Clinical Study Protocol	
Drug Substance	Durvalumab
Study Code	D933AC00001
Version	7.0
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A Phase III Randomized, Double-Blind, Placebo-Controlled, Multi-Regional, International Study of Durvalumab in Combination with Gemcitabine plus Cisplatin versus Placebo in Combination with Gemcitabine plus Cisplatin for Patients with First-Line Advanced Biliary Tract Cancers (TOPAZ-1)

Sponsor: AstraZeneca AB

Local Sponsor in Japan: AstraZeneca K.K.

Regulatory Agency Identifying Number(s): IND 141072; EudraCT 2018-004688-30

VERSION HISTORY

Version 1.0, 19 December 2018	
Initial creation	
Version 2.0, 21 March 2019	
Section	**Summary of change**
6.1.3 Duration of treatment and criteria for treatment through progression	Clarification of the requirement for treatment beyond progression as follows: • Patients with RECIST 1.1 defined radiological PD who continue to receive their assigned treatment at the discretion of the Investigator and patient (following consultation with AstraZeneca) can receive treatment until no longer having clinical benefit, and imaging for tumor assessments should be continued at a maximum scan interval of 8 weeks for the duration of treatment unless there is unacceptable toxicity, or another discontinuation criterion is met. • The decision of treatment through progression should be made after careful assessment of derived clinical benefit and risk of assigned treatment, followed by discussion and agreement between the investigators and the patients.
Version 3.0, 18 Sep 2019	
Section	**Summary of change**
1.1 Schedule of activities	This section updated with several changes as below • Added treatment discontinuation visit • Added additional assessment: Coagulation (aPTT and INR) • Patients with known diagnosis of hepatitis B and Patients without history of hepatitis B will be monitored during study period. This activity is added into SoA. • Changed the ePRO assessment schedule to align with the Durvalumab dose. • Added the collection of Serum sample for biomarkers • Footnote was updated per SOA activities • Updated the title of follow-up assessments and note
1.2 Synopsis	This section updated with several changes as below • Clarified the secondary endpoint of ADA • Updated the exploratory objective and endpoint of TMB and MSI and make it more clearly. • Removed the exploratory biomarkers in overall design since it is exploratory research. • Clarified the interim analysis to align with analysis plan • Clarified the PFS analysis to align with analysis plan
3. Objective and endpoint	This section updated with several changes as below • Clarified the secondary endpoint of ADA

	• Updated the exploratory objective and endpoint of TMB and MSI and make it more clearly. • Clarified the exploratory objective and endpoint of ctDNA
5.1 Inclusion criteria	This section updated with several changes as below • Updated the inclusion criteria of serum bilirubin, AST and ALT • Updated the inclusion criteria 3 • Added the inclusion criteria for patients with virology
5.2 Exclusion criteria	This section updated with several changes as below • Removed the exclusion criteria for patients with HBV infection • Clarified the exclusion criteria for active infection of hepatitis C
6.1.1 Investigational products	Updated table 7 with information on Placebo and packing and labeling.
6.1.1.1 Durvalumab	This section updated with several changes as below • Corrected that the Durvalumab must be prepared by the unblinded site staff • Clarified the Durvalumab preparation to maintain double-blind conditions
6.1.1.3 Placebo	Updated the placebo preparation method
6.1.2.1 Durvalumab (MEDI4736) or placebo plus gemcitabine/cisplatin	Updated information on dosing schedule and treatment discontinuation.
6.1.3 Duration of treatment and criteria for treatment through progression	Removed some redundant wording
6.2.1 Patient enrollment and randomization	Removed that “patients with a single TL, if the screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired.”
6.2.4 Method for ensuring blinding	This section updated with several changes as below • Clarified the Durvalumab and placebo preparation to maintain double-blind conditions • Removed the sponsor must be notified before the blind is broken
6.5 Dose modification	Updated information on discontinuation visit.
7.1 Discontinuation of study treatment	Added discontinuation visit.
8.1.1 Central reading of scans	Updated information on BICR
8.1.3.5 Administration of patient-reported outcome questionnaires	Updated the instructions when collecting the PRO data
8.2.1 Clinical safety laboratory assessments	Added the requirement of data collection for subject with hepatitis
8.2.4 Electrocardiograms	Removed the requirement of obtaining ECG in triplicate

8.3.13 Adverse events of special interest	Updated information of AESI
8.4.2 Regulatory Reporting Requirements for SAE	Added the Regulatory Reporting Requirements for SAE
8.4.6.1 Specific toxicity management and dose modification information – durvalumab	Added additional more information of TMG as an Annex of the protocol.
8.5.2 Collection of samples to measure for the presence of ADAs	Added information on specific requirements for PK collection.
8.7.2 Additional Exploratory Genetic testing	Added additional exploratory genetic testing
8.8.1 Collection of tumor sample for biomarker assessment	This section updated with several changes as below • Clarified the importance of sample integrity and structural morphology • Removed that patients with a single TL, if the screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired.”
8.8.3 Exploratory biomarkers	This section updated with several changes as below • Added the collection of microsatellite instability (MSI) and tumor mutation burden (TMB) • Updated tumor microenvironment biomarkers • Updated soluble factors – plasma • Added the collection of serum sample for biomarkers
9.2 Sample size determination	This section updated with several changes as below • Removed the content of analysis period • Added information on analysis methods
9.3 Populations for analyses	Updated the summary of outcome variables and analysis populations
9.4.1.1 RECIST 1.1-based endpoints	Clarified the BICR
9.3.4 ADA analysis set	This section updated with several changes as below • Added ADA analysis set
9.4.3 Calculation or derivation of patient-reported outcome variables	Updated the description way for the score evaluation
9.5 Statistical analyses	This section updated with several changes as below • Clarified the objective response rate and duration of response • Updated the number which will be applied to OS IA-2 and FA to align the analysis plan
9.5.1.1 Primary endpoint: overall survival	Clarified the PD-L1 status

9.5.6 Methods for multiplicity control	This section updated with several changes as below • Clarified the methods for multiplicity control to align the analysis plan • Updated figure 3
9.6 Interim analyses	• Added ORR assumption information
Appendix B	Added definition on AEs for Malignant tumor
Appendix E	This section updated with several changes as below • Updated the report process of Potential Hy's law and Hy's law cases. • Definition of 'significant change' moved to section F-4.2, where it is first mentioned.
Appendix F	This section updated with several changes as below • Removed that "patients with a single TL, if the screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired." • Added clarification for TL has had any intervention
Version 4.0, 17 Apr 2020	
Section	**Summary of change**
Version History	Updated summary of changes provided to the version 3.0 but not incorporated in the table.
1.1 Schedule of activities	This section updated with several changes as below • Updated HCV RNA test for patients with known diagnosis of hepatitis B • Removed HCV genotype for patients without history of hepatitis B • Updated HCV RNA test for patients without history of hepatitis B • Added new footnote for HCV RNA testing • Updated footnote for virology tests for patients with known diagnosis of hepatitis B • Added a specific window for virology tests in case of dosing delay • Updated footnote for virology tests for patients without history of hepatitis B • Removed "CT or MRI" from tumor evaluation description • Corrected footnote for PK collection at C7D1 • Updated the timing of the ePRO assessment • Added information on EORTC BIL21 for patients in India • Footnotes was updated per SOA activities
1.2 Synopsis	This section updated with several changes as below • Clarified the exploratory endpoints of biomarkers • Updated the sample size and the statistical assumptions • Clarified the number of randomized patients from China • Updated estimated date of the last patient enrolled
3 Objectives	Clarified the exploratory endpoints of biomarkers
4.1 Overall design	This section updated with several changes as below

	• Updated the sample size • Clarified the number of randomized patients from China
5.1 Inclusion criteria	This section updated with several changes as below • Added a clarification for biliary obstruction in inclusion criterion 11 • Clarified inclusion criterion 16
6.1.1 Investigational products	Added % of saline and dextrose solution for placebo
6.1.1.1 Durvalumab (MEDI4736)	This section updated with several changes as below • Added a description of product appearance • Added further clarification for the preparation and storage of IP, blinding measures and IV line flushing
6.1.1.3 Placebo	Clarified infusion details, to align with section 6.1.1.1
6.1.2.1 Durvalumab (MEDI4736) or placebo plus gemcitabine/cisplatin	Removed some redundant wording
6.1.3 Duration of treatment and criteria for treatment through progression	This section updated with several changes as below • Corrected an error of the wording in the criteria for treatment through progression • Clarified the requirement for treatment beyond progression
6.1.4 Storage	Updated the storage instruction for cisplatin and gemcitabine
6.2.4 Methods for ensuring blinding	Updated the wording to match in the other section
8.1.2 Survival assessments	Updated the OS events
8.1.3.5 Administration of patient-reported outcome questionnaires	This section updated with several changes as below • Added information on EORTC BIL21 for patients in India • Clarified the timing of the ePRO assessment
8.2.1 Clinical safety laboratory assessments	This section updated with several changes as below • Removed HCV genotype • Added Coagulation (aPTT and INR) to the Table 11
8.7.2 Additional Exploratory Genetic testing	Updated buffy coats usage
8.8.3 Exploratory biomarkers	This section updated with several changes as below • Added a clarification of the measurement of biomarkers • Added a method for the test of tumor microenvironment biomarkers • Added usage of the whole blood samples
9.2 Sample size determination	This section updated with several changes as below • Updated the sample size and the statistical assumptions • Clarified the number of randomized patients from China
9.4.1.1 RECIST 1.1-based endpoints	Updated BICR description

9.4.1.4 Objective response rate	Updated ORR evaluation at IA-1
9.4.1.5 Duration of response	Updated DoR evaluation at IA-1
9.5.1 Efficacy analyses	This section updated with several changes as below • Updated the OS events at the IA-2 and FA and maturity at the IA-2 • Updated Table 17 to align with sections 9.4.1.4 and 9.4.1.5
9.5.1.1 Primary endpoint: overall survival	Removed high versus low/negative from the PD-L1 status in the section of subgroup analysis
9.5.1.3 Objective response rate	Updated ORR evaluation at IA-1
9.5.1.4 Duration of response	Updated DoR evaluation at IA-1
9.5.6 Methods for multiplicity control	This section updated with several changes as below • Updated the sample size and the statistical assumptions • Updated Figure 3
9.6 Interim analyses	This section updated with several changes as below • Clarified the population for IA1 • Updated the timing of IA1 and IA2 • Updated the statistical assumption of IA2
Appendix C	This section updated with several changes as below • Updated instruction for withdrawal of consent for biological samples • Updated IATA 6.2 Guidance document
Appendix D	This section updated with several changes as below • Changed appendix title to Optional Genomics initiative sample • Genotype changed to genetic in DM part • Removed Statistical methods and determination of sample size part
Appendix F	This section updated with several changes as below • Progressive disease corrected for partial response in RECIST 1.1 NLT assessment follow-up part • Updated instruction for follow-up scan evaluation

Version 6.0, 28 Oct 2020

Note: **Version 5.0, 07 Oct 2020** won't be implemented due to text formatting errors found after document finalization. Therefore version 6.0 is following CSP v 4.0 and implementing all changes below.

Section	**Summary of change**
1.2 Synopsis	Updated the information fraction for OS at IA2 to 80% and the related numbers (number of events, maturity, significance levels, critical HR and timing of IA2) accordingly.
8.1.2 Survival assessments	Updated the information fraction for OS at IA2 to 80% and the related numbers (number of events and significance levels)

9.2 Sample size determination	Updated the information fraction for OS at IA2 to 80% and the related numbers (number of events, maturity, significance levels, critical HR and timing of IA2) accordingly.
9.5.1 Efficacy analyses	Updated the information fraction for OS at IA2 to 80% and the related numbers (number of events and maturity) accordingly.
9.5.6 Methods for multiplicity control	Updated the information fraction for OS at IA2 to 80% and the related numbers (number of events, maturity, significance levels, powers, critical HRs and timing of IA2) accordingly. Updated Figure 3.
9.6 Interim analyses	Updated the information fraction for OS at IA2 to 80% and the related numbers (number of events, maturity, significance levels and timing of IA2) accordingly.

Version 7.0, 01 Mar 2021	
Section	**Summary of change**
Table of Contents	Formatting of document and Table of Contents was revised to ensure correct sections, tables and figures listing.
1.2 Synopsis	Statistical methods: Added notes about FH(0, 1) OS analysis at FA and power at IA-2.
2.3.2.1 Durvalumab 8.3.13 Adverse events of special interest	Durvalumab risks updated as per Investigator Brochure v.16.
4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	Subsection added detail for mitigation in case of study disruption due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis i.e. COVID 19.
8.1.2 Survival assessments	Deleted a paragraph with references to power calculations and multiplicity adjustments, since Section 8.1.2 should describe data collection to support survival analysis.
8.4.6.1 Specific toxicity management and dose modification information – durvalumab	The name of document describing Toxicity Management Guidelines as Annex to Protocol was updated to currently used title: “Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy Sentence referring to TMG portal link was removed as portal was decommissioned.
9.2 Sample size determination	Added power calculations for FH(0, 1) and clarified that other calculations were for log-rank test.
9.5.1 Efficacy analyses	Changed testing method for OS at FA from stratified log-rank to FH(0, 1). Changed ORR analysis method from logistic regression to stratified CMH test following feedback from FDA.

9.5.1.1 Primary endpoint	Changed testing method for OS at FA from stratified log-rank to FH(0, 1). Updated text about the Cox sensitivity model. Added stratified log-rank test as a sensitivity model for p-value at FA. Included rational for using FH(0, 1) test instead of a log-rank test at FA.
9.5.1.2 Progression-Free Survival	Corrected “Confirmatory secondary PFS” to “Secondary PFS”.
9.5.1.3 Objective Response Rate	Following FDA feedback changed ORR analysis method from logistic regression to stratified CMH test.
9.5.6 Methods for multiplicity control	Clarified statistical significance determination at FA using FH(0.1). Deleted Figure 3 after the method of testing for OS at FA was changed to FH(0, 1)
10 References	Included one new reference.
Appendix I	Appendix added detail for mitigation in case of study disruption due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis i.e. COVID 19.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 PROTOCOL SUMMARY

1.1 Schedule of activities

The procedures for the screening and treatment periods in this study are presented in Table 1, and the procedures for the follow-up period are presented in Table 2.

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw (eg, pharmacokinetic [PK] blood sample) to occur at the timepoints indicated in the schedule of activities (SoAs). Whenever electrocardiograms (ECGs), vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in the SoAs.

For durvalumab (or placebo)

- Patients may delay dosing under certain circumstances.
  - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines due to either an immune or a non-immune-related adverse event (AE).
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
  - Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (Response Evaluation Criteria in Solid Tumors [RECIST]) and patient-reported outcome (PRO) assessments. Subsequent time between 2 consecutive doses cannot be <21 days based on the half-lives of durvalumab (see the current Investigator's Brochure [IB] for durvalumab).

For gemcitabine/cisplatin

- Patients may delay and subsequently resume dosing per local standard clinical practice.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible.

Table 1 Schedule of assessments for screening and treatment period

	Screening	1 cycle=3 weeks (during chemotherapy)[a]																1 cycle =4 weeks	Treatment discontinuation visit[ee]	For details, see Section
		C1D1	C1D8	C2D1	C2D8	C3D1	C3D8	C4D1	C4D8	C5D1	C5D8	C6D1	C6D8	C7D1	C7D8	C8D1	C8D8	C9 to PD[b] (q4w)		
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**13**	**15**	**16**	**18**	**19**	**21**	**22**	**24**		
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	**85**	**92**	**106**	**113**	**127**	**134**	**148**	**155**	**169**		
Window (days)[a]	**NA**	**NA**	**Window for each assessment ±3 days, window for tumor assessment ±7 days**																	
Informed consent for study procedures, including biomarker sample collection[c]	X																			5.1
Consent: Genetic sample and analysis (optional)[d]	X																			8.7, Appendix D
Study Procedures																				
Full physical examination	X																			8.2.2
Targeted physical examination (based on symptoms)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.2

	Screening	1 cycle=3 weeks (during chemotherapy)[a]																1 cycle =4 weeks	Treatment discontinuation visit[ee]	For details, see Section
		C1D1	C1D8	C2D1	C2D8	C3D1	C3D8	C4D1	C4D8	C5D1	C5D8	C6D1	C6D8	C7D1	C7D8	C8D1	C8D8	C9 to PD[b] (q4w)		
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**13**	**15**	**16**	**18**	**19**	**21**	**22**	**24**		
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	**85**	**92**	**106**	**113**	**127**	**134**	**148**	**155**	**169**		
Window (days)[a]	**NA**	**NA**	**Window for each assessment ±3 days, window for tumor assessment ±7 days**																	
Vital signs (temperature, respiratory rate, blood pressure, pulse rate, and weight)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.3
12-lead ECG[e]	X	At each infusion visit as clinically indicated																		8.2.4
Concomitant medications	X	At each infusion visit AND as clinically indicated																		6.4
Demography, including baseline characteristics	X																			5.1
Eligibility criteria	X																			5.1, 5.2
Brain MRI (preferred) or CT scan[f]	X																			5.2
Laboratory assessments																				
Clinical chemistry[g,h]	X[i]	X[i]	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	Table 10

	Screening	1 cycle=3 weeks (during chemotherapy)[a]																1 cycle =4 weeks	Treatment discontinuation visit[ee]	For details, see Section
		C1D1	C1D8	C2D1	C2D8	C3D1	C3D8	C4D1	C4D8	C5D1	C5D8	C6D1	C6D8	C7D1	C7D8	C8D1	C8D8	C9 to PD[b] (q4w)		
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**13**	**15**	**16**	**18**	**19**	**21**	**22**	**24**		
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	**85**	**92**	**106**	**113**	**127**	**134**	**148**	**155**	**169**		
Window (days)[a]	**NA**	**NA**	**Window for each assessment ±3 days, window for tumor assessment ±7 days**																	
Hematology[g,h]	X[i]	X[i]	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	Table 11
Coagulation (aPTT and INR)	X[i]	X[i]	As clinically indicated																	Table 11
CA-19-9 and CEA (serum)		X		X		X		X		X		X		X		X		X	X	8.2.1.1
TSH, free T3, and free T4[j]	X	X		X		X		X		X		X		X		X		X	X	Table 10
Urinalysis	X[i]	X[i]		X		X		X		X		X		X		X		X	X	8.2.1
HIV	X																			8.2.1

	Screening	1 cycle=3 weeks (during chemotherapy)[a]																1 cycle =4 weeks	Treatment discontinuation visit[ee]	For details, see Section
		C1D1	C1D8	C2D1	C2D8	C3D1	C3D8	C4D1	C4D8	C5D1	C5D8	C6D1	C6D8	C7D1	C7D8	C8D1	C8D8	C9 to PD[b] (q4w)		
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**13**	**15**	**16**	**18**	**19**	**21**	**22**	**24**		
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	**85**	**92**	**106**	**113**	**127**	**134**	**148**	**155**	**169**		
Window (days)[a]	**NA**	**NA**	**Window for each assessment ±3 days, window for tumor assessment ±7 days**																	
Patients with known diagnosis of hepatitis B Qualitative HBsAg, qualitative HBeAg, anti-HBc, anti-HBs, anti-HBe, quantitative HBV DNA, anti-HCV, HCV RNA[k] and anti-HDV[l]	X	X		X		X		X		X		X		X		X		X	X	8.2.1

	Screening	1 cycle=3 weeks (during chemotherapy)[a]																1 cycle =4 weeks	Treatment discontinuation visit[ee]	For details, see Section
		C1D1	C1D8	C2D1	C2D8	C3D1	C3D8	C4D1	C4D8	C5D1	C5D8	C6D1	C6D8	C7D1	C7D8	C8D1	C8D8	C9 to PD[b] (q4w)		
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**13**	**15**	**16**	**18**	**19**	**21**	**22**	**24**		
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	**85**	**92**	**106**	**113**	**127**	**134**	**148**	**155**	**169**		
Window (days)[a]	**NA**	**NA**	**Window for each assessment ±3 days, window for tumor assessment ±7 days**																	
Patients without history of hepatitis B, anti-HCV, HCV RNA[k], qualitative HBsAg, quantitative HBV DNA, anti-HBc, and anti-HBs[m]	X	As clinically indicated																		8.2.1
Pregnancy test[n]	X	X		X		X		X		X		X		X		X		X		8.2.1
Efficacy assessments																				
Tumor evaluation (RECIST 1.1)[o]	X[p]	On-study tumor assessments will be done q6w±1w for the first 24 weeks (relative to the date of randomization) and then q8w±1w thereafter (relative to the date of randomization) until RECIST 1.1-defined radiological PD plus at least 1 additional follow-up scan. This on-study imaging schedule MUST be followed regardless of any delays in dosing. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression), every attempt should be made to acquire subsequent images at the next regularly scheduled imaging visit.																		8.1, Appendix F
PK																				
Durvalumab PK sample		X[q,r]		X[r]						X[q,r]				X[r]					X	8.5
Monitoring																				

	Screening	1 cycle=3 weeks (during chemotherapy)[a]																1 cycle =4 weeks	Treatment discontinuation visit[ee]	For details, see Section
		C1D1	C1D8	C2D1	C2D8	C3D1	C3D8	C4D1	C4D8	C5D1	C5D8	C6D1	C6D8	C7D1	C7D8	C8D1	C8D8	C9 to PD[b] (q4w)		
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**13**	**15**	**16**	**18**	**19**	**21**	**22**	**24**		
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	**85**	**92**	**106**	**113**	**127**	**134**	**148**	**155**	**169**		
Window (days)[a]	**NA**	**NA**	**Window for each assessment ±3 days, window for tumor assessment ±7 days**																	
WHO/ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.2.5
AE/SAE assessment	X	At each infusion visit AND as clinically indicated																		8.3
IP administration (interval between 2 consecutive doses cannot be <21 days)																				
Durvalumab (or placebo)[s]		X		X		X		X		X		X		X		X		X		6.1.1.1, 6.1.1.3 6.1.2.1
Cisplatin[s,t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			6.1.1.2, 6.1.2.1
Gemcitabine[s,t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			6.1.1.2, 6.1.2.1
PRO assessments																				

	Screening	1 cycle=3 weeks (during chemotherapy)[a]																1 cycle =4 weeks	Treatment discontinuation visit[ee]	For details, see Section
		C1D1	C1D8	C2D1	C2D8	C3D1	C3D8	C4D1	C4D8	C5D1	C5D8	C6D1	C6D8	C7D1	C7D8	C8D1	C8D8	C9 to PD[b] (q4w)		
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**13**	**15**	**16**	**18**	**19**	**21**	**22**	**24**		
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	**85**	**92**	**106**	**113**	**127**	**134**	**148**	**155**	**169**		
Window (days)[a]	**NA**	**NA**	**Window for each assessment ±3 days, window for tumor assessment ±7 days**																	
EORTC QLQ-C30/BIL21, PGIS, EQ-5D-5L, and PRO-CTCAE[u,v]		X		X		X		X		X		X		X		X		X[w]		8.1.3
Other laboratory assessments and assays																				
Immunogenicity assessment for durvalumab (ADA sampling to identify ADA responses in patient circulation)		X[r]								X[r]				X[r]					X	8.5.2
Circulating soluble factors (plasma)		X[r,x]				X				X				X				X[y]		8.8.3
Whole blood for gene expression (PAXgene RNA tubes)		X[r]	X															X[y]		8.8.3

	Screening	1 cycle=3 weeks (during chemotherapy)[a]																1 cycle =4 weeks	Treatment discontinuation visit[ee]	For details, see Section
		C1D1	C1D8	C2D1	C2D8	C3D1	C3D8	C4D1	C4D8	C5D1	C5D8	C6D1	C6D8	C7D1	C7D8	C8D1	C8D8	C9 to PD[b] (q4w)		
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**13**	**15**	**16**	**18**	**19**	**21**	**22**	**24**		
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	**85**	**92**	**106**	**113**	**127**	**134**	**148**	**155**	**169**		
Window (days)[a]	**NA**	**NA**	**Window for each assessment ±3 days, window for tumor assessment ±7 days**																	
Mandatory provision of tumor biopsy sample (newly acquired[z] or archival FFPE ≤3 years old)[aa]	X																			8.8.1
Optional additional tumor biopsy		At time of progression[bb]																		8.8.1
Clinical care tumor biopsy		Additional tumor biopsies collected as part of clinical care (eg, for mixed responses) can be submitted for further analysis[cc].																		8.8.1
Genetic sample (optional DNA element for long-term storage/future use)[d]		X																		8.7, Appendix D
Serum sample for biomarkers		X				X														8.8.3
Health economics measurements																				
HOSPAD[dd]	X	X		X		X		X		X		X		X		X		X		8.9

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated. Every effort should be made to minimize the time between randomization and starting treatment. It is strongly recommended that patients commence study drug on the same day as randomization. If same-day treatment is not possible, then the study treatment must occur within 3 days of randomization. Patients must not be randomized and treated unless all eligibility criteria have been met. Screening procedures must take place on Days -28 to -1 with respect to randomization.
Note: For patients who have discontinued gemcitabine/cisplatin due to treatment-related toxicity before completion of Cycle 8, treatment with durvalumab/placebo may continue at the Investigator's discretion. when toxicity resolves to Grade 2 or less; in that case, durvalumab/placebo monotherapy will be administered q4w.
Note: During the first 8 cycles of durvalumab or placebo in combination with gemcitabine/cisplatin, if durvalumab or placebo must be delayed due to durvalumab- or placebo- related toxicity, treatment with Gemcitabine/Cisplatin may continue at the discretion of the investigator. In that case, the all of the assessment except PK, ADA and PRO should be completed as described in table1.

[a] For durvalumab treatment schedules, if there is a dosing delay while on the q3w schedule, all future dosing days should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days. For gemcitabine/cisplatin, dosing delays should be managed according to local prescribing guidelines. If treatment with durvalumab/placebo is delayed, the cycle number and week number should be delayed until treatment with durvalumab/placebo resumes.

[b] Treatment to continue until clinical progression or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Patients will be offered the opportunity to continue their assigned study treatment regimen after RECIST 1.1-defined radiological PD, at the discretion of the Investigator and patient, provided certain criteria (as outlined in Section 6.1.3) are met.

[c] If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes, with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization (except for screening clinical chemistry and hematology assessments, which must be obtained within 7 days prior to randomization).

[d] The sample for genetic research will be obtained at Day 1 pre-dose (at or after randomization). If, for any reason, the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study.

[e] Echocardiograms will be performed as needed per patient status at the discretion of the Investigator or Physician Designee if the patient exhibits any symptoms (eg, myocarditis or any myocardial imAE). Patients with past medical history of ischemic heart disease or arrhythmia or patients who develop myositis during the course of study are examples of patients who need ECG at each infusion visit.

[f] Mandatory only for patients with suspected brain metastases at screening.

[g] Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion (samples must have been obtained within 3 days prior to the infusion).

[h] Serum or plasma clinical chemistry (including liver function test monitoring) and hematology may be performed more frequently, if clinically indicated.

[i] Screening clinical chemistry and hematology assessments must be obtained within 7 days prior to randomization. If screening clinical chemistry, hematology coagulation and urinalysis assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

[j] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1. Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[k] HCV RNA testing is required at screening for patients who test positive for anti-HCV. For patients with diagnosis of HBV, HCV RNA testing is required only for patients with inactive infection as evidenced by negative HBsAg and undetectable HBV DNA at baseline.

[l] In patients with known hepatitis B, anti-HCV, anti-HDV, anti-HBc, and anti-HBs will only be collected at screening.
Note: In the case of dosing delay the on-treatment virology tests (Qualitative: HBsAg, HBeAg, anti-HBe and Quantitative: HBV DNA) do not need to be repeated if collected within 14 days of the rescheduled dose of durvalumab/placebo.

[m] If the HBsAg or anti-HBc are positive or HBV DNA is detectable at screening, then the assessments should be according to the requirements for patients with known diagnosis of hepatitis B. HBV DNA testing is required at screening for patients who test positive for HBsAg and/or anti-HBc.

[n] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then on Day1 of every cycle. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

[o] Baseline RECIST 1.1 assessments (selection of TLs and NTLs) should be performed on images from CT scans (preferred) or MRI scans, each preferably with IV contrast, of the chest, abdomen, and pelvis, acquired no more than 28 days before the date of randomization and, ideally, should be performed as close as possible to and prior to the date of randomization. Additional anatomy should be imaged based on the signs and symptoms of individual patients at baseline and follow-up. The follow-up scan collected after a RECIST 1.1-defined radiological PD should be performed preferably at the next (and no later than the next) scheduled imaging visit and no less than 4 weeks after the prior assessment of PD; this follow-up scan is evaluated using the criteria outlined in Appendix F. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression), every attempt should be made to perform the subsequent assessments at their next regularly scheduled visit. Copies of all images are retained at the investigative site as source documents, and all images are preferably submitted electronically to the AstraZeneca-appointed iCRO for QC, storage, and BICR. See Section 8.1 and Appendix F for additional details relevant to imaging and tumor assessments.

[p] A patient's diagnostic scan may be used as a baseline scan if it is taken within 28 days prior to randomization and it is in full accordance with the image acquisition guidelines provided by the AstraZeneca-appointed iCRO and as outlined in Appendix F, ie, IV contrast-enhanced CT/MRI of the chest, abdomen, and pelvis.

[q] PK sampling should be performed within 60 minutes after the end of infusion.

[r] Pre-dose samples should be collected within 60 minutes pre-dose.

[s] The immunotherapy agents are infused first, followed by the gemcitabine/cisplatin regimen.

[t] IV cisplatin is given on Days 1 and 8 of each cycle (q3w), infused according to local labeling. IV gemcitabine is given on Days 1 and 8 of each cycle (q3w), infused according to local labeling. Treatment with gemcitabine/cisplatin on Days 1 and 8 of each cycle is continued up to 8 cycles until clinical progression or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

[u] PRO questionnaires will be administered using a site-based ePRO tablet device, which should be completed in private and prior to treatment administration, and ideally before discussion of health status, to avoid biasing the patient's responses to the questions. As feasible, site staff should ensure PRO questionnaires are completed prior to other study procedures, such as laboratory samples, to further minimize bias. If there are dose delays, the PRO assessment schedule should continue to follow the Durvalumab treatment schedule. EORTC BIL21 will not be used in India except for patients, who are able to complete the questionnaire in Bengali or English languages.

[v] PRO-CTCAE will be administered only in the languages where a linguistically validated version exists.

[w] After Cycle 16 Day 1, administer PRO questionnaires every other cycle.

[x] The buffy coat layer will be collected during the plasma isolation process.

[y] Samples will be collected upon progression.

[z] Tumor lesions used for biopsies acquired during screening should not be the same lesions used as RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy; in this instance, only core needle (not excisional/incisional) biopsy is allowed.

[aa] Provision of a newly acquired tumor sample during screening (preferred) or archival FFPE obtained ≤3 years prior to screening is mandatory for this study.

[bb] The collection of tumor biopsies at the time of progression is optional but strongly encouraged.

[cc] The collection of tumor biopsies as part of clinical care (eg, for mixed responses) is optional but strongly encouraged.

[dd] At each scheduled visit, sites are to review if a hospital admission has been made since the last visit; if it has, then HOSPAD is completed. This module should be completed whenever the patient has attended or been admitted to the hospital (ie, each hospital admission, outpatient, or emergency room attendance encountered). It excludes routine study-related follow-up clinic visits.

[ee] Treatment discontinuation visit must be performed at the time the decision is made to permanently discontinue durvalumab/placebo. If durvalumab/placebo must be discontinued due to durvalumab- or placebo-related toxicity while the patient is receiving treatment with SOC (eg during cycles 1-8), patients must complete the treatment discontinuation visit and enter the follow-up period. Treatment with Gemcitabine/cisplatin may continue at the discretion of the investigator during the follow up period when toxicity resolves to grade 2 or better, and should be recorded in the eCRF as subsequent anticancer treatment.

ADA Anti-drug antibody; AE Adverse event; BICR Blinded independent central review; C Cycle; CA-19-9 Carbohydrate antigen 19-9; CEA Carcinoembryonic antigen; CT Computed tomography; D Day; DNA Deoxyribonucleic acid; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; ePRO Electronic patient-reported outcome; EQ-5D-5L EuroQol 5-dimension, 5-level health state utility index; FFPE Formalin-fixed and paraffin-embedded; HIV Human immunodeficiency virus; HOSPAD Hospital resource use module; iCRO Imaging Contract Research Organization; imAE Immune-mediated adverse event; IP Investigational product; IV Intravenous; MRI Magnetic resonance imaging; NA Not applicable; NTL Non-Target Lesion; PD Progressive disease; PD-L1 Programmed cell death ligand-1; PGIS Patient Global Impression of Severity; PK Pharmacokinetic(s); PRO Patient-reported outcome; PRO-CTCAE Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; q3w Every 3 weeks; q4w Every 4 weeks; q6w Every 6 weeks; q8w Every 8 weeks; QC Quality control; QLQ-BIL21 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire; QLQ-C30 30-Item Core Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; RNA Ribonucleic acid; SAE Serious adverse event; T3 Triiodothyronine; T4 Thyroxine; TL Target Lesion; TSH Thyroid-stimulating hormone; w Weeks; WHO World Health Organization.

Table 2 Schedule of follow-up assessments for patients who have discontinued durvalumab/placebo treatment

Evaluation	Time since the last dose of IP (Durvalumab/Placebo)								For details, see Section
	Day (±3)[l]	Months (±1 week)						12 months and every 6 months (±2 weeks)	
	30	2	3	4	6	8	10		
Physical examination (full)	X	X	X						8.2.2
Vital signs	X	X	X						8.2.3
Pregnancy test[a]	X	As clinically indicated							8.2.1
AE/SAE assessment[b]	X	X	X						8.3
Concomitant medications	X	X	X						6.4
WHO/ECOG PS[c]	At timepoints consistent with tumor assessments; at 30, 60, and 90 days; and then at the initiation of subsequent anticancer therapy								8.2.5
Survival status: For all patients, including phone contact with patients who refuse to return for evaluations and agree to be contacted[d]		X		X	X	X	X	X (every 2 months)	8.1.2
Subsequent anticancer therapy[e]	X	X	X	X	X	X	X	X	8.1.2
Serum or plasma chemistry	X	X	X						Table 10
Hematology	X	X	X						Table 11
CA-19-9 and CEA (serum)	X	X	X						8.2.1.1
Thyroid function tests (TSH, free T3, and free T4)[f]	X								Table 10
Durvalumab PK sample (serum)	X[g]		X[g]						8.5
Immunogenicity assessment (ADA sampling [including ADA neutralizing antibodies] to identify ADA responses in patient circulation) for durvalumab	X[h]		X[h]						8.5.2

Evaluation	Time since the last dose of IP (Durvalumab/Placebo)								For details, see Section
	Day (±3)[l]	Months (±1 week)						12 months and every 6 months (±2 weeks)	
	30	2	3	4	6	8	10		
EORTC QLQ-C30/BIL21, PGIS and EQ-5D-5L[i]	X	X	X	Patients who completed/discontinued treatment without RECIST 1.1-defined radiological PD will continue assessments relative to tumor scan assessment (q6w ±1w for the first 24 weeks and then q8w±1w thereafter) until RECIST 1.1-defined radiological PD, subsequent therapy, withdrawal from study, or death, whichever occurs first							8.1.3
PRO-CTCAE[i]	X	X	X						8.1.3
Health resource use (HOSPAD module)[j]	X								8.9
Tumor assessment (RECIST 1.1)[k]	On-study tumor assessments will be done q6w±1w for the first 24 weeks (relative to the date of randomization) and then q8w±1w thereafter (relative to the date of randomization) until RECIST 1.1-defined radiological PD plus at least 1 additional follow-up scan. This on-study imaging schedule MUST be followed regardless of any delays in dosing. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression), every attempt should be made to acquire subsequent images at the next regularly scheduled imaging visit.								8.1

[a] For women of childbearing potential. A urine or serum pregnancy test is acceptable.
[b] AEs and SAEs will be collected until 90 days following discontinuation of study treatment (ie, the last dose of durvalumab [or placebo] plus gemcitabine/cisplatin or the last dose of durvalumab [or placebo] monotherapy).
[c] ECOG PS will be collected, if available, at the calls every 2 months to obtain subsequent anticancer therapy and survival status. WHO/ECOG performance status should also be collected at other site visits that the patient attends, if appropriate site staff are available to collect such information. In addition, WHO/ECOG performance status should be provided when information on subsequent anticancer therapy is provided, where possible.
[d] Patients may be contacted within 7 days following DCOs to confirm survival status.
[e] Will be collected until the end of the clinical phase of the study (final study visit). Details of any treatment for BTC (including surgery) after the last dose of study treatment must be recorded in the eCRF.
[f] Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[g] The PK follow-up sample is to be taken 30 days±3 days and 90 days±7 days after the last dose of durvalumab.
[h] A sample to look for antibodies to durvalumab will be taken 30 days±3 days and 90 days±7 days after the last dose of durvalumab.

[i] PRO questionnaires will be administered using a site-based ePRO tablet device, which should be completed in private and ideally before discussion of health status, to avoid biasing the patient's responses to the questions. As feasible, site staff should ensure PRO questionnaires are completed prior to other study procedures, such as laboratory samples, to further minimize bias. PRO-CTCAE will be administered only in the languages where a linguistically validated version exists. EORTC BIL21 will not be used in India except for patients, who are able to complete the questionnaire in Bengali or English languages.

[j] The site should complete the HOSPAD form at every scheduled study clinic visit up to, and including, the study treatment discontinuation follow-up visit. If the patient discontinues study treatment for reasons other than RECIST 1.1-defined radiological PD, the HOSPAD form should continue to be completed until RECIST 1.1-defined radiological PD has been assessed.

[k] RECIST 1.1 assessments will be performed on images from CT scans (preferred) or MRI scans, each preferably with IV contrast, of the chest, abdomen, and pelvis. Additional anatomy should be imaged based on the signs and symptoms of individual patients at baseline and follow-up. The follow-up scan collected after a RECIST 1.1-defined radiological PD should be performed preferably at the next (and no later than the next) scheduled imaging visit and no less than 4 weeks after the prior assessment of PD; this follow-up scan is evaluated using the criteria outlined in Appendix F). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression), every attempt should be made to perform the subsequent assessments at their next regularly scheduled visit. Copies of images are retained at the investigative site as source documents, and all images are preferably submitted electronically to the AstraZeneca-appointed iCRO for QC, storage, and BICR. See Section 8.1 and Appendix F for additional details relevant to imaging and tumor assessments.

[l] If the day of treatment discontinuation visit is in the window of Day30 since the last dose of IP, the overlapping tests do not need to be repeated.

ADA Anti-drug antibody; AE Adverse event; BICR Blinded independent central review; BTC biliary tract cancer; CA-19-9 Carbohydrate antigen 19-9; CEA Carcinoembryonic antigen; CSP Clinical study protocol; CT Computed tomography; DCO Data cutoff; eCRF Electronic case report form; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EORTC European Organisation for Research and Treatment of Cancer; EOT End of treatment; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; iCRO Imaging Contract Research Organization; IP Investigational product; IV Intravenous; MRI Magnetic resonance imaging; NA Not applicable; PD Progressive disease; PGIS Patient Global Impression of Severity; PK Pharmacokinetic; PRO Patient-reported outcome; PRO-CTCAE Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; PS Performance status; q6w Every 6 weeks; q8w Every 8 weeks; QC Quality control; QLQ-BIL21 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire; QLQ-C30 30-Item Core Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid-stimulating hormone; w Weeks; WHO World Health Organization.

1.2 Synopsis

International Co-ordinating Investigator

Protocol Title:

A Phase III Randomized, Double-Blind, Placebo-Controlled, Multi-Regional, International Study of Durvalumab in Combination with Gemcitabine plus Cisplatin versus Placebo in Combination with Gemcitabine plus Cisplatin for Patients with First-Line Advanced Biliary Tract Cancers (TOPAZ-1)

Short Title: A Global Phase III Study of Durvalumab or Placebo in Combination with Gemcitabine/Cisplatin in Patients with First-Line Advanced Biliary Tract Carcinoma.

Rationale:

Advanced, unresectable biliary tract cancer (BTC) represents an area of unmet medical need due to its very aggressive nature, limited treatment options, and poor prognosis.

It has been shown that interaction between the programmed cell death ligand-1 (PD-L1) of cancer cells and the programmed cell death 1 (PD-1) receptor of T cells inhibits T-cell activation, leading to the decline of immune control to cancer cells. Previous biomarker studies on BTC tumor samples have reported various rates of expression of PD-L1 in these tumors (Sabbatino et al 2016, Salem et al 2018, Ye et al 2009). Higher levels of soluble PD-L1 have been shown to portend poorer prognosis in BTC patients treated with standard chemotherapy regimens (Ha et al 2016). Durvalumab, an antibody that blocks the interaction between PD-L1 and its receptors, may relieve PD-L1-dependent immunosuppressive effects and therefore enhance the cytotoxic activity of antitumor T cells. This hypothesis is supported by AstraZeneca's data as well as data from other monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway (Brahmer et al 2012, Topalian et al 2012).

There is also a rationale for the use of a PD-1/PD-L1 antagonist such as durvalumab in combination with cytotoxic chemotherapy based on emerging evidence of activity of this combination in a variety of cancers (Langer et al 2016). The combination of these agents may provide a complementary benefit in mounting an effective antitumor immunity by promoting antigen presentation, increasing the production of protective T cells, and overcoming immunosuppression in the tumor bed (Mellman et al 2011, Bracci et al 2014). An immunotherapy agent that aids in the recognition of cancer cells by T cells may lead to long-lived tumor destruction, helping to prolong the early tumor responses seen with cytotoxic agents (Vanneman and Dranoff 2012).

Continued clinical development of durvalumab in advanced BTC is supported by the following 2 ongoing durvalumab clinical studies: i) a Phase I AstraZeneca-sponsored Study D4190C00002 (NCT01938612), hereinafter referred to as Study 2, showing durable responses with durvalumab (10 mg/kg every 2 weeks [q2w]) and the combination of durvalumab (20 mg/kg every 4 weeks [q4w]) with tremelimumab (1 mg/kg q4w × 4 doses) in heavily pretreated patients with advanced BTC, and ii) a Phase II Investigator-initiated clinical study supported by AstraZeneca (NCT03046862), hereinafter referred to as Study ESR-O, where the combination of durvalumab (1120 mg every 3 weeks [q3w]) with or without tremelimumab (75 mg q3w) demonstrated additive and possibly synergistic efficacy when combined with gemcitabine/cisplatin (1000 mg/m^2 and 25 mg/m^2, respectively, on Days 1 and 8 of a 21-day cycle). All the regimens listed above were well tolerated with a manageable safety profile.

In Study 2, a numerical improvement in the median overall survival (mOS) was observed with durvalumab (8.1 months) and durvalumab plus tremelimumab (10.1 months) in comparison to the range of mOS reported with chemotherapy in prior studies (6.5 months to 7.5 months) in the context of a heavily pretreated population (Lamarca et al 2014, Kim et al 2017, Brieau et al 2015, Walter et al 2013). These results are presented in Table 3.

In Study ESR-O (NCT03046862), of the 30 evaluable patients enrolled in Part 1 of this study (who received durvalumab, tremelimumab, gemcitabine, and cisplatin), 15 reported an objective response (2 complete response [CR] and 13 partial response [PR]), resulting in an objective response rate (ORR) of 50.0%. Preliminary data from Part 2 (in which patients received either durvalumab or durvalumab plus tremelimumab in combination with gemcitabine/cisplatin) indicate an ORR of 50% (3 PR) and 57% (4 PR) in patients receiving the 3-drug and 4-drug combination regimens, respectively, suggesting that the addition of durvalumab to the chemotherapy is likely sufficient to drive the majority of the benefit. These preliminary data are impressive and suggest additive and potentially synergistic activity when placed in the context of ORRs from historical studies (Valle et al 2010, Valle et al 2015, Okusaka et al 2010). A summary of these results is presented in Table 4.

Taken together, these data support the hypothesis that combining durvalumab, gemcitabine, and cisplatin has the potential to improve clinical outcomes in patients with advanced BTC; therefore, AstraZeneca has designed the proposed Phase III study (Study D933AC00001) to evaluate the clinical benefit of adding durvalumab to the established chemotherapy regimen of gemcitabine and cisplatin for the treatment of patients with previously untreated, unresectable locally advanced or metastatic BTC.

Objectives	**Endpoints**
Primary objective	**Endpoint/Variable**
To assess the efficacy of Arm A compared to Arm B in terms of OS in patients with first-line advanced BTC	OS
Secondary objectives	**Endpoints/Variables**
To further assess the efficacy of Arm A compared to Arm B in terms of PFS, ORR, and DoR in patients with first-line advanced BTC	PFS, ORR, and DoR according to RECIST 1.1 using Investigator assessments
For IA-1: To summarize the efficacy of Arm A compared to Arm B in terms of ORR and DoR in patients with first-line advanced BTC	ORR and DoR according to RECIST 1.1 using BICR assessments
To assess disease-related symptoms, impacts, and HRQoL in patients treated with Arm A compared to Arm B	• EORTC QLQ-C30: Global health status/QoL and impacts (eg, physical function); multi-term symptoms (eg, fatigue); and single items (eg, appetite loss, insomnia) • EORTC QLQ-BIL21: Single-item symptoms (eg, abdominal pain [item 42], pruritus [item 36], jaundice [item 35])
To assess the efficacy of Arm A compared to Arm B by PD-L1 expression	Association of PD-L1 expression level with PFS, ORR, DoR, and DCR according to RECIST 1.1 using Investigator assessments and OS
To assess the PK of durvalumab when used in combination with gemcitabine/cisplatin	Serum concentration of durvalumab (peak and trough concentrations)
To investigate the immunogenicity of durvalumab	Reporting tiered results of ADAs for durvalumab
Safety objective	**Endpoint/Variable**
To assess the safety and tolerability profile of Arm A compared to Arm B in patients with first-line advanced BTC	AEs, physical examinations, laboratory findings, WHO ECOG/PS, ECG and vital signs
Exploratory objectives	**Endpoints/Variables**
To investigate the efficacy of Arm A compared to Arm B by candidate biomarkers (for example but not limited to TMB and MSI) that may correlate with drug activity or identify patients likely to respond to treatment	Association of candidate biomarkers including, but not limited to TMB, MSI and/or tumor mutations with: OS and PFS, ORR, DoR, and DCR according to RECIST 1.1 using Investigator assessments
To evaluate circulatory-based biomarkers and associations with efficacy parameters, including, but not limited to, ctDNA It is not applicable in China.	Association with circulatory-based biomarkers, including, but not limited to, ctDNA-based TMB, whole blood gene expression, etc, with efficacy assessments
To assess patient-reported treatment tolerability using PRO-CTCAE and global assessment of treatment tolerability	PRO-CTCAE (pre-selected items based on treatment arms) and global assessment of treatment tolerability (QLQ-BIL21 item 49)

Objectives	Endpoints
To assess the patients' global impression of the severity of cancer symptoms	PGIS
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	The EQ-5D-5L health state utility instrument will be used to derive health state utility based on patient-reported data.
To explore the impact of treatment and disease on healthcare resource use	The HOSPAD module will be used to collect information on key healthcare resource use beyond study mandated visits.

Note: Patients in Arm A will receive durvalumab plus gemcitabine/cisplatin combination therapy; patients in Arm B will receive placebo plus gemcitabine/cisplatin therapy.
ADA Antidrug antibody; AE Adverse event; BICR Blinded independent central review; BTC Biliary tract cancer; ctDNA Circulating tumor deoxyribonucleic acid; DCR Disease control rate; DoR Duration of response; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; HOSPAD Hospital resource use module; HRQoL Health-related quality of life; IA-1 Interim Analysis 1; MSI Microsatellite instability; ORR Objective response rate; OS Overall survival; PD-L1 Programmed cell death ligand-1; PFS Progression-free survival; PGIS Patient Global Impression of Severity; PK Pharmacokinetics; PRO-CTCAE Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; PS Performance status; QLQ-BIL21 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire; QLQ-C30 30-Item Core Quality of Life Questionnaire; QoL Quality of life; RECIST Response Evaluation Criteria in Solid Tumors; TMB Tumor mutational burden; WHO World Health Organization.

Overall design:

This is a Phase III randomized, double-blind, placebo-controlled, multi-regional, international study to assess the efficacy and safety of first-line treatment with durvalumab in combination with gemcitabine/cisplatin versus placebo in combination with gemcitabine/cisplatin in patients with previously untreated, unresectable locally advanced or metastatic BTC.

Patients will be asked to provide a recent tumor biopsy or an available unstained archived tumor tissue sample (taken ≤3 years prior to screening). These samples will be analyzed for biomarker and other molecular analysis.

Approximately 672 patients with previously untreated, unresectable locally advanced or metastatic BTC will be randomized 1:1 to receive one of the following treatments (approximately 336 patients are to be randomized to each arm):

- **Arm A:** Durvalumab plus gemcitabine/cisplatin combination therapy. Durvalumab 1500 mg via intravenous (IV) infusion q3w, starting on Cycle 1 in combination with cisplatin 25 mg/m2 and gemcitabine 1000 mg/m2 (each administered on Days 1 and 8 q3w) up to 8 cycles, followed by durvalumab 1500 mg as monotherapy q4w until clinical progression or RECIST 1.1-defined radiological progressive disease (PD), unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

- **Arm B**: Placebo plus gemcitabine/cisplatin therapy. Placebo via IV infusion q3w, starting on Cycle 1 in combination with cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 (each administered on Days 1 and 8 q3w) up to 8 cycles, followed by placebo monotherapy q4w until clinical progression or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

The primary objective of the study is to confirm the superiority of Arm A compared to Arm B in terms of overall survival (OS) in patients with first-line advanced BTC.

Randomization will be stratified by disease status (initially unresectable versus recurrent) and primary tumor site (intrahepatic cholangiocarcinoma versus extrahepatic cholangiocarcinoma versus gallbladder cancer).

Approximately 130 Chinese patients will be randomized in this study. The Sponsor will close the global study enrolment to all sites apart from sites in China at an appropriate time to ensure approximately 672 patients are randomized to global study population. Recruitment of patients from sites in China will continue until 130 Chinese patients are randomized. Patients randomized in China prior to the last patient randomized in the global cohort will be included in both Global Cohort and China Cohort. Enrolment of patients from sites in China will be actively managed by the Sponsor to ensure there is no significant over recruitment of patients from sites in China. Patients randomized in China after last patient randomized in the global cohort will only be analyzed in the China Cohort. The analysis in China cohort will be performed when the OS data from the Chinese patients is of similar maturity to those of the global cohort where significant clinical efficacy is established, eg, if OS efficacy is established at the primary analysis, a similar maturity to this will be used for the consistency evaluation.

For an overview of the study design, see Figure 1. For details on treatments given during the study, see Section 6.1. For details on the efficacy and safety endpoints, see Section 3.

Study period:

Estimated date of the first patient enrolled: Q1 2019

Estimated date of the last patient enrolled: Q4 2020

Number of patients:

Approximately 672 patients will be randomized in the Global Cohort. Patients will be randomized 1:1 to Arm A or Arm B. Approximately 130 Chinese patients will be randomized in this study.

After global enrolment is closed, enrolment will continue in China until 130 Chinese patients have been randomized. Patients randomized in China will also be analyzed as the China Cohort.

Treatments and treatment duration:

- Patients will receive cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 (each administered on Days 1 and 8 q3w) plus durvalumab 1500 mg (Arm A) or placebo (Arm B) via IV infusion q3w, starting on Cycle 1, for up to 8 cycles. After treatment with gemcitabine/cisplatin is complete, the patients will receive 1500 mg durvalumab (Arm A) or placebo (Arm B) via IV infusion q4w until clinical progression or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See Figure 2. (Note that if a patient's weight falls to ≤30 kg, the patient should receive a weight-based dosing equivalent to 20 mg/kg of durvalumab [or placebo] q3w or q4w after consultation between the Investigator and the Study Physician, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg [or placebo] q3w or q4w.)

Duration of treatment

Patients will receive durvalumab (or placebo) in combination with gemcitabine/cisplatin for up to 8 cycles q3w, followed by durvalumab (or placebo) monotherapy q4w until clinical progression or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met, per Section 7.

Progression during treatment

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined radiological PD may continue to receive study treatment at the discretion of the Investigator and patient. A follow-up scan is to be collected after the initial RECIST 1.1-defined radiological PD, preferably at the next (and no later than the next) scheduled imaging visit and no less than 4 weeks after the prior assessment of PD; this follow-up scan is evaluated using the criteria outlined in Appendix F.

Patients with RECIST 1.1-defined radiological PD who continue to receive their assigned treatment at the discretion of the Investigator and patient (following consultation with AstraZeneca) can receive treatment until no longer having clinical benefit, and imaging for tumor assessments should continue on their regular imaging schedule for the duration of treatment.

Follow-up of patients post discontinuation of study drug

Patients who have discontinued treatment due to toxicity, clinical progression (for patients with unclear radiological progression), or symptomatic deterioration or who have commenced subsequent anticancer therapy will be followed up with tumor assessments until RECIST 1.1-defined radiological PD plus an additional follow-up scan or until death (whichever comes first) and followed up for survival.

Survival

All randomized patients should be followed up for survival.

Data monitoring committee:

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

An independent data monitoring committee (IDMC) composed of independent experts will be convened and will meet approximately every 6 months to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. For the interim analyses (both Interim Analysis-1 [IA-1] and IA-2), the IDMC will review unblinded interim efficacy data, as outlined in Section 9.6. The IDMC will inform the Sponsor of its recommendation according to the IDMC charter, which will be developed separately. Formal implementation and communication of IDMC recommendations will be managed by the AstraZeneca Executive Committee, which will be unrelated to the study team.

Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

Statistical methods

The primary objective of the study is to confirm the superiority of Arm A compared to Arm B in terms of OS in patients with first-line advanced BTC.

The primary endpoint OS is defined as the time from the date of randomization until death due to any cause. Secondary efficacy endpoints include progression-free survival (PFS), ORR, duration of response (DoR), disease control rate (DCR), and PRO measures.

The Full Analysis Set (FAS) will include all randomized patients. The FAS will be used for all efficacy analyses, including PROs. Treatment groups will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment group to which they were randomized.

A hypothesis of improved OS will be tested when:

- Approximately 397 OS events have occurred across Arm A and Arm B (59% maturity) Interim Analysis 2 (IA-2) AND
- Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity) final analysis (FA).

The primary analysis of OS is based on log-rank test for interim analysis and Fleming-Harrington (FH) (0, 1) test for final analysis. A sensitivity analysis using the log-rank test will also be performed at the final analysis. If the true average OS hazard ratio (HR) is 0.745, approximately 496 OS events will provide 90% power to demonstrate statistical significance at the 4.20% level (using a 2-sided log-rank test), allowing for 1 interim analysis for clinical activity assessed by ORR and DoR and 1 interim analysis for early testing for superiority in OS improvement at approximately 80% of target events. The smallest treatment difference that could be statistically significant at the FA is an average HR of 0.833 using log-rank test. With a 21-month recruitment period and a minimum follow-up period of 19 months assumed, it is anticipated that this analysis will be performed approximately 40 months after the first patient is randomized. With log-rank test for the second interim analysis and FH(0, 1) as the final analysis, the overall power is at least 86% under various scenarios considered (Section 9.2).
Two interim analyses and 1 FA are planned for the evaluation of efficacy:

- IA-1: The objective of IA-1 is to assess clinical activity. ORR and DoR will be summarized to support early registration of durvalumab when administered in combination with gemcitabine/cisplatin. The summary will be done both for Investigator assessments and for blinded independent central review (BICR) assessments according to RECIST 1.1. The planned data cutoff (DCO) for IA-1 will occur when at least 200 patients have had the opportunity to be followed for at least 32 weeks or the last patient has been randomized to the global cohort, whichever comes later. The analysis set will include all randomized patients who have had the opportunity for at least 32 weeks of follow-up at the time of the IA-1 DCO (ie, randomized $\geq$ 32 weeks prior to IA-1 DCO).

  Based on enrollment assumptions, it is expected that this will occur approximately 21 months after randomization of the first patient.
- IA-2: The second interim analysis will test for early superiority of the durvalumab regimen relative to control. This analysis will be performed when approximately 397 OS events have been observed in the study (59% maturity or 80% information fraction with respect to log-rank test) with 75% power. Based on enrollment assumptions, it is expected that this will occur approximately 31 months after randomization of the first patient.

IA-2 will evaluate the efficacy of Arm A compared to Arm B in terms of OS (primary objective). OS will be analyzed using a stratified log-rank test (stratified by disease status and

primary tumor location). The treatment effect will be estimated by the HR, 95% confidence interval (CI), and p-value.

A small alpha expenditure of 0.001 (0.1%) will be allocated to IA-1. Strong control of the familywise error rate (FWER) at the remaining 4.9% level (2 sided) across the testing of OS and PFS endpoints will be achieved through a combined approach of alpha allocation to the OS analyses (IA-2 and the FA) via alpha spending function and a hierarchical testing procedure; that is, PFS will be tested only if OS met statistical significance at IA-2 or FA (Glimm et al 2010). The IA-2 for OS will be conducted when approximately 397 of the 496 expected OS events (ie, 80% information fraction with respect to log-rank test) have occurred. Using the Lan-DeMets spending function approximating O'Brien-Fleming boundaries, 2-sided significance levels of 0.0238 and 0.0420 will be applied to OS IA-2 and FA, respectively using log-rank test (Lan and DeMets 1983). The significance level of FH(0, 1) test at the final analysis will be determined based on the correlation between interim data and final data (Tsiatis 1982).

PFS will be formally tested using PFS information collected up to each DCO if OS meets statistical significance at that DCO (IA-2 or FA). Significance levels for PFS at IA-2 and FA will be derived based on the alpha spending function approximating Pocock boundaries, which strongly controls the Type I error at the 0.049 level (2-sided). Assuming approximately 506 PFS events and 590 PFS events are available at the time of each PFS analysis, PFS testing will be carried out with 2-sided significance levels of 0.0444 and 0.0236 at IA-2 and FA based on log-rank test, respectively. Since DCO timing will be determined based on the number of OS events, the nominal significance level for PFS analysis might be adjusted for the actual information fraction for PFS at IA-2 relative to FA.

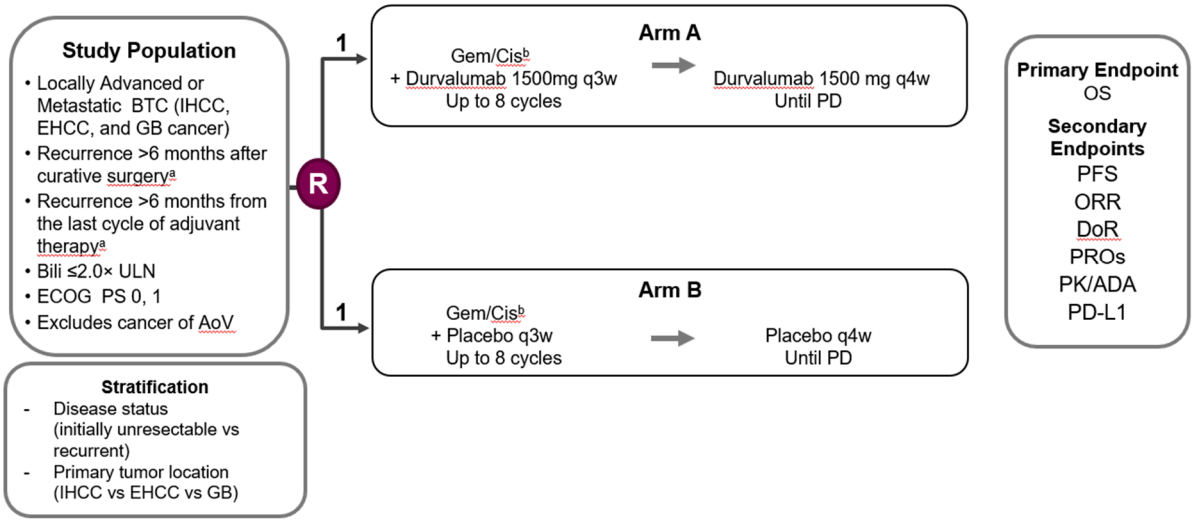
Safety data will be summarized descriptively and will not be formally analyzed.

Details of China subgroup analysis on efficacy and safety will be covered in the China supplementary Statistical Analysis Plan (SAP).

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



[a] Patients with recurrence >6 months after curative surgery without adjuvant therapy or >6 months after adjuvant therapy will be included.

[b] Cisplatin (25 mg/m^2) and gemcitabine (1000 mg/m^2), each administered on Days 1 and 8, q3w for 8 cycles.

ADA Antidrug antibody; AoV Ampulla of Vater; Bili Bilirubin; BTC Biliary tract cancer; DoR Duration of response; ECOG Eastern Cooperative Oncology Group; EHCC Extrahepatic cholangiocarcinoma; GB Gallbladder; Gem/Cis Gemcitabine plus cisplatin; IHCC Intrahepatic cholangiocarcinoma; ORR Objective response rate; OS Overall survival; PD Progressive disease; PD-L1 Programmed cell death ligand-1; PFS Progression-free survival; PK Pharmacokinetic; PRO Patient-reported outcome; PS Performance status; q3w Every 3 weeks; q4w Every 4 weeks; ULN upper limit of normal.

2 INTRODUCTION

BTC refers to a heterogeneous group of gastrointestinal cancers that arise from the bile ducts (cholangiocarcinoma), the gallbladder, or the ampulla of Vater (AoV). These cancers are often difficult to diagnose due to their anatomical location and the paucity or non-specificity of their symptoms; therefore, >75% of BTC patients present with advanced, unresectable disease (Lamarca et al 2014, Takahashi et al 2013). The randomized Study ABC-02 has established the combination of gemcitabine and cisplatin for first-line advanced BTC (Valle et al 2010), and this treatment is recommended by the clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) as well as the European Society for Medical Oncology (ESMO) and Japanese guidelines (Valle et al 2016, Miyazaki et al 2015, NCCN Guidelines 2018).

In Study ABC-02, 410 patients with locally advanced or metastatic BTC and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2 were randomized 1:1 to receive gemcitabine/cisplatin or gemcitabine alone. After a median follow-up of 8.2 months, the mOS was 11.7 months versus 8.1 months, respectively (HR: 0.64; 95% CI: 0.52, 0.80). The ORR was 26.1% versus 15.5%, respectively, and the DCR was 81.4% versus 71.8%, respectively. Safety observations were similar regardless of treatment arm, with the exception of Grades 3 and 4 neutropenia events, which were more frequent in the gemcitabine/cisplatin group; neutropenia-associated infections were similar across treatment arms (Valle et al 2010).

Consistency of these results was reported in Study BT22. In Study BT22, 84 patients with unresectable, locally advanced, or metastatic BTC with no prior chemotherapy and a PS of 0 or 1 were randomized 1:1 to receive gemcitabine/cisplatin or gemcitabine alone. The mOS was 11.2 months versus 7.7 months, respectively (HR: 0.69; 95% CI: 0.42, 1.13); the ORR was 19.5% versus 11.9%, respectively; and the DCR was 68.3% (95% CI: 51.9, 81.9) versus 50.0% (95% CI: 34.2, 65.8), respectively. Safety observations were consistent with the known safety profile of gemcitabine/cisplatin (Okusaka et al 2010).

These results indicate an improved OS in patients treated with gemcitabine/cisplatin compared with patients treated with gemcitabine alone; however, patients with advanced BTC treated with gemcitabine/cisplatin continue to have a poor prognosis, with an mOS of <1 year and a 5-year OS rate of <10% (Eckel and Schmid 2007, Valle et al 2017, Yachimski and Pratt 2008). Advanced, unresectable BTC represents an area of unmet medical need due to its very aggressive nature, limited treatment options, and poor prognosis.

2.1 Study rationale

Current treatment options for patients with advanced BTC are limited. Thus, new therapeutic models are required.

It has been shown that interaction between the PD-L1 of cancer cells and the PD-1 receptor of T cells inhibits T-cell activation, leading to the decline of immune control to cancer cells. Previous biomarker studies on BTC tumor samples have reported various rates of expression of PD-L1 in these tumors (Sabbatino et al 2016, Salem et al 2018, Ye et al 2009). Higher levels of soluble PD-L1 have been shown to portend poorer prognosis in BTC patients treated with standard chemotherapy regimens (Ha et al 2016). Durvalumab, an antibody that blocks the interaction between PD-L1 and its receptors, may relieve PD-L1-dependent immunosuppressive effects and therefore enhance the cytotoxic activity of antitumor T cells. This hypothesis is supported by AstraZeneca's data as well as data from other mAbs targeting the PD-L1/PD-1 pathway (Brahmer et al 2012, Topalian et al 2012).

There is also a rationale for the use of a PD-1/PD-L1 antagonist such as durvalumab in combination with cytotoxic chemotherapy based on emerging evidence of activity of this combination in a variety of cancers (Langer et al 2016). The combination of these agents may provide a complementary benefit in mounting an effective antitumor immunity by promoting antigen presentation, increasing the production of protective T cells, and overcoming immunosuppression in the tumor bed (Mellman et al 2011, Bracci et al 2014). An immunotherapy agent that aids in the recognition of cancer cells by T cells may lead to long-lived tumor destruction, helping to prolong the early tumor responses seen with cytotoxic agents (Vanneman and Dranoff 2012). Consequently, combination of gemcitabine and cisplatin with immune checkpoint inhibitors such as durvalumab may result in enhanced efficacy and improved outcome in BTC based on these complementary mechanisms of action (MOAs), preliminary evidence of which has been observed, as discussed below.

Continued clinical development of durvalumab in advanced BTC is supported by the following 2 ongoing durvalumab clinical studies: i) a Phase I AstraZeneca-sponsored Study D4190C00002 (NCT01938612), hereinafter referred to as Study 2, showing durable responses with durvalumab (10 mg/kg q2w) and the combination of durvalumab (20 mg/kg q4w) with tremelimumab (1 mg/kg q4w × 4 doses) in heavily pretreated patients with advanced BTC, and ii) a Phase II Investigator-initiated clinical study supported by AstraZeneca (NCT03046862), hereinafter referred to as Study ESR-O, where the combination of durvalumab (1120 mg q3w) with or without tremelimumab (75 mg q3w) demonstrated additive and possibly synergistic efficacy when combined with gemcitabine/cisplatin (1000 mg/m^2 and 25 mg/m^2, respectively, on Days 1 and 8 of a 21-day cycle). All the regimens listed above were well tolerated with a manageable safety profile.

Study 2 is an ongoing Phase I, open-label, multi-center, dose-escalation, dose-expansion study evaluating the safety, tolerability, PK, and efficacy of durvalumab monotherapy and durvalumab plus tremelimumab in patients with advanced solid tumors. The dose-expansion phase included 2 cohorts of patients with advanced or metastatic BTC who received durvalumab monotherapy or durvalumab plus tremelimumab as second- or greater-line

therapy for up to 12 months. Forty-two patients received durvalumab monotherapy, and 65 patients received durvalumab plus tremelimumab. The ORR observed for durvalumab (ORR: 4.8% [2 PR]) or durvalumab plus tremelimumab (ORR: 10.8% [7 PR]) was within the range of ORRs reported for historical studies in a similar population treated with chemotherapy alone (3% to 11.8%); additionally, the observed responses were durable (median DoR: durvalumab, 9.7 months; durvalumab plus tremelimumab, 8.4 months). A numerical improvement in the mOS was observed with durvalumab (8.1 months) and durvalumab plus tremelimumab (10.1 months) in comparison to the range of mOS reported with chemotherapy in prior studies (6.5 months to 7.5 months) in the context of a heavily pretreated population (Lamarca et al 2014, Kim et al 2017, Brieau et al 2015, Walter et al 2013). These results are presented in Table 3.

Table 3 Durvalumab and durvalumab plus tremelimumab in 2L advanced BTC compared to prior studies with chemotherapy

	IO in 2L+BTC		Chemo in 2L/2L+BTC (retrospective and Phase II)			
Study	**Study 2[a]**		**Lamarca A[b]**	**Kim BJ[c]**	**Brieau B[d]**	**Walter T[e]**
Drug	**D**	**D+T**	**Various regimens (meta-analysis)**	**Fluoro-pyrimidine-based**	**FOLFIRI/ XELIRI/ FOLFOX/ XELOX, etc**	**Gem/5-FU combo**
N	42	65	761	321	196	96
ORR (%)[f] (95% CI)	4.76 (0.58, 16.16)	10.77 (4.44, 20.94)	7.7 (4.6, 10.9)	3	11.8	9
mOS (mo) (95% CI)	8.1 (5.6, 10.1)	10.1 (6.2, 11.4)	7.2 (6.2, 8.2)	6.5 (5.9, 7.0)	6.7 (5.6, 7.8)	7.5 (4.8, 10.2)
mPFS (mo) (95% CI)	1.5 (1.4, 2.6)	1.6 (1.4, 2.8)	3.2 (2.7, 3.7)	1.9 (1.6, 2.2)	3.2 (2.8, 4.0)	2.8 (2.2, 3.4)
mDoR (mo)	9.7	8.4	NR	NR	NR	NR

[a] AZ Study 2 (D4190C00002) (on file)
[b] Lamarca et al 2014
[c] Kim et al 2017
[d] Brieau et al 2015
[e] Walter et al 2013
[f] Only PRs were reported.

2L Second-line; 5-FU 5-Fluorouracil; BTC Biliary tract cancer; CI Confidence interval; D Durvalumab; Gem Gemcitabine; IO Immuno-oncology (agent); mDoR Median duration of response; mo Months; mOS Median overall survival; mPFS Median progression-free survival; NR Not reported; ORR Objective response rate; PR Partial response; T Tremelimumab.

The second study (Study ESR-O) is an ongoing Investigator-initiated Phase II, open-label study to evaluate the safety and efficacy of durvalumab and tremelimumab in combination

with gemcitabine/cisplatin in patients with previously untreated unresectable or recurrent BTC who were suitable candidates for first-line standard chemotherapy.

Preliminary data as of 13 September 2018 from Study ESR-O have provided encouraging efficacy of the combination of durvalumab, tremelimumab, gemcitabine, and cisplatin. Of the 30 evaluable patients enrolled in Part 1 of this study (who received durvalumab, tremelimumab, gemcitabine, and cisplatin), 15 reported an objective response (2 CR and 13 PR), resulting in an ORR of 50.0%. Preliminary data from Part 2 (in which patients received either durvalumab or durvalumab plus tremelimumab in combination with gemcitabine/cisplatin) indicate an ORR of 50% (3 PR) and 57% (4 PR) in patients receiving the 3-drug and 4-drug combination regimens, respectively, suggesting that the addition of durvalumab to the chemotherapy is likely sufficient to drive the majority of the benefit. These preliminary data are impressive and suggest additive and potentially synergistic activity when placed in the context of ORRs from historical studies (Valle et al 2010, Valle et al 2015, Okusaka et al 2010). A summary of these results is presented in Table 4. In addition, administration of durvalumab in combination with tremelimumab, gemcitabine, and cisplatin in patients with advanced BTC has so far demonstrated an acceptable safety profile.

Table 4 Durvalumab and durvalumab plus tremelimumab in 1L advanced BTC compared to prior studies with chemotherapy

	Chemo+IO (1L BTC)			**Chemo (1L BTC)**		
Study	**ESR-O[a]**			**ABC-02[b]**	**BT22[c]**	**ABC-03[d]**
	Part 1	**Part 2**				
Drug	**Gem/Cis +D+T**	**Gem/Cis +D+T**	**Gem/Cis +D**	**Gem/Cis**	**Gem/Cis**	**Gem/Cis**
N	30	7	6	161	41	54
ORR (%) (N of CR and PR)	50 (2 CR, 13 PR)	57 (4 PR)	50 (3 PR)	26.1 (1 CR, 41 PR)	19.5 (0 CR, 8 PR)	19 (0 CR, 10 PR)
mPFS (mo) (95% CI)	NE	NE	NE	8.0 (6.6-8.6)	5.8 (4.1-8.2)	7.4 (5.7-8.5)
mOS (mo) (95% CI)	NE	NE	NE	11.7 (9.5-14.3)	11.2 (9.1-12.5)	11.9 (9.2-14.3)
mDoR (mo) (95% CI)	11.0 (7.8-14.2)	NE	NE	NR	NR	5.8 (0.5-22.4)

[a] ESR-O (NCT03046862).
[b] Valle et al 2010.
[c] Okusaka et al 2010.
[d] Valle et al 2015.

1L First-line; BTC Biliary tract cancer; CI Confidence interval; CR Complete response; D Durvalumab; Gem/Cis Gemcitabine plus cisplatin; IO Immuno-oncology (agent); mDoR Median duration of response; mo Month; mOS Median overall survival; mPFS Median progression-free survival; NE Not evaluable; ORR Objective response rate; PR Partial response; T Tremelimumab.

Taken together, these data support the hypothesis that combining durvalumab, gemcitabine, and cisplatin has the potential to improve clinical outcomes in patients with advanced BTC; therefore, AstraZeneca has designed the proposed Phase III study (Study D933AC00001) to evaluate the clinical benefit of adding durvalumab to the established chemotherapy regimen of gemcitabine and cisplatin for the treatment of patients with previously untreated, unresectable locally advanced or metastatic BTC.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of durvalumab is provided in the current IB. Background information on gemcitabine/cisplatin is provided in the local prescribing information.

2.2.1 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors (Dunn et al 2004).

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (cluster of differentiation [CD] 279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki and Honjo 2007). PD-1 and PD-L1/PD-L2 belong to a family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T-cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages (Qin et al 2016). Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment (Pardoll 2012). PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T cells, leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous antitumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the

PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes the PD-L1-mediated inhibition of antitumor immunity. Although the functional blockade of PD-L1 results in T-cell reactivation, this MOA is different from the direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of pre-clinical and clinical studies of mAbs targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in patients with cancer (Brahmer et al 2012, Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012, Zhang et al 2008), with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al 2014, Rizvi et al 2015, Segal et al 2015). In addition, high mutational burden (eg, in bladder carcinoma; Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon the binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells (Fife and Bluestone 2008). Blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data has now been added to a wealth of clinical data showing that blockade of negative regulatory signals to T cells such as CTLA-4 and PD-L1 has promising clinical activity. Ipilimumab was first granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies. Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and atezolizumab, an anti-PD-L1 agent, have been granted approval by agencies for the treatment of a number of malignancies, including metastatic melanoma, squamous and non-squamous cell non-small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), and urothelial carcinoma (UC). In addition, there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

2.2.2 Durvalumab

Durvalumab is a human mAb of the immunoglobulin (Ig) G1 kappa subclass that blocks the interaction of PD-L1 (but not PD-L2) with PD-1 on T cells and CD80 (B7.1) on immune cells (ICs). It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer.

(MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed MOA for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in the restored proliferation of IFN-γ (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to >6000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 4.3.1 and Section 8.3.13. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information, including safety, efficacy, and PK.

2.2.3 Gemcitabine plus cisplatin

Two randomized studies (Study ABC-02 and Study BT22) have established gemcitabine/cisplatin as the standard-of-care (SoC) regimen for first-line advanced BTC (Okusaka et al 2010, Valle et al 2010). These studies are summarized in Section 2. Gemcitabine/cisplatin combination therapy is the most commonly used standard treatment regimen across the world in first-line BTC and is the regimen recommended for first-line BTC treatment according to NCCN, ESMO, and Japanese guidelines (NCCN Guidelines 2018, Valle et al 2016, Miyazaki et al 2015).

Different gemcitabine/oxaliplatin combination regimens have been assessed in several Phase II clinical studies, and both gemcitabine/oxaliplatin and gemcitabine/cisplatin regimens are used in clinical practice. A meta-analysis across several Phase II and III studies using weighted mOS suggests that gemcitabine/cisplatin has been associated with a survival advantage over gemcitabine/oxaliplatin (Fiteni et al 2014).

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of durvalumab may be found in the current IB. Similar information for gemcitabine/cisplatin may be found in the local prescribing information.

See Section 9.6.1 for information regarding the IDMC.

2.3.1 Potential benefits

2.3.1.1 Durvalumab

As of the DCO date (12 July 2018), across the entire clinical development program, approximately 5127 patients have received durvalumab in AstraZeneca or MedImmune-sponsored interventional studies in multiple tumor types, stages of disease, and lines of therapy. Of these, 2229 patients received durvalumab monotherapy, 1573 patients received durvalumab in combination with tremelimumab, and 1325 patients received durvalumab in combination with an investigational and/or an approved product. An estimated 8252 patients are currently enrolled in blinded studies.

Descriptions of the ongoing and completed sponsored clinical studies of durvalumab are provided in the current durvalumab IB.

2.3.1.2 Durvalumab in combination with standard of care (chemotherapy)

Over the recent years, it has been shown that controlling the progression of cancer cells can be achieved by using immune checkpoint inhibitors such as PD-L1. Further, accumulating evidence indicates that immune checkpoint inhibitors combined with cytotoxic chemotherapy may provide a complementary benefit in mounting an effective antitumor immunity by promoting antigen presentation, increasing the production of protective T cells, and overcoming immunosuppression in the tumor bed (Mellman et al 2011, Bracci et al 2014). An immunotherapy agent that aids in the recognition of cancer cells by T cells may lead to long-lived tumor destruction, helping to prolong the early tumor responses seen with cytotoxic agents (Vanneman and Dranoff 2012). Therefore, combining a PD-L1 antagonist such as durvalumab with cytotoxic agents may result in enhanced efficacy and improved outcome via different but synergistic MOAs.

In addition, preliminary data (Table 4) from an ongoing study (Study ESR-O) of durvalumab (with or without tremelimumab) in combination with gemcitabine/cisplatin in patients with first-line advanced BTC provide initial evidence supporting the thesis of combining conventional anticancer chemotherapy with durvalumab as a potential approach to significantly improve clinical outcomes. AstraZeneca has therefore designed the proposed Phase III study to evaluate the clinical utility of adding durvalumab to the established chemotherapy regimen of gemcitabine and cisplatin in patients with previously untreated, unresectable locally advanced or metastatic BTC.

2.3.2 Overall risks

mAbs directed against immune checkpoint proteins such as PD-L1, as well as those directed against PD-1 or CTLA-4, aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system, however, there is the potential for adverse effects on normal tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune-mediated mechanism and that may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune-mediated effects can occur in nearly any organ system and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as liver enzyme elevations, skin events such as rash and dermatitis, and endocrinopathies including hypothyroidism and hyperthyroidism.

2.3.2.1 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyperthyroidism, hypothyroidism, type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis (including pemphigoid), immune thrombocytopenia, myocarditis, myositis/polymyositis, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less-frequent inflammatory events including neuromuscular toxicities (e.g. Guillain Barre syndrome, myasthenia gravis).

For information on all identified and potential risks with durvalumab, always refer to the current version of the durvalumab IB.

In monotherapy clinical studies, AEs that are reported at an incidence of ≥20% include events such as fatigue, cough, decreased appetite, dyspnea, and nausea. Approximately 10% of patients discontinued the drug due to an AE. See the current version of the IB for a detailed summary of the monotherapy data, including AEs, serious adverse events (SAEs), and CTC Grade 3 to 5 events reported across the durvalumab program.

The majority of treatment-related AEs were manageable, with dose delays, symptomatic treatment, and, in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 8.4.6).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

2.3.2.2 Durvalumab in combination with standard of care (chemotherapy)

Two ongoing studies are evaluating the safety and tolerability of combining durvalumab and tremelimumab with different chemotherapy regimens in patients with solid tumors. One study is an AstraZeneca internal study (Study D419SC00001), and the other is CCTG Study NCT02537418.

As of 12 July 2018, a total of 22 patients with advanced solid tumors have been treated with durvalumab and tremelimumab in combination with chemotherapy in Study D419SC00001. All patients had at least 1 AE (regardless of causality). AEs (all grades) reported in >20% of patients were nausea (68.2%); neutrophil count decreased (63.6%); decreased appetite (50.0%); cough, diarrhea, and rash (36.4% each); anemia and pyrexia (31.8% each); constipation, dizziness, insomnia, myalgia, platelet count decreased, and pruritus (27.3% each); and ALT increased, alopecia, dyspepsia, peripheral sensory neuropathy, vomiting, and white blood cell count decreased (22.7% each). All patients had AEs considered by the Investigator to be related to study treatment. Treatment-related AEs reported in >20% of patients were neutrophil count decreased (63.6%); nausea (59.1%); decreased appetite, diarrhea, and rash (31.8% each); platelet count decreased and pruritus (27.3% each); and alopecia and peripheral sensory neuropathy (22.7% each). The majority (19 patients [86.4%]) of patients reported ≥Grade 3 treatment-emergent AEs (TEAEs); 16 (72.7%) patients reported ≥Grade 3 treatment-related TEAEs.

SAEs were reported in a total of 10 patients (45.5%). With the exception of pneumonia and pyrexia (3 patients each) and diarrhea and neutrophil count decreased (2 patients each), all other SAEs were reported in 1 patient each. One patient had a fatal AE of lung infection that was considered treatment-related. A total of 13.6% of patients had AEs that led to permanent discontinuation of treatment.

A total of 17 patients (77.3%) had at least 1 AE of special interest (AESI). AESI grouped terms reported with an incidence of >10% were dermatitis/rash (59.1%); diarrhea/colitis (36.4%); hepatic events (22.7%); and infusion/hypersensitivity reactions (18.2%). The majority of the AESIs were Grade 1 or 2 in severity. Grade 3 and Grade 4 events were reported in 2 patients (9.1%) each. There were no Grade 5 AESIs.

In the CCTG study (NCT02537418), 118 patients were exposed to >700 cycles of treatment, which began with chemotherapy combined with durvalumab ± tremelimumab until 4 to 6 cycles of chemotherapy ended; afterward, patients received further durvalumab ± tremelimumab treatment (Daaboul et al 2017). Recent data from the CCTG study show that chemotherapy combined with durvalumab ± tremelimumab did not increase immune-related adverse events (irAEs), giving support to the combination being tolerable and manageable. Overall, 50% of patients had irAEs of any grade, and 10% had ≥Grade 3 irAEs. Differences between the chemotherapy combination period and the durvalumab ± tremelimumab alone period were not significant, with the exception of biochemistry irAEs (chemotherapy combination 74% versus durvalumab ± tremelimumab 48%; p=0.003) and ALT/AST changes (41% versus 16% and 38% versus 9%, respectively; p=0.005). The irAEs that led to discontinuation of treatment in 15 patients were pneumonitis, hepatitis, nephritis, adrenal, myocarditis, gastrointestinal, thrombocytopenia, hyperthyroidism, and encephalitis.

Pneumonitis and gastrointestinal irAEs were the most common, followed by nephritis. The few significant findings are likely due to the nature of combining numerous agents.

Overall, the above data demonstrate that anti-PD-L1 immunotherapy (including durvalumab) in combination with chemotherapy is reasonably well tolerated and has an acceptable safety profile.

2.3.3 Overall benefit/risk

Durvalumab is a potential anticancer biologic for the treatment of multiple tumor types, including BTC. Initial therapeutic benefits are presented in Section 2.1.

As of the DCO date (12 July 2018), across the entire clinical development program, approximately 5127 patients have received durvalumab in AstraZeneca or MedImmune-sponsored interventional studies in multiple tumor types, stages of disease and lines of therapy. Of these, 2229 patients received durvalumab monotherapy, 1573 patients received durvalumab in combination with tremelimumab, and 1325 patients received durvalumab in combination with an investigational and/or an approved product. An estimated 8252 patients are currently enrolled in blinded studies. Most adverse drug reactions (ADRs) seen with durvalumab are consistent with the immune checkpoint inhibitor class of agents, which are thought to be due to the effects of inflammatory cells on specific tissues. The clinical reported ADRs are presented in Section 2.3.2.

Although the combination of gemcitabine/cisplatin is recommended as first-line chemotherapy for patients with unresectable or advanced BTC, the response rates and OS demonstrate limited efficacy. Therefore, new treatment options are needed for this patient population.

3 OBJECTIVES AND ENDPOINTS

Table 5 Study objectives, timing, and endpoints

Objectives	**Endpoints**
Primary objective	**Endpoint/Variable**
To assess the efficacy of Arm A compared to Arm B in terms of OS in patients with first-line advanced BTC	OS
Secondary objectives	**Endpoints/Variables**
To further assess the efficacy of Arm A compared to Arm B in terms of PFS, ORR, and DoR in patients with first-line advanced BTC	PFS, ORR, and DoR according to RECIST 1.1 using Investigator assessments
For IA-1: To summarize the efficacy of Arm A compared to Arm B in terms of ORR and DoR in patients with first-line advanced BTC	ORR and DoR according to RECIST 1.1 using BICR assessments

Objectives	**Endpoints**
To assess disease-related symptoms, impacts, and HRQoL in patients treated with Arm A compared to Arm B	• EORTC QLQ-C30: Global health status/QoL and impacts (eg, physical function); multi-term symptoms (eg, fatigue); and single items (eg, appetite loss, insomnia) • EORTC QLQ-BIL21: Single-item symptoms (eg, abdominal pain [item 42], pruritus [item 36], jaundice [item 35])
To assess the efficacy of Arm A compared to Arm B by PD-L1 expression	Association of PD-L1 expression level with PFS, ORR, DoR, and DCR according to RECIST 1.1 using Investigator assessments and OS
To assess the PK of durvalumab when used in combination with gemcitabine/cisplatin	Serum concentration of durvalumab (peak and trough concentrations)
To investigate the immunogenicity of durvalumab	Reporting tiered results of ADAs for durvalumab
Safety objective	**Endpoint/Variable**
To assess the safety and tolerability profile of Arm A compared to Arm B in patients with first-line advanced BTC	AEs, physical examinations, laboratory findings, WHO ECOG/PS, ECG and vital signs
Exploratory objectives	**Endpoints/Variables**
To investigate the efficacy of Arm A compared to Arm B by candidate biomarkers (for example but not limited to TMB and MSI) that may correlate with drug activity or identify patients likely to respond to treatment	Association of candidate biomarkers including but not limited to TMB, MSI and/or tumor mutations with: OS and PFS, ORR, DoR, and DCR according to RECIST 1.1 using Investigator assessments
To evaluate circulatory-based biomarkers and associations with efficacy parameters, including, but not limited to, ctDNA It is not applicable in China.	Association with circulatory-based biomarkers, including, but not limited to, ctDNA-based TMB, whole blood gene expression, etc, with efficacy assessments
To assess patient-reported treatment tolerability using PRO-CTCAE and global assessment of treatment tolerability	PRO-CTCAE (pre-selected items based on treatment arms) and global assessment of treatment tolerability (QLQ-BIL21 item 49)
To assess the patients' global impression of the severity of cancer symptoms	PGIS
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	The EQ-5D-5L health state utility instrument will be used to derive health state utility based on patient-reported data.
To explore the impact of treatment and disease on healthcare resource use	The HOSPAD module will be used to collect information on key healthcare resource use beyond study mandated visits.

Note: Patients in Arm A will receive durvalumab plus gemcitabine/cisplatin combination therapy; patients in Arm B will receive placebo plus gemcitabine/cisplatin therapy.

ADA Antidrug antibody; AE Adverse event; BICR Blinded independent central review; BTC Biliary tract cancer; ctDNA Circulating tumor deoxyribonucleic acid; DCR Disease control rate; DoR Duration of response; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L EuroQoL 5-dimension, 5-level health state utility index; HOSPAD Hospital resource use module; HRQoL Health-related quality of life; IA-1 Interim Analysis 1; MSI Microsatellite instability; ORR Objective response rate; OS Overall survival; PD-L1 Programmed cell death ligand-1; PFS Progression-free survival; PGIS Patient Global Impression of Severity; PK Pharmacokinetics; PRO-CTCAE Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; PS Performance status; QLQ-BIL21 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire; QLQ-C30 30-Item Core Quality of Life Questionnaire; QoL Quality of life; RECIST Response Evaluation Criteria in Solid Tumors; TMB Tumor mutational burden; WHO World Health Organization.

4 STUDY DESIGN

4.1 Overall design

This is a Phase III randomized, double-blind, placebo-controlled, multi-regional, international study to assess the efficacy and safety of first-line treatment with durvalumab in combination with gemcitabine/cisplatin versus placebo in combination with gemcitabine/cisplatin in patients with previously untreated, unresectable locally advanced or metastatic BTC.

Patients will be asked to provide consent to supply a recent tumor biopsy or their archival tumor blocks if a sample recently taken at the time of diagnosis is available. These samples will be analyzed for biomarker and other molecular analysis, TMB, and oncogenic variants in addition to exploratory analyses such as, but not limited to, molecular profiling and gene expression profiling.

Approximately 672 patients will be randomized in the Global Cohort. Patients will be randomized 1:1 to Arm A or Arm B. Approximately 130 Chinese patients will be randomized in this study.

- **Arm A**: Durvalumab plus gemcitabine/cisplatin combination therapy. Durvalumab 1500 mg via IV infusion q3w, starting on Cycle 1 in combination with cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 (each administered on Days 1 and 8 q3w) up to 8 cycles, followed by durvalumab 1500 mg as monotherapy q4w until clinical progression or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (per Section 7). Durvalumab dose modification for patients ≤30 kg is presented in Section 6.1.1.1.
- **Arm B**: Placebo plus gemcitabine/cisplatin therapy. Placebo via IV infusion q3w, starting on Cycle 1 in combination with cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 (each administered on Days 1 and 8 q3w) up to 8 cycles, followed by placebo monotherapy q4w until clinical progression or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (per Section 7).

The primary objective of the study is to confirm the superiority of Arm A compared to Arm B in terms of OS in patients with first-line advanced BTC.

Randomization will be stratified by disease status (initially unresectable versus recurrent) and primary tumor site (intrahepatic cholangiocarcinoma versus extrahepatic cholangiocarcinoma versus gallbladder cancer).

For an overview of the study design, see Figure 1. For details on treatments given during the study, see Section 6.1. For details on the efficacy and safety endpoints, see Section 3.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] or similar pandemic infection), which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimise risks to study integrity. Where allowable by local health authorities, ethics committees, health care provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining reconsent for the mitigation procedures (note, in the case of verbal reconsent, the informed consent form [ICF] should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study clinical lead.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix I.

4.2 Scientific rationale for study design

4.2.1 Rationale for efficacy endpoints

The primary endpoint of the proposed study will be OS, defined as the time from the date of randomization until death due to any cause. OS is considered the most reliable cancer endpoint in this Phase III study supported by the FDA and European Medicines Agency (EMA) guidelines (FDA 2007 and EMA 2012). OS is considered the most appropriate endpoint, given that the mOS in patients with advanced BTC receiving gemcitabine and cisplatin is <1 year (Valle et al 2010, Okusaka et al 2010).

4.2.2 Rationale for other endpoints

The secondary efficacy endpoints will include PFS, ORR, DoR, DCR, and PRO measures. All tumor-related endpoints will be assessed by the site Investigator according to RECIST 1.1; ORR and DoR will also be assessed by a BICR according to RECIST 1.1 for IA-1.

Assessment of AEs and relatedness to the medicinal product will be performed and analyzed. Further, blood samples will be used to measure systemic PK parameters of durvalumab and to investigate the immunogenicity of durvalumab by assessing the presence of anti-drug antibodies (ADAs). Note that PD-L1 is the target of durvalumab, and its expression is hypothesized to be associated with clinical efficacy; thus, potential relationship between PD-L1 expression and response to durvalumab therapy in combination with gemcitabine/cisplatin will also be evaluated.

PROs have become important in evaluating effectiveness of treatments in cancer clinical studies (Kluetz et al 2018). Published qualitative research, including that involving direct patient input, has identified significant symptomatic, functional, and health-related quality of life (HRQoL) burden experienced by patients with advanced BTC (Butt et al 2012, Darwish et al 2013, Elberg et al 2017). The secondary PRO endpoints assessing disease-related symptoms, impacts, and HRQoL, measured using the European Organisation for Research and Treatment of Cancer (EORTC) 30-Item Core Quality of Life Questionnaire (QLQ-C30) and the complementary EORTC-21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire (QLQ-BIL21), will show the overall influence of the benefits and toxicity of the treatment from a patient's perspective and will aid in understanding of the benefit/risk evaluation. The EORTC QLQ-C30/BIL21 questionnaires are validated and well-established instruments with evidence of content validity and psychometric properties for use in clinical studies (Aaronson et al 1993, Friend et al 2011, Kaup-Robberts et al 2016). The additional exploratory PROs of the Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE), Patient Global Impression of Severity (PGIS), and EuroQoL 5-dimension, 5-level health state utility index (EQ-5D-5L) will further inform treatment benefit and risk from the patient's perspective. The assessment of health economic resource

use data and derivation of health state utility will provide important information for payers and will be used within economic evaluations of investigational treatment.

4.2.3 Rationale for gemcitabine/cisplatin as comparator

A large randomized Phase III study (Study ABC-02) and a small (n=84) randomized Phase II Japanese study (Study BT22) have established gemcitabine/cisplatin for first-line advanced BTC (Okusaka et al 2010, Valle et al 2010). These studies are summarized in Section 2. Gemcitabine/cisplatin combination therapy is the most commonly used regimen across the world for the treatment of first-line BTC and is the regimen recommended for first-line BTC treatment according to NCCN, ESMO, and Japanese guidelines (Valle et al 2016, Miyazaki et al 2015, NCCN Guidelines 2018). Based on this information, gemcitabine/cisplatin combination therapy is considered to be the most appropriate comparator for this study.

4.3 Justification for dose

Patients in this study will receive a fixed dose of either durvalumab treatment (1500 mg q3w IV) in combination with cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 (each administered on Days 1 and 8 q3w) or placebo in combination with cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 (each administered on Days 1 and 8 q3w) for up to 8 cycles, followed by durvalumab (1500 mg q4w IV) or placebo monotherapy.

4.3.1 Durvalumab dose and treatment regimen justification

4.3.1.1 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg q4w is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumors and from a Phase I study performed in Japanese patients with advanced solid tumor (Study D4190C00002).

PK/pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 mg/kg to 10 mg/kg q2w or 15 mg/kg q3w, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg q2w, suggesting near-complete target saturation (membrane bound and soluble PD-L1) and further showing that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral soluble PD-L1 was observed over the dose range studied, consistent with the engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (for further information on immunogenicity, see the current durvalumab IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 mg/kg to 10 mg/kg q2w or 15 mg/kg q3w; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by AUC_{ss} (4 weeks). The median $C_{max,ss}$ is expected to be higher with 20 mg/kg q4w (~1.5-fold), and the median $C_{trough,ss}$ is expected to be higher with 10 mg/kg q2w (~1.25-fold). Clinical activity with the 20-mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg q2w, with the proposed similar dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in the majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the serum drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete soluble PD-L1 suppression at trough, and the available clinical data, the 20-mg/kg q4w and 10-mg/kg q2w regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg q4w.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information, including safety, efficacy, and PK at the 20-mg/kg q4w regimen.

4.3.1.2 Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from Study 1108 (N=292; doses=0.1 mg/kg to 10 mg/kg q2w or 15 mg/kg q3w; solid tumors). The population PK analysis indicated only a minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg q2w) and fixed dosing (750 mg q2w) of durvalumab was evaluated by comparing predicted steady-state PK concentrations (5^{th}, median, and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on the median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40 kg to 120 kg. Simulation results demonstrate that the body-WT-based and fixed-dosing regimens yield similar median steady-state PK concentrations, with slightly less overall between-patient variability with the fixed-dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 mAbs and found that fixed and body-size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed-dosing approach is preferred by the prescribing community due to its ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed-dosing regimens. Based on the average body WT of 75 kg, a fixed dose of 1500-mg q4w durvalumab (equivalent to 20 mg/kg q4w) is sufficient to provide therapeutic effects.

4.3.1.3 Durvalumab q3w dose rationale

During gemcitabine/cisplatin administration in this study, durvalumab will be administered at 1500 mg q3w, rather than the standard q4w schedule, in order to conform to the gemcitabine/cisplatin schedule.

The safety of a q3w dosing schedule in combination with chemotherapy has been explored in the ongoing Study D419SC00001, where durvalumab plus tremelimumab was given in combination with chemotherapy to patients with advanced solid tumors. The combination has been declared tolerable and manageable.

There is also an ongoing Phase III study (Study D419MC00004) to investigate the efficacy and safety of durvalumab in combination with platinum-based chemotherapy for the treatment of patients with NSCLC, where the fixed dose of durvalumab 1500 mg q3w dosing is used in combination with gemcitabine 1000 or 1250 mg/m^2 via IV infusion on Days 1 and 8 q3w plus cisplatin 75 mg/m^2 via IV infusion on Day 1 q3w for 4 to 6 cycles. No safety events related to this combination have been reported through IDMC review. The combination of durvalumab 1500 mg q3w with gemcitabine plus cisplatin q3w has been also tolerable.

The relative increase in the dose density of durvalumab (ie, 1500 mg q3w instead of q4w) is supported by the fact that toxicities attributable to durvalumab do not appear dose dependent, and PK modeling reveals no meaningful differences in drug levels between q3w and q4w dosing.

In this study, AstraZeneca also proposes to use the Phase III fixed dose of durvalumab q3w, so this study will use 1500-mg durvalumab q3w in combination with chemotherapy.

After treatment with gemcitabine/cisplatin is complete, durvalumab will be administered at 1500 mg q4w.

4.3.2 Gemcitabine/cisplatin dose and treatment regimen justification

As described in Section 4.2.3, the combination of gemcitabine and cisplatin is the most commonly used first-line treatment regimen for patients with advanced BTC across the world (NCCN Guidelines 2018, Valle et al 2016, Miyazaki et al 2015). The recommended dose and dosing regimen for gemcitabine/cisplatin for advance BTC is adopted in this study, as presented in Section 4.3.

In Study ABC-02, the patients were treated for up to 8 cycles and discontinued gemcitabine/cisplatin irrespective of response. In the real-world practice, patients responding to gemcitabine/cisplatin with tolerability often continue chemotherapy over 8 cycles until disease progression, but the benefit of continued therapy is uncertain. Hyung and colleagues retrospectively evaluated the survival benefit of continuing gemcitabine/cisplatin after 6 to 8 cycles (maintenance group) versus no further cycles of gemcitabine/cisplatin after 6 to 8 cycles (observation group) in patients with advanced BTC (n=740). OS and PFS did not show statistically significant differences between the 2 treatment groups. The results were consistent with the multivariate analyses for OS and PFS after the adjustment of prognostic factors. Considering the potential disadvantages such as cumulative toxicities, maintenance therapy may not be beneficial in patients who did not progress on 6 to 8 cycles of gemcitabine/cisplatin (Hyung et al 2018). Therefore, continuing gemcitabine/cisplatin or gemcitabine monotherapy after 8 cycles should not be allowed in this study to avoid the imbalance of chemotherapy in both arms.

4.4 End of study definition

The end of study is defined as the last visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when he/she has completed his/her last scheduled procedure shown in the SoAs.

Patients may be withdrawn from the study if the study itself is stopped. The study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings.

In the event that a rollover or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The rollover or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new Informed Consent.

See Appendix A 6 for guidelines on the dissemination of study results.

5 STUDY POPULATION

The study population includes patients ≥18 years of age with previously untreated, unresectable locally advanced or metastatic BTC (eg, intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer). Cancer of AoV has a different genetic profile than other subtypes of BTC (Yachida et al 2016). To minimize the diversity of the study population, the patients with cancer of AoV were excluded from the study.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be randomized to a study intervention. Under no circumstances can there be exceptions to this rule.

In this protocol, "enrolled" patients are defined as those who sign an informed consent and receive an enrollment number. "Randomized" patients are defined as those who undergo randomization and receive a randomization number.

Patients who do not meet the entry requirements are screen failures; refer to Section 5.4. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

For procedures for withdrawal of incorrectly enrolled patients, see Section 7.3.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2 Provision of a signed and dated written ICF prior to any mandatory study-specific procedures, sampling, and analyses.

3 Provision of a signed and dated written informed consent prior to the collection of sample for optional genetic analysis.

The ICF process is described in Appendix A 3.

Age

4 Age ≥18 years at the time of screening. For patients aged <20 years and enrolled in Japan, a written informed consent should be obtained from the patient and his/her legally acceptable representative.

Type of patient and disease characteristics

5 Histologically confirmed, unresectable advanced or metastatic adenocarcinoma of biliary tract, including cholangiocarcinoma (intrahepatic or extrahepatic) and gallbladder carcinoma.

6 Patients with previously untreated disease if unresectable or metastatic at initial diagnosis will be eligible.

7 Patients who developed recurrent disease >6 months after surgery with curative intent and, if given, >6 months after the completion of adjuvant therapy (chemotherapy and/or radiation) will be eligible.

8 A World Health Organization (WHO)/ECOG PS of 0 or 1 at enrollment.

9 At least 1 lesion that qualifies as a RECIST 1.1 Target Lesion (TL) at baseline.

10 No prior exposure to immune-mediated therapy, including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines.

11 Adequate organ and marrow function, as defined below:

- Hemoglobin ≥9.0 g/dL.
- Absolute neutrophil count ≥1.5 × 10^9 /L.
- Platelet count ≥100 × 10^9/L.
- Serum bilirubin ≤2.0 × the upper limit of normal (ULN); This will not apply to patients with confirmed Gilbert's syndrome. Any clinically significant biliary obstruction should be resolved before randomization.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST ≤5 × ULN.
- Creatinine clearance (CL) >50 mL/min per 24hr urine or as calculated by Cockcroft-Gault (using actual body weight):

  Males

  $$\text{Creatinine CL (mL/min)} = \frac{Weight\ (kg) \times (140 - Age)}{72 \times serum\ creatinine\ (mg/dL)}$$

  Females:

  $$\text{Creatinine CL (mL/min)} = \frac{Weight\ (kg) \times (140 - Age) \times 0.85}{72 \times serum\ creatinine\ (mg/dL)}$$

12 Patients must have a life expectancy of at least 12 weeks at the time of screening.

Weight

13 Body weight >30 kg.

Sex

14 Male and/or female.

Other

15 Patients must provide a recent tumor biopsy or an available unstained archived tumor tissue sample in a quantity sufficient to allow for analysis (taken ≤3 years prior to screening). The tumor lesions to be used for biopsy should not be those used as RECIST TLs, unless there are no other lesions suitable for biopsy.

16 Patients with HBV infection (as characterized by positive hepatitis B surface antigen [HBsAg] and/or anti-hepatitis B core antibodies (anti-HBc) with detectable HBV deoxyribonucleic acid (DNA) [≥10 IU/mL or above the limit of detection per local laboratory]) must receive antiviral therapy prior to randomization per institutional practice to ensure adequate viral suppression. Patients must remain on antiviral therapy for the study duration and for 6 months after the last dose of study treatment. Patients who test positive for anti-HBc with undetectable HBV DNA (<10 IU/mL or under the limit of detection per local laboratory) do not require antiviral therapy unless HBV DNA exceeds 10IU/mL or reaches detectable limits per local laboratory during the course of treatment. Patients with active co-infection of HBV and HCV as evidenced by positive anti-HCV antibody and actively co-infected with HBV and hepatitis D virus are not eligible.

5.2 Exclusion criteria

Medical conditions

1 Ampullary carcinoma.

2 History of allogeneic organ transplantation.

3 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

- Patients with vitiligo or alopecia.
- Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.
- Any chronic skin condition that does not require systemic therapy.
- Patients without an active disease in the last 5 years may be included but only after consultation with the Study Physician.
- Patients with celiac disease controlled by diet alone.

4 Uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active interstitial lung disease (ILD), serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase the risk of incurring AEs, or compromise the ability of the patient to give written informed consent.

5 History of another primary malignancy, except for:
   - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of investigational product (IP) and of low potential risk for recurrence.
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
   - Adequately treated carcinoma in situ without evidence of disease.

6 History of leptomeningeal carcinomatosis.

7 History of active primary immunodeficiency.

8 Active infection, including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), or **human immunodeficiency virus** (positive HIV 1/2 antibodies).

9 Any unresolved toxicity NCI Common Terminology Criteria for Adverse Event (CTCAE) Grade ≥2 from a previous anticancer therapy, with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
   - Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
   - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.

10 Brain metastases or spinal cord compression (including asymptomatic and adequately treated disease). Patients with suspected brain metastases at screening should have an MRI (preferred) or CT scan, each preferably with IV contrast, of the brain prior to study entry.

11 Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

Prior/concomitant therapy

12 Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.

13 Radiation therapy, including palliative radiation, is not allowed before the study, with an exception of radiation given in an adjuvant setting.

14 Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note that patients, if enrolled, should not receive live vaccine while receiving IP and up to 30 days after the last dose of IP.

15 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note that minor surgery of isolated lesions for palliative intent is acceptable if performed more than 14 days prior to the first dose of IP.

16 Patients who have received prior immune-mediated therapy, including, but not limited to, other anti-PD-1, anti PD-L1, or anti CTLA-4.

17 Prior locoregional therapy such as radioembolization.

18 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:

- Intranasal, inhaled, or topical steroids or local steroid injections (eg, intra-articular injection).
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
- Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

Prior/concurrent clinical study experience

19 Participation in another clinical study with an IP administered in the last 3 months.

20 Previous IP assignment in the present study.

21 Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

22 Prior randomization or treatment in a previous durvalumab clinical study, regardless of treatment arm assignment.

Other exclusions

23 Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to use effective birth control from screening to 180 days after the last dose of gemcitabine/cisplatin or 90 days after the last dose of durvalumab/placebo monotherapy.

24 Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.

25 Genetic research study (optional).

Exclusion criteria for participation in the optional (deoxyribonucleic acid [DNA]) genetic research component of the study include the following:

- Previous allogeneic bone marrow transplant.
- Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection.

26 Active infection of hepatitis C as evidenced by detectable HCV RNA per local laboratory. Patients who test positive for hepatitis C (HCV) antibody may be enrolled if HCV RNA is undetectable.

5.3 Lifestyle restrictions

The following restrictions apply while the patient is receiving IP and for the specified times before and after:

1 Female patient of child-bearing potential

- Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 6) from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of gemcitabine/cisplatin or 90 days after the last dose of durvalumab/placebo monotherapy). Non-sterilized male partners of female patients of childbearing potential must use a male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding throughout this period.

2 Male patients with a female partner of childbearing potential

- Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of gemcitabine/cisplatin or 90 days after the last dose of durvalumab/placebo monotherapy). True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 6).

Note that females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for ≥12 months following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for ≥12 months following cessation of all exogenous hormonal treatments, had radiation-induced menopause with the last menses >1 year ago, or had chemotherapy-induced menopause with the last menses >1 year ago.
- Women who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) are eligible.

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, <1% per year) when used consistently and correctly, are described in Table 6. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper-containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel, which is considered highly effective]; and triphasic combined oral contraceptive pills).

Serum levels of contraceptive hormones may be altered by concomitant use of other drugs. Therefore, drug interactions should always be considered when prescribing hormonal contraception; there could be a risk of contraceptive failure or other adverse effects.

For patients receiving gemcitabine/cisplatin (both arms), the local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for these agents should be followed.

Table 6 Highly effective methods of contraception (<1% failure rate)

Barrier/intrauterine methods	Hormonal methods
• Copper T intrauterine device. • Levonorgestrel-releasing intrauterine system (eg, Mirena®).[a]	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®).[b] • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®). • Injection: Medroxyprogesterone injection (eg, Depo-Provera®). • Combined pill: Normal and low-dose combined oral contraceptive pill. • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®). • Minipill: Progesterone-based oral contraceptive pill using desogestrel. Cerazette® is currently the only highly effective progesterone based pill.

[a] This is also considered a hormonal method.
[b] Not approved for use in Japan.

3 All patients: Patients should not donate blood or blood components while participating in this study and through 180 days after the last dose of gemcitabine/cisplatin or 90 days after the last dose of durvalumab/placebo monotherapy or until alternate anticancer therapy is started.

4 Restrictions relating to concomitant medications are described in Section 6.4.

5.4 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study and, therefore, must not be randomized. These patients should have the reason for study withdrawal recorded as “eligibility criteria not fulfilled” (ie, the patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized patients). Patients may be rescreened a single time, but they may not be re-randomized.

If the patient is ineligible and not randomized, the interactive voice/web response system (IVRS/IWRS) should be contacted to terminate the patient in the system (screen failed).

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

6 STUDY TREATMENTS

Study treatment is defined as any IPs (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to durvalumab, placebo, and gemcitabine/cisplatin.

6.1 Treatments administered

6.1.1 Investigational products

Study treatments/IP are described in Table 7. Rescue and concomitant medications are included in Section 6.4.

AstraZeneca will supply durvalumab (MEDI4736). The SoC (chemotherapy) agents (gemcitabine and cisplatin) and the 0.9% (w/v) saline or 5% (w/v) dextrose solution for placebo will be supplied locally. Under certain circumstances, when local sourcing is not feasible, an SoC (chemotherapy) treatment may be supplied centrally through AstraZeneca.

Table 7 Study treatments

	Durvalumab	**Placebo**	**Standard of care**
Study treatment name:	**Durvalumab (MEDI4736)**	**Sterile saline or dextrose solution**	**Standard of care (chemotherapy)[a]**
Dosage formulation:	500 mg vial solution for infusion after dilution, 50 mg/mL	Sterile solution of 0.9% (w/v) sodium chloride or 5% (w/v) dextrose for injection	As sourced locally
Route of administration	IV	IV	IV
Dosing instructions[b]:	1500 mg IV q3w or q4w	0.9% (w/v) saline or 5% (w/v) dextrose volume matching durvalumab volume	Cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 on Day 1 and Day 8 q3w for up to 8 cycles
Packaging and labelling	Study treatment will be provided in 500 mg vials Each vial will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.[C]	Sourced locally by site	Sourced locally by site

Provider	AstraZeneca	Sourced locally by site	Sourced locally by site[a]

[a] Under certain circumstances, when local sourcing is not feasible, an SoC (chemotherapy) treatment may be supplied centrally through AstraZeneca.
[b] Detailed instructions on IP administration are provided in Sections 6.1.1.1, 6.1.1.2, and 6.1.1.3. Refer to Section 6.1.2 for details on the duration of treatment.
[c] Label text prepared for durvalumab (MEDI4736) will show the product name as "MEDI4736" or "durvalumab (MEDI4736)," depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.
IV Intravenous; IP Investigational product; q3w Every 3 weeks; q4w Every 4 weeks; SoC Standard of care; w/v, weight/volume.

6.1.1.1 Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10.0 mL.

Durvalumab (MEDI4736) is a sterile, clear to opalescent, colourless to slightly yellow solution, free from visible particles.

IP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. IP should be kept in original packaging until use to prevent prolonged light exposure.

Preparation of durvalumab (MEDI4736) doses for administration with an IV bag

The dose of durvalumab (MEDI4736) for administration must be prepared by the unblinded site staff using aseptic technique. The total time from the needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

  If the final product is stored at both refrigerated and ambient temperatures, the total time should not exceed 24 hrs.

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2-µm or 0.22-µm filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, 1500 mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final

concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

The IV bag should be covered with a translucent colored or opaque sleeve after preparation by the unblinded pharmacist prior to dispensing to other study personnel, sleeve cover should be secured (e.g. using stapling, heat-sealing), to maintain double-blind conditions. Once the IP infusion is completed, the infusion bag must be discarded with the sleeve covering in place to ensure that the blind is maintained.

If patient's weight falls to ≤30 kg, weight-based dosing at 20 mg/kg will be administered using an IV bag size selected such that the final concentration is within 1 to 15 mg/mL.

Standard infusion time is 1 hour, however if there are interruptions during the infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

If either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

6.1.1.2 Standard of care (chemotherapy)

The SoC (chemotherapy) agents (gemcitabine/cisplatin) will be either locally sourced or centrally supplied by AstraZeneca and will be administered according to prescribing information or treatment guidance in general use by the investigating site. Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally supply the drugs, and the drugs will be labelled with local-language-translated text in accordance with regulatory guidelines.

6.1.1.3 Placebo

An IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose (approximately) matching the IV bag volume containing active drug will be used for placebo. The IV bag should be covered with a translucent coloured or opaque sleeve after preparation by the unblinded pharmacist prior to dispensing to other study personnel, sleeve cover should be secured (e.g. using stapling, heat-sealing) to maintain double-blind conditions. Once the IP infusion is completed, the infusion bag must be discarded with the sleeve covering in place to ensure that blind is maintained.

Standard infusion time is one hour, however if there are interruptions during the infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

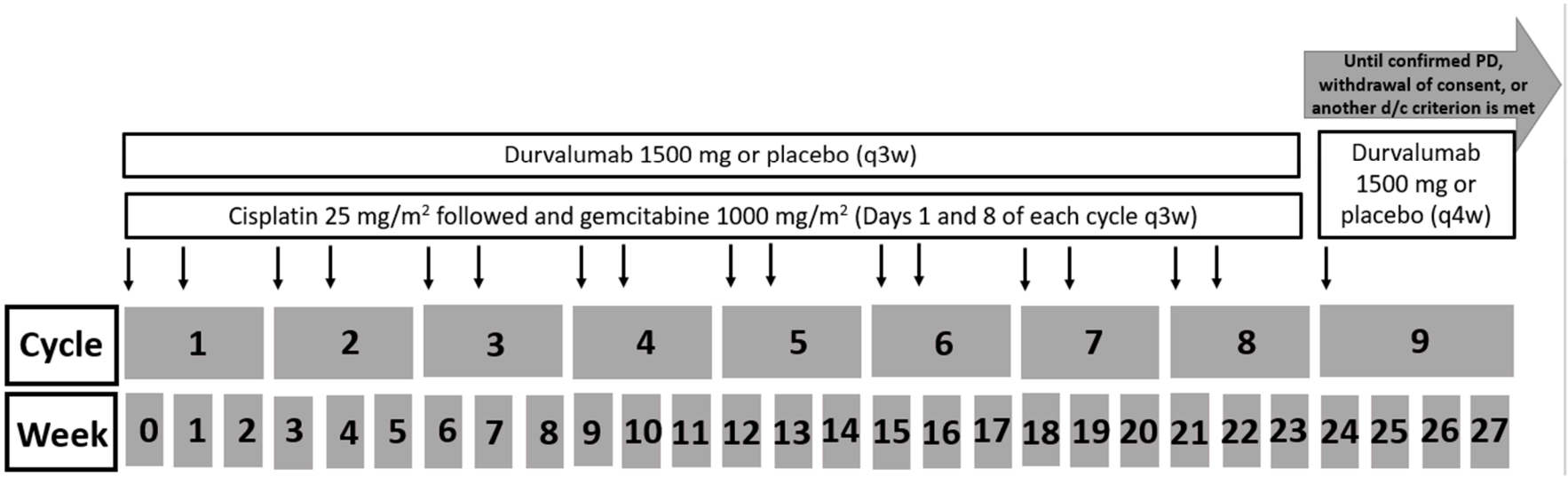
If either preparation time or infusion time exceeds the time limits a new placebo dose must be prepared.

6.1.2 Dose and treatment regimens

6.1.2.1 Durvalumab (MEDI4736) or placebo plus gemcitabine/cisplatin

Patients will receive cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 (each administered on Days 1 and 8 q3w) plus durvalumab 1500 mg (Arm A) or placebo (Arm B) via IV infusion q3w, starting on Cycle 1, for up to 8 cycles. During Day 1 visits of each cycle, treatment administration of durvalumab/placebo should occur first (as described in Table 1), followed by chemotherapy. After treatment with gemcitabine/cisplatin is complete, patients will receive 1500-mg durvalumab (Arm A) or placebo (Arm B) as monotherapy via IV infusion q4w until clinical progression or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See Figure 2. (Note that if a patient's weight falls to ≤30 kg, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab [or placebo] q3w or q4w after consultation between the Investigator and the Study Physician, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg [or placebo] q3w or q4w.)

Figure 2 Durvalumab or placebo plus gemcitabine/cisplatin dosing schedule



Note: Patients in Arm A will receive durvalumab plus gemcitabine/cisplatin combination therapy; patients in Arm B will receive placebo plus gemcitabine/cisplatin therapy.
Note: For patients who have discontinued gemcitabine/cisplatin due to treatment-related toxicity before completion of Cycle 8, treatment with durvalumab/placebo may continue at the Investigator's discretion when toxicity resolves to Grade 2 or less; in that case, durvalumab/placebo monotherapy will be administered q4w. During the first 8 cycles of durvalumab or placebo in combination with gemcitabine/cisplatin, if durvalumab or placebo must be discontinued due to durvalumab- or placebo-related toxicity, the patient must complete the treatment discontinuation visit as outlined in Table 1, and enter the Follow-Up Period. Treatment with Gemcitabine/cisplatin may be continued at the Investigator's discretion of the investigator during the follow-up period, and should reported in the eCRF as subsequent anticancer treatment.
Note: For durvalumab treatment schedules, if there is a dosing delay while on the q3w schedule, all future dosing days should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days. For gemcitabine/cisplatin, dosing delays should be managed according to local prescribing guidelines. If any cycle is delayed, cycle number and week number should be delayed.
d/c Discontinuation; PD Progression of disease; q3w Every 3 weeks; q4w Every 4 weeks.

6.1.3 Duration of treatment and criteria for treatment through progression

Durvalumab [Arm A] or placebo [Arm B] plus gemcitabine/cisplatin will be administered up to 8 cycles q3w. Patients will subsequently receive durvalumab (Arm A) or placebo (Arm B) q4w until clinical progression or RECIST 1.1-defined radiological PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined radiological PD may continue to receive study treatment at the discretion of the Investigator and patient as long as they are deemed to be receiving clinical benefit. A follow-up scan is to be collected after the initial RECIST 1.1-defined radiological PD, preferably at the next (and no later than the next) scheduled imaging visit and no less than 4 weeks after the prior assessment of PD; this follow-up scan is evaluated using the criteria outlined in Appendix F.

Patients with RECIST 1.1-defined radiological PD who continue to receive their assigned treatment at the discretion of the Investigator and patient can receive treatment until no longer having clinical benefit, and imaging for tumor assessments should be continued at a maximum scan interval of 8 weeks for the duration of treatment unless there is unacceptable toxicity, withdrawal of consent or another discontinuation criterion is met.

The decision of treatment through progression should be made after careful assessment of derived clinical benefit and risk of assigned treatment, followed by discussion and agreement between the investigators and the patients.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible for continuing durvalumab (or placebo).

For all patients who are treated through progression, the Investigator should ensure that the patients do not have any significant, unacceptable, or irreversible toxicities that indicate continuing would not further benefit them.

Crossover within the study will not be permitted.

For all patients who are treated through progression, the Investigator should ensure that:

- The patient does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The patient may not have experienced a toxicity that required permanent discontinuation of study treatment.
- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG PS to >1.

- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g. central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention. The patient still fulfills the eligibility criteria for this study (see Sections 5.1 and 5.2), with the exception of inclusion criteria 6, 7, 10, and 12 and exclusion criteria 5, 10, 13, 16, and 22.

Patients who AstraZeneca and the Investigator determine may not continue treatment after RECIST 1.1-defined radiological PD will be followed up for survival. Patients without radiological PD and who have discontinued treatment due to toxicity, clinical progression (for patients with unclear radiological progression), or symptomatic deterioration or who have commenced subsequent anticancer therapy will be followed up with tumor assessments until RECIST 1.1-defined radiological PD plus an additional follow-up scan or until death (whichever comes first) and followed up for survival.

Post final Data Cutoff (DCO)

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician consider they are gaining clinical benefit. For patients continuing to receive durvalumab treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patients' safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dosing Modification and Toxicity Management Guidelines (see Section 8.4.6).

In the event that a rollover or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The rollover or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new Informed Consent.

6.1.4 Storage

The Investigator, or an approved representative (e.g. pharmacist), will ensure that all IP is stored in a secured area and in refrigerated temperature (2°C to 8°C for durvalumab). . Cisplatin and gemcitabine must be stored according to the applicable manufacturer labelled storage conditions. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature-monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

6.1.5 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language. Label text prepared for durvalumab (MEDI4736) will show the product name as "MEDI4736" or "durvalumab (MEDI4736)," depending on the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period. IP will be provided with either single panel labels or multi language booklet labels.

6.2 Measures to minimize bias: randomization and blinding

6.2.1 Patient enrollment and randomization

Patients will be randomized in a 1:1 ratio to Arm A or Arm B. Randomization will be stratified by disease status (initially unresectable versus recurrent) and primary tumor location (intrahepatic cholangiocarcinoma versus extrahepatic cholangiocarcinoma versus gallbladder cancer).

All patients will be centrally assigned to randomized study treatment using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

If a patient withdraws from the study, then his/her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

Investigators should keep a record (i.e. the patient screening log) of patients who entered screening.

At screening/baseline (Days -28 to -1), the Investigators or suitably trained delegate will:

- Obtain a signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes, with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization (except for screening clinical chemistry and hematology assessments, which must be obtained within 7 days prior to randomization).
- Obtain a unique 7-digit enrollment number (E-code) through the IVRS/IWRS in the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the patient enrollment code at the center). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).
- Determine patient eligibility (see Sections 5.1 and 5.2).

- Obtain a signed informed consent for the genetic research study (optional).

At randomization, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will:

- Obtain a unique randomization number via the IVRS/IWRS. Numbers will start at 001 and will be assigned strictly sequentially by the IVRS/IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 2 treatment groups.

If the patient is ineligible and not randomized, the IVRS/IWRS should be contacted to terminate the patient in the system (screen failed).

Patients will begin treatment on Day 1. Every effort should be made to minimize the time between randomization and starting treatment. It is strongly recommended that patients commence study drug on the same day as randomization. If same-day treatment is not possible, then the study treatment must occur within 3 days of randomization. Patients must not be randomized and treated unless all eligibility criteria have been met.

6.2.2 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca Study Physician must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the patient.

6.2.3 Methods for assigning treatment groups

The actual treatment given to patients will be determined by the randomization scheme in the IVRS/IWRS. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers.
One randomization list will be produced for each of the randomization stratum. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment group.

Patients will be identified to the IVRS/IWRS per country regulations. Randomization codes will be assigned strictly sequentially, within each stratum, as patients become eligible for randomization. The IVRS/IWRS will provide the kit identification number to be allocated to the patient at the randomization visit and subsequent treatment visits.

6.2.4 Methods for ensuring blinding

The study will be conducted in a double-blind manner. For durvalumab, the IV bag should be covered with a translucent colored or opaque sleeve after preparation by the unblinded pharmacist prior to dispensing to other study personnel, sleeve cover should be secured (e.g. using stapling, heat-sealing), to maintain double-blind conditions. Once the IP infusion is completed, the infusion bag must be discarded with the sleeve covering in place to ensure that the blind is maintained.. The patient, the Investigator, and study center staff will be blinded to the durvalumab/placebo allocation and will remain blinded to each patient's assigned study treatment throughout the course of the study. To maintain this blind, an otherwise uninvolved third party (ie, the unblinded pharmacist) will be unblinded to the durvalumab/placebo allocation and will prepare durvalumab or placebo for a patient as specified by the randomization scheme and IVRS (only the unblinded pharmacist will know the randomization/treatment allocation details). The IVRS/IWRS will provide to the unblinded pharmacists the kit identification number to be allocated to the patient at the dispensing visit. Pharmacists will be given specific instructions for durvalumab/placebo preparation and will note if the double-blind conditions have been compromised or the blind has been broken. Kit numbers of durvalumab dispensed will be recorded by the pharmacist and monitored by an unblinded monitor. Other study center staff and monitors will not be given access to kit number information. Blinded and unblinded access and notifications will be controlled using the IVRS/IWRS.

No member of the extended study team at AstraZeneca, at the investigational centers, or any blinded Contract Research Organization handling data will have access to the randomization scheme until the time of the final data analysis (ie, the primary OS analysis) or any interim analysis data where a decision is made to unblind the study. At such time, AstraZeneca and any Contract Research Organization handling data will have access to the randomization scheme. Exceptions are relevant persons within the Pharmaceutical Development Supply Chain at AstraZeneca or their designee, where the information is needed to package the study treatment; the drug safety departments at AstraZeneca; and the pharmacists required to dispense the study treatment at the study site. Investigators will be unblinded to treatment allocation only in cases of medical emergency.

The treatment codes and results will be kept strictly within AstraZeneca to safeguard the integrity of the blind and hence to minimize any possible bias in data handling.

The IDMC will be provided with unblinded data for their review, but AstraZeneca staff and Investigators involved in the study will remain blinded.

In the event that the treatment allocation for a patient becomes known to the Investigator or other study staff involved in the management of study patients or needs to be known to treat an individual patient for an AE, the Sponsor must be notified promptly by the Investigator and, if possible, before unblinding. The IVRS/IWRS will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the Investigator, it is in the patient's best interest for the Investigator to know the study treatment assignment. In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. Study unblinding should not occur until database lock, and all decisions on the evaluability of the data from each individual patient have been made and documented.

6.3 Treatment compliance

Any change from the dosing schedule, dose delays/interruptions, dose reductions, and dose discontinuations should be recorded in the eCRF.

The Investigational Product Storage Manager is responsible for managing the IP, from receipt by the study site until the destruction or return of all unused IP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IP.

6.4 Concomitant therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical treatment phase of the study, including the 90-day follow-up period following the last dose of study drug.

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrollment or receives during the study, must be recorded along with:

- Reason for use
- Dates of administration, including the start and end dates
- Dosage information, including the dose, unit, and frequency

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer also to the Dosing Modification and Toxicity Management Guidelines (see

Section 8.4.6). For gemcitabine/cisplatin, refer to the local prescribing information with regard to warnings, precautions, and contraindications.

Table 8 Prohibited concomitant medications

Prohibited medication/class of drug	Usage
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment.
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment.
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding TLs, for palliative intent is acceptable [eg, radiotherapy for bone metastasis].)
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP.
Immunosuppressive medications, including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly or used for premedication prior to the IO infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs • Short-term premedication for patients receiving gemcitabine/cisplatin, where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted • A temporary period of steroids, which will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy-related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea)
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days after the last dose of durvalumab. Increased incidences of pneumonitis (with third-generation EGFR TKIs) and transaminase increases (with first-generation EGFR TKIs) have been reported when durvalumab has been given concomitantly.

Prohibited medication/class of drug	Usage
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly, unless agreed by the Sponsor.

AE Adverse event; CTLA-4 Cytotoxic T-lymphocyte associated protein 4; EGFR Epidermal growth factor receptor; IO Immuno-oncology (agent); IP Investigational product; mAbs monoclonal antibody; PD-1 Programmed cell death 1; PD-L1 Programmed cell death ligand-1; TKI Tyrosine kinase inhibitors; TL Target Lesion.

Table 9 Supportive medications

Supportive medication/class of drug	Usage
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to NTLs [ie, for bone metastasis], etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

NTL Non-Target Lesion.

6.4.1 Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form (CRF).

6.4.2 Durvalumab drug-drug interactions

There is no information to date on drug-drug interactions with durvalumab, either pre-clinically or in patients. Because durvalumab is a mAb and, therefore, a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that durvalumab will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected PK drug-drug interactions. The MOA of durvalumab involves binding to PD-L1, and therefore, significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential drug-drug interactions.

6.4.3 Rescue medication

As a result of immune-mediated adverse events (imAEs) that could potentially be experienced by patients on durvalumab, steroids and other immunosuppressant rescue medications have to be made available to this patient population. The 2 products that fall into the category of immunosuppressants are infliximab (e.g. for colitis) and mycophenolate (e.g. for hepatitis). AstraZeneca supply chain will be responsible for sourcing these 2 rescue medications to the sites if local regulations prevent the use of infliximab and mycophenolate in this indication, as they are considered off label for management of immunotherapy-related toxicities. These rescue medications must be receipted, controlled, and dispensed by the unblinded pharmacist and stored according to the labelled storage conditions, with temperature excursions reported accordingly by the unblinded pharmacist. If required for use as a result of an imAE, then the IVRS/IWRS will provide to the unblinded pharmacists the kit identification number to be allocated to the patient at the time. Blinded and unblinded access and notifications will be controlled using the IVRS/IWRS.

6.5 Dose modification

Dose delays are permitted for durvalumab (or placebo) therapy (see the Dosing Modification and Toxicity Management Guidelines. However, **dose reduction for durvalumab (or placebo) therapy is not permitted.**

The Investigator should follow local standard clinical practice regarding dose modifications for gemcitabine/cisplatin. For specific information regarding the individual agents used in this study, refer to the local prescribing information for the relevant agent.

With regard to gemcitabine/cisplatin, patients may delay and subsequently resume dosing per local standard clinical practice. If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible. In the event that chemotherapy is discontinued due to treatment-related toxicity, treatment with durvalumab/placebo may continue at the Investigator's discretion when toxicity resolves to Grade 2 or less; in that case, durvalumab/placebo monotherapy will be administered q4w. Note that if the Investigator feels a patient is ready to restart treatment prior to the toxicity resolving to Grade 2 or less, AstraZeneca should be consulted for an exception to this rule.

During the first 8 cycles of durvalumab or placebo in combination with gemcitabine/cisplatin, if durvalumab or placebo must be discontinued due to durvalumab- or placebo-related toxicity, the patient must complete the treatment discontinuation visit as outlined in Table 1, and enter the Follow-Up Period. Treatment with Gemcitabine/cisplatin may continue at the discretion of the investigator during the follow-up period and should reported in the eCRF as subsequent anticancer treatment. Subsequent anticancer treatment should be held until the toxicity resolves to Grade 2 or less.

6.6 Treatment after the end of the study

After the FA, AstraZeneca will continue to supply open-label drug to patients receiving durvalumab therapy up to the time that they discontinue the treatment (see Section 6.1.2).

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

An individual patient will not receive any further study treatment (durvalumab, placebo, or gemcitabine/cisplatin) if any of the following occur in the patient in question:

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study (e.g. for safety and survival follow-up), unless he/she specifically withdraws consent to all further participation in any study procedures and assessments (see Section 7.3).
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets the criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.6) or as defined in the local prescribing information for gemcitabine/cisplatin. NOTE: Patients who permanently discontinue treatment with durvalumab or placebo for durvalumab/placebo related toxicity, should complete the treatment discontinuation visit as described in Table 1 and enter the Follow-up Period. If this occurs while patient is receiving SOC (e.g. cycles 1-8), treatment with gemcitabine/cisplatin may continue during the follow up period at the investigator's discretion as described in section 6.5
- Pregnancy or intent to become pregnant.
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (e.g. refusal to adhere to scheduled visits).
- Initiation of alternative anticancer therapy, including another investigational agent.
- Clinical progression or radiological progression (refer to Appendix F) and Investigator determination that the patient is no longer benefiting from treatment with IP.

7.1.1 Procedures for discontinuation of study treatment

Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending

subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who are permanently discontinued from further receipt of durvalumab/placebo, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will complete the treatment discontinuation visit and enter follow-up (see Table 2).

Patients who permanently discontinue drug for reasons other than RECIST 1.1-defined radiological PD should continue to have RECIST scans performed q6w±1w for the first 24 weeks (relative to the date of randomization) and then q8w±1w thereafter (relative to the date of randomization) until RECIST 1.1-defined radiological PD plus at least 1 additional follow-up scan or death (whichever comes first), as defined in the SoAs.

If a patient is discontinued for RECIST 1.1-defined radiological PD, then the patient should have 1 additional follow-up scan performed, preferably at the next (and no later than the next) scheduled imaging visit and no less than 4 weeks after the prior assessment of PD.

All patients will be followed up for survival until the end of the study.

Patients who decline to return to the site for evaluations should be contacted by telephone, as indicated in the SoAs, as an alternative.

Patients who have permanently discontinued from further receipt of all study medications (durvalumab/placebo, gemcitabine, and cisplatin) will need to be discontinued from the IVRS/IWRS.

7.2 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 4.3.1.3) such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." The Investigator should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up, and evaluations should resume according to the protocol.

In order to support key endpoints of PFS and OS analyses, the survival status of all patients in the FAS and the Safety Analysis Set (SAS) should be re-checked; this includes those patients who withdrew consent or are classified as "lost to follow-up."

- Lost to follow-up: Site personnel should check hospital records, the patient's current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable CRF modules will be updated.)
- In the event that the patient has actively withdrawn consent to the processing of his/her personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available), where it is possible to do so under applicable local laws, to obtain a current survival status. (The applicable CRF modules will be updated.)

7.3 Withdrawal from the study

Patients are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or undergo further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws consent, he/she will be specifically asked if he/she is withdrawing consent to:

- All further participation in the study, including any further follow-up (eg, survival contact telephone calls)
- Withdrawal to the use of any samples (see Section 8.8.7)

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoAs (Table 1 and Table 2).

The Investigator will ensure that data are recorded on the eCRFs.

The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoAs, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count and imaging assessments) and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoAs.

8.1 Efficacy assessments

This study will evaluate the primary endpoint of OS. The secondary efficacy endpoints of PFS, ORR, DoR, and DCR will be derived (by AstraZeneca) using Investigator RECIST 1.1 assessments; ORR and DoR will also be assessed by a BICR according to RECIST 1.1 for IA-1. PRO-related assessment will be evaluated using quality-of-life questionnaires.

Baseline RECIST 1.1 assessments (selection of TLs and Non-Target Lesions) should be performed on images from CT scans (preferred) or MRI scans, each preferably with IV contrast, of the chest, abdomen (including the entire liver and both adrenal glands), and pelvis, acquired no more than 28 days before the date of randomization and, ideally, should be performed as close as possible to and prior to the date of randomization. Additional anatomy should be imaged based on the signs and symptoms of individual patients at baseline and follow-up. It is important to follow the tumor assessment schedule as closely as possible (refer to Table 1 and Table 2). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression), every attempt should be made to perform the subsequent assessments at their next regularly scheduled visit. The follow-up scan collected after a RECIST 1.1-defined radiological PD should be performed preferably at the next (and no later than the next) scheduled imaging visit and no less than 4 weeks after the prior assessment of PD; this follow-up scan is evaluated using the criteria outlined in Appendix F. Copies of all images are retained at the investigative site as source documents, and all images are preferably

submitted electronically to the AstraZeneca-appointed Imaging Contract Research Organization (iCRO) for quality control (QC), storage, and BICR. See Appendix F for additional details relevant to imaging and tumor assessments.

8.1.1 Central reading of scans

Images, including unscheduled scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed iCRO for QC, storage, and for Blinded Independent Central Review (BICR). Guidelines for image acquisition, de-identification, storage of digital copies at the investigative site (as source documents), and transfer to the iCRO will be provided in a separate document. Electronic image transfer from the sites to the iCRO is strongly encouraged A BICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part on the results of the RECIST 1.1 assessment conducted by the Investigator. Further details of the BICR will be documented in an Independent Review Charter.

8.1.2 Survival assessments

Assessments for survival must be made every 2 months following treatment discontinuation. Survival information may be obtained via telephone contact with the patient or the patient's family or by contact with the patient's current physician. Details of the first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

In addition, patients on treatment or in survival follow-up will be contacted following the DCO for the interim and final analyses (i.e. IA-1, IA-2, and FA) to provide complete survival data. These contacts should generally occur within 7 days of the DCO.

8.1.3 Clinical outcome assessments

A clinical outcome assessment is an assessment of a clinical outcome made through report by a clinician, a patient, or a non-clinician observer or through a performance-based assessment (DA-NIH BEST Resource). A clinical outcome assessment may be used in clinical studies to provide either direct or indirect evidence of treatment benefit. PRO is a type of clinical outcome assessment. PRO is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become important in evaluating effectiveness of study treatments in clinical studies and will aid in understanding of the benefit/risk evaluation (Kluetz et al 2018). The following PROs will be administered in this study: EORTC-QLQ-C30, EORTC-QLQ-BIL21, PRO-CTCAE, PGIS, and EQ-5D-5L (see Appendix G). Each is described below. PROs will be translated into the language of the country in which they are being administered, with the exception of PRO-CTCAE that will only be administered in languages where a linguistically validated version is available.

8.1.3.1 EORTC QLQ-C30 and EORTC QLQ-BIL21

The EORTC-QLQ-C30 and the EORTC QLQ-BIL21 are selected to assess the impact of treatment and disease state on symptoms, impacts, and HRQoL. The EORTC scales include many of the key BTC symptoms and impacts, such as abdominal pain, fatigue, pruritus, jaundice, lack of appetite, physical functioning, and insomnia.

The EORTC QLQ-C30 includes 30 items and assesses HRQoL/health status through the following 9 multi-item scales: 5 functional scales (ie, physical, role, cognitive, emotional, and social), 3 symptom scales (ie, fatigue, pain, and nausea and vomiting), and 1 global health status/QoL scale. It also includes 6 single-item symptom/impact measures: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties (Aaronson et al 1993).

The EORTC QLQ-BIL21 was developed to measure QoL in patients with BTC and is used as an accompaniment to the EORTC QLQ-C30. The EORTC QLQ-BIL21 consists of 21 questions: 3 single-item assessments relating to treatment side effects, difficulties with drainage bags/tubes, and concerns regarding weight loss, in addition to 18 items grouped into 5 scales, which are pain symptoms (4 items), tiredness symptoms (3 items), jaundice symptoms (3 items), anxiety symptoms (4 items), and eating symptoms (4 items).

The EORTC QLQ-BIL21 has evidence of content validity in BTC patients. It was developed based on a literature review, in-depth patient interviews, and healthcare provider interviews specific to BTC populations (Friend et al 2011). Its measurement properties have also been tested in BTC populations and include good evidence of internal consistency reliability, test-retest reliability (reproducibility), and construct validity (Kaup-Robberts et al 2016).

8.1.3.2 PRO-CTCAE

The PRO-CTCAE is included to address tolerability from the patients' perspective. It was developed by the National Cancer Institute (NCI). It was developed in recognition that collecting treatment-related symptom data directly from patients can improve accuracy and efficiency. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate treatment-related symptom onset, frequency, and severity in comparison with patient ratings (Basch et al 2009, Litwin et al 1998, Sprangers and Aaronson 1992). The PRO-CTCAE is an item-bank of symptoms, and the items have undergone extensive qualitative review among experts and patients. To date, 78 symptoms of the CTCAE have been identified to be amenable to patient reporting, but not all items are administered in any one clinical study. Six different symptomatic AEs were selected for the PRO-CTCAE based on available safety reports of durvalumab and gemcitabine/cisplatin. Generally, symptomatic AEs that were not included in the EORTC were prioritized for the PRO-CTCAE to reduce patient burden per published recommendations (Trask et al 2018). The PRO-CTCAE will only be administered in the languages where a linguistically validated version exists.

8.1.3.3 PGIS

The PGIS item is included to assess how a patient perceives his/her overall severity of cancer symptoms over the past 7 days. This is a single-item questionnaire, and patients will choose from response options ranging from "no symptoms" to "very severe."

8.1.3.4 EQ-5D-5L

The EQ-5D-5L, developed by the EuroQoL Group, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status for economic appraisal (EuroQol Group 2015). The EQ-5D-5L questionnaire comprises 5 questions that cover 5 dimensions of health (ie, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Respondents also assess their health today using the EQ-visual analog scale (VAS), which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

8.1.3.5 Administration of patient-reported outcome questionnaires

Patients will complete the PRO assessments using electronic patient□reported outcome (ePRO) tablet devices at study sites. Each study site must allocate the responsibility for the administration of the ePRO tablet devices to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover for that individual if he/she is absent.

The PRO questionnaires should be completed before treatment dosing and before any other study procedures are conducted at the visit in the following order: EORTC QLQ-C30, EORTC QLQ-BIL21, PGIS, EQ-5D-5L, and PRO-CTCAE. EORTC BIL21 will not be used in India except for patients, who are able to complete the questionnaire in Bengali or English languages. It takes about 15 to 20 minutes for patients to complete the PRO questionnaires. The PRO questionnaires must be administered and completed at the clinic per the SoAs (Table 1 and Table 2).

PRO data collection will be discontinued due to the following:

- Patient withdrawal of consent
- Post-PD patient receives non-study treatment regimen
- Death
- Study termination or completion

PRO data collection will continue during the following:

- Discontinuation of study treatment due to toxicity, patient is not receiving non-study treatment regimen and is being followed for safety/efficacy.
- Patient is post-PD and remains on study treatment.

- Patient is not receiving non-study treatment regimen and is being followed for safety/efficacy.

The following instructions should be followed when collecting PRO data via an electronic device:

- The research nurse or appointed site staff must explain the value and relevance of participation to patients and inform them that these questions are being asked to find out from them directly how they feel. This can help motivate patients to comply with data collection.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if patients have any medical problems, they should discuss them with the doctor or research nurse separately from the PRO assessment.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided by the ePRO vendor. All questionnaires must be completed using the ePRO device; paper questionnaires are not allowed in this study.
- PRO questionnaires must be completed prior to treatment administration, and ideally before discussion of health status, to avoid biasing the patient's responses to the questions. As feasible, site staff should ensure PRO questionnaires are completed prior to other study procedures, such as laboratory samples, to further minimize bias.
- PRO questionnaires should be completed by the patient in a quiet and private location.
- The patient should be given sufficient time to complete the questionnaires at their own speed.
- The research nurse or appointed site staff will review the completion status of questionnaires during the scheduled site visit and document in the eCRF the reason(s) why a patient could not complete assessments.
- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and must avoid introducing bias by not clarifying items.
- The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires.
- If a patient uses visual aids (eg, spectacles or contact lenses) for reading and does not have them when he or she attends the clinic, the patient will be exempted from completing the ePROs at that clinic visit. Site staff must not read or complete the PRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (eg, is blind or illiterate), that patient should be exempted from completing the PRO questionnaires but may still participate in the study. Patients exempted in this regard

should be flagged appropriately by the site staff in the source documents and in the eCRF.

- The study nurse or appointed site staff must administer questionnaires available in the language that the patient speaks and understands. Questions should not be read in an available language and translated into another language for the patient.
- Train the patients on how to use the ePRO device using the materials and training provided by the ePRO vendor.
- It is vital that the ePRO reporting is initiated at randomization, as specified in the study plan, to capture the effect of study treatment.

The research nurse or appointed site staff must monitor compliance to ensure all data are captured. Compliance must be checked at each study visit to identify problems early. It is important that the PRO device is charged and fully functional. If a patient's compliance drops to or below 85%, they will be flagged in the routine compliance report generated by the ePRO system.

8.2 Safety assessments

Planned timepoints for all safety assessments are provided in the SoAs.

8.2.1 Clinical safety laboratory assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see Table 1 and Table 2).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary, depending on the laboratory method used and routine practice at the site. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 hours to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables to be measured are presented in Table 10 (clinical chemistry), Table 11 (hematology), and Table 12 (urinalysis).

Other safety tests to be performed include the following (see Table 1 for details):

- Qualitative HBsAg, qualitative hepatitis B envelope (HBe) antigen, anti-hepatitis B core, hepatitis B surface antibody, HBe antibody, anti-HCV, hepatitis D antibody, quantitative HBV DNA and HCV RNA
- HIV antibodies (per local standards)

Note: HBV-positive patients must remain on antiviral therapy for the study duration and must continue therapy for 6 months after the last dose of study treatment.

The following laboratory variables will be measured:

Table 10 Clinical chemistry

Albumin	Lipase[b]
Alkaline phosphatase	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Bicarbonate[c]	Total protein
Calcium	TSH[e]
Chloride[c]	T3 free[f] (reflex)
Creatinine[d]	T4 free[f] (reflex)
Gamma glutamyltransferase[c]	Urea or blood urea nitrogen, depending on local practice
Glucose	
Lactate dehydrogenase	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × the upper limit of normal (and there is no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.

[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured, either lipase or amylase is acceptable.

[c] Bicarbonate (where available), chloride, creatinine clearance, gamma-glutamyltransferase, and magnesium testing are to be performed at baseline, on Day 1 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 1), and if clinically indicated.

[d] Creatinine clearance will be calculated using Cockcroft-Gault (using actual body weight) or by measured 24 hour urine collection for determination.

[e] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.

[f] Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

ALT Alanine aminotransferase; AST Aspartate aminotransferase; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid-stimulating hormone.

Table 11 Hematology

Absolute neutrophil count[a]	Absolute lymphocyte count[a]
Hemoglobin	Platelet count

Absolute neutrophil count[a]	Absolute lymphocyte count[a]
Total white cell count	
Coagulation (aPTT and INR)[b]	

[a] Can be recorded as absolute counts or as percentages. Total white cell count therefore has to be provided.
[b] For coagulation parameters, activated partial thromboplastin time [either as a ratio or as an absolute value, in seconds] and international normalized ratio are to be assessed at baseline, on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and as clinically indicated.

Table 12 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Microscopy is preferred to investigate white blood cells and should use the high-power field for red and white blood cells; dipstick can be used as well.

If a patient shows an AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, refer to Appendix E for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law (HL). These cases should be reported as SAEs if, after evaluation, they meet the criteria for a PHL or HL case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at 30 days (±3 days), 2 months (±1 week), and 3 months (±1 week) after permanent discontinuation of IP (see Table 2).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.7.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IP must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.2.1.1 Disease-specific tumor marker samples

As part of the routine safety blood samples, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA-19-9) assessment will take place as described in the SoAs (Table 1 and Table 2). It is important to follow the assessment schedule as closely as possible. A rise in CEA or CA-19-9 alone is not sufficient to declare progression and discontinue treatment.

Progression events should be determined by radiographic evidence of progression based on RECIST 1.1.

Further assessment of CEA and CA-19-9 after radiological progression will be at the discretion of the Investigator according to local clinical practice.

8.2.2 Physical examinations

Physical examinations will be performed according to the assessment schedules (see the SoAs). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.

8.2.3 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the SoAs. Body weight is also recorded at each visit, along with vital signs.

First infusion

On the first infusion day, patients will be monitored, and vital signs will be collected/recorded in eCRF prior to, during, and after infusion of IP, as presented in the bulleted list below.

BP and pulse will be collected from patients before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes [±5 minutes])

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles described above or be taken more frequently, if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab.

Subsequent infusions

BP, pulse, and other vital signs should be measured and collected/recorded in the eCRF prior to the start of the infusion. Patients should be carefully monitored, and BP and other vital signs should be measured during and after infusion per institution standard and as clinically

indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

On days where gemcitabine/cisplatin is administered without durvalumab/placebo, patients will be monitored pre-dose and as clinically indicated before every infusion or administration.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.7. For any AEs of infusion reactions, the vital signs values should be entered into the CRF.

8.2.4 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated at each infusion visit throughout the study (see Table 1). Patients with past medical history of ischemic heart disease or arrhythmia or patients who develop myositis during the course of study are examples of patients who need ECG at each infusion visit. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position. Echocardiograms will be performed as needed per patient status at the discretion of the Investigator or Physician Designee if the patient exhibits any symptoms (e.g. myocarditis or any myocardial imAE).

In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g. 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 8.3.7.

8.2.5 WHO/ECOG PS

The WHO/ECOG PS will be assessed at the times specified in the assessment schedules (see Table 1 and Table 2) based on the following:

0 Fully active; able to carry out all usual activities without restrictions

1 Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work)

2 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about >50% of waking hours

3 Capable of only limited self-care; confined to bed or chair >50% of waking hours

4 Completely disabled; unable to carry out any self-care and totally confined to bed or chair

5 Dead

Any significant change from baseline or screening must be reported as an AE.

8.2.6 Other safety assessments

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.6) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc.) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered, and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath, and pyrexia, etc), including auscultation for lung field, will be assessed.
- SpO2
  - Saturation of peripheral oxygen (SpO_2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured, where possible:
    - ILD markers (KL-6, SP-D) and β-D-glucan
    - Tumor markers: Particular tumor markers that are related to disease progression
    - Additional clinical chemistry: C-reactive protein and lactate dehydrogenase

8.3 Collection of adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the contents of this section.

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow up AEs, see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

AEs and SAEs will be collected from the time of the patient signing the ICF until the follow-up period is completed (90 days after the last dose of IP). If an event that starts after the defined safety follow-up period noted above is considered to be due to a late-onset toxicity to study drug, then it should be reported as an AE or SAE, as applicable.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator should notify the Sponsor.

The method of recording, evaluating, and assessing the causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow up each patient at subsequent visits/contacts. All SAEs/non-serious AEs/AESIs (as defined in Section 8.3.13) will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated (this may be beyond the 90 days after the last dose of durvalumab) but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day)
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 8.3.5
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.5 Causality collection

The Investigator will assess causal relationship between the IP and each AE and answer ‘yes’ or ‘no’ to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the IP?”

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as "yes."

A guide to the interpretation of the causality question is found in Appendix B.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study site staff: "Have you had any health problems since the previous visit/you were last asked?", or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol-mandated laboratory tests and vital signs will be summarized in the Clinical Study Report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, etc, should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE, unless it is unequivocally related to the disease under study (DUS); see Sections 8.3.9 and 8.3.10.

8.3.8 Potential Hy's Law and Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN will need to be reported as SAEs. Refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.9 Disease under study

Symptoms of DUS are those that might be expected to occur as a direct result of BTC. Events that are unequivocally due to the DUS should not be reported as an AE during the study, unless they meet the SAE criteria or lead to discontinuation of the IP.

8.3.10 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the DUS and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

8.3.11 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

8.3.12 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the DUS, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the postmortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined safety follow-up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow-up period and the

event is considered to be due to a late-onset toxicity to study drug, then it should also be reported as an SAE.

8.3.13 Adverse events of special interest

An AESI is one of scientific and medical interest specific to understanding of the IP and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP.

AESIs for durvalumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and that may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated MOA and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions with regard to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESI/imAEs observed with anti PD-L/PD-1 agents such as durvalumab include pneumonitis, hepatitis, diarrhea/colitis, intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), nephritis, rash/dermatitis (including pemphigoid), immune thrombocytopenia, myocarditis,myositis/polymyositis, pancreatitis and rare/less frequent imAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome.

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, hematological, rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines on their evaluation and treatment are described in detail in the Dose Modification and Toxicity Management Guidelines (see Section 8.4.6). These guidelines have been prepared by the Sponsor to assist the Investigator

in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

8.3.14 Safety data to be collected following the final DCO of the study

For patients continuing to receive durvalumab treatment after the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patients' safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.6). All data after the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving durvalumab treatment (or within 90 days following the last dose of durvalumab treatment) after the final DCO and database closure must be reported as detailed in Section 8.4.1.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel will inform the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

Once the Investigators or other site personnel indicate that an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff on how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.4.2 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure or and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.3 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study drug

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.4.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy, and the PREGOUT is used to report the outcome of the pregnancy.

8.4.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of gemcitabine/cisplatin or 90 days after the last dose of durvalumab/placebo monotherapy. Please follow the local prescribing information relating to contraception and the time limit for such precautions for gemcitabine/cisplatin agents.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of gemcitabine/cisplatin or 90 days after the last dose of durvalumab/placebo monotherapy should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment and will enter follow-up (see the SoAs).

8.4.4 Overdose

8.4.4.1 Durvalumab

Use of durvalumab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of durvalumab, and possible symptoms of overdose are not established.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply (see Section 8.3.2). For other overdoses, reporting must occur within 30 days.

8.4.4.2 Gemcitabine/cisplatin

For gemcitabine/cisplatin, refer to the local prescribing information for treatment of cases of overdose. If any overdose is associated with an AE or SAE, record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

8.4.5 Medication error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (ie, immediately but no later than 24 hours of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.4.6 Management of investigational product-related toxicities

The following general guidance should be followed for management of toxicities:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to NCI CTCAE, version 5.0.

8.4.6.1 Specific toxicity management and dose modification information – durvalumab

Comprehensive toxicity management guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors, durvalumab [MED4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either drug is used alone or both drugs are used in combination and, also other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) are administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

The most current version of the TMGs is provided to the investigative site as an Annex to Protocol document entitled, “Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy” and is maintained within the Site Master File.

Patients should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 7.1 and the Dosing Modification and Toxicity Management Guidelines).

Following the first dose of IP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the durvalumab regimen by the reporting Investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

8.4.6.2 Specific toxicity management and dose modification information – gemcitabine/cisplatin

Investigators should follow local standard clinical practice regarding dose modifications for gemcitabine/cisplatin. For specific information regarding gemcitabine/cisplatin, please refer to the local prescribing information for the relevant agent.

8.5 Pharmacokinetics

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5.1 Collection of samples for pharmacokinetics analysis

Blood samples for determination of durvalumab concentration in serum will be obtained according to the SoAs (Table 1 and Table 2).

Samples for determination of durvalumab concentration in serum will be analyzed by a designated third party on behalf of AstraZeneca. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

8.5.2 Collection of samples to measure for the presence of ADAs

The presence of ADA will be assessed in serum samples taken according to the SoAs (Table 1 and Table 2). PK and immunogenicity samples for each immunotherapy drug are collected at 30days (+/- 3days) and 90 days (3 months) (+/- 7 days) after treatment with durvalumab.

Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies for durvalumab using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive negative cut points previously statistically determined from drug-naïve validation samples will be used.

8.5.3 Storage and destruction of pharmacokinetic/ADA samples

PK and ADA samples will be destroyed within 5 years of CSR finalization.

PK and ADA samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Validation Report.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AstraZeneca-assigned Biobank).

For China: Durvalumab PK and ADA samples collected in China will be stored and disposed according to local laws and regulations. PK and ADA samples collected in China will be destroyed after finalization of bioanalytical report or completion of CSR.

8.6 Pharmacodynamics

Pre-defined pharmacodynamic parameters are not evaluated in this study, but exploratory analyses may be conducted to understand pharmacodynamics.

8.7 Genetics

8.7.1 Optional exploratory genetic sample

If the patient agrees to participate in the optional genetic research study, a blood sample will be collected. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the patient. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix D for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D or in the Laboratory Manual.

Note: this sample will not be collected in China.

8.7.2 Additional Exploratory Genetic testing

Buffy coat layers obtained during plasma isolation (see section 8.8.3), may be retained and analysed for germline mutations and/or in identification of tumor-specific mutations for MSI/TMB assessment to distinguish more accurately tumor-specific mutations, according to local regulations.

Note: Additional exploratory genetic testing will be conducted in countries where local regulations permit.

8.7.3 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of 15 years or per local regulations from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA.

8.8 Biomarkers

By participating in this study, the patient consents to the mandatory collection and use of donated biological samples as described here. Tissue samples will be obtained from all screened patients.

Pretreatment tumor PD-L1 expression will be evaluated (retrospectively) in all randomized patients. Data will be compared between arms to determine if baseline PD-L1 status is prognostic and/or predictive of outcomes associated with Arm A versus Arm B. Baseline tumor requirements are briefly described in Section 8.8.1.

Based on availability of tissue, additional exploratory biomarkers may be evaluated as described in Section 8.8.3. Also, descriptions of exploratory, peripheral measures are described in this section. Samples will be obtained according to the assessment schedules provided in the SoA (Table 1).

Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

All samples collected for biomarker analyses will be stored at the study site, a reference laboratory, or at AstraZeneca facilities and may be used for subsequent research relevant to evaluating biological and/or clinical response to immunotherapy as described in the exploratory analyses section.

The results may be pooled with biomarker data from other durvalumab studies to evaluate biological responses across indications and to compare results in monotherapy versus combination settings.

8.8.1 Collection of tumor samples for biomarker assessments

The following tumor samples will be requested during the study:

- MANDATORY: At screening, provision of a tumor biopsy sample, formalin-fixed and embedded in paraffin, for the purpose of retrospective PD-L1 expression analyses and for enabling exploratory analyses as described in the proceeding section. A newly acquired tumor biopsy sample is strongly preferred; however, if not feasible with an acceptable clinical risk, an archival sample taken ≤3 years prior to screening can be submitted.

Samples should be collected via an image-guided core needle (at least 18 gauge) or by excision and must maintain sample integrity and morphology. Fine-Needle Aspirate (FNAs) specimens that comprise loose cellular content with no integrity and structural morphology are not acceptable. Where institutional practice, in this setting, uses a smaller gauge needle, samples must maintain sample integrity and morphology and be of sufficient quantity for PD-L1 immunohistochemical (IHC) analyses (i.e., total tissue quantity submitted should be similar to core needle or excisional biopsy requirements described briefly here and outlined in the laboratory manual).

When tissue is newly obtained by biopsy at screening for this study, effort should be made to maximize material for downstream analyses. Two cores, using an 18-gauge or larger needle, are required for determining PD-L1 expression. These should be placed in formalin and processed to a single paraffin-embedded block, as described in the Pathology Manual. As a guidance, it is anticipated that 4 passes of an 18-gauge core needle will provide sufficient tissue for both PD-L1, and exploratory analyses (as described below). Whenever feasible, additional cores beyond the 2 mandated for PD-L1 analyses should be obtained, embedded in the same block, and processed as described in the Laboratory Manual. When a smaller gauge needle is used, the number of cores required to ensure a PD-L1 result rises to 3 or 4.

The tumor specimen should be of sufficient quantity to allow for PD-L1 immunohistochemistry (IHC) analyses (see the Laboratory Manual). Newly acquired or archived specimens with limited tumor content and fine needle aspirates are inadequate for defining tumor PD-L1 status.

Tumor lesions used for fresh biopsies should not be the same lesions used as RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy; in this instance, only core needle (not excisional/incisional) biopsy is allowed.

- OPTIONAL: The collection of tumor biopsies at the time of progression is optional but strongly encouraged. Note: this sample will not be collected in China.

- OPTIONAL: Additional tumor biopsies collected as part of clinical care (eg, for mixed responses) can be submitted for further analysis. Note: this sample will not be collected in China.

See the Laboratory Manual for further details of requirements including sample QC and shipping.

A brief description of exploratory tumor markers likely to be explored by IHC or ribonucleic acid (RNA) analysis is provided in Section 8.8.3.

8.8.2 PD-L1 expression assessment

The Ventana PD-L1 IHC assay will be used to determine PD-L1 status in the tumor samples.

To meet the requirement of Food and Drug Administration (FDA) approval of a companion diagnostic, sections of the tumor will be retained by AstraZeneca or a contracted third party for potential additional studies, as requested by the FDA, to support potential test approval.

8.8.3 Exploratory biomarkers

Blood and tumor samples for exploratory biomarker analyses will be obtained according to the schedules presented in the SoA (Table 1). Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

Baseline measurements and/or changes in measurements in on-treatment samples from baseline will be correlated with outcomes and/or drug treatment. Note that samples will be obtained from patients randomized to each treatment arm. Comparisons will be made between baseline measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes.

Additional sample collections and analyses may be completed at select study sites by site-specific amendment. All samples collected for such exploratory analyses will be stored at site, a reference laboratory, or at AstraZeneca's facilities and may be used for subsequent research relevant to evaluating response to immunotherapy.
The exploratory biomarker plan is described by sample type below.

Note: Biomarker samples will be collected only if local laws and regulations allow

Microsatellite instability (MSI) and tumor mutation burden (TMB)

Tumor tissue remaining after PD-L1 testing may be analyzed retrospectively for microsatellite instability (MSI) using a Next Generation Sequencing (NGS)-based method such as whole exome sequencing (WES) or a targeted NGS assay. The MSI-H/MSS status and TMB will be determined based on the MSI events or somatic variants detected in the tumor sequence data and correlated with efficacy as an exploratory objective. Blood-based MSI or TMB testing may also be performed in cases of insufficient tissue material, unsuccessful tissue-based MSI

testing or for evaluation of blood-based MSI/TMB with clinical outcomes and other biomarkers. The matched normal DNA obtained from buffy coat layer collected during plasma isolation may be used in identification of tumor-specific mutations for MSI/TMB assessment. The incorporation of a matched normal DNA in the mutation analysis helps distinguish more accurately tumor-specific mutations in heterogeneous tumor cell populations and thus may also reduce or prevent unintentional inclusion of normal inherited germline mutations in the final analysis or study reports.

In the event NGS-based MSI testing is not feasible or fails, MMR testing by IHC or similar methods will be performed.

Note: Biomarker samples will be collected only if local laws and regulations allow.

Tumor microenvironment biomarkers

Based on the availability of tissue (described in section 8.8.1), a panel of additional immune-relevant markers expressed in TILs or tumor cells may be assessed using immunohistochemistry (IHC), gene expression profiling or other technically-feasible methods. Markers of special interest include, but are not limited to, CD8, FOXP3, CD68, CD3, CD73, NKp46, CXCL9 and LAG3.

Other tissue-based approaches may be pursued including but not limited to neo-antigen prediction, T cell receptor clonality assessment, molecular profiling and/or somatic variant detection methodologies.

Note: This analysis will not be conducted in China

Whole blood gene expression (PaxGene RNA)

Whole blood samples will be obtained for RNA analysis. Total RNA will be prepared for quantification of RNA, micro-RNA, and/or other non-coding RNA using reverse transcription quantitative polymerase chain reaction, microarray, sequencing, or other technology. Focus is likely to be given to the expression of immunomodulatory genes. Baseline and/or on-treatment correlations with outcome data will be completed on select candidate predictive markers, with the aim of identifying useful expression thresholds for identifying patients likely to receive benefit. These samples may also be used for other molecular analyses of features associated with immune responses such as, but not limited to, T cell receptor clonality and HLA type.

Note: This sample will not be collected in China.

Soluble factors - plasma

Blood samples will be collected at multiple timepoints for analysis of circulating factors such as circulating tumor deoxyribonucleic acid (ctDNA) in plasma, as specified in the Schedule of

Assessments (Table 1). Analyses may include, but not be limited to evaluating baseline sensitizing mutations to treatment and correlations with clinical outcomes, changes in levels and variant frequencies of ctDNA and potentially minimal residual disease. Plasma may also be evaluated for relevant cytokines, chemokines and other soluble biomarkers.

The buffy coat layer obtained during the plasma isolation process of the baseline sample may be retained and analyzed per local regulations. DNA isolated from the buffy coat will be used as a patient-specific normal DNA reference to determine whether mutations identified in ctDNA or tumor mutational analysis are tumor-specific (somatic).

Note: This analysis will not be conducted in China.

Serum sample for biomarkers

Serum will be obtained to explore the expression of cytokines and chemokines, including but not limited to IFN-γ, interleukin 18, CXCL9, and CXCL10. Similarly, the concentrations of a battery of IC ligands, receptors, or other soluble factors may be assessed. Proteins of special interest include CTLA-4, PD-1, PD-L1, B7-1, B7-2, and IL6R. In addition, serum proteome may be explored using mass-spectrometry based or similar technologies. Circulating exosomes may also be isolated from serum to evaluate exosome RNA, DNA, and/or protein contents.

Note: This sample will not be collected in China.

Management of biomarker data

The biomarker data will have unknown clinical significance. AstraZeneca will not provide biomarker research results to patients, their family members, any insurance company, an employer, a clinical study investigator, a general physician, or any other third party, unless required to do so by law. The patient's samples will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

8.8.4 Storage, re-use, and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. Summaries and analyses for exploratory biomarkers may be reported outside the CSR in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies involving durvalumab to generate hypotheses to be tested in future research.

For China: The unused tumor samples will be destroyed or repatriated maximally 5 years after study drug is approved for marketing in China. The stained tissue slides will be retained at the central labs as raw data for a minimum of 10 years after study closure and repatriated or discarded at the end of the retention period or otherwise as required by local regulation

8.8.5 Labeling and shipment of biological samples

The Principal Investigator will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B, Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see Appendix C 3.

Any samples identified as Infectious Category A materials will not be shipped, and no further samples will be taken from the involved patients unless agreed upon with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

8.8.6 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The Principal Investigator at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and will keep documentation of sample shipments.

The sample receiver will keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and will keep documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks and will be registered with the AstraZeneca Biobank Team during the entire life cycle.

8.8.7 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed, and the action will be documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator will:

- Ensure that AstraZeneca is immediately notified of the patients' withdrawal of informed consent to the use of donated samples.

- Ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of or destroyed and the action documented.
- Ensure that the organization(s) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented, and the signed document is returned to the study site.
- Ensure that the patient and AstraZeneca are informed about the sample disposal.

8.9 Healthcare resource use

The assessment of healthcare resource use will increase the understanding regarding the relationship between treatment and tumor-related cancer symptoms on resource use, such as the need for palliative procedures to address obstruction and bleeding. This will be captured and analyzed to inform submissions to payers.

9 STATISTICAL CONSIDERATIONS

The primary objective of the study is to confirm the superiority of Arm A compared to Arm B in terms of OS in patients with first-line advanced BTC.

- All personnel involved with the analysis of the study will remain blinded until database lock for the FA and protocol deviations identified.
- Analyses will be performed by AstraZeneca or its representatives.
- Refer to the statistical analysis plan (SAP) for details.

9.1 Statistical hypotheses

The formal statistical analysis will be performed to test the following main hypotheses:

- H0: No difference between Arm A and Arm B
- H1: Difference between Arm A and Arm B

9.2 Sample size determination

Approximately 672 patients will be randomized in the Global Cohort. Patients will be randomized 1:1 to Arm A or Arm B. Approximately 130 Chinese patients will be randomized in this study. Once the Global Cohort is closed, sites in China will continue until 130 Chinese patients will be randomized.

Randomization will be stratified by disease status (initially unresectable versus recurrent) and primary tumor site (intrahepatic cholangiocarcinoma versus extrahepatic cholangiocarcinoma versus gallbladder cancer).

The study is powered to demonstrate superiority in the OS benefit of durvalumab plus gemcitabine/cisplatin (Arm A) versus placebo plus gemcitabine/cisplatin (Arm B) in patients with previously untreated, unresectable locally advanced or metastatic BTC.

A hypothesis of improved OS will be tested when:

- Approximately 397 OS events have occurred across Arm A and Arm B (59% maturity) (IA-2) AND
- Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity) (FA).

The primary analysis of OS is based on a log-rank test for the interim analysis and a FH(0, 1) test for the final analysis. The log-rank test will also be performed at the final analysis as a sensitivity analysis.
If the true average OS HR is 0.745, corresponding to an approximate 4-month improvement in median OS compared to Arm B of 11.7 months, approximately 496 OS events will provide 90% power to demonstrate statistical significance at the 4.20% level (using a 2-sided log-rank test) for the FA. The 4.9% (2-sided) alpha allocation for the OS analysis will be controlled at the IA-2 and FA timepoints by using the Lan-DeMets (Lan and DeMets 1983) spending function that approximates the O'Brien-Fleming approach, where the significance level applied depends upon the proportion of information (ie, information fraction) available. For example, if the information fraction for OS at IA-2 is 80% and overall alpha level is 4.9% then the two-sided significance levels of 2.38% and 4.20% will be applied to IA-2 and FA for OS, respectively. The smallest treatment difference that could be statistically significant at the FA is an average HR of 0.833 using log-rank test, or 2.3-month improvement in median OS. With a planned 21-month non-linear recruitment period with accrual weight equal to 1.5 and a minimum follow-up period of 19 months assumed, it is anticipated that this analysis will be performed approximately 40 months after the first patient is randomized. With a log-rank test at IA-2 and a FH(0, 1) test at the final analysis, the overall power is at least 86% based on an assumed average HR of 0.745 under the assumption of proportional hazards or up to a 6-month delayed effect (i.e., delayed separation of the OS curves by up to 6 months).

9.3 Populations for analyses

Definitions of the analysis sets for each outcome variable are provided in Table 13.

Table 13 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy Data	
OS	Full Analysis Set
PFS	Full Analysis Set
ORR, DoR, and PRO endpoints	Full Analysis Set

Outcome variable	**Populations**
Demography and other baseline characteristics	Full Analysis Set
PK data	PK Analysis Set
Biomarker data	
Biomarker data	Full Analysis Set
Safety Data	
Exposure	Safety Analysis Set
AEs	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
Vital Signs and other safety	Safety Analysis Set
ADA data	ADA Analysis Set

AE Adverse event; DoR Duration of response; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PK Pharmacokinetics; PRO Patient-reported outcome.

9.3.1 Full analysis set

The FAS will include all randomized patients. The FAS will be used for all efficacy analyses, including PROs. Treatment groups will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment group to which they were randomized.

Analysis for ORR will be based on patients in the FAS, who had a measurable disease at baseline. Analysis of DoR will be based on patients in the FAS who achieved objective response.

9.3.2 Safety analysis set

The SAS will consist of all patients who received at least 1 dose of study treatment. Safety data will not be formally analyzed but summarized descriptively using the SAS according to the treatment received; that is, erroneously treated patients (eg, those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

9.3.3 Pharmacokinetic analysis set

All patients who receive at least 1 dose of durvalumab per the protocol for whom any post-dose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK Analysis Set. The population will be defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

9.3.4 ADA analysis set

The ADA analysis set will include all subjects who have non-missing baseline ADA and at least 1 non-missing post-baseline ADA results. All major ADA analyses will be based on the ADA analysis set.

9.4 Outcome measures for analyses

9.4.1 Calculation or derivation of efficacy variables

9.4.1.1 RECIST 1.1-based endpoints

The analysis of the secondary efficacy endpoints, PFS, ORR, DoR, and DCR, will be primarily based on the site Investigator assessments using RECIST 1.1.

However, a BICR will be performed to validate the ORR/DoR evaluation at IA-1 to support early registration.

Investigator RECIST 1.1-based assessments

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anticancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD, depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within 28 days prior to enrollment. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE; unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Appendix F for the definitions of CR, PR, SD, and PD.

BICR

The independent review will be conducted on all scheduled and unscheduled on-protocol scans acquired up to IA-1 data cutoff for all the randomized subjects who have had the opportunity to be followed for at least 32 weeks (± 1 week). All other images will be collected and stored for potential BICR if considered necessary by AstraZeneca.

All images will be collected centrally. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each timepoint (ie, for visits where response or progression is/is not identified). If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be

assigned as PD). Endpoints (of PFS) will be derived from the overall visit response date and the scan dates.

Further details of the BICR will be documented in the Imaging Charter.

9.4.1.2 Overall survival

The primary endpoint OS is defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made following the date of DCO for the analysis (these contacts should generally occur within 7 days of the DCO). If patients are confirmed to be alive or if the death date is post the DCO date, these patients will be censored at the date of DCO. Death dates may be found by checking publicly available death registries.

9.4.1.3 Progression-free survival

The secondary endpoint PFS (per RECIST 1.1 as assessed by the site Investigator) will be defined as the time from the date of randomization until the date of RECIST 1.1-defined radiological PD or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression (ie, date of event or censoring – date of randomization + 1). Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the patient has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline, then they will be treated as an event with date of death as the event date.

The PFS time will always be derived based on scan/assessment dates and not on visit dates.

RECIST 1.1 assessments/scans contributing toward a particular visit may be performed on different dates. The following rules will be applied:

- For Investigator assessments, the date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that indicates progression.
- When censoring a patient for PFS, the patient will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

9.4.1.4 Objective response rate

The secondary endpoint ORR (per RECIST 1.1 using Investigator assessments) is defined as the number (%) of patients with at least 1 visit response of CR or PR. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

At IA-1, the ORR evaluation will be repeated with tumor data as assessed by BICR according to RECIST 1.1 for the randomized patients who have had the opportunity to be followed for at least 32 weeks.

9.4.1.5 Duration of response

The secondary endpoint DoR (per RECIST 1.1 using Investigator assessment) will be defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression (ie, date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 PFS endpoint.

The time of the initial response will be defined as the latest of the dates contributing toward the first visit response of CR or PR. If a patient does not progress following a response, then their DoR will be censored at the PFS censoring time. DoR will not be defined for those patients who do not have documented response.

At IA-1, the DoR evaluation will be repeated with tumor data as assessed by BICR according to RECIST 1.1 for the randomized patients who have had the opportunity to be followed for at least 32 weeks.

9.4.1.6 Disease control rate

DCR (per RECIST 1.1 as assessed by the Investigator) is defined as the rate of best objective response of CR, PR, or SD according to RECIST 1.1.

DCR-24w is defined as the percentage of patients who have a best objective response of CR or PR or who have SD for at least 24 weeks (±7 days), following the start of study treatment. DCR-32w is defined as the percentage of patients who have a best objective response of CR or PR or who have SD for at least 32 weeks (±7 days), following the start of treatment.

9.4.2 Calculation or derivation of safety variables

9.4.2.1 Adverse events

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, and exposure. These will be collected for all patients. Data from all cycles of treatment will be combined in the presentation of safety data. “On treatment” will be defined as assessments between date of start dose and 90 days following discontinuation of IP

(ie, the last dose of durvalumab). For AEs, on treatment (or TEAEs) will be defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment.

Adverse events observed up until 90 days following discontinuation of the IP or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of the AE summary tables. This will more accurately depict AEs attributable to study treatment only, as a number of AEs up to 90 days following discontinuation of the IP are likely to be attributable to subsequent therapy. However, to assess the longer term toxicity profile, AE summaries will also be produced containing AEs observed up until 90 days following discontinuation of the IP (ie, without taking subsequent therapy into account). Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

The SAS will be used for reporting of safety data.

A separate data listing of AEs occurring >90 days after discontinuation of IP will be produced. These events will not be included in AE summaries.

9.4.2.2 Safety assessments

For the change from baseline summaries for vital signs, laboratory data, ECGs, and physical examinations, the baseline value will be the latest result obtained prior to the start of study treatment.

QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT) using the following formula:

$QTcF = QT/RR^{1/3}$, where RR is in seconds

Corrected calcium product will be derived during creation of the reporting database using the following formula:

Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 – albumin (G/L)] × 0.02)

The denominator used in laboratory summaries will only include evaluable patients, ie, those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded.

- If a CTCAE criterion does not consider changes from baseline to be evaluable, the patient need only have 1 post-dose value recorded.

The denominator in vital signs data should include only those patients with recorded data.

9.4.3 Calculation or derivation of patient-reported outcome variables

9.4.3.1 EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and global health status/QoL scale. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 Scoring Manual (Fayers et al 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales, each of the functional scales, and the global measure of health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global measure of health status and functional scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity. For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded.

Definition of clinically meaningful changes - visit response and best overall response

The global health status/QoL scale includes 2 items from the EORTC QLQ-C30: "How would you rate your overall health during the past week?" (item 29) and "How would you rate your overall QoL during the past week?" (item 30). Definition of clinically meaningful changes in score compared with baseline will be evaluated. A clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales from the EORTC QLQ-C30 (Osoba et al 1998). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥10, whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥10. At each post-baseline assessment, the change in global health status/QoL, symptoms, and functioning score from baseline will be categorized as improvement, no change, or deterioration as shown in Table 14.

Table 14 Mean change and clinically meaningful change - EORTC QLQ-C30

Score	Change from baseline	Visit response
	≥ 10-point increase	Improvement

Score	Change from baseline	Visit response
EORTC QLQ-C30 global quality-of-life score	≥10-point decrease or "Patient too sick to complete the questionnaires (disease under investigation)"	Deterioration
	Otherwise	No change
EORTC QLQ-C30 symptom score	≥10-point increase or "Patient too sick to complete the questionnaires (disease under investigation)"	Deterioration
	≥10-point decrease	Improvement
	Otherwise	No change
EORTC QLQ-C30 functional score	≥10-point increase	Improvement
	≥10-point decreaseor "Patient too sick to complete the questionnaires (disease under investigation)"	Deterioration
	Otherwise	No change

EORTC European Organisation for Research and Treatment of Cancer; QLQ-C30 30-item core quality-of-life questionnaire.

A patient's best overall response in symptoms, function, or global health status/QoL will be derived as the best response the patient achieved based on evaluable PRO data collected during the study period. The criteria in Table 15 will be used to assign a best response in symptoms, function, or global health status/QoL.

Table 15 Best response in EORTC QLQ-C30 and EORTC QLQ-BIL21 scores: FAS

Overall score response	Criteria
Missing	Patient has no evaluable baseline or post-baseline PRO assessment.
Improved	Patient meets one of the following criteria: 1 Has 2 consecutive visit responses of "improvement" at least 14 days apart 2 Has 1 visit response of "improvement" with no further assessments and did not die within 2 PRO assessment visits
No Change	Patient does not qualify for an overall score response of "improved" and meets one of the following criteria: 1 Has 2 consecutive visit responses of "no change" at least 14 days apart 2 Has 1 visit response of "no change" with no further assessments and did not die within 2 PRO assessment visits

Overall score response	Criteria
Deterioration	Patient does not qualify for an overall score response of "improved" or "no change" and meets one of the following criteria: 1 Has 2 consecutive visit responses of "deterioration" at least 14 days apart 2 Has 1 visit response of "deterioration" and no further assessments 3 Has 1 visit response of "improvement" or "no change" followed by death within 2 PRO assessment visits
Other	Does not qualify for one of the above (improved, no change, or deterioration).

EORTC European Organisation for Research and Treatment of Cancer; FAS Full analysis set; PRO Patient-reported outcome; QLQ-C30 30-item core quality-of-life questionnaire; QLQ-BIL21 21-item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire.

Time to HRQoL or function deterioration

Time to QoL or function deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful deterioration that is confirmed at a subsequent visit (except if it was the patient's last available assessment) or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient discontinues the study treatment(s) or receives another anticancer therapy prior to global health status/QoL or function deterioration. Death will be included as an event only if it occurs within 2 PRO assessment visits from the last available PRO assessment. A sensitivity analysis will be conducted, in which deaths will be censored at the date of death.

Patients whose global health status/QoL or function (as measured by EORTC QLQ-C30) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment, where the global health status/QoL or function could be evaluated. Also, if global health status/QoL or function deteriorates or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment, where global health status/QoL or function could be evaluated prior to the 2 missed visits.

The population for the analysis of time to global health status/QoL or function deterioration will include a subset of the FAS who have baseline scores of ≥10.

Symptom improvement rate

Responses in symptoms for each visit (improvement, deterioration, and no change) based on Table 15 as well as the best overall response will be presented by treatment group. The symptom improvement rate will be defined as the number (%) of patients with a best overall score response of "improved" in symptoms.

The denominator will consist of a subset of the FAS who have a baseline symptom score ≥10.

Global health status/QoL or function improvement rate

The global health status/QoL or function improvement rate will be defined as the number (%) of patients with a best overall response of "improved" in QoL or function.

The denominator will consist of a subset of the FAS who have a baseline global health status/QoL or function score ≤90.

9.4.3.2 EORTC QLQ-BIL21

The QLQ-BIL21 is a BTC-specific module from the EORTC comprising 21 questions to assess BTC symptoms. The module includes 5 multi-item domain scales and 3 single-item scales. For all items and scales, high scores indicate increased symptomatology/more problems.

The scoring approach for the QLQ-BIL21 is identical in principle to that for the symptom scales/single items of the EORTC QLQ-C30. Similar to the symptom scales of the EORTC QLQ-C30, higher scores represent greater symptom severity.

Definition of clinically meaningful change - visit response and best overall response

Changes in score compared with baseline will be evaluated. A clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales/items from QLQ-BIL21. For example, a clinically meaningful deterioration or worsening in pain (as assessed by QLQ-BIL21) is defined as an increase in the score from baseline of ≥10. At each post-baseline assessment, the change in symptom score from baseline will be categorized as improved, no change, or deterioration, as shown in Table 16. A patient's best overall response in symptoms will be derived as the best response the patient achieved based on evaluable PRO data collected during the study period. The criteria in Table 15 will be used to assign a best response in symptom score.

Table 16 Mean change and clinically meaningful change - EORTC QLQ-BIL21

Score	Change from baseline	Visit response
QLQ-BIL21 symptom scales and items	≥+10 (increase of at least 10) or "Patient too sick to complete the questionnaires (disease under investigation)"	Deterioration
	≥-10 (decrease of at least 10)	Improved
	Otherwise	No change

EORTC European Organisation for Research and Treatment of Cancer; QLQ-BIL21 21-item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire.

Time to symptom deterioration

For each of the symptom scales/items in the QLQ-BIL21, time to symptom deterioration will be defined as the time from randomization until the date of the first clinically meaningful symptom deterioration that is confirmed at a subsequent visit (except if it was the patient's last available assessment) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient discontinues the study treatment(s) or receives another anticancer therapy prior to symptom deterioration. Only deaths occurring within 2 PRO assessment visits from the last available PRO assessment will be included as events. A sensitivity analysis will be conducted in which deaths will be censored at the date of death.

Patients whose symptoms (as measured by the QLQ-BIL21) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment, where the symptom could be evaluated. Also, if symptoms progress or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment, where the symptom could be evaluated prior to the 2 missed visits.

The population for the analysis of time to symptom deterioration will include a subset of the FAS who have baseline scores ≤90.

9.4.3.3 EQ-5D-5L

The EQ-5D-5L questionnaire comprises 6 questions that cover 5 dimensions of health (eg, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a VAS. For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (eg, no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems).

A unique EuroQoL 5-dimension (EQ-5D) health state, termed the EQ-5D-5L profile, is reported as a 5-digit code with a possible 3125 health states based on these responses. For example, state 11111 indicates no problems on any of the 5 dimensions. This EQ-5D-5L profile will be converted into a weighted health state utility value, termed the EQ-5D index, by applying a country-specific equation to the profile that represents the comparative value of health states. This equation is based on national valuation sets elicited from the general population, and the base case will be the UK perspective. Where a valuation set has not been published, the EQ-5D-5L profile will be converted to the EQ-5D index using a crosswalk algorithm (Van Hout et al 2012).

The evaluable population will comprise a subset of the FAS who have a baseline EQ-5D-5L assessment.

9.4.3.4 PGIS

PGIS data will be presented using summaries and descriptive statistics. Additionally, PGIS data will be further explored to support anchor-based analyses of clinically meaningful change supplemented with empirical cumulative distribution function and probability density function curves. Further details will be provided in the SAP.

9.4.3.5 PRO-CTCAE

The PRO-CTCAE consists of nominal categories (eg, "none" to "very severe" for some items in the questionnaire) as described in Appendix G.

9.4.4 Calculation or derivation of pharmacokinetic variables

9.4.4.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model will be developed using a non-linear mixed-effects modeling approach. The impact of physiologically relevant patient characteristics (covariates) and disease on PK will be evaluated. The relationship between the PK exposure and the effect on safety and efficacy endpoints will be evaluated. The results of such an analysis will be reported in a separate report. The PK, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or exposure-response/safety analysis.

9.4.4.2 Pharmacokinetic analysis

Non-compartmental analysis will not be performed to calculate PK parameters due to sparse sampling. Durvalumab serum concentration data and summary statistics will be tabulated. Individual and mean serum concentration-time profiles will be generated. Samples below the lower limit of quantification will be treated as missing in summary statistics.

9.4.4.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against durvalumab. The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, efficacy, and safety will be evaluated, if the data allow.

9.4.5 Calculation or derivation of biomarker variables

PD-L1 status, as defined in the secondary objectives, will be assessed for evaluable patients in each cohort according to prespecified criteria that will be detailed in the SAP.

9.4.6 Calculation or derivation of pharmacogenetic variables

In the case of genetic data, only the date that the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database. The genetic data generated from the study will be stored in the

AstraZeneca Laboratory Information Management System (LIMS) database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the dataset from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis. Data will be reported outside the CSR (please see Appendix D).

9.4.7 Calculation of healthcare resource use

To investigate the impact of treatment and disease on healthcare resource use, the following variables will be captured:

- Planned and unplanned hospital attendances beyond study protocol-mandated visits (including physician visits, emergency room visits, day cases, and admissions)
- Primary sign or symptom the patient presents with
- Length of hospital stay
- Length of any time spent in an intensive care unit

Where admitted overnight, the length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date) and the start date of hospitalization or start of study drug if the start of study drug is after start date of hospitalization (length of hospital stay = end date of hospitalization – start date of hospitalization + 1). Patients with missing discharge dates will be calculated as the difference between the last day with available data and the start date of hospitalization. The length of intensive care unit stay will be calculated using the same method.

9.5 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be developed and finalized before database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.5.1 Efficacy analyses

A hypothesis of improved OS will be tested when:

- Approximately 397 OS events have occurred across Arm A and Arm B (59% maturity) (IA-2) AND
- Approximately 496 OS events have occurred across Arm A and Arm B (74% maturity) (FA).

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment group. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of IP, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to randomization.

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the FAS. PK data will be summarized and analyzed based on the PK Analysis Set. Safety data will be summarized on the SAS.

Results of all statistical analysis will be presented using a 95% CI and 2-sided p-value, unless otherwise stated.

The following table details which endpoints are to be subjected to formal statistical analysis, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint. Note, all endpoints compare Arm A versus Arm B in all randomized patients (FAS), unless otherwise indicated.

Table 17 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Overall survival	<u>Primary confirmatory analysis</u> IA-2: Stratified log-rank test adjusting for disease status and primary tumor location for primary comparison of survival between randomized treatment groups FA: Stratified FH(0, 1) test adjusting for disease status and primary tumor location for primary comparison of survival between randomized treatment groups <u>Sensitivity and supplemental analysis</u> Stratified log-rank test adjusting for disease status and primary tumor location will be performed at final analysis as sensitivity. KM plot of time to censoring where the censoring indicator of the primary analysis is reversed – attrition bias Cox proportional hazards models to determine the effect of covariates on the HR estimates Subgroup analysis using Cox model

Endpoints analyzed	Notes
Progression-free survival	Only PFS according to RECIST 1.1 based on Investigator assessments will be analyzed as a secondary variable. Secondary confirmatory analysis Stratified log-rank tests adjusting for disease status and primary tumor location, using PFS according to RECIST1.1 using Investigator assessments Sensitivity and supplemental analysis Interval-censored analysis - evaluation time bias Analysis using alternative censoring rules – attrition bias Cox proportional hazards models to determine the effect of covariates on the HR estimate Subgroup analysis using Cox proportional hazards model
Objective response rate	Stratified Cochran-Mantel-Haenszel (CMH) test adjusted for disease status and primary tumor location, using tumor data according to RECIST1.1 by Investigator assessment Sensitivity analysis with tumor data according to RECIST 1.1 based on BICR for the randomized patients who have had the opportunity to be followed for at least 32 weeks
Duration of response	KM plots based on the tumor data using Investigator assessment of RECIST 1.1. Median DoR calculated from the KM curve. Sensitivity analysis with tumor data according to RECIST 1.1 based on BICR for the randomized patients who have had the opportunity to be followed for at least 32 weeks
Disease control rate	Summary statistics using DCR, DCR-24w, and DCR-32w as assessed by the Investigator according to RECIST 1.1
Each scale/item of EORTC QLQ-C30 and QLQ-BIL21	Summary and descriptive statistics Unadjusted change from baseline
Key symptoms, functions, global health status/QoL of EORTC QLQ-C30 and QLQ-BIL21	MMRM analysis (overall and by each visit)
Time to symptom, function, or HRQoL deterioration of key PRO endpoints using EORTC QLQ-C30 and QLQ-BIL21	Stratified log-rank test
Improvement rates for key PRO endpoints (EORTC QLQ-C30 and QLQ-BIL21)	Logistic regression
Patient global and treatment-related symptoms (PGIS, PRO-CTCAE)	Summary and descriptive statistics Additional analyses may be included in the SAP

BICR Blinded independent central review; CR Complete response; DCR Disease control rate; DCR-24w Percentage of patients who have a best objective response of CR or PR or who have SD for at least 24 weeks (±7 days), following the start of study treatment; DCR-32w Percentage of patients who have a best objective response of CR or PR or who have SD for at least 32 weeks (±7 days), following the start of treatment; DoR Duration of response; EORTC European Organisation for Research and Treatment of Cancer; FAS Full analysis set; HR Hazard ratio; HRQoL Health related quality of life; KM Kaplan Meier; MMRM Mixed-effect model repeated measure; OS Overall survival; PFS Progression-free survival; PGIS Patient Global Impression of Severity; PR Partial response; PRO Patient-reported outcomes; PRO-CTCAE Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; QLQ-BIL21 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire; QLQ-C30 30-Item Core Quality of Life Questionnaire; QoL Quality of life; RECIST Response Evaluation Criteria in Solid Tumors; SAP Statistical analysis plan; SD Stable disease .

9.5.1.1 Primary endpoint: overall survival

OS in the FAS will be analyzed using a stratified log-rank test, adjusting for disease status (initially unresectable or recurrent) and primary tumor location (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer) at IA-2 and using stratified FH(0, 1) test at FA. The effect in Arm A versus Arm B will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment arm. Summaries of the numbers and percentages of patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the mOS for each treatment.

Sensitivity analysis

The assumption of proportionality will be assessed first by examining the plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time-periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be a result of treatment-by-covariate interactions, which will be investigated. In addition, the Kaplan Meier (KM) curve along with landmark analyses (eg, 1-year OS rate) will also help in understanding the treatment benefit.

Attrition bias will be investigated by a KM plot of the time to censoring using the OS data from the primary analysis and where the censoring indicator of the OS analysis is reversed.

Cox proportional hazards modeling will be used to assess the effect of covariates on the HR estimate. A model will be constructed, containing treatment and the stratification factors, to ensure that any output from the Cox modeling is likely to be consistent with the results of the stratified log-rank test.

Interactions between treatment and stratification factors will also be tested to rule out any qualitative interaction using the approach of Gail and Simon 1985.

At FA OS will be analyzed using a stratified log-rank test, adjusting for disease status (initially unresectable or recurrent) and primary tumor location (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer) to ensure that any output from the stratified log-rank test is likely to be consistent with the methods of the FH(0, 1) test.

Delayed effect, i.e., delayed separation of survival curves is expected in immunotherapy trials, and has been noted in the majority of IO+chemo vs chemo Phase III trials reported to date. The strategy of using log-rank test at the interim analysis and FH(0, 1) test at final analysis provides robust statistical power and inference under various scenarios including proportional hazards and delayed effects. Log-rank test is the most powerful approach in the scenario of proportional hazards and FH(0, 1) is more powerful in the scenario of delayed effects. In addition, at the final analysis, the data maturity is high and consequently the weight function of FH(0, 1) test is stable.

Subgroup analysis

Subgroup analyses will be conducted comparing OS between Arm A versus Arm B in the following subgroups of the FAS (but not limited to):

- Sex (male versus female)
- Age at randomization (<65 versus ≥65 years of age)
- PD-L1 status
- Disease status (initially unresectable versus recurrent)
- Primary tumor location (intrahepatic cholangiocarcinoma versus extrahepatic cholangiocarcinoma versus gallbladder cancer)
- Race (Asian versus non-Asian)

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment arms. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors. Forest plots will be presented.

Additionally, for each subgroup, the HR (Arm A:Arm B) and 95% CI will be calculated from a Cox proportional hazards model with treatment as the only covariate. These will be presented on a forest plot including the HR and 95% CI from the overall population.

No adjustment to the significance level for testing of the subgroup and sensitivity analyses will be made, since all these analyses will be considered supportive of the analysis of OS and PFS.

9.5.1.2 Progression-free survival

The secondary PFS analysis will also be based on the programmatically derived RECIST 1.1 using the Investigator tumor assessments. The analysis will be performed in the FAS using a stratified log-rank test, adjusting for disease status and primary tumor location. The effect of Arm A versus Arm B will be estimated by the HR together with its corresponding 95% CI and p-value.

Kaplan-Meier plots of PFS will be presented by treatment arm. Summaries of the number and percentage of patients experiencing a PFS event and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each treatment.

Sensitivity analysis

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled timepoints. The midpoint between the time of progression and the previous evaluable RECIST assessment will be analyzed using a log-rank test. For patients whose death was treated as PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust even in highly asymmetric assessment schedules (Sun and Chen 2010).

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following 2 or more non-evaluable tumor assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a Kaplan-Meier plot of the time to censoring where the censoring indicator of the PFS analysis is reversed.

The assumption of proportionality will be assessed first by examining the plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time-periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be a result of treatment-by-covariate interactions, which will be investigated. In addition, the Kaplan-Meier curve along with landmark analyses (eg, 1-year PFS rate) will also help in understanding the treatment benefit.

Cox-proportional hazards modeling will be used to assess the effect of covariates on the HR estimate. A model will be constructed, containing treatment and the stratification factors, to ensure that any output from the Cox modeling is likely to be consistent with the results of the stratified log-rank test.

Interactions between treatment and stratification factors will also be tested to rule out any qualitative interaction using the approach of (Gail and Simon 1985).

Further sensitivity analysis may be documented in the SAP.

Subgroup analysis

Subgroup analyses will be conducted comparing PFS (per RECIST 1.1 using Investigator assessments) between Arm A and Arm B in the subgroups of the FAS, as specified in Section 9.5.1.1.

9.5.1.3 Objective response rate

ORR will be based on the programmatically derived RECIST using the Investigator tumor data. ORR will be compared between Arm A and Arm B using a stratified CMH test adjusting for the same factors as the primary endpoint (disease status and primary tumor location). The results of the analysis will be presented in terms of a p-value. This analysis will be performed in the subset of patients in the FAS who had a measurable disease at baseline.

Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR). Overall visit response data will be listed for all patients (ie, the FAS). For each treatment arm, best overall response (BoR) will be summarized by n (%) for each category (CR, PR, SD, PD, and NE). No formal statistical analyses are planned for BoR.

At IA-1, the ORR evaluation will be repeated with tumor data as assessed by BICR according to RECIST 1.1 for the randomized patients who have had the opportunity to be followed for at least 32 weeks.

9.5.1.4 Duration of response

KM plots of DoR based on the Investigator assessment of RECIST 1.1 will be presented. Median DoR will also be summarized and calculated from the KM curve. Only patients who have a confirmed response will be included in this summary table. Swimmer plots that clearly show the profile of each patient who responds will also be produced.

At IA-1, the DoR evaluation will be repeated with tumor data as assessed by BICR according to RECIST 1.1 for the randomized patients who have had the opportunity to be followed for at least 32 weeks.

9.5.1.5 Disease control rate

The DCR, DCR-24w, and DCR-32w based on Investigator assessments per RECIST 1.1 will be summarized (ie, number of patients [%]) per treatment arm.

9.5.1.6 Patient-reported outcomes

EORTC QLQ-C30

The primary assessment of symptoms, impacts, and HRQoL will focus on time to deterioration (TTD), which will be analyzed using a stratified log-rank test as described for the PFS endpoint. Separate analyses will be conducted for global health status/QoL, function (physical, role, cognitive, social, and emotional), multi-term symptoms (fatigue and pain), and single items (appetite loss and insomnia). The effect of durvalumab therapy versus placebo will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment group. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians for each treatment.

Additional analyses of HRQoL, impacts, and symptoms will focus on comparing mean change from baseline in the global health status/QoL, functions (physical, role, cognitive, social, and emotional), multi-term symptoms (fatigue and pain), and single items (appetite loss and insomnia) score between treatment groups. The analysis population for mean change in HRQoL, impacts, or symptoms data will be the FAS and will include all randomized patients with an evaluable baseline assessment and at least 1 evaluable post-baseline assessment. Change from baseline will be derived using a mixed model repeat measures (MMRM) analysis of all the post-baseline scores for each visit. The model will include treatment, visit, and treatment-by-visit interaction as explanatory variables and the baseline score as a covariate. Adjusted mean change from baseline estimates per treatment group and corresponding 95% CIs will be presented along with an overall estimate of the treatment difference, 95% CI, and p-value.

Summary tables of visit responses for each EORTC QLQ-C30 scale/item score (global health status/QoL, 5 functions, and all symptoms) and for each visit (improvement, deterioration, and no change) will be presented by treatment group. In addition, summary tables of the best overall response will be provided for the following domains by treatment group: global health status/QoL, function (physical, role, cognitive, social, and emotional), multi-term symptoms (fatigue and pain), and single items (appetite loss and insomnia). Occurrence of symptom, impacts, and QoL/function improvement based on best overall response will be compared between treatment groups using a logistic regression model adjusting for the same factors as the primary endpoint (disease status and primary tumor location). The odds ratio, p-value, and 95% CI will be presented graphically on a forest plot.

Finally, summaries of absolute and unadjusted change from baseline values of each EORTC QLQ-C30 scale/item will be reported by visit for each treatment group. Graphical presentations may also be produced as appropriate.

Additional supportive/exploratory analyses may be conducted. Further details will be provided in the SAP.

EORTC QLQ-BIL21

The primary assessment of TTD, as described for the EORTC QLQ-C30, will be evaluated for single-item abdominal pain (item 42), pruritus (item 36), and jaundice (item 35) symptoms of the EORTC QLQ-BIL21.

For TTD in abdominal pain, pruritus, and jaundice, single items of the EORTC QLQ-BIL21 will be presented using a Kaplan-Meier plot as well as the HR together with the corresponding 95% CI and p-values. Summaries of the number and percentage of patients experiencing a clinically meaningful deterioration or death and the median TTD will also be provided for each treatment group.

Additionally, comparing mean change from baseline using the MMRM as described for the EORTC QLQ-C30 will be repeated for abdominal pain, pruritus, and jaundice symptoms of the EORTC QLQ-BIL21. All assumptions and outputs as described for the EORTC QLQ-C30 are applicable.

Summary tables of visit responses for each EORTC QLQ-BIL21 scale/item score and for each visit (improvement, deterioration, and no change) will be presented by treatment group. In addition, summary tables of best overall response will be provided for abdominal pain, pruritus, and jaundice symptoms by treatment group. Occurrence of improvement based on best overall response will be compared between treatment groups using a logistic regression model. The odds ratio, p-value, and 95% CI will be presented graphically on a forest plot.

As described for the EORTC QLQ-C30, summaries of absolute and unadjusted change from baseline values of each EORTC QLQ-BIL21 scale/item will be reported by visit for each treatment group. Graphical presentations may also be produced as appropriate. This descriptive analysis includes item 49 of the EORTC QLQ-BIL21 (“To what extent have you been troubled with side-effects from your treatment?”) assessing patient’s global impression of treatment tolerability, which will complement exploratory findings of the PRO-CTCAE assessment.

Additional supportive/exploratory analyses may be conducted. Further details will be provided in the SAP.

PRO-CTCAE

PRO-CTCAE data will be presented using summaries and descriptive statistics based on the FAS. EORTC QLQ-BIL21 item 49 ("To what extent have you been troubled with side-effects from your treatment?") descriptive statistics will complement PRO-CTCAE findings. Refer to the section above. Further details will be provided in the SAP.

PGIS

Responses on the PGIS will be summarized descriptively as number of patients and corresponding percentages for each category in the questionnaire at each visit by treatment group. Further details will be provided in the SAP.

EQ-5D-5L

Descriptive statistics will be calculated for each scheduled visit/timepoint in the study, for each study arm, and as a total. This will report the number of patients, the number of EQ-5D questionnaires completed at each visit, and the number and proportion responding to each dimension of the EQ-5D-5L. Additionally, summary statistics (eg, n, mean, median, SD, min, and max) will be reported for the EQ-5D index score and the EQ-VAS score, as well as the change from baseline for the EQ-5D index score and the EQ-VAS score.

Graphical plots of the mean EQ-5D index score and EQ-VAS score, including change from baseline, and associated 95% CI by scheduled visits/timepoints in the study may be produced. To support submissions to payers, additional analyses may be undertaken, and these will be outlined in a separate Payer Analysis Plan.

9.5.1.7 Healthcare resource use

The potential impact the disease and treatment have on healthcare resource use will be analyzed for the purposes of submissions to payers. Descriptive statistics (as appropriate, including means, median, ranges or frequencies, and percentages) will be provided for each arm on the different types of hospital admissions, the length of stay of people admitted in to the hospital for at least 1 overnight stay and the length of stay of people admitted to the intensive care/high dependency units, as well as the primary sign or symptom the patient presents with. To support submissions to payers, additional analyses may be undertaken, and these will be outlined in a separate Payer Analysis Plan.

9.5.2 Safety analyses

All safety analyses will be performed on the SAS.

Safety and tolerability data will be presented by treatment arm using the safety population.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms

and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by treatment arm and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, WHO ECOG/PS, and ECGs. Exposure to durvalumab plus gemcitabine/cisplatin combination therapy and gemcitabine/cisplatin will be summarized. Time on study, durvalumab plus gemcitabine/cisplatin combination therapy, and gemcitabine/cisplatin dose delays/dose reductions will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

9.5.3 Pharmacokinetic data

Durvalumab serum concentration data will be listed for each patient with Durvalumab treatment and each dosing day, and a summary will be provided for all evaluable patients.

Note: In China, all the PK (patient with Durvalumab treatment and placebo) will be analysed.

9.5.4 Immunogenicity data

Immunogenicity results will be listed by patient, and a summary will be provided by the number and percentage of patients who develop detectable anti-durvalumab antibodies. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-durvalumab antibodies.

The effect of immunogenicity as well as the effect of its neutralizing properties on PK, efficacy, and safety will be evaluated, if the data allow. A detailed plan will be written by the AstraZeneca Clinical Pharmacology group or designee.

9.5.5 Biomarker data

The relationship of PD-L1 expression and, if applicable, of exploratory biomarkers to clinical outcomes (including but not restricted to) of PFS, ORR, and OS may be evaluated.

PD-L1 expression determined by IHC will be reported in the CSR. Summaries and analyses for exploratory biomarkers may be reported outside the CSR in a separate report.

9.5.6 Methods for multiplicity control

A small alpha expenditure of 0.001 (0.1%) will be allocated to IA-1. Strong control of the FWER at the remaining 4.9% level (2 sided) across the testing of OS and PFS endpoints will be achieved through a combined approach of alpha allocation to the OS analyses (IA-2 and the FA) via alpha spending function and a hierarchical testing procedure; that is, PFS will be tested only if OS met statistical significance at IA-2 or FA (Glimm et al 2010). The IA-2 for OS will be conducted when approximately 397 of the 496 expected OS events (ie, 80%

information fraction) have occurred. Using the Lan-DeMets spending function approximating O'Brien-Fleming boundaries, 2-sided significance levels of 0.0238 and 0.0420 will be applied to OS IA-2 and FA for log-rank test, respectively (Lan and DeMets 1983).

The statistical significance at OS final analysis using FH(0, 1) will be determined based on the alpha spending at IA using log-rank test according to the correlation structure between IA log-rank statistic and FA FH(0, 1) (Tsiatis 1982).

PFS will be formally tested using PFS information collected up to each DCO if OS meets statistical significance at that DCO (IA-2 or FA). Significance levels for PFS at IA-2 and FA for log-rank test will be derived based on the Lan-DeMets alpha spending function approximating Pocock boundaries, which strongly controls the Type I error at the 4.9% level (2-sided). If the true average HR for PFS is 0.70, corresponding to an approximate 3-month improvement in median PFS compared to Arm B of 7.0 months, approximately 506 PFS events will provide 98% power to demonstrate statistical significance at the 4.44% level (using a 2-sided test) at IA-2, and approximately 590 PFS events will provide 98% power to demonstrate statistical significance at the 2.36% level (using a 2-sided test) at FA. The smallest treatment difference that could be statistically significant at the IA-2 and FA is an average HR of 0.836 and 0.830 for log-rank test, or 1.3 and 1.4-month improvement in median PFS. Since DCO timing will be determined based on the number of OS events, the nominal significance level for PFS analysis might be adjusted for the actual information fraction for PFS at IA-2 relative to FA.

9.6 Interim analyses

Two interim analyses and a FA are planned for the evaluation of efficacy:

- IA-1: The objective of IA-1 is to assess clinical activity. ORR and DoR will be summarized to support early registration of durvalumab when administered in combination with gemcitabine/cisplatin. The summary will be done both for Investigator assessments and for BICR assessments according to RECIST 1.1. The assumption for ORR in Arm B is approximately 26%, as observed in ABC-02 (Valle, 2010). Regarding Arm A, an ORR of 40%-50% is estimated based on data from Study ESR-O. Assuming true ORRs of 40% in Arm A and 26% in Arm B, a sample size of 100 patients/arm would yield an approximate 76% probability that the exact 95% CI lower bound of ORR in Arm A excludes the point estimate of ORR in Arm B. The planned DCO for IA-1 will occur when at least 200 patients have had the opportunity to be followed for at least 32 weeks or the last patient has been randomized to the global cohort whichever comes later. The analysis set will include all randomized patients who have had the opportunity for at least 32 weeks of follow-up at the time of the IA1 DCO (ie, randomized ≥ 32 weeks prior to IA1 DCO). Based on enrollment assumptions, it is expected that this will occur approximately 21 months after randomization of the first patient.

- IA-2: The second interim analysis will test for early superiority of the durvalumab regimen relative to control. This analysis will be performed when approximately 397 OS events have been observed in the study (59% maturity or 80% information fraction). Based on enrollment assumptions, it is expected that this will occur approximately 31 months after randomization of the first patient.

IA-2 will evaluate the efficacy of Arm A compared to Arm B in terms of OS (primary objective). OS will be analyzed using a stratified log-rank test (stratified by disease status and primary tumor location). The treatment effect will be estimated by the HR, 95% CI, and p-value.

A small alpha expenditure of 0.001 (0.1%) will be allocated to IA-1. Strong control of the FWER at the remaining 4.9% level will be achieved through alpha allocation to the OS analyses (IA-2). Based on the Lan-DeMets spending function approximating O'Brien-Fleming boundaries (Lan and DeMets 1983), when approximately 397 of the 496 expected OS events (ie, 80% information fraction) have occurred (ie, at the time of IA-2), a 2-sided significance level of 0.0238 will be applied to IA-2.

As described in Section 9.5.6, the first interim analysis for OS (ie, IA-2) will be conducted when approximately 397 of the 496 expected OS events (ie, 80% information fraction) have occurred.

The SAP will describe the planned interim analyses in greater detail.

9.6.1 Data monitoring committee

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

An IDMC composed of independent experts will be convened and will meet approximately every 6 months to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. For the interim analyses (both IA-1 and IA-2), the IDMC will review unblinded interim efficacy data, as outlined in Section 9.6. The IDMC will inform the Sponsor of its recommendation according to the IDMC Charter, which will be developed separately. Formal implementation and communication of IDMC recommendations will be managed by the AstraZeneca Executive Committee, which will be unrelated to the study team.

Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

Interim safety monitoring will be conducted by an IDMC. Details of the plan and communication process will be provided in an IDMC Charter.

The recommendations from the IDMC will not reveal the results of the analyses but will take the form of "Continue/Modify/Recommend early submission/Stop."

The study may also be stopped based on the findings of the interim safety analysis conducted by the IDMC.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators

are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

If a patient's partner becomes pregnant during or within 180 days after the last dose of gemcitabine/cisplatin or 90 days after the last dose of durvalumab/placebo monotherapy, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document. AstraZeneca will not provide individual genotype results to patients, their family members, their general physician, any insurance company, any employer, or any other third party, unless required to do so by law.

Precautions are taken to preserve confidentiality and prevent genetic data from being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and might also have access to his/her genetic data. Also, regulatory authorities may require access to the relevant files. Even so, the patient's medical information and the genetic files would remain physically separate.

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information that would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of clinical study data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the *main* study results when they are available. The clinical study and/or summary of *main* study results may also be available on other websites according to the regulations of the countries in which the *main* study is conducted.

A 7 Data quality assurance

All patient data relating to the study will be recorded on printed or electronic Case Report Form (CRF) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Event Definitions and Additional Safety Information

B 1 Definition of adverse events

An adverse event (AE) is the development of an undesirable medical condition (other than the progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea and chest pain), signs (eg, tachycardia and enlarged liver), or the abnormal results of an investigation (eg, laboratory findings and electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study drug(s) has/have been administered.

The term AE is used to include both serious and non-serious AEs.

B 2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up) that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical treatment to prevent one of the outcomes listed above
- Adverse Events (AEs) for malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.
- Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia

into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

B 3 Life-threatening

"Life-threatening" means that the patient was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the patient's death. Life-threatening does not mean that had an AE occurred in a more severe form, it might have caused death (e.g. hepatitis that resolved without hepatic failure).

B 4 Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g. bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

The hospital admission and procedure for scheduled-stent exchange are not considered SAE(s). The unexpected serious or life-threatening events that occur during the procedure or post-procedure requiring unexpected prolongation of the planned hospitalization (e.g. perforation, infection) are the SAEs that are reported.

B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring intravenous (IV) hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

B 6 CTCAE grade

The grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) Version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the criteria recommended in the CTCAE manual that converts severity levels into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A guide to interpreting the causality question

When assessing causality, consider the following factors when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of "related" is made if following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as "not related."

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process-related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error (e.g. medication prepared incorrectly, even if it was not actually given to the participant)
- Drug not administered as indicated; for example, wrong route or wrong site of administration
- Drug not taken as indicated (e.g. tablet dissolved in water when it should be taken as a solid tablet)
- Drug not stored as instructed (e.g. kept in the fridge when it should be at room temperature)

- Wrong participant received the medication (excluding Interactive Voice Response System/Interactive Web Response System [IVRS/IWRS] errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) (e.g. forgot to take medication)
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication or standard-of-care medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of informed consent for donated biological samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca or delegate.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified and disposed of/destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

C 3 International Airline Transportation Association (IATA) 6.2 guidance document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx classifies biohazardous agents into 3 categories: Category A, Category B or Exempt.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are e.g., Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf)
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D Optional Genomics Initiative Sample

D 1 Use/analysis of DNA

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and Institutional Review Board/Independent Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting patients.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, to better diagnosis of diseases or other improvements in healthcare, and to the discovery of new diagnostics, treatments, or medications.

In addition, collection of DNA samples from populations with well-described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the patient's DNA (ie, the entire genome).

The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on durvalumab continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary, and if a patient declines to participate, there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, patients must fulfill all of the inclusion criteria described in the main body of the Clinical Study Protocol and: Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined Appendix C 2.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patient's pre-dose at the first dosing visit. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at the first dosing visit, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction, replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

The link between the patient enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

The genetic component of this study is optional, and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study, the patient must sign and date both the consent form for the main study and also the genetic component of the form. A copy of the signed and dated consent form must be given to the patient, and the original filed at the study center. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that he/she may freely withdrawal from the genetic aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his/her genetic data. In addition, Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data management

Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyses the samples.

AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can

only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Serious Adverse Events (SAEs) and Adverse Events (AEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

E 2.1 Potential Hy's Law

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

E 2.2 Hy's Law

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

Local laboratories being used:

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the subject meets PHL criteria (see Section 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not Met

If the subject does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law Criteria Met

If the subject does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Appendix E, Section 6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the subject's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
  - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  - Complete the three Liver CRF Modules as information becomes available

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
- The 'Medically Important' serious criterion should be used if no other serious criteria apply.
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions Required When Potential Hy's Law Criteria Are Met Before and After Starting Study Treatment

This section is applicable to subjects *with liver metastases* who meet PHL criteria on study treatment, having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met the Investigator will determine if there has been a **significant change** in the subjects' condition[#] compared with the last visit where PHL criteria were met[#]

- If there is no significant change no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix E, Section 4.2.

E 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease or did the subject meet PHL criteria prior to starting study treatment and at their first on-study treatment visit as described in section 6 of this Appendix?

If **No**: follow the process described in Appendix E, Section 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the subject's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Appendix E, Section 4.2 for reporting PHL as an SAE

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 8 Laboratory Tests

To evaluate the underlying etiology of PHL cases, relevant laboratory tests will be performed as outlined in Section 8.2.1 and described below. Additional laboratory assessments may be performed as clinically indicated.

Table 18 represents the standard, comprehensive list of follow-up tests which are recommended when using a central laboratory. Some of the tests may also be considered for use with local laboratories that have respective testing capabilities. Any test results need to be recorded in the CRF.

Table 18 Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgG anti-HCV HCV RNA* IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)**
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive
** Carbohydrate deficient transferrin (CD-transferrin) is not available in China. Study teams should amend this list accordingly

Appendix F Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for this study with regard to Investigator assessment of tumor burden including protocol-specific requirements for this study. Additional special guidance is provided for assessing follow-up scans acquired after RECIST 1.1-defined radiological progression.

Imaging modalities and acquisition specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of Target Lesions (TLs), Non-Target Lesions (NTLs), and New Lesions (NLs) is provided in Table 19.

Table 19 Summary of imaging modalities for tumor assessment

Target Lesions	Non-Target Lesions	New Lesions
CT[a]	CT[a]	CT[a]
MRI[a]	MRI[a]	MRI[a]
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan
		FDG-PET/CT

CT Computed tomography; MRI Magnetic resonance imaging; FDG-PET/CT ^{18}F-Fluoro-deoxyglucose positron emission tomography/CT;

It is essential that the same imaging modality [computed tomography (CT) or magnetic resonance imaging (MRI)] and image acquisition parameters (e.g. imaged anatomy, IV contrast imaging phases, etc.), imaging facility, and method of tumor assessment (e.g. RECIST 1.1) are used consistently for each patient throughout the study. The use of the same scanner for serial scans, if possible, is highly recommended. It is important to follow the image collection/tumor assessment schedule as closely as possible (refer to the schedule of assessments [SoAs]). If an unscheduled assessment is performed (e.g. to investigate clinical signs/symptoms of progression), every attempt should be made to perform the subsequent scan acquisitions during scheduled visits.

CT and MRI

CT and MRI, each preferably with IV contrast, are generally considered to generate the best currently available and reproducible anatomical images for measurement of TL, assessment of NTL, and identification of NLs. The most critical CT and MRI image acquisition parameters

for optimal tumor evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

For standard RECIST 1.1 assessments, it is recommended that IV contrast-enhanced CT examinations of the chest, abdomen (including the entire liver and both adrenal glands), and pelvis will be used to assess tumor burden at baseline and follow-up visits. In patients who are sensitive to IV CT contrast, a non-contrast CT examination of the chest and an MRI with IV MRI contrast of the abdomen and pelvis is appropriate. In patients who develop sensitivity to both CT and MRI IV contrast or have significantly compromised renal function, a non-contrast CT examination of the chest, abdomen, and pelvis is appropriate. Any other areas of disease involvement (e.g. brain) should be additionally imaged based on the signs and symptoms of individual patients. For brain lesion assessment, MRI with IV contrast is the preferred method over IV contrast-enhanced CT.

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis (and other anatomies e.g. neck) with T1 and T2 weighted imaging preferably with fat suppression along with T1 weighted imaging with fat suppression following IV injection of gadolinium-based contrast agent is performed. The field of view, matrix, number of excitations, phase encoding steps, use of fat suppression and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized. CT of the chest is typically recommended over MRI due to significant motion artifacts (heart, major blood vessels, breathing) associated with MRI. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans for each patient. Body scans should be performed with breath-hold scanning techniques if possible. For these reasons, CT is typically the imaging modality of choice.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as an NL representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up timepoints. This will enable better consistency not only of tumor measurements but also identification of new disease.

b. IV contrast administration: Optimal visualization and measurement of metastases in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumor lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. Oral contrast is recommended to help visualize and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/ reconstructed as contiguous (no gap) with ≤5 mm slice thickness for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the measurements should be performed using the same window setting for repeated examinations throughout the study.

Chest X-ray

Chest X-ray assessment will not be used for assessment of TL. Chest X-ray can, however, be used to assess NTL and to identify the presence of NLs.

Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment (CT, MRI, or X-ray).

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. NLs may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan which cannot be verified with correlative imaging (CT, MRI, X-ray) of the same anatomical region shall not be the only trigger for a progressive disease (PD) assessment at that timepoint.

FDG-PET/CT

^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography/CT (FDG-PET/CT) scans may be used as a method for identifying NLs, according to the

following algorithm: NLs will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[1] not present on baseline or a prior FDG-PET scan or in a location corresponding to an NL on a companion CT/MRI collected close in time to the FDG-PET scan. The PET portion of the PET/CT introduces additional data that may bias an Investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior FDG-PET scan available for comparison, and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule in order to verify the unequivocal presence of NLs.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically-based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with intravenous contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumor assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation and may not provide an accurate assessment of true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Other tumor assessments

Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used as they are not validated in the context of tumor assessment.

[1] A positive FDG-PET scan lesion should be reported only when an uptake (eg, SUV) greater than twice that of the surrounding tissue or liver is observed.

Histology and cytology

Histology or tumor markers on tumor biopsy samples will not be used as part of the tumor response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment as per RECIST 1.1.

Measurability of tumor lesions at baseline

RECIST 1.1 measurable lesions at baseline:

A tumor lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis[2] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements.

Non-measurable lesions at baseline:

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component)
  - Leptomeningeal disease
  - Ascites, pleural, or pericardial effusion
  - Inflammatory breast disease
  - Lymphangitic involvement of skin or lung
- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline[3]).
- Previously irradiated lesions[4]
- Brain metastasis

Special considerations regarding lesion measurability at baseline:

- Bone lesions

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[2] The short axis is defined as the longest in-plane axis perpendicular to long axis

[3] Lymph nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

[4] Localized post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

  - Bone scan, PET scan or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.
  - Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability.
  - Blastic bone lesions are considered non-measurable.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected over cystic lesions as TLs.

RECIST 1.1 TL selection at baseline:

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TLs at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph node locations as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented as well as the longest axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

A previously irradiated lesion may be selected as a TL provided it fulfils the criteria for reproducible measurability and is the only lesion available.

Special cases for TL assessment at baseline:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.

- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

RECIST 1.1 NTL selection at baseline:

All other lesions, including non-measurable lesions and surplus measurable lesions not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of tumor response and progression

RECIST 1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimeters. The sum of the diameters for all TL at each follow-up visit will be compared to the baseline sum of diameters (for response or stable disease) or to the smallest prior (nadir) sum of diameters (for progression).

Special cases for TL assessment at follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.
- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TLs merge then the sum of the diameters of the combined lesion should be recorded for 1 of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually discernable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter of the nodal mass.
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion. The choice of 'Too large to measure' in the case report form (CRF) will trigger an overall visit response of PD.
- If a Target Lesion has had an Intervention, e.g. radiotherapy, surgery, embolization, or excisional biopsy (but not core-needle or fine-needle biopsy) that is not a part of study treatment and that might adversely affect the size and measurability of that Target Lesion, then the following apply:
  - If an Intervention on a Target Lesion is ticked in the case report form, the diameter of the lesion is still recorded (0mm if no longer present) and is included in the sum of diameters.
  - If a Target Lesion Intervention is ticked in the case report form, the Intervention must be reported for all subsequent assessments of that Target Lesion.
  - If a Target Lesion has an Intervention, the only Overall Visit Responses allowed to be recorded by the Investigator are NE or PD, with PD if the sum of diameters exceeds at least a 20% increase and at least a 5mm absolute increase in the visit sum of diameters compared to the previous minimum (nadir) sum of diameters.
  - No visit with a recorded Target Lesion Intervention can be used as the minimum (nadir) sum of TL diameters; i.e. nadir sum of TL diameters is identified from any imaging visit prior to that of the TL Intervention.

Evaluation of TLs

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see Table 20).

Table 20 Evaluation of Target Lesions

Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable disease (SD)	Neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir) – this includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg missing anatomy) or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; TL Target Lesion.

RECIST 1.1 NTL assessment at follow-up

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease or partial response in TLs, the overall tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of stable disease (SD) or partial response (PR) of target disease will therefore be extremely rare.

This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table 21).

Table 21 Evaluation of Non-Target Lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NTL Non-Target Lesion; TL Target Lesion.

RECIST 1.1 NL identification at follow-up

Details including the imaging modality, the date of scan, and the location of any NLs will be recorded in the CRF. The presence of 1 or more NLs is assessed as progression. The finding of an NL should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. If an NL is equivocal, for example because of its small size, the treatment and tumor

assessments should be continued until the previously (pre-existing) NL has been assessed as unequivocal at a follow-up visit, and then the progression date should be declared using the date of the initial scan when the NL first appeared.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered an NL and will indicate disease progression.

RECIST 1.1 evaluation of overall visit response at follow-up

The overall visit response will be derived using the algorithm shown in Table 22.

Table 22 Overall visit response algorithm

Target Lesions	Non-Target Lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non-CR/Non-PD	No	SD (Non-CR/non-PD*)
NE	Non PD or NE	No	NE
NA	NE	No	NE
NA	NA	No	NED
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NA Not applicable (only relevant if there were no TLs or NTLs at baseline), NED No Evidence of Disease (only relevant if there were neither TLs nor NTLs at baseline); NTL Non-Target Lesion; TL Target Lesion.
*Non-CR/Non-PD for Overall Response if only NTLs (no TLs) are present at baseline.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For subjects with TLs (at baseline): CR, PR, SD, PD, or NE
- For subjects with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE
- For subjects with no disease at baseline: NED (no evidence of disease; available as an option in the electronic CRF), PD, or NE

Symptomatic deterioration

Symptomatic (clinical) deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective radiologic evidence of disease progression at that time should continue to undergo scan acquisitions and tumor assessments where clinically feasible.

Evaluation of scans subsequent to RECIST 1.1-defined progression

A follow-up scan is requested at least 4 weeks after a RECIST 1.1-defined radiological progression and no longer than the next regularly scheduled imaging visit. The follow-up scans provide additional information to the Investigator for patient management and further treatment decisions, and since the published RECIST 1.1 criteria (Eisenhauer et al 2009) do not provide guidance on how to assess scans acquired after RECIST 1.1-defined PD, supplemental instructions for Investigators on how to evaluate these follow-up scans are provided below. A subsequent follow-up scan would be considered as having Progressive Disease if any of the following criteria are met:

- ≥20% increase and at least a 5-mm increase in the sum of TL diameters compared with the prior minimum (nadir) sum of TL diameters at 2 consecutive visits and a further increase of ≥5 mm in the sum of TL diameters at the second scan timepoint compared with the prior timepoint
- significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint
- significant progression (worsening) of previously NLs (pre-existing NLs) at the follow-up scan timepoint compared with the immediate prior timepoint
- additional brand new unequivocal lesions at the follow-up scan timepoint

Central review

Images, including unscheduled scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging Contract Research Organization (iCRO) for QC and storage. Guidelines for image acquisition, de-identification, storage at the investigative site as source data, and transfer to the iCRO will be provided in a separate document. A blinded independent central review (BICR) of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part upon the results of the RECIST 1.1 assessment conducted by the Investigator. Further details of the BICR will be documented in an Independent Review Charter.

References

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix G Patient-Reported Outcomes

This appendix includes example copies of the following patient-reported outcome (PRO) questionnaires:

- European Organisation for Research and Treatment of Cancer (EORTC) 30-Item Core Quality of Life Questionnaire
- EORTC 21-item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire
- PRO-Common Terminology Criteria for Adverse Event
- Patient Global Impression of Severity
- EuroQoL 5-Dimension, 5-Level health state utility index

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋
Your birthdate (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋
Today's date (Day, Month, Year): 31 ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ – BIL21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Have you had trouble with eating?	1	2	3	4
32. Have you felt full up too quickly after beginning to eat?	1	2	3	4
33. Have you had problems with your sense of taste?	1	2	3	4
34. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
35. Have your skin or eyes been yellow (jaundiced)?	1	2	3	4
36. Have you had itching?	1	2	3	4
37. Have you been worried about your skin being yellow?	1	2	3	4
38. Have you been less active than you would like to be?	1	2	3	4
39. Have you felt "slowed down"?	1	2	3	4
40. Have you felt lacking in energy?	1	2	3	4
41. Did you have pain during the night?	1	2	3	4
42. Have you had pain in your stomach area?	1	2	3	4
43. Have you had pain in your back?	1	2	3	4
44. Did you have a bloated feeling in your abdomen?	1	2	3	4
45. Have you felt stressed?	1	2	3	4
46. Have you felt less able to enjoy yourself?	1	2	3	4
47. Have you worried about your health in the future?	1	2	3	4
48. Were you worried about your family in the future?	1	2	3	4
49. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
50. Have you had difficulties with drainage tubes/ bags?	1	2	3	4
51. Have you worried about losing weight?	1	2	3	4

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 10 October 2018

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
2.	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
3.	In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
4.	In the last 7 days, did you have any RASH?				
	○ Yes	○ No			
5.	In the last 7 days, did you have any HAIR LOSS?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
6.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Patient Global Impression of Severity
Please choose the response below that best describes the severity of your overall cancer symptoms over the past 7 days. ☐ No Symptoms ☐ Very Mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very Severe

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

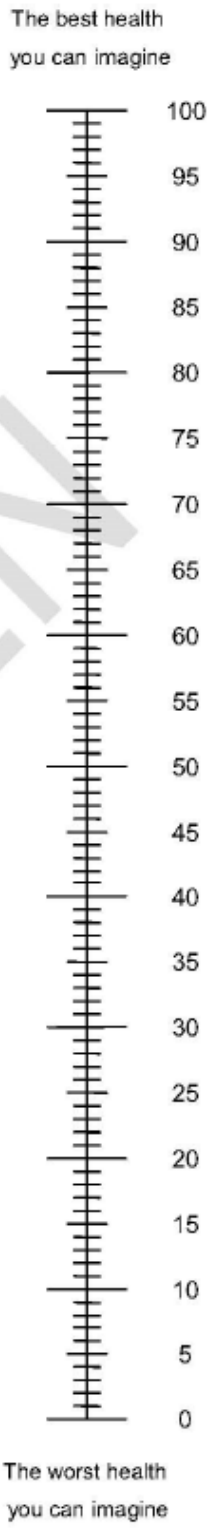
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix H Abbreviations

Abbreviation or special term	Explanation
ADA	Antidrug antibody
AE(s)	Adverse event(s)
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AoV	Ampulla of Vater
AST	Aspartate aminotransferase
AUC	Area under the serum drug concentration-time curve
BICR	Blinded independent central review
Bili	Bilirubin
BP	Blood pressure
BTC	Biliary tract cancer
CA-19-9	Carbohydrate antigen 19-9
CD	Cluster of differentiation
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
C_{max}	Maximum observed concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRF	Case Report Form
CRO	Contact Research Organization
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumor deoxyribonucleic acid
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DCO	Data cutoff
DCR	Disease control rate

Abbreviation or special term	Explanation
DCR-24w	Percentage of patients who have a best objective response of CR or PR or who have SD for at least 24 weeks (±7 days), following the start of study treatment.
DCR-32w	Percentage of patients who have a best objective response of CR or PR or who have SD for at least 32 weeks (±7 days), following the start of treatment
DGR	Dangerous Goods Regulations
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DoR	Duration of response
DUS	Disease under study
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EHCC	Extrahepatic cholangiocarcinoma
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
ePRO	Electronic patient□reported outcome
EQ-5D	EuroQoL 5-dimension
EQ-5D-5L	EuroQoL 5-dimension, 5 level health state utility index
ESMO	European Society for Medical Oncology
ESR/IIT	Externally sponsored/investigator-initiated clinical trial
EU	European Union
FDG-PET	^{18}F-Fluoro-deoxyglucose positron emission tomography
FA	Final analysis
FAS	Full analysis set
FDA	Food and Drug Administration
FH	Fleming-Harrington
FU	Follow-up
FWER	Familywise error rate
GB	Gallbladder
GCP	Good Clinical Practice

Abbreviation or special term	Explanation
Gem/Cis	Gemcitabine plus cisplatin
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HAV	Hepatitis A virus
HBc	Hepatitis B core
HBeAg	Hepatitis B e-antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HL	Hy's Law
HOSPAD	Hospital resource use module
HR	Hazard ratio
HRCT	High-resolution computed tomography
HRQoL	Health-related quality of life
HSV	Herpes simplex virus
IA-1/2	Interim Analysis 1/2
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCRO	Imaging Contract Research Organization
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
IHCC	Intrahepatic cholangiocarcinoma
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
INR	International normalized ratio

Abbreviation or special term	Explanation
IO	Immuno-oncology
IP	Investigational product
irAE	immune related adverse events
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
KM	Kaplan Meier
LD	Limited-stage disease
LDH	Lactate dehydrogenase
LIMS	Laboratory Information Management System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MHC-1	Major histocompatibility complex Class 1
MMRM	Mixed model repeat measures
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MOA	Mechanism of action
mOS	Median overall survival
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NL	New Lesion
NMIBC	Non-muscle-invasive bladder cancer
NOAEL	No-observed-adverse-effect level
NSCLC	Non-small cell lung cancer
NTL	Non-Target Lesion
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death 1 (CD279)
PD-L1	Programmed cell death ligand-1 (also known as B7 homolog 1, CD274)
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
PGIS	Patient Global Impression of Severity

Abbreviation or special term	Explanation
PHL	Potential Hy's Law
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events
PS	Performance status
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
QC	Quality control
QLQ-C30	30-Item Core Quality of Life Questionnaire
QLQ-BIL21	21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
qXw	Every X weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SoA	Schedule of activities
SoC	Standard of care
SpO_2	Saturation of peripheral oxygen
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TL	Target Lesion
TMB	Tumor mutational burden
TME	Tumor microenvironment
TSH	Thyroid-stimulating hormone
TTD	Time to deterioration
UC	Urothelial carcinoma

Abbreviation or special term	Explanation
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
w/v	Weight/volume
WHO	World Health Organization
WT	Body weight

Appendix I Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID-19 Outbreak

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor.

I 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections I 2 to I 4. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

I 2 Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study clinical lead.

In addition, during study disruption there may be a delay between confirming eligibility of participants and either enrolment into the study or commencing of dosing with study intervention. If this delay is outside the screening window specified in Section 6.2.1 the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 6.2.1.

I 3 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs, concomitant medicationto be reported and documented.

I 4 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the participant themselves.

I 5 COVID-19 Risk Assessment

The safety of participants is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to COVID-19 outbreak, should be weighed against the anticipated benefit (see also principle 2.2 of ICH GCP). Investigators are advised to use clinical judgment in determining infection prevention precautions for study participants.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Participants enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to participants receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID-19, and actions to be taken on study treatment (see Section I 8). With these measures in place, it is considered that the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks. All implemented measures prioritise trial participant safety and data validity; in case these two conflict with each other, trial participant safety should always prevail (see also European Medicines Agency Guidance on the management of clinical trials during the COVID-19 [coronavirus] pandemic [EMA 2020]).

Notably, participants with active COVID-19 infection confirmed by local laboratory testing will not be eligible for study enrolment (see CSP Section 5.2, Exclusion Criterion 1).

I 6 Potential Risks during COVID-19

Every effort should be made to follow the CSP. Section I 9 provides a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with study intervention durvalumab. The risk-benefit assessment should be carefully considered for each participant enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for participants and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

The sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimise any potential risks.

I 7 New Participant Enrolment

Study sites may continue to recruit new participants into the study provided the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enrol and manage new participants effectively and in compliance with the protocol.
- Data will continue to be entered into the eCRF and queries resolved in a timely manner. Per CSP Exclusion Criterion 1 (see CSP Section 5.2), participants with uncontrolled intercurrent illness, including but not limited to, ongoing or active infection are not eligible for the study participation and hence such participants (including those who have confirmed COVID 19) should not be included for study participation.

I 8 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the participants' treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the CSP.

AEs, SAEs, cycle delays and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the End of Treatment Form(s) completed

I 9 Ongoing Participants

Participants receiving study intervention should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, study intervention should be interrupted until such assessments can be completed.

I 9.1 If a Participant has an Event Suspected to be COVID-19

Delay or omit study intervention as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing and sometimes abnormal chest imaging and may be similar to those of an imAE.

- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.
- If COVID-19 is ruled out, study intervention may be resumed per the CSP.
- If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

I 9.2 Participants with Confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have study intervention withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids as per the durvalumab/tremelimumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual participant's presentation (Curigliano et al 2020).

I 9.3 Restarting Study Intervention

Study intervention must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, lab testing and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The study clinical lead should be contacted if any additional guidance or clarification is needed.

I 9.4 Vaccination Against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk-benefit of other types of COVID-19 vaccines for participants in clinical trials. Ideally, administration of the vaccine should be done on a different day other than the day of study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

I 10 References

Curigliano et al 2020
Curigliano G, Banerjee S, Cervantes A, Garassino M, Garrido P, Girard N. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol 2020;31(10):1320-35.

EMA 2020
EMA, Clinical Trials Facilitation and Coordination Group, European Commission. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 2, 27 March 2020. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed: 17 December 2020.

SIGNATURE PAGE

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