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Initial phase I safety study of gedatolisib plus cofetuzumab pelidotin for patients with metastatic triple-negative breast cancer

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Abstract

Purpose: The PI3K pathway is dysregulated in the majority of triple-negative breast cancer(TNBCs), yet single agent inhibition of PI3K has been ineffective in TNBC. PI3K inhibition leads to an immediate compensatory up-regulation of the Wnt pathway. Dual targeting of both pathways is highly synergistic against TNBC models *in vitro* and *in vivo*. We initiated a Phase I clinical trial combining gedatolisib, a pan-class I isoform PI3K/mTOR inhibitor, and cofetuzumab pelidotin, an antibody-drug conjugate against the cell-surface PTK7 protein (Wnt pathway co-receptor) with an auristatin payload.

Experimental Design: Participants(pts) had metastatic TNBC or ER low (ER and PgR<5%, HER2-negative) breast cancer, and had received at least one prior chemotherapy for advanced disease. The primary objective was safety. Secondary endpoints included objective response(ORR), clinical benefit at 18 weeks(CB_{18}), progression-free survival(PFS), and correlative analyses.

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Results: 18 pts were enrolled in 3 dose cohorts: gedatolisib 110 mg weekly + cofetuzumab pelidotin 1.4mg/kg every 3 weeks (n=4), 180mg + 1.4mg/kg (n=3), and 180mg + 2.8mg/kg (n=11). Nausea, anorexia, fatigue, and mucositis were common but rarely reached ≥Grade 3 severity. Myelosuppression was uncommon. ORR was 16.7% (3/18). An additional 3 pts had stable disease, of these 2 had stable disease for >18 weeks; CB_{18} was 27.8%. Median PFS was 2.0 months (95%CI for PFS:1.2-6.2). Pts with clinical benefit were enriched with genomic alterations in the PI3K and PTK7 pathways.

Conclusions: The combination of gedatolisib + cofetuzumab pelidotin was well tolerated and demonstrated promising clinical activity. Further investigation of this drug combination in metastatic TNBC is warranted.

Trial Registration: NCT03243331

Keywords

PI3K; PTK7; Gedatolisib; Cofetuzumab Pelidotin; Triple-negative breast cancer

INTRODUCTION

Triple-negative breast cancer (TNBC) is a heterogeneous disease that comprises a minority (15-20%) of breast cancer cases, but has a disproptionally higher mortality (1). TNBC is characterized by the absence of estrogen-receptor (ER), progesterone-receptor (PR), and human epidermal growth factor receptor 2 (HER2) over-expression (2-4). Patients with TNBC have a higher probability of relapse in the first three years after surgery, higher rates of visceral metastases, and shortened overall survival upon onset of metastatic disease when compared to hormone receptor positive and HER2-positive breast cancers(5). Despite the recent FDA approval of immune checkpoint inhibition using pembrolizumab for early-stage (6) and late-stage disease (7), cytotoxic chemotherapy remains the mainstay treatment for metastatic TNBC. Previous attempts to introduce targeted therapies in TNBC by inhibiting the EGFR and c-KIT receptors were unsuccessful(8-11). PARP inhibitors are effective, but only in the subset of patients with deleterious BRCA1/2 mutations(12,13). Sacituzumab govitecan, an antibody drug conjugate (ADC) targeting TROP2 was recently approved by the (FDA) for metastatic TNBC, based on an overall response rate (ORR) of 33.3% in a single-arm Phase II study unselected for TROP2 expression(14). These results were recently confirmed in the Phase III ASCENT study demonstrating an ORR of 35% with sacituzumab compared to 5% with single-agent chemotherapy in patients treated with two prior lines of therapy(15). Clearly there remains a critical need to identify additional novel targeted therapies for TNBC.

The majority of TNBCs (~70%) harbor a genomic aberration in the PI3K pathway(16), most commonly an activating mutation or somatic copy number change in one of the canonical components(17). Somewhat surprisingly, single-agent inhibition of PI3K has been ineffective as a treatment for TNBC(18). We have previously reported that PI3K inhibition in TNBC results in an immediate compensatory upregulation of the Wnt pathway(19). Activation of the Wnt pathway is well-known for its role in cancer metastases and confers resistance to PI3K inhibition in TNBC, pancreatic, and colorectal cell lines(20-22).

Simultaneous dual targeting of both pathways is synergistic against TNBC models *in vitro* and *in vivo*(19).

Building on our preclinical observations, we initiated a Phase I clinical trial of gedatolisib(23,24), a pan-class I isoform PI3K/mTOR inhibitor, and cofetuzumab pelidotin(25,26), an antibody-drug conjugate against the cell-surface PTK7 protein with an auristatin payload. PTK7 is a pseudo-receptor tyrosine kinase involved in non-canonical Wnt signaling that maintains developmental planar cell polarity in normal cells(27). PTK7 is over-expressed in a variety of cancers including TNBC(25), and its expression is induced by PI3K inhibition therefore providing rationale for exploring the combination of a PI3K inhibitor with a PTK7-targeting ADC in TNBC. The payload for cofetuzumab pelidotin, auristatin, is in itself synergistic with gedatolisib, providing another potential mechanism of synergy for the combination(28).

METHODS

Study population

Pts had metastatic TNBC or ER low (ER and PgR <5%, HER2 negative) breast cancer, and had received at least one prior chemotherapy for metastatic disease. Pts were excluded if previously treated with a PI3K or an mTOR inhibitor or if they had previous exposure to cofetuzumab pelidotin. Pts were required to have an ECOG PS ≤1 with adequate hematologic, hepatic, and renal function. Pts with treated and stable CNS involvement were allowed. Given the potential for hypergylcemia with gedatolisib, pts with uncontrolled diabetes were excluded.

Trial Design and Statistical analyses

This single-center, phase I dose-escalation trial utilized a traditional 3+3 schema with a small expansion cohort at the recommended phase II dose to better characterize safety (Supplementary Figure 1). The primary objective was safety as assessed by NCI CTC v4.0 criteria. Dose limiting toxicity (DLT) was defined as grade 4 neutropenia lasting ≥ 7 days; febrile neutropenia; grade 3 thrombocytopenia associated with bleeding or grade 4 thrombocytopenia lasting ≥ 4 days; any non-hematological grade 3 ≥ toxicity despite the use of adequate/maximal medical interventions and/or prophylaxis; ALT or AST > 3X upper limit of normal (ULN) and total bilirubin >2X ULN with serum alkaline phosphatase normal; any toxicity that resulted in a >14 day delay in treatment; or any death not clearly due to underlying disease or extraneous causes. Secondary endpoints included objective response rate (ORR), clinical benefit at 18 weeks (CB_{18}, prospectively defined as all pts with a complete response, partial response, or stable disease for at least 18 weeks), and progression-free survival (PFS). Exploratory analyses probed for association between genomic/pathologic features and clinical efficacy to identify putative biomarkers for consideration in subsequent trials. The Kaplan-Meier method was used to analyze for PFS and OS (with median times and 95% confidence intervals calculated) using SAS Version 9.4 (Cary, NC). The study was approved by the Institutional Review Board (IRB) at Indiana University; all pts provided written informed consent prior to study entry. This study was conducted in accordance with United States Common Rule.

Treatment plan

The recommended phase 2 dose (RP2D) and toxicity profile had been established for each agent as monotherapy. As overlapping toxicity and pharmacokinetic interactions were not expected, we planned limited dose escalation, starting with 50% of the monotherapy RP2D for each agent in cohort one. The full RP2D of each agent as monotherapy was delivered in cohort 3 (Table 1). Gedatolisib was infused first followed by cofetuzumab pelidotin. Pts were treated prophylactically with a steroid mouthwash prior to administration of gedatolisib to minimize mucositis. Pts were evaluated clinically each week during the first 2 cycles and on day 1 of each subsequent cycle. Serum chemistry was obtained at the start of each cycle; complete blood counts were obtained prior to each gedatolisib infusion. Dose modifications for hematologic and non-hematologic toxicity were pre-specified. Response was evaluated according to RECIST 1.1 criteria every 2 cycles (6 weeks) through week 18, then every 3 cycles thereafter. Tumor biopsies for correlative analyses were obtained at screening and Cycle 1 Day 15 in pts with accessible lesions.

PTK7 and p-AKT Immunohistochemistry

PTK7 immunohistochemistry (IHC) was performed by Flagship Biosciences (Westminster, CO) using a proprietary antibody for staining under a protocol developed by Pfizer(29). Staining for phospho-AKT (pAKT, Ser473), was performed using antibody #4060 procured from Cell Signaling Technology (Beverly, MA) as described previously(30). PTK7 and pAKT. IHC results were assessed by a certified pathologist and quantified by H-score.

Exome library preparation and sequencing

DNA from tumor and matched blood normal was extracted using the Qiagen AllPrep DNA/RNA FFPE kit and QIAamp DNA Blood Mini kit, respectively. DNA library preparation utilized the SureSelect XTHS Target Enrichment System for Illumina Paired-End Multiplexed Sequencing Version A1, July 2017 (Agilent Technologies). Libraries were then hybridized, captured, and amplified with the Agilent Human All Exon V7 probe set (48Mb, hg38). Libraries were sequenced on a NovaSeq 6000 sequencer using 150bp paired-end chemistry (Illumina, Inc.). A Phred quality score (Q score) was used to measure the quality of sequencing. More than 90% of the sequencing reads reached Q30 (99.9% base call accuracy).

Exome variant and copy number analysis

FASTQ files were aligned to the human reference genome (b37/hg19) using BWA (v. 0.7.17, https://bio-bwa.sourceforge.net/).(31) PCR duplicates were removed and coverage metrics were calculated using Picard-tools (v.2.21.2, https://picard.sourceforge.net/). The Genome Analysis Toolkit (GATK, v. 4.1.4.1, https://www.broadinstitute.org/gatk/) was used for SNP and INDEL discovery according to GATK best practices.(32) Copy number variants (CNV) were analyzed using CODEX2 (v.1.3.0).(33)

Data Availability

Raw sequencing data for this study were generated by The Center for Medical Genomics at Indiana University School of Medicine. Derived data supporting the findings of this study are available in the Supplementary Data.

RESULTS

Participant characteristics

We enrolled 18 pts; 10 in three dose escalation cohorts and 8 in expansion at cohort 3. Baseline characteristics are shown in Table 2. Pts were heavily pretreated with the majority having prior exposure to an anthracycline, taxane, platinum, and capecitabine.

Safety

Dose escalation was completed with no dose limiting toxicities (DLTs); an additional pt was included in cohort 1 to accommodate an immediate clinical need for treatment. A small expansion cohort proceeded at the full RP2D for monotherapy for both agents. The most common adverse events of any grade were nausea (n=16, 89%), anorexia (n=13, 72%), constipation (n=12, 67%), fatigue (n=12), and mucositis (n=12). Grade 3 or greater toxicity (nausea, n=1; fatigue, n=2) and myelosuppression (Grade ≥3 neutropenia, n=2) were uncommon (Table 3).

Efficacy

16 of 18 pts enrolled were evaluable for response; two pts discontinued treatment prior to the first disease assessment that was not due to toxicity or progression. Three pts achieved a confirmed partial response (ORR 16.7%, 3/18 including the two non-evaluable patients). An additional 3 pts had stable disease (SD), of these 2 had SD for > 18 weeks. The clinical benefit rate at 18 weeks (CB_{18}) was 27.8% (5/18) (Figure 1). Of note, one pt with SD with Inflammatory TNBC (Pt #: 0613-25) had their only target lesion biopsied and therefore were not eligible for measurement per RECIST criteria, however has had a prolonged exceptional response of ~ 2 years. The pt has been off all anti-cancer treatment for > 15 months. Overall, after a median follow-up of 7.9 months, median progression-free survival (PFS) was 2.0 months (95% CI for PFS:1.2-6.2) (Figure 2A); median overall survival (OS) was 9.4 months (95% CI for OS:4.3-15.8, Figure 2B).

Correlative analyses

Using whole exome sequencing, we set out to observe if somatic DNA variants were associated with clinical response (Table 4). Of the 18 pts on trial, 15 had successful whole exome sequencing of the baseline biopsy sample. We did not detect abberations in the PI3K pathway or PTK7 in 6 out of 15 pts. In pts who had a partial response (n=3), we observed a PTEN I101N mutation in one pt and a high gain of AKT2 in another. In pts who had stable disease (n=3), one harbored a high gain of AKT2; another a PIK3CA E545A gain-of-function mutation and PTEN single copy deletion; and a third had high gains in AKT2, PIK3CG, and PTK7. In those pts with progressive disease (n=10), we observed an AKT2 S268L gain-of-function mutation in one pt, a PIK3CA H1047R gain-of-function

mutation in one pt, a PTK7 variant (of unknown significance), and high gains of AKT2 in 3 pts and PIK3CB in 2 pts. Overall, 5 of 5 pts with either a PR or SD and matched exome sequencing harbored an aberration in the PI3K pathway or PTK7, compared to 4 of 9 pts with progressive disease.

Of note, in our pt with exceptional response to therapy (Pt #: 0613-25) we observed that the pt had a concurrent PIK3CA E545A gain-of-function mutation and a PTEN deletion. These data demonstrate two mutations that are consistent with potential activation of the PI3K pathway and may help explain the exceptional response seen in this pt.

Tissues from research biopsies obtained prior to therapy and at C1D15 were stained for the expression of PTK7 as well as phospho-AKT, a pharmacodynamic marker of PI3K inhibition (Table 4). There was no correlation between IHC H-Scores for either marker and timepoint with clinical benefit. However, due to the small sample size this observation is preliminary.

DISCUSSION

In this study, we have shown that the novel combination of gedatolisib and cofetuzumab pelidotin can be delivered in combination at full doses with manageable toxicity and has clinical activity in pts with heavily pretreated metastatic TNBC. While the PI3K pathway is genomically and transcriptomically aberrant in the majority of TNBCs, single agent treatment with inhibitors of this pathway has resulted in only modest clinical activity, contrary to the theory of oncogene addiction(34,35). Transcriptome reprogramming has emerged as a common response mechanism in tumor cells when exposed to small molecule perturbations(36). Four independent groups have reported that up-regulation of the Wnt pathway is a common compensatory response to PI3K inhibition driving resistance(19-22). Inhibition of both pathways resulted in synergistic anti-tumor efficacy in preclinical models(19). We theorized that we could leverage this compensatory mechanism to inform clinical combination therapy by using a PI3K inhibitor (gedatolisib) to potentially drive up-regulation of PTK7, such that synergy would be achieved with co-treatment with a PTK7-ADC (cofetuzumab pelidotin). Further, previously reported data has also shown that the payload for cofetuzumab pelidotin, auristatin, is in itself synergistic with gedatolisib, providing another potential mechanism for synergistic action of this combination(28).

In this phase I trial, we report the first clinical experience of combining a PI3K pathway inhibitor with an agent that targets a component of the Wnt pathway. The trial successfully completed its dose escalation to RP2D of both agents with no DLTs. Safety data from the dose escalation and our expansion cohort found the combination to be generally well tolerated. Further, while our sample size was limited, we observed clinical activity of the combination with a CB_{18} of 27.8%. Given the paucity of targeted agents for the majority of patients with TNBC, this combination provides a promising avenue for increasing the clinical armamentarium. Our study was not powered to definitely detect biomarkers of response, however, patients with genomic aberrations in the PI3K pathway or PTK7 may preferentially benefit. Taken together, these data set the stage for larger Phase II studies of the combination in metastatic TNBC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TRANSLATIONAL RELEVANCE

Targeted therapy options for metastatic triple-negative breast cancer (TNBC) are limited. Previous genomic analyses of large cohorts of TNBC have consistently demonstrated activation of the PI3K pathway. However, single-agent PI3K inhibition has had modest clinical efficacy. Preclinical data from our group and others have demonstrated that up-regulation of the Wnt pathway induces resistance to PI3K inhibition. Herein, we report a Phase I clinical trial of gedatolisib (PI3K/mTOR inhibitor) in combination with cofetuzumab pelidotin, an antibody-drug conjugate targeting the Wnt pathway receptor PTK7, in patients with metastatic TNBC. In this first clinical trial combining a PI3K and Wnt pathway agent we report a favorable safety profile and anti-tumor activity. Further clinical trials testing combinations targeting these two pathways are warranted.

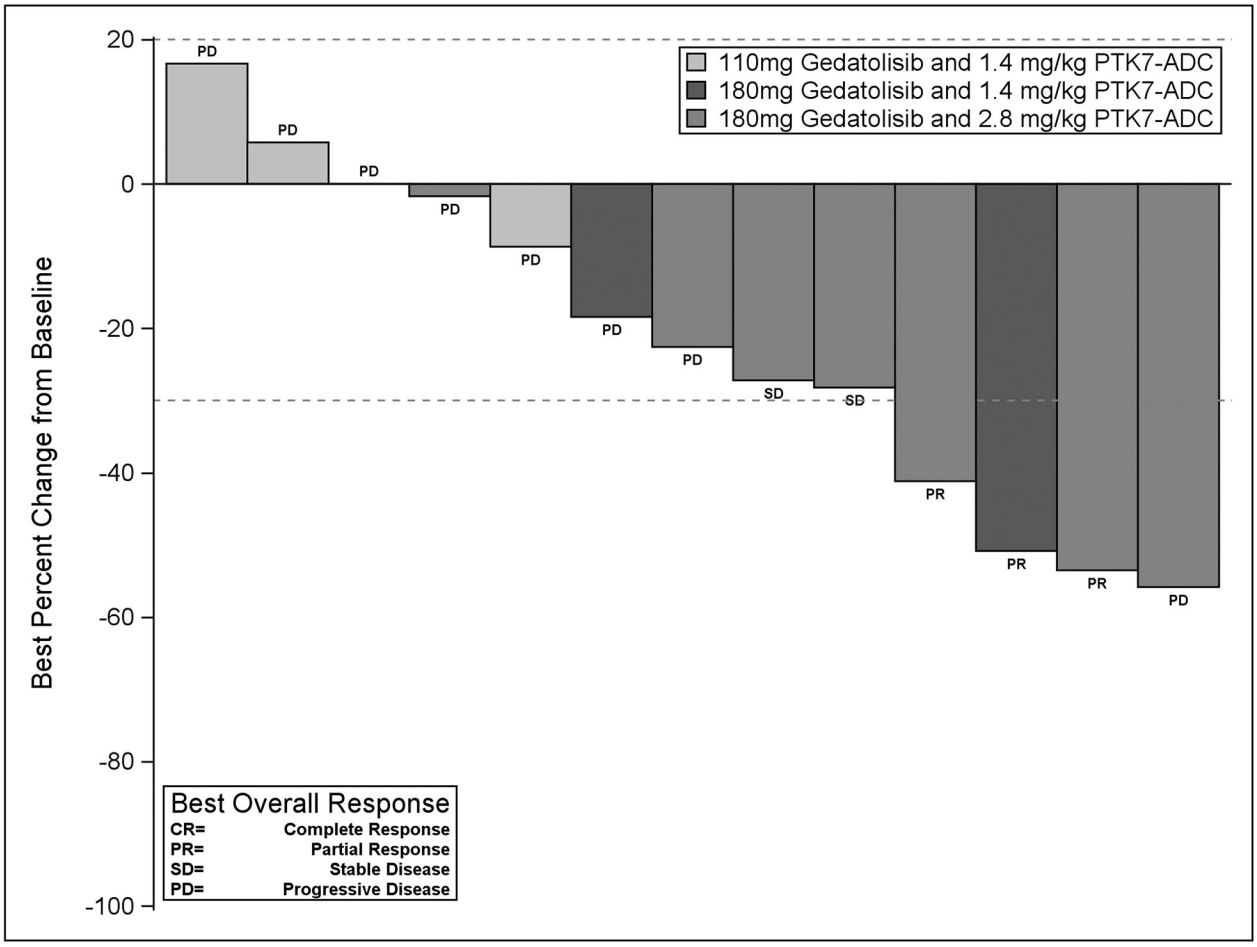

Figure 1.

Waterfall plot demonstrating best tumor response from baseline (y-axis). 18 pts enrolled on trial, 16 were evaluable for response, 13 pts with measurable disease reached at least the first pre-specified imaging timepoint for disease assessment. Pts are color-coded by dose cohort. PR=Partial Response; SD=Stable Disease; PD=Progressive Disease. Of note, the pt with best percent change for the target lesions, unfortunately, in the same visit had increasing/PD for the non-target lesions, resulting in overall best response as PD.

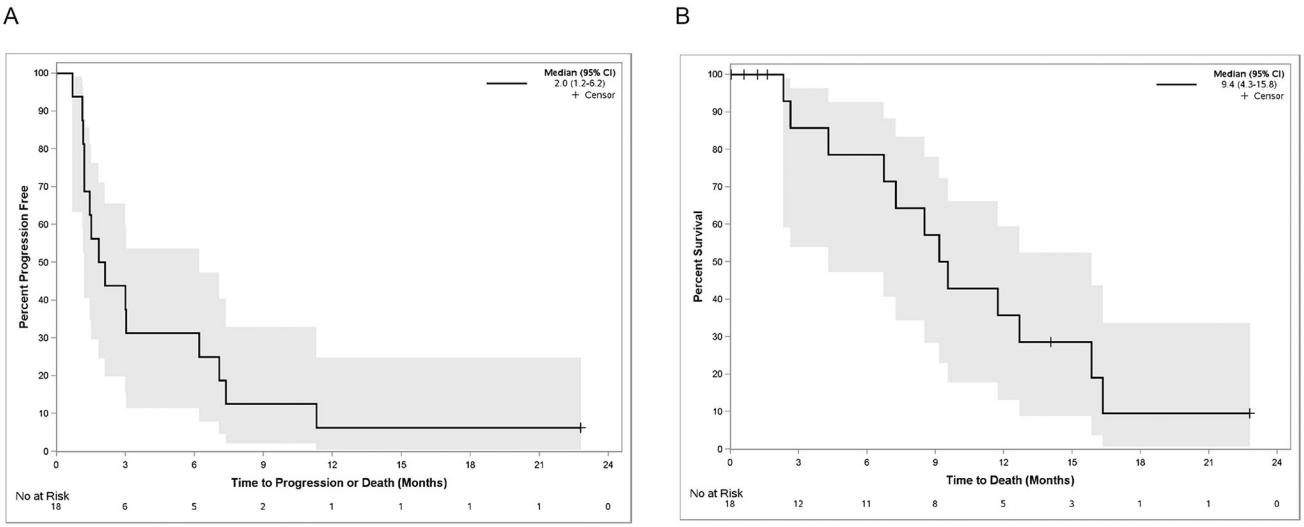

Figure 2.

(A) Kaplan-Meier plot of progression free survival (PFS) demonstrating a median PFS of 2.0 months (95% CI for PFS:1.2-6.2). (B) Kaplan-Meier plot of overall survival (OS) demonstrating a median OS of 9.4 months (95% CI for OS:4.3-15.8).

Table 1.

Treatment plan

No. of pts	Cohort	Gedatolisib			Cofetuzumab Pelidotin		
		Dose	Frequency of administration	Route of administration	Dose	Frequency of administration	Route of administration
4	1	110 mg	D1,8,15 every 21 days	IV	1.4 mg/kg	D1 every 21 days	IV
3	2	180 mg	D1,8,15 every 21 days	IV	1.4 mg/kg	D1 every 21 days	IV
11	3	180 mg	D1,8,15 every 21 days	IV	2.8 mg/kg	D1 every 21 days	IV

Table 2.

Participant Characteristics

Characteristic	Overall (N=18)
Age (year)	
Median (Range)	53 (32-77)
Gender, n (%)	
Female	18 (100%)
Race, n (%)	
White	17 (94.4%)
Black or African American	1 (5.6%)
Ethnicity	
Not Latino or Hispanic	17 (94.4%)
Unknown	1 (5.6%)
Prior Therapies	
Taxane	18 (100%)
Platinum	18 (100%)
Anthracycline	17 (94.4%)
Capecitabine	13 (72.2%)
Gemcitabine	8 (44.4%)
Eribulin	6 (33.3%)
Vinorelbine	5 (27.8%)
Immunotherapy	4 (22.2%)
PARP inhibitor	3 (16.7%)
Other	3 (16.7%)

Table 3.

Observed toxicities in >10% of pts or observed as grade ≥ 3 using CTCAE criteria.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Total Percent	Grade 3-5	Grade 3-5 Percent
Nausea	11	4	1	0	0	16	88.89	1	5.56
Anorexia	9	4	0	0	0	13	72.22	0	0.00
Constipation	10	2	0	0	0	12	66.67	0	0.00
Fatigue	2	8	2	0	0	12	66.67	2	11.11
Mucositis oral	10	2	0	0	0	12	66.67	0	0.00
Back pain	6	3	2	0	0	11	61.11	2	11.11
Dyspnea	6	1	3	1	0	11	61.11	4	22.22
Vomiting	6	2	3	0	0	11	61.11	3	16.67
Alopecia	4	6	0	0	0	10	55.56	0	0.00
Pruritus	9	0	0	0	0	9	50.00	0	0.00
Diarrhea	6	1	1	0	0	8	44.44	1	5.56
Dyspepsia	4	4	0	0	0	8	44.44	0	0.00
Headache	6	2	0	0	0	8	44.44	0	0.00
Anemia	1	4	2	0	0	7	38.89	2	11.11
Cough	7	0	0	0	0	7	38.89	0	0.00
Insomnia	6	1	0	0	0	7	38.89	0	0.00
Neutrophil count decreased	0	4	1	1	0	6	33.33	2	11.11
Anxiety	2	3	0	0	0	5	27.78	0	0.00
Hyperglycemia	5	0	0	0	0	5	27.78	0	0.00
Pain	1	2	2	0	0	5	27.78	2	11.11
Blurred vision	4	0	0	0	0	4	22.22	0	0.00
Dysgeusia	3	1	0	0	0	4	22.22	0	0.00
Edema limbs	4	0	0	0	0	4	22.22	0	0.00
Hypokalemia	1	2	1	0	0	4	22.22	1	5.56
Pain in extremity	3	1	0	0	0	4	22.22	0	0.00
Peripheral sensory neuropathy	2	2	0	0	0	4	22.22	0	0.00
Aspartate aminotransferase increased	2	1	0	0	0	3	16.67	0	0.00
Chest wall pain	1	2	0	0	0	3	16.67	0	0.00
Chills	3	0	0	0	0	3	16.67	0	0.00
Lung infection	1	0	2	0	0	3	16.67	2	11.11
Mucosal infection	1	1	1	0	0	3	16.67	1	5.56
Rash acneiform	3	0	0	0	0	3	16.67	0	0.00
Rash maculo-papular	2	0	1	0	0	3	16.67	1	5.56
Urinary tract pain	2	1	0	0	0	3	16.67	0	0.00
Abdominal pain	1	0	1	0	0	2	11.11	1	5.56
Alanine aminotransferase increased	2	0	0	0	0	2	11.11	0	0.00

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Total Percent	Grade 3-5	Grade 3-5 Percent
Allergic rhinitis	2	0	0	0	0	2	11.11	0	0.00
Bone pain	1	1	0	0	0	2	11.11	0	0.00
Dry mouth	2	0	0	0	0	2	11.11	0	0.00
Infections and infestations - Other, specify	0	2	0	0	0	2	11.11	0	0.00
Lymphedema	2	0	0	0	0	2	11.11	0	0.00
Nasal congestion	1	1	0	0	0	2	11.11	0	0.00
Oral pain	2	0	0	0	0	2	11.11	0	0.00
Paresthesia	2	0	0	0	0	2	11.11	0	0.00
Skin and subcutaneous tissue disorders - Other, specify	2	0	0	0	0	2	11.11	0	0.00
Thromboembolic event	0	2	0	0	0	2	11.11	0	0.00
Urinary tract infection	0	2	0	0	0	2	11.11	0	0.00
Urinary urgency	1	1	0	0	0	2	11.11	0	0.00
Colitis	0	0	1	0	0	1	5.56	1	5.56
Dehydration	0	0	1	0	0	1	5.56	1	5.56
Investigations - Other, specify	0	0	1	0	0	1	5.56	1	5.56
Respiratory failure	0	0	0	1	0	1	5.56	1	5.56
Skin infection	0	0	1	0	0	1	5.56	1	5.56
White blood cell decreased	0	0	1	0	0	1	5.56	1	5.56

* There were no grade 5 events observed

Table 4.

Genomic alterations and immunohistochemistry results with best response. DNA aberrations and copy number variation of focus were in the PI3K pathway (PIK3CA, PIK3CB, PIK3CD, PIK3CG, AKT1, AKT2, AKT3, PTEN) and PTK7. N/A = samples did not have mutations in the PI3K or PTK7 pathway. NS = Not sequenced.

Patient ID	Dose Cohort	Best Response	CB_{18}	PFS (Months)	DNA variants	Copy number variation	PTK7 H-score (Screen)	PTK7 H-score (C1D15)	NUC-pAKT (Screen)	Cyto-pAKT (Screen)	NUC-pAKT (C1D15)	Cyto-pAKT (C1D15)
2	1	Progressive disease		1.12	N/A	N/A	120	166	0	0	0	10
3	1	Progressive disease		1.22	N/A	N/A	16	25	0	0	0	2
4	1	Progressive disease		1.15	N/A	High Gain: AKT2, PIK3CB	N/A	232	0	0	N/A	N/A
5	1	Progressive disease		2.1	PTK7 E139Q	High Gain: AKT2, PIK3CB	101	22	0	0	0	0
7	2	Progressive disease		0.69	AKT2 S268L	N/A	197	N/A	20	1	N/A	N/A
8	2	Partial Response	Yes	11.31	PTEN I101N	N/A	116	N/A	1	200	0	10
9	2	Progressive disease		1.22	N/A	N/A	224	116	0	0	10	0
10	3	Progressive disease		1.84	N/A	N/A	68	82	0	0	0	6
12	3	Progressive disease		1.51	N/A	N/A	111	N/A	2	60	N/A	N/A
15	3	Partial Response	Yes	6.21	N/A	High Gain: AKT2	144	N/A	0	20	N/A	N/A
16	3	Progressive disease		1.45	PIK3CA H1047R	High Gain: AKT2	168	N/A	4	140	N/A	N/A
18	3	Not Evaluable		-	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
19	3	Partial Response	Yes	7.36	NS	NS	N/A	N/A	N/A	N/A	N/A	N/A
20	3	Stable disease	Yes	7.07	N/A	High Gain: AKT2	3	120	120	200	N/A	N/A
21	3	Progressive disease		3.02	NS	NS	N/A	N/A	N/A	N/A	N/A	N/A
22	3	Not Evaluable		-	NS	NS	N/A	N/A	N/A	N/A	N/A	N/A
25	3	Stable disease	Yes	22.78	PIK3CA E545A	One copy deletion: PTEN	0	N/A	0	0	N/A	N/A
29	3	Stable disease		2.99	N/A	High Gain: AKT2, PIK3CG, PTK7	175	15	0	0	0	100