

Safety and Efficacy of Durvalumab and Tremelimumab Alone or in Combination in Patients with Advanced Gastric and Gastroesophageal Junction Adenocarcinoma



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ABSTRACT

Purpose: This randomized, multicenter, open-label, phase Ib/II study assessed durvalumab and tremelimumab in combination or as monotherapy for chemotherapy-refractory gastric cancer or gastroesophageal junction (GEJ) cancer.

Patients and Methods: Second-line patients were randomized 2:2:1 to receive durvalumab plus tremelimumab (arm A), or durvalumab (arm B) or tremelimumab monotherapy (arm C), and third-line patients received durvalumab plus tremelimumab (arm D). A tumor-based IFN γ gene signature was prospectively evaluated as a potential predictive biomarker in second- and third-line patients receiving the combination (arm E). The coprimary endpoints were objective response rate and progression-free survival (PFS) rate at 6 months.

Results: A total of 113 patients were treated: 6 in phase Ib and 107 (arm A, 27; arm B, 24; arm C, 12; arm D, 25; arm E, 19) in phase II. Overall response rates were 7.4%, 0%, 8.3%, 4.0%, and 15.8% in the five arms, respectively. PFS rates at 6 months were 6.1%, 0%, 20%, 15%, and 0%, and 12-month overall survival rates were 37.0%, 4.6%, 22.9%, 38.8%, and NA, respectively. Treatment-related grade 3/4 adverse events were reported in 17%, 4%, 42%, 16%, and 11% of patients, respectively.

Conclusions: Response rates were low regardless of monotherapy or combination strategies. No new safety signals were identified. Including use of a tumor-based IFN γ signature and change in baseline and on-treatment circulating tumor DNA are clinically feasible and may be novel strategies to improve treatment response in this difficult-to-treat population.

Introduction

Responses to approved treatments in the first- and second-line metastatic gastric cancer and gastroesophageal junction (GEJ) cancer settings are short lived, with virtually all patients experiencing disease

progression (1, 2). For patients receiving two or more lines of treatment, options are limited, and treatment regimens involving novel approaches are urgently needed (3). Increasing understanding of tumor immunity and gastric cancer/GEJ cancer pathogenesis has

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Translational Relevance

In this randomized, multicenter phase 1b/II clinical study of metastatic/recurrent gastric or gastroesophageal junction cancer ($n = 113$), durvalumab plus tremelimumab demonstrated low response rates, a 12-month overall survival (OS) rate similar to that reported previously for checkpoint inhibitor combination, and a tolerable safety profile. Prospectively screening patients using a novel RNA-based IFN γ signature from archival tissue was feasible, but this patient selection did not improve clinical response. Changes in circulating tumor DNA variant allele frequency correlated with median progression-free survival and OS, suggesting utility as an early indicator of clinical benefit.

fueled investigations of immune checkpoint inhibitors (ICI) in the setting of chemotherapy-refractory advanced or metastatic gastric cancer/GEJ cancer. Trials of anti-PD-1 and anti-CTLA-4 (CTLA-4) ICIs (4–9), including pembrolizumab (5, 9) and nivolumab (7) as monotherapy and nivolumab in combination with ipilimumab, have shown durable clinical responses with acceptable toxicity profiles (6).

Although the antitumor effect and long-term durability observed in responders treated with ICI monotherapy and combination therapy are encouraging, the identification of novel predictive biomarkers to predict response is paramount. Approximately 40% of patients with gastric cancer/GEJ cancer express PD-L1 on tumor and immune cells (5, 10). In addition, microsatellite instability status (MSI) is associated with an improved prognosis as well as a reduced risk of lymph node metastasis, tumor invasion, and mortality (11, 12).

Interferon-gamma (IFN γ) produced by activated T cells and natural killer cells can directly upregulate PD-L1 expression and promote cytotoxicity through tumor-infiltrating macrophages recruitment, cytotoxic T-cell proliferation, and nitric oxide production. T-cell inflamed tumors show a high IFN γ signature (13). An IFN γ gene signature associated with improved response to pembrolizumab in multiple tumor indications, including gastric cancer/GEJ cancer has been identified (14). Similarly, patients with non-small-cell lung cancer receiving durvalumab with high expression of a four-gene signature comprising *IFN γ* , *CD274*, *LAG3*, and *CXCL9* had higher overall response rates, longer progression-free survival (PFS), and improved overall survival (OS) than those with low expression, and these findings were replicated in an independent urothelial cancer cohort (15). Given the moderate-to-high expression of IFN γ signature in a subset of gastric cancer/GEJ tumors, we performed a prospective evaluation of patients based on signature status.

The anti-PD-L1 antibody durvalumab has demonstrated durable clinical activity and a manageable safety profile in multiple tumor types, including gastric cancer/GEJ cancer (16–19). In addition, the anti-CTLA-4 antibody tremelimumab has the potential to interrupt a key coinhibitory signal, thus leading to T-cell activation in advanced gastric cancer/GEJ cancer (10, 20). In this study, we investigated the potential clinical benefits of durvalumab and tremelimumab in combination and as monotherapy in chemotherapy-refractory advanced gastric cancer/GEJ cancer. We also prospectively evaluated the ability of a tumor-based IFN γ gene signature to identify a subset of second- and third-line patients with gastric cancer/GEJ cancer who were most likely to respond to dual ICI therapy.

Patients and Methods

Study design and treatments

This study is registered with ClinicalTrials.gov (NCT02340975) and was conducted at 30 centers globally, including sites in Canada (2), Japan (3), Korea (4), Singapore (2), Taiwan (3), and the United States (16), from March 2015 to January 2018. The study protocol and amendments were approved by local institutional boards and performed in accordance with the Declaration of Helsinki and is consistent with International Conference on Harmonisation, Good Clinical Practice, and applicable regulatory requirements. All patients provided written informed consent.

The phase 1b portion of the study ($N = 6$) involved a safety run-in assessment of durvalumab and tremelimumab at doses and schedules selected for dose expansion in patients with gastric or GEJ adenocarcinoma. Patients received durvalumab 20 mg/kg plus tremelimumab 1 mg/kg i.v. every 4 weeks (Q4W) for four cycles, followed by durvalumab 10 mg/kg every 2 weeks (Q2W) for up to 12 months (16). Patients were monitored for dose-limiting toxicities before enrollment in phase II (Supplementary Fig. S1).

In the phase II portion ($N = 88$), 63 patients with disease refractory to one platinum- or fluoropyrimidine-based chemotherapy regimen were randomized 2:2:1 to one of three second-line treatment arms: A, B, or C. Third-line patients who had progressed on two regimens enrolled in arm D ($n = 25$). Patients in all arms were treated for up to 12 months. Patients in arms A and D received durvalumab 20 mg/kg plus tremelimumab 1 mg/kg Q4W for four cycles, followed by durvalumab 10 mg/kg Q2W. Patients in arm B received durvalumab monotherapy (10 mg/kg) Q2W. Patients in arm C received tremelimumab monotherapy (10 mg/kg) Q4W for seven doses and then every 12 weeks for two doses (for a total of up to 9 doses). Patients in the durvalumab and tremelimumab monotherapy arms could cross over to combination therapy at the time of disease progression if they met specific criteria. Those who did not have progression during the first 12 months and entered follow-up were eligible for retreatment for up to 12 months at the time of progression.

An additional arm (arm E; $n = 19$) was added per a study amendment to prospectively evaluate the ability of a tumor-based IFN γ gene signature in second- and third-line patients to identify patients with an increased likelihood of response. Prescreening was undertaken using archival formalin-fixed paraffin-embedded tissue to assign IFN γ signature status with a custom, targeted RNA sequencing assay using Ion AmpliSeq (Thermo Fisher Scientific) sequencing technologies. The positive cutoff was established at the upper tertile of IFN γ expression from an existing dataset, including data from arms A–D (15). Patients who were positive were eligible to be screened upon progression while receiving first- or second-line therapy. Patients enrolled in this arm received durvalumab 20 mg/kg and tremelimumab 1 mg/kg i.v. Q4W for four cycles, followed by durvalumab 10 mg/kg Q2W for ≤ 12 months.

A prespecified interim analysis was performed on arms A and B after 20 patients were enrolled and followed for ≥ 8 weeks to assess whether the criterion for expansion [≥ 2 of 20 patients with complete response (CR), partial response (PR), or stable disease (SD) for 8 weeks] was met. If the criterion was not met, enrollment in arms A, B, and C could be stopped. Preliminary biomarker data could be used to support the decision to continue or stop enrollment. Similar interim analyses were planned for arm D (enrollment could stop if ≤ 2 of 25 patients had CR or PR) and arm E (enrollment could stop if ≤ 3 of 20 patients had CR or PR).

Patients

Key inclusion criteria included histologic or cytologic confirmation of metastatic or recurrent gastric or GEJ adenocarcinoma that progressed after ≤ 2 lines of systemic platinum- or fluoropyrimidine-based chemotherapy and presence of a measurable lesion amenable to biopsy. Key exclusion criteria included HER2-overexpressing metastatic or recurrent gastric cancer/GEJ cancer; active or prior documented autoimmune or inflammatory disease within 3 years; and prior treatment with any immunotherapy.

Study assessments

The coprimary efficacy endpoints for the phase II portion were the confirmed objective response rate (ORR) and PFS at 6 months (PFS-6) based on investigator assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Clinical activity was assessed by imaging every 8 weeks through end of treatment.

Secondary endpoints included the safety of durvalumab and tremelimumab in combination, durvalumab monotherapy, and tremelimumab monotherapy, including adverse events (AE) and serious AEs based on laboratory parameters, vital signs, and electrocardiograms. AEs were assessed and graded using the National Cancer Institute Common Terminology Criteria for AEs, version 4.0 (21). Clinical activity of durvalumab and tremelimumab in combination and as monotherapy was further assessed by disease control rate, duration of response, PFS, and OS.

PD-L1 expression was determined by IHC [Ventana PD-L1 (SP263) assay] and analyzed for correlation with clinical activity of durvalumab and tremelimumab. PD-L1 expression was determined to be positive if the proportion of tumor cells with staining at any intensity was $\geq 1\%$.

Prognostic scores

Prognostic scores were retrospectively calculated to characterize the baseline features of the different treatment arms in phase II and allow retrospective analysis. These scores included the Royal Marsden Hospital (RMH) prognostic score (22) and the Gustave-Roussy Immune (GRIm)-score (23). The RMH score is based on three objective variables: number of metastatic sites (< 3 or ≥ 3 sites), lactate dehydrogenase level [less than the upper limit of normal (ULN) or greater than or equal to the ULN], and serum albumin level (< 3.5 or ≥ 3.5 g/dL). For each variable, the score was validated in patients treated with cytotoxic and targeted therapies (22). Patients with a lower RMH score at baseline (0 or 1) had a longer median OS than patients with a poor prognostic score (2 or 3). The GRIm score is based on serum albumin level, lactate dehydrogenase level, and neutrophil-to-lymphocyte ratio. Patients with a high GRIm score (> 1) had inferior OS compared with those with a lower score (0 or 1). This has been prospectively validated for patients in phase I trials receiving immunotherapy (23).

Circulating tumor DNA

A 73-gene panel measured DNA variants using the Guardant360 assay in plasma circulating tumor DNA (ctDNA). Treatment arms were combined to demonstrate associations of changes in mutation variant allele frequencies (VAF) with clinical response. Mutation VAFs and total mutation count of patient single-nucleotide variants and insertions/deletions were correlated with clinical outcomes. ORR was calculated according to RECIST 1.1. Cox proportional HRs were calculated while adjusting for age, sex, Eastern Cooperative Oncology Group performance status, line of therapy, and treatment arm.

Statistical analyses

All analyses were performed for the as-treated population, which included patients who received one or more dose of any study drug. The coprimary efficacy endpoints of ORR and PFS-6 were based on RECIST 1.1. For ORR, the two-sided 95% exact confidence intervals (CI) were estimated using binomial distribution. For PFS-6, Kaplan–Meier estimates were provided along with two-sided 95% CIs. Sample size determination was based primarily on providing sufficient precision for estimating ORR and PFS-6. The targeted ORR range was approximately 35%; with full enrollment the study would have had 85% power to detect a difference in ORR of 35% in arm A and 10% in arm B. The targeted PFS-6 rate was 53%, corresponding to a median PFS of 6.6 months or a 50% improvement over the median PFS reported for ramucirumab + paclitaxel (24).

Results

At the data cutoff of August 24, 2018, 107 patients had been enrolled in the phase II portion. Before the phase II portion, six patients were enrolled in a phase Ib safety run-in period. Three patients received one prior line of therapy, and the remaining had two or more lines. Although no responses were observed, two patients had SD (Supplementary Table S1). Five of six patients had a treatment-related AE (TRAE).

Fifty-two patients had received durvalumab in combination with tremelimumab (27 second line and 25 third line), 24 had received durvalumab monotherapy, and 12 had received tremelimumab monotherapy. The median duration of follow-up was 9.2, 3.5, 9.2, and 10.7 months in arms A, B, C, and D, respectively. An additional 19 second- or later-line patients received durvalumab and tremelimumab in the IFN γ -high group. Baseline characteristics of patients in arms A through E are shown in **Table 1**.

At the prespecified interim analysis, further enrollment in arms A, B, and C was stopped at the sponsor's discretion despite meeting the prespecified criteria for expansion, based on the evolving immunotherapy landscape in gastric cancer/GEJ cancer. The discontinuation of enrollment in arms A, B, and C was not due to safety concerns. Similarly, an interim analysis on data for 19 patients in arm E also led to discontinuation of enrollment for that cohort.

Efficacy

No significant differences among the treatment arms were observed in ORR and PFS (**Table 2**; Supplementary Fig. S2). The confirmed ORR was 7.4% (two of 27 patients; 95% CI, 0.9%–24.3%) in arm A compared with 0% in arm B (durvalumab monotherapy; 0 of 24 patients; 95% CI, 0%–14.2%) and 8.3% in arm C (tremelimumab monotherapy; one of 12 patients; 95% CI, 0.2%–38.5%; **Table 2**; **Fig. 1**). The PFS rate at 6 months was 6.1% (95% CI, 0.5%–22.2%), 0% (95% CI, NA), and 20.0% (95% CI, 3.1%–47.5%), respectively.

The median OS was 9.2 months (95% CI, 5.4–12.6 months), 3.4 months (95% CI, 1.7–4.4 months), and 7.7 months (95% CI, 2.1–13.7 months) in the combination therapy (arm A), durvalumab monotherapy (arm B), and tremelimumab monotherapy (arm C) arms, respectively (**Fig. 2**). The OS rate at 12 months in the combination therapy arm (arm A) was 37.0% (95% CI, 19.6%–54.6%) compared with 4.6% (95% CI, 0.3%–19.0%) and 22.9% (95% CI, 3.5%–52.4%) in the durvalumab monotherapy and tremelimumab monotherapy arms, respectively. The OS rate at 24 months was 18.5% (95% CI, 6.7%–34.8%) in the combination therapy arm, 0% in the durvalumab monotherapy arm, and 11.5% (95% CI, 0.6%–39.6%) in the tremelimumab monotherapy arm.

Table 1. Baseline characteristics.

Characteristics No. of patients	Arm A 2L D+T (n = 27)	Arm B 2L D (n = 24)	Arm C 2L T (n = 12)	Arm D 3L D+T (n = 25)	Arm E 2L/3L D+T IFN γ + (n = 19)
Median age (range), years	64.0 (27–78)	60.0 (29–79)	54.0 (19–74)	59.0 (35–75)	57.0 (32–82)
Male, n (%)	20 (74.1)	19 (79.2)	8 (66.7)	16 (64.0)	14 (73.7)
Race, n (%) ^a					
Asian	7 (25.9)	11 (45.8)	5 (41.7)	12 (48.0)	13 (68.4)
Other	0	0	1 (8.3)	0	0
White	20 (74.1)	13 (54.2)	6 (50.0)	13 (52.0)	6 (31.6)
Extent of disease at study entry, n (%) ^b					
Locoregionally recurrent only	2 (7.4)	1 (4.2)	2 (16.7)	0	0
Locoregionally recurrent with metastasis	14 (51.9)	14 (58.3)	2 (16.7)	13 (52.0)	9 (47.4)
Metastasis without locoregional recurrence	11 (40.7)	9 (37.5)	8 (66.7)	12 (48.0)	10 (52.6)
PD-L1 status, n (%) ^c					
High ^d	14 (51.9)	9 (37.5)	6 (50.0)	5 (20.0)	9 (47.4)
Low/negative	10 (37.0)	11 (45.8)	4 (33.3)	15 (60.0)	3 (15.8)
Unknown ^e	3 (11.1)	4 (16.7)	2 (16.7)	5 (20.0)	7 (36.8)
RMH score, n (%) ^f					
0	15 (55.6)	5 (20.8)	6 (50.0)	11 (44.0)	5 (26.3)
1	6 (22.2)	4 (16.7)	3 (25.0)	9 (36.0)	7 (36.8)
2	6 (22.2)	15 (62.5)	3 (25.0)	4 (16.0)	5 (26.3)
3	0	0	0	0	2 (10.5)
Unknown	0	0	0	1 (4.0)	0
GRIIm score, n (%) ^f					
0	12 (44.4)	7 (29.2)	3 (25.0)	15 (60.0)	7 (36.8)
1	12 (44.4)	10 (41.7)	8 (66.7)	6 (24.0)	6 (31.6)
2	1 (3.7)	4 (16.7)	1 (8.3)	2 (8.0)	5 (26.3)
3	0	2 (8.3)	0	1 (4.0)	1 (5.3)
Unknown	2 (7.4)	1 (4.2)	0	1 (4.0)	0

^aEach race category counts patients who selected only that category.

^bInformation is missing for one patient in arm B.

^cPD-L1 expression was determined using the VENTANA SP263 assay.

^dPD-L1 high was defined as $\geq 1\%$ tumor cells at baseline.

^ePD-L1 unknown was defined as percentage of tumor cells not available at baseline.

^fRMH or GRIIm score of 2 or 3 was classified as a high score.

Table 2. Efficacy endpoints.

Endpoint	Arm A 2L D+T (n = 27)	Arm B 2L D (n = 24)	Arm C 2L T (n = 12)	Arm D 3L D+T (n = 25)	Arm E 2L/3L D+T IFN γ + (n = 19)
ORR, n (%; 95% CI)	2 (7.4; 0.9–24.3)	0 (0; 0–14.2)	1 (8.3; 0.2–38.5)	1 (4.0; 0.1–20.4)	3 (15.8; 3.4–39.6)
Complete response	0	0	0	0	1 (5.3)
Partial response	2 (7.4)	0	1 (8.3)	1 (4.0)	2 (10.5)
Stable disease	5 (18.5)	3 (12.5)	2 (16.7)	6 (24.0)	1 (5.3)
Progressive disease	15 (55.6)	14 (58.3)	5 (41.7)	14 (56.0)	12 (63.2)
Nonevaluable ^a	5 (18.5)	7 (29.2)	4 (33.3)	4 (16.0)	3 (15.8)
Ongoing response rate	2 (100)	NA	0	0	1 (33.3)
DCR, n (%; 95% CI)	7 (25.9; 11.1–46.3)	3 (12.5; 2.7–32.4)	3 (25.0; 5.5–57.2)	7 (28.0; 12.1–49.4)	4 (21.1; 6.1–45.6)
DCR24, n (%; 95% CI)	2 (7.4; 0.9–24.3)	0 (0; 0–14.2)	3 (25.0; 5.5–57.2)	3 (12.0; 2.5–31.2)	3 (15.8; 3.4–39.6)
Median time to response, weeks (95% CI)	16.1 (8.1–24.0)	NA	11.6 (NA–NA)	31.1 (NA–NA)	7.7 (7.3–8.0)
Median duration of response (95% CI), weeks	NA	NA	20.1 (NA–NA)	32.3 (NA–NA)	13.3 (8.1–NA)
Median PFS (95% CI), months	1.8 (1.6–3.3)	1.6 (1.0–1.8)	1.7 (0.8–5.3)	1.8 (1.6–3.5)	1.8 (1.6–1.9)
PFS-6 (95% CI), %	6.1 (0.5–22.2)	NA	20.0 (3.1–47.5)	15.0 (4.0–32.6)	NA
Median OS (95% CI), months	9.2 (5.4–12.6)	3.4 (1.7–4.4)	7.7 (2.1–13.7)	10.6 (4.8–14.8)	7.0 (2.4–7.5)
OS-12 (95% CI), %	37.0 (19.6–54.6)	4.6 (0.3–19.0)	22.9 (3.5–52.4)	38.8 (19.2–58.1)	NA
OS-24 (95% CI), %	18.5 (6.7–34.8)	0 (0–0)	11.5 (0.6–39.6)	9.7 (1.7–26.5)	NA

Abbreviations: 2L, received treatment in the second-line setting; 3L, received treatment in the third-line setting; D, durvalumab; DCR, disease control rate (complete response + partial response + stable disease); DCR24, DCR at 24 weeks (complete response + partial response + stable disease ≥ 24 weeks); NA, not applicable; OS-12, OS rate at 12 months; OS-24, OS rate at 24 months; T, tremelimumab.

^aNonevaluable includes patients with only a baseline assessment or a response of complete response, partial response, or stable disease at an interval of < 54 days (the minimum criteria for stable disease duration) without subsequent disease evaluation and patients who had all overall response evaluations assessed as nonevaluable.

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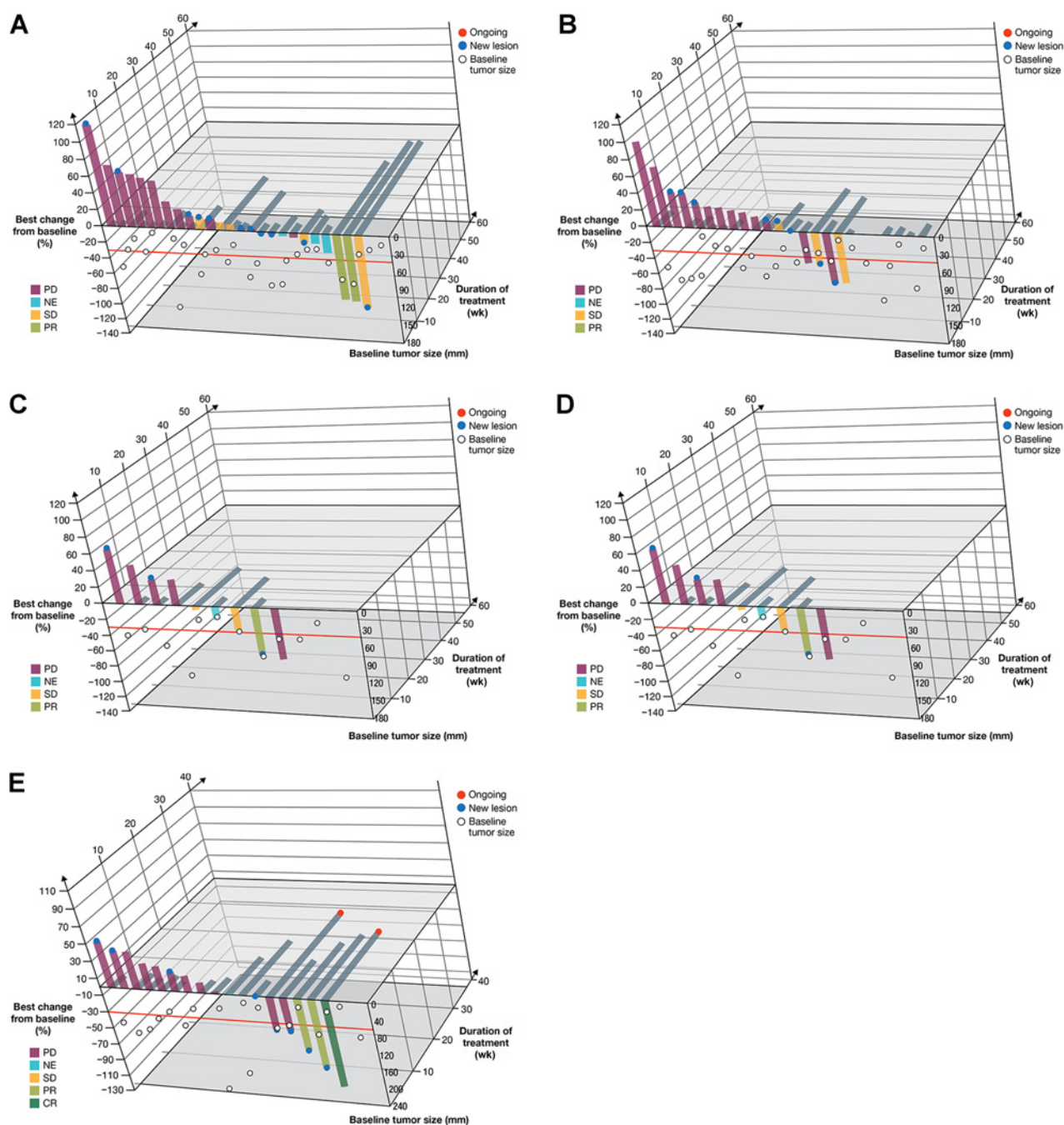


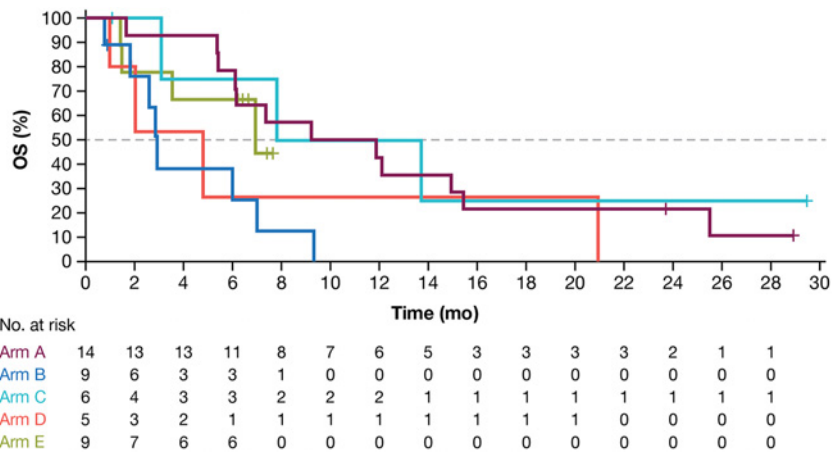
Figure 1. Three-dimensional waterfall and swim plots of arm A (**A**), arm B (**B**), arm C (**C**), arm D (**D**), and arm E (**E**). The x-axis depicts individual patients; the y-axis depicts best change from baseline (%). CR, PD, SD, PR, and SD were all per RECIST 1.1. Blue dot represents new lesion. The z-axis represents duration of treatment (weeks); red dot, ongoing therapy. White dot, baseline tumor size (mm); NE, not evaluable.

In arm D, in which 25 third-line patients were enrolled and received combination durvalumab and tremelimumab, the observed ORR was 4.0% (1 of 25 patients; 95% CI, 0.1%–20.4%) and median OS was 9.2 months (95% CI, 5.4–12.6 months). The PFS rate at 6 months was 15.0% (95% CI, 4.0%–32.6%). The OS rates at 12 and 24 months were 38.8% (95% CI, 19.2%–58.1%) and 9.7% (95% CI, 1.7%–26.5%), respectively.

In arm E, 176 patients had tumor samples submitted for prescreening; 27 were ultimately screened. Nineteen patients were enrolled, with a median follow-up duration of 5.8 months. Among the samples prescreened for potential enrollment, the IFN γ gene signature assay had a 70% success rate. The primary reason for failure was insufficient tissue resulting in insufficient nucleic acid available for RNA sequencing. The distribution of patients observed in the cohort was as

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Figure 2.
Overall survival.



expected, with 37.5% of prescreened patients having an elevated signature and 62.5% not having elevated expression. There was one CR (5%), two confirmed PRs (10.5%), and one patient (5%) with SD; the ORR was 15.8% (3 of 19 patients; 95% CI, 3.4%–39.6%). Duration of response was 13.3 weeks (range, 8.1–16.3 weeks). Median PFS was 1.8 months (95% CI, 1.6–1.9 months), PFS rate at 6 months was 0% (95% CI, NA), and median OS was 7.0 months (95% CI, 2.4–7.5 months). We correlated the degree of IFN γ gene signature intensity with best overall response (Supplementary Fig. S3). Interestingly, in patients achieving CR or PR ($n = 3$), there was no difference in IFN γ intensity (-2.84 vs. -2.83 ; $P = 0.99$) compared with those who had progressive disease (PD; $n = 14$).

Prognostic scores

RMH and GRiM prognostic scores were retrospectively evaluated for all treatment arms. The proportion of those with low RMH scores (0–1 vs. >1) was 77.8%, 37.5%, 75.0%, 80.0%, and 63.2% for arms A through E, respectively, indicating that more patients enrolled in arms B and E were likely to have a poorer prognosis than patients in the other treatment arms. A lower percentage of low

GRiM scores (0–1 vs. >1) was observed in arms B and E than in other treatment arms (92.6%, 70.8%, 91.7%, 84.0%, and 68.4%, respectively), which may explain in part the decreased OS rates observed in these patients.

Biomarker evaluations

MSI status was obtained for patients in all study cohorts (A–E), characterized using whole-exome sequencing (MSIsensor; ref. 25). A cutoff score of ≥ 10 was used to define MSI-high (MSI-H; ref. 26). One patient in arm C was MSI-H (score 13) and was a nonresponder. All other patients ($n = 72$) were microsatellite stable (Fig. 3). PD-L1 status was available for 80.4% of patients (86/107). Clinical activity regarding PFS and OS was not affected by PD-L1 status (Supplementary Table S2). Furthermore, tumor mutation burden (TMB) was calculated using whole-exome sequencing. Median TMB in arms A–D was 2.13 mutations per megabase (Mb). There was no correlation with PFS or OS when comparing high versus low TMB based on median, upper tertile, and upper quartile cutoff points. In addition, no differences were observed on the basis of response status (Supplementary Fig. S4). In arm E, median TMB was 5.00 mutations per Mb (range, 2.02–7.59;

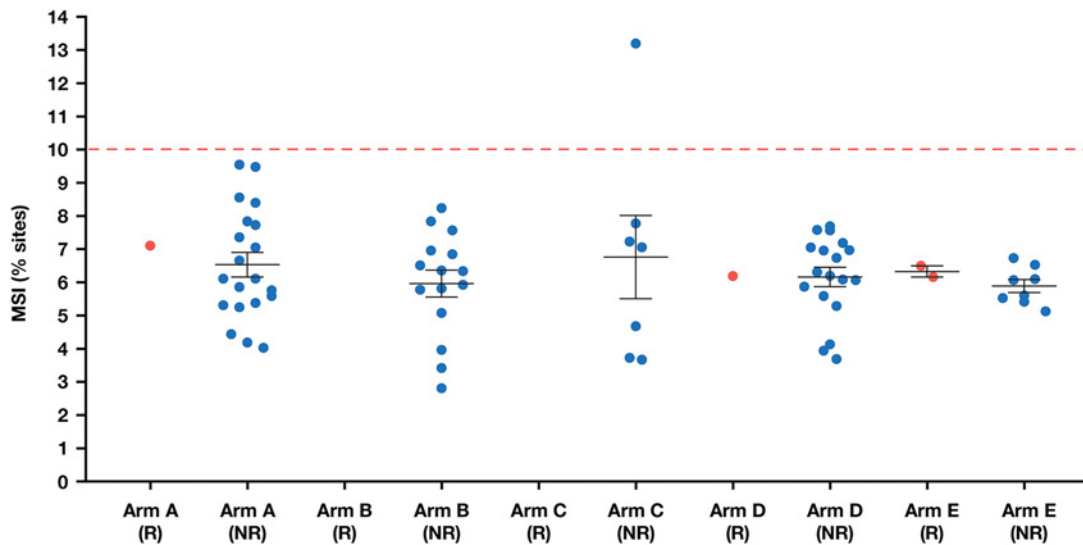


Figure 3. MSI status based on responder status by arm. Data based on MSIsensor, which uses whole-exome sequencing for characterization of MSI status. Cut-off value ≥ 10 designates MSI-H. Red dots, responders (R); blue dots, nonresponders (NR).

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Table 3. Treatment-related AEs, $\geq 10\%$ any grade in any arm.

Adverse event	Arms A + D + E 2L/3L D+T (n = 71)		Arm B 2L D (n = 24)		Arm C 2L T (n = 12)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Diarrhea	12 (16.9)	2 (2.8)	1 (4.2)	0	3 (25.0)	1 (8.3)
Aspartate aminotransferase increased	2 (2.8)	0	0	0	3 (25.0)	1 (8.3)
Dyspnea	4 (5.6)	0	0	0	3 (25.0)	0
Fatigue	14 (19.7)	2 (2.8)	2 (8.3)	0	2 (16.7)	1 (8.3)
Decreased appetite	11 (15.5)	1 (1.4)	3 (12.5)	0	1 (8.3)	0
Colitis	4 (5.6)	3 (4.2)	0	0	2 (16.7)	2 (16.7)
Pruritus	8 (11.3)	0	0	0	2 (16.7)	0
Rash ^a	9 (12.7)	1 (1.4)	0	0	2 (16.7)	0
Alanine aminotransferase increased	1 (1.4)	1 (1.4)	0	0	2 (16.7)	0
Lipase increased	2 (2.8)	2 (2.8)	0	0	2 (16.7)	1 (8.3)
Dermatitis acneiform	1 (1.4)	0	0	0	2 (16.7)	1 (8.3)
Nausea	6 (8.5)	1 (1.4)	1 (4.2)	0	1 (8.3)	0
Dry skin	2 (2.8)	0	0	0	2 (16.7)	0
Amylase increased	2 (2.8)	2 (2.8)	0	0	2 (16.7)	0
Vomiting	4 (5.6)	0	0	0	1 (8.3)	0
Weight decreased	4 (5.6)	0	0	0	0	0
Hyperglycemia	3 (4.2)	2 (2.8)	0	0	0	0
Blood thyroid-stimulating hormone increased	3 (5.8)	0	0	0	0	0
Hypothyroidism	3 (5.8)	0	0	0	0	0

^aPooled data for rash and rash maculopapular.

$n = 11$). Similar to other arms, there was no correlation of TMB with response status.

ctDNA samples were obtained from 72 patients at baseline and 31 patients at both baseline and 9 weeks on treatment. Patients with PR showed a decrease (Δ , -10.05% ; $P = 0.26$) in VAF posttreatment, compared with a significant increase in mean VAF in patients with PD (Δ , $+8.14\%$; $P = 0.03$; Supplementary Fig. S5). This correlation was also observed in total mutation count in patients with PR (Δ , -6.7 ; $P = 0.17$) compared with patients with PD (Δ , $+2.2$; $P = 0.06$). Patients with a decrease in VAF at week 9 had longer median PFS [5.4 months; 95% CI, 3.7–not reached (NR); ref. 27] and OS (median, 13.8 months; 95% CI, 7.0–NR) than those with an increase in VAF [median PFS, 1.9 months (95% CI, 1.8–NR); HR, 0.33; 95% CI, 0.09–1.21] and median OS, 8.2 months (95% CI, 6.2–NR); HR, 0.07; 95% CI, 0.01–0.66]. In addition, by using ctDNA, KRAS mutation (nonsynonymous single variant nucleotide) was identified in 2 of 113 patients (1.8%), both of whom had PD.

Safety and tolerability

In the phase Ib portion, one of six patients had a dose-limiting toxicity of grade 3 hepatic function abnormality (transaminitis), which was initially attributed as possibly related to the investigational drug; further evaluation revealed that the patient had disease progression of liver metastases. The dose of 20 mg/kg durvalumab and 1 mg/kg tremelimumab was confirmed safe and tolerable for the phase II portion.

In the phase II part of this study, the proportion of patients reporting one or more TRAE was 33.3% in the durvalumab monotherapy arm and 66.7% in the tremelimumab monotherapy arm. The incidence of AEs varied between the combination treatment arms (A, 70.4%; D, 56.0%; E, 42.1%). The most frequently observed TRAEs ($\geq 10\%$ any grade in any treatment arm) included fatigue, diarrhea, decreased appetite, and pruritus (Table 3). TRAEs leading to treatment discontinuation occurred in 14.8% (4/27), 20.0% (5/25), and 5.3% (1/19) in

the three combination therapy arms (arms A, D, and E), compared with 33.3% of patients (4/12) in the tremelimumab monotherapy arm and 4.2% of patients (1/24) in the durvalumab monotherapy arm. No TRAEs leading to death were observed.

Discussion

This completed phase Ib/II study is the first to evaluate a PD-L1 and CTLA-4 combination strategy in metastatic gastric cancer/GEJ adenocarcinoma and shows that the combination of durvalumab and tremelimumab demonstrated numerically higher rates of confirmed response than durvalumab monotherapy. Twelve-month OS rates in the combined therapy arms were comparable with the combination of nivolumab with ipilimumab in the CheckMate 032 study (37% vs. 35%; ref. 6). As anticipated, the incidence of TRAEs was higher in the combination arm and the tremelimumab monotherapy arm than in the durvalumab monotherapy arm.

In this study, we prospectively screened patients with a novel RNA-based IFN γ gene expression signature comprising *IFN γ* , *CD274*, *LAG3*, and *CXCL9*. We found this approach to be feasible for patient selection with predictable assay performance. Although the ORRs with durvalumab and tremelimumab were higher in the IFN γ signature-high group than those in unselected populations, survival outcomes remained similar. One important distinction between the assessment of the IFN γ gene signature in this study and that used in previous studies (15) was the use of archival tissue rather than fresh tissue. We postulate that IFN γ is a dynamic marker and scores can vary based on multiple factors, including timing of tissue acquisition, number of previous lines of therapy, and location of tissue acquisition (primary tumor vs. metastatic site). In this study, archival tissue was used due to availability and for pragmatic reasons to prevent delay in initiation of therapy in this fragile patient population. Given the added complexity of patient preselection and lack of substantial improvement in clinical outcomes, these results do not support further implementation

of the IFN γ gene signature for patient selection, as designed, in this population.

The use of PD-L1 expression as a biomarker for patient selection in advanced gastric cancer/GEJ cancer continues to evolve. In studies of pembrolizumab, PD-L1 status was assessed using the combined positive score (CPS), which counts PD-L1 staining in both tumor and peritumoral mononuclear cells (5). With the CPS, PD-L1-negative (CPS 0) tumors are associated with worse outcomes than PD-L1-positive tumors (CPS \geq 1). These findings are consistent with a recent meta-analysis, suggesting that PD-L1 expression levels are associated with OS (28). However, in the current study, no clear difference in clinical activity based on PD-L1 status was observed. This may be explained by our use of PD-L1 staining in tumor cells only, as well as differences in patient cohorts and immunohistochemistry antibodies.

To validate additional biomarkers, we evaluated pretreatment and on-treatment levels of ctDNA in a subset of patients in this study. Although our sample size was small, ctDNA VAFs were consistently reduced after 9 weeks of therapy in responders but not in non-responders. A decrease in VAF following 9 weeks of treatment correlated with longer PFS and OS, suggesting utility as an early indicator of clinical benefit (Supplementary Fig. S5). These findings have also been observed independently in other cancers and suggest that ctDNA may be a promising biomarker of response to ICIs in gastric cancer. Importantly, the utilization of ctDNA VAF changes should be evaluated in future studies as a method of determining response to treatment rather than relying solely on radiographic changes as measured by the RECIST criteria. This is particularly because clinical responses may be delayed and can infrequently be preceded by apparent progression (so-called pseudoprogression).

One possibility for the differences in efficacy observed in arm B (durvalumab monotherapy) and arm E (IFN γ signature-high, durvalumab plus tremelimumab) compared with the other study arms may be a higher rate of enrolled patients with poor prognostic factors, as measured by RMH and GRIM scores. In a separate phase I trial, durvalumab monotherapy demonstrated a higher rate of OS in patients with eligibility characteristics similar to those in this study (17). The possibility that patients with more adverse features were enrolled in this study is supported by the observation that only 1 of 72 evaluated patients (1.4%) had an MSI-high tumor; this is lower than the 4% incidence normally noted in patients with metastatic disease and the 12% of patients (7/59) treated with nivolumab alone in CheckMate 032 (6).

A limitation of this study is the relatively small sample size in each cohort, which affected the statistical power and precluded the ability to distinguish between treatment arms. Per protocol, enrollment was stopped following interim analyses of efficacy. In addition, although pembrolizumab was active in patients who were MSI-H and those with EBV-associated gastric cancer/GEJ cancer (29), we are unable to conclude how the therapies in our study would perform in these specific populations. As mentioned above, there was a very low proportion of MSI-H patients. EBV status was not available, as testing viral status was not a standard practice at the time of this trial. Furthermore, a lack of available tissue precluded EBV testing retrospectively.

In summary, this is the second trial to investigate the efficacy of combination checkpoint inhibitors in gastric cancer/GEJ cancer and the first to assess a PD-L1 inhibitor with a CTLA-4 inhibitor. Although responses rates with durvalumab or tremelimumab monotherapy or in combination were low, the combination approach resulted in a 12-month OS rate of approximately 37%. These results highlight that a

better understanding of the underlying immune microenvironment is paramount to prospectively identify which patients should receive combined checkpoint inhibitors. Biomarker strategies beyond PD-L1 expression, MSI status, and the use of *IFN* gene expression are ongoing.

Disclosure of Potential Conflicts of Interest

R.J. Kelly is an advisory board member/paid consultant for AstraZeneca, Bristol-Myers Squibb, Merck, Eli Lilly, Astellas, and Novartis. Y. Bang is an employee/paid consultant for AstraZeneca, Novartis, Genentech/Roche, MSD, Merck Serano, Bayer, Bristol-Myers Squibb, Eli Lilly, Taiho, Daiichi-Sankyo, Astellas, BeiGene, Green-Cross, Samyang Biopharm, Hanmi, Genexine, and GlaxoSmithKline, and reports receiving commercial research grants from AstraZeneca, Novartis, Genentech/Roche, MSD, Merck Serano, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Eli Lilly, Boehringer-Ingelheim, MacroGenics, Boston Biomedical, FivePrime, Curis, Taiho, Takeda, Ono, Daiichi-Sankyo, Astellas, BeiGene, Green-Cross, CKD Biopharma, and Genexine. D.V.T. Catenacci is an employee/paid consultant for Bristol-Myers Squibb, Merck, Taiho, Gritstone, Lilly, Genentech/Roche, Seattle Genetics, and Daiichi Sankyo, and reports receiving speakers bureau honoraria from Foundation Medicine, Merck, Lilly, Guardant Health, Tempus, and Genentech/Roche. Zev A. Wainberg is an employee/paid consultant for AstraZeneca, Bayer, Merck, Lilly, and Bristol-Myers Squibb. J.C. Bendell is an employee/paid consultant for Gilead, Genentech/Roche, Bristol-Myers Squibb, Five Prime, Lilly, Merck, MedImmune, Celgene, Taiho, MacroGenics, GlaxoSmithKline, Novartis, OncoMed, LEAP, TG Therapeutics, AstraZeneca, BI, Daiichi Sankyo, Bayer, Incyte, Apexigen, Array, Sanofi, ARMO, Ipsen, Merrimack, Oncogenex, FORMA, Arch Oncology, Prelude Therapeutics, Phoenix Bio, Cytair, Molecular Partners, Innate, Torque, Tizona, Janssen, Tolero, Translational Drug Development, Amgen, Settle Genetics, Moderna therapeutics, Tanabe Research Laboratories, Beigene, Continuum Clinical, and Agois, reports receiving commercial research grants from Gilead, Genentech/Roche, Bristol-Myers Squibb, Five Prime, Lilly, Merck, MedImmune, Celgene, EMD Serono, Taiho, MacroGenics, GlaxoSmithKline, Novartis, OncoMed, LEAP, TG Therapeutics, AstraZeneca, BI, Daiichi Sankyo, Bayer, Incyte, Apexigen, Koltan, SynDevRex, Forty Seven, AbbVie, Array, Onyx, Sanofi, Takeda, Eisai, Celldex, Agios, Cytomx, Nektar, ARMO, Boston Biomedical, Ipsen, Merrimack, Tarveda, Tyrogenex, Oncogenex, Marshall Edwards, Pieris, Mersana, Calithera, Blueprint, Evelo, FORMA, Merus, Jacobio, Effector, Novocare, Arrys, Tracoon, Sierra, Innate, Arch Oncology, Prelude Oncology, Unum Therapeutics, Vyriad, Harpoon, ADC, Amgen, Pfizer, Millennium, ImClone, Acerta Pharma, Rgenix, Bellicum, Gossamer Bio, and Arcus Bio, and other remuneration from Gilead, Genentech/Roche, Bristol-Myers Squibb, Lilly, Merck, MedImmune, Celgene, Taiho, Novartis, OncoMed, BI, ARMO, Ipsen, Oncogenex, and FORMA. C.S. Denlinger is an employee/paid consultant for Merck, Bristol-Myers Squibb, Eli Lilly, Astellas, Exelixis, QED Therapeutics, Carevive, Bayer, and Beigene. R. Leidner reports receiving commercial research grants from Bristol-Myers Squibb. H. Lenz is an advisory board member/unpaid consultant for Bristol-Myers Squibb, Merck KG, and Bayer. M.C. Rebelatto is an employee/paid consultant for and holds ownership interest (including patents) in AstraZeneca. P. Brohawn is an employee/paid consultant for AstraZeneca and Immunocore Ltd. P. He is an employee/paid consultant for AstraZeneca. J. McDevitt is an employee/paid consultant for MedImmune. J.M. Englert is an employee/paid consultant for MedImmune/AstraZeneca. G.Y. Ku is an employee/paid consultant for Merck, Pieris, Bristol-Myers Squibb, and Eli Lilly, reports receiving commercial research grants from AstraZeneca and Arog, other commercial research support from Bristol-Myers Squibb, Pieris, and Zymeworks, and speakers bureau honoraria from Dava Oncology. No potential conflicts of interest were disclosed by the other authors.

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