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Dual MAPK / PI3K pathway inhibition with trametinib and GSK2141795 does not yield clinical benefit in metastatic NRAS mutant and wild type melanoma

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Summary

Aberrant MAPK and PI3K pathway signaling may drive the malignant phenotype in NRAS mutant and $BRAF^{WT}$ $NRAS^{WT}$ metastatic melanoma.

To target these pathways NRAS mutant and $BRAF^{WT}$ $NRAS^{WT}$ patients received oral trametinib at 1.5 mg daily and GSK2141795 at 50 mg daily in a 2-cohort Simon 2-stage design. Participants had adequate end organ function and no more than 2 prior treatment regimens. Imaging assessments were performed at 8-week intervals.

10 NRAS mutant and 10 $BRAF^{WT}$ $NRAS^{WT}$ patients were enrolled. No objective responses were noted in either cohort. The median PFS and OS were 2.3 and 4.0 months in the NRAS mutant cohort 2.8 and 3.5 months in the wild-type cohort. Grade 3 and 4 adverse events, primarily rash, were observed in 25% of patients.

We conclude that the combination of trametinib and GSK2141795 does not have significant clinical activity in NRAS mutant or $BRAF^{WT}$ $NRAS^{WT}$ melanoma.

Keywords

NRAS; wild type; MEK; AKT; melanoma; trametinib; GSK2141795

The most active immune checkpoint inhibitor regimen yields objective tumor responses only in about half of metastatic melanoma patients (Larkin et al., 2015). In BRAF mutant melanoma, which accounts for approximately 50% of cases overall, BRAF plus MEK inhibitor combinations yield rapid objective response in 64 to 68% of patients with a median

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PFS of 9.9 to 11.4 months (e. g. Larkin et al., 2014), but there are limited options for patients with BRAF wild type melanoma who do benefit from immune therapy.

Abnormal signaling through the MAPK and PI3K pathways is a potential therapeutic target even in BRAF wild type melanoma. NRAS exon 1 and 2 mutations, observed in approximately 30% of BRAF wild type melanoma metastases (Colombino et al., 2012), are associated with poor overall survival (e. g. Thomas et al., 2015). Clinical trials to date have focused on inhibition of downstream mediators of canonical RAS signaling (Bedard et al., 2015), the PI3 kinase and MAP kinase pathways. ATP-competitive BRAF inhibitors lead to paradoxical activation of the MAP kinase pathway in NRAS mutant melanoma (Su et al., 2012), but MEK inhibitors induce objective responses in about 20% of NRAS mutant melanoma patients, with a median progression free survival of 3.6 months (Ascierto et al., 2013). Increased signaling through the MAPK and PI3K pathways as assessed by pERK, pAKT, and pS6 levels has also been identified in melanoma lesions harboring either BRAF or NRAS mutations, suggesting that inhibition of these pathways could have clinical activity in wild type melanoma patients as well (Krayem et al., 2014). There have been no studies to date examining combined MEK and PI3K pathway inhibition in metastatic melanoma.

Trametinib is an allosteric inhibitor of MEK1/2 that decreases MAPK signaling in RAS mutant melanoma (Infante et al., 2012) and GSK2141795 is an ATP competitive pan-AKT inhibitor with preliminary evidence of activity in patients whose tumors demonstrated significant PI3K pathway activity. The combination of trametinib and GSK2141795 shows evidence of clinical activity at tolerable doses in gynecologic malignancies (Kurzrock et al., 2011). In the current phase II clinical trial, we test the hypothesis that the combination of trametinib and GSK2141795 will overcome the resistance associated with single agent MEK inhibitors by decreasing PI3K pathway activity in NRAS mutant melanoma. We also examine the clinical activity of the study combination in BRAF / NRAS wild type patients.

Design:

This was a nonrandomized, multicenter phase II study of trametinib in combination with GSK2141795 accrued at UCSF and MSKCC with 2 separate cohorts: Patients with NRAS exon 1 and 2 mutations (NRAS mutant) identified by Sanger sequencing or exon-capture next-generation sequencing (Wagle et al., 2012) and patients without these mutations (wild-type). The sample size for each arm was based on a Simon 2-stage stage design and the primary end point was best overall response rate (H_0 = 15%, H_1 = 35%). According to pre-planned stopping rules, further testing of trametinib and GSK2141795 would be halted if none of the first 10 patients enrolled in each cohort had an objective response to treatment.

Patients:

Patients were required to have unresectable stage III or stage IV melanoma, measurable disease by RECIST version 1.1, ECoG performance status of 0–2, and adequate end organ function. Patients with tumors harboring BRAF exon 15 mutations, significant heart disease, retinal or fundal disease, prior treatment and an AKT or MEK inhibitor, or untreated central nervous metastases were excluded from the study.

Treatment:

Patients received trametinib 1.5 mg daily and GSK2141796 at 50 mg daily continuously until disease progression, the development of unacceptable adverse events, or withdrawal of consent. Up to 2 dose reductions were permitted for treatment associated toxicity.

Assessments:

Radiographic response assessments compared to pretreatment baseline were performed at 8-week intervals. Adverse event assessments were performed weekly for the first 8 weeks of therapy and every 4 weeks thereafter. Additional safety assessments included safety laboratories, EKGs, and echocardiograms.

Enrollment:

Enrollment began in September 2013. Enrollment was completed in April 2014 after 10 patients in the NRAS mutant cohort and 10 patients in the NRAS wild-type cohort were enrolled and futility endpoints were met in both cohorts. The patient demographics are described in Table 1. The average number of prior regimens was 1.75 (Table S1) and 70% of patient received prior immune checkpoint inhibitor therapy.

Response and survival:

The best overall response in both cohorts was stable disease. In the NRAS mutant cohort, 4 patients had transient stabilization of disease, all lasting less than 6 months including 2 patients with mucosal melanoma. In the wild type cohort, 5 patients had transient stabilization of disease lasting less than 6 months including 3 patients with uveal melanoma, one of whom had a 13.2% reduction in tumor burden after 2 months of therapy. The median PFS estimates in the NRAS mutant and wild type cohorts were 2.3 months (95% CI 2.1 to 2.5 months) and 2.8 months (95% CI 2.6 to 2.9 months) and the median OS estimates were 4.0 months (95% CI 0.9 to 7.0 months) and 3.5 months (95% CI 0.6 to 6.4 months) respectively. Kaplan-Meier curves for PFS and OS are shown in Figure 1.

Adverse events:

The most common adverse events associated with treatment on study were rash (70%), diarrhea (55%), mucositis (40%), fever (30%), and nausea (25%). Grade 3 and 4 rash was common (20%) and grade 3 diarrhea and dehydration were also noted. Treatment associated adverse events are summarized in Table 2.

The combination of trametinib and GSK2141795 failed to produce objective responses in patients with either NRAS mutant or wild-type melanoma. In the NRAS patient population, this is somewhat surprising given that MEK inhibitors alone can induce objective responses in up to 20% of patients. One problem could be the therapeutic index of the agents used in the study. MEK inhibitors block signaling equally in BRAF mutant, RAS mutant, and wild-type cells (Su et al., 2012). Perhaps because of this, the MEK inhibitor trametinib induces objective responses in only 22% of BRAF-mutant melanoma patients compared to the 53%

response rate conferred by the BRAF inhibitor dabrafenib (e. g. Robert et al., 2015). Efforts to block oncogenic signaling in NRAS-mutated melanoma is further complicated by the potential for escape through the PI3 kinase pathway (Jaiswal et al., 2009), but the recommended phase 2 doses of trametinib and GSK2141795 when administered in combination are lower than the doses for either drug when administered as monotherapy. Thus, we may have induced a partial blockade of signaling through both pathways to a degree that was insufficient to induce significant tumor regressions.

Treatment was not particularly well tolerated. Four of 20 patients developed grade 3 or 4 rash. Mucositis and diarrhea were also common, and although these adverse effects were not severe in most patients, they had a significant impact on their quality of life. The toxicity profile observed in the current study is similar to prior studies of combined MEK and PI3K pathway inhibition (Bedard et al., 2015; Tolcher et al., 2015).

The heterogeneity of the patient population and the advanced disease stage of the patients who participated may also have negatively impacted outcomes. The wild-type cohort included several patients with uveal melanoma, a melanoma subtype with a distinct molecular phenotype (Van Raamsdonk et al., 2010) and limited responses to commonly used melanoma therapeutics including PD-1 antibodies (Algazi et al., 2016). There are data, however, suggesting that uveal melanoma tumors can respond to MEK inhibitor monotherapy (Carvajal et al., 2014), and the best response trend observed on the current trial was in a uveal melanoma patient. 80% of the patients enrolled in this study had stage IV M1c disease, many with elevated LDH values. These factors have been identified as independent negative prognosticators associated with poorer outcomes in advanced melanoma (Ribas A, Hamid O, Daud A, & et al, 2016).

In summary, the combination of trametinib and GSK2141795 did not induce objective responses in NRAS mutant melanoma nor in uveal and cutaneous melanoma patients whose tumors harbored neither BRAF nor NRAS mutations. The combination does not warrant further evaluation and therapeutic alternatives should be explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance

NRAS mutations leading to aberrant MAP kinase and PI3 kinase pathway activity are observed in 15% of patients with advanced melanoma and signaling through these pathways may also contribute to the malignant phenotype in $BRAF^{wt}$ / $NRAS^{wt}$ melanoma patients. This is the first study to examine the safety and efficacy of combined MAPK / PI3K pathway blockade with MEK and AKT inhibitors in NRAS mutant and $BRAF^{wt}$ / $NRAS^{wt}$ populations. The combination had a poor therapeutic index suggesting that either more selective agents or alternative strategies may be required to yield significant clinical benefits in these patients.

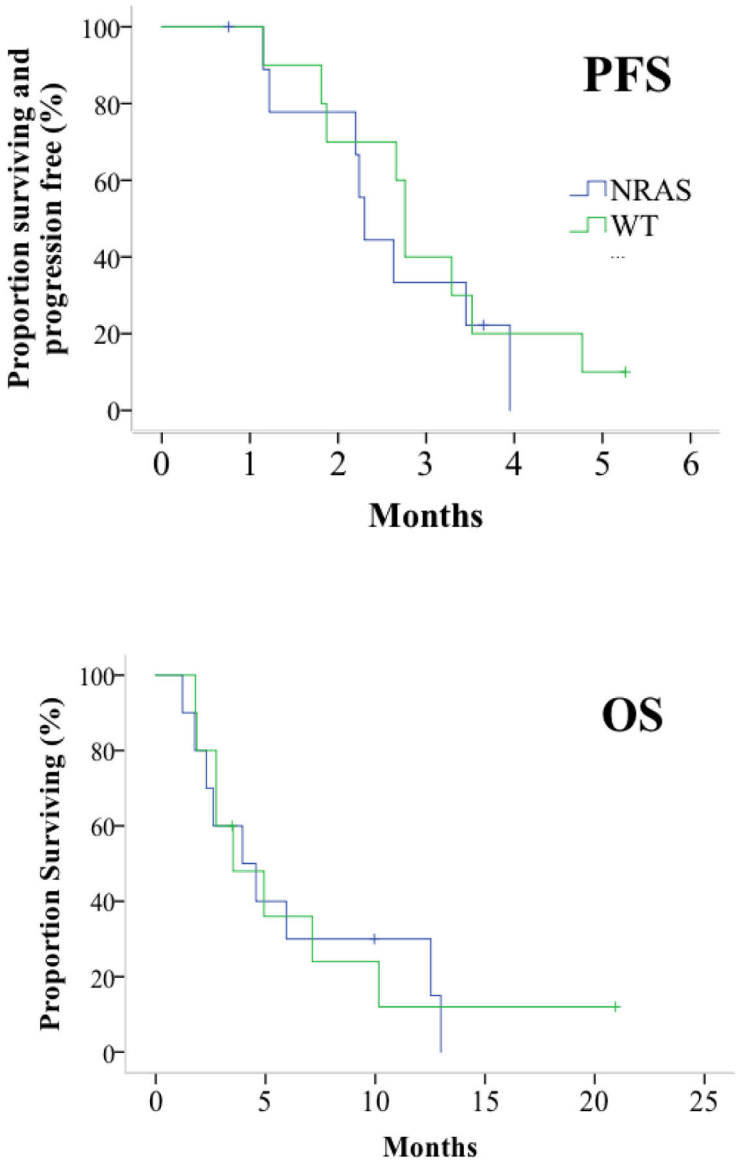

Figure 1.
Kaplan-Meier analysis of PFS and OS in NRAS mutant and wild type patients.

Table 1.

Patient demographics.

		NRAS WT (n=10)	NRAS Mutant (n=10)
Mean Age (range)		59.3 (40–86)	56.8 (19–67)
Gender	**Male**	8 (80%)	7 (70%)
	Female	2 (20%)	3 (30%)
ECOG Status	**0**	6 (60%)	2 (20%)
	1	4 (40%)	8 (80%)
Stage	**M1a**	0	2 (10%)
	M1b	0	2 (10%)
	M1c	10 (100%)	6 (80%)
LDH	**Normal**	2 (20%)	2 (20%)
	Elevated	8 (80%)	8 (80%)
Genotype	**$NRAS^{Q61H}$**	-	1
	$NRAS^{Q61K}$	-	3
	$NRAS^{Q61L}$	-	1
	$NRAS^{Q61R}$	-	5
	$BRAF^{WT}/NRAS^{WT}$	10	-
Subtype	**Cutaneous**	6	8
	Mucosal	-	2
	Acral	1	-
	Uveal	3	-

Table 2.

All adverse events at least possibly due to study treatment.

		Highest grade toxicity				
		1	**2**	**3**	**4**	**Total (%)**
Constitutional	Fatigue	1	1			2 (10%)
	Fever	**5**	**1**			**6 (30%)**
	Malaise		1			1 (5%)
	Dehydration			1		1 (5%)
ENT	Dysphagia		1			1 (5%)
	Epistaxis	1				1 (5%)
	Mucositis	**4**	**4**			**8 (40%)**
	Odynophagia		1			1 (5%)
Eyes	blurry vision	1				1 (5%)
Cardiovascular	Hypertension		2			2 (10%)
	Tachycardia	1				1 (5%)
Respiratory	Dyspnea	1				1 (5%)
GI	Anorexia	1				1 (5%)
	Diarrhea	**3**	**7**	**1**		**11 (55%)**
	Constipation	1				1 (5%)
	Dysgeusia	1				1 (5%)
	Indigestion		1			1 (5%)
	Nausea	**3**	**2**			**5 (25%)**
	Vomiting		1			1 (5%)
GU	Vaginal spotting	1				1 (5%)
Integument	Alopecia	1				1 (5%)
	Dry skin	2				2 (10%)
	Folliculitis		2			2 (10%)
	Itching	1				1 (5%)
	Rash	**4**	**6**	**3**	**1**	**14 (70%)**
Neurological	Headache	1				1 (5%)
Laboratory	Elevated alk phos		1			1 (5%)
	Elevated AST/ALT	2				2 (10%)
	Hyperglycemia		1			1 (5%)
	Hypokalemia	1				1 (5%)
	Increased creatinine	1	1			1 (5%)
	Thrombocytopenia	1				1 (5%)