CHRONOLOGICAL EVOLUTION IN THE DEVELOPMENT OF ANTICANCER DRUGS: A COMPREHENSIVE REVIEW

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ABSTRACT

The development of anti-cancer drugs has undergone a significant transformation over the past century, reflecting advances in scientific understanding, technology, and clinical practice. This paper traces the chronological evolution of cancer therapeutics, beginning with the discovery of cytotoxic chemotherapy in the mid-20th century, followed by the introduction of hormone therapies and the rise of combination chemotherapy regimens. In recent decades, breakthroughs in immunotherapy, personalized medicine, and nanotechnology have further revolutionized treatment approaches. This evolving landscape highlights a shift from broad-spectrum cytotoxic agents to more precise, individualized strategies aimed at maximizing efficacy and

minimizing toxicity. Understanding this historical progression provides critical context for current innovations and future directions in oncology drug development.

Key words: Cancer; Chemotherapy; Targeted therapy; Immunotherapy; Nanotechnology

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, posing a significant challenge to global health systems. Over the decades, the therapeutic landscape of cancer has undergone a remarkable transformation, shaped by scientific advancements and a growing understanding of tumour biology. The journey began with the advent of chemotherapy in the mid-20th century—an approach that, while groundbreaking, often lacked specificity and was associated with considerable toxicity[1].

As research progressed, newer classes of anticancer agents emerged, including targeted therapies that disrupted specific molecular pathways, and more recently, immunotherapies that harness the body's own immune system to combat malignancies. This chronological evolution marks a paradigm shift in cancer treatment, moving from broadly cytotoxic strategies to more precise, individualized approaches[2].

This review aims to provide a comprehensive overview of the historical development of anticancer drugs, tracing their evolution from traditional chemotherapeutic agents to the cutting-edge field of immunotherapy. By examining key milestones and therapeutic innovations, we highlight the scientific progress that has shaped modern oncology and discuss future directions in the search for more effective and less toxic cancer treatments.

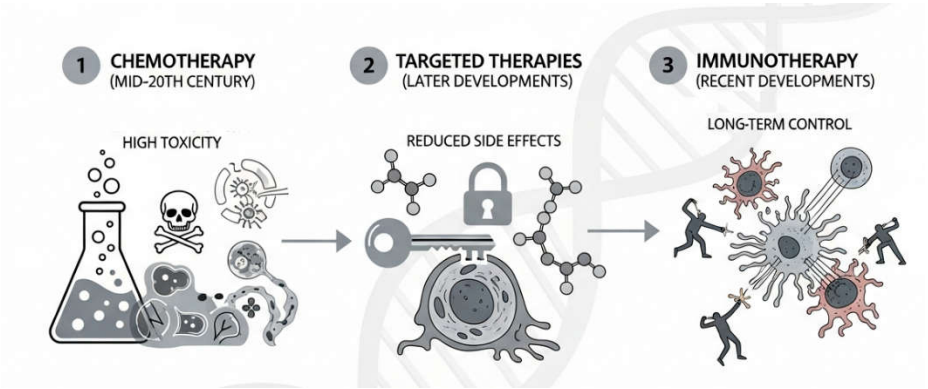

Fig.1. *A Historical Progression of Anticancer Drug Development*

Origins and Evolution of Cancer therapies

The earliest approaches to cancer treatment were primarily surgical, focusing on the physical removal of tumors. With the advent of radiation therapy in the late 19th and early 20th centuries, clinicians gained a powerful modality capable of controlling localized disease. The mid-20th [Fig. 1.] century marked a turning point with the introduction of systemic chemotherapy, enabling treatment of disseminated cancers.

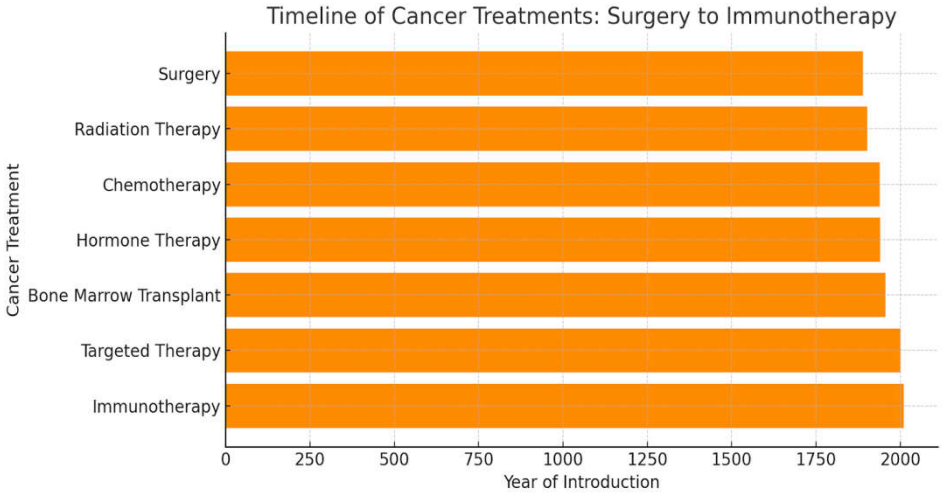

Fig.2. *A horizontal bar graph illustrating the timeline of key cancer treatments from surgery (1890) to immunotherapy (2011).*

Over time, cancer therapy evolved through distinct phases, including the development of hormone therapies, combination chemotherapy regimens, targeted therapies, and immunotherapies. This progression reflects a gradual transition from broadly cytotoxic interventions to biologically informed and immune-based strategies, as illustrated by the historical timeline of cancer treatments[3].

Hormone Therapy

Hormone therapy represents one of the earliest examples of targeted cancer treatment. Certain malignancies, particularly breast and prostate cancers, depend on endogenous hormones for growth and survival[4]. Hormone therapy aims to either reduce hormone production or block hormone-receptor interactions, thereby inhibiting tumour progression.

Two principal strategies are employed in hormone therapy: suppression of hormone synthesis and interference with hormone action at the receptor level[5]. Agents such as selective estrogen receptor modulators, aromatase inhibitors, and androgen deprivation therapies have

significantly improved outcomes in hormone-dependent cancers. However, hormone therapy is not universally applicable and may be contraindicated in hormone-independent tumors[6].

Radiation Therapy

Radiation therapy uses ionizing radiation to damage the DNA of cancer cells, leading to cell death or loss of reproductive capacity. It can be administered as a definitive treatment, adjuvant therapy following surgery, or palliative intervention to relieve symptoms[7].

Technological advancements, including intensity-modulated radiation therapy and image-guided radiation therapy, have enhanced precision and reduced damage to surrounding normal tissues. Radiation therapy is often combined with chemotherapy or targeted agents to enhance therapeutic efficacy, forming the basis of multimodal cancer treatment strategies[8, 9].

Chemotherapy

Chemotherapy involves the use of cytotoxic drugs that interfere with cell division or DNA synthesis, thereby inhibiting tumour growth. Early chemotherapeutic agents, such as alkylating agents and antimetabolites, were non-specific and associated with substantial toxicity. Nevertheless, they demonstrated that systemic pharmacotherapy could achieve tumour regression and cure in certain cancers[10, 11].

Over time, combination chemotherapy regimens were developed to improve efficacy and reduce resistance. Advances in drug formulation, dosing strategies, and supportive care have improved tolerability and patient outcomes. Despite the emergence of newer therapies, chemotherapy remains a cornerstone of cancer treatment, often used in combination with targeted therapy or immunotherapy[12, 13].

Targeted Therapy

Targeted therapy represents a major paradigm shift in anticancer drug development. These agents are designed to selectively inhibit molecular targets that drive cancer initiation and progression, such as growth factor receptors, kinases, and signalling proteins[14, 15].

Targeted therapies include small-molecule inhibitors and monoclonal antibodies that block oncogenic pathways, induce apoptosis, or deliver cytotoxic agents directly to cancer cells[16]. By exploiting specific genetic and molecular abnormalities, targeted therapies have improved

efficacy and reduced off-target toxicity compared to traditional chemotherapy. However, resistance and tumour heterogeneity remain significant challenges[17, 18].

Immunotherapy to Chemotherapy: A Revolution in Cancer Treatment

Immunotherapy has emerged as one of the most transformative advances in oncology. Unlike chemotherapy, which directly targets cancer cells, immunotherapy harnesses the patient's immune system to recognize and eliminate malignant cells[19 - 21].

Major immunotherapeutic approaches include immune checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy, cancer vaccines, cytokine therapies, and bispecific antibodies. These strategies have produced durable responses in cancers previously considered refractory to treatment. The integration of immunotherapy with chemotherapy and targeted therapy has further expanded treatment options and reshaped clinical practice[22 - 24].

Recent Advances: Approved and Investigational Therapies (2016–2025)

The past decade has witnessed an unprecedented number of regulatory approvals and clinical trial advancements in oncology [Table 1,2 & Fig. 3, 4]. Tissue-agnostic therapies, cell-based treatments, antibody–drug conjugates, and precision-targeted agents have expanded the therapeutic arsenal.

Table 1. *FDA-Approved Cancer Therapy Drugs (2016–2025)*

Year	Drug Name	Cancer Type	Mechanism/Indication	Latest Update
2016	Olaratumab (Lartruvo)	Soft Tissue Sarcoma	PDGFRA monoclonal antibody; accelerated approval for advanced sarcoma with doxorubicin	Removed from market in 2019 due to lack of efficacy in confirmatory trials[26]
2016	Atezolizumab (Tecentriq)	Urothelial Carcinoma	PD-L1 inhibitor; first FDA-approved checkpoint inhibitor for bladder cancer	Expanded to NSCLC, SCLC, and other cancers later[27]
2017	Pembrolizumab (Keytruda)	Multiple (MSI-H/dMMR cancers)	PD-1 inhibitor; first tissue-agnostic approval for	Landmark for biomarker-

			MSI-H/dMMR solid tumors	driven therapy[28]
2018	Larotrectinib (Vitrakvi)	Solid Tumors (NTRK fusion)	TRK inhibitor; tissue-agnostic approval for NTRK gene fusion cancers	Accelerated approval; rare cancer focus[29]
2019	Erdafitinib (Balversa)	Urothelial Carcinoma	FGFR inhibitor; first targeted therapy for FGFR-altered bladder cancer	Accelerated approval[30]
2020	Selpercatinib (Retevmo)	Lung, Thyroid Cancers	RET inhibitor; for RET fusion-positive NSCLC and thyroid cancers	Precision oncology advancement[31]
2021	Sotorasib (Lumakras)	Non-Small Cell Lung Cancer (NSCLC)	KRAS G12C inhibitor; first approved therapy targeting KRAS mutations	Accelerated approval[32]
2022	Tebentafusp (Kimmtrak)	Uveal Melanoma	Bispecific T-cell engager; first approved therapy for metastatic uveal melanoma	Novel mechanism targeting gp100[32]
2023	Talquetamab-tgvs (Talvey)	Multiple Myeloma	Bispecific T-cell engager (GPRC5D-targeted); for relapsed/refractory multiple myeloma	Part of 13 novel oncology approvals in 2023[33]
2024	Lifileucel (Amtagvi)	Melanoma	Tumor-infiltrating lymphocyte (TIL) therapy; first TIL therapy for unresectable/metastatic melanoma	Objective response rate of 31.5%[34]
2024	Afamitresgene autoleucel (Tecelra)	Synovial Sarcoma	TCR therapy; first TCR therapy for MAGE-A4-positive metastatic synovial sarcoma	Accelerated approval[35]
2025	Sunvozertinib (Zegfrovy)	NSCLC	EGFR TKI; for EGFR exon 20 insertion	Accelerated approval on July 2, 2025[36]

			mutations in advanced NSCLC	
2025	Datopotamab deruxtecan-dlnk (Datroway)	NSCLC, Breast Cancer	Antibody-drug conjugate; for EGFR-mutated NSCLC and HR+/HER2- breast cancer	Accelerated approval in June 2025[37]
2025	Tislelizumab-jsgr (Tevimbra)	Esophageal Squamous Cell Carcinoma (ESCC)	PD-1 inhibitor; first-line treatment with chemotherapy for PD-L1-positive ESCC	Approved March 4, 2025[37]
2025	Pembrolizumab (Keytruda)	Head and Neck Squamous Cell Carcinoma (HNSCC)	PD-1 inhibitor; perioperative use for PD-L1-positive HNSCC	Approved in Q2 2025, based on KEYNOTE-689 trial[38]

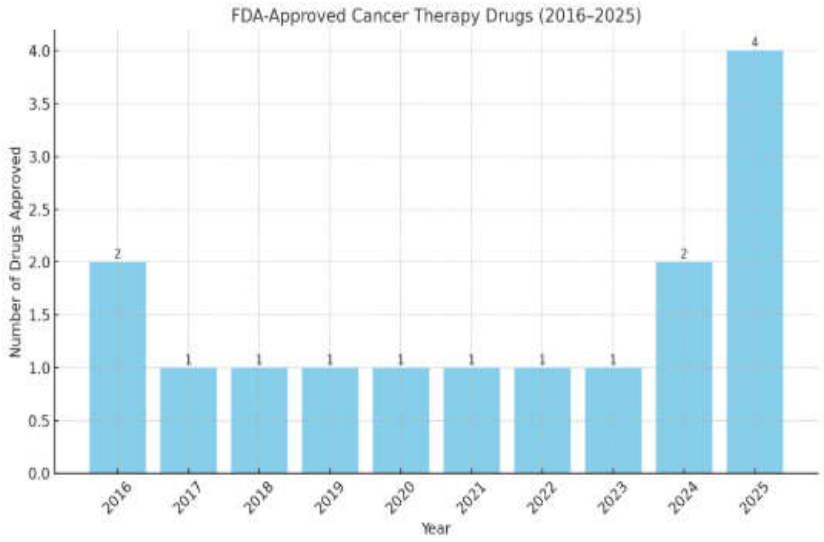

Fig. 3. *Bar graph representing the number of FDA-approved cancer therapy drugs from 2016 to 2025.*

Table 2. *Clinical Trial Cancer Therapy Drugs (2016–2025)*

Year	Drug Name	Cancer Type	Mechanism/ Indication	Trial Details	Status/Notes
2016	Venetoclax	Chronic Lymphocytic Leukemia (CLL)	BCL-2 inhibitor; Phase 3 trials (MURANO, NCT02005471)	Combined with rituximab; later approved in 2018	Showed improved PFS[39]
2017	Tisagenlecleucel	Acute Lymphoblast	CAR T-cell therapy;	First CAR T-cell therapy;	Pediatric and young adult ALL

		ic Leukemia (ALL)	ELIANA trial (NCT02435849)	approved in 2017	
2018	Ipatasertib	Breast Cancer	AKT inhibitor; LOTUS trial (NCT02162719)	For triple-negative breast cancer	Ongoing; no FDA approval by 2025
2019	177Lu-PSMA-617	Prostate Cancer	Radiopharmaceutical; VISION trial (NCT03511664)	For PSMA-positive mCRPC	Approved in 2022 as Pluvicto
2020	Lurbinectedin	Small Cell Lung Cancer (SCLC)	Transcription inhibitor; ATLANTIS trial (NCT02566993)	Combined with doxorubicin	Approved in 2020 under accelerated approval
2021	Belzutifan	Renal Cell Carcinoma (RCC)	HIF-2α inhibitor; MK-6482-004 trial (NCT02974738)	For VHL-associated RCC	Approved in 2021 for VHL-associated tumors
2022	Adagrasib	NSCLC, Colorectal Cancer	KRAS G12C inhibitor; KRYSTAL-1 trial (NCT03785249)	For KRAS G12C-mutated cancers	Approved in 2022 for NSCLC; 2024 for colorectal cancer
2023	Pirtobrutinib	CLL/SLL	BTK inhibitor; BRUIN trial (NCT03740529)	For post-BTK inhibitor treatment	Approved in 2023
2024	Uza-cel	Multiple Cancers	TCR therapy targeting MAGE-A4; NCT03132922	For MAGE-A4-positive solid tumors	Promising results in synovial sarcoma; ongoing
2025	PEP-010	Pancreatic Cancer	Orphan drug designation; Phase 3 trial planned	For metastatic pancreatic cancer	Orphan drug status granted March 17, 2025
2025	MRANK-106	Solid Tumors	WEE1/YES1 kinase inhibitor; Phase 1 trial (NCT not specified)	For advanced solid tumors	IND cleared March 7, 2025
2025	CTD402	T-Cell ALL/LBL	CD7-targeted CAR T-cell therapy; Phase 1 trial (NCT not specified)	For relapsed/refractory T-ALL/LBL	IND cleared March 5, 2025[40]

These developments reflect a growing emphasis on biomarker-driven treatment selection and personalized medicine.

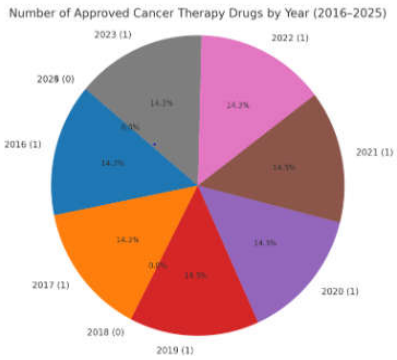

Fig. 4. *Pie chart displaying the number of approved cancer therapy drugs each year from 2016 to 2025.*

Each slice represents a year and is labelled with the number of approvals in parentheses. Years like 2018, 2024, and 2025 show **0 approvals**, reflecting ongoing or early-stage trials

CONCLUSION

The chronological evolution of anticancer drug development highlights the remarkable progress achieved through sustained scientific innovation. From early non-specific cytotoxic agents to sophisticated targeted therapies and immunotherapies, each era has contributed to improved survival and quality of life for cancer patients. Contemporary oncology increasingly relies on combination strategies that integrate chemotherapy, targeted therapy, and immunotherapy to address tumour heterogeneity and therapeutic resistance. As research continues to advance, future cancer treatments are expected to become even more precise, effective, and patient-centred, bringing the goal of durable cancer control and cure closer to reality.

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Conflict of Interest: The authors declare no conflicts of interest.

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