



# Phase Ib Trial of the PI3K Inhibitor Copanlisib Combined with the Allosteric MEK Inhibitor Refametinib in Patients with Advanced Cancer

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## Abstract

**Background** Dual inhibition of PI3K and MAPK signaling is conceptually a promising anticancer therapy.

**Objective** This phase Ib trial investigated the safety, maximum tolerated dose (MTD), recommended phase II dose, pharmacokinetics, tumor response, fluorodeoxyglucose positron emission tomography (FDG-PET) pharmacodynamics, and biomarker explorations for the combination of pan-PI3K inhibitor copanlisib and allosteric MEK inhibitor refametinib in patients with advanced solid tumors.

**Patients and methods** This was an adaptive trial with eight dose cohorts combining dose escalation and varying schedules in repeated 28-day cycles. Patients received copanlisib (0.2–0.8 mg/kg intravenously) intermittently (days 1, 8, 15) or weekly (days 1, 8, 15, 22) each cycle, and refametinib (30–50 mg twice daily orally) continuously or 4 days on/3 days off. Patients with *KRAS*, *NRAS*, *BRAF*, or *PI3KCA* mutations were eligible for the expansion cohort.

**Results** In the dose-escalation ( $n=49$ ) and expansion ( $n=15$ ) cohorts, the most common treatment-emergent adverse events included diarrhea (59.4%), nausea, acneiform rash, and fatigue (51.6% each). Dose-limiting toxicities included oral mucositis ( $n=4$ ), increased alanine aminotransferase/aspartate aminotransferase ( $n=3$ ), acneiform rash, hypertension ( $n=2$  each), and diarrhea ( $n=1$ ). MTD was copanlisib 0.4 mg/kg weekly and refametinib 30 mg twice daily. No pharmacokinetic interactions were identified. Decreased tumor FDG uptake and MEK-ERK signaling inhibition were demonstrated during treatment. Best response was stable disease ( $n=21$ ); median treatment duration was 6 weeks.

**Conclusions** Despite sound rationale and demonstrable pharmacodynamic tumor activity in relevant tumor populations, a dose and schedule could not be identified for this drug combination that were both tolerable and offered clear efficacy in the population assessed.

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## 1 Introduction

Aberrant activation of phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and RAS/RAF/MAPK signaling is frequently implicated in tumorigenesis. These signaling pathways are interconnected,

allowing for compensatory signal transduction when one pathway is inhibited [1, 2]. Dual inhibition of these pathways in vitro and in vivo has demonstrated synergistic tumor stasis and antitumor efficacy [3, 4]; hence, combination therapy may provide improved clinical outcomes in cancer patients.

Copanlisib (Bayer AG, Berlin, Germany) is an intravenous, pan-class I PI3K inhibitor with predominant activity against PI3K- $\alpha$  and PI3K- $\delta$  isoforms [5, 6]. In a first-in-human study, copanlisib demonstrated antitumor activity in patients with solid tumors; the maximum tolerated dose (MTD) was 0.8 mg/kg (equivalent to a 60-mg fixed dose) [7]. In a recent phase II study, copanlisib 60 mg demonstrated significant efficacy and manageable toxicity in heavily pre-treated patients with indolent lymphoma [8]. Based on these

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### Key Points

Inhibition of two separate yet interconnected oncogenic signaling pathways (PI3K and MEK) is a promising approach for anticancer therapy, to avoid compensatory signaling if only one pathway alone was inhibited.

In this phase Ib study, the combination of the pan-PI3K inhibitor copanlisib plus allosteric MEK inhibitor refametinib was tolerated only at a sub-clinically active dose in patients with advanced solid tumors, and optimal dosing for PI3K-MEK inhibitor combination regimens remains to be established.

results, copanlisib was approved by the US Food and Drug Administration for the treatment of patients with relapsed follicular lymphoma [9]. Refametinib (BAY 86-9766; Bayer AG, Berlin, Germany) is a highly selective, orally administered allosteric MEK1/2 inhibitor [10] that demonstrated good tolerability and clinical activity in a phase I study; the MTD was 50 mg twice daily (BID) [11]. Copanlisib combined with refametinib has demonstrated synergy, with observed tumor stasis in colorectal cancer (CRC) tumor cell lines (with wild-type or mutant *KRAS*) [12], non-small-cell lung cancer (NSCLC) cell lines [13] and biliary tract cancer models [14] with various genetic alterations; tumor progression was observed with either agent alone. These data supported further study of the combination, especially in patients with metastatic *KRAS*-mutant CRC and NSCLC (with wild-type or mutant *EGFR*).

Previous combination studies using oral PI3K and MEK inhibitors have demonstrated antitumor activity, although long-term tolerability is challenging due to frequent dose interruptions and reductions, often due to gastrointestinal toxicities [15, 16]. Intravenous copanlisib, administered intermittently, has demonstrated manageable safety and is potentially advantageous compared with oral PI3K inhibitors, with low incidences of fatal hepatic and/or gastrointestinal toxicity [8], supporting the rationale for the study of intravenous copanlisib combined with oral refametinib.

The primary objectives of this phase Ib study were to determine the safety, tolerability, MTD, and recommended phase II doses (RP2D) of intravenous copanlisib combined with oral refametinib in patients with advanced cancer, and to determine any possible pharmacokinetic interaction. Secondary objectives were to assess antitumor activity and to explore potentially predictive and pharmacodynamic biomarkers.

## 2 Patients and Methods

### 2.1 Study Design and Treatments

This was a multicenter, open-label, non-randomized, dose-escalation study comprising a dose-escalation scheme plus an expansion cohort (NCT01392521). Dose escalation followed an adaptive design in repeated 28-day cycles (Supplementary Fig. S1). Copanlisib dosing started at 0.2 mg/kg (25% of the single-agent MTD [7]) administered intravenously over 1 h, intermittently on days 1, 8, and 15 of each cycle [7, 8], or in later cohorts on days 1, 8, 15, and 22 of each cycle, and was to be escalated to the MTD of 0.8 mg/kg, with a maximum dose of 65 mg. Refametinib dosing started at 30 mg BID (60% of the single-agent MTD) administered continuously from cycle 1, day 4, or in later cohorts intermittently for 4 days on/3 days off starting on cycle 1, day 6, and was to be escalated to the MTD of 50 mg BID [11].

If  $\leq 1/6$  patients in a cohort experienced a dose-limiting toxicity (DLT) in the first cycle, escalation to the next dose level would commence. If  $\geq 2/6$  patients experienced a DLT, the MTD would have been exceeded and dose escalation would cease. Criteria for DLTs are provided in the Online Supplementary Material. Following tolerability assessment of cohorts 2A, 2B, and 2C, and review of the data from all dose levels tested by the investigators, the highest tolerable combination was selected for  $\geq 12$  additional patients enrolled into an expansion cohort for further safety, preliminary efficacy, and biomarker evaluations (Supplementary Fig. S1).

The study was compliant with the Declaration of Helsinki and Good Clinical Practice, and was approved by the appropriate ethics committees. All patients provided written, informed consent.

### 2.2 Inclusion Criteria

Patients aged  $\geq 18$  years with histologically or cytologically confirmed incurable and refractory advanced solid tumors were eligible. Patients must have had  $\geq 1$  measurable lesion or evaluable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST), life expectancy of  $\geq 12$  weeks, and an Eastern Cooperative Oncology Group performance status of  $\leq 1$ . Enrollment into the expansion cohort required the presence of an activating tumor mutation in *KRAS*, *NRAS*, *BRAF*, and/or *PI3KCA*. Patients could be enrolled into the expansion cohort with mutation data based on either historical results (any tumor mutation result generated before enrollment into the trial) or prospectively generated central laboratory mutation analysis

of circulating tumor DNA isolated from plasma collected during screening.

### 2.3 Assessments

Tumors were measured by computed tomography or magnetic resonance imaging at screening, within 7 days of the start of each odd-numbered cycle, and within 30 days of the last dose. Tumor response was assessed using RECIST. Ophthalmologic examinations were performed at screening and day 1 ( $\pm$  7 days) of every third cycle. Safety, pharmacokinetic, pharmacodynamic, and biomarker assessments are detailed in the Online Supplementary Material.

### 2.4 Statistical Analysis

Statistical analyses are detailed in the Online Supplementary Material.

## 3 Results

### 3.1 Patients and Treatment

Eighty-seven patients were screened and 64 were assigned to copanlisib and refametinib treatment: 49 in dose-escalation cohorts and 15 in the expansion cohort (Supplementary Fig. S1). The mean age was 58.4 years; 38 patients (59.4%) had received  $\geq$  3 prior regimens. Common cancer types included CRC (34.4%) and NSCLC (14.1%) (Table 1).

Patients received a median of two copanlisib cycles (range 1–6) and two refametinib cycles (range 1–7). Patients received a median of six copanlisib infusions (range 1–22) and a median daily dose of refametinib 58.7 mg (range 20–100). Median duration of treatment for copanlisib and refametinib was 6.1 weeks (range 0.1–28.0) and 6.9 weeks (range 0.6–28.0), respectively.

### 3.2 Dose Escalation and Dose-Limiting Toxicities

Sixteen patients (25.0%) had DLTs, including oral mucositis and increased alanine aminotransferase/aspartate aminotransferase (Table 2). Dose 3A was considered intolerable because of a DLT in one patient and multiple adverse events (AEs) leading to dose reduction or dropout. Doses 3B and 3BN were considered intolerable because 4/6 and 2/6 patients, respectively, had DLTs during cycle 1. No patients were enrolled to planned cohorts 3AN, 4, or 4N. DLTs were observed in 1/4, 2/4, and 1/7 patients, respectively, in cohorts 2A, 2B, and 2C. Therefore, the MTD for the combination was established as copanlisib 0.4 mg/kg once weekly plus refametinib 30 mg BID (dose 2C). Of the 15 patients

treated at the MTD in the expansion cohort, two presented with AEs that met protocol-defined DLT criteria (Table 2).

### 3.3 Safety and Tolerability

At least one treatment-emergent AE (TEAE) was observed in all patients; TEAEs considered related to copanlisib or refametinib were reported in 60 (93.8%) and 61 (95.3%) patients, respectively. The most common TEAEs of any grade (in  $>$  50% of patients) were diarrhea, nausea, acneiform rash, and fatigue (Table 3). Eight patients (12.5%) experienced  $\geq$  1 treatment-emergent eye disorder of any grade: blurred vision ( $n = 4$  [6.3%]), other disorders ( $n = 2$  [3.1%]; optic hemorrhage and conjunctival pallor), conjunctivitis, dry eye, and keratitis ( $n = 1$  each [1.6%]). Eye disorders were grade 1 in six patients and grade 2 or 3 in one patient each (one patient had grade 3 optic disc hemorrhage which recovered). TEAEs of worst grade 3 or 4 were reported in 68.8% ( $n = 44$ ) and 10.9% ( $n = 7$ ) of patients, respectively. The most common grade 3 TEAEs (in  $\geq$  5 patients) were hypertension (26.6%;  $n = 17$ ), diarrhea (10.9%;  $n = 7$ ), anemia, hyponatremia, maculopapular rash (9.4% each;  $n = 6$ ), acneiform rash, dyspnea, and oral mucositis (7.8% each;  $n = 5$ ). The most common grade 4 TEAE was increased creatine phosphokinase (3.1% [all-grade, 15.6%]).

Twelve patients (18.8%) experienced  $\geq$  1 serious TEAE related to either copanlisib or refametinib, most commonly worst grade 3 (Table 4). All drug-related serious TEAEs were considered related to the combination therapy, except for one case of grade 1 pneumonitis (copanlisib only) and one case each of grade 3 acneiform rash and grade 3 diarrhea (refametinib only).

Dose modifications (interruptions, delays, or reductions) occurred in 45 patients (70.3%) and were attributed to copanlisib-related TEAEs in 25 patients (39.1%) and refametinib-related TEAEs in 34 patients (53.1%). Twenty-one patients (32.8%) had TEAEs leading to permanent discontinuation, including 6/22 patients (27.3%) treated at the MTD. Most events leading to treatment discontinuation were grade 3 (23.4%;  $n = 15$ ), most commonly oral mucositis and maculopapular rash (3.1% each;  $n = 2$ ); grade 4 events were reported in two patients (ileus and respiratory failure,  $n = 1$  each).

Nine deaths were reported within 30 days after treatment discontinuation, including one deemed copanlisib-related following grade 2 renal insufficiency and dehydration (assessed as a DLT).

### 3.4 Pharmacokinetics

Single-agent pharmacokinetics were measured on days 1 and 14 for copanlisib and refametinib, respectively, and in

**Table 1** Patient demographics and baseline characteristics

	Dose-escalation cohorts							Expansion cohort (n = 15)	Total (N = 64)	
	Cohort 1 (n = 6)	Cohort 2 (n = 6)	Cohort 3A (n = 10)	Cohort 3B (n = 6)	Cohort 3BN (n = 6)	Cohort 2A (n = 4)	Cohort 2B (n = 4)			Cohort 2C (n = 7)
Males, n (%)	5 (83.3)	3 (50.0)	3 (30.0)	1 (16.7)	2 (33.3)	1 (25.0)	3 (75.0)	4 (57.1)	11 (73.3)	33 (51.6)
Mean (SD) age, years	62.0 (7.5)	55.2 (16.8)	62.2 (14.1)	56.7 (11.6)	52.0 (7.8)	46.5 (21.0)	59.0 (13.1)	61.4 (14.8)	60.7 (8.8)	58.4 (12.6)
Mean (SD) body weight, kg	74.9 (9.8)	69.7 (19.5)	79.6 (32.7)	74.0 (16.3)	63.1 (17.5)	61.7 (11.5)	78.8 (5.6)	73.6 (15.7)	82.4 (15.2)	74.9 (18.8)
ECOG PS, n (%)										
0	1 (16.7)	2 (33.3)	5 (50.0)	1 (16.7)	1 (16.7)	1 (25.0)	1 (25.0)	2 (28.6)	4 (26.7)	18 (28.1)
1	5 (83.3)	4 (66.7)	5 (50.0)	5 (83.3)	5 (83.3)	3 (75.0)	3 (75.0)	5 (71.4)	11 (73.3)	46 (71.9)
Cancer histology, n (%)										
CRC	2 (33.3)	2 (33.3)	0	1 (16.7)	2 (33.3)	1 (25.0)	0	3 (42.9)	11 (73.3)	22 (34.4)
NSCLC	0	1 (16.7)	3 (30.0)	0	1 (16.7)	0	1 (25.0)	1 (14.3)	2 (13.3)	9 (14.1)
Ovarian	0	1 (16.7)	2 (20.0)	0	0	1 (25.0)	1 (25.0)	0	1 (6.7)	6 (9.4)
Pancreatic adenocarcinoma	2 (33.3)	0	1 (10.0)	0	0	1 (25.0)	1 (25.0)	1 (14.3)	0	6 (9.4)
Breast	0	0	3 (30.0)	1 (16.7)	0	0	0	0	0	4 (6.3)
Gastric	0	1 (16.7)	0	0	1 (16.7)	0	0	0	0	2 (3.1)
Cervical	1 (16.7)	0	0	0	0	0	0	0	0	1 (1.6)
Uterine	0	0	0	1 (16.7)	0	0	0	1 (14.3)	0	2 (3.1)
Other <sup>a</sup>	1 (16.7)	1 (16.7)	2 (20.0)	3 (50.0)	2 (33.3)	1 (25.0)	1 (25.0)	0	1 (6.7)	12 (18.8)
Median time since initial diagnosis, months (range)	67.5 (5–105)	17.3 (9–58)	17.4 (1.4–67)	43.0 (12–263)	31.0 (9–59)	71.5 (18–137)	35.1 (16–75)	28.2 (10–50)	20.3 (6–73)	26.5 (1.4–263)
Prior systemic treatments, n (%)										
0	0	0	1 (10.0)	1 (16.7)	0	0	0	0	0	2 (3.1)
1	1 (16.7)	0	3 (30.0)	0	2 (33.3)	0	0	0	2 (13.3)	8 (12.5)
2	1 (16.7)	5 (83.3)	2 (20.0)	1 (16.7)	0	0	1 (25.0)	2 (28.6)	4 (26.7)	16 (25.0)
≥3	4 (66.7)	1 (16.7)	4 (40.0)	4 (66.7)	4 (66.7)	4 (100)	3 (75.0)	5 (71.4)	9 (60.0)	38 (59.4)

CRC colorectal cancer, ECOG PS Eastern Cooperative Oncology Group performance status, NSCLC non-small-cell lung cancer, SD standard deviation

<sup>a</sup>Other includes ampullary carcinoma, apocrine carcinoma, epithelioid malignant mesothelioma, hepatobiliary cancer, intracranial hemangiopericytoma, kidney cancer, neuroendocrine tumor of right lower lobe lung, undifferentiated sarcoma, unknown primary, urothelial carcinoma of the bladder and vulva

**Table 2** Overview of dose-limiting toxicities and relationship to study drug

Cohort	Copanlisib dose	Refametinib dose	Patients with DLT(s)/treated patients	DLT <sup>a</sup>
1	0.2 mg/kg 3 weeks on/1 week off	30 mg BID	1/6	Grade 3 pancreatitis
3A	0.8 mg/kg 3 weeks on/1 week off	30 mg BID	1/10	Grade 3 diarrhea
3B	0.4 mg/kg 3 weeks on/1 week off	50 mg BID	6/6	Grade 3 acneiform rash, grade 3 oral mucositis, grade 3 dehydration, grade 3 dry skin, grade 4 hypernatremia, grade 3 increased AST, grade 3 hypertension, grade 3 fatigue <sup>b</sup>
3BN	0.4 mg/kg weekly	50 mg BID	2/6	Grade 3 increased ALT, grade 3 increased ALT
2A	0.6 mg/kg weekly	30 mg BID	1/4	Grade 3 hypertension
2B	0.6 mg/kg 3 weeks on/1 week off	30 mg BID	2/4	Grade 3 oral mucositis, grade 3 hypertension
2C	0.4 mg/kg weekly	30 mg BID	1/7	Grade 3 oral mucositis
Expansion	0.4 mg/kg weekly	30 mg BID	2/15	Grade 3 acneiform rash, grade 3 oral mucositis

*ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BID* twice daily, *DLT* dose-limiting toxicity

<sup>a</sup>DLTs assessed using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; patients may have more than one DLT

<sup>b</sup>Grade 3 fatigue started during treatment cycle 2 in two patients

**Table 3** Summary of treatment-emergent adverse events<sup>a</sup>

<i>n</i> (%)	Total ( <i>N</i> =64)		
Any TEAE	64 (100)		
Grade 1	0		
Grade 2	5 (7.8)		
Grade 3	44 (68.8)		
Grade 4	7 (10.9)		
Grade 5	9 (14.1)		
TEAEs occurring in $\geq 20\%$ of patients	All-grade	Grade 3	Grade 4
Diarrhea	38 (59.4)	7 (10.9)	0
Acneiform rash	33 (51.6)	5 (7.8)	0
Fatigue	33 (51.6)	4 (6.3)	0
Nausea	33 (51.6)	0	0
Vomiting	27 (42.2)	2 (3.1)	0
Hyperglycemia	26 (40.6)	2 (3.1)	0
Hypertension	25 (39.1)	17 (26.6)	0
Maculopapular rash	24 (37.5)	6 (9.4)	0
Oral mucositis	24 (37.5)	5 (7.8)	0
Limb edema	21 (32.8)	0	0
Anorexia	20 (31.3)	2 (3.1)	0
Abdominal pain	19 (29.7)	3 (4.7)	0
Dyspnea	17 (26.6)	5 (7.8)	0
Pruritus	17 (26.6)	0	0
Constipation	15 (23.4)	0	0
Fever	15 (23.4)	2 (3.1)	0
Investigations – other, specify	15 (23.4)	2 (3.1)	0
Hypokalemia	14 (21.9)	2 (3.1)	1 (1.6)

*TEAE* treatment-emergent adverse event

<sup>a</sup>Adverse events classified and graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

**Table 4** Serious treatment-emergent adverse events of grade  $\geq 3$  considered related to copanlisib or refametinib<sup>a</sup>

<i>n</i> (%)	Total ( <i>N</i> =64)
Patients with $\geq 1$ TEAE	
Grade 3	
Diarrhea	4 (6.3) <sup>b</sup>
Hyperglycemia	2 (3.1)
Abdominal pain	1 (1.6)
Acneiform rash	1 (1.6) <sup>b</sup>
Anemia	1 (1.6)
Dehydration	1 (1.6)
Fatigue	1 (1.6)
Lung infection	1 (1.6)
Pancreatitis	1 (1.6)
Pleural effusion	1 (1.6)
Syncope	1 (1.6)
Vomiting	1 (1.6)
Grade 4	
Increased creatine phosphokinase	1 (1.6)
Grade 5	
Death—not otherwise specified <sup>c</sup>	1 (1.6)

TEAE treatment-emergent adverse event

<sup>a</sup>Adverse events classified and graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

<sup>b</sup>Includes one serious TEAE related to refametinib only

<sup>c</sup>Death following grade 2 renal insufficiency assessed as drug-related and grade 3 dehydration assessed as dose-limiting toxicity

combination on day 15. Following a single copanlisib infusion at doses of 0.2–0.8 mg/kg (cycle 1, day 1), the geometric mean maximum drug concentration ( $C_{max}$ ) reached 118–403  $\mu\text{g/L}$  at a median time of 0.50–1.03 h, with coefficients of variation (CVs) of 16.6–146% (Table 5). The area under the curve from time 0 to 25 h after the start

of infusion ( $AUC_{(0-25)}$ ) from 0.2–0.8 mg/kg ranged from 305–1,210  $\mu\text{g}\cdot\text{h/L}$ , with CVs of 16.0–63.1%. Within each cohort, copanlisib  $C_{max}$  and  $AUC_{(0-25)}$  were comparable between day 1 and day 15.

Following multiple doses of refametinib 30 mg or 50 mg BID, geometric mean  $C_{max}$  reached 484–1,220  $\mu\text{g/L}$  at a median time of 1.50–4.00 h, with CVs of 20.6–101% (Table 6). AUC from time 0 to 8 h ( $AUC_{(0-8)}$ ) ranged from 2,510–5,310  $\mu\text{g}\cdot\text{h/L}$ , with CVs of 20.5–126%.  $C_{max}$  and  $AUC_{(0-8)}$  were slightly lower with refametinib monotherapy versus concomitant copanlisib.

### 3.5 Clinical and Pharmacodynamic Activity

No complete or partial responses were observed. Seven patients (10.9%) had stable disease lasting 2–4 cycles as best response. Thirty-one patients (48.4%) had progressive disease, one (1.6%) had non-complete response/non-progressive disease (defined as the response in one non-target lesion due to no measurable target lesion at baseline), and 11 (17.2%) were not evaluable (Fig. 1). Of 51 patients for whom tumor shrinkage values by investigator assessment were available, modest improvements in the best change in target lesion size from baseline were observed (Fig. 2). In cohort 2C, 4/7 patients (57.1%) had tumor shrinkage and stable disease as best response, contributing to the decision to use this dose in the expansion cohort. In the expansion cohort in patients treated at the MTD, 5/15 patients (33.3%) had stable disease as best response, with three patients having some degree of tumor shrinkage (Fig. 2).

#### 3.5.1 Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) Tumor Response

Paired FDG-PET scans were evaluable in 23/30 patients from cohorts 2A, 2B, 2C, and the expansion cohort

**Table 5** Copanlisib geometric mean (% coefficient of variation) pharmacokinetic parameters on cycle 1, day 1 (copanlisib alone) and day 15 (copanlisib and refametinib)

[ <i>n</i> ] Cohort	Day 1		Day 15	
	$C_{max}$ ( $\mu\text{g/L}$ )	$AUC_{(0-25)}$ ( $\mu\text{g}\cdot\text{h/L}$ )	$C_{max}$ ( $\mu\text{g/L}$ )	$AUC_{(0-25)}$ ( $\mu\text{g}\cdot\text{h/L}$ )
1	126 (146) [6]	305 (57.3) [5]	123 (168) [6]	362 (135) [4]
2	189 (84.9) [6]	564 (16.0) [5]	185 (10.9) [6]	632 (35.0) [6]
3A	353 (65.8) [10]	1080 (49.6) [10]	319 (84.5) [5]	1090 (49.7) [5]
3B	247 (29.9) [6]	693 (49.6) [6]	246 (14.4) [4]	956 (45.0) [3]
3BN	118 (16.6) [6]	432 (44.9) [6]	154 (38.9) [5]	482 (34.1) [5]
2A	403 (72.5) [3]	1210 (24.9) [3]	194 (88.6) [3]	619 (123) [3]
2B	212 (44.1) [3]	947 (32.9) [3]	371 (148) [4]	1250 (76.4) [4]
2C	241 (104) [7]	725 (45.5) [7]	303 (84.6) [6]	743 (37.5) [6]
Expansion	312 (111) [15]	890 (63.1) [15]	257 (108) [14]	770 (33.8) [14]

$AUC_{(0-25)}$  area under the curve from time 0 to 25 h after the start of infusion,  $C_{max}$  maximum drug concentration

**Table 6** Refametinib geometric mean (% coefficient of variation) pharmacokinetic parameters on cycle 1, day 14 (refametinib alone) and day 15 (refametinib and copanlisib)

[n] Cohort	Day 14		Day 15	
	$C_{max}$ (µg/L)	$AUC_{(0-8)}$ (µg·h/L)	$C_{max}$ (µg/L)	$AUC_{(0-8)}$ (µg·h/L)
1	484 (101) [6]	2510 (126) [6]	433 (77.9) [6]	2240 (101) [6]
2	943 (52.3) [6]	5110 (55.3) [6]	795 (47.2) [6]	4920 (46.7) [6]
3A	822 (55.3) [8]	4530 (44.3) [8]	625 (34.3) [7]	3790 (36.4) [7]
3B	1220 (80.0) [3]	4910 (98.4) [3]	672 (102) [4]	4130 (118) [4]
3BN	— <sup>a</sup>	— <sup>a</sup>	1080 (39.7) [5]	6170 (48.5) [5]
2A	743 (24.2) [3]	3300 (47.7) [3]	452 (60.2) [3]	2560 (65.0) [3]
2B	607 (32.1) [3]	3750 (21.1) [3]	631 (31.8) [3]	3810 (29.9) [3]
2C	873 (38.1) [6]	4770 (48.3) [6]	766 (46.4) [6]	3900 (50.6) [5]
Expansion	845 (20.6) [14]	5310 (20.5) [14]	691 (34.7) [15]	4420 (31.6) [15]

$AUC_{(0-8)}$  area under the curve from time 0 to 8 h after the start of infusion,  $C_{max}$  maximum drug concentration

<sup>a</sup>Not sampled per protocol

(including 16 treated at the MTD in cohort 2C and the expansion cohort). Eighteen patients (78.3%) showed a decline in FDG standardized uptake values (SUV) from baseline in all target lesions (range – 3% to – 74%). All 16 evaluable patients treated at the MTD demonstrated a decrease in  $SUV_{max}$  values during treatment; mean decrease was 25.8% (Supplementary Fig. S2). A weak negative correlation was observed between changes in FDG  $SUV_{max}$  and drug exposure ( $AUC_{(0-25)}$ ,  $R^2=0.1828$ ;  $AUC$  from time 0 to the last data point,  $R^2=0.2158$ ) (Supplementary Fig. S3).

### 3.5.2 Biomarkers

All 22 patients treated at the MTD had mutation data available for  $\geq 1$  gene of interest and had a mutation in  $\geq 1$  of the four genes assessed (Table 7). Tumor mutations were observed in 19/21 patients (90.5%) for *KRAS*, 7/18 (38.9%) for *PI3KCA*, and 1/19 (5.3%) for *BRAF*. No patients evaluated for *NRAS* harbored an *NRAS* tumor mutation. *PIK3CA* mutational status did not clearly associate with best response (stable disease rates were 3/6 [50%] and 3/9 [33%] for mutant and wild-type *PIK3CA*, respectively;  $p=0.622$ ) or progression-free survival (PFS) (Supplementary Fig. S4A).

All patients with next-generation sequencing data ( $n=13$ ) had 5–29 tumor genetic mutations, most commonly (besides *KRAS*) in *TP53* (10/13, 76.9%) and *APC* (7/13, 53.8%; all CRC) (Supplementary Fig. S5).

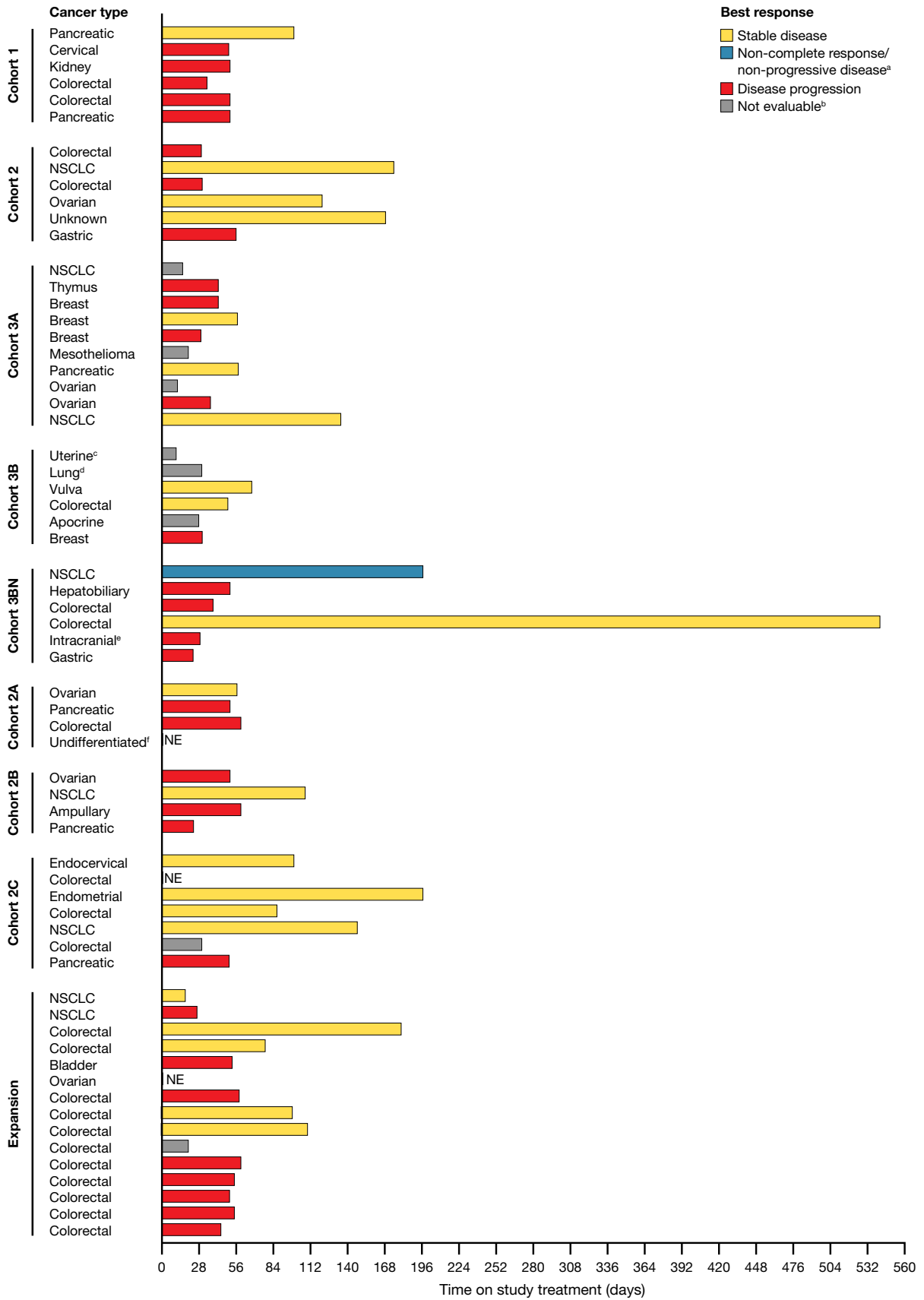
Nineteen of 22 patients treated at the MTD had immunohistochemistry data for pretreatment PTEN, pAKT, pERK, and Ki-67. Four patients (21.1%) had complete tumor PTEN protein loss, including three (75.0%) with stable disease as best response, including the individual patient with the greatest tumor shrinkage (– 28%; Fig. 2). Three of 11 patients (27%) with detectable PTEN had stable disease as best response. Patients with PTEN loss also showed a trend

towards longer PFS (Supplementary Fig. S4B). The sole patient with DNA-level *PTEN* loss had stable disease as best response, but had insufficient tumor sample for PTEN immunohistochemistry. Patients with high (above median) pretreatment pERK levels had shorter PFS than those with low pERK (Supplementary Fig. S4C). A relationship between high baseline Ki-67 and shorter PFS was observed (analyzed as a continuous variable,  $p=0.027$ ; hazard ratio 1.012; suggesting that the risk of progression increases by 1.2% for every 1-point increase in Ki-67 H-score), and Ki-67 dichotomization showed a similar trend (Supplementary Fig. S4D).

Five patients in the expansion cohort had evaluable paired tumor biopsies collected before and during treatment; all demonstrated a reduction in pERK levels during treatment versus baseline, three had reduced pAKT levels, and four had reduced Ki-67 levels (Supplementary Fig. S6). Stronger inhibition of pERK, pAKT, and/or Ki-67 did not clearly correspond with improved response, as the two patients with the greatest total decreases in pERK, pAKT, and Ki-67 tumor levels had progressive disease as best response.

## 4 Discussion

This phase Ib study evaluated the safety, tolerability, and RP2D of intravenous copanlisib (intermittent dosing, weekly or 3 weeks on/1 week off) combined with oral refametinib (continuous or intermittent dosing) in patients with advanced cancer. The MTD for the combination was determined as copanlisib 0.4 mg/kg weekly and refametinib 30 mg BID, doses lower than for the individual drugs as monotherapy (0.8 mg/kg and 50 mg, respectively) [7, 11]. DLTs included class-effect toxicities associated with PI3K inhibitors (e.g., diarrhea [8, 17]) and MEK inhibitors (e.g., rash [18, 19]), and toxicities previously reported with dual inhibition of





**Fig. 1** Time on study treatment by cohort and by RECIST best response; 28 days=1 cycle. <sup>a</sup>Response only valid for non-target lesions. <sup>b</sup>Eleven patients had missing imaging for post-baseline RECIST assessment and were classified as not evaluable. <sup>c</sup>Leiomyosarcoma. <sup>d</sup>Neuroendocrine tumor. <sup>e</sup>Hemangiopericytoma. <sup>f</sup>Sarcoma. *NE* not evaluable, *NSCLC* non-small-cell lung cancer, *RECIST* Response Evaluation Criteria in Solid Tumors version 1.1

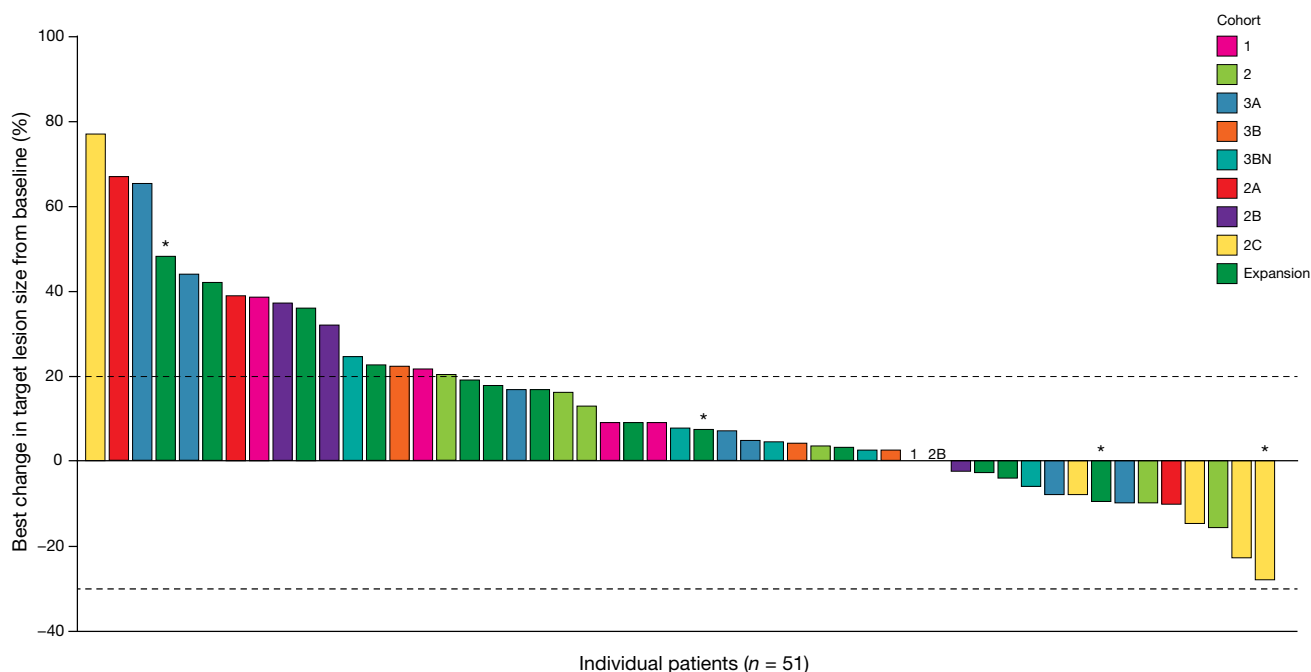
the PI3K/AKT/mTOR and RAS/RAF/MAPK pathways [20]. Based on TEAEs leading to discontinuation at the MTD, short treatment duration (6–7 weeks), and lack of objective responses, an RP2D and schedule that were both tolerable and offered clear efficacy in the population assessed could not be identified for this drug combination.

The most common TEAEs (> 50% incidence) included gastrointestinal toxicities, dermatologic toxicities, and fatigue, consistent with those observed in monotherapy studies of refametinib [11] and copanlisib [21]. The incidence of dermatologic toxicities was consistent with reports of other MEK inhibitors [18, 19, 22]. Rash TEAEs were generally mild (grade 1 or 2); although infrequent, rash was among the most common grade 3 TEAEs leading to discontinuation. Hyperglycemia (all-grade, 40.6%) is an on-target effect of PI3K inhibitors and was treatment-related and reversible, similar to copanlisib monotherapy reports [8, 21, 23]. The incidence of hypertension (all-grade, 39.1%) was also consistent with reports of copanlisib monotherapy [7, 8, 21]. Increased creatine phosphokinase was the most common grade 4 TEAE (3.1%), consistent with reports of

PI3K and MEK inhibitor combination therapies [15, 24–26]. High rates of ophthalmologic toxicities have been associated with some MEK inhibitors (e.g., 19% incidence [all-cause] with trametinib and 27% incidence with RO4987655) [27], although were infrequent here (all-grade, 12.5%) and mostly mild in severity [18].

Pharmacokinetic characteristics for copanlisib combined with refametinib were consistent with those reported for copanlisib monotherapy [7]. Copanlisib exposure ( $C_{max}$  and  $AUC_{(0-25)}$ ) was comparable between day 1 (copanlisib alone) and day 15 (copanlisib and refametinib), suggesting that co-administration with refametinib did not influence copanlisib pharmacokinetics. Pharmacokinetic characteristics for refametinib in combination generally reflected those for refametinib monotherapy [11]; however, refametinib exposure ( $C_{max}$  and  $AUC_{(0-8)}$ ) was slightly reduced with concomitant copanlisib. No clinically relevant pharmacokinetic interactions between copanlisib and refametinib were observed.

No objective responses were observed, consistent with the inadequate efficacy reported from studies with other PI3K and MEK inhibitor combinations [25, 26, 28–30]. This was unexpected based on preclinical evidence of such combinations being synergistic [3, 4]. Furthermore, in combination with gemcitabine, the current standard-of-care therapy for many advanced cancers, copanlisib and refametinib have demonstrated promising clinical responses in patients with advanced cancer [31, 32]. In this study, the response rate was



**Fig. 2** Best change in target lesion size from baseline by cohort. Each bar represents one patient; the best change in target lesion size per investigator assessment could not be determined in 13 patients. “Asterisk”—patients with PTEN loss

**Table 7** Tumor mutations in cohort 2C and the expansion cohort ( $n=22$ )

Cohort/tumor type	Gene	Historic <sup>a</sup>	ctDNA <sup>b</sup>	NGS <sup>b</sup>
Expansion/bladder	<i>PIK3CA</i>	E545K	E545K	–
Cohort 2C/cervical	<i>KRAS</i>	A146V	–	–
Cohort 2C/colorectal	<i>KRAS</i>	G12A	–	G12A
Cohort 2C/colorectal	<i>KRAS</i>	G12A	–	–
Cohort 2C/colorectal	<i>KRAS</i>	–	–	CN: 17
Expansion/colorectal	<i>KRAS</i>	G13D	G13D	G13D
Expansion/colorectal	<i>KRAS</i>	G12V	G12V	–
Expansion/colorectal	<i>KRAS</i>	G12D	G12D	G12D
Expansion/colorectal	<i>KRAS</i>	G12A	G12A	–
Expansion/colorectal	<i>KRAS</i>	G12D	G12D	G12D
Expansion/colorectal	<i>KRAS</i>	G13D	WT	G13D
Expansion/colorectal	<i>KRAS</i>	G12D	WT	WT
Expansion/colorectal	<i>KRAS</i>	G12V	G12V	–
Expansion/colorectal	<i>PIK3CA</i>	–	E542K	–
	<i>KRAS</i>	G13D	G13D	G13D
Expansion/colorectal	<i>PIK3CA</i>	–	WT <sup>c</sup>	CN: 28
	<i>KRAS</i>	G12D	G12D	G12D
Expansion/colorectal	<i>PIK3CA</i>	E542K	E542K	E542K
	<i>KRAS</i>	G12S	G12S	G12S
Expansion/colorectal	<i>PIK3CA</i>	–	E545K	WT
	<i>PIK3CA</i>	–	–	N1044K
Cohort 2C/endometrial	<i>PIK3CA</i>	–	–	–
Cohort 2C/NSCLC	<i>KRAS</i>	G12C	–	–
Expansion/NSCLC	<i>KRAS</i>	G12C	WT	–
Expansion/NSCLC	<i>KRAS</i>	G12R	G12R	G12R
	<i>PIK3CA</i>	–	E545K	WT
Expansion/ovarian	<i>BRAF</i>	Complex rearrangement	–	–
Cohort 2C/pancreatic	<i>KRAS</i>	–	–	G12D

CN copy number, ctDNA circulating tumor DNA, NGS next-generation sequencing, NSCLC non-small-cell lung cancer, WT wild-type, — not tested/not available

<sup>a</sup>Any tumor mutation result generated before enrollment into the trial

<sup>b</sup>Test performed centrally

<sup>c</sup>ctDNA test cannot detect copy number alterations

similar to that observed in the phase I study of refametinib monotherapy (partial response rate 0% vs. 2%, respectively), although stable disease was more frequent here (32.8% vs. 16%) [11]. The lack of objective responses observed here, despite enrichment for tumor types with RAS-MAPK or PI3K signaling pathway mutations in the expansion cohort, may be partially explained by the MTD of the combination being lower than that of the individual compounds as monotherapy [7, 11]. This is consistent with a recent pharmacodynamic study showing that copanlisib 0.4 mg/kg as monotherapy was less active than 0.8 mg/kg [33]. Further, median duration of treatment was short due to toxicities, likely resulting in insufficient exposure.

Patients with complete tumor PTEN loss showed a trend towards better outcomes, suggesting these patients may be more responsive to treatment, whereas patients with high baseline pERK, pAKT, and Ki-67 levels showed a trend towards shorter PFS, possibly indicative of a poorer prognosis. Some indicators of a pharmacodynamic effect were seen in patients with relevant evidence of tumorigenic activity (decreases in FDG-PET signal and tumor pERK levels). The limited number of patients with relevant gene mutations might contribute to the lack of observed response; favorable objective response rates have been observed in studies of MEK inhibitors in monotherapy or combined with PI3K inhibitors in patients with RAS- and/or BRAF-mutant solid tumors [15, 34]. Optimal dosing for PI3K-MEK inhibitor combinations remains to be confirmed.

In conclusion, despite the scientific rationale for combining PI3K and MEK inhibitors, the copanlisib plus refametinib combination was not tolerated at doses expected to be clinically active. Further development of the combination is not warranted.

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## Compliance with Ethical Standards

**Conflict of Interest** R. K. Ramanathan is currently employed by Merck and received research funding from Bayer for the conduct of the study. D.D. Von Hoff is employed as a consultant at McKesson; reports stock and ownership at Anthem, Inc., CerRx, Medtronic, Stromatis Pharma, SynDevRx, Systems Oncology, and UnitedHealthcare; has participated in a consulting or advisory role for Aadi, Actinium Pharmaceuticals, Adicet Bio, Aeglea BioTherapeutics, Agenus, AiMed Bio, Alpha Cancer Technologies, Amunix, APEIRON, Aptose Biosciences, Arvinas, Athenex, Bellicum Pharmaceuticals, BioLineRx, BioSpecifics Technologies, BioXcel Therapeutics, Boston Scientific, Bryologyx, CanBas, Celgene, Codiak Biosciences, Corcept Therapeutics, CORONA, CV6 Therapeutics, CytomX Therapeutics, Decoy Biosystems, DNATrix, EMD Serono, Erimos Pharmaceuticals, Esperance Pharmaceuticals, Evelo Biosciences, Fate Therapeutics, FibroGen, Five Prime Therapeutics, Fujifilm, Geistlich Pharma, Genzada Pharmaceuticals, Gimbal, GiraPharma, Globe Life Sciences, Helix BioPharma, Hills Pharma, Histogen, Horizon Discovery, HUYA Bioscience International, Imaging Endpoints, Immodulon Therapeutics, Immunophotonics, Innokeys, Intezyme Technologies, Ipsen, Jounce Therapeutics, Kalos Therapeutics, Kelun-Klus Pharma, Kura, L.E.A.F. Pharmaceuticals, Lixte Biotechnology, Medical Prognosis Institute, Novita Pharmaceuticals, Novocure, NuCana BioMed, Oncology Venture, Oncolyze, Pfiz-

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