Clinical Study Synopsis

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## 2. Synopsis

<table>
<thead>
<tr>
<th>Date of report:</th>
<th>30 MAR 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study title:</td>
<td>Phase Ib trial of the combination of PI3K inhibitor BAY 80-6946 and allosteric-MEK inhibitor BAY 86-9766 in subjects with advanced cancer</td>
</tr>
<tr>
<td>Sponsor’s study number:</td>
<td>12876</td>
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<tr>
<td>NCT number:</td>
<td>NCT01392521</td>
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<td>EudraCT number:</td>
<td>2010-024082-45</td>
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<td>Bayer HealthCare</td>
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<tr>
<td>Clinical phase:</td>
<td>Ib</td>
</tr>
<tr>
<td>Study objectives:</td>
<td>The primary objectives of this study were to:</td>
</tr>
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<td></td>
<td>• Determine the safety, tolerability and recommended Phase II doses (RP2D) for the combination of phosphatidylinositol 3’-kinase (PI3K) inhibitor copanlisib (BAY 80-6946) and mitogen-activated protein kinase (MEK) inhibitor refametinib (BAY 86-9766)</td>
</tr>
<tr>
<td></td>
<td>• Determine any possible pharmacokinetic interaction of the two drugs when administered concomitantly</td>
</tr>
<tr>
<td></td>
<td>The secondary objectives of this study were to:</td>
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<tr>
<td></td>
<td>• Assess the clinical benefit and response to the combination</td>
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<tr>
<td></td>
<td>• Explore biomarkers of pathway activation that could be predictive of response to this combination, as well as pharmacodynamic biomarkers reflecting drug activity</td>
</tr>
<tr>
<td>Test drug (IMP 1):</td>
<td>Copanlisib (BAY 80-6946)</td>
</tr>
<tr>
<td>Name of active ingredient(s):</td>
<td>BAY 80-6946</td>
</tr>
</tbody>
</table>
Starting dose: 0.2 mg/kg/day
Maximum dose: 0.8 mg/kg/day

Effective from 09 FEB 2012 (Protocol Version 3.0), the total daily dosage of copanlisib should not have exceeded 65 mg in subjects assigned to 0.8 mg/kg, regardless of the body weight. Similarly, for subjects assigned to 0.4 mg/kg copanlisib, the total daily dosage of copanlisib should not have exceeded 32.5 mg.

Intravenously (IV) in 100 mL normal saline solution infused over 1 hour (1-hour IV infusion)

Refametinib (BAY 86-9766)

BAY 86-9766 (1 capsule contained 10 mg of BAY 86-9766)

Starting dose: 30 mg twice daily (60 mg/day)
Maximum dose: 50 mg twice daily (100 mg/day)

Orally (po) twice a day (BID dosing)

Combination therapy with copanlisib and refametinib were tested under a dose-escalation scheme in repeated treatment cycles (cycle length = 28 days). Figure 2–1 shows the 3 dosing schemes used in this study. Subjects continued on study drugs until disease progression, unacceptable toxicity, consent withdrawal or withdrawal from the study at the discretion of the investigator.

Figure 2–1: Schematic diagram of combination therapy schedules of copanlisib and refametinib:

Cohorts 1, 2, 3B: Copanlisib (3 Wks On / 1 Wk Off) + Refametinib (Daily)

Cohorts 2A, 2C: Copanlisib (Weekly) + Refametinib (Daily)

Cohorts 3BN, 4N: Copanlisib (Weekly) + Refametinib (4 Days On / 3 Days Off)

1h: Copanlisib (PI3K inhibitor) 1-hour (1h) intravenous infusion
xx: Refametinib (MEK inhibitor) capsules orally twice daily (BID)
**: Copanlisib PK sampling (C1D1 + C1D15): before (pre-dose) and 0.5, 1, 1.5, 2, 4, 6, 8, 12, 25, 49, 73 hour(s) post infusion
^^: Refametinib PK sampling (C1D14 + C1D15): before (pre-dose) and 0.5, 1, 2, 4, 6, 8, 12 hour(s) post morning dose
Reference drug: Not applicable

Indication: Refractory, locally advanced or metastatic solid tumors

### Diagnosis and main criteria for inclusion:

Subjects had to fulfill all of the following criteria before receiving any dose of the study medication:

- Subjects, at least 18 years of age, with incurable and refractory advanced or solid tumors that had progressed on or failed to respond to therapies known to provide clinical benefit.
- Histological or cytological documentation of non-hematologic, malignant solid tumor, excluding primary brain or spinal tumors, with no current involvement of the central nervous system (CNS). Subjects who had brain metastases that had been treated and had been stable for > 3 months could be included in the study.
- At least one measurable lesion or evaluable disease, as per RECIST 1.1
- ECOG Performance Status of 0 or 1
- Life expectancy of at least 12 weeks.
- LVEF (left ventricular ejection fraction) ≥ LLN (lower limit of normal) for the institution
- Women of childbearing age and men enrolled in this study had to use adequate birth control measures prior to, during the course of the study and 30 days after the last administration of either copanlisib (BAY 80-6946) or refametinib (BAY 86-9766). An adequate contraception included a hormonal contraception with implants or combined oral, transdermal, or injectable contraceptives, certain intrauterine devices, bilateral tubal ligation, hysterectomy, or vasectomy of the partner. In addition, the use of condoms for subjects or their partners was required unless the woman had had a hysterectomy.
- ALT (alanine aminotransferase) and AST (aspartate aminotransferase) ≤ 2.5 x ULN (upper limit of normal) (≤ 5 x ULN for subjects with liver involvement of their cancer)
### Diagnosis and main criteria for inclusion:
(continued)
- Total bilirubin ≤ 1.5 x ULN
- Serum creatinine ≤ 1.5 x ULN
- PT-INR (prothrombin-international normalized ratio) and PTT (partial thromboplastin time) < 1.5 x upper limit of normal (Subjects being therapeutically anti-coagulated with an agent such as coumadin or heparin were allowed to participate provided that no prior evidence of underlying abnormality in these parameters existed). Low dose aspirin was permitted (≤ 100 mg daily).
- Adequate bone marrow function as assessed by the following:
  - Hemoglobin ≥ 9.0 g/dL (transfusion was permitted)
  - Absolute neutrophil count (ANC) ≥ 1,500/mm³
- Platelet count ≥ 100,000/mm³
- Ability to understand and follow study related instructions
- Only for subjects enrolled into the expansion cohort: Presence of a tumor mutation in one or more of the following genes: KRAS (Kirsten rat sarcoma viral oncogene homolog), NRAS (neuroblastoma RAS viral (v-ras) oncogene homolog), BRAF (B-Raf proto-oncogene, serine/threonine kinase gene), or PI3KCA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha gene)

### Study design:
This was a Phase Ib, multi-center, multi-regional, open-label, non-randomized, dose-escalation study of copanlisib in combination with refametinib in sequential cohorts of subjects with refractory, locally advanced or metastatic solid tumors.

The study was designed to determine the maximum tolerated dose (MTD) and toxicities of combination therapy of intravenous copanlisib and oral refametinib (capsules) in subjects with advanced solid tumors using an adaptive dose escalation design and expansion of cohort at MTD.

### Methodology:
The study consisted of a screening period (within 14 days before the first IV infusion of copanlisib on C1D1), a treatment period with repeated 28-day treatment cycles starting on C1D1 (with the duration of combined treatment with copanlisib and refametinib limited by toxicity to the subject), and a follow-up period (follow-up within 30 days of the last dose and post-treatment follow-up 30 days after the last visit).
<table>
<thead>
<tr>
<th><strong>Methodology:</strong> (continued)</th>
<th><strong>Treatment</strong></th>
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<tbody>
<tr>
<td>Increasing doses and varying schedules of combination therapy with copanlisib (0.2-0.8 mg/kg IV; 3 Wks On/ 1 Wk Off and Weekly) and refametinib (30 mg and 50 mg BID po; Daily or 4 Days On/ 3 Days Off) on 28-day cycles were studied at 8 dose levels (cohorts 1, 2, 2A, 2B, 2C, 3A, 3B, 3BN) and in one expansion cohort (dose level 2C).</td>
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**Determination of the MTD**

A 3+3 dose escalation design was used to determine the MTD of the combination therapy with copanlisib and refametinib. A minimum of 3 and up to 6 subjects were enrolled at each dose level. A total of 6 subjects were required, with dose limiting toxicity (DLT) in ≤ 1/6 subjects in the first cycle, before a combination dose level will be designated as either a MTD level for the combination, or as Recommended Phase II Dose (RP2D) if different from the MTD. Dose interruptions and/or dose reductions could be required based on individual safety and tolerability.

**Efficacy**

Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of all anatomic regions involved with the disease was performed at screening (baseline), within 7 days of the start of each odd cycle (3, 5, 7, etc.), and at the safety FU visit to assess tumor response using the Response Evaluation Criteria in Solid Tumors, Version 1.1. (RECIST 1.1). CT/MRI scans were not required at the safety FU visit if the subject discontinued due to progressive disease.

**Pharmacodynamics**

- Tumor glucose metabolism

Subjects enrolled in cohorts 2A, 2B and 2C during dose escalation as well as the MTD expansion cohort(s) underwent mandatory positron emission tomography using $^{18}$Ffluorodeoxyglucose (FDG-PET) at screening as well as on Day 22 of Cycle 1 in order to assess the PD effects of the tested drug combination (copanlisib and refametinib) on tumor glucose metabolism at the doses administered.

**Biomarkers**

Since the copanlisib/refametinib combination could lead to a MTD for each drug that is lower than the individual MTD of each drug when administered as monotherapy. A demonstration of
Methodology: (continued)

mechanistic biological activity in the expansion cohort(s) supported decision making on whether dose levels and / or schedule provided sufficient pathway inhibition to warrant advancement for further study. As such, emphasis was placed on obtaining PD biomarker data.

Biomarkers reflecting the pharmacodynamic (PD) activity of the drug combination (copanlisib + refametinib) at the various doses administered and candidate biomarkers that could predict drug response were examined in dose escalation cohorts 2A, 2B and 2C and in the expansion cohort(s) using blood (plasma) and tissue samples.

Blood/ tissue samples obtained at screening were used to determine subject eligibility for enrollment in the MTD expansion cohort(s). In addition, optional fresh paired tumor biopsies for both tumor genetics and / or PD biomarker studies were requested from subjects enrolled in the dose escalation cohorts 2A, 2B and 2C, and were mandatory in the expansion cohort(s). Genetic and non-genetic biomarker testing consent was mandatory for subjects being enrolled into the dose escalation cohorts 2A, 2B and 2C as well as into the expansion cohort(s).

Biomarker analysis in blood and plasma samples

Plasma samples for analysis of circulating tumor DNA for activating mutations (e.g., KRAS, NRAS, BRAF, PIK3CA), and perhaps other genomic (e.g., circulating miRNA isolated from plasma) and non-genomic assays were collected at screening, pre-dose on Days 1, 8 and 15 of Cycle 1 and Cycle 2, and at the follow-up within 30 days after the last dose. Whole blood samples were to be collected at screening for signal-transduction pathway analysis by Prometheus; however, this assay was not performed due to insufficient assay validation.

Biomarker analysis in tumor tissue

Archival formalin-fixed/paraffin-embedded (FFPE) tumor tissue specimens (mandatory when available) were collected during screening. Optional fresh paired tumor biopsies were collected at screening and on Day 15 of Cycle 1 (within 48 hours after copanlisib IV infusion) from subjects enrolled in the dose escalation cohorts 2A, 2B and 2C, and were mandatory in the expansion cohort.

Tumor tissue was to be used for analysis of tumor mutations (e.g., KRAS, NRAS, BRAF, PIK3CA), protein expression (e.g., pAKT, PTEN, pERK, Ki67), and / or other assays such as gene copy number analysis (e.g., PIK3CA) or other genomic assays (e.g.,
### Methodology:
(continued)

mRNA, miRNA).

**Pharmacokinetics**

Single- and multiple-dose pharmacokinetic (PK) assessments of copanlisib and/or refametinib and their metabolites were evaluated in all subjects in the dose escalation phase and in approximately 12 subjects in the expansion phase.

Plasma samples for PK evaluation were collected in Cycle 1, on Day 1 (up to 73 hours after IV infusion of copanlisib), on Day 14 (up to 12 hours after morning dose of refametinib), and on Day 15 (up to 73 hours after IV infusion of copanlisib).

**Safety/ tolerability**

Safety and tolerability of combination therapy with copanlisib and refametinib were assessed by close monitoring and timely assessment of adverse events (AEs)/toxicities, vital signs (blood pressure, pulse, respiratory rate, body temperature), subject’s medical condition (physical examination including weight and evaluation of the mouth and respiratory status), and laboratory parameters (hematology, biochemistry including plasma glucose and insulin profiles, and urinalysis).

The National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0) was used to grade toxicities/AEs.

Further safety measures performed at screening and within 7 days prior to dosing on Day 1 of every third cycle (3, 6, 9, etc.) included multiple gated acquisition (MUGA) scans/echocardiograms to measure LVEF, 12-lead electrocardiograms (ECGs) and ophthalmologic examinations to exclude subjects with a history of, or high risk of developing, retinal vein occlusion, and to detect treatment emergent changes.

The Eastern Cooperative Oncology Group [ECOG] performance status was used to quantify subject’s general well-being and activities of daily life.

Subjects were instructed on the importance of using topical sunblock and UV blocking sunglasses, due to the demonstrated prolonged half-life of copanlisib in pigmented tissues including the eye wall.

If systemic corticosteroids had to be given to treat rash, refametinib was to be held during steroid therapy.
**Methodology:** (continued)

**Recommended Phase II dose (RP2D)**

The Phase II dose (RP2D) for the combination of copanlisib and refametinib was determined by the investigators and the sponsor at the end of the study after review of the data from all of the dose levels evaluated.

**Study center(s):**

8 study centers in 3 countries: 1 center in Germany, 1 center in the Netherlands, and 6 centers in the USA

**Publication(s) based on the study (references):**


**Study period:**

First subject, first visit: 13 JUL 2011

Last subject, last visit: 13 APR 2014

**Early termination**

Not applicable

**Number of subjects:**

Planned: Up to a maximum of 92 subjects were to be enrolled in the study. Minimum 12 subjects for evaluation of safety/ tolerability and PD in the RP2D cohort.

Analyzed: 64 subjects total: 49 subjects in 8 dose escalation cohorts, 15 subjects in 1 expansion cohort.

**Criteria for evaluation Efficacy:**

Tumor response using RECIST 1.1 criteria
Clinical pharmacology:

- MTD
- Pharmacodynamic (PD) evaluation:
  - Tumor glucose metabolism
  - PD biomarkers evaluation including analysis of pathway activation in blood and plasma
  - PD biomarker evaluation analysis using paired tumor biopsies

Clinical pharmacology: (continued)

- Pharmacokinetic (PK) evaluation:
  - Single-dose and steady state PK of copanlisib when given alone and in combination with refametinib (C1D1 vs. C1D15): $C_{\text{max}}$, AUC(0-25), AUC(0-t<sub>last</sub>)
  - Single-dose and steady state PK of refametinib when given alone and in combination with copanlisib (C1D14 vs. C1D15): $C_{\text{max}}$, AUC(0-8), AUC(0-12), AUC(0-t<sub>last</sub>)

Safety:

- Adverse events (AEs) / DLTs
- Blood / urine laboratory parameters (hematology, clinical chemistry, urinalysis)
- ECOG performance status
- Vital signs (blood pressure, pulse, respiratory rate, body temperature)
- Physical examination (including weight, oral findings, respiratory status)
- Electrocardiogram (ECG)
- Left ventricular ejection fraction (LVEF)
- Ophthalmologic examinations

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1 The effect of refametinib on the PK of copanlisib and vice versa was not evaluated in cohort 3BN (copanlisib Weekly + refametinib BID 4 Days On/3 Days Off) due to limited number of continuous dosing days.
### Interim analysis

A formal statistical interim analysis was planned to support regulatory filing. The interim analysis was not done because regulatory filing was postponed and thus, there was no longer a need for an interim report.

### Final analysis

Efficacy, safety/tolerability, PD and PK parameters were summarized using frequency tables for qualitative data and descriptive statistics for quantitative data.

To investigate a potential PK interaction of copanlisib with refametinib and *vice versa*, an explorative Analysis Of Variance (ANOVA) with study day as the fixed effect and subject as a random effect was performed on the log-transformed values of PK parameters $C_{max}$, $AUC(0-t_{last})$, and $AUC$ (if possible). Based on these analyses point estimates (LS-Means) and exploratory 90% Confidence Intervals (90% CI) for the ratio $C1D15/C1D1$ of copanlisib PK parameters were calculated to assess the effect of refametinib on the PK of copanlisib. Similarly, point estimates (LS-Means) and exploratory 90% CI for the ratio $C1D15/C1D14$ of refametinib PK parameters were calculated to assess the effect of copanlisib on the PK of refametinib.

All statistical analyses were explorative. A confirmatory statistical analysis was not intended. Medical history and AE data were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.1.

### Substantial protocol changes:

There were three amendments to the original Clinical Study Protocol (CSP), Version 1.0, dated 09 MAR 2011.

- Protocol Version 2.0, dated 25 MAY 2011 introduced the following changes:
  - Clarification of the subject population to include only those subjects with incurable and refractory solid tumors who have failed or progressed on standard of care treatments.
  - Addition of criteria for screening LVEF within normal ranges
  - Clarification that subjects with brain metastases that have been stable for greater than 12 months were eligible for inclusion
  - Addition that subjects with known G6PD deficiency
were to be excluded from study participation
- Clarification anticancer hormonal therapies were to be discontinued within 2 weeks of first study treatment.

### Protocol Version 3.0, dated 09 FEB 2012, introduced the following changes:
- Addition of dose levels 3AN, 3BN and 4N to test an intermittent dosing regimen of refametinib at the higher dose levels.
- Identification of the maximum dose for obese subjects, i.e. the total daily dosage of copanlisib was not to exceeded 65 mg in subjects assigned to 0.8 mg/kg; regardless of the body weight (subjects assigned to 0.4 mg/kg copanlisib were to receive a proportionally reduced maximum dose of 32.5 mg).

- Clarification about the order of cohort enrollment (dose Level 1 → 2 → 3A/3B)
- Clarification of the PK sampling schedule / evaluation for subjects on an intermittent dosing schedule of refametinib.
- Definition of Grade 3 elevation of CPK and some instances of Grade 4 as additional non-hematologic DLT.
- Clarification that transient hypertension on the same day as study drug administration of copanlisib was not considered a DLT if it was manageable with medication.
- Addition of CPK measurements to the chemistry panel
- Addition of CPK increase ≥ CTCAE Grade 3 as AE of special interest for this study.

### Protocol Version 4.0, dated 15 JAN 2013, introduced the following changes:
- Extending secondary study objectives to explore pharmacodynamics biomarkers reflecting drug activity.
- Addition of dose levels 2A, 2B, and 2C.
- Addition of further AEs of special interest (interstitial lung disease and pneumonitis).
- Addition of criteria for expansion cohort(s) at the newly-determined MTD(s), i.e., limitation to subjects with cancer mutations in selected genes (KRAS, NRAS, BRAF, PI3KCA), mandatory genetic and non-genetic biomarker testing consent, FDG-PET scans and paired
tumor biopsies in Cycle 1.
The synopsis of this report is based on Protocol Version 4.0.

Study subjects

In this study, 87 adult male or female subjects with incurable and refractory advanced or solid tumors were screened in 3 countries. Twenty-three subjects (26.4% of 87) were screening failures and 64 subjects (73.6% of 87) were assigned to combination therapy with copanlisib and refametinib (11 subjects in Germany, 11 subjects in the Netherlands and 42 subjects in the USA). Of 64 (100%) subjects assigned to treatment, 49 (76.6%) subjects were included in the dose-escalation part of the study, and 15 subjects were included in 1 dose expansion cohort (Dose Level 2C) (Table 2–1). All 64 (100%) treated subjects received at least 1 dose of copanlisib and 63 (98.4%) subjects received at least 1 dose of refametinib.

<table>
<thead>
<tr>
<th>Cohort / Dose Level</th>
<th>Number of subjects</th>
<th>Dose and dosing regimen</th>
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<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>0.2 mg/kg copanlisib 3 Wks On/1 Wk Off + 30 mg refametinib BID Daily</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>0.4 mg/kg copanlisib 3 Wks On/1 Wk Off + 30 mg refametinib BID Daily</td>
</tr>
<tr>
<td>2B</td>
<td>4</td>
<td>0.6 mg/kg copanlisib 3 Wks On/1 Wk Off + 30 mg refametinib BID Daily</td>
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<tr>
<td>3A</td>
<td>10</td>
<td>0.8 mg/kg copanlisib 3 Wks On/1 Wk Off + 30 mg refametinib BID Daily</td>
</tr>
<tr>
<td>2C</td>
<td>7</td>
<td>0.4 mg/kg copanlisib Weekly + 30 mg refametinib BID Daily</td>
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<tr>
<td>Expansion</td>
<td>15</td>
<td>0.4 mg/kg copanlisib Weekly + 30 mg refametinib BID Daily</td>
</tr>
<tr>
<td>2A</td>
<td>4</td>
<td>0.6 mg/kg copanlisib Weekly + 30 mg refametinib BID Daily</td>
</tr>
<tr>
<td>3B</td>
<td>6</td>
<td>0.4 mg/kg copanlisib 3 Wks On/1 Wk Off + 50 mg refametinib BID Daily</td>
</tr>
<tr>
<td>3BN</td>
<td>6</td>
<td>0.4 mg/kg copanlisib Weekly + 50 mg refametinib BID 4 Days On/3 Days Off</td>
</tr>
<tr>
<td>Total:</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

Discontinuation of treatment was primarily due to disease progression (37 subjects, 57.8% of 64). The next common reason for treatment discontinuation was the occurrence of an AE (21 subjects, 32.8% of 64). Further reasons for discontinuation included withdrawal of consent by subject (3 subjects, 4.7% of 64), death (1 subject, 1.6%), deterioration of general conditions (1 subject, 1.6%), and loss to follow-up (1 subject, 1.6%). All 64 subjects assigned to treatment were valid for the analysis of safety (SAF=64), efficacy/pharmacodynamics (ITT: N=64), and pharmacokinetics (PKS: N=64).

Efficacy / clinical pharmacology evaluation

The interpretation of the results in terms of clinical benefit and tumor response to copanlisib/refametinib combination therapy (efficacy) needs to take into account that efficacy was a secondary objective of this study.
Based on the data collected on the SAF population (64 subjects with different types of non-hematologic, malignant solid tumors Stage III-IV treated for a median of 6 to 7 weeks corresponding to a median of 2 cycles), there is no evidence of clinical efficacy of copanlisib therapy in combination with refametinib:

Best overall response (using RECIST 1.1 criteria) was progressive disease (PD) in 31 subjects (48.4% of 64), stable disease (SD) in 21 subjects (32.8%), and non-complete response / non-progressive disease in 1 subject (1.6%). Considering the clinical assessment, a PD was observed in 36 subjects (56.2% of 64). There were no partial (PR) or complete (CR) responses in the 64 subjects treated in this study (median time under treatment was 6 to 7 weeks corresponding to a median of 2 cycles). SD lasted up to Cycle 2 in 14 subjects, and up to Cycle 4 in 7 subjects. The time to progression (TTP) ranged from 1 to 210 days. The duration of SD showed no relationship to the dose level of combination therapy, the cancer type, or to the tumor stage at study entry.

Declines in FDG SUV\textsubscript{max} (maximum standardized uptake value) of target lesions between 3 to 74% of the baseline value were seen 3 weeks (i.e. 21 / 17 days) after start of copanlisib / refametinib combination. The correlation between %changes in FDG SUV\textsubscript{max} and AUC(0-25) or AUC(0-\text{tlast}) of copanlisib was weak (R=0.1828 and R\textsuperscript{2}=0.2158, respectively).

Biomarkers of pathway activation that could be predictive of response to copanlisib / refametinib combination therapy, as well as pharmacodynamic biomarkers reflecting drug activity were evaluated exploratively in the expansion cohort of Dose Level 2 C. For enrollment in the expansion cohort, subjects’ tumor samples were required to harbor a mutation in one or more of the following genes: KRAS, NRAS, BRAF, and / or PIK3CA.

- KRAS was the most common mutation in the expansion cohort, occurring in 13 out of 15 subjects tested; PIK3CA mutations occurred in 5 subjects (1 alone and 4 in the presence of KRAS mutations), and a BRAF activating rearrangement was detected in 1 subject. However, despite activation of the MEK-ERK and / or PI3K signaling pathways based on the presence of these mutations, no objective tumor responses were observed in this cohort.

- In the 5 subjects with usable paired biopsies collected at baseline and C1D15, mean pERK levels decreased from baseline by 62.4 ± 38.5% and 71.1 ± 32.1% for percent cells positive and H-score, respectively; pERK reduction was detected in 5/5 subjects. Mean pAKT levels decreased by a smaller magnitude, 25.9 ± 48.5% and 29.4 ± 54.3% for percent cells positive and H-score, respectively; pAKT reduction was detected in 4/5 and 3/5 subjects for percentage of cells staining positive and H-score, respectively. Mean Ki67 levels also decreased by 16.9 ± 19.4% and 19.6 ± 22.9% for percent cells positive and H-score, respectively; Ki67 reduction was detected in 4/5 subjects. This data suggests consistent inhibition of the MEK-ERK signaling pathway during copanlisib-refametinib treatment, and less consistent inhibition of the PI3K signaling pathway. More impressive inhibition of pERK, pAKT and/or Ki67 did not result in a more favorable best response, since the 2 subjects with the strongest decreases in pERK, pAKT, and Ki67, both had PD as best response.
Whether a relationship exists between responses, duration of response, and activated PI3K / MEK pathway in subjects with solid tumors is not clear.

**Pharmacokinetic evaluation**

All 64 subjects who received treatment were valid for PK analysis. Any subject with a valid PK profile of copanlisib at both C1D1 and C1D15 was valid for the evaluation of the effect of refametinib on the PK of copanlisib. Any subject with a valid PK profile of refametinib at both C1D14 and C1D15 was valid for the evaluation of the effect of copanlisib on the PK of refametinib.

**Copanlisib and metabolite M-1**

Selected PK parameters for copanlisib are shown in Table 2–2.

Following an IV infusion of copanlisib over 1 h, highest concentrations in plasma were observed at a median time between 30 min after the start of the infusion and the end of the infusion. There was no obvious difference observed in time to reach maximum plasma concentrations of copanlisib when co-administered with refametinib. After reaching $C_{\text{max}}$, the concentration time profiles follow a multiple-phase pattern showing a steep decline within the first 2 h after the end of the infusion which might be attributed to a quick distribution of the compound throughout the body. A second distribution / elimination phase was observed between 2 and 6 to 8 h after the end of the infusion followed by a flattened curve afterwards possibly representing wide distribution into tissues. Concentrations of copanlisib in plasma were measurable for a median time of at least 24.7 h.

Overall, variability in copanlisib PK parameters was minor to high (CV 10.9 to 183%). Dose-normalized $C_{\text{max}}$, $AUC(0-t_{\text{last}})$ and $AUC(0-25)$ of copanlisib in plasma showed evidence for dose-proportionality of maximum plasma concentrations and overall exposure following IV dosing from 0.2 to 0.8 mg/kg.

Co-administration of refametinib did not influence the pharmacokinetic behaviour of copanlisib.

Maximum plasma concentrations and overall exposure of the metabolite M-1 were much lower than those observed for the parent compound. M-1 maximum plasma concentrations were observed at a median time between 1.25 and 9.93 h after the start of the infusion. Concentrations of the metabolite M-1 in plasma were measurable for a median time of at least 8.33 h. The metabolite ratios of $AUC(0-t_{\text{last}})$ and $AUC(0-25)$ of metabolite M-1 to copanlisib had a high inter-individual variability but seemed to be independent of the dose with a median ratio from 6.8% to 16.5% and from 9.0% to 17.1%, respectively. Furthermore, there appeared to be no substantial difference in the PK parameters of M-1 when copanlisib was co-administered with refametinib.

**Refametinib and metabolite M-17**

Selected PK parameters for refametinib are shown in Table 2–3.

After multiple oral dosing of 30 or 50 mg refametinib capsules the compound was well absorbed from the gastro-intestinal tract reaching peak plasma levels at a median time between 1.0 and 4.0 h with low to moderate inter-individual variability. Co-administration of copanlisib did not influence the time to reach peak plasma concentrations of refametinib.
After attainment of $C_{\text{max}}$, mean plasma concentrations of refametinib declined in an essentially monophasic manner in most of the subjects. All subjects had concentrations above LLOQ until the next dosing after 12 h.

Overall, variability in refametinib PK parameters was minor to high (CV 20.5 to 156%). Dose-normalized $C_{\text{max}}$, AUC(0-8) and AUC(0-12) of refametinib in plasma did not show an obvious difference between the dosing regimens applied in this study.

Maximum plasma concentrations and overall exposure of refametinib was slightly lower when copanlisib was administered concomitantly. However, according to the results from the ANOVA a substantial decrease in maximum plasma concentrations and overall exposure after co-administration of copanlisib was only evident in 1 or 2 cohorts, mostly pronounced in the expansion cohort (0.4 mg/kg copanlisib Weekly + 30 mg refametinib BID Daily).

Following multiple oral dosing of refametinib, mean maximum plasma concentrations of the metabolite M-17 were observed at a median time between 2.00 and 4.00 h. Afterwards the mean plasma concentration time profiles of metabolite M-17 followed a more or less monophasic pattern in most of the subjects and concentrations of M-17 in plasma were measurable until the next dosing of refametinib after 12 h.

Maximum plasma concentrations and overall exposure of the metabolite M-17 were much lower than those observed for the parent compound. The metabolite ratios of AUC(0-$t_{\text{last}}$), AUC(0-8) and AUC(0-12) of metabolite M-17 to refametinib had a high inter-individual variability but seemed to be independent of the dosing regimen with a median ratio from 13.2% to 60.8%, from 12.9% to 61.7%, and from 13.1% to 73.2%, respectively.

As already seen for the parent compound, maximum concentrations and overall exposure of the metabolite M-17 was slightly lower when refametinib was co-administered with copanlisib.

In conclusion, concomitant administration of the MEK inhibitor refametinib did not have a clinically relevant effect on copanlisib PK or its metabolite M-1, and vice versa, there was no clinically relevant effect of copanlisib on the PK of refametinib or its metabolite M-17.
Table 2–2: Selected pharmacokinetic parameters of copanlisib in plasma after dosing at C1D1 and C1D15 in the dose-escalation cohorts and expansion cohort (geo. mean/CV% (range); PKS)

<table>
<thead>
<tr>
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<th>Cohort 1</th>
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<th>Cohort 2</th>
<th>n</th>
<th>Cohort 3A</th>
<th>n</th>
<th>Cohort 3B</th>
<th>n</th>
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<tr>
<td>AUC(0-25)</td>
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<td>5</td>
<td></td>
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<td>5</td>
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</tr>
<tr>
<td>AUC(0-t&lt;sub&gt;last&lt;/sub&gt;)</td>
<td>µg·h/L</td>
<td>1</td>
<td>6</td>
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<td>µg·h/L</td>
<td>1</td>
<td>3</td>
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Table 2–3: Selected pharmacokinetic parameters of refametinib in plasma after dosing at C1D14 and C1D15 in the dose-escalation cohorts and expansion cohort (geo. mean/CV% (range); PKS)

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<th>Cohort 2</th>
<th>n</th>
<th>Cohort 3A</th>
<th>n</th>
<th>Cohort 3B</th>
<th>n</th>
<th>Cohort 3BN</th>
<th>n</th>
<th>Expansion cohort</th>
</tr>
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<tbody>
<tr>
<td>(C_{\text{max}})</td>
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<td>6</td>
<td>484/101</td>
<td>(124-1180)</td>
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<td>(552-1680)</td>
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<td>822/55.3</td>
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<td>1220/80.0</td>
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<tr>
<td>AUC(0-8)</td>
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<td>433/77.9</td>
<td>(121-843)</td>
<td>6</td>
<td>795/47.2</td>
<td>(438-1310)</td>
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<td>625/34.3</td>
<td>(373-958)</td>
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<td>672/102</td>
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<tr>
<td>AUC(0-12)</td>
<td>µg·h/L</td>
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<td>5</td>
<td>2510/126</td>
<td>(486-850)</td>
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<td>5110/55.3</td>
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<td>AUC(0-t\text{last})</td>
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<td>6</td>
<td>2240/101</td>
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<th>n</th>
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<th>Cohort 3B</th>
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<th>Cohort 3BN</th>
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<th>Expansion cohort</th>
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<td>µg/L</td>
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<td>3</td>
<td>743/24.2</td>
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<td>AUC(0-12)</td>
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<td>3300/47.7</td>
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<td>3</td>
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<td>12</td>
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<td>(2410-8950)</td>
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<tr>
<td>Cohort 3A</td>
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<td>Cohort 2BN</td>
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<td>Expansion cohort</td>
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Safety evaluation

All 64 (100%) subjects included in the SAF population reported at least 1 treatment-emergent adverse event (TEAE), and 61 (95.3%) subjects reported at least 1 drug-related TEAE. TEAEs related to protocol-required procedures occurred in 10 (15.6%) subjects.

The most common TEAEs were diarrhea (59.4%), nausea (51.6%), rash acneiform (51.6%) and fatigue (51.6%).

Common TEAEs reported for >20% of 22 subjects treated at the MTD level (0.4 mg/kg copanlisib Weekly + 30 mg refametinib BID Daily) were diarrhea (63.6%), nausea (50.0%), rash acneiform (50.0%), fatigue (45.5%), hypertension (45.5%), vomiting (40.9%), abdominal pain (36.4%), hyperglycemia (31.8%), mucositis oral (31.8%), anorexia (31.8%), creatine phosphokinase (CPK) increased (31.8%), rash maculo-papular (27.3%), pruritus (27.3%), investigations – other (27.3%), platelet count decreased (27.3%), edema limbs (22.7%), dyspnea (22.7%), constipation (22.7%), fever (22.7%), and hypokalemia (22.7%).

Fifty-nine subjects (92.2% of 64) reported at least 1 TEAE of severity Grade ≥3. The most common TEAEs of CTCAE Grade 3 were hypertension (26.6%), diarrhea (10.9%), anemia, hyponatremia, rash maculo-papular (9.4% each), rash acneiform, mucositis oral, and dyspnea (7.8% each). TEAEs of CTCAE Grade 4 included ileus (1.6%), and laboratory abnormalities [alkaline phosphatase increased, CPK increased, lipase increased, neutrophil count decreased, hypokalemia, hyponatremia] (≤3.1%).

Thirty-nine subjects (60.9% of 64) reported at least 1 drug-related TEAE of severity Grade ≥3. Copanlisib-related TEAEs of CTCAE Grade ≥3 occurring in ≥5% of subjects were hypertension (23.4%) and mucositis oral (6.3%). Refametinib-related TEAEs of CTCAE Grade ≥3 occurring in ≥5% of subjects were diarrhea (10.9%), rash maculo-papular (9.4%), rash acneiform (7.8%), mucositis oral (7.8%), and hypertension (6.3%).

Dose modifications (i.e., interruptions, reductions or increases) of copanlisib or refametinib due to TEAE were necessary for 45 (70.3%) subjects, and 21 (32.8%) subjects permanently discontinued combination therapy due to a TEAE.

TEAEs of CTCAE Grade 3 leading to drug discontinuation included oral mucositis, maculo-papular rash, ascites, diarrhea, increases in aspartate aminotransferase (AST) or alanine aminotransferase (ALT), acneiform rash, anorexia, dehydration, sepsis, chest wall pain, other vascular disorders and urticaria, confusion and other respiratory / thoracic and mediastinal disorders (the latter 3 TEAEs led only to discontinuation of copanlisib). TEAEs of CTCAE Grade 4 leading to drug discontinuation were ileus and respiratory failure.

Thirteen subjects (20.3% of 64) experienced a dose limiting toxicity (DLT). CTCAE Grade ≥ 3 non-hematologic toxicities included mucositis oral, pancreatitis, diarrhea, fatigue, and dehydration (considered related to both copanlisib and refametinib), rash acneiform and dry skin (considered related to refametinib, only), and hypertension (considered related to copanlisib, only). CTCAE Grade ≥ 3 hematologic and biochemical toxicities included increase in AST, increase in ALT and hyponatremia considered related to copanlisib and / or refametinib. No DLTs were reported for the 15 subject in the expansion cohort treated at the MTD level (0.4 mg/kg copanlisib Weekly + 30 mg refametinib BID Daily). However,
2 subjects had a drug-related TEAE of CTCAE Grade 3 that met protocol-defined criteria for a DLT but were not rated as DLT by the investigators (oral mucositis related to copanlisib and refametinib and rash maculo-papular not adequately controlled by medical intervention related to refametinib).

Serious TEAEs were reported for 37 (57.8%) subjects. Serious TEAEs reported for 3 subjects or more (≥4.7% of 64) were diarrhea (6.3%), other infections and infestations (6.3% [port infection, device related infection, infection of unknown origin, pyelonephritis]), infectious pneumonitis (6.3%), urinary tract infection (4.7%), fever (4.7%), and other benign, malignant and unspecified neoplasms (4.7% [tumor progressions]). Drug-related serious TEAEs of CTCAE Grade 3 were diarrhea (3 subjects), hyperglycemia (2 subjects), vomiting (1 subject), abdominal pain (1 subject), pancreatitis (1 subject), lung infection (1 subject), pleural effusion (1 subject), fatigue (1 subject), dehydration (1 subject), syncope (1 subject), and anemia (1 subject); a drug-related serious TEAE of CTCAE Grade 4 was increase in CPK (1 subject).

In total, 12 (14.1%) subjects died: 9 subjects died during or within 30 days after permanent discontinuation of study drugs and 3 subjects died later than 30 days after permanent treatment discontinuation. Seven deaths were due to tumor progression, 2 deaths were due to respiratory failure associated with tumor progression, 1 death was due to undiagnosed coronary artery disease not associated with tumor progression, 1 death was due to subdural hematoma caused by fall, and 1 death was associated with renal insufficiency and dehydration. The investigators assessed all deaths as not drug-related except one (renal insufficiency and dehydration). This 71-year old man with apocrine carcinoma, died 27 days after last dosing of copanlisib respectively 16 days after the last dose of refametinib (treatment duration: 15 / 23 days). Two weeks before death, the subject was hospitalized for renal insufficiency (CTCAE Grade 2) and dehydration (CTCAE Grade 3). According to the investigator, renal insufficiency and dehydration were related to copanlisib / refametinib combination therapy.

**Dermatology / skin toxicities**

Skin and subcutaneous tissue disorders were observed in 57 subjects (89.1% of 64), most commonly rash acneiform (51.6%), rash maculo-papular (37.5%), pruritus (26.6%), and dry skin (18.8%). Treatment with refametinib was associated with a higher incidence of acneiform rash (51.6% vs. 20.3%), and maculo-papular rash (35.9% vs. 21.9%), pruritus (25.0% vs. 12.5%) or dry skin (18.8% vs. 9.4%) compared to copanlisib treatment. Rash, acneiform or maculo-papular was generally mild to moderate (CTCAE Grade 1-2). There was only one case of severe rash (acneiform), which was assessed as being related to refametinib. Of note, rash of any type was the most frequent TEAE related to copanlisib and / or refametinib that led to permanent discontinuation of treatment.

**Hyperglycemia**

Reversible hyperglycemia as a consequence of copanlisib treatment was observed in all 41 (100%) subjects who had a normal or lower than normal blood / plasma glucose value at baseline. Drug-related hyperglycemia of CTCAE Grade 3 occurred in 2 (3.1%) out of 64 treated subjects, none was classified as DLT.
Adverse events of special interest

Interstitial lung disease and non-infectious pneumonitis were not reported in this study. The term ‘pneumonitis’ (related to copanlisib) was reported for 1 (1.6%) out of 64 subjects but chest CT showed no evidence of pneumonitis and the physician later on stated that subject did not have pneumonitis at any time. The term ‘pneumonia’ was reported for 5 (7.8%) subjects with no causal relationship to copanlisib or refametinib (all 5 cases were coded as ‘pneumonitis’ using the CTCAE terminology). All subjects recovered after antibiotic treatment except for 1 subject where outcome of post-operative pneumonia is unknown (subject died due to subdural hematoma caused by an accidental fall not related to study treatment).

Laboratory toxicities

Most hematological and biochemical toxicities were of CTCAE Grade 1-2. CTCAE Grade 3 laboratory toxicities reported for ≥5% of subjects included lymphocyte count decreased (27.0% of 63), AST increased (11.1% of 63), anemia (7.9% of 63), hyponatremia (7.8% of 64), CPK increased (7.7% of 39), activated partial thromboplastin time prolonged (6.9% of 58), lipase increased (6.7% of 60), hypoalbuminemia (6.3% of 64), and hypokalemia (6.3% of 64).

CTCAE Grade 4 laboratory toxicities were hyperuricemia (4.8% of 63), increase in CPK (5.1% of 39), increase in lipase (3.3% of 60), decrease in lymphocyte count (3.2% of 63), increases in alkaline phosphatase (1.6% of 61), increase in serum amylase (1.6% of 61), and hypokalemia (1.6% of 64).

ECOG performance status rating (ECOG PSR)

In most subjects (45.8% of 48), the ECOG performance status worsened by 1 rating score. Worsening of subjects’ ECOG performance status was in agreement with the observed progression of cancer disease (48.4% of 64).

Vital signs / physical examination

No clinically relevant changes were observed in mean values of heart rate, respiratory rate, body temperature and weight. Mean values for blood pressure (BP) were higher post infusion compared to pre-infusion. IV infusion of copanlisib resulted in an increase in BP directly after start of the infusion with peak mean BP rises occurring at 90 minutes after start of the infusion (mean BP increase by 16.8 ± 11.9 mmHg systolic and by 11.2 ± 9.6 diastolic at 1 hour 30 min post infusion on C1D1). Mean systolic / diastolic BP returned to baseline values 3 days after the infusion.

12-lead ECG

Based on post-baseline ECGs available for 18 subjects (28.6% of 63), there was no increased occurrence of ST segment, T and U wave abnormalities or atrial and ventricular conduction abnormalities after start of treatment. The incidence of abnormal post-baseline findings showed no relationship to the dosage of copanlisib / refametinib combination therapy. A QTc interval increase from baseline >30-60 msec (according to Bazett’s and / or Fridericia’s correction formula) was registered for 2 (11.1%) out of 18 subjects with post-baseline ECG
data (1 out of 6 subjects in cohort 3BN and 1 out of 7 subjects in cohort 2C). QTc interval increases >60 msec did not occur.

**Left ventricular ejection fraction (LVEF)**

A decrease in LVEF >10% occurred in 6 out of 29 subjects who had post-baseline MUGA scans and/or echocardiograms. The decrease in LVEF from baseline 65% to 45% on C3D1 determined for 1 subject in cohort 2 was reported as CTCAE Grade 3 left ventricular dysfunction. This subject additionally had Grade 1 right ventricular dysfunction (right bundle branch block, considered as medically significant on C3D1). The investigator considered Grade 3 left ventricular dysfunction to be related to both copanlisib and refametinib; Grade 1 right ventricular dysfunction was considered unrelated to treatment.

**Ophthalmologic examination**

Blurred vision (4.7% of 64), dry eye and keratitis (1.6% each) were reported as drug-related TEAEs.

**Recommended Phase II dose (RP2D)**

The MTD for the copanlisib-refametinib combination is 0.4 mg/kg copanlisib given intravenously in a weekly schedule and refametinib 30 mg BID given orally, doses which are below the MTDs of either compound alone. Due to the fact that even at this dose the time under treatment remains short (median 3 cycles), that permanent discontinuation of treatment due to a drug-related TEAE has been observed in 2 subjects, and no CR or PR were observed, a Phase II dose (RP2D) could not be determined.

**Overall conclusions**

- The MTD for the combination was determined as copanlisib 0.4 mg/kg IV once-weekly and refametinib 30 mg bid po which is lower than the MTD for the individual components.
- The safety profile of the combination is consistent to the class-effect toxicities of PI3K inhibitors (e.g., hypertension, oral mucositis, rash, hyperglycemia) and MEK inhibitors (e.g., diarrhea, rash, CPK increase) and the previously observed toxicities for copanlisib and refametinib.
- No indication for any clinically relevant PK interactions between copanlisib and refametinib was found.
- In the expansion cohort treated with the combination MTD, frequent dose modifications due to drug related toxicities became necessary including permanent discontinuation of treatment due to a TEAE in 2 out of 15 patients. The treatment durations were short (median 3 cycles).
- No evidence of objective response (PR or CR) per RECIST criteria has been observed in KRAS, BRAF, PI3KCA mutation selected expansion cohort.
- Consequently, a recommended Phase II dose (RP2D) could not be determined.