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An open-label phase IB study to evaluate GSK3052230 in combination with paclitaxel and carboplatin, or docetaxel, in FGFR1-amplified non-small cell lung cancer

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ABSTRACT

Objectives: GSK3052230 (FP-1039) is a soluble fusion protein that acts as ligand trap sequestering fibroblast growth factors (FGFs) involved in tumor growth and angiogenesis, while sparing the hormonal FGFs. Because of this selectivity, the molecule is predicted to avoid toxicities associated with small molecule inhibitors of FGFR, including hyperphosphatemia and retinal, nail, and skin toxicities. Herein we report the results of a phase 1b study where GSK3052330 was administered with standard of care chemotherapy in FGFR1-amplified squamous non-small cell lung cancer (sqNSCLC) patients.

Methods and Methods: Eligible patients with stage IV or recurrent metastatic sqNSCLC harboring *FGFR1* gene amplification received escalating doses of GSK3052230 in combination with paclitaxel and carboplatin at the starting doses 200 mg/m^2 and AUC of 6, respectively, in the first line setting (Arm A) or docetaxel 75 mg/m^2 in second line (Arm B). The primary endpoints of the study were safety and tolerability, to identify a maximum tolerated dose (MTD), and to assess overall response rate (ORR) based on investigator assessment.

Results: Twenty-nine patients were enrolled into the study, including 20 patients on Arm A and 9 patients on Arm B. There were no dose limiting toxicities in either Arm and the MTD was not reached. The most common adverse events (AEs) were compatible with the chemotherapy backbone used in each Arm, including neutropenia, alopecia, nausea, arthralgia, asthenia, diarrhea and peripheral neuropathy. The overall response rate and median progression-free survival were 47% and 5.5 months, respectively, for Arm A and 0% and 4.6 months, respectively, for Arm B.

Conclusion: GSK3052230 is a novel FGFR pathway inhibitor, which is well tolerated in combination with chemotherapy. Importantly, AEs associated with small molecule inhibitors of FGFR were not observed, as predicted by the unique mechanism of action of this drug.

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1. Introduction

Fibroblast growth factors (FGFs) and their receptors (FGFRs) regulate many physiological processes including embryonic development, differentiation, proliferation, survival, and angiogenesis [1]. FGFRs constitute a family of four highly conserved transmembrane receptor tyrosine kinases designated FGFR1 through FGFR4 [2]. Each receptor comprises an extracellular domain composed of three immunoglobulin (Ig)-like domain (domains I to III), a transmembrane domain and an intracellular tyrosine kinase domain. Although the nomenclature of FGF family describes 23 members, the mammalian FGF family includes 18 ligands since there is no human *FGF15* gene and four members that are not secreted and do not function as FGF ligands (FGF11 to FGF14) [3]. The secreted FGFs may be further subdivided into mitogenic (canonical) and hormone-like subfamilies. Canonical FGFs are promptly sequestered by the extracellular matrix and the cell surface by heparin sulfate proteoglycans (HPSG), which stabilize their interaction with FGFR, whereas hormone-like FGFs (FGF 19, FGF21 and FGF23) have low affinity to HPSG, can diffuse from the source of production into the circulation, and rely on the transmembrane klotho proteins as co-receptors for high-affinity binding.

Molecular aberrations in the FGF-FGFR signaling pathway have been implicated in oncogenesis and may occur through several mechanisms including receptor amplification, activating mutation or oncogenic fusions, and aberrant autocrine or paracrine loops through increased secretion of FGFs by tumor or stromal cells [4]. Deregulation of FGFR signaling may occur in many malignancies, including squamous non-small cell lung cancer (sqNSCLC), where amplification of *FGFR1* occurs in approximately 20% of patients [5,6].

GSK3052230 (FP-1039) is a soluble decoy receptor where the extracellular domain of the FGFR1c isoform was fused with the Fc domain of IgG1 to create a trap for FGF ligands [7]. Preclinical studies showed that GSK3052230 binds with high affinity to several mitogenic FGFs and to low affinity with FGF23. There was no measurable binding to FGF19 and FGF21 or other classes of growth factors including epidermal growth factor, platelet-derived growth factor and vascular endothelial growth factor. Antitumor activity was demonstrated in xenograft models with *FGFR1* amplification, including the lung cancer cell line NCIH1581 [7]. In a prior phase I first time in human study, 39 patients with solid tumors were treated with escalating doses of GSK3052230 on a 3 + 3 design, ranging from 0.5 mg/kg to 16 mg/kg intravenous weekly [8]. There was no maximum tolerated dose (MTD) and the maximum feasible dose (MFD) was established at 16 mg/kg. The most common adverse events (AEs) were diarrhea (43.6%), fatigue (43.6%) and nausea (25.6%). Neutropenia was observed in only one patient, with grade 3 at the dose of 1 mg/kg. Patients in the study were not selected by FGFR pathway deregulation and there were no objective responses observed. Following the completion of the trial, FP-1039 was renamed GSK3052230 and with the change in methodology to determine the drug concentration, the 16 mg/kg MFD became equivalent to 20 mg/kg.

Based on these data, we conducted a phase IB study (NCT01868022) to evaluate the combination of GSK3052230 and standard of care chemotherapy in patients with stage IV sqNSCLC harboring *FGFR1* amplification or with malignant pleural mesothelioma (MPM). Here we describe the results on patients with sqNSCLC.

2. Methods

2.1. Patient selection and study oversight

Eligible patients were 18 or older, had histologically or cytologically confirmed stage IV or recurrent metastatic squamous cell NSCLC with *FGFR1* gene amplification by central laboratory testing, radiologically documented measurable disease by Response Evaluation Criteria in Solid Tumor (RECIST) 1.1, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, adequate organ function, and no other current active malignancy requiring anticancer therapy. Patients with brain or leptomeningeal metastases were eligible in case of stable central nervous system disease for at least 4 weeks after local therapy assessed by contrast enhanced magnetic resonance imaging or computed tomography. Additional key exclusion criteria included corrected QT (QTc) interval ≥ 480 msec or hemoptysis greater than half teaspoon of red blood within 2 weeks prior to the first dose of therapy.

To assess FGFR1 amplification, a Fluorescence In Situ Hybridization (FISH)-based FGFR1 assay was performed by a central laboratory on archived formalin-fixed, paraffin embedded (FFPE) tissue specimens. The FGFR1 FISH probe used in this assay (Kreatech, Cat# 08P003B550) was a probe mixture that measured the FGFR1 gene locus (8p11.22–23) and the alpha satellite region (D8Z1) of chromosome 8 as a control site. Scoring guidelines and criteria for FGFR1 amplification were described previously [9]. Briefly, evaluations were performed independently by two technologists, evaluating 120 nuclei per sample. For inclusion in this study, FGFR1 gene amplification had to meet one of the following criteria: ratio of FGFR1/CEP 8 of ≥ 2; or average number of FGFR1 signals per tumor nucleus of ≥ 6; or the percentage of tumor nuclei containing ≥5 FGFR1 signals is ≥ 50%.

The study was approved by the institutional review board or independent ethics committee at participating sites and conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent prior to treatment initiation.

2.2. Study design

This study was an open label, multicenter phase IB study (NCT01868022) where patients were treated with GSK3052230 in combination with chemotherapy. The study had 3 Arms. In Arm A, patients with previously untreated stage IV squamous cell lung cancer received GSK3052230 intravenous in combination with paclitaxel and carboplatin. To avoid delay in the initiation of therapy, patients in this Arm were allowed to receive the first cycle of chemotherapy while waiting for the eligibility based on *FGFR1* testing. In Arm B, patients with tumor progression after at least one prior line of platinum-containing combination chemotherapy in the metastatic setting, received GSK3052230 in combination with docetaxel. Arm C included patients with previously untreated MPM and will be reported in a separate publication.

Dose escalation followed a 3 + 3 design as described in Table 1. The starting dose for GSK3052230 was 5 mg/kg intravenous weekly in combination with paclitaxel 200 mg/m^2 plus carboplatin AUC 6 every 21 days on Arm A or docetaxel 75 mg/m^2 every 3 weeks on Arm B. On both Arms, the dose levels 1 and 2 for GSK3052230 were 10 mg/kg and 20 mg/kg. An additional fourth patient was allowed in each cohort to ensure that at least 3 patients were evaluable for the determination of dose-limiting toxicity (DLT). The evaluation of safety data required that at least 3 patients had a minimum follow-up of 21 days. DLT was defined for each cohort as toxicities occurring in the first 21 days that

Table 1
Combination Therapy Dose Levels.

Dose Level	GSK3052230 (weekly)	Paclitaxel + Carboplatin[1] (once every 21 days)	Docetaxel (once every 21 days)
Dose Level -2	5 mg/kg	135 mg/m^2 + AUC 4	40 mg/m^2
Dose Level -1	5 mg/kg	175 mg/m^2 + AUC 5	55 mg/m^2
Starting Dose Level	**5 mg/kg**	**200 mg/m^2 + AUC 6**	**75 mg/m^2**
Dose Level 1	10 mg/kg	200 mg/m^2 + AUC 6	75 mg/m^2
Dose Leve 2	20 mg/kg	200 mg/m^2 + AUC 6	75 mg/m^2

[1] Carboplatin dose based on Calvert's formula.

were unlikely to be from disease progression, accidents or known effects from the cytotoxic chemotherapy and including grade 3 or 4 clinically significant non-hematologic toxicity, grade 4 neutropenia lasting more than 7 days, febrile neutropenia, grade 4 thrombocytopenia, grade 4 clinically significant laboratory abnormalities lasting more than 48 h, or treatment delay of at least 14 days due to unresolved drug-related toxicity. The maximum tolerated dose (MTD) was defined as the highest dose level at which less than 33% of patients experience DLT. If the MTD was not reached, the highest dose evaluated was described as the maximum feasible dose (MFD). In each Arm, dose escalation was followed by a cohort expansion. Expansion cohorts of 12 to 30 subjects were planned with stopping rules for futility using a response-based predictive probability design. Enrollment was ultimately stopped in both Arms either because of enrollment difficulties or due the changing standard of care in these indications.

2.3. Study evaluations

Disease assessment included imaging studies within 30 days prior to the first dose of therapy and every other treatment cycle for the first year. Tumor responses and progression were determined according to the RECIST 1.1 criteria [10]. Patients who had either a partial response (PR) or complete response (CR) required confirmatory disease assessment performed at least 4 weeks after the prior imaging studies. Safety was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

2.4. Outcomes

The primary endpoints of the study were safety and tolerability, MTD, MFD and overall response rate (ORR) based on investigator assessment using RECIST version 1.1. Secondary endpoints included progression-free survival (PFS) in the intent-to-treat (ITT) population, defined as the time from the first dose of GSK3052230 to the date of disease progression or death from any cause and pharmacokinetics (PK).

2.5. Study procedures

Blood samples for PK were collected on cycle 1 days 1 and 8, and on the first days of cycles 2, 6 and 12 of GSK3052230, as well as at the end of treatment and 30 days later. Plasma concentrations of GSK3052230 were determined using a validated FGF2 ligand-binding enzyme-linked immunosorbent assay as described previously [8].

2.6. Statistical analyses

For analysis of the efficacy, ORR data from dose expansion cohorts were compared against historical control rates [11,12]. A test that the response rate is less than or equal to the null hypothesis rate versus the response rate is greater than or equal to the alternative rate was performed using the pre-specified stopping rules for futility based on the Bayesian predictive probability methodology. For Arm A, the null hypothesis was ORR $\leq$ 25% and the alternative hypothesis was ORR $\geq$ 45%. For Arm B, the null hypothesis was ORR $\leq$ 10% and the alternative hypothesis was ORR $\geq$ 25%. Descriptive statistics was used to describe the observed response rates at the dose used in the expansion cohorts for each of the Arms.

3. Results

3.1. Patients

Among the 176 patients with squamous cell lung carcinoma screened for the study, 34 (19%) were positive for *FGFR1* amplification. Twenty-nine patients were enrolled between October 2013 and December 2015, including 20 patients in Arm A and 9 patients in Arm B (Table 2). The median age was 67 years and most patients were men (93%) and current or former smokers (97%).

Table 2
Patient characteristics.

Characteristic	Number (%) Arm A	Arm B
Number of patients	20	9
Sex (male)	19 (95%)	8 (89%)
Median age (range)	67 (50-77)	67 (51-79)
Current of former smokers	19 (95%)	9 (100%)
History of brain metastases	0 (0%)	0 (0%)
Prior radiation therapy	1 (5%)	6 (67%)

3.2. Pharmacokinetic results

Following dosing, plasma GSK3052230 concentrations were measurable in all available plasma samples. For patients in Arm A, the mean maximum observed concentration (Cmax) values after their first treatment were 92775, 155,457 and 354,534 ng/ml following 5, 10 and 20 mg/kg GSK3052230, respectively (Supplementary Table 1). Variability in Cmax was moderate to high between samples from patients given the same dose of GSK3052230, but Cmax values increased in a dose proportional manner and did not increase from Cycle 1 to later cycles. The median time of maximum concentration (Tmax) was between 0.5 and 0.8 h across all dose groups. Similar PK results were observed for Arm B, where mean Cmax values on Cycle 1 Day 1 were 78508, 165,583 and 216,050 ng/ml following 5, 10 and 20 mg/kg GSK3052230, respectively, and median Tmax was between 0.4 and 1.3 h across the dose groups (Supplementary Table 2). Overall, a trend for a lack of PK drug-drug interaction between GSK3052230 and cotherapies was observed.

3.3. Safety

There were no DLTs in either Arm and MTD was not reached. Therefore, a dose of 20 mg/kg was declared the MFD for GSK3052230 in combination with chemotherapy in both Arms. AEs were observed in all patients on both Arms. On Arm A, no patient had to permanently discontinue therapy whereas dose delays of GSK3052230 were reported in 6 (30%) patients, half of which were due to AEs. Two patients had 3 or more dose delays and 4 (20%) had dose reduction. Serious adverse events (SAEs) were seen in 8 patients (40%), of which 5 (25%) were related to the study treatment (asthenia, diabetes mellitus, febrile neutropenia, neutropenia, and respiratory tract infection). In Arm B, 3 patients (33%) experienced GSK3052230 treatment delays, with 75% of delays due to AEs, and 3 patients (33%) required dose reduction. SAEs were observed in 6 patients (67%), of which 3 (33%) were related to the study treatment (febrile neutropenia in 2 patients and abdominal pain in 1 patient which led to study withdrawal). The most common AE causing dose delay in both arms was neutropenia. While there were no fatal SAEs on the study, a total of 8 patients died on study (5 in Arm A and 3 in Arm B) due to disease progression.

The most common AEs in Arm A were neutropenia (80%), alopecia (55%), diarrhea (50%), anemia, arthralgia, constipation, anemia, and decreased appetite (all at 40%) (Table 3). In Arm B, the most common AEs were alopecia, asthenia, fatigue, and pyrexia (all at 44%). There were no Grade 5 AEs, but Grade 3 or 4 neutropenia was observed in both Arms. Importantly, no AEs of hyperphosphatemia or any other toxicities associated with pan-FGFR kinase inhibitors were reported.

3.4. Efficacy

According to the investigator assessments, 9 out of 19 evaluable

Table 3
Most common adverse events reported in patients across both Arms.

Adverse event	Arm A		Arm B	
	All grades	Grades 3-4	All grades	Grades 3-4
Neutropenia	16 (80%)	14 (70%)	3 (33%)	3 (33%)
Alopecia	11 (55%)		4 (44%)	1 (11%)
Diarrhea	10 (50%)	2 (10%)	3 (33%)	1 (11%)
Anemia	8 (40%)	2 (10%)	2 (22%)	
Arthralgia	8 (40%)	1 (5%)	3 (33%)	
Constipation	8 (40%)		2 (22%)	
Decreased appetite	8 (40%)	1 (5%)	1 (11%)	
Asthenia	7 (35%)	2 (10%)	4 (44%)	1 (11%)
Cough	7 (35%)		2 (22%)	
Fatigue	6 (30%)		4 (44%)	
Nausea	6 (30%)		3 (33%)	
Peripheral neuropathy	6 (30%)		1 (11%)	
Pyrexia	5 (25%)		4 (44%)	
Back pain	4 (20%)		3 (33%)	

patients (47%) achieved confirmed partial response and 7 (37%) had stable disease in Arm A (Table 4). Patients received a median of 8 treatment cycles with a maximum of 20. Among the 13 evaluable patients treated with 20 mg/kg of GSK3052230, 6 (46%) achieved PR (95% CI: 19.2, 74.9) and 5 (38%) achieved SD (95% CI: 13.9, 68.4), with a disease control rate (DCR) of 84% (95% CI: 54.6, 98.1). In Arm B, patients received a median of 6 treatment cycles with a maximum of 14. There were no responders and 6 (67%) achieved stable disease (not shown). The maximum percent reduction from baseline in tumour measurements for both Arms is shown in Fig. 1. The median PFS for the 20 mg/kg GSK3052230 groups in Arms A and B were 5.5 months (95% CI: 3.9, 6.2) and 4.6 months (95% CI: 1.3, 9.5), respectively. In Arm A, there was no correlation between *FGFR1* amplification levels and response to therapy or PFS (Supplementary Fig. 1 and not shown). The small number of patients in Arm B precluded an evaluation of the correlation between *FGFR1* amplification levels and outcomes.

4. Discussion

GSK3052230 in combination with chemotherapy in patients with *FGFR1*-amplified stage IV squamous cell lung cancer did not increase the toxicity compared to historical data on chemotherapy alone. The dose was successfully escalated to 20 mg/kg in combination with both carboplatin plus paclitaxel in the first line setting and docetaxel in previously treated patients, with no MTD reached. The toxicity profile in both Arms was similar to what has been described in patients treated with chemotherapy alone, with neutropenia, alopecia, nausea, arthralgia, asthenia, and peripheral neuropathy commonly observed [11,13–17]. The only notable exception is diarrhea in Arm A, which was more common in this study compared to previous studies including carboplatin plus paclitaxel, where it was often not reported due to the low incidence [11,18]. When reported, diarrhea ranged from approximately 7% to 23% of cases [13,19].

Notably absent in our study was hyperphosphatemia, which has been described as the most common treatment emergent adverse event among patients treated with selective anti-FGFR tyrosine kinase inhibitors such as JNJ-42756493 and BJG398 [20,21]. This class-specific mechanism-based toxicity frequently required treatment interruptions and led to the use of intermittent dose schedules for both JNJ-42756493 and BJG398. The hyperphosphatemia is caused by the inhibition of FGF23, which acts primarily on the renal proximal tubule inhibiting phosphate reabsorption [22]. Consistent with the mechanism of action described in preclinical studies, GSK3052230 did not bind hormonal FGFs, including FGF23, and was not associated with hyperphosphatemia.

Although there were no responders among patients treated with GSK3052230 plus docetaxel, the results from the combination with carboplatin and paclitaxel are encouraging, with PR and DCR of 46% and 84%, respectively, among the 13 patients treated with the target dose of 20 mg/kg. Overall response rates for patients with stage IV NSCLC treated with carboplatin and paclitaxel have ranged from 16% to 25% [11,18,23,24]. PFS, on the other hand, was similar to what has been previously observed in historical data, with the 20 mg/kg GSK3052230 group demonstrating 5.5 months of PFS compared to previous data ranging between 4 to 5.7 months [10,17,22,23]. One caveat to this study is that patients were selected based on FGFR1 amplification, whereas historical data comes from an unselected population. Thus, it is difficult to ascertain the actual contribution of GSK3052230 to the results observed in this study. A randomized trial would be necessary to determine the benefits of GSK3052230.

Overall, the results from single agent FGFR inhibitors in patients with *FGFR1* amplification have been disappointing. A possible explanation for this low efficacy is the lack of uniform addiction to FGFR signaling among patients with *FGFR* aberrations, particularly among patients with FGFR1 alterations, where co-aberrant genes in the 8p12 amplicon may also have a role in oncogenesis and not all tumors depend on FGFR signaling for survival [4]. Another mechanism is the sustained mitogen activated protein kinase (MAPK) pathway activation. Binding of FGF to FGFR leads to receptor dimerization, transphosphorylation of the tyrosine kinase domains and activation of downstream signaling pathways including MAPK, phosphatidylnositide 3-kinase (PI3K) and signal transducer and activator of transcription (STAT). MAPK is the pathway most strongly activated by FGFR aberrant signaling. Both NRAS and MET amplifications with increased MAPK signaling have been observed in preclinical studies of drug resistance in

Table 4
Investigator-assessed best response with confirmation according to RECIST 1.1 criteria for Arm A.

GSK3052230 + Paclitaxel + Carboplatin	Starting Dose Level (N = 3)	Dose Level 1 (N = 3)	Dose Level 2 (N = 13)
Best Response, n (%)			
Complete response	0	0	0
Partial response	1 (33)	2 (67)	6 (46)
Stable disease	1 (33)	1 (33)	5 (38)
Non-CR/Non-PD	0	0	0
Progressive disease	1 (33)	0	2 (15)
Not evaluable	0	0	0
Unknown	0	0	0
Response Rate			
CR + PR, n (%)	1 (33)	2 (67)	6 (46)
95% CI*	0.8, 90.6	9.4, 99.2	19.2, 74.9

Abbreviations: CI = Confidence interval; CR = Complete response; PD = Progressive disease; PR = Partial response. *95% confidence intervals are calculated based on the unconditional exact method.

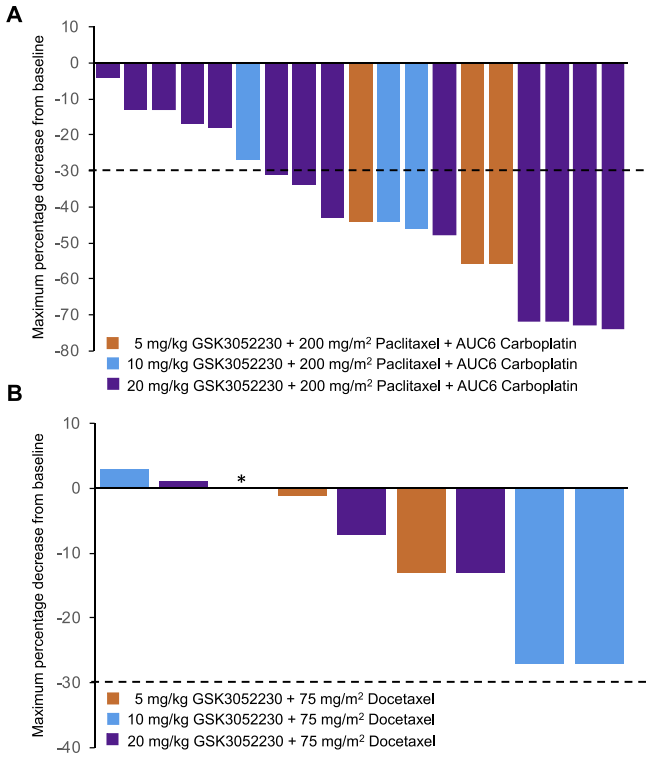

Fig. 1. Antitumor activity of GSK3052230 in combination with standard therapy in first line (A) or second line (B) FGFR1-amplified sqNSCLC patients. Maximum percentage decrease from baseline in target lesions according to RECIST 1.1 criteria. *Maximum percentage decrease from baseline = 0%.

FGFR1 amplified lung cancers [25]. It is expected that the good tolerability of GSK3052230 may allow safer and possibly effective combination therapies with MET or MAPK pathway inhibitors.

Since the initiation of the trial, the standard treatment for patients with stage IV squamous cell lung cancer has changed, with the use of pembrolizumab, either alone or in combination with carboplatin and a taxane representing the best available treatment for patients without contraindications for the use of immune checkpoint blockers (ICBs) [26,27]. Therefore, further exploration of the cohort A regimen will likely need to include an ICB.

In summary, GSK3052230 is a novel FGFR pathway inhibitor that affects primarily the mitogenic FGFs, avoiding the toxicities from hormonal FGF blockade. The good tolerability allowed the combination with chemotherapy in both first and second line settings for patients with squamous cell lung cancer harboring *FGFR1* amplifications. Further studies are required to better define the role of GSK3052230 in tumors with *FGFR* aberrations including optimization of patient selection and novel combination therapies.

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Declaration of Competing Interest

D. Morgensztern is a consultant/advisory board member for Takeda, AbbVie, Bristol-Myers Squibb (BMS), and PharmaMar. E. Felip reports receiving speakers' bureau honoraria and is a consultant/advisory board member for AbbVie, AstraZeneca (AZ), Blueprint Medicines, Boehringer Ingelheim (BI), BMS, Celgene, Eli Lilly, Guardant Health, Janssen, Medscape, Merck KGaA, Merck, Novartis, Pfizer, Roche, Takeda, and Touchtime. M. Dómine reports receiving speakers' bureau honoraria and is a consultant/advisory board member for AZ, BMS, BI, Celgene, MSD, Roche-Genentech, Pfizer, and AbbVie. P.K. Paik reports receiving commercial research grants from Celgene and EMD Serono, speakers' bureau honoraria and travel expenses from AbbVie, Celgene, EMD Serono, Lilly, Takeda, and is a consultant/advisory board member for AbbVie, BMS, Celgene, Lilly, and Takeda. *J.*Trigo reports receiving speakers' bureau honoraria and is a consultant/advisory board member for AZ, BMS, BI, Merck, and Takeda. K. Baker-Neblett, X. Wang, L. Yan, I. Mitrica, and M.P. DeYoung are employees of and hold ownership interest in GlaxoSmithKline (GSK). *J.* Vasquez is an employee of GSK. P. Garrido reports receiving commercial research grants from GSK, Celgene, Sanofi, PharmaMar, Theradex, Roche, BMS, Lilly, Guardant, Sysmex, Takeda, AZ, BI, and Novartis and is a consultant/advisory board member for Roche, MSD, BMS, BI, Pfizer, Abbvie, Guardant, Novartis, Lilly, AZ, Janssen, Sysmex, Blueprint Medicines, and Takeda. No potential conflicts of interest were disclosed by the other authors.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.08.011.

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