

# Immuno-Oncology Brings New Opportunities for Developers of Targeted Cytotoxics

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Among the highlights of this year's American Society of Clinical Oncology Annual Meeting were outstanding data from the combination of Bristol-Myers Squibb's nivolumab and ipilimumab, which produced a longer progression-free survival than ipilimumab alone in non-BRAF-mutated melanoma. Companies are furiously mixing and matching combinations of their immuno-oncology therapies to determine their greatest benefit. But a strong case can also be made for participation by developers of targeted therapies, including receptor kinase inhibitors and antibody-drug conjugates. The time is right to partner with immunotherapy firms, and for immunotherapy firms similarly to collaborate with those makers of targeted agents.

Ultimately, the value to patients will lie in combination therapies including, but not limited to, immunotherapy agents. But companies developing immunotherapies cannot feasibly run all of the early-stage trials needed to ascertain the types of combinations that will be safe and effective in given indications. The number of possible combinations is daunting, and absent better preclinical modeling, at least for today, deciding which classes of targeted cytotoxics to combine with immunotherapies and how to sequence treatment remains a process of trial and error.

The development of combination therapies using

targeted agents offers immunotherapy developers several potential advantages. These include the ability to differentiate in a crowded indication; maintain leadership in an indication; or provide an entry point in an indication where immunotherapy has not yet made significant progress as monotherapy, such as breast cancer; or where the tumor microenvironment renders it difficult for immunotherapies to be truly effective. Targeted agents may also make tumors more immunogenic and/or trigger antigen release upon cell death, creating a favorable microenvironment and boosting the efficiency of immunotherapies. But it needs to be shown case by case that the targeted agents do not also diminish the ability of T cells to infiltrate a tumor or hamper their activation in any way.

Underappreciated, however, is the value that companies developing cytotoxic modalities bring to the table in terms of knowledge and development resources, as well as funding. Our sense is that many of these companies have yet to realize the power they hold if they are willing to make an investment in early-stage combination trials with immunotherapies. As we discussed in a Q&A in this journal in May 2015, partnerships make the overall economics better for an immunotherapy developer seeking to rapidly penetrate a broad range of indications across many lines. Introducing a targeted agent in combination with an immunotherapy, assuming higher efficacy for the duo, may help bring competitive advantage to one immunotherapy versus another—especially if the targeted agent carries with it a biomarker so that the combination is “locked in” with a defined patient population, which would help to define and segment that market in favor of that specific combination and potentially smooth the commercialization path. Plus, key opinion leaders and industry experts do not expect immunotherapy by itself to be sufficient in many indications, thus requiring a combination approach with targeted cytotoxics.

For developers of targeted agents, the ability to combine their compounds with an immunotherapy could help them establish a leading position in crowded indi-

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cations where many other companies are pursuing the same target. Companies have begun to see this, as large pharmaceutical firms including Novartis, Eli Lilly, and Pfizer have begun running combination trials of their targeted agents with the most clinically advanced checkpoint-inhibiting compounds. Incyte is testing its inhibitor of indoleamine 2,3-dioxygenase 1, INCB24360, with each of the leading checkpoint inhibitors—nivolumab, Merck's pembrolizumab, Roche's atezolizumab, and AstraZeneca's MEDI4736. According to clinicaltrials.gov, of the 143 clinical trials of those 4 checkpoint inhibitors initiated between June 1, 2014, and May 28, 2015, 25 are testing combinations with targeted agents from other companies and are being sponsored by the developers of those targeted agents.

That percentage is sure to increase, because the window of opportunity is now for developing combinations of immunotherapies and targeted agents. The leaders in checkpoint inhibition are jockeying for position among themselves with little knowledge of what will differentiate one compound or target (programmed death-1 [PD-1] vs its ligand PD-L1, for example) from another—including the use of biomarkers—or of how to segment populations of cancer patients. Those without a first-mover advantage who are playing catch-up to the leaders especially need to differentiate their immunotherapies from others in specific indications.

That makes for a favorable competitive situation for companies that have assets to combine and are seeking access to immunotherapies. Some companies have negotiated more complex deals, but the majority of partnerships with immunotherapy companies have been simple clinical trial collaborations, without specific deal terms for future codevelopment or co-commercialization. Immunotherapy companies with limited discovery capabilities may also be interested in arrangements where the targeted agent developer also brings a discovery platform to the table. Accessing novel mechanisms may be of particular interest. As one business development executive at a leading immunotherapy company puts it: “New mechanisms of action have the sizzle and provide interest in new investments.”

Although for regulatory reasons it may be easier to combine an early-stage asset with an approved immunotherapy, combinations of assets at the same stage of development offer symmetry in partnering negotiations. Having a late-stage clinical product to combine

with an immunotherapy may make patient recruitment easier as well.

Already it's clear that this new age of immunotherapy is changing the game for developing targeted agents in oncology. They will now be positioned either as combination agents with immunotherapies or for use in patients who either don't respond to or are not expected to respond to immunotherapy. With checkpoint inhibitors fast becoming the backbone in multiple indications, the market will demand answers to the questions of whether and how to combine and sequence them with other treatment modalities. Developers of targeted agents may be in a better position to show a strong scientific rationale for a combination with an immunotherapy, having already developed models relevant to the cytotoxic target, that may help determine the degree of T-cell infiltration in a tumor and that the targeted agent does not ablate those cells.

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Pricing of combinations is a large looming issue, especially if the assumption is that, at some point, payers will try to cap their reimbursement costs. Introducing a combination with a currently approved immunotherapy whose price is already set could put pricing pressure on the targeted agent. But the power of negotiation could also lie with the targeted agent, assuming a greater level of efficacy for an immunotherapy combined with it.

There is an abundance of checkpoint inhibitors with which to work, especially if the goal is to establish activity and safety quickly and not necessarily look for the highest efficacy right off the bat. In a sense, the immunotherapy is serving as a tool compound. That gives the developer of a targeted agent a range of choices for early trial work. The time is now for developers of targeted agents to gain more understanding of the clinical impact of combination therapy at a relatively low partnering cost, a situation that may not last as second-generation immunotherapies enter the market and immunotherapy companies refine their approaches. ♦