These results are supplied for informational purposes only.
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Sponsor / Company: Sanofi **Drug substance(s):** SAR260301	**Study Identifiers:** NCT01673737, UTN U1111-1129-2696 **Study code:** TCD12739
Title of the study: A Phase I/Ib study for the evaluation of SAR260301, administered orally in monotherapy in patients with advanced solid tumors or lymphomas, and in combination with vemurafenib in patients with unresectable/metastatic BRAF mutated melanoma	
Study center(s): 1 site in Canada and 3 sites in the US	
Study period: Date first patient enrolled: 07/Aug/2012 Date last patient completed: 02/Feb/2015	
Phase of development: Phase 1/1b	

Objectives:

Primary

Part A

- To determine the maximum tolerated dose (MTD) of SAR260301 administered as monotherapy and either on a once daily (QD) or twice daily (BID) schedule, to patients with advanced solid tumors or lymphomas.

Part B

- To determine the MTD of SAR260301 administered in combination with the recommended standard dosage of vemurafenib to patients with unresectable/metastatic *BRAF* mutated melanoma.

Secondary

- To characterize the overall safety and tolerability profile of SAR260301 administered as monotherapy (Part A) and in combination with vemurafenib (Part B).
- To characterize the pharmacokinetic (PK) profile of SAR260301 administered as monotherapy (Part A) and in combination with vemurafenib (Part B) as well as vemurafenib PK in combination with SAR260301 (Part B).
- To evaluate the food effect on SAR260301 PK (Part A).
- To assess preliminary antitumor activity according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
- To assess the preliminary antitumor activity using volumetric computed tomography (CT) or magnetic resonance imaging (MRI).
- To evaluate the pharmacodynamic (PD) effects of SAR260301 in the blood and tumor.
- To evaluate the PK/PD relationships.
- To identify the recommended Phase 2 dose (RP2D) of SAR260301 in combination with vemurafenib (Part B only).
- To assess the potential induction effect of SAR260301 on CYP3A (Part A).

Exploratory

- To explore predictive markers of response. To evaluate pre-existing phosphatase and TENsin homologue (PTEN) status in archival or fresh tumor samples and correlate PTEN deficiency with clinical outcome in subjects treated with SAR260301.
- To evaluate other potential genetic alterations in the context of PTEN deficiency and correlate with clinical outcome.
- To explore the platelet function assay PFA100® as a potential useful point-of-care biomarker of PI3Kβ (phosphoinositol-3-kinase beta) inhibition.

Methodology: This was an open-label, non-randomized, dose-escalation, safety, tolerability, PK and PD evaluation study of SAR260301, given alone or in combination with vemurafenib, following a continuous daily schedule of 28-day cycles.

This study planned to initially include 2 parts (Part A and B):

Part A:

- Dose escalation study for the evaluation of the tolerability, safety, PK, and PD of SAR260301 administered as monotherapy in patients with solid tumors or lymphomas, with enrichment for tumor types with a high expected rate of PTEN deficiency.

Part B:

- Dose escalation study for the evaluation of the tolerability, safety, PK, and PD of SAR260301 administered in combination with the approved dose of 960 mg BID of the BRAF inhibitor vemurafenib in patients with *BRAF* mutated melanoma.

Initially, enrollment of the first cohort in the Part B combination phase was to start after the completion of DL2 in Part A for an escalation in parallel thereafter. Following preliminary PK, the recruitment for Part B was put on hold until completion of dose escalation in Part A, and the protocol was amended to allow for testing additional dose levels, and to adjust the dose according to body surface area (BSA) to partly control exposure variability (Further details can be found in protocol Amendment 4 located in Appendix 16.1.1).

Dose levels according to the latest protocol amendment are listed in the following table.

SAR260301 Dose Levels (DL) in Part A

DL[a]	SAR260301	
	Up to Amendment 3	Amendment 4[b]
A-DL1	100 mg QD	
A-DL2	100 mg BID	
A-DL3	200 mg BID	
A-DL4	400 mg BID	
A-DL5	600 mg BID	*or* 330 mg/m² BID[b]
A-DL6	800 mg BID	*or* 440 mg/m² BID[b]
A-DL7	-	550 mg/m² BID
A-DL8	-	660 mg/m² BID

a Intermediate dose levels could be tested, after agreement between the Sponsor and investigators (Study Committee).

b Adjustment of dose according to body surface was implemented in new patients to be treated at the DL being tested at the time of implementation of the Amendment 4. Further details can be found in protocol Amendment 4 located in Appendix 16.1.1.

Dose escalation for Part A and B:

A Study Committee was set up, including at least the investigators, Sponsor team members (the Clinical Study Director, Global Safety Officer, the Biostatistician and the Clinical Trial Operation Manager) and ad hoc experts (biomarkers, PK and statistic representatives) when appropriate.

During Study Committee meetings, the committee decided on whether to escalate (or not) to the next dose level on the basis of knowledge of the whole safety and tolerability profile, PK profile, and the Bayesian design recommendation (for details, refer to the "Statistical Methods" section).

Although the dose-escalation process is guided by the safety evaluation during Cycle 1 of treatment, cumulative or irreversible toxicities observed after subsequent administrations had to be considered also for the dose-escalation and dose-selection decisions (ie, expansion of a given dose level, intermediate dose levels), upon recommendation from the Study Committee.

As a general definition, the MTD was defined as the highest dose with a tolerable global safety profile, controlling the risks of overdose (true DLT rate above 35%) and the risks of unacceptable toxicity (true DLT rate above 60%). One MTD was to have been assessed for the single agent (Part A) and another MTD was to have been assessed for the dose of SAR260301 in combination with vemurafenib (Part B).

The dose escalation in Part A (SAR260301 monotherapy) and Part B (SAR260301 combined with vemurafenib) were to have been stopped as soon as the determination of the doses not tolerated and/or MTDs.

The first dose level of SAR260301 that was planned to have been tested in the Part B combination study (B-DL1) was to have been 2 dose levels below the MTD or the highest dose tested in Part A. The initial dose of vemurafenib to have been tested in combination was to have been 720 mg BID, corresponding to 75% of the full dose for that drug. In dose level B-DL2, the vemurafenib dosage was to have been increased to 960 mg BID, while SAR260301 was to have remained the same as that tested in B-DL1. Once B-DL2 was found safe, the SAR260301 dose escalation in combination was to have been pursued.

Expansion cohort in Part A and B (to confirm the MTD):

Upon completion of the dose escalation phase, a preliminary RP2D (pRP2D) was to have been assessed by the Study Committee for the expansion cohorts (in Part A and in Part B), primarily based on safety, tolerability and PK data. However, PK and PD results could have supported the determination of the RP2D (especially in the case of situations where the MTD could not have been determined in the absence of DLT at the maximal administrated dose). At the end of each escalation phase of both parts (A and B), the pRP2D was to have been determined taking into account overall safety and tolerability occurring at all cycles (early and late toxicities), PK, PD, PK/PD relationships, and antitumor activity.

In Part A (SAR260301 administered in monotherapy), 10 additional patients with PTEN deficient solid tumors or lymphomas were planned to have been added at the pRP2D to further assess safety (especially any cumulative toxicity, which had to be taken into account), antitumor activity, and PD.

In Part B (SAR260301 administered in combination with vemurafenib), it was planned to have 15 additional patients who were PTEN deficient, *BRAF* mutated melanomas treated at this pRP2D for confirmation of safety (especially any cumulative toxicity, which had to be taken into account), and evaluation of PK, PD, PK/PD, and antitumor activity. Determination of the RP2D in combination was to have taken into consideration the same parameters as those used for determination of the SAR260301 pRP2D in monotherapy.

The study was terminated prematurely due to preliminary PK data indicating a rapid elimination associated with a nonsaturable SAR260301 apparent clearance preventing the achievement of the minimum exposure required for a sustained PD effect.

Number of patients**:**	Planned: approximately 75 (around 40 in Part A and 35 in Part B)
	Treated: 21 (Part A only)
Evaluated:	
	Efficacy: 20
	DLT assessment: 21
	Safety: 21

Pharmacokinetics: 21
Diagnosis and criteria for inclusion: *Specific to Part A* Enrollment included patients with locally advanced or metastatic solid tumor disease as well as lymphoma for which no alternative therapy was available. *Specific to Part B* Enrollment was planned to include patients with unresectable or metastatic $BRAF^{V600}$ mutated melanoma confirmed using an institutional validated assay in a CLIA-certified laboratory or a local Health Authority-approved assay: • During the escalation phase: With or without prior exposure to vemurafenib or other BRAF inhibitor. Patients with only a partial response to a BRAF inhibitor (<50% decrease in tumor volume by RECIST after 4 months of treatment) could have been included. • During the expansion phase: Patients who received ≤4 months of vemurafenib or other BRAF inhibitor, or prior regimen combining a BRAF inhibitor with a MEK inhibitor, and who had either progressive disease, or <50% decrease in tumor volume by RECIST after 4 months of treatment. • Anterior scans pre-vemurafenib and on vemurafenib treatment had to be made available to the Sponsor or Sponsor designated central imaging analysis. *Part A & Part B* Patients who were ≥18 years old and had at least 1 measurable lesion by RECIST Version 1.1; archived primary tumor biopsies or surgical specimens, or biopsies of recurrence or metastasis (requested for all subjects for PTEN analyses and additional molecular profiling); and at least 75 microns (preferably 125 microns) of formalin-fixed paraffin-embedded (FFPE) tissue or a tissue block available for enrollment and for shipment to the Sponsor, or to a laboratory designated by the Sponsor (or sufficient material for key evaluations based on Sponsor judgment). PTEN status: • During the escalation phases, inclusion was not restricted to, but was enriched for PTEN deficiency: - Documented PTEN deficiency (loss of protein expression by immunohistochemistry [IHC] confirmed retrospectively by Sponsor or a Sponsor-designated central laboratory). Tumor tissue was also used for assessment of PTEN status via a variety of other assay platforms. - Or, in Part A: Tumor types known to have a significant prevalence for PTEN deficiency including, but not restricted to, *KRAS* wild-type colorectal, Cowden syndrome malignancies, endometrioid, melanoma (including *BRAF* wild type in Part A), prostate, gastric, breast, lung, kidney, pancreas, liver, ovarian, squamous-cell carcinoma of the head and neck, and thyroid. • During the expansion phases, the patient had to have PTEN-deficient tumors as confirmed prospectively by loss of protein expression via IHC on archival tumor tissue either locally or by the Sponsor or a Sponsor-designated central laboratory.
Study treatments **Investigational medicinal product(s):** SAR260301 Formulation: 100 mg film-coated tablets Route(s) of administration: oral

Dose regimen: SAR260301 was administered at assigned dose levels QD or BID (~12 hours apart), within a 28-day cycle. Patients were to have received all doses at a fasted condition (1 hour before breakfast and following an overnight fast in the morning, and at least 2 hours after an afternoon snack and 1 hour before dinner, or 2 hours after dinner in the evening). For patients participating in the food effect substudy, at a day convenient to the patient in Cycle 2, SAR260301 was to have been taken within 30 minutes of a moderate-fat breakfast (fed condition). PK was characterized in the fed and fasted conditions. This food effect evaluation was carried out in the escalation phase of Part A until 6 evaluable patients were included. On the basis of the PK and safety findings, a recommendation was to have been made by the Study Committee to give all subsequent doses for all patients in the study at all dose levels in the fed or fasted condition.

In Part B, SAR260301 was planned to be administered BID and concomitantly with vemurafenib.

Noninvestigational medicinal product(s): Vemurafenib (ZELBORAF™)

Formulation: 240 mg film-coated tablets

Route(s) of administration: oral

Dose regimen: Vemurafenib was planned to be administered, but was not due to early study termination. Except at dose level B-DL1, where vemurafenib was to have been administered at 720 mg BID during Cycle 1, it was planned to be administered at the recommended dose of 960 mg (four 240 mg tablets) BID (~12 hours apart), within a 28-day cycle. Administration in relation with food was to have depended on the recommendation previously made for SAR260301 administration. Dose reductions were not to have gone below 480 mg BID.

Duration of treatment: SAR260301 was administered continuously in 28-day cycles. Unless toxicity requiring premature drug discontinuation occurred during the first cycle, each patient had to receive at least 4 weeks of treatment.

Duration of observation: The duration of the study for an individual patient included a period to assess eligibility (screening period) of up to 4 weeks (28 days), a treatment period of at least 1 cycle (28 days) of study treatment, and an end-of-treatment visit at least 30 days (or until the patient receives another anticancer therapy, whichever was earlier) following the last administration of study treatment. Treatment could have continued until precluded by toxicity, progression, death, or upon patient's request.

Criteria for evaluation:

Safety:

Primary endpoint

The primary safety endpoint was the incidence of DLTs at Cycle 1 (Day 1 to Day 28). A DLT was defined as any of the following using the National Cancer Institute of Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 whether related or not to the study treatment in the absence of clear evidence to the contrary, and if not related to a disease progression:

- ≥Grade 3 toxicities excluding:
  - Grade 3 nausea and vomiting resolving to Grade ≤1 within 48 hours.
  - Grade 3 diarrhea, if controlled with adequate anti-diarrheal therapy and lasting less than 48 hours.
- Other "non-gradable" toxicities:
  - Cutaneous and non-cutaneous squamous-cell carcinoma, known to be related to vemurafenib, will not be considered a DLT.
  - If ≥25% (≥14 doses with twice daily dosing or ≥7 doses with once daily dosing) of SAR260301 (in Part A) or SAR260301/vemurafenib (in Part B) were not administered during C1 due to toxicity.
  - A treatment-emergent adverse event (TEAE), which in the opinion of the Study Committee, was of potential clinical significance such that further dose escalation would have exposed patients to unacceptable risk.

If multiple toxicities were seen, the presence of DLT was based on the most severe toxicity experienced. At the end of each cycle, each patient had to have been assessed by the Investigator as to whether or not the patient experienced DLT, and this information had to have been recorded on the appropriate electronic case report forms (e-CRFs).

Secondary endpoints

Secondary safety endpoints included the overall safety profile of SAR260301 administered in monotherapy (Part A) or in combination with vemurafenib (Part B), and characterization in terms of the type, frequency, severity, timing, and relationship to study therapy of any adverse events or abnormalities of physical findings, laboratory tests, vital signs, ECGs or LVEF evaluations (ophthalmologic and dermatologic examinations in Part B); drug discontinuation due to adverse events; or serious adverse events.

Pharmacokinetics: SAR260301 venous blood concentrations obtained after a once daily or twice daily regimen were used to determine the following PK parameters on Day 1 and Day 28 of Cycle 1 in fasted conditions and on a selected day (Day X) of Cycle 2 for food effect pilot study (moderate fat breakfast) using standard non-compartmental analysis: C_{max} (maximum blood concentration observed), t_{max} (time to reach C_{max}), AUC_{last} (area under the blood concentration versus time curve calculated using the trapezoidal method from time zero to the real time corresponding to the last concentration above the limit of quantification), AUC_{τ} (area under the blood concentration versus time curve calculated using the trapezoidal method over the dosing interval), Rac (AUC_{tau} Day28/Day1), RacC_{max} (C_{max} D28/Day 1), and CL_{ss}/F (apparent total body clearance at steady state after oral route); $t_{1/2z}$ (apparent elimination half-life associated with the terminal slope) and the ratio of C_{max} and AUC_{τ} in fed (Cycle 2 Day X) versus fasted (Cycle 1 Day 28) state were also calculated.

In the expansion phase of Part A, the plasma 4β-hydroxycholesterol on Day 15 versus Day 1 concentration ratios were to have been calculated to evaluate the potential for CYP3A4 enzyme induction and inhibition by SAR260301 after repeated doses.

PK sampling times and assay methods: Venous blood samples (using dried blood spot technology [DBS]) were collected at Cycle 1 at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24* (*QD regimen only) hours after the first daily administration on Day 1 and Day 28 and on a selected day of Cycle 2 for the food effect pilot study. Additional blood samples were collected before the first daily dose (predose) on Day 2 (BID regimen), Day 8, Day 15, and Day 29 (corresponding to the Cycle 2 Day 1, BID regimen).

In addition DBS samples were collected by finger prick for investigation purposes at the following time points: predose (0), 2, and 6 hours after oral dosing of Cycle 1 Day 28 (not presented in this report).

Bioanalytical PK method: SAR260301 concentrations were determined in blood using a validated LC-MS/MS method with a lower limit of quantification (LLOQ) of 1.00 ng/mL (Method DOH1109).

Pharmacodynamic biomarkers:

Blood (all patients) and tumor (expansion cohort only – optional) samples were obtained to document the PD effect of SAR260301 on the PI3K pathway. 8.5 mL blood samples were collected at various time points within Cycle 1 (predose on Day 1, 2, 15, and 28 and at 1 hour and 6 hours after SAR2060301 administration on Day 1 and 28) and processed to obtain platelet-rich plasma (PRP) on which the level of pAKT inhibition was determined. On treatment tumor biopsies, planned to be done predose and during Cycle 1 Day 15 (±3 days) in the expansion phases, were not done.

Efficacy: Tumor response was to have been assessed using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 locally for all patients and was planned to be assessed centrally in the expansion cohort of Part B. Patients had to be assessed using magnetic resonance imaging (MRI) or computerized tomography (CT) scan at least every 2 cycles, or less frequently, if indicated. Responses had to be confirmed by repeat assessments performed at least 4 weeks after response criteria were first met (RECIST, Version 1.1). International Workshop Group (IWG) response and revised criteria was planned to be used to assess response in patients with lymphoma.

Exploratory endpoints

Predictive biomarkers:

The objective of this endpoint was to evaluate pre-existing PTEN status in archival or fresh tumor samples and correlate PTEN deficiency with clinical outcome.

Archival tumor sample: Archived primary tumor biopsies or surgical specimens, or biopsies of recurrence or metastasis, were requested for all subjects for PTEN analyses and additional molecular profiling. At least 75 microns (preferably 125 microns) of formalin-fixed paraffin-embedded (FFPE) tissue or a tissue block should have been available for enrollment and shipment to the Sponsor, or a laboratory designated by the Sponsor. PTEN protein expression was tested using a validated immunohistochemistry either locally or by Sponsor or laboratory designated by the Sponsor. For prospective enrolment in expansion phase, the validated IHC was performed in a CLIA-certified laboratory. If less material was available, the patient could have still been eligible after discussion with the Sponsor who assessed and confirmed that there was sufficient material for key evaluations.

Fresh tumor biopsy: Tumor sampling was not required for the escalation cohorts, but was mandatory at baseline for the expansion cohorts.

The objective was to evaluate other potential genetic markers of response in the context of PTEN deficiency in tumor tissue and whole blood.

Whole blood: One whole blood sample (10 mL) was collected during screening and processed for plasma circulating tumor DNA genotyping for genetic alterations relevant to components of the PI3K and MAPK pathways, as well as other relevant signaling pathways.

Other genetic markers could also have been assessed in archived and/or fresh tumor tissue samples when sufficient material was available.

Optional genotyping or pharmacogenetics:

One optional blood sample was collected on Day-1 (predose) to investigate allelic variants of drug metabolism enzymes and/or drug transporters as intrinsic factors associated with PK or PD variability of SAR260301.

Evaluation of platelet function: The impact of the PI3K pathway modulation in platelet on platelet function was done using the point-of-care assay PFA100® by the measure of closure time using both a collagen/epinephrine cartridge and a P2Y PGE1/ADP cartridge. For that purpose, 2.7 mL whole blood samplings were drawn predose on Days 1, 2, 15, and 28, and 1 and 3 or 6 hours postdose on Days 1 and 28 and 24 hours predose on Day 28.

Statistical methods:

Determination of sample size:

This study aimed to establish the MTD of SAR260301 according to DLTs observed and the RP2D of SAR260301 to be administered:

- as a single agent,
- in combination with the approved dose of the BRAF inhibitor, vemurafenib 960 mg BID, in patients with BRAF mutated melanoma.

Based on different simulated scenarios (1000 simulated trials on 8 different scenarios), it was anticipated that almost likely around 25 to 30 safety-evaluable patients would be enrolled in Part A and 15 to 20 safety evaluable patients in Part B during the escalation phase of the study. The actual sample size could have varied depending on the DLTs observed and number of dose levels actually explored.

In order to complete the assessment of the global safety profile at the MTD, approximately 10 patients had to be enrolled in the dose expansion cohort of Part A and approximately 15 patients in the dose expansion cohort of Part B. If 3 clinical objective responses (or less) were observed among 15 patients in the Part B expansion, a response rate of 40% would be ruled out with less than 10% (precisely, 9.1%) chance to falsely rejecting the drug.

A total of approximately 75 patients were to have been enrolled in the study.

Analysis populations:

Safety population: all patients who received at least 1 dose of study treatment.

Patients evaluable for DLT evaluation: patients who had received a complete first cycle with at least 75% dosing unless the patient was discontinued early during Cycle 1 due to a DLT.

Efficacy population: patients who had received at least 1 cycle of study treatment, and provided a baseline and at least 1 post baseline tumor assessment. Patients with early progression as per RECIST 1.1 were also included in this population.

Adaptive Bayesian design providing recommendation on SAR260301 dose escalation:

An adaptive Bayesian design with overdose control was used to provide dose recommendations on SAR260301 dose escalation. This adaptive dose escalation was based on a statistical (2-parameter logistic) model for the probability of dose-limiting toxicity (DLT) in the whole population as a function of dose. The model was used to estimate whether the probability of DLT (also called DLT rate) at each candidate dose level was within a targeted interval of 16% to 33% after each new cohort of DLT evaluable patients.

Dose escalation was indicated by the design if the probability of DLT within the targeted interval at the next level was greater than at the current level or de-escalation if the probability of DLT within the targeted interval at a lower level was greater than at the current level. Otherwise, subsequent patients were treated at the current dose level. Intrapatient dose escalation was not allowed. Intrapatient dose escalation for vemurafenib was to have been allowed only within the initial combination dose level B-DL1, where vemurafenib 720 mg BID could have been increased to 960 mg BID if no DLT had occurred in Cycle 1.

In addition, escalation occurred when the overdosing and unacceptable toxicity risks were controlled at the levels of 25% and 5%, respectively. That is to say, the risks of a DLT rate above 33% and above 60% could not have exceeded pre-specified tolerated risk levels of 25% and 5%, respectively. To further increase the safety of dose escalation, the maximum increase in dose from 1 level to the next was 100%. In addition, if 2 or more patients in the current cohort had a Grade 2 related SAR260301 toxicity or if any patient had a DLT, then the maximum increase in dose from 1 level to the next was to have been no greater than 50%.

Enrollment at the next dose level could have proceeded only if a minimum of 3 patients completed treatment without a DLT at the current dose level for at least the duration of 28 days (1 cycle).

Only DLTs reported during Cycle 1 have been considered in the modeling.

Safety analyses:

Safety endpoints included:

- DLTs,
- Treatment-emergent AEs (TEAEs), including serious adverse events (SAEs),
- Deaths,
- Laboratory assessments,
- Vital signs,
- Electrocardiograms.

All safety analyses were descriptive and performed on the safety population by actual dose level.

Dose-limiting toxicities occurring during Cycle 1 were provided by dose level, with details provided by patient. Moreover, AEs meeting DLT criteria and occurring after Cycle 1 were also listed.

The primary focus of AE reporting was TEAEs, defined as any AEs that occurred or worsened during the on-treatment period (ie, from the first administration of study treatment up to 30 days after the last dose). Treatment-emergent AEs were coded using MedDRA Version 17.1, with intensity graded by the National Cancer Institute (NCI) Common Toxicity Criteria Adverse Event (CTCAE) Version 4.03. Adverse event incidence tables presented the number and percentage of patients by primary system organ class (SOC) and preferred term (PT) and sorted by SOC internationally agreed order.

Summaries of all TEAEs, related TEAEs, treatment-emergent SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification (delay, reduction, omission), and TEAEs leading to dose interruption were provided. Worst grades were summarized. Some AE tables presenting data by high level group term (HLGT), high level term (HLT), and PT were also presented.

Clinical laboratory values were converted to standard international units by data management, then were graded according to the NCI-CTCAE version 4.03 whenever applicable, using laboratory ranges provided by the laboratory analyzing the sample whenever possible and using generic normal ranges for other parameters. The maximum grade (worst) per patient was summarized. When the NCI-CTCAE was not applicable, laboratory values "out of normal ranges" were summarized.

Vital sign data were not described.

Left ventricular ejection fraction (LVEF) data were listed.

Efficacy analyses:

The endpoint was ORR (CR + PR), which was summarized by dose level.

Due to the early termination of the study, all analyses planned in the protocol were not performed.

Summary: This study was planned to include 2 parts (Part A and B), of which the second part (Part B) was never initiated due to the unfavorable PK properties of SAR260301; therefore, only results from Part A are presented in this synoptic report.

Population characteristics:

Twenty-one patients were enrolled and treated as follows:

- 3 in the A-DL1 (100 mg QD) cohort;
- 3 in the A-DL2 (100 mg BID) cohort;
- 3 in the A-DL3 (200 mg BID) cohort;
- 6 in the A-DL4 (400 mg BID) cohort;
- 4 in the A-DL5 (600 mg BID) cohort;
- 2 in the A-DL6 (440 mg/m^2 BID) cohort.

Of those 21 patients, 19 discontinued due to disease progression and 2 discontinued due to other reasons (ie, "physician and patient decision" for 1 patient and "patient decision" for 1 patient).

All 21 patients were included in the treated population and were evaluable for DLTs. Twenty patients were included in the efficacy evaluable population; 1 patient in the A-DL5 cohort was not evaluable for efficacy since her radiological tumor assessment was performed in an outside facility, albeit disease progression was based on evidence of symptomatic deterioration.

The primary tumor sites (for >1 patient) at initial diagnosis were the colon/rectum (7 patients), skin (3 patients), breast and ovary (2 patients each); and the most common histology types (>1 patient) were adenocarcinoma (12 patients) and melanoma (3 patients). No patients with lymphoma were enrolled. All patients had metastatic disease. Most patients had Stage IV (11 patients) or Stage III cancer (5 patients) at initial diagnosis. Median time from initial diagnosis and date of first study treatment dose for all patients was 4.50 years (range: 1.3 to 22.2 years). Most patients (19) had ≥2 organs involved at baseline, with the most commons organs (for >10 patients) identified as the lungs (16 patients), lymph nodes (12 patients), and liver (11 patients). The median number of prior lines of anticancer treatment regimen was 4 (ranging from 1 to 9). Eighteen patients had prior cancer surgery, and 9 patients had prior radiotherapy.

Some level of tumor molecular characterization was available for 15 of the 21 treated patients at study entry. Genetic alterations had been documented in 8 of these 15 patients and involved the following genes: *PTEN* (1 patient), *PIK3CA* (4 patients), *EGFR* (1 patient), *NRAS* (2 patients), *KRAS* (3 patients), *TP53* (3 patients), *BRCA2* (1 patient), *ATM* (1 patient), and *APC* (1 patient). Three patients had PTEN-null disease documented at the level of PTEN protein expression by the study site.

Grade 3-4 laboratory abnormalities at baseline included Grade 3 lymphopenia (2 patients) and Grade 3 GGT increased (2 patients).

Safety results:

Exposure

The median number of days on treatment was 36.0 for the A-DL1; 30.0 for the A-DL2; 28.0 for the A-DL3; 56.0 for the A-DL4; 28.0 for the A-DL5; and 109.5 for the A-DL6 cohort. Most patients received between 1 cycle (8 patients) and 2 cycles (9 patients) of treatment. Two patients received at least 6 cycles. Median relative dose intensity (RDI) was 0.97 for the A-DL1; 0.85 for the A-DL2; 1.04 for the A-DL3; 0.54 for the A-DL4; 0.76 for the A-DL5; and 0.94 for the A-DL6 cohort.

Based on the exposure dataset, 9 patients had dose administration as planned and 12 patients had at least 1 dose omission. No patient had a cycle delayed.

Dose-Limiting Toxicities

Two DLTs occurred during dose escalation:

- Grade 3 pneumonitis: 1 patient treated at A-DL4 (400 mg BID), was discontinued from the study after completion of Cycle 1 for disease progression. Grade 1 pneumonitis was incidentally documented on CT scan. The event worsened from Grade 1 to Grade 3 seventeen days after the last SAR260301 administration. No other cause could be incriminated. The event resolved with corticosteroids. Further details can be found in the patient's safety narrative in Section 15.3.
- Grade 3 GGT increased: 1 patient treated at A-DL5 (600 mg BID), was discontinued from the study midway through Cycle 1 for disease progression, at which time, Grade 3 GGT increased was documented in the context of liver metastases (Grade 1 at baseline). Grade 3 GGT increased resolved promptly after discontinuation of SAR260301 and in the absence of initiation of another anticancer treatment. The event was retrospectively attributed to study treatment. Further details can be found in the "Treatment-Emergent Adverse Events" section.

Treatment-Emergent Adverse Events

All 21 patients had at least 1 TEAE (all grades), of which 13 had treatment-related TEAEs. Nine patients had at least 1 ≥Grade 3 TEAE, of which 2 had treatment-related ≥Grade 3 TEAEs (1 pneumonitis and 1 GGT increased).

The most common TEAEs (reported by ≥3 patients) in all cohorts (all grades), regardless of relationship to treatment, were fatigue (11 patients); nausea (6 patients); diarrhea and abdominal pain (5 patients each); cough and vomiting (4 patients each); decreased appetite, headache, constipation, myalgia, back pain, and GGT increased (3 patients each). Five infectious events were documented: urinary tract infection (1 patient), pneumonia (1 patient), viral infection (1 patient), mucosal infection (1 patient), and upper respiratory tract infection (1 patient). Three bleeding events were documented: hemorrhoids (1 patient), vaginal hemorrhage (1 patient), and pulmonary hemorrhage (1 patient). The only ≥Grade 3 TEAEs reported by more than 1 patient were GGT increased (3 patients, of which 1 had a treatment-related TEAE [Grade 3 GGT increased DLT]); pleural effusion and disease progression (2 patients each).

Nine patients had at least 1 treatment-emergent SAE, of which 1 patient had a treatment-related SAE (Grade 3 pneumonitis DLT). Treatment-emergent SAEs included the following: pleural effusion, abdominal pain, and disease progression (2 patients each); autoimmune disorder, hypercalcemia, confusional state, syncope, pneumonitis, pulmonary hemorrhage, upper abdominal pain, and bile duct obstruction (1 patient each). Further details on these patients can be found in the patients' safety narratives in Section 15.3.

Two patients (1 in the A-DL1 cohort and 1 in the A-DL5 cohort) died as the result of a treatment-emergent SAE that was unrelated to study treatment (disease progression) within 30 days of the last study treatment dose. Further details on these patients can be found in the patients' safety narratives in Section 15.3. An additional patient in the A-DL2 cohort died due to disease progression post-study, 77 days after the last study treatment dose.

No patient had a TEAE that led to permanent discontinuation or dose modification of study treatment.

Based on the AE dataset, 6 patients had at least 1 TEAE (all grades) leading to dose interruption as follows:

- A patient in the A-DL1 cohort, presented with recurrent pleural effusion due to malignant disease. Study treatment was interrupted for insertion of a chest tube, but was never reinitiated due to disease progression.
- A patient in the A-DL2 cohort, had intermittent abdominal pain at baseline in the context of liver metastases. Study treatment was interrupted at the end of Cycle 1 for worsening gastrointestinal symptoms and Grade 3 GGT increase consistent with progression of liver metastases, which was retrospectively confirmed.
- A patient in the A-DL2 cohort, presented with syncope on Cycle 1 Day 1, 1 to 2 hours after the evening dose of study treatment. Study treatment was interrupted and quickly resumed after establishing a diagnosis of post-tussive syncope due to the pneumonia. Furthermore, the patient had study treatment interrupted at the end of Cycle 5 because of increased uric acid in the context of persisting diarrhea related to malignant disease (Good's syndrome - autoimmune process related to thymic carcinoma). Uric acid was quickly normalized following hydration and allopurinol, but study treatment was never reinitiated due to evidence of progressive disease.
- A patient in the A-DL5 cohort, presented with Grade 2 dehydration (unrelated to study treatment) on Day 15 of Cycle 1 for which the study treatment was interrupted (1 dose omission) but resumed on the same day. There was a slight drop in the patient's hemoglobin at 85 g/L from 91 g/L at baseline (Grade 2). The patient was rehydrated with normal saline and received a transfusion with red blood cells. The event of dehydration resolved on the same day. The patient's hemoglobin stabilized at 101 g/L (Grade 1) at the end of Cycle 1.
- A patient in the A-DL5 cohort, had study treatment interrupted midway through Cycle 1 for headache and Grade 3 GGT increased (Grade 1 at baseline). The patient was found to have new punctate brain lesions and an increase in size of liver lesions. The patient was discontinued from the study for disease progression, and Grade 3 GGT increased recovered promptly after discontinuation of SAR260301 and in the absence of initiation of another anticancer treatment. GGT increase was retrospectively attributed to study treatment and was considered to be a DLT.
- A Patient in the A-DL6 cohort, midway through Cycle 2, had vomiting, fever and increased transaminases (Grade 3) found later to be due to obstruction of a biliary stent due to disease progression. The event resolved with replacement of the stent.

Laboratory Results

Overall, there were no relevant laboratory abnormalities.

The only ≥Grade 3 hematologic abnormalities were 3 cases of lymphopenia (all Grade 3). For all of these patients, lymphopenia was present at baseline (Grade 3 in 1 patient and Grade 2 in 2 patients), and there was no clear evidence of worsening while on treatment.

≥Grade 3 chemistry abnormalities included:

- 5 patients with ≥Grade 3 GGT increased, of which only 1 patient had an increase related to SAR260301 (DLT); all others had an increase related to the underlying malignant disease.
- 2 patients with ≥Grade 3 ALT increased, of which 1 patient also had concomitant Grade 3 AST increased; all were related to the underlying malignant disease.
- 1 patient with Grade 3 hypokalemia (concomitant to Grade 3 decrease in bicarbonate and increased uric acid) occurring 20 days after the last administration of SAR260301. The patient was discontinued from the study due to progressive disease, in the context of thymoma-associated autoimmune enteropathy.

One patient, with metastatic hepatocellular carcinoma with bone involvement, had serious Grade 2 hypercalcemia, which was considered to be related to disease progression.

No patient had a ≥Grade 3 coagulation abnormality during the study.

Other safety results:

Thyroid function

Overall, a small number of patients had at least 1 non-gradable thyroid function abnormality as follows:

- 4 patients (2 in the A-DL4 and 2 in the A-DL5 cohort) had thyroid stimulating hormone (TSH) >ULN during the on-treatment period; 2 had above normal TSH present at baseline. One patient with increased TSH at baseline and at Cycle 2 also had <LLN free thyroxine 4 (FT4) levels at baseline and on treatment.

Cardiac function

No drop in LVEF was documented.

Pharmacokinetic results:

Pharmacokinetic parameters were obtained in 21 patients during Cycle 1 Day 1 and 15 patients during Cycle 1 Day 28. During Cycle 1 Day 1, 1 patient was not excluded from the PK analysis despite having a single episode of vomiting (approximately 40 minutes after oral dosing) since there was no evidence of pill presence in the vomit and the PK parameters of SAR260301 (C_{max} and AUC_T) were in the range of those observed in the same dose level for the other patients.

Among the 7 patients treated during Cycle 2 in fed conditions (moderate fat breakfast), 6 patients were evaluable for the optional pilot food effect study part. One patient was excluded due to a protocol deviation (SAR260301 oral dosing was taken 1.8 hours after moderate fat breakfast instead of within 30 minutes, as per protocol).

Mean PK profiles of SAR260301 concentrations in blood at Day 1 and Day 28 in fasted conditions are presented in Figure 1 and Figure 2, respectively. Mean PK profiles of SAR260301 concentrations in blood in fed conditions are presented in Figure 3.

In fasted conditions, mean PK parameters of SAR260301 in blood at Day 1 and 28 are presented in Table 1 and Table 2, respectively; PK parameters as a function of dose are illustrated in Figure 4 and Figure 5; the accumulation ratios on C_{max} and AUC_T (Day 28/Day 1) are presented in Table 3; PK parameters of SAR260301 in blood in fed conditions are presented in Table 4; and the pilot food-effect study results are presented in Table 5.

Figure 1 - Mean concentration-time course of SAR260301 after oral administration of SAR260301 during Cycle 1 – DAY 1 (fasted)

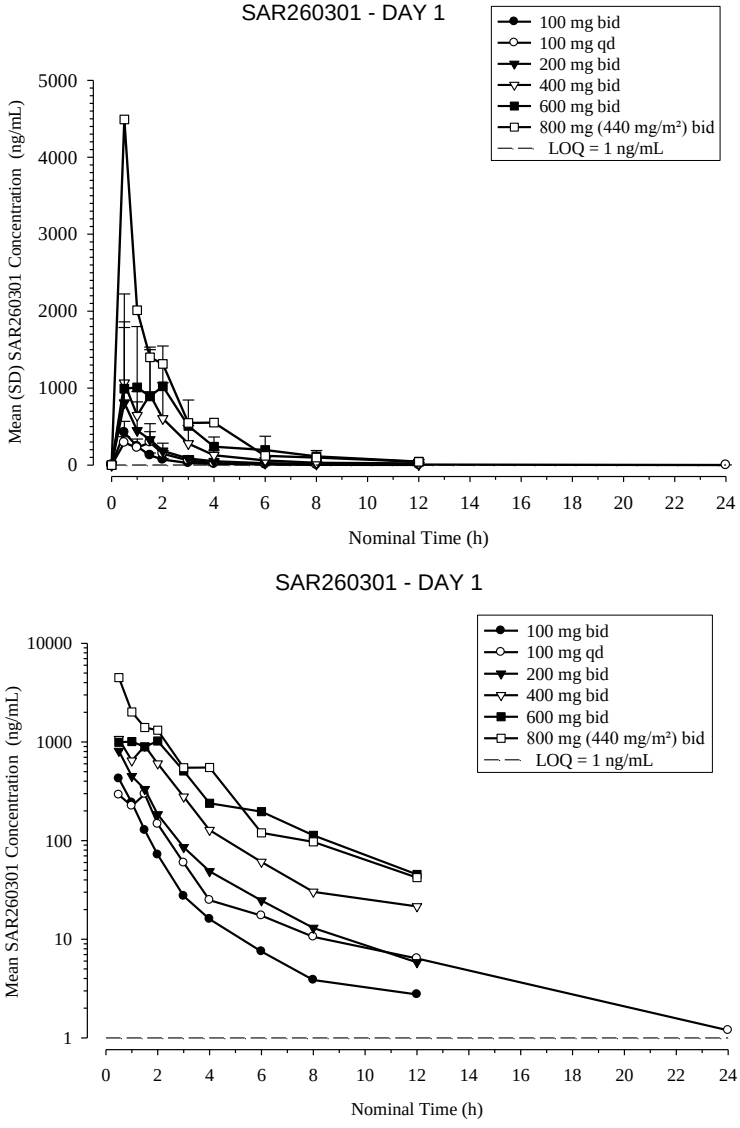


Figure 2 - Mean concentration-time course of SAR260301 after oral administration of SAR260301 during Cycle 1 – DAY 28 (fasted)

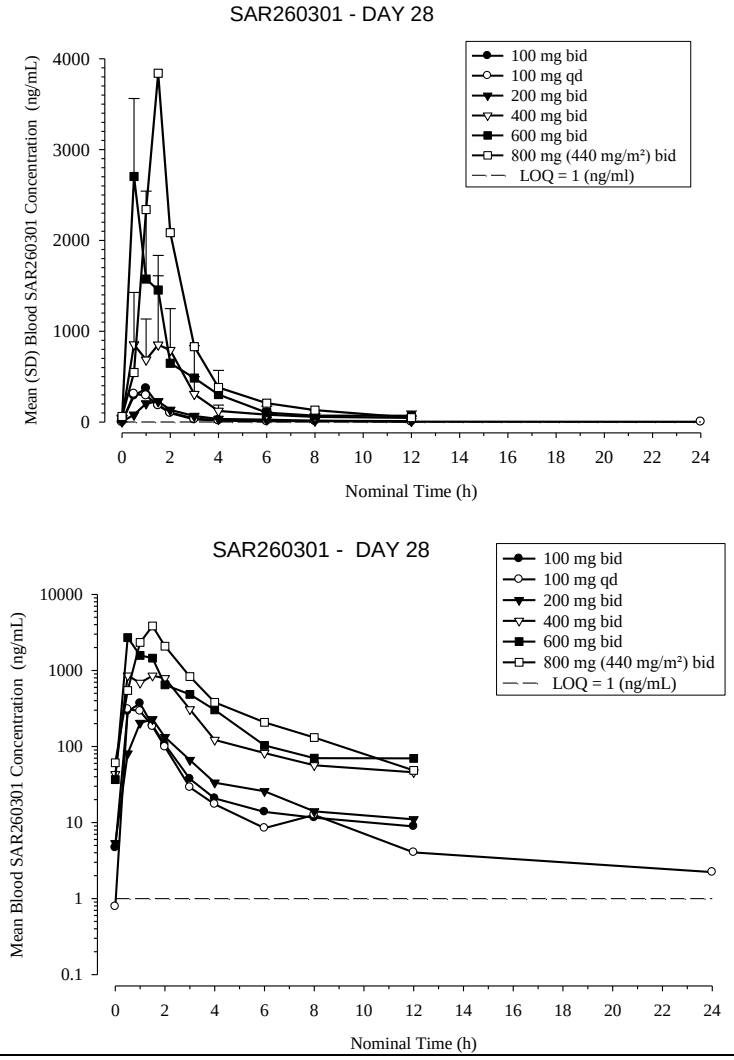


Figure 3 - Mean concentration-time course of SAR260301 after oral administration of SAR260301 on fed conditions during Cycle 2

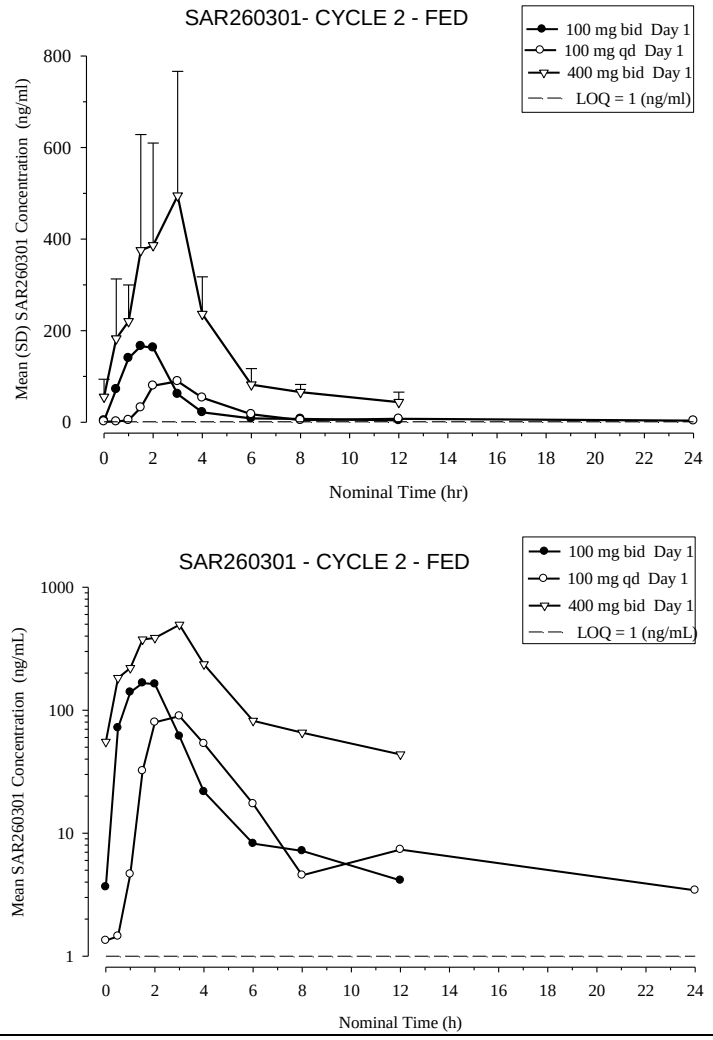


Table 1 - Summary of SAR260301 PK parameters in blood following oral administration of SAR260301 on Day 1

Mean ± SD (Geometric Mean) [CV%]	**Dried Blood SAR260301 – DAY 1**					
	100 mg QD	100 mg BID	200 mg BID	400 mg BID	600 mg BID	800 mg BID (440 mg/m^2 BID)[b]
N	3	3	3	6	4	2
C_{max} (ng/mL)	322 ± 93.2 (312) [29]	424 ± 145 (405) [34]	825 ± 961 (465) [116]	1570 ± 908 (1330) [58]	1540 ± 487 (1480) [32]	4660 ± NC (3080) [NC]
t_{max}[a] (h)	1.5 (0.50 - 1.50)	0.5 (0.50 - 0.55)	0.58 (0.48 - 1.50)	1.15 (0.50 - 2.02)	0.78 (0.42 - 2.00)	1.24 (0.48 - 2.00)
AUC_{last} (ng•h/mL)	730 ± 192 (713) [26]	539 ± 105 (531) [20]	1190 ± 929 (957) [78]	2440 ± 909 (2300) [37]	3810 ± 1490 (3610) [39]	6840 ± NC (6220) [NC]
AUC_{0-12} (ng•h/mL)	694 ± 230 (668) [33]	541 ± 105 (534) [19]	1200 ± 928 (961) [77]	2460 ± 914 (2320) [37]	3840 ± 1480 (3650) [38]	6880 ± NC (6260) [NC]
AUC_{0-24} (ng•h/mL)	734 ± 199 (716) [27]	NA	NA	NA	NA	NA
$t_{1/2z}$ (h)	5.19 ± 2.44 (4.71) [47]	NA	NA	NA	NA	NA

SD: standard deviation; CV: coefficient of variation; QD: daily; BID: twice daily; NC: not calculated; NA: not applicable

a Median (Min - Max)

b According to their body surface area, 1 patient received 700 mg BID and the other received1000 mg BID

Table 2 - Summary of SAR260301 PK parameters in blood following repeated oral administration of SAR260301 on Day 28

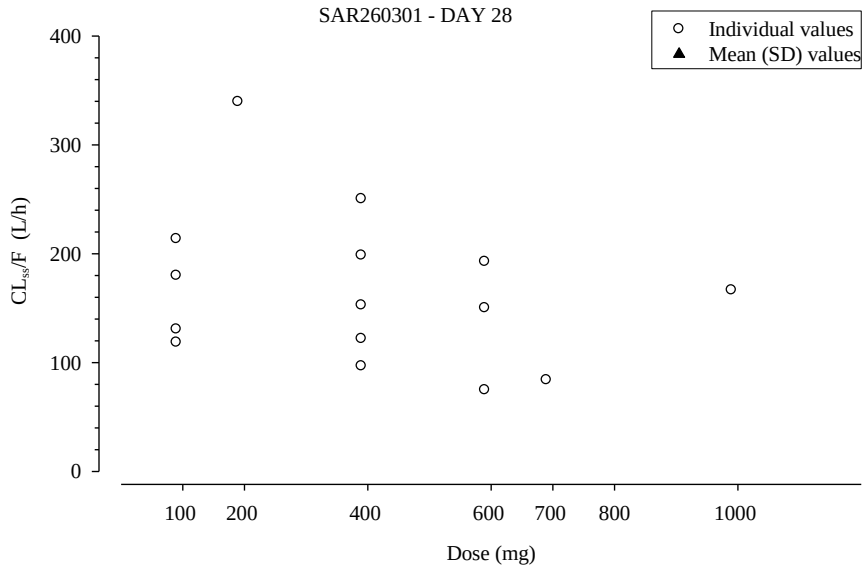
Mean ± SD (Geometric Mean) [CV%]	**Dried Blood SAR260301 – DAY 28**					
	100 mg QD	100 mg BID	200 mg BID	400 mg BID	600 mg BID	800 mg BID (440 mg/m^2 BID)[b]
N	2	2	1	5	3	2
C_{max}	344 ± NC	445 ± NC	228 ± NC	1240 ± 535	2700 ± 859	3870 ± NC
(ng/mL)	(296) [NC]	(441) [NC]	(228) [NC]	(1140) [43]	(2620) [32]	(3860) [NC]
t_{max}[a]	0.78	0.77	1.5	1.03	0.5	1.24
(h)	(0.55 - 1.00)	(0.52 - 1.02)	(1.50 - 1.50)	(0.50 - 2.13)	(0.47 - 0.55)	(0.95 - 1.52)
AUC_{last}	618 ± NC	647 ± NC	589 ± NC	2650 ± 990	4940 ± 2510	7130 ± NC
(ng•hr/ml)	(600) [NC]	(640) [NC]	(589) [NC]	(2500) [37]	(4560) [51]	(7030) [NC]
AUC_{τ}	617 ± NC	700 ± NC	589 ± NC	2730 ± 1010	5050 ± 2620	7180 ± NC
(ng•hr/ml)	(599) [NC]	(685) [NC]	(589) [NC]	(2580) [37]	(4640) [52]	(7080) [NC]
CL_{ss}/F	172 ± NC	149 ± NC	339 ± NC	164 ± 61.4	139 ± 59.7	125 ± NC
(L/h)	(167) [NC]	(146) [NC]	(339) [NC]	(155) [37]	(129) [43]	(118) [NC]
$t_{1/2z}$	7.59 ± NC	NA	NA	NA	NA	NA
(h)	(7.59) [NC]					

SD: standard deviation; CV: coefficient of variation; QD: daily; BID: twice daily; NC: not calculated; NA: not applicable

a Median (Min - Max)

b According to their body surface area, 1 patient received 700 mg BID and the other received1000 mg BID

Figure 4 - $CL_{ss/F}$ over the dose range tested



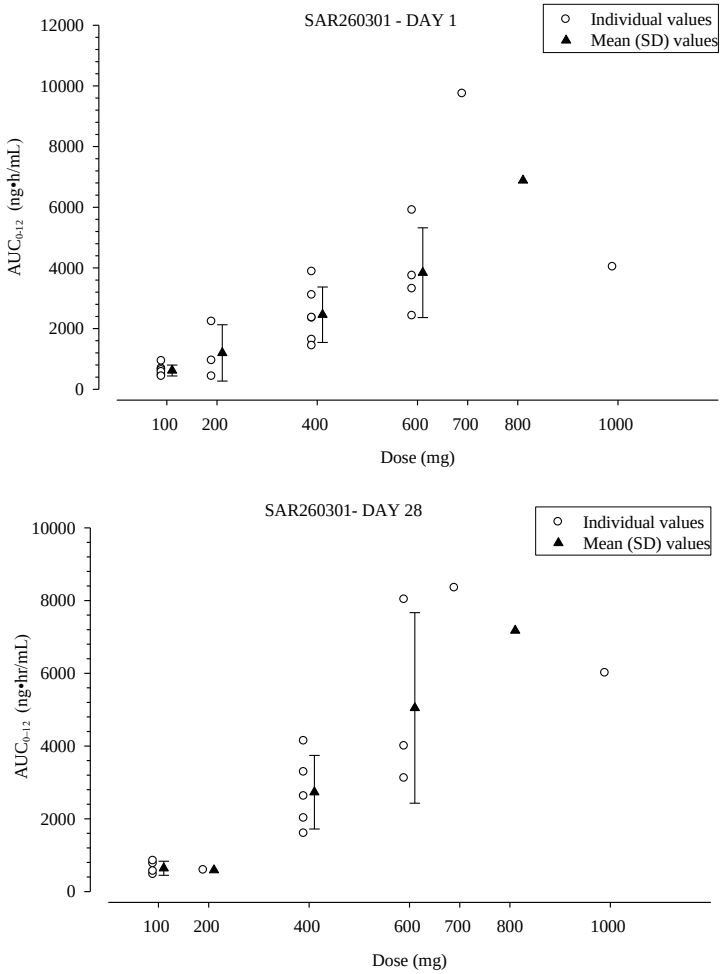
SAR260301 maximal concentrations were rapidly reached with t_{max} ranging from 0.5 to 1.5 hours post oral dosing, either on Day 1 and Day 28 (Table 1 and Table 2). Then concentrations decreased rapidly up to the last sampling time, 24 hours for QD or 12 hours for BID regimens (Figure 1 and Figure 2).

Overall, a moderate to high variability was observed for C_{max} with CV ranging from 29 % to 116%. A low to high variability was observed for AUC_T (CV ranging from 20 to 77%).

Based on mean values, the apparent total body clearance at steady state (CL_{ss}/F) remained almost constant over the dose range tested (100 mg BID to 800 mg BID) after repeated oral BID administration. Overall, CL_{ss}/F was 165 L/h (CV=42%).

After a single daily dose of 100 mg QD, the mean apparent elimination half-life was 5.2 hours.

Figure 5 - SAR260301 PK parameters (AUCτ) as a function of dose on Day 1 and Day 28 during Cycle 1



Based on mean values, exposure increased almost in proportion to the increase of dose, over the dose range 100 mg BID to 800 mg BID (440 mg/m² BID). For an 8-fold increase in dose, C_{max} and AUCτ increased by 11- and 13-fold, respectively, on Day 1 and by 9- and 10-fold on Day 28.

Table 3 - Accumulation ratio D28/D1: Geometric mean value by dose levels

Treatment		R_{accmax}	R_{ac}
	N	D28/D1 C_{max} ratio	D28/D1 AUC_T ratio
100 mg QD	2	1.00	0.840
100 mg BID	2	1.20	1.32
200 mg BID	1	1.90	1.39
400 mg BID	5	1.02	1.18
600 mg BID	3	1.64	1.23
800 mg BID (440 mg/m^2 BID)	2	1.26	1.13
Overall (BID regimen only)	13	1.26	1.22

QD: daily; BID: twice daily

The PK of SAR260301 was similar between Day 1 and Day 28; no accumulation was observed during Cycle 1 between Day 1 and Day 28 (overall, 1.22-fold increase of AUC_T).

Table 4 - Summary of SAR260301 PK parameters in blood following repeated oral administration of SAR260301 in fed conditions during Cycle 2

Mean ± SD (Geometric Mean) [CV%]	**Blood SAR260301 PK parameters – fed conditions**		
	100 mg QD	100 mg BID	400 mg BID
N	1	1	4
C_{max} (ng/mL)	89.4 ± NC (89.4) [NC]	166 ± NC (166) [NC]	503 ± 265 (456) [53]
t_{max} [a] (h)	3.00 (3.00 - 3.00)	1.88 (1.88 - 1.88)	2.53 (1.42 - 3.10)
AUC_{last} (ng•h/mL)	370 ± NC (370) [NC]	438 ± NC (438) [NC]	1990 ± 770 (1890) [39]
AUC_T (ng•h/mL)	375 ± NC (375) [NC]	443 ± NC (443) [NC]	2030 ± 814 (1920) [40]

SD: standard deviation; CV: coefficient of variation; QD: daily; BID: twice daily; NC: not calculated

a Median (Min - Max)

Table 5 - Food effect pilot study – fed over fasted conditions (geometric mean)

		FASTED - C1D28	**FED - C2Dx**	**Ratio Fed/Fasted**	
Treatment	N	$C_{predose}/C_{max}$ (%)	$C_{predose}/C_{max}$ (%)	C_{max}	AUC_T
100 mg QD	1	0.929	1.50	0.529	0.801
100 mg BID	1	1.27	2.20	0.428	0.797
400 mg BID	4	2.53	9.23	0.430	0.787
Geometric mean	6	NA	NA	0.444	0.791

QD: daily; BID: twice daily; NA: not applicable

Patient 840002008 was excluded from the food-effect study.

After a moderate fat breakfast, a negative food effect was observed. Median t_{max} was slightly delayed when compared to fasted conditions (Cycle 1 Day 28). C_{max} and AUC_T decreased respectively, by 56% and 21%, when compared to fasted conditions.

Biomarker results:

Secondary PD objective:

- Near complete (≥80%) and sustained (≥6 hours) pathway inhibition was observed in only 2 patients (1 from the A-DL5 cohort and one from the A-DL6 cohort). For both patients, C_{max} read over 10µM, consistent with the SAR260301 total drug concentration threshold required to induce significant pathway inhibition as predicted from nonclinical studies. The results indicated collectively that pharmacologically active concentrations are reached and mechanistic proof-of-concept is clinically established. Pharmacodynamic data are provided in the Pharmacodynamic Biomarker Analysis Report.
- A preliminary PK/PD analysis indicates that maximum inhibition of phosphor-AKT/total AKT significantly correlated with exposure parameters on Day 28. According to regression lines, the thresholds to reach 60% and 80% inhibition on C_{max} were respectively 7µM and 11µM, and the threshold to reach 60% and 80% inhibition on AUC_{0-12} were 12 µM.h and 20 µM.h, respectively. The results of this PK/PD analysis are preliminary and may be part of a separate report at a later date.

Exploratory objectives:

- For all 21 treated patients, archival tumor tissue samples were available for retrospective documentation of PTEN expression. Tumor sample for 1 patient was nonevaluable. The 3 PTEN-null cases were confirmed by central testing. All remaining cases expressed PTEN. Data will be provided in a separate translational medicine report at a later date.
- The impact of SAR260301 on platelet function using the point-of-care PFA100® assay was assessed from A-DL4. Although inconsistent, there was a trend for closure time prolongation ≥1.3 compared to baseline with C_{max} ≥6µM. These data are preliminary and may be part of a separate translational medicine report at a later date.

Efficacy results:

Twenty patients were evaluable for tumor response by RECIST Version 1.1. No patient had confirmed CR or PR, and most patients progressed quickly after completion of the first or second cycle. Five patients had stable disease (1 PTEN-null heavily pretreated patient with colorectal cancer at A-DL6 showed stable disease lasting for 6 months), 14 patients had progressive disease, and 1 patient was not evaluable.

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