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COMBINATION THERAPY IN ONCOLOGY:

Key Trends, Drivers, and Future Management Among US Payers

KEY OBJECTIVES

- Briefly identify key trends and drivers associated with the expanded use of combination therapies in oncology
- Understand US payer expectations for management of combination therapies
- Discuss future strategies for innovator development in the context of key trends

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KEY TAKEAWAYS

- IO therapies are the key growth driver of oncology combinations and future spend
- Payers defer broadly to clinical guidelines in their management decision-making, despite increasing cost of combination therapies
- Innovators must ensure new combinations remain value-added in an evolving market or risk low market access at launch and beyond

Key Trends and Drivers for Oncology Combination Therapies

Perhaps no other segment of the pharmaceutical market has reached a greater level of therapeutic complexity in recent years than oncology. With the advent of immune-oncology (IO) approaches – in particular, the broad penetration of PD-1/PD-L1 targeted therapies and the strong clinical proofs of concept shown by various cell therapy platforms – the efficacy threshold continues to rise for novel therapies in development.

Unsurprisingly, manufacturers face challenges to improve upon the standard of care in oncology indications through monotherapy alone, and increasingly have turned to combination therapy to create differentiated value and maximize revenue. Over the past decade, the rate of clinical trial starts for combination therapies has increased rapidly (~14% CAGR 2013-2021), with nearly all growth being driven by novel IO combinations (Figure 1).[1] The recent approval of Opdualag

(nivolumab + relatlimab-rmbw combination) uniquely underscores these trends, as relatlimab-rmbw is approved exclusively for use as combination therapy.[2] Payers have taken note of these trends as well, with one medical director at a national MCO (~5M covered lives) observing that "more and more, [checkpoint inhibitors] are looking to be very similar," that "more and more tumor-agnostic trials" are being conducted.[3]

Industry-Sponsored Combination Therapy Trial Starts in Oncology: IO Combinations are the Key Driver of Growth

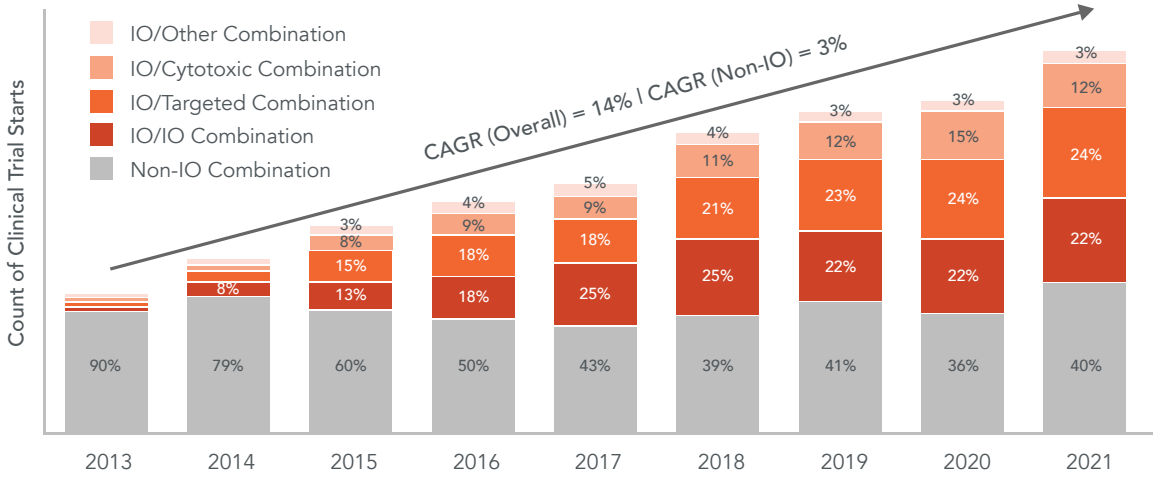

Figure 1: Clinical Development Trends in Oncology Combination Therapy.
Innovators are increasingly incorporating IO therapies into combination trials in oncology, with IO therapies involved in roughly 60% of combination trial starts in oncology in 2021.[1]

Together, increasing therapeutic complexity, growth in combination trials, and broader penetration across oncology indications will continue to place further pricing and reimbursement pressure on payer organizations. As novel combinations not only gain initial approval, but escalate into earlier lines of therapy, per-patient cost of care is primed to accelerate. In the words of another medical director at a national MCO (~44M covered lives), "I find myself torn here, because the vast majority of these drugs are really good. Whether the combination of these drugs is as good as I would like it to be? That, I'm still not sure of – when it's priced out of our ability to pay for it. I've been fighting this [fight] for probably a decade now, and it just doesn't seem to be getting better."[3]

For manufacturers, considerable challenges arise regarding value attribution and appropriate pricing strategies associated with combination therapies.

- Which therapy is considered the backbone vs add-on and what does that mean for differential value when negotiating with payers?
- In the case of multiple manufacturers across classes and combinations, how much does one product's pricing and value proposition influence the market access outcomes relative to the combination partner?

With these looming questions in mind for manufacturers, and the per-patient cost plus value attribution issues likely to escalate on payer agendas, we sought to better understand how oncology combination therapies may be managed in the future, and to characterize core considerations for manufacturers to optimize the value of their product within a combination.

Anticipated Payer Response in the US Market

Near-Term Expectations: Maintaining the Status Quo

As competition increases within classes where combination therapies are common (e.g., PD-1/PD-L1), and as outsourcing of development and manufacturing to lower-cost emerging markets comes under increased scrutiny,[4] innovators have expressed concern over the potential for greater management of oncology products – particularly as payers have begun implementing formulary exclusions in oncology for single-source brands.[5] However, consensus among a mix of national MCO and PBM payers (covering appx. ~140M lives in the US) suggests limited near-term changes and a continued deference to treatment guidelines (e.g., NCCN, ASCO). Without direct comparator trials or guideline preferences within the class, US payers' ability to more closely manage combination therapies is expected to be limited in the near-term. In addition, the high overall cost of emerging durable monotherapies such as cell therapies was referenced as a barrier to increased management of combinations (Figure 2).[3]

For the near-term, US payer's hands are generally tied with regards to the escalating cost of combination therapies in oncology as these complex regimens drive the clinical bar higher and guidelines continue to recommend combination use.

Increased Competition in Classes where Combinations are Common (e.g., PD-1/PD-L1

"[My organization's management of combinations] would only change based on data and/or guidelines."

-National MCO, ~18M Covered Lives

"For the most part, competition isn't increasing in oncology - manufacturers don't typically do comparator trials. PD-L1 may be exception... in the near future, NCCN may say 'it doesn't matter which one you use', but not at the moment."

-National MCO, ~5M Covered Lives

Emergence of Durable Monotherapies in Earlier Lines of Therapy (e.g., Cell Therapies)

"We may then step through the monotherapy - especially if it's a more cost-effective option."

~National PBM, ~80M Covered Lives

"We'll move to monotherapy if there's strong evidence that it's just as good [and lower-cost], but that doesn't seem to happen in oncology. It may happen with cell therapies, but they're already expensive anyway."

~National MCO, ~5M Covered Lives

Effect of Entry of Biosimilars into the Oncology Market on Reference Brands

"We would move to the biosimilar and place a step edit on the parent brands."

~National MCO, ~5M Covered Lives

"Even if the cost reduction sat somewhere around 10%, is the savings significant? No, but we'll substitute [for the biosimilar] regardless. Brands in most cases don't reduce their price."

~National MCO, ~44M Covered Lives

Figure 2: US Payer Expectations for Near-Term Management of Combination Therapies in Oncology.
National MCO and PBM payers (~140M lives) were interviewed to gather perspectives on near-term competitive risk faced by combination therapies.[3]

Long-Term Expectations: Broader Market Evolution, Limited Payer Evolution

In contrast to ex-US markets, where HTA/payer bodies exert significant influence over the price of and access to treatments,[6] US anti-trust regulations and payers' regulatory (in Medicare) and ethical expectations to cover oncology therapies makes the most common international recommendations (Figure 3) challenging, if not impossible, to implement in the near-term. Where payers perceived the most potential for management evolution was increasing the clinical value demonstrated by the combinations (i.e., by the manufacturer) and by negotiating lower prices for the combination through flexible payment mechanisms and/or multi-indication pricing for single-source combinations.[3]

Challenges in Combination Value Attribution/Payment: Recommendations from a Recent International Multi-Stakeholder Workshop

Increase the Value of the Combination (i.e., via clinical development)	Decide to Pay More for the Combination (i.e., via HTA or HTA-like processes)	Negotiate Lower Price(s) for the Combination (i.e., via flexible payment and pricing)
▶ Optimize clinical trial design ▶ Optimize dosing schedule ▶ Optimize supportive care requirements	▶ Higher cost-effectiveness or willingness-to-pay thresholds (in organizations that control market access) ▶ Modifications to deliberative frameworks or decision rules (in organizations that control market access)	▶ Establish flexible payment mechanisms ▶ Re-visit price of "backbone" therapy ▶ Establish value attribution mechanisms ▶ Establish multi-indication pricing ▶ Re-develop combination therapy as "one combined product"

Figure 3: International Recommendations on Value Attribution and Payment for Combination Therapies in Oncology. Fifty-three stakeholders from patient groups, regulatory agencies, HTA/payer organizations, universities, and life sciences companies from North America, Europe, Australasia, and Asia recommended three categories of approaches to potentially tackle value attribution and payment challenges. Interestingly, US-based payer organizations were not included in the discussion. Triangle Insights followed up with stakeholders from MCO and PBM payers (~140M covered lives) to pressure-test these recommendations. Note: Categories and approaches do not represent a consensus statement from attendees. Adapted from [6].

Overall, payers desire evolution in the oncology treatment landscape to stem steeply escalating costs – US sales of checkpoint inhibitors alone are projected to double from ~$19B in 2021 to ~$38B in 2028.[7] However, the same payers feel increasingly burdened by the current policy environment. According to a national MCO (~44M covered lives), "The only way this will change is if something happens at the federal level to give us the opportunity to work in some more common way with manufacturers. We're getting triplet combos now, going from $300K to $500K per year now. Unless we get more of a consensus nationally… we're running out of the ability to provide these drugs."[3] With drug pricing reform finally achieved in Medicare, including (among other changes) negotiated pricing for the highest-spend single-source drugs and inflationary penalties across the channel,[8] oncology combination innovators may benefit from thoughtful selection of and partnering with certain backbone therapies for which price reductions may be required by statute in the coming years.

Implications for Combination Therapy Manufacturers

The increasing penetration, cost, and burden on payers of combination therapies in oncology suggests that manufacturers will need to take a proactive approach early in development to craft their product's value story. It is entirely possible that early-phase combination assets today will be subject to an evolved market access landscape as they approach launch, particularly given the strain placed on Medicare coverage already by ultra-high-cost specialty therapies. With these factors in mind, Triangle Insights recommends a multi-faceted strategic approach for oncology manufacturers that are grappling with pricing considerations and the value attribution concern for combination therapies (i.e., clinical and value considerations; Figure 4):

Oncology Combination Therapy Development:
Recommended Strategic Framework from Triangle Insights

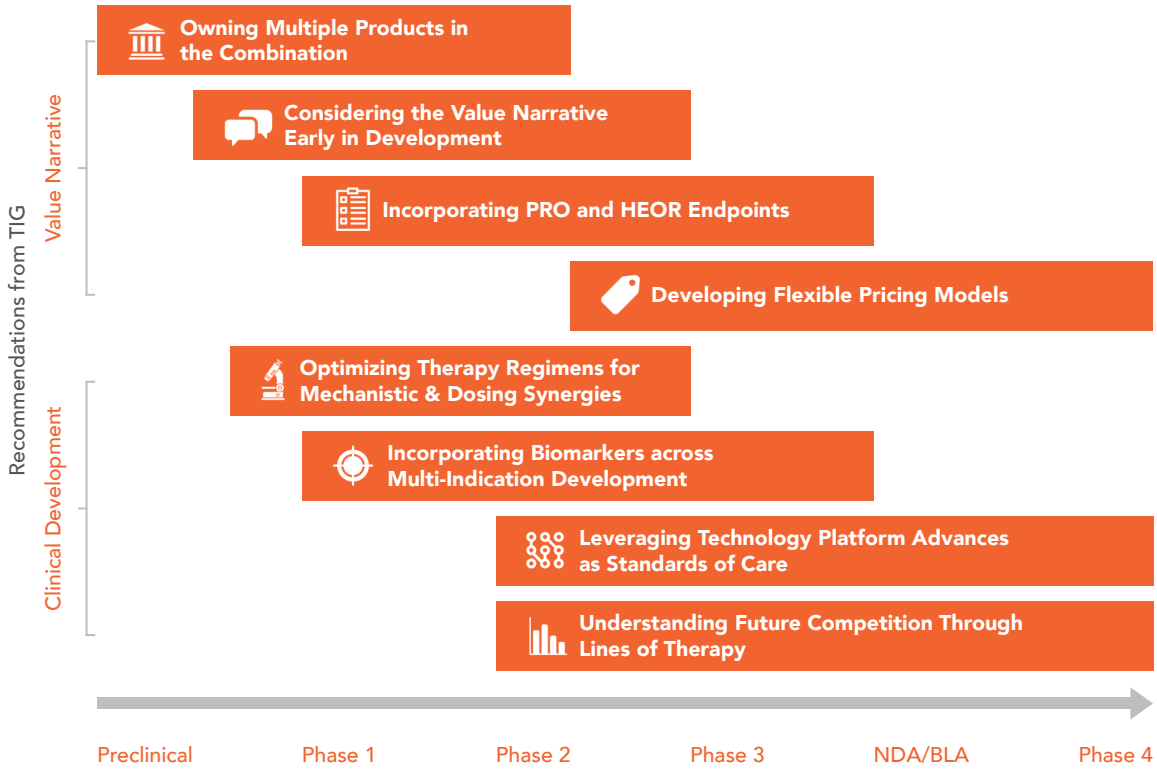

Figure 4: Strategic Framework for Oncology Combination Therapy Development.
Triangle Insights recommends an eight-factor approach to strategic planning for combination therapies in oncology, with clinical development approaches and insights paired with a robust value narrative to achieve optimal future market access from payers.

Clinical Development Recommendations

Understanding Future Competition Through Lines of Therapy

As innovative oncology therapies extend overall survival for patients, more volume will be generated in later lines of therapy. Thus, attention should be paid by early-stage oncology manufacturers not only to the current and future competition, but also to the evolution of the entire treatment paradigm. Oncology combination manufacturers that enter the market with a value story that is less compelling than those of their competitors will be unable to move up in future lines of therapy.

Leveraging Technology Platform Advances as Standards of Care

As treatment paradigms advance, novel therapies with differentiated value propositions will become the backbone for combination therapies upon which manufacturers will be expected to build. In the cell therapy space, where off-the-shelf approaches present opportunity for significantly reduced cost of care compared to autologous treatment,[9] the opportunity for payers to better manage spend is clear. Oncology combination manufacturers that do not carefully consider their choice of combination in their development plan early on (cell therapy or otherwise) may be left with an outdated approval by the time they reach the market.

Incorporating Biomarkers across Multi-Indication Development

Incorporation of biomarkers into trial design should be carefully considered, as they allow for expansion into indications beyond the "Big Six" early in development, and can maximize a combination's value in a specific patient population based on the biomarker rather than the indication. Manufacturers that do not incorporate a "biomarker first" mindset run the risk of non-preferential access if a leading clinical guideline recommendation is not attained.

Optimizing Therapy Regimens for Mechanistic and Dosing Synergies

While complementary mechanisms of action are being developed across a variety of combination therapies, synergies in efficacy (as well as toxicity) can also be found at sub-MTD doses for the monotherapies, and dose escalation/de-escalation strategies that can capture these synergies may be a foundational component of a combination therapy development program.[10-12] Oncology combination manufacturers that do not optimize their regimens for dose as well as mechanism for efficacy may leave potential value on the table when they look to negotiate with payers.

Value Narrative Recommendations

Considering the Value Narrative Early in Development

In addition to thoughtfully designing the clinical development program, manufacturers should proactively consider the development of the value narrative and payer engagement strategy early in the development process, particularly for 'add-ons' in a combination therapy that may be more carefully scrutinized. Manufacturers that do not engage with payers early and often may end up with a value narrative at launch that does not resonate with payers long-term needs in cost of care.

Incorporating PRO and HEOR Endpoints

Careful incorporation of appropriate non-clinical endpoints should be a priority to highlight the asset's holistic value, prepare for HTA/ICER assessments, and optimize the value narrative. While payers in the near-term do not expect significant changes to their management of oncology combinations, the market has already observed restrictions and even non-coverage being put in place for oncology therapies today.[3,5] Manufacturers that do not heed the cost of care concerns presented by payers today may be the first ones to be viewed as lower value as they enter the market.

Developing Flexible Pricing Models

Manufacturers should also consider flexible pricing models with payers based on the biomarker as well as the indication. Payers interviewed discussed the challenges with implementing flexible pricing (e.g., emphasizing no more than a 3-year amortization), but were open to predictable contracts based on share of up-front payment and/or utilization-based pricing models. [3] Manufacturers that proactively consider solutions throughout the development process may be rewarded by payers with preferential access.

Owning Multiple Products in the Combination

To maximize pricing flexibility and PRO/HEOR endpoint incorporation, as well as the value narrative overall, manufacturers should consider taking a portfolio approach to combination therapy development. Owning multiple products in the combination reduces the challenges in defining backbone vs add-on therapy while simplifying early conversations and later negotiations with payers. Manufacturers that own only one component of a proposed combination therapy risk being relegated to add-on therapy status to an already-established treatment paradigm.

As combination therapy utilization in oncology accelerates and costs continue to climb, payers may find themselves in a more and more favorable negotiating position, dependent on the continued evolution of regulatory and policy initiatives. Oncology manufacturers should take proactive steps to best position their combination assets and ensure patient access through implementation of preemptive clinical and value strategies early in the development process. Manufacturers that become complacent with respect to developing the value narrative for combination therapies may find themselves in a challenging position at the negotiating table in years to come.

Citations:

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