Precision Oncology, Cell Signaling and Targeted Therapy: A Holistic Approach to Molecular Cancer Therapeutics

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Abstract: In recent decades, there has been a deluge in the large-scale production of anticancer agents, primarily due to advances in genomic technologies enabling precise targeting of oncogenic pathways involved in disease progression. This initiated a paradigm shift in cancer research and therapeutics based on the ability to study molecular changes throughout the genome. It provided a unique opportunity in the field of translational cancer research and have led to the concept of precision medicine in cancer therapy, raising hopes of developing better diagnostic and therapeutic means for the management of cancer. The purpose of this article is to briefly review the tools and techniques involved in precision oncology research and their applications in the field of cancer treatment.

Keywords: Gene Mutation; Cancer Genomics; Targeted Therapy; Immunotherapy, Precision Medicine

1. Introduction

Cancer is one of the leading causes of death worldwide. It is considered that genetic factors and epigenetic changes allow cells to proliferate in an uncontrolled manner by escaping essential regulatory mechanisms. Rigorous cancer research in the past few decades supported by advances in cell and molecular biology has led scientists to clearly understand there are genetic changes associated with cancer incidences that cause the disease to grow and spread to other parts of the body. Cancer is initiated as the result of uncontrolled cell division and proliferation leading to tumor formation which culminates in metastasis that involves the dissemination of tumor cells to new sites in the body forming secondary tumors, and is responsible for about 90% of cancer-related deaths in reality. Cell proliferation requires a balanced rate of cell growth and division to maintain the increase in cell numbers for growth and development, maintenance of tissue homoeostasis and wound healing. Cancer progression is frequently associated with increased cell proliferation, metabolic dysregulation, resistance to apoptosis, genetic instability, initiation ofangiogenesis, invasion and increased migration of cells. Genetic changes appearing in the information system of cells that program its unregulated growth and proliferation gradually lead to the manifestation of cancer and therapeutic options must be directed accordingly [1]. The critical roles played by some of the molecules associated with specific oncogenic pathways and the cellular microenvironment that lead to cancer progression and metastasis have been precisely described in recent years based on findings from the Human Genome Project. New developments in DNA and RNA analysis have made it possible to study underlying genetic changes systematically [2]. These advances have allowed researchers to have a more in-depth understanding of the signaling pathways and processes involved. in carcinogenesis and have led to the identification of critical pathways that can be successfully targeted for therapeutic purposes [3]. Over the years, technological advances in the field of molecular biology have been exploited to unravel genomic changes to fully understand the pathogenesis of human cancer. The range of cancer-causing mutations is known to be huge, and the mutational landscape differs from one another depending on the type of cancer and even people suffering from the same cancer type are found to have considerably different mutation patterns. Moreover, it has long been observed that every patient responds differently to particular treatments despite having the same type and stage of cancer. These observations have been compelling and led researchers to adopt a precision medicine approach to cancer therapy necessitating the study of genetic features of vulnerable individuals for a patient-specific treatment regimen towards the most effective treatment of cancer. Precision oncology has evolved as a form of cancer therapy focused on genetic profiling of tumors to identify molecular alterations involved in cancer development for tailored individualized treatment of the disease [4,5]. The emergence of next-generation sequencing (NGS) in 2005 has proved to be massively important in this direction as the technology is used to determine the order of nucleotides in entire genomes or targeted regions of DNA or RNA and has revolutionized biological research, allowing scientists to study biological systems at a level never tried before. It can provide new insights into the nature of genes and proteins thought to be associated with cancer, and the application of evolving molecular techniques to the study of cancer has also provided markers that have led to new advances in tumor diagnosis, prognosis, and treatment which have proven to be immensely helpful in advancing precision oncology [6].

Cancer development generally is a multi-step process triggered by mutations leading to the activation of specific oncogenic pathways with the concurrent inactivation of tumor suppressor genes that act as sentinels to control unwanted cell growth, proliferation, tumor microenvironment (TME) remodeling, epithelial to mesenchymal transition (EMT), etc. Scientists have been trying to analyze the totality of cancer-causing gene mutations regarded as the “mutational landscape’, of different types of cancer types and to target them effectively for cancer cure [7,8]. Most of these biochemical processes are conserved in model organisms such as the free-living transparent nematode Caenorhabditis elegans and the fruit fly Drosophila melanogaster alongsidemice and other large animal models, and are widely used due to the ease of their genetic manipulation to study the complex biology of cancer. The somatic cell mutations, called somatic structural variants (SVs), have been shown to account for more than half of all cancer- causing mutations. These are the variants or mutations different from the hereditary or germline variants that have

passed from parents to offspring and become incorporated into the DNA of every cell in the body [9]. The somatic SVs can be noticed in the transformed cells and in their daughter cells that may continue to grow because of errors in DNA copying and their repair mechanisms during cell division thereby altering the genomic structure which will become more numerous with time. Although somatic SVs play a crucial role in cancer development, relatively little has been known about their mode of action in cancer development. Methods to detect and identify the functional effects of these SVs are sure to enable researchers to understand the molecular consequences of individual somatic mutations in cancer. The findings related to the mutation-specific alterations could be used to develop therapies that target the mutated cells, opening new possibilities in cancer therapy. Furthermore, most of the human genome consists of noncoding regions, and studies on variations in the noncoding regions of the cancer cells reveal additional mechanisms underlying cancer progression. For example, changes in noncoding regions such as point mutations and complex genomic rearrangements can disrupt or create transcription factor-binding sites or even affect non-coding RNA loci leaving options for unwanted changes in the gene expression pattern of the cell. Cancer whole-genome sequencing (WGS) remains the most comprehensive method for identifying variants in non-coding regions as targeted approaches like exome sequencing (WES) may miss certain variants residing outside the coding regions. Pieces of evidence suggest oncogenesis typically involves interplay between germline and somatic variants and different modes of action of non-coding variants could further potentiate these developments. Thus, a systematic approach to unraveling the roles of the non-coding genome in cancer progression should help improve cancer diagnosis and therapy [10].

2. Initiatives to identify tumor cell reprogramming and targeted cancer therapy

The landmark Cancer Genomics Program launched in 2006 has contributed immensely to the awareness of the importance of cancer genomics in our understanding of cancer over the past decade and has begun to change the way the disease is treated in clinic. A large number of mutations contribute to cancer and predicting the effects of mutations using in silico tools has become a frequently used approach, but the use of next-generation sequencing-based approaches in clinical diagnosis has also led to a considerable increase in data and a vast number of variants of uncertain significance that require further analysis and validation to achieve the development goals. These data cannot be analyzed simply by using the tools and techniques traditionally available to better understand the origin and evolution of cancer and therefore to achieve this goal, a cancer reference framework through modeling of genome sequencing data has been proposed for the systematic identification of representative driver networks to predict cancer progression and associated clinical phenotypes. It is based on the consideration that possible observable combinations of these mutations must converge on a few common signaling pathways and networks responsible for tumor growth and cancer progression. In this way, it aims to analyze data to explain how different genetic mutations in different patients have the same downstream effects on the protein machinery, ultimately leading to the analysis of the characteristic pathway of cancer progression. In this regard, The Cancer Genome Atlas Program (TCGA) is the landmark cancer genomics program initiated by the NIH, and has contributed immensely to realizing the importance of genomics in cancer research [11,12]. It has molecularly characterized over 20,000 primary cancer and successfully matched normal samples spanning 33 cancer types. The synchronized vision of oncogenic processes based on PanCancer Atlas analyzes attempts to elucidate the possible consequences of genome alterations on the different signaling pathways involved in human cancers, also reflecting on their influence on the tumor microenvironment and immune cells, to provide new information about development of new forms of targeted drugs and immunotherapies. Considering the genes and pathways affecting different cancer types and individual tumors vary considerably, a complete understanding of these alterations becomes essential to identify vulnerabilities and discover precise therapeutic solutions. A comprehensive analysis of tumors based on their genomic studies must reveal the alterations in signaling pathways indicating patterns of vulnerabilities and the means to identify prospective targets for the development of personalized treatments and new combination therapies. The TCGA Research Network has profiled and analyzed a large number of

human tumors to discover molecular aberrations at the DNA, RNA, protein, and epigenetic levels and thereby provided reliable diagnostic and prognostic biomarkers for different cancer types since then [13,14]. Further, the Cancer Cell Map Initiative (CCMI), launched in 2015 by researchers at the University of California, San Francisco and the University of California, San Diego, allowed researchers to determine how hundreds of genetic mutations involved in a few types of cancer affect the activity of certain crucial proteins which ultimately lead to the manifestation of cancer [15]. As there is a large amount of sequence data from many different cancer types, efforts are being made to extract mechanistic insights from the available information, requiring an integrated computational and experimental strategy that will help place these alterations in the higher order contexts of signaling mechanisms in cancer cells. This is the defined goal of the CCMI and has the potential to create a resource that can be used for cancer genome interpretation, enabling the identification of key complexes and pathways to be studied more mechanistically to better understand the biology underlying different cancer types and conditions [16]. Additionally, the Cancer Dependency Map (DepMap) initiative at the Broad Institute of MIT and Harvard, an academic-industry partnership program officially announced in 2019, is devoted to cancer research aimed at accelerating precision cancer medicine by creating a comprehensive map of tumor vulnerabilities and identifying key cancer biomarkers. This program focuses on screening thousands of cancer cell lines using RNA interference (RNAi) and CRISPR-Cas9 gene editing strategies to identify genes whose expression may be affected and found to be essential for cell transformation. CRISPR-Cas9 gene editing is an efficient method of modifying the genome of almost any cell type. CRISPR editing and screening have emerged as powerful tools for studying nearly all aspects of cellular behaviors which have greatly influenced our understanding of cancer biology and continue to contribute to new discoveries [17,18]. A related project called Cancer Cell Line Encyclopedia (CCLE), started as a collaboration between the Broad Institute and the Novartis Institute for Biomedical Research in 2008, appears well suited for large-scale genetic characterization of thousands of cancer cell lines in order to link characteristics genetic alterations with distinct pharmacological vulnerabilities, and to translate integrative genomics into patients stratification for personalized cancer treatments. By accessing critical genomic data via CCLE, such as gene mutations, chromosome copy number, gene expression and methylation profiles, scientists can now predict new synthetic lethality and identify new molecular markers for selectively targeting cells with specific genetic changes. Thus, the initiative provides a rigorous foundation on which to study genetic variants and candidate targets, identify new marker-based cancer diagnostics, and design anticancer agents for critical cancers therapies p[19,20]. The challenge of identifying relevant genes and signaling molecules for different types of cancer using cutting-edge technologies will remain an essential part of cancer research and precision oncology and will most likely help vulnerable individuals receive effective treatment for cancer.

3. Single-cell Technology Reveals Tumor Heterogeneity Critical to Cancer Therapy

Tumor heterogeneity is a hallmark property of cancer development and broadly refersto the differences between tumors of the same type in different patients, the differences betweena primary and a secondary tumor, and the differences in genomic and phenotypic profiles displayed by cells within a single tumor. Heterogeneity within a single tumor, referred to as genetic intratumoral heterogeneity (ITH), has been documented across most cancers as an outcome of genome instability and clonal evolution [21,22]. Tumor heterogeneity appears to be a critical phenomenon in the history of individual cancers, as its translational significance may reflect on tumor progression, disease recurrence, treatment response, and resistance [23]. Recent investigations on drug resistance and tumor heterogeneity have confirmed the clonal organization of tumors as the underlying basis for drug resistance, thus indicating the need to fully understand the structure and dynamics of ITH to develop advanced treatment strategies for cancer [24,25]. More precisely the cellular composition of a tumor is known, the underlying mechanism of disease progression is understood, and/or molecules and pathways involved in the process are identified, and more specific therapeutic strategies could be devised to get the desiredresult. It is the stated goal of precision oncology

and the emergence of single-cell technologies for biological analysis has become the crucial tool in this regard as they can carry out accurate single-cell measurements to provide a clear picture of tumor heterogeneity and reveal how structural changes in chromosomes can lead to the complex biological processes involved with carcinogenesis [26,27]. The rapid progress in the development of NGS in recent years has provided many valuable insights into cancer genomics, and NGS-based technologies for genomics, transcriptomics, and epigenomics have enabled laboratories to carry out related single-cell measurements efficiently. Single-cell genomics now facilitates the simultaneous measurement of thousands of genes in thousands of 'single' cells from a single specimen, allowing researchers to compare genomes of individual cells to determine the mutational profile of the affected cells to better understand the molecular consequences of different variants presentin the tumor. The single-cell template strand sequencing (Strand-seq), a special single-cell sequencing technology now enables independent and efficient analysis of the two parental DNA strands resolving homologous chromosomes similar in shape and structure but not identical within single cells which is crucial to identifying somatic SVs, understanding genomic rearrangements and unmask tissue heterogeneity. Moreover, single-cell sequencing can also be combined with CRISPR knockout screening that exploits the efficiency and flexibility of CRISPR–Cas9 genome editing to enable large-scale studies regarding how genetic modification can affect cell behavior or gain insights into a specific physiological condition required to fully understand the underlying cellular events [28]. Combining the CRISPR-Cas system with single-cell techniques for studying gene functions with the concurrent use of single-cell resolution techniques, such as flow cytometry, microfluidics, manual cell picking, or micromanipulation, can be exploited in cancer research in many ways, including identifying novel drug targets, studying unknown mechanisms of action of drugs and designing treatment regimen [29]. The importance of epigenetic reprogramming in cancer is well understood, as evidenced by the fact that chromatin regulators are often mutated in the affected cells and the widespread epigenetic, changes throughout cancer genomes can be identified and linked to the activities of different known oncogenes and tumor suppressor genes. Abnormal epigenetic changes are usually influenced by aging, viruses, and dietary and environmental factors that frequently contribute to cancer development. The interrelationship between genetic and epigenetic changes needs to be further examined for the discovery of screening markers to optimize pathways of diagnosis and prognosis and to develop strategies for individualized cancer treatment [30]. For example, DNA methylation is known to be associated with cell differentiation, aging, and diseases including cancer. A considerable amount of understanding exists regarding tissue- specific DNA methylation patterns, but it would reveal much less information about person- specific DNA methylation causing cancer. Thus, the premise of single-cell epigenome profiling holds great possibilities for deciphering the cellular states and characterizing tumor heterogeneity with an option for therapeutic interventions to pin specific mutations having profound effects on epigenetic pathways. The inclusion of epigenetics in clinical practice would require identifying epigenetic signatures that mediate distinct phenotypical changes of clinical relevance, such as mesenchymal transition, stems, dormancy, and quiescence or therapy resistance.

Single-cell sequencing technologies have largely been successful in leading scientists to understand the cell types and features associated with the tumor yet, the spatial context of this development is essential to better understand how cells organize and communicate across the tissue to fully unlock the repertoire of tumor heterogeneity. It requires a clear understanding of which cells are present, where they are situated in tissue, their biomarker expression patterns, and how they organize and interact to influence the tissue microenvironment. This is an essential part of spatial biology and adds another dimension to single-cell analysis to unmask tumor heterogeneity [31,32]. Spatial biology simply tries to combine whole-slide imaging (WSI), commonly referred to as 'virtual microscopy', at single-cell resolution to visualize and quantitate biomarker expression and reveal how cells interact and organize across the entire tissue landscape. This technique can support research for early biomarker discovery to late-stage translational research and therapy development. The latest development in this direction is spatial transcriptomics which has enabled researchers to visualize and quantify RNA down to the subcellular level and simultaneously compare gene expression in situ. It is a groundbreaking molecular profiling method that exploits multi-omics technologies allowing researchers to measure all the gene activity in a tissue sample and assay the

genetic information of single cells within their native tissue environment [33,134]. The growing ability to demonstrate the role and function of distinct cell types present in the tissue has paved the way for a new understanding of the tissue-specific cellular pathways and interactions that lead to cancer manifestation. Thus, molecular analysis of cancer cells based on single-cell technologies aims to present an accurate picture of the most recent developments regarding changes in genes and proteins responsible for alterations in cellular processes, enabling a better understanding of prognosis and pathways of development of cancer. New advances in multi-omics techniques powered by AI h now enable researchers to integrate genomic, transcriptomic, epigenomic, and other related data to gain the most accurate information on the activity state of individual genes and proteins to reveal the novel cancer drivers and genetic vulnerabilities for prevention and cure [35,36]. The emerging field of single-cell technology thus provides an unprecedented insight into the complex genetic and epigenetic heterogeneity within individual tumors for advanced precision oncology-based treatment and is likely to streamline future research directions [37,38].

4. Signaling Pathway Deregulation and Targeted Drug Therapy of Cancer

The root cause underlying cancer progression is genetic and epigenetic alterations in the affected cells leading them to grow and proliferate uncontrollably, although the progression of cancer remains dependent on a complex interplay between the tumor cells and surrounding non- neoplastic stromal cells and ECM present in the tumor microenvironment [39,40]. Cell signaling network as the foremost system of communication between cells and the surroundings that involve a variety of chemical and mechanical signals to regulate different signaling pathways comes into consideration here as all the essentials of cellular behaviors like cell growth and proliferation, cell polarity, cell metabolism, differentiation, survival, and migration can be seen guided by the components of these pathways working in a collaborative manner in the cell. The signaling pathways together maintain an internal circuitry inside cells guided by external stimuli enabling them to sense whether their state of attachment to ECM and other cells is appropriate and if different growth factors, hormones, and cytokines guide them to proliferate or differentiate, move, or stay put for now, or to commit to cell death by apoptosis or autophagy 41]. Almost all gene modifications can be related to one or more of these signaling pathways that are deregulated in the affected cells to acquire hallmark properties of cancer. Cancer cell signaling displays altered expressions of the components of the signaling network that include many secreted protein receptors, growth factors, protein kinases, phosphatases, different cytoplasmic proteins, and transcription factors leading individual cells to respond to the changes with appropriate physiological behaviors. Cell division is mainly regulated by a group of extracellular growth factors that signal resting cells to divide by exploiting the intrinsic regulatory process of the cell. Cytokines ordinarily signal the immune cells to mount coordinated attacks on invading bacteria, and viruses and play essential roles in cancer prevention. Thus, signals propagated by growth factors and cytokines can simply tell individual cells to divide or not under particular conditions whose alterations could lead to the pathophysiology of cancer. The earliest information regarding the relationship between cancer and growth factors camefrom the observation that normal cells in culture often required serum for proliferation, while cancer cells had a much less requirement for serum. The serum is known for providing growth factors among other ingredients needed for the overall regulation of the cell cycle. The other hints came from gene mutations found in cancer cells observed to cause changes in cell behaviors very similar to those related to the activities of growth factors and their receptors. Theoncogenic mutations disrupt the cellular circuits that control cell adhesion and signaling, enabling cells that carry them to over-proliferate and invade the other tissues in an uncontrolled fashion. Many of these mutations have been directly linked to the growth factors and their receptor proteins involved with tumor growth, angiogenesis, invasion, and metastases [42,43].

A critically important finding of cell signaling is that one kind of cell membrane receptor can mediate many different downstream intracellular pathways and one pathway can also be activated by several of the upstream surface receptors revealing common signaling components in multiple signaling pathways. For example, the RTKs, like EGFR, FGFR, IGFR, VEGFR, PDGFR, and the GPCRs, can all activate the

MAPK cascade while the widely studied RTKs such as EGFR/HER family receptor can initiate different signaling pathways including mitogen- activated protein kinase (MAPK), phosphoinositide-3-kinase (PI3K)/AKT, and mammalian target of rapamycin (mTOR) pathways involved in regulations of cell growth, proliferation, differentiation, and survival. This feature of the signaling process evidently presents the option for crosstalk between components of different signaling pathways at different stages of the cellular process. A molecule participating in crosstalk can affect the activation of alternate signaling pathways, and receptors can also have an altered ability to bind to the ligands which can swiftly lead to cancer manifestation. As generally observed, most of the cell signaling pathways contribute to the development of cancer and seldom does a cancer type arise from the deregulation of a single pathway. Breast cancer can arise due to elevated expression of the estrogen receptor (ER), EGFR/HER, or IGFR, but in many cases, molecules and intermediates of multiple signaling pathways can be interactively involved in the process. In this way, the many signaling molecules affecting cancer cells together could beconsidered to create elaborate integrated circuits within the cell, derived from the usual signaling circuits that operate in normal cells. The transformed intracellular circuit could be divided into distinct subcircuits specialized in specific cellular activities to promote hallmark features of cancer [44] (Fig. 1).

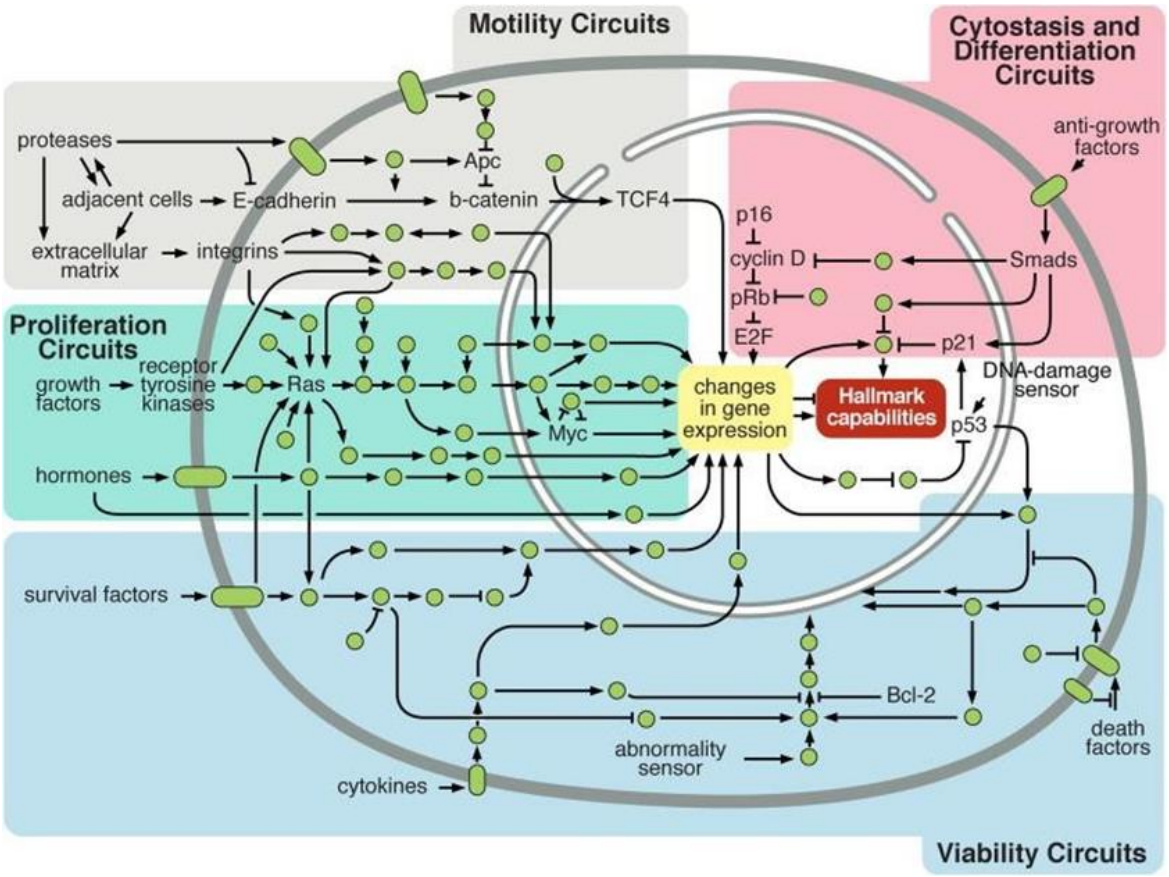

Figure 1. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell.
An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate sub-circuits, depicted here in differently colored fields, are specialized to orchestrate the various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such sub-circuits. In addition, because each cancer cell is exposed to a complex mixture of signals from its microenvironment, each of these sub-circuits is connected with signals originating from other cells in the tumor microenvironment. (Hanahan and Wienberg [44]. With permission from Elsevier)

Signal transduction leading to tumor growth, cancer cell migration, metastasis, and drug resistance are often complex processes, as cancer cells typically develop abnormalities in multiple signaling pathways or rely on crosstalk between different pathways and some redundant pathways for maintenance of growth and survival. As cancer progression involves alterations in signaling pathways due to mutations in the relevant genes, it is satisfying and mechanistically well-founded that a therapeutic intervention taking into account this biology of the affected cells can pave the way for a very effective cancer treatment [45,46]. Further, it has been established in clinical practice that targeting a single intermediateor pathway brings considerable results toward recovery, possibly because it impedes the synergistic signaling process of disease progression. Yet, the constitutive activation of a molecular event that contributes to cancer development can be sustained by different mechanisms, and strategies to inhibit multiple targets or redundant pathways simultaneously with molecular-targeted agents could prove to be an even more effective way to treat cancer and overcome resistance in cancer therapy [47]. Targeted drug therapy is the form of cancer therapeutics that targets specific genes and proteins of cancer cell reprogramming, the signaling molecules, and others in the tumor microenvironment that contribute to cancer development. This contrast with the single-target approach employed in chemotherapy to primarily target and kill actively dividing cancer cells with serious side effects and so the emergence of targeted drug therapy can be seen as a natural outcome of decades of studies on molecular reprogramming of affected cells in different cancers. Some noticeable breakthroughs have come in certain cancers as a renewed understanding of the signaling pathways underlying cancer development has led to the development of specific targeted drugs that have really revolutionized the treatment of cancer. This form of cancer therapy can be thoroughly optimized by means of precision oncology that enables taking advantage of genomic profiling of patient samples for insights into the mutational changes underlying pathway alterations responsible for cancer initiation and progression [48]. Precision oncology-based treatment strategies pledge to diagnose and prognosis the disease using specific molecular-level information about a patient's tumor to treat the ill with desired results. Inthis way, it qualifies to be a theranostic approach to cancer treatment satisfactorily. The term, theranostics literally means a combination of diagnosis and therapeutics and refers to the pairing of diagnostic methods such as the proteogenomics approach to biomarker discovery, with appropriate therapeutic interventions for effective management of the disease. Theranostics focuses on patient-centered care and thus provides a transition from conventional to personalized medicine for targeted, efficient and safe pharmacotherapy relevantly applicable in precision oncology [49,50].

The anticancer drugs employed in targeted therapy are mainly designed to target selected molecules directly involved with cancer cell signaling or those in the tumor microenvironment essentially required for tumor growth and cancer manifestation [51]. They are broadly classified as monoclonal antibodies (mAbs) and small-molecule drugs. The small molecule drugs are designed to directly approach the cell membrane and interact with targets inside the cell and usually inhibit the enzymatic activity of target proteins such as the proteasome complex, cyclin- dependent kinases and a variety of signaling proteins. Kinase family proteins such as tyrosine kinases, Rho kinase, Bruton tyrosine kinase, ABL kinases, NAK kinases, etc. play an essential role in modulating signaling pathways associated with cancer progression and therefore constitute a valuable source of biological targets against cancers (Table 1).

A type of targeted therapy, called tumor-agnostic therapy uses drugs and other substances to target cancer-specific genetic changes or markers to treat the problem without requiring focusing on the cancer type or where the disease may have started in the body. Therapeutic targeting of DNA damage response (DDR) signaling is another emerging field of targeted cancer therapy that exploits the options of targeting cancer cells with exceeding deficiencies in homologous recombination (HR) signaling which includes BRCA-mutated cancers. Poly(ADP-ribose) polymerase (PARP) and Inhibitors of poly(ADP-ribose)glycohydrolase (PARG) are the most important DNA repair enzymes that work synergistically in many different DDR pathways, including base excision repair, non- homologous end joining, nucleotide excision repair, homologous recombination (HR), maintenance of replication fork stability and nucleosome remodeling. These enzymes are essentially involved in the process of single-strand break (SSB) repair whose failure leads to the conversion of SSB into double-strand breaks (DSB) requiring repair by HR to

prevent cell death. Such lethal genetic interactions, known as synthetic lethality, can be exploited to develop anticancer therapeutics and the enzymes of DDR signaling fit the needs satisfactorily. Overexpression of these proteins has been witnessed in different cancer types such as pancreatic, prostate, breast, ovarian, and oral cancers, providing scope for inhibiting PARP activity as an effective therapeutic strategy. PARP and PARG inhibitors have shown improved results in different forms of tumors, and are under investigation for being used in combination therapy safely. [52,53].

The therapeutic mAbs are modified monoclonal antibodies that target antigens found on the cancer cells or cytotoxic T-lymphocytes in targeted cancer therapy. mAbs are important in cancer treatment as they may be exploited for potentiating the natural immune system by successfully mutualizing changes in immunogenicity of the affected cells during oncogenesis. The mAbs may be designed to coat the cancer cells to be opsonized and destroyed by the immune cell, block the activity of different cancer-specific antigens called neoantigens, generated by cancer cells, or inhibit the activities of immune checkpoint proteins that promote immune evasion in cancer development [54,55]. Several immune checkpoint proteins are expressed by immune cells, such as T cells, and cancer cells capable of binding with other partner proteins to help cancer cells escape immune responses. Their activation limits vital immune cell activities like T-cell infiltration and other effector cell functions resulting in tumor formation. CTLA-4 is a checkpoint protein present on the T-cell surface that binds to another protein called B7, preventing T cells from killing other target cells, including cancer cells. Certain mAbs, also called anti-CTLA4 monoclonal antibodies, are used to block CTLA-4 and are widely used as immune checkpoint inhibitors in a variety of human cancers. Different forms of monoclonal antibody-based therapy have proven to be efficacious in cancer treatment and are becoming increasingly important tools in targeted cancer therapy [56,57]. Importantly, cancer cells express a number of protein antigens that can be recognized by cytotoxic T lymphocyte (CTL) T cells, thus providing means for CTL-mediated cancer therapy. Targeting transformed cells by CTL may be crucial to the prevention of both hematological and solid tumors and its roles are being explored in cancer immunotherapy. T-cell transfer therapy, also called adoptive immunotherapy or immune cell therapy is a new form of cancer treatment designed to exploit enhanced anti-tumor immune response of the tumor antigen-specific CTL found in the tumors, and has been tried against neoantigen-possessing cells effectively in recent times. Two types of T-cell transfer therapy, tumor-infiltrating lymphocytes or TIL therapy and CAR T-cell therapy are in use, and both involve harvesting autologous T cells infiltrated into the tumor, growing largenumbers of these cells in vitro, and administering to the patient for desired results. CAR T- cell therapy is similar to TIL therapy except that the T cells are designed to express a type of protein known as CAR (CAR for chimeric antigen receptor) to target specific antigens expressed in cancer cells in the body. Although CAR T cells have significantly improved the landscape for hematological malignancies, it has shown limited results in solid tumors as the solid tumors present certain obvious barriers to adoptive T-cell transfer and localization, but a variety of approaches are being deliberated to overcome these barriers to increase its specificity, efficacy, and safety in the treatment of different malignancies. The development of CAR T cell therapy forsolid tumors has been impaired also because most target antigens are common with normal cells.Research is being directed to develop a ‘toolbox’ of novel chimeric antigen receptors (CARs) that could be programmed to use logic to discriminate between normal and cancerous cells to prevent toxicity. This development could help to overcome some of the barriers to the application of CAR-T cells against solid tumors [58]. Furthermore, therapeutic cancer vaccines, such as the dendritic cell (DC) vaccine, peptide vaccine, and RNA-based neoantigen vaccines have been developed for inducing CTLs against the antigens in cancer patients and have shown encouraging results. These vaccines can be designed to induce the production of biomolecules capable of targeting the shared antigens expressed by cancer cells through appropriate immune response and, are being investigated for their efficacy as neoantigen-targeted individualized cancer vaccines. Dendritic cells (DCs) are specialized Antigen-presenting cells (APCs) known for their ability to present antigens to T cells, and this property of DCs has been exploited for their application in therapeutic cancer vaccines which have been shown to induce protective anti-tumor activities [59]. Besides that, the transposable elements (REs) usually present in the tumor microenvironment are of potential therapeutic importance to create a pan-cancer vaccine that can aid in the prevention of a range of cancers. There is an

enumerable number of regions with TEs involved with the expression of proteins in the cancer cell. Many of these are shared across tumors of the same type and could provide means for destruction by the immune system. The goal of immunotherapy remains to activate the individual's own immune system against the evolving tumors to successfully target the transformed cells with high selectivity, low toxicity, and appropriate results. Thus, immunotherapy remains the frontline area of targeted cancer therapies, and precision oncology will be focused on immunotherapy accordingly (Fig. 2).

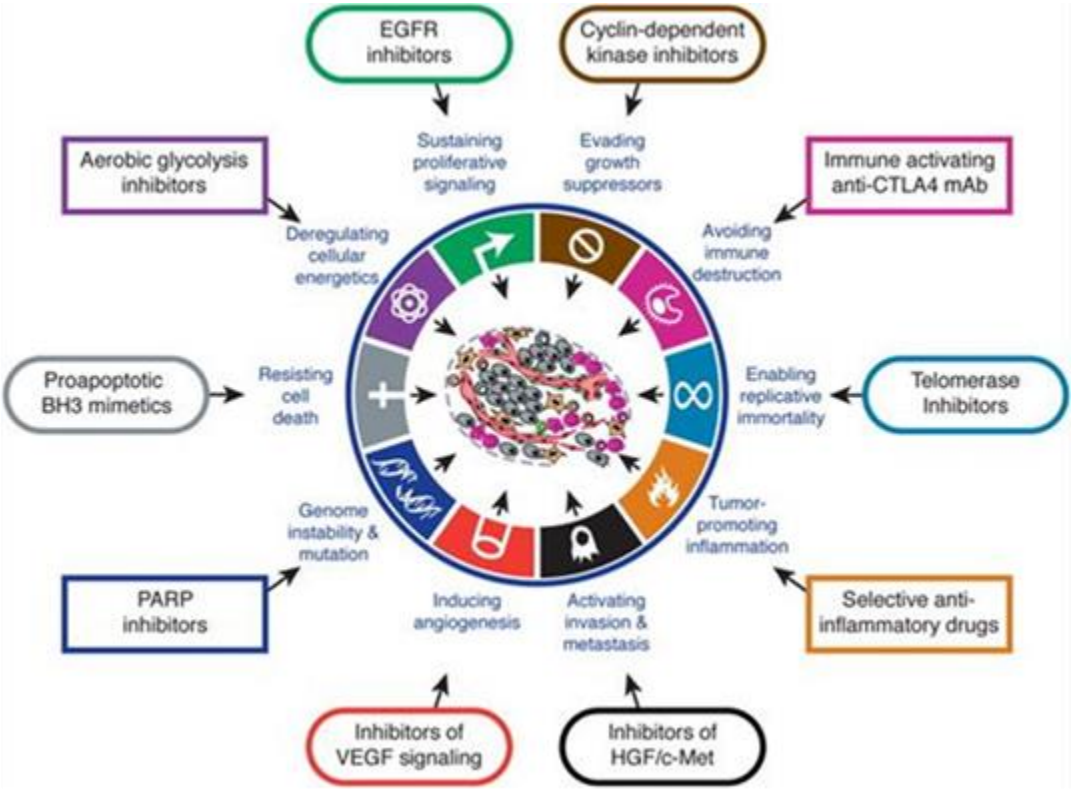

Figure 2. Therapeutic Targeting of the Hallmarks of Cancer
Therapeutic agents that can mitigate the acquired capabilities necessary for tumor growth and cancer progression are being developed for clinical use in treating different cancer types. These drugs are being developed in clinical trials to target each of the emerging neoplastic characteristics and the enabling hallmarks capabilities towards effective cancer therapy. The listed drugs are just illustrative examples; there is a deep pipeline of investigational drugs in development to target different signaling molecules that lead to the hallmark capabilities. (Hanahan and Wienberg [44]. With permission from Elsevier)

A major concern in cancer therapeutics is the proper drug delivery to the affected cells and tissue for the desired outcomes. Conventional chemotherapeutics may possess some serious side effects due to nonspecific targeting or inability to enter the core of the tumors, resulting in impaired treatment and a low survival rate. Researchers have been trying to address the issue with more specific methods of drug delivery including the use of nanotechnology in cancer therapeutics. Nanoparticles (NP)-based systems can be programmed to recognize cancerous cells for selective and accurate drug delivery with increased drug localization, cellular uptake, and bioavailability, avoiding encounters with healthy cells. The newly developed quantum dots (QDs) are the class of heterogeneous fluorescent nanoparticle, nanoscale materials with sizes ranging from 1 to 10 nm, with unique optical properties and optimal surface chemical properties to link with targets such as antibodies, peptides, and other small molecule drugs. Named so as the photoluminescent nanostructures can have fully quantized energy states with superior fluorescence characteristics, they are thought to be more specific and effective methods with wide applications in the

diagnostics and molecular targeting of the transformed cells. The NP-based drug delivery system, in general, displays better pharmacokinetic and pharmacodynamic profiles including efficient targeting of cancer cells and reduction in side effects, they are sure to serve the needs of precision oncology-based therapy satisfactorily [60,61]. Further, antibody-drug conjugates (ADC) are a fast-expanding therapeutic strategy designed to selectively deliver drugs to cancer cells. ADCs are monoclonal antibodies linked with small molecule cytotoxic drugs through a chemical linker capable of approaching the cancer cells and attaching to the specific tumor antigens on the cell surface for direct drug delivery sparing healthy cells in the surroundings. They are designed to exploit the featuresof antigen-antibody specificity for efficient drug delivery and are considered to be the magic bullets in targeted cancer therapy [62, 63]. In this way, precision oncology seems to be the best fit for strategizing effective means of targeted drug therapy by exploiting the genomic peculiarities of individuals or a cohort of patients for effective personalized cancer treatment. It will remain dedicated to studying the genetic profile of cancer cells to gain a thorough understanding of the alterations in key signaling pathways and related molecular events during cancer progression, therapy resistance, and recurrence to help improve targeted cancer therapy (Suppl. 1 & 2).

Recent advances in cancer genomics and single-cell technologies have certainly made targeted therapy the accepted form of cancer treatment, and yet a huge amount of investment willbe needed for future research, drug discovery, and diagnostics to fully unlock its potential and for their application in the management of cancer. Let us not forget that the socioeconomic burden of cancer remains high as the treatment options for most common cancers have been limited so far and is an indication for a renewed approach to expedite drug development to bring effective anticancer agents from bench to bedside in a cost-effective manner. The lack of understanding of the genetic heterogeneity of individual cancers has traditionally been limiting the search for efficacious agents for cancer treatment and missing a wide range of possibly suitable agents from other disease areas. The use of molecular characterization of different cancer types through cancer genomics can help resolve drug-related issues to a reasonable extentby repurposing the use of certain existing drugs as anticancer agents for a wide range of applications, and it will remain at the forefront of precision oncology [64,65]. Moreover, the move from tissue-based cancer-specific treatments to genome-based targeted treatments entails the reuse of anticancer drugs prescribed for one type of cancer to treat other cancer types as well.It is envisaged that, with the ever-greater understanding of cell signaling mechanisms and geneticalterations in carcinogenesis, considerable progress in cancer treatment will be realized in the near future. Considering that academia, industries, and civil society will be working in tandem tocater to the contemporary needs of the system, it is hoped that a wide range of people with cancer will benefit from this new development in cancer research in the future to benefit the system as a whole [66,67].

5. Conclusion

Genome-based cancer therapies propose developing treatments that target the specific molecular features of an individual's tumor instead of targeting common features of cancer to find a cure. Genomic databases produced as part of different cancer initiatives now provide a large amount of information on mutation profiles with significant genetic associations with diseases to facilitate targeted molecular therapies. Furthermore, an in-depth understanding of the genetic composition and heterogeneity of an individual's tumor is now becoming possible using single-cell technologies. This should help individuals successfully get the right treatment at the right time without requiring them to undergo more generalized treatment with excessive side effects. Importantly, drug resistance has traditionally been a serious problem in cancer treatment, but the emergence of targeted drug therapy based on precision oncology can greatly improve outcomes. Advances in genetic detection methods, liquid biopsy, and single-cell sequencing technology could facilitate deciphering the molecular mechanism of tumor drug resistance to help develop updated and effective anticancer agents in response to drug resistance, All of these developments in fact reflect natural outcomes of cancer genome research, the level of support coming from multi-omics platforms is very encouraging and is on path to satisfactorily achieve the intended goal of the cancer initiatives. The growing

success of this form of treatment is sure to further strengthen our belief in the possibility of effective cancer treatment over time.

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References:

1. Loftus LV, Amend SR, Pienta KJ. Interplay between Cell Death and Cell Proliferation Reveals New Strategies for Cancer Therapy. International Journal of Molecular Sciences. 2022; 23(9):4723. https://doi.org/10.3390/ijms23094723

2. Takeshima, H., Ushijima, T. Accumulation of genetic and epigenetic alterations in normal cells and cancer risk. npj Precis. Onc. 3, 7 (2019). https://doi.org/10.1038/s41698-019-0079-

3. You JS, Jones PA. Cancer genetics and epigenetics: two sides of the same coin? Cancer Cell. 2012 Jul 10;22(1):9-20. doi: 10.1016/j.ccr.2012.06.008. PMID: 22789535; PMCID: PMC3396881.

4. Advani D, Sharma S, Kumari S, Ambasta RK, Kumar P. Precision Oncology, Signaling, and Anticancer Agents in Cancer Therapeutics. Anticancer Agents Med Chem. 2022;22(3):433-468. doi: 10.2174/1871520621666210308101029. PMID: 33687887.

5. Tsimberidou AM, Fountzilas E, Nikanjam M, Kurzrock R. Review of precision cancer medicine: Evolution of the treatment paradigm. Cancer Treat Rev. 2020 Jun;86:102019. doi: 10.1016/j.ctrv.2020.102019. Epub 2020 Mar 31. PMID: 32251926; PMCID: PMC7272286.

6. van Dijk EL, Auger H, Jaszczyszyn Y, Thermes C. Ten years of next-generation sequencing technology. Trends Genet. 2014 Sep;30(9):418-26. doi: 10.1016/j.tig.2014.07.001. Epub 2014 Aug 6. PMID: 25108476.

7. Feitelson MA, Arzumanyan A, Kulathinal RJ, Blain SW, Holcombe RF, Mahajna J, Marino M, Martinez-Chantar ML, Nawroth R, Sanchez-Garcia I, Sharma D, Saxena NK, Singh N, Vlachostergios PJ, Guo S, Honoki K, Fujii H, Georgakilas AG, Bilsland A, Amedei A, Niccolai E, Amin A, Ashraf SS, Boosani CS, Guha G, Ciriolo MR, Aquilano K, Chen S, Mohammed SI, Azmi AS, Bhakta D, Halicka D, Keith WN, Nowsheen S. Sustained proliferation in cancer: Mechanisms and novel therapeutic targets. Semin Cancer Biol. 2015 Dec;35 Suppl(Suppl):S25-S54. doi: 10.1016/j.semcancer.2015.02.006. Epub 2015 Apr 17. PMID: 25892662; PMCID: PMC4898971.

.

8. Sivaraman K, Muthukumar K, Shanthi C. A potential bioactive peptide candidate for biomaterial and tissue engineering applications. Life Sci. 2019 Jun 1;226:140-148. doi: 10.1016/j.lfs.2019.04.010. Epub 2019 Apr 12. PMID: 30986446.

9. Geeleher P, Huang RS. Exploring the Link between the Germline and Somatic Genome in Cancer. Cancer Discov. 2017 Apr;7(4):354-355. doi: 10.1158/2159-8290.CD-17-0192. PMID: 28373166; PMCID: PMC5404740.

10. Scacheri CA, Scacheri PC. Mutations in the noncoding genome. Curr Opin Pediatr. 2015 Dec;27(6):659-64. doi: 10.1097/MOP.0000000000000283. PMID: 26382709; PMCID: PMC5084913.

11. Cancer Genome Atlas Research Network, Weinstein JN, Collisson EA, Mills GB, Shaw KR, Ozenberger BA, Ellrott K, Shmulevich I, Sander C, Stuart JM. The Cancer Genome Atlas Pan-Cancer analysis project. Nat Genet. 2013 Oct;45(10):1113-20. doi: 10.1038/ng.2764. PMID: 24071849; PMCID: PMC3919969.

12. Tomczak K, Czerwińska P, Wiznerowicz M. The Cancer Genome Atlas (TCGA): an immeasurable source of knowledge. Contemp Oncol (Pozn). 2015;19(1A):A68-77. doi: 10.5114/wo.2014.47136. PMID: 25691825; PMCID: PMC4322527.

13. Tatlow, P., Piccolo, S. A cloud-based workflow to quantify transcript-expression levels in public cancer compendia. Sci Rep 6, 39259 (2016). https://doi.org/10.1038/srep39259

14. Li, Y., Kang, K., Krahn, J.M. et al. A comprehensive genomic pan-cancer classification using The Cancer Genome Atlas gene expression data. BMC Genomics 18, 508 (2017). https://doi.org/10.1186/s12864-017-3906-0

15. Krogan NJ, Lippman S, Agard DA, Ashworth A, Ideker T. The cancer cell map initiative: defining the hallmark networks of cancer. Mol Cell. 2015 May 21;58(4):690-8. doi: 10.1016/j.molcel.2015.05.008. PMID: 26000852; PMCID: PMC5359018.

16. Zheng F, Kelly MR, Ramms DJ, Heintschel ML, Tao K, Tutuncuoglu B, Lee JJ, Ono K, Foussard H, Chen M, Herrington KA, Silva E, Liu SN, Chen J, Churas C, Wilson N, Kratz A, Pillich RT, Patel DN, Park J, Kuenzi B, Yu MK, Licon K, Pratt D, Kreisberg JF, Kim M, Swaney DL, Nan X, Fraley SI, Gutkind

JS, Krogan NJ, Ideker T. Interpretation of cancer mutations using a multiscale map of protein systems. Science. 2021 Oct;374(6563):eabf3067. doi: 10.1126/science.abf3067. Epub 2021 Oct 1. PMID: 34591613; PMCID: PMC9126298.

17. Tsherniak A, Vazquez F, Montgomery PG, Weir BA, Kryukov G, Cowley GS, Gill S, Harrington WF, Pantel S, Krill-Burger JM, Meyers RM, Ali L, Goodale A, Lee Y, Jiang G, Hsiao J, Gerath WFJ, Howell S, Merkel E, Ghandi M, Garraway LA, Root DE, Golub TR, Boehm JS, Hahn WC. Defining a Cancer Dependency Map. Cell. 2017 Jul 27;170(3):564-576.e16. doi: 10.1016/j.cell.2017.06.010. PMID: 28753430; PMCID: PMC5667678.

18. Pacini C, Duncan E, Gonçalves E, Gilbert J, Bhosle S, Horswell S, Karakoc E, Lightfoot H, Curry E, Muyas F, Bouaboula M, Pedamallu CS, Cortes-Ciriano I, Behan FM, Zalmas LP, Barthorpe A, Francies H, Rowley S, Pollard J, Beltrao P, Parts L, Iorio F, Garnett MJ. A comprehensive clinically informed map of dependencies in cancer cells and framework for target prioritization. Cancer Cell. 2024 Feb 12;42(2):301-316.e9. doi: 10.1016/j.ccell.2023.12.016. Epub 2024 Jan 11. PMID: 38215750.

19. Warren A, Chen Y, Jones A, Shibue T, Hahn WC, Boehm JS, Vazquez F, Tsherniak A, McFarland JM. Global computational alignment of tumor and cell line transcriptional profiles. Nat Commun. 2021 Jan 4;12(1):22. doi: 10.1038/s41467-020-20294-x. PMID: 33397959; PMCID: PMC7782593.

20. Ghandi M, Huang FW, Jané-Valbuena J, Kryukov GV, Lo CC, McDonald ER 3rd, Barretina J, Gelfand ET, Bielski CM, Li H, Hu K, Andreev-Drakhlin AY, Kim J, Hess JM, Haas BJ, Aguet F, Weir BA, Rothberg MV, Paolella BR, Lawrence MS, Akbani R, Lu Y, Tiv HL, Gokhale PC, de Weck A, Mansour AA, Oh C, Shih J, Hadi K, Rosen Y, Bistline J, Venkatesan K, Reddy A, Sonkin D, Liu M, Lehar J, Korn JM, Porter DA, Jones MD, Golji J, Caponigro G, Taylor JE, Dunning CM, Creech AL, Warren AC, McFarland JM, Zamanighomi M, Kauffmann A, Stransky N, Imielinski M, Maruvka YE, Cherniack AD, Tsherniak A, Vazquez F, Jaffe JD, Lane AA, Weinstock DM, Johannessen CM, Morrissey MP, Stegmeier F, Schlegel R, Hahn WC, Getz G, Mills GB, Boehm JS, Golub TR, Garraway LA, Sellers WR. Next-generation characterization of the Cancer Cell Line Encyclopedia. Nature. 2019 May;569(7757):503-508. doi: 10.1038/s41586-019-1186-3. Epub 2019 May 8. PMID: 31068700; PMCID: PMC6697103.

21. Junker JP, van Oudenaarden A. Every cell is special: genome-wide studies add a new dimension to single-cell biology. Cell. 2014 Mar 27;157(1):8-11. doi: 10.1016/j.cell.2014.02.010. PMID: 24679522.

22. Reddy RB, Khora SS, Suresh A. Molecular prognosticators in clinically and pathologically distinct cohorts of head and neck squamous cell carcinoma-A meta-analysis approach. PLoS One. 2019 Jul 16;14(7):e0218989. doi: 10.1371/journal.pone.0218989. PMID: 31310629; PMCID: PMC6634788.

23. Saadatpour A, Lai S, Guo G, Yuan GC. Single-Cell Analysis in Cancer Genomics. Trends Genet. 2015 Oct;31(10):576-586. doi: 10.1016/j.tig.2015.07.003. PMID: 26450340; PMCID: PMC5282606.

.24 Lim, ZF., Ma, P.C. Emerging insights of tumor heterogeneity and drug resistance mechanisms in lung cancer targeted therapy. J Hematol Oncol 12, 134 (2019). https://doi.org/10.1186/s13045-019-0818-2

25. Dagogo-Jack, I., Shaw, A. Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol 15, 81–94 (2018). https://doi.org/10.1038/nrclinonc.2017.166

26. Hong, T.H., Park, WY. Single-cell genomics technology: perspectives. Exp Mol Med 52, 1407–1408 (2020). https://doi.org/10.1038/s12276-020-00495-6

27. Hu P, Zhang W, Xin H, Deng G. Single Cell Isolation and Analysis. Front Cell Dev Biol. 2016 Oct 25;4:116. doi: 10.3389/fcell.2016.00116. PMID: 27826548; PMCID: PMC5078503.

28. González-Silva L, Quevedo L, Varela I. Tumor Functional Heterogeneity Unraveled by scRNA-seq Technologies. Trends Cancer. 2020 Jan;6(1):13-19. doi: 10.1016/j.trecan.2019.11.010. Epub 2020 Jan 3. Erratum in: Trends Cancer. 2021 Mar;7(3):265. PMID: 31952776.

29. Di Palma S, Bodenmiller B. Unraveling cell populations in tumors by single-cell mass cytometry. Curr Opin Biotechnol. 2015 Feb;31:122-9. doi: 10.1016/j.copbio.2014.07.004. Epub 2014 Aug 11. PMID: 25123841.

30. Guo M, Peng Y, Gao A, Du C, Herman JG. Epigenetic heterogeneity in cancer. Biomark Res. 2019 Oct 31;7:23. doi: 10.1186/s40364-019-0174-y. PMID: 31695915; PMCID: PMC6824025.

31. Yuan Y. Spatial Heterogeneity in the Tumor Microenvironment. Cold Spring Harb Perspect Med. 2016 Aug 1;6(8):a026583. doi: 10.1101/cshperspect.a026583. PMID: 27481837; PMCID: PMC4968167.

32. Brady, L., Kriner, M., Coleman, I. et al. Inter- and intra-tumor heterogeneity of metastatic prostate cancer determined by digital spatial gene expression profiling. Nat Commun 12, 1426 (2021). https://doi.org/10.1038/s41467-021-21615-4

33. Levy-Jurgenson, A., Tekpli, X., Kristensen, V.N. et al. Spatial transcriptomics inferred from pathology whole-slide images links tumor heterogeneity to survival in breast and lung cancer. Sci Rep 10, 18802 (2020). https://doi.org/10.1038/s41598-020-75708-z

34. Ye F, Huang W, Guo G. Studying hematopoiesis using single-cell technologies. J Hematol Oncol. 2017 Jan 21;10(1):27. doi: 10.1186/s13045-017-0401-7. PMID: 28109325; PMCID: PMC5251333.

35. Zheng, B., Fang, L. Spatially resolved transcriptomics provide a new method for cancer research. J Exp Clin Cancer Res 41, 179 (2022). https://doi.org/10.1186/s13046-022-02385-3

36. Xu, Y., Su, GH., Ma, D. et al. Technological advances in cancer immunity: from immunogenomics

to single-cell analysis and artificial intelligence. Sig Transduct Target Ther 6, 312 (2021). https://doi.org/10.1038/s41392-021-00729-7

37. Dai, Z., Gu, Xy., Xiang, Sy. et al. Research and application of single-cell sequencing in tumor heterogeneity and drug resistance of circulating tumor cells. Biomark Res 8, 60 (2020). https://doi.org/10.1186/s40364-020-00240-1

38. Schmidt F, Efferth T. Tumor Heterogeneity, Single-Cell Sequencing, and Drug Resistance. Pharmaceuticals. 2016; 9(2):33. https://doi.org/10.3390/ph9020033

39. Popova, N.V.; Jücker, M. The Functional Role of Extracellular Matrix Proteins in Cancer. Cancers 2022, 14, 238. https://doi.org/10.3390/cancers14010238

40. Kessler T, Hache H, Wierling C. Integrative analysis of cancer-related signaling pathways. Front Physiol. 2013 Jun 4;4:124. doi: 10.3389/fphys.2013.00124. PMID: 23760067; PMCID: PMC3671203.

41. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000 Jan 7;100(1):57-70. doi: 10.1016/s0092-8674(00)81683-9. PMID: 10647931.

42. Lee EY, Muller WJ. Oncogenes and tumor suppressor genes. Cold Spring Harb Perspect Biol. 2010 Oct;2(10):a003236. doi: 10.1101/cshperspect.a003236. Epub 2010 Aug 18. PMID: 20719876; PMCID: PMC2944361.

43. Orr B, Compton DA. A double-edged sword: how oncogenes and tumor suppressor genes can contribute to chromosomal instability. Front Oncol. 2013 Jun 27;3:164. doi: 10.3389/fonc.2013.00164. PMID: 23825799; PMCID: PMC3695391.

44. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144(5):646-74. doi: 10.1016/j.cell.2011.02.013. PMID: 21376230.

45. Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022 Jan;12(1):31-46. doi: 10.1158/2159-8290.CD-21-1059. PMID: 35022204.

46. Adjei AA, Hidalgo M. Intracellular signal transduction pathway proteins as targets for cancer therapy. J Clin Oncol. 2005 Aug 10;23(23):5386-403. doi: 10.1200/JCO.2005.23.648. Epub 2005 Jun 27. PMID: 15983388.

47. Bayat Mokhtari R, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, Yeger H. Combination therapy in combating cancer. Oncotarget. 2017 Jun 6;8(23):38022-38043. doi: 10.18632/oncotarget.16723. PMID: 28410237; PMCID: PMC5514969.

48. Liotta L, Petricoin E. Molecular profiling of human cancer. Nat Rev Genet. 2000 Oct;1(1):48-56. doi: 10.1038/35049567. PMID: 11262874.

49. Karagiannakos A, Adamaki M, Tsintarakis A, Vojtesek B, Fåhraeus R, Zoumpourlis V, Karakostis K. Targeting Oncogenic Pathways in the Era of Personalized Oncology: A Systemic Analysis Reveals Highly Mutated Signaling Pathways in Cancer Patients and Potential Therapeutic Targets. Cancers (Basel). 2022 Jan 28;14(3):664. doi: 10.3390/cancers14030664. PMID: 35158934; PMCID: PMC8833388.

50. Te Beek ET, Teunissen JJM, Postema JWA, Lafeber A, Ten Broek MRJ. Precision medicine and theranostics using radiopharmaceuticals in oncology. Br J Clin Pharmacol. 2022 Jan;88(1):359-361. doi: 10.1111/bcp.14942. Epub 2021 Jun 22. PMID: 34159632.

51. Zahavi D, Weiner L. Monoclonal Antibodies in Cancer Therapy. Antibodies (Basel). 2020 Jul 20;9(3):34. doi: 10.3390/antib9030034. PMID: 32698317; PMCID: PMC7551545.

52. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017 Mar 17;355(6330):1152-1158. doi: 10.1126/science.aam7344. Epub 2017 Mar 16. PMID: 28302823; PMCID: PMC6175050.

53. Slade D. PARP and PARG inhibitors in cancer treatment. Genes Dev. 2020 Mar 1;34(5- 6):360-394. doi: 10.1101/gad.334516.119. Epub 2020 Feb 6. PMID: 32029455; PMCID: PMC7050487.

54. Rossi JF, Céballos P, Lu ZY. Immune precision medicine for cancer: a novel insight based on the efficiency of immune effector cells. Cancer Commun (Lond). 2019 Jun 14;39(1):34. doi: 10.1186/s40880-019-0379-3. PMID: 31200766; PMCID: PMC6567551.

55. Pfohl, U.; Pflaume, A.; Regenbrecht, M.; Finkler, S.; Graf Adelmann, Q.; Reinhard, C.; Regenbrecht, C.R.A.; Wedeken, L. Precision Oncology Beyond Genomics: The Future Is Here— It Is Just Not Evenly Distributed. Cells 2021, 10, 928. https://doi.org/10.3390/cells10040928

56. Baghban, R., Roshangar, L., Jahanban-Esfahlan, R. et al. Tumor microenvironment complexity and therapeutic implications at a glance. Cell Commun Signal 18, 59 (2020). https://doi.org/10.1186/s12964-020-0530-4

57. Kareva I. A Combination of Immune Checkpoint Inhibition with Metronomic Chemotherapy as a Way of Targeting Therapy-Resistant Cancer Cells. International Journal of Molecular Sciences. 2017; 18(10):2134. https://doi.org/10.3390/ijms18102134

58. Chen G, Bodogai M, Tamehiro N, Shen C, Dou J. Cancer Immunotherapy: Theory and Application.

J Immunol Res. 2018 Jun 21;2018:7502161. doi: 10.1155/2018/7502161. PMID: 30035133; PMCID: PMC6033242.

59. Kiyotani K, Toyoshima Y, Nakamura Y. Personalized immunotherapy in cancer precision medicine. Cancer Biol Med. 2021 Aug 9;18(4):955–65. doi: 10.20892/j.issn.2095- 3941.2021.0032. Epub ahead of print. PMID: 34369137; PMCID: PMC8610159.

60. Zhao, B.; Chen, S.; Hong, Y.; Jia, L.; Zhou, Y.; He, X.; Wang, Y.; Tian, Z.; Yang, Z.; Gao, D. Research Progress of Conjugated Nanomedicine for Cancer Treatment. Pharmaceutics 2022, 14, 1522. https://doi.org/10.3390/pharmaceutics14071522

61. Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, Wu S, Deng Y, Zhang J, Shao A. Nanoparticle-Based Drug Delivery in Cancer Therapy and Its Role in Overcoming Drug Resistance. Front Mol Biosci. 2020 Aug 20;7:193. doi: 10.3389/fmolb.2020.00193. PMID: 32974385; PMCID: PMC7468194.

62. Dupont CA, Riegel K, Pompaiah M, Juhl H, Rajalingam K. Druggable genome and precision medicine in cancer: current challenges. FEBS J. 2021 Nov;288(21):6142-6158. doi: 10.1111/febs.15788. Epub 2021 Mar 19. PMID: 33626231.

63. Pereira M.A. et al. (2020). Cancer Genomics in Precision Oncology: Applications, Challenges, and Prospects. In: Masood, N., Shakil Malik, S. (eds) 'Essentials of Cancer Genomic, Computational Approaches and Precision Medicine. Springer, Singapore. https://doi.org/10.1007/978-981-15-1067-0_21

64. Pantziarka P, Bouche G, André N. "Hard" Drug Repurposing for Precision Oncology: The Missing Link? Front Pharmacol. 2018 Jun 14;9:637. doi: 10.3389/fphar.2018.00637. PMID: 29962954; PMCID: PMC6010551.

65. Oprea TI, Bauman JE, Bologa CG, Buranda T, Chigaev A, Edwards BS, Jarvik JW, Gresham HD, Haynes MK, Hjelle B, Hromas R, Hudson L, Mackenzie DA, Muller CY, Reed JC, Simons PC, Smagley Y, Strouse J, Surviladze Z, Thompson T, Ursu O, Waller A, Wandinger-Ness A, Winter SS, Wu Y, Young SM, Larson RS, Willman C, Sklar LA. Drug Repurposing from an Academic Perspective. Drug Discov Today, Ther Strateg. 2011 Winter;8(3-4):61-69. doi: 10.1016/j.ddstr.2011.10.002. PMID: 22368688; PMCID: PMC3285382.

66. Yip HYK, Papa A. Signaling Pathways in Cancer: Therapeutic Targets, Combinatorial Treatments, and New Developments. Cells. 2021 Mar 16;10(3):659. doi: 10.3390/cells10030659. PMID: 33809714; PMCID: PMC8002322.

67. Dugger SA, Platt A, Goldstein DB. Drug development in the era of precision medicine. Nat Rev Drug Discov. 2018 Mar;17(3):183-196. doi: 10.1038/nrd.2017.226. Epub 2017 Dec 8. PMID: 29217837; PMCID: PMC6287751.

Supplementary File 1: New FDA-Approved Oncology Drugs (2021–2022) (https://ascopost.com/issues/june-3-2022-narratives-special-issue/new-fda-approved-oncology- drugs-2021-2022/#.ZDUJRrQ2lAE.)

Supplementary File 2: Ongoing/Cancer Accelerated Approvals (https://www.fda.gov/drugs/resources-information-approved-drugs/ongoing-cancer- accelerated- approvals)

Table 1. List of Protein Kinase Inhibitors approved by FDA.
(NRY, non-receptor protein-tyrosine kinase; RTK, receptor protein-tyrosine kinase; S/T, protein-serine/threonine kinase; T/Y, dual-specificity protein kinase)

Protein kinase inhibitor	Approval year	Primary targets	Target kinase family	Indications
Abemaciclib	2017	CDK4/6	S/T	Breast cancer
Acalabrutinib	2017	BTK	NRY	Lymphoma
Afatinib	2013	ErbB1/2/4	RTK	Lung cancer
Alectinib	2015	ALK, RET	RTK	Lung cancer
Avapritinib	2020	PDGFR	RTK	Gastrointestinal Cancer
Axitinib	2012	VEGFR1/2/3	RTK	Kidney cancer
Binimetinib	2018	MEK1/2	T/Y	Melanoma
Bosutinib	2012	BCR-Abl	NRY	Leukemia
Brigatinib	2017	ALK	RTK	Lung cancer
Cabozantinib	2012	RET, VEGFR2	RTK	Thyroid. kidney, hepatocellular cancer
Capmatinib hydrochloride	2020	c-MET	RTK	Lung cancer
Ceritinib	2014	ALK	RTK	Lung cancer
Cobimetinib	2015	MEK1/2	T/Y	Melanoma
Crizotinib	2011	ALK, ROS1	RTK	Lung cancer
Dabrafenib	2013	B-Raf	S/T	Melanoma; lung, thyroid Cancer
Dacomitinib	2018	EGFR	RTK	Lung cancer
Dasatinib	2006	BCR-Abl	NRY	Leukemia
Encorafenib	2018	B-Raf	S/T	Melanoma, colorectal cancer
Entrectinib	2019	TRKA/B/C, ROS1	RTK	Lung cancer; solidTumors
Erdafitinib	2019	FGFR1/2/3/4	RTK	Urothelial carcinoma

Erlotinib hydrochloride	2004	EGFR	RTK	Lung, Pancreatic cancer
Everolimus	2009	FKBP12/mTOR	S/T	Breast, kidney cancer, Neuroendocrine tumors
Fedratinib	2019	JAK2	NRY	Myelofibrosis
Futibatinib	2022	FGFR2	RTK	Cholangiocarcinomas
Gefitinib	2003	EGFR	RTK	Lung cancer
Gilteritinib	2018	Flt3	RTK	Leukemia
Ibrutinib	2013	BTK	NRY	Lymphoma
Imatinib mesylate	2001	BCR-Abl	NRY	Leukemia; Gastrointestinal
Infigratinib	2021	FGFRs	RTK	Cholangiocarcinoma
Lapatinib ditosylate	2007	ErbB1/2/HER2	RTK	Breast cancer
Larotrectinib	2018	TRKA/B/C	RTK	Solid tumors
Lenvatinib	2015	VEGFR, RET	RTK	Hepatocellular, endometrial, Thyroid, Kidney cancer
Lorlatinib	2018	ALK	RTK	Lung cancer
Midostaurin	2017	Flt3	RTK	Leukemia
Mobocertinib	2021	EGFR with exon 20 insertions	RTK	Lung cancer
Neratinib	2017	ErbB2/HER2	RTK	Breast cancer
Nilotinib	2007	BCR-Abl	NRY	Leukemia
Osimertinib	2015	EGFR T790M	RTK	Lung cancer
Pacritinib	2022	JAK2	RTK	Myelofibrosis
Palbociclib	2015	CDK4/6	S/T	Breast cancer
Pazopanib hydrochloride	2009	VEGFR1/2/3	RTK	Kidney cancer; soft tissue sarcoma
Pemigatinib	2020	FGFR2	RTK	Cholangiocarcinoma

Pexidartinib	2019	CSF1R	RTK	Tenosynovial giant cell tumor
Pirtobrutinib	2023	BTK	NRY	Lymphoma
Ponatinib hydrochloride	2012	BCR-Abl	NRY	Leukemia
Pralsetinib	2020	RET	RTK	Lung cancer
Quizartinib	2023	FLT3/STK1	RTK	Leukemia
Regorafenib	2012	VEGFR1/2/3	RTK	Gastrointestinal, Colorectal, Hepatocellular cancer
Ribociclib	2017	CDK4/6	S/T	Breast cancer
Ripretinib	2020	KIT/PDGFR	RTK	Gastrointestinal cancer
Ruxolitinib phosphate	2011	JAK1/2/3, Tyk	NRY	Myelofibrosis
Selpercatinib	2020	RET	RTK	Lung, thyroid cancer
Selumetinib	2020	MEK1/2	T/Y	Neurofibroma
Sorafenib tosylate	2005	VEGFR1/2/3	RTK	Thyroid, Kidney, Hepatocellular cancer
Sunitinib malate	2006	VEGFR2	RTK	Gastrointestinal, kidney, pancreatic cancer
Temsirolimus	2007	FKBP12/mTOR	S/T	kidney cancer
Tepotinib	2021	Met	RTK	Lung cancer
Tivozanib	2021	VEGFR2	RTK	kidney cancer
Trametinib	2013	MEK1/2	T/Y	Melanoma
Trilaciclib	2021	CDK4/6	S/T	Lung cancer
Tucatinib	2020	ErbB2/HER2	RTK	Breast cancer
Vandetanib	2011	VEGFR2	RTK	Thyroid cancer
Vemurafenib	2011	B-Raf	S/T	Melanoma; histiocytic sarcoma
Zanubrutinib	2019	BTK	NRY	Lymphoma

Table 1. List of Protein Kinase Inhibitors approved by FDA.
(NRY, non-receptor protein-tyrosine kinase; RTK, receptor protein-tyrosine kinase; S/T, protein-serine/threonine kinase; T/Y, dual-specificity protein kinase)

Protein kinase inhibitor	Approval year	Primary targets	Target kinase family	Indications
Abemaciclib	2017	CDK4/6	S/T	Breast cancer
Acalabrutinib	2017	BTK	NRY	Lymphoma
Afatinib	2013	ErbB1/2/4	RTK	Lung cancer
Alectinib	2015	ALK, RET	RTK	Lung cancer
Avapritinib	2020	PDGFR	RTK	Gastrointestinal Cancer
Axitinib	2012	VEGFR1/2/3	RTK	Kidney cancer
Binimetinib	2018	MEK1/2	T/Y	Melanoma
Bosutinib	2012	BCR-Abl	NRY	Leukemia
Brigatinib	2017	ALK	RTK	Lung cancer
Cabozantinib	2012	RET, VEGFR2	RTK	Thyroid. kidney, hepatocellular cancer
Capmatinib hydrochloride	2020	c-MET	RTK	Lung cancer
Ceritinib	2014	ALK	RTK	Lung cancer
Cobimetinib	2015	MEK1/2	T/Y	Melanoma
Crizotinib	2011	ALK, ROS1	RTK	Lung cancer
Dabrafenib	2013	B-Raf	S/T	Melanoma; lung, thyroid Cancer
Dacomitinib	2018	EGFR	RTK	Lung cancer
Dasatinib	2006	BCR-Abl	NRY	Leukemia
Encorafenib	2018	B-Raf	S/T	Melanoma, colorectal cancer
Entrectinib	2019	TRKA/B/C, ROS1	RTK	Lung cancer; solidTumors
Erdafitinib	2019	FGFR1/2/3/4	RTK	Urothelial carcinoma

Erlotinib hydrochloride	2004	EGFR	RTK	Lung, Pancreatic cancer
Everolimus	2009	FKBP12/mTOR	S/T	Breast, kidney cancer, Neuroendocrine tumors
Fedratinib	2019	JAK2	NRY	Myelofibrosis
Futibatinib	2022	FGFR2	RTK	Cholangiocarcinomas
Gefitinib	2003	EGFR	RTK	Lung cancer
Gilteritinib	2018	Flt3	RTK	Leukemia
Ibrutinib	2013	BTK	NRY	Lymphoma
Imatinib mesylate	2001	BCR-Abl	NRY	Leukemia; Gastrointestinal
Infigratinib	2021	FGFRs	RTK	Cholangiocarcinoma
Lapatinib ditosylate	2007	ErbB1/2/HER2	RTK	Breast cancer
Larotrectinib	2018	TRKA/B/C	RTK	Solid tumors
Lenvatinib	2015	VEGFR, RET	RTK	Hepatocellular, endometrial, Thyroid, Kidney cancer
Lorlatinib	2018	ALK	RTK	Lung cancer
Midostaurin	2017	Flt3	RTK	Leukemia
Mobocertinib	2021	EGFR with exon 20 insertions	RTK	Lung cancer
Neratinib	2017	ErbB2/HER2	RTK	Breast cancer
Nilotinib	2007	BCR-Abl	NRY	Leukemia
Osimertinib	2015	EGFR T790M	RTK	Lung cancer
Pacritinib	2022	JAK2	RTK	Myelofibrosis
Palbociclib	2015	CDK4/6	S/T	Breast cancer
Pazopanib hydrochloride	2009	VEGFR1/2/3	RTK	Kidney cancer; soft tissue sarcoma
Pemigatinib	2020	FGFR2	RTK	Cholangiocarcinoma

Pexidartinib	2019	CSF1R	RTK	Tenosynovial giant cell tumor
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Regorafenib	2012	VEGFR1/2/3	RTK	Gastrointestinal, Colorectal, Hepatocellular cancer
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Ripretinib	2020	KIT/PDGFR	RTK	Gastrointestinal cancer
Ruxolitinib phosphate	2011	JAK1/2/3, Tyk	NRY	Myelofibrosis
Selpercatinib	2020	RET	RTK	Lung, thyroid cancer
Selumetinib	2020	MEK1/2	T/Y	Neurofibroma
Sorafenib tosylate	2005	VEGFR1/2/3	RTK	Thyroid, Kidney, Hepatocellular cancer
Sunitinib malate	2006	VEGFR2	RTK	Gastrointestinal, kidney, pancreatic cancer
Temsirolimus	2007	FKBP12/mTOR	S/T	kidney cancer
Tepotinib	2021	Met	RTK	Lung cancer
Tivozanib	2021	VEGFR2	RTK	kidney cancer
Trametinib	2013	MEK1/2	T/Y	Melanoma
Trilaciclib	2021	CDK4/6	S/T	Lung cancer
Tucatinib	2020	ErbB2/HER2	RTK	Breast cancer
Vandetanib	2011	VEGFR2	RTK	Thyroid cancer
Vemurafenib	2011	B-Raf	S/T	Melanoma; histiocytic sarcoma
Zanubrutinib	2019	BTK	NRY	Lymphoma

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New FDA-Approved Oncology Drugs (2021–2022)

By Compiled by Donna Bell

June 3, 2022 - Narratives Special Issue

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Over the past year (May 2021–May 2022), the U.S. Food and Drug Administration (FDA) approved and expanded indications for many drugs related to the treatment of different types of cancers and adverse events. The new approvals and accelerated approvals are listed below.

FAM-TRASTUZUMAB DERUXTECAN-NXKI (ENHERTU) was approved for patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2–based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy. May 4, 2022.

ALPELISIB (VIJOICE) was approved for adult and pediatric patients two years of age and older with severe manifestations of *PIK3CA*-related overgrowth spectrum who require systemic therapy.

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AXICABTAGENE CILOLEUCEL (YESCARTA) was approved for adult patients with large B-cell lymphoma who are refractory to first-line chemoimmunotherapy or who experienced relapse within 12 months of first-line chemoimmunotherapy. April 1, 2022.

LUTETIUM (LU-177) VIPIVOTIDE TETRAXETAN (PLUVICTO) was approved for prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer after other therapies. March 23, 2022.

PEMBROLIZUMAB (KEYTRUDA) was approved as a single agent for patients with advanced endometrial carcinoma that is microsatellite instability–high or mismatch repair–deficient. Eligible patients have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. March 21, 2022.

NIVOLUMAB AND RELATLIMAB-RMBW (OPDUALAG) was approved for unresectable or metastatic melanoma. March 18, 2022.

OLAPARIB (LYNPARZA) was approved for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated, HER2-negative, high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Patients must be selected for therapy based on an FDA-approved companion diagnostic for olaparib. March 11, 2022.

NIVOLUMAB (OPDIVO) was approved in combination with platinum-doublet chemotherapy for the neoadjuvant treatment of early-stage non–small cell lung cancer (NSCLC). March 4, 2022.

PACRITINIB (VONJO) was approved for adults with intermediate- or high-risk primary or secondary (post–polycythemia vera or post–essential thrombocythemia) myelofibrosis with a platelet count below 50×10^9/L. February 28, 2022.

CILTACABTAGENE AUTOLEUCEL (CARVYKTI) was approved for the treatment of adults with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

TEBENTAFUSP-TEBN (KIMMTRAK) was approved for HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. January 25, 2022.

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PEMBROLIZUMAB (KEYTRUDA) was approved for the adjuvant treatment of adult and pediatric (≥ 12 years of age) patients with stage IIB or IIC melanoma following complete resection. December 3, 2021.

RITUXIMAB (RITUXAN) was approved in combination with chemotherapy for pediatric patients with previously untreated, advanced-stage, CD20-positive diffuse large B-cell lymphoma, Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia. December 2, 2021.

DARATUMUMAB PLUS HYALURONIDASE-FIHJ (DARZALEX FASPRO) was approved for adult patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy. December 1, 2021.

CARFILZOMIB (KYPROLIS) was approved combined with dexamethasone for adult patients with relapsed/refractory multiple myeloma who have received one to three prior lines of therapy. December 1, 2021.

PAFOLACIANINE (CYTALUX), an imaging drug, received approval for use in adult patients with ovarian cancer to help identify cancerous lesions during surgery. November 29, 2021.

SIROLIMUS PROTEIN-BOUND PARTICLES FOR INJECTABLE SUSPENSION (FYARRO) was approved for treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor. November 22, 2021.

PEMBROLIZUMAB (KEYTRUDA) was approved for the adjuvant treatment of patients with renal cell carcinoma at intermediate-high or high risk of disease recurrence following nephrectomy or nephrectomy and resection of metastatic lesions. November 17, 2021.

ASCIMINIB (SCEMBLIX) received accelerated approval for Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, previously treated with two or more tyrosine kinase inhibitors, and was approved for adult patients with Ph+ CML in chronic phase with the T315I mutation. October 29, 2021.

ATEZOLIZUMAB (TECENTRIQ) was approved for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥1% of tumor cells. October 15, 2021.

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PEMBROLIZUMAB (KEYTRUDA) combined with chemotherapy, with or without bevacizumab (Avastin), was approved for patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (combined positive score ≥ 1). October 13, 2021.

ABEMACICLIB (VERZENIO) combined with endocrine therapy was approved for adjuvant treatment of patients with hormone receptor–positive, HER2-negative, node-positive early breast cancer who are at high risk of disease recurrence and who have a Ki67 score ≥ 20%. October 12, 2021.

BREXUCABTAGENE AUTOLEUCEL (TECARTUS) received approval for adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). October 1, 2021.

CETUXIMAB (ERBITUX) was approved combined with encorafenib (Braftovi) for the treatment of adults with metastatic colorectal cancer and a *BRAF* V600E mutation after prior therapy. September 28, 2021.

RUXOLITINIB (JAKAFI) was approved for the treatment of chronic graft-vs-host disease (GVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients aged 12 years and older. September 22, 2021.

TISOTUMAB VEDOTIN-TFTV (TIVDAK) was approved to treat adult patients with recurrent or metastatic cervical cancer who experienced disease progression on or after chemotherapy. September 20, 2021.

CABOZANTINIB (CABOMETYX) was approved to treat adult and pediatric patients aged 12 years and older with locally advanced or metastatic differentiated thyroid cancer that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine–refractory or ineligible. September 17, 2021.

MOBOCERTINIB (EXKIVITY) was granted accelerated approval to treat adults with locally advanced or metastatic NSCLC and epidermal growth factor receptor exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. September 15, 2021.

ZANUBRUTINIB (BRUKINSA) received accelerated approval for the treatment of adult patients with relapsed or refractory marginal zone lymphoma who have received at least one anti–CD20-based regimen. September 15, 2021.

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ZANUBRUTINIB (BRUKINSA) was approved for the treatment of adult patients with Waldenström's macroglobulinemia. August 31, 2021.

IVOSIDENIB (TIBSOVO) was granted approval for previously treated locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 *(IDH1)* mutation. August 25, 2021.

NIVOLUMAB (OPDIVO) was approved for the adjuvant treatment of patients with urothelial carcinoma who are at high risk of disease recurrence after undergoing radical resection. August 19, 2021.

DOSTARLIMAB-GXLY (JEMPERLI), an anti–PD-1 antibody, received accelerated approval for adult patients with mismatch repair–deficient (dMMR) recurrent or advanced solid tumors who have had disease progression on or following prior treatment and who have no satisfactory alternative treatment options. August 17, 2021.

LENVATINIB (LENVIMA) PLUS PEMBROLIZUMAB (KEYTRUDA) received approval for the first-line treatment of adult patients with advanced renal cell carcinoma. August 10, 2021.

PEMBROLIZUMAB (KEYTRUDA) was approved for high-risk, early-stage triple-negative breast cancer in combination with chemotherapy as a neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery. July 26, 2021.

PEMBROLIZUMAB (KEYTRUDA) PLUS LENVATINIB (LENVIMA) was granted approval for treatment of patients with advanced endometrial carcinoma that is not microsatellite instability–high or dMMR. July 21, 2021.

BELUMOSUDIL (REZUROCK) was approved for adult and pediatric patients aged 12 years and older with chronic GVHD after failure of at least two prior lines of systemic therapy. July 16, 2021.

ENFORTUMAB VEDOTIN-EJFV (PADCEV) was approved for adults with locally advanced or metastatic urothelial cancer who have previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy. It also was approved for patients who are ineligible for cisplatin-containing chemotherapy and have received one or more prior lines of therapy. July 9, 2021.

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DARATUMUMAB AND HYALURONIDASE-FIHJ (DARZALEX FASPRO) combined with pomalidomide and dexamethasone was approved to treat adult patients with multiple myeloma who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor. July 9, 2021.

ASPARAGINASE ERWINIA -CHRYSANTHEMI (RECOMBINANT)-RYWN (RYLAZE) was approved for ALL and lymphoblastic lymphoma in patients allergic to *Escherichi coli*–derived asparaginase products, as a component of a chemotherapy regimen. June 30, 2021.

AVAPRITINIB (AYVAKIT) was approved to treat adult patients with advanced systemic mastocytosis, including those with aggressive systemic mastocytosis, systemic mastocytosis with an associated hematologic neoplasm, and mast cell leukemia. June 16, 2021.

INFIGRATINIB (TRUSELTIQ) received accelerated approval for adults with previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 fusion or other rearrangement. May 28, 2021.

SOTORASIB (LUMAKRAS) was approved as the first treatment for adult patients with NSCLC whose tumors have a *KRAS* G12C genetic mutation and who have received at least one prior systemic therapy. May 28, 2021.

PIFLUFOLASTAT F-18 INJECTION (PYLARIFY) was approved for the identification of suspected metastasis or recurrence of prostate cancer. May 27, 2021.

AMIVANTAMAB-VMJW (RYBREVANT) received accelerated approval for adult patients with locally advanced or metastatic NSCLC and *EGFR* exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. May 21, 2021.

NIVOLUMAB (OPDIVO) was approved for patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy. May 20, 2021.

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Ongoing | Cancer Accelerated Approvals

This listing includes accelerated approvals (/drugs/nda-and-bla-approvals/accelerated-approval-program) (AAs) for malignant hematology and oncology indications that have postmarketing requirement(s) for ongoing clinical trial(s) to verify clinical benefit. Please refer to Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/) for the latest approvals and prescribing information for specific products. Visit the verified (https://www.fda.gov/drugs/resources-information-approved-drugs/verified-clinical-benefit-cancer-accelerated-approvals) and withdrawn (https://www.fda.gov/drugs/resources-information-approved-drugs/withdrawn-cancer-accelerated-approvals) AA indication pages for more information and the Postmarket Requirements and Commitments (https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm) page for the status of specific requirements.

Indications may remain on this page until FDA updates product labeling or publishes a Federal Register notice regarding a change in status.

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Drug Name	Accelerated Approval (AA) Indication	AA Date	AA Post-Marketing Requirement	Original Projected Completion [1]
Elrexfio (elranatamab-bcmm)	Adults with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. (/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-elranatamab-bcmm-multiple-myeloma)	8/14/2023	4476-1: Complete a randomized clinical trial in patients with relapsed or refractory multiple myeloma. Patients should be randomized to receive an elranatamab-based regimen compared to standard therapy for relapsed or refractory multiple myeloma. The primary endpoint should be progression-free survival and secondary endpoints should include overall survival and overall response rate. The trial should enroll sufficient numbers of older patients (ages 65-74 years and 75 years and above) to enable an evaluation of elranatamab in a study population that reflects the age of the U.S. population of patients with multiple myeloma.	9/30/2026

Drug Name	Accelerated Approval (AA) Indication	AA Date	AA Post-Marketing Requirement	Original Projected Completion [1]
Talvey (talquetamab-tgvs)	Adults with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody (/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-talquetamab-tgvs-relapsed-or-refractory-multiple-myeloma)	8/9/2023	4473-1: Conduct a randomized clinical trial that evaluates the clinical efficacy and safety of talquetamab in patients with relapsed or refractory multiple myeloma. Patients should be randomized to receive a talquetamab-based regimen compared to standard therapy for relapsed or refractory multiple myeloma. The primary endpoint should be progression-free survival and secondary endpoints should include overall survival and overall response rate. The trial should enroll sufficient numbers of racial and ethnic minority patients and older patients (ages 65-74 years and 75 years and above) to enable an evaluation of talquetamab in a study population that reflects the U.S. population of patients with multiple myeloma.	12/31/2026

Drug Name	Accelerated Approval (AA) Indication	AA Date	AA Post-Marketing Requirement	Original Projected Completion [1]
Columvi (glofitamab-gxbm)	Relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified or large B-cell lymphoma arising from follicular lymphoma, after two or more lines of systemic therapy (/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-glofitamab-gxbm-selected-relapsed-or-refractory-large-b-cell)	6/15/2023	4464-1 Complete a randomized clinical trial that evaluates the clinical benefit of glofitamab in patients with diffuse large B-cell lymphoma. The trial should compare glofitamab in combination with gemcitabine and oxaliplatin (GemOx) to rituximab in combination with GemOx for patients with relapsed or refractory diffuse large B-cell lymphoma. The primary endpoint should be overall survival with secondary endpoints that include progression-free survival and response rate.	9/30/2024
Epkinly (epcoritamab-bysp)	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy. (/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-epcoritamab-bysp-relapsed-or-refractory-diffuse-large-b-cell)	5/19/2023	4435-1: Complete a randomized clinical trial in patients with relapsed or refractory large B-cell lymphoma. The trial should compare epcoritamab monotherapy to an investigator's choice of standard therapies for patients with relapsed or refractory large B-cell lymphoma. The primary endpoint should be OS with secondary endpoints that include PFS and response rate.	6/30/2025

Drug Name	Accelerated Approval (AA) Indication	AA Date	AA Post-Marketing Requirement	Original Projected Completion [1]
Keytruda (pembrolizumab)	In combination with enfortumab vedotin-ejfv for the treatment of adult patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing chemotherapy (/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-enfortumab-vedotin-ejfv-pembrolizumab-locally-advanced-or-metastatic)	4/3/2023	4429-1: Conduct clinical trial EV-302, “Enfortumab Vedotin and Pembrolizumab vs. Chemotherapy Alone in Untreated Locally Advanced or Metastatic Urothelial Cancer” and submit the final OS, PFS, ORR and DoR results, intended to verify and describe the clinical benefit of enfortumab vedotin in combination with pembrolizumab in patients with untreated locally advanced or metastatic urothelial cancer.	9/30/2025
Padcev (enfortumab vedotin-efjv)	In combination with pembrolizumab for the treatment of adult patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing chemotherapy (/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-enfortumab-vedotin-ejfv-pembrolizumab-locally-advanced-or-metastatic)	4/3/2023	4428-1: Conduct clinical trial EV-302, “Enfortumab Vedotin and Pembrolizumab vs. Chemotherapy Alone in Untreated Locally Advanced or Metastatic Urothelial Cancer” and submit the final OS, PFS, ORR and DoR results, intended to verify and describe the clinical benefit of enfortumab vedotin in combination with pembrolizumab in patients with untreated locally advanced or metastatic urothelial cancer.	9/30/2025

Drug Name	Accelerated Approval (AA) Indication	AA Date	AA Post-Marketing Requirement	Original Projected Completion [1]
Zynyz (retifanlimab-dlwr)	Adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC). (/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-retifanlimab-dlwr-metastatic-or-recurrent-locally-advanced-merkel)	3/22/2023	4412-1: Conduct a multicenter clinical trial intended to confirm the clinical benefit of retifanlimab-dlwr in patients with metastatic or recurrent locally advanced MCC who have not received prior systemic therapies for metastatic or recurrent locally advanced MCC. The trial will enroll at least 100 patients to be followed for a minimum of 12 months to establish the ORR and characterize the DOR. Include an analysis of OS, when 70% of patients have died, or all patients have been followed for at least three years.	3/31/2025

Drug Name	Accelerated Approval (AA) Indication	AA Date	AA Post-Marketing Requirement	Original Projected Completion [1]
Jaypirca (pirtobrutinib)	Adult patients with relapsed or refractory mantle cel lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor. (/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-relapsed-or-refractory-mantle-cell-lymphoma)	1/27/2023	4389-1: Complete a randomized clinical trial to obtain data on the clinical efficacy and safety of pirtobrutinib in patients with MCL. The trial should compare pirtobrutinib monotherapy to an investigator's choice of approved BTK inhibitors in patients with MCL. The primary endpoint should be PFS as assessed by an independent review committee, with secondary endpoints that include OS and objective response rate. The trial should enroll a sufficiently representative study population to reflect the racial and ethnic diversity of the U.S. patient population with MCL and allow for interpretation of the results in these patient populations.	12/31/2026

Drug Name	Accelerated Approval (AA) Indication	AA Date	AA Post-Marketing Requirement	Original Projected Completion [1]
Tukysa (tucatinib)	In combination with trastuzumab for the treatment of adult patients with RAS wild-type, HER2-positive, unresectable or metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy (/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tucatinib-trastuzumab-colorectal-cancer)	1/19/2023	4388-1: Conduct a randomized clinical trial to obtain data on the clinical efficacy of tucatinib for patients with RAS wild type, HER2-positive, unresectable or metastatic colorectal carcinoma. The trial should compare tucatinib in combination with trastuzumab with the standard of care in patients with RAS wild type, HER2-positive, unresectable or metastatic colorectal carcinoma. The primary endpoint should be PFS per blinded assessment or OS. The trial should enroll a sufficiently representative study population to reflect the racial and ethnic diversity of the U.S. patient population with RAS wild type, HER2-positive, unresectable or metastatic colorectal carcinoma and allow for interpretation of the results across this representative study population.	04/30/2026

Drug Name	Accelerated Approval (AA) Indication	AA Date	AA Post-Marketing Requirement	Original Projected Completion [1]
Lunsumio (mosunetuzumab-axgb)	Adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy. (/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mosunetuzumab-axgb-relapsed-or-refractory-follicular-lymphoma)	12/22/2022	4375-1: Conduct a randomized clinical trial in patients with relapsed or refractory follicular lymphoma (FL), with patients randomized to receive mosunetuzumab in combination with lenalidomide or rituximab in combination with lenalidomide. The primary endpoint should be PFS, with secondary endpoints that include RR and OS. The trial should enroll a sufficiently representative study population to reflect the racial and ethnic diversity of the U.S. patient population with FL and allow for interpretation of the results in these patient populations.	12/31/2025

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1 If multiple PMRs were required, the latest date is reported here. This date represents the original agreed-upon Final Study Report date and does not include any updated deadlines submitted by the Applicant.

2 [a] [b] [c] The original AA indication was modified to include an expanded population.