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## REVIEW ON IMMUNOONCOLOGY DRUGS FOR THE TREATMENT OF CANCER

Mekala Bhaskar\*, M. Rajesh, Budagala. Gayathri, Ch Babu Rao

Priyadarshini Institute of Pharmaceutical Education and Research, 5th mile, pulladigunta, Guntur-522017, Andhra Pradesh, India

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### Abstract

Over the past decade, immunotherapy has revolutionized cancer treatment by leveraging the body's immune system to target and eliminate cancer cells, leading to significant advancements and improved patient outcomes across various malignancies. Checkpoint Inhibitors: Drugs targeting immune checkpoints, such as CTLA-4 and PD-1, have been pivotal in cancer therapy. For instance, a long-term follow-up of the Check Mate 067 trial demonstrated that patients with advanced melanoma treated with a combination of nivolumab and ipilimumab had a median overall survival of approximately six years, marking a substantial improvement in survival rates. CAR-T Cell Therapy: Chimeric Antigen Receptor (CAR) T-cell therapy has emerged as a promising treatment, particularly for hematologic malignancies. Recent developments aim to enhance these therapies by improving antigen selection and delivery methods, thereby reducing tumor escape rates and increasing efficacy. Microbiome Modulation: Innovative approaches combining immunotherapy with microbiome modulation have shown potential. For example, a clinical trial reported that a patient with stage III small bowel cancer achieved remission after receiving a combination of immunotherapy and fecal microbiota transplantation from a "superdonor." Melanoma: The introduction of immunotherapy has significantly improved outcomes for melanoma patients. Notably, the five-year survival rate for advanced melanoma has risen from less than 10% to more than 50% since the advent of these therapies..

**Keywords:** biomarkers; cancer; immune checkpoint inhibitors; immune-oncology; oncology.

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### \*Corresponding Author

MEKALA.BHASKAR

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### Introduction

The field of immuno-oncology has transformed the care of cancer patients. William B. Coley, widely regarded as the father of immunotherapy, first tried to use the power of the immune system to treat cancer at the end of the 19th century [1]. In addition, Tasuko Honjo, a co-nobel prize winner, showed that a basic mechanism activated induced cell death in lymphocytes, mediated by program cell death [2] Cancer immunotherapy (also called immunooncology) is a type of cancer treatment that uses body's own immune system to prevent, control, and eliminate cancer. improving on the immune system's natural ability to fight the disease. The growth rate of cancer is steadily increasing over the past years. The number of variation rate is now more than 200 which is growing further to more. Treatment has undergone a slow evolution from its start in the 1800s, with the sequential development of four main recognised modes of treatment. The first was

surgery, which was performed after the discovery of general anesthesia in the late 1800s.

Immunotherapy has a central role in the treatment of cancer with the approval of several immuno-oncology (IO) agents in different indications. Trials supporting the approval of these drugs has demonstrated that acting on the immune system can be a successful therapeutic approach [3]. In this article, we describe the current status, limitations and options for improvement for the clinical development of immunotherapy in cancer including: (i) the limitations of preclinical models to predict biological activity in humans (ii) special pharmacologic considerations for the development of these agents (iii) the selection of indication, line of treatment and backbone partner, and (iv) the threshold of activity that has to be reached for the compound to be considered as clinically meaningful [4].

Cancer incidence rates have steadily increased over the past 20 years, while mortality rates have shown a considerable decline<sup>1</sup>. Although significant variation in survival rates is still observed across cancer types (i.e. there are more 200 distinct diseases recognised), for most types, survival is improving owing to earlier diagnosis and improved treatments[5] The second development was

radiotherapy, established at the end of the 19th century, which utilises X-rays and/or G-rays to damage the DNA within tumour cells, thus blocking essential biochemical processes and leading to cell death<sup>4</sup>. The third development, chemotherapy, was discovered in the 1940s, during World War II, when it was observed that individuals exposed to mustard gas suffered myelosuppression [6]. The fourth development was targeted cancer therapies (also known as precision therapies). This was established with the discovery of imatinib (Glivec; Novartis) in the late 1990s—a small molecule kinase inhibitor targeted to the mutant BCR-ABL protein present in the tumour cells of patients with chronic myeloid leukaemia (CML), but not in their healthy cells [7].

### History of immune-oncology

It has long been known, but is now increasingly appreciated, that tumour cells can be recognised and disabled by the immune system. Some tumours show evidence of spontaneous regression early in their development, suggesting that the immune system may be capable of recognising and eliminating early-stage tumour cells. William Coley was the first to investigate the potential for IO, and successfully treated malignancies based on immune stimulation in the 1890s<sup>16</sup>. After discovering that cancer patients who contracted post-surgical infections seemed to improve faster than those who did not, he investigated the use of bacteria to stimulate and enhance the body's natural immune response to fight cancer. Through these studies, he later developed Coley's toxin, which was based on attenuated bacteria and is thought to be the first known IO therapy. A later development involved the Bacillus Calmette-Guerin (BCG) vaccine, originally produced in the early 1900s for use against tuberculosis (TB), and first used therapeutically for TB in the 1920s.

### Types of Immuno-Therapy

#### Cellular immunotherapy

Dendritic cell treatment stimulates anti-tumor responses by forcing dendritic cells to offer tumour antigens to lymphocytes, activating them and priming them to destroy additional antigen-presenting cells. Antigen presentation cells (APCs) in the mammalian immune system are called dendritic cells. They help tumour antigen targeting in cancer treatment. Sipuleucel-T is the only licenced cellular cancer treatment based on dendritic cells.

Vaccination with autologous tumour lysates or short peptides is one way to get dendritic cells to present tumour antigens (small parts of protein that correspond to the protein antigens on cancer cells). To boost immunological and anti-tumor responses, these peptides are frequently given in combination with adjuvants (particularly immunogenic chemicals). Proteins or other substances that attract and/or activate dendritic cells, such as granulocyte.

### Drugs

In 2010, Sipuleucel-T (Provenge) received FDA approval for the treatment of asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer. Antigen-presenting cells are removed from the blood via leukapheresis and grown with the fusion protein PA2024, which is made up of GM-CSF and prostate-specific prostatic acid phosphatase (PAP), before being reinfused. This

#### Cart-t cell therapy

The idea of CAR-T immunotherapy is to alter T cells so that they can recognise cancer cells and target and destroy them more efficiently. Scientists take T cells from humans, genetically modify them to add a chimeric antigen receptor (CAR) that targets cancer cells precisely, and then inject the CAR-T cells into patients to attack their tumours.

#### Approved drugs

In 2017, the FDA authorised tisagenlecleucel (Kymriah), a chimeric antigen receptor (CAR-T) therapy for the treatment of acute lymphoblastic leukaemia (ALL). CD19 positive cells (B-cells) are removed from the body with this treatment (including the diseased cells, but also normal antibody producing cells)

intracellular antigen fragments than CAR-T can recognise cell surface antigens. TCR-T cell treatment, on the other hand, is dependent on MHC molecules, which limits its utility. Multifunctional alginate scaffolds for T cell engineering and release MASTER (Multifunctional alginate scaffolds for T cell engineering and release) is a technology for in situ genetically modified T cell engineering, replication, and release. CAR-T cell treatment has progressed in this way. T cells are taken from the patient and combined with a virus that **Combination immunotherapy**

Patients who react to IO monotherapy exhibit dramatic and long-lasting clinical responses, with none of the adverse effects associated with standard cytotoxic medicines. However, only about 25–50% of patients treated with ICPs belong to this group of responders. Because of the low ORR, there has been a lot of interest in combining ICPs with other therapy modalities, such as other IO agents, in order to improve response rates and durability. The current increase in combination clinical studies demonstrates this. For example, between 2014 and 2017, there was a 705 percent rise in the number of combination studies but a 42 percent decrease in individual trial enrollment levels, owing in part to more targeted clinical trials. Combination therapy is appealing because it allows researchers to target many pathways of tumour cell killing at the same time, reducing tumour growth and resistance. The only licenced checkpoint inhibitor combo is ipilimumab plus nivolumab, which targets CTLA-4 and PD-1 at the same time. It was authorised by the FDA in 2015 and the EMA in 2016 for treatment in individuals with advanced melanoma. The FDA additionally approved this combination in 2018 for individuals with intermediate- or poor-risk advanced RCC

who had previously gone untreated. While combining two ICPIs may increase the risk of toxicity, other clinical trials are now looking into whether this combination could be beneficial in different cancer types. Given the capacity of modified T-cells to establish an inflammatory tumour microenvironment, there is growing interest in using PD-1/PD-L1 inhibitors in combination with CAR-T cell treatment. Some targeted medicines, such as BRAF inhibitors, have been linked to some degree of immunomodulation, and it has been suggested that combining these with IO drugs could have a synergistic impact. In support of this, a pre-

**Current challenges:** And managing toxicity are the two most significant hurdles for IO treatments. However, there is a dearth of knowledge on pertinent biomarkers, as well as the high expense of research, development, and treatment. Some experts also believe that future research should focus on lowering toxicity as a way to improve total clinical benefit.

#### ➤ **Unpredictability of clinical efficacy**

Newly developed drugs have an unpredictably high efficacy rate. The presence of distinct gene mutations and differing degrees of activation of certain signalling pathways in individual individuals are two probable causes for these variances in clinical outcomes. The main goal is to develop therapies that are consistently effective in the majority of patients with the majority of cancer types. With the current increase of indications, things look to be headed in this way. For example, in 2018, the European Medicines Agency (EMA) enhanced pembrolizumab's marketing authorization by adding a new indication for the adjuvant treatment of stage III melanoma. It's been proposed that the widespread use of chemotherapy as a first-line treatment for the majority of cancer types is delaying the development and usage of IO agents that aren't currently extensively approved for first-line use. They are now given to patients who are immunocompromised as a result of past chemotherapy, making the restoration of antitumour immune function difficult. As a result, it has been proposed that greater efficacies may be attained if IO drugs are used early in the treatment plan in order to fully use the immune system's capabilities. Another issue is that, in order to minimise off target effects, IO drugs should preferably be aimed against tumor-specific antigens that are only expressed by tumour cells. If precise predictive biomarkers could be identified and produced, there would be considerable therapeutic and economic benefits, as those patients who are most likely to respond would be treated. However, like with PD-L1 expression tests, there is currently a lack of confidence in the use of IO related biomarkers to guide treatment. The treatment and/or prediction of drug-drug interactions is another emerging concern. Patients who got proton pump inhibitors (PPIs) or antibiotics had a worse overall survival (OS) than those who did not<sup>114</sup>, according to a study published in 2020. Patients in the POPLAR and OAK trials who received either second-line atezolizumab

therapy (n=757) or docetaxel therapy (n=755) were included in this analysis. Antibiotics were given to 22.3 percent (n=169) of atezolizumab patients and 26.8% (n=202) of docetaxel patients, respectively, while PPIs were given to 30.9 percent (n=234) and 34.4 percent (n=260) of atezolizumab and docetaxel patients, respectively, 30 days before or after starting atezolizumab or docetaxel. For docetaxel treated patients, there was no significant link between OS and the usage of antibiotics/PPIs. Patients treated with atezolizumab who also received antibiotics had an OS of 8.5 months, compared to 14.1 months for those who did not, while patients treated with PPIs had an OS of 9.6 months, compared to 14.5 months for those who did not. Overall, our findings imply that some commonly given medicines can have a major impact on immunological checkpoint efficacy [8].

#### **Overview of check point inhibitors:**

Cancer immuno-editing is the process by which various components of the immune system protect the host from the development of primary tumors or increase the evacuation of tumors, or both, by shaping tumour immunogenicity or attenuating immune responses to cancer. The process is closely regulated by immune checkpoints, which are surface receptors that control the activation or inhibition of immune responses of the immune cells. The activation of the immune system is, on the one hand, the desired result for controlling the discovery and development of monoclonal antibodies against ctla-4 and PD-1 inhibitory immune checkpoints have led to dramatic antitumor responses by increasing immune activation at various stages of the immune cycle [9-10].

#### **The Cancer Immunity Cycle**

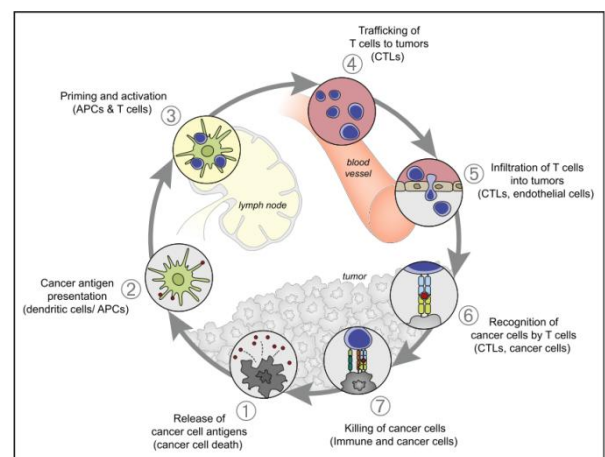


Figure: 1 Cancer Immunity Cycle

The model of the cancer immune cycle, which summarizes our scientific knowledge on each step of an effective immune response against cancer, begins with the recognition of tumor antibodies by the immune system.<sup>[11]</sup> Genetic instability or mutation is one of the characteristics of cancer. All cancers, regardless of their tissue origin, have genetic mutations ranging from small

mutations in paediatric tumors to dozens or hundreds in adult cancers [12]. Once activated, T-cells act in a systemic way, infiltrate the cancer site, recognize cancer cells expressing tumor antigen peptides presented by the Major Histocompatibility Complex (MHC) and kill target cancer cells. In turn, cancer cells release the neoantigens transposed by APC, leading to further expansion of the anticancer immune response, allowing more T cells to be detected and activated, and allowing the end stage of the anticancer response to be controlled by a complex network of stimulation and inhibitory pathways. The PD-1/PD-L1 pathway is one of the main inhibitory pathways. The involvement of the TCR with its known antigen-MHC combination, together with cytokine stimulation (e.g. IL-2 stimulation), induces PD-1 expression. The binding of PD-1 with PD-L1 on target cells inhibits T cell proliferation and IL-2 production, the immune response. Thus, rational combination immunotherapy must aim to coordinate the activation and function of T cells and the suppression of the inhibitory mechanisms of T cells

### benefits of immunotherapy

Immunotherapies are still less commonly used to treat cancer than surgery or chemotherapy. However, for some cancers, these medicines are now a viable treatment choice. Many other immunotherapies are still in the early stages of development. Because they employ the body's own strength to combat the tumour rather than injecting drugs into the body, immunotherapies have the potential to be more comprehensive and less damaging than other types of cancer treatments. Risks of immunotherapy Immunotherapies are a hot topic in cancer research, with new treatments being authorised all the time [13].

### Futures of Immunotherapy

There have been two comprehensive assessments of the worldwide IO landscape to date. The global IO pipeline increased by 67 percent between September 2017 and August 2018, with cell therapy showing the most significant increase of 113 percent in the number of active agents, followed by other immunomodulatory (e.g. aldesleukin and interferons; 79 percent) and T-cell-targeted immunomodulatory therapies (76 percent ). interest and enthusiasm for the IO field. Furthermore, clinical evidence suggests that IO drugs have a bright future ahead of them, with the potential to lead to a number of breakthrough treatments that could improve the standard of care in a variety of cancer types. Benefits of immunotherapy Immunotherapies are still less commonly used to treat cancer than surgery or chemotherapy. However, for some cancers, these medicines are now a viable treatment choice. Many other immunotherapies are still in the early stages of development. Because they employ the body's own strength to combat the tumour rather than injecting drugs into the body, immunotherapies have the potential to be more comprehensive and less damaging than other types

of cancer treatments. Risks of immunotherapy Immunotherapies are a hot topic in cancer research, with new treatments being authorised all the time. The type of immunotherapy, the type of cancer, the stage, the patient's overall condition, and the existing treatment regimen all influence the risks. Every medication has its own set of side effects, and patients may react to the same treatment in different ways. When you raise the immune system's function to "high," there are usually adverse consequences. Because the immune system is doing its job, you may suffer flu-like symptoms such as fever, chills, , followed by other immunomodulatory (e.g. aldesleukin and interferons; 79 percent) and T-cell-targeted immunomodulatory therapies (76 percent).

This area appears to be far from the development of selective agents for a particular type of cancer. IO agents are now rarely approved for specific types of cancers, but focus on pathways and expression of specific biomarkers in tumours, regardless of their origin or location (i.e., 'tissue-agnostic' therapies). This pan-cancer approach was demonstrated by the FDA's first tumor -agnostic approval of Keytruda in 2017, in patients with non- resectable or metastatic solid tumors based on their MSI-high and dMMR status, as opposed to the location or origin of the tumor. Merck, the company that developed Keytruda, is now seeking a second pancancer indicator for TMB biomarkers, with the aim of further expanding patient access[16] ii) In the field of small molecule oncology, a similar trend has been to adopt a cancer-agnostic approach; for example, in the past two years, kinase inhibitors and entrectinib have been accelerated by the FDA for use in patients with any type of solid tumors that have NTRK fusion mutation[14] iii)To date, two comprehensive studies of the global IO landscape have been carried out. Between September 2017 and August 2018, the global IO pipeline was estimated to have increased by 67%, and cell therapy was the most significant to increase the number of active substances by 113%, followed by other immunomodulatory therapies (e.g. aldesleukin and interferon; 79%) and T cell targeted immunomodulatory therapies (76%) [15].

iv) The number of IO targets also increased by 50% between September 2017 and August 2018, indicating that the IO landscape could expand significantly in the future. Both studies concluded that of the many IOs in clinical development, a large percentage are concentrated on a few targets (e.g., PD-1, PD-L1, CTLA4). In addition to the five antibodies already approved by the FDA and EMA, the British Cancer Research Institute has identified 164 drugs for the development of PD-1 or PD-L1, of which 50 are in clinical development. This indicates significant overlaps in product development and raises concerns as to whether the current approach to focusing on a small number of biomarker objectives is restricting further innovation. It is remarkable that the number of agents developed against non-toxic antigens actually decreased over the same period, which explains that IO is

increasingly focused on certain specific targets. However, interest and enthusiasm in the IO field has increased in the pharmaceutical industry and academia. In addition, clinical data indicate that I.O. drugs have significant potential in the future and may lead to some breakthrough treatments that improve the standard of care of many different types of cancer [16-17].

### Toxicity

GI toxicity is the most frequently reported irAE of any grade associated with anti-CTLA4 therapy and is managed with a combination of fluids and anti-diarrhoeal agents, and Owing to their mechanism of action, IO agents are associated with a unique but variable spectrum of toxicities, known as irAEs<sup>84,85</sup>. While the toxicities can vary greatly depending on the patient, the risk of serious clinical problems developing limits the use of IO agents to specialist clinicians with the experience to deal with irAEs should they arise. The most serious concern is potential supra-physiologic stimulation of the immune system leading to a potentially life-threatening uncontrolled and rapid production of pro-inflammatory cytokines (a so-called 'cytokine storm')<sup>85</sup>. Since there are several potential irAEs that can present following initiation of IO therapy, it is important to have clear and robust guidelines of when to refer to other medical specialists who are able to provide input to managing individual patients. For this to work in practice, it is essential that good relationships are developed with other specialties, perhaps most importantly gastroenterology, endocrinology and dermatology. The European Society for Medical Oncology (ESMO) clinical practice guidelines, 'Management of toxicities from immunotherapy', contain comprehensive guidance for the use of IOs in the clinic (see Figure 2)[18]. A Meta-Analysis, Published In 2017, Has Revealed That

### Side Effects

#### (1) Skin Reaction

Skin redness, blistering, and dryness are common reactions to immunotherapy. Skin on the fingertips may crack. Skin may also become more sensitive to sunlight. A lot of scratching can break the skin, making it more prone to infections. Inflammation around the nails can make grooming, dressing, and other activities painful or difficult. Read more about managing and treating skin irritations and reactions [19]

#### (2) Flu-Like Symptoms

Fatigue (feeling tired), fever, chills, weakness, nausea (feeling sick to your stomach), vomiting (throwing up), dizziness, body aches, and high or low blood pressure are all possible side effects of immunotherapy[20].

These are particularly common in non-specific immunotherapy and in oncolytic virus therapy. When experiencing these symptoms, it is very important to remain hydrated. If you cannot keep liquids, seek medical attention and talk to your doctor about how to manage these side effects. Many side effects will disappear by themselves, but others can be very serious and require immediate attention [21].

### (3) Other Possible Side Effects

- Muscle aches
- Shortness of breath (trouble breathing)
- Swelling of legs (edema)
- Weight gain from retaining fluid
- Diarrhoea
- Hormone changes, including hypothyroid which is when the thyroid gland does not make enough thyroid hormones and can cause fatigue and weight gain [22]

### Conclusion

Immuno-oncology (IO) is transforming cancer treatment, redefining the management of both solid and hematological tumors. However, this emerging therapy still requires optimization to minimize toxicities and integrate effectively into current treatment standards. Additionally, the high cost of IO therapies poses challenges for sustainable incorporation into healthcare systems while ensuring broader patient access. Immune checkpoint inhibitors (ICPis), such as pembrolizumab and ipilimumab, have led the IO revolution by targeting PD-1/PD-L1 and CTLA-4, respectively. Their success has driven interest in combining IO agents with conventional therapies. However, despite their efficacy, ICP is can cause significant and distinct toxicities.

### Author Contributions

All authors are contributed equally

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### Declaration of Competing Interest

The Authors have no Conflicts of Interest to Declare.

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