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Clinical Trial Results

Phase I Dose-Escalation Study of Pilaralisib (SAR245408, XL147) in Combination with Paclitaxel and Carboplatin in Patients with Solid Tumors

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT00756847
- **Sponsor(s)**: Sanofi
- **Principal Investigator**: Jennifer Wheler
- **IRB Approved**: Yes

Lessons Learned

- Despite involvement of PI3K pathway activation in tumorigenesis of solid tumors, single-agent PI3K inhibitors have shown modest clinical activity.
- Preclinical evidence suggests that combining PI3K pathway inhibitors and chemotherapy can enhance antitumor effects.
- In patients with solid tumors, the PI3K inhibitor pilaralisib had a favorable safety profile but did not enhance the antitumor activity of paclitaxel plus carboplatin.
- Further clinical evaluation is warranted to identify effective combination strategies with PI3K pathway inhibitors.

Abstract

Background. Pilaralisib (SAR245408) is an oral, pan-class I phosphoinositide 3-kinase (PI3K) inhibitor. This phase I dose-escalation study evaluated the maximum tolerated dose (MTD), safety, pharmacokinetics (PK), and pharmacodynamics of pilaralisib in capsule and tablet formulations, administered in combination with paclitaxel and carboplatin in patients with advanced solid tumors.

Methods. A 3 + 3 design was used. Pilaralisib was administered once daily (QD); paclitaxel (up to 175 mg/m^2) and carboplatin (up to area under the curve [AUC] of 6) were administered on day 1 of 21-day cycles. An MTD expansion cohort of patients with endometrial carcinoma was included.

Results. Fifty-eight patients were enrolled. Six patients (10.3%) had dose-limiting toxicities, of which only rash (two patients, 3.4%) occurred in more than one patient. The MTD of pilaralisib tablets in combination with paclitaxel and carboplatin was determined to be 200 mg QD. The most frequently reported adverse events (AEs) of any grade were neutropenia (67.2%) and thrombocytopenia (67.2%). PK data showed no interaction between pilaralisib and paclitaxel/carboplatin. Tumor tissue showed moderate inhibition of PI3K and mitogen-activated protein kinase (MAPK) pathways. Seven of 52 evaluable patients had a partial response (PR; 13.5%).

Conclusion. Pilaralisib had a favorable safety profile but did not enhance the antitumor activity of paclitaxel plus carboplatin in solid tumors. ***The Oncologist*** 2017;22:377–e37

Discussion

Despite the involvement of PI3K pathway activation in tumorigenesis of solid tumors, single-agent PI3K inhibitors have shown modest clinical activity. Preclinical evidence suggests that combining PI3K pathway inhibitors and chemotherapy can enhance antitumor effects in solid tumors, providing a rationale for clinical evaluation. The pan-class I PI3K inhibitor pilaralisib showed preliminary antitumor activity in a phase I monotherapy study in advanced solid tumors, which established the MTD of pilaralisib capsules as 600 mg QD. This study aimed to determine the safety and MTD of pilaralisib in capsule and tablet formulations in combination with paclitaxel and carboplatin in patients with advanced solid tumors.

Fifty-eight patients were enrolled, of which 25 received pilaralisib capsules (100–600 mg) and 33 received pilaralisib

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Table 1. Adverse events of any grade occurring in >25% of patients and of grade ≥3 occurring in >10% of patients treated with pilaralisib plus paclitaxel plus carboplatin[a]

Adverse event	Patients, *n* = 58 *n* (%)
Any grade	
Neutropenia	39 (67.2)
Thrombocytopenia	39 (67.2)
Anemia	34 (58.6)
Fatigue	34 (58.6)
Nausea	28 (48.3)
Diarrhea	22 (37.9)
Vomiting	22 (37.9)
Hypomagnesemia	19 (32.8)
Decreased appetite	16 (27.6)
Peripheral neuropathy	16 (27.6)
Rash	16 (27.6)
Urinary tract infection	16 (27.6)
Alopecia	15 (25.9)
Dyspnea	15 (25.9)
Grade ≥3	
Neutropenia	37 (63.8)
Thrombocytopenia	21 (36.2)
Anemia	14 (24.1)
Decreased neutrophil count	11 (19.0)
Leukopenia	10 (17.2)
Decreased white blood cell count	9 (15.5)
Decreased platelet count	6 (10.3)

tablets. The tablet starting dose was 200 mg, which was shown to provide exposure similar to 400 and 600 mg capsules in preliminary analyses (Sanofi data on file). Most frequent tumors types included endometrial (33%), lung (12%), breast (9%), and ovarian (9%).

The most frequently occurring AEs were consistent with the known safety profiles of carboplatin, paclitaxel, and pilaralisib (Table 1). Pilaralisib PK findings were consistent with previous studies of pilaralisib monotherapy; paclitaxel/carboplatin did not appear to affect pilaralisib PK. In serial tumor biopsies from two patients (with colorectal adenocarcinoma and cervical carcinoma), inhibition of PI3K/mTOR and MAPK pathways was observed (67%–76% reduction in pAKT, 64%–69% reduction in phosphorylated EIF4E-binding protein-1 [p4EBP1], and 70%–73% reduction in phosphorylated extracellular signal-regulated kinase [pERK]) alongside modest reductions in proliferation and induction of apoptosis (Fig. 1). Of 52 evaluable patients, 13.5% had a PR and 42.3% had stable disease or a progression-free period lasting ≥12 weeks. Median progression-free survival was 3.2 months. Molecular alterations in the PI3K pathway did not appear to correlate with response. Adding pilaralisib to paclitaxel and carboplatin did not appear to enhance antitumor efficacy in patients with solid tumors, including patients with endometrial cancer. Similarly, previous studies showed modest efficacy for pilaralisib monotherapy in solid tumors and endometrial cancers. The combination of pilaralisib, paclitaxel, and carboplatin is no longer being investigated in solid tumors.

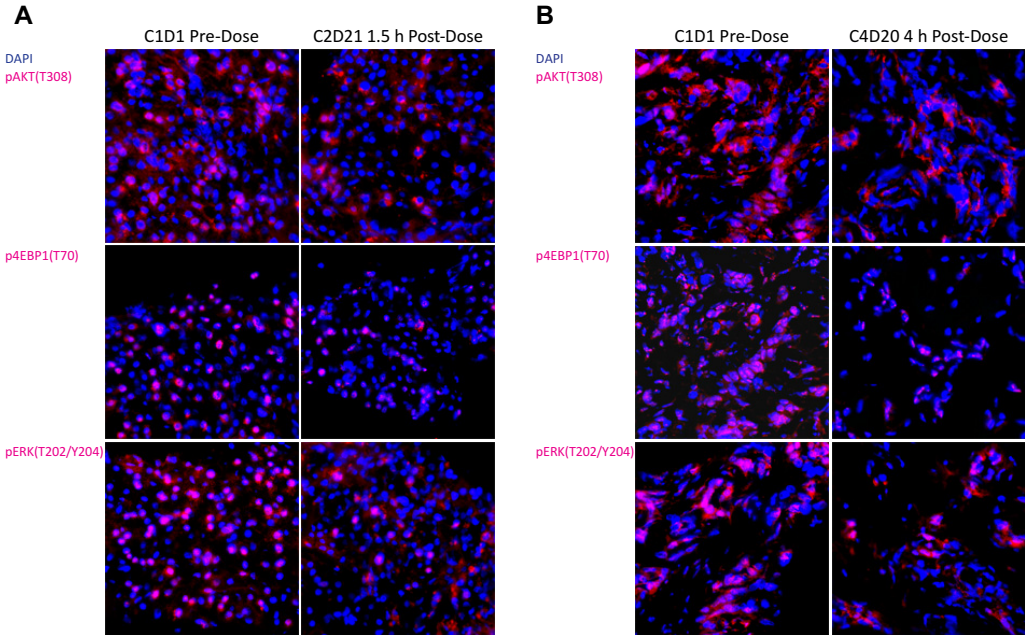

Figure 1. PI3K and MAPK pathway inhibition in paired tumor biopsies. Cryopreserved tumor biopsy samples were serially sectioned at 10 microns; representative fields were captured at ×400 magnification. **(A)**: A patient with colon adenocarcinoma (liver metastasis biopsies) receiving 200 mg pilaralisib/150 mg/m^2 paclitaxel/AUC 5 carboplatin. Tumor molecular alterations were detected in *KRAS, PIK3CA,* and *TP53* genes. **(B)**: A patient with cervical adenocarcinoma receiving 200 mg pilaralisib/175 mg/m^2 paclitaxel/AUC 6 carboplatin. Tumor molecular alteration was detected in *PIK3CA* gene (I391M polymorphism).

Abbreviations: AUC, area under the curve; EBP1, EIF4E-binding protein-1; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase.

Trial Information	
Disease	Advanced cancer/solid tumor only
Stage of disease/treatment	Metastatic/Advanced
Prior Therapy	No designated number of regimens
Type of study - 1	Phase I
Type of study - 2	Other
Primary Endpoint	MTD
Primary Endpoint	Toxicity

Additional Details of Endpoints or Study Design

Phase I, open-label, nonrandomized, dose-escalation study. A standard 3 + 3 design was used. Treatment was administered in 21-day cycles. Pilaralisib (starting dose 200 mg) was administered once daily starting on day 1. Paclitaxel (at doses up to 175 mg/m^2) and carboplatin (at doses up to a targeted AUC of 6) were administered on day 1. Patients with advanced solid tumors were enrolled in the dose-escalation phase. An expansion cohort enrolled patients with endometrial carcinoma. Primary objectives were to evaluate safety and determine the MTD. Secondary objectives were to investigate the relationship between selected biomarkers and efficacy and safety outcomes, to assess PK, and to evaluate preliminary antitumor activity. Eligible patients were aged $\geq$18 years and had an Eastern Cooperative Oncology Group (ECOG) performance status $\leq$1 (subjects with performance status 2 were considered following discussion and agreement with the sponsor). In the dose-escalation phase, patients were required to have a histologically or cytologically confirmed solid tumor that was metastatic or unresectable, and refractory to standard therapy, or for which no known effective therapy existed. An MTD expansion cohort enrolled patients with advanced or recurrent endometrial carcinoma (endometrioid, serous, clear cell adenocarcinoma, adenosquamous carcinoma, or mixed histology, any grade). All patients were required to have adequate organ and bone marrow function and fasting plasma glucose $\leq$160 mg/dL. Patients who had previously received treatment with a PI3K inhibitor were excluded. All patients provided written informed consent.

Investigator's Analysis	Evidence of target inhibition but no or minimal antitumor activity

Drug Information	
Drug 1	
Generic/Working name	Pilaralisib
Drug type	Small molecule
Drug class	PI3 kinase
Dose	100–600 mg capsules or 200–300 mg tablets QD
Route	oral (p.o.)
Schedule of Administration	100–600 mg capsules or 200–300 mg tablets QD
Drug 2	
Generic/Working name	Paclitaxel
Drug type	Small molecule
Drug class	Microtubule-targeting agent
Dose	Doses up to 175 mg/m^2 on day 1 of 21-day cycles
Route	IV
Schedule of Administration	Doses up to 175 mg/m^2 on day 1 of 21-day cycles
Drug 3	
Generic/Working name	Carboplatin
Drug type	Other
Drug class	Platinum compound
Dose	Doses up to a targeted AUC of 6 on day 1 of 21-day cycles
Route	IV
Schedule of Administration	Doses up to a targeted AUC of 6 on day 1 of 21-day cycles

Patient Characteristics	
Number of patients, male	14
Number of patients, female	44

Stage at diagnosis	I: 1 II: 1 III: 7 IV: 32 Unknown: 17
Age	Median (range): 56.5 (25–82)
Number of prior systemic therapies	Median (range): 3 (1–10)
Performance Status: ECOG	0 — 13 1 — 44 2 — 3 — unknown —
Other	Not Collected
Cancer Types or Histologic Subtypes	Endometrium 19 Lung 7 Breast 5 Ovaries 5 Skin 4 Cervix 2 Colon 1 Lymph nodes 1 Other 14

Primary Assessment Method

Control Arm: Total Patient Population	
Number of patients screened	84
Number of patients enrolled	58
Number of patients evaluable for toxicity	58
Number of patients evaluated for efficacy	52
Response assessment CR	0
Response assessment PR	13.5%
Response assessment SD	48.1%
Response assessment PD	38.5%
(Median) duration assessments PFS	3.2 months
(Median) duration assessments duration of treatment	13 weeks

Adverse Events

All Dose Levels, All Cycles	**AEs are shown in Tables 1–3.**

Dose-Limiting Toxicities

Dose Level	Dose of Drug: Pilaralisib	Dose of Drug: Paclitaxel	Dose of Drug: Carboplatin	Number Enrolled	Number Evaluable for Toxicity	Number with a Dose-Limiting Toxicity	Dose-Dose-limiting Toxicity Information
Pilaralisib capsules							
1	100 mg	150 mg/m^2	5 AUC	3	3	0	
2	150 mg	150 mg/m^2	5 AUC	3	3	0	
3	200 mg	150 mg/m^2	5 AUC	3	3	0	
4	200 mg	175 mg/m^2	6 AUC	3	3	0	

5	400 mg	175 mg/m^2	6 AUC	3	3	0	
6	600 mg	175 mg/m^2	6 AUC	3	3	0	
5E	400 mg	175 mg/m^2	6 AUC	3	3	2	Allergic reaction
6E	600 mg	175 mg/m^2	6 AUC	1	1	1	Grade 3 rash
4E	200 mg	175 mg/m^2	6 AUC	3	3	0	
Pilaralisib tablets							
7	200 mg	175 mg/m^2	6 AUC	3	3	0	
8	300 mg	175 mg/m^2	6 AUC	3	3	1	Failure to receive 75% of dose due to skin rash
8E	300 mg	175 mg/m^2	6 AUC	3	3	1	Grade 3 skin rash
7E	200 mg	175 mg/m^2	6 AUC	3	3	1	Grade 3 dehydration, grade 4 neutrophil count decreased, grade 3 staphylococcal bacteremia

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Pharmacokinetics/Pharmacodynamics	Not Collected
Investigator's Assessment	Evidence of target inhibition but no or minimal antitumor activity

Paclitaxel plus carboplatin is a standard treatment for various solid tumors, including first-line treatment of advanced/recurrent endometrial cancer [1]. However, most patients eventually become resistant to this regimen and experience disease progression. The phosphoinositide 3-kinase (PI3K) pathway is pivotal for growth in normal cells, and dysregulation of the pathway is involved in tumorigenesis of solid tumors [2–7]. In endometrial cancers, activation of the PI3K/mTOR pathway is associated with aggressive disease and poor prognosis [3]. Upregulation of PI3K/mTOR pathway signaling has been identified as a mechanism of tumor resistance to paclitaxel and carboplatin. In addition, PI3K/mTOR pathway inhibitors have been shown to augment the cytotoxicity of paclitaxel and carboplatin in cancer cell lines [8–10]. Therefore, combining paclitaxel plus carboplatin with PI3K inhibition is a rational therapeutic strategy in solid tumors and endometrial cancer.

Pilaralisib is a selective, reversible, pan-class I PI3K inhibitor that has shown preliminary antitumor activity in a phase I study in advanced solid tumors. Pilaralisib is stable in human hepatocytes in vitro (Sanofi data on file); in patients, $<$0.1% is excreted unchanged in urine, independent of dose [11]. The maximum tolerated dose (MTD) of pilaralisib capsules was established as 600 mg once daily (QD) [11]. The current study aimed to determine the safety and MTD of pilaralisib capsule and tablet formulations administered in combination with paclitaxel and carboplatin in patients with advanced solid tumors.

Fifty-eight patients were enrolled. Initially, 25 patients were treated with pilaralisib capsules (100–600 mg). After a protocol amendment, newly enrolled patients ($n = 33$) received a tablet formulation at 200–300 mg QD. A planned expansion cohort in ovarian cancer was not enrolled due to shortage of pilaralisib supply; the expansion cohort was limited to patients with endometrial cancer ($n = 16$).

The median duration of pilaralisib treatment was 13 weeks (range 1–80); 51.7% of patients received pilaralisib for $>$12 weeks. Reasons for treatment discontinuation were disease progression (69.0%), adverse events (AEs)/serious AEs (SAEs, 17.2%), investigator's decision other than AEs (6.9%), patient request (5.2%), and death (1.75%).

Six patients (10.3%) had dose-limiting toxicities (DLTs): 2/6 receiving 400 mg pilaralisib capsules, 1/4 receiving 600 mg capsules, 1/27 receiving 200 mg tablets, and 2/6 receiving 300 mg tablets. The only DLT occurring in more than one patient was rash (two patients, 3.4%). The MTD of pilaralisib tablets administered in combination with 175 mg/m^2 paclitaxel and area under the curve (AUC) 6 carboplatin was determined to be 200 mg QD.

The most frequently occurring AEs were consistent with carboplatin, paclitaxel, and pilaralisib known safety profiles (Tables 1–3). No difference in toxicity was observed between capsule and tablet formulations. Grade 3/4 treatment-related AEs occurred in 87.9% of patients.

Treatment-related grade $\geq$3 events of increases in aspartate aminotransferase and gamma glutamyltransferase were reported for two (3.4%) and one patient (1.7%), respectively; no patient met the criteria for Hy's law. Fifteen patients had treatment-related AEs in the rash grouping; four (6.9%) had grade $\geq$3 events. Four patients (6.9%) had treatment-related AEs in the hyperglycemia grouping; two (3.4%) had grade $\geq$3 events.

Twenty-eight patients (48.3%) had an SAE, which was considered treatment related in 12 patients (20.7%). Treatment-

related SAEs occurring in more than one patient were mental status changes, neutropenia, rash, and thrombocytopenia (two patients each, 3.4%). Twelve patients (21.0%) had AEs that led to discontinuation of any study treatment, most commonly fatigue (seven patients, 12.1%), nausea, vomiting, and urinary tract infection (six patients each, 10.3%). Three deaths occurred within 30 days of last study drug dose: one due to disease progression and two due to unknown cause.

Pilaralisib was absorbed with a median t_{max} of 6–11 hours after repeated doses of 100 to 600 mg pilaralisib QD in combination with paclitaxel and carboplatin (Table 4). On cycle 2 day 1, exposure of pilaralisib was within the range of previous data with pilaralisib monotherapy at steady state (Fig. 2) [11]. There was no apparent impact of coadministration of paclitaxel and carboplatin on pilaralisib pharmacokinetics.

Modulation of PI3K/mTOR and mitogen-activated protein kinase (MAPK) pathway biomarkers was assessed in serial tumor biopsies from three patients (Fig. 1 and Table 5). Tumor biopsies from two patients receiving 200 mg pilaralisib capsules showed inhibition of PI3K/mTOR and MAPK pathways and modest reduction of proliferation and induction of apoptosis, whereas no pharmacodynamic impact was observed in biopsies from the third patient tested (200 mg tablets).

Of 52 evaluable patients, best overall response was confirmed partial response (PR) in seven patients (13.5%). Twenty-two patients (42.3%) had stable disease or a progression-free period of $\geq$12 weeks. One of 18 evaluable patients with endometrial cancer had a PR (5.6%). Median progression-free survival (PFS) was 3.2 months overall and 3.3 months in patients with endometrial cancer. The longest PFS observed was 77.4 weeks in a patient with squamous cell carcinoma of the neck treated with 400 mg capsules. Maximum change in size of target lesions according to prior paclitaxel and carboplatin treatment is shown in Figure 3. No responses occurred in patients who had previously received both paclitaxel and carboplatin.

Molecular profiling of tumor tissue was performed in 21 patients in the dose-escalation phase (Fig. 4A). *PIK3CA*, *KRAS*, and *BRAF* status in cell-free circulating tumor DNA from peripheral blood sampled at enrollment was also assessed in 17 patients with endometrial cancer (Fig. 4B); four patients (23.54%) had a *PIK3CA* mutation, including H1047R (two patients), K111E, and R93W (one patient each). No obvious associations between PI3K pathway alterations and responses were observed, consistent with previous studies [11, 12].

Despite promising preclinical data, PI3K inhibitors have shown only modest single-agent activity in solid tumors to date [11, 13–16]. However, combination regimens could reveal therapeutic utility for these agents. In this study, adding pilaralisib did not appear to enhance the antitumor efficacy of paclitaxel plus carboplatin. This is consistent with the limited efficacy observed with pilaralisib monotherapy in solid tumors [11] and endometrial cancers [12] and findings for other PI3K inhibitors in various solid tumors [13–16]. Further clinical evaluation is warranted to identify effective combination strategies with PI3K pathway inhibitors.

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Disclosures

Joanne Lager: Sanofi (E); **Christelle Castell:** Sanofi (E); **Li Liu:** Sanofi (E); **Jason Jiang:** Sanofi (E). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Experttestimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

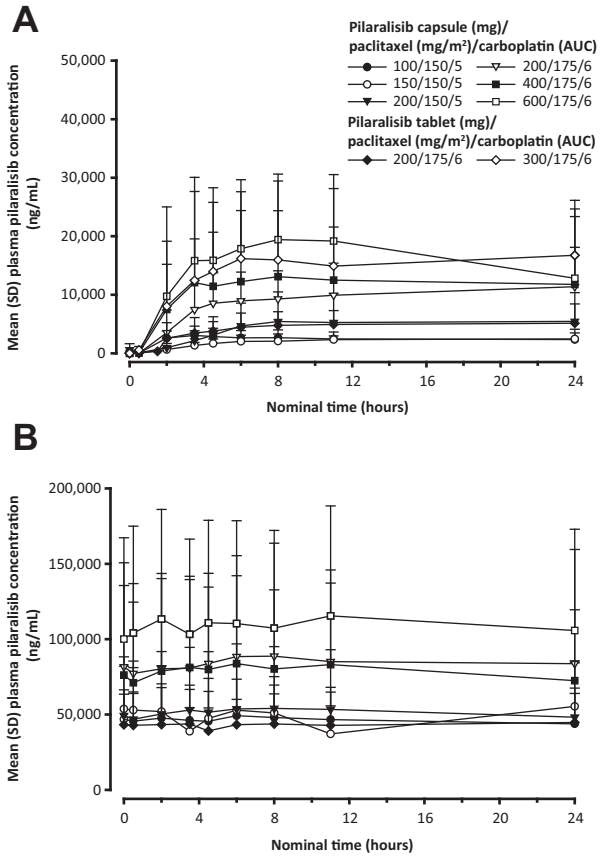

Figure 2. Mean plasma concentration of pilaralisib over time on cycle 1, day 1 **(A)** and cycle 2, day 1 **(B)**.

Abbreviations: AUC, area under the curve; SD, standard deviation.

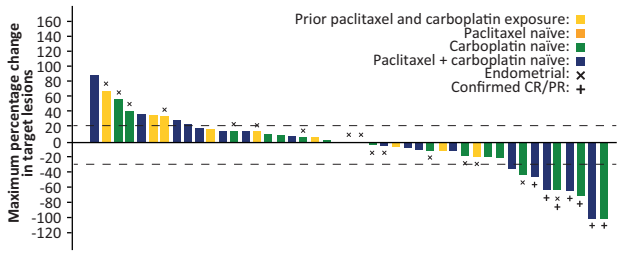

Figure 3. Maximum change in target lesions in patients treated with the combination of pilaralisib, paclitaxel, and carboplatin. Bar colors indicate prior treatment with paclitaxel and/or carboplatin.

Abbreviations: CR, complete response; PR, partial response.

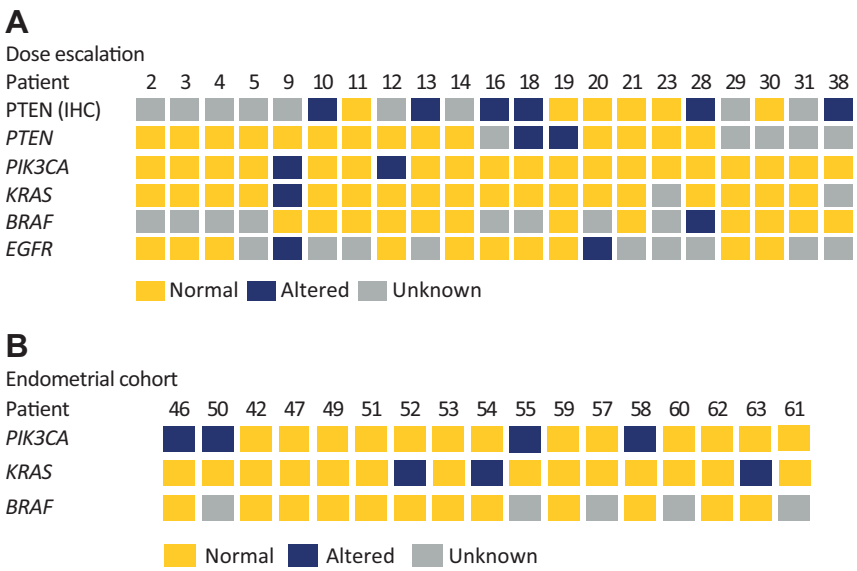

Figure 4. Mutational analysis of tumor tissue and circulating tumor DNA. **(A)**: Dose-escalation cohort: molecular profiling for gene alterations was performed on archival tumor tissue samples using Sanger sequencing ($n = 21$), and PTEN protein expression status was evaluated using IHC ($n = 12$). **(B)**: Endometrial cohort ($n = 17$). *KRAS, PIK3CA, BRAF* mutational status at start of pilaralisib treatment (cycle 1, day 1) was assessed in cell-free circulating tumor DNA obtained from peripheral blood samples using BEAMing assays (Sysmex Inostics). Key: yellow, no alteration detected; blue, gene alteration or altered protein expression (H score <50); grey, status unknown.

Abbreviations: EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; PTEN, phosphatase and tensin homolog.

Table 2. Adverse events irrespective of causality occuring in >20% of patients

AE	Pilaralisib capsules, mg/paclitaxel, mg/m^2/carboplatin, AUC						Pilaralisib tablets, mg/paclitaxel, mg/m^2/carboplatin, AUC	
	100/150/5 ($n = 3$)	150/150/5 ($n = 3$)	200/150/5 ($n = 3$)	200/175/6 ($n = 6$)	400/175/6 ($n = 6$)	600/175/6 ($n = 4$)	200/175/6 ($n = 27$)	300/175/6 ($n = 6$)
Any AE	3 (100)	3 (100)	3 (100)	6 (100)	6 (100)	4 (100)	27 (100)	6 (100)
Neutropenia	2 (66.7)	3 (100)	2 (66.7)	5 (83.3)	4 (66.7)	3 (75.0)	18 (66.7)	2 (33.3)
Thrombocytopenia	2 (66.7)	2 (66.7)	1 (33.3)	6 (100)	3 (50.0)	3 (75.0)	21 (77.8)	1 (16.7)
Anemia	3 (100)	2 (66.7)	2 (66.7)	5 (83.3)	2 (33.3)	2 (50.0)	17 (63.0)	1 (16.7)
Fatigue	2 (66.7)	1 (33.3)	2 (66.7)	4 (66.7)	6 (100)	3 (75.0)	14 (51.9)	2 (33.3)
Nausea	3 (100)	0	2 (66.7)	2 (33.3)	4 (66.7)	2 (50.0)	13 (48.1)	2 (33.3)
Diarrhea	1 (33.3)	0	2 (66.7)	2 (33.3)	3 (50.0)	2 (50.0)	10 (37.0)	2 (33.3)
Vomiting	1 (33.3)	0	3 (100)	3 (50.0)	4 (66.7)	1 (25.0)	10 (37.0)	0
Hypomagnesemia	1 (33.3)	0	0	3 (50.0)	2 (33.3)	3 (75.0)	6 (22.2)	4 (66.7)
Decreased appetite	1 (33.3)	0	2 (66.7)	2 (33.3)	2 (33.3)	1 (25.0)	8 (29.6)	0
Peripheral neuropathy	2 (66.7)	2 (66.7)	0	2 (33.3)	0	3 (75.0)	7 (25.9)	0
Rash	2 (66.7)	0	2 (66.7)	3 (50.0)	2 (33.3)	2 (50.0)	3 (11.1)	2 (33.3)
Urinary tract infection	0	0	0	3 (50.0)	0	2 (50.0)	10 (37.0)	1 (16.7)
Alopecia	0	2 (66.7)	2 (66.7)	1 (16.7)	2 (33.3)	1 (25.0)	5 (18.5)	2 (33.3)
Dyspnea	1 (33.3)	0	2 (66.7)	0	0	2 (50.0)	9 (33.3)	1 (16.7)
Abdominal pain	0	0	2 (66.7)	1 (16.7)	1 (16.7)	2 (50.0)	6 (22.2)	1 (16.7)
Hypokalemia	0	0	1 (33.3)	2 (33.3)	0	1 (25.0)	7 (25.9)	2 (33.3)
Peripheral edema	0	0	0	3 (50.0)	2 (33.3)	1 (25.0)	4 (14.8)	3 (50.0)
Dizziness	0	0	1 (33.3)	1 (16.7)	1 (16.7)	2 (50.0)	6 (22.2)	1 (16.7)
Leukopenia	1 (33.3)	1 (33.3)	0	1 (16.7)	1 (16.7)	0	8 (29.6)	0
Decreased neutrophil count	0	0	1 (33.3)	1 (16.7)	1 (16.7)	1 (25.0)	4 (14.8)	4 (66.7)
Decreased white blood cell count	0	0	1 (33.3)	1 (16.7)	1 (16.7)	1 (25.0)	4 (14.8)	4 (66.7)

Data is shown as n (%).
Abbreviations: AE, adverse event; AUC, area under the curve.

Table 3. Treatment-related adverse events occurring in >10% of patients

AE	Pilaralisib capsule, mg/paclitaxel, mg/m^2/carboplatin, AUC						Pilaralisib tablet, mg/paclitaxel, mg/m^2/carboplatin, AUC	
	100/150/5 ($n = 3$)	150/150/5 ($n = 3$)	200/150/5 ($n = 3$)	200/175/6 ($n = 6$)	400/175/6 ($n = 6$)	600/175/6 ($n = 4$)	200/175/6 ($n = 27$)	300/175/6 ($n = 6$)
Any treatment-related AE	3 (100)	3 (100)	3 (100)	6 (100)	6 (100)	4 (100)	25 (92.6)	6 (100)
Neutropenia	2 (66.7)	3 (100)	2 (66.7)	5 (83.3)	4 (66.7)	3 (75.0)	12 (44.4)	2 (33.3)
Thrombocytopenia	2 (66.7)	1 (33.3)	1 (33.3)	6 (100)	3 (50.0)	3 (75.0)	15 (55.6)	1 (16.7)
Fatigue	2 (66.7)	1 (33.3)	2 (66.7)	4 (66.7)	5 (83.3)	2 (50.0)	13 (48.1)	2 (33.3)
Anemia	3 (100)	2 (66.7)	2 (66.7)	5 (83.3)	2 (33.3)	2 (50.0)	10 (37.0)	1 (16.7)
Nausea	3 (100)	0	2 (66.7)	2 (33.3)	4 (66.7)	2 (50.0)	8 (29.6)	2 (33.3)
Diarrhea	1 (33.3)	0	1 (33.3)	2 (33.3)	1 (16.7)	2 (50.0)	7 (25.9)	1 (16.7)
Hypomagnesemia	1 (33.3)	0	0	3 (50.0)	2 (33.3)	3 (75.0)	3 (11.1)	2 (33.3)
Alopecia	0	2 (66.7)	2 (66.7)	1 (16.7)	2 (33.3)	1 (25.0)	3 (11.1)	2 (33.3)
Vomiting	1 (33.3)	0	3 (100)	2 (33.3)	2 (33.3)	1 (25.0)	4 (14.8)	0
Peripheral neuropathy	1 (33.3)	2 (66.7)	0	2 (33.3)	0	3 (75.0)	4 (14.8)	0
Rash	1 (33.3)	0	1 (33.3)	2 (33.3)	2 (33.3)	2 (50.0)	2 (7.4)	2 (33.3)
Decreased appetite	1 (33.3)	0	1 (33.3)	1 (16.7)	1 (16.7)	0	7 (25.9)	0
Decreased neutrophil count	0	0	1 (33.3)	1 (16.7)	1 (16.7)	1 (25.0)	3 (11.1)	4 (66.7)
Decreased white blood cell count	0	0	1 (33.3)	1 (16.7)	1 (16.7)	1 (25.0)	3 (11.1)	4 (66.7)
Leukopenia	1 (33.3)	1 (33.3)	0	1 (16.7)	1 (16.7)	0	6 (22.2)	0
Decreased hemoglobin	0	0	0	1 (16.7)	0	1 (25.0)	4 (14.8)	2 (33.3)
Hypokalemia	0	0	0	2 (33.3)	0	1 (25.0)	4 (14.8)	1 (16.7)

(continued)

Table 3. (continued)

AE	Pilaralisib capsule, mg/paclitaxel, mg/m^2/carboplatin, AUC						Pilaralisib tablet, mg/paclitaxel, mg/m^2/carboplatin, AUC	
	100/150/5 ($n = 3$)	150/150/5 ($n = 3$)	200/150/5 ($n = 3$)	200/175/6 ($n = 6$)	400/175/6 ($n = 6$)	600/175/6 ($n = 4$)	200/175/6 ($n = 27$)	300/175/6 ($n = 6$)
Increased aspartate aminotransferase	0	1 (33.3)	1 (33.3)	0	0	2 (50.0)	2 (7.4)	0
Peripheral edema	0	0	0	3 (50.0)	2 (33.3)	0	0	1 (16.7)
Decreased platelet count	0	1 (33.3)	0	0	0	1 (25.0)	1 (3.7)	3 (50.0)
Pruritus	0	0	0	2 (33.3)	0	1 (25.0)	1 (3.7)	2 (33.3)

Data is shown as n (%).
Abbreviations: AE, adverse event; AUC, area under the curve.

Table 4. Pilaralisib pharmacokinetic parameters after treatment with pilaralisib in combination with paclitaxel and carboplatin on cycle 1 day 1 (C1D1) and cycle 2 day 1 (C2D1)

PK parameter, mean ± SD (geometric mean) [CV%]	Pilaralisib capsule, mg/paclitaxel, mg/m^2/carboplatin, AUC						Pilaralisib tablet, mg/paclitaxel, mg/m^2/carboplatin, AUC	
	100/150/5	150/150/5	200/150/5	200/175/6	400/175/6	600/175/6	200/175/6	300/175/6
C1D1								
n	3	3	3	6	6	4	24	6
C_{max}, μg/mL	3.1 ± 1.6	3.1 ± 1.2	5.7 ± 4.89	12.5 ± 6.81	13.2 ± 16.3	21.6 ± 12.6	6.15 ± 3.4	18.0 ± 8.4
	(2.72) [51.6]	(2.87) [39.8]	(3.69) [85.5]	(8.50) [54.5]	(5720) [123.90]	(17.9) [58.6]	(5.170) [55.6]	(16.4) [46.4]
t_{max}[a], hour	3.5	11.0	24.0	15.0	8.0	15.0	8.0	9.5
	(3.5–3.5)	(8.0–24.0)	(6.0–24.0)	(4.5–24.0)	(4.5–24.0)	(3.5–24.0)	(2.0–24.0)	(6.0–24.0)
AUC_{0-24}, μg*hour/mL	57.7 ± 27.8	48.1 ± 19.5	108 ± 95.3	218 ± 114	271 ± 338	371 ± 198	105 ± 50.8	344 ± 152
	(51.9) [48.3]	(44.8) [40.6]	(62.5) [88.6]	(146) [52.4]	(116) [124.6]	(315) [53.5]	(91.8) [48.2]	(313) [44.3]
C2D1								
n	3	3	3	5	4	4	20	4
C_{max}, μg/mL	50.3 ± 23.2	56.3 ± 29.4	55.9 ± 40.1	94.9 ± 71.2	85.7 ± 57.8	119 ± 74.9	50.8 ± 24.3	89.3 ± 31.7
	(46.2) [46.1]	(50.2) [52.2]	(44.8) [71.8]	(77.5) [75.1]	(71.1) [67.4]	(93.8) [63.0]	(46.2) [47.7]	(85.7) [35.5]
t_{max}[a], hour	6.0	8.0	8.0	6.0	7.25	11.0	6.0	7.0
	(0–11.0)	(2.0–24.0)	(6.0–11.0)	(0.0–8.0)	(2.0–11.0)	(4.5–11.0)	(0–24.0)	(0.5–11.0)
AUC_{0-24}, μg*hour/mL	1110 ± 506	1150 ± 594	1230 ± 950	2030 ± 1600	1890 ± 1270	2640 ± 1660	1050 ± 482	1940 ± 605
	(1010) [45.7]	(1020) [51.8]	(946) [76.9]	(1620) [79.1]	(1580) [67.2]	(2080) [62.8]	(952) [46.1]	(1880) [31.2]

[a]Median (range)
Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; C1D1, cycle 1 day 1; C2D1, cycle 2 day 1; CV%, coefficient of variation; PK, pharmacokinetics, SD, standard deviation; t_{max}, time to maximum concentration.

Table 5. Summary of pharmacodynamic activity in tumor biopsy sets

Tumor type	Pilaralisib, mg/paclitaxel, mg/m^2/carboplatin, AUC	Sampling time	Decrease, %				Fold induction
			pAKT^{T308}	p4EBP1^{T70}	pERK$^{T202/Y204}$	Ki67	TUNEL
CRC adenocarcinoma	200 (capsule)/150/5	Cycle 2 day 21	67	64	73	32	2.4
Cervical adenocarcinoma	200 (capsule)/175/6	Cycle 4 day 20	76	69	70	33	2.3
SCC (skin, lower lip)	200 (tablet)/175/6	Cycle 2 day 20	7	31	29	−25	1.5

Modulation of PI3K and MAPK pathway biomarkers was assessed in serial tumor biopsies collected from three patients. Levels of PI3K and ERK pathway components (pAKT^{T308}, p4EBP1^{T70} and pERK$^{T202/Y204}$) were evaluated using immunofluorescence staining protocols with pixel- and intensity-based quantitative readouts. Proliferation and apoptosis were measured by decrease in Ki67 and fold induction in TUNEL, respectively.
Abbreviations: EBP1, EIF4E-binding protein-1; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase.