Clinical trial results:
Phase II Single-arm Study evaluating Neo-adjuvant (pre-radical radiotherapy) Abiraterone acetate (plus prednisolone) and Gonadotropin-Releasing Hormone (GnRH) agonist in high risk localised prostate carcinoma

Summary

EudraCT number	2014-001128-31
Trial protocol	IE
Global end of trial date	19 January 2021

Results information

Result version number	v1 (current)
This version publication date	25 June 2022
First version publication date	25 June 2022

Trial information

Trial identification

Sponsor protocol code	13-23

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02160353
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cancer Trials Ireland
Sponsor organisation address	Ardilaun House, Dublin, Ireland, D02 VN51
Public contact	Head of Clinical Operations, Cancer Trials Ireland, +353 16677211, info@cancertrials.ie
Scientific contact	Head of Clinical Operations, Cancer Trials Ireland, +353 16677211, info@cancertrials.ie

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 January 2021
Global end of trial reached?	Yes
Global end of trial date	19 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective:
To evaluate the clinical tumour and biochemical response, and mean percentage reduction in prostate gland volume; achieved by 126 days of neo-adjuvant combined treatment by abiraterone acetate, prednisolone and GnRH agonist - in treatment naïve high-risk localised prostate carcinoma patients (prior to radical radiotherapy).

Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations SI 190 of 2004 as amend and European Directive 2001/20/EC. The study was approved by the HPRA and Clinical REC of the Cork Teaching Hospital.

Background therapy:

Prednisolone and GnRH agonist injection(s) are non IMP treatments/therapies used in this study. These are mandatory standard supportive care concomitant medication

Evidence for comparator:

The role of the proposed study is to focus on the potential role of abiraterone acetate in treatment-naïve patients newly diagnosed with high-risk localised prostate cancer requiring combined hormonal therapy and radiotherapy (External Beam Radiation Therapy and/or Brachytherapy). This was a single-arm, Phase II prospective study with a primary efficacy objective of evaluating 126 days of neo-adjuvant hormonal therapy by abiraterone acetate (plus prednisolone) and GnRH agonist in high-risk localised prostate carcinoma.

Actual start date of recruitment	01 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	9
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

45 Participants were consented from Ireland from July-2015 to March-2020

Pre-assignment

Screening details:

This study will involve patients undergoing neo-adjuvant hormonal therapy for localised prostate carcinoma. All patients will fulfil the eligibility criteria

Pre-assignment period milestones

Number of subjects started	45
Number of subjects completed	45

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This study was a single arm non blinded study

Arms

Arm title	Single Arm

Arm description:

A single arm study where all patients will receive IMP Abiraterone acetate for 126 as well as Mandatory standard supportive care concomitant medication (nIMP): Prednisolone for 126 days and GnRH agonist for a minimum of 112 days

Arm type	Experimental
Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	Zytiga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/day - four 250 mg tablets, orally once a day (unless otherwise instructed by the study doctor in the case of a dose adjustment) for 126 days - commencing 14 days prior to 1st GnRH agonist injection.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	Deltacortril®, Deltastab®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg/day (orally once a day, concomitant to abiraterone acetate) for 126 days - commencing 14 days prior to 1st GnRH agonist injection.
[Following the 126 days of treatment, prednisolone dose should be gradually reduced at clinician’s advice to avoid patient withdrawal symptoms]. Prednisolone is being used to manage mineralocorticoid excess; abiraterone acetate is always taken with low-dose prednisolone.

Investigational medicinal product name	GnRH agonist:
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Injection

Dosage and administration details:

First injection should be administered 14 days after first dose of concomitant abiraterone acetate (and prednisolone) and continued throughout the study for minimum duration of 112 days (e.g. either four one-monthly injections at 28-day intervals, or two x 3-monthly injections, or one 6-monthly injection - per Investigator's choice). GnRH agonist is being used in this study as a standard treatment, therefore continuing this treatment beyond 112 days is the investigator decision and should be managed as per standard practice.

Number of subjects in period 1	Single Arm
Started	45
Completed	44
Not completed	1
Withdrawn, prohibited medication	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study (overall period)

Reporting group description: -

Reporting group values	Overall Study (overall period)	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
Adults (18-64 years)	8	8	
From 65-84 years	37	37	
Age continuous Units: years			
median	69		
full range (min-max)	57 to 81	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	45	45	

End points

End points reporting groups

Reporting group title	Single Arm

Reporting group description:

A single arm study where all patients will receive IMP Abiraterone acetate for 126 as well as Mandatory standard supportive care concomitant medication (nIMP): Prednisolone for 126 days and GnRH agonist for a minimum of 112 days

Subject analysis set title	Single Arm Study
Subject analysis set type	Full analysis

Subject analysis set description:

As this is a 1 armed study this statistical arm is created as a workaround so that statistical anlysis of the study can be posted

Primary: Tumour Response: Mean % Reduction in Prostatic Gland Volume

End point title	Tumour Response: Mean % Reduction in Prostatic Gland Volume

End point description:

Tumour Response at 126 was assessed 3 ways. This is the first way: Mean % Reduction in Prostatic Gland Volume: The mean prostatic volume at baseline was 45.8 cm3, with a median of 38.1 cm3 (range of 30.2 - 102). The mean reduction from baseline at Day 99 was 19.6 cm3, with a median of 17.4 cm3 (range of 7.2 – 77.4). The mean percentage reduction from baseline at Day 99 was 42.4%, with a median of 42.3% (range of 21.2 – 75.9). The 95% CI for mean percentage reduction from baseline at Day 99 was [38.6 - 46.2]. This is consistent with the assumption in Section 4 that the mean percentage reduction was expected to be at least 35% and no greater than 46%.
In addition, 29/42 patients (69.0%) had prostatic volume within the range 20 – 50 cm3 at baseline, decreasing slightly to 23/36 (63.9%) at Day 99.

End point type	Primary

End point timeframe:

Baseline to Day 99 to Day 126

End point values	Single Arm	Single Arm Study		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	42[1]	42[2]		
Units: cm3				
median (full range (min-max))				
Baseline	38.1 (30.2 to 102.0)	38.1 (30.2 to 102.0)		
Day 99	22.2 (13.2 to 62.7)	22.2 (13.2 to 62.7)		
Day 126	19.0 (16.7 to 21.0)	19.0 (16.7 to 21.0)		

Notes:

[1] - Baseline n =42
Day 99 n=36
Day 126 n=4
[2] - This set is used as a workaround for statistical analysis as this is a single arm study

Statistical analyses

Statistical analysis title	Percentage reduction in prostatic volume
Comparison groups	Single Arm v Single Arm Study
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[3]
Method	Mean percentage reduction at D99 and CI
Parameter estimate	Median difference (final values)
Point estimate	42.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	38.6
upper limit	46.2
Variability estimate	Standard deviation
Dispersion value	11.2

Notes:

[3] - Mean percentage reduction and confidence interval

Primary: Tumour Response at 126 Days: Median Change in PSA Levels

End point title	Tumour Response at 126 Days: Median Change in PSA Levels[4]

End point description:

Assessment 2 for Tumour Response at 126 days: Median Change in PSA Levels: One patient had screening assessment outside window and is excluded from the results. One further patient did not have a PSA assessment at Day 126. The median PSA at baseline was 14.1 ng/mL (range of 2.86 – 147.2), and the median reduction from baseline at Day 126 was 13.7 ng/mL (range of 3 – 146). A total of 33 patients (80.5%) achieved a PSA value of <0.1 ng/mL at Day 126.

End point type	Primary

End point timeframe:

After 126 days as compared to Baseline (PSA prior to treatment and on Day 126)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: the statistical analysis for this endpoint doesn't fit into the format provided but the median reduction from baseline in PSA at Day 126 was 13.7 ng/mL (range of 3 – 146).

End point values	Single Arm	Single Arm Study		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	42[5]	42[6]		
Units: ng/ML				
median (full range (min-max))				
Baseline	14.1 (2.86 to 147.2)	14.1 (2.86 to 147.2)		
Day 126	0.05 (0.03 to 0.87)	0.05 (0.03 to 0.87)		

Notes:

[5] - Baseline n=42
Day126 n=41
[6] - This arm has been created as a workaround as this is only a single am study

Statistical analyses

No statistical analyses for this end point

Primary: Tumour Response at 126 Days: DRE and Complete Response

End point title	Tumour Response at 126 Days: DRE and Complete Response

End point description:

Assessment 3 for measuring tumour response at 126 days: DRE and Complete Response: 1 patient had his screening examination outside window and his screening T stage of T1c is excluded from the table. 4 patients did not have an examination performed at Day 126. The most common category at baseline was T1c with 11 patients (26.2%), and the highest category was T3b with just one patient. All FAS patients were T1c or higher at baseline.
At Day 126, 5 patients (13.2%) could not have their primary tumour assessed. The most common category was T1c with 12 patients (31.6%), with one patient achieving T0 and one patient having the highest category of T3a.
A total of 19 patients (57.6% of the 33 patients with a Day 126 assessment of tumour) had normalisation of DRE (T1c or less).
A total of 16 patients (48.5% of the 33 patients with a Day 126 assessment of tumour) had a complete clinical and biochemical response as defined by a normalisation of DRE and an achieved PSA <0.1 ng/ml on Day 126.

End point type	Primary

End point timeframe:

Baseline vs Day 126

End point values	Single Arm	Single Arm Study		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	42[7]	42[8]		
Units: Percent				
number (not applicable)				
BL: T1c	26.2	26.2		
BL: T2	2.4	2.4		
BL: T2a	7.1	7.1		
BL: T2b	16.7	16.7		
BL: T2c	21.4	21.4		
BL: T3	11.9	11.9		
BL: T3a	11.9	2.4		
BL: T3b	2.4	2.6		
D126: T0	2.6	15.8		
D126: T1	15.8	31.6		
D126: T1C	31.6	2.6		
D126: T2	5.3	5.3		
D126: T2a	2.6	2.6		
D126: T2c	5.3	5.3		
D126: Y3	13.2	13.2		
D126: T3a	2.6	2.6		
D126: TX	13.2	13.2		
D126: T2b	7.9	7.9		

Notes:

[7] - Baseline (BL) n=42
Day 126 n=38
[8] - This arm was created as a workaround as this is a single arm study

Statistical analyses

Statistical analysis title	Complete Clinical and Biochemical Response

Statistical analysis description:	
Response rate	
Comparison groups	Single Arm v Single Arm Study
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[9]
Method	Complete clin & biochem response & CI
Parameter estimate	Response rate
Point estimate	48.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	32.5
upper limit	64.8

Notes:

[9] - Response rate and confidence interval

Secondary: Decrease in Testosterone Levels

End point title	Decrease in Testosterone Levels

End point description:

The median testosterone at baseline was 16.1 nmol/L (range of 4.8 – 34.5). At Day 15, just 8 patients (18.6%) had a value > 1.7 nmol/l. The median reduction from baseline at Day 126 was 16.1 nmol/L (range of 4.4 – 34.4), a reduction that was first achieved at Day 43 and maintained through to Day 126.

End point type	Secondary

End point timeframe:

Prior To Treatment & on Days 15, 43, 71, 99 and 126

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	43[10]			
Units: Testosterone nmol/L				
median (full range (min-max))				
Baseline	16.1 (4.80 to 34.5)			
Day 15	0.40 (0.10 to 11.9)			
Day 43	0.12 (0.05 to 0.45)			
Day 71	0.15 (0.06 to 0.45)			
Day 99	0.10 (0.05 to 0.40)			
Day 126	0.15 (0.02 to 0.45)			

Notes:

[10] - Baseline & Day 15 n=43
Day 43,71,99,126 n=42

Statistical analyses

No statistical analyses for this end point

Secondary: PSA kinetics and response

End point title	PSA kinetics and response

End point description:

End point type	Secondary

End point timeframe:

The PSA kinetics and response on the studied treatment evaluated by serial PSA measurements prior to treatment and on days 15, 43, 71, 99, and 126

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	42[11]			
Units: ng/ML				
median (full range (min-max))				
Baseline	14.1 (2.86 to 147.2)			
Day 126	0.05 (0.03 to 0.87)			

Notes:

[11] - Baseline =42, Day 126=41

Statistical analyses

No statistical analyses for this end point

Secondary: Impact on Urinary Symptoms

End point title	Impact on Urinary Symptoms

End point description:

The studied treatment impact on urinary symptoms evaluated by serial International Prostate Symptom Score (IPSS) prior to treatment and on days 15, 43, 71, 99, and 126. The IPSS total score is calculated across 7 symptoms scores, with a maximum possible total score of 35.
The median total score at baseline was 9.0 (range of 0 – 32), and the median change from baseline at Day 126 was -1.0 (range of -30 – 10), indicating a minimal change from baseline.

End point type	Secondary

End point timeframe:

Baseline and Days 15, 43, 71, 99, and 126

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	43[12]			
Units: IPSS Score				
median (full range (min-max))				
Baseline	9.0 (0 to 32)			
Day 15	7.0 (0 to 26)			

Day 43	7.0 (0 to 26)			
day 71	7.0 (0 to 20)			
Day 99	5.5 (1 to 19)			
Day 126	4.0 (1 to 18)			

Notes:

[12] - Baseline & Day 15 n=43
Day 43, 71, 99 n=42
Day 126 n=41

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Beginning on or after the start date of study treatment and up to 30 days after the end of study treatment

Adverse event reporting additional description:

Evaluations include periodic physical examination, vital sign measurement, and clinical lab tests. (cardiac function may be assessed by MUGA scan or ECHO)
AEs/ toxicities, incl. lab AEs, are graded and summarised. Any clinically significant abnormalities persisting at EoS will be followed until resolution or clinically stable endpoint reached.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Single Arm

Reporting group description:

A single arm study where all patients will receive IMP Abiraterone acetate for 126 as well as Mandatory standard supportive care concomitant medication (nIMP): Prednisolone for 126 days and GnRH agonist for a minimum of 112 days

Serious adverse events	Single Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 45 (8.89%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oedema peripheral			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Single Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 45 (100.00%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	36 / 45 (80.00%)		
occurrences (all)	51		
Hypertension			
subjects affected / exposed	26 / 45 (57.78%)		
occurrences (all)	60		
Hypotension			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 45 (40.00%)		
occurrences (all)	31		
Influenza like illness			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Oedema peripheral			

subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 3		
Reproductive system and breast disorders Ejaculation disorder subjects affected / exposed occurrences (all) Erectile dysfunction subjects affected / exposed occurrences (all)	 1 / 45 (2.22%) 1 9 / 45 (20.00%) 11		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all) Upper-airway cough syndrome subjects affected / exposed occurrences (all)	 2 / 45 (4.44%) 3 1 / 45 (2.22%) 1 1 / 45 (2.22%) 1 1 / 45 (2.22%) 1 1 / 45 (2.22%) 1		
Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Libido decreased	 3 / 45 (6.67%) 3 1 / 45 (2.22%) 1 7 / 45 (15.56%) 8		

subjects affected / exposed	9 / 45 (20.00%)		
occurrences (all)	11		
Loss of libido			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Mood swings			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	21 / 45 (46.67%)		
occurrences (all)	50		
Aspartate aminotransferase increased			
subjects affected / exposed	20 / 45 (44.44%)		
occurrences (all)	46		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Blood cholesterol increased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blood urea increased			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Cardiac murmur			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Glycosylated haemoglobin increased subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Haematocrit decreased subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2		
Haemoglobin decreased subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 6		
Red blood cell count decreased subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Weight decreased subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Injury, poisoning and procedural complications Skin laceration subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Cardiac disorders Sinus bradycardia subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Nervous system disorders Amnesia subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Cognitive disorder subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Dizziness			

subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Memory impairment subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4 1 / 45 (2.22%) 1 1 / 45 (2.22%) 1 2 / 45 (4.44%) 3 1 / 45 (2.22%) 1 1 / 45 (2.22%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all) Dry Eye subjects affected / exposed occurrences (all) Vision blurred subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1 1 / 45 (2.22%) 1 1 / 45 (2.22%) 1		
Gastrointestinal disorders			

Abdominal discomfort				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Abdominal Pain				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Abdominal pain upper				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences (all)	3			
Anal Incontinence				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	5 / 45 (11.11%)			
occurrences (all)	5			
Diarrhoea				
subjects affected / exposed	4 / 45 (8.89%)			
occurrences (all)	4			
Dry Mouth				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Dyspepsia				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences (all)	3			
Flatulence				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences (all)	3			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Haematochezia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	4 / 45 (8.89%)			
occurrences (all)	5			

Proctalgia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Night sweats			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Skin induration			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Dysuria			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Lower urinary tract symptoms			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Micturition urgency			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	8		
Nocturia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Pollakiuria			

subjects affected / exposed	9 / 45 (20.00%)		
occurrences (all)	10		
Urinary hesitation			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Urinary incontinence			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Urinary retention			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Urine flow decreased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Groin pain			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Muscle atrophy			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Myopathy			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Infections and infestations			
Gingivitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Lower respiratory tract infection			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Onychomycosis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Tooth abscess			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Hyperkalaemia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	5		
Increased appetite			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2016	First Approved Protocol V3.0 24-Jun-2014: This Amendment was for Protocol V4.0/01-APr-2016: The protocol was amended to clarify the RSI to be used in this study.
28 September 2016	Protocol v5.0 05Sept2016: Rationale for all protocol changes detailed in summary of Amendment Protocol V4.0 to V5.0. Includes update of ICORG to Cancer Trials Ireland , updates to abbreviations, admin updates, TRU assessment update, end point update
16 January 2019	Protocol V6.0/ 07-Dec-2018: Updates due to changes in conduct or mgmt of the trial. A key change to the protocol is the reduction of the follow up period to 6 months based on data reported from other trials, including the large international randomised phase III trials LATITUDE and STAMPEDE, which have demonstrated no significant concerns for late onset toxicities. Its safety profile is well characterised. The CI and study team therefore determine that 6 months follow up post last patient last treatment should provide an adequate duration of follow up and safety monitoring on this single arm phase II trial.
24 April 2020	Protocol V6.1/25Jun2019: updated to IB JNJ-212082 ZYTIGA Ed14 14Jun2019 led to non substantial amendments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported