original reports

Safety, Efficacy, and Pharmacodynamics of Tremelimumab Plus Durvalumab for Patients With Unresectable Hepatocellular Carcinoma: Randomized Expansion of a Phase I/II Study

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abstract

PURPOSE This phase I/II study evaluated tremelimumab (anticytotoxic T-lymphocyte–associated antigen-4 monoclonal antibody) and durvalumab (antiprogrammed death ligand-1 monoclonal antibody) as monotherapies and in combination for patients with unresectable hepatocellular carcinoma (HCC), including a novel regimen featuring a single, priming dose of tremelimumab (ClinicalTrials.gov identifier: NCT02519348).

PATIENTS AND METHODS Patients with HCC who had progressed on, were intolerant to, or refused sorafenib were randomly assigned to receive T300 + D (tremelimumab 300 mg plus durvalumab 1,500 mg [one dose each during the first cycle] followed by durvalumab 1,500 mg once every 4 weeks), durvalumab monotherapy (1,500 mg once every 4 weeks), tremelimumab monotherapy (750 mg once every 4 weeks [seven doses] and then once every 12 weeks), or T75 + D (tremelimumab 75 mg once every 4 weeks plus durvalumab 1,500 mg once every 4 weeks [four doses] followed by durvalumab 1,500 mg once every 4 weeks). Safety was the primary end point. Secondary end points included objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors v1.1 and overall survival; exploratory end points included circulating lymphocyte profiles.

RESULTS A total of 332 patients were enrolled (T300 + D, n = 75; durvalumab, n = 104; tremelimumab, n = 69; and T75 + D, n = 84). Tolerability was acceptable across arms, with grade ≥ 3 treatment-related adverse events occurring in 37.8%, 20.8%, 43.5%, and 24.4%, respectively. Confirmed ORRs (95% CI) were 24.0% (14.9 to 35.3), 10.6% (5.4 to 18.1), 7.2% (2.4 to 16.1), and 9.5% (4.2 to 17.9), respectively. An early expansion of CD8+ lymphocytes was associated with response across arms, with highest proliferating CD8+ lymphocyte levels occurring in the T300 + D arm. The median (95% CI) overall survival was 18.7 (10.8 to 27.3), 13.6 (8.7 to 17.6), 15.1 (11.3 to 20.5), and 11.3 (8.4 to 15.0) months in the T300 + D, durvalumab, tremelimumab, and T75 + D arms, respectively.

CONCLUSION All regimens were found to be tolerable and clinically active; however, the T300 + D regimen demonstrated the most encouraging benefit-risk profile. The unique pharmacodynamic activity and association with ORR of the T300 + D regimen further support its continued evaluation in HCC.

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INTRODUCTION

Despite advances in treatment for unresectable hepatocellular carcinoma (uHCC), few patients achieve durable benefit and long-term survival rates remain poor.[1-4] An immune-suppressed tumor microenvironment in hepatocellular carcinoma (HCC), mediated in part by activated immune checkpoint signaling pathways, contributes to therapeutic resistance[5] and provides the rationale to evaluate immunotherapy in this difficult cancer. Programmed cell death receptor-1 and ligand-1 (PD-1/PD-L1) and cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) operate via complementary immunosuppressive signaling pathways,[6] and a combination regimen designed to inhibit both pathways may improve outcomes in patients with uHCC.

In solid tumors, combination regimens incorporating anti-CTLA-4 with anti-PD-L1 agents are associated with improved radiologic response and survival compared with monotherapies alone. Combinations

ASSOCIATED CONTENT

Appendix

Data Sharing Statement

Data Supplement

Protocol

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

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CONTEXT

Key Objective

Patients with unresectable hepatocellular carcinoma have a poor prognosis. Immune checkpoint inhibitors (programmed cell death ligand-1 [PDL-1]/PD-L1; cytotoxic T-lymphocyte–associated antigen-4 [CTLA-4]) have shown promise, but are currently insufficient as single agents and, in the case of anti–CTLA-4, can be accompanied by challenging toxicities. We hypothesized that combination of a single, priming dose of tremelimumab (anti-CTLA-4) and durvalumab (anti-PDL1) every 4 weeks (T300 + D regimen) may provide the benefit of tremelimumab combination therapy while minimizing associated toxicity.

Knowledge Generated

The T300 + D regimen showed reduced toxicity compared with other tremelimumab-containing regimens and the highest efficacy compared with durvalumab and tremelimumab as monotherapy or in combination. T300 + D also stimulated CD8+ T-cell production, enhancing response and efficacy.

Relevance

The T300 + D regimen displayed the most encouraging benefit-risk profile. These findings suggest that a single dose of tremelimumab may be sufficient to activate the tumor-fighting potential of the immune system. Both T300 + D and durvalumab monotherapy are being evaluated in the HIMALAYA study.

incorporating higher doses of anti-CTLA-4 improved efficacy but were also associated with increased anti-CTLA-4 dose-dependent toxicity.[7-11] Collective evidence indicates that prolonged or multiple exposures to CTLA-4 inhibitors may not be required for effective antitumor responses. A single dose of the CTLA-4 inhibitor tremelimumab was sufficient to provide long-lasting responses in patients with melanoma.[12,13] In a phase Ib study of tremelimumab combined with the PD-L1 inhibitor, durvalumab, an expansion of CD4+ and CD8+ T cells was observed after the initial tremelimumab dose.[14] The increased T-cell count was not observed with repeat dosing and largely subsided after 15 days.[14] Similar results were seen in patients with melanoma after treatment with ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD-1).[15] As CTLA-4–related toxicity is typically observed after repeat dosing,[11] we evaluated whether a single, priming dose of tremelimumab in combination with durvalumab could limit toxicity while maintaining the pharmacodynamic effect with similar or improved efficacy versus monotherapies.

The combination of tremelimumab (75 mg intravenous [IV], once every 4 weeks for four cycles) and durvalumab (1,500 mg IV once every 4 weeks; T75 + D) showed promising safety and initial efficacy in uHCC in the previously reported phase I cohort of this study.[16] Expansion to a phase II portion initially enrolled patients to receive tremelimumab and durvalumab as monotherapies and in combination (T75 + D). After emergence of pharmacodynamic data,[14,15] a second combination regimen featuring a single, priming dose of tremelimumab (300 mg IV, cycle 1) combined with durvalumab (1,500 mg IV once every 4 weeks; termed T300 + D) was added. The study was then subsequently expanded to part 3 to comprehensively evaluate all four regimens to determine whether either of the combination regimens could improve efficacy over monotherapies and whether the single, priming dose of tremelimumab in T300 + D could minimize the toxicity that may accompany repeat anti-CTLA-4 dosing (Appendix Fig A1, online only).

PATIENTS AND METHODS

Study Design and Conduct

This open-label, phase I/II study was conducted at 19 sites in nine countries (ClinicalTrials.gov identifier: NCT02519348) according to the Declaration of Helsinki. All patients provided written informed consent. Protocol approval was obtained from institutional review boards or ethics committees at each site.

The study was conducted in four parts (Appendix Fig A1). Part 1[16] evaluated T75 + D for initial safety and efficacy gating. In part 2A (n = 115), patients were randomly assigned 1:1:1 (via an interactive response system) to receive durvalumab monotherapy (1,500 mg IV once every 4 weeks), tremelimumab monotherapy (750 mg IV every 4 weeks × 7 doses and then once every 12 weeks thereafter), or the T75 + D regimen. Patients were then allocated to part 2B (n = 10) to examine the safety of the T300 + D regimen. In part 3 (n = 207), patients were randomly assigned 2:2:1:2 across four randomized arms: T300 + D, durvalumab monotherapy, tremelimumab monotherapy, and T75 + D. See the Data Supplement (online only) for patient stratification factors and treatment discontinuation details.

Patients

Eligible patients (≥ 18 years or ≥ 20 years [Japan]) had uHCC confirmed by previous histologic diagnosis and/or by radiologic criteria[17,18]; all patients were required to provide a fresh or archival tumor tissue sample. Patients were

immunotherapy-naïve; had progressed on, were intolerant to, or refused treatment with sorafenib; and had Child-Pugh Score class A and Eastern Cooperative Oncology Group performance status 0-1. Patients with hepatitis B virus or hepatitis C virus infection were permitted. Additional enrollment criteria and definitions for sorafenib intolerance are provided in the Data Supplement.

Assessments

The primary end point was safety. Adverse events (AEs) were monitored and graded by investigators using the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03. Treatment-related AEs (trAEs) were determined based on investigator assessment of relationship to treatment, and immune-mediated AEs (imAEs) were also assessed.

Response measurements were collected every 8 weeks (RECIST 1.1) and assessed locally by site investigators for treatment decisions and centrally by a blinded independent central review (BICR) radiologist. Secondary end points per BICR included objective response rate (ORR), duration of response (DoR), time to response, and progression-free survival (PFS), as well as overall survival (OS; per investigator assessment only). See the Data Supplement for biomarker assessments, including associated discriminant analyses.

Statistical Analyses

In part 2A, a sample size of 108 patients was estimated to yield approximately 12 patients per viral status cohort in the monotherapy arms, providing ≥ 72% probability of observing ≥ 1 AE in each cohort, assuming the incidence of 10%-15%. In part 3, an estimated total of 64 patients treated with durvalumab monotherapy would provide a 96% probability of observing ≥ 1 AE, assuming the incidence of 5%. The combined total estimated sample size was approximately 200.

Safety data were analyzed using descriptive statistics for patients who received ≥ 1 dose of study treatment. Efficacy outcomes were summarized by arm, including frequency and ORR; median and corresponding 95% CIs were estimated for OS, PFS, and DoR using the Kaplan-Meier method.

See the Data Supplement for biomarker methods.

RESULTS

Patients

As of February 28, 2020, 332 patients were enrolled in parts 2 and 3 (T300 + D, n = 75; durvalumab, n = 104; tremelimumab, n = 69; and T75 + D, n = 84; Fig 1). Patient demographics and baseline characteristics were generally balanced across groups (Table 1 and Data Supplement). Most patients had advanced HCC (ie, Barcelona Clinic Liver Cancer stage B or C) and Child-Pugh score A; 2.4% declined to B/7 between screening and random assignment or treatment. The majority progressed on (51.8%) or were intolerant to (15.4%) sorafenib. The median duration of previous sorafenib therapy was 3.9 months.

Safety

The safety analysis included 326 patients from parts 2 and 3. The median (range) duration of exposure was 3.7 (0.8-27.1) months for T300 + D, 3.7 (0.7-34.3) months for durvalumab, 3.7 (0.9-31.2) months for tremelimumab, and 2.4 (0.6-31.4) months for T75 + D. trAEs and grade ≥ 3 trAEs were highest with tremelimumab (Table 2). For T300 + D, the most common trAEs were grade 1 or 2 cutaneous AEs. The most common grade ≥ 3 trAEs overall included increased aspartate aminotransferase, increased lipase, increased amylase, and diarrhea. However, these increased laboratory values were transient and/or asymptomatic. Serious trAEs were highest with tremelimumab monotherapy (24.6%); incidences were 17.6%, 10.9%, and 14.6% with T300 + D, durvalumab, and T75 + D, respectively. trAEs requiring systemic steroids were distributed across system organ class, and grade 3 or 4 rates were low overall. They were reported at higher frequency in the tremelimumab-containing arms (T300 + D: 24.3%, tremelimumab: 26.1%, and T75 + D: 24.4%) versus durvalumab (9.9%; Data Supplement). imAEs were also reported at a higher frequency in the tremelimumab-containing arms (T300 + D: 31.1%, T: 24.6%, T75 + D: 26.8%) versus the D arm (15.8%; Data Supplement). The frequencies of hepatic standardized MedDRA Query AEs were comparable across arms (Data Supplement), as was the frequency of hepatic standardized MedDRA Query AEs considered causally related by investigators (T300 + D: 28.4%, D: 18.8%, T: 18.8%, and T75 + D: 23.2%). AEs of hepatitis and hepatic failure were low for all arms (n = 1-2 per arm for each). One (1.4%), 4 (4.0%), 1 (1.4%), and 3 (3.7%) patients on T300 + D, D, T75 + D, and T, respectively, required steroids for hepatobiliary disorders (Data Supplement). An antidrug antibody (ADA) response to durvalumab was found in only one patient on study who was receiving T75 + D. ADA-positive responses for tremelimumab at any visit were identified in 7 (13%), 5 (16.1%), and 3 (7.3%) patients receiving T300 + D, tremelimumab, and T75 + D, respectively. Treatment-emergent ADA incidences were 7.4% (n = 4) with T300 + D, 16.1% (n = 5) with T, and 7.3% (n = 3) with T75 + D (Data Supplement).

The most frequent reasons for treatment discontinuation were disease progression (210 [64.4%]) and AEs (34 [10.4%]). Discontinuation because of trAEs was similar across arms; 10.8%, 7.9%, 13.0%, and 6.1% discontinued T300 + D, durvalumab, tremelimumab, and T75 + D, respectively. Discontinuation because of imAEs was also similar across arms. Possible trAEs that led to death (grade 5 trAEs) occurred in one patient who received T300 + D (pneumonia), three patients who received durvalumab

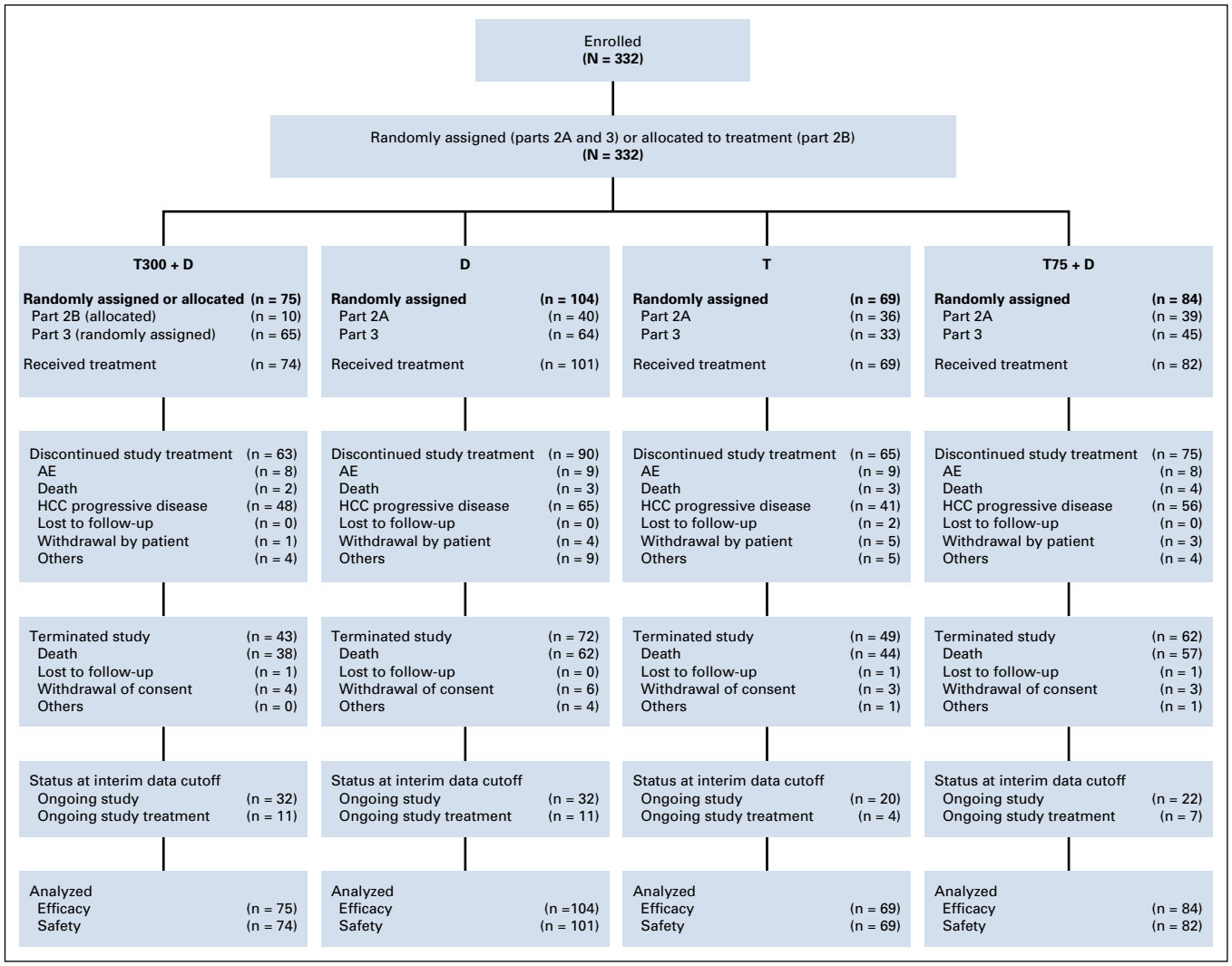

FIG 1. CONSORT diagram of patient disposition in parts 2 and 3. AE, adverse event; D, durvalumab; HCC, hepatocellular carcinoma; T, tremelimumab; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks.

(pneumonitis, abnormal hepatic function, and hepatic failure), none who received tremelimumab, and one who received T75 + D (hepatic failure). Another patient in the T300 + D arm died from an unknown cause where relationship to treatment could not be determined by the investigator.

Efficacy

Efficacy analyses were performed for each treatment arm for parts 2A, 2B, and 3 combined, and for part 3 alone. Overall, the results were consistent between parts, and therefore, only the results of the combined data are presented here. See the Data Supplement for part 3 alone (Appendix Figs A2 and A3, online only; Data Supplement). The confirmed ORR by BICR was highest for T300 + D (24.0%; 95% CI, 14.9 to 35.3; Table 3). Confirmed complete responses were achieved by one patient receiving T300 + D and two receiving T75 + D. Median time to response was shortest with T300 + D (1.86 months) and tremelimumab (1.81 months). The median DoR was not reached with T300 + D and was 11.17 months, 23.95 months, and 13.21 months with durvalumab, tremelimumab, and T75 + D, respectively (Table 3). Responses occurred across PD-L1 and viral status subgroups (Appendix Fig A4, online only). One patient in each of the tremelimumab-containing arms had an initial ≥ 5% increase in tumor size from baseline at first scan, but subsequently achieved partial or complete responses (Appendix Fig A5, online only).

The median PFS (95% CI) was 2.17 (1.91 to 5.42) months with T300 + D, 2.07 (1.84 to 2.83) months with durvalumab, 2.69 (1.87 to 5.29) months with tremelimumab, and 1.87 (1.77 to 2.53) months with T75 + D (Appendix Fig A6, online only). The median (95% CI) OS was highest

TABLE 1. Demographic and Clinical Characteristics of Patients With Unresectable Hepatocellular Carcinoma

Characteristic	T300 + D (n = 75)	Durvalumab (n = 104)	Tremelimumab (n = 69)	T75 + D (n = 84)
Median age, years (range)	66.0 (26-86)	64.5 (32-89)	62.0 (37-81)	61.5 (28-82)
Sex, male, No. (%)	65 (86.7)	92 (88.5)	57 (82.6)	70 (83.3)
Race and ethnicity, No. (%)				
White	27 (36.0)	35 (33.7)	26 (37.7)	30 (35.7)
Black	4 (5.3)	10 (9.6)	2 (2.9)	5 (6.0)
Asian	44 (58.7)	55 (52.9)	39 (56.5)	47 (56.0)
Hispanic or Latino	4 (5.3)	5 (4.8)	4 (5.8)	5 (6.0)
Others	0	4 (3.8)	2 (2.9)	2 (2.4)
ECOG PS, No. (%)				
0	46 (61.3)	52 (50.0)	45 (65.2)	51 (60.7)
1	29 (38.7)	52 (50.0)	24 (34.8)	33 (39.3)
Child-Pugh score, No. (%)				
A/5	51 (68.0)	79 (76.0)	44 (63.8)	54 (64.3)
A/6	23 (30.7)	23 (22.1)	24 (34.8)	26 (31.0)
B/7	1 (1.3)	2 (1.9)	1 (1.4)	4 (4.8)
BCLC score, No. (%)				
A	1 (1.3)	1 (1.0)	2 (2.9)	1 (1.2)
B	13 (17.3)	9 (8.7)	13 (18.8)	17 (20.2)
C	58 (77.3)	80 (76.9)	42 (60.9)	57 (67.9)
Unknown or missing[a]	3 (4.0)	14 (13.5)	12 (17.4)	9 (10.7)
Extent of disease, No. (%)				
Macrovascular invasion	16 (21.3)	30 (28.8)	17 (24.6)	20 (23.8)
Extrahepatic disease	53 (70.7)	63 (60.6)	31 (44.9)	48 (57.1)
AFP, ≥ 400 ng/mL, No. (%)	35 (46.7)	39 (37.5)	33 (47.8)	34 (40.5)
Viral status, No. (%)				
HBV infection	27 (36.0)	40 (38.5)	27 (39.1)	29 (34.5)
HCV infection	21 (28.0)	28 (26.9)	20 (29.0)	26 (31.0)
Uninfected	27 (36.0)	36 (34.6)	22 (31.9)	29 (34.5)
PD-L1 status, No. (%)				
TC/IC[b] ≥ 1%	27 (36.0)	55 (52.9)	40 (58.0)	41 (48.8)
TC/IC < 1%	38 (50.7)	35 (33.7)	24 (34.8)	31 (36.9)
Missing	10 (13.3)	14 (13.5)	5 (7.2)	12 (14.3)
Prior sorafenib therapy, No. (%)				
Progressed	43 (57.3)	52 (50.0)	30 (43.5)	47 (56.0)
Intolerant[c]	12 (16.0)	15 (14.4)[c]	14 (20.3)	10 (11.9)[c]
Refused	20 (26.7)	37 (35.6)	25 (36.2)	27 (32.1)
Previous treatment modalities, No. (%)				
Systemic therapy	55 (73.3)	66 (63.5)	44 (63.8)	55 (65.5)
Radiation	22 (29.3)	16 (15.4)	15 (21.7)	22 (26.2)
Cancer-related surgery	34 (45.3)	37 (35.6)	23 (33.3)	37 (44.0)

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; IC, immune cell; PD-L1, programmed cell death ligand-1; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks; TC, tumor cell.

[a]At the start of the study, the Protocol required the use of modified TNM staging together with the fibrosis score. The study was amended to include BCLC at a later date. Thus, BCLC scores are missing for some patients.

[b]Defined as PD-L1 staining of any intensity in TC membranes and/or tumor-associated ICs in the tumor area.

[c]Includes three patients (one durvalumab and two T75 + D) confirmed with documented contraindication to sorafenib. Thus, they were not offered sorafenib and could not refuse. These patients are captured as intolerant although sorafenib therapy is not recorded.

with T300 + D at 18.73 (10.78 to 27.27) months, followed by 15.11 (11.33 to 20.50) months with tremelimumab, 13.57 (8.74 to 17.64) months with durvalumab, and 11.30 (8.38 to 14.95) months with T75 + D (Fig 2). Analysis of OS and ORR by previous sorafenib/vascular endothelial growth factor receptor tyrosine kinase inhibitor exposure and viral status found that T300 + D was associated with the longest median OS independent of line of therapy (Data Supplement) and the highest ORR independent of viral etiology (Data Supplement). No differences in efficacy from the overall population were observed for any viral subgroup. Five (6.7%) and 3 (3.6%) patients were treated with T300 + D and T75 + D, respectively, beyond progression, per investigator assessment. After treatment completion, 42.7%, 35.6%, 31.9%, and 38.1% in the T300 + D, durvalumab, tremelimumab, and T75 + D arms, respectively, received subsequent therapy; most received systemic therapy (Data Supplement).

Biomarker Analyses

Baseline immune cell profiles were similar across all arms (Data Supplement). Quadratic discriminant analysis of 26 lymphocyte population values on day 15 revealed that patients were maximally discriminated by two discrete combinations of lymphocyte populations, canon-1 and canon-2, which were associated with CD4+ and CD8+ T cells, respectively. Patients receiving T300 + D exhibited the highest canon-2 scores (Fig 3A). Linear regression analysis revealed that canon-2 was predominantly associated with elevations in the Ki67+ subset of CD8+ T cells (Appendix Fig A7, online only). Response was associated with an expansion of these CD8+Ki67+ lymphocytes occurring early during treatment (day 15). The highest median counts were observed with T300 + D (Fig 3B, Appendix Fig A8, online only), consistent with the observation that T300 + D yielded the highest ORR (Table 3).

DISCUSSION

This is the first randomized study in a predominantly second-line uHCC population who received PD-L1 or CTLA-4 inhibitors as monotherapies or combinations. Among regimens investigated, T300 + D provided the best benefit-risk profile.[19-22] The toxicity profile for T300 + D was favorable when compared with other anti-CTLA-4/PD-1(L1) combinations[23-25] and consistent with published monotherapies.[19-22] Additionally, although durable responses occurred across arms, T300 + D demonstrated the greatest efficacy, including a confirmed ORR of 24%, median DoR that was not reached, and a median OS of 18.73 months. All treatment regimens were tolerable and had manageable safety profiles in the target patient population; no new safety signals were identified.

Previous data for nivolumab (1 mg/kg) and high-dose ipilimumab (3 mg/kg once every 3 weeks for four doses) combination followed by nivolumab monotherapy in uHCC (CheckMate-040) and other tumors[23-25] resulted in the

TABLE 2. Common trAEs (≥ 5% in Any Group)[a]

	T300 + D (n = 74), No. (%)		Durvalumab (n = 101), No. (%)		Tremelimumab (n = 69), No. (%)		T75 + D (n = 82), No. (%)	
AE	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Patients with any trAE	61 (82.4)	28 (37.8)	61 (60.4)	21 (20.8)	58 (84.1)	30 (43.5)	58 (70.7)	20 (24.4)
Pruritus	24 (32.4)	0	11 (10.9)	0	19 (27.5)	1 (1.4)	13 (15.9)	0
Rash	24 (32.4)	2 (2.7)	7 (6.9)	0	15 (21.7)	2 (2.9)	11 (13.4)	0
AST increased	12 (16.2)	9 (12.2)	8 (7.9)	3 (3.0)	10 (14.5)	6 (8.7)	12 (14.6)	7 (8.5)
ALT increased	11 (14.9)	3 (4.1)	5 (5.0)	0	7 (10.1)	3 (4.3)	8 (9.8)	2 (2.4)
Amylase increased	11 (14.9)	5 (6.8)	2 (2.0)	1 (1.0)	3 (4.3)	0	6 (7.3)	1 (1.2)
Lipase increased	9 (12.2)	5 (6.8)	1 (1.0)	0	9 (13.0)	4 (5.8)	4 (4.9)	4 (4.9)
Fatigue	8 (10.8)	0	9 (8.9)	1 (1.0)	11 (15.9)	0	8 (9.8)	0
Diarrhea	7 (9.5)	1 (1.4)	9 (8.9)	1 (1.0)	14 (20.3)	6 (8.7)	10 (12.2)	1 (1.2)
Alkaline phosphatase increased	6 (8.1)	3 (4.1)	7 (6.9)	1 (1.0)	1 (1.4)	0	1 (1.2)	0
Hyperthyroidism	6 (8.1)	0	2 (2.0)	0	0	0	4 (4.9)	1 (1.2)
Hypothyroidism	6 (8.1)	0	10 (9.9)	0	2 (2.9)	0	7 (8.5)	0
Bilirubin increased	4 (5.4)	1 (1.4)	3 (3.0)	0	2 (2.9)	0	5 (6.1)	0
Abdominal pain	2 (2.7)	0	0	0	5 (7.2)	0	4 (4.9)	0
Rash maculopapular	2 (2.7)	1 (1.4)	2 (2.0)	0	7 (10.1)	0	5 (6.1)	0

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks; trAE, treatment-related adverse event.

[a]Listed by frequency in T300 + D arm.

TABLE 3. Response Outcomes

Outcome	T300 + D (n = 75)	Durvalumab (n = 104)	Tremelimumab (n = 69)	T75 + D (n = 84)
ORR, % (95% CI)[a]	24.0 (14.9 to 35.3)	10.6 (5.4 to 18.1)	7.2 (2.4 to 16.1)	9.5 (4.2 to 17.9)
CR, No. (%)	1 (1.3)	0	0	2 (2.4)
PR, No. (%)	17 (22.7)	11 (10.6)	5 (7.2)	6 (7.1)
SD, No. (%)	16 (21.3)	28 (26.9)	29 (42.0)	23 (27.4)
Disease control rate, No. (%)	34 (45.3)	39 (37.5)	34 (49.3)	31 (36.9)
Median time to response, months	1.86	3.65	1.81	2.86
Median DoR from onset of response, months	NR	11.17	23.95	13.21
Median (95% CI) PFS, months	2.17 (1.91 to 5.42)	2.07 (1.84 to 2.83)	2.69 (1.87 to 5.29)	1.87 (1.77 to 2.53)
Patients achieving SD > 6 months, No. (%)	6 (8.0)	4 (3.8)	10 (14.5)	4 (4.8)

Abbreviations: CR, complete response; DoR, duration of response; NR, not reached; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks.
[a]Confirmed response by blinded independent central review according to RECIST 1.1.

longest median OS, but are also associated with high rates of immune toxicity; in uHCC, more than 50% of patients in CheckMate-040 required systemic corticosteroids and the discontinuation rate because of trAEs was 22%.[26,27] By contrast, trAEs requiring discontinuation in this study occurred in 6%-13% of patients across arms and were highest with tremelimumab. Moreover, incidence of trAEs requiring systemic steroids for the T300 + D regimen was 24.3%, and the safety profile appeared favorable; only 10.8% discontinued because of trAE. Furthermore, incidences of imAEs of hepatitis or hepatic failure were low for all arms (≤ 2 patients per arm).

ADA rates reported for other immunotherapies in uHCC are varied (28% with atezolizumab and 45%-56% with

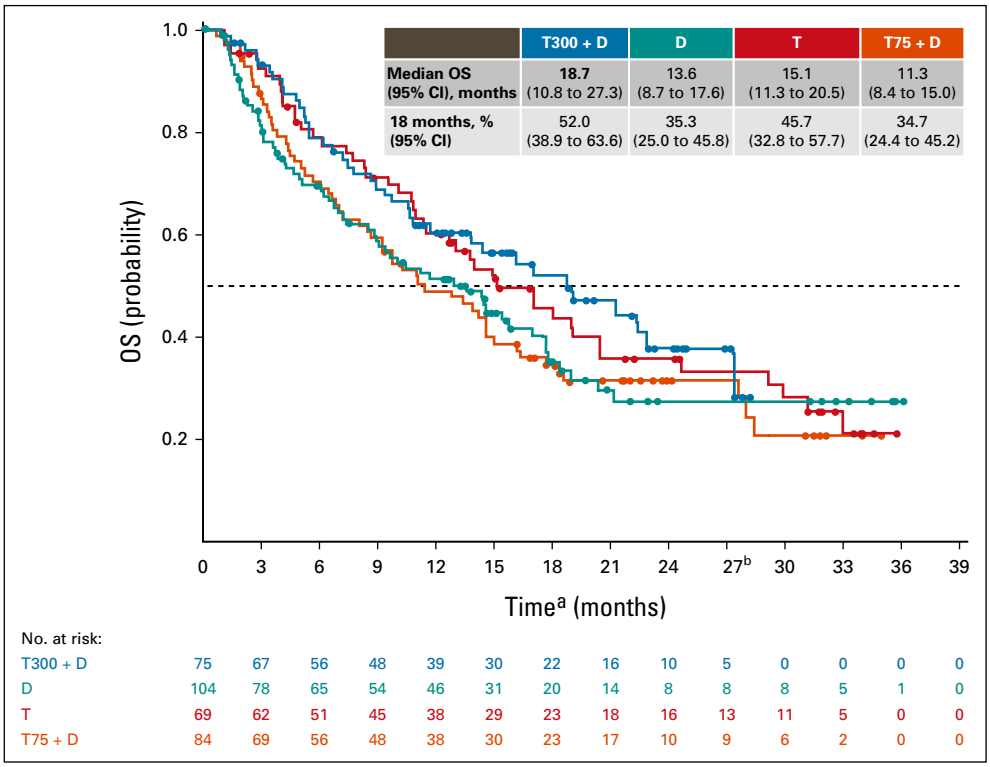

FIG 2. Kaplan-Meier analysis of OS. [a]Time from random assignment (parts 2A and 3) or first dose (part 2B). [b]One event observed at 27 months in the T300 + D arm. D, durvalumab; OS, overall survival; T, tremelimumab; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks.

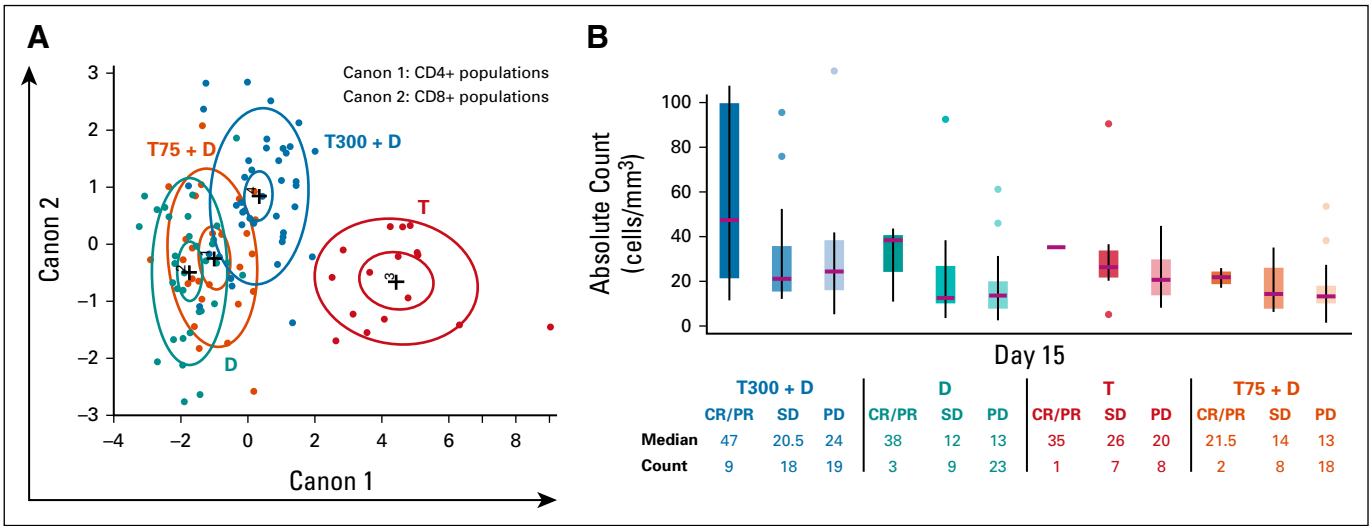

FIG 3. Biomarker analysis of day 15 patient whole-blood samples. (A) Canonical score plot derived from quadratic discriminant analysis of 26 lymphocyte population values that identified two combinations of populations (canons) that best classify each patient into the assigned treatment arm. Canon 1 is composed of CD4+ T-cell populations and canon 2 of CD8+ T-cell populations. Percent misclassified: 1.7% (2 of 117); entropy R^2: 0.92. (B) Analysis of patient CD8+ Ki67+ T-cell counts stratified by treatment arm and response. CR, complete response; D, durvalumab; PD, progressive disease; PR, partial response; SD, stable disease; T, tremelimumab; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks.

nivolumab, dose-dependent).[28-31] Although ADAs associated with atezolizumab can affect clinical efficacy,[30] the same has not been shown for nivolumab,[28] despite the higher frequency. These results suggest that absolute ADA rates alone may not be predictive of an impact on clinical activity, and understanding the role of neutralizing antibodies as part of the ADA response could be critical. Here, durvalumab and tremelimumab had lower rates across all arms (≤ 2.3% and ≤ 16.1%, respectively). Although most occurrences of ADAs for tremelimumab were classified as persistently positive, > 90% were because a single ADA response was recorded at the final assessment. Overall, the full impact of ADAs on clinical efficacy for immunotherapies warrants further exploration.

Proliferative CD8+Ki67+ T-cell counts were associated with radiographic response regardless of treatment received but were highest after T300 + D, supporting the mechanism of enhanced immune activation. Moreover, the T-cell profile observed via quadratic discriminant analysis in patients treated with T300 + D was distinct from those treated with durvalumab monotherapy and T75 + D, which were similar. These data reflect results in non–small-cell lung cancer[14] and other solid tumors,[15] suggesting that combinations may not simply be additive but rather yield distinct expression profiles.[32] In summary, favorable clinical outcomes with T300 + D, coupled with unique proliferative T-cell response, warrant further studies of this approach.

The tremelimumab monotherapy arm represents the first large cohort of patients with HCC to receive treatment with an anti-CTLA-4 monotherapy. Although ORR was lowest in this arm, median OS was the second longest and median DoR was prolonged (23.95 months). This suggests that tremelimumab alone is capable of driving sustained, durable responses and is consistent with existing data from patients treated with anti-CTLA-4 agents across multiple tumor types.[26,33] The apparent disconnect between ORR and OS suggests that anti-CTLA-4 therapy can drive sustained or delayed immune-mediated effects for some patients with HCC, despite a lack of radiologic response. The disparity between OS and ORR may result from using RECIST 1.1, which does not account for different patterns of clinical response and progression.[34,35] Increases in tumor size followed by reduction can occur with immunotherapies[36]; a phenomenon termed pseudoprogression.[36-38] Although pseudoprogression with checkpoint inhibition is rare, there may be a broader potential for atypical patterns of response with CTLA-4 inhibition with or without PD-1/PD-L1 inhibition.[39-43] Additionally, disease stabilization after initial progression has been documented for PD-1 inhibitors and is associated with prolonged survival.[26]

In this study, patients in tremelimumab-containing arms demonstrated cases of atypical patterns of response (Appendix Fig A4), indicating that early progression per conventional criteria does not always imply a poor survival prognosis and can confound PFS interpretation. The potential for anti-CTLA-4 agents to provide a survival benefit despite a lack of response per RECIST 1.1 may warrant treatment after initial progression and/or alternative means of assessing progression after immunotherapy, such as

immune-related RECIST.[36,44] Previous studies with other immunotherapies in HCC reported strong improvements in ORR evaluated using these other methods versus RECIST v1.1.[34,45]

Perhaps the most remarkable finding for immunotherapies is the capacity to provide durable, long-term survival, leading to substantial survival tails in the Kaplan-Meier OS curves associated with anti-CTLA-4[12,13] and anti-PD-1 agents.[21,46,47] In Checkmate-067, both anti-CTLA-4 and anti-PD-1 agents were shown to drive the formation of the survival tail; however, the greatest benefit was observed when both were given in combination. Another key finding observed with immunotherapies is that the separation between the survival curves of checkpoint inhibitors and standard-of-care agents can be delayed,[21,46,47] suggesting that longer periods of follow-up may be required to ascertain OS benefit when studying novel immunotherapy combinations like T300 + D.[47,48] This may also complicate the comparison of OS in randomized controlled trials using the proportional risk methods.

A limitation of this study was the absence of a standard-of-care control. Although data from parts 2 and 3 were pooled, the four arms were not powered for direct comparison and between-arm comparisons were further confounded by the differences in start times, patient random assignment, and stratification factors between parts 2 and 3. At study initiation, a modified TNM staging approach including fibrosis and Child-Pugh scores was used, resulting in the underreporting of Barcelona Clinic Liver Cancer scores in part 2A. Although most patients were enrolled after progressing on or intolerance to sorafenib, a subset in each arm refused sorafenib therapy and were treated as first line. This limitation was mitigated in part 3 where stratification included sorafenib status. Notably, ORRs were consistent regardless of sorafenib usage, suggesting that T300 + D provides the best all-around response benefit. Finally, the analysis of circulating lymphocytes was limited by the number of patients with accompanying evaluable tumor specimens and lack of paired on-treatment tumor specimens to evaluate changes in the tumor immune microenvironment. Baseline and on-treatment tumor analyses of immune microenvironment and PD-L1 expression are ongoing.

The treatment landscape for uHCC has evolved rapidly, with regulatory approval of atezolizumab plus bevacizumab in 2020.[4] In addition, other immunotherapy-containing regimens are being evaluated, including combinations of immune checkpoint inhibitors with antiangiogenic agents lenvatinib (ClinicalTrials.gov identifier: NCT03517449) and cabozantinib (ClinicalTrials.gov identifier: NCT03755791), and nivolumab plus ipilimumab (ClinicalTrials.gov identifier: NCT04039607). With multiple new treatments likely to be available, T300 + D may offer distinct differentiating features beyond demonstration of durable objective responses and promising OS, including a favorable safety profile with a relatively low steroid requirement, rare ADA formation, and a single, priming dose of tremelimumab followed by monthly durvalumab administration schedule. Moreover, the absence of an antiangiogenic partner allows for treatment of patients who are contraindicated for antiangiogenics because of bleeding risks or comorbidities like cardiovascular disease.

In conclusion, the encouraging safety profile and clinical activity of a single priming dose of tremelimumab combined with durvalumab once every 4 weeks suggest that this regimen may provide improved safety and durable responses versus either agent alone or versus a combination (including a lower, repeated dose of tremelimumab) in patients with uHCC. The unique pharmacodynamic activity of the tremelimumab priming dose on proliferative T cells substantiates its clinical efficacy. The T300 + D regimen and durvalumab monotherapy are being evaluated versus sorafenib in the ongoing phase III HIMALAYA study (ClinicalTrials.gov identifier: NCT03298451).

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DISCLAIMER

The sponsor (AstraZeneca) designed the study in collaboration with members of the trial steering committee. Data were collected by each study site and submitted to the sponsor for analysis. The sponsor collaborated with the academic authors regarding data interpretation and writing of the report. All authors had access to study data. The corresponding author had final responsibility for the decision to submit for publication.

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Safety, Efficacy, and Pharmacodynamics of Tremelimumab Plus Durvalumab for Patients With Unresectable Hepatocellular Carcinoma: Randomized Expansion of a Phase I/II Study

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Expert Testimony: AbbVie, Alfasigma, Actial, Sanofi, MSD, Gilead Sciences, Eisai

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Research Funding: Boston Biomedical, miRNA Therapeutics, Senhwa Biosciences, MedImmune, BiolineRx, Agios, Halozyme, Celgene, Threshold Pharmaceuticals, Toray Industries, Dicerna, Sillajen, Eisai, Taiho Pharmaceutical, EMD Serono, Isis Pharmaceuticals, Incyte, Sun Biopharma, ARIAD, ImClone Systems, QED Therapeutics, Puma Biotechnology, Adaptimmune, Merck Serono, RedHill Biopharma, Basilea
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Gritstone Oncology, Evelo Therapeutics, FORMA Therapeutics, Forty Seven, EMD Serono, Merus, Jacobio, eFFECTOR Therapeutics, Novocure, Sorrento Therapeutics, Arrys Therapeutics, TRACON Pharma, Sierra Oncology, Innate Pharma, Prelude Therapeutics, Arch Oncology, Harpoon therapeutics, Phoenix Biotech, Unum Therapeutics, Vyriad, Harpoon therapeutics, Cyteir, Molecular Partners, Innate Pharma, ADC Therapeutics, Torque, Tizona Therapeutics Inc, Janssen, Amgen, BeiGene, Pfizer, Millenium Pharmaceuticals, ImClone Systems, Acerta Pharma, Rgenix, Bellicum Pharmaceuticals, Arcus Biosciences, Gossamer Bio, Seattle Genetics, Tempest Therapeutics, Shattuck Labs, Synthorx, Revolution Medicines, Bicycle Therapeutics, Zymeworks, Relay Therapeutics, Evelo Therapeutics, Scholar Rock, NGM Biopharmaceuticals, Numab, AtlasMedx, Treadwell Therapeutics, IGM, MabSpace Biosciences, Hutchison MediPharma, Repare Therapeutics, NeoImmuneTech, Regeneron, PureTech, G1 Therapeutics, Erasca Inc, Rubius Therapeutics, Pionyr, Loxo/Lilly, BioNTech AG, Elicio Therapeutics
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Research Funding: Bayer, Exelixis, CASI Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, Incyte, Agios, Polaris, Puma Biotechnology, QED Therapeutics
Travel, Accommodations, Expenses: Polaris

No other potential conflicts of interest were reported.

APPENDIX

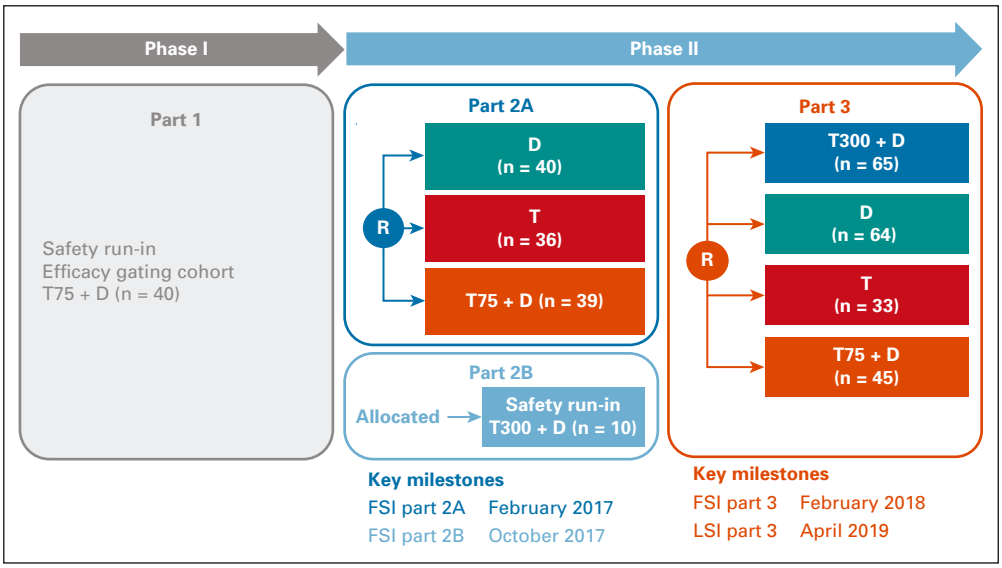

FIG A1. Study design for parts 1-3 (part 4 evaluated durvalumab plus bevacizumab in patients with first-line unresectable hepatocellular carcinoma and will be published separately). D, durvalumab; FSI, first subject in; LSI, last subject in; n, No. of enrolled patients; R, randomly assigned; T, tremelimumab; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks.

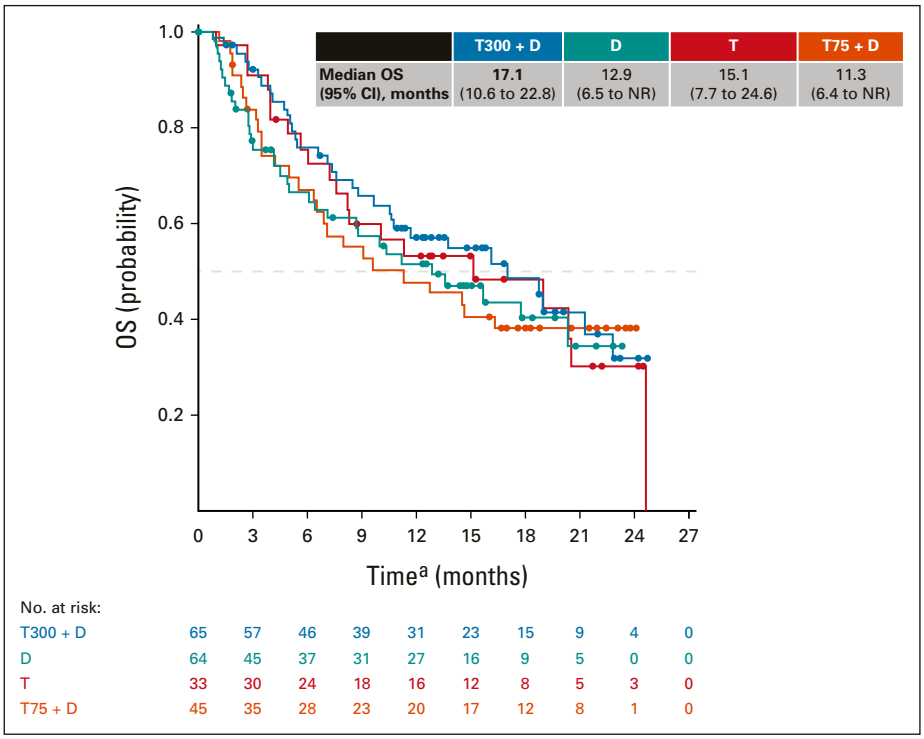

FIG A2. Kaplan-Meier analysis of OS, part 3 only. [a]Time from random assignment. D, durvalumab; NR, no response; OS, overall survival; T, tremelimumab; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks.

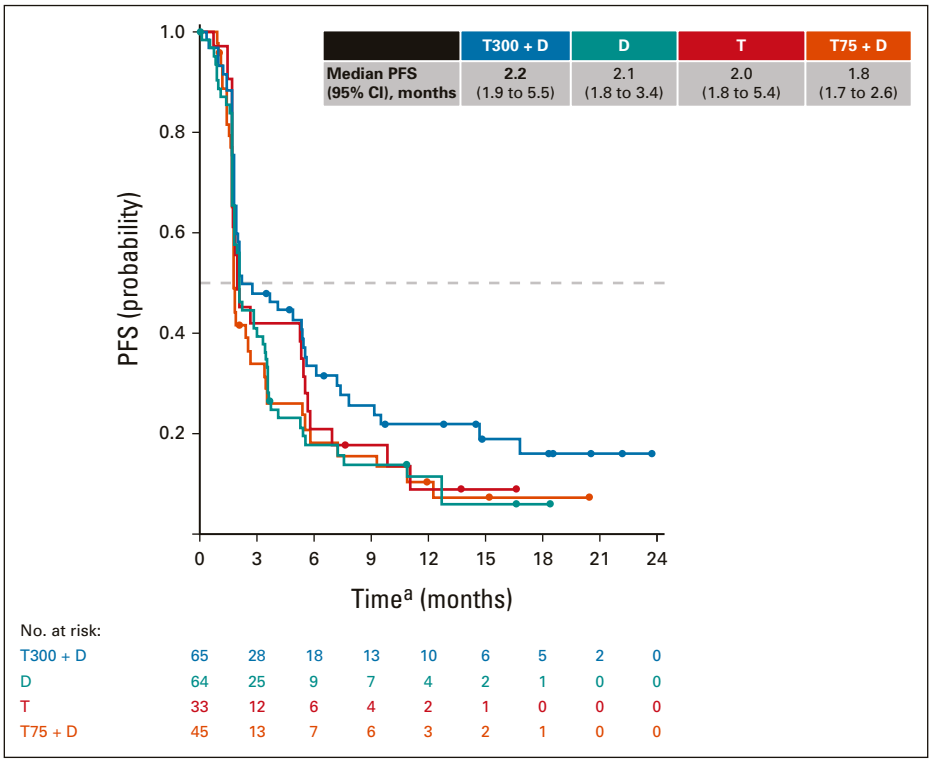

FIG A3. Kaplan-Meier analysis of progression-free survival, part 3 only. [a]Time from random assignment. D, durvalumab; PFS, progression-free survival; T, tremelimumab; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks [four doses] plus durvalumab 1,500 mg once every 4 weeks.

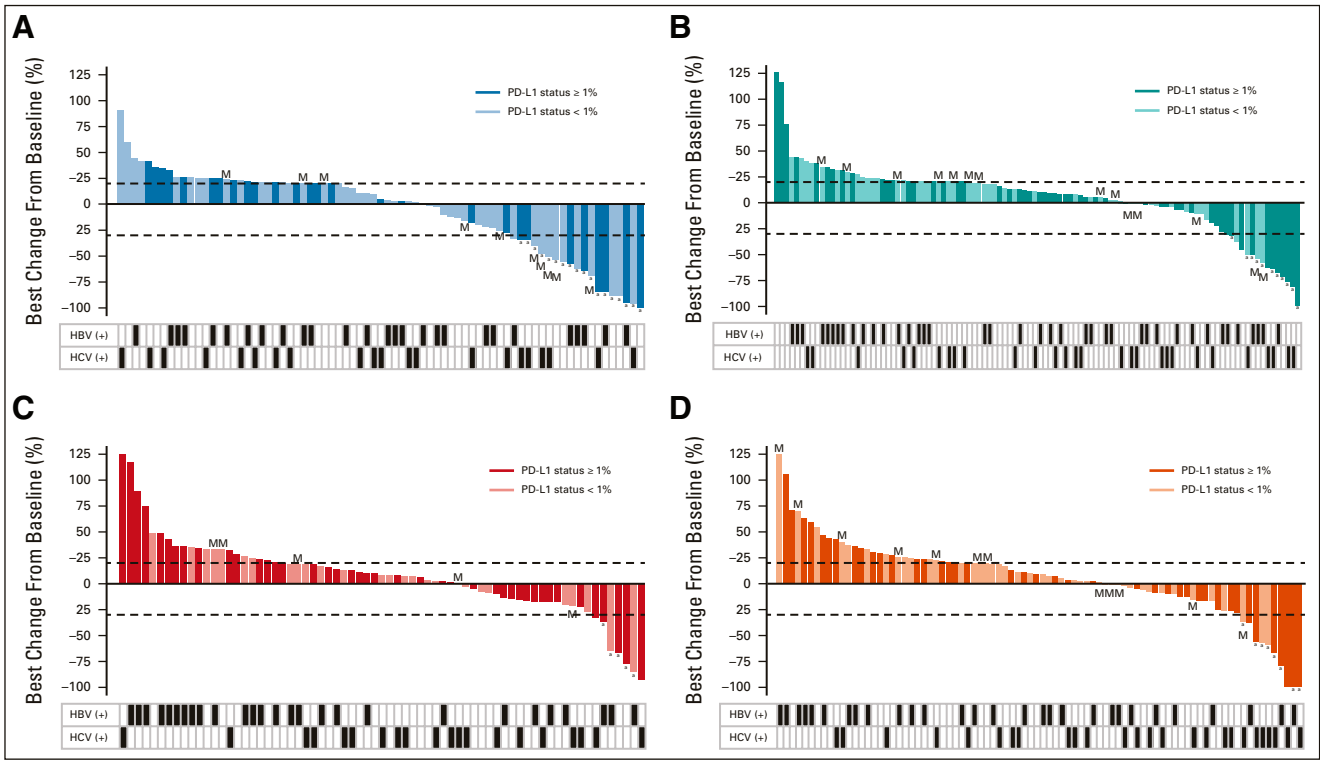

FIG A4. Target lesion response for (A) T300 + D (ORR = 24.0%), (B) durvalumab (ORR = 10.6%), (C) tremelimumab (ORR = 7.2%), and (D) T75 + D treatment cohorts (ORR = 9.5%) in parts 2 and 3. [a]Patients who achieved a response. D, durvalumab; HBV, hepatitis B virus; HCV, hepatitis C virus; M, PD-L1 status missing; ORR, overall response rate; PD-L1, programmed cell death ligand-1; T, tremelimumab; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks.

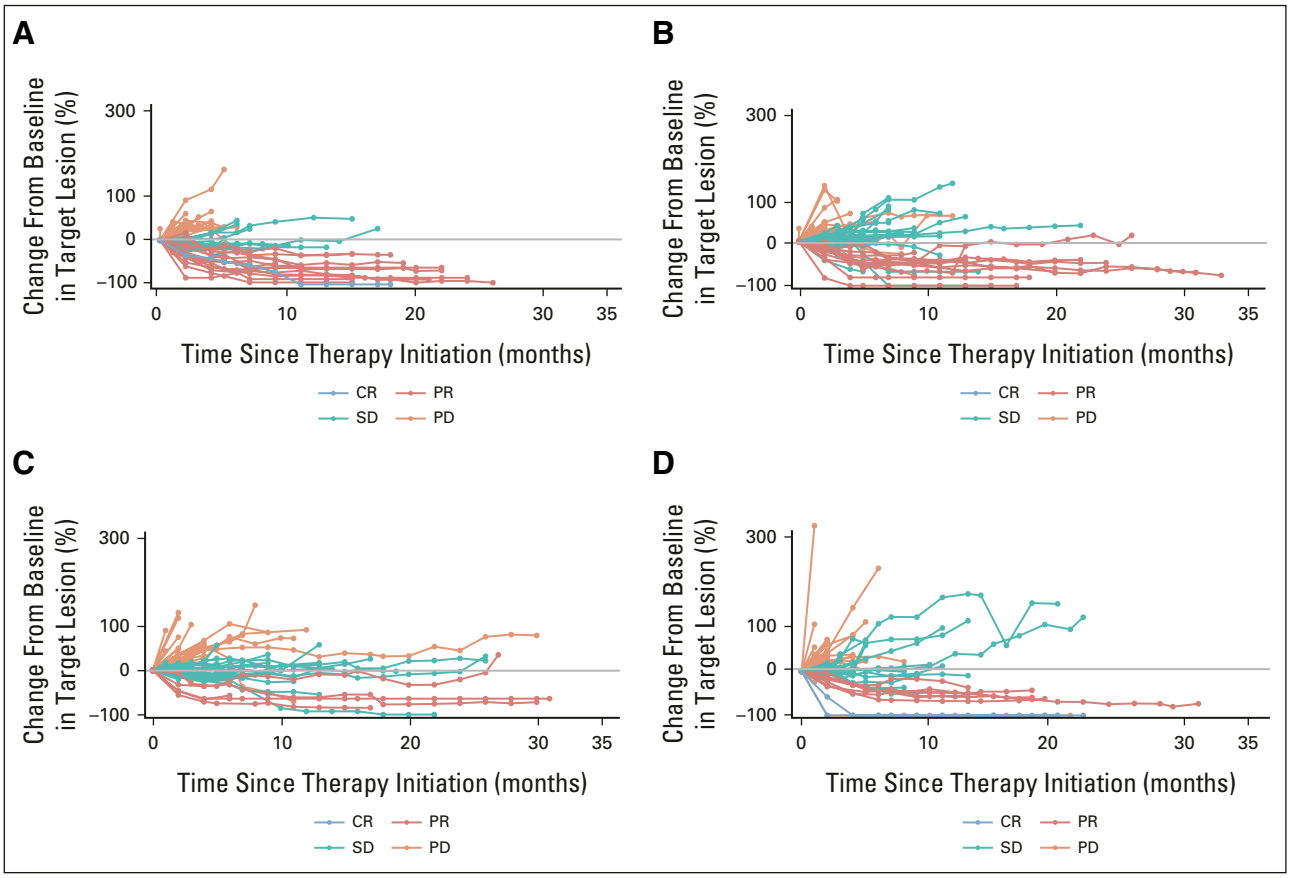

FIG A5. Best response for target lesion from baseline. (A) T300 + D. (B) Durvalumab. (C) Tremelimumab. (D) T75 + D. CR, complete response; D, durvalumab; PD, progressive disease; PR, partial response; SD, stable disease; T, tremelimumab; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks.

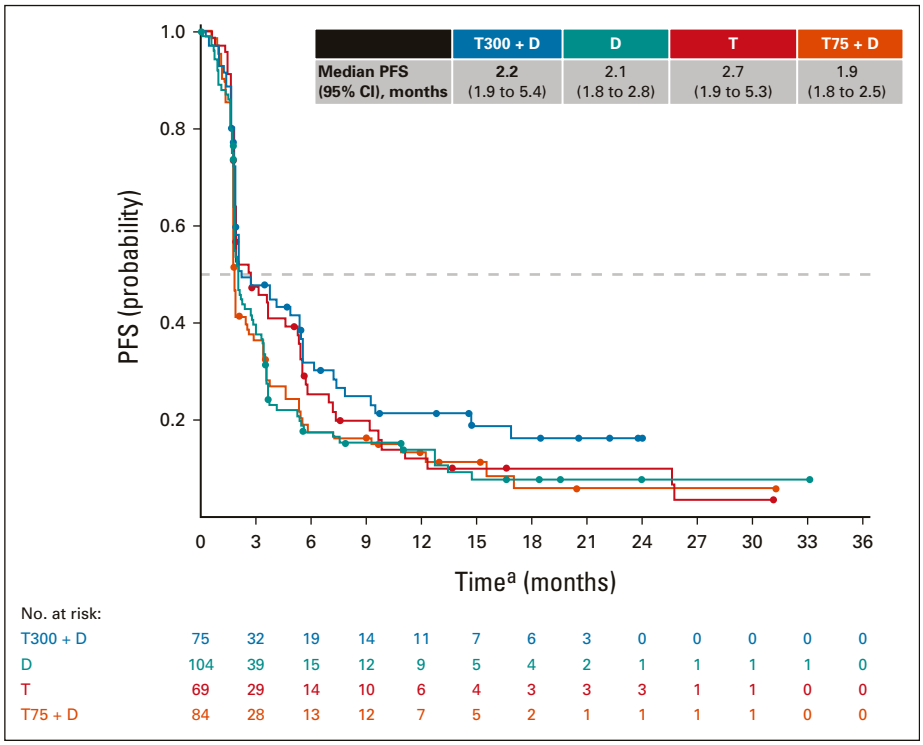

FIG A6. Kaplan-Meier analysis of PFS, parts 2 and 3. [a]Time from random assignment (part 2A, 3) or first dose (part 2B). D, durvalumab; PFS, progression-free survival; T, tremelimumab; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks.

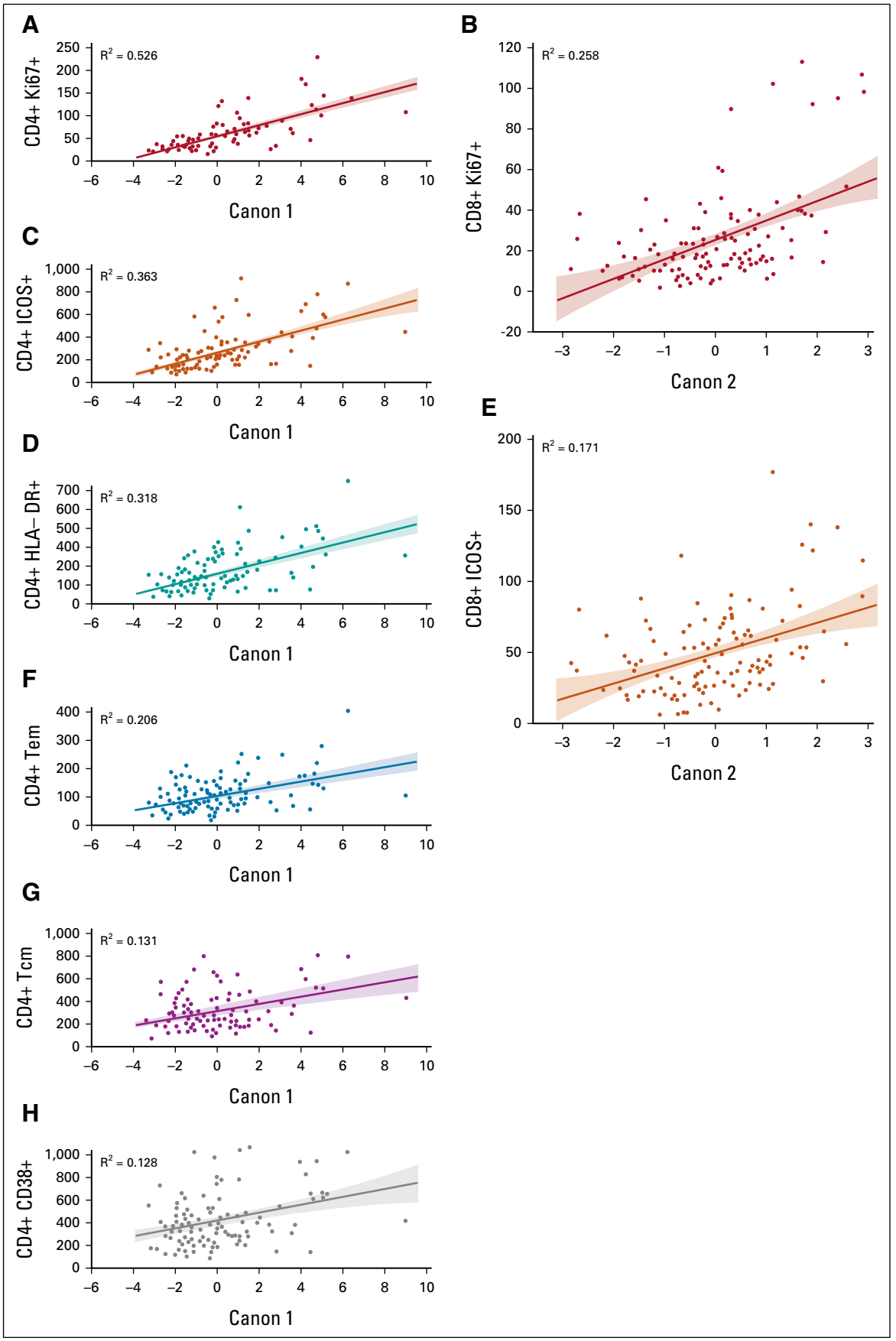

FIG A7. Correlation (correlation coefficient > 0.1) of lymphocyte population counts for all treatment arms combined with canon-1 or canon-2 scores. ((A) CD4+Ki67+ T cells. (B) CD8+Ki67+ T cells. (C) CD4+ICOS+ T cells. (D) CD4+HLA-DR+ T cells. (E) CD8+ICOS+ T cells. (F) CD4+ Tem cells. (G) CD4+ Tcm cells. (H) CD4+CD38+ T cells. HLA-DR, Human Leukocyte Antigen of the DR type; ICOS, inducible T cell costimulator; Tcm, central memory T cells; Tem, effector memory T cells.

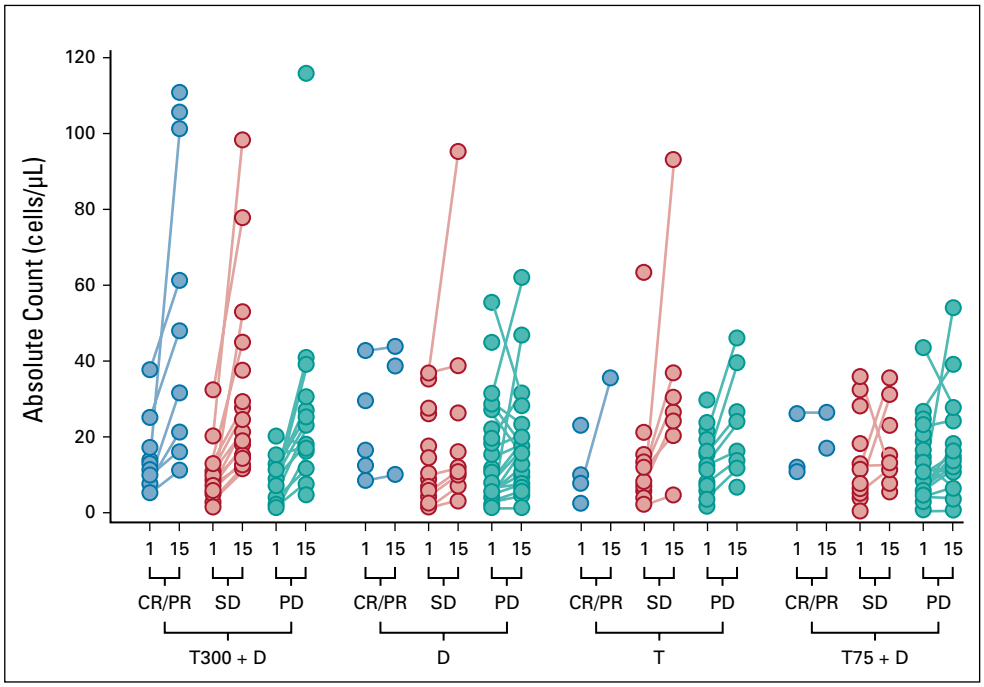

FIG A8. CD3+ CD8+ Ki67+ T-cell analysis of patient samples by response at day 1 and day 15. CR, complete response; D, durvalumab; PD, progressive disease; PR, partial response; SD, stable disease; T, tremelimumab; T300 + D, tremelimumab 300 mg plus durvalumab 1,500 mg for one dose each during the first cycle followed by durvalumab 1,500 mg once every 4 weeks; T75 + D, tremelimumab 75 mg once every 4 weeks (four doses) plus durvalumab 1,500 mg once every 4 weeks.