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XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer (TROPIC)

This study has been completed.

Sponsor:	Sanofi
Collaborators:	
Information provided by:	Sanofi
ClinicalTrials.gov Identifier:	NCT00417079

Purpose

This is a randomized, open-label, multi-center study comparing the safety and efficacy of XRP6258 plus prednisone to mitoxantrone plus prednisone in the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere®-containing regimen. The primary objective is overall survival. Secondary objectives include progression free survival, overall response rate, prostate-specific antigen (PSA) response/progression, pain response/progression, overall safety, and pharmacokinetics. Patients will be treated until disease progression, death, unacceptable toxicity, or for a maximum of 10 cycles. Patients will have long-term follow-up for a maximum of up to 2 years.

Condition	Intervention	Phase
Neoplasms Prostatic Neoplasms	Drug: cabazitaxel (XRP6258) (RPR116258) Drug: mitoxantrone Drug: prednisone	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Open Label, Randomized, Efficacy Study
Official Title: A Randomized, Open Label Multi-Center Study of XRP6258 at 25 mg/m^2 in Combination With Prednisone Every 3 Weeks Compared to Mitoxantrone in Combination With Prednisone For The Treatment of Hormone Refractory Metastatic Prostate Cancer Previously Treated With A Taxotere®-Containing Regimen

Further study details as provided by Sanofi:

Primary Outcome Measure:

- Overall Survival [Time Frame: From the date of randomization up to 104 weeks (study cut-off)] [Designated as safety issue: No]
  Overall survival was defined as the time interval from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, the survival time was censored at the last date patient was known to be alive or at the cut-off date, whichever had come first.

Secondary Outcome Measures:

- Time to Progression Free Survival (PFS) [Time Frame: From the date of randomization up to 104 weeks (study cut-off)] [Designated as safety issue: No]
  Progression free survival was defined as a composite endpoint evaluated from the date of randomization to the date of tumor progression, PSA progression, pain progression, or death due to any cause, whichever occurred first
- Overall Tumor Response [Time Frame: From the date of randomization up to 104 weeks (study cut-off)] [Designated as safety issue: No]
  Tumor Overall Response Rate (ORR) (only in patients with measurable disease): Objective responses (Complete Response and Partial Response) for measurable disease as assessed by investigators according to RECIST criteria. Complete Response (CR) is defined as: Disappearance of all target lesions. Partial Response (PR) is defined as: At least a 30% decrease in the sum of longest diameter (LD) of target lesions taking as reference baseline sum LD. Confirmation of objective responses will be performed by repeat tumor imaging (CT scans, MRI, bone scans) after the first documentation of response.
- Time to Tumor Progression [Time Frame: From the date of randomization up to 104 weeks (study cut-off)] [Designated as safety issue: No]
  Time to tumor progression is defined as the number of months from randomization until evidence of progressive disease (RECIST)
- Time to Prostatic Specific Antigen (PSA) Progression [Time Frame: at screening, day 1 of every treatment cycle, up to 104 weeks (study cut-off)] [Designated as safety issue: No]
  In PSA non-responders, progression will be defined as a 25% increase over nadir and increase in the absolute value PSA level by at least 5 ng/ml and confirmed by a second value at least 4 weeks later. In PSA responders and in patients not evaluable for PSA response at baseline, progression will be defined as a ≥50% increase over nadir, provided that the increase is a minimum of 5 ng/ml and confirmed by a second value at least 1 week later.
- PSA (Prostate-Specific Antigen) Response [Time Frame: from baseline up to 104 weeks (study cut-off)] [Designated as safety issue: No]
  PSA response was defined as a ≥ 50% reduction in serum PSA, determined only for patients with a serum PSA ≥ 20ng/mL at baseline, confirmed by a repeat PSA ≥ 3 weeks later.
- Time to Pain Progression [Time Frame: from baseline up to 104 weeks (study cut-off)] [Designated as safety issue: No]
  Pain Progression is defined as an increase of ≥1 point in the median Personal Pain Intensity (PPI) from its nadir noted on 2 consecutive 3-week-apart visits or ≥25 % increase in the mean analgesic score compared with the baseline score & noted on 2 consecutive 3-week-apart visits or requirement for local palliative radiotherapy. Evaluation of the PPI & analgesic scores are based on the short-form McGill Pain Questionnaire which consists of 15 descriptors (11 sensory; 4 affective) which are rated on an intensity scale as 0=none (best) 1=mild 2=moderate 3=severe (worst) (TOTAL: 0=best 45=worst)
- Pain Response [Time Frame: from baseline up to 104 weeks (study cut-off)] [Designated as safety issue: No]
  Pain Response was defined as a two-point or greater reduction from baseline median Present Pain Intensity (PPI) score without an increased Analgesic Score (AS) or a decrease of ≥50% in the AS without an increase in the PPI score, maintained for at least 3 weeks.

Enrollment: 755
Study Start Date: January 2007
Primary Completion Date: September 2009
Study Completion Date: September 2009

Arms	Assigned Interventions
Active Comparator: Mitoxantrone + Prednisone	Drug: mitoxantrone

Arms	Assigned Interventions
Mitoxantrone + Prednisone	12 mg/m^2 administered by intravenous (IV) route over 15-30 minutes on day 1 of each 21-day cycle Drug: prednisone 10 mg daily administered by oral route
Experimental: Cabazitaxel + Prednisone Cabazitaxel + Prednisone	Drug: cabazitaxel (XRP6258) (RPR116258) 25 mg/m^2 administered by intravenous (IV) route over 1 hour on day 1 of each 21-day cycle Other Names: Jevtana Drug: prednisone 10 mg daily administered by oral route

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Male
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria

1. Histologically or cytologically confirmed adenocarcinoma of the prostate that is refractory to hormone therapy and previously treated with a Taxotere®-containing regimen.
2. Documented progression of disease (demonstrating at least one visceral or soft tissue metastatic lesion, including a new lesion). Patients with non-measurable disease must have documented rising prostate-specific antigen (PSA) levels or appearance of new lesion.
3. Surgical or hormone-induced castration
4. Life expectancy > 2 months
5. Eastern Cooperative Oncology Group (ECOG) performance status 0 - 2

Exclusion criteria

1. Previous treatment with mitoxantrone
2. Previous treatment with <225 mg/m^2 cumulative dose of Taxotere (or docetaxel)
3. Prior radiotherapy to ≥ 40% of bone marrow
4. Surgery, radiation, chemotherapy, or other anti-cancer therapy within 4 weeks prior to enrollment in the study
5. Other prior malignancy, except for adequately treated superficial basal cell skin cancer, or any other cancer from which the patient has been disease-free for less than 5 years
6. Known brain or leptomeningeal involvement
7. Other concurrent serious illness or medical conditions
8. Inadequate organ function evidenced by unacceptable laboratory results

The investigator will evaluate whether there are other reasons why a patient may not participate.

Contacts and Locations

Locations

- United States, New Jersey
  - sanofi-aventis US
    - Bridgewater, New Jersey, United States, 08807
- Argentina
  - sanofi-aventis Argentina
    - Buenos Aires, Argentina
- Belgium
  - sanofi-aventis Belgium
    - Diegem, Belgium
- Brazil
  - sanofi-aventis Brazil
    - Sao Paulo, Brazil
- Canada, Quebec
  - sanofi-aventis Canada
    - Laval, Quebec, Canada
- Chile
  - sanofi-aventis Chile
    - Santiago, Chile
- Czech Republic
  - sanofi-aventis Czech Republic
    - Praha, Czech Republic
- Denmark
  - sanofi-aventis Denmark
    - Horsholm, Denmark
- Finland
  - sanofi-aventis Finland
    - Helsinki, Finland
- France
  - sanofi-aventis France
    - Paris, France
- Germany
  - sanofi-aventis Germany
    - Berlin, Germany
- Hungary
  - Sanofi-Aventis Hungaria
    - Budapest, Hungary
- India
  - sanofi-aventis India
    - Mumbai, India
- Italy
  - sanofi-aventis Italy

Milano, Italy
Korea, Republic of
sanofi-aventis South Korea
Seoul, Korea, Republic of
Mexico
sanofi-aventis Mexico
Mexico, Mexico
Netherlands
sanofi-aventis Netherlands
Gouda, Netherlands
Russian Federation
sanofi-aventis Russia
Moscow, Russian Federation
Singapore
sanofi-aventis Singapore
Singapore, Singapore
Slovakia
sanofi-aventis Slovakia
Bratislava, Slovakia
South Africa
sanofi-aventis South Africa
Midrand, South Africa
Spain
sanofi-aventis Spain
Barcelona, Spain
Sweden
sanofi-aventis Sweden
Bromma, Sweden
Taiwan
sanofi-aventis Taiwan
Taipei, Taiwan
Turkey
sanofi-aventis Turkey
Istanbul, Turkey
United Kingdom
sanofi-aventis UK
Guildford, Surrey, United Kingdom

Investigators

Study Director:	ICD	sanofi-aventis

More Information

Responsible Party: sanofi-aventis (International Clinical Development Study Director)

Study Results

Participant Flow

Recruitment Details	Multicenter study: 146 actives sites from 26 countries in Europe, USA, South America and Asia Pacific region. Study initiation date: January 2nd, 2007; study completion date/study cut off date: September 25th, 2009.
Pre-Assignment Details	165 patients signed informed consent but were not randomized and considered as screen failure. Intention to Treat Population (ITT or randomized patients): 755 patients (377 mitoxantrone, 378 cabazitaxel). Safety population (treated patients): 742 patients (371 mitoxantrone, 371 cabazitaxel) (Patients not treated: 6 mitoxantrone, 7 cabazitaxel).

Reporting Groups

	Description
Mitoxantrone + Prednisone	mitoxantrone 12 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily
Cabazitaxel + Prednisone	cabazitaxel 25 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily

Overall Study

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
Started	377 [1]	378 [1]
Completed	46 [1]	105 [1]
Not Completed	331	273
Disease progression	267	180
Adverse Event	32	67
Non-compliance to protocol	0	1
Lost to Follow-up	2	0
Withdrawal by Subject	17	8

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
Not treated	6	7
Screened failure	2	1
Investigator's decision	1	4
Non-confirmed Disease progression	1	1
Clinical deterioration	1	0
Screening error	2	1
Withdrawal by subject's family	0	1
Patient unable to come to the clinic	0	1
abnormal liver function tests	0	1

[1] Randomized patients

Baseline Characteristics

Reporting Groups

	Description
Mitoxantrone + Prednisone	mitoxantrone 12 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily
Cabazitaxel + Prednisone	cabazitaxel 25 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily

Baseline Measures

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone	Total
Number of Participants	377	378	755
Age, Continuous [units: years] Median (Full Range)	67.0 (47 to 89)	68.0 (46 to 92)	67 (46 to 92)
Gender, Customized Male [units: participants]	377	378	755
Region of Enrollment [units: participants]			
United States	106	97	203
Taiwan	4	7	11

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone	Total
Slovakia	1	1	2
Spain	10	9	19
Chile	9	12	21
Russian Federation	6	4	10
Italy	17	18	35
India	11	9	20
France	44	46	90
Denmark	19	26	45
South Africa	7	9	16
Netherlands	8	9	17
Korea, Republic of	8	7	15
Finland	4	1	5
Turkey	17	19	36
United Kingdom	17	20	37
Hungary	8	7	15
Czech Republic	10	12	22
Mexico	2	3	5
Canada	16	16	32
Argentina	7	3	10
Brazil	7	4	11
Belgium	16	15	31
Singapore	6	3	9
Germany	6	11	17
Sweden	11	10	21
Eastern Cooperative Oncology Group (ECOG) Performance Status [units: Participants]			

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone	Total
0 - Fully Active	120	141	261
1 - Ambulatory, Restricted Activity	224	209	433
2 - Ambulatory, No Work Activities	33	28	61
Prostatic Specific Antigen PSA [units: ng/mL] Median (Full Range)	127.5 (2 to 11220)	143.9 (2 to 7842)	135.00 (2 to 11220)
Measurable disease [1] [units: Participants]			
Measurable disease	204	201	405
Not Measurable disease	173	177	350
Extent of disease [2] [units: Participants]			
Metastatic	356	364	720
Locoregional Recurrence	20	14	34
Missing	1	0	1
Tumor Location: number of sites involved [units: Participants]			
1	134	146	280
2	117	112	229
3	78	73	151
4 or more	43	44	87
Missing	5	3	8

[1] Measurability of the disease per Response Evaluation Criteria in Solid Tumors (RECIST) criteria:

Patients with measurable disease have at least one visceral or soft tissue metastatic lesion (including new lesion).

Patient with non-measurable disease have documented rising PSA levels or appearance of new lesion.

[2] Extent of the disease at screening stage:

- Metastatic: bone or visceral metastases.

- Locoregional recurrence includes local recurrent tumor at the primary site, along the draining lymphatic channels, or within the draining lymphatic nodal basin.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Overall Survival
Measure Description	Overall survival was defined as the time interval from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, the survival time was censored at the last date patient was known to be alive or at the cut-off date, whichever had come first.
Time Frame	From the date of randomization up to 104 weeks (study cut-off)
Safety Issue?	No

Analysis Population Description

Analysis was performed on the intention To Treat (ITT) population. The ITT population is composed of all randomized patients (i.e. patients assigned to a treatment group by the randomization, regardless of whether patients received any study drug or received a different study drug from which they were randomized).

Reporting Groups

	Description
Mitoxantrone + Prednisone	mitoxantrone 12 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily
Cabazitaxel + Prednisone	cabazitaxel 25 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily

Measured Values

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
Number of Participants Analyzed	377	378
Overall Survival [units: Months] Median (95% Confidence Interval)	12.7 (11.6 to 13.7)	15.1 (14.1 to 16.3)

Statistical Analysis 1 for Overall Survival

Statistical Analysis Overview	Comparison Groups	Mitoxantrone + Prednisone, Cabazitaxel + Prednisone

	Comments	The study required an estimated sample size of 720 patients (360 per arm) in order to detect a 25% reduction in the hazard ratio for death in the cabazitaxel group relative to the mitoxantrone group with 90% power. The final analysis was planned for when 511 deaths had occurred.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	A 2-sided significance level of 0.0452 was used for the final analysis based on an interim analysis performed after 307 events with an adjusted significance level of 0.016 based on the O'Brien-Fleming type 1 error spending function.
	Method	Log Rank
	Comments	Analysis was performed by using a log-rank comparisons stratified according to disease measurability and ECOG performance status (0-1 versus 2)

2. Secondary Outcome Measure:

Measure Title	Time to Progression Free Survival (PFS)
Measure Description	Progression free survival was defined as a composite endpoint evaluated from the date of randomization to the date of tumor progression, PSA progression, pain progression, or death due to any cause, whichever occurred first
Time Frame	From the date of randomization up to 104 weeks (study cut-off)
Safety Issue?	No

Analysis Population Description

Analysis was performed on the intention To Treat (ITT) population. The ITT population is composed of all randomized patients (i.e. patients assigned to a treatment group by the randomization, regardless of whether patients received any study drug or received a different study drug from which they were randomized).

Reporting Groups

	Description
Mitoxantrone + Prednisone	mitoxantrone 12 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily
Cabazitaxel + Prednisone	cabazitaxel 25 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily

Measured Values

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
Number of Participants Analyzed	377	378

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
Time to Progression Free Survival (PFS) [units: Months] Median (95% Confidence Interval)	1.4 (1.4 to 1.7)	2.8 (2.4 to 3.0)

Statistical Analysis 1 for Time to Progression Free Survival (PFS)

Statistical Analysis Overview	Comparison Groups	Mitoxantrone + Prednisone, Cabazitaxel + Prednisone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Overall Tumor Response
Measure Description	Tumor Overall Response Rate (ORR) (only in patients with measurable disease): Objective responses (Complete Response and Partial Response) for measurable disease as assessed by investigators according to RECIST criteria. Complete Response (CR) is defined as: Disappearance of all target lesions. Partial Response (PR) is defined as: At least a 30% decrease in the sum of longest diameter (LD) of target lesions taking as reference baseline sum LD. Confirmation of objective responses will be performed by repeat tumor imaging (CT scans, MRI, bone scans) after the first documentation of response.
Time Frame	From the date of randomization up to 104 weeks (study cut-off)
Safety Issue?	No

Analysis Population Description

Tumor response rate was evaluated only for patients, in the Intention-To-Treat (ITT) population, with measurable disease by Response Evaluation Criteria in Solid Tumor (RECIST).

Reporting Groups

	Description
Mitoxantrone + Prednisone	mitoxantrone 12 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily
Cabazitaxel + Prednisone	cabazitaxel 25 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily

Measured Values

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
Number of Participants Analyzed	204	201
Overall Tumor Response [units: percentage of participants] Number (95% Confidence Interval)	4.4 (1.6 to 7.2)	14.4 (9.6 to 19.3)

Statistical Analysis 1 for Overall Tumor Response

Statistical Analysis Overview	Comparison Groups	Mitoxantrone + Prednisone, Cabazitaxel + Prednisone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0005
	Comments	[Not specified]
	Method	Chi-squared
	Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Time to Tumor Progression
Measure Description	Time to tumor progression is defined as the number of months from randomization until evidence of progressive disease (RECIST)
Time Frame	From the date of randomization up to 104 weeks (study cut-off)
Safety Issue?	No

Analysis Population Description

Analysis was performed on the intention To Treat (ITT) population. The ITT population is composed of all randomized patients (i.e. patients assigned to a treatment group by the randomization, regardless of whether patients received any study drug or received a different study drug from which they were randomized).

Reporting Groups

	Description
Mitoxantrone + Prednisone	mitoxantrone 12 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily
Cabazitaxel + Prednisone	cabazitaxel 25 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily

Measured Values

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
Number of Participants Analyzed	377	378
Time to Tumor Progression [units: Months] Median (95% Confidence Interval)	5.4 (4.7 to 6.5)	8.8 (7.4 to 9.6)

Statistical Analysis 1 for Time to Tumor Progression

Statistical Analysis Overview	Comparison Groups	Mitoxantrone + Prednisone, Cabazitaxel + Prednisone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Log Rank
	Comments	Log-rank comparisons stratified according to disease measurability and ECOG performance status.

Method of Estimation	Estimation Parameter	Cox Proportional Hazard
	Estimated Value	0.61
	Confidence Interval	(2-Sided) 95% 0.49 to 0.76

	Estimation Comments	Hazard ratio (HR) < 1 favours the cabazitaxel group and > 1 favours the mitoxantrone group.

5. Secondary Outcome Measure:

Measure Title	Time to Prostatic Specific Antigen (PSA) Progression
Measure Description	In PSA non-responders, progression will be defined as a 25% increase over nadir and increase in the absolute value PSA level by at least 5 ng/ml and confirmed by a second value at least 4 weeks later. In PSA responders and in patients not evaluable for PSA response at baseline, progression will be defined as a ≥50% increase over nadir, provided that the increase is a minimum of 5 ng/ml and confirmed by a second value at least 1 week later.
Time Frame	at screening, day 1 of every treatment cycle, up to 104 weeks (study cut-off)
Safety Issue?	No

Analysis Population Description

Analysis was performed on the intention To Treat (ITT) population. The ITT population is composed of all randomized patients (i.e. patients assigned to a treatment group by the randomization, regardless of whether patients received any study drug or received a different study drug from which they were randomized).

Reporting Groups

	Description
Mitoxantrone + Prednisone	mitoxantrone 12 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily
Cabazitaxel + Prednisone	cabazitaxel 25 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily

Measured Values

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
Number of Participants Analyzed	377	378
Time to Prostatic Specific Antigen (PSA) Progression [units: Months] Median (95% Confidence Interval)	3.1 (2.2 to 4.4)	6.4 (5.1 to 7.3)

Statistical Analysis 1 for Time to Prostatic Specific Antigen (PSA) Progression

Statistical Analysis Overview	Comparison Groups	Mitoxantrone + Prednisone, Cabazitaxel + Prednisone
	Comments	[Not specified]

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0010
	Comments	[Not specified]
	Method	Log Rank
	Comments	Log-rank comparisons stratified according to disease measurability and ECOG performance status.

Method of Estimation	Estimation Parameter	Cox Proportional Hazard
	Estimated Value	0.75
	Confidence Interval	(2-Sided) 95% 0.63 to 0.90
	Estimation Comments	Hazard ratio (HR) < 1 favours the cabazitaxel group and > 1 favours the mitoxantrone group.

6. Secondary Outcome Measure:

Measure Title	PSA (Prostate-Specific Antigen) Response
Measure Description	PSA response was defined as a ≥ 50% reduction in serum PSA, determined only for patients with a serum PSA ≥ 20ng/mL at baseline, confirmed by a repeat PSA ≥ 3 weeks later.
Time Frame	from baseline up to 104 weeks (study cut-off)
Safety Issue?	No

Analysis Population Description

Prostate Specific Antigen (PSA) response was evaluated only in patients, in the Intention-To-Treat population, with a baseline PSA >20ng/mL.

Reporting Groups

	Description
Mitoxantrone + Prednisone	mitoxantrone 12 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily
Cabazitaxel + Prednisone	cabazitaxel 25 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily

Measured Values

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
Number of Participants Analyzed	325	329
PSA (Prostate-Specific Antigen) Response [units: Percentage of participants] Number (95% Confidence Interval)	17.8 (13.7 to 22.0)	39.2 (33.9 to 44.5)

Statistical Analysis 1 for PSA (Prostate-Specific Antigen) Response

Statistical Analysis Overview	Comparison Groups	Mitoxantrone + Prednisone, Cabazitaxel + Prednisone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0002
	Comments	[Not specified]
	Method	Chi-squared
	Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Time to Pain Progression
Measure Description	Pain Progression is defined as an increase of ≥1 point in the median Personal Pain Intensity (PPI) from its nadir noted on 2 consecutive 3-week-apart visits or ≥25 % increase in the mean analgesic score compared with the baseline score & noted on 2 consecutive 3-week-apart visits or requirement for local palliative radiotherapy. Evaluation of the PPI & analgesic scores are based on the short-form McGill Pain Questionnaire which consists of 15 descriptors (11 sensory; 4 affective) which are rated on an intensity scale as 0=none (best) 1=mild 2=moderate 3=severe (worst) (TOTAL: 0=best 45=worst)
Time Frame	from baseline up to 104 weeks (study cut-off)
Safety Issue?	No

Analysis Population Description

Analysis was performed on the intention To Treat (ITT) population. Data from 265 and 279 patients in the cabazitaxel and mitoxantrone groups, respectively, were censored as a results of > 2 PPI and/or AS assessments being missed during the same week (unless a complete evaluation of ≥5 values showed pain progression).

Reporting Groups

	Description
Mitoxantrone + Prednisone	mitoxantrone 12 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily
Cabazitaxel + Prednisone	cabazitaxel 25 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily

Measured Values

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
Number of Participants Analyzed	377	378
Time to Pain Progression [units: Months] Median (95% Confidence Interval)	NA (NA to NA) [1]	11.1 (8.1 to NA) [2]

[1] Median not reached
[2] Upper confidence interval unevaluable

Statistical Analysis 1 for Time to Pain Progression

Statistical Analysis Overview	Comparison Groups	Mitoxantrone + Prednisone, Cabazitaxel + Prednisone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5192
	Comments	[Not specified]
	Method	Log Rank
	Comments	Log-rank comparisons stratified according to disease measurability and ECOG performance status.

Method of Estimation	Estimation Parameter	Cox Proportional Hazard
	Estimated Value	0.91
	Confidence Interval	(2-Sided) 95% 0.69 to 1.19
	Estimation Comments	Hazard ratio (HR) < 1 favours the cabazitaxel group and > 1 favours the mitoxantrone group.

8. Secondary Outcome Measure:

Measure Title	Pain Response
Measure Description	Pain Response was defined as a two-point or greater reduction from baseline median Present Pain Intensity (PPI) score without an increased Analgesic Score (AS) or a decrease of ≥50% in the AS without an increase in the PPI score, maintained for at least 3 weeks.
Time Frame	from baseline up to 104 weeks (study cut-off)
Safety Issue?	No

Analysis Population Description

Pain Response (applies only to patients, in the Intention-To-Treat (ITT) population, with median PPI ≥2 on McGill-Melzack scale and/or mean Analgesic Score ≥10 points at baseline)

Reporting Groups

	Description
Mitoxantrone + Prednisone	mitoxantrone 12 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily
Cabazitaxel + Prednisone	cabazitaxel 25 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily

Measured Values

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
Number of Participants Analyzed	168	174
Pain Response [units: Percentage of participants] Number (95% Confidence Interval)	7.7 (3.7 to 11.8)	9.2 (4.9 to 13.5)

Statistical Analysis 1 for Pain Response

Statistical Analysis Overview	Comparison Groups	Mitoxantrone + Prednisone, Cabazitaxel + Prednisone
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6286
	Comments	[Not specified]

	Method	Chi-squared
	Comments	[Not specified]

Reported Adverse Events

Time Frame	Adverse events are collected from the time to the first patient signed an informed consent form until 30 days after the administration of the last cycle of the study treatment to the last patient (i.e. 104 weeks).
Additional Description	The safety analyses are performed on the safety population which includes all randomized patients who received at least part of one dose of the study drug.

Reporting Groups

	Description
Mitoxantrone + Prednisone	mitoxantrone 12 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily
Cabazitaxel + Prednisone	cabazitaxel 25 mg/m^2 (Day 1) by intravenous (IV) every 3 weeks, and prednisone 10 mg orally given daily

Serious Adverse Events

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
	Affected/At Risk (%)	Affected/At Risk (%)
Total	77/371 (20.75%)	145/371 (39.08%)
Blood and lymphatic system disorders		
Anaemia [A] *	2/371 (0.54%)	2/371 (0.54%)
Febrile neutropenia [A] *	4/371 (1.08%)	25/371 (6.74%)
Leukopenia [A] *	0/371 (0%)	3/371 (0.81%)
Neutropenia [A] *	3/371 (0.81%)	18/371 (4.85%)
Pancytopenia [A] *	1/371 (0.27%)	0/371 (0%)
Thrombocytopenia [A] *	0/371 (0%)	2/371 (0.54%)
Cardiac disorders		
Atrial fibrillation [A] *	1/371 (0.27%)	2/371 (0.54%)
Cardiac arrest [A] *	0/371 (0%)	2/371 (0.54%)

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
	Affected/At Risk (%)	Affected/At Risk (%)
Cardiac failure [A] *	0/371 (0%)	2/371 (0.54%)
Cardiotoxicity [A] *	1/371 (0.27%)	0/371 (0%)
Myocardial infarction [A] *	1/371 (0.27%)	0/371 (0%)
Ventricular fibrillation [A] *	0/371 (0%)	1/371 (0.27%)
Gastrointestinal disorders		
Abdominal pain [A] *	0/371 (0%)	6/371 (1.62%)
Abdominal pain lower [A] *	0/371 (0%)	1/371 (0.27%)
Caecitis [A] *	0/371 (0%)	1/371 (0.27%)
Constipation [A] *	1/371 (0.27%)	3/371 (0.81%)
Diarrhoea [A] *	0/371 (0%)	9/371 (2.43%)
Duodenal ulcer perforation [A] *	0/371 (0%)	1/371 (0.27%)
Dysphagia [A] *	0/371 (0%)	1/371 (0.27%)
Enterocolitis [A] *	0/371 (0%)	1/371 (0.27%)
Enterovesical fistula [A] *	0/371 (0%)	1/371 (0.27%)
Gastric ulcer [A] *	0/371 (0%)	1/371 (0.27%)
Haematemesis [A] *	2/371 (0.54%)	0/371 (0%)
Haemorrhoidal haemorrhage [A] *	0/371 (0%)	1/371 (0.27%)
Intestinal obstruction [A] *	0/371 (0%)	3/371 (0.81%)
Mesenteric vein thrombosis [A] *	0/371 (0%)	1/371 (0.27%)
Nausea [A] *	1/371 (0.27%)	3/371 (0.81%)
Oesophageal ulcer [A] *	0/371 (0%)	1/371 (0.27%)
Pancreatic mass [A] *	1/371 (0.27%)	0/371 (0%)

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
	Affected/At Risk (%)	Affected/At Risk (%)
Pancreatitis [A] *	1/371 (0.27%)	0/371 (0%)
Proctalgia [A] *	1/371 (0.27%)	0/371 (0%)
Rectal haemorrhage [A] *	0/371 (0%)	2/371 (0.54%)
Vomiting [A] *	2/371 (0.54%)	6/371 (1.62%)
General disorders		
Asthenia [A] *	0/371 (0%)	2/371 (0.54%)
Chest pain [A] *	0/371 (0%)	2/371 (0.54%)
Disease progression [A] *	11/371 (2.96%)	1/371 (0.27%)
Fatigue [A] *	0/371 (0%)	1/371 (0.27%)
Influenza like illness [A] *	0/371 (0%)	1/371 (0.27%)
Oedema peripheral [A] *	0/371 (0%)	1/371 (0.27%)
Pain [A] *	0/371 (0%)	1/371 (0.27%)
Pyrexia [A] *	1/371 (0.27%)	6/371 (1.62%)
Sudden death [A] *	0/371 (0%)	1/371 (0.27%)
Hepatobiliary disorders		
Bile duct stone [A] *	0/371 (0%)	1/371 (0.27%)
Biliary colic [A] *	0/371 (0%)	1/371 (0.27%)
Cholangitis [A] *	1/371 (0.27%)	0/371 (0%)
Cholecystitis [A] *	0/371 (0%)	1/371 (0.27%)
Hepatic failure [A] *	1/371 (0.27%)	0/371 (0%)
Immune system disorders		
Anaphylactic shock [A] *	0/371 (0%)	1/371 (0.27%)
Infections and infestations		

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
	Affected/At Risk (%)	Affected/At Risk (%)
Bacteraemia [A] *	0/371 (0%)	1/371 (0.27%)
Bacterial sepsis [A] *	1/371 (0.27%)	0/371 (0%)
Bronchopneumonia [A] *	0/371 (0%)	1/371 (0.27%)
Campylobacter infection [A] *	0/371 (0%)	1/371 (0.27%)
Cellulitis [A] *	2/371 (0.54%)	1/371 (0.27%)
Cystitis [A] *	1/371 (0.27%)	1/371 (0.27%)
Febrile infection [A] *	1/371 (0.27%)	0/371 (0%)
Fungal sepsis [A] *	0/371 (0%)	1/371 (0.27%)
Groin abscess [A] *	0/371 (0%)	1/371 (0.27%)
Implant site cellulitis [A] *	0/371 (0%)	1/371 (0.27%)
Infection [A] *	2/371 (0.54%)	2/371 (0.54%)
Lobar pneumonia [A] *	1/371 (0.27%)	1/371 (0.27%)
Neutropenic infection [A] *	0/371 (0%)	2/371 (0.54%)
Neutropenic sepsis [A] *	1/371 (0.27%)	3/371 (0.81%)
Oesophageal candidiasis [A] *	0/371 (0%)	1/371 (0.27%)
Pneumococcal sepsis [A] *	1/371 (0.27%)	0/371 (0%)
Pneumonia [A] *	2/371 (0.54%)	6/371 (1.62%)
Pneumonia klebsiella [A] *	0/371 (0%)	1/371 (0.27%)
Salmonellosis [A] *	0/371 (0%)	2/371 (0.54%)
Sepsis [A] *	0/371 (0%)	4/371 (1.08%)
Septic shock [A] *	0/371 (0%)	4/371 (1.08%)
Urinary tract infection [A] *	3/371 (0.81%)	4/371 (1.08%)

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
	Affected/At Risk (%)	Affected/At Risk (%)
Urinary tract infection enterococcal [A] *	0/371 (0%)	1/371 (0.27%)
Urinary tract infection fungal [A] *	0/371 (0%)	1/371 (0.27%)
Urosepsis [A] *	2/371 (0.54%)	1/371 (0.27%)
Injury, poisoning and procedural complications		
Accidental overdose [A] *	1/371 (0.27%)	0/371 (0%)
Alcohol poisoning [A] *	1/371 (0.27%)	0/371 (0%)
Ankle fracture [A] *	0/371 (0%)	1/371 (0.27%)
Femur fracture [A] *	0/371 (0%)	1/371 (0.27%)
Fracture [A] *	1/371 (0.27%)	0/371 (0%)
Hip fracture [A] *	1/371 (0.27%)	2/371 (0.54%)
Multiple fractures [A] *	1/371 (0.27%)	0/371 (0%)
Tibia fracture [A] *	1/371 (0.27%)	0/371 (0%)
Investigations		
Eastern cooperative oncology group performance status worsened [A] *	0/371 (0%)	1/371 (0.27%)
Metabolism and nutrition disorders		
Dehydration [A] *	1/371 (0.27%)	4/371 (1.08%)
Electrolyte imbalance [A] *	0/371 (0%)	1/371 (0.27%)
Hyperglycaemia [A] *	0/371 (0%)	1/371 (0.27%)
Hyperkalaemia [A] *	0/371 (0%)	1/371 (0.27%)
Hypoalbuminaemia [A] *	0/371 (0%)	1/371 (0.27%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] *	1/371 (0.27%)	0/371 (0%)

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
	Affected/At Risk (%)	Affected/At Risk (%)
Back pain [A] *	4/371 (1.08%)	3/371 (0.81%)
Flank pain [A] *	0/371 (0%)	1/371 (0.27%)
Osteonecrosis [A] *	2/371 (0.54%)	1/371 (0.27%)
Pain in extremity [A] *	2/371 (0.54%)	2/371 (0.54%)
Spinal column stenosis [A] *	1/371 (0.27%)	0/371 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Cancer pain [A] *	1/371 (0.27%)	1/371 (0.27%)
Gastric cancer [A] *	1/371 (0.27%)	0/371 (0%)
Metastases to meninges [A] *	1/371 (0.27%)	0/371 (0%)
Metastases to spine [A] *	1/371 (0.27%)	0/371 (0%)
Metastatic pain [A] *	1/371 (0.27%)	1/371 (0.27%)
Prostate cancer metastatic [A] *	1/371 (0.27%)	0/371 (0%)
Nervous system disorders		
Altered state of consciousness [A] *	1/371 (0.27%)	0/371 (0%)
Cerebral haemorrhage [A] *	0/371 (0%)	1/371 (0.27%)
Cerebral infarction [A] *	1/371 (0.27%)	0/371 (0%)
Cerebrovascular accident [A] *	1/371 (0.27%)	0/371 (0%)
Cranial nerve paralysis [A] *	1/371 (0.27%)	0/371 (0%)
Epiduritis [A] *	1/371 (0.27%)	0/371 (0%)
Grand mal convulsion [A] *	0/371 (0%)	1/371 (0.27%)
Metabolic encephalopathy [A] *	0/371 (0%)	1/371 (0.27%)
Neuropathy peripheral [A] *	0/371 (0%)	1/371 (0.27%)

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
	Affected/At Risk (%)	Affected/At Risk (%)
Peripheral motor neuropathy [A] *	1/371 (0.27%)	0/371 (0%)
Presyncope [A] *	0/371 (0%)	1/371 (0.27%)
Speech disorder [A] *	0/371 (0%)	1/371 (0.27%)
Spinal cord compression [A] *	3/371 (0.81%)	4/371 (1.08%)
Syncope [A] *	1/371 (0.27%)	2/371 (0.54%)
Vestibular nystagmus [A] *	1/371 (0.27%)	0/371 (0%)
Vith nerve paralysis [A] *	0/371 (0%)	1/371 (0.27%)
Psychiatric disorders		
Confusional state [A] *	3/371 (0.81%)	1/371 (0.27%)
Psychotic disorder [A] *	1/371 (0.27%)	0/371 (0%)
Suicidal ideation [A] *	0/371 (0%)	1/371 (0.27%)
Renal and urinary disorders		
Bladder neck obstruction [A] *	0/371 (0%)	1/371 (0.27%)
Haematuria [A] *	3/371 (0.81%)	10/371 (2.7%)
Hydronephrosis [A] *	1/371 (0.27%)	4/371 (1.08%)
Postrenal failure [A] *	1/371 (0.27%)	0/371 (0%)
Renal colic [A] *	0/371 (0%)	1/371 (0.27%)
Renal failure [A] *	0/371 (0%)	6/371 (1.62%)
Renal failure acute [A] *	0/371 (0%)	5/371 (1.35%)
Ureteric obstruction [A] *	0/371 (0%)	4/371 (1.08%)
Ureteric stenosis [A] *	1/371 (0.27%)	1/371 (0.27%)
Urethral pain [A] *	0/371 (0%)	1/371 (0.27%)

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
	Affected/At Risk (%)	Affected/At Risk (%)
Urethral stenosis [A] *	0/371 (0%)	1/371 (0.27%)
Urinary retention [A] *	2/371 (0.54%)	2/371 (0.54%)
Urinary tract obstruction [A] *	0/371 (0%)	1/371 (0.27%)
Reproductive system and breast disorders		
Penile oedema [A] *	1/371 (0.27%)	0/371 (0%)
Respiratory, thoracic and mediastinal disorders		
Aspiration [A] *	0/371 (0%)	1/371 (0.27%)
Chronic obstructive pulmonary disease [A] *	1/371 (0.27%)	0/371 (0%)
Chylothorax [A] *	0/371 (0%)	1/371 (0.27%)
Dyspnoea [A] *	1/371 (0.27%)	3/371 (0.81%)
Hypoxia [A] *	0/371 (0%)	1/371 (0.27%)
Pleural effusion [A] *	1/371 (0.27%)	0/371 (0%)
Pneumonitis [A] *	0/371 (0%)	1/371 (0.27%)
Pulmonary embolism [A] *	6/371 (1.62%)	5/371 (1.35%)
Respiratory failure [A] *	0/371 (0%)	2/371 (0.54%)
Vascular disorders		
Deep vein thrombosis [A] *	2/371 (0.54%)	2/371 (0.54%)
Extremity necrosis [A] *	1/371 (0.27%)	0/371 (0%)
Haematoma [A] *	0/371 (0%)	1/371 (0.27%)
Hypotension [A] *	0/371 (0%)	1/371 (0.27%)
Orthostatic hypotension [A] *	0/371 (0%)	1/371 (0.27%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA 12.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
	Affected/At Risk (%)	Affected/At Risk (%)
Total	323/371 (87.06%)	350/371 (94.34%)
Blood and lymphatic system disorders		
Anaemia [A] *	18/371 (4.85%)	38/371 (10.24%)
Neutropenia [A] *	38/371 (10.24%)	66/371 (17.79%)
Gastrointestinal disorders		
Abdominal pain [A] *	13/371 (3.5%)	38/371 (10.24%)
Abdominal pain upper [A] *	5/371 (1.35%)	20/371 (5.39%)
Constipation [A] *	56/371 (15.09%)	73/371 (19.68%)
Diarrhoea [A] *	39/371 (10.51%)	170/371 (45.82%)
Dyspepsia [A] *	6/371 (1.62%)	25/371 (6.74%)
Nausea [A] *	84/371 (22.64%)	127/371 (34.23%)
Vomiting [A] *	36/371 (9.7%)	80/371 (21.56%)
General disorders		
Asthenia [A] *	46/371 (12.4%)	76/371 (20.49%)
Fatigue [A] *	102/371 (27.49%)	136/371 (36.66%)
Mucosal inflammation [A] *	10/371 (2.7%)	22/371 (5.93%)
Oedema peripheral [A] *	34/371 (9.16%)	34/371 (9.16%)
Pain [A] *	18/371 (4.85%)	19/371 (5.12%)
Pyrexia [A] *	22/371 (5.93%)	40/371 (10.78%)
Infections and infestations		
Urinary tract infection [A] *	9/371 (2.43%)	24/371 (6.47%)

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
	Affected/At Risk (%)	Affected/At Risk (%)
Investigations		
Weight decreased [A] *	28/371 (7.55%)	32/371 (8.63%)
Metabolism and nutrition disorders		
Anorexia [A] *	39/371 (10.51%)	59/371 (15.9%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] *	31/371 (8.36%)	39/371 (10.51%)
Back pain [A] *	41/371 (11.05%)	58/371 (15.63%)
Bone pain [A] *	19/371 (5.12%)	19/371 (5.12%)
Muscle spasms [A] *	10/371 (2.7%)	27/371 (7.28%)
Musculoskeletal pain [A] *	20/371 (5.39%)	18/371 (4.85%)
Pain in extremity [A] *	27/371 (7.28%)	29/371 (7.82%)
Nervous system disorders		
Dizziness [A] *	21/371 (5.66%)	30/371 (8.09%)
Dysgeusia [A] *	15/371 (4.04%)	41/371 (11.05%)
Headache [A] *	19/371 (5.12%)	28/371 (7.55%)
Neuropathy peripheral [A] *	4/371 (1.08%)	30/371 (8.09%)
Peripheral sensory neuropathy [A] *	5/371 (1.35%)	20/371 (5.39%)
Renal and urinary disorders		
Dysuria [A] *	5/371 (1.35%)	25/371 (6.74%)
Haematuria [A] *	13/371 (3.5%)	58/371 (15.63%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] *	22/371 (5.93%)	40/371 (10.78%)
Dyspnoea [A] *	16/371 (4.31%)	43/371 (11.59%)

	Mitoxantrone + Prednisone	Cabazitaxel + Prednisone
	Affected/At Risk (%)	Affected/At Risk (%)
Skin and subcutaneous tissue disorders		
Alopecia [A] *	18/371 (4.85%)	37/371 (9.97%)
Vascular disorders		
Hypotension [A] *	9/371 (2.43%)	19/371 (5.12%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 12.0

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Publication of the study will be made jointly in the name of all wholehearted collaborators. Other papers will be authored based on the contributions of the individuals to the overall study. Substudies with scientific merit which have received prior approval from the Steering Committee (SC) may be published in the names of the contributing investigators. A copy of all manuscripts will be provided to the sponsors for their review. The final decision to publish articles will be made by the SC.

Results Point of Contact:

Name/Official Title: International Clinical Development Study Director
Organization: sanofi-aventis
Phone:
Email: GV-Contact-us@sanofi-aventis.com