

MATCHMAKING IN ONCOLOGY

CHALLENGES AND COMBINATION STRATEGY FOR NOVEL TARGETED AGENTS

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Recent advances in oncology, such as biomarkers and targeted therapeutics, have raised the bar for success, requiring drug developers to think beyond the traditional R&D model. Oncology treatment is changing, and as targeted agents gain adoption and use in the clinic, demand is increasing for products with high (and durable) efficacy and low toxicity. Approval based on incremental efficacy gains may soon be a thing of the past. Companies playing in oncology are faced with a dizzying number of options, high pipeline competition, and many are pursuing the same target in a race to be first to market and demonstrate significant differentiation versus their competitors.

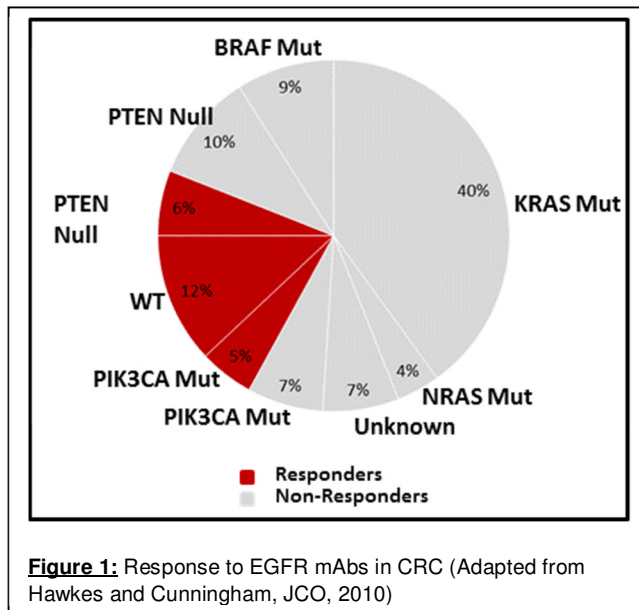
In order to maximize chances of success, and move beyond incremental efficacy, many companies are pursuing novel combinations of targeted agents that disrupt key signaling pathways critical to tumorigenesis (Table 1). The idea of combination therapy is not new in oncology. Many oncology indications are treated

Companies	Combination Regimen	MOA	Indications
GSK	Dabrafenib, trametinib	BRAF, MEK1/2	Melanoma, other solid tumors
Novartis	BEZ235, MEK162	PI3K-mTOR, MEK1/2	Solid tumors
Merck and Sanofi	MSC1936369B, SAR245409	MEK1/2, PI3K-mTOR	Solid tumors
	MSC1936369B, SAR245408	MEK1/2, PI3K	Solid tumors
AstraZeneca and Merck	Selumetinib, MK-2206	MEK1/2, Akt	NSCLC, CRC, melanoma

Table 1: Selected novel-novel combination programs ongoing in oncology; CRC = colorectal cancer; NSCLC = non-small cell lung cancer

with a combination approach, be it a combination chemotherapy regimen (e.g., platinum doublet therapy for NSCLC) or a targeted agent combined with chemotherapy (e.g., Rituxan-CHOP for DLBCL). However, the combination of novel targeted agents is an emerging phenomenon, ushering in an era of rationale treatment approaches based on knowledge that tumors are often driven by several factors, including multiple molecular changes (e.g., genetic mutations, protein overexpression, etc.) and the tumor microenvironment. Thus targeting more than one molecular target may result in a better therapeutic outcome in oncology — multi-tyrosine kinase inhibitors are real life examples reflecting such a concept. Similarly, many hope that combination approaches, by targeting two or more molecular targets simultaneously, will increase the chance of success for many targeted agents, and meet the high efficacy bar that has eluded other agents in the past.

A combination strategy to co-develop unapproved agents raises a unique set of questions for companies, ranging from selection of synergistic MOAs, biomarkers, and optimal patient segment(s), to regulatory uncertainties, pricing strategy, and market access. In this article, we suggest that a



combination strategy in oncology could be crucial to ensure maximum success, and discuss the specific impact / implications on decision-making for drug development.

WHY COMBINATION THERAPY IS IMPORTANT FOR ONCOLOGY

As new targets are identified, cancer therapy has become increasingly complex, with multiple therapy options per indication, depending on a patient’s somatic and germ line genetic / molecular makeup; especially given that a tumor’s molecular makeup may be heterogeneous and evolve over time. This evolution is clear in NSCLC – what used to be a

single disease treated with chemotherapy has evolved into a highly segmented group of indications, defined by a patient’s EGFR, KRAS, and ALK status, and tumor histology.

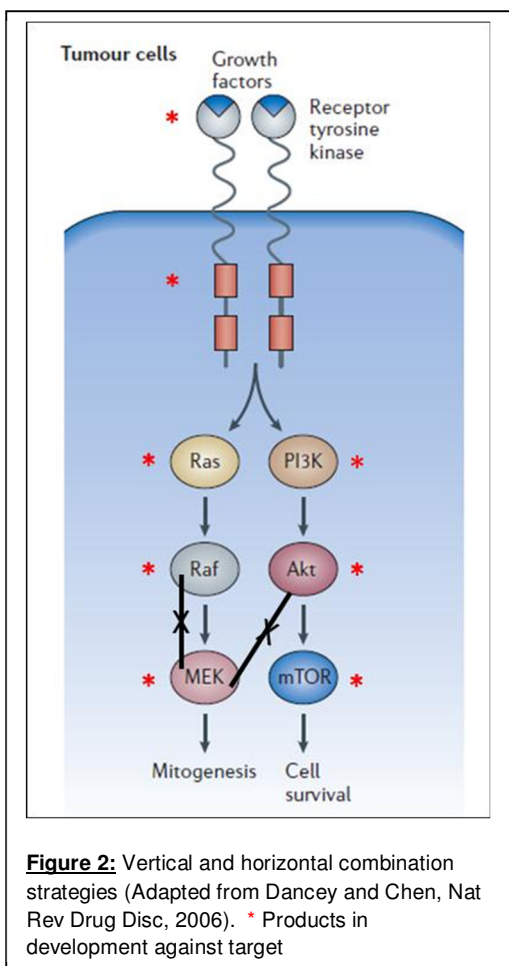
In some ways, the combination of novel targeted agents is a logical step in oncology R&D, and we see it to be critical from both a clinical and commercial standpoint.

Scientific and Clinical Rationale

The combination of novel targeted products has obvious scientific and clinical benefits. Most tumors are driven by multiple driver mutations / molecular aberrations, and as a result, targeting a single pathway is likely to be insufficient to fully halt tumor growth and induce cell death. This phenomenon is clearly the case in CRC, in which the EGFR targeted mAbs Erbitux and Vectibix are only effective in ~23% of patients. While KRAS mutation testing is able to eliminate 40% of CRC patients who will not respond to EGFR targeted therapy, a significant proportion of KRAS WT patients have mutations / aberrations (e.g., PTEN loss, PI3KCA mutations, NRAS mutations), causing resistance to EGFR targeted therapy (Figure 1). Based on this, one could hypothesize that a combination of EGFR directed therapy with a second targeted agent may be beneficial in a subset of CRC patients.

Combination strategies for targeted products can encompass either a vertical combination, targeting different nodes in the same pathway (e.g., BRAF and MEK), or a horizontal combination, targeting parallel pathways (e.g., MEK and PI3K) (Figure 2). Vertical combinations address dependency on one or multiple genes (e.g., oncogene addiction) and their downstream signaling pathway for maintenance of tumor growth. On the other hand, horizontal combinations to target multiple pathways can address compensatory mechanisms such as feedback inhibition or activation. Consequently, patients who may not respond well to a certain therapy due to either downstream mutations (e.g., KRAS mutation for EGFR inhibitors) or compensatory mechanism at parallel pathways could actually respond to vertical and





/ or horizontal combination therapies, leading to a synergistic effect between the two combined products. As a result, such combination strategies may ultimately provide the best chance for maximum response (in terms of response rate and survival benefits, etc.), thereby also increasing duration of response and preventing resistance. Resistance is a significant concern with targeted therapy, evidenced by the recent data with Roche’s BRAF inhibitor Zelboraf in melanoma. While Zelboraf induces striking tumor shrinkage in BRAF V600E mutation patients, median PFS is short (approximately 5.3 months) due to onset of resistance. Consequently, GSK, who is developing its BRAF inhibitor dabrafenib in melanoma, is pursuing a combination approach with its MEK inhibitor trametinib, and Phase I/II data so far suggest improved progression free survival compared to historical data with Zelboraf monotherapy (7.4 months with combination therapy).

Commercial Rationale

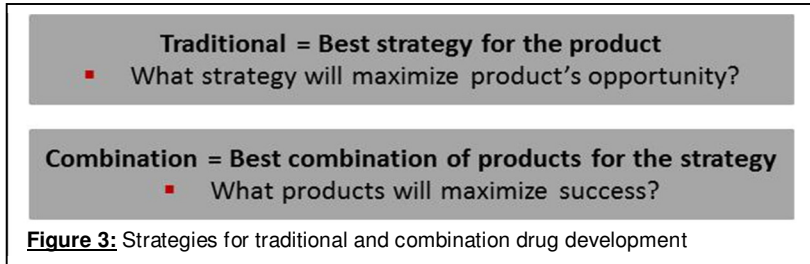
For companies competing in the oncology space, a combination strategy may also bring some critical commercial benefits. Perhaps one of the most impactful consequences of a combination strategy is the potential

for differentiation versus the competition resulting from the synergistic benefits of combination therapies—significantly enhanced efficacy (response rate, survival benefits, duration of response, etc.), and / or reduction of resistance. In the highly competitive oncology market, differentiation versus similar MOAs / products in development is critical, and can provide a competitive edge, improving penetration, access, and the probability of commercial success. For example, GSK is the leader in the MEK and BRAF combination space, differentiating them from Zelboraf, and putting them ahead of the curve as other competitors scramble to find suitable combination partners for their BRAF inhibitors.

Dual combinations of novel targeted products can also leverage synergy across a company’s portfolio, increasing options for competing in the oncology market. Selection of the product to combine with can broaden the opportunity for a given asset, improving its efficacy and potentially allowing it to play in a particular patient segment that it otherwise would not be successful in.

The potential benefits of combination therapy are significant; however, there are unique questions that companies must address to ensure success.



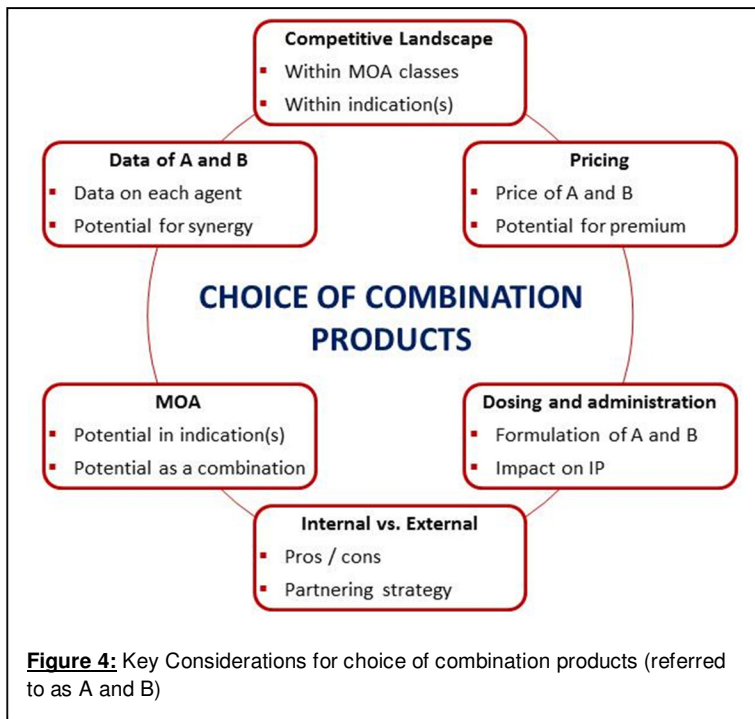


KEY CHALLENGES FOR COMBINATION STRATEGIES

Companies face a complex set of challenges and questions in the development of novel combination regimens. In traditional single product

development, companies must address the question of “what is the best strategy for the product” (Figure 3). Typically, after identification of a drug candidate in the discovery stage, product teams address the scientific and clinical questions around MOA and target indication(s) to support pre-clinical and early Phase I trials. In this case, commercial inputs come later in development, once the potential indication(s) have been identified and evaluated by R&D and clinical teams.

On the other hand, we believe that a combination strategy requires a different approach, addressing a second critical question, “what is the best combination of products for the strategy” (Figure 3). Pursuing a combination strategy brings a complex and unique set of challenges, which requires both clinical and commercial inputs during the development of the combination regimen. Central to these challenges is the key decision around the products to use in the combination program. Product choice is critical, and can be impacted by several factors, including MOA, potential for synergy, choice of internal versus external product, competitive landscape within the MOA and indication, dosing, and pricing strategy (Figure 4).



Multiple Options for Combination

Contributing to the complexity of a combination strategy is the availability of multiple combination options for a given indication. Companies are not only faced with selecting the relevant MOA (e.g., BRAF versus PI3K versus Akt), but also the appropriate drug candidate within a MOA class as there may be multiple products under development for a given class. Furthermore, companies are also faced with the choice to use an internal pipeline asset, or pursue a collaboration or partnership with a competitor to gain access to their pipeline – for example, GSK is

combining their MEK1/2 inhibitor with their internal BRAF inhibitor, while AstraZeneca has partnered with Merck to combine with their Akt inhibitor. The choice of a combination product requires early decision making and tradeoff analysis from both a clinical and commercial perspective to ensure maximum opportunity in a given indication.

Implications for Monotherapy Programs

For most combination programs under development, the two products are likely also being investigated as monotherapies, both in the same and additional indications. As a result, certain scientific and clinical decisions may have been taken with regards to the products, including drug design, dosing, target indications, etc., and therefore, a combination decision cannot be made in isolation without considering the monotherapy programs. For example, GSK and AstraZeneca are developing their MEK1/2 inhibitors in NSCLC as monotherapies and / or with standard of care chemotherapy, while also running combination trials with BRAF and Akt inhibitors, respectively, for other indications. Implications for the monotherapy programs must also be taken into consideration, to address issues such as launch timing (e.g., should the single or combination program be launched first), impact on pricing strategy, and value proposition for both the single and combination therapy.

Clinical Development Costs

While the clinical development and regulatory pathways are still somewhat unclear today, combination trials have the potential to be costly, particularly if the FDA requires multi-arm trials for both single and combination therapy. Accordingly, the decisions to pursue a combination strategy, and the subsequent decisions around the products and indication(s) may have significant impact, and robust decision analysis should be performed to support the level of investment that may be required.

KEY IMPLICATIONS FOR DRUG DEVELOPMENT

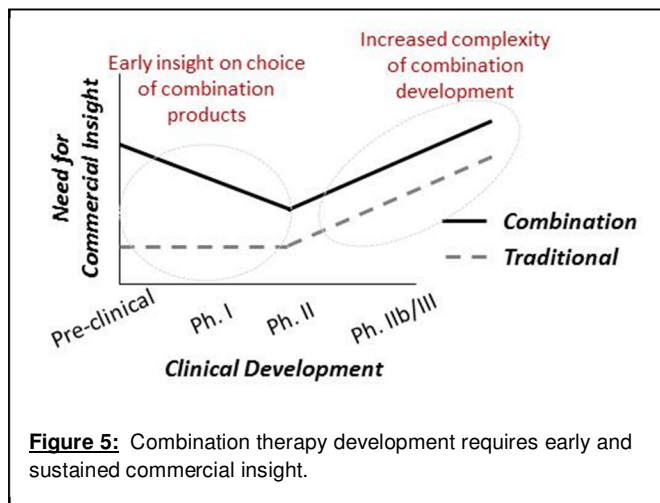
We believe that commercial analytics early on are crucial in order to properly address the key questions that arise during the development of a combination therapy. Product teams must determine how the combination of two products impacts the opportunity in a given segment, and the implications for patients, prescribers and payers. Will the combination therapy provide sufficient clinical value and a favorable benefit / risk ratio to ensure adoption by physicians and patients? To address those questions, it is essential to understand how “combo-friendly” the target indication will be – the unmet needs in the target indication, and the level of clinical utility / value the combination therapy would provide based on its differentiating efficacy and / or safety profile. For example, if overall survival is already significant, as is the case for many follicular lymphoma patients, a combination regimen providing a limited incremental survival benefit may face access and clinical adoption challenges, even if regulatory approval is secured. As the selection of combination products is so closely linked to the optimal target segment / indication, these two topics must be addressed simultaneously, drawing on both clinical and commercial analyses. Furthermore, the potential for a biomarker / personalized medicine approach is an important consideration, particularly for a combination therapy with two highly targeted products.

Accordingly, product teams must assess whether a dual biomarker approach will be required, or whether one biomarker will be sufficient to identify the appropriate patient population.

Pricing strategy is another critical topic that companies must address, and many teams are unsure of how to tackle pricing of a combination therapy. As mentioned above, one of the potential benefits for combination therapy is the boost in efficacy from targeting two targets or pathways central to tumorigenesis. To-date in oncology, we have seen highly targeted and efficacious agents garnering significant price premiums. However, a combination therapy involving two separate products raises another set of considerations around pricing of the single products versus the combination therapy, and whether payers will be willing to pay for synergy. Central to this question, companies must understand the impact on value of bringing the products to the market separately as well as in combination – timing here is critical, particularly if the single products have a set price before the combination therapy is approved. Based on our analysis, we do not expect payers to necessarily deny high priced combination therapies, should their value be justified by their pharmacoeconomic / comparative values; however, cost containment measures may be implemented to limit their use, including prior-authorization, step therapy and inclusion in pathways. In Europe, high priced combination therapies may experience pushback, particularly from countries like the UK. Furthermore, as Germany has ended free pricing, and implemented their health reform – AMNOG, it is unclear what benchmarks will be used to set combination therapy price, and what impact this will have on other European countries given the historical importance of Germany in reference pricing. It is clear though that companies will need a well-defined and defensible value proposition to ensure approval and access in Europe.

CONCLUDING REMARKS

In conclusion, given the increased complexity of developing a combination therapy with two unapproved products in oncology, we see a critical need for early commercial insight to address the challenges discussed above. Involving commercial teams at the pre-clinical stage is important to help decide on the optimal combination product, and identify the indications and clinical strategies that will ensure maximal opportunity and success of the program. Additionally, commercial insight will become critical again to support the late stage development process to ensure high penetration and access to therapy once launched (Figure 5). The combination of novel targeted agents has the potential to increase efficacy and create better outcomes for oncology patients – and oncology players should be prepared in order to realize these goals.



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