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Sponsor (Collaborator): sanofi-aventis (Regeneron) **Drug substance(s):** Aflibercept (AVE0005)	**Study Identifier:** NCT00876044 **Study code:** TES10897(QUTIE)
Title of the study: A randomized, double-blind, placebo-controlled study comparing aflibercept versus placebo on the QTc interval in cancer patients treated with docetaxel (TES10897 QUTIE study)	
Study center(s): 20 centers in 7 countries: 4 centers in Germany, 3 centers in Italy, 3 center in Belgium, 3 centers in Romania, 3 centers in the USA, 2 centers in Denmark and 2 centers in Turkey.	
Study period: Date first patient enrolled: 08 April 2009 Date study completion (last patient last visit): 08 November 2010	
Phase of development: Phase 1	
Objectives: ***Primary objective*** • To assess the effect on QTcF interval (QTc Fridericia) of aflibercept versus placebo, in cancer patients ***Secondary objectives*** • to assess the effects of aflibercept versus placebo on heart rate (HR), QT, QTcB (Bazett's correction), and QTcN (population specific correction formula) intervals • to assess the overall clinical safety of the two treatment arms • to assess the pharmacokinetic (PK) profile of aflibercept (administered every 3 weeks) at Cycle 1 and Cycle 3	
Methodology: This was a prospective multicenter, international, randomized, double-blind, parallel-group study that enrolled patients with solid malignancy and for which treatment with single agent docetaxel (administered every 3 weeks at dose <75 mg/m^2) was planned. Patients received for at least 3 cycles, double-blind treatment (aflibercept or placebo) on top of docetaxel and then continued to be treated until occurrence of unacceptable toxicity, decision from the patient or Investigator to discontinue double-blind treatment, need to use anti-cancer treatment other than aflibercept and docetaxel, or until a maximum of 15 cycles, whichever came first. QTc and other ECG intervals were assessed at Cycle 1 and Cycle 3 using a 12-lead Holter ECG monitor. Concomitant serial PK blood sampling was also performed at Cycle 1 and Cycle 3. In addition, the use of concomitant medications known to significantly prolong QT interval were controlled as best as practically possible from screening until Cycle 3. In particular, the use of anti-emetics of the 5 HT-3 receptor antagonist class (or setron class) was strictly controlled, and restricted to palonosetron during screening and the first 3 cycles. Clinical safety was assessed during the entire study. Anti-cancer treatment other than study treatment (docetaxel, aflibercept) was not authorized during the study, with the exception of hormonal therapy such as steroids, antiestrogen (ie, tamoxifene, aromatase inhibitors), antiandrogen and LH-RH agonist therapies.	
Number of patients: Planned: approximately 80 patients (ie, 40 patients per arm); Randomized: 88; Treated: 87 **Evaluated:** Safety: 87; Pharmacodynamic: 84; Pharmacokinetics: 87	
Diagnosis and criteria for inclusion: Patients with solid malignancy and for which treatment with single agent docetaxel (administered every 3 weeks at dose ≤ 75 mg/m^2) was planned.	

Investigational product: Aflibercept at a concentration of 25 mg/ml.

Dose/administration: Patients were randomly assigned to receive either aflibercept 6 mg/kg over 1 hour IV on Day 1 every 3 weeks or matching placebo.

Combination therapy: Docetaxcel (Taxotere®)

Dose/administration: 75 mg/m^2 (or lower dose) in 250 mL dextrose 5% or NaCl 0.9% IV over 1 hour, once on Day 1 every 3 weeks immediately after aflibercept or matching placebo administration. Pre- and post-medication: Dexamethasone 8 mg PO (or equivalent) was administered as pre- and post- medication for docetaxel in the evening before Day 1, on Day 1 (early morning, 1 hour before docetaxel treatment, and evening), and on Day 2 (morning and evening). In case of Body Surface Area (BSA) >2.2 m², the actual dose of docetaxel was to be adjusted to a maximum BSA of 2.2 m² for safety reasons. Dose reduction and/or treatment delay and/or treatment discontinuation were planned in case of severe toxicity.

Duration of treatment: After randomization, every effort was to be made to administer the double-blind treatment to patients for at least 3 cycles. Patients were to be treated until unacceptable toxicity, decision from the patient or investigator to discontinue double-blind study treatment, need to introduce anti-cancer treatment other than aflibercept and docetaxel, or until a maximum of 15 cycles, whichever came first.

Duration of observation: Patients were considered on study upon signing the informed consent to the last dose of double-blind study treatment + 60 days follow-up.

Criteria for evaluation:

Pharmacodynamics: ECG intervals (QTcF, QTcB, QTcN, HR, PR, QRS)

Safety: Adverse events, laboratory data (hematology, biochemistry, and urinalysis), 12-lead ECG (at screening, then as clinically indicated), vital signs, and immunogenicity.

Pharmacokinetics: Individual free aflibercept and VEGF-bound aflibercept plasma concentrations at Cycle 1 and Cycle 3 over 6 hours post administration and $C_{max,}$ were calculated.

Pharmacokinetic sampling times and bioanalytical methods: Pharmacokinetic (PK) blood samples for measurement of free and VEGF-bound aflibercept were to be collected at 5 time points at Cycle 1 and at Cycle 3. Predose (T-0.5h, before start of aflibercept/placebo [A/P] infusion), then 0.5h , 1h , 3h and 6h after start of the infusion. One additional PK sample was also to be collected at the final Day 60 follow-up visit. Free and VEGF-bound aflibercept were measured in plasma by ELISA methods (lower limit of quantification [LOQ] of 15.6 and 43.9 ng/mL, respectively).

Immunogenicity assays: A validated non-quantitative titer based bridging assay was used to detect anti-drug antibodies (ADA) in serum samples. The presence of anti-aflibercept neutralizing antibodies (Nab) in ADA positive samples was assessed using a validated non-quantitative ligand binding assay.

Statistical methods: The main ECG analyses (including QT intervals) were performed on the evaluable patient population. Clinical safety was performed on the all-treated population. The evaluable patient population was defined as all randomized and treated patients who had at least two valid QT measurements (at baseline, and during the first 3 cycles). Patient must also have received adequate double-blind treatment (aflibercept or placebo). The all-treated population consisted of all patients who received at least part of the double-blind study medication.

Analysis of the ECG intervals (incl. QTcF) was based on (triplicate) ECGs extracted by the central ECG core lab from the 12-lead ECG Holter, at the following time points:

- Cycle 1, pre-dose (baseline): T(-1.5h), T(-1h) and T(-0.5h)
- Cycle 1, post-dose: T0.5h, T1h (end of aflibercept/placebo infusion), T2h, T3h, T4h, T6h
- Cycle 3, pre-dose: T(-0.5h)
- Cycle 3, post-dose: T(0.5h), T([1h], ie, end of aflibercept/placebo infusion), T2h, T3h, T4h, T6h

All statistical analyses were presented as differences between aflibercept and placebo.

The baseline value for QTcF and other ECG intervals was defined as the average of 3 measurements (each measurement in triplicate) 1.5h, 1h and 0.5h before the start of the first dose on Cycle 1.

Primary analysis: Summary of least square mean difference calculated on the QTcF change from baseline over the interval T1h (end of infusion) to T3h (2h post end of infusion), on Cycle 3, Day 1.

Secondary analyses:

- Summary of least square mean (LSM) difference calculated on the QTcF change from baseline over the interval T0.5h (midpoint during the infusion) to T6h (5h post end of infusion) on Cycle 3, Day 1
- Estimate and 1-sided 95% confidence interval of the largest time-matched mean difference among all timepoints at Cycle 3 (QTcF)
- All QTcF above analyses performed at Cycle 3, were also performed at Cycle 1
- Estimate and 2-sided 90% confidence intervals (CIs) in mean QTcF change from baseline, at all individual post-baseline time points in Cycle 1, and all time points in Cycle 3

The secondary endpoints (HR, QT, QTcB, and QTcN) were analyzed in a similar way as the primary parameter QTcF.

Analysis of ECGs was also performed based on the review of descriptive statistics (N, mean, SD, minimum and maximum for quantitative variables and frequencies for qualitative variables). Individual ECG intervals were flagged for potentially clinically significant abnormalities (PCSAs).

Clinical Safety: Pre-treatment and treatment-emergent adverse events (TEAEs) were to be summarized with respect to the type as assessed by the Medical Dictionary for Regulatory Activities (current version or immediate previous version), frequency, cycle, severity, according to the NCI CTCAE v.3.0., seriousness, and relatedness. Laboratory abnormalities were assessed according to the NCI CTCAE v.3.0.

Pharmacokinetics: Descriptive statistics on free and bound aflibercept concentrations and C_{max} determined at Cycle 1 and Cycle 3.

Study cutoff date and clinical study report (CSR)

The cutoff date for the pharmacodynamic analysis (main analysis of the study), defined when all randomized patients completed at least 3 treatment cycles (or discontinued study treatment), was determined on 05 February 2010. For this main analysis, the corporate study team (Sponsor) were internally unblinded to the study data after the database lock to allow preparation of the CSR, while the investigators and local monitoring teams remained blinded, as some patients continued to receive blinded treatments (for up to 15 treatment cycles) after cutoff date. For these patients, data for the safety and investigational products (IPs) were collected and presented as an addendum to the initial CSR.

This final CSR comprises the addendum safety data (disposition, exposure and overview of TEAEs) for patients ongoing in the study after primary cutoff as well as updated safety data for patients in the follow-up period with an ongoing SAE, or related AE at cutoff at cutoff.

Summary:

A total of 88 patients with solid malignancy were enrolled and randomized; one randomized patient failed inclusion criteria (had more than 2 prior lines of cytotoxic treatment) and did not receive study treatment.

The other 87 patients were randomized between 08-Apr- and 23-Nov-09 and received double-blind treatment with aflibercept or placebo in 7 countries and 20 centers worldwide as follows: 27 patients in 3 centers in Belgium, 13 in 2 centers in Turkey, 12 in 3 centers in Romania, 11 in 4 centers in Germany, 11 in 3 centers in the US, 9 in 2 centers in Denmark and 4 in 3 centers in Italy. At the 05-Feb-10 clinical cutoff for primary analysis, a total of 73 (83.9%) patients had discontinued the study treatment while 14 (16.1%) were still receiving treatment. Primarily, treatment was stopped for disease progression (41 patients), adverse events (16 patients), and different reasons (16 patients) including patient decision (6 patients), Investigator's decision (5 patients), withdrawal of consent (3 patients) and other reason (2 patients).

Of the 87 patients treated, all except 1 were Caucasian/White, 49 (56.3%) were males, 38 (43.7%) were females; median age was 61 years (range: 31 to 81 years) with 63 (72.4%) patients in the category <65 years, 17 (19.5%) in the category 65 - 75 years and 7 (8.0%) in the category ≥75 years. Median BSA was 1.82 m^2 (range: 1.3 to 2.5 m^2). Blood pressure, ECOG performance status and ECG values showed similar distribution between the aflibercept and placebo arms at baseline. In the majority of patients, ECG was normal or abnormal but not clinically significant.

Overall, primary tumor sites included lungs for 20 (23.0%) patients, "other sites" for 17 (19.5%) patients, breast for 14 (16.1%) patients, while the skin, stomach, pancreas and prostate were primary tumor sites in most of the remaining patients. Other primary tumor sites in the above 17 patients included gallbladder (2 patients), cardia (2 patients), endometrium (2 patients), ocular (3 patients), and 1 patient each, respectively, for urethra, cancer of unknown primary tumor site, cortico supra renal, mouth bottom, malignant melanoma, cholangiocarcinoma, thyroid, thyroid medullary carcinoma. Over half of the patients (44 or 50.6%) had adenocarcinoma while "other" tumor histology was reported for the other patients. The median time from the first diagnosis to randomization was 22.8 months.

Two-thirds of the patients entering the study had one or two prior anticancer chemotherapy mostly anthracycline (25 patients or 28.7%). Prior anti-cancer surgeries were performed in 48 (55.2%) patients and no patient received radiotherapy. Overall, medical history data were recorded at study entry for 64 (73.6%) patients and included thrombovascular events (mostly deep vein thrombosis and pulmonary embolism) and/or history of cardiovascular risk factors (mostly hypertension, tobacco users, and diabetes mellitus).

Pharmacodynamic results: For the 87 patients randomized and treated, 84 had evaluable ECG Holter (post-baseline and baseline) while 3 patients were excluded from the pharmacodynamic evaluable population for missing ECG Holter at Cycle 1 due to a FedEx plane crash during transfer of the ECG flash memory card to the core ECG laboratory. For these patients only Cycle 3 ECG Holter recordings were available in the clinical database.

The analysis of the QT was done by time difference and by time points using the following patient populations with at least one baseline (T-0.5h, Cycle 1) and post-baseline (ECG available Cycle 1 or Cycle 3 whichever was the last) evaluations:

- evaluable pharmacodynamic (EP) population: 84 patients (43 placebo, 41 aflibercept) with a baseline and post-baseline ECG Holter available
- Cycle 1 only versus baseline for all 84 patients (43 placebo, 41 aflibercept) in the EP population
- Cycle 3 only versus baseline for the 59 patients (31 placebo, 28 aflibercept) in the EP population with Cycle 3 evaluations

Cycle 3 was missing for 25 patients (12 aflibercept, 13 placebo) during the study and therefore only Cycle 1 ECG Holter was used instead. Cycle 3 ECG Holter was not performed for 24 of the 25 patients since they discontinued the study treatment before receiving Cycle 3 for different reasons (disease progression, AEs, withdrawal of consent,..) and for 1 patient, Cycle 3 was administered but ECG Holter was lost.

It is to be noted for one patient that Cycle 3 Holter was done but became irrecoverable following a FedEx plane crash during transfer and Cycle 5 Holter was used instead. Also, a 2-hour ECG Holter was planned during follow-up in case patients discontinued the study before Cycle 3 ECG Holter but was finally not performed as Cycle 1 measurement could be used instead.

Analysis by time difference (primary and secondary endpoints) :

Repeated measures analysis for change from baseline between T1h and T3h for post-baseline ECG - EP population

	Placebo (N=43)		Aflibercept (N=41)			90% CI of LS Mean Difference	
Change from baseline in ECG parameters	Number	LS Mean (se)	Number	LS Mean (se)	LS Mean Difference[a] (se)	Lower	Upper
QTcF (ms)	43	2.7 (2.26)	41	6.4 (2.35)	3.8 (3.24)	-1.6	9.2
HR (bpm)	43	-0.6 (1.65)	41	-4.3 (1.72)	-3.6 (2.41)	-7.7	0.4
QTcN (ms)	43	2.8 (2.21)	41	5.1 (2.29)	2.3 (3.16)	-2.9	7.6
QTcB (ms)	43	2.9 (2.44)	41	2.1 (2.53)	-0.8 (3.51)	-6.6	5.1
QT (ms)	43	2.3 (3.91)	41	13.7 (4.07)	11.5 (5.65)	2.1	20.9

[a] LS Mean Difference = LS mean of Aflibercept - LS mean of placebo. Note: LS = Least Square; CI = Confidence Interval.

In the EP population, for the 84 patients who received Cycle 1 or Cycle 3, QTcF LS mean difference of the change from baseline on Day 1 in the time interval T1h to T3h was +3.8 (3.24) ms with variations for secondary parameters as presented in the table above. The upper 90% CI of LS mean difference of the change from baseline was below 10 ms for all parameters but QT uncorrected for which LS mean difference of the change from baseline was +11.5 (5.65) ms and the upper 90% CI limit was +20.9 ms as shown in the table.

Repeated measures analysis for change from baseline between T1h and T3h for Cycle 3 only - EP population

	Placebo (N=43)		Aflibercept (N=41)			90% CI of LS Mean Difference	
Change from baseline in ECG parameters	Number	LS Mean (se)	Number	LS Mean (se)	LS Mean Difference[a] (se)	Lower	Upper
QTcF (ms)	31	3.0 (3.04)	28	6.3 (3.26)	3.4 (4.51)	-4.2	10.9
HR (bpm)	31	-1.0 (2.04)	28	-3.1 (2.16)	-2.0 (3.07)	-7.2	3.1
QTcN (ms)	31	3.1 (2.96)	28	5.3 (3.17)	2.3 (4.38)	-5.1	9.6
QTcB (ms)	31	3.2 (3.18)	28	2.9 (3.40)	-0.3 (4.68)	-8.1	7.5
QT (ms)	31	3.3 (4.96)	28	11.3 (5.33)	8.0 (7.47)	-4.6	20.5

[a] LS Mean Difference = LS mean of Aflibercept - LS mean of placebo. Note: LS = Least Square; CI = Confidence Interval.

For Cycle 3 only, QTcF LS mean difference of the change from baseline on Day 1 in the time interval T1h to T3h was +3.4 (4.51) ms with variations for secondary parameters as presented in the table above. The upper 90% CI of LS mean difference of the change from baseline was 10.9 ms for QTcF and below 10 ms for secondary parameters. QT uncorrected LS mean difference of the change from baseline was +8.0 (7.47) ms and the upper 90% CI limit was 20.5 ms as shown in the table.

Repeated measures analysis for change from baseline between T1h and T3h on Day 1 Cycle 1 - EP population

Change from baseline in ECG parameters	Placebo (N=43)		Aflibercept (N=41)			90% CI of LS Mean Difference	
	Number	LS Mean (se)	Number	LS Mean (se)	LS Mean Difference[a] (se)	Lower	Upper
QTcF (ms)	43	2.8 (1.32)	41	3.2 (1.37)	0.4 (1.90)	-2.8	3.6
HR (bpm)	43	-1.1 (1.15)	41	-5.6 (1.19)	-4.4 (1.67)	-7.2	-1.7
QTcN (ms)	43	2.9 (1.25)	41	1.5 (1.30)	-1.4 (1.79)	-4.3	1.6
QTcB (ms)	43	2.9 (1.42)	41	-2.5 (1.47)	-5.4 (2.04)	-8.8	-2.0
QT (ms)	43	2.7 (2.69)	41	12.3 (2.80)	9.6 (3.89)	3.1	16.1

[a] LS Mean Difference = LS mean of Aflibercept - LS mean of placebo. Note: LS = Least Square; CI = Confidence Interval.

For Cycle 1 only, QTcF LS mean difference of the change from baseline on Day 1 in the time interval T1h to T3h was +0.4 (1.90) ms with variations for secondary parameters as presented in the table above. The upper 90% CI of LS mean difference of the change from baseline was below 10 ms for all parameters. QT uncorrected LS mean difference of the change from baseline was +9.6 (3.89) ms and the upper 90% CI limit was below 20 ms as shown in the table.

In the longer interval (T0.5h and T6h), QTcF LS mean difference of the change from baseline on Day 1 was +2.9 (2.96) ms for Cycle 1 or Cycle 3 (postbaseline), +2.2 (4.07) ms for Cycle 3 only and +0.2 (1.79) ms for Cycle 1 only. In all EP populations, the upper 90% CI of LS mean difference of the change from baseline was below 10 ms for all parameters (primary and secondary). Corresponding QT were 10.8 (5.19) ms post-baseline, 7.7 (6.94) ms Cycle 3 only and 9.4 (3.46) ms Cycle 1 only. The upper 90% CI of LS mean difference of the change from baseline was below 20 ms for all QT values.

By time point analysis, results for QTcF change from baseline were consistent with findings by time difference as described above in the shorter and longer intervals.

By categorical analysis, overall, 27 patients (15 placebo, 12 aflibercept) had abnormal QTcF values (borderline or marked elevations) during Cycle 1 or Cycle 3. No patient had QTcF ≥ 500 msec or QTcF change from baseline >60 msec.

Safety results:

At the cutoff date of 5 Feb 2010, a total of 194 cycles (range: 1 to 9) was received in the placebo treatment group versus 179 cycles (range: 1 to 8) in the aflibercept treatment group with a median number of cycles of 5 and 4 in the placebo and aflibercept treatment groups, respectively.

A total of 70 (80.4%) patients had no cycle delay and no dose modification (reduction or omission) while only one patient receiving aflibercept had dose reduction (0 mg/kg - <4.5 mg/kg) versus 7 under docetaxel (infusion: ≥52.5 - <67.5 mg/ m^2).

A total of 97.7% of patients in the placebo group and all patients (100%) in the aflibercept group experienced at least 1 clinical TEAE (regardless of relationship) and amongst them, 60 (69.0%) had Grade 3 or 4 TEAE, 44 (50.6%) had TEAEs that were SAEs, which led to death for 10 (11.5%) patients and to permanent or premature discontinuations for 18 (20.7%) patients.

Overall, the safety profile of the 2 treatment groups included the main following TEAEs (all grades, ≥10% frequency) occurring more frequently for both treatment groups regardless of relationship: asthenia/fatigue, nausea, diarrhea, stomatitis, constipation, vomiting, alopecia, nail disorder, decreased appetite, cough, dyspnea, and pyrexia.

In the aflibercept treatment group, the following all grades events were more commonly observed compared to placebo: with a difference of more than 10%: gastrointestinal events (nausea, stomatitis, constipation, GI and abdominal pains), decrease appetite, dysphonia, dyspnea, cough, hypertension, hemorrhage (including mainly epsitaxis and bleeding from GI origin), and infections and neutropenic complications.

Fewer patients in the placebo group experienced at least 1 Grade 3/4 TEAEs regardless of the relationship to the study medication compared to the aflibercept group (56.8% vs 81.4%). The increased incidence of Grade 3/4 AEs in the aflibercept group was due to the higher percentages of Grade 3 or 4 neutropenia/febrile neutropenia (32.6% vs 18.2%), fatigue/asthenia (27.9% vs 6.8%) and hypertension (11.6% vs 0%).

For both treatment arms, the most common Grade 3/4 nonhematological events observed in ≥5% of patients were asthenia/fatigue and the most common Grade 3/4 hematological events observed in ≥5% of patients were neutropenias (including febrile neutropenia). Grade 3 or 4 progression disease, proteinuria, nausea, stomatitis, dyspnea, hypertension, and decreased appetite were more common in the aflibercept treatment group compared to placebo.

Using selected grouped clinical terms for possible aflibercept drug class events, the greatest differences between the placebo and aflibercept groups were seen for hypertension (all grades reported at 2.3% and Grade 3/4 events at 0% in the placebo group, and all grade events reported at 20.9% and Grade 3/4 events at 11.6% in the aflibercept group), and for hemorrhage (all grade events reported at 4.5% and Grade 3/4 events at 2.3% in the placebo group and all grades events reported at 34.9% and Grade 3/4 events at 0% in the aflibercept group). The difference in all grades hemorrhage in the aflibercept group was mostly due to 9 events of all grades epistaxis versus 2 in the placebo group (none were Grade 3 or 4 in either treatment group) and bleeding from GI origin 5 versus 0 patients.

No patients in either treatment group experienced Grade 3 or 4 arterial thromboembolic events. Fewer venous thromboembolic events were observed in the aflibercept group compared to the placebo group: Grade 3/4 pulmonary embolism occurred in 4.5% of placebo patients and 2.3% of aflibercept patients; Grade 3/4 vena cava thrombosis occurred in 2.3% of placebo patients and 0% of aflibercept patients.

Neutropenic complications were higher in the aflibercept group (23.3% vs 9.1%) and all were Grade 3 or 4 in both treatment groups.

Gastrointestinal fistulae were uncommon (2.3% all grades events in the placebo group and 0% in the aflibercept group; no Grade 3 or 4 events). One Grade 3 or 4 gastrointestinal perforation was observed in one patient in the aflibercept group. The event was non study drug related and recovered after corrective treatment.

All grades drug reaction (acute drug reaction - tbc) events were observed at 31.8% under placebo versus 37.2% in the aflibercept group. One Grade 3 serious study drug related hypersensitivity reaction was reported in one patient in the aflibercept group. The event recovered after corrective treatment.

Deaths were reported for a total of 32 patients (16 placebo, 16 aflibercept) during the study mostly due to malignant disease with 9 occurring within 30 days of last dose (4 placebo, 5 aflibercept).

Discontinuation due to TEAEs was comparable between treatment groups: 16 (18.4%) patients (9 placebo, 7 aflibercept) permanently discontinued treatment due to TEAEs.

At study entry, 30 patients (17 placebo, 13 aflibercept) or 34.5% had preexisting hypertension, which was ongoing without change during the study for 25 of them (16 placebo, 9 aflibercept) and worsened to Grade 2 or 3 (mostly at Cycle 1) for 5 of them (1 placebo, 4 aflibercept). Amongst the patients without hypertension at baseline (27 placebo, 30 aflibercept), 5 aflibercept patients (11.6%) experienced new hypertension during the study; 2 were Grade 3 and none led to a change in the study treatment administration. No Grade 4 hypertension was reported in either treatment group.

One patient in the aflibercept group experienced Grade 3 or 4 ejection fraction decreased versus none in the placebo group. The patient had a medical history of pulmonary embolism with occlusion of segmental arteries of lower left lobe of lung and no prior exposure to treatment with anthracycline. The event of LVEF recovered after corrective treatment.

A total of 28 (32.2%) patients (9 placbo, 19 aflibercept) had proteinuria during the study, (mostly Grade 1). Study drug related proteinuria (grade 2 and 3), resulted in delay of aflibercept dosing for 2 patients and in permanent discontinuation for 2 other patients. More than half of the cases of proteinuria under aflibercept were observed within the 2 first cycles. There was no Grade 4 proteinuria (nephrotic syndrome) reported in this study.

There were no events of reversible posterior leukoencephalopathy syndrome (RPLS) or thrombotic microangiopathy (TMA) reported in either treatment group. Considering SMQ events, syncope was reported for 3 patients during the study (1 placebo, 2 aflibercept) occurring at cycle 1 or 2 of the study treatment. All 3 patients (2 with breast cancer, 1 with thyroid cancer) had a history of high blood pressure (ongoing for 2 patients and past for one patent) had received prior QT-prolonagtion drugs (mainly epirubicin) 2 to 3 years before study entry. All events of syncope recovered the day after onset without corrective treatment and did not require study drug action.

During treatment, the main Grade 3 or 4 hematologic abnormalities was neutropenia with more patients experiencing G3/4 neutropenia in the aflibercept group and more Grade 1/2 anemia in the the placebo treated patients.

A total of 32 patients in the placebo group and 30 patients in the aflibercept group were evaluated for immunogenicity. No immune response was observed in the placebo group. One patient treated with aflibercept developed a drug specific immune response and returned to a negative response after end of treatment. This immune response did not correspond to neutralizing antibodies.

Overall, 1/43 (0.02%) patient showed an immune response in this study. Antibodies were not neutralizing.

Addendum safety data: At cutoff for primary analysis, 46 patients were in follow-up (23 placebo, 23 aflibercept) and 14 (9 placebo, 5 aflibercept) were still receiving the study treatment. An addendum to the initial CSR was done and included safety update for the 14 patients still on treatment as well as safety update for the 46 patients who were under follow-up period with an ongoing SAE, or related AE. The last patient last visit occurred on 08 November 2010 and final database lock took place on 03 December 2010. The additional safety data obtained did not impact the safety profile described above.

Pharmacokinetic results:

In the aflibercept (6mg/kg) treated population, free aflibecept mean C_{max} was 132±39 µg/mL and 125±45 µg/mL at cycles 1 and 3, respectively. Bound VEGF C_{max} increased from 0.058± 0.0381 to 3.42±0.913 µg/mL between Cycle 1 and Cycle 3.

PK/PD relationship results:

The QT-exposure and relationship with free aflibercept were calculated at Cycle 1 and Cycle 3. At Cycle 1, the estimated slope of the relationship (95%CI) was - 0.013 (-0.044;0.019) versus + 0.048 (0.013;0.082) at Cycle 3 showing that the PK/PD relationship between QTcF change from baseline and free aflibercept concentrations was established during the study.

Date of issue: 25-July-2012