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Journal Title: Journal of the American Medical Association
Volume: Volume 311, Number 23
Publisher: American Medical Association (AMA): JAMA | 2014-06-18, Pages 2397-2405
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1001/jama.2014.6096
Permanent URL: https://pid.emory.edu/ark:/25593/s2v1n

Final published version: http://dx.doi.org/10.1001/jama.2014.6096

Original Investigation

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A Randomized Clinical Trial

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IMPORTANCE Uveal melanoma is characterized by mutations in *GNAQ* and *GNA11*, resulting in mitogen-activated protein kinase pathway activation.

OBJECTIVE To assess the efficacy of selumetinib, a selective, non–adenosine triphosphate competitive inhibitor of MEK1 and MEK2, in uveal melanoma.

DESIGN, SETTING, AND PARTICIPANTS Randomized, open-label, phase 2 clinical trial comparing selumetinib vs chemotherapy conducted from August 2010 through December 2013 among 120 patients with metastatic uveal melanoma at 15 academic oncology centers in the United States and Canada.

INTERVENTIONS One hundred one patients were randomized in a 1:1 ratio to receive selumetinib, 75 mg orally twice daily on a continual basis (n = 50), or chemotherapy (temozolomide, 150 mg/m^2 orally daily for 5 of every 28 days, or dacarbazine, 1000 mg/m^2 intravenously every 21 days [investigator choice]; n = 51) until disease progression, death, intolerable adverse effects, or withdrawal of consent. After primary outcome analysis, 19 patients were registered and 18 treated with selumetinib without randomization to complete the planned 120-patient enrollment. Patients in the chemotherapy group could receive selumetinib at the time of radiographic progression.

MAIN OUTCOMES AND MEASURES Progression-free survival, the primary end point, was assessed as of April 22, 2013. Additional end points, including overall survival, response rate, and safety/toxicity, were assessed as of December 31, 2013.

RESULTS Median progression-free survival among patients randomized to chemotherapy was 7 weeks (95% CI, 4.3-8.4 weeks; median treatment duration, 8 weeks; interquartile range [IQR], 4.3-16 weeks) and among those randomized to selumetinib was 15.9 weeks (95% CI, 8.4-21.1 weeks; median treatment duration, 16.1 weeks; IQR, 8.1-25.3 weeks) (hazard ratio, 0.46; 95% CI, 0.30-0.71; $P < .001$). Median overall survival time was 9.1 months (95% CI, 6.1-11.1 months) with chemotherapy and 11.8 months (95% CI, 9.8-15.7 months) with selumetinib (hazard ratio, 0.66; 95% CI, 0.41-1.06; $P = .09$). No objective responses were observed with chemotherapy. Forty-nine percent of patients treated with selumetinib achieved tumor regression, with 14% achieving an objective radiographic response to therapy. Treatment-related adverse events were observed in 97% of patients treated with selumetinib, with 37% requiring at least 1 dose reduction.

CONCLUSIONS AND RELEVANCE In this hypothesis-generating study of patients with advanced uveal melanoma, selumetinib compared with chemotherapy resulted in a modestly improved progression-free survival and response rate; however, no improvement in overall survival was observed. Improvement in clinical outcomes was accompanied by a high rate of adverse events.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01143402

JAMA. 2014;311(23):2397-2405. doi:10.1001/jama.2014.6096

Supplemental content at jama.com

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Uveal melanoma arises from melanocytes within the choroid of the eye, has an incidence of 1500 cases per year in the United States, and is biologically distinct from cutaneous melanoma.[1,2] Despite enucleation or definitive radiotherapy of the primary lesion, metastases develop in 50% of patients and outcomes are subsequently poor, with a median survival of less than 12 months.[3-5] Although improved outcomes have been achieved in patients with advanced cutaneous melanoma, no effective therapy has been identified for those with metastatic uveal melanoma.

Oncogenic mutations in *GNAQ* or *GNA11*, genes encoding for widely expressed G-protein-α subunits, are observed in more than 80% of primary uveal melanomas and activate signaling pathways including the mitogen-activated protein kinase (MAPK) pathway.[6-8] We and others demonstrated the genotype-dependent antitumor effects of inhibition of the MAPK pathway at the level of the mitogen-activated protein kinase kinase (MEK) enzymes MEK1 and MEK2 in preclinical models.[9-11] Furthermore, subset analysis of 20 patients with advanced uveal melanoma treated in a previously completed trial of selumetinib (AZD6244; ARRY-142886), a selective, orally available, non-adenosine triphosphate competitive small molecule inhibitor of MEK1/2,[12,13]vs temozolomide demonstrated a progression-free survival time with selumetinib double that achieved with chemotherapy.[14]

ERK *extracellular signal-regulated kinase*

MAPK *mitogen-activated protein kinase*

MEK *mitogen-activated protein kinase kinase*

pERK *phosphorylated extracellular signal-regulated kinase*

RECIST *Response Evaluation Criteria in Solid Tumors*

We therefore developed and conducted this National Cancer Institute (NCI) Cancer Therapy Evaluation Program–sponsored, multicenter, randomized phase 2 trial of selumetinib vs chemotherapy to formally assess the efficacy of MEK inhibition in advanced uveal melanoma.

Methods

Study Design

This trial assessed the efficacy of selumetinib in patients with metastatic uveal melanoma who had not received prior therapy with temozolomide or dacarbazine (see trial protocol in Supplement 1). Enrollment began on August 25, 2010, with 10 patients receiving therapy as of the data-lock date of December 31, 2013. Tumor samples from all patients were prospectively genotyped for mutations in exon 5 of *GNAQ* and *GNA11*.

Eligible patients were randomized in a 1:1 ratio using the method of random permuted block to receive open-label treatment with (1) chemotherapy with either temozolomide, 150 mg/m^2 orally daily for 5 of every 28 days, or dacarbazine, 1000 mg/m^2 intravenously every 21 days (investigator choice) or (2) selumetinib, 75 mg orally twice daily on a continual basis.[13] Randomization was stratified by mutation status (*GNAQ* mutant vs *GNA11* mutant vs *GNAQ* and *GNA11* wild type), American Joint Committee on Cancer cutaneous melanoma staging criteria (stage M1a/b vs M1c), and number of prior systemic therapies for metastatic disease (0 vs ≥1). Dose modification was permitted for toxic effects (eTable 1 in Supplement 2). Patients received study treatment until the first occurrence of disease progression, death, intolerable toxic effects, or withdrawal of consent. Clinical and laboratory assessments were conducted at baseline, every 2 weeks for 4 weeks, and every 4 weeks subsequently for up to 30 days following the off-study date or until resolution of treatment-associated toxic effects. Patients treated with selumetinib at Memorial Sloan Kettering Cancer Center, New York, New York, who had accessible tumor underwent tumor biopsies at baseline and after 14 (±3) days of therapy. Adverse events were graded using the NCI Common Terminology Criteria for Adverse Events, version 4.0. Investigator-determined tumor response was measured radiographically every 4 weeks for 8 weeks and every 8 weeks subsequently using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[15] Those randomized to chemotherapy who experienced disease progression could receive selumetinib subsequently if they remained eligible for study therapy.

Selumetinib was supplied by the Division of Cancer Treatment and Diagnosis of the NCI and was provided to the NCI under a collaborative agreement with AstraZeneca. Temozolomide and dacarbazine were obtained as commercially available agents.

Patients

Eligible patients had documented metastatic uveal melanoma; age older than 18 years; life expectancy longer than 3 months; Eastern Cooperative Oncology Group performance status of 1 or less (able to conduct normal activity or carry out work of a light nature); measurable disease by RECIST, version 1.1[15]; adequate organ function; and either untreated metastatic uveal melanoma or disease that progressed while receiving prior anticancer therapy in the opinion of the investigator. Prior therapy with an MEK inhibitor, temozolomide, or dacarbazine was not permitted.

Both men and women and members of all races and ethnic groups were eligible. The protocol and amendments were approved by relevant institutional review boards. All participants provided written informed consent before initiating study procedures.

Statistical Analysis

The primary end point was progression-free survival. Secondary end points included overall survival, response rate, and safety/tolerability. Patients who received at least 1 dose of therapy or who experienced objective disease progression during the first cycle of therapy were evaluable for the primary end point. Progression-free survival was calculated as time from randomization to the earlier date of disease progression by RECIST version 1.1 or death due to any cause in the absence of progression, and overall survival was calculated as time to death due to any cause, with distributions estimated via Kaplan-Meier methods and compared

between treatment groups using the log-rank test. Hazard ratios were estimated using a Cox proportional hazards model. Proportional hazards assumptions were assessed using a plot of the log(−log[survival] vs log[time]). We tested for proportional hazard assumption by including in a Cox model a term for the interaction between treatment group and progression-free survival time. We used SAS version 9.2 (SAS Institute Inc) and considered a 2-tailed $P<.05$ as significant. All data available on December 31, 2013, are reported.

A randomized phase 2 design was used to evaluate the primary end point. Assuming a median progression-free survival of 1.5 months, a 24-month accrual period, and a 12-month follow-up period, the design had 80% power (10% significance level, 1-sided) to detect a treatment difference if the true hazard ratio was 0.6. Final analysis was prespecified to occur after 68 or more progression events were observed in patients with tumor harboring a *GNAQ* or *GNA11* mutation. Randomization of 80 or more patients with tumor harboring a *GNAQ* or *GNA11* mutation was planned. Because antitumor effects were observed in *GNAQ* and *GNA11* wild-type uveal melanoma in preclinical models, 40 or fewer additional patients could be randomized regardless of mutational status.[10] Following this analysis, randomization to the inferior treatment group was discontinued; however, accrual could continue to complete the planned 120-patient enrollment. An unplanned analysis of progression-free and overall survival that included 72 patients with a data cutoff of September 25, 2012, was performed. No correction for multiplicity across testing of the primary and secondary end points was performed, as the goal of this hypothesis-generating study was to assess for a signal rather than proof of efficacy.

Correlative Analyses

Mutational analysis of exon 5 of *GNAQ* and *GNA11* was conducted in a Clinical Laboratory Improvement Amendments-certified laboratory. Standard polymerase chain reaction amplification of a 250-bp and 245-bp fragment for *GNAQ* and *GNA11*, respectively, including the entire coding region of exon 5, was performed in duplicate using HotStar Taq DNA polymerase (Qiagen) and primers listed in eTable 2 in Supplement 2. Polymerase chain reaction was also performed using standard primers with a 10mer locked nucleic acid oligonucleotide designed to suppress amplification of wild-type DNA. Sequencing and analysis were performed using the BigDye Terminator version 3.1 Cycle Sequencing Kit (Applied Biosystems) on an ABI3730 running ABI Prism DNA Sequence Analysis Software.

Western blotting was performed for phosphorylated extracellular signal-regulated kinase (pERK) and cyclin D1 and quantitated by densitometry using ImageJ software. Cells were lysed in radioimmunoprecipitation assay buffer supplemented with protease inhibitor cocktail tablets (Roche Diagnostics) and 1 mmol/L of sodium orthovanadate. Equal amounts of protein were loaded on 4% to 12% polyacrylamide gel electrophoresis gels (Invitrogen, Life Technologies). Polyvinylidene difluoride membranes were blocked with 5% nonfat dried milk and probed with pERK, ERK, cyclin D1, and α-tubulin (Cell Signaling Technology). The Wilcoxon rank-sum test was used to evaluate associations between radiographic regression (RECIST response or stable disease for >16 weeks) and suppression of pERK and cyclin D1.

Results

Patient Characteristics

Between August 25, 2010, and July 23, 2013, 101 patients from 15 centers (eTable 3 in Supplement 2) were randomized, with 51 assigned to chemotherapy and 50 to selumetinib. One patient in each group was randomized but not treated because of rapid clinical decline. Patient characteristics (**Table 1**) were balanced between treatment groups. The median treatment duration for those randomized to chemotherapy was 8 weeks (interquartile range, 4.3-16 weeks) and for those randomized to selumetinib was 16.1 weeks (interquartile range, 8.1-25.3 weeks), respectively. Nineteen patients were subsequently registered and 18 treated with selumetinib without randomization to complete the planned 120-patient enrollment.

Mutational testing was performed on 117 metastatic and 3 primary specimens, with 37% harboring mutations in exon 5 of *GNAQ* (Q209L: n=13; Q209P: n=26; Q209H: n=4; and Q209R: n=1) and 45% harboring mutations in exon 5 of *GNA11* (Q209L: n=53; Q209P: n=1).

Clinical Activity

The primary end point of progression-free survival was analyzed using data available as of April 22, 2013. At that time, 98 patients were randomized and 96 evaluable for progression-free survival (**Figure 1**). The median progression-free survival time was 7 weeks (95% CI, 4.3-8.4 weeks) in the chemotherapy group (n = 49) and 15.9 weeks (95% CI, 8.4-21.1 weeks in the selumetinib group (n = 47) (**Figure 2**A). The hazard ratio for progression-free survival was 0.46 (95% CI, 0.30-0.71; $P < .001$) in favor of selumetinib. Similar improvement was observed when limiting analysis to patients with tumor harboring a *GNAQ* or *GNA11* mutation (n = 80) (Figure 2B). Two patients randomized to chemotherapy were progression-free with a median follow-up of 12.8 weeks (range, 7.9-17.9 weeks). Eight patients randomized to selumetinib were progression-free with a median follow-up of 15.2 weeks (range, 4-80 weeks). Four- and 6-month progression-free survival rates were 8.5% and 5.7% with chemotherapy and 43.1% and 22.9% with selumetinib. As of April 22, 2013, the median overall survival time was 9.4 months (95% CI, 6.0-11.4 months) with chemotherapy and 10.8 months (95% CI, 7.5-12.9 months) with selumetinib, with a hazard ratio of 0.79 (95% CI, 0.46-1.37; $P = .40$) (eFigure 1 in Supplement 2).

Ninety-nine patients were ultimately treated, with 98 patients stopping active therapy by December 31, 2013 (Figure 1). At that time, the median progression-free survival time was 7.3 weeks (95% CI, 4.3-10.1 weeks) in the chemotherapy group (n = 50) and 16 weeks (95% CI, 8.4-23 weeks) in the selumetinib

Table 1. Baseline Participant Characteristics for All Patients Treated as of December 31, 2013

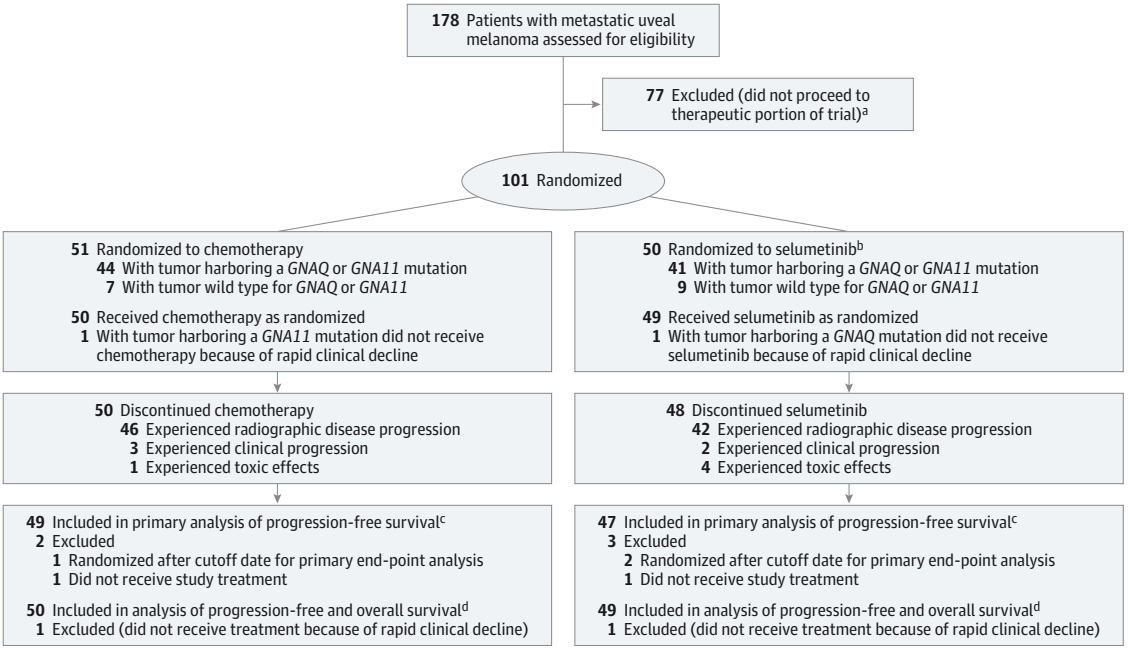
Characteristics	Randomized to Chemotherapy (n = 51)	Randomized to Selumetinib (n = 50)	Allocated Without Randomization to Selumetinib (n = 19)
Age, median (range), y	62 (34-86)	62 (32-86)	63 (42-81)
Sex, No. (%)			
Male	31 (62)	26 (52)	9 (47)
Female	20 (39)	24 (48)	10 (53)
Performance status, median (range)[a]	0 (0-1)	0 (0-1)	0 (0-1)
American Joint Committee on Cancer stage, No. (%)			
M1a/b	3 (6)	2 (4)	0
M1c	48 (94)	48 (96)	19 (100)
Elevated lactate dehydrogenase level, No. (%)[b]	30 (59)	25 (50)	14 (74)
No. of prior systemic therapies, median (range)	0 (0-2)	0 (0-3)	0 (0-2)
Ipilimumab, No. (%)	11 (22)	8 (16)	4 (21)
No. of prior liver-directed therapies, median (range)	0 (0-2)	0 (0-2)	0 (0-1)
No. (%) with			
Radiofrequency ablation	3 (6)	5 (10)	0
Chemoembolization	5 (10)	4 (8)	0
Immunoembolization	1 (2)	1 (2)	0
Other	2 (4)	4 (8)	1 (5.3)
Tumor mutation, No. (%)			
GNAQ mutant	19 (37)	20 (40)	6 (32)
GNA11 mutant	25 (49)	21 (42)	8 (42)
Wild type[c]	7 (14)	9 (18)	5 (26)

[a] As defined by the Eastern Cooperative Oncology Group (range, 0-5).

[b] Exceeding institutional laboratory upper limit of normal range.

[c] Wild type for Q209 mutations in *GNAQ*/*GNA11*.

Figure 1. Flow of Study Participants



[a] Data regarding why patients did not proceed to the therapeutic portion of the protocol were not collected.

[b] After primary outcome analysis, 19 additional patients were registered and 18 treated with selumetinib without randomization to complete the planned 120-patient enrollment.

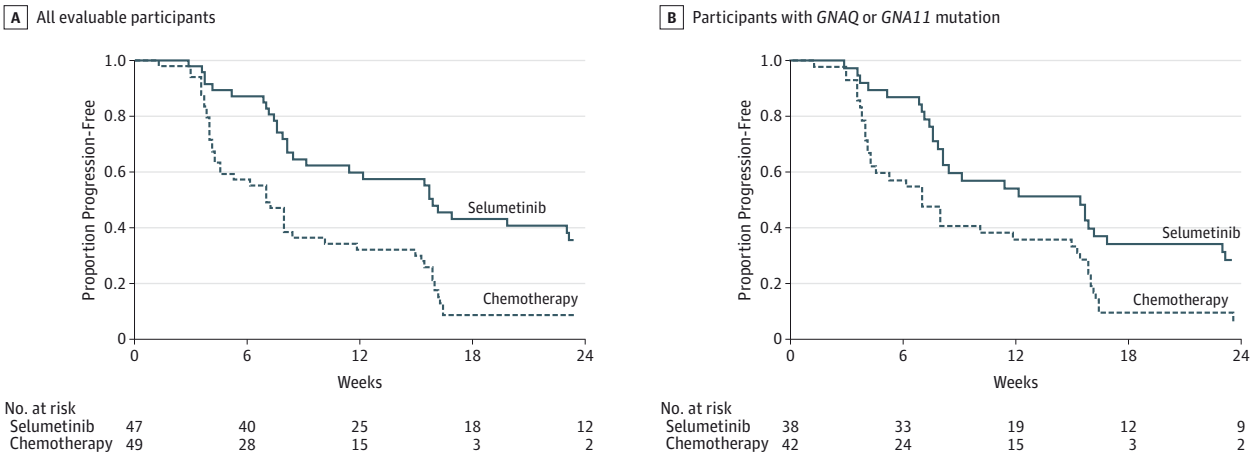
[c] As of April 22, 2013.

[d] As of December 31, 2013.

group (n = 49) (eFigure 2 in Supplement 2). The median overall survival time was 9.1 months (95% CI, 6.1-11.1 months) with chemotherapy and 11.8 months (95% CI, 9.8-15.7 months) with selumetinib, with a hazard ratio of 0.66 (95% CI, 0.41-1.06; *P* = .09) (eFigure 3A in Supplement 2). Ten patients randomized to chemotherapy were alive with a median follow-up of 14.2 months (range, 8.8-23.8 months). Sixteen patients randomized to selumetinib were alive with a median follow-up of 12.8 months (range, 6-35.2 months). No difference in overall survival was observed when limiting analysis to patients with tumor harboring a *GNAQ* or *GNA11* mutation (n = 83; eFigure 3B in Supplement 2).

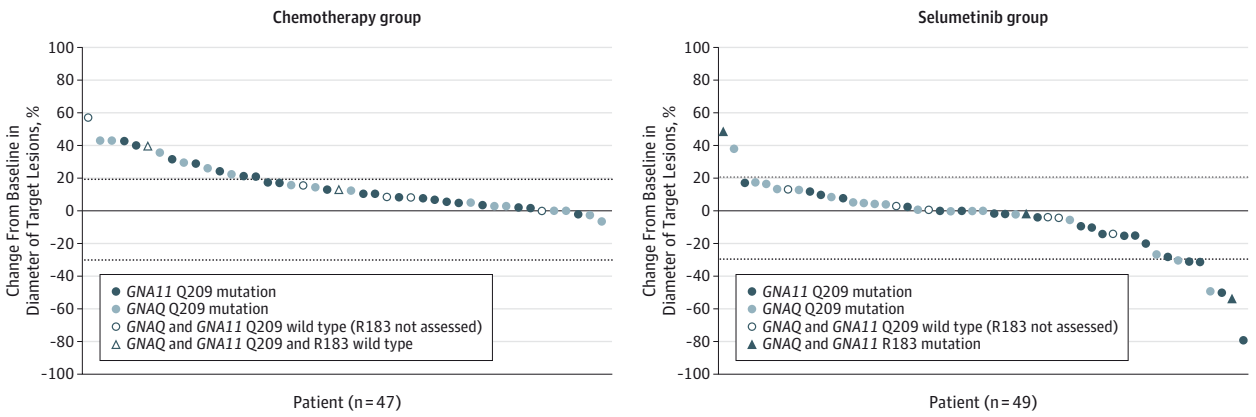
Tumor regression was uncommon with chemotherapy, with no RECIST responses observed (**Figure 3**A). In contrast, 49% of patients randomized to selumetinib achieved tumor regression (Figure 3B), with 7 (14%) of 49 patients evaluable for response achieving a 30% or greater tumor regression, consistent with a RECIST partial response. Five partial responses were confirmed on subsequent imaging studies, with durations of response of 23, 23.4, 25.3, 31.7, and 40.3 weeks. Two

Figure 2. Progression-Free Survival



Kaplan-Meier estimates of progression-free survival in all evaluable patients (n = 96; panel A) and in patients with tumor harboring mutations in exon 5 of *GNAQ* or *GNA11* (n = 80; panel B) treated as of April 22, 2013, are shown. The median progression-free survival was 7 weeks (95% CI, 4.3-8.4 weeks) among evaluable patients randomized to chemotherapy (n = 49) and 15.9 weeks (95% CI, 8.4-21.1 weeks) for evaluable patients randomized to selumetinib (n = 47). The hazard ratio for progression-free survival in all evaluable patients was 0.46 (95% CI, 0.30-0.71; *P* < .001) in favor of selumetinib (panel A). When limiting analysis to the 80 patients with tumor harboring a mutation (chemotherapy, n = 42; selumetinib, n = 38), the hazard ratio was 0.55 (95% CI, 0.34-0.87; *P* = .01) in favor of selumetinib (panel B).

Figure 3. Best Tumor Response for Each Patient



Data regarding the best tumor response are shown for the 47 patients evaluable for response in the chemotherapy group (panel A) and the 49 patients evaluable for response in the selumetinib group (panel B) who had undergone at least 1 tumor assessment after treatment and before the clinical cutoff date on December 31, 2013. Each marker represents data for an individual patient. The percentage change from baseline in the sum of the diameter of the target lesions is shown on the y-axis. Negative values indicate tumor shrinkage. The horizontal dashed lines indicate 20% tumor enlargement consistent with progression of disease by Response Evaluation Criteria in Solid Tumors (RECIST) and 30% tumor shrinkage consistent with a partial response by RECIST. Five patients with wild-type tumors for exon 5 of *GNAQ* and *GNA11* were tested for exon 4 mutations in *GNAQ* and *GNA11* and are indicated by triangles.

Table 2. Select Adverse Events Observed in More Than 5% of Patients and Adjudicated as Possibly, Probably, or Definitely Related to Therapy

	No. (%) of Participants[a]					
	Randomized to Chemotherapy (n = 50)[b]		Randomized to Selumetinib (n = 49)[c]		Allocated Without Randomization to Selumetinib (n = 8)[b]	
Adverse Events	Grade 1/2	Grade 3	Grade 1/2	Grade 3	Grade 1/2	Grade 3
Hematologic						
Anemia	8 (16)		15 (31)		5 (28)	1 (6)
Leukopenia	9 (18)		6 (12)		6 (33)	
Lymphopenia	4 (8)	1 (2)	1 (2)	3 (6)	2 (11)	2 (11)
Neutropenia	4 (8)	1 (2)	3 (6)		3 (17)	
Thrombocytopenia	8 (16)		5 (10)		5 (28)	
Nonhematologic						
Alanine aminotransferase elevation	4 (8)		17 (35)	4 (8)	7 (39)	
Alopecia			6 (12)		1 (6)	
Anorexia	7 (14)		4 (8)		1 (6)	
Arthralgias			5 (10)			
Aspartate aminotransferase elevation	6 (12)		20 (41)	5 (10)	7 (39)	
Blurred vision			3 (6)		1 (6)	
Constipation	15 (30)		3 (6)		1 (6)	
Creatine kinase elevation			18 (37)	8 (16)	13 (72)	1 (6)
Diarrhea	4 (8)		20 (41)		8 (44)	
Dyspnea			7 (14)	1 (2)	2 (11)	
Edema, face			6 (12)		3 (17)	
Edema, limbs	1 (2)		14 (29)	1 (2)	10 (56)	
Eye disorder			4 (8)		1 (6)	
Fatigue	22 (44)		30 (61)		8 (44)	
Mucositis	1 (2)		6 (12)			
Nausea	20 (40)		18 (37)		7 (39)	
Pruritus			8 (16)		1 (6)	
Rash, acneiform	3 (6)		37 (76)	1 (2)	12 (67)	
Vomiting	12 (24)		11 (22)		3 (17)	

[a] Data are presented for all participants treated as of December 31, 2013. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. No grade 4 adverse events were observed in more than 5% participants in any group.

[b] One participant in each of the randomized treatment groups and 1 participant in the nonrandomized portion of the trial did not receive study therapy and are not included.

[c] Adverse events observed in participants initially randomized to selumetinib only; does not include events observed in those receiving selumetinib after experiencing disease progression with chemotherapy.

were unconfirmed, with durations of response of 7.9 and 15.7 weeks. Representative images from 1 patient are presented in eFigure 4 in Supplement 2.

Forty-two patients (86%) randomized to chemotherapy experienced disease progression and subsequently received selumetinib. The median progression-free survival time was 8 weeks (95% CI, 8-12 weeks) (eFigure 5 in Supplement 2). Although tumor regression was observed in 11 (28%) of 40 patients evaluable for response, no objective RECIST response was observed (eFigure 6 in Supplement 2).

Nineteen patients were registered to receive selumetinib without randomization. Eighteen were treated and 17 were evaluable for progression-free survival. With 9 progression events and a median follow-up for those without progression of 12 weeks, the median progression-free survival time was 16 weeks (95% CI, 6-not reached) (eFigure 7 in Supplement 2). Of 17 patients evaluable for response, 1 (6%) achieved a partial response.

Tolerability

Select adverse events observed in more than 5% of patients attributed to temozolomide, dacarbazine, and selumetinib are presented in **Table 2**. All observed adverse events attributed to therapy and all observed adverse events regardless of attribution are presented in eTables 4 through 7 in Supplement 2.

Treatment-related adverse events (any grade) were observed in 65 (97%) of 67 patients treated with selumetinib, with the most common being acneiform rash (75%), creatine kinase elevation (60%), fatigue (57%), aspartate aminotransferase elevation (48%), and alanine aminotransferase elevation (42%). Blurred vision (6%) and other visual changes (7%) were observed. Twenty-five (37%) experienced grade 3 to 4 treatment-related adverse events, including creatine kinase elevation (13%), aspartate aminotransferase elevation (7%), and alanine aminotransferase elevation (6%). Most cases of creatine kinase elevation were asymptomatic and clinically insignificant; however, neck myopathy or myositis was observed in 3

patients (4%).[16] Twenty-five patients (37%) required at least 1 dose reduction of selumetinib because of adverse events (eTable 1 in Supplement 2). Four patients (6%) discontinued therapy because of treatment-related adverse events.

One patient (2%) treated with chemotherapy required dose reduction because of toxic effects. Eight patients (16%) initially randomized to chemotherapy did not receive selumetinib after disease progression because of death or declining performance status.

Pharmacodynamic Analysis

We observed sustained MAPK pathway inhibition in available tumor specimens, with median decreases in pERK and cyclin D1 of 48% (P = .03) and 76% (P = .03 by sign test), respectively (eTable 8 in Supplement 2). Of the 18 patients for whom specimens were available, 5 achieved radiographic regression, with 2 achieving RECIST partial responses. Six achieved clinical benefit as defined as a RECIST response or stable disease for longer than 16 weeks. Radiographic regression correlated with suppression of pERK (P = .03) but not cyclin D1 (P = .97 by Wilcoxon rank-sum test). No statistically significant association between pERK suppression and clinical benefit was observed (P = .07).

Discussion

In this hypothesis-generating phase 2 clinical trial, selumetinib compared with chemotherapy resulted in improved progression-free survival in patients with uveal melanoma not previously treated with temozolomide or dacarbazine. The median progression-free survival time was improved from 7 weeks with chemotherapy to 15.9 weeks with selumetinib. The 4-month progression-free survival rate was improved from 8.5% with chemotherapy to 43.1% with selumetinib. Tumor regression was more common with selumetinib, occurring in 50% of patients treated, with only 2 patients experiencing greater than 20% tumor growth (consistent with RECIST disease progression) at the time of the first scan. No effect on overall survival was observed.

Our results are similar to those of an unplanned subset analysis of patients with advanced uveal melanoma treated in a prior trial of selumetinib.[14] This analysis demonstrated a median progression-free survival time of 16.3 weeks (80% CI, 10-28.8 weeks) in 7 patients randomized to selumetinib vs 7.1 weeks (80% CI, 6.1-11.8 weeks) in 13 patients randomized to temozolomide. The limited activity observed with temozolomide is similar to that achieved in a phase 2 study of temozolomide[17] that reported a median time to disease progression of 1.84 months (range, 0.7-3.8 months) and to that observed in our study, which demonstrated a progression-free survival time of 7 weeks with chemotherapy.

The efficacy of MEK inhibition in uveal melanoma is predicted by the frequent activation of the MAPK pathway by functionally activating mutations in *GNAQ* or *GNA11*. This strategy may be applicable to other tumors characterized by MAPK pathway activation via additional mechanisms including receptor tyrosine kinase activation,[18] *RAS* mutation,[19] *NF1* loss,[20] and others. Single-agent activity has been observed with MEK162, another small molecule inhibitor of MEK, in *NRAS*-mutant melanoma.[21] Selumetinib has been demonstrated to enhance iodine update and retention in radioiodine-refractory thyroid cancer, with the most prominent activity observed in *NRAS*-mutant tumors.[22] Additionally, phase 2 trials comparing the efficacy of chemotherapy alone vs in combination with selumetinib have demonstrated improved outcomes with combination therapy in *KRAS*-mutant non-small cell lung cancer and *BRAF*-mutant melanoma, with hazard ratios for progression of 0.58 (P < .001) and 0.63 (P = .02), respectively.[23,24]

Our data suggest that progression-free survival is greater in the *GNAQ* and *GNA11* wild-type population (25.9 weeks [range, 3.7-40.4 weeks] vs 15.4 weeks [range, 8.1-16.9 weeks]). This observation may be explained by the presence of other mechanisms of MAPK pathway activation in exon 5 of *GNAQ* or *GNA11* wild-type tumors. After study initiation, activating mutations affecting exon 4 of *GNAQ* and *GNA11* were reported to occur in 12% of metastatic uveal melanomas in a pattern mutually exclusive with exon 5 mutations.[8] Thus, it is likely that the majority of the cases classified as wild type in this study had tumors harboring exon 4 *GNAQ* or *GNA11* mutations. Of the 5 exon 5 wild-type cases with sufficient remaining tumor material, we identified exon 4 mutations in 3 patients, 1 of whom achieved a major response to selumetinib.

As of December 31, 2013, we observed a median overall survival of 9.1 months and 11.8 months for those randomized to chemotherapy and selumetinib, respectively, which did not reach statistical significance. Because 86% of patients received selumetinib after experiencing disease progression with chemotherapy, which was permitted to maximize accrual from this rare cancer population, analysis of survival data are confounded. We observed that the efficacy of selumetinib may be affected by prior therapy with temozolomide or dacarbazine. The median progression-free survival time was 15.9 weeks and median progression-free response rate was 14% for those initially randomized to selumetinib; survival time was 8 weeks and response rate was 0% for those receiving selumetinib after experiencing disease progression with chemotherapy. Although our study was not designed to assess the effects of prior therapy on clinical outcome with selumetinib, these observations may reflect the induction of survival pathways or enhancement of angiogenesis with chemotherapy that confer resistance to MEK inhibition, or the more advanced disease in patients who have received prior therapies.[25]

Treatment-related adverse events were observed in 97% patients treated with selumetinib and were consistent with those observed with other inhibitors of MEK, including rash, creatine kinase elevation, edema, and visual changes.[21,26] Most events were manageable with supportive measures, but 37% required at least 1 dose reduction and 6% discontinued therapy because of toxic effects.

We previously observed effective MAPK pathway inhibition as demonstrated by pERK suppression with selumetinib in uveal melanoma cell lines.[10] Using human tumor specimens, we similarly demonstrated effective and sustained pathway blockade after 14 days of therapy, with inhibition of both

pERK and cyclin D1. Furthermore, radiographic regression correlated with the degree of pERK suppression, suggesting that optimal antitumor effects require more complete pathway inhibition.

Limitations of this study include the unblinded trial design and lack of central review of imaging studies. Additionally, this trial was designed before activating mutations in exon 4 of *GNAQ* and *GNA11* were reported; thus, prospective assessment for these alterations was not performed.

Conclusions

In this hypothesis-generating study of patients with advanced uveal melanoma, selumetinib compared with chemotherapy resulted in a modestly improved progression-free survival time and rate of response; however, no improvement in overall survival was observed. Improvement in clinical outcomes was accompanied by a high adverse event rate.

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Statistical analysis: Carvajal, Panageas, Schwartz.
Obtained funding: Carvajal, Doyle, Schwartz.
Administrative, technical, or material support: Carvajal, Sosman, Quevedo, Joshua, Linette, Flynn, Sato, Doyle, Bluth, Erinjeri, Marr, Abramson, Dickson, Schwartz.
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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Kudchadkar reports consulting/honoraria and speaker's fees from Genentech and Bristol-Myers Squibb and payment for development of educational presentations from RMEI and CancerNet; Dr Gajewski reports grants from Roche/Genentech, Bristol-Myers Squibb, Incyte, and Merck and consulting fees from Jouncs, Bayer, Boehringer-Ingelheim, and Abbvie; Dr Lutzky reports speaker's fees from Genentech and Bristol-Myers Squibb; Dr Panageas reports travel reimbursement from AstraZeneca; and Dr Wolchok reports grants and other personal fees and nonfinancial support from Bristol-Myers Squibb, Medimmune, Merck, GlaxoSmithKline, ImClone/Eli Lilly, Ziopharm, Polynoma, and Psioxus. No other disclosures were reported.

Funding/Support: This study was sponsored by the Cancer Therapy Evaluation Program. Financial support for this trial was provided by the National Cancer Institute, the Conquer Cancer Foundation, Cycle for Survival, and the Fund for Ophthalmic Knowledge. The Division of Cancer Treatment and Diagnosis at the National Cancer Institute provided selumetinib for this clinical trial.

Role of the Sponsor: The Cancer Therapy Evaluation Program worked jointly with the academic coauthors under a confidentiality agreement to participate in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the review and approval of the manuscript; and the decision to submit the manuscript for publication. All drafts of the manuscript were written and prepared by the authors. The authors vouch for the accuracy and completeness of the reported data and the fidelity of this report to the protocol.

Previous Presentations: Presented in part at the Cancer Therapy Evaluation Program Early Drug Development meeting, October 3-4, 2011, Bethesda, Maryland; the 15th biennial meeting of the International Society of Ocular Oncology, November 14-17, 2011, Buenos Aires, Argentina; Macula 2012, January 20-21, 2012, New York, New York; the fourth annual Scientific Retreat of the Melanoma Research Alliance, March 1-2, Washington, DC; the 48th annual meeting of the American Society of Clinical Oncology, June 1-5, 2012, Chicago, Illinois; the 2012 Beijing International Melanoma Congress, November 2-4, 2012, Beijing, China; and the 49th annual meeting of the American Society of Clinical Oncology, May 31–June 4, 2013, Chicago, Illinois.

Additional Contributions: We acknowledge Daniel J. Paucar, BS, Sloane Smith, MPH, and Anne Fusco, MPA, all from Memorial Sloan Kettering Cancer Center, for their contributions to this study, which included data acquisition, data analysis, and administrative support. No compensation was provided for this work.

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