A Phase 1 study of gefitinib combined with durvalumab in EGFR TKI-naive patients with EGFR mutation-positive locally advanced/metastatic non-small-cell lung cancer

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BACKGROUND: EGFR tyrosine kinase inhibitors (TKIs) induce cytolyis and release of tumour proteins, which can stimulate antigen-specific T cells. The safety and efficacy of durvalumab and gefitinib in combination for TKI-naive patients with advanced EGFRm NSCLC was evaluated.

METHODS: This Phase 1 open-label, multicentre trial (NCT02088112) was conducted in 56 patients with NSCLC. Dose expansion permitted TKI-naive patients, primarily with activating L858R or Ex19del EGFRm. Arms 1+1a received concurrent therapy; Arm 2 received 4 weeks of gefitinib induction followed by concurrent therapy.

RESULTS: From dose escalation, the recommended dose of durvalumab was 10 mg/kg Q2W with 250 mg QD gefitinib. Pharmacokinetics were as expected, consistent with inhibition of soluble PD-L1 and no treatment-emergent immunogenicity. In dose expansion, 35% of patients had elevated liver enzymes leading to drug discontinuation. In Arms 1+1a, objective response rate was 63.3% (95% CI: 43.9–80.1), median progression-free survival (PFS) was 10.1 months (95% CI: 5.5–15.2) and median response duration was 9.2 months (95% CI: 3.7–14.0).

CONCLUSIONS: Durvalumab and gefitinib in combination had higher toxicity than either agent alone. No significant increase in PFS was detected compared with historical controls. Therefore, concurrent PD-L1 inhibitors with gefitinib should be generally avoided in TKI-naive patients with EGFRm NSCLC.

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Durvalumab is a selective, high-affinity human IgG1κ monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80. Objective response rates of approximately 12% have been reported with durvalumab monotherapy in EGFR TKI-resistant tumours with strong PD-L1 expression. We hypothesised that the combination of gefitinib with durvalumab would exert therapeutic synergy by inducing differentiation and engraftment of memory T cells immediately after initial TKI treatment, therefore inducing more durable clinical remissions with the EGFR TKI. We performed a Phase 1 study to assess the safety and efficacy of concurrent gefitinib and durvalumab for the treatment of TKI-naive patients with EGFR mutation-positive NSCLC.

METHODS

Study design
This was an open-label, multicentre Phase 1 trial (NCT02088112) with a modified 3+3 dose-escalation phase followed by a multi-arm dose-expansion phase, conducted at seven sites in the US, Japan and Korea. A fixed dose of gefitinib 250 mg daily (QD) was selected for all cohorts, based upon the established maximal biologic activity in vivo. In the dose-escalation phase (Fig. 1), patients received gefitinib 250 mg QD plus durvalumab (MEDI4736) at 3 or 10 mg/kg intravenously (IV) every 2 weeks (Q2W). Cohort A received durvalumab at 3 mg/kg IV Q2W. Next, a subsequent Cohort B and a Japan Cohort received durvalumab at 10 mg/kg. Dose-limiting toxicity (DLT) was defined as any possible treatment-related Grade ≥3 adverse event (AE), regardless of duration, within the first treatment cycle of 28 days. This included any Grade 4 immune-mediated AEs that were not attributable to lung cancer.

The dose-expansion phase comprised three arms. Patients enrolled in Arm 1 received gefitinib 250 mg QD plus durvalumab 10 mg/kg IV Q2W. Arm 1 was intended to address whether concurrent gefitinib and durvalumab could achieve a more durable response than historical gefitinib monotherapy. Patients enrolled in Arm 2 received gefitinib monotherapy induction for 28 days followed by concurrent gefitinib plus durvalumab. The rationale for the induction Arm 2 was that gefitinib would induce tumour autophagy with MHC class I cross-presentation of tumour antigens and the activation of CD8+ T cells over time, thereby priming T cells for durvalumab at Day 28. Arm 1a was later added to the study protocol to further explore the safety and clinical activity of the dosing schedule used in Arm 1. For all cohorts, concurrent therapy was given for up to 12 months; and thereafter patients continued with gefitinib monotherapy until disease progression.

Patients
Screening was conducted between March 2014 and February 2015. Patients were required to have tissue-confirmed metastatic or advanced NSCLC by AJCC seventh edition cancer staging criteria that was not amenable to definitive surgery or radiation. The dose-escalation phase permitted patients with any relapsed/refractory NSCLC or those who were intolerant or not eligible for any line of standard treatment. This cohort did not require an activating EGFR mutation, and prior treatment with EGFR TKIs was permitted. The dose-expansion phase permitted only EGFR TKI-naive patients with tumours harbouring a sensitising EGFR mutation. Mandatory tumour biopsies were required at screening and on Day 10 of treatment. Patients in Arm 1a were permitted to submit an archival tissue sample in place of the screening sample, if collected within 90 days prior to the first dose (N = 12). For additional patient eligibility criteria, please see Supplementary Data 1. All patients provided written informed consent; the final protocol was approved by the local ethics committee or Institutional Review Board at each site.

Assessments
In the dose-escalation phase, the primary objective was to assess the safety and tolerability of concurrent gefitinib plus durvalumab and establish a recommended dose of durvalumab for use in the dose-expansion phase. In the dose-expansion phase, the primary objective was to confirm the safety and tolerability of the gefitinib plus durvalumab combination in the intent-to-treat population, for use in future studies. Secondary objectives included pharmacokinetics, durvalumab immunogenicity, durvalumab pharmacodynamics and efficacy. Efficacy endpoints included overall response rate (ORR), disease control rate (DCR), DCR at 16 weeks, duration of response and progression-free survival (PFS). Overall survival was added as a protocol amendment later in the course of the study; however, few patients could subsequently consent to this protocol amendment.

EGFR mutation was determined by local site laboratories. Exploratory objectives included correlation of baseline tumour PD-L1 expression with efficacy. Tumour cell (TC) PD-L1
immunohistochemistry (Ventana, clone SP263) was blindly scored by a pathologist using an established scoring protocol. An exploratory cut-point (PD-L1 TC ≥20%) was empirically chosen as it provided more meaningful group numbers for analysis (PD-L1 TC ≥20%: N = 12; PD-L1 TC <20%: N = 24) than the more typical cut-off of PD-L1 TC ≥25% (N = 7; PD-L1 TC: <25%: N = 29). Safety and tolerability were assessed in the safety population of all patients who received at least one dose of study medication. Pharmacokinetics were assessed in all patients who had at least one measurable post-dose pharmacokinetic concentration. Tumour response was assessed in all patients with a baseline tumour assessment who received study medication. Study sample size was based on the design to obtain adequate tolerability, safety, pharmacokinetic and pharmacodynamic data while exposing as few subjects as possible to the investigational product and procedures. Further details are provided in Supplementary Data 1.

RESULTS

Patient characteristics

Of the 70 patients screened, 56 were eligible and treated (Supplementary Fig. 1). Patient demographics and baseline characteristics are reported in Supplementary Table 1. Overall, in the dose-escalation and dose-expansion phases, patients had a median age of 61 years (range: 27–83) and 55% were female. There was a slightly higher prevalence of Asian (55%) patients, compared with Caucasian (43%) and Black (4%) patients. EGFR mutation status in the dose-expansion phase included 2 patients with exon 18 mutations, 21 with exon 19 deletions, 16 with exon 20 patients were enrolled into the concomitant dosing group, Arm 1a (Supplementary Table 2). Common AEs included diarrhoea (24%), elevated ALT (47% [8/17]) and AST (35% [6/17]). Although these patients discontinued as a result of AEs, most frequently due to elevated ALT (47% [8/17]) and AST (35% [6/17]). Despite cessation of both drugs, administration of a corticosteroid, usually 1 mg/kg oral prednisone, was initiated. Once AST/ALT levels improved, corticosteroid dose was tapered over the course of 3–5 weeks. With this management, hepatic AEs of special interest resolved for most patients (87.1%) but remained a pervasive problem during the trial. The majority of patients discontinued gefitinib plus durvalumab combination treatment before the full 1-year treatment period ended (N = 28; 70.0%). Of these, 17 patients discontinued as a result of AEs, most frequently due to elevated ALT (47% [8/17]) and AST (35% [6/17]). Although these patients stopped combination treatment, they continued on gefitinib monotherapy. Patients with hepatic AEs that led to treatment discontinuation are shown in Table 1.

Pharmacokinetics and pharmacodynamics in the dose-expansion phase

The pharmacokinetics of each compound were similar to those previously reported in gefitinib and durvalumab monotherapy trials, indicating no drug–drug interaction between gefitinib and durvalumab (Supplementary Table 4 and Supplementary Fig. 2).
| Patient (cohort) | AE (max. CTCAE grade) | Onset | ALT | AST | BIL | Last available value | TRAE<sup>a</sup> | Outcome |
|-----------------|-----------------------|-------|-----|-----|-----|----------------------|----------------|---------|
| 1 (Arm 1a)      | DILI<sup>b</sup> (Grade 4) | D41 D55 | D41: 86 U/L | D41: 76 U/L | D41: 27 µmol/L | FU (D125): ALT: 10 U/L; AST: 15 U/L; BIL: 21 µmol/L | No | Recovered/resolved |
| 2 (Arm 1a)      | Transaminases increased<sup>b</sup> (Grade 4) | D44 D44 | D44: 992 U/L | D44: 829 U/L | D44: 24 µmol/L | FU (D86): ALT: 13 U/L; AST: 22 U/L | Yes | Recovered/resolved |
| 3 (Arm 1a)      | Transaminases increased<sup>b</sup> (Grade 3) | D36 D36 | D36: 309 U/L | D36: 193 U/L | D36: 9 µmol/L | FU (D120): ALT: 29 U/L; AST: 27 U/L | Yes | Recovered/resolved |
| 4 (Arm 1a)      | ALT increased (Grade 4) | D42 D42 | D42: 1109 U/L | D42: 665 U/L | D42: 32 µmol/L | FU (D61): ALT: 120 U/L; AST: 99 U/L; BIL: 19 µmol/L | Yes | Recovered/resolved |
| 5 (Arm 1a)      | ALT increased (Grade 3) | D88 | D88: 462 U/L D157: 266 U/L | D88: 197 U/L D157: 225 U/L | D88: 15 µmol/L D157: 24 µmol/L | FU (D183): ALT: 98 U/L; AST: 102 U/L | Yes | Recovered/resolved |
|                 | ALT increased (Grade 3) | D157 | | | | | Yes | Recovered/resolved |
| 6 (Arm 1a)      | ALT increased (Grade 3) | D70 | D70: 404 U/L | D70: 310 U/L | D70: 12 µmol/L | EOCT (D84): ALT: 168 U/L; AST: 137 U/L | Yes | Not recovered/resolved |
|                 | ALT increased (Grade 3) | D70 | | | | | Yes | Recovered/resolved |
| 7 (Arm 1a)      | ALT increased<sup>b</sup> (Grade 3) | D57 D71 | D57: 87 U/L D71: 566 U/L | D57: 59 U/L D71: 301 U/L | D57: 7 µmol/L D71: 9 µmol/L | FU (D99): ALT: 424 U/L; AST: 132 U/L | Yes | Not recovered/resolved |
|                 | ALT increased<sup>b</sup> (Grade 3) | D57 | | | | | Yes | Recovered/resolved |
| 8 (Arm 1a)      | ALT increased (Grade 2) | D44 D44 | D44: 80 U/L | D44: 56 U/L | D44: 9 µmol/L | FU (D310): ALT: 17 U/L; AST: 30 U/L | Yes | Recovered/resolved |
|                 | ALT increased<sup>b</sup> (Grade 3) | D142 D142 | D142: 201 U/L | D142: 109 U/L | D142: 12 µmol/L | FU (D118): ALT: 82 U/L; AST: 100 U/L | Yes | Recovered/resolved |
| 9 (Arm 2)       | ALT increased<sup>b</sup> (Grade 4) | D41 D41 | D41: 753 U/L | D41: 585 U/L | D41: 14 µmol/L | FU (D124): ALT: 186 U/L; AST: 53 U/L | Yes | Not recovered/resolved |
|                 | ALT increased (Grade 3) | D41 | | | | | Yes | Not recovered/resolved |
| 10 (Arm 2)      | ALT increased (Grade 3) | D71 D71 | D71: 275 U/L | D71: 330 U/L | D71: 12 µmol/L | EOCT (D83): ALT: 186 U/L; AST: 53 U/L | Yes | Not recovered/resolved |
|                 | ALT increased (Grade 3) | D71 | | | | | Yes | Not recovered/resolved |
| 11 (Arm 2)      | ALT increased (Grade 2) | D57 | Plasma: D57: 32 U/L D73: 102 U/L D85: 141 U/L D101: 257 U/L D108: 402 U/L | Plasma: D57: 41 U/L D73: 67 U/L D85: 78 U/L D101: 128 U/L D108: 183 U/L | Plasma: D57: 10 µmol/L D73: 9 µmol/L D85: 12 µmol/L D101: 12 µmol/L D108: 10 µmol/L | FU (D124): ALT: 68 U/L; AST: 31 U/L | Yes | Recovered/resolved |

<sup>A</sup>AE adverse event, ALT alanine aminotransferase, AST aspartate aminotransferase, BIL bilirubin, CTCAE Common Terminology Criteria for Adverse Events, D day, DILI drug-induced liver injury, EOCT end of combination treatment, FU follow-up, Max maximum.

<sup>b</sup>Possibly causally related to any study treatment, as assessed by the investigator.

<sup>q</sup>Listed as a serious adverse event.
No treatment-emergent anti-drug antibodies were observed for
durvalumab when combined with gefitinib. Complete inhibition of
soluble PD-L1, a pharmacodynamic biomarker for durvalumab
activity, was observed in all patients (Supplementary Fig. 3),
consistent with durvalumab monotherapy at this dose. 30

Efficacy in the dose-expansion phase
ORR was 63.3% and 70.0% in Arms 1 + 1a and Arm 2, respectively
(Table 2). DCR was 100.0% in Arms 1 + 1a and 90.0% in Arm 2,
indicating that almost all patients in the dose-expansion phase
achieved disease control.

Table 2. Antitumour activity (tumour response analysis set).

| BOR, n (%) | Arms 1 + 1a (N = 30) | Arm 2 (N = 10) |
|-----------|----------------------|---------------|
| CR        | 0                    | 0             |
| PR        | 19 (63.3)            | 7 (70.0)      |
| SD ≥ 8 weeks | 10 (33.3)        | 2 (20.0)      |
| Unconfirmed response | 1 (3.3)          | 0             |
| PD        | 0                    | 1 (10.0)      |
| ORR, % (95% CI) | 63.3 (43.9–80.1) | 70.0 (34.8–93.3) |
| DCR, % (95% CI) | 100.0 (88.4–100.0) | 90.0 (55.5–99.7) |
| DCR at 16 weeks, % (95% CI) | 90.0 (73.5–97.9) | 80.0 (44.4–97.5) |
| Median DoR, months (95% CI) | 9.2 (3.7–14.0)   | 12.6 (5.5–20.4) |
| Median PFS, months (95% CI) | 10.1 (5.5–15.2) | 12.0 (2.7–15.6) |

BOR best overall response, CI confidence interval, CR complete response,
DCR duration of response, N number of patients assigned to treatment, ORR overall response rate, PD progressive disease,
PFS progression-free survival, PR partial response SD stable disease.

Median duration of response was 9.2 months (95% confidence interval [CI]: 3.7–14.0) in Arms 1 + 1a and 12.6 months (95% CI 5.5–20.4) in Arm 2, while median PFS was 10.1 (95% CI 5.5–15.2) in Arms 1 + 1a and 12.0 months (95% CI 2.7–15.6) in Arm 2 (Fig. 3). However, given the small number of patients in Arm 2, these results should be interpreted with caution. The duration of PFS for individual patients in Arms 1 + 1a and Arm 2 is shown in Fig. 4. In an exploratory analysis, a trend towards favourable PFS was noted in patients expressing baseline PD-L1 TC ≥20% (N = 12 vs. 24; hazard ratio: 0.46; 95% CI: 0.19–1.03; Figs. 3 and 4). It was not possible to compare the median duration of response for patients expressing PD-L1 TC ≥20%, due to small patient numbers.

DISCUSSION
In this trial combining geftinib with durvalumab immunotherapy,
no synergistic efficacy signal was detected, and the incidence of AEs was higher than expected. The incidence of hepatic AEs with concurrent geftinib plus durvalumab was notably higher than previously reported for gefitinib (2.4%) and durvalumab (2.8%) monotherapy. 5,30,39 The observed transaminitis led to treatment discontinuation in >25% of patients, potentially compromising the dose intensity of the EGFR inhibitor. Although some patients were successfully managed with dose interruption or corticosteroids,
this remained a significant concern during the course of the trial.
Owing to the small numbers of patients in the study, it is difficult to draw definite conclusions around the impact of AEs on PFS, which was no better than historical reports of PFS with gefitinib monotherapy (Supplementary Fig. 4). It is possible that PFS was reduced due to toxicity; however, when considering the width of the CIs, the PFS in each of the groups was not dissimilar despite the observed differences in the number of patients discontinuing treatment due to AEs. This hepatic phenomenon suggests a potential synergy in liver toxicity. Interestingly, treatment-related AEs associated with elevations in ALT and AST have been observed in other first-generation EGFR TKI/immunotherapy combinations, such as erlotinib plus atezolizumab (14.3%),

and particularly gefitinib plus pembrolizumab (71.4%).

Recruitment to the latter trial was stopped after seven patients enrolled, due to frequency and severity of transaminitis. Hepatotoxicity may be due to the formation of reactive gefitinib metabolites in the liver, leading to inflammation when combined with an immune checkpoint inhibitor.

Since this study was initiated, the third-generation EGFR TKI osimertinib is now available for first-line treatment of patients with EGFR-mutant metastatic NSCLC. In contrast to gefitinib, osimertinib had a high incidence of interstitial lung disease when combined with durvalumab (13/34; 38%).

This resulted in early termination of the subsequent Phase 3 CAURAL combination trial. In the first 13 ALK+ patients treated with nivolumab plus crizotinib, 5 developed severe hepatic toxicities leading to drug discontinuation. Of these, two patients died and the presence of severe hepatic toxicities may have contributed to death. Taken together, the safety profiles associated with EGFR/ALK TKI plus PD-(L)1 inhibitor combinations have generally shown somewhat higher toxicity than expected, reflecting the potential exacerbation of intrinsic but typically minimal toxicities of various TKIs.

In this Phase 1 trial, there was no improvement in PFS or ORR compared to that previously reported with gefitinib monotherapy in similar patient populations. Similar trials of TKI plus PD-1 axis inhibitors have also had no clear evidence of therapeutic synergy, compared with EGFR TKI monotherapy. In a small Phase 1b study of erlotinib plus atezolizumab, response rate of 75% and median PFS of 15 months was observed; likewise erlotinib plus either pembrolizumab or nivolumab had modestly favourable median PFS and ORR. Perhaps due to this unfavourable efficacy-to-toxicity ratio, the clinical investigation of EGFR TKI plus PD-1 axis inhibitor combinations has largely curtailed in the past 2 years, particularly for TKI-naive patients. To the best of our knowledge, no Phase 3 trials with an EGFR TKI plus PD-1 inhibitor for EGFR TKI-naive patients are currently planned or actively accruing.

Although our trial did observe numerically greater improvement in median PFS in patients with baseline PD-L1 TC ≥20%, this finding needs to be interpreted with caution due to the small sample size. Similarly, an association between PD-L1 expression and improved efficacy was suggested with another EGFR TKI/immunotherapy combination in KEYNOTE-021, in which partial response was reported in all patients with baseline PD-L1 tumour proportion scores ≥50%. Although PD-L1 TC ≥25% was associated with efficacy of durvalumab monotherapy in patients with EGFR-mutant NSCLC with acquired TKI resistance, a recent Phase 2 study found that pembrolizumab monotherapy was ineffective for the treatment of EGFR TKI-naive patients with PD-L1 TC ≥1%, in which many were ≥50%. Although higher PD-L1 and
tumour mutational burden may also be predictive for early relapse for EGFR-mutant patients while receiving EGFR TKI monotherapy, these reports remain largely exploratory and inconclusive.4,24,27,48

In summary, results from this Phase 1 study do not support the combination of TKIs and anti-PD-L1 in the EGFR TKI treatment-naive setting. Given the diverse array of resistance mutations and clonal heterogeneity for EGFR TKI-resistant patients, it is possible that the relapsed/refractory setting may be a more opportune setting for T cell or immune checkpoint-based therapy. Further trials are warranted to elucidate the role of anti-PD-1/PD-L1 agents in the treatment paradigm for patients with EGFR-mutant NSCLC and determine whether baseline tumour PD-L1 expression is predictive of improved durability of response.

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AUTHOR CONTRIBUTIONS

B.C.C. (Site Principal Investigator) contributed to the study design, recruitment and management of patients and interpretation of data. T.C.Y. (Translational Sciences Lead) contributed to the development and implementation of the biomarker strategy; was responsible for the delivery and oversight of pharmacokinetics, soluble PD-L1, anti-drug antibodies and exploratory biomarker data (i.e. PD-L1) and contributed to the interpretation of data. S.-W.K. (Site Principal Investigator) contributed to the study design, recruitment and management of patients and interpretation of data. N.N. (Site Principal Investigator) contributed to the recruitment and management of patients, assisted with the provision of study materials/patients, and was responsible for the collection and assembly of data. D.-W.K. and S.K. (Site Principal Investigators) assisted with the provision of study materials/patients, were responsible for the collection and assembly of data and contributed to the interpretation of data. R.T. contributed to the study design, oversaw the analysis and contributed to the interpretation of data. W.T. (Clinical Pharmacologist) was responsible for the analysis and interpretation of the gefitinib pharmacokinetics data. M.T. (Clinical Pharmacologist) was responsible for the analysis and interpretation of the durvalumab pharmacokinetics, soluble PD-L1 and anti-drug antibodies data. H.K.A. was responsible for the analysis of PD-L1 in tumour samples and contributed to the interpretation of data. M.P.R was responsible for the assessment of tumour PD-L1 expression in tissue sections. M.M. (Clinical Lead) contributed to the study design, development of the protocol and interpretation of data. D.L.G. (Site Principal Investigator) contributed to the study design, recruitment and management of patients, protocol and interpretation of data. All authors contributed to the development of the manuscript and have given final approval for the final version to be published.

ADDITIONAL INFORMATION

Ethics approval and consent to participate This study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. All patients provided written informed consent, including for exploratory biomarker research. The study protocol, and all other written information and/or materials provided to patients, were approved by the following Ethics Committees/Institutional Review Boards: National Cancer Center Hospital, Chuo-ku, Japan; National Hospital Organization Shikoku Cancer Center, Matsuyama-shi, Japan; Seoul National University Hospital, Seoul, South Korea; Asan Medical Center, Seoul, South Korea; Liberty Institutional Review Board, DeLand, USA; MD Anderson Cancer Center, Houston, USA; Western Institutional Review Board, Puyallup, USA.

Data availability Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca’s data sharing policy described at https://astrazenecagrouptrials.pharmacom.com/ST/Submission/Disclosure.

Competing interests B.C.C. has received institutional research grants/supplies from Biodexis; Boehringer Ingelheim, Bristol-Myers Squibb, Iovance Biotherapeutics, Neo-genomics and Prometheus; participated in speaker b ur eas for A chilles, AstraZeneca, Bristol-Myers Squibb, Foundation Medicine, F. Hoffmann-La Roche AG, Gilead and Takeda; and has participated in advisory boards for AbbVie, BergenBio, Bristol-Myers Squibb and GlaxoSmithKline. T.C.Y., R.T., W.T. and H.K.A. are employees or contracted employees of AstraZeneca and may be shareholders of AstraZeneca. S.-W.K. has received clinical research support from AstraZeneca, Boehringer Ingelheim and Eli Lilly. N.N. has received research grants from AstraZeneca, Boehringer Ingelheim, Chugai Pharmaceutical, Kyowa Hakko Kirin, ONO Pharmaceutical and Taiho Pharmaceutical and personal fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Kyowa Hakko Kirin, Meiji Seika Pharma, Merck Sharp & Dohme, Nikkire Business Publications, ONO Pharmaceutical, Pfizer Japan, Reno Medical and Taiho Pharmaceutical. D.-W.K. has received research funding from Alpha Biopharma, AstraZeneca/MedImmune, Hammi, Jansson, Merus, Mirati Therapeutics, MSD, Novartis, ONO Pharmaceutical, Pfizer Inc., Roche/Genentech, Takeda, TP Therapeutics, Coveryo and Yuhani. L.Q.M.C. is an employee of the University of Texas, Austin and a former employee of the University of Washington/Seattle Cancer Care Alliance. L.Q.M.C.’s institution has received research funding from Alkermes, AstraZeneca/MedImmune, Bristol-Myers Squibb, Dynavax, Eli Lilly, Genentech, Incyte, Merck, Novartis, Pfizer Inc., Seattle Genetics and Ventrx; and the University of Washington/Seattle Cancer Care Alliance received institutional funding from AstraZeneca for this study. L.Q.M.C. has received honoraria from Amgen and has participated in advisory boards for Alkermes, Amgen, AstraZeneca, Bristol-Myers Squibb, Dynavax, Genentech, Merck, Novartis, Pfizer Inc., Sanofi Genzyme, Seattle Genetics, Synthorx and Takeda. S.K. has received research grant funding from AbbVie, AstraZeneca and ONO Pharmaceutical; honoraria from AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Novartis and ONO Pharmaceutical; and has participated in advisory boards for AstraZeneca. M.T. is an employee of Astellas Pharma US and a former employee of AstraZeneca. M.P.R. is an employee of the Institute for Prostate Cancer Research and a former employee of AstraZeneca. M.M. is a former employee of AstraZeneca. D.L.G. has received research grants from AstraZeneca, Janssen Research & Development and Takeda; has participated in advisory boards for AstraZeneca, GlaxoSmithKline and Sanofi; and has received travel expenses from AstraZeneca. D.L.G.’s institution has received compensation for conducting the study.

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