FRIENDS of CANCER RESEARCH

OPPORTUNITIES FOR COMBINATION DRUG DEVELOPMENT:

DATA SOURCES AND INNOVATIVE STRATEGIES TO ASSESS CONTRIBUTION OF COMPONENTS

Friends of Cancer Research (*Friends*) convened a multi-stakeholder meeting consisting of representatives from the U.S. Food and Drug Administration (FDA), the National Cancer Institute (NCI), the pharmaceutical industry, academia, and professional and patient advocacy organizations. This meeting served as a platform for characterizing key challenges and proposing forward-looking solutions in the development and regulation of combination therapies. This can include combinations 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 a novel combination therapy. The roundtable discussion was segmented into two parts:

Part I: Innovative Methods to Facilitate Combination Drug Development

Part II: Strategies for the Development of Unapproved PD-(L)1s Intended for Use in Combination Therapies

The issue of combination therapy development is especially timely and important for patient access. As the number of combination therapies and codeveloped new investigational drugs increases, clinical trials are requiring increasingly complex study designs to accommodate more trial arms and the accrual of an extensive number of patients. Trial sponsors and regulators will need to balance the level of evidence needed for approval in the context of data that may already be available to ensure equipoise and expedite development. Innovative methods for assessing contribution of components in combination regimens are necessary to facilitate expedited approval. It must also be acknowledged that the goal of all stakeholders in the drug development process is to promote the rapid availability of safe and effective drug products, at the lowest possible cost, for the benefit of patients, while minimizing patients' exposure to

ABOUT FRIENDS OF CANCER RESEARCH

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.

potentially ineffective and harmful agents.

This document is meant to facilitate ongoing discussions to further develop concepts extracted from the roundtable discussion as well as encourage additional input and proposals designed to facilitate the development of combination therapies.

PART I: INNOVATIVE METHODS TO FACILITATE COMBINATION DRUG DEVELOPMENT

The *Friends* multi-stakeholder roundtable began with two case-study presentations by representatives from Bristol-Myers Squibb (BMS) and Janssen. Below are key points from these presentations:

Case Study 1: Nivolumab-Ipilimumab Renal Cell Carcinoma Development Experience

Combination: Nivolumab (A) + Ipilimumab (B) v. Sunitinib (C)[1]

The nivolumab-ipilimumab combination was approved by the FDA for patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma. The pivotal phase III trial was a randomized open-label study. It was randomized 1:1 and compared nivolumab plus ipilimumab with sunitinib. The primary endpoints were overall survival (OS) and objective response rate (ORR). Previous clinical trials investigating single agent efficacy and in combination had been conducted, which contributed to the safety and efficacy information on the contribution of each agent.[2,3,4] Bristol-Myers Squibb noted that the key challenges of combination development are understanding and demonstrating the additional benefit necessary for justifying added toxicity and demonstrating the contribution of each component of a combination.

Case Study 2: Daratumumab-Pomalidomide-Dexamethasone Multiple Myeloma Development Experience

Combination: Daratumumab (A) + Pomalidomide (B) + Dexamethasone (C)

The daratumumab-pomalidomide-dexamethasone (D-Pd) combination was evaluated in patients with relapsed/refractory multiple myeloma (MM) with ≥ 2 prior lines of therapy who were refractory to their last treatment. FDA approval was based on a non-randomized, multi-center, multi-cohort, phase 1b study. The treatment cohorts evaluated daratumumab in combination with multiple regimens. The primary endpoints included maximum tolerated dose (MTD) and ORR.

[1] Motzer R, Tannir N, McDermott D, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 2018;378:1277-1290.
[2] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23-34.
[3] Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 2016;17:883-895.
[4] Hammers HJ, Plimack ER, Infante JR, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. J Clin Oncol 2017;35:3851-3858.

Daratumumab had previously been approved as a monotherapy for the treatment of patients with heavily treated MM.[5] Pom-dex has also demonstrated progression free survival (PFS) benefit in patients with relapsed and refractory MM compared with pom alone.[6] External data supporting the findings from this single-arm combination study includes the results from two recently completed Phase 3 studies (POLLUX and CASTOR). The POLLUX phase 3 study, in which a combination of daratumumab with lenalidomide and dexamethasone and the CASTOR phase 3 study in which daratumamb plus bortezomib/dexamethasone (Vd) was evaluated against Vd alone induced a high ORR and significantly reduced the risk for disease progression and death in patients with relapsed or refractory MM compared with lenalidomide and dexamethasone. In an indirect comparison with historical data, D-Pd showed a clear benefit over individual components, existing therapy, and other historical datasets.

Table 1. Summary of Case Study Presentations.

Combination	Pivotal Trial Design	Use of External Data
Nivolumab (A) + Ipilimumab (B)	Nivolumab (A) + Ipilimumab (B) v. Sunitinib (C)	Previous clinical trials investigating single agent efficacy and in combination contributed to the safety and efficacy information on the contribution of each agent
Daratumumab (A) + Pomalidomide (B) + Dexamethasone (C)	Daratumumab (A) + Pomalidomide (B) + Dexamethasone (C)	Supported approval of a combination therapy based on a single-arm trial

These case studies were intended to frame the issue of combination therapy development and highlight real-world examples of the use of external data sources in the combination development and approval processes.

[5] US Food and Drug Administration. FDA approves Darzalex for patients with previously treated multiple myeloma [press release]. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm472875.htm. Accessed 18 January 2019.
[6] Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014;123(12):1826-1832.

INTRODUCTION

In 2013, the FDA released the "Codevelopment of Two or More New Investigational Drugs for Use in Combination" guidance for industry.[7] This guidance acknowledged that advances in the understanding of the pathophysiological processes underlying disease had, in many cases, necessitated the use of multiple targeted therapeutic agents to improve treatment response, reduce development of resistance, or minimize adverse events. The guidance was intended to be a high-level description of an approach for the development of two or more new investigational drugs[8] and describes criteria for determining when codevelopment is appropriate, recommends development strategies, and addresses certain regulatory concerns. This guidance also describes the necessity of demonstrating the contribution of each component to the effect of the novel combination therapy. While meeting this expectation is required, there may be more efficient processes and methods for data generation in scenarios involving the combination therapies discussed in this paper.

Although the FDA's 2013 guidance provides an overview of the development and regulatory processes for two or more new investigational drugs in combination, additional opportunities and learnings exist that may warrant exploration of whether a follow-on guidance specific to oncology is needed. Specifically, guidance may be warranted to complement the 2013 guidance, which was limited in scope to two or more novel drugs in combination. Opportunities to streamline combination therapy development programs, which may include the use of external data sources, are discussed. These discussions should be aimed at answering the following questions about demonstration of contribution of individual components to the effect of the combination in the context of a development program that investigates two or more agents that have not been previously approved for the indication:

1. Which trial design is most appropriate (e.g., factorial, adaptive, etc.)?
2. What is the biological rationale?
3. What are the endpoints and opportunities for earlier evidence aside from response?
4. What is the strength of external data needed to say that a therapeutic arm should not be included?

These questions served as the basis for identifying opportunities to use external data to inform development strategies and considerations for combination drug development.

[7] "Codevelopment of Two More New Investigational Drugs for Use in Combination" Guidance for Industry https://www.fda.gov/downloads/drugs/guidances/ucm236669.pdf
[8] Defined in the FDA's "Codevelopment of Two or More New Investigational Drugs for Use in Combination" guidance for industry as being a drug that has not been previously developed for any indication
[9] The concepts discussed in this whitepaper may be most applicable to combinations involving at least one previously approved agent

EARLY ISSUES TO ADDRESS IN A COMBINATION THERAPY DEVELOPMENT PROGRAM

The FDA guidance for the codevelopment of two or more new investigational drugs outlines four criteria that should be met by sponsors:

1. The combination is intended to treat a serious disease or condition
2. There is a strong biological rationale for use of the combination
3. It appears that the combination may provide a significant therapeutic advance over available therapy and is superior to the individual agents
4. There is a compelling reason why the new investigational drugs cannot be developed independently

It is important for sponsors pursuing the development of a combination to initiate conversations with the FDA early in their development programs to determine if they meet the above criteria and, if so, whether they are pursuing the most efficient path forward. These conversations are context-dependent and specific to the drug, indication, and need of the patient population at the time of development. For example, the risk-benefit of developing a novel combination with a relatively small improvement in objective response rate (ORR) in a disease setting where there is a high objective response rate to monotherapy would need to be discussed. While the FDA's 2013 guidance encourages early interaction between sponsors and the appropriate Center for Drug Evaluation and Research (CDER) review division, further work is needed to define the parameters of these early interactions between drug sponsors and the FDA and types of data that can inform strategies.

In addition to the need for context-dependent conversations between drug sponsors and the FDA, there is a need for the FDA to further clarify and provide guidance on strategies for demonstrating early activity for drugs being developed in combination and efficient design of development programs for combination therapy products.

Strategies for Demonstrating Early Activity for Combination Therapy Products

Guidance from the FDA on strategies for demonstrating early activity for combination therapy products is needed, especially as the prevalence of codeveloped immune therapies increases. This guidance should more clearly define how sponsors can demonstrate the biological rationale for use of the combination and that their combination has a significant therapeutic advance over existing therapeutic options.

The FDA's 2013 guidance establishes that "sponsors should develop evidence to support the biological rationale for the combination in an in vivo (preferable) or in vitro model relevant to the human disease or condition the product is intended to treat." Sponsor experiences have demonstrated, however, that findings in animal models are not easily translated to clinical predictions, indicating a need for better pre-clinical models. Additionally, while drug sponsors and the FDA have identified the indication of activity as being critical early in development, stakeholders have expressed uncertainty about what can be defined as "activity" or how to demonstrate this activity to the FDA.

Combination therapy products may have greater toxicities (including late on-set toxicities) than monotherapies, making it critical for sponsors to demonstrate a substantial improvement over other available therapies and individual agents on a clinically significant endpoint(s). The magnitude of benefit needed to justify increased toxicities, however, is not always apparent during the early evaluation of combination therapies and codeveloped new investigational drugs. Defining generally what is considered a clinically meaningful benefit and the level of added toxicity that is acceptable given this benefit will be context dependent.

Efficient Design of Development Programs for Combination Therapy Products

Determining when a factorial design is necessary to demonstrate the contribution of each component

In addition to making recommendations for how sponsors may demonstrate early activity of their combination products, the FDA should make recommendations around the efficient design of development programs for codeveloped combination therapies.

Traditionally, clinical trial designs of novel combinations intended for registration have demonstrated the effect of each of the individual components using a multi-arm Phase 3 trial that isolates the contribution of each drug to the overall treatment effect, including time-to event endpoints. To facilitate efficient drug development and better use of resources, FDA has recommended a common control arm when several drugs are being developed for the same population at the same time, and the ineffective investigational arms are discontinued earlier (discussed in more detail in the section of this manuscript titled "Sources of Data and Considerations"). Alternatively, an accelerated approval may be considered based on ORR and a regular approval based on OS results in the same trial.

In combination therapy development programs, the evaluation of the individual drugs as single agents often occurs in earlier phase trials. The utilization of these and other data sources creates opportunities to augment data collected in the pivotal study, reduce the number of patients randomized to a single-agent arm, or replace single-agent arms in phase III trials when appropriate. Situations when factorial designs are not necessary or not appropriate to demonstrate the contribution of each component should therefore be considered.

It has been proposed to develop criteria to assist with the decision-making process to determine when it may be permissible to pursue a more accelerated development strategy. The below suggested criteria could serve as the basis for these early conversations between sponsors and the FDA:

1. The combination shows activity in a population resistant to the individual agent(s)
2. The combination has biomarker driven/associated activity
3. The biological rationale for the combination differs from that of the single agent (this criterion would not be sufficient alone)
4. The combination is in a disease setting where there is no or very little single agent activity

These four suggested criteria are not intended to be binding as it is unlikely that a single combination therapy would meet all four criteria. Additionally, it will be important to consider criteria in the context of the specific disease setting in which the combination therapy is being developed. There may be more confidence in disease settings where the reported ORR has been low compared to where high ORRs have been documented. It may be easier to consider non-factorial trial designs when the single agents to be used in combination have demonstrated efficacy and safety in the randomized trials in that disease.

When a factorial design is not a viable option for trial design, alternative approaches must be pursued to demonstrate the contribution of individual components to the FDA and provide sufficient evidence to assess benefit-risk. These innovative approaches will ensure that an application for approval of a combination therapy will provide the required evidence of the contribution of the individual drugs to the effect of the combination. Alternative approaches will be discussed in further detail in the section of this paper titled "Sources of Data and Considerations."

Determining Which Endpoints Should be Selected

It is also important for the FDA to provide further guidance to sponsors on the appropriate selection of endpoints in clinical trials evaluating two or more drugs for use in combination in a new indication. Endpoint selection for clinical trials evaluating combination therapy products must depend on the research question and the intent of the study. Because combination therapy development may involve the use of external data sources that utilize different endpoints, endpoint selection can be challenging, and different endpoints may provide varying levels of information depending on the trial design. Potential primary and secondary endpoints traditionally used in oncology development are: ORR, PFS, OS, patient reported outcomes (PROs) or clinical outcome assessments, and complementary endpoints such as circulating tumor cells and biomarker-based endpoints (Table 1).

Table 2. Select Endpoints for Oncology Combination Development Trials

Endpoint	Comments
Overall Survival (OS)	Universally accepted "gold standard"; May require larger trial population and longer follow-up to show clinical benefit; Can be impacted by cross-over or subsequent therapies; incorporates impact of a drug's toxicities on survival
Progression-Free Survival (PFS)	Can require smaller patient populations; Definition may vary among trials and measurement may be subject to bias; Requires balanced timing of assessment among treatment arms
Objective Response Rate (ORR)	Can be assessed in single arm trials and requires smaller patient populations; Not a comprehensive measure of drug activity; In rare cancers or rare subpopulations of more common cancers, ORR/DoR may be appropriate
Biomarker-based endpoints	Can enable faster and more efficient clinical trials; Limited availability of validated biomarker-based endpoints
Clinical Outcome Assessments (COAs); Patient Reported Outcomes (PROs)	Useful for the assessment of toxicity and safety; assess whether clinical benefit impacts patient symptoms and quality of life; Can support direct or indirect evidence of treatment benefit; Need to minimize missing data points; Can be subject to bias and judgement

It is important for selected endpoints, such as ORR, to demonstrate the contribution of each component of the combination therapy. Additionally, clarity is needed to determine the strength of clinical evidence required to support the assessment of the contribution of each drug, including the number of patients and clinical trial data evaluating the drug(s) in other disease settings. The assessment of external data can be challenging when different endpoints may be utilized or criteria for defining response may differ among clinical trials.

Sources of Data and Considerations

A range of data sources exist that could help support combination therapy applications and regulatory decision-making. Again, it is imperative for sponsors to present data to the FDA demonstrating the contribution of individual components to the safety and efficacy of the combination therapy. These data sources include randomized pivotal clinical trials, randomized supportive trials, pivotal single-arm trials, supportive single-arm trials, patient registries, real-world data, and published clinical data. While randomized controlled trials remain the gold standard, opportunities may exist to use other data sources to augment clinical trial data to potentially reduce the necessary number of patients or control arms to support a more streamlined development path. As external data sources are considered, the advantages and limitations associated with the various sources and whether patient-level data is available will need to be evaluated when designing an

efficient combination development program.

It will also be important for drug sponsors and regulators to evaluate the population for which the combination therapy is being developed when making decisions about data sources to support the drug application. Sponsors should clarify with regulators if the combination is being developed for all relevant patients, a histology or site-specific indication, a particular disease stage, or a biomarker enriched population before committing to a development strategy. There will be different data quality measures such as data quantity, magnitude of effect, type of data, and directionality of data associated with each source that must be considered.

Appropriate statistical methods will also need to be utilized. Sponsors should present a pre-specified statistical analysis plan (SAP) that clearly lays out all hypotheses to be tested and the allocation of significance level for testing multiple hypotheses controlling the overall type I error rate. Principles for utilizing statistical methodologies for leveraging external data in a regulatory setting have also been described in a recent publication.[10] Methodology for augmenting clinical trial control arms is currently being explored by *Friends* and preliminary data is discussed in a recent whitepaper.[11] The necessary number of trial arms, the adequate number of patients, or decisions to remove an arm will be context dependent and will rely on the quality and type of data informing decisions.

Randomized pivotal clinical trials, randomized supportive trials, pivotal single-arm trials, supportive single-arm trials

A 2 x 2 factorial clinical trial design is an optimal design to isolate the treatment effect in a combination therapy (e.g. SOC vs. A vs. B vs. A+B). As mentioned previously, these trials can be inefficient and could produce duplicative data because the evaluation of individual drugs as single agents often occurs in earlier phase trials in combination therapy development programs or in pivotal trials that lead to a monotherapy approval in a different indication. Furthermore, based on the mechanisms of action, clinical activity of the monotherapy may not be anticipated, thus necessitating the initiation of combination therapy investigations earlier in development and making the factorial trial design unethical.

The benefits of randomized Phase 2 clinical trials were acknowledged by multiple stakeholders and were discussed as being optimal for demonstrating the contribution of individual components in a combination therapy. These trials allow sponsors to more readily produce data to identify when a drug or biologic is not going to be active. They also allow sponsors to more readily identify the more active arm to focus development efforts on.

Supportive single-arm trials may also be preferred by some sponsors due to the challenges associated with conducting randomized phase 2 clinical trials and translating their results into

[10] Lim, J., Walley, R., Yuan, J., et al. (2018). Minimizing Patient Burden Through the Use of Historical Subject-Level Data in Innovative Confirmatory Clinical Trials: Review of Methods and Opportunities. Therapeutic Innovation & Regulatory Science, 52(5), 546–559.
[11] Exploring whether a synthetic control arm can be derived from historical clinical trials: Case study in non-small cell lung cancer. https://www.focr.org/sites/default/files/pdf/SCA%20White%20Paper.pdf

predictions of Phase 3 benefit and risk. In the absence of randomized trials, however, a comprehensive evaluation of the contribution of each respective component in both preclinical and clinical data is needed. Additionally, in the absence of a randomized trial, time-to-event endpoints, such as OS, will likely not be informative.

As mentioned previously, the FDA has supported the use of a common control in clinical trials as seen in the I-SPY2 trial to minimize the time sponsors need to accrue patients and the number of patients assigned to a standard of care (SOC) control arm.[12] This clinical trial design was also previously discussed at a round-table co-hosted by *Friends* that focused on the optimal development of PD-1 inhibitors and included the proposal of a non-comparative collaborative trial to test multiple PD-1 inhibitors using a common control.[13] The utilization of these methods has been lacking; therefore, further work must be undertaken to describe optimal master protocol designs that collect high-quality data to increase sponsor uptake.

Patient Registries, Real-World Data, Patient-Level Data, and Published Clinical Data

Data collected outside of a traditional clinical trial is becoming more commonly explored for use in regulatory settings. In fact, the 21st Century Cures Act mandates FDA explore the potential use of real-world evidence (RWE) to help support regulatory decisions. FDA recently released their framework for implementing the RWE program.[14] Several challenges were noted with the use of these potential data sources:

- **Confidence in Data Source and Data Quality.** No uniform data standards or standardized definitions of real-world endpoints. Potential biases in data collection and variability in rigor of data collection and missingness.
- **Utilization of Different Endpoints.** Real-world endpoints are typically different than those utilized in clinical trials. There is a need for a better understanding of how real-world endpoints relate to traditional endpoints.
- **Recency of Data.** Age of data and relevance to current clinical practices are important.
- **Access to Patient Level Data.** Patient level data is helpful for propensity score to ensure comparability of patient populations, other statistical methods for making historical data more usable are needed.
- **Publication Bias.** Published data tends to reflect positive or supportive outcomes, which may not provide an accurate or complete picture.
- **Selection bias.** Patients captured by real-world data sources may come from socio-economically disadvantaged groups and there may be unobserved factors that could confound the results.

Patient registries, real-world data, and published clinical data present attractive opportunities for patients, regulatory decision-makers, and drug sponsors. Because these data sources are most often derived from broader populations, they are often more indicative of how a real-world patient population will respond to a given treatment.

The use of data collected outside of a traditional clinical trial is accompanied by multiple challenges. For regulatory decision-makers to be confident in these data it is important for sponsors to consider the age,

[12] https://www.ispytrials.org/i-spy-platform/i-spy2
[13] Friends of Cancer Research and Parker Institute for Cancer Immunotherapy Summit: Optimizing the Use of Immunotherapy. https://www.focr.org/events/friends-and-parker-institute-cancer-immunotherapy-summit-optimizing-use-immunotherapy
[14] Framework for FDA's Real-World Evidence Program. https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

relevance, accuracy, intent, biases in collection, rigor of collection, and missingness of data. First, because rapid advancements are being made in science and medicine, older data may no longer be relevant. Second, caution must be taken to ensure patient populations are comparable between differing data sources. Although this method may not produce the same point estimates of component contribution of the combination therapy, it would be an indicator of whether the benefit exists. Additionally, time intervals between radiographic imaging, differences in dosing and scheduling, and endpoints used to assess treatment benefit may present challenges when aggregating and evaluating data. One possible approach to validating these endpoints would be to compare the SOC RWE results to the SOC results derived from clinical trials. Access to patient-level data from publications would also allow for more robust comparisons as opposed to relying on summary statistics.

Prior to implementation, sponsors should discuss the potential contribution(s) external data could play in regulatory decision-making taking into consideration the challenges cited in the preceding paragraph.

CONCLUSION

The codevelopment of two or more drugs for use in combination in a new indication presents challenges, but the growing availability of external data and development of innovative statistical methods create new opportunities. Improvements are critical to getting safer and more effective therapies to patients quickly and at a lower cost.

Several areas of opportunity were identified to help advance the concepts outlined in this discussion document:

- Define parameters and timing for conversations between FDA and sponsors evaluating two or more drugs for use in combination
- Outline types of data to demonstrate biologic rationale and early activity
- Establish general criteria for when factorial clinical trial designs are not needed and data that could inform this decision
- Provide guidance for the selection of endpoints and acceptable strength of clinical evidence needed to demonstrate contribution
- Organize and collect quality information on the use of external data sources to improve understanding and provide more sophisticated methodologies to more readily use these data sources (possible role for AI and machine learning)

PART II: STRATEGIES FOR THE DEVELOPMENT OF UNAPPROVED PD-(L)1s INTENDED FOR USE IN COMBINATION

INTRODUCTION

Sponsors seeking to develop novel drugs in combination with PD-(L)1s have approached the FDA citing problems accessing approved PD-(L)1s, which inhibit their development processes. These sponsors have noted challenges of partnering with drug sponsors of approved PD-(L)1 agents and thus have elected to develop their own novel PD-(L)1. While the extent of this issue is unknown, the challenges of maintaining equipoise and recruiting patients to an investigational PD-(L)1 arm is clear. One recent analysis of ongoing oncology trials identified 1,716 trials assessing PD-(L)1 immune checkpoint inhibitors in combination with other cancer therapies.[15] Based on accrual needs, more than 380,000 patients would be required for trials containing immunotherapy agents.

Potential trial design strategies for combinations containing an unapproved PD-(L)1

With noted challenges in mind, the following case study was proposed to inform potential trial design strategies:

> A PD-(L)1 checkpoint inhibitor is the approved SOC for the indication to be studied (Control = C). The study objective is to evaluate treatment effect of an unapproved PD-1 checkpoint inhibitor (A) in combination with another experimental drug (B). The treatment effect of A and B are unknown. The primary endpoint of the study is overall survival (OS). The intermediate endpoint is objective response rate (ORR).

Two potential proposals were discussed in the context of a randomized trial of an unapproved PD-(L)1 and an approved PD-(L)1 that incorporates an interim analysis to stop enrollment into one or more arms based on ORR (Figure 1).

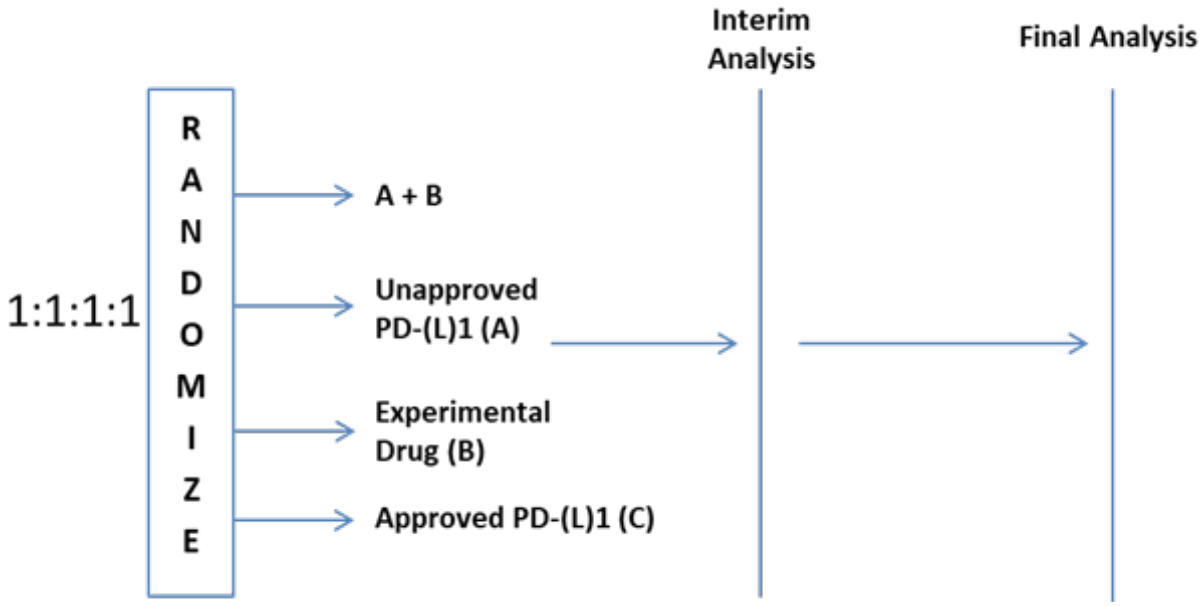
Proposal 1: The interim analysis would be based on ORR and would evaluate A vs. A+B; B vs. A+B. Decision criteria would be utilized to stop enrollment into the arm containing monotherapy A, B, or both. Enrollment for either monotherapy arm would stop if shown to have significantly lower ORR than the combination. The final analysis would be based on OS; comparisons would be conducted in A+B vs. C (followed by B vs. C and A vs. C).

Proposal 2: The interim analysis would be based on ORR and would evaluate A vs. C, in which enrollment into arm C would stop if the ORR is similar within a pre-specified margin (no non-inferiority or biosimilar claim); interim analysis would also compare A+B vs B with decision criteria to stop enrollment into arm B, if shown to have significantly lower ORR than the combination. The control arm (C) would be dropped if shown to have equivalent ORR (based on

[15] Tang J. et al. The clinical trial landscape for PD1/PDL1 immune checkpoint inhibitors. Nature Reviews Drug Discovery. 17, pages 854–855 (2018)

a pre-specified margin of error) to monotherapy of same class (in this case, another PD(L)-1). Enrollment into the arm with the other monotherapy (B) would stop if shown to have significantly lower ORR than the combination. The final analysis would be based on OS; comparisons would be conducted in A+B vs A (followed by A vs. B, B vs. C and A vs. C).

Figure 1. Clinical trial design for approval consideration of a combination treatment (no monotherapy indication approval)



The proposed trial designs are not intended to make a superiority claim by comparison of the monotherapy arms. In addition, it would not support biosimilarity or exchangeability of the experimental PD-(L)1 with the approved PD-(L)1 nor would it support approval of an individual component of the combination.

In addition to clinical trial data, preclinical data to demonstrate the experimental PD-(L)1 is blocking the intended target is necessary. Safety was noted as not being a major concern among unapproved PD-(L)1s particularly given the similarities in the spectrum of toxicities across the approved PD-(L)1s. However, some challenges, in part due to the disease-area/tumor type, were noted in recent combination development programs due to safety concerns.[16] In addition, if the unapproved PD-(L)1 single agent arm is dropped in the clinical trial design proposed in proposal 1, it would limit the amount of long-term data available and would introduce some uncertainty as compared to approved PD-(L)1s. An additional concern was raised around relying on similarities between ORR at the interim analysis due to concern that it may not always translate to similarity in long-term outcomes.

[16] Keytruda: US FDA Reflects On Lessons Learned From Failed Myeloma Studies. https://pink.pharmaintelligence.informa.com/PS122072/Keytruda-US-FDA-Reflects-On-Lessons-Learned-From-Failed-Myeloma-Studies

CONCLUSION

The purpose of considering these proposed clinical trial strategies is to accelerate development of combination therapies that include an unapproved PD-(L)1 through regulatory flexibility, to accelerate the potential utilization of combination therapies across a more diverse range of tissue types, and to potentially alleviate noted challenges by some drug developers.

Additional considerations may also need to be explored to further facilitate the development of combination therapies containing immuno-oncology agents.

- Obtaining sufficient data on safety and efficacy will be important to consider both in the context of regulatory decision-making and in providing adequate data for patients and physicians who may be considering several therapeutic options.
- Improving the understanding of how preclinical analytical data or animal models can inform the toxicity profiles between an approved PD-(L)1 and an unapproved PD-(L)1 should be further defined.
- Creating incentives or policies to encourage greater collaboration between sponsors of approved PD-(L)1s and sponsors seeking to conduct combination studies with a PD-(L)1 backbone could be explored.

FUTURE CONSIDERATIONS

Areas that may require additional guidance:

- **Interactions Between FDA and Drug Sponsors.**
  - » Define parameters and timing for conversations between FDA and sponsors evaluating two or more drugs for use in combination.
  - » Define parameters for FDA input on adaptations or for the pre-specification of adaptations
- **Class Definition.**
  - » Define process for determining a drug class
  - » Demonstration of early activity
  - » Define how preclinical analytical data or animal models can inform the toxicity profiles between an approved PD-(L)1 and an unapproved PD-(L)1
  - » Suggest strategies for demonstrating early activity for drugs being developed in combination
  - » Suggest strategies for demonstrating the biological rationale for use of a combination
  - » Suggest strategies for demonstrating a combination has a significant therapeutic advance over existing therapeutic options
  - » Establish general criteria for when factorial clinical trial designs are not needed and data

that could inform this decision
  - » Provide clarity on the appropriate selection of endpoints in clinical trials evaluating two or more drugs for use in combination in a new indication
  - » Provide clarity around dosing strategies (i.e., could it possible to have a FIH dose in the monotherapy arm of a 2x2 factorial study?)
  - » Provide clarity on the strength of clinical evidence required to support the assessment of the contribution of each drug (i.e., number of patients)
- **External Data Sources in Regulatory Decision-Making.**
  - » Indicate which data sources and methodologies are generally recommended or preferred by FDA
  - » Provide clarity on how sponsors can incorporate RWE for the identification of the contribution of effect in a combination regimen and for augmenting clinical trial controls
  - » Provide clarity on how efficacy data can be extrapolated from one disease setting to another and the value of single agent data in multiple disease settings in subsequent combination approvals in other disease settings
  - » Provide clarity on the strength of clinical evidence generated in a clinical trial in different disease settings required to support the assessment of the contribution of each drug

Areas identified as needing further work by all stakeholders include:

- **Pre-competitive Collaborative Partnerships.**
  - » Invest time and resources in the improvement of pre-clinical models
  - » Discuss further how external data can be shared among sponsors (i.e., consortium opportunities). Patient level data will allow for the most robust comparisons
  - » Formulate optimal master protocol designs that collect high-quality data to increase sponsor uptake
  - » Consider incentives or policies to encourage greater collaboration between sponsors of approved PD-(L)1s and sponsors seeking to conduct combination studies with a PD-(L)1 backbone
- **Utility of External Data Sources.**
  - » Invest resources in the evaluation of the utility of different external data sources
- **Impact Monitoring.**
  - » Identify possible metrics for evaluating the impact of streamlined combination therapy development (i.e., opportunity cost, time, number of studies, number of patient participants)