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Assessing Contribution of Effect (COE) in Oncology Combination Therapies: Lessons Learned to Inform and Optimize Future Registrational Trial Designs

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Executive Summary

The pace of oncology drug development has accelerated significantly over the past decade, with a growing emphasis on the use of combination drug therapies and their potential to offer patients earlier access to novel treatments that can significantly improve outcomes. However, introducing more drugs into a regimen may also increase the risk of toxicity, making it important to ensure that each drug contributes meaningfully to the overall therapeutic benefit. To evaluate this, researchers study the contribution of effect (COE), or the impact of each individual drug in a combination therapy. The recommended trial design to assess COE is a factorial trial design, in which each component (e.g., Drug A and Drug B) is tested individually, in combination (A+B), and against a control (C), across four arms: (A, B, A+B, and C).

As many modern combination therapies are increasingly co-developed from the outset, rather than by combining data from separately developed therapies, demonstrating each component's contribution to the overall effect can be more challenging. While understanding COE in combination therapies is essential, there are often limitations to a fully factorial study design. To address these, alternative trial designs may be considered, provided they generate sufficient COE data and are agreed with regulators before studies are initiated.

Friends of Cancer Research (*Friends*) convened a multi-stakeholder working group including experts from the U.S. Food and Drug Administration (FDA), National Cancer Institute (NCI), pharmaceutical companies, academia, and patient advocacy organizations to discuss best practices for generating COE data. The group explored several strategies and considerations:

- Alternative trial designs: Exploring options beyond traditional factorial designs for registrational trials to evaluate COE, including adaptive designs, 2-arm, and 3-arm trials, as well as trials that include descriptive statistical comparisons.
- Leveraging data from previously approved examples:
    - Using early evidence of COE in one cancer type to support streamlined development across other cancer types, especially for rare cancers or high unmet need settings.
    - Analyzing data using simple comparisons to assess COE of drugs with the same mechanism of action (MOA) as the comparator when similar outcomes are expected.
    - Considering data from early-phase trials, especially when both components demonstrate activity, to justify excluding monotherapy arms.
    - Omitting arms when there is a strong biological rationale, such as when one drug is known to lack monotherapy activity.
- Additional considerations: While we focus on contribution of effect in doublets, safety and the complexity of multi-drug regimens must be carefully evaluated when designing combination trials.

These insights emphasize the importance of integrating thoughtful trial design and practical considerations into combination therapy development in ways that maximize patient benefit while maintaining scientific rigor. By adopting more flexible approaches, clinicians can better understand the COE of each drug, paving the way for more effective treatment options in oncology.

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This white paper was developed through discussions that included these experts and other perspectives representing academia, industry, the U.S. Food and Drug Administration, and the patient advocacy community. The views expressed here represent the collective insights from working group discussions and do not necessarily reflect the official positions of any individual organization.

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Introduction

The speed of oncology combination drug development has accelerated over the past decade. While this can enable earlier access to novel, highly effective treatment options for patients, it can also present challenges in demonstrating that each component meaningfully contributes to the efficacy observed in the combination, with an acceptable safety profile. Ideally, drugs combine synergistically, where their efficacies are greater than the sum of the individual effects, or additively, where the combined effect equals that of the sum of the individual components. Conversely, an unfavorable situation occurs if the combination provides no meaningful benefit relative to either of the components administered alone, highlighting the importance of ensuring contribution of effect (COE) is well understood.

Traditionally, when the pace of advancing combination therapies was less rapid, it was more common for sponsors to evaluate drugs in combination after the approval of one or more parts of the combination in that clinical setting. Increasingly, however, therapies are intentionally developed and studied as part of a combination from the outset due to scientific or clinical factors, and/or the expected safety and efficacy, which can lead to limited or unavailable monotherapy data. As such, isolating and understanding the COE of each component can be challenging, given overlapping effects, the need for methodological rigor and pressures for meeting unmet clinical needs.

Demonstrating the COE of each component can ensure that a combination therapy provides a clinically meaningful benefit over its individual components, while avoiding unnecessary toxicity and informing decisions about the adoption of treatments that may offer only marginal improvements at the cost of increased burden to patients. The U.S. Food and Drug Administration (FDA) recently released draft guidance for establishing clinical evidence to demonstrate the COE in novel combinations in oncology.[1] Building on this guidance, this white paper explores practical design considerations for registrational trials demonstrating COE, highlighting areas where additional clarity, flexibility, or alternative approaches may help to operationalize these principles effectively in clinical development programs.

Scope

The gold standard for demonstrating COE in a registrational trial is a factorial design where the individual components (A and B) are evaluated both individually and together across four arms: A, B, AB, and C (standard of care [SOC] control). While this approach may provide the most rigorous evidence, it may be infeasible due to recruitment and logistical challenges as well as the potential for added statistical complexity, particularly in rare populations or aggressive disease settings. Furthermore, the use of factorial designs may not be appropriate in settings where there is sufficient evidence that either A or B is inactive or poorly active as a single agent.

This white paper examines scenarios where alternative designs may be considered to provide sufficient evidence of COE in registrational trials. For each scenario, we provide examples of previous registrational trials and discuss 1) the data that supported deviating from a traditional factorial design, and 2) key considerations for ensuring the alternative approach remains scientifically robust, interpretable, and supportive of regulatory decision-making.

We focus on efficacy assessments rather than dosing decisions (which should ideally be established prior to registrational trials) or safety assessments (which are evaluated as part of the overall benefit-risk assessment). Discussions outlined herein are framed around patient-centricity and multi-disciplinary

perspectives, recognizing both scientific rigor and operational realities in the development of oncology combination therapies.

Factorial Design

In addition to providing treatment effect estimates for each experimental arm (A, B, and AB) relative to C, the factorial design isolates the contribution of each component by allowing either formal or exploratory comparisons of AB vs. A and B. From a statistical perspective, using a factorial trial design and making comparisons across all arms (i.e., AB vs. A, B, C and C vs. A and B) requires additional multiplicity adjustment and ultimately, more patients enrolled, prolonging the time to readout, approval, and patient access.

While statistical methods can help to minimize sample size inflation,[2] additional concerns may arise if there are sufficient data that either of the individual components is less active or have outcomes that are worse, than current SOC. Patients may be hesitant to join trials due to concerns about randomization to a less active arm, so it is critical to describe trial designs to patients as part of their consent as well as to carefully consider these aspects during study design. Clinical equipoise should be maintained, and trials should only include arms that have valid scientific questions about their effectiveness. A variety of alternative trial designs can be considered to demonstrate COE based on data availability.

Alternative Trial Designs

Many oncology combination trials do not use a factorial design. Instead, they use data to justify alternative approaches including adaptive designs, 2- or 3-arm trials, or analyses with descriptive comparisons. In some cases, more than one approach can be considered. For each, the approach should be discussed and agreed upon with regulatory agencies before initiating the trial.

Adaptive Study Design

An adaptive study design includes a pre-determined interim analysis plan to assess early signals from the experimental arms. Based on these results, the trial may undergo modifications, such as dropping one of the experimental arms that demonstrates futility, adjusting sample size, or adapting randomized probabilities to favor arms performing better. Early dropping of monotherapy arm(s) should be carefully considered to ensure that sufficient evidence has been acquired to demonstrate COE. These approaches use methods such as group-sequential testing to maintain statistical validity and control for type I error. For example, the STAMPEDE trial in advanced or metastatic prostate cancer was designed to evaluate the efficacy of adding various agents to standard androgen deprivation therapy. Arms that did not show survival benefit were discontinued and those that did were eventually incorporated into clinical SOC.[3]

3- Arm Trial Design

If one of the monotherapy arms (B) is known to be ineffective, poorly effective, or has well known activity demonstrating inferiority to the combination, a 3-arm design (AB, A, and C) could be considered where both investigational arms are compared to C. Alternatively, although less common, one of the monotherapy arms may already be the established SOC. Often, 3-arm trial designs include parallel testing (i.e., A vs. C and AB vs. C) or sequential testing (e.g., AB vs. C then, A vs. C), but do not formally test AB vs. A. Isolating the contribution of B to the combination would still require comparing AB vs. A if both AB and A are shown to be better than C.[4]

2- Arm Trial Design

A 2-arm design may be used to demonstrate the additional benefit of a second drug, particularly when it involves adding a new agent (B) to the SOC (A), where the efficacy of A is already well established and B alone would not be considered an effective treatment option. Other scenarios include when COE has already been established or where A and B are both inactive or poorly active as monotherapies. Confirming that any inactive comparator arms are indeed pharmacologically or clinically inactive to ensure the validity of the observed treatment effect would be necessary. Data from previously completed clinical trials often support an understanding of COE for comparisons that do not include all monotherapy arms.

Trials that Include Descriptive Comparisons

In some cases, the primary analysis will focus on AB vs. C while comparing AB vs. monotherapy arm(s) may be adequately guided by a less stringent exploratory rule, as long as limitations of this less stringent approach are understood by all stakeholders.[5–7] It should be appreciated that the less stringent approaches that do not involve a reproducible or quantifiable decision rule, either in favor or against the comparison, should be considered on a case-by-case basis. Furthermore, in the absence of a prespecified decision rule, the ability of the approach to address COE cannot be quantified. Decisions regarding thresholds for efficacy improvements should also be prespecified and safety profiles would need to support a positive benefit risk assessment.

Data to Support COE

Data developed before the registrational trial can support efficacy of individual components to guide decisions on choosing an alternative trial design to the factorial design. However, there is no single definition or threshold for what constitutes “sufficient” evidence to demonstrate efficacy, and the relevance of any data source depends on the molecule, mechanism of action (MOA), and the specific context of the trial. Additionally, many studies demonstrate activity, or anti-tumor effect, which does not always guarantee there is long-term clinical benefit. Below, we outline potential sources for data that support an understanding of efficacy.

Clinical Data

Clinical data, either from earlier phases of the program of interest or other trials from the sponsor, can support an understanding of COE. The strongest COE evidence may come from the early phase clinical trials that use randomized designs and report definitive clinical endpoints. Depending on the circumstance, data may be extrapolated from other settings such as different cancer types, molecules, or biomarker populations.

Early endpoints that support an understanding of potential efficacy are critical. Objective response rate (ORR), alone or in conjunction with duration of response (DOR), is an early endpoint that can be considered as a marker for activity. Other tumor markers, such as prostate specific antigen (PSA) or circulating tumor DNA (ctDNA), may be used as early signals of activity depending on the disease and drug, but they should not replace adequate demonstration of COE. Early endpoints should be relevant to the clinical setting/registrational trial. In general, assessing COE would ideally use clinical endpoints that have served for other regulatory decision-making (e.g., progression free survival (PFS), overall survival (OS), ORR) and evaluating the totality of evidence across multiple early readouts.

Data Modeling and Non-Clinical Pharmacology

Modeling can support expectations around drug activity. Pharmacokinetics (PK)/ pharmacodynamics (PD) modeling and Tumor Growth Inhibition modeling using clinical or pre-clinical data can support a mechanistic rationale to support the clinical data established in early phase studies and strengthen the evidence base. Model based meta-analysis (MBMA) uses study-level covariates to build a quantitative model of treatment-response relationships in clinical data. MBMA can be used to identify class-level COE interactions regarding ORR, PFS, and OS.[8] Other non-clinical data (e.g., *in vivo* patient-derived xenograft models, organoids, etc.) can provide supportive evidence. These approaches would not be considered adequate to establish COE on their own.

Data from Other Settings

Data including preclinical data, activity, or efficacy data from other setting(s) can support the design approach in a new setting, including different cancer types or populations (e.g., different disease stages, biomarker studies, studies completed in other countries). Additionally, real-world data and evidence from off-label use of components can support an understanding of COE and ultimately, an alternative registrational design from the factorial design when available. Why the data support the alternative trial approach should be justified with consideration for the natural history of the disease, SOC, and biomarkers, which may differ in different settings.

Scenarios

To demonstrate when each of the alternative trials could be considered and what data might justify their use, we identified scenarios for registrational trial designs of previously FDA reviewed combinations. The default assumption when designing registrational trials that assess COE is that both components of the combination are individually effective and thus a factorial design could be used. Below, we outline data that may support an alternative approach to demonstrating COE. We categorized the scenarios based on data supporting COE that were available ahead of the registrational trial and led to the use of an alternative trial design.

For the combinations where each component is anticipated to be active as a monotherapy, we considered 3 categories of data:

1) Other tumor types – Certain therapies are effective in multiple cancer types and there may be opportunities to leverage the totality of data across tumor types.
2) Drugs with similar MOA – For drugs with similar MOA that are expected to behave similarly, it may be possible to use informal comparisons (i.e., control arm vs. investigational agent with same MOA and expectation of similar activity in the disease setting).
3) Other trials in the same cancer setting – As development programs for combinations evolve, there may be opportunities to leverage data from other trials in the sponsor's portfolio that demonstrate COE for the monotherapy arms compared to the combination (e.g., earlier phase trials, other phase III trials).

Lastly, we include a section focused on scenarios where we do not anticipate activity in one or more of the arms as a monotherapy and the data that might be used to justify this.

Other Tumor Types

Anti-PD-(L)1 + anti-CTLA-4

Anti–PD-(L)1 and anti–CTLA-4 therapies are immune checkpoint inhibitors. Anti-PD-(L)1 blocks the interaction between PD-1 on T cells and PD-L1 on tumor cells, preventing immune suppression and allowing T cells to recognize and attack cancer cells. Anti-CTLA-4 targets a separate checkpoint that regulates early T-cell activation, thereby enhancing T-cell proliferation and activity. Studying these agents in combination leverages complementary mechanisms with known class effects: CTLA-4 blockade primes and expands T-cells, while PD-(L)1 inhibition sustains their activity within the tumor microenvironment, often resulting in more durable and robust anti-tumor responses. This combination strategy has been shown to improve outcomes in multiple cancer types, including melanoma, non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and others, and has become an important approach in treatment of solid cancers. The development programs for subsequent cancer types relied on data from previous trials that support demonstration of COE. To demonstrate the stepwise data analyses across cancer types, Table 1 outlines the various trials, outcomes, and key takeaways.

Throughout the development of anti-CTLA-4 and anti-PD-(L)1 combination therapies, data from other cancer types supported decisions to not investigate certain monotherapy arms for COE in the registrational trial. Initially, the anti-CTLA-4 alone arm was not included because evidence suggested that anti-CTLA-4 inhibition had limited efficacy as monotherapy. Eventually, the anti-PD-(L)1 arm alone became SOC for many settings or was not included due to lessons learned from other settings. Sponsors used their own internal data from earlier phase clinical trials as well as publicly available data from others to justify the decision about which arms to include.

Table 1. Anti-CTLA4 + anti-PD-(L)1

Trial {Primary Source} Cancer type (Setting) Year of FDA Approval	Trial arms	Findings *(Confidence Intervals [CI] included in parenthesis)**	Trial Design Takeaways
CheckMate 067[9] Unresectable or metastatic melanoma (First line) 2016	1:1:1 ratio: • Nivo + ipi (combo) • Nivo • Ipi	**mPFS** Combo = 11.5 mos (8.9-16.7) Nivo = 6.9 mos (4.3-9.5) Ipi = 2.9 mos (2.8-3.4) HR for combo vs. ipi = 0.42 (0.31-0.57); p<0.001 HR for nivo vs. ipi = 0.57 (0.43-0.76); p<0.001	• First approval of the combo – ipi and nivo were each approved separately for unresectable or metastatic melanoma • Formal planned statistics compared the combo and nivo arm with the ipi arm – when the trial started, ipi was not fully established as SOC but had shown efficacy over other options (i.e., chemo) • The 10-year follow-up[10] suggested potentially non-trivial 8% improvement in 5-year OS rates for nivo-ipi vs. nivo alone, however the study was not designed with formal comparison for the nivo-ipi vs. nivo alone
CheckMate 214[11] Advanced RCC (First line) 2018	1:1 ratio: • Nivo + ipi (combo) • Sunitinib (SOC)	**mOS** Combo = not reached Sunitinib = 26.0 mos HR = 0.63 (0.44-0.89); p<0.001	• No nivo or ipi monotherapy arm included – previous data from single-arm studies had demonstrated substantially lower ORR for each monotherapy in the first-line RCC setting compared to ORR for the combo • Supportive data of similar ORR trends for nivo or ipi monotherapy vs. the combo across other tumor types • Melanoma data supported the biological rationale that the combination may be beneficial
CheckMate 227[12] Metastatic NSCLC (First line) 2020	1:1:1 ratio (PD-L1 ≥1%): • Nivo + ipi (combo) • Nivo • Chemo (SOC)	**mOS** Combo = 17.1 mos (15.0-20.1) Nivo = 15.7 mos (13.3-18.1) SOC = 14.9 mos (12.7-16.7) HR for combo vs. SOC = 0.79 (0.65-0.96); p=0.007	• No ipi only arm • Primary comparisons were made to the SOC arm (chemo – nivo not approved at time of trial design) • Supported by data across tumor types, including data used in review of melanoma and RCC applications

Trial {Primary Source} Cancer type (Setting) Year of FDA Approval	Trial arms	Findings *(Confidence Intervals [CI] included in parenthesis)**	Trial Design Takeaways
CheckMate9LA[13] Metastatic NSCLC (First line) 2020	1:1 ratio: • Nivo + ipi + 2 cycles chemo (combo) • Chemo (SOC)	mOS Combo = 15.8 mos (13.9-19.7) SOC = 11.0 mos (9.5-12.7) HR = 0.74 (0.62-0.87); p<0.001	• Assessed whether reducing the amount of chemo with addition of nivo + ipi enhanced benefit • Trials showing no improvement in OS with addition of nivo alone to chemo already completed • Contribution of ipi was adequately established based on available data from CheckMate-227 and across other tumor types
SWOGS1616[14] Unresectable stage III or IV melanoma (After progression on anti-PD-(L)1) N/A	3:1 ratio: • Nivo + ipi (Combo) • Ipi	OS HR = 0.63 (0.41-0.97); p=0.036	• At this point, anti-PD-(L)1 was first-line therapy and there were ethical concerns about including an anti-PD-(L)1 alone arm after progression
CheckMate-9DW[15] Unresectable HCC (First line) 2025	1:1 ratio: • Nivo + ipi • Investigator's choice of lenvatinib or sorafenib (SOC)	mOS Combo = 23.7 mos (18.8-29.4) SOC = 20.6 mos (17.5-22.5) HR = 0.79 (0.65-0.96); p=0.018	• Other settings (e.g., CheckMate-067, CheckMate-214, CheckMate-227) supported not including a nivo only arm • Phase II data from CheckMate-040 further supported COE for nivo vs. combo[16,17]

*Trials differed in their definition of CI (i.e., 95-98% CI).

Nivo = nivolumab (anti-PD-1); ipi = ipilimumab (anti-CTLA-4); mPFS = median progression free survival; combo = combination; HR = Hazard ratio; mOS = median overall survival; RCC = renal cell carcinoma; NSCLC = non-small cell lung cancer; mos = months; SOC = standard of care; HCC = hepatocellular carcinoma; lenvatinib = multikinase inhibitor; sorafenib = multikinase inhibitor

BRAFi + MEKi

BRAF and MEK inhibitors (BRAFi and MEKi) are targeted therapies that disrupt signaling through the MAP kinase pathway, a key driver of tumor growth in BRAF V600–mutant cancers. BRAFi block the mutant BRAF kinase directly, halting downstream signaling and tumor proliferation, while MEKi act one step further along the cascade, overcoming resistance mechanisms that can limit the efficacy of BRAF inhibition alone. Studying these agents in combination leverages complementary mechanisms: BRAFi produce rapid tumor responses, while MEKi suppress resistance mechanisms and mitigate paradoxical MAP kinase activation. The development programs for subsequent cancer types built on the clinical proof of concept established in melanoma and demonstrated COE across multiple trials. To demonstrate the stepwise data analyses across cancer types, Table 2 outlines the various trials, outcomes, and key takeaways.

Lessons learned from other cancer types supported an understanding of COE and eventually alternative trial design approaches for BRAFi/MEKi combinations. Early clinical data, combined with biological rationale for the value of MEKi supporting BRAFi, supported initial decisions to not include the MEKi arm. In some cases, like BEACON CRC, the BRAFi arm was included, however, there were no formal comparisons between the BRAFi arm (doublet with EGFR inhibitor) and the combination arm (triplet with MEKi) for efficacy.[18] Given the similar efficacy data, the totality of data including safety and toxicity led to conclusions that there was little additional benefit from the triplet. While BREAKWATER CRC did not include a pre-specified adaptive trial design, protocol amendments allowed for the doublet arm to be dropped when it was clear there was not an efficacy benefit in that arm.[19]

When there is an unmet need, there is a particular urgency to establish effective regimens rapidly. Additionally, when the disease is rare, patient populations sizes are small, which can make it challenging to include multiple arms and randomize patients. As outlined in Table 2, trials like ROAR and CDRB436G2201 included 10-20 patients per arm due to rarity of the patient population.[20,21] Additionally, these patients often have limited treatment options, and treatments that do exist have limited efficacy, suggesting it may be appropriate to not include an SOC arm as was seen in ROAR. Because of the severity of the disease, such development approaches may rely on endpoints like ORR combined with DOR to demonstrate efficacy.

Overall Takeaways from Other Tumor Types

Early demonstrations of COE in one tumor type can serve as the foundation for expansion across multiple cancers. Initial trials developed relevant evidence, often including single-agent and SOC arms to establish COE, but over time sponsors streamlined designs by leveraging prior data and biological rationale including expected class effects. While combinations may have more durable and deeper responses than single agents, toxicity concerns and a lack of clear head-to-head analyses sometimes raise questions about risk–benefit trade-offs. Additionally, there may be differences in feedback mechanisms among cancer types. Particularly in rare or high-unmet-need populations, single-arm or small randomized trials relying on ORR and DOR can be considered. Overall, these programs show how the totality of evidence across tumor types can justify streamlined development strategies, while also highlighting the ongoing challenge of balancing efficacy, toxicity, and interpretability of COE.

Table 2. Anti-CTLA4 + anti-PD-(L)1

Trial {Primary Source} Cancer type (Setting) Year of FDA Approval	Trial arms	Findings *(Confidence Intervals [CI] included in parenthesis)**	Trial Design Takeaways
COMBI-d[22,23] BRAF V600-mutant advanced melanoma (First line) 2014	1:1 ratio: • Dabrafenib + trametinib (combo) • Dabrafenib	**mPFS** Combo = 9.3 mos Dabrafenib = 8.8 mos HR = 0.75 (0.57-0.99); p=0.03	• BRAFi were SOC before trial began • Provided a comparison of COE vs. dabrafenib to demonstrate the added value of trametinib • Study also showed a large OS benefit
COMBI-v[24] BRAF V600-mutant aNSCLC (First line) 2014	1:1 ratio: • Dabrafenib + trametinib (combo) • Vemurafenib (SOC)	**Interim OS (mOS)** Combo = 28% death (not reached) SOC = 35% death (17.2 mos) HR = 0.69 (0.53-0.89); p=0.005	• Review of COMBI-v also included data from COMBI-d as supportive data for COE assessment • Demonstrated superiority over SOC
BRF113928[25] BRAF V600-mutant aNSCLC (First line) 2014	Single arm: Dabrafenib + trametinib (combo)	**ORR** Combo = 64% (46%-79%) DOR = 10.4 mos (8.3-17.9)	• While not randomized, this study did include a cohort of patients treated with dabrafenib alone[26] • Assessment was supported by melanoma data on COE • The unmet need was a key driver that influenced the acceptance of the combination in aNSCLC in a smaller study using ORR and DOR endpoints
COLUMBUS[27] BRAF V600-mutant advanced melanoma (First line) 2018	1:1:1 ratio: • Encorafenib + binimetinib (combo) • Encorafenib • Vemurafenib (SOC)	**mPFS** Combo = 14.9 mos (11.0-18.5) Encorafenib = 9.6 mos (7.5-14.8) SOC = 7.3 mos (5.6-8.2) HR for combo vs. SOC = 0.54 (0.41-0.71); p<0.0001 HR for combo vs. encorafenib = 0.68 (0.52-0.90); p<0.001	• Historical data supported not including MEKi only arm (binimetinib) due to biological rationale and data from COMBI-d/ COMBI-v • Original findings from the study showed that combo was better than BRAFi alone (encorafenib) • Long-term OS:[28] HR for combo vs. encorafenib = 0.93 (0.73 to 1.18)
COMBI-AD[29] BRAF V600-mutant stage III melanoma (Adjuvant) 2018	1:1 ratio: • Dabrafenib + trametinib (combo) • Placebo (SOC)	**RFS (Investigator)** Combo = 38% SOC = 57% HR = 0.47 (0.39-0.58)	• Single-agent efficacy of dabrafenib in metastatic melanoma already demonstrated when the trial began • No SOC in adjuvant setting before this trial • Natural history supported the use of placebo as comparator

Trial {Primary Source} Cancer type (Setting) Year of FDA Approval	Trial arms	Findings *(Confidence Intervals [CI] included in parenthesis)**	Trial Design Takeaways
BEACON CRC[18] BRAF V600-mutant metastatic CRC (Second or third line) 2020	1:1:1 ratio: • Encorafenib, cetuximab, binimetinib (triplet) • Encorafenib + cetuximab (doublet) • Chemo (SOC)	mOS Triplet = 9.0 mos (8.0-11.4) Doublet = 8.4 mos (7.5-11.0) SOC = 5.4 mos (4.8-6.6) HR for triplet vs. SOC = 0.52 (0.39-0.70); p<0.001 HR for doublet vs. SOC = 0.60 (0.45-0.79); p<0.001	• The design did not have a formal comparison of triplet vs. doublet arms • The results showed that the doublet was sufficient and that the triplet did not provide a significant additional benefit but did add more adverse events • Ultimately, doublet was the approach moving forward
BREAKWATER CRC[19] BRAF V600-mutant metastatic CRC (First line) 2024	1:1:1 ratio: • Encorafenib + Cetuximab + mFOLFOX6 (doublet + SOC) • Encorafenib + Cetuximab (doublet) • Chemotherapy with or without bevacizumab (SOC)	mPFS Doublet + SOC = 12.8 mos (11.2-15.9) SOC = 7.1 mos (6.8-8.5) HR for doublet + SOC vs. SOC = 0.53 (0.41-0.68); p<0.001	• Protocol amendment led to closing the doublet arm early due to interim efficacy showing superiority of the doublet + SOC arm • Not an adaptive design (i.e., not prespecified) but resembled an adaptive approach
BRF117019 (ROAR)[20] BRAF V600-mutant rare cancers (mixed) 2022[30]	Single arm basket trial: Dabrafenib + trametinib (combo)	ORR (Investigator) ATC = 56% (38.1%-72.1%) BTC = 53% (37.7%-68.8%) ASI = 67% (9.4%-99.2%) LGG = 54% (25.1%-80.8%) HGG = 33% (20.0%-49.0%) HCL = 89% (77.8%-95.9%) MM = 50% (18.7%-81.3%)	• Rare tumors with no effective standard of care justified the use of a single arm and ORR as primary endpoint • This approach was considered acceptable due to extensive prior experience with the combo vs. monotherapy in other tumor types demonstrating COE • Demonstrated high and durable response rates

Trial {Primary Source} Cancer type (Setting) Year of FDA Approval	Trial arms	Findings *(Confidence Intervals [CI] included in parenthesis)**	Trial Design Takeaways
CDRB436G2201[21] BRAF V600-mutant pediatric glioma (First line) 2023	2:1 ratio • Dabrafenib + trametinib (combo) • Chemotherapy (SOC)	ORR (Central) Combo = 47% (35%-59%) SOC = 11% (3%-25%) Odds ratio (CI)= 7.19 (2.30-22.40)	• Data from prior clinical trials of dabrafenib and trametinib as single agents in pediatric patients with glioma supported trial design • Body of data across other BRAF V600E mutation-positive tumor types also supported combo vs. SOC

* Trials differed in their definition of CI (i.e., 95-98% CI).

Dabrafenib = BRAFi; trametinib = MEKi; vemurafenib = BRAFi; encorafenib = BRAFi; binimetinib = MEKi; cetuximab = EGFRi; mFOLFOX6 = modified folinic acid + fluorouracil + oxaliplatin; combo = combination; SOC = standard of care; mos = months; mPFS = median progression free survival; mOS = median overall survival; RFS = recurrence free survival; ORR = objective response rate; HR = Hazard ratio; RCC = renal cell carcinoma; NSCLC = non-small cell lung cancer; CRC = colorectal cancer; ATC = anaplastic thyroid cancer; BTC = biliary tract cancer; ASI = adenocarcinoma of the small intestine; LGG = low-grade glioma; HGG = high-grade glioma; HCL = hairy cell leukemia; MM = multiple myeloma

Drugs with Similar MOA

Targeting EGFRm in aNSCLC

Tyrosine kinase inhibitors (TKIs) targeting EGFR mutations (EGFRm) were introduced in the early 2000s and iterative improvements to drug design resulted in better outcomes for patients treated with TKI monotherapy over the next two decades. The evolution of targeting EGFRm provided a multitude of studies that led to confidence in the biology of EGFRm aNSCLC and a clearer understanding of the TKIs. Subsequent combination studies that incorporated EGFRm targeting agents used data to support decisions about trial designs.

The MARIPOSA[31] trial assessed patients with untreated EGFRm aNSCLC who were randomized in a 2:2:1 fashion to first-line treatment with amivantamab + lazertinib (combo): osimertinib (SOC): lazertinib (unapproved monotherapy with similar outcomes expected as compared to SOC). The lazertinib monotherapy arm was unpowered and comparisons between the lazertinib monotherapy arm and the other arms were included as descriptive analyses with any statistical comparisons included as secondary or exploratory. The combination arm showed a mPFS (CI) of 23.7 (19.1-27.7) months compared to 16.6 (14.8-18.5) months with osimertinib (HR = 0.70 [0.58-0.85]; p<0.001). The mPFS for the lazertinib only arm was 18.5 (14.8-20.1) months.

This setting was an add on design of amivantamab to an EGFR TKI compared to osimertinib, another EGFR TKI, where outcomes were anticipated to be similar between the two EGFR TKIs. The SOC at the time was osimertinib and when designing the trial, it was appreciated that patients and providers would not forgo a third generation EGFR TKI (i.e., osimertinib) as first-line treatment to receive amivantamab alone. The lazertinib single agent arm was necessary because lazertinib was not approved in the U.S. as a single agent and had not been evaluated against osimertinib in a phase 3 trial. To show that amivantamab was necessary, the trial needed to demonstrate that the effect of lazertinib alone on efficacy endpoints was consistent with the effect osimertinib. In this scenario, the contribution of amivantamab to the efficacy observed with the combination could be projected from the demonstration of superiority of the combination compared to osimertinib, with supportive data provided by informal comparison between the combination and lazertinib alone arms. This approach was supported by data from a previous phase 3 trial comparing lazertinib to gefitinib as first-line treatment for patients with EGFR-mutated NSCLC, which demonstrated outcomes for lazertinib were similar to those reported with osimertinib.[32]

While the 2:2:1 allocation limited the size of the unapproved lazertinib arm, there were over 1000 patients in the trial, allowing for a descriptive efficacy characterization without diluting power from the main combination vs. SOC comparison. The trial was powered for the analysis comparing PFS for the combination vs. SOC and no formal alpha was spent on combination vs. lazertinib comparisons, avoiding the consequence of inflating sample size for multiple primary hypotheses. Once the combination was demonstrated to be superior to SOC, the comparison of the combination vs. lazertinib was performed by examining the magnitude of effect and confidence intervals rather than a pre-specified p-value. Given the resultant approval, the non-powered analysis was deemed to provide sufficient descriptive findings that support COE for monotherapy.

The MARIPOSA-2 trial also employed a 2:2:1 (amivantamab + lazertinib + chemotherapy [combination]: chemotherapy [SOC]: amivantamab + chemotherapy [experimental monotherapy + SOC]) design when treating patients with EGFRm aNSCLC who had progressed on osimertinib. The trial was originally designed to include the comparison of the combination to SOC for assessing COE but was later updated to include

dual hypothesis testing due to emerging Phase I data demonstrating the benefit of amivantamab + chemotherapy. The study reported PFS effects with HRs of 0.44 and 0.48, respectively, for the combination and experimental monotherapy arms compared with SOC.[33] Operational characteristic of this less stringent (i.e., unequal randomization ratio) approach should be carefully examined at the design stage.

Overall Takeaways on Drugs with Similar MOA

Therapies with similar MOA may sometimes leverage data from earlier trials suggesting similar efficacy outcomes to support COE and enable alternative registrational trial designs. Iterative improvements to therapies over time establish strong data about the biology of the MOA and associations with outcomes, providing confidence in the biology and mechanism that inform combination trials. With strong background about the MOA, designs with appropriately calibrated traditionally less stringent evidentiary thresholds may be considered to provide findings that support COE for monotherapy and help overcome ethical and practical concerns without diluting power. Across these settings, leveraging prior data can allow for efficient trial designs that preserve power for primary comparisons while providing descriptive evidence of the added value of combination therapies.

Other Trials in the Same Cancer Setting

Anti-P(D)-L1 + nectin-4 antibody drug conjugate (ADC) in urothelial carcinoma (UC)

Data from early UC clinical trials with monotherapy anti-PD-(L)1 or nectin-4 ADC arms demonstrated that each exhibited benefit as monotherapies. The biological rationale for the potential additive benefit of these two therapies together was based on high expression of nectin-4 in UC. Targeting UC with nectin-4 ADCs may increase neoantigen presentation in some patients who do not respond to anti-PD-(L)1 monotherapy, theoretically turning "cold" tumors "hot" and allowing for anti-PD-(L)1 to function in larger populations. COE data were leveraged from previously completed randomized control trials in advanced UC to build the data over time:

- *Pembrolizumab alone:* KEYNOTE-052 was a phase II trial that assessed pembrolizumab alone (ORR = 24% [19%-27%]).[34]
- *Pembrolizumab vs. chemotherapy:* KEYNOTE-045 was a phase III trial assessing pembrolizumab (mOS = 10.1 mos [8.0-12.3]) vs. chemotherapy (mOS = 7.3 months [6.1-8.1]) and a HR (CI) = 0.70 (0.57-0.85); p<0.001.[35]
- *Enfortumab vedotin alone*: EV-201 was a phase II single arm trial that assessed enfortumab vedotin monotherapy after progression on platinum chemotherapy with an anti-PD-(L)1 (confirmed ORR = 44% (CI 35.1% - 53.2%; mDOR = 7.6 months [3.6-11.3]).[36]
- *Enfortumab vedotin vs. chemotherapy*: EV-301 was a phase II trial that assessed enfortumab vedotin (mOS = 12.9 months [11.01-14.92]) vs. chemotherapy (mOS = 8.94 months [8.25-10.25]) with HR (CI) = 0.704 (0.581-0.852); p=0.00015.[36]
- *Enfortumab vedotin vs. enfortumab vedotin + pembrolizumab*: EV-103 was a phase II trial that assessed enfortumab vedotin (ORR = 45.2% [33.5-57.3]) vs. enfortumab vedotin with pembrolizumab (ORR = 64.5% [52.7%-75.1%]).[37]

In the registrational trial EV-302/KEYNOTE-A39,[38] patients with untreated advanced UC were treated with pembrolizumab + enfortumab vedotin or chemotherapy (mPFS = 12.5 months [10.4-16.6] vs. 6.3 months

[6.2-6.5]) with HR (CI) = 0.45 (0.38-0.54); p<0.001. FDA approved the combination for patients with advanced UC in 2023.[39]

Head-to-head comparisons of each component to the combination and each other were assessed in individual clinical trials rather than being analyzed all at once. These previous trials set the foundation for COE of the components and led to a 2-arm trial as the alternative registrational trial.

VEGFi + PD-(L)1 in advanced Renal Cell Carcinoma (aRCC)

aRCC is a highly vascular disease and VEGF signaling is central to disease progression. To overcome this, TKIs targeting the VEGF receptor (VEGFi) were established as SOCs in in the 2000s. aRCC is also immunogenic and responsive to immune-based therapies, so it was hypothesized that there may be synergy between VEGFi and anti-PD-(L)1 to enhance immune infiltration and T-cell activity. Early phase studies showed promising response rates and acceptable safety initially as monotherapies and later as a combination. As such, to demonstrate COE, the registrational trials used previous data to justify not including the monotherapy arms.

We include the following list to demonstrate the multitude of studies using previously completed trials to support COE in this space:

- CheckMate 9ER compared nivolumab plus cabozantinib (mPFS = 16.6 months [12.8-19.5]) vs. sunitinib (mPFS = 8.4 months [7.0-9.7]), demonstrating a HR (CI) = 0.59 (0.49-0.71).[40]
- CLEAR (KEYNOTE-581) compared lenvantinib plus pembrolizumab (mPFS = 23.9 months [20.8-27.2]) vs. sunitinib (mPFS = 9.2 months [6.0-11.0]), demonstrating a HR (CI) = 0.39 (0.32-0.49); p<0.001. Additionally, it compared lenvantinib plus everolimus (mPFS = 14.7 months [11.1-16.7]) vs. sunitinib, demonstrating a HR (CI) = 0.65 (0.53-0.80); p<0.001.[41]
- Among patients with PD-L1 positive tumors, JAVELIN Renal 101 compared avelumab plus axitinib (mPFS =13.8 months [11.1-not estimable]) vs. sunitinib (mPFS = 7.2 months [5.7-9.7]) demonstrating a HR (CI) = 0.61 (0.47-0.79); p<0.001.
- KEYNOTE-426 compared pembrolizumab plus axitinib (mPFS = 15.1 months [12.6-17.7]) vs. sunitinib (mPFS = 11.1 months (12.6-17.7)), demonstrating a HR (CI) = 0.69 (0.57-0.84); p<0.001.[42]

There were multiple sponsors with programs in this space and rather than relying on data from other programs, each used data from their own internal programs to demonstrate COE.

Overall Takeaways on Other Trials in the Same Cancer Setting

Early-phase studies may suggest that combining two agents could improve response rates beyond what either could achieve alone. In settings where an increase in response rates is known to translate into OS benefit registrational trials can subsequently focus on the comparison between the combination and SOC, omitting active monotherapy arms in part because each agent already had established single-agent activity. To demonstrate COE, the relied-on trials should ideally be randomized, include a sufficient sample size of patients treated with monotherapy compared with the combination, and demonstrate a strong indication of response rate. The absence of formal monotherapy comparators means that COE is inferred rather than directly measured, highlighting the trade-offs between trial efficiency and the ability to fully characterize the added value of each component.

One Monotherapy Arm is Inactive

KRASmuti + EGFRi in metastatic Colorectal Cancer (mCRC)

KRAS mutations are prevalent in refractory CRC, and treating with KRAS mutation inhibitors (KRASmuti) can prevent growth by blocking downstream signaling through the MAP kinase pathway. CRC tumors use the compensatory mechanism of re-activating EGFR in response to KRAS inhibition, suggesting using an EGFRi may overcome resistance. Preclinical studies showed EGFR signaling allowed cancer cells to evade KRAS inhibition, so adding EGFRi addresses a key resistance mechanism.[43] Additionally, modeling guided the rational selection of combination therapies to overcome resistance mechanisms like EGFR feedback activation.

Clinical trial data assessing cetuximab in KRAS mutant CRC demonstrated that cetuximab alone was ineffective (i.e., no difference in mOS between cetuximab vs. SOC). Additionally, mechanistic studies demonstrated that the KRASmut confers resistance to EGFRi monotherapy. As a result, the EGFRi cetuximab carries a warning that treatment could lead to increased tumor progression, increased mortality, or lack of benefit for the patient population with KRASmut CRC.[44]

As such, KRYSTAL-1 was a phase 1/2 trial that tested adagrasib (KRASmuti) and cetuximab (EGFRi) vs. adagrasib in refractory KRAS G12C mutated CRC and did not include a cetuximab monotherapy arm.[45] ORR for the combination was 34% with all partial responses and mDOR of 5.8 months, while the single arm adagrasib showed ORR of 19% and mDOR of 4.3 months. The combination was approved under accelerated approval without a phase 3 study. Subsequently, KRYSTAL-10 was a phase 3 trial that included two arms: the combination vs. chemotherapy.[45] CodeBreaK 300 also assessed sotarasib (KRASmuti at two different doses) and panitumumab (EGFRi) vs. investigator's choice (SOC) and the combination was subsequently approved.[46] Pre-clinical and clinical data demonstrated a mechanistic understanding and subsequent lack of activity with EGFRi alone, leading to a registrational trial that did not include an EGFRi monotherapy.

Anti-SLAMF7 + Immunomodulary Agents (IMiDs) + Dexamethasone in Multiple Myeloma (MM)

Anti-SLAMF7 antibodies combined with IMiDs and dexamethasone enhance complementary mechanisms of action. Anti-SLAMF7 marks MM cells for immune-mediated destruction and simultaneously activates natural killer (NK) cells. IMiDs further potentiate this effect by stimulating NK cell and T-cell activity, increasing cytokine production, and sensitizing myeloma cells to immune attack. Elotuzumab, an anti-SLAMF7 monoclonal antibody, demonstrated limited single-agent efficacy in relapsed/refractory MM as demonstrated by early-phase studies that reported ORR near 0%. This lack of efficacy was supported by clinical data demonstrating insufficient natural killer (NK) cell activation when used alone, as expected based on the MOA. Consequently, subsequent registrational trials, including ELOQUENT-2 and ELOQUENT-3, evaluated elotuzumab exclusively in combination with IMiDs (i.e., lenalidomide or pomalidomide) and dexamethasone, as a monotherapy was deemed unlikely to provide clinically meaningful benefit.[47,48] Again, pre-clinical MOA data and early clinical trial data supported not including the elotuzumab monotherapy arm for the registrational trial to demonstrate COE.

Overall Takeaways when One Monotherapy Arm is Inactive

Early pre-clinical and clinical data from clinical trials that demonstrate a single agent has very limited or no efficacy can support not investigating that agent as monotherapy in a registrational study to demonstrate COE. Preclinical data can support mechanistic understandings of single agent vs. combination activity and

limit the patients who may be exposed to poorly effective monotherapies. Clear biological rationale, supported by non-clinical and clinical data, can demonstrate that a single drug is inactive and thus support not including such a monotherapy arm as a comparator for COE in the registrational trial.

Additional Considerations

Above, we outline key considerations for determining COE, but it is critical to recognize additional considerations and settings.

Safety as Part of the Totality of Evidence

While the FDA draft guideline and this white paper do not address safety, for approvals, evidence needs may vary depending on the safety profile of the drug. Additionally, the value of a component is judged not just by its efficacy but also by its toxicity level. Patient reported outcomes can support an understanding of toxicity that includes the patient's perspective, rather than just relying on clinical safety endpoints.

Contribution of Phase

As therapies move into earlier stages of disease, they are often provided either in the neoadjuvant (i.e., before surgery) or adjuvant (i.e., after surgery) setting. Many times, therapies are provided in both, however, whether both are necessary may be unknown. Like combination therapies, understanding the contribution of efficacy of each phase is important to prevent overtreating and may necessitate a factorial design comparing treatment in adjuvant only, neoadjuvant only, both neoadjuvant, or none. This approach is further complicated when the therapy under investigation is given in combination, and a demonstration of COE is needed. This white paper provides approaches for considering alternative trial designs that could be pulled through into contribution of phase trials, specifically the need for robust evidence before adjusting the factorial approach.

Complex Combinations with Multiple Components

Demonstrating the individual contribution of each drug in a triplet or higher-order combination can be highly complex, particularly when the SOC is already a combination regimen. One common approach is to build on an existing doublet by adding a third agent, but questions often arise regarding whether all components must be evaluated individually or if some can be substituted. As combinations become more complex, it may not always be feasible or necessary to evaluate every component separately, though careful consideration in trial design is essential. Additional factors, such as market utility, also play a role: a triplet may receive approval but see limited adoption if it does not demonstrate clear superiority or practical advantage over simpler regimens. This challenge is further compounded in biomarker-selected subgroups, where a SOC may not yet exist.

Conclusions

The development of combination therapies in oncology continues to rapidly evolve, requiring a balance between methodological rigor, feasibility, and patient need. While factorial designs remain the methodological gold standard for demonstrating COE, alternative approaches supported by prior data can be considered if they are scientifically sound and operationally practical. Sponsors should engage regulatory agencies as they build strategies to demonstrate COE. The scenarios outlined in this white paper highlight the importance of carefully justifying trial design choices, prespecifying decision rules, and leveraging the totality of available evidence to support regulatory and clinical confidence in the benefit of the combination

beyond that of each monotherapy. Going forward, clearer consensus on evidentiary standards, greater use of adaptive and innovative trial designs, and thoughtful integration of early endpoints and modeling may enable more efficient development while maintaining scientific integrity. Continued dialogue between sponsors, regulators, clinicians, and patients will be essential to refine expectations for COE, ensure trial designs support the delivery of safe and effective therapies, and accelerate the availability of effective, safe, and meaningful combination treatments.

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