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Results from a single arm, single stage phase II trial of trametinib and GSK2141795 in persistent or recurrent cervical cancer

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HIGHLIGHTS

- Strong pre-clinical rationale supports combining PI3K/AKT and MEK inhibitors in cervical cancer.
- The combination of the MEK inhibitor trametinib and the pan-AKT inhibitor GSK2141795 had limited activity.
- Major toxicities of the combination included rash, diarrhea, nausea, and ALT elevation.
- Alterations in PI3K or RAS signaling did not predict for activity of the combination.

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ABSTRACT

Background. Improved treatment for advanced cervical cancer is needed; currently, treatment options include combined chemotherapy and bevacizumab or pembrolizumab monotherapy for PD-L1 positive disease. *PIK3CA* and *KRAS* mutations have been reported in cervical cancers; this study therefore tested dual inhibition of PI3K and RAS signaling by combining the MEK inhibitor trametinib and the AKT inhibitor GSK2141795 in recurrent cervical cancer.

Methods. This was an investigator-initiated phase II study combining trametinib and GSK2141795 in patients with recurrent cervical cancer. Primary endpoint was best tumor response; secondary endpoints included progression free survival, overall survival, and safety assessment. Translational objectives included characterization of molecular alterations in PI3K and RAS signaling pathway genes.

Results. Planned accrual was 35 patients; 14 patients were enrolled and received at least one dose of study drug before the study was terminated due to discontinuation of GSK2141795 development. There were no confirmed responses; 1 patient had an unconfirmed PR, 8 had stable disease, 3 had progression as best response, and 2 were unevaluable. Toxicities were mostly grade 1 and 2, although 57% of patients experienced grade 3/4 adverse events and 50% patients required a dose reduction.

Conclusions. The combination of trametinib and GSK2141795 was feasible but required dose holds and modifications for adverse events; however, anti-cancer activity was minimal, even in patients with PI3K or RAS pathway alterations. Although the study was terminated early after GSK2141795 development was halted, the findings in these 14 patients do not support further development of this combination in cervical cancer.

1. Introduction

Cervical cancer is the fourth most common cancer diagnosed in women worldwide and also ranks fourth in mortality [1]. There are 569,847 new diagnoses of cervical cancer per year, and 311,365 women die from the disease per year worldwide [1]. Recent advances have been made in the treatment of advanced and/or recurrent cervical cancer, including the findings from GOG240 which demonstrated improvement of overall survival (OS) to 17.5 and 15.0 months respectively when bevacizumab was added to platinum or non-platinum-based chemotherapy [2,3]. Additionally, in June 2018, the PD-1 inhibitor pembrolizumab received United States Food and Drug Administrative

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(FDA) approval for treatment of PD-L1 positive cervical cancer as defined by a combined positive score of 1 or higher. Two trials demonstrated the single agent activity of pembrolizumab; the first consisted of a 24-patient cohort of PD-L1 positive cervical cancer with a 17% response rate (KEYNOTE 028; [4]). KEYNOTE 158 study included 98 women, 77 of whom had PD-L1 positive cervical cancer, and the overall response rate was 14.3% [5]. No responses were observed in women whose cancers were PD-L1–negative [5]. Despite these advances, metastatic cervical cancer remains incurable, and new options and strategies are needed.

Multiple examples exist of treatment advances for advanced cancer based on successful targeting of molecular alterations in the tumor, and several studies have identified genomic alterations in cervical cancer that could serve as targets for biologic therapies. PI3 kinase pathway alterations have been identified in both squamous cell and adenocarcinomas of the cervix [6–9] with identification of a *PIK3CA* mutation rate of 36% in squamous cervical cancer in one trial. Additionally, *KRAS* and *HRAS* mutations have also each been reported at frequencies of 10% and 22% [8–11]. In our own study at DFCI, in a group of 80 patients with either squamous cell or adenocarcinoma of the cervix, validated mutations were detected in 60.0% (48/80) of tumors examined [8]. The highest mutation rates were *PIK3CA* (31.3%) and *KRAS* (8.8%). *PIK3CA* mutations were found at similar rates in both adenocarcinoma and squamous cell carcinomas (25.0% vs. 37.5%, $p = 0.33$). In contrast, *KRAS* mutations were identified only in adenocarcinoma (17.5% vs. 0%, $p = 0.01$) [8]. These data served as the initial rationale for this study.

Preclinical and translational studies support the combination of PI3K/AKT and MEK inhibitors in order to target these pathways given their redundancy and cross talk and the resultant feedback loops; for example, mouse models of KRAS driven tumors do not respond to either PI3K or MEK inhibition alone but respond to the combination [12–16]. PI3K pathway inhibition can result in the activation of several receptor tyrosine kinases that can signal through RAS-ERK thus giving rationale for both inhibitors to be combined. In the phase II study reported here, we tested the combination of the MEK inhibitor trametinib and the pan-AKT inhibitor GSK2141795; this combination was previously studied in a phase I clinical trial that determined the recommended phase II dosing [17].

2. Methods

Patients were enrolled from the Dana-Farber Cancer Institute and Beth Israel Deaconess Medical Center in Boston MA, and all patients were required to sign an informed consent that had been approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board. This study was an investigator-initiated study, and UAM held the FDA IND. The study was funded by the National Comprehensive Cancer Network, and study drugs were provided by Glaxosmithkline.

2.1. Eligibility

Eligibility included the following: histologically or cytologically confirmed cervical cancer which was deemed recurrent or metastatic and was refractory to established treatments, age 18 or older, ECOG performance status 0–2, normal organ and bone marrow function, controlled blood pressure, ability to tolerate oral medications since both study drugs were administered orally, measurable cancer per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, and no prior treatment with drugs that targeted the PI3K pathway (including PI3K inhibitors or mTOR inhibitors) or the RAS-ERK pathway. All histologic types of cervical origin were permitted. Patients were required to have received one prior chemotherapeutic regimen for management of cervical carcinoma. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer was not counted as a systemic chemotherapy regimen. Patients were allowed, but were not required, to receive one additional prior treatment regimen (including a single chemotherapeutic, a combination of chemotherapeutics, or biologic drugs such as bevacizumab) for management of recurrent cancer.

2.2. Study design

This was an open-labeled single arm study. Each cycle was 28 days. The starting doses of agents were: trametinib 1.5 mg orally daily and GSK2141795 50 mg orally daily, self-administered at the same time each day. Dose reductions for trametinib to 1.0 mg and for GSK2141795 to 25 mg per day were allowed for certain pre-specified toxicities such as grade 3 rash and ophthalmologic toxicities. Treatment was continued until disease progression or adverse effects prohibited further treatment. Patients were assessed radiographically by RECIST 1.1 using CT or MRI every 8 weeks (every 2 cycles) until disease progression was confirmed. Toxicities were measured by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The primary endpoint of this study was best objective tumor response [complete response (CR) + partial response (PR)] per RECIST version 1.1. Secondary endpoints included progression-free survival (PFS) and overall survival (OS) following initiation of therapy with trametinib and GSK2141795, toxicities, the mutation and co-mutation rates of genes in the PI3K and RAS-ERK signaling pathways in recurrent cervical cancer using high throughput targeted mutational analysis on participant tumor samples, and exploration of the association of mutational status with clinical benefit from trametinib and GSK2141795.

2.3. Mutational analysis

Mutational and copy number assessment was performed by OncoPanel on formalin-fixed paraffin embedded archival samples. The OncoPanel assay surveys exonic DNA sequences of 447 cancer genes and 191 regions across 60 genes for rearrangement. DNA is isolated from tissue containing at least 20% tumor nuclei and analyzed by massively parallel sequencing using a solution-phase Agilent SureSelect hybrid capture kit and an Illumina HiSeq 2500 sequencer. The OncoPanel assay has been previously described and validated for the detection of genomic alterations and somatic mutations in cancers [18,19].

2.4. Statistical considerations

With the planned accrual of 35 participants, the study had a 91% power to detect an improvement in response rate from 0.07 to 0.22 using a one-sided 0.09-level exact binomial test. Therefore, the null hypothesis was rejected if 5 or more participants responded to combination therapy with trametinib and GSK2141795. The null hypothesis of 0.07 was based on a weighted average of the observed response rates from the 11 cohorts enrolled to GOG 127 and 227 series.

The analyses included all participants who initiated study treatments. The objective response [complete response (CR) + partial response (PR)] rate (ORR) was estimated with 90% exact binomial confidence interval. PFS was defined as the time from registration to the study until documented disease progression or death without progression, whichever occured first. Participants not experiencing a PFS event were censored at the last date of documented disease evaluation. OS was defined as the time from study registration to the time of death from any cause, with follow-up censored at the last date known to be alive. The PFS and OS analyses were summarized using the Kaplan-Meier product-limit estimator with reported event rate and estimate of median survival using Greenwood's formula with 95% confidence intervals (CI). Safety data were described by the number and proportion of patients who had treatment-related adverse events using CTCAE v4.0.

3. Results

The trial was opened in October 2013 and closed in June 2015. The study closed early because the AKT inhibitor GSK2141795 was

discontinued and because GSK determined the drug combination had an unacceptable toxicity profile in other populations, including breast cancer and melanoma. The planned accrual was 35 patients; 16 patients were consented, 2 never started therapy because of ineligibility, and 14 patients enrolled on the study and received at least 1 dose of study treatment.

Table 1 lists the patient and tumor characteristics; 93% of the patients were white, the median age was 52 (range 46 to 61) years, 71% had ECOG PS status of 0, 50% of patients had histology type of squamous cell cancer, and the median number of prior line therapies received was 2 (range 1–3). 10 patients (71%) had received prior RT; 7 patients (50%) had received prior chemoradiation. The follow-up time was estimated as 6.3 (interquartile range 2.4 to 12.9) months based on the known follow-up time for all patients, via summary statistics of median and interquartile range. The median number of cycles completed by patients on study was 3 (range 0 to 22). All 14 treated patients came off treatment; 8 patients had progressive disease and 6 patients went off-treatment without a documented progression. Of those patients who went off treatment without progression, 2 were by treating investigator decision (1 in setting of 16% tumor burden increase, 1 in setting of clinical decline related to disease and entry into hospice care), 2 patient withdrawals, and 2 for toxicity (1 colon perforation and 1 grade 3 diarrhea who declined dose reduction).

One patient had an unconfirmed partial response for a response rate of 7.1%. Eight patients (57.1%) had stable disease; in 5 patients this was confirmed, while in 3 patients this remained unconfirmed. The median duration of stable disease was 1.9 months. Three patients (21.4%) had progressive cancer as their best response. Two patients (14.3%) were unevaluable. Fig. 1 shows the waterfall plot of maximum tumor shrinkage in the 12 patients with available response data.

Kaplan Meier curves for PFS and OS are depicted in Fig. 2. A total of 11 PFS events (6 by RECIST 1.1, 3 by clinical progression, 2 deaths) were reported; 8 total deaths were reported during study follow-up, 5 patients had previous documentation of progression (4 RECIST 1.1, 1 clinical progression). At 6.3 months of median follow-up (maximum 24.5 months), the median PFS (RECIST 1.1) was 3.7 months (95% CI: 1.9, NA); median PFS (RECIST 1.1 + clinical progression) was 3.6 months (95% CI: 1.6, NA); and median OS was 14.8 months (95% CI: 6.7, NA).

Table 2 describes toxicities that were deemed related to study treatment which occurred in at least 10% of patients. All 14 enrolled patients received at least one treatment and had adverse event (AE) forms submitted. The overall rate of grade 3/4 AEs possibly, probably or definitely related to treatment was 57.1% (8/14): 7 with grade 3, 1 with grade 4. Grade 3 AEs related to study drug include 3 rashes (2 acneiform, 1 maculopapular), 2 diarrhea, 1 mucositis, 1 hypertension, 1 hyponatremia, 1 INR increase, and 1 thromboembolic event. There was one grade 4 treatment-related AE of colonic perforation. The most common occurring AEs (any grade) included acneiform rash (71.4%), diarrhea (64.3%), nausea (36%), and ALT elevation (29%), mostly grade 1 or 2. Dose reductions occurred in 50% of patients due to AEs.

Fig. 3 shows the observed mutations and amplifications in genes related to PI3K or RAS signaling in the 13 patients with tissue available for testing. One patient did not have archival tissue available for testing. Two of the 7 squamous cell carcinoma and 2 of the 5 adenocarcinoma cancers had a *PIK3CA* mutation. The only cancer with a *PIK3CA* amplification was of adenocarcinoma histology. Three cancers had *KRAS* aberrations; the one mucinous cancer had a *KRAS* mutation, and the other 2 were adenocarcinomas (one mutation and one amplification). Of note, while the one patient with prolonged stable disease (>20 months) had a *PIK3CA* mutation, there was no clear pattern of association between time on drug and any detected genomic alteration.

Table 1
Patient and tumor characteristics.

Characteristics		Total, N = 14
White, N (%)		13 (92.9)
Age (years)	Median (range)	52 (46 to 61)
Performance status, N (%)	0	10 (71.4)
	1	1 (7.1)
	2	3 (21.4)
Histology, N (%)	Adenocarcinoma	5 (35.7)
	Adenosquamous	1 (7.1)
	Mucinous	1 (7.1)
	Squamous cell carcinoma	7 (50.0)
Grade, N (%)	Well differentiated	2 (14.3)
	Moderately differentiated	4 (28.6)
	Poorly differentiated	8 (57.1)
Stage, N (%)	I	3 (21.4)
	II	5 (35.7)
	III	1 (7.1)
	IV	5 (35.7)
Median lines of systemic therapy	Median (range)	2 (1 to 3)
Number of prior lines of systemic therapy, N (%)	1	5 (36)
	2	8 (57)
	3[a]	1 (7)
Prior chemotherapy received (as systemic therapy), N (%)	Platinum	13 (92.8)
	Taxane	11 (78.6)
	Gemcitabine	5 (35.7)
	Topotecan	3 (21.4)
	Bevacizumab	9 (64.3)
Prior radiation therapy (RT), N (%)		10 (71.4)
Prior chemoradiation, N (%)		7 (50.0)

[a] Patient received cisplatin/gemcitabine twice, separated by 17 months, and one line of nab-paclitaxel. A deviation was approved by the IRB to consider her two treatments of cisplatin/gemcitabine as one line of therapy.

4. Discussion

This study tested the combination of a MEK inhibitor and a PI3Kinase pathway inhibitor, specifically a pan-AKT inhibitor in this study, for the treatment of relapsed and advanced cervical cancer. The study was terminated early because of discontinuation of the clinical development of GSK2141795 and the determination by GSK that the combination had significant toxicity as observed in other cancer populations. In the 14 patients enrolled into this study, the combination was tolerable, but no confirmed responses were observed.

Because of the promising pre-clinical activity of combined MEK and PI3K pathway inhibition and the strong rationale for combining these agents, multiple phase I and II studies have tested this strategy, in addition to ours. A study examining the results of 236 patients enrolled on PI3K pathway inhibitor studies with or without a MAPK pathway inhibitor seemed to support this dual inhibition approach, reporting that dual inhibition of these pathways may have improved efficacy compared to inhibiting either pathway alone [20].

The combination of trametinib and GSK2141795 has previously been tested in phase I and II studies. In the initial phase I studies, the maximally tolerated doses of this combination were established at trametinib/GSK2141795 doses of 1.5 mg/50 mg, 2 mg/25 mg and 0.5 mg/75 mg dosing [17]; in our study, trametinib 1.5 mg daily and GSK2141795 50 mg daily was selected for the dosing regimen. Adverse events in the phase I study were similar to those observed in our study, with AEs including gastrointestinal events, fatigue, and rash. Of note the rate of grade 3 events was lower (13% of 62 patients), and included diarrhea, stomatitis, and increase in AST. Partial responses were observed at 8 weeks in three patients: one with triple negative breast cancer (TNBC), one with endometrial cancer, and one with ocular melanoma [17].

In addition to our trial in advanced cervical cancer, phase II testing of the trametinib/GSK2141795 combination has occurred in endometrial cancer [21], TNBC [22], and melanoma [23]. In each of these studies, efficacy was felt to be limited, with 1 response in 26 endometrial patients [21], 1 unconfirmed partial response in 16 TNBC patients [22], and no

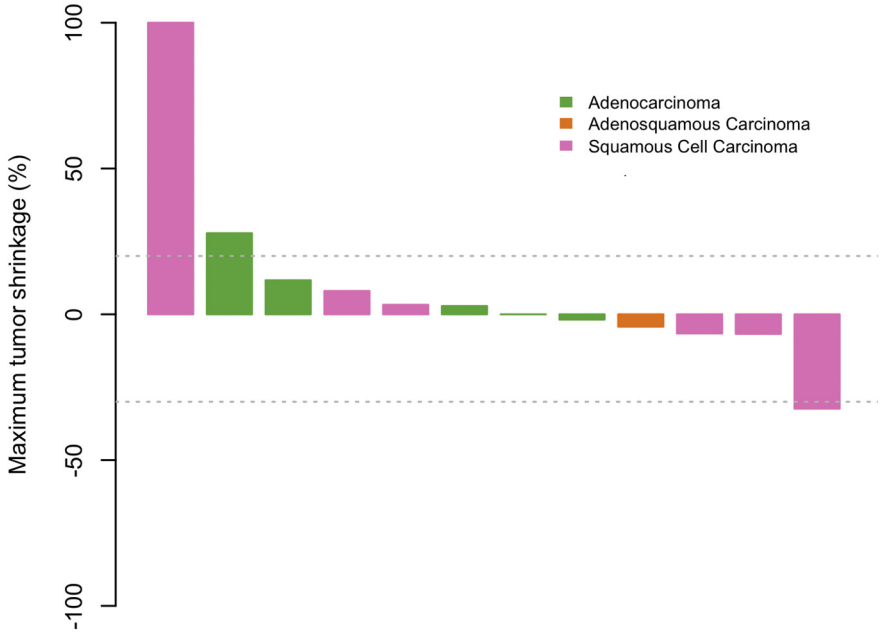

Fig. 1. Waterfall plot of maximum tumor shrinkage from baseline.

responses in 20 (10 *NRAS*-mutated and 10 *NRAS*-wildtype) melanoma patients [23]. The most common adverse events in our study, rash and diarrhea, occurred at a rate comparable to that observed with the same combined dose of trametinib 1.5 mg daily and GSK 2141795 50 mg in the melanoma study, although the overall rate of grade 3 or higher adverse events was higher in our study. This may reflect the eligibility in this trial allowing patients with performance status of 2 or possibly increased sensitivity to this drug combination in the study population. In other studies, increased toxicity has also been observed in endometrial cancer patients. In the phase II endometrial cancer study, 8 dose limiting toxicities (2 hypertension, 2 mucositis, 2 rash, 1 dehydration, and 1 acute kidney injury) were observed at the initial dose level of trametinib 1.5 mg daily and GSK 2141795 50 mg daily that was utilized in each of the other phase II studies, including ours [21]. A lowered dose was then tested in 12 patients using trametinib 1.5 mg daily and GSK2141795 25 mg daily; this was better tolerated with no dose limiting toxicities. However, given the overall lack of efficacy observed in multiple patient populations and the observed toxicities of the combination, our trial was closed early prior to meeting its accrual goal, and the clinical development of the AKT inhibitor GSK2141795 terminated.

Trametinib or other MEK inhibitors have also been combined with other inhibitors of the PI3K pathway [15]. A phase I trial in 20 patients of trametinib with another AKT inhibitor, afuresertib (GSK2110183) reported toxicities including liver enzyme elevation, stomatitis, rash, and diarrhea [24]. One partial response was seen in a *BRAF* wild-type melanoma. Continuous dosing was poorly tolerated, while intermittent dosing was better tolerated. Similarly, another trial reported poor tolerability of continuously dosed trametinib with everolimus [25]. Combinations of MEK inhibitors and PI3K inhibitors have also been explored. A phase I/II trial of BKM120, a pan-PI3K inhibitor, together with trametinib reported dose limiting toxicities of stomatitis, diarrhea, dysphagia, and creatine kinase elevation, with grade 3/4 toxicities of creatine kinase elevation, stomatitis, liver enzyme elevation, and rash [26]. Interestingly, activity was observed in the 21 patients with ovarian cancer who were enrolled (4 in the dose escalation and 17 in the dose expansion phases), with an overall response rate was 29% and median PFS of 7 months [26]. Of these 21 patients, 71% had low grade serous histology and 91% had a *KRAS* mutation. A phase I trial of BYL719, an alpha specific PI3K inhibitor, together with the MEK inhibitor binimetinib (MEK162) enrolled 58 patients and reported grade 3/4 toxicities of diarrhea, increased creatine kinase, rash, nausea, and hyperglycemia [27]. Again, activity was observed in ovarian cancer patients, with 3 of the 4 ovarian cancer patients enrolled achieving a partial response. Two of the 3 responders had a known *KRAS* mutation; the 3rd patient did not have somatic sequencing results. The fourth patient with ovarian cancer also had a somatic *KRAS* mutation and had stable disease for 41+ weeks [27].

A few MEK inhibitor/PI3K pathway inhibitor combinations have been tested in both phase I and randomized phase II settings; these include the combination of the AKT inhibitor MK2206 with the MEK inhibitor selumetinib and the combination of SAR24509, an oral PI3K and mTORC1/TORC2 inhibitor, with the MEK inhibitor pimasertib. In the phase I trial of MK2206 and selumetinib, RECIST 1.0-confirmed partial responses were observed in patients with non-small cell lung cancer and low-grade ovarian cancer [28]. However, further single arm phase 2 testing of this combination in colorectal cancer showed no responses [29]. Additionally, this combination was compared to modified FOLFOX chemotherapy in an open-label phase 2 randomized trial; there was no statistical difference in OS between the two groups, and median PFS was shorter with the MEK/AKT inhibitor combination [30]. Toxicities were also higher in the MK2206/selumetinib arm, with increased grade 3 or higher toxicities [30]. Phase I testing of SAR245409 and pimasertib demonstrated significant toxicity; at the recommended phase 2 dosing, 74 patients needed to be dose interrupted (73%), 20% required dose reduction (20%), and 26% of patients discontinued treatment due to adverse events [31]. There was also limited anti-cancer activity in patients with advanced solid tumors. In a randomized phase 2 study in recurrent low grade serous ovarian cancer of pimasertib and SAR245409 versus pimasertib alone (NCT01936363), only 65 patients were enrolled before the trial was closed for futility after an interim analysis in May 2016.

The totality of experience with dual inhibition of the PI3K and RAS signaling pathways, with low overall response rates in unselected populations, emphasizes the importance of identifying those patients who are most likely to derive benefit, especially as these drug combinations impart significant toxicities. Given the presence of alterations in both PI3K and RAS signaling in cervical cancers, there was significant preclinical rationale to consider dual inhibition in this disease. Molecular characterization of tumors from the patients enrolled to our study demonstrated a pattern of alterations consistent with the literature [7–9],

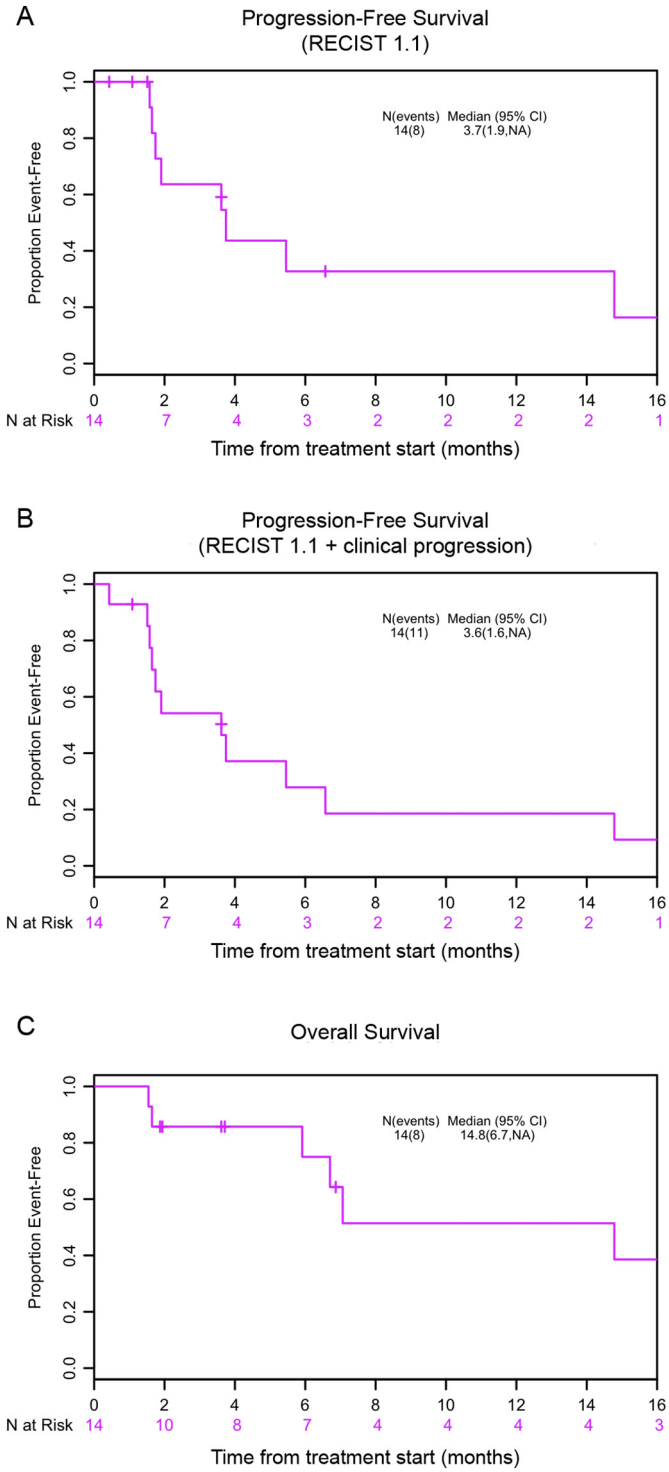

Fig. 2. Median PFS as measured by (A) RECIST 1.1 and (B) RECIST 1.1 and clinical progression events, and median OS in study participants.

with no clear difference in frequency of *PIK3CA* mutations between squamous cell and adenocarcinoma histologies, but with alterations in *KRAS*, *ERBB2*, and *ERBB3* observed only adenocarcinoma patients. In The Cancer Genome Atlas, while alterations in *KRAS*, *ERBB2*, and *ERBB3* do occur in squamous cell carcinomas, the frequency was lower [9], and with the small number of patients in this study, it is not unexpected that we would not have observed alterations in these patients. However, although the molecular characteristics of the study population appear to be consistent with what has been reported in the literature, the presence or absence of alterations in PI3K or RAS signaling did not

Table 2
Treatment related toxicities occurring in >10% of patients.

	Maximum grade								Total	
	1		2		3		4			
	N	%	N	%	N	%	N	%	N	%
Toxicity (CTCAEv4.0)										
Rash acneiform	6	42.9	2	14.3	2	14.3	–	–	10	71.4
Diarrhea	5	35.7	2	14.3	2	14.3	–	–	9	64.3
Nausea	5	35.7	–	–	–	–	–	–	5	35.7
Aspartate aminotransferase increased	4	28.6	–	–	–	–	–	–	4	28.6
Alanine aminotransferase increased	3	21.4	–	–	–	–	–	–	3	21.4
Fatigue	2	14.3	1	7.1	–	–	–	–	3	21.4
Mucositis oral	2	14.3	–	–	1	7.1	–	–	3	21.4
Rash maculo-papular	2	14.3	–	–	1	7.1	–	–	3	21.4
Vomiting	3	21.4	–	–	–	–	–	–	3	21.4
Dehydration	1	7.1	1	7.1	–	–	–	–	2	14.3
Dry skin	2	14.3	–	–	–	–	–	–	2	14.3
Edema limbs	–	–	2	14.3	–	–	–	–	2	14.3
Epistaxis	2	14.3	–	–	–	–	–	–	2	14.3
Hyperglycemia	2	14.3	–	–	–	–	–	–	2	14.3

appear to have any significant correlation with activity of the combination. While the patient who experienced long-term stable disease did have a *PIK3CA* mutation, other patients with *PIK3CA* alterations had short durations of treatment or rapid progression.

Overall, while a strong pre-clinical rationale suggests that dual inhibition of PI3K and RAS signaling has significant promise as a therapeutic strategy, the clinical implementation of this strategy has been challenging. While occasional signals of activity have been observed, identifying a biomarker of response has been elusive, and the overall toxicities for these combinations have been significant. Our trial in cervical cancer patients failed to demonstrate significant clinical activity of the MEK/AKT inhibitor combination of trametinib and GSK2141795. Additionally, while expected alterations in the PI3K and RAS signaling pathways were identified, these did not appear to be biomarkers for clinical activity. Of note, 93% of the patients on this study were white, and therefore the results may not be generalizable across all racial and ethnic backgrounds. Nonetheless, although this trial was stopped early due to termination of the clinical development of GSK2141795, the findings in these 14 patients do not support further exploration of combination MEK and PI3K inhibition in an unselected advanced cervical cancer population.

Author contributions

All authors contributed to writing, review, and/or revision of the manuscript. JFL, AAW, and UAM contributed to the conception and design of the study. JFL, AAW, SC, PAK, AP, KM, SM, CW, DD, and UAM contributed to data collection. JFL, KPG, AAW, PAK, DD, and UAM contributed to data analysis and interpretation.

Declaration of Competing Interest

This trial was supported by a grant provided by the National Comprehensive Cancer Network. JFL reports advisory board participation for AstraZeneca, Tesaro, Clovis, and Mersana Therapeutics and is the institutional PI on industry-sponsored trials from Genentech/Roche, AstraZeneca, Boston Biomedical, Atara Biotherapeutics, Acetylon, Bristol-Myers Squibb, Agenus, CytomX Therapeutics, Regeneron, Tesaro, and Clovis Oncology. PAK reports advisory board participation for AstraZeneca, Merck, Pfizer, and Tesaro. DD reports consulting work for Novartis and advisory board participation for Oncology Analytics, Inc. UAM reports consulting work for Merck, 2× Oncology, and Immunogen and advisory board participation for AstraZeneca, Myriad Genetics,

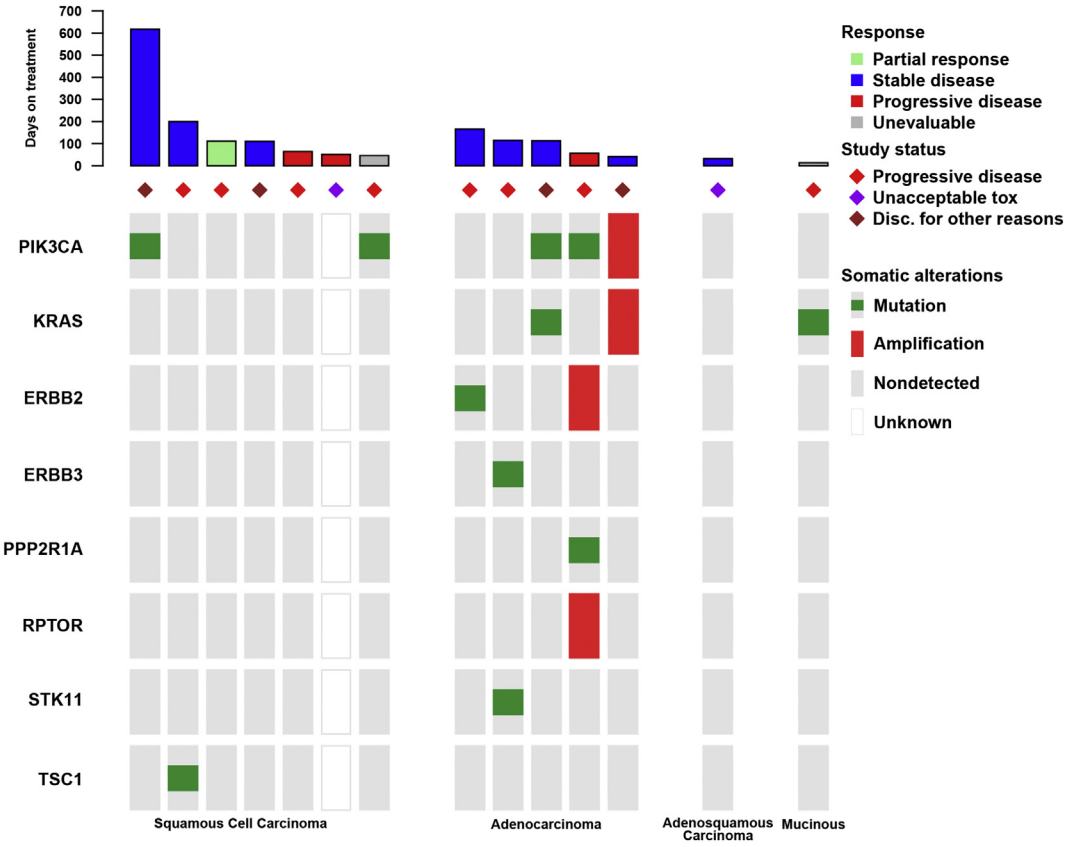

Fig. 3. Molecular alterations in PI3K and RAS signaling pathway genes observed in each study participant.

Clovis, Eli Lilly, Mersana, Geneos, FujiFilm, and Cerulean. KPG, AAW, SC, AP, KM, SM, and CW report no additional conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.05.003.

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