

IMMUNO-ONCOLOGY COMBINATION DRUG DEVELOPMENT FOR PATIENTS WITH DISEASE PROGRESSION AFTER INITIAL ANTI-PD-(L)1 THERAPY

BACKGROUND

During the past five years, one CTLA-4 and six PD-(L)1 inhibitors have gained approval by the Food and Drug Administration (FDA) for a variety of malignancies including melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), lymphoma, urothelial carcinoma, and microsatellite instability-high (MSI-H) cancers.^{1,2} The use of PD-(L)1 inhibitors as single agent therapies in first- and second-line settings is becoming the standard of care for several indications, such as NSCLC, increasing the number of patients being exposed to these IO therapies earlier in the course of their disease.³ However, durable benefit from these PD-(L)1 monotherapies is only observed in a small fraction of patients as many of these patients appear to develop primary resistance.

Novel combination immunotherapy regimens using PD-(L)1 inhibitors as a backbone that modulate different immune pathways simultaneously or in tandem and override the risk of acquired resistance to a single immunotherapy agent are being developed and studied in different indications.⁴⁻⁸

Given the potential for overcoming anti-PD-(L)1 resistance using a combination drug approach, many patients who could benefit from these combination therapies are those whose disease has progressed during or after anti-PD-(L)1 monotherapy. However, it is not fully understood how these previously treated patients will respond to re-exposure to additional anti-PD-(L)1 therapies given in combination with additional agents. In some cases, the PD-(L)1 inhibitors or their combination agents may be already FDA-approved, but there may be cases in which they are not. Several scenarios exist, including the combination of two or more investigational drugs, an investigational drug with a previously approved drug for a different indication, or two (or more) previously approved drugs for a different indication as

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Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients.

a novel combination therapy. These scenarios have been previously explored and innovative strategies that properly assess the contribution of components of the combination drug regimen have been discussed.⁹

The mechanisms of resistance to PD-(L)1 inhibitors are not well understood as some patients may not respond to these inhibitors at all and develop progressive disease right away, while others may respond to treatment initially or partially, and eventually develop progressive disease. A better understanding of the mechanisms by which patients develop refractory or relapsed disease will help guide subsequent drug alternatives for patients whose disease progressed during or after PD-(L)1 inhibitors. Moreover, refining the definition of disease that has relapsed or has become refractory to treatment will also further elucidate the population being studied, which will help guide the interpretation of the study findings.

Exploring the development of promising combination therapies using PD-(L)1 therapy as a backbone is imperative and a rational next-step to overcome resistance to monotherapies. However, knowing that the study population will most likely be composed of both PD-(L)1 inhibitor-pre-treated and PD-(L)1 inhibitor-naïve patients, it is crucial to discuss any additional considerations that the pre-treated population may require to closely monitor the safety and efficacy of the novel combination drugs while maintaining proper equipoise. For instance, would there be a lack of equipoise if a patient whose tumor progressed after anti-PD-(L)1 therapy is randomized to the single-agent PD-(L)1 inhibitor control arm in a late-stage randomized controlled clinical trial? And would this be dependent on disease type? Because there are not enough data to guide treatment decisions in this rapidly-growing pre-treated population, there is great uncertainty as to whether a patient's tumor would respond when re-exposed to the same agent in combination, to monotherapy with another same-in-class agent, or even if the patient would respond to an inhibitor that targets PD-(L)1 if they have received a PD-1 inhibitor (or vice-versa). It is not fully understood whether the patient's immune system will behave similarly to an immunotherapy-naïve patient, or if further considerations, such as timing or a specific washout period from anti-PD-(L)1 therapies, will impact subsequent response to re-exposure to additional anti-PD-(L)1 therapy.

Friends of Cancer Research (*Friends*) convened a group of experts from various healthcare sectors to discuss important considerations to keep in mind that patients whose disease has progressed after anti-PD-(L)1 therapies face when seeking to enroll in clinical trials testing combination therapies including a PD-(L)1 inhibitor. The objectives of the working group and this whitepaper encompass the development of a framework that will help harmonize the definition of a population whose disease has progressed after PD-(L)1 inhibitors, and the identification of flexible trial design strategies and innovative approaches that allow for earlier exploration and modifications based on interim analyses, and the characterization of roles that external data may have to support immuno-oncology combination trials. The primary goal of these discussions is to propose actionable, practical, and rational solutions for the unique needs of patients whose tumors have progressed after anti-PD-(L)1 therapies, which will promote the development of drug combinations and increase accessibility to better treatment options for this growing population.

Framework for the Harmonization of a Definition for a Population Whose Disease has Progressed After Initial Anti-PD-(L)1 Therapies

Disease that has progressed past treatment can be referred to as (1) relapsed disease when the disease has initially responded positively to treatment but later reappeared or grew after having been in remission for a time, or (2) refractory disease when the disease has not responded positively to treatment or even progressed during treatment. However, relapsed disease can become refractory to the treatment it once responded to, so it is not surprising that these two terms are often confused, or at times used interchangeably. Actually, various publications have repeatedly combined both relapsed and refractory (r/r) diseases into a single category. As the use of this combined term to define solid tumors that ultimately fail to respond to treatment increases, and as the community learns more about the unique patterns of response to immunotherapies, it is important to accurately define what is meant by r/r disease and refine these terms within the context of immunotherapies, more specifically, after PD-(L)1 inhibitors.

Assessing response to PD-(L)1 inhibitors is complex because clinical response to immunotherapies is unique and does not follow the established patterns observed with cytotoxic therapies. Various reports have shown delayed clinical responses in studies with immunotherapies where patients have shown an increase in total tumor burden, either by growth of existing lesions or appearance of new lesions, followed by decreased tumor burden¹⁰. This atypical response pattern is known as pseudoprogression and seems to be unique to immunotherapy. If such a response was evaluated using the conventional Response Evaluation Criteria In Solid Tumors (RECIST) criteria established to assess whether a solid tumor responded, stayed the same, or progressed, patients receiving immunotherapies would be classified as having progressive disease even if their tumors actually responded to treatment.^{11–14} Several efforts subsequently addressed this challenge,^{10,15–17} which led to the development of response criteria that incorporated RECIST 1.1 recommendations, but is better able to address the atypical patterns of response associated with immunotherapies: iRECIST.¹⁸ Use of iRECIST would ensure consistency in the way the trials were designed and the way data was collected, which would enable the comparison of results across trials. It is important to note, however, that to date, no drug has been approved based on immune-related response criteria only.

The complexity of identifying clinical efficacy, or lack thereof, in patients receiving PD-(L)1 inhibitors is one of the remaining challenges that confounds the definition of a population of patients whose disease has truly progressed past PD-(L)1 inhibitors. These remaining challenges have been acknowledged by the research community, launching several initiatives that further investigate, discuss and develop strategies to align definitions to better characterize patients with r/r disease after initial anti-PD-(L)1 therapy, such as the Society for Immunotherapy of Cancer (SITC) PD-(L)1 Resistance Definition Task Force. Open discussion among experts will drive research that investigates mechanisms of resistance to PD-(L)1 inhibitors, and thus promote a greater understanding on how patients who progress past these therapies should be treated.

Friends conducted a survey with six pharmaceutical companies that have a marketed FDA-approved PD-(L)1 inhibitor to better assess the variability in definitions for r/r disease being utilized in current clinical trials of PD-(L)1 inhibitors, and to learn whether the definition is harmonized across each pharmaceutical company. All six companies surveyed expressed interest in the idea of a harmonized definition of r/r disease and commented this is an area where further guidance is necessary. Three of the six companies (50%) surveyed had

a company-wide harmonized definition of *r/r* disease, and those who did not mentioned they are working on incorporating a more consistent definition of disease progression into their clinical trials (Table 1). The survey also asked sponsors to share their definition of *r/r* disease (if available) in order to compare the variability across company definitions.

When analyzing the definitions provided by the different sponsors, three main principles emerged. These revolved around 1) identifying adequate exposure to anti-PD-(L)1 therapies by specifying dose or length of anti-PD-(L)1 therapy that was used before disease progression; 2) identifying and confirming progression of disease, including the type of scan, or the timing at which this scan would be done; and 3) identifying the likelihood of responding to re-exposure of anti-PD-(L)1 therapies (Table 2).

Some pharmaceutical companies raised concerns about a harmonized *r/r* definition as they acknowledge there are considerations that need to be taken into account when defining *r/r* disease in different populations, as there are various factors that may influence the evaluation of disease progression. Seeing as how the assessment of disease progression in patients treated with PD-(L)1 inhibitors is so nascent, the influence of factors such as cancer type, the natural history of disease, the biology of the drug assessed, and the timing of scans need to be further investigated within this unique context.

Table 1: State of Harmonization of Relapsed/Refractory Disease Definitions of Six Major Pharmaceutical Companies with a Marketed FDA-approved PD-(L)1 Inhibitor

Question	Sponsor A	Sponsor B	Sponsor C	Sponsor D	Sponsor E	Sponsor F
Harmonized r/r disease definition within company	Yes	Yes	No	No	No	Yes
Comments	Variations can occur related to specific tumor types	Definitions are specific for primary, secondary, and adjuvant resistance	Due to differences in disease setting, prior therapy, and stage of drug development	Company does not have enough studies in this space yet	Company has proposed criteria but no harmonized language yet	Terminology for "progressed on or recurred after an anti-PD-1 agent"
Definitions	<p>Patients must have progressed on treatment with an anti-PD1/(L)1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD-1 treatment progression is defined by meeting all of the following criteria:</p> <ul style="list-style-type: none"> Has received at least 2 doses of an approved anti-PD-1/(L)1 mAb. Has demonstrated disease progression after PD-1/(L)1 as defined by RECIST v1.1. The initial evidence of disease progression (PD) is to be confirmed by a second assessment no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression.^{1,2} Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/(L)1 mAb. 	<p>The recommendation is to generally include all categories of resistance, but use "primary," "secondary," and "adjuvant" resistance for patient stratification purposes.</p> <ul style="list-style-type: none"> <u>Primary Resistance:</u> patients must have experienced progressive disease (PD) within 12 weeks of initiation of PD-(L)1 inhibitor-based treatment. Radiographic confirmation of the PD must be documented*, after a minimum of 4 weeks after the initial identification of progression, unless: i) investigator confirms clinical progression/deterioration attributed to PD, or ii) the first radiographic assessment indicated critical tumor growth by imaging (size or location). <p>*The purpose of radiographic confirmation is to minimize inclusion of patients with pseudoprogression; however, study teams have the option to waive this requirement.</p>	<p>Generally, we have incrementally modified our definition of progression to be more consistent across clinical trials that include anti-PD-(L)1 therapies in solid and hematological diseases, to account for tumor flare, and to incorporate feedback received from Health Authorities in our programs.</p> <p>» For proof-of-concept studies only: - CPI refractory: best response by RECIST is PD - CPI-responsive: best response by RECIST is PR or SDx 6 months followed by PD</p>	<p>At present definitions are still being discussed</p>	<p>We will be happy to share the definition, when harmonized</p>	<p>We believe there are at least 3 distinct patient populations:</p> <ul style="list-style-type: none"> Patients who do not respond & progress on anti-PD-(L)1 (or within 6 months of treatment) Patients who progress after initial response while on anti-PD-(L)1 Patients who progress after initial response to anti-PD-(L)1 off drug

Question	Sponsor A	Sponsor B	Sponsor C	Sponsor D	Sponsor E	Sponsor F
<p>Definitions (con't)</p>	<p>1. Seymour et al; iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 18; e143-52</p> <p>2. This determination is made by the investigator. Once PD is confirmed, the initial date of PD documentation will be considered the date of disease progression.</p>	<ul style="list-style-type: none"> Secondary Resistance: patients must have experienced progressive disease (PD), either during or within 3 months of discontinuing treatment with anti-PD-(L)1-based therapy, occurring after previous clear benefit (any complete (CR) or partial response (PR)), or after previous stable disease (SD). No requirement for radiographic confirmation of progression. Adjuvant Resistance: patients with documented loco-regionally and/or systemic relapse of their disease occurring <6 months after the last dose of anti-PD-(L)1-based systemic adjuvant treatment. <p>In an effort to ensure that Phase 1/2 signal-finding studies are conducted in a population that is not potentially still sensitive to their prior anti-PD-(L)1 therapy, we are not including patients that experience progression > 3 months after cessation of anti-PD-(L)1-based therapy in the metastatic setting or > 6 months in the adjuvant setting, regardless of the rationale for cessation of treatment. In addition, we are generally recommending exclusion of patients that have received intervening systemic therapy following prior anti-PD-(L)1-based therapy.</p>				<p>We believe it is important to study these patient populations separately. An additional patient population to consider in this context (and not covered by "relapsed/refractory" definitions) is patients with stable disease while on PD-(L)1 inhibitors</p> <p><u>Additional criteria:</u></p> <ul style="list-style-type: none"> Patients must have confirmed disease progression on anti-PD-(L)1 therapy as defined by RECISTv1.1 and further defined as: <ul style="list-style-type: none"> Previous exposure to anti-PD-1 containing regimen for at least 12 consecutive weeks, and Progression must be while on treatment with anti-PD-1 or within 6 months of discontinuing anti-PD-1, and regardless of any intervening therapy

Table 2: Principles and Considerations for the Definition of Relapsed/Refractory Disease

Principle	Considerations	Example
1. Identifying adequate exposure to anti-PD-(L)1 therapies	<ul style="list-style-type: none"> • Dose of anti-PD-(L)1 therapies • Length of anti-PD-(L)1 therapies 	Has received at least 2 doses of an approved anti PD-(L)1 therapy.
2. Identifying progression of disease		
Evaluation of progression	<ul style="list-style-type: none"> • Tumor-specific criteria • Adequacy of measurement method 	<ul style="list-style-type: none"> • Different cancer types may require different approaches to evaluate progression. • Progression in prostate cancer is evaluated using the PCWG3 criteria,¹⁹ and in glioblastoma, the modified RANO criteria.²⁰
Confirmation of progression	<ul style="list-style-type: none"> • Ability to address pseudo-progression • Timing • Equipoise: patients with immediate life-altering disease & timing 	<ul style="list-style-type: none"> • Radiographic confirmation of disease. • Documented after a minimum of 4 weeks of initial identification of progression.
3. Identifying likelihood of responding to re-exposure of anti-PD-(L)1 therapies	<ul style="list-style-type: none"> • Time from anti PD-(L)1 therapy initiation • Time from last anti-PD-(L)1 therapy administration • Refractory – disease progressed because it did not respond to drug • Relapsed – disease initially responded to drug & then progressed • Adjuvant vs. metastatic setting • Intervening treatment • Does resistance to one drug within class mean resistance to all drugs within class? 	

Considerations for the Assessment of Combination Drugs Using a PD-(L)1 Inhibitor Backbone in Patients Whose Disease Progressed After PD-(L)1 Inhibitors

Combination drug trial design strategies: maintaining a fine balance between efficiency and equipoise in patients who have been previously treated with PD-(L)1 inhibitors

The development of innovative combination drug clinical trial designs, such as master protocol platform designs and seamless adaptive designs that allow for modifications based on interim analyses while achieving the appropriate statistical rigor, would greatly benefit patients and enable the collection of data to support clinical decision making in this unique population of previously-treated patients.

In addition to striking the right balance between providing potentially life-saving therapies to advanced cancer patients with very few therapeutic options, and minimizing a patient's exposure to ineffective and harmful therapies by rapidly identifying patients who do not derive any benefit from their assigned therapy (via early efficacy or futility evaluation), combination drug trials must also determine the contribution of each of the investigational drugs assessed in combination.

Several combination drug trial designs and approaches have been previously explored to help isolate the treatment effects of the agents used in combination.

- **2x2 factorial design.** Several reports have comprehensively reviewed the benefits and challenges of using the most optimal 2x2 factorial clinical trial design (e.g. SOC vs. A vs. B vs. A+B) to understand the attribution of effects for the single agents and their combination; however, this approach may generate duplicative data and reduce the lack of equipoise created when patients are assigned to the control arm knowing they are predicted to receive no benefit from it.
- **Randomized early-stage clinical trials.** Assessing efficacy and safety through randomized early-stage clinical trials, such as randomized, open label, phase 2 trials that incorporate a "master" protocol framework (such as umbrella, basket, or platform trials) would enable sponsors to identify a treatment arm that shows the best activity in a smaller number of patients and would signal the need to increase development efforts.
- **Single-arm trials.** Another alternative method involves supportive single-arm trials, when randomized trials may not be feasible. In such cases a single-arm trial may be the next best approach to translate preliminary results into predictions of Phase 3 benefit and risk. In the absence of randomized trials, however, a comprehensive evaluation of the contribution of each individual component in both preclinical and clinical data would be needed, given that time-to-event endpoints, such as OS, will likely not be informative.
- **Common controls.** The use of a common control may incorporate the flexibility needed to better assess efficacy and safety when there is a desire to minimize the number of patients randomized to a control arm. The i-SPY2 trial used this method to more rapidly accrue patients and minimize the number of patients assigned to a standard of care (SOC) control arm that may be lacking equipoise as in the case of previously-treated patients enrolling in a combination drug trial using a PD-(L)1 backbone.²¹ In the i-SPY2 trial, the FDA supported the use of a common control arm, but additional guidance and further work to better characterize this type of design is necessary given that this is not a common method to assess clinical benefit.

Additionally, the FDA has generated guidance on the Codevelopment of Two or More New Investigational Drugs Used in Combination, which describes criteria for knowing when codevelopment is appropriate, and identifies various development strategies as well as regulatory considerations.²²

All these strategies seek to address one of the main concerns about investigating the efficacy and safety of a combination regimen that has a PD-(L)1 inhibitor backbone in patients whose disease has progressed after an initial PD-(L)1 inhibitor: **Will the patient's disease be able to respond to the challenge by either the same PD-(L)1 inhibitor or a similar in-class inhibitor when used in combination with another drug or biologic?** This is not a particularly novel question, given that there have been several studies where patients treated with earlier-generation therapies have been subsequently re-challenged with a same-in-class novel agents and demonstrated clinical benefit (e.g., retreatment of advanced NSCLC patients with later-generation ALK inhibitors after becoming resistant to a first-generation ALK inhibitor^{23,24}). However, if focusing on immunotherapy, much can be learnt from the first trials assessing the use of PD-1 inhibitors (nivolumab and pembrolizumab) in patients who developed melanoma that is refractory to CTLA-4 inhibitor (ipilimumab), another immune checkpoint inhibitor (Table 3).

Table 3: Characteristics of KEYNOTE-001, KEYNOTE-002 and CheckMate 037, Clinical Trials Investigating the Efficacy of PD-1 Inhibitors in Patients with Advanced Melanoma who Progressed After Anti-CTLA-4 Therapy

	KEYNOTE-001 (Robert et al., 2014)	KEYNOTE-002 (Ribas et al., 2015 & Hamid et al., 2017)	CheckMate 037 (Weber et al., 2015 & Larkin et al., 2017)
Clinical trial type	Randomized, dose-comparison, open label, expansion cohort of a phase 1 international trial	Randomized, controlled, phase 2 international trial	Randomized, controlled, open label, phase 3 international trial
Number of patients	173 given pembrolizumab, 89 at 2mg/kg, and 84 at 10mg/kg	357 given pembrolizumab (178 at 2mg/kg, 179 at 10mg/kg) and 171 given investigators choice chemotherapy (ICC)	268 given nivolumab and 102 given ICC
Definition of anti-CTLA-4 refractory melanoma population	<ul style="list-style-type: none"> • Progressive, measurable, unresectable melanoma • Previously treated with at least 2 doses of ipilimumab 3 mg/kg or higher administered every 3 weeks • Confirmed disease progression using immune related response criteria within 24 weeks of the last dose of ipilimumab • Previous BRAF or MEK inhibitor therapy or both (if BRAF V600 mutant-positive) and no limitations on the number of previous treatments 	<ul style="list-style-type: none"> • Histologically or cytologically confirmed unresectable stage III or stage IV melanoma not amenable to local therapy • Confirmed disease progression within 24 weeks of the last ipilimumab dose • Minimum two doses, 3 mg/kg once every 3 weeks; • Previous BRAF or MEK inhibitor therapy or both (if BRAF V600 mutant-positive) 	<ul style="list-style-type: none"> • Histologically confirmed, unresectable stage IIIC or IV metastatic melanoma • Patients with BRAF wild-type tumors must have had progression after anti-CTLA-4 treatment, such as ipilimumab, and patients with a BRAF V600 mutation-positive tumor mutation must have had progression on anti-CTLA-4 treatment and a BRAF inhibitor
Crossover	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • Allowed • Effective crossover rate= 58% 	<ul style="list-style-type: none"> • Prohibited until the interim analyses • High percentage of patients in the ICC arm withdrawing consent (17%)

KEYNOTE-001 started as a phase 1 adaptive clinical trial that sought to define the safety and tolerability of pembrolizumab in patients with advanced solid tumors (reviewed in Kang et al.).²⁵ Although these initial study cohorts were not powered for efficacy, a substantial antitumor activity was observed, which provided the necessary rationale for an expansion randomized dose-comparison cohort of a phase 1 trial investigating pembrolizumab in patients with advanced and ipilimumab-refractory melanoma.²⁶ The definition of their study cohort used the recently developed immunotherapy-related response criteria guidelines¹⁵ to ensure they were studying patients who had truly progressed after their initial immunotherapy (ipilimumab). Moreover, the adaptive design used in this trial was key in the early identification of substantial antitumor activity that led to the accelerated approval of pembrolizumab for unresectable or metastatic melanoma with disease progression after ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Following KEYNOTE-001, KEYNOTE-002, a randomized, controlled, phase 2 trial, conducted a safety and efficacy study between patients treated with two different doses of pembrolizumab and investigator's choice of chemotherapy (ICC) in an equally defined population of ipilimumab-refractory melanoma.²⁷ This trial had planned two interim analyses that would allow for the identification of early response outcomes.

CheckMate 037 was a randomized, controlled, open-label, phase 3 trial that compared nivolumab with ICC in a population of ipilimumab-refractory melanoma patients. The trial design included an interim analysis assessing objective response as the primary analysis in a predefined population.¹⁰ Moreover, a descriptive interim progression-free survival (PFS) analysis was also conducted in the intention-to-treat population at the same timepoint as the first analysis.

These trials initially demonstrated clinically meaningful improvements in objective response and PFS respectively, as well as fewer toxic effects compared to patients treated with ICC. Final analyses for KEYNOTE-002 and CheckMate 037 trials showed improvement in overall survival as well as durable response with the PD-1 inhibitors; however, these were not statistically significant.^{28,29} Various factors could have contributed to the lack of significance in overall survival between the treatment and control arms, including allowing crossover between treatment groups. In KEYNOTE-002, the effective crossover rate was 58%, while in CheckMate 037, prohibiting crossover until the interim analysis could have been the reason why a high fraction of patients in the ICC arm withdrew consent.

Trial design determinations, such as whether crossover would be allowed or not, hinge on a fine balancing act between a trial's ability to detect significant drug efficacy and maintaining proper equipoise. All data derived from all stages of drug development (e.g. preclinical, early clinical trial, late and confirmatory trial, etc.) should be considered to make these determinations, and trialists are required to make trial design and statistical determinations that provide patients the care most likely to benefit them. This is the impetus behind the need for more flexible clinical trial designs that are able to meet the necessary statistical rigor for approval while placing the patient's safety and interests first and providing them a choice when preliminary findings reveal a potential lack of equipoise.

Currently, a few active trials are assessing the clinical utility of combination drugs using PD-(L)1 inhibitors as a backbone in patients whose disease progressed after anti-PD-(L)1 therapy, while adopting a flexible trial design, which allows for greater adaptability to changes driven by earlier assessment of patient safety and efficacy outcomes. As trial data becomes available, it will be important to assess how the added flexibility

of the platform trials contributes to a finer balance between trial efficiency and equipoise. Examples of such trials include:

- The HUDSON study is a phase 2 study that assesses novel biomarker-directed drug combinations that include durvalumab, an approved PD-(L)1 inhibitor, as a backbone in patients with NSCLC who progressed on an anti-PD-(L)1 containing therapy (NCT03334617).³⁰ This ongoing trial is an umbrella study with a modular design, which is able to conduct initial assessments of efficacy, safety, and tolerability in multiple treatment arms. This flexible design also allows trialists to add future treatment arms as needed via protocol amendment.
- The PLATforM study is a randomized phase 2 study of the novel PD-1 inhibitor Spartalizumab in combination with novel drugs and biologics in patients with unselected, unresectable, or metastatic melanoma previously-treated with PD-(L)1 ± CTLA-4 inhibitors, and a BRAF inhibitor, alone or in combination with a MEK inhibitor, if BRAF mutation positive (NCT 03484923).³¹ In addition, based on an extensive tumor biopsy and blood sampling at baseline and on treatment, a key secondary endpoint of the study is to assess the percentage of patients with a favorable biomarker profile, as defined by favorable changes in number of cells expressing T-cell markers.

Challenges for the Assessment of Combination Immuno-oncology Therapies in the Adjuvant Setting

Combination IO trials are not only assessing response in patients with advanced disease who no longer have treatment options. Immune checkpoint inhibition is also being used earlier in the disease course, more specifically, in the adjuvant setting. A couple of scenarios that are becoming increasingly common in the clinic include the use of adjuvant anti-PD-(L)1 therapy in patients with Stage III/IV resected melanoma and anti-PD-(L)1 therapy after definitive chemoradiation therapy in patients with Stage IIIB NSCLC.

- Scenario A: Patient with Stage III melanoma treated with PD-(L)1 inhibitor monotherapy recurs while on adjuvant anti-PD1 therapy. This recurrence represents resistance to therapy.
- Scenario B: Patient with Stage III melanoma treated with PD-(L)1 inhibitor monotherapy develops recurrent disease after completing the planned treatment cycles or sooner (e.g., in case of toxicity). Recurrence may represent resistance to therapy, but this determination is less clear.

It is well described that patients with Stage IV melanoma who have a complete response and then discontinue therapy may again respond when re-challenged with the same or similar therapy. It stands to reason that patients who discontinue therapy after completing a planned year of adjuvant therapy may respond to re-treatment in the setting of disease recurrence. However, the magnitude of the effect may be smaller if there is ongoing target engagement of the PD-1 antibody with T-cells. As this occurs for at least 12 weeks and perhaps up to 6 months, by convention, it has been accepted generally to consider a patient resistant to anti-PD-(L)1 therapy if the last dose was within 3 months, and in some definitions, 6 months. This convention is reflected in Table 1. It is imperative to develop and implement a consistent framework for the proper documentation of response in patients who are re-challenged with immune checkpoint inhibitors. Whether these are given as monotherapies or in combination, either on clinical trials or off study, it will be critical to determine what the true rate of “resistance” is in patients whose disease progress after adjuvant

PD-(L)1 inhibitor therapy and whether there are predictive factors, including timing of last adjuvant dose to time of recurrence or specific biomarkers that may be useful in patient risk stratification.

Advantages to the Use of External Data for the Assessment of Combination Immuno-oncology Therapies

It is important to explore the use of external data to complement clinical trial data and further confirm the benefit of the combination regimen. Several efforts are being carried out to better understand the use of synthetic control arms derived from historical clinical trial data to augment clinical trial data, especially in instances where assigning a randomized control arm lacks equipoise or is not possible due to scarcity of patients, or when elevated crossover rates may compromise control arm data and make it unusable (2018 and *Friends* 2019 Annual Meeting whitepaper on external controls).³²

Assessing the safety and efficacy of combination drugs with an anti-PD-(L)1 therapy backbone in patients whose disease has progressed after an initial PD-(L)1 inhibitor is not straight forward and will require out-of-the-box thinking. There are several remaining questions that need to be further discussed and potentially several areas that require further evidence development to better inform treatment alternatives for this unique and growing population of patients previously treated with an immunotherapy.

Remaining Questions or Areas that Warrant Evidence Development and Continued Discussion

- What type of data needs to be collected to enable a better understanding of potential patient response to re-challenge by either the same PD-(L)1 inhibitor or a similar in-class inhibitor when used in combination with another drug or biologic?
- Consistency in collecting data to determine timing of progression—will a harmonized method for data collection help investigate the association with likelihood of response to re-challenge?
- What preclinical models or clinical translational data would be helpful to identify combinations most likely to be effective in patients who have progressed on PD-(L)1 therapies?
- What is the role of biomarkers in better understanding the drug combinations most likely to be effective in patients who have progressed on PD-(L)1 therapies?
- Randomization approaches that allow for earlier examination of effect via interim analyses
 - Earlier identification of patients who may not be deriving benefit from monotherapy arm using, for example, response adaptive randomization
- What are some statistical considerations or approaches to evaluate early efficacy or early futility in these trials?
- Statistical considerations for addressing crossover
 - Knowing that crossover is a common issue when preclinical and early phase data for a novel

- agent demonstrates significant antitumor activity, what are some innovative statistical strategies to properly deal with crossover?
- An example may include crossover-adjusted overall survival using rank preserved structural failure time (RPSFT). Under certain assumptions, the RPSFT model can be used to identify what survival difference would have been observed had all patients remained on the original assigned treatment
 - Not all statistical approaches apply to all cases. Several approaches may be needed.
- Is there a role for non-invasive monitoring of treatment response in the adjuvant setting (i.e. ctDNA monitoring)? Would this enhance the identification of patients who respond to treatment vs. patients who never achieved a benefit?

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