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A Phase 1b/2 Dose-Escalation Study of ARRY-382, an Oral Inhibitor of Colony-Stimulating Factor-1 Receptor, in Combination With Pembrolizumab for the Treatment of Patients With Advanced Solid Tumors

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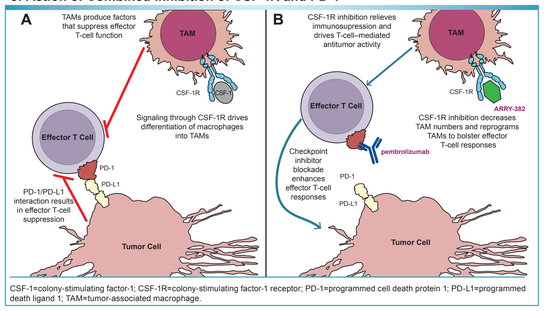
Presented at the 32nd Annual Meeting of the Society for Immunotherapy of Cancer • November 8–12, 2017 • National Harbor, MD, USA

INTRODUCTION

- Tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells are critical modulators of immune response in the tumor microenvironment.[1]
- Colony-stimulating factor-1 receptor (CSF-1R) signaling drives recruitment and differentiation of TAMs, which in turn enables tumor progression by suppressing antitumor immune responses, promoting angiogenesis, and facilitating tumor cell metastasis.[2,3]
- Inhibition of CSF-1R signaling reduces the number of TAMs and alters their function, alleviating immunosuppression, enhancing antigen presentation, and inducing antitumor T-cell responses.[4]
- CSF-1R inhibition also upregulates molecules associated with T-cell checkpoint signaling, which act as negative regulators of T-cell activity and cytokine production.[4,5]
- Preclinical studies have shown that combined CSF-1R inhibition and immune checkpoint blockade enhances antitumor activity, providing a rationale for testing combined inhibition in clinical studies **(Figure 1)**.[2]
  - The combination of CSF-1R inhibition with agents that block cell surface molecules responsible for checkpoint inhibition (programmed cell death protein 1 [PD-1] and cytotoxic T-lymphocyte–associated protein 4) reduced tumor progression by >90% and reduced established tumors by 15% in pancreatic cancer models.[4]

Figure 1. (A) Immunosuppressive Tumor Microenvironment; (B) Putative Mechanism of Action of Combined Inhibition of CSF-1R and PD-1[4]



CSF-1=colony-stimulating factor-1; CSF-1R=colony-stimulating factor-1 receptor; PD-1=programmed cell death protein 1; PD-L1=programmed death ligand 1; TAM=tumor-associated macrophage.

- The PD-1–blocking antibody pembrolizumab is approved for the treatment of multiple tumor types[6]; however, the majority of patients do not respond to treatment.[7]
- ARRY-382 is a highly selective oral inhibitor of the CSF-1R intracellular tyrosine kinase.[8]
- The maximum tolerated dose (MTD) of ARRY-382, as monotherapy, is 400 mg once daily (QD). Pharmacodynamic effects on circulating nonclassical monocytes were seen at ARRAY-382 doses ≥200 mg QD.[8]
  - Reductions in nonclassical monocytes of 65%, 96%, and 85% were seen at doses of 200-mg, 400-mg, and 500-mg QD, respectively.
- Here, we describe the initial findings from a phase 1b/2 study assessing ARRY-382 in combination with pembrolizumab in patients with advanced solid tumors.

OBJECTIVE

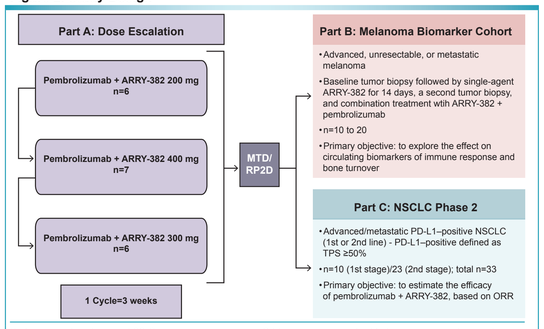
- The objective of the phase 1b portion of the study (Part A) is to determine the MTD and/or recommended phase 2 dose (RP2D) of ARRY-382 in combination with intravenous pembrolizumab 2 mg/kg every 3 weeks, based on the incidence of dose-limiting toxicities (DLTs).

METHODS

Study Design

- This is a 3-part, open-label, multicenter study (NCT02880371; **Figure 2**).
- Part A (phase 1b) included a dose-escalation component with 2 planned dose cohorts (intravenous pembrolizumab 2 mg/kg every 3 weeks with oral ARRY-382 200 mg QD and intravenous pembrolizumab 2 mg/kg every 3 weeks with oral ARRY-382 400 mg QD) and the potential for a third planned cohort.
- A third cohort was enrolled with pembrolizumab 2 mg/kg every 3 weeks and an intermediate dose of ARRY-382 of 300 mg QD, based on the results from the first 2 dose cohorts.
- Following the determination of RP2D/MTD, Parts B and C will enroll patients with advanced/metastatic melanoma and non–small cell lung cancer (NSCLC), respectively.

Figure 2. Study Design



MTD=maximum tolerated dose; NSCLC=non–small cell lung cancer; ORR=overall response rate; PD-L1=programmed death ligand 1; RP2D=recommended phase 2 dose; TPS=tumor proportion score.

Key Eligibility Criteria in Part A

- Adult patients with confirmed diagnosis of the following disorders:
  - Bladder cancer, head and neck squamous cell cancer, ovarian cancer, triple-negative breast cancer, gastric cancer, metastatic colorectal cancer, or pancreatic ductal adenocarcinoma, refractory to standard of care, with no standard therapy available or for which the patient refused standard therapy
  - Advanced, unresectable, or metastatic melanoma with or without prior treatment
  - Advanced/metastatic PD-L1–positive NSCLC meeting any of the following criteria:
    - Tumors without *EGFR* or *ALK* genomic aberrations in patients who had received no prior systemic chemotherapy or had disease progression on or after platinum-containing chemotherapy
    - Tumors with *EGFR* or *ALK* genomic aberrations in patients with disease progression on a US Food and Drug Administration–approved therapy for *EGFR* or *ALK* genomic tumor aberrations
- Patients who received prior immune checkpoint inhibitor treatment were excluded.

Assessments

- DLTs were determined using standard definitions.
- Adverse events (AEs) and serious AEs were collected to analyze the safety and tolerability of treatment.
- Blood samples for plasma pharmacokinetic (PK) analysis for ARRY-382 and its metabolites were drawn predose and at specified time points predose (trough) and postdose (1, 2, 4, and 8 hours after administration of ARRY-382) on cycle 1 day 1 and cycle 2 day 1.
- Blood samples for pharmacodynamic analysis of circulating biomarkers, including CSF-1, were collected on days 1, 8, and 15 of cycle 1 and on day 1 of all subsequent cycles.
- Preliminary antitumor activity was analyzed using the following methods:
  - Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1: investigator-determined overall response rate (ORR)
  - Immune-related response criteria (irRC)[9]: investigator-determined immune-related response rate

RESULTS

Patients

- Overall, 19 patients were treated in Part A **(Table 1)**.
  - 53% of patients were male, 63% had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (the remaining patients were ECOG PS 1), and the most common tumor type was pancreatic ductal adenocarcinoma (6 patients; 32%).
  - Patients had received a median of 2 (range, 0–5) prior regimens of systemic treatment; 42% had received ≥3 prior regimens of systemic treatment.

Table 1. Demographic and Clinical Characteristics at Baseline

	ARRY-382 200 mg + Pembrolizumab (n=6)	ARRY-382 400 mg + Pembrolizumab (n=7)	ARRY-382 300 mg + Pembrolizumab (n=6)	All Patients (N=19)
Median (range) age, y	66 (42–77)	51 (40–76)	43 (32–61)	59 (32–77)
Male, n (%)	4 (67)	3 (43)	3 (50)	10 (53)
ECOG PS, n (%)				
0	5 (83)	2 (29)	5 (83)	12 (63)
1	1 (17)	5 (71)	1 (17)	7 (37)
Initial diagnosis, n (%)				
Gastric cancer	1 (17)	1 (14)	0	2 (11)
Melanoma	0	1 (14)	1 (17)	2 (11)
Metastatic colorectal cancer	2 (33)	2 (29)	1 (17)	5 (26)
Ovarian cancer	1 (17)	0	2 (33)	3 (16)
Pancreatic ductal adenocarcinoma	2 (33)	2 (29)	2 (33)	6 (32)
Triple-negative breast cancer	0	1 (14)	0	1 (5)
Number of previous systemic regimens, n (%)				
0	0	1 (14)	1 (17)	2 (11)
1	1 (17)	1 (14)	0	2 (11)
2	4 (67)	1 (14)	2 (33)	7 (37)
≥3	1 (17)	4 (57)	3 (50)	8 (42)

ECOG PS=Eastern Cooperative Oncology Group performance status.

- 6 patients were enrolled in the ARRY-382 200-mg cohort. No DLTs occurred, and the study proceeded with the ARRY-382 400-mg cohort.
- 2 of 7 patients in the ARRY-382 400-mg cohort experienced a DLT; therefore, an intermediate dose cohort (300 mg) was enrolled (n=6).
- Of the treated patients, 3 (16%) were still on treatment and 16 discontinued treatment as of the data cutoff of September 11, 2017 **(Table 2)**.

Table 2. Patient Disposition

	ARRY-382 200 mg + Pembrolizumab (n=6)	ARRY-382 400 mg + Pembrolizumab (n=7)	ARRY-382 300 mg + Pembrolizumab (n=6)	All Patients (N=19)
Treatment ongoing	1 (17)	0	2 (33)	3 (16)
Treatment discontinued	5 (83)	7 (100)	4 (67)	16 (84)
Primary reason for treatment discontinuation				
Changes in patient condition or development	0	1 (14)	0	1 (5)*
Unacceptable AEs or failure to tolerate study drug	1 (17)	0	0	1 (5)†
Withdrawal of consent	0	1 (14)	0	1 (5)
Progressive disease	4 (67)	5 (71)	4 (67)	13 (68)

AE=adverse event.
*Progression of underlying disease resulting in death, as noted below.
†Pneumonitis, as noted below.

Dose-Limiting Toxicities

- 2 patients in the ARRY-382 400-mg dose cohort experienced DLTs.
  - 1 patient experienced a grade 3 creatine phosphokinase (CK) increase lasting >7 days.
    - The patient remained on study on a reduced ARRY-382 dose.
  - 1 patient experienced grade 3 alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin increases.
    - The patient remained on study on a reduced ARRY-382 dose.
- 1 patient in the ARRY-382 300-mg dose cohort had a DLT of grade 3 acute pancreatitis.
  - The patient remained on study on a reduced ARRY-382 dose.

Adverse Events

- The most common all-grade AEs were increased laboratory values (AST, CK, ALT, alkaline phosphatase [ALP], lipase, amylase), fatigue, pyrexia, and nausea **(Table 3)**.
- The most common grade 3/4 events (>10%) were increased AST, increased CK, rash, lipase increased, increased ALP, increased ALT, and anemia **(Table 3)**. All of these events were grade 3, with the exception of one grade 4 event of increased blood CK.
  - There were 5 patients with grade 3 AST elevation.
    - 3 of these patients had hepatic metastases at baseline.
    - Grade 3 elevation occurred once each in 4 patients. In 1 patient, grade 3 elevation resolved following interruption of ARRY-382 and recurred a second time; the second occurrence resolved with a drug reduction.
  - AST and CK elevations resolved in all patients following interruption of ARRY-382.
    - Dose reduction was required in 2 patients with AST elevation.
    - Dose reduction was required in 3 patients with CK elevation.

Table 3. Percentage of Patients With Treatment-Emergent Adverse Events Regardless of Causality by Preferred Term (≥15% of All Patients)

	ARRY-382 200 mg + Pembrolizumab (n=6)		ARRY-382 400 mg + Pembrolizumab (n=7)		ARRY-382 300 mg + Pembrolizumab (n=6)		All Patients (N=19)	
	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Any adverse event	6 (100)	4 (67)	6 (86)	5 (71)	6 (100)	6 (100)	18 (95)	15 (79)
AST increased	2 (33)	1 (17)	5 (71)	2 (29)	6 (100)	2 (33)	13 (68)	5 (26)*
Blood creatine phosphokinase increased	2 (33)	0	3 (43)	1 (14)	3 (50)	2 (33)	8 (42)	3 (16)
ALT increased	1 (17)	0	3 (43)	1 (14)	3 (50)	1 (17)	7 (37)	2 (11)*
Blood alkaline phosphatase increased	1 (17)	1 (17)	4 (57)	1 (14)	2 (33)	0	7 (37)	2 (11)*
Fatigue	2 (33)	0	3 (43)	0	2 (33)	1 (17)	7 (37)	1 (5)*
Pyrexia	2 (33)	0	3 (43)	0	2 (33)	0	7 (37)	0
Lipase increased	1 (17)	0	1 (14)	0	4 (67)	3 (50)	6 (32)	3 (16)*
Amylase increased	1 (17)	0	1 (14)	0	3 (50)	0	5 (26)	0
Nausea	1 (17)	0	3 (43)	1 (14)	1 (17)	0	5 (26)	1 (5)*
Anemia	1 (17)	1 (17)	3 (43)	1 (14)	0	0	4 (21)	2 (11)
Rash	1 (17)	1 (17)	1 (14)	1 (14)	2 (33)	1 (17)	4 (21)	3 (16)*
Chills	2 (33)	0	1 (14)	0	0	0	3 (16)	0
Dry mouth	2 (33)	0	0	0	1 (17)	0	3 (16)	0
Headache	1 (17)	0	1 (14)	0	1 (17)	0	3 (16)	0
Pruritus	2 (33)	1 (17)	0	0	1 (17)	0	3 (16)	1 (5)*
Thrombocytopenia	0	0	2 (29)	0	1 (17)	0	3 (16)	0
Vomiting	1 (17)	0	1 (14)	1 (14)	1 (17)	0	3 (16)	1 (5)*

ALT=alanine aminotransferase; AST=aspartate aminotransferase.
*No grade 4 events were reported.

- AST and CK increases may also be caused by on-target effects of CSF-1R inhibition in macrophages and Kupffer cells.[10]
- Immune-related AEs, as classified by the investigators, were identified in 5 patients **(Table 4)**.

Table 4. Immune-Related Adverse Events

Patient (Dose Cohort)	Grade	Cycle and Day of Onset	Recovered/Resolved
Pt 1 (ARRY-382 200 mg)			
Hypothyroidism	1	C2D1	No/No
Pt 2 (ARRY-382 300 mg)			
Rash	3	C1D12	Yes/Yes with sequelae
Pt 3 (ARRY-382 300 mg)			
Generalized joint pain	1	C1D1	Yes/Yes
Rash	2	C2D1	Yes/Yes
AST increased	3	C2D7	Yes/Yes
ALP increased	2	C2D7	Yes/Yes
Pt 4 (ARRY-382 300 mg)			
Amylase increased	1	C1D13	Yes/Yes
Lipase increased	1	C1D13	Yes/Yes
AST increased	1	C3D15	Yes/Yes
CK elevation	4	C3D15	Yes/Yes
Thyroiditis	1	C5D1	Yes/Yes
Pt 5 (ARRY-382 400 mg)			
Hot flashes	1	C1D2	No/No

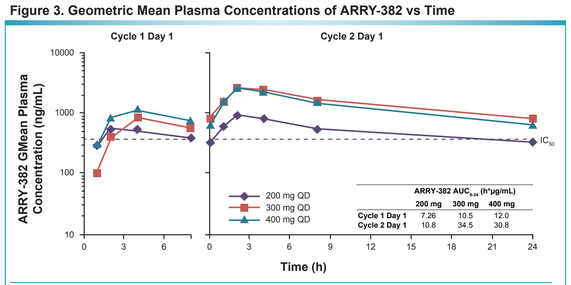
ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; C=cycle; CK=creatine phosphokinase; D=day

- 1 patient in the ARRY-382 200-mg cohort with stage IIIA ovarian cancer discontinued treatment because of an AE of pneumonitis with onset in cycle 4 (approximately 3 months after starting therapy). The patient had not received previous radiation therapy and had no known lung metastasis.
- There were 3 on-study deaths (on treatment or within 30 days of last dose); cause of death was disease progression in all cases.
  - 1 patient with stage IV metastatic colorectal cancer treated in the ARRY-382 300-mg cohort was discontinued in cycle 3 because of disease progression.
  - 1 patient with stage IV gastric cancer treated in the ARRY-382 400-mg cohort completed 2 cycles of therapy and was discontinued for disease progression.
  - 1 patient with stage IV pancreatic cancer treated in the ARRY-382 400-mg cohort completed 14 days of dosing and was discontinued because of changes in the patient's condition determined by the investigator to be due to disease progression.
- Dose reductions occurred in 3 patients in the ARRY-382 300-mg cohort.
  - 2 patients had a dose reduction from ARRY-382 300 mg to 200 mg in cycle 2 (one due to grade 3 pancreatitis and one due to grade 3 rash); one of these patients had a further dose reduction to ARRY-382 100 mg in cycle 6 due to increased CK.
  - The third patient had a dose reduction in cycle 4 (due to grade 3 CK increase) and had a further dose reduction to 100 mg in cycle 8 due to a recurrence of increased CK.

Pharmacokinetics/Pharmacodynamics

- There was no evidence of any PK interactions between ARRY-382 and pembrolizumab.
- ARRY-382 exposures were generally dose-proportional **(Figure 3)**.
- Mean plasma concentrations of ARRY-382 were ≥790 ng/mL over the full dosing interval following repeat dosing of ≥300 mg QD (cycle 2 day 1 minimum drug concentration [C_{min}]).
  - The half-maximal inhibitory concentration (IC_{50}) of CSF-1R by ARRY-382 was 0.38 µg/mL,[11] determined using an ex vivo cell assay in which ARRY-382 inhibited CSF-1–mediated phosphorylation of extracellular signal-regulated kinase (ERK) in monocytes.
- The mean ARRY-382 C_{min} was greater than the IC_{50} with the 300-mg QD regimen, which suggested that continual target engagement is achievable **(Figure 3)**.

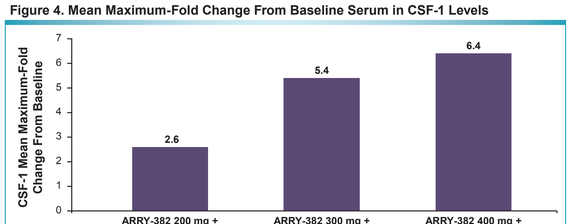
Figure 3. Geometric Mean Plasma Concentrations of ARRY-382 vs Time



AUC_{0-24}=area under the plasma concentration-time curve over the dosing interval of 0–24 hours; GMean=geometric mean; IC_{50}= half-maximal inhibitory concentration; QD=once daily.

- Treatment with ARRY-382 300 mg QD resulted in an average maximum 5.4-fold increase in CSF-1 levels from baseline **(Figure 4)**.

Figure 4. Mean Maximum-Fold Change From Baseline Serum in CSF-1 Levels



CSF-1=colony-stimulating factor-1.

Efficacy

- Best overall response and the objective response rate as measured via RECIST v1.1 and irRC are summarized in **Table 5**.

Table 5. Investigator-Determined Confirmed Response by RECIST v1.1 and by irRC

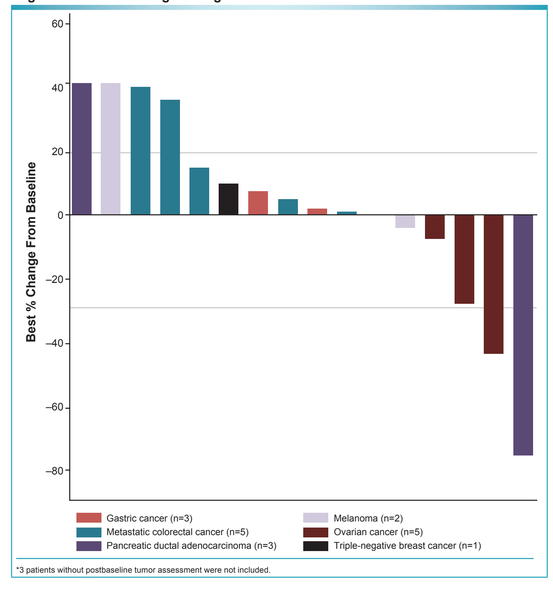
	All Patients (N=19)	
	RECIST v1.1	irRC
Best overall response, n (%)		
Complete response	0	0
Partial response*	2 (11)	2 (11)
Stable disease	5 (26)	9 (47)
Progressive disease	9 (47)	1 (5)
Unevaluable	3 (16)	7 (37)
Objective response rate,† n (%)	2 (11)	2 (11)

irRC=immune-related response criteria; RECIST=Response Evaluation Criteria in Solid Tumors.
*2 patients (1 in the ARRY-382 200-mg cohort and 1 in the ARRY-382 300-mg cohort) achieved partial response by both RECIST and irRC criteria.
†Objective response rate = complete response + partial response.

RESULTS (continued)

- 2 patients achieved a partial response by both RECIST and irRC.
  - 1 patient treated with ARRY-382 200 mg had stage III pancreatic ductal adenocarcinoma that had previously been treated with gemcitabine and paclitaxel in the neoadjuvant setting and FOLFOXIRI and FOLFOX in the adjuvant setting. The patient remains on study treatment in cycle 14.
  - 1 patient treated with ARRY-382 300 mg had stage IV ovarian cancer with liver metastasis and had previously been treated with paclitaxel, gemcitabine, carboplatin, cisplatin, and doxorubicin in the neoadjuvant setting. The patient remains on study treatment in cycle 8.
- In the ARRY-382 300-mg cohort, stable disease was achieved by 2 patients (33%) per RECIST and 3 patients (50%) per irRC.
- Best percentage change from baseline in tumor measurement is illustrated in **Figure 5**.

Figure 5. Best Percentage Change From Baseline*



*3 patients without postbaseline tumor assessment were not included.

CONCLUSIONS

- A total of 19 patients with various tumor types were treated
  - Patients were heavily pretreated, with 42% having received ≥3 prior systemic regimens.
- The RP2D of ARRY-382 administered continuously on a daily basis is 300 mg QD in combination with pembrolizumab 2 mg/kg given intravenously every 3 weeks.
- ARRY-382 plus pembrolizumab has a manageable safety profile.
  - The most common AEs of any grade, regardless of relationship to study drug, were increased laboratory values (AST, ALT, CK, ALP, lipase, and amylase), fatigue, pyrexia, and nausea.
  - Grade 3 elevations of AST and CK were observed and were reversible following ARRY-382 dose interruption and, in some cases, dose reductions.
  - Immune-related AEs (regardless of relationship to study drug) were observed and were manageable.
- ARRY-382 PK: at the 300-mg dose, exposure continually exceeded the IC_{50} for CSF-1R inhibition in cell-based assays.
  - Exposure at cycle 2 day 1 was similar in the 300-mg and 400-mg dose cohorts.
- Increases from baseline in CSF-1 levels were correlated with increasing ARRY-382 exposure.
  - The average maximum increase in CSF-1 levels from baseline was similar in the 300-mg and 400-mg cohorts.
- 11% (n=2) of patients had a partial response and 26% (n=5) and 47% (n=9) had stable disease (by RECIST v1.1 and irRC, respectively).
  - Partial response occurred in a patient with pancreatic ductal adenocarcinoma (ARRY-382 200-mg cohort; currently in cycle 14) and a patient with ovarian cancer (ARRY-382 300-mg cohort; currently in cycle 8).
- ARRY-382 300-mg QD plus pembrolizumab 2 mg/kg every 3 weeks is currently being evaluated in Parts B and C of the study in patients with melanoma and NSCLC, respectively.

REFERENCES

1. Pollard JW. *Nat Rev Immunol.* 2009;9(4):259-270.
2. Hao NB, et al. *Clin Dev Immunol.* 2012;2012:948098.
3. Qian BZ and Pollard JW. *Cell.* 2010;141(1):39-51.
4. Zhu Y, et al. *Cancer Res.* 2014;74(18):5057-5069.
5. Postow MA, et al. *J Clin Oncol.* 2015;33(17):1974-1982.
6. KEYTRUDA (pembrolizumab). Full Prescribing Information. Merck Sharp & Dohme Corp., Whitehouse Station, NJ, 2017.
7. Sharma P, et al. *Cell.* 2017;168(4):707-723.
8. Bendell JC, et al. *Mol Cancer Ther.* 2013;12(11):A252.
9. Wolchok JD, et al. *Clin Cancer Res.* 2009;15(23):7412-7420.
10. Radi ZA, et al. *Am J Pathol.* 2011;179(1):240-247.
11. Data on File. Array BioPharma Inc., Boulder, CO. 2017.

DISCLOSURES

WAH, MLJ, AW, JC, AZD, and CLC report no conflicts of interest. JWG reports research funding from and speakers bureau participation for Merck. SZ, KM, and AG are employees of, and may hold stock or stock options in, Array BioPharma Inc. RG has served on advisory boards for Roche/Genentech, Amgen, Castle Biosciences, Novartis, and Bristol-Myers Squibb; has received honoraria from Roche/Genentech, Amgen, Castle Biosciences, Novartis, and Bristol-Myers Squibb; has had travel expenses paid by Amgen, Prometheus Lab, Castle Biosciences, Novartis, and Bristol-Myers Squibb; and has received research funding from Roche/Genentech, Amgen, Prometheus Lab, Castle Biosciences, Novartis, Millennium, Bristol-Myers Squibb, Merck, Dynavax Technologies, Reata Pharmaceuticals, Celidex Therapeutics, Takeda Pharmaceuticals, Boston BioMedical, Checkmate, Incyte, Syndax Pharmaceutical, and Array BioPharma. JFG reports consulting for/honoraria received from Pfizer, Ariad/Takeda, Novartis, Genentech/Roche, Bristol-Myers Squibb, Merck, Incyte, and Theravance.

Available at: www.arraybiopharma.com/files/5515/0955/3643/ARRY-382_SITC_Dose_Escalation.pdf

Acknowledgments

Array BioPharma Inc. acknowledges the patients who participated in this study and their families. The authors further acknowledge Kevin Litwiler, PhD, and Christopher Conn, PhD, for their contributions to this presentation. Editorial support for development of this manuscript was provided by Bret Fulton at Complete Healthcare Communications, LLC (West Chester, PA), a CHC Group company, and was funded by Array BioPharma Inc.

This study is sponsored by Array BioPharma Inc.