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Cancer Immunotherapy
Current Landscape and Future Directions

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List of Abbreviations

TME	Tumor Microenvironment
TCR	T Cell Receptor
MHC	Major Histocompatibility Complex
TNF	Tumor Necrosis Factor
Rb	Retinoblastoma
TP53	Tumor Protein 53
VEGF	Vascular Endothelial Growth Factor
TSP-1	Thrombospondin-1
ATP	Adenosine Triphosphate
TIL	Tumor Infiltrating Lymphocyte
T_{Reg}	Regulatory T lymphocyte
ROS	Reactive Oxygen Species
HIF	Hypoxia Inducible Factor
CTL	Cytotoxic T Lymphocyte
NK	Natural Killer Cell
DC	Dendritic Cell
EGF	Epidermal Growth Factor
TAA	Tumor Associated Antigen
TSA	Tumor Specific Antigen
APC	Antigen Presenting Cell
CTLA-4	Cytotoxic T Lymphocyte Associated Protein - 4
IL	Interleukin
IFN	Interferon
IL-12R	Interleukin 12 Receptor
PD-1	Programmed Death - 1
MDSC	Myeloid Derived Suppressor Cell
LAG-3	Lymphocyte-Activation Gene - 3
PD-L1	Programmed Death Ligand - 1
PD-L2	Programmed Death Ligand - 2
FDA	Food and Drug Administration
mAb	Monoclonal Antibody
BCG	Bacillus Calmette–Guérin
HBV	Hepatitis B Virus
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
ICI	Immune Checkpoint Inhibitor
CAR	Chimeric Antigen Receptor
irAEs	Immune Related Adverse Events
BCMA	B-Cell Maturation Antigen
CRS	Cytokine Release Syndrome
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
EMA	European Medicines Agency
HER	Human Epidermal Growth Factor Receptor
HPV	Human Papillomavirus
EBV LMP	Epstein-Barr Virus Latent Membrane Protein
HTLV	Human T cell Leukemia Virus type-1
CMV	Cytomegalovirus

MAGE	Melanoma Antigen Gene
BAGE	B Melanoma Antigen Gene
SEREX	Serological Analysis of Recombinant Tumor cDNA Expression Libraries
HORMAD1	HORMA domain-containing protein 1
CT83	Cancer Testis Antigen 83
ACTL8	Actin-like Protein 8
SSX-2	Synovial Sarcoma X Protein
GAGE	G Antigen
SOX-2	Sex determining Region Y Box
OCT-4	Octamer binding Transcription Factor 4
TERT	Telomerase Reverse Transcriptase
PAP	Prostatic Acid Phosphatase
PSA	Prostate-Specific Antigen
gp100	Glycoprotein 100
MART-1	Melanoma-associated Antigen Recognized by T Cells
VEGF-R	Vascular Endothelial Growth Factor Receptor
B-Raf	B-Rapidly Accelerated Fibrosarcoma
MUC-1	Mucin 1
K-Ras	Kirsten Rat Sarcoma
BCR-ABL	Breaking Cluster Region-Abelson Fusion Gene
ETV6	E26 Transformation-specific Variant 6
NPM-ALK	Nucleophosmin-Anaplastic Lymphoma Kinase Fusion Protein
ALK	Anaplastic Lymphoma Kinase
EGFR	Epidermal Growth Factor Receptor
WT1	Wilms' Tumor Gene
CEA	Carcinoembryonic Antigen
STn-KLH	Sialyl-Tn-Keyhole Limpet Hemocyanin
CDK-4	Cyclin-Dependent Kinase 4
mRNA	Messenger RNA
PFS	Progression-Free Survival
OS	Overall Survival
CAGR	Compound Annual Growth Rate
dMMR	Deficient Mismatch Repair
MSI-H	Microsatellite Instability High
TMB	Tumor Mutational Burden
ORR	Overall Response Rate
ctDNA	Circulating Tumor DNA
CT	Chemotherapy
TT	Targeted Therapy
RT	Radiotherapy
TGF	Transforming Growth Factor
NP	Nanoparticle
PEG	Polyethylene Glycol
TIM-3	T Cell Immunoglobulin and Mucin Domain 3
VISTA	V-domain Ig Suppressor of T Cell Activation

Resumo

De acordo com a Organização Mundial de Saúde, o cancro é um importante problema de saúde pública e uma das principais causas de morte em todo o mundo. Nos últimos anos, tem-se verificado um considerável crescimento no mercado global das terapias contra o cancro. O cancro é principalmente caracterizado pela proliferação desregulada das células do corpo, que, em vez de responderem adequadamente aos sinais que controlam o comportamento celular normal, crescem e dividem-se de forma descontrolada. As características distintas do cancro, inicialmente propostas em 2000 por Hanahan e Weinberg, revolucionaram a terapia do cancro e abriram caminho para o desenvolvimento de novas abordagens terapêuticas capazes de superar as limitações dos tratamentos convencionais.

Dada a reduzida eficácia e/ou efeitos adversos extensos dos tratamentos convencionais contra o cancro, como cirurgia, radioterapia e quimioterapia, surgiu a necessidade de desenvolver terapias novas, direcionadas, seguras e eficazes. A imunoterapia surgiu como uma estratégia inovadora para o tratamento do cancro e agora está firmemente estabelecida como um pilar da oncologia para inúmeros tipos de cancro. A imunoterapia estimula o sistema imunitário para atacar e eliminar indiretamente as células tumorais, melhorando a imunidade anti-tumoral e reduzindo os efeitos *off target*. Embora esta terapia tenha se mostrado altamente bem-sucedida para alguns doentes, a sua eficácia não é abrangente, não sendo aplicável e eficaz para vários tipos de cancro. Além disso, ainda existem efeitos adversos associados que devem ser tidos em consideração. Nesse sentido, várias estratégias que visam superar essas limitações estão a ser estudadas, incluindo o uso de biomarcadores preditivos, combinação de terapias, utilização de sistemas de entrega e desenvolvimento de estratégias imunoterapêuticas inovadoras.

A presente dissertação tem como objetivo descrever e compreender as principais características do cancro e fornecer uma visão geral do estado atual da imunoterapia, incluindo a identificação dos diferentes tipos de imunoterapia, bem como as suas principais vantagens e desafios. Além disso, será fornecida uma análise do estado atual do mercado no campo da imuno-oncologia, incluindo a identificação dos produtos aprovados. Por fim, esta dissertação avalia o potencial dos biomarcadores preditivos, estratégias de combinação e sistemas de entrega como mecanismos para ajudar a superar os desafios associados às abordagens imunoterapêuticas tradicionais.

Palavras-chave: cancro, imunologia do cancro, imunoterapia, estado do mercado, perspetivas futuras.

Abstract

According to the World Health Organization, cancer is a major public health problem and a leading cause of death worldwide. In the last years, considerable growth in the global market of cancer therapies has been witnessed. Cancer is mainly characterized by the unregulated proliferation of the body's cells which, rather than responding appropriately to the signals that control the normal cell behavior, grow and divide in an uncontrolled manner. The hallmarks of cancer, initially proposed in 2000 by Hanahan and Weinberg, have revolutionized cancer therapy and opened the road for the development of novel therapeutic approaches capable of overcoming the limitations of conventional treatments.

Given the lack of efficacy and/or extensive adverse effects of standardized cancer treatments such as surgery, radiotherapy, and chemotherapy, the need for new, targeted, safe, and effective therapies has emerged. Immunotherapy arose as a groundbreaking strategy for cancer treatment and has now firmly been established as a pillar of cancer care for numerous cancer types. Immunotherapy stimulates the immune system to indirectly attack and kill tumor cells, improving anti-tumor immunity while reducing off-target effects. Although this therapy has proved to be highly successful for some patients, its efficacy is not all-encompassing, not being applicable and effective for several cancer types. In addition, there are still associated adverse effects that must be taken into consideration. To this end, several strategies that aim to overcome these limitations are being studied, which include using predictive biomarkers, combining therapies, employing delivery systems, and developing innovative immunotherapeutic strategies.

The present dissertation aims to describe and understand the main features of cancer and provide an overview of the current status of immunotherapy, including the identification of the different types of immunotherapy, as well as its key advantages and challenges. Furthermore, the current market landscape of the immuno-oncology field, including the identification of the approved products, will be provided. Finally, this dissertation reviews the potential of predictive biomarkers, combination strategies and delivery systems as mechanisms to help to overcome the challenges associated with traditional immunotherapeutic approaches.

Key-words: cancer, cancer immunology, immunotherapy, market status, future perspectives.

“Everything is theoretically impossible, until it is done.”

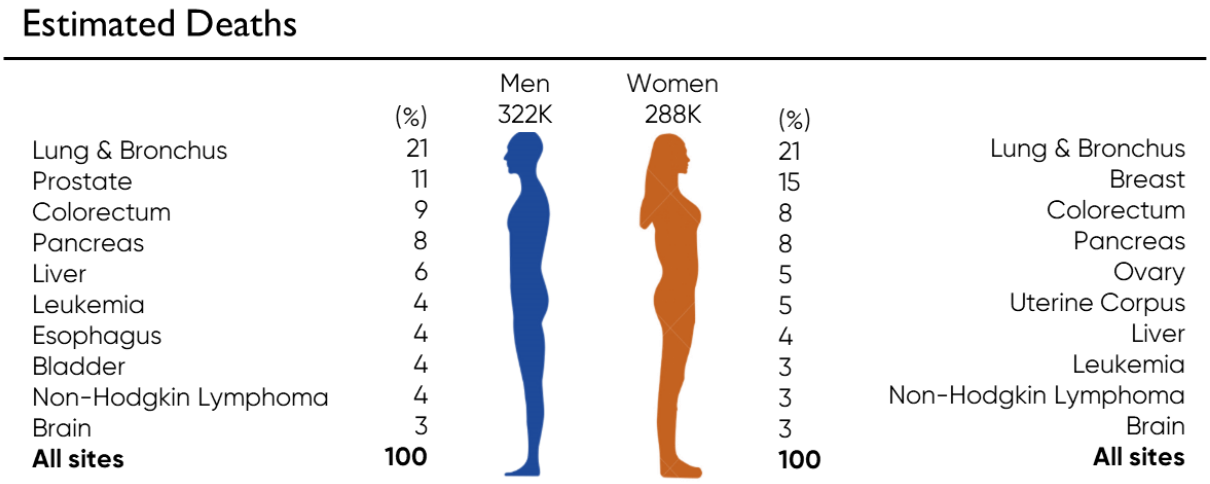
Robert A. Heinlein

Chapter I – Journey into Cancer: Fundamental Concepts and Key Principles

1.1. Introduction

Cancer is a major public health problem and a leading cause of death worldwide, according to the World Health Organization[1], with an estimated 19.3 million new cancer cases and almost 10 million cancer deaths in 2020[2]. In 2023, 1,958,310 new cancer cases and 609,820 cancer deaths are predicted to occur in the United States[3;4], which represents about 1,670 deaths per day[5]. Figure 1A depicts the most common cancers projected to be diagnosed in men and women in the United States in 2023. Prostate, lung and bronchus, and colorectal cancer account for almost half of the incident cases in men, with 29% of the diagnoses of prostate cancer[4]. For women, breast cancer, lung cancer, and colorectal cancer represent more than half of the diagnosed cases, being breast cancer responsible for 31% of female cancers. In terms of estimated deaths, as shown in Figure 1B, lung cancer is, for both men and women, the leading cause of death, responsible for 21% of estimated deaths for 2023[4]. It is also important to highlight prostate cancer and colorectal cancer as leading causes of cancer death in men and breast cancer and colorectal cancer in women[4].

A



B

Estimated New Cases

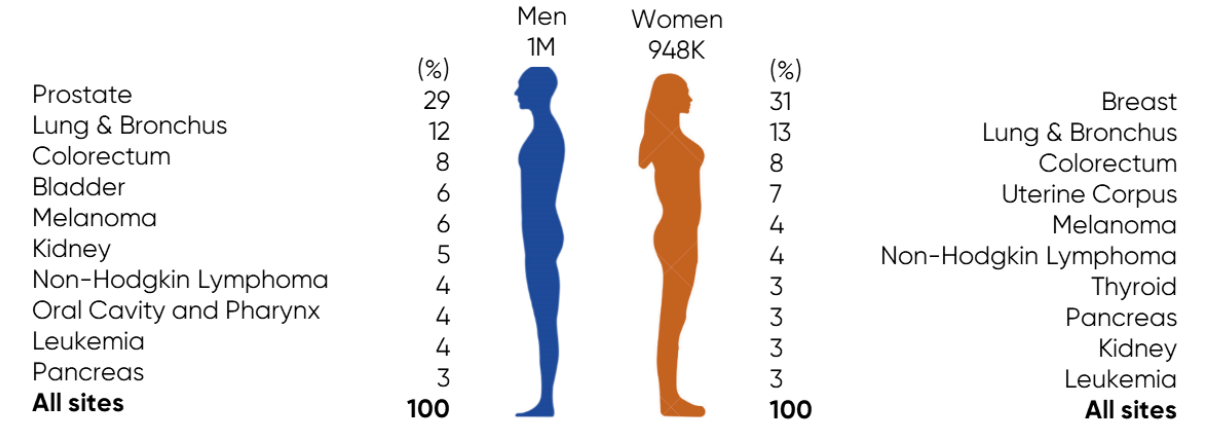


Figure 1 - Ten Leading Cancer Types for the Estimated New Cancer Cases (A) and Estimated Deaths (B) by Sex in 2023 for the United States. Estimates exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. The ranking is based on modeled projections. Adapted from Siegel et al. 2023[4].

It is estimated that about 42% of the new cancers are potentially avoidable, including the 19% of cancers that are caused by smoking habits and at least 18% induced by a combination of excessive body weight and alcohol consumption, poor nutrition and physical inactivity[5]. Furthermore, cancer incidence is expected to continue to increase, following the past decades' landscape, reaching 27.5 million new cancer cases worldwide by 2040, a 62% increase since 2018[6].

Cancer is, by definition, a multifactorial disorder involving complex modifications in the genome[7]. It involves various genetic or epigenetic changes which ultimately drive the malignant transformation of the normal cells[7; 8]. The mutations required for the development of a malignant status can either be acquired gradually during an individual's lifetime or hereditary[8]. These mutations can produce oncogenes with dominant gain of function, such as those involved in cellular communication and growth, or recessive loss of function[8; 9]. Tumor suppressor genes achieve oncogenic effects through recessive loss of function[8; 9]. Their inactivation, essential for controlling cell growth and preventing cancer, promotes tumorigenesis[8; 9].

The accumulation of abnormalities is the basis of the multi-step process through which malignant transformation occurs, known as carcinogenesis[10]. The carcinogenic process involves an irreversible alteration to a cell's DNA, either a strand break or a nucleotide alteration, which alters the sequence of the encoded protein[10]. If such error is related to a protein involved in growth regulation, it could potentially confer a growth advantage to the cell[10]. In the following stages of carcinogenesis, the altered cell's selective proliferation is promoted, and it becomes predisposed to additional alterations that arise in regulatory genes[10;

[11]. The carcinogenic process is complete when the malignant conversion occurs. This step is induced by the acquisition of additional mutations that drive the cell to acquire specific characteristics associated with malignancy, referred to as hallmarks of cancer, which will be further discussed in the following subsection[10]. These mutations may cause structural changes to cell morphology and architecture, and biochemical changes to metabolic pathways that enhance the tumor cell's resistance to normal apoptosis-inducing signals[10]. The highly mutated cell then grows in an uncontrolled and unregulated manner, eventually leading to the formation of the primary tumor[10].

1.2. Hallmarks of Cancer

The Hallmarks of Cancer comprise the biological capabilities, acquired during the multi-step development of tumors, that are shared by all types of cancer cells. This concept constitutes an organizing principle for rationalizing the complex phenotypes of diverse human tumor types and variants in terms of a common set of underlying cellular parameters[8; 12; 13].

The six original hallmarks were proposed in 2000 by Douglas Hanahan and Robert A. Weinberg[8] (Figure 2A). In 2011, the same authors revisited the original hallmarks (Evading Growth Suppressors, Enabling Replicative Immortality, Activating Invasion and Metastasis, Inducing or Accessing Vasculature, and Resisting Cell Death) and added two additional hallmarks (Sustaining Proliferative Signaling and Avoiding Immune Destruction) and two enabling characteristics (Tumor-Promoting Inflammation and Genome Instability and Mutation) (Figure 2B)[12]. The enabling characteristics were described as molecular and cellular mechanisms by which hallmarks are acquired, being, therefore, vital for malignant transformation[12; 13].

The extensive developments in cancer research and the better understanding of the mechanistic underpinnings of each hallmark resulted in the creation of a new version of the Hallmarks of Cancer, published in 2022[13]. This version provided additional two emerging hallmarks (Unlocking Phenotypic Plasticity and Senescent Cells) and two enabling characteristics (Non-mutational Epigenetic Reprogramming and Polymorphic Microbiomes) that better addressed the complexity of cancer pathogenesis (Figure 2C). Apart from hallmarks and enabling characteristics, the tumor microenvironment (TME) was also critical to cancer pathogenesis, adding another complexity to cancer[13].

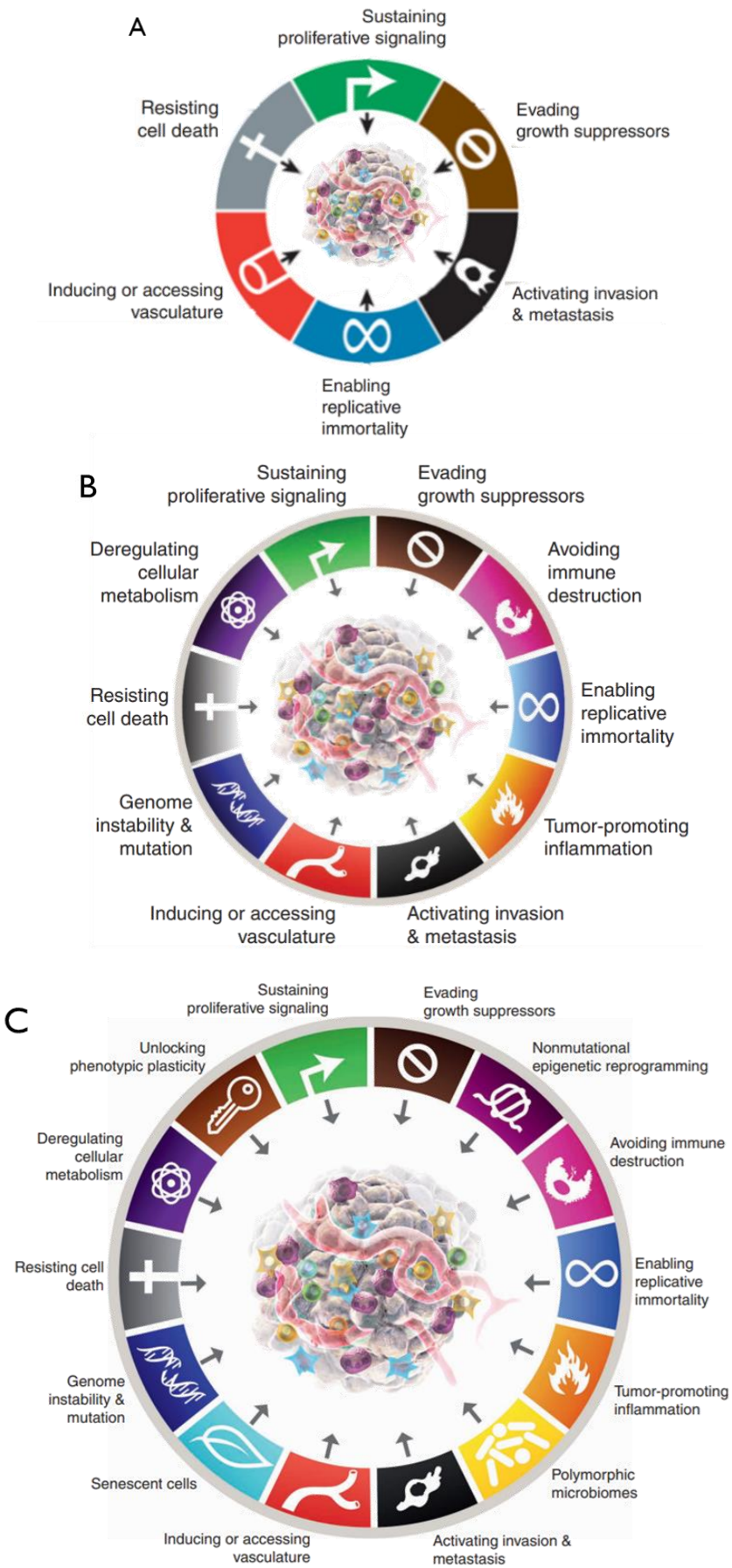


Figure 2 - The Hallmarks of Cancer. This concept comprises the biological capabilities acquired during the carcinogenic process. In addition to the six original acquired capabilities proposed in 2000 (Figure 2A), two additional hallmarks and two enabling characteristics were introduced and published in 2011 (Figure 2B). In 2022, this concept was reviewed, and two new hallmarks and two enabling characteristics were incorporated (Figure 2C). Adapted from Hanahan et al. 2000[8], Hanahan et al. 2011[12] and Hanahan 2022[13].

The ten hallmarks that have been established over 22 years are described below and depicted in Figure 3.

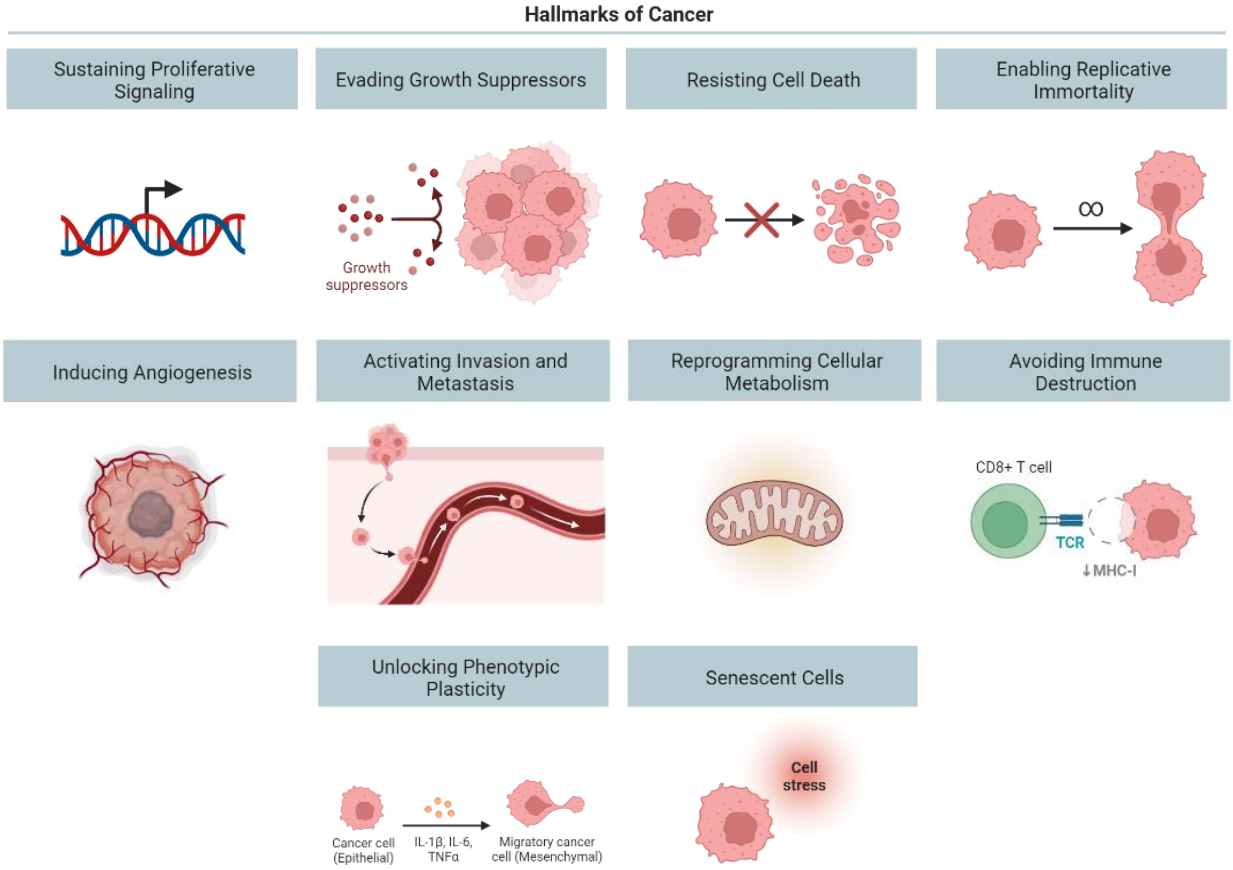


Figure 3 - Representation of the Hallmarks of Cancer. The original hallmarks include Sustained Proliferative Signaling, Evading Growth Suppressors, Enabling Replicative Immortality, Activating Invasions and Metastasis, Inducing Angiogenesis and Resisting Cell Death. Emerging hallmarks include Avoiding Immune Destruction, Unlocking Phenotypic Plasticity, Deregulating Cellular Energetics and Senescent Cells. Abbreviations are as follows: TCR – T Cell Receptor; MHC – Major Histocompatibility Complex; TNF – Tumor Necrosis Factor. Created in BioRender.com.

i. Sustaining Proliferative Signaling

The ability to sustain chronic proliferation is perhaps the most fundamental trait of cancer cells. Normal tissue growth is tightly regulated by the production and release of growth factors and hormones that control the progression through the cell growth and division cycle[12]. Cancer cells, however, are unresponsive to such regulation, which may happen due to several mechanisms[12; 14]:

- Cancer cells may produce their growth factors, resulting in autocrine proliferative stimulation;
- Cancer cells may send signals to surrounding normal cells, which respond by producing the necessary growth factors;
- Receptor signaling may be deregulated through receptor overexpression which renders cancer cells hypersensitive to otherwise limiting amounts of growth factor;

- Structural modifications in the receptor may facilitate ligand-free firing;
- Activation of components downstream to the receptors may provide cancer cells with a growth factor-independent activation of the pathway.

ii. Evading Growth Suppressors

In addition to inducing and sustaining chronic growth stimulatory signals, cancer cells must also counteract the mechanisms that negatively regulate cell proliferation, which mainly depend on the action of tumor suppressor genes[12]. Tumor suppressor genes prevent the transformation of normal cells into cancer cells by inhibiting the proliferation of mutated or damaged cells by averting the cell cycle and inducing programmed cell death – apoptosis[15].

In cancer cells, however, tumor suppressor genes, such as retinoblastoma (Rb) and tumor protein 53 (TP53), often suffer mutations that result in the suppression of their activity[16; 17]. Rb protein plays a crucial role in the negative control of the cell cycle and tumor progression[18]. It is a major checkpoint of the G1 phase of the cell cycle, blocking the cell from entering the S-phase of cell division and, therefore, inhibiting cell growth[19]. p53 protein receives inputs from stress and abnormality sensors that function within the cell's intracellular operating systems. If the degree of damage to the genome is excessive, or if the levels of nucleotides, growth-promoting signals, glucose, or oxygenation are suboptimal, p53 can stop cell-cycle progression until these conditions have been normalized or, if such damage is overwhelming or irreparable, trigger apoptosis[12; 14]. Thus, Rb and TP53 loss of function may induce cell cycle deregulation and lead to a malignant phenotype[19].

In solid tumors, the most common genetic changes observed are losses of tumor suppressor genes, which emphasizes the need to restore the function of these genes, whether they have been lost or mutated, in every cell - a feat that remains unachieved[12].

iii. Resisting Cell Death

Under physiological conditions, in response to stressful stimuli, the cell triggers a cellular stress response to ensure survival, which limits tissue damage[20]. In cancer cells, however, the activation of pathways that favor cell survival under stressful conditions contributes to carcinogenesis, tumor progression, and therapy resistance[20]. Such mechanisms involve the up-regulation of anti-apoptotic proteins and/or downregulation or dysfunction of pro-apoptotic molecules, including[20]:

- Downregulation of receptors surface expression, such as Tumor Necrosis Factor (TNF) receptor, which is crucial for inducing apoptotic signals;
- Increase in the ratio of anti- to pro-apoptotic B cell Lymphoma proteins;
- Regulation of the redox state of cytochrome c, since the reduced form is unable to induce activation of proteins responsible for the execution phase of apoptosis;
- Aberrant overexpression of Inhibitor of Apoptosis Proteins.

iv. Enabling Replicative Immortality

For over two decades, it has been widely accepted that cancer cells require unlimited replicative potential to generate macroscopic tumors[12]. Under normal conditions, healthy cells have a limited replicative ability before entering cell senescence or programmed death[21]. However, cancer cells exhibit unlimited replicative proliferation without evidence of senescence or cell death, a process referred to as immortalization[12]. This immortalization is achieved through the expression of the enzyme telomerase, a DNA polymerase whose role is to lengthen telomeres[22].

Telomeres are specialized structures located at the end of chromosomes, comprised of tandem DNA repeats, that play a crucial role in protecting the DNA from recombination and degradation activities[22; 23]. Telomerase is almost absent in normal cells, but in immortalized cells such as cancer cells, it is expressed in significant levels[12]. Telomeres progressively lose repeats in a way coupled with cell division due to the inability to completely replicate linear chromosomes by conventional DNA polymerases[23]. Telomere shortening to a critical length results in loss of telomeric protection, which leads to chromosomal instability and loss of cell viability[24]. Defects in telomere length have been implicated in age-related diseases, premature aging syndromes and cancer[23].

v. Inducing Angiogenesis

Under physiological conditions, angiogenesis is a highly regulated process responsible for forming new blood and lymphatic vessels from pre-existing vasculature, transiently turned on in adults[25; 26]. In tumor cells, however, the angiogenic switch is almost always activated. As such, cancer cells can produce an erratic pattern of new blood vessels – the tumor-associated neovasculature – that provides their required substantial metabolic sustenance[12; 27]. In addition, angiogenesis promotes the entry of cancer cells into the newly formed blood and lymphatic system and their subsequent metastasis and proliferation to distant sites in the body[25; 28].

The angiogenic switch is an imbalance between regulatory agents that induce and inhibit angiogenesis, such as vascular endothelial growth factor (VEGF) and thrombospondin-1 (TSP-1), respectively[25; 29]. The VEGF gene encodes ligands that are involved in the formation of new blood vessels[30; 31]. VEGF signaling is regulated at multiple levels, and its expression is upregulated by hypoxia and activation of various oncogenic proteins[30; 31]. On the other hand, TSP-1 is a crucial counteractive in the angiogenic switch, evoking suppressive signals that can counteract pro-angiogenic stimuli[32]. The expression of TSP-1 is downregulated by oncogene signaling and upregulated by tumor suppressor genes such as p53[33]. Thus, increased expression of VEGF and decreased expression of TSP-1 leads to a pro-angiogenic state, which is associated with the malignant phenotype[34].

The lack of adequate blood supply to the tumor might stop tumor growth, possibly leading to cancer cell death[35]. Thus, targeting angiogenic molecules, such as those mentioned above, may be an important approach to cancer treatment. However, despite promising results in mice having been achieved, success in human cancer has been limited[25].

vi. Activating Invasion and Metastasis

Metastasis refers to the formation of secondary tumors located in a different part of the body from the site of the original tumor[36; 37]. It is the leading cause of cancer treatment failure, responsible for over 90% of cancer-related deaths, making it a critical factor to address in cancer treatment strategies[36; 37].

The development of metastasis involves a series of consecutive steps, including local invasion of cancer cells, their entry into nearby blood and lymphatic vessels, through a process called intravasation, and transit through the lymphatic and hematogenous systems. Subsequently, cancer cells extravasate from these vessels and form small nodules of that eventually grow into macroscopic tumors[38]. This last phase is called colonization and is considered the final step of the metastatic cascade[38]. The ability to detach and disseminate into other tissues requires specific alterations on the cancer cell itself, rendering them more deformable and contractile, which facilitates intravasation and extravasation[39]. Additionally, alterations must occur in their attachment to other cells and the extracellular matrix[12]. While multiple mechanisms can induce these changes[36], the epithelial-mesenchymal transition has been extensively studied. Epithelial-mesenchymal transition is characterized by several modifications, including the loss of adherens junctions, adoption of a fibroblastic morphology, expression of matrix-regulating enzymes, increased motility, and elevated resistance to

apoptosis[40]. Through epithelial-mesenchymal transition, cancer cells can acquire the ability to invade, resist apoptosis, and disseminate to other tissues[41].

vii. Reprogramming Energy Metabolism

During cancer progression, cancer cells are exposed to various types of metabolic stress. Thus, cancer cells must reprogram their metabolism to survive in different environments.

Tumor cells, even in normoxic conditions, limit their energy production (adenosine triphosphate - ATP) almost exclusively to aerobic glycolysis. This metabolic shift results in lactate production and contributes to the hypoxic TME, which promotes angiogenesis, metastasis, and resistance to therapy[42; 43]. Cancer cells compensate for the 18-fold lower yield of ATP production efficacy afforded by glycolysis relative to mitochondrial oxidative phosphorylation by upregulating glucose receptors and increasing the expression of glycolytic enzymes[44]. The reliance on the glycolytic pathway is associated with activated oncogenes and mutated suppressor genes that contribute to several hallmark capabilities[44; 45].

viii. Evading Immune Destruction

According to immune surveillance theory, lymphocytes act as sentinels to identify and eliminate somatic cells transformed by spontaneous mutations[46]. This constant monitoring is responsible for recognizing and eliminating the vast majority of incipient cancer cells and, hence, nascent tumors, emphasizing the importance of the immune system in protecting against cancer[12]. However, subsets of tumor cells may evade immunosurveillance, progressively grow into immunologically sculpted tumors and establish an immunosuppressive TME[47]. This process is referred to as immunoediting[47].

The strongest evidence of cancer immunoediting in humans comes from the existence of tumor-infiltrating lymphocytes (TILs)[48]. Tumor cells are able to suppress TILs through various mechanisms. Such mechanisms involve the direct suppression of anti-tumor immune cells or the release of immunosuppressive factors and recruitment of immunosuppressive cell subsets, such as regulatory T cells (T_{Reg}). This phenomenon results in diminished host anti-tumor immune responses[49]. Therefore, the immunogenic capacity of cancer has steered cancer therapy research in the direction of harnessing the immune system's ability to survey and eliminate cancer cells[12].

ix. Unlocking Phenotypic Plasticity

Phenotypic plasticity describes the ability of cancer cells to undergo reversible molecular and phenotypic changes, driven by epigenetic, transcriptional and/or translational mechanisms, that allow them to adapt to environmental stresses[50]. This phenomenon amplifies cancer heterogeneity and promotes metastasis and therapy evasion[50]. Epithelial-mesenchymal transition is one of the best described examples of phenotypic plasticity, which induces both morphological and molecular changes in the cancer cell that facilitate the metastatic process[51].

x. Senescent Cells

Cell senescence is a stress response that elicits a typically irreversible form of proliferative arrest that allows inactivation and posterior removal of diseased, dysfunctional, or otherwise unnecessary cells[13]. It is triggered by microenvironmental stresses such as genotoxic agents, nutrient deprivation, hypoxia, mitochondrial dysfunction, DNA damage and aberrant oncogene activation[52; 53]. Senescent cells produce a complex secretome (senescence-associated secretory phenotype) that stimulates malignant formation and tumor development[52; 53]. It is believed that this secretome is responsible for conveying signaling molecules and proteases to viable cancer cells in proximity, as well as to other cells in the TME, which activates and/or releases them from their sequestered state, allowing them to acquire the hallmark capabilities associated with cancer[13].

In addition, senescent cancer cells have the ability to transition through reversible senescent cell states, enabling them to escape from their non-proliferative, senescent secretome-expressing condition and resume cell proliferation and manifestation of the capabilities associated with fully viable oncogenic cells[54]. The phenomenon of transient senescence is extensively documented in cases of therapy resistance[54].

Enabling Characteristics

To acquire multiple hallmark capabilities, cancer cells require initial molecular and cellular alterations. Such modifications, referred as enabling characteristics enable cancer cells to adopt these functional traits. They include genome instability and mutation, non-mutational epigenetic reprogramming, tumor-promoting inflammation, and polymorphic microbiomes, represented in Figure 4.

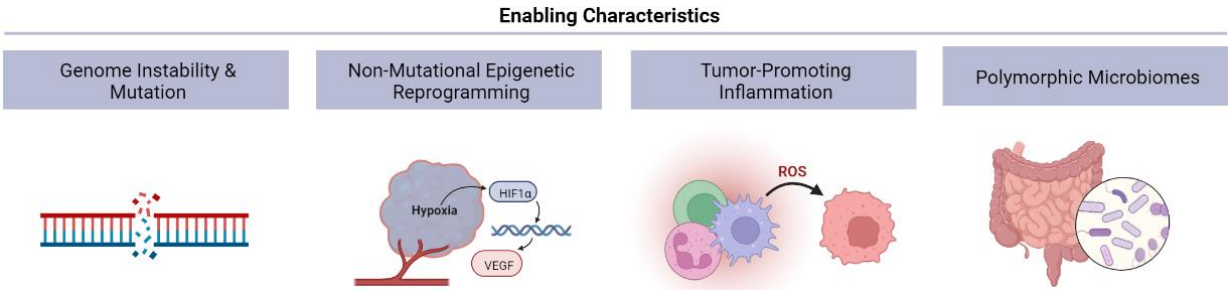


Figure 4 - Representation of the Emerging Characteristics. They include Tumor-Promoting Inflammation, Non-mutational Epigenetic Reprogramming and Polymorphic Microbiomes. Abbreviations are as follows: ROS – Reactive Oxygen Species; HIF – Hypoxia Inducible Factor; VEGF – Vascular Endothelial Growth Factor. Created in BioRender.com.

Changes in the genome of neoplastic cells, for example, lead to the development of mutant genotypes and genomic instability[12]. Mutant genotypes confer selective advantages to cells, allowing their outgrowth and eventual dominance in a specific environment[12]. This mutability is achieved through increased sensitivity to mutagenic agents and/or breakdown in one or several components of the genomic maintenance systems that detect and resolve defects in the DNA and force genetically damaged cells into either senescence or apoptosis[12; 55]. Genomic instability, on the other hand, enables the acquisition of hallmark capabilities by loss of telomeric DNA, which leads to amplification and deletion of chromosomal segments[56].

Gene expression can be modulated not only by genomic alterations, but also by independent modes of genome reprogramming that involve epigenetic regulation[57]. This concept is referred to as non-mutational epigenetic reprogramming[57]. In fact, aberrant physical properties of the TME, such as hypoxia, can cause changes in the epigenome that result in clonal outgrowth of cancer cells with enhanced fitness for proliferative expansion[13]. Furthermore, the accessory cells in the TME that functionally contribute to the acquisition of hallmark capabilities are thought to suffer epigenetic reprogramming upon their recruitment by soluble and physical factors that define the TME[58].

Additionally, the acquisition of hallmark capabilities also depends on the establishment of inflammatory conditions that supply bioactive molecules such as growth factors, survival factors, proangiogenic factors, extracellular matrix-modifying enzymes, among others[59]. Inflammatory cells can also release chemicals, notably reactive oxygen species, that are actively mutagenic for nearby cancer cells, accelerating their genetic evolution toward states of heightened malignancy[60].

Finally, the microbiome and its polymorphic variability between individuals are able to have a significant impact on cancer phenotypes, particularly tumor growth, inflammation, immune evasion, genome instability and therapy resistance[61]. While gut microbiome has pioneered the research in this area, multiple tissues and organs have associated microbiomes,

including the TME itself, which affects, both positively and negatively, the acquisition of hallmark capabilities[13]. Furthermore, a correlation has been established between the presence of intratumor bacteria and response to immunotherapy as well as survival rates[62].

Tumor Microenvironment

The TME is both a cause and a consequence of tumorigenesis, critical to its initiation and maintenance[63]. The TME is impacted on a molecular and cellular level through interactions between cancer cells, host structural cells and adaptive and innate immune cells, which promotes cancer progression and induces many hallmark capabilities[12]. It is comprised of a complex network that includes cancer cells, cancer stem cells, structural cells, such as endothelial cells and pericytes, fibroblasts, blood vessels, endothelial cell precursors, immune cells and secreted factors, such as cytokines[63; 64]. Inflammatory and immune cells infiltrated within the TME include cytotoxic T lymphocytes (CTLs), B lymphocytes, natural killer cells (NK), macrophages, neutrophils and dendritic cells (DC)[60]. They release signaling molecules that, due to immunoediting, serve as effectors of their tumor-promoting actions, such as tumor growth factors (epithelial growth factor - EGF), angiogenic growth factors (VEGF), cytokines that amplify the inflammatory state and matrix-degrading enzymes[12]. Considering the TME's role in cancer progression, its manipulation could be used as an approach to treat and prevent cancer.

1.3. Cancer Immunology

Neoplastic cells rely on the diversity of normal resident and recruited accessory cells to support their evolution, including a prominent presence of diverse assemblages of immune cells recruited to the TME due to inflammation. These are referred to as "hot" tumors[67]. These immune infiltrates are co-opted into sustaining tumor proliferation, regulating the immune response and suppressing surveillance functions[67]. These immune aggregates comprise cells of both myeloid and lymphoid lineages:

- Myeloid cells include macrophages, DCs, mast cells, monocytes and granulocytes and have multiple homeostatic functions that are co-opted by evolving neoplasms[67]. Due to their functional plasticity, their activity can be altered in response to environmental signals which dictate antigen degradation/presentation, tissue repair/inflammation and protective/non-protective T-cell immunity[68];
- The lymphoid compartment in tumors includes NK cells, NK T cells, $CD4^+$ T cells, $CD8^+$ T cells and B cells. These cells can release different types of cytokines based on their effector function. These cytokines can either promote cytotoxic activity, facilitate antigen processing and expression, or trigger T cell anergy leading to a decrease in T-cell-mediated cytotoxicity[67; 69; 70].

Despite contributing to cancer progression, it is important to recognize that immune cells also play a crucial role in identifying and targeting cancer cells. While it may seem contradictory, immune cells possess a vital surveillance function that allows them to detect and respond to abnormal cells within the body, including cancerous ones. Indeed, during carcinogenesis, cells of the innate immunity, such as NK cells, recognize non-specific alterations in endogenous cells and unleash a broad response[71]. Due to the widespread expression of the recognition molecules used by the innate system in a large number of cells, this system is poised to act rapidly and thus constitutes the initial host response[72]. If this primary response is unsuccessful in eliminating the cancer cell, the adaptive immune system is induced. The adaptive response is characterized by its ability to manifest immune memory, thus prominently contributing to a more effective host response when antigens are encountered a second time, even decades following the initial encounter[72]. The main features of innate and adaptive immunity are compared in Table I.

Table 1 - Main features of Innate and Adaptive Immunity. Adapted from Moyano et al. 2019[73].

	Innate	Adaptive
Speed of Onset	+	-
Regulation	±	+
Potency	±	+
Duration	-	+
Memory Function	-	+
Activity	Always Present	Normally Silent
Specificity	-	+

+ (Favorable); - (Unfavorable); ± (Intermediate)

The adaptive immune system stimulation requires the activation of T and B cells with unique proteins synthesized by cancer cells, named antigens. Antigens are classified as tumor-associated antigens (TAA) or tumor-specific antigens (TSA)[74] (Figure 5). TAA are encoded by normal cellular genes that, in tumors, undergo dysregulation, resulting in increased expression in cancer cells[74; 75]. In contrast, TSA are highly immunogenic non-self antigens whose expression is restricted to tumor cells[75].

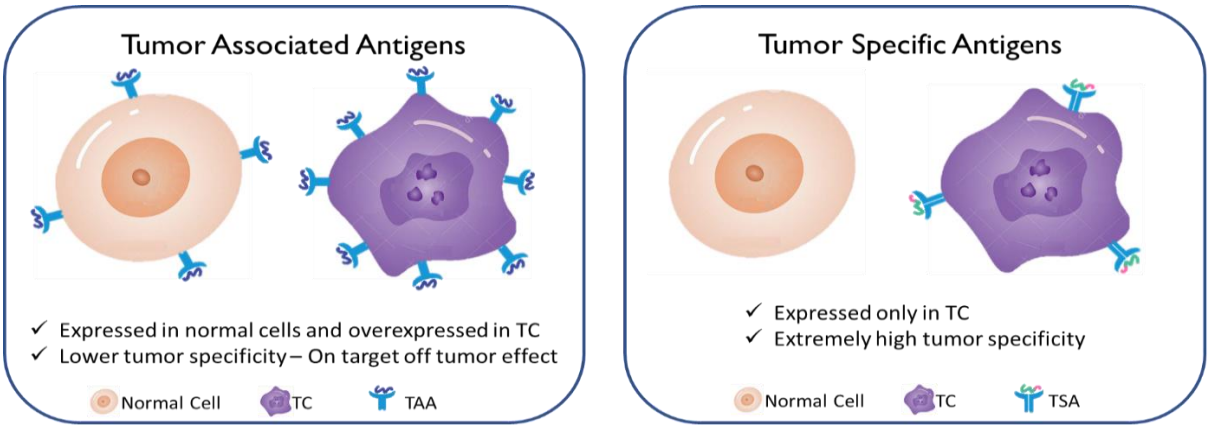


Figure 5 - Tumor Associated Antigens and Tumor Specific Antigens. Abbreviations are as follows: TC – Tumor Cell; TAA – Tumor Associated Antigen; TSA – Tumor Specific Antigen.

The exceptional specificity to the target antigen is due to the presence of antigen-specific receptors expressed on the surface of T cells, known as the T cell receptor (TCR), and B cells, known as the B cell antigen receptor[72], represented in Figure 6A and B, respectively.

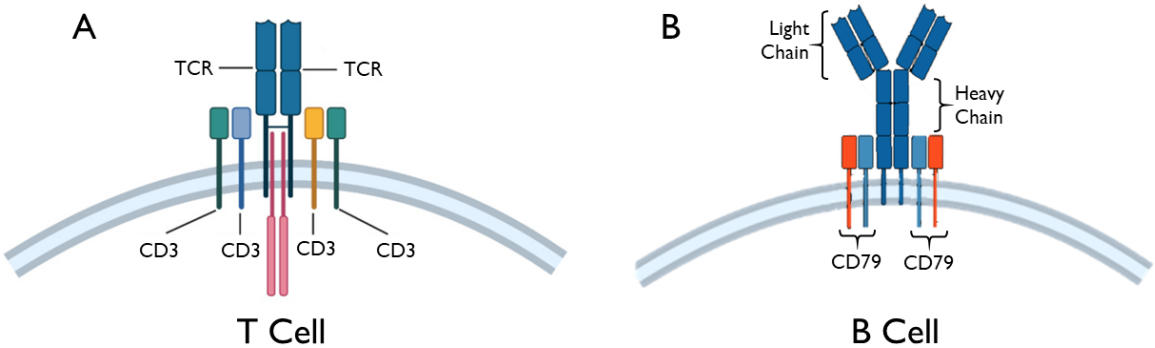


Figure 6 - Structure of T and B cell receptors. Representation of the **A** | T cell receptor, a protein complex, and the **B** | B cell receptor, a membrane-bound immunoglobulin. Abbreviation is as follows: TCR – T Cell Receptor. Adapted from Sun et al. 2021[76].

The TCR plays a crucial role in stimulating T cell-mediated immune responses. However, since it can only identify peptide fragments of antigens, protein antigens must be processed by antigen-presenting cells (APC) before they can be recognized[72; 77]. This processing step is essential for T cell activation and for an effective immune response to be initiated[72; 77]. Contrariwise, B cell receptors can recognize soluble or cell-bound antigens without prior modifications, including proteins in their native or denatured conformations, simple chemical groups, lipids, carbohydrates, nucleic acids and other molecules[77]. However, B cell action cannot go much further than antigen recognition without the role of helper T cells, crucial for establishing B cell-mediated responses[77].

Professional APCs, such as DCs, B cells and macrophages, are the only ones capable of inducing complete T cell activation[78; 79]. Dendritic cells are the most efficient APC due to their ability to attract and activate naïve $CD4^+$ and $CD8^+$ T cells, thereby playing a crucial role in inducing antigen-specific immune responses[67]. DCs present antigen fragments to T cells complexed to the major histocompatibility complex (MHC) surface molecule[72; 77]. These glycoproteins bind and display peptides derived from antigens expressed in intracellular compartments to cytotoxic $CD8^+$ T cells via MHC class I molecules (Figure 7A)[80; 81]. On the other hand, peptides derived from extracellular sources are presented by APCs to $CD4^+$ T cells via MHC class II molecules (Figure 7B)[80; 81]. Upon activation, $CD8^+$ T cells assume the role of CTLs that induce cell death upon target recognition[77]. In contrast, when naïve $CD4^+$ T are activated, they differentiate into helper T cells that secrete cytokines, which help to activate B cells, macrophages and cytotoxic $CD8^+$ T cells[77; 82].

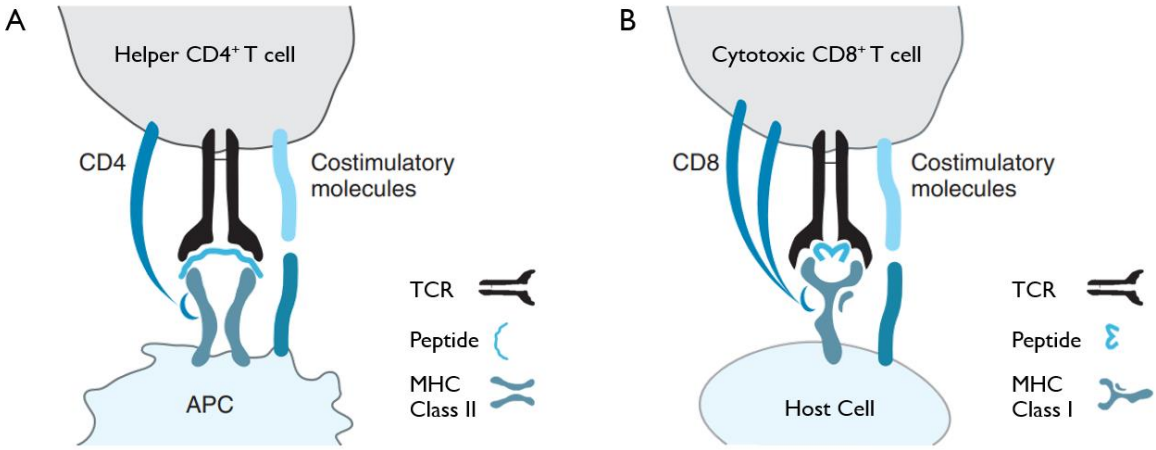


Figure 7 - Peptide presentation to T cells. A | The TCR on a helper CD4+ T cell binds to the peptide associated with an MHC class II molecule on the surface of an APC. Th cells also express the CD4 coreceptor that binds to MHC class II. **B** | The TCR on a cytotoxic $CD8^+$ T cell recognizes the peptide associated with an MHC class I molecule on the surface of any nucleated host cell. Cytotoxic T cells also express the CD8 coreceptor that binds to MHC class I. The activation of both helper and cytotoxic T cells depends not only on TCR engagement by the peptide-MHC complex, but also on the engagement of co-stimulatory molecules. Abbreviations are as follows: APC – Antigen Presenting Cell; TCR – T Cell Receptor; MHC – Major Histocompatibility Complex. Adapted from Mak et al. 2006[77].

Figure 8 depicts the process for a complete T cell activation, where three signals must be provided:

I. Signal 1: Binding of Peptide–MHC to the TCR

The binding of the peptide-MHC complex to the TCR (Figure 8) is vital but, in itself, inefficient in triggering T cell activation. TCR signaling depends greatly on the action of adhesion molecules that hold the T cell and the APC together since transient TCR engagement could lead to T cell anergy rather than activation[83].

II. Signal 2: Co-stimulatory Molecules

Complete T cell activation requires co-stimulatory contacts in addition to antigen binding to the TCR. These include engagement with CD28, CD27, CD40, OX40, among many others.

The most crucial co-stimulatory interaction occurs between the CD28 receptor on T cells and the B7 ligands on the APC[84] (Figure 8). CD28 binds with moderate affinity two cell surface ligands, B7-1 (CD80) and B7-2 (CD86), which are extensively upregulated on APCs in response to TRC engagement[84]. Signaling through CD28 sustains the survival of T cells whose TCRs are engaged by peptide-MHC and contributes to the production of IL-2, which stimulates the proliferation and differentiation of naïve T cells. Additionally, other co-stimulatory and regulatory molecules, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), are also dependent on TCR signaling[84]. Contrarily, in the absence of CD28 co-stimulation, the binding of the peptide-MHC to the TCR often induces apoptosis or anergy[83].

III. Signal 3: Cytokine Secretion

The last step in triggering complete T cell activation consists of the transcription of genes required for T cell proliferation and differentiation[84]. These include expression on IL-2 and various other cytokines (such as interleukins (IL) 3, 4, 5, 12 and interferon (IFN)), chemokines and growth factors that bind to receptors upregulated on the activated T cell[84]. This enables the initiation of a complex signaling cascade that allows naïve $CD8^+$ T cell activation, forming cytotoxic T lymphocytes.

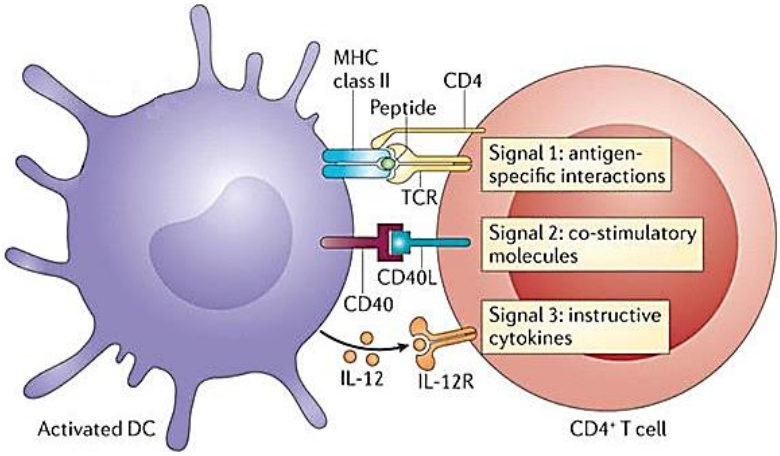


Figure 8 - Molecular mechanisms for T cell activation. Representation of the three signals required for T cell activation and expansion. Signal 1 involves antigen presentation by interaction between the peptide-MHC complex and the TCR. Signal 2 comprises the co-stimulation through interaction with stimulatory molecules. Signal 3 includes the release of cytokines, crucial for T cell expansion and differentiation. Abbreviations are as follows: DC – Dendritic Cell; MHC – Major Histocompatibility Complex; TCR – T Cell Receptor; IL – Interleukin; IL-12R – Interleukin 12 Receptor. Adapted from Kambayashi et al. 2014[85].

The process that describes how the immune system can effectively eliminate cancer cells is called the cancer-immunity cycle[86], and it is schematized in Figure 9. This cycle starts with the release of neoantigens created by oncogenesis, which are then captured by DCs for processing (step 1). Subsequently, DCs present the captured antigens to T cells (step 2), resulting in the priming and activation of effector T cell responses against the cancer-specific antigens (step 3). Finally, the activated effector T cells migrate to (step 4) and infiltrate the tumor (step 5), where they recognize and bind to cancer cells (step 6) and eliminate them (step 7). The killing of tumor cells either via immune mechanisms or anti-cancer therapy releases additional tumor-associated antigens (step 1), thereby initiating the restart of the cycle[67].

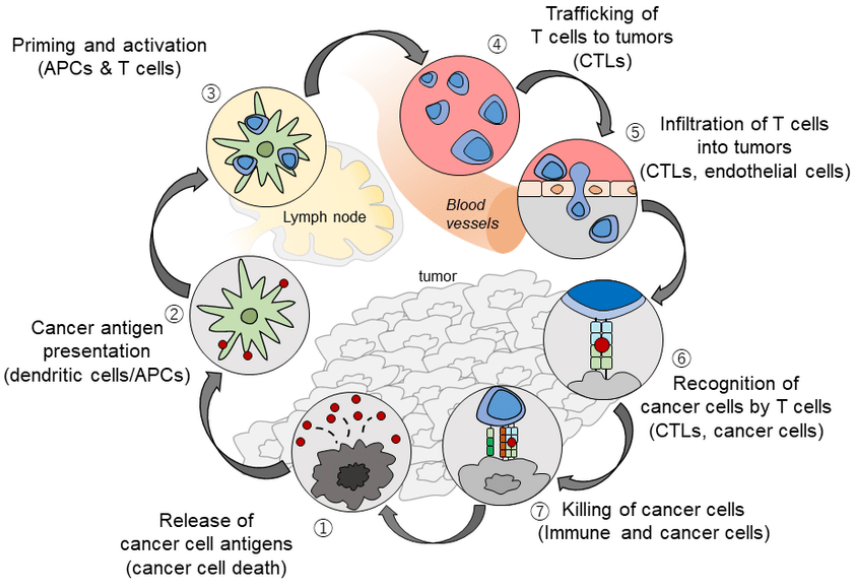


Figure 9 - The Cancer-Immunity Cycle. The generation of immunity to cancer is a cyclic process that can be self-propagating, leading to an accumulation of immune-stimulatory factors that, in principle, should amplify and broaden T cell responses. The cycle is also characterized by inhibitory factors that lead to immune regulatory feedback mechanisms, which can halt the development or limit immunity. This cycle can be divided into seven major steps, starting with the release of antigens from the cancer cell and ending with the elimination of cancer cells. Adapted from Kudo 2020[91].

In cancer patients, the cancer-immunity cycle does not perform optimally. This is primarily due to the ability of cancer cells to create immune-suppressive networks at each stage of the cancer-immunity cycle[86; 87]. To this end, tumor antigens might go undetected, as DCs and T cells could recognize these antigens as self rather than foreign, leading to the development of T regulatory cell responses instead of effector responses. Moreover, T cells may encounter obstacles in effectively homing to tumor sites due to inhibited infiltration, and even if they do reach the tumor, their effector function can be suppressed by certain factors present in the TME. For example, tumor cells can suppress the immune response by tuning down stimulatory signaling (e.g., downregulating MHC-I) and/or upregulating the activity of inhibitory immunoreceptors (e.g., Programmed Death-1 (PD-1))[88; 89; 90]. These factors collectively contribute to the complex dynamics that can limit the efficacy of immune responses against tumors. Some of the major players in this regulatory process are the immune checkpoints, myeloid-derived suppressor cells (MDSC) and T_{Reg} cells.

IC refer to a plethora of inhibitory pathways of the immune system that play a crucial role in ensuring self-tolerance as well as modulating the duration and amplitude of physiological immune responses in order to minimize collateral tissue damage. While IC plays an essential role in preventing autoimmunity and maintaining immune homeostasis, cancer cells can use these checkpoints to evade the immune system's attack. The most studied ICs in cancer include CTLA-4, PD-1 and lymphocyte activation gene 3 (LAG-3).

CTLA-4 is an inhibitory molecule homologous to CD28, expressed in T_{Reg} and activated T cells[67] (Figure 10A). While the binding of B7 ligands to CD28 promotes T cell activation, their binding to CTLA-4 downregulates T cell activation[67; 84]. Although resembling CD28 in structure, CTLA-4 binds the B7 ligands with much higher affinity than CD28, causing B7 displacement from CD28, thus mediating immunosuppression by disrupting co-stimulatory signaling[84; 92]. CTLA-4 is, therefore, an essential component for maintaining homeostasis, helping to "deactivate" effector cells and control their numbers. While CTLA-4 serves as an essential regulator of immune responses, excessive or prolonged CTLA-4 signaling can dampen the immune system's ability to recognize and eliminate cancer cells. This can hinder the natural anti-tumor immune responses and promote tumor growth.

PD-1 operates on the regulation of previously activated T cells once an immune response has been established[84; 92]. PD-1 binds two ligands, Programmed Death Ligand-1 (PD-L1) and Programmed Death Ligand-2 (PD-L2) (Figure 10B). PD-1–PD-L1/PD-L2 interaction inhibits T lymphocyte proliferation, survival and effector functions, induces apoptosis of tumor-specific T cells and promotes the differentiation of $CD4^+$ T cells into T_{Reg} cells. Furthermore,

it enables tumor cell resistance to CTL attack. Summarily, the interaction negatively regulates T-cell activation when engaged with an APC and/or effector function when engaged with other PD-L1 positive cells[67; 84].

Finally, LAG-3 exerts multiple biological activities over T cell activation and effector functions, and is upregulated in activated, cytokine-expressing T cells[93; 94]. LAG-3 associates with the TCR-CD3 complex at the T cell membrane (Figure 10C) and negatively regulates TCR signal transduction, resulting in cell proliferation and cytokine secretion inhibition[95]. LAG-3 expression is frequently associated with exhausted T cells, which often occur in response to repetitive antigen stimulation in cancer and chronic viral infections[93; 96].

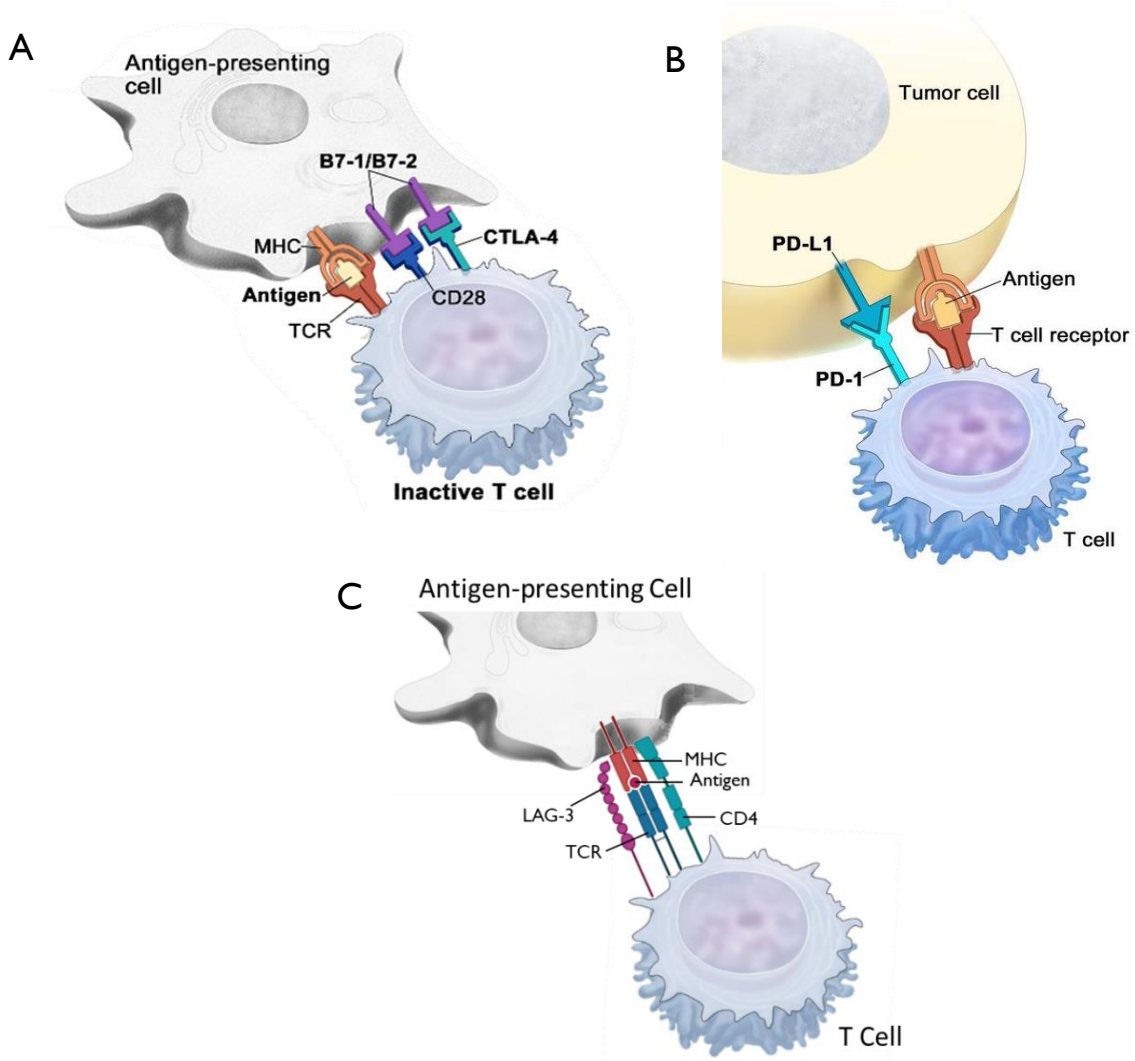


Figure 10 - CTLA-4, PD-1 and LAG-3 mediated immunosuppression. A | Representation of CTLA-4 interaction with B7 ligands. CTLA-4 mediates immunosuppression by indirectly diminishing signaling through the co-stimulatory receptor CD28. Although both receptors bind CD80 and CD89, CTLA-4 does so with much higher affinity, effectively outcompeting CD28. By limiting CD28-mediated signaling during antigen presentation, CTLA-4 increases the activation threshold for T cell activation, reducing immune responses to weak antigens such as self and tumor antigens. **B |** Representation of the PD-1-PD-L1 that controls the induction and maintenance of immune tolerance within the TME by inhibiting T cell activation, proliferation, survival and effector functions (cytotoxicity and cytokine release). **C |** Representation of the LAG-3 interaction with peptide-MHC-II complex (expressed by tumor cells and APCs). This interaction triggers inhibitory signaling that suppresses T-cell function. Abbreviations are as follows: MHC – Major Histocompatibility Complex; TCR – T Cell Receptor; CTLA-4 – Cytotoxic T Lymphocyte Associated Protein 4; PD-1 – Programmed Death 1; PD-L1 – Programmed Death Ligand 1; LAG-3 – Lymphocyte Activation Gene 3. Adapted from National Cancer Institute[97,98].

Immune suppression is induced not only by IC but also by MDSC and T_{Reg} cells.

During cancer progression or states of chronic inflammation, myeloid cells are reprogrammed into MDSC by factors in the TME (e.g., cytokines and growth factors), which play a crucial role in suppressing anti-tumor immunity and promoting tumor growth[99]. MDSC exert their immunosuppressive role mainly through the inhibition of T cell functions by engaging their inhibitor receptors[99]. In addition, in the TME, MDSC can induce upregulation of checkpoint molecules, produce reactive oxygen species, that decrease T cell proliferation, and activate other immunosuppressive cells, such as T_{Reg} cells via IL-10 secretion[99].

T_{Reg} cells are a $CD4^+$ T cell subset and the primary mediators of peripheral tolerance, exhibiting a diverse TCR repertoire that specifically recognizes self-antigens[100]. When exposed to inflammatory conditions, T_{Reg} cells acquire strongly enhanced suppressive functions. From a functional perspective, the suppression mechanisms used by T_{Reg} cells can be grouped into four basic modes of action[100], depicted in Figure 11:

i. Suppression by inhibitory cytokines;
ii. Suppression by cytolysis;
iii. Suppression by metabolic disruption;
iv. Suppression by modulation of dendritic-cell maturation/function.

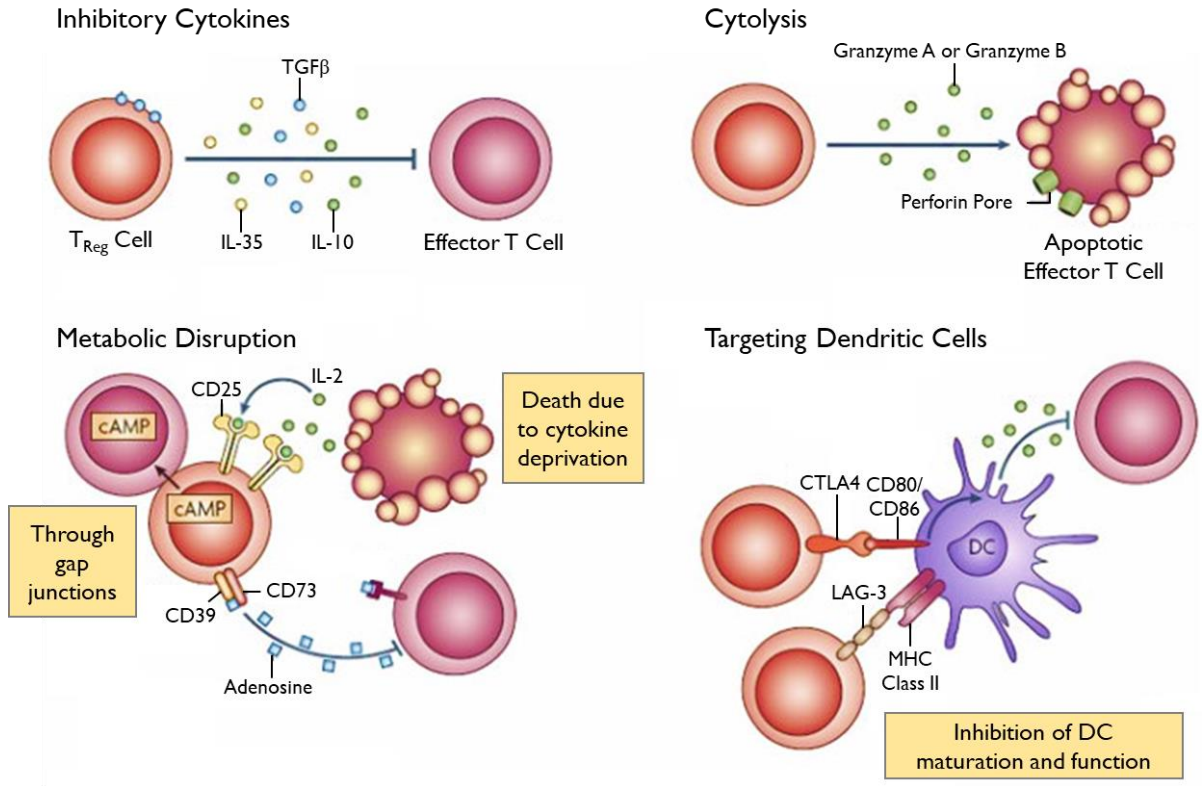


Figure 11 - Basic suppressive mechanisms used by T_{Reg} cells. T_{Reg} cell regulatory mechanisms are centered around four basic modes of action: **A** | The action of inhibitory cytokines (IL-10, IL-35 and TGF-β); **B** | Cytolysis through granzyme-dependent killing mechanism; **C** | Metabolic disruption through, among others, high-affinity CD25 (IL-2 receptor)-dependent cytokine-deprivation-mediated apoptosis; **D** | Targeting DC maturation and/or function. Adapted from Vignali et al. 2008[100].

T_{Reg} cells can play their immunosuppressive role by releasing inhibitory cytokines such as IL-10, IL-35 and TGFβ[100] (Figure 11A) or by inducing cytolysis of CTLs, NK cells and $CD4^+$ T cells through granzyme secretion (Figure 11B)[100]. Additionally, metabolic effects are also employed by T_{Reg} to inhibit the immune response. This mechanism involves competition for IL-2, which possesses a higher affinity towards T_{Reg} cells[101]. Thus, by limiting the IL-2 levels, T_{Reg} cells thwart the stimulation of T effector cells in the periphery, triggering metabolic disturbance and culminating in cellular apoptosis (Figure 11C)[102]. Finally, the functional state of DC is also a key regulator of T cell activation and tolerance, which can be modulated through T_{Reg} interaction with the APC[103]. Such interaction may alter the maturation state and function of DCs by blocking their co-stimulatory ability required for T cell activation (Figure 11D)[102]. Additionally, it induces suppression of protein synthesis, resulting in cell cycle arrest and inactivity or anergy of T effector cells. Together these processes further suppress DC maturation and their antigen-presenting/immunostimulatory ability (Figure 12).

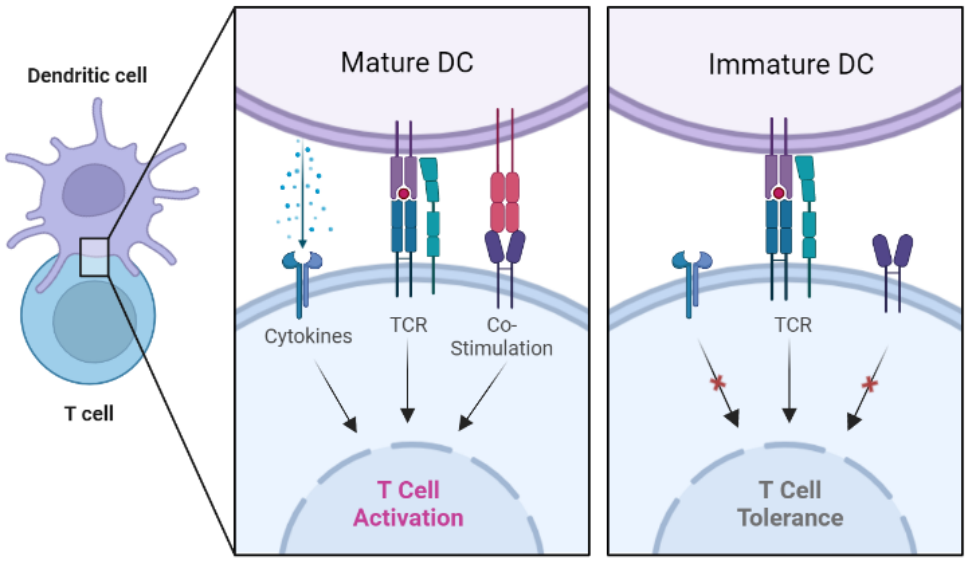


Figure 12 - Influence of the DC maturation status on T cell activation and tolerance. Mature DCs provide T cells with signals through the TCR, co-stimulatory receptors and cytokines, which then result in T cell activation. Immature DCs, however, are able to only deliver signals through the TCR, which leads to T cell tolerance. It is, thus, used by T_{Reg} cells as an immunoregulatory mechanism. Created in BioRender.com.

Chapter II - Diving into Immunotherapy as a Cancer Treatment Modality

2.1. Cancer Treatment Modalities

Cancer treatment aims to cure, prolong, and improve the quality of life of patients. Throughout history, cancer treatment has often been associated with limited efficacy, as well as extensive side effects.. Currently, over half of the ongoing clinical trials are focusing on cancer treatments, which have led to the discovery of potentially curative modalities for several types of cancer[104].

The most common conventional cancer treatment strategies include surgical resection of the tumors followed by radiotherapy and/or chemotherapy[105]. It is one of the most effective treatments in early-stage solid tumor cancers. However, specific treatment varies with the type of cancer, the extent of the disease, its progression rate, the condition of the patient, and the response to therapy.

Chemotherapy was originally developed to treat infectious diseases, and its potential use in cancer treatment wasn't discovered until the 1930s. In 1943, the first chemotherapy agent, nitrogen mustard, was successfully used to treat lymphoma[105]. Since then, numerous chemotherapeutic agents have been discovered, leading to a current count of over 130 Food and Drug Administration (FDA)-approved chemotherapy drugs[106].

Chemotherapy is a commonly used treatment for cancer, either on its own or in combination with other therapies[104]. These drugs target specific stages of the cell cycle and are particularly effective against rapidly dividing cells, such as cancer cells. By causing DNA damage, mainly through the production of reactive oxygen species, chemotherapy agents can halt tumor growth, preventing cell division and promoting apoptosis[107]. Moreover, evidence has shown that the anti-tumor activity of chemotherapy also relies on several off-target effects that stimulate the host immune system, cooperating for successful tumor eradication[108]. Among these mechanisms are the following[108; 109]:

- Trigger immunogenic cell death;
- Reduction of the production of immunosuppressive factors;
- Increase of the antigenicity of cancer cells;
- Decrease in the number of immunosuppressive cells, such as T_{Reg} cells;

- Increase antigen processing and presentation.

Although this therapy has demonstrated effectiveness in certain types of cancer, such as lymphoma, its success in achieving a cure may be limited in other types, such as carcinoma, mainly due to resistance to therapy[110]. Acquired drug resistance is a major obstacle to chemotherapy treatment, which may be developed through several mechanisms, such as inactivation of the drug, cell death inhibition, altering drug metabolism, epigenetic changes and mutations in the chemotherapeutic targets[111]. Furthermore, cells' DNA repair mechanisms may be enhanced to repair damage caused by cytotoxic chemotherapy, and gene amplification may occur, leading to an overproduction of the target protein[111]. Additionally, while chemotherapy has higher efficacy on cancer cells, they also act against healthy cells that either possess higher mitotic rates than normal cells, such as hair follicles and bone marrow precursor cells, or cells undergoing division at the time of treatment[112; 113]. Thus, chemotherapy treatment is limited by the associated toxicity, which leads to a variety of side effects, namely alopecia, nausea, fatigue, vomiting and neurotoxicity[112]. Furthermore, patients may become immunocompromised and potentially develop serious infections[106].

Radiotherapy is another conventional modality that holds a significant part in treatment plans and remains an important curative treatment modality for uncomplicated locoregional tumors[114]. This approach uses ionizing radiation that either directly kills cancer cells or genetically alters them so that the damaged DNA is unable to replicate, which results in apoptosis[106]. In addition, radiotherapy holds several synergistic effects on immune pathways that improve the control of distant systemic diseases[115]. Some of these include[115]:

- Generation of DC maturation stimuli required for T-lymphocyte activation;
- Upregulation of proteins necessary for the effection of a T cell-mediated response (e.g., MHC Class 1);
- Increase of the expression of death receptors on tumor cells (e.g., Fas).

The efficacy of radiotherapy in treating cancer has improved with advancements in technology and a better understanding of tumor biology, achieving significant overall survival rates in some head and neck cancers[114]. There are still several concerns associated with this cancer treatment approach. Firstly, despite being a local treatment, radiotherapy also damages the healthy surrounding cells, organs, and tissues[104]. Thus, radiotherapy is limited by the maximum tolerated dose by the adjacent normal tissues due to off-target effects. Indeed, DNA damage affecting cell cycle signaling and tumor suppressor genes can promote malignant transformation and subsequent malignancies years after radiotherapy treatment[116].

Additionally, intrinsic or acquired resistance can render many tumor types insensitive to radiotherapy, resulting in treatment failure or cancer recurrence shortly after therapy[114].

The limited efficacy and significant side effects associated with traditional cancer treatment methods emphasize the need for innovative cancer treatments that can provide potent anti-tumor effects in a targeted and safe manner. Furthermore, since chemotherapy and radiotherapy can induce secondary immune-mediated antineoplastic effects, combining them with immunotherapy, has shown great potential in counteracting local immunosuppressive mechanisms responsible for immune evasion[115]. Such combination have the potential to stimulate, expand, and enhance antitumor immune responses and may prove to be highly beneficial[115].

Conventional cancer treatments have been used for decades to treat cancer patients. However, the emergence of novel fields of cancer research has led to a renewed interest in developing innovative approaches that can overcome the challenges associated with conventional treatments. This is the case of immunotherapy, which will be thoroughly explored in the present chapter.

2.2. The Basis of Immunotherapy

Immunotherapy represents an innovative approach to cancer treatment that harnesses the power of the immune system to identify, attack and destroy cancer cells[117]. Unlike traditional therapies that directly target tumor cells, immunotherapy seeks to stimulate and enhance different elements of the immune system to engage in specific phases of the immune response and modulate natural defenses against cancer cells[118].

Cancer immunotherapy is based on two mechanisms of action: passive and active immunotherapy. Passive immunotherapy involves administering monoclonal antibodies (mAbs), cytokines, or *ex vivo* activated cells to enhance the body's natural anti-cancer defenses[119]. On the other hand, active immunotherapy relies on the host's ability to elicit an anti-tumor T-cell-mediated immune response through vaccination strategies, antibodies that target critical T-cell activation checkpoints, and oncolytic viruses[118; 119].

The effectiveness of immunotherapy relies on its ability to produce sustainable T-cell responses that can overcome the various immune evasion mechanisms utilized by tumors[120]. The success of anti-cancer immunotherapy depends on multiple factors, such as the patient's immune system, genetics, the type of cancer, tumor characteristics (e.g. immunogenicity and heterogenicity), the expression of certain biomarkers (e.g. PD-1), as well as the development of resistance to therapy[121]. Additionally, tumor immune characteristics can impact the effectiveness of immunotherapy, mainly the presence of immune aggregates on immune inflammatory tumors, which correlate with high response rates to immunotherapy[122]. Besides, the composition of the TME, such as the number of immune cells, as well as the acidic and hypoxic conditions, promote tumor growth and inhibit T-cell activation and toxicity[123]. The gut microbiome has also been shown to affect not only the incidence of cancer but also the sensitivity to immunotherapy, resulting from higher numbers of $CD4^+$ and $CD8^+$ cells[124]. Finally, higher tumor mutational burdens promote the release of neoantigens which trigger T-cell responses and induce greater responsiveness to immune therapy[125].

2.2.1. The Evolution of Immunotherapy

Immunotherapy is often perceived as a relatively recent advance in medicine when, in fact, from Ancient Egypt to the early XVIII century, there are multiple reports of tumors disappearing after patients suffered infections with associated febrile episodes[126]. The historical highlights that contributed to the immuno-oncology field are described below and represented in Figure 13.

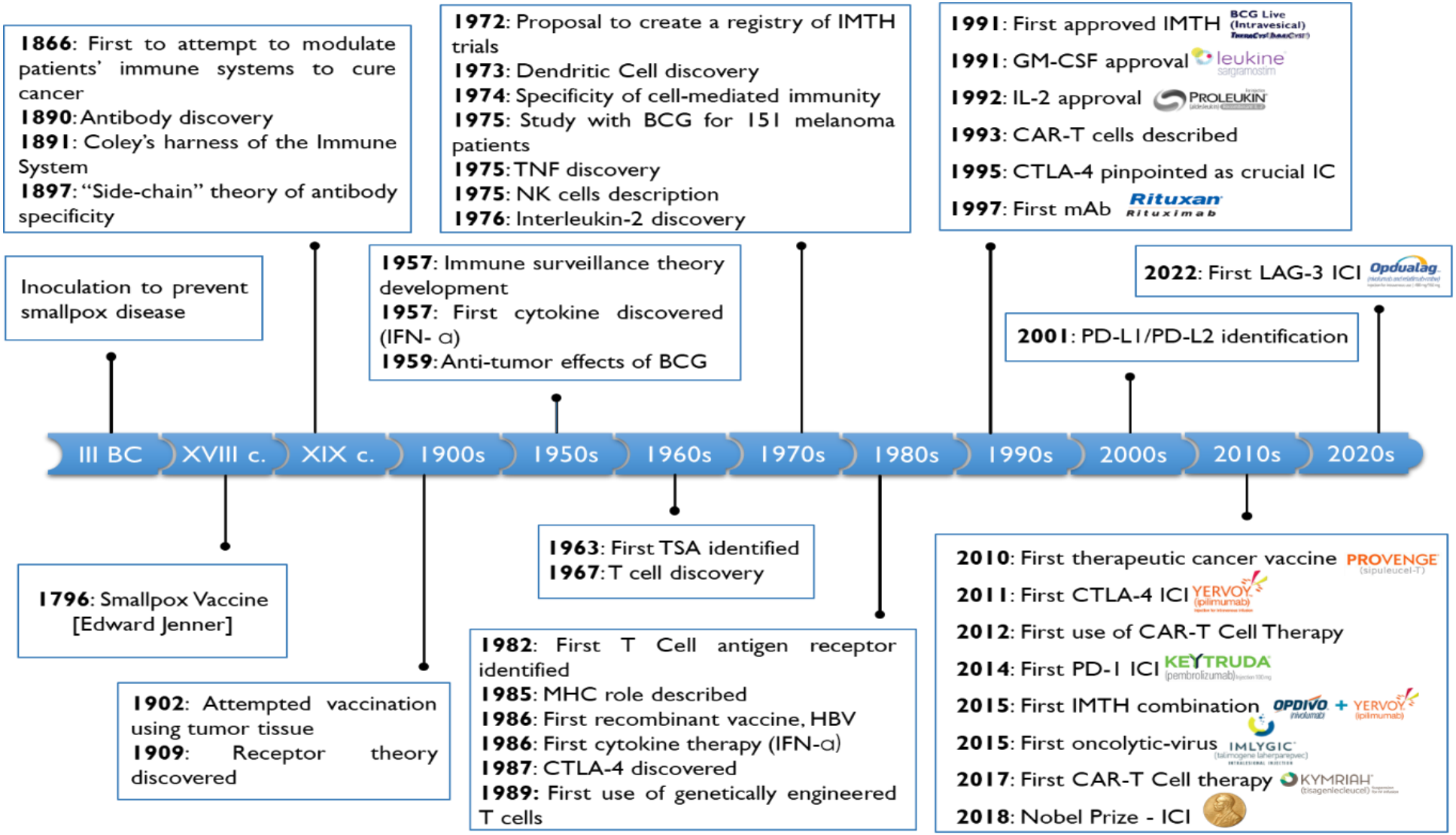


Figure 13 - Historical Timeline of the Major Highlights in Cancer Immunotherapy. Abbreviations are as follows: BCG - Bacillus Calmette–Guérin; TSA – Tumor Specific Antigen; IMTH – Immunotherapy; MHC – Major Histocompatibility Complex; HBV – Hepatitis B Virus; IFN – Interferon; GM-CSF - Granulocyte-Macrophage Colony-Stimulating Factor; IL – Interleukin; mAb – Monoclonal Antibody; ICI – Immune Checkpoint Inhibitor.

The first attempts to modulate patients' immune systems to cure cancer occurred after the German physicians Busch and Fehleisen independently noticed tumor regression after erysipelas infection[127]. In 1868, Busch became the first to intentionally infect a cancer patient with erysipelas, and he observed a shrinkage of the malignancy. Fehleisen repeated the experiment in 1882 and, eventually, identified the bacteria responsible for causing erysipelas[126]. Then, in 1891, William B. Coley, known as the Father of Immunotherapy, developed important work in the treatment of patients with inoperable cancers, such as sarcoma, lymphoma, and testicular carcinoma, through the administration of heat-inactivated bacteria[128]. Remarkably, Coley reported a substantial number of durable complete remissions, marking a significant milestone in the history of cancer immunotherapy[129]. The administered cocktail of bacteria became known as "Coley's toxin" and became the first documented active cancer immunotherapy intervention, commercially available since 1899[130]. However, oncologists' skepticism regarding the unknown mechanism of actions of Coley's toxin and the risks of deliberately infecting cancer patients with pathogenic bacteria limited its use in clinical practice[131]. Later, in 1902, Blumenthal and E. von Leyden first attempted to vaccinate patients against cancer using tumor tissue derived from the patients themselves. However, this approach did not yield significant tumor reduction[127; 132]. More than half a century later, in 1959, Old and his team conducted a study that demonstrated the anti-tumor effect of Bacillus Calmette–Guérin (BCG) bacteria in mice models with bladder cancer[133]. This study was the first direct evidence of the immune system's ability to prevent cancer. In 1976, Morales conducted an experiment to examine the effect of BCG, used as a tuberculosis vaccine, to prevent the recurrence of bladder cancer, which achieved promising results[134].

The immuno-oncology field was historically marked by several achievements in immunology, such as the discovery of the antibody (Paul Ehrlich, Emil von Behring and Kitasato Shibasaburo, 1890)[127; 135], the development of the "Side-chain" theory of antibody specificity[136], the receptor-ligand theory (Ehrlich, 1909)[136] and the immune surveillance theory (Lewis Thomas and Sir Frank Burnet, 1957[135]). It is also important to highlight the discovery of the first cytokine, IFN-α (1957)[137], the identification of T cells and enlightenment of their crucial role in immunity (Jacques Miller, 1967)[128; 138], the discovery of dendritic cells (Steinman, 1973)[139], the publishment of the first report regarding the high specificity of cell-mediated immunity (Doherty and Zinkernagel, 1974)[140] and the discovery of NK cells (Klein, 1975)[141]. Additionally, in 1975, Milstein and Köhler pioneered the production of mAbs in the laboratory using hybridomas[142]. In the same year, tumor necrosis factor was discovered and identified as the first immune molecule with anti-cancer properties[143]. In 1976, the T cell growth factor,

later named IL-2, was discovered, which allowed the culture of T cells[144]. Later, in 1982, the T cell antigen receptor was identified[128], and in 1985, the functional role of MHC in the immune response was described. In the forthcoming years, the first immune checkpoint molecule, CTLA-4, was discovered (Burnet, 1987)[145], and the genetically engineered T cells that targeted cancer cells - chimeric antigen receptor (CAR) T cells (1989) were described[146]. In the 1990s, the immune molecule granulocyte macrophage-colony stimulating factor (GM-CSF) was discovered to strengthen immunity against tumors[127], the first CTLA-4 blocking antibody was developed[147], and PD-1 was identified as a crucial checkpoint molecule[148].

In 1972, the US National Cancer Institute made a significant recommendation to establish an international registry of immunotherapy trials[127]. This recommendation not only demonstrated the groundbreaking progress and potential of this novel cancer therapy but also settled the debate surrounding its use in oncology. Subsequently, several notable achievements emerged, leading to remarkable breakthroughs and instilling hope in cancer patients worldwide. One of the pivotal milestones that paved the way for significant advancements was the commercialization of anti-tumor cytokines[149]. The first immunotherapy agent approved by the FDA was the anti-tumor cytokine IFN-α (Intron A®, Schering) in 1986[149]. In 1991, the FDA approved a new type of immunotherapy: a BCG vaccine against bladder cancer. The following year, IL-2 (Proleukin®, Chiron) became the second anti-tumor cytokine approved by the FDA[150]. Later, in 1997, the FDA approved the first mAb for the treatment of cancer, rituximab (Rituxan®, Genentech Inc.)[151].

The first decade of the XXI century was also marked by many achievements in cancer immunotherapy: the first ipilimumab clinical trial, an anti-CTLA-4 mAb (2000)[127], the identification of the PD-1 ligands (PD-L1, 2000[152] and PD-L2, 2001[153]) and the first clinical trial using an anti-PD-1 mAb (2008)[127]. In 2010, the FDA approved sipuleucel-T (Provenge®, Dendreon Pharmaceuticals LLC), a cancer vaccine for metastatic hormone-refractory prostate cancer[154]. In the subsequent year, ipilimumab (Yervoy®, Bristol-Myers Squibb) became the first immune checkpoint inhibitor (ICI) to be approved by the FDA[155]. In 2012, the first child with leukemia was treated with CAR-T cell Therapy[127]. During the following years, many products were approved, including the first anti-PD-1 mAb, pembrolizumab (Keytruda®, 2014)[156], the anti-PD-1 mAb nivolumab (Opdivo®, Bristol-Myers Squibb, 2014)[157], the first OV, Imlygic® (Amgen Inc., 2015)[158] and the CAR-T cell therapy, Kymriah® (Novartis Pharmaceutical Corporation, 2017)[159]. In 2018, James P. Allison and Tasuku Honjo received a Nobel prize for their pioneering work with immune checkpoints, establishing that these pathways act as "brakes" on the immune system[160]. Finally, in 2022, the FDA approved Opdualag® (Bristol-

Myers Squibb), a combination therapy used to treat melanoma that contains nivolumab, an anti-PD-1 mAb and relatlimab, an anti-LAG-3 mAb[161].

Today, more than a century after the first steps in the modulation of the immune system to treat cancer, immunotherapy has dramatically transformed survival and quality of life for oncology patients. However, despite encouraging advances in the last decades, the application of immunotherapy in oncology is still in its relative infancy, with numerous limitations and hurdles yet to be overcome, mainly in terms of efficacy and safety, which will be discussed throughout this chapter[162].

2.3. Immunotherapy Strategies for Cancer Treatment

In the past years, several immunotherapies have achieved promising results in cancer therapy, some of which have led to the approval of several products. These include ICIs, CAR-T cells, mAbs, cytokines, cancer vaccines and oncolytic viruses[121; 163; 164]. Moreover, despite the absence of currently approved products for NK cell therapy, this approach has been attracting considerable attention within the research and medical communities[124; 165]. Each of the previously mentioned therapeutic modalities, which are represented in Figure 14, will be described in the following subsections.

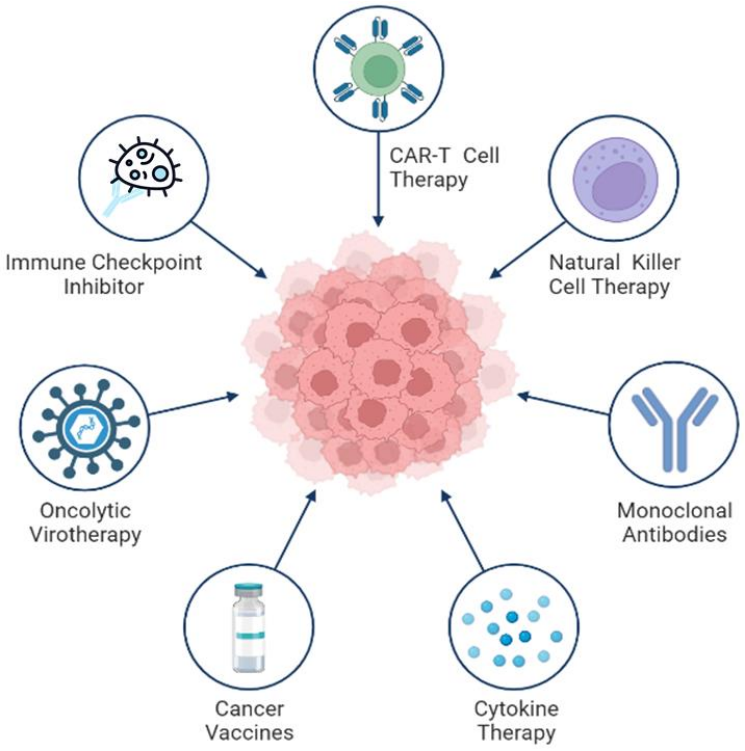


Figure 14 - Representation of the Immunotherapy Strategies for Cancer Treatment. These therapeutic modalities include Immune Checkpoint Inhibitors, CAR-T Cell Therapy, Natural Killer Therapy, Monoclonal Antibodies, Cytokine Therapy, Cancer Vaccines and Oncolytic Virotherapy. Created with BioRender.com.

2.3.1. Immune Checkpoint Inhibitors

Immune responses are tightly regulated by checkpoints that enable effective protective immunity and tolerance. These immunoregulatory checkpoints control the innate and adaptive immune systems, regulating the resolution of inflammation, preventing autoimmunity and maintaining homeostasis[166]. Cancer cells can hijack checkpoint regulation to block anti-tumor responses and, thus, promote immune evasion[92].

ICI therapies are designed to inhibit factors responsible for suppressing T-cell function, leading to the activation of the immune system[167]. ICIs play a crucial role in immunotherapy by blocking several targets that interfere with T cell activation and proliferation, such as CTLA-4 (Figure 15A), PD-1/PD-L1 (Figure 15B) and LAG-3 (Figure 15C)[167].

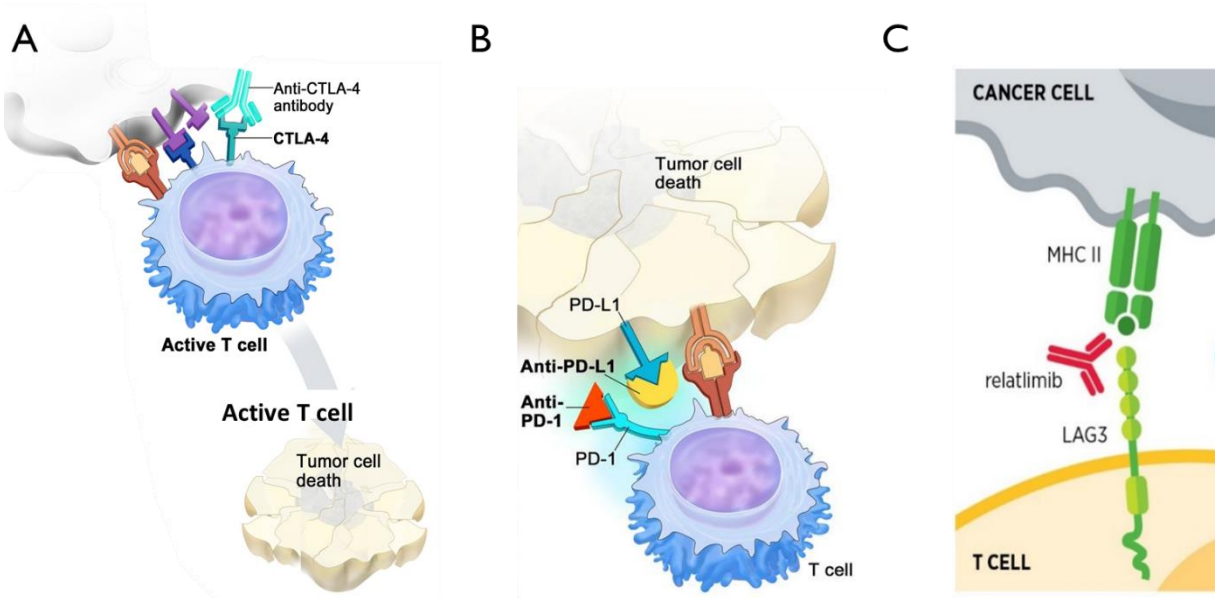


Figure 15 - Effects of CTLA-4 and PD-1/PD-L1 blocking antibodies. A | anti-CTLA-4 therapies operate by inhibiting T cell responses, acting as an antagonist of CD28-mediated costimulation. CTLA-4 raises the activation threshold for T-cell priming, downregulating T cell activation while inhibiting T_{Reg} function. **B |** Activated T cells express PD-1, which engages its specific ligand PD-L1/PD-L2 to dampen T cell activation. Therefore, blocking this interaction prevents inhibitory stimulation and unleashes antitumoral T lymphocyte activity by promoting increased T cell activation and proliferation, enhancing their effector functions and supporting the formation of memory cells. **C |** LAG-3 associates with the TCR-CD3 complex at the T cell membrane and negatively regulates TCR signal transduction, LAG-3 inhibitors can negatively regulate and suppress T cell proliferation and activation through combination with MHC II ligand. Adapted from National Cancer Institute[101,102] and American Association for Cancer Research[172].

ICI therapy has produced durable clinical responses and improved survival across a variety of cancers. This approach was translated to the clinic with Ipilimumab (Yervoy®, Bristol-Myers Squibb), a humanized mAb designed to inhibit CTLA-4, which was approved by the FDA in 2011 to treat advanced melanoma[168]. Clinical trials evidenced its ability to induce long-lasting tumor repression, with over 20% of patients demonstrating improved long-term survival[168]. Additionally, tremelimumab (Imjudo®, AstraZeneca AB) was approved in 2022 for patients with hepatocellular carcinoma and non-small cell lung cancer. Similarly, PD-1 targeting antibodies have demonstrated significant clinical responses in multiple tumor types[169] which resulted in the FDA approval of nivolumab (Opdivo®, Bristol-Myers Squibb) and pembrolizumab (Keytruda®, Merck Sharp Dohme) in 2014, atezolizumab (Tecentriq®, Genentech Inc.) in 2016, avelumab (Bavencio®, EMD Serono Inc.) and durvalumab (Imfinzi®, AstraZeneca UK Ltd) in 2017, cemiplimab (Libtayo®, Regeneron Pharmaceuticals) in 2018 and dostarlimab (Jemperli®, GlaxoSmithKline) in 2021. Since CTLA-4 and PD-1 regulate different inhibitory pathways in T cells, combination therapy using both anti-CTLA-4 and anti-PD-1 mAbs (ipilimumab and nivolumab) was suggested. A clinical trial was conducted to evaluate the efficacy of this combination. The trial demonstrated remarkable results, with over 50% of patients diagnosed with advanced melanoma experiencing an impressive 80% reduction in tumor size[170]. These results led to the FDA approval of nivolumab in combination with

ipilimumab to treat patients with unresectable or metastatic melanoma in 2015. Finally, in 2022, Opdualag®, a combination therapy developed by Bristol-Myers Squibb, received approval for use in patients with metastatic melanoma. Opdualag® consists of nivolumab and relatlimab, an anti-LAG-3 mAb, working together to enhance its therapeutic effects[171].

Despite their great potential, ICIs also hold several challenges. By blocking signaling pathways that regulate the immune system, ICIs activate it and trigger inflammation, which contributes to the development of immune-related Adverse Effects (irAEs). During therapy, irAEs of various natures can be observed, which include skin disorders (pruritus, rash, eczema, vitiligo), gastrointestinal diseases (diarrhea, colitis), and respiratory diseases (dyspnea, cough), among others[173]. Furthermore, ICI therapy is often accompanied by other adverse events, which include arthralgia, abdominal pain, fatigue, nausea and vomiting[174].

Furthermore, various mechanisms can cause primary or acquired resistance in patients, with a key factor being the absence of tumor-infiltrating T cells, which differentiates "cold" tumors from "hot" tumors [163]. As such, and because immune cell infiltrates can serve as prognostic markers for assessing responses to ICI therapy, several methods of turning cold tumors into hot tumors are currently under investigation[163]. These strategies, which focus on enhancing T cell priming and activation, expansion, trafficking to the tumor, and infiltration, will be further explored in the following chapter[175].

2.3.2. Adoptive Cell Therapy

Adoptive Cell Therapy has emerged as a powerful and potentially curative therapy that relies on the immune cells' ability to eliminate cancer cells. Adoptive cell therapy involves the transfer of immune cells, primarily expanded T cells, to promote amplified anti-tumor responses. The adoptive cell therapies can be classified into three types, namely adoptive cell therapy with TILs, adoptive cell therapy using TCR gene therapy and adoptive cell therapy with CAR modified T cells[176]. In addition to T cells, other immune cell types, such as NK cells, have been areas of study and are currently being developed in clinical trials.

Current TIL therapy consists of *ex vivo* expansion of TILs from resected tumor material and adoptive transfer into the patient. This approach has yielded impressive objective tumor responses of approximately 50% in patients with metastatic melanoma during several phase I/II clinical trials[176]. Additionally, the generation of TILs from solid tumors such as cervical cancer, renal cell cancer, breast cancer and non-small cell lung cancer has been explored, with varying rates of tumor reactivity[176].

Furthermore, peripheral blood T cells can be isolated and genetically modified *in vitro* to express TCRs that target specific tumor antigens[176]. This approach has facilitated the creation of large populations of tumor specific T cells, exhibiting potent anti-tumor activity. Adoptive cell therapy using TCR gene therapy has achieved objective clinical responses in up to 30% of treated patients[176]. For the recognition by the modified TCR, antigen presentation via MHC is required. However, it is widely recognized that numerous cancer types can escape T cell-mediated immune responses by downregulation or loss of MHC expression[176]. To overcome the requirement of MHC presence on tumor cells for recognition by tumor-specific T cells, alternative receptors such as CAR have been developed, which will be explored below[176].

The ultimate goal of adoptive cell therapy is to create an optimized and personalized cellular product specifically reactive to the tumor[176]. Although significant accomplishments have been achieved, further optimization of this promising therapeutic modality is required to enhance the anti-tumor effect and reduce adverse events.

2.3.2.1. CAR-T Cell Therapy

CAR-T Cell Therapy comprises the only adoptive cell therapy found to have received FDA approval. CARs, whose structure is illustrated in Figure 16, are hybrid recombinant receptors that possess tumor-specific antigen recognition capabilities, as well as intracellular signaling components derived from the TCRs[177].

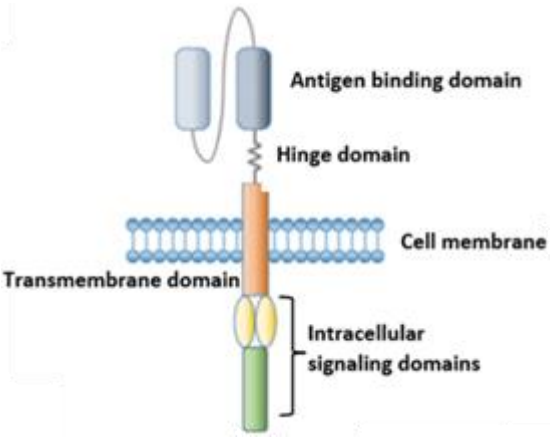


Figure 16 - Basic Structure of a typical CAR. A CAR is composed of the extracellular, transmembrane and intracellular domains. The extracellular domain of a CAR is the antigen recognition domain, which is derived from an immunoglobulin and provides CARs with the ability to specifically bind to target antigens and give the primary activation signal required for T cell activation. The extracellular domain also includes the linker and hinge domains. The intracellular domain encompasses the stimulatory signals and co-stimulatory signals, such as CD27, CD28, OX40 and 4-1BB. The extracellular and intracellular domains are linked through a transmembrane domain. Adapted from Han et al. 2017[179].

The complex and multistep process towards the development of CAR-T cells is depicted in Figure 17. They are derived from T cells of the patient's blood, which are modified *in vitro* to express specific CARs that recognize tumor cell antigens and, following stimulation and expansion, are re-transferred into the same patient[178]. Upon infusion, tumor cells are specifically recognized and killed by CAR-T cells, which are able to maintain their activity for more than a decade after administration[178].

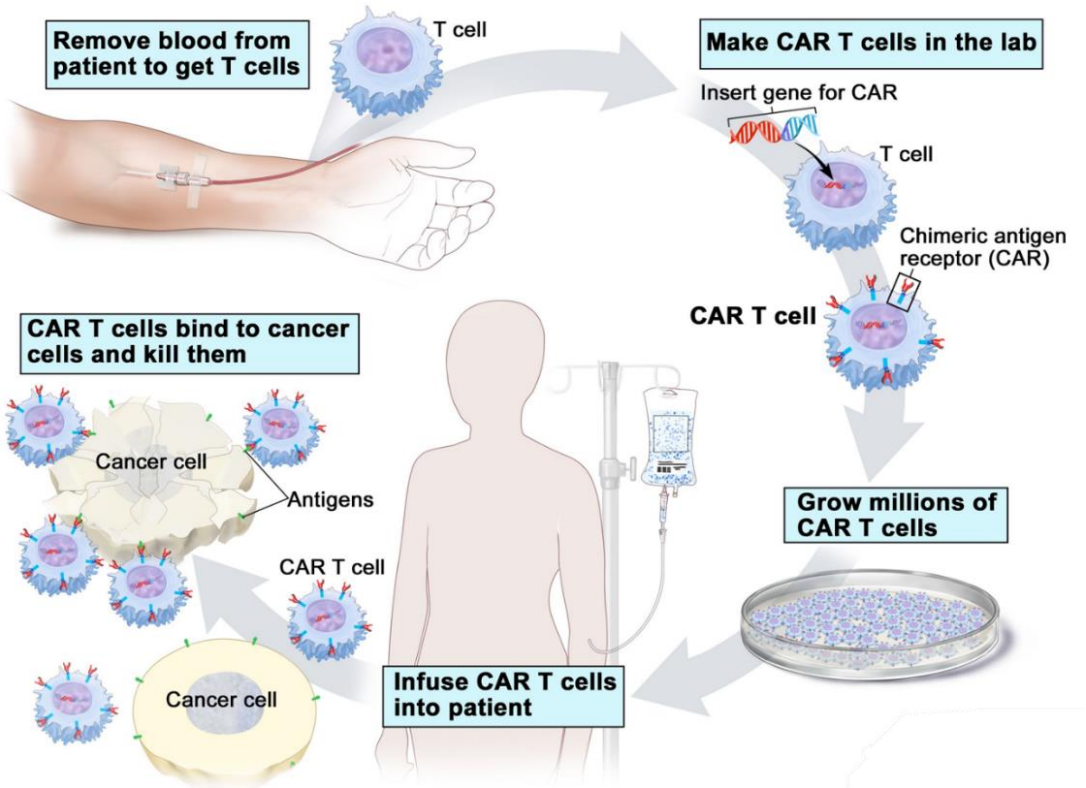


Figure 17 - The process of clinical application and development of CAR-T cells. To develop CAR-T cells, primary T cells from the patient's peripheral blood are isolated via leukapheresis and apheresis. These T cells are then transduced by viral vectors, usually retrovirus, to express CARs and expanded and purified until they reach sufficient numbers. Finally, the genetically modified T cells are re-infused back into the patient. Adapted from National Cancer Institute[180].

The most studied target for CAR-T cells is CD19, a cell surface transmembrane protein expressed in the B cell lineage, used in the treatment of hematologic malignancies[120]. Out of the six encountered FDA approved CAR-T Cell Therapies, four are CD19 targeted, which include tisagenleucel (Kymriah®, Novartis Pharmaceutical Corporation), axicabtagene ciloleucel (Yescarta®, Kite Pharma Inc.), brexucabtagene autoleucel (Tecartus®, Kite Pharma Inc.) and lisocabtagene maraleucel (Breyanzi®, Bristol-Myers Squibb). These products were approved for the treatment of patients with B-cell acute lymphoblastic leukemia (Tecartus® and Kymriah®), B-cell lymphoma (Kymriah®, Breyanzi® and Yescarta®), follicular lymphoma (Kymriah®, Breyanzi® and Yescarta®) and mantle cell lymphoma (Tecartus®). Remission rates in hematologic malignancies after CD19 CAR-T cell treatment range from 50% to 90%, having been reported to be as high as 100%[181]. Furthermore, two more therapies have been approved: idecabtagene vicleucel (Abecma®, Bristol-Myers Squibb) and ciltacabtagene autoleucel

(Carvykti®, Janssen Biotech Inc.). These treatments specifically target B Cell Maturation Antigen (BCMA) and have been authorized for administration to patients who suffer from relapsed or refractory multiple myeloma.

While these therapies have been marked by their efficacy, a common observation in all clinical studies involving CAR-T cells is the associated toxicity, namely cytokine release syndrome (CRS) and neurotoxicity[120; 124; 167; 182]. CRS is the result of activation of the infused T cells through antigen recognition, which leads to colossal cytokine release, namely IFN-γ, IL-1 and IL-6[176]. Neurological complications, specifically immune effector cell-associated neurotoxicity syndrome (ICANS), have also been observed associated with CAR-T cell treatment[167; 176]. In more severe cases, these complications manifest as symptoms such as speech impairment, confusion, delirium, seizures and cerebral edema, often resulting in death[167; 176]. Severe or life-threatening CRS and ICANS can effectively be treated with mAbs blocking cytokine receptors, such as tocilizumab (anti-IL-6 receptor mAb), anakinra (anti-IL-1 receptor mAb) and etanercept (anti-TNF-α receptor) as well as corticosteroids[183]. In addition, because CD19 is expressed in B cells, targeting CD19 is passive of triggering ablation of this cell compartment. Fortunately, B cell aplasia can be successfully alleviated with immunoglobulin replacement therapy, making it a serious but manageable on-target/off-tumor toxicity[184].

Unfortunately, CAR-T cell therapy's success in hematologic malignancies has not yet been consistently reproduced for individuals with solid tumors[185]. Despite the application and development of CAR-T cells for solid tumors still being in the early stages, major obstacles have been encountered that limit the efficacy of CAR-T therapy in this aspect. Several clinical challenges contribute to these limitations, including antigen selection, poor trafficking to the tumor site, limited persistence and proliferation within the host and functional suppression within the hostile TME[185].

Undoubtedly, CAR-T cell therapy has revolutionized cancer therapy and has been most advantageous, particularly for patients who have experienced cancer progression after several lines of therapies and have almost exhausted all potential treatments. The continuous research has led to new findings, such as the ability of CAR-T cells to circulate within the central nervous system, which provides the possibility of effective use against central nervous system cancers[182]. A better understanding of the CAR-T cell approach will hopefully continue moving forward in the area of hematologic malignancies, but also towards solid tumors, in order to generate cures for patients with previously therapeutically resistant cancers[185].

2.3.3. Natural Killer Cell Therapy

The essential role of NK cells in anti-tumor immunity has been evidenced by higher susceptibility to cancer and metastasis associated with diminished NK activity, which attracted attention in the immuno-oncology field[165; 186]. Tumor cells have mechanisms capable of inhibiting NK cells to achieve immune escape. Currently, several approaches aim to control NK cell paralysis and improve anti-tumor immunity, which include *ex vivo* expanded allogenic NK cells, CAR-NK cells and autologous induced pluripotent stem cell-derived NK cells[187].

While treatments with autologous NK cells have not shown persistent anti-tumor activity, researchers have demonstrated the improved efficacy of *ex vivo* expanded allogeneic NK cells co-cultured with cytokines (such as IL-12, IL-15, and IL-18) for treating hematological and solid cancers[187]. An example of this approach is Glycostem Therapeutics' oNKord®. oNKord® is an off-the-shelf, *ex vivo*-cultured allogeneic NK cell immunotherapy for patients with acute myeloid leukemia. After delivering promising results in a phase I clinical trial, it is currently under investigation in a phase II study (NCT04632316) which aims to determine its safety and efficacy[239,240]. Notably, oNKord® has received an orphan drug designation for acute myeloid leukemia from both the European Medicines Agency (EMA) (2014) and FDA (2016)[188].

Additionally, autologous or allogenic NK cells may be genetically modified to achieve prolonged and increased expression of CARs and cytokines receptors. CAR-NKs aim to address the limitations of current CAR-T therapies, including safety concerns, tumor targeting and manufacturing time and cost. To this end, several phase I clinical trials are being conducted. Nkarta's allogenic CAR-NK cell targeting CD19, NKX019, is being studied in patients with relapsed/refractory non-Hodgkin lymphoma, chronic lymphocytic leukemia and B cell acute lymphoblastic leukemia (NCT05020678)[190; 191]. This monotherapy has achieved 70% complete responses and promising safety profiles[190; 191]. Additionally, Fate Therapeutics' FT576, an induced pluripotent stem cell line that expresses an anti-BCMA CAR and an IL-15 receptor, is being evaluated in combination with the mAb daratumumab for patients with multiple myeloma (NCT05182073)[192; 193]. As of now, no results from this study have been published.

Furthermore, NK cells generated from autologous iPSCs are regarded as effective potentiators of tumor lysis[187]. This approach was first evaluated in 2019, when Fate Therapeutics and the University of California undertook the first clinical trial for evaluating the effect of FT500 cell therapy[187]. FT500 is an off-the-shelf induced pluripotent stem cell line-derived NK cell product. In this ongoing trial (NCT04106167), FT500 is being tested for safety, along with patient responses to its different doses for the treatment of various tumors[194].

2.3.4. Antibody therapy

mAbs have emerged as efficacious therapeutic agents due to their ability to identify and recognize proteins associated with tumors[164]. mAbs can be classified as naked, conjugated, or bispecific[163]:

- Naked mAbs are the most common mAb and work by themselves, targeting a specific antigen that initiates an immunologic response (Figure 18A).
- Conjugated mAbs, or antibody-drug conjugates, are composed of mAbs bearing cytotoxic drugs or cytokines that allow targeted delivery of the drug to the antigen-expressing tumor cell (Figure 18B).
- Bispecific mAbs combine two different mAbs, this way being able to target two antigens at the same time (Figure 18C).

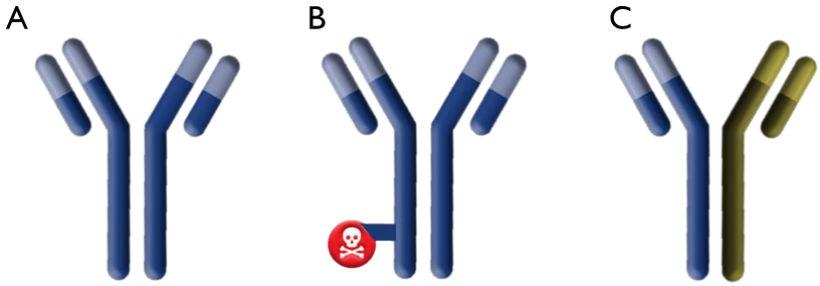


Figure 18 - Representation of the basic structure of naked, conjugated and bispecific mAbs. A | Naked, monovalent mAbs are the most common type of antibody for cancer treatment. **B |** An ADC is comprised of a monoclonal antibody and the payload attached via a linker. More than one payload can be attached. **C |** Bispecific mAbs are able to simultaneously recognize and engage two different epitopes or antigens.

Antibodies are the most commonly used and approved cancer immunotherapeutic method in clinical practice. The first mAb approved by the FDA was rituximab (Rituxan®, Genentech Inc.) for the treatment of relapsed or refractory non-Hodgkin's lymphoma, achieving an overall response rate of 50-70%[195; 196]. Since then, many other therapeutic mAbs have been approved by the FDA for use in a wide range of clinical indications, some of which were listed in the top 10 most sold mAbs for cancer in 2021[197]. Such mAbs include bevacizumab (Avastin®, Genentech Inc.) for colorectal cancer, non-small cell lung cancer, renal cell carcinoma, hepatocellular carcinoma, among others, trastuzumab (Herceptin®, Genentech Inc.) for human epidermal growth factor receptor 2 (HER-2)-positive breast cancer and gastric and gastroesophageal cancer, daratumumab (Darzalex®, Janssen Biotech Inc.) for multiple myeloma, and panitumumab (Vectibix®, Amgen Inc.) for colorectal cancer[198].

Due to their specific targeting, adverse events associated with therapeutic mAbs are generally considered to be mild compared to other immunotherapeutic modalities[199]. However, when mAbs are conjugated with other substances or when bispecific antibodies are employed, higher levels of toxicity can be observed[167].

Despite the discovery of the anti-tumor potential of mAbs and their demonstrated therapeutic efficacy in treating several types of solid and hematologic cancers, there are still some challenges that must be addressed, mainly the development of tumor resistance, which limits their potential[167]. Nonetheless, antibody therapy is considered a main component of cancer therapy.

2.3.5. Cytokine therapy

Cytokines, small protein molecular messengers, play a crucial role in mediating growth, differentiation and inflammatory or anti-inflammatory signals[167]. In addition, they possess the ability to exert an immunomodulatory effect on immune cells, enabling the generation of a coordinated, robust, but self-limited response to a target antigen[118; 121; 167]. The most prominent cytokines include IFN-α (Intron A®, Schering), GM-CSF (Leukine®, Berlex Laboratories) and IL-2 (Proleukin®, Chiron), which received FDA approval in 1986, 1991 and 1992, respectively.

Although cytokines have demonstrated clinical benefits, their poor tolerability and severe toxicity hamper their further application as monotherapies. However, their potential is still being investigated in combination with other immunotherapies[200].

2.3.6. Cancer Vaccines

Cancer vaccines seek to drive T cell activation by priming tumor-specific T cells with tumor antigens[120]. They are subclassified based on their therapeutic or prophylactic interventions[115]:

- Prophylactic Vaccines

  Prophylactic vaccines aim to reduce cancer incidence, morbidity and mortality by initiating a specific immune response against pathogenic microorganisms or oncogenic viruses that contribute to the development of cancer[115; 201]. These include Human Papillomavirus (HPV) and Hepatitis B virus (HBV).

  Several prophylactic vaccines are already commercially available and are highly effective. These include HPV vaccines such as Cervarix® (GlaxoSmithKline Biologicals), Gardasil® (Merck Sharp & Dohme LLC) and Gardasil-9® (Merck Sharp & Dohme LLC). Gardasil-9 protects against HPV types linked to about 90% of cervical cancers[202] for at least 9 years, although some projections point to 20-30 years of immunization[167]. On the other hand, HBV vaccines such as Heplisav-B® (Dynavax GmbH), HbVaxPro® (Merck Sharpe & Dohme B.V.) and Engerix-B®

(GlaxoSmithKline Biologicals), among others, are also examples of prophylactic vaccines. Since 1982, HBV vaccines have prevented new HBV infections and decreased rates of chronic liver disease and hepatocellular carcinoma[92].

- Therapeutic Vaccines

Therapeutic vaccines aim to activate specific $CD8^+$ CTLs that can eliminate cancer cells and, consequently, treat existing malignancies[167].

In terms of therapeutic vaccines, the offer range is much narrower. BCG vaccines, which were initially developed to prevent tuberculosis, were discovered to have an anti-tumor effect. Therefore, BCG vaccines, such as Tice® BCG (Merck Teknika LLC) and TheraCys® (Sanofi Pasteur Limited), were approved for patients with bladder cancer. Additionally, Sipuleucel-T (Provenge®, Dendreon Pharmaceuticals LLC), an autologous cell-based cancer vaccine, was approved by the FDA in 2010 for use in patients with metastatic castrate-resistant prostate cancer. This vaccine has shown the ability to improve OS while maintaining a low toxicity profile[164].

Recently, personalized neoantigen vaccines have demonstrated immense promise in the field of cancer immunotherapy, as a consequence of the significant advances in sequencing methods[203]. These vaccines are customized to target specific neoantigens found in each patient's tumor, making them highly effective and tailored to individual needs[203].

Vaccines utilizing neoantigens offer numerous advantages, including the ability to specifically target cancer cells and avoid off-tumor effects[203]. Moreover, they can stimulate long-lasting immune responses that specifically target neoantigens, potentially offering protection against disease recurrence[203]. However, this approach has certain limitations that must be addressed. Such limitations include the high cost involved, the time-consuming process of manufacturing individualized vaccines and the uncertainty surrounding the optimal delivery platform[203]. To overcome these challenges, further studies are necessary to develop strategies that can efficiently stimulate effective, long-lasting and tumor-specific immune responses in cancer patients.

Both prophylactic and therapeutic anti-cancer vaccines are designed to induce tumor-specific and tumor-reactive immune responses *in vivo*[118]. To this end, vaccines usually consist of immunogenic epitopes from tumor-specific or tumor-associated antigens. The most studied targets include products of mutated oncogenes or tumor suppressor genes, oncogenic viruses, oncofetal proteins, overexpressed self-proteins, cancer germline and cancer stem cell antigens and tissue lineage and differentiation antigens. Some of these antigens, which were mentioned in several reviews, are represented in Figure 19[115; 204; 205; 206; 207; 208].

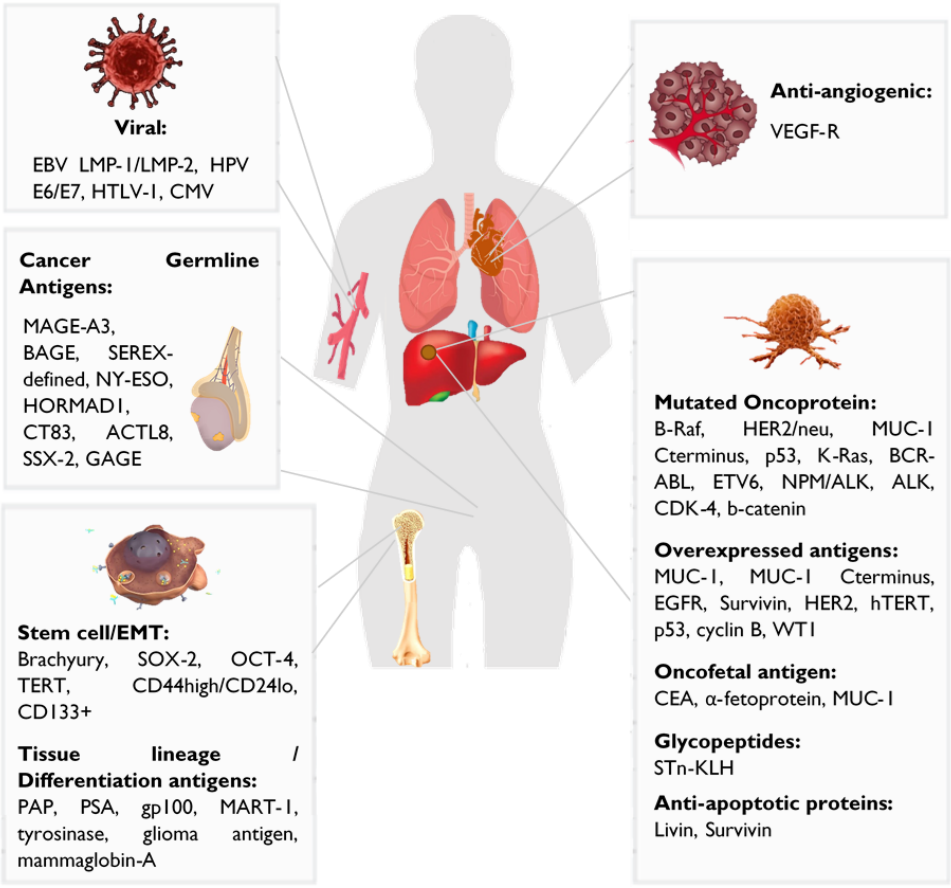


Figure 19 - Representation of Cancer Vaccines Targets. The choice of antigen to target in any cancer vaccine is extremely important for it to be effective. The ideal antigen should be specifically expressed on cancer cells, necessary for cell survival and highly immunogenic. Several categories of cancer target antigens have been identified, including viral antigens, antiangiogenic antigens, cancer germline antigens, cancer stem cell, tissue lineage and differentiation antigens, mutated oncoproteins, overexpressed antigens, oncofetal antigens, glycopeptides and anti-apoptotic proteins. Abbreviations are as follows: EMT – Epithelial-Mesenchymal Transition; EBV LMP - Epstein-Barr Virus Latent Membrane Protein; HPV – Human Papillomavirus; HTLV - Human T cell Leukemia Virus type-1; CMV – Cytomegalovirus; MAGEE - Melanoma Antigen Gene; BAGE – B Melanoma Antigen Gene; SEREX - Serological Analysis of Recombinant Tumor cDNA Expression Libraries; HORMAD1 - HORMA domain-containing protein 1; CT83 – Cancer Testis Antigen 83 ; ACTL8 - Actin-like Protein 8; SSX-2 - Synovial Sarcoma X Protein; GAGE – G Antigen; SOX-2 - Sex determining Region Y Box; OCT-4 - Octamer-binding Transcription Factor 4; TERT - Telomerase Reverse Transcriptase; PAP - Prostatic Acid Phosphatase; PSA - Prostate-Specific Antigen; gp100 - Glycoprotein 100; MART-1 - Melanoma-associated Antigen Recognized by T-cells; VEGF-R - Vascular Endothelial Growth Factor Receptor; B-Raf – B-Rapidly Accelerated Fibrosarcoma ; HER - Human Epidermal Growth Factor Receptor; MUC-1 – Mucin 1; K-Ras - Kirsten Rat Sarcoma; BCR-ABL – Breaking Cluster Region-Abelson Fusion Gene; ETV6 - E26 Transformation-specific Variant 6; NPM-ALK – Nucleophosmin-Anaplastic Lymphoma Kinase Fusion Protein; ALK - Anaplastic Lymphoma Kinase; EGFR – Epidermal Growth Factor Receptor ; WT1 - Wilms' Tumor Gene 1; CEA - Carcinoembryonic Antigen ; STn-KLH – Sialyl-Tn-Keyhole Limpet Hemocyanin; CDK-4 - Cyclin-Dependent Kinase 4.

Cancer vaccines vary not only by their target antigens but also by vaccine platform, according to which they can be divided into peptide-based vaccines, cell-based vaccines, viral-based vaccines and nucleic acids-based vaccines[209]. The major features of different vaccine platforms are described below and are summarily represented in Table II.

Peptide-Based Vaccines

Peptide-based vaccines commonly comprise a sequence of amino acids derived from TSA or TAAs[210]. These vaccines have shown to be stable, safe, and manufacture-wise, relatively simple and cost-efficient to develop[211]. Although peptide-based cancer vaccines have demonstrated promising results in the pre-clinical setting, there is still significant room for improvement to achieve desirable clinical efficacy[210]. As such, they often require a combination with immune adjuvants that further enhance the development of the immune response[209].

Cell-Based Vaccines

Cell-based cancer vaccines hold significant potential as therapeutic options for various cancer types. They offer several advantages, including the ability to stimulate a customized immune response tailored to the patient's unique tumor profile and induce immune memory, potentially providing long-term protection against cancer recurrence. The two main categories of cell-based cancer vaccines are tumor cell vaccines and immune cell vaccines, mainly DCs, which can be allogenic or autologous.

Tumor-cell Vaccines

Whole tumor-cell vaccines represent the first therapeutic vaccines to be developed. They can present a wide variety of TAAs, but are characterized by low specificity and immunogenicity[209]. Consequently, these characteristics result in the development of lower magnitude immune responses[209].

Due to the results obtained in various clinical trials in the past decades, tumor cell-based cancer vaccines have been considered to lack sufficient evidence in terms of inducing strong immune responses and therapeutic responses[212].

Dendritic Cells

The majority of therapeutic DCs are autologous and manipulated *ex vivo* to enhance the immune response[213]. Such manipulation may include pulsing isolated/recombinant antigens, transfection with tumor messenger RNA (mRNA), transduction with antigen-coding genes and loading with tumor cell lysates or apoptotic tumor cells[213]. Despite having demonstrated

favorable response rates, DC-based vaccines are limited by a complex, time-consuming and costly manufacturing process that must meet rigorous quality control parameters[167].

The only DC-based vaccine approved was sipuleucel-T (Provenge®, Dendreon Pharmaceuticals LLC), in 2010 by the FDA and by EMA in 2013, for the treatment of patients with castration-resistant prostate cancer[154; 214]. However, within two years of obtaining European Union-wide marketing authorization, Provenge® was withdrawn due to commercial reasons[214].

Viral-Based Vaccines

Viral-based vaccines are based on viral vectors, which are intrinsically immunogenic pathogens that have been engineered to encode tumor antigens. These viral vectors can be further modified to increase their potency by co-expressing immunomodulatory costimulatory molecules[212].

Although very successful in the infectious diseases sector, clinical trials using viral vaccines in oncology have not yielded comparable results thus far[205]. Nevertheless, this platform is highly promising due to the effective induction of the immune system, the possibility of its off-the-shelf nature and the relatively simple manufacture and storage, which is associated with a fairly low cost of production[215].

Nucleic Acid-Based Vaccines

Nucleic acid-based vaccines (DNA and RNA) have been gaining increasing prominence in virology and oncology[216]. This recognition is exemplified by the remarkable success of mRNA-based vaccines developed for Covid-19[216]. Nucleic acid vaccines deliver genetic information encoding tumor antigens to the host, initiating the synthesis of antigenic proteins. These proteins, in turn, trigger antigen-specific immune responses within the body. Some of the major advantages of genetic vaccines include the easy delivery of multiple antigens in one immunization, the self-adjuvating ability, and the simple, rapid, cost-effective and easily scalable production methods[216].

Extracellular Vesicles-Based Vaccines

Extracellular vesicles are natural particles released from almost all cell types to the extracellular environment. They are involved in many biological processes, including intracellular communication during inflammation, cell proliferation and immune response, carrying various biomolecules (DNA, RNA, proteins)[218; 219]. Extracellular vesicles derived from DCs and cancer cells have been evaluated in their ability to induce anti-tumor immune

responses[218]. Despite modest results in clinical trials, which demonstrated their ability to activate and recruit cells of the innate immune system, extracellular vesicle-based vaccines have failed to induce antigen-specific immune responses[218].

Despite great promise in cancer therapy, therapeutic cancer vaccines have not yet lived up to their potential[220]. One of the key challenges lies in unleashing a significant anti-tumor response in patients who have inherent tolerance mechanisms that actively suppress immune recognition in oncology patients[220]. Consequently, it is very challenging for larger tumors to be eliminated when treated only with vaccines[163]. This difficulty is further amplified in patients with compromised immune systems[163].

Furthermore, cancer vaccines are associated with several adverse events, that may vary according to the type of vaccine and the specific target. Still, common side effects include but are not limited to, flu-like symptoms, fever, chills, nausea, vomiting, headache, fatigue, dyspnea, myalgia, hypertension and tachycardia[221]. In addition, cancer vaccines targeting TAAs can potentially cause irAEs due to the expression of target antigens on normal cells[164].

2.3.7. Oncolytic Virotherapy

Oncolytic viruses are capable of selective viral replication in tumor tissues, which results in cancer cell lysis. Cell lysis consequently leads to the release of oncolytic viruses and tumor antigens, which induces systemic anti-tumor immune responses. Oncolytic viruses may be genetically modified to further enhance their oncolytic properties, which renders them a versatile tool for treating malignant diseases[118].

The only oncolytic virus-based therapy found to have received FDA approval is Talimogene laherparepvec (T-VEC) (Imlygic®, Amgen Inc.), a genetically enhanced herpes simplex virus[118]. T-VEC was approved by the FDA in 2015 for use in patients with melanoma after demonstrating impressive clinical benefits (overall response rates ~60%)[223]. T-VEC therapy exhibits a good safety profile, with the majority of patients experiencing absence or mild adverse events, which included fever, fatigue, nausea and light-headedness[223].

Table II – Main features of cancer vaccine platforms. Abbreviations are as follows: TC – Tumor Cell; DC – Dendritic Cell; EV – Extracellular Vesicle.

			Tumor Cell					Genetic	
		Peptide	Autologous	Allogenic	Viral	DC	EV	DNA	RNA
Effectiveness	Efficacy	±	-	-	±	±	-	±	±
	Specificity	+	-	-	±	+	±	+	+
	Immunogenicity	-	-	-	+	+	+	±	+
	Stability	+	±	±	±	-	+	+	±
Safety	Adverse Events	+	-	-	+	±	+	±	+
Versatility		+	-	-	±	±	+	+	+
Manufacturing	Harvest	+	+	-	+	-	±	+	+
	Production Complexity	+	-	-	±	-	±	+	+
	Production Cost	+	-	-	+	-	+	+	+
Storage	Conditions Requirements	+	-	-	±	-	-	+	-

+ (Favorable); ± (Intermediate); - (Unfavorable)

2.4. Immunotherapies Comparative Assessment

Over the past decade, immunotherapy has become a significant player in the field of cancer care, with demonstrated efficacy across various malignancies. This success has led to the integration of immunotherapies into clinical practice. In fact, positive responses have been reported more frequently, achieving significant lost-lasting responses, complete responses and cures, even in patients with solid tumors or aggressive malignancies[224].

When selecting the most appropriate treatment, multiple factors require careful consideration. Firstly, the patient's condition and tumor type play a crucial role as each cancer type is distinct, and individual patients may respond differently to treatment[224]. Secondly, the limited therapeutic window in oncologic patients demands careful evaluation of the complexity and duration of therapy production[224]. Lastly, the efficacy of the treatment and the potential adverse events must also be thoroughly assessed[224]. Table III provides a concise overview of the key characteristics of different immunotherapies.

Preclinical and clinical studies have demonstrated the effectiveness of immunotherapies, resulting in improved response rates and overall survival for patients. Notably, CAR-T therapy has shown remarkable efficacy in hematological cancers, leading to substantial investment in this treatment modality[181]. Although research on the use of CAR-T therapy in solid tumors is ongoing, the results have yet to yield similarly encouraging outcomes. In addition, immune checkpoint inhibitors have emerged as a promising therapeutic strategy, achieving favorable therapeutic outcomes that have led to their approval as first-line treatments for certain cancers[225]. Furthermore, therapeutic mAbs have also proven successful in various malignancies and have been successfully integrated into clinical practice[226].

Although certain immunotherapies have showcased substantial efficacy, the safety considerations cannot be overlooked. The safety profile varies depending on the therapeutic strategy, route of administration and mechanism of action[224]. Broad immune system activation approaches, such as ICIs and cytokines, are more likely to induce severe and systemic adverse events. In contrast, therapies targeting specific tumor antigens, such as vaccines and mAbs, tend to result in milder and localized adverse events[224]. CAR-T therapy, in particular, is associated with severe and potentially life-threatening toxicities, limiting its application[164].

Moreover, in terms of production duration and complexity, CAR-T and NK therapies present notable challenges, rendering them particularly intricate and demanding immunotherapies. The process of extracting blood, modifying therapeutic cells, and reintroducing them to the patient typically takes three to four weeks[227]. This extended

timeframe imposes limitations on the application of these therapies, rendering them unsuitable for patients with rapidly progressing cancers.

The aforementioned factors have played a crucial role in the incorporation of various immunotherapies into clinical practice. This achievement is particularly evident with therapeutic mAbs, which have emerged as the leading class of commercialized cancer immunotherapies, representing the largest share among approved immunotherapeutic products. Nevertheless, over the past decade, immune checkpoint inhibitors and CAR-T therapies have also received significant approvals from regulatory agencies, highlighting their importance and potential in cancer treatment. The ongoing advancements and integration of these therapeutic approaches signify a promising future for immunotherapy in improving patient outcomes.

Table III – Main features of Cancer Immunotherapeutic Modalities

		ICI	CAR-T	NK	mAbs	Cytokine	Vaccines	OV
Effectiveness	Efficacy	++	+++	+	+	-	±	±
	Specificity	+	+	±	++	-	+	±
Safety	Adverse Events	-	--	-	±	-	±	±
Versatility		-	+	±	±	-	+	±
Manufacturing	Harvest	+	-	-	+	+	±	+
	Production Complexity	+	-	-	+	+	±	±
	Production Cost	+	-	-	+	+	±	+
Storage	Conditions Requirements	+	+	+	+	+	±	+
Applicability	Indications	+	±	±	+	±	±	±
Market Success	Approved Products	10	6	0	62	3	13	1
	Market Share	+	+	-	+	±	-	-

+++(Extremely Favorable); ++ (Highly Favorable); + (Favorable); ± (Intermediate); - (Unfavorable); -- (Highly Unfavorable)

2.5. Exploring the Benefits and Drawbacks of Immunotherapy

The clinical efficacy of various immunotherapies has been well established, with significant advantages over traditional anti-tumor therapy in terms of prolonging progression-free survival (PFS) and overall survival (OS). Immunotherapy offers tumor specificity and sophisticated mechanisms of self-tolerance, which prevent autoimmune reactions and maintain tissue and organ integrity[110]. Furthermore, this modality induces powerful, specific, and targeted anti-cancer responses that can be widely adaptable to kill multiple types of tumors[124]. Immunotherapy is also associated with memory functions that induce long-lasting anti-cancer responses, whereas standard therapies exert their role as long as treatment is maintained[110].

Side effects are generally less extensive and frequent than in traditional treatments[124]. However, immunotherapy is marked by inherent complexity and uncertainty, influenced by various factors that render the survival rate and prognosis of patients indeterminate[124].

Despite offering high selectivity based on individual patients and specific cancer types, immunotherapy's benefits for the broader population remain relatively limited. The limitations of immunotherapy include the frequency and heterogeneity of treatment responses, which vary significantly among individuals[228]. In addition, most patients either do not respond to immunotherapy or inevitably develop resistance to treatment after a certain period of time[229]. Immunotherapy may also cause severe adverse reactions due to an overactive immune system, leading to the development of autoimmune diseases and hyper-progressive diseases, which can accelerate mortality[124]. Finally, the high treatment cost is another limiting factor, with some therapies reaching over US$1 million in expenses[230].

2.6. Market Forecast and Approved Products Landscape

The global cancer market has been growing throughout the years. It has gone up from a valuation of US$54 billion in 2010 to US$265.1 billion in 2020[231]. It is projected that the market will continue to expand and reach a value of US$581.25 billion by 2030, with an impressive Compound Annual Growth Rate (CAGR) of 8.2% from 2020 to 2030[231]. The rise of oncology products is evident, with 31% of the drugs approved by the FDA in 2022 being cancer-related[232]. The increasing prevalence of oncology across the globe, coupled with a surge in R&D efforts for the development of novel oncology therapeutics, are the major driving factors for the oncology market[233].

The global cancer immunotherapy market held a valuation of US$ 115.01 billion in 2022, and it is expected to expand at a noteworthy CAGR of 8,7% from 2023 to 2028[234]. By 2028,

it is predicted to reach a market value of US$200.95 billion[234]. This growth is fueled by the high efficacy of immunotherapy compared to other therapies, fewer side effects and reduced chance of cancer recurrence[234]. Technological advances in clinical therapies and the increasing R&D for cancer treatment are also significant driving factors.

In terms of revenue, North America leads the global immunotherapy market, mainly due to the presence of leading players in the immuno-oncology field, promotion of research activities, and approval of novel drugs and combination therapies[234]. However, in the forthcoming years, the Asia Pacific market is expected to witness the fastest growth rate, which may be due to the increase in the geriatric population, who are at an increased risk of oncologic disease[234].

mAbs, including ICI, dominate the therapy type market with the largest share[233; 234] (Figure 20). By 2021, they already accounted for more than 70% of the market share, and this upward trend is expected to continue in the upcoming years[234]. The high market value can be attributed to their high prescription rates, high efficacy, minimal side effects, and impressive commercial performance and sales of leading immune checkpoint inhibitors, such as Keytruda® (Merck Sharp & Dohme), Yervoy® (Bristol-Myers Squibb), and Opdivo® (Bristol-Myers Squibb)[233]. Furthermore, the field of oncolytic virotherapy and cancer vaccines is expected to see significant expansion until 2030 due to the growing demand for novel treatment regimens[234] (Figure 20).

In terms of the area of therapy, the immuno-oncology market is dominated by the lung cancer segment. This dominance can be credited to the rising prevalence of lung cancer, the increasing adoption of immunotherapeutic treatment regimens even as first-line therapy, and the presence of robust pipelines[233]. There has also been significant investment in R&D in lung cancer, further promoting the growth of this segment[233]. The breast cancer segment holds the second-largest share, primarily driven by the growing prevalence and the increasing need for effective therapies[233]. It is worth noting that prostate cancer is expected to experience the fastest growth until 2030[233].

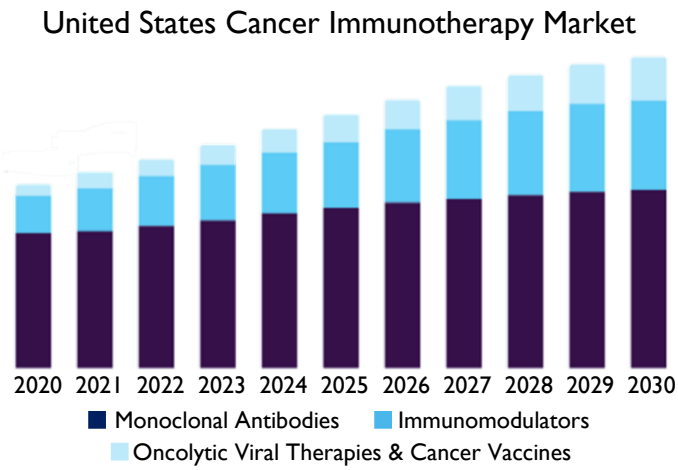


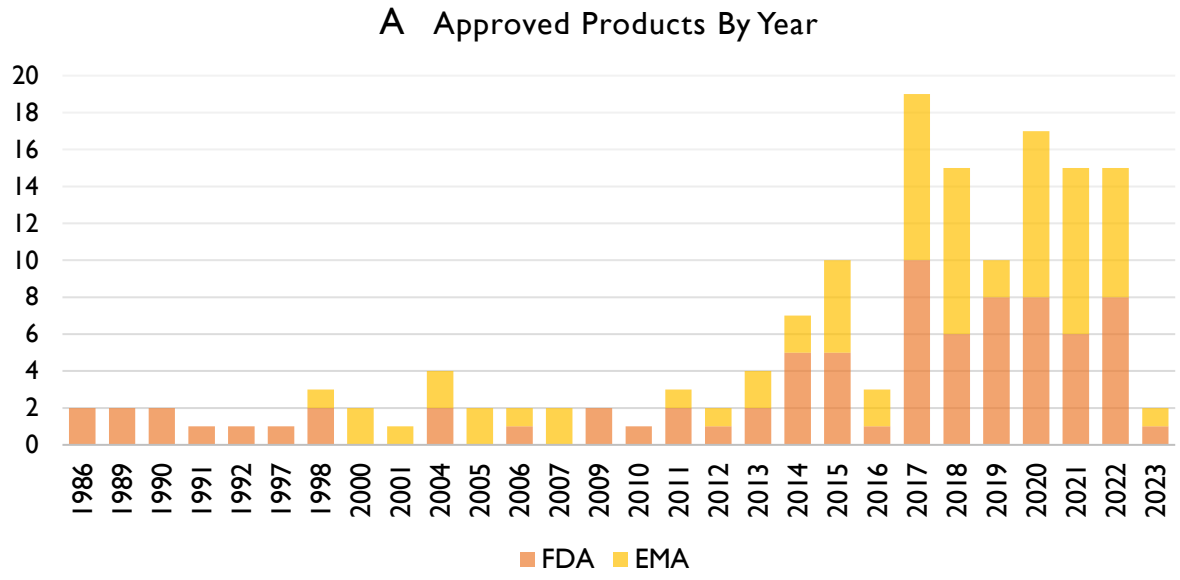
Figure 20 - Unites States' Cancer Immunotherapy Market Forecast by type of therapy. Monoclonal antibodies, including ICI, encompass the largest share of the onco-immunotherapy market. This dominance of the market is expected to be maintained in the forthcoming years. Immunomodulators, Oncolytic Viral Therapies and Cancer Vaccines are predicted undergo a significant growth until 2030, asserting their important role in the immunotherapeutic field. Adapted from Grand View Research[233].

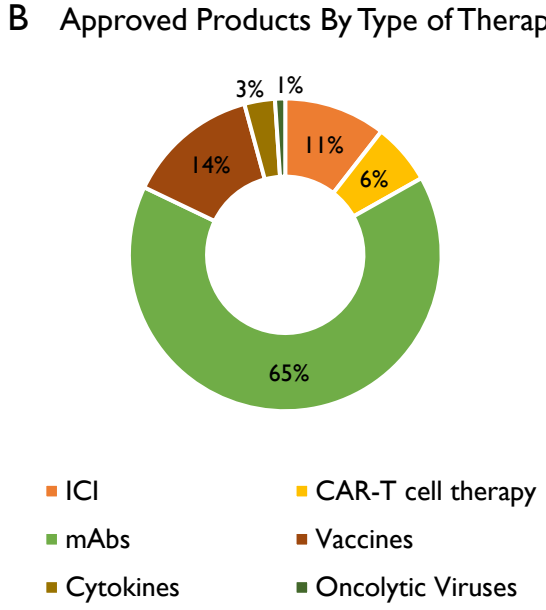
The impact of immunotherapy, particularly ICI, is evident when examining the leading pharmaceutical product sales worldwide in 2022. Merck Sharp & Dohme's Keytruda is ranked the fourth most sold drug, with US$21 billion in revenue[235]. However, it is worth noting that the first and second places are occupied by COVID-19 vaccines, which have topped the ranking since 2021. Additionally, Keytruda® is projected to be the top-selling drug in 2023, with US$24 billion in sales, while Bristol-Myers Squibb's Opdivo ranks sixth with US$11.5 billion in revenue[236]. When considering the best-selling cancer drugs in 2022, the list includes not only the ICIs Keytruda® and Opdivo®, but also Genentech's ICI Tecentriq® and mAb Rituxan®, Janssen Biotech's mAb Darzalex® and Roche's mAb Gazyva®[237].

Following an extensive search using Cortellis™ (a Clarivate Analytics database) and reviewing current literature, numerous immuno-oncology products that have received FDA and/or EMA approval were successfully identified. Throughout this search, it was possible to identify 95 approved products for cancer immunotherapy. The approved products were categorized according to the type of therapy, including ICI, CAR-T cell therapy, mAbs, Vaccines, Cytokines and Oncolytic Viruses. While the major results of this search will be briefly discussed below, a more detailed version can be found in Table I in the Appendix.

Figure 21A offers an insight into the evolving landscape of cancer treatment and the historical progression and distribution of approvals by both FDA and EMA within the immuno-oncology field over the course of several years. It is notorious that this number has been increasing, with the year of 2017 accounting for the highest number of approvals. From that year on, this trend seems to have been maintained, with at least 10 products approved per year. It is important to note that as the year 2023 is still ongoing, these numbers are not yet

representative of the current year. Out of the identified products, mAbs account for a significant number of approvals across the years, as depicted in Figure 21B. This dominance demonstrates their established role, but the presence of various other therapies, including ICI (10%) and CAR-T cell therapy (6%), indicates a dynamic market that's continually expanding and adapting. Figure 22C provides insight into the top 10 indications for approved cancer immunotherapy products, presenting a comprehensive overview of the therapeutic priorities within the field. Hematologic cancers, such as lymphoma and leukemia, and lung cancer stand out as the top three most common indications. Nonetheless, breast cancer, colorectal cancer, and several other types of cancer are also features, demonstrating the versatility of immunotherapy across a range of cancer types and highlighting its potential to redefine treatment approaches In diverse clinical contexts.





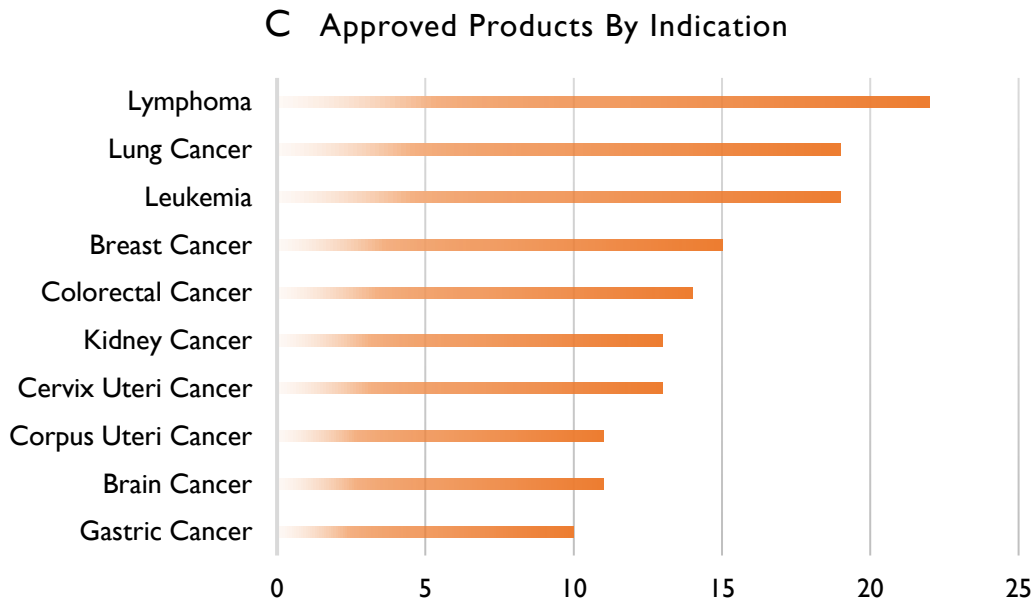
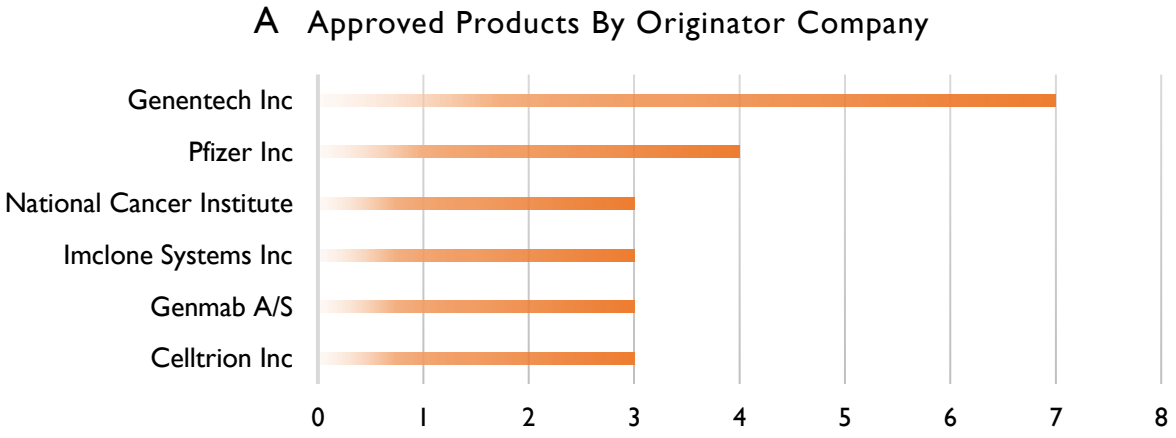


Figure 21 - Approved Products for Cancer Immunotherapy Landscape. This overview includes a graphical representation of the: **A |** Approved products by year; **B |** Approved products by type of therapy; **C |** Top 10 most common indications.

The major originator and active companies, with a minimum of three approvals, are represented in Figure 22A and Figure 22B, respectively. Genentech Inc (headquartered in the United States of America) stands out as the leading originator company with the highest number of approved products and maintains its prominent position among active companies in this regard. This distinction validates Genentech's enduring commitment to advancing cancer immunotherapy and reinforces its pivotal role in shaping the evolving treatment landscape. It is also important to highlight Pfizer Inc. as the second leading originator company in terms of approvals. Furthermore, among active companies, it is noteworthy to mention Roche Holding AG, Chugai Pharmaceutical Co Ltd, which have achieved the same numbers as Genentech. Additionally, Bristol-Myers Squibb Co has emerged as a key player in the field.



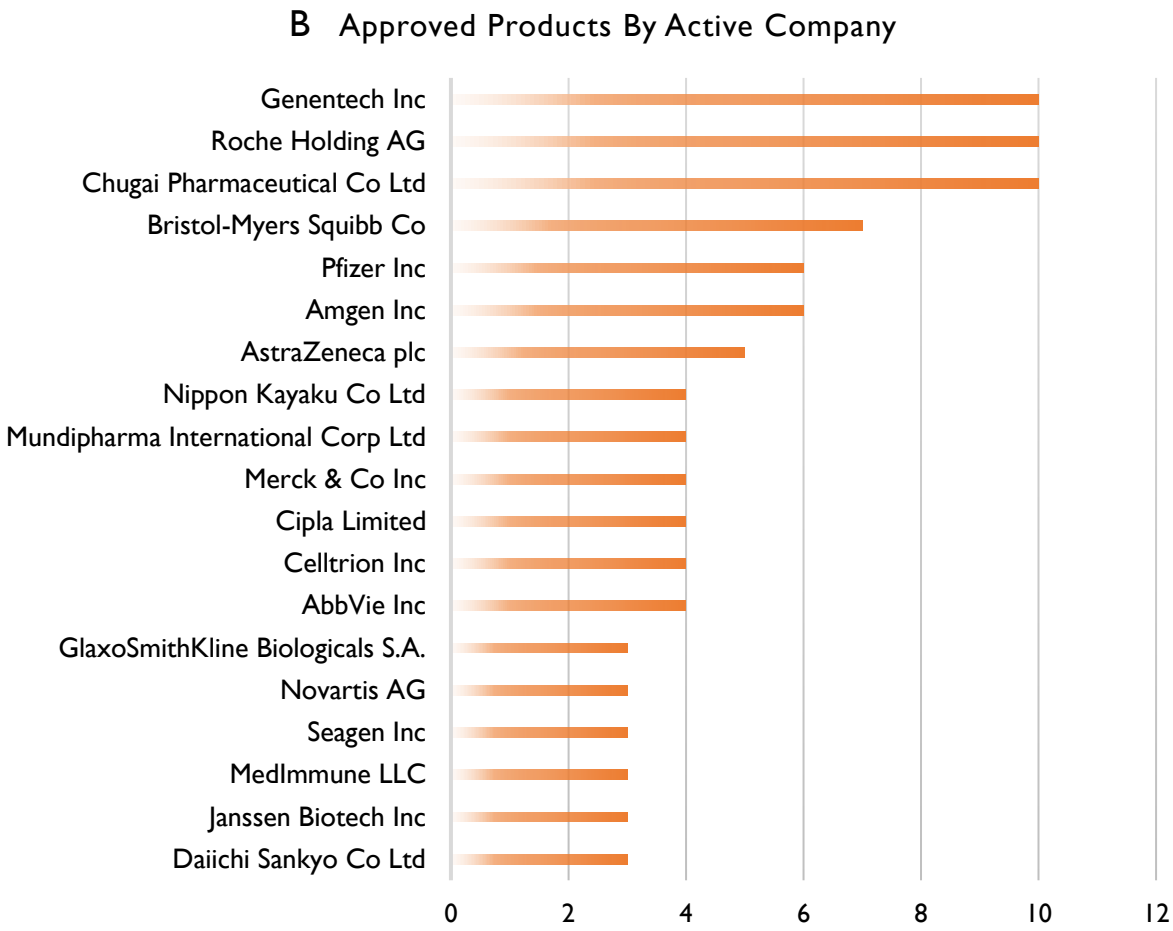


Figure 22 - Key-Players of Immuno-Oncology. This includes a graphical representation of the: **A |** Approved products by originator company, excluding those with fewer than three approvals; **B |** Approved products by active company, excluding those with fewer than three approvals.

Chapter III – Beyond the Horizon: The Promising Future of Immunotherapy

3.1. Introduction

As highlighted in the previous chapter, the field of immuno-oncology is rapidly advancing, offering numerous benefits in the battle against cancer. These advantages encompass the prevention of metastasis and recurrence. However, it is still in its relative infancy, with many challenges yet to be overcome[162]. Indeed, the clinical benefit of cancer immunotherapy is restricted by a range of factors, including inefficient delivery, overall low efficacy, limited tumor penetration, off-target effects, and high toxicity[238]. Additionally, the hypoxic and nutrient-deficient TME, as well as the heterogeneity of tumor cells, significantly inhibit the action of immune cells[238]. Overcoming these challenges and achieving precision anti-tumor therapy is a major direction of immunotherapy research[124]. To this end, several strategies may be implemented, which will be further discussed throughout the chapter:

- Detection of therapeutic response and prognostic biomarkers that accurately indicate the predictions for the patient's response to therapy;
- Combination of immunotherapy with different therapies, such as chemotherapy, radiotherapy and targeted therapy, and with other types of immunotherapies;
- Use of delivery technologies and targeted release mechanisms;
- Development of novel immunotherapies.

3.2. Predictive Biomarkers

The lack of reliable predictive biomarkers of durable response and the limited understanding of clinically relevant determinants of progression are major limitations of immunotherapy[239]. Therefore, the identification of prognostic and predictive biomarkers may help to define tumors that are either immune-responsive or immune-resistant to therapy, illuminate the mechanism of action of novel immunotherapeutic approaches, and potentially inform which patients require single-agent versus combination therapy[120; 163; 198].

As highlighted in the previous chapter, the efficacy of immunotherapy is not determined by only a single factor. Instead, it depends on a combination of variables, which ultimately affect the interactions between tumor and host genomics, TME and immune function[240]. Thus, establishing a predictive model that considers the various elements influencing these interactions holds great importance, as it provides a unique opportunity to evaluate their contribution to the response to immunotherapy[240]. These predictive models will require a continuous process of update and re-evaluation as more knowledge on the molecular determinants of response to immunotherapy is unraveled[240].

Biomarkers that can predict the response to immunotherapy, particularly ICI and CAR-T cell therapy, in advanced malignancies are being extensively studied. Moreover, some biomarkers associated with ICI therapy have been clinically validated. These biomarkers, represented in Table IV may be detected and measured in the tissue, such as tumor tissue and gut tissue, which entails a biopsy, or in the peripheral blood, which requires a blood draw. The subsequent subsections will delve deeper into exploring these types of biomarkers. The evaluation of the samples occurs by next-generation sequencing assays, polymerase chain reactions, or immunohistochemistry assays, depending on the biomarker being analysed[240].

Table IV – Potential Predictive Biomarkers for Immunotherapy.

Source	Biomarker	Association with Favorable Clinical Outcome	Clinical Significance
Tumor Tissue	PD-L1	Positive	High levels are correlated with benefit from ICI therapy[241; 242]
		Negative	High levels are inversely related to patient survival after CAR-T therapy[243]
	TMB	Positive	High TMB is correlated with improved PFS, ORR and OS in anti-PD1/PD-L1 therapy[241; 242; 244]
	dMMR/MSI-H	Positive	Predicts clinical benefit to anti-PD-1/PD-L1 therapy[245]
Gut Tissue	TILs	Positive	High density of TILs is a good prognostic marker and is correlated with increased OS in ICI therapy[241; 242]
	MHC	Positive	Low levels are associated with poor prognosis in anti-CTLA-4 therapy[242]
	Microbiome	Positive or Negative	Increased *Bacteroides* in ICI non-responders and *Akkermansia* in ICI responders have been reported[242]
Peripheral Blood	Absolute Lymphocyte Count	Positive	Low count is correlated with poor prognosis and poor response to immunotherapy[242; 245]
	PD-1	Positive	Expression is a potential predictor of response to PD-1 blockade therapy[242]
		Negative	High levels are associated with decreased patient survival in CAR-T[243]
	Neutrophil/ Lymphocyte Ratio	Negative	Higher ratio is associated with reduced progression-free survival in ICI therapy[242] and is prognostic for IL-2 treatment failure and shorter OS[245]
	MDSC	Negative	High levels are negatively correlated with clinical benefit from ICIs and CAR-T cell therapy[246]

CAR-T Cells	Positive	High counts are associated with increased response to CAR-T therapy[247]
ctDNA	Negative	Early decrease in concentration is correlated with improved OS in ICI therapy[242; 244]
IFN-γ	Positive	High levels correlate with improved response, PFS, and OS in anti-PD-L1 therapy[242]
	Negative	High levels are associated with development of CRS and/or ICANS[246]
IL-6		High IL-6 is a prognostic marker for failure of ICI and CAR-T therapy[243; 248]
	Negative	On-therapy increase is predictive of development of irAEs in ICI treatment[243]
	Negative	High levels correlate with decreased survival with CAR-T therapy[243]
		High levels are associated with development of CRS and/or ICANS[246]
IL-8	Negative	High IL-8 levels are correlated with decreased survival with CAR-T therapy[243]
IL-10	Negative	High levels are associated with development of CRS and/or ICANS[246]
VEGF	Negative	High levels are associated with decreased OS in ICI therapy[245]
C-reactive Protein	Negative	High levels are a prognostic marker for treatment failure and shorter OS after ICI[245]
Lactate Dehydrogenase	Negative	High levels predict poor response to ICI and CAR-T therapy[245]

Abbreviations are as follows: PD-L1 – Programmed Death Ligand 1; ICI – Immune Checkpoint Inhibitors; dMMR – Deficient Mismatch Repair; MSI-H – Microsatellite Instability High; PD-1 – Programmed Death 1; TMB – Tumor Mutational Burden; PFS – Progression-Free Survival; ORR – Overall Response Rate; OS – Overall Survival; TILs – Tumor Infiltrating Lymphocytes; MHC – Major Histocompatibility Complex; CTLA-4 – Cytotoxic T Lymphocyte Associated Protein 4; IL – Interleukin; MDSC – Myeloid Derived Suppressor Cells; INF – Interferon; irAEs – Immune Related Adverse Events; CRS – Cytokine Release Syndrome; ICANS–- Immune Effector Cell-Associated Neurotoxicity Syndrome; ctDNA – Circulating Tumor DNA; VEGF – Vascular Endothelial Growth Factor.

3.2.1. Tissue Biomarkers

The current landscape of FDA-approved tissue biomarkers for solid malignancies includes PD-L1 expression, tumor mutational burden (TMB) and microsatellite instability, all associated with ICI therapy. The use of each of these biomarkers has played a significant role in assisting the appropriate selection of patients for ICI treatment[249].

PD-L1 is the most investigated and clinically used predictive biomarker for ICI[249]. In fact, numerous clinical trials have established its predictive potential, consistently revealing that patients with elevated PD-L1 levels experience more significant benefits from ICI therapy[241]; [250]. These outcomes resulted in the approval of PD-L1 evaluation as a standard procedure for anti-PD1 therapy in patients diagnosed with non-small cell lung cancer in 2015[249]. Since then, the FDA has approved the assessment of levels of PD-L1 for six additional tumor types, gastric or gastroesophageal junction adenocarcinoma, cervical cancer, urothelial carcinoma, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma and triple-negative breast carcinoma[249]. However, PD-L1 is, by itself, an imperfect biomarker, as its expression can be influenced by active immune responses[242]. Consequently, alternative biomarkers predictive of ICI efficacy, independent of PD-L1 status, are being evaluated.

One such biomarker is the TMB, which is a measure of the number of mutations carried by tumor cells[242]. Thus, it correlates with the likelihood of generating immunogenic neoantigens and, thus, eliciting an immune response[242]. In a study conducted by Lee and collaborators, which included over 1,600 patients treated with ICI, the patients whose tumors obtained the 10% highest TMB scores experienced 10-20% longer overall survival, better objective response rates and progression-free survival[251]. For this reason, the analysis of the TMB was approved for pembrolizumab for the treatment of patients with unresectable or metastatic solid tumors in 2020[249].

Another example is a defective DNA mismatch repair system. Tumors with this deficiency accumulate several mutations across the genome[249]. Mismatch errors are particularly prone to occur in short tandem repeats, referred to as microsatellite regions[249]. This condition is known as microsatellite instability[249]. Tumors with deficient mismatch repair or high microsatellite instability have increased TMB, which promotes the infiltration of T cells within the TME, and leads to improved response with anti-PD1/PD-L1 therapies[242; 252]. Several clinical trials, including "Keynote 177" (NCT02563002), determined that patients with metastatic colorectal cancer exhibiting high microsatellite instability and/or mismatch repair deficiency have better outcomes when receiving first-line ICIs compared with

chemotherapy[253]. In 2017, the FDA announced a biomarker-based approval for pembrolizumab for patients with unresectable or metastatic solid tumors exhibiting high microsatellite instability or mismatch repair deficiency[254].

Despite the already approved biomarkers playing a vital role in predicting the response to ICI therapy, the ongoing research of experimental cancer tissue biomarkers reveals immense potential. These emerging biomarkers hold the promise of enhancing our understanding of tumor behavior and improving patient outcomes. These include TILs, leucocytes, MHC and the microbiome.

TILs, particularly $CD4^+$ and $CD8^+$ T cells within the TME, have been identified as potentially predictive biomarkers of ICI efficacy since they are the main effectors of ICI's anti-tumoral activity[249]. A higher density of TILs has been associated with improved outcomes, specifically increased overall survival, in different tumor types, including ovarian and colorectal cancer[242; 255]. Additionally, TILs' immunophenotypes, mainly high PD-1 and CTLA-4 expression, have been correlated with better responses to ICI therapy[256].

Moreover, MHC class I molecules, essential for CTL activation, are occasionally downregulated in cancer cells as an immune evasion mechanism, which is frequently associated with poor prognosis[242]. Major (>50%) or total loss of MHC-I expression on the surface of melanoma cells was linked to poor prognosis and served as a reliable marker of resistance to anti-CTLA-4 ICI therapy[242; 257]. In addition, low levels of MHC have been correlated with a reduced density of the immune infiltrate[258].

Finally, the gastrointestinal microbiota has emerged as a significant factor in anti-tumor immunity. A balanced, healthy microbiota was suggested to enhance the anti-tumor effect of immune cells and increase tumor cell immunogenicity. This beneficial impact may occur through several mechanisms, such as the release of metabolites that may promote DC maturation, NK cell activation and T cell infiltration and activation, thus leading to improved therapeutic responses[259]. For example, increased *Akkermansia* has been detected in ICI-responding pre-clinical models[242]. However, elevated numbers of certain bacteria in the microbiota can inhibit the anti-tumor response by impairing immune cell activity. Indeed, increased *Bacteroides* have been detected in ICI non-responders[242]. Despite these observations, further research is necessary to elucidate the correlation between microbiota composition and diversity, immunotherapy response, and toxicity, as well as validate the effects of microbiota alterations on treatment outcomes[242].

3.2.2. Peripheral Blood Biomarkers

Peripheral blood-based biomarkers hold significant appeal in cancer research due to their non-invasive nature. These biomarkers offer the advantage of being easily accessible and hold promise for their potential applications in cancer screening, prognosis, and monitoring of treatment response. Within this realm, both cellular and soluble biomarkers have been extensively investigated. Examples of cellular biomarkers include peripheral T lymphocytes, their expression level of PD-1, neutrophil-to-lymphocyte ratio, MDSCs and CAR-T cells. These cell populations can provide insights into the immune response and, in some cases, potential immunosuppressive mechanisms in cancer. On the other hand, soluble biomarkers encompass circulating tumor DNA (ctDNA), inflammatory cytokines, and other soluble factors.

Cellular Biomarkers

The peripheral T lymphocyte count has been identified as an indicator of response to immunotherapy. A lower pre-treatment lymphocyte count is associated with poor prognosis in terms of overall survival, relapse and metastasis in ICI therapy[260]. In addition, the immunophenotype of peripheral $CD8^+$ T cells, particularly the expression of PD-1, has been proposed as a potential predictor of response to PD-1 blockade therapy[242]. Contrarily, high PD-1 levels are associated with decreased patient survival in CAR-T therapy, since PD-1 expression in tumor cells directly inhibits CAR T-cell effector functions[243].

Furthermore, the neutrophil-to-lymphocyte ratio was established as a method to assess the balance between pro-tumoral inflammatory status and anti-tumor immune response[242]. Higher values of this ratio have been associated with reduced progression-free survival, suggesting its potential as a predictive biomarker for assessing the effectiveness of immunotherapy[261].

Moreover, MDSCs are negatively correlated with clinical benefit due to their ability to foster an immunosuppressive TME, which hinders the efficacy of ICIs, as well as CAR-T cell therapy[246]. Thus, MDCSs present as potential predictive biomarkers for identifying patients who may derive the most benefit from immunotherapy[246; 262].

Finally, regarding predicting benefit for CAR-T cell therapy, an important factor is the expansion of CAR-T cells after infusion into the patient, which results in a significant increase in their numbers and correlates with improved objective responses to therapy[247].

Soluble Biomarkers

The use of ctDNA has emerged as a valuable biomarker for screening and predicting the clinical response to ICI in a cost-effective and accessible manner. Tumor-derived ctDNA enters the bloodstream through various mechanisms, including necrotic, apoptotic or circulating tumor cells, or exosomes released by tumor cells[263]. By studying ctDNA, researchers can detect gene mutations and specific changes in cancer cells, providing a clinical foundation for treatment decisions and prognosis[244]. Notably, in patients with advanced solid tumors undergoing pembrolizumab treatment, a significant reduction in ctDNA levels early on has been strongly associated with improved overall survival, regardless of tumor type, TMB, or PD-L1 status[264]. This observation highlights the potential of ctDNA as a dynamic biomarker to monitor treatment response.

Furthermore, as discussed in the previous chapter, cytokines play a pivotal role in modulating the immune system. Indeed, high levels of INF-γ were correlated with improved response, progression-free survival and overall survival in anti-PD-L1 therapy[242]. Moreover, evidence suggests that elevated IL-6 is a negative biomarker of prognosis for ICI and CAR-T treatment[243; 248]. High levels of IL-6, as well as IL-8, are also associated with decreased patient survival when treated with CAR-T cell therapy[243]. Cytokines have also been studied as biomarkers of the development of toxicity, particularly with CAR-T treatment. Elevated levels of IL-6, IL-10 and INF-γ have been reported as robust biomarkers of development of severe CRS and/or ICANS[246]. On-therapy increase in IL-6 has been suggested to be predictive for irAEs in ICI treatment[243]. However, it is important to acknowledge that the expression of cytokines can be affected by various factors, such as tumor burden, the presence of brain metastasis, and co-existing conditions like stress and infection[265]. These factors can limit the sensitivity and specificity of cytokines as predictive biomarkers[265].

Finally, elevated levels of VEGF and C-reactive protein are associated with decreased overall survival in patients treated with ICI therapy[245]. Similarly, high concentrations of lactate dehydrogenase are linked with poor responses in both ICI and CAR-T therapy[245; 247].

3.2.3. Concluding Thoughts and Future Considerations of Predictive Biomarkers

The success of immunotherapy, particularly ICI therapy, relies heavily on predictive biomarkers. However, their development and implementation into clinical practice face numerous challenges. A significant challenge arises from the intra-tumoral and inter-tumoral heterogeneity[242; 243]. Indeed, in both the primary tumor and distant metastatic sites, certain clones may not be accurately represented in the tumor biopsy[242]. Furthermore, intra-tumoral heterogeneity gives rise to diverse patterns of biomarker expression among distinct regions or cell subpopulations within the tumor. This diversity extends to treatment-resistant subsets, increasing the risk of therapy failure and undermining treatment efficacy.

The variability in the host immunity and the intricate interactions between tumor cells and immune cells within the TME also pose significant limitations on the utilization of biomarkers[242; 243]. Immune cells within the TME are known to play pivotal roles in either the amplification or suppression of the immune response and relying solely on biomarkers that represent cancer cells may not accurately reflect the actual response to immunotherapy[242].

Moreover, cancer itself may undergo evolutionary changes throughout treatment[242; 243]. Unfortunately, obtaining multiple tissue biopsies at different treatment stages is infeasible, mainly due to the invasiveness of the procedure, the risk of complications, the financial burden, and, in some cases, the tumor's location and accessibility[242]. This aspect restricts the widespread use of biomarkers[242].

The current use of biomarkers also faces challenges due to substantial variability In pre-analytical processing and subsequent clinical interpretation[266]. Therefore, it is imperative to establish tighter control and further validate and standardize the techniques employed to ensure reproducibility in biomarker validation within clinical trials[266].

Despite these challenges, biomarkers are anticipated to form the cornerstone of immunotherapy for all cancer types[243]. However, since it is unlikely that a single biomarker will be predictive for every type of cancer immunotherapy, comprehensive immune profiling of individual tumors will likely be required to develop predictive biomarkers that can accurately guide patient selection for immunotherapy[243]. This approach recognizes the complexity and individuality of each patient's tumor and immune response, leading to a more personalized and effective application of immunotherapy. As the repertoire of biomarkers expands, it will be possible to unlock new avenues for personalized cancer therapies, leading to more precise

and effective treatments tailored to individual patients. In addition, as research progresses, the identification and validation of these experimental biomarkers will undoubtedly contribute to the ever-evolving field of oncology and pave the way for transformative breakthroughs in cancer care.

3.3. Combination Strategies

The field of cancer treatment has been transformed by immunotherapy, especially for patients whose condition was previously considered untreatable. Nevertheless, the effectiveness of monotherapy is often hindered by resistance mechanisms, leading to treatment failure[109]. Furthermore, only a small fraction of patients achieve long-lasting benefits[109].

Combining therapies has emerged as a viable approach to enhance the effectiveness of cancer immunotherapy, enabling significant improvements in outcomes[267]. Such a strategy may encompass sequential or simultaneous administration of two or more immunotherapies and/or combinations with conventional cancer therapies, effectively overcoming the limitations of individual therapies[167]. This field is rapidly advancing, with new combinations of treatments being evaluated almost on a monthly basis[267].

The aim of combining immunotherapies with other treatment modalities is to enhance the immune response, mitigate immunosuppression, and target signaling and resistance pathways. This integrated approach leads to durable, long-lasting, and effective treatment options for cancer patients, surpassing the outcomes achieved with traditional therapies and single-agent treatments[120] (Figure 23). Several combination therapies have been approved by the FDA (Table V), and numerous clinical trials, which have reported clinical benefits, are currently underway[268].

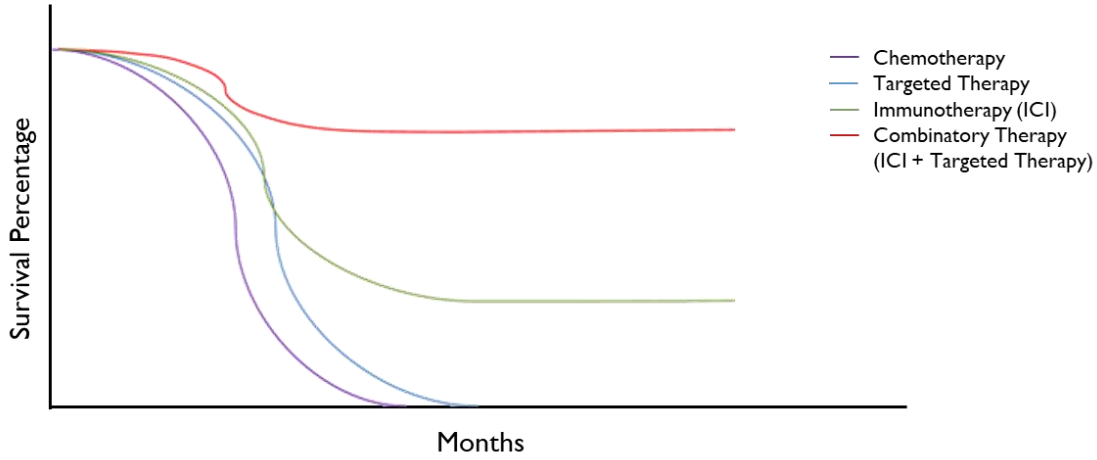


Figure 23 - Depiction of Kaplan-Meier survival curve with chemotherapy, targeted therapy, immunotherapy and combinatory therapy. Improved median overall survival and durable responses are demonstrated in a fraction of patients treated with immune checkpoint therapy (green line) and in the majority of patients treated with combinatory therapy (red line). Adapted from Sharma 2015[169] .

Table V – Approved Immunotherapy Combinations.

Combination	Drugs	Indications and FDA Approval Year	References
ICI + CT	Pembrolizumab + Chemotherapy	Non-Squamous NSCLC (2017, 2018), HNSCC (2019), TNBC (2020), Esophageal and GEJ Carcinoma (2021)	109; 269
ICI + CT ± mAb	Pembrolizumab + Chemotherapy ± Bevacizumab	Cervical Cancer (2021)	269
ICI + CT + mAb	Pembrolizumab + Chemotherapy + Trastuzumab	HER-2^{+} Gastric or GEJ Adenocarcinoma (2021)	109; 269
ICI + TT	Pembrolizumab + Lenvatinib	Endometrial Carcinoma (2019), RCC (2021)	109; 269
ICI + TT	Pembrolizumab + Axitinib	RCC (2019)	109; 269
ICI + CT	Atezolizumab + Chemotherapy	NS NSCLC (2019), SCLC (2019), TNBC (2019)	109; 269
ICI + mAb	Atezolizumab + Bevacizumab	HCC (2020)	109; 269
ICI + mAb + CT	Atezolizumab + Bevacizumab + Chemotherapy	NSCLC (2018)	109; 269
ICI + TT	Atezolizumab + Cobimetinib + Vemurafenib	Metastatic Melanoma (2020)	109; 269
ICI + CT + RT	Durvalumab + Chemotherapy + Radiotherapy	NSCLC (2018)	109; 269
ICI + CT	Durvalumab + Chemotherapy	SCLC (2020), Biliary Tract Cancer	109; 269

ICI + ICI	Nivolumab + Ipilimumab	Metastatic Melanoma (2015, 2016), RCC (2018), CRC (2018), HCC (2020), NSCLC (2020), Pleural Mesothelioma (2020)	109; 269
ICI + ICI + CT	Nivolumab + Ipilimumab + Chemotherapy	NSCLC (2020)	109
ICI + CT	Nivolumab + Chemotherapy	GC (2021), Esophageal Adenocarcinoma (2021), NSCLC (2022)	269
ICI + TT	Nivolumab + Cabozantinib	RCC (2021)	109; 269
ICI + CT	Avelumab + Chemotherapy	Bladder Cancer (2020)	109; 269
ICI + TT	Avelumab + Axitinib	RCC (2019)	109; 269
ICI + ICI	Tremelimumab + Durvalumab	HCC (2022)	270
ICI + ICI + CT	Tremelimumab + Durvalumab + Chemotherapy	NSCLC (2022)	271
mAb + CT + TT	Daratumumab + Chemotherapy + Carfilzomib	Multiple Myeloma (2020)	272
mAb + CT	Rituximab + Chemotherapy	Lymphoma (2021), B-cell Acute Leukemia (2021)	273
mAb + TT	Rituximab + Ibrutinib	Lymphocytic Leukemia (2020)	274

Abbreviations are as follows: ICI–- Immune Checkpoint Inhibitor; CT – Chemotherapy; mAb – Monoclonal Antibody; TT – Targeted Therapy; RT – Radiotherapy; HNSCC–- Head and Neck Squamous Cell Carcinoma; TNBC – Triple Negative Breast Cancer; GEJ – Gastroesophageal Junction; RCC – Renal Cell Carcinoma; SCLC – Small Cell Lung Cancer; CRC – Colorectal Cancer; HCC – Hepatocellular Carcinoma.

3.3.1. Combining Immunotherapy with Other Therapies

The synergistic interaction between immunotherapy and chemotherapy has been firmly established. As mentioned in the previous chapter, chemotherapy induces several effects on the immune system, such as triggering immunogenic cell death, reducing the production of immunosuppressive factors and the number of immunosuppressive cells, and increasing antigen processing and presentation[108; 109]. As such, chemoimmunotherapy has become a standard option in some cancers, particularly associated with ICI[120].

The use of these combinations has ”ed t’ significant overall improvements in patient outcomes, surpassing those achieved with chemotherapy alone[109]. Lung cancer has been a prime example of the synergistic benefits of such combinations. For non-small cell lung cancer, the combination of chemotherapy with ICIs such as pembrolizumab (Keytruda®, Merck Sharp & Dohme), atezolizumab (Tecentriq®, Genentech Inc.), and nivolumab (Opdivo®, Bristol-Myers Squibb) has been approved, resulting in over 4 months of increased OS[275; 276; 277]. In the case of small cell lung cancer, the combination of chemotherapy with two ICIs, atezolizumab (Tecentriq®, Genentech Inc.) and durvalumab (Imjudo®, AstraZeneca AB), have been approved, leading to OS benefits of 2 and 2.7 months, respectively[278; 279].

In addition to ICIs, various mAbs have demonstrated improved efficacy and survival when used in combination with chemotherapy[280; 281]. Some of these mAbs include rituximab (Rituxan®, Genentech Inc.), which achieved a 13% improvement in one year event-free survival[40], and brentuximab vedotin (Adcetris®, Seattle Genetics), which resulted in a 59% lower risk of an event or death[280; 281]. Moreover, the FDA has approved combinations of ICIs, chemotherapy and mAbs or targeted therapies for the treatment of cervical cancer, HER-2 positive gastric cancer, lung cancer, metastatic melanoma, and multiple myeloma.

Furthermore, radiotherapy has shown synergy with various immunotherapy approaches, particularly anti-PD-1/PD-L1 antibodies[282]. In fact, the combination of radiotherapy, chemotherapy and durvalumab (Imjudo®, AstraZeneca AB) has been approved for patients diagnosed with non-small cell lung cancer[283]. The combination demonstrated a remarkable enhancement, with a 20% increase in one-year progression-free survival, a 12% rise in response rates, and a substantial extension of approximately 9 months in the duration until the occurrence of distant metastasis or death[283].

Finally, the combination of targeted therapies, which target proteins that control how cancer cells grow, divide, and spread[284], and immunotherapy, particularly ICI, has emerged as

a highly effective strategy for maximizing therapeutic benefits due to synergistic action and reducing toxicity in cancer treatment. Notably, the use of ICI in combination with anti-angiogenic agents has gained significant attention, leading to the approval of several combinations as first-line therapies for major cancer types[269]. In renal cell carcinoma, four combinations involving anti-angiogenic agents, namely pembrolizumab (Keytruda®, Merck Sharp & Dohme) plus lenvatinib (Lenvima®, Sun Pharm Inds Inc. Inc)[285], pembrolizumab plus axitinib (Inlyta®, Teva Pharms Inc.)[286], nivolumab (Opdivo®, Bristol-Myers Squibb) plus cabozantinib (Cabometyx®, Teva Pharms Inc.)[287], and avelumab (Bavencio®, EMD Serono Inc.) plus axitinib[288], have significantly improved patient survival compared to targeted therapy monotherapy. Apart from angiogenic inhibitors, other targeted therapies have exhibited immune-related benefits. For instance, the combination of the ICI atezolizumab (Tecentriq®, Genentech Inc.) with targeted molecules cobimetinib (Cotellic®, Genentech Inc.) and vemurafenib (Zelboraf®, Genentech Inc.) gained approval for metastatic melanoma, resulting in a significant increase in progression-free survival for patients with this condition[289]. Moreover, targeted small molecules have received approval in combination with mAbs such as daratumumab (Darzalex®, Janssen Biotech Inc.) with chemotherapy and carfilzomib (Kyprolis®, Dr Reddys) for multiple myeloma[290], and rituximab (Rituxan®, Genentech Inc.) with ibrutinib (Imbruvica®, Sandoz Inc.) for lymphocytic leukemia[291], achieving notable improvements in terms of progression-free survival. The previously mentioned combinations represent exciting advancements in cancer treatment, highlighting the potential of targeted therapies to enhance the immune response and improve patient outcomes.

3.3.2. Combining Immunotherapies

The combination of different types of immunotherapy agents has garnered significant attention and shown great potential in the fight against cancer.

For example, the combination of the PD-1/PD-L1 blockade with the CTLA-4 blockade, which inhibits two IC, has been demonstrated to induce higher response rates and significantly improve overall survival, achieving an unprecedented five-year overall survival above 50% in metastatic melanoma[292]. These outcomes resulted in the approval of nivolumab (Opdivo®, Bristol-Myers Squibb) and ipilimumab (Yervoy®, Bristol-Myers Squibb) for metastatic melanoma, renal cell carcinoma, colorectal cancer, hepatocellular carcinoma, metastatic non-small cell lung cancer and pleural mesothelioma. In addition, this combination was approved with chemotherapy for patients with metastatic non-small cell lung cancer.

Additionally, Opdualag® (Bristol-Myers Squibb), a combination of relatlimab (a LAG-3 mAb) and nivolumab (a PD-1 mAb), was approved by the FDA in 2022 as a first-line treatment for melanoma[293]. The use of Opdualag® resulted in a significant improvement in progression-free survival, with a duration of 10.1 months[293]. This value represents more than double the duration observed in patients treated with nivolumab (Opdivo®, Bristol-Myers Squibb) alone without worsening the side effects associated with the treatment[293].

Furthermore, ICIs have been approved in combination with mAbs, such as bevacizumab (Avastin®, Genentech Inc.) and trastuzumab (Herceptin®, Genentech Inc.). Pembrolizumab (Keytruda®, Merck Sharp & Dohme), for instance, has been approved in combination with chemotherapy and either bevacizumab (Avastin®, Genentech Inc.) or trastuzumab (Herceptin®, Genentech Inc.) for cervical cancer[294] and HER-2 positive gastric cancer[295], respectively. Similarly, atezolizumab (Tecentriq®, Genentech Inc.) in combination with bevacizumab (Avastin®, Genentech Inc.) has received approval with and without chemotherapy for hepatocellular carcinoma[296] and non-small cell lung cancer[297], respectively.

Currently, multiple ongoing studies are investigating various other combinations that have shown promising and encouraging results. Of particular interest is the combination of CAR-T cell therapy and ICI, given the functional inhibition of CAR-T cells by PD-1/PD-L1[298]. Indeed, preclinical studies have demonstrated the effective enhancement of the anti-tumor effect when employing this strategy[298]. Additionally, the combination of oncolytic viruses with CAR-T cell therapy has emerged as a potentially safer and more effective treatment approach for solid tumors[299]. Preliminary evidence suggests that this combination may lead to better therapeutic outcomes and long-lasting responses while using lower dosages, which will reduce adverse events[299]. The use of immunostimulatory cytokines alongside cancer vaccines has also been the subject of extensive research in various clinical trials[109]. Cytokines like IL-2 have shown promise in enhancing vaccine efficacy, leading to significant improvements in overall response rates and progression-free survival[109]. Beyond IL-2, several other immunostimulatory cytokines are also under exploration to harness their potential in boosting the immune response against cancer cells[109]. Interest has also arisen in the combination of cancer vaccines and ICI. Both preclinical and clinical studies are actively investigating this strategy, which has shown promising results in improving responses to therapy[109]. The potential synergy between cancer vaccines and ICIs offers new possibilities for enhancing the body's ability to recognize and target cancer cells effectively. In addition to those mentioned above, the future of combinatory regimens may involve the use of [167]:

- Immune Checkpoint Inhibitors and oncolytic viruses;
- Immune Checkpoint Inhibitors and NK cell therapy;
- mAbs and oncolytic viruses;
- CAR-T cell therapy and cytokines;
- CAR-T cell therapy and NK cell therapy;
- CAR-T cell therapy and oncolytic viruses;

3.3.3. Concluding Thoughts and Future Considerations of Combination Strategies

In the dynamic landscape of cancer treatment, the quest to unlock the full potential of immunotherapy combinations is accompanied by several challenges that require innovative strategies and collective efforts to overcome.

One of the foremost challenges lies in balancing the synergistic effects of combining therapies and the potential for increased toxicity and adverse events. While each combination may possess unique mechanistic synergism, extensive research is still required to determine the optimal dosage, sequence, and schedule that yields optimal efficacy while maintaining manageable toxicities[120].

Additionally, as mentioned in previous subsections, the identification of reliable biomarkers for predicting patient response to combination immunotherapy is hindered by the complex interactions between the immune system and cancer cells[120]. For instance, the predictive value of PD-L1 expression may become challenging to determine in the context of combination therapy due to the complex mechanistic interactions between the different therapeutics involved.

The regulatory and clinical trial design also presents unique challenges, Iding the selection of appropriate endpoints, patient populations, and control groups. Overcoming these challenges requires the application of innovative approaches, collaborative research efforts, and careful consideration of patient safety and efficacy. Furthermore, the economic aspect poses an additional obstacle, as the cost of immunotherapy treatments averages nearly $150,000, per year, for ICI[126]. Combination therapies, such as ipilimumab (Yervoy®, Bristol-Myers Squibb) and nivolumab (Opdivo®, Bristol-Myers Squibb), commonly used for advanced melanomas, naturally entail greater costs[126]. The emergence of combination strategies with newer modalities such as adoptive cellular therapy, which are inherently more expensive Furthermore, despite the administration of combinatory therapies, many patients still fail to

achieve satisfactory responses, and treatment-related adverse events persist, sometimes increasing with the combinations. A comprehensive understanding of the intricate interactions between diverse immunotherapeutic agents and their impact on the TME is indispensable for optimizing combination strategies. This way, to achieve the desired effect, it is crucial to individually determine which combinatory approach will demonstrate the best results in treating a specific oncological disease for each patient[167].

Finally, in order to improve the response to therapy in immune-resistant cancers, the combination strategy has achieved enthusiastic results. Indeed, the combinatorial approach is now regarded as the most promising to convert immunologically cold tumors into hot tumors. Therapeutic strategies aimed at establishing a hot phenotype focus on enhancing T cell priming and activation, expansion, trafficking to the tumor, and infiltration[175]. These approaches encompass the utilization of immune adjuvants, chemotherapy, radiotherapy, oncolytic viruses, and other methods to facilitate antigen release, presentation, and subsequent T cell activation[175]. Additionally, cancer vaccines and adoptive cellular therapies, such as CAR-T cells, have been employed to increase the numbers of tumor-specific T lymphocytes that will, therefore, enhance the efficacy of immunotherapy[175]. Different therapeutic approaches have also been used to promote T-cell trafficking and infiltration into the tumor[175]. Such therapies include oncogenic pathway inhibitors (e.g., RAS), inhibitors of epigenetic modifications, anti-angiogenic therapies, and TGFβ inhibitors[175].

As researchers and clinicians continue to deepen their understanding of tumor biology, the immune system, and the mechanisms of treatment resistance, novel combination strategies are being developed. Personalized treatment approaches, tailored to individual patients based on their specific tumor characteristics and biomarker profiles, will become a cornerstone of cancer care. With advancements in immunotherapy, targeted therapies, and precision medicine, combination regimens will be designed to optimize therapeutic responses while minimizing side effects, thus improving patient outcomes.

3.4. Delivery Systems

Delivery systems have been widely employed in clinical practice due to their ability to introduce a therapeutic substance into the body and improve therapy outcomes. Delivery technologies can increase the accumulation of therapeutic agents within diseased tissues, enable more effective targeting of the tumor and/or immune cells and reduce off-target adverse effects, thus facilitating patient compliance[300]. Such systems have been extensively applied to increase the efficacy of immunotherapy and reduce untargeted cytotoxicity, functioning as an integrated platform to deliver individual or multiple therapies and modulate immune responses against cancer cells[238].

Based on delivering biomaterials, delivery systems may be grouped into viral (e.g., lentivirus, retrovirus and adenovirus) and non-viral approaches (e.g., nanoparticle (NP)-based, cell-based and biomaterial delivery)[301]. Viral strategies, particularly oncolytic viruses, enable the development of robust anti-tumor immune responses[301]. However, the use of viral delivery systems in cancer immunotherapy is limited, mainly due to safety concerns and manufacturing challenges[302]. Alternatively, non-viral systems, which are the focus of the following subsections, have been demonstrated to be an attractive strategy that can address these challenges, characterized by simple manufacture and low cost[303] (Table VI). Interestingly, researchers have attempted to form virus encapsulated in non-viral vectors[304]. These hybrid vectors form a new class of gene delivery vectors which overcome the limitations of each vector and simultaneously augment desirable features[304].

Table VI – Advantages and challenges of viral and non-viral delivery systems. Adapted from Wang et al., 2022[305], Park et al., 2019[306] and Dogbey et al., 2023[307].

	Advantages	**Challenges**
Viral Delivery Systems	High transduction efficiency Sustained vector expression Specificity	Highly immunogenic Risk of insertion mutagenesis Limited packaging capacity Difficulty of production
Non-Viral Delivery Systems	Low immunogenicity High loading capacity Chemical design flexibility Low toxicity Low risk of mutagenesis Simple and cost-effective synthesis Scalable production	High quantity for therapeutic effect

3.4.1. Viral Delivery Systems

Viral vectors have been engineered for a wide range of applications in drug and gene delivery as well as in vaccines[307]. In the field of immuno-oncology, these vectors can elicit an immune response through various mechanisms. They can induce immunogenic cell death, facilitate the recruitment of dendritic cells, and enhance the uptake and presentation of antigens, thereby triggering a robust immune response[301]. The use of viral delivery systems for local immunotherapies offers several advantages over systemically administered immunotherapies[301]. These advantages include a reduced risk of systemic side effects and the potential for higher concentrations of therapeutic molecules within the tumor site[301]. However, viral vectors possess intrinsic limitations. These drawbacks include challenges in their production, limited opportunities for repeated administrations due to acute inflammatory responses, and the risk of insertional mutagenesis[308].

Various viruses, including adenovirus, retrovirus, and herpes simplex virus, have been harnessed for the treatment of cancer, which are often genetically engineered to demonstrate oncolytic abilities. Oncolytic viruses have gained significant attention and thorough investigation due to their remarkable ability to specifically induce tumor cell destruction and stimulate immune responses[309]. These oncolytic viruses are often genetically modified to augment their anti-tumor effectiveness. These modifications involve incorporating immunostimulatory transgenes into the viral genome, such as GM-CSF, IL-12, CD40 and 4-1BB ligands, IL-2, TNF-α, OX-40 ligand, and others[309]. Additionally, combining oncolytic viruses with checkpoint inhibitors has emerged as a promising strategy to achieve prolonged control of tumors in patients who are unresponsive to systemic immune checkpoint blockade[309]. This strategy relies on the action of the oncolytic virus to reverse immune suppression and create a more favorable microenvironment for ICI therapy[309].

3.4.2. Non-Viral Delivery Systems

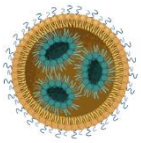
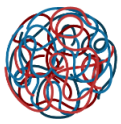
Non-viral vectors can be originated from either organic or inorganic sources. They are known for their biosafety, low immunogenicity, and lack of pathogenicity[310]. One of their key advantages is the flexibility in design, enabling easy and rapid modifications to achieve desired physicochemical properties tailored for delivering specific types of cargos[310].

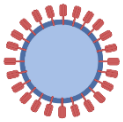
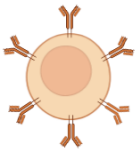
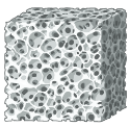
Delivery systems must be able to remain stable in the blood, escape immune recognition, penetrate the tumor interstitial fluid of the TME and interact exclusively with the target cells[311]. These objectives can be achieved through passive or active targeting. Passive targeting

strategies are based on the characteristics of the carrier (e.g., size and circulation time) and tumor biology (e.g., vascularity, leakiness, etc.) to facilitate accumulation in the tumor[311]. This accumulation is promoted by the Enhanced Permeability and Retention (EPR) effect, characterized by the discontinued epithelium that arises in tumor vasculature due to inflammatory and hypoxic conditions[311; 312]. Conversely, active targeting strategies involve coating the surface of the delivery system with ligands (e.g., receptor ligands, antibodies, proteins, peptides, aptamers, etc.) that promote the specific binding to cancer cells[311].

Ongoing research is focused on developing novel delivery systems for immunotherapy that mitigate the limitations associated with this therapy. These strategies include nanoparticles (lipidic, polymeric, inorganic and virus-like particles), cell-based platforms and biomaterials[300]. The main advantages and challenges associated with these delivery systems are represented in Table VII.

Table VII - Advantages and challenges of lipid-based, polymer-based, bio-inspired, inorganic-based, virus-like particle-based, cell-based and biomaterial-based delivery systems. Adapted from Lin et al., 2020[313], Caffery et al., 2022[314], Li et al., 2021[315], Dai et al., 2018[316] and Cui et al., 2021[317].

	Advantages	**Challenges**
Lipid-based 	Simple preparation Good biocompatibility Biodegradability Low immunogenicity Possibility of functionalization Payload flexibility Versatility	Limited stability Easy leakage of payloads Rapid clearance
Polymer-based 	Good biocompatibility Biodegradability (natural and natural-derived) Low cost of production Easy surface modification Possibility of functionalization Payload flexibility Versatility	Toxicity Non-degradability (in some cases)
Inorganic-based 	Multimodal use (diagnostic and therapy) Easy surface modification Good reproducibility Possibility of functionalization	Non-biodegradability (in some cases) Toxicity

Virus-like Particles 	Safety Flexibility Easily scalable Immunogenicity	Limited stability
Cell-based 	Prolonged circulation Specific tissue tropism Biological barrier crossing capability Versatility Low immunogenicity Biodegradable Biocompatibility	Complex manufacture High cost Limited stability
Biomaterials 	Good biocompatibility Good biodegradability Simple production Versatility Local delivery Stability Low cost	Difficulty in maintaining a therapeutic dose (due to uncontrolled degradation) Invasive application (implantable) Inaccessibility to some tumors

3.4.2.1. Nanoparticle-Based Delivery Systems

NP-based delivery systems have been increasingly used in diagnostics and treatment, offering a safer and more effective approach to therapy[318]. They can be composed of a variety of materials such as lipids, polymers, proteins and metals, presenting with several well-defined shapes such as spheres, rods, tubes, among others[311]. These delivery systems can be employed for delivering antibodies or their fragments, peptides, proteins, nucleic acids and small molecules, such as cytokines[238].

NP-based delivery systems have demonstrated several advantages, holding promise for overcoming certain limitations associated immuno-oncology therapy, regulating the immunosuppressive TME and enhancing therapy effectiveness, thus providing more effective treatment options[319]. Such advantages involve[319]:

- Enhancing drug accumulation at the tumor site by leveraging the unique permeability and retention effect of tumor vasculature. This targeted delivery reduces off-target activity and minimizes side effects;
- Stabilizing and protecting the biological activity of protein and nucleic acid drugs, ensuring their efficacy during delivery;

- Improving the solubility of insoluble drugs, enabling their effective administration;
- Enhancing the therapeutic index of drugs by enabling targeted delivery, sustained release, reducing immunogenicity, etc., thus maximizing their therapeutic benefits;
- Reducing systemic toxicity, making treatments safer for patients.

Current NP platforms can be classified into three major categories, including organic (e.g., lipid-based, polymer-based, bio-inspired and virus-like particles), inorganic (e.g., gold, silica, iron oxide, ceramic and carbon) and hybrid NPs. Hybrid NPs have recently been developed to address the specific limitations associated with organic or inorganic vectors[320]. These hybrid vectors encompass polymer-lipid, and organic-inorganic NPs[320].

3.4.2.1.1. Lipid-Based Vectors

Lipid-based nanoparticles are the most represented and commonly FDA-approved type of nanomedicines. They are spherical vesicles of various sizes, primarily composed of natural phospholipids or their derivates[321]. Thus, they have a natural tendency to interact with the cell membrane, facilitating cellular uptake of the drug[313]. Additionally, lipid-based NPs are characterized by simple preparation, low manufacturing costs, scalable production, good biocompatibility, biodegradability and safety, allowing both passive and active targeting strategies[313]. However, there are several challenges, including limited stability, easy leakage of payloads and rapid clearance by the kidneys[313].

The widely used lipid vectors, which have been Id as promising platforms to deliver a variety of therapeutic agents, include liposomes, lipid NPs and micelles[322].

Liposomes are among the most advanced drug delivery systems[323]. They are spherical vesicles composed of one or more lipid bilayers enveloping a hydrophilic core[324]. Liposomes are formed via self-assembly in an aqueous solution and are composed mainly of helper lipids, such as phospholipids, and polyethylene glycol (PEG)-derivatized lipids[321]. These vesicles can transport hydrophilic drugs enclosed in the internal aqueous core, while hydrophobic drugs are enclosed within the lipid bilayer[18]. Liposomes can improve the delivery of antigens and other stimulatory molecules to APCs or T cells and deliver drugs selectively to the TME to overcome the immune-suppressive state[325].

On the other hand, lipid NPs are the main nanocarriers for cancer treatment due to their high drug loading capacity, low leakage, stability, and simple, scalable manufacturing. The

general composition of these nanocarriers consists of different types of lipids, mainly ionizable lipids, helper lipids, cholesterol and PEG-derivatized lipids[322; 324]. The lipid composition of lipid NPs greatly influences particle size, morphology, encapsulation efficiency and surface properties[326]. Due to the complex internal lipid architectures, lipid NPs are considered more suitable for encapsulating genetic payloads with long-term stability[322].

Lipidic micelles are colloidal systems formed spontaneously by amphiphilic molecules, presenting a monolayer with the lipophilic tails forming the inner core[323]. Thus, micelles are usually used as nanocarriers for the delivery of hydrophobic drugs[320; 323]. The major limitation of micelles includes the low drug loading capacity as well as the tendency to dissociate upon dilution to a concentration lower than the critical micelle concentration - the concentration from which molecules start rearranging to form the micellar structure[323].

Lipid-based NPs hold tremendous potential in various aspects of immunotherapy, such as *in vivo* CAR-T cell induction[327] and cancer vaccines, the latter currently being extensively explored in clinical trials. Leading pharmaceutical companies like ModernaTX, Inc., Merck & Co., and BioNTech SE have directed their focus toward harnessing the potential of lipid-based nanoparticles in developing innovative immunotherapeutic approaches. A completed phase I clinical trial conducted by BioNTech SE has been mentioned in multiple reviews[178; 303; 310]. This clinical trial aims to assess the safety and tolerance of intravenous administration of a tetravalent mRNA cancer vaccine designed to target four TSAs in individuals with advanced melanoma (NCT02410733)[328]. This vaccine employs a lipid-based delivery system. Moreover, an ongoing phase I clinical trial (NCT03739931) is actively investigating the safety and tolerability of intra-tumoral administration of mRNA-2752 in individuals with relapsed/refractory solid tumor malignancies or lymphoma[329]. This study employs lipid nanoparticles to deliver mRNAs encoding the costimulatory molecule OX40 ligand, along with IL-23 and IL-36γ, which stimulate the immune response. This approach is being studied alone and in combination with durvalumab (Imjudo®, AstraZeneca AB)[329]. At the moment, no results have been published for these studies.

The Integration of lipid-based nanoparticles into immunotherapy holds great promise, not only for mRNA-based cancer vaccines but also for other applications. These nanoparticles can be tailored to encapsulate various therapeutic molecules, including small interfering RNA, immune checkpoint inhibitors, cytokines, among others[330; 331; 332]. This way, they can enhance the efficacy of these therapies by increasing the concentration of the drug in the target site, reducing off-target effects, and decreasing adverse events. The versatility of these delivery

systems allows for the development of personalized and precise immunotherapies, ultimately leading to better patient outcomes.

As research and clinical trials progress, lipid-based NPs are anticipated to revolutionize the field of immunotherapy. The collaboration between prominent industry players and scientific advancements in this area holds the potential to transform the landscape of cancer treatment and significantly improve patient care.

3.4.2.1.2. Polymer-Based Vectors

Polymeric systems have been exploited as excellent carriers for therapeutic immunogenic agents[333]. These vectors hold several advantages, including biocompatibility, biodegradability, stability, low immunogenicity and tunable size[333; 334]. Additionally, these vectors allow structural and component diversity, easy and controllable production and high loading capacity[333]. Similarly to lipid-based delivery systems, polymer vectors can improve the stability and specificity of the loaded drug by preventing their rapid metabolization and excretion[334].

Polymeric-based vectors may be synthesized using biodegradable or non-biodegradable sources that can be natural or synthetic. Due to its lower toxicity, biodegradable polymers are intensively studied in drug delivery.

Notably, polymeric systems can protect and preserve the activity of bioactive agents, insulating them from unfavorable immune reactions or promoting favorable ones in the body[333]. For these reasons, they can perform several functions in immunotherapy, such as stimulating the immune system, modifying and activating T cells, delivering cargo, or acting as artificial antigen-presenting cells.

Over the past decade, various polymeric systems have been evaluated for use in targeted cancer therapy, including polymeric NPs, dendrimers and micelles.

Polymeric nanoparticles are solid and colloidal particles with sizes ranging from a few nanometers to 1000 nm, with versatile structures and morphologies[335]. They are usually structured via spontaneous and sophisticated self-assembly, during which therapeutic compounds are entrapped within the nanoparticle core[336]. On the other hand, dendrimers are highly ordered, symmetric, branched polymeric molecules[333] formed by a central core and internal branching (dendrons). Dendrimers are monodisperse, water-soluble, biodegradable polymers that have attracted attention as drug carriers[326]. Additionally, polymeric micelles are

self-assembled globular structures with sizes ranging from 10 to 100 nm[326]. Structurally, they are very similar to lipidic micelles. They are composed of amphiphilic molecules that form an outer corona of hydrophilic polar heads and an interior core of hydrophobic tails[326]. Polymeric micelles are very employed in drug delivery due to their unique core-shell structure. The hydrophobic core provides an ideal scenario for the encapsulation of poorly water-soluble drugs and can also be modified to control drug release kinetics.

Polymeric systems offer versatile encapsulation capabilities for a range of molecules, such as antigens, adjuvants, immune checkpoint inhibitors, and cytokines, enabling precise modulation of the immune response against cancer. Recently, polymeric-based delivery systems are being explored for immune checkpoint blockade, with small interfering RNA gene transfection targeting the PD-1/PD-L1 immunosuppressive pathway showing promising results in cancer treatment[333]. Additionally, polymeric nanoparticles emerged as potential gene delivery systems candidates for *in vivo* CAR-T cell induction[337]. Furthermore, studies involving polymeric micelles encapsulating anti-PD-L1 antibodies have demonstrated significant anti-tumor effects[319]. Dendrimers, on the other hand, have shown potential in delivering genetic and peptide vaccines, as well as in NK cell-related cancer immunotherapy, effectively promoting their amplification[302].

3.4.2.1.3. Inorganic Material-Based Vectors

Recently, inorganic materials as nanocarriers have shown great potential in drug delivery systems[338]. These vectors serve as skeletons, capable of loading and releasing drugs, keeping an intact framework in circulation. They are characterized by high stability, low biodegradability and intrinsic electronical and optical properties, which make them suitable for cancer imaging and therapy[320]. Inorganic-based nanocarriers include metallic nanoparticles (e.g., gold, iron oxide, manganese oxide, etc.), silica nanoparticles and carbon nanotubes.

Metallic NPs offer a promising approach for targeted delivery of immunotherapeutic agents in cancer treatment. Gold NPs have long been used in drug delivery due to their chemical and physical characteristics, such as tunable size, optical properties, easy surface modification, stability, and biocompatibility[339]. The application of gold nanoparticles has been studied in various therapeutics, including the delivery of proteins, peptides, small interfering RNA, antibodies and cytokines incorporated with gold NPs[340]. In a phase I clinical trial, PEGylated gold NPs were utilized to deliver TNF-α into cancer cells, which resulted in selective TNF storage in tumor cells[341]. Results showed that this nanomedicine could target

tumors and be administered systemically in doses of TNF that were previously shown to be toxic[341]. However, the clinical application of gold NPs has been limited mostly due to insufficient knowledge and the absence of coherent information, which has led to controversy and disagreement regarding the potential of gold NPs for clinical use[342].

Iron oxide NPs, another class of magnetic nanoparticles, are excellent drug carriers due to their biodegradable, biocompatible, and magnetic features[339]. These nanocarriers enable localized delivery of payload drugs due to the intrinsic targeting ability of macrophages and surface functionalization[343]. They have been studied as carriers of immunomodulatory drugs, therapeutic vaccines, and adoptive cell therapies[343; 344].

Manganese oxide nanomaterials have also received tremendous research interest in the biomedical field due to their unique physiochemical features and excellent biosafety[339]. Within the acidic TME, this material degrades, releasing the loaded drug and oxygen, which alleviates the hypoxic TME, which has an immunosuppressive effect on $CD8^+$ T cell function[339]. Manganese oxide NPs have been designed to load PD-L1-targeting small interfering RNA[345]. *In vivo* experiments showed that this nanocarrier was able to effectively transport the carried cargo to tumor sites and remarkably improve the hypoxic condition of the TME, which results in enhanced efficacy of ICI therapy[345].

Silica-based vectors are commonly used biodegradable and biocompatible inorganic nanomaterials[339]. While there are other silica-based vectors, mesoporous silica NPs have drawn research interest due to their honeycomb-ordered porous structure, which allows the protection of several bioactive molecules[320; 339]. Notably, mesoporous silica NP-loaded vaccines can be internalized into APCs to deliver antigenic information[339].

Lastly, carbon nanotubes, elongated and hollow cylindrical nanostructures, can be utilized as nanocarriers to deliver antibodies, proteins, peptide-based drugs, and nucleic acids for cancer treatment[339]. This material has been reported to stimulate immune responses, which is advantageous when using therapeutic strategies such as immunotherapy. Furthermore, drug-loaded carbon nanotubes are capable of entering APCs and, thus, exhibit significant research potential in anti-cancer immunotherapy[339].

Owing to their unique physiochemical properties, inorganic nanomaterials play a crucial role in anti-cancer drug delivery. However, the overall safety profile of inorganic-based vectors is still uncertain and requires further characterization[320]. Furthermore, the clinical translation

of metallic NPs, in particular, remains challenging due to their tendency to aggregate after systemic injection and their potential long-term toxicity resulting from liver accumulation[320].

3.4.2.1.4. Virus-like Particles

Virus-like particles are self-assembled complexes of viral proteins that closely resemble the morphology, biochemical composition, and size of native viruses[346; 347]. However, they do not contain viral genetic material and are, therefore, incapable of replication or causing infections[346; 347]. Virus-like particles can be functionalized with specific ligands, and allow the delivery of peptides, genes, and drugs to target tissues or the immune system[346].

The immune response triggered by virus-like particles is a result of their interactions with various components of the immune system[346]. DCs internalize virus-like particles, leading to antigen presentation and the activation of both helper $CD4^+$ and cytotoxic $CD8^+$ T cells[346]. This dual action induces humoral and cellular responses, making them an effective strategy for preventive and therapeutic vaccines[347]. Indeed, preventive vaccines based on virus-like particles have been successfully developed for HBV and HPV)[346]. These vaccines, such as Cervarix® (GlaxoSmithKline Biologicals), Gardasil® (Merck Sharp & Dohme LLC), Gardasil 9® (Merck Sharp & Dohme LLC) (protecting against HPV), and Heplisav-B® (Dynavax GmbH) (preventing liver cancer caused by HBV infection), have received approval from international regulatory agencies for human use[115; 128; 201]. Furthermore, for example, Ensoma has developed a virus-like particle-based *in vivo* gene editing platform, named Engenious™. This approach allows the direct transduction of both immune cells and hematopoietic stem cells. This way, it empowers the body's natural defenses against the immunosuppressive properties of cancer[348].

3.4.2.2. Cell-Based Delivery Systems

Cell-based delivery systems have gained significant attention for biomedical applications, particularly in the field of immunotherapy[315]. These systems utilize cells, natural carriers of proteins and molecules, and have shown promising progress[315]. Compared to traditional delivery systems, cell-based delivery systems offer multiple advantages, such as prolonged circulation, flexibility, low immunogenicity, low toxicity, biodegradability, and biocompatibility[315; 349; 350]. They also exhibit the ability to cross biological barriers, along with controlled drug release and active tissue targeting[315; 349]. As a result, cell-mediated delivery systems are a promising strategy to maximize therapeutic outcomes and minimize the side effects of immuno-oncology therapy[349].

One notable advantage of cell-based delivery systems is their biomimetic nature[349]. This property allows cell-based drug carriers to act as a platform that mimics the body's natural processes and delivers therapeutic agents to specific sites[349]. Researchers aim to create effective cell-based delivery systems by utilizing a diverse range of cell types, including erythrocytes, platelets, immune cells, stem cells, and cell-derived extracellular vesicles. Furthermore, other cell types like adipocytes and bacteria have also been explored as drug carriers[351].

For example, erythrocytes have unique characteristics, such as a biconcave shape, which results in a high surface area for conjugation of drugs, high drug loading capacity and long half-life, which render them an attractive option for the delivery of various cargos, including protein antigens, nucleic acids, and cytokines[349; 350]. One notable approach was developed by Xiao Han and colleagues, which involves fusing the membranes of erythrocytes with tumor cell membranes, enabling the delivery of TAAs[352]. *In vivo* delivery demonstrated that nanoerythrosomes formed by the membrane fusion can effectively reach APCs and stimulate T cell immune responses in mice, therefore holding potential as a personalized tumor vaccine[352].

Additionally, platelets have emerged as promising delivery systems due to their inherent targeting abilities toward surgical wounds, circulating tumor cells, and sites of inflammation. Platelets' cytokine-releasing capacity also enhances their potential for therapeutic applications[315]. Preclinical studies involving the conjugation of anti-PD-1 antibodies to the surface of platelets have been conducted, which were able to prevent tumor recurrence and metastasis following surgery and extend the survival time of tumor-bearing mice[315].

Immune cells, particularly DCs, have also gathered attention as promising cell-based delivery systems due to their inherent transport mechanisms[349]. In a study carried out by Cheng and collaborators, a biomimetic nanovaccine derived from DCs was created. Biomimetic vaccines aim to mimic natural infectious agents and mechanisms in order to stimulate a targeted and effective immune response. This nanovaccine was constructed by incorporating the cell membrane of DCs pulsed with a tumor cell lysate and coating them with IL-2-loaded polymeric NPs[353]. This strategy has demonstrated improved T cell responses[353]. Additionally, Liu and associates have investigated the fusion of DCs with cancer cells to develop a cancer vaccine[354]. This hybrid cell retains the antigenic properties of tumor cells and the costimulatory molecules of DCs[354], effectively activating DCs and presenting antigens to T cells[354].

Stem cells have also received attention as promising candidates for cell-based drug delivery because they can survive in cancerous environments[349]. They possess low immunogenicity and inherent homing abilities, enabling them to migrate to sites of inflammation, including tumor sites, thereby facilitating targeted delivery[315]. Although stem cells have been mainly employed to regenerate diseased tissues, their properties have propelled their investigation as carriers for therapeutic agents[349]. For example, Hu and collaborators have developed hematopoietic stem cells conjugated with blood platelets decorated with anti-PD-1 mAbs[355]. This combination-mediated drug delivery strategy effectively suppressed the growth and recurrence of leukemia in mice, making it a promising approach to augment the therapeutic efficacy of checkpoint blockade[355].

In addition, extracellular vesicles, vital in cellular communication, have been utilized as nanocarriers for drug delivery in cancer therapy due to their inherent ability to package molecules, low immunogenicity, and efficient uptake[320]. Tumor cells, dendritic cells, T cells, NK cells, platelets, bacteria and macrophages have all been described as feasible cell sources for producing carrier exosomes, a type of extracellular vesicle, for therapeutic use in cancer immunotherapy[356]. Particularly, DC-derived exosomes have garnered significant attention, since they contain antigen-presenting molecules and costimulatory molecules required for generating powerful immune responses[357]. DC-derived exosomes have been studied in the context of cancer vaccines, where they have been the subject of numerous preclinical and clinical trials[357]. Two phase II clinical trials focused on exploring the efficacy of DC-derived exosome vaccines, one using DC-derived exosomes loaded with cancer antigens and conjugated with IFN-γ[358] and the other loaded with tumor antigens[359], both tailored for the treatment of non-small cell lung cancer. While the first has no published results at the moment, the second clinical trial was able to confirm the capacity of DC-derived exosomes to boost the NK cell arm of anti-tumor immunity. Several other clinical trials have confirmed the safety and feasibility of exosome-based cancer vaccines[357]. Nevertheless, the lack of content standardization and large-scale production methods still hinders their clinical use[320].

Overall, cell-based delivery systems present a promising strategy to enhance therapeutic outcomes and minimize side effects in immuno-oncology therapy[349].

3.4.2.3. Biomaterial Delivery

In addition to the aforementioned systemic administration approaches, there is growing interest in exploring technologies for local delivery in cancer immunotherapy[300]. Local delivery holds promise for improving therapeutic outcomes, particularly in cancers with low immunogenicity that are less responsive to therapy, while potentially reducing the toxic side effects associated with systemic administration[300]. Biomaterial-based approaches, such as scaffolds and hydrogels, have garnered attention due to their high biocompatibility and ability to mimic the properties of natural tissues[317]. These delivery systems offer advantages such as ease of synthesis, low raw material costs, and potential applicability to multiple immunological therapeutics[317].

Implantable scaffolds are predominantly polymeric and have shown promise in delivering therapeutic agents such as GM-CSF and CAR-T cells, yielding positive therapeutic effects[317]. However, their use requires invasive surgery, limiting their application to inaccessible sites[317].

On the other hand, injectable scaffolds, including injectable hydrogels are composed of hydrophilic polymer chains[317]. One of the major advantages lies in their soft texture, which can minimize the created inflammatory response in contact with adjacent cells and tissues[360]. In addition, injectable scaffolds have the ability to be precisely positioned using a needle, eliminating the requirement for surgical implantation[178]. This approach offers a relatively simple and minimally invasive procedure that reduces tissue damage, inflammation, and related complications[178].

Hydrogels can serve as carriers for various cargos, including cytokines (such as IL-12 and GM-CSF), checkpoint inhibitors, antigen-loaded NPs, tumor cell lysates, immune cells like TILs, activated $CD8^+$ T cells, and antigen-loaded DCs[317]. In the future, injectable hydrogels could be further engineered to achieve precise control over the release kinetics of loaded therapies, enabling sustained treatment regimens[300].

Currently, an injectable scaffold is being assessed in a phase I clinical trial. This study aims to evaluate the feasibility of an investigational melanoma tumor lysate vaccine, termed WDVAX, which has been licensed to Novartis (NCT01753089), and determine the safety and biological activity of vaccination with a dendritic cell activation scaffold[300; 361].

3.4.3. Concluding Thoughts and Future Considerations of Delivery Systems

The development of effective delivery systems for cancer immunotherapy faces several challenges. One of the key hurdles is ensuring the targeted and efficient delivery of immunotherapeutic agents to the target site. Moreover, optimizing the biodistribution and pharmacokinetics of the delivery system is crucial to maintain therapeutic efficacy and minimize off-target effects. The size of the delivery systems is a significant aspect of this subject. Indeed, NPs less than 200 nm can circulate in the body and have more chances of reaching the target[178]. Furthermore, selecting suitable materials and formulations that provide controlled release, stability, and biocompatibility further adds to the challenges[178].

Regarding the translation to clinic, scalability, manufacture, and costs are major limitations[178]. Indeed, the scalability and manufacturability of delivery systems need to be addressed to ensure their practical application. Moreover, delivery systems can increase the complexity and cost of manufacture and commercialization, which is detrimental to the clinical translation of delivery systems-based immunotherapy[178].

Currently in its early stages, the delivery technology for cancer immunotherapy is witnessing the introduction of novel strategies for controlled release, local delivery, and improved stability[178]. Many of the described delivery technologies not only enhance immunotherapy efficacy, but also address the diverse nature of cancer, overcoming its inherent heterogeneity[178]. For this reason. it is anticipated that these technologies will gain increasing recognition in the future. Furthermore, delivery systems that can accommodate various therapeutic agents customized based on patient-specific targets, will lead to personalized treatments which will potentially cure cancer patients[178]. As drug delivery continues to advance, it will significantly contribute to their broader application of cancer immunotherapy in the foreseeable future.

3.5. Novel Immunotherapeutics

While significant progress has been made in the field of immunotherapy, challenges persist within the currently available strategies. These challenges encompass issues such as low efficacy, adverse events, and restricted applicability to various cancer types. Despite efforts to address these challenges through the investigation of predictive biomarkers, combination therapies, and drug delivery systems, these approaches also come with limitations that might impede their broad adoption. As a result, novel categories of immunotherapies are now on the rise, offering a promising perspective for overcoming the constraints of earlier cancer immunotherapies[364].

A comprehensive understanding of the tumor immune microenvironment biology within the immuno-oncology field is imperative for developing next-generation immuno-oncology therapeutic strategies. This comprehension drives advancements in ICI, CAR-T and other cell-based therapies, which will continue to lead the way in clinical immunotherapy. As part of the future of the ICI approach, ongoing investigations are exploring the utilization of checkpoint molecules, such as T Cell Immunoglobulin and Mucin Domain 3 (TIM-3) and V-domain Ig suppressor of T cell activation (VISTA)[120]. Additionally, Siglec-15, mainly expressed by myeloid cells, was identified and may be a newly-defined T cell immune checkpoint target[364]. Furthermore, co-stimulatory molecules, including 4-1BB and OX40, have also been a target of intensive research due to their immune stimulatory properties, which could improve the efficacy of immunotherapies[120].

In CAR-T therapy, several targets are already being evaluated in pre-clinical and/or clinical studies[365]. Innovative designs of CAR-T cells to enhance their efficacy and function were also described. Some of the strategies being explored include genetic edition using CRISPR/Cas9 technology to eliminate CAR-T cell expression of endogenous TCRs and PD-1, as well as co-expression of a fusion protein to rescue them from hypofunction and enhance their tumor-killing effects[364]. Additionally, effector memory T cells and DC-activated cytokine-induced killer cells have been identified and investigated as new strategies for cellular therapy[364].

Furthermore, researchers are putting valuable efforts into designing techniques that may improve their efficacy. These strategies include targeting immunosuppressive cells, such as T_{Regs} cells[124; 366] and myeloid-derived suppressor cells[367; 368].

As mentioned above, targeting T_{Regs} cells has been considered a hopeful method to improve the body's ability to fight against tumors. Such strategies may include blocking their recruitment to the TME, administration of small molecule antagonists for T_{Regs} depletion, employment of T_{Regs} targeted ICIs or conversion of T_{Regs} into inflammatory cells[124; 366]. Furthermore, when considering MDSC, several approaches that aim to improve patient benefit from immunotherapy treatment have been investigated. These strategies include promoting the differentiation and maturation of MDSC into tumor associated macrophages and inflammatory DCs, reducing their accumulation and expansion, inhibiting immunosuppressive functions and preventing migration and recruitment[367; 368].

In conclusion, innovation in cancer immunotherapy has transformed the landscape of cancer treatment, providing new hope for patients to combat the disease. The ongoing advancements and discoveries in this field hold tremendous promise for the future, promising more effective, personalized, and less toxic therapies. By encouraging innovation, supporting research, and ensuring accessibility, we can continue to push the boundaries of cancer immunotherapy and bring us closer to the goal of defeating cancer.

Chapter IV – Final Considerations

Cancer remains one of the most challenging diseases of our time, affecting millions worldwide. Despite the long history of cancer cases, finding a definitive cure has been an arduous journey. Over the years, therapies have shown limited success in eradicating cancer due to the disease's complex nature and the ability of cancer cells to mutate and evade treatment.

The current approach to treating cancer primarily relies on chemotherapeutic and radiotherapeutic methods. Although these strategies have been used as standard treatments, they often come with severe side effects and are not consistently effective in eradicating cancer. As a result, researchers and medical professionals have been driven to explore alternative therapeutic approaches that can overcome these limitations. Furthermore, the significant progress in understanding the biology of cancer and advancing medical technologies has allowed the treatment landscape for cancer to undergo a revolutionary transformation.

Immunotherapy, in particular, has emerged as a game-changer in the field of cancer care. It has established itself as a major pillar of cancer treatment, significantly improving patient outcomes and offering new hope for those whose cancer was once deemed untreatable. Unlike conventional therapies that directly target cancer cells, immunotherapy aims to harness and enhance our immune system to recognize and attack cancer cells more effectively.

Despite these impressive advancements, particularly with ICI and CAR-T cell therapy, challenges persist. These include the inefficacy observed in a majority of patients with immune-resistant tumors, as well as the associated adverse effects. Furthermore, increasing access to cutting-edge treatments for all patients remains a critical issue. Ensuring that these innovative therapies are affordable and available to people from all walks of life is essential to reducing the global burden of cancer.

To overcome these limitations, several strategies are being explored, such as using predictive biomarkers, combining different therapeutic approaches, employing delivery systems, and developing innovative approaches for immuno-oncology. Their strategic integration allows for personalized and more effective treatments, enabling medical professionals to combat cancer with increased precision and potency. Embracing these

advancements holds significant promise for further enhancing cancer care and improving patient outcomes in the battle against this challenging disease.

In conclusion, while cancer continues to be one of the most problematic diseases, significant progress has been made in recent years. Immunotherapy, coupled with a deeper understanding of cancer biology, has revolutionized the field of cancer care. The ongoing research and collaborative efforts hold the promise of continuing this positive trajectory toward finding more effective treatments and, ultimately, a cure for cancer.

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Appendix

Table I - Approved immunotherapeutic products for cancer.

IMTH	Active Substance, Trade Name	Indications	Approval Year		Originator Company	Active Company	References
			FDA	EMA			
CAR-T	Axicabtagene ciloleucel, Yescarta®	Large B-cell Lymphoma Follicular Lymphoma	2017	2018	Cabaret Biotech Ltd	Daiichi Sankyo Co Ltd Fosun Kite Biotechnology Co Ltd Kite Pharma Inc	1; 2; 3; 4
CAR-T	Brexucabtagene Autoleucel, Tecartus®	Mantle Cell Lymphoma Acute Lymphoblastic Leukemia	2020	2020	Cabaret Biotech Ltd	Kite Pharma Inc	1; 5; 6; 7
CAR-T	Ciltacabtagene autoleucel, Carvykti®	Relapsed Or Refractory Multiple Myeloma	2022	2022	Nanjing Legend Biotech Co Ltd	Janssen Biotech Inc Nanjing Legend Biotech Co Ltd	1; 8; 9; 10
CAR-T	Idecabtagene Vicleucel, Abecma®	Relapsed Or Refractory Multiple Myeloma	2021	2021	Bluebird Bio Inc	2seventy bio Inc Bristol-Myers Squibb Co Celgene Corporation	1; 11; 12; 13
CAR-T	Lisocabtagene maraleucel, Breyanzi®	Large B-cell Lymphoma Diffuse Large B-cell Lymphoma High-grade B-cell Lymphoma Primary Mediastinal Large B-cell Lymphoma Follicular Lymphoma Grade 3B	2022	2022	Juno Therapeutics Inc	Bristol-Myers Squibb Co	1; 14; 15; 16

CAR-T	Tisagenlecleucel, Kymriah®	B-cell Acute Lymphoblastic Leukemia Diffuse Large B-cell Lymphoma Follicular Lymphoma	2017	2018	Abramson Cancer Center of the University of Pennsylvania	Abramson Cancer Center of the University of Pennsylvania Novartis AG	1; 17; 18; 19
Cytokine	Aldesleukin, Proleukin®	Metastatic Renal Cell Carcinoma	1992	Not Approved	Ceutus Corporation	CHIRON Clinigen	20; 21
Cytokine	Interferon α-2b, Intron A®	Hairy Cell Leukemia Melanoma Follicular Lymphoma AIDS-related Kaposi Sarcoma	1986	Withdrawn	Biogen Inc	SCHERING Merck Sharp & Dohme	21; 22; 23
Cytokine	Sargramostim, Leukine®	Acute Myeloid Leukemia	1991	Not Approved	Immunex Corporation	BERLEX LABS Partner Therapeutics, Inc.	21; 24
ICI	Atezolizumab, Tecentriq®	Urothelial Carcinoma Non-Small Cell Lung Cancer Small Cell Lung Cancer Hepatocellular Carcinoma Melanoma Alveolar Soft Part Sarcoma	2016	2017	Genentech Inc	Chugai Pharmaceutical Co Ltd Genentech Inc Roche Holding AG	1; 25; 26; 27
ICI	Avelumab, Bavencio®	Merkel Cell Carcinoma Urothelial Carcinoma Renal Cell Carcinoma	2017	2017	Merck KGaA	Merck KGaA Merck Serono SA Pfizer Inc	1; 28; 29; 30
ICI	Cemiplimab, Libtayo®	Cutaneous Squamous Cell Carcinoma Basal Cell Carcinoma Non-Small Cell Lung Cancer	2018	2019	Regeneron Pharmaceuticals Inc	Regeneron Pharmaceuticals Inc Sanofi SA	1; 21; 31; 32

ICI	Dostarlimab, Jemperli®	Mismatch Repair Deficient Recurrent or Advanced Endometrial Cancer Mismatch Repair Deficient Recurrent or Advanced Solid Tumors	2021	2021	AnaptysBio Inc	GSK plc	1; 33; 34; 35
ICI	Durvalumab, Imfinzi®	Non-Small Cell Lung Cancer Small Cell Lung Cancer Biliary Tract Cancers	2017	2018	AstraZeneca plc	AstraZeneca plc Bristol-Myers Squibb Co MedImmune LLC	1; 21; 36; 37
ICI	Ipilimumab, Yervoy®	Melanoma Renal Cell Carcinoma Colorectal Cancer Hepatocellular Carcinoma Non-Small Cell Lung Cancer Malignant Pleural Mesothelioma Esophageal Cancer	2011	2011	Medarex Inc	Bristol-Myers Squibb Co Ono Pharmaceutical Co Ltd	1; 21; 38; 39
ICI	Nivolumab, Opdivo®	Melanoma Non-Small Cell Lung Cancer Malignant Pleural Mesothelioma Renal Cell Carcinoma Classical Hodgkin Lymphoma Squamous Cell Carcinoma of the Head and Neck Urothelial Carcinoma Colorectal Cancer Hepatocellular Carcinoma Esophageal Cancer Gastric Cancer Gastroesophageal Junction Cancer Esophageal Adenocarcinoma	2014	2015	Ono Pharmaceutical Co Ltd	Bristol-Myers Squibb Co Ono Pharmaceutical Co Ltd	1; 40; 41; 42

ICI	Pembrolizumab, Keytruda®	Melanoma Non-Small Cell Lung Cancer Head and Neck Squamous Cell Cancer Classical Hodgkin Lymphoma Primary Mediastinal Large B-Cell Lymphoma Urothelial Carcinoma Microsatellite Instability-High or Mismatch Repair Deficient Cancer Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer Gastric Cancer Esophageal Cancer Cervical Cancer Hepatocellular Carcinoma Merkel Cell Carcinoma Renal Cell Carcinoma Endometrial Carcinoma Tumor Mutational Burden-High Cancer Cutaneous Squamous Cell Carcinoma Triple-Negative Breast Cancer Large B-Cell Lymphoma	2014	2015	LifeArc	Merck & Co Inc	1; 43; 44; 45
ICI	Relatlimab Nivolumab, Opdualag®	Unresectable Or Metastatic Melanoma	2022	2022	Bristol-Myers Squibb Co	Bristol-Myers Squibb Co	1; 21; 46; 47
ICI	Tremelimumab, Imjudo®	Hepatocellular Carcinoma Non-Small Cell Lung Cancer	2022	2023	Pfizer Inc	AstraZeneca plc	1; 48; 49; 50
mAb	Amivantamab, Rybrevant®	Non-Small Cell Lung Cancer	2021	2021	Janssen Research & Development LLC	Janssen Research & Development LLC	1; 21; 51; 52

mAb	Belantamab Mafodotin, Blenrep®	Multiple Myeloma	2020	2020	GSK plc	GSK plc	1; 21; 53; 54
mAb	Bevacizumab, Abevmy®	Metastatuc CRC Metastatic Breast Cancer Non-Small Cell Lung Cancer Non-Squamous Non-Small Cell Lung Cancer Advanced and/or Metastatic Renal Cell Cancer Advanced Persistent, Recurrent, or Metastatic Carcinoma of the Cervix Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Not Approved	2021	Biocon Ltd	Biocon Ltd Mylan NV	1; 55
mAb	Bevacizumab, Alymsys®	Metastatic Colorectal Cancer First-Line Non-Squamous Non–Small Cell Lung Cancer Recurrent Glioblastoma Metastatic Renal Cell Carcinoma Persistent, Recurrent, or Metastatic Cervical Cancer Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	2022	2021	mAbxience SA	Amneal Pharmaceuticals Inc ApoBiologix Laboratorio Elea Libbs Farmaceutica Ltda Sandoz KK Zentiva a.s. Praha mAbxience SA	1; 21; 56; 57
mAb	Bevacizumab, Oyavas®	Metastatic Colorectal Cancer First-Line Non-Squamous Non–Small Cell Lung Cancer Recurrent Glioblastoma Metastatic Renal Cell Carcinoma Persistent, Recurrent, or Metastatic Cervical Cancer Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	2022	2021	Stada Arzneimittel AG	Stada Arzneimittel AG	1; 21; 58; 59

mAb	Bevacizumab, Avastin®	Metastatic Colorectal Cancer First-Line Non-Squamous Non–Small Cell Lung Cancer Recurrent Glioblastoma Metastatic Renal Cell Carcinoma Persistent, Recurrent, or Metastatic Cervical Cancer Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	2004	2005	Genentech Inc	Chugai Pharmaceutical Co Ltd Cipla Limited F. Hoffmann-La Roche Ltd Genentech Inc Roche Holding AG	1; 21; 60; 61
mAb	Bevacizumab, Mvasi®	Metastatic Colorectal Cancer First-Line Non-Squamous Non-Small Cell Lung Cancer Recurrent Glioblastoma Metastatic Renal Cell Carcinoma Persistent, Recurrent, or Metastatic Cervical Cancer Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	2017	2018	Amgen Inc	AbbVie Inc Amgen Inc Daiichi Sankyo Co Ltd	1; 21; 62; 63
mAb	Bevacizumab, Onbevzi/Aybintio®	Metastatic CRC Metastatic Breast Cancer Non-Small Cell Lung Cancer Non-Squamous Non-Small Cell Lung Cancer	Not Approved	2020	Samsung Bioepis Co Ltd	3SBio Inc Merck & Co Inc Mundipharma International Corp Ltd Organon & Co Samsung Bioepis Co Ltd	1; 64
mAb	Bevacizumab, Vegzelma®	Metastatic Colorectal Cancer First-Line Non-Squamous Non-Small Cell Lung Cancer Recurrent Glioblastoma Metastatic Renal Cell Carcinoma Persistent, Recurrent, or Metastatic Cervical Cancer Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	2022	2022	Celltrion Inc	Celltrion Inc Nippon Kayaku Co Ltd	1; 21; 65; 66

mAb	Bevacizumab, Zirabev®	Metastatic Colorectal Cancer First-Line Non-Squamous Non-Small Cell Lung Cancer Recurrent Glioblastoma Metastatic Renal Cell Carcinoma Persistent, Recurrent, or Metastatic Cervical Cancer Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	2019	2019	Pfizer Inc	Pfizer Inc	1; 21; 67; 68
mAb	Blinatumomab, Blincyto®	CD19-Positive B-Cell Precursor Acute Lymphoblastic Leukemia	2014	2015	Amgen Research (Munich) GmbH	Amgen Inc Amgen KK Astellas Pharma Inc BeiGene Co Ltd Dr Reddy's Laboratories Ltd	1; 21; 69; 70
mAb	Brentuximab vedotin, Adcetris®	Hodgkin Lymphoma Systemic Anaplastic Large Cell Lymphoma	2011	2012	Seagen Inc	Seagen Inc Takeda Pharmaceutical Co Ltd	1; 71; 72; 73
mAb	Cetuximab, Erbitux®	Squamous Cell Carcinoma of the Head and Neck K-Ras Wild-type, EGFR-expressing Colorectal Cancer BRAF V600E Mutation-Positive Metastatic Colorectal Cancer	2004	2004	Imclone Systems Inc	Imclone Systems Inc Merck KGaA Merck Serono SA	1; 21; 74; 75
mAb	Daratumumab + Hyaluronidase, Darzalex Faspro®	Multiple Myeloma	2020	Not Approved	Janssen Biotech Inc	Janssen Biotech Inc	1; 21; 76
mAb	Daratumumab, Darzalex®	Multiple Myeloma	2015	2016	Genmab A/S	Janssen Biotech Inc Xian-Janssen Pharmaceutical Ltd	1; 77; 78; 79

mAb	Dinutuximab beta, Qarziba®	Neuroblastoma	Not Approved	2017	EMD Lexigen Research Center Corp	Apeiron Biologics GmbH BeiGene Co Ltd EUSA Pharma Emerge Health Pty Ltd Gen Ila Medison Pharma Ltd Paladin Labs Inc	1; 80
mAb	Dinutuximab, Unituxin®	Neuroblastoma	2015	Withdrawn	National Cancer Institute	National Cancer Institute United Therapeutics Corp	1; 21; 81; 82
mAb	Elotuzumab, Empliciti®	Multiple Myeloma	2015	2016	PDL BioPharma Inc	AbbVie Inc Bristol-Myers Squibb Co	1; 21; 83; 84
mAb	Enfortumab Vedotin, Padcev®	Metastatic Urothelial Cancer	2019	2021	Agensys Inc	Agensys Inc Astellas Pharma Inc Baxter Oncology GmbH Seagen Inc	1; 21; 85; 86
mAb	Fam-Trastuzumab Deruxtecan, Enhertu®	Metastatic HER2-Positive Breast Cancer Metastatic HER2-Low Breast Cancer Metastatic Non-Small Cell Lung Cancer Metastatic HER2-Positive Gastric or Gastroesophageal Junction Adenocarcinoma	2019	2020	Daiichi Sankyo Co Ltd	AstraZeneca plc Daiichi Sankyo Co Ltd	1; 21; 87; 88
mAb	Gemtuzumab Ozogamicin, Mylotarg®	CD33-positive Acute Myeloid Leukemia	2017	2018	Wyeth Research	Pfizer Inc	1; 21; 89; 90

mAb	Ibritumomab tiuxetan, Zevalin®	Non-Hodgkin Lymphoma	2002	2004	IDEC Pharmaceuticals Corp	Acrotech Biopharma Inc CASI Pharmaceuticals Inc FUJIFILM Holdings Corp Mundipharma International Corp Ltd Servier Canada Inc	1; 21; 91; 92
mAb	Inotuzumab Ozogamicin, Besponsa®	B-cell Precursor Acute Myeloid Leukemia	2017	2017	Wyeth Research	Pfizer Inc	1; 21; 93; 94
mAb	Isatuximab, Sarclisa®	Multiple Myeloma	2020	2020	ImmunoGen Inc	Sanofi SA	1; 21; 95; 96
mAb	Loncastuximab tesirine, Zynlonta®	Large B-cell Lymphoma	2021	2022	ADC Therapeutics SA	ADC Therapeutics SA Mitsubishi Tanabe Pharma Corp Overland ADCT BioPharma (CY) Limited Swedish Orphan Biovitrum AB (Publ)	1; 21; 97; 98
mAb	Margetuximab, Margenza®	HER2-Positive Breast Cancer	2020	Not Approved	MacroGenics Inc	Green Cross Holdings Corp MacroGenics Inc Zai Lab Limited	1; 21; 99
mAb	Mirvetuximab Soravtansine, Elahere®	Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cance	2022	Not Approved	ImmunoGen Inc	Hangzhou Zhongmei Huadong Pharmaceutical Co Ltd ImmunoGen Inc	1; 21; 100
mAb	Mosunetuzumab, Lunsumio®	Follicular Lymphoma	2022	2022	Genentech Inc	Chugai Pharmaceutical Co Ltd Genentech Inc	1; 21; 101; 102

mAb	Moxetumomab Pasudotox, Lumoxiti®	Hairy Cell Leukemia	2018	Withdrawn	National Cancer Institute	AstraZeneca plc Innate Pharma SA MedImmune LLC	1; 21; 103; 104
mAb	Naxitamab, Danyelza®	Neuroblastoma	2018	Not Approved	Memorial Sloan Kettering Cancer Center	Adium Pharma SA SciClone Pharmaceuticals LLC Takeda Israel Ltd Y-mAbs Therapeutics Inc	1; 21; 105
mAb	Necitumumab, Portrazza®	Squamous Non-Small Cell Lung Cancer	2015	Withdrawn	Imclone Systems Inc	Eli Lilly & Co Imclone Systems Inc Nippon Kayaku Co Ltd	1; 21; 106; 107
mAb	Obinutuzumab, Gazyva/Gazyvaro®	Chronic Lymphocytic Leukemia Follicular Lymphoma	2013	2014	Roche GlycArt Ag	Biogen Inc Chugai Pharmaceutical Co Ltd F. Hoffmann-La Roche Ltd Genentech Inc Nippon Shinyaku Co Ltd Roche Holding AG	1; 21; 108; 109
mAb	Ofatumumab, Arzerra®	Chronic Lymphocytic Leukemia	2009	Withdrawn	Genmab A/S	Novartis AG	1; 21; 110; 111
mAb	Panitumumab, Vectibix®	Metastatic Colorectal Cancer	2006	2007	Abgenix Inc	Amgen Inc Amgen-Beta Pharmaceuticals Co Ltd Dr Reddy's Laboratories Ltd Takeda Pharmaceutical Co Ltd	1; 21; 112; 113
mAb	Pertuzumab + Trastuzumab, Phesgo®	Early Breast Cancer Metastatic Breast Cancer	2020	2020	Roche Holding AG	Chugai Pharmaceutical Co Ltd Roche Holding AG	1; 21; 114; 115

mAb	Pertuzumab, Perjeta®	Metastatic Breast Cancer Early-Stage Breast Cancer	2012	2013	Genentech Inc	Chugai Pharmaceutical Co Ltd Genentech Inc Roche Holding AG	1; 116; 117; 118
mAb	Polatuzumab vedotin, Polivy®	Diffuse Large B-cell Lymphoma	2019	2020	Genentech Inc	Chugai Pharmaceutical Co Ltd Genentech Inc	1; 21; 119; 120
mAb	Ramucirumab, Cyramza®	Gastric Cancer Non-Small Cell Lung Cancer Colorectal Cancer Hepatocellular Carcinoma	2014	2014	Imclone Systems Inc	Eli Lilly & Co	1; 21; 121; 122
mAb	Rituximab + Hyaluronidase, Rituxan Hycela®	Follicular Lymphoma Diffuse Large B-Cell Lymphoma Chronic Lymphocytic Leukemia	2017	Not Approved	Roche Holding AG	Roche Holding AG	1; 21; 123
mAb	Rituximab, Blitzima®	Non–Hodgkin's Lymphoma Chronic Lymphocytic Leukemia Rheumatoid Arthritis Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and mAb Microscopic Polyangiitis Pemphigus Vulgaris	Not Approved	2017	Celltrion Inc	Celltrion Inc Hikma Pharmaceuticals plc Mundipharma International Corp Ltd Nippon Kayaku Co Ltd Orion Corp Teva Pharmaceutical Industries Ltd Vcell Healthcare Limited	1; 124
mAb	Rituximab, Riabni®	Non–Hodgkin's Lymphoma Chronic Lymphocytic Leukemia Rheumatoid Arthritis Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis Pemphigus Vulgaris	2020	Not Approved	Amgen Inc	AbbVie Inc; Amgen Inc	1; 21; 125

mAb	Rituximab, Rituxan/Mabthera®	Non–Hodgkin's Lymphoma Chronic Lymphocytic Leukemia	1997	1998	IDEC Pharmaceuticals Corp	Biogen Inc Chugai Pharmaceutical Co Ltd Cipla Limited Genentech Inc Roche Holding AG Zenyaku Kogyo Co Ltd	1; 126; 127; 128
mAb	Rituximab, Rixathon®	Non–Hodgkin's Lymphoma Chronic Lymphocytic Leukemia Rheumatoid Arthritis Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis Pemphigus Vulgaris	Not Approved	2017	Sandoz International GmbH	Kyowa Kirin Co Ltd Novartis AG Sandoz International GmbH	1; 129
mAb	Rituximab, Riximyo®	Non–Hodgkin's Lymphoma Chronic Lymphocytic Leukemia Rheumatoid Arthritis Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis Pemphigus Vulgaris	Not Approved	2017	Sandoz GmbH	Sandoz GmbH	1; 130
mAb	Rituximab, Ruxience®	Non–Hodgkin's Lymphoma Chronic Lymphocytic Leukemia Rheumatoid Arthritis Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis Pemphigus Vulgaris	2019	2020	Pfizer Inc	Pfizer Inc	1; 21; 131; 132

mAb	Rituximab, Truxima®	Non–Hodgkin's Lymphoma Chronic Lymphocytic Leukemia Rheumatoid Arthritis Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis Pemphigus Vulgaris	2018	2017	Celltrion Healthcare Co.,Ltd.	Celltrion INC Celltrion Healthcare Hungary Kft.	21; 133; 134
mAb	Sacituzumab Govitecan, Trodelvy®	Metastatic Triple-Negative Breast Cancer Metastatic Urothelial Cancer	2020	2020	Immunomedics Inc	Everest Medicines Ltd Gilead Sciences Inc	1; 21; 135; 136
mAb	Tafasitamab, Monjuvi/Minjuvi®	Diffuse Large B-Cell Lymphoma	2020	2021	Xencor Inc	Incyte Corp InnoCare Pharma Ltd Knight Therapeutics Inc MorphoSys AG Specialised Therapeutics Asia Pte Ltd	1; 21; 137; 138
mAb	Talquetamab, Talvey®	Multiple Myeloma	2023	Not Approved	Janssen Pharmaceuticals Inc	Janssen Pharmaceuticals Inc	1; 21; 139
mAb	Tebentafusp, Kimmtrak®	Uveal Melanoma	2022	2022	Immunocore Ltd	Immunocore LTD Immunocore Ireland Limited	21; 140; 141
mAb	Teclistimab, Tecvayli®	Multiple Myeloma	2022	2022	Janssen Research & Development LLC	Janssen Research & Development LLC	1; 21; 142; 143
mAb	Tisotumab vedotin, Tivdak®	Recurrent or Metastatic Cervical Cancer	2021	Not Approved	Genmab A/S	Genmab A/S Seagen Inc Zai Lab Limited	1; 21; 144

mAb	Trastuzumab + Hyaluronidase, Herceptin Hylecta®	Adjuvant Breast Cancer Metastatic Breast Cancer	2019	Not Approved	Halozyme Therapeutics Inc	Genentech Inc Roche Holding AG	1; 21; 145
mAb	Trastuzumab Emtansine, Kadcyla®	Metastatic Breast Cancer Early Breast Cancer	2013	2013	Genentech Inc	Chugai Pharmaceutical Co Ltd Genentech Inc Roche Holding AG	1; 21; 146; 147
mAb	Trastuzumab, Herceptin®	Metastatic Breast Cancer	1998	2000	Genentech Inc	Chugai Pharmaceutical Co Ltd Cipla Limited Genentech Inc Roche Holding AG	1; 148; 149; 150
mAb	Trastuzumab, Herzuma®	Breast Cancer Metastatic Breast Cancer Metastatic Gastric Cancer	2018	2018	Celltrion Inc	Celltrion Inc; EGIS Gyogyszergyar RT Hikma Pharmaceuticals plc Mundipharma International Corp Ltd Nippon Kayaku Co Ltd Teva Pharmaceutical Industries Ltd Vcell Healthcare Limited	1; 21; 151; 152
mAb	Trastuzumab, Kanjinti®	Breast Cancer Metastatic Breast Cancer Metastatic Gastric Cancer	2019	2018	Synthon BV	AbbVie Inc Amgen Inc Daiichi Sankyo Co Ltd	1; 21; 153; 154
mAb	Trastuzumab, Ogivri®	Breast Cancer Metastatic Breast Cancer Metastatic Gastric Cancer	2017	2018	Biocon Ltd	Alvogen Korea Biocon Ltd Libbs Farmaceutica Ltda Mylan NV	1; 21; 155; 156

mAb	Trastuzumab, Ontruzant®	Breast Cancer Metastatic Breast Cancer Metastatic Gastric Cancer	2019	2017	Samsung Bioepis Co Ltd	AffaMed Therapeutics Ltd Daewoong Pharmaceutical Co Ltd Organon & Co Samsung Bioepis Co Ltd	1; 21; 157; 158
mAb	Trastuzumab, Trazimera®	Breast Cancer Metastatic Breast Cancer Metastatic Gastric Cancer	2019	2018	Pfizer Inc	Pfizer Inc	1; 21; 159; 160
mAb	Trastuzumab, Zercepac®	Breast Cancer Metastatic Breast Cancer Metastatic Gastric Cancer	Not Approved	2020	Shanghai Henlius Biotech Inc	Abbott Laboratories Accord Healthcare Inc Cipla Limited Eurofarma Henlius Biopharmaceuticals Inc Jacobson Pharma Corp Ltd Shanghai Henlius Biotech Inc mAbxience SA	1; 161
Oncolytic Virus	Talimogene Leherparepvec, Imlygic®	Melanoma	2015	2015	BioVex Inc	Amgen Inc BioVex Inc	1; 162; 163; 164
Vaccine	BCG Live, TheraCys®	Carcinoma *in situ* of the Urinary Bladder Papillary Tumors	1990	Not Approved	Not Found	Sanofi Pasteur Limited	1; 165; 166
Vaccine	BCG Live, Tice BCG®	Carcinoma *in situ* of the Urinary Bladder Papillary Tumors	1998	Not Approved	Not Found	Merck Teknika LLC	1; 167; 168
Vaccine	Hepatitis B Surface Antigen, Engerix-B®	Prevention of Infection by Hepatitis B Virus	1989	Not Approved	Not Found	GlaxoSmithKline Biologicals S.A.	169

Vaccine	Hepatitis B Vaccine, Fendrix®	Prevention of Infection by Hepatitis B Virus	Not Approved	2005	Not Found	GlaxoSmithKline Biologicals S.A.	170
Vaccine	Hepatitis B Vaccine, HBVaxPro®	Prevention of Infection by Hepatitis B Virus	Not Approved	2001	Not Found	Merck Sharp & Dohme B.V.	171
Vaccine	Hepatitis B Surface Antigen, Heplisav-B®	Prevention of Infection by Hepatitis B Virus	2017	2021	Dynavax Technologies Corporation	Dynavax Technologies Corporation	172; 173; 174
Vaccine	Human Papillomavirus 9-valent Vaccine, Gardasil 9®	Cervical, Vulvar, Vaginal, Anal, Oropharyngeal and other Head And Neck Cancers	2014	2015	Merck & Co Inc	CSL Ltd Korea Kolmar Holdings Co Ltd MSD KK Merck & Co Inc	1; 175; 176; 177
Vaccine	Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Cervarix®	Cervical Cancer Adenocarcinoma *in situ*	2009	2007	GlaxoSmithKline Biologicals S.A.	GlaxoSmithKline Biologicals S.A.	178; 179
Vaccine	Human Papillomavirus quadrivalent- types 6, 11, 16, and 18 Vaccine, Gardasil®	Cervical, Vulvar, Vaginal, and Anal Cancer	2006	2006	UniQuest Pty Ltd	Korea Kolmar Holdings Co Ltd MSD KK Merck & Co Inc Seqirus Inc	1; 180; 181; 182
Vaccine	Infanrix Hexa®, Hepatitis B Vaccine	Prevention of Infection by Hepatitis B Virus	Not Approved	2000	Not Found	GlaxoSmithKline Biologicals S.A.	183; 184
Vaccine	Prehevbrio®, Hepatitis B Vaccine	Prevention of Infection by Hepatitis B Virus	2021	Not Approved	VBI Vaccines (Delaware), Inc.	VBI Vaccines (Delaware), Inc.	185

Vaccine	Hepatitis B Vaccine, Recombivax Hb®	Prevention of Infection by Hepatitis B Virus	1986	Not Approved	Not Found	Merck Sharp & Dohme LLC	186
Vaccine	Sipuleucel-T, Provenge®	Metastatic Castrate-Resistant (Hormone-Refractory) Prostate Cancer	2010	Withdrawn	Dendreon Corporation	Dendreon Corp Shanghai Danrui BioPharmaceutical	1; 187; 188; 189

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