Addressing resistance to PD-1/PD-(L)1 pathway inhibition: considerations for combinatorial clinical trial designs

Tian Zhang,1 Patrick M Forde,2 Ryan J Sullivan,3 Elad Sharon,4 Elizabeth Barksdale,5 Wendy Selig,6 Scot Ebbinghaus,7 Gina Fusaro,8 Damla Gunenc,1 Dena Battle,9 Robyn Burns,10 Marc S Hurlbert,11 Mark Stewart,12 Michael B Atkins13

ABSTRACT
With multiple PD-(L)1 inhibitors approved across dozens of indications by the US Food and Drug Administration, the number of patients exposed to these agents in adjuvant, first-line metastatic, second-line metastatic, and refractory treatment settings is increasing rapidly. Although some patients will experience durable benefit, many have either no clinical response or see their disease progress following an initial response to therapy. There is a significant need to identify therapeutic approaches to overcome resistance and confer clinical benefits for these patients. PD-1 pathway blockade has the longest history of use in melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). Therefore, these settings also have the most extensive clinical experience with resistance.

In 2021, six non-profit organizations representing patients with these diseases undertook a year-long effort, culminating in a 2-day workshop (including academic, industry, and regulatory participants) to understand the challenges associated with developing effective therapies for patients previously exposed to anti-PD-(L)1 agents and outline recommendations for designing clinical trials in this setting. This manuscript presents key discussion themes and positions reached through this effort, with a specific focus on the topics of eligibility criteria, comparators, and endpoints, as well as tumor-specific trial design options for combination therapies designed to treat patients with melanoma, NSCLC, or RCC after prior PD-(L)1 pathway blockade.

INTRODUCTION: IMMUNE CHECKPOINT INHIBITION AND MECHANISMS OF RESISTANCE
With the US Food and Drug Administration (FDA) approving immune checkpoint inhibitors (ICIs) across multiple indications, the number of patients exposed to ICIs for adjuvant, first-line or second-line metastatic, and refractory treatment settings is increasing rapidly. While a minority of patients will achieve durable clinical responses, many others will demonstrate no response or will progress following an initial period of response. Identifying therapies that can overcome resistance and confer clinical benefits for these patients, therefore, represents an area of significant unmet clinical need.

Patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC) have had the longest history with ICI treatment. As a result, patients with these three solid tumors who have documented therapeutic resistance to PD-(L)1 inhibitors pose an increasingly difficult clinical conundrum for treating oncologists. Despite some unique considerations among the three cancer types, efforts to tackle this problem for each of these tumor types can benefit from focused input from basic science researchers defining mechanisms of ICI resistance as well as clinical investigators, clinicians, and patient advocates across cancer types to facilitate clinical development of treatments targeting those ICI resistance mechanisms.

Over the past two decades, fundamental discoveries of the mechanisms by which tumors evade the host immune response have successfully translated into therapeutic opportunities. The advent of ICIs such as CTLA-4 and PD-(L)1 inhibitors has dramatically improved clinical outcomes across solid tumors. These ICIs improve immune activation by inhibiting negative regulatory pathways for tumor immune evasion. Genomic changes, chemokines, and dynamic processes that shift toward immunosuppression can lead to ICI treatment resistance.

To identify key considerations and develop consensus among experts, a consortium of patient advocacy organizations, including the LUNGevity Foundation, Kidney Cancer Cure (KCCure), Melanoma Research Alliance, Melanoma Research Foundation, and Friends of Cancer Research, joined together to launch a working group effort (including leading clinicians, industry leaders, and regulatory officials) to discuss the issues related to
ICI resistance in patients with melanoma, NSCLC, and RCC.

This effort built on the 2019 work of Friends of Cancer Research to identify rational trial designs for evaluating combination therapies for tumors that have progressed after anti-PD-(L)1 therapy and the resistance-related definitions and recommendations put forth by the Society for Immunotherapy of Cancer (SITC) Immunotherapy Resistance Taskforce in 2020. The working group designed a collaborative process, culminating in a 2-day virtual workshop in October 2021 to identify and tackle shared challenges in conducting clinical trials for patients previously exposed to anti-PD-(L)1 therapy across the three tumor types. This paper summarizes meeting findings and subsequent recommendations for future trials (figure 1).

Treatment resistance overview

To date, only a few immune-regulatory pathways have been successfully targeted with ICIs for patient benefit. Response rates of 30–45% have been reported with single-agent anti-PD-(L)1 therapy for certain solid tumor frontline metastatic settings. At best, some regimens reach near 50% objective response rates with combination treatments, as reported in melanoma, lung, and renal cancers. In the majority of patients treated with ICIs, however, tumors can exhibit either primary resistance or secondary/acquired resistance after initial response.

The most common strategy to overcome primary resistance is developing combination therapies that can attack multiple targets simultaneously. ICIs have been added to front-line combinations for chemo-immunotherapy approaches in NSCLC and anti-angiogenic immunotherapy approaches in RCC. However, crosstalk between T cells, antigen-presenting cells, and cancer cells occurs within the tumor microenvironment (TME) and includes many more molecules and interactions. Moreover, the immune response against cancer is not limited to the TME. Many molecular interactions play a role in the process, from T-cell activation after recognition of a cancer antigen, immune cell trafficking to cancer cells, infiltration of these cells into the tumor, and killing of the target cancer cell. This process has been termed the “Cancer-Immunity Cycle” (figure 2). The tumor cell can escape from immune surveillance at several points within this cycle. The most complex and least understood parts of immune resistance involve the dynamic processes taking place in the steps of this cycle that lead to acquired resistance.

Mechanisms of resistance

Generally, tumors with low tumor mutational burden or low immune cell infiltration in the TME (cold tumors) respond poorly to immunotherapies. Therefore, the TME affects the immune response and, thus, the success of the treatment, both in immune activation and in cytotoxicity of tumor cells. Changes in TME content can contribute to immunotherapy resistance. For anti-PD-(L)1 therapy to be effective, there must be a pre-existing T-cell-mediated immune response. Interferon-gamma, released from T cells and natural killer cells, causes the expression of various genes that provide immune activation via the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, and JAK1/2 mutations make up one mechanism identified for primary resistance (figure 3).

Beyond the expression of specific molecules, it has been shown that intact tumor antigen presentation is critical to T-cell activation. The expression of MHC class I and II, which are involved in antigen presentation, engage the T cell through the T-cell receptor, and key chemokines are released, which change the TME immune activation level. Through a series of elegant studies, acquired and/or selected mutations in β2 microglobulin, a component of MHC class I molecules, have been implicated in the impaired T-cell antigen recognition, immune activation,
would have difficulty selecting a homogeneous patient cohort. To date, early trials in this setting have adopted a 6-month cut-off to define primary (duration of prior PD-(L)1 therapy being ≥6 months) versus acquired (prior PD-(L)1 therapy for ≥6 months) resistance; however, efforts are ongoing to create a more nuanced definition.13

The studies to be designed may need to be handled on a tumor-specific basis, as suggested by Schoenfeld et al, as tumor biology differs between histologies.32 For a better understanding of resistance mechanisms and their difference between tumor types, serial tumor biopsies should be obtained in clinical trials. These biopsies can use panels of biomarkers to associate with clinical outcomes, thus allowing for correlation of tumor responses with candidate predictive biomarkers—of both response and resistance. In addition, ongoing analysis of existing patient samples collected since the introduction of ICIs, including those collected in “negative” trials, will provide us with important data.

It is, however, necessary to acknowledge the feasibility and difficulties of serial biopsies within the scope of these clinical trial designs. In obtaining research-related serial biopsies, it is important to ensure proper informed consent with careful risk assessment. Liquid biopsies may soon replace conventional biopsies as a less invasive method, as sequencing technologies improve in sensitivity and specificity for long-term monitoring.

Several candidate biomarkers are being investigated as predictive for ICI responses. These include the PD-(L)1 level as well as transcriptome gene expression signatures. However, it is not enough to find out what is predictive for tumor response to ICIs. Standardizing definitions and methods, for example, to uniformity in definitions of positive or negative PD-L1 status, can improve our understanding of what is transferrable or not across cancer types. In NSCLC, for example, low PD-(L)1 expression is linked to ICI resistance.32–34 For NSCLC, the most used and FDA-approved methodology for PD-(L)1 expression is the tumor proportion score (TPS),33 35 the percentage of viable tumor cells showing partial or complete membrane staining. For other tumors, PD-(L)1 protein expression is determined by using combined positive score,37 which is the number of PD-(L)1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells. Measuring PD-(L)1 expression is further complicated by the variety of antibodies (eg, Ventana PD-(L)1 (SP142) for atezolizumab, Dako 73-10 for avelumab, Ventana PD-(L)1 (SP263) for durvalumab, Dako 28-8 pharmDx for nivolumab) and different cut-offs to define positivity in each tumor type. The panel, therefore, called for consistency across biomarker definitions as they are developed, which will enable more consistent patient selection and analysis in subsequent post-IO trials.

**Clinical trial endpoints**

Overall survival (OS) remains the gold standard clinical endpoint for randomized registration trials. Because demonstration of OS benefit often requires large numbers of patients and long follow-up periods,
alternative endpoints in immunotherapy trials have been explored, with progression-free survival (PFS) successfully used as a primary endpoint (and surrogate of OS) for registrational trials in the metastatic setting. Given both the difficulty of assessing the overall benefit from early radiographic progression, as well as the prolonged duration of effect in patients who have marked responses to checkpoint inhibitor regimens, landmark OS or PFS have also been proposed as intermediate endpoints (eg, for accelerated approval), but require validation before being used for regulatory approval.48

Overall response rate (ORR) is more useful in early analyses and/or in signal-seeking studies than in RCTs with registrational intent. Evaluation of ORR does not always require a comparator and thus is often used in single-cohort studies as an endpoint for accelerated approval. However, ORR may need a comparator for combination treatments to isolate contribution of effect in order to guide subsequent randomized trials. Cross-study comparisons with ORR may also be problematic due to the heterogeneity of different study populations with disparate potentials to respond. Moreover, unless there is a large treatment effect, the apparent clinical benefit seen with this early endpoint may not always translate into PFS or OS improvements.

SPECIFIC CONSIDERATIONS AND RECOMMENDED TRIAL DESIGN CRITERIA

Non-small cell lung cancer

Efforts are ongoing among the thoracic oncology community to define primary and acquired resistance to immunotherapy, recognizing that this is a key trial design question when developing new treatments for both advanced and earlier-stage lung cancer. Unfortunately, success with either novel agent monotherapy or combination immune-checkpoint modulation for patients with PD-(L)1 resistant tumors have been limited.45 49 50 Thus, many development programs for novel, multiple immunotherapy combinations for NSCLC have moved to the first-line setting, typically adding a novel checkpoint inhibitor to a PD-(L)1 backbone.41–45 48

Limited data reported thus far indicate that patients with acquired tumor resistance may have a better prognosis irrespective of the next line of therapy used. A recent systematic review of 59 trials with I-O therapy in NSCLC found that in patients with PFS >6 months with stable disease (SD), outcomes were similar to those with partial response, defining a population of “SD responders.”45 These similar outcomes were observed when either standard chemotherapy or investigational agents were used as next line of therapy.46 47

Specific challenges in the lung cancer space include defining resistance when the initial PD-(L)1 therapy is given in combination with other agents, most frequently chemotherapy. Here, at least a proportion of tumors are likely responding to the chemotherapy component rather than to immunotherapy and would be more appropriately triaged to an immunotherapy-resistant group for next-line treatment. It is possible that early use of novel technologies, eg, ctDNA and/or immune monitoring with T-cell receptor (TCR) sequencing, may allow more refined definitions of clinical benefit from combination immunotherapy treatment, thus allowing appropriate patient selection for ICI resistance trials.48

Patients with NSCLC harboring actionable driver mutations (eg, EGFR, ALK, ROS-1) generally have poor outcomes with ICIs.49 50 However, effective therapeutic options are limited when patients progress on front-line targeted therapies, and ICI outcomes in patients with actionable driver mutations remain an important question for sequential trials. Therefore, the panel advocated that this group of patients should be included when designing clinical trials for refractory NSCLC.

It is possible that combining agents that are not primarily immunologic in their mechanism of action with PD-(L)1 pathway blockade may have a synergistic effect. As an example, initial data from phase I and II trials of lenvatinib with pembrolizumab were encouraging, driving a phase III trial of this combination (LEAP 007). LEAP 007 was conducted in the PD-(L)1 naive setting in patients whose PD-(L)1 TPS is greater than or equal to 1%, and although the study showed longer median PFS for the combination, it met futility criteria for overall survival.51 Other therapies with mechanisms to augment immunotherapy effects are direly needed. With promising early data from both antibody–drug conjugates and DNA damage repair inhibitors, it is likely that combinations of novel agents, not primarily immunologic in mechanism of action, with PD-(L)1 pathway blockade will still be a major focus in the ICI-resistant NSCLC setting. The panel had consensus to define patient populations carefully and for post-ICI trials to be as inclusive as possible of patients with prior treatments.

Renal cell carcinoma

There are now five ICI-based combinations available for clinical use in the front-line setting in RCC, including the combination of nivolumab with ipilimumab or an anti-PD-(L)1 therapy with one of several tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor (VEGF) receptor.11–14 These combinations have extended survival outcomes and shown long-term disease control rates (3-year PFS rates); however, treatment resistance develops in the majority of cases. Understanding the critical mechanisms of resistance and effective sequential therapies are necessary to improve therapeutic options in ICI-refractory disease.

Because the first-line immunotherapy combinations are different in their mechanisms of action, resultant resistance mechanisms will also differ. Therefore, in clinical trials for patients with refractory metastatic RCC, an important consideration should be made to include information on prior therapies, as well as stratification on any randomized efforts to ensure the balance between patients who were treated with nivolumab and
ipilimumab as opposed to an immunotherapy/VEGF receptor-targeting regimen. Patient selection based on prior therapies can be done in trial design in designated separate cohorts, or as stratification based on prior therapies. These prior treatments should be specifically detailed in the eligibility criteria for ongoing and future trials for refractory disease.

The panel also focused on being inclusive in the refractory RCC trial population to allow situations more specific to the RCC patient population. For example, the panel advocated for sufficient flexibility in the inclusion criteria for lower thresholds for glomerular filtration rates (as many patients have had prior nephrectomies causing impaired renal function), for patients with prior non-life-threatening immune-related adverse events, and for patients with stable, treated brain metastases which are common in RCC. These relaxed criteria have been previously developed by an ASCO—Friends of Cancer Research working group and subsequently integrated as inclusion criteria for National Cancer Institute (NCI) Cancer Therapy Evaluation Program trials. Finally, given the likelihood of patients with metastatic RCC who may have received multiple lines of therapies, it is important to avoid limiting the number of prior lines of therapies. These eligibility considerations should be considered to include more diversity of disease in future industry-funded and investigator-initiated trials.

Melanoma

The treatment of patients with advanced melanoma has been transformed by the development of ICIs. With the approval of ipilimumab in 2011, pembrolizumab and nivolumab in 2014, two dual checkpoint inhibitor combinations—ipilimumab and nivolumab in 2015 and nivolumab and relatlimab (an anti-LAG3 agent) in 2022—as well as the first triplet approval in 2020 (vemurafenib, cobimetinib, and atezolizumab), immunotherapy has become the dominant standard-of-care treatment modality for patients with melanoma. Unfortunately, the majority of patients do not have prolonged PFS and will require additional systemic therapy after initial treatment with frontline ICIs.

Importantly, data leading to these approvals are mainly in the adjuvant and frontline settings. There are no routine biomarkers to predict which treatment should be used for a particular patient either as initial therapy or in the event of disease progression. To that end, there is very little known about the benefit of any of these treatments in the post-PD-(L)1 setting. SWOG S1616 was a recent NCI-sponsored effort that addressed this question. Patients with metastatic melanoma who were primarily refractory to a frontline anti-PD-(L)1 monotherapy but naive to a CTLA-4 inhibitor were randomized 3:1 to the combination of nivolumab and ipilimumab or ipilimumab alone, respectively. Patients treated with the combination had an improved PFS as well as an ORR of 28%, compared with 9% for those treated with single-agent ipilimumab. Unfortunately, this trial was initially designed prior to the establishment of definitions for acquired resistance by SITC and other professional societies. Therefore, even with the impressive results that showed a benefit for patients who received combination ipilimumab/nivolumab, there remains a question whether this applies to the patient population who had an initial response to an immunotherapy treatment followed by acquired resistance.

To develop better treatment strategies in the anti-PD-(L)1 resistance space, there are many factors that need to be considered when planning clinical trials. First of these critical factors, nearly half of patients with metastatic melanoma have a V600E mutation of BRAF in their tumors. Since 2011, patients with melanoma have had access to potent, highly selective inhibitors targeting the BRAF V600E mutation. BRAF inhibitors have also been combined with MEK inhibitors. This combination blocks the growth and proliferation of cells that have BRAF mutations. Patients with tumors containing BRAF mutations should be considered separately, particularly given good early response to BRAF/MEK combination therapies. Therapeutic strategies with or without ICIs must consider the availability of alternative regimens for these patients. Finally, the panel recommended that trials for patients with anti-PD-(L)1 resistant melanoma need to account for whether patients have received prior BRAF-targeted therapy.

While designing a clinical trial for sequential use in ICI resistance, apart from currently targetable mutations, a second critical factor is the type of resistance pattern to immunotherapy (primary vs acquired). Retrospective analyses suggest that patients with primary resistance have worse clinical outcomes. Thus, when a randomized trial is planned, the type of resistance could be considered as a stratification factor in randomized trials and also for patient selection in single-cohort studies.

A third important consideration for melanoma trials, as for RCC trials above, is the presence or absence of brain metastases and whether these are treated, stable, and/or symptomatic. And finally, the initial therapy received (single-agent, combination) and whether it was in the adjuvant or metastatic setting should also be key considerations.

In summary, for future trials including patients with melanoma resistant to anti-PD-(L)1 therapy, pertinent patient characteristics to consider include tumor BRAF mutation status, the pattern of resistance, extent of central nervous system metastases, first-line treatment regimen, and the treatment setting of prior therapy. Accounting for these factors will help with patient selection and more homogeneous patient populations.
FUTURE WORK

Ongoing challenges for sequencing therapies and overcoming ICI resistance

With the ongoing challenges of ICI resistance, defining optimal treatment sequencing is of particular importance. One prospective effort from ECOG-ACRIN, the DREAMSeq trial, enrolled patients with metastatic BRAF-mutant melanoma, and randomized to either first-line targeted BRAF/MEK combinations followed by immunotherapy on progression, or the reverse sequence. This trial was completed and recently reported, demonstrating that patients with tumors containing BRAF mutations receive more benefit from frontline treatment with the ipilimumab–nivolumab combination, as opposed to frontline therapy with the BRAF/MEK inhibitors, dabrafenib, and trametinib. With expanding therapeutic options in each disease type, subsequent sequencing trials are clinically critical to defining optimal sequential approaches.

Sequencing trials have been an ongoing central principle for adjuvant clinical trials. The therapies employed in the adjuvant setting are typically the same agents used in the metastatic setting, so adjuvant trials essentially ask whether early treatment for micrometastatic disease is better than delayed treatment in the metastatic setting for solely the patients who have disease recurrence. Adjuvant cytotoxic therapy was generally considered to be more effective in the micrometastatic/minimal residual disease setting, but it is uncertain if this principle applies to patients treated with ICIs. These questions will become more common as more patients receive ICIs in the approved adjuvant disease settings across an increasing number of tumor types. Furthermore, both clinicians and researchers must ask if patients who have disease progression after adjuvant ICIs are truly ICI resistant and whether re-treatment or escalation of treatment will be effective.

Pertinent to the adjuvant versus metastatic disease discussions, some researchers have suggested that giving ICI in the presence of more tumor burden can potentially enhance an immune-based anti-tumor response. This is the strategy behind giving neoadjuvant therapy in combination with ICIs, a strategy recently approved in NSCLC, and shown to have a dramatic benefit in melanoma, but yet to show substantial impact in RCC.

Offering ICIs in earlier lines of treatment adds treatment pressure for resistant clones of cancer cells. Clinicians and researchers are tasked with the quandary of subsequent treatment selection for patients who have already experienced immunotherapy. Therefore, defining windows after adjuvant therapy, where ICIs are thought still to be effective strategies, is critically important for trials enrolling patients who have had prior adjuvant ICI treatment. Trials are already underway across melanoma, NSCLC, and RCC to find efficacious treatments in PD-(L)1 refractory disease with some allowance for treatment in the adjuvant setting (example trials include NCT03991130, NCT03833440, NCT05068427, NCT03858486, NCT05061134, NCT04250246, NCT04987203, and NCT03793166).

Salvage alternative immunotherapy versus enhancing frontline options

The development path for a new immunotherapy or immunotherapy combination has often included launching clinical trials with registration intent in the frontline setting in the selected patient populations most likely to benefit. Another approach would explore the efficacy and, ideally, biomarkers of benefit in smaller, randomized trials such as a randomized phase II trial or even a phase II/III study which includes an interim analysis before enrolling the entire phase III cohort. In fact, such an approach was used in the RELATIVITY 047 trials and the ECOG-ACRIN 6141 trial. In addition, establishing efficacy in an ICI-resistant population would likely justify moving a second-line or later regimen into the frontline space. Most importantly, while it is critical to optimize frontline therapy, the greatest unmet needs in the field are to determine which currently approved frontline regimens should be offered and to develop salvage treatment options for patients with anti-PD-(L)1 resistant disease.

Determining contribution of effect: demonstrating single-agent activity/inactivity versus definitive activity of anti-PD-(L)1 combinations in PD-(L)1 resistant disease

The FDA has a published a guidance document regarding demonstration of the contribution of components when developing two or more investigational agents in combination for a particular condition. One challenge is delineating the contribution of effect from a novel agent and any potential activity from switching the PD-(L)1 targeted agent. While the contribution of effect from the novel agent is a key consideration in this setting, there is substantially less equipoise that switching between PD-1 pathway directed agents has a clinically significant effect. Concern has also been raised about potential lack of equipoise if, for example, a single-agent PD-(L)1 antibody trial arm was a requirement for phase III trials testing a PD-(L)1-based combination in patients with disease progression on a frontline PD-(L)1 antibody regimen.

Most critically, it is incumbent on the sponsor and investigators to design a development strategy that can clearly evaluate whether an effective combination requires each of the regimen’s agents to be effective. The simplest example would be a plan to develop as a combination in the anti-PD-(L)1 resistant disease with Drug X plus an anti-PD-(L)1. If effective, it is not hard to understand that Drug X adds value to the patient since the patient previously developed progressive disease on anti-PD-(L)1 therapy; however, it is not clear whether Drug X needs to be used in combination with anti-PD-(L)1.

Conversely, it is important that the contribution of effect from any novel agent be assessed, particularly in settings where the novel agent has not been approved. This can occur from data sets arising from external trials, for example, data on single-agent activity in a similar PD-(L)1-resistant population from prior phase I or phase
II trials or from a single-agent cohort (with an early stopping rule) within a registrational phase III trial. Therefore, wherever possible, consensus opinion is to minimize or eliminate single-agent PD-(L)1 inhibitor therapy cohorts for trials that focus on PD-(L)1 refractory disease.

A randomized design that includes a cohort treated with single-agent Drug X and a cohort treated with the combination of Drug X plus anti-PD-(L)1 therapy may be an appropriate design, considering what is known about the anti-PD-(L)1 therapy effect in that given population. If the anti-PD-(L)1 therapy effect alone is not known, then an additional arm of monotherapy may be included, with a planned futility analysis to drop any ineffective therapies. Furthermore, if there was evidence from other clinical trials with Drug X that showed benefit as a single agent, but the trial of the combination suggests significantly more benefit, then a single-agent Drug X cohort may not be necessary. In general, the workshop panel recommended minimizing cohorts of patients when possible, while also providing enough justification for contribution of components when testing novel agents in combination with anti-PD-(L)1 therapy.

CONCLUSION

As frontline immunotherapy approaches expand across multiple solid tumors, addressing ICI resistance represents the next frontier in cancer research. The disease types of interest combined in this workshop represented the three solid tumor types with the earliest approvals of ICIs, thereby the most patients who have now developed resistant disease. Through this workshop, we explored putative mechanisms of immunotherapy resistance and discussed commonalities across tumor types for designing the next wave of trials for immunotherapy-resistant disease. As a notable limitation, this workshop summary is not comprehensive in addressing all the complexities of combination therapy clinical trial design. Stratifying for prior therapies remains a common priority for future trial design in post-ICI settings across tumor types. Many PD-(L)1 resistance mechanisms are likely yet to be discovered. Finally, many questions on optimal treatment sequencing or combinations still remain for NSCLC, melanoma, and renal cell carcinoma, and uniformity of clinical trial design in the refractory disease setting will improve future clinical development of effective therapies.

Author affiliations
1Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, Texas, USA
2Johns Hopkins Kimmel Cancer Center, Baltimore, Maryland, USA
3Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA
4Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland, USA
5LUNGeVity Foundation, Chicago, Illinois, USA
6WSCollaborative, McLean, Virginia, USA
7Merck & Co Inc, Kenilworth, New Jersey, USA
8Bristol-Myers Squibb Co Summit, Summit, New Jersey, USA
9Kidney Cancer Research Alliance, Alexandria, Virginia, USA
10Melanoma Research Foundation, Washington, District of Columbia, USA
11Melanoma Research Alliance, Washington, District of Columbia, USA
12Friends of Cancer Research, Washington, District of Columbia, USA
13Georgetown Lombardi Comprehensive Cancer Center, Washington, District of Columbia, USA
14Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, Texas, USA
15Kidney Cancer Research Alliance, Alexandria, Virginia, USA
16Johns Hopkins Kimmel Cancer Center, Baltimore, Maryland, USA
17Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA
18Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland, USA
19LUNGeVity Foundation, Chicago, Illinois, USA
20WSCollaborative, McLean, Virginia, USA
21Merck & Co Inc, Kenilworth, New Jersey, USA
22Bristol-Myers Squibb Co Summit, Summit, New Jersey, USA
23Kidney Cancer Research Alliance, Alexandria, Virginia, USA

Acknowledgements

We are grateful for the support and input from all participants of the “Addressing Resistance to PD1/PDL1 pathway inhibition: a workshop to identify effective clinical trial designs” workshop, which was held virtually in October 2021. Support from LUNGeVity, KC Cure, Melanoma Research Alliance, and Friends of Cancer Research was critical to the workshop discussions and in the development of this final manuscript.

Contributors

Conception and design: WS, EB, DB, TZ, PMF, RJS. Administrative support and supervision: WS, EB, DG. Drafting of the manuscript: all authors. Review and final approval of manuscript: all authors.

Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

TZ reports grants or contracts from Acerta, Novartis, Merrimack, Abbvie/StemCentrex, Merck, Regeneron, Mirati Therapeutics, Janssen, AstraZeneca, Pfizer, OmneGen, Personal Genome Diagnostics, Astellas, Eli Lilly, Elexis, Sanofi-Aventis, Janssen, AstraZeneca, Pfizer, Amgen, BMS, Pharmacyclics, SeaGen, Calithera, QED Therapeutics, Eisai, Aveo, Eli Lilly, Aravive, and Bayer; honoraria from MJH Associates, Vianam, Apptitude Health, Peerview, Clinical Care Options, KCA, SIU, and ASCO; all unrelated to submitted work. DB reports grants from BMS, Elexis, AVEO Pfizer, Eisai, EMD Serono, leadership or fiduciary role in KC Cure (President), NCI GU Steering Committee, and Alliance Cooperative Group GU Committee, all outside the submitted work. WS reports support for the present manuscript from LUNGeVity Foundation paid to her company WSCollaborative. Outside the submitted publication, she reports consulting fees from LUNGeVity Foundation, National Brain Tumor Society, Ovarian Cancer Research Alliance, Cholangiocarcinoma Foundation, Pfizer, Daichi Sankyo, Target Cancer Foundation, CancerCare, Childhood Cancer Coalition, and TriSalus Life Sciences paid to her company; honoraria from American Institutes of Cancer Research; leadership or fiduciary role in Rising Tide Foundation for Clinical Cancer Research; and owns stock in TriSalus Life Sciences. EB reports grants from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, EMD Serono, Genentech, Johnson&Johnson, Merck (MSD), and Natera outside the submitted work. RJS reports grants from Merck, loyalty to Up-to-date, consulting fees from AstraZeneca, Merck, BMS, Novartis, Eisai, Pfizer, and Ivance; and participation on a data safety monitoring/advisory board for Yale and Duke Universities, all outside the submitted work. MSA reports grants from the NCI (P30CA010508, R21CA270585, P50CA109192, R01CA231291, and DoD (KC170216), consultant fees from BMS, Merck, Novartis, Eisai, Aveo, Pfizer, Werewolf, Fathom, Pyxis Oncology, PACT, Epis, X4Pharma, ValeHealth, ScholarRock, Surface, Takeda, Roche, SAB Bio, Elexis, Ivance, Ivance, COTA, Idera, Ageron, Asher Bio, AstraZeneca, Calithera, SeaGen, Sanofi, OncoRena, and GSK; honoraria from Medscape, OncLive, PRIME, Clinical Education Alliance, LivDerm, and ASCO; participation on a data safety monitoring board or advisory board for Novartis, BMS, Pfizer, SIMCHA, Genentech/Roche, and Melanoma Research Foundation; and owns stock in Werewolf, Pyxis Oncology, and Epis, all outside the submitted work. PMF reports research funding to his affiliated institution from AstraZeneca, BMS, Corvus, Kyowa, Novartis, and Regeneron; consultant fees from Amgen, AstraZeneca, BMS, Daiichi, G-Star, G1, Genentech, Jansen, Iteos, Merck, Sanofi, Novartis, and Surface; and participation on a data safety monitoring board for Polaris, outside the submitted work. GF owns stock in Bristol Myers Squibb and works for BMS. MSH is the CEO of the Melanoma Research Alliance. SE is an employee of Merck&Co. The remaining authors report no conflicts of interest.

Patient consent for publication

Not applicable.

Ethics approval

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See http://creativecommons.org/licenses/by-nc/4.0/.


Open access
REFERENCES


