# Protocol OSE2101C301

## A randomized parallel group Phase III trial of OSE2101 as 2nd or 3rd line compared with standard treatment (docetaxel or pemetrexed) in HLA-A2 positive patients with advanced Non-Small-Cell Lung Cancer with progressive disease after last treatment with immune checkpoint inhibitors (ICI) (OSE2101C301)

**Study Name: ATALANTE 1**

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| Drug | OSE2101 |
| Indication | Treatment of Non-Small-Cell Lung Cancer (NSCLC) in patients expressing HLA-A2 |
| Development phase | III |
| EudraCT number | 2015-003183-36 |
| IND number | BB-IND 10802 |
| Sponsor | OSE Immunotherapeutics |
| Steering Committee | [redacted] |
| Protocol version | Version 6.0 of 02 February 2022 |

## Signature page

| **Sponsor** | | |
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| **Coordinating investigators – Co-Chairs of the Steering Committee** | | |
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| **Principal Investigator** | | |
| | *Signature* | *Date* |

As an investigator, I have read and approve this protocol. My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that this clinical study will be conducted in accordance with the protocol and all related documents, and in accordance with all applicable laws and regulations including but not limited to the Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), Directive 2001/20/EC, the ethical principles of the Declaration of Helsinki and its amendments.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

## Main contact details

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# Revision History

| Study protocol version | Summary of main changes |
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| Version 1.0 on 27-Jul-2015 | Initial version submitted to Authorities (not applicable in countries) |
| Version 1.2 on 02-Oct-2015 | Exclusion criteria n°9 added to exclude patients treated with corticosteroids within 3-weeks before inclusion (except if low dose) |
| Version 2.0 on 30-Nov-2015 | Exclusion criteria n°1 modified to exclude patients with Large Cell Carcinoma; Inclusion criterion n°5 clarified to authorize patients as 2nd line after failure of prior platinum-based chemotherapy **or** as 3rd line after failure of platinum-based chemotherapy then immune checkpoint inhibitor (ICI) |
| Version 3.0 on 14-Feb-2017 | Inclusion criterion n°5 modified to authorize patients as 2nd line or 3rd line after failure of platinum-based chemotherapy **and/or** failure of ICI (sequential or combined with chemo) *as ICIs may be used either as 1st or 2nd line therapy;* PDL-1 expression on tumor biopsy not further mandatory for inclusion; clarification on inclusion criteria n°9 to authorize only patients with asymptomatic brain metastases |
| Version 4.0 on 21-Dec-2017 and Version 4.1 on 28-Feb-2018 | Inclusion criterion n°5 modified to only authorize the subgroup of **patients previously treated with ICI and who have progressed after ICI** (as 2nd line after ICI + chemotherapy first line or as 3rd line after platinum-based chemotherapy in first line then ICI in second line); Study design modified for a Phase II (Step 1) / Phase III (Step 2) design with a first step Fleming non comparative Phase II design; First secondary criterion modified for disease control rate instead of progression-free survival; Clarification on population for analysis for Step 1 and Step 2 (*in version 4.1 per request after the voluntary harmonized procedure (VHP) in the European Union*); *Per IDMC request, the recruitment was temporarily halted from June 2017 to November 2017 before the decision to restart the recruitment only in the subgroup of patients who progressed after ICI was taken based on the IDMC independent analysis of data (safety and death events) reported in the first 131 patients randomized until June 2017; This analysis was blinded from the investigators and the Sponsor.* |
| Version 5.0 on 29-Mar-2019 | Implementation of the 8th edition of TNM instead of 7th edition leading to modify the study title with no modification of the target study population; Inclusion criterion n°7 modified to authorize patient with progression during or within 12 months after the end of ICI as sequential or concomitant platinum-based chemotherapy ± radiation for locally advanced disease (stage III); Study design modified to remove the possibility of a sample size reassessment of Step 2 based on the Step 1 Phase II results, to continue with the 2:1 randomization ratio in Step 2 and, as a consequence, to increase the number of events in Step 2 from 250 to 278 and to increase accordingly the number of patients, also to not consider for the final analysis the 38 patients with previous ICI treatment randomized before the recruitment hold; Implementation of NCI CTCAE version 5.0 instead of CTCAE version 4.0 leading to clarifying the definition of cytokine release syndrome (CRS) as well as the management of CRS still per Lee recommendation; A translational study has been added for patients/sites who agreed, in order to assess immunogenicity before and under treatment. |
| Version 6.0 on 02-Feb-2022 | To notify the decision to early stop the recruitment in April 2020 per the IDMC recommendation due to the impact of the COVID-19 pandemic on the primary endpoint of the study (OS) and the risk on data integrity, and to harmonize the study protocol with the final Statistical Analysis Plan (SAP) completed on 23-jul-21 before database lock. |

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| | Main changes of the analysis plan compared to protocol v5.0 were to reorder the secondary endpoints and to add Post-Progression Survival (PPS) and Time to worsening of ECOG PS as first secondary endpoints to better reflect the efficacy of a cancer vaccine, to consider a Population of Interest (PoI) identified during Step-1 as the main population for the final analysis, and to estimate the study power considering that half of patients have been finally included due to the early study discontinuation. Additional analysis of COVID-19 impact, and quality of life based on EORTC and FDA guidance's were added. |

## Protocol Summary

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| **Title** | A randomized parallel group Phase III trial of OSE2101 as 2nd or 3rd line compared with standard treatment (docetaxel or pemetrexed) in HLA-A2 positive patients with advanced Non-Small-Cell Lung Cancer with progressive disease after last treatment with immune checkpoint inhibitors (ICI) (OSE2101C301) |
| **Objectives** | **Step 1 (Phase II) 2:1 randomized non-comparative one stage Fleming Phase II**<br>**Primary objective**<br>• To evaluate the overall survival (OS) rate at 12 months in HLA-A2 positive patients with advanced NSCLC as 2nd or 3rd line therapy after failure of checkpoint-inhibitor regimens<br>**Secondary objectives**<br>• To describe secondary measures of clinical efficacy including OS (median), disease control rate (DCR) at 6 and 12 months, Health-related Quality of life (QoL), progression free survival (PFS), objective response rate (ORR) and evaluate duration of response (DR)<br>• To assess the safety and tolerability<br>• To describe patient reported outcomes (PRO) disease/treatment-related symptoms of lung cancer<br><br>**Step 2 (conditional Phase III) 2:1 comparative randomized Phase III**<br>**Primary objective**<br>• To demonstrate that OSE2101 is superior to control treatment with respect to OS in HLA-A2 positive patients with advanced NSCLC as 2nd or 3rd line therapy after failure of checkpoint-inhibitor regimens; primary population will be the Population of Interest (PoI) defined as patients with secondary resistance to ICI monotherapy with ICI given 2nd line; sensitivity analysis will be done in all patients<br>**Secondary objectives**<br>• To compare secondary measures of clinical efficacy including Post progression Survival (PPS), Time to worsening of ECOG PS, Health-related QoL, DCR at 6 and 12 months, and PFS<br>• To assess the safety and tolerability of OSE2101 compared to the control treatment<br>**Exploratory objectives**<br>• To compare other efficacy criteria (ORR, DR), other QoL criteria, time to next lung cancer therapy and COVID-19 impact in both treatment arms. |
| **Design** | Open-label, multicenter, controlled, randomized, parallel group, 2-step Phase II/III study; Randomization 2:1 in experimental Arm A OSE2101 or Arm B Standard of Care (SoC) docetaxel or pemetrexed using the following stratification factors: histology (squamous vs. non squamous), best response to first line treatment (objective response vs. no objective response), line rank of |

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| | previous treatment with ICI (ICI first line vs. ICI second line) | | | |
| **Study planned duration** | **First subject**<br>***First visit*** | Q1 2016 | **Last subject**<br>***Last visit (Step 1)***<br>***Last visit (Step 2)*** | ≈Q1 2020<br>Q1 2021 |
| **Centers / Country** | Approximately 80 to 125 centers in the European Union, North America and other countries. The study includes IND and non-IND centers (21 CFR 312.120 compliant). | | | |
| **Subjects / Groups** | **Step 1 (Phase II)**<br>A total of 38 patients with previous ICI treatment have been recruited before protocol version 4.0. After implementation of protocol version 4.0, 108 new patients are to be randomized with a 2:1 randomization ratio in order to reach a total of 84 patients in arm A (OSE2101) evaluable at 12 months (death observed within 12 months or follow-up time of 12 months or more).<br>**Step 2 (Phase III)**<br>After end of randomization in Step 1, the same 2:1 randomization ratio will be continued for patients entering Step 2 until a cumulated total of new 363 patients or a cumulated total of 278 deaths (both counts excluding the 38 patients enrolled before protocol 4.0) is reached.<br>Step-1 analysis was reviewed by the independent data monitoring committee (IDMC) in March 2020. Step-1 data showed that the predefined thresholds of 12 months-OS rate in OSE2101 arm was achieved. At this time, the IDMC was concerned about the impact of the COVID-19 pandemic on the primary endpoint of the study (OS), on the risk on data integrity and recommended to stop accrual early.<br>The Sponsor decided to stop the accrual in April 2020. At that date, 219 patients have been enrolled and planned to be followed for survival up to mid-January 2021. From Step-1 analysis, a population of interest (PoI) consisting of patients from the 2d line ICI stratification factor with secondary resistance to ICI (duration of ICI ≥ 12 weeks) was identified as having a benefit over SoC and being proposed as the main population for final analysis (Kluger et al., 2020).<br><br>N.B.: All patients included in the study will be monitored until death-events or termination of the study or decision to withdraw from the study, even after a change in therapy for progression, as the main criterion is OS and as all patients included in the post-ICI stratum will be kept for the final analysis.<br>Patients included within the subgroup "no previous treatment with ICI" before recruitment hold in this subgroup will continue treatment as planned. They will be described separately in the final analysis. | | | |

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| **Study periods** | The total study duration for an individual subject will depend on the survival of the subject, including the following periods:<br>• **Pre-screening:** HLA-A2 testing (using PCR methods) can be done at any time before inclusion (a specific consent form is available).<br>• **Screening:** 1 to 35 days before treatment administration.<br>• **Randomization:** treatment allocation and baseline for OS calculations.<br>• **Treatment:**<br>– For OSE2101 (Arm A): Day 1 each 21-day cycle for 6 cycles, then every 8 weeks for the remainder of year one and, finally every 12 weeks beyond year one (*see Figure 2: Schedule of OSE2101 administration)*<br>– For docetaxel or pemetrexed (Arm B): Day 1 each 21-day cycle (i.e. every 3 weeks)<br>– In both arms, treatment cycles will be repeated until unequivocal RECIST 1.1-defined disease progression as determined by the investigator, unacceptable toxicity, or consent withdrawal. Should pseudo progression or delayed response to treatment be suspected in arm A, investigator may continue treatment beyond the time of RECIST-defined progression, if the patient is perceived to be experiencing clinical benefit.<br>• **End of treatment:** 4 weeks after the final treatment administration to obtain assessments from the 4 previous weeks.<br>• **Post-treatment follow-up:** every 2 months after discontinuation of treatment for the post-treatment survival status. |
| **Inclusion criteria** | **Protection of study subjects and compliance**<br>1. Signed and dated informed consent document indicating that the patient has been informed of all the pertinent aspects of the trial prior to enrollment<br>2. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures<br>**Demography**<br>3. Female or male, 18 years of age or older<br>**Cancer Diagnosis and treatment**<br>4. Histologically or cytologically proven diagnosis of NSCLC that is locally advanced (stage III) unsuitable for radiotherapy or metastatic (stage IV) according to the 8th edition of tumor, node, metastasis (TNM) in Lung Cancer published by the International Union Against Cancer and the American Joint Committee on Cancer<br>5. Subjects with disease recurrence or progression after therapy with an immune checkpoint inhibitor and platinum-based chemotherapy: |

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| | • either 1st line chemotherapy followed by 2nd line checkpoint inhibitor<br>• or 1st line combination of checkpoint inhibitor and chemotherapy<br>Patients with progression during or within 12 months after the end of ICI as sequential or concomitant platinum-based chemotherapy ± radiation for locally advanced disease (stage III) are eligible<br>6. Subjects with measurable or non-measurable lesions<br>7. Subjects must express HLA-A2 phenotype as assessed serologically<br>8. Subjects must be considered suitable for chemotherapy with either single-agent pemetrexed or docetaxel<br>9. Subjects with brain metastases are eligible if treated (whole brain radiotherapy, stereotaxic radiotherapy, surgery) at least 3 weeks prior to initiation of study treatment and have no symptoms related to brain metastases for at least 2 weeks before initiation of study treatment and are not taking any forbidden medications (see Section 4.3.5 of the protocol)<br>10. Any prior chemotherapy, immunotherapy, hormonal therapy, radiation therapy or surgeries must have been completed at least 3 weeks prior to initiation of study treatment<br>11. Any toxicity from prior therapy must have recovered to ≤ Grade 1 (except alopecia)<br>**Clinical status**<br>12. ECOG performance status 0-1<br>13. Adequate organ function as defined by all the following criteria:<br>• Albuminemia > 25 g/L<br>• Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤1.5 x upper limit of normal (ULN) with alkaline phosphatase ≤ 2.5 x ULN, or AST and ALT ≤ 5 x ULN if liver function abnormalities are due to liver metastases<br>• Total serum bilirubin ≤ 1.5 x ULN<br>• Absolute neutrophil count (ANC) ≥ 1500/µL<br>• Platelets ≥ 100000/µL<br>• Hemoglobin ≥ 9.0 g/dL (in the absence of transfusion within 2 weeks before randomization)<br>• Creatinine clearance (based on modified Cockcroft-Gault formula) ≥ 45 ml/min |
| **Exclusion criteria** | **Cancer Diagnosis and treatment**<br>1. Small-cell lung cancer/mixed NSCLC with small cell component or other neuroendocrine lung cancers (typical and atypical carcinoids, large-cell neuroendocrine carcinomas) |

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| | 2. Patients with squamous cell carcinoma histology, and who had docetaxel as part of his prior chemotherapy will not be eligible to the trial<br>3. Current or previous treatment with investigational therapy in another therapeutic clinical trial (interrupted less than 4 weeks before study treatment initiation)<br>4. Patients whose tumor harbors EGFR gene mutation that sensitizes tumors to TKI (EGFR exon 18-21) or ALK rearrangement<br>5. Ongoing immunotherapy (checkpoint inhibition, antigen immunotherapy that would be scheduled to continue concomitantly to the study)<br>6. Spinal cord compression (unless treated with the patient attaining good pain control and stable or recovered neurologic function), carcinomatous meningitis, or leptomeningeal disease<br>7. Patients with squamous cell histology or non-squamous cell histology previously treated by pemetrexed, with a contraindication for docetaxel with grade ≥ 2 neuropathy or hypersensitivity reaction to medications formulated with polysorbate 80 (Tween 80) as they could be randomly assigned to Arm B<br>**Medical history and clinical status**<br>8. Patients with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications<br>9. Treatment with corticosteroids in the last 3-week period before inclusion, c corticosteroids with minimal systemic absorption (*e.g.* with a dose ≤ 500 microgram beclomethasone equivalent for inhaled steroids), or steroid doses ≤ 10 mg daily prednisone equivalent which are permitted<br>10. A recognized immunodeficiency disease including human immunodeficiency virus (HIV) infection and other cellular immunodeficiencies, hypogammaglobulinemia or dysgammaglobulinemia; subjects who have hereditary, congenital or acquired immunodeficiencies<br>11. Patients with auto-immune disease, with the exception of type I diabetes or treated hypothyroidism<br>12. Patients with interstitial lung disease<br>13. Patients with active B or C hepatitis<br>14. Other malignancy: patients will not be eligible if they have evidence of other active invasive cancer(s) (other than NSCLC) within 5 years prior to screening (except appropriately treated non-melanoma skin cancer or localized cervical cancer, or other local tumors considered cured (e.g. localized and presumed cured prostate cancer)<br>15. Other severe acute or chronic medical or psychiatric conditions, or |

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| | laboratory abnormalities that would impart, in the judgment of the investigator and/or sponsor, excess risk associated with study participation or study drug administration, and which would, therefore, make the patient inappropriate for entry into this study<br>16. Female patients must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of the trial and for at least 90 days after completion of treatment (See Appendix 4: Guidance on Contraception)<br>17. Male patients sexually active with a woman of childbearing potential must be surgically sterile or must agree to use effective contraception during the period of the trial and for at least 90 days after completion of treatment. The decision of effective contraception will be based on the judgment of the principal investigator (See Appendix 4: Guidance on Contraception)<br>18. Breastfeeding women<br>19. Women with a positive pregnancy test |
| **Investigational drug** | OSE2101 is combination of 10 synthetic peptides targeting 5 tumor–associated antigens. It is a T-cell specific immunotherapy.<br><br>OSE2101 will be administered as a 1 mL-subcutaneous injection on Day 1 every three weeks for six cycles, then every eight weeks for the remainder of year one and finally every twelve weeks beyond year one until unequivocal RECIST 1.1-defined disease progression as determined by the investigator, unacceptable toxicity, or consent withdrawal. Should pseudo progression or delayed response to treatment suspected in arm A, investigator may continue treatment beyond the time of RECIST-defined progression, if the patient is perceived to be experiencing clinical benefit.<br><br>OSE2101 dose will be 5 mg of peptide (0.5 mg for each peptide). |
| **Control treatment** | **Docetaxel**, 75 mg/m$^2$, will be administered by intravenous infusion over 1 hour on Day 1 of a 21-day cycle to patients with squamous cancer or to patients with non-squamous cancer who had previously been treated with pemetrexed.<br>**Pemetrexed**, 500 mg/m$^2$, will be administered by intravenous infusion over 10 minutes on Day 1 of a 21-day cycle to patients with non-squamous cancer and who have not previously received pemetrexed.<br>Docetaxel and pemetrexed will be continued until unequivocal RECIST 1.1-defined disease progression as determined by the investigator, unacceptable toxicity, or consent withdrawal. |
| **Concomitant therapies** | • Mandatory concomitant therapies (premedication) for patients in Arm B (Docetaxel / Pemetrexed) are detailed in Section 4.3.5 of the protocol.<br>• and authorized and prohibited therapies for patients in Arm A and B are detailed in Section 4.3.5 of the protocol. |

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| **Efficacy endpoints** | **Primary efficacy endpoint**:<br>• Overall survival (OS):<br>  o In Step 1: OS rate at 12 months in experimental Arm A (OSE2101) in 84 evaluable patients exposed to OSE2101<br>  o In Step 2: comparison of OS between experimental Arm A (OSE2101) and control Arm B (docetaxel or pemetrexed) when 278 events observed; due to early study discontinuation (219 patients included instead of 363 patients), statistical hypothesis was revised with a comparison of OS between experimental Arm A and control Arm B in the PoI (refer statistical methodology section)<br>**Secondary efficacy endpoints** (in Steps 1 & 2):<br>• Disease control rate (DCR) at 6 and 12 months based on RECIST1.1<br>• QLQ-C30 (EORTC QLQ questionnaire): "Global health status/QoL" score based on questions 29 (*How would you rate your overall health during the past week?*) and 30 (*How would you rate your overall quality of life during the past week?*)<br>• QLQ-LC13 (lung cancer module from EORTC QLQ questionnaire): time to 1st ≥ 10-point deterioration in chest pain (question 40), dyspnea (questions 33, 34, 35) or cough (question 31) (in Step-1 only)<br>• Post Progression Survival<br>• Time to worsening of ECOG PS<br>• QLQ-C30 Global health status score change from baseline (in Step 2 only)<br>• QLQ-C30 Functional scores change from baseline (in Step 2 only)<br>• QLQ-C30 Symptom scores change from baseline (in Step 2 only)<br>• QLQ-LC13 Symptom scores change from baseline (in Step 2 only)<br>• Progression free survival based on RECIST1.1<br>• Objective Response Rate (ORR) (in Step 1 only)<br>• Duration of Response (DR) (in Step 1 only) |
| **Exploratory endpoints** | In Step 2 only:<br>• ORR<br>• DR<br>• All the other scores of QoL<br>• COVID-19 impact<br>In Steps 1:<br>• Time to deterioration (TTD) in patient reported chest pain<br>• TTD in patient reported dyspnea<br>• TTD in patient reported cough<br>In Steps 1 & 2:<br>• Time to next lung cancer therapy |
| **Tolerability / Safety** | • Incidence, severity, seriousness and relationship to study treatments of adverse events (AE), immune-related adverse events (irAE) and any |

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| **endpoints** | laboratory abnormalities |
| **Translational study** | Patient can agree to participate in all or some parts of the translational study. Patient can refuse to participate in the translational study without compromising his/her participation in the main study.<br>The main objectives are to explore biomarkers and pharmacodynamic parameters before and after the start of study treatment (OSE2101 or chemotherapy) in a population of NSCLC patients who progressed after ICI treatment.<br><u>Blood samples:</u><br>• Pre-, on-treatment and after treatment collection of peripheric blood mononuclear cells (PBMCs) for:<br>o Immunophenotyping<br>o OSE2101 vaccine antigen-specific T-cell frequency<br>• Pre-, on-treatment and after treatment collection of liquid biopsies (e.g. cell free DNA (cfDNA)):<br>o Tumor Mutational Burden (TMB) and/or other mutation of interest (e.g. gene profiling of OSE2101 vaccine TAA)<br>Blood samples will be taken at baseline, then every 6 weeks until Cycle 7 (e.g. Day 1 of Cycles 3, 5 and 7), then every 12 weeks (e.g. at time of CT scan) until end of treatment and/or progression in all arms.<br><br><u>Tumor samples:</u><br>• Specimens from archiving tumor biopsies (at first diagnosis and/or at any time before study entry) will be collected.<br>• If possible, a new tumor biopsy will be collected <u>within 35 days prior to the first study treatment administration (during the screening period</u>). An archiving tumor biopsy collected before the screening period is acceptable, should the biopsy be collected after the end of ICI treatment. A second tumor biopsy (e.g. in the same tumor site) will be undertaken between cycle 3 and cycle 6 and/or at time of the disease progression. *Of note*, a blood sample will be collected for Whole-Exome sequencing (WES) for:<br>o Determination of HLA class I expression in tumor (e.g. HLA-A2 and Beta-2 microglobulin)<br>o Tumor and tumor microenvironment (TME) characterization by multiplex IHC and gene profiling (i.e. CD8 exhausted T cells, TIL infiltration, …)<br>All blood and tumor samples will be stored in certified biobanks before being submitted to central laboratories for analysis.<br>If the patient agrees, remaining specimens after analysis will be biobanked for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby. |

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| **Statistical methodology** | **Step 1 – Phase II sample size**<br>The primary objective of Step 1 is to evaluate the overall survival rate after 12 months in OSE2101 arm. The following statistical hypotheses are considered:<br>- H0 (null): 25% of overall survival rate at 12 months (uninteresting to pursue any further investigation)<br>- H1 (alternative): 40% of overall survival rate at 12 months (clinically relevant to discuss the interest of further investigation in a Phase III comparative trial).<br>According to the previous hypotheses and a Fleming one step Phase II design with a 2.5% one-sided type I error and a power of 80%, 84 evaluable patients have to be enrolled in the arm A.<br><br>Fleming decision rules<br>Amongst the first 84 evaluable patients:<br>To reject H0 we have to observe at least 30 (35.7%) patients alive at 12 months then it will be interesting to run the next step of Phase III comparative trial.<br>If less than 30 patients are alive at 12 months, H0 will not be rejected and it will be considered uninteresting to pursue any further investigation.<br>The probability to conclude for inefficacy whereas the true rate is 40% is $\beta$=18.1%.<br>The probability to conclude for efficacy whereas the true rate is 25% is $\alpha$=1.9%.<br>In order to limit the total number of patients needed in Step 1, a 2:1 randomization ratio to receive OSE2101 (Arm A) or pemetrexed or docetaxel (Arm B) has been used for new patients recruited since version 4.0 of the protocol came into effect. A total of 38 patients with previous ICI treatment have been recruited before protocol version 4.0, from whom 18 patients randomized in arm A (OSE2101), thus 84 – 18 = 66 new evaluable patients need to be recruited in arm A (OSE2101). Based on a 2:1 randomization ratio, 66/2 = 33 |
| | new patients need to be randomized in arm B, leading to a total of 99 new evaluable patients. With an expected 7% rate of patients not evaluable at 12 months or withdrawn, a total of 108 new patients will be randomized for Step 1.<br><br>**Step 2 – Phase III sample size**<br>For Step 2, the same 2:1 randomization ratio will be continued. All the 38 patients randomized before protocol version 4.0 in the subgroup of patients with previous ICI treatment and all new patients included in Step 1 / Phase II will be followed during Step 2 /Phase III. However, the final analysis of Phase II/Phase III will exclude the 38 patients with previous ICI treatment randomized before the recruitment hold.<br>In order to reach a power of 80% for the two-sided log rank test at the 5% significance level when assuming a median OS of 7 months for the control and 10 months for the experimental arm, a total of 278 events is required. If the new patients are uniformly included over an accrual period of 36 months followed by |

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| | a follow-up of 6 months after the last inclusion, observing 278 events would require a total of 363 new patients. The actual number of new patients may be reduced if the 278 events are observed earlier (this is an event-driven study). Both counts exclude the 38 patients enrolled before protocol 4.0.<br>Due to early study discontinuation due to COVID-19 (219 patients included instead of 363 patients), the power decreased to 62% with the same hypotheses (HR=0.70).<br>Considering Step 1 results in the PoI, the following hypotheses have been proposed for final analysis:<br>Assuming a HR of 0.55 observed in PoI in Step-1 and a median OS of 7 months in SoC (unchanged as initially planned), a total of 90 events in the PoI will provide a power of 80% and a 2-sided logrank test at a 5% two-sided level, if the patients are included over an accrual period of 48 months followed by a follow-up of 6 months after the last inclusion. |
| **Steering Committee** | A Steering Committee including representatives from the investigators, the Sponsor and other experts will be responsible of the study supervision. |
| **Independent Data Monitoring Committee** | An independent Data Monitoring Committee (IDMC) will review the safety and tolerability data and assess the risk/benefit ratio of the investigational drug on a regular basis. The IDMC membership, role and responsibilities will be detailed in a specific IDMC charter. |

## Table 1: Visits and assessments schedule (Arm A: OSE2101)

| Period | Pre-screening | Screening | Treatment | | | | | End of treatment | |
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| **Visit** | | **Screening and randomization** | **Cycle 1 (3 week-cycle)** | | **Cycles 2 to 6 (3 week-cycle)** | **Cycles 7 to 9 (8 week-cycle)** | **Cycles ≥ 10 or EOT (12-week cycle)** | **End of treatment[1]** | **Post-treatment Follow-up[2]** |
| **Cycle day** | | **-35 Day/ -1 Day** | **Day 1 (±2)** | **Day 15 (±2)** | **Day 1 (±2)** | **Day 1 (±4)** | **Day 1 (±8)** | | |
| Informed consent for HLA-A2 determination and biobanking | X | | | | | | | | |
| HLA-A2 determination[3] | X | | | | | | | | |
| Informed consent | | X | | | | | | | |
| Medical/ Oncological history | | X | | | | | | | |
| Previous medications | | X | | | | | | | |
| EGFR/ALK alterations, PD-L1[4] | | X | | | | | | | |
| Body height | | X | | | | | | | |
| Body weight | | X | X | | X | X | X | X | |
| Physical examination | | X | X | | X | X | X | X | |
| Vital signs (Body temperature, BP/PR, oxygen saturation) | | X | X | | X | X | X | X | |
| 12-lead ECG | | X | | | X | X | X | X | |
| ECOG Performance status | | X | X | | X | X | X | X | |
| Hematology/ Biochemistry[5] | | X | X | X | X | X | X | X | |
| Coagulation/ HIV test[6] | | X | | | | | | | |
| Pregnancy test (as appropriate) | | X | | | | | | X | |
| Tumor assessments (including scans) | | X | every 6 (± 1) weeks until documented RECIST 1.1 progression[7] | | | | | | (X)[8] |
| Randomization | | X | | | | | | | |
| OSE2101 administration[9] | | | X | | X | X | X | | |
| EORTC QLQ-C30, QLQ-LC13 | | | X | | X | X | X | X | |
| Survival follow-up | | | | | | | | | X |
| Concomitant medications | | X | X | X | X | X | X | X | |
| Adverse Events | | X | X | X | X | X | X | X | |
| Serious Adverse Events | | X | X | X | X | X | X | X | |
| Hospitalizations | | X | X | X | X | X | X | X | |
| Informed consent for translational study and biobanking (optional)[10] | | X | | | | | | | |
| Blood samples for biomarkers (optional)[11] | | X | | | every 6 (± 3) weeks (e.g. at D1 of Cycles 3, 5 & 7) | every 12 (± 3) weeks (e.g. at time of imaging) until EOT and/or progression | | | |
| Tumor samples for biomarkers (optional)[12] | | X | | | X (e.g. between Cycles 3 & 6) | | | X (e.g. at tumor progression) | |

1 End of treatment: visit to obtain last assessments after the study drug stop from the 4 previous weeks.
2 Post-treatment follow-up: data collection on survival status and any subsequent cancer therapy (if any) every 2 months after study drug discontinuation until death.
3 HLA-A2 testing can be done at any time during patient management before inclusion. A pre-screening consent is available to test patients for instance during 1st or 2nd line therapy.
4 EGFR/ALK alterations and PD-L1 expression on tumor tissue: if these results are not available, they have to be done in local or central laboratories during the screening period. EGFR/ALK alterations is mandatory before randomization in patients with non-squamous cancer or never/light smokers with squamous cancer. If PD-L1 expression is not documented and no tumor tissue available to perform the testing, then the PD-L1 status can be omitted.
5 Hematology and biochemistry tests: to be done at Day 1 Cycle 1 only if screening assessment done more than 7 days before. Thereafter at Day 1 of each subsequent cycle, local laboratory tests will be done every 3 weeks (less than 72 hours (3 days) before study treatment administration) until Cycle 6, then every 8 weeks (less than 4 days before study administration) until Cycle 9, then every 12 weeks (less than 8 days before each subsequent administration.
6 HIV test: to be done for all eligible patients with HIV status unknown.
7 Tumor assessments (CT scan of thorax, abdomen and brain CT or brain MRI) to be done every 6 weeks (± 1-week allowance) after Day 1 Cycle 1, meaning it could be between 2 treatment visits; CT scan of the pelvis will be performed only upon request according to clinical suspicion. In case of clinical suspicion of bone metastasis out of the area reported by CT scan, imaging test will be performed under discretion of the investigator and will be repeated every 12 weeks. **For Germany**, with respect to brain metastases, MRI should be the privileged imaging technic and CT should only be considered when there are contra-indications to MRI.
8 Tumor assessments should be continued until documented RECIST 1.1 disease progression for patients who have not progressed during the treatment period.
9 OSE2101 treatment will continue until unequivocal RECIST 1.1-defined disease progression as determined by the investigator, unacceptable toxicity, or consent withdrawal. Should pseudo progression or delayed response to treatment suspected in arm A, investigator may continue treatment beyond the time of RECIST-defined progression, if the patient is perceived to be experiencing clinical benefit.
10 Separate informed consent (optional) will be obtained from the patient who agreed to participate in a translational study and authorizing the bio banking of the remaining samples to be used for future biomarker research and drug development projects. Patient can agree to participate in all and/or some parts of the translational study. Patient can refuse to participate in the translational study without compromising his/her participation in the main study.
11 Blood samples for biomarkers will be taken at baseline (during the screening period), then every 6 (± 3) weeks until Cycle 7 (e.g. at D1 of Cycles 3, 5 and 7), then every 12 (± 3) weeks (e.g. at time of imaging) until end of treatment and/or progression.
12 Specimens from archiving tumor biopsies (at first diagnosis and/or at any time during previous treatment) will be collected. As possible, a new tumor biopsy will be collected within 35 days prior to the first study treatment administration (during the screening period). An archiving tumor biopsy collected before the screening period is acceptable, should the biopsy be collected after the end of ICI treatment. A second tumor biopsy (e.g. in the same tumor site) will be undertaken between Cycle 3 and Cycle 6 and/or at time of the disease progression. A blood sample will be collected for Whole-Exome sequencing (WES) at screening.

## Table 2: Visits and assessments schedule (Arm B: Docetaxel or Pemetrexed)

| Period | Pre-screening | Screening | Treatment | | | | End of treatment | |
|---|---|---|---|---|---|---|---|---|
| **Visit** | | **Screening and randomization** | **Cycle 1 (3 week-cycle)** | | **Cycle 2 (3 week-cycle)** | **Cycles ≥3 (3 week-cycle)** | **End of treatment[1]** | **Post-treatment Follow-up[2]** |
| **Study day** | | **-35 Day/ -1 Day** | **Day 1 (±2)** | **Day 15 (±2)** | **Day 1 (±2)** | **Day 1 (±2)** | | |
| Informed consent for HLA-A2 determination and biobanking | X | | | | | | | |
| HLA-A2 determination[3] | X | | | | | | | |
| Informed consent | | X | | | | | | |
| Medical/ Oncological history | | X | | | | | | |
| Previous medications | | X | | | | | | |
| EGFR/ALK alterations, PD-L1[4] | | X | | | | | | |
| Body height | | X | | | | | | |
| Body weight | | X | X | | X | X | X | |
| Physical examination | | X | X | | X | X | X | |
| Vital signs (Body temperature, BP/PR, oxygen saturation) | | X | X | | X | X | X | |
| 12-lead ECG | | X | | | X | X | X | |
| ECOG Performance status | | X | X | | X | X | X | |
| Hematology/ Biochemistry[5] | | X | X | X | X | X | X | |
| Coagulation/ HIV test[6] | | X | | | | | | |
| Pregnancy test (as appropriate) | | X | | | | | X | |
| Tumor assessments (including scans) | | X | every 6 (± 1) weeks until documented RECIST 1.1 progression[7] | | | | | (X)[8] |
| Randomization | | X | | | | | | |
| Docetaxel or Pemetrexed[9] | | | X | | X | X | | |
| EORTC QLQ-C30, QLQ-LC13 | | | X | | X | X | X | |
| Survival follow-up | | | | | | | | X |
| Concomitant medications | | X | X | X | X | X | X | |
| Adverse Events | | X | X | X | X | X | X | |
| Serious Adverse Events | | X | X | X | X | X | X | |
| Hospitalizations | | X | X | X | X | X | X | |
| Informed consent for translational study and biobanking (optional)[10] | | X | | | | | | |
| Blood samples for biomarkers (optional)[11] | | X | | every 6 (± 3) weeks (e.g. at D1 of Cycles 3, 5 & 7), then every 12 (± 3) weeks (e.g. at time of imaging) until EOT and/or progression | | | | |
| Tumor samples for biomarkers (optional)[12] | | X | | | | X (e.g. between Cycles 3 & 6) | X (e.g. at tumor progression) | |

1 End of treatment: visit to obtain last assessments after the study drug stop from the 4 previous weeks.

2 Post treatment follow-up: data collection on survival status and any subsequent cancer therapy (if any) every 2 months after study drug discontinuation until death.

3 HLA-A2 testing can be done at any time during patient management before inclusion. A pre-screening consent is available to test patients for instance during 1st or 2nd line therapy.

4 EGFR/ALK alterations and PD-L1 expression on tumor tissue: if these results are not available, they have to be done in local or central laboratories during the screening period. EGFR/ALK alterations is mandatory before randomization in patients with non-squamous cancer or never/light smokers with squamous cancer. If PD-L1 expression is not documented and no tumor tissue available to perform the testing, then the PD-L1 status can be omitted.

5 Hematology and biochemistry tests: to be done at Day 1 Cycle 1 only if screening assessment done more than 7 days before. Thereafter at Day 1 of each subsequent cycle, local laboratory tests will be done every 3 weeks (less than 72 hours (3 days) before study treatment administration) until Cycle 6, then every 8 weeks (less than 4 days before study administration) until Cycle 9, then every 12 weeks (less than 8 days before each subsequent administration.

6 HIV test: to be done for all eligible patients with HIV status unknown.

7 Tumor assessments (CT scan of thorax, abdomen and brain CT or brain MRI) to be done every 6 weeks (± 1-week allowance) after Day 1 Cycle 1 meaning it could be between 2 treatment visits; CT scan of the pelvis will be performed only upon request according to clinical suspicion. In case of clinical suspicion of bone metastasis out of the area reported by CT scan, imaging test will be performed under discretion of the investigator and will be repeated every 12 weeks. **For Germany**, with respect to brain metastases, MRI should be the privileged imaging technic and CT should only be considered when there are contra-indications to MRI.

8 Tumor assessments should be continued until documented RECIST 1.1 disease progression for patients who have not progressed during the treatment period.

9 Docetaxel and pemetrexed treatment will continue until unequivocal RECIST 1.1-defined disease progression as determined by the investigator, unacceptable toxicity, or consent withdrawal. Premedication is required with docetaxel and pemetrexed. Premedication will occur before Day 1 (i.e. Day 1 of each cycle will be injection day for chemotherapy).

10 Separate informed consent (optional) will be obtained from the patient who agreed participating in a translational study and authorizing the bio banking of the remaining samples to be used for future biomarker research and drug development projects. Patient can agree to participate in all and/or some parts of the translational study. Patient can refuse to participate in the translational study without compromising his/her participation in the main study.

11 Blood samples will be taken at baseline (during the screening period), then every 6 (± 3) weeks until Cycle 7 (i.e. at D1 of Cycles 3, 5 and 7), then every 12 (± 3) weeks (e.g. at time of CT imaging) until end of treatment and/or progression.

12 Specimens from archiving tumor biopsies (at first diagnosis and/or at any time during previous treatment) will be collected. As possible, a new tumor biopsy will be collected within 35 days prior to the first study treatment administration (during the screening period). An archiving tumor biopsy collected before the screening period is acceptable, should the biopsy be collected after the end of ICI treatment. A second tumor biopsy (e.g. in the same tumor site) will be undertaken between Cycle 3 and Cycle 6 and/or at time of the disease progression. A blood sample will be collected for Whole-Exome sequencing (WES) at screening.

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| | |
|---|---|
| AE | Adverse Event |
| ALK | Anaplastic Lymphoma Kinase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase |
| ATC | Anatomic Therapeutic Chemical Classification |
| BP | Blood Pressure |
| Bpm | beats per minute |
| CBC | Complete blood count |
| CEA | Carcinoembryonic Antigen |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CR | Complete response |
| CRF | Case Report Form |
| CRS | Cytokine Release Syndrome |
| CT | Chemotherapy |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTL | Cytotoxic T-lymphocyte |
| CYP3A4 | Cytochrome P450, family 3, subfamily A, polypeptide 4 |
| DCR | Disease control rate |
| DNA | Desoxyribonucleic Acid |
| DoR | Duration of response |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EGFR | Epidermal Growth Factor Receptor |
| ELISA | Enzyme Linked Immunosorbent Assay |
| ELISPOT | Enzyme-Linked Immuno Spot |
| EORTC QLQ | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire |
| EOS | End of Study |
| EOT | End of Treatment |
| FDA | Food and Drug Administration |
| FDG-PET | Fluorodeoxyglucose Positon Emission Tomography |
| FFPE | Formaldehyde Fixed-Paraffin Embedded |
| FISH | Fluorescence in situ hybridization |
| G-CSF | Granulocyte Colony Stimulating Factor |
| GCP | Good Clinical Practice |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HER-2/neu | Human Epidermal Receptor-2/neurological |

| | |
|---|---|
| HIV | Human Immunodeficiency Virus |
| HLA | Human Leukocyte Antigen |
| HR | Hazard Ratio |
| HRQoL | Health Related Quality of Life |
| HTL | Helper T-lymphocyte |
| ICH | International Conference on Harmonization |
| ICI | Immune Checkpoint Inhibitor |
| IDMC | Independent Data Monitoring Committee |
| IFN | Interferon |
| IND | Investigational New Drug |
| INR | International Normalized Ratio |
| irAE | Immune-related Adverse Event |
| IRB | Institutional Review Board |
| ITT | Intent to treat |
| IUD | intrauterine device |
| IV | Intravenous or intravenously |
| IVD | In Vitro Diagnostics Device |
| IVRS/IWRS | Interactive voice/web response system |
| LDH | Lactate Dehydrogenase |
| LLT | Low level terms |
| MAGE 2/3 | Melanoma Antigens 2/3 |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic Resonance Imaging |
| NE | Not evaluable |
| NSCLC | Non Small Cell Lung Cancer |
| ORR | Objective response rate |
| OS | Overall survival |
| p53 | A nuclear –regulatory protein |
| PADRE | Pan-DR-Epitope |
| PBMCs | Peripheral-blood mononuclear cells |
| PCSA | Potential clinically significant abnormality |
| PD | Pharmacodynamics |
| PD | Progressive disease |
| PET | Positon Emission Tomography |
| PFS | Progression free survival |
| PR | Partial response |
| PR | Pulse Rate |
| PRO | Patient reported outcomes |
| PT | Preferred Term |
| QLQ-C30 and QLQ-LC13 | Lung cancer module in EORTC QLQ |
| QoL | Quality of life |
| RANK-L | Receptor Activator of Nuclear Factor Kappa B ligand |

| | |
|---|---|
| RECIST | Response Evaluation Criteria in Solid Tumors |
| rIL | Recombinant Interleukin |
| RNA | Ribonucleic Acid |
| ROS1 | c-ros oncogene 1, receptor tyrosine kinase |
| SAE | Serious Adverse Event |
| SAP | Statistical analysis plan |
| SD | Standard Deviation |
| SD | Stable disease |
| SE | Standard Error |
| SOC | System Organ Class |
| TAA | Tumor-associated antigen |
| TKI | Tyrosine-Kinase Inhibitor |
| TSH | Thyroid Stimulation Hormone |
| TTD | Time to deterioration |
| ULN | Upper limit of normal |
| WES | Whole-Exome sequencing |
| WHO | World Health Organization |
| WOCBP | Women of childbearing potential |
| WT | Wild type |

# 1 BACKGROUND AND RATIONALE

## 1.1 Target indication

Worldwide, lung cancer has the highest incidence (2.09 million) and mortality (1.76 million) among all cancers (Globocan 2018; 30). It is the leading cause of cancer death among males in both more and less developed countries, and has surpassed breast cancer as the leading cause of cancer death among females in more developed countries (30). Cancer stage at diagnosis determines treatment options and has a strong influence on the length of survival. In the SEER database (39), 57% of patients are diagnosed with advanced stage (metastatic) disease, with a 5y-overall survival (OS) of 4.2%. For the overall population 5y OS is 17.4%. Lung cancer is diagnosed at a median age of 70 years.
Non-small-cell lung cancers (NSCLC) account for 85%–90% of lung cancers, while small-cell lung cancer (SCLC) has been decreasing in frequency in many countries over the last two decades (39).
Tumor subtypes are considered in therapeutic decisions. Adenocarcinoma is the most common histologic subtype. Approximately 63% of advanced NSCLC are diagnosed as adenocarcinoma, 17% as squamous, and 20% as not otherwise specified (37).

Platinum-based doublet chemotherapy is the standard first-line treatment for non-selected patients with advanced NSCLC who have a good performance status. Platinum-based doublet chemotherapy prolongs survival and improves quality of life (QoL) in patients with PS 0–2. For most patients, four cycles of chemotherapy are recommended, notably when maintenance treatment is considered, with a maximum of six cycles. Several regimens of first-line treatment have shown comparable efficacy. Cisplatin compared to carboplatin globally has reported better response rate (RR) and in the subgroup of patients with non-squamous histology when cisplatin is added to third-generation regimens has reported better OS. There is no single platinum-based doublet standard chemotherapy. Pemetrexed use should be restricted to non-squamous NSCLC and bevacizumab combined with paclitaxel–carboplatin regimen improves OS in patients with non-squamous histology and PS 0– 1, and may be offered after exclusion of contraindications (65).

Personalized treatment has changed the diagnostic and treatment approach in NSCLC and could have an impact on patients' outcome (44) as 30% of advanced NSCLC have some kind of actionable oncogenic driver mutation. The most common are sensitizing *EGFR* mutation (around 17% in non-Asian population), *ALK*-rearrangements (8%) and others such as *ROS1*-rearrangements. These oncogenic drivers are almost always mutually exclusive in patients with NSCLC. Targeted agents currently approved for the treatment of NSCLC and include the first-generation, reversible EGFR-targeted tyrosine-kinase inhibitors (TKIs) erlotinib and gefitinib; the second-generation irreversible EGFR-TKI, afatinib; and the ALK inhibitor, crizotinib. New treatments indicated for acquired resistance are being tested.

Erlotinib, docetaxel and pemetrexed are approved second-line therapies for advanced NSCLC patients who progress after first-line treatment (65). The OS for these second line therapies ranged from 5.5 to 8.3 for chemotherapy and 5.3 to 6.7 for erlotinib (15, 24, 34, 73). Some differences exist among these therapies. Pemetrexed has shown a similar efficacy to docetaxel in

second-line setting but with a significantly better toxicity profile (34). Efficacy of pemetrexed compared to docetaxel according to histology has been reviewed (71) and this favored pemetrexed specifically in large cell carcinoma, although this histologic category has been revised subsequently (77). The TITAN trial reported that erlotinib was equivalent to pemetrexed or docetaxel in refractory patients (progression during first-line chemotherapy) unselected for EGFR status (15). In molecularly selected wild-type (wt) EGFR population, the TAILOR trial showed that docetaxel was superior to erlotinib as second-line therapy with respect to OS and progression free survival (PFS) (24). However, in the subset analysis of EGFR-wt tumors, the DELTA trial failed to demonstrate a gain in OS for docetaxel *vs*. erlotinib (42), reinforcing erlotinib as a potential second-line treatment option independently of EGFR status.
Currently, the efficacy of approved drugs for second-line treatment in NSCLC or their response rate are limited and new treatment options are awaited.

Tumor angiogenesis is critical for tumor progression. Recently two randomized Phase III trials have tested the efficacy of antiangiogenic therapies in second-line for advanced NSCLC. The LUME-lung 1 trial (64) was conducted in 1314 patients and demonstrated that docetaxel plus a multi-antiangiogenic (VEGFR, PDGFR, FGFR) angiokinase inhibitor, nintedanib, improved PFS, the primary endpoint of the trial (3.4 mo. *Vs*. 2.7 mo., HR 0.79, 95%CI 0.68-0.79, p=0.0019). Although an OS benefit was not noted in the study population (10.1 mo. *Vs*. 9.1 mo., HR 0.94, 95%CI 0.83-1.05, p=0.27), in the hierarchical analysis, nintedanib plus docetaxel significantly improved OS in the subgroup of adenocarcinomas (12.6 mo. *Vs*. 10.3 mo., HR 0.83, 95%CI 0.7-0.99, p=0.0359), as well as in those adenocarcinoma tumors with a more aggressive behavior (defined progression within 9 months of starting prior first-line therapy; 10.9 mo. *Vs*. 7.9 mo., HR 0.75, 95%CI 0.6-0.92, p=0.0073). Toxicity grade 3 or higher was more common in combination arm than monotherapy (31.3% vs. 26.7%, mainly diarrhea, and reversible increase in transaminases) (64), however, it did not have an impact on patient self-reported QoL (56). The OS benefit with nintedanib and docetaxel may have been optimized by the fact that the population included in the trial–was highly selected (the study excluded patients with brain metastasis or radiological evidence of blood vessel involvement or cavitation or with hemoptysis or thrombosis; and median age was only 60). These results have led to the approval of nintedanib in Europe, not in the US (as of April 2015) as second-line treatment in combination with docetaxel in locally advanced or metastatic NSCLC patients.

Another product, ramucirumab, a monoclonal antibody anti VEGFR-2 was tested in the REVEL trial (25, 61). A total of 1253 patients were included in this Phase III study and the addition of ramucirumab, to standard therapy with docetaxel improved OS, the primary endpoint of the trial, (10.5 mo. *Vs*. 9.1 mo., HR 0.86, 95%CI 0.75-0.98, p=0.023), PFS (4.5 mo. Vs. 3 mo., HR 0.76, 95%CI 0.68-0.86, p<0.0001) and overall response rate (ORR: 23% *vs*. 14%, p <0.001), without detrimental effect on quality of life. Ramucirumab has been approved in this indication by FDA but not by EMA (as of April 2015).

Immunotherapeutic approach has been tested in the treatment of NSCLC. Several Immune checkpoint inhibitors (ICIs) exist (such as CTLA-4 and programmed death 1 (PD-1) receptor) which dampen the T-cell immune response to antigens expressed by tumor cells. Checkpoint

inhibition with Ipilimumab, a monoclonal antibody against CTLA-4, has been tested in NSCLC and reported a significant improvement in immune-related PFS compared to placebo when administered concomitantly with chemotherapy (47). The PD-1 receptor is another checkpoint molecule expressed on activated T cells and engaged by ligands PD-L1 and PD-L2, which are expressed by tumor cells and infiltrating immune cells. Tumor PD-L1 expression is prevalent in NSCLC, and the interaction of PD-1 with the PD-L1 and PD-L2 ligands inhibits T-cell activation and promotes tumor immune escape. In 2015, two randomized Phase III trials have reported the efficacy of nivolumab, a fully human IgG4 monoclonal antibody antiPD-1, in advanced NSCLC patients who had disease progression during or after first-line chemotherapy. In squamous NSCLC subtype, 272 patients were randomized to nivolumab (3 mg/kg every 2 weeks) or docetaxel (75 mg/m$^2$ every 3 weeks). Nivolumab reported a significant improvement in OS over docetaxel (9.2 months *vs*. 6 months, p<0.001), with 1-y OS of 42% versus 24%, respectively. The response rates were also significantly improved with nivolumab compared with docetaxel, 20% vs. 9%, respectively (p=0.008) (10). Nivolumab has been approved by FDA and EMA for 2$^{nd}$ line treatment of stage IV squamous cell NSCLC following results of this trial. In the second Phase III trial, 582 non-squamous patients were randomized to nivolumab or docetaxel at the same schedule. Nivolumab significantly improved OS (12.2 months *vs*. 9.4 months, p= 0.0015), 1-yOS (51% *vs*. 39%) and median duration of response (17.1 months *vs*. 5.6 months) compared to docetaxel, respectively (60). In both trials the toxicity profile was in favor of nivolumab. Of note, in squamous subtype, the expression PD-L1 was neither prognostic nor predictive of benefit with nivolumab. However, in non-squamous histology, PD-L1 expression was a predictive marker of efficacy of nivolumab. The full results of this trial (8) led to approval of Nivolumab by FDA in non-squamous NSCLC as well. These results reinforce immunotherapy as a new strategy in the treatment of NSCLC patients.

Other ICIs have been tested in NSCLC. Pembrolizumab, an anti-PD1 inhibitor, has been tested in a phase I study in advanced NSCLC patients. Pembrolizumab reported an objective response rate of 19.4% with a median duration of response of 12.5 months, with an acceptable toxicity profile. In those patients with high expression of PD-L1 (expression in at least 50% of tumor cells) the response rate was 45.2% with a median PFS of 6.3 months, suggesting that the expression of PD-L1 correlated with improved the efficacy of pembrolizumab (26). The updated results of this trial in 101 treatment-naïve PD-L1+ NSCLC patients reported an ORR of 24% and a median PFS of 6 months with no significant between-dose differences, with the greatest efficacy observed in patients with PD-L1 staging in ≥ 50% of tumor cells (70). Preliminary results of pembrolizumab in a Phase II trial in 10 advanced NSCLC patients with untreated asymptomatic brain metastasis has reported a 44% and 34% of brain and systemic response rate, respectively (31). The results of the Keynote 010 trial led to approval of pembrolizumab in patients with NSCLC with PD-L1 expression on at least 1% of tumor cells as both doses tested improved OS over docetaxel with a favorable benefit risk ratio (36).

Two anti-PD-L1 antibodies, atezolizumab (MPDL3280A) and durvalumab (MEDI4736), have been tested in NSCLC. Updated results of atezolizumab in a phase I trial with 88 advanced NSCLC patients, reported an ORR of 21%, with a median duration of response of 67 weeks and 1-year OS of 82%. PD-L1 expression in the tumor microenvironment appeared to be a

predictive biomarker for MPDL3280 clinical efficacy (38). In a single arm Phase II study in 205 PD-L1 selected patients with NSCLC, atezolizumab have reported clinical efficacy in both chemo-naïve and previously treated patients (ORR 29% and 17%, respectively) and some evidence of clinical efficacy in previously treated patients with asymptomatic brain metastases (75). In a randomized Phase II trial (POLAR study) with 287 previously treated NSCLC patients, atezolizumab has been compared to docetaxel. Atezolizumab has reported a trend toward OS improvement (11.4 months *vs*. 9.5 months, HR 0.77; 95 CI 0.55-1,06, p=0.11) with an improved overall survival benefit observed with increasing PD-L1 expression (76). The complete results of the POPLAR study were published later by Fehrenbacher et al (19).

Eventually the OAK Phase III study in 2nd or 3rd line therapy of advanced NSCLC showed improved median OS (13.8 *vs* 9.6 months) with atezolizumab compared to docetaxel (68).
In 198 NSCLC patients, MEDI4736 administered at 10 mg/kg IV every 2 weeks until unacceptable toxicity, disease progression, or for up to 12 months, has reported an ORR of 16% (27% in PD-L1+ and 5% in PD-L1-), and DCR at 12 weeks of 42%. The ORR was higher in squamous (21%) than non-squamous (13%) patients. The duration of response ranged from 0.1 to 54.4 weeks. Preliminary OS data suggests that PD-L1+ patients appear to have improved OS compared with patients with PD-L1- tumors (NA vs. 8.9 months) (69).

All of these results suggest immunotherapy as an important therapeutic approach in NSCLC patients and thus our study will consider previous checkpoint inhibitor therapy as a stratification criterion for randomization.

New results have been published and address the possible benefit of using immune checkpoint inhibitors in 1st line therapy of advanced NSCLC. These results are conflicting with very positive results for anti PD-1 therapy with pembrolizumab in patients with PD-L1 expression over 50% of tumor cells (66) but not with anti PD-1 therapy with nivolumab in patients included whatever was the level of PD-L1 expression (28). Yet, various combination therapies may be beneficial with reports by Hellmann et al (35) or Langer et al (45). Thus, it has been advised by the Steering Committee of our study during its December 13th 2015 session that there should be an amendment to the current protocol to allow for inclusion of patients treated with checkpoint inhibitors alone or in combination as 1st line therapy and that patient should anyhow be offered also platinum-based chemotherapy (1st or 2nd line) before entering the trial. This led to version 3.0 of the protocol.

Numerous studies evaluating ICIs as stand-alone and in combination are ongoing in early stage. In 2017, durvalumab as maintenance treatment for one year after radical treatment with concurrent chemo-radiotherapy in locally advanced unresectable NSCLC showed an improvement in median time to death or distant metastasis of 23.2 months in durvalumab arm vs. 14.6 months in placebo arm (1).

In 2019, immunotherapies play an important role in the treatment of NSCLC (62). Since 2015, four anti PD-(L)1 monoclonal antibodies (nivolumab, pembrolizumab, atezolizumab and durvalumab), alone and in combination with various compounds (i.e. ipilimumab, or

chemotherapy ± bevacizumab), have consistently demonstrated a superiority of overall survival in first and second-line treatment in advanced NSCLC and in locally advanced unresectable NSCLC. Overall, in advanced NSCLC, a meaningful improvement of long-term OS rate at 3 and 5 years of 25% is maintained with ICIs (62).

This major improvement in therapy, albeit with limited response rate (10, 60) when ICI are used as monotherapy, led us to consider that, where available, checkpoint inhibition would be offered before moving to investigational therapy and thus that the current Phase II/III target should include 2nd or 3rd line therapy in patients with no therapeutic alternative after failure of platinum and immune checkpoint inhibition. In 2018, data of durvalumab + tremelimumab were reported in 78 immunotherapy-pretreated advanced NSCLC patients (27). 94% of patients received ≥ 2 lines of prior therapy including PD-1 or PD-L1 inhibitors. 40 (51%) patients "relapsed" after ICI (defined as responders, then progression; prior median time to progression of 7 mo) and 38 (49%) were "refractory" to previous ICI (defined as no response; prior median time to progression of 2.6 mo). The combination durvalumab + tremelimumab was manageable. Severe (Grade 3 and 4) related AEs occurred in 28% of patients, with diarrhea (6%) being most common. 5 patients (6%) discontinued due to a treatment-related AE. No treatment-related deaths were observed. Objective response rate was reported in 4 (5.1%) patients [2(5%) patients in relapsed group, 2(5.3%) patients in refractory group]. Median progression-free survival (PFS) was 1.8 mo (95% CI; 1.6-2.5) [2.5 mo (95% CI; 1.6-3.5) in relapsed group, 1.7 mo (95% CI; 1.6-1.7) in refractory group]. Median overall survival (OS) was 8.4 mo (95% CI; 6.2-10.4) [8.5 mo (95% CI; 4.0-14.3) in relapsed group, 8.3 mo (95% CI; 6.0-10.4) in refractory group. OS rate at 12 months was 34.1% (37.5% in relapsed group, 30.1% in refractory group).

These limited data comfort our current statistical assumption that an OS-rate at 12 months of 40% is a relevant efficacy target in this population. However, the continuation of the study in Step 2 which plans to demonstrate a better survival of OSE2101 over the control group (HR 0.7), will be discussed at the end of Step 1 between the steering committee (SC) and the Sponsor based on the recommendations of the independent data monitoring committee (IDMC). Since the start of the study in 2015, there have been major forward advances in the management of NSCLC. The decision of continuing the study in Step 2 (Phase 3) will consider the expected benefit of OSE2101 as well the relevance of the specific design of the Phase 3 in regards of the state of the art in the management of advanced NSCLC known at time of the analysis (see Section 6.7).

Moreover, different vaccines have been designed for specific peptide epitopes in NSCLC (79). In the adjuvant setting, the Phase III MAGRIT trial did not report improvement in disease free survival with the recMAGE-A3 + AS15 cancer immunotherapeutic (MAGE-A3 CI) as adjuvant therapy compared with placebo in patients with stage IB-IIIA completely resected MAGE-A3-positive NSCLC, even in the population who did not receive adjuvant chemotherapy (78). In locally advanced disease, the Phase III START trial, randomly assigned 1,513 patients with unresectable stage IIIB NSCLC following definitive chemoradiation to L-BLP25 (liposomal vaccine) with best supportive care (BSC) or placebo plus BSC. The trial failed to meet its primary endpoint of improved OS with L-BLP25 (25.6 vs. 22.3 months for placebo; P=0.123)

(13). In advanced disease, different vaccines have been tested such as Belagenpumatucel-L (54), EGF vaccine (32), TG4010 vaccine (TIME trial) (63) or IDO vaccine (40). However, heterogeneity of tumor-associated antigen (TAA) expression, the potential for tumor associated antigen (TAA) loss, and variability of the human T-cell repertoire suggest that effective cancer T-specific immunotherapies require induction of a wide breadth of cytotoxic T lymphocytes (CTL) specificities. This can best be achieved with T-specific immunotherapies targeting multiple TAAs.

## 1.2 OSE2101

The OSE2101 T-specific immunotherapy was designed to induce CTLs against five TAAs frequently overexpressed in NSCLC (i.e. carcinoembryonic antigen [CEA], p53, HER-2/neu, and melanoma antigens MAGE2 and 3). These TAAs have been used alone in previous studies involving NSCLC patients. OSE2101 is composed of 10 synthetic peptides from these TAAs, nine of the peptides representing CTL epitopes and one pan-DR epitope. Each CTL epitope is restricted by HLA-A2.1 and at least one other member of the HLA-A2 superfamily of major histocompatibility complex class I molecules. HLA-A2 phenotype is expressed by approximately 45% of the general population as well as cancer patients. These epitopes being HLA-A2 restricted means that they can bind only HLA-A2 molecules to be presented to the T-lymphocyte and thus, can only be effective in patients having HLA-A2 phenotype.

The pan-DR epitope (PADRE) is a rationally designed helper T-lymphocyte (HTL) epitope included to augment the magnitude and duration of CTL responses (5). The innovation is to associate epitopes designed and modified chemically (analogs), of different tumor antigens in the same combination. Some of these analogs will increase the HLA-A2 binding and others will increase the T cell receptor binding.

It was previously demonstrated that all of the epitopes selected were immunogenic. The utility of the analog peptides was further documented, as the CTLs generated were capable of recognizing wild-type epitopes expressed on tumor cell lines. Moreover, others have demonstrated measurable recall or post-vaccination CTL responses against most of the nine CTL epitopes (including the wild-type versions of analogs in the current product). The immunogenicity of OSE2101 after in vivo immunization was also demonstrated in HLA-A2.1/Kb transgenic mice, which express the human HLA-A2.1 molecule (refer to investigator brochure)

### OSE2101 clinical trials

In two phase I trials in stage IIB-IIIA NSCLC (NCT00054899) and stage III colon cancer (NCT00054912) patients, subcutaneous OSE2101 was administered at 5 mg peptide/dose at 3-week schedule for a total of 6 doses. The objectives were to evaluate the safety and immunogenicity of OSE2101 measured by IFN-γ ELISPOT assays. A total of 16 out of 24 enrolled patients completed six injections over 18 weeks (6 out of 10 NSCLC patients, and 10 out of 14 colon cancer patients).

The most common adverse event in the 24 patients who received at least one dose of the

OSE2101 was reaction at the site of injection (erythema, pain, granuloma, and induration). Other side effects were: fatigue, rigors, nausea, vomiting, arthralgia, myalgia, pain in the extremities and dyspnea. Only 1 out of 24 patients reported an immune-related adverse event with a cytokine release reaction (fever, chills, chest pain, nausea and apnea) that was resolved within 24 hours of hospitalization**.**
A strong CTL response was observed in the majority of patients tested.
Immune response was defined in the protocol as one (or more) epitope-specific response greater than two standard deviations above background values as assessed by the ELISPOT assay. 15 out of 16 patients receiving 6 injections were responding (93%) indicating that the T-specific immunotherapy was immunogenic and effective at inducing strong and broad CTL responses in a high frequency of patients (only one patient out of the 16 failed to respond to the T-specific immunotherapy, the expression of a less cross-reactive subtype in the HLA-A2 supertype family, HLA-A*0207, most likely accounted for the lack of immunogenicity in this patient). With respect to breadth of responses, eight of the 15 patients generated CTL responses to over half (five or more) of the epitopes in OSE2101 and, on average, each patient induced CTL responses to approximately four epitopes.

In NSCLC patients, HLA-A2 is expressed as in the general population (22, 74) and is thought to be between 40 and 50%. Interestingly, HLA-A2 positivity appears as being an independent negative prognostic factor in cancers (48) and also in NSCLC: the role of HLA-A2 measured by blood sampling has been established by different and independent teams in large series of patients. Serological HLA-A2 expression appears as an independent risk factor of lymph node involvement and distant metastasis (12, 51, 47). However, a more recent analysis has shown that the HLA-A2 status was not identified as a prognostic factor in a large advanced NSCLC population treated with platinum-based chemotherapy (84).

A Phase II, open-label, multicenter, single dose-group, multiple administration study of OSE2101 in patients with HLA-A2 positive advanced NSCLC was performed (NCT00104780) (4, 53, 54).
The study was designed to evaluate the safety, efficacy (response and survival), and immunogenicity of OSE2101 in patients with advanced NSCLC who were HLA-A2 positive. The T-specific immunotherapy was administered subcutaneously at a dose of 5 mg every 3 weeks for the first 15 weeks, then every 2 months through year 1, then quarterly through year 2, for a total of 13 doses.
Patients were to be followed at three months after the last injection. Survival status was then to be ascertained every three months through year three then annually until year five.
Tumor assessment was performed at baseline with reassessment at weeks 9 and 18 and at months 6, 9, and 12. Leukapheresis was performed before vaccination (at screening) and at weeks 9 and 18 to obtain sufficient cells to conduct the immunogenicity assays. Hematology, electrolytes, liver, other organ functions, urinalysis, and antinuclear antibody titer were assessed. Toxicity was monitored and graded according to the National Cancer Institute Common Toxicity Criteria. All patients signed the protocol-specific local institutional review board approved informed consent form. Response Evaluation Criteria in Solid Tumors were used to evaluate response.

Eligible patients for this study were 18 years or older with histologic confirmation of stage IIIB or IV or recurrent NSCLC. Patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1, an absolute granulocyte count ≥ 1,500/µL, platelet count ≥100,000/µL, hemoglobin ≥ 10 g/dL, total bilirubin ≤ 2 mg/dL, AST and ALT 2 ≤ 5 times the upper limit of normal, and serum creatinine ≤ 2 times the upper limit of normal. Patients with brain metastases were eligible if the disease was clinically stable for at least 2 months before study entry.
A second group of patients who were HLA-A2 negative when screened for the study were identified to use as an observational comparator group. The patients were assessed for survival via access to the social security death index.

Overall survival was estimated using the Kaplan-Meier method. Progression-free survival was to be determined from time of patient registration to date of progression, death or last assessment of tumor response.

To measure CTL responses, $2*10^6$ peripheral-blood mononuclear cells (PBMCs)/well (three to four wells per epitope) were stimulated in vitro with each peptide (10 µg/mL). Ten U/mL of rIL-2 was added after 24 hours. After 10 days of culture, the in vitro–expanded PBMCs were tested for epitope-specific (T-specific immunotherapy epitope and wild-type epitope of an analog) CTL responses, measured by an 18-hour interferon gamma ELISPOT assay.
Immune response relationship to survival was done by comparing the number of epitopes with measurable enzyme-linked immunosorbent spot assay (ELISPOT) responses in relation to survival using the log-rank statistic.

*Results:*
A total of 135 patients were enrolled; 64 patients were positive for HLA-A2 and 72 patients were HLA-A2 negative with the information provided only for survival.

The 64 HLA-A2 positive patients were treated with one or more dose(s) of OSE2101 and represent the ITT population and the safety population. Of these 64 treated patients, 31 (48%) completed the treatment phase and 11 (36%) subsequently completed the follow-up phase.

The majority of the early withdrawals from the treatment phase (27%, 17/64 patients) as well as from the continuation and follow-up phases (19%, 12/64) were due to disease progression and/or decline in health status. Eight patients (13%) completed all phases of the study. Four patients (6%) withdrew from the study due to an AE.
The characteristics of the 64 HLA-A2 positive patients were as follows:

- Median age 64 (26-87)
- Male 55%; Female 45%
- Caucasian 83%, African American 9%, Asian 8%

The majority of patients (43/64, 67%) had Stage IV NSCLC at inclusion. The median number of days since first diagnosis was 416 (range of 74 to 1921 days).
Prior treatment lines for OSE2101 treated patients were:

- one previous line in 31% of patients;

- two previous lines: 28%
- 3 or more previous lines (up to 6 lines): 37.5%

92% of the treated population had previously received a platinum-based chemotherapy and 34% a TKI (gefinitib or erlotinib).
6 patients (9.4 %) had received previous radiotherapy for brain metastasis.
18 patients were considered as progressive disease at entry, representing 28% of this treated OSE2101 population.
The HLA-A2-negative non-treated population demographics were similar to the HLA-A2 positive treated population: 72 patients: age 65 (33- 91); male 37 (51%), female 35 (49%); Caucasian 57 (79%). One out of the 72 patients was lost of follow-up.

*Overall survival*
Median survival for HLA-A2-positive treated patients was 17.3 months. In the HLA-A2-negative non-treated group, the median survival was 12.0 months.
One-year survival in OSE2101 treated patients was 60%, compared to 49% in the HLA-A2-negative group (53). The two-year and three-year survival estimates for OSE2101 treated patients were 39% and 27%.

*Clinical evaluation on the 64 HLA-A2+ treated patients (ITT population)*
One patient had a complete response and one a partial response. Stable disease of 3 months or greater was observed in 54 (86%) additional patients, translating into a clinical benefit in 89% of patients. Seventeen (27%) patients continued treatment for one year and demonstrated no evidence of progressive disease. Fourteen (22%) patients completed two years of dosing and remained without evidence of progressive disease.
Progression free survival was 285 days (median time to progression)

*Immune Response*
Immune response was assessed in 33 treated patients.

All 9 epitopes were immunogenic in at least 1 patient. Five epitopes showed strong responses that cross-reacted with wild type (WT) peptide. In analyzing the strongest 5 epitopes, 91% of patients demonstrated CTL epitope response to at least one antigen. Eighty-five percent demonstrated responses to 2 or more, 64% to 3 or more, 39% to 4 or more, and 18% to 5 or more.

Correlation with survival was demonstrated in patients generating immune response.
Longer survival was correlated with a higher number of positive epitopes (response was assessed by ELISPOT for the 5 strongest, CEA24, CEA605, HER2.369, MAGE2.157 and MAGE3.112). The Log Rank test showed decreased survival among those with a low immune response level compared to those with a medium or high immune response level ($p<0.001$).

- Low: 0-1-epitopes: 406 ± 58 days of survival (n=5; 95% CI for mean 292 -520)
- Medium: 2 to 3-epitopes: 778 ± 72 days of survival (n=15; 95% CI for mean 637 -919)
- High: 4 to 5-epitopes: 875 ± 67 days of survival (n=13; 95% CI for mean 743- 1007).

Interferon-γ producing helper T cells against PADRE were detected in 18 of 33 (55%) patients tested in a direct ELISA assay.
The durability of the CTL induction was also demonstrated by responses to 4 of 5 epitopes in 3 of 4 patients tested at 12 months.

In conclusion, the OS difference observed is 17.3 months of median OS in the OSE2101 treated group versus 12 months in the observational HLA-A2 negative group. The OS rate at one year was 59% in the treated HLA-A2 positive group versus 49% in the observational HLA-A2 negative group. The HLA-A2 observational group represents a "worst case" control group given that the prognosis is superior to the treated HLA-A2 positive group. The data collected from the observational group is adequate to allow a meaningful comparison of one-year OS to the OSE2101 treated group. The median survival achieved is important for the OSE2101 Phase II highly pretreated population (65.5% received more than 2 lines, 92% received previous platinum-based chemotherapy). The median survival for the three registered treatments (docetaxel, pemetrexed and erlotinib) after first line therapy is approximately 8 months and the one-year survival rate is 33%. In the OSE2101 Phase II, longer survival was significantly correlated with a higher number of positive epitopes. Furthermore, the long–term survival achieved at 4 years for the treated patients was complemented by a favorable safety profile.

These OSE2101 clinical data support a recommendation that OSE2101 move forward to a Phase III trial in HLA-A2 positive patients with advanced NSCLC who have previously failed first or subsequent line of therapy.

Additional information on OSE2101 is available in the investigator's brochure.

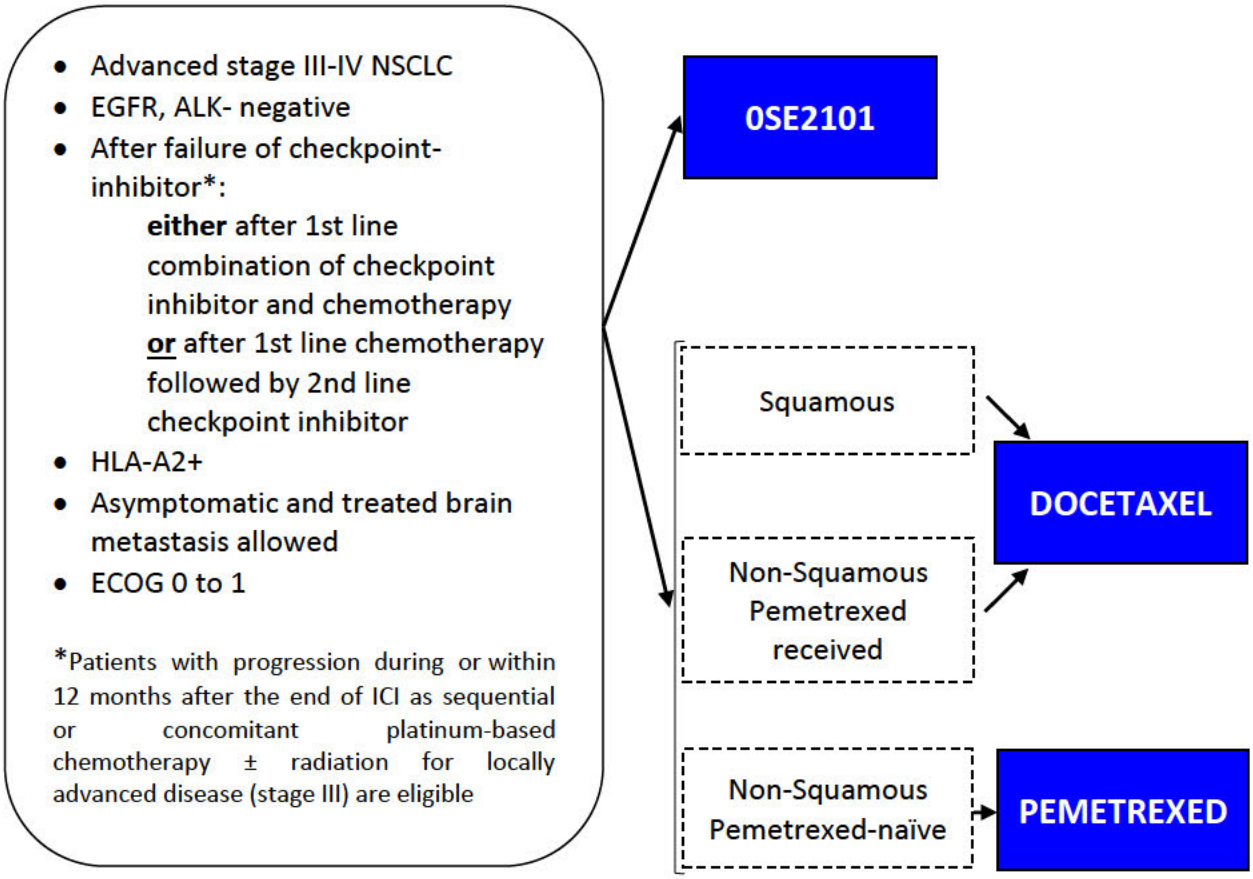
### 1.3 Design considerations

Target indication:
Based on the Phase II OSE2101 results and ESMO and ASCO treatment guidelines (2, 3, 65, 62), the targeted population in a Phase III trial should be patients with stage III unsuitable for radiotherapy or metastatic stage IV NSCLC in second- or third-line treatment. Since 2015, immunotherapies (PD-(L)1 ± CTL-A4 inhibitors) play an important role in the treatment of NSCLC with a meaningful improvement of long-term OS rate at 3 and 5 years of 25% in advanced disease. More recently in 2017, durvalumab as maintenance treatment for one year after radical treatment with concurrent chemo-radiotherapy in locally advanced unresectable NSCLC shown an improvement in median time to death or distant metastasis of 23.2 months in durvalumab arm vs. 14.6 months in placebo arm (1). This major improvement in therapy, albeit with limited response rate (10, 60) when used as monotherapy, led us to consider that, where available, checkpoint inhibition would be offered before moving to investigational therapy and thus that the Phase III target should include 2$^{nd}$ or 3$^{rd}$ line therapy in patients with no therapeutic alternative after failure of platinum and immune checkpoint inhibition.

Therapy:
Reference therapy should be available and approved alike in the US and Europe as the trial extent needed to reach these 2 regions and thus only docetaxel and pemetrexed meet this

criterion (2, 3, 65), docetaxel being reference in squamous cancer and pemetrexed having a better safety profile combined with proven efficacy in non-squamous NSCLC. Thus, treatment will be allocated as shown in Figure 1

**Figure 1: Control group treatment allocation**




With respect to duration of treatment in the Phase II trial for OSE2101 treatment was administered for 2 years (13 injections). As some patients had longer survival (over 4 years) and as safety profile was good, it is proposed that study treatment with OSE2101 should continue on a 12-weekly basis, beyond 2 years, provided individual benefit to the patient is shown. With respect to reference therapy docetaxel needs usually to be stopped for safety reasons often after 6 cycles but pemetrexed is usually continued as long as patients benefit. Patients will continue the study with the assigned study treatment until RECIST1.1-defined progression of disease as determined by the investigator, unacceptable toxicity or consent withdrawal. Pseudo-progression has been reported with immunotherapy in cancer patients, be it related to initial increased inflammation or delayed response to treatment. Investigators should consider this possibility in patients treated with immunotherapy and may continue treatment as assigned beyond the time of RECIST-defined progression, at his discretion if the patient is perceived to be experiencing clinical benefit.

Randomization:
This Phase III study needs to be randomized but cannot be blinded as study treatment and reference therapies have different routes of administration, need concomitant therapy that would not be allowed for OSE2101 (steroids) and safety profile would easily help to recognize treatment allocated. Thus, the study will be open-labelled (not blind).
The design of the study needs to consider prognostic factors in the randomization process.
Although both patients with squamous and non-squamous NSCLC were included in the Phase II study for OSE2101, histology is a key prognostic factor as reference therapies do not have efficacy over the full range of NSCLC histologic subtypes. Pemetrexed for instance is not approved in squamous NSCLC, survival with docetaxel seems longer in non-squamous than in squamous cancer (10, 60) and some treatments (64) have positive results in non-squamous and negative in squamous.
Best response to chemotherapy is documented as a prognostic factor (59) although patients will only be included in the trial once 1st line chemotherapy failed.
Last, previous treatment with checkpoint inhibitors needs to be considered as 2nd or 3rd line therapy patients. They will be selected after failure of checkpoint-inhibitor regimens. Interaction between checkpoints inhibitors and T-specific immunotherapy with OSE2101 will have to be considered, supporting stratification as well on this criterion.

Thus, randomization will be stratified by:
- histology (squamous *vs.* non-squamous),
- best response to first line treatment (objective response: complete or partial response, *vs.* no objective response: stabilization or progressive disease), and
- *before protocol v4.0 only:* previous treatment with immune checkpoint inhibitors (yes *vs.* no).
- *from protocol v4.0*: line rank of previous treatment with immune checkpoint inhibitor (first line *vs.* second line).

Target endpoints:
As recommended in current FDA and EMA (18, 21) guidelines the primary endpoint will be overall survival, secondary endpoint will be linked to assessment of tumor response with a cancer vaccine (adding post progression survival and time to ECOG deterioration as secondary endpoints) but a specific attention will also be paid to quality of life as patient reported outcome and analyzed per EORTC guidelines (https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf) and the FDA Guidance on June 2021 "Core Patient-Reported Outcomes in Cancer Clinical Trials" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials).

## 2 STUDY OBJECTIVES

**Step 1 (Phase II): 2:1 randomized non-comparative one stage Fleming Phase II**

**Primary objective**

- To evaluate the overall survival (OS) rate at 12 months in HLA-A2 positive patients with advanced NSCLC as 2nd or 3rd line therapy after failure of checkpoint-inhibitor regimens

**Secondary objectives**

- To describe secondary measures of clinical efficacy including OS (median), disease control rate (DCR) at 6 and 12 months, Health-related Quality of life (QoL), progression free survival (PFS), objective response rate (ORR) and evaluate duration of response (DR)
- To assess the safety and tolerability
- To describe patient reported outcomes (PRO) disease/treatment-related symptoms of lung cancer

**Step 2 (conditional Phase III): 2:1 comparative randomized Phase III**

**Primary objective**

- To demonstrate that OSE2101 is superior to control treatment with respect to OS in HLA-A2 positive patients with advanced NSCLC as 2nd or 3rd line therapy after failure of checkpoint-inhibitor regimens; primary population will be the Population of Interest (PoI) defined as patients with secondary resistance to ICI and ICI 2nd line; sensitivity analysis will be done in all patients

**Secondary objectives**

- To compare secondary measures of clinical efficacy including Post Progression Survival (PPS), Time to worsening ECOG PS deterioration, Health-related QoL, DCR at 6 and 12 months, and PFS
- To assess the safety and tolerability of OSE2101 compared to the control treatment

**Exploratory objectives**

- To compare other efficacy criteria (ORR, DR), other QoL criteria, time to next lung cancer therapy and COVID-19 impact in both treatment arms.

# 3 ETHICAL CONSIDERATIONS

## 3.1 Ethics and Good Clinical Practice

The investigator must ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" and its amendments, and with the laws and regulations of the country in which the clinical research is conducted. This study must follow the ICH/GCP guidelines and applicable regulations and laws, including if applicable, the European Directive on Clinical Trials and the Code of Federal Regulations. The investigator agrees to the terms and conditions relating to this study as defined in the protocol, CRF and any other protocol-related documents.

The investigator fully understands that any changes without previous agreement with the sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on study subjects/patients (other than those procedures necessary for the wellbeing of the subjects/patients).

### 3.2 Ethics Committee/ Institutional Review Board

The investigator will submit this protocol and any related document provided to the subject (such as subject information used to obtain informed consent) to an EC/IRB. Approval from the EC/ IRB must be obtained before starting the study, and should be documented in a dated letter to the investigator, clearly identifying the trial, the documents reviewed and the date of approval. A list of members participating in the meeting must be provided, including the functions of these members. If study staff were present, it must be clear that none of these persons voted.

Modifications made to the protocol after receipt of the EC/IRB approval must also be submitted as amendments by the investigator to the EC/IRB in accordance with local procedures and regulations (see section 7.1.1).

### 3.3 Informed consent and subject information

It is the responsibility of the investigator to obtain signed informed consent from each of the subjects participating in this study before any study-mandated procedure, and after adequate explanation of the aims, methods, objectives and potential hazards of the study. The investigator must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. Appropriate forms for documenting written informed consent will be provided to the site prior to the study. The Informed Consent Form and Subject Information Sheet will be provided in the local language with validated translations as appropriate. One signed informed consent form will be kept by the subject, and one will be filed by the investigator in the investigator's file.

### 3.4 Governance of the study

A Steering Committee has been appointed by OSE Immunotherapeutics; it is comprised of investigators (national coordinators). Representatives of OSE Immunotherapeutics will attend the Steering Committee meetings. The Steering Committee is responsible for scientific validity of the protocol and will assess the study quality and conduct on a regular basis.

An Independent Data Monitoring Committee (IDMC) will review the safety and tolerability data and assess the risk/benefit ratio of the investigational drugs on a regular basis and give recommendations to the Steering Committee and the sponsor regarding continuation of the study.

## 4 INVESTIGATIONAL PLAN

### 4.1 Overall Study Design and Plan

- This is an open-label, multicenter, controlled, randomized, parallel group, 2-step design Phase II/III trial of OSE2101 (Arm A – experimental treatment) versus docetaxel or pemetrexed (Arm B – control treatments) as second or third line treatment in HLA-A2 positive patients with advanced NSCLC.
- Patients will be recruited and monitored in experienced oncology/pulmonology centers.

- Randomization to Arms A and B and will be stratified according to:
  - histology (squamous *vs.* non-squamous),
  - best response to first line treatment (objective response: complete or partial response, *vs.* no objective response: stabilization or progressive disease), and
  - and for new patients from version 4.0 of the protocol the 3rd stratification factor will be previous treatment with immune checkpoint inhibitors (used in 1st line *vs.* used in 2nd line).

  Treatment allocation will be made by IVRS/IWRS.
- The total study duration for an individual subject will depend on the survival of the subject, including the following periods:
  - **Pre-screening**: HLA-A2 testing (using PCR methods) can be done at any time before inclusion (a specific consent form is available).
  - **Screening:** 1 to 35 days before treatment administration.
  - **Randomization:** treatment allocation and baseline for OS calculations.
  - **Treatment:**
    - For OSE2101 (Arm A): Day 1 each 21-day cycle for 6 cycles, then every 8 weeks for the remainder of year one and, finally every 12 weeks beyond year one (*see Figure 2: Schedule of OSE2101 administration)*
    - For docetaxel or pemetrexed (Arm B): Day 1 each 21-day cycle (i.e. every 3 weeks)
    - In both arms, treatment cycles will be repeated until unequivocal RECIST 1.1-defined disease progression as determined by the investigator, unacceptable toxicity, or consent withdrawal. Should pseudo progression or delayed response to treatment suspected in arm A, investigator may continue treatment beyond the time of RECIST-defined progression, if the patient is perceived to be experiencing clinical benefit.
  - **End of treatment:** 4 weeks after the last treatment administration to obtain assessments from the 4 previous weeks.
  - **Post-treatment follow-up:** every 2 months after discontinuation of treatment for the post-treatment survival status.
- The study key time points are the following:
  - Randomization: when screening is completed, baseline for OS calculation
  - Day 1 Cycle 1 for treatment administration (performed in a time to allow for premedication if needed) and baseline for schedule of on-treatment tumor assessments.
  - Tumor assessments every 6 (± 1) weeks
  - Survival assessments after treatment stop every 2 months.
- Study duration

  The study design is built as a 2-step design. Analysis of the 1st step will decide whether the 2nd step is clinically relevant and analysis of the combined population included in Step 1 and 2 is planned when the target number of events is reached. However, the final analysis will exclude the 38 patients with previous ICI treatment randomized before the recruitment hold.

## 4.2 Study Population

### 4.2.1 Subject population

Patients will be enrolled into the clinical study after having been checked for their eligibility during the screening period.

### 4.2.2 Inclusion criteria

**Protection of study subjects and compliance**

1. Signed and dated informed consent document indicating that the patient has been informed of all the pertinent aspects of the trial prior to enrollment
2. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures

**Demography**

3. Female or male, 18 years of age or older

**Cancer Diagnosis and treatment**

4. Histologically or cytologically proven diagnosis of NSCLC that is locally advanced (stage III) unsuitable for radiotherapy or metastatic (stage IV) according to the 8$^{th}$ edition of tumor, node, metastasis (TNM) in Lung Cancer published by the International Union Against Cancer and the American Joint Committee on Cancer (11)
5. Subjects with disease recurrence or progression after therapy with an immune checkpoint inhibitor and platinum-based chemotherapy:
   - either 1$^{st}$ line chemotherapy followed by 2$^{nd}$ line checkpoint inhibitor
   - or 1$^{st}$ line combination of checkpoint inhibitor and chemotherapy

   Patients with progression during or within 12 months after the end of ICI as sequential or concomitant platinum-based chemotherapy ± radiation for locally advanced disease (stage III) are eligible
6. Subjects with measurable or non-measurable lesions
7. Subjects must express HLA-A2 phenotype as assessed serologically
8. Subjects must be considered suitable for chemotherapy with either single-agent pemetrexed or docetaxel
9. Subjects with brain metastases are eligible if treated (whole brain radiotherapy, stereotaxic radiotherapy, surgery) at least 3 weeks prior to initiation of study treatment and have no symptoms related to brain metastases for at least 2 weeks before initiation of study treatment and are not taking any forbidden medications (see Section 4.3.5 of the protocol)
10. Any prior chemotherapy, immunotherapy, hormonal therapy, radiation therapy or surgeries must have been completed at least 3 weeks prior to initiation of study treatment
11. Any toxicity from prior therapy must have recovered to ≤ Grade 1 (except alopecia)

**Clinical status**

12. ECOG performance status 0-1
13. Adequate organ function as defined by all the following criteria:
    - Albuminemia > 25g/L
    - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤1.5 x upper limit of normal (ULN) with alkaline phosphatase ≤ 2.5 x ULN, or AST and ALT ≤ 5 x ULN if liver function abnormalities are due to liver metastases
    - Total serum bilirubin ≤ 1.5 x ULN
    - Absolute neutrophil count (ANC) ≥ 1500/µL
    - Platelets ≥ 100000/µL
    - Hemoglobin ≥ 9.0 g/dL (in the absence of transfusion within 2 weeks from before randomization)
    - Creatinine clearance (based on modified Cockcroft-Gault formula) ≥ 45 ml/min.

### 4.2.3 Exclusion criteria

**Cancer Diagnosis and treatment**

1. Small-cell lung cancer/mixed NSCLC with small cell component or other neuroendocrine lung cancers (typical and atypical carcinoids, large-cell neuroendocrine carcinomas)
2. Patients with squamous cell carcinoma histology, and who had docetaxel as part of their prior chemotherapy will not be eligible for this trial
3. Current or previous treatment with investigational therapy in another therapeutic clinical trial (interrupted less than 4 weeks before study treatment initiation)
4. Patients whose tumor harbors EGFR gene mutation that sensitizes tumors to TKI (EGFR exon 18-21) or ALK rearrangement
5. Ongoing immunotherapy (checkpoint inhibition, antigen immunotherapy that would be scheduled to continue concomitantly to the study)
6. Spinal cord compression (unless treated with the patient attaining good pain control and stable or recovered neurologic function), carcinomatous meningitis, or leptomeningeal disease
7. Patients with squamous cell histology or non-squamous cell histology previously treated by pemetrexed with a contraindication for docetaxel with grade ≥ 2 neuropathy or hypersensitivity reaction to medications formulated with polysorbate 80 (Tween 80) as they could be randomly assigned to Arm B

**Medical history and clinical status**

8. Patients with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications

9. Treatment with corticosteroids in the last 3-week period before inclusion, except for topical, ocular, intra-articular, intranasal, and inhaled corticosteroids with minimal systemic absorption (*e.g.* with a dose ≤ 500 microgram beclomethasone equivalent for inhaled steroids), or steroid doses ≤ 10 mg daily prednisone equivalent which are permitted
10. A recognized immunodeficiency disease including human immunodeficiency virus (HIV) infection and other cellular immunodeficiencies, hypogammaglobulinemia or dysgammaglobulinemia; subjects who have hereditary, congenital or acquired immunodeficiencies
11. Patients with auto-immune disease, with the exception of type I diabetes or treated hypothyroidism
12. Patients with interstitial lung disease
13. Patients with active B or C hepatitis
14. Other malignancy: patients will not be eligible if they have evidence of other active invasive cancer(s) (other than NSCLC) within 5 years prior to screening (except appropriately treated non-melanoma skin cancer or localized cervical cancer, or other local tumors considered cured (e.g. localized and presumed cured prostate cancer)
15. Other severe acute or chronic medical or psychiatric conditions, or laboratory abnormalities that would impart, in the judgment of the investigator and/or sponsor, excess risk associated with study participation or study drug administration, and which would, therefore, make the patient inappropriate for entry into this study
16. Female patients must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of the trial and for at least 90 days after completion of treatment (See Appendix 4: Guidance on Contraception)
17. Male patients sexually active with a woman of childbearing potential must be surgically sterile or must agree to use effective contraception during the period of the trial and for at least 90 days after completion of treatment. The decision of effective contraception will be based on the judgment of the principal investigator (See Appendix 4: Guidance on Contraception)
18. Breastfeeding women
19. Women with a positive serum pregnancy test at screening

## 4.3 Study Drugs

### 4.3.1 Description, packaging and labelling

The investigational drug OSE2101 will be provided to the site in vials containing OSE2101 1 mg/mL suspension for emulsion for subcutaneous (sc) injection. It is manufactured in accordance with Good Manufacturing Practice (GMP) as required by the current GCP. It is packaged and labelled in accordance with GMP and local regulations.

Two kits (one for OSE2101 and one for Montanide), corresponding to a single administration, will be provided to the sites. Each OSE2101 kit will contain 1 vial of OSE2101 and all ancillary materials to prepare the full treatment for one single administration.

Control treatments (i.e. docetaxel and pemetrexed) will be market-approved presentations. Suppliers may vary according to country/center.

### 4.3.2 Storage

The investigational drug OSE2101 will be provided by the Sponsor as vials to be stored at -20°C/-4°F protected from light and the adjuvant Montanide ISA51™ will be provided as vials to be stored at 5°C/41°F.

Control treatments must be stored at room temperature according to manufacturer's recommendations.

### 4.3.3 Study drug administration

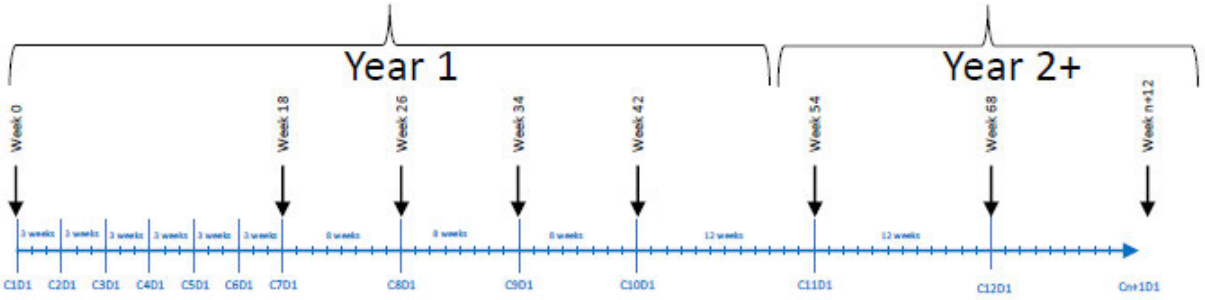
**Study treatment administration in Arm A (OSE2101)**

Study treatment to be injected will be prepared (emulsification) by the pharmacist within one hour of administration, according to a specific study drugs preparation manual.

Patients randomized to OSE2101 will receive 1 mL of OSE2101 administered subcutaneously on Day 1 every three weeks for six cycles, then every eight weeks for the remainder of year one and, finally every twelve weeks beyond year one until unequivocal RECIST 1.1-defined disease progression as determined by the investigator, unacceptable toxicity, or consent withdrawal. Should pseudo progression or delayed response to treatment suspected in arm A, investigator may continue treatment beyond the time of RECIST-defined progression, if the patient is perceived to be experiencing clinical benefit. (Figure 2: Schedule of OSE2101 administration).

It is intended that all OSE2101 injections be given at the same site (either the anterior thigh or deltoid region of the non-dominant arm).
If pain or granuloma formation prevents using the same site, other areas may be used. If the 1-mL injection cannot be given by a single injection, then it may be divided into two injections, preferably in the same lymph node drainage area.

**Figure 2: Schedule of OSE2101 administration**




OSE2101 treatment will be continued until unequivocal RECIST 1.1-defined disease progression as determined by the investigator, unacceptable toxicity, or consent withdrawal. Should pseudo progression or delayed response to treatment suspected, investigator may continue treatment beyond the time of RECIST-defined progression, if the patient is perceived to be experiencing clinical benefit.

Patients are to be monitored for at least 4 hours after each injection, in order to detect any immediate allergic reaction or later symptoms related to possible cytokine release syndrome with appropriate equipment and treatment which may be needed for immediate intervention.

Patients should be instructed to the risk of infrequent and delayed flu-like syndrome, malaise, fever, low blood pressure which would need to make contact with the investigator (refer to 5.8 Management of adverse events, dosing adaptations and risk minimization strategy and the Investigator's Brochure).

The investigator or his/her designee will administer the study drugs to the patients, exercising accepted medical practices. Under no circumstances will the investigator allow study drugs to be used otherwise than as directed by this clinical study protocol. All study drug administrations will be done under direct medical supervision.

**Study treatment administration in Arm B (control treatment)**

Patients randomized to docetaxel will receive standard approved NSCLC dose: 75 mg/m$^2$ in 1-hour infusion every 3 weeks. Docetaxel will be prepared as per the manufacturer's recommendations. Patients will also be required to take dexamethasone, 8 mg orally, twice daily, the day before, the day of and the day after docetaxel dosing. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities at the discretion of the investigator.

Patients randomized to pemetrexed will receive standard approved NSCLC dose: 500 mg/m$^2$ in 10-minute infusion every 3 weeks. Pemetrexed will be prepared as per the manufacturer's recommendations. Patients will also be required to take folic acid, 350-1000 µg orally daily beginning approximately 1 to 2 weeks before the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed. Vitamin $B_{12}$, 1000 µg, will be injected intramuscularly approximately 1 to 2 weeks before the first dose of pemetrexed and will be repeated approximately every 9 weeks until discontinuation. Patients will also be required to take dexamethasone, 4 mg orally, twice daily, the day before, the day of and the day after pemetrexed dosing.

**Cross-over in Arm B is not permitted**
Patients in Arm B (docetaxel or pemetrexed) cannot receive OSE2101 at time of treatment interruption whichever the cause.

### 4.3.4 Treatment Exposure and Compliance

Records of study drug used, and dosages administered will be kept during the study. Study drug accountability will be performed on an ongoing basis by the study staff and checked by the monitor during site visits and at the completion of the study.

### 4.3.5 Concomitant medications

**Patients in Arm A with OSE2101**
***Authorized:***
Subjects can use topical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption) with a dose ≤ 500 microgram beclomethasone equivalent. Steroid doses ≤ 10 mg daily prednisone equivalent are permitted.

Systemic steroids are only allowed for a brief (less than 1 week) course when prophylaxis (e.g., contrast dye allergy) or for acute treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen).

***Precautions:***
The potential for overlapping toxicities with radiotherapy and OSE2101 is not known currently: therefore, palliative radiotherapy is not recommended while receiving OSE2101.
If palliative radiotherapy is required, then OSE2101 should be withheld for at least 3 days before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs considered related to radiotherapy should resolve to Grade 1 prior to resuming OSE2101.

**Patients in Arm B**

Patients in Arm B will require premedication as per product information (refer to 3.3.3 study treatment administration in Arm B). Unless started earlier for other reasons, the premedication should start before day 1 of each cycle (i.e. day 1 of each cycle will be injection day for chemotherapy).

- **Patients in Arm B with docetaxel**

***Mandatory/Authorized:***
Patients will be required to take dexamethasone, 8 mg orally, twice daily, the day before, the day of and the day after docetaxel dosing. Intramuscular or intraperitoneal administration of dexamethasone with the same total dose as oral dexamethasone, or equivalent corticosteroids, will be allowed per country regulations. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities.

***Prohibited***
The following strong CYP3A4 inhibitors should be avoided for subjects receiving docetaxel during the study. This includes (but is not limited to): Ketoconazole, Itraconazole, Clarithromycin, Atazanvir, Indinavir, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, Voriconazole.

- **Patients in Arm B with Pemetrexed**

***Mandatory/Authorized:***
Patients will be required to take folic acid, 350-1000 μg orally daily beginning approximately 1 to 2 weeks before the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed.
Vitamin $B_{12}$, 1000 μg, will be injected intramuscularly approximately 1 to 2 weeks before the first dose of pemetrexed and will be repeated approximately every 9 weeks until discontinuation.
Patients will also be required to take dexamethasone, 4 mg orally, twice daily, the day before, the day of and the day after pemetrexed dosing. Intramuscular or intraperitoneal administration of dexamethasone with the same total dose as oral dexamethasone will be allowed per country regulations.

***Precautions:***
Refer to product labelling/SPC

**Patients in Arm A or Arm B**
***Authorized palliative radiotherapy***
Only non-target bone lesions that do not include lung tissue in the planned radiation field or CNS lesions may receive palliative radiotherapy while on study treatment.
Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. Subjects requiring palliative radiotherapy should be assessed for disease progression. Subjects considered as having progressive disease should be considered for discontinuing study treatment, except if the patient is perceived to be experiencing clinical benefit.

***Prohibited for all patients***
The following are prohibited for all subjects during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated above in "allowed concomitant medication")
- Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, surgical resection of lesions, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC). Unless a localised progression with a global control of the disease with a clinical benefit for the patient and under discretion of the investigator, may warrant continuing study treatment should be discussed with the sponsor.

***Authorized***
Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates and RANK-L inhibitors) is allowed if initiated prior to first dose of study treatment (prior radiotherapy must have been completed at least 3 weeks prior to initiation of study treatment).

#### 4.3.6 Study instructions, restrictions and exclusion period

Subjects with active, known or suspected autoimmune disease cannot be enrolled. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

### 4.4 Study premature discontinuation and withdrawal

#### 4.4.1 Premature discontinuation

Subjects who will prematurely discontinue the study for example for an AE will undergo whenever possible the study assessments scheduled at the end of treatment visit.

A subject will be considered as withdrawn from the study if, and only if, he/she has withdrawn his/her consent. The potential follow-up of subjects after their withdrawal of consent will depend upon local regulations or specific agreement with the subjects. However, subjects who withdraw their consent after first study drug administration will be advised to undergo the study assessments scheduled at the end of treatment visit. They will be advised that participation to the end of treatment visit is voluntary but is in their best interest.
If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (eCRF) page.

In this study, overall survival is a key endpoint of the study. Post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required until death or the conclusion of the study. Tumor assessments should be continued until documented RECIST 1.1 disease progression. Cancer treatment received after discontinuation of study treatment must be recorded as well.

Subjects should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.

In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

### 4.4.2 Lost to Follow Up

A subject will be considered as lost to follow-up only after having exhausted all means of contact; all reasonable efforts must be made to locate subjects to determine and report their ongoing vital status.
Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes or emails as well as lack of response by the subject to one registered mail/letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.
If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

## 4.5 Treatment Assignment

### 4.5.1 Identification of subjects

The identification of subjects in this study is based on the obligation for pseudonomysation.

Eligible subjects will be assigned by the investigator a unique study number identifying the country, the site and the patient.

### 4.5.2 Randomization

Treatment assignment will be done through an IVRS/IWRS system. Phone number / Web address and information required for randomization (identification of the patient/center, criteria for inclusion, stratification and criteria for selection of appropriate Arm B treatment) will be specified in the study manual.

Subjects will receive OSE2101 (Arm A) or docetaxel or pemetrexed (according to histology and previous treatment, refer to Figure 1) (Arm B).
Before protocol 4.0, the randomization ratio was 1:1. From protocol 4.0, the randomization is 2:1.

Patients should be treated as soon as possible with the allocated treatment, and preferably within 15 days after randomization.

## 4.6 Study Endpoints

### 4.6.1 Efficacy endpoints

**Primary efficacy endpoint**:

- OS:

- In Step 1: OS rate at 12 months in experimental Arm A (OSE2101) in 84 evaluable patients exposed to OSE2101
- In Step 2: comparison of OS between experimental Arm A (OSE2101) and control Arm B (docetaxel or pemetrexed) when 278 events observed; due to early study discontinuation (219 patients included instead of 363 patients), statistical hypothesis was revised with a comparison between experimental Arm A and control Arm B in the PoI (refer statistical methodology section)

**Secondary efficacy endpoints** (in Steps 1 & 2):

- DCR at 6 and 12 months based on RECIST 1.1
- QLQ-C30 (EORTC QLQ questionnaire): "Global health status/QoL" score based on questions 29 (*How would you rate your overall health during the past week?)* and 30 (*How would you rate your overall quality of life during the past week?)* (in Step 1 only)
- QLQ-LC13 (lung cancer module from EORTC QLQ questionnaire): time to 1st ≥ 10-point deterioration in chest pain score (question 40), dyspnea score (question 33, 34, 35) or cough score (question 31) (in Step 1 only)
- Post Progression Survival
- Time to worsening of ECOG PS
- QLQ-C30 Global health status score change from baseline (in Step 2 only)
- QLQ-C30 Functional scores change from baseline (in Step 2 only)
- QLQ-C30 Symptom scores change from baseline (in Step 2 only)
- QLQ-LC13 Symptom scores change from baseline (in Step 2 only
- PFS based on RECIST1.1
- ORR (in Step 1 only)
- DR (in Step 1 only)

**Exploratory efficacy endpoints:**

In Step 2 only:

- ORR
- DR
- All the other scores of QoL
- COVID-19 impact

In Steps 1:

- TTD in patient reported chest pain
- TTD in patient reported dyspnea
- TTD in patient reported cough

In Steps 1 & 2:

- Time to next lung cancer therapy

### 4.6.2 Safety and tolerability endpoints

- Incidence, severity, seriousness and relationship to study treatments of adverse events (AE) and immune-related adverse events (irAE) and any laboratory abnormalities.

### 4.6.3 Exploratory translational endpoints

Patients who agreed to participate in this exploratory translational study, will have to sign a specific inform consent. Patient can agree to participate in all or some parts of the translational study. Patient can refuse to participate in the translational study without compromising his/her participation in the main study.

The predicted mode of action of OSE2101 includes to increase the tumor associated antigen (TAA) presentation of the multiple neoepitope OSE2101 vaccine and to increase the priming and activation of T cell in the intent to increase the recognition of cancer cell by specific T cells (5, 72).

The main objectives of the translational research in the present study are to explore biomarkers and pharmacodynamic parameters before and after the start of study treatment (OSE2101 or chemotherapy) in a population of NSCLC patients who progressed after ICI treatment (41, 67, 72).
Therefore, the following exploratory translational studies will be done:

**In blood samples:**

- Pre-, on-treatment and after treatment collection of peripheric blood mononuclear cells (PBMCs) for:
    - Immunophenotyping
    - OSE2101 vaccine antigen-specific T-cell frequency
- Pre-, on-treatment and after treatment collection of liquid biopsies (e.g. cell free DNA (cfDNA)):
    - Tumor Mutational Burden (TMB) and/or other mutation of interest (e.g. gene profiling of OSE2101 vaccine TAA)

Blood samples will be taken at baseline, then every 6 weeks until Cycle 7 (e.g. Day 1 of Cycles 3, 5 and 7), then every 12 weeks (e.g. at time of CT scan) until end of treatment and/or progression in all arms (see flow charts Table 1).

**In tumor tissue samples**:

- Specimens from archiving tumor biopsies (at first diagnosis and/or at any time before study entry) will be collected.
- If possible, a new tumor biopsy will be collected within 35 days prior to the first study treatment administration (during the screening period). An archiving tumor biopsy collected before the screening period is acceptable, should the biopsy be collected after the end of ICI treatment. A second tumor biopsy (e.g. in the same tumor site) will be undertaken between cycle 3 and cycle 6 and/or at time of the disease progression; *Of note*, a blood sample will be collected for Whole-Exome sequencing (WES) for:
    - Determination of HLA class I expression in tumor (e.g. HLA-A2 and Beta-2 microglobulin)

- Tumor and tumor microenvironment (TME) characterization by multiplex IHC and gene profiling (i.e. CD8-exhausted T cells, TIL infiltration…)

**Handling and shipping of blood and tumor samples for biomarkers analysis**
All blood and tumor samples will be stored in certified biobanks before being submitted to central laboratories for analysis. The procedure for collection, handling and shipping of the samples will be provided in a separate manual.

**Blood and tumor tissue banking for future biomarker analyses**

If the patient agrees, remaining specimens after analysis will be biobanked for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby. All sample will be stored at an external biobanking facility contracted by the Sponsor.

Participation in biobanking is voluntary and not a prerequisite for participation in the trial or in the translational study. Biobanking will only occur after patient agreed for biobanking and having signed the specific informed consent in accordance with local ethical and regulatory requirements. Samples and/or data may be transferred to third parties and other countries as specified in the informed consent form (ICF).

## 4.7 Study Assessment Procedures

The study assessments and their timing are depicted in Table 1 (Arm A) and Table 2 (Arm B). Informed consent must be obtained before any study related procedure. All assessments should be performed prior to dosing with study treatment unless otherwise indicated. All cycles are 21 days in duration.

### 4.7.1 Screening assessments

Screening assessments and procedures must be completed within 35 days of randomization, in accordance with Table 1 and Table 2:

- A complete medical history including oncology history (information on prior treatments and regimen) and concomitant medications
- HLA-A2 testing (if there are local results with PCR methods, they can be used for inclusion, but a central determination is required posteriori. If PCR methods is not available on local sites, a central determination of HLA-A2 testing is mandatory)
- EGFR & ALK determination, PD-L1 status: if there is not documented results in subject's medical file, a central determination is recommended if tumor tissue is available (see section 4.7.3)
- Tumor assessments: CT scan of thorax, abdomen and brain CT or brain MRI. CT scan of the pelvis will be performed only upon request according to clinical suspicion. In case of clinical suspicion of bone metastasis out of the area reported by CT scan, imaging test will be performed under discretion of the investigator. If imaging were realized as part as

routine practice before patient signed the ICF, these radiologic exams can be considered as baseline assessments if performed within 35 days of randomization

- Assessment of pretreatment signs and symptoms from the screening visit (at least from 14 days before randomization)
- Vital signs
- Physical examination
- ECOG performance status
- The safety laboratory (within 14 days prior to randomization):
    - Hematology: blood for complete blood count (CBC) with differential, including neutrophil and lymphocyte count
    - Biochemistry: serum for urea, creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, bicarbonate, glucose, LDH, bilirubin, ALT, AST, gamma GT, alkaline phosphatase, total proteins, albumin, TSH, free T3 and free T4
    - Coagulation: aPTT, PT/INR, fibrinogen
    - Virology: Hepatitis B (HBV HbsAg) and Hepatitis C (HCV RNA), HIV test
- Female subjects with child-bearing potential are required to have a negative serum pregnancy test at screening. The test should be repeated whenever one menstrual cycle is missed during treatment or a potential pregnancy is otherwise suspected.

Clinically relevant findings that exist prior to study treatment start must be recorded on the relevant Medical History CRF page.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified timeframe.

### 4.7.2 HLA-A2 testing

HLA-A2 testing can be done at any time before inclusion to screen potential patients. Remaining DNA will be stored until the end of the study for further HLA-A2 testing as necessary. A specific informed consent will be signed for this pre-screening.
HLA-A genotype will be determined centrally by PCR in all patients (laboratory to be specified in laboratory manual). If there are local results with PCR methods, they can be used for inclusion, but a central determination will be done posteriori. If PCR methods is not available on local sites, a central determination of HLA-A2 testing is mandatory. HLA-A2 positive phenotype is mandatory for inclusion.

This test is done on serum; one 4mL blood sample will be collected on an EDTA tube by venipuncture. Serum will be sent to central laboratory at ambient temperature.

All details on sample preparation and shipment will be described in the laboratory manual.

For patients who agreed (optional):
In order to be able to address future scientific questions, pre-screened patients will be asked to voluntarily donate remaining biospecimens for banking. If the patient agrees, banked samples may be used for future biomarker research and drug development projects (e.g. for future development a companion diagnostic).

### 4.7.3 EGFR and ALK determination, PD-L1 expression at screening

EGFR and ALK negative determination must be known before randomization. Patients must have their tumor screened for the absence of *EGFR* gene mutation that sensitizes tumors to TKI (EGFR exon 18-21) or ALK rearrangement. As per current recommendations EGFR and ALK determination need to be done only in patients with non-squamous cancer or never/light smokers (<15 pack*years) with squamous cancer.

PD-L1 expression will be documented if local test has been done or, if remaining tumor tissue for central determination is possible.

ALK *analysis*
ALK testing will be performed in local laboratories with validated tests. If not available on site, a central determination will be performed by a selected central laboratory, should tumor tissue available.
Samples will be FFPE blocks or slides.

*EGFR analysis*
EGFR testing will be performed in local laboratories with validated tests. If not available on site, a central determination will be performed by a selected central laboratory, should tumor tissue available.
Biopsy samples will be FFPE blocks.

*PD-L1 expression*
PD-L1 testing will be performed in local laboratories with validated tests. If not available on site, a central determination will be performed by a selected central laboratory, should tumor tissue be available.

Preparation and shipment details will be described in the laboratory manual.

### 4.7.4 Tumor assessments

CT scan of chest and abdomen and CT scan or MRI of the brain will be performed at screening. CT scan of the pelvis will be performed only upon request at screening according to clinical suspicion or during follow-up according to clinical suspicion or for monitoring purpose of identified target/non-target lesions. In case of clinical suspicion of bone metastasis out of the area included by the basal CT scan, radiological test will be performed under discretion of the

investigator. Then CT scan will be performed every 6 weeks after randomization with 1 week of allowance even it is between 2 study visits. Brain imaging must be included in subsequent tumor assessments if a patient has brain metastases, otherwise brain will only be evaluated when clinically indicated. **For Germany**, with respect to brain metastases, MRI should be the privileged imaging technic and CT should only be considered when there are contra-indications to MRI. Specific tests for bone metastasis are required every 12 weeks only if bone metastases are present at baseline or are diagnosed later, at investigator discretion. CT scan or MRI, where appropriate, should also be performed whenever disease progression is suspected (e.g. symptomatic deterioration).

If imaging were realized as part as routine practice before patient signed the ICF, these radiologic exams can be considered as baseline assessments if performed within 35 days of randomization.

### 4.7.5 Quality of life

The questionnaires EORTC QLQ-C30, QLQ-LC13 (specific to lung cancer) will be used in this study (see Appendix 2). These questionnaires must be self-administered by the patient on his/her own. These questionnaires will be proposed in the local language to the patient at each study visit. A member of the onsite clinical study team can help the patient if he/she does not understand the question but must not suggest or impose any answer.

The investigator will ensure that the questionnaires are complete and ask the patient to complete them should there be any missing answers.

### 4.7.6 Safety laboratory assessments

The safety parameters (Complete blood count with differential, Serum chemistry BUN or serum urea, creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, bicarbonate, glucose, LDH, total bilirubin, ALT, AST, gamma GT, alkaline phosphatase, total proteins, albumin, TSH, free T3 and free T4, aPTT, PT/INR, fibrinogen) will be measured by the local laboratories of investigational sites. All laboratories will provide OSE Immunotherapeutics or its designee with the name, professional degree and curriculum vitae of the laboratory director, the laboratory certification documents, validations methods, normal ranges, and all other appropriate documents. These laboratory references must be forwarded to OSE Immunotherapeutics or its designee before study start and updated whenever necessary.

### 4.7.7 Vital signs

It includes body temperature, blood pressure, heart rate, respiratory rate and oxygen saturation. Blood pressure (systolic and diastolic) will be recorded after 10 minutes resting in supine position. Oxygen saturation will be measured by pulse oximetry.

### 4.7.8 Physical examination

A complete physical examination including an examination of major body systems, height (baseline visit only) and weight is performed during the study.

### 4.7.9 ECG

Standard digital 12-lead ECG (at least 3 complexes for each standard lead) will be recorded with the subject in the supine position for a 10-minute period. ECG will include date, time, subject's identification, and physician's signature, and will be kept as source document.

### 4.7.10 Day 1 of study treatment cycle assessments

These assessments must be done before study drug administration in accordance with Tables 1&2. Clinically relevant findings meeting the definition of an AE must be recorded on an AE page of the CRF.

### 4.7.11 End of treatment / withdrawal assessments

These assessments must be obtained for the 4 previous weeks on study, meaning this visit is occurring 4 weeks after the last study drug administration.

### 4.7.12 Post treatment follow-up assessments

Monitoring of patients continues after the end of study treatment:

- Tumor assessments should be continued until documented RECIST 1.1 disease progression (Arm A or B).
- Survival status shall be recorded. Post study-treatment survival status will be collected every 2 months until death; telephone contact is acceptable. Date and reason of death will be recorded.
- Assessment of adverse events and hospitalizations: Subjects must be followed for adverse events until 28 days after the last study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is later. Hospitalizations will be recorded until the last day of study drug administration.
- Collection of subsequent anticancer therapies after study drug discontinuation.

## 4.8 Post-study access to study treatment

At the conclusion of the study, subjects treated with OSE2101 who continue to have clinical benefit will be offered to continue treatment with OSE2101 at the request of the investigator and the patient either via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through local procedures for compassionate use at the

discretion of the sponsor. The sponsor reserves the right to terminate access to study drug if any of the following occur:

a) the marketing application is rejected by responsible Health Authority;
b) the study is terminated due to safety concerns or development of the product is stopped or development strategy modified (e.g. other indication, population, and/or combination approach);
c) the subject can obtain medication from a government sponsored or private health program; or
d) therapeutic alternatives become available in the local market.

# 5 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

## 5.1 Reporting of adverse events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational medicinal product(s) are to be reported by the investigator.

For all AEs**,** the investigator must pursue and obtain information adequate to determine the outcome of the AE, assess whether it meets the criteria for classification as a SAE requiring immediate notification to OSE Immunotherapeutics or its designated representative, and determine the causality of the AE. For AEs with a causal relationship to the investigational medicinal product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and OSE Immunotherapeutics concurs with that assessment.

## 5.2 Reporting period

All SAEs require immediate notification to OSE Immunotherapeutics or its designated representative beginning from the time that the subject/patient provides informed consent, which is obtained prior to the subject's participation in the clinical trial, i.e., prior to undergoing any trial-related procedure and/or receiving an investigational medicinal product, through the study treatment period until the last injection and including 28 calendar days after the final administration of the investigational medicinal product.

Any SAE occurring any time after the end of treatment visit must be promptly reported if a causal relationship to investigational product is suspected. These SAEs will only be entered in the drug safety database, and hence will not affect study closure.

All AEs (serious and non-serious) must be recorded on an AE specific CRF page from the time of consent through last subject visit.

## 5.3 Assessment of causality

The investigator's assessment of causality (drug relationship) must be provided for all AEs (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational medicinal product caused or contributed to an AE. If the investigator's final determination of causality is unknown and the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on trial records.

In addition, if the investigator determines a SAE is associated with trial procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

Guidelines to determine whether an event might be considered related include (but are not limited to) the following:

- The event occurred in close temporal relationship to study drug administration.
- The event abated (diminished) or disappeared when treatment with the study drug was down-titrated, interrupted, or discontinued.
- The event re-occurred when treatment was re-introduced.
- Environmental factors such as clinical state and other treatments could equally have caused the event.

## 5.4 Definitions of Adverse Events

An AE is any untoward medical occurrence in a patient or healthy subject administered an investigational medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.
Examples of adverse events include but are not limited to:

- Clinically significant symptoms and signs.
- Clinically significant changes in physical examination findings.
- Hypersensitivity.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Lack of efficacy in the acute treatment of a life-threatening disease.
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Events considered by the investigator to be related to study-mandated procedures.

- Clinically significant abnormal test findings.

The criteria for determining whether an abnormal objective test finding (e.g., laboratory test, ECG) should be reported as an AE are as follows:

Test result is associated with accompanying signs or symptoms; and/or requires additional diagnostic testing or medical/surgical intervention; and/or leads to a change in study drug trial dosing (outside of protocol-stipulated dose adjustments), dose reduction, interruption or permanent discontinuation; and/or significant additional concomitant drug treatment, or other therapy; and/or is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Additionally, AEs may include the signs or symptoms resulting from:

- Drug overdose.
- Drug withdrawal.
- Drug abuse.
- Drug misuse.
- Drug interactions.
- Drug dependency.
- Extravasation.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, endoscopy, tooth extraction, transfusion should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

## 5.5 Severity of adverse events

The NCI Common Terminology Criteria for Adverse Events will be used for assessing severity of adverse events reporting according to version CTCAE v5.0 (52).
A grading (severity) scale is provided for each AE term.

**Components and Organization SOC**
System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results).
CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).
**CTCAE Terms**
An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical

treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.
Each CTCAE v5.0 term is a MedDRA LLT (Lowest Level Term).

**Definitions**
A brief definition is provided to clarify the meaning of each AE term.

**Grades**
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:
Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) *.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.
A Semi-colon indicates 'or' within the description of the grade. A single dash (-) indicates a grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

**Grade 5**
Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

**Activities of Daily Living (ADL)**
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

## 5.6 Serious Adverse Events

### 5.6.1 Definition

A SAE or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death.
- Is life-threatening; Life-threatening refers to an event in which the subject/patient was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.
- Important medical event.

Medical judgment should be exercised in determining whether an event is an important medical event to be reported as a SAE. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

### 5.6.2 Hospitalization - Prolongation of existing hospitalization

Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room.
An additional overnight stay defines a prolongation of existing hospitalization.
All AEs associated with hospitalization or prolongation of hospitalization are considered serious.
Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from a medical floor to a coronary care unit).
Hospitalization does not include the following:

- Rehabilitation facilities.
- Hospice facilities.
- Nursing homes.
- Routine emergency room admissions.
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself a SAE. Examples include:

- Planned hospitalization for a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for chemotherapy for cancer, elective hip replacement for arthritis, coronary angiography for a patient with stable angina pectoris.
- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep).
- Administrative admission (e.g., for yearly physical exam).
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery);
- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the trial protocol).

### 5.6.3 Serious Adverse Events related to study-mandated procedures

They are defined as SAEs that appear to have a reasonable possibility of causal relationship (i.e., a relationship cannot be ruled out) to study-mandated procedures (excluding administration of

study drug) such as an event related to the discontinuation of subject's previous treatment during a washout period, or complication of a mandated invasive procedure (e.g., blood sampling), or car accident on the way to the hospital for a study visit.

## 5.7 Reporting of serious and non-serious adverse events

### 5.7.1 Reporting requirements

Each AE is to be assessed to determine if it meets the criteria for SAE. If a SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

All SAEs must be recorded on SAE forms, irrespective of the study drug received by the subject, whether or not this event is considered by the investigator to be related to study drug. These SAE forms must be faxed or scanned to the Clinical Research Organisation (CRO) in charge of pharmacovigilance for OSE Immunotherapeutics:

STRAGEN SERVICES

fax: +33 (0) 4 78 42 55 71 or email: OsePV@stragen.fr

All AEs will be reported on the AE page(s) of the CRF. The SAE form and the AE CRF page must be completed in a consistent manner (e.g., same AE date, terms and drug relationship).

### 5.7.2 Serious adverse event reporting requirements

All SAEs must be reported by the investigator to Stragen Services in charge of pharmacovigilance within 24 hours of awareness of the event by the investigator. If the SAE is fatal or life-threatening, notification to Stragen Services must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports. Stragen Services acknowledges the receipt of the SAE information by email to the investigational site within one working day. In the absence of email acknowledging the receipt or in case of issue in sending the fax or email, the investigator shall contact Stragen Services by any means for ensuring the receipt of SAE information at the earliest opportunity.

In the rare case that the investigator does not become aware of the occurrence of a SAE immediately (e.g., if an outpatient trial subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Stragen Services in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Stragen Services to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE case report form. In general, this will include a description of the AE in sufficient detail to allow for a

complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Stragen Services.

**REFERENCE SAFETY INFORMATION**

The reference safety information (RSI) to guide for expedited reporting of Suspected Unexpected Serious Adverse Reaction is Investigator's Brochure for OSE2101 and the EU Summary of Product Characteristics for pemetrexed and docetaxel available at SUSAR processing date.

## 5.8 Management of adverse events, dosing adaptations and risk minimization strategy

**OSE2101**

Skin/injection site reactions

- If grade 1 local toxicity [defined per NCI CTCAE v5.0 as tenderness ± associated symptoms (e.g. warmth, erythema, itching)] or grade 2 local toxicity [defined per NCI CTCAE v5.0 as pain, lipodystrophy, edema, phlebitis]:
  - apply a hot or cold compress to the injection site and consider giving an analgesic or antipruritic medication.
  - It is intended that all injections be given at the same site: either the anterior thigh or deltoid region of the non-dominant arm (see section 4.3.3). If pain or granuloma formation limit dosing in a patient despite measures such as pain medication or local hot or cold compresses, other areas may be used. If the 1-mL injection cannot be given by a single injection, then it may be divided into two injections, preferably in the same lymph node drainage area.
- If grade 3 local toxicity [defined per NCI CTCAE v5.0 as ulceration or necrosis; severe tissue damage; operative intervention indicated] or grade 4 local toxicity (defined per NCI CTCAE v5.0 as life-threatening consequences; urgent intervention needed], local toxicity shall be considered dose limiting, and the patient will not to receive further injections.

Cytokine release syndrome (CRS)

CRS has been reported in the completed Phase I and Phase II studies. In 88 patients exposed to OSE2101 in these completed studies, 2 cases of CRS (1 grade 2, 1 grade 3) have been reported in 2 patients (2.3%). Both adverse effects were resolutive.

CRS caused by T cell-engaging therapies is related to elevation in effector cytokines, such as interferon gamma (Maude 2014, Lee 2014) and abnormal elevation in cytokines associated with macrophage activation and hemophagocytic syndrome, such as interleukin 6 and 10 (Lee 2014). CRS is a constellation of inflammatory symptoms resulting from cytokine elevations associated with T cell engagement and proliferation. In most patients, CRS symptoms are mild and flulike, with fevers and myalgias. However, some patients experience a severe inflammatory syndrome,

including vascular leak, hypotension, pulmonary edema, and coagulopathy, resulting in multi-organ system failure.
Serious adverse events that may be associated with CRS include pyrexia, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, and increased total bilirubin. These events may lead to treatment discontinuation.
Disseminated intravascular coagulation, capillary leak syndrome, and hemophagocytic lympho-histiocytosis/macrophage activation syndrome have been reported in the setting of CRS.
Patients will be closely monitored for signs or symptoms of these events. Management of these events may require either temporary interruption or discontinuation of OSE2101, corticosteroids and other symptomatic treatments.

The risk minimization strategy of CRS consists of:

- As a first step, patients should be monitored at least 4h after injection and be informed of possible later symptoms like flu-like syndrome, malaise, fever, low blood pressure which would need to make contact with the investigator.
- Should symptoms occur, CRS should be classified according to CTCAE 5.0 or other adapted classification (Lee 2014) in order to adapt treatment strategy (Lee 2014).

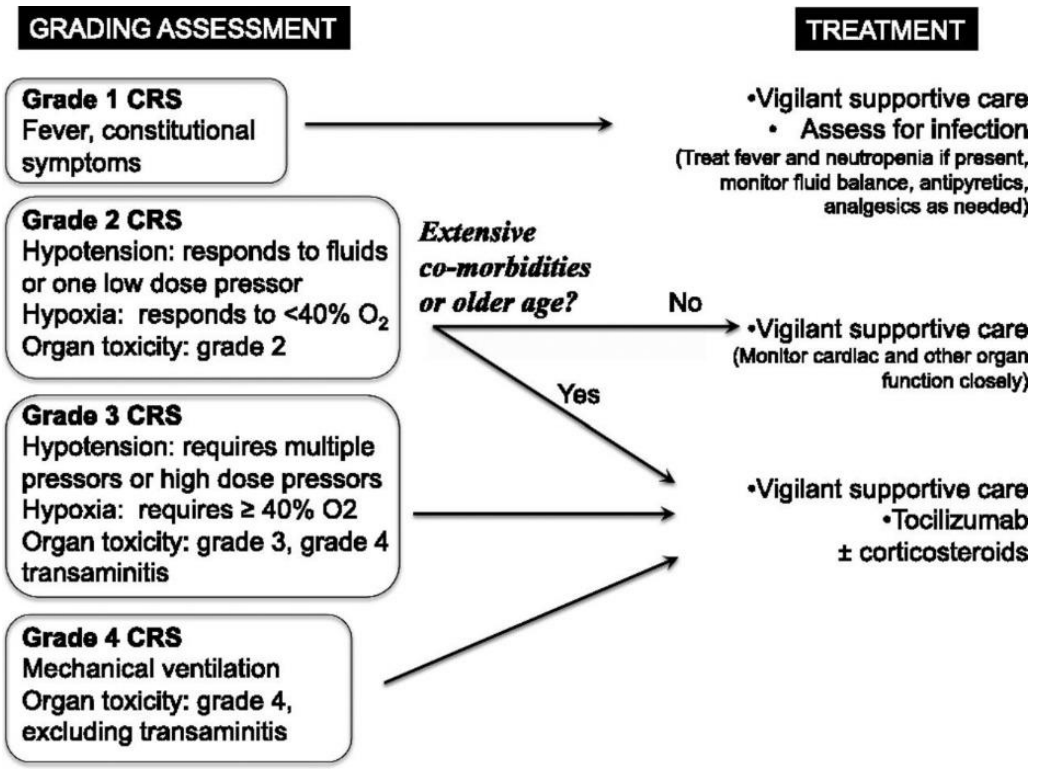
Per NCI CTCAE v5.0 definition, CRS is a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. Also consider reporting other organ dysfunctions including neurological toxicities such as psychiatric disorders (e.g. hallucinations or confusion), nervous system disorders (e.g. seizure, dysphasia, tremor, or headache).

Overall, in every grade of CRS, a vigilant supportive care including empiric treatment of concurrent bacterial infections and maintenance of adequate hydration and blood pressure. Immunosuppression should be used in all patients with grade 3 or 4 CRS and instituted earlier in patients with extensive comorbidities or older age (Lee 2014):

- Grade 1 [defined per NCI CTCAE v5.0 as fever ± constitutional symptoms]: vigilant support care, assess for infection (e.g. treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed).
- Grade 2 [defined per NCI CTCAE v5.0 as hypotension responds to fluid, hypoxia responding to <40% oxygen]: vigilant supportive care, monitor cardiac and other organ function closely, consider corticosteroids or other specific therapy according to comorbidities and expected benefit vs. cancer treatment needs.
- Grade 3 [defined per NCI CTCAE v5.0 as hypotension managed with one pressor; hypoxia requiring ≥ 40% oxygen] and Grade 4 [defined per NCI CTCAE v5.0 as life-threatening consequences, urgent intervention needed]: vigilant supportive care and intensive care monitoring for Grade 4 events, adapted vasopressor support and oxygen; specific treatment required : corticosteroids and/or tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor (Actemra®) which has been FDA-approved for grade 3 or grade 4 CRS induced by CAR-T cell therapy, although off-label in Europe and off-label for other indications than CAR-T cell).

- Decision to continue subsequent injections of OSE2101 shall be taken considering condition of the patient, response to therapy with OSE2101 and alternate anticancer treatment options and the severity of CRS.
    - In grade 1 and 2 CRS, continuation of OSE2101 may be considered under strict surveillance if patient is having benefit of OSE2101 therapy; it has been reported that CRS did not systematically recur at subsequent injections in an instance where grade 2 CRS was reported with OSE2101
    - In grade 3 and 4 CRS, treatment with OSE2101 shall not be continued and alternate cancer therapy should be considered. Patient trial assessments shall continue as scheduled in the protocol. In case of reversible grade 3 CRS, if the investigator considers the patient to be experiencing clinical benefit with OSE2101, continuation of OSE2101 may be considered under strict surveillance after discussion and approval of the Sponsor. In case of grade 4 CRS, OSE2101 will be permanently discontinued.

**Figure 3: Treatment algorithm for management of cytokine release syndrome (per Lee, 2014)**




Anaphylactic and severe immunoallergic reactions

Anaphylactic reaction should be treated with immediate adrenaline subcutaneous injection followed by intensive care management.

Immunoallergic reactions will require corticosteroids.
In case of anaphylactic and severe (grade 3 and 4) immunoallergic reactions, OSE2101 will be permanently discontinued.

**OSE2101 dosing adaptation**
There will be no dose reduction of OSE2101.

Treatment administration of OSE2101 may be delayed allowing enough time for recovery from toxicity. Toxicities must have improved to NCI CTCAE Grade ≤ 1 prior to re-treatment or NCI CTCAE as of baseline.

A patient who has not received any study drug(s) for > 16 weeks since last OSE2101 administration, should be permanently discontinued from study treatment.

**Pemetrexed**
Monitoring
Complete blood cell counts, including platelet counts, should be performed on all patients receiving pemetrexed. Patients should be monitored for nadir and recovery, which were tested in the clinical study before each dose and on days 8 and 15 of each cycle. Patients should not begin a new cycle of treatment unless the ANC is ≥1500 cells/$mm^3$, the platelet count is ≥100,000 cells/$mm^3$, and creatinine clearance is ≥45 mL/min. Periodic chemistry tests should be performed to evaluate renal and hepatic function.

Dose Reduction Recommendations
Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy. Treatment may be delayed allowing sufficient time for recovery. Upon recovery, patients should be retreated using the guidelines in Table 3, Table 4 and Table 5, which are suitable for using pemetrexed as a single-agent or in combination with cisplatin.

**Table 3: Dose Reduction for Pemetrexed – Hematologic Toxicities**

| | |
|---|---|
| Nadir Absolute neutrophil count (ANC) <500/$mm^3$ and nadir platelets ≥50,000/$mm^3$ | 75% of previous dose |
| Nadir platelets <50,000/$mm^3$ without bleeding regardless of nadir ANC | 75% of previous dose |
| Nadir platelets <50,000/$mm^3$ with bleeding, regardless of nadir ANC | 50% of previous dose |

If patients develop non-hematologic toxicities (excluding neurotoxicity) ≥ Grade 3, treatment should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed according to guidelines in Table 4.

**Table 4: Dose Reduction for Pemetrexed – Non-hematologic Toxicities**

| | Dose of pemetrexed ($mg/m^2$) |
|---|---|
| Any Grade 3 or 4 toxicities except mucositis | 75% of previous dose |
| Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea | 75% of previous dose |
| Grade 3 or 4 mucositis | 50% of previous dose |

In the event of neurotoxicity, the recommended dose adjustments for pemetrexed are described in Table 5. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is experienced.

**Table 5: Dose Reduction for Pemetrexed - Neurotoxicity CTC Grade**

| | Dose of pemetrexed ($mg/m^2$) |
|---|---|
| 0-1 | 100% of previous dose |
| 2 | 100% of previous dose |

Discontinuation Recommendation

Pemetrexed therapy should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

Renal Impaired Patients

In clinical studies, patients with creatinine clearance ≥45 mL/min required no dose adjustments other than those recommended for all patients. Insufficient numbers of patients with creatinine clearance below 45 mL/min have been treated to make dosage recommendations for this group of patients. Therefore, pemetrexed should not be administered to patients whose creatinine clearance is <45 mL/min using the standard Cockcroft and Gault formula (below) or GFR measured by Tc99m-DTPA serum clearance method:

[140 - Age in years] × Actual Body Weight (kg) = mL/min

Males: 72 × Serum Creatinine (mg/dL)

Females: Estimated creatinine clearance for males × 0.85

Caution should be exercised when administering pemetrexed concurrently with NSAIDs to patients whose creatinine clearance is <80 mL/min.

**Docetaxel**

Patients who are dosed initially at 75 $mg/m^2$ and who experience either febrile neutropenia, neutrophils <500 cells/$mm^3$ for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 $mg/m^2$. Patients who develop ≥grade 3 peripheral neuropathy should have Docetaxel Injection, USP treatment discontinued entirely.

**Pemetrexed and docetaxel adaptation**
Dose reduction of pemetrexed and docetaxel will follow the guidance's as their respective SCPs. Treatment administration may be delayed allowing sufficient time for recovery from toxicity.

A patient who has not received any study drug(s) for > 6 weeks (e.g. equivalent to 2 cycles of 21 days) since last study drug administration should be discontinued from study treatment.

# 6 STATISTICAL METHODOLOGY AND ANALYSES

## 6.1 Statistical Analysis Plan

A statistical analysis plan (SAP) will be written and finalized before the database lock. The SAP will provide full details of analyses, data displays and algorithms to be used for data derivations.

The SAP will include the definition of major and minor protocol deviations and the link of major protocol deviations to the analysis sets. Major and minor protocol deviations will be identified before the study closure.

The final SAP v2.2 was finalized on 23-july-2021 before the database lock. This SAP also details the subgroup analyses and variables used to define subgroups, and precisely describes the hierarchical order to test secondary endpoints.

## 6.2 Analysis Sets

Three different analysis sets are defined **for the patients with previous treatment with ICI**. The primary population will be a Population of Interest (PoI) identified during Step-1 analysis consisting of patients from the 2d line ICI stratification factor with secondary resistance to ICI (i.e. duration of ICI ≥ 12 weeks) having shown a benefit over SoC and being proposed as the main population for final analysis. Sensitivity analyses on primary endpoint (OS) will be done in all population (Kluger et al., 2020).

Subjects not having a valid or substituted post-baseline value for a particular endpoint are excluded from the relevant analysis sets.

- **Safety set**

This analysis set includes all patients who were randomized and received at least one dose of study treatment. Patients will be analyzed in the group according to the treatment they actually received. All safety data analyses will be analyzed using the safety set.

- **Intent-to-Treat (ITT) set**

This analysis set includes all randomized patients. Patients will be analyzed in the group as randomized. All efficacy data analyses will be analyzed using the ITT set.

- **Modified Intent-to-Treat (mITT) set for testing the null hypothesis of the one stage Fleming Phase II design (at end of Step 1)**

For testing the null hypothesis of the one stage Fleming Phase II design at the end of Step 1 (Phase II part), this analysis set includes all patients of the ITT set, enrolled up to the end of Step 1, who received at least one dose of OSE2101 and are evaluable at 12 months after

randomization, "evaluable" meaning either known alive for at least 12 months or having experienced death within 12 months. Patients will be analyzed in the group according to the treatment they actually received.

- **Per-protocol set**

This analysis set includes all patients of the ITT set who did not violate the protocol in a way that might affect the evaluation of the effect of the study drugs on the main endpoints, i.e., without major protocol deviations. Major protocol deviations will be defined in the SAP. Selected sensitivity efficacy data analyses will be performed using the per-protocol set.

- **Per protocol set for testing the null hypothesis of the one stage Fleming Phase II design (at end of Step 1)**

This analysis set includes all patients of the mITT set (for testing the null hypothesis of the one stage Fleming Phase II design) who have no major protocol deviations and comply with the revised inclusion criterion #5. Major protocol deviations will be defined in the SAP. Selected sensitivity efficacy data analyses will be performed using the per-protocol set.

**Nota bene:** In addition, patients **without** previous treatment with ICI (included before recruitment hold) will be described separately.

## 6.3 Sample size

**Step 1 - Phase II**

The primary objective of Step 1 is to evaluate the overall survival rate after 12 months in OSE2101 arm. The following hypotheses are considered:
- H0 (null): 25% of overall survival rate at 12 months (uninteresting to pursue any further investigation)
- H1 (alternative): 40% of overall survival rate at 12 months (clinically relevant to discuss the interest of further investigation in a Phase III comparative trial).

According to the previous hypotheses and a Fleming one step Phase II design with a 2.5% one-sided type I error and a power of 80%, 84 evaluable patients have to be enrolled in the arm A.

Fleming decision rules:

Amongst the first 84 evaluable patients:
To reject H0 we have to observe at least 30 (35.7%) patients alive at 12 months, then it will be interesting to run the next step of Phase III comparative trial.
If less than 30 patients are alive at 12 months, H0 will not be rejected and it will be considered uninteresting to pursue any further investigation.
The probability to conclude for inefficacy whereas the true rate is 40% is $\beta$=18.1%.
The probability to conclude for efficacy whereas the true rate is 25% is $\alpha$=1.9%.

In order to limit the total number of patients needed in Step 1, a 2:1 randomization ratio to receive OSE2101 (Arm A) or pemetrexed or docetaxel (Arm B) will be used for new patients recruited when version 4.0 of the protocol comes into effect. A total of 38 patients with previous ICI treatment have been recruited before protocol version 4.0, from whom 18 patients

randomized in arm A (OSE2101), thus 84 - 18 = 66 new patients need to be recruited in arm A (OSE2101). Based on a 2:1 randomization ratio, 66/2 = 33 new patients need to be randomized in arm B, leading to a total of 99 new evaluable patients. With an expected 7% rate of patients not evaluable at 12 months or withdrawn, a total of 108 new patients will be randomized for Step 1.

The analysis of the Phase II data will take place once 84 subjects of the OSE2101 arm are evaluable for survival at 12 months (meaning that death was observed within 12 months or that the patient has a follow-up time of 12 months or more). With this sample size, the lower limit of the exact binomial two-sided 95% confidence interval will be above 25% as soon as at least 30 subjects will be alive at 12 months. In the situation where exactly 30 subjects out of 84 would be seen alive at 12 months, the observed survival rate at 12 months would be 35.7%, which seems reasonable in light of the 34.1% overall survival rate at 12 months published for 78 patients on durvalumab plus tremelimuab after failure to previous ICI (27).

It may be noted that as soon as 55 deaths within 12 months are observed by the IDMC, there is no need to wait for 84 evaluable patients at 12 months since there is no possibility left to reach 30 or more patients alive at 12 months among 84 patients evaluable at 12 months. Conversely as soon as 30 patients or more are observed alive at 12 months by the IDMC in patients evaluable at 12 months, there is no need to wait for 84 patients evaluable at 12 months since the number of patients alive at 12 months cannot decrease with the additional observations (and since the lower limit of the 95% confidence interval is already above 25%).

**Step 2 - Phase III**

For Step 2, the same 2:1 randomization ratio will be continued. All the 38 patients randomized before the recruitment hold in the subgroup of patients with previous ICI treatment and all new patients included in Step 1 / Phase II will be followed during Step 2 /Phase III. However, the final analysis of Phase II/Phase III will exclude the 38 patients with previous ICI treatment randomized before protocol version 4.0.

In order to reach a power of 80% for the two-sided log rank test at the 5% significance level when assuming a median OS of 7 months for the control and 10 months for the experimental arm, a total of 278 events is required. If the new patients (randomized since version 4.0 of the protocol came into effect) are uniformly included over an accrual period of 36 months followed by a follow-up of 6 months after the last inclusion, observing 278 events requires a total of 363 new patients. The actual number of new patients may be reduced if the 278 events are observed earlier (this is an event-driven study). Both counts exclude the 38 patients enrolled before protocol 4.0.

Step-1 analysis was reviewed by the independent data monitoring committee (IDMC) in March 2020. Step-1 data showed that the predefined thresholds of 12 months-OS rate in OSE2101 arm was achieved. At this time, the IDMC was concerned about the impact of the COVID-19 pandemic on the primary endpoint of the study (OS), on the risk on data integrity and recommended to stop accrual early.

The Sponsor decided to stop the accrual in April 2020. At that date, 219 patients have been enrolled instead of 363 patients and planned to be followed for survival up to mid-January 2021. From Step-1 analysis, a population of interest (PoI) consisting of patients from the 2d line ICI stratification factor with secondary resistance to ICI (duration of ICI ≥ 12 weeks) was identified as having a benefit over SoC and being proposed as the main population for final analysis (Kluger et al., 2020).

Due to early study discontinuation due to COVID-19 (219 patients included instead of 363 patients), the power decreased to 62% with the same hypotheses (HR=0.70).
Considering Step 1 results in the PoI, the following hypotheses have been proposed for final analysis:
Assuming a HR of 0.55 observed in PoI in Step-1 and a median OS of 7 months in SoC (unchanged as initially planned), a total of 90 events in the PoI will provide a power of 80% and a 2-sided logrank test at a 5% two-sided level, if the patients are included over an accrual period of 48 months followed by a follow-up of 6 months after the last inclusion.

### 6.4 Primary and secondary efficacy endpoints

The primary endpoint is OS, defined as time from randomization to death, will be summarized on the ITT set using the Kaplan-Meier method and displayed graphically. The median event time for each treatment arm and the corresponding 2-sided 95% confidence interval (CI) will be provided. A 2-sided log-rank test stratified for the same stratification factors as used for the randomization will be used to compare OS between the two treatment arms. The Cox regression model, stratified for the same stratification factors, will be fitted, and the estimated hazard ratio and 2-sided 95% CI will be provided.

2-sided unstratified log-rank test and an unstratified Cox regression model will also be used as secondary analyses for OS.

Subgroups analyses of OS will be performed to determine whether treatment effect is consistent among subgroups. The hazard ratios (obtained via a separate unstratified Cox model within each subgroup) and their 95% confidence intervals will be displayed as a forest-plot, the test of interaction between treatment and subgroup will be derived from an unstratified Cox model applied on the whole study population. The following variables will be used to define subgroups:

- histology (squamous *vs.* non-squamous),
- initial response to first line treatment (objective response, that is either complete or partial response, *vs.* no objective response, that is either stabilization or progressive disease)
- line rank of ICI therapy ($2^{nd}$ line *vs.* $1^{st}$ line).
- best response to ICI (objective response, *vs* no objective response)
- presence vs absence of brain metastases
- tumor stage (III *vs.* IV)
- previous number of systemic treatment lines (1 *vs.* 2 or more)
- gender (male vs female)
- age (< 75 *vs.* ≥ 75)
- Smoking status: never, former or current smoker
- baseline ECOG score (0 *vs*. 1)

- duration of PFS since previous treatment (shorter or longer than 6 months)

Additionally, a Cox regression model, stratified for the same stratification factors as used for the randomization, will be used to explore the potential influences of the other factors (those defining subgroups in the text above) on the primary OS endpoint. The full list of subgroups of interest will finalized before database lock and detailed in the SAP.

The 6-months survival probability will be estimated using the Kaplan-Meier method and a 2-sided 95% CI for the log [-log(6-months survival probability)] will be calculated using a normal approximation and then back transformed to give a confidence interval for the 6-months survival probability itself. The 1-year survival probability will be estimated similarly.

Once the primary objective will be established (significant result on OS), each of the secondary efficacy endpoints will be tested at 5% significance level using a further hierarchical order (OS (PP), PPS, Time to worsening of ECOG PS, QLQ-C30 Global health status score change from baseline, QLQ-C30 Functional scores change from baseline, QLQ-C30 Symptom scores change from baseline, QLQ-LC13 Symptom scores change from baseline, DCR at 6 months, DCR at 12 months, , followed by PFS) in order to control the overall type I error. If the primary objective is not established, these endpoints will still be analyzed but interpreted as exploratory endpoints, similarly if one secondary endpoint in the sequence is not significant, the lower rank secondary endpoint(s) will be considered exploratory.

Based on the randomized patients with measurable lesions at baseline, the best response (CR, PR, SD or PD) will be determined by radiology review for each patient and will be summarized by treatment arm. Assessment of response will be made using RECIST version 1.1 (Appendix 1). Then DCR at 6 and 12 months will be calculated as the number of patients remaining within CR, PR or SD responses within the considered time period divided by the total number of randomized patients with measurable lesions at baseline in each treatment group. DCR will be analyzed as described for ORR. The corresponding exact 2-sided 95% confidence interval will be calculated. The Mantel Haenszel test will be used to compare DCR at 6 months between the treatment arms, using the randomization strata, the corresponding odds-ratio will be provided with its 95% confidence interval. In addition, the difference in DCR at 6 months between the two treatments will be provided and its 95% confidence interval will be calculated based on the normal approximation.

The secondary efficacy endpoints associated with HRQoL will be the change from baseline in the EORTC QLQ-C30 “Global health status/QoL” score (based on questions 29 and 30), for EORTC QLQ-C30 functional scores, and for EORTC QLQ-C30 and QLQ-C13 symptoms according to repeated measures mixed-effects modeling.

The composite endpoint time to 1$^{st}$ $\geq$ 10-point deterioration in EORTC QLQ-LC13 “Chest pain symptom” score (based on question 40), “Dyspnea symptom” score (based on questions 33, 34, 35) or “Coughing symptom” score (based on question 31), whichever happens first. Scores will

be derived from the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires items according to the respective scoring manuals.

PFS, defined as time from randomization to the first documented disease progression or death whichever occurs first, will be analyzed similarly as described for OS. A log-rank test, stratified by the same stratification factors as used for the randomization, will be used in analyzing PFS.

PPS, defined as time from the first documented disease progression in patients having experienced a progression to death, will be analyzed similarly as described for OS.

Time to worsening of ECOG PS, defined as the time from randomization to the earliest time when the ECOG becomes greater than 1 ignoring all assessments performed after the analysis cut-off date. Patients who die without having recorded an ECOG >1 will be assigned an ECOG = 5 (Dead) at the time of death. Patients without worsening ECOG will be censored at the last time when an ECOG value was recorded. By protocol, ECOG is not collected anymore when a subject discontinues study treatment while the time between study treatment discontinuation and death can be quite long, an additional analysis without imputation for death will be performed. This analysis will exclude patients without any post-baseline ECOG assessment and censor patients without observed ECOG worsening at their last ECOG assessment. The endpoint will be analyzed as described for the PFS.

## 6.5 Exploratory efficacy endpoints

ORR will be calculated as the number of patients with a best response of CR or PR divided by the total number of randomized patients with measurable lesions at baseline in each treatment group. ORR will be analyzed as described for DCR at 6 months.

DR will be calculated for the subgroup of patients with objective disease response and summarized using the Kaplan-Meier method.

The 3 endpoints TTD in patient reported pain (QLQ-LC13 “Chest pain symptom” score), TTD in patient reported dyspnea (QLQ-LC13 “Dyspnea symptom” score), and TTD to patient reported cough (QLQ-LC13 “Coughing symptom” score), will be defined as the time from randomization to the earliest time the patient’s score shows a 10-point or higher increase after baseline (7, 6). Patients will be censored at the last time when they completed an assessment for chest pain, dyspnea and cough if they have not deteriorated. A 10 point or higher change in the score is perceived by patients as clinically significant (58). TTD of each these 3 pre-specified symptoms (chest pain, dyspnea, and cough) scales will be summarized using Kaplan-Meier methods. The estimated Kaplan-Meier plots will be provided for each symptom and the unstratified log-rank test will be the primary method to compare the time to first deterioration between the two treatment groups. The median time and the corresponding 2-sided 95% CI also will be provided. The Hochberg procedure will be used to adjust for multiplicity of the three pre-specified symptoms.

Patient reported HRQoL will also be assessed in a detailed manner in the SAP. Summary statistics (mean [and SE], median, range and 95% CI) will be reported by treatment arm and visit for the items and scales of the EORTC QLQ-C30 and QLQ-LC13 questionnaires**.** The mean change from baseline (and 95% CI) will also be reported. Line charts depicting the means and mean changes of subscales over time will be provided for each treatment arm. The number and proportion of patients who improved, worsened, or remained stable for each of the symptom and functional domains, global QOL, and single items of the EORTC QLQ-C30 and QLQ-LC-13 questionnaires will be summarized in a table and compared between the two treatment arms. Additional analyses may be performed such as repeated measures mixed-effects modeling.

Time to next lung cancer therapy, defined as time from randomization to the first recording a lung cancer therapy, will be analyzed similarly as described for OS. A log-rank test, stratified by the same stratification factors as used for the randomization, will be used.

COVID-19 Impact: it is proposed to test COVID-19 impact in the ITT population following FDA Guidance (Updated January 27, 2021 then August 2021 on "*Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards.*" and "*Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency: Guidance for Industry*" June 2020. The complete description of COVID-19 impact analyses is described in the SAP.

### 6.6 Safety and tolerability endpoints

All AEs and SAEs will be coded using the MedDRA dictionary. All AEs will be tabulated by system organ class (SOC), preferred terms (PT) and low-level terms (LLT) within each SOC. The incidence of subjects who experienced AEs coded with the same preferred term will be tabulated (in descending order according to the incidence in the investigational study drug group). Adverse events will also be tabulated by severity and by relationship to study drug. Summary tables will be accompanied by individual subject listings.
AEs corresponding to hypersensitivity reactions will be considered as adverse events of special interest and will be detailed in additional summary tables.
SAEs occurring after study drug initiation will be listed and summarized similarly to AEs, while SAEs occurring before study drug initiation (only those related to study- mandated procedures) will be listed only.
The same analyses will also be conducted on the irAEs.
Vital signs (blood pressure and pulse rate) and ECG will be summarized by descriptive statistics by treatment group. Individual subject listings of vital signs and ECG data will be provided.
Values for safety laboratory parameters will be summarized by descriptive statistics by treatment group. Individual subject listings will be provided.

### 6.7 Interim analysis

No interim analysis of the primary endpoint will be performed.

However, OS rate at 12 months will be analyzed on Arm A at end of Step 1 by the IDMC, before a decision to continue Step 2 can be made by the Steering Committee after recommendation by

the IDMC. The decision of moving forward in Step 2 (Phase III) will consider the expected benefit of OSE2101 as well the relevance of the specific design of the Phase III with regards to the state-of-the-art in the management of advanced NSCLC known at time of the analysis.

## 6.8 Exposure to study drugs

Exposure to study drugs will be described in terms of administered doses. The exposure will be tabulated using the usual location and scale statistics.

## 6.9 Baseline Parameters and Concomitant Medications

Continuous demographic variables (age, height, weight) will be summarized by descriptive statistics (mean, median, SD, minimum, maximum and number of available observations). Individual subject listings will be provided.

Qualitative demographic characteristics (gender) will be summarized by counts and percentages. Other subject characteristics (medical history, physical examination findings, previous and concomitant medications) will only be listed.

Previous and concomitant medications will be coded according to the WHO drug code and the ATC code. They will be summarized by type (i.e., previous and concomitant) by tabulating the number and percentages of subjects having received each medication.

# 7 PROCEDURES AND QUALITY ASSURANCE

## 7.1 Procedures

### 7.1.1 Protocol amendments

Any change to a protocol has to be considered as an amendment as soon as these documents have been submitted to Ethics Committee (ECs)/Institutional Review Board (IRB) and Health Authorities. Therefore, an amendment could occur before or after the approval of these documents by ECs/IRBs and Health Authorities. Potential amendments must be approved by the Sponsor after discussion within the Steering Committee, as appropriate.

Changes in the core Subject Information sheet and Informed Consent form requested by ECs/IRBs are not considered as amendments, as long as they do not significantly affect the protocol.

- **Non-substantial amendment**

Administrative or logistical minor changes require a non-substantial amendment. Such changes include but are not limited to changes in study staff or contact details, change in laboratory normal ranges, or minor changes in the packaging of study drug, etc.

The implementation of a non-substantial amendment could be done with or without (according to national regulations) notification to the appropriate ECs/IRBs and Health Authorities. It does not require their approval or to be signed by the investigators.

- **Substantial amendment**

Significant changes require a substantial amendment. They include but are not limited to: new data affecting the safety of subjects/patients, change of the objectives/endpoints of the study, eligibility criteria, dose regimen, study assessments/procedures, treatment or study duration, with or without the need to modify the Subject Information and Informed Consent.

Substantial amendments are to be approved by the appropriate ECs/IRBs and in some countries by the Health Authorities. The implementation of a substantial amendment can only occur after formal approval by the appropriate ECs/IRBs and/or Health Authorities and must be signed by the investigators.

- **Urgent amendment**

An urgent amendment might become necessary to preserve the safety of the subjects included in the study. The requirements for approval should in no way prevent any immediate action being taken by the Investigator or OSE Immunotherapeutics in the best interest of the subjects. Therefore, if deemed necessary, an investigator can implement an immediate change to the protocol for safety reasons. This means that, by exception, the implementation of urgent amendments will occur before submission to and approval by ECs/IRBs and Health Authorities.

In such cases, the investigator must notify OSE Immunotherapeutics within 24 hours. A related substantial amendment will be written within 10 working days by OSE Immunotherapeutics and submitted to the appropriate ECs/IRBs and Health Authorities.

### 7.1.2 Monitoring

The OSE Immunotherapeutics monitor(s) or its designee will contact and visit the investigator regularly and will be allowed, on request, to have access to all source documents needed to verify the entries in the eCRF and other protocol- related documents; provided that subject confidentiality is maintained in agreement with local regulations. It will be the monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered in them. OSE Immunotherapeutics monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of the main safety and tolerability and efficacy endpoints.

The investigator must ensure that subjects' anonymity will be maintained. On eCRFs or other documents submitted to OSE Immunotherapeutics, subjects should not be identified by their names, but by birth date (upon local regulation) and number. The investigator must keep a subject/patient log showing the subject’s number, name, date of birth and address or any other locally accepted identifiers. Documents identifying the subjects/patients (e.g., signed informed consent forms) must not be sent to OSE Immunotherapeutics and must be kept by the investigator in strict confidence.

The investigator and co-investigators agree to cooperate with the monitor(s) to ensure that any issues detected in the course of monitoring visits are resolved. If the subject is hospitalized or dies in a hospital other than the study center, the investigator is in charge of contacting this hospital in order to document this SAE.

The investigator will supply OSE Immunotherapeutics or its designee on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

An initiation visit will be performed before the first subject is included. Monitoring visits and contacts will occur at regular intervals thereafter. A close-out visit will be performed after the database lock and resolution of all pending queries and follow-up of ongoing AEs/SAEs.

### 7.1.3 Data management

#### 7.1.3.1 *Data collection*

An eCRF must be completed and signed by the principal investigator or co-investigator only when a patient has been randomized. This also applies to those subjects who prematurely discontinue the study. If a subject withdraws from the study, the reason must be noted on the eCRF. The eCRFs are to be completed on an ongoing basis.

#### 7.1.3.2 *Database management and quality control*

All study data will be entered into the study database, according to validated procedures described in specific data management documents. Subsequently, the data will be systematically checked using specific quality control procedures. When the database will be declared complete, clean and accurate, it will be locked. Any changes to the database after that time can only be made by joint written agreement between the Clinical Research Physician and the Trial Statistician.

### 7.1.4 Recording of data and retention of documents

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: investigator's file, and subject clinical source documents.

The investigator's file will contain the protocol/amendments, FDA form 1572 for studies conducted under an US IND, financial disclosure form, EC/IRBs and Health Authority approval with correspondence, informed consent forms, drug records, staff curriculum vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence as per ICH/GCP guidelines and local regulations. Electronic filing of eCRF must also occur.

Subject clinical source documents include, but are not limited to subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, etc.

These two categories of documents must be kept on file by the investigator for as long as needed to comply with national and international regulations (2 years after the last marketing

authorization in an ICH/GCP region or following local requirements is it is a longer period). No study document should be destroyed without prior written approval from OSE Immunotherapeutics or its designee. Should the investigator wish to assign the study records to another party, or move them to another location, OSE Immunotherapeutics or its designee must be notified in advance.

When source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

### 7.1.5 Audit

OSE Immunotherapeutics or its designee may conduct audits of clinical research activities in accordance with its internal Quality System to evaluate compliance with the protocol and the principles of ICH/GCP related guidelines. Health Authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by Health Authorities, the investigator must inform OSE Immunotherapeutics or its designee immediately that such request has been made.

The investigator will permit such audits by OSE Immunotherapeutics (and its designee) or Health Authorities and facilitate them by providing access to the relevant source documents.

### 7.1.6 Publication of study results

The clinical study report will be signed by the chair of the Steering Committee.

In accordance with standard editorial and ethical practice, results of OSE Immunotherapeutics sponsored studies will be published.

Authors will be defined as meeting requirements of the International Committee of Medical Journal Editors. The list of authors will consider for ranking Committee members, investigators according to the number of inclusions, region representation. Other contributions may be acknowledged.

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

### 7.1.7 Disclosure and confidentiality

By signing the protocol, the investigator agrees to keep all information provided by OSE Immunotherapeutics in strict confidence and to request similar confidentiality from his/her staff and the EC/IRB. Study documents provided by OSE Immunotherapeutics (Investigators'

Brochure, protocol, CRF and any other protocol-related documents) will be stored appropriately to ensure their confidentiality. The information provided by OSE Immunotherapeutics to the investigator may not be disclosed to others without direct written authorization from OSE Immunotherapeutics, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

Furthermore, the investigator agrees that the sponsor is allowed to enter and utilize his/her professional contact details in an electronic database for internal purposes and for submission to worldwide Health Authorities.

### 7.1.8 Premature termination or suspension of the study

Both OSE Immunotherapeutics and the investigator reserve the right to terminate the study at any time.

If a study is prematurely terminated or suspended, OSE Immunotherapeutics will promptly inform the investigator, the ECs/IRBs and Health Authorities, as appropriate, and provide the reason(s) for the termination or suspension. If the study is prematurely terminated or suspended for any reason, the investigator in agreement with OSE Immunotherapeutics should promptly inform the enrolled subjects and ensure their appropriate treatment and follow-up.

In addition, if the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should promptly inform OSE Immunotherapeutics and the EC/IRB, and should provide the sponsor and the EC/IRB with a detailed written explanation of the termination or suspension.

If the EC/IRB terminates or suspends its approval/favorable opinion of a study, the investigator should promptly notify OSE Immunotherapeutics and provide OSE Immunotherapeutics with a detailed written explanation of the termination or suspension.

## 7.2 Insurance and Compensation to subjects and investigators

The sponsor is providing insurance in order to indemnify (legal and financial coverage) the investigator/center against claims arising from the study, except for claims that arise from malpractice and/or negligence. The compensation of the subject in the event of study-related injuries will comply with the applicable regulations.

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# 9 APPENDICES

# APPENDIX 1: RECIST 1.1 CRITERIA

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47. doi: 10.1016/j.ejca.2008.10.026.

This Appendix has been excerpted from the full RECIST 1.1 criteria. For information pertaining to RECIST 1.1 criteria not contained in the study protocol or in this Appendix, please refer to the full publication (17).

## 1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

### 1.1 Measurability of tumor

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

**Measurable lesions** must be accurately measured in at least one dimension (longest diameter inthe plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT scan - (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymphnode must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axiswill be measured and followed.

All measurements should be recorded in metric notation, using calipers if clinically assessed.
Special considerations regarding lesion measurability

**Bone lesions:**

- Bone scan, PET scan or plain films 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, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be

considered as measurable lesions if the soft tissue component meets the definition ofmeasurability described above.
- Blastic bone lesions are non-measurable.

**Cystic lesions:**
- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

**Lesions with prior local treatment:**
Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

**Non-measurable lesions** are all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

**1.2 Method of assessment**
The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.
CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

**Chest x-ray**: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

**Clinical lesions**: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted

above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

**Ultrasound**: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

**Endoscopy, laparoscopy**: The utilization of these techniques for objective tumor evaluation is not advised.
Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

## 2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

**Target lesions:** When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.
Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum.

All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

**Non-target lesions:** All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

# 3 TUMOR RESPONSE EVALUATION AND RESPONSE CRITERIA

## 3.1 Evaluation of target lesions

**Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

**Partial Response (PR**): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

**Progressive Disease (PD)**: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (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.
Note: the appearance of one or more new lesions is also considered progression.

**Stable Disease (SD**): Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
*Special notes on the assessment of target lesions*

- **Lymph nodes:** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.
- **Target lesions that become 'too small to measure':** All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:
(i) if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

(ii) if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

**Lesions that split or coalesce on treatment:** When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have

coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

**3.2 Evaluation of non-target lesions**

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

**Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

**Progressive Disease (PD)**: Unequivocal progression of existing non-target lesions.
(Note: the appearance of one or more new lesions is also considered progression).

- The concept of progression of non-target disease requires additional explanation as follows:
- *When the patient also has measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- *When the patient has only non-measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include
  an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point.

**3.3 New lesions**

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For

example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion,which it is not. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be constitute PD even if he/she did not have brain imaging at baseline.If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

### 3.4 Tumor markers

Tumor markers alone cannot be used to assess objective tumor responses. If markers are initiallyabove the upper normal limit, however, they must normalize in order for a patient to be considered as having attained a complete response.

## 4 EVALUATION OF BEST OVERALL RESPONSE

### 4.1 Time point response

A response assessment should occur at each time point specified in the protocol.
For patients who have measurable disease at baseline Appendix **Table 6** provides a summary of the overall response status calculation at each time point.

**Table 6: Summary of the Overall Response Status**
**Calculation [Time point response - patients with target ± non-target disease]**

| Target lesions | Non-target lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

### 4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an

assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

### 4.3 Best overall response: all timepoints

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. In this circumstance, the best overall response can be interpreted as in Appendix Table 7.

**Table 7: Best overall response when confirmation of CR and PR required**

| Overall Response First Timepoint | Overall Response Subsequent Timepoint | Best Overall response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR[a] |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| NE | NE | NE |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR).
Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

### 4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal'size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Appendix **Table 6** and Table 7.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

## 5 ADDITIONAL CONSIDERATIONS

### 5.1 Duration of response

***Duration of overall response:*** The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

***Duration of stable disease:*** Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

### 5.2 Lesions that disappear and reappear

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorization is based upon

the realization that most lesions do not actually 'disappear' but are not visualized because they are beyond the resolving power of the imaging modality employed.

### 5.3 Use of FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. Confirmatory CT is recommended.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

# APPENDIX 2: EORTC QOL QUESTIONNAIRES

As consulted on July 16th, 2015 at

http://groups.eortc.be/qol/sites/default/files/img/specimen_lc13_english.pdf
and
http://groups.eortc.be/qol/sites/default/files/img/slider/specimen_qlq-c30_english.pdf


specimen_lc13_english.pdf


specimen_qlq-c30_english.pdf

# APPENDIX 3: ECOG

## ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair (57)
Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

| GRADE | ECOG PERFORMANCE STATUS |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any selfcare; totally confined to bed or chair |
| 5 | Dead |

# APPENDIX 4: GUIDANCE ON CONTRACEPTION

## ACCEPTABLE METHODS FOR PROTOCOLS WITH A TERATOGENIC DRUG OR WHEN THERE IS INSUFFICIENT INFORMATION TO DETERMINE TERATOGENICITY

(CHOOSE ONE OF THE FOLLOWING 3 OPTIONS)[a]

OPTION 1: Any TWO of the following methods

- Hormonal methods of contraception [b, c, d]
- IUD [c, d, e]
- Vasectomy [d, f]
- Tubal Ligation[d]
- A Barrier method (Female or Male Condom with spermicide, Cervical Cap with spermicide,Diaphragm with spermicide)

OPTION 2: Male condom (with spermicide) and diaphragm[g]

OPTION 3: Male condom (with spermicide) and cervical cap[g]

[a] The theoretical failure rate for any of the options listed is considerably less than 1% per year
[b] Excludes progestin-only pills
[d] A highly effective method of birth control with a failure rate less than 1% per year
[e] IUDS used should have a failure rate less than 1% (highly effective method), such as Mirena and ParaGard
[f] Must be at least 90 days from date of surgery with a semen analysis documenting azoospermia
[g] These 2 barrier methods together are acceptable for a teratogenic drug

## UNACCEPTABLE METHODS OF CONTRACEPTION

Abstinence (including periodic abstinence)
No method
Withdrawal
Rhythm
Vaginal Sponge
Any barrier method without spermicide
Spermicide
Progestin only pills
Concomitant use of female and male condom

In countries where spermicide is not available or its use is not considered compatible with male condoms, use of a male condom without spermicide in conjunction with a hormonal method, IUD, or tubal ligation will be acceptable to fulfill this recommendation. Any barrier method when used alone (without spermicide) or the concomitant use of a female and male condom, is not considered a sufficient method of contraception, as each carries a failure rate of > 1%.

Women of childbearing potential (WOCBP) receiving OSE2101 will be instructed to adhere to contraception for a period of 90 days after the last dose of investigational product. Men receiving

OSE2101 and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 90 days after the last dose of investigational product.

For women of childbearing potential (WOCBP) randomized to receive docetaxel, they will be instructed to adhere to contraception for a period of 33 days after the last dose of investigational product.
Men randomized to receive docetaxel must follow instructions for birth control as per the SmPC (6 months after discontinuation of treatment), or package insert.

Women of childbearing potential should be advised to use effective contraceptive measures to prevent pregnancy during the treatment with pemetrexed