BRIEF REPORT

SWOG S1400B (NCT02785913), a Phase II Study of GDC-0032 (Taselisib) for Previously Treated PI3K-Positive Patients with Stage IV Squamous Cell Lung Cancer (Lung-MAP Sub-Study)

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ABSTRACT

Background: S1400B is a biomarker-driven Lung-MAP substudy evaluating the phosphatidylinositol 3-kinase (PI3K) inhibitor taselisib (GDC-0032) in patients with PI3K pathway-activated squamous NSCLC (sqNSCLC).

Methods: Eligible patients had tumoral phosphatidylinositol-4,5-biphosphate 3 kinase catalytic subunit alpha (*PIK3CA*) alterations by next-generation sequencing and disease progression after at least one line of platinum-based therapy. Patients received 4-mg taselisib orally daily. The primary analysis population (PAP) was a subset of patients having substitution mutations believed to be associated with clinical benefit of PI3K inhibitors. Primary endpoint was response by Response Evaluation Criteria in Solid Tumors version 1.1; secondary endpoints included

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progression-free survival, overall survival and duration of response.

Results: Twenty-six patients treated with taselisib comprised the full evaluable population (FEP); 21 patients comprised the PAP. Median age for patients in the FEP was 68 years (range: 53–83 years), 19 were male (73%). The study was closed for futility at interim analysis with one responder in the PAP (5% response rate, 95% confidence interval [CI]: 0%–24%). Two possibly treatment-related deaths (one respiratory failure, one cardiac arrest) were observed; one patient had grades 4 and 11 had grade 3 adverse events. Median progression-free survival and overall survival in the PAP group were 2.9 months (95% CI: 1.8–4.0 mo) and 5.9 months (95% CI: 4.2–7.8 mo), respectively. These numbers were nearly the same in the FEP.

Conclusions: Study S1400B evaluating taselisib in PIK3CA-altered sqNSCLC failed to meet its primary endpoint and was closed after an interim futility analysis. The trial is unique in cataloguing the diversity of *PIK3CA* mutations in sqNSCLC.

Keywords: Lung cancer; Targeted therapy; Master protocol

Introduction

The Lung Master Protocol (Lung-MAP, SWOG 1400) is an umbrella protocol with a screening component and multiple independently conducted and analyzed treatment substudies.[1] Herein we report on the results of SWOG S1400B, a phase II Lung-MAP substudy evaluating taselisib, a phosphoinositide-3 kinase (PI3K) inhibitor in patients with chemorefractory squamous NSCLC (sqNSCLC) tumors harboring alterations in phosphatidylinositol-4,5-biphosphate 3 kinase catalytic subunit alpha (*PIK3CA*).

PI3Ks are a family of lipid kinases involved in tumor cell proliferation, survival, and migration upon activation by growth factor receptors and integrins. PI3Ks catalyze phosphorylation of phosphatidylinositol-4, 5 bisphosphate to generate phosphatidylinositol-3,4,5 trisphosphate, a second messenger involved in phosphorylation of AKT and associated proteins in the AKT/mammalian target of rapamycin pathway.[2,3] Activating and transforming mutations, as well as amplification, in the p110 alpha isoforms of PI3K are commonly found in solid and hematologic tumors.[4] Additionally, the PI3K/AKT pathway is activated in numerous types of cancer by receptor tyrosine kinase signaling, loss of phosphatase and tensin homolog (PTEN), or RAS mutations.[2,5-8] PI3K alterations, including PI3K mutations and PTEN loss or mutations, are observed in 30% to 50% of squamous lung cancers. PI3K mutations are observed in 2% to 5% of nonsquamous and in 8% to 10% of sqNSCLC, and human tumors carrying mutated *PIK3CA* or deleted PTEN have responded favorably to PI3K inhibition.[6,7]

Taselisib is a potent, selective, small molecule inhibitor of class 1 PI3Ks developed by Genentech (South San Francisco, California) as an anticancer therapeutic agent that is a potent growth inhibitor in nonclinical models of PI3K mutant tumors.[8,9]

Methods

Patients with previously treated advanced sqNSCLC were eligible for the S1400 screening study. Briefly, eligibility for S1400B stipulated age greater than or equal to 18 years, Zubrod performance scale (PS) of 0–2 (modified to 0–1 during the study), measurable disease by Response Evaluation Criteria in Solid Tumors, and adequate hematologic, hepatic, and cardiac function with no supplemental oxygen requirement. Calcium and phosphate levels had to be within institutional limits. Patients had to be able to take oral medications with no impairment of gastrointestinal function or gastrointestinal disease that could significantly alter the absorption of taselisib. Patients with leptomeningeal disease, symptomatic untreated brain metastases, and chemotherapy within 21 days before registration were excluded.

Table 1. *PIK3CA* Mutations in Patients Eligible for Treatment With Taselisib

Eligible Populations	Number of Patients	Base Substitution Mutations Allowed[a]
Full Evaluable Population	26	R38C, R38H, E81K, R88Q, R93Q, R93W, P104L, P104R, G106V, G106R, P104_G106>R, R108H, E110del, E110K, K111E, K111N, K111del, G118D, V344G, V344M, N345K, N345I, E365K, C378F, E418K, C420R, E453K, E453Q, P539R, E542K, E542A, E542V, E542G, E542Q, E545A, E545G, E545K, E545Q, E545D, Q546E, Q546H, Q546K, Q546L, Q546P, Q546R, E726K, G1007R, D1017H, Y1021C, Y1021H, T1025A, A1035V, A1035T, M1043I, M1043L, M1043V, H1047L, H1047R, H1047Y, H1047N, H1047Q, G1049R, G1049S, I1058L
Primary Analysis Population	21	E542K, E545A, E545G, E545K, E545Q, H1047L, H1047R, or H1047Y

[a]Base substitutions, small insertions and deletions, focal copy number amplifications, homozygous gene deletions, and genomic rearrangements were analyzed. Patients with disease characterized by *PI3KCA* gene amplifications and fusions were not eligible

Eligibility for treatment with taselisib required base substitutions in *PIK3CA* (see Table 1). The primary analysis population (PAP) was defined by the presence of alterations expected to derive the greatest benefit from PI3K inhibition. Mutational analysis was performed on archival formalin-fixed paraffin-embedded tumor specimens using FoundationOne (Foundation Medicine, Cambridge, Massachusetts). Tumor mutational burden (TMB) was calculated as the number of somatic, coding, short variants, excluding known driver mutations, per megabase of genome interrogated.

Taselisib was administered orally at 4 mg daily on an empty stomach in 21-day treatment cycles. Disease assessment occurred every two cycles, and treatment was continued until disease progression or untoward toxicity. Dose reductions and adjustments were discussed with the study chair and were followed as specified in the protocol.

This study was originally designed as a randomized trial of taselisib versus docetaxel in the second line setting post-progression on platinum-based treatment. However, upon approval of immunotherapy in the second-line setting in December 2015, the S1400B trial was redesigned and became a single-arm phase II study[10-13]; the docetaxel arm permanently was closed to accrual and eligibility criteria were modified to allow second and later lines of therapy and only allow PS 0–1. Patients on the docetaxel arm were not included in the analyses presented in this article.

Statistical Considerations

The primary objective was evaluation of the Response Evaluation Criteria in Solid Tumors version 1.1 response rate (RR; confirmed and unconfirmed, complete, and partial) in patients in the PAP. The accrual goal was 40 response-evaluable PAP patients. The sample size (n=40) was based on a design with 91% power to rule out a RR of 15% at the one-sided 5% level if the true rate was 35%. The observation of 10 of 40 (25% RR) responses in the PAP was considered evidence to rule out the null RR and to pursue a randomized phase III trial. If at least three responses were observed on interim analysis of 20 evaluable patients, the trial would continue accrual to 40 patients. Other objectives included assessment of response in the full evaluable population (FEP), progression-free survival (PFS), and overall survival (OS) in the PAP and FEP, duration of response among all responders, and evaluation of the frequency and severity of toxicities in the FEP. A key secondary objective was investigator assessment of median PFS (mPFS) in the PAP. An RR rate less than 25% with mPFS greater than or equal to 4.5 months would have been considered sufficient evidence to continue to a follow-up phase III.

Results

Between June 16, 2014, and December 12, 2016, 55 patients (5% of those screened on S1400 while S1400B was actively accruing) were assigned to S1400B; 39 were enrolled and 31 were registered to receive taselisib.

Five of those registered were deemed ineligible (two with inadequate baseline disease assessment; one with chemotherapy within 21 days, one with last radiotherapy within 14 days of registration; and one death before treatment). Twenty-one of 26 (81%) in the FEP group had at least one of the PAP alterations. Baseline patient characteristics are enumerated in Table 2 and mutations for FEP and PAP are listed in Tables 1 and 3.

The most common concomitant gene alterations included mutations in tumor protein p53 (*TP53*), lysine methyltransferase 2D (*MLL2*), and notch receptor 1 (*NOTCH1*), and copy number alterations in cyclin dependent kinase inhibitor 2A (*CDKN2A*) and cyclin dependent kinase inhibitor 2B (*CDKN2B*) (see Table 3).

Table 2. Patient Demographics

	All Eligible Patients (n = 26)	Primary Analysis Population (n = 21)
Age median (range), years	68.1 (52.9-82.9)	70.5 (52.9-82.9)
Male	19 (73)	16 (76%)
Performance status		
0	7 (27)	6 (29)
1	18 (69)	14 (67)
2	1 (4)	1 (5)
Race/ethnicity		
White	19 (73)	15 (71)
Black	4 (15)	4 (19)
Asian	1 (4)	1 (5)
Native American	1 (4)	0 (0)
Unknown	1 (4)	1 (5)
Hispanic ethnicity	1 (4)	1 (5)
Number of prior lines of therapy for stage IV disease		
0	3 (12)	1 (5)
1	14 (54)	12 (57)
2 or more	9 (35)	8 (38)
Smoking status		
Current smoker	8 (31)	5 (24)
Former smoker	17 (65)	15 (71)
Never-smoker	1 (4)	1 (5)
In primary analysis population	21 (81)	21 (100)

Values are shown as n (%) unless otherwise stated.

Table 3. Gene Alterations Detected on FoundationOne Screening in Eligible Taselisib Patients

	Taselisib (n = 26)
PI3K study gene alterations	
E545K*	11 (42)
E542K*	6 (23)
H1047R*	4 (15)
N345K	2 (8)
E453K	1 (4)
G1049R	1 (4)
M1043I	1 (4)
Number of PI3K gene alterations	
1	26 (100)
Tumor mutation burden	
Median	9.67
Range	2.42–41.11
Interquartile range	6.05–16.93
<10	15 (58)
≥10	11 (42)
Other concomitant gene alterations	
Short Variants	
TP53	23 (88)
MLL2	8 (31)
NOTCH1	5 (19)
CDKN2A, NF1	4 (15)
BRAF, LRP1B, NFE2L2	3 (12)
FBXW7, PMS2, RB1, STK11	2 (8)
APC, ARID1A, ASXL1, ATR, ATRX, BRCA1, BRCA2, BRIP1, CDK12, CREBBP, EGFR, EP300, ERBB2, FANCC, FANCD2, FGFR3, GRIN2A, KDM6A, MUTYH, NOTCH3, PBRM1, PIK3C2G, PIK3CG, RUNX1T1, SETD2, SMARCA4, SPEN, STAG2, TGFBR2	1 (4)
Copy number alterations	
CDKN2A	6 (23)
CDKN2B	5 (19)
CCND1, FGF12, FGF19, FGF3, FGF4, SOX2	4 (15)
MYC, RICTOR	3 (12)
AKT2, FGF10, FGFR1, MDM2, PIK3CA, ZNF703	2 (8)
AXL, BRCA2, CCNE1, CDK4, EGFR, EPHB1, ERBB2, FGFR4, FLT4, KDM5A, KDM6A, KRAS, NFKBIA, NKX2-1, RET, TOP1	1 (4)
Rearrangements	
MAP3K13, PBRM1	1 (4)

Values are n (%) unless otherwise stated. PAP, primary analysis population.
*Included in PAP.

The median and range TMB scores were 9.62 (range: 2.42–41.11), with 11 (42%) patients with TMB scores greater than or equal to 10.

Two on-study deaths possibly related to treatment occurred, one due to respiratory failure and one due to cardiac arrest. In addition, one patient experienced multiple grade 4 adverse events (AEs) (dyspnea, thrombocytopenia, and pneumonitis). Eleven additional patients experienced grade 3 AEs including five patients each with hyperglycemia or diarrhea, and three with lymphopenia. Patients received a median of 3.5 cycles (range: 2–13, interquartile range: 2–4) of taselisib. Five patients were removed from treatment due to toxicity, 18 due to progression/relapse, 2 due to death, and 1 patient for other reasons. No patients remain on treatment. See Table 4 for a full listing of AEs.

Table 4. Adverse Events Attributable to Treatment

	Grade		
AE (n = 26)	3	4	5
Cardiac arrest			1 (4)
Dehydration	1 (4)		
Diarrhea	5 (19)		
Dyspnea	2 (8)	1 (4)	
Fatigue	3 (12)		
Hyperglycemia	5 (19)		
Hypertension	1 (4)		
Hyponatremia	1 (4)		
Hypoxia	1 (4)		
Lung infection	1 (4)		
Lymphocyte count decreased	3 (12)		
Nausea	1 (4)		
Platelet count decreased		1 (4)	
Pneumonitis	1 (4)	1 (4)	
Pneumothorax	1 (4)		
Rash maculopapular	1 (4)		
Respiratory failure			1 (4)
Vomiting	1 (4)		
Maximum grade of any AE	11 (42)	1 (4)	2 (8)

Values are n (%). AE, adverse event.

One patient in the PAP group with an E545K gene alteration responded (5% RR, 95% confidence interval [CI]: 0%–24%). This patient was removed from treatment due to toxicity and subsequently exhibited disease progression (duration of response = 4.4 mo). There were no additional responses in the FEP group resulting in a study-wide RR of 4% (95% CI: 0%–20%), but 16 patients had stable disease for a disease control rate of 65% (95% CI: 47%–84%). Figure 1 depicts the waterfall plot for individual responses by mutational status with no obvious pattern in terms of magnitude of change in tumor measurements or PI3K alteration type.

In the PAP group, mPFS was 2.9 months (95% CI: 1.8–4.0 mo) and median OS was 5.9 months (95% CI: 4.2–7.8 mo). These figures were virtually identical in the FEP group (see Fig. 2). The 1- and 2-year OS estimates were 23.8% and 17.9% in the PAP group, respectively; and 30.8% and 22.4% in the FEP group, respectively. The analysis evaluating the association between patient characteristics and PFS and OS in the FEP group yielded limited results. Current versus former or never-smokers were associated with worse prognosis (OS hazard ratio [HR] = 2.85, $p = 0.03$), and number of lines of previous therapy for stage IV (0 versus 1 or more) was associated with shorter time to progression (PFS HR = 7.88, $p = 0.006$); however, this observation was

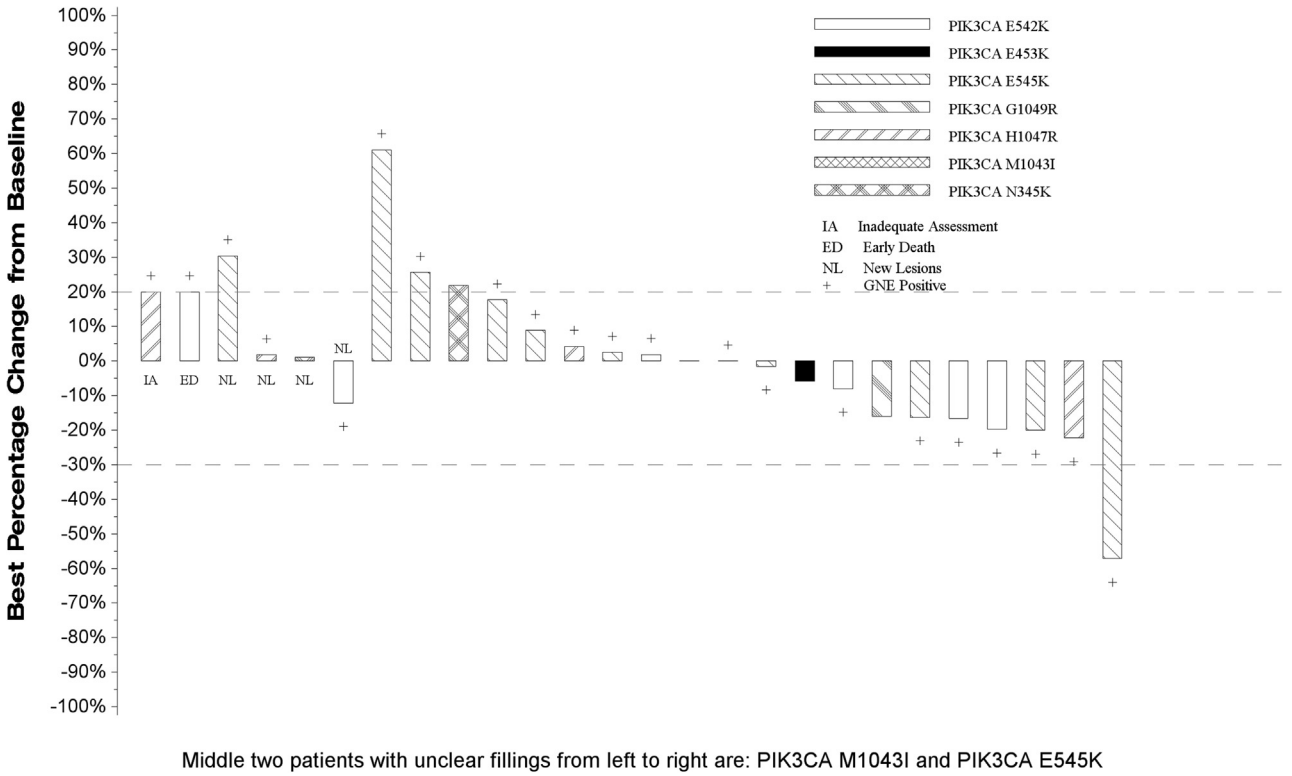

Figure 1. Waterfall plot with annotations for individual alterations. This plot depicts the response magnitude/status for all patients in the full eligible population. Patients who did not have a follow-up tumor disease assessment are presented at the very left of the plot marked with "inadequate response assessment." In addition, patients who expired due to causes other than disease progression before their first disease assessment were coded as an early death (ED and are also presented at the left of the plot. Patients who had new lesions appear at their first follow-up assessment were presented with percentage change in target lesions and marked with new lesions (NL). Patients who expired due to disease progression before the first scheduled disease assessment are represented graphically as a 100% increase in tumor burden. For the remaining patients with follow-up disease assessments, the vertical bars represent the best percent decrease in tumor burden when compared to baseline as defined by Response Evaluation Criteria in Solid Tumors version 1.1. Negative numbers represent decrease in tumor burden from baseline whereas positive numbers represent increase in tumor burden from baseline. + indicates a patient was in the primary analysis population.

based on only three patients with no prior lines of therapy for stage IV NSCLC, and these results should be interpreted with caution. Age, sex, PS, type of PI3K alteration, and TMB were not associated with PFS or OS (see Fig. 3).

Discussion

The paradigm for second-line therapy for sqNSCLC has changed significantly since 2015 with the approval of checkpoint inhibitors of programmed death receptor pathway based on phase III studies showing superior OS compared with the erstwhile standard, docetaxel.[10-13] Recently, molecular genotyping has become the "norm" in the evaluation of patients with advanced nonsquamous NSCLC and has led to major interest in applying targeted agents for mutations and other genetic aberrations prevalent in sqNSCLC. Genetic alterations within lung adenocarcinomas and sqNSCLC are generally distinct. sqNSCLC tends to be genetically more complex and is usually characterized by a high overall mutational burden. Because of the genetic diversity and lack of clear oncogenic drivers in this disease, we recognized the need to develop clinical trials solely focused on sqNSCLC that could evaluate single-agent as well as combination targeted therapies along with newer immunotherapeutic approaches.

Lung-MAP substudy S1400B was one such effort. Unfortunately, this study failed to meet its primary endpoint and was closed after an interim analysis for futility. The lone response observed on taselisib was brief; both the median PFS of 2.9 months and the median OS of 5.9 months in the targeted population proved disappointing. Although single-agent taselisib resulted in a fair amount of hyperglycemia and fatigue, toxicities were manageable. The trial, although unsuccessful, proved unique in cataloguing the diversity of mutations in the PI3K pathway in sqNSCLC, some of which may prove targetable in the future if a more active agent emerges. It is unclear why this agent failed. It is

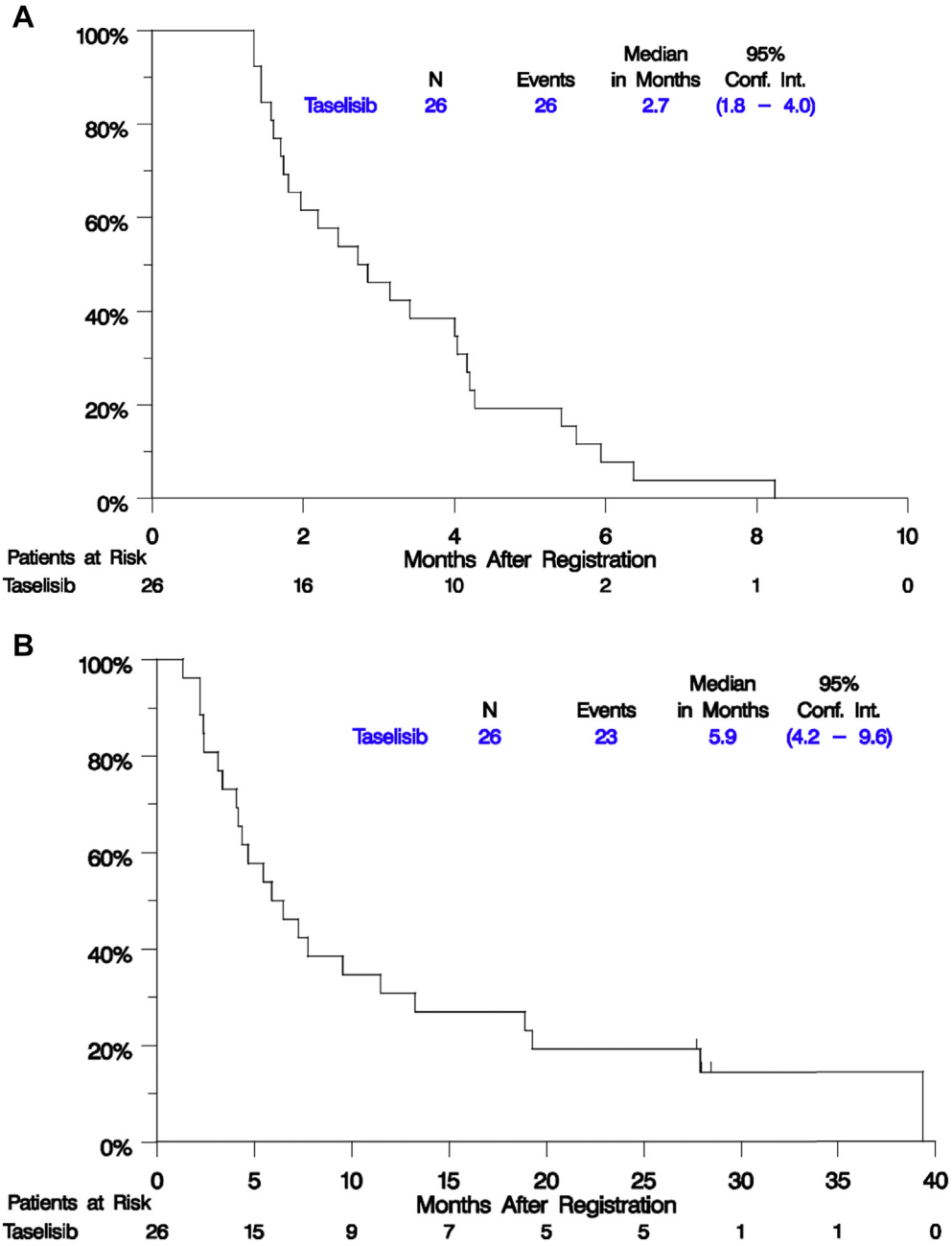

Figure 2. Kaplan-Meier plots of progression-free survival (PFS) and overall survival (OS) in the full eligible population. (*A*) PFS. (*B*) OS. Survival distributions were estimated using the Kaplan-Meier method and the Brookmeyer-Crowley method was used to estimate confidence intervals (Conf. Int.) for median times.

conceivable that PI3KA is not a true driver of tumor growth in sqNSCLC, or that bypass pathways circumvented the potential benefit of taselisib. Another PI3K inhibitor, buparlisib, was negative in a broader NSCLC population with a wider range of PI3K-activating mutations.[14] In contrast, taselisib in combination with fulvestrant yielded a modest PFS benefit of 2 months compared with fulvestrant alone in patients with estrogen receptor–positive *PIK3CA* mutant locally advanced or metastatic breast cancer.[15] Based on the experience in breast, it is conceivable that taselisib may work better in combination with other agents in advanced NSCLC, but this is speculative; there are no preclinical data to suggest this might be the case.

Also, the heterogeneity of molecular aberrations in advanced sqNSCLC suggests that targeting a single pathway may be insufficient. In this regard, additional genetic alterations detailed in Table 3 were present in the majority of patients enrolled on this substudy. It is

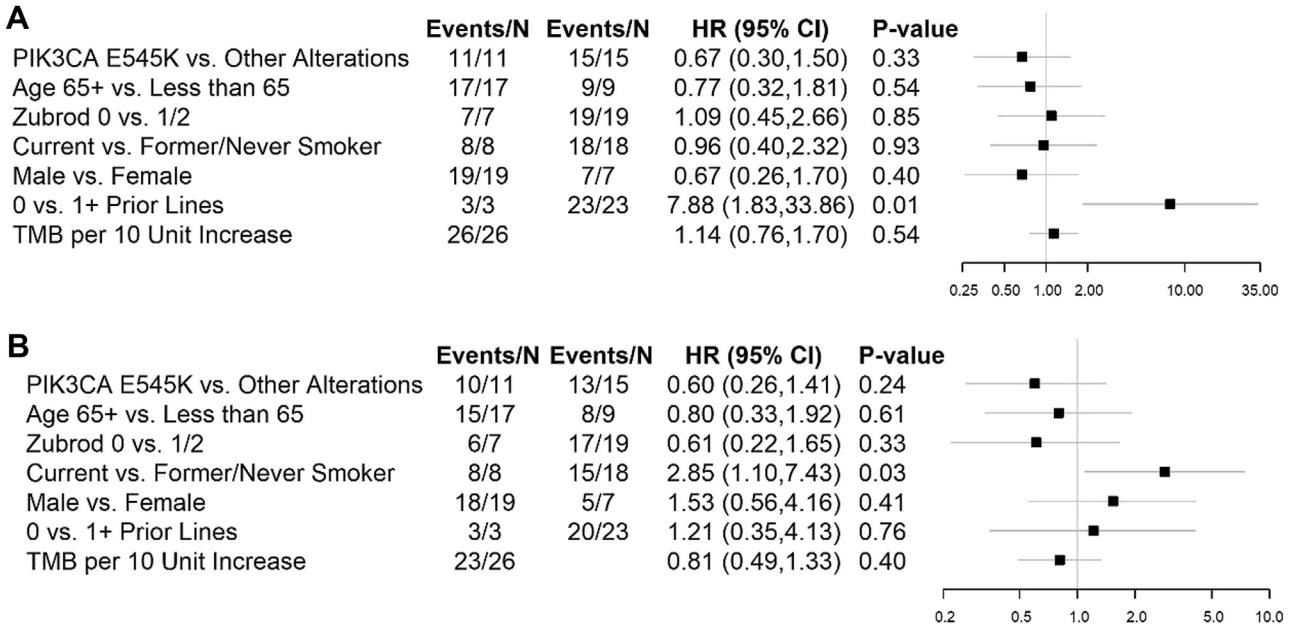

Figure 3. Forest plot comparison of patient characteristics and progression-free survival (PFS) and overall survival (OS) in the full eligible population. (*A*) Forest plot for PFS. (*B*) Forrest plot for OS. Hazard ratios and associated confidence intervals (CIs) were estimated using a Cox proportional hazards model. Confidence intervals were based on Greenwood's formula for the variance. HR, hazard ratio; TMB, tumor mutational burden.

also posited that PI3K alterations may simply not be as powerful oncogenic drivers as we have observed with EGFR mutations and ALK rearrangements in advanced nonsquamous NSCLC.

Although S1400B failed to identify a promising agent targeting PI3K, the study design of Lung-MAP has proven promising. Under a single-umbrella protocol, in a single-disease venue, with a single–institutional review board approval, we are now able to separately investigate multiple different pathways of interest, quickly discarding agents that prove inactive and focusing resources on new agents that may prove efficacious. This model of protocol design, under the aegis of the cooperative group system in the United States, may be the most efficient means of investigating less common, as well as newly identified, oncogenic drivers.

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