International Journal of Recent Research and Review, Vol. XVIII, Issue 1, March 2025
ISSN 2277 – 8322

SMALL MOLECULE INHIBITORS IN ONCOLOGY: A COMPREHENSIVE REVIEW OF TARGETED THERAPIES AND THEIR IMPLICATIONS IN CANCER TREATMENT

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Abstract- Small molecule inhibitors have emerged as a pivotal magnificence of focused remedies in oncology, offering new avenues for the treatment of numerous cancers. These sellers are designed to selectively inhibit precise molecular pathways that pressure tumor boom and progression, thereby offering a extra specific technique to cancer therapy in comparison to traditional chemotherapy. This overview pursuits to offer a comprehensive evaluate of small molecule inhibitors utilized in cancer treatment, focusing on their mechanisms of action, molecular goals, and medical packages. Key focused pathways consist of tyrosine kinases, serine/threonine kinases, and epigenetic regulators, amongst others. The healing implications of these inhibitors are explored throughout a number malignancies, inclusive of solid tumors and hematological cancers. The assessment additionally discusses resistance mechanisms, aspect consequences, and aggregate strategies to conquer limitations and decorate efficacy. As studies advances, small molecule inhibitors keep to enlarge the healing panorama, providing the capacity for personalised medicinal drug and improved affected person consequences in oncology. This paper aims to summarize current information even as highlighting rising trends and future instructions within the improvement of small molecule-focused treatment options for most cancers treatment.

Keywords- Magnificence, Small molecule, inhibitors, oncology, hematological, resistance, tyrosine kinases

I. INTRODUCTION

Cancer is a collection of diseases characterized by way of the uncontrolled boom and spread of odd cells. It happens

whilst regular regulatory tactics that govern cellular division, differentiation, and loss of life are disrupted, leading to the formation of malignant tumors. These tumors can invade nearby tissues and, in some instances, spread to distant parts of the body thru the bloodstream or lymphatic gadget, a system referred to as metastasis.[1]

Cancer remains one of the main reasons of mortality worldwide, accounting for millions of deaths each year. Traditional most cancers remedies together with chemotherapy and radiation therapy, at the same time as effective in positive cases, frequently come with massive drawbacks, consisting of non-unique toxicity to normal cells and the improvement of resistance. [2]

Targeted healing procedures aim to interfere with unique molecular drivers of cancer increase, offering a extra tailor-made method to treatment. Among the diverse forms of targeted treatment options, small molecule inhibitors (SMIs) have emerged as a key magnificence of medicine designed to disrupt aberrant signaling pathways that power tumor progression. These inhibitors usually consist of low molecular weight compounds that can penetrate cell membranes and modulate the feature of intracellular goals such as enzymes, receptors, and other proteins concerned in most cancers cellular signaling.[3]

The use of small molecule inhibitors in oncology has revolutionized the control of many cancers through offering extra personalized treatment options that directly goal the molecular abnormalities inside tumor cells. As adversarial to conventional chemotherapy, which affects each cancerous and healthful unexpectedly dividing cells, small molecule inhibitors are designed to target unique proteins or pathways which are dysregulated in cancer cells. This specificity lets in for more effective cancer manipulate with fewer facet outcomes.[4]

This complete overview explores the mechanisms of action, healing goals, clinical programs, challenges, and future guidelines of small molecule inhibitors in oncology. It objectives to provide a thorough information of ways those centered cures have reshaped cancer treatment and what lies ahead in the pursuit of more effective and customized cancer care.

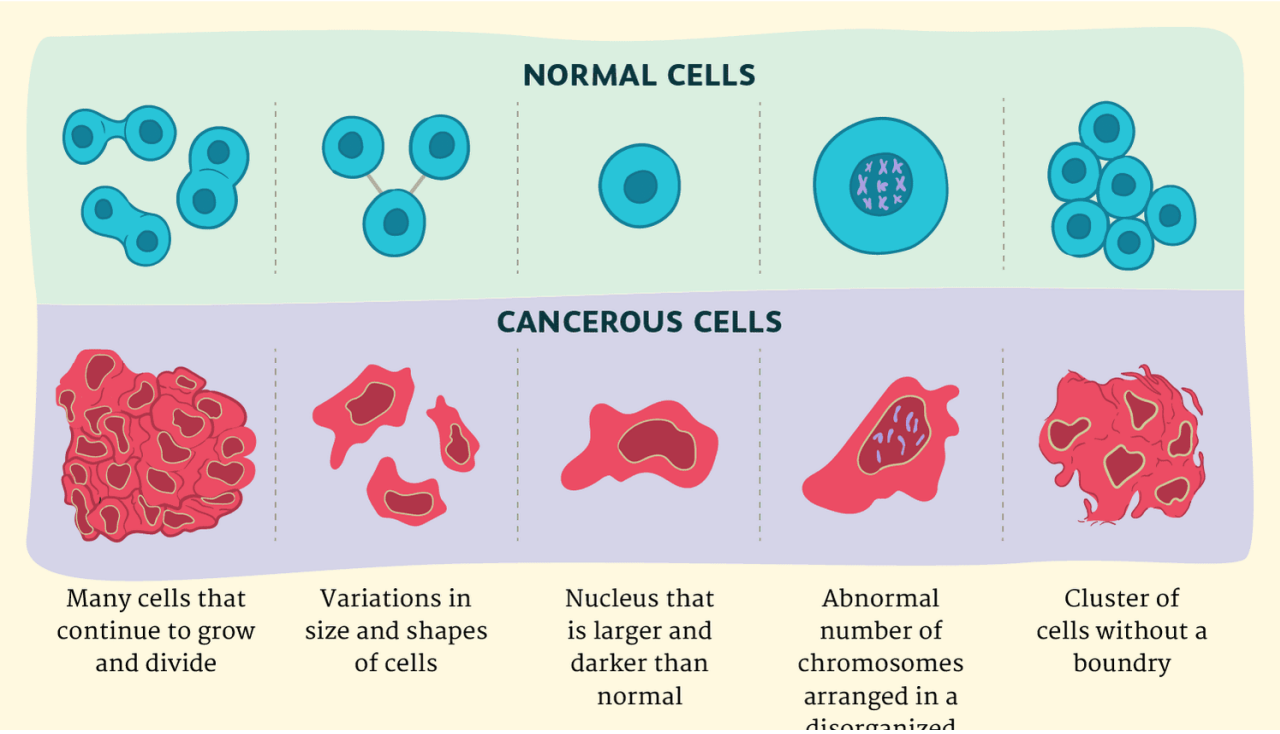

Fig. 1 Normal and Cancer cell Diagram

II. MECHANISMS OF ACTION

Small molecule inhibitors are designed to intervene with precise proteins or enzymes that play important roles in cancer mobile proliferation, survival, angiogenesis, and metastasis. These inhibitors generally characteristic via binding to energetic web sites or allosteric web sites on target proteins, thereby inhibiting their activity. The fundamental categories of SMIs in oncology encompass:Fig.1.2. show mechanisms of action[5]

1. **Tyrosine Kinase Inhibitors (TKIs):**These inhibit tyrosine kinases, which can be enzymes that catalyze the switch of phosphate companies to tyrosine residues on proteins, thereby activating signaling pathways that promote cellular increase. Examples consist of imatinib (concentrated on BCR-ABL in chronic myeloid leukemia) and erlotinib .[6]
2. **Proteasome Inhibitors:**These block the proteasome, a cellular complex chargeable for degrading broken or unneeded proteins. [7]By inhibiting proteasome activity, cancer cells collect poisonous proteins, leading to cell death. Bortezomib is a outstanding instance

used in more than one myeloma treatment.

3. **Histone Deacetylase Inhibitors (HDACis):**These inhibit histone deacetylases, which cast off acetyl agencies from histone proteins, leading to chromatin condensation and reduced gene transcription. HDAC inhibitors which includes vorinostat have shown efficacy in treating cutaneous T-mobile lymphoma.[8]
4. **Poly (ADP-ribose) Polymerase (PARP) Inhibitors:**These goal PARP enzymes, which are worried in DNA repair tactics. Inhibiting PARP leads to accumulation of DNA harm, particularly in most cancers cells with faulty DNA repair mechanisms like BRCA-mutant cancers. Olaparib is a exquisite PARP inhibitor utilized in ovarian and breast cancers.

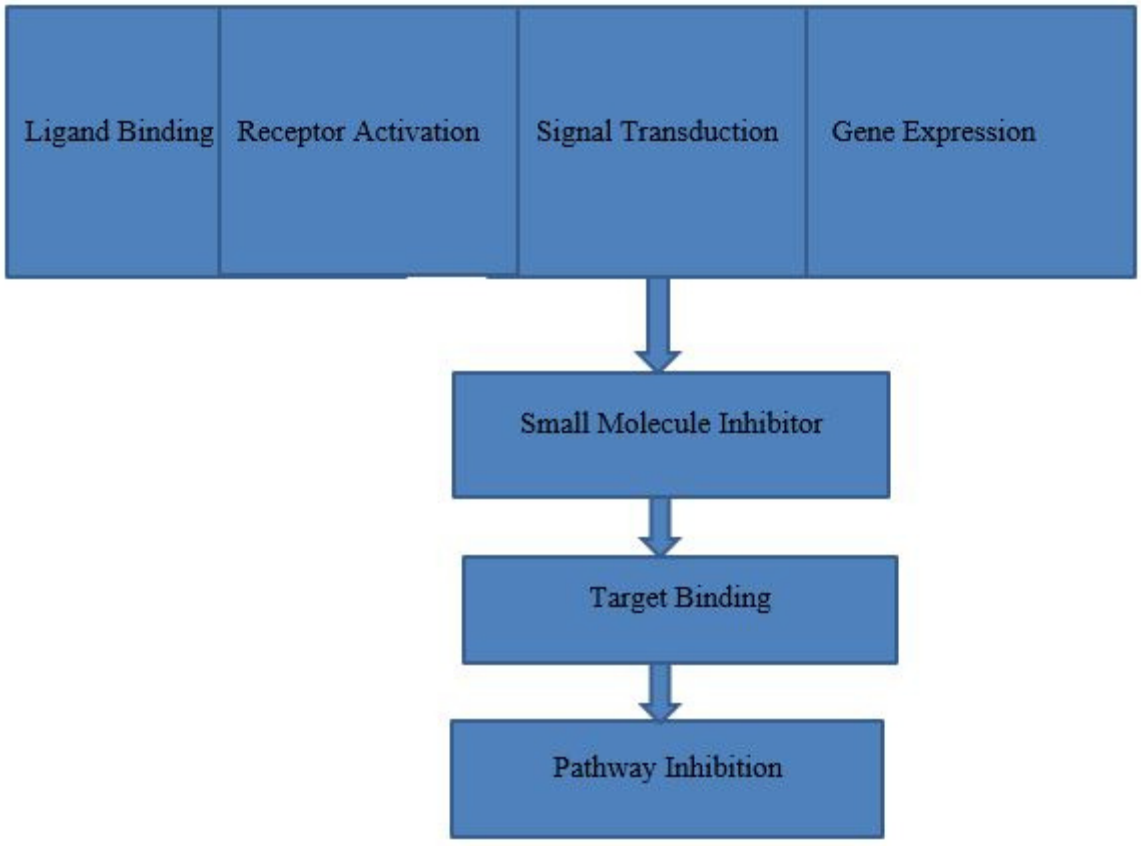

Fig. 2Mechanisms of Action of Small molecules Inhibitors

Table1.Summary of some approved selective small molecule kinaseinhibitors[10]

Class	Drug Name	Company	First Approval	Target	Protein Substrate	Administration pathway	Indication
ABL	Imatinib (Gleevec)	Novartis	2001	BCR–ABL, PDGFR, SCF, KIT	Tyrosine	Oral	Ph-positive CML, Ph-positive ALL, PDGFR rearrangements MDS/MPD, ASM, HES, CEL, DFSP, KIT-positive GIST
ABL	Dasatinib (Sprycel)	Bristol-Myers Squibb	2006	BCR–ABL, SRC family (SRC, LCK, YES, FYN), and KIT, EPHA2, PDGFRβ	Tyrosine	Oral	Ph-positive CML, Ph-positive ALL,
ABL	Nilotinib (Tasigna)	Novartis	2007	BCR–ABL, PDGFRB, KIT	Tyrosine	Oral	Ph-positive CML
ABL	Bosutinib (Bosulif)	Wyeth Inc	2012	BCR–ABL, SRC-family (SRC, LYN, andHCK)	Tyrosine	Oral	Ph-positive CML
ABL	Ponatinib (Iclusig)	Ariad	2012	BCR–ABL, BCR–ABL (T315I), VEGFR, PDGFR, FGFR, EPH receptors, SRC families of kinases, KIT,	Tyrosine	Oral	Ph-positive CML and Ph-positive ALL resistant/intolerant to therapy, T315I-positive CML, T315Ipositive/ Ph-positive ALL

				RET, TIE2, FLT3			
ABL	Asciminib (Scemblix)	Novartis	2021	BCR–ABL, BCR–ABL (T315I)	Tyrosine	Oral	Ph-positive CML-CP resistant to therapy, T315I-positive CML
KIT	KIT Ripretinib (Quinlock)	Deciphera	2020	KIT, PDGFRA, PDGFRA mutations, PDGFRB, TIE2, VEGFR2, BRAF	Tyrosine	Oral	GIST
KIT	Avapritinib (Ayvakit)	Blueprint Medicines	2020	KIT, KIT D816V, KIT exon 11, 11/17, and 17 mutants, PDGFRA and PDGFRA D842 mutants, PDGFRB, and CSFR1	Tyrosine	Oral	PDGFRA exon 18 mutation (including D842V) positive GIST, advanced systemic mastocytosis
HER	Gefitinib (Iressa)	AstraZeneca	2003	EGFR and HER family	Tyrosine	Oral	NSCLC
HER	Erlotinib (Tarceva)	OSI	2004	EGFR and HER family	Tyrosine	Oral	NSCLC with EGFR 19del or L858R, pancreatic cancer
HER	Afatinib (Gilotrif)	Boehringer Ingelheim	2013	EGFR and HER family	Tyrosine	Oral	NSCLC with nonresistant EGFR mutations, squamous NSCLC
HER	Osimertinib (Tagrisso)	AstraZeneca	2015	EGFR and HER family	Tyrosine	Oral	NSCLC with EGFR 19del or L858R, NSCLC with T790M positive

HER	Dacomitinib (Vizimpro)	Pfizer	2018	EGFR and HER family	Tyrosine	Oral	NSCLC with EGFR 19del or L858R
HER	Mobocertinib (Exkivity)	Takeda Pharmaceuticals	2021	EGFR and HER family	Tyrosine	Oral	NSCLC with EGFR 20 exon insertion
HER	Lapatinib (Tykerb)	SmithKline Beecham	2007	EGFR and HER family	Tyrosine	Oral	HER2-positive breast cancer
HER	Neratinib (Nerlynx)	Puma Biotechnology	2017	EGFR and HER family	Tyrosine	Oral	HER2-positive breast cancer
ALK	Crizotinib (Xalkori)	PF Prism CV	2011	ALK, HGFR, c-Met, ROS1, RON	Tyrosine	Oral	ALK- or ROS1-positive NSCLC, ALK-positive anaplastic large cell lymphoma
ALK	Ceritinib (Zykadia)	Novartis	2014	ALK, IGF-1R, InsR, ROS1	Tyrosine	Oral	ALK-positive NSCLC

III. KEY THERAPEUTIC TARGETS IN CANCER

Small molecule inhibitors (SMIs) were advanced to target specific proteins and pathways that play critical roles in cancer mobile survival, proliferation, angiogenesis, and metastasis. These centered treatment options aim to disrupt the signaling cascades that power tumor progression, supplying extra effective and less poisonous remedy alternatives in comparison to traditional chemotherapy. Here, we speak the important thing healing goals in oncology that have been effectively exploited by using small molecule inhibitors.

1. Epidermal Growth Factor Receptor (EGFR) The epidermal boom factor receptor (EGFR) is a transmembrane tyrosine kinase receptor this is overexpressed or mutated in several cancers, along with non-small cellular lung most cancers (NSCLC), colorectal

most cancers, and head and neck cancers. EGFR activation triggers a cascade of downstream signaling pathways that sell cellular proliferation, survival, and angiogenesis. Mutations within the EGFR gene, which include exon 19 deletions and L858R point mutations, can cause constitutive activation of the receptor, driving oncogenesis.[11]

- EGFR Inhibitors: Tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, and osimertinib specifically target mutated EGFR, inhibiting its kinase activity and blocking downstream signaling.[12]

2. BCR-ABL Fusion Protein The BCR-ABL fusion protein outcomes from the Philadelphia chromosome translocation (t(nine;22)(q34;q11)), that's a hallmark of chronic myeloid leukemia (CML). [13]

- BCR-ABL Inhibitors: Imatinib (Gleevec) became the first small molecule inhibitor advanced to target the BCR-ABL kinase, revolutionizing the treatment of CML through reworking it from a deadly sickness to a practicable continual situation. Second- and 0.33-technology BCR-ABL inhibitors, consisting of dasatinib, nilotinib, and ponatinib, have been advanced to triumph over resistance to imatinib and target additional mutations within the BCR-ABL gene.[14]

3. Vascular Endothelial Growth Factor Receptor (VEGFR) VEGFR performs a critical role in angiogenesis, the process by which new blood vessels are fashioned to deliver vitamins and oxygen to tumors. Many solid tumors, along with renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), and gastrointestinal stromal tumors, depend upon angiogenesis for boom and metastasis.[15]
4. Anaplastic Lymphoma Kinase (ALK) ALK is a receptor tyrosine kinase that, while rearranged or mutated, acts as an oncogenic motive force in certain cancers, including non-small cellular lung cancer (NSCLC), anaplastic large mobile lymphoma, and neuroblastoma. The maximum not unusual alteration in ALK is the EML4-ALK fusion, which leads to a constitutively energetic kinase selling tumor mobile survival and proliferation.[16]

- ALK Inhibitors: Crizotinibbecome the primary ALK inhibitor authorized for the remedy of ALK-high quality NSCLC, followed with the aid of more

moderen-generation inhibitors together with ceritinib, alectinib, and lorlatinib. These subsequent-era inhibitors are designed to overcome resistance mutations and improve crucial frightened device penetration, enhancing remedy results for sufferers with ALK-rearranged cancers.[17]

5. BRAF and MEK in the RAS/RAF/MEK/ERK Pathway The RAS/RAF/MEK/ERK signaling pathway is often dysregulated in cancers, playing a important role in cell division and survival. Mutations within the BRAF gene, particularly the V600E mutation, are normally discovered in cancer, colorectal cancer, and thyroid most cancers, main to constitutive pathway activation.[18]

- BRAF and MEK Inhibitors: Vemurafenib and dabrafenib are BRAF inhibitors utilized in treating BRAF V600E-mutant melanoma. MEK inhibitors such as trametinib and cobimetinib goal downstream components of the same pathway, and their mixture with BRAF inhibitors has proven stronger efficacy and delayed resistance development.[19]

6. Poly (ADP-ribose) Polymerase (PARP) PARP enzymes are concerned in DNA restore methods, specially in repairing unmarried-strand breaks through the base excision repair pathway. In cancers with defective homologous recombination restore (HRR), inclusive of BRCA1/2-mutated breast and ovarian cancers, PARP inhibition ends in the buildup of DNA harm and next cellular loss of life.[20]
7. Cyclin-Dependent Kinases (CDKs) CDKs are crucial regulators of the cell cycle, and their dysregulation can lead to uncontrolled mobile proliferation. CDK4/6, in particular, performs a key position inside the G1-S phase transition of the cellular cycle and is regularly overactive in cancers which includes breast most cancers.[22]
8. Histone Deacetylases (HDACs) HDACs are enzymes concerned in editing chromatin structure and regulating gene expression. In cancer, HDACs can emerge as dysregulated, main to extraordinary gene silencing and promoting of tumor increase.[23]

- HDAC Inhibitors: Vorinostat and romidepsin are HDAC inhibitors which have shown efficacy in treating cutaneous T-cellular lymphoma (CTCL). These inhibitors work by using inducing cancer cellular differentiation, apoptosis, and growth arrest through epigenetic modulation.[24]

Table 2.New strategies for targeting kinases[25]

Target	Compound Name	Drug Type	Indication in Research	Highest Clinical Phase
NTRK	CG□001419	PROTACs	Solid tumors	Phase 1/2 Cullgen, Inc. (San Diego, CA, USA). CXHL2200331 *
EGFR	HSK40118	PROTACs	EGFR□positive NSCLC	Phase 1 Haisco Pharmaceutical Group Co., Ltd. (Chengdu, China). CTR20230926
GSPT1 × HER2	ORM□5029	PROTACs	HER2□positive solid tumors or breast cancer	Phase 1 Orum Therapeutics, Inc. (Daejeon, Republic of Korea). NCT05511844
EGFR L858R	CFT□8919	PROTACs	EGFR□positive NSCLC	Investigational new drug (IND) by FDA C4 Therapeutics, Inc. (Watertown, MA, USA). Company pipeline

IV. CHALLENGES AND LIMITATIONS

Despite the success of SMIs, several challenges remain:

- Drug Resistance: Cancer cells can expand resistance to focused therapies via secondary mutations, activation of opportunity signaling pathways, or phenotypic modifications. Combination treatments and next-technology inhibitors are being explored to overcome resistance.[26]
- Toxicity: While SMIs are normally greater selective than chemotherapy, they can nevertheless motive aspect consequences including pores and skin rash, diarrhea, cardiotoxicity, and myelosuppression. Patient monitoring and dose modifications are often required.[27]

- Cost: The high cost of targeted cures may be a barrier to get admission to, mainly in low- and middle-profits nations. Efforts to lessen fees thru generics and biosimilars are underway.[28]

Clinical Applications of Small Molecule Inhibitors in Cancer Treatment

Small molecule inhibitors (SMIs) have extensively transformed the control of diverse cancers by using focused on precise molecular pathways that pressure tumor growth a27nd survival. These inhibitors were included into fashionable treatment protocols for more than one malignancies, frequently leading to progressed outcomes.

1. Chronic Myeloid Leukemia (CML) Chronic myeloid leukemia (CML) is a hematologic malignancy characterized by way of the presence of the BCR-ABL fusion gene, which ends from the Philadelphia chromosome translocation. The BCR-ABL fusion protein acts as a constitutively active tyrosine kinase, promoting unregulated cellular proliferation. The development of BCR-ABL inhibitors has revolutionized CML treatment.[29]

- Key Inhibitors: Imatinib (Gleevec) become the primary small molecule inhibitor to goal the BCR-ABL tyrosine kinase, dramatically changing the analysis for CML patients. Imatinib has proven high efficacy in inducing long lasting responses and reworking CML from a deadly disorder right into a potential chronic condition. Subsequent generations of BCR-ABL inhibitors, together with dasatinib, nilotinib, and ponatinib, were evolved to deal with resistance and intolerance to imatinib and to target additional mutations within the BCR-ABL gene.[30]
- Clinical Impact: The availability of these inhibitors has led to significant improvements in survival rates for CML patients, with many achieving long-term remission. The introduction of BCR-ABL inhibitors has set a precedent for targeted therapy development in other cancers.[31]

2. Non-Small Cell Lung Cancer (NSCLC) Non-small mobile lung cancer (NSCLC) accounts for the majority of lung most cancers cases, and sure subtypes are driven with the aid of specific genetic mutations that may be targeted with the aid of small molecule inhibitors. The most exceptional goals in NSCLC

consist of the epidermal increase thing receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS1.

- EGFR Inhibitors: EGFR mutations, observed in a subset of NSCLC patients, cause constitutive receptor activation and tumor boom. EGFR tyrosine kinase inhibitors (TKIs) consisting of erlotinib, gefitinib, and osimertinib are used to target these mutations. Osimertinib, a third-technology EGFR inhibitor, has proven advanced efficacy in treating patients with sensitizing EGFR mutations and in overcoming resistance associated with the T790M mutation.[32]
- ALK and ROS1 Inhibitors: ALK rearrangements and ROS1 fusions are also actionable targets in NSCLC. ALK inhibitors like crizotinib, ceritinib, and alectinib, in addition to ROS1 inhibitors, have proven considerable blessings in sufferers with these genetic alterations. Newer dealers along with lorlatinib offer more advantageous vital worried device penetration and effectiveness against resistance mutations.[33]

3. Breast Cancer Breast cancer is one of the most common malignancies worldwide, and various molecular subtypes have been identified, some of which are suitable for targeted therapies. The use of small molecule inhibitors has been particularly successful in hormone receptor-positive (HR+) breast cancer and BRCA-mutated breast cancer.

- CDK4/6 Inhibitors: Palbociclib, ribociclib, and abemaciclib are cyclin-dependent kinase (CDK) four/6 inhibitors used in combination with endocrine therapy for HR /HER2- superior breast most cancers. These inhibitors induce mobile cycle arrest, thereby slowing tumor progression. The addition of CDK4/6 inhibitors to standard endocrine therapy has improved progression-loose survival and common survival on this patient population.[34]
- PARP Inhibitors: Patients with BRCA1/2 mutations are at a better risk for developing breast cancer, as those mutations impair DNA repair. PARP inhibitors consisting of olaparib and talazoparib goal faulty DNA repair mechanisms, main to cancer mobile demise. They are authorised for the remedy of BRCA-mutated metastatic breast cancer.

- Clinical Impact: The incorporation of CDK4/6 inhibitors and PARP inhibitors into treatment regimens has significantly superior the healing landscape for unique subtypes of breast cancer, supplying more tailor-made and effective treatment alternatives.[35]

4. Multiple Myeloma :It is characterized by the clonal proliferation of plasma cells within the bone marrow. The development of proteasome inhibitors has been a chief advancement in the remedy of this sickness.
   - Proteasome Inhibitors: Bortezomib, carfilzomib, and ixazomib are proteasome inhibitors that block the degradation of proteins involved in cell cycle law and apoptosis, leading to most cancers cell loss of life. Bortezomib, the primary proteasome inhibitor accredited for multiple myeloma, considerably stepped forward affected person results and is now used as part of general combination regimens.[36]
5. Ovarian Cancer Ovarian most cancers is often identified at an advanced stage, making it tough to deal with. The improvement of PARP inhibitors has been a recreation-changer for patients with BRCA-mutated ovarian cancer and those with homologous recombination deficiency (HRD).
   - PARP Inhibitors: Olaparib, niraparib, and rucaparib are utilized in ovarian most cancers remedy, in particular for protection therapy following a response to platinum-based totally chemotherapy. They have verified tremendous blessings in prolonging development-loose survival in sufferers with BRCA mutations or HRD. [37]
6. Renal Cell Carcinoma (RCC) Renal mobile carcinoma, a not unusual kind of kidney cancer, is tremendously depending on angiogenesis for boom. Targeting the vascular endothelial growth issue (VEGF) pathway has end up a cornerstone of RCC remedy.
7. Melanoma Melanoma, a type of pores and skin cancer, often harbors mutations inside the BRAF gene, specially the V600E mutation, which activates the MAPK signaling pathway.

- BRAF and MEK Inhibitors: Targeted inhibitors along with vemurafenib and dabrafenib (BRAF inhibitors) and trametinib and cobimetinib (MEK inhibitors) had been evolved to block this pathway. Combination remedy with BRAF and MEK inhibitors has shown advanced efficacy in comparison to BRAF inhibition alone, resulting in better response prices and delayed resistance. [38]
- Clinical Impact: These inhibitors have dramatically stepped forward outcomes for sufferers with BRAF-mutant cancer, remodeling the management of this competitive cancer.[39]

V. FUTURE DIRECTIONS AND EMERGING THERAPIES

The future of SMIs in oncology is promising, with ongoing research focused on:

1. **Biomarker-Driven Therapy:** The identity of predictive biomarkers is important for deciding on patients who are most probably to benefit from particular SMIs. Liquid biopsy and subsequent-era sequencing are advancing precision medication tactics.
2. **Combination Therapy:** Combining SMIs with different remedies, consisting of immunotherapy, chemotherapy, or radiation, may additionally beautify therapeutic efficacy and triumph over resistance mechanisms.
3. **Novel Targets:** Newer targets, which include KRAS, MYC, and epigenetic modulators, are being explored with innovative inhibitors. For instance, the current development of KRAS G12C inhibitors like sotorasib has opened new avenues for treating previously untreatable cancers.

VI. CONCLUSION

The creation of small molecule inhibitors (SMIs) has revolutionized most cancers treatment, offering a extra specific and centered method compared to standard therapies along with chemotherapy and radiation. By selectively interfering with unique molecular pathways that power tumor increase, survival, and metastasis, SMIs have grow to be a cornerstone of modern-day oncology. The improvement and achievement of those inhibitors, beginning with imatinib for chronic myeloid leukemia, have transformed several previously untreatable or hard-to-deal with cancers into extra possible chronic situations, considerably enhancing affected

person consequences and exceptional of lifestyles.

Targeted treatment plans have validated speciallyeffective in cancers in which properly-described molecular drivers, together with EGFR mutations, BCR-ABL fusions, and BRAF changes, are gift. Small molecule inhibitors targeting these and different key proteins, consisting of VEGFR, ALK, PARP, and CDK4/6, have shown considerable advantages across various malignancies, which includes non-small cell lung cancer, breast cancer, cancer, multiple myeloma, and ovarian most cancers. The clinical achievement of these marketers has validated the approach of tailoring treatments primarily based on specific molecular abnormalities inside tumors, ushering in an era of precision oncology.

Additionally, at the same time as small molecule inhibitors are usually extra selective than traditional chemotherapies, they can still purpose destructive outcomes that need to be cautiously managed. The high price of targeted treatment options additionally limits get entry to, especially in resource-constrained settings. Future guidelines inside the area of small molecule inhibitors consist of the development of next-technology inhibitors to overcome resistance, the identity of recent healing goals, and the use of biomarkers to higher pick out patients who will benefit from unique treatments.

References

1. Merino D, Kelly GL, LesseneG,Wei AH, Roberts AW, Strasser A. BH3-mimetic drugs: blazing the trail for new cancer medicines. Cancer Cell. 2018;34(6):879-891.
2. Nakayama A, Nagashima T, Nishizono Y, et al. Characterisation of a novel KRAS G12C inhibitor ASP2453 that shows potent anti-tumour activity in KRAS G12C-mutated preclinical models. Br J Cancer. 2022;126(5):744-753.
3. Hong DS, Fakih MG, Strickler JH, et al. KRAS(G12C) inhibition with sotorasib in advanced solid tumors. N Engl J Med. 2020;383(13):1207-1217.
4. Case LB. Membranes regulate biomolecular condensates. Nat Cell Biol. 2022;24(4):404-405.
5. Kurreck A, StintzingS,Modest DP. Efficacy, molecular biology, quality of life, or economic aspects: what do we really focus on? J Clin Oncol. 2022;40(11):1260-1262.

6. Aggarwal C, Albelda SM. Molecular characterization of malignant mesothelioma: time for new targets? Cancer Discov. 2018;8(12):1508-1510.
7. Dietlein F, Wang AB, Fagre C, et al. Genome-wide analysis of somatic noncoding mutation patterns in cancer. Science. 2022;376(6589):eabg5601.
8. Schrag D. The price tag on progress—chemotherapy for colorectal cancer. N Engl J Med. 2004;351(4):317-319.
9. Neyt M, Albrecht J, Cocquyt V. An economic evaluation of Herceptin in adjuvant setting: the Breast Cancer International Research Group 006 Trial. Ann Oncol. 2006;17(3):381-390.
10. Mohamed MK, Ramalingam S, Lin Y, Gooding W, Belani CP. Skin rash and good performance status predict improved survival with gefitinib in patients with advanced non-small cell lung cancer. Ann Oncol. 2005;16(5):780-785.
11. Park J, Park BB, Kim JY, et al. Gefitinib (ZD1839) monotherapy as a salvage regimen for previously treated advanced non-small cell lung cancer. Clin Cancer Res. 2004;10(13):4383-4388.
12. Ullrich A, Schlessinger J. Signal transduction by receptors with tyrosine kinase activity. Cell. 1990;61:203–12.
13. Ward CW, Lawrence MC, Streltsov VA, Adams TE, McKern NM. The insulin and EGF receptor structures: new insights into ligand-induced receptor activation. Trends Biochem Sci. 2007;32:129–37.
14. Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell. 2000;103:211–25. 62. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer. 2007;7:169–81.
15. Libermann TA, Nusbaum HR, Razon N, Kris R, Lax I, Soreq H, Whittle N, Waterfield MD, Ullrich A, Schlessinger J: Amplification, enhanced expression and possible rearrangement of EGF receptor gene in primary human brain tumours of glial origin. 1985.
16. Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science. 1989;244:707.
17. Liu, L. et al. The BRAF and MEK inhibitors dabrafenib and trametinib: effects on immune function and in combination with immunomodulatory antibodies targeting PD-1, PD-L1, and CTLA-4. Clin. Cancer Res. 21, 1639–1651 (2015).

18. MD, H. et al. Phase Ib study of atezolizumab combined with cobimetinib in patients with solid tumors. Ann. Oncol. 30, 1134–1142 (2019).
19. Eng, C. et al. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 20, 849–861 (2019).
20. Callahan, M. K. et al. Phase 1 study to evaluate the safety and tolerability of MEDI4736 (durvalumab, DUR) + tremelimumab (TRE) in patients with advanced solid tumors. J. Clin. Oncol. 35, 3069–3069 (2017).
21. Erin, N., Grahovac, J., Brozovic, A. &Efferth, T. Tumor microenvironment and epithelial mesenchymal transition as targets to overcome tumor multidrug resistance. Drug Resist. Updat. 53, 100715 (2020).
22. Bukowski, K., Kciuk, M. &Kontek, R. Mechanisms of multidrug resistance in cancer chemotherapy. Int. J. Mol. Sci. 21, 3233 (2020). 599. Mele, L. et al. The role of autophagy in resistance to targeted therapies. Cancer Treat. Rev. 88, 102043 (2020).
23. Adam K, Hunter T. Histidine kinases and the missing phosphoproteome from prokaryotes to eukaryotes. Lab Investig. 2018;98:233–47.
24. Ciesla J, Fraczyk T, Rode W. Phosphorylation of basic amino acid residues in proteins: important but easily missed. Acta Biochim Pol. 2011;58:137–48.
25. Greaves, P., and Gribben, J. G. (2013). The role of B7 family molecules in hematologic malignancy. Blood 121, 734–744. doi: 10.1182/blood-2012-10-385591 Guengerich, F. P. (2020). Cytochrome P450 2E1 and its roles in disease. Chem. Biol. Interact. 322:109056. doi: 10.1016/j.cbi.2020.109056
26. Hanahan, D., and Folkman, J. (1996). Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 86, 353–364. doi: 10.1016/s0092- 8674(00)80108-7
27. Heinhuis, K. M., Ros, W., Kok, M., Steeghs, N., Beijnen, J. H., and Schellens, J. H. M. (2019). Enhancing antitumor response by combining immune checkpoint inhibitors with chemotherapy in solid tumors. Ann. Oncol. 30, 219–235. doi: 10.1093/annonc/mdy551

28. Gupta, D.; Kumar, M.; Saifi, S.; Rawat, S.; Ethayathulla, A.S.; Kaur, P. A Comprehensive Review on Role of Aurora Kinase Inhibitors (AKIs) in Cancer Therapeutics. Int. J. Biol. Macromol. 2024, 265, 130913. [CrossRef] [PubMed]
29. Zhang, X.; Li, X.; Bi, M.; Su, C.; Fang, Y.; Wang, Z.; Yuan, Y.; Du, X.; Lv, T.; Li, Y. Phase Ib/IIa Study Assessing the Safety and Efficacy of AL8326 Monotherapy in Patients with ≥3rd Line Small Cell Lung Cancer (SCLC) Treatment. J. Clin. Oncol. 2023, 41, 8585. [CrossRef]
30. Piha□Paul, S.A.; Xu, B.; Dumbrava, E.E.; Fu, S.; Karp, D.D.; Meric□Bernstam, F.; Hong, D.S.; Rodon, J.A.; Tsimberidou, A.M.; Raghav, K.; et al. First□In□Human Phase I Study of Tinengotinib (TT□00420), a Multiple Kinase Inhibitor, as a Single Agent in Patients with Advanced Solid Tumors. Oncologist 2024, 29, e514–e525. [CrossRef] [PubMed]
31. Lahiry, P.; Torkamani, A.; Schork, N.J.; Hegele, R.A. Kinase Mutations in Human Disease: Interpreting Genotype–Phenotype Relationships. Nat. Rev. Genet. 2010, 11, 60–74. [CrossRef] [PubMed]
32. Attwood, M.M.; Fabbro, D.; Sokolov, A.V.; Knapp, S.; Schiöth, H.B. Author Correction: Trends in Kinase Drug Discovery: Targets, Indications and Inhibitor Design. Nat. Rev. Drug Discov. 2021, 20, 798. [CrossRef] [PubMed]
33. Ferguson, F.M.; Gray, N.S. Kinase Inhibitors: The Road Ahead. Nat. Rev. Drug Discov. 2018, 17, 353–377. [CrossRef] [PubMed]
34. Bhullar, K.S.; Lagarón, N.O.; McGowan, E.M.; Parmar, I.; Jha, A.; Hubbard, B.P.; Rupasinghe, H.P.V. Kinase□Targeted Cancer Therapies: Progress, Challenges and Future Directions. Mol. Cancer 2018, 17, 48. [CrossRef] [PubMed]
35. Ye, F.; Dewanjee, S.; Li, Y.; Jha, N.K.; Chen, Z.□S.; Kumar, A.; Vishakha; Behl, T.; Jha, S.K.; Tang, H. Advancements in Clinical Aspects of Targeted Therapy and Immunotherapy in Breast Cancer. Mol. Cancer 2023, 22, 105. [CrossRef] [PubMed]
36. Zeng, Z.; Fu, M.; Hu, Y.; Wei, Y.; Wei, X.; Luo, M. Regulation and Signaling Pathways in Cancer Stem Cells: Implications for Targeted Therapy for

Cancer. Mol. Cancer 2023, 22, 172. [CrossRef] [PubMed]

37. Wu, J.; Lin, Z. Non□Small Cell Lung Cancer Targeted Therapy: Drugs and Mechanisms of Drug Resistance. Int. J. Mol. Sci. 2022, 23, 15056. [CrossRef] [PubMed]
38. Bansal, I.; Pandey, A.K.; Ruwali, M. Small□Molecule Inhibitors of Kinases in Breast Cancer Therapy: Recent Advances, Opportunities, and Challenges. Front. Pharmacol. 2023, 14, 1244597. [CrossRef] [PubMed]
39. Arter, C.; Trask, L.; Ward, S.; Yeoh, S.; Bayliss, R. Structural Features of the Protein Kinase Domain and Targeted Binding by Small□Molecule Inhibitors. J. Biol. Chem. 2022, 298, 102247. [CrossRef] [PubMed]