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PHASE I STUDIES

A phase 1b dose expansion study of the pan-class I PI3K inhibitor buparlisib (BKM120) plus carboplatin and paclitaxel in PTEN deficient tumors and with dose intensified carboplatin and paclitaxel

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Summary *Purpose* We previously reported the phase I dose escalation study of buparlisib, a pan-class 1A PI3K inhibitor, combined with platinum/taxane-based chemotherapy in patients with advanced solid tumors. The combination was well tolerated and promising preliminary efficacy was observed in PTEN deficient tumors. This phase I dose expansion study now evaluates buparlisib plus high dose carboplatin and paclitaxel in unselected patients with advanced solid tumors and buparlisib plus standard dose carboplatin and paclitaxel in patients with PTEN deficient tumors (ClinicalTrials.gov, NCT01297452). *Methods* There were two expansion cohorts: Cohort A received continuous buparlisib (100 mg/daily) orally plus high dose carboplatin AUC 6 and paclitaxel 200 mg/m2; Cohort B treated patients with PTEN deficient tumors only and they received the recommended phase II dose (RP2D) of continuous buparlisib (100 mg/daily) orally plus standard dose carboplatin AUC 5 and paclitaxel 175 mg/m2. Both cohorts received chemotherapy intravenously on day 1 of the 21-day cycle with pegfilgrastim support. Primary endpoint in Cohort A was to evaluate the safety and tolerability of chemotherapy dose intensification with buparlisib and in Cohort B was to describe preliminary efficacy of the combination among patients with tumors harboring a PTEN mutation or homozygous deletion. *Results* 14 subjects were enrolled, 7 in Cohort A and 7 in Cohort B. Dose reductions were required in 5 (71%) and 3 (43%) patients, in cohort A and B respectively. Grade 3 adverse events in Cohort A included lymphopenia (n = 5 [71%]), hyperglycemia (n = 2, [29%]), diarrhea (n = 2, [29%]) and rash (n = 2, [29%]) and in cohort B included lymphopenia (n = 5 [71%]), hyperglycemia (n = 4 [57%]) and neutropenia (n = 2 [29%]. The mean number of cycles on protocol was 6. The overall objective response rate was 14% (2 /14). No objective responses were observed in the PTEN deficient cohort. Four out of 6 patients with stable disease (SD) had SD or better for ≥6 cycles, 2 of which had PTEN deficient tumors. *Conclusion* The addition of buparlisib to high dose carboplatin and paclitaxel was not tolerable. The combination did not reveal significant clinical activity amongst a small and heterogenous group of PTEN deficient tumors,

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Introduction

Phosphatidylinositol-3-kinase (PI3K)–AKT pathway activation is a well-known initiator of tumor development in a range of malignancies and can occur due to somatic mutations in the gene encoding the catalytic subunit of PI3K (*PIK3CA*), activation of receptor tyrosine kinases upstream of PI3K, mutations in Akt or other downstream signaling molecules or through loss or inactivation of the PTEN (phosphatase and tensin homologue) tumor suppressor gene (a negative regulator of the pathway) [1–4]. PTEN also has a nuclear role in promoting chromosome stability and DNA repair and therefore, loss of PTEN function increases genomic instability [5–7]. PTEN deficiency is a frequent event in many cancer subtypes and offers a potential therapeutic target [5, 8]. In fact, inhibitors of various nodes of the PI3K-AKT pathway are now in active development.

Buparlisib (BKM120) is an oral pure and potent pan-class I (p110α, β, γ, and δ) PI3K inhibitor with modest single agent activity [9–13]. Preclinical data have shown that as a class, PI3K inhibitors can enhance the antitumor activity of cytotoxic chemotherapy and combinatorial strategies with buparlisib are being explored with preliminary signs of clinical activity [14–17]. We previously reported a single-center dose escalation study (*n = 30)* of daily buparlisib combined with two parallel schedules of carboplatin (AUC 5) and paclitaxel (175 mg/m2 on day 1 with pegfilgrastim support or 80 mg/m2 on day 1, 8, and 15 without pegfilgrastim support) of an every 3 (q3) or q4 week cycle, respectively. We established the MTD/ recommended phase II dose (RP2D) for the combination and reported that the addition of buparlisib to q3 weeks carboplatin (AUC 5) and paclitaxel (175 mg/m2) was well tolerated and permitted full dosing of buparlisib (100 mg/daily) compared with the alternate q4 weeks carboplatin (AUC 5) and paclitaxel schedule of 80 mg/m2 (days 1, 8, and 15) that limited buparlisib escalation to 80 mg/day [18]. Additive clinically significant myelosuppressive effects were not seen with the q3 weeks combination. In view of the favorable safety profile seen with the combination in the q3 week schedule, we sought to explore a higher dose of this regimen in an expansion cohort. Notably, we also observed in the dose escalation study, promising activity against tumors with loss of PTEN expression [18]. An observation with some mechanistic rationale, given PTEN deficient tumors are dependent on p110β PI3K signaling and buparlisib having activity against this isoform, is potentially desirable for these tumors [19, 20]. Indeed pre-clinical studies have shown synergistic lethality with the combination of buparlisib and platinum-based chemotherapy in PTEN deficient xenografts [21]. Moreover, all 3 patients with *PTEN* loss (IHC score = 0) in the dose escalation study, had objective radiographic tumor reductions or clinical benefit, 2 of which were prolonged [18].

Here, we report two dose expansion cohorts of this Phase Ib trial; cohort A evaluating buparlisib (100 mg/daily) plus higher dose carboplatin (AUC 6) and paclitaxel (200 mg/m2) q3 weeks and cohort B evaluating the RP2D for the combination [buparlisib (100 mg/daily) plus standard dose carboplatin (AUC 5) and paclitaxel (175 mg/m2)] q3 weeks in PTEN deficient tumors only. The primary aim was to evaluate the safety and tolerability of chemotherapy dose intensification with buparlisib and to describe preliminary efficacy of the combination in patients with PTEN deficient tumors. We also present pharmacodynamic biomarker data for the higher dose chemotherapy cohort (cohort A).

Materials and methods

This study was approved by the institutional review board at Memorial Sloan Kettering Cancer Center and registered with the National Cancer Institute, ClinicalTrials.gov, NCT01297452.

Patient eligibility

Eligibility was based on the following criteria: histologically confirmed advanced solid tumor considered incurable with standard therapy (with PTEN mutation or homozygous deletion required for cohort B enrollment), performance status of ECOG ≤1, ≥ than 18 years old, life expectancy ≥3 months, adequate electrolyte, organ function and hematologic parameters and ≤2 prior chemotherapy regimens for metastatic disease (with ≤1prior chemotherapies required for cohort A enrollment).

Exclusion criteria included prior treatment with a PI3K inhibitor, untreated brain metastases, history of major depressive episode or other significant psychiatric history, mood rating score of ≥10 on PHQ-9[22] and/or ≥15 of GAD-7 [23], uncontrolled diabetes, ≥grade 2 diarrhea, prior whole pelvic radiation therapy, current use of strong inhibitors or inducers of CYP3A or QT-prolonging medications, or any uncontrolled medical conditions that could compromise participation in the study.

Study design and treatment

This was a Phase I, single-center, open-label study, which consisted of two parts: a dose-escalation part (previously reported) [18] and a dose-expansion part (presented here) with a planned enrollment of up to 6 patients in Cohort A and up to 10 patients in Cohort B.

All patients received buparlisib 100 mg/day orally continuously. Cohort A received carboplatin AUC 6 and paclitaxel 200 mg/m2 intravenously on day 1 of the 21-day cycle. Cohort B (PTEN deficient tumors) received carboplatin AUC 5 and paclitaxel 175 mg/m2 intravenously on day 1 of the 21-day cycle. Both cohorts received mandatory pegfilgrastim support subcutaneously 24–48 h following chemotherapy due to anticipated neutropenia. Premedication regimens followed standard institutional guidelines with the exclusion of aprepitant and cimetidine due to their moderate CYP3A4 inhibition and with tapering of dexamethasone permitted at the discretion of the investigator. The premedication dose of dexamethasone administered ranged between 10 mg and 20 mg IV.

Patients in both cohorts were evaluated by the physician in clinic and completed the patient self-rating mood questionnaires PHQ-9 (depression) and GAD-7 (anxiety) on days 1, 8, and 15 of cycle 1 and at the start of each subsequent cycle, with additional visits as clinically indicated. Symptomatic patients (≥ Grade 1 anxiety/depression) continued with questionnaires on a weekly basis until resolution to grade 0. Labs including a complete blood count (CBC), comprehensive metabolic panel COMP) and lipid panel were obtained on Day 1 of every cycle. In cohort A, research bloods for pharmacokinetics were also drawn on Day 1 and Day 8 of Cycle 1 only.

Patients who remained on study after cycle 6 had the option to continue on protocol with buparlisib monotherapy until progression of disease or unacceptable toxicity. For patients who continued on buparlisib monotherapy after cycle 6 at a dose of <100 mg/day, it was allowable to increase to buparlisib 100 mg/day, per investigator discretion and patient preference. AEs were assessed using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Restaging imaging studies were obtained every 6 weeks for the first 6 cycles and every 9 weeks thereafter and response was assessed using RECIST 1.1.

Definition of a dose-limiting toxicity (DLT) for cohort a

DLTs were monitored per protocol in Cohort A only, during cycle 1. As previously described, [18] a DLT was defined as any toxicity resulting in a treatment delay of >7 days in cycle 1, or any toxicities of grade 3 or higher (NCI Common Toxicity Criteria version 4) felt to be at least possibly related to buparlisib. Protocol-specified exceptions to this DLT definition included grade 3 hypomagnesemia, hypokalemia, or hypocalcemia if corrected within 24 h; grade 3 diarrhea lasting ≤48 h; grade 3 fatigue, nausea, vomiting, or uncomplicated hyperglycemia if resolved within 72 h; or grade 3 lymphopenia. Grade 3 hypersensitivity reaction to any of the study drugs was not deemed a DLT, given such events are not strictly dose related. Uncomplicated grade 3 or 4 neutropenia lasting ≤7 days or uncomplicated grade 3 thrombocytopenia lasting ≤7 days were also not considered DLTs.

Dose reductions

Hematologic toxicities required dose reductions for carboplatin, paclitaxel and BKM120. Hepatic toxicity or neurotoxicity required dose reductions for paclitaxel and BKM120. The dose reduction schema for each cohort is summarized in Supplementary Table 1, below.

Biomarker and pharmacodynamic assessments

Enrollment in cohort B required a documented genetic alteration (inactivating mutation or homozygous deletion) in the PTEN gene identified by the clinically validated, custom hybrid capture targeted next generation sequencing (NGS) assay, MSK-IMPACT, using methods previous described [24].

Archival formalin-fixed paraffin-embedded (FFPE) tumor specimens were collected from patients in cohort A (where available) and subjected to mass spectrometry genotyping using the iPLEX system (Sequenom, San Diego, CA) using a multiplexed system for genotyping *PIK3CA*, *AKT1*, *KRAS*, *NRAS*, and *BRAF* [25–27]. For patients in cohort A and B, tumor PTEN expression was scored as 0, 1+, or 2+, according to previously described immunohistochemistry (IHC) methods (Dako, clone 6H2.1) [28]. For Cohort A only, to characterize the drug elimination phase, plasma levels of buparlisib were determined from samples collected at the following time points on cycle 1/day 1: 0, 15, 30, and 60 min; 2, 3, 4.5, 6, and 8 h. On cycle 1/ day 8, an additional PK blood sample was collected prior to treatment with buparlisib. Day 8, 0 h was considered as 168-h post-dose to perform the PK analysis for AUC0–168 h. The area under the curve ($AUC_{0\rightarrow\infty}$), half-life (t½), and maximum concentration (Cmax) for buparlisib were determined by noncompartmental analysis, as previously described [11, 18].

Statistical considerations

The statistical design for Cohort A, was that following initial enrollment of 3 patients. If ≤1/3 patients experienced a DLT, up to 3 additional patients were enrolled and treated at the same dose level. If >1/3 or >1/6 patients experienced DLT, the regimen would be deemed inappropriate for further study.

No formal analysis of response rate was planned in this phase I study due to the small sample. As such, radiographic response data were tabulated and presented in descriptive form. The preliminary assessment of efficacy in Cohort B was descriptive, and for the purposes of hypothesis generation.

Results

Patient population

Between May 2013 and October 2015, 14 patients were enrolled on the dose expansion protocol, 7 patients in Cohort A and 7 in Cohort B. (Table 1, below).

Toxicity

Dose limiting toxicities of grade 3 rash requiring holding of drug for greater than 7 days during cycle 1 occurred in 2 patients in Cohort A. All toxicities are summarized in Table 2, below. The most common adverse events in cohort A were hyperglycemia (n = 7 [100%]), anemia (n = 7 [100%]), sensory neuropathy (n = 6 [86%]), rash (n = 6 [86%]) and diarrhea (n = 6[86%]) and in cohort B were hyperglycemia (n = 7 [100%]), fatigue (n = 7 [100%]) and anemia (n = 6 [86%]).

Table 1 Patient characteristics, n = 14

	N (number of patients)
Evaluable Patients	14
Toxicity only	5
Toxicity and response	9
Gender	
Male	2
Female	12
Age (at consent)	
Median	59
Range	41–76
ECOG PS (pre-treatment)	
0	5
1	9
Tumor type	
Gynecologic	5
Ovarian (HG Serous)	1
Endometrial (LG Adenocarcinoma)	3
Endometrial (Papillary Serous)	1
Head and neck	6
Thyroid (Anaplastic or poorly differentiated)	3
Squamous Cell Carcinoma	2
Adenocarcinoma	1
Sarcoma	2
Prostate	1
Visceral Metastases	7
Number of prior systemic therapies (metastatic)	
0	5
1	3
≥ 2	6
Received prior RT	9
Number of cycles on protocol	
Mean	6
Median	3

Table 2 Adverse events regardless of attribution occurring in ≥33% of subjects at any grade, or ≥Grade 3 in two or more subjects, in Cohort A or B

Adverse event	Any grade [n (%)]	≥Grade 3 [n (%)]
Cohort A (n = 7)		
Anemia	7 (100%)	
Hyperglycemia	7 (100%)	2 (29%)
Neuropathy, sensory	6 (86%)	
Diarrhea	6 (86%)	2 (29%)
Hypertension	6 (86%)	
Rash maculo-papular	6 (86%)	2 (29%)
Nausea	5 (71%)	
Hypercholesterolemia	5 (71%)	
Alkaline phosphatase increased	5 (71%)	
Lymphopenia	5 (71%)	5 (71%)
Thrombocytopenia	5 (71%)	
Constipation	4 (57%)	
Fatigue	4 (57%)	
Hypokalemia	4 (57%)	
Hypomagnesemia	4 (57%)	
Hyponatremia	4 (57%)	
Abdominal pain	3 (43%)	
Dysgeusia	3 (43%)	
Headache	3 (43%)	
Myalgia	3 (43%)	
Pruritus	3 (43%)	
ALT and/or AST elevation	3 (43%)	
Hypoalbuminemia	3 (43%)	
Adverse event	Any grade [n (%)]	≥Grade 3 [n (%)]
Cohort B (n = 7)		
Fatigue	7 (100%)	
Hyperglycemia	7 (100%)	4 (57%)
Anemia	6 (86%)	
Lymphopenia	5 (71%)	5 (71%)
Hyponatremia	5 (71%)	
Hypoalbumenia	5 (71%)	
Hypertension	4 (57%)	
Nausea	4 (57%)	
Alkaline phosphatase increased	4 (57%)	
Hypomagnesemia	4 (57%)	
Thrombocytopenia	4 (57%)	
Alopecia	3 (43%)	
Anorexia	3 (43%)	
Cough	3 (43%)	
Dizziness	3 (43%)	
Rash maculo-papular	3 43%)	
Leukopenia	3 (43%)	
Neutropenia		2 (29%)

Table 3 Summary of dose reductions in cohort A: Buparlisib 100 mg/day + Carbo (AUC 6) + Paclitaxel (200 mg/m2)

Buparlisib (mg/day)	Paclitaxel dose (mg/m^2)	Carboplatin Dose	Tumor type	Age (yr) at treatment start	Gender	Dose reduction description	Timing of dose reduction
100 mg	175	AUC 5	Ovarian	59	F	G2 Neuropathy	Cycle 3
80 mg	175	AUC 5				G2 Maculo-papular Rash	Cycle 5
60 mg	-	-				G2 Maculo-papular Rash	Cycle 7
80 mg	200	AUC 6	Endometrial	64	F	G2 Increased ALT	Cycle 2
60 mg	200	AUC 6				G3 Maculo-papular Rash	Cycle 6
100 mg	175	AUC 5	Thyroid	60	F	G2 Fatigue	Cycle 2
100 mg	175	AUC 5	Thyroid	62	F	G1 Neuropathy	Cycle 3
100 mg	160	AUC 6	HEENT	60	F	G2 Neuropathy	Cycle 6

Grade 3 or higher adverse events in Cohort A included lymphopenia (n = 5 [71%]), hyperglycemia (n = 2, [29%]), diarrhea (n = 2, [29%]) and rash (n = 2, [29%]) and in cohort B included lymphopenia (n = 5 [71%]), hyperglycemia (n = 4 [57%]) and neutropenia (n = 2 [29%]. Of note, the incidence of febrile neutropenia was 0% and there were no treatment-related deaths.

Treatment exposure

Dose reductions were required in 5 (71%) and 3 (43%) of patients in Cohort A and B respectively, none of which occurred during the first cycle of therapy. All dose reductions are detailed in Tables 3 and 4, below. The mean number of cycles on protocol was 6 (Table 1, below).

Pharmacokinetics

Plasma exposure (AUC0–8 h) and mean concentration–time profiles in cohort A were slightly higher, but still largely comparable with those observed in the dose escalation study (Table 5, below) [18].

Clinical efficacy

Nine of 14 patients who had measurable disease at baseline were evaluable for response. Five patients were not evaluable for response assessment due to the following events that occurred during cycle 1: hypersensitivity reaction to buparlisib (n = 1) and clinical progression prior to completion of response period/first scan (n = 4). Among 14 patients with measureable disease who received any treatment on study, the confirmed objective response rate was 14% (2 /14).

Best responses among patients measureable by RECIST criteria (n = 9), were complete response (CR) (n = 1), partial response (PR) (n = 1), stable disease (SD) (n = 6) and progression of disease (PD) (n = 1), (Table 6, below). Four out of 6 patients with SD by RECIST criteria had SD or better for ≥6 cycles, 2 of which were seen in the PTEN deficient cohort B (Table 6, B5 and B6).

Table 4 Summary of dose reductions in cohort B: Buparlisib 100 mg/day + Carbo (AUC 5) + Paclitaxel (175 mg/m2)

Buparlisib (mg/day)	Paclitaxel dose (mg/m^2)	Carboplatin Dose	Tumor type	Age (years) at treatment start	Gender	Dose reduction description	Timing of Dose reduction
80 mg	175	AUC 5	Endometrial	62	F	Intolerable G2 Fatigue	Cycle 1
80 mg	140	AUC 4				Intolerable G2 Fatigue, G3 nausea	Cycle 2
80 mg	140	Discontinued				G4 Carboplatin hypersensitivity	Cycle 3
60 mg	On Buparlisib only					Intolerable G1 Fatigue	Cycle 8
80 mg	175	AUC 5	Endometrial	65	F	G2 Mood disorder	Cycle 1
80 mg	175	Discontinued				G2 Carboplatin hypersensitivity	Cycle 4
100 mg	140	AUC 4	Endometrial	57	F	G3 Thrombocytopenia	Cycle 3
100 mg	140	Discontinued				G2 Carboplatin hypersensitivity	Cycle 6

Table 5 Mean pharmacokinetic parameters in Cohort A

Dose level	*T*max (h)	*C*max (ng/mL)	AUC0–8 h (h × ng/mL)
100 mg Buparlisib	2.29	1102.43	2288.14
SD	0.95	388.99	890.22

AUC area under the plasma concentration time curve, Cmax maximum concentration, Gp group, SD standard deviation, Tmax time of occurrence of Cmax

Correlative studies

Results of the molecular analysis of tumor samples obtained at baseline are also summarized in Table 6, below. Genomic analysis was performed in 11 of 14 patients, by MSK-IMPACT, $n = 9$; Sequenom, $n = 1$; and Foundation one, $n = 1$. PTEN IHC analysis was performed in 11 of 14 patients.

In the PTEN deficient cohort B ($n = 7$), 5 had PTEN IHC analysis, 3 of whom were also found to have PTEN loss by IHC (score = 0). One of these 3 patients experienced stable disease control for almost 9 months.

In cohort A ($n = 7$), 2 patients were found to have a PTEN alteration by NGS and 1 other patient had PTEN loss by IHC.

Overall, 6 patients found to have a PTEN alterations by NGS, were evaluable for response ($n = 2$ from cohort A and $n = 4$ from cohort B), 5 of whom had stable disease as their best response on study.

Discussion

This phase 1 expansion trial firstly aimed to determine if chemotherapy dose intensification combined with buparlisib was tolerable and safe. Given, DLT's were observed in 2 patients and dose reductions were required in the majority (5/7, 71%) of patients enrolled in the high dose cohort (A), we conclude that high dose chemotherapy is not a feasible or safe combination therapy with buparlisib. Secondly, based upon a strong preclinical rationale and initial observations in the dose escalation portion of our study, we aimed in the second expansion cohort (B) reported here, to evaluate preliminary efficacy of the combination in patients with PTEN deficient tumors. We observed disease stability in 3 of 4 evaluable patients in this cohort, 2 of which lasted in excess of 6 months. Thirdly, we performed correlative studies evaluating tumor PTEN status at both a genomic and protein level in patients in both cohorts. As a result of which we identified 2 additional patients among cohort A to have PTEN mutations, one of whom achieved a partial response lasting 11 months and the second experiencing a minor response but who withdrew consent after 2 cycles, declining

Table 6 Best response and Tumor molecular analysis in cohort A and B

Cohort, pt. no.	Tumor type	PTEN alteration	PTEN IHC	PIK3CA alteration	RAS alteration	Best response	Cycles
A1	Anaplastic thyroid cancer	No	+2	PIK3CA E545K,	NRAS Q61R	N/E	0.5
A2	Ovarian	PTEN Deletion (Fold Change: −3.8)	+2	No	No	PR	16.4
A3	Anaplastic thyroid cancer	No	+2	No	KRAS -Q61R	SD	6.0
A4	Poorly differentiated thyroid cancer	PTEN K144*	N/A	No	No	SD	2.3
A5	Endometrial (Serous)	N/A	+1	N/A	N/A	CR	7.4
A6	Chondrosarcoma	N/A	0	N/A	N/A	N/E	1.2
A7	Head &Neck (HN) Adenocarcinoma (Maxillary sinus)	N/A	+1	N/A	N/A	SD	12.8
B1	Prostate	PTEN Intragenic deletion	0	No	No	N/E	0.1
B2	HN Squamous Cell Carcinoma (SCC) (Hypopharyngeal)	PTEN Deletion (Fold Change: −2.3)	+2	No	No	N/E	1.3
B3	HN SCC (unknown site)	PTEN - Intragenic deletion	N/A	No	No	N/E	0.8
B4	Uterine Sarcoma	PTEN - Intragenic deletion	0	No	No	PD	2.0
B5	Endometrial	PTEN N292 fsPTEN R130G	+1	No	No	SD	8.5
B6	Endometrial	PTEN R130G	N/A	No	No	SD	4.3
B7	Endometrial	PTEN I168fs	0	PIK3CA - K111E, PIK3CA - P449R	KRAS -G12A	SD	13.3

*NE, Not Evaluable, NA, Not available

further therapy and ultimately succumbing to her illness 8 months later. Taken together 5 out of 6 evaluable patients with a PTEN tumor alteration in this study had stable disease or better on combination chemotherapy and buparlisib. It is worth noting that in our 1 patient who achieved a complete response and remained on study for 5 months before coming off for toxicity and who ultimately did not develop progression of her disease until 20 months after beginning study therapy, tumor tissue was unfortunately unavailable for genomic testing to further understand the genomic basis of this response. Interestingly, among the 6 patients with an inactivating PTEN mutation who also had PTEN IHC testing, only 3 showed loss of the PTEN protein by IHC.

This study highlights the challenges of identifying the clinical activity of a novel agent in a small, molecularly enriched expansion study, when combined with chemotherapy and conducted amongst a diverse patient population in terms of prior treatment exposure, tumor histology and genomics- acknowledging the impact of co-mutated genes within the tumor and both intra- and inter-tumoral heterogeneity [29, 30].

PTEN has been linked to poor outcome and therapeutic resistance in a number of cancers [5, 31–40]. Numerous ongoing clinical trials are evaluating the benefit of PI3K inhibitors in patients with tumors harboring *PIK3CA* mutations or PTEN deficiency. Certainly, the experience with PIK3CA mutation status thus far with buparlisib and letrozole has been that it does not predict for benefit, among ER+ metastatic breast cancer patients [15]. In the phase I study of buparlisib in patients with advanced solid tumors, no association between PTEN status and clinical response was seen [11]. It may be that, owing to PTEN-deficient cancers dependence on the p110β isoform of Class IA PI3K, p110β-specific inhibitors may be required to impede growth signaling in these cancers [5, 41–43]. The current report explored the possibility that PTEN-deficient tumors may be sensitive to the combination of buparlisib and platinum-based chemotherapy, as suggested by pre-clinical modeling and preliminary phase I observations [18, 21]. Poor tolerability may have limited the potential for clinical benefit with the combination regimen in this clinical experience.

Certainly in other clinical trials exploring the addition of buparlisib to chemotherapy, similar challenges have been noted. The phase II randomized study (Neophobia, NCT01816594) testing neoadjuvant Trastuzumab and paclitaxel +/− buparlisib in early-stage breast cancer patients, was stopped prematurely owing to a lack of pCR benefit and higher toxicity in the Buparlisib arm [13, 44]. Notably no additional benefit was seen in the PIK3CA mutant subgroup receiving the pan- PI3K inhibitor. In stage IV squamous non-small cell lung cancer patients, both phase Ib/II trials testing the addition of Buparlisib in the first- line setting to 3-weekly carboplatin and paclitaxel (BASALT2; NCT01820325) and in the second-line setting to 3-weekly docetaxel (BASALT-3; NCT01911325), were terminated due to the challenging safety profile and marginal anti-tumor activity observed [45]. It is worth noting that early results from the phase II randomized study (BERIL-1; NCT01852292) of weekly paclitaxel +/− Buparlisib in recurrent/metastatic HNSCC progressing after platinum-based therapy has demonstrated improved PFS and a manageable safety profile [45, 46].

In conclusion, although some activity was observed among PTEN deficient tumors, greater numbers are needed to assess whether PTEN mutation status is predictive of response to inhibitors of the PI3K pathway in combination with platinum-based chemotherapy, and motivation for further study of this combination strategy must be balanced against the observed toxicity.

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Compliance with ethical standards

Conflict of interest M.F., K.J., A.H., M.L, and M.V. have served on advisory boards and/or consulted for Novartis.

LMS: Advisory- Genentech, Research - AstraZeneca.

KJ: Consulting/Advisory - Novartis.

DH: Consulting - Chugai, CytomX, Atara, Research/Grants- AstraZeneca, PUMA, LOXO.

AH: Advisory/ Speaker- Novartis.

MV: Consulting- Novartis, Exelixis, Pfizer, Alexion, Research- BMS, Genentech.

No potential conflict of interest was disclosed by the other authors.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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