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Oncogenetics: Unraveling the Genetic Underpinnings of Cancer for Improved Immunotherapeutic Outcomes

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Abstract In this review article we will highlight the evidences that how oncogenes are formed due to the physical genetic variations in proto-oncogenes and tumor suppressor genes and various planned immunotherapies which will include- The immune checkpoint inhibitor-opposing antibodies, adoptive cell treatments, and biologic modifiers (cytokines and vaccines). We will make an effort to provide guidance and potential fixes for these issues, along with pertinent sources for foundational research. For suitable studies, a literature search was undertaken from various database sources such as PubMed, EMBASE, and Google Scholar. One type of gene known as an oncogene—a cellular gene that becomes dysfunctional owing to mutation and overexpression—is the cause of cancer. Certain oncogenes seem to inhibit the homeostatic mechanism by limiting the single cell lineage of leukemia stem cells. According to the clonal theory of oncogenes, tumors are thought to begin in a single cell, Moreover, the growth of tumors is closely linked to the prevention of apoptosis, or programmed cell death. These activities of oncogene can be minimized by some immunological therapies.

Keywords Oncogene, proto-oncogene, gene expression, paradoxes, Immune checkpoints inhibitors, vaccines, monoclonal antibodies, combination therapy

1. Introduction

The function of tumor suppressor genes is blocked, resulting in the activation of cell cycle checkpoints, the prevention of cell growth, and DNA repair. Due to the notable increase in cancer patients' survival rates, a wide range of immunotherapeutic medications are being used more frequently. These include immune checkpoint inhibitors (ICIs), tumor vaccines, cellular immunotherapeutic agents, immunomodulatory

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medications targeting T cells, oncolytic virotherapy, and immunomodulatory drugs [1]. Patients with stage I–IV tumors are gradually being administered these medications. Many large-scale cancer genome initiatives, such as The Cancer Genome Atlas (TCGA), The International Cancer Genome Consortium (ICGC), and The Wellcome Trust Sanger Institute' s Cancer Genome Project, have recently generated multi-dimensional genome-wide big data. Genetic modifications are important factors in the etiology of cancer and offer valuable insights for identifying therapeutic targets and developing new medications. Cancer driver genes are those that carry "DRIVER" mutations that influence cancer development [2,3].

The treatment of cancer patients has been revolutionized by the field of immune-oncology. In the late 19th century, William B. Coley—who is now regarded as the father of immunotherapy—made an initial attempt to harness the immune system to treat cancer. Gain-of-function mutations that promote cell division and proliferation typically activate oncogenes, while loss-of-function mutations (such as transcript insertion/deletion) inactivate tumor suppressor genes [4]. The precision and scope of discovering cancer-related genes that may promote or inhibit cancer development have been improved by genome-wide studies. Although thousands of mutations have been identified through large-scale sequencing data, no new therapeutic targets, aside from the already known ones, have been discovered thus far. There is now a renewed push to apply these cutting-edge discoveries to cancer therapy [5].

This review paper highlights the current standards for understanding and strengthening knowledge of the molecular and cellular drivers of cancer, while researching more effective therapeutic approaches. Physicians and researchers have had some success with innovative techniques, targeting and developing combination therapies and strategies. Special emphasis is placed on immune checkpoint inhibitors (ICIs), their limitations, pitfalls, and the promising novel approaches in cancer patient care practices [6].

2. Oncogenes and Proto-oncogenes

A gene that mutates and becomes capable of causing cancer is called an oncogene. Before mutation, it is known as a proto-oncogene and plays a crucial role in regulating normal cell division. The mutation of a proto-oncogene into an oncogene (Figure 1), leading to uncontrolled cell division and proliferation, is associated with the development of cancer. Certain oncogenes act like an accelerator pedal in a car, driving cells to divide uncontrollably, while others function like a broken brake on a car stopped on a hill, causing cells to divide without regulation [7].

The term "oncogenes" refers to their ability to induce cancer. These genes were initially discovered in viruses that could cause cancer in animals. Subsequent studies revealed that oncogenes can be mutant versions of specific normal cellular genes, referred to as proto-oncogenes. Proto-oncogenes regulate normal cellular growth, division, and apoptosis—programmed and controlled cell death. As positive growth regulators, proto-oncogenes promote the differentiation and multiplication of normal cells [8]. Different proto-oncogenes are involved in various stages of cell development, and changes in their sequence or protein synthesis can disrupt their usual function in cell division and regulation. This disruption can lead to neoplastic transformation, or unchecked cell growth, eventually resulting in the formation of a malignant tumor [9].

In the mid-1970s, American microbiologists Harold Varmus and John Michael Bishop explored the idea that dominant viral oncogenes, when activated, could cause cancer in normal body cells. While oncogenes and proto-oncogenes share similar DNA sequences, oncogenes differ by being activated or mutated forms. Proto-oncogenes are naturally present in the genomes of mammals, including humans [10].

2.1 Events take place at the oncogene formation

In humans, proto-oncogenes can transform into oncogenes through three distinct mechanisms, all of which result in a loss or reduction of cell regulation. Gain of function occurs when proto-oncogenes are converted into oncogenes, which can happen in both

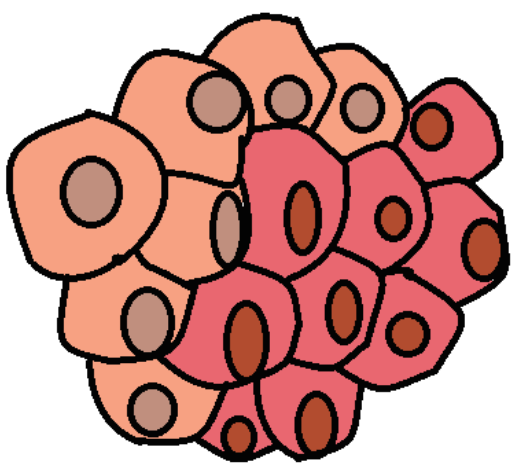

Figure 1: Structure of oncogene.

quantitative and qualitative ways [7,9]. These changes lead to abnormal cell division, eventually contributing to tumor growth. Quantitative types of oncogene activation can occur through gene amplification or transposition to an active chromatin domain. In contrast, qualitative types of activation can result from point mutations or the production of a novel product from a chimeric gene [10]. In summary, there are three primary mechanisms (Figure 2) by which oncogenes are activated, transforming proto-oncogenes and potentially leading to cancer:

1. Translocation or transposition,
2. Gene amplification, and
3. Point mutation.

(i) Translocation or transposition

An oncogene may over-proliferate as a result of chromosomal translocations that disrupt transcriptional control, such as the (8;14) translocation, which affects 75% of lymphoma patients. This specific translocation has been linked to several human tumors. A chromosomal translocation occurs when a chromosome breaks off and joins with another. The Philadelphia chromosome, the first translocation associated with a human cancer (Figure 3)—chronic myelogenous leukemia—is an example of two distinct genes fusing together [11]. A well-known example of this translocation is the fusion of the chromosome 9 proto-oncogene c-ABL with the chromosome 22 breakpoint cluster region (BCR). This fusion produces the hybrid oncogene BCR-ABL, which generates a mutant protein that disrupts the normal regulation of cell division [12].

In Burkitt's lymphoma patients, translocations of chromosomes 8 and 14 occur. As a result of this unusual translocation, the strong immunoglobulin heavy chain gene (IGH) promoter on chromosome 14 takes control of the MYC proto-oncogene from chromosome 8 [13]. Normally, the MYC protein signals promote cell proliferation; however, this translocation causes overexpression of MYC in lymphoid cells, where the IGH promoter is usually active. These gene rearrangements, in which genes relocate to new chromosomal sites, lead to increased gene expression. Such chromosomal rearrangements often result from errors in the normal rearrangement of immunoglobulin or T-cell receptor genes. Refer to Figure 3 for an illustration of how these reciprocal chromosome rearrangements activate the c-ABL and c-MYC proto-oncogenes in Burkitt's lymphoma and chronic myelogenous leukemia [8,11, 14].

(ii) Gene amplification

The term 'gene amplification' refers to the process of adding multiple copies of a gene to a genome. In response to signals from other cells or external stimuli, cancer cells can replicate a gene several times. This phenomenon significantly impacts the development of various solid tumors in humans [15]. Moreover, oncogene amplification may indicate genomic instability in solid tumor cells. A major genetic mechanism for regulating gene expression is the amplification of gene dosage through deoxyribonucleic acid (DNA) amplification. Gene amplification in organisms can occur in one of two ways: intentionally or accidentally. The overexpression of the amplified gene, which is a hallmark of cancer, is closely associated with the result of chromosome fragment amplification. Amplified genes may be scattered throughout the genome, appear as repeating units at a single locus, or exist as extrachromosomal elements [16]. Notably, amplicons have been found to contain amplified oncogenes such as MYC, MYCN, EGFR, and v-erb-b2 avian erythroblast leukemia viral oncogene homolog 2 (ERBB2). MYC was the first oncogene shown to be amplified in various tumor cells, including those derived from mouse osteosarcoma, colon carcinoma, small cell lung carcinoma, and plasma cell leukemia [17]. Numerous techniques can be used to evaluate the process of oncogene amplification, including DNA-based methods (PCR or Southern blot), molecular cytogenetic methods (Fluorescence In Situ

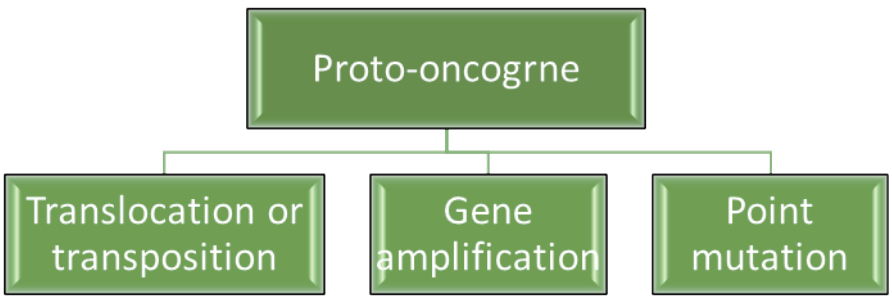

Figure 2: Mechanism of oncogene activation

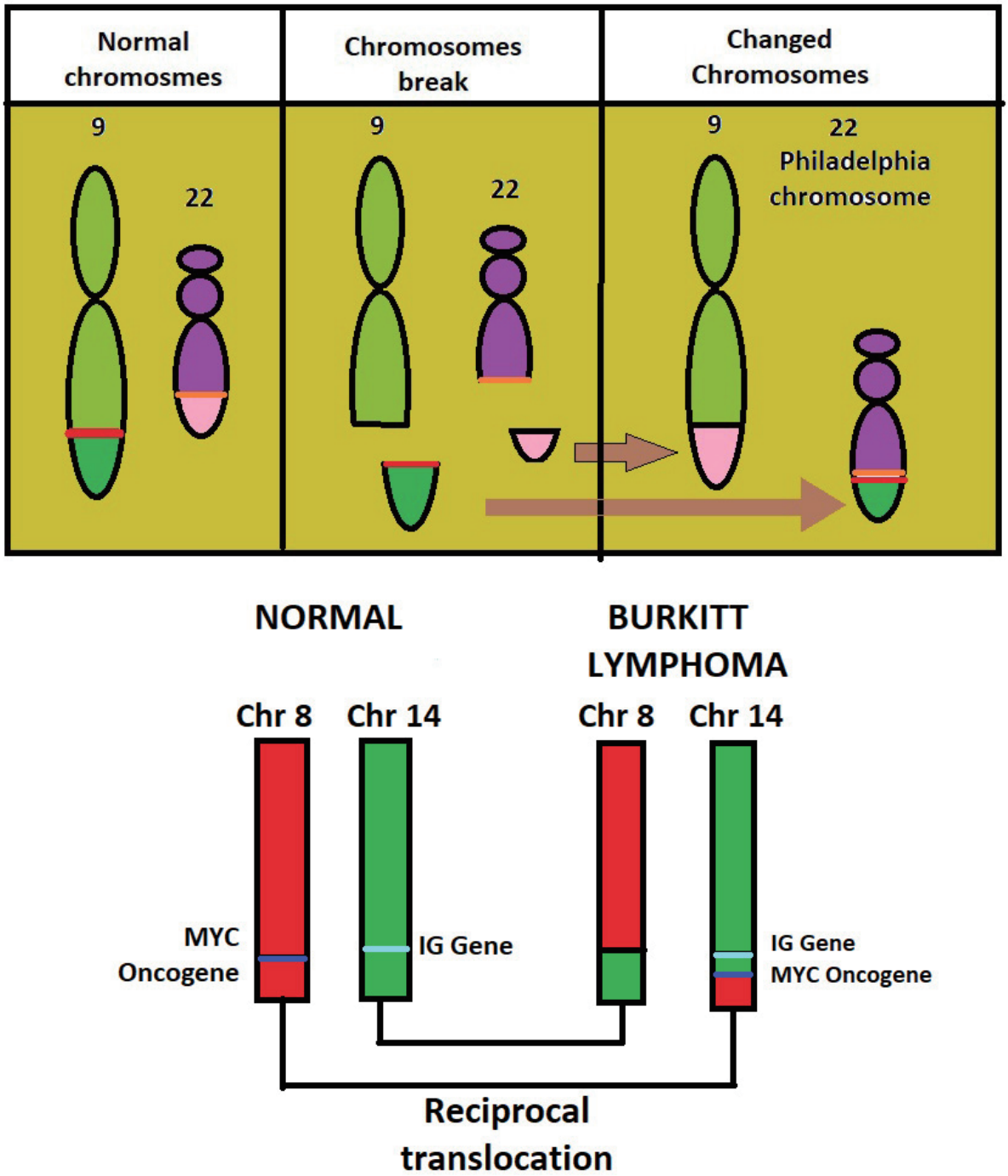

Figure 3: Reciprocal translocation at chromosome (9; 22) and at (8; 14) leading to activation of c-ABL proto-oncogene and activation of c-MYC proto-oncogene.

Hybridization, or FISH) using gene-specific probes, and Comparative Genomic Hybridization (CGH) [18].

(iii) Point mutation

One of the most common genetic alterations observed in humans is mutations in the RAS proteins (Figure 4). Point mutations, also known as point variations, are genetic changes that occur when one nucleotide is replaced by another. These mutations can activate proto-oncogenes by altering the structure of the proteins they encode. Proto-oncogenes can be activated by point mutations through various mechanisms, such as base substitutions, deletions, and insertions [12, 19]. Mutations in the RAS proteins are among the most frequent genetic alterations found in human proteins. Several molecular techniques can be used to evaluate gene amplification for oncogenes, including molecular cytogenetic techniques like Fluorescence In-

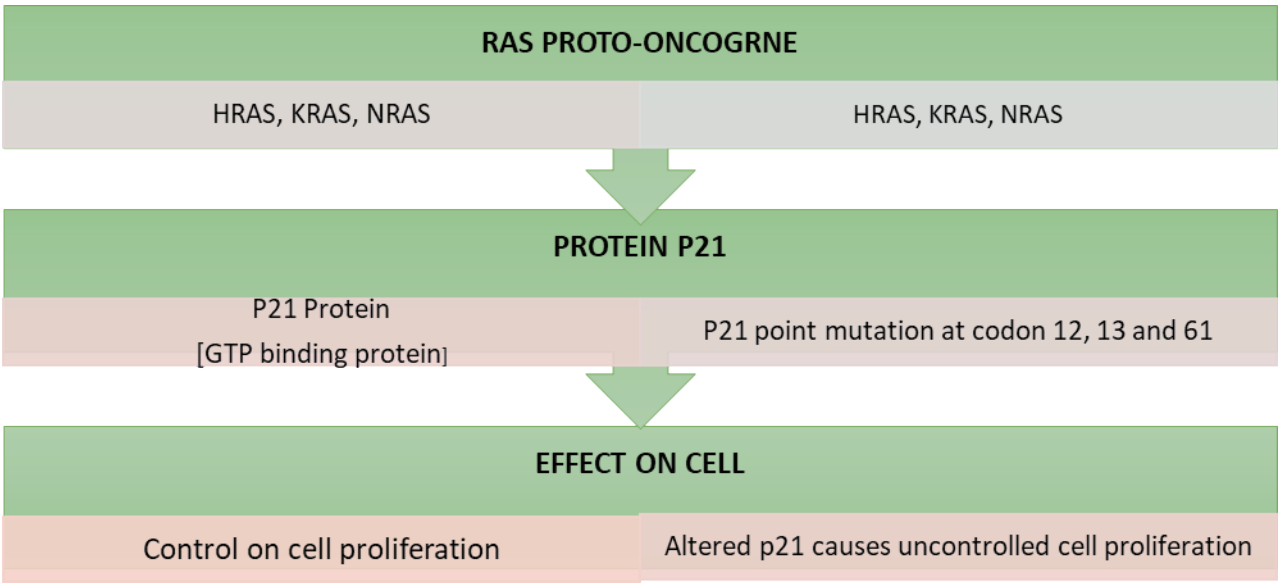

Figure 4: The effect of RAS-mutation on cell proliferation.

Situ Hybridization (FISH) with gene-specific probes, DNA-based techniques like Polymerase Chain Reaction (PCR) and Southern blot, and Comparative Genomic Hybridization (CGH) [20].

K-ras mutations are primarily detected in carcinomas and are responsible for 90% of pancreatic carcinomas, 30% of lung carcinomas, and 50% of colon carcinomas. In contrast, N-ras mutations are more commonly associated with hematologic malignancies and can be found in up to 25% of cases of myelodysplastic syndromes and acute myeloid leukemia. RAS mutations have also been discovered in the majority of thyroid cancer cases. These mutations are not restricted to any particular member of the RAS family but are distributed among K-ras, H-ras, and N-ras. However, they are particularly correlated with differentiated follicular-type thyroid carcinomas [21,22].

3. Structures of Most Common Oncognes

Oncogenes are genes that can cause cancer, often as a result of mutations or increased expression levels. These genes have the ability to transform healthy cells into cancerous ones, initiating the process that leads to tumor development. When certain structural features of well-known oncogenes are altered, they can contribute to the development of cancer in the body. Some of the most commonly associated oncogenes include RAS-GTPase, the Bcl-2 gene, the Myc gene, the HER2 protein, the RET proto-oncogene, the BRCA2 gene, and the C-Met protein [12-14].

RAS-GTPase

Cancer can result from mutations in the proteins encoded by the Ras genes. As GTPases, all Ras proteins act as molecular switches that regulate various cellular interactions and signaling pathways. Disruption of Ras protein function, caused by different point mutations in the gene, is a well-established predictor of cancer development. The involvement of H-Ras, K-Ras, and N-Ras in the Ras-Raf-MAPK pathway within cellular signaling networks is crucial for regulating the growth, differentiation, and survival of eukaryotic cells. Mutations in Ras genes have been linked to the development of numerous cancers and have been identified in various cancer types. These mutations can lead to molecular changes in other signaling pathway components, such as B-Raf, EGFR, and NF-1 [6,9,14]. In addition to cancer and developmental disorders, altered Ras signaling may also contribute to other diseases. For example, H-Ras activation has been associated with non-obese diabetes and diabetic retinopathy, resulting in the formation of abnormal vascular structures. Changes in the expression patterns of K-Ras and H-Ras have also been occasionally linked to glomerulonephritis. Notably, while specific mutations are responsible for oncogenic changes, the majority of mutations associated with these diseases tend to affect a broader range of amino acids in Ras proteins [22].

MYC gene

Transcription factor-coding regulator genes and proto-oncogenes of the MYC (Figure 5) family play a significant role in many human malignancies. The MYC

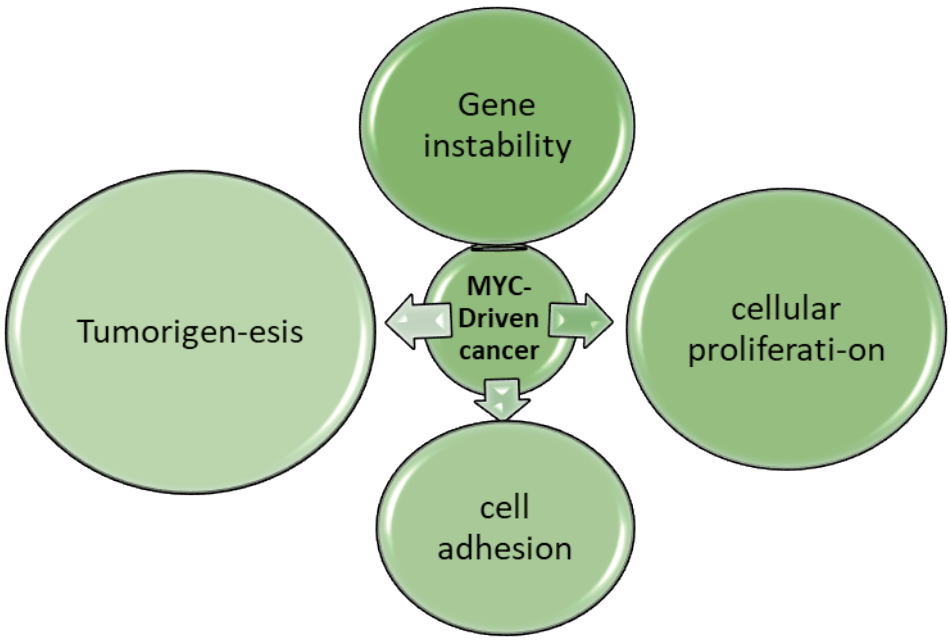

Figure 5: MYC driven cancer and structure of MYC oncogene.

gene is a major contributing factor in a large number of cancers. Early research on aggressive chicken tumors caused by oncogenic retroviruses led to the discovery of MYC by identifying the v-MYC oncogene, which induces myelocytomatosis, or leukemia and sarcoma [6, 21]. Although retroviral integration, chromosomal rearrangements, activation of the gene's super-enhancer, modifications to MYC-related signaling pathways, and MYC overexpression are all linked to cancer and contribute to MYC instability, the MYC expression pattern is tightly regulated under normal conditions. Numerous studies have extensively examined the critical role of MYC in regulating the cell cycle and cell proliferation. Research has also investigated the role of MYC in cell destruction. In response to DNA damage caused by UV irradiation and other agents, MYC levels are reduced through various mechanisms, including protein turnover, transcriptional regulation, and MYC alteration [19, 23].

ER2 Protein

There is an overexpression of the oncogene HER2 and membrane tyrosine kinase, which initiates strong signals that prevent apoptosis and promote cell growth. This overexpression plays a key role in the development and spread of tumors in certain cancers, such as breast cancer. The HER2 protein can drive the formation of cancer cells, particularly in breast cancers [18]. Approximately 1 in 5 cases of breast cancer have amplified copies of these proteins. In HER2-positive breast cancers, the overexpression of HER2 is a significant factor (Figure 6). The HER2 pathway is a complex biological network, which systems biology describes as having three layers: an input layer consisting of membrane receptors and their ligands that trigger signals from outside the cell; a core system that processes signals via kinase proteins, transmitting them to the nucleus; and an output layer that regulates genes affecting various cellular functions [20, 22].

HER2 overexpression occurs in 20% of breast cancers, as well as some ovarian and gastric cancers, but in breast cancer, it leads to more aggressive biological behavior and clinical outcomes. Breast cancer malignancies may have up to 25–50 copies of the HER2 gene, resulting in the expression of approximately 2 million receptors on the surface of the tumor cells. Analyzing the variation in HER2 expression between normal tissues and tumors helps determine the optimal therapeutic target. HER2 amplification is a relatively early event in the development of human breast tumors, often associated with co-amplification of the topoisomerase-2 gene. These tumors exhibit distinct biological and clinical characteristics, including a high proliferation rate, increased aneuploidy, and are associated with a worse prognosis for patients [11, 24].

RET Proto-oncogene

A chromosomal segment at 10q11.2 encodes the receptor tyrosine kinase, known as the RET proto-oncogene, which is expressed in tumors and tissues derived from neural crests. Pheochromocytoma

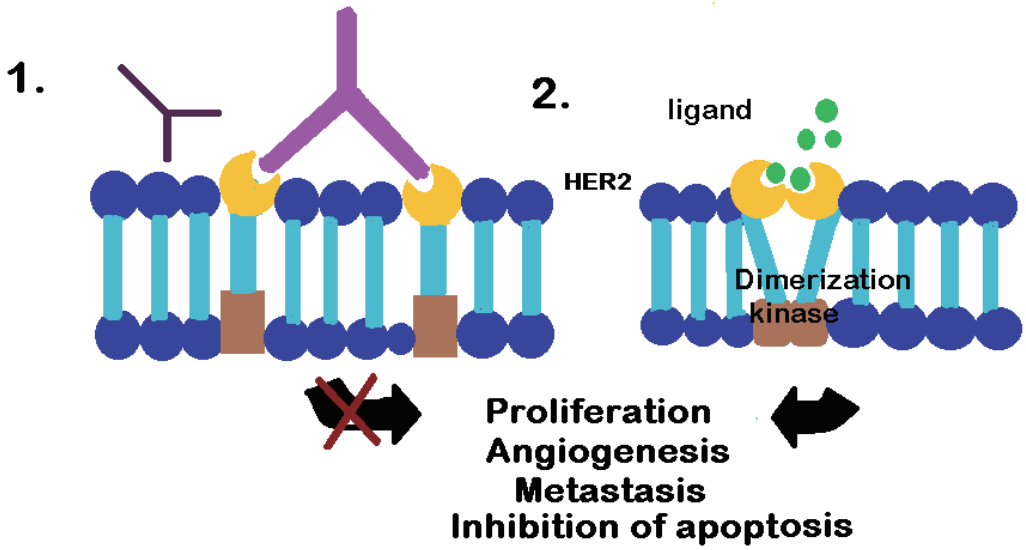

Figure 6: the 1st structure shows the drug TRASTUZUMAB binds to HER2 cancer causing protein in breast cancer and 2nd structure shows the effect of HER2 protein causing proliferation, angiogenesis and metastasis.

(PC), medullary thyroid carcinoma (MTC), and hyperparathyroidism (HPT) are all part of multiple endocrine neoplasia type 2, an inherited cancer syndrome caused by mutations in the RET gene. The most frequent mutation, TGC → CGC (cysteine → arginine) at codon 634, occurs in the cysteine-rich region of the extracellular domain and results in the substitution of cysteine with arginine. RET fusions with other partner genes have been linked to numerous human malignancies, such as non-small cell lung cancers (NSCLCs) and papillary thyroid carcinomas (PTCs). RET fusion has been identified in 5%–35% of adult PTCs, with the most common rearrangement involving the CCDC6 gene [5, 8, 24]. The RET and CCDC6 genes are located on the long arm of chromosome 10, and the gene fusion is caused by intrachromosomal inversion.

The following are additional partner genes associated with RET fusion in PTC: TRIM24, TRIM33, GOLGA5, PRKAR1A, NCOA4, and KTN1. All of these genes cause fusion with RET through intrachromosomal translocation, except for NCOA4, which is located on chromosome 10. Moreover, congenital central hypoventilation syndrome (CCHS) and congenital kidney and urinary tract abnormalities are less frequently linked to RET mutations (Figure 7). Future research on RET functions will provide additional insights into the molecular mechanisms controlling kidney development, spermatogenesis, and enteric neuronal systems [25].

3.1 Concept of immunotherapy

A cancer treatment called immunotherapy works by strengthening a patient's immune system. It can change or bolster the immune system's capacity to identify and destroy malignant cells. The immune system is a highly developed system that the body employs to fight cancer, involving cells, organs, and proteins. Cancer frequently evades the immune system's built-in defenses, allowing cancer cells to multiply. Different types of immunotherapy work in various ways [19]. Some treatments help the immune system stop or slow the growth of cancer cells, while others prevent the disease from spreading to other parts of the body or support the immune system's attack on cancer cells. The immune system's everyday job is to protect the body from intruders, including viruses, allergens, and potentially cancerous cells [24]. It has special cells that constantly scour the body for intruders, eliminating any damaged or cancerous cells they encounter. This process helps prevent cancerous tumors from growing and spreading. That said, cancer is a shifting target. Malignant cells are always looking for ways to evade the defenses of the immune system. Immunotherapy often serves as a first-line or initial treatment for many types of metastatic cancer, which is cancer that has spread. Chemotherapy, targeted therapy, and other cancer therapies may be used in conjunction with immunotherapy [26].

Healthcare professionals employ diverse types of immunotherapy to address different kinds of cancer, with each type utilizing a different part of the immune system. The immune system uses receptor proteins on specific immune cells to identify invaders. Based

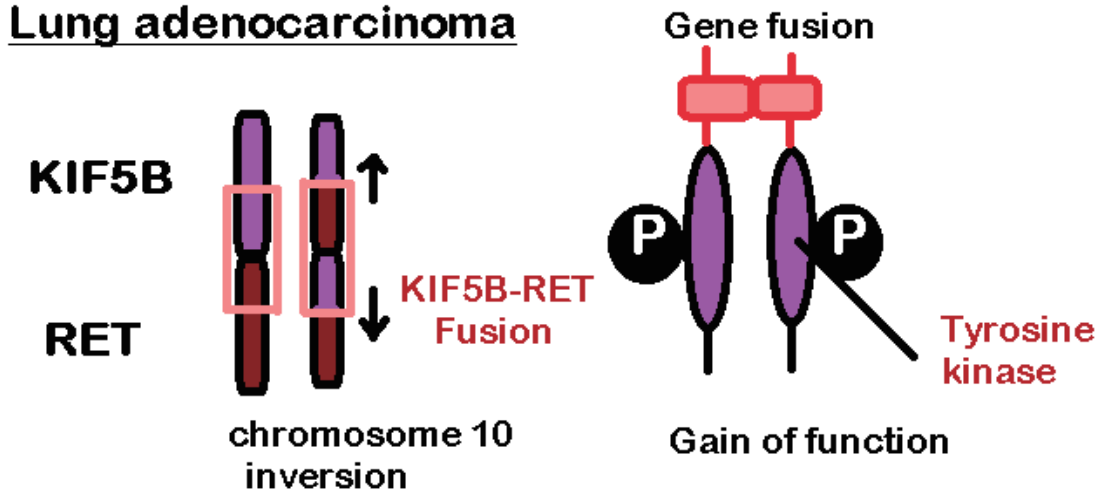

Figure 7: Molecular process of oncogene fusion

on whether these receptors are active or silenced, it can distinguish between healthy and invasive cells at particular checkpoints, which are essential for preventing the immune system from attacking healthy cells [21]. Cancer cells, however, behave differently from healthy cells and often do not elicit an immune response because they are simply altered cells of the body. The immune system struggles to differentiate between these harmful cells, allowing them to proliferate, divide, and spread throughout the body. Oncologists prescribe immunotherapies for various cancers, as they have been approved in numerous countries worldwide. Years of research and testing have led to these approvals, demonstrating the efficacy of these treatments. Immunotherapies can also be accessed through clinical trials, which are closely supervised and controlled studies involving volunteer patients [22-26].

Not every patient responds to immunotherapy, and some treatment forms have mild to moderate adverse effects that can still be managed. Scientists are working to determine which patients will benefit from treatment and which will not. This research is paving the way for new strategies to broaden the patient base that may benefit from immunotherapy. Immunology has already led to significant advances in treating some cancers, such as the first drug shown to extend the survival of patients with metastatic melanoma and vaccines against cervical and liver cancer [27]. However, each type of cancer is distinct, and immunology and immunotherapy affect cancers differently. Below are a few types of cancer along with their respective immunotherapy treatments:

As the above-mentioned cancer immunotherapies have various different methods to be performed to have the effect of immunotherapy i.e. why here are some ways to give immunotherapies.

3.2 Immune checkpoint inhibitors

T cells help the immune system combat cancer. These

Table 1: Various cancers with their respective immunotherapies [25-39].

CANCER TYPE	IMMUNOTHERAPY
Bladder cancer Among the most common cancers worldwide is bladder cancer. The transitional epithelial cells that make up the bladder's inner lining are where the majority of bladder tumors start. These tumors have the potential to spread into the nearby muscle and connective tissue as they grow. Tumors in advanced stages of the disease can metastasis to tissues farther away, like the liver, lungs, or bone, or they can move beyond the bladder to adjacent lymph nodes or pelvic organs.	Treatment for people whose bladder cancer has not spread to the muscular tissue involves surgically excising the tumor and administering one dose of intra-bladder chemotherapy (also known as intravesical chemotherapy), which usually consists of mitomycin C.

Brain cancer Both adults and children can be affected by brain and nervous system cancers, which can take many different forms. It is yet unclear what causes these tumors. Despite the fact that there have been substantial advancements in tumor diagnosis, treatment, and patient quality of life, there is still a lack of understanding regarding the biology of these tumors. Based on the kind of cell they originate from, brain cancer can be categorized into numerous forms, such as meningiomas, gliomas, and astrocytomas. Neuroblastoma and ependymoma are examples of cancers that affect the central and peripheral nervous systems.	When it comes to treating brain cancer, immunotherapy provides some specific alternatives to the standard regimen of chemotherapy, radiation therapy, and surgery.
Breast cancer One of the cancers that women worldwide are diagnosed with the most frequently is breast cancer. In 2023, there will be 44,000 breast cancer-related fatalities and an estimated 300,000 new cases of the disease. At some time in their lives, 1 in 8 women and 1 in 1,000 males will experience invasive breast cancer. Therefore, there is an urgent need for long-lasting, effective breast cancer treatment.	Surgery is usually used in the treatment of breast cancer if the condition is discovered early. Treatment options for breast cancer may include chemotherapy, hormone therapy, surgery, radiation therapy, and/or other modalities, depending on the cancer's molecular features and stage upon diagnosis.
Cervical cancer Affected by more than half a million cases annually, cervical cancer is also the most common malignancy among women worldwide. Nearly every instance of cervical cancer is linked to an HPV infection. Moreover, anal, vaginal, and head and neck malignancies have been connected to this widespread virus.	The FDA has approved three immunotherapy vaccines (listed below) to prevent HPV infection. There have been substantially fewer new occurrences of cervical cancer since the first HPV vaccine was released in 2006. There is some indication from studies that the HPV vaccinations (Gardasil®, Cervarix®, and Gardasil-9®) may also help those who have already had an HPV infection.
Kidney cancer Renal cell carcinomas, or tumors that originate in the kidney's tubule lining, account for around 90% of all kidney cancer cases. Clear cell carcinoma is a subtype that affects about 7 out of 10 patients with renal cell carcinoma. The symptoms of a growing tumor can include pain or swelling in the lower back or abdomen, weariness, weight loss, and swelling in the ankles or legs. Blood in the urine is another common sign.	The precise location, stage, and overall health of the patient are among the specific characteristics that determine how kidney cancer is treated. Kidney cancer treated in its early stages (stages 1-3) can be treated with surgery, laparoscopy, ablation, and targeted therapy. Immunotherapy and targeted therapy are two components of the systemic therapy used to treat patients with metastatic or advanced kidney cancer.
Leukemia Leukemia is a malignancy that affects both adults and children that starts in the lymphatic and bone marrow systems. In leukemia, aberrant bone marrow-produced cells start to replace and supplant healthy blood and marrow cells.	Leukemia treatment varies based on the patient's age, the type of cancer, and the extent of the illness. Chemotherapy is typically the initial course of treatment for this illness; but, in certain circumstances, a stem cell transplant is necessary to completely eradicate the leukemia. There are presently 10 FDA-approved immunotherapy treatments for leukemia in addition to stem cell transplantation.
Lung cancer Lung cancer is the most frequent disease in the world, affecting over 2.1 million people year and causing an estimated 1.7 million deaths. It is also the primary cause of cancer-related fatalities in both genders.	**Immunotherapy:** Radiation, chemotherapy, and surgery were once the standard lung cancer treatments. These treatments are unlikely to be completely curative because most lung cancer patients have advanced illness (stage 3b/4). Immunotherapy patients have significantly improved in clinical trials when treated with it either on its own or in conjunction with other therapies.

Prostate cancer A little gland that resembles a walnut, the prostate is a component of the male reproductive system. The prostate encircles the upper part of the urethra and is situated just beneath the bladder. Prostate cancer, the second most frequent cancer in men worldwide, affects over 1.3 million individuals and claims over 360,000 lives annually, accounting for approximately 4% of all cancer-related fatalities globally.	Radiation and surgery are the standard therapies for prostate cancer in its early stages. Early-stage tumors are also treated with hormonal therapy, which can lower levels of male hormones (androgens like testosterone) that promote tumor growth. Another treatment option for metastatic or advanced prostate cancer is chemotherapy.
Skin cancer Skin cancer is frequently identified early on, when treatment options are more favorable. Of 500 instances, just a tiny percentage—roughly 1 to 2—prove fatal. Ninety percent of skin cancer cases are related to ultraviolet radiation exposure. As a result, most cases of skin cancer occur in sun-exposed areas including the face, head, neck, arms, and legs, and they are more common in those with lighter (less-pigmented) skin.	Localized early-stage skin malignancies can be effectively treated with radiation treatment, photodynamic therapy, topical chemotherapy, and other medical interventions. Patients can choose from a variety of chemotherapies and immunotherapies for advanced instances that cannot be treated with surgery.
Ovarian cancer Frequently, ovarian cancer advances considerably before a patient receives a diagnosis. This is due to the fact that signs of ovarian cancer are sometimes mistaken for less serious digestive problems such gas, bloating, and constipation. An estimated 300,000 people receive an ovarian cancer diagnosis each year, and the disease is responsible for 180,000 fatalities.	Surgery is the first line of treatment for ovarian cancer, and it is followed by a chemotherapy regimen that combines a platinum-based treatment (often carboplatin) with a taxane-based treatment (typically paclitaxel). Patients may be eligible for maintenance therapy with a new class of medications called PARP inhibitors after upfront chemotherapy is finished. These medications have been shown to significantly delay and in some cases even prevent disease relapse in certain patients, especially those whose tumors contain mutations in the BRCA1 and BRCA2 genes.

highly potent specialized cells have the capacity to harm healthy cells. "Immune checkpoints," which can be positive or negative, regulate T cell activity. Positive immune checkpoints activate T cells and facilitate their continued activity, while negative immune checkpoints prevent T cells from functioning by stopping their activity [22]. As a result, when these negative checkpoints are inhibited, the immune system is reactivated, enabling T cells to locate and destroy cancer cells. The negative effects of immune checkpoint inhibitors can vary. Furthermore, not all cancers can currently be treated with this type of immunotherapy. The suitability of specific immune checkpoint inhibitors for a patient depends on the type of cancer and the patient's overall health [25].

Many regulators, or "checkpoints," are in place to ensure that once foreign or tumor antigens trigger a response, the immune inflammatory response is not perpetually activated. Most of these checkpoints are characterized by T-cell receptors attaching to ligands on neighboring cells to establish immunological synapses. These synapses subsequently control the actions of the T cell, which polarizes or becomes specialized to perform various tasks [26].

As mentioned earlier, the first step in T-cell activation is the presentation of antigens to the appropriate T-cell receptor (TCR) on naive T cells by the MHC molecules on antigen-presenting cells (APCs). Full activation of the costimulatory T-cell receptor CD28 is dependent on its interaction with the B7 ligand to prevent collateral damage from autoimmunity. This interaction is either strictly regulated or inhibited by inhibitory checkpoint receptor/ligand combinations [27].

3.3 Mechanism of immune check point inhibitors

Immune checkpoint inhibitors (ICIs) are a revolutionary class of cancer treatments that enhance the body's immune response against tumors by targeting the immune checkpoints, which are regulatory pathways that control T cell activation and proliferation. These checkpoints are essential for maintaining immune tolerance and preventing autoimmune responses; however, cancer cells often

exploit these mechanisms to evade detection and destruction by the immune system [28]. Immune checkpoints include proteins such as programmed cell death protein 1 (PD-1), its ligand PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). When T cells encounter cancer cells expressing PD-L1 or ligands for CTLA-4, these interactions inhibit T cell activation and function, effectively allowing cancer cells to escape immune surveillance. Immune checkpoint inhibitors work by blocking these inhibitory signals, thereby restoring T cell activity and enhancing the immune system's ability to identify and eliminate cancer cells [29]. For instance, PD-1 inhibitors bind to the PD-1 receptor on T cells, preventing it from interacting with PD-L1 on tumor cells, which enhances T cell activation, proliferation, and the subsequent anti-tumor response. Similarly, CTLA-4 inhibitors block the interaction between CTLA-4 and its ligands, promoting T cell activation and augmenting immune responses against tumors [30]. The effectiveness of ICIs can vary among patients and types of cancer, influenced by factors such as tumor mutation burden, the presence of specific biomarkers, and the overall immune landscape within the tumor microenvironment. Additionally, while ICIs can lead to remarkable and durable responses in some patients, they can also result in immune-related adverse effects due to the unleashing of T cells, which may attack healthy tissues [31]. Ongoing research is focused on understanding the precise mechanisms of action, identifying predictive biomarkers for response, and developing combination therapies that enhance the efficacy of immune checkpoint inhibitors while minimizing their adverse effects. Overall, the advent of immune checkpoint inhibitors represents a paradigm shift in cancer immunotherapy, offering new hope for patients with various malignancies. The checkpoint inhibitors work by blocking the receptors that cancer cells use to send signals to T cells when the signal is blocked, T cells may be better able to differentiate a cancer cell from a healthy cell and launch an attack [32].

The immune system needs to be able to discriminate between substances or cells that are "self," or a part of the body, and "non-self," or not a part of the body but potentially dangerous, when it reacts to an outside invader. Your body's cells' surfaces or contents contain proteins that help the immune system identify those cells as belonging to you. A subset of these proteins are called immunological checkpoints, and they help your immune system identify "self" cells. By putting up a barrier made of these immune checkpoint proteins, cancer cells can occasionally avoid being recognized by the immune system and attacked [14, 33]. T cells are immune system cells that scavenge the body for indications of illness or infection. T lymphocytes recognize other cells by identifying certain proteins on their surface through analysis. The T cell ignores the cell if the surface proteins indicate that it is sound and normal. The T cell launches an assault on the cell if the surface proteins indicate that it is malignant or unhealthy in any other way [34]. The immune system produces more specialized proteins once T cells launch an attack in order to stop the attack from harming the body's normal cells and tissues. Immune checkpoints are these specialized proteins that maintain the safety of healthy cells and tissues [35].

PD-1 and PD-L1 inhibitor

One type of checkpoint protein present on T cells is called PD-1, while another checkpoint protein found on many healthy cells in the body is PD-L1. When PD-1 attaches to PD-L1, T cells cannot destroy the cell. However, a high concentration of PD-L1 on certain cancer cells prevents T lymphocytes from eradicating these cancer cells. Immune checkpoint inhibitor medications enable T cells to target cancer cells by preventing PD-1 from binding to PD-L1 [36]. Interferon gamma (IFN-γ), produced by activated T cells, can upregulate PD-L1 on the surface of tumor cells. The PD-1/PD-L1 signaling pathway plays a significant role in tumor immunosuppression, as it can enhance tumor cellular immunological tolerance and prevent T lymphocyte stimulation, thereby enabling tumor immune escape. To summarize, the binding of PD-1 to PD-L1 reduces T cell-mediated immune surveillance, leading to decreased immune reactions or even T cell death. This interaction also suppresses tumor-infiltrating CD4+/CD8+ T cells (CD4+/CD8+ TILs) and causes a decline in cytokines such as tumor necrosis factor (TNF), IFN-γ, and interleukin-2 (IL-2) [12, 37].

PD-1/PD-L1 inhibitors reverse the immunological inhibition of anti-tumor T cells, allowing T cells to proliferate, penetrate the tumor microenvironment (TME), and trigger an anti-tumor response. Current anti-PD-1/PD-L1 therapies effectively stimulate depleted immune cells and initiate an anti-tumor immune response by blocking the interaction between PD-1 and PD-L1 [38]. Pembrolizumab, the chemical name for Keytruda, is approved by the FDA to treat certain types of triple-negative breast cancer as a PD-L1 inhibitor. Keytruda may be used in conjunction with the chemotherapy drug that you and your doctor have selected. Jemperli, also known by its chemical name dostarlimab-gxly, is a PD-1 inhibitor licensed to

treat advanced-stage breast cancer that has progressed during or after therapy and is mismatch repair deficient (dMMR) when no other therapeutic options are available [39].

CTLA-4 inhibitor

On certain T cells, CTLA-4 is an additional checkpoint protein. When CTLA-4 attaches to the B7 protein on another cell, it prevents the T cell from killing the target cell. The medication Yervoy (chemical name: ipilimumab) targets the CTLA-4 protein, preventing it from binding to B7 on other immune cells. This forces the T cells to become activated in order to combat cancer cells. The FDA has approved Yervoy for the treatment of advanced-stage skin cancer, and research is ongoing for its use in treating tumors other than breast cancer. CTLA-4 induces immunosuppression by indirectly decreasing signaling through the co-stimulatory receptor CD28 [29, 32]. Although both receptors bind CD80 and CD86, CTLA-4 has a considerably higher binding affinity than CD28, making it more effective at inhibiting T cell activation. CTLA-4 can remove CD80 and CD86, along with their cytoplasmic domains, from the surfaces of antigen-presenting cells through the process of trans-endocytosis. This procedure reduces the accessibility of these stimulatory receptors to additional CD28-expressing T cells. In reality, regulatory T cells (Tregs) play a vital role in mediating immune suppression in bystander cells. By increasing the activation threshold for T cells, CTLA-4 diminishes immune responses to weak antigens, such as self-antigens and tumor antigens [35, 38].

Tumor lesions may express CTLA-4 not only from the tumor cells themselves but also from invasive Tregs or exhausted conventional T cells. Comparisons of CTLA-4 and PD-1 checkpoint inhibitors to traditional chemotherapies have shown improved patient survival in several studies, including those focused on melanoma, renal cell carcinoma, squamous cell carcinoma, and non-small cell lung cancer [39]. Anti-PD-1 therapy for melanoma was particularly successful in patients with smaller tumors. In a Phase III clinical trial, a direct comparison of the two checkpoint inhibitors revealed that patients treated with the anti-PD-1 antibody nivolumab had a better response rate (44%) and longer survival rates (6.9 months progression-free survival) than those treated with the anti-CTLA-4 antibody ipilimumab (19% response rate and 2.8 months progression-free survival). When nivolumab and ipilimumab were administered together, even greater response rates (58%) and longer survival times (11.5 months) were observed. It appears that underlying immune responses are necessary for checkpoint inhibitor treatment to be effective, as both CTLA-4 and PD-1 function as independent brakes on CD3/CD28-dependent signaling [37-40].

3.4 Adoptive cell therapy

Adoptive cell therapy (ACT) is an innovative form of immunotherapy that harnesses the body's own immune cells to combat cancer. This therapeutic approach involves the extraction of T cells from a patient's blood, followed by their activation and expansion in the laboratory before being reinfused into the patient. The most common type of ACT is chimeric antigen receptor (CAR) T cell therapy, where T cells are genetically modified to express CARs that specifically recognize and bind to antigens present on tumor cells [41]. This modification enhances the T cells' ability to identify and eliminate cancer cells. Once reinfused, the CAR T cells proliferate in the patient's body, targeting and destroying malignant cells. Another form of ACT involves tumor-infiltrating lymphocytes (TILs), which are immune cells that have already infiltrated the tumor microenvironment. These TILs are isolated from the tumor, expanded, and then reinfused, leveraging their natural ability to recognize and attack cancer cells [42]. ACT has shown remarkable efficacy in certain hematologic malignancies, such as acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma, with some patients achieving complete remission. However, challenges remain, including the potential for severe side effects, such as cytokine release syndrome (CRS) and neurotoxicity, which can occur due to the rapid activation and proliferation of the infused T cells. Furthermore, the effectiveness of ACT can be limited by the immunosuppressive tumor microenvironment and the heterogeneity of tumor antigens [35, 41]. Ongoing research is focused on improving the safety and efficacy of ACT through the development of next-generation CAR T cells, combination therapies that enhance the tumor microenvironment, and strategies to identify and target additional tumor antigens. Overall, adoptive cell therapy represents a promising and rapidly evolving area of cancer treatment, with the potential to transform the therapeutic landscape for various malignancies and provide new hope for patients who have exhausted traditional treatment options [42].

Adoptive cell therapy, sometimes referred to as cellular immunotherapy, is a medical procedure that targets and eradicates cancer by means of immune system cells. Not only can our immune system identify and eradicate damaged or ill cells, but it can also

identify and eradicate malignant cells. Because of their capacity to attach to antigens, or surface marks, on cancer cells, immune cells known as killer T cells are very effective against the disease [43]. Utilizing this innate capability, cellular immunotherapies can be applied in many ways.

- Tumor-Infiltrating Lymphocyte (TIL) Therapy
- Engineered T Cell Receptor (TCR) Therapy
- Chimeric Antigen Receptor (CAR) T Cell Therapy
- Natural Killer (NK) Cell Therapy

Tumor-Infiltrating Lymphocyte (TIL) Therapy

Naturally occurring T cells seen in cancer patients are frequently able to target the cancer cells themselves. These T cells, which come in several varieties, are among the most potent immune cells in our body. Particularly the "killer" T cells have the ability to precisely identify and eradicate cancer cells. In essence, TIL treatment uses transformed tumor cells to eradicate the tumor [44]. TIL therapy involves the extraction of TILs from the tumor via biopsy or surgical excision, followed by their massive cultivation in a lab setting using interleukin-2 (IL-2), a protein that stimulates TIL proliferation. Because this procedure usually takes several weeks, patients will only be eligible for TIL therapy if their tumor is stable enough to endure the interim waiting period [45]. Tumor-infiltrating lymphocyte (TIL) therapy is one type of adoptive cell therapy that aims to solve these problems. Using this method, naturally occurring T cells that have already penetrated the malignancies of patients are harvested, activated, and expanded [4, 44]. After that, patients receive massive doses of these activated T cells again, enabling them to find and eliminate cancers.

Step 1: Tumors Resected: One or more tumors are surgically removed from the patient.

Step 2: TILs Extracted: The tumors are dissected to remove immune cells that have penetrated the tumor. These cells are known as tumor infiltrating lymphocytes (TILs)

Step 3: TILs Expanded: The TILs are cultured and expanded (multiplied) using interleukin-2, resulting in a large population of immune cells

Step 4: Infusion of TILs: Patient receives chemotherapy to help make room for the new immune cells. The TILs are then infused into the patient to bolster an immune response against the cancer cells, leaving healthy cells untouched.

Engineered T cell Receptor (TCR) Therapy

Engineered T cell receptor (TCR) therapy is an innovative approach in cancer immunotherapy that involves modifying a patient's own T cells to enhance their ability to recognize and attack cancer cells. This therapy begins with the extraction of T cells from the patient's blood, which are then genetically engineered in the laboratory to express a specific TCR that targets tumor-associated antigens [45]. These antigens are proteins expressed on the surface of cancer cells, which may not be present on healthy cells, making them ideal targets for T cell-mediated destruction. The engineered TCRs are designed to recognize these unique antigens, enabling the modified T cells to distinguish between cancerous and non-cancerous cells [46]. After the T cells are successfully modified and expanded in number, they are infused back into the patient, where they can seek out and destroy cancer cells. This approach holds great promise, particularly for cancers that express specific antigens, such as melanoma, lung cancer, and certain leukemias. Unlike traditional treatments, TCR therapy can provide a more precise and targeted attack on tumors, potentially leading to better outcomes and fewer side effects. Moreover, ongoing research is focused on improving the specificity and efficacy of engineered TCRs by exploring novel antigen targets, enhancing T cell persistence in the body, and overcoming the immunosuppressive tumor microenvironment. While engineered TCR therapy has shown encouraging results in clinical trials, challenges remain, including the risk of off-target effects, which can lead to damage to normal tissues, and the need for personalized approaches that may require extensive time and resources [47-49]. Nevertheless, as research progresses, TCR therapy has the potential to become a cornerstone of personalized cancer treatment, offering new hope to patients with challenging malignancies.

Not all patients have T cells that recognize their cancers. Some people may be able to reject their cancers, but these T cells may not be able to become adequately activated and expanded for a variety of reasons. For these patients, doctors may employ a procedure known as tailored T cell receptor (TCR) therapy. This approach also makes use of T cells that have been removed from patients; however, the T cells may also be altered to gain a novel T cell receptor, enabling them to target specific cancer antigens, in addition to activating and increasing the quantity of anti-tumor T cells available [50].

Chimeric Antigen Receptor (CAR) T cell Therapy

Only cancer cells presenting their antigens in a certain context—when the antigens are bound by the major histocompatibility complex, or MHC—can be targeted and eliminated by TIL and TCR treatments. The benefit of CARs is their capacity to attach to cancer

cells even in the absence of MHC-presented antigens on the surface, potentially making more cancer cells susceptible to their attacks. But unlike TCRs, the spectrum of possible antigen targets is restricted since CAR T cells are only able to identify antigens that are naturally produced on the cell surface. When foreign substances enter the body, the immune system identifies them by looking for proteins on the surface of those cells known as antigens [22-26]. T cells are immune cells with their own proteins called receptors that bind to foreign antigens and assist in inducing other immune system components to eliminate the foreign material. Antigens and immunological receptors have a lock and key interaction. Like a lock that requires the proper key to open, every foreign antigen has a distinct immune receptor that can attach to it in CAR T-cell therapy, a patient's blood is used to modify T cells in the lab. A gene for a receptor—known as a chimeric antigen receptor, or CAR—those aids in the T cells' attachment to a particular cancer cell antigen is added. After that, the patient receives their CAR T cells back [8, 51]. The patient may get chemotherapy a few days before to the CAR T-cell infusion in order to assist reduce the quantity of other immune cells. This increases the likelihood that the CAR T cells will become activated to combat the malignancy. Because CAR T cells function best while there are still some cancer cells to assault, this chemotherapy is typically not very strong. While CAR T-cell therapy has demonstrated remarkable efficacy in treating certain tumors that are difficult to treat, it can occasionally result in severe or even fatal side effects. As a result, it must be administered at a hospital with specialized training in its use, and patients must be constantly monitored for a few weeks following their administration of CAR T cells. When CAR T cells proliferate, a significant quantity of molecules known as cytokines are released into the bloodstream, which might strengthen the immune system [52-55]. This release may cause serious adverse effects, which include:

- High fever and chills
- Trouble breathing
- Severe nausea, vomiting, and/or diarrhea
- Feeling dizzy or lightheaded
- Headaches
- Fast heartbeat
- Feeling very tired
- Muscle and/or joint pain
- Allergic reactions during the infusion
- Abnormal levels of minerals in the blood, such as low potassium, sodium, or phosphorous levels
- A weakened immune system, with an increased risk of serious infections
- Low blood cell counts, which can increase the risk of infections, fatigue, and bruising or bleeding

4. Cancer Vaccines

It has been demonstrated that vaccines are effective in preventing viral and bacterial infections. Since the first vaccine was developed more than 200 years ago, vaccines have helped avoid some of the deadliest diseases of the 20th century and saved hundreds of millions of lives worldwide. However, the development of vaccines to prevent or treat cancer has been hampered by the fact that the situation is more complex in the case of cancer for various reasons (more on this below). In particular, cancer cells resemble normal, healthy cells more than viruses and bacteria, which appear foreign to our immune system [56]. Furthermore, each person's tumor is unique in some way and is distinguished from others by specific antigens. Therefore, more advanced methods are required to create effective cancer vaccines. Specific malignancies caused by viruses can be prevented in healthy individuals by receiving certain vaccinations. These vaccines shield the body from these viruses, similar to vaccinations against the flu or chickenpox [57]. This type of vaccine is only effective if administered to a person prior to viral infection. Cancer vaccines enhance the immune system's ability to identify and eliminate antigens. Cancer-specific antigens are substances present on the surface of cancer cells but not on healthy cells. When a person receives a vaccine containing one of these substances, they act as antigens that instruct the immune system to find and destroy cancer cells displaying them on their surface [58]. Individualized cancer immunizations are also available, suggesting that they are designed for a single person. This type of vaccine is created using tumor samples removed from the patient after surgery. In contrast, certain cancer vaccines that lack customization target cancer antigens that are not specific to an individual [59].

4.1 Therapeutic Cancer Vaccines

In essence, tumors are unique and contain a particular set of antigens. Therefore, more advanced techniques are required to develop cancer vaccines. Fortunately, by pinpointing specific targets in patients' tumors, medical professionals can now differentiate between dangerous and healthy cells. These targets can occasionally be normal proteins, such as prostatic acid phosphatase (PAP), which is frequently overexpressed

in prostate cancer cells, that cancer cells produce in abnormally large quantities. Based on these data, the FDA granted approval for the sipuleucel-T vaccination in 2010 to treat patients with metastatic prostate cancer [13, 22]. Numerous approaches to therapeutic vaccination have been developed, including:

• Whole Tumor Cell Vaccines: These vaccines use whole tumor cells as the antigen source.

• Tumor-Cell Lysates or Gene-Modified Tumor Cells: Some vaccines employ tumor-cell lysates or genetically modified tumor cells.

• Protein- or Peptide-Based Vaccines: These vaccines utilize specific proteins or peptides associated with the tumor.

• RNA and DNA Vaccines: RNA and DNA vaccines involve genetic material to trigger an immune response.

• Viral Vectors Engineered for Tumor Antigen Expression: Viral vectors are engineered to express tumor antigens.

• Dendritic Cell (DC)-Based Vaccines Loaded with DNA, RNA, or Peptides: Dendritic cells, a type of immune cell, are loaded with tumor-related DNA, RNA, or peptides to stimulate the immune system.

• The tuberculosis vaccine Bacillus Calmette-Guérin (BCG), which is now utilized as a general immune stimulant, is an exception to this rule.

• These diverse strategies show how the field of cancer vaccine development is changing, with the goal of improving the body's capacity to identify and fight cancer while reducing damage to healthy cells.

4.2 Personalized Neo-antigen Vaccines

Tumor cells from every cancer patient have genetic alterations in them, most of which are unique to each patient. These tumor cells can undergo mutations that produce novel self-antigens called neo-epitopes or neo-antigens. The immune system can identify and combat neo-antigens, which are molecular changes caused by a certain subset of these somatic mutations. Because of the overexpression of some proteins, such as PAP, which results from mutations, tumors also have specific targets [60]. Depending on the kind of cancer, neo-antigens can result from a variety of mutational events, with the quantity and kinds of mutations changing. Point mutations, insertions, deletions, and gene fusions are all included in this category of mutational events. These neo-antigens can be identified by cytotoxic CD8+ T lymphocytes that have infiltrated tumors. Neo-antigens are only expressed by tumor cells in a patient's body; no healthy cells do this. Neo-antigen vaccines present the possibility of triggering immune responses that selectively target tumor cells in a patient while protecting healthy cells from immunological attacks, hence lowering the likelihood of adverse events. These vaccines have the ability to minimize the toxicities frequently associated with checkpoint blockade medicines, such as PD-1 and CTLA-4 inhibitors, by enhancing the immune response while maintaining its precision when paired with other immunotherapeutic techniques [61-63].

5. Oncolytic Virus Therapy

A novel form of immunotherapy known as "oncolytic viruses" use viruses to enter cancer cells and destroy them. Viruses are minute organisms that infiltrate human cells, use the genetic machinery of the host cell to multiply, and then spread to other cells that are not yet infected. Certain viruses, such as the human papillomavirus (HPV) in cervical and head and neck cancer and the hepatitis B virus (HBV) in liver cancer, have occasionally been linked to the development of particular cancers. The idea of utilizing viruses to specifically target and fight tumors that have already advanced led to the development of a class of viruses known as oncolytic viruses, some of which have undergone modifications [33, 41, 58]. These viruses possess the following crucial characteristics that make them a promising cancer therapeutic option:

Susceptibility of Cancer Cells: Cancer cells often exhibit compromised antiviral defenses, rendering them more vulnerable to viral infection [58].

Engineered Advantages: It is possible to genetically modify these naturally existing viruses to improve their characteristics. Changes may involve lessening their capacity to infect healthy cells and giving them the ability to transport therapeutic payloads straight to tumor locations. Additionally, after invading tumor cells, many oncolytic viruses might release chemicals that strengthen the immune system [59].

Inducing Cancer Cell Destruction: Oncolytic viruses have the ability to induce lysis, or "bursting," in cancer cells after infection, which results in the cancer cells' demise. Carcinogens are also released during this procedure. These antigens have the capacity to set off immune reactions that aggressively seek out and eradicate any tumor cells that may still be present nearby or in other areas of the body [60].

In summary, oncolytic viruses offer a promising avenue in cancer treatment due to their ability to exploit the vulnerabilities of cancer cells, their capacity for genetic modification to enhance targeting, and their potential to trigger an immune response against

cancer cells beyond the site of infection.

6. Targeted Antibodies

One type of cancer immunotherapy treatment that inhibits the growth of cancer cells and alerts the immune system to identify and destroy cancer cells is targeted antibody therapy. B cells are immune cells that create these naturally occurring proteins that are called antibodies. They are essential for protecting our body against various infections, such as those caused by bacteria, viruses, and cancerous cells. They accomplish this by precisely recognizing and attaching to antigens, which are surface identifiers for cells. The variety of antibodies that our immune system is capable of producing is amazing [56-61]. Advance technologies enhance immune system by customizing antibodies in the lab to target particular cancer signals. Because of their similar structural makeup, these customized antibodies are frequently referred to as monoclonal antibodies. Targeted antibodies come in many varieties that are used:

"Naked" Monoclonal Antibodies (mAbs): These antibodies are administered without any additional components and work by directly targeting cancer cells.

Antibody-Drug Conjugates (ADCs): In ADCs, monoclonal antibodies are coupled with potent cytotoxic drugs. When they bind to cancer cells, they deliver the drug, enhancing the cell-killing effect while minimizing damage to healthy cells.

Bispecific Antibodies: Bispecific antibodies target two different antigens at once by combining components from two separate antibodies. Some of these targets both immune (T cells) and cancer cells; they are referred to as "bispecific T cell engagers" (BiTEs).

Since most targeted antibodies specifically target tumor cells rather than immune cells, they fall under the category of "passive" immunotherapies. But because they involve immune cells, more recent developments have led to targeted antibody variants that are categorized as "active" immunotherapies. Many targeted antibodies are currently being tested in clinical trials for a variety of cancer types, both as stand-alone therapies and in conjunction with other therapy strategies. Antibodies attach themselves to cancer cells and obstruct important channels that control their activity, like the ones that allow uncontrolled growth (i.e., death by the "front" end). These antibodies also have the capacity to notify other immune cells to initiate "back-end" immune mediated death, which involves eliminating the cancer cells [57, 60].

6.1 Naked" Monoclonal Antibodies (mAbs)

"Naked" monoclonal antibodies are a type of targeted therapy that has gained significant attention in the field of oncology for their ability to selectively bind to specific antigens present on the surface of cancer cells. Unlike conjugated or labeled antibodies, which are linked to drugs, toxins, or radioactive particles, naked monoclonal antibodies function independently to elicit an immune response against cancer cells [39, 45]. These antibodies are engineered in the laboratory to recognize and attach to specific proteins that are overexpressed or uniquely expressed on cancer cells, such as CD20 in B-cell malignancies or HER2 in certain breast cancers. Once bound to their target, naked monoclonal antibodies can trigger a variety of anti-tumor mechanisms, including direct induction of apoptosis (programmed cell death), recruitment of immune effector cells to destroy the tumor, and blocking signaling pathways that promote tumor growth and survival. For instance, the binding of naked antibodies can activate complement-mediated cytotoxicity, where the body's complement system is recruited to create pores in the cancer cell membrane, leading to cell lysis. Additionally, these antibodies can facilitate antibody-dependent cellular cytotoxicity (ADCC), wherein natural killer cells recognize and kill the antibody-coated cancer cells [48]. Notable examples of naked monoclonal antibodies include rituximab, which targets CD20 and is used to treat various B-cell lymphomas and leukemias, and trastuzumab, which targets HER2 and is utilized in HER2-positive breast cancer. Although naked monoclonal antibodies have shown promising results in clinical settings, their effectiveness can vary based on tumor type, the presence of specific biomarkers, and individual patient factors. Furthermore, while they are generally well-tolerated, some patients may experience infusion-related reactions or other adverse effects. Ongoing research is focused on enhancing the efficacy of naked monoclonal antibodies through combination therapies, understanding mechanisms of resistance, and identifying biomarkers that predict response, thereby improving treatment outcomes for cancer patients [49-51].

6.2 Antibody-drug conjugates (ADCS)

Antibody-drug conjugates (ADCs) represent a type of therapy wherein a specific antibody is armed with anti-cancer drugs (Figure 8). This strategic combination allows the antibody, upon binding to cancer cells, to

transport a potent cytotoxic drug capable of eradicating the cancer cells. This precise delivery of chemotherapy drugs directly to tumor sites holds the promise of mitigating the adverse effects typically associated with the untargeted dissemination of these toxic agents. Antibody-drug conjugates (ADCs) represent a groundbreaking approach in cancer therapy that combines the specificity of monoclonal antibodies with the potent cytotoxic effects of chemotherapy agents. By linking an antibody that targets specific tumor-associated antigens to a cytotoxic drug, ADCs are designed to deliver the drug directly to cancer cells while sparing normal healthy tissues, thus minimizing systemic toxicity [62]. The mechanism of action involves the antibody binding to its target antigen on the surface of cancer cells, facilitating internalization of the conjugate. Once inside the cell, the cytotoxic drug is released, leading to cell death through mechanisms such as disruption of DNA synthesis or induction of apoptosis. This targeted approach enhances the therapeutic index of chemotherapy, allowing for the use of higher doses of cytotoxic agents without significantly increasing side effects. Several ADCs have been approved for clinical use, particularly in the treatment of hematological malignancies and solid tumors [33], such as brentuximab vedotin for Hodgkin lymphoma and trastuzumab emtansine for HER2-positive breast cancer. Ongoing research aims to identify new targets for ADCs, optimize linker technology for improved stability and drug release, and explore combination strategies with other therapies, including immune checkpoint inhibitors. Despite their promising potential, challenges remain, including the development of resistance mechanisms and the need for careful patient selection based on biomarker expression. As research progresses, ADCs are poised to become a crucial component of personalized cancer treatment, offering hope for improved outcomes in patients with various malignancies [26].

6.3 Bispecific antibodies

Bispecific antibodies are a class of engineered therapeutic antibodies that possess the unique ability to simultaneously bind to two different antigens or epitopes. This innovative design allows bispecific antibodies to engage multiple targets, enhancing their therapeutic efficacy in various medical applications, particularly in oncology and immunotherapy [16]. One of the most promising uses of bispecific antibodies is in the treatment of cancer, where they can bridge the gap between T cells and tumor cells. By binding to both CD3, a component of the T cell receptor, and a specific tumor-associated antigen, bispecific antibodies facilitate the direct engagement of T cells with cancer cells, effectively recruiting the immune system to attack and destroy tumors. This dual-targeting mechanism not only improves the specificity of the immune response but also minimizes potential off-target effects, as the T cells are directed to the tumor environment. Additionally, bispecific antibodies can enhance the activation and proliferation of T cells, further amplifying the anti-tumor response. Several bispecific antibodies have shown promising results in clinical trials for various malignancies [34], including hematological cancers such as acute lymphoblastic leukemia (ALL) and solid tumors like breast cancer and melanoma. Furthermore, the versatility of bispecific antibodies extends beyond oncology; they

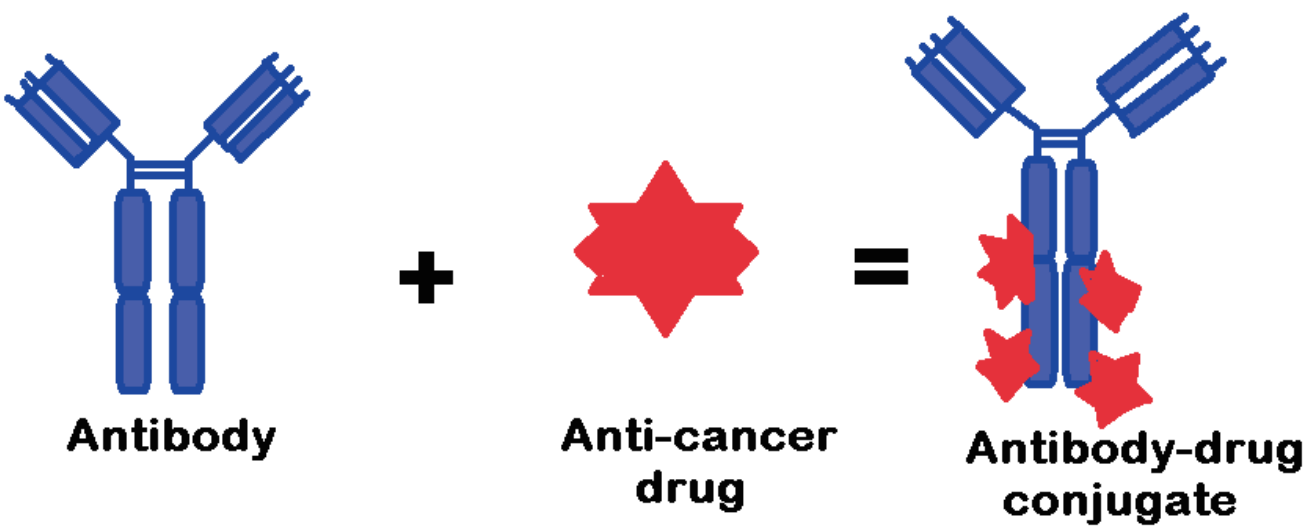

Figure 8: Conjugate of antibody and anti-cancer drug.

are being explored for use in autoimmune diseases, infectious diseases, and even in combating viral infections by simultaneously targeting pathogens and enhancing immune responses. Despite their potential, the development and clinical application of bispecific antibodies come with challenges, including complex manufacturing processes, potential immunogenicity, and the need for careful dosing and administration strategies. However, ongoing research and advancements in antibody engineering techniques continue to improve the efficacy and safety profiles of bispecific antibodies, positioning them as a significant breakthrough in targeted therapy and personalized medicine. Using bispecific antibodies is a newly developed type of antibody-based immunotherapy [44]. The targeting areas of two separate antibodies are combined to create these particular antibodies, which allow them to attach to two different targets. Some bispecific antibodies are made to target T cells, which are immunological cells, as well as cancer cells. Bites, or bispecific T cell engagers, are the name given to these antibodies. Because bites can directly target immune cells, they are categorized as "active" immunotherapies [63].

7. Conclusion

The continuous ongoing researches on the cancer genetics and therapies led the various changes associated with this problem. The various drugs are being developed to increase the survival rate of the patients. It has very good progress in the last 2 decades various drugs were approved and some are still in ongoing trials and it future it will be definitely approved. Some of the somatic and germ-line therapies will be will be developed in the future. The use of gene therapies i.e. the defective genes can be corrected in order to cure the diseases (the cancer). The investigations are going in several ways that can give the method that how the mutated gene can be replaced with healthy gene.

Conflict of interest

The writers attest that there is not a conflict between their interests in the article's content.

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