A randomised Phase II study of Enzalutamide (MDV3100) in combination with AZD5363 in Patients with Metastatic Castration - Resistant Prostate Cancer (RE-AKT)

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Coordinating Trials Unit: ICR Clinical Trials and Statistics Unit (ICR-CTSU)
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FINAL PROTOCOL

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The RE-AKT trial has been approved by the Cancer Research UK's Clinical Trials Advisory & Awards Committee (CTAAC). The RE-AKT trial is part of the National Institute for Health Research Clinical Research Network Trial Portfolio

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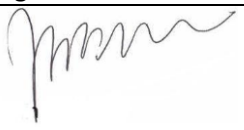
Professor Johann de Bono (Chief Investigator)		24/5/2019

This protocol describes the RE-AKT trial and provides information about procedures for entering participants into this trial. The protocol should not be used as a guide for the treatment of other patients. Every care was taken in the preparation of this protocol, but corrections or amendments may be necessary. Protocol amendments will be circulated to participating sites as they occur, but sites entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version

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TRIAL SUMMARY

TITLE	A randomised Phase II study of enzalutamide (MDV3100) in combination with AZD5363 in Patients with Metastatic Castration- Resistant Prostate Cancer.
TARGET DISEASE	Metastatic Castration- Resistant Prostate Cancer (mCRPC)
STUDY OBJECTIVES	**Phase I – safety run in** ▪ To identify safety and tolerability of enzalutamide and AZD5363 ▪ To identify dose-limiting toxicities, estimate the maximum tolerated dose and identify recommended phase II dose of AZD5363 **Randomised Phase II** ▪ To estimate and compare the antitumour activity of AZD5363 + enzalutamide and placebo + enzalutamide as measured by response **Single Stage phase II - expansion cohort** ▪ To estimate the antitumour activity of AZD5363 + enzalutamide in patients who have previously progressed on enzalutamide alone
TRIAL DESIGN	A multicentre prospective, randomised, phase II interventional study in mCRPC patients previously treated with 1-2 lines of chemotherapy and at least 12 weeks of abiraterone with a safety run-in and single stage phase II expansion cohort
TRIAL POPULATION	Patients with metastatic Castrate Resistant Prostate Cancer (mCRPC) who progressed after docetaxel-based chemotherapy and prior abiraterone or enzalutamide
RECRUITMENT TARGET	**Phase I - safety run-in** - Approximately 18 patients **Randomised Phase II** - 100 patients will be randomised in a 1:1 ratio for the enzalutamide + AZD5363 vs. enzalutamide + placebo group comparison. **Single stage phase II - expansion cohort** - 18 patients will be recruited.
TREATMENT REGIMEN	**Phase I – safety run in** ▪ Enzalutamide 160mg od and AZD5363 dose escalation bid on an intermittent schedule (4days on 3days off) with a starting dose of 320mg **Randomised Phase II** ▪ Enzalutamide 160mg od and AZD5363 400mg bid (recommended phase II dose) 4 days on 3 days off OR matching placebo **Single stage phase II - expansion cohort** ▪ Following progression on enzalutamide alone enzalutamide 160mg od and AZD5363 400mg bid (recommended phase II dose) 4 days on 3 days off
PRIMARY ENDPOINTS	**Phase I – safety run in** ▪ Type, frequency, severity, seriousness and relatedness of adverse events ▪ Laboratory abnormalities. **Randomised Phase II** ▪ Best overall tumour response by RECIST (v1.1), PCWG2 criteria and CTC response. **Single stage phase II expansion cohort** ▪ Best overall tumour response by RECIST (v1.1), PCWG2 criteria and CTC response.
SECONDARY ENDPOINTS	**Phase I – safety run in** ▪ PK assay analyses ▪ Antitumour activity of the combination **Randomised Phase II and single stage phase II - expansion cohort** ▪ Overall survival and radiographic progression free survival ▪ Maximum PSA decline and circulating tumour cell (CTC) fall ▪ Pain palliation (using BPI-SF) (randomised phase II only) ▪ Safety ▪ PK assay analyses
EXPLORATORY ENDPOINTS	**Phase I – safety run in** ▪ Pharmacodynamic analyses **Randomised Phase II and single stage phase II expansion cohort** ▪ Molecular characterisation of the tumour ▪ Assessment of mRNA signature ▪ Pharmacodynamic analyses (single stage expansion only)
FOLLOW UP	Treatment should continue until confirmed disease progression. Patients will be assessed 30 days after the last dose of study drug. In the randomised phase II and single stage phase II expansion cohorts patients will be followed up for survival data.

1. INTRODUCTION

1.1. Prostate Adenocarcinoma

Prostate adenocarcinoma is the most common malignancy affecting men in the Western world, with over 570,000 new cases annually and an estimated 94, 000 deaths in Europe in 2008 and 32,050 deaths in the United States [1]. Up to 40% of men initially diagnosed with localized prostate cancer will eventually develop metastases. In patients with advanced disease, androgen deprivation with either orchiectomy or medical castration with GnRH agonists is highly effective in shrinking tumour burden, decreasing prostate-specific antigen (PSA) levels, and enhancing quality of life. However, nearly all patients experience disease progression following hormonal manipulations, and develop castration-resistant prostate cancer (CRPC). Mitoxantrone was the first chemotherapy to show a palliative benefit for patients with CRPC, and was subsequently approved by the US Food and Drug Administration (FDA). In 2003, the TAX327 trial showed, for CRPC patients treated with 3 weekly docetaxel had a survival advantage over mitoxantrone [2] (OS: 19.2 mo. vs. 16.3 mo., p = 0.009). Until recently, cytotoxic chemotherapy had been the only therapy shown to improve survival for patients with CRPC. In the last five years, five novel treatments have shown survival gains in phase III trials, including sipuleucel-T [3] abiraterone acetate [4], alpharadin, cabazitaxel [5] and enzalutamide [6].

1.2. PI3K / AKT signalling

It is estimated that the majority of metastatic prostate cancers have activation of the PI3K/AKT pathway by diverse mechanisms, including loss/mutations of PTEN, INPP4B, PHLPP or PI3K. More than 60% of metastatic prostate cancers have functional loss of PTEN [7]. The PI3K/AKT pathway is believed to play a critical role in tumour growth, proliferation, metabolism, survival, and resistance to therapy[8] [9] [10] [11]. Functional loss of PTEN has been reported as a result of gene deletion, mutation, microRNA expression, post-translational modification or epigenetic silencing [12]. Furthermore, PTEN loss has been associated with increased AKT phosphorylation, advanced disease and Gleason stage, as well as a poorer prognosis [13]. Together, these data provide a strong rationale for developing therapeutics to target the PI3K / AKT pathway in human cancers.

1.3. PI3K / AKT pathway and androgen receptor interaction

Many studies have demonstrated crosstalk between the AR and PI3K / AKT signalling pathways. In vitro data suggest that over-expression and activation of AKT can result in androgen escape in tumour cells by altering AR sensitivity and activation [14]. There is increasing evidence that the PI3K / AKT pathway may regulate the expression and transcription of AR. Additionally, studies of matched hormone-sensitive and -resistant tissues from progressing CRPC patients demonstrated that up-regulation of the PI3K / AKT pathway was associated with AR phosphorylation during the transition from a hormone-sensitive to refractory state [15].

Recent pre-clinical data also suggest that the AR and PI3K / AKT pathways cross-regulate one another through reciprocal feedback. Thus, inhibition of either pathway leads to activation of the other, thereby maintaining cell survival. Carver et al. (2011) showed that simultaneous pharmacological inhibition of PI3K/mTOR and AR caused near complete prostate cancer regression in PTEN deficient prostate cancer models [16].

1.4. Background on the molecules

1.4.1. Enzalutamide

Enzalutamide XTANDI™ (formerly MDV3100) is a novel small molecule designed to have increased affinity for the androgen receptor and more effective suppression of the androgen pathway. Enzalutamide slows growth and induces cell death in bicalutamide-resistant cancers via three complementary actions: blocking testosterone binding to the androgen receptor, impeding nuclear translocation, and by inhibiting binding of

the AR to DNA. Enzalutamide has been granted FDA and EMA approval for the treatment of adult men with CRPC.

1.4.1.1. Summary of Clinical Experience with Enzalutamide

The pharmacokinetics (PK), tolerability, and antitumour activity of enzalutamide were first studied in a multi-centre, open-label, first-in-human, dose-escalation study of enzalutamide (MDV3100) in 140 patients with castration-resistant prostate cancer (S-3100-1-01 study, Scher et al). Patients who were chemotherapy-naïve or who had previously failed docetaxel-based chemotherapy were treated with enzalutamide at doses of 30 to 600 mg/day until disease progression or intolerable side effects developed. The maximum tolerated dose was determined to be 240 mg daily. After review of all data available, the optimal dose of enzalutamide for evaluation in Phase III clinical trials was determined to be 160 mg/day. Two Phase III studies and a similar Phase II study have evaluated enzalutamide in men with prostate cancer:

i. CRPC2 (AFFIRM, NCT00974311): A Phase III, randomised, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 (160 mg daily) in patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy was conducted in 1199 men, 800 of whom received treatment with enzalutamide. All patients continued androgen deprivation therapy. Patients were allowed, but not required to continue or initiate glucocorticoids [17].
ii. MDV3100-03 (PREVAIL, NCT01212991): A multinational Phase III, randomised, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy was conducted in 1717 men, 871 of whom received treatment with enzalutamide [18, 19].
iii. 9875-CL-0222 (TERRAIN): A randomised, double-blind, Phase 2 efficacy and safety study of MDV3100 versus bicalutamide in castrate men with metastatic prostate cancer was conducted in 375 men, 184 of whom received treatment with enzalutamide[20].

1.4.1.2. Enzalutamide Efficacy

In the Phase I S-3100-1-01 study, enzalutamide demonstrated antitumour activity across multiple endpoints in patients both with and without previous exposure to chemotherapy. The antitumour activity endpoints included prostate-specific antigen (PSA) reduction from baseline, median time to PSA progression, responses on imaging, and circulating tumour cell conversion from unfavourable to favourable counts.

In the AFFIRM study, a formal interim analysis of overall survival was performed at 520 events (80% of the 650 targeted number of events for final analysis) and demonstrated a statistically-significant increase in the duration of survival among patients treated with enzalutamide compared with patients treated with placebo (hazard ratio [HR] = 0.63, [95% CI: 0.53, 0.75], $p < 0.0001$). Median survival was 18.4 months in the enzalutamide arm and 13.6 months in the placebo arm ($\Delta = 4.8$ months). There were also statistically significant increases in time to PSA progression; radiographic progression-free survival (assessed by computed tomography [CT] or magnetic resonance imaging [MRI] and by bone scan); time to first skeletal-related event; PSA response, and overall objective soft tissue radiographic response among patients treated with enzalutamide compared to placebo. In addition, statistically significant differences favouring enzalutamide over placebo in pain palliation and pain progression rate at week 13 were also observed [17].

In the PREVAIL study, 1717 men were randomized (1715 treated) between September 2010 and September 2012 to receive either enzalutamide (160 mg) or placebo once daily. The study was stopped after a planned interim analysis, conducted when 540 deaths had been reported, showed a benefit of the active treatment: enzalutamide improved OS (HR=0.71; [95% CI: 0.60–0.84]; P <

0.0001) and rPFS (HR=0.19; [95% CI: 0.15–0.23]; P < 0.0001) [18]. The final analysis at 784 deaths with a median follow-up of 31 months confirmed the overall survival benefits of Enzalutamide with a 23% reduction in risk of death (HR= 0.77; [95% CI: 0.67–0.88]; P = 0.0002) and a 4-month improvement in median overall survival (35.3 months [95% CI 32.2–NYR]) vs 31.3 months [95% CI 28.8–34.2]) [19]. 42% of Enzalutamide and 49% of placebo patients had died; 52% of Enzalutamide and 81% of placebo patients (including 167 patients who crossed over to Enzalutamide) received ≥ 1 subsequent life-extending prostate cancer therapy.

In the TERRAIN study, 375 patients were randomly assigned, 184 to enzalutamide and 191 to bicalutamide. Median follow-up time was 20·0 months (IQR 15·0–25·6) in the enzalutamide group and 16·7 months (10·2–21·9) in the bicalutamide group. Patients in the enzalutamide group had significantly improved median progression-free survival (15·7 months [95% CI: 11·5–19·4]) compared with patients in the bicalutamide group (5·8 months [4·8–8·1]; HR=0·44 [95% CI: 0·34–0·57]; p<0·0001) [20].

1.4.1.3. Enzalutamide Safety

98.1% of the enzalutamide-treated patients in the AFFIRM study (n = 1199) reported at least 1 treatment-emergent adverse event as compared to 97.7% of placebo patients (at data cut-off date of 25th September 2011). Serious adverse events were reported in 33.5% of enzalutamide-treated patients as compared with 38.6% of placebo-treated patients. Of the enzalutamide-treated patients, 7.6% discontinued study drug due to adverse events as compared with 9.8% of placebo patients. Adverse events reported by those treated with enzalutamide with an incidence at least 2% greater than that among those who received placebo included fatigue, diarrhoea, hot flush, musculoskeletal pain, headache, insomnia, anxiety, hypertension, nasopharyngitis, pollakisuria, fall, pruritus, dry skin, and musculoskeletal stiffness. Serious adverse events reported with an incidence of at least 0.5% and more frequently by enzalutamide-treated patients compared to placebo patients were spinal cord compression, general physical health deterioration, haematuria, pneumonia, bone pain, pathologic fracture, urinary tract obstruction, cauda equina syndrome, metastases to central nervous system, and urosepsis. The most common adverse events leading to treatment discontinuation among those receiving enzalutamide were fatigue, dysphagia, vomiting, nausea, and cerebrovascular accident, and were reported with incidence between 0.4% and 0.6%.

As an inhibitor of the GABA-gated chloride channel, enzalutamide has the potential to cause seizures. A dose-dependent relationship between enzalutamide exposure and seizure incidence was seen in both a nonclinical mouse study and the Phase I S-3100-1-01 study in which seizures were reported at supra-clinical doses in 3 patients (all with other seizure risk factors such as use of concomitant medication that may lower seizure threshold). Seizures have also rarely been reported at the 160 mg dose (<1% frequency); however, there were confounding factors that may have contributed to the occurrence of seizures in the majority of these cases. In the Phase III AFFIRM study, seizures were reported in 5 (0.6%) patients treated with enzalutamide (160 mg daily) and no placebo patients as of the data cut-off date of 25th September 2011. Two of these patients had brain metastases, 1 had inadvertently received an intravenous lidocaine overdose, 1 had an unwitnessed fall after recently initiating haloperidol in the context of heavy alcohol use with brain atrophy, and 1 had cortical atrophy with microvascular disease. These observations suggest that enzalutamide may lower the seizure threshold at the clinical dose of 160 mg daily. Overall, enzalutamide (160 mg daily) was well tolerated in the AFFIRM study.

1.4.1.4. Pharmacokinetics and Drug Metabolism of Enzalutamide and of AZD5363

Enzalutamide was absorbed rapidly after oral administration, with the time to maximum plasma concentration (tmax) after a single dose typically occurring at 1-hour post dose. No major

deviations from dose proportionality were observed over the dose range 30 to 600 mg. Due to the long t1/2 (~ 5.8 days) it took approximately 1 month to reach steady state concentrations. With daily oral administration, enzalutamide accumulation was observed at steady state with an 8.3-fold higher exposure (steady-state area under the curve [AUC]) relative to a single dose. Based on the mean peak-to-trough ratio, the average difference between the peak (C_{max}) and trough (minimum plasma concentration [Cmin]) concentrations was ≤ 25%. As a result of the low daily fluctuations, plasma profiles at steady state resembled a constant infusion. The Cmin values in individual patients remained constant beyond Day 28 of chronic therapy, suggesting time-linear PK once a steady state was achieved.

In mice, rats, and dogs, oral MDV3100 had a half-life ($t_{1/2}$) of approximately 0.25 to 3 days. The $t_{1/2}$ did not appear to be affected by dose; however, the bioavailability appeared to decrease with increasing dose. *In vitro* drug metabolism studies suggest that MDV3100 undergoes very slow rates of metabolism. Plasma protein binding of MDV3100 in human plasma ranged from 97% - 98% and was similar in mice, rats, rabbits, and dogs. *In vitro* drug metabolism studies suggest that MDV3100 may have the potential to induce cytochrome P450 (CYP) 3A4 and to directly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. In consideration of time-dependent inhibition data, a metabolite of MDV3100 may inhibit CYP1A2.

The metabolism of AZD5363 has been investigated *in vitro* in study KMN010 using rat, dog and two human donor hepatocyte preparations, and in study KMX013 in human liver microsomes and expressed CYP and UGT enzymes. There was moderate metabolism of AZD5363 by rat and dog hepatocytes. Human hepatocytes metabolised AZD5363 more slowly (77.7% to 78.8% remaining after 180 minutes incubation) and the metabolite profiles from the 2 human preparations appeared to be qualitatively and quantitatively similar. Across the species, at least 14 different metabolites were identified by high-performance liquid chromatography with radioactivity detection and high-performance liquid chromatography mass spectrometry. All the metabolites generated by human hepatocytes were also formed by rat or dog hepatocytes indicating that the species used in the toxicology studies have been exposed to the major metabolites produced in human in vitro incubations.

The major metabolite in dog and human was a direct glucuronide conjugate whereas the major metabolite in the rat was a direct sulfate conjugate of AZD5363. Six monooxygenated metabolites were also identified and, in the presence of aminobenzotriazole, the major human peak was still the glucuronide of [14C]-AZD5363 whereas the levels of monooxygenated metabolites were all reduced in the presence of aminobenzotriazole. This suggests that the formation of the monooxygenated metabolites was mediated by CYP enzymes.

Experiments performed to identify the UGT and CYP isozymes responsible for the metabolism of AZD5363 suggested that UGT1A9 and UGT2B7 are responsible for the formation of the major human metabolite, the glucuronide conjugate. UGT1A4 produced a glucuronide metabolite, which was not observed in incubations with human hepatocytes and therefore is a potential metabolite in human. AZD5363 was metabolised following incubation with heterologous expressed CYP2D6, CYP3A4, CYP3A5, CYP2C9, CYP1A1, CYP2C19 and CYP2B6. Based on the relative expression levels of these CYP isozymes, and the fact that inhibitory antibodies against CYP3A4 reduce the levels of the monooxygenated metabolites, it is likely that CYP3A4 will play the largest role in vivo, with contributions from CYP2C9 and CYP3A5.

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, enzalutamide reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate).. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot

be avoided, conduct additional INR monitoring. Single 160 mg oral dose of Enzalutamide was administered alone or after multiple oral doses of gemfibrozil (strong CYP2C8 inhibitor). Gemfibrozil increased the $AUC_{0\text{-}inf}$ of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold with minimal effect on C_{max}.

Single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of itraconazole (strong CYP3A4 inhibitor). Itraconazole increased the $AUC_{0\text{-}inf}$ of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold with no effect on C_{max}.

1.4.1.5. Summary of Nonclinical Experience with Enzalutamide

For full details of the pre-clinical information, please refer to the Investigator Brochure.

1.4.2. AZD5363

AZD5363 is a potent and selective ATP-competitive inhibitor of the serine / threonine kinase AKT / PKB (protein kinase B). AKT is a key member of the AGC family of kinases. Mammalian cells express three closely related AKT isoforms: AKT1 (PKBα), AKT2 (PKBβ) and AKT3 (PKBγ), all encoded by different genes. AKT is a critical node along multiple signalling pathways that is involved in the regulation of cellular apoptosis, proliferation, and growth. The activation of all 3 AKT isoforms have been implicated in different tumour types, including breast, prostate, ovarian, pancreatic and gastric cancers, and this activation is often associated with resistance to established antitumour treatments, as well as the progression of advanced malignancies [21]. AKT hyperactivation in tumours is mainly due to deregulated input from genetic and epigenetic aberrations upstream of AKT or along parallel signalling pathways (e.g. mutation of oncogenes such as Ras, Bcr-abl, mutations of receptor tyrosine kinases such as EGFR, amplification of HER2, loss of PTEN function and PIK3CA mutations), although AKT mutations or amplification may also result in the hyperactivation of this pathway. The development of potent inhibitors against AKT is thus a rational anticancer strategy [22].

Single agent antitumour activity with AKT inhibitors has, to date, been modest in the initial phase I clinical trials conducted [23] [24]. This is likely to be related to critical issues of crosstalk between signalling pathways, disruption of feedback loops and tumoural heterogeneity. As such, the optimal application of AKT inhibitors is hypothesized to be in combination regimens with other molecular targeted agents, cytotoxic chemotherapies or anti-hormonal therapies. AZD5363 inhibits all three AKT isoforms (AKT1, AKT2 and AKT3) and has the potential to provide clinical benefit over a range of therapeutic indications.

1.4.2.1. Pharmacokinetics and Drug Metabolism of AZD5363

Time-dependent inhibition of cytochrome P450 (CYP) 3A4/5 was observed during the non- clinical *in vitro* evaluation of the metabolism of AZD5363.

1.4.2.2. Summary of Clinical Experience with AZD5363

AZD5363 is currently being assessed in a first-in-human Phase I clinical trial (NCT01226316). The main objectives include the assessment of the safety and tolerability of AZD5363, dose-limiting toxicities, and the establishment of the maximum tolerated dose. Secondary objectives include the assessment of pharmacokinetics, pharmacodynamics and preliminary antitumour effects.

AE reports of hyperglycaemia, rash, diarrhoea and hypersensitivity are causally associated with the use of AZD5363. To date, the most commonly reported AEs, regardless of dose or causality, are: diarrhoea, hyperglycaemia, fatigue, maculo-papular rash, vomiting, dyspnoea and nausea. The

majority of AEs reported in patients receiving AZD5363 have been CTCAE Grade 1 or Grade 2 in toxicity.

Ten DLTs of maculo-papular rash have been reported in studies D3610C00001 and D3610C00004 under a continuous dosing schedule: three at 320 mg bid cohort (CTCAE grade 3) two at 400 mg bid cohort (CTCAE grade 3), three at 480 mg bid cohort (CTCAE grade 3) and two at 600 mg bid cohort (CTCAE grade 4).

No DLTs of maculo-papular rash have been reported in studies D3610C00001 and D3610C00004 under any of the intermittent continuous dosing schedule (4 days on and 3 days off or 2 days on and 5 days off).

Five DLTs of diarrhoea have been reported in studies D3610C00001 and D3610C00004 under a continuous dosing schedule: two at 320 mg bid cohort (CTCAE grade 3), one at 400 mg bid cohort (CTCAE grade 3) and two at 480 mg bid cohort (CTCAE grade 3).

No DLTs of diarrhoea have been reported in studies D3610C00001 and D3610C00004 under any of the intermittent continuous dosing schedule (4 days on and 3 days off or 2 days on and 5 days off).

Two DLTs of hyperglycaemia have been reported in study D3610C00001 under the intermittent continuous dosing of 2 days on and 5 days off: plasma glucose levels of 31.1mmol/L (560.3 mg/dL) and 31.6 mmol/L (569.3 mg/dL) at 640 mg bid and 800 mg bid, respectively.

4 patients have experienced hypersensitivity events, 2 in study D3610C00001, 1 in D3610C00004 and a fourth patient was enrolled in a combination study with paclitaxel (D3610C00002). The events manifested as rash with one or more associated clinical features such as flushing, pruritus, urticaria, throat itchiness, pyrexia and facial and/or lip oedema. Time to onset of events ranged from 11 to 120 days (median: 21 days) from start of therapy with AZD5363. In each case the event resolved with study drug discontinuation and treatment with antihistamines and steroids. This information from clinical studies suggests that AZD5363 can cause hypersensitivity in some patients.

There have been no clinically significant findings identified on review of electrocardiograms (ECGs) or left ventricular ejection fraction (LVEF) decreases attributed to AZD5363.

One female patient with cervical carcinoma (*PIK3CA* mutation positive) with metastasis to the lymph nodes, receiving 400 mg bid in the continuous dosing regimen, had a confirmed partial response for 20 weeks prior to disease progression. The patient had previously received adjuvant and first-line chemotherapy and radiation. Another female patient, Asian, 38 years old, endometrioid cancer of the ovary had a best response of PR (-30.2% tumour decrease from baseline) after 89 days of AZD5363 480 mg bid (4 days on and 3 days off), confirmed at Day 139 (-38.4% tumour decrease from baseline) still ongoing.

Five patients treated with the continuous dosing regimen had stable disease with duration of response (DoR) of at least 12 weeks. These were: advance cervical carcinoma (n=1), advanced osteosarcoma (n=1) at 80 mg bid; colorectal carcinoma (n=1) at 240 mg bid; urothelial carcinoma (n=1) and liposarcoma (n=1) both at 400 mg bid.

Continuous schedule doses of 80, 160, 240 and 320 mg bid have been declared tolerable, and 400, 480 and 600 mg bid have been declared non-tolerable.

Intermittent schedule (4days on and 3days off) dose of 240, 480 and 640 mg bid have been declared the tolerated, maximum tolerated/optimal long term and not chronically tolerated

exposure doses respectively. Intermittent schedule (2days on and 5days off) dose of 640 was declared tolerated and 800 mg bid is ongoing.

Based on the efficacy and safety accumulated data the intermittent schedule, 4days on and 3days off is being investigated in this study and depending on the AZD5363 programme emerging data and SRC agreement the 2 days on and 5 days off schedule could be investigated in this study.

Further information on AZD5363 can be found in the Investigator's Brochure.

1.4.2.3. Summary of Non-clinical Experience with AZD5363

For full details of the pre-clinical information, please refer to the Investigator Brochure

1.4.2.4. Rationale for AZD5363 dosing regimen

Emerging data from the continuous and intermittent dose schedule part of studies D3610C00001 (Western) and D3610C00004 (Japan) showed that AZD5363 bid given for 4 days on, 3 days off therapy is the preferred regimen due to the following:

AZD5363 480 mg bid given for 4 days on and 3 days off therapy in a weekly based regimen was considered tolerated by the SRC as no patients presented any DLTs out of the 11 patients dosed in this cohort level. All patients had transiently elevated plasma glucose levels elevation after approximately 2 to 4 hours, returning to baseline levels within 6 hours after AZD5363 dosing. Four patients required metformin to control the transient hyperglycaemia.

1.5. Rationale for performing the study

The activity of anti-androgen therapies, including bicalutamide and gonadotropin-releasing hormone analogues, resulted in improved survival for patients with prostate cancer. However, nearly all patients who present with "hormone-sensitive" prostate cancer inevitably progress to CRPC and will eventually require further forms of antitumour therapy.

Activation of PI3K / AKT signalling, often manifested by PTEN loss, is a frequent hallmark of CRPC. Deregulation of this pathway results in the activation of downstream targets (e.g. PRAS40, MTOR, GSK3β, FOXO, etc.), which are involved in the regulation of cellular survival, proliferation, cell cycle progression, growth, migration, and angiogenesis. Notably, prostate-specific deletion of PTEN in preclinical mouse models recapitulates features of human prostate cancer, and *AKT1* deletion in a conditional PTEN knockout model has been demonstrated to significantly reduce prostate cancers [25] [26] [27]. Additionally, PTEN deletion promotes androgen independence in cell lines and mouse models of prostate cancer [28] [29]. In patients with prostate cancer, PTEN loss is associated with higher Gleason scores, disease recurrence post-prostatectomy, bone metastasis, and progression to castration resistance. In addition, PTEN loss is associated with worse survival. Overall, these results suggest that the activation of the PI3K/AKT signalling pathway is an important driver of prostate cancer.

Recent preclinical data suggest that reciprocal crosstalk between the AR and PI3K/AKT signalling pathways occur in PTEN-deficient CRPC. Specifically, activation of the PI3K / AKT pathway can be associated with decreased androgen receptor signalling, and inhibition of the PI3K / AKT pathway increases AR signalling in PTEN-deficient prostate cancer cells. Proposed mechanisms to account for these observations include PI3K / AKT pathway inhibition resulting in feedback activation of AR via the up regulation of HER kinases, while inhibition of AR relieves feedback inhibition of AKT by the phosphatase PHLPP. Such reciprocal cooperativity between PI3K / AKT and AR pathways suggests that the inhibition of either one pathway, without the other, would lead to the achievement of sub-optimal clinical efficacy. Carver and co-workers actually showed that the simultaneous pharmacological inhibition of the PI3K/mTOR pathway and AR

caused near complete prostate cancer regression in PTEN-deficient prostate cancer preclinical mouse models. Therefore, the combined inhibition of the AR and PIK3/AKT pathways may result in more complete inhibition of tumour cell viability and potentially more durable clinical benefit in patients with CRPC [16].

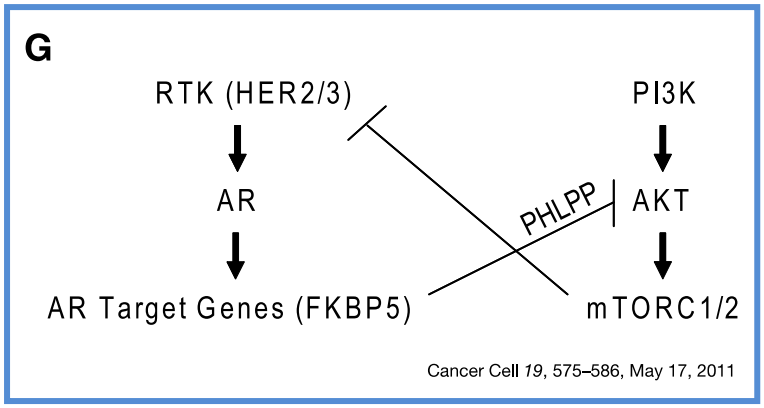


Figure 1 Reciprocal feedback regulation of PI3K and androgen receptor signalling in PTEN-deficient prostate cancer cells.

Finally, despite the success of the enzalutamide studies, CRPC remains an incurable disease with a limited duration of PFS and OS. The purpose of this study is to evaluate if the combined inhibition of androgen signalling (with enzalutamide) and AKT signalling (with AZD5363) is safe and will significantly improve the efficacy of single agent enzalutamide in patients with CRPC. Collection of archival tumour samples will be required for all patients for the analysis of PTEN status. Prospective PTEN analysis will be performed in the single stage phase II expansion cohort with upfront testing (prior to entry) introduced part way through the study.

2. TRIAL OBJECTIVES

2.1. Phase I – safety run in

Recruitment to the phase 1 safety run-in completed in April 2016. AZD5363 400mg bd 4 days on 3 days off with Enzalutamide 160mg continuous was selected as the recommended phase 2 dose.

2.1.1. Primary Objective

- To identify the safety and tolerability of enzalutamide and AZD5363 when given in a combination of once daily enzalutamide (MDV3100) with twice daily AZD5363 administered in a four days on and three days off regimen
- To identify dose-limiting toxicities (DLTs), estimate the maximum tolerated dose (MTD) and identify a recommended Phase II dose (RP2D) of AZD5363 administered in combination with enzalutamide 160mg daily

2.1.2. Secondary Objectives

- To characterize the pharmacokinetics (PK) of AZD5363 and enzalutamide when administered in combination.
- To study the antitumour activity of this combination by PSA, radiological and CTC evaluation.

2.1.3. Exploratory Objectives

- To characterize the pharmacodynamics (PD) of AZD5363 and enzalutamide when administered in combination.

2.2. Randomised Phase II

2.2.1. Primary Objective

- To estimate and compare the antitumour activity of AZD5363 + enzalutamide versus placebo + enzalutamide as measured by response. Response will be defined on the basis of the following outcomes; if any of these occur without evidence of RECIST progression, patients will be considered to have responded:

    - PSA decline ≥50% confirmed by a second reading 4 weeks or later and/or,
    - Confirmed soft tissue objective response (RECIST v1.1) and/or
    - ONLY for patients with detectable circulating tumour cell count (CTC) of ≥5/7.5ml blood at baseline, conversion of CTC to <5/7.5ml blood nadir confirmed by a second reading 4 weeks or later.

Only PSA and CTC assessments from week 12 onwards (to coincide with the first RECIST assessment) will be considered to evaluate response.

The RECIST (v1.1) criteria will be used to determine soft tissue response, (APPENDIX A).

2.2.2. Secondary Objectives

- To estimate and compare the duration of radiological progression free survival (rPFS) of patients on AZD5363 + enzalutamide versus placebo + enzalutamide.
- To estimate the duration of overall survival (OS) of patients on AZD5363 and enzalutamide versus placebo + enzalutamide.

- To estimate the number of skeletal-related events in patients on AZD5363 + enzalutamide versus placebo + enzalutamide.
- To establish maximum PSA decline at any point on the trial (as per PCWG2 criteria) and at 12 weeks of patients on AZD5363 + enzalutamide versus placebo + enzalutamide.
- To assess the effect of AZD5363 + enzalutamide versus placebo + enzalutamide on numbers of circulating tumour cells (CTCs).
- To compare the differences in pain symptoms as measured by the modified Brief Pain Inventory-Short Form (BPI-SF).
- To evaluate the safety and tolerability of AZD5363 + enzalutamide versus placebo + enzalutamide

2.2.3. Exploratory Objectives

- To assess the effect of tumour cell PI3K/AKT pathway alterations on response rate utilizing tumour tissue, CTCs or circulating tumour DNA from plasma using molecular data obtained by one or more of the following methods:

    - Immunohistochemistry/Immunofluorescence for PTEN loss and other markers of pathway activating including INPP4B loss, PhLPP1 loss
    - FISH for PTEN loss in tissue and CTC.
    - PIK3Ca mutation
    - Other genomic changes or biomarkers activating the PI3K/AKT pathway or implicated in resistance/sensitivity to AR or AKT blockade.

- To explore whether selected genes of interest from plasma DNA/RNA are predictive of response to the combination of enzalutamide and AZD5363.
- To explore the predictive and prognostic value of the mRNA expression signature from whole blood at baseline and on treatment [30] and to evaluate if treatment alters this signature.

2.3. Single Stage Phase II Expansion cohort

2.3.1. Primary Objective

To estimate the antitumour activity of AZD5363 + enzalutamide in patients who have previously progressed (by PSA according to PCWG2 criteria or in soft tissue by RECIST 1.1) on enzalutamide alone.

Response will be defined on the basis of the following outcomes; if any of these occur without evidence of RECIST progression of disease, patients will be considered to have responded to combination treatment:

- PSA decline ≥50% confirmed by a second reading 4 weeks or later and/or,
- Confirmed soft tissue objective response (RECIST v1.1) and/or
- ONLY for patients with detectable circulating cell count (CTC) or ≥5/7.5ml blood at baseline, conversion of CTC to <5/7.5ml blood nadir confirmed by a second reading 4 weeks or later.

Only PSA and CTC assessments from week 12 onwards (to coincide with the first RECIST assessment) will be considered to evaluate response.

The RECIST (v1.1) criteria will be used to determine soft tissue response, (Appendix A).

2.3.2. Secondary Objectives

- To report maximal PSA change at any time on the trial and PSA changes at 12 weeks (as per PCWG2 criteria) by a waterfall plot analyses.
- To estimate overall survival (OS) in these patients.
- To estimate the radiologic progression free survival (rPFS) on the combination of AZD5363 + enzalutamide (radiographic progression defined 15.3.2) in these patients.
- To assess the effect of the combination AZD5363 and enzalutamide on numbers of circulating tumour cells (CTCs) in these patients.
- To evaluate the safety and tolerability of the addition of AZD5363 to patients who progress on enzalutamide alone.
- To further assess the pharmacokinetic (PK) profile of AZD5363 and enzalutamide when administered in combination.

2.3.3. Exploratory Objectives

- To assess the effect of tumour cell PI3K/AKT pathway alterations on response rate utilizing tumour tissue, CTCs or circulating tumour DNA from plasma using molecular data obtained by one or more of the following methods:

    - Immunohistochemistry/Immunofluorescence for PTEN loss and other markers of pathway activating including INPP4B loss, PHLPP1 loss
    - FISH for PTEN loss in tissue and CTC.
    - PIK3CA mutation
    - Other genomic changes or biomarkers activating the PI3K/AKT pathway or implicated in resistance/sensitivity to AR or AKT blockade.

- To explore whether selected genes of interest from plasma DNA/RNA are predictive of response to enzalutamide and AZD5363.
- To explore the predictive and prognostic value of the mRNA expression signature from whole blood at baseline and on treatment [30] and the impact of treatment on this signature.
- To further assess the pharmacodynamic (PD) profile of AZD5363 and enzalutamide when administered in combination.

3. TRIAL DESIGN

A multicentre prospective, randomised, phase II interventional study in mCRPC patients previously treated with 1-2 lines of chemotherapy and at least 12 weeks of abiraterone with a phase I safety run-in and single stage phase II expansion cohort.

The randomised phase II and single stage phase II expansion cohort will commence on completion of the phase I safety run in and will run in parallel. Patients eligible for the single stage phase II expansion cohort are patients that have progressed on enzalutamide, so would not be eligible for the randomised phase II part of the study.

3.1. Phase I – safety run in

Approximately 18 patients will receive the combination of enzalutamide and AZD5363 to determine the AZD5363 dose to be used for the randomised phase II and single stage phase II expansion cohort. In phase I, a cohort size of at least 3 and up to 6 patients will be employed at each dose level (starting at dose level 1) in a 3+3 design.

3.1.1. Dose escalation schedule

Approximately three dose-levels of AZD5363 in combination with enzalutamide are planned although higher dose levels may be required since enzalutamide may induce AZD5363 clearance. Intermediate dose levels (1A or 2A) may also be explored depending on drug tolerability. In case of significant interaction with reduced or increased enzalutamide exposure different doses of enzalutamide may be explored. The dose of enzalutamide will be increased or decreased at increments of 40mg.

Table 1 – Dose escalation schedule

Dose level	AZD5363 – commence Cycle 0 Day 1	MDV3100 – commence Cycle 1 Day 1
-2	160mg bid 4 days on 3 off	160mg od
-1	240mg bid 4d on 3d off	160mg od
1	320mg bid 4d on 3d off	160mg od
1A (optional)	400mg bid 4d on 3d off	160mg od
2	480mg bid 4d on 3d off	160mg od
2A (optional)	560mg bid 4d on 3d off	160mg od
3	640mg bid 4d on 3d off	160mg od

- Patients will receive a single dose of AZD5363 at Cycle 0 Day 1 (i.e. Cycle 1 Day -7). A week later, on Cycle 1 Day 1, continuous oral dosing of enzalutamide with intermittent oral AZD5363 will be started.
- At least three patients will be enrolled at dose level 1 (320mg) of AZD5363 bid given on an intermittent schedule 4 days on and 3 days off. The first patient will be treated (Cycle 0, Day 1) and the next two patients staggered to be treated at the earliest one week after the first patient started treatment of combination therapy on C1D1.
- After this first cohort has cleared the 35-day DLT window (Cycle 0 Day 1 to Cycle 1 Day 28) without DLT, dose escalation will occur to level 2 (480 mg) of AZD5363 based on the dose escalation rules. If a DLT occurs in this first cohort then the dose will be de-escalated to dose level -1 (240 mg).
- Further dose escalation or de-escalation may be explored (see Table 1). These doses and schedules of AZD5363 have been explored and been declared safe and tolerable in the current phase I study (NCT01226316). A different schedule of AZD5363 and / or a different dose may be investigated in the run-in phase of the trial depending on emerging safety and PK / PD data (for example two days on, 5 days off). Other dose levels of AZD5363 may be investigated but are unlikely to be required. Decisions on dose escalation or de-escalation will be made by the Safety Review Committee (SRC). Cycle 0 duration is 7 days and all cycles thereafter (C1 D1 onwards) are 28-day treatment cycles.

3.1.2. Phase I Safety Run In: Definition of Dose-Limiting Toxicity (DLT)

A DLT is defined as one of the following toxicities occurring mainly but not exclusively during the DLT assessment window of Cycle 0 Day 1 to Cycle 1 Day 28 (35 day assessment window) and is highly probably or probably related to either AZD5363 or enzalutamide (see causal attribution guidance in Table 8):

- Grade ≥3 non-haematologic, non–hepatic major organ adverse event, excluding the following:
    - Grade 3 nausea, vomiting, or diarrhoea that resolves to Grade ≤1 within 7 days with appropriate supportive care
    - Grade 3 rash that resolves rapidly upon discontinuation of drug with appropriate supportive measures.
    - Grade 3 laboratory abnormality that is asymptomatic and deemed by the investigator not to be clinically significant
- Grade ≥3 febrile neutropenia
- Grade ≥4 neutropenia (absolute neutrophil count $< 500/\mu L$) lasting > 7 days
- Grade ≥3 thrombocytopenia associated with acute haemorrhage
- Grade ≥4 thrombocytopenia
- Grade ≥4 anaemia
- One episode of fasting Grade ≥4 hyperglycaemia (>27.8mmol/l) or two episodes of symptomatic fasting Grade 3 hyperglycaemia (>13.9 – 27.8mmol/l) on separate days within 7 days, as determined by laboratory blood glucose evaluation.
- Any Grade >3 elevation of hepatic transaminases (ALT or AST) OR total bilirubin lasting >48 hours will be considered a DLT with the following exceptions:
    - For patients with elevated hepatic transaminase at baseline due to documented liver metastasis (i.e. <5 x ULN), hepatic transaminase >8x ULN for >48 hours will be considered a DLT;
    - For patients with elevated total bilirubin at baseline due to documented liver metastasis or Gilbert's disease (i.e. ≥1.5 x ULN), total bilirubin of >2.5x ULN will be considered a DLT.
- Any case involving an increase in hepatic transaminase >3 x ULN and an increase in total bilirubin >2 x ULN, without any findings of cholestasis AND in the absence of other contributory factors (e.g. worsening of metastatic disease or concomitant exposure to known hepatotoxic agent) is suggestive of potential drug-induced liver injury according to Hy's Law and will be considered a DLT.
- Any other toxicity, which in the view of the investigators is considered to be a DLT, at any time during the study. These cases will be discussed at the SRC meetings.

3.1.3. Patients Evaluable for Assessment of Dose-Limiting Toxicities

DLTs will be primarily assessed during the 35-day DLT assessment window (Cycle 0 Day 1 to Cycle 1 Day 28). A patient can have multiple toxicities that meet the criteria of DLT but only the first will be considered for dose escalation decisions. The following patients will not be considered evaluable for DLTs and will be replaced:

- Patients who withdraw or are withdrawn from the study prior to completing the DLT assessment window for any reason other than a DLT.
- Patients who miss ≥7 total days of scheduled AZD5363 or enzalutamide dosing (e.g. 80% of the total intended dose of AZD5363 or enzalutamide within the 35 day cycle) during the DLT assessment window for reasons other than a DLT. Patients will not make up missed doses of AZD5363 or enzalutamide.

3.1.4. Dose-Escalation Rules

Dose escalation of AZD5363 will occur in accordance with the rules listed below:

- A minimum of 3 patients will initially be enrolled per cohort.
- If none of the first 3 patients experiences a DLT, dose escalation may proceed.
- If 1 of the first 3 patients enrolled in a given cohort experiences a DLT, 3 additional patients (for a total of 6) will be enrolled in that cohort.
- If less than one-third of the patients in a given cohort experience a DLT (e.g. DLTs in less than 1 of 3 or 2 of 6 patients), dose escalation may proceed.
- If a DLT is observed in one-third or more of the patients in a given cohort (e.g. 2 or more of up to 6 patients), the MTD will have been exceeded and dose escalation will be stopped. An additional 3 patients will be evaluated for DLTs at the preceding dose cohort (if 6 patients had not already been evaluated at that level).The highest dose level with a minimum of 6 patients at which fewer than one-third of patients experience a DLT will be declared the MTD, and the recommended phase II dose (RP2D).
- If the initial dose levels evaluated are not safely cleared, a lower dose and / or alternate schedule of AZD5363 (e.g. 2 days on 5 days off weekly) may be examined.

Dose escalation or de-escalation may only proceed following confirmation from the RE-AKT Safety Review Committee (see section 16.4).

3.2. Phase II - Randomised

A randomised, double blind phase II trial of enzalutamide in combination with AZD5363 versus enzalutamide alone will determine if the antitumour activity of the combination therapy is superior to the antitumour activity to enzalutamide alone **(enzalutamide + AZD5363 vs. enzalutamide + placebo)**.

Patients will be randomised using a minimisation algorithm, incorporating a random element, in a 1:1 ratio.

3.3. Phase II - single stage expansion cohort

A single stage phase II expansion cohort of enzalutamide and AZD5363 in patients with previous progression on enzalutamide to explore whether the addition of AZD5363 to enzalutamide can reverse resistance **(enzalutamide → enzalutamide + AZD5363).**

This cohort includes patients that have been previously treated with enzalutamide for at least 12 weeks and have documented progression by PSA or soft tissue (PCWG2 and/or RECIST 1.1). Patients with purely bone scan progression in the absence of PSA and / or soft tissue progression will not qualify for the single stage phase II expansion. Early changes in PSA (<12 weeks from baseline) will be ignored and enzalutamide treatment must have been given for a minimum of 12 weeks to ensure adequate drug exposure before they can be eligible for treatment on this single stage phase II expansion cohort.

Patients may have either recently progressed on Enzalutamide within 12 weeks of trial registration with Enzalutamide having been their last line of treatment (Recent Group) or have progressed on Enzalutamide during a previous line of treatment and subsequently stopped Enzalutamide treatment > 12 weeks from trial registration (Elapsed Group). Patients in the Elapsed Group will be treated with sole Enzalutamide for at least 4 weeks until confirmed progression via weekly PSA as part of the study protocol.

Patients in this cohort will have their archival tumour tissue analysed for PTEN loss. This single stage phase II expansion cohort will attempt to include 9 patients with PTEN loss (as determined by immunohistochemistry and defined as any part of the tumour having an H score <30) and 9 patients with normal PTEN by immunohistochemistry or/and FISH (-/-). Once 9 patients with PTEN loss or PTEN normal status have been accrued, the IDMC will advise on whether further enrolment will be dependent on the

patient's tumour having the PTEN status criteria required to ensure sufficient PTEN loss patients are enrolled.

3.4. Discontinuation of Study Treatment (all stages)

Patients will receive study treatment until disease progression (clinical or radiological progression see Appendix A for definition of soft tissue and bone progression) or unacceptable toxicity or patient withdrawal from the RE-AKT study, or study completion or termination. Patients with pure PSA progression in the absence of clinical or radiological progression should remain on trial. If a patient is withdrawn for any reason prior to radiological progression then the patient should be assessed until radiological progression has occurred or a subsequent line of treatment is started.

3.5. Replacement of patients

Patients that stop treatment with AZD5363 and enzalutamide within the first 12 weeks of treatment for reasons other than progression (soft tissue by RECIST 1.1 or bone scan progression or skeletal related event (SRE)) or tolerability issues directly related to either of the compounds will be replaced. The IDMC will advise on the replacement of patients in the randomised phase II part of the study. Patients in the Elapsed Group of the Single Stage expansion Cohort who do not receive combination treatment will be replaced.

3.6. Definition of disease progression (all stages)

For disease progression the PCWG2 criteria will be followed. A patient will be considered to have progressed on study if the following findings occur:

i. Progression by bone scan:

Progression is defined as the appearance of 2 or more new bone metastases detected by bone scan compared with the baseline scan. However, if the 2 or more new lesions are detected at week 12, a confirmatory scan 6-12 weeks later with additional 2 or more new lesions will be required in order to qualify for disease progression ("2+2" rule). If on the confirmatory scan less than 2 additional new lesions are detected, patients are classified as having stable disease.

ii. Progression of soft tissue /visceral disease by RECIST v1.1 (Appendix A):

A patient will be determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions, or the appearance of one or more new lesions by RECIST v1.1.

iii. Progression by PSA

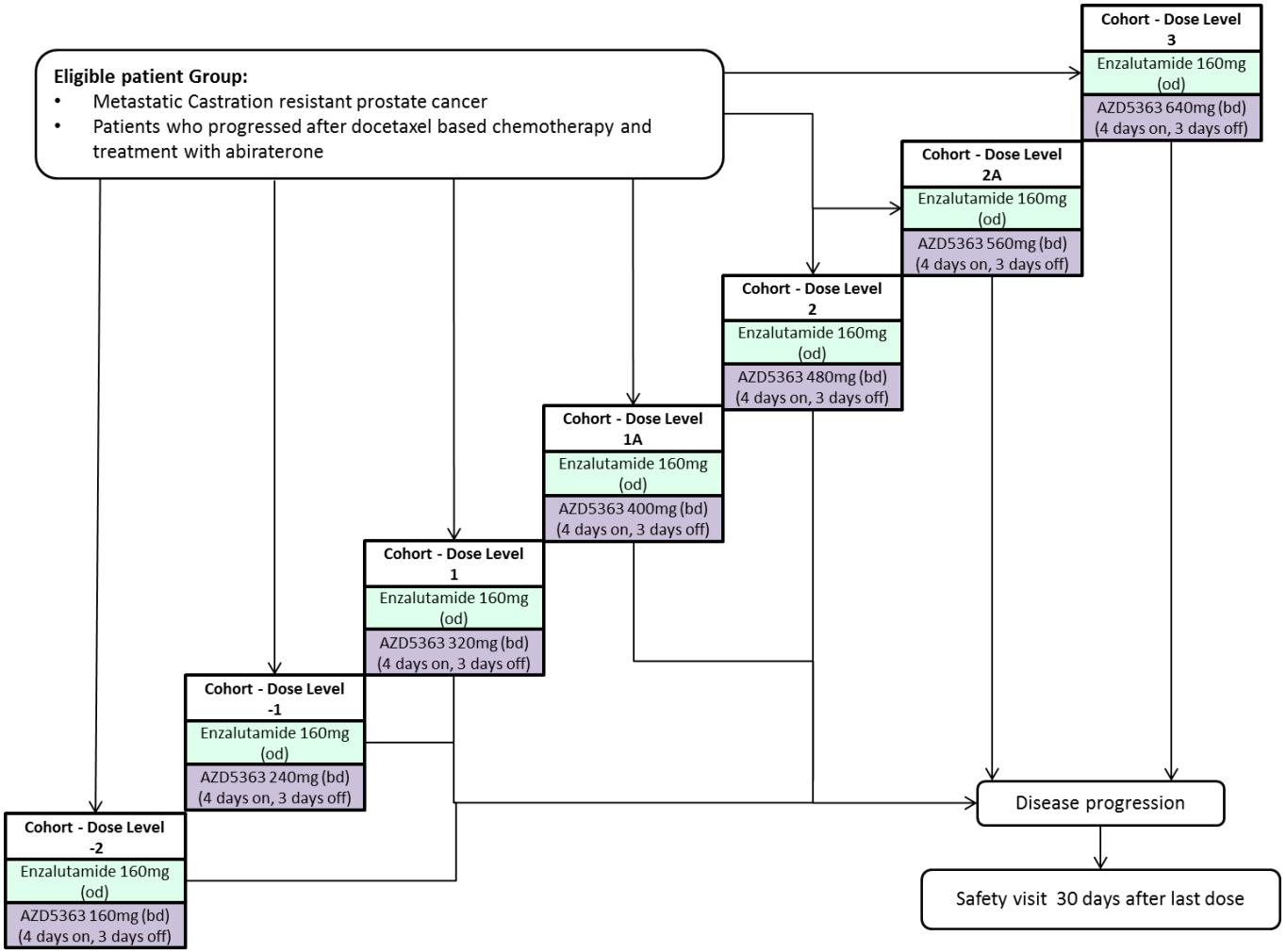
PSA progression is defined as a 25% or greater increase and an absolute increase of 2 ng/mL or more from the baseline value or a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir if PSA decreases from baseline after treatment, which is confirmed by a second value obtained 4 or more weeks later. PSA progression should only be defined on or after 12 weeks (3 cycles) of treatment. In the first 12 weeks PSA will not be measured. It is strongly recommended that in case of PSA progression in the absence of objective soft tissue or bone progression, patients will remain on study treatment.

iv. Unequivocal evidence of clinical progression:

Discontinuation of treatment is discouraged unless the patient has progressed by clinical and radiological measures. Nevertheless, a patient can be taken off trial treatment at the discretion of the treating clinician under the following circumstances:

- Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy.
- Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumour progression even in the absence of radiological progression.
- Marked deterioration in ECOG performance status to grade 3 or higher felt by the investigator to indicate clinical progression.
- Decision of investigator that in the best interest of the patient to discontinue trial treatment due to clinical progression.

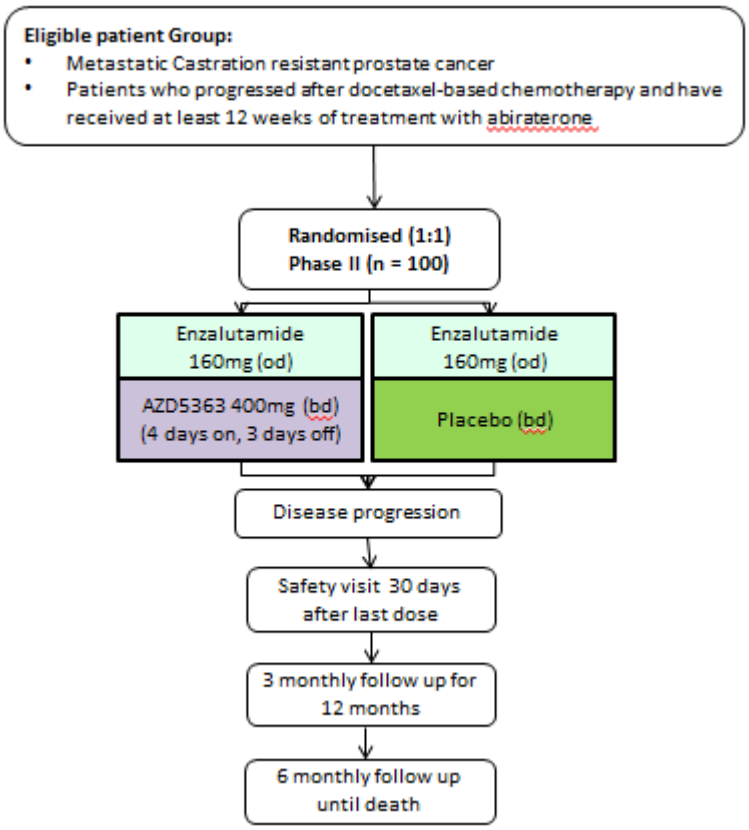
3.7. Figure 2: STUDY FLOW CHART – Part 1 – Phase I safety run in



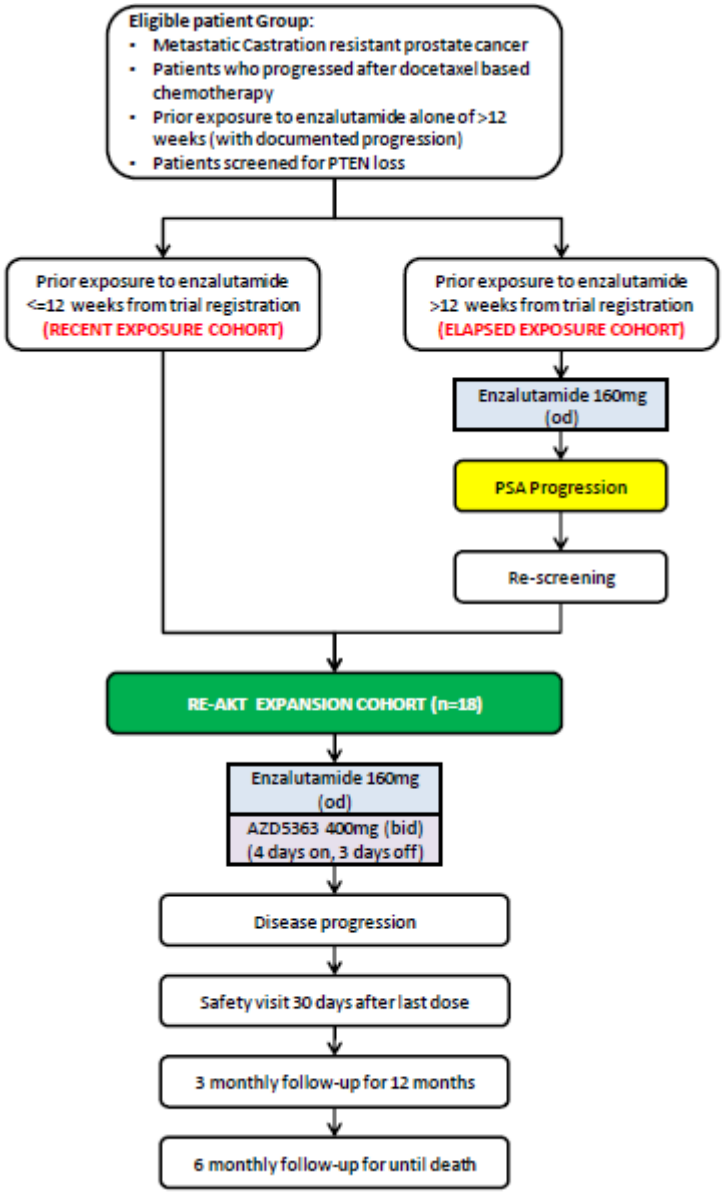
Please note

- **figure is illustrative with respect to the highest dose of AZD5363**
- **cohorts 1A and 2A are optional.**

3.8. Figure 3: STUDY FLOW CHART – Part 2 - Randomised Phase II



3.9. Figure 4: STUDY FLOW CHART –Part 2 – Phase II Single Stage Expansion Cohort



4. PATIENT SELECTION & ELIGIBILITY

4.1. Number of Patients

- **Phase I safety run-in :** Approximately 18 patients
- **Randomised Phase II**: 100 patients will be randomised in a 1:1 ratio for the Enzalutamide + AZD5363 vs. Enzalutamide + placebo group comparison.
- **Single stage phase II** (expansion cohort): 18 patients will be recruited. It is intended the expansion cohort will include 9 fully evaluable patients with PTEN loss and 9 patients without.

4.2. Source of Patients

The target population is patients with metastatic Castrate Resistant Prostate Cancer (mCRPC) who progressed after docetaxel-based chemotherapy and:

- **Phase I safety run-in:** patients must have progressed on prior abiraterone OR enzalutamide.
- **Randomised phase II:** patients must have progressed on prior abiraterone
- **Single stage phase II expansion:** patients must have progressed on prior enzalutamide.

Patients will be recruited from approximately 15 oncology centres for the randomised phase II portion of the study. The phase I safety run in will be conducted at the Royal Marsden NHS Foundation Trust only. The phase II single stage expansion cohort will be run at the Royal Marsden and some but not all of the selected centres participating in the phase II randomised stage of the study.

4.3. Inclusion Criteria

1. Written informed consent.
2. Histological diagnosis of adenocarcinoma of the prostate and with tumour tissue accessible for research analyses for this trial (e.g. PTEN testing). Patients who have no histological diagnosis must be willing to undergo a biopsy to prove prostate adenocarcinoma.
3. Metastatic Castration-Resistant Prostate Cancer (mCRPC).
4. Progressed after 1 or 2 lines of taxane based chemotherapy.
5. Progressed after abiraterone (pre or post chemotherapy).

    - Patients must have received at least 12 weeks of treatment with abiraterone or enzalutamide (Phase I safety run-in)
    - Patients must have received at least 12 weeks of treatment with abiraterone (Randomised phase II).

6. Age ≥18 years.
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 – 2.
8. PSA ≥ 10ng/ml.
9. Documented willingness to use an effective means of contraception while participating in the study and for 12 months post last dose of treatment (see section 4.5).
10. Documented ongoing castrate serum testosterone <50 ng/dL (<1.7 nmol/L).
11. Received prior castration by orchiectomy and/or ongoing Luteinizing Hormone-Releasing Hormone (LH-RH) agonist treatment.
12. Progression of disease by PSA utilizing PCWG2 criteria and at least another of the following criteria;
    a. Bone scan: disease progression as defined by at least 2 new lesions on bone scan.
    b. Soft tissue disease progression defined by modified RECIST 1.1.
    c. Clinical progression with worsening pain and the need for palliative radiotherapy for bone metastases.

PHASE I SAFETY RUN IN and EXPANSION COHORT - inclusion criteria:

13. Willing to have a biopsy to obtain tumour tissue for biomarker analyses prior to and after treatment.

SINGLE STAGE PHASE II EXPANSION COHORT ONLY - inclusion criteria:

14. Prior exposure to enzalutamide of at least 12 weeks is required with documented disease progression biochemically and/or radiologically by PCWG2 or RECIST 1.1 criteria. Patients should have received at least 12 weeks of enzalutamide with evidence of disease progression (by PSA with 3 rising values as per PCWG2 criteria or soft tissue progression as per RECIST v1.1). Patients who have progressed on Enzalutamide within 12 weeks prior to trial registration are defined as 'Recent' patients. Patients who have progressed on Enzalutamide outside the 12 week window prior to trial registration are defined as 'Elapsed' patients.

15. Archival tumour tissue available for the analysis of PTEN loss by the central laboratory.

Note: Inclusion Criteria 5 - Prior Abiraterone treatment will not be mandated for the Single Stage Phase II Expansion but is allowed

4.4. Exclusion Criteria

1. Prior treatment with enzalutamide (MDV3100) (not applicable for the phase I safety run in or for the single stage phase II expansion cohort, see inclusion criteria 14).
2. Prior treatment with PI3K, AKT, TOR kinase or mTOR inhibitors (see Appendix C).
3. Surgery, chemotherapy, or other anti-cancer therapy within 4 weeks prior to trial entry / randomisation into the study (6 weeks for bicalutamide). Any other therapies for prostate cancer, other than GnRH analogue therapy, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (e.g., finasteride or dutasteride), must be discontinued at least 2 weeks before the first dose of study drug.
4. Participation in another clinical trial and any concurrent treatment with any investigational drug within 4 weeks prior to trial entry / randomisation.
5. Prior limited field radiotherapy within 2 weeks or wide field radiotherapy within 4 weeks of trial entry / randomisation.
6. History of seizure or any condition that may predispose to seizure including, but not limited to underlying brain injury, stroke, primary brain tumours, brain metastases, or alcoholism.
7. History of loss of consciousness or transient ischemic attack within the previous 12 months of trial entry / randomisation.
8. Known brain or leptomeningeal involvement.
9. Use of potent inhibitors or inducers of CYP3A4, CYP2C9, CYP2C19 and CYP2D6 substrates (see Appendix B) within 2 weeks before trial entry / randomisation (3 weeks for St John's Wort) must be avoided.
10. Clinically significant abnormalities of glucose metabolism as defined by any of the following:
    a. Diabetes mellitus type I.
    b. Fasting plasma glucose [fasting is defined as no calorific intake for at least 8 hours]:
       ≥ 7.0mmol/L (126 mg/dL) for those patients without a pre-existing diagnosis of Type 2 diabetes mellitus
       ≥ 9.3 mmol/L (167mg/dL) for those patients with a pre-existing diagnosis of Type 2 diabetes mellitus
    c. Glycosylated haemoglobin (HbA1C) ≥8.0% (63.9 mmol/mol)
    d. Requirement for insulin for routine diabetic management and control
    e. Requirement for more than two oral hypoglycaemic medications for routine diabetic management and control
11. Inadequate organ and bone marrow function as evidenced by:
    a. Haemoglobin <85 g/L
    b. Absolute neutrophil count <1.0 x 10^9/L

c. Platelet count < 75 x 10^9/L
d. Albumin ≤25 g/L
e. AST / SGOT and/or ALT / SGPT ≥ 2.5 x ULN (≥ 5 x ULN if liver metastases present)
f. Total bilirubin ≥ 1.5 x ULN (except for patient with documented Gilbert's disease)
g. Serum Creatinine > 1.5 x ULN

12. Inability or unwillingness to swallow oral medication.
13. Malabsorption syndrome or other condition that would interfere with enteral absorption.
14. Any of the following cardiac criteria;
    a. Mean resting corrected QT interval (QTcF) >470msec obtained from 3 consecutive ECGs taken within 5 minutes
    b. Any clinically important abnormalities in rhythm, conduction, or morphology of a resting ECG (e.g., complete left bundle branch block, third degree heart block)
    c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication known to prolong the QT interval or with a potential for Torsades de pointes
    d. Experience of any of the following procedures or conditions in the preceding six months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure NYHA ≥ Grade2
    e. Uncontrolled hypotension defined as – systolic blood pressure (BP) <90mmHg and/or diastolic BP <50mmHg
15. Clinically significant history of liver disease consistent with Child-Pugh Class B or C, including viral or other hepatitis, current alcohol abuse, or cirrhosis.
16. Any other finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patients at high risk from treatment complications.
17. Need for chronic corticosteroid therapy of >10 mg of prednisolone or >0.5mg of dexamethasone per day or an equivalent dose of other anti-inflammatory corticosteroid**, for the use of concomitant steroids on this trial please refer to section 12.1.** Patients in which corticosteroids cannot be stopped prior to entering the trial are allowed a maximum of 10mg of prednisolone per day or equivalent. **In the case of corticosteroid discontinuation, a 2-week (14 days) washout is required with a mandatory PSA check prior to starting the trial. If the PSA has declined compared to the value obtained prior to stopping corticosteroids, patients will not be eligible for study. Patients can only enter the study with a confirmed PSA increase.**
18. Malignancies other than prostate cancer within 5 years prior to trial entry / randomisation, except for adequately treated basal or squamous cell skin cancer.
19. Unresolved clinically significant toxicity from prior therapy except for alopecia and Grade 1 peripheral neuropathy.
20. Inability to comply with study and follow-up procedures.
21. Patients with predominately small cell or neuroendocrine differentiated prostate cancer are not eligible.

4.5. Lifestyle Guidelines

Male participants must be surgically sterile or must agree to use effective contraception during the period of the therapy and for 12 months after the last dose of study treatment. Effective contraception is defined as double barrier contraception (e.g. condom plus spermicide in combination with a female condom, diaphragm, cervical cap or intrauterine device). Note: It is not known whether the preclinical changes seen in the male animal reproductive organs, after treatment with AZD5363, will be fully reversible or will permanently affect the ability to produce healthy sperm following treatment. Therefore, if male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

Due to the increased risk of seizure and hallucination for patients receiving enzalutamide patients should be advised to avoid drinking large amounts of alcohol and avoid medicines that can cause seizures or that can increase the susceptibility for having seizures.

5. SCREENING

5.1. Screening Log

All participating sites will be required to keep a log of all participants with mCRPC that are potentially eligible for this study. The information collected on the log will include:

- Date patient identified
- Screening outcome (patient approached/accepted participation/declined participation)
- Reasons for not approaching / declining participation (if available)
- Trial ID (if applicable)

This information will be used to monitor recruitment activity. No patient identifiable data will be sent to ICR-CTSU at this stage.

5.2. Procedure for obtaining informed consent

The Principal Investigator (or designated individual) must ensure that each trial patient is fully informed about the nature and objectives of the trial and possible risks associated with participation. Participants should be given the current REC approved RE-AKT patient information sheet for their consideration. Patients should only be asked to consent to the study after they have had sufficient time to consider the trial, and the opportunity to ask any further questions.

No protocol required assessments should be conducted until the RE-AKT consent form has been signed and dated by both the patient and the Investigator, unless they are performed routinely as part of standard patient care.

Patients who consent to RE-AKT consent to having archival tumour tissue, CTCs, blood and urine collected for translational studies.

- **Phase I safety run –in** – patients also consent to the collection of fresh tissue and hair follicles.
- **Randomised phase II** - Patients will be asked to consent to donate fresh tissue for translational studies. Patients should be made aware that participation in the tissue sub-studies is entirely voluntary and refusal to participate will not result in ineligibility to participate in the main clinical trial and will not impact the medical care received.
- **Single stage phase II expansion cohort** - patients also consent to the collection of fresh tissue and hair follicles.

Confirmation of the patient's consent and the informed consent process must be documented in the patient's medical notes. A copy of the signed consent form should be provided to the patient and the original retained in the investigator site file, which must be available for verification by ICR-CTSU study staff or for regulatory inspection at any time.

5.3. Participation in other clinical trials

Patients who fulfil the eligibility criteria will be given the opportunity to participate in RE-AKT if they have participated in other clinical trials prior to recruitment.

RE-AKT patients will not be permitted to participate in any other trials of investigational medicinal products whilst they are being treated within RE-AKT or for two weeks after the last dose of study drug.

6. REGISTRATION

Participants must be registered centrally with the trials unit (ICR-CTSU) before protocol required screening assessments commence. Blank registration forms will be provided to sites with the Investigator Site File. The following information will be requested on the registration form and will be required when registering the patient for screening:

- Stage of trial patient registered into screening for (phase I safety run-in, randomised phase II or single stage phase II expansion cohort)
- Name of treating hospital, consultant and person registering patient
- Confirmation that patient has given written informed consent for the trial
- Patient's full name, hospital number, date of birth, NHS number, postcode
- Confirmation of diagnosis of adenocarcinoma of the prostate

Patients should be registered by telephoning ICR-CTSU on:
020 8643 7150
09.00-17.00 (UK time) Monday to Friday

The caller will be given the patient's unique trial registration number.

7. ELIGIBILITY STATUS and TRIAL ENTRY/RANDOMISATION

Patients must be enrolled (phase I safety run-in and single stage phase II expansion cohort) or randomised (randomised phase II) centrally into the trial by the trials unit (ICR-CTSU) before trial treatment can commence. Following written informed consent and completion of all screening procedures, an eligibility checklist should be completed and eligibility must be confirmed by a clinician by signing the eligibility checklist. Patients can then be enrolled / randomised to study treatment. Blank trial entry / randomisation forms will be provided to sites with the Investigator Site File prior to study initiation. The following information will be requested on the trial entry / randomisation form:

- Name of centre, Principal Investigator and person entering / randomising patient;
- Patient registration number;
- Confirmation of the stage of trial patient registered into screening for (phase I safety run-in, randomised phase II or single stage phase II expansion cohort);
- Confirmation that written informed consent has been obtained;
- Patient's full name (if applicable) and date of birth;
- Date of confirmation that the patient is eligible and that an eligibility checklist has been completed by the clinician.
- Randomised Phase II only: Prior lines of taxane based chemotherapy (1 or 2) and prior response to abiraterone (Yes or No). The response to abiraterone is defined as a ≥50% PSA decline or an objective soft tissue response as per RECIST 1.1.
- Single Stage Phase II Expansion Cohort only: Time since progression on Enzalutamide i.e.
    - Recent: Patients who have progressed on Enzalutamide within 12 weeks prior to trial registration
    - Elapsed: Patients who have progressed on Enzalutamide outside the 12 week window prior to trial registration. Elapsed patients will be treated with single treatment Enzalutamide for at least 4 weeks until confirmed progression via weekly PSA as part of the study protocol.

Trial entry / randomisation should take place as close to the planned start date of treatment as possible.

Patients should been enrolled / randomised by telephoning ICR-CTSU on:
020 8643 7150
09.00-17.00 (UK time) Monday to Friday

The caller will be given the patient's unique trial number (Trial ID) and treatment allocation/study code (see section 10).

ICR-CTSU will fax the data management contact and pharmacist at the recruiting site to confirm a patients' entry into the trial. The fax confirmation for the safety-run in component will confirm the dose level for the patient. For details of the randomised phase II medication allocation see section 10.6.

8. TRIAL ASSESSMENTS

Please note for all components of the trial the term 'week 12' is used and counted from Cycle 1 Day 1 (not Cycle 0 Day 1 for the phase I safety run-in).

Please note the potential for AZD5363 to cause hyperglycaemia and the requirement for regular monitoring.

8.1. Phase I Safety Run-in Trial Assessments

8.1.1. Post Registration / Screening Assessments

The following assessments should be conducted after consent/registration and within 28 days of start of trial treatment (C0D1) to confirm eligibility for trial entry (refer also to section 9.1 and 9.2);

- **Demography –** including age, sex and ethnicity
- **Medical history** - including clinically significant diseases within the previous 5 years, smoking history, prostate cancer history and complete cardiovascular history and family history
- **Acquire archival tissue** - (or fresh biopsy for patients with no prior tissue diagnosis of prostate cancer)
- **Vital signs** – HR, BP and body temperature
- **Physical examination** - including height and weight
- **Concomitant medications** – including investigational and anti-cancer therapies used within 28 days prior to Day 1 of Cycle 0.
- **ECOG status**
- **ECG**
- **ECHO or MUGA -** if not performed in the 3 months prior to C0D1
- **Local laboratory blood test**
    - Full blood count
    - Biochemistry – including LFTs, electrolytes, fasting glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
    - Thyroid function – including TSH and FT4
    - Follicle stimulating hormone
    - HbA1C
    - PSA
    - Serum testosterone
- **CT and bone scan**
- **Research samples** - refer to table 2b

8.1.2. Pre-treatment / Baseline Assessments (C0D1)

Pre-treatment / baseline assessments should be performed before the first dose of study drug on C0D1 (refer also to section 9.1 and 9.2);

- **Vital signs -** HR, BP and body temperature
- **Physical examination** (if clinically indicated) – including weight
- **Concomitant medications – including** investigational and anti-cancer therapies used within 28 days prior to Day 1 of Cycle 0.
- **Baseline conditions** - on-going signs, symptoms and toxicities
- **ECOG status**
- **Local laboratory blood test**
    - Full blood count
    - Biochemistry - including LFTs, electrolytes, fasting glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
    - Thyroid function – including TSH and FT4

- Follicle stimulating hormone
- HbA1C
- PSA

- **Research samples** - refer to table 2b

8.1.3. On-treatment Assessments

(Refer also to section 9.1 and 9.2)

8.1.3.1. C0D2, C0D3, C2D2, C2D3 and C2D4

- **Trial treatment administration and compliance** (C2D2, C2D3 and C2D4)
- **Research samples** (blood and urine) - refer to table 2b

8.1.3.2. C1D1, C2D1 and C3D1 (visit window + / - 1 day)

- **Vital signs -** HR, BP and body temperature
- **Physical examination** (if clinically indicated) – including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Trial treatment administration and compliance**
- **Local laboratory blood test**
  - Full blood count
  - Biochemistry - including LFTs, electrolytes, fasting glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  -
- **Research samples** - refer to table 2b

8.1.3.3. C1D4

- **Concomitant medications**.
- **Adverse events**
- **ECOG status**
- **Trial treatment administration and compliance**
- **Local laboratory blood test**
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - Fasting blood glucose pre-dosing
  - Random blood glucose – **2-4 HOURS POST DOSE**

- **Research samples** - refer to table 2b

8.1.3.4. C1D11 (visit window + / - 1 day)

- **Concomitant medications**.
- **Adverse events**
- **ECOG status**
- **Trial treatment administration and compliance**
- **Local laboratory blood test**
  - Full blood count

- Biochemistry including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
- Thyroid function – including TSH and FT4
- Follicle stimulating hormone
- Fasting blood glucose pre-dosing
- Random blood glucose – **2-4 HOURS POST DOSE**

- **Research samples** - refer to table 2b

8.1.3.5. C2D11 (visit window + / - 1 day)

- **Concomitant medications**.
- **Adverse events**
- **ECOG status**
- **Trial treatment administration and compliance**
- **Local laboratory blood test**
  - Full blood count
  - Biochemistry including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH

- **Research samples** - refer to table 2b

8.1.3.6. C4D1 and D1 of every cycle therafter (visit window + / - 2 days)

- **Vital signs -** HR, BP and body temperature
- **Physical examination** (if clinically indicated) – including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Trial treatment administration and compliance**
- **Local laboratory blood test**
  - Full blood count
  - Biochemistry - including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - HbA1C - 12 weekly from C4D1
  - PSA
- **CT and bone scan -** 12 weekly from C4D1
- **Research samples** - refer to table 2b

8.1.4. Procedure at Disease Progression / treatment discontinuation

At disease progression the treatment discontinuation assessments should be performed (refer also to section 9.1 and 9.2);

- **Vital signs-** HR, BP and body temperature
- **Physical examination** – including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Trial treatment compliance**
- **Local laboratory blood test**

- Full Blood count - including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
- Biochemistry

- **Research samples** - refer to table 2b

8.1.5. Post treatment / safety follow up visit

The post treatment / safety follow-up visit should be performed 30 days (+/-7) after treatment discontinuation for all patients (refer also to section 9.1 and 9.2);

- **Vital signs -** HR, BP and body temperature
- **Physical examination** (if clinically indicated) – including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG Status**
- **Local laboratory blood test**
  - Full Blood count including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Biochemistry
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - HbA1C
  - PSA
  - Serum testosterone

8.2. Randomised Phase II Trial Assessments

8.2.1. Post registration / screening assessments

The following assessments should be conducted after consent/registration and within 28 days of start of trial treatment (C1D1) to confirm eligibility for trial entry (see also section 9.3, 9.4);

- **Demography –** including age, sex and ethnicity
- **Medical history** - including clinically significant diseases within the previous 5 years, smoking history, prostate cancer history, complete cardiovascular history and family history
- **Acquire archival tissue** (or fresh biopsy for patients with no prior tissue diagnosis of prostate cancer)**.** Previous biopsy samples taken prior to RE-AKT consent but processed as per the RE-AKT Laboratory Manual may be used if within the appropriate window.
- **Vital signs -** HR, BP and body temperature
- **Physical examination** – including height and weight
- **Concomitant medications** – including investigational and anti-cancer therapies used within 28 days prior to Day 1 of Cycle 1.
- **ECOG status**
- **ECG**
- **ECHO or MUGA -** if not performed in the 3 months prior to C1D1
- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  -
  - Biochemistry - including LFTs, electrolytes, fasting glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - HbA1C
  - PSA
  - Serum testosterone

- **CT and bone scan**
- **Brief pain inventory (BPI) questionnaire** – to be completed by the patient before any trial-specific procedures are undertaken
- **Research samples** - refer to table 3b

8.2.2. Pre- treatment / Baseline Assessments (C1D1)

Pre-treatment / baseline assessments should be performed before the first dose of study drug on C1D1 (see also section 9.3, 9.4);

- **Vital signs -** HR, BP and body temperature
- **Physical examination** (if clinically indicated) – including weight
- **Concomitant medications** - including investigational and anti-cancer therapies used within 28 days prior to Day 1 of Cycle 1.
- **Baseline Conditions** - on-going signs, symptoms and toxicities
- **ECOG status**
- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  - Biochemistry- including LFTs, electrolytes, fasting glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - PSA
- **BPI questionnaire -** to be completed by the patient before any trial-specific procedures are undertaken
- **Research samples** - refer to table 3b

8.2.3. On-treatment Assessments

(See also section 9.3, 9.4)

8.2.3.1. C1D8 and C1D15 (visit window + / - 1 day)

- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Trial treatment administration and compliance**
- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  - Biochemistry- including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - Random blood glucose – 2-4 HOURS POST DOSE

8.2.3.2. C2D1 (visit window + / - 1 day)

- **Vital signs -** HR, BP and body temperature
- **Physical examination (**if clinically indicated) - including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Trial treatment administration and compliance**

- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  - Biochemistry – including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - PSA

- **BPI questionnaire –** to be completed by the patient before any trial-specific procedures are undertaken
- **Research samples** - refer to table 3b

8.2.3.3. C3D1 (visit window + / -2 days)

- **Vital signs -** HR, BP and body temperature
- **Physical examination (**if clinically indicated) - including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Trial treatment administration and compliance**
- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  - Biochemistry – including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - PSA

- **BPI questionnaire -** to be completed by the patient before any trial-specific procedures are undertaken

8.2.3.4. C4D1 and D1 of every cycle thereafter (visit window + / - 2 days)

- **Vital signs -** HR, BP and body temperature
- **Physical examination** (if clinically indicated) - including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Trial treatment administration and compliance**
- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  - Biochemistry – including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - HbA1C – 12 weekly from C4D1
  - PSA

- **BPI questionnaire -** to be completed by the patient before any trial-specific procedures are undertaken
- **CT and bone scan -** 12 weekly from C4D1
- **Research samples** - refer to table 3b

8.2.4. Procedure at Disease Progression / treatment discontinuation

At disease progression the treatment discontinuation assessments should be performed (see also section 9.3, 9.4);

- **Vital signs -** HR, BP and body temperature
- **Physical examination** - including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Trial treatment compliance**
- **Local laboratory blood test**
    - Full blood count - including PT, PTT and INR coagulation tests
    - Biochemistry – including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
    - PSA
- **Research samples** - refer to table 3b

8.2.5. Post treatment / safety follow up visit

The post treatment / safety follow-up visit should be performed 30 days (+/-7) after treatment discontinuation for all patients (see also section 9.3, 9.4);

- **Vital signs -** HR, BP and body temperature
- **Physical examination** (if clinically indicated) - including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Local laboratory blood test**
    - Full blood count - including PT, PTT and INR coagulation tests
    - Biochemistry – including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
    - Thyroid function – including TSH and FT4
    - Follicle stimulating hormone
    - HbA1C
    - PSA
    - Serum testosterone
- **CT and bone scan –** if more than 8 weeks since last scans
- **BPI questionnaire -** to be completed by the patient before any trial-specific procedures are undertaken.

8.3. Single Stage Phase II Expansion Cohort Trial Assessments (Recent patients)

Recent patients are defined as patients who have progressed on Enzalutamide within 12 weeks prior to Trial Registration.

8.3.1. Post registration / screening Assessments

The following assessments should be conducted after consent/registration and within 28 days of the start of the combination trial treatment (C1D1) to confirm eligibility for trial entry (see also section 9.5 and 9.7);

- **Demography –** including age, sex and ethnicity

- **Medical history** - including clinically significant diseases within the previous 5 years, smoking history, prostate cancer history and complete cardiovascular history and family history.
- **Acquire archival tissue** (and fresh biopsy for patients with no prior tissue diagnosis of prostate cancer). Previous biopsy samples taken prior to RE-AKT consent but processed as per the RE-AKT Laboratory Manual may be used if within the appropriate window.
- **Vital signs -** HR, BP and body temperature
- **Physical examination** - including height and weight
- **Concomitant medications** – including investigational and anti-cancer therapies used within 28 days prior to Day 1 of Cycle 1.
- **ECOG status**
- **ECG**
- **ECHO or MUGA -** if not performed in the 3 months prior to C1D1
- **Local laboratory blood test**
    - Full blood count - including PT, PTT and INR coagulation tests
    - Biochemistry – including LFTs, electrolytes, fasting glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
    - Thyroid function – including TSH and FT4
    - Follicle stimulating hormone
    - HbA1C
    - PSA
    - Serum testosterone
- **CT and bone scan** (if not performed in the last 28 days)
- **Research samples** - refer to table 4c

8.3.2. Pre- treatment / Baseline Assessments (C1D1)

Pre-treatment / baseline assessments should be performed before the first dose of study drug on C1D1 (see also section 9.5 and 9.7);

- **Vital signs -** HR, BP and body temperature
- **Physical examination** (if clinically indicated) – including weight
- **Concomitant medications** - including investigational and anti-cancer therapies used within 28 days prior to Day 1 of Cycle 1.
- **Baseline conditions** - on-going signs, symptoms and toxicities
- **Trial treatment administration**
- **ECOG status**
- **Local laboratory blood test**
    - Full Blood count - including PT, PTT and INR coagulation tests
    - Biochemistry – including LFTs, electrolytes, fasting glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
    - Thyroid function – including TSH and FT4
    - Follicle stimulating hormone
    - PSA
- **Research samples** - refer to table 4c

8.3.3. On-treatment Assessments

(See also section 9.5 and 9.7)

8.3.3.1. C1D2 and C1D3

- **Research samples** - refer to table 4c

8.3.3.2. C1D4 (visit window +/- 1 day)

- **Concomitant medications**

- **Adverse events**
- **ECOG status**
- **Trial treatment administration and compliance**
- **Local laboratory blood test**
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - Fasting blood glucose pre-dosing
  - Random blood glucose – **2-4 HOURS POST DOSE**

- **Research samples -** refer to table 4c

8.3.3.3. C1D11 (visit window +/- 1 day)

- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  - Biochemistry – including LFTs, electrolytes, fasting glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH all pre-dose
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - Random blood glucose – **2-4 HOURS POST DOSE**

- **Research samples** - refer to table 4c

8.3.3.4. C2D1, C3D1(visit window +/- 1 day)

- **Vital signs -** HR, BP and body temperature
- **Physical examination** (if clinically indicated) – including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Trial treatment administration and compliance**
- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  - Biochemistry – including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - PSA

- **Research samples** - refer to table 4c

8.3.3.5. C2D4 (visit window +/- 1 day)

- **Research samples** - refer to table 4c

8.3.3.6. C2D11 (visit window +/- 1 day)

- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  - Biochemistry – including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH

- **Research samples -** refer to table 4c

8.3.3.7. C4D1 and D1 of every cycle thereafter (visit window + / - 2 days)

- **Vital signs -** HR, BP and body temperature
- **Physical examination** (if clinically indicated) – including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Trial treatment administration and compliance**
- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  - Biochemistry – including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - HbA1C – 12 weekly from C4D1
  - PSA

- **CT and bone scan** - 12 weekly from C4D1
- **Research samples** - refer to table 4c

8.3.4. Procedure at Disease Progression / treatment discontinuation

At disease progression the treatment discontinuation assessments should be performed (see also section 9.5 and 9.7);

- **Vital signs -** HR, BP and body temperature
- **Physical examination** (if clinically indicated) – including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Trial treatment compliance**
- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  - Biochemistry – including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - PSA
- **Research samples** - refer to table 4c

8.3.5. Post treatment / safety follow up visit

The post treatment / safety follow-up visit should be performed 30 days (+/-7) after treatment discontinuation for all patients (see also section 9.5and 9.7);

- **Vital signs -** HR, BP and body temperature
- **Physical Examination** (if clinically indicated) – including weight
- **Concomitant medications**
- **Adverse events**
- **ECOG status**
- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests

- Biochemistry – including LFTs, electrolytes, random glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
- PSA
- Serum testosterone
- Thyroid function – including TSH and FT4
- Follicle stimulating hormone
- HbA1C

- **CT and bone scan -** if more than 8 weeks since last scans

8.4. Single Stage Phase II Expansion Cohort Trial Assessments (Elapsed patients)

Elapsed patients are defined as patients who progressed on Enzalutamide outside the 12 week window prior to Trial Registration.

8.4.1. Post registration / Screening Assessments

The following assessments should be conducted after consent/registration and within 28 days of start of sole Enzalutamide treatment to confirm eligibility for trial entry (see also sections 9.6 and 9.7);

- **Demography –** including age, sex and ethnicity
- **Medical history** - including clinically significant diseases within the previous 5 years, smoking history, prostate cancer history and complete cardiovascular history and family history.
- **Acquire archival tissue** (and fresh biopsy for patients with no prior tissue diagnosis of prostate cancer). Previous biopsy samples taken prior to RE-AKT consent but processed as per the RE-AKT Laboratory Manual may be used if within the appropriate window.
- **Vital signs -** HR, BP and body temperature
- **Physical examination** - including height and weight
- **Concomitant medications** – including investigational and anti-cancer therapies used within 28 days prior to the first day of Enzalutamide treatment.
- **ECOG status**
- **ECG**
- **ECHO or MUGA -** if not performed in the 3 months prior to the start of trial treatment
- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  - Biochemistry – including LFTs, electrolytes, fasting glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - HbA1C
  - PSA
  - Serum testosterone
- **CT and bone scan** (if not performed in the last 28 days)
- **Research samples** - refer to table 4c

8.4.2. On-treatment Assessments for sole Enzalutamide run-in

Assessments to be carried out on a weekly basis (See also section 9. 6)

Local laboratory blood test

- PSA

Assessments to be carried out at the end of each Enzalutamide cycle (See also section 9.6)

- **Concomitant medications**

- **Trial treatment administration and compliance**

Assessments to be reported throughout sole Enzalutamide treatment (See also sections 9.6)

- **Serious adverse events**
- **CT and bone scan** (scans carried out as part of standard care)

8.4.3. Procedure at sole treatment discontinuation/Rescreening

When disease progression is confirmed by weekly PSA or soft tissue progression as per RECIST 1.1, the following treatment discontinuation assessments should be performed (see also section 9.6);

- **Vital signs -** HR, BP and body temperature
- **Physical examination** - including height and weight
- **Concomitant medications** – including investigational and anti-cancer therapies used within 28 days prior to the first day of combination treatment.
- **ECOG status**
- **ECG**
- **ECHO or MUGA**
- **Trial treatment compliance**
- **Local laboratory blood test**
  - Full blood count - including PT, PTT and INR coagulation tests
  - Biochemistry – including LFTs, electrolytes, fasting glucose, BUN (or urea), creatinine, uric acid, amylase, total protein and LDH
  - Thyroid function – including TSH and FT4
  - Follicle stimulating hormone
  - HbA1C
  - PSA
  - Serum testosterone
- **CT and bone scan** (if not performed in the last 28 days)

8.4.4. On-treatment Assessments (Elapsed patients starting combination treatment)

(See also section 9.6)

Patients will start C1D1 of combined treatment as detailed in Sections 8.3.2., 8.3.3., 8.3.4. and 8.3.5. Combination treatment should commence within 28 days of the rescreening visit.

8.5. Post treatment follow up – all stages

- **Phase I Safety –run in** – the safety follow up visit is the last study assessment performed
- **Randomised phase II** – patients should be followed up for survival status every 3 months from the safety follow up visit for the first 12 months and then 6 monthly thereafter.
- **Single Stage Phase II Expansion cohort** patients should be followed up for survival status every 3 months from the safety follow up visit for the first 12 months and then 6 monthly thereafter.

Note: there is no requirement to follow-up Elapsed patients who do not receive combination treatment after the treatment discontinuation and 30 day safety follow-up visits.

NB – If a patient withdraws for any reason prior to radiological progression then the patient should be assessed until radiological progression has occurred or a subsequent line of treatment is started.

8.6. Discontinuation from treatment or follow up – all stages

Participants may discontinue from trial treatment at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator. Reasons for discontinuation may include:

- Disease progression
- Unacceptable toxicity
- Co-morbidities

Participants who discontinue treatment should continue to be followed up. If a patient withdraws consent for further follow-up it should be clarified whether they no longer wish to attend trial specific follow up visits or wish to stop contributing further data to the study. A trial deviation form should be completed for any patient who withdraws consent for information to be sent to the ICR-CTSU or for attending trial follow up visits. In the very rare event that a patient requests that their data is removed from the study entirely, the implications of this should be discussed with the patient first to ensure that this is their intent and, if confirmed, ICR-CTSU should be notified in writing. If this request is received after results have been published the course of action will be agreed between the Sponsor and independent Trial Steering Committee/Independent Data Monitoring and Steering Committee.

If a patient withdraws for any reason prior to radiological progression then the patient should be assessed until radiological progression has occurred or a subsequent line of treatment is started.

For patients who refuse or are unable to attend further clinic study visits, telephone contact should be attempted to follow up for adverse events 30 days -/+ 7 days after the last dose of study drug. All serious adverse events will be followed until resolution, until the event has stabilized and/or become chronic, until it has been determined that the event was caused by aetiology other than the study drug, or through 30 days, whichever comes first. Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete study-related assessments and retrieve any outstanding data and study drug. Such efforts should be documented in the source documents.

9. SCHEDULE OF ASSESSMENTS

9.1. Table 2a – Phase I Safety Run in Schedule of Assessments

Procedures & Assessments	Screening Day -28 to Day C0D1	C0D1 (=C1D-7)	C0D2 & C0D3	C1D1 +/-1 day	C1D4 & C1D11 +/-1 day	C2D1 +/- 1day	C2D2, 3,4	C2D11 +/-1 day	C3D1 +/-2 days	C4D1 & D1 each subsequent cycle +/- 2 days	Treatment discontinuation	Safety Follow-up (30 +/-7 days after last dose)
Informed consent	X											
Medical History [1]	X											
Acquire archival tumour tissue [2]	X											
Physical Examination and vital signs [3,4]	X	X		X		X			X	X	X	X
Concomitant medication [5]	X	X		X	X	X		X	X	X	X	X
Adverse events [6]		X		X	X	X		X	X	X	X	X
ECOG status	X	X		X	X	X		X	X	X	X	X
Enzalutamide - od continuously[16]				X	X	X	X	X	X	X		
AZD5363 – bid 4days on 3 days off from C1D1[16]		X		X	X	X	X	X	X	X		
ECG [7]	X											
ECHO / MUGA[13]	X											
FBC [8]	X	X		X	C1D11	X		X	X	X	X	X
Biochemistry [9]	X	X		X	C1D11	X		X	X	X	X	X
Thyroid function tests[15]	X	X		X	X	X			X	X		X
FSH	X	X		X	X	X			X	X		X
HbA1c	X	X								12 weekly		X
Blood glucose	X[10]	X[10]		X[10]	X[10, 14]	X[10]		X	X[10]	X	X	X
PSA	X	X								X		X
Serum testosterone	X											X
CT and bone scan [12]	X									12 weekly		
Research sample collection (table 2b)	X	X	X	X	X	X	X	X	X	X	X	

9.2. Table 2b – Phase I Safety Run in Research Sample Collection Schedule

Time Points	Tissue		Germ line DNA		Blood based biomarkers							Urine biomarker	Hair follicles
	Archival	Fresh	Saliva	Buccal Swab	CTC	Plasma: DNA & RNA analysis	PAXgene miRNA	Serum proteomic profile (ETH Zurich)	PK - AZD5363[18]	PK - Enzalutamide[1 8]	PD - PRP (3x2.7ml CPT each timepoint)	Hormone analyses	
Screening	X	X	X	X	2x10ml	3x10ml	1x2.5ml	1x8.5ml				24 hour	
C0D1 (pre-dose)					2x10ml	3x10ml	1x2.5ml	1x8.5ml	X		X	24 hour	X
C0D1 (post dose)									30min, 1,2,4,8h		2,4,8h		4h
C0D2 (24h post-dose)									X		X		
C0D3 (48h post-dose)									X		X		
C1D1 (5min pre-dose)											X		
C1D4 (4h post-dose)		C1D4 or C1D11									X same as fresh tissue		X same as biopsy
C1D11 (4h post-dose)													
C2D1 (pre-dose)					2x10ml	3x10ml		1x8.5ml	X	X	X	24 hour	X
C2D1 (post-dose)									30min, 1,2,4,8h	30min,1h	2,4,8h		4h
C2D2 & C2D3 (24h & 48h post-dose)									X		X		
C2D4 (pre-dose)									X	X			
C2D4 (post dose)											4h		4h
C2D11 (pre-dose)									X	X			
C2D11 (post-dose)											4h		
C3D1						3x10ml	1x2.5ml						
C4D1 & each subsequent					2x10ml & C7D1	3x10ml 12 weekly	1x2.5ml	1x8.5ml C4D1 only				24 hour C4D1 only	
Treatment discontinuation[17]		Optional			2x10ml	3x10ml	1x2.5ml	1x8.5ml			X	24 hour	X

9.3. Table 3a – Randomised Phase II Schedule of Assessments

Procedures & Assessments	Screening Day -28 to Day -1	C1D1	C1D8 +/- 1day	C1D15 +/- 1day	C2D1 +/- 1day	C3D1 +/- 2days	C4D1 & each subsequent cycle +/- 2 days	Treatment discontinuation	Safety Follow-up 30 +/-7 days after last dose	Follow Up	
										3/12 for 12 months	6/12 from 12 months
Informed consent	X										
Medical History [1]	X										
Archival tissue acquisition [2]	X										
Physical Examination & vital signs[3,4]	X	X			X	X	X	X	X		
Concomitant medication [5]	X	X	X	X	X	X	X	X	X		
Adverse Events [6]		X	X	X	X	X	X	X	X		
ECOG status	X	X	X	X	X	X	X	X	X		
Enzalutamide – od, continuously[16]		X	X	X	X	X	X				
AZD5363 – bid, 4 days on 3 days off[16]		X	X	X	X	X	X				
ECG [7]	X										
ECHO / MUGA[13]	X										
FBC [8]	X	X	X	X	X	X	X	X	X		
Biochemistry [9]	X	X	X	X	X	X	X	X	X		
Thyroid function tests[15]	X	X	X	X	X	X	X		X		
FSH	X	X	X	X	X	X	X		X		
Blood glucose	X[10]	X[10]	X[14]	X[14]	X	X	X	X	X		
HbA1c	X						12 weekly		X		
PSA	X	X			X	X	X	X	X		
Serum testosterone	X								X		
CT and bone scan[12]	X						12 weekly		X (if >8 weeks from last scan)		
BPI questionnaire[19]	X	X			X	X	X		X		
Survival										X	X
Research sample collection (table 3b)	X	X			X		X	X			

9.4. Table 3b - Randomised Phase II Research Sample Collection Schedule

Time Points	Tissue		Germline DNA		Blood based biomarkers				Urine biomarkers
	Archival	Fresh (optional)	Saliva	Buccal Swab	CTC	Plasma: DNA and RNA analysis	PAXgene miRNA	Serum proteomic profile (ETH Zurich)	Hormone analyses
Screening	X	X Optional unless archival not available	X	X	2x 10ml	3x10ml	1x2.5ml	1x8.5ml	24 hour
C1D1 (pre-dose)		X Optional			2x10ml	3x10ml	1x2.5ml	1x8.5ml	24 hour
C2D1					2x10ml	3x10ml	1x2.5ml	1x8.5ml	24 hour
C4D1 & each subsequent					2x10ml C4D1 & C7D1 only	3x10ml 12 weekly	1x2.5ml	1x8.5ml C4D1 only	24 hour C4D1 only
Treatment discontinuation[17]		X Optional			2x10ml	3x10ml	1x2.5ml	1x8.5ml	24 hour

9.5. Table 4a - Single Stage Phase II Expansion Cohort Schedule of Assessments

Recent Patients: Patients progressed on Enzalutamide within 12 weeks prior to Trial Registration

Procedures & Assessments	Screening D-28 to D-1	Enzalutamide and AZD5363										Safety follow up 30 +/-7 days after last dose	Follow up	
		C1D1 +/- 1day	C1D2& D3	C1D4 +/- 1day	C1D11 +/- 1day	C2D1 +/- 1day	C2D4 +/- 1day	C2D11 +/- 1day	C3D1 +/- 1day	C4D1 & each subsequent cycle +/- 2 days	Treatment discontinuation		3/12 for 12 months	6/12 from 12 months
Informed consent	X													
Medical History [1]	X													
Archival tissue aquisition[2]	X													
Physical Examination and vital signs [3,4]	X	X				X			X	X	X	X		
Concomitant medication [5]	X	X		X		X			X	X	X	X		
Adverse Events [6]		X		X		X			X	X	X	X		
ECOG status	X	X		X		X			X	X	X	X		
Enzalutamide – od continuously[16]		X		X		X			X	X				
AZD5363 – bid 4 days on 3 days off[16]		X		X		X			X	X				
ECG [7]	X													
ECHO / MUGA[13]	X													
FBC [8]	X	X			X	X		X	X	X	X	X		
Biochemistry [9]	X	X			X	X		X	X	X	X	X		
Thyroid function tests[15]	X	X		X	X	X			X	X		X		
FSH	X	X		X	X	X			X	X		X		
Blood glucose	X[10]	X[10]		X[10, 14]	X[10, 14]	X		X	X	X	X	X		
HbA1c	X									12 weekly		X		
PSA	X	X				X			X	X	X	X		
Serum testosterone	X											X		
CT and bone scan[12]	X[11]									12 weekly		X (if >8weeks from last scan)		
Survival													X	X
Research sample collection (table 4c)	X	X	X	X	X	X	X	X	X	X	X			

9.6. Table 4b - Single Stage Phase II Expansion Cohort with sole Enzalutamide run-in Schedule of Assessments

Elapsed Patients: Patients progressed on Enzalutamide outside the 12 week window prior to Trial Registration

Procedures & Assessments	Screening D-28 to D-1	Sole Enzalutamide		Enzalutamide and AZD5363										Safety follow up 30 +/-7 days after last dose	Follow up	
		Weekly visits until Treatment discontinuation of sole Enzalutamide Run-In Data collected at the end of each cycle	Treatment discontinuation / Rescreening D-28 to C1D1-1	C1D1 +/- 1day	C1D2&D3	C1D4 +/- 1day	C1D11 +/- 1day	C2D1 +/- 1day	C2D4 +/- 1day	C2D11 +/- 1day	C3D1 +/-2days	C4D1 & each subsequent cycle +/- 2 days	Treatment discontinuation		3/12 for 12 months	6/12 from 12 months
Informed consent	X															
Medical History [1]	X															
Archival tissue aquisition[2]	X															
Physical Examination and vital signs [3,4]	X		X	X				X			X	X	X	X		
Concomitant medication [5]	X	X	X	X		X		X			X	X	X	X		
Adverse Events [6]		SAEs only		X		X		X			X	X	X	X		
ECOG status	X		X	X		X		X			X	X	X	X		
Enzalutamide – od continuously[16]		X at each new cycle	X	X		X		X			X	X				
AZD5363 – bid 4 days on 3 days off[16]				X		X		X			X	X				
ECG [7]	X		X													
ECHO / MUGA[13]	X		X													
FBC [8]	X		X	X			X	X		X	X	X	X	X		
Biochemistry [9]	X		X	X			X	X		X	X	X	X	X		
Thyroid function tests[15]	X		X	X		X	X	X			X	X		X		
FSH	X		X	X		X	X	X			X	X		X		
Blood glucose	X[10]		X[10]	X[10]		X[10,14]	X[10,14]	X		X	X	X	X	X		
HbA1c	X		X									12 weekly		X		
PSA	X	Weekly	X	X				X			X	X	X	X		
Serum testosterone	X		X											X		
CT and bone scan[12]	X[11]	Routine CT scan results collected	X[11]									12 weekly		X (if >8weeks from last scan)		
Survival															X	X
Research sample collection (table 4c)	X			X	X	X	X	X	X	X	X	X	X			

9.7. Table 4c –Single Stage Phase II Expansion Cohort Research Sample Collection Schedule

Time Points	Tissue		Germline DNA		Blood based biomarkers							Urine biomarkers	Hair follicles
	Archival	Fresh	Saliva	Buccal Swab	CTC	Plasma - DNA and RNA analysis	PAXgene - miRNA	Serum proteomic profile (ETH Zurich)	PK AZD5363	PK - Enzalutamide	PD - PRP (3x2.7ml CPT at each timepoint)	Hormone analyses	
Screening	X	X	X	X	2x 10ml	3x10ml	1x2.5ml	1x8.5ml				24 hour	
C1D1 (5min pre-dose)					2x10ml	3x10ml	1x2.5ml	1.8.5ml	X	X	X	24 hour	X
C1D1 (post-dose)									30min, 1,2,4,8h	30min, 1h	2,4,8h		
C1D2 & C1D3 (24h and 48h post-dose)									X		X		
C1D4 (4h post-dose)		C1D4 or C1D11									X (same as fresh tissue)		X (same as biopsy)
C1D11 (4h post-dose)													
C2D1 (pre-dose)					2x10ml	3x10ml		1x8.5ml	X	X	X	24 hour	X
C2D4 (pre-dose)									X	X			
C2D4 (post-dose)											4h		4h
C2D11 (pre-dose)									X	X			
C2D11 (post-dose)											4h		
C3D1						3x10ml	1x2.5ml						
C4D1 & each subsequent					2x10ml & C7D1	3x10ml 12 weekly	1x2.5ml	1x8.5ml C4D1 only				24 hour C4D1 only	
Treatment discontinuation[17]		X Optional			2x10ml	3x10ml	1x2.5ml	1x8.5ml			X	24 hour	

Legend for tables 2a, 2b, 3a, 3b, 4a, 4b and 4c

1	Medical history includes clinically significant diseases within the previous 5 years, smoking history, prostate cancer history, prior cancer therapies and procedures, and complete cardiovascular history (including prior LVEF values, if available) and family history. Demographic data include age, sex and ethnicity.
2	Patients who have never had a tissue diagnosis of prostate cancer must be willing to undergo a fresh biopsy that confirms adenocarcinoma of the prostate as inclusion criteria is histological confirmation of adenocarcinoma of the prostate.
3	Vital signs include measurements of heart rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature
4	Complete physical examination should include height and weight and the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems and measurement of weight. A complete physical examination should be performed at screening and treatment discontinuation and as clinically indicated at the other visits.
5	Concomitant medications include prescription medication, over-the-counter preparations, and herbal/homeopathic remedies and therapies used within 7 days prior to screening visit and investigational and anti-cancer therapies used within 28 days prior to Day 1 of Cycle 1. Concomitant medications and supplements are collected to account for any possible interactions with CYP3A4, CYP2C9 and CYP2C19.
6	Adverse events including baseline conditions, signs, symptoms and toxicities. They should be recorded from baseline (C0D1/C1D1) until 30 days after the last dose of study drug.
7	ECGs to be performed in triplicate i.e. 3 consecutive ECGs taken within 5 minutes
8	FBC includes: Includes RBC count, haemoglobin, haematocrit, WBC count with differential and platelet count, coagulation factors. Coagulation tests should be reported as PT, PTT and INR.
9	Biochemistry includes: serum chemistry includes glucose, BUN (or urea), creatinine, sodium, potassium, magnesium, bicarbonate, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, GGT, amylase, chloride, LDH, phosphate and uric acid. Patients on warfarin must have their INR regularly monitored (minimum 4 weekly).
10	Glucose sample taken after overnight fast of 8 hours
11	If not performed in the last 28 days.
12	Assessments should be according to RECIST 1.1
13	If not performed in the 3 months prior to C1D1 and if clinically indicated.
14	Glucose sample taken 2-4 hours post dose
15	Thyroid function test includes; TSH (thyroid stimulating hormone) and FT4
16	Compliance to study treatment should be assessed
17	If possible, the fresh biopsy should be collected before treatment is stopped.
18	Phase I safety run in - unscheduled PK sampling may be undertaken where clinically indicated.
19	The BPI Questionnaire should be completed by the patient before any trial-specific procedures are undertaken.

10. TRIAL TREATMENT

Enzalutamide and AZD5363 / matching placebo are the Investigational Medicinal Products under study in RE-AKT.

10.1. Drug Manufacturer

AZD5363 (also known as Capivasertib) and matching placebo are manufactured and provided free of charge by AstraZeneca to participating centres.

Enzalutamide (also known as MDV3100, Xtandi) is manufactured and provided free of charge by Astellas to participating centres.

10.2. Drug Dose and Schedule

From C1D1 a treatment cycle is 28 days. In the phase I safety run in patients will commence treatment on C0D1 which is a 7 day cycle.

Patients will be given sufficient supplies for one course (28 days) of treatment plus a small overage. Patients in the phase I safety run in will also be given supplies for the single dose on C0D1.

Patients should be advised to withhold study drug on the morning of their clinic appointments for trial assessments.

10.2.1. Enzalutamide (MDV3100)

Patients will be prescribed 160mg enzalutamide once daily. Enzalutamide dose should be taken as close as possible to the same time each day. Study patients will take four capsules of study drug once daily. If dosing is missed on one day for any reason, double dosing should NOT occur the following day. The capsules should be swallowed whole with water, and can be taken with or without food.

For patients participating in the safety run-in component, enzalutamide will commence on Cycle 1 Day 1 (AZD5363 will commence 7 days prior on Cycle 0 Day 1 – see section 10.2.2).

10.2.2. AZD5363 (Capivasertib) and matching placebo

Phase I safety run-In

At C0D1 patients will receive a single dose of AZD5363 followed by serial PK/PD measurements. The starting dose and schedule of AZD5363 on dose level I will be 320 mg twice daily. The dose and schedule of AZD5363 in this study were selected on the basis of safety data from the single-agent Phase I trial of AZD5363 (NCT01226316). In this study, AZD5363 was generally well tolerated when administered daily at doses of 80 – 640 mg bid in different schedules. Continuous and intermittent (4 days on and 3 days off, and 2 days on and 5 days off) schedules have been explored. The starting dose of AZD5363 in combination with enzalutamide in the Phase I portion will be lower (320 mg twice daily) than the single agent (intermittent (4 days on and 3 days off) MTD of 480mg. Overall, AZD5363 at the chosen starting dose and enzalutamide were generally well-tolerated, and no clinically significant overlapping toxicities are expected.

Patients will be prescribed AZD5363 in accordance with the dose and schedule described in section 3.1.

Randomised phase II and single stage phase II expansion cohort

The randomised phase II and single stage phase II expansion cohort parts of the study will begin at the recommended dose and schedule of AZD5363, as determined in the safety run-in. Following completion of the Phase I safety run-in stage, the recommended dose and schedule for the randomised Phase II and single stage phase II expansion cohort is; Enzalutamide 160mg od and AZD5363 400mg bid 4 days on 3 days off.

10.2.3. Directions for Administration for AZD5363 / matching placebo

AZD5363 or matching placebo will be administered orally, twice daily on an intermittent (4 days on and 3 days off) weekly dosing schedule. Where possible all doses should be taken at approximately the same times each day, in a fasted state (water only) from at least 2 hours prior to the dose to at least 1 hour post dose.

In the safety run-in part patients will be administered a single dose on C0D1 and then commence twice daily dosing thereafter.

10.2.3.1. Missed doses of AZD5363 / matching placebo

In the event that the patient vomits, the following should be adhered to:

- If vomiting occurs within 30 minutes after AZD5363 / matching placebo dosing, or later if the capsule(s) can be identified in the vomit content, the patient can retake new capsule(s), as appropriate.

Should a patient miss a scheduled dose, the patient will be allowed to take the dose up to a maximum of 2 hours after the scheduled dose time. If it is greater than 2 hours after the scheduled dose time the missed dose should not be taken and the patient should take their allotted dose at the next scheduled time. If a patient needs to take the dose earlier for whatever reason, the patient can take the dose up to 2 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the AZD5363 capsule(s) on time.

10.3. Drug Presentation, Packaging and Labelling

Enzalutamide is presented as 40mg white to off white capsules. The capsules are provided in high-density polyethylene bottles, with an induction seal and a child-resistant closure.

Following a change to commercial formulation for AZD5363 during the course of the trial, and subsequent run-down period of previous stock, two different formulations may be dispensed to patients in the trial, as described below.

The phase II trial stock AZD5363 and matching placebo are presented as plain, round, biconvex, beige, film-coated tablets containing 80mg and 200mg of AZD5363 / matching placebo.

The new formulation (commercial formulation) AZD5363 and matching placebo are presented as plain beige film-coated caplet shaped tablets containing 200mg of AZD5363 / matching placebo and plain, round, biconvex, beige, film-coated tablets containing 160mg of AZD5363 / matching placebo.

The tablets are packed in white, high-density polyethylene bottles, with an induction seal and a child-resistant closure.

The packaging and tablets will appear identical for both active and matching placebo treatments. To ensure that the patient and research team remain blind to the treatment allocation during the randomised phase II double blind component of the study, the drug label will be identifiable by means of a kit number that is linked to the randomisation system.

AstraZeneca has employed Fisher Clinical Services to coordinate IMP packaging, labelling and distribution for this trial.

Labelling will be the responsibility of Fisher Clinical Services and will be compliant with Annex 13 of the Good Manufacturing Guidelines (GMP) and all applicable local regulatory requirements.

10.4. Drug Storage

AZD5363 / matching placebo and enzalutamide should be stored in the original packaging in a secure location, with limited access as per the storage conditions on the drug label.

Patients will be instructed to store study drugs as per the storage conditions on the drug label and out of the reach of children.

Participating centres will be responsible for reporting any temperature excursions from the storage conditions to ICR-CTSU for approval from the manufacturer. The local pharmacy is responsible for ensuring that the study medication is stored appropriately and in a secured area.

10.5. Distribution of drugs to site

Drug will only be distributed to participating centres once ICR-CTSU is satisfied that the required approvals and agreements and initiation procedures are complete.

In the phase I safety run-in and single stage phase II expansion phases, medication will be provided as open label supplies. Participating pharmacy departments should contact the ICR-CTSU trial management team to request drug supplies. Contact details will be provided in trial specific guidance documents. Once a supply request is received, delivery will take up to 5 working days.

For the randomised phase II component of the study, distribution of blinded drug supplies will be coordinated via an Interactive Web Response System (IWRS) provided by Cenduit, a commercial organisation who have been contracted on behalf of AstraZeneca/Fisher Clinical Services to provide this service.

10.6. Kit number allocation (randomised phase II only)

At trial entry the site staff will be provided the Trial ID for the patient by ICR-CTSU. Site staff will be provided access to the Cenduit IWRS. The site staff will enter the Trial ID and patient's date of birth into the system which will generate the details of the allocated drug pack numbers to be dispensed for the patient. An email will be sent to the Site Pharmacist and ICR-CTSU personnel confirming the allocation.

Site staff will be able to access the Cenduit IWRS via a secure website, using individual access codes. Full telephone support is available via a toll free telephone number. Study specific guides and PIN details will be sent to each site after site activation.

The toll free access line for Cenduit helpdesk is 00 800 1012 1960.

The Cenduit IWRS will track trial drug supply at each site and will automatically order drug/placebo to maintain adequate stock based on consumption of the trial supplies at the site.

10.7. Pharmacy Responsibilities and Drug Accountability

The study drugs must not be used outside the context of the RE-AKT protocol.

For the open label components (phase I safety run-in and single stage phase II expansion cohorts) the local pharmacy department must ensure there is sufficient supply of study drug for the patients' continued treatment and in a timely manner, contact the ICR-CTSU for re-supply of stock. Additionally they should ensure that study drug expiry dates are monitored and used in order of expiry date i.e. earliest expiry first.

In the blinded component (randomised phase II) the IWRS controls the supply and stock and expiry dates.

Records must be kept of all deliveries, dispensing and destruction in accordance with the RE-AKT Pharmacy Guidance Notes. These records may be requested by ICR-CTSU during the trial to monitor supply and usage of stock. Account must be given of any discrepancies and certificates of delivery and return must be signed.

10.8. Drug Complicance

Patients must be asked to bring all their trial medication every time they attend the clinic for the purposes of treatment compliance assessment and drug accountability. Every effort should be made to encourage patients to return the unused medication and empty bottles. The unused tablets should be collected by the Investigator/study nurse and counted to ascertain patient compliance.

10.9. Emergency Code Breaking

Treatment is blinded during the phase II randomised double blind part of the study. During this time, in the absence of disease progression, unblinding is restricted to emergency situations and should only be used under circumstances where knowledge of the treatment is necessary for the proper clinical care of the patient. Un-blinding will be controlled via the IWRS. In addition to the trial statistician(s), delegated individuals at each centre will have

access to the unblinding form in the IWRS and information on how to perform the unblinding will be provided in the RE-AKT trial guidance notes. Details divulged to the clinician must only be in regard to specific treatment for the patient for whom the code is broken. If no-one is available to perform the unblinding the patient should be treated as if they are on active drug.

10.10. Patient cards

Small wallet sized cards will be produced by ICR-CTSU on request by the participating centre. Each card will state:

- the name of the participating centre
- that the patient is participating in the RE-AKT trial and the part of that trial
- that the patient is taking AZD5363/placebo and / or enzalutamide.
- An emergency contact number

10.11. Duration of Trial Treatment

Treatment should continue until confirmed disease progression, death or withdrawal from treatment (i.e. due to unacceptable toxicity). See section 3.4 and 8.5 for further details on treatment discontinuation.

11. TOXICITY MANAGEMENT

Common toxicities are listed in the respective investigator brochures. Toxicities should be treated with maximum supportive care. For definition of DLTs in the phase1 safety run in please refer to section 3.1.2.

Patients who experience Grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have both enzalutamide and AZD5363 / placebo interrupted until the toxicity improves to Grade 1 or lower severity. Patients may subsequently be re-started on study drug. Treatment with enzalutamide is generally well tolerated and dose reductions are very rarely necessary. One level of dose reduction of enzalutamide will be allowed. For specific AZD5363 toxicities and their management please refer to the sections below.

11.1. ENZALUTAMIDE DOSE REDUCTION / DOSE ADJUSTMENT

Patients who experience Grade 3 or greater toxicity that is related to enzalutamide in the opinion of the investigator and that cannot be ameliorated by the use of adequate medical intervention should have their enzalutamide treatment interrupted until the toxicity improves to Grade 1 or lower severity. Patients may subsequently be re-started on study drug, including at a reduced dose of 120mg (3 capsules) of enzalutamide. No further dose reductions for enzalutamide will be allowed on this trial.

Table 5 – Enzalutamide dose reductions

Standard dose of Enzalutamide	All dose levels	160mg OD
Dose reduction in case of toxicity attributed to enzalutamide	Dose level -1 for enzalutamide	120mg OD

11.1.1. Seizures

Enzalutamide has been associated with a small risk of seizures and hallucinations. Patients with pre-disposing factors such as brain metastases, leptomeningeal spread of the cancer, a history of stroke or epilepsy will be excluded from this trial. Patients who experience a seizure, or unexplained loss of consciousness of any grade on trial while receiving treatment with enzalutamide will discontinue trial treatment (enzalutamide and AZD5363).

11.1.2. Posterior reversible encephalopathy syndrome

There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving enzalutamide. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of enzalutamide in patients who develop PRES is recommended.

11.1.3. Drug interaction risks

Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products (please refer to SmPC). A review of concomitant medicinal products should therefore be conducted when initiating enzalutamide treatment. Concomitant use of enzalutamide with medicinal products that are sensitive substrates of many metabolising enzymes or transporters should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.
Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If enzalutamide is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted.

11.2. COMBINATION TREATMENT / AZD5363 & / OR MATCHING PLACEBO

11.2.1. General toxicity management

If a patient experiences a clinically significant and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted or the dose reduced and supportive therapy administered as required (see Figure 5). If the toxicity resolves or reverts to ≤ CTCAE grade 2 within 8 days of onset and the patient is showing clinical benefit, treatment with AZD5363 may be restarted without using the rules below for dose modifications (see figure 5). If the patient is still showing clinical benefit, but toxicity takes between 8 and 14 days to resolve or revert to ≤ CTCAE grade 2, treatment with AZD5363 may be restarted using the rules below for dose modifications only following agreement with the local Principal Investigator, Chief Investigator (or Chief Investigators delegate) (see figure 5). Patients who are at the lowest possible dose i.e., in Cohort 1 or who have their dose previously reduced to the Cohort 1 dose and who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the Investigator.

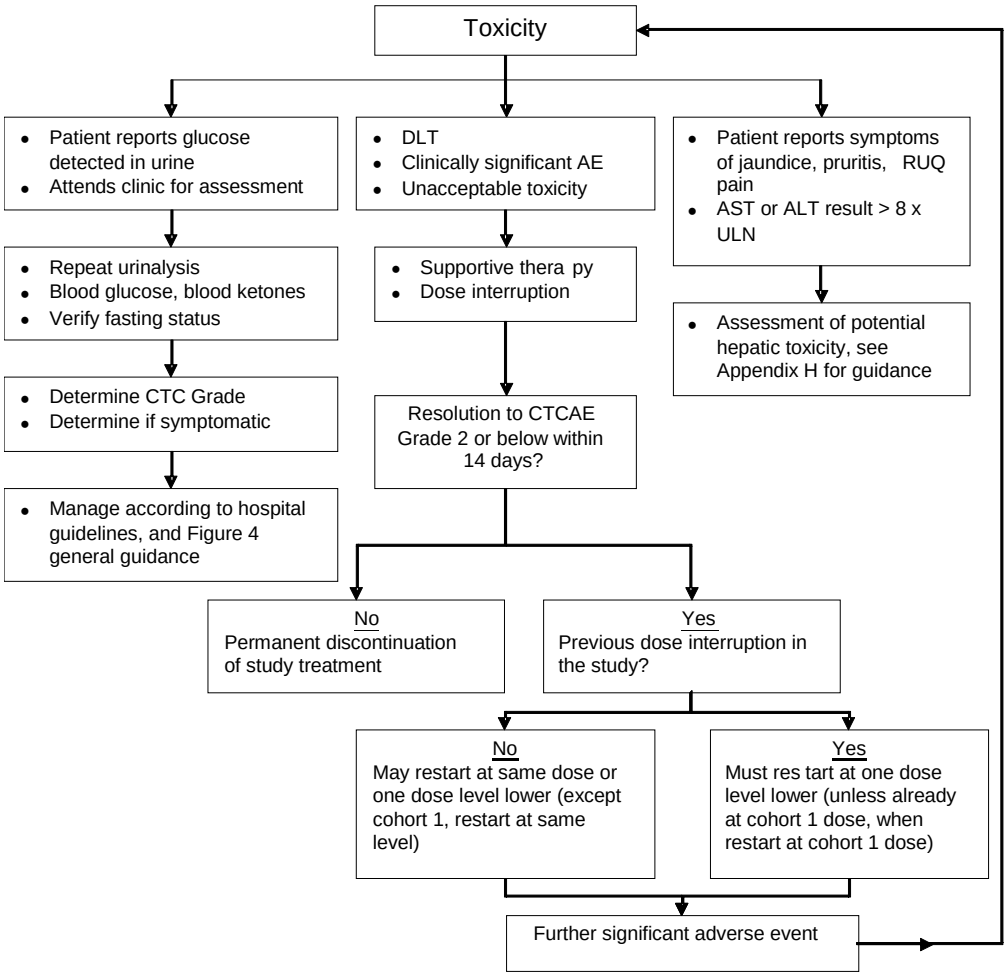
For all other events, if the toxicity does not resolve to ≤ CTCAE grade 2 after 14 days, then the patient should be discontinued from AZD5363 treatment and observed until resolution of the toxicity. Patients who permanently discontinue AZD5363 will be allowed to continue treatment with Enzalutamide.

Specific management of the hyperglycaemia will be according to local practice; however, the principles in the blood glucose intervention plan (see appendix E) should be followed. General advice based upon previous clinical experience with related agents suggests that Initial medical intervention should be an oral-antidiabetic agent e.g. metformin per local prescribing information, on days when AZD5363 is given, unless otherwise clinically indicated.

Following discharge from the clinic, any patients experiencing symptoms consistent with acute liver dysfunction such as unexplained pruritus, jaundice or right upper quadrant pain will be advised to temporarily stop study treatment and promptly contact the clinic for clinical assessment and liver biochemistry testing. Investigation and management of these patients and any patients with AST or ALT results > 8 x ULN identified at any time during the study will be according to local practice, however, the principles of the hepatotoxicity management algorithm (see appendix H) and the FDA Draft Guidance for evaluation of Drug-Induced Liver Injury (REF needed) should be followed. If a patient exhibits an AST, ALT result

in excess of 10 x ULN, or AST or ALT in excess of 8 x ULN in combination with a doubling of bilirubin from baseline, which is considered to be related to study drug, they will not be permitted to restart study treatment. If a patient experiences a maculo-papular rash, guidance provided in Appendix F and G should be followed.

Figure 5 – General Toxicity Management



11.2.2. Dose reductions for AZD5363 and /or matching placebo (all stages)

The dose reductions indicated in this table may change according to emerging safety data.

Table 6 – AZD5363 / matching placebo dose reductions

Following completion of the Phase I safety run-in stage, **Dose level 1A** was confirmed as the recommended dose and schedule for the Phase II stages of the study. The schedule below is applicable to patients receiving the phase II trial stock with tablet strengths of 200mg and 80 mg.

Dose level	AZD5363 – commence Cycle 0 Day 1	First reduction to next lower dose level	Second reduction of AZD5363 to next dose level
-2	160mg bid 4 days on 3 off	80mg bid 4 days on 3 off	NA
-1	240mg bid 4d on 3d off	160mg bid 4 days on 3 off	80mg bid 4 days on 3 off

1	320mg bid 4d on 3d off	240mg bid 4 days on 3 off	160mg bid 4 days on 3 off
1A (optional)	400mg bid 4d on 3d off	320mg bid 4 days on 3 off	240mg bid 4 days on 3 off
2	480mg bid 4d on 3d off	400mg bid 4 days on 3 off	320mg bid 4 days on 3 off
2A (optional)	560mg bid 4d on 3d off	480mg bid 4 days on 3 off	400mg bid 4 days on 3 off
3	640mg bid 4d on 3d off	560mg bid 4 days on 3 off	480mg bid 4 days on 3 off

For patients receiving the new commercial formulation of AZD5363, with tablet strengths of 200mg and 160 mg, the second dose reduction is to 200mg AZD5363 bid 4 days on 3 days off as indicated in the table below.

AZD5363 – Starting dose	First reduction to next lower dose level	Second reduction of AZD5363 to next dose level
400mg bid 4d on 3d off	320mg bid 4 days on 3 off	200mg bid 4 days on 3 off

11.2.3. Hyperglyceamia

Increases in blood glucose and concurrent elevated insulin levels have been noted in pre-clinical and clinical studies 2-4 hours following oral administration of AZD5363. In general, within 4-6 hours after AZD5363 dosing, these values returned to normal levels. The mechanism for hyperglycaemia due to AKT inhibition is not yet clear, but it may be due to interference with insulin signalling in addition to peripheral insulin resistance. The glucose management algorithm (Appendix E) should, where possible, be followed to minimise metabolic risks, allow patients to continue receiving the same dose of AZD5363 therapy where possible, and avoid compliance issues.

11.2.4. Diarrhoea

Diarrhoea has been observed in patients treated with AZD5363. Its effects can be minimised by prompt treatment as symptoms arise. Diarrhoea is also associated with enzalutamide however dose reductions of enzalutamide because of diarrhoea have very rarely been necessary. For guidance on how to manage diarrhoea please see table 7.

Table 7 - Management guidelines for diarrhoea:

Grade of Diarrhoea	AZD5363	Enzalutamide
G1- Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Continue	Continue
	Treat with Loperamide - Take 4mg after the first loose stool then 2mg after each loose stool. Maximum 16mg in 24 hours	
G2 - Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output	Continue	Continue
	Treat with Loperamide - Take 4mg after the first loose stool then 2mg after each loose stool. Maximum 16mg in	

compared to baseline	24 hours	
G3 - Increase of >=7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Discontinue AZD5363, treat symptomatically Re-start once diarrhoea has resolved to ≤G1. Follow AZD5363 general toxicity management (figure 5) at a reduced dose once diarrhoea has resolved to ≤G1	Discontinue Enzalutamide Re-start once diarrhoea has resolved to ≤G1
G4 - Life-threatening consequences; urgent intervention indicated	Discontinue permanently from trial treatment	Discontinue permanently from trial treatment

11.2.5. Skin reactions

Dermatological effects have been observed in patients treated with AZD5363. A maculo-papular rash is the most frequently observed condition, with incidence of pruritus. AZD5363 is also in a class of compounds with a known potential for phototoxicity. To minimise the risk of skin sensitivity or reaction severity, and to help ensure a consistent treatment approach, it is recommended that the guidance on Appendix F be followed.

11.2.5.1. Maculo-papular rash

A maculo-papular rash may occur at any time, but it most commonly starts within one week of commencing AZD5363 study treatment. It affects patients to varying degrees and frequently improves over time with the appropriate treatment. For guidance of how to manage rash and pruritus please follow the recommendations in Appendix F.

11.2.5.2. General dermatological guidance

During the study, patients should use sunglasses and sunscreen (SPF ≥30), reapplied as necessary on areas of skin directly exposed to sunlight. Investigators may consider issuing patients with a prescription for topical treatments, used at their discretion. However, topical or oral steroids should not be implemented prophylactically and treatment should only be started once confirmed with the investigator. Patients must notify the study site if a skin rash develops, and they should obtain study site approval before using any prescribed topical treatments. They should also be instructed to contact the site if the rash changes (e.g. if it spreads or becomes painful). It may be beneficial to warn patients to avoid skin products that may cause irritation (e.g. perfumed soaps, products containing retinol, retinoic comedogenic or non-pore blocking) during study treatment.

11.2.5.3. Hypersensitivity

In the case of hypersensitivity reactions, AZD5363 should be discontinued and symptomatic / supportive therapy should be initiated (including with antihistamines and/or steroids) as considered appropriate by the investigator/treating physician. Any subsequent decision on rechallenge with AZD5363 at the same or a lower dose, with its potential for recurrence of such or more severe AEs should be carefully considered against the potential benefits to the individual patient from continuation of AZD5363 treatment. Further management should follow local guidelines on management of hypersensitivity reactions.

11.2.5.4. Stomatitis, dry skin, and pruritus

Patient reports of stomatitis, dry skin, and pruritus are to be evaluated and treated by investigators according to local practice. The need for an interruption in dosing with AZD5363 should be considered according to the Appendix G.

11.2.6. Hepatotoxicity

Investigators should remain especially vigilant for changes in liver biochemistry for early identification of potential drug-induced liver injury. The protocol details reporting requirements associated with elevated levels of liver enzymes with respect to Hy's law (Appendix H). The management algorithm presented here provides guidance on management of patient reported symptoms of potential acute liver dysfunction and of liver transaminase results in excess of 8x upper limit of normal occurring at any time during the study.

12. CONCURRENT MEDICATIONS

All concomitant medications (including start/stop dates, dose frequency, route of administration and indication) must be recorded in the patient's source documentation.

12.1. Non-permissible concurrent medications/therapies to be avoided

Non-permissible concurrent medications/therapies include:

- Supplements or complementary medications (conventional multivitamin supplements are allowed);
- Other approved or investigational systemic anticancer treatments, including chemotherapy, hormone therapy and immunotherapy;
- Other investigational drugs.

12.1.1. Enzalutamide

In vitro drug metabolism studies suggest that enzalutamide induces CYP3A4 and may inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 CYP2D6, and CYP3A4/5; therefore, concomitant medications that are substrates of any of these enzymes should be used with caution, and relevant monitoring should be considered, especially for substrates known to cause seizure, and for substrates with a narrow therapeutic index because the possibility of drug-drug interactions cannot be fully excluded. Appendix B provides a list of potent CYP enzyme inhibitors and inducers that may have a theoretical concern of potential drug-drug interactions with MDV3100. Patients on warfarin must have their INR regularly monitored while on this trial (minimum 4 weekly).

To determine if a particular drug is a potent CYP inhibitor or inducer, Investigators should consult Appendix B and refer to the current Investigators Brochure.

12.1.2. AZD5363

AZD5363 is metabolised *in vitro* by CYP2D6, CYP3A4, CYP3A5, CYP2C9, CYP1A1, CYP2C19 and CYP2B6, based on relative expression levels CYP3A4 is likely to play the main role in oxidative metabolism. *In vitro* incubation data suggest that glucuronidation, via UGT1A9 and UGT2B7 isoforms, is likely to be the major metabolic route. The contribution of metabolism to the overall clearance of AZD5363 is currently unknown, however, drugs that inhibit or induce CYP3A4 and CYPD2D6 substrates are currently restricted in clinical studies with AZD5363 (Please see appendix B for list of drugs). The effect of cytochrome P450 induction by enzalutamide will be explored as part of this study.

The potential for AZD5363 to inhibit cytochrome P450 (CYP) isoforms has been explored *in vitro* by microsomal incubation. AZD5363 demonstrated a reversible inhibition of CYP2D6 inhibition (IC_{50} 5.3 µmol/L), compared to the free exposure of AZD5363 being explored in clinical studies, drug interactions through this mechanism are considered possible. Minor evidence of reversible inhibition of CYP2C9, CYP2B6 and CYP2C19 was also demonstrated *in vitro*, but considered unlikely to translate to a clinically significant inhibition. *In vitro* microsomal and hepatocyte incubations with AZD5363 have demonstrated that it is a time dependent inhibitor of CYP3A4, with time dependent kinetic parameters, K_I and K_{Inact}, for hepatocyte incubations of 0.027 /min and 24 µmol/L, respectively. Based on the exposure of AZD5363 explored in clinical studies, drug interactions through this mechanism are

considered possible. Current restrictions to the co-administration of drugs that are metabolised by CYP3A and CYP2D6 in clinical studies with AZD5363 mitigate these drug interaction liabilities.

AZD5363 is an *in vitro* inhibitor of the renal transporter OCT-2 with an IC_{50} of 1.3 µmol/L which is responsible for the active secretion in to urine of endogenous components such as creatinine and drugs such as metformin. Although there is a potential for interaction between AZD5363 and metformin, metformin is recommended for the management of AZD5363 treatment-related hyperglycaemia and co-administration is permitted as described in Appendix E of this protocol.

Additionally concomitant medications known to prolong the QT are not permitted in RE-AKT.

12.1.3. Corticosteroids

It is strongly recommended that patients considered for this trial be taken off any chronic low-dose steroid treatments before entering the trial. Refer to section 4.4 for details of wash out period.

In case of emergency (e.g. spinal cord compression, G3 skin rash) short courses of high-dose steroids are allowed (<21 days). Careful home glucose monitoring is mandated in this situation due to hyperglycaemia associated with AZD5363 treatment.

Low dose of steroids is allowed (maximum prednisolone 10 mg per day or dexamethasone 0.5mg per day) prior to the study treatment. If chronic corticosteroid therapy is stopped, study treatment can only be started if PSA is not declining within the 2 weeks prior to study treatment initiation.

12.2. Permissible concurrent medications/therapies include:

- Luteinizing hormone-releasing hormone (LHRH) analogue to maintain a testosterone level <50g/dL should be administered in patients who have not undergone an orchiectomy.
- Conventional multi-vitamins and minerals.
- Initiating bisphosphonate or denosumab therapy or adjusting bisphosphonate dose/regimen within 30 days prior to Cycle 1 Day 1 is prohibited. Patients on a stable bisphosphonate regimen are eligible and may continue.
- Blood transfusions and growth factor support as per standard of care and institutional guidelines
- Anticoagulant Therapy: It is recommended that patients who are taking warfarin should preferably be switched to an equivalent dose of LMWH. Subcutaneous heparin is permitted and is preferable given the potential for myelosuppression.
- Palliative radiotherapy: may be used for treatment of pain at the site of bony metastases that were present at baseline, providing the Investigator does not feel that this is an indication for the patient to discontinue treatment due to disease progression.
- Concurrent radionuclide treatment is not permitted.
- Prophylactic antiemetics as required.

13. PHARMACOVIGILANCE

13.1. Definitions

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered an investigational medicinal product; the event does not necessarily have a causal relationship with the treatment or usage.

Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that occurs after the commencement of study treatment and within 30 days of the last administration and:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious. The event does not necessarily have a causal relationship with the treatment or usage

Progression of the indicated disease and death due to progression of the indicated disease are not considered SAEs.

Pregnancy or aid in the conception of a child whilst participating in a trial is not itself considered an SAE but should be followed up for congenital anomalies or birth defects.

Serious Adverse Reaction (SAR)

A serious adverse reaction is an SAE that is suspected as having a causal relationship to the investigational medicinal product, as assessed by the investigator responsible for the care of the patient. A suspected causal relationship is defined as possibly, probably or definitely related (see definitions of causality table).

Table 8 - Definitions for causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other

	concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the safety information provided in the applicable Investigator's Brochure (IB) and is assessed as unexpected by the Chief Investigator.

13.2. Reporting Adverse Events to ICR-CTSU

Any toxicity, sign or symptom that occurs after commencement of study treatment and within 30 days of the last administration of study treatment, which is not unequivocally due to progression of disease, should be considered an AE.

All AEs must be reported on the relevant CRF and submitted to ICR-CTSU.

The severity of AEs should be graded according to the NCIC-CTC criteria version 4. For each toxicity/sign/symptom, the highest grade observed since the last visit should be reported.

Whenever one or more toxicity/sign/symptom corresponds to a disease or a well-defined syndrome only the main disease/syndrome should be reported.

13.3. Reporting of Serious Adverse Events to ICR-CTSU

Any SAE that occurs after the commencement of study treatment and up to 30 days following the last dose of study drug must be reported.

All SAEs should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or designated representative) becoming aware of the event, by completing the RE-AKT SAE form and faxing to:

The ICR-CTSU safety desk

Fax no: **0208 722 4368**

For the attention of the RE-AKT Trial team

As much information as possible, including the Principal Investigator's assessment of causality, must be reported to ICR-CTSU in the first instance. Additional follow up information should be reported as soon as it is available.

All SAE forms must be completed, signed and dated by the Principal Investigator or designated representative.

All reported SAEs and follow up information will be forwarded to AstraZeneca and Astellas upon receipt at ICR-CTSU.

13.4. Review of Serious Adverse Events

The Chief Investigator (or designated representative) will assess all reported SAEs for causality and expectedness (NB. The Chief Investigator cannot down-grade the Principal Investigator's assessment of causality.)

SAEs assessed as having a causal relationship to study drug and as being unexpected (SUSARs) will undergo expedited reporting to the relevant authorities by ICR-CTSU (see Figure 6 for SAE reporting).

Sites should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of an SAE.

13.5. Expedited Reporting of SUSARs

If an SAE is identified as being a SUSAR by the Chief Investigator, and is fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the main REC, the Co-sponsor(s) and AstraZeneca and Astellas within 7 days of being notified of the event.

If an SAE is identified as a SUSAR by the Chief Investigator, and is not fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the main REC, the Co-sponsor(s) and AstraZeneca and Astellas within 15 days of ICR-CTSU being notified of the event.

ICR-CTSU will report any additional relevant information to the MHRA, main REC, Co-sponsor(s) and AstraZeneca and Astellas as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR.

The Principal Investigators at all actively recruiting sites will be informed of any SUSARs occurring within the trial at regular intervals.

13.6. Follow up of Serious Adverse Events

SAEs should be followed up until clinical recovery is complete or until disease has stabilised. SAE outcomes should be reported to ICR-CTSU using the relevant section of the SAE form as soon as the Principal Investigator becomes aware of the outcome.

NB. Any female partner of any male patient who fathers a child whilst on study medication, must be followed up and the outcome reported to ICR-CTSU who will then forward the details to AstraZeneca and Astellas.

13.7. Annual Reporting of Serious Adverse Reactions

An annual report will be provided to the MHRA and the main REC by ICR-CTSU and copied to the Co-sponsor(s) at the end of the reporting year.

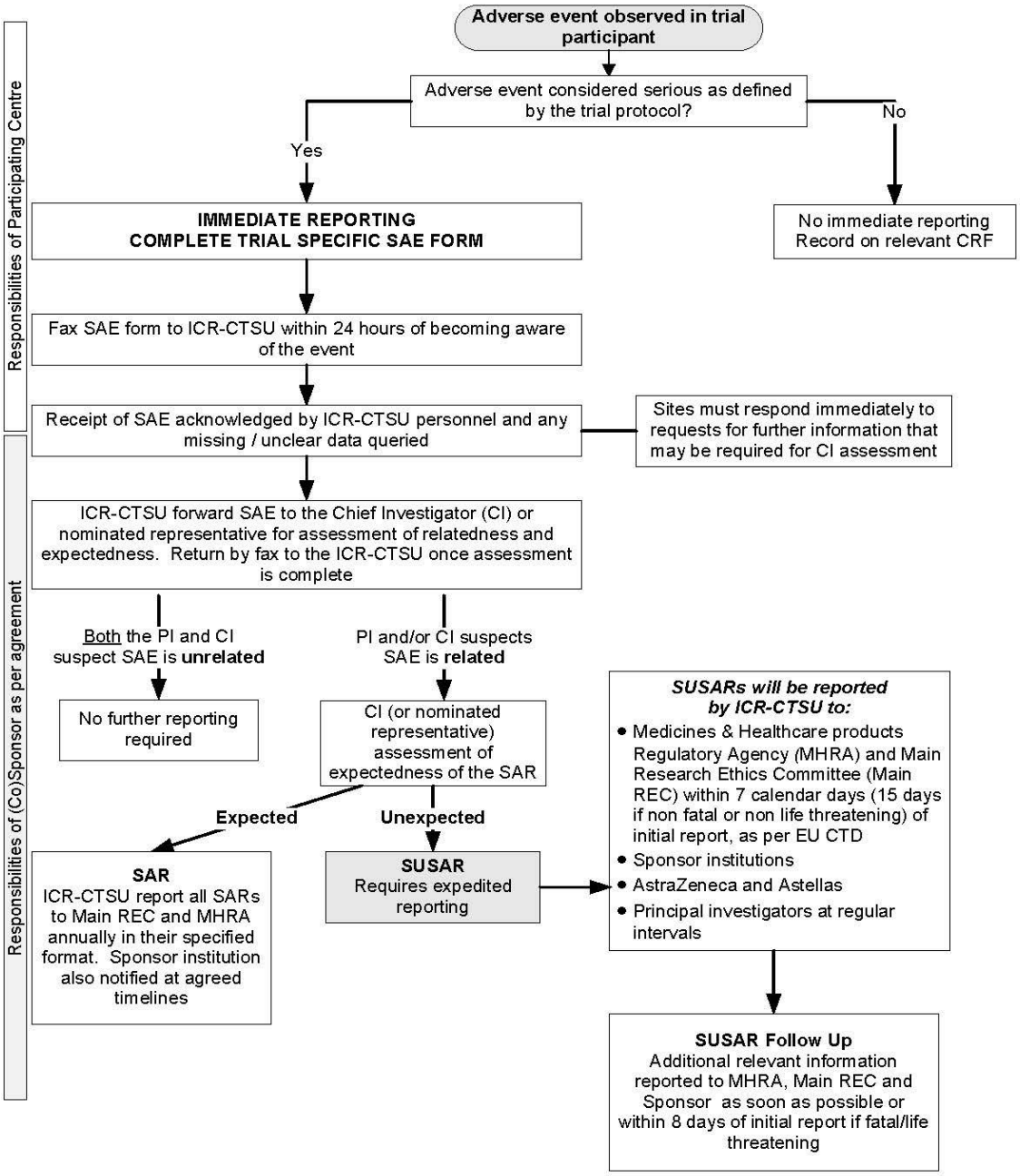
13.8. Reporting Pregnancies

If a trial participants' partner becomes pregnant while receiving study drug or up to 12 months days after receiving study drug, this should be reported to ICR-CTSU using the pregnancy reporting form. Pregnancies should be followed up until conclusion and all follow-up information should be reported to ICR-CTSU. If the outcome of the pregnancy meets the definition of serious (i.e. congenital abnormality) this should be reported to ICR-CTSU following the serious adverse event reporting procedures described above.

13.9. Unblinding of SUSARs

Unblinding of SUSARs for regulatory reporting purposes will be done centrally at ICR-CTSU by the trial statistician to ensure that individual clinicians and staff directly involved in the conduct of the trial remain blinded to study treatment.

Figure 6 - Flow diagram for SAE reporting, and action following report



NB. All SAEs should continue to be followed up as specified in the protocol

14. PHARMACOKINETICS, PHARMACODYNAMICS AND TRANSLATIONAL RESEARCH

Collection, processing, handling and shipment of all biological samples are detailed in the RE-AKT Laboratory Manual.

14.1. Pharmacokinetics (PK)

Samples for PK characterization of AZD5363 and enzalutamide will be collected as outlined in Tables 2b and 4c during the phase I safety run-in and single stage phase II expansion parts of the study. PK samples will not be collected in the randomised phase II part of the study.

Note: During the Phase I safety run in stage of the trial, unscheduled PK sampling may be undertaken where clinically indicated.

14.2. Pharmacodynamics (PD)

14.2.1. Platelet rich plasma (PRP)

PRP samples will be taken during the phase I safety run-in and single stage phase II expansion cohort (as outlined in Tables 2b and 4c). Analyses of markers of the PI3K/AKT pathway will be performed including pGSK3beta and pPRAS40. These assays have already been developed, validated and implemented on multiple Phase I clinical trials of PI3K/AKT inhibitors at the RM.

Further studies to assess AKT inhibition will include measurements of FKBP5 levels and PHLPP function.

14.2.2. Hair follicles (PD)

Hair (eyebrow) determination of concentrations of exploratory biomarkers will be taken for the phase I safety run-in and the single stage phase II expansion cohort (as outlined in tables 2b and 4c). A minimum of five hair follicles will also be collected at each time point. Hair follicles should preferably be collected from the eyebrow, however scalp is acceptable.

14.3. Tumour Tissue

14.3.1. Archival tumour tissue

For all parts of RE-AKT an adequately sized (minimum of 2 mm x 2 mm) archival tumour tissue paraffin block from resection or a core biopsy from the time of the original diagnosis or from a biopsy / resection of metastatic disease at any time prior to study entry is required. Alternatively, unstained slides prepared from the block can be provided.

14.3.2. Fresh tumour biopsies

Fresh tumour biopsies will be mandatory in the phase I safety run-in and the single stage phase II expansion cohort and will be collected at baseline and at C1D4 or C1D11. Fresh tumour biopsies will be collected from either bone or soft tissue disease. The most appropriate method of collection will be used including ultrasound- and CT-guided approaches. An optional tumour biopsy may be collected at the end of treatment (treatment

discontinuation visit of safety follow up visit). The precise timing of the second biopsy may vary contingent on the results of the PK/PD analyses. Fresh tumour biopsies will be used for molecular characterisation (including but not exclusively ERG, PTEN, INPP4B, PHLLP2, AR status) and for PD analyses.

The fresh tumour biopsy may be obtained from either the prostate or a metastatic site that is safe and amenable to a biopsy. Tumour biopsies may be obtained from the prostate itself (if it has not been surgically resected and has not been treated with radiotherapy) via an ultrasound-guided transrectal biopsy. Local recommendations for the procedure will be followed. Alternative sites where a biopsy can be obtained include lymph nodes, bone or liver where there is evidence of cancer on imaging. Patients who do not have evidence of visceral disease but do have evidence of bone metastasis on the bone scan may undergo a standard bone marrow biopsy. Ideally, the pre- and post-treatment biopsies will be from the same site.

14.4. Rationale for the Translational Research

14.4.1. Archival Tissue for Examining PTEN as a Potential Diagnostic Marker

In vitro and *in vivo* prostate cancer models harbouring PTEN deletions or mutations in PIK3CA are generally exquisitely sensitive to PI3K / AKT inhibition [31], suggesting a potentially useful positive predictive value for PIK3CA and / or PTEN status with respect to these agents. Because PTEN loss can happen by more than one mechanism (e.g. gene deletions, miRNA, methylation, and mutation) and prostate cancer can exhibit varying degrees of PTEN loss (e.g. homozygous vs. hemizygous deletion), PTEN status will be determined both at the gene level by FISH and at the protein level by IHC. In addition to testing for PTEN status, patient tumour tissue will be used to evaluate other exploratory biomarkers including PTEN-independent mechanisms for activation of the PI3K / AKT pathway (i.e. PIK3CA mutations, INPP4B by IHC and PhLPP loss). Taken together, these data support the collection of archival tissue (and / or fresh biopsy if archival tissue is not available) from patients to evaluate the activity of AZD5363 in combination with enzalutamide

14.4.2. Circulating Tumour Cells (CTCs): Enumeration and molecular analyses

The use of CTCs as a potential surrogate biomarker of treatment efficacy has been examined in CRPC [32] [33], and prospective trials are ongoing to evaluate the clinical significance of CTCs. In the Phase II trials, abiraterone had a high CTC conversion rate, 34% and 42% [34] [35] respectively. CTC conversion is defined as a change from a prognostically unfavourable CTC count (≥5 CTC / 7.5mls blood) at baseline to a favourable CTC count on therapy (<5 CTC / 7.5mls blood). In the abiraterone COU-AA-301 Phase III trial, CTC conversion was significantly higher in the abiraterone arm relative to the placebo arm, 48% vs. 17% respectively [36]. In addition to enumeration of CTCs, exploratory analyses of CTCs for pathway activation and/or genetic aberrations may inform of patients most likely to benefit from combination therapy and will be examined using various platforms at multiple time points. PTEN loss, AR and TMRSS2/ERG will also be analysed in CTC by FISH and multicolour immunofluorescence (IF) for predictive biomarker analyses.

14.4.3. Plasma nucleic acids

There is increasing evidence that tumour DNA representing the mutational status of tumour cells can be obtained through the isolation of circulating DNA from blood specimens of patients with cancer [37] [38]. An assay has been developed to identify the major mutations in the PIK3CA / AKT genes on the basis of the analysis of circulating tumour DNA (ctDNA) in plasma. A blood sample will be collected at various time points to evaluate oncogenic mutations at baseline and the emergence of new mutations after treatment. Mutations will be evaluated in relevant genes including but not limited to PIK3CA and AKT. This will be correlated with mutations detected in submitted tumour specimens. According to the Sanger database, up to 30% of prostate cancers harbour PIK3CA mutation. Identifying potential discordances in the PIK3CA and AKT status of the primary and metastatic lesions through the analysis of archival tumour samples and ctDNA, respectively, may help clarify the prognostic and predictive significance of PIK3CA mutations in patients treated with the experimental regimens.

14.4.4. miRNA signature

A 9-gene mRNA expression signature has been shown to classify CRPC patients into distinct subgroups that are associated with significant differences in survival. (latent process decomposition LPD1 overall survival 10·7 months [95% CI 4·1-17·2] vs. non-LPD1 25·6 months [18·0-33·4]; p<0·0001) [30]. The prognostic value of this signature will be prospectively tested in this trial. This signature detects immune suppression. AKT/TOR blockade can impact immune function and therefore this signature will be evaluated in whole blood assays. Whole blood samples will be collected as outlined in schedule of events.

14.4.5. Endocrine Panel

Endocrine panels in urine for high-sensitive hormonal assays will be collected for correlative studies.

14.4.6. Proteomic analyses

Plasma and potentially tumour tissue will be analysed in collaboration with the ETH in Zurich (Prof Ruedi Aebersold) and employ proteomics techniques to assess the acute state of molecular pathways in bulk tissue and on the single cell level. Some of the methods used have been pioneered by members of the project team, some (SWATH-MS, Cy-TOF, multiplexed quantitative imaging and the corresponding computational efforts). Prof Aebersolds group has previously described and published a predictive serum biomarker signatures for patients with mCRPC[39].

14.5. Pain Assessment

The modified Brief Pain Inventory-short form (mBPI-sf; see Appendix D) is a simple, validated and reliable self-report questionnaire that consists of 9 questions that assess intensity of pain, as well as the degree of interference with daily life as a result of pain [40]. The questionnaire should be completed by the patient before any trial-specific procedures are undertaken.

14.6. Radiology assessment

14.6.1. Prospective evaluation of SCC signature on CTs

As part of the CT review pre-defined CT based signs that may precede malignant spinal cord compression will be analysed and correlated with clinical outcome. These features consist of epidural disease, malignant paravertebral fat infiltration and periosteal reaction (Omlin et al. ESMO 2012, manuscript submitted).

14.6.2. Prospective validation of bone scan index software

Bone scans will be analysed using the semi-automated bone scan index method [41].

15. STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

15.1. Phase I – safety run in

15.1.1. Primary Endpoint

- Type according to MedDRA (Medical Dictionary for Regulatory Activities), frequency and severity according to NCICTCAE V4, seriousness, and relatedness of study treatment-emergent adverse events will be assessed.
- Laboratory abnormalities will be assessed according to the NCI CTCAE v.4.

15.1.2. Secondary Endpoints

- Pharmacokinetic assay analyses.
- Antitumour activity of the combination.

15.1.3. Exploratory Endpoints

- Pharmacodynamic assay analyses.

15.2. Randomised Phase II

15.2.1. Primary Endpoint

- The primary endpoint of response will be defined on the basis of the following outcomes; if any of these occur without evidence of RECIST progression patients will be considered to have responded:
    - PSA decline of ≥ 50% confirmed by a second reading after 4 weeks or later,
    - Confirmed objective response (complete and/or partial response) by RECIST v1.1
    - ONLY for patients with detectable circulating tumour cell count (CTC) of ≥5/7.5ml blood at baseline, conversion of CTC to <5/7.5ml blood nadir confirmed by a second reading after 4 weeks or later

Only PSA and CTC assessments from week 12 onwards (to coincide with the first RECIST assessment) will be considered to evaluate response.

The RECIST (v1.1) criteria will be used to determine soft tissue response, Appendix A).

15.2.2. Secondary Endpoints

- Radiographic progression-free survival (rPFS- according to PCWG2 criteria & RECIST v1.1) measured from date of randomisation until:
    - Bone scan progression- a patient is considered to have progressed by bone scan if:
        i. The first bone scan with ≥2 new lesions compared to baseline is observed at 12 weeks from randomization and is confirmed by a

second bone scan taken ≥6 weeks later showing ≥2 additional new lesions (a total of ≥4 new lesions compared to baseline).

ii. A bone scan obtained later than the 12 week assessment shows ≥2 new lesions.

- Progression of soft tissue lesions measured by CT or MRI
- Death from any cause

If a patient is withdrawn for any reason prior to radiological progression then the patient should be assessed until radiological progression has occurred. If however they have started another treatment then they will be censored at the start of the new treatment.

- Overall survival measured from the date of randomisation to the date of death (whatever the cause). Survival time of living patients will be censored on the last date a patient is known to be alive or lost to follow up.
- Number of skeletal-related events defined as either the use of external beam radiotherapy to relieve skeletal symptoms or the occurrence of new symptomatic bone fractures (vertebral or non-vertebral) or the occurrence of spinal cord compression or a tumour related orthopaedic surgical intervention.
- Maximum PSA decline at any time during the trial and PSA decline at 12 weeks (as per PCWG2 criteria) presented as a waterfall plot.
- Circulating Tumour Cell (CTC) fall by >30%: This will be expressed as the proportion of patients that have demonstrated a CTC fall of >30%. Also the maximum CTC decline at any time during the trial and CTC decline at 12 weeks will be presented as a waterfall plot.
- Pain palliation will be assessed using the BPI-SF worst pain intensity score. Standard scoring algorithms will be used with a focus on worst pain intensity score and analgesic score. A composite of the four pain items (worse, least, average, right now) will be presented as supplemental information.
- Safety: Using the safety population the extent of exposure of study drug will be summarised. Adverse events will be graded according to NCI-CTCAEv4.

15.2.3. Exploratory Endpoints

- Molecular characterisation of tumours, in particular (but not exclusively) characterisation of PTEN status.
- Assessment of mRNA signature at baseline and on treatment.

15.3. Single Stage Phase II Expansion cohort

15.3.1. Primary Endpoint

- Response after the addition of AZD5363 in patients who progress after 12 weeks of enzalutamide alone will be defined on the basis of the following outcomes. If any of these occur without evidence of RECIST progression patients will be considered to have responded:

  - PSA decline ≥50% confirmed by a second reading after 4 weeks or later

- Confirmed objective response (complete and/or partial response) by RECIST v1.1

- ONLY for patients with detectable circulating tumour cell count (CTC) of ≥5/7.5ml blood at baseline, conversion of CTC to <5/7.5ml blood nadir confirmed by a second reading after 4 weeks or later.

Only PSA and CTC assessments from week 12 onwards (to coincide with the first RECIST assessment) will be considered to evaluate response.

15.3.2. Secondary Endpoints

- Maximum PSA decline at any time during the trial and PSA decline after 12 weeks (as per PCWG2 criteria) of combination treatment will be presented as a waterfall plot.
- Overall survival: It will be measured from the date of AZD5363 addition to enzalutamide to the date of death (whatever the cause). Survival time of living patients will be censored on the last date a patient is known to be alive or lost to follow up.
- Radiographic progression-free survival (rPFS) measured from the date of AZD5363 addition to enzalutamide until:

    - Bone scan progression: A patient is considered to have progressed by bone scan if:

        i. The first bone scan with ≥2 new lesions compared to baseline is observed at 12 weeks from randomization and is confirmed by a second bone scan taken ≥6 weeks later showing ≥2 additional new lesions (a total of ≥4 new lesions compared to baseline).
        ii. A bone scan obtained later than the 12 week assessment shows ≥2 new lesions.

    - Progression of soft tissue lesions measured by CT or MRI as defined by RECIST v1.1.
    - Death from any cause.

    If a patient is withdrawn for any reason prior to radiological progression then the patient should be assessed until radiological progression has occurred. If however they have started another treatment then they will be censored at the start of the new treatment.

- CTC fall by >30% will be expressed as the proportion of patients that have demonstrated a CTC fall of >30% after 12 weeks of combination treatment.
- Safety: Using the safety population the extent of exposure of study drug will be summarised. Adverse events will be graded according to NCI-CTCAEv4.
- Pharmacokinetic assay analyses.

15.3.3. Exploratory Endpoint

- Pharmacodynamic assay analyses
- Molecular characterisation of tumours, in particular (but not exclusively) characterisation of PTEN status.
- Assessment of mRNA signature at baseline and on treatment.

15.4. Stratification & treatment allocation

For the randomised phase II trial, a 1:1 treatment allocation will be performed via a minimisation algorithm, balancing for centre and the following factors:

- 1 or 2 prior lines of taxane based chemotherapy
- Prior response to abiraterone (yes or no). The response to abiraterone is defined as a ≥50% PSA decline or an objective soft tissue response as per RECIST 1.1

Minimisation is a widely recognised method of ensuring balance between treatment groups for several prognostic factors in clinical trials with smaller sample sizes. Treatment allocation to the next participant enrolled depends on the characteristics of the patients already involved, thus minimising the imbalance across the prognostic factors. To make the allocation of treatment more unpredictable, a random element will be incorporated in the algorithm.

15.5. Trial Design and sample size calculations

Phase I safety run-in: Approximately 18 patients will be treated in a run-in phase. A cohort size of at least 3 and up to 6 patients will be employed at each dose level (starting at dose level 1)in a 3+3 design.

Randomised double-blinded phase II: Assuming a response rate of 17% with enzalutamide alone in the post-docetaxel post-abiraterone setting, 50 patients per arm will allow us to detect a response rate of at least 40% in the enzalutamide + AZD5363 combination arm i.e. a detectable difference of 23% (one-sided $\alpha = 0.05$, power = 82%). The target sample size is therefore **100 patients**.

For secondary time-to-event outcomes with the same number of patients and a target of 70 events and with one-sided $\alpha = 0.10$ and power = 80% we can detect a hazard ratio of 0.60. This equates to an increase of median PFS from 5 months to 8.3 months and to an increase in OS from 10 months to 16.7 months.

Single stage phase II (expansion cohort): The single stage phase II trial will explore reversion of resistance to enzalutamide with the addition of AZD5363. A single stage A'Hern design will be employed to explore the response rate after addition of AZD5363 in patients who progress on enzalutamide alone. Assuming a p_0=10%, p_1=45%, α=0.05 and power 90%, 13 evaluable patients (see below for a definition of evaluable patients) are needed; if 4 or more responses are observed then further research with this treatment strategy will be considered feasible. Non-evaluable patients will be replaced; 18 patients will be recruited to allow for a 25% dropout rate. To allow exploratory analyses by PTEN status, the aim is to recruit 9 patients with PTEN loss and 9 patients with normal PTEN. PTEN status figures will be reviewed by the IDMC who will advise whether subsequent recruitment should be

dependent on the patient's tumour having the PTEN status criteria required to ensure sufficient PTEN loss patients are enrolled.

15.6. Analysis populations

Safety population: This population includes all enrolled patients who received at least 1 treatment dose of either of the trial drugs.

Intention to treat (ITT) applicable to the randomised phase only: This population includes all patients enrolled into the study regardless of whether they are later found to be ineligible, a protocol violator or not evaluated. Patients for whom the primary endpoint cannot be evaluated will be treated as non-responders. For patients who receive the wrong treatment, analysis will be carried out by the treatment assigned rather than the treatment received.

Evaluable-patient population: This population contains all enrolled patients for whom the primary endpoint can be evaluated. Where evaluability is difficult to define the final decision will rest with the IDMC.

- For phase I: Patients who complete the DLT period or experience a DLT during the DLT period are considered evaluable.
- For the randomised phase II and single stage expansion: Patients who meet all of the relevant inclusion and exclusion criteria and who start combination trial treatment are considered evaluable, unless they discontinue treatment prior to 12 weeks for reasons which aren't drug or disease related. Those who discontinue treatment prior to 12 weeks for reasons related to drug or disease will be classed as non-responders.

For the phase II trials comparison will be performed in all patients independent of results from the diagnostic assessments of the tumour (e.g. AR status, PTEN loss).

In the randomised phase II, analysis of the primary endpoint will use the evaluable-patient population with sensitivity analyses in the ITT population. Analysis of all other outcome endpoints will use the ITT population.

In the single stage phase II expansion, analysis of the primary endpoint will use the evaluable-patient population with sensitivity analyses in the safety population (patients for whom the primary endpoint cannot be evaluated will be treated as non-responders). Analysis of all other outcome endpoints will use the safety population.

The safety population will be used to characterise the safety and tolerability profile of the treatment regimens in the phase I safety run-in and phase II trials.

15.7. Analysis plan

15.7.1. Phase I safety run - in

Analyses for the run-in phase will be descriptive. Toxicity grades will be tabulated and the proportion of patients with grade 3 or 4 toxicities (NCI-CTC v4) and the number and type of

SAEs will be reported. All enrolled patients that received at least 1 dose of AZD5363 (safety population) will be included in the safety analysis. The plasma concentration/ time data will be analysed using non-compartmental methods. The pharmacokinetic (PK) parameters include maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), the area under the plasma concentration time curve (AUC), the terminal elimination half- life ($T_{1/2}$), mean residence time (MRT), total body clearance (CLT) and steady/ state volume of distribution (V_{ss}). Documenting anti-tumour activity is a secondary objective for the safety run-in phase and will be described by PSA, radiological criteria and CTC evaluation. Patients must receive 12 weeks of trial treatment to be evaluable for response.

15.7.2. Randomised Phase II & Single Stage Phase II Expansion cohort

For the randomised phase II trial it is planned that the primary analysis will take place once all patients have been evaluated 12 weeks post randomisation or have progressed prior to that, and after the data have been through quality control checks. This strategy will be reviewed by the IDMC in light of PFS events and the likely duration of response. If the target of accrued rPFS events (n=70) has not been reached by the time of the primary analysis it is planned that an additional analysis of rPFS and other secondary endpoints will take place once these have been observed. For the single stage phase II expansion cohort, primary analysis will be triggered once 13 patients have been evaluated 12 weeks post starting combination treatment.

The last value of PSA, CTC count (if available), CT or bone scan up to 4 weeks before the C1D1 will be used as baseline value for the response assessment. The best overall response rate will be presented along with its exact two-sided confidence interval. The Fisher's exact test will be used to compare the differences in response rates between the two randomised groups. Logistic regression models will be used to assess and control for stratification and important prognostic factors (to be identified in the statistical analysis plan).

Kaplan Meier curves will be used to summarize the survival data and the log-rank test will be used to assess any differences in OS or rPFS between groups. The median rPFS and OS estimates will be reported along with 95% CIs.

For the randomised phase II part Cox regression will be used to adjust for potential confounding factors relating to rPFS and OS. Methods for non-proportional hazards will be used as required and other models, e.g. exponential, Weibull, will also be explored to determine if any of these distributions are a more suitable fit for the data.

Response criteria will each be presented separately as waterfall plots for PSA (maximum PSA decline and PSA change), CTC (% fall) and RECIST measurement changes for each arm. Baseline and nadir CTC counts will be presented below the waterfall plot.

The proportion of patients with at least a 30% fall in CTC will be reported along with its 95% CI. The number of skeletal-related events will be presented by allocated treatment and the proportion of patients with an event will be estimated along with the 95% CI. Chi-squared tests will be used to assess any differences between the randomised groups.

Pain palliation will be assessed using the Brief Pain Inventory's (BPI Short Form) in the randomised phase II only. Standard scoring algorithms will be used [42] with a focus on worst pain intensity score and analgesic score. A composite of the four pain items (worse,

least, average, right now) will be presented as supplemental information. The analgesic relief received will be described.

Exploratory analyses to evaluate putative predictive biomarkers, specifically PTEN loss and INPP4B, optional fresh biopsies and CTC (multi-colour IF; IHC), will investigate whether there is a differential response rate or OS or rPFS in patients with and without these biomarkers. Resistance mechanisms will be explored on the single stage phase II expansion cohort. In the absence of prospective hypotheses, p-values for interaction will be required to satisfy $p<0.01$ for any subgroup results to be considered valid.

Interim analyses will take place frequently to examine safety.

15.8. Follow up post the primary analysis

Any patients still receiving study medication at the time of the primary analysis will be able to continue to receive AZD5363 / matching placebo and enzalutamide if in the opinion of the investigator and chief investigator they are continuing to derive clinical benefit, and in the absence of discontinuation criteria. For patients continuing, SAEs will be collected until 30 days post the last dose. The level and intensity of additional safety monitoring (collection of AE data) for continuing patients will be agreed when required and will be informed by emerging safety data from the trial (and any external advice) in discussion with the IDMC and TMG.

16. TRIAL MANAGEMENT

16.1. Trial Management Group (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, ICR-CTSU scientific lead, co-investigators and identified collaborators, the Trial Statistician and the Trial Managers. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. Where possible, membership will include a lay/consumer representative. The TMG will meet at regular intervals, and at least annually. Notwithstanding the legal obligations of the co-sponsors and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

16.2. Trial Steering Committee (TSC)

The ICR-CTSU metastatic Castration Resistant Prostate Cancer (mCRPC) Trial Steering Committee (TSC) will provide expert independent oversight of the trial on behalf of co-sponsors and funders. The mCRPC TSC includes an independent Chairman (not involved directly in the trial other than as a member of the TSC) and not less than two other independent members. The TSC will meet annually. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

The TSC will approve the dose to be used in the randomised and single stage phase II expansion cohort stages of the trial based on advice from the Safety Review Committee / IDMC.

16.3. Independent Data Monitoring Committee (IDMC)

An IDMC will be instigated to monitor the progress of the randomised phase II and single stage phase II expansion cohort parts of the trial. Membership of the IDMC will be proposed by the TMG and approved by the TSC. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU. The IDMC will meet in confidence at regular intervals, and at least annually. A summary of the findings and any recommendations will be produced following each meeting. This summary will be submitted to the TMG and TSC, and if required, the main REC and the MHRA.

The IDMC reserve the right to release any data on outcome or side effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it. The replacement of patients who withdraw from the study or who are unevaluable for reasons deemed not to be treatment related will be based on the advice of the committee.

16.4. Safety Review Committee (SRC)

A SRC will be set up for the Phase I – safety run in part of the study. After each dose level during the dose escalation phase the SRC will evaluate the safety and tolerability of the combination of AZD5363 and enzalutamide to decide if it is safe to proceed to the next dose. The SRC will also review the emerging PK and PD data. Data may be shared with the IDMC or TSC at any point.

The SRC will consist of:

- Chief Investigator
- Pharmacokinetic Lead
- Pharmacodynamic Lead
- Principal Investigator or delegate from each participating site
- ICR-CTSU Pharmacovigilance officer
- ICR-CTSU Senior Trial Manager or delegate
- ICR-CTSU statistician
- Senior ECMC clinician (who is not the Chief Investigator)

Representatives of AstraZeneca will also be invited to attend the SRC meetings as non-voting participants. Further internal or external experts may be consulted by the SRC as necessary.

The SRC will recommend the dose to be used for the randomised and single stage phase II expansion cohort stage of the study.

17. RESEARCH GOVERNANCE

17.1. Sponsor Responsibilities

The co-sponsors of the RE-AKT trial are the Institute of Cancer Research (ICR) and Royal Marsden NHS Foundation Trust (RM). Sponsor responsibilities, as defined by The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, are allocated between ICR and RM, as set out in an agreement letter between ICR and RM.

Responsibilities delegated to participating sites are defined in an agreement between the Co-sponsors and the individual site.

17.2. AstraZeneca and Astellas Responsibilities

AstraZeneca (AZD5363) and Astellas (enzalutamide) are responsible on behalf of the co-sponsors for the manufacture, packing, labelling and distributing of study drug and matching placebo to site in accordance with Good Manufacturing Practice and all applicable local legislation. Some of these responsibilities have been delegated to Fisher Clinical Services. and are defined in an agreement.

18. TRIAL ADMINISTRATION & LOGISTICS

18.1. Site Activation

Before activating the trial, participating sites are required to sign an agreement accepting responsibility for all trial activity which takes place within their site.

Sites may commence recruitment once the site agreement has been signed by all required signatories, the required trial documentation is in place (as specified by ICR-CTSU) and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

18.2. Data Acquisition

Electronic (e) Case Report Forms (CRF) will be used for the collection of trial data. ICR-CTSU will provide guidance to sites to aid the completion of the eCRFs. The Trial Management Group reserves the right to amend or add to the eCRF template as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by sites in accordance with the guidelines provided by ICR-CTSU.

18.3. Central Data Monitoring

Once data has been entered on the eCRF by the site personnel, ICR-CTSU will review it for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be raised for resolution by the site.

Any systematic inconsistencies identified through central data monitoring may trigger an on-site monitoring visit.

18.4. On-Site Monitoring

If a monitoring visit is required, ICR-CTSU will contact the site to arrange the visit. Once a date has been confirmed, the site should ensure that full patient notes of participants selected for source data verification are available for monitoring.

ICR-CTSU staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the clinical trial agreement and trial protocol. If any problems are detected during the course of the monitoring visit, ICR-CTSU will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

18.5. Completion of the study and Definition of Study End Date

The study end date is deemed to be the last date of data capture.

18.6. Archiving

Essential trial documents should be retained according to local policy and for a sufficient period for possible inspection by the regulatory authorities (at least 5 years after the date of last data capture). Documents should be securely stored and access restricted to authorised personnel.

19. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

19.1. Trial Approvals

This trial has been formally assessed for risk by the Sponsor.

ICR-CTSU, on behalf of the Sponsor, will ensure that the trial has received ethics approval from a research ethics committee for multi-centre trials, regulatory approval from the MHRA and the relevant NHS permissions. Before recruiting patients, the Principal Investigator at each site is responsible for gaining local approvals.

19.2. Trial Conduct

This trial will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by the Co-sponsors and in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, the Research Governance Framework for Health and Social Care and the principles of GCP.

19.3. Informed Consent

Patients should be asked to sign the current main REC approved RE-AKT consent form at trial registration after receiving both verbal and written information about the trial, having been given sufficient time to consider this information. All consent forms must be countersigned by the Principal Investigator or a designated individual. A signature log of delegated responsibilities, listing the designated individuals and the circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The current main REC approved RE-AKT patient information sheets should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice.

19.4. Patient Confidentiality

Patients will be asked to consent to their full name being collected at registration in addition to their date of birth, hospital number, postcode and NHS number or equivalent to allow linkage with routinely collected NHS data and ensure accuracy in handling biological samples.

Each investigator should keep a separate log of all participants' Trial IDs, names, addresses and hospital numbers. The investigator must retain trial documents (e.g. participants' written consent forms) in strict confidence. The investigator must ensure the participants' confidentiality is maintained at all times.

Representatives of ICR-CTSU and the regulatory authorities will require access to participants' hospital notes for quality assurance purposes. ICR-CTSU will maintain the confidentiality of participants at all times and will not reproduce or disclose any information by which participants could be identified.

19.5. Data Protection Act (DPA)

ICR-CTSU will comply with all aspects of the DPA 1998.

19.6. Liability

19.6.1. Manufacturers Liability

The Co-Sponsors have secured indemnity from the manufacturers for patients in relation to adverse side effects for medicine-induced injury.

19.6.2. Management & Design

The Co-Sponsors are responsible for harm arising from the experimental treatment given to patients recruited to this study.

19.6.3. Conduct (Hospital)

Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements for clinical negligence. A copy of the relevant insurance policy/indemnity scheme or summary shall be provided to the Co-Sponsors on request.

19.6.4. Non-fault

ICR has in force a non-fault compensation insurance for any potential injury caused in connection with your participation in this clinical trial. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to ICR's insurers, via the Purchasing office.

20. FINANCIAL MATTERS

This trial is investigator designed and led, has been endorsed by Clinical Trials Awards & Advisory Committee (CTAAC) of Cancer Research UK, and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

The trial is part of the National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio. CRN resources should therefore be made available for the trial to cover UK specific research costs.

ICR has received an Investigator Initiated Research grant (IIR) from AstraZeneca for the central coordination of the trial. If further funding is received from any other source this will be made apparent in the patient information sheet and to the main REC, but will not require a protocol amendment.

21. PUBLICATION POLICY

The main trial results will be published in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, consisting of members of the TMG and key collaborators and led by the chief investigator. Participating investigators may be selected to join the writing group on the basis of intellectual and time input. All participating clinicians will be acknowledged in the publication.

Any presentations and publications relating to the trial must be authorised by the TMG. Authorship of any secondary publications e.g. those relating to sub-studies, will reflect the intellectual and time input into these studies.

No investigator may present or attempt to publish data relating to the RE-AKT trial without prior permission from the TMG.

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Appendix A. RECIST v1.1

Selected sections from the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, are presented below, with slight modifications and the addition of explanatory text as needed for clarity.

A. Measurability of Tumour at Baseline

At baseline, tumour lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

1. Measurable Tumour Lesions

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 as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with callipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes - To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5mm).

2. Non-measurable Tumour Lesions

Non-measurable tumour lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with short axis ≥10 but <15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

B. Target Lesions: Specifications by Methods of Measurements

1. Measurement of Lesions

All measurements should be recorded in metric notation, with use of callipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of treatment.

2. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CT / MRI - CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT

scan on the basis of the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrolment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumour type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine whether substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

C. Tumour Response Evaluation

1. Assessment of Overall Tumour Burden and Measurable Disease

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

2. Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is $>$10mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs but, in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumour. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge whether a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial

plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20mm×30 mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15mm) should be considered non-target lesions. Nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

D. Response Criteria

1. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

- **Complete response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- **Partial response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters

- **Progressive disease (PD)**: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
- **Stable disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

2. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. Whereas some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **CR**: Disappearance of all non-target lesions and (if applicable) normalization of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- **Non-CR/Non-PD**: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumour marker level above the normal limits
- **PD**: Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

3. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease - In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-measurable Disease - This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider whether the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease; that is, an increase in tumour burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. Although it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

4. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal; that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumour (e.g., some “new” bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify whether it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

E. Evaluation of Response

1. Time Point Response (Overall Response)

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 9 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 10 is to be used.

Table 9 - Time Point Response: Patients with Target Lesions (With or Without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.			

Table 10 - Time Point Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD a
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD
CR=complete response; NE=not evaluable; PD=progressive disease. "Non-CR/non-PD" is preferred over "stable disease" for non-target disease, since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.		

2. Special Notes on Response Assessment

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

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

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumour should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumour is still present but not evaluated as a target or non-target lesion.

F. ASSESSMENT OF BONE LESIONS

In this study, bone lesions will be assessed by bone scintigraphy (bone scans).

On-study assessments should be performed on at week 12 and then at every third follow-up visit thereafter until progression, discontinuation of study treatment or withdrawal of consent. A final assessment (exit scan) should be performed at the time of discontinuation from study drug if a scan has not been taken in the 8 weeks preceding discontinuation.

1. Assessment of progression in bone lesions

Progression is defined as the appearance of 2 or more new bone metastases detected by bone scan compared with the baseline scan at any time point on the study after 12 weeks of treatment. However, if the 2 or more new lesions are detected at week 12, a confirmatory scan 6-12 weeks later with additional 2 or more new lesions will be required in order to qualify for disease progression (2+2 rule). If on the confirmatory scan less than 2 additional new lesions are detected, patients are classified as having stable disease.

2. New lesions

New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan (or confirmatory CT, MRI or X-ray) performed at any time during the study. The finding of a new lesion should be unequivocal:

i.e., not attributable to differences in scanning technique or suggestive for a flare reaction. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesions.

Note if fewer than 2 new bone metastases are present, then it will not be considered that disease progression as defined by bone criteria has occurred. Patients may continue to

receive treatment (if they are still receiving benefit) and continue radiological assessment as per the study plan.

If the investigator is in doubt as to whether progression has occurred, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated.

3. Evaluation of visit response for bone lesions

Table 11 - provides the definitions of the criteria to determine tumour visit response for bone lesions.

Overall response for bone lesions	
Complete response (CR)	Disappearance of all bone lesions since baseline
Stable disease (SD)	Persistence of bone lesions or appearance of 1 new lesion. At the first bone scan at week 12 the appearance of new lesions will also be considered SD.
Progressive disease (PD)	Two or more bone lesions compared to baseline. For patients having 2 or more new lesions at week 12, a subsequent scan 6-12 weeks later needs to confirm additional ≥2 lesions (2+2 rule).

Appendix B. Potent CYP Inhibitors and Inducers

CYP Inhibitors	CYP Inducers
amiodarone	carbamazepine
atazanavir	Rifampicin
clarithromycin	
disulfiram	
fluconazole	
fluoxetine	
fluvoxamine	
gemfibrozil	
indinavir	
itraconazole	
ketoconazole	
moclobemide	
nefazodone	
nelfinavir	
paroxetine	
quinidine	
ritonavir	
saquinavir	
telithromycin	

For additional CYP inhibitors and inducers please refer to;

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#cypEnzymes

Guidance regarding potential interactions of AZD5363 (Capivasertib) with concomitant medications

Drugs that may influence capivasertib pharmacokinetics

Based on results from in vitro studies, capivasertib is a substrate of CYP3A4, although data suggests that glucuronidation may be the major metabolic route. Co-administration of some CYP3A4 inhibitors may increase exposure to capivasertib and hence potentially affect toxicity, while CYP3A4 inducers may decrease the exposure to capivasertib and may potentially affect efficacy.

The following lists (Table 1) are not intended to be exhaustive and a similar restriction will apply to other agents that are known to modulate CYP3A4 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

Table 1 CYP3A4-interacting medication that should be avoided or used with caution

Medication	Recommendation	Rationale
Clarithromycin Cobicistat Itraconazole Ketoconazole Nefazodone Posaconazole Protease inhibitors (danoprevir, ritonavir, saquinavir, indinavir, tipranavir, telaprevir, elvitegravir, lopinavir, nelfinavir, boceprevir) Telithromycin Troleandomycin Voriconazole	**Should be avoided** 2 weeks prior to capivasertib administration and for 2 days following discontinuation of capivasertib.	Potent CYP3A4 inhibitors, which may increase the capivasertib exposure.
Carbamazepine Enzalutamide Phenobarbital Phenytoin Rifabutin Rifampicin Mitotane St John's wort	**Should be avoided** 2 weeks (3 weeks for St John's Wort and 4 weeks for enzalutamide) prior to capivasertib administration.	Potent CYP3A4 inducers, which may reduce the capivasertib exposure.

Medication	Recommendation	Rationale
Aprepitant Diltiazem Erythromycin Fluconazole Verapamil	May be used with caution[a].	Moderate CYP3A4 inhibitors which might increase the capivasertib exposure.

[a] Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with capivasertib.

Drugs that may be influenced by capivasertib

There are currently no data confirming that there are any pharmacokinetic (PK) interactions between capivasertib and CYP3A4, CYP2D6 or CYP2C9 substrates. The potential interactions detailed below (Table 2) are considered on the basis of preclinical data and physiologically based pharmacokinetic (PBPK) modelling. The following list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to be sensitive to CYP3A4, CYP2D6, and/or CYP2C9 metabolism inhibition and/or have a narrow therapeutic window. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

Table 2 CYP3A4, CYP2D6 or CYP2C9 substrates that should be avoided or used with caution

Medication	Recommendation/	Rationale
Alfentanil Atorvastatin Carbamazepine Cerivastatin Cyclosporin Diergotamine Ergotamine Fentanyl Lovastatin Simvastatin Sirolimus Tacrolimus	**Should be avoided** 1 week prior to capivasertib administration and for 1 week following discontinuation of capivasertib.	CYP3A4 substrates, whose exposure may be increased by capivasertib.

Medication	Recommendation/	Rationale
Amitriptyline Atomoxetine Desipramine Doxepin Metoprolol Nefazodone Nebivolol Perphenazine Tolterodine Trimipramine Tropisetron	**Should be avoided** 1 week prior to capivasertib administration and for 1 week following discontinuation of capivasertib.	CYP2D6 substrates, whose exposure may be increased by capivasertib.
Haloperidol Tramadol	**Should be avoided** 1 week prior to capivasertib administration and for 1 week following discontinuation of capivasertib.	Combined CYP3A4 and CYP2D6 substrates, whose exposure may be increased by capivasertib.
Alprazolam Domperidone Erythromycin Felodipine Isradipine Midazolam Methylprednisolone Nifedipine Pimozide Quinidine Sertraline Tamoxifen Trazodone Triazolam	May be used with caution[a].	CYP3A4 substrates, whose exposure may be increased by capivasertib.
Fluoxetine Paroxetine Venlafaxine	May be used with caution[a].	CYP2D6 substrates, whose exposure may be increased by capivasertib.
Warfarin	May be used with caution[a].	CYP2C9 substrate, whose exposure may be increased by capivasertib.

[b] Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with capivasertib.

Guidance for statins

Atorvastatin, cerivastatin, lovastatin, and simvastatin should be avoided due to the potential for increased exposure through inhibition of CYP3A4 by capivasertib (Table 2).

Fluvastatin, pravastatin, and rosuvastatin are minimally influenced by CYP3A4 inhibitors, conveying a relatively low potential for clinically significant drug-drug interactions via this mechanism.

Capivasertib also has a potential to inhibit the organic-anion-transporting polypeptide 1B1 (OATP-1B1) transporter, which is implicated in the distribution and clearance of many of the statins. The predicted increase in the area under the plasma concentration time curve (AUC) is 1.3-fold for pravastatin and 1.5-fold for rosuvastatin. It is, therefore, recommended that doses of pravastatin be capped to 40 mg once daily and rosuvastatin be capped to 10 mg once daily when combined with capivasertib, including 1 week prior to capivasertib administration and for 1 week following discontinuation of capivasertib.

In summary, rosuvastatin (up to 10 mg once daily), pravastatin (up to 40 mg once daily) and fluvastatin are appropriate agents to be used in patients included in capivasertib studies who require statin therapy.

Additional resources

For additional inhibitors, inducers and substrates please refer to:

https://drug-interactions.medicine.iu.edu/Clinical-Table.aspx

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Appendix C. Expansion of Exclusion Criteria 2

Previous exposure to agents with the following mechanisms of action:

- inhibition of AKT (e.g., MK2206, GDC0068, GSK2110183, GSK2141795)
- any inhibitor with PI3K pharmacology (e.g., GDC0941, XL147, BKM120, PX866, BYL719, AMG319, GDC0032, INK1117, INK119)
- any compound with

    - mixed PI3K and mTOR kinase pharmacology (e.g., BEZ235, GDC0980, PF04691502, PF05212384, GSK2126458, XL765)or
    - any mTOR kinase inhibitor (e.g., AZD8055, AZD2014, OSI027, INK128)

      Note: Do not exclude patients previously treated with a rapalogue (allosteric inhibitor of mTOR; mTORC1 complex inhibitor) – including temisirolimus (Torisel; Pfizer), everolimus (Affinitor; Novartis), ridoforolimus (Ariad).

Appendix D. Brief Pain Inventory (Short Form)

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

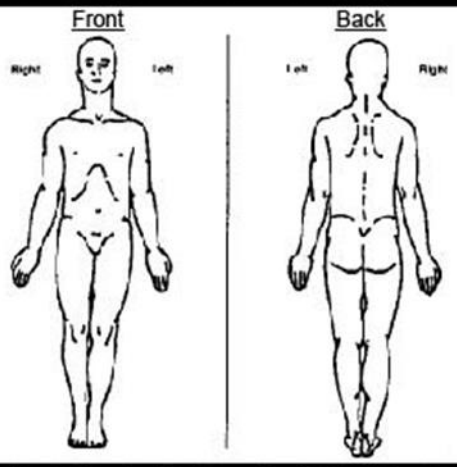
Revision: 07/01/05

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

B. Mood

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

C. Walking ability

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

E. Relations with other people

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

F. Sleep

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

G. Enjoyment of life

☐0 Does Not Interfere ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Completely Interferes

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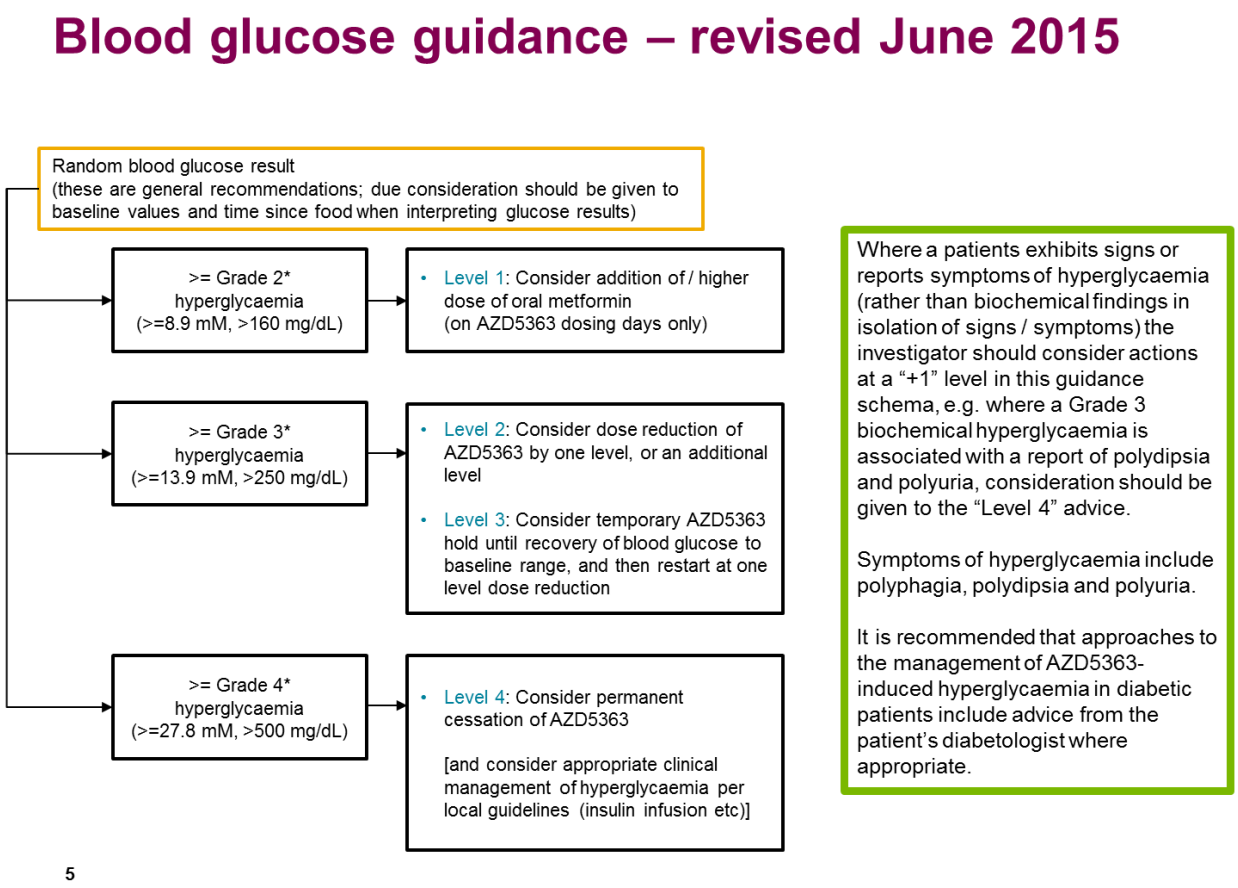
Appendix E. Glucose Management Algorithm

Note where AZD5363 is written = AZD5363 and / or matching placebo



*These grade thresholds based on CTCAE cut-offs for fasting glucose, but applied to random glucose here.

Appendix F. Maculo-Papular Rash Guidelines

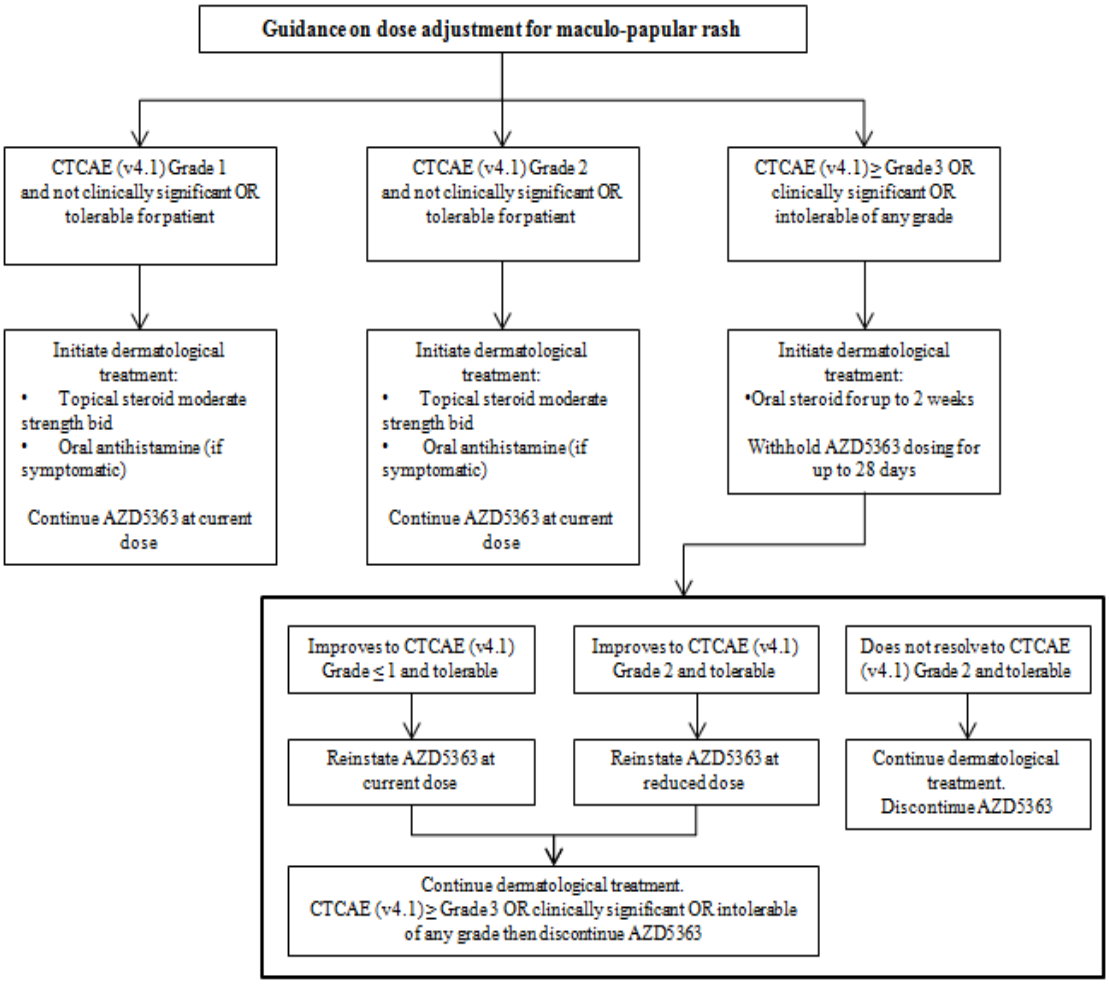
CTCAE Grade 1	
▪ <10% body surface area (BSA) covered with macules/papules ▪ With or without symptoms (e.g. pruritis, burning, tightness)	▪ Topical steroid moderate strength *bid ▪ Oral antihistamine (if symptomatic)
CTCAE Grade 2	
▪ 10% - 30% BSA covered with macules/papules ▪ With or without symptoms (e.g. pruritis, burning, tightness); limiting instrumental activities or daily living (ADL)	▪ Topical steroid moderate strength *bid ▪ Oral antihistamine (if symptomatic)
CTCAE Grade ≥ 3	
▪ >30% BSA covered with macules/papules ▪ With or without associated symptoms; limiting self-care ADL	▪ Topical steroid moderate strength *bid ▪ Oral antihistamines ▪ Oral steroid for up to 2 weeks

Examples of topical steroids and antibiotics

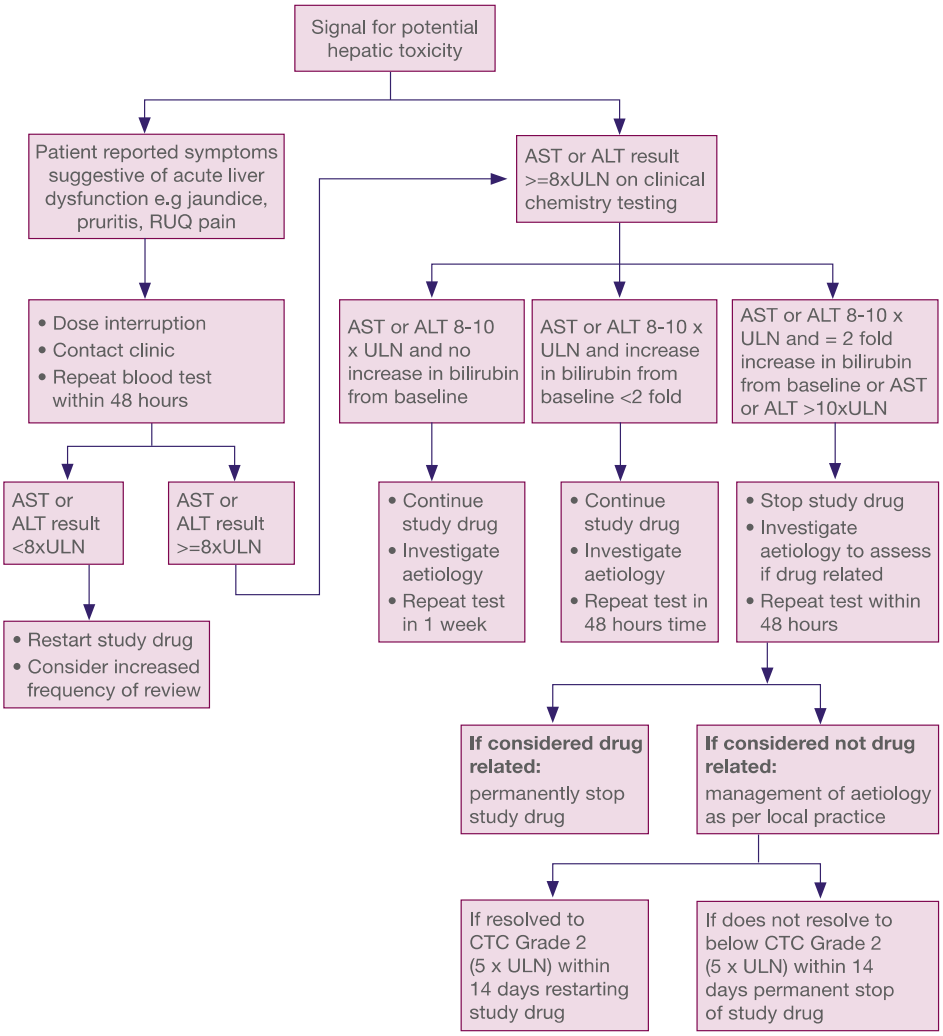
Topical steroid moderate strength	Fluticasone proprionate 0.05% Aclometasone 0.05%
Oral Antihistamines	Dipenhydramine 25-50mg every 8 hours Hydroxyzine 25mg every 8 hours Chlorpheniramine 4mg 4-6 hourly
Oral Steroids	Prednisolone: 5mg – 60mg per day. Before the drug is stopped it is recommended that it be withdrawn gradually rather then abruptly. Doses > the equivalent of 10 mg/day of prednisolone can only be given for a maximum of 21 days.

Appendix G. Dose Adjustment for Maculo-Papular Rash

Note where AZD5363 is written = AZD5363 and / or matching placebo



Appendix H. Guidance on Management of Hepatotoxicity



Appendix I. Total Volume of Blood Collected

Phase I safety run – in

	Blood volumes (ml)				
Visit	**Safety Blood**	**Research**	**PK (AZD5363)**	**PK (enzalutamide)**	**PD**
Screening	36.7	61	0	0	0
C0D1	36.7	61	12	0	32.4
C0D2	0	0	2	0	8.1
C0D3	0	0	2	0	8.1
C1D1	27.7	0	0	0	8.1
C1D4	22	0	0	0	8.1
C1D11	27.7	0	0	0	0
C2D1	27.7	58.5	12	30	32.4
C2D2	0	0	2	0	8.1
C2D3	0	0	2	0	8.1
C2D4	0	0	2	10	8.1
C2D11	11.7	0	2	10	8.1
C3D1	27.7	32.5	0	0	0
C4D1	36.7	61	0	0	0
C7D1	33.7	52.5	0	0	0
C10D1	33.7	32.5	0	0	0
Treatment Discontinuation	11.7	61	0	0	8.1
Safety Follow -up	36.7	0	0	0	0
Total	**370.4**	**420**	**36**	**50**	**137.7**

Randomised phase II

	Blood volumes (ml)		**Urine volume (ml)**
Visit	**Safety Blood**	**Research**	**Research**
Screening	36.7	61	20
C1D1	36.7	61	20
C1D8	27.7	0	0
C1D15	27.7	0	0
C2D1	27.7	61	20
C3D1	27.7	0	0
C4D1	36.7	61	20
C7D1	33.7	52.5	0
C10D1	33.7	32.5	0
Treatment Discontinuation	11.7	61	20
Safety Follow -up	36.7	0	0
Total	**336.7**	**390**	**100**

Single Stage Phase II Expansion Cohort

	Blood volumes (ml)				
Visit	**Safety Blood**	**Research**	**PK (AZD5363)**	**PK (enzalutamide)**	**PD**
Screening	36.7	61	0	0	0
C1D1	36.7	61	12	30	32.4
C1D2	0	0	2	0	8.1
C1D3	0	0	2	0	8.1
C1D4	22	0	0	0	8.1
C1D11	27.7	0	0	0	0
C2D1	27.7	58.5	2	10	8.1
C2D4	0	0	2	10	8.1
C2D11	11.7	0	2	10	8.1
C3D1	27.7	32.5	0	0	0
C4D1	36.7	61	0	0	0
C7D1	33.7	52.5	0	0	0
C10D1	33.7	32.5	0	0	0
Treatment Discontinuation	22.7	61	0	0	8.1
Safety Follow -up	36.7	0	0	0	0
Total	**353.7**	**420**	**22**	**60**	**89.1**

Volumes calculated on the basis of;

- Full blood count = 5.7 ml
- Biochemistry (including glucose) = 6 ml
- PSA = 6 ml
- Testosterone and FSH = 6 ml
- Thyroid function = 10 ml
- HbA1C = 3 ml
- AZD5363 PK = 2 ml
- Enzalutamide PK = 10 ml
- PD = 8.1 ml

Appendix J. Glossary

AD	Androgen deprivation
APTT	Activated partial thromboplastin time
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
AE	Adverse Event
ALT	Alanine Transaminase (SGPT)
ALP	Alkaline Phosphatase
Ha	Alternative Hypothesis
AR	Androgen receptor
ADC	Apparent diffusion coefficient
AUC	Area under curve
AST	Aspartate Transaminase (SGOT)
AZ	AstraZeneca
BER	Base excision repair
BP	Blood Pressure
BUN	Blood urea nitrogen
BPI-SF	Brief pain inventory - short form
CRF	Case Report Form
CRPC	Castration Resistant Prostate Cancer
cm	Centimetre
CTC	Circulating Tumour Cell
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete Response
CT	Computerised Tomography
CI	Confidence Interval
CrCl	Creatinine clearance
CYP	Cytochrome P450 isoenzymes
D	Day (as in treatment day)
dL	Decilitres
ºC	Degrees Celsius
DNA	Deoxyribonucleic acid
DNA	Deoxyribonucleic acid
DRE	Digital rectal exam
IC50	Dose for 50% inhibition
DLT	Dose Limiting Toxicity
DSB	Double Strand Breaks
ECOG	Eastern Co-operative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
FISH	Fluorescent in-situ hybridisation
FDA	Food and Drug Administration
FBC	Full Blood Count
FSH	Follicle Stimulating Hormone
GGT	Gamma glutamyltransferase
HbA1c	Glycosylated haemoglobin
GCP	Good Clinical Practice
GMP	Good manufacturing practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GCIG	Gynaecologic Cancer Intergroup
t1/2	Half life
H2AX	Histone H2AX
HR	Homologous Recombination
HER2	Human Epidermal Growth Factor Receptor 2
IF	Immunoflourescence
IHC	Immunohistochemistry
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INPP4B	Inositol polyphosphate-4-phosphatase, type II
IRB	Institutional Review Board
ITT	Intention To Treat
ICH	International Conference on Harmonisation
INR	International Normalised Ratio
IMP	Investigational Medicinal Product
IB	Investigator Brochure
kg	Kilogram
LDH	Lactic Dehydrogenase
LD	Longest Diameter
LHRH	Luteinizing Hormone Releasing Hormone
MRI	Magnetic Resonance Imaging
mTOR	Mammalian target of rapamycin
C_{max}	Maximum (or peak) concentration

MTD	Maximum tolerated dose
µM	Micromolar
miRNAs	MicroRNAs
mg	Milligram
Cmin	Minimum (trough) concentration
nM	Nanomolar
NCI	National Cancer Institute
NCICTC	National Cancer Institute Common Terminology Criteria
NYHA	New York Heart Association
NAD	Nicotine adenine dinucleotide
Ho	Null hypothesis
NRS	Numeric Rating Scale
od	Once daily
ORR	Overall Response Rate
PR	Partial Response
PICF	Patient Informed Consent Form
PO	Per Oral (by mouth)
PBMC	Peripheral Blood Mononuclear Cells
PHLPP	PH domain and Leucine rich repeat Protein Phosphatases
PD	Pharmacodynamic
PK	Pharmacokinetic
PTEN	Phosphatase and Tensin Homologue
PI3K	Phosphatidylinositide 3-kinases
PRP	Platelet rich plasma
PARP	Poly (ADP-ribose) polymerase
PT	Preferred Term
PFS	Progression Free Survival
PD	Progressive Disease
PCWG2	Prostate Cancer Working Group 2
PIN	Prostatic Intraepithelial Neoplasm
PSA	Prostatic Specific Antigen
AKT	Protein Kinase B
rPFS	Radiographic progression-free survival
RP2D	Randomised phase II dose
Ras	Rat sarcoma
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
SRC	Safety review committee
SAE	Serious Adverse Event
SAR	Serious adverse reaction
SUSAR	Serious unexpected suspected adverse (drug) reaction
SGPT	Serum Glutamic Pyruvate Transaminase
SGOT	serum glutamic-oxaloacetic transaminase
SSB	Single Strand Break
SD	Stable disease
SOC	System Organ Class
SBP	Systolic blood pressure
TSH	Thyroid Stimulating Hormone
tmax	Time to peak concentration
BID	Twice daily
bid/bd	twice daily
ULN	Upper Limit of Normal
UA	Urinalysis
WBC	White Blood Cells
GABA	γ-Aminobutyric