

MSCI Thematic Insight

Subject Area: **Immuno-Oncology**

# Harnessing Immunity in the Fight Against Cancer



This is an **interactive brochure**





# Contents



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# Introduction

Cancer is a major and growing cause of disease and death. A 2022 study estimated that, globally, in 2019, there were almost 24 million new cancer cases, 10 million cancer deaths and 250 million disability life-adjusted years (DALYs) taken from cancer sufferers.<sup>1</sup> The incidence of new cancer cases has seen a compounding annual growth of approximately 2% since 2010. The US National Cancer Institute estimated that there will be more than 1.9 million new cases and greater than 600,000 cancer deaths in 2022 in the US alone.<sup>2</sup> In the US, cancer is consistently ranked as the second leading cause of death behind cardio-vascular disease.<sup>3</sup>

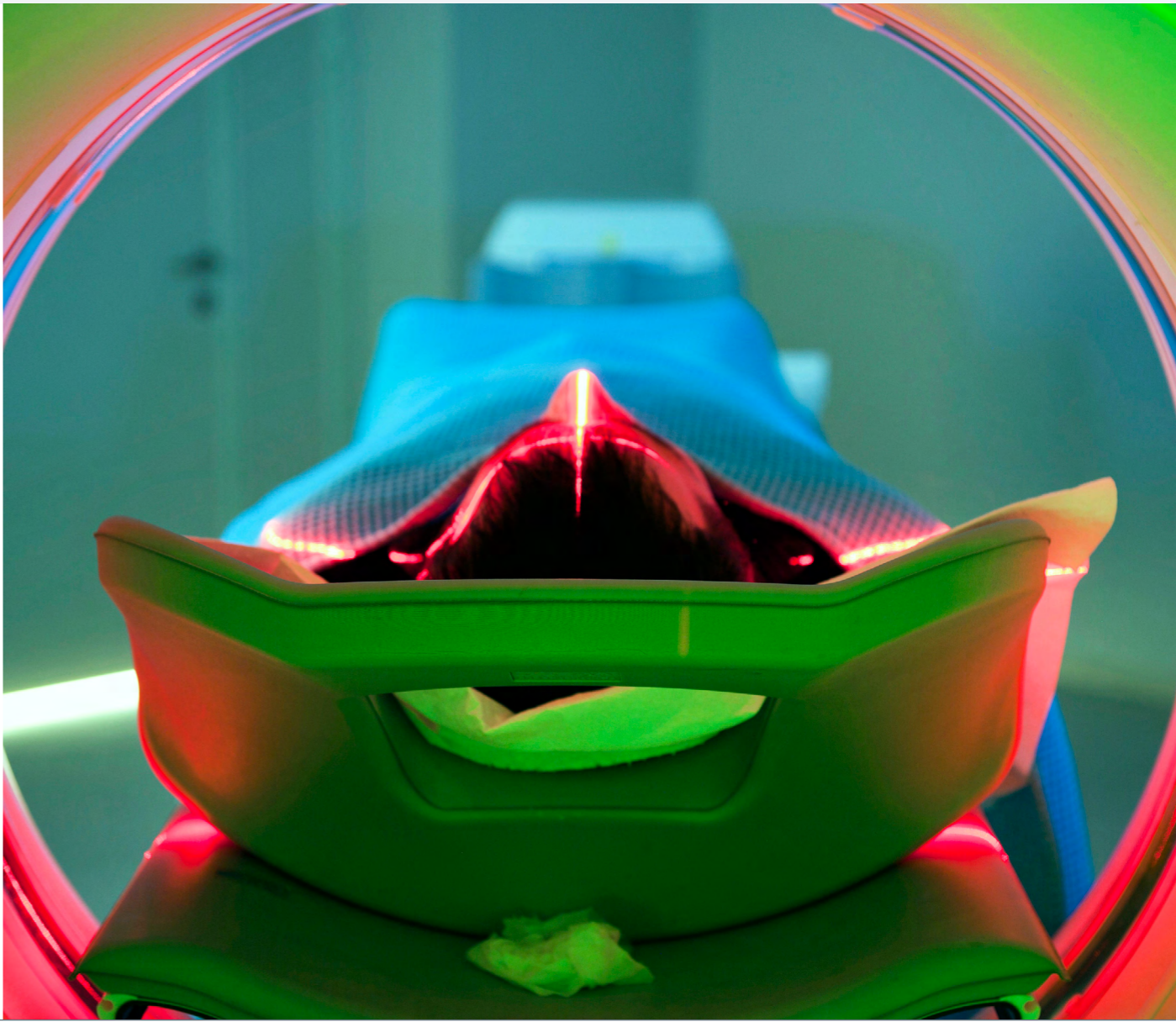
Cancer comes in many forms but in all of them, there is a characteristic rapid growth of abnormal cells that spread to healthy organs and tissues, disrupting their function. Surgery, radiotherapy, chemotherapy, bone marrow transplants and hormone protocols are some of the familiar toolkit available for oncologists to treat their patients. However, advanced cancers and solid tumors are still highly challenging and against a backdrop of growing cancer incidence, novel therapies are greatly needed.

Immuno-oncology (IO; sometimes called cancer immunotherapy) is one of the fastest growing areas of scientific investigation and product development. Its techniques are now a major presence in most major types of cancer, even though the first drug approval only occurred in 2011<sup>4</sup>. There are currently 23 marketed IO products in the 7 major markets<sup>5</sup> with prophylactic and therapeutic cancer vaccines leading the category with 9 products, followed by “checkpoint modulators” (8) and cell therapies (4).

As of February 2023, there are almost three thousand active or planned, industry sponsored, randomized clinical trials investigating immuno-oncology therapies across the 7MM spanning almost 18 thousand investigators, over seven hundred industry sponsors and studying over a thousand investigational drugs in clinical development.

Checkpoint modulation has emerged as the critical IO sub-sector by size. These are treatments that seek to stop or moderate the suppression of different pathways of the body's immune system by cancers (we will describe this key category in more detail later). Without these blocks, the natural action of the body may be able to reverse the cancer development. Checkpoint modulators (or inhibitors) have been some of the first non-chemotherapy drugs for indications that had been without major progress for many years.<sup>6</sup> Their introduction has resulted in a paradigm shift in modern oncology, one was recognized by the award of the Nobel Prize in Physiology or Medicine in 2018 to Tasuku Honjo and James Allison “for their discovery of cancer therapy by inhibition of negative immune regulation”.<sup>7</sup> Key patent expiries for these drugs will occur in the second half of the 2020s, likely leading to a shift from branded agents into biosimilars and novel mechanisms (to extend sales past the patent cliff).

Nevertheless, the high cost of these therapies<sup>8</sup> and the need for highly personalized treatment using biomarkers (often in a limited number of treatment centers in a given country) currently risk limiting the scale of future use. Better and cheaper biomarkers are a key element of a change to this landscape.



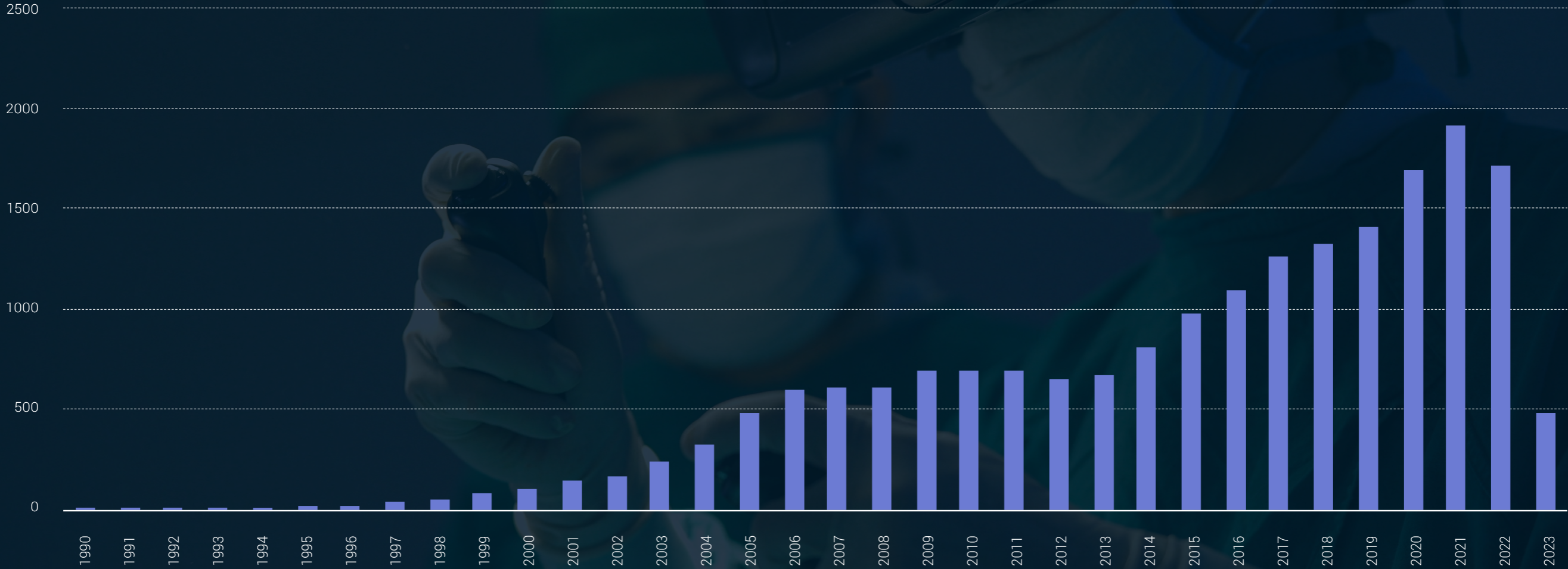
1 J. M. Kocarnik et al, (2022) “Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019”. JAMA Oncology, 8(3), p.420–444.  
2 K. D. Miller et al (2022), “Cancer treatment and survivorship statistics, 2022”. CA: A Cancer Journal for Clinicians, issue 0 pages 1-28.  
3 <https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm>  
4 Yervoy (ipilimumab)  
5 US, Japan, Germany, UK, France, Spain, Italy

6 E.g. melanoma, lung cancer, Hodgkin's lymphoma  
7 <https://www.nobelprize.org/prizes/medicine/2018/summary/>  
8 The high cost has currently been justified by the risk and expense of development programs by drug companies – even at these levels (up to multiples of \$100,000) the avoidance of more toxic conventional treatments (e.g. chemotherapy/radiation) and the gain in quality adjusted life years (QALY) has been sufficient to secure reimbursement in publicly funded health systems.



### Exhibit 1: Commercial IO Trial Starts

Source: Evaluate Pharma (accessed 2/28/2023)





# What is Immuno-oncology?

Immuno-oncology is the therapeutic strategy of harnessing a patient's immune system to recognize and attack cancer cells that employs pharmaceutical products or biologics.<sup>9</sup> This may be achieved with the stimulation of a patient's own immune system, or with the administration of modified products with oncolytic<sup>10</sup> properties.

How does IO work within the immune system? An essential characteristic of the immune system is its ability to differentiate "threats", including tumor cells, from normal "self" cells. Although technically part of "self", tumor cells can be tagged as "foreign" threats because they selectively express cancer markers ("antigens"<sup>11</sup>) whose existence can be used to activate and direct immune responses. IO uses therapies that seek in this way to exploit the body's own immune processes to attack cancer. Such therapeutics are leading to a transformational shift in cancer treatment paradigms: therapies tailored to leverage the unique immune biology within each cancer patient while minimizing toxicities. Given comparable efficacy and the fact that IO agents avoid chemotherapy's trademark signs and symptoms (e.g. loss of hair and nails, nausea, and hearing loss), IO is now part of the "standard of care" paradigm<sup>12</sup> for a multitude of cancers (e.g. melanoma, lung cancer, kidney cancer, colon cancer) and the trend (as usual in oncology) is towards use across more cancer types and earlier in therapy.<sup>13</sup> Precision medicine approaches based on better understanding of disease biology and individual differences may reveal better-defined patient segments in which the risk/benefit profile could be even more favorable.



9 A "biologic" is a biological substance (such as proteins, including antibodies) created synthetically or naturally from a living organism or their products, that may be used as a diagnostic or in the prevention or treatment of a disease.  
10 Oncolytic refers to the destruction of a tumour or cancerous cells.

11 A toxin or foreign substances which can induce an immune response in the body  
12 E.g. recommended in several society/NCCN guidelines  
13 E.g. [Real-world trends in first-line checkpoint inhibitor use \(CPI\) in advanced urothelial cell carcinoma \(aUC\)](#), *J. Journal of Clinical Oncology* ([ascopubs.org](#)).

# What are the different types of Immuno-oncology treatments?

Some key examples of immune-oncology therapies include:

- cancer vaccines: to teach the immune system how to recognize tumors
- immune stimulators: for example, IL-2/Proleukin, which is a protein that directly stimulates immune cells (as opposed to a CPI which disrupts native inhibitory signaling, see below)
- checkpoint inhibitors/CPI: for example, those inhibit the PD-1 molecules expressed on the surface of T-cells and hence reduce the cancer's immunosuppressive signals,
- bispecific antibodies: for example, T cell "engagers" that target immune cells to the tumor by linking between different antigens on the surface of each
- immune cell therapies: for example, infusions of CAR T cells ("Chimeric Antigen Receptor" T-cells i.e. genetically engineered T-cell receptors) and NKs (enhanced and modified Natural Killer cells) to directly attack the tumor,

alongside other approaches that seek to make the tumor more recognizable by the immune system or the immune system better at recognizing the tumor.

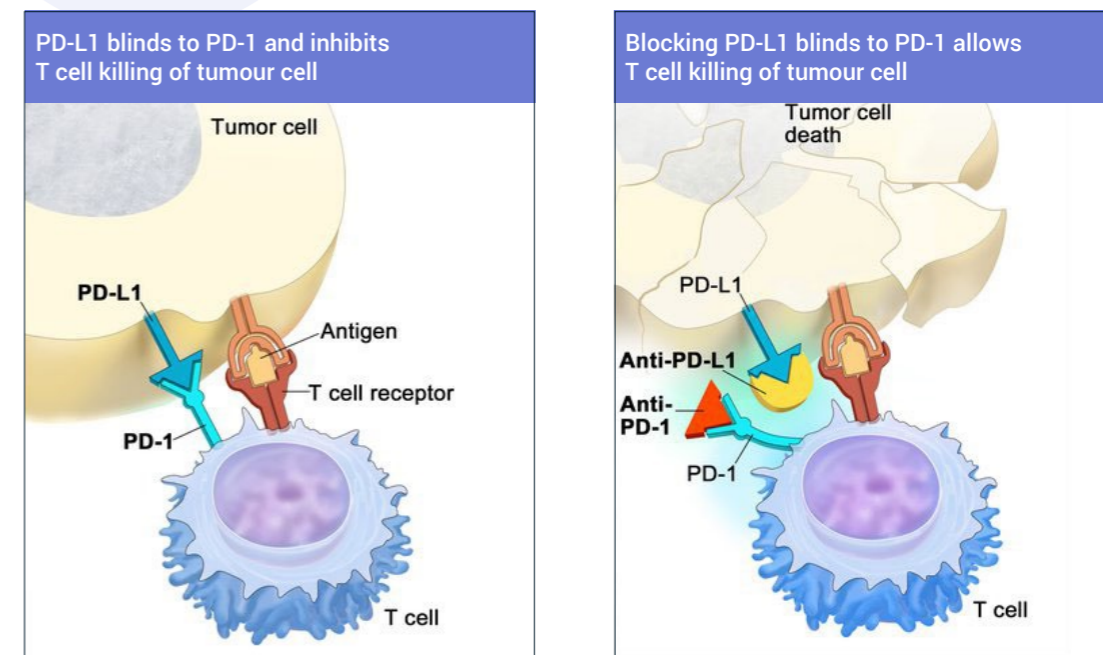
To date, approved IO drugs have generally been immune checkpoint inhibitors ("CPIs") or CAR T cell therapies. So, let's dig a little deeper into how they each work.

"Checkpoint inhibitors" have been a mainstay in cancer immunotherapy since their initial approvals in the beginning of last decade. Today, they are used against a broad swath of malignancies, ranging from lung and kidney cancer to melanoma and lymphoma. Several immune system processes are characterized by the presence of signaling "checkpoints" that serve to contain and control potentially harmful aberrant immune response activity. For example, in the process of T-cell activation, T cells expressing the protein PD-1<sup>14</sup> can be suppressed in the presence of the ligand protein PD-L1 (from a tumor). Antibodies that, in turn, inhibit PD-1 or PD-L1 are called checkpoint inhibitors. These have been shown to remove the immunosuppression and thus allow T cells to attack the tumor.

However, currently these therapies remain high risk with the patient vulnerable to suffering from immune-related adverse events such as dermatologic, gastrointestinal, endocrine, or hepatic autoimmune reactions.

## Exhibit 2: Mechanism of action of PD-1 and PD-L1 checkpoint inhibitors

Source: [Mechanism of action of PD-1 and PD-L1 inhibitors. Tumor cells develop... | Download Scientific Diagram \(researchgate.net\)](#)



14 PD-1 is a protein on the surface of T and B cells that can down-regulate the immune system by suppressing T cell inflammatory activity. This helps prevent autoimmune diseases.



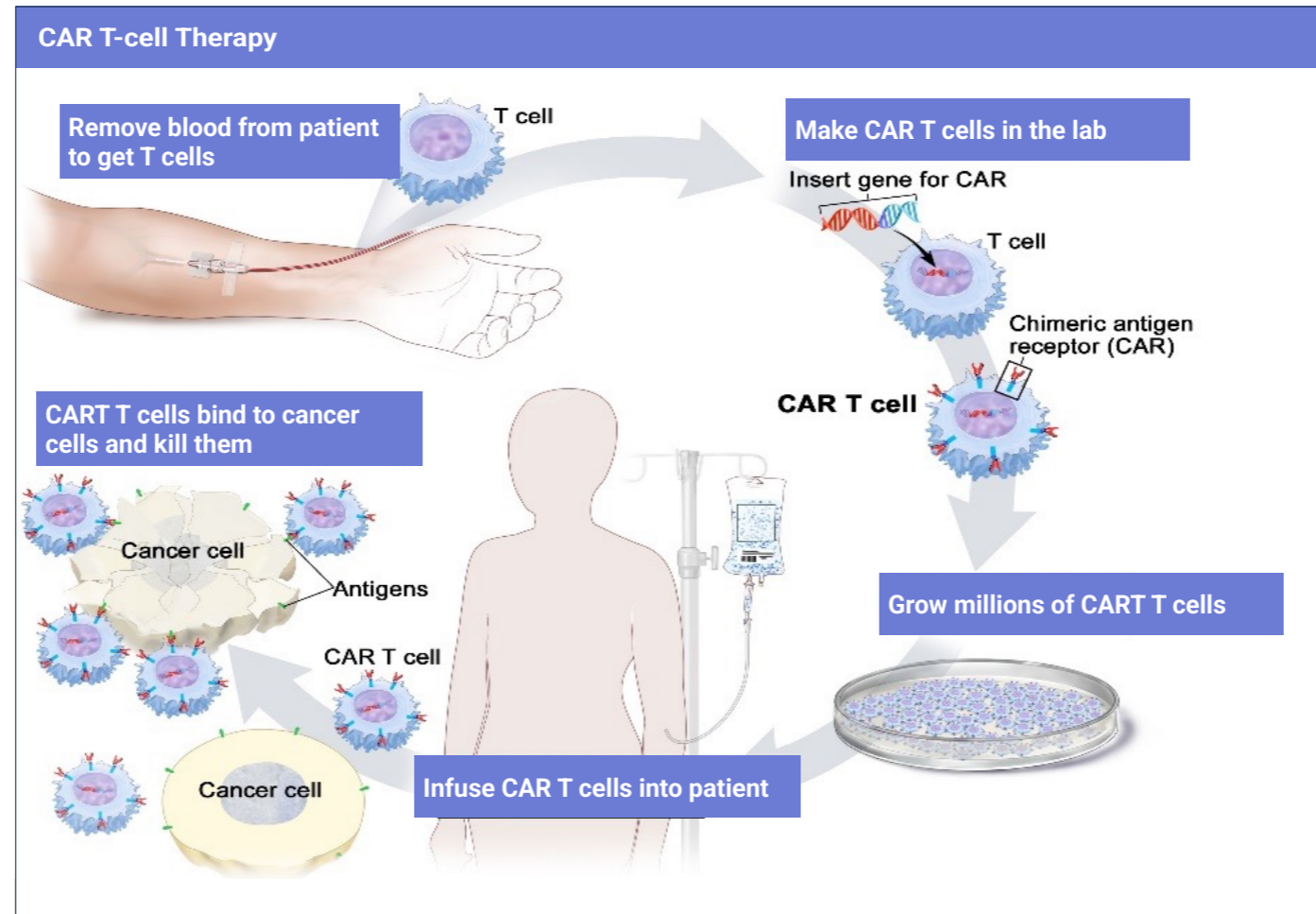
Chimeric Antigen Receptor (CAR) T cells are immune cells that have been reprogrammed to recognize and attack a cancer antigen. These therapies can be manufactured “just-in-time” from a sample of the patients’ own blood cells (“autologous CAR T”) or “off the shelf” from donor immune cells (“allogeneic CAR T”). After the source cells have been collected, their genome is edited so as, at a minimum, to insert the genetic sequence encoding for the Chimeric Antigen Receptor recognizing the tumor. Other changes may also be introduced to bias the cells to be more strongly activated, longer lasting or even inducible/switchable for increased specificity and patient safety.

Although CAR T therapies have given hope to many patients and their families, their adoption has been limited by the complexity around manufacturing currently approved therapies, as well as by outstanding questions regarding the safety and durability of such treatments. Moreover, to-date, approved CAR T therapies have been limited to blood cancers like multiple myeloma.

However, there is some cause for optimism as the number of clinical trials testing IO therapies grew >10X in the 90s, tripled in the 200s and doubled again in the 2010s.<sup>15</sup> The acceleration of the pace of IO clinical trial starts has been particularly notable in the 5 years. No year before 2016 saw more than 1000 IO trial starts, whereas every year since then has had more than that. From 2014-2021, annual clinical trial starts have increased at a 18.5% CAGR.<sup>16</sup>

**Exhibit 3:  
 Autologous CAR-T cell Therapy Process**

Source: [nci-vol-11776-150.jpg \(970x776\)](https://www.cancer.gov/nci-vol-11776-150.jpg). (cancer.gov)



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# Where next for immuno-oncology?

The limitations sketched above show that, despite groundbreaking scientific advances, much work remains to be done to achieve the potential of IO therapies for patients. Efforts are currently underway to find novel treatable targets to combine with approved CPIs. Therapeutic goals include:

- “raising the tail” of the survival curves, that is, extending the duration of immune responses (e.g. by addressing the challenge of T-cell exhaustion;
- increasing response rates - by further stimulation of the immune system, by making “cold” tumors “hot” (visible to the host immune system), or by tighter selection of patient populations through predictive biomarkers;
- improving on therapy safety by targeting anti-cancer immunity more selectively among the intracellular immune checkpoints and other T-cell specific signaling pathways;
- improving tolerability and reducing the burden of therapy via new formulations and routes of administration.

On the cell therapy front, the lead priorities have been improving safety and extending the in-scope indications including solid tumors e.g.

- improving turnaround in cell therapy manufacture by increasing usability of “off the shelf” allogeneic products,
- introducing exogenous “switches” to improve patient safety as the infused cells could be “turned off” if an adverse reaction arises

- developing more targeted, efficacious and safer therapies with longer duration by selecting only specific subtypes of T cells to expand, or by making the “activation” effect of the infused cells more precise
- widening therapy options beyond CAR T cells with cellular immunotherapies such as TIL (tumor infiltrating lymphocytes) and NK (natural killer) cells.

Another promising approach in IO relies on “immunizing” the body against the tumor through cancer vaccines. Using special viruses, mRNA or other gene therapy technologies, these vaccines introduce one or more tumor-associated antigen. This primes, activates and guides an immune response against the cancer. These approaches can also help enhance other IO therapies, since they can turn immunologically cold tumors “hot” (i.e. immunologically active). Other current efforts seek to explore combinations of these strategies.

The distinct and independent mechanisms of action of these different IO therapies means that IO has tended to be what is termed an “additive” market. New drugs can potentially command premium prices without seeing the full displacement of the prevailing “standard of care” treatment paradigm (at least initially). The area remains highly active: a third of all the IO trials ever run are still ongoing as of mid-2022 and about 20% are currently open to enrollment.<sup>17</sup> Companies in the space have been quick to recognize the importance of novel IO discoveries with several recent takeovers in biopharma triggered by breakthrough IO data.<sup>18</sup>



<sup>17</sup> Evaluate Pharma

<sup>18</sup> E.g. the recent approval this year of the first dual combination checkpoint inhibitor targeting PD-L1 and LAG-3, Opdualag



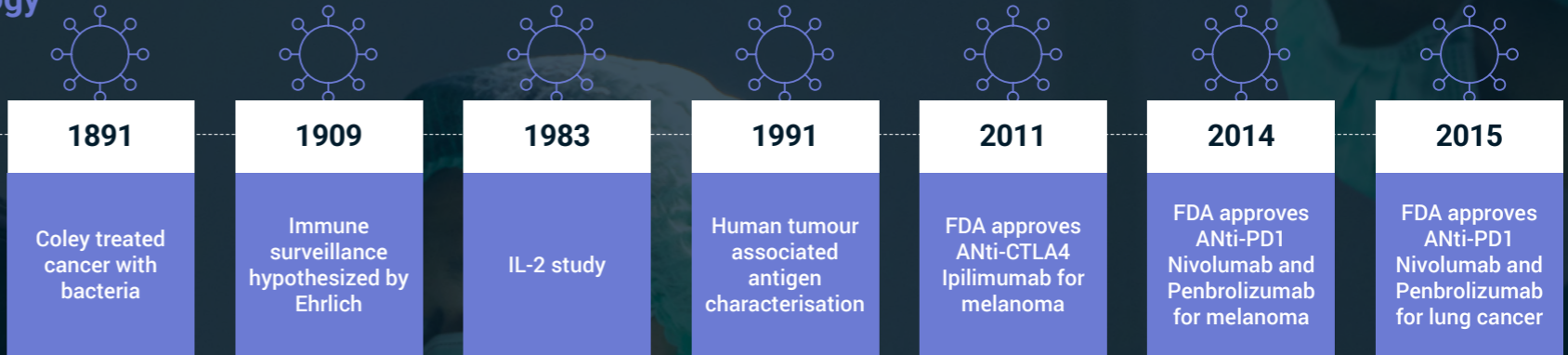
# Conclusion

Despite many recent advances that have revolutionized cancer care for patients, oncology remains one of the areas with the largest unmet need in medicine. The field of immuno-oncology is now consolidating its presence in the frontline of treatments for most major types of cancer. Challenges remain related to treatment complexity and control, cost and patient safety but all of these are seeing rapid progress and high levels of research activity and trials.

## Exhibit 4: Mechanism of action of PD-1 and PD-L1 checkpoint inhibitors

Source; [The Rise of Immunotherapies - Strategies to Accelerate Their Advance Into Clinical Trials - Drug Discovery World \(DDW\) \(ddw-online.com\)](#)

### Key events in the Immuno-oncology timeline



MSCI would like to thank **Royalty Pharma** for useful discussions and insightful analysis of this megatrend which have greatly facilitated the preparation of this document.

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