Redacted protocol to accompany manuscript:

Phase III, randomized, placebo-controlled study of zibotentan (ZD4054) in combination with docetaxel in patients with metastatic castration-resistant prostate cancer

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A Phase III, Randomised, Double-bind, Placebo-controlled Study to Assess the Efficacy and Safety of 10 mg Zibotentan (ZD4054) in Combination with Docetaxel in comparison with Docetaxel in Patients with Metastatic Hormone-resistant Prostate Cancer

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CONTENTS

Source material

Taken from Clinical Study Protocol (study code D4320C00033), dated 15 February 2011.

1. SELECTION OF STUDY POPULATION

1.1 Study selection record

Investigator(s) must keep a record of patients who were considered for enrolment but were never enrolled eg, patient screening log. This information is necessary to establish that the patient population was selected without bias.

1.2 Inclusion criteria

For inclusion in the study patients must fulfil all of the following criteria:

1. Provision of informed consent
2. Male, aged 18 years or older
3. Histological or cytological confirmation of adenocarcinoma of the prostate
4. Documented evidence of bone metastasis on bone scan. Patients must have disease involvement <75% of the spine, pelvis and ribs in the anteroposterior (AP) or posteroanterior (PA) view. Patients with ≤3 lesions seen on bone scan will require a CT scan, MRI or x-ray to confirm
5. Biochemical progression of prostate cancer, defined as at least 2 stepwise increases in a series of any 3 prostate-specific antigen (PSA) values collected while the patient is castrate. The 3 PSA values selected do not need to be consecutive, and do not need to include the most recent PSA collected at or prior to study enrolment but must meet the following criteria:
    - There must be at least 14 days between each of the 3 PSA values, and each must be collected no more than 1 year before enrolment into the study
    - The last PSA value in the series of 3 must be either an increase of ≥25% of the first PSA or an absolute increase of ≥10 ng/mL over the first PSA
    - The last PSA value in the series of 3 must be ≥1.2 ng/mL in patients who have had a radical prostatectomy and ≥5 ng/mL in all other patients
    - Each of the 3 PSA values must be collected whilst the patient is under medical castration or is surgically castrated.
6. Continuously medically castrated with stable treatment for at least 8 weeks prior to study randomisation or surgically castrated. Acceptable medical castration includes luteinising hormone-releasing hormone analogues

(LHRHa), estradiol, estramustine or other estrogen based preparations. Anti-androgens can be taken in conjunction with medical castration. Serum testosterone must be ≤2.4nmol/L (70ng/dL) at enrolment despite method of castration.

7. WHO Performance score of 0–1
8. Life expectancy of 3 months or more

1.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Radiotherapy to bone lesion or prostatic bed within 4 weeks of starting study treatment
2. Prior cytotoxic chemotherapy (such as paclitaxel, docetaxel and mitoxantrone) for the treatment of recurrent prostate cancer (prior estramustine therapy is allowed). Prior targeted cancer therapies, such as EGF, EGFR, VEGF and VEGFR, or immune cell therapy, are only permitted if the patient received them during participation in a previous clinical trial
3. Systemic radionuclide therapy (ie, strontium chloride Sr89, 186Relabeled HEDP, or ^{153}Sm-EDTMP pentasodium) within 12 weeks of starting study treatment
4. Use of potent CYP450 inducers (such as phenytoin, rifampicin, carbamazepine, phenobarbitone, St John's Wort) within 2 weeks of starting study treatment. Dexamethasone is a known inducer of CYP2D6 and CYP3A4 but is acceptable for this study when used as part of the standard docetaxel regime
5. Use of systemic retinoids within 2 weeks of starting study treatment
6. Have received investigational drug in another clinical study of anti-cancer therapy, within 4 weeks of starting study treatment
7. Prior therapy with endothelin receptor antagonists or family history of hypersensitivity to endothelin antagonists
8. Acute or evolving spinal cord compression or neurological symptoms or signs consistent with this. If a patient has neurologic symptoms, an MRI must be performed that demonstrates no impending or actual spinal cord compression. Stable, previously treated patients are allowed

9. Symptomatic peripheral neuropathy of CTCAE grade 2 or higher
10. Known or suspected central nervous system metastases.
11. History of past or current epilepsy, epilepsy syndrome, or other seizure disorder
12. Stage II, III or IV cardiac failure (classified according to New York Heart Association (NYHA) classification) or myocardial infarction within 6 months prior to study entry
13. QT interval corrected for heart rate eg, by Bazett's correction >470 msec
14. Previous history or presence of another malignancy within the preceding 5 years except treated squamous/basal cell carcinoma of the skin or melanoma that has been fully excised with no signs of residual disease or recurrence at the time of study enrolment
15. In the opinion of the investigator, any evidence of severe or uncontrolled systemic disease, (eg, currently unstable or uncompensated respiratory, cardiac, hepatic or renal disease) or evidence of any other significant clinical disorder or laboratory finding that makes it undesirable for the patient to participate in the study
16. Absolute Neutrophil Count (ANC) <1.5 x 10^9/L (1,500/mm^3); haemoglobin (Hb) <9 g/dL; platelet count <100 x 10^9/L (100,000/mm^3). Concomitant use of erythropoietin or blood transfusions is allowed
17. Serum bilirubin >1.5 times the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of evidence of haemolysis or hepatic pathology), who will be allowed in consultation with their physician
18. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 times the ULN or 5 times the ULN in the presence of liver metastases
19. Creatinine clearance of <50 mL/minute, determined using the Cockcroft-Gault equation or by 24-hour creatinine clearance
20. Patients who have been previously randomised in this study cannot be rerandomised. Patients who fail to meet the inclusion/exclusion criteria may be reconsidered once for participation in the study
21. Involvement in the planning and conduct of the study (applies to ICON and AstraZeneca staff or staff at the study site)

2. SCHEMA AND TREATMENT PLAN

2.1 Overall study design and flow chart

This is a randomised, double-blind, parallel-group, multi-centre, 2-arm, placebo-controlled Phase III study to assess the efficacy and safety of zibotentan (ZD4054) (10 mg) in combination with docetaxel, compared with docetaxel, in patients with metastatic hormone-resistant prostate cancer.

Approximately 1044 (522/arm) metastatic hormone resistant prostate cancer patients who have progressive disease defined by rising serum prostate specific antigen levels despite medical or surgical castration will be recruited into approximately 150 hospital-based centres globally.

Total study duration is approximately 50 months, which includes an estimated 26 months for recruitment, an estimated 12-month follow-up for survival for primary analysis (primary analysis is at approximately 508 deaths) and an additional 12-month follow-up for survival for final analysis. If the primary analysis does not demonstrate a statistically significant effect in overall survival the follow-up survival analysis will not take place.

Patients will be randomised 1:1, stratified by centre to receive zibotentan plus docetaxel or placebo plus docetaxel.

Zibotentan (10 mg) or matched placebo is administered orally once daily in combination with docetaxel (75 mg/m^2) administered intravenously over 1 hour on day 1 of each 21-day cycle (dose reductions and alteration to frequency of administration are allowed as appropriate if toxicity seen or anticipated).

Patients will receive 10 cycles of docetaxel as long as they meet no withdrawal criteria. Following completion of 10 cycles of docetaxel plus zibotentan/placebo, patients who, in the investigator's opinion, are experiencing benefit from study treatment may continue on docetaxel. Patients may continue on blinded

zibotentan/placebo with or without docetaxel, for as long as they meet no withdrawal criteria.

Following randomisation, patients may receive additional standard prostate cancer therapies which may include any of the following: regular follow-up; symptomatic therapy for pain control or urinary obstruction therapies including prednisolone, ketoconazole, megace or antiandrogens at the investigator's discretion without being considered treatment failures or having to stop zibotentan or placebo therapy. Following disease progression, patients may continue on randomised study treatment unless or until another discontinuation criterion is met. Further chemotherapy may also be administered in addition to study treatment at the investigator's discretion after objective progression if the patient is considered likely to derive benefit; though it should be noted that experience with zibotentan in combination with chemotherapy is limited at the time of initiation of this study.

The primary analysis will be performed when approximately 508 deaths have occurred. Based on a recruitment period of 26 months and a median overall survival for the docetaxel group of 19 months, it is estimated that 508 deaths will occur approximately 38 months after the first patient entered the study. A follow-up survival analysis will occur approximately 1 year after the primary survival analysis. If the primary analysis does not demonstrate a statistically significant effect in overall survival the follow-up survival analysis will not take place.

Patients will attend study visits and have assessments performed according to the schedule detailed in the Study Plan, Table 1. Study visits will be aligned with the docetaxel administration while patients are receiving docetaxel. If docetaxel treatment is deferred for any reason such as toxicity then the visit schedule should be re-aligned with the change in docetaxel schedule. Bone scintigraphy and tumour assessment by CT/MRI should be performed at entry, at 24 weeks post study entry and 48 weeks post study entry to assess for progression and tumour size, irrespective of whether patients remain on trial therapy or not. Patients may also undergo additional bone scans and/or CT/MRI scans if considered clinically indicated by the Investigator.

As per the Study Flow Chart (Figure 1) and Study Plan (Table 1), patients who discontinue docetaxel before completion of 10 cycles but continue zibotentan or placebo should be assessed every 4 weeks for the first 24 weeks and thereafter every 12 weeks. Patients who discontinue zibotentan or placebo should be assessed, 28 days post discontinuation of study therapy and thereafter every 12 weeks during the survival follow-up. In all cases tumour assessment by bone scintigraphy and CT/MRI should still be performed at 24 and 48 weeks. Additional visits may be performed as clinically indicated.

Following the primary analysis data cut-off, data collection will reduce to AE, SAEs, drug accountability, subsequent cancer therapies and survival status as per the study plan (Table 1).

Following the primary analysis AstraZeneca will inform Investigators of the study results and, if there is appropriate approval of Protocol Amendment 2, the medication allocation of patients at their centre. In the absence of any relevant safety concerns, patients who were receiving blinded zibotentan may either choose to continue receiving zibotentan via open label supplies or discontinue from treatment. Patients who were randomised to placebo will discontinue from study treatment and will not be offered open label zibotentan. These patients should be managed according to local clinical practice.

If the primary analysis demonstrates a statistically significant effect in overall survival the study will continue to the follow-up survival analysis. All patients should be followed for survival until the data cut-off which will take place approximately 12 months after the primary analysis data cut-off. After this second data cut-off data collection will reduce to SAE and drug accountability data for patients that continue to derive benefit from open label zibotentan. The study will close for all patients that are not receiving open label zibotentan.

If the primary analysis does not demonstrate a statistically significant effect in overall survival the follow-up survival analysis will not take place. However, AstraZeneca will supply open label zibotentan to patients that are deriving clinical benefit. Data collection will reduce to SAE and drug accountability for patients that receive open

label zibotentan. The study will close following the primary analysis to all patients that are not receiving open label zibotentan.

Tissue, serum biomarker samples, plasma biomarker samples and genetic samples (from consenting patients only) will be obtained and stored for long-term experimental purposes.

Adverse events will be collected throughout the study. There will be an Independent Data Monitoring Committee (IDMC) responsible for the review of safety data on an ongoing basis.

The overall study design is depicted in Figure 1.

Figure 1. Study flow chart

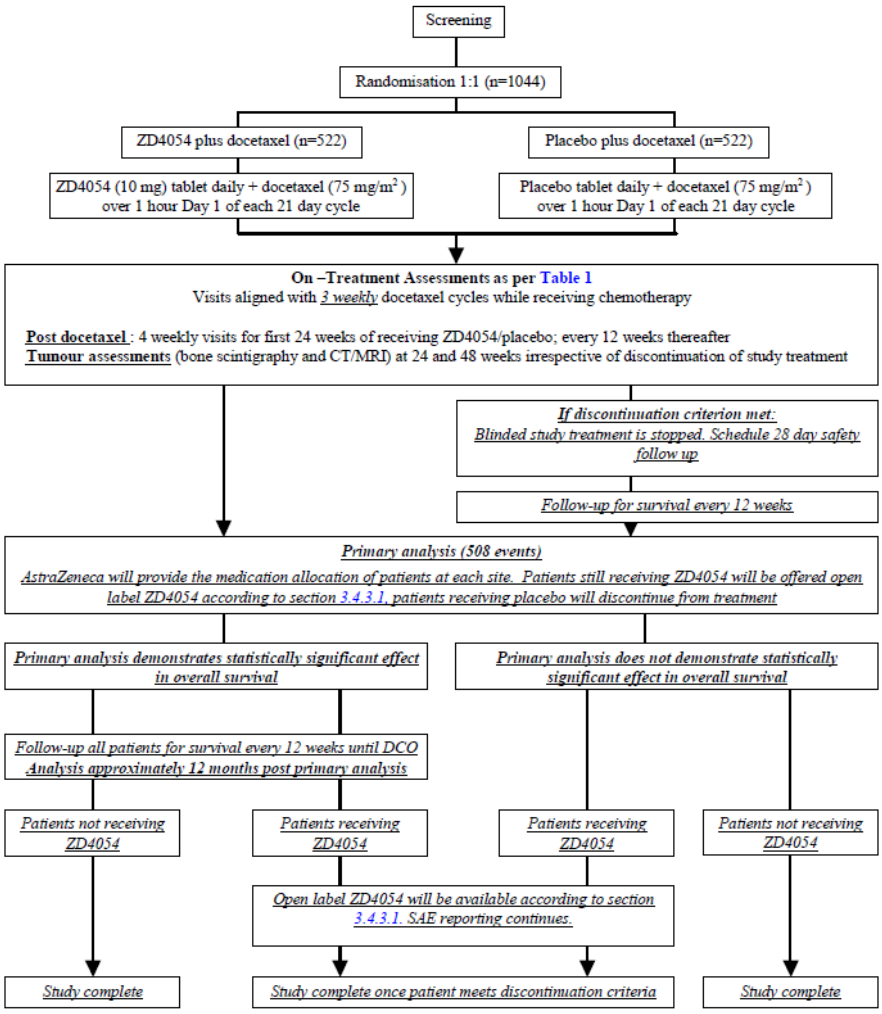

Table 1. Study plan

Cycle	Screen	1			2			3-9	10	Additional cycles of docetaxel (ZD4054/ placebo continues)	Post docetaxel follow-up for patients remaining on ZD4054/ placebo	Discontinuation of ZD4054/ placebo [a]	28-day safety follow-up	Off-treatment follow-up for survival and progression up to primary analysis data cut-off	12 month Survival follow-up after primary analysis data cut-off
		Baseline/ Randomisation			3- weekly chemotherapy cycle			3- weekly chemotherapy cycle			4-weekly then every 12 weeks after 24 weeks			Every 12 weeks [b,c]	Every 12 weeks [b,c]
Day	-28 to -1	1	8	15	22/1	8	15	22/1	22/1	1					
Visit [d]	1	2	3	4	5	6	7	8-14	15	16, 17 etc	100, 101, etc	200	201	300, 301, etc	
Informed consent	X [e]														
Inclusion/exclusion criteria	X	X													
Medical history	X														
Physical examination	X				X			X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECG [f]	X				X							X			
Adverse events [g]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Clinical chemistry/ haematology	X [h]	X	X [i]	X [i]	X	X [i]	X [i]	X	X	X	X	X	X		
BNP [j]		X			X			X	X	X	X	X	X		
Urinalysis	X	X			X			X	X	X	X	X	X		
Prostate specific antigen (PSA) [k]		X			X			X	X	X	X	X			
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X [l]	X [l]	
Cancer therapies [v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication dispensing [m]		X			X			X	X	X	X				X [n]
Bone scintigraphy [o]	X								at 24 and 48 weeks						
Tumour assessment (by CT/MRI) [o]	X								at 24 and 48 weeks						
Brief Pain Inventory [p]	X	X						X	X	X	X	X	X	X [q]	
EQ-5D (Health Status) [p]	X	X						X	X	X	X	X	X	X [r]	
FACT-P [p]	X	X						X	X	X	X	X	X	X [r]	

Cycle	Screen	1			2			3-9	10	Additional cycles of docetaxel (ZD4054/ placebo continues)	Post docetaxel follow-up for patients remaining on ZD4054/ placebo	Discontinuation of ZD4054/ placebo [a]	28-day safety follow-up	Off-treatment follow-up for survival and progression up to primary analysis data cut-off	12 month Survival follow-up after primary analysis data cut-off
		Baseline/ Randomisation			3- weekly chemotherapy cycle			3- weekly chemotherapy cycle			4-weekly then every 12 weeks after 24 weeks			Every 12 weeks [b,c]	Every 12 weeks [b,c]
Day	-28 to -1	1	8	15	22/1	8	15	22/1	22/1	1					
Visit [d]	1	2	3	4	5	6	7	8-14	15	16, 17 etc	100, 101, etc	200	201	300, 301, etc	
Exploratory biomarker serum sample		X							X			X			
Exploratory cell death biomarker plasma sample [g]		X	X	X	X	X	X								
Genetic blood sample (optional) [f]		X													
Survival											X			X	X

a Discontinuation procedures should be completed as soon as possible once a decision is made to discontinue study treatment (up to primary analysis data cut-off only)

b These visits are to occur 12 weeks from previous visit date in order to maintain the 12 week intervals needed for survival analysis

c Telephone contact permissible for these visits (there may be additional telephone contact calls for survival data close to data cut-off for each analysis and any additional data cut-off points)

d Visits must occur within +/- 3 days of the scheduled date (or rescheduled date if there is a delay to docetaxel dosing) for the 3 or 4 weekly visits and +/- 2 weeks of the scheduled date for the 12 weekly visits

e Informed consent is to be obtained within 6 weeks before randomisation

f 12-Lead ECGs (2 identical copies at each time point) obtained. Additional ECGs may be collected as clinically indicated

g During the additional 12 month follow-up for survival, AE's and SAE's should still be collected. Any supportive laboratory data, ECG or vital signs should be reported as comments in the eCRF because these assessments are no longer recorded routinely in the study. After final data cut-off for follow up survival analysis, patients continuing on study treatment will be followed for SAEs only.

h Clinical chemistry and haematology to establish eligibility are to be performed a maximum of 4 weeks prior to randomisation by the central laboratory

i Weekly clinical chemistry and haematology assessments are recommended but not mandatory, however these assessments must, at minimum, be performed prior to every docetaxel administration.

j The utility of BNP data will be reviewed and if not found to be predictive of development of cardiac failure it will cease to be performed

k PSA assessments will be from the central laboratory. PSA assessment to be performed a maximum of 4 weeks prior to randomisation

l Once the patient has discontinued blinded study treatment, only the first opiate usage (initiation of strong opiate, or increase from baseline of at least 25%, for minimum 1 week) for symptoms of metastatic prostate cancer is required to be captured in the opioid medication module.

m Docetaxel IV and zibotentan/placebo oral are both started at randomisation (visit 2). Zibotentan/placebo will be administered as once daily tablet. Docetaxel will be administered in combination with dexamethasone and prednisone/prednisolone

n A bone scan to confirm eligibility is to be performed a maximum of 6 weeks prior to randomisation, thereafter at 24 and 48 weeks post study entry and as clinically indicated. The scan must occur within +/- 2 weeks of the scheduled date.

o Tumour assessment by CT/MRI is to be performed a maximum of 4 weeks prior to randomisation, thereafter at 24 and 48 weeks post study entry and as clinically indicated . CT or MRI scans performed will be expected to cover pelvis and abdomen. Additional regions (eg chest) should be included where clinically indicated for soft tissue lesions at baseline and follow-up (eg pulmonary metastases). The scan must occur within +/- 2 weeks of the scheduled date. Additional scans may be performed for new or worsening symptoms (eg, brain MRI)

p Once the patient is in the off-treatment follow-up phase, EQ-5D and FACT-P questionnaires are optional every 12 weeks. Questionnaires should be completed before patient receives docetaxel (even delayed) and before given the results of their tumour assessment

q BPI questionnaire is to be completed until patient reported pain progression only

r If the survival visit is conducted by telephone and the patient is confirmed to be alive, the optional QoL questionnaires can be completed by mail.

s Pre-dose and 8, 15, 22 days for first 2 cycles only

t If sample not drawn at visit 2, sample can be taken at any visit until last study visit

u Drug dispensing after the primary analysis will be open label zibotentan only. Drug accountability of blinded IP will be collected on the WBDC system, but accountability of open label zibotentan will be collected on paper forms until the patient discontinues from treatment.

v All treatments for cancer including radiotherapy and surgical procedures due to patient's metastatic disease are recorded throughout the study for all patients until follow-up survival analysis

3. DOSE MODIFICATION

3.1 Management of toxicity

Dose interruptions may be used to manage any zibotentan/placebo-related toxicity, dose reductions are not possible. Docetaxel and associated steroid therapy doses and frequency of administration may be adjusted to manage toxicity.

To protect patient safety, if the patient has a grade 3 or 4 non-haematological or grade 4 haematological toxicity attributable to zibotentan/placebo, consideration must be given to withdrawal of zibotentan/placebo. Patients must have recovered to grade 2 or below before zibotentan/placebo is next administered.

Dose interruptions

Zibotentan may be stopped for up to 2 weeks without consultation with the Study Team Physician. If a dose delay is greater than 2 weeks, or if there have been greater than 2 dose delays, approval from the Study Team Physician must be obtained prior to restarting zibotentan/placebo. In the case of CTCAE Grade 3 or 4 cardiac failure, study treatment must not be restarted unless the case has been discussed with the Study Team Physician, and agreement made for the study medication to restart.

Interruptions in dosing will be recorded on the eCRF.

At the investigator's discretion, patients may continue docetaxel if zibotentan or placebo have been discontinued and will continue to be followed up for progression and survival.

Management of docetaxel related toxicity

Standard practise and local prescribing information should be followed to manage docetaxel related toxicity; in particular blood count, liver function tests and other aspects of safety should be carefully monitored to ensure patients remain suitable to receive docetaxel.

Treatment for headache

Any patient experiencing headache should be strongly encouraged to take appropriate analgesia eg, paracetamol/acetaminophen 1 g (unless otherwise contraindicated), as soon as the headache is experienced. If the headache continues to worsen despite the administration of full dose simple analgesia such as paracetamol/acetaminophen, then the choice of further treatment for the headaches is at the discretion of the investigator using an approved treatment within the recommendations for use as described by the product label. Patients with ongoing headaches should be advised to take appropriate analgesics. Concomitant medication and adverse event information must be reported on the appropriate eCRF.

Treatment for rhinitis/nasal congestion

Any patient experiencing rhinitis/nasal congestion may be treated with over-the-counter decongestants or antihistamines. Concomitant medication and adverse event information must be reported on the appropriate eCRF.

Treatment for peripheral oedema or cardiac failure

Any patient experiencing peripheral oedema or cardiac failure may be treated with a diuretic such as frusemide and/or other appropriate medication. If cardiac failure develops or there is suspicion of cardiac failure then cardiovascular assessment should be performed. Concomitant medication and adverse event information must be reported on the appropriate eCRF.

Other treatment

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the eCRF.

4. MEASUREMENT OF TREATMENT EFFECT AND METHODS OF MEASUREMENT

Before administration of the Investigational Product, patients will be assessed to ensure that eligibility criteria are met. Any patient not meeting the criteria must not be entered into the study and must be documented as a screen failure. The Investigator must ensure that all entry criteria are met before the patient commences treatment.

4.1 Primary variable

The primary outcome variable is overall survival, where overall survival is defined as time to death (from randomisation) from any cause.

4.2 Screening and demographic measurements

The data listed below will be collected:

- Inclusion/exclusion criteria
- Patient demography – date of birth, sex, race, ethnic group
- Significant medical and surgical history
- Details of previous cancer treatment
- Full physical examination
- Vital signs – HR, BP, weight and height
- WHO performance status
- Clinical chemistry, BNP, haematology and urinalysis
- Baseline PSA
- Bone scan
- CT/MRI
- 12-Lead ECG
- Concurrent illnesses and therapies at time of entry to the study
- BPI
- FACT-P

4.3 Efficacy and pharmacodynamic objectives and variables

Table 2 shows how efficacy and pharmacodynamic variables relate to efficacy objectives.

Table 2

Objective	**Variable(s)**
Primary To determine the effect of zibotentan in combination with docetaxel on overall survival compared with docetaxel	Assessment of overall survival, defined as time to death (from randomisation) from any cause
Secondary To assess the effect of zibotentan in combination with docetaxel on progression free survival compared with docetaxel	Clinical progression is defined as one of the following: Four or more new bony lesions confirmed by either bone scan, CT scan or MRI (In the event that bone scans cannot be performed due to a Technetium 99(Tc-99) radioisotope shortage, Increased pain Skeletal Related Event Appearance of new malignant soft tissue disease or objective progression of malignant soft-tissue disease assessed according to modified RECIST criteria Death from any cause in absence of progression
To assess the effect of zibotentan in combination with docetaxel on skeletal related events compared with docetaxel	Skeletal related events, defined as: Pathologic fracture Vertebral compression fracture not related to trauma Prophylactic surgery or radiation for impending fracture or spinal cord compression Spinal cord compression
To investigate the effect of zibotentan in combination with docetaxel on time to prostate-specific antigen (PSA) progression compared with docetaxel	PSA progression defined as the time to the first PSA value >50% higher compared with baseline, seen in at least 2 consecutive PSA values

Objective	Variable(s)
To assess the effect of zibotentan in combination with docetaxel on time to pain progression compared with docetaxel	Time to pain progression, defined as significantly increased pain due to metastasis, defined as: The initiation of opiate medication or an increase from baseline of analgesic use of at least 25% for a duration of 1 week or more with or without a change in BPI score. (Note that there must be a relationship between the pain and a metastatic site) Pain due to metastasis that has an increase in the level of pain from baseline of at least 2 units (a movement from no/mild to moderate pain or moderate to severe pain) to a minimum score of 5 points in the worst pain item of the Brief Pain Inventory (BPI), with no decrease in analgesic use Pain due to metastasis requiring radionuclide therapy, radiation therapy, surgery or continuous glucocorticoid therapy (which is not part of the standard docetaxel regime)
To assess the effects of zibotentan in combination with docetaxel on pain response compared to docetaxel	Defined as a decrease in worst pain item of the Brief Pain Inventory (BPI) of at least 2 points from baseline in patients who had a BPI score of ≥2 at baseline in the absence of increased analgesic use, OR a decrease from baseline of analgesic use of at least 25% for a duration of 1 week or more without an increase in BPI score
To investigate the effect of zibotentan in combination with docetaxel on PSA response compared to docetaxel	PSA response is defined as a >50 % decrease in serum PSA from baseline on 2 occasions at least 2 weeks apart
Exploratory To assess the effect of zibotentan in combination with docetaxel on change in tumour size	All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions overall, and representative of all involved organs will be identified as target lesions and will be measured at baseline, at 24 and 48 weeks post study entry. Percentage change in tumour size from baseline will be calculated for assessments at 24 and 48 weeks

Overall survival

Methods of assessment

Cause and date of death will be recorded.

Derivation or calculation of outcome variable

Time to death will be calculated from the date of randomisation to date of death from any cause. Patients who have not died or have been lost to follow-up at the time of statistical analysis will be censored at the time they were last known to be alive.

Progression-free survival

Methods of assessment

A clinical progression event is defined as any of:

- Four or more new bone lesions confirmed by either bone scan, CT scan or MRI (In the event that bone scans cannot be performed due to a Technetium 99(Tc-99) radioisotope shortage
- Increased pain
- Skeletal Related Event
- Appearance of new malignant soft tissue disease or objective progression of malignant soft-tissue disease assessed according to modified RECIST criteria
- Death from any cause in absence of progression.

Derivation or calculation of outcome variable

Progression free survival (PFS) will be measured from date of randomisation to the first of any clinical progression event. In the event that the date of progression has been reported in 2 different places as 2 distinct dates, the earlier date will be used. Patients who have not had a clinical progression event at the time of statistical analysis will be censored at the time they were last assessed for clinical progression.

Skeletal related events

Methods of assessment

Skeletal related events are defined as:

- Pathological fracture
- Vertebral compression fracture not related to trauma

- Prophylactic surgery or radiation for impending fracture or spinal cord compression
- Spinal cord compression.

Derivation or calculation of outcome variable

Time to skeletal events will be calculated from the date of randomisation. Patients who have not had a skeletal related event at the time of statistical analysis will be censored at their last available assessment date.

PSA progression

Methods of assessment

Blood samples for PSA analysis will be collected using serum separation gel tubes. Assessments will be performed at Quintiles Laboratories at the time points specified in the Study Plan, Table 1. PSA progression is defined as the time to the first PSA value >50% higher compared with baseline, seen in at least 2 consecutive PSA values.

Derivation or calculation of outcome variable

Time to PSA progression will be calculated from date of randomisation to date of first sample which shows an increase in PSA of at least 50% compared with baseline. Patients who have not had a PSA progression at the time of the analysis will be censored using the last available assessment date.

Time to pain progression

Methods of assessment

Progression is defined as significantly increased pain due to metastasis, defined as:

- the initiation of opiate medication or an increase from baseline of analgesic use of at least 25% for a duration of 1 week or more with or without a change in BPI score. Note that there must be a relationship between the pain and a metastatic site, or
- pain due to metastasis that has an increase in the level of pain from baseline of at least 2 units (a movement from no/mild to moderate pain or moderate to

severe pain) to a minimum score of 5 points in the worst pain item of the Brief Pain Inventory (BPI), with no decrease in analgesic use

- pain due to metastasis requiring radionuclide therapy, surgery or glucocorticoid therapy (which is not part of the chemotherapy regimen).

Note, there must be a relationship between the pain and a metastatic site or pain due to metastasis requiring radionuclide therapy, radiation therapy, surgery or glucocorticoid therapy.

Table 3. Definition of pain level[a]

BPI worst pain item score	Pain level
0	None
1–4	Mild
5–6	Moderate
7–10	Severe

[a] Serlin et al. *Pain* 1995;61:277–84.

Derivation or calculation of outcome variable

Time to pain progression will be assessed from date of randomisation. Patients who have not had a pain progression at the time of the analysis will be censored using the last available assessment date.

Pain response

Methods of assessment

Pain response will be assessed using the BPI.

Derivation or calculation of outcome variable

Pain response will be defined as a decrease in worst pain item of the Brief Pain Inventory (BPI) of at least 2 points from baseline in patients who had a BPI score of ≥2 at baseline in the absence of increased analgesic use. OR a decrease from baseline of analgesic use of at least 25% for a duration of 1 week or more without an increase in BPI score.

PSA response

Methods of assessment

Blood samples for PSA analysis will be collected using serum separation gel tubes. Assessments will be performed at Quintiles Laboratories at the time points specified in the Study Plan, Table 1.

Derivation or calculation of outcome variable

PSA response is defined as >50% decrease in serum PSA from baseline on 2 occasions at least 2 weeks apart.

Bone lesions (bone scintigraphy)

Bone scintigraphy (bone scans) will be performed at the time points specified in the Study Plan, Table 1, with confirmatory CT scan or MRI, where there are ≤3 lesions. Bone scintigraphy may also be performed when clinically indicated.

Methods of assessment

Bone scans must be performed locally in accordance with any local protocol, and will be reviewed by the Investigator.

In the event that bone scan is not possible due to a Technetium 99 (Tc-99) shortage, individual patients will be allowed to use an alternate form of imaging. The alternative imaging modality must be approved by the AZ study physician prior to scanning and randomisation. The imaging modality used should remain consistent for that patient throughout the course of the study.

Ongoing patients who had a Tc-99 bone scan at baseline should continue to be assessed using this modality. If supplies of Tc-99 are so limited that bone scan is not possible, the AZ study physician must be contacted so an acceptable alternate modality can be assigned.

Alternate imaging modalities can only be used when pre-approved by the AZ study physician on a case by case basis.

The Web Based Data Capture (WBDC) system will collect information on whether a bone scan has been performed, the date of the bone scan and outcome data.

Derivation or calculation of outcome variable
The number of metastatic bone lesions at baseline, 24 and 48 weeks will be read locally and recorded.

Objective progression of malignant soft-tissue disease (RECIST) and change in tumour size
Methods of assessment
CT or MRI of the pelvis and abdomen is to be performed at the time points specified in the Study Plan, Table 1, with additional CT or MRI performed as clinically indicated (eg, chest CT for pulmonary metastases) at baseline and subsequent follow-up visits. Lesions must be assessed using the same method and technique on each occasion.

Modified RECIST criteria will be used to perform the objective tumour assessments and the scans will also determine a patient's change in tumour size (Appendix).

Baseline radiological tumour assessments should be performed no more than 4 weeks before the start of study treatment and at all time points defined in the Study Plan (Table 1). Previously irradiated lesions will not be considered measurable.

All measurable lesions, up to a maximum of 5 lesions per organ and 10 lesions overall, and representative of all involved organs will be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline. The baseline sum will be used as reference to further characterize the objective tumour response of the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these

lesions should be followed at each tumour assessment and recorded as “present”, “absent”, or “present with progression”. In addition the Investigator will also provide an overall assessment of the non target lesions at each visit as “complete response”, “incomplete response/stable disease” or “progressive disease” (Appendix).

Lesions must be assessed using the same method and technique on each occasion. Lesions will be recorded on the eCRF in the same order as they were recorded at screening. Details of any new lesions will also be collected.

For patients who have target lesions that have been subjected to local/regional radiotherapy for symptom control (palliative radiotherapy) during the course of the study the following rules will be applied. The patient will not be allowed a complete response or partial response following radiotherapy. The patient will be assessed for evidence of disease progression. If there is no evidence of disease progression the patient can be assigned a response of stable disease. A patient is 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 (see Appendix). Progression of target lesions is defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as references the smallest sum of longest diameter recorded. Death will be regarded as a progression event in those patients who die before documented disease progression. Unequivocal malignant disease identified on additional anatomical imaging eg, CT or MRI or bone scan (confirmed by x-ray if necessary), prompted by symptoms is considered disease progression and should be recorded as new lesions. If the Investigator is in doubt as to whether progression has occurred, particularly with respect to non-target lesions and the appearance of a new lesion then it is advisable to pursue treatment for 4 additional weeks (and then repeat the assessment to confirm progression).

Patients who discontinue study medication prior to objective disease progression assessment will continue to have objective tumour assessments at 24 and 48 weeks unless the patient withdraws consent.

Derivation or calculation of outcome variable

Tumour size is the sum of the longest dimensions of the target lesions. The change in tumour size will be assessed using the ratio of each follow-up visit tumour size over the baseline tumour size (baseline sum LD) for each patient. More details on target lesions and measurement can be found in the Appendix. Non-measurable lesions will be given an artificial value of 1.5 cm, which is less than the pre-defined limit of 2 cm. This would allow for patients with non-measurable lesions at baseline to be included in the assessment. If the lesions remain non-measurable then the ratio will be 1.

5. REASONS FOR EARLY CESSATION OF TREATMENT THERAPY

5.1 Discontinuation of patients from treatment or assessments

Termination from study

Patients will be considered to have terminated the study only in the event of death, loss to follow-up, or withdrawal of informed consent. No data will be collected from patient confidential medical records after the date of withdrawal of informed consent. Voluntary discontinuation of the study treatment does not result in study termination. The patient should still be followed for progression (where applicable) and survival, unless they withdraw consent.

Patients may withdraw consent at any time without prejudice to further treatment.

Procedures for termination

Patients who withdraw consent from all study assessments should always be asked the reason(s) for their withdrawal of consent. If the reason for withdrawal of consent is that the patient is unable to attend the study visits, then the patient should be informed that survival follow-up visits could be conducted by telephone.

If the patient is unwilling for any follow-up information to be collected (including via telephone follow-up), the Investigator should record the date and reason for termination. The Investigator should also inform ICON (or other approved AZ representative) immediately of the patient's termination from the study.

If possible, the patient should be seen and assessed by the Investigator. They should be asked about the presence of any AEs if terminating the study within 28 days of receiving the last dose of study drug. The patient should return all investigational products.

Criteria for discontinuation of study treatment

Patients may be discontinued from study treatment at any time. Following discontinuation of study treatment, all patients will be followed for progression (where progression has not already been confirmed) and survival, until death or termination from the study. Specific reasons for discontinuing a patient from study treatment are:

- Voluntary discontinuation by the patient who is at any time free to discontinue study treatment, without prejudice to further treatment. Patients who discontinue study treatment should be followed for progression and survival, until a criterion is met for study termination
- Safety reasons as judged by the Investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca
- Incorrect randomisation. Patients who are found not to meet the required inclusion/exclusion criteria for the study must be discussed with the study team physician or delegate. Each case will be reviewed individually and a decision made as to whether the patients must be discontinued.

Discontinuation of blinded study therapy is not required at disease progression. The protocol allows the co-administration of additional prostate cancer therapies as outlined. The Investigator can discuss with the study team physician before making a judgement.

Following the primary analysis and subsequent unblinding of patients, all patients who were randomised to placebo will discontinue from study treatment and will not be offered open label zibotentan. Discontinuation of open label zibotentan should be managed according to the criteria specified in this section.

Procedures for discontinuation of study treatment

Patients who discontinue study treatment should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. The procedures for progression (where applicable) and survival follow-up should be explained. If a patient discontinues study treatment prior to disease progression, then they should continue to be followed for progression as per the protocol schedule. Following progression, the patient should be followed for survival unless they withdraw consent. The patient should return all investigational products.

Where possible, the Principal Investigator/Sub-investigator should perform all relevant procedures for the discontinuation visit (see Table 1). In addition, they will record the date and reason for discontinuation. They will also immediately inform

ICON (or other approved AZ representative) of the discontinuation of study treatment. Duration of post-treatment follow-up. Any serious adverse events should be communicated to ICON within the usual timelines.

After discontinuation of study treatment, all on-going study-related toxicities and SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

All patients who have any CTC grade 3 or 4 laboratory values at the time of discontinuation should have further tests performed and the results recorded on the appropriate eCRF until the laboratory values have returned to CTC grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

The date of death will be recorded until the final analysis of the study (estimated to be 1 year after approximately 508 deaths have occurred), then the patients will no longer be followed for survival.

AEs/SAEs will be collected post data cut off for those patients still on treatment. After the final efficacy analysis of the study, those patients who are considered, by the investigator, to be deriving clinical benefit will be allowed to continue to receive study treatment where local regulations allow and will be assessed for safety until they are no longer deriving benefit. No additional follow-up for survival will be conducted in this instance.

6. OBJECTIVES AND STATISTICS

6.1 Primary objective

The primary objective of this study is to determine the effect of zibotentan in combination with docetaxel on overall survival compared with docetaxel; overall survival is defined as time to death (from randomisation) from any cause.

6.2 Secondary objectives

The secondary objectives of the study are:

1. To assess the effect of zibotentan in combination with docetaxel on progression free survival compared with docetaxel. Clinical progression of disease is defined as any one of:

- Four or more new bone lesions confirmed by either bone scan, CT scan or MRI (In the event that bone scans cannot be performed due to a Technetium 99(Tc-99) radioisotope shortage.)
- Increased pain, defined as one of the following:
  - The initiation of opiate medication or an increase from baseline of analgesic use of at least 25% for a duration of 1 week or more with or without a change in BPI score. Note that there must be a relationship between the pain and a metastatic site
  - Pain due to metastasis that has an increase in the level of pain from baseline of at least 2 units (a movement from no/mild to moderate pain or moderate to severe pain) to a minimum score of 5 points in the worst pain item of the Brief Pain Inventory (BPI), with no decrease in analgesic use
  - Pain due to metastasis requiring radionuclide therapy, radiation therapy, surgery or continuous glucocorticoid therapy (which is not part of the standard docetaxel regime)
- Skeletal Related Event
  - Pathologic fracture
  - Vertebral compression fracture not related to trauma
  - Prophylactic surgery or radiation for impending fracture or spinal cord compression
  - Spinal cord compression
- Appearance of new malignant soft tissue disease or objective progression of existing malignant soft-tissue disease assessed according to modified RECIST criteria (including development of visceral or brain metastasis, malignant pleural effusion or malignant ascites)
- Death from any cause in the absence of progression.

2. To assess the safety and tolerability profile of zibotentan in combination with docetaxel compared with docetaxel

- Adverse events

- Vital signs
- Laboratory data
- ECGs
- Physical Exam.

3. To assess the effect of zibotentan in combination with docetaxel on skeletal-related events compared with docetaxel, defined as:

- Pathologic fracture
- Vertebral compression fracture not related to trauma
- Prophylactic surgery or radiation for impending fracture or spinal cord compression
- Spinal cord compression.

4. To investigate the effect of zibotentan in combination with docetaxel on time to PSA progression compared to docetaxel, where time to progression is defined as the time to the first PSA value >50% higher compared with baseline, seen in at least 2 consecutive PSA values

5. To assess the effects of zibotentan in combination with docetaxel on time to pain progression compared with docetaxel, where pain progression is defined as one or more of:

- The initiation of opiate medication or an increase from baseline of analgesic use of at least 25% for a duration of 1 week or more with or without a change in BPI score. Note that there must be a relationship between the pain and a metastatic site
- Pain due to metastasis that has an increase in the level of pain from baseline of at least 2 units (a movement from no/mild to moderate pain or moderate to severe pain) to a minimum score of 5 points in the worst pain item of the Brief Pain Inventory (BPI), with no decrease in analgesic use
- Pain due to metastasis requiring radionuclide therapy, radiation therapy, surgery or continuous glucocorticoid therapy (which is not part of the standard docetaxel regime).

6. To assess the effects of zibotentan in combination with docetaxel on pain response compared to docetaxel defined as a decrease in worst pain item of the Brief Pain Inventory (BPI) of at least 2 points from baseline in patients who had a BPI score of ≥2 at baseline in the absence of increased analgesic use OR a decrease from baseline of analgesic use of at least 25% for a duration of 1 week or more without an increase in BPI score

7. To assess the effect of zibotentan in combination with docetaxel on Health-related Quality of Life (HRQoL) compared with docetaxel, as measured by the Functional Well Being (FWB) domain of the Functional Assessment of Cancer Therapy for Prostate Cancer (FACT-P) and the Total FACT-P score

8. To investigate the effect of zibotentan in combination with docetaxel on PSA response compared to docetaxel, defined as >50 % decrease in serum PSA from baseline on 2 occasions at least 2 weeks apart.

6.3 Description of outcome variables in relation to objectives and hypotheses

Primary objectives - efficacy and pharmacodynamic measurement variables

The primary objective is to determine the effect of zibotentan in combination with docetaxel on overall survival compared with docetaxel.

Secondary objectives – efficacy and pharmacodynamic measurement variables

The secondary objectives of the study are to investigate the effect of zibotentan in combination with docetaxel on the following:

- Progression free survival in metastatic hormone resistant prostate cancer, where clinical progression is defined as one of following:
  - Four or more new bone lesions confirmed by either bone scan, CT scan or MRI (In the event that bone scans cannot be performed due to a Technetium 99(Tc-99) radioisotope shortage.)
  - Increased pain
  - Skeletal-related event
  - Objective progression
  - Death from any cause in absence of progression

- Skeletal related event
- Time to PSA progression, defined as the time to the first PSA value >50% higher compared with baseline, seen in at least 2 consecutive PSA values
- Pain Progression
- Pain Response
- Health related Quality of Life measured using FACT-P
- PSA response.

Secondary objective - safety measurement variables

- Tolerability and safety
- Adverse events
- Laboratory data
- ECGs
- Vital signs.

Exploratory objectives – efficacy and pharmacodynamic measurement variables

The exploratory objectives of the study are to investigate the effect of zibotentan in combination with docetaxel on the following:

- Change in tumour size

Exploratory objectives – BNP measurements

BNP levels will be summarised by timepoint and treatment groups. The relationship between BNP and development of cardiac adverse events will be explored.

Secondary and exploratory objective – patient reported outcomes

The patient reported outcome questionnaires that will be summarised are the FACT-P and BPI. Data will be summarised by treatment group, and changes in different domains and scales will be correlated with clinical changes. Compliance in completion of the questionnaires for each treatment group will be summarised at each time point. Change in pain level over time will be assessed according to the BPI assessment scale

6.4 Description of analysis sets

Three patient analysis sets will be defined in this study:

Intention to Treat (ITT) set

The ITT set will be defined as all patients randomised.

The ITT set will be the primary set used for the efficacy analyses.

Patients in the ITT set will be analysed according to the treatment they were randomised to rather than the treatment they actually received.

Safety set

The safety set will include patients who received at least 1 dose of study medication. Patients in the safety set will be analysed according to the treatment they received. This will be the primary set used for the safety analyses.

Quality of life set

The quality of life set will be defined as a subset of the ITT set but including only those patients who have valid baseline quality of life data and at least one evaluable follow-up visit data. This analysis set will be the primary set analysed for all quality of life endpoints.

6.5 Method of statistical analysis

Baseline data

Summaries of demographic and other baseline characteristics will be produced for the ITT population. Summaries will be produced for all patients in each population.

Listings of demographic and other baseline characteristics will be produced, including surgical history, medical history which will be summarised by System Organ Class and High Level term using the Medical Dictionary for Regulatory Activities (MedDRA).

Compliance

Compliance and exposure of daily usage of investigational product will be listed and summarised.

Primary variable

Overall survival

Time to death will be analysed using a log-rank test. Death is from any cause. Patients who have not died at the time of the analysis will be censored using the last available assessment date.

The primary analysis will include a factor for treatment. The analysis results will be presented as hazard ratios. A hazard ratio less than 1 would indicate that, on average, overall survival is longer on active treatment than on placebo. The hazard

ratios will be presented with 95% confidence intervals and p-values. Kaplan-Meier plots of the times to death will be produced. Additional analyses, plots and summaries by covariate may be presented if appropriate.

Secondary variables

The interpretation of the analyses will consider the number of assessments being undertaken.

Progression Free Survival

The number of progression events occurring in each period will be compared between the treatment groups using the interval censoring method of Whitehead, with the intervals defined by the scheduled scans at 24 and 48 weeks; i.e. fitting a logistic regression model with a complementary log-log function and including a factor for treatment (Whitehead. Statistics in Medicine 1989;8:1439–1454). The relative risk of a progression event for the combination therapy compared to docetaxel alone will be reported together with the corresponding 95% confidence interval and p-value. Kaplan-Meier plots of times to progression free survival will be produced.

Skeletal related events

Time to skeletal events will be analysed using a log-rank test. Patients who do not have skeletal events at the time of the analysis will be censored using the last available assessment date.

The primary analysis will include a factor for treatment. The analysis results will be presented as hazard ratios. A hazard ratio less than 1 would indicate that, on average, times to skeletal events are longer on active treatment than on placebo. The hazard ratios will be presented with 95% confidence intervals and p-values. Kaplan-Meier plots of the times to skeletal event will be produced. Additional plots and summaries by covariate may be presented if appropriate.

Time to PSA progression will be analysed using a log-rank test. Patients who have not had a PSA progression at the time of the analysis will be censored using the last available assessment date.

The analysis will be presented as hazard ratios. A hazard ratio less than 1 would indicate that, on average, times to PSA progression are longer on active treatment than on placebo. The hazard ratios will be presented with 95% confidence intervals and p-values. Kaplan-Meier plots of the times to PSA progression will be presented.

Pain progression

Time to pain progression will be analysed using a log-rank test. Patients who have not had a pain progression at the time of the analysis will be censored using the last available assessment date.

The primary model will include a term for treatment.

The analysis will be presented as hazard ratios. A hazard ratio less than 1 would indicate that, on average, times to pain progression are longer on active treatment than on placebo. The hazard ratios will be presented with 95% confidence intervals and p-values. Kaplan-Meier plots of the times to pain progression will be presented.

Brief Pain Inventory (BPI)

Each patient's BPI assessment at baseline and all time points will be listed individually. The raw data, and the change from baseline at each time point will be presented for each treatment group using standard summary statistics.

Pain response

Time to pain response will be analysed using a log-rank test. Patients who do not have a response to pain at the time of the analysis will be censored using the last available assessment date.

The primary analysis will include a factor for treatment. The analysis results will be presented as hazard ratios. A hazard ratio greater than 1 would indicate that, on average, times to pain response are shorter on active treatment than on placebo. The hazard ratios will be presented with 95% confidence intervals and p-values. Kaplan-Meier plots of the times to pain response will be produced. Additional plots and summaries by covariate may be presented if appropriate.

Change in tumour size

The tumour size is the sum of the longest diameters of the target lesions. The change in tumour size will be assessed using the ratio of each follow-up visit tumour size over the baseline tumour size for each patient. These data have been assumed to be log-normally distributed. Data will therefore be log-transformed prior to analysis. Change in size of soft tissue metastases will be analysed by an analysis of covariance (ANCOVA) model including terms for treatment (zibotentan or placebo) as well as a covariate for baseline tumour size. The results of the analysis will be back-transformed and presented in terms of adjusted geometric means (glsmeans) for each treatment together with their 2-sided 90% confidence intervals. An estimate of the treatment effect (ratio of the glsmeans, zibotentan:placebo) will be calculated together with its 2-sided 95% confidence interval and pvalues.

Assumptions will be explored and, if necessary, an appropriate transformation or nonparametric technique will be used to validate the results of the main analysis.

For patients with missing baseline results, the data will be considered missing at randomisation and the patients will be excluded from the analysis. For patients with nonmeasurable disease at baseline, the tumour size is assumed to be 1.5 cm.

The data will summarised graphically using the waterfall plot.

PSA response

Patients will be categorised according to whether or not they experienced a PSA response during the study. For each treatment arm, the percentage of patients with a PSA response will be presented.

A logistic regression model will compare the proportion of patients with PSA response in the treatment groups: the primary analysis will include factors for treatment and centre. The analysis will be repeated with additional covariates. The analysis results will be presented as odds ratios, with 95% confidence intervals and p-values. An odds ratio greater than 1 would indicate that, on average, there are more PSA responses on active treatment than on placebo.

Functional well being and FACT-P total score

- FWB
- FACT-P

The raw data and the change from baseline will be presented for each treatment group for each subscale score.

The number of and percentage of patients who have worsened or improved at each visit will be summarised by treatment. In addition, the overall response will be summarised by treatment.

PSA concentration

The raw data collected at baseline and during the study plus changes and percentage changes from baseline will be presented using standard summary statistics.

Other secondary endpoints will be presented and may be analysed to investigate trends in the data.

Exploratory variables

Safety data

The Safety analysis set will be used as the primary analysis dataset for the reporting of safety data. All safety data will be listed.

Adverse events

The number of patients reporting at least one AE in any system organ class will be presented.

AEs will be summarised by preferred term within each system organ class. For each preferred term, the number and percentage of patients reporting at least one occurrence will be presented. Similar summaries of the number of patients reporting the most frequently reported AEs during the treatment period. Most frequent AEs will be those reported, at preferred term level, in a pre-defined minimum percentage of patients within at least one treatment group; this defined minimum will be set at Blind Review of data before analysis.

AEs will be summarised by causality and CTC grade. All AEs will be listed for all patients. Separate listings of all serious AEs (SAEs), deaths, other significant AEs (OAEs) or discontinuations due to AEs will be presented.

Laboratory variables

Scheduled laboratory results will be used for the summary tables. All recorded laboratory data will be listed.

All continuous laboratory parameters will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline. Categorical laboratory parameters will be summarised by frequency counts and percentages at each visit by treatment group.

All laboratory safety data will be listed, with clinically relevant abnormalities, as defined by the AstraZeneca extended reference ranges explicitly noted on the listings.

ECG

The overall evaluation will be listed and summarised by treatment group.

Vital signs

The vital signs data will be summarised by absolute value at each visit by treatment group. The corresponding changes from baseline will also be presented.

Scheduled vital sign results will be used for the summary tables. All recorded vital sign data will be listed with clinically relevant abnormalities noted on the listings.

Physical examination

Physical examination details will be listed and summarised by treatment group using standard summary statistics.

6.6 Determination of sample size

A total of 1044 patients will be recruited into this study. The primary analysis will be performed when approximately 508 deaths have occurred. Based on a recruitment period of 26 months and a median overall survival for the docetaxel group of 19 months, it is estimated that 508 deaths will occur approximately 38 months after the first patient entered the study. If the true hazard ratio for zibotentan versus placebo is 0.75, then the analysis will have 90% power to demonstrate a statistically significant effect in overall survival at the 5% significance level.

6.7 Data monitoring board

An Independent Data Monitoring Committee (IDMC) will be responsible for safeguarding the interests of study participants, via review of accumulating safety data for this study and the other Phase III zibotentan studies. The IDMC will be composed of therapeutic area experts and statisticians who do not have significant conflicts of interests and therefore, will be neither zibotentan study investigators nor individuals employed by AstraZeneca. The IDMC will review safety data at least every 6-monthly for the first year and thereafter will recommend the intervals for subsequent reviews.

APPENDIX: Objective Tumour Response Criteria (RECIST)

Definition of measurable and non-measurable lesions

Measurable: Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan.

Non-measurable: All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly non-measurable lesions.

Lesions that are considered as truly non-measurable include the following:

- Leptomeningeal disease;
- Ascites;
- Pleural / pericardial effusion;
- Inflammatory breast disease;
- Lymphangitis cutis/pulmonis;
- Abdominal masses that are not confirmed and followed by imaging techniques;
- Cystic lesions.

Note: Lesions previously irradiated will not be considered as measurable lesions.

Methods of measurement

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. All measurements should be recorded in metric notation by use of a ruler, callipers or electronic callipers etc.

Computed tomography (CT) and magnetic resonance imaging (MRI)

Computed tomography (CT) and magnetic resonance imaging (MRI) are the best currently available, and most reproducible methods, for measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm; this specification

applies to the tumours of the chest, abdomen and pelvis, while head and neck tumours and those of the extremities usually require specific protocols.

In this study, CT examinations of the abdomen and pelvis will be used to assess tumour burden at study entry. Further CT/MRI scans will be performed at 24 and 48 weeks and as clinically indicated. Additional regions eg, chest should be included where clinically indicated for soft tissue lesions at baseline and follow-up eg, pulmonary metastases. Any other sites at which new disease is suspected should also be appropriately imaged. CT examination with intravenous (iv) contrast media administration is the preferred method. If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study, then the recommended methods are: CT chest examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT without iv contrast is an option for the chest, abdomen and pelvis examination.

Clinical lesions

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended.

In this study, as CT or MRI examinations are being performed, clinical examination will not be used as part of RECIST assessment for measurable lesions. Clinical examination will however be used to assess non-target and new lesions.

Chest x-ray

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

In this study, chest x-ray assessment will not be used as part of RECIST assessment for measurable lesions, as CT or MRI examinations are being performed, which provide a more precise measurement. Chest radiograph will, however, be used to assess non-target and new lesions.

Ultrasound

Ultrasound should not be used to measure tumour lesions for objective response evaluation. It is however a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

In this study, ultrasound examination will not be used as part of RECIST assessment for measurable lesions as it is not a reproducible method and does not provide an accurate assessment of tumour size. If new or worsening clinical symptoms occur and an ultrasound is performed then new lesions or progression of the existing lesions needs to be confirmed by CT or MRI examination..

Endoscopy and laparoscopy

The utilisation of these techniques for objective tumour evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centres. Therefore, the utilisation of such techniques for objective tumour response should be restricted to validation purposes in reference centres. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

In this study, these methods will not be used as part of the RECIST assessment as they are not validated in the context of tumour assessments. .

Tumour markers

Tumour markers alone cannot be used to assess response. However, if markers are initially above the upper normal limit, they must normalise for a patient to be considered in complete clinical response when all tumour lesions have disappeared.

In this study, tumour markers will not contribute to the response assessment.

Cytology and histology

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours, where known

residual benign tumours can remain). However, this is not an issue in this disease setting and histology/cytology will not be used to differentiate between PR and CR.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to differentiate between response or stable disease. In the absence of negative cytology findings for pleural effusion that worsens or appears, this will be considered to be disease progression due to new lesions or progression of non-target lesions..

Tumour response evaluation

Assessment of overall tumour burden and measurable disease

To assess the response during the study, it is necessary to estimate the overall tumour burden at baseline to which subsequent assessments will be compared. Presence of soft tissue metastatic lesions are not an inclusion criterion for this study, however, a patient will be determined to have progressed if objective progression of visceral or nodal disease, assessed according to modified RECIST criteria (including development of visceral or brain metastasis or malignant pleural effusion), is seen. Patients who discontinue study medication prior to objective disease progression assessment will continue to have objective tumour assessments at 24 and 48 weeks unless the patient withdraws consent.

Documentation of "target" and "non-target" lesions

All measurable lesions up to a maximum of 10 lesions representative of all involved organs (maximum of 5 lesions per organ) should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD.

The longest diameter will be measured and recorded for all target lesions identified at baseline at follow-up assessments and the sum LD calculated.

If a lesion splits into two or more parts, then the sum of the LDs of those parts is recorded.

If two or more lesions merge, then the LD of the combined lesion should be recorded for one of the lesions and zero recorded for the other lesion.

If a lesion becomes too small to measure, then the size below which measurement cannot be accurately obtained should be substituted for the LD and used in the sum LD.

If a lesion cannot be measured accurately due to progression, then the maximum measurable LD should be used in the sum LD and response assessment.

If a lesion cannot be measured accurately due to it being too large, and was measurable previously, then the maximum measurable size should be recorded as the LD and should be used in the sum LD and response assessment.

All other lesions (or sites of disease) should be identified as non-target lesions on CT or MRI and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present”, “absent” or “present with progression.”

Response criteria

Evaluation of target lesions

Table 4. Evaluation of target lesions

Response	Evaluation
Complete Response (CR)	Disappearance of all target lesions.
Partial Response (PR)	At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.
Progressive disease (PD)	At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since treatment started.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Note: The appearance of new lesions only counts towards the overall visit response, not towards the response of target or non-target lesions.

Evaluation of non-target lesions

Table 5. Evaluation of non-target lesions

Response	Evaluation
Complete Response (CR)	Disappearance of all non-target lesions.
Non-Complete Response/stable disease	Persistence of one or more non-target lesion
Progression (PD)	Unequivocal progression of existing non-target lesions.

Note: The appearance of new lesions only counts towards the overall visit response, not towards the response of target or non-target lesions.

Evaluation of Overall response

Best Overall Response

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Best overall response will be derived as part of the study analysis by the sponsor as necessary.

Overall Visit Response

Overall visit response will be derived by the Investigator at site. Overall visit response will be derived from assessment of target, non-target and new soft tissue lesions as part of the analysis for this study.

Table 6. Overall visit response algorithm

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. See text for more details.

Specifications for radiological imaging

The use of standardised protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

CT

CT scans of the thorax, abdomen and pelvis should be contiguous throughout the anatomical region of interest.

The type of CT scanner is important regarding the slice thickness and minimum sized lesion. For spiral (helical) CT scanners, the minimum size of any given lesion at baseline may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. For conventional CT scanners, the minimum sized lesion should be 20 mm using a contiguous slice thickness of 10 mm. For other body parts, where CT scans examination are of different slice thickness eg, neck, which are typically of 5 mm thickness, the minimum sized lesion allowable will be different.

In patients where the abdomen and pelvis have been imaged, oral contrast agents should be given to accentuate the bowel from other soft tissue masses.

Contrast (iv) agents should also be given (unless contraindicated for medical reasons such as allergy) to accentuate vascular structures from adjacent lymph node masses and to help enhance liver and other visceral metastases.

The method of administration of iv contrast agents is variable. It is appropriate to suggest that an adequate volume of a suitable contrast agent should be given such that the metastases are better differentiated; a consistent method should be used on subsequent examinations for any given patient. All window settings should be included, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the target lesions should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included and not selected images of the apparent lesion.

MRI

MRI is a complex issue. MRI is entirely acceptable and capable of providing images in different anatomical planes. It is important therefore that when it is used lesions must be measured in the same anatomical plane using the same imaging sequences on subsequent examinations. MRI scanners vary in the images produced. Wherever possible, the same scanner should be used.

Moreover, many patients with advanced malignancy are in pain, so their ability to remain still for the duration of a scan sequence, in the order of 2 to 5 minutes is limited. Any movement during the scan time leads to motion artifacts, degradation of image quality such that the examination will probably be useless.

For these reasons, CT is at this point in time the imaging modality of choice.

The same imaging modality must be used throughout the study to measure disease. Different imaging techniques have differing sensitivities, so any given lesion may have different dimensions at any given time if measured with different modalities. It is therefore, not acceptable to interchange different modalities throughout this study.

References

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