

Phase Ib Study of Combination Therapy with MEK Inhibitor Binimetinib and Phosphatidylinositol 3-Kinase Inhibitor Buparlisib in Patients with Advanced Solid Tumors with *RAS/RAF* Alterations

ADITYA BARDIA,^{a,†} MRINAL GOUNDER^{b,†},[‡] JORDI RODON,^c FILIP JANKU,^d MARTIJN P. LOKKEMA,^e JOE J. STEPHENSON,^f PHILIPPE L. BEDARD,^g MARTIN SCHULER^{b,h},[‡] CRISTIANA SESSA,ⁱ PATRICIA LORUSSO,^j MICHAEL THOMAS,^k HEIKO MAACKE,^l HELEN EVANS,^l YONGJIAN SUN,^l DANIEL S.W. TAN^m

^aDepartment of Hematology/Oncology, Massachusetts General Hospital Cancer Center; Harvard Medical School, Boston, Massachusetts, USA; ^bDepartment of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, New York, USA; ^cMedical Oncology Department, Vall D'Hebron Institute of Oncology, VHIO, Barcelona, Spain; ^dDepartment of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; ^eDepartment of Medical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands; ^fDepartment of Medical Oncology, GHS Cancer Institute, Greenville, South Carolina, USA; ^gDivision of Medical Oncology & Hematology, Princess Margaret Cancer Centre, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; ^hDepartment of Medical Oncology, West German Cancer Center, University Duisburg-Essen, and German Cancer Consortium (DKTK), Partner Site University Hospital Essen, Essen, Germany; ⁱDepartment of Medical Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; ^jDepartment of Medical Oncology, Yale Cancer Center, New Haven, Connecticut, USA; ^kInternistische Onkologie der Thoraxtumoren, Thoraxklinik im Universitätsklinikum Heidelberg, Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany; ^lNovartis Pharma AG, Basel, Switzerland; ^mDepartment of Medical Oncology, National Cancer Centre Singapore, Singapore

[†]Contributed equally.

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Binimetinib • Buparlisib • *RAS/RAF* • Phase Ib • Ovarian cancer

ABSTRACT

Background. This multicenter, open-label, phase Ib study investigated the safety and efficacy of binimetinib (MEK inhibitor) in combination with buparlisib (phosphatidylinositol 3-kinase [PI3K] inhibitor) in patients with advanced solid tumors with *RAS/RAF* alterations.

Materials and Methods. Eighty-nine patients were enrolled in the study. Eligible patients had advanced solid tumors with disease progression after standard therapy and/or for which no standard therapy existed. Evaluable disease was mandatory, per RECIST version 1.1 and Eastern Cooperative Oncology Group performance status 0-2. Binimetinib and buparlisib combinations were explored in patients with *KRAS*-, *NRAS*-, or *BRAF*-mutant advanced solid tumors until the maximum tolerated dose and recommended phase II dose (RP2D) were defined. The expansion phase comprised patients with epidermal growth factor receptor (*EGFR*)-mutant, advanced non-small cell lung cancer, after progression on an *EGFR* inhibitor; advanced *RAS*- or *BRAF*-mutant

ovarian cancer; or advanced non-small cell lung cancer with *KRAS* mutation.

Results. At data cutoff, 32/89 patients discontinued treatment because of adverse events. RP2D for continuous dosing was buparlisib 80 mg once daily/binimetinib 45 mg twice daily. The toxicity profile of the combination resulted in a lower dose intensity than anticipated. Six (12.0%) patients with *RAS/BRAF*-mutant ovarian cancer achieved a partial response. Pharmacokinetics of binimetinib were not altered by buparlisib. Pharmacodynamic analyses revealed downregulation of pERK and pS6 in tumor biopsies.

Conclusion. Although dual inhibition of MEK and the PI3K pathways showed promising activity in *RAS/BRAF* ovarian cancer, continuous dosing resulted in intolerable toxicities beyond the dose-limiting toxicity monitoring period. Alternative schedules such as pulsatile dosing may be advantageous when combining therapies. *The Oncologist* 2020;25:e160–e169

Correspondence: Mrinal Gounder, M.D., Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, New York 10065, USA. Telephone: 646-888-4167; e-mail: gounder@mskcc.org Received April 16, 2019; accepted for publication June 18, 2019; published Online First on August 8, 2019. <http://dx.doi.org/10.1634/theoncologist.2019-0297>

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Implications for Practice: Because dysregulation of the mitogen-activated protein kinase (MAPK) and the phosphatidylinositol 3-kinase (PI3K) pathways are both frequently involved in resistance to current targeted therapies, dual inhibition of both pathways may be required to overcome resistance mechanisms to single-agent tyrosine kinase inhibitors or to treat cancers with driver mutations that cannot be directly targeted. A study investigating the safety and efficacy of combination binimetinib (MEK inhibitor) and buparlisib (PI3K inhibitor) in patients harboring alterations in the RAS/RAF pathway was conducted. The results may inform the design of future combination therapy trials in patients with tumors harboring mutations in the PI3K and MAPK pathways.

INTRODUCTION

The mitogen-activated protein kinase (MAPK [RAS/RAF/MEK/ERK]) and phosphatidylinositol 3-kinase (PI3K [PI3K/AKT/mTOR]) pathways are frequently dysregulated in cancer. Oncogenic mutations in RAS and its downstream signals occur in a variety of tumors, including non-small cell lung cancer (NSCLC; 20%–30%), melanoma (30%–60%), thyroid (30%–50%), colorectal (2%–45%), and ovarian cancers (3%–11%) [1–8]. Furthermore, the PI3K and MAPK pathways are interconnected; inhibition of one pathway can lead to compensatory activation of the other. Therefore, dual blockade of both pathways may be required [9, 10]. Synergistic antitumor efficacy by dual PI3K/MAPK pathway inhibition has been demonstrated in pre-clinical in vitro and in vivo models of basal-like breast cancer and lung cancer, and has shown promise in the clinical setting [11], thus supporting this hypothesis [12, 13].

Binimetinib (MEK162) is a potent, highly selective, orally bioavailable, non-ATP-competitive allosteric inhibitor of MEK1 and MEK2 [14–16]. The maximum tolerated dose (MTD) of single-agent binimetinib is 60 mg b.i.d. [17]; single-agent binimetinib has shown preliminary clinical activity in solid tumors such as NRAS- and BRAF-mutant melanoma (objective response rate 11% and 6%, respectively) [14, 17, 18]. A phase III study (NEMO) of binimetinib versus dacarbazine in unresectable or metastatic NRAS-mutant melanoma met its primary endpoint of improvement in progression-free survival (PFS; hazard ratio = 0.62; 95% confidence interval [CI]: 0.47–0.80; $p < .001$) [19].

Buparlisib (BKM120) is an oral pan-class I PI3K inhibitor that selectively targets all four isoforms of class I PI3K [20, 21]. The MTD of single-agent buparlisib is 100 mg once daily (q.d.) [20, 22]. Although only modest improvements in PFS were reported in a randomized clinical trial in estrogen receptor-positive breast cancer, higher activity was seen in patients with PIK3CA-activating mutations [23].

Given the preclinical rationale for dual inhibition of the PI3K and MAPK pathways, a phase Ib basket trial was conducted to evaluate the safety and MTD of binimetinib/buparlisib combination therapy in patients with advanced solid tumors harboring selected genomic alterations in the RAS/RAF pathway (ClinicalTrials.gov, number NCT01363232). Secondary objectives of the study were evaluation of efficacy, pharmacokinetics (PK), and pharmacodynamics (PD).

MATERIALS AND METHODS

Study Design

This was a multicenter, open-label, phase Ib study to determine the MTD and/or recommended phase II dose (RP2D)

for combination buparlisib/binimetinib, followed by an expansion phase to further assess safety and efficacy in patients with advanced solid tumors harboring selected genomic alterations in the RAS/RAF pathway. Dose escalation was conducted in patients with KRAS-, NRAS-, or BRAF-mutant advanced solid tumors. Upon determination of RP2D, two expansion arms were then opened in order to further assess safety and preliminary antitumor activity.

Eligibility Criteria

Patients >18 years of age with advanced solid tumors and disease progression after standard therapy and/or for whom no standard anticancer therapy exists were eligible. Evaluable disease was mandatory as determined by RECIST version 1.1 and Eastern Cooperative Oncology Group performance status 0–2. Patients with diabetes mellitus, impaired cardiovascular function, clinically significant cardiovascular diseases, history of depression, or ocular disease (with a history or current evidence of central serous retinopathy [CSR], retinal vein occlusion [RVO], or ophthalmopathy that would be considered a risk factor for CSR/RVO) were excluded.

Dose escalation was performed in patients with advanced refractory colorectal cancer harboring KRAS, NRAS, or BRAF mutations; NSCLC with KRAS mutation; cutaneous malignant melanoma with NRAS or BRAF mutations; pancreatic cancer (irrespective of RAS/RAF mutation status, because most have KRAS mutations); triple-negative breast cancer (because tumors have high prevalence of RAS/MAPK pathway activation) [24]; and other advanced solid tumors with documented KRAS, NRAS, or BRAF mutations. For evaluation of RP2D, patients were enrolled in one of two expansion arms. Arm 1 comprised patients with epidermal growth factor receptor (EGFR)-mutant, advanced NSCLC (including NSCLC with documented T790M activating mutations), with disease progression on a prior EGFR-inhibitor treatment. Arm 2 comprised patients with advanced ovarian cancer with documented RAS or RAF mutations, or advanced NSCLC with documented KRAS mutation.

The study was conducted in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice as defined by the International Conference on Harmonisation. Patients provided written informed consent, and regulatory approval was obtained from participating institutions.

Treatments

Starting doses for the combination were 30 mg binimetinib b.i.d. and 50 mg buparlisib q.d. (both 50% of the single-

agent MTD). Combinations of doses were explored based on an adaptive Bayesian logistic regression model (BLRM) for dose-escalation with overdose control (EWOC) [25] until the MTD and RP2D were defined (supplemental online Table 1). At all decision time points, the adaptive BLRM permitted alterations in the dose increments based on the observed dose-limiting toxicities (DLTs). Only one of the two combination partners could be escalated, and the maximum intercohort dose escalation for a combination partner was limited to 100%. Following determination of the RP2D, patients enrolled in Arm 1 ($n \geq 15$) and Arm 2 (advanced ovarian cancer with documented *RAS* or *RAF* mutations [$n \geq 15$], or advanced NSCLC with documented *KRAS* mutation [$n \geq 10$]) received the recommended RP2D: 80 mg buparlisib q.d. and 45 mg binimetinib b.i.d.

Safety and Efficacy Assessments

A treatment cycle was defined as 28 days. Clinical and laboratory assessments were conducted at baseline, throughout the study, and up to 30 days after the last treatment dose.

Safety assessments included monitoring and recording all adverse events (AEs) with their severity and relationship to study drug, according to Common Terminology Criteria for Adverse Events (version 4.0). Given known pulmonary, ophthalmic, and psychiatric effects of the drugs, patients were monitored at baseline and during the study with pulmonary function tests, mood questionnaires (Patient Health Questionnaire [PHQ-9] depression scale and the Generalized Anxiety Disorder 7-item [GAD-7] anxiety scale), and detailed ophthalmic examination [10, 20]. Supportive medications to manage side effects were permitted.

Efficacy assessments were conducted at baseline and every 8 weeks and evaluated by RECIST version 1.1 criteria.

Pharmacokinetic Assessments

Pharmacokinetic assessments were performed for binimetinib, its primary active metabolite (AR00426032), and buparlisib; plasma levels were determined from samples collected before dose and 0.5, 1.5, 3, 5, 8, and 24 hours after dose on Day 1 and Day 15 of Cycle 1 from all patients in the dose-escalation phase and expansion arm 2. The pharmacokinetics of binimetinib and buparlisib were investigated after a single dose (Day 1) and multiple doses (Day 15) in Cycle 1. The potential impact of coadministration of buparlisib on binimetinib was assessed by examining maximum plasma concentration (C_{max}) and area under the concentration curve (AUC_{tau}) at the same level of binimetinib across doses of buparlisib on Day 15.

Pharmacodynamic Assessments

Paired fresh tumor biopsy samples were collected at baseline and Day 15. Biopsies were recommended for all patients in the dose-escalation phase and were required for patients in the dose-expansion phase. Specimens were flash frozen and analyzed by immunohistochemistry for the PD markers pS6 and pERK (IPG, Belgium) to confirm target modulation of the MAPK and PI3K pathway, respectively. Immunohistochemistry results were semiquantitatively evaluated using the H-score. The percentage of cells with positive staining was estimated for each intensity level

(0, no staining; 1+, weak staining; 2+, moderate staining; 3+, strong staining). The H-score is calculated using the following equation: $[1 \times (\% \text{ cells } 1+) + 2 \times (\% \text{ cells } 2+) + 3 \times (\% \text{ cells } 3+)]$. The H-score ranges from 0 to 300.

Statistical Analyses

A BLRM guided by EWOC principle was used to guide dose escalation of the combination treatment to its MTD and RP2D. A five-parameter BLRM for combination treatment was fitted on Cycle 1 DLT data accumulated throughout the dose escalation to model the dose-toxicity relationship of buparlisib and binimetinib when given in combination. Dose recommendation was based on the probability that the true DLT rate for each dose combination lies in one of the following categories: underdosing (0%, 16%), targeted toxicity (16%, 35%), or excessive toxicity (35%, 100%). The MTD and/or RP2D was expanded by enrolling additional patients eligible for the safety set to be evaluated for safety, tolerability, pharmacokinetics, and biologic activity of buparlisib and binimetinib. A sample size of 40 patients in the expansion cohort had an 87% probability of detecting an AE with a true incidence rate of $\geq 5\%$.

RESULTS

Patient Characteristics

From August 15, 2011, to March 24, 2014 (data cutoff date), 89 patients were enrolled and received at least one dose of the buparlisib/binimetinib combination (Table 1). One patient withdrew consent before receiving the first dose of study drug; 48 and 41 patients were treated in the escalation and expansion phases, respectively. Baseline characteristics were similar across treatment groups in the escalation phase.

Patient Disposition

At the cutoff date, 84 patients (94.4%) had discontinued study treatment; 5 patients in the expansion phase were still ongoing. The most common reasons for discontinuation were disease progression (43 patients, 48.3%) and AEs (32 patients, 36.0%). Other reasons included withdrawal of consent (seven patients, 7.9%), death due to disease progression (one patient, 1.1%), and administrative problems (one patient, 1.1%).

MTD and RP2D Determination

Thirteen patients (20.3%) experienced at least one DLT during the first cycle; the most frequent DLTs were diarrhea (four patients, 6.3%), CSR, and stomatitis (two patients each, 3.1%). Both CSRs were grade 1, reversible, and manageable. In the dose-escalation phase, no DLTs were reported in the buparlisib 50-mg/binimetinib 45-mg group or the buparlisib 60-mg/binimetinib 45-mg group. The dose at which DLTs occurred in both the dose-escalation and dose-expansion phases are specified in supplemental online Table 2.

The MTD for the dose combination was buparlisib 90 mg q.d. and binimetinib 45 mg b.i.d. in a continuous schedule; however, a lower RP2D of buparlisib (80 mg q.d.)

Table 1. Baseline patient characteristics

Characteristic	Buparlisib/binimetinib dose, mg q.d./b.i.d.							All patients (n = 89)
	50/30 (n = 11)	50/45 (n = 5)	60/45 (n = 5)	70/30 (n = 6)	80/30 (n = 6)	80/45 (n = 50)	90/45 (n = 6)	
Sex, male/female, n (%)	5 (46)/6 (55)	3 (60)/2 (40)	2 (40)/3 (60)	1 (17)/5 (83)	3 (50)/3 (50)	17 (34)/33 (66)	3 (50)/3 (50)	34 (38)/55 (62)
Age, median (range), years	64 (36–77)	57 (47–75)	52 (52–78)	50 (42–69)	56 (43–73)	54 (30–77)	66 (54–76)	57 (30–78)
WHO PS, n (%)								
0	3 (27)	0	1 (20)	4 (67)	4 (67)	21 (42)	2 (33)	35 (39)
1	8 (73)	5 (100)	4 (80)	2 (33)	2 (33)	28 (56)	3 (50)	52 (58)
2	0	0	0	0	0	1 (2)	1 (17)	2 (2)
Primary cancer site, n (%)								
Lung	0	1 (20)	0	1 (17)	0	24 (48)	1 (17)	27 (30)
Ovary	1 (9)	0	0	0	0	18 (36)	0	19 (21)
Colon	4 (36)	0	1 (20)	4 (67)	1 (17)	2 (4)	1 (17)	13 (15)
Rectum	4 (36)	1 (20)	1 (20)	0	0	2 (4)	1 (17)	9 (10)
Other ^a	0	2 (40)	1 (20)	0	1 (17)	1 (2)	2 (33)	7 (8)
Breast (triple negative)	2 (18)	0	0	1 (17)	2 (33)	1 (2)	0	6 (7)
Pancreas	0	1 (20)	2 (40)	0	2 (33)	0	1 (17)	6 (7)
Melanoma	0	0	0	0	0	2 (4)	0	2 (2)
No. of prior antineoplastic regimens, median (range)	3.0 (2.0–12.0)	3.5 (1.0–6.0)	2.0 (1.0–4.0)	3.0 (2.0–3.0)	2.5 (1.0–5.0)	3.0 (1.0–12.0)	2.0 (1.0–5.0)	3.0 (1.0–12.0)

^aOther sites included unknown/unspecified (n = 3) and cervix, head and neck, small intestine, and thyroid (n = 1 each).

Abbreviations: PS, performance status; q.d., once daily; WHO, World Health Organization.

and binimetinib (45 mg b.i.d.) was recommended. During the dose escalation phase, there were fewer DLTs reported in the buparlisib (80 mg q.d.) and binimetinib (45 mg b.i.d.) group (1/7 reported grade 3 maculo-papular rash) than in the buparlisib (90 mg q.d.) and binimetinib (45 mg b.i.d.) group (2/6 reported DLTs; grade 3 diarrhea [n = 1] and grade 3 anaphylactic reaction and grade 3 swelling face [n = 1]); the Bayesian model estimated the probability of excessive toxicity was higher for buparlisib 90 mg q.d. and binimetinib 45 mg b.i.d. (0.052) than for buparlisib 80 mg q.d. and binimetinib 45 mg b.i.d. (0.012), and the true DLT rate lies in the excessive toxicity category. Therefore, both dose combinations satisfied EWOC criterion (less than 25% chance that true DLT rate \geq 35%). The lower buparlisib dose was chosen to limit DLTs and excessive toxicity while still meeting EWOC criterion.

Patient Exposure and Safety

The most common all-grade AEs (\geq 10%) suspected of being study drug related included increased blood creatine phosphokinase (CPK; 59.6%), diarrhea (57.3%), and increased aspartate aminotransferase (AST; 49.4%; Table 2). The most common grade 3/4 AEs suspected of being study drug related included increased CPK (27%), increased alanine aminotransferase (ALT; 14.6%), and increased AST (13.5%; Table 2). The most common (\geq 10%) all-cause all-grade AEs and all-cause grade 3/4 AEs are shown in supplemental online Table 3.

Fifty-three patients (59.6%) reported a grade 3/4 AE that required dose interruption and/or change; 54 patients (60.7%) with a grade 3/4 AE required additional therapy for diarrhea, pneumonia, nausea, and vomiting. At the RP2D dose, 26 patients (29.2%) discontinued study treatment for drug-related AEs. The most commonly occurring AEs leading to discontinuation were maculopapular rash (7.9%), symptomatic blood CPK elevation, diarrhea, and ALT increase (3.4% each). One patient died while on treatment as a result of disease progression, and 10 patients died within 30 days after the last dose of study drug as a result of disease progression (n = 7), pneumonia (n = 2), and disseminated intravascular coagulation (n = 1). No deaths were suspected to be study drug related.

Efficacy

Sixty-nine patients (77.5%) were evaluable for tumor response according to RECIST version 1.1 (Fig. 1A). Six patients (12.0%) from the dose-expansion arm achieved a partial response (PR) and remained on treatment for 57 to 169 days. In patients treated with the RP2D (Fig. 1B; supplemental online Table 4), PR was most frequently observed in *RAS/BRAF* ovarian cancer (27.8%); one patient (7.7%) in the *EGFR*-mutant NSCLC group achieved a PR. In the RP2D population, the highest disease control rate (the proportion of patients with a best overall response of complete response, PR, or stable disease) was reported for patients with *RAS/BRAF* ovarian cancer (61.1%; 95% CI: 35.7%–82.7%; supplemental online Table 4). The longest median PFS based on Kaplan-Meier estimates was

Table 2. Adverse events, suspected to be related to study drug, reported by ≥10% of patients (all grades; safety set)

Preferred term	Buparlisib/binimetinib dose, mg q.d./b.i.d.															
	50/30 (n = 11)		50/45 (n = 5)		60/45 (n = 5)		70/30 (n = 6)		80/30 (n = 6)		80/45 (n = 49)		90/45 (n = 7)		All patients (N = 89)	
	All n (%)	G3/4 n (%)	All n (%)	G3/4 n (%)	All n (%)	G3/4 n (%)	All n (%)	G3/4 n (%)	All n (%)	G3/4 n (%)	All n (%)	G3/4 n (%)	All n (%)	G3/4 n (%)	All n (%)	G3/4 n (%)
Total	11 (100)	5 (45.5)	5 (100)	5 (100)	5 (100)	3 (60.0)	5 (83.3)	3 (50.0)	6 (100)	4 (66.7)	44 (89.8)	33 (67.3)	7 (100)	4 (57.1)	83 (93.3)	57 (64.0)
Blood CPK increased	5 (45.5)	2 (18.2)	4 (80.0)	2 (40.0)	3 (60.0)	2 (40.0)	3 (50.0)	2 (33.3)	3 (50.0)	0	32 (65.3)	15 (30.6)	3 (42.9)	1 (14.3)	53 (59.6)	24 (27.0)
Diarrhea	5 (45.5)	0	3 (60.0)	1 (20.0)	2 (40.0)	0	2 (33.3)	0	4 (66.7)	0	29 (59.2)	5 (10.2)	6 (85.7)	1 (14.3)	51 (57.3)	7 (7.9)
AST increase	3 (27.3)	0	3 (60.0)	0	4 (80.0)	1 (20.0)	3 (50.0)	1 (16.7)	2 (33.3)	1 (16.7)	25 (51.0)	8 (16.3)	4 (57.1)	1 (14.3)	44 (49.4)	12 (13.5)
Stomatitis	2 (18.2)	1 (9.1)	2 (40.0)	1 (20.0)	1 (20.0)	0	2 (33.3)	0	4 (66.7)	1 (16.7)	20 (40.8)	3 (6.1)	2 (28.6)	0	33 (37.1)	6 (6.7)
ALT increase	2 (18.2)	0	1 (20.0)	0	2 (40.0)	1 (20.0)	2 (33.3)	0	1 (16.7)	1 (16.7)	20 (40.8)	10 (20.4)	4 (57.1)	1 (14.3)	32 (36.0)	13 (14.6)
Nausea	2 (18.2)	0	1 (20.0)	0	2 (40.0)	0	2 (33.3)	0	1 (16.7)	0	21 (42.9)	0	3 (42.9)	0	32 (36.0)	0
Maculopapular rash	1 (9.1)	0	1 (20.0)	1 (20.0)	2 (40.0)	1 (20.0)	2 (33.3)	1 (16.7)	4 (66.7)	2 (33.3)	17 (34.7)	4 (8.2)	3 (42.9)	2 (28.6)	30 (33.7)	11 (12.4)
Rash	4 (36.4)	0	3 (60.0)	0	1 (20.0)	1 (20.0)	1 (16.7)	0	4 (66.7)	0	14 (28.6)	3 (6.1)	1 (14.3)	0	28 (31.5)	4 (4.5)
Dermatitis acneiform	1 (9.1)	1 (9.1)	2 (40.0)	1 (20.0)	3 (60.0)	0	2 (33.3)	1 (16.7)	1 (16.7)	0	15 (30.6)	1 (2.0)	2 (28.6)	0	26 (29.2)	4 (4.5)
Fatigue	4 (36.4)	0	1 (20.0)	0	0	0	2 (33.3)	0	2 (33.3)	0	12 (24.5)	1 (2.0)	2 (28.6)	0	23 (25.8)	1 (1.1)
Vomiting	3 (27.3)	0	0	0	0	0	1 (16.7)	0	3 (50.0)	0	13 (26.5)	0	2 (28.6)	0	22 (24.7)	0
Decreased appetite	3 (27.3)	0	1 (20.0)	0	1 (20.0)	0	1 (16.7)	0	3 (50.0)	0	9 (18.4)	0	2 (28.6)	0	20 (22.5)	0
Amylase increased	1 (9.1)	0	1 (20.0)	1 (20.0)	0	0	2 (33.3)	0	1 (16.7)	1 (16.7)	11 (22.4)	2 (4.1)	1 (14.3)	0	17 (19.1)	4 (4.5)
Hyperglycemia	3 (27.3)	0	0	0	2 (40.0)	0	0	0	0	0	10 (20.4)	0	2 (28.6)	0	17 (19.1)	0
Chorioretinopathy	2 (18.2)	0	2 (40.0)	0	0	0	1 (16.7)	0	1 (16.7)	0	7 (14.3)	0	3 (42.9)	0	16 (18.0)	0
Lipase increased	1 (9.1)	0	0	0	1 (20.0)	0	1 (16.7)	0	1 (16.7)	1 (16.7)	11 (22.4)	6 (12.2)	1 (14.3)	0	16 (18.0)	7 (7.9)
Peripheral edema	2 (18.2)	0	2 (40.0)	0	1 (20.0)	0	0	0	2 (33.3)	0	7 (14.3)	0	0	0	14 (15.7)	0
Pruritus	2 (18.2)	0	1 (20.0)	0	1 (20.0)	0	1 (16.7)	0	0	0	6 (12.2)	1 (2.0)	1 (14.3)	0	12 (13.5)	1 (1.1)
Dry skin	0	0	2 (40.0)	1 (20.0)	1 (20.0)	0	1 (16.7)	0	0	0	3 (6.1)	0	2 (28.6)	0	9 (10.1)	1 (1.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; G, grade; q.d., once daily.

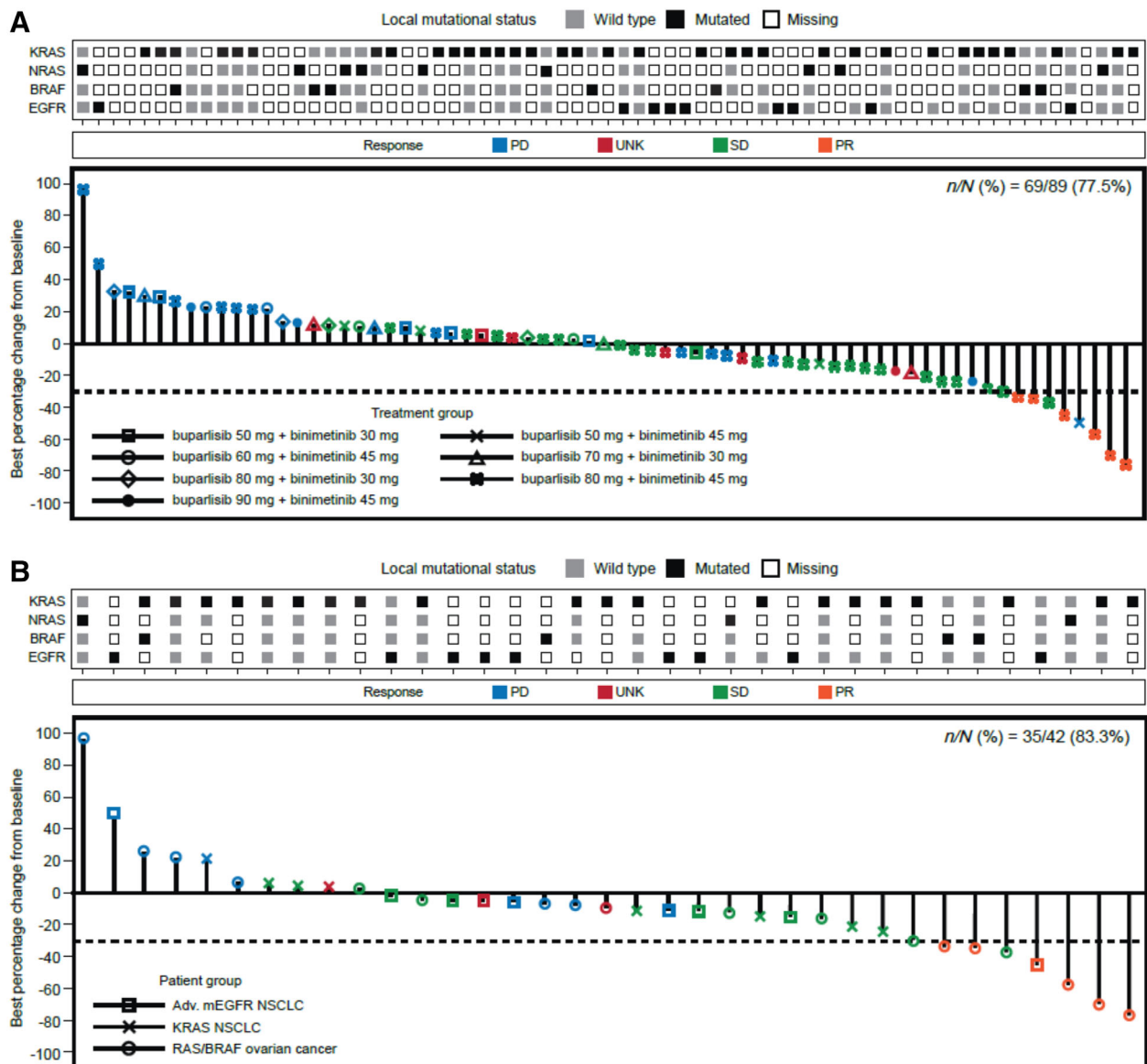


Figure 1. Best percentage change from baseline in sum of tumor diameters. **(A):** By local mutational status and treatment group (full analysis set). **(B):** By local mutational status (recommended phase II dose).

Abbreviations: Adv, advanced; mEGFR, mutant epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD, progressive disease; SD, stable disease; UNK, unknown.

also reported in patients with *RAS/BRAF* ovarian cancer (median 3.7 months; 95% CI: 1.8 to not estimable).

Pharmacokinetics

The potential impact of coadministration of buparlisib and binimetinib was assessed by examining C_{max} and AUC_{tau} at the same level of binimetinib across doses of buparlisib on Day 15 (Fig. 2).

For the combination of binimetinib 45 mg b.i.d. and buparlisib 80 mg q.d., the mean AUC_{tau} of 2,668 ng•hour/mL (supplemental online Table 5) was comparable to or higher than the expected exposure (2,679 ng•hour/mL) derived from the population PK model developed for binimetinib monotherapy and that seen in the single-agent phase I study (mean AUC_{tau} [1,740 ng•hour/mL]) using the same dosing schedule [17]. In the present study, the AUC_{tau}

and C_{max} were 11,690.71 hour•ng/mL and 764.3 ng/mL, respectively. In the single-agent study, AUC_{tau} and C_{max} were 15,413 ng•hour/mL and 1,098 ng/mL, respectively [22]. Overall, the peak concentration of buparlisib and exposure at steady state were lower than expected from single-agent data (supplemental online Table 5), and the PK of binimetinib was not altered by buparlisib. When combined with binimetinib, C_{max} and AUC_{tau} of buparlisib were reduced by >50% in many patients, but this reduction is within the variability of buparlisib exposure and clinical relevance is unclear.

Pharmacodynamics

Biomarker analyses on baseline and postbaseline fresh tumor samples (20 evaluable baseline and postbaseline pairs for pERK analysis; 19 evaluable baseline and

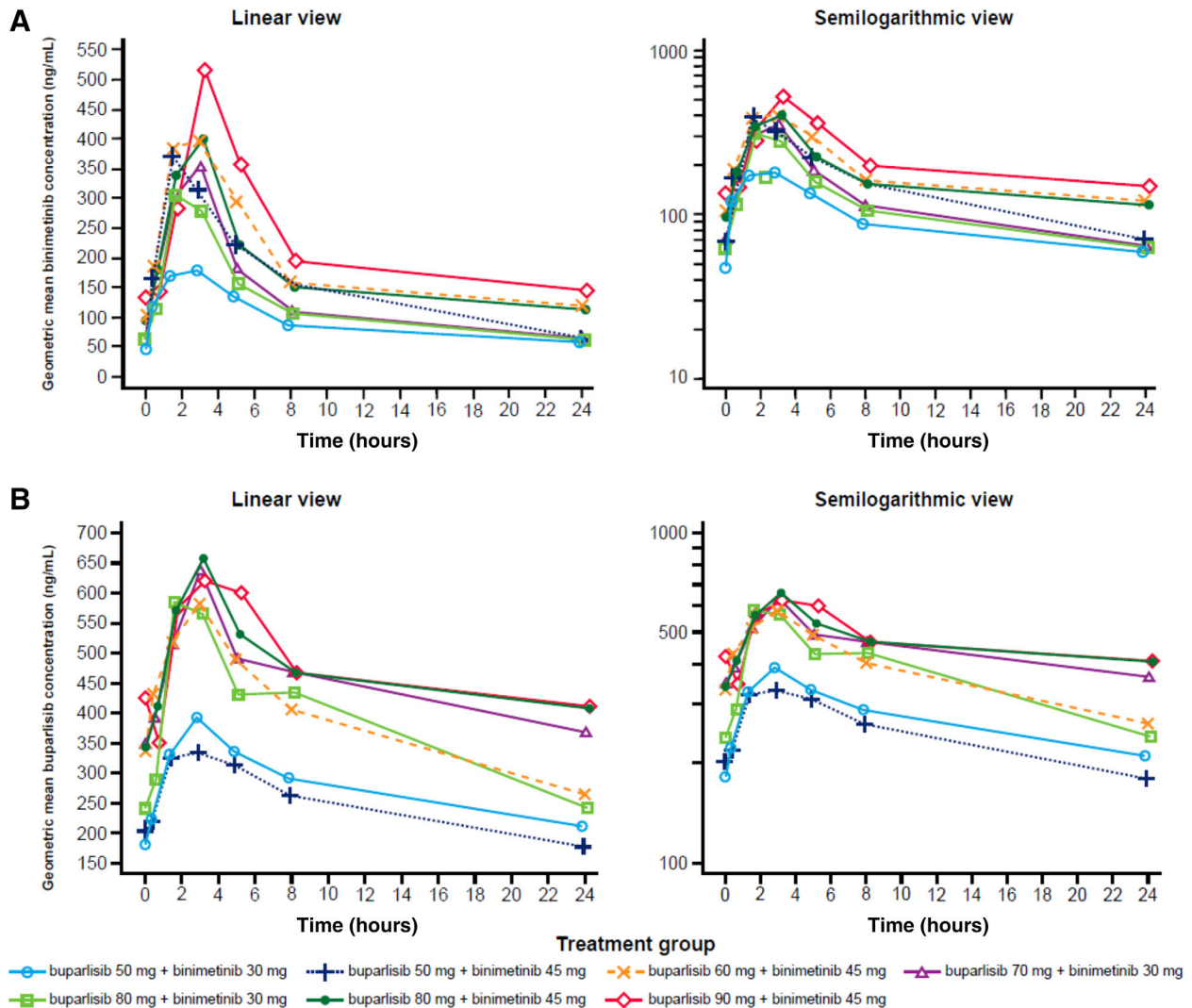


Figure 2. Geometric mean plasma concentration-time profiles after repetitive (Day 15) daily combination doses of buparlisib and binimetinib by treatment group. **(A):** Binimetinib. **(B):** Buparlisib. “tau” represents the dosing interval; tau = 12 hours for binimetinib, tau = 24 hours for buparlisib.

postbaseline pairs for pS6 analysis) showed that inhibition of MAPK and PI3K signaling by combination therapy resulted in downregulation of pERK and pS6 (Fig. 3). At the RP2D dose combination, median cytoplasmic pERK H-score at baseline and postbaseline was 210 (range, 0–300) and 190 (range, 60–300), respectively; the median nuclear pERK H-score at baseline and postbaseline was 180 (range, 0–300) and 160 (range, 0–300). Median cytoplasmic pS6 (Ser235 and Ser240) H-score at baseline and postbaseline was 120 (range, 3–280) and 110 (range, 9–140). H-score could not be analyzed for nuclear pS6 levels.

DISCUSSION

In this study, we show that buparlisib, an oral pan-PI3K inhibitor, and binimetinib, an oral MEK1/2 inhibitor, have overlapping toxicities when given in combination; the RP2D of this combination is lower than the MTD for single-agent buparlisib (100 mg/day) and binimetinib (60 mg b.i.d.) [17, 20, 22]. Although the pharmacokinetics of binimetinib are comparable to those observed in a single-agent phase I

study, the peak concentration of buparlisib and exposure at steady state were lower than expected from single-agent data [17]. Despite the lower exposures of buparlisib, there was significant interpatient variability, and a significant proportion of patients required dose reductions and treatment discontinuation even at the RP2D.

In terms of efficacy, the most striking responses were seen in *KRAS/NRAS/BRAF*-mutant ovarian cancer, where standard therapies are ineffective [26]. In contrast, a phase II study of single-agent selumetinib reported a 15% response rate irrespective of *BRAF* or *KRAS* status [26]. The doubling of response rates seen in our study was similarly observed in a previous MEK-PI3K trial [11], thereby lending support to a combination strategy. A phase III study (MILO; NCT01849874) of single-agent binimetinib compared with standard chemotherapy in genomically unselected patients with low-grade serous (LGS) ovarian cancer failed to meet its futility endpoint [27]. Based on findings from our study, further exploration of combination therapy in this patient population with selected genomic alterations is warranted.

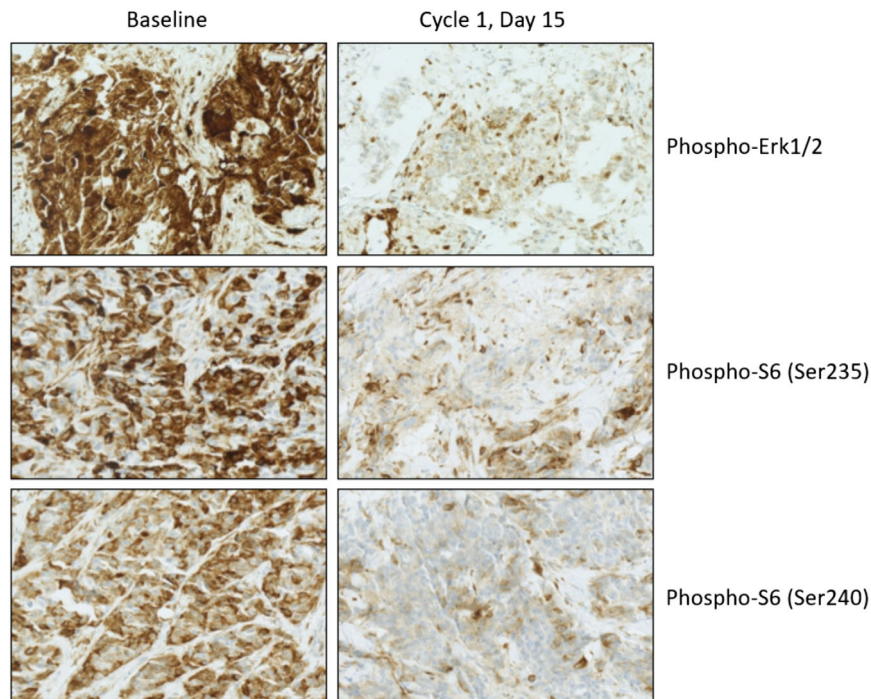


Figure 3. Immunohistochemical staining on pre- and postbaseline tumor biopsies (representative images shown at $\times 25$ magnification).

Although dual PI3K and MAPK pathway inhibition has strong preclinical rationale across a range of cancer types, the efficacy of the combination was not as robust in the clinic, perhaps with the exception of ovarian cancer (PR in 5/18 [27.8%] patients treated at RP2D). Several factors should be considered. First, toxicities from the combination resulted in frequent dose reductions, and the consequent suboptimal pathway modulation likely contributed to reduced efficacy. Second, although tumors may share common driver alterations, coexisting mutations and their genomic context—whether truncal, shared, or private—may explain the significant differences in responses between the cancers. In support, whole exome sequencing of LGS has shown a high prevalence of activating mutations in the MAPK pathway ($\sim 70\%$) with few “passenger” mutations likely explaining the sensitivity of this histology to combination strategy [28]. Dual inhibition of PI3K and MEK in colon cancer cell lines demonstrated antitumor activity except in those harboring *TP53* gene mutations [29]. In targeting PI3K- and MAPK-mutant pathways, the impact of “passenger” mutations needs further elucidation. Third, beyond genomic alterations, the dependency of a tumor on a particular pathway can be mediated by epigenetic factors that dictate therapeutic vulnerabilities, requiring different doses of targeted therapy to achieve sufficient pathway inhibition. This was previously illustrated in a histology-independent, *BRAF V600E*-mutant basket study with vemurafenib that showed differential activities between histologies [30].

In this study, toxicity with the combination generally required dose reduction of both agents, and many patients discontinued because of intolerable toxicities. Data from other phase Ib studies have suggested that long-term tolerability of the combination at RP2D is challenging [11, 31] and that overlapping toxicities of rash, diarrhea, and fatigue

limits the ability to dose both agents continuously [22, 32]. Pharmacodynamic studies in *BRAF*-mutant melanoma indicate that profound ($>80\%$) inhibition of the pathway is required for clinical responses [33]. In this study, RP2D patient biopsies at baseline and after treatment (Day 15) demonstrated median pERK H-score (cytoplasm) of 210 (range, 0–300) and 190 (range, 60–300), respectively; median pERK H-score (nucleus) of 180 (range, 0–300) and 160 (range, 0–300); and median pS6 (Ser235 and Ser240) H-score (cytoplasm) of 120 (range, 3–280) and 110 (range, 9–140). This shows that with continuous dosing, the downstream targets of MAPK and PI3K pathway are not adequately inhibited at the Day 15 time point, likely because of early and acquired compensatory resistance. Furthermore, we found elevated ERK signaling after treatment, which can paradoxically have antiproliferative effects [34].

A potential way of overcoming toxicities while achieving adequate PD inhibition is to evaluate alternate schedules and doses. MEK inhibitors are limited by a narrow therapeutic index and accumulative toxicities. Pulsatile dosing of buparlisib and/or binimetinib may overcome issues related to toxicities [35]. This strategy was successfully used in the combination study of selumetinib, a MEK inhibitor, with MK-2206, an AKT inhibitor, where pulsatile dosing was better tolerated than a continuous dosing schedule [36]. The advantage of pulsatile dosing may not only mitigate toxicities but also delay resistance (acquired mutations or receptor upregulations) [37–39]. To the best of our knowledge, clinical trials have not formally evaluated the PK/PD relationship of pulsatile dosing strategies, where the degree of PD inhibition at early time points (24–72 hours after dosing) would be critical. Based on our findings, we advocate clinical trial designs in which either one or both drugs are administered at or above the established MTD in a pulsatile

fashion [40] to induce tumor regression and mitigate toxicities.

This study further expands the “basket” concept from selection based on a single genomic mutation (e.g., *BRAF* V600E) to selection based on multiple genomic alterations that converge on a common pathway. It should be noted that tissue type and quality are important for these genomic studies, as highlighted by the BELLE-2 trial of buparlisib plus fulvestrant that showed that *PIK3CA* mutations in circulating tumor DNA, but not tissue specimens, may help select patients who could benefit from PI3K-inhibitor therapy [23]. Moving forward, comprehensive molecular profiling of fresh tissue or liquid biopsies might be important for matching patients with rational combinations of targeted drugs and may address some of the challenges associated with biomarker development.

Limitations

The study limitations include the relatively small number of patients in each tumor group of the expansion phase and the limited number of tumor samples available for PD analyses.

CONCLUSION

The toxicity profile of the combination regimen evaluated in this study resulted in a lower dose intensity than anticipated. However, an encouraging signal was observed in patients with ovarian cancer. Based on these data, further exploration of this combination may be warranted to define a better-tolerated dose and/or schedule, such as alternative scheduling with noncontinuous/pulsatile dosing of either agent, which could be explored further in *RAS/BRAF*-mutant tumors.

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Erasmus Medical Center Cancer Center, Erasmus Medical Center, Rotterdam, The Netherlands.

AUTHOR CONTRIBUTIONS

Conception/design: Novartis Pharmaceuticals Corporation

Provision of study material or patients: Aditya Bardia, Mrinal Gounder, Jordi Rodon, Filip Janku, Martijn P. Lolkema, Joe J. Stephenson, Philippe L. Bedard, Martin Schuler, Cristiana Sessa, Patricia LoRusso, Michael Thomas, Heiko Maacke, Helen Evans, Yongjian Sun, Daniel S.W. Tan

Collection and/or assembly of data: Aditya Bardia, Mrinal Gounder, Jordi Rodon, Filip Janku, Martijn P. Lolkema, Joe J. Stephenson, Philippe L. Bedard, Martin Schuler, Cristiana Sessa, Patricia LoRusso, Michael Thomas, Heiko Maacke, Helen Evans, Yongjian Sun, Daniel S.W. Tan

Data analysis and interpretation: Aditya Bardia, Mrinal Gounder, Jordi Rodon, Filip Janku, Martijn P. Lolkema, Joe J. Stephenson, Philippe L. Bedard, Martin Schuler, Cristiana Sessa, Patricia LoRusso, Michael Thomas, Heiko Maacke, Helen Evans, Yongjian Sun, Daniel S.W. Tan

Manuscript writing: Aditya Bardia, Mrinal Gounder, Jordi Rodon, Martijn P. Lolkema, Joe J. Stephenson, Philippe L. Bedard, Martin Schuler, Cristiana Sessa, Patricia LoRusso, Michael Thomas, Heiko Maacke, Helen Evans, Yongjian Sun, Daniel S.W. Tan

Final approval of manuscript: Aditya Bardia, Mrinal Gounder, Jordi Rodon, Filip Janku, Martijn P. Lolkema, Joe J. Stephenson, Philippe L. Bedard, Martin Schuler, Cristiana Sessa, Patricia LoRusso, Michael Thomas, Heiko Maacke, Helen Evans, Yongjian Sun, Daniel S.W. Tan

DISCLOSURES

Aditya Bardia: Novartis, Pfizer, Genentech/Roche, Radius Health, Merck, Spectrum Pharmaceuticals, Immunomedics, Daiichi, Sanofi (C/A), Biotheranostics (RF); **Mrinal Gounder:** Amgen, Daiichi Sankyo, Karyopharm Therapeutics, TRACON Pharmaceuticals, Epizyme (H); Amgen, Daiichi Sankyo, Karyopharm Therapeutics; Epizyme (C/A); Amgen (speaker’s bureau); Amgen, Daiichi Sankyo, Karyopharm Therapeutics, Epizyme (travel); **Jordi Rodon:** GlaxoSmithKline (H), Novartis, Eli Lilly, Orion Pharmaceuticals, Servier Pharmaceuticals, Peptomyc, Merck Sharp & Dohme, Kelun Pharmaceutical/Klus Pharma, Spectrum Pharmaceuticals Inc, Pfizer, Roche Pharmaceuticals, Ellipses Pharma (C/A, travel), Bayer, Novartis, Spectrum Pharmaceuticals, Tocagen, Symphogen, BioAtla, Pfizer, GenMab, CytomX, KELUN-BIOTECH, Takeda-Millennium, GlaxoSmithKline, Ipsen (RF), Ellipses Pharma (SAB); **Filip Janku:** Novartis, Genentech, BioMed Valley Discoveries, Astellas, Agios, Plexxikon, Deciphera, Piquor, Symphogen, Bristol-Myers Squibb, Asana, Upsher-Smith Laboratories (RF), Guardant Health, IFM Therapeutics, Synlogic, Deciphera (SAB), Trovogene, Immunomet (C/A), Trovogene (OI); **Martijn P. Lolkema:** Novartis Pharmaceuticals (C/A); **Philippe L. Bedard:** Bristol-Myers Squibb, Roche/Genentech, Sanofi, Pfizer (C/A), Bristol-Myers Squibb, Roche/Genentech, Novartis, Servier, Nektar, Oncothyreon, Seattle Genetics, Eli Lilly, Sanofi, Merck, AstraZeneca, GlaxoSmithKline, PTC Therapeutics, Mersana, Zymeworks (RF); **Martin Schuler:** Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, Roche (C/A); AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis (RF); **Patricia LoRusso:** Agenus, Agios, Cybrexa, CytomX, FivePrime, Genentech, Halozyne (SAB), Roche-Genentech, imCORE Alliance, Sotio (C/A); **Heiko Maacke:** Novartis (E, OI); **Helen Evans:** Novartis (E, OI); **Daniel S.W. Tan:** Merck, Pfizer, Novartis, Boehringer Ingelheim, Roche, Takeda (H), Novartis, Bayer, Boehringer Ingelheim, Celgene, Astra Zeneca, Eli-lilly, Loxo (C/A), Novartis, Astra Zeneca, GlaxoSmithKline, Bayer, Pfizer (RF). The other authors indicated no financial relationships.

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