Review Article

A Comprehensive Review of Targeted Therapies for Skin Cancer

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Received: 18-03-2025; **Revised:** 21-06-2025; **Accepted:** 27-06-2025; **Published online:** 15-07-2025.

ABSTRACT

Skin cancer is a disease that is life-threatening for anybody and has that potential to cause morbidity and mortality to individuals suffering from it, and this disease is not easy to cure. For many years, people have been diagnosed with skin cancer, because of many factors like prolonged UV exposure, chemicals and environmental causes and treatment for skin cancer includes chemotherapy and surgery which is effective to some extent. But this review is highlighted for skin cancer and demonstrating the treatment for it, which is most likely to cure because somehow with advanced science, molecular biology, and cancer genetics, scientists have introduced this method as a cure for skin cancer, which is targeted therapy. This directly acts on the site of cause and tries not to harm healthy cells. This includes some inhibitors like BRAF, MEK, the hedgehog pathway, PD-1, mTOR, etc. These treatment approaches help in personalised medicines for individuals with respect to their genetic profile to achieve remarkable progress with less toxicity and more effective outcomes. This review has explained therapy based on small molecule inhibitors and monoclonal antibodies. Targeted therapies ensure promising, revolutionizing treatment and promoting a quality of life to patients and society.

Keywords: Skin cancer, Targeted therapy, small molecule inhibitors, monoclonal antibodies BRAF inhibitors, Hedgehog Pathway inhibitors.

1. INTRODUCTION

According to the extensive harm caused by this disease and its high occurrence, there has been an increase in interest in the topic of skin cancer in recent years.[1] Skin cancer is an important disease that places a significant economic burden on society because it is a cancer that can be prevented or its effects reduced with early detection and treatment. [2] The prognosis is improved for both melanoma and non-melanoma skin cancers when they are diagnosed and treated early. [3] The skin is the body's first organ to come into contact with the environment. This member has notches, lines, grooves, and hairs in certain places, it is not entirely flat. The skin is responsible for producing body odour, which can sometimes stimulate sexual behaviour, as well as regulating pressure, pain, and temperature. Controlling body temperature and water content is one of the skin's most important functions. The vascular system and sweat glands of the skin do this. Survival and resilience to environmental changes depend on all of these actions and tasks. [4] One of the most, deadly forms of cancer are skin cancer, which is brought on by aberrant cell division. Squamous, basal, and melanocyte cells are the three primary types of skin cells. [5] The prevalence of non-melanoma skin cancer (NMSC), which includes both squamous and basal cell carcinomas of the skin. [6]

2. TYPES OF SKIN CANCER

There are two types of skin cancer: 1) Melanoma skin cancer (MSC) and 2) Nonmelanoma skin cancer (NMSC). MSC is linked to the highest percentage of fatalities, while NMSC is the most often diagnosed form of cancer globally. [7] The primary cause of skin cancer is exposure to UV radiation, which can occur naturally from the sun or as a result of using solarium. As aging populations in countries reach the prime ages for keratinocyte skin malignancies (i.e., squamous and basal cell carcinomas), the incidence will continue to rise. Among all types of skin malignancies, malignant melanoma is the most dangerous and is becoming more common in both young individuals and older persons. [8]

2.1. Melanoma

It is the most, deadly type of skin cancer, while being less common than BCC and SCC. It is the leading cause of death from skin cancer, while making up a very tiny portion of all cases. Since melanoma requires high, sporadic UV exposure, blistering sunburns in kids and teens are especially dangerous. Genetic predispositions that have a major impact on the progression of melanoma include mutations in the BRAF and NRAS genes. Scientist suggests that these genetic changes may result in carcinogenic signalling pathways that encourage unbridled cell survival and proliferation. [9]

2.2. Carcinomas with basal cells (BCCs)

The outermost layer of skin, the epidermis, is where basal cell carcinomas form, and they are distinguished by their aberrant, unchecked proliferation. Most often, cancer develops in the "face, ears, neck, scalp, shoulders, and back," which are the areas, most frequently exposed to the sun's rays. BCCs may result from prolonged exposure to the sun's UV radiation or from high exposure periods that occur intermittently. In the absence of early detection and treatment, cell carcinomas have the potential to cause local destruction. However, these malignancies can occasionally spread to other parts of the body through metastasis, which can sometimes result in death.

2.3. SCC or squamous cell carcinoma

With uncontrolled proliferation of aberrant cells, this carcinoma begins with squamous cells in the skin's outermost layer of the epidermis. SCCs are frequently observed on the face, ears, scalp, neck, and hands areas of the skin that receive the most sun exposure and exhibit signs of UV damage, such as wrinkles or age spots. SCCs are mostly brought on by prolonged exposure to UV rays from the sun and tanning salons. SCCs have the potential to develop more quickly and metastasize to other tissue locations in the body if they are not detected early. [10]

3. DIAGNOSIS OF SKIN CANCER [4]

The following are the four primary features of this approach:

3.1. Asymmetry

When there is asymmetry, the two parts are not the same. Moles in nature are symmetrical. When analyzing the patches or spots, compare two half moles to one another and visualize a hypothetical line in the centre of the spot. The patient should see a doctor for further testing if the half moles are not similar.

3.2. Border

Because melanoma skin lesions have irregular margins, one should also consult a doctor if the mole's margin is uneven, fading, or unusual in form.

3.3. Colour

A mole is abnormal if it lacks a consistent colour and is thought to have a second mixed colour, such as brown, tan, black, blue, white, or red. Typically, a typical mole is monochrome. A doctor should examine the mole, which is darker in some places and brighter in others.

3.4. Diameter

The mole, bigger than the end of a pencil, is suspected. Typically, benign moles are less than 6 mm in size.

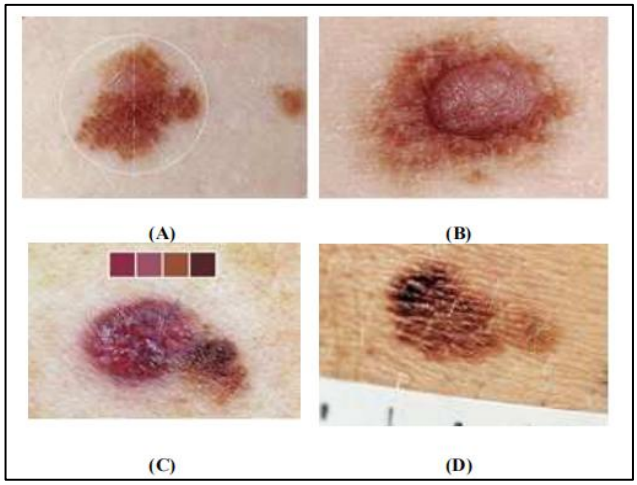

Figure 1: ABCD rule for suspected parts of melanoma cancer. [4]

One of the most important steps in stopping the spread of melanoma and preventing it from progressing into irreversible stages is recognizing its early symptoms. The American Cancer Society states that in both clinical practice and at-home inspections, the acronym ABCDE is used to recognize warning indicators in skin growths or moles. The letters "A" stands for the mole's asymmetry, "B" for its jagged edges and borders, "C" for colour and any colour variations within a single region, "D" for a diameter larger than six millimetres (mm), and "E" for the mole's form or appearance progression. The presumed growths of malignant melanocytes can be surgically eliminated by biopsy without any problems if they are discovered early in the course of the disease. [11]

4. DERMASCOPE

One important diagnostic technique in the toolbox of doctors who screen patients for skin cancer is dermoscopy. Dermoscopy, also known as nonpolarized dermoscopy, is a procedure that applies a liquid interface to the skin and then employs portable magnifying equipment that looks like an otoscope. The clinical unassisted diagnostic accuracy of a skilled dermatologist's eye is only around 60%. The accuracy of diagnosis is improved by dermoscopy. [12] Dermoscopy, often referred to as dermatoscope or epiluminescence microscopy, makes it possible to see anatomical features in the papillary dermis and epidermis that are otherwise invisible to the human eye. This is accomplished by using a handheld dermatoscope to magnify the skin's surface and lessen the corneal layer's ability to refract light.

There are two varieties of dermatoscopes: the original, non-polarized version is better at seeing comedo-like openings (a sign of seborrheic keratosis), milia-like cysts, and blue-white patches (frequently linked to regression). It requires an immersion medium (oil, alcohol). It has been discovered that the alternative dermatoscope, which employs polarized light, is more effective in evaluating vascular systems and gleaming white streaks that may indicate fibrosis. [13]

5. TARGETED THERAPY

The goal of targeted therapy is to deliver medications to specific genes or proteins that are unique to cancer cells or the tissue milieu that supports the formation of cancer. Targeted therapeutic release at the illness site with minimal off-target adverse effects to healthy tissues is the key to the therapy's effectiveness. It is frequently used with other cancer therapies, such as chemotherapy. Drugs that inhibit the growth of cancer cells, regulate the cell cycle, or trigger apoptosis or autophagy are developed as part of targeted therapy. Toxic compounds are delivered to cancer cells selectively to kill them. Oral tiny medicines or monoclonal antibodies are used in targeted therapy. [14]

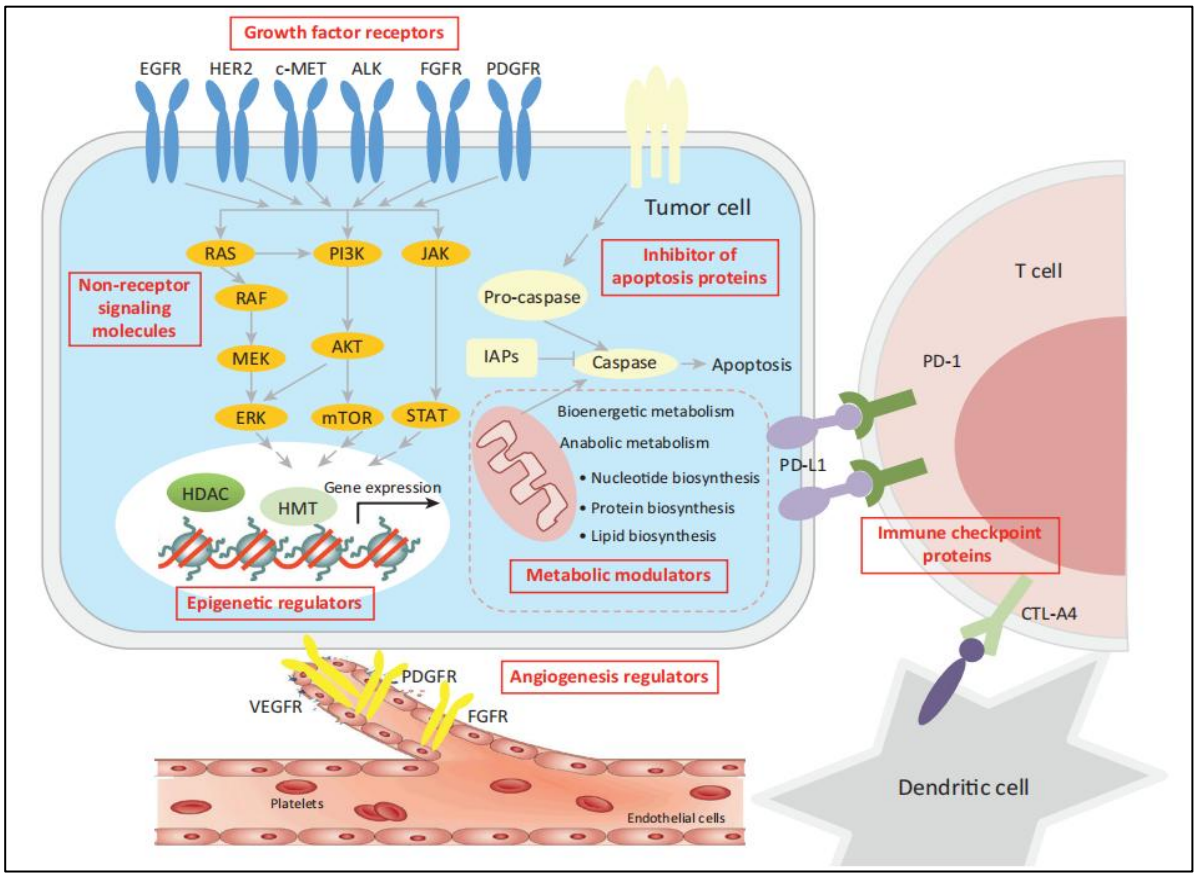

Figure 2: New targets being discovered for cancer treatment that targets molecules. Following more than ten years of development, the most actively pursued drug discovery targets are still growth factor receptor and downstream non-receptor signalling. [15]

Table 1: Targeted therapy for skin cancer can be classified into several categories based on the specific molecular targets and mechanism of action:

Inhibitors	Target	Drugs	Indications
Receptor Tyrosine Kinase (RTK) Inhibitors	EGFR, PDGFR, VEGFR,	Erlotinib, Gefitinib, Sunitinib	Melanoma, Basal cell carcinoma, Squamous cell carcinoma
BRAF Inhibitors	BRAF mutation V600E	Vemurafenib, Dabrafenib	Melanoma with BRAF V600E mutation
MEK Inhibitors	MEK1/2	Trametinib, Cobimetinib	Melanoma with BRAF V600E mutation
PI3K/AKT/mTOR Inhibitors	PI3K, AKT, mTOR	Everolimus, Temsirolimus	Advanced melanoma, Basal cell carcinoma
Angiogenesis Inhibitors	VEGF, VEGFR	Bevacizumab, Ranibizumab, Sorafenib	Advanced melanoma, Basal cell carcinoma
Immune Checkpoint Inhibitors	CTLA-4, PD-1, PD-L1	Ipilimumab, Pembrolizumab, Nivolumab	Advanced melanoma, Markel cell carcinoma
Hedgehog Pathway Inhibitors	SMO, GLI	Vismodegib, Sonidegib	Basal cell carcinoma
CDK4/6 Inhibitors	CDK4, CDK6	Palbociclib, Ribociclib	Advanced melanoma
Other Targeted Therapies	c-KIT, FLT3	Imatinib, Sunitinib	Rare skin cancers
Combination Therapies	Multiple pathways	BRAF + MEK inhibitors, CTLA-4 + PD-1 inhibitors	Advanced melanoma, Basal cell carcinoma

5.1. Small molecule inhibitors

Small molecule inhibitors, which target certain molecules and pathways involved in controlling the immune response to malignancies, are important in cancer immunotherapy. Through a variety of ways, these inhibitors alter the tumour microenvironment and strengthen the immune system's defences against the tumour.

As prospective adjuvants in cancer immunotherapy, small molecule inhibitors that target important signalling molecules within these pathways have surfaced. In order to effectively boost anti-tumour immunity, small molecule inhibitors can fine-tune immune responses by specifically targeting particular nodes within these signalling pathways. Gaining insight into the complicated connections between signal transduction pathways and utilizing small molecule inhibitors' therapeutic potential present intriguing opportunities to broaden the scope of cancer immunotherapy recuperation and enhance the outcomes for patients. To improve the immune response in the tumour microenvironment, small molecule inhibitors target important routes and mechanisms such as angiogenesis, extracellular matrix remodelling, and immune cell infiltration. [16]

A. BRAF Inhibitor

The RAS and RAF family members in the ERK/MAPK pathway that contain mutations and are connected to melanoma include BRAF, NRAS, HRAS, and KRAS. In this route, BRAF, a serine/threonine kinase of the RAF family, controls cell proliferation, survival, and differentiation. BRAF is activated by membrane-bound receptors such as G-protein-coupled receptors and tyrosine kinases. Several potent BRAF inhibitors have been developed as potential treatments for melanoma [17]. Most B-RAF mutations are found in the activation segment and surrounding regions, as well as the glycine-rich P loop of the N lobe. A Glu-forVal substitution at position 599 in the activation region, adjacent to the conserved DFG motif, accounts for 90% of B-RAF mutations in human cancers. The characteristics of a typical oncogene are present in the B-RAF V599E mutation. This mutant protein significantly increases its kinase activity, constitutively promotes ERK activity in vivo without the need for RAS and transforms NIH3T3 cells.

It's interesting to note that Val599 is flanked by the conserved regulatory phosphorylation sites Thr598 and Ser601 within the B-RAF activation section, which suggests that the Glu substitution at this location acts as a phospho-mimetic. Similar to V599EB-RAF, analysis of three more oncogenic B-RAF mutations revealed that they also enhance kinase activity. The question of how these mutations promote tumorigenesis is intriguing, though, as a thorough examination of B-RAF mutations in cancer reveals that seven of the mutations involve highly conserved or invariant residues in the catalytic domain that are known to be necessary for optimal catalytic activity in other kinases.[18]

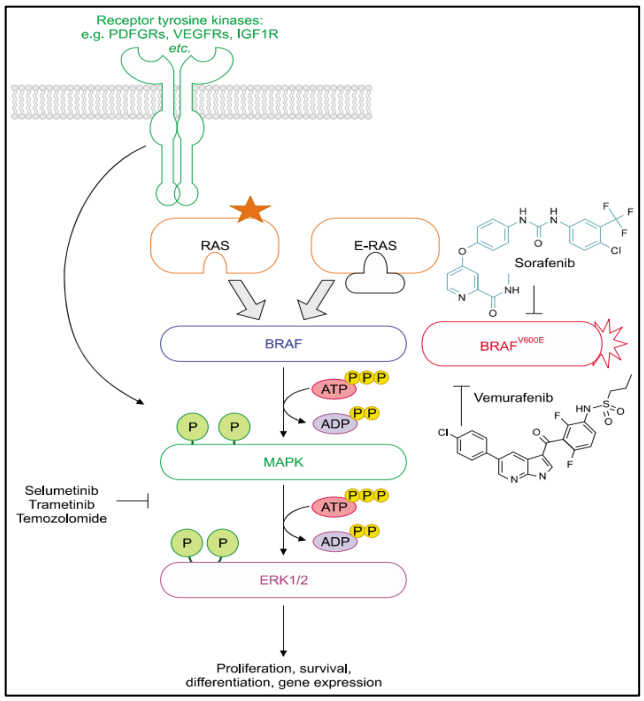

Figure 3: Representation of BRAF Inhibitors. [19]

I. Vemurafenib

First manufactured in early 2005, vemurafenib is a powerful inhibitor of the B-RAFV600E mutant that has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with metastatic and late-stage melanoma. Strongly bound to the ATP binding domain, the active "DFG-in" version of the kinase is inhibited by vemurafenib. In biochemical tests, vemurafenib's selectivity for B-RAFV600E is moderate compared to wildtype BRAF; nevertheless, in melanoma cell lines, it is remarkably selective for B-RAFV600E. Most notably in B-RAFV600E-positive tumour models, these medications produce tumour regression in vivo, induce cell cycle growth arrest and apoptosis in vitro, and strongly decrease MEK phosphorylation. Vemurafenib, in contrast, exclusively inhibits MEK phosphorylation in BRAF-mutant cells, whereas MEK inhibitors do so in cells of any genotype. Because vemurafenib works only on cells that have the BRAF mutation at codon 600, which changes valine (V) to glutamic acid (E), it prevents B-RAFV600E melanoma, colorectal cancer, and papillary thyroid cancer cell lines from proliferating. [19]

II. Dabrafenib

BRAF is an upstream activator in the MAPK pathway, and between 40 and 60 percent of cutaneous melanomas have a mutation in it. This protein kinase is indeed one of the most commonly mutated ones in all human malignancies. Because of this mutation, melanocytes proliferate excessively, which causes melanomas to form. As a BRAF kinase inhibitor, dabrafenib stops melanocytes from proliferating excessively. Using it to treat BRAF-mutated non-small cell lung cancer was approved. [20] As a therapy for individuals with 8RAF V600E mutations in unresectable or metastatic melanoma, dabrafenib (Tafinlar®) received FDA

approval on May 29, 2013. 150 mg dosages of dabrafenib are taken orally twice a day until the disease worsens or an unfavourable toxicity arises. It is recommended that doses be taken either two hours after or at least one hour before meals. It is possible to deliver missed dosages up to six hours before the subsequent dose. Do not administer if there are less than six hours left before the next dose is due. Dabrafenib is classified as a medication that increases the risk of pregnancy. Dabrafenib should not be taken by women who are pregnant or may become pregnant. Dabrafenib's approval was predicated on the fact that it enhanced progression-free survival (PFS) when compared to chemotherapy. [11]

B. EGFR – inhibitor

The ErbB family of receptor tyrosine kinases include the human epidermal growth factor receptor (EGFR). Receptor dimerization and subsequent intracellular tyrosine residue autophosphorylation are caused by extracellular ligand binding. Numerous downstream cells signalling pathways that affect cellular proliferation, apoptosis, migration, and survival can be triggered by the EGFR. [21] Two categories of anti-EGFR-targeting agents small-molecule inhibitors of EGFR tyrosine kinase enzymatic activity and monoclonal antibodies (MAbs) have advanced clinical development. [22] Gefitinib and erlotinib are two small compounds that have been researched intensively in the past ten years as selective, reversible, and orally active EGFR-tyrosine kinase inhibitors. [23]

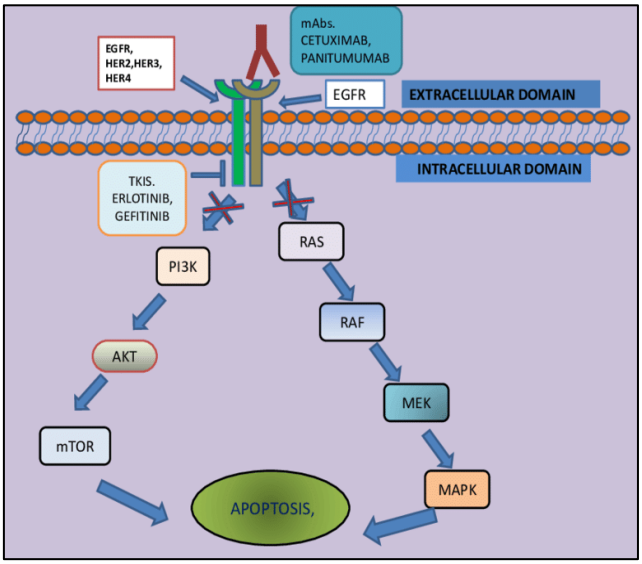

Figure 4: A representation of EGFR Inhibitors working. [24]

I. Erlotinib

Erlotinib is a small chemical quinazoline derivative that inhibits the autophosphorylation of EGFR tyrosine kinase (Tarceva; Roche, Genentech, OSI Pharmaceuticals, Northbrook, IL). Erlotinib reduces proliferation and increases apoptosis by causing cell cycle arrest and acting as a reversible ATP-competitive inhibitor. [25] Erlotinib, inhibited the growth of tumour cells by specifically blocking the EGFR downstream signalling pathway. Erlotinib was licensed by the FDA in 2004 to treat patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who had not responded to chemotherapy. According to clinical trials, it may increase patients' chances of surviving. [26] It is a derivative of 4-anilinoquinazoline that inhibits EGFR. The medication is categorized as an inhibitor of Type I and Type I1/2B kinases. It functions as a type I inhibitor if it attaches itself to the ATP binding pocket of activated EGFR. But it can also operate as a Type I1/2B inhibitor by binding to EGFR with its inactive DFG-in and C-helix-out conformation. It participates in an H-bonding network with a water molecule and Thr766 in both situations, and it forms an H-bond with Met769 as well. With IC50 values in the low nanomolar range, its selectivity has been evaluated in cells as well as against the recombinant EGFR kinase; inhibition of other tyrosine kinases necessitates concentrations that are more than 1000 times greater than those required for EGFR. [27]

II. Gefitinib

AstraZeneca's gefitinib, which suppressed wild-type EGFR to a lesser degree, was approved by the FDA for marketing in 2003 for the treatment of patients with locally advanced or metastatic non-small cell lung cancer. [26] Gefitinib's function as a first-line therapy option for individuals who were molecularly chosen. Patients chosen based on the existence of an EGFR mutation are treated with gefitinib as their first line of treatment. [23] An oral tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR), gefitinib competes with ATP for the ATP-binding site located in the cytoplasmic tail of EGFR. Additionally, patients with EGFR mutations have been shown to respond better to gefitinib. In 2004, it was demonstrated that the responsiveness to two tyrosine kinase inhibitors, gefitinib, is highly correlated with mutations in the EGFR gene. [28]

C. Targeting KIT

Patients who have an activating c-KIT mutation on exons 9, 11, or 13 and have CSD, acral, or mucosal melanoma may benefit from targeting KIT as a treatment approach. [29]

I. Imatinib

Imatinib, a tyrosine kinase inhibitor, is approved for the treatment of metastatic or incurable gastrointestinal stromal tumors (GIST). An unselected group of patients with advanced melanoma tested it and found it to be ineffective. Nonetheless, there are cases in the literature when individuals with acral and mucosal melanoma reacted totally or partially to imatinib treatment. According to a retrospective examination of responses in unselected cohorts of melanoma patients treated with it and data from case reports, imatinib-sensitive mutations were most frequently detected in exons 11 and 13 of c-KIT, but individuals with other mutations did not respond to the treatment. The effectiveness of imatinib therapy in advanced c-KIT mutant or amplified melanoma is now being explored in three clinical trials. [29]

II. Sunitinib

The oral multitargeted receptor tyrosine kinase (RTK) inhibitor sunitinib malate (Sutent, SU11248; Pfizer Inc.) inhibits the receptors for macrophage colony-stimulating factor (CSF1R), glial cell-line-derived neurotrophic factor receptor (Rearranged during Transfection; RET), vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), stem cell factor receptor (KIT), and FMS-like tyrosine kinase-3 (FLT3). International approval has been granted for sunitinib to treat advanced renal cell carcinoma (RCC) and gastrointestinal stromal tumours (GIST) that are intolerant to or resistant to imatinib mesylate. Sunitinib suppression of VEGFRs and PDGFRs produced by vascular or perivascular endothelial cells is expected to generate anti-angiogenic effects on a wide range of solid tumours because angiogenesis is necessary for the continuing development of the majority of solid tumours. In isolated GIST cells or cells bioengineered to express constitutively active KIT exon 9 and exon 11 mutants, which are frequently present in naïve GIST, sunitinib has been demonstrated to potently suppress KIT autophosphorylation. In a similar vein, Ikezoe and colleagues showed that sunitinib prevented downstream effector phosphorylation in addition to KIT autophosphorylation in naive GIST-T1 cells with activating mutations. It's important to note that sunitinib also strongly suppressed KIT's exon 13 and exon 14 mutant versions, or V654A and T670I, which are linked to decreased binding affinity and imatinib resistance. [30]

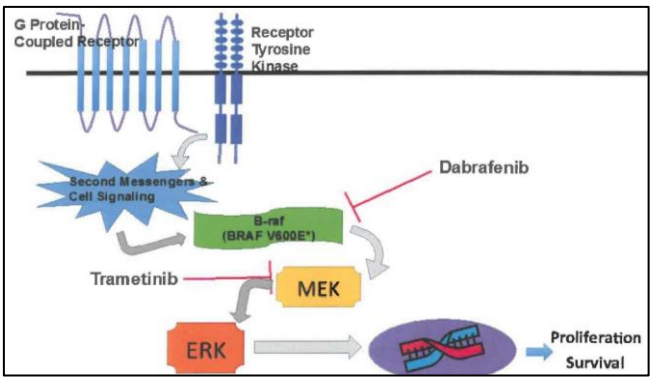

Figure 5: Schematic representation of B-raf and MEK signalling in Melanoma. [11]

D. MEK inhibitors

The PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signalling pathways have recently been recognized as prospective therapeutic targets for cancer treatment. The control of cellular functions like growth, proliferation, survival, and death is carried out by protein kinases. Oncogenesis is largely caused by signalling pathways that are overactivated. MEK, sometimes referred to as mitogen-activated protein kinases (MAPKs), is a downstream kinase of the RAS pathway that comes in two distinct forms, MEK1/2. These kinases become extracellular signal regulated kinases (ERK1 and 2) when they become phosphorylated. They are the sole RAF kinase catalytic substrates that are known to exist. [31]

I. Trametinib

Within the MAPK signalling pathway, MEK is a therapeutic target that can be used to allosterically and reversibly reduce MEK1 and MEK2 activity. Metastatic melanoma with the BRAF V600E mutation is treated with it because of its strong anticancer properties. [20] On May 29, 2013, the FDA authorized trametinib (Mekinist®) for the treatment of cancer patients with BRAF V600E or V600K mutations who have metastatic or incurable melanoma. In the cell proliferation pathway, MEK is B-Raf's next effector. Trametinib induces tumour cell death, promotes cell cycle arrest, and reduces cellular proliferation by blocking the activation of MEK 1 and MEK 2. Trametinib should be taken orally at a dose of 2 mg once daily until toxicity or disease progression is determined. It is recommended that trametinib be taken at least one hour prior to or two hours following a meal. It is not recommended to take missed dosages within 12 hours of the subsequent dose. Trametinib is classified as a medication that increases the risk of pregnancy. Trametinib should not be taken by women who are pregnant or attempting to conceive. Trametinib's approval as a melanoma treatment was predicated on its higher PFS in comparison to chemotherapy. [11]

E. Hedgehog pathway inhibitor

The development of organs and tissues during the embryonic and postnatal stages is significantly influenced by the Hh pathway. It plays a role in the development of motor neurons in the growing spinal cord as well as the location of finger growth in the limb buds. The Hh signalling pathway is inhibited in normal settings and becomes active when the Hh ligand binds to the transmembrane receptor known as Patched (PTCH1). The transmembrane protein smoothened (SMO) can transmit signals across other proteins when the Hh pathway is activated. A mutation in the Hh pathway, paracrine or autocrine activation by Hh ligands, stromal involvement, or activation of cancer stem cells (CSCs) could all be the cause of the aberrant Hh signalling that causes new tumours or accelerates existing tumours. Uncontrolled self-renewal of tumour cells and the development of metastases have been attributed to the activation of cancer stem cells (CSCs) through aberrant Hh signalling. [32]

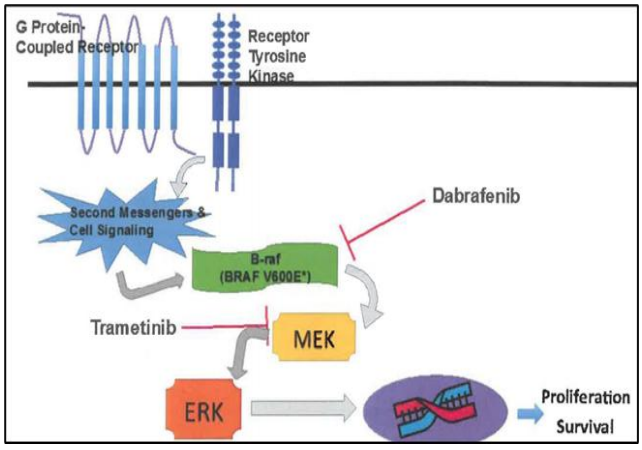

Figure 6: A visual representation of hedgehog pathway inhibitors working. [33]

I. Vismodegib

The US Food and Drug Administration's (US FDA) priority review program approved vismodegib on January 30, 2012, for the treatment of an advanced form of basal-cell carcinoma by inhibiting the Hh pathway. The US FDA has approved vismodegib, a new small molecule Hh inhibitor, for advanced BCC. It works by blocking the SMO protein involved in Hh signal transduction, and it has demonstrated encouraging anti-tumour responses in advanced BCC [32]. Vismodegib is an SMO inhibitor that is the first of its kind. Vismodegib is an oral synthetic inhibitor of the Hedgehog signalling system, which is nearly inactivated in maturity but plays a crucial role in cell proliferation and differentiation during embryogenesis. [34]

II. Erismodegib / Sonidegib

In the TM3 mouse Leydig cell line, Novartis' Erismodegib showed potential potency through SMO antagonism, and in animal studies, it showed favourable pharmacokinetics. The FDA authorized it in July 2015 for the treatment of adult patients with locally advanced BCC who had recurred after surgery or radiation therapy or those with advanced BCC who were not responsive to either treatment. Additionally, medulloblastoma, triple-negative breast cancer, small cell lung cancer, pancreatic adenocarcinoma, haematological malignancies, and advanced solid tumours are being studied as possible therapy options. [35] On tumour cells, it has shown a range of effects, such as increased apoptosis, decreased GLI homolog activity, and decreased cell survival. Sonidegib has an elimination half-life of about 28 days. The primary metabolizer of sonidegib is cytochrome P450 (CYP) 3A. Sonidegib remains the primary component in circulation. Muscle spasms (54%), musculoskeletal discomfort (32%), and myalgia (19%) were the most frequent musculoskeletal adverse events. In addition to being embryotoxic, fetotoxic, and teratogenic in animals, sonidegib can result in serious birth abnormalities or embryo-foetal mortality when given to a pregnant woman.[36]

F. PI3K/Akt/mTOR Inhibitors

The PI3K/Akt/mTOR pathway regulates cell proliferation, survival, growth, and metabolism. Deregulation of the PI3K/Akt/mTOR pathway, including mutation or amplification of PIK3CA (encoding the p110α subunit of PI3K), loss or inactivation of phosphatase and tensin homolog (PTEN), and hyperactivation of mTOR, has been linked to various cancer types and anticancer drug resistance. As a result, inhibitors of PI3K, Akt, and mTOR have been tested in preclinical studies and clinical trials, with some inhibitors being used clinically to treat cancer. Examples of clinically used PI3K inhibitors include idelalisib, duvelisib, copanlisib, and alpelisib, as well as mTOR inhibitors such as sirolimus, temsirolimus, and everolimus. PI3K inhibitors targeting PI3Kδ or PI3Kγ are used to treat lymphoma. Some mTOR inhibitors, particularly rapamycin analogs (rapalogs), which form a compound with FK506-binding protein 12 (FKBP12) and inhibit mTORC1 (but not mTORC2) activity, are licensed for clinical usage. [37]

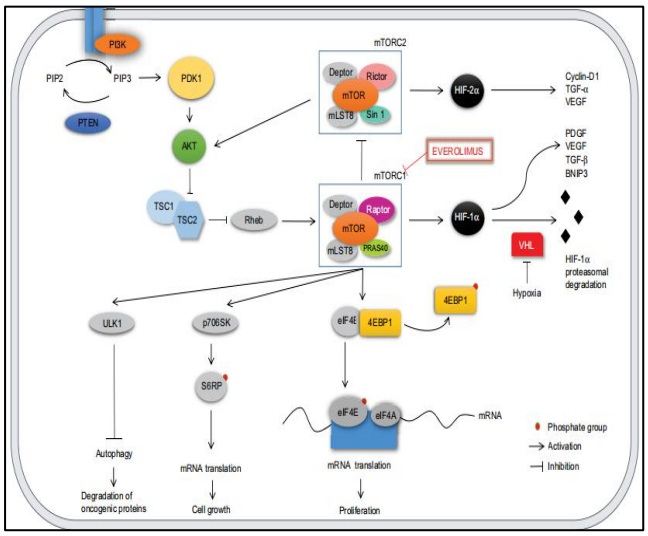

Figure 7: Schematic representation of PI3K/AKT/MTOR Inhibitors. [38]

I. Everolimus

Everolimus (RAD001, afinitor; Novartis International AG, Basel, Switzerland) is a rapamycin derivative that suppresses the mTOR serine/threonine kinase. It binds to the intracellular receptor protein FKBP12 with great affinity, forming the FKBP12/everolimus complex, which specifically inhibits mTORC1. In cancer treatment, the first preclinical findings showed dose dependent antitumor efficacy with everolimus administered daily or weekly. After treatment with everolimus, the mTOR effectors 4EBP1 and p-S6K1 were found in tumour, skin, and peripheral-blood mononuclear cell (PBMC) extracts, indicating that tumour growth reduction was associated with p-S6K1 inactivation and reduced 4EBP1 phosphorylation. Everolimus is taken orally at a daily dose of 10 mg, which results in consistent suppression of mTOR signalling. A weekly dose of 70 mg did not result in the same level of target inhibition as an equivalent daily dose. [38]

G. Multikinase Inhibitors

More specific targets have been identified to improve therapy efficacy while reducing toxicity. Multikinase inhibitors (MKIs), which include tyrosine kinase inhibitors, are one of the most promising groups of targeted anticancer medicines. MKIs target specific tyrosine kinases inside tumour cells, where they play an important role in signal transduction, gene transcription, and DNA synthesis. MKIs are divided into two categories: small molecules and big molecules. We will primarily concentrate on small molecule MKIs. Small molecule MKIs are taken orally, giving them a distinct advantage over traditional chemotherapy in terms of flexibility and patient convenience. [39]

I. Sorafenib

A dual-action multi-kinase inhibitor, sorafenib targets both tumour cells and tumour vasculature cells. By strongly suppressing the Raf serine/threonine kinases, it prevents the growth of tumours: Raf-1, oncogenic B-Raf V600E, and wild-type B-Raf kinases in the MAPK pathway determined

the mechanism of melanoma carcinogenesis and the significance of V599E B-Raf in the disease. Sorafenib-induced inhibition of V599E B-Raf decreased MAPK cascade activity, hindered vascular growth by lowering VEGF secretion, and subsequently boosted tumour cell death.

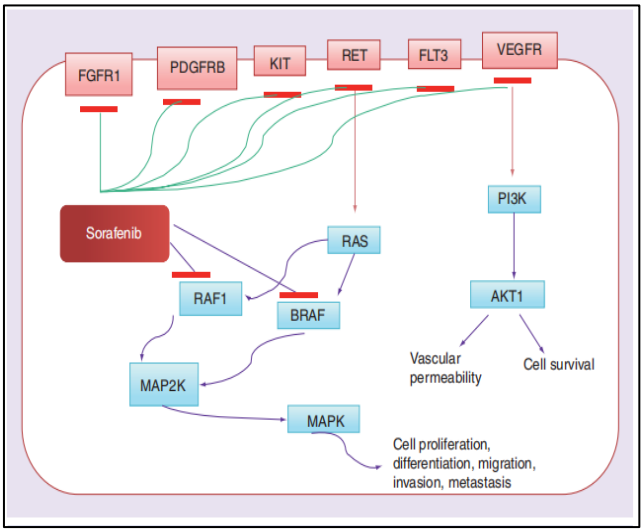

Figure 8: The mechanism of action of Sorafenib. [40]

It has been demonstrated that sorafenib monotherapy is less effective in treating some malignancies, such as melanomas and sarcomas, for reasons such as medication resistance and patient insensitivity. However, sorafenib is a desirable option for combination therapy due to its numerous targets. Therefore, the combination of sorafenib with other drugs has been extensively investigated, indicating clinical benefits in many cancer types. A phase II randomized discontinuation trial that evaluated the efficacy and safety of sorafenib in advanced melanoma. Best responses for patients on sorafenib were 19% stable disease and 62% progressive disease; overall median PFS was 11 weeks. Most common adverse effects were dermatological. Sorafenib was well-tolerated but had little or no antitumor activity. [41]

5.2. Monoclonal Antibodies

Since Kohler and Milstein first described the manufacture of mAbs using hybridoma technology in 1975, considerable breakthroughs in the utilization of mAbs and their derivatives in clinical practice have been made. Targeting specific cellular targets has been effective in hematologic malignancies and solid tumours, with dramatically enhanced patient survival. Cutaneous lymphomas have also been successfully addressed with specific mAbs targeting Bcell or T-cell lymphomas, as well as nonspecific wide anticancer action. mAbs and their derivatives can be classified using a variety of criteria. mAbs can be classified according to their targets or roles, which include direct tumour cell assassins, checkpoint blockade inhibitors, tumour microenvironment modifiers, and immune primers, among others. Currently available mAbs can also be classed based on changes to the immunoglobulin scaffold and/or the addition of a conjugation that enhances immune activation or causes direct cell killing. Immunotoxins (ITs), such as diphtheria toxin (DT), radioisotopes (radioimmunoconjugates, such as yttrium 90), and cytotoxic medicines (antibody-drug conjugates [ADC], such as auristatins), are examples of mAb-conjugated agents. The majority of licensed mAbs in clinical use are unconjugated antibodies that have anticancer effects via complement- or antibody dependent cell-mediated cytotoxicity (ADCC). The US Food and Drug Administration (FDA) has now approved more than 20 mAbs for clinical usage in a variety of malignancies, with over 350 more mAbs in the works, including clinical studies in lymphomas. mAbs are currently widely used as targeted therapy for cancer, transplant rejection, autoimmune and infectious illnesses, and a variety of other indications. [42]

A. Immune Checkpoint Inhibitors

The introduction of immune checkpoint inhibitors like pembrolizumab and nivolumab has changed the therapy landscape for melanoma. These immunotherapies have proved long-term efficacy and boosted survival rates by instructing the immune system to target and destroy cancer cells. [9]

I. CTLA-4-Blocking Antibodies

The first inhibitory immunological checkpoint molecule to be examined in a clinical setting was cytotoxic T-lymphocyte antigen (Ag)-4 (CTLA-4; CD152), which enhanced survival for patients with metastatic melanoma. Direct inhibition at the TCR immunological synapse in a cell-intrinsic manner,46 reduction of CD28 or its, signalling pathway, or enhanced T cell mobility leading to a reduced ability to engage with APC are characteristics of CTLA-4mediated inhibitory signalling. [43] Two antibodies that block CTLA-4 in humans have been developed based on encouraging preclinical data from mouse models: ipilimumab (formerly known as MDX-010; Medarex, Princeton, NY, USA, and Bristol-Myers Squibb, Princeton, NJ, USA) and tremelimumab (formerly known as CP-675,206 or ticilimumab; Pfizer, New York, NY, USA, and currently Medimmune, Gaithersburg, MD, USA). [44]

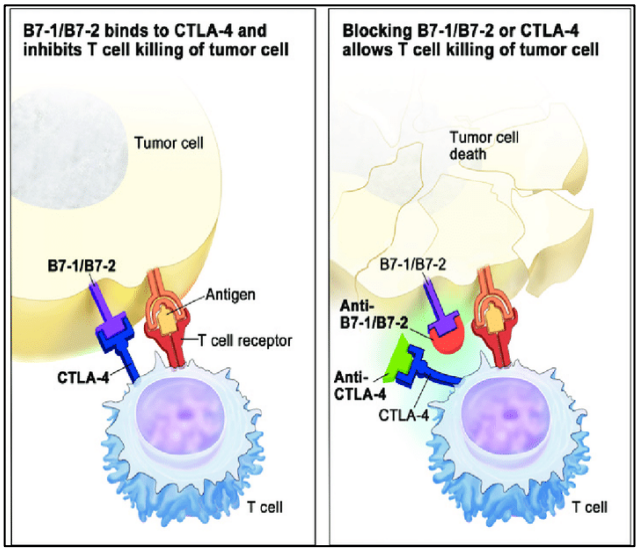

Figure 9: A visual representation of CTLA-4 blocking inhibitors. [45]

a. Ipilimumab

The FDA approved ipilimumab (marketed under the brand name Yervoy) on March 25, 2011, for the treatment of metastatic or incurable melanoma. [44] It was recently demonstrated that Ipilimumab increases the survival rate of patients with metastatic melanoma. Ipilimumab is a fully human monoclonal antibody (IgG1) that enhances antitumor immunity by blocking cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), an immunological checkpoint protein that blocks T-cell activation pathways. For four sessions, ipilimumab was administered at a dose of 3 mg/kg body weight every three weeks. Since ipilimumab has been shown to be effective, it may soon be used as a standard treatment. However, researchers should now concentrate on determining the predictive factors that influence treatment response. Additionally, ipilimumab is presently being investigated in a number of clinical trials in combination therapy with other drugs like bevacizumab, dacarbazine, and fotemustine. It will soon be tested in combination with vemurafenib. [29]

II. PD-1-Blocking Antibodies

Originally identified in a T cell line undergoing planned cell death, the type I transmembrane protein known as Planned Death 1 (PD-1) has since been linked to lymphocyte activation rather than cell death. Activated T and B cells, as well as a minority of thymocytes, expressed PD-1, according to our earlier research using an anti-mouse PD-1 mAb (J43). PD-1 shares a single Ig V-like domain in its extracellular region, making it physically similar to the CD28/CTLA-4 subgroup of the Ig superfamily. There are two tyrosine residues in the cytoplasmic domain of PD-1: An immunoreceptor tyrosine-based switch motif (ITSM) contains the C-terminal tyrosine, while an immunoreceptor tyrosine-based inhibitory motif contains the N-terminal tyrosine. According to in vivo studies using mice lacking PD-1, PD-1 controls peripheral tolerance and inhibits autoimmunity. [46]

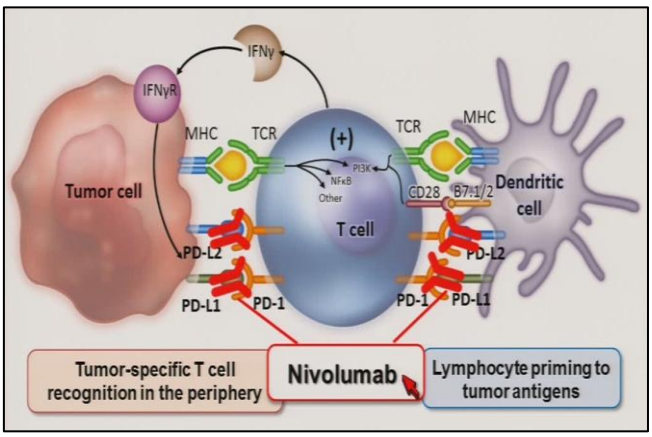

Figure 10: A visual representation of role of the PD-1 in suppressing anti-tumour immunity.[47]

T cells have a second coinhibitory receptor called PD-1, which may be a target for treatment. Through its interactions with PD-L1 and PD-L2, PD-1 seems to have a more significant role in controlling T cell activation in peripheral tissues. PD-L2 expression in DCs, macrophages, mast cells, and B cells, and PD-L1 expression in hematopoietic and nonhematopoietic tissues. Human tumours that express PD-L2 include glioblastoma, melanoma, non-small cell lung cancer, ovarian, breast, cervical, colon, pancreatic, and gastric cancers. These results suggest that by reducing the inhibition of the immune response in the tumour microenvironment, blocking the PD-1: PD-L1/PD-L2 interaction may be a useful anticancer treatment. Numerous antibodies that disrupt the PD-1 pathway have been created, either by blocking PD-L1 or the PD-1 molecule. [44]

a. Nivolumab

Targeting PD-1, nivolumab is an immune checkpoint inhibitor that helps the immune system combat cancer cells. Nivolumab seeks to strengthen the body's defences against cancer cells that are still present. [48] Nivolumab is a humanized monoclonal antibody that attaches itself competitively to tumour cell PD-Ligand 1 (PD-L1) and T-cell Programmed Death 1 (PD-1) receptors. By impeding T-cell anergy, this interaction strengthens the immune response against cancerous cells. T-lymphocyte activation is thought to be related to PD-1 inhibitor-induced cutaneous responses. [49] The Food and Drug Administration initially authorized nivolumab for individuals with advanced malignant melanoma who were not responding to other forms of treatment. It was authorized in 2015 to treat metastatic malignant melanoma as a first-line treatment. The PD-1 on the surface of monocytes, B cells, natural killer cells, and activated T cells is highly favoured by nivolumab. [50]

III. VEGF Inihibitor

when molecularly targeted medications that block VEGF activity are administered, such as multi-kinase inhibitors that block VEGF receptors. By regulating the tumour vasculature, these medications also enhance T cell migration from the lymph nodes to the tumour site and encourage T cell activation during the priming phase. The immunosuppressive microenvironment is reprogrammed into an immunologically stimulatory microenvironment as a result of anti-VEGF antibodies' inhibition of MDSC, Treg, and TAM activity (reprogramming). Activated T cells effectively assault tumours when the VEGF-suppressed tumour microenvironment is normalized with molecule-targeted anti-VEGF drugs. [51]

a. Bevacizumab

All VEGF-A isoforms are bound with high affinity by bevacizumab, a recombinant, humanized monoclonal antibody that targets the VEGF ligand (VEGF-A). At dosages up to 10 mg/kg, bevacizumab was safely administered without dose-limiting toxicities in patients with advanced tumours in the primary phase I trial. 0.3 mg/kg dosages of bevacizumab were shown to be well tolerated in pharmacokinetic studies. The terminal half-life of bevacizumab was II– approximately 21 days, and its pharmacokinetic profile was linear. The availability of phase

III randomized controlled studies and meta-analyses supports the efficacy of bevacizumab and its toxicity behaviour when used as a main treatment for metastatic large bowel cancer. [52]

IV. EGFR Inhibitor

The involvement of EGFR in the development and progression of different malignancies. Examples include colorectal cancer and pancreatic carcinoma. Human carcinomas frequently overexpress EGFR and EGF-like peptides, and data suggest that these proteins promote cell transformation both in vitro and in vivo. EGFR gene amplification and tyrosine kinase domain mutation have been observed in patients with cancer. Interestingly, both of these EGFR genetic alterations are typically sensitive to EGFR-targeting drugs. [53]

a. Cetuximab

A high-affinity recombinant immunoglobulin G1 (IgG1), cetuximab (Erbitux2), inhibits ligand binding and encourages EGFR interiorization and downregulation. The direct blockage of EGFR tyrosine kinase, cell cycle restriction, increased activity and quantity of cell death inducing molecules like Bcl-2 and Bax, and enhanced anti-cancer effects of chemotherapy and radiation therapy are some of the mechanisms thought to be responsible for cetuximab's anticancer action. Furthermore, cetuximab has been shown in clinical trials to reduce angiogenesis, invasion, and metastasis. [53]

6. COMBINATION THERAPY

Combination therapies with dual drugs with separate mechanisms of action have demonstrated lower morbidity and a higher likelihood of attaining clinical remission than monotherapy with a single agent. [54]

- Combination therapy with BRAF and MEK inhibitors may be more effective in treating metastatic melanoma. The combination of dabrafenib and trametinib, which target BRAF and MEK, in patients with metastatic melanoma with BRAFV600E. [17] Patients with advanced BRAF-mutant melanoma treated with dabrafenib plus trametinib outperformed those treated with BRAF inhibitor (BRAFi) monotherapy, with significant improvements in overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). Dabrafenib and trametinib proved to be well tolerated, with a manageable safety profile. [55] A phase II trial of trametinib revealed no risk of squamous cell cancer. These two novel substances clearly outperform prior MAPK pathway inhibitors. [11]
- The Sarah Cannon Oncology Research Consortium's phase II trial indicated that combining bevacizumab, an angiogenesis inhibitor, and everolimus, an mTOR inhibitor, had modest activity and was well tolerated in treating metastatic melanoma. [17]
- Combining anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) increased the 3-year survival rate by 58%, compared to 52% in the nivolumab group and 34% in the ipilimumab group. 23 Although the combination (ipilimumab + nivolumab) increased activity and efficacy, it also increased the incidence of severe irAEs in the combo arm (59% of Grades 3-4 irAEs) compared to 21% in the nivolumab group and 28% in the ipilimumab group, especially in patients with PD-L1 negative tumours. [43] In a recent clinical trial, Larkin et al. found that in previously untreated patients with metastatic melanoma, nivolumab coupled with ipilimumab resulted in considerably greater survival than ipilimumab alone. [50]

A phase I trial found that the combination of sorafenib plus erlotinib was well-tolerated and showed potential efficacy. In a phase II trial for the combination, EGFR wild-type and EGFR FISH-negative patients had longer PFS and OS than with erlotinib alone. [42]

7. CONCLUSION

Targeted therapy helps treat skin cancer by attacking the cancer cells directly. It can be more effective and have fewer side effects. This treatment can help people with skin cancer live longer and healthier lives. It works well when caught early and can reduce the need for harsh treatments. This treatment can give hope to cancer-surviving patients. In this review, we tried to explain how cancer can be treated with targeted therapies. Researchers are still working to make more and give patients better care.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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