Long-term Benefit of PD-L1 Blockade in Lung Cancer Associated with JAK3 Activation


Abstract

PD-1 immune checkpoint blockade occasionally results in durable clinical responses in advanced metastatic cancers. However, mechanism-based predictors of response to this immunotherapy remain incompletely characterized. We performed comprehensive genomic profiling on a tumor and germline sample from a patient with refractory lung adenocarcinoma who achieved marked long-term clinical benefit from anti–PD-L1 therapy. We discovered activating somatic and germline amino acid variants in JAK3 that promoted PD-L1 induction in lung cancer cells and in the tumor immune microenvironment. These findings suggest that genomic alterations that deregulate cytokine receptor signal transduction could contribute to PD-L1 activation and engagement of the PD-1 immune checkpoint in lung cancer. Cancer Immunol Res 3(8): 1–9. ©2015 AACR.

Introduction

The programmed cell death-1 (PD-1) protein is a coinhibitory receptor that restraints immune signaling by inhibiting T-cell function. Tumors that express its major inducible ligand, PD-L1, evade immunosurveillance by engaging the PD-1 immune checkpoint (1, 2). In preclinical models, blockade of PD-L1 interaction with PD-1 promotes immune-mediated antitumor activity (3). Clinical trials of PD-1 and PD-L1 inhibitors have uncovered durable tumor regression in a subset of patients with a variety of aggressive cancers (4–7). Although studies have suggested that PD-L1 expression in tumors or tumor-infiltrating immune cells (8) appear more likely to respond to immune checkpoint inhibition, the specific determinants of this enhanced responsiveness remain incompletely characterized.

Identifying genomic mechanisms of inhibitor sensitivity may inform patient selection for agents targeting immune checkpoints and suggest approaches to enhance the efficacy of these agents in otherwise resistant patients. Comprehensive genomic profiling of exceptional responders has revealed the genomic mechanism of extraordinary response to targeted therapies (9–13), but has not yet been applied to immunotherapies.

We identified a patient with advanced, chemoresistant stage IV lung adenocarcinoma who achieved a long-term durable response on a phase 1 clinical trial of MPDL3280A (atezolizumab), an engineered anti–PD-L1 antibody (8). To identify genomic mechanisms associated with this sensitivity, we performed genomic profiling of the patient’s tumor and germline samples.

Case report

A 57-year-old male with a 40-pack-year smoking history presented with left shoulder discomfort. Magnetic resonance imaging (MRI) revealed a 1 × 2 cm lytic abnormality in the left humeral head. Biopsy of this lesion identified CK7 and TTF-1 positive adenocarcinoma, suggestive of primary lung origin. Chest computed tomography (CT) showed a 4 × 3.2 cm left apical mass. Positron emission tomography (PET) confirmed that this mass, the left humeral lesion, and left paratracheal lymphadenopathy were FDG-avid. Brain MRI revealed four lesions consistent with additional metastatic spread.

The patient received palliative whole-brain and left-shoulder radiotherapy, followed by a single cycle of carboplatin and paclitaxel, which he tolerated poorly (Fig. 1A). He then responded to dose-reduced carboplatin, pemetrexed, and bevacizumab for three additional cycles, and was transitioned to maintenance pemetrexed and bevacizumab.
After 8 months of maintenance therapy, CT scans showed growth of a left adrenal mass. Laparoscopic left adrenalectomy was performed for palliation of severe flank pain and for further molecular profiling. Clinical testing for oncogenic alterations revealed wild-type EGFR, ALK, and KRAS status. Three months later the patient developed a new right adrenal mass and recurrence of the left paratracheal lymphadenopathy. Hospice was considered in the setting of worsening pain and weight loss (Fig. 1B). Immunohistochemistry (IHC) performed on the excised left adrenal tumor revealed PD-L1 reactivity, prompting enrollment of the patient on Dana-Farber/Harvard Cancer Center (DF/HCC) clinical trial 11-314, a phase I study of MPDL3280A (atezolizumab). B, change in patient weight (kg) during the same time period. C, serial chest computed tomography scans showing reduction in size of the paratracheal mass over time (arrows). D, serial abdominal computed tomography scans showing recurrence and retreatment response of the right adrenal mass (arrows).

Given the patient’s extraordinary and repeated response to PD-L1 immune checkpoint blockade, comprehensive genomic profiling of the patient’s tumor and germline DNA was performed.

**Materials and Methods**

**Patient informed consent and tumor/blood samples**

All patients provided written informed consent for research biopsies and genomic profiling of tumor and normal DNA, as approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board (DF/HCC Protocol 11-104). In addition, the patient provided written informed consent to participate in a clinical trial of MPDL3280A (11-314; NCT 01375842). A blood sample was obtained from the patient for germline testing after the complete response was identified, and whole blood was stored at −80°C until DNA extraction was performed. Tumor specimens for PD-L1 IHC and blood samples were obtained from additional patients consented through DF/HCC Protocol 11-104. Normal blood donor samples were accessed through DF/HCC Protocol 10-145.
Histology and staining

Histopathologic analysis of the surgically resected left adrenal gland revealed metastatic adenocarcinoma, consistent with metastasis from the patient’s lung primary tumor. Surgical resection margins were negative for tumor and the tumor was confined by the adrenal capsule. IHC for tumor PD-L1 expression was performed as described (14–16). In brief, PD-L1 (9A11, 1:125) was performed on the Leica BOND III platform using Bond’s Polymer Refine Detection kit. Heat-induced antigen retrieval was performed in Bond ER2 solution for 30 minutes online. Sections were incubated at room temperature in primary antibody for 120 minutes at room temperature. Upon staining completion, slides were dehydrated and coverslipped offline. S.J. Rodig performed all IHC interpretation and was blinded to JAK3 V722I or P132T status when assessing PD-L1 stain. A random control set of 9 lung cancers identified by an independent pathologist was stained in parallel to determine relative enrichment. Scoring was performed by measuring the average number of positive cells in a given sample and the average intensity of staining (0, no staining; 1+, weak; 2, moderate; 3, intense positive staining, with all positive staining considered over background). Determination of statistically significant differences between the groups was performed by calculating an adjusted expression (H) score (% positive cells × staining intensity; refs. 14, 17). Macrophage cells were identified through morphologic determination in intratumoral or alveolar spaces.

Targeted sequencing

Standard techniques were used to extract genomic DNA from tumor within the left adrenalectomy specimen and from blood. Initial sequencing of tumor DNA was performed using the OncoMap assay, which detects mutations in 41 cancer genes at 471 different loci using multiplex PCR to amplify the region containing the variant of interest (18). Following primer extension of the allele-specific DNA products, DNA analyses were measured using chip-based mass spectrometry (Sequenom MassARRAY 4). Additional tumor samples that harbored variants of interest in JAK3 were identified through the Dana-Farber Cancer Institute PROFILE project using the OncoMap assay, which included V722I and P132T variants. All lung cancer tumor samples from patients who provided written informed consent (DF/HCC Protocol 11-104) with adequate tumor tissue who underwent OncoMap assay testing done between 2010 and 2013 was included in the query. The OncDRS clinical-genomics database system that links genomic data from PROFILE with salient clinical annotations was searched through the Dana-Farber Cancer Institute (DF/HCC) database. Heuristic analysis of all somatic alterations was performed using Integrated Genomics Viewer (26, 27). Somatic alterations were manually reviewed using PHIAL (25). Somatic alterations were manually reviewed using Integrated Genomics Viewer (26, 27).

Whole-exome sequencing

Library construction and sequencing. Whole-exome capture was performed using the Agilent SureSelect Human All Exon 44 Mb v2.0 bait set (Agilent Technologies). In summary, genomic DNA was sheared, end repaired, ligated with barcoded Illumina sequencing adapters, amplified, size selected, and subjected to in-solution hybrid capture using the Agilent SureSelect Human All Exon v2.0 bait set (19, 20). Resulting exome Illumina sequencing libraries were then qPCR quantified, pooled, and sequenced with 76 base-paired-end reads using HiSeq2500 sequencers (Illumina). Raw BAM files are deposited in phs000694.v1.p1.

Sequence data processing and quality control. Exome sequence data processing was performed using established analytical pipelines at the Broad Institute. Tumor and normal sequences were aligned to the hg19 human genome built from Illumina sequencing reads using the Picard pipeline (http://picard.sourceforge.net/). The BAM was uploaded into Firehose (http://www.broadinstitute.org/cancer/cga/Firehose), which manages input and output files. Comparison of the origin for tumor and normal genotypes was performed to assess fingerprinting concordance, and cross-contamination of samples was estimated using ContEst (21).

Alteration identification. MuTect (22) was applied to identify somatic single-nucleotide variants. DNA oxidation artifacts induced during sequencing were computationally removed using a filter-based method (23). Indelocator (http://www.broadinstitute.org/cancer/cga/indelocator) was applied to identify small insertions or deletions. Annotation of identified variants was done using Oncotator (http://www.broadinstitute.org/cancer/cga/oncotator). Copy ratios were calculated for each captured target by dividing the tumor coverage by the median coverage obtained in a set of reference normal samples. The resulting copy ratios were segmented using the circular binary segmentation algorithm. Genes in copy ratio regions with segment means of greater than log2(4) were evaluated for focal amplifications, and genes in regions with segment means of less than log2(0.5) were evaluated for deletions. Genome-wide copy ratios were estimated from whole-exome sequencing (WES) data by comparison of the observed depth of coverage at each exon with that achieved in normal samples. Allelic copy ratios were then estimated by analysis of allelic fractions for all heterozygous SNPs identified in the paired normal sample. Purity and ploidy evaluations to derive absolute copy number were made using ABSOLUTE (24). Heuristic analysis of all somatic alterations was performed using PHIAL (25). Somatic alterations were manually reviewed using Integrated Genomics Viewer (26, 27).

Experimental procedures

Cell culture. 293T and Calu-1 cells were maintained in DMEM and RPMI-1640, respectively, with 10% FBS. Beas-2B was maintained in Keratinocyte SFM, supplemented with human recombinant EGF and BPE (Gibco). All media were supplemented with 1% penicillin/streptomycin.

Plasmids, immunoblotting, and flow cytometry. JAK3-mutant alleles were generated from pDONR223-JAK3-WT (Broad Institute, The RNAi Consortium) using the QuickChange Lightning Site-Directed Mutagenesis Kit (Agilent Technologies), and transferred into the plX304 vector using the Gateway LR Clonase II enzyme mix from Life Technologies. 293T cells were transfected using XtremeGENE HP DNA Transfection Reagent (Roche) with plX304 EGFP, JAK3-WT, or JAK3 constructs as described (28). Lysates were harvested after 48 hours and immunoblotting was also performed according to a standard protocol (28). JAK3 (#8827) and Y980/981 pJAK3 (#5031) antibodies were from Cell Signaling Technologies. Beas-2B and Calu-1 cells were infected with lentivirus generated from plX304 empty control or the same JAK3 constructs and selected in blasticidin to derive stably infected cell lines as described (28). Flow cytometry for PD-L1 expression was performed 72 hours after plating, as described in ref. 29. In brief, cells were stained with an anti–PD-L1 antibody

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PBMC isolation and stimulation. Peripheral blood mononuclear cells (PBMC) from patients identified as having JAK3 V722I or P132T variants (see ‘Targeted sequencing’ section above) and healthy donors were isolated from fresh blood and platelet-depleted blood collars, respectively, by Ficoll method. PBMCs were plated at a density of 7.5 × 10^6 cells/mL in a 48-well plate and stimulated with 250 ng/mL IFN-γ (PBL Interferon Source). No stimulation controls were set up for each donor. At 48 hours after stimulation, cells were treated with 2 mmol/L EDTA and collected for flow cytometry to assess for PD-L1 expression on CD14+ myeloid cells. Cells were stained with Live/Dead yellow viability dye (Invitrogen), as well as antibodies (BD Biosciences) against CD14 (M522), CD11b (ICRF44), and PD-L1 (MH11) for 30 minutes at 4°C, and then fixed in BD Cytofix buffer before analyses on BD LSR Fortessa SORT HTS flow cytometer. Given the need to compare the difference between two means in relation to the variation in the data, a t test was used to compare PD-L1 inducibility between V722I and non-V722I monocytes.

T-cell proliferation assay. PBMCs were isolated from patient blood samples immediately before and 1 hour after treatment with MPDL3280A, as well as from a normal donor by Ficoll and plated in a density of 4 × 10^6 cells/mL to a 96-well plate. After 2 hours at 37°C nonadherent cells (lymphocyte portion) were removed by pipetting and remaining adherent cells (monocyte portion) were cultured with or without 250 ng/mL IFN-γ. At 24 hours, nonadherent lymphocytes were labeled with CFSE; monocytes (IFN-γ treated or untreated) were harvested by 5 mmol/L EDTA treatment and resuspended in fresh medium. Both lymphocytes and monocytes were then plated to a 96-well plate precoated with 10 μg/mL OKT3 antibody. Proliferation of CD4+ T cells and CD8+ T cells was monitored at 72 hours after stimulation by CSFE dilution.

Results
Genomic profiling identifies selection for two JAK3 mutations in the tumor

The only variant observed in the mass spectrometric genotyping panel was JAK3 V722I. This variant, which is located in the pseudokinase or JH2 domain of JAK3 (Fig. 2A and Supplementary Fig. S1A), has been described and functionally characterized as an activating allele in patients with acute megakaryocytic leukemia (30), acute lymphoblastic leukemia (31), and extranodal nasal-type natural killer cell lymphoma (32). JAK3 V722I has also been identified in peripheral blood from normal subjects (33), and the population frequency of this hyperactive germline variant is approximately 1% (34).

Whereas tumor WES revealed neutral copy of the JAK3 locus on chromosome 19 in aggregate (Fig. 2B and Supplementary Fig. S2), allele-specific copy-number segmentations demonstrated near complete conversion to the mutant allele in this region (Fig. 2C and Supplementary Fig. S3). The allelic fraction of the JAK3 V722I locus was 0.88 (131 of 149 reads) in the tumor and 0.47 (90 of 190 reads) in the germline sample, consistent with homozygosity of the JAK3 V722I allele in the tumor sample (which was 76% pure) and similar to the selection that occurs for activating JAK2 V617F alleles in myeloproliferative neoplasms (MPN; ref. 35).

Next, the 1,767 nonsynonymous somatic alterations observed in the WES data were ranked for clinical and biologic relevance (Supplementary Fig. S4 and Supplementary Table S1; ref. 25). Among the clinically relevant events, a second somatic JAK3 missense mutation at codon 61 (S→C) was observed and orthogonally validated in tumor DNA with PCR (Fig. 2A and Supplementary Fig. S1B). This mutation occurred in the FERM domain and has not been described previously. Because we identified two distinct genomic events in JAK3 undergoing tumor somatic selection in cis, a scenario described in hematologic malignancies (36), and Epstein–Barr Virus (EBV) induces PD-L1 expression via JAK3 (37), we sought to determine whether these JAK3 mutations were activating and might contribute to PD-L1–mediated immune checkpoint evasion in lung cancer.

Molecular basis of JAK3 autoactivation and PD-L1 overexpression

We generated constructs that express JAK3 WT, JAK3 S61C/V722I, JAK3 V722I, JAK3 S61C/V722I, and compared activity with an additional known activating JH2-domain mutation (JAK3 R657Q; ref. 28), identified as a somatic mutation in squamous cell lung cancer (38). Consistent with the known impact of JH2 domain mutation on relieving JAK3 autoinhibition (30), transfection of 293T cells revealed that JAK3 V722I, JAK3 S61C/N722I, or JAK3 R657Q overexpression resulted in increased JAK3 autophosphorylation and autoactivation compared with the wild-type control as measured by immunoblotting (Fig. 2D). Although levels of JAK3 S61C phosphorylation did not differ significantly from JAK3 WT, expression of JAK3 S61C/N722I caused the highest levels of JAK3 phosphorylation among all mutants, consistent with the positive selection observed in the tumor and cooperative gain of function.

We next examined the consequences of stable JAK3 transduction on PD-L1 cell surface expression in immortalized lung epithelial cells (BEAS-2B) and lung cancer cells (Calu-1; Fig. 3A). Low-level JAK3 S61C/N722I expression in BEAS-2B cells modestly induced PD-L1 by flow cytometry relative to control, as compared with no induction at all in JAK3 WT-expressing cells (Fig. 3B). In contrast, 5-fold greater expression of JAK3 in Calu-1 increased PD-L1 levels more demonstrably, irrespective of the allele (Fig. 3B). We also examined the consequence of exposure to factors in the lung tumor microenvironment such as EGF, since activation of EGFR signaling is known to enhance PD-L1 expression in lung cancer (17, 29). Levels of PD-L1 in Calu-1 cells expressing JAK3 S61C/N722I were as high as control cells stimulated with EGF, and we observed an additive further increase of PD-L1 expression in mutant cells upon EGF exposure (Fig. 3C). These findings reveal that JAK3 activation in lung airway and cancer cells induces PD-L1, including wild-type kinase when overexpressed at high levels. Furthermore, activated JAK3 cooperates with factors such as EGF to boost PD-L1 expression even further.

Dual impact on the tumor and immune microenvironment

Consistent with these results, IHC of the patient’s tumor using a validated antibody (16) revealed strong positive membrane PD-L1 expression on both tumor and immune cells (macrophages), coupled with increased nuclear pSTAT3 staining, a marker of JAK
pathway activation (Fig. 4A). To assess the generalizability of this relationship, we identified 10 out of 500 lung adenocarcinoma patients (2%) previously genotyped for the JAK3V722I mutation at our institution (39), including this index case. PD-L1 positivity was observed in tumor cells and more strikingly in macrophages in 9 of 10 JAK3V722I-mutated cases (Fig. 4B). PD-L1 positivity was substantially enriched as compared with a random control set of lung cancers (tumor cells: $P = 0.02$; immune cells: $P < 0.01$; Mann–Whitney; Supplementary Fig. S5), including 4 patients carrying the JAK3P132T variant, with the exception of high level PD-L1 tumor expression associated with an ALK rearrangement and another tumor with high level PD-L1 expression in macrophages (Fig. 4B).

Because of the strong activation in the immune compartment, and the presence of JAK3V722I in the germline, we also measured the inducibility of PD-L1 expression in available matched patient PBMCs. Stimulation with IFNγ, another cytokine known to trigger PD-L1 in the tumor immune microenvironment, resulted in
modest but significantly increased expression of PD-L1 on CD14+ myeloid cells from JAK3V722I-positive patients compared with a JAK3V7132I-positive patient or negative blood donor controls (Fig. 4C). Next, to determine if this increased PD-L1 expression directly inhibits T cells, we collected blood from the index patient immediately before and 1 hour after MPDL3280A infusion and exposed monocytes from these samples to the patient’s own activated T cells, or from allogeneic T cells from a different donor. In both instances we found that T-cell activation was significantly greater in the presence of circulating MPDL3280A, especially when monocytes were primed with IFNγ (Fig. 4D and Supplementary Fig. S6). This enhanced T-cell activity correlated with the clinical response we observed upon MPDL3280A rechallenge (Fig. 1D). Thus, monocytes/macrophages that carry the JAK3V722I allele also express increased levels of PD-L1, with can contribute directly to T-cell suppression.

Taken together, these findings suggest that, in addition to somatic alteration in lung cancer cells, germline expression of the JAK3V722I allele in infiltrating immune cells may represent a key contributor of PD-L1 tumor immune checkpoint engagement.

Discussion

Immune targeting of the PD-L1/PD-1 interaction is emerging as an effective therapy for multiple aggressive tumor types, including non–small-cell lung cancer (5), and results in occasional long-term responses. While tumor or immune cell PD-L1 expression may indicate a suppressed immune microenvironment and
enrich for clinical activity (40), the molecular basis and markers of response remain unclear.

We genomically characterized a patient with metastatic lung adenocarcinoma who experienced an exceptional and durable response to PD-L1 inhibition. We discovered one germline JAK3 variant and one somatic JAK3 mutation in the patient’s tumor in cis, and we demonstrated that these genetic alterations act in concert to activate JAK3. Stable transduction of this double-mutant increased PD-L1 expression in lung cells. Furthermore, the presence of JAK3V722I in the germline, the strong tumor immune cell PD-L1 positivity, and the enhanced PD-L1 induction by IFNγ in monocytes, which inhibits T-cell activation in an MPDL3280A-sensitive manner, also suggest a more complex interaction with the tumor microenvironment. To our knowledge, this is the first report that illustrates how a genomic mechanism that affects both tumor cells and the host response may enhance PD-L1 expression and immune evasion by engaging the PD-1 immune checkpoint.

Multiple reports have identified candidate mechanisms that may predict response to immune checkpoint blockade. These may include high levels of tumor-specific neoantigens (41, 42) or inherited immune-related characteristics (43). It is unclear yet whether the specific genomic mechanism of JAK3 activation reported here is generalizable to other patients who achieve such responses, whether this patient’s tumor harbored a rare genotype, or whether the genotype in this patient acted in concert with other somatic or germline alterations. Notably, JAK3 signaling regulates EBV-mediated PD-L1 expression in lymphomas (37) and has...
been implicated in response to PD-1 blockade in Hodgkin lymphoma (6), STAT3 binds directly to the PD-L1 promoter (44), and been implicated in response to PD-1 blockade in Hodgkin lymphoma (6), STAT3 binds directly to the PD-L1 promoter (44), and been implicated in response to PD-1 blockade in Hodgkin lymphoma (6), STAT3 binds directly to the PD-L1 promoter (44), and been implicated in response to PD-1 blockade in Hodgkin lymphoma (6), STAT3 binds directly to the PD-L1 promoter (44), and been implicated in response to PD-1 blockade in Hodgkin lymphoma (6), STAT3 binds directly to the PD-L1 promoter (44), and been implicated in response to PD-1 blockade in Hodgkin lymphoma (6), STAT3 binds directly to the PD-L1 promoter (44), and been implicated in response to PD-1 blockade in Hodgkin lymphoma (6), STAT3 binds directly to the PD-L1 promoter (44). Thus, functional SNP variants, somatic alterations resulting in activation of other JAK family members (e.g., JAK1, JAK2, or TYK2), or inactivation of negative regulators such as suppressor of cytokine signaling (SOCS) family members may serve as a common pathway for upregulating PD-L1 expression and predicting responsiveness to this immune therapy. Indeed, as this particular JAK3Y222C variant is present in the germline at a significantly lower frequency (1%-2%) compared with the frequency of PD-L1 positivity in lung cancer overall (at least 20%), it may only explain a small subset of tumors that engage this pathway. However, as long-term durable remissions are much rarer, it is possible that studies in patients enriched for this genotype may now similarly reverse responsiveness to those seen in this case. Regardless, further studies in larger patient cohorts are necessary to establish definitively the role of this and other somatic/germline JAK alterations as a mechanism-based predictive marker of response to PD-L1 inhibition.

Broadly, this result expands the concept of studying extraordinary responses to cancer therapeutics beyond classic targeted therapies to include approved or investigational immunotherapies. The identification of these and other genomic mechanisms of sensitivity to immune checkpoint inhibitor blockade will not only help tailor this therapy in a personalized fashion, but may also suggest pharmacologic approaches to induce sensitivity in otherwise resistant patients. Finally, profiling patients who demonstrate initial responses but develop acquired resistance may further illuminate the spectrum of pathways that restrict tumor immunity and implicate additional rational modalities for therapeutic development.

Disclosure of Potential Conflicts of Interest

E.M. Van Allen is a consultant/advisory board member for Roche Ventana and Synapsee. L.M. Sholl is a consultant/advisory board member for Genentech.

G.R. Oxnard is a consultant/advisory board member for AstraZeneca and Genentech. P.A. Janne is a consultant/advisory board member for AstraZeneca and Roche. P.S. Hammerman is a consultant/advisory board member for Janssen Oncology. L.A. Garraway reports receiving a commercial research grant from Novartis, has ownership interest (including patents) in Foundation Medicine, and is a consultant/advisory board member for Boehringer Ingelheim, Foundation Medicine, and Novartis. F.S. Hodi reports receiving commercial research support from Bristol-Myers Squibb (to the institution), other commercial research support from Bristol-Myers Squibb, Genentech, and Merck; and is a consultant/advisory board member for Bristol-Myers Squibb, Merck, Novartis, and Roche. S.J. Rodig reports receiving a commercial research grant from Bristol-Myers Squibb; has ownership interest (including patents) for use of monoclonal antibodies for PD-L1 IHC; and is a consultant/advisory board member for AstraZeneca. G. Dranoff reports receiving commercial research support from Bristol-Myers Squibb and Novartis and is a consultant/advisory board member for Novartis. D.A. Barbie is a consultant/advisory board member for N-of-One. No potential conflicts of interest were disclosed by the other authors.

The Editor-in-Chief is an author on this article. In keeping with the AACR's editorial policy, the peer review of this submission was managed by a senior member of Cancer Immunology Research's editorial team; a member of the AACR Publications Committee rendered the final decision concerning acceptability.

Authors' Contributions

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