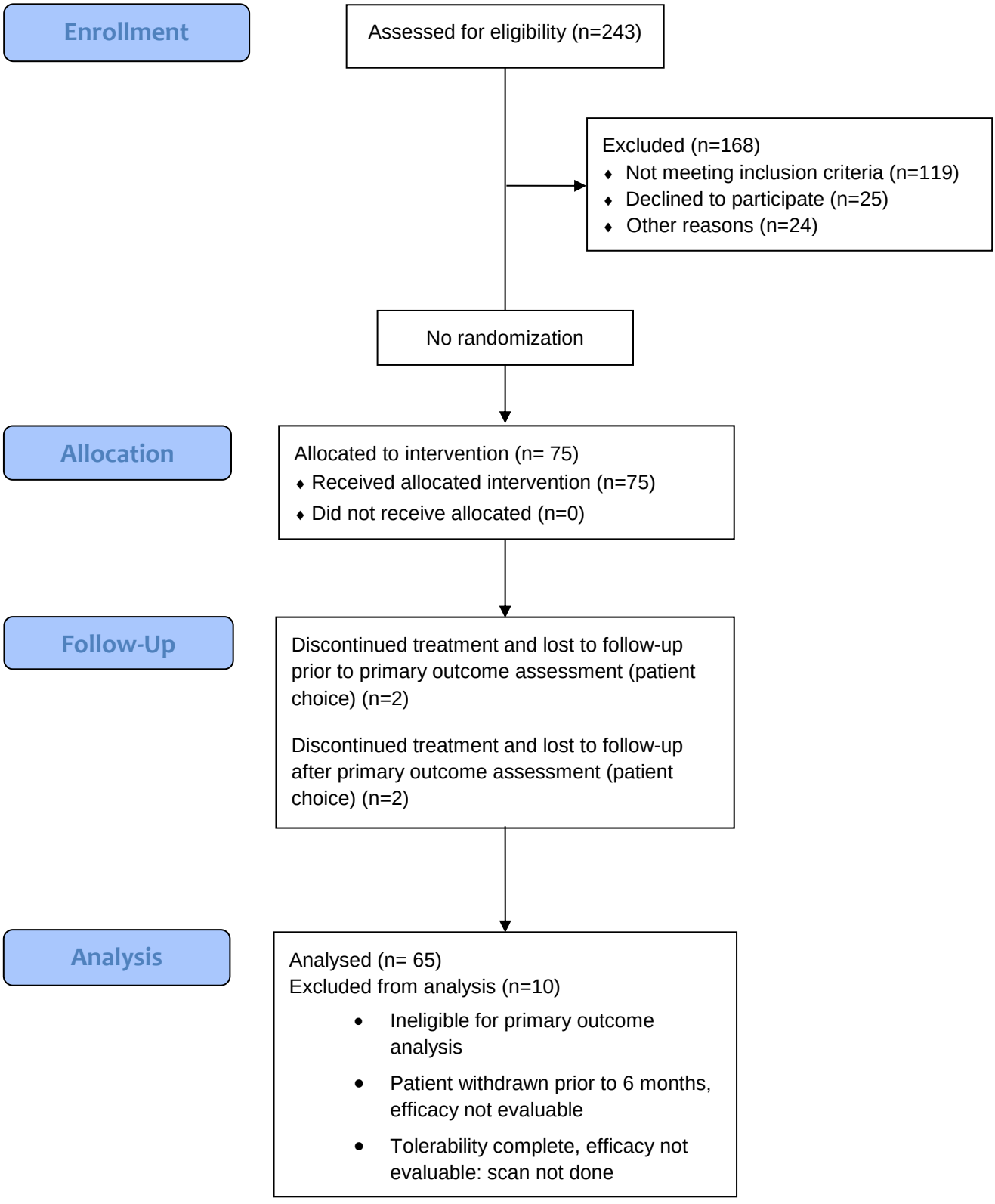
ISRCTN Trial Summary Report

Acronym: PAZO2
Title: A study of pazopanib efficacy and safety in patients with advanced clear cell renal cell carcinoma and ECOG Performance Status 2
Sponsor: University of Birmingham
Sponsor Ref Number: RG 10-177
EudraCT Number: 2011-01211-31
REC Reference Number: 11/EM/0450
Countries with participating centres: United Kingdom
Paediatric regulatory details: The trial is not part of a Paediatric Investigation Plan (PIP)
Details of Investigational Medicinal Product(s): Pazopanib (Votrient)
Details of Non-Investigational Medicinal Product(s): None
Arms: Pazopanib
Analysis Stage: Complete
Start Date: 24-Aug-2012
End of Trial: 30-Jun-2019

Participant Flow Diagram



Baseline Characteristics

Patient demographics:

The following table shows patient demographics collected at baseline:

Years from diagnosis to registration	
N	75
Mean (sd)	2.4 (4.3)
Median	0.3
IQR	0.1, 3.4
Range	0.0, 23.0
Age(Yrs)	
N	75
Mean (sd)	69.3 (9.2)
Median	68.6
IQR	64.6, 76.0
Range	48.2, 87.4
Sex	**N (%)**
Male	54 (72.0)
Female	21 (28.0)
Physical Exam Performed	**N (%)**
Yes	75 (100.0)
Days from physical exam to registration	
N	75
Mean (sd)	4.0 (5.9)
Median	1.0
IQR	0.0, 7.0
Range	-4.0, 30.0

Previous treatments:

The table below provides an overview of all patient's previous treatments.

No patients reported having prior systemic treatment.

Months from surgery to registration	
N	39
Mean (sd)	54.1 (60.9)
Median	39.2
IQR	8.3, 79.4
Range	2.1, 275.9
Surgery Type	**N (%)**
Radical nephrectomy	37 (94.9)
Partial nephrectomy	1 (2.6)
Unknown	1 (2.6)
Tumour Location	
Left Only	16 (41.0)
Right Only	23 (59.0)

Details of the 25 patients who had previous radiotherapy are provided in the table below.

Months from last radiotherapy to registration	
N	25
Mean (sd)	11.7 (45.5)
Median	1.5
IQR	0.7, 2.1
Range	0.5, 229.3

Histopathology:

Histopathology data for all 75 patients is provided in the tables below.

Months from diagnosis to development of metastases	
N	75
Mean (sd)	23.4 (49.2)
Median	0.8
IQR	0.0, 28.1
Range	-2.5, 273.0
Months from metastases to registration	
N	75
Mean (sd)	5.1 (12.6)
Median	2.1
IQR	1.1, 3.6
Range	0.0, 97.5
Metastases	**N (%)**
Bone	7 (9.3)
Bone & Liver	1 (1.3)
Bone & Lung	6 (8.0)
Bone & Other	1 (1.3)
Bone, Liver & Lung	5 (6.7)
Bone, Liver & Other	1 (1.3)
Bone, Liver, Lung & Other	2 (2.7)
Bone, Lung & Other	3 (4.0)
Bone, Lymph & Lung	3 (4.0)
Liver	1 (1.3)
Liver & Lung	1 (1.3)
Liver, Lung & Other	1 (1.3)
Liver, Lymph & Lung	2 (2.7)
Lung	22 (29.3)
Lung & Other	2 (2.7)
Lymph	1 (1.3)
Lymph & Lung	5 (6.7)
Lymph & Other	3 (4.0)
Lymph, Lung & Other	3 (4.0)
Other	5 (6.7)
Clear Cell Component	
No	1 (1.3)
Yes	74 (98.7)

Sarcomatoid	**N (%)**
No	66 (88.0)
Yes	8 (10.7)
Unknown	1 (1.3)
T Stage	
TX	12 (16.0)
T0	5 (6.7)
T1	10 (13.3)
T2	15 (20.0)
T3	9 (12.0)
T3a	10 (13.3)
T3b	3 (4.0)
T4	4 (5.3)
T1a	1 (1.3)
T1b	2 (2.7)
T2a	1 (1.3)
T2b	3 (4.0)
N Stage	
NX	8 (10.7)
N0	41 (54.7)
N1	19 (25.3)
N2	3 (4.0)
Unknown	4 (5.3)
M Stage	
M0	4 (5.3)
M1	69 (92.0)
Unknown	2 (2.7)
Grade	
Grade 2	23 (30.7)
Grade 3	20 (26.7)
Grade 4	17 (22.7)
Grade Unknown	15 (20.0)

Outcome Measures

Primary outcome measures:

Tolerability

The tolerability endpoint is defined as the proportion of patients who have not developed 'intolerable' adverse events within 183 days (6 months) from the date of registration.

Adverse events deemed 'Intolerable' must meet all the following criteria:

1. Grade 3 or 4 according to CTCAE version 4 **AND**
2. Rated as being possible, probably or definitely related to Pazopanib by the investigator **AND**
3. Result in either an SAE **OR** discontinuation of pazopanib for a period greater than 21 days.

In cases where the adverse event meeting criteria 1 and 2 result in an SAE the date of onset of the SAE will be used as the date the treatment was deemed intolerable, for those which result in pazopanib discontinuation the first day that treatment was stopped will be considered the intolerable date. This date will be used to indicate whether or not the event occurred within 6 months of registration.

Patients who died prior to completing 6 months of treatment without having an event which meets the tolerability criteria are counted as tolerable and included in the denominator.

Stage 2 required 34 out of 68 patients to tolerate the treatment.

Efficacy

Efficacy is defined as the proportion of patients who entered the trial who are radiologically progression free and alive at 6 months (183 days) post registration.

Progression is defined in terms of RECIST 1.1 as follows:

1. The appearance of one or more new lesions **OR**
2. A 20% increase and absolute increase of 5mm in the sum of the longest diameter of the target lesions compared to the smallest sum of the longest diameter of target lesions **OR**
3. The unequivocal progression of non target lesions

The occurrence of any one of the changes listed above constitutes radiological progression. In addition to this it is assumed that all deaths will be disease related and thus constitute progression. Any progression or death within 183 days are deemed to show a lack of efficacy and will be counted as events.

The efficacy part of the primary outcome is reliant on RECIST data obtained from a scan at 6 months (183 days) post registration. As it is likely scans will not be exact a window of 21 days around 183 day time-point has been agreed with the chief investigators as acceptable for the 6 month scan. This means that to count as the 6 months scan the scan must be done within 162 and 204 days. If multiple scans are done within this time frame the closest to day 183 will be used.

If no scan occurs within this time frame and the patient is alive and no prior progression has been reported then the following rules will be applied to determine whether the patient should be excluded from the analysis.

- In addition to the baseline scan if the patient has two scans one before the time frame and one after that show the same response this will be taken as the response at 6 months and used in the analysis
- If the patient does not have scan either side of the time frame or if the response on those scans differs then it is impossible to say with any certainty what the response was at 6 months and this patient will be excluded from the primary analysis.

The sample size for this study was increased by 10% from 68 to 75 to allow for this type of drop out.

At the end of stage 2 there need to be at least 23 out of 68 patients who are progression free and alive at 183 days.

The table below shows the status for all 75 patients in the study.

Patient Status	**N (%)**
Ineligible for primary outcome analysis	2 (2.7)
Efficacy and tolerability complete	65 (86.7)
Patient withdrawn prior to 6 months, efficacy none evaluable	2 (2.7)
Tolerability complete, efficacy non evaluable: Scan not done	6 (8.0)
Total	75 (100.0)

6 patients have been excluded from the primary analysis because they did not have a scan at the required time (between 162 and 204 days post registration). It was reported that one additional patient (TNO 61) also missed the 28 week scan however this patient did have a scan at 164 days post registration which is within the allowed timeframe and thus was used to determine the primary outcome. This means that both primary outcomes can only be calculated for 65 patients. The required number of evaluable patients was 68. The table below shows how many patients have contributed to each of the dual primary outcomes.

Efficacy	**Not efficacious N(%) (28)**	**Alive & progression free N(%) (37)**	**Overall (65)**
Tolerability			
Intolerable	13 (46.4)	6 (16.2)	19 (29.2)
Tolerable	15 (53.6)	31 (83.8)	46 (70.8)
Total	28 (100.0)	37 (100.0)	65 (100.0)

Tolerability

Tolerable
Total number of observations = 65
Number of patients tolerating treatment = 46
Proportion (95% CI) = 0.708 (0.588, 0.804)

In the sample size calculation alpha = 5%, power = 85%. Undesirable tolerability = 0.4 and the desired tolerability = 0.6

Sensitivity Analysis
Independent Analysis
The details below are for all available tolerability data regardless of whether efficacy data is available.
Total number of observations = 73
Number of patients tolerating treatment = 49
Proportion (95% CI) = 0.671 (0.557, 0.768)

Worst Case Senario
All patients for which the data is unknown are classified as intolerable.
Total number of observations = 75
Number of patients tolerating treatment = 49
Proportion (95% CI) = 0.653 (0.541, 0.751)

Efficacy

Efficacy
Total number of observation = 65
Number of patients alive & progression free at 6 months = 37
Proportion (95% CI) = 0.569 (0.448, 0.682)

The sample size calculation set the alpha to be 5% and power to be 85%.
The undesirable efficacy was set at 0.25 and the desired efficacy was set at 0.44

Sensitivity Analysis
Independent Analysis
The details below are for all available efficacy data regardless of whether tolerability data is available. This is exactly the same as the primary outcome as no patients have been excluded on the basis of tolerability alone.

Worst Case Scenario
This include as efficacy failures those patients for which the scan was not done which includes those who withdrew prior to completing 6 months treatment.
Total number of observation = 73
Number of patients alive & progression free at 6 months = 37
Proportion (95% CI) = 0.507 (0.395, 0.618)

Clinical Progression
There are currently no instances where clinical progression has been reported within 6 months of registration but efficacy is missing or favourable. All patients with clinical progression within 6 months have also been deemed none efficacious using radiological and death data, therefore accounting for clinical progression made no difference to the outcome.

Secondary outcome measures:

1) **Progression free survival (PFS):**
Defined as the number of whole days from the date of entry into trial until evidence of radiological disease progression or death by any cause. Patients who are alive and progression free will be censored at the date last known to be progression free.

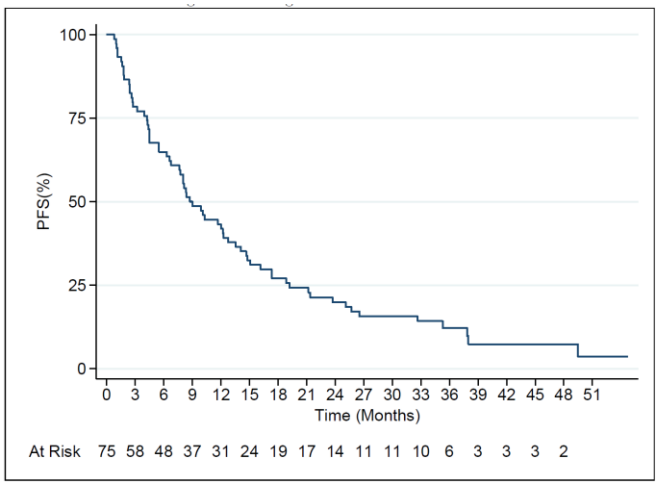
67 patients radiologically progressed or died and 8 patients were included as alive and progression free.

1 patient is censored less than one month after registration and one patient at 17 months post registration both due to patients withdrawal of consent. The remaining 6 patients were followed up for between 33 and 54 months post registration.

The median progression free survival is 9.00 months (95% CI 6.77, 12.74).

The 6 month progression free survival percentage is 65% (95 %CI 53, 75).

The Kaplan Meier graph below shows progression free survival.



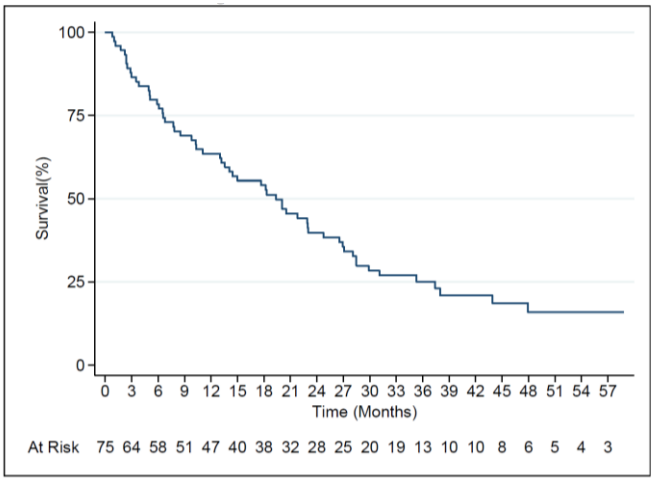
2) **Overall survival (OS):**
Defined as the number of whole days from date of entry into the trial until death by any cause. Patients alive at the end of the trial will be censored at the date last know to be alive.

58 patients had died by the end of the follow up period. Of the 17 patients alive 1 patient is censored less than one month after registration, one at 17 months and one at 14 months post registration all due to patients withdrawal of consent. The remaining 14 patients were followed up for between 33 and 58 months post registration.

The median overall survival is 19.4 months (95% CI 13.2, 24.7).

The 6 month overall survival percentage is 78% (95 %CI 67, 86).

The Kaplan Meier graph below shows overall survival



3) **Response Rate also referred to as objective response rate (ORR):**
Defined as the proportion of patients who achieve either a complete or partial radiological response as defined by RECIST criteria.

Total number of observations = 75

Number of patients achieving CR or PR = 22

Proportion (95% CI) = 0.29 (0.20, 0.40)

4) **Clinical benefit rate:**
Defined as the proportion of patients who achieve either a complete, partial or stable radiological response as defined by the RECIST 1.1 criteria.

The number reported below related to all patients within the study.

Total number of observation = 75

Number of patients achieving CR, PR or SD = 62

Proportion (95% CI) = 0.83 (0.73, 0.90)

5) **Treatment safety:**
Defined as the proportion of patients developing Adverse Events (AEs). Adverse Events will be collected from the date of entry in the trial until 28 days after drug discontinuation and graded according the NCI-CTC version 4. Adverse Events will be classified by causality, grade, type, duration and system involved.

Treatment safety included the collection of all CTCAE grade 3 or greater adverse events which are reported by category, toxicity, relatedness to Pazopanib and severity.

This data is reported in the Adverse Events section.

6) **Drug dose administered:**
Defined as the incidence of dose reductions, interruptions, escalations and discontinuations.

In total 407 dose modifications have been reported. Details of these modifications can be found in the following tables.

Type of modification	**N (%)**
Reduction	25 (6.2)
Interruption	152 (37.4)
Escalation	154 (37.9)
Discontinuation	75 (18.5)
Total	406 (100.0)

Table 4.17: Treatment Reductions

Duration of reduction (Days)	
N	25
Mean (sd)	103.2 (151.5)
Median	42.0
IQR	14.0, 126.0
Range	0.0, 721.0
Type of reduction	**N (%)**
800 to 600 mg	17 (68.0)
600 to 400 mg	7 (28.0)
800 to 400 mg	1 (4.0)
Reason for reduction	
Clinical Decision	3 (12.0)
Patient Choice	2 (8.0)
Serious Adverse Event	1 (4.0)
Toxicities Improved - General	1 (4.0)
Toxicities Worsened - Asthenia/ Fatigue	5 (20.0)
Toxicities Worsened - Nausea	1 (4.0)
Toxicities Worsened - Other specify	1 (4.0)
Toxicities worsened - General	6 (24.0)
Toxicities worsened - Diarrhoea	2 (8.0)
Toxicities worsened - Mucositis	2 (8.0)
Toxicity Improved - Specify	1 (4.0)

Table 4.18: Treatment Interruptions

Duration of interruption (Days)	
N	152
Mean (sd)	12.5 (22.7)
Median	7.0
IQR	2.0, 14.0
Range	1.0, 191.0
Type of interruption	**N (%)**
800 to 0 mg	68 (44.7)
600 to 0 mg	58 (38.2)
400 to 0 mg	26 (17.1)
Total	152 (100.0)
Reason for interruption	
Clinical Decision	3 (2.0)
Medical Procedure	6 (3.9)
Patient Choice	8 (5.3)
Patient Missed Dose	13 (8.6)
Serious Adverse Event	12 (7.9)
Surgical Procedure	2 (1.3)
Toxicities Worsened - ALT Increased	1 (0.7)
Toxicities Worsened - Asthenia/ Fatigue	7 (4.6)
Toxicities Worsened - Nausea	10 (6.6)
Toxicities Worsened - Other specify	40 (26.3)
Toxicities Worsened - Proteinuria	5 (3.3)
Toxicities Worsened - Vomiting	1 (0.7)
Toxicities worsened - General	19 (12.5)
Toxicities worsened - Diarrhoea	8 (5.3)
Toxicities worsened - Haematuria	2 (1.3)
Toxicities worsened - Hypertension	10 (6.6)
Unknown	5 (3.3)
Total	152 (100.0)

Table 4.19: Treatment Escalations

Type of escalation	**N (%)**
0 to 400 mg	38 (24.7)
0 to 600 mg	69 (44.8)
0 to 800 mg	43 (27.9)
400 to 600 mg	1 (0.6)
600 to 800 mg	2 (1.3)
400 to 800 mg	1 (0.6)
Total	154 (100.0)

Table 4.20: Treatment Discontinuations

Reasons for permanent discontinuation	**N (%)**
Clinician Choice	3 (4.0)
Death	1 (1.3)
Other	3 (4.0)
Patient Choice	1 (1.3)
Patient, Clinician & Other	1 (1.3)
Progression	24 (32.0)
Progression & Clinician	12 (16.0)
Progression & Toxicity	2 (2.7)
Progression, Toxicity & Clinician	4 (5.3)
Progression, Toxicity & Patient	1 (1.3)
Progression, Toxicity, Clinician & Other	2 (2.7)
Progression, Toxicity, Patient & Clinician	1 (1.3)
Toxicity	5 (6.7)
Toxicity & Clinician	7 (9.3)
Toxicity & Pt Choice	2 (2.7)
Toxicity, Pt & Clinician	5 (6.7)
Toxicity, Pt, Clinician & Other	1 (1.3)
Total	75 (100.0)

7) **Dose intensity**:

Defined as the total dose prescribed to each patient as a proportion of the planned protocol dose of 800mg per day for the 6 months during which time treatment tolerability was assessed.

The table below shows the dose intensity percentages both for the first 6 months and over the study as a whole.

Table 4.42: Dose Intensity

Overall Dose Intensity	
N	75
Mean (sd)	81.0 (18.6)
Median	87.4
IQR	66.5, 100.0
Range	41.8, 100.0
Dose Intensity for first 6 months	
N	75
Mean (sd)	84.0 (18.2)
Median	91.8
IQR	72.2, 100.0
Range	37.7, 100.0

8) **Duration of response:**

Defined as the number of whole days between date of first evidence of response (complete or partial) until date of disease progression or death as defined by the RECIST 1.1 criteria.

No patients reported complete response. 2 of the 20 patients who did report partial response were alive and progression free at the end of the trial so the duration of response is unknown.

Table 4.43: Duration of Response

Partial Response	**N (%)**
No	55 (73.3)
Yes	20 (26.7)
Duration of Response (mths)	
N	18
Mean (sd)	12.3 (11.1)
Median	7.5
IQR	5.7, 13.7
Range	3.0, 45.2

Adverse Events

All adverse events have been graded using the CTCAE v4.0. It is the highest grade which has been observed within the visit period which is recorded.

In total 66 patients have reported 581 adverse events which were either grade 3 or above or for which the grade was missing or unknown. 65 patients have reported 375 adverse events graded as 3, 4 or 5. In addition to this 206 events have been reported without a grade, these relate to 24 patients. In total 95 different types of adverse events were reported.

No events are missing both grade and relatedness information.

Grade and relatedness for all adverse events reported are shown in the table below:

Number of Adverse Events

CTCAE Grade	**N (%)**
Grade 3	357 (61.4)
Grade 4	12 (2.1)
Grade 5	6 (1.0)
Unknown	206 (35.5)
Relatedness	
1. Unrelated	232 (39.9)
2. Unlikely to be related	94 (16.2)
3. Possibly related	78 (13.4)
4. Probably related	43 (7.4)
5. Definitely related	51 (8.8)
Unknown	83 (14.3)

Number of Patients

Highest CTCAE grade	**N (%)**
Grade 3	36 (69.2)
Grade 4	5 (9.6)
Grade 5	1 (1.9)
Unknown	10 (19.2)
Highest relatedness of event	
1. Unrelated	2 (3.8)
2. Unlikely to be related	1 (1.9)
3. Possibly related	7 (13.5)
4. Probably related	6 (11.5)
5. Definitely related	8 (15.4)
Unknown	28 (53.8)

The tables below list all grade 3, 4, 5 or ungraded adverse events, the events are ordered by category and toxicity.

- Exposed = number of patients treated within the trial
- Affected = number of patients who experienced this event at least once
- Occurrences = total number of each event reported by those affected
- Related = number of occurrences which were classed as related to trial treatment
- Relatedness Unknown = number of occurrences for which the relatedness information has not been reported

Category	Toxicity	Exposed	Occurences		Related	Related Unknown
			Affected		Related	
Blood and lymphatic system disorders	Anemia	75	9	25	1	2
	Leukocytosis	75	1	1	0	0
	Low Red Cells	75	1	1	0	0
	Raised red cell distribution	75	1	1	0	0
	Thrombocytopenia	75	1	1	0	1
Cardiac disorders	Heart failure	75	1	1	1	0
	Sick sinus syndrome	75	1	1	0	1
	Tachycardia	75	2	2	0	1
Ear and labyrinth disorders	Vertigo	75	1	1	0	0
Endocrine disorders	Hypothyroidism	75	1	1	0	1
Eye disorders	Eye pain	75	1	1	1	0
Gastrointestinal disorders	Abdominal pain	75	4	5	1	4
	Anal hemorrhage	75	1	1	0	1
	Constipation	75	1	1	0	1
	Diarrhea	75	4	6	4	0
	Dry mouth	75	2	2	0	0
	Duodenal ulcer	75	1	1	0	1
	Dyspepsia	75	2	2	1	0
	Fecal incontinence	75	1	1	0	1
	Gastritis	75	1	1	0	1
	Mucositis oral	75	3	3	2	0
	Nausea	75	4	5	2	1
	Nausea and Vomitting	75	1	1	0	1
	Vomiting	75	4	4	2	1
General disorders and administration site conditions	Collapse	75	1	1	0	1
	Edema limbs	75	1	1	0	0
	Fatigue	75	22	32	25	2
	Feeling of pressure in chest	75	1	1	0	0
	Mild right sided chest pain	75	1	1	0	0
	Night sweats	75	1	1	0	0
	Non-cardiac chest pain	75	1	1	0	0
	Pain	75	6	8	0	2
Hepatobiliary disorders	Bileduct obstruction	75	1	1	0	1
Vascular disorders	Hypertension	75	25	117	71	1
	Hypotension	75	1	1	0	0
	Pulmonary Embolus	75	1	1	0	1

	Hepatoxicity	75	1	1	0	1
Infections and infestations	Bronchial infection	75	1	1	0	1
	Chest infection	75	1	1	0	1
	Cold sore	75	1	1	0	0
	Hospital acquired pneumonia	75	1	1	0	0
	Infection	75	2	2	0	1
	Lower respiratory tract infection	75	1	1	0	1
	Lung infection	75	2	2	0	2
	Pneumonia	75	1	2	0	1
	Respiratory infection	75	1	1	0	0
	Sepsis	75	2	2	0	1
	Upper respiratory infection	75	1	1	0	1
	Urinary tract infection	75	3	3	0	3
	Urine infection	75	1	2	0	0
	Wound infection	75	1	2	0	0
Injury, poisoning and procedural complications	Fall	75	1	1	0	1
Investigations	Alanine aminotransferase increased	75	8	9	4	4
	Alkaline phosphatase increased	75	1	2	2	0
	Aspartate aminotransferase increased	75	3	3	1	1
	Blood bilirubin increased	75	2	2	0	2
	Creatinine increased	75	3	3	1	0
	Fibrinogen decreased	75	1	1	0	0
	GGT increased	75	5	7	3	1
	INR increased	75	2	4	4	0
	Investigations - Other, specify	75	18	145	11	1
	Lymphocyte count decreased	75	3	7	1	0
	Platelet count decreased	75	1	1	1	0
	Serum amylase increased	75	4	4	0	0
Metabolism and nutrition disorders	Anorexia	75	6	10	2	0
	Dehydration	75	1	1	0	0
	Hypercalcemia	75	1	2	0	1
	Hyperglycemia	75	1	1	1	0
	Hyperkalemia	75	4	4	0	1
	Hypertriglyceridemia	75	4	11	9	0
	Hypoalbuminemia	75	5	6	0	0
	Hypocalcemia	75	1	1	0	0
	Hypoglycemia	75	1	1	0	0
	Hypomagnesemia	75	1	1	0	0
	Hyponatremia	75	8	11	3	1
	Hypophosphatemia	75	8	8	1	0
	Low Protein	75	1	1	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	75	2	4	0	0
	Back pain	75	3	4	0	2
	Bone pain	75	7	10	1	6
	Cramp in hands	75	1	1	1	0
	Flank pain	75	1	1	0	0
	Muscle cramps	75	1	1	0	0
	Muscle weakness lower limb	75	4	5	0	4
	Pain in extremity	75	2	3	1	0
	Pain right leg	75	1	1	0	1
Nervous system disorders	Aphonia	75	1	1	1	0
	Headache	75	1	1	0	0
	Paresthesia	75	2	3	1	1
	Syncope	75	2	2	0	1
Psychiatric disorders	Confusion	75	2	2	0	1
Renal and urinary disorders	Chronic kidney disease	75	1	3	3	0
	Proteinuria	75	3	6	6	0
	Urinary frequency	75	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Bronchial obstruction	75	1	1	0	0
	Cough	75	1	1	0	1
	Dyspnea	75	5	8	0	7
	Emphysema	75	1	1	0	1
	Epistaxis	75	1	2	0	1
	Hoarseness	75	1	1	0	0
	Hypoxia	75	1	2	0	1
	Intermittent small amounts of haemoptysis	75	1	1	0	0
	Pleural effusion	75	1	1	0	0
	Pneumothorax	75	1	1	0	1
	Respiratory failure	75	1	2	0	1
	Shortness of breath	75	1	1	0	1
	Wheezing	75	1	1	0	1
Skin and subcutaneous tissue disorders	Alopecia	75	1	1	1	0
	Palmar-plantar erythrodysesthesia syndrome	75	1	1	1	0
	Skin ulceration	75	1	1	1	0
	Urticaria	75	1	1	1	0

Serious Adverse Events

SAEs are defined as any untoward medical occurrence or effect that at any dose:

- 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/birth defect
- Or is otherwise considered medically significant by the Investigator

In total 77 SAEs have been reported by 49 patients.
Details of all SAE reported can be found in the following table. The toxicities reported in this table were those identified by sites as being the primary cause of each SAE.

TNO	Days from entry to SAE	Reason for reporting	Toxicity	Grade	Outcome	Category
2	12	Hospitalisation	Abdominal pain	3	Resolved - no sequelae	SAR
3	54	Hospitalisation	Bone pain	3	Death	Unrelated SAE
4	77	Hospitalisation	Hyperkalemia	3	Resolved - no sequelae	SAR
6	423	Hospitalisation	Gastrointestinal disorders - Other, specify	3	Resolved - no sequelae	Unrelated SAE
7	28	Other	Alanine aminotransferase increased	3	Resolved - with sequelae	SAR
7	331	Hospitalisation	Vascular disorders - Other, specify	1	Resolved - no sequelae	Unrelated SAE
10	49	Hospitalisation	Anal hemorrhage	3	Resolved - no sequelae	Unrelated SAE
11	146	Hospitalisation	Bone pain	3	Resolved - no sequelae	Unrelated SAE
17	267	Hospitalisation	Hepatobiliary disorders - Other, specify	2	Resolved - no sequelae	SAR
17	308	Hospitalisation	Hepatobiliary disorders - Other, specify	3	Resolved - no sequelae	Unrelated SAE
17	956	Hospitalisation	Abdominal pain	3	Resolved - no sequelae	Unrelated SAE
18	533	Hospitalisation	Transient ischemic attacks	2	Resolved - no sequelae	SAR
18	541	Hospitalisation	Bone pain	3	Resolved - with sequelae	Unrelated SAE
18	549	Hospitalisation	Bone pain	3	Resolved - with sequelae	Unrelated SAE
19	149	Hospitalisation	Laryngeal hemorrhage	2	Resolved - no sequelae	SAR
19	170	Hospitalisation	Vomiting	3	Resolved - no sequelae	SAR
20	34	Hospitalisation & disability	Muscle weakness lower limb	3	Death	Unrelated SAE
22	855	Other	Vascular disorders - Other, specify	2	Resolved - with sequelae	SAR
23	3	Hospitalisation	Hypercalcemia	2	Resolved - no sequelae	Unrelated SAE
23	134	Hospitalisation	Hypercalcemia	4	Resolved - no sequelae	Unrelated SAE
23	153	Hospitalisation	Upper gastrointestinal hemorrhage	2	Resolved - no sequelae	Unrelated SAE
24	551	Hospitalisation & disability	Cough	3	Resolved - with sequelae	Unrelated SAE
26	503	Other	Vascular disorders - Other, specify	3	Resolved - no sequelae	SAR
26	509	Hospitalisation	Vomiting	2	Resolved - no sequelae	SAR
26	520	Hospitalisation	Seizure	2	Resolved - with sequelae	Unrelated SAE
27	93	Hospitalisation	Pain	3	Resolved - no sequelae	Unrelated SAE
27	104	Hospitalisation	Upper gastrointestinal hemorrhage	2	Death	Unrelated SAE
28	67	Death, life threatening & Hospitalisation	Hypoxia	5	Death	Unrelated SAE
30	0	Life threatening & Hospitalisation	Dyspnea	3	Resolved - with sequelae	Unrelated SAE
31	280	Other	Blood and lymphatic system disorders - Other, specify	1	Resolved - with sequelae	Non fatal / life-threatening SUSAR

32	7	Hospitalisation	Bronchial infection	3	Resolved - no sequelae	SAR
34	85	Death & Hospitalisation	Abdominal pain	2	Resolved - no sequelae	Unrelated SAE
35	224	Hospitalisation	Lung infection	3	Resolved - no sequelae	Unrelated SAE
36	386	Hospitalisation	Dyspnea	3	Resolved - no sequelae	Unrelated SAE
36	448	Hospitalisation	Lung infection	3	Resolved - no sequelae	Unrelated SAE
37	31	Hospitalisation	Abdominal pain	3	Resolved - no sequelae	Unrelated SAE
38	528	Life threatening, Hospitalisation & disability	Muscle weakness lower limb	3	Resolved - with sequelae	Unrelated SAE
39	12	Hospitalisation	Vomiting	2	Resolved - no sequelae	SAR
41	8	Hospitalisation	Sinus bradycardia	2	Resolved - no sequelae	SAR
42	208	Hospitalisation	Fever	1	Resolved - with sequelae	Unrelated SAE
42	235	Hospitalisation	Urinary tract infection	3	Resolved - with sequelae	Unrelated SAE
47	24	Hospitalisation	Hepatobiliary disorders - Other, specify	3	Resolved - no sequelae	SAR
48	66	Hospitalisation	Dyspnea	2	Resolved - with sequelae	Unrelated SAE
48	88	Hospitalisation	Dyspnea	3	Resolved - with sequelae	Unrelated SAE
48	116	Hospitalisation	Dyspnea	3	Resolved - with sequelae	Unrelated SAE
48	147	Hospitalisation	Abdominal pain	3	Resolved - no sequelae	Unrelated SAE
50	111	Other	Alanine aminotransferase increased	3	Resolved - with sequelae	Unrelated SAE
53	112	Hospitalisation	Fatigue	3	Death	SAR
54	5	Hospitalisation	Lung infection	2	Resolved - no sequelae	SAR
55	25	Hospitalisation	Bone pain	3	Resolved - no sequelae	Unrelated SAE
56	49	Other	Alanine aminotransferase increased	3	Resolved - no sequelae	SAR
57	69	Hospitalisation	Syncope	3	Resolved - no sequelae	Non fatal / life-threatening SUSAR
59	432	Hospitalisation	Urinary tract infection	3	Resolved - with sequelae	Unrelated SAE
59	447	Hospitalisation	Rash maculo-papular	2	Resolved - no sequelae	Unrelated SAE
61	268	Hospitalisation	Sick sinus syndrome	3	Resolved - with sequelae	Unrelated SAE
61	947	Hospitalisation	Hyponatremia	3	Resolved - no sequelae	Unrelated SAE
62	220	Hospitalisation	Infections and infestations - Other, specify	3	Resolved - no sequelae	SAR
62	256	Hospitalisation	Dyspnea	3	Resolved - with sequelae	Unrelated SAE
62	264	Hospitalisation	Dyspnea	3	Resolved - with sequelae	Unrelated SAE
63	31	Hospitalisation	Gastritis	3	Resolved - no sequelae	Unrelated SAE
63	58	Hospitalisation	Pain	3	Resolved - with sequelae	Unrelated SAE
64	453	Hospitalisation	Abdominal pain	2	Resolved - no sequelae	Unrelated SAE
65	104	Hospitalisation	Hypothyroidism	3	Resolved - no sequelae	SAR
65	120	Hospitalisation	Fatigue	3	Resolved - no sequelae	SAR
67	235	Hospitalisation & disability	Confusion	3	Resolved - with sequelae	Unrelated SAE
67	279	Hospitalisation & disability	Pneumothorax	3	Resolved - no sequelae	Unrelated SAE
68	12	Hospitalisation	Presyncope	2	Resolved - with sequelae	SAR
69	192	Hospitalisation	Diarrhea	1	Resolved - no sequelae	SAR
70	42	Hospitalisation	Respiratory, thoracic and mediastinal disorders - Other, specify	3	Resolved - no sequelae	Unrelated SAE
70	220	Hospitalisation	Respiratory, thoracic and mediastinal disorders - Other, specify	3	Resolved - no sequelae	Unrelated SAE
71	7	Hospitalisation	Back pain	3	Resolved - no sequelae	Unrelated SAE
73	135	Hospitalisation	Epistaxis	4	Resolved - no sequelae	SAR
73	146	Hospitalisation	Epistaxis	4	Resolved - no sequelae	SAR
73	158	Hospitalisation	Upper respiratory infection	3	Resolved - no sequelae	Unrelated SAE
73	174	Hospitalisation & disability	Bone pain	3	Death	Unrelated SAE
75	14	Hospitalisation	Musculoskeletal and connective tissue disorder - Other, specify	3	Resolved - no sequelae	SAR
75	142	Hospitalisation	Sepsis	4	Resolved - no sequelae	Unrelated SAE

6 SAE reasons have been reported as `other', the details of these are in the table below.

TNO	Reason 'Other'
7	Raised ALT, greater than 8xULN
22	Thrombotic event - Left inferior quadrantanopia
26	Pulmonary embolus - possibly tumour from IVC filling defect.
31	Information from GSK regarding pulmonary fibrosis and Pazopanib.
50	Increased ALT on 12-MAY-2015 520 U/L which is >8.0 x ULN - asked to report this by Pazo2 monitor .
56	Raised Alanine Aminotransferase = 533 U/L on 05 AUG 2015