Journal for ImmunoTherapy of Cancer

ARID1A alterations function as a biomarker for longer progression-free survival after anti-PD-1/PD-L1 immunotherapy

Ryosuke Okamura ,[1] Shumei Kato,[1] Suzanna Lee,[1] Rebecca E Jimenez,[1] Jason K Sicklick ,[1,2] Razelle Kurzrock [1]

To cite: Okamura R, Kato S, Lee S, *et al*. *ARID1A* alterations function as a biomarker for longer progression-free survival after anti-PD-1/PD-L1 immunotherapy. *Journal for ImmunoTherapy of Cancer* 2020;**8**:e000438. doi:10.1136/jitc-2019-000438

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jitc-2019-000438).

Accepted 11 February 2020

[1]Center for Personalized Cancer Therapy, UC San Diego Moores Cancer Center, La Jolla, California, USA
[2]Division of Surgical Oncology, Department of Surgery, UC San Diego Moores Cancer Center, La Jolla, California, United States

Correspondence to
Dr Ryosuke Okamura; ryokamura@health.ucsd.edu

ABSTRACT

Background Several cancer types harbor alterations in the gene encoding AT-Rich Interactive Domain-containing protein 1A (ARID1A), but there are no approved therapies to address these alterations. Recent studies have shown that *ARID1A* deficiency compromises mismatch repair proteins. Herein, we analyzed 3403 patients who had tumor tissue next-generation sequencing.

Findings Among nine cancer subtypes with >5% prevalence of *ARID1A* alterations, microsatellite instability-high as well as high tumor mutational burden was significantly more frequent in *ARID1A*-altered versus *ARID1A* wild-type tumors (20% vs 0.9%, p<0.001; and 26% vs 8.4%, p<0.001, respectively). Median progression-free survival (PFS) after checkpoint blockade immunotherapy was significantly longer in the patients with *ARID1A*-altered tumors (n=46) than in those with *ARID1A* wild-type tumors (n=329) (11 months vs 4 months, p=0.006). Also, multivariate analysis showed that *ARID1A* alterations predicted longer PFS after checkpoint blockade (HR (95% CI), 0.61 (0.39 to 0.94), p=0.02) and this result was independent of microsatellite instability or mutational burden; median overall survival time was also longer in *ARID1A*-altered versus wild-type tumors (31 months vs 20 months), but did not reach statistical significance (p=0.13).

Conclusions Our findings suggest that *ARID1A* alterations merit further exploration as a novel biomarker correlating with better outcomes after checkpoint blockade immunotherapy.

INTRODUCTION

The *ARID1A* gene encoding AT-Rich Interactive Domain-containing protein 1A is known as a member of the switching/sucrose non-fermentable (SWI/SNF) complex involved in chromatin remodeling.[1] Mutations in and loss of the *ARID1A* gene mostly lead to its inactivation and ARID1A protein loss.[2] Certain types of cancer, including clear cell ovarian carcinoma (46%–50%), gastric adenocarcinoma (10%–35%), and cholangiocarcinoma (15%–27%), frequently harbor *ARID1A* alterations.[2–4] To date, clinical and preclinical data indicate that *ARID1A* alterations may sensitize tumors to drugs targeting the ataxia telangiectasia and Rad3-related (ATR) protein, the enhancer of zeste 2 (EZH2), or the phosphatidylinositol-3-kinase (PI3K) pathway,[5–10] but no therapies targeting *ARID1A* alterations have been approved. Importantly, Shen *et al* demonstrated that *ARID1A* alterations interact with the mismatch repair (MMR) protein MSH2 and, hence, compromise MMR.[3] Tumors formed by an *ARID1A*-deficient ovarian cancer cell line in syngeneic mice exhibited higher mutation load, as well as increased numbers of tumor-infiltrating lymphocytes and elevated programmed cell death-ligand 1 (PD-L1) expression. Furthermore, administration of anti-PD-L1 antibody decreased cancer burden and extended survival of mice bearing *ARID1A*-deficient but not *ARID1A* wild-type ovarian tumors.[3] Interestingly, alterations in the polybromo-1 (*PBRM1*) gene, which is another member of the SWI/SNF complex, have been reported to correlate with salutary effects in cancer patients receiving checkpoint blockade inhibitors, though the clinical evidence remains controversial.[11 12] In gastric cancers, *ARID1A* alterations are associated with Epstein-Barr virus infection, which is in turn associated with checkpoint blockade response.[13] Herein, for the first time to our knowledge, we investigated the clinical correlation between *ARID1A* alterations and treatment benefit after anti-programmed cell death-1 (PD-1)/PD-L1 immunotherapy in the human pan-cancer setting.

MATERIALS AND METHODS

Study population and next-generation sequence

In a cohort of 3403 eligible patients at the Center for Personalized Cancer Therapy

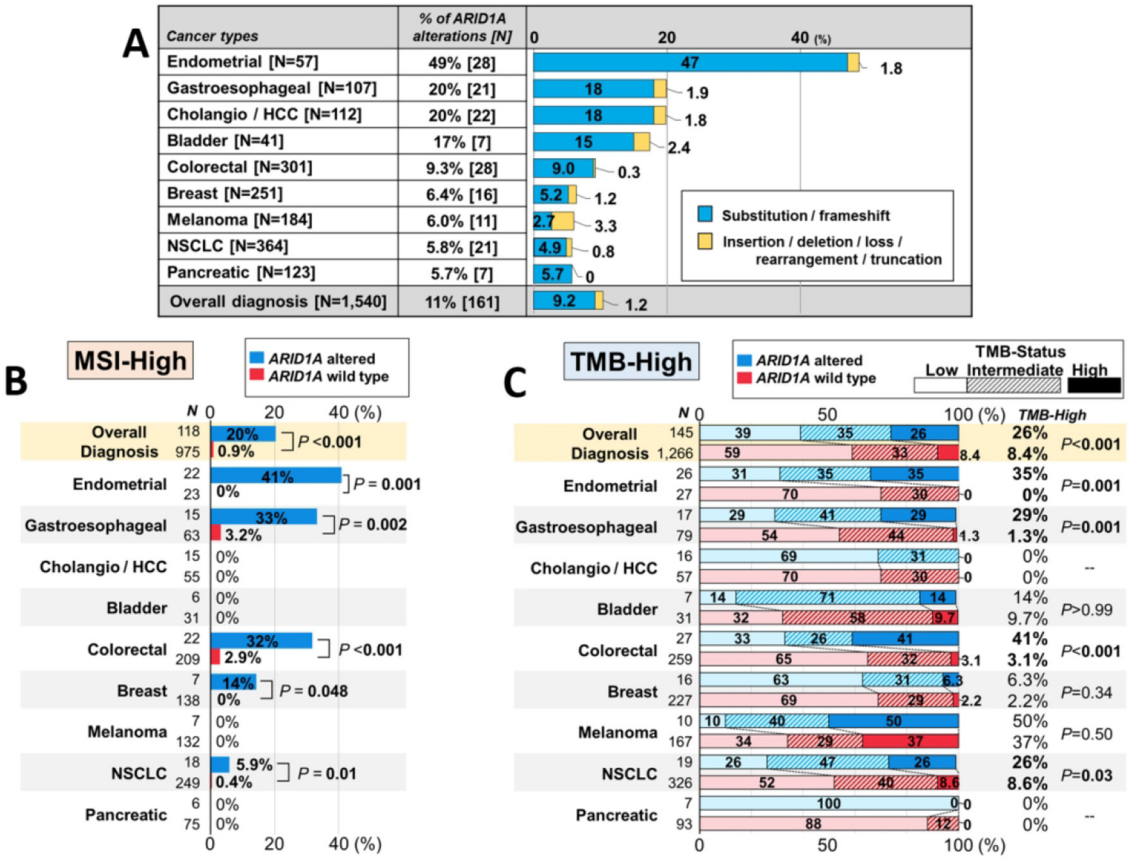

Figure 1 (A) Prevalence of characterized *ARID1A* alterations in tissue DNA NGS according to cancer types (n=1540). (B) Frequency of MSI-high according to *ARID1A* status (microsatellite status was available in 1093 patients (71.0%)). (C) Frequency of TMB-high according to *ARID1A* status (TMB-status was available in 1411 patients (91.6%); p values are for TMB-high rates): TMB-high (≥20 mutations/mb); TMB-intermediate (6–19 mutations/mb); TMB-low (<6 mutations/mb). *ARID1A*, AT-Rich Interactive Domain-containingprotein 1A; bladder, urothelial bladder carcinoma; breast, breast cancer; cholangio/HCC, cholangiocarcinoma and hepatocellular carcinoma; colorectal, colorectal adenocarcinoma; endometrial, uterine/ovary endometrial (endometrioid) carcinoma; gastroesophageal, gastric/esophageal adenocarcinoma; MSI, microsatellite instability; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; pancreatic, pancreatic ductal adenocarcinoma; TMB, tumor mutational burden.

(University of California San Diego Moores Cancer Center), whose tissue DNA was analyzed by next-generation sequencing (NGS) by Foundation Medicine, Inc. (CLIA-licensed and CAP-accredited laboratory. Cambridge, Massachusetts, USA https://www.foundationmedicine.com), we reviewed the clinicopathological and genomic information of patients whose tumors were pathologically diagnosed as one of nine types of cancer that frequently harbored *ARID1A* alterations (>5% of prevalence in this cohort): non-small cell lung cancer, colorectal adenocarcinoma, breast cancer, melanoma, pancreatic ductal adenocarcinoma, cholangiocarcinoma/hepatocellular carcinoma, gastric/esophageal adenocarcinoma, uterine/ovary endometrial (endometrioid) carcinoma (including clear-cell carcinoma), and urothelial bladder carcinoma. Tissue DNA sequencing at the laboratory was approved by the US Food and Drug Administration in November 2017 and designed to include all genes somatically altered in human solid malignancies that were validated as targets for therapy, either approved or in clinical trials, and/or that were unambiguous drivers of oncogenesis based on available knowledge.[14 15] Although the gene panel expanded with time (236–324 genes), the interrogation of the *ARID1A* gene was considered consistent. Only characterized *ARID1A* alterations were considered in this study (variants of unknown significant were excluded). In terms of microsatellite instability (MSI) status, 114 intron homopolymer repeat loci with adequate coverage are analyzed for length variability and compiled into an overall score via principal components analysis.[16 17] Measuring genes interrogated on the tissue DNA NGS and extrapolating to the genome as a whole as previously validated determined tumor mutational burden (TMB).[18] TMB was classified to three categories: high (≥20 mutations/mb), intermediate (6–19 mutations/mb), and low (<6 mutations/mb).

Statistics

Using the Mann-Whitney U test and Fisher's exact test, respectively, we compared categorical and continuous data. Progression-free survival (PFS) and overall survival (OS) data were measured from date of the initiation of

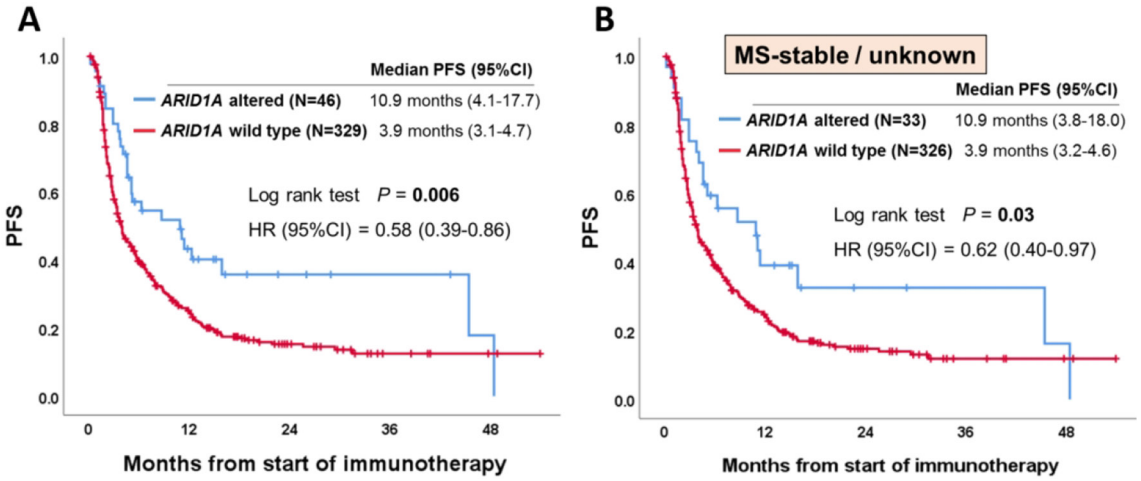

Figure 2 Kaplan-Meier curve of PFS according to *ARID1A* status. (A) Among patients who received anti-programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) immunotherapy (n=375). (B) Among patients without microsatellite instability-high who received anti-PD-1/PD-L1 immunotherapy (n=359). Similar results were seen even if the MS-unknown (n=60) were excluded (p=0.02). *ARID1A*, AT-Rich Interactive Domain-containingprotein 1A; MS, microsatellite status; PFS, progression-free survival.

anti-PD-1/PD-L1 immunotherapy and plotted by the Kaplan-Meier method. Data were censored if patient was progression free or alive (for PFS and OS, respectively) at last follow-up. The curves were compared by using the log-rank test. In multivariate analysis to investigate independent predictive factors for the PFS after anti-PD-1/PD-L1 immunotherapy, we used Cox's proportional hazard model for estimating HR and its 95% CI (variables with p<0.1 in the univariate analyses were entered into the multivariate analysis). RO performed and verified statistical analysis using SPSS V.24 software.

RESULTS AND DISCUSSION

Starting with 3403 eligible patients who underwent tissue DNA NGS, we found 1540 patients with nine types of cancer diagnoses that had >5% prevalence of characterized *ARID1A* alterations in tissue DNA NGS (figure 1A and online supplementary figure 1). Of 161 patients with ≥1 characterized *ARID1A* alteration in diverse types of cancer, 142 had *ARID1A* substitution or frameshift alterations, while the remaining 19 had insertions, deletions, allelic loss, rearrangement, or truncation. Endometrial and gastroesophageal cancers were the tumor types in which *ARID1A* alterations were most frequent—49% and 20% of cases, respectively (figure 1A). The median number of genomic coalterations among tumors with *ARID1A* alterations was 6 (range, 1–72) (not including *ARID1A* alterations), which was significantly higher than the median of 4 alterations (range, 0–61) among those cancers with wild-type *ARID1A* (p<0.001). The rate of MSI-high was significantly higher in tumors with *ARID1A* alterations than in those with wild-type *ARID1A* (20% vs 0.9%; p<0.001) and in multiple individual tumor types as well (eg, MSI-high in *ARID1A*-altered vs wild-type endometrial cancer, 41% vs 0%, p=0.001) (figure 1B). Similarly, TMB-high (≥20 mutations/mb) was more often observed in tumors with *ARID1A* alterations than in those with wild-type *ARID1A* (26% vs 8.4%; p<0.001) and in individual tumor types (eg, endometrial cancer, 35% vs 0%, p=0.001) (figure 1C).

Overall, 375 patients (24%) among the 1540 patients with the nine types of cancer with >5% *ARID1A* alterations received anti-PD-1/PD-L1 immunotherapy in the advanced/metastatic disease setting (see online supplementary figure 1). MSI-high and TMB-high were seen in 4.3% (n=16) and 17% (n=65) of these 375 patients, respectively. As shown in figure 2A, patients with *ARID1A*-altered tumors showed a significantly longer PFS than those with the wild-type tumors (10.9 months vs 3.9 months, p=0.006) from the start of anti-PD-1/PD-L1 immunotherapy. When PFS was analyzed according to cancer diagnosis (only tumor types with ≥5 patients with *ARID1A* alterations), similar sensitivity was observed in individual tumor types (eg, colorectal cancer (5.2 months vs 2.1 months, p=0.005); endometrial cancer (4.6 months vs 3.0 months, p=0.02)) (see online supplementary figure 2). Importantly, even when only patients without MSI-high were included to the analysis, *ARID1A*-altered tumors showed a significantly longer PFS than those with wild-type tumors: HR (95% CI), 0.62 (0.40 to 0.97); p=0.03 (figure 2B). In the same way, when only patients without TMB-high were included to the analysis, patients with *ARID1A*-altered tumors (vs *ARID1A* wild-type) showed a trend towards longer PFS: HR (95% CI), 0.69 (0.43 to 1.08) although not statistically significant (p=0.10) (see online supplementary figure 3) (small numbers of patients precluded analysis of patients with MSI-high or TMB-high who had *ARID1A* alterations vs not). When examining OS in *ARID1A*-altered versus the wild-type patients, median OS time was longer in the *ARID1A*-altered group (30.8 months vs 20 months), but this did not reach statistical significance (p=0.13) (see online

Table 1 Characteristics of patients who underwent anti-PD-1/PD-L1 immunotherapy (n=375)

Variables	*ARID1A*-altered (n=46)	*ARID1A*-wild type (n=329)	P value
Basic characteristics and tissue DNA next-generation sequencing			
Age at tissue DNA analysis, years			
Median (range)	65.1 (34.0–89.4)	63.0 (22.3–93.7)	0.49
Gender			
Female	25 (54.3%)	142 (43.2%)	0.16
Male	21 (45.7%)	187 (56.8%)	–
Diagnosis			
Lung cancer, non-small cell	7 (15.2%)	104 (31.6%)	**0.02**
Colorectal adenocarcinoma	12 (26.1%)	37 (11.2%)	**0.009**
Breast cancer	1 (2.2%)	24 (7.3%)	0.34
Melanoma	6 (13.0%)	91 (27.7%)	**0.046**
Pancreatic ductal adenocarcinoma	1 (2.2%)	7 (2.1%)	>0.99
Cholangiocarcinoma/hepatocellular carcinoma	2 (4.3%)	13 (4.0%)	0.71
Gastric/esophageal adenocarcinoma	5 (10.9%)	16 (4.9%)	0.16
Endometrial carcinoma	10 (21.7%)	13 (4.0%)	<**0.001**
Urothelial bladder carcinoma	2 (4.3%)	24 (7.3%)	0.76
Characterized alterations			
Median (range)	8 (2–57)*	5 (1–24)	<**0.001**
Microsatellite status			
MSI-high	13 (28.3%)	3 (0.9%)	<**0.001**
Stable	31 (67.4%)	268 (81.5%)	**0.03**
Unknown	2 (4.3%)	58 (17.6%)	**0.02**
Tumor mutational burden, mutations/mb			
Median (range)†	16.0 (1.0–321.0)	6.1 (0.0–222.0)	<**0.001**
≥20 (high)	18 (39.1%)	47 (14.3%)	<**0.001**
6–19 (intermediate)	16 (34.8%)	129 (39.2%)	0.63
<6 (low)	8 (17.4%)	133 (40.4%)	**0.002**
Unknown	4 (8.7%)	20 (6.1%)	0.52
Anti-PD-1/PD-L1 immunotherapy			
Administered as			
1st line	8 (17.4%)	113 (34.3%)	**0.03**
≥2nd line	38 (82.6%)	216 (65.7%)	–
Regimen of anti-PD-1/PD-L1 immunotherapy			
Anti-PD-1/PD-L1 monotherapy	25 (54.3%)	170 (51.7%)	0.76
With molecular targeting drug	7 (15.2%)	36 (10.9%)	0.46
With CTLA4 inhibitor	6 (13.0%)	56 (17.0%)	0.67
With cytotoxic chemotherapy	4 (8.7%)	33 (10.0%)	>0.99
With molecular targeting and cytotoxic drugs	2 (4.3%)	2 (0.6%)	0.08
Others‡	2 (4.3%)	32 (9.7%)	0.41

All p-values <0.05 are listed in bold.
*Excluded *ARID1A* alterations.
†Among 1411 patients whose TMB data were available.
‡With NKG2A inhibitor (n=9); with CD73 inhibitor (n=8); with IDO1 inhibitor (n=6); with CD122-preferential IL-2 pathway agonist (n=5); with CTLA4 inhibitor and molecular targeting drug (n=2); with OX40 agonist (n=2); with CEA/BiTE inhibitor (n=1); with 4-1BB inhibitor (n=1).
ARID1A, AT-Rich Interactive Domain-containing protein 1A gene; bladder, urothelial bladder carcinoma; breast, breast cancer; cholangio/HCC, cholangiocarcinoma and hepatocellular carcinoma; colorectal, colorectal adenocarcinoma; CTLA4, cytotoxic T lymphocyte antigen 4; endometrial, uterine/ovary endometrial (endometrioid) carcinoma; gastroesophageal, gastric/esophageal adenocarcinoma; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; pancreatic, pancreatic ductal adenocarcinoma; PD-1/PD-L1, programmed cell death-1 and its ligand.

Table 2 Univariate and multivariate analyses for progression-free survival after anti-PD-1/PD-L1 immunotherapy (n=375). Variables with p<0.10 in the univariate analyses were entered into the multivariate analysis

	Progression-free survival			
	Univariate analysis		Multivariate analysis	
Characteristics	**Median, months**	**P value**	**HR (95% CI)**	**P value**
Age, years*				
≥63 (n=195) vs <63 (n=180)	4.6 vs 4.0	0.57	–	–
Gender				
Female (n=167) vs male (n=208)	3.8 vs 5.1	0.08	1.16 (0.91 to 1.47)	0.23
Diagnosis				
NSCLC (n=111) vs not (n=264)	4.9 vs 4.1	0.99	–	–
Colorectal (n=49) vs not (n=326)	2.9 vs 4.6	**0.02**	1.38 (0.98 to 1.97)	0.07
Melanoma (n=97) vs not (n=278)	7.8 vs 3.7	**<0.001**	0.69 (0.50 to 0.95)	**0.02**
Endometrial (n=23) vs not (n=352)	3.7 vs 4.2	0.64	–	–
Number of characterized alteration in tissue DNA†				
≥6 (n=195) vs <6 (n=180)	4.2 vs 4.2	**0.03**	1.09 (0.84 to 1.41)	0.51
MSI-status				
MSI-high (n=16) vs not‡ (n=359)	12.3 vs 4.0	**0.01**	0.74 (0.33 to 1.64)	0.46
TMB, mutations/mb				
TMB-high (≥20) (n=65) vs not‡ (n=310)	13.6 vs 3.7	**<0.001**	0.47 (0.31 to 0.71)	**<0.001**
ARID1A status				
ARID1A-altered (n=46) vs wild type (n=329)	10.9 vs 3.9	**0.006**	0.61 (0.39 to 0.94)§	**0.02**
Regimen of anti-PD-1/PD-L1 immunotherapy				
Administered as 1st line (n=121) vs ≥2nd line (n=254)	7.4 vs 3.7	**0.001**	0.80 (0.60 to 1.07)	0.13

All p-values <0.05 are listed in bold.
*Age at tissue DNA analysis. Dichotomized by the median.
†Dichotomized by the median.
‡Including patients whose data were not reported.
§The HR (95% CI) was similar (0.55 (0.34 to 0.88), p=0.01) even if patients with MS-unknown or TMB-unknown (n=70) were excluded.
ARID1A, AT-Rich Interactive Domain-containing protein 1A gene; CI, confidence interval; HR, hazard ratio; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; PD-1/PD-L1, programmed cell death-1 and its ligand; TMB, tumor mutational burden.

supplementary figure 4). In order to better determine if the correlation between *ARID1A* alterations and longer PFS was independent of specific confounding variables, we performed a multivariate analysis (patient characteristics of *ARID1A*-altered vs wild-type patients are shown in table 1). Our Cox-regression model demonstrated that *ARID1A* alterations were selected as an independent predictor of better outcome (PFS) after anti-PD-1/PD-L1 immunotherapy (HR (95% CI), 0.61 (0.40 to 0.94); p=0.03) (table 2).

In conclusion, 28% of *ARID1A*-altered tumors (n=32 of 114 patients whose microsatellite and TMB status were both available) had either MSI-high or TMB-high (or both), and the rate of MSI-high and TMB-high was significantly higher in *ARID1A*-altered versus wild-type tumors. These findings are consistent with previous reports that *ARID1A* deficiency is correlated with MMR deficiency.[3 19] *ARID1A* alterations were independently and significantly associated with longer PFS after anti-PD-1/PD-L1 immunotherapy (regardless of microsatellite and TMB status). This study has several limitations such as the small number of patients with each cancer type, which restricted our ability to analyze individual tumor histologies. Nevertheless, the results suggest generalizability across tumor types. Another limitation was that improvement in OS in *ARID1A*-altered patients (vs wild-type) did not reach statistical significance; larger numbers of patients are needed to validate this endpoint. Therefore, *ARID1A* alterations may be a genomic marker of checkpoint blockade sensitivity, in addition to other putative markers such as MSI-high and TMB-high.[20–22] Our observations indicate that *ARID1A* alterations warrant further studies with longer follow-up and larger numbers of patients in order to confirm if they can be added to the armamentarium of genomic markers that are exploitable for matching patients to immunotherapy in the pan-cancer setting.[23 24]

Contributors Study conception and design: RO, SK, JKS, and RK; data acquisition: RO, SL, and REJ; statistical analysis: RO and SK; data interpretation: RO, SK, JKS, and RK; drafting the manuscript or revising it critically: all authors; final approval of the manuscript: all authors.

Funding This work was funded in part by the Joan and Irwin Jacobs Fund and NIH P30 CA023100 (RK). We appreciate funding support from Hope for a Cure Foundation, Jon Strong, NIH R01 CA226803, and FDA R01 FD006334 (JKS).

Competing interests SK serves as a consultant fee (Foundation Medicine) and speaker's fee (Roche). JKS has the following disclosure information: Research funding (Novartis Pharmaceuticals, Amgen Pharmaceuticals, and Foundation Medicine); Consultant fee (Grand Rounds (2015–2019), Loxo Oncology (2017–2018), Deciphera (2019), and Roche (2019)). RK has the following disclosure information: Stock and Other Equity Interests (IDbyDNA, CureMatch, and Soluventis); Consulting or Advisory role (Gaido, LOXO, X-Biotech, Actuate Therapeutics, Roche, NeoMed, Soluventis, and Pfizer); Speaker's fee (Roche); Research Funding (Incyte, Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, Guardant Health, Grifols, Konica Minolta, DeBiopharm, Boerhringer Ingelheim, and OmniSeq (All institutional)); Board Member (CureMatch).

Patient consent for publication Not required.

Ethics approval This study was approved by the Internal Review Board at UC San Diego Moores Cancer Center. All investigations followed the guidelines of the *Profile-Related Evidence Determining Individualized Cancer Therapy* study (UCSDPREDICT study: NCT02478931) for data collection and any investigational therapies for which the patient gave consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of our study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID iDs
Ryosuke Okamura http://orcid.org/0000-0001-7352-8621
Jason K Sicklick http://orcid.org/0000-0003-4403-0271
Razelle Kurzrock http://orcid.org/0000-0003-4110-1214

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