ARRY-382 in Combination with Pembrolizumab in Patients with Advanced Solid Tumors: Results from a Phase 1b/2 Study

Melissa Johnson[1], Arkadiusz Z. Dudek[2], Ammar Sukari[3], Justin Call[4], Paul R. Kunk[5], Karl Lewis[6], Justin F. Gainor[7], John Sarantopoulos[8], Patrice Lee[9], Adele Golden[9], Allison Harney[9], S. Michael Rothenberg[9], Yuanyuan Zhang[9], and Jonathan W. Goldman[10]

ABSTRACT

Purpose: ARRY-382 (PF-07265804) is a selective inhibitor of colony-stimulating factor-1 receptor. We evaluated the safety and preliminary efficacy of ARRY-382 plus pembrolizumab in patients with advanced solid tumors.

Patients and Methods: This was an open-label, multicenter, Phase 1b/2 study (NCT02880371) performed over September 1, 2016 to October 24, 2019. In the Phase 1b dose-escalation, patients with selected advanced solid tumors received ARRY-382 [starting dose 200 mg once daily (QD) orally] plus pembrolizumab [2 mg/kg intravenously (IV) every 3 weeks (Q3W)]. Phase 2 patients had: Pancreatic ductal adenocarcinoma (PDA); programmed cell death protein-1 (PD-1)/PD-ligand 1 (PD-L1) inhibitor-refractory (PD-1/PD-L1 IR) advanced solid tumors; or platinum-resistant ovarian cancer (prOVCA). Patients received ARRY-382 at the maximum tolerated dose (MTD) of 300 mg QD plus pembrolizumab 200 mg IV Q3W.

Results: Primary endpoints of dose-limiting toxicities (DLT; Phase 1b) and objective response rate (Phase 2) were met. In Phase 1b, 19 patients received ARRY-382 200–400 mg. Three patients reported DLTs. The MTD of ARRY-382 (plus pembrolizumab) was 300 mg QD. In Phase 1b, 2 patients (10.5%) had confirmed partial response (PR): 1 with PDA and 1 with ovarian cancer, lasting 29.2 and 3.1 months, respectively. In Phase 2, there were 27, 19, and 11 patients in the PDA, PD-1/PD-L1 IR, and prOVCA cohorts, respectively. One patient (3.7%) with PDA had a PR lasting 2.4 months. The most frequent ARRY-382–related adverse events were increased transaminases (10.5%–83.3%) and increased creatine phosphokinase (18.2%–50.0%).

Conclusions: Although limited clinical benefit was observed, ARRY-382 plus pembrolizumab was well tolerated.

Introduction

Cancer immunotherapies, which work by overcoming the barriers to an antitumor immune response, have transformed modern oncology treatment (1, 2). Pembrolizumab is a potent and highly selective humanized monoclonal antibody that blocks the interaction between programmed cell death protein-1 (PD-1) and its ligands, programmed death-ligand 1 and 2 (PD-L1 and PD-L2; refs. 3, 4). On the basis of the results from a number of pivotal KEYNOTE clinical trials, pembrolizumab, as monotherapy or as part of a combination regimen, is approved for the treatment of a variety of tumor types, including melanoma, non–small cell lung carcinoma (NSCLC), head and neck squamous cell cancer (HNSCC), classical Hodgkin's lymphoma, and urothelial carcinoma (3, 4).

Intrinsic or primary resistance to anti–PD-1 therapy may arise from immune regulatory factors in the tumor microenvironment that suppress specific immune responses to the tumor or allow tumor cells to evade recognition (5, 6). Tumor-associated macrophages (TAM) and myeloid-derived suppressor cells (MDSCs) are critical drivers of immune escape in the tumor microenvironment (7). Mouse models have shown that depleting or modifying TAMs and MDSCs reverses immunosuppression and/or improves the efficacy of anti–PD-1 agents (7, 8).

ARRY-382 (PF-07265804) is a potent, highly specific, small-molecule inhibitor of colony-stimulating factor 1 receptor (CSF-1R). CSF-1, which signals via CSF-1R, regulates both TAMs and MDSCs (8). Inhibition of CSF-1R with ARRY-382 in preclinical models decreased the number of tumor infiltrative macrophages (e.g., TAMs) in the tumor microenvironment and reprogrammed macrophages to increase antigen presentation and support T-cell activation (7). In a Phase 1 dose-escalation study, ARRY-382 monotherapy was well tolerated and demonstrated CSF-1 pathway suppression in patients with advanced or metastatic cancers (9).

In a pancreatic cancer model, the combination of anti–PD-1 with CSF-1R inhibitors improved the response to anti–PD-1 therapy versus anti–PD-1 alone (7). In addition, preliminary data from clinical studies of anti–PD-1/PD-L1 therapies in combination with other CSF-1 pathway inhibitors have shown encouraging antitumor responses (10–13). Therefore, the rationale for exploring ARRY-382 in combination with pembrolizumab is to inhibit both TAMs and MDSCs, two immune populations that negatively regulate immune-mediated tumor control,

[1]Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, Tennessee. [2]HealthPartners Institute, Regions Cancer Care Center, St. Paul, Minnesota. [3]Karmanos Cancer Institute, Detroit, Michigan. [4]Utah Cancer Specialists, Salt Lake City, Utah. [5]University of Virginia, Charlottesville, Virginia. [6]University of Colorado Cancer Center, Aurora, Colorado. [7]Massachusetts General Hospital, Boston, Massachusetts. [8]Institute for Drug Development, Mays Cancer Center at University of Texas Health San Antonio MD Anderson Cancer Center, San Antonio, Texas. [9]Pfizer Inc., Boulder, Colorado. [10]David Geffen School of Medicine at UCLA, Los Angeles, California.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Author: Melissa Johnson, Thoracic Medical Oncology, Sarah Cannon Research Institute at Tennessee Oncology, PLLC, 250 25th Avenue, North, Nashville, TN. Phone: 615-329-7274; E-mail: mjohnson@tnonc.com

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Translational Relevance

Resistance to programmed cell death protein-1 (PD-1) pathway therapies may arise from immune regulatory factors in the tumor microenvironment that suppress specific immune responses to the tumor or allow tumor cells to evade recognition. In preclinical and preliminary clinical studies, combining PD-1 pathway inhibitors with colony-stimulating factor 1 (CSF-1) pathway inhibitors showed synergistic antitumor responses. This Phase 1b/2 study evaluated the selective CSF-1 receptor (CSF-1R) inhibitor, ARRY-382, plus the anti–PD-1 agent, pembrolizumab, in patients with advanced solid tumors. Although no further evaluation of these drugs in combination is planned, the safety profile of the combination was generally tolerable, manageable, and consistent with the known safety profiles of ARRY-382 and single-agent pembrolizumab. Despite on-target modulation of CSF-1R activity by ARRY-382, limited clinical benefit was observed. Confirmed partial responses were observed in 2 patients in the dose-escalation portion and 1 patient in the Phase 2 pancreatic ductal adenocarcinoma cohort.

resulting in a double-blockade of cancer-induced immune suppression. The overall objectives of this Phase 1b/2 study were to determine the MTD of ARRY-382 plus pembrolizumab in patients with advanced solid tumors, as well as to assess the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics of the combination regimen. The primary objective for the Phase 1b study (MTD) was assessed by the incidence of dose-limiting toxicities (DLT). The primary objective of the Phase 2 study (efficacy) was assessed by evaluation of the objective response rate (ORR), per RECIST v1.1, as determined by the investigator.

Patients and Methods

Study design

This was an open-label, multicenter Phase 1b/2 study (ClinicalTrials.gov identifier: NCT02880371) at 12 centers in the United States between September 1, 2016 and October 24, 2019. The Phase 1b portion was a dose-escalation study in adult patients with selected advanced solid tumors. The starting dose of ARRY-382 was 200 mg orally (PO) once daily (QD), with planned escalation to 400 mg PO QD. Pembrolizumab was administered intravenously (IV) at 2 mg/kg every 3 weeks (Q3W). The Phase 2 portion included patients with: Pancreatic ductal adenocarcinoma (PDA); advanced solid tumors that were refractory to PD-1 or PD-L1 inhibitor therapy (PD-1/PD-L1 IR); or platinum-resistant ovarian cancer (prOVCA). Across all cohorts in Phase 2, ARRY-382 was administered orally at 300 mg PO QD (MTD from the Phase 1b portion). Pembrolizumab was administered at the approved fixed dose of 200 mg IV Q3W.

The study was approved by institutional review boards and independent ethics committees at each center. The study was conducted in accordance with all local legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Guidelines for Good Clinical Practice, and the Declaration of Helsinki. All patients provided written informed consent.

Patients

All patients were ≥18 years with a histologically or cytologically confirmed cancer diagnosis. All patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 with adequate bone marrow, renal, and hepatic function at screening. Patients had measurable or evaluable, non-measurable disease per RECIST v1.1. Patients were excluded if they had symptomatic brain metastases, a history of autoimmune disease, impaired gastrointestinal function or disease that could significantly alter the absorption of ARRY-382, or any other clinically significant disease.

In the Phase 1b portion, solid tumor patients had one of the following cancer types: Ovarian cancer, triple-negative breast cancer, HNSCC, bladder cancer, metastatic colorectal cancer, gastric cancer, or PDA that was refractory to currently available therapies, for which no standard therapy was available or the patient declined standard therapy; or advanced, unresectable, or metastatic melanoma with or without prior treatment; or advanced/metastatic PD-L1+ NSCLC [defined as tumor proportion score (TPS) ≥50% according to the initial accelerated approval for pembrolizumab in NSCLC; this was later updated to TPS >1% to reflect the updated pembrolizumab label].

In the Phase 2 portion, patients were assigned to 1 of the following 3 cohorts. Cohort 1 (PD-1/PD-L1 IR): Advanced/metastatic solid tumor with progressive disease [PD; per RECIST or immune-related Response Criteria (irRC)] on anti–PD-1/PD-L1 therapy. Cohort 2 (prOVCA): Advanced/metastatic epithelial ovarian, peritoneal, or fallopian tube cancer that progressed ≤6 months following ≥4 cycles of platinum-based therapy. Cohort 3 (PDA): Advanced/metastatic PDA in patients who had received ≥1 prior line of systemic therapy.

Patients previously treated with an immune checkpoint inhibitor were excluded from the Phase 1b study and Cohorts 2 and 3 of the Phase 2 study. Patients previously treated with CSF-1R or CSF-1 (or macrophage colony-stimulating factor, MCSF) inhibitors were excluded from the Phase 2 study.

Endpoints

The primary endpoint of the Phase 1b study was the incidence of DLTs. The primary endpoint across cohorts in the Phase 2 study was ORR per RECIST v1.1 as determined by the investigator. Secondary efficacy endpoints across the Phase 1b and 2 studies were: ORR per RECIST v1.1 as determined by the investigator (Phase 1b only); duration of response (DOR), progression-free survival (PFS), and overall survival (OS) per RECIST v1.1 as determined by the investigator; immune-related (ir) response rate (irRR) and PFS (irPFS) as determined by the investigator. Safety parameters were assessed as secondary endpoints and included adverse events (AE), serious AEs (SAE), laboratory evaluations, and vital signs. PK parameters for ARRY-382 and metabolites were also assessed as secondary endpoints and included area under the plasma concentration–time curve (AUC) over the dosing interval (AUC_{tau}), maximum observed plasma concentration (C_{max}), pre-dose concentration (C_{trough}), and time to first occurrence of C_{max} (T_{max}).

Several exploratory endpoints were evaluated in both the Phase 1b and 2 portions. Biomarkers were assessed across the Phase 1b and 2 studies, for example, levels of growth factors, cytokines (CSF-1), C-terminal telopeptide of type 1 collagen (CTX), urinary N-terminal telopeptide of type I collagen (NTX), and non-classical monocytes (NCM). Antitumor activity in relation to PD-L1 expression (Phase 1b only) and pharmacodynamic and tumor genomic alterations and/or gene expression profiles (Phase 2 only) were also evaluated.

Pharmacokinetic and pharmacodynamic analyses

Blood samples for PK analyses of ARRY-382 and metabolites [AR00469099 (an N-oxide metabolite), AR00469100 (an N-desmethyl metabolite), and AR00470870 (a sulfate metabolite)] were collected

pre-dose and at 1, 2, 4, and 8 hours after administration of ARRY-382 on day 1 of cycles 1 and 2. Trough PK blood samples were collected pre-dose (≤120 minutes before ARRY-382 administration) on cycle 1 day 15 and day 1 of cycles 3–6. Blood samples for circulating cytokines (CSF-1), growth factors, and markers of bone turnover (CTX), and urine sample for markers of bone turnover (NTX), were collected pre-dose, and at treatment discontinuation. Further details on both PK and PD analyses can be found in the Supplementary Materials.

Molecular biomarkers

At screening, a fresh biopsy or archived tissue samples, plus a blood sample were assessed for PD-L1 expression (Phase 1b only), tumor genomic alterations (including microsatellite instability (MSI) status/mismatch repair (MMR) proficiency), tumor mutational burden (TMB), and/or gene expression profiling (Phase 2 only). Results were reported by local testing laboratories based on validated thresholds for the test at the time of analysis. Blood and urine samples for biomarkers were collected on cycle 1 days 1, 8, and 15; on day 1 of subsequent cycles; and at treatment discontinuation.

Statistical analyses

Overall, 90 patients were planned for enrollment. The full analysis set (FAS) population included all patients who received ≥1 dose (partial or full) of ARRY-382 or pembrolizumab. The safety analysis set was the same as the FAS. Additional details on sample size and analysis populations can be found in the Supplementary Materials.

All safety analyses were based on the safety analysis set and summarized descriptively. All AEs and laboratory abnormalities were graded using CTCAE version 4.03. Definitions for DLTs can be found in the Supplementary Materials. All efficacy analyses were based on the FAS. Definitions for efficacy endpoints can be found in the Supplementary Materials. ORR was based on confirmed responses and 2-sided 95% confidence intervals (CI) calculated using the Clopper–Pearson exact binomial method. DOR, PFS, and OS were estimated using the Kaplan–Meier method and 2-sided 95% CIs calculated using the Brookmeyer–Crowley method. All PK analyses were based on the PK analysis set. Non-compartmental PK parameters were estimated for each patient with Phoenix WinNonlin v8.0 or higher (Certara USA, Inc.), and PK parameters were summarized descriptively. No formal tests were performed on the biomarker analyses. Pharmacodynamic outcomes were summarized descriptively; data with outliers excluded were reported.

Statistical analyses were conducted using SAS v9.4 or higher (SAS Institute, Inc.). Original sample size calculations for Phase 2 were conducted using R v3.4.3. The data cutoff date for these analyses was March 3, 2020.

Data availability

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Results

Patients and disposition

Phase 1b

In Phase 1b, 20 patients were enrolled and 19 patients were treated and included in the FAS (Supplementary Fig. S1). Most patients were male (52.6%) and white (94.7%), with a median age of 59 years (range, 32–77; **Table 1**). Overall, 63.2% and 36.8% had an ECOG PS of 0 and 1, respectively.

In Phase 1b, 6 patients received ARRY-382 200 mg plus pembrolizumab, 6 received ARRY-382 300 mg plus pembrolizumab, and 7 received ARRY-382 400 mg plus pembrolizumab. The median duration of ARRY-382 treatment was 3.3, 2.9, and 1.3 months in the 200, 300, and 400 mg cohorts, respectively. Corresponding median duration of pembrolizumab treatment was 2.8, 3.1, and 1.4 months. Four patients in each cohort had ≥1 dose reduction or interruption of ARRY-382; all were due to AEs, with 3 patients also having other reasons. Two patients in the 200-mg cohort, and 1 each in the 300 and 400-mg cohorts, had ≥1 dose interruption of pembrolizumab; 3 were due to AEs and 1 was due to other reasons. Respectively in the 200, 300, and 400 mg cohorts, treatment discontinuations occurred in 6 (100.0%), 6 (85.7%), and 7 (100.0%) patients, most commonly due to disease progression [4 (66.7%), 6 (100.0%), and 6 (85.7%) patients]. One patient (16.7%) in the 200-mg cohort discontinued due to AEs (primary reason).

Phase 2

In Phase 2, 59 patients were enrolled and 57 were treated and included in the FAS (Supplementary Fig. S2). There were 27, 19, and 11 patients in the PDA, PD-1/PD-L1 IR, and prOVCA cohorts, respectively (**Table 1**). Most patients were female (61.4%) and white (82.5%), with a median age of 63 years (range, 30–87). Overall, 28.1% and 71.9% had an ECOG PS of 0 and 1, respectively.

In total, one patient (1.8%) was MSI-High, occurring in the PD-1/PD-L1 IR cohort. Across cohorts, most patients were MSI-Stable [PDA: 14 (51.9%); PD-1/PD-L1 IR: 10 (52.6%); prOVCA: 11 (100%)] or other/unknown/test not done [PDA: 13 (48.1%); PD-1/PD-L1 IR: 8 (42.1%); prOVCA: 0 (0.0%)]. In the PDA, PD-1/PD-L1 IR, and prOVCA cohorts, respectively, 5 (18.5%), 4 (21.1%), and 0 (0.0%) were MMR proficient, whereas 22 (81.5%), 15 (78.9%), and 11 (100%) were other/unknown/test not done, and 7 (25.9%), 5 (26.3%), and 3 (27.3%) were TMB-Low. The majority of patients were PD-L1 negative [19 (70.4%), 14 (73.7%), and 11 (100.0%) in the PDA, PD-1/PD-L1 IR, and prOVCA cohorts, respectively]. No patients had CSF-1R mutations.

The median duration of ARRY-382 treatment was 1.1, 2.0, and 1.4 months in the PDA, PD-1/PD-L1 IR, and prOVCA cohorts, respectively. Corresponding median duration of pembrolizumab treatment was 1.4, 2.8, and 2.0 months. In the PDA, PD-1/PD-L1 IR, and prOVCA cohorts, respectively, 16 (59.3%), 15 (78.9%), and 7 (63.6%) patients had ≥1 dose reduction or interruption of ARRY-382; of which 10 (37.0%), 13 (68.4%), and 7 (63.6%) were due to AEs. One patient in each dose cohort had ≥1 dose interruption of pembrolizumab; all were due to AEs. Respectively in the PDA, PD-1/PD-L1 IR, and prOVCA cohorts, treatment discontinuations occurred in 27 (96.4%), 19 (95.0%), and 11 (100.0%) patients; most commonly due to disease progression [16 (57.1%), 14 (70.0%), and 7 (63.6%) patients]. Corresponding discontinuations due to AEs (primary reason) occurred in 5 (17.9%), 3 (15.0%), and 2 (18.2%) patients.

Safety

MTD and recommended phase 2 dose

The Phase 1b primary endpoint was met. Overall, 3/19 patients reported DLTs (primary endpoint) in the Phase 1b portion. DLTs were observed in 2/7 patients in the 400-mg cohort: Grade 2 increased blood creatine phosphokinase (CPK) in 1 patient, and Grade 3 increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin in another patient. In the 300-mg cohort, 1/6 patients

Table 1. Baseline demographics and characteristics: Phase 1b and Phase 2.

	Phase 1b				Phase 2			
n **(%)**	**ARRY-382 200 mg (*N* = 6)**	**ARRY-382 300 mg (*N* = 6)**	**ARRY-382 400 mg (*N* = 7)**	**Total (*N* = 19)**	**PDA (*N* = 27)**	**PD-1/PD-L1 IR (*N* = 19)**	**prOVCA (*N* = 11)**	**Total (*N* = 57)**
Sex								
Male	4 (66.7)	3 (50.0)	3 (42.9)	10 (52.6)	15 (55.6)	7 (36.8)	0 (0.0)	22 (38.6)
Female	2 (33.3)	3 (50.0)	4 (57.1)	9 (47.4)	12 (44.4)	12 (63.2)	11 (100.0)	35 (61.4)
Median (range) age, y	66 (42–77)	51 (32–76)	51 (40–76)	59 (32–77)	65 (46–87)	63 (30–80)	58 (35–81)	63 (30–87)
Race								
White	5 (83.3)	6 (100.0)	7 (100.0)	18 (94.7)	23 (85.2)	15 (78.9)	9 (81.8)	47 (82.5)
Black	—	—	—	—	2 (7.4)	3 (15.8)	0 (0.0)	5 (8.8)
Asian	—	—	—	—	0 (0.0)	0 (0.0)	1 (9.1)	1 (1.8)
Other	1 (16.7)	0 (0.0)	0 (0.0)	1 (5.3)	2 (7.4)	1 (5.3)	1 (9.1)	4 (7.0)
ECOG PS								
0	5 (83.3)	5 (83.3)	2 (28.6)	12 (63.2)	5 (18.5)	7 (36.8)	4 (36.4)	16 (28.1)
1	1 (16.7)	1 (16.7)	5 (71.4)	7 (36.8)	22 (81.5)	12 (63.2)	7 (63.6)	41 (71.9)
Prior radiation therapy	1 (16.7)	2 (33.3)	4 (57.1)	7 (36.8)	5 (18.5)	13 (68.4)	2 (18.2)	20 (35.1)
Prior surgery	4 (66.7)	6 (100.0)	7 (100.0)	17 (89.5)	18 (66.7)	18 (94.7)	11 (100.0)	47 (82.5)
Prior lines of systemic therapy	6 (100.0)	5 (83.3)	6 (85.7)	17 (89.5)	26 (96.3)	19 (100.0)	11 (100.0)	56 (98.2)
0	0 (0.0)	1 (16.7)	1 (14.3)	2 (10.5)	1 (3.7)	0 (0.0)	0 (0.0)	1 (1.8)
1	1 (16.7)	0 (0.0)	1 (14.3)	2 (10.5)	4 (14.8)	2 (10.5)	0 (0.0)	6 (10.5)
2	4 (66.7)	2 (33.3)	1 (14.3)	7 (36.8)	8 (29.6)	6 (31.6)	3 (27.3)	17 (29.8)
≥3	1 (16.7)	3 (50.0)	4 (57.1)	8 (42.1)	14 (51.9)	11 (57.9)	8 (72.7)	33 (57.9)
MSI status								
MSI-S	—	—	—	—	14 (51.9)	10 (52.6)	11 (100.0)	35 (61.4)
MSI-H	—	—	—	—	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.8)
Other[a]	—	—	—	—	13 (48.1)	8 (42.1)	0 (0.0)	21 (36.8)
MMR deficiency								
pMMR	—	—	—	—	5 (18.5)	4 (21.1)	0 (0.0)	9 (15.8)
Other[a]	—	—	—	—	22 (81.5)	15 (78.9)	11 (100.0)	48 (84.2)
TMB[b]								
Low	—	—	—	—	7 (25.9)	5 (26.3)	3 (27.3)	15 (26.3)
Intermediate	—	—	—	—	7 (25.9)	5 (26.3)	8 (72.7)	20 (35.1)
High	—	—	—	—	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.8)
Other[a]	—	—	—	—	13 (48.1)	8 (42.1)	0 (0.0)	21 (36.8)
PD-L1 status[c]								
Positive	—	—	—	—	1 (3.7)	4 (21.1)	0 (0.0)	5 (8.8)
Negative	—	—	—	—	19 (70.4)	14 (73.7)	11 (100.0)	44 (77.2)
Other[a]	—	—	—	—	7 (25.9)	1 (5.3)	0 (0.0)	8 (14.0)
BRCA1 positive	—	—	—	—	1 (3.7)	0 (0.0)	3 (27.3)	4 (7.0)
BRCA2 positive	—	—	—	—	0 (0.0)	0 (0.0)	1 (9.1)	1 (1.8)
Tumor type								
PDA	2 (33.3)	2 (33.3)	2 (28.6)	6 (31.6)	25 (92.6)	0 (0.0)	0 (0.0)	25 (43.9)
Metastatic CRC	2 (33.3)	1 (16.7)	2 (28.6)	5 (26.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ovarian	1 (16.7)	2 (33.3)	0 (0.0)	3 (15.8)	0 (0.0)	0 (0.0)	10 (90.9)	10 (17.5)
Gastric	1 (16.7)	0 (0.0)	1 (14.3)	2 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Melanoma	0 (0.0)	1 (16.7)	1 (14.3)	2 (10.5)	0 (0.0)	3 (15.8)	0 (0.0)	3 (5.3)
Breast	0 (0.0)	0 (0.0)	1 (14.3)[d]	1 (5.3)	0 (0.0)	2 (10.5)	0 (0.0)	2 (3.5)
Pancreatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.4)	0 (0.0)	0 (0.0)	2 (3.5)
Bladder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.8)
CRC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.8)
Hepatocellular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.8)
NSCLC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (21.1)	0 (0.0)	4 (7.0)
Other[e]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (36.8)	1 (9.1)	8 (14.0)

Note: Full analysis set.

Abbreviations: CRC, colorectal carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance score; IR, inhibitor refractory; MMR, mismatch repair; MSI, microsatellite instability; MSS, MSI-Stable; MSI-H, MSI-High; NSCLC, non–small cell lung cancer; PDA, pancreatic ductal adenocarcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; pMMR, MMR proficient, intact, normal; prOVCA, platinum-resistant ovarian cancer; TMB, tumor mutational burden; TNBC, triple-negative breast cancer.

[a]Includes unknown, other, test not done/unsure.

[b]Low = 1–6 mutations/Mb; Intermediate = 6–16 mutations/Mb; High = ≥17 mutations/Mb.

[c]Positive staining defined as ≥5% immune cells for TNBC; ≥1% immune cells for urothelial carcinoma; and 2+/5% in tumor cells for all other indications.

[d]TNBC.

[e]In the PD-1/PD-L1 IR cohort, patients had penile cancer, anal cancer, neuroendocrine carcinoma, leiomyosarcoma, anaplastic sacral ependymoma, endometrium cancer, and small-cell carcinoma ($n = 1$ each). In the prOVCA cohort, 1 patient had a diagnosis of peritoneal carcinoma.

experienced a DLT of Grade 3 acute pancreatitis. The MTD and RP2D of ARRY-382 in combination with pembrolizumab were determined to be 300 mg QD. This was based on reported DLTs in 2 patients at the 400-mg QD dose, 1 patient at the 300-mg QD dose, and consideration by the investigators of the overall safety profile for all treated patients. Pancreatitis was the only DLT not previously identified in the safety profile of ARRY-382; however, increased amylase and lipase were reported with ARRY-382. Pancreatitis is a known toxicity during pembrolizumab treatment. In Phase 2, the pembrolizumab dose was changed from 2 mg/kg to 200 mg to reflect a change in the pembrolizumab prescribing information.

Phase 1

In Phase 1b, the majority of patients (94.7%) had ≥1 treatment-emergent AE (TEAE), and 2 (10.5%) permanently discontinued due to AEs of pneumonitis in the 200-mg cohort (considered pembrolizumab-related by the investigator) and peritonitis and ascites in the 400-mg cohort (neither event was considered related to study treatment; Supplementary Table S1). Overall, 9 (47.4%) patients had a Grade 3 AE, and 6 (31.6%) had a Grade 4 AE. Fifteen deaths occurred during Phase 1b, of which 3 occurred within 30 days of the last dose and were attributable to disease progression. Of the remaining 12 deaths, 9 were due to disease progression and 3 for reasons unknown.

AEs considered to be related to ARRY-382 were reported in 16 (84.2%) patients: 5 (83.3%), 6 (100.0%), and 5 (71.4%) patients in the 200, 300, and 400-mg cohorts, respectively. Corresponding rates of ARRY-382–related grade ≥3 AEs were 50.0%, 100.0%, and 42.9%. One patient (16.7%) in the 300-mg cohort reported a SAE that was considered to be related to ARRY-382: Grade 3 ALT and AST increased. The most frequently reported AEs considered to be related to ARRY-382 treatment were increased AST (42.1%), increased ALT (36.8%), and increased CPK (36.8%; **Table 2**).

AEs considered to be related to pembrolizumab were reported in 12 (63.2%) patients. The most frequently reported AEs were increased AST (36.8%) and increased lipase (26.3%; Supplementary Table S2). AE causality was determined by the Investigator at the time of the event and based on their clinical judgment.

Phase 2

In Phase 2, the majority of patients (>90%) in each cohort had ≥1 TEAE (Supplementary Table S3). Permanent discontinuations due to AEs occurred in 4 (14.8%), 1 (5.3%), and 1 (9.1%) patients in the PDA, PD-1/PD-L1 IR, and prOVCA cohorts, respectively. The AEs were: Ileus and pneumonia in 1 patient, and abdominal pain and ascites in 1 patient, aspiration, and anal fistula in the PDA cohort; somnolence in the PD-1/PD-L1 IR cohort; and autoimmune hepatitis increased AST in 1 patient in the prOVCA cohort. None of the AEs were considered related to study treatment, except the prOVCA cohort, where both events were considered by the investigator to be related to ARRY-382 and pembrolizumab. Overall, 33 (57.9%) patients had a grade 3 AE, 7 (12.3%) patients had a Grade 4 AE, and 3 (5.3%) patients had a grade 5 AE. Deaths occurred in 20 (74.1%), 10 (52.6%), and 5 (45.5%) patients in the PDA, PD-1/PD-L1 IR, and prOVCA cohorts, respectively, mostly due to disease progression. A total of 16 deaths occurred during treatment or within 30 days of the last dose; 3 of these deaths (5.3% of patients) were attributed to fatal AEs (enterocolitis, gastric perforation, and aspiration), and none were considered related to study treatment.

AEs considered to be ARRY-382 related were reported in 43 (75.4%) patients: 17 (63.0%), 17 (89.5%), and 9 (81.8%) in the PDA, PD-1/PD-L1 IR, and prOVCA cohorts, respectively (**Table 3**). Rates of ARRY-382–related SAEs and grade ≥3 AEs were 11.1% and 25.9% in the PDA cohort, 15.8% and 57.9% in the PD-1/PD-L1 IR cohort, and 0.0% and 45.5% in the prOVCA cohort. The most frequent ARRY-382–related AEs were fatigue (33.3%), and increased CPK, nausea, and increased AST (18.5% each) in the PDA cohort. Similarly, the most frequent ARRY-382–related AEs were fatigue (47.4%), increased CPK (47.4%), and nausea (42.1%) in the PD-1/PD-L1 IR cohort. In the prOVCA cohort, the most frequent ARRY-382–related AEs were increased AST (36.4%), increased ALT (36.4%), and increased CPK and pyrexia (18.2% each).

AEs considered to be related to pembrolizumab were reported in 36 (63.2%) patients. The most frequently reported AEs were fatigue and increased AST in the PDA and PD-1/PD-L1 IR cohorts, and increased transaminases in the prOVCA cohort (Supplementary Table S4).

Table 2. Most common ARRY-382–related AEs reported in ≥10% of patients overall: Phase 1b.

n (%)	ARRY-382 200 mg (*N* = 6)	ARRY-382 300 mg (*N* = 6)	ARRY-382 400 mg (*N* = 7)	Total (*N* = 19)
All AEs	5 (83.3)	6 (100.0)	5 (71.4)	16 (84.2)
AST increased	1 (16.7)	5 (83.3)	2 (28.6)	8 (42.1)
ALT increased	2 (33.3)	3 (50.0)	2 (28.6)	7 (36.8)
Blood CPK increased	2 (33.3)	3 (50.0)	2 (28.6)	7 (36.8)
Lipase increased	1 (16.7)	4 (66.7)	1 (14.3)	6 (31.6)
Amylase increased	1 (16.7)	3 (50.0)	1 (14.3)	5 (26.3)
Blood alkaline phosphatase increased	1 (16.7)	2 (33.3)	2 (28.6)	5 (26.3)
Fatigue	2 (33.3)	2 (33.3)	0 (0.0)	4 (21.1)
Pruritus	2 (33.3)	2 (33.3)	0 (0.0)	4 (21.1)
Rash maculo-papular	1 (16.7)	2 (33.3)	1 (14.3)	4 (21.1)
Nausea	0 (0.0)	1 (16.7)	2 (28.6)	3 (15.8)
Chills	1 (16.7)	0 (0.0)	1 (14.3)	2 (10.5)
Pyrexia	1 (16.7)	0 (0.0)	1 (14.3)	2 (10.5)
Thrombocytopenia	0 (0.0)	1 (16.7)	1 (14.3)	2 (10.5)

Note: Safety set.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.

Table 3. Most common ARRY-382–related AEs reported in ≥10% of patients overall: Phase 2.

n (%)	PDA (*N* = 27)	PD-1/PD-L1 IR (*N* = 19)	prOVCA (*N* = 11)	Total (*N* = 57)
All AEs	17 (63.0)	17 (89.5)	9 (81.8)	43 (75.4)
Fatigue	9 (33.3)	9 (47.4)	0 (0.0)	18 (31.6)
Blood CPK increased	5 (18.5)	9 (47.4)	2 (18.2)	16 (28.1)
Nausea	5 (18.5)	8 (42.1)	3 (27.3)	16 (28.1)
AST increased	5 (18.5)	6 (31.6)	4 (36.4)	15 (26.3)
ALT increased	4 (14.8)	2 (10.5)	4 (36.4)	10 (17.5)
Vomiting	2 (7.4)	7 (36.8)	1 (9.1)	10 (17.5)
Diarrhea	4 (14.8)	5 (26.3)	0 (0.0)	9 (15.8)
Decreased appetite	5 (18.5)	3 (15.8)	0 (0.0)	8 (14.0)
Amylase increased	2 (7.4)	4 (21.1)	0 (0.0)	6 (10.5)

Note: Safety set.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; IR, inhibitor refractory; PDA, pancreatic ductal adenocarcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; prOVCA, platinum-resistant ovarian cancer.

Efficacy

Phase 1b

In Phase 1b, both confirmed ORR and confirmed irORR were 10.5% (95% CI, 1.3–33.1; **Table 4**). One patient with MSI-High PDA in the 200-mg cohort had a confirmed PR, with a DOR of 29.2 months. Several genomic alterations were detected in this patient, including those in *AKT2*, *KRAS*, *MTOR*, *PI3KCA*, *FANCC*, *SMARCB1*, and *TP53* genes. Further details on prior therapy were unknown. One patient with ovarian cancer in the 300-mg cohort also had a confirmed PR, with a DOR of 3.1 months. Details on TMB, MSI, and prior therapy were unknown.

Median PFS was 4.7 (95% CI, 1.4–33.1), 2.3 (95% CI, 1.3–5.7), and 1.4 (95% CI, 0.5–2.6) months in the 200, 300, and 400-mg cohorts, respectively. Corresponding median irPFS per irRC was 3.0 (95% CI, 1.4–16.1), 2.5 (95% CI, 1.4–7.1), and 1.3 (95% CI, 0.5–1.5) months. Median OS was 14.7 [95% CI, 5.2–not reached (NR)], 6.5 (95% CI, 1.0–NR), and 7.4 (95% CI, 2.1–14.1) months in the 200, 300, and 400-mg cohorts, respectively.

Phase 2

In Phase 2, the primary endpoint of confirmed ORR, as well as confirmed irORR per irRC, was 3.7% (95% CI, 0.1–19.0) for the PDA cohort (**Table 4**). Confirmed ORR and irORR were 0.0% for each of the PD-1/PD-L1 IR and prOVCA cohorts. One patient (3.7%) in the PDA cohort had a confirmed PR, with a DOR of 2.4 months (**Fig. 1**). This patient was MSI-Stable, TMB-Low, and PD-L1 negative (based on historical data). Stable disease (SD) was the best response observed for patients in the PD-1/PD-L1 IR and prOVCA cohorts: 8 (42.1%) and 4 (36.4%) patients, respectively. In the PDA cohort, 5 patients (18.5%) had SD. Confirmed PD was observed in 7 (25.9%), 9 (47.4%), and 5 (45.5%) patients in the PDA, PD-1/PD-L1 IR, and prOVCA cohorts, respectively.

Table 4. Summary of efficacy endpoints: Phase 1b and Phase 2.

	Phase 1b				Phase 2		
n (%)	ARRY-382 200 mg (*N* = 6)	ARRY-382 300 mg (*N* = 6)	ARRY-382 400 mg (*N* = 7)	Total (*N* = 19)	PDA (*N* = 27)	PD-1/PD-L1 IR (*N* = 19)	prOVCA (*N* = 11)
Best overall response							
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	1 (16.7)	1 (16.7)	0 (0.0)	2 (10.5)	1 (3.7)	0 (0.0)	0 (0.0)
SD	3 (50.0)	2 (33.3)	0 (0.0)	5 (26.3)	5 (18.5)	8 (42.1)	4 (36.4)
PD	1 (16.7)	3 (50.0)	5 (71.4)	9 (47.4)	7 (25.9)	9 (47.4)	5 (45.5)
NE	1 (16.7)	0 (0.0)	2 (28.6)	3 (15.8)	14 (51.9)	2 (10.5)	2 (18.2)
ORR, % (95% CI)	16.7 (0.4–64.1)	16.7 (0.4–64.1)	0.0 (0.0–41.0)	10.5 (1.3–33.1)	3.7 (0.1–19.0)	0.0 (0.0–17.6)	0.0 (0.0–28.5)
Immune-related best overall response							
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	1 (16.7)	1 (16.7)	0 (0.0)	2 (10.5)	1 (3.7)	0 (0.0)	0 (0.0)
SD	3 (50.0)	3 (50.0)	2 (28.6)	8 (42.1)	7 (25.9)	7 (36.8)	6 (54.5)
PD	1 (16.7)	0 (0.0)	1 (14.3)	2 (10.5)	0 (0.0)	1 (5.3)	0 (0.0)
NE	1 (16.7)	2 (33.3)	4 (57.1)	7 (36.8)	19 (70.4)	11 (57.9)	5 (45.5)
ir-ORR, % (95% CI)	16.7 (0.4–64.1)	16.7 (0.4–64.1)	0.0 (0.0–41.0)	10.5 (1.3–33.1)	3.7 (0.1–19.0)	0.0 (0.0–17.6)	0.0 (0.0–28.5)

Note: Full analysis set. Exact 2-sided 95% CI using the Clopper–Pearson method. Tumor assessment was based on investigator assessment. Confirmed best overall response was derived per visit-level overall response.
Abbreviations: CI, confidence interval; CR, complete response; ir, immune-related; IR, inhibitor refractory; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PDA, pancreatic ductal adenocarcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PR, partial response; prOVCA, platinum-resistant ovarian cancer; SD, stable disease.

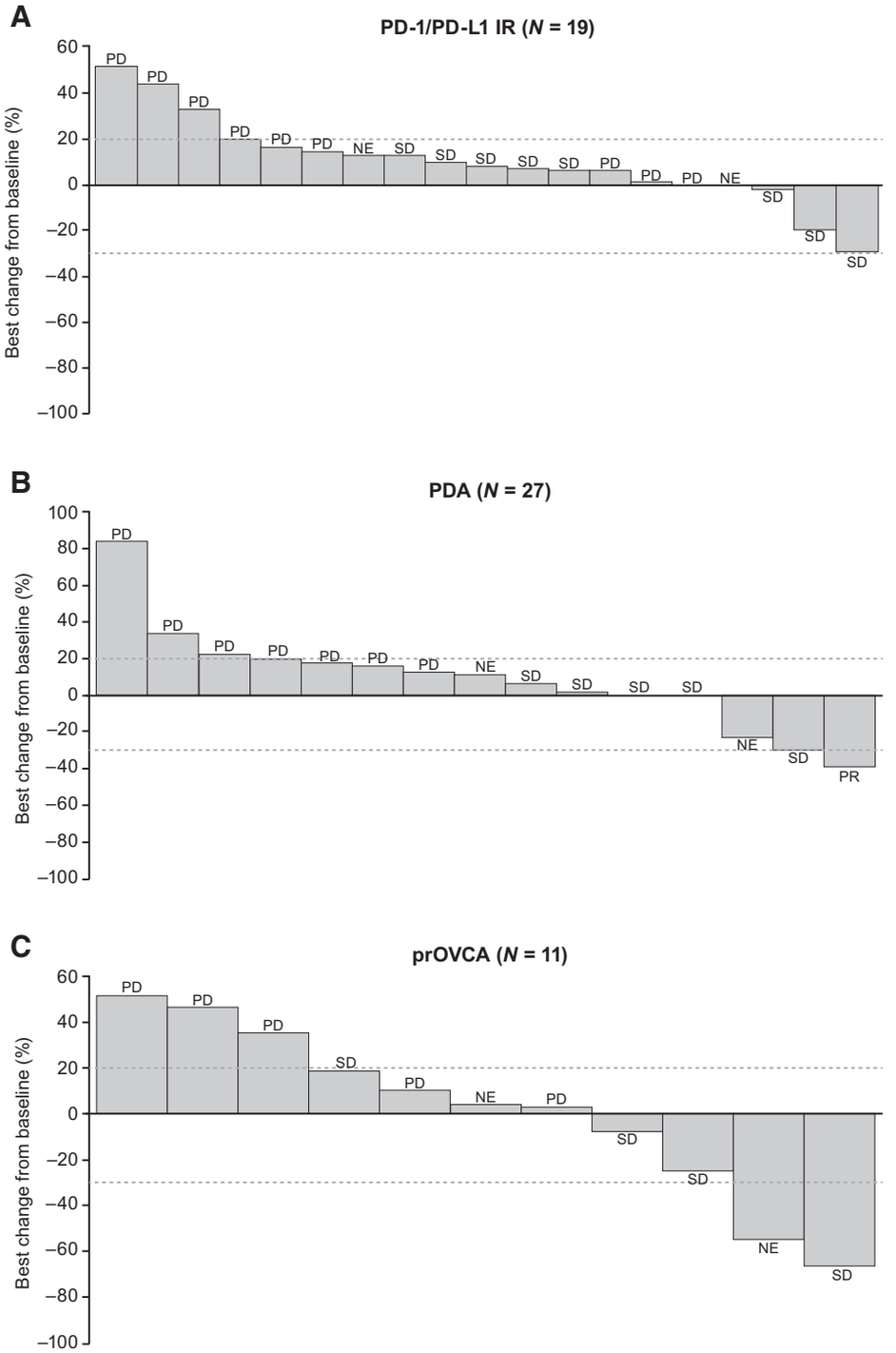

Figure 1.
Best percentage change from baseline in sum of longest diameters in Phase 2. **A,** PDA cohort; **B,** PD-1/PD-L1 IR cohort; **C,** prOVCA cohort.

Median PFS was 1.4 (95% CI, 0.9–2.8), 1.6 (95% CI, 1.3–4.4), and 2.1 (95% CI, 1.2–4.1) months in the PDA, PD-1/PD-L1 IR, and prOVCA cohorts, respectively (Supplementary Fig. S3). Corresponding median irPFS per irRC was 1.3 (95% CI, 0.9–2.7), 1.5 (95% CI, 1.3–4.3), and 2.5 (95% CI, 1.2–NR) months. Median OS was 2.2 (95% CI, 1.5–4.9) months in the PDA cohort, 12.4 (95% CI, 3.6–NR) months in the PD-1/PD-L1 IR cohort, and NR (95% CI, 5.3–NR) months in the prOVCA cohort (Supplementary Fig. S4).

Pharmacokinetics

In Phase 1b, ARRY-382 exposure based on C_{max} and AUC from time 0 to last measurable timepoint (AUC_{last}) increased on day 1 of cycles 1 and 2 with increasing doses (**Table 5**). A similar trend was observed for the exposures of the metabolites (Supplementary Table S5). The exposures of the 3 metabolites were <20% that of the parent compound.

In Phase 2, ARRY-382 exposure based on C_{max} and AUC_{last} on cycle 1 day 1 were similar in all 3 cohorts, and accumulated about

Table 5. Summary of ARRY-382 PK parameters: Phase 1b and Phase 2.

	Phase 1b			Phase 2			
	ARRY-382 200 mg (*N* = 6)	**ARRY-382 300 mg (*N* = 6)**	**ARRY-382 400 mg (*N* = 7)**	**PDA (*N* = 27)**	**PD-1/PD-L1 IR (*N* = 19)**	**prOVCA (*N* = 11)**	**Overall (*N* = 57)**
Cycle 1 day 1							
N	6	6	7	26	18	11	55
AUC_{last}, h·ng/mL	3,720 (44.4)	4,890 (58.8)	6,790 (39.5)	6,350 (70.4)	6,320 (53.2)	6,210 (48.8)	6,310 (59.7)
C_{max}, ng/mL	773 (60.2)	995 (68.9)	1,330 (39.6)	1,290 (75.6)	1,240 (62.1)	1,260 (53.9)	1,270 (65.8)
T_{max}, h	2.00 (1.00–7.95)	4.01 (1.25–4.05)	4.07 (0.98–8.00)	2.00 (0.97–8.00)	1.97 (0.95–4.17)	2.00 (1.00–4.10)	2.00 (0.95–8.00)
Cycle 2 day 1							
N	4	4	3	4	6	5	15
AUC_{last}, h·ng/mL	22,800 (44.2)	30,600 (26.6)	30,800 (130)	47,100 (10.2)	26,600 (80.3)	20,700 (70.6)	28,500 (70.8)
AUC_{tau}, h·ng/mL	22,800 (44.2)	30,600 (26.6)	30,800 (130)	47,100 (10.2)	32,100 (65.7)	20,700 (70.6)	30,600 (65.2)
C_{max}, ng/mL	1,560 (41.3)	2,260 (36.6)	2,560 (117)	2,820 (15.1)	2,130 (60.4)	1,580 (64.8)	2,080 (55.7)
C_{trough}, ng/mL	576 (59.5)	667 (27.7)	627 (126)	1,480 (17.5)	878 (70.1)	438 (86.5)	796 (86.9)
RAUC[a]	3.03 (47.9)	1.92 (NC)	3.52 (NC)	3.41 (23.6)	2.67 (36.2)	1.87 (16.7)	2.49 (35.6)
RC_{max}	2.53 (48.2)	2.51 (95.7)	2.28 (54.2)	2.07 (53.6)	2.52 (39.9)	1.62 (24.7)	2.06 (41.9)
T_{max}, h	2.00 (2.00–7.95)	4.18 (1.85–7.48)	1.98 (1.97–2.00)	3.03 (2.00–4.08)	2.00 (1.00–7.50)	2.00 (1.83–4.17)	2.00 (1.00–7.50)

Note: PK Set. Geometric mean (geometric %CV) reported for all except median (range) for T_{max}.
Abbreviations: AUC_{last}, area under the concentration–time curve from zero to the last measurable time point; AUC_{tau}, area under the plasma concentration–time curve over the dosing interval; C_{max}, maximum observed concentration; C_{trough}, pre-dose concentration; CV, coefficient of variation; IR, inhibitor refractory; NC, not calculated; PDA, pancreatic ductal adenocarcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PK, pharmacokinetic; prOVCA, platinum-resistant ovarian cancer; R, accumulation ratio; T_{max}, time to C_{max}.
[a]n = 3, 2, and 2 for 200-, 300-, and 400-mg cohorts, respectively; n = 3, 3, and 4 for PDA, PD-1/PD-L1 IR, and prOVCA cohorts, respectively.

2- to 3-fold on cycle 2 day 1 (**Table 5**). ARRY-382 metabolite exposures were <20% of the parent compound on day 1 of cycles 1 and 2 across the 3 cohorts, except for the exposures of the AR00469099 metabolite in the PD-1/PD-L1 IR and PDA cohorts on cycle 2 day 1, and the exposure of the AR00470870 metabolite in the prOVCA cohort on cycle 2 day 1 (Supplementary Table S5). Plasma concentration–time profiles for ARRY-382 and metabolites across the Phase 1b and 2 studies are shown in Supplementary Fig. S5.

Pharmacodynamics

In the Phase 1b portion, mean serum CSF-1 increased 4.5-fold on cycle 1 day 15 versus cycle 1 day 1 ($P < 0.05$). There were no changes in mean CTX or NTX on cycle 1 day 15 compared with cycle 1 day 1. This is likely due to the small number of patients treated in Phase 1b.

Across cohorts in Phase 2, mean serum CSF-1 increased 6.7-fold on cycle 1 day 15 versus cycle 1 day 1 ($P < 0.05$). In addition, mean serum osteoprotegerin (OPG) increased 1.5-fold on cycle 1 day 15 compared with cycle 1 day 1 ($P < 0.001$). Overall, mean NCM decreased by 70% on cycle 1 day 15 versus cycle 1 day 1 ($P < 0.05$). There were no significant changes in mean CTX or NTX on cycle 1 day 15 compared with cycle 1 day 1.

Corresponding to the biomarker analysis, the correlation of trough concentrations of ARRY-382 with a percentage of change of biomarker levels from the baseline at cycle 1 day 1 (CSF-1, CTX, NCM, NTX, and OPG) were evaluated in the pooled patients of Phase 1b Part A and Phase 2. Higher levels of NCM were generally associated with lower trough concentrations of ARRY-382, whereas higher levels of circulating CSF-1 and OPG were associated with higher trough concentrations of ARRY-382. No obvious relationships were observed between trough concentrations of ARRY-382 with the percentage of changes of circulating CTX or NTX.

Discussion

In Phase 1b, the MTD/RP2D of the selective CSF-1R inhibitor, ARRY-382, in combination with pembrolizumab was determined to be 300 mg QD. This was based on reported DLTs in 2 patients at the 400-mg QD dose and in 1 patient at the 300-mg QD dose. Pancreatitis was the only DLT not previously identified in the safety profile of ARRY-382; however, increased amylase and lipase were reported with ARRY-382. Pancreatitis is a known toxicity during pembrolizumab treatment.

Overall, the most common TEAEs included fatigue, pyrexia, nausea, vomiting, and increase in AST, ALT, and blood CPK. These events are consistent with the known safety profiles of ARRY-382, pembrolizumab, or the underlying disease, or were isolated events (3, 4, 9, 14). The TEAEs observed in the current study are in line with the safety profiles of CSF-1 pathway inhibitors (both small molecules and monoclonal antibodies; refs. 14, 15), as well as the TEAEs reported in other clinical trials investigating CSF-1 pathway-targeting agents in combination with immune checkpoint inhibitors (10–13, 16). In particular, transaminase elevations are believed to be a class effect of CSF-1 pathway-targeting agents and are thought to occur as a result of Kupffer cell depletion or senescence within the liver (15). Increased ALT and AST have also been reported with pembrolizumab—both as monotherapy and in combination with other medications (3, 4). Periorbital edema has been reported during treatment with CSF-1R–targeting antibodies; data from the current study are consistent with this finding, with periorbital edema occurring in <10% of patients overall in both the Phase 1b (5.3%) and Phase 2 portions (7.0%; ref. 15).

Preliminary clinical activity was observed during the Phase 1b study, with a confirmed ORR of 10.5%. PRs were observed in 1 patient with MSI-High PDA in the 200-mg cohort (DOR 29.2 months) and 1 patient with ovarian cancer in the 300-mg cohort (DOR 3.1 months). Although no patients with TMB-High pancreatic cancer were treated with pembrolizumab in KEYNOTE-158, a recent retrospective study

in Japanese patients reported an ORR of 4% in patients with TMB-High pancreatic cancer treated with anti–PD-1/PD-L1 therapy (17). In the Phase 2 portion, patients received ARRY-382 300-mg QD with pembrolizumab 200-mg Q3W. No confirmed objective responses were observed in the PD-1/PD-L1 IR and prOVCA cohorts, but 1 patient in the PDA cohort had a PR; this patient was MSI-Stable, TMB-Low, and PD-L1 negative. Given the lack of genomic instability, low mutational burden, absence of PD-L1 staining, and the limited clinical activity of immune checkpoint inhibitor therapy in patients with pancreatic cancer, the pathophysiology for this patient's tumor response is not clear, although the DOR was limited (2.4 months; refs. 18, 19). Median PFS ranged from 1.4 to 2.1 months across cohorts in Phase 2, whereas median OS ranged from 2.2 to NR months. No patients in the Phase 2 portion had a mutation in CSF-1R.

The results from the current study are consistent with other combination studies evaluating CSF-1 pathway inhibitors and suggest that although some antitumor activity has been observed, it is unclear if the efficacy of the combination is greater than that expected for single-agent immune checkpoint inhibitors. In a Phase 1 study of cabiralizumab, a CSF-1R–targeting antibody, plus nivolumab (anti–PD-1) in pancreatic cancer ($N = 31$), 3 patients who were MSI-Stable had a PR (16). However, the Phase 2 trial (NCT03336216) failed to meet its primary endpoint and the combination is no longer under investigation. Another CSF-1R–targeting antibody, AMG 820, was evaluated in combination with pembrolizumab in a Phase 1b/2 study in patients with advanced solid tumors. Two patients with metastatic colorectal cancer (MMR-proficient) had an irPR and 1 patient with NSCLC (low PD-L1 expression) had an irPR; however, none of the Phase 2 cohorts met the predefined efficacy threshold and the combination is no longer under evaluation (10). In a Phase 1 study in patients with advanced/metastatic PDA or colorectal cancer, 4 patients had stable disease following treatment with the multikinase inhibitor, pexidartinib (targets CSF1-R, cKIT, and FLT3), plus durvalumab (anti–PD-L1; ref. 11). The anti–PD-1 agent, spartalizumab, has been investigated in 2 Phase 1/2 clinical trials in combination with CSF-1 pathway inhibitors (12, 13). One patient with HNSCC and 2 patients with relapsed/refractory glioblastoma had a PR when treated with BLZ945, a brain-penetrant CSF-1R kinase inhibitor, plus spartalizumab (12). One patient with pancreatic cancer had a PR following treatment with lacnotuzumab, a CSF-1–targeting monoclonal antibody, plus spartalizumab (13). A number of trials investigating CSF-1 pathway inhibitors in combination with anti–PD-1/PD-L1 therapies (or other immune checkpoint inhibitors) are ongoing (15).

Although modest antitumor activity was observed in the current study and in studies of other combination regimens, there are several possible reasons why the response rates were lower than expected. Across cohorts, the majority of patients in this study had received ≥2 prior therapies and/or were relapsed/refractory to previous treatments; therefore, it is difficult to evaluate response, and response evaluation should ideally be performed in Phase 2 tumor type-specific studies. Prior therapies could also have had an impact on alterations in the tumor microenvironment and/or promoted the development of cancer cell populations with resistance to CSF-1 pathway blockade. The current trial aimed to investigate whether the addition of CSF-1R inhibitor could re-invigorate the immune system in patients who had been previously treated with anti–PD-1/PD-L1 or activate the primary antitumor immune response in patients with traditionally "less sensitive" tumors. Therefore, it is possible that this combination strategy was insufficient to overcome exhausted T cells and/or deplete immunologically "cold" tumors of TAMs and MDSCs.

In Phase 1b, the exposure of ARRY-382 and metabolites increased with increasing doses, with metabolite exposures <20% of the parent compound. In Phase 2, ARRY-382 exposure was similar across the 3 cohorts on cycle 1 day 1 and accumulated about 2- to 3-fold on cycle 2 day 1. Serum CSF-1 increased with ARRY-382 plus pembrolizumab, indicating inhibition by ARRY-382 of CSF-1R (consistent with previous studies) and CSF-1R kinase (9, 20). Decreased peripheral NCM with the combination therapy is also consistent with CSF-1R inhibition and resulting downstream effects of CSF-1R inhibition on macrophage cellular maturation (9). However, there was no significant correlation between trough concentrations of ARRY-382 and the percentage of changes of circulating CTX or NTX osteoclast bone resorption markers upon treatment with ARRY-382 plus pembrolizumab; based on previous results with ARRY-382 monotherapy, it was expected that both biomarkers would decrease (9). Therefore, although the observed effects on CSF-1 and NCM levels indicate robust CSF-1R target downmodulation by ARRY-382, it is possible that combination treatment with pembrolizumab may be altering downstream processes in a different manner to ARRY-382 monotherapy.

Conclusion

In this 2-part Phase 1b/2 study, the selective CSF-1R inhibitor, ARRY-382, was combined with the anti–PD-1 agent, pembrolizumab. The MTD and RP2D of ARRY-382 plus pembrolizumab were determined to be 300 mg QD. ARRY-382 and ARRY-382 metabolites exposures increased in a dose-dependent manner. The safety profile of ARRY-382 plus pembrolizumab was generally tolerable, manageable, and consistent with the known safety profiles of ARRY-382 and single-agent pembrolizumab. Despite on-target modulation of CSF-1R activity by ARRY-382, as evidenced by increased serum CSF-1 and decreased peripheral NCM, limited clinical benefit was observed. Confirmed PRs were observed in 2 patients (1 MSI-High PDA; 1 ovarian cancer) in the dose-escalation portion and 1 patient (MSI-Stable, TMB-Low, and PD-L1 negative) in the Phase 2 PDA cohort. No confirmed responses were observed in the Phase 2 PD-1/PD-L1 IR or prOVCA cohorts. No further evaluation of these drugs in combination is planned.

Authors' Disclosures

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Authors' Contributions

M. Johnson: Conceptualization, writing–original draft, writing–review and editing. **A.Z. Dudek:** Conceptualization, writing–original draft, writing–review and editing. **A. Sukari:** Conceptualization, writing–original draft, writing–review and editing. **J. Call:** Conceptualization, writing–original draft, writing–review and editing. **P.R. Kunk:** Conceptualization, writing–original draft, writing–review and editing. **K. Lewis:** Conceptualization, writing–original draft, writing–review and editing. **J.F. Gainor:** Conceptualization, writing–original draft, writing–review and editing. **J. Sarantopoulos:** Conceptualization, writing–original draft, writing–review and editing. **P. Lee:** Writing–original draft, writing–review and editing. **A. Golden:** Conceptualization, writing–original draft, writing–review and editing. **A. Harney:** Conceptualization, writing–original draft, writing–review and editing. **S.M. Rothenberg:** Conceptualization, writing–original draft, writing–review and editing. **Y. Zhang:** Conceptualization, writing–original draft, writing–review and editing. **J.W. Goldman:** Conceptualization, writing–original draft, writing–review and editing.

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