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Sponsor: Sanofi **Drug substance(s):** SAR566658	**Study Identifiers:** U1111-1116-4129, IND 106861, NCT01156870 **Study code:** TED10499
Title of the study: Dose escalation, safety and pharmacokinetic, first in man study, of SAR566658 administered as single agent by intravenous infusion in adult patients with CA6 positive and refractory solid tumors	
Study center(s): 5 centers in the US (2), Spain (2), and France (1)	
Study period: Date first participant enrolled: 07/Sep/2010 Date last participant completed: 09/Mar/2017 Study Status: Completed	
Phase of development: 1	

Objectives:

The primary objective was to determine the maximum tolerated dose (MTD) of SAR566658 according to the investigational medicinal product (IMP)-related dose-limiting toxicities (DLTs) observed in patients with CA6-positive and refractory solid tumors.

The secondary objectives were:

- To characterize the global safety profile including cumulative toxicities
- To evaluate the pharmacokinetic (PK) profile of SAR566658
- To assess the potential immunogenicity of SAR566658
- To assess preliminary antitumor activity in patients, according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria for SAR566658 administered according to 3 different schedules and volumetric tumor response in evaluable patients for SAR566658 administered in D1 every 3 weeks (Q3W) schedule, included in the expansion part.
- To estimate the response rate according to RECIST 1.1 criteria in a cohort of breast patients treated with SAR566658 every 3 weeks
- To assess the effect of SAR566658 at the recommended dose on the PK profile of midazolam.
- To assess the incidence of ocular corneal toxicity and to explore the safety profile of alternative schedule(s) of SAR566658 administration.

Methodology:

This was a first in man, open-label Phase 1 oncology study with a primary objective of determining the MTD of SAR566658 according to IMP related DLTs observed in patients with CA6-positive and refractory solid tumors.

The study included accelerated dose escalation for the 2 first doses followed by classical "3+3" dose escalation and an expansion part testing different selected doses and schedules of administration. In addition, the effect of SAR566658 at the selected doses on CYP3A enzyme activity using midazolam as probe in an additional cohort of patients was assessed.

Preliminary antitumor activity, CA6 expression on tumor samples, and pharmacodynamic markers of SAR566658 activity was also assessed.

Ocular and pulmonary toxicity were monitored closely.

Patients who benefited from receiving SAR566658 were allowed to continue study treatment beyond the study cut-off date, if applicable.

Dose-limiting toxicities

Dose limiting toxicities were defined as any of the following adverse events (graded using NCI CTCAE scale version 4.03 [Appendix B in the protocol in Appendix 16.1.1]), unless unrelated to the IMP:

- Grade 4 neutropenia for 7 or more consecutive days
- Febrile neutropenia or neutropenic infection (defined as a documented infection with neutrophil count decreased Grade 3 or 4)
- Grade 4 thrombocytopenia
- Bleeding requiring transfusion with Grade 3 thrombocytopenia
- Grade 4 infusion reaction or Grade 3 infusion reaction if the infusion reaction does not resolve within 24 hours and the entire dose of IMP cannot be administered
- Grade 4 vomiting or Grade 3 nausea and vomiting not resolved to Grade ≤1 within 48 hours despite adequate antiemetic treatment
- Any other Grade 3 or higher non-hematological clinical AE
- Any Grade 3 or higher laboratory abnormalities
- Any toxicity related to SAR566658 resulting in a treatment delay of more than 2 weeks due to delayed recovery to baseline or Grade ≤1.

The maximum administered dose (MAD) was achieved when an IMP-related DLT was observed in at least 2 of a maximum of 6 treated patients at that dose level. Once the MAD was reached, no further dose escalation occurred.

The dose level below the MAD was considered the predefined MTD, provided that IMP related DLTs were observed in fewer than 2 of 6 treated patients at that dose level (or fewer than one third of treated patients if more than 6 patients at that dose level).

Midazolam interaction

Twelve evaluable patients with solid tumors treated at the recommended dose in the expansion part were to be enrolled in the midazolam interaction sub-study to assess any potential interactions between SAR566658 and CYP3A inhibitors. A single sequence, 2 treatment crossover study with 24 hour washout period was performed. Patients received 2 mg midazolam under fasting conditions.

Number of participants:

Planned: 1-6 patients at dose levels 10 and 20 mg/m^2;

3-6 patients at dose levels ≥30 mg/m^2 (dose escalation)
66 (dose expansion)

Enrolled: 114

Treated: 114

Evaluated:

Efficacy: 112

Safety: 114

Pharmacokinetics: 114

Diagnosis and criteria for inclusion:

Patients ≥18 years of age with a diagnosis of CA6-positive solid tumors, defined as moderate to intense membrane staining of ≥15% of tumor cells in patients with measurable and/or non-measurable disease (in the dose escalation part only), for which no standard therapy was available

Study products:

Investigational medicinal product(s): SAR566658

Formulation: 25 mL extractable concentrate for solution; each 30 mL glass vial contained 125 mg of SAR566658

Route of administration: Intravenous (IV)

Dose regimen:

Dose escalation: 10, 20, 40, 60, 90, 120, 150, 190, and 240 mg/m^2 every 3 weeks (Q3W)

Dose expansion: 150 and 190 mg/m^2 Q3W, 90 mg/m^2 D1D8 Q3W, 120 mg/m^2 every 2 weeks (Q2W)

Non investigational medicinal product(s): Midazolam

Formulation: 2 mL of 1 mg/mL solution (2 mg) mixed with 40 mL of 5% glucose solution for injection

Route of administration: Oral

Dose regimen: Once

Duration of treatment: Patients continued treatment until disease progression, unacceptable toxicity, or willingness to stop.

Duration of observation:

The follow-up period was 30 days after last infusion. SAEs regardless of relationship with study treatment, IMP-related AEs ongoing at the end of study treatment, and new IMP-related AE/SAEs were followed until resolution or stabilization. Patients achieving stable disease (SD), complete response (CR), partial response (PR) or non-CR/non-progressive disease (PD) were followed until disease progression or initiation of another specific anti-tumor treatment.

Criteria for evaluation:

Safety:

Safety was assessed by reported adverse events, deaths, clinical laboratory evaluations, vital signs, respiratory function (diffusing capacity of the lung for carbon monoxide [DL_{CO}], chest X-ray, and chest computerized tomography [CT] scan) , ECGs, and anti-therapeutic antibodies (ATA; anti-SAR566658 and anti-huDS6 antibodies).

DLT were assessed during DLT observation period as well as AE meeting DLT criteria in subsequent cycles.

Efficacy:

The following efficacy variables were calculated:

- Overall response rate (ORR) according to RECIST 1.1 criteria: number of patients with objective response (best overall response [BOR]=CR or PR or not [ie, BOR=SD, PD, NE]) was tabulated by initial planned dose level in the all treated population.
- Duration of the best overall response, defined for patients who reached CR or PR as BOR, as the time from the first documentation of RECIST-defined objective response to the first documentation of tumor progression or death in the absence of prior documentation of disease progression.
- Overall volumetric response rate based on central review (for expansion part only)
- Time to progression (TTP) defined as the time from first treatment administration to first documentation of RECIST-defined disease progression.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

- Q3W dosing: Samples were collected pre-infusion, within 5 minutes of change infusion rate (if infusion duration was less than 30 minutes, samples were collected at the middle of the infusion), end of infusion, 6h post-infusion, and Days 2 (24h) , 3 (48h), 8 (168h), 15 (336h), and 21 (480h) post-infusion in Cycle 1. Samples were collected pre-infusion, post-infusion and Days 8, 15, and 21 in Cycle 2, pre- and post-infusion of subsequent cycles, end of treatment, and Day 30 post-treatment.
  Samples for SPA/SPD were collected pre-infusion and Days 8, 15, and 21 in Cycle 1, Day 21 of subsequent cycles, and Day 30 post-treatment.
  Samples for ATA were collected pre-infusion and Day 21 of Cycle 1 and Day 21 of subsequent cycles, and Day 30 post-treatment.
- Q2W dosing: Samples were collected pre-infusion, end of infusion, 7h post-infusion, and Days 2 (24h) , 3 (48h), and 8 (168h) post-infusion in Cycles 1 and 3. Samples were collected pre- and post-infusion in Cycle 2, odd-numbered weeks beginning with Cycle 5, end of treatment, and Day 30 post-treatment.
  Samples for SPA/SPD and ATA were collected pre-infusion Day 1 of Cycles 1 to 3 and odd cycles beginning at Cycle 5.
- D1D8 Q3W dosing: During Cycle 1, samples were collected pre-infusion, end of infusion, 7h post-infusion, and Days 2 (24h) and 3 (48h) post first infusion, Day 8 pre-infusion, end of infusion, 7h post-infusion, and Days 9 (24h), 10 (48h), and 15 (168h) post-infusion 2. Samples were collected pre- and post-infusion in cycle 2. Samples in Cycle 3 were collected as for Cycle 1. Samples were collected pre- and post-infusion Day 1 for odd-numbered weeks beginning with Cycle 5, end of treatment, and Day 30 post-treatment.
  Samples for SPA/SPD were collect pre-infusion Days 1 and 8 and Day 15 of Cycles 1 and 3, pre-infusion Day 1 in Cycle 2, pre-infusion Day 1 at odd cycles beginning with Cycle 5, end of treatment, and Day 30 post-treatment..
  Samples for ATA were collected pre-infusion Day 1 of Cycles 1 to 3, pre-infusion at odd cycles beginning with Cycle 5, end of treatment, and Day 30 post-treatment.

Statistical methods:

Analysis populations

- The all treated/safety population was defined as all registered patients who received at least 1 dose or part of the dose of SAR566658.
- The evaluable population for DLT was the subset of patients from the all treated population:
  - 3-week cycle: completed the initial 3-week period of treatment (ie, 1 cycle) or experienced a DLT validated by the Study Committee before the completion of Cycle 1.
  - 2-week cycle (only for 120 mg/m² Q2W: completed 2 cycles of treatment or experienced a DLT validated by the Study Committee before the completion of the 2 first cycles.
- PK analyses were performed for patients with samples available for analysis of PK parameters.
- The activity/efficacy population included patients evaluable for anti-tumor response, defined as all treated patients (see above) who provided a baseline and had at least 1 evaluable postbaseline tumor assessment according to RECIST 1.1 criteria. Patients with early progression as per RECIST 1.1 criteria were also included in this population.
- Biomarker analyses were performed on all treated patients who had available biomarker data.

Safety

Dose-limiting toxicities were summarized by DL, with by patient details were provided.

Adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 4.03 from the time the informed consent form was signed until at least 30 days after the last IMP administration. Adverse events were classified by SOC/PT according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA). The incidence of ocular AEs was summarized. The results of pulmonary function tests were summarized.

For clinical laboratory evaluations, the maximum grade (worst) per patient and/or per cycle was used. Laboratory results were graded by NCI CTC (version 4.03).

The number of patients with potentially clinically significant abnormalities (PCSAs) of blood pressure was summarized.

Pharmacokinetic analyses

Pharmacokinetic parameters of SAR566658, naked huDS6, total huDS6, DM4, Me-DM4 and midazolam were summarized by treatment group by descriptive statistics by DSAR, except for the derived parameters: (1) metabolic ratio (Rmet) for Q3W, Q2W, and day1-day 8 Q3W schedules. DM4 or Me-DM4 over SAR566658, taking into account molecular weights at each full PK cycle for Cmax, AUC (only at cycle 1) and AUCtau (at cycle 3); (2) accumulation ratio (R) (cycle 3 to cycle 1 ratio) for Cmax and AUCtau of SAR566658, DM4, and Me-DM4; and (3) CL/BSA and Vss/BSA at cycle 1 and cycle 3 considering actual BSA for SAR566658. Tau was the dosing interval (ie, 14 days or 21 days, depending on the study schedule).

Individual values and descriptive statistics by treatment group were provided with the 90% confidence interval (CI).

Efficacy

The following variables were determined:

- Overall response rate (ORR) according to RECIST 1.1 criteria: number of patients with objective response (best overall response [BOR]=CR or PR or not [ie, BOR=SD, PD, NE]) was tabulated by initial planned dose level in the all treated population. In this table, the number of patients in each category was detailed.
- Duration of best overall response, defined for patients who reached CR or PR as BOR, as the time from the first documentation of RECIST-defined objective response to the first documentation of tumor progression or death in the absence of prior documentation of disease progression.
- Overall volumetric response rate based on central review (for expansion part only)
- Time to progression (TTP) defined as the time from first treatment administration to first documentation of RECIST-defined disease progression.

Overall response rate, response duration, and TTP were described along with relevant parameters (characteristics of patients/disease). If appropriate, summaries (including 95% confidence interval) were provided.

Biomarkers and pharmacodynamics analyses

The levels of CA6 antigen expression was assessed for pretreatment samples.

Posttreatment analyses included DM4 tumor content, level of CA6 expression, markers of proliferation (Ki67), cell cycle arrest (phosphohistone H3), and apoptosis (cleaved caspase-3) were described and compared to baseline for patients who consented in the biomarker sub-study.

The relationship between antitumor activity and CA6 expression level and between antitumor activity and PD biomarkers of SAR566658 activity were assessed.

Immunogenicity

Immunogenicity was evaluated. Human anti-SAR566658 and anti-huDS6 antibodies (ATA) were described categorically as negative (below detection limits) or positive, and were displayed by patient per DL. A patient was considered to have positive antibody levels if antibodies were detected above the quantification limits at least once during the course of the study.

Summary:

Population characteristics:

One hundred fourteen patients with heavily pretreated solid tumors expressing CA6 (in ≥30% tumor cells with intensity 2+/3+ by IHC in almost all patients) were enrolled and treated: 34 in the dose escalation part and 80 in the expansion part. All patients had an ECOG performance status of Grade 0 or 1. About half the patients were enrolled with an ovarian cancer (47.4%), mostly likely due to a high prevalence of CA6 in this indication, followed by patients with breast cancer (20.2%), and patients with pancreas cancer (15.8%).

The 34 patients in the DE phase had a mean age of 57.3 years (range 32 to 77), and patients were predominantly White (97.1%), female (67.6%), and <65 years old (67.6%).

The 89 patients in the dose expansion phase (includes 3 and 6 patients who received 150 and 190 mg/m2 Q3W from the DE phase, respectively) had a mean age of 57.9 years (range 36 to 79), and patients were predominantly White (96.6%), female (77.5%), and younger than 65 years old (74.2%).

Safety results:

Overall, SAR566658 was well tolerated with few related Grade 3 AEs and limited Grade 3 laboratory abnormalities.

Dose levels of 10 mg/m² to 240 mg/m² Q3W were evaluated during the DE phase, with DLTs observed in 1 of 8 patients at Cycle 1 (Grade 3 diarrhea) at the highest dose of 240 mg/m² Q3W. Two of these 8 patients presented with an AE meeting the DLT definition at Cycle 2 (Grade 3 keratitis), The dose of 240 mg/m² Q3W was defined as the MAD and the dose of 190 mg/m² Q3W was initially considered the MTD, but due to a high incidence of corneal toxicity impacting study treatment, this dose was stopped and 150 mg/m² was considered the MTD.

Ocular corneal events, particularly keratitis or punctuated keratitis, were the main related TEAEs and DLTs, with a higher incidence at the highest selected dose of 190 mg/m² Q3W during the expansion part. At doses ≥50 mg/m²/week, keratitis was reversible for 84.7% of events. Assessment of alternative schedules giving a dose intensity of ≥50 mg/m²/week proposed after PK/safety simulations (90 mg/m² D1D8 Q3W and 120 mg/m² Q2W) resulted in a decrease in the incidence of keratitis. The lowest incidence was observed at 120 mg/m² Q2W. While the sample size was small, implementation of primary corneal prophylaxis in the alternative schedules did not appear to affect the incidence of keratitis, but appeared to mitigate the impact of ocular events on study treatment modification; 3 of 10 patients (30.0%) who received primary prophylaxis had keratitis compared with 7 of 23 patients (30.4%) who did not receive primary prophylaxis. Ocular events, such as keratitis and dry eye are expected events with SAR566658 and are attributed to DM4-loaded ADC.

In addition, 40.4% of patients experienced TEAEs of peripheral neuropathy; all were Grade 1 or 2 except for 1 Grade 3 event. Of note, most of the patients were previously treated with a platinum-based therapy.

With regard to pulmonary events, 18 out of 114 patients (15.8%) had a decrease of >20% DL_{CO} during treatment that in some patients was in the context of pleural effusion or lung metastases. Six patients (5.2%) experienced a related pulmonary event of ILD, pneumonitis, or organizing pneumonia.

No clinically relevant findings were observed for laboratory assessments, vital signs, or ECGs.

Other safety conclusions during the DE phase were:

- The frequency and severity of AEs was generally similar across the 9 dose levels, except for corneal TEAEs (expected events with SAR566658) and peripheral neuropathy. The most frequent TEAEs (occurring in ≥6 of 34 patients) of all grades, regardless of relationship to study drug, and excluding lab abnormalities were asthenic conditions, decreased appetite, keratitis, gastrointestinal and abdominal pains, nausea, peripheral neuropathies, dry eye, constipation, vomiting, musculoskeletal and connective tissue pain, diarrhea, anxiety, edema peripheral, and weight decreased.
- Eighteen patients (52.9%) had at least 1 grade 3-4 TEAE (regardless of relationship to study treatment): 1 patient at each at dose levels 20 and 40 mg/m²; 2 patients at each dose levels 60, 90, 120, and 150 mg/m²; 3 patients (50%) at the 190 mg/m² dose level; and 5 patients (62.5%) at the 240 mg/m² dose level.
- Ocular corneal events were more frequently observed at doses ≥150 mg/m². The main TEAE was keratitis (12 of 34 patients [35.3%]) with the following pattern: first occurrence mainly at Cycle 2; grade 2 severity (except at the 240 mg/m² DL at which 2 patients developed a grade 3 keratitis); reversible; and with limited impact on study treatment up to the 190 mg/m² DL.
- Peripheral neuropathy was observed with no clear dose-dependency in 10 of 34 patients (29.4%). All were Grade 1 or 2

Other safety conclusions at the RDs and selected doses of interest (150 and 190 mg/m² Q3W, 120 mg/m² Q2W and 90 mg/m² D1D8 Q3W) were:

- The frequency and severity of TEAEs were generally similar in comparison to the escalation part. All patients experienced at least 1 TEAE, and 78 of 89 patients (87.6%) had a related TEAE. Grade ≥3 events occurred in 45 of 89 patients [50.6%]), but 13 of 89 patients (14.6%) had Grade ≥3 related TEAEs.
- Eye disorders were reported in 56 of 89 patients (62.9%), which were mainly keratitis (PT keratitis or punctate keratitis) in 37 of 89 patients (41.6%) and blurred vision in 17 of 89 patients (19.1%). Other eye disorders PTs were abnormal sensation in eye (dry eye sensation) in 15 of 89 patients (16.9%) and dry eye in 13 of 89 patients (14.6%). These eye disorders occurred more often at the 190 mg/m²Q3W or 90 mg/m² D1D8 Q3W DLs. The corneal events occurred from the dose level of 150 mg/m² in the Q3W schedule. Eye disorders leading to dose delay and/or dose reduction or drug discontinuation were considered for the dose selection. Eye disorders leading to dose modification occurred in 14 of 23 patients (60.9%) at 190 mg/m² Q3W, 8 of 33 patients (24.2%) at 150 mg/m² Q3W, 5 of 17 patients (29.4%) at 90 mg/m² D1D8 Q3W, and 2 of 16 patients (12.5%) at 120 mg/m² Q2W. The incidence and severity of ocular TEAEs was lower at the 120 mg/m² Q2W dose. Ocular corneal events seemed to be dose and schedule dependent. These ocular toxicities occurred mainly during Cycle 2 (23 of 34 patients [67.6%]) with Grade 2 as the worst grade in 24 of 34 patients (70.6%).
- The HLT peripheral sensory neuropathies (PTs peripheral sensory neuropathy and neuropathy peripheral) were reported in 32 of 89 patients (36.0%). All except one were Grade ≤2; peripheral sensory neuropathy events were related in 21 patients (23.6%) and the PT neuropathy peripheral events were related in 4 patients (4.5%).
- The other most frequent TEAEs of all grades, regardless of relationship to study drug, occurring in more than 10% of the patients overall were: asthenic conditions (fatigue or asthenia) in 51 of 89 patients (57.3%); gastrointestinal and abdominal pains (PTs abdominal pain, abdominal pain upper, and gastrointestinal pain) in 31 of 89 patients (34.8%); nausea in 23 of 89 patients (25.8%); diarrhea in 22 of 89 patients (24.7%); constipation and decreased appetite in 21 of 89 patients (23.6%) each; musculoskeletal and connective tissue pain (PTs back pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, and neck pain) in 17 of 89 patients (19.1%); carbon monoxide diffusing capacity decreased in 13 of 89 patients (14.6%); vomiting in 12 of 89 patients (13.5%), weight decreased in 11 of 89 patients (12.4%); peripheral oedema in 10 of 89 patients (11.2%); pyrexia in 9 of 89 patients (10.1%).
- The incidence of immunogenicity was 4.5% (5 positive ATA patients out of 114 patients). All were receiving the D1 Q3W schedule at DLs 60, 150, and 190 mg/m².

Pharmacokinetic results:

- The pharmacokinetics of SAR566658 following IV administration were characterized by a bi-phasic profile, a mean plasma clearance of approximately 0.75 L/day, a volume of distribution of 4 L and a terminal half-life of around 5 days.
- Over the dose range 20 to 240 mg/m² in a Q3W administration schedule, SAR566658 showed a peak of concentration generally at the end of infusion, its exposure (Cmax and AUC) increased in a dose proportional manner and no dose effect was observed on clearance and terminal half-life. Its both metabolites, DM4 and Me-DM4, were quantified at low levels in plasma (mean Cmax of 5.56 ng/mL and 16.5 ng/mL, respectively, at 190 mg/m²). DM4 was quantified rapidly in plasma (tmax around 7 h) while Me-DM4 was characterized by a later tmax (around 1 to 4 days). DM4 exposure increased with no major deviation from dose proportionality within the limited 90 to 240 mg/m² dose range while no conclusion could be drawn on Me-DM4 dose proportionality due to its high variability. On a molar basis, at either, 150 or 190 mg/m² dose levels, DM4 and Me-DM4 accounted for about 0.5 % and 4 % of SAR566658 exposure, respectively.
- The maximum concentration after repeated administration (Ctrough) was reached by the end of first cycle (ie, Predose Cycle 2) for SAR566658, DM4 and Me-DM4 independently of the study schedule used - 150/190 mg/m² Q3W, 90 mg/m² D1D8Q3W or 120 mg/m² Q2W- while for naked huDS6, the maximum Ctrough was reached by Cycle 3, Cycle 7 and Cycle 8, respectively. This is consistent with the 1.7 to 2-fold accumulation in naked huDS6 exposure at Cycle 3 compared to Cycle 1 whereas the other analytes, SAR566658, DM4 or Me-DM4 did not accumulate over cycles.
- Total variability on exposure PK parameters (Cmax and AUCs) was consistent across schedules and was low for SAR566658 and DM4 (CV<30%), moderate (CV around 40%) for naked huDS6 and high (CV>60%) for Me-DM4.
- Compared to the 190 mg/m² Q3W schedule, both alternative schedules - 90 mg/m² D1D8Q3W and 120 mg/m² Q2W - led to a decrease in mean SAR566658 Cmax at Cycle 1 by around 30% for a similar dose intensity of approximately 60 mg/m²/week; both schedules showing similar Cmax.

- Pharmacokinetic/pharmacodynamic analyses showed a strong relationship between SAR566658 exposure and the occurrence of ocular toxicity. Both AUCs (AUC0-7d, AUC0-14d, AUC) and Cmax at Cycle1 were significant ($p<0.0001$ for AUCs and $p = 0.0005$ for Cmax in univariate logistic regression analyses).
- **Midazolam interaction study:** Following administration of SAR566658 at 150 or 190 mg/m², mean midazolam exposure was increased by approximately 20% indicating a weak effect of SAR566658 administration on midazolam (a CYP3A probe substrate) pharmacokinetics.

Efficacy results:

- SAR566658, an ADC, is an active drug with responses and tumor shrinkage per RECIST 1.1 criteria at least in breast, lung, bladder, and ovarian cancers. Responses were observed at for doses of 150 mg/m² Q3W and higher at DLs with a dose intensity ≥50mg/m²/week.

- A similar antitumor activity was observed at the alternative schedule of 90 mg/m² D1D8 Q3W when compared to the initial MTD of 190 mg/m² Q3W, with an ORR of 18.8%, a probability of non-progression at 12 weeks of 63.0%, and a 29.4% frequency of ocular toxicity leading to dose modification.

- All patients except one treated at ≤60 mg/m2 Q3W (10 mg/m² Q3W) were evaluable for CA6 expression by IHC at study entry. Based on analysis of CA6 levels of expression by primary tumor site, there were no significant differences in CA6 H-score between indications. Only weak correlations were noted for ovarian and pancreatic tumor between tumor shrinkage and level of CA6 expression.
- Decreased CA125 (ovarian cancer) and CA15-3 (breast cancer) levels were recorded during the treatment and especially in patients with PR or CR.
- No obvious differences in SPA and SPD levels according to initial planned dose level of SAR566658 or cycle number during the treatment or correlation with respiratory parameters (DL_{CO}, forced expiratory volume) were noted.

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