# The Emergence of Immunotherapies: From Tumour Immunity to The Clinic

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Cancer has been the predominant cause of deaths around the world. The immune system has been shown to be a critical regulator of tumour development and clearance. As our knowledge of tumour-immune interactions develops, we could see new immunotherapies change the way in which cancer is treated. In this review, I discuss the importance of the immune system in fighting cancer by referring specifically to the functioning of T cells and how they interact with cancer cells to destroy them and promote tumour clearance. I will then describe the importance of immunotherapies, as well as the advantages and limitations to this type of cancer treatment therapy. Current immunotherapies, such as Adoptive T Cell Transfer Therapy, Immune Checkpoint Inhibitors, Monoclonal Antibodies and Immune System Modulators, will be discussed, and the emergence of new immunotherapies, such as CAR T cell Therapy, will also be discussed.

## Introduction

Cancer is the leading cause of premature death across the globe. According to the World Health Organisation, close to 20 million people have been affected by cancer annually[1], with around 10 million people dying each year from this lethal, agonising disease, with cancer being responsible for the death of 1 in 6 people[2]. Cancer has become a global problem, affecting people of all ages, and there is still much more that needs to be uncovered in order to fully understand the effects of this disease. The research of cancer is important in order to develop our understanding about this disease and to develop appropriate strategies that will hopefully have the ability to save countless lives.

Cancer is a disease in which cells in the body proliferate and begin to spread uncontrollably around the body. By spreading into surrounding tissue and producing enzymes that break down normal cells and tissue, these cancerous cells destroy the normal, healthy cells in your body, and they dysregulate the correct functioning of major organs in the body[3]. Cancer is a major leading cause of death worldwide, and with no specific cure developed to treat cancer, it remains a mystery in how we can effectively treat cancer. Previously, the various forms of cancer treatment involved using radiation to damage or destroy cancer cells[4], and chemotherapy, which works by damaging the cancer cell's DNA, preventing cell division from occurring[5]. These treatments aren't always effective treatments in reducing or eliminating cancer cells in an individual and have off-target effects that may often be harmful to the body themselves.

The immune system plays a crucial role in defending the body against cancer by recognising any foreign or abnormal cells and killing them. Thus, cancer cells must avoid the immune system in order to continue growing and proliferating. However, cancer cells undermine, subvert and suppress the immune system, promoting tumour survival and tumour growth. T-cells are a type of white blood cell that determine the immune response to antigens in the body. Cancer cells are able to undermine the immune system through overexpression of programmed death-ligand (PD-L1). PD-L1. When binding to PD-1 (Programmed Cell Death Protein 1), a protein expressed on the surface of T cells, cancer cells can trigger strong intra-cellular signalling that can restrain T cell activation and then undermine immune responses[6,7]. Cancer cells have the ability to suppress the body's immune system, ultimately stopping the correct function of the immune system, thus reducing the immune system's ability to fight off diseases and infections. For example, tumours, through the process of tumour editing, can downregulate the expression of cancer-specific proteins located on its surface, that are recognised by the immune system[8]. Tumours can also secrete suppressive cytokines, small proteins that are crucial in cell signalling, and ligands to inhibit T cell priming, the subsequent response of T cell after its initial encounter with the tumour[9]. Increased levels of signalling proteins (VEGF) have been linked to a decreased expression of ICAM - 1(a protein what plays a role in the T cell defence system) and VCAM - 1(a protein that helps regulate inflammation), contributing to T cell death and a reduced accumulation of these cells[10].

Therefore, by harnessing the immune system to fight and mitigate the effects that cancer cells have on our body, we could develop better treatments against cancer that may be

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more effective than the conventional treatments you see today, and we have already seen this approach take place through the development of immunotherapies. Immunotherapy is an approach to cancer therapy that helps support the immune system in fighting cancer, by helping T-cells better distinguish cancer cells from healthy cells by recognizing molecules uniquely expressed in cancer cells [11,12]. Immunotherapies aim to support or restore endogenous immune function and clearance of tumour cells [13]. Therefore, the development of immunotherapies is important in stimulating the response of the immune system in order to strengthen its ability to fight off cancer.

Unlike traditional treatments, immunotherapy is an innovative treatment that is used to strengthen the immune system and can attack and clear tumour cells at many crucial nodes in the inflammatory pathways and metabolic pathways [14] of the immune system. Immunotherapies have been proven, through certain cases, to be more effective than traditional methods of treatment, and have been discovered to prolong progression-free survival (Figure 1) [15]. A major advantage of using immunotherapies over traditional forms of therapies, such as chemotherapy, is that immunotherapies offer the possibility for long-term cancer remission, as opposed to chemotherapy which only prevents the metastasis of cancer and lasts for the period of time that the drug remains in the body. The immune-tumour co-evolution is the interaction between the evolving tumour and the adaptive immune system. This co-evolution causes immunotherapies to be robust as they are able to ultimately reduce tumour-evolved resistance. Epitopes are a part of an antigen molecule that an antibody binds to. Epitope spreading represents the process of diversification of the immune response from the initial dominant epitope to a secondary epitope over time [16]. In immunotherapies, tumour-specific T cells that were induced upon vaccination or were adoptively transferred could eliminate malignant cells through epitope spreading [17]. Immunotherapies are able to provide long-term protection to the human body, as it provides the immune system with the ability to recognise and remember the appearance of cancer cells. Another advantage of the use of immunotherapies over conventional forms of treatments is that it is very selective of cancer cells. Immunotherapies have the potential to be fitted accordingly to an individual's type of cancer (a customised treatment), as it works to enhance the immune system in selecting and targeting only the malignant cells.

Specific immunotherapies result in fewer side effects than chemotherapy and radiation therapy, as these traditional treatments are non-specific, causing them to have adverse reactions on areas of the body that are not specific to the disease and its treatment. As a result, they can cause damage to cells that may be non-cancerous as well. Immunotherapies also prove to be a very effective way in which many types of cancer can be treated, as the immune system has the ability to eliminate most cancer types when under the right conditions. Therefore, an advancement of these therapies can help modify conditions experienced to enhance the ability of the immune response [18]. Current immunotherapies have had profound effects in certain individuals, exemplifying the power of the immune system in fighting cancer (Figure 1). For example, Pembrolizumab has been more effective in progression-free survival than chemotherapy.

Immunotherapies have been more effective in its treatment of cancer and has thus resulted in a greater progression-free survival rate as opposed to that of Chemotherapy (Figure 1).

## Importance of Immunotherapies

### An Overview of Immunotherapies

Cancer immunotherapies can be classified as either an active immunotherapy or a passive immunotherapy, depending on the encouragement of the host's immune system.

Active immunotherapies stimulate the host's defences and can be arranged as either specific or nonspecific treatments [20]. Immunogenicity is the ability of a foreign substance to stimulate an immune response. Non-specific immunotherapies boost the general function of the immune system and help improve the immunogenicity of specific treatments or immune challenges. Non-specific treatments use chemicals, such as cytokines, small proteins that are crucial in cell signalling, and ligands to inhibit T cell priming [21], and interferons, substances that help the immune system fight diseases such as cancer, which provide resistance against virus infections and diseases. Specific immunotherapies enhance the body's targeting or response to antigens located on the surface of pathogens that have entered the body. Specific therapies include the injection of particular antigens, found on the pathogen, into the body in order for an immune response to be activated. The result of this is that the immune system then produces the necessary antibodies to combat this antigen so that when the foreign substance enters the body again, the immune system will be well prepared with the needed antibodies to eliminate the antigen. Passive immunotherapy is an immunity that results from the introduction of effector agents that do not cause an immune response but rather act on their own accord within the body. Passive immunotherapies do not rely on the body's natural immune system to attack cancerous cells, but rather uses components of it, such as antibodies, to provide cancer patients with antibodies that allow these patients to adopt an immune response that has been developed in a laboratory [22,23]. Any modified cell that is introduced into the body can therefore be considered 'Passive'. Passive immunotherapies are used in patients with weak or unresponsive immune systems to compensate for missing or deficient immune functions [24]. For ex-


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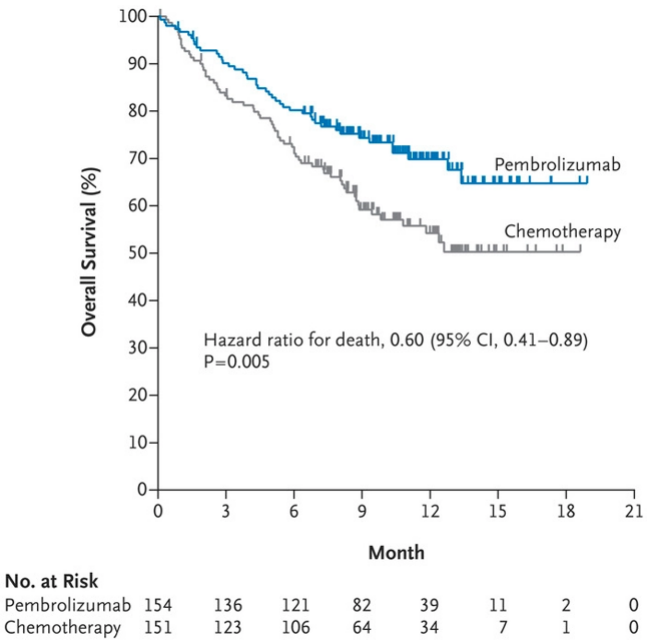


**Fig. 1** Kaplan Meier Curve Of Progression-Free Survival Comparing The Treatment of Non Small Cell Lung Cancer Using Pembrolizumab vs Chemotherapy. The blue curve representing Pembrolizumab (a cancer immunotherapy) and grey Chemotherapy highlights the advantageous effect of immunotherapy over the conventional treatment. This is seen by the two curves portraying the percentage of progression-free survival for patients undergoing these types of treatments – 'Martin Reck M.D. 2016' [19].

ample: The amplification of T cells that are specific to tumours in adoptive transfer models (an immunotherapy that involves the introduction of specific T-cells into the patient's body to help fight cancer) is a form of passive immunotherapy.

## Types of Immunotherapies

### Adoptive T Cell Transfer Therapy

Adoptive T cell Transfer Therapy is a passive immunotherapy that enhances the natural ability of T cells to fight cancer by increasing the number of immune cells able to fight cancer in your body. This therapy involves T cells being removed from the body, either taken from the tumour site or from the blood. Traditional methods of treatment are then used on patients after this transfer, to increase the probability of T cells growing and activating robustly once placed back into the body [25]. This approach to immunotherapy is given to the patient through an infusion and it aims to control the spread of tumour cells and decrease the proliferation and metastasis of tumours [26].

Cancer can promote T cell exhaustion (Figure 2 a) (Figure 2 b), a dysfunctional state caused by chronic stimulation of T cells. Adoptive T cell transfers can reintroduce functional T cells into a population of otherwise exhausted unfunctional T cells (Figure 2 c), thus restoring T cell immunity to tumours.

**0.0.1 CAR-T Cell Therapy**Chimeric Antigen Receptor (CAR) T-cell therapy has revolutionised the way in which cancer is treated today, having shown remarkable effects on patients suffering from cancer [28]. CARs are engineered, artificial receptors that operate to predominantly divert T cells to recognise and destroy cells displaying a particular target antigen. The process of this therapy involves the extraction of T cells from the body, which are genetically engineered to have a receptor (CAR) that interacts with the receptors of tumour cells, eventually killing these cells (Figure 4). CARs consist of 4 important constituents: an extracellular target antigen-binding domain, a hinge region, a transmembrane domain, and one or more intracellular signalling domains (Figure 3) [29]. The antigen-binding domain in a CAR consists of any target-binding protein. This domain interacts with possible target molecules and is responsible for acquiring the CAR T-cell to any cell expressing a match to the target molecule [30]. The hinge region is the extracellular structural region that extends the binding components from the transmembrane domain. The hinge region targets membrane-distal epitopes, and it also functions to provide flexibility to enter the targeted antigen [31]. The transmembrane domain is a membrane-spanning protein domain that spans the inner core of the lipid bilayer. It functions to anchor the CAR to the T cell membrane, arranging triggers through the regulation of bilayer absorption [32,33].

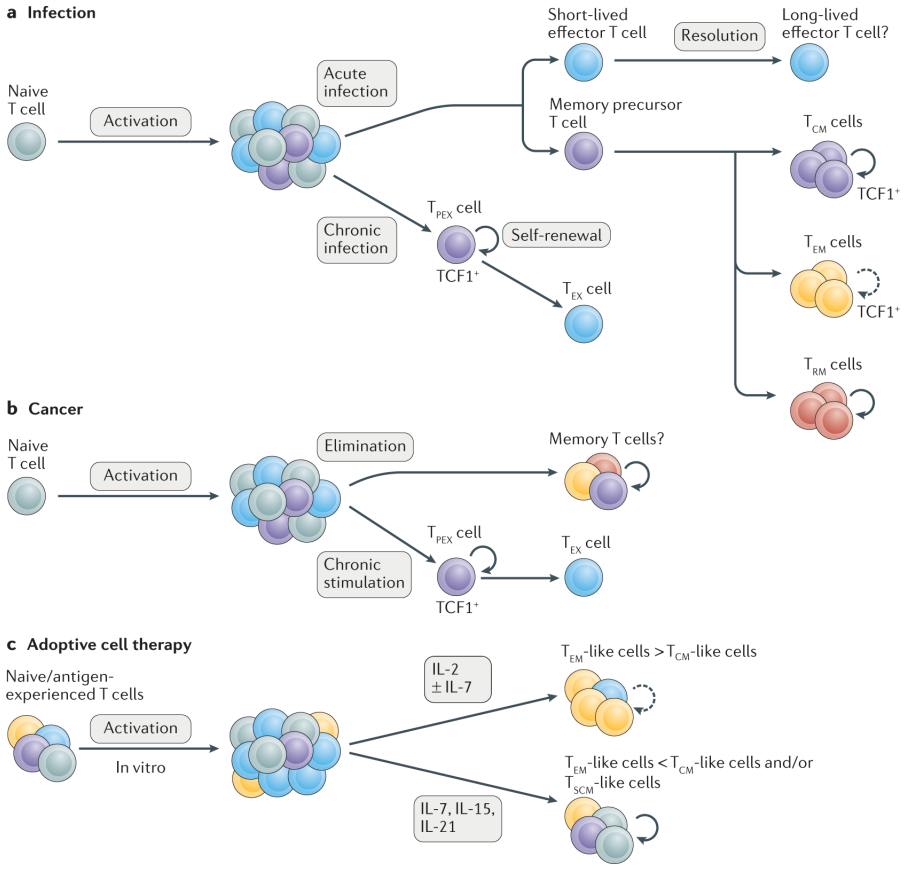


**Fig. 2** The modification of T cells when using Adoptive T Cell Transfer Therapy. The use of Adoptive T Cell Therapy results in the introduction of a greater amount of T cells that are able to recognise and attack the tumour cells. As a result, the tumour cells are eradicated by the T cells, and a greater amount of T cells remain in the body after the treatment has taken place. 'Cellular Networks controlling T cell persistence in adoptive T cell Therapy - Nature Reviews Immunology', Jack D. Chan - 2021 [27].

The intracellular signalling domains trigger signalling pathways that communicate signals. They are recognised by specific cofactor proteins, proteins that assist with a biological chemical reaction in the body, and activate numerous proteins inside the cell, thus driving an appropriate response. They ultimately function to regulate gene expression in reply to extracellular stimuli.

CAR T-cell therapy faces limitations including 'Antigen escape', where tumours develop resistance to a single antigen targeting the CAR, either through antigen-loss or downregulation of protein expression. CAR T-cell therapy also faces the limitation of off-tumour effects, which occurs during the treatment of solid tumours primarily, as the solid tumour antigens are also expressed on normal tissue on a differing level [35]. CAR T-cell therapy also incurs a great cost ranging from $373,000-475,000$, which is extremely expensive and can therefore not be accessed by everyone [36].

CAR T-cells are also being developed so that they can also overcome some of the suppressive features of the tumour environment. For example, T cells often lack the required co-stimulatory signalling when targeting tumour cells and CARs are being developed so that they don't require this co-stimulation [37].

**0.0.2 Kymriah (Tisagenlecleucel)**Kymriah is a specific type of CAR T-cell therapy [39]. Kymriah is a genetically modified autologous T-cell immunotherapy, used for the treatment of individuals up to the age of 25 years. Kymriah holds a patient's T cells so that the cells can be modified so that they can make a CAR protein. When this treatment is given to a patient, the T cells attach to and destroy the cancer cells, thereby helping in the clearance of tumours (Figure 5). Kymriah involves modifying the patient's T cells with a CAR protein that has an extracellular binding domain that recognizes CD19, a protein overexpressed in tumours, thus making CAR T-cells preferentially target tumour cells (Figure 5). Kymriah has been shown to be very effective in the treatment of cancer as it has shown to have around a complete response in 66% of


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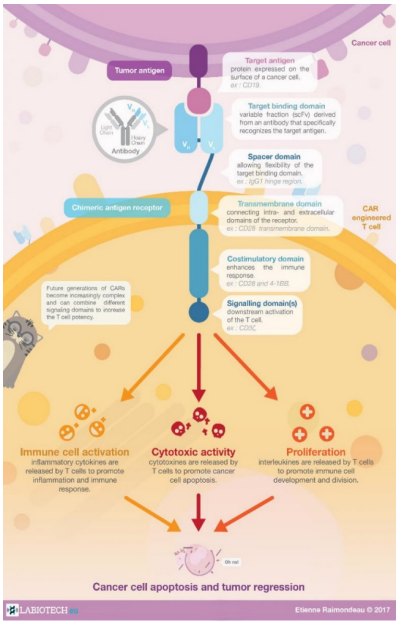


**Fig. 3** An infographic expressing the 4 domains of the receptor involved in CAR-T cell therapy. 'Rodriguez Fernandez, 2017' [34]

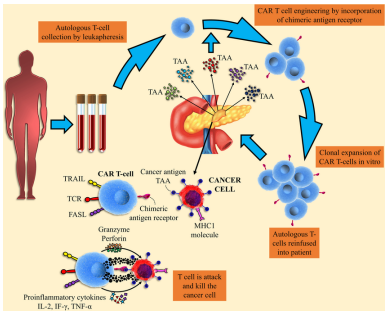


**Fig. 4** The T cell collection is extracted from the human body. The T cells are then engineered to incorporate the chimeric antigen receptor (CAR), and the CAR T cells are then cloned inside of a lab. The re-engineered T cells (CAR T cells) are then infused back into the human body. The chimeric antigen receptor then interacts with the receptor on the tumour cell, and the T cell then attacks and kills the cancer cell. 'Isolation of CAR T cells and its interaction with tumour-associated antigens (TAA) in solid tumours' [38]

the people tested[40].

However, the new generation of CAR T-cells are being developed to target proteins exclusively expressed by tumours, unlike CD19 which is also expressed in some healthy cells, thus leading to the autoimmune cytokine storm side effects[41]. However, there are certain side effects that could result from this treatment. This includes CRS (Cytokine Release Syndrome), which is a life-threatening disease that can cause fevers, a shortness of breath and vomiting. However, this treatment has proven to be more effective than other kinds of treatment, as it has led to the complete remission in patients that had not responded to previous treatments[42].

Patients that have been treated with more active CAR-T cell products have experienced inflammatory toxicities, and studies have shown that specific domains relating to the use of this therapy have been linked to the susceptibility to inflammatory toxicities[44]. Kymriah, a CAR T-cell product, has also shown correlation amongst signalling domains and toxicity in the treatment of cancer and it is therefore important to better understand the effect of the various costimulatory domains on inflammatory toxicities, so that emerging CAR T-cell therapies can be made safer and more effective[44].

## Immune Checkpoint Inhibitors

Immune Checkpoint Inhibitors are nonspecific active drugs that block immune checkpoints. The immune checkpoints are an ordinary component of the body's immune system. They prevent an immune response from being so strong that it destroys healthy cells in the body. Immune checkpoints function when the proteins on the surface of T cells recognise and interact with a partner protein located on the tumour cell, promoting T cell activation. In consequence to T cell activation, the T cell progressively upregulates the expression of immune checkpoint proteins as part of an integral immune homeostatic process, dampening T cell activation after a prolonged period, to prevent autoimmune consequences. Tumours can co-opt this mechanism, over-expressing the ligand for immune checkpoints, reducing T cell activation before it is able to effectively clear the tumour. This immunotherapy works by blocking the proteins on the T cell from binding to their partner proteins, thus preventing the dysregulation of the T cells, therefore allowing these immune cells to then properly function to kill the tumour cells[45]. An example of this form of therapy includes PD-1 (Programmed Cell Death Protein 1) inhibitors and PD-L1 (Programmed Cell Death Ligand) inhibitors, which block the activity of the PD-1 and PD-L1 proteins present on the surface of the T cell and the tumour cell. As a result, the two proteins can't interact with each other, thus preventing the tumour cell from dysregulating the function of the T cell[46].

The dysregulation of the immune checkpoints, which are a set of inhibitory signals to the immune system that play a useful role in adaptive immune response, has become a crucial mechanism for tumour cells to avoid immune destruction[47,48]. PD-L1 (programmed death-ligand) proteins, helps to prevent immune cells from attacking healthy cells in the body. The upregulation of PD-L1 proteins, by tumours interacting with the PD-1 proteins, proteins expressed on the surface of T cells that play a vital role in restoring T cell function, drives strong

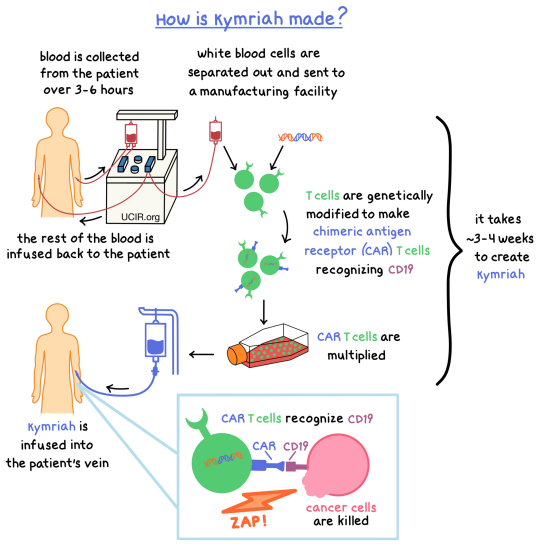


**Fig. 5** A person undergoing this treatment requires blood to be collected from their body. The white blood cells (T cells) are then separated from the collected blood and are sent to a laboratory where the cells are genetically modified to produce CAR proteins that recognise cancerous cells. These modified T cells then replicate and are infused back into the patient. These T cells then recognise the cancer cell, and the CAR receptor binds to the CD19 receptor to eliminate the cancer cell. 'Tisagenlecleucel Drug Information', Novartis - 2021[43].

inhibitory signalling in the T cell, thus preventing T cell activation reversion through the inhibition of PD-L1 or PD-1. As a result of this suppressive axis, T cell activation and function in the tumour site can be restored, leading to a greater survival rate of patients undergoing cancer, as shown by the improved survival rates with Nivolumab, a therapeutic PD-1 blockade antibody therapy, compared to traditional chemotherapy (Figure 6).

### Immune System Modulators: Monoclonal Antibodies

Immune system modulators are a type of specific and nonspecific immunotherapy that boosts the body's immune response against cancer. This therapy strives to achieve tumour destruction of the cancer cells[50]. An example of an immune system modulator is 'Monoclonal Antibodies", as antibodies are introduced into the body to help boost the immune system in its response to cancer. An antibody is a protein produced by the immune system to recognise and destroy foreign molecules. Monoclonal antibodies are immune system proteins formed in a lab, designed to bind to specific proteins, and are thus a passive form of immunotherapies. They are referred to as "monoclonal" because they are identical and bind to a specific target protein[51]. This therapy can detect and identify any pathogenic agent unpinning an infection. Monoclonal antibodies intervene in the signalling on tumour cells, through the cross-linking of antigens present on the surface of the tumour cell, eventually leading to cell death[52]. Monoclonal antibodies are able to inhibit the interaction between the Anti-PD1 and Anti-PDL1 receptors (Figure 7), which in turn prevents the immune cells from being dysregulated, therefore enhancing anti-tumour activity. This treatment also has the ability to block an activation signal that is crucial for cell growth to continue, thus preventing the tumour cells from growing and further metastasizing around the body[53]. Furthermore, this treatment can also increase the development of an active anti-tumor immune response[53]. An example of a monoclonal antibody treatment is 'rituximab' which binds to a specific protein (CD20), located on particular types of cancer cells, marking these cancer cells for the immune system, causing the immune system to destroy these cells[54].

**0.0.3 Daratumumab (Darzalex)**Darzalex is a monoclonal antibody that is used for the treatment of multiple myeloma, a type of cancer that affects certain white blood cells[56]. This targeted therapy attaches itself to CD38, a highly expressed protein found on a multiple myeloma cell. Through this attachment, this immunotherapy directly kills multiple myeloma cells or helps your immune system function to destroy these cells. This proves to be effective as multiple myeloma cells can go undetected by the body's immune system. However, this treatment attaches itself to a protein found on multiple myeloma cells, thus allowing the immune system to identify these cells. Darzalex either destroys the cells directly, or it marks these cells for the immune system to destroy. Darzalex has proven to be very effective in its treatment of multiple myeloma, whether alone or accompanied with other cancer-fighting drugs[57].

Darzalex can cause some mild to serious side effects, such as the common side effects of tiredness, muscle spasms, fevers, joint pain, and other symptoms associated with the common flu. However, more serious side effects include trouble breathing, pneumonia, nerve damage as well as allergic reactions leading to rashes or even swelling. Thus, a large amount of work is required to better this immunotherapy and lower the risk of experiencing potential side effects that may be severe[57].

## Discussion

Cancer is a disease in which cells in the body proliferate and begin to spread uncontrollably around the body. These cancerous cells destroy the normal, healthy cells in your body, and they dysregulate the correct functioning of major organs in the body. Immunotherapies are an approach to cancer therapy that helps support the immune system to fight cancer. Im-


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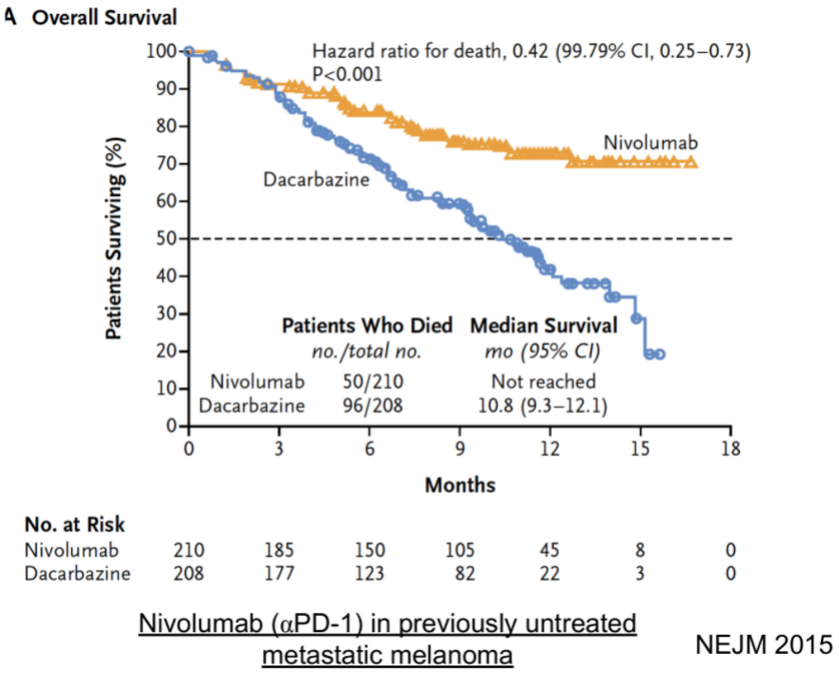


**Fig. 6** The drug, Nivolumab (orange), targets the protein, PD-1, found on T cells and it interrupts the interaction between PD-1 and PD-L1 and has been proven to result in a better survival rate compared to traditional chemotherapeutic Dacarbazine (blue). NEJM, 2015 - 'Society for Immunotherapy of Cancer', Patrick Hwu MD - 2015[49].

munotherapies aim to support or restore endogenous immune function and clearance of tumour cells. Some of the current immunotherapies available include Adoptive T Cell Transfer Therapy, Immune Checkpoint Inhibitors, Monoclonal Antibodies and Immune System Modulators. With the development of immunotherapies, we are seeing the emergence of new immunotherapies: CAR T cell Therapy, Kymriah and Daratumumab.

Immunotherapies are limited by the need for additional biomarkers (a traceable substance instituted into the body to examine the function of organs and the body's health) to assess an individual's risk of developing cancer, evaluate cancer recurrence, and predict the probability of whether a treatment will be effective[58]. The incomplete understanding of tumour-immunosuppression suggests that many patients are not accurately diagnosed or do not respond to immunotherapies. Novel immunotherapies have still had to be developed in order to make immunotherapies a more effective treatment that can facilitate patients that were non-responsive to previous immunotherapies. However, there are still lots of non-responding patients when using immunotherapies, resulting in only about a 40% - 50% progression-free survival after 15 months (Figure 1). As a result, a more complete understanding of immune-tumour interaction is required in non-responding patients, and this understanding then needs to be applied to the development of new immunotherapies in order to restore these patients' immune function. There is still more to be done on the development of immunotherapies in order to make them successful in the treatment of cancer, and there is still much more research that needs to be done on immunotherapies in order to understand its interactions with tumours during the treatment of cancer.

There are currently many limitations with the use of immunotherapies, including a high proportion of patients that are non-responsive to the use of this therapy, as well as tumours developing a further resistance to make the treatment of immunotherapies ineffective. However, novel therapies such as CAR T cell therapy involves the alternation of genes within the T cell that help the T cell attack the cancer, proving to be a more effective form of treatment as no foreign material is needed to be introduced into the body, thus reducing autoimmune responses and associated side effects with other forms of immunotherapy[59]. CARs can be developed to target neoantigens, tumour specific antigens, and thus have vastly reduced off target effects and associated side effects compared to early CARs that targeted tumour associated antigens. CAR T cell therapy has also shown to have an exceptional efficacy for patients who have undergone this treatment, with complete remission rates as high as 68% - 93%[60]. Therefore, as we see the development of new immunotherapies such as CAR T cell

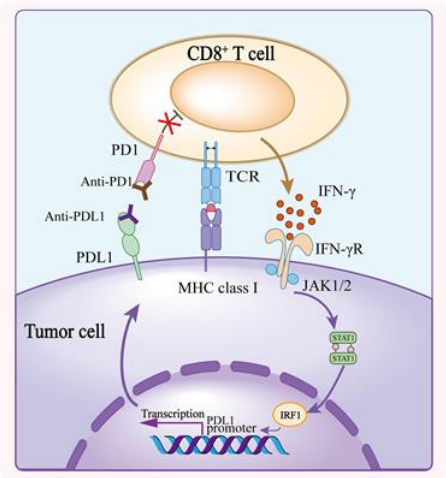


**Fig. 7** . Resistance Mechanisms of Anti-PD 1/PDL1 Therapy in Solid Tumours. The figure highlights the interaction between the PD-1 and PD-L1 proteins present on the tumour cell and the T cell. 'Cell and Developmental Biology', Qingyang Lei - 2020.[55]

Therapy, we could see these limitations reduce and witness more effective treatments with the use of immunotherapy.

Therefore, as our understanding about tumour-immune interaction increases, new treatment approaches will soon be developed to revert the immunosuppression and lack of response observed to currently approved therapies in patients. Immunotherapies have ultimately helped in strengthening the function of the immune system to fight cancer and have produced more effective results than conventional forms of treatment (Figure 1), leading to tumour clearance and immune escape, restricting tumour outgrowth. Immunotherapies have also provided long-term protection against cancer and have revolutionised the way in which we see cancer to be treated today[61]. Immunotherapies will likely never be applicable for everyone, as the development of this form of treatment is fairly new and will thus incur larger costs as opposed to traditional forms of treatments[62]. They therefore represent one weapon in the ever-growing arsenal of cancer therapeutics.

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