Cell-Based Cancer Immunotherapies: Commercial Risk, Curative Reward

White Paper
Cell-Based Cancer Immunotherapies: Commercial Risk, Curative Reward

Until recently, cancer treatments for advanced disease were palliative in nature, seeking to reduce tumor burden and prolong life. Curing metastatic disease was not considered possible. But over the past few decades, a new class of cancer treatments has demonstrated curative potential even in late stage patients: cancer immunotherapies.

So far, the approved “checkpoint inhibitor” cancer immunotherapies have been successful in only a subset of tumor types and patients. However, the cancer immunotherapy landscape is expanding to include several new and promising types of immunotherapies, such as cell-based immunotherapies, cancer viruses, and personalized vaccines. Here, we:

- Provide an overview of cancer immunity and how cell-based immunotherapies work
- Review each type of cell-based immunotherapy
- Place each type into a broader context of therapeutic potential and market competitiveness
- Discuss the development and commercialization outlook for each type and the class as a whole

<table>
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<tr>
<th>Glossary</th>
<th>Definition</th>
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<tr>
<td>Adaptive Immunity</td>
<td>Recognizes previously unidentified targets as “non-self,” then expands highly targeted Cytotoxic T Lymphocytes to identify and kill cells expressing the newly-identified “non-self” target antigens</td>
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<tr>
<td>Adoptive Cell Transfer (ACT)</td>
<td>Process of isolating living immune cells, manipulating them to boost or force cancer immune biology, then (re)infusing into the patient</td>
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<tr>
<td>Antigen</td>
<td>Fragment of a protein that is recognized by a TCR; typically presented at the cell surface (via the MHC) for the Adaptive Immune system to scan and classify as either “self” or “non-self”</td>
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<tr>
<td>Apoptosis</td>
<td>Programmed cell death; immune cells like Natural Killer Cells and Cytotoxic T Lymphocytes induce apoptosis in targeted “non-self” cells</td>
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<tr>
<td>Chimeric Antigen Receptor T Cell (CAR-T Cell)</td>
<td>T Cell (CTL) that expresses a genetically-engineered TCR that recognizes a tumor-specific cell surface protein</td>
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<td>Cytotoxic T Lymphocytes (CTLs)</td>
<td>Adaptive immunity effector T Cell; once activated into a CTL, recognizes “non-self” antigens and kills cells expressing those antigens by inducing apoptosis; also referred to generically as “T Cells” within this article</td>
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<tr>
<td>Dendritic Cells (DCs)</td>
<td>Digest dead cells, capture various antigens and present to naive T Lymphocytes for classification of novel “non-self” antigens, therefore bridging Innate to Adaptive Immune response to new antigens</td>
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<tr>
<td>Innate Immunity</td>
<td>Recognizes and kills general classes of “non-self” entities based on cell surface molecular patterns</td>
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<tr>
<td>Major Histocompatibility Complex (MHC)</td>
<td>Set of surface proteins that organizes antigens (either from inside the cell or digested by a DC), and presents them at the cell surface for scanning by Cytotoxic T Lymphocytes</td>
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<tr>
<td>Natural Killer (NK) Cells</td>
<td>Innate immunity effector cell; recognizes a limited class of “non-self” cells and kills them by inducing apoptosis</td>
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<tr>
<td>Naïve T Lymphocytes</td>
<td>Each one has a different T Cell Receptor (TCR); once there is a match between a TCR and a “non-self” antigen, the naïve T Lymphocyte activates into a Cytotoxic T Lymphocyte</td>
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<tr>
<td>T Cell</td>
<td>See “Cytotoxic T Lymphocyte”</td>
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<tr>
<td>T Cell Receptor (TCR)</td>
<td>Receptor on a CTL; Scans MHC-presented antigens for a match; if there is a match then it binds and triggers immune response</td>
</tr>
<tr>
<td>Tumor-Specific Antigen (TSA)</td>
<td>A tumor-expressed antigen that is identifiable as “non-self” by the immune system</td>
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Cancer Immunity: How the Immune System Can Attack Cancer

The immune system’s core function is to differentiate between “self” and “non-self”, and to target and destroy “non-self” entities within the body. These entities can include infectious viruses and bacteria, as well as cancer cells - if they can be recognized as “non-self”.

There are two types of immunity: Innate and Adaptive (historically called Acquired). Innate Immunity is the intrinsic ability of the immune system to mount a rapid response against general classes of targets based on patterns of molecules on the cell surface. The key innate immune cells are called Natural Killer (NK) Cells and Dendritic Cells (DCs), which recognize these patterns and force apoptosis (programmed cell death) upon their targets, then capture the released antigens (protein fragments that the immune system can recognize as either “self” or “non-self”). Innate immunity is fast, but it is fixed on the same limited set of targets; it cannot be triggered for newly-identified “non-self” antigens.

The immune system has a complementary type of immunity, Adaptive Immunity, which refers to the immune system’s ability to identify a previously unrecognized target antigen as “non-self” and mount a highly specific response. The key adaptive immune cells are called Cytotoxic T Lymphocytes (CTLs), or just “T Cells” for our purposes here.

Each immature T Cell has receptors with unique variations that enable it to recognize different potential antigens. No two immature T Cells recognize the same antigen. Adaptive Immunity is prompted when the Innate Immune system presents a novel antigen to an immature T Cell which recognizes and binds to it. This binding triggers activation and amplification of that single T Cell into a population of activated T Cells that roam throughout the body and kill any cell bearing the target antigen. This results in a slower but more targeted response than Innate Immunity, as well as one that “remembers” (if more cells with the target antigen show up in the future, the antigen-specific T Cells will rapidly expand and

Cancer Immunity identifies and targets tumor-specific antigens: Cancer cells arise after a series of mutations which may include some that affect the antigens presented on the cell surface. If the innate immune system then recognizes an individual cancer cell as “non-self”, that cancer cell is destroyed. If Dendritic Cells obtain and present a tumor-specific antigen to a naive T Cell that can recognize it, adaptive immunity is triggered, and a clonal population of Cytotoxic T Lymphocytes can find and destroy the rest of the tumor.
Both types of immunity can play a role in the immune system’s ability to detect and fight cancer. Cancer occurs when the body’s own cells undergo a series of mutations that result in uncontrollable growth and spreading throughout the body. These mutations can change the cancer cell enough that it becomes recognizable as “non-self,” enabling the immune system to detect and destroy tumor cells through Innate and / or Adaptive immune responses. This is the likely cause of at least some cases of reported spontaneous cancer remissions. Understandably, there has been significant interest in how to induce or boost this process via therapeutic interventions.

It is very likely that the immune system identifies and destroys many new cancers before they grow and spread. But any cancer that still exists and is being treated is one that has not yet been successfully handled by the immune system. Understanding how cancer immunity fails suggests ways we might assist it therapeutically. The immune system fails to mount a successful defense against cancer in one of two ways:

1. No immune response occurs: Cancer cells are not identifiable to the immune system as “non-self” because they do not express surface molecules or present antigens that the innate immune system can recognize, so no adaptive immunity or tumor-specific T Cells are generated.

2. Immune response occurs but is evaded: Cancer cells can be initially successfully targeted by the adaptive immune system, but subsequently develop resistance mechanisms. For example, they can establish barriers that block or depress the activity of T Cells or mutate so they no longer present antigens for T Cell recognition (effectively “hiding” from the immune system).

Cancer Immunotherapy: How Therapeutic Interventions Can Trigger and / or Boost Cancer Immunity

Cancer immunotherapy can be loosely defined as any therapeutic intervention which is intended to assist an immune response against the cancer. This includes the historical use of induced infection at tumor sites to attempt spontaneous regression, as well as more recently the checkpoint inhibitor drugs that act by blocking immune suppressor proteins such as CTLA4 and PD1/PDL1. These drugs have been approved in several tumor types including melanoma and lung, with a subset of individuals experiencing deep and durable responses.

As opposed to classic drug approaches that stimulate or block various molecular pathways, cell-based cancer immunotherapies are actual intact, living immune cells that are removed from the body and either grown to increase their amount and potency, or genetically-modified to boost (or artificially force) their ability to find and kill tumor cells.

The end goal for this approach is to generate and expand tumor-specific T Cells that find, invade, and kill tumors. Cell-based cancer immunotherapies have unique potential because they directly force (or bypass) existing cancer immune pathways to create more effective T Cells, vs working indirectly via molecular pathways as do classic drug-based interventions.
Cell-Based Cancer Immunotherapies: Commercial Risk, Curative Reward

Of the numerous cell types playing critical roles in cancer immunity, only two have been extensively targeted for cell-based therapies to-date, namely Cytotoxic T Lymphocytes (T Cells) and Dendritic Cells. This is because these cell types play uniquely direct roles in either classifying a cancer cell as “non-self” to trigger immune response (Dendritic Cells) or targeting and killing a “non-self”-classified cancer cell (T Cells).

In addition to which immune cell type to build from, the other key decision in cell-based immunotherapy design is which tumor antigen to target. There are several important considerations to boost the likelihood of clinical efficacy while minimizing risks of toxicity:

- **Efficacy**: Antigen must be expressed by the tumor cells as well as recognizable by immune cells to be targeted and killed. Depending on the design of the cell-based immunotherapy, this may mean it is expressed on the cell surface and/or via the classic MHC presentation.
- **Safety**: Antigen must be differentially expressed by tumor cells but not healthy cells, otherwise serious side effects including death can result as immune cells attack healthy tissue. In practice, this results in three classes of antigens:
  - **Tissue-Restricted** (expressed by tumor cells, only expressed in a small subset of healthy tissues): MAGE, NYESO-1, CEA
  - **Overexpressed** (expressed much more in tumor cells than in healthy tissues): HER2, WT1
  - **Viral** (expressed in viral-infected tumor cells only): HPV, EBV

All cell-based immunotherapy approaches work via the same general process of Adoptive Cell Transfer (ACT), with the intent of either boosting or forcing normal cancer immune biology towards a tumor-specific target antigen. ACT involves:

1. **Isolation**: The immune cell type of interest is extracted from the body and isolated, usually from the patient but sometimes from a donor.
2. **Modification**: Immune cells are genetically-engineered to specifically target their actions to tumor cells (note: there are some cell-based immunotherapies that simply...
CAR-T Cells

CAR-T Cells are made using living T Cells and are named for their genetically-modified Chimeric Antigen Receptor (CAR) that replaces the normal T Cell Receptor.

A CAR is different than the typical T Cell Receptor because it directly binds proteins expressed on the tumor cell surface, whereas the typical T Cell Receptor can only bind antigens that are presented by the MHC proteins. This is an important feature of CAR-T because MHC presentation failure is a common mechanism of tumor resistance to the immune system, which this design circumvents.

CAR-T Cells are made by removing healthy T Cells from either the blood of the patient or a donor, then genetically-modifying them to express a CAR that is specific to a selected tumor cell surface protein (for example, CD19 in leukemias), then infusing them back into the patient’s bloodstream where they circulate throughout the body to find and kill cells expressing the CAR-T target antigen. Because CAR-T Cells can be made from donors, they have the potential for a more “off the shelf” and scalable manufacturing approach than some of the other cell-based immunotherapies.

CAR-T cell design has evolved through several generations to-date. The first-generation CAR-T Cells expressed the CAR, as well as a co-stimulatory molecule designed to prompt immune activation.

This design has been successful in liquid tumors, culminating in two FDA approved products: Novartis’ tisagenlecleucel “KYMRIAH” (first approved in August 2017), and Kite’s axi-cabtagene ciloleucel “YESCARTA” (first approved in October 2018). Both CAR-Ts target CD19-expressing leukemia cells and include a co-stimulatory molecule to boost efficacy.

CAR-T efficacy has been more mixed in solid tumors, likely due to challenges in appropriate tumor cell surface protein targeting, tumor microenvironment-mediated suppression, and “T Cell exhaustion” (from repeated killing). Because it is difficult to find truly tumor-specific cell surface expressed proteins, there is also an inherent risk of immune attack on healthy tissues that also express whatever marker is targeted.

To address observed and anticipated autoimmune issues, as well as to counter tumor-mediated immune suppression, CAR-T design has expanded into subsequent generations, with third-generation CAR-T expressing multiple co-stimulatory molecules, and fourth-generation CAR-T expressing cytokines (immune boosters) directly. Some CAR-Ts are also being designed to require binding to two distinct tumor antigens to activate (reducing the risks of autoimmune side effects).

CAR-T is currently the most active category of cell-based therapy in clinical development. As of November 2018, about 250 clinical trials are ongoing in both liquid and solid tumors.
TCR

Like CAR-T, T-Cell Receptor (TCR) therapies also involve modified T Cells. The key design difference is that instead of adding in a Chimeric Antigen Receptor, they substitute in a known T Cell Receptor that recognizes a particular MHC-presented Tumor Specific Antigen (TSA).

Unlike CAR-T, which can theoretically be used somewhat off-the-shelf, TCR cells must be uniquely created for each patient using T Cells from the patient or an MHC-matched donor. Clinical studies have shown some efficacy with a limited set of TSAs first in melanoma, then other solid tumors including synovial sarcoma, as well as esophageal and colorectal cancers.

TCR therapies have a potentially broader applicability than CAR-T because they can be designed to recognize any protein expressed by a tumor cell, not just those that are naturally surface-expressed (as long as it can be presented by the MHC proteins). But while some efficacy has been observed in clinical trials, there have also been severe toxicities and deaths due to immune recognition of healthy tissues. These serious adverse events, as well as the more robust efficacy seen in CAR-T cells, have shifted clinical development focus away from TCR. The requirement for more personalized manufacturing also makes these less appealing from a cost and timing standpoint.

TILs

Tumor-Infiltrating Lymphocytes (TILs), a purified population of naturally-occurring T Cells, were the first cell-based therapy successfully attempted. This approach is based on the rationale that simply expanding the number of existing tumor-specific T Cells could be sufficient to overcome resistance to cancer immunity.

Immune cells are extracted from the inside the tumor, then selected against either known Tumor Specific Antigens (TSA) or against cell lines generated from the tumor itself. The tumor-specific T Cells purified via this screening are then expanded via cell culture and reinfused into the patient along with the immune booster IL-12. TILs infusion can be effective for
some patients with melanomas, as well as a few other tumor types including breast. Several later stage (Ph2) clinical trials are ongoing. Because TILs are obtained from the patient, they are typically very specific and targeted to the tumor, so the risk of adverse events from inappropriate immune responses is hypothetically lower. However, not all tumor types or individual patients have a suitable population of TILs to draw from, which has limited the scope of this therapy.

DC Vaccines

Unlike TILs, TCR, and CAR-T Cells, DC vaccines do not involve direct manipulation of T Cells. Instead, the focus is modulating the adaptive immunity trigger of Dendritic Cell-mediated antigen presentation. To create a DC Vaccine, Dendritic Cells are extracted and either “primed” to Tumor-Specific Antigens (TSA) by exposing them to tumor cell lysate, or genetically-engineered to directly express a chosen TSA. Then, once they are added back into the body, they present those TSAs to naïve T Lymphocytes, triggering the adaptive immune response. This is similar to how vaccines work, hence the name.

One DC therapy has been FDA-approved (Dendreon’s sipuleucel-T “PROVENGE” in prostate cancer), but like other cell-based immunotherapy approaches, efficacy has been mixed in other solid tumors. There has also been controversy about the high price given the relatively modest efficacy ($100,000 for a 4-month increase in median overall survival), which also suggests that DC vaccines may not share the curative potential of other cell-based immunotherapies. Several clinical trials are ongoing for other DC Vaccines, including some in glioblastoma, that are reporting promising early signs of durable efficacy.

**Commercial Opportunity and Challenges**

As a class, cell-based immunotherapies have already demonstrated significant potential as well as risks and challenges pertaining to both drug development and commercial success. The key factors are outlined below.

<table>
<thead>
<tr>
<th>CAR-T: T Cell that targets tumor cell surface proteins</th>
<th>TCR: T Cell that targets tumor cell MHC-presented antigens</th>
<th>TILs: Purified population of tumor-targeting T Cells</th>
<th>DC Vaccine: Dendritic Cell that activates T Cells to tumor</th>
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<tr>
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<td>Broad (vs All or None) Efficacy</td>
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<td><strong>Liquid Tumor Efficacy</strong></td>
<td><strong>T Cell that targets tumor cell MHC-presented antigens</strong></td>
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<td><strong>Solid Tumor Efficacy</strong></td>
<td><strong>T Cell that targets tumor cell MHC-presented antigens</strong></td>
<td><strong>TILs: Purified population of tumor-targeting T Cells</strong></td>
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<tr>
<td><strong>Time to Manufacture</strong></td>
<td><strong>T Cell that targets tumor cell MHC-presented antigens</strong></td>
<td><strong>TILs: Purified population of tumor-targeting T Cells</strong></td>
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<tr>
<td><strong>Lower Cost / Price</strong></td>
<td><strong>T Cell that targets tumor cell MHC-presented antigens</strong></td>
<td><strong>TILs: Purified population of tumor-targeting T Cells</strong></td>
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<td><strong>Safety / Tolerability</strong></td>
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**DC Vaccine Design & Rationale**

- **Dendritic Cells (DC)** are either exposed to tumor lysate, or genetically engineered to express a **Tumor-Specific Antigen (TSA)**; They then present the TSA to various TCRs; once a matching **T Cell Receptor (TCR)** is found, the associated **Cytotoxic T Lymphocytes (CTL)** is activated to find and induce apoptosis in TSA-presenting tumor cells, **triggering adaptive immunity to the tumor cells**

- Clinical Efficacy: Some efficacy seen in solid tumors (prostate, GBM)
- Development Status: One approval (Provenge in prostate), and several ongoing clinical trials (GBM)
- Key Biological Challenges: TSA selection; Can only work for MHC-presented tumor antigens; DC presentation to CTLs may not be sufficient to trigger successful adaptive immunity given solid tumor challenges (microenvironment)
Curative Potential

In both liquid and solid tumors, cell-based immunotherapies have delivered such durable complete responses that they are essentially “cures.” For those tumors that do not respond—or that eventually recur via various resistance mechanisms—theoretically, cell-based immunotherapies could be personalized to adapt, shifting metastatic disease into something chronic that can be managed rather than a rapidly fatal condition.

This differentiates immunotherapies from other systemic (chemo, radiation) and targeted therapies which offer a temporary disease control but ultimately cannot prevent progression in metastatic or otherwise advanced disease. If cell-based immunotherapies can be designed and developed that have either broader or more personalized efficacy, particularly in solid tumors, it will dramatically shift the standard of care, pushing current therapies back to later or salvage lines.

All-or-None / Limited Breadth of Efficacy

Like the broader class of immunotherapies, these therapies tend to work dramatically well in a (sometimes very small) subset of recipients, while the rest receive next to no clinical benefit. This response profile is challenging for clinical development because trials may fail if the responding subset is too small.

Because there are no known predictive markers, in clinical practice there is also a potential opportunity cost if an individual chooses an immunotherapy over something like a targeted therapy which won’t be curative but offers a more “guaranteed” clinical benefit of several months of disease control (for example). This is a commercial challenge because the high cost of therapy may be less palatable with no guarantee of any clinical benefit. In addition to development of cell-based immunotherapies with broader applicability, better prediction of responders will be critical in overcoming both development and commercialization challenges.

Liquid Tumor Efficacy but Solid Tumor Barriers

While leukemias and lymphomas are by their nature very accessible to cell-based immunotherapies (which circulate via the blood), solid tumors have been more challenging to address. This is likely due to several issues. One key challenge is that the surrounding tissue and the tumor itself, referred to as the “tumor microenvironment,” frequently develops both physical and chemical signaling barriers to cancer immunity. This means that even if tumor-specific T Cells are in the body, they may not be able to enter the tumor. Or, if they do enter, they may be suppressed and unable to kill efficiently. The checkpoint-inhibitor immunotherapies make an appealing combination partner for cell-based immunotherapies, as the former address at least one signaling mechanism of tumor-mediated immune suppression.

Long Time to Manufacture, Long Time to Work

Producing patient-specific cell-based immunotherapies takes several weeks at a minimum. In addition, immunotherapies in general take longer to generate a response than do classical therapies because they require inducing and expanding the adaptive immune response (vs just killing cancer cells directly like the classic approaches).

This is a challenge in clinical practice when a patient has a high tumor burden or rapidly-growing tumor. They may not be able to wait weeks or months for a cell-based immunotherapy to be effective. While the biological delay in efficacy may be inherent, it is possible to avoid manufacturing delays for cell-based immunotherapies that are generated in bulk from a donor, i.e., not patient-specific. In clinical practice, protocols could be designed that aggressively treat tumors with either a systemic (chemotherapy and/or radiation) or targeted therapy to “buy some time” while the personalized cell-based immunotherapies are being generated.

High Manufacturing Cost and High Price

For the “personalized” cell-based immunotherapies that must be generated from the patient’s own immune cells, the cost of manufacture can be quite high, contributing to a price of ~$100,000-$500,000 for the currently approved cell-based immunotherapies. Insurance companies will demand robust evidence of significant improvement over standard of care to cover this high price, and out of pocket payment may not be possible for most patients.

It is possible that “pay for performance” models where the price is adjusted based on the individual outcome could make the high end of the price range more acceptable. This would also strongly incentivize manufacturers to design more adaptive protocols that maximize the benefit for each individual patient (adjusting doses, combination and sequencing regimens with other therapies, etc.).

Potential for Severe-to-Lethal Side Effects

The incredibly specific targeting and efficacy of cell-based immunotherapies can be a double-edged sword. In the subset of patients where these therapies are active, they can trigger a positive feedback loop of general immune activation that ultimately impacts the rest of the body, resulting...
in what is known as Cytokine Release Syndrome, or a “cytokine storm.” This overactive inflammatory syndrome occurs to at least some degree in nearly all recipients and when severe, can damage or destroy key organs, and even be fatal.

Recently, the immunosuppressive drug tocilizumab has been repurposed to manage this side effect, with reasonable success. Another risk of these therapies is when the tumor-targeted T Cells recognize and attack healthy tissues that express similar antigens. For example, in one notable case a MAGE-A3 TCR therapy ended up targeting a similar brain-expressed protein and killed 2 out of 9 patients in an early trial.

One more theoretical risk is that cell-based immunotherapies developed from donor immune cells could trigger Graft vs Host Disease (this has not yet been observed in clinic, however). To address these risks, some cell-based immunotherapies are being designed with “kill switches” that can be used to self-destruct the cells upon recognition of a serious adverse event.

Outlook (Intra-Class Comparison)

While CAR-T therapies are currently the most intense area of focus, they have significant limitations around solid tumor efficacy, toxicity, and manufacturing costs and time. The other types of cell-based immunotherapies are unlikely to displace CAR-T in leukemias, but if they can successfully address these issues, they may find their own niches in other tumor types.

Development and Commercial Outlook

Cell-based immunotherapies must find their position within the broader class of immunotherapies

The curative potential of cell-based immunotherapies is confirmed in at least one other class of immunotherapies: the checkpoint inhibitors (CPIs). CPIs also share the downside of the “all or none” response, and no truly predictive marker is yet identified. It remains to be seen whether cell-based immunotherapies can achieve broader efficacy in more tumor types. In parallel, other classes of immunotherapies such as personalized cancer vaccines and bispecific antibodies are being heavily invested in and showing strong clinical promise as well. Some of these therapies may be combination partners for cell-based therapies, while others are more likely to be competitors for their same niche of “immune response trigger” immunotherapies.

Cancer Immunotherapy Inter-Class Comparison: Cell-based Immunotherapies have a similar therapeutic goal to Vaccines/Viruses and the T Cell Bispecific Antibodies, which can be considered direct competitors. The other classes of cancer immunotherapies are not competitors to cell-based immunotherapies, but in fact may be useful or even required combination partners to boost efficacy.
**Combinatorial regimens may be required (challenging pricing and reimbursement)**

It seems likely that some tumor types or individual patients may require immunotherapy combinations to maximize the cancer immune response. This could involve inter-class (e.g., CAR+T plus anti-PD1 checkpoint inhibitor) or intra-class (e.g., DC Vaccine + CAR-T). These combinations are already being explored in the clinic. One potential future landscape involves a “toolbox” of various cancer immunotherapies that can be mixed and matched for each individual patient and adapted over time to address resistance. This would result in both immense clinical complexity (how do we capture this in guidelines) as well as pricing challenges (additive pricing would result in astronomically high prices).

Over the next few years, numerous clinical datasets will be reading out, providing important insights into which individual therapies or immunotherapy classes could have the commercial potential to either displace or partner with the currently dominant checkpoint inhibitors and CAR-T therapies.

**For some tumors, personalized targeting could be required (bumping time and cost of manufacture).**

Right now, cell-based immunotherapies are mostly focused on a few known TSAs that are indication-specific, i.e., specific cell surface proteins or tumor antigens that are known to be broadly expressed in specific tumor types. It may be that for tumor types that are more heterogeneous, a personalized approach will be required, e.g., determining potential TSAs from each tumor using bioinformatic approaches, and generating targeted T Cells accordingly. While this has potential to dramatically broaden efficacy, the manufacturing cost and complexity would be much higher. It remains to be seen whether the market can bear a higher price, even with curative efficacy.

**Outlook**

Cell-based immunotherapies are well-poised from a scientific standpoint to effectively trigger cancer immunity and have already demonstrated curative impact in some settings. However, the approved / late stage therapies are only active in specific indications or in subsets of patients within an indication (with no known predictive marker). It may be that some individual tumors are simply intractable to cell-based immunotherapies, or it may be that they require a more personalized antigen selection and / or a combination strategy to boost immunity or address resistance mechanisms.

Numerous therapy and regimen designs to address these issues are under development. As more are tested in trials and deliver clinical data, we expect to see clarity around the true potential of cell-based immunotherapies within the next few years.

Aside from efficacy, cell-based immunotherapies face competitive threat from other immune triggering cancer immunotherapies (viruses / vaccines, bispecific antibodies). Many of these alternatives are significantly easier and cheaper to manufacture. Therefore, equivalent or greater clinical efficacy from a more cost-effective therapy remains a significant development risk for cell-based immunotherapies. That said, some types of cell-based immunotherapies (namely CAR-T) are exploring “off the shelf” / donor-based manufacturing strategies that could make them more competitive in terms of pricing.

To make a long story short: There is no crystal ball that will tell us exactly how cell-based therapies will evolve—or how successful they’ll be—in the coming years. They do, however, show tremendous potential, and we are confident that some cell therapies will have a disruptive effect on the market in the coming years, becoming a key part of the oncologist’s armamentarium.
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This paper authored by the Blue Matter team.