IO's Impact On Strategic Decision-Making In The Broader Oncology Landscape

Market signals from the pioneering immuno-oncology therapies suggest a paradigm shift across multiple oncology indications in the coming years. To ensure that non-IO products become successful components of the standard of care in cancer, drug developers must consider how IO may impact clinical development, market access, and commercialization strategies.

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- The initial success of checkpoint inhibitors and engineered T cell therapies has spawned a surge of investment in the field of immuno-oncology.
- More than 750 IO agents are currently under investigation across a broad range of tumor types, which will likely drive rapid and significant changes in oncology treatment.
- This evolution will consequently impact decision-making for all novel oncology assets, and in particular for non-IO therapies.
- Moving forward, it will therefore be critical for drug developers to factor in the advancement of IO for strategic planning across clinical development, market access and commercialization.

Oncology is one of the fastest expanding therapeutic areas in health care, and a strong contributor to this growth is the burgeoning field of immuno-oncology (IO). Heralded as the next big revolution in cancer care, a week rarely passes without an announcement of an IO deal or a clinical development update. Recent reports of transformative efficacy, from dramatic remissions in hematologic cancer to overall survival improvements in solid tumors, are fueling interest in IO, which has the potential to dramatically alter the way we treat cancer.

Given IO's likely impact, all cancer drug companies, particularly those that are developing novel, non-IO agents, should consider their strategic decision-making accordingly. Emphasis on and expectations for higher response rates and greater durability will raise the efficacy bar across tumor types. As such, the growth of IO will increase the burden on oncology drug manufacturers to demonstrate additional, clinically meaningful value. To compete in this future environment, non-IO drug developers need to think strategically regarding the identification of attractive white space opportunities and when positioning their agents within the broader oncology landscape.

DEPTH OF IO THERAPEUTIC APPROACHES

While much of IO in clinical practice is currently centered on anti PD-1/PD-L1 and anti CTLA-4 agents, these checkpoint inhibitors represent the tip of the iceberg for the field. The next wave of IO therapies exploits a wide range of pathways in tumor immunology. These approaches can be divided into four classes: T Cell Stimulation, Engineered T Cells, Antigen Presentation and Other Anti-immunosuppression. (*See Exhibit 1.*)

Within these classes, T Cell Stimulation is the most prominent in

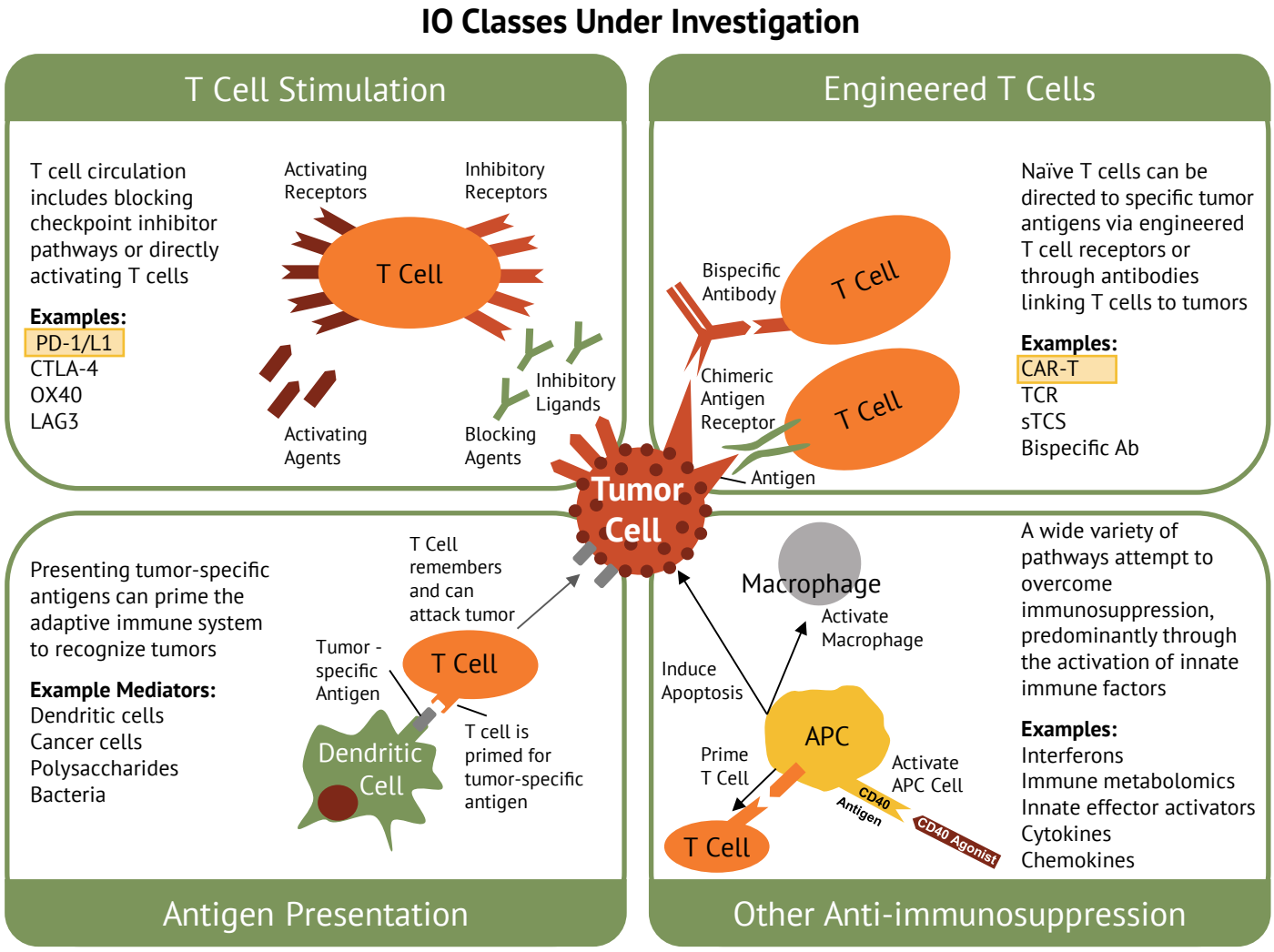
the market, including the approved PD-1 inhibitors *Opdivo* (nivolumab) from **Bristol-Myers Squibb Co.** and *Keytruda* (pembrolizumab) from **Merck & Co. Inc.**, as well as BMS' CTLA-4 antagonist *Yervoy* (ipilimumab). Nevertheless, these are not the only mechanistic options for T cell stimulation. Others in development (e.g., lymphocyte-activation gene 3 [LAG3] and OX40 [CD134]) seek to inhibit regulatory T cell suppression or drive expansion of effector and memory T cells.

Another widely publicized class of IO agents is Engineered T Cells. Such programs prime T cells to induce antigen-specific immune reactions. The most prominent are chimeric antigen receptor T cell (CAR-T) therapies, with preliminary yet breathtaking hematologic data from innovators such as Juno, Kite and Novartis. Bispecific CD3 antibodies such as **Amgen Inc.**'s *Blincyto* (blinatumomab) are another potentially exciting approach, aiming to collocate T cells to tumors for their destruction.

The two other classes of IO therapies are Antigen Presentation and Other Anti-immunosuppression. Promoting antigen presentation through vaccines could sensitize the immune system to tumor antigens, and is being harnessed in clinical-stage therapies such as **MedImmune LLC/Inovio Pharmaceuticals Inc.**'s DNA vaccine for HPV-associated cancers. Meanwhile, other anti-immunosuppression approaches aim to capitalize on innate effectors of the immune system and the tumor microenvironment to induce heightened responses to cancer cells, as exemplified by **Janssen Biotech Inc./Alligator Bioscience AB**'s CD40 agonist under investigation for solid and hematologic tumors.

Exhibit 1

Potential Approaches To Harness The Immune System Against Cancer

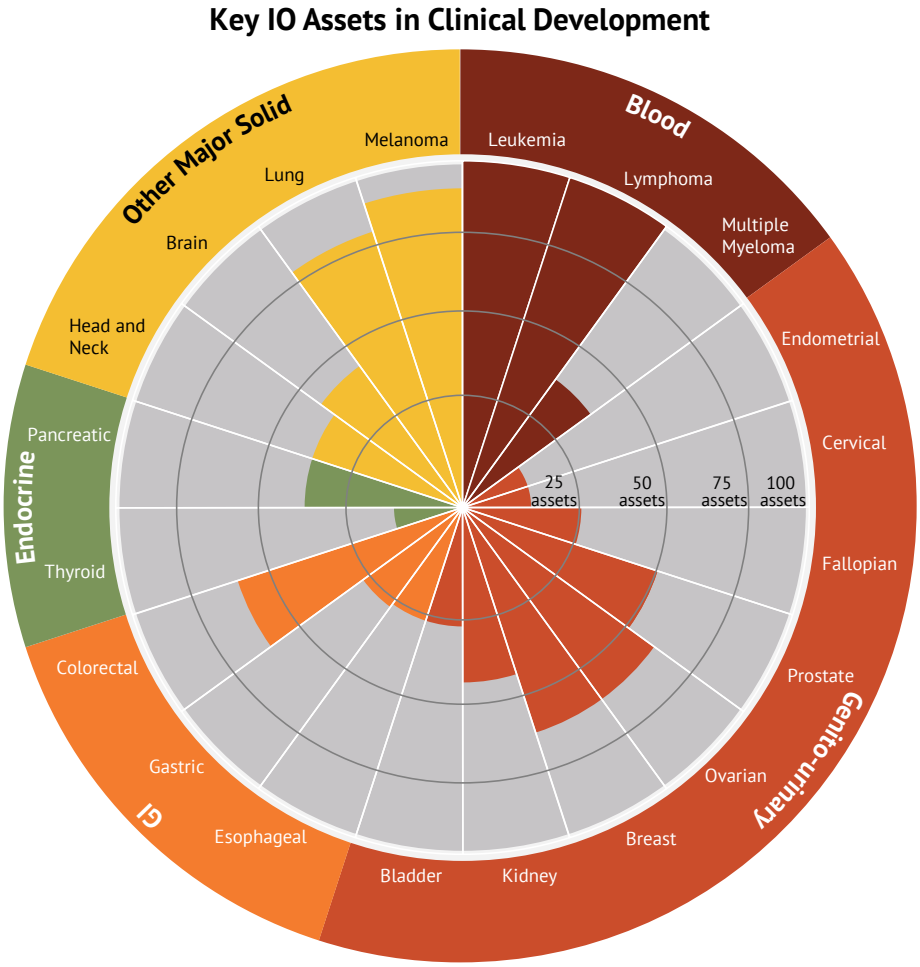


PD-1/L1 and CAR-T therapies represent only a fraction of the various approaches to harness the immune system against tumors

SOURCE: Citeline | Pharma Intelligence, 2016

Exhibit 2

Potential Approaches To Harness The Immune System Against Cancer



SOURCE: Citeline | Pharma Intelligence, 2016

Although the field of IO is still in its nascency, it is already apparent that an abundance of pathways may be targeted to induce the immune system to attack cancer.

BREADTH OF APPLICATION FOR IO THERAPY

The breadth of application for IO agents also appears to be substantial. Since the approval of the checkpoint inhibitors Yervoy, Opdivo and Keytruda, clinical trials of IO agents have been expanding at an exponential rate. As of the beginning of 2016, over 750 unique agents were being investigated across more than 20 hematologic and solid tumors. (*See Exhibit* 2.)

At this time, a general dichotomy currently exists across IO, with T cell stimulatory agents primarily targeting solid tumors and engineered T cells favoring liquid tumors. But this separation may not last long. Biopharmaceutical companies are investigating combination therapies that span IO classes. For example, **Roche**'s **Genentech Inc.** is partnering its PD-L1 checkpoint inhibitor with **Kite Pharma Inc.**'s CAR-T in non-Hodgkin lymphoma. Many other clinical trials are underway that also demonstrate the potential applicability of IO across either solid or liquid tumors. The result is the potential for substantial breadth of application for IO across the spectrum of liquid and solid tumors.

IMPLICATIONS FOR NON-IO ASSET STRATEGY

Given the depth and breadth of IO, this field is expected to inspire a dramatic shift in treatment paradigms. In this future environment, it will become increasingly critical to consider how IO will impact strategic decision-making for novel, non-IO agents. Specifically, non-IO drug developers will need to consider the implications of IO across three key dimensions: clinical development strategy, pricing and market access, and commercialization.

Impact On Clinical Development Strategy

Tumors are highly heterogeneous and in most cases unlikely to be cured through a single therapy or target. Accordingly, the role of non-IO therapies should remain a dynamic component of the strategies implemented to treat cancer. Nevertheless, IO drugs will be highly effective in many instances, resulting in evolving tumor treatment paradigms, which consequently may affect white space opportunities for non-IO assets in development. Manufacturers of non-IO therapies will thus need to carefully consider how IO approaches may impact clinical development strategy and trial design decisions.

Efficacy: When evaluating the white spaces for a non-IO asset, a key factor to keep in mind is that the excitement surrounding IO does not dictate that these drugs are definitively the best option for a patient. A non-IO therapy may in fact be positioned to deliver meaningful efficacy to patients. In non-small cell lung cancer, EGFR inhibitors such as Genentech/**OSI Pharmaceuticals LLC**'s *Tarceva* (erlotinib) remain a first-line option for patients with EGFR mutations, despite the availability of Opdivo and Keytruda. In melanoma, B-Raf and MEK inhibitors such as **Novartis AG**'s *Tafinlar* + *Mekinst* (dabrafenib + trametinib) may be prescribed ahead of IO agents. Even without a companion diagnostic test, a non-IO agent may deliver better efficacy than alternative IO drugs. In this scenario, drug developers may seek to position a non-IO asset as an independent, superior option for treatment.

Patient Stratification: Non-IO therapies may also take advantage of patient stratification stemming from IO approaches. As understanding of IO agents increases, and as diagnostics improve, select patients may be identified who would benefit more, or less, from a non-IO approach. PD-1/L1 products arguably demonstrate better efficacy in patients with higher levels of

PD-L1. This may open the door for a novel targeted therapy to prove superior benefit in patients exhibiting low levels of PD-L1. Alternatively, individuals with poor health or compromised immune systems may be better candidates for a non-IO drug compared with antigen presentation or engineered T cell approaches, which may be less safe for such patients. These and other patient stratification scenarios may create favorable opportunities for non-IO drugs to become the preferred treatment choice, rather than playing second fiddle to IO.

IO/Non-IO Combination: Combination regimens may represent another attractive opportunity for a non-IO agent. Instead of going toe-to-toe with an IO agent on efficacy benefit, it may be preferable to demonstrate additive benefit in tandem with an IO drug. In certain indications, this may be the best approach to achieve faster and greater non-IO drug adoption. A combination regimen may be especially compelling if synergistic benefit with an IO agent is suspected. Research to date suggests Raf-MEK-ERK inhibitors increase T cell target antigen recognition, and therefore a drug developer may determine it is best to pair a novel inhibitor of this pathway with an IO agent to demonstrate the greatest clinical value.

Therapeutic Sequencing: Alternatively, it may be best to sequence therapies to achieve optimal efficacy, perhaps positioning a non-IO therapy ahead of or subsequent to an IO treatment. For instance, a non-IO drug may up-regulate immune response, suggesting that the non-IO drug should be administered prior to an IO treatment. Conversely, delivery of an IO product may maximize the anti-tumor effect of a non-IO chemotherapy, positioning the non-IO agent subsequent to IO administration.

Clinical Trial Design: Identifying the future white space opportunities comprises only the first piece of the clinical strategy equation. An equally important yet difficult decision relates to late-stage clinical trial design. It is not necessarily straightforward to identify the most appropriate comparator, patient inclusion and exclusion criteria, or treatment sequence. Making this more challenging is that cancer treatment paradigms are not static. For example, PD-1/L1 agents are in late-stage development for

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for squamous cell carcinoma of the head and neck (SCCHN), and while regulatory approval is anticipated, it is not guaranteed. Moreover, there is a question of whether PD-L1 diagnostics will or will not be used in clinical practice. For a non-IO agent in development for SCCHN, it will be important to identify how to approach Phase III trial design. Should a monotherapy approach be pursued in later-line patients, and if so, is the best comparator a chemotherapy or PD-1/L1 drug? Is the best business decision to target all patients, or only include those with low levels of PD-L1? Is it possible to target earlier-line patients with a combination regimen? Answering such questions will be critical to determining the appropriate clinical trial design for a non-IO asset.

The rise of IO is likely to complicate clinical development of a non-IO drug. It is therefore important to reevaluate and prioritize white space opportunities, and to align on the appropriate clinical trial program to demonstrate value for those indications. Doing so is one of the first steps to ensure downstream commercial success.

Impact On Pricing And Market Access Strategy

Decision-making regarding clinical development should not be made in a vacuum. Pricing and market access (P&MA) considerations, which may factor into clinical trial strategy, are equally if not more important to maximizing the commercial potential of a novel drug.

Historically, oncology has been regarded as an untouchable therapeutic area. New products would typically be fully accessible and reimbursed. However, this mentality has been shifting.

In Europe, cost-effectiveness and overall value proposition are becoming increasingly relevant. Germany's Institute of Quality and Efficiency in Healthcare (IQWiG) recently issued negative assessments to three oncology therapies: **Gilead Sciences Inc.**'s *Zydelig* (idelalisib), **Valeant Pharmaceuticals International Inc.**'s *Provenge* (sipuleucel-T) and **Vifor Pharma Ltd.**'s *Velphoro* (sucroferric oxyhydroxide). The rationale for each was that the products did not provide added benefit over comparator therapies. In the UK, drastic cost-cutting measures resulted in removal of over half of the reimbursed agents in the Cancer Drug Fund in 2015. Among these were **Celgene Corp.**'s widely used *Imnovid* (pomalidomide) and *Revlimid* (lenalidomide) for refractory multiple myeloma, and *Abraxane* (nab-paclitaxel) for metastatic pancreatic cancer.

Movement in the US similarly suggests a growing scrutiny of oncology drug pricing. A number of non-profit organizations and for-profit enterprises have launched tools that evaluate drug pricing and value. The American Society for Clinical Oncology (ASCO) has recommended that alternative payment programs and innovative care models be tested to promote high-value cancer care. As part of this effort, ASCO developed an initial value framework to assess the relative value of new cancer therapies compared with established treatments. Memorial Sloan Kettering published DrugAbacus, a tool to evaluate the price of oncology therapies relative to their perceived value. Finally, the National Comprehensive Cancer Network (NCCN) is incorporating cost scores into the information it publishes for clinicians and patients.

Granted, drastic P&MA changes will not

happen overnight, particularly in the US. Nevertheless, pricing and market access are key considerations when evaluating a new oncology product strategy. Moreover, if IO delivers on its promise and raises the bar for efficacy, the burden on emerging non-IO therapies to demonstrate additional, meaningful value will be even greater.

With this in mind, drug developers should carefully evaluate the indications for which a non-IO agent may demonstrate the greatest value. For example, consider a scenario in which a non-IO asset is being pursued in two indications. Indication A has a larger patient population, but the anticipated efficacy improvement with the non-IO drug will be modest. Indication B, on the other hand, is smaller in terms of addressable patients, but the expected efficacy benefit is more substantial. In the future P&MA landscape, this analysis, while oversimplified, may suggest that Indication B is more attractive given the potential for higher pricing and more favorable access.

In a similar vein, P&MA considerations may impact the decision to pursue combination therapy with an IO agent versus a non-IO monotherapy. Envision a situation in which combining a non-IO agent with an IO drug may lead to additive benefit. Although beneficial, the additional clinical value may not be perceived as sufficient to justify the total cost of the combination regimen. This may then suggest that executing clinical development as a monotherapy, potentially in a different indication, may be preferable.

Finally, the clinical landscape is likely to evolve. New treatment paradigms can be adopted into practice relatively quickly. Given a stricter future P&MA environment, it will become increasingly important to forecast the future standard of care (SOC) and determine its impact for a non-IO agent in development. It may be that the non-IO asset provides compelling value relative to current treatments but is less favorable compared with the anticipated future SOC. This may influence clinical development decisions regarding which indications and patient populations to prosecute against.

Ultimately, P&MA has become more than a check-the-box exercise for new oncology products. As the market access landscape becomes more restrictive, it will be imperative to plan early and pragmatically to ensure commercial success following regulatory approval.

Impact On Commercialization Strategy

The growth of IO also creates a need for early consideration of commercialization strategy for non-IO developers. This is important across two dimensions. First, drug developers should ensure that the marketing and sales teams possess the information required for a successful product positioning strategy. Second, non-IO drug developers must plan ahead for life cycle management and portfolio planning, particularly given the fast-paced market changes stemming from IO.

Regarding product positioning, drug developers may need to preemptively plan for future competitors, IO and otherwise. For example, while incorporation of patient-reported outcomes (PROs) and quality of life (QOL) measures may not be necessary for regulatory approval, collecting these data may prove important if a competitor IO agent is launched with similar overall survival data.

Another scenario is if a non-IO drug is complementary to a marketed IO therapy. In this case, there may be value in generating data to support messaging that acknowledges the ability to prescribe multiple drugs to attack a tumor. Through such an effort, a novel non-IO agent will be in the best position to achieve commercial success while providing physicians with the information needed to make informed prescribing decisions.

Notably, all of the decisions regarding a new, non-IO agent should take into account the impact to a company's broader oncology portfolio. A drug manufacturer should ensure that the messaging platform for a new, non-IO agent is coordinated with other products that are already launched or in development. In so doing, the overall therapeutic area franchise will possess harmonized product positioning across the portfolio that enables optimal commercialization.

CONCLUSIONS

Although the full impact of IO remains to be seen, market signals from the pioneering checkpoint inhibitors and next-generation CAR-T therapies suggest a paradigm shift across multiple oncology indications in the coming years. However, IO will not be the silver bullet to cure all cancer. Oncologists will be eager to take advantage of all novel therapies, including non-IO, thereby providing additional arrows in the quiver for tumor treatment. To ensure that a novel, non-IO product becomes a successful component of future oncology standard of care, drug developers should carefully consider how IO may impact clinical development, pricing and market access, and commercialization strategies. IV

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