A RANDOMIZED PHASE II STUDY OF SEQUENCING ABIRATERONE ACETATE AND ENZALUTAMIDE IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER
GUTG-001

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STUDY CHAIR: DR. KIM N. CHI

COGNITIVE STUDY CO-CHAIR: DR. BERNHARD EIGL

STUDY COORDINATOR: MS. LEANNE SETO

BCCA – VCC PI: Dr. Kim N. Chi

BCCA – AC PI: Dr. Muhammad Zulfiqar

BCCA – CN PI: Dr. Christian Fibich

BCCA – CSI PI: Dr. Daygen Finch

BCCA – FVC PI: Dr. Conrad Oja

BCCA – VIC PI: Dr. Joanna Vergidis

Vancouver Prostate Centre – PI: Dr. Martin Gleave

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1.0 PROTOCOL SUMMARY

Title	A randomized phase II study of sequencing abiraterone acetate and enzalutamide in metastatic castration-resistant prostate cancer
Background and rationale	Abiraterone acetate and enzalutamide have emerged as standard therapies in metastatic castration-resistant prostate cancer (mCRPC). Both agents improve outcomes in patients previously treated with docetaxel and in those that are chemotherapy-naive[1-4]. Although their mechanisms of action differ, both abiraterone and enzalutamide target persistent androgen receptor (AR) signaling. Abiraterone inhibits CYP17 and testicular and extragonadal androgen production whereas enzalutamide directly antagonises the AR. Whether cross resistance occurs between these agents if used in sequence is unknown, but theoretically disparate mechanisms of resistance may allow for successful sequencing of these agents. Prior studies have reported PSA response rates of under 10% in patients treated with abiraterone after enzalutamide[5,6] and 13%-29% in patients treated with enzalutamide after abiraterone[7,8]. Since these data were generated in small, retrospective series, a prospective clinical trial is warranted to evaluate effects of sequencing abiraterone and enzalutamide. A randomized phase II study is proposed in which patients with PSA progression on abiraterone or enzalutamide will be crossed over to the opposite agent. Although not a surrogate for clinical outcomes, PSA changes will be used to assess treatment efficacy since PSA expression is driven by AR activation. Apart from determining optimal sequencing of abiraterone and enzalutamide in mCRPC patients, a key issue associated with the use of these agents is identifying circulating biomarkers associated with treatment response and resistance. Our group has preliminary data showing that a high proportion of enzalutamide-resistant mCRPC patients and some abiraterone-resistant mCRPC patients possess focal AR amplification in cell-free tumour DNA extracted from plasma. In pre-clinical studies, other potential mechanisms of resistance to these agents include increased expression of AR splice variants (abiraterone and enzalutamide)[9,10], increased expression of CYP17 (abiraterone)[6,9], upregulation of the stress-activated chaperone protein clusterin (enzalutamide only)[11] and a point mutation (F876L) in the ligand-binding domain of the AR (enzalutamide only)[12,13]. Non-coding RNAs (ncRNAs) are additional biomarkers of interest since they are implicated in tumorigenesis and are readily detectable in plasma of mCRPC patients[14]. Examination of these biomarkers in serum and plasma is planned, with the aim of identifying potentially novel factors associated with treatment efficacy and resistance in mCRPC patients receiving abiraterone and enzalutamide. The cognitive effects of abiraterone and enzalutamide are not well described. Enzalutamide is known to cross the blood-brain barrier and infrequently causes seizures, possibly related to effects on the γ-aminobutyric acid–gated chloride channel[15]. In the enzalutamide registration study, a small subset (< 5%) of patients also developed mental impairment disorders including amnesia, memory impairment, cognitive disorder and disturbance in attention[16]. Conversely, no central nervous system effects of abiraterone have been reported. Cognitive testing will therefore be undertaken in this study to evaluate potential differences between these agents.
Hypothesis	That the differing mechanisms through which abiraterone acetate and enzalutamide target AR signaling will permit effective sequencing of these agents.
Primary Objectives	1. To evaluate the PSA response rate (defined as a ≥ 30% decline in PSA from baseline confirmed on repeat measurement ≥ 28 days later) in mCRPC

	patients with PSA progression on first-line therapy with abiraterone acetate or enzalutamide when crossed over to second-line therapy with the opposite agent. 2. To evaluate the time to second PSA progression of combined first and second-line therapy (from start of first-line therapy to PSA progression on cross-over second-line therapy).
Secondary Objectives	1. To collect whole blood, serum and plasma to identify potential biomarkers that are associated with treatment efficacy and/or resistance in mCRPC patients receiving abiraterone acetate and enzalutamide. 2. To evaluate the PSA response rate in mCRPC patients treated with first-line abiraterone acetate or enzalutamide. 3. To evaluate time to PSA progression with first or second-line abiraterone acetate or enzalutamide. 4. To evaluate duration of second-line therapy and time to clinical progression on second-line therapy. 5. To evaluate cognitive, depressive, and functional effects of abiraterone acetate and enzalutamide 6. To evaluate overall survival in patients treated with sequential abiraterone acetate and enzalutamide 7. To evaluate safety and toxicity profiles of second-line abiraterone acetate or enzalutamide.
Study Population	Patients with metastatic castration-resistant prostate cancer
Study Design	Randomized phase II with 1:1 randomization to either Arm A or Arm B (see Figure 1): Arm A: Patients will receive abiraterone acetate 1000 mg PO OD with prednisone 5 mg PO BID or 10 mg OD as per standard of care. At time of PSA progression (see Section 5.5), patients will receive enzalutamide 160 mg PO daily until clinical progression as per standard of care. Arm B: Patients will receive enzalutamide 160 mg PO OD as per standard of care. At time of PSA progression (see Section 5.5) patients will receive abiraterone acetate 1000 mg PO OD with prednisone 5 mg PO BID or 10 mg OD until clinical progression as per standard of care.
Inclusion Criteria	Patients must meet **ALL** of the following criteria: 1. Willing and able to provide informed consent 2. Adult males ≥ 18 years age 3. History of adenocarcinoma of the prostate diagnosed histologically without evidence of neuroendocrine or small cell differentiation, or if patient does not have pathology of adenocarcinoma of the prostate, patient has metastatic disease typical of prostate cancer (i.e., involving bone or pelvic lymph nodes or para-aortic lymph nodes) AND a serum concentration of PSA that is rising and >20ng/mL at the time of when the patient was clinically diagnosed with prostate cancer. 4. Prior surgical orchiectomy or if on LHRH agonist/antagonist then testosterone < 1.7 nmol/L at screening visit (patients must maintain LHRH agonist/antagonist therapy for duration of study treatment if not surgically castrated)

	5. Evidence of metastatic disease on bone scan or CT scan 6. Evidence of biochemical or imaging progression in the setting of surgical or medical castration. Progressive disease for study entry is defined by one of the following three criteria: a. PSA progression: minimum of two rising PSA values from a baseline measurement with an interval of ≥ 1 week between each measurement. Minimum PSA at screening visit is > 2.0 ug/L b. Soft tissue or visceral disease progression (see Appendix B for definition of measurable disease as per RECIST 1.1 criteria) c. Bone progression: ≥ 2 new lesions on bone scan 7. ECOG performance status 0-2 (see Appendix C) 8. Eligible for treatment with either abiraterone acetate or enzalutamide as per standard of care guidelines 9. Adequate organ function defined as: a. Absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L and hemoglobin ≥ 80 g/L b. Creatinine clearance ≥ 30 ml/min (calculated by Cockcroft-Gault formula, see Appendix D) c. Serum potassium > than lower limit of normal range d. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) except for patients with known Gilbert's syndrome (direct bilirubin ≤ 1.5 x ULN) e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5 x ULN 10. Able to swallow study drug and comply with study requirements including provision of peripheral blood samples at specified time points for correlative studies 11. Recovery from all prior treatment-related toxicity to grade ≤ 2 (as per CTC AE 4.0)
Exclusion Criteria	Patients must **NOT** meet any of the following criteria: 1. Severe concurrent illness or co-morbid disease that would make the subject unsuitable for enrolment 2. Prior therapy with CYP17 inhibitors (including abiraterone acetate, TAK-700, TOK-001 and ketoconazole), enzalutamide or other experimental anti-androgens (e.g. ARN-509, TOK-001) 3. Prior systemic chemotherapy for mCRPC 4. Life expectancy < 6 months 5. Active concurrent malignancy (with the exception of non-melanomatous skin cancer) 6. Wide-field radiotherapy or radioisotopes such as Strontium-89 or Radium-223 ≤ 28 days prior to starting study drug (limited-field palliative radiotherapy for 1-5 fractions is permitted) 7. Brain metastases or active epidural disease (treated epidural disease is permitted) 8. Use of herbal products that may lower PSA level (e.g. saw palmetto) 9. Contraindication to prednisone therapy including poorly controlled diabetes mellitus 10. History of seizure or seizure disorder, or history of any cerebrovascular event

	within 6 months of study entry. 11. Gastrointestinal disorder affecting absorption 12. Major surgery within 4 weeks of starting study treatment
Laboratory and imaging assessments (see Table 1)	1. Screening visit: CBC, electrolytes, creatinine, random glucose, AST, ALT, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), bilirubin, gamma-glutamyl transpeptidase (GGT), PSA, testosterone, albumin, bone scan, CT chest (or X-Ray chest), CT abdomen and pelvis (CT C/A/P; or CXR and CT A/P) 2. Start of first-line therapy: CBC, electrolytes, creatinine, AST, ALT, ALP, LDH, bilirubin, random glucose, GGT, PSA & albumin, **correlative studies** 3. On Study: PSA every 28 days, other labs for safety will be performed as per standard of care, bone scan and CT A/P + Chest imaging (CT or Chest X-ray as was done at baseline) every 12 weeks from cycle 1 (or more frequently as clinically indicated), patients on Abiraterone arm are required to have safety labs from cycles 1-3 (inclusive) 4. Start of second-line therapy: CBC, electrolytes, creatinine, random glucose, AST, ALT, ALP, LDH, bilirubin, GGT, PSA, albumin, **correlative studies, bone and CT scans required +/- 4 weeks from cross-over** 5. End of second-line therapy or End of first-line therapy if subject will not cross-over to second-line therapy: CBC, electrolytes, creatinine, AST, ALT, ALP, LDH, bilirubin, GGT, PSA, albumin, **correlative studies**
Correlative studies (see Table 1)	**Participation in correlative studies is mandatory for study enrolment.** In addition to routine laboratory tests, peripheral blood samples will be collected at **start of first-line therapy, start of second-line therapy and end of study treatment** (i.e. maximum 3 draws per patient). A total of 4 EDTA tubes (6 ml per tube), 1 SST tube (5 ml), and 1 PAXgene (2.5mL) will be collected per patient at each time point. If subject will not cross-over to second-line therapy, correlative studies are required at the end of first-line therapy.
Primary End Points	1. PSA response rate in subjects with PSA progression on first-line abiraterone acetate or enzalutamide when crossed over to second-line therapy with the opposite agent. PSA response is defined as ≥ 30% decline in PSA value from commencement of second-line therapy confirmed on repeat measurement ≥ 28 days later.
Secondary End Points	1. Correlation of serum and plasma biomarker expression with PSA response to first-line and second-line abiraterone acetate or enzalutamide 2. PSA response rates to first-line abiraterone acetate or enzalutamide 3. Time to PSA progression on first-line and second-line abiraterone acetate or enzalutamide 4. Time on study treatment and time to clinical progression on second-line abiraterone acetate or enzalutamide 5. Overall survival in patients treated with sequential abiraterone acetate and enzalutamide 6. Safety of second-line treatment with abiraterone acetate or enzalutamide
Duration of therapy	**First-line therapy** Study treatment will continue until **ANY** of the following occur: 1. Development of PSA progression, which is defined as: a. **In patients without a PSA decline**: A PSA that is ≥ 25% and ≥ 2 ug/L above baseline after ≥ 12 weeks of study treatment. b. **In patients with a PSA decline at any time on first-line therapy:**

	A PSA increase of ≥ 25% and ≥ 2 ug/L above nadir, confirmed by a repeat measurement ≥ 28 days later (confirmed rising trend). 2. Treatment of symptomatic bone metastases with wide-field radiation, as this would indicate treatment failure 3. Unacceptable treatment-related toxicity. 4. Withdrawal of consent. **Second-line therapy** Treatment will continue until **ANY** of the following occur: 1. Symptomatic or clinical progression that, in the opinion of the Investigator, signifies the subject is no longer benefiting from study treatment. **NB: PSA progression on second-line therapy will be documented but does not mandate cessation of study treatment.** 2. Unacceptable treatment-related toxicity. 3. Withdrawal of consent.
Statistical design	The primary clinical endpoint is the proportion of patients with a PSA response defined as a PSA decline ≥ 30% from baseline with second-line therapy. A "pick the winner" randomized phase 2, Simon's Optimal two-stage design will be employed. A PSA response rate in either arm of 10% or less would not be of interest for further study (null hypothesis). If the PSA response rate for either arm were 30% or greater, then this would be considered of interest to further evaluate in larger trials. Using an alpha error of 0.1 and a beta error of 0.1, 12 patients per arm will be initially accrued. If 2 or more patients respond in either arm, both arms will be expanded to 35 evaluable patients. Accounting for a 10% drop-out/non-evaluable rate, approximately 78 evaluable patients (39 per arm) will be required to meet the statistical end points to address this objective. The other primary endpoint of this study is time to second PSA progression, calculated from time of start of first-line therapy to time of PSA progression on cross-over second-line therapy. Accrual will continue to a total of 200 patients (100 per arm). The probability is 70 percent that the study will detect a treatment sequence difference at a two sided 0.05 significance level, if the true hazard ratio is 1.519. This is based on the assumption that the accrual period will be 18 months, the follow up period will be 18 months and a median time to PSA progression of 12 months (null hypothesis). The total number of events will be 140.

FIGURE 1: STUDY DESIGN

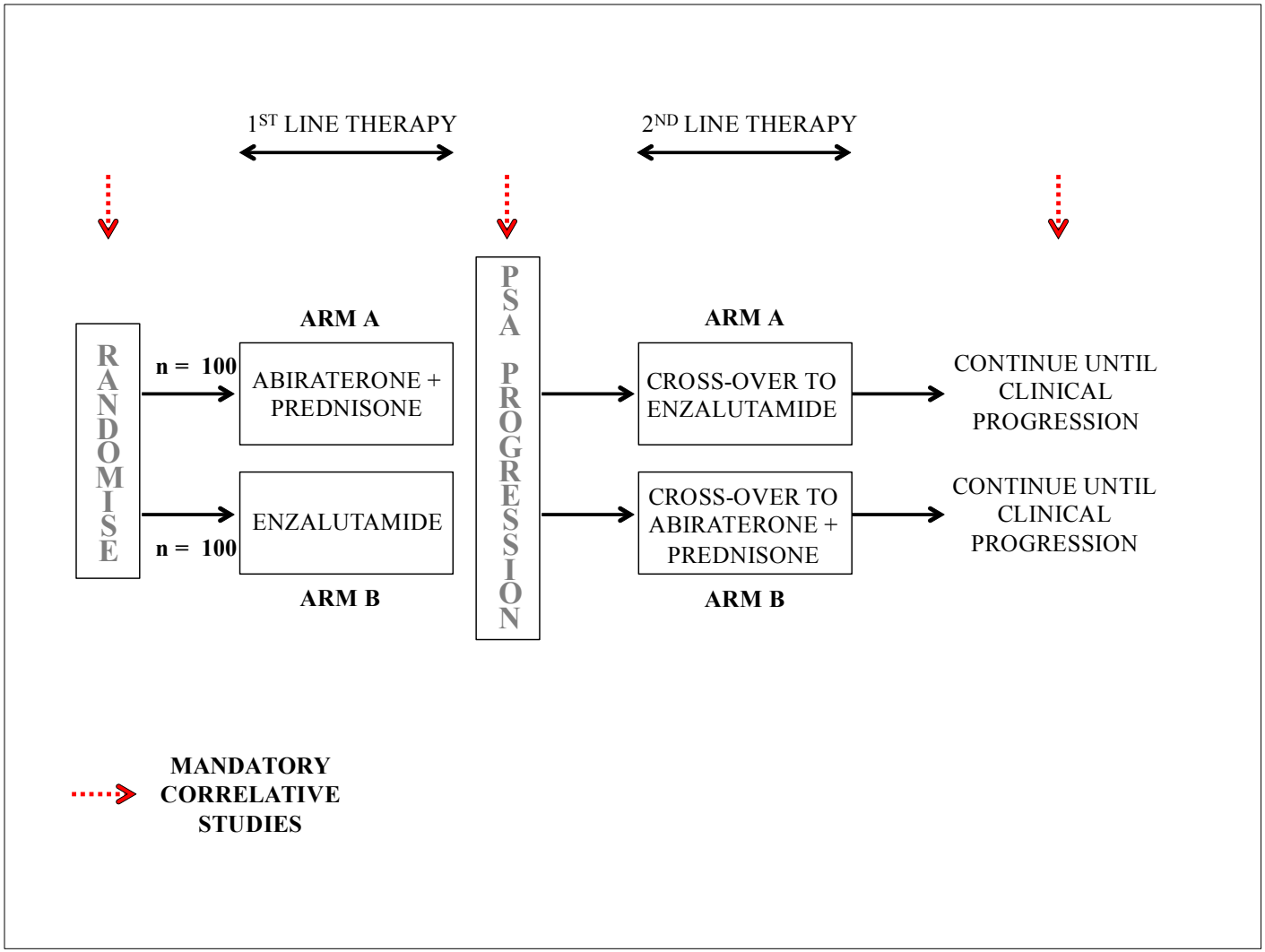


TABLE 1: STUDY ASSESSMENTS

		FIRST-LINE THERAPY			SECOND-LINE THERAPY				
Study Day	**Screening Visit**	**C1**	**C2 - C4[a]**	**Subsequent Cycles[q]**	**C1[b]**	**C2 - 4[a]**	**Subsequent Cycles**	**End of second-line therapy[p]**	**Follow-Up**
Timeline	Day -28 to Day -1[r]	Day 1 (Baseline)	Day 1 of every cycle	Day 1 of cycle	Day 1 (Baseline)	Day 1 of every cycle	Day 1 of cycle	Last dose	
Window (days)			± 5 days	± 5 days	- 5 days[s]	± 5 days	± 5 days	± 5 days	
Protocol Section	**8.1**	**8.2.1**	**8.2.2**	**8.2.3**	**8.3.1**	**8.3.2**	**8.3.3**	**8.4**	
Informed consent	×								
Medical history & demographics	×								
Inclusion/exclusion criteria	×	×[c]							
Randomisation		×							
Vital signs	×	×[c]	×		×	×		×	
Physical examination	×	×[c]	×		×	×		×	
PHQ-9 Questionnaire[m]	×	×[c]	×	x	×	×	x	×	
FACT-P Questionnaire[n]	×	×[c]	x	x	×	×	x	×	
Montreal Cognitive Assessment[ou]	×		Cycle 4 visit only		×[l]	Cycle 4 visit only		×[u]	
ECOG	×	×[c]	×		×	×		×	
AEs (of interest & Grade ≥ 3 only)[d]		×	×	x	×	×	x	×	
Concomitant medications	×	×	×	x	×	×	x	×	
Clinical labs[e]	×	×[ch]	× Safety labs for subjects on Abiraterone[h]		×[h]	× Safety labs for subjects on Abiraterone[h]		×	
PSA[f]	×	×[c]	x	x	×	×	x	×	
Correlative studies[g]		×			×			×	
CT chest (or X-Ray chest) and CT abdomen/pelvis	×[i]		Every 12 (+/- 1) weeks[j]	Every 12 (+/- 1) weeks[j]	×[t]	Every 12 (+/- 1) weeks[j]	Every 12 (+/- 1) weeks[j]		
Whole body bone scan	×[i]		Every 12 (+/- 1) weeks[j]	Every 12 (+/- 1) weeks[j]	×[t]	Every 12 (+/- 1) weeks[j]	Every 12 (+/- 1) weeks[j]		
Study drug treatment		×	×	x	×	×	x		
Overall survival[k]									×

[a]Study visits for cycles 2-4 (inclusive) on first-line therapy will be every 4 weeks from commencement of study medication.
[b]**Cross-over from first-line therapy to second-line therapy is mandatory when PSA progression occurs.** Patients who cease first-line therapy due to PSA progression will immediately commence second-line therapy. Please refer to Section 11.1 for instructions on initiation of second-line therapy in patients who cease first-line therapy in the absence of PSA progression.
[c]If cycle 1, day 1 occurs within 7 days of screening visit, the following assessments can be omitted: Inclusion/exclusion criteria, vital signs, physical examination, ECOG, clinical labs, PSA, questionnaires. However, correlative studies must be performed at commencement of first-line therapy.
[d]See Appendix A for AEs of interest
[e]See Section 8.1 to 8.4 Bilirubin, AST and ALT can be performed as per standard of care.
[f]**PSA must be performed every 4 weeks while subjects are on study (even if on treatment break due to toxicity or recovery from radiation). Wherever possible, PSA testing should be performed at the same laboratory throughout the study.**
[g]**Mandatory correlative studies at start of first-line therapy, start of second-line therapy and end of second-line therapy. Mandatory correlative studies are required at the end of first-line therapy if subject will not cross-over to second-line therapy.**
[h]Electrolytes, Bilirubin, AST and ALT as per standard of care on D15 of cycles 1, 2, and 3 for patients on abiraterone acetate + prednisone
[i]Standard of care CT and bone scans performed within 6 weeks of commencing first-line therapy can be used even if done prior to consent being signed
[j]CT and bone scan are required at a minimum of every 12 weeks from cycle 1 (+/- 1 week) or more frequently at Investigator discretion. Patients without pulmonary or mediastinal metastatic disease on screening CT or Chest X-ray are permitted to have CT abdomen/pelvis only on follow-up scans.
[k]After discontinuation of second-line therapy or first-line therapy if subject does not cross over to second-line therapy, survival data will be collected every 12 weeks.
[l] A baseline cognitive assessment will be undertaken prior to initiation of second line therapy.
[m] PHQ-9 depression assessments will be completed at screening, at the beginning of cycles 1- 4 and subsequent cycles, and at the end of second-line therapy or end of first-line therapy if subject will not be crossing over to second-line therapy. Not required after July 1, 2018
[n]FACT-P questionnaire will be completed at screening, at the beginning of cycles 1 – 4 and subsequent cycles, and at the end of the second-line therapy or end of first-line therapy if subject will not be crossing over to second-line therapy. Not required after July 1, 2018.
[o] Use alternate versions of assessment if done within 3 months or less from previous one. Not required after July 1, 2018
[p] Complete End of second-line therapy visit if subject will not be crossing over to second-line therapy.
[q] All subsequent cycle visits will be as per standard of care **(however, PSA must be performed every 4 weeks).**
[r] First-line therapy, Cycle 1/ Day 1 (Baseline) visit may be completed on the same day as Screening visit if feasible however, subject's eligibility will need to be confirmed prior to correlatives sample collection, randomization, and study drug treatment.
[s] Second –line therapy Cycle 1 assessments can be completed up to 5 days prior to commencing second-line therapy.
[t] CT and bone scans are required +/- 4 weeks from cross-over.

" MoCA is required to be completed at end of therapy *only if* it is before the Cycle 4 visit (i.e. patient discontinues therapy before Cycle 4). Not required after July 1, 2018

2.0 BACKGROUND AND RATIONALE

2.1 PROSTATE CANCER

Prostate cancer is the most common cancer among men and the third most common cause of cancer deaths in males in the developed world[17]. Although the majority of men with metastatic prostate cancer initially respond to androgen deprivation therapy, development of castration-resistant disease is inevitable. Until recently, docetaxel remained the only available systemic agent proven to prolong overall survival in mCRPC[18]. In the past three years however, five novel agents including abiraterone acetate[1], enzalutamide[3], cabazitaxel[19], radium-223 dichloride[20] and sipuleucel-T[21] have demonstrated a significant overall survival benefit in phase III trials in mCRPC. Although the development of these agents has greatly expanded the therapeutic armamentarium for mCRPC, it has also led to questions about optimal sequencing of systemic therapy.

2.2 ABIRATERONE ACETATE AND ENZALUTAMIDE

It is now well established that the androgen receptor (AR) pathway remains active in CRPC[22] and this knowledge has provided a rationale for developing novel hormonal compounds such as abiraterone acetate and enzalutamide. Abiraterone is a potent, selective and irreversible inhibitor of CYP17, a cytochrome P450 (CYP) enzyme centrally involved in extra-gonadal androgen biosynthesis[23]. Enzalutamide is a potent AR antagonist that remains active in the setting of increased AR expression and has been shown to inhibit nuclear translocation and peptide co-activator recruitment of the ligand-receptor complex[24]. Importantly, both agents have demonstrated efficacy in mCRPC irrespective of prior chemotherapy use (see Section 3.2). In post-docetaxel mCRPC patients, abiraterone plus prednisone significantly improved median overall survival by 4.6 months over prednisone monotherapy (COU-AA-301 trial)[1] while enzalutamide significantly increased median overall survival by 4.8 months compared to placebo (AFFIRM trial)[3]. In chemotherapy-naïve mCRPC patients, abiraterone plus prednisone was shown to significantly improve radiological progression-free survival (PFS) compared with prednisone in the COU-AA-302 trial[2]. As radiological PFS was a co-primary endpoint of the COU-AA-302 trial, this study was terminated prior to statistical significance being met for a difference in overall survival. Nevertheless, treatment with abiraterone plus prednisone resulted in longer median overall in comparison to prednisone alone (HR 0.75). Enzalutamide also has activity in chemotherapy-naïve mCRPC, with recent results released from the PREVAIL study demonstrating a significant increase in median overall survival for enzalutamide over placebo (HR 0.70)[4].

Thus, both abiraterone acetate and enzalutamide have proven and comparable activity in mCRPC. Despite their efficacy however, an unresolved question regarding the use of abiraterone acetate and enzalutamide is the best sequence in which these agents should be used. While both agents target androgen-AR signaling, their mechanisms of action differ and theoretically disparate mechanisms of resistance may allow for successful sequencing of these agents. Prior studies have reported PSA response rates (PSA decline $\geq$ 50% from baseline) of under 10% in patients treated with abiraterone after enzalutamide[5,6] and 13%-29% in patients treated with enzalutamide after abiraterone[7,8]. These data were generated in small, retrospective series, highlighting the need for a randomized clinical trial to examine the activity of second-line abiraterone and enzalutamide after treatment with the opposite agent.

2.3 RESISTANCE MECHANISMS TO ABIRATERONE ACETATE AND ENZALUTAMIDE

Despite their proven activity in mCRPC, resistance to abiraterone acetate and enzalutamide ultimately occurs in all patients. Various mechanisms have been identified as being associated with resistance to these agents, mainly from pre-clinical studies. Among these mechanisms is induction of AR splice variants, increased expression of CYP17, a novel mutation (F876L) of the ligand-binding domain (LBD) of the AR and increased expression of a stress-activated chaperone protein (clusterin).

AR splice variants are truncated AR isoforms which, despite lacking a C-terminal LBD, enhance the transcription of AR-regulated genes in a ligand-independent manner[25]. The transcriptional activity of splice variants results from the fact that the N-terminal domain contains AF1, the principal transactivation domain of the AR[26]. Pre-clinical studies indicate that induction of AR splice variants accompanies resistance to both abiraterone[9,27] and enzalutamide[9,10,28]. Resistance to abiraterone has also been linked to increased expression of its primary target, CYP17, in pre-clinical models[27,29] and a solitary clinical study[29]. Resistance to enzalutamide in prostate cancer cells has been associated with a novel point mutation in the AR LBD (F876L), which produces a conformational change that leads to enzalutamide aberrantly behaving as an AR agonist rather than as an antagonist[13,30]. Lastly, a recent pre-clinical report identified upregulation of the PI3K and MAPK signaling pathways by the stress-activated chaperone protein clusterin as a novel resistance mechanism to enzalutamide[11]. Collectively, these predominantly pre-clinical data indicate that multiple mechanisms may contribute to resistance of mCRPC to abiraterone and enzalutamide. This in turn highlights the importance of further examining resistance to abiraterone and enzalutamide in patient-derived clinical samples.

2.4 CIRCULATING CELL-FREE TUMOUR DNA

A major obstacle to examining molecular markers in mCRPC is the ability to readily access metastatic tumour tissue from bone or intra-abdominal lymph nodes. As a consequence, capturing circulating cell-free tumor DNA from plasma represents a highly attractive approach for molecular characterisation of mCRPC. Importantly, it has previously been shown that cell-free tumour DNA is present in plasma from patients with mCRPC and its amount and copy number profile can be modulated by therapeutic interventions[31,32]. Our group has preliminary data suggesting that most enzalutamide-resistant mCRPC patients and some abiraterone-resistant mCRPC patients possess focal AR amplification in cell-free tumour DNA extracted from plasma. Further evaluation of biomarkers in cell-free tumour DNA and correlation of treatment outcome with abiraterone acetate and enzalutamide may uncover novel molecular factors associated with treatment efficacy and resistance.

2.5 COGNITIVE EFFECTS OF ABIRATERONE ACETATE AND ENZALUTAMIDE

The cognitive effects of abiraterone and enzalutamide are not well described. Enzalutamide is known to cross the blood-brain barrier and infrequently causes seizures, possibly related to effects on the γ-aminobutyric acid–gated chloride channel[15]. In the enzalutamide registration study, a small subset (< 5%) of patients also developed mental impairment disorders including amnesia, memory impairment, cognitive disorder and disturbance in attention[16]. Conversely, no

central nervous system effects of abiraterone have been reported. Cognitive testing will therefore be undertaken in this study to evaluate potential differences between these agents.

3.0 BACKGROUND THERAPEUTIC INFORMATION

Abiraterone acetate and enzalutamide will be purchased from commercial supply and provided though the BC Cancer Agency. Abiraterone acetate and enzalutamide are both approved by Health Canada for treatment of mCRPC. Please refer to product monograph for full details. The following information is for summary purposes only.

3.1 PHARMACOLOGY

Abiraterone acetate is converted *in vivo* to abiraterone, which is an irreversible inhibitor of the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is upregulated in CRPC tissue and is required for extra-gonadal androgen biosynthesis in the adrenal gland and within prostate cancer tissue. CYP17 catalyses the conversion of pregnenolone and progesterone into the testosterone precursors, DHEA and androstenedione, respectively.

Enzalutamide is an AR antagonist that has more than 10 times the affinity for the AR when compared to bicalutamide. Unlike bicalutamide it also inhibits nuclear co-localisation of the AR and peptide co-activator recruitment.

3.2 CLINICAL EFFICACY DATA

TABLE 2: EFFICACY OF ABIRATERONE ACETATE (AA) AND ENZALUTAMIDE IN RANDOMIZED PHASE III STUDIES IN mCRPC PATIENTS

Study	Population	Treatment	PSA RR[a]	Time to PSA progression (median, months)	Radiological PFS[b] (median, months)	Overall survival (median, months)
COU-AA-301[33]	Post-docetaxel	AA + prednisone (n=797) vs. prednisone (n=398)	30% vs. 6% p<0·0001	8.5 vs. 6.6 HR 0.63, p<0·0001	5.6 vs. 3.6 HR 0.66, p<0·0001	15.8 vs. 11.2 HR 0.74, p<0·0001
COU-AA-302[2]	Docetaxel-naïve	AA + prednisone (n=546) vs. prednisone (n=542)	62% vs. 24% p<0.001	11.1 vs. 5.6 HR 0.49, p<0·001	16.5 vs. 8.3 HR 0.53, p<0·001	NR vs. 27.2 HR 0.75, p=0.01[c]
AFFIRM[3]	Post-docetaxel	Enzalutamide (n=800) vs. placebo (n=399)	54% vs. 2% p<0.001	8.3 vs. 3.0 HR 0.25, p<0·001	8.3 vs. 2.9 HR 0.40, p<0·001	18.4 vs. 13.6 HR 0.63, p<0·001
PREVAIL[d]	Docetaxel-naive	Enzalutamide vs. placebo	NR	NR	NR vs. 3.9 HR 0.19, p<0.0001	32.4 vs. 30.2 HR 0.70, p<0.0001

[a] PSA RR (response rate): PSA decline ≥ 50%
[b] PFS: Progression-free survival
[c] Not significant
[d] Unpublished data
NR: Not reported

3.3 CLINICIAL TOXICITY DATA

3.3.1 Abiraterone acetate + prednisone

ORGAN SITE	SIDE EFFECTS
Cardiovascular	**Hypertension** (9%, severe < 1%) Atrial fibrillation (4%, severe 1%) Cardiac failure (2%, severe < 1%) Angina (1%, severe < 1%)
Gastrointestinal	Diarrhoea (18%, severe < 1%) Dyspepsia (6%)
General	Fatigue (39%) **Peripheral oedema** (28%, severe < 1%) Hot flashes (19%) Fracture (6%, severe 1%)
Laboratory	**ALT, increased** (12%, severe 5%) **AST, increased** (11%, severe 3%) **Hypokalaemia** (17%, severe 2%)
Musculoskeletal	Bone pain (20%)
Renal	Urinary symptoms (7%)

3.3.2 Enzalutamide

ORGAN SITE	SIDE EFFECTS
Cardiovascular	**Hypertension** (6%, severe 2%) Myocardial infarction (2%, severe < 1%)
Gastrointestinal	Diarrhoea (21%, severe 1%)
General	**Fatigue** (34-51%, severe 6%) Hot flashes (20%) Peripheral oedema (15%) Headache (12%, severe 1%) Fracture (4%)
Laboratory	ALT increased (10%, severe < 1%) AST increased (23%, severe < 1%)
Musculoskeletal	Musculoskeletal pain (14%, severe 1%)
Neurological	**Seizure** (< 1%)
Renal	Urinary symptoms (7%)

Clinically significant side effects of interest are in **bold**.

4.0 STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVES

i. To evaluate the PSA response rate (defined as a ≥ 30% decline in PSA from baseline confirmed on repeat measurement ≥ 28 days later) in mCRPC patients with PSA progression on first-line therapy with abiraterone acetate or enzalutamide when crossed over to second-line therapy with the opposite agent.

ii. To evaluate the time to second PSA progression of combined first and second-line therapy (from start of first-line therapy to PSA progression on cross-over second-line therapy).

4.2 SECONDARY OBJECTIVES

i. To collect whole blood, serum and plasma to potentially identify biomarkers that are associated with treatment efficacy and/or resistance in mCRPC patients receiving abiraterone acetate and enzalutamide.

ii. To evaluate the PSA response rate in mCRPC patients treated with first-line abiraterone acetate or enzalutamide.

iii. To evaluate time to PSA progression with first or second-line abiraterone acetate or enzalutamide.

iv. To evaluate duration of second-line therapy and time to clinical progression on second-line therapy.

v. To evaluate cognitive, depressive, and functional effects of abiraterone acetate and enzalutamide

vi. To evaluate overall survival in patients treated with sequential abiraterone acetate and enzalutamide.

vii. To evaluate safety and toxicity profiles of second-line abiraterone acetate or enzalutamide.

5.0 STUDY DESIGN AND ENDPOINTS

5.1 DESCRIPTION OF STUDY DESIGN

This is a multi-centre, randomized phase II study of sequencing abiraterone acetate and enzalutamide in patients with mCRPC. Subjects will be allocated to either Arm A (first-line abiraterone acetate plus prednisone followed by second-line enzalutamide) or Arm B (first-line enzalutamide followed by second-line abiraterone acetate plus prednisone). Total accrual of 200 subject is planned, 100 per arm.

5.2 SCREENING PHASE

Patients must sign an Informed Consent Form before any study-related procedures can commence. Eligibility for enrollment will be determined on the basis of Inclusion and Exclusion Criteria as outlined in Sections 6.2 and 6.3 respectively. A list of procedures to be undertaken at screening is summarized in Table 1 and Section 8.1.

5.3 RANDOMIZATION AND TREATMENT ALLOCATION

After completing screening procedures and determining eligibility for trial enrollment, subjects will be randomized 1:1 to either Arm A or Arm B as outlined in Section 12.2.

5.4 FIRST-LINE THERAPY

5.4.1 Cycle 1

Subjects will commence cycle 1 on first-line therapy within 5 days of randomization. A list of study-related procedures **(including mandatory correlative studies)** required at commencement of cycle 1 on first-line therapy is summarized in Table 1 and outlined in Section 8.2.1. Subjects randomized to Arm A will receive abiraterone acetate 1000 mg PO daily plus prednisone 5 mg PO BID or 10 mg OD as per standard of care. Subjects randomized to Arm B will receive enzalutamide 160 mg PO OD as per standard of care.

5.4.2 Cycle 2 and subsequent cycles

Treatment will be organized into 28-day cycles. A list of study-related procedures required for cycle 2 and subsequent cycles on first-line therapy is summarized in Table 1 and outlined in Sections 8.2.2 and 8.2.3.

5.5 CROSS-OVER FROM FIRST-LINE TO SECOND-LINE THERAPY

Cross-over from first-line to second-line therapy is mandated when subjects develop PSA progression. Other reasons for discontinuation of first-line therapy are outlined in Section 11.1. For the purposes of determining time of cross-over to second-line therapy, PSA progression is defined as:

i. **In patients without a PSA decline**: A PSA that is ≥ 25% and ≥ 2 ug/L above baseline after ≥ 12 weeks of study treatment.

ii. **In patients with a PSA decline at any time on first-line therapy:** A PSA increase of ≥ 25% and ≥ 2 ug/L above nadir, confirmed by a repeat measurement ≥ 28 days later (confirmed rising trend).

Patients who cease first-line therapy due to PSA progression will immediately commence second-line therapy. Please refer to Section 11.1 for instructions on initiation of second-line therapy in patients who cease first-line therapy in the absence of PSA progression. If subject will not be crossing over to second-line therapy, subject will still be required to complete end of second-line therapy visit.

5.6 SECOND-LINE THERAPY

5.6.1 Cycle 1

Patients randomized to Arm A will cease abiraterone acetate and commence enzalutamide 160 mg PO OD. It is recommended that subjects be weaned off prednisone when ceasing abiraterone acetate although Investigators have the option of continuing prednisone. A suggested weaning programme would be to administer prednisone 5mg PO daily for 2 weeks, reduce to 2.5 mg PO daily for 2 weeks and then to cease. Patients randomized to Arm B will cease enzalutamide and commence abiraterone acetate 1000 mg PO OD plus prednisone 5 mg PO BID or 10 mg PO OD.

A list of study-related procedures **(including mandatory correlative studies)** at commencement of cycle 1 on second-line therapy is summarized in Table 1 and outlined in Section 8.3.1.

5.6.2 Cycle 2 and subsequent cycles

Treatment will be organized into cycles of 28 days. A list of study-related procedures required for cycle 2 and subsequent cycles on second-line therapy is summarized in Table 1 and outlined in Sections 8.3.2 and 8.3.3.

5.7 END OF SECOND-LINE THERAPY

Second-line therapy will be continued until the Investigator deems a subject is no longer benefitting from treatment. **NB: PSA progression on second-line therapy will be documented but does not mandate cessation of study treatment.** Other reasons for discontinuing second-line therapy are outlined in Section 11.2. A list of study-related procedures **(including mandatory correlative studies)** is summarized in Table 1 and outlined in Section 8.4.

6.0 STUDY POPULATION

6.1 PATIENT POPULATION

Patients with metastatic castration-resistant prostate cancer.

6.2 INCLUSION CRITERIA

Patients must meet **ALL** of the following criteria:

1. Willing and able to provide informed consent
2. Adult males ≥ 18 years age
3. History of adenocarcinoma of the prostate diagnosed histologically without evidence of neuroendocrine or small cell differentiation, or if patient does not have pathology of adenocarcinoma of the prostate, patient has metastatic disease typical of prostate cancer (i.e., involving bone or pelvic lymph nodes or para-aortic lymph nodes) AND a serum concentration of PSA that is rising and >20ng/mL at the time of when the patient was clinically diagnosed with prostate cancer
4. Prior surgical orchiectomy or if on LHRH agonist/antagonist then testosterone < 1.7 nmol/L at screening visit (patients must maintain LHRH agonist/antagonist therapy for duration of study treatment if not surgically castrated)
5. Evidence of metastatic disease by bone scan or CT scan
6. Evidence of biochemical or imaging progression in the setting of surgical or medical castration. Progressive disease for study entry is defined by one of the following three criteria:
    a. PSA progression: minimum of two rising PSA values from a baseline measurement with an interval of ≥ 1 week between each measurement. Minimum PSA at screening visit is > 2.0 ug/L
    b. Soft tissue or visceral disease progression: (see Appendix B for definition of measurable disease as per RECIST 1.1 criteria)

c. Bone progression: ≥ 2 new lesions on bone scan

7. ECOG performance status 0-2 (see Appendix C)
8. Eligible for treatment with either abiraterone acetate or enzalutamide as per standard of care guidelines
9. Adequate organ function defined as:
    a. Absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L and hemoglobin ≥ 80 g/L
    b. Creatinine clearance ≥ 30 ml/min (calculated by Cockcroft-Gault formula, see Appendix D)
    c. Serum potassium > than lower limit of normal range
    d. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) except for patients with known Gilbert's syndrome (direct bilirubin ≤ 1.5 x ULN)
    e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5 x ULN
10. Able to swallow study drug and comply with study requirements including provision of peripheral blood samples at specified time points for correlative studies
11. Recovery from all prior treatment-related toxicity to grade ≤ 2 (as per CTC AE 4.0)

6.3 EXCLUSION CRITERIA

Patients must **NOT** meet any of the following criteria:

1. Severe concurrent illness or co-morbid disease that would make the subject unsuitable for enrolment
2. Prior therapy with CYP17 inhibitors (including abiraterone acetate, TAK-700, TOK-001 and ketoconazole), enzalutamide or other experimental anti-androgens (e.g. ARN-509, TOK-001)
3. Prior systemic chemotherapy for mCRPC
4. Life expectancy < 6 months
5. Active concurrent malignancy (with the exception of non-melanomatous skin cancer)
6. Wide-field radiotherapy or radioisotopes such as Strontium-89 or Radium-223 ≤ 28 days prior to starting study drug (limited-field palliative radiotherapy for 1-5 fractions is permitted)
7. Brain metastases or active epidural disease (treated epidural disease is permitted)
8. Use of herbal products that may lower PSA level (e.g. saw palmetto)
9. Contraindication to prednisone therapy including poorly controlled diabetes mellitus
10. History of seizure or seizure disorder, or history of any cerebrovascular event within 6 months of study entry.
11. Gastrointestinal disorder affecting absorption
12. Major surgery within 4 weeks of starting study treatment

7.0 TREATMENT

7.1 STUDY TREATMENT

7.1.1 Dosing

Arm A: Patients will receive abiraterone acetate 1000 mg PO OD with prednisone 5 mg PO BID or 10 mg OD as per standard of care. At time of PSA progression (see Section 5.5), patients will receive enzalutamide 160 mg PO daily until symptomatic or clinical progression that, in the opinion of the Investigator, signifies the subject is no longer benefiting from study treatment.

Arm B: Patients will receive enzalutamide 160 mg PO OD as per standard of care. At time of PSA progression (see Section 5.5), patients will receive abiraterone acetate 1000 mg PO OD with prednisone 5 mg PO BID or 10 mg OD until symptomatic or clinical progression that, in the opinion of the Investigator, signifies the subject is no longer benefiting from study treatment.

7.1.2 Dose modification

Dose modification for treatment-related toxicity will be at Investigator discretion as per standard of care.

7.1.3 Compliance

Formal monitoring of compliance with study treatment will not be performed. Investigators are encouraged to reinforce the importance of medication compliance to subjects.

7.1.4 Treatment duration

First-line and second-line therapy will be administered until discontinuation as outlined in Sections 11.1 and 11.2 respectively.

7.2 PRIOR TREATMENT

Prior therapy with CYP17 inhibitors (including abiraterone acetate, TAK-700, TOK-001 and ketoconazole), enzalutamide or other experimental anti-androgens (e.g. ARN-509, TOK-001) is not permitted. Patients previously treated with chemotherapy for mCRPC (including but not limited to docetaxel, cabazitaxel and mitoxantrone) will not be recruited to this study.

7.3 PROHIBITED CONCOMITANT TREATMENT

The following treatments are not permitted at any time while on study drugs:

- Anti-androgens (bicalutamide, flutamide, nilutamide)
- 5-α reductase inhibitors (finasteride, dutasteride)
- Estrogens
- Chemotherapy
- Androgens (testosterone, DHEA)
- Radioisotopes (including but not limited to Strontium-89 and Radium-223)
- Herbal products that may lower PSA (e.g. saw palmetto)
- **Treatment of symptomatic metastases with radiation is allowed (NB: except for wide-field (i.e. hemibody)).**

7.4 PERMITTED CONCOMITANT MEDICATIONS AND TREATMENT

- Bisphosphonates or RANKL inhibitors
- Topical, inhaled or local corticosteroid preparations
- Supportive care medications including anti-emetics, laxatives, analgesics
- Radiation to symptomatic bone metastases (except wide-field (i.e. hemibody) is allowed at first and second line therapies. No washout required prior to starting second-line therapy).

8.0 VISIT SCHEDULE

8.1 SCREENING

After signing the informed consent form, subjects will undergo screening assessments as outlined in Table 1 ≤ 28 days prior to commencing study treatment. As part of screening, the following assessments will be performed:

- Medical history including prior anti-neoplastic therapies (surgery, radiation, chemotherapy, biological, immunological and other investigational), co-morbid medical conditions and concomitant medications (from time of screening visit), and demographics (race and ethnicity).
- Physical examination including vital signs (blood pressure, heart rate, weight, height)
- Cognitive, depression, and functional assessments
- ECOG performance status
- Laboratory tests including CBC, electrolytes, creatinine, random glucose, AST, ALT, ALP, LDH, bilirubin, GGT, PSA, testosterone, and albumin
- Bone scan and CT chest (or X-ray chest) and CT abdomen/pelvis

8.2 FIRST-LINE THERAPY

8.2.1 Cycle 1 (Day 1 – Baseline)

As outlined in Table 1, the following assessments will be performed at commencement of first-line therapy:

- Concomitant medications
- Physical examination including vital signs (blood pressure, heart rate, weight)
- ECOG performance status
- Depression and functional assessments (not required after July 1, 2018)
- Adverse events (those of interest (see Appendix A) and Grade ≥ 3 only)
- Laboratory tests including CBC, electrolytes, creatinine, AST, ALT, ALP, LDH, bilirubin, random glucose, GGT, PSA, and albumin
- **Correlative studies including processing and shipping (see Section 14.2 & 14.3)**
- Electrolytes, bilirubin, AST and ALT on Day 15 for subjects on abiraterone acetate + prednisone.

8.2.2 Cycles 2 - 4

Study visits will be scheduled for every 4 weeks from commencement of study medication. As outlined in Table 1, the following assessments will be performed:

- Concomitant medications
- Physical examination including vital signs (blood pressure, heart rate)
- ECOG performance status
- Cognitive testing at cycle 4 visit only (not required after July 1, 2018)
- Depression and functional assessments at the beginning of every cycle (not required after July 1, 2018)
- Adverse events (those of interest (see Appendix A) and Grade ≥ 3 only) (reporting not required after July 1, 2018)
- **PSA every 4 weeks**; other labs for safety will also be performed as per standard of care
- Electrolytes, bilirubin, AST and ALT on Day 15 of cycles 2 and 3 for patients on abiraterone acetate + prednisone.
- Bone scan and CT abdomen/pelvis + chest imaging (CT or Chest X-ray as was done at baseline). Imaging is required every 12 weeks from Cycle 1.

8.2.3 Subsequent Cycles

Study visits following Cycle 4 will be as per standard of care. As outlined in Table 1, the following will be measured:

- Depression and functional assessment at the beginning of each subsequent cycle's visit (not required after July 1, 2018)
- Adverse events (those of interest (see Appendix A) and Grade ≥ 3 only) (reporting not required after July 1, 2018)
- Concomitant medications
- **PSA every 4 weeks must be performed;** other labs for safety will be performed as per standard of care.
- Bone scan and CT abdomen/pelvis + chest imaging (CT or Chest X-ray as was done at baseline). Imaging is required every 12 weeks from Cycle 1.

8.3 SECOND-LINE THERAPY

8.3.1 Cycle 1 (Day 1 – Baseline)

Treatment with first-line therapy will be continued until any of the criteria outlined in Section 11.1 are met. Patients on Arm A (abiraterone plus prednisone) will be weaned off prednisone at discretion of Investigator (please see Section 5.6.1).

Patients who cease first-line therapy due to PSA progression will immediately commence second-line therapy. Please refer to Section 11.1 for instructions on initiation of second-line therapy in patients who cease first-line therapy in the absence of PSA progression.

At commencement of second-line therapy, subjects will undergo the following assessments (see Table 1):

- Concomitant medications
- Physical examination including vital signs (blood pressure, heart rate, weight)
- Cognitive, functional, and depression assessments (not required after July 1, 2018)
- ECOG performance status
- Adverse events (those of interest (see Appendix A) and Grade ≥ 3 only) (reporting not required after July 1, 2018)
- Laboratory tests including CBC, electrolytes, creatinine, random glucose, AST, ALT, ALP, LDH, bilirubin, GGT, PSA & albumin .
- **Correlative studies including processing and shipping (see Section 14.2 & 14.3)**
- Electrolytes, bilirubin, AST and ALT on D15 for subjects on abiraterone acetate + prednisone.
- CT and bone scans required +/- 4 weeks from cross-over.

8.3.2 Cycle 2 - 4

Study visits will be scheduled for every 4 weeks from commencement of second-line study medication. Study visits will be scheduled every 4 weeks. As outlined in Table 1, the following assessments will be performed:

- Concomitant medications
- Physical examination including vital signs (blood pressure, heart rate)
- ECOG performance status
- Cognitive testing at cycle 4 visit only (not required after July 1, 2018)
- Depression and functional assessments at the beginning of every cycle (not required after July 1, 2018)
- Adverse events (those of interest (see Appendix A) and Grade ≥ 3 only) (reporting not required after July 1, 2018)
- **PSA every 4 weeks**; other labs for safety will also be performed as per standard of care
- Electrolytes, bilirubin, AST and ALT on Day 15 of cycles 2 and 3 for patients on abiraterone acetate + prednisone.
- Bone scan and CT abdomen/pelvis + chest imaging ((CT or Chest X-ray as was done at baseline). Imaging is required every 12 weeks from Cycle 1.

8.3.3 Subsequent Cycles

Study visits following Cycle 4 will be at the beginning of every cycle. As outlined in as outlined in Table 1, the following will be measured:

- Depression and functional assessments at the beginning of every cycle (not required after July 1, 2018)
- Adverse events (those of interest (see Appendix A) and Grade ≥ 3 only) (reporting not required after July 1, 2018)
- Concomitant medications
- **PSA every 4 weeks**; other labs for safety will be performed as per standard of care
- Bone scan and CT abdomen/pelvis +chest imaging (CT or Chest X-ray as was done at baseline). Imaging is required every 12 weeks from Cycle 1.

8.4 END OF SECOND-LINE THERAPY

Treatment with second-line therapy will be continued until any of the criteria outlined in Section 11.2 are met. Subjects who will not cross-over to second-line therapy from first-line therapy, is also required to complete this study visit and the following assessments will be performed (see Table 1):

- Concomitant medications
- Physical examination including vital signs (blood pressure, heart rate, weight)
- ECOG performance status
- Depression and functional assessments (not required after July 1, 2018)
- Cognitive assessment is required *only* if end of therapy visit is before Cycle 4 visit (i.e. patient discontinues therapy before Cycle 4). Otherwise not required at the end of therapy visit. Not required after July 1, 2018.
- Adverse events (those of interest (see Appendix A) and Grade ≥ 3 only) (reporting not required after July 1, 2018)
- Laboratory tests including CBC, electrolytes, creatinine, AST, ALT, ALP, LDH, bilirubin, GGT, PSA & albumin.
- **Correlative studies including processing and shipping (see Section 14.2 & 14.3)**

9.0 ASSESSMENTS

9.1 EFFICACY

PSA measurements will be performed as outlined in Table 1 and Section 8.1-8.4. The following definitions will be employed:

9.1.1 PSA response

A ≥ 30% decline in PSA from baseline confirmed on repeat measurement ≥ 28 days later.

9.1.2 PSA progression

Patients without a PSA decline: A PSA that is ≥ 25% and ≥ 2 ug/L above baseline after ≥ 12 weeks of study treatment.

Patients with a PSA decline: A PSA increase of ≥ 25% and ≥ 2 ug/L above nadir, confirmed by a repeat measurement ≥ 28 days later (confirmed rising trend).

9.1.3 Radiological Tumour Assessments

Visceral/soft tissue disease: Tumour assessments in patients with measurable disease will be based on RECIST criteria version 1.1 (see Appendix B).

Bone disease: Progression on bone scan will be defined as the appearance of ≥ 2 new lesions with a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions.

9.2 COGNITIVE, DEPRESSION, AND FUNCTIONAL TESTING

Cognitive testing will be conducted via the Montreal Cognitive Assessment (MoCA), a validated screening tool for cognitive impairment (see Appendix E)[34]. This test will be administered by study staff at screening, at cycle 4 on first-line treatment, prior to initiation of second line treatment and at cycle 4 on second-line treatment. If patient's end of therapy visit is before the Cycle 4 visit, then MoCA is required to be completed. Alternate versions of assessment should be used if done within 3 months or less from previous assessment.

The Patient Health Questionnaire-9 (PHQ-9) is a validated, self-administered depression-rating tool[35] (see Appendix F). It will be administered to patients at as outlined on Table 1.

Functional Assessment of Chronic Illness Therapy is a validated tool to evaluate quality of life of patients with prostate cancer[36] (see Appendix G). This assessment will be self-administered at as outlined on Table 1.

All questionnaires and assessments will only record subject's unique study code and initials in place of the fields for personal identifying information.

After July 1, 2018, subjects will not be required to perform the MoCA, PHQ-9 and FACT-P.

9.3 SAFETY AND TOLERABILITY

Safety will be monitored by assessing physical examination, vital signs, ECOG performance status (see Appendix C), laboratory evaluations and adverse events (refer to Sections 10.1 & 10.2).

9.4 CORRELATIVE STUDIES

Please refer to Sections 14.2 & 14.3.

10.0 SAFETY MONITORING AND REPORTING

10.1 ADVERSE EVENTS

10.1.1 Definition and reporting

Adverse events will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 4.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. As the adverse event profiles for abiraterone acetate and enzalutamide are well characterized and these are approved medications, **only adverse events of interest (see**

Appendix A) and Grade ≥ 3 adverse events will be collected for this study on case report forms. Adverse events will no longer be required for case report forms after July 1, 2018.

10.2 SERIOUS ADVERSE EVENTS

10.2.1 Definition and reporting

Serious adverse events (SAE) will be captured following commencement of therapy. A serious adverse event is any adverse event that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
- results in persistent or significant disability or incapacity is a congenital anomaly/birth defect

All serious adverse events must be reported as follows:

Within 24 hours:	Report event by email to: safetyreporting@bccancer.bc.ca
Within 7 days:	Email completed Serious Adverse Event Form to: safetyreporting@bccancer.bc.ca (signed by the investigator and updated as much as possible)

All Serious Adverse Event Forms will be reviewed by Dr. Chi.

11.0 CRITERIA FOR TREATMENT DISCONTINUATION

11.1 FIRST-LINE THERAPY

Study treatment will continue until **ANY** of the following occur:

i. Development of PSA progression, which is defined as:
   a. **In patients without a PSA decline**: A PSA that is ≥ 25% and ≥ 2 ug/L above baseline after ≥ 12 weeks of study treatment.
   b. **In patients with a PSA decline at any time on first-line therapy:** A PSA increase of ≥ 25% and ≥ 2 ug/L above nadir, confirmed by a repeat measurement ≥ 28 days later (confirmed rising trend).

ii. Treatment of symptomatic bone metastases with wide-field radiation, as this would indicate treatment failure. Cross-over to second-line therapy will be permitted once ≥ 14 days have elapsed from completion of radiation and treatment-related toxicity has recovered to grade ≤ 2.

iii. Unacceptable treatment-related toxicity. These patients will be eligible to commence second-line therapy once toxicity has recovered to grade ≤ 2.

iv. Withdrawal of consent.

11.2 SECOND-LINE THERAPY

Treatment will continue until **ANY** of the following occur:

i. Symptomatic or clinical progression that, in the opinion of the Investigator, signifies the subject is no longer benefiting from study treatment. **NB: PSA progression on second-line therapy will be documented but does not mandate cessation of study treatment.**

ii. Unacceptable treatment-related toxicity. These patients will cease study treatment.

iii. Withdrawal of consent.

11.3 POST-PROTOCOL THERAPY AND FOLLOW-UP

Further treatment, if any, is at the discretion of the Investigator. Follow-up data on overall survival will be collected.

12.0 STATISTICAL METHODS AND DATA ANALYSIS

12.1 STATISTICAL DESIGN

The primary clinical endpoint is the proportion of patients with a PSA response defined as a PSA decline ≥ 30% from baseline with second-line therapy. A "pick the winner" randomized phase 2, Simon's Optimal two-stage design will be employed. A PSA response rate in either arm of 10% or less would not be of interest for further study (null hypothesis). If the PSA response rate for either arm were 30% or greater, then this would be considered of interest to further evaluate in larger trials. Using an alpha error of 0.1 and a beta error of 0.1, 12 patients per arm will be initially accrued. If 2 or more patients respond in either arm, both arms will be expanded to 35 evaluable patients. Accounting for a 10% drop-out/non-evaluable rate, approximately 78 evaluable patients (39 per arm) will be required to meet the statistical end points of this objective.

The other primary endpoint of this study is time to second PSA progression, calculated from time of start of first-line therapy to time of PSA progression on cross-over second-line therapy. Accrual will continue to a total of 200 patients (100 per arm). The probability is 70 percent that the study will detect a treatment difference at a two sided 0.05 significance level, if the true hazard ratio is 1.519. This is based on the assumption that the accrual period will be 18 months, the follow up period will be 18 months and the median survival is 12 months (null hypothesis). The total number of events will be 140. The design is based on the null hypothesis assumption is that sequential therapy is of no benefit (median PSA progression-free survival in chemotherapy-naïve patients approximately 12 months based on the COU-302 trial[2]), and that a 6-month improvement in median time to PSA progression of one treatment sequence over another would be a clinically significant benefit. Patients that do not cross over to second-line protocol therapy will not be censored and the date of first-line PSA progression used as the date of progression for the purposes of this analysis which seeks to evaluate the overall efficacy of planned sequential therapy.

12.2 RANDOMIZATION METHOD

Subjects will be centrally randomized using a random number generator. Patients will be assigned at random to Arm A and Arm B in 1:1 ratio, respectively. First-line study treatment must begin within 5 working days of randomization.

12.3 PRIMARY ENDPOINTS

The primary end points are:

i. PSA response rate in subjects with PSA progression on first-line abiraterone acetate or enzalutamide when crossed over to second-line therapy with the opposite agent. PSA response is defined as ≥ 30% decline in PSA value from commencement of second-line therapy confirmed on repeat measurement ≥ 28 days later.

ii. To evaluate the time to second PSA progression of combined first and second-line therapy (from start of first-line therapy to PSA progression on cross-over second-line therapy).

12.4 SECONDARY ENDPOINTS

The secondary end points are:

i. Correlation of serum and plasma biomarker expression with PSA response to first-line and second-line abiraterone acetate or enzalutamide

ii. PSA response rates to first-line abiraterone acetate or enzalutamide

iii. Time to PSA progression on first-line and second-line abiraterone acetate or enzalutamide

iv. Time on study treatment and time to clinical progression on second-line abiraterone acetate or enzalutamide

v. Change in Montreal Cognitive Assessment score on first-line and second-line abiraterone acetate and enzalutamide

vi. Overall survival in patients treated with sequential abiraterone acetate and enzalutamide

vii. Safety of second-line abiraterone acetate or enzalutamide.

13.0 ETHICAL AND ADMINISTRATIVE PROCEDURES

13.1 REGULATORY AND ETHICAL COMPLIANCE

This study will be conducted in accordance with ICH Harmonized Tripartite Guidelines for Good Clinical Practice and with the ethical principles laid down in the Declaration of Helsinki.

13.2 RESPONSIBILTIES OF THE INVESTIGATOR AND IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to the sponsor before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these

documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the sponsor, IRBs/IECs/REBs and regulatory authorities as required.

13.3. INFORMED CONSENT PROCEDURES

Eligible subjects will only be enrolled on this study after a signed informed consent form has been obtained. This information should be recorded in the patient source documents. No additional consent form will be provided for correlative studies.

13.5 PUBLICATION OF STUDY PROTOCOL AND RESULTS

The sponsor will post a summary of this study on a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database.

13.6 STUDY DOCUMENTATION, RECORD KEEPNG AND RETENTION

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. Investigators must retain on file all patient records and study files, including but not limited to Case Report Forms, SAE reporting forms, patient files, patient exclusion logs, informed consent forms, informed consent log, and all correspondence and other documents pertaining to the conduct of the study for a minimum of 2 years after the trial is discontinued.

13.7 CONFIDENTIALITY OF STUDY DOCUMENTS AND PATIENT RECORDS

All patient data must be kept anonymous with no identifying information being recorded in documents submitted to the sponsor. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at each participating centre. All questionnaires will only record subject's unique study code and initials in place of the fields for personal identifying information.

13.8 AUDITS AND INSPECTIONS

In addition to the routine review of case report forms and supporting documents sent to the sponsor, site monitoring will be conducted at participating centres in the course of the study as part of the overall quality assurance programme. The monitors/auditors will require access to patient medical records to verify the data, as well as essential document binders and standard operating procedures (including electronic information).

14.0 CORRELATIVE STUDIES

14.1 BACKGROUND AND RATIONALE

Apart from determining optimal sequencing of abiraterone and enzalutamide in mCRPC patients, a key issue associated with the use of these agents is identifying circulating biomarkers associated with treatment response and resistance. Our group has preliminary data showing that a

high proportion of enzalutamide-resistant mCRPC patients and some abiraterone-resistant mCRPC patients possess focal AR amplification in cell-free tumour DNA extracted from plasma. In pre-clinical studies, other potential mechanisms of resistance to these agents include increased expression of AR splice variants (abiraterone and enzalutamide)[9,10], increased expression of CYP17 (abiraterone)[6,9], upregulation of the stress-activated chaperone protein clusterin (enzalutamide only)[11] and a point mutation (F876L) in the ligand-binding domain of the AR (enzalutamide only)[12,13]. Recently, the presence of AR splice variants was linked to primary resistance to abiraterone and enzalutamide in mCRPC patients[35] supporting further assessment of the link between splice variants and treatment outcome with novel hormonal agents. Non-coding RNAs (ncRNAs) are additional biomarkers of interest since they are implicated in tumorigenesis and are readily detectable in plasma of mCRPC patients[14]. Examination of these biomarkers in serum and plasma is planned, with the aim of identifying novel biomarkers associated with treatment efficacy and resistance in mCRPC patients receiving abiraterone and enzalutamide.

14.2 SAMPLE COLLECTION

Peripheral blood samples will be collected at **start of first-line therapy, start of second-line therapy and end of study treatment** (i.e. maximum 3 draws per patient). Mandatory correlative samples are required at the end of first-line therapy if subject will not be crossing over to second-line therapy. A total of 2 Streck tubes (10 ml per tube) for cell-free DNA (ctDNA), 1 SST tube (5 ml) for non-coding RNA (ncRNA), and 1 PAXgene tube (2.5 ml) for assessing AR splice variants and other cancer associated mRNA transcripts will be collected per patient at each time point. Please refer to laboratory manual for full details of sample processing and collection.

14.3 SAMPLE PROCESSING AND ANALYSIS

Please refer to Laboratory Manual.

15.0 APPENDICES

15.1 APPENDIX A - ADVERSE EVENTS OF INTEREST

In addition to grade ≥ 3 adverse events, the following adverse events are considered of interest and will be recorded irrespective of grading:

i. Hypertension
ii. Fatigue
iii. Hypokalaemia
iv. Peripheral edema
v. Elevated liver enzyme tests
vi. Seizure

Any adverse event irrespective of grading leading to treatment interruption, delay, discontinuation or dose adjustment must also be documented and reported.

15.2 APPENDIX B - RECIST 1.1 CRITERIA

15.2.1 Criteria for Measurable Disease

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan.

Malignant lymph nodes: Must be ≥ 15 mm in short axis when assessed by CT scan. Only the short axis will be measured at baseline and followed.

All other lesions are considered non-target for the purposes of RECIST response.

15.2.2 Response Criteria for Target Lesions

Response Criteria	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline

15.2.3 Response Criteria for Non-target Lesions

Response Criteria	Evaluation of Non-target Lesions
Complete Response (CR)	Disappearance of all non-target lesions. In addition, all lymph nodes assigned as non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions.
Stable Disease (SD)	Neither CR nor PD.
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

15.3 APPENDIX C - ECOG PERFORMANCE STATUS

Grade	Description
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 self-care 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

15.4 APPENDIX D – CREATININE CLEARANCE

Calculated creatinine clearance (Cockcroft-Gault formula):

N x (140-Age) x weight in kg ÷ Serum Creatinine in µmol/L

* For males N=1.23; for females N=1.04

15.5 APPENDIX E – MONTREAL COGNITIVE ASSESSMENT TOOL

Montreal Cognitive Assessment
(MoCA)

Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. Alternating Trail Making:

Administration: The examiner instructs the subject: "Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."

Scoring: Allocate one point if the subject successfully draws the following pattern: 1 −A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuoconstructional Skills (Cube):

Administration: The examiner gives the following instructions, pointing to the **cube**: "Copy this drawing as accurately as you can, in the space below".

Scoring: One point is allocated for a correctly executed drawing.

- Drawing must be three-dimensional
- All lines are drawn
- No line is added
- Lines are relatively parallel and their length is similar (rectangular prisms are accepted)

A point is not assigned if any of the above-criteria are not met.

3. Visuoconstructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions: "Draw a **clock**. Put in all the numbers and set the time to 10 after 11".

Scoring: One point is allocated for each of the following three criteria:

- Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
- Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
- Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centred within the clock face with their junction close to the clock centre.

A point is not assigned for a given element if any of the above-criteria are not met.

4. Naming:

Administration: Beginning on the left, point to each figure and say: "Tell me the name of this animal".

Scoring: One point each is given for the following responses: (1) camel or dromedary, (2) lion, (3) rhinoceros or rhino.

5. Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: "This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them". Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: "I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time." Put a check in the allocated space for each word the subject recalls after the second trial.

At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, "I will ask you to recall those words again at the end of the test."

Scoring: No points are given for Trials One and Two.

6. Attention:

Forward Digit Span: Administration: Give the following instruction: "I am going to say some numbers and when I am through, repeat them to me exactly as I said them". Read the five number sequence at a rate of one digit per second.

Backward Digit Span: Administration: Give the following instruction: "Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order." Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (N.B.: the correct response for the backwards trial is 2-4-7).

Vigilance: Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: "I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand".

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

Serial 7s: Administration: The examiner gives the following instruction: "Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop." Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond "92 – 85 – 78 – 71 – 64" where the "92" is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. Sentence repetition:

Administration: The examiner gives the following instructions: "I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: **I only know that John is the one to help today."** Following the response, say: "Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: **The cat always hid under the couch when dogs were in the room.**"

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.).

8. Verbal fluency:

Administration: The examiner gives the following instruction: "Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter F. [time for 60 sec]. Stop."

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject's response in the bottom or side margins.

9. Abstraction:

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: "Tell me how an orange and a banana are alike". If the subject answers in a concrete manner, then say only one additional time: "Tell me another way in which those items are alike". If the subject does not give the appropriate response (fruit), say, "Yes, and they are also both fruit." Do not give any additional instructions or clarification.

After the practice trial, say: "Now, tell me how a train and a bicycle are alike". Following the response, administer the second trial, saying: "Now tell me how a ruler and a watch are alike". Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:

Train-bicycle = means of transportation, means of travelling, you take trips in both;

Ruler-watch = measuring instruments, used to measure.

The following responses are **not** acceptable: Train-bicycle = they have wheels; Ruler-watch = they have numbers.

10. Delayed recall:

Administration: The examiner gives the following instruction: "I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember. Make a check mark (✓) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: **Allocate 1 point for each word recalled freely without any cues**.

Optional:

Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (✓) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, "Which of the following words do you think it was, NOSE, FACE, or HAND?"

Use the following category and/or multiple-choice cues for each word, when appropriate:

FACE: category cue: part of the body multiple choice: nose, face, hand

VELVET: category cue: type of fabric multiple choice: denim, cotton, velvet

CHURCH: category cue: type of building multiple choice: church, school, hospital

DAISY: category cue: type of flower multiple choice: rose, daisy, tulip

RED: category cue: a colour multiple choice: red, blue, green

Scoring: **No points are allocated for words recalled with a cue.** A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

11. Orientation:

Administration: The examiner gives the following instructions: "Tell me the date today". If the subject does not give a complete answer, then prompt accordingly by saying: "Tell me the [year, month, exact date, and day of the week]." Then say: "Now, tell me the name of this place, and which city it is in."

Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

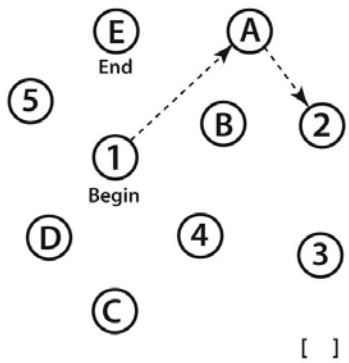
TOTAL SCORE: Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



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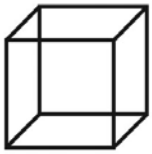


[ ] [ ]

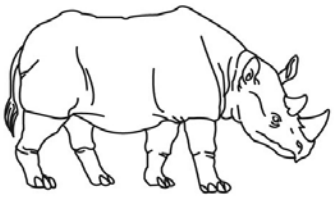
Draw CLOCK (Ten past eleven)
(3 points)

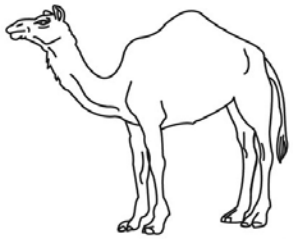
[ ] Contour [ ] Numbers [ ] Hands

POINTS

__/5

NAMING





[ ] [ ] [ ]

__/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

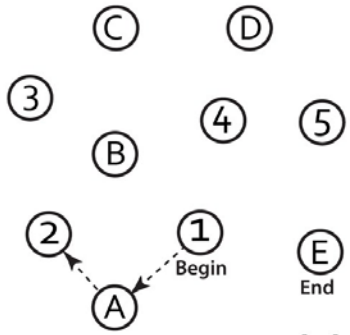
Add 1 point if ≤ 12 yr edu

Administered by: _____

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.2 Alternative Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



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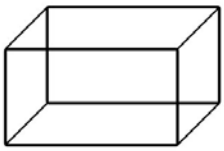


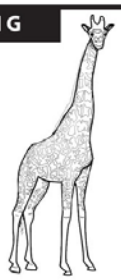
[ ] [ ]

Draw CLOCK (Five past four)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING



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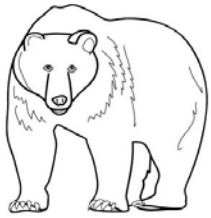

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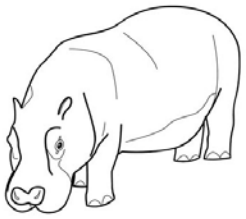


[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	TRUCK	BANANA	VIOLIN	DESK	GREEN
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 3 2 9 6 5
Subject has to repeat them in the backward order [ ] 8 5 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 90 [ ] 83 [ ] 76 [ ] 69 [ ] 62 [ ] 55
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : A bird can fly into closed windows when it's dark and windy. [ ]
The caring grandmother sent groceries over a week ago. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter S [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] diamond - ruby [ ] cannon - rifle

__/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	TRUCK	BANANA	VIOLIN	DESK	GREEN	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD
 www.mocatest.org
Administered by: _____

Normal ≥ 26 / 30

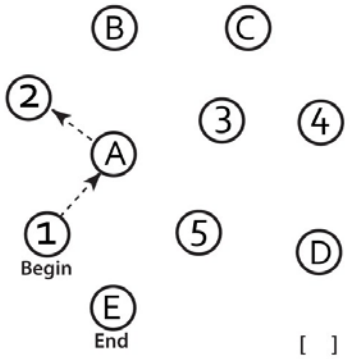
TOTAL __/30
Add 1 point if ≤ 12 yr edu

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.3 Alternative Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



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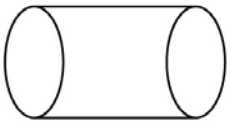


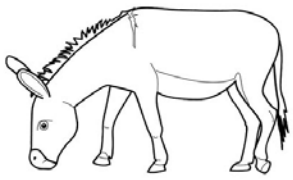
[ ] [ ]

Draw CLOCK (Ten past nine)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

NAMING



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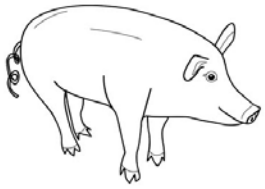

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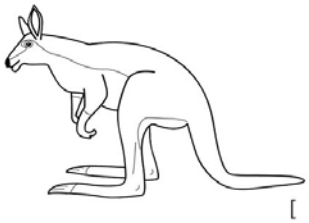

[ ]

__/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	TRAIN	EGG	HAT	CHAIR	BLUE
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 5 4 1 8 7

Subject has to repeat them in the backward order [ ] 1 7 4

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 80 [ ] 73 [ ] 66 [ ] 59 [ ] 52 [ ] 45

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE

Repeat : She heard his lawyer was the one to sue after the accident. [ ]

The little girls who were given too much candy got stomach aches. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter B [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] eye – ear [ ] trumpet – piano

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	TRAIN	EGG	HAT	CHAIR	BLUE	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD

 www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

15.6 APPENDIX F – PATIENT HEALTH QUESTIONNAIRE

PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 □s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 □s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 □s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.
Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up √s by column. For every √: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every √ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

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PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: _____ **DATE:** _____

Over the last *2 weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
	add columns		+	+
	TOTAL:			

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult _____

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15.7 APPENDIX G – FACT-P QUESTIONNAIRE

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

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