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Advanced Antibodies Will Revolutionize The Future Of IO

by Hannah Hall

Immuno-oncology is a key area for biological drug development and activity has exploded over the past decade. Today, IO therapies represent a third of the biologics pipeline, and antibody development remains the focus.

The launch of monoclonal antibody (MAb) immune checkpoint inhibitors (ICIs) in the past decade has been game changing and provided new treatment options across the spectrum of solid tumor types and hematological cancers.

However, ICIs are limited by the fact that they target one singular pathway to mediate T-cell cytotoxicity, which means patient response is low and immune-related adverse events can occur. This approach does not consider the interactions of other immune cells and complex signaling pathways in the tumor microenvironment (TME).

There is, therefore, a great need for more efficacious and safer drugs that precisely direct cytotoxicity to tumor cells and simultaneously disrupt multiple signaling pathways. Next-generation multi-specific antibodies are designed to do just that and are anticipated to revolutionize IO in the future. This article explores the past, present, and future of IO antibody development using data and insights from Informa Pharma Intelligence's suite of products.

Historical Development Trends

The biologics market is growing, and the number of pipeline candidates continues to climb even though development is complex, lengthy, and expensive. This has been driven by advances in biotechnology as well as the clear clinical advantages biologics have demonstrated in multiple therapy areas. They have proven to be very effective in treating autoimmune conditions, specifically targeting pathogenic immune signaling pathways with fewer side effects compared to small molecules. Their improved target specificity, high efficacy, and favorable safety profiles also make them revolutionary treatments for cancer.

There have also been great advances in understanding the role of immunology in cancer pathogenesis over the past two decades, which has triggered huge industry interest in IO development platforms. The number of IO pipeline candidates has boomed since 2011 when ipilimumab became the first ICI MAb approved for cancer, increasing roughly 15-fold. Over this time, IO has become a significant area of biological therapy development, and IO candidates now represent around a third (33%) of all biologics in development (see Exhibit 1).

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There are many forms of IOs including fusion proteins, CAR-T therapies, oncolytic viruses, anticancer vaccines, and antibodies which have been investigated over the last 20 years. Antibodies are notably the most popular type of IO in investigation as they have consistently dominated the development pipeline. Based on data from the last decade, they represent around 40% of IO drugs in development per year on average (see Exhibit 2).

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So far, clinical development programs for IO drugs have proven significantly more successful than those for traditional oncology drugs. Biomedtracker estimates that likelihood of approval (LOA) of an IO candidate in Phase I is significantly higher than the average oncology candidate LOA (12.4% vs. 5.3%). Moreover, according to the Informa Pharma Intelligence report *Clinical Development Success Rates and Contributing Factors 2011-2020*, IO drugs have a notably high Phase II to Phase III transition rate of 42%, compared to 24.6% for the general oncology pipeline. This is the critical step during which proof-of-concept efficacy and safety is established in the desired target population. To date there have been 55 IOs approved, and the rapid growth and depth of the development pipeline will lead to more becoming available to patients in the future.

Immune Checkpoint Inhibitor MAbs

The most common forms of immunotherapy available for patients today are ICI MAbs (targeting PD-L1, PD-1, CTLA-4, and LAG3). To date, 18 have been approved and the majority are targeted to PD-1 (see table 1). Most of these approvals have occurred in the past in the past five years specifically. The first ICI to be approved was ipilimumab (targeting CTLA-4) in the US in 2011 for the treatment of unresectable or metastatic melanoma.

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In March 2022, Opdualag became the first fixed-dose combination ICI therapy to be approved, which includes nivolumab and an antibody that binds to a new ICI target, LAG3 (relatlimab). (Also see "*BMS Wins Competition For Novel Checkpoint Inhibitors With Relatlimab Approval*" - Scrip, 21 Mar, 2022.) Melanoma and Hodgkin's lymphoma are the most common diseases ICIs are

first approved for. However, their clinical utility extends much more broadly and PD-1 MAbs have subsequently received approvals in an expanded range of indications, including almost every solid tumor type.

ICIs have dramatically changed the treatment paradigm and dominated the market for certain indications. Most notably, PD-1/PD-L1-targeted MAbs are the best-selling class of drugs for NSCLC, according to analysis conducted by Datamonitor Healthcare. Keytruda was the first to gain regulatory approval for first-line NSCLC patients without an oncogenic driver and has risen to dominance, representing 22% of the total NSCLC patient share in 2021 in the US, Japan, and 5EU. This equates to revenues of $7.5bn in NSCLC alone, out of a total $17.2bn reported by *Merck & Co., Inc.* in 2021 for all Keytruda's indications globally.

The arrival of ICIs has certainly been groundbreaking for some patients, but they are limited by the fact they have a relatively low response rate, do not work universally in all cancer patients, and are associated with significant adverse side effects. While ICI trials have shown that they improve survival and clinical outcomes in selected indications (such as NSCLC, melanoma, and Hodgkin lymphoma), patient response to these types of therapy is relatively low. Recent estimates suggest that up to 38.5% of cancer patients in the US are eligible for immune checkpoint therapy, and only up to 11.4% of these patients are expected to respond to this treatment. They are also associated with a broad spectrum of immune-related adverse events affecting multiple organs including, hepatitis, pneumonitis, and encephalitis.

ICIs aim to generally enhance T-cell mediated immune response against tumor cells. But T cells are not the only immune cell that play a role in tumor immunology. The tumor microenvironment (TME) contains multiple types of immune cells, including dendritic cells (DCs), natural killer (NK) cells, B cells, and neutrophils. There are many levels of complex interactions between immune cells in the TME that determine their ability to control a tumor. Furthermore, there are many different mutations and characteristics of tumor cells that influence their ability to suppress the immune cells and determines a patient's response to immunotherapy. So, targeting a single pathway such as PD-1 is unlikely to attain the full therapeutic potential of ICIs.

There is a need for more targeted IO therapies with enhanced efficacy and safety. Rather than functioning to generally enhance immune response, and risk inducing immune-related adverse events, next-generation therapeutics need to be better targeted to tumors to allow more precise delivery of cytotoxicity. Moreover, there will be a move away from targeting singular pathogenic pathways towards using combinations of IOs, or IOs that can simultaneously target multiple pathways involved in controlling the tumor.

Current Pipeline And Next-Generation Antibodies

As of April 2022, there are currently 2,809 IO therapies in development. The pipeline mostly

consists of very early-stage candidates, with ~62% (N=1,759) of all drugs in preclinical stages. There are 1,035 drugs in clinical trials, and 15 are awaiting approval in pre-registration phase (see Exhibit 3). Almost all the candidates in the pipeline are novel chemical or biological entities as there are just 19 biosimilars in development, including ipilimumab, nivolumab, and pembrolizumab, and rituximab biosimilars.

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After the success of MAbs in cancer therapy, it is not surprising that antibodies remain the most common type of IO in development, with 411 currently in clinical trials. Over a third (N=147/411) of these are next-generation multi-specific antibodies, which target multiple antigens or epitopes on the same antigen.

Multi-specific antibodies are very promising as they can be designed to target multiple cells in the TME, rather than a singular molecular pathway. They aim to influence tumor death through various mechanisms including T cell co-stimulation, engagement of innate and adaptive immune cells, inhibition of specific mutation driven signaling pathways, simultaneous blockade of two immune checkpoints, and targeting multiple antigens to increase tumor selectivity. Bispecific antibodies (BsAbs), which can act upon two targets, are more prevalent in the pipeline compared to the more complex trispecific antibodies (TsAbs) (see exhibit 4).

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Bispecific T cell engagers (BiTEs) are a major class of BsAbs, representing 40% of total BsAbs in development. They simultaneously bind to T cells and cancer cells to more precisely target T-cell mediated cytotoxicity in the TME only, and therefore minimize immune adverse events.

Amgen, Inc.'s Blincyto (blinatumamab) is the only BiTE that has achieved approval, indicated for the treatment of B cell tumors such as leukemia and lymphoma. (Also see "*FDA Grants Blincyto Accelerated Approval Based On MRD Response Endpoint*" - Pink Sheet, 30 Mar, 2018.) There are six other similar BiTE candidates, in late-stage development for hematological malignancies, all targeting CD3 on T cells along with antigens on B cells (including BCMA, CD19). Three of these, *Johnson & Johnson*'s teclistamab and *Roche Holding AG*'s glofitimab and mosunetuzumabare in both in pre-registration, undergoing review with major regulatory bodies.

One other BsAb, *Genmab A/S* and Johnson & Johnson's Rybrevant (amivantamab), recently achieved approval in 2021 for the treatment of NSCLC patients with EGFR mutation. (Also see "*J&J's Rybrevant May Find Limited Uptake Outside Academic Centers*" - Scrip, 24 May, 2021.) It functions to disrupt the EGFR and cMet pathway which leads to tyrosine kinase therapy resistance in these patients.

There are several other candidates in clinical trials that aim to overcome therapy resistance through targeting other mutational pathways. For example, *Systimmune Inc.*'s SI-B001 is a Phase III BsAb targeting the EGFR/HER3 pathway that is also involved in anti-EGFR resistance in multiple solid tumor indications. Targeting two checkpoint inhibitors is another popular strategy for BsAb development programs. *Akeso Inc.*'s cadonilimab is the most advanced bispecific checkpoint inhibitor (targeting both PD-1 and CTLA-4) and is likely to be the first of its kind to be approved. In clinical trials it has demonstrated its efficacy in both PD-L1 positive and negative patients, significantly improving progression-free survival.

Further advances in antibody research have led to the debut of cutting-edge TsAb research programs. They offer even more clinical possibilities than BsAbs as they can be engineered to specifically target three pathways simultaneously, or alternatively co-localize three different antigens to engineer a powerful and tailored immune response. The vast majority are currently in early preclinical studies, but eleven have entered clinical trials (see Table 2).

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The most common class in development are trispecific T cell engagers (TriTEs). Improving T cell activation efficacy is a major goal in IO development and TriTEs may be a promising solution. There is therefore huge interest in funding the development of these novel therapies.

In 2018, UK-based *Crescendo Pharmaceuticals Corp.* raised $70m through series B financing to progress CB-307 into Phase I trials. At the time of reporting, this was the largest disclosed series B biotech financing round in Europe in that year. (Also see "*Crescendo Raises $70m In Largest European Biotech Series B Of Year*" - Scrip, 30 Apr, 2018.) More recently, a Swiss biotech, *CDR-Life, Inc.*, raised an impressive $76m in series A financing to advance its platform of multi-specific T cell engagers, including a preclinical multiple myeloma trispecific antibody (CDR101). (Also see "*CDR-Life Raises $76m To Develop Next-Generation T-Cell Engagers*" - Scrip, 13 Apr, 2022.)

Engaging innate natural killer (NK) cells rather than T cells to mediate cytotoxicity is another new approach being investigated. It is theorized that NK therapies are likely to have better safety profiles than T-cell based treatments, due to the observation that graft-vs-host reactions do not occur in patients receiving NK cell infusions.

The NK cell approach may also open alternative antigens beyond the common CD19 and BCMA approaches that are favored by T cell developers. Cell-based NK therapies have shown some benefits in hematological malignancies especially. However, the development of NK therapies for solid tumors is challenging because NK cells do not easily infiltrate solid tumor sites. The emergence of bispecific, and especially trispecific, NK cell engagers is likely to revolutionize NK

cell IO as they can be designed to utilize multiple targets to direct NK cells to tumors.

Multi-specific antibodies are a very promising tool, allowing for precision targeting of cytotoxicity and simultaneous disruption of multiple cancer pathways. Considering their specificity and unique targeting capabilities, it is likely that these drugs will prove more effective and safer than current MAbs and entry of these drugs into the market could revolutionize IO.

As our understanding of the complex interactions between tumor and immune cells in the TME advances, it is likely we will identify new targets and immune signatures specific to certain cancer types and individuals. Cancer treatment is inexorably becoming more personalized and one day it may be possible that IO therapy combinations can be routinely tailored for patients based on their specific immune signature. As the depth of investigation into multi-specific antibodies increases, these powerful drug classes can be adapted to new target combinations in the future and therefore they will play an important role in personalized combination therapy.

As IO development has boomed, antibody drugs have proved themselves as pivotal tools in cancer therapy. The arrival of ICI MAbs has been trailblazing in the field and provided much needed new treatment options for patients. But they are not the holy grail and advances in antibody research and development in IO will lead to the next generation of cancer therapies. Current ICIs are limited by low response rates, and association with immune adverse events. Therefore, a major goal of developers in the IO space is to build on the success of MAbs and advance antibody technology to discover new therapies with improved safety and efficacy. Multi-specific antibodies are particularly promising as they can be designed to simultaneously target multiple pathogenic pathways in the TME, and better direct cytotoxicity to tumor cells. They are a major focus of development currently, and will revolutionize IO as they enter the market in the future.

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