FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

DATA GENERATION TO SUPPORT CROSS-LABELING OF INDICATIONS FOR COMBINATION PRODUCTS

INTRODUCTION

The field of oncology is increasingly shifting from use of single agent, broad spectrum chemotherapies to more targeted treatments that can require combination strategies to overcome redundant and evolving oncogenic pathways in cancers. This is particularly common for hematologic cancers such as multiple myeloma and non-Hodgkin's lymphoma where combination therapies are quickly becoming the standard of care and extending patients' lives. Yet, as two-drug combinations replace monotherapies as standard of care, combination regimens that include 3 or more drugs and novel-novel drug combinations are already being developed. Continued progress in this area will require parallel advances in both clinical and regulatory science.

Traditional clinical trials often utilize factorial study designs to identify the contributions of individual drugs in a combination with a high level of rigor and statistical power. In cases where a new combination includes an approved monotherapy, the traditional approach may result in inclusion of irrelevant, and sometimes unethical, trial arms and repetitive data generation. For example, when a monotherapy is being tested in combination with standard of care (SOC), only the trial arms that assessed the SOC and SOC + monotherapy would be relevant, not the monotherapy alone. Risk/benefit approaches which utilize available knowledge regarding approved oncology treatments, including toxicology, mechanism of action, and efficacy of monotherapies, will be needed to enable greater flexibility of clinical trials designed to extract adequate safety and efficacy data without impeding development. Streamlined approaches to clinical trials (see Appendix, Table 1) will become increasingly important as combination therapies evolve from double and triple combinations to include quadruplet, or larger, combinations.

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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.

As oncology shifts to large combination therapies some uncertainty regarding the regulatory and legal implications of cross-labeling (listing of information regarding a new combination therapy on labels of all treatments included in a combination) and public health have been created. The composition of a combination therapy often includes monotherapies developed by different sponsors, sometimes with active market exclusivity or patent protection, which contribute to disparity in cross-labeling for drugs used in combinations. Although labels are not the only source of prescribing information used by physicians, inadequate cross-labeling may limit sharing of product information with patients and providers, potentially affecting patient care. Clarity in cross-labeling guidelines, which support maintenance of up-to-date labels for combination therapies and enhance information sharing on safety and effectiveness, will better promote appropriate use of the most effective combination therapies. More robust development of combination therapies can be achieved by updating regulatory pathways to address the challenges presented by cross-labeling.

The objective of this whitepaper is to develop a framework that will help inform the level of evidence to consider for combination therapies, alternative trial designs to generate that data, and suggest regulatory modifications to better facilitate up-to-date labeling of combination therapies without compromising FDA standards that protect the safety of patients. The framework will help trial sponsors to streamline clinical trials that more efficiently identify the contribution of each drug in a combination while minimizing redundancy of data generation and the number of patients required for enrollment in new clinical trials. The whitepaper will also discuss approaches in which streamlined trial designs can be used to provide evidence of contribution for each agent in a combination therapy that supports cross-labeling. Combinations of approved therapies, but not fixed-dose combination drugs which are regulated under a different framework,[1] indicated for hematologic cancers will serve as case studies to inform the framework development with the intent to direct future expansion of guidance to address other cancer types and novel-novel drug combinations. Further, it will be discussed how the proposed framework can generate the necessary evidence needed for cross-labeling and regulatory and legal challenges associated with cross-labeling.

CLINICAL TRIAL DESIGN

With greater number of and more diverse components incorporated into combination therapies, traditional clinical trials will require increasingly complex designs to accommodate more trial arms and accrual of an extensive number of patients. Trial sponsors and regulators, alike, will need to balance the level of evidence needed for approval with the speed of development to maintain equipoise. This is particularly important for therapies which benefit from the breakthrough therapy designation and accelerated approval where expedited approval is meant to enhance patient access. Innovative methods for assessing contribution of components in combination therapies are necessary to facilitate expedited approval.

Innovation in clinical trial design in oncology/hematology, especially in early stages of product development (e.g., I-SPY, BATTLE) has led to more adaptive trials that minimize redundant and expensive data collection while maintaining statistical rigor. These models have enabled sponsors to tease out contribution of therapies in a combination while avoiding large randomized trials, which can lead to a shortened development process and reduced number of patient accruals. Regulatory agency and stakeholder emphasis on collaboration and shared data collection between sponsors of clinical trials could considerably advance these goals. Further, FDA guidance "Adaptive Design Clinical Trials for Drugs and Biologics" specifically highlighted that there can be multiple prespecified timepoints within a clinical trial to evaluate the contribution of a drug such that the development pathway can be streamlined without requiring a factorial trial.[2] This will be particularly beneficial in immuno-oncology, where unique development challenges associated with kinetics of response and the types and timing of associated toxicity are often encountered. Add-on trials can also be a more efficient method to identify contribution while allowing quick advancement to phase III clinical trials. This, however, is dependent upon prior agreement of appropriate endpoints, inclusion of a heterogeneous population, and pre-specified level of evidence to support clinical trial flexibility. As the mechanism of action for immuno-oncology therapies is more thoroughly elucidated, a more adaptive framework will be possible that will better facilitate clinical trial design.

Another important consideration for clinical trial design is to minimize redundancy in data generation. Streamlined trial designs such as single arm trials have already been employed to expedite monotherapy development for cancer. Of the thirty most recent oncology therapies to receive accelerated approval, nineteen were based on results from single arm trials. This approach should be used prospectively to streamline the clinical trial process of combinations therapies as well.[3] Depending upon the potential risk/benefits and pharmacologic understanding of a new therapy, use of historical data is often an appropriate replacement for an active control arm in support of a combination therapy, particularly when evaluating non-inferiority in response rate of a new treatment or for applying inclusion/exclusion criteria based upon patient level demographics and risk factors to the single arm trial. For example, daratumumab was approved in 2016 for combination with pomalidomide and dexamethasone in multiple myeloma using only a single arm trial after the FDA determined that a previous randomized trial for pomalidomide and dexamethasone combination could appropriately be used as a control for the three-drug combination study. When such data exist, sponsors should consider use of historical data as the control in a n+1 trial or for trial designs including adaptive, umbrella, basket, or common control trials. Another opportunity to generate data without impacting clinical trial size or complexity is to use sources of real-world evidence, such as the American Society of Clinical Oncologist's CancerLinQ. Provided that adequate standards are established for quality of data and guidelines formed for collection, real-world evidence can enhance, although not replace, safety and efficacy data. Last, surrogate endpoints offer an accepted mechanism to reduce the length of clinical trials necessary for approval. Overall survival is the typical endpoint assessed in clinical trials for oncology despite that many novel therapeutics extending over-

all survival up to years beyond previous therapies, making it a difficult endpoint to measure. Surrogate endpoints such as response rate and progression free survival offer opportunities to balance evidence gathered in clinical trials with access to new therapeutics. Increasingly complicated combination therapies will benefit from consideration of appropriate endpoints that promote streamlined data collection.

Box 1: Select Master Protocols in Cancer

Innovative trials that established the "proof of concept" for adaptive trial designs such as umbrella and basket trials include the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) program, the Lung Master Protocol (LUNG-MAP), and National Cancer Institute-Molecular Analysis for Therapy Choice (MATCH) Trial.[4] Neither BATTLE nor MATCH were developed with the intention of, nor did they lead to, a pharmaceutical registration, however, the proof of concept realized by completion of these groundbreaking approaches to clinical trials can be leveraged to translate to pivotal studies.

The **BATTLE program** was an umbrella trial that used adaptive randomization to assign patients with a single cancer type, advanced non-small cell lung cancer, to a trial arm for a targeted therapy based upon the presence of one of several tumor biomarkers detected by real-time biopsies. Completion of the BATTLE program signaled a pivotal shift to innovation in streamlining clinical trials.

LUNG-MAP is another umbrella trial that has harnessed the power of innovative designs to minimize patient screening and accruals for trials in advanced squamous cell lung cancer. Similar to BATTLE, LUNG-MAP assigns patients to trial arms based upon tumor biomarkers, but the trial arms in LUNG-MAP are more diverse, including drugs sponsored by different manufacturers or an immunotherapy for patients with unmatched tumor biomarkers. LUNG-MAP establishes a master protocol for phase 2-3 clinical trials that assigns all patients to a treatment and minimizes patient attrition at screening with the intention of supporting drug approval.

NCI-MATCH is an example of a pioneering basket trial, which studied targeted therapies in patients with specific biomarkers, whose cancers have progressed or did not respond to standard therapies. MATCH streamlined clinical trials by assessing treatment efficacy in patients with diverse cancer types that shared a biomarker in a single trial.

A NOTE OF CAUTION

A different dynamic is created in the clinical trial process as increasing numbers and complexity of combination therapies affect the extent of innovation achievable. Clinical trials can become consistently complex as combinations grow in number of components, making assessment of the independent value and side effects associated with additional components more difficult. The particular components and level of available information concerning those additions to a combination can also exacerbate an already complicated clinical trial. For components where the science and biology of a therapy is less well understood, as in novel or immunomodulatory therapies, different levels of data are needed to assess each component. Specifically, the unique challenges and unexpected drug interactions possible with use of immunomodulatory therapies in combinations require added caution. Accelerated development and innovation should be balanced with caution when considering these combinations, particularly in immune suppressed populations.

LABELING FRAMEWORK

Streamlining trials for combination therapies while still capturing necessary contributions of components to inform labeling is vitally important. However, beyond data collection, marketing exclusivity, patent life, and labeling updates should also be considered especially when combination therapies may involve drugs from different sponsors. Gaps in regulatory policy and uncertainty regarding legal implications have likely contributed to multiple practices for cross-labeling when approval of new combinations expands indications of an existing approved drug. Although labels do not comprise the sole source of information for physician prescribing, there is a potential that the resulting label disparities may cause uncertainty among patients and physicians about to find up-to-date safety and efficacy. Ultimately, this raises concern that some patients may not receive the most efficacious or safe treatment available. Regulatory requirements already mandate that a sponsor must update a label when it becomes inaccurate, false, or misleading but a framework that outlines the scenarios when cross-labeling may be appropriate is necessary to better promote consistency of labels in representation of new safety and efficacy information and ensure patient access. For example, the combination of Revlimid, Velcade, and dexamethasone was shown clinically superior to a combination of only Velcade and dexamethasone but the indication for Revlimid, Velcade, and dexamethasone is listed only on the label for Revlimid[5]. A provider or patient who searched only the Velcade or dexamethasone label could potentially miss information concerning a more efficacious treatment. Consistent representation of safety and effectiveness on all labels could ensure practitioners can locate relevant information and bolster optimal patient care.

In the interest of public health, a successful framework development will require regulators to consider the various stakeholders and scenarios in which labeling guidelines apply. Specifically, reasons for updating a label may include an effort to effectively communicate up-to-date information for patient care, expand the label's indications for marketing purposes, update the label with new safety information, or to ensure global access to the combination therapy in countries where the initial product label is used as the basis for coverage determinations. Guidance will need to consider the motivation of stakeholders when clarifying the regulatory process to encourage maintenance of comprehensive labels and incentivize innovation with combinations, particularly when incorporating approved monotherapies.

A well-defined framework for labeling combination therapies must address standards for the type and level of evidence necessary to contribute to a label. Specifically, what level of evidence will be sufficient to support a label change when, as for expedited regulatory pathways, the precise contribution of components may not be as thoroughly dissected. Different levels of evidence may be required to support label changes depending on the type of change specified and should be considered in a framework guidance.

Finally, additional legal and regulatory issues associated with cross-labeling need to be addressed. Currently, a drug's sponsor is responsible for maintenance of and updating the drug label; however, the drug sponsor may not necessarily have access to the proprietary data generated from a combination trial which would support a label change. In the event where a clinical trial is conducted by an entity other than the drug sponsor, the mechanism to obtain a right to reference proprietary data and update a label may be cumbersome and pose a disincentive to the drug sponsor. A framework to streamline this process may, at least in part, address some barriers to cross-labeling and encourage maintenance of up-to-date labels for combination therapies. Further, there are instances where the holder of an approved new drug application (NDA) ceases to manufacture a drug and withdraws the NDA, leaving only the generic manufacturer(s) on the market with no legislative language or legal precedent to clarify the entity responsible to update the label. The FDA has issued draft ANDA Labeling Guidance to provide insights on some circumstances where ANDA holders can update labeling[6]. In cases that are not addressed by the draft guidance, incentives to encourage the NDA holder to continue manufacturing the drug or to maintain an up-to-date label despite cessation of manufacturing may be helpful. Alternatively, a new mechanism to allow FDA or a generic drug manufacturer to update a label may be necessary.

Numerous examples of combination therapies for hematologic cancers can be found where disparity in labels exists, highlighting the need for a labeling framework. Darzalex (Janssen Biotech), a monotherapy for multiple myeloma with accelerated approval, received approval in 2016 for two new indications in multiple myeloma. These included combinations with Revlimid (Celgene) and dexamethasone and combination with Velcade (Millennium) and dexamethasone. The new indications are listed only on the Darzalex label. Further, Elotuzumab (PDL Biopharma) received its first NDA for multiple myeloma in combination with Revlimid and dexamethasone. Similar to Darzalex, the indication is listed only on the label of the new molecular entity. For each of these examples, a regulatory framework which accounted for various stakeholder incentives and standards for supporting evidence could facilitate a streamlined process to update labels and ensure parity in labels.

EMERGING CHALLENGES

Standard of Care

It is becoming increasingly unsuitable for standard of care (SOC) to serve as controls in clinical trials amid a rapidly changing practice of medicine. SOC can change quickly, often in less time than it takes to complete the clinical trial process and regulatory approval which, in oncology, averages 8 years.[7] If the SOC for an indication in cancer changes during the clinical trial process, use of the investigational drug may no longer be appropriate in the clinical trial population, resulting in a different patient population ultimately receiving the treatment. Further, whether the indication for which SOC is used in the clinical trial is indicated for on-label use will impact global access to new therapies which are compared to the SOC. Substantial disagreement can also exist amongst the medical community regarding which therapies constitute SOC, as there is regarding the use of autologous stem cell transplantation as first or second line therapy for multiple myeloma. When rapid changes or disparity of SOC exists, comparisons with SOC and accrual to clinical trials become problematic and create discordance between the practice of medicine, clinical research and registration trials, and drug labeling. In multiple myeloma, the combination therapy of lenalidomide and dexamethasone is most frequently used as a first line therapy, despite its use in clinical trials and indication on the lenalidomide label as SOC for relapsed myeloma, not first-line therapy. Most patients with relapsed myeloma are likely already resistant to lenalidomide/dexamethasone therapy. Using lenalidomide/dexamethasone as SOC in clinical trials for relapsed multiple myeloma results in approval and labeling of novel therapies that have not been tested in the most common form of relapsed multiple myeloma, which is lenalidomide/dexamethasone resistant. These issues will continue to pose a barrier to drug development as combinations increase in complexity. Alternative strategies, including validation of trial designs that replace components of a treatment with add-on to SOC designs, may need to be employed to establish an appropriate control arm.

Regulatory and Legal Ramifications

The regulatory and legal ramifications of updating a label for an approved monotherapy when used in a combination remain largely uncharted by the pharmaceutical industry. The uncertainty created, particularly when market exclusivity or patent life exist for a component of the combination therapy, can pose additional challenges to cross-labeling and impede consistency of labeling between monotherapies used in combination.

The FDA has used its regulatory authority to facilitate and encourage cross-labeling, albeit in a case specific manner which was highly dependent upon the level of cooperation that existed between sponsors. For example, when both sponsors agree to coordinate efforts to cross-label, the FDA has, in the past, either negotiated language for an indication for use in each label or encouraged use of a Drug Master File (DMF). In the latter, the initial sponsor could file a DMF and permit the second sponsor a right of reference to amend its current label using a supplemental NDA. Conversely, the scenario in which sponsors do not agree to collaborate (this may occur for a variety of reasons), has presented greater difficulty and ambiguity as to the regulatory and legal mechanisms necessary to cross-label. In these cases, the result has most commonly meant that the level of information on the individual labels remained disproportionate. A new approach could be taken where the FDA, with the permission of the trial sponsor, allows the manufacturer

of each component of the combination to independently update its label by referencing the new study that tested the monotherapies in combination.

While the FDA has authority to mediate cross-labeling of combination therapies, the disadvantage of these regulatory solutions rests upon the necessity for drug and trial sponsor cooperation. A legislative fix, similar to that which was recently enacted in the Food and Drug Administration Reauthorization Act of 2017 (FDARA) regarding labeling of medical imaging products, would likely provide a more effective solution for cross-labeling of combination therapies. Section 706 of the Food, Drug, and Cosmetics Act was amended in FDARA to allow imaging devices approved for a new indication, dosage, etc., to reference existing imaging agents that are labeled for use with other marketed devices. The legislative update now allows the imaging agent's label to be modified by referencing a device master file or through right of reference to research conducted by a device company through a supplemental NDA. A similar approach could be used to simplify cross-labeling for combinations. However, any of the preceding approaches would also need to consider any patent rights pertaining to the combination or any individual agent, as discussed below.

Whether regulatory or legislative, attempts to incentivize cross-labeling for combination therapies must consider the potential impact that cross-labeling could have on market access for follow-on products such as abbreviated new drug applications (ANDAs) and 505(b)(2) applications. ANDAs are particularly vulnerable to market delay when patents/exclusivities are extended because of the "same labeling" rule that requires the ANDA to incorporate the same information from the reference listed drug (RLD) label onto its own. Further, follow-on products are listed in the FDA "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) and, when associated with an innovator drug with current patent life, must include certification that the applicant does not infringe on and will not seek market approval until all relevant innovator patents are expired or submit a "paragraph IV certification" to challenge the validity of the patent. It is possible that certain circumstances exist where an innovator label could be updated to include use in combination, thereby extending patent life or exclusivity, and subsequently block generic market entry. However, there is a regulatory mechanism that allows use of a "skinny label" that may mitigate this effect. In the event the innovator product is protected by exclusivity or method of use patents, which are still in effect after the initial exclusivity/patents expire, generic or 505(b)(2) application could still be filed but would have to account for the protected indication by "carving out" the indication under active exclusivity/method of use patent from the label. The skinny label would list only the non-protected information on the label but should not prevent market entry. It is important to note that this discussion pertains to drug-drug (or NDA-NDA) combinations and does not address potential regulatory or legal implications associated with drug-biologic (or NDA-BLA) combinations, which are approved via a separate regulatory pathway for combination products, and are outside the scope of this whitepaper. A thorough legal and regulatory examination regarding market exclusivity and patent life, including case study analysis of the potential outcomes of previous combination approvals, will be needed to inform future policy solutions.

CASE STUDIES TO INFORM LABELING POLICY

In each scenario below, consider the implications to patent life and market exclusivity of an innovator drug if that drug's label were updated to include an indication for use in a new combination therapy. Additionally, where possible, the economic incentives and implications of such cross-labeling would be of further interest to inform policy.

Issues to Consider
To best inform this analysis, it may be most helpful to consider the following questions:

- Would this impact regulatory exclusivity? How?
- Are there issues with sharing or giving rights to use combination study data with or to a manufacturer whose drug is used in the combination?
- Are there economic incentives or outcomes that would impact the sponsor's or the other manufacturer(s)' decision to update a label that should be considered in these scenarios?
- What impact would patent rights for a drug included in the combination, or for the combination, have?

Scenario 1: A novel therapeutic in combination with a drug that has existing exclusivity/patents and a generic.

Elotuzumab (PDL Biopharma) was approved for multiple myeloma in combination with lenalidomide (Revlimid, Celgene) and dexamethasone (generic)[8].

- Only the Elotuzumab label reflects this indication. This combination is also included in NCCN guidelines for previously treated multiple myeloma.
- This case study will address the implications that cross-labeling may have on market exclusivity and patent life because it includes a novel therapeutic (elotuzumab), a brand product with existing market exclusivity and patent life (Revlimid),[9,10] and a generic (dexamethasone) where the clinical trial led to approval of combination without a label change to the patented therapeutic.
- The compound patent for Revlimid (US 5,635,517) will expire in October 2019 and the polymorph patent (US 7,465,800) will expire in 2027.
- The compound, or composition of matter, patent for Revlimid (US 5,635,517) expires in October 2019. It also has two method of use patents (US 7,189,740 and US 7,968,569) expire in 2023. Market exclusivity will end in 2018 but several orphan drug exclusivities exist which will last through 2020, 2022, or 2024.[11]

Scenario 2: A monotherapy approved initially through accelerated approval and later regular approval receives an additional indication in combination with another therapy that has existing exclusivity/patents and a generic.

Daratumumab[12] (Darzalex, Janssen Biotech) was approved for multiple myeloma in combination with:[13]
a. lenalidomide[14] (Revlimid, Celgene) and dexamethasone (generic)

b. bortezomib[15] (Velcade, Takeda/Millennium) and dexamethasone (generic)

- Both combinations are listed as preferred regimens (class 1) in NCCN guidelines for patients previously treated multiple myeloma.
- Only the daratumumab label reflects this indication in either combination.
- There are many patents for Revlimid, an expanded indication exclusivity which ends in 2018, and orphan drug exclusivities which end in 2020, 2022, or 2024.
- Velcade has three patents (US 5,780,454; US 6,713,446; and US 6,958,319), pediatric exclusivities which expire in 2018, 2019, or 2022, and an orphan drug exclusivity which expires in 2021.

Scenario 3: Brand product combined with brand product.

A combination of palbociclib (Ibrance, Pfizer) and fulvestrant (Falsodex, AstraZeneca), both brand products with current patents and exclusivities, was approved for breast cancer following endocrine therapy after a single clinical trial. Both drug labels were approved independently.

a. Ibrance[16] received approval in combination with Falsodex in February, 2016. Ibrance has three patents (US 6,936,612; US 7,208,489; and US 7,456,168) and a new chemical entity exclusivity.
b. Falsodex[17] received approval in combination with Ibrance in March, 2016. Falsodex has four patents (US 6,774,122; US 7,456,160; Us 8,329,680; and US 8,466,139) and pediatric exclusivity.

In this example, both innovator drugs in the combination updated their labels to include the new indication. This will be an interesting case to study the economic incentives which influenced this decision and how patent life and exclusivity was impacted to inform cases in Scenarios 1 and 2.

APPENDIX

Table 1: Comparison of different clinical trial design for combination therapies.

Trial Design	Pro	Con
Basket Trial	Beneficial for matching patients with low prevalence mutations to targeted gene therapies. Compares effectiveness of multiple drugs simultaneously.	Measurement of genotype status is static and does not account for change in tumor composition over time. Can become increasingly complex as additional arms are added. There is also a risk of overlooking or failing to tease out impact of a mutation in different tumor types (e.g. BRAF in melanoma vs. BRAF in colorectal cancer).
Umbrella Trial	Streamlines clinical trials by testing multiple drugs in a single cancer type and targets patients to the most appropriate therapy based upon specific molecular aberrations. There are potentially less screen failures and more patients may benefit from a treatment under an umbrella design.	Measurement of genotype status is static and does not account for change in tumor composition over time. Can become increasingly complex as additional arms are added.
Common Control	Reduces clinical trial recruitment by comparing multiple trial arms to a single control. Enables faster time to data for multiple agents in a more rigorous statistical fashion (if randomized and in the same study).	Can be difficult to determine an appropriate control arm that is a suitable comparator for multiple experimental arms. There is the additional need to demonstrate "similarity" or relevance of patients to compare if done in separate trials or without direct randomization.
Adaptive Trials	Speeds the clinical trial by approving modification protocols before the trial starts and interim analyses gives the flexibility to adapt the trial in real-time and respond to unexpected events.	Adaptations or trial decisions based on highly uncertain data early in patient accrual can lead to erroneous conclusions and frequent interim analyses may jeopardize the integrity of a trial. Patient accrual sometimes occurs too quickly to allow time for impactful trial adaptations. Further, practical challenges of executing adaptive trials and complicated statistics may prove difficult for study investigators and sponsors.

Table 2: Comparison of modifications to comparator arms for clinical trials of combination therapies.

Approaches to Comparator Arms	Pro	Con
Add-on	Streamlines the clinical trial by eliminating the lag phase which requires patients to stop current treatments.	Must consider possibility of developing drug resistance during the first phase, before addition of a second therapy. There is added difficulty in selection of an optimal endpoint(s) to demonstrate benefit/risk in the various phases.
Parallel	Allows direct comparison of multiple therapies (or combinations versus individual components) in parallel or interrogation of therapy efficacy in different cancer settings.	Can require additional experimental arms and increasing number of patients to enroll.

APPENDIX

Table 3: Framework to streamline clinical trial design for combination therapies by optimizing use of historical data.

- **Identify historical data sources.**
- **Determine intended use for data. Comparator or experimental arm?**
- **Determine if historical data meets guidelines for similarity to current clinical arms to provide for robust assessments.**

Considerations for use of historical data	Questions
What is the intended use?	• Are the data intended to provide an objective response rate for comparison, or are they intended to serve as a control group (requiring patient level data and covariates)? • Do the data support an evaluation of safety or efficacy? • Are the data intended to supplement or replace a clinical trial arm (provided patient-level data are available)? • Is the length of time since collection relevant for intended use/to intended population? • What is the clinical trial design of the prospective study?
Do data meet guidelines for robustness?	• How applicable are existing data to the patient population in the prospective trial? • (Are patient-level covariates available and of sufficient quality for use in accounting for differences?) • How applicable are existing data to the disease setting? • Are the data collection methods and timing of collection similar? • Are the endpoints used relevant to new intended use? • Were the clinical trial sites similar?

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