DKN-01 in Combination With Tislelizumab and Chemotherapy as First-Line Therapy in Advanced Gastric or Gastroesophageal Junction Adenocarcinoma: DisTinGuish

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ABSTRACT

PURPOSE The outcomes of anti–PD-1 agents plus fluoropyrimidine/platinum in frontline advanced gastroesophageal adenocarcinomas (aGEAs) remain poor. We investigated the safety, tolerability, and activity of fluoropyrimidine/oxaliplatin and tislelizumab with the DKK1-neutralizing antibody DKN-01 in aGEAs in a phase IIa open-label study.

PATIENTS AND METHODS Patients had untreated human epidermal growth factor receptor 2–negative aGEAs, RECIST v1.1 measurable disease, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, and adequate organ function. Patients received intravenous DKN-01 300 mg once every 2 weeks, tislelizumab 200 mg once every 3 weeks, oxaliplatin 130 mg/m² once every 3 weeks, and capecitabine 1,000 mg/m² twice daily on days 1-15 of each 21-day cycle. The primary end point was safety and tolerability. Key secondary end points included objective response rate (ORR) by RECISTv1.1, progression-free survival (PFS), and overall survival (OS).

RESULTS Between September 18, 2020, and April 8, 2021, 25 patients were enrolled. All patients who received at least one dose of DKN-01 were included in the safety analysis. Most patients had gastroesophageal junction tumors, median age was 61 years, 76% were male, and 55% were ECOG of 0. All patients reported at least one treatment-emergent adverse event. The ORR was 73% (95% CI, 49.8 to 89.3), with a disease control rate of 95%. The ORR was 90% (95% CI, 55.5 to 99.7) in the DKK1-high tumor patients and 67% (95% CI, 29.9 to 92.5) in the DKK1-low tumor patients. The median PFS was 11.3 months (95% CI, 5.8 to 12.0) and the 12-month PFS rate was 33%. The median OS was 19.5 months (95% CI, 15.2 to 24.4) with a 12-month OS rate of 76% and an 18-month OS rate of 55%.

CONCLUSION DKN-01 can be safely combined with frontline fluoropyrimidine/oxaliplatin and tislelizumab and demonstrates encouraging activity independent of PD-L1 expression levels. A randomized phase II trial is ongoing (ClinicalTrials.gov identifier: NCT04363801).

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Advanced gastroesophageal adenocarcinomas (aGEAs) represent a major cause of cancer-related mortality.[1] Modern frontline phase III trials combining fluoropyrimidine and platinum chemotherapy with an anti–PD-1 antibody have improved survival, primarily among PD-L1–positive patients.[2-4] Despite improvements in survival from anti–PD-1 with chemotherapy (2.5-4 months), the majority of aGEAs develop resistance manifesting as clinical disease progression, and only 40%-60% of patients will receive subsequent therapy.[5,6] Development of strategies to expand the proportion of patients who benefit from anti–PD-1–containing strategies is needed.

The composition and adaptive changes in the tumor microenvironment (TME) modulate response to chemotherapy and immunotherapies, across solid tumors.[7-10] We have shown M2-like macrophages in the TME to be associated with inferior outcomes to fluorouracil (FU)/oxaliplatin in

CONTEXT

Key Objective

Preclinically, depleting DKK1 enhances the efficacy of anti–PD-1 in gastroesophageal models. We sought to determine whether the frontline combination of the anti-DKK1 antibody DKN-01 with fluorouracil (FU)/oxaliplatin + anti–PD-1 is safe and assess preliminary antitumor activity in advanced human epidermal growth factor receptor 2–negative advanced gastroesophageal adenocarcinomas (aGEAs).

Knowledge Generated

DKN-01 in combination with FU/oxaliplatin and the anti–PD-1 tislelizumab was well tolerated as frontline therapy for aGEA. Exploratory efficacy demonstrated a high objective response rate of 73% in the overall population and 90% in DKK1-high patients. The durable progression-free survival of 11.3 months supports the ongoing confirmatory randomized phase II trial.

Relevance *(R.G. Maki)*

Anti-DKK1 therapy may be a useful adjunct to chemotherapy in metastatic gastroesophageal adenocarcinoma. A randomized trial will determine if these promising data are upheld under greater scrutiny.*

*Relevance section written by *JCO* Associate Editor Robert G. Maki, MD, PhD, FACP, FASCO.

combination with pembrolizumab in advanced gastric cancer, and similar findings were seen in bulk-RNA analysis from pretreatment samples in the phase III frontline CM-649 trial.[7,11,12] The secreted protein Dickkopf-related protein (DKK1) regulates Wnt and PI3K/AKT signaling pathways, and increased DKK1 expression is associated with shorter survival in gastric cancer.[13–15] The TME of gastric cancers with high DKK1 expression is notable for increased tumor promoting M2-like macrophages, and lower CD4 and NK cell infiltrates consistent with an immunosuppressive microenvironment.[16] DKN-01 (Leap Therapeutics, Inc, Cambridge, MA) is a humanized IgG4 monoclonal antibody that binds and neutralizes circulating DKK1. In cancer models, DKK1 blockade with DKN-01 repolarizes macrophage subsets toward antitumor M1-like phenotype, increases CD8 T-cell recruitment, and enhances the activity of PD-1 blockade.[16,17] The combination of DKN-01 and pembrolizumab showed encouraging safety and clinical efficacy signals in previously treated aGEAs in a phase Ib trial.[18]

On the basis of the evolution of PD-1 incorporation in frontline aGEA management, the phase IIa DisTinGuish trial was designed to determine the safety, tolerability, and clinical efficacy of DKN-01 in combination with the anti–PD-1 antibody tislelizumab and fluoropyrimidine/oxaliplatin chemotherapy in patients with untreated human epidermal growth factor receptor 2 (HER2)–negative aGEA. The study was designed in three parts: part A is a single-arm evaluation of DKN-01 plus tislelizumab in combination with capecitabine and oxaliplatin (CAPOX) in 1L HER2-negative aGEA; part B is a single-arm evaluation of DKN-01 plus tislelizumab in 2L DKK1-high aGEA; and part C is a randomized evaluation of DKN-01 plus tislelizumab in combination with CAPOX or fluorouracil, leucovorin, and oxaliplatin (FOLFOX) in 1L HER2-negative aGEA population. Parts B and C are ongoing and part A is reported here.

PATIENTS AND METHODS

Study Design

DisTinGuish is a phase IIa open-label study of DKN-01 in combination with tislelizumab with or without chemotherapy as first-line or second-line therapy in HER2-negative inoperable locally advanced or metastatic aGEA (ClinicalTrials.gov identifier: NCT04363801). Here, we report part A of the study, which was designed to characterize the safety and tolerability of DKN-01 in combination with tislelizumab and CAPOX in patients with treatment-naïve, inoperable, locally advanced, or metastatic aGEA. The study protocol and all amendments were approved by the local institutional review boards. The study was performed in accordance with the protocol, its amendments, and good clinical practice guidelines. All patients provided written informed consent as per the Declaration of Helsinki principles. The study protocol and statistical analysis plan are included in the Protocol (online only), which includes all parts (A-C) of the study.

Study Population and Methods

Part A enrolled patients with aGEA who had received no previous systemic treatment in the locally advanced/metastatic setting. Patients could have received previous neoadjuvant or adjuvant therapy if completed without disease recurrence for at least 6 months since last treatment.

Key eligibility criteria included Eastern Cooperative Oncology Group (ECOG) 0-1, histologically confirmed gastric cancer or Siewert I-III gastroesophageal junction (GEJ) adenocarcinoma, and at least one measurable lesion as defined by RECIST v1.1. Tumor tissue for DKK1 and PD-L1 was required. Patients had to have adequate hepatic function, defined as total bilirubin ≤2.0 times the upper limit of normal (ULN), and AST and ALT ≤three times ULN (unless liver metastases were present, then ≤five times ULN was allowed); serum creatinine ≤1.5 times ULN or estimated glomerular filtration rate >30 mL/min; and hematologic parameters including an absolute neutrophil count of ≥1.5 × 10^9/L, platelet count ≥100 × 10^9/L, and hemoglobin ≥9 g/dL. Key exclusion criteria included a diagnosis of HER2-positive gastroesophageal adenocarcinoma (GEA), inability to swallow or absorb capsules, partial or complete bowel obstruction, previous therapy with anti–PD-1/L1 antibodies or antibodies specifically targeting T-cell costimulatory molecules, or previous therapy with an anti-DKK1 agent. Patients with active autoimmune disease, any condition requiring >10 mg once daily prednisone or equivalent, or with unstable brain metastases were also excluded. Because of the known role of DKK1 in regulating bone development during organogenesis and potential bone remodeling effects of DKN-01, patients with a history of osteonecrosis of the hip or osteoblastic bony metastases were excluded.[19] Complete inclusion and exclusion are provided in the protocol.

Biomarker Analysis

Tumor tissue (fresh or archived) was required during the screening period for DKK1 and PD-L1 expression by central testing. DKK1 RNA expression was assessed using an analytically validated RNAscope chromogenic in situ hybridization (CISH) assay and an H-score (0-300) was determined for the tumor compartment (Flagship Biosciences, Broomfield, CO; Advanced Cell Diagnostics, Newark, CA[20]). An H-score of ≥35 was used to define the DKK1-high population. The previous phase Ib trial was used to define this threshold.[19] PD-L1 IHC was performed using the SP263 antibody and a visual combined positive score (vCPS; tumor area positivity) was reported (Roche Tissue Diagnostics, Tucson, AZ). Tumor genomic data were obtained from circulating tumor DNA (ctDNA; Foundation Medicine, Cambridge, MA).

Patient Treatment

After institutional standard premedication, patients received intravenous DKN-01 (300 mg) once every 2 weeks, intravenous tislelizumab (200 mg) once every 3 weeks, intravenous oxaliplatin (130 mg/m²) once every 3 weeks, and oral capecitabine (1,000 mg/m²) twice daily on days 1-15 of each 21-day cycle. The order of IV administration was DKN-01, tislelizumab, followed by oxaliplatin. Capecitabine may have been taken at any time on day 1. Dose modifications, including dose reduction, delay, and omission, were per

TABLE 1. Baseline Patient Demographics and Tumor Characteristics in the Enrolled Trial Population

Clinicopathologic Feature	N = 25
Age, years	
Median (min-max)	61.0 (22-80)
Sex, No. (%)	
Male	19 (76)
Female	6 (24)
Region, No. (%)	
The United States	25 (100)
Ethnicity, No. (%)	
Hispanic or Latino	3 (12)
Not Hispanic or Latino	22 (88)
Race, No. (%)	
White	20 (80)
Asian	1 (4)
Other	4 (16)
Tumor location, No. (%)	
GEJ	17 (68)
Gastric	8 (32)
Disease stage, No. (%)	
III	4 (16)
IV	20 (80)
Unknown	1 (4)
GEJ Siewert category, No. (%)	
I	4 (16)
II	3 (12)
III	10 (40)
Liver involvement, No. (%)	
Yes	7 (28)
No	18 (72)
Performance status (ECOG), No. (%)	
0	14 (56)
1	11 (44)
MMR or MSI status, No. (%)	
MMRp/MSS	19 (76)
MMRd/MSI-H	0
Unknown	6 (24)
Tumor mutational burden, No. (%)	
≥10	2 (8)
≤10	17 (68)
Unknown	6 (24)
Tumor PD-L1, No. (%)	
vCPS <5 (low)	16 (64)
vCPS ≥5 (high)	6 (24)
vCPS unknown	3 (12)
Tumor DKK1, No. (%)	
DKK1 low (H-score <35)	9 (36)
DKK1 high (H-score ≥35)	12 (48)
DKK1 unknown	4 (16)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction; max, maximum; min, minimum; MMR, mismatch repair; MMRd, MMR deficient; MMRp, MMR proficient; MSI, microsatellite instability; MSI-H, MSI-high; MSS, microsatellite stable; vCPS, visual combined positive score.

protocol. Study treatments were maintained until disease progression, unacceptable toxicity, or at the discretion of patients or treating physicians. Patients were allowed to discontinue oxaliplatin, capecitabine, and/or tislelizumab treatment, and permitted to continue in the study with DKN-01 monotherapy or any combination of agents, if they were receiving clinical benefit from the treatment.

Safety and Efficacy Evaluation

Safety was evaluated by assessing the incidence of treatment-emergent adverse events (TEAEs), grade ≥3 TEAEs, treatment-related TEAEs, treatment-emergent serious adverse events (SAEs), treatment-related SAEs, and TEAEs leading to study drug discontinuation. Additional safety evaluations included the incidence of treatment-emergent immune-related adverse events, changes from baseline in clinical laboratory parameters, changes from baseline in vital signs and electrocardiogram parameters, and a shift from baseline in ECOG performance status. Toxicities were graded and documented according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v5.0 guidelines). Radiologic assessment of tumor-response status was performed every 6 weeks (±7 days) after C1D1 for the first 24 weeks, then every 9 weeks (±7 days) after 24 weeks on the basis of RECIST v1.1. Tumor response was assessed by the investigator. Immune-related response criteria were investigator-assessed in patients continuing treatment beyond progressive disease.

Study End Points

The primary safety end point was the incidence of TEAEs, grade ≥3 TEAEs, treatment-related TEAEs, treatment-emergent serious adverse events (TESAEs), treatment-related TESAEs, and TEAEs leading to study drug discontinuation. All efficacy end points were secondary objectives in part A. The key efficacy end point was objective response rate (ORR) as assessed by the investigator using RECIST v1.1. Other efficacy end points included disease control rate (DCR; complete response + partial response + stable disease at ≥6 weeks), as assessed by the investigator using RECIST v1.1, duration of response (DoR), progression-free survival (PFS), and overall survival (OS). PFS is defined as the time from first study drug dose to first radiographic progressive disease, on the basis of investigator-assessed RECIST v1.1, or death due to any cause, whichever comes earlier. Patients known to be progression-free and have a baseline and at least one disease assessment after dosing are censored at the date of the last objective disease assessment that verified lack of disease progression. OS is defined as the time from first study drug dose to death due to any cause. If the patient is alive or lost to follow-up by the time of data analysis, OS data will be censored at the last date the patient is known to be alive. Exploratory correlatives included DKK1 tumor RNA expression by CISH, tumor PD-L1 expression by IHC, serum DKK1, and association with outcomes. See statistical section of online protocol for additional details.

Statistical Analyses

The sample size for part A is not based on formal statistical calculations. Data collected from previous clinical studies indicate that DKN-01 is well tolerated, therefore 20 patients were determined to be sufficient to assess the safety and tolerability of DKN-01 in combination with tislelizumab ± CAPOX. For ORR, the primary efficacy end point, a sample size of 20 evaluable patients provides 50%, 80%, or 90% power for observed ORR rates of 69%, 77%, or 80%, respectively, to be greater than the 50% expected success rate at a 0.05

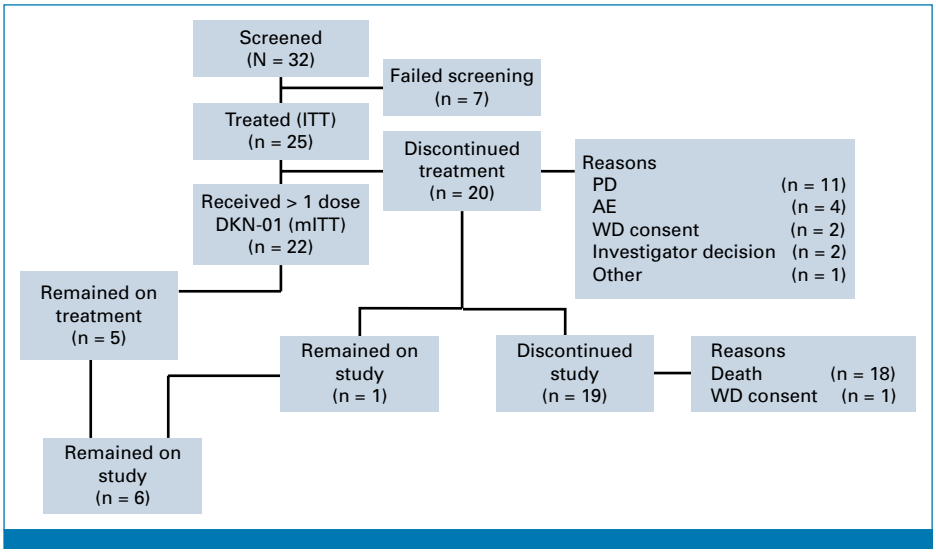

FIG 1. Overall study flow for part A of the DisTinGuish trial. AE, adverse event; ITT, intention-to-treat; mITT, modified intention-to-treat; PD, progressive disease; WD, consent withdrawn by patient.

TABLE 2. Adverse Events by System Occurring in ≥10% of Patients in the Safety Population (N = 25)

Adverse Event	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)	Grade 5, No. (%)	Any Grade, No. (%)
Any adverse event	1 (4.0)	7 (28.0)	13 (52.0)	1 (4.0)	1 (4.0)	25 (100.0)
GI						
Nausea	14 (56.0)	5 (20.0)	0	0	0	19 (76.0)
Diarrhea	11 (44.0)	2 (8.0)	5 (20.0)	0	0	18 (72.0)
Constipation	7 (28.0)	4 (16.0)	1 (4.0)	0	0	12 (48.0)
Vomiting	7 (28.0)	3 (12.0)	1 (4.0)	0	0	11 (44.0)
Abdominal pain	1 (4.0)	4 (16.0)	1 (4.0)	0	0	6 (24.0)
Dry mouth	5 (20.0)	0	0	0	0	5 (20.0)
Dysphagia	2 (8.0)	1 (4.0)	1 (4.0)	0	0	4 (16.0)
Abdominal distension	2 (8.0)	1 (4.0)	0	0	0	3 (12.0)
Investigations						
Neutrophil count decreased	2 (8.0)	8 (32.0)	1 (4.0)	0	0	11 (44.0)
Platelet count decreased	1 (4.0)	5 (20.0)	2 (8.0)	0	0	8 (32.0)
Blood potassium decreased	2 (8.0)	1 (4.0)	4 (16.0)	0	0	7 (28.0)
Hemoglobin decreased	1 (4.0)	3 (12.0)	3 (12.0)	0	0	7 (28.0)
Weight decreased	2 (8.0)	3 (12.0)	0	0	0	5 (20.0)
Blood bilirubin increased	3 (12.0)	0	1 (4.0)	0	0	4 (16.0)
AST increased	1 (4.0)	2 (8.0)	0	0	0	3 (12.0)
Lymphocyte count decreased	0	1 (4.0)	1 (4.0)	1 (4.0)	0	3 (12.0)
General						
Fatigue	8 (32.0)	7 (28.0)	2 (8.0)	0	0	17 (68.0)
Edema peripheral	6 (24.0)	0	0	0	0	6 (24.0)
Pyrexia	2 (8.0)	2 (8.0)	0	0	0	4 (16.0)
Temperature intolerance	4 (16.0)	0	0	0	0	4 (16.0)
Chills	3 (12.0)	0	0	0	0	3 (12.0)
Mucosal inflammation	3 (12.0)	0	0	0	0	3 (12.0)
Nervous system						
Peripheral sensory neuropathy	3 (12.0)	8 (32.0)	0	0	0	11 (44.0)
Headache	6 (24.0)	1 (4.0)	0	0	0	7 (28.0)
Dizziness	3 (12.0)	1 (4.0)	0	0	0	4 (16.0)
Dysgeusia	3 (12.0)	1 (4.0)	0	0	0	4 (16.0)
Neuropathy peripheral	1 (4.0)	3 (12.0)	0	0	0	4 (16.0)
Skin and subcutaneous tissue						
Palmar-plantar erythrodysesthesia	4 (16.0)	6 (24.0)	0	0	0	10 (40.0)
Dry skin	4 (16.0)	1 (4.0)	0	0	0	5 (20.0)
Rash	4 (16.0)	0	0	0	0	4 (16.0)
Rash maculopapular	3 (12.0)	1 (4.0)	0	0	0	4 (16.0)
Musculoskeletal and connective tissue						
Arthralgia	6 (24.0)	1 (4.0)	0	0	0	7 (28.0)
Back pain	2 (8.0)	2 (8.0)	0	0	0	4 (16.0)
Muscular weakness	1 (4.0)	1 (4.0)	1 (4.0)	0	0	3 (12.0)
Infections and infestations						
COVID-19	1 (4.0)	2 (8.0)	0	0	0	3 (12.0)
Respiratory, thoracic, and mediastinal						
Cough	3 (12.0)	3 (12.0)	0	0	0	6 (24.0)
Dyspnea	1 (4.0)	4 (16.0)	1 (4.0)	0	0	6 (24.0)
Pulmonary embolism	0	1 (4.0)	1 (4.0)	0	1 (4.0)	3 (12.0)
Metabolism and nutrition						
Decreased appetite	7 (28.0)	2 (8.0)	1 (4.0)	0	0	10 (40.0)

(continued on following page)

TABLE 2. Adverse Events by System Occurring in ≥10% of Patients in the Safety Population (N = 25) (continued)

Adverse Event	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)	Grade 5, No. (%)	Any Grade, No. (%)
Eye						
Visual impairment	0	3 (12.0)	0	0	0	3 (12.0)
Injury, poisoning, and procedural						
Fall	2 (8.0)	2 (8.0)	0	0	0	4 (16.0)
Vascular						
Deep vein thrombosis	0	3 (12.0)	0	0	0	3 (12.0)
Psychiatric						
Insomnia	2 (8.0)	2 (8.0)	0	0	0	4 (16.0)
Endocrine						
Hypothyroidism	0	3 (12.0)	0	0	0	3 (12.0)

one-sided significance level. The emphasis of the final analyses was on estimation of key summary statistics. No formal hypotheses were tested, all study centers were pooled, and no adjustments were made for covariates or multiplicity. Any statistical results are interpreted in the perspective of the exploratory nature of the study. The primary efficacy analysis for ORR was conducted on the modified intention-to-treat (mITT) population. PFS and OS were determined for the intention-to-treat (ITT) population.

RESULTS

Patients

Between September 18, 2020, and April 8, 2021, a total of 32 patients were screened and 25 patients were enrolled in part A of the DisTinGuish study (Table 1; Fig 1). All patients who signed the consent and received at least one dose of DKN-01 (ITT population) were included in the safety analysis. Efficacy analyses were conducted on the ITT and mITT (all patients who received more than one dose of DKN-01) populations. Most patients had GEJ tumors, the median age was 61 years (range, 22-80), 76% were male, and 56% had an ECOG of 0. Molecular features included a low tumor mutation burden (<10 mut/Mb) in 90% of tested samples (17/19 tested), no evidence of microsatellite instability–high tumor types (19/19 tested), and a predominance of tumor PD-L1 expression of <5 (vCPS <5 = 73% of tested samples). Twenty-three percent of patients had PD-L1 vCPS <1. Tumor DKK1 expression was high (H-score ≥35) in 12 patients (48%), low in nine patients (36%), and unknown in four (16%) patients (three with insufficient tumor cells for testing and one with RNA degradation; Table 1). At a data cutoff of February 3, 2023, the median duration of treatment was 11.3 months (minimum-maximum [min-max], 0.76-24.41) and median duration on study was 18.73 months (min-max, 0.92-24.64). The median follow up is 19.48 months (min-max, 0.92-24.64). Treatment was ongoing in five patients; 11 patients discontinued treatment owing to disease progression; and seven were alive. The median number of cycles was 14 (min-max, 1-34) for DKN-01, tislelizumab, and oxaliplatin and 12.5 (min-max, 1-34) for capecitabine.

Safety

In the ITT safety population (N = 25), all patients experienced one or more TEAE, the majority (96%) of which were attributed to CAPOX chemotherapy (Table 2). Grade 3 or higher adverse events were seen in 60% of patients, with the most common reported as diarrhea (n = 5), decreased potassium (n = 4), and decreased hemoglobin (n = 3). DKN-01–related events reported in ≥10% of patients included the following: fatigue, diarrhea, decreased neutrophil count (seven patients each); nausea (six patients); decreased appetite and headache (four patients each); and vomiting, rash, dyspnea, decreased platelet count, and decreased hemoglobin (three patients each). Six patients experienced grade 3 or higher events attributed to DKN-01 including diarrhea (n = 1), vomiting (n = 1), neutrophil count decreased (n = 1), blood phosphorus decreased (n = 2), and pulmonary embolism (PE; n = 2). Two patients had a

TABLE 3. DKN-01–Related TEAEs Occurring in ≥10% of Patients

Adverse Event	Patients (N = 25), No. (%)
All patients reporting ≥one DKN-01–related TEAEs	15 (60.0)
Fatigue	7 (28.0)
Diarrhea	7 (28.0)
Neutrophil count decreased	7 (28.0)
Nausea	6 (24.0)
Decreased appetite	4 (16.0)
Headache	4 (16.0)
Dyspnea	3 (12.0)
Hemoglobin decreased	3 (12.0)
Platelet count decreased	3 (12.0)
Rash	3 (12.0)
Vomiting	3 (12.0)

Abbreviation: TEAE, treatment-emergent adverse event.

regimen-related event that led to DKN-01 discontinuation (fatigue [1] and PE [1]). One patient had a TEAE leading to death (PE) reported as related to DKN-01 and the study regimen (Tables 3 and 4). The PE events were noted to be possibly related to DKN-01. Notably, patients with aGEA have a known baseline rate of thromboembolic events of 9%-24%.[21] In the aggregate data set for DKN-01–exposed patients (N = 583), only nine (1.5%) had a reported treatment-emergent SAE of PE, with only two (0.5%) deemed possibly related to DKN-01.

Efficacy

The mITT population included 22 patients, all of whom had measurable disease as per protocol criteria. Three of the total 25 patients were not included in the mITT analysis as they only received one dose of DKN-01 on C1D1 because of rapid clinical progression. All evaluable patients in the mITT population had a reduction in tumor size from baseline. The mITT ORR was 73% (95% CI, 49.8 to 89.3), with a DCR of 95% (Figs 2A-2D; Appendix Table A1, online only). The ORR was 90% (95% CI, 55.5 to 99.7) in patients whose tumors were DKK1-high (n = 10). The one patient without a response in this population was not evaluable. The ORR was 67% (95% CI, 29.9 to 92.5) in DKK1-low (n = 9) tumors. Among the PD-L1 vCPS strata, the ORR was 86% (95% CI, 57.2 to 98.2) in patients with tumor vCPS <5 (n = 16) and 67% (95% CI, 22.3 to 95.7) in patients with tumor vCPS ≥5 (n = 6; Figs 2C and 2D; Appendix Table A1). With five patients remaining on treatment, the median DoR was 10 months (first-third quartiles, 7.0-19.2). In the ITT population (n = 25), the median PFS was 11.3 months (95% CI, 5.7 to 12.0) and was similar across tumor DKK1 and PD-L1 expression levels (Fig 3A; Appendix Table A2 and Figs A1A and A1B). The 12-month PFS rate was 33% across the ITT population. The median OS was 19.5 months (95% CI, 15.2 to 24.4) with a 12-month OS rate of 76% and an 18-month OS rate of 55% (Fig 3B; Appendix Table A2 and Figs A1C and A1D). OS by DKK1 status is shown in Appendix Figure A1D.

TABLE 4. DKN-01–Related Serious TEAEs, TEAEs Leading to DKN-01 Drug Discontinuation, and TEAEs Leading to Death

Adverse Event	Patients (N = 25), No. (%)
Patients reporting ≥one DKN-01–related serious TEAEs	3 (12.0)
Vomiting	1 (4.0)
PE	2 (8.0)
Patients reporting ≥one TEAEs leading to DKN-01 drug discontinuation	4 (16.0)
Cardiogenic shock	1 (4.0)
Hepatic failure	1 (4.0)
Pneumonia aspiration	1 (4.0)
PE	1 (4.0)
Acute kidney injury	1 (4.0)
Patients reporting ≥one TEAEs leading to death	3 (12.0)
Hepatic failure	1 (4.0)
Pneumonia aspiration	1 (4.0)
PE	1 (4.0)

Abbreviations: PE, pulmonary embolism; TEAE, treatment-emergent adverse event.

Biomarker Analyses

In exploratory analyses, tumor PD-L1 and DKK1 expression levels did not correlate, suggesting that they are independent biomarkers (Appendix Fig A2). As DKK1 is involved in Wnt-signaling, we examined pretreatment ctDNA for alterations in Wnt pathway genes (*APC*, *AXIN1*, *CTNNB1*, *RNF43*, and *RSPO2*). Among patients tested (n = 19), three with DKK1-high tumors also had Wnt-activating mutations and three with DKK1-low tumors had Wnt-activating mutations. There was no significant difference in ORR on the basis of pretreatment serum DKK1 levels, when comparing patients with DKK1 serum levels above or below the median (3.8 ng/mL; not shown).

DISCUSSION

Strategies to build on frontline anti–PD-1 in combination with FU/platinum are a major focus of clinical and translational research in aGEA. In part A of the DisTinGuish trial, we demonstrate safety and tolerability of the novel DKK1-neutralizing antibody DKN-01 in combination with frontline tislelizumab and CAPOX in HER2-negative aGEA. In an unselected Western patient population, enriched for GEJ adenocarcinoma, we observed an ORR of 73%, and an overall PFS and OS of 11.3 and 19.5 months, respectively. These preliminary efficacy end points should be interpreted in the context of the phase III KeyNote-859, Checkmate-649, and Rationale-305 trials.[2,3] Consistent with previous combination with pembrolizumab, the addition of DKN-01 was safe and the toxicity profile was largely consistent with the expected adverse events seen in phase III trials with FU/platinum and anti–PD-1 in GEA.[2,3,18,22] The primary DKN-01–related adverse events were gastrointestinal and generally low grade. Although DKK1 is implicated in bone remodeling during normal development, we did not observe any skeletal-related events, nor was this observed in the previously reported phase Ib trial in this patient population.[18,19]

DKK1 expression is associated with unfavorable biology and poor prognosis, suggesting elevated DKK1 may define a more refractory population.[16,17] In this trial, we observed a DKK1-high prevalence of 48% suggesting a recurrent feature in aGEA. Interestingly, the ORR was numerically better in patients with high tumor DKK1 expression compared with those with low tumor DKK1 expression (90.0% *v* 66.7%, respectively), suggesting that these patients may benefit most from the addition of DKN-01. The combination was active in patients with low tumor PD-L1 expression (vCPS <5), and the PD-L1–low

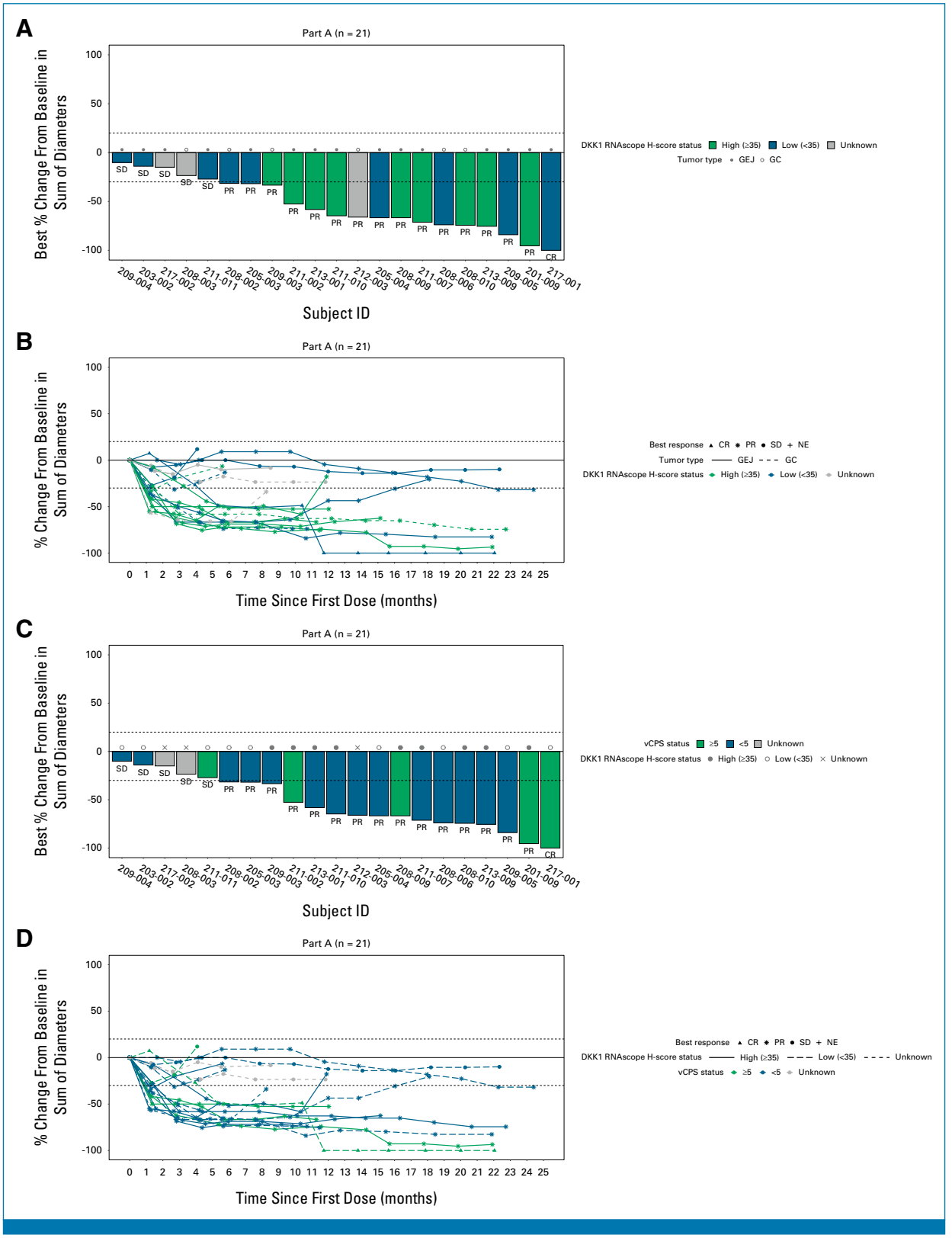

FIG 2. Changes in tumor burden in the mITT population (n = 21). (A) Maximal percentage change in tumor from baseline, colored by DKK1 expression level, (B) percentage change from baseline over time colored by DKK1 expression level, (C) maximal percentage change in tumor from baseline, colored by PD-L1 expression level, (D) percentage change from baseline over time colored by PD-L1 expression level. Includes patients from the mITT Population with evaluable postbaseline assessments. One patient had only baseline tumor measurement data and was not included. CR, complete response; GC, gastric cancer; GEJ, gastroesophageal junction; mITT, modified intention-to-treat; NE, not evaluable; PR, partial response; SD, stable disease; vCPS, visual combined positive score.

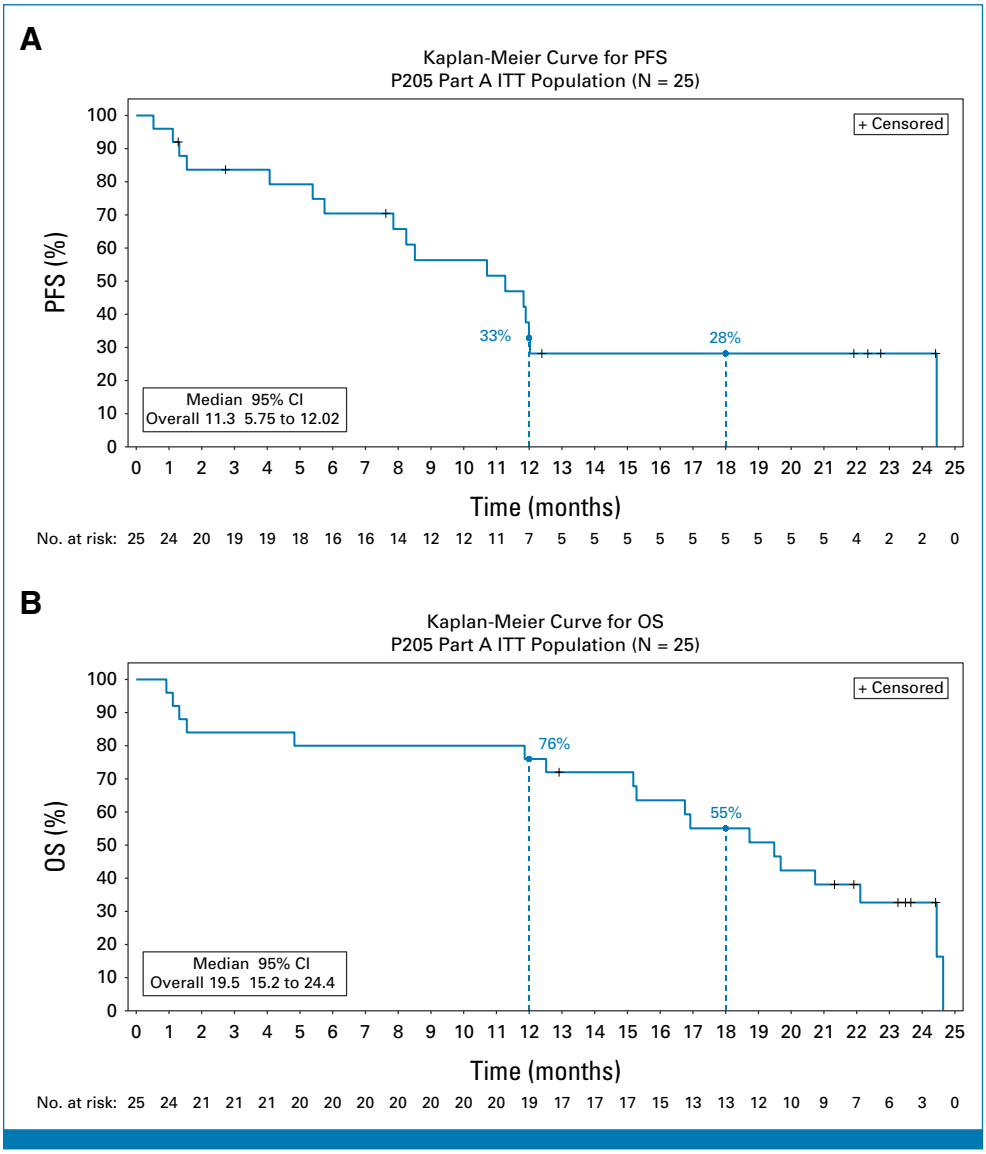

FIG 3. Survival in the ITT population (N = 25). (A) PFS and (B) OS. ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

population represented most of the enrolled patients. If borne out in the ongoing confirmatory randomized phase II, these data could support the preclinical hypothesis that DKN-01 upregulates PD-L1 expression and enhances anti–PD-1 treatment, thereby expanding the portion of patients with aGEA benefiting from immune checkpoint therapies.[16,17] These data should be interpreted with caution in the setting of the smaller sample size. Although OS was noted to be higher in patients with DKK1-low tumors versus those with higher expression levels, the OS in DKK1-high patients treated with DKN-01 (16.9 months) was still favorable. The lower OS for DKK1-high patients versus DKK1-low may reflect the poor prognosis associated elevated tumor levels of DKK1.[14,16]

The current US Food and Drug Administration label for frontline FU/platinum and nivolumab in aGEA is independent of PD-L1 expression status. However, the benefit from anti–PD-1 plus fluoropyrimidine/platinum is largely restricted to PD-L1+ patients, particularly those with higher PD-L1–expressing tumors.[6,23-25] The proportion of PD-L1–negative aGEA (defined as CPS <1) is ≥20% and the proportion of PD-L1–low (defined as CPS <5) ranges from 40% to 60%, depending on the assay used and population studied.[23,25-27] We used the SP263 clone (Roche) and noted nearly three fourths of our population (72.7%) had tumors that were vCPS <5 and 22.7% had tumors that were PD-L1–negative (vCPS <1). Despite a limited sample size, data from this study are aligned with DKN-01 cooperativity independent of PD-L1 expression levels.

Our study has limitations including the small sample size, single-arm design, and the exploratory nature of the efficacy findings. Although our study population is consistent with

Western phase III trial demographics, it is underpowered for PFS and OS, and these results should be considered exploratory. However, similarly sized trials have defined important observations in aGEA, supporting subsequent confirmatory efforts.[28-30] Collectively, these data support the ongoing randomized phase II portion of the trial comparing FU/oxaliplatin plus tislelizumab with or without DKN-01 (ClinicalTrials.gov identifier: NCT04363801).

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APPENDIX

TABLE A1. Best Overall Response Within Patient Subgroups of the mITT Population

Best Overall Response	Objective Response Rate (95% CI)	Complete Response, No. (%)	Partial Response, No. (%)	Stable Disease, No. (%)	Progressive Disease
mITT population (n = 22)	73% (49.8 to 89.3)	1 (5)	15 (68)	5 (23)	0
PD-L1 expression					
vCPS <5 (n = 16)	86% (57.2 to 98.2)	0	12 (86)	2 (14)	0
vCPS ≥5 (n = 6)	67% (22.3 to 95.7)	1 (17)	3 (50)	1 (17)	0
Unknown (n = 2)	0	0	0	2 (100)	0
DKK1 expression					
DKK1-high (n = 12)	90% (55.5 to 99.7)	0	9 (90)	0	0
DKK1-low (n = 9)	67% (29.9 to 92.5)	1 (11)	5 (56)	3 (33)	0
Unknown (n = 3)	33% (0.84 to 90.6)	0	1 (33)	2 (67)	0

Abbreviations: mITT, modified intention-to-treat; vCPS, visual combined positive score.

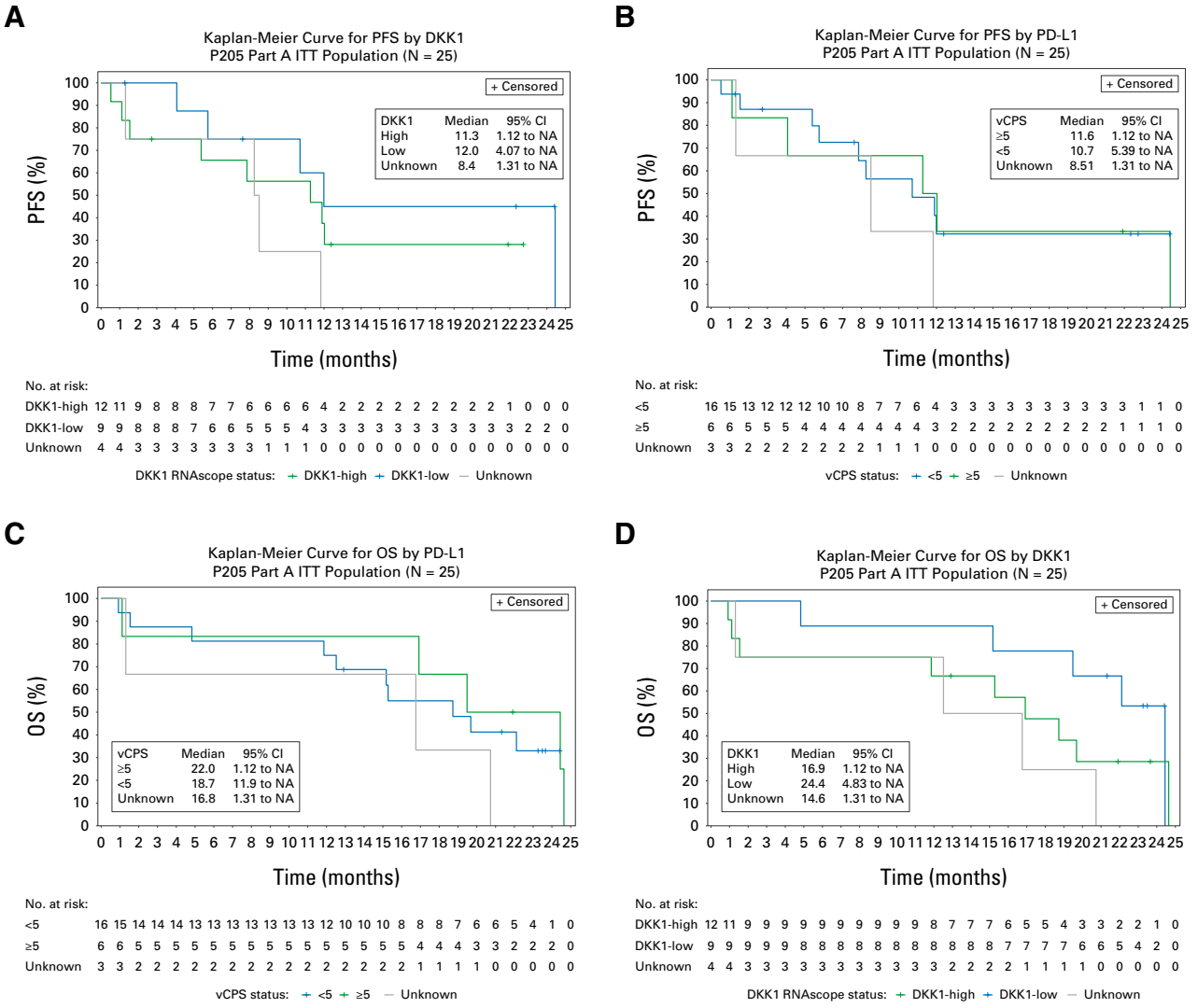

FIG A1. Survival by DKK1 and PD-L1 in the overall population. PFS by (A) DKK1 and (B) PD-L1 expression in the overall population. OS by (C) PD-L1 and (D) DKK1 expression level. ITT, intention-to-treat; NA, not applicable; OS, overall survival; PFS, progression-free survival; vCPS, visual combined positive score.

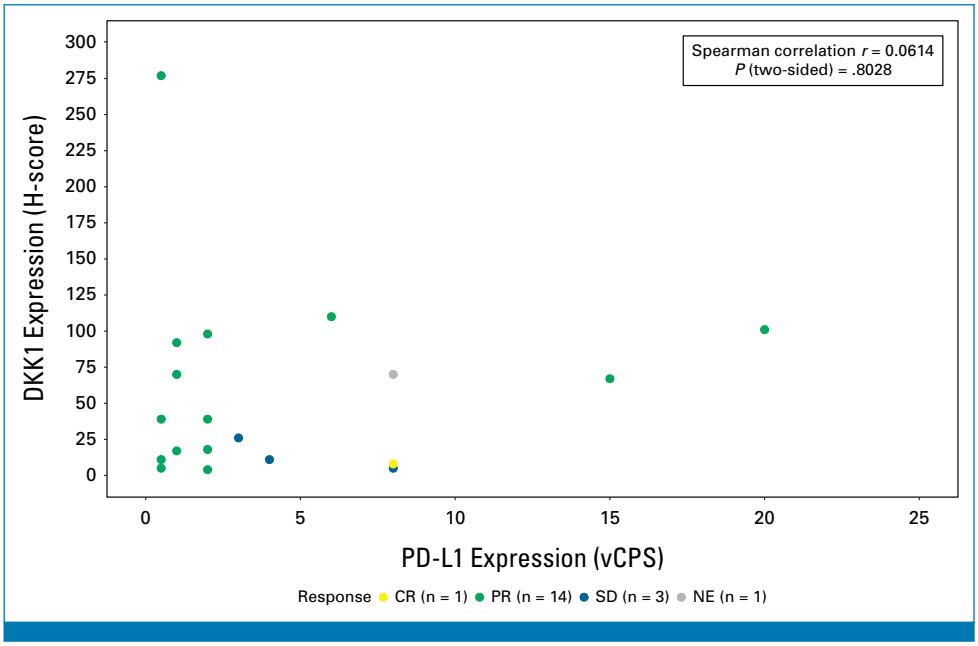

FIG A2. DKK1 and PD-L1 expression level are not correlated in the overall population (Spearman correlation $r = 0.06$). CR, complete response; NE, not evaluable; PR, partial response; SD, stable disease; vCPS, visual combined positive score.

TABLE A2. PFS and OS Within Biomarker Groupings in the Overall Population (ITT, n = 25)

Biomarker Group	PFS (months), Median (95% CI)	OS (months), Median (95% CI)
Overall (N = 25)	11.3 (5.75 to 12.0)	19.5 (15.2 to 24.4)
PD-L1 expression		
vCPS <5 (n = 16)	10.7 (5.39 to NA)	18.7 (11.9 to NA)
vCPS ≥5 (n = 6)	11.6 (1.12 to NA)	22.0 (1.12 to NA)
DKK1 expression		
DKK1-high (N = 12)	11.3 (1.12 to NA)	16.9 (1.12 to NA)
DKK1-low (N = 9)	12.0 (4.07 to NA)	24.4 (4.83 to NA)

Abbreviations: ITT, intention-to-treat; NA, not applicable; OS, overall survival; PFS, progression-free survival; vCPS, visual combined positive score.