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ORIGINAL REPORT

# Selumetinib in Combination With Dacarbazine in Patients With Metastatic Uveal Melanoma: A Phase III, Multicenter, Randomized Trial (SUMIT)

*Richard D. Carvajal, Sophie Piperno-Neumann, Ellen Kapiteijn, Paul B. Chapman, Stephen Frank, Anthony M. Joshua, Josep M. Piulats, Pascal Wolter, Veronique Cocquyt, Bartosz Chmielowski, T.R. Jeffry Evans, Lauris Gastaud, Gerald Linette, Carola Berking, Jacob Schachter, Manuel J. Rodrigues, Alexander N. Shoushtari, Delyth Clemett, Dana Ghiorghiu, Gabriella Mariani, Shirley Spratt, Susan Lovick, Peter Barker, Elaine Kilgour, Zhongwu Lai, Gary K. Schwartz, and Paul Nathan*

Author affiliations and support information (if applicable) appear at the end of this article.

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Corresponding author: Richard D. Carvajal, MD, Division of Hematology/Oncology, Columbia University Medical Center, New York, NY 10032; e-mail: carvajal@columbia.edu.



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## ABSTRACT

### Purpose

Uveal melanoma is the most common primary intraocular malignancy in adults with no effective systemic treatment option in the metastatic setting. Selumetinib (AZD6244, ARRY-142886) is an oral, potent, and selective MEK1/2 inhibitor with a short half-life, which demonstrated single-agent activity in patients with metastatic uveal melanoma in a randomized phase II trial.

### Methods

The Selumetinib (AZD6244: ARRY-142886) (Hyd-Sulfate) in Metastatic Uveal Melanoma (SUMIT) study was a phase III, double-blind trial (ClinicalTrial.gov identifier: NCT01974752) in which patients with metastatic uveal melanoma and no prior systemic therapy were randomly assigned (3:1) to selumetinib (75 mg twice daily) plus dacarbazine (1,000 mg/m$^2$ intravenously on day 1 of every 21-day cycle) or placebo plus dacarbazine. The primary end point was progression-free survival (PFS) by blinded independent central radiologic review. Secondary end points included overall survival and objective response rate.

### Results

A total of 129 patients were randomly assigned to receive selumetinib plus dacarbazine (n = 97) or placebo plus dacarbazine (n = 32). In the selumetinib plus dacarbazine group, 82 patients (85%) experienced a PFS event, compared with 24 (75%) in the placebo plus dacarbazine group (median, 2.8 *v* 1.8 months); the hazard ratio for PFS was 0.78 (95% CI, 0.48 to 1.27; two-sided $P = .32$). The objective response rate was 3% with selumetinib plus dacarbazine and 0% with placebo plus dacarbazine (two-sided $P = .36$). At 37% maturity (n = 48 deaths), analysis of overall survival gave a hazard ratio of 0.75 (95% CI, 0.39 to 1.46; two-sided $P = .40$). The most frequently reported adverse events (selumetinib plus dacarbazine *v* placebo plus dacarbazine) were nausea (62% *v* 19%), rash (57% *v* 6%), fatigue (44% *v* 47%), diarrhea (44% *v* 22%), and peripheral edema (43% *v* 6%).

### Conclusion

In patients with metastatic uveal melanoma, the combination of selumetinib plus dacarbazine had a tolerable safety profile but did not significantly improve PFS compared with placebo plus dacarbazine.

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## INTRODUCTION

Uveal melanoma arises from the uveal tract of the eye, which includes the choroid, ciliary body, and iris, and is the most common primary intraocular malignancy in adults.[1] Uveal melanoma is biologically distinct from cutaneous melanoma[2] and accounts for approximately 3% to 5% of all melanomas in the United States. There are currently no approved or effective systemic therapies specifically for these patients.

Mutations in *GNAQ* or *GNA11* are found in > 80% of uveal melanomas, resulting in constitutive activation of the RAS/RAF/MEK/ERK (RAS-ERK) pathway.[3-5] Selumetinib (AZD6244, ARRY-142886) is an oral, potent, and highly selective MEK1/2 inhibitor[6] that has a short half-life of approximately 5 hours.[7,8] In vitro, selumetinib plus temozolomide, an oral prodrug of dacarbazine,

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enhanced tumor growth inhibition, DNA damage, and apoptosis in a *KRAS*-mutant colorectal tumor model compared with temozolomide monotherapy.[9] In vivo studies demonstrated that selumetinib increases the levels of the proapoptotic protein BIM, a mediator of chemotherapy-induced cell death; therefore, addition of selumetinib to chemotherapy may increase cytotoxicity compared with chemotherapy alone.[9,10] Clinical trials assessing efficacy of selumetinib plus chemotherapy have shown activity in patients with mutations associated with the RAS-ERK pathway.[11]

In an open-label phase II study, patients with metastatic uveal melanoma who had not received prior treatment with temozolomide or dacarbazine achieved improved median progression-free survival (PFS) with selumetinib 75 mg twice daily versus temozolomide or dacarbazine (15.9 *v* 7 weeks; hazard ratio [HR] 0.46; 95% CI, 0.30 to 0.71; one-sided $P < .001$).[12]

Building on this evidence, we initiated a phase III trial to assess efficacy and safety of selumetinib plus dacarbazine in patients previously untreated with systemic therapy for metastatic uveal melanoma (Clinicaltrials.gov identifier: NCT01974752).[13]

## METHODS

### Study Design

Selumetinib (AZD6244: ARRY-142886) (Hyd-Sulfate) in Metastatic Uveal Melanoma (SUMIT) was a randomized, international, double-blind, placebo-controlled, phase III trial in which patients from 29 centers across 11 countries were enrolled (ClinicalTrials.gov identifier: NCT02768766). The protocol was approved by the local institutional review board or ethics committee of each participating site. The study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. All patients gave informed consent before undergoing any study-specific procedures.

Patients were randomly assigned 3:1 to receive selumetinib or matched placebo, plus dacarbazine, stratified by presence or absence of liver metastases.

### Patients

Patients were eligible if they had histologically or cytologically confirmed metastatic uveal melanoma, one or more lesions that could be accurately measured using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Patients were excluded if they had previously received systemic anticancer therapy (prior surgery and intrahepatic or other nonsystemic therapies were permitted); history of retinal pigmented epithelial detachment, central serous retinopathy, or retinal vein occlusion in the unaffected eye; or intraocular pressure > 21 mm Hg or uncontrolled glaucoma (irrespective of intraocular pressure) in the unaffected eye.

### Procedures

Patients received selumetinib (75 mg twice daily, continuous oral administration) or matched placebo, plus dacarbazine (1,000 mg/m$^2$ intravenously on day 1 of every 21-day cycle) until objective disease progression (confirmed by blinded independent central review [BICR]), intolerable toxicity, or another discontinuation criterion was met. Upon confirmation of objective disease progression, patients could receive open-label selumetinib monotherapy or selumetinib plus dacarbazine.

All patients were assessed by computed tomography (CT) scan or magnetic resonance imaging (MRI) at screening, week 6, and every 6 weeks thereafter until objective disease progression. Tumor response to treatment was assessed by BICR using RECIST 1.1.

Adverse events (AEs) were recorded from the time of informed consent, and graded using the National Cancer Institute Common Terminology Criteria for AEs (version 4.0). Baseline tumor samples from 106 patients were submitted to Foundation Medicine for prospective molecular profiling.

### Study End Points

The primary end point was efficacy of selumetinib plus dacarbazine compared with placebo plus dacarbazine in terms of PFS assessed by BICR of CT or MRI scans according to RECIST 1.1.[14] Secondary end points included objective response rate (ORR), duration of response, change in tumor size at week 6, overall survival (OS), safety and tolerability, and quality of life. Investigative site–based analysis of PFS was performed as a sensitivity analysis of the primary end point.

### Statistical Analysis

Assuming a true PFS HR of 0.46,[12] 93 PFS events would provide 90% power to demonstrate a statistically significant difference for PFS at a two-sided significance level of 5%. Approximately 128 patients were required for 3:1 randomization to selumetinib plus dacarbazine (n = 96 patients) or placebo plus dacarbazine (n = 32 patients) groups to obtain a minimum of 93 PFS events. Additional information on randomization, masking, statistical analysis, and procedures is given in the Supplemental Data.

## RESULTS

### Patients

From April 2014 to February 2015, 152 patients were screened (Fig 1). Twenty-three patients were excluded and 129 were randomly assigned to either to the study treatment with selumetinib plus dacarbazine (n = 97) or placebo plus dacarbazine (n = 32). Patient demographics were generally balanced between treatment groups at baseline, with the exception of sex and number of sites of disease (Table 1).

### Efficacy

The primary end point of PFS assessed by BICR was not met. In the selumetinib plus dacarbazine group, there were 82 events (85%) compared with 24 (75%) for placebo plus dacarbazine; the HR for PFS was 0.78 (95% CI: 0.48 to 1.27) with a two-sided *P* value of 0.32 (Fig 2A), showing no significant benefit of selumetinib plus dacarbazine for PFS. Median estimated PFS was 2.8 months in the selumetinib plus dacarbazine group and 1.8 months in the placebo plus dacarbazine group. Median follow-up for PFS (ie, time from random assignment to death or progression for patients with an event, and time from random assignment to censoring for censored patients) in the selumetinib plus dacarbazine and placebo plus dacarbazine groups was 2.7 and 1.5 months, respectively. Three- and 6-month PFS rates were 38% and 10%, respectively, in the selumetinib plus dacarbazine group, and 26% and 18%, respectively, in the placebo plus dacarbazine group.

The sensitivity analysis of ascertainment bias (based on investigational site–based assessment of PFS) was inconsistent with the primary analysis, showing statistically significant improvement in PFS for selumetinib plus dacarbazine compared with placebo plus dacarbazine (3.8 *v* 2.1 months; HR, 0.49; 95% CI, 0.28 to 0.84; $P = .01$; Data Supplement). The sensitivity analysis of evaluation

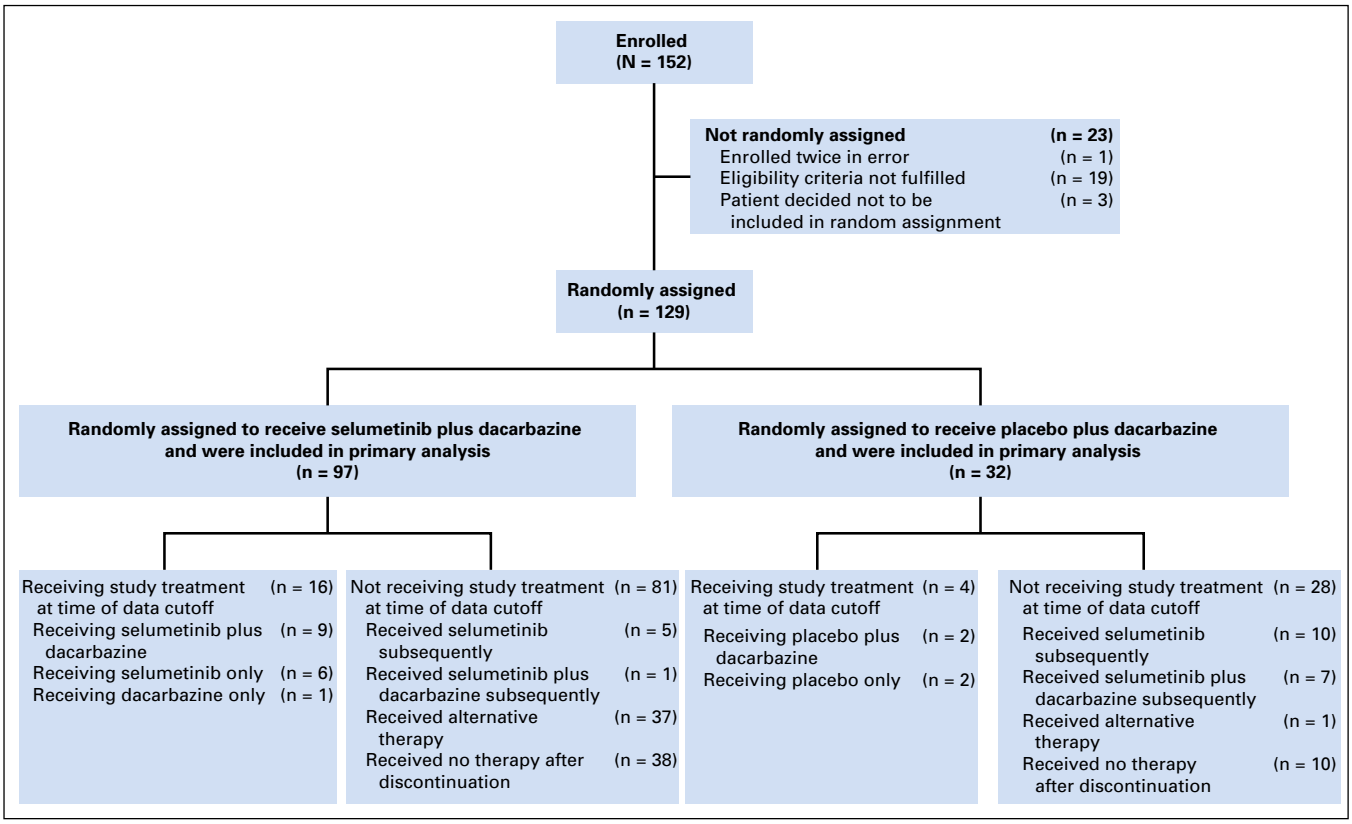


**Fig 1.** CONSORT diagram. Of the 97 patients randomly assigned to receive the combination of selumetinib and dacarbazine, all received the assigned therapy. At the time of data cutoff, 16 continued to receive the assigned study treatment and did not meet criteria for discontinuation. Of the 81 patients who did meet criteria for discontinuation, the subsequent treatment received is listed. Of the 32 patients randomly assigned to receive the combination of placebo and dacarbazine, all received the assigned therapy. At the time of data cutoff, four continued to receive the study treatment and did not meet criteria for discontinuation. Of the 28 patients who did meet criteria for discontinuation, the subsequent treatment received is listed. Data cutoff was May 15, 2015.

time bias (based on BICR of CT and MRI scans according to RECIST 1.1) was consistent with the primary analysis (HR, 0.82; 95% CI, 0.51 to 1.33; $P = .42$). The interaction test assessing consistency of treatment effect across potential prognostic factors was statistically significant ($P = .046$; Fig 3), mainly due to ECOG performance status, where there was a larger treatment effect in a small subgroup of patients with ECOG performance status of 1 (HR, 0.28; 95% CI, 0.13 to 0.69) compared with ECOG performance status of 0 (HR, 1.05; 95% CI, 0.62 to 1.88). This suggests that patients with a higher tumor burden may have a larger treatment effect; however, no firm conclusions can be made because of the low patient number.

Analysis of the secondary efficacy end points of OS, ORR, and percentage change in tumor size at week 6 showed no statistically significant differences between treatment groups. Preliminary analysis of OS (n = 48 deaths; 37% maturity) by log-rank test gave an HR of 0.75 (95% CI, 0.39 to 1.46; two-sided $P = .40$; Fig 2B). Given the results of the primary analysis, additional analysis of OS with additional events is not planned. ORR was similar between the selumetinib plus dacarbazine (n = 3 of 97; 3%) and placebo plus dacarbazine (n = 0 of 32; 0%) groups (two-sided $P = .36$). Three patients achieved partial responses with durations of 43, 56, and 146 days. Target lesion size at week 6 increased in both groups, with a geometric mean fold change of 1.06 in the selumetinib plus dacarbazine group and 1.16 in the placebo plus dacarbazine group, and with a geometric least squares mean ratio 0.94 (95% CI, 0.88 to 1.02; two-sided $P = .13$). Waterfall plots of best percentage change in tumor size from baseline for all patients are shown in the Data Supplement.

At data cutoff, 16 patients (17%) from the selumetinib plus dacarbazine group and four (13%) from the placebo plus dacarbazine group remained on their randomly assigned study arm. Twenty-three patients (18%) received open-label selumetinib after disease progression while in the initially assigned study arm (n = 15 with selumetinib monotherapy and n = 8 with selumetinib plus dacarbazine). The majority of these patients (n = 17 of 23) had been randomly assigned to placebo plus dacarbazine in the double-blind phase. Four patients (3%) were receiving ongoing open-label treatment at the time of data cut off (three patients continued receiving selumetinib monotherapy and one continued receiving selumetinib plus dacarbazine). Disease progression was the most common reason for discontinuation of open-label treatment.

### *Safety*

A summary of AEs is provided in Table 2 and Table 3; AEs of special interest because of their association with selumetinib are highlighted in Table 3. Incidence of AEs of special interest was more frequent with selumetinib plus dacarbazine; however, these were generally grade 1/2. One patient in the selumetinib plus

  

**Table 1.** Baseline Characteristics

| Characteristic | Selumetinib + Dacarbazine (n = 97), No. (%) | Placebo + Dacarbazine (n = 32), No. (%) |
|---|---|---|
| Sex | | |
| Female | 42 (43) | 19 (59) |
| Male | 55 (57) | 13 (41) |
| Age, years, median (range) | 63 (2-86) | 58 (42-84) |
| Race | | |
| White | 96 (99) | 31 (97) |
| Other | 1 (1) | 1 (3) |
| ECOG PS | | |
| 0 | 72 (74) | 22 (69) |
| 1 | 25 (26) | 10 (31) |
| Primary tumor location | | |
| Choroid | 86 (89) | 29 (91) |
| Ciliary body | 7 (7) | 4 (13) |
| Iris | 1 (1) | 0 |
| Missing | 3 (3) | 0 |
| Presence of liver metastases* | | |
| Yes | 89 (92) | 30 (94) |
| No | 8 (8) | 2 (6) |
| Number of organ sites involved with disease | | |
| 1 | 53 (55) | 11 (34) |
| 2 | 20 (21) | 9 (28) |
| 3 | 18 (19) | 9 (28) |
| 4 | 6 (6) | 1 (3) |
| ≥ 5 | 0 | 2 (6) |
| Time from primary tumor diagnosis to random assignment | | |
| ≤ 18 months | 26 (27) | 7 (22) |
| > 18 to ≤ 36 months | 28 (29) | 6 (19) |
| > 36 months | 43 (44) | 18 (56) |
| Missing | 0 | 1 (3) |
| Mutation status† | (n = 60) | (n = 18) |
| *GNAQ* mutation positive | 23 (38) | 9 (50) |
| *GNA11* mutation positive | 33 (55) | 8 (44) |
| *GNAQ* and *GNA11* mutation negative | 4 (7) | 1 (6) |

NOTE. Population: full analysis set, data cutoff: May 15, 2015.
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
*Stratification factor.
†Tumor tissue samples from 106 patients were submitted to Foundation Medicine for genomic profiling: 78 were successfully analyzed; tumor material was insufficient for testing for 28 patients; samples were not available from 23 patients.

dacarbazine group, who died of uveal melanoma progression, had grade 5 cardiac failure considered by the investigator to be unrelated to study treatment. Safety and tolerability data from patients receiving open-label therapy were consistent with the mild to moderate toxicities observed during the double-blind phase.

Despite the AE rate, most patients could be treated with single-dose interruptions or reductions. The actual treatment duration of selumetinib or placebo was within 5 days of the intended duration in each group (Table 2), and the actual dose intensity relative to intended dose intensity was > 88% for selumetinib, placebo, and dacarbazine in both groups despite dose reductions or interruptions. The longer treatment with selumetinib was due to longer disease control compared with placebo. Few AEs led to study drug discontinuation; disease progression was the main reason for study drug discontinuation (Table 2).

### *Molecular Analysis*

Prior groups have demonstrated uveal melanoma to be a disease characterized by a low mutational burden and recurrent chromosomal alterations[15]; however, most of this work has been performed using primary uveal melanoma samples.

Of 106 baseline tumor samples (obtained primarily from metastatic sites of disease) submitted to Foundation Medicine for genomic profiling, 78 were successfully analyzed. There was a median of nine mutations per sample (range, two to 21 mutations). We observed mutually exclusive *GNAQ* or *GNA11* mutations in 94% of samples (n = 73 of 78), a frequency higher than observed in The Cancer Genome Atlas (TCGA) for uveal melanoma data set (Data Supplement). All *GNA11* (n = 41 of 41), and most *GNAQ* mutations (n = 29 of 32) occurred in exon 5; the remaining *GNAQ* mutations occurred in exon 4 (n = 2). One additional patient had a variant of unknown significance in GNAQ (G48L, exon 2).

Comparison of data from TCGA, reanalyzed using VarDict, showed the most significant difference between SUMIT and TCGA analyses was the incidence of *BAP1* mutations, with 62.3% and 30.0% mutation rates, respectively ($P = .00006$). This is reflective of the increased risk for development of metastatic disease in primary uveal melanomas harboring BAP1 mutations.[16] There were no significant differences for *GNA11*, *GNAQ*, or *SF3B1* mutations, nor for *MYC* amplification. *CDKN2A/B* deletions, *GNAS* amplification, and *TP53* mutations were only detected in the SUMIT cohort and at a low frequency (< 10%). Previous reports have highlighted recurrent mutations in CYSLTR2[17] and PLCB4,[18] but these were not assessed in this study.

## DISCUSSION

Selumetinib plus dacarbazine did not improve clinical outcomes for patients with metastatic uveal melanoma compared with placebo plus dacarbazine. Although the previous phase II trial of selumetinib monotherapy demonstrated an HR of 0.46 (one-sided $P \leq .001$) for PFS in favor of selumetinib over chemotherapy,[12] no significant improvement in PFS was observed with selumetinib plus dacarbazine over placebo plus dacarbazine (HR, 0.78; two-sided $P = .32$) in this study. Fourteen percent of patients achieved a partial response with selumetinib in the phase II trial,[12] whereas only 3% treated with selumetinib plus dacarbazine achieved a response in the SUMIT trial.

Results of this study differ from others evaluating selumetinib plus chemotherapy in other tumor types characterized by mitogen-activated protein kinase (MAPK) pathway activation, which demonstrate improved clinical activity with combinatorial therapy over chemotherapy alone.[11,19] These studies also demonstrate how the various mechanisms of MAPK activation can respond differently to MAPK inhibition. In a phase II trial of selumetinib plus dacarbazine versus placebo plus dacarbazine in patients with *BRAF*-mutant cutaneous or unknown primary melanoma, median PFS was 5.6 and 3.0 months, respectively (HR, 0.63; 80% CI, 0.47 to 0.84; one-sided $P = .021$), with an ORR of 40% versus 26%.[11] A phase II trial of selumetinib plus docetaxel versus placebo plus docetaxel in patients with *KRAS*-mutant non–small-cell lung

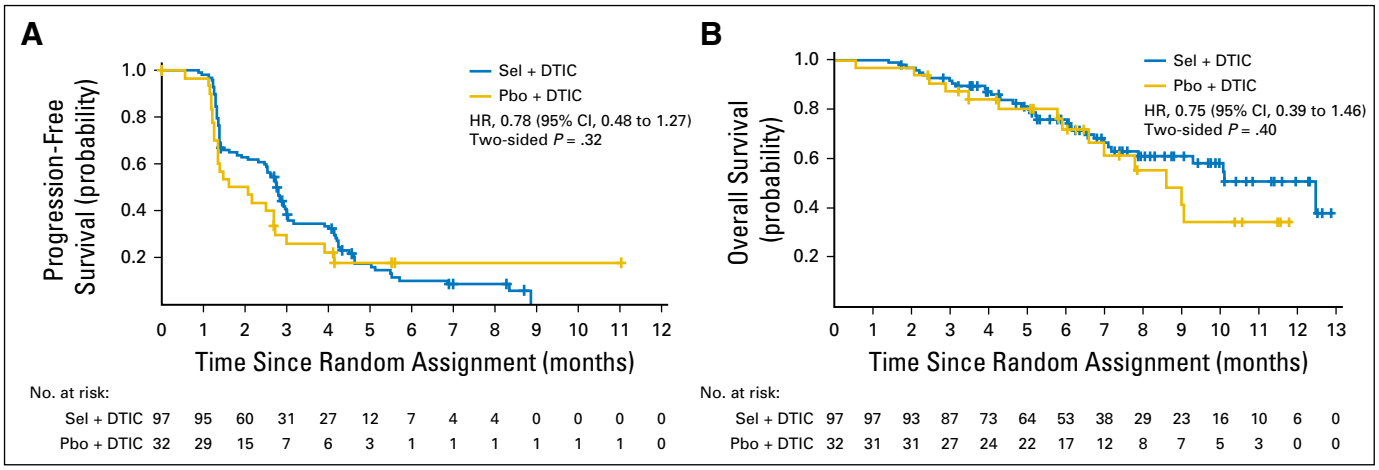


**Fig 2.** Kaplan-Meier estimates of progression-free survival and overall survival. (A) Blinded independent central review of progression-free survival. (B) Overall survival. Population: full analysis set, data cutoff: May 15, 2015. Crosses denote censored observations. Overall survival data are immature, with 34 events (35%) and 14 events (44%) in the selumetinib plus dacarbazine and placebo plus dacarbazine groups, respectively. DTIC, dacarbazine; HR, hazard ratio; Pbo, placebo; Sel, selumetinib.

cancer demonstrated a median PFS of 5.3 versus 2.1 months, respectively (HR for progression, 0.58, 80% CI, 0.42 to 0.79; one-sided $P = .014$), with an ORR of 37% versus 0%.[19] However, more recently, selumetinib plus docetaxel failed to meet the primary end point of PFS in the phase III SELECT-1 trial.[20]

Effects of *GNAQ* and *GNA11* mutations on downstream growth pathways differ from those associated with *BRAF* and *KRAS* mutations, and include activation of the MAPK pathway[21] via phospholipase C[22] and protein kinase C activation,[23] the phosphatidylinositol-3 kinase (PI3K)/AKT pathway,[24] and the

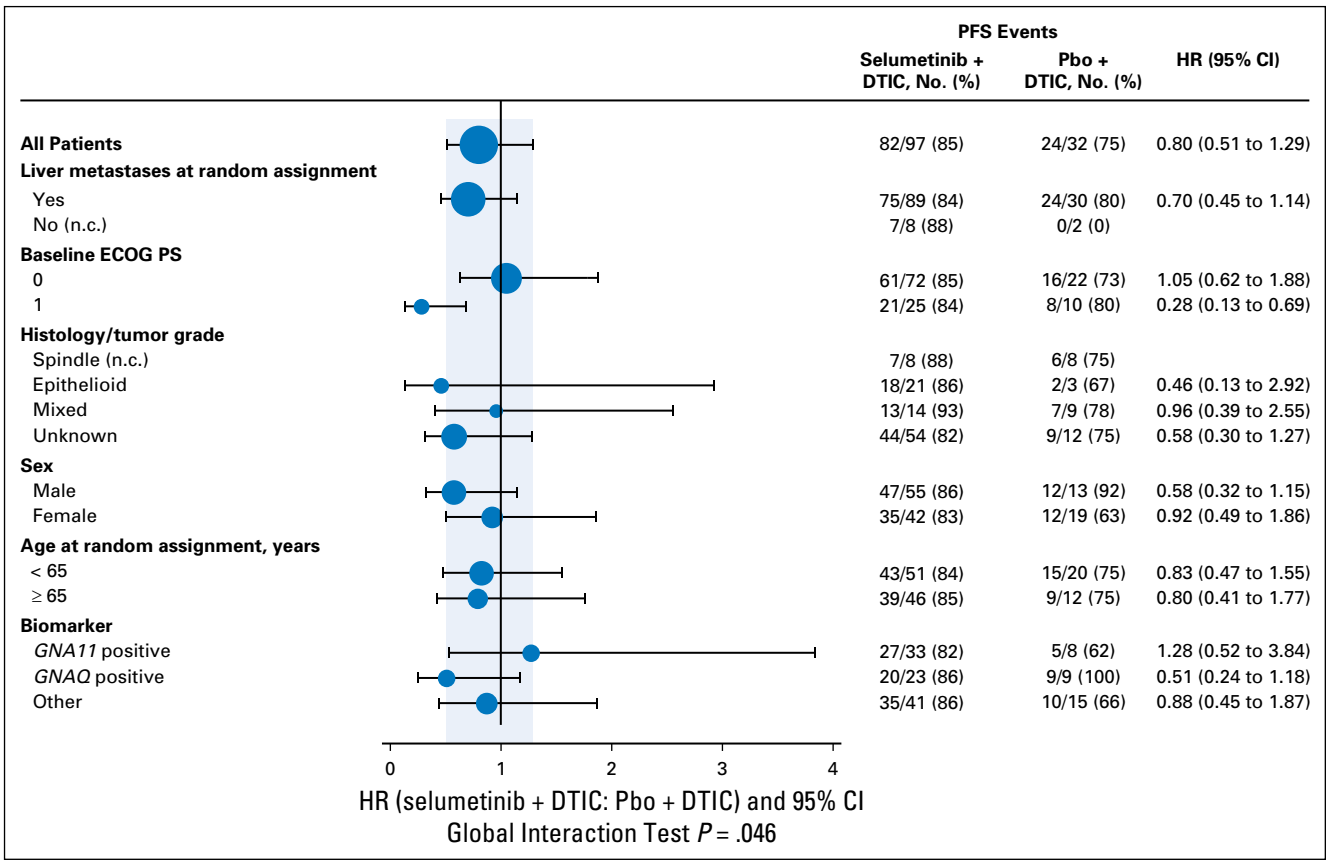


**Fig 3.** Progression-free survival by prespecified subgroup. Population: full analysis set, data cutoff: May 15, 2015. Hazard ratios were not calculated for subgroups with < 20 events. With the exception of liver metastases at randomization (yes/no), all analyses were performed using a Cox proportional hazards model. The size of the circle is proportional to the number of events. Progression includes deaths in the absence of RECIST progression. Progression events occurring 14 weeks after last evaluable assessment (or randomization) are censored and, therefore, excluded. DTIC, dacarbazine; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; n.c., not calculated; Pbo, placebo.

  

**Table 2.** Adverse Events During Randomized Treatment

| Category | Selumetinib + Dacarbazine (n = 97) | Placebo + Dacarbazine (n = 32) |
|---|---|---|
| Any AE | 97 (100) | 32 (100) |
| Any AE CTCAE ≥ grade 3 | 61 (63) | 17 (53) |
| Any SAE | 20 (21) | 2 (6) |
| Any AE leading to hospitalization | 17 (18) | 2 (6) |
| Any AE with outcome of death | 1 (1)* | 0 |
| Selumetinib/placebo | | |
| Any AE leading to discontinuation | 6 (6)† | 1 (3)‡ |
| Any AE leading to dose interruption | 35 (36) | 7 (22) |
| Any AE leading to dose reduction | 20 (21) | 4 (13) |
| Duration of treatment, days, median (range)§ | 112 (21-400) | 68 (8-418) |
| Dacarbazine | | |
| Any AE leading to discontinuation | 7 (7) | 2 (6) |
| Any AE leading to dose delay | 20 (21) | 11 (34) |
| Any AE leading to dose reduction | 28 (29) | 11 (34) |
| No. of cycles, median (range)§ | 5 (1-17) | 3 (1-8) |

NOTE. Data given as no. (%) unless otherwise indicated. Population: safety analysis set, data cutoff: May 15, 2015.§

Abbreviations: AE, adverse event; CTCAE, common terminology criteria for adverse events; SAE, serious adverse event.

*Grade 5 cardiac failure considered unrelated to treatment.

†Retinal vein occlusions (n = 2); blood creatinine phosphokinase increased (n = 1); febrile neutropenia (n = 1); cardiac failure (n = 1); peripheral edema (n = 1); lung infection (n = 1).

‡Blood bilirubin increased and hypoalbuminemia (n = 1).

§Treatment summaries as of addendum data cutoff: February 18, 2016.

Hippo pathway.[25] This, as well as other cell context–dependent differences between uveal melanoma, *BRAF*-mutant cutaneous melanoma, and *KRAS*-mutant non–small-cell lung cancer, in part may explain the discrepant results observed in these trials; however, additional investigation into these differences is needed. Limited work conducted in parallel to the SUMIT trial in three xenograft models derived from patients with uveal melanoma, derived from metastatic tumor specimens and characterized by *GNAQ* and *GNA11* mutations, demonstrated that dacarbazine alone and in combination with selumetinib induced strong tumor growth inhibition in one model, and selumetinib continued after combination treatment significantly delayed disease progression compared with dacarbazine maintenance. However, combination of selumetinib and dacarbazine did not increase tumor response in these models compared with either agent alone, comparable to the results observed in the SUMIT trial.[26] These xenograft models derived from patients with uveal melanoma were difficult to generate; therefore, these data were not available at the time of trial design.

Median PFS in this study was 2.8 months in the selumetinib plus dacarbazine group, numerically but not statistically greater than the 1.8 month median PFS observed in the placebo plus dacarbazine group. Given the 6-week interval for restaging studies in this trial, these results are comparable to the PFS of 3.6 months observed in the selumetinib monotherapy group and 1.6 months observed in the chemotherapy group in the phase II monotherapy trial, during which imaging was performed every 4 weeks for 8 weeks, and every 8 weeks thereafter. It was hypothesized that the lack of significant benefit for selumetinib plus dacarbazine in this study may have been caused by increased toxicity, decreased compliance, or decreased dose density. However, the actual treatment duration for selumetinib or placebo being within 5 days of the intended treatment duration in each group, and the actual dose intensity relative to intended dose intensity > 88% for each treatment across both groups, provides evidence against this hypothesis.

The modest improvement in PFS observed with selumetinib alone or plus dacarbazine in uveal melanoma suggests that any clinical activity of MEK inhibitors in G-protein–driven tumors may be limited by the rapid development of adaptive resistance to MEK inhibition or progression of primarily resistant tumor clones. This hypothesis is supported by the results of the phase III trial of binimetinib, an oral selective adenosine triphosphate–uncompetitive inhibitor of MEK1/2 versus dacarbazine in *NRAS*-mutant cutaneous melanoma, where, despite an overall response rate of 15% with binimetinib, demonstrating objective radiographic evidence of antitumor activity, only a modest improvement in median PFS of 2.8 versus 1.5 months in favor of binimetinib was reported (HR, 0.62; 95% CI, 0.47 to 0.80; $P \leq .001$).[27]

Radiographic assessment of treatment response in liver metastases is associated with unique challenges, with interobserver agreement dependent on radiologist experience and the imaging modality used.[28] These challenges are amplified in uveal melanoma, a disease with a predilection for hepatic metastasis and associated with greater radiographic heterogeneity compared with other tumor types as a result of the presence of hemorrhage, methemoglobin, and melanin.[29] These factors may have contributed to the discordance in our results based on central and site-based radiologic reviews. Although the HR for the primary analysis of PFS assessed by BICR was a statistically insignificant 0.78 in favor of selumetinib plus dacarbazine (two-sided $P = .32$), the HR of PFS assessed by investigative site–based review was 0.49 in favor of selumetinib plus dacarbazine (two-sided $P = .01$), with a median PFS of 3.8 versus 2.1 months in the selumetinib plus dacarbazine and placebo plus dacarbazine groups, respectively. In 88 of the 106 patients (83%) with PFS events, there was concordance between central and site-based imaging reviews regarding the development of disease progression; however, a difference was observed in the timing of progression events, which was the primary driver in the difference in PFS as determined by central and site-based reviews. Despite the double-blinded study design and the use of independent reference radiologists for review of imaging studies at most of the participating centers, the distinct toxicity profile associated with selumetinib that includes easily observable toxicities such as rash, peripheral edema, and creatine phosphokinase elevation may have introduced bias into the site-based determination of PFS.

In conclusion, selumetinib plus dacarbazine was not associated with a significant improvement in PFS or ORR for patients with metastatic uveal melanoma compared with placebo plus dacarbazine. Given the lack of effective treatment options for patients with advanced uveal melanoma, rapid development and testing of novel therapeutic strategies are critical. The SUMIT trial began 6 years after initial reports of frequent, functionally activating *GNAQ* mutations in uveal melanoma and demonstrates feasibility of the rapid conduct of pivotal clinical trials in this rare tumor type. Despite the results of this study, additional assessment of MEK inhibitors in uveal

**Table 3.** Most Frequent Adverse Events (All Causality) Reported in ≥ 10% of Patients During Randomized Treatment

| Preferred Term | Selumetinib + Dacarbazine (n = 97), No. (%) | | | Placebo + Dacarbazine (n = 32) , No. (%) | | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 |
| Nonlaboratory parameters | | | | | | |
| Patient with any adverse event | 97 (100) | 47 (48) | 13 (13) | 32 (100) | 10 (31) | 7 (22) |
| Nausea* | 60 (62) | 1 (1) | 0 | 6 (19) | 0 | 0 |
| Rash* | 55 (57) | 2 (2) | 0 | 2 (6) | 0 | 0 |
| Fatigue* | 43 (44) | 1 (1) | 0 | 15 (47) | 2 (6) | 0 |
| Diarrhea* | 43 (44) | 2 (2) | 0 | 7 (22) | 0 | 0 |
| Peripheral edema* | 42 (43) | 2 (2) | 0 | 2 (6) | 0 | 0 |
| Constipation | 37 (38) | 1 (1) | 0 | 14 (44) | 0 | 0 |
| Dermatitis acneiform* | 30 (31) | 1 (1) | 0 | 1 (3) | 0 | 0 |
| Vomiting* | 27 (28) | 1 (1) | 0 | 6 (19) | 0 | 0 |
| Asthenia | 21 (22) | 2 (2) | 0 | 4 (13) | 0 | 0 |
| Dyspnea | 19 (20) | 0 | 0 | 3 (9) | 0 | 0 |
| Hypertension* | 18 (19) | 8 (8) | 0 | 1 (3) | 1 (3) | 0 |
| Decreased appetite | 17 (18) | 1 (1) | 0 | 9 (28) | 0 | 0 |
| Anemia | 17 (18) | 1 (1) | 0 | 4 (13) | 1 (3) | 0 |
| Stomatitis* | 15 (16) | 0 | 0 | 2 (6) | 0 | 0 |
| Pruritus | 14 (14) | 0 | 0 | 3 (9) | 0 | 0 |
| Headache | 13 (13) | 2 (2) | 0 | 3 (9) | 1 (3) | 0 |
| Myalgia | 12 (12) | 0 | 0 | 1 (3) | 0 | 0 |
| Skin fissures | 12 (12) | 0 | 0 | 0 | 0 | 0 |
| Urinary tract infection | 11 (11) | 1 (1) | 0 | 4 (13) | 1 (3) | 0 |
| Dysgeusia | 11 (11) | 0 | 0 | 3 (9) | 0 | 0 |
| Dyspepsia | 11 (11) | 0 | 0 | 2 (6) | 0 | 0 |
| Dry skin* | 11 (11) | 0 | 0 | 0 | 0 | 0 |
| Abdominal pain | 10 (10) | 1 (1) | 0 | 3 (9) | 1 (3) | 0 |
| Vision blurred* | 10 (10) | 0 | 0 | 1 (3) | 0 | 0 |
| Pyrexia* | 9 (9) | 0 | 0 | 5 (16) | 0 | 0 |
| Insomnia | 7 (7) | 0 | 0 | 4 (13) | 0 | 0 |
| Arthralgia | 5 (5) | 0 | 0 | 4 (13) | 0 | 0 |
| Laboratory parameters† | | | | | | |
| Blood creatinine phosphokinase level increased*‡ | 36 (37) | 8 (8) | 2 (2) | 2 (6) | 0 | 0 |
| Aspartate aminotransferase level increased | 28 (29) | 6 (6) | 0 | 5 (16) | 1 (3) | 0 |
| Alanine aminotransferase level increased | 27 (28) | 6 (6) | 1 (1) | 5 (16) | 2 (6) | 0 |
| Thrombocytopenia | 26 (27) | 8 (8) | 4 (4) | 4 (13) | 0 | 0 |
| Neutropenia | 25 (26) | 12 (12) | 7 (7) | 11 (34) | 3 (9) | 7 (22) |

Note. Population: safety analysis set, data cutoff: May 15, 2015. Adverse events reported in ≥ 10% patients, ordered by frequency in patients receiving selumetinib plus dacarbazine.
*Adverse event of special interest because of known association with selumetinib.
†Deterioration compared with baseline in protocol-mandated laboratory values were reported as adverse events if they fulfilled any of the serious adverse event criteria or were the reason for discontinuation of treatment with the investigational product.
‡Creatinine phosphokinase increase was prospectively measured in the battery of laboratory parameters.

melanoma is warranted. It remains a possibility that dacarbazine limits the efficacy of MEK inhibitors in this disease, and the exploration selumetinib as monotherapy or in alternative combinations, other than with alkylating agents, remains of interest. A trial evaluating selumetinib plus paclitaxel for metastatic uveal melanoma is underway (EudraCT: 2014-004437-22). On the basis of the hypotheses that greater efficacy and improved tolerability may be achieved by delivering selumetinib in greater doses, with more complete target inhibition using a pulsatile dosing schedule, a phase Ib dose-escalation study of intermittent selumetinib in patients with advanced uveal melanoma who have not been previously treated with a MEK inhibitor is also ongoing (ClinicalTrials.gov: NCT02768766).

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Disclosures provided by the authors are available with this article at jco.org.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Richard D. Carvajal, Gary K. Schwartz, Paul Nathan
**Provision of study materials or patients:** Richard D. Carvajal, Sophie Piperno-Neumann, Ellen Kapiteijn, Paul B. Chapman, Stephen Frank, Anthony M. Joshua, Josep M. Piulats, Pascal Wolter, Veronique Cocquyt, Bartosz Chmielowski, T.R. Jeffry Evans, Lauris Gastaud, Gerald Linette, Carola Berking, Jacob Schachter, Manuel J. Rodrigues, Alexander N. Shoushtari, Gary K. Schwartz, Paul Nathan
**Collection and assembly of data:** Richard D. Carvajal, Stephen Frank, Anthony M. Joshua, Josep M. Piulats, Pascal Wolter, Veronique Cocquyt, T.R. Jeffry Evans, Gerald Linette, Carola Berking, Jacob Schachter, Alexander N. Shoushtari, Dana Ghiorghiu, Gabriella Mariani, Susan Lovick, Elaine Kilgour, Zhongwu Lai, Gary K. Schwartz, Paul Nathan
**Data analysis and interpretation:** All authors
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors

  

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### *Affiliations*


**Richard D. Carvajal** and **Gary K. Schwartz**, Columbia University Medical Center; **Paul B. Chapman** and **Alexander N. Shoushtari**, Memorial Sloan Kettering Cancer Center, New York, NY; **Sophie Piperno-Neumann** and **Manuel J. Rodrigues**, Institut Curie, Paris; **Lauris Gastaud**, Centre Antoine-Lacassagne, Nice, France; **Ellen Kapiteijn**, Leiden University Medical Center, Leiden, the Netherlands; **Stephen Frank**, Hebrew University Hadassah Medical School – The Sharett Institute of Oncology, Jerusalem; **Jacob Schachter**, Sheba Medical Center at Tel Hashomer, and Tel-Aviv University Medical School, Tel Aviv, Israel; **Anthony M. Joshua**, Princess Margaret Cancer Centre, Toronto, ON, Canada; **Josep M. Piulats**, Institut Catala d'Oncologia L'Hospitalet, L'Hospitalet de Llobregat, Barcelona, Spain; **Pascal Wolter**, University Hospitals Leuven, Leuven, Belgium; **Veronique Cocquyt**, Ghent University Hospital, Ghent, Belgium; **Bartosz Chmielowski**, University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA; **T.R. Jeffry Evans**, University of Glasgow, Glasgow; **Delyth Clemett**, **Shirley Spratt**, **Susan Lovick**, and **Elaine Kilgour**, AstraZeneca, Macclesfield; **Dana Ghiorghiu** and **Gabriella Mariani**, AstraZeneca, Cambridge; **Paul Nathan**, Mt Vernon Cancer Centre, Northwood, United Kingdom; **Gerald Linette**, Washington University School of Medicine, St Louis, MO; **Carola Berking**, University Hospital of Munich, Munich, Germany; **Peter Barker**, AstraZeneca, Gaithersburg, MD; and **Zhongwu Lai**, AstraZeneca, Waltham, MA.


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**Richard D. Carvajal**
**Consulting or Advisory Role:** AstraZeneca, Bristol-Myers Squibb, Castle Biosciences, Foundation Medicine, Iconic Therapeutics, Immunocore, Incyte, Merck, Roche
**Other Relationship:** Aura Biosciences, Chimeron, Rgenix

**Sophie Piperno-Neumann**
No relationship to disclose

**Ellen Kapiteijn**
No relationship to disclose

**Paul B. Chapman**
**Honoraria:** Bristol-Myers Squibb, GlaxoSmithKline, Roche, Provectus, Momenta Pharmaceuticals, Daiichi Sankyo
**Consulting or Advisory Role:** Bristol-Myers Squibb, GlaxoSmithKline, Roche, Daiichi Sankyo, Provectus, Momenta Pharmaceuticals
**Research Funding:** GlaxoSmithKline, Roche, Bristol-Myers Squibb, Pfizer
**Travel, Accommodations, Expenses:** Bristol-Myers Squibb

**Stephen Frank**
No relationship to disclose

**Anthony M. Joshua**
No relationship to disclose

**Josep M. Piulats**
No relationship to disclose

**Pascal Wolter**
No relationship to disclose

**Veronique Cocquyt**
No relationship to disclose

**Bartosz Chmielowski**
**Consulting or Advisory Role**: Amgen, Bristol-Myers Squibb, Merck, Roche, Eisai, Immunocore
**Speakers' Bureau:** Roche, Janssen Oncology
**Travel, Accommodations, Expenses:** Roche, Bristol-Myers Squibb, Janssen, Merck

**T.R. Jeffry Evans**
**Honoraria:** Bristol-Myers Squibb, Clovis Oncology, Karus Therapeutics, Baxalta, Bayer, Celgene, Eisai, Glaxo Smith Kline, Otsuka, Roche, TC Biopharm, Transgene/Jennerex
**Consulting or Advisory Role:** Bristol-Myers Squibb, Clovis Oncology, Karus Therapeutics (Inst), Baxalta (Inst), Bayer (Inst), Celgene (Inst), Eisai (Inst), Glaxo Smith Kline (Inst), Otsuka (Inst), Roche (Inst), TC Biopharm (Inst), Immunova (Inst), Transgene/Jennerex (Inst)
**Research Funding:** AstraZeneca, Bristol Myers Squibb, Clovis Oncology (Inst), Bayer (Inst), Celgene (Inst), Eisai (Inst), Glaxo Smith Kline (Inst), Otsuka (Inst), Roche (Inst), TC Biopharm (Inst), Pharmamar (Inst), Basilea (Inst), e-Therapeutics (Inst), Immunocore (Inst), Vertex (Inst), Daiichi (Inst), Merck (Inst)
**Travel, Accommodations, Expenses:** Bristol-Myers Squibb

**Lauris Gastaud**
No relationship to disclose

**Gerald Linette**
No relationship to disclose

**Carola Berking**
**Honoraria**: Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, Amgen, Pierre Fabre
**Consulting or Advisory Role:** Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, Amgen, Sanofi/Regeneron, Pierre Fabre, AstraZeneca, Incyte, Merck Serono
**Travel, Accommodations, Expenses:** Amgen, Merck Sharp & Dohme

**Jacob Schachter**
No relationship to disclose

**Manuel J. Rodrigues**
**Honoraria:** AstraZeneca
**Consulting or Advisory Role**: AstraZeneca
**Research Funding:** Bristol-Myers Squibb, Merck Sharp& Dohme

**Alexander N. Shoushtari**
**Consulting or Advisory Role:** Vaccinex, Castle Biosciences, Immunocore, Bristol-Myers Squibb
**Research Funding:** Bristol-Myers Squibb, Immunocore, Xcovery
**Travel, Accommodations, Expenses:** Bristol-Myers Squibb

**Delyth Clemett**
**Employment:** AstraZeneca
**Stock or Other Ownership:** AstraZeneca
**Consulting or Advisory Role:** AstraZeneca

**Dana Ghiorghiu**
**Employment:** AstraZeneca, AstraZeneca (I)
**Stock or Other Ownership:** AstraZeneca, AstraZeneca (I)

**Gabriella Mariani**
**Employment:** AstraZeneca
**Stock or Other Ownership:** AstraZeneca

**Shirley Spratt**
**Employment:** AstraZeneca
**Stock or Other Ownership:** AstraZeneca

**Susan Lovick**
**Employment:** AstraZeneca
**Stock or Other Ownership:** AstraZeneca

**Peter Barker**
**Employment:** AstraZeneca
**Stock or Other Ownership:** AstraZeneca

**Elaine Kilgour**
**Employment:** AstraZeneca
**Stock or Other Ownership:** AstraZeneca

**Zhongwu Lai**
**Employment:** AstraZeneca
**Stock or Other Ownership:** AstraZeneca

**Gary K. Schwartz**
No relationship to disclose

**Paul Nathan**
**Consulting or Advisory Role:** AstraZeneca, Bristol-Myers Squibb, MSD, Immunocore, Pfizer, Pierre Fabre, Novartis, GlaxoSmithKline, Ipsen
**Speakers' Bureau:** Bristol-Myers Squibb, Novartis
**Travel, Accommodations, Expenses:** Bristol-Myers Squibb, MSD

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