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Sponsor / Company: Sanofi	**Study Identifiers:** NCT00436839
Drug substance(s): Taxotere/docetaxel / XRP6976	**Study code:** DOCET_L_01833

Title of the study: A Multicenter, Parallel Controlled, Open-label, 1:1 Randomized Clinical Trial Comparing the Three-weekly Docetaxel Regimen in Combination with Prednisone versus Mitoxantone in Combination with Prednisone for Metastatic Hormone Refractory Prostate Cancer

Study center(s): 15 Active sites in China

Study period:

Date first patient enrolled: 09/Jan/2007

Date last patient completed: 30/Jun/2012

Phase of development: 3

Objectives:

Primary objective

To compare the overall survival (OS) after docetaxel (Taxotere®) and Prednisone (Arm A) versus mitoxantrone and prednisone (Arm B) in patients with metastatic hormone refractory prostate cancer.

Secondary objectives

To compare the following indicators between 2 treatment groups:

- Progression-free survival (PFS)
- Pain improvement (incidence and duration)
- Prostate specific antigen (PSA) response (incidence and duration)
- Quality of Life (QoL)
- Overall response rate (ORR) in patients with measurable lesions
- Safety

Methodology: prospective, multicenter, active control, open-label, randomized (1:1), parallel group study conducted in patients with metastatic hormone refractory prostate cancer. Randomization was centralized and stratified for present pain intensity (PPI; mean PPI≥2 versus <2) and Karnofsky Performance Status (KPS; KPS≥80 versus ＜80).

Number of patients:	Planned: 240 Randomized: 228 Treated: 220
Evaluated:	Efficacy (per protocol): 189 Safety: 220

Diagnosis and criteria for inclusion:

Patients with metastatic prostate adenocarcinoma that were unresponsive or refractory to hormone therapy were included in the study after giving written informed consent. Patients had to have documented progression detected by PSA increase, physical examination and/or imaging; and had to have achieved stable analgesia for a minimum of 7 consecutive days prior to randomization. Prior treatment with corticosteroids, prior radiation therapy (to ≤25% of the bone marrow only were allowed in the study). Patients had to have Karnfoskys Performance Status ≥ 70, normal left ventricular ejection fraction (LVEF) and standard routine laboratory requirement, and life expectancy ≥ 3 months.

Study treatments

Investigational medicinal products:

The dosing regimen could be modified by dose reduction and/or treatment delay and/or treatment discontinuation in case of severe hematological and/or non-hematological toxicities.

Arm A: Docetaxel (taxotere®) (TXT) and Prednisolone (PRE)	**Arm B: Mitoxantone (MIT) and Prednisolone (PRE)**
Formulation: Docetaxel: infusion solution Prednisolone: capsules Route of administration: Docetaxel: IV infusion every 3 weeks for 10 cycles Prednisolone: oral Dose regimen: Docetaxel: 75 mg/m^2 Prednisolone: 10 mg	Formulation: Mitoxantone: infusion solution Prednisolone: capsules Route of administration: Mitoxantone: IV infusion every 3 weeks for 10 cycles Prednisolone: oral Dose regimen: Mitoxantone: 12 mg/m^2 Prednisolone: 10 mg

Duration of treatment: 10 cycles in both groups.

Duration of observation: Follow-up will continue after end of treatment monthly until death. If the patient goes off study before disease progression, clinical and radiological assessments of all lesions will be performed every 2 months at the visits until tumor progression.

Criteria for evaluation:

Efficacy:

Overall survival, PFS, response rate and response duration were assessed in both treatment groups to evaluate efficacy. Scheduled assessment of the 3 variables (Present Pain Intensity [PPI]/Analgesics Score [AS], PSA values and tumor lesions) was planned to define response and progression according to established criteria for each set of efficacy variables. Pain response applied only to patients with a median PPI ≥ 2 on the McGill Melzack scale and/or a mean AS ≥ 10 at baseline, was defined as a 2-point or greater reduction with no increase in analgesic score, or a reduction of at least 50% in analgesic use from baseline analgesic score with an increase in pain (only for patients with baseline AS>10) maintaining for 3 weeks. PSA response applied only to patients with PSA ≥20 ng/ml at baseline was defined as a reduction of at least 50% maintaining for 3 weeks. Tumor response applied to patients who presented uni- or bi-dimensionally measurable lesions or non-measurable but evaluable lesions, using World Health Organization assessment criteria (ie, complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]). Event progression-free survival was calculated among all patients. Event progression-free survival (EPFS), ie, the time interval between randomization and the date of event progression, further antitumor therapy, or the date of death, was calculated for pain, PSA, tumor lesions and disease.

Safety:

Safety data included AEs, clinical examinations, vital signs, KPS and clinical tests (ie, hematology and biochemistry, electrocardiograms, LVEF measurement, and chest X-ray). Clinical and laboratory toxicity/symptom was graded according to NCI-CTC toxicity standard (version 3.0). Prior to dose administration of every cycle, AE, disease symptom/signs, and blood chemistry were assessed once. Blood routine was assessed once weekly.

Statistical methods:

Efficacy analysis

The primary analysis was to compare OS in the intent to treat (ITT) population using Kaplan-Meier curve and log-rank test, stratified by baseline pain (PPI ≥2 versus <2) and performance status (KPS ≥80 versus < 80) as specified at randomization. Testing at two-sided 5% significance level was performed. The Kaplan-Meier curve was used to describe survival data, in each analysis, hazard ratios (HR) and 95% confidence intervals (CI) were presented.

Secondary efficacy analyses for event progression-free survival in both ITT and PPS population were conducted using Kaplan-Meier curve and log-rank test for pain, PSA, tumor, and disease. Hazard ratios and corresponding 95% CIs were presented. Response rates for pain and PSA were calculated in both ITT and PPS population, tumor response rate was calculated in ITT population only using chi-square or Fisher's exact test. Duration of pain response and duration of PSA response were analyzed using the log-rank test among those who responded. Quality of life analyses included the change from baseline for domain scores (ie, physical well-being, social/family well-being, emotional well-being, functional well-being, and prostate specific concerns). QoL and clinical benefit time-to-event endpoints were analyzed similarly to secondary efficacy endpoints.

Two supportive multivariate analyses were introduced to analyze the potential effect on hazard risk or response rate. In the first multiple analysis, Cox proportional hazard model was applied to assess potential effect of 2 prognostic variables (baseline PPI and KPS) on hazard risk. In the second multiple analysis, logistic regression model was used to evaluate potential effect of following prognostic factors on response rate: age, visceral metastases, prior hormone therapy, prior estramustine therapy, increase of PSA, baseline hemoglobin, and baseline alkaline phosphatases. Pre-specified subgroup analysis about OS and PFS were conducted for consistency check of treatment effect. A backward elimination (stepwise) was applied to screen prognostic factors, and the final model excluded all interaction terms and the terms that were not significant at a two-sided 10% level.

Safety analysis

The safety analyses were to include a comparison of the safety parameters between the 2 treatment groups in the safety population. All AEs were summarized with counts and percentages. The selected safety endpoints profile was analyzed using Fisher's exact test.

Treatment-emergent adverse events (TEAEs) were to be summarized as the primary assessment of safety and determined programmatically. A TEAE was considered as any event not present prior to the initiation of treatment that developed during the on-study period or any event already present that worsened in intensity during the on-study period, where the on-study period was determined by a valid on-study cycle.

TEAEs were summarized by patient and by cycle for each of the 2 treatment groups. The worst NCI grade (for NCI gradable AEs) and maximum severity [for Medical Dictionary for Regulatory Activities (MedDRA) classifications] were presented for TEAEs. In addition, grade 3-5 NCI gradable AEs and severe non-NCI gradable AEs were also summarized for TEAEs.

Serious AEs were listed and summarized by patient and by cycle for each of the 2 treatment groups. The number of deaths, cause of death, and the number of days since the last infusion of the study drug (≤ 30 days and >30 days) were summarized by treatment group.

Interim analysis

Two interim analyses were performed in November 2008 and September 2009, separately. Sixty patients were included in the first interim analysis and 109 patients in the second interim analysis. The major aim for interim analyses was to evaluate the safety of study medication. Both reports summarized TEAE and TE-SAE, and assessment made on hematologic toxicity, biochemical toxicity and specific safety events. In addition, the second interim analysis was performed to evaluate pain response, tumor response, and PSA response. The results of these 2 interim analyses were submitted to State Food and Drug Administration (SFDA) for new indication application, which was approved in August 2010.

Summary:

Population characteristics:

A total of 228 patients were randomized in the 15 center between 9 January 2007 and 16 December 2010 as ITT population; 220 patients were treated and entered into safety population; 189 patients without major protocol deviation were included into PPS population. The patients were followed through June 30, 2012 (ie, the cut-off date for ascertainment of survival).

All patients had completed study medication or discontinued therapy by the cut-off date for analysis. The table below presents reasons for therapy discontinuation, as determined by Investigators, according to treatment group in the ITT population.

Reason for therapy discontinuation*, ITT population

	Treatment group		
	TXT + PRE N (%)	**MIT + PRE N (%)**	**All N (%)**
Randomized ITT	113	115	228
Completed study medication	50 (44.25)	27 (23.48)	77 (33.77)
Progressive disease/death	31 (27.43)	41 (35.65)	72 (31.58)
Adverse event	9 (7.96)	15 (13.04)	24 (10.53)
Lost to follow-up	3 (2.65)	4 (3.48)	7 (3.07)
Other major deviation	2 (1.77)	2 (1.74)	4 (1.75)
Other therapy/procedure not permitted	2 (1.77)	3 (2.61)	5 (2.19)
Consent withdrawn	1 (0.88)	0 (0.00)	1 (0.44)
Other	15 (13.27)	23 (20.00)	38 (16.67)

* as determined by investigator

Eight patients were randomized but never treated. Information on chemotherapy and prednisone dosage and duration in the table below are provided for the safety population, which consisted of all patients who started at least one infusion of study drug or who received at least one dose of corticosteroids, regardless of study eligibility.

Drug delivery and duration of chemotherapy, safety population

	Treatment group	
	TXT + PRE	**MIT + PRE**
No. of patients who received study chemotherapy	111	109
Median cumulative dose, mg/m^2	567.18	46.58
Median actual dose intensity, mg/m^2/wk	22.78	3.78
Median relative dose intensity (% of planned)	0.91	0.95
Median duration of study chemotherapy (weeks)	25	12.14
Total no. of cycles received	786	529
Median No. of cycles by patient	8	4
No. of patients (%) receiving at least		
5 cycles of study chemotherapy	81 (72.97)	47 (43.12)
10 cycles of study chemotherapy	49 (44.14)	21 (19.27)

Demographics and baseline characteristics of the ITT population are summarized in the table below.

Demographics and baseline characteristics, ITT population

	Treatment group		
	TXT + PRE N (%)	**MIT + PRE N (%)**	**All N (%)**
No. of patients	113	115	228
Age			
Median (range)	70.69 (44.2-82.32)	70.80 (49.56-81.13)	70.75 (44.28-82.32)
≥65y	81 (71.68)	84 (73.04)	165 (72.37)
KPS			
Median (range)	90 (70-100)	90 (60-100)	90 (60-100)
≥80	102 (90.27)	96 (83.48)	198 (86.84)
PPI			
Median (range)	1 (0-5)	1 (0-4.17)	1 (0-5)
≥2	32 (28.32)	29 (25.22)	61 (26.75)
Duration of prostate cancer			
Median (range)	2.05 (0.5-10.14)	1.91 (0.35-10.31)	1.98 (0.35-10.31)
Type of site involved*			
No site involved	2 (1.8)	8 (7.0)	10 (4.4)
Bone	87 (77.0)	87 (75.7)	174 (76.3)
Lymph nodes	9 (8.0)	12 (10.4)	21 (9.2)
Visceral	9 (8.0)	8 (7.0)	17 (7.5)
Liver	1 (0.9)	3 (2.6)	4 (1.8)
Lung	6 (5.3)	4 (3.5)	10 (4.4)
Other organs	2 (1.8)	1 (0.9)	3 (1.3)
Other soft tissues	6 (5.3)	0 (0)	6 (2.6)
Baseline PSA			
Median (range)	44.35 (0.99-1065.50)	82.21 (0.06-2092.74)	68.97 (0.06-2092.74)
Prior anticancer therapy			
Surgery**	27 (23.89)	29 (25.22)	56 (24.56)
Radiotherapy	21 (18.58)	22 (19.13)	43 (18.86)
Hormonal therapy	112 (99.12)	109 (94.78)	221 (96.93)
Castration	110 (97.35)	107 (93.04)	217 (95.18)
Anti-androgen	108 (95.58)	106 (92.17)	214 (93.86)
Estramustine	15 (13.27)	9 (7.83)	24 (10.53)

*Sites included bone, lymph nodes, soft tissue, liver, lung and other organs.
**Surgery for hormonal control is included in hormonal therapy.

Therefore, based on the demographics and baseline characteristics, the study population could be considered as being representative of patients with metastatic hormone refractory prostate cancer for treatment with the study medication.

Efficacy results:

The prospective statistical analysis plan specified that the survival cut-off was to be chosen to include at least 160 deaths (70% endpoint events). As a consequence, the survival status of all patients was determined as of 30 June 2012, the date on which the 160th notification of a death was received. All patients known to be alive at the cut-off date were censored either on the date of last assessment or, on the date of cut-off if the last contact had taken place at a later time. The median follow-up time was 39.13 months for TXT group and 28.45 months for MIT group.

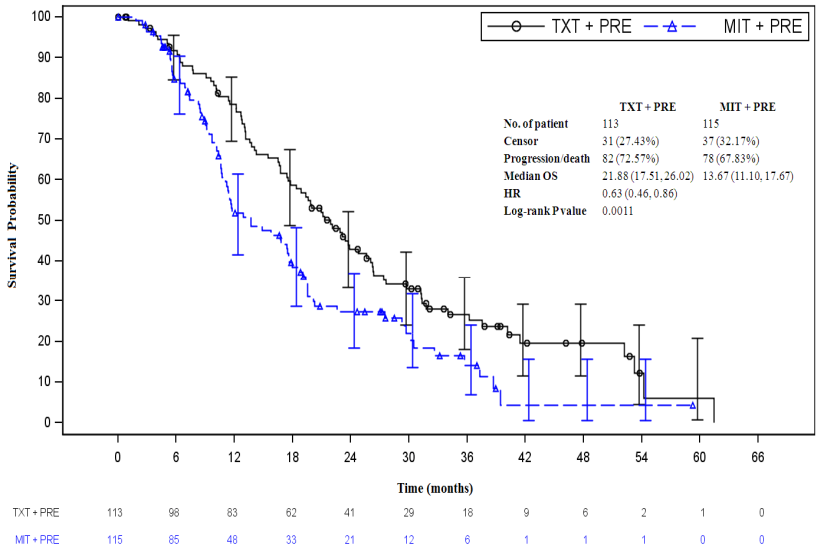
It was prospectively specified that the stratified log-rank test, stratified on baseline pain and KPS, would be the primary means of determining if TXT group increased survival compared with MIT group.

Efficacy results of this study demonstrated that TXT group achieved significant and consistent improvements over MIT group on both primary endpoint and secondary endpoints that were used to establish the effectiveness of anticancer drugs (OS, PFS, RR).

Primary endpoint

Overall survival was significantly superior in the TXT group compared with the MIT group (P = 0.0011, hazard ratio = 0.63, 95% CI [0.46-0.86]). The median overall survival was 21.88 months in TXT group versus 13.67 months in MIT group.

Kaplan-Meier plot for OS in each treatment group, ITT population

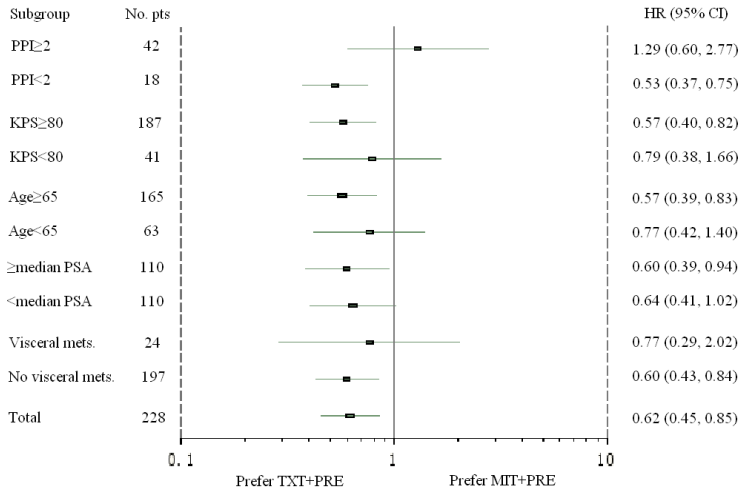


	TXT + PRE	MIT + PRE
No. of patient	113	115
Censor	31 (27.43%)	37 (32.17%)
Progression/death	82 (72.57%)	78 (67.83%)
Median OS	21.88 (17.51, 26.02)	13.67 (11.10, 17.67)
HR	0.63 (0.46, 0.86)	
Log-rank P value	0.0011	

Subgroup analyses

The primary analysis on OS was repeated in a number of patient subsets defined by the stratification variables (baseline PPI and KPS) or the prognostic factors of interest (age, baseline PSA, visceral involved). The figure below present the Hazard Ratio and 95% CI for the ITT population and all subgroups analyzed. These results demonstrate that the overall survival results comparing TXT with MIT in the subgroups were consistent with the results in the ITT population.

Hazard Ratio and 95% CI for OS Comparing TXT with MTZ



Secondary endpoints

The analyses on event progression-free survival (pain, PSA, tumor and disease) in both ITT and PPS populations were all significantly in favor of TXT group over MIT group. In ITT population, median pain PFS was higher in TXT group (12.71 months, P=0.0008, HR=0.51) compared with MIT group (5.55 months). Median PSA PFS was higher in TXT group (12.71 months, P=0.0005, HR=0.53) compared with MIT group (5.55 months). Median tumor PFS was higher in TXT group (12.19 months, P=0.0306, HR=0.65) compared with MIT group (9.13 months). Median disease PFS was higher in TXT group (3.42 months, P=0.0021, HR=0.66) compared with MIT group (2.14 months).

In ITT population, pain response rate was higher in TXT group (61.11%, P=0.0011) than in MIT (23.08%). Median duration of pain response was 3.71 months for TXT group, but not reached statistical significance compared with MIT group (2.17 months, P=0.23). PSA response rate was higher in TXT group (35.11%, P=0.0155) than in MIT group (19.39%). Median duration of PSA response was 4.20 months for TXT group and 2.83 months for MIT groups (P=0.0792). Tumor response rate was 24.14% for TXT group and 16.13% for MIT group (P=0.5269).

In QoL population, TOI scores increased over time (indicating improved QoL) for the 2 treatment groups. Observed response rate was higher in TXT group (19.75%) than in MIT group (15.79%), but the difference between the 2 groups was not statistically significant (P=0.5393).

Safety results:

The safety population consisted of 220 patients who received at least one dose of study medication, regardless of study eligibility. The analysis of the safety data demonstrated that the tolerability and overall safety of Docetaxel in combination with prednisone was generally comparable to that of mitoxantrone plus prednisone.

A summary of the incidence of TEAEs in the safety population, by subjects and by cycles, is presented in the table below. Overall, 203 patients (92.27%) experienced at least 1 TEAE, regardless of relationship to study treatment. When considering only grade 3-4 AEs, regardless of relationship to study treatment, a higher percentage of patients were recorded with at least 1 TEAE in the TXT group (74.77%) than in the MIT group (66.06%).

Overview of patients and cycles with TEAEs

	Treatment group	
	TXT + PRE N (%)	**MIT + PRE N (%)**
No. of patients	111	109
With at least one TEAE regardless of relationship to study treatment	105 (94.59)	98 (89.91)
With at least one TEAE possibly or probably related to study treatment	102 (91.89)	94 (86.24)
With at least one grade 3-5 TEAE regardless of relationship to study treatment	83 (74.77)	72 (66.06)
With at least one grade 3-5 TEAE possibly or probably related to study treatment	79 (71.17)	68 (62.39)
No. of cycles	786	529
With at least one TEAE regardless of relationship to study treatment	495 (62.98)	343 (64.84)
With at least one TEAE possibly or probably related to study treatment	477 (60.69)	332 (62.76)
With at least one grade 3-5 TEAE regardless of relationship to study treatment	286 (36.39)	180 (34.03)
With at least one grade 3-5 TEAE possibly or probably related to study treatment	276 (35.11)	173 (32.7)

The 10 most common TEAEs observed in the TXT group were anticipated based on the known safety profile for docetaxel. These events, in order of decreasing frequency, were neutropenia, leucopenia, alopecia, infection, fever, anemia, nausea, fatigue, diarrhea, febrile neutropenia. The incidences of the same 10 events in the MTZ group were similar to those of the TXT group for neutropenia, infection, anemia, nausea, and febrile neutropenia, but were lower for alopecia, fever, diarrhea while were higher for leucopenia, fatigue. Events of all grades that were reported less often but whose incidences were higher in the TXT group than in the MTZ group were peripheral edema, allergic reactions, erythra, and cardiac failure. Vomiting, bone pain and hyponatremia had higher incidences in the MTZ group than TXT group.

TEAEs of patients in each treatment group- regardless of relationship to study drug -by NCI terms ordered by the TXT group

AE	Treatment group			
	TXT + PRE (N=111)		MIT + PRE (N=109)	
	All grades N (%)	Grade 3-5 N (%)	All grades N (%)	Grade 3-5 N (%)
Neutropenia	65 (58.56)	64 (57.66)	58 (53.21)	50 (45.87)
Leucopenia	22 (19.82)	19 (17.12)	33 (30.28)	25 (22.94)
Alopecia	9 (8.11)	4 (3.6)	3 (2.75)	1 (0.92)
Infection	6 (5.41)	5 (4.5)	6 (5.5)	5 (4.59)
Fever	6 (5.41)	4 (3.6)	1 (0.92)	1 (0.92)
Anemia	5 (4.5)	4 (3.6)	4 (3.67)	3 (2.75)
Nausea	5 (4.5)	0 (0.00)	4 (3.67)	1 (0.92)
Fatigue	4 (3.6)	0 (0.00)	10 (9.17)	4 (3.67)
Diarrhea	4 (3.6)	2 (1.8)	0 (0.0)	0 (0.0)
Febrile neutropenia	2 (1.8)	2 (1.8)	0 (0.0)	0 (0.0)
Pharyngitis	2 (1.8)	1 (0.9)	2 (1.83)	0 (0.0)
Oral ulcer	2 (1.8)	1 (0.9)	2 (1.83)	0 (0.0)
Hypokalemia	2 (1.8)	2 (1.8)	1 (0.92)	1 (0.92)
Cardiac failure	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
Peripheral edema	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Erythra	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	1 (0.9)	0 (0.0)	3 (2.75)	1 (0.92)
Bone pain	1 (0.9)	0 (0.0)	3 (2.75)	2 (1.83)
Hyponatremia	1 (0.9)	1 (0.9)	2 (1.83)	2 (1.83)
Allergic reactions	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)

Overall, 17 of 220 patients (7.73%) experienced at least 1 treatment-emergent (TE) SAE: 8 patients (7.21%) treated with TXT and 9 patients (8.26%) treated with MIT. When considering only grade 3-5 TE-SAE, regardless of relationship to study treatment, the number of patients experienced at least 1 TE-SAE in the TXT group and MIT group was 7 (6.31%) and 6 (5.5%), respectively.

TE-SAEs of all Grades regardless of relationship to study drug-by NCI category ordered by the TXT group

SAE	Treatment group	
	TXT + PRE (N=111)	MIT + PRE (N=109)
	N (%)	N (%)
Infection	4 (3.6)	4 (3.67)
Pulmonary	1 (0.9)	0 (0.0)
Renal/Genitourinary	0 (0.0)	2 (1.83)
Gastrointestinal	2 (1.8)	0 (0.0)
Cardiovascular	1 (0.9)	2 (1.83)
Coagulation	1 (0.9)	0 (0.0)
Blood/Lymphatic	0 (0.0)	1 (0.92)

The incidences of TE-SAE and TEAEs that led to discontinuation in TXT group (8.11%) were lower than those in MIT group (13.76%).

At the time of the cut-off date for survival (30 June 2012), 160 of the 220 treated patients (72.73%) had died: 5 patients (2.27 %) during the study treatment period (within 30 days of their last study-treatment infusion), and 155 (70.45%) after more than 30 days from their last study treatment infusion.

Death within 30 days of the last administration of study medication was rare in both treatment groups (TXT: 2.70% versus MIT: 1.83%). Most mortality (TXT: 71.17% versus MIT: 69.72%) occurred beyond 30 days after last administration of study medication, usually attributed to progressive disease.

Summary of deaths by cause of death and by day from last infusion of study chemotherapy, Safety population

	Treatment group		
	TXT + PRE (N=111)	**MIT + PRE (N=109)**	**All (N=220)**
	N (%)	**N (%)**	**N (%)**
Death	82 (73.87)	78 (71.56)	160 (72.73)
During Study-treatment within 30 days of last infusion	3 (2.70)	2 (1.83)	5 (2.27)
Due to progression	0 (0.00)	1 (0.92)	1 (0.45)
Due to drug-related toxicity	3 (2.70)	1 (0.92)	4 (1.82)
Due to other causes	0 (0.00)	0 (0.00)	0 (0.00)
More than 30 days after last study treatment infusion	79 (71.17)	76 (69.72)	155 (70.45)
Due to progression	65 (58.56)	61 (55.96)	126 (57.27)
Due to drug-related toxicity	13 (11.71)	11 (10.09)	24 (10.91)
Due to other causes	1 (0.90)	4 (3.67)	5 (2.27)

Issue date: 23-Aug-2013