Review Article

A Comprehensive Pan-Cancer Review on Molecular Targeted Therapy in Cancer: Mechanisms of Action, Drug Resistance, and Emerging Strategies

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Abstract | The emergence of molecularly targeted therapy has fundamentally transformed the treatment paradigm of human malignancies. Unlike conventional cytotoxic chemotherapy, targeted agents exploit specific oncogenic vulnerabilities aberrant kinase signalling, gain-of-function mutations, angiogenic cascades, and DNA repair defects to selectively eliminate malignant cells while preserving normal tissue. Over the past two decades, more than 80 small-molecule inhibitors and monoclonal antibodies have received regulatory approval across a spectrum of tumour types. This review systematically appraises the mechanistic landscape of molecular targeted therapies across cancer types, delineates the molecular pathways underpinning intrinsic and acquired resistance, and evaluates next-generation strategies designed to circumvent treatment failure. A narrative synthesis was performed of landmark randomised controlled trials, translational studies, and mechanistic investigations published between 2000 and 2024, identified through PubMed, Embase, and ClinicalTrials.gov. Studies were selected for clinical relevance, methodological rigour, and impact in high-ranking peer-reviewed journals. Targeted therapies demonstrate superior progression-free survival (PFS) and objective response rates (ORR) compared with conventional chemotherapy in biomarker-selected populations, including EGFR-mutated non-small-cell lung cancer (median PFS: 18.9 vs. 10.2 months; HR 0.46; p<0.001), BCR-ABL-positive chronic myeloid leukaemia (complete cytogenetic response: 74% vs. 31%), and BRAF V600E-mutated melanoma (ORR: 84% vs. 64%). However, acquired resistance develops universally through on-target secondary mutations, activation of bypass signalling pathways, and phenotypic plasticity. Molecular targeted therapy has redefined the oncological treatment landscape, converting several previously lethal malignancies into manageable chronic conditions. Overcoming resistance necessitates rational combinatorial strategies, longitudinal liquid biopsy monitoring, and artificial intelligence-guided therapeutic sequencing.

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Introduction

Cancer remains one of the foremost global health challenges, accounting for approximately 19.3 million new diagnoses and 10.0 million deaths in 2020, with projections estimating 28.4 million incident cases by 2040 (Sung *et al.*, 2021). Despite decades of progress, conventional cytotoxic chemotherapy predicated on the non-selective inhibition of cell division confers limited tumour specificity, resulting in systemic toxicity and modest improvements in long-term survival for most advanced solid tumours (DeVita and Chu, 2008). The elucidation of the molecular hallmarks of cancer sustained proliferative signalling, evasion of growth suppressors, replicative immortality, resistance to apoptosis, induction of angiogenesis, and activation of invasion and metastasis provided the conceptual framework for a rational, biology-driven therapeutic approach (Hanahan and Weinberg, 2011). The introduction of imatinib in 2001, targeting the BCR-ABL fusion kinase in chronic myeloid leukaemia (CML), marked a paradigmatic inflexion: a mechanistically defined, molecularly targeted agent capable of inducing durable complete cytogenetic responses in >80% of patients and transforming a previously fatal disease into a manageable chronic condition (Druker *et al.*, 2006; Hochhaus *et al.*, 2020). This conceptual breakthrough catalysed a global effort to identify and therapeutically exploit oncogenic driver alterations across tumour types. Today, the landscape encompasses receptor tyrosine kinase inhibitors (TKIs), monoclonal antibodies, proteolysis-targeting chimaeras (PROTACs), antibody-drug conjugates (ADCs), PARP inhibitors, CDK4/6 inhibitors, and immune checkpoint modulators (Hyman *et al.*, 2017; Hanahan, 2022). Yet a fundamental challenge persists: virtually all patients who initially respond to targeted therapy eventually develop acquired resistance, with relapse occurring at a median of 9–18 months depending on tumour type and agent (Vasan *et al.*, 2019). Understanding the molecular underpinnings of resistance is therefore not merely an academic pursuit but a clinical imperative.

Figure 1 illustrates a timeline of landmark FDA-approved molecular targeted therapies in oncology (2001–2024). Events are colour-coded by mechanistic class. The accelerating pace of approvals from 2014 onwards reflects both the expansion of tumour genomic profiling and the adoption of tumour-agnostic indications. CML, chronic myeloid leukaemia; NSCLC, non-small-cell lung cancer; CRC, colorectal cancer; RCC, renal cell carcinoma; MEL, melanoma; BC, breast cancer.

The present review systematically examines the mechanistic classes of molecular targeted therapies, their clinical efficacy across a spectrum of cancer types, the biology of intrinsic and acquired resistance, and translational strategies including combination regimens, drug sequencing, and liquid biopsy-guided monitoring directed at overcoming resistance and sustaining therapeutic benefit.

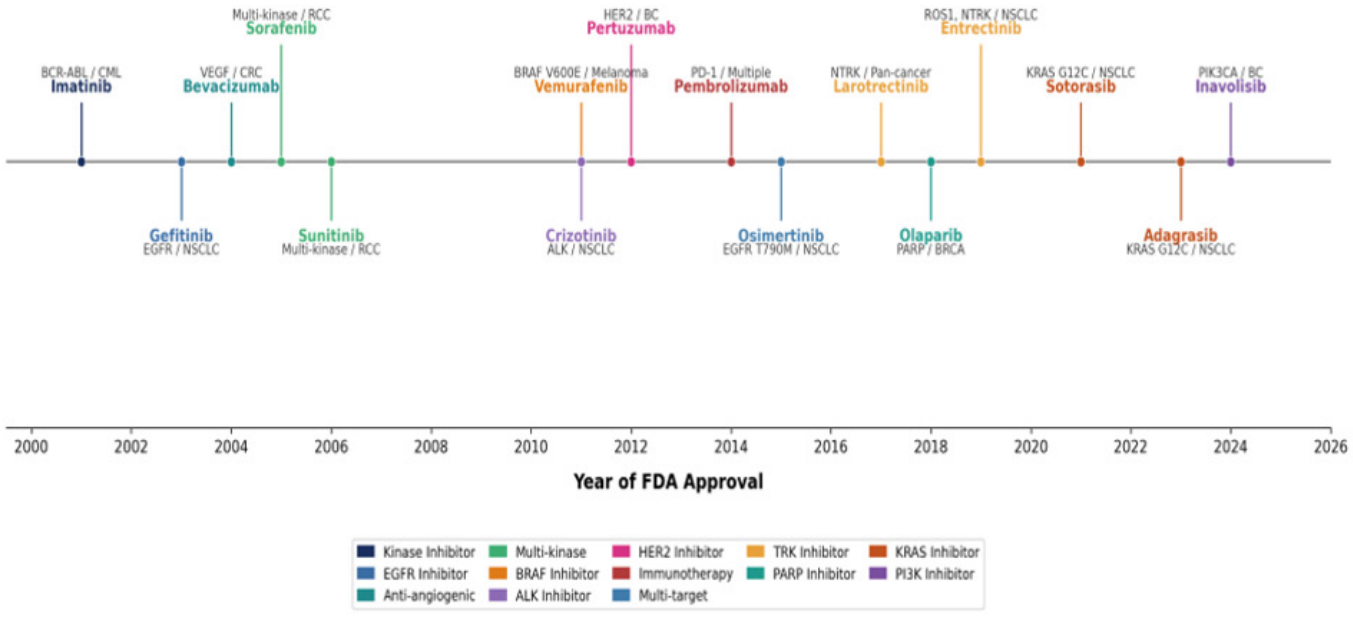

Figure 1: *Timeline of landmark FDA-approved molecular targeted therapies in oncology (2001–2024).*

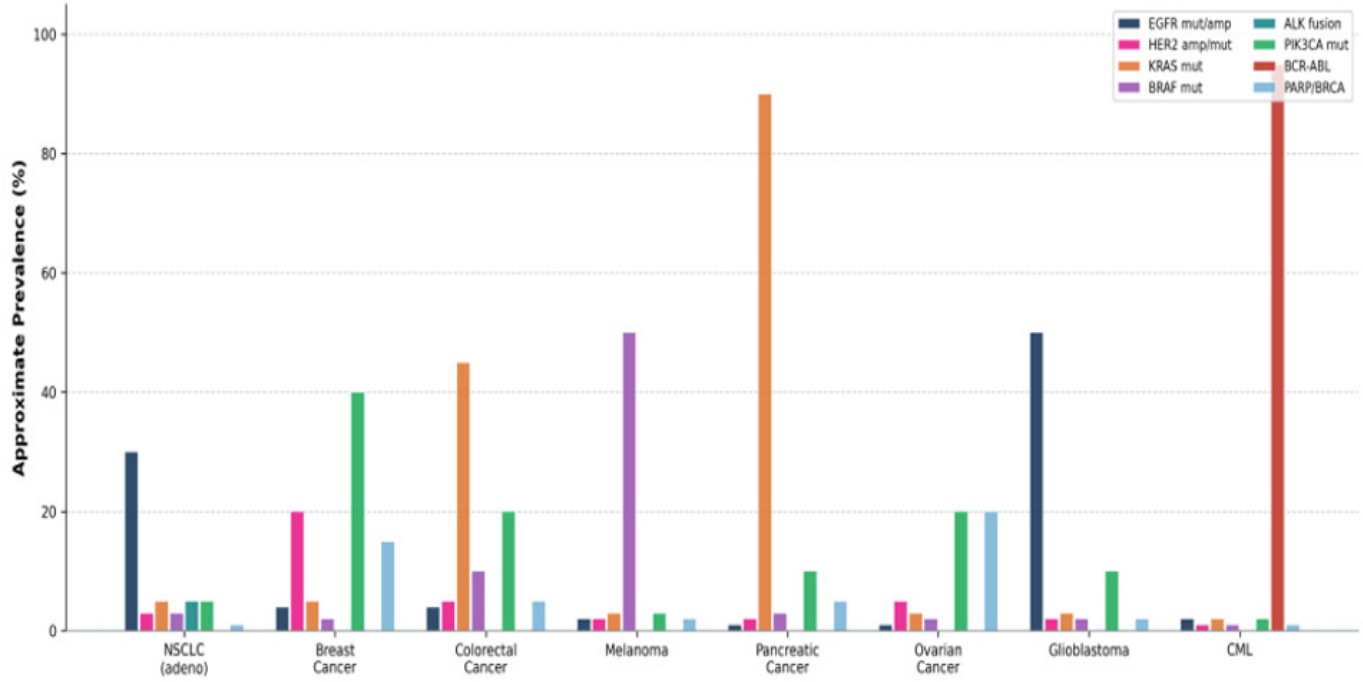

Figure 2: *Pan-cancer prevalence of key actionable oncogenic alterations across major tumour types.*

Landscape of oncogenic driver alterations in human malignancies

The genomic revolution, accelerated by next-generation sequencing (NGS) and the Cancer Genome Atlas (TCGA) programme, has delineated a complex network of somatic alterations that drive tumourigenesis (TCGA Research Network, 2014). These include point mutations, gene amplifications, chromosomal translocations, copy number variations, and epigenetic modifications. While thousands of somatic variants per tumour characterise cancer, a critical subset represents 'driver' alterations conferring a selective proliferative or survival advantage and constituting actionable therapeutic targets (Figure 2) (Bailey *et al.*, 2018).

Figure 2 illustrates the pan-cancer prevalence of key actionable oncogenic alterations across major tumour types. Frequencies are approximate values derived from TCGA genomic databases and published clinical genomic studies (TCGA Research Network, 2014; Bailey *et al.*, 2018; Prior *et al.*, 2020; Fakih *et al.*, 2022). EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral proto-oncogene; BRAF, v-Raf murine sarcoma viral oncogene homolog B; ALK, anaplastic lymphoma kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; CML, chronic myeloid leukaemia.

Receptor tyrosine kinases and their downstream effectors

Receptor tyrosine kinases (RTKs) including the epidermal growth factor receptor (EGFR) family, vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), and mesenchymal-epithelial transition factor (MET) are among the most frequently dysregulated oncoproteins in human cancer (Bhullar *et al.*, 2018). Activating mutations in EGFR (exon 19 deletions and L858R substitution) occur in 10–15% of Western and 40–55% of East Asian patients with lung adenocarcinoma, conferring sensitivity to EGFR-TKIs with ORRs exceeding 60–80% (Mok *et al.*, 2009; Wu *et al.*, 2020). HER2 (ERBB2) amplification, present in approximately 20% of breast cancers and 2–4% of gastric cancers, drives oncogenic signalling through PI3K/AKT/mTOR and RAS/MAPK cascades, and is targeted by trastuzumab, pertuzumab, and the highly potent antibody-drug conjugate trastuzumab deruxtecan (T-DXd) (Swain *et al.*, 2020; Modi *et al.*, 2022).

RAS–RAF–MEK–ERK signalling axis

The RAS family of GTPases (KRAS, NRAS, HRAS) constitutes the most frequently mutated oncogene class in human cancer, harbouring alterations in approximately 30% of all tumours (Prior *et al.*, 2020). KRAS mutations are particularly prevalent in pancreatic ductal adenocarcinoma (PDAC; ~90%), colorectal cancer (CRC; 40–45%), and non-small-cell

lung cancer (NSCLC; 25–30%) (Fakih *et al.*, 2022). For decades, RAS was considered 'undruggable' due to the absence of a discernible drug-binding pocket and its picomolar affinity for GTP; however, the discovery of a cryptic allosteric switch-II pocket in KRAS G12C led to the development of covalent inhibitors sotorasib and adagrasib (Skoulidis *et al.*, 2021; Janne *et al.*, 2022). BRAF V600E mutations, occurring in approximately 50% of cutaneous melanomas, 8–10% of CRCs, and 1–3% of NSCLCs, are targeted by vemurafenib, dabrafenib, and encorafenib in combination with MEK inhibitors (Robert *et al.*, 2019; Dummer *et al.*, 2018).

PI3K/AKT/mTOR pathway

The phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR signalling axis regulates fundamental cellular processes including growth, survival, metabolism, and motility (Alzahrani, 2019). PIK3CA encoding the catalytic subunit of PI3Kα is mutated in approximately 40% of hormone receptor-positive (HR+) breast cancers at hotspot codons E542K, E545K, and H1047R (Andre *et al.*, 2019). The selective PIK3CA inhibitor alpelisib combined with fulvestrant demonstrated superior PFS in PIK3CA-mutated HR+/HER2-negative metastatic breast cancer in the SOLAR-1 trial (median PFS 11.0 vs. 5.7 months; HR 0.65; 95% CI 0.50–0.85; p<0.001) (Andre *et al.*, 2019). mTOR inhibitors (everolimus, temsirolimus) have regulatory approval in renal cell carcinoma, HR+ breast cancer, and neuroendocrine tumours (Yardley, 2015).

DNA damage response and repair pathways

Germline and somatic mutations in BRCA1 and BRCA2 encoding homologous recombination repair (HRR) proteins confer sensitivity to PARP inhibitors through the concept of synthetic lethality: simultaneous impairment of HRR and base excision repair (via PARP trapping) creates an irrecoverable DNA double-strand break burden selectively in tumour cells (Lord and Ashworth, 2017). In BRCA-mutated, platinum-sensitive relapsed ovarian cancer, olaparib maintenance prolonged median PFS to 19.1 vs. 5.5 months (HR 0.30; 95% CI 0.22–0.41; p<0.001; SOLO2 trial) (Pujade-Lauraine *et al.*, 2017). This paradigm has since expanded to castration-resistant prostate cancer (PROfound trial; HR 0.34) and BRCA-mutated PDAC (POLO trial; HR 0.53) (De Bono *et al.*, 2020; Golan *et al.*, 2019); As summarised in Table 1.

Mechanisms of Acquired Resistance to Molecular Targeted Therapy

Acquired resistance to targeted therapy is a near-universal phenomenon that critically limits long-term clinical benefit. Resistance mechanisms are broadly classified into (i) on-target alterations mutations within the drug-binding domain that impair drug accommodation and (ii) off-target alterations, which activate alternative pro-survival signalling pathways bypassing the inhibited oncogene (Vasan *et al.*, 2019; Holohan *et al.*, 2013). A third category encompasses non-mutational adaptive mechanisms, including epigenetic reprogramming, phenotypic plasticity, and tumour microenvironment (TME)-mediated paracrine signalling (Boumahdi and de Sauvage, 2020; Shintani *et al.*, 2013). Understanding this taxonomy is essential for the rational design of sequential or combinatorial therapeutic strategies (Figure 3).

On-target secondary and tertiary mutations

The acquisition of gatekeeper or solvent-front mutations within the ATP-binding domain of the target kinase is the prototypical and best-characterised resistance mechanism. The EGFR T790M gatekeeper mutation, detected in approximately 50–60% of NSCLC patients progressing on first- or second-generation EGFR-TKIs, increases the kinase's affinity for ATP and sterically impairs inhibitor binding (Kobayashi *et al.*, 2005). This insight directly motivated the development of osimertinib a mutant-selective, irreversible third-generation covalent EGFR-TKI that potently inhibits both sensitising and T790M resistance mutations while sparing wild-type EGFR, reducing dermatological and gastrointestinal toxicity (Soria *et al.*, 2018). Upon osimertinib therapy, tertiary EGFR C797S mutation or amplification abrogates covalent drug–cysteine bond formation, necessitating fourth-generation agents (Leonetti *et al.*, 2019). Similarly, BCR-ABL T315I the 'gatekeeper' resistance mutation to first- and second-generation ABL inhibitors is effectively targeted by the third-generation agent ponatinib, and by the allosteric STAMP inhibitor asciminib (ABL myristoyl pocket binding), which demonstrated superior major molecular response rates vs. bosutinib in the ASCEMBL trial (25.5% vs. 13.2%; p=0.029) (Rea *et al.*, 2021).

Table 1: *Major oncogenic targets, approved therapeutic agents, and key clinical data.*

Oncogenic target	Alteration	Cancer type	Approved agent(s)	Mechanism	Key trial / outcome	Ref.
BCR-ABL	t(9;22) translocation	CML, Ph+ ALL	Imatinib; Dasatinib; Ponatinib; Asciminib	ATP-competitive / allosteric ABL inhibitor	IRIS: 5-yr OS 89% vs. 68% (imatinib vs. IFN+AraC)	Druker *et al.*, 2006; Hochhaus *et al.*, 2020
EGFR (exon 19 del / L858R)	Activating point mutation	NSCLC (adenocarcinoma)	Gefitinib; Erlotinib; Afatinib; Osimertinib	1st/2nd/3rd-generation EGFR TKI	FLAURA: mPFS 18.9 vs. 10.2 mo (osimertinib vs. std-TKI; HR 0.46)	Soria *et al.*, 2018; Ramalingam *et al.*, 2020
HER2 (ERBB2)	Amplification / overexpression	Breast; Gastric; Lung	Trastuzumab; Pertuzumab; Lapatinib; T-DXd; Tucatinib	Anti-HER2 mAb; HER2/EGFR TKI; ADC	CLEOPATRA: mOS 57.1 vs. 40.8 mo (pertu+tras+doce vs. tras+-doce)	Swain *et al.*, 2020; Swain *et al.*, 2023
BRAF V600E	Point mutation (codon 600)	Melanoma; CRC; NSCLC; PTC	Vemurafenib; Dabrafenib+Trametinib; Encorafenib+Binimetinib	BRAF-selective + MEK inhibitor doublet	COMBI-d: 5-yr OS 34% (dabraf+trame); BEACON: mOS 9.3 mo (triplet CRC)	Robert *et al.*, 2019; Dummer *et al.*, 2018; Kopetz *et al.*, 2019
ALK fusion	EML4-ALK rearrangement	NSCLC (~5%)	Crizotinib; Alectinib; Brigatinib; Lorlatinib	1st/2nd/3rd-gen ALK/ROS1 TKI	ALEX: mPFS 34.8 vs. 10.9 mo (alectinib vs. crizotinib; HR 0.43)	Peters *et al.*, 2017
KRAS G12C	Point mutation (codon 12)	NSCLC; CRC; PDAC	Sotorasib; Adagrasib	Covalent switch-II pocket KRAS G12C inhibitor	CodeBreaK 200: mPFS 5.6 vs. 4.5 mo (HR 0.66); KRYSTAL-1: ORR 43%	Skoulidis *et al.*, 2021; De Langen *et al.*, 2023; Janne *et al.*, 2022
PIK3CA	Hotspot mutation (E542K/ E545K/ H1047R)	HR+/ HER2- breast cancer	Alpelisib; Inavolisib	PI3Kα-selective inhibitor	SOLAR-1: mPFS 11.0 vs. 5.7 mo (HR 0.65; p<0.001)	Andre *et al.*, 2019; Jhaveri *et al.*, 2024
BRCA1/2 / HRR deficiency	Germline/ somatic LOF mutation	Ovarian; Breast; Prostate; PDAC	Olaparib; Niraparib; Rucaparib; Talazoparib	PARP trapping → synthetic lethality in HRR-deficient cells	SOLO2: mPFS 19.1 vs. 5.5 mo (HR 0.30); PROfound: HR 0.34	Pujade-Lauraine *et al.*, 2017; De Bono *et al.*, 2020
CDK4/6	Rb pathway dysregulation (loss of p16, Cyclin D amp)	HR+/ HER2- breast cancer	Palbociclib; Ribociclib; Abemaciclib	Selective CDK4/6 inhibitor → G1 cell cycle arrest	MONALEESA-2: mPFS 25.3 vs. 16.0 mo; MONALEESA-3: mOS 53.7 vs. 41.5 mo	Finn *et al.*, 2016; Slamon *et al.*, 2020
VEGF/ VEGFR	Overexpression / pathway activation	RCC; CRC; HCC; NSCLC; GBM	Bevacizumab; Sunitinib; Sorafenib; Cabozantinib; Ramucirumab	Anti-VEGF mAb; multi-target VEGFR TKI	AXIS: mPFS 8.3 vs. 5.0 mo (axitinib vs. sorafenib, 2nd-line RCC)	Rini *et al.*, 2011
NTRK1/2/3 fusion	Pan-cancer chromosomal fusion (tumour-agnostic)	17 cancer types (TRK fusion+)	Larotrectinib; Entrectinib	Pan-TRK kinase inhibitor	Pooled analysis: ORR 75% across 17 tumour types (larotrectinib)	Drilon *et al.*, 2018
MET exon 14 skip	Splice-site mutation → loss of ubiquitination domain	NSCLC (~3%)	Capmatinib; Tepotinib	Selective MET TKI	GEOMETRY mono-1: ORR 68% (treatment-naïve); mDOR 12.6 mo	Wolf *et al.*, 2020

Abbreviations: CML, chronic myeloid leukaemia; ALL, acute lymphoblastic leukaemia; Ph+, Philadelphia chromosome–positive; NSCLC, non–small-cell lung cancer; CRC, colorectal cancer; PDAC, pancreatic ductal adenocarcinoma; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; GBM, glioblastoma multiforme; PTC, papillary thyroid cancer; HR+, hormone receptor–positive; HRR, homologous recombination repair; ADC, antibody-drug conjugate; mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor; LOF, loss-of-function; amp, amplification; mPFS, median progression-free survival; mOS, median overall survival; ORR, objective response rate; mDOR, median duration of response; mo, months; HR, hazard ratio; doce, docetaxel; tras, trastuzumab; pertu, pertuzumab; IFN, interferon; AraC, cytarabine. Data from pivotal registration trials as cited; all agents approved by FDA and/or EMA.

Bypass and parallel signalling pathway activation

Off-target resistance arises when tumour cells activate alternative RTKs or downstream effectors that transduce identical pro-survival signals independently of the inhibited driver. In EGFR-mutated NSCLC, MET amplification detectable in 5–20% of T790M-negative osimertinib-resistant specimens activates PI3K/AKT and RAS/MAPK signalling in a parallel fashion (Sequist *et al.*, 2011). The bispecific EGFR–MET antibody amivantamab effectively neutralises both resistance mechanisms simultaneously, demonstrating a 29% ORR in osimertinib-pretreated patients in the MARIPOSA-2 trial (Passaro *et al.*, 2023). In BRAF V600E melanoma treated with vemurafenib monotherapy, paradoxical MAPK reactivation via RAS mutations, BRAF amplification, or alternative splicing is detected in >80% of resistant tumours (Nazarian *et al.*, 2010). This biological insight underpinned the BRAF+MEK inhibitor combinatorial strategy (dabrafenib + trametinib; encorafenib + binimetinib), which significantly delayed resistance emergence and improved 5-year OS to 34% in metastatic melanoma (Robert *et al.*, 2019; Dummer *et al.*, 2018).

Downstream pathway reactivation

Loss-of-function alterations in negative regulators of downstream signalling represent an additional tier of resistance. PTEN deletion the primary negative regulator of PI3K activates AKT/mTOR signalling downstream of RTK inhibition, thereby negating the effect of upstream blockade (Fruman *et al.*, 2017). Concurrent KRAS mutations in CRC patients receiving anti-EGFR antibody therapy (cetuximab, panitumumab) reactivate MAPK signalling downstream of EGFR, explaining the lack of efficacy in KRAS-mutant CRC and the historical ~40% primary resistance rate in unselected populations (Karapetis *et al.*, 2008). Critically, in BRAF V600E-mutated CRC, EGFR-mediated feedback reactivation of RAS/MAPK a resistance mechanism operationally absent in melanoma due to low basal EGFR expression renders BRAF monotherapy largely ineffective; cotargeting of BRAF + MEK + EGFR in the BEACON-CRC trial (encorafenib + binimetinib + cetuximab) overcame this feedback and extended median OS to 9.3 vs. 5.9 months (HR 0.60; p<0.001) (Kopetz *et al.*, 2019).

Phenotypic plasticity and lineage switching

Phenotypic transformation represents a non-mutational but clinically devastating resistance mechanism characterised by tumour cell reprogramming to an alternative lineage that is intrinsically insensitive to the employed agent. Approximately 3–10% of EGFR-mutated NSCLC tumours undergo histological transformation to small-cell lung cancer (SCLC) upon TKI pressure, acquiring a neuroendocrine phenotype characterised by co-inactivation of RB1 and TP53 (Yu *et al.*, 2013). This SCLC transformation is generally irreversible, renders tumour cells unresponsive to EGFR-directed therapy, and necessitates a shift to platinum-etoposide-based SCLC regimens; concurrent atezolizumab may provide additional benefit (Marcoux *et al.*, 2019). Epithelial to mesenchymal transition (EMT) characterised by loss of E-cadherin, upregulation of vimentin and N-cadherin, and acquisition of cancer stem cell properties mediates resistance across multiple tumour types by conferring enhanced drug efflux, anti-apoptotic signalling, and transcriptional reprogramming through ZEB1/SNAIL/TWIST transcription factors (Shintani *et al.*, 2013).

Epigenetic reprogramming and drug-tolerant persister cells

Emerging evidence implicates non-genetic, reversible epigenetic mechanisms in the initial survival of residual tumour cells under targeted therapy a subpopulation termed drug-tolerant persister (DTP) cells. DTP cells were first characterised in EGFR-mutated NSCLC and are defined by reversible upregulation of the histone H3K27 demethylase KDM5A (JARID1A), leading to global chromatin compaction and transcriptional dormancy that reduces sensitivity to EGFR-TKIs (Sharma *et al.*, 2010). These cells exhibit high IGF-1R signalling and are sensitive to combined EGFR-TKI and histone deacetylase inhibitor treatment in preclinical models (Sharma *et al.*, 2010). Chromatin remodelling factors (ARID1A, SMARCA4) are recurrently mutated or lost in resistant tumours across cancer types, further underscoring the role of epigenetic dynamics in therapeutic failure (Kadoch and Crabtree, 2015). SWI/SNF complex loss correlates with enhanced sensitivity to EZH2 inhibitors a synthetic lethal interaction with direct therapeutic implications.

Tumour microenvironment-mediated resistance

The TME comprising cancer-associated fibroblasts (CAFs), tumour-associated macrophages (TAMs), immune effector cells, and the extracellular matrix

modulates therapeutic sensitivity through paracrine ligand secretion and structural barriers. HGF secreted by CAFs activates MET signalling in a bypass fashion, conferring context-dependent resistance to EGFR, ALK, and BRAF inhibitors (Straussman *et al.*, 2012). Tumour immunosuppression mediated by PD-L1 upregulation, TGF-β secretion, and myeloid-derived suppressor cell (MDSC) recruitment attenuates the immune-mediated tumour clearance component of targeted agent activity (Chen and Mellman, 2013). The combination of targeted agents with immune checkpoint inhibitors (ICIs) aims to eradicate proliferating tumour cells and reinstate immune surveillance simultaneously; however, concurrent toxicity notably hepatotoxicity with EGFR-TKI + ICI combinations has mandated careful clinical evaluation (Ahn *et al.*, 2023).

Figure 3 illustrates the evidence matrix of acquired resistance mechanisms across major targeted therapeutic classes. Levels are graded: High (strongly supported by clinical or large translational datasets), Moderate (supported by translational or retrospective studies), Low (primarily preclinical evidence) (Vasan *et al.*, 2019; Boumahdi and de Sauvage, 2020; Holohan *et al.*, 2013; Shintani *et al.*, 2013; Kobayashi *et al.*, 2005; Leonetti *et al.*, 2019; Rea *et al.*, 2021; Sequist *et al.*, 2011; Passaro *et al.*, 2023; Nazarian *et al.*, 2010; Fruman *et al.*, 2017; Karapetis *et al.*, 2008; Yu *et al.*, 2013; Marcoux *et al.*, 2019; Sharma *et al.*, 2010; Kadoch and Crabtree, 2015; Straussman *et al.*, 2012; Chen and Mellman, 2013; Ahn *et al.*, 2023). PARP, poly (ADP-ribose) polymerase; VEGFR, vascular endothelial growth factor receptor (Table 2).

Clinical outcomes of molecular targeted therapy: A pan-cancer appraisal

The clinical impact of molecular targeted therapy has been most profound in biomarker-selected patient populations where oncogenic driver alterations are validated therapeutic targets. The following subsections synthesise landmark efficacy data across major tumour types, contextualised by mechanistic insights and resistance considerations (Figure 4) (Hyman *et al.*, 2017; Hanahan, 2022; Kargule *et al.*, 2026).

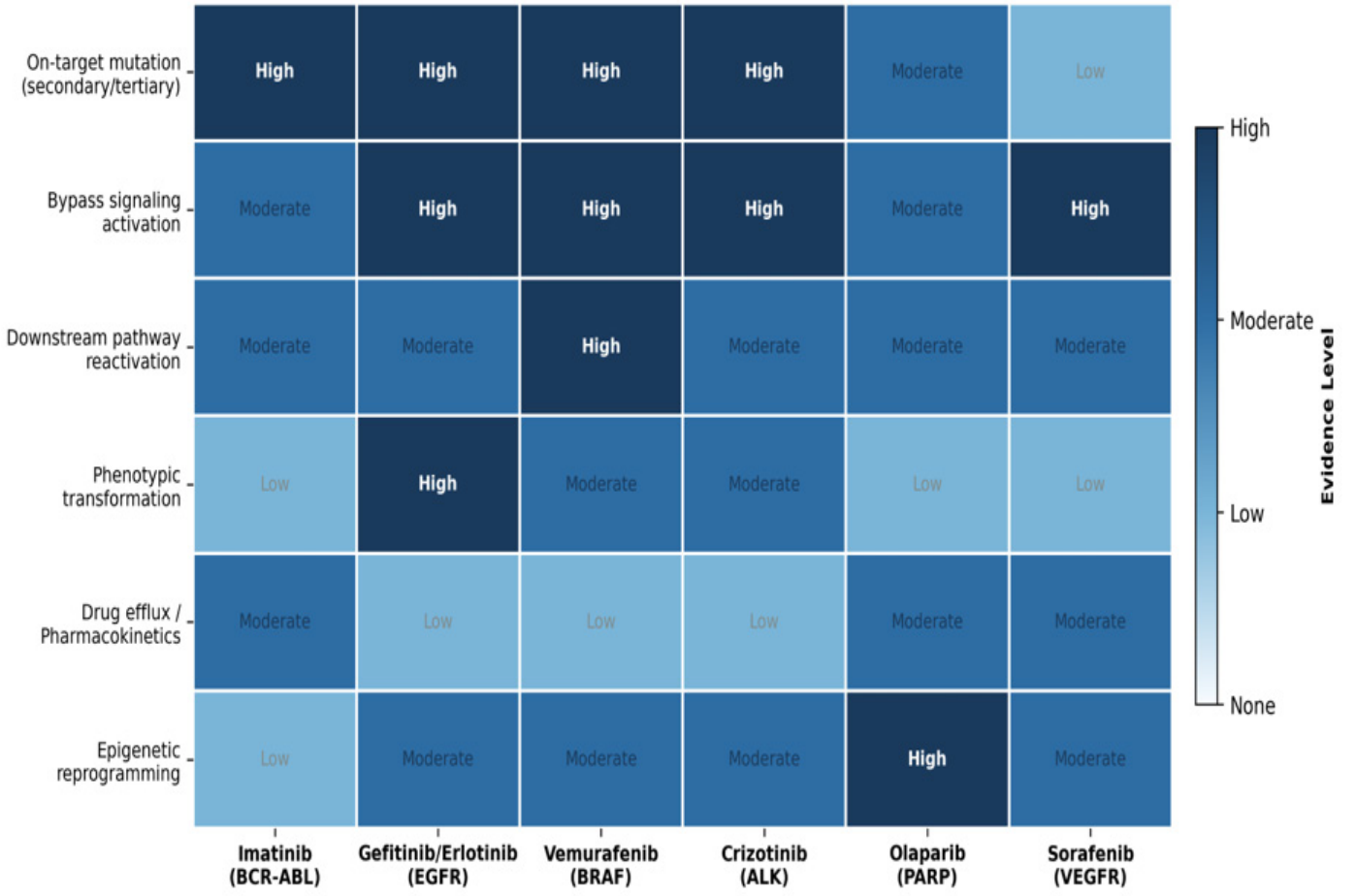

Figure 3: *Evidence matrix of acquired resistance mechanisms across major targeted therapeutic classes.*

Table 2: *Molecular mechanisms of acquired resistance: Clinical evidence and therapeutic strategies.*

Drug (Target)	Resistance mechanism	Molecular basis (Frequency)	Detection method	Therapeutic strategy	Ref.
Gefitinib/ Erlotinib (EGFR 1st-gen TKI)	On-target gatekeeper mutation	EGFR T790M (50–60% of cases)	Liquid biopsy ctDNA; tissue NGS	Osimertinib (3rd-gen mutant-selective TKI)	Kobayashi *et al.*, 2005
Osimertinib (EGFR 3rd-gen TKI)	Tertiary on-target mutation / amp.	EGFR C797S (~22%); EGFR amplification (~10%)	NGS; ddPCR; plasma ctDNA	4th-gen agents (BTP-168, BBT-176); EGFR PROTAC	Leonetti *et al.*, 2019
Osimertinib (EGFR 3rd-gen TKI)	RTK bypass signalling	MET amplification (15%); ERBB2 amp (8%)	FISH; plasma NGS	Amivantamab + lazertinib (MARIPOSA-2 trial)	Sequist *et al.*, 2011; Passaro *et al.*, 2023
Osimertinib (EGFR 3rd-gen TKI)	Phenotypic transformation	SCLC histological transformation (3–10%); RB1+TP53 co-loss	Histological rebiopsy; IHC (Rb, p53)	Platinum + etoposide ± atezolizumab	Yu *et al.*, 2013; Marcoux *et al.*, 2019
Vemurafenib (BRAF inhibitor)	Paradoxical MAPK reactivation	RAS mutation/amplification; MEK1/2 mutation; BRAF alternative splicing (>80%)	Targeted NGS panel	BRAF+MEK doublet (dabrafenib+trametinib); encorafenib+binimetinib	Nazarian *et al.*, 2010; Dummer *et al.*, 2018
Dabrafenib+Trametinib (BRAF+MEK)	ERK reactivation; EGFR feedback (CRC)	BRAF amp.; CRAF switch; EGFR reactivation (CRC-specific)	WES; ddPCR; IHC	BRAF+MEK+EGFR triplet (BEACON CRC); ERK inhibitor (ulixertinib)	Kopetz *et al.*, 2019; Fruman *et al.*, 2017
Sotorasib (KRAS G12C)	On-target switch-II pocket mutation	KRAS Y96D; H95Q/R; KRAS amp. (~20%); co-occurring RAS/RAF/MAPK alterations	ctDNA serial monitoring; NGS	Adagrasib + cetuximab (KRYSTAL-10); next-gen KRAS+SOS1 combo	Skoulidis *et al.*, 2021; Janne *et al.*, 2022
Imatinib (BCR-ABL 1st-gen)	Kinase domain point mutations	BCR-ABL T315I gatekeeper (15–20%); BCR-ABL amplification	Sanger / NGS sequencing	Ponatinib (pan-BCR-ABL); asciminib (STAMP) (ASCEMBL: MMR 25.5% vs. 13.2%)	Hochhaus *et al.*, 2020; Rea *et al.*, 2021
Crizotinib (ALK TKI 1st-gen)	ALK kinase domain mutations	L1196M, G1269A, F1174C (20–30%)	Tumor NGS; ctDNA	Alectinib; brigatinib; lorlatinib (sequential generation strategy)	Peters *et al.*, 2017
Olaparib (PARP inhibitor)	BRCA reversion mutation; 53BP1 loss	BRCA2 reversion restoring ORF (~40%); 53BP1/REST loss; CDK12 activation	ctDNA reversion testing; WGS	Platinum rechallenge; WEE1/ATR inhibitor combination; RAD51 foci assay guided	Pujade-Lauraine *et al.*, 2017; Tobalina *et al.*, 2021
Palbociclib (CDK4/6 inhibitor)	Cell cycle bypass	CDK4 amplification; RB1 loss; Cyclin E1 amplification (~30%)	IHC (Rb); FISH; NGS	PI3K/mTOR inhibitor; CDK2 inhibitor; abemaciclib (residual CDK4 activity)	Finn *et al.*, 2016; Pandey *et al.*, 2019
Bevacizumab (anti-VEGF mAb)	Alternative pro-angiogenic pathway	FGF2 upregulation; Ang-2/Tie2; pericyte coverage of vessels	Plasma cytokine profiling; IHC	Multi-target VEGFR+FGFR TKI; Ang-2/VEGF bispecific (vanucizumab)	Rini *et al.*, 2011; Shojaei and Ferrara, 2008

Abbreviations: SCLC, small-cell lung cancer; EMT, epithelial-to-mesenchymal transition; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; NGS, next-generation sequencing; ddPCR, droplet digital PCR; ctDNA, circulating tumour DNA; WES, whole-exome sequencing; WGS, whole-genome sequencing; MMR, major molecular response; amp, amplification; ORF, open reading frame; STAMP, specifically targeting the ABL myristoyl pocket. Resistance frequencies are approximate and context-dependent.

Chronic myeloid leukaemia: The proof-of-concept paradigm

CML represents the definitive proof-of-concept for molecular targeted oncology. Driven by the constitutively active BCR-ABL tyrosine kinase arising from the t (9;22) Philadelphia chromosome translocation, CML was historically fatal in blast crisis within 3–5 years without allogeneic stem cell transplantation (Druker *et al.*, 2006). The IRIS trial established imatinib as transformative: Estimated 5-year OS 89% vs. 68% with IFN + cytarabine, with complete cytogenetic response in 74% of imatinib-

treated patients at 12 months (Druker *et al.*, 2006). Second-generation inhibitors (dasatinib, nilotinib, bosutinib) achieve deeper and faster molecular responses, enabling treatment-free remission (TFR) attempts in patients who achieve sustained deep molecular response (MR4.5) (Hochhaus *et al.*, 2020). Asciminib the first STAMP inhibitor demonstrated superior MMR rates in the ASCEMBL trial (25.5% vs 13.2%; OR 2.27; p=0.029) and activity against T315I in a dedicated cohort (Rea *et al.*, 2021).

Non-small-cell lung cancer: Exemplar of multi-driver precision oncology

NSCLC has emerged as the paradigmatic example of actionable molecular stratification, with clinical guidelines mandating comprehensive biomarker profiling for EGFR, ALK, ROS1, BRAF, KRAS, MET exon 14, RET, NTRK1/2/3, and ERBB2 alterations at diagnosis (Planchard *et al.*, 2018). The FLAURA trial established osimertinib as standard first-line therapy for EGFR-mutated NSCLC (mPFS 18.9 vs. 10.2 months; HR 0.46; 95% CI 0.37–0.57; p<0.001; mOS 38.6 vs. 31.8 months; HR 0.80) (Soria *et al.*, 2018; Ramalingam *et al.*, 2020). FLAURA2 subsequently demonstrated that adding platinum-doublet chemotherapy to osimertinib further extended mPFS to 25.5 months (HR 0.62; p < 0.001), at the cost of increased toxicity (Planchard *et al.*, 2023). In ALK-rearranged NSCLC, the ALEX trial demonstrated superior alectinib over crizotinib (mPFS 34.8 vs. 10.9 months; HR 0.43), with the third-generation pan-ALK inhibitor lorlatinib achieving mPFS of 76.7% at 12 months in the CROWN trial (Peters *et al.*, 2017; Shaw *et al.*, 2020). Sotorasib became the first approved KRAS G12C inhibitor following the phase II CodeBreaK 100 study (ORR 37.1%; mDOR 11.1 months) (Skoulidis *et al.*, 2021), with superiority over docetaxel confirmed in CodeBreaK 200 (mPFS 5.6 vs. 4.5 months; HR 0.66; p=0.002) (De Langen *et al.*, 2023).

Breast cancer: Subtype-driven targeted therapy

Molecular stratification of breast cancer into HR+/HER2-, HER2-enriched, and triple-negative (TNBC) subtypes directly informs targeted therapeutic strategy. In HER2-amplified disease, the CLEOPATRA trial established the pertuzumab + trastuzumab + docetaxel triplet as standard first-line care (mOS 57.1 vs. 40.8 months; HR 0.69; p<0.001) (Swain *et al.*, 2020). The transformative DESTINY-Breast04 trial demonstrated the efficacy of T-DXd in HER2-low breast cancer (IHC 1+ or 2+/ISH-) expanding the HER2-targetable population to ~60% of breast cancer patients with mPFS of 9.9 vs. 5.1 months (HR 0.50; p<0.001) in HR+ patients (Modi *et al.*, 2022). In the HR+/HER2- subtype, CDK4/6 inhibitors combined with endocrine therapy have consistently extended PFS by approximately 9–10 months, with the MONALEESA-3 trial establishing an OS benefit for ribociclib + fulvestrant vs. Placebo (mOS 53.7 vs. 41.5 months; HR 0.73; p=0.004) (Slamon *et al.*, 2020). The INAVO120 trial (inavolisib + palbociclib + fulvestrant) demonstrated dramatic mPFS improvement of 15.0 vs. 7.3 months in PIK3CA-mutated HR+ disease (HR 0.43) (Jhaveri *et al.*, 2024).

Melanoma: Dual pathway targeting and immunotherapy integration

The BRAF V600E inhibitor vemurafenib demonstrated, for the first time, that targeting a single oncogene could induce rapid and dramatic tumour regression in advanced melanoma (ORR 48% vs. 5% for dacarbazine; HR for PFS 0.26) (Chapman *et al.*, 2011). However, median PFS of 6.9 months reflected rapid acquired MAPK resistance. The COMBI-d and COMBI-v trials established the dabrafenib + trametinib doublet as superior (5-yr OS 34%; 5-yr PFS 19%), representing unprecedented survival achievement in metastatic melanoma (Robert *et al.*, 2019). Concurrent immune checkpoint blockade with nivolumab + ipilimumab (CheckMate 067) achieves 5-year OS of 52% in unselected patients (Larkin *et al.*, 2019). Ongoing trials are evaluating the combination of BRAF/MEK inhibitors with PD-1 blockade to maximise and sustain response rates.

Figure 4 illustrates the magnitude of clinical benefit conferred by molecular targeted therapy relative to conventional or first-generation comparators across six pivotal trials spanning four tumour types. Panel A reports median progression-free survival, most directly comparable in the two EGFR/ALK-driven NSCLC trials FLAURA (osimertinib vs. standard EGFR-TKI: 18.9 vs. 10.2 months; HR 0.46) and ALEX (alectinib vs. crizotinib: 34.8 vs. 10.9 months; HR 0.43) where a shared endpoint and randomised design permit direct effect-size comparison. For CML (IRIS), melanoma (COMBI-d/COMBI-v) and HER2-positive breast cancer (CLEOPATRA), the underlying trials report benefit on OS- or landmark-survival endpoints (5-year OS 89% vs. 68%

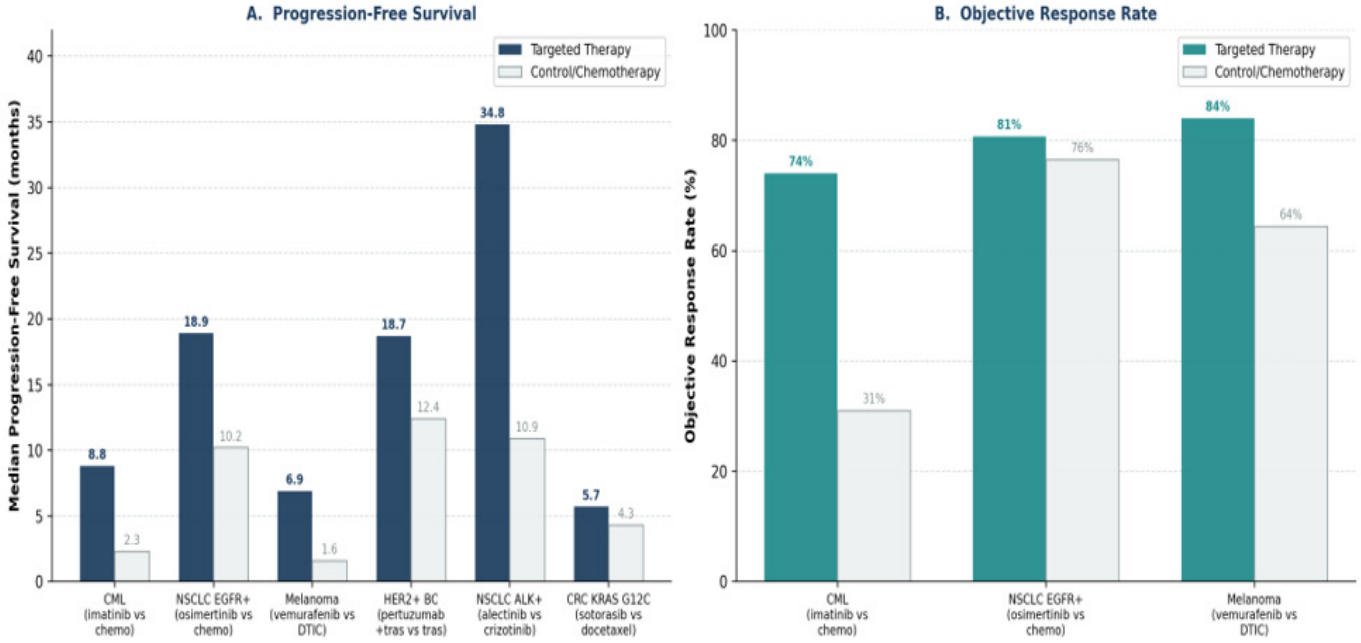

Figure 4: *Clinical outcomes of molecular targeted therapy versus conventional treatment across selected pivotal randomised controlled trials. Panel A: Median progression-free survival (months). Panel B: Objective response rates (%) for comparisons with published data. Data sourced from registration trials (Soria et al., 2018; Druker et al., 2006; Robert et al., 2019; Swain et al., 2020; Skoulidis et al., 2021; Peters et al., 2017). Error bars reflect reported confidence intervals where available. CML, chronic myeloid leukaemia; NSCLC, non-small-cell lung cancer; BC, breast cancer; CRC, colorectal cancer; DTIC, dacarbazine; tras, trastuzumab.*

for imatinib vs. interferon-α/cytarabine; 5-year OS 34% for dabrafenib plus trametinib; mOS 57.1 vs. 40.8 months for pertuzumab-trastuzumab-docetaxel) rather than a directly comparable mPFS, and are plotted alongside the PFS-based trials for illustrative rather than statistically pooled comparison. Panel B presents objective response rate data for the same trial set; the KRAS G12C NSCLC data point (Skoulidis *et al.*, 2021) derives from the single-arm phase II CodeBreaK100 study (ORR 37.1%) rather than a randomised comparator arm, and should be interpreted as a benchmark rather than a head-to-head effect estimate. Taken together, the panel underscores a consistent direction of benefit for biomarker-matched targeted therapy across mechanistically distinct settings, while highlighting that the magnitude of benefit is not directly poolable across trials owing to heterogeneity in endpoint definition, comparator selection, and trial phase. Error bars represent the 95% confidence intervals reported in the original publications, where available.

Strategies to Overcome Acquired Resistance

Sequential next-generation inhibitors

The most clinically validated resistance-overcoming strategy is the sequential deployment of structurally distinct inhibitors designed to target the specific resistance mutation identified upon disease progression an approach exemplified by the imatinib → dasatinib/nilotinib → ponatinib cascade in CML, and the gefitinib/erlotinib → osimertinib → fourth-generation agents pathway in EGFR-mutated NSCLC (Vasan *et al.*, 2019; Leonetti *et al.*, 2019; Rea *et al.*, 2021). This paradigm necessitates comprehensive molecular characterisation of resistant tumours through tissue rebiopsy or preferably ctDNA-based liquid biopsy at the time of clinical progression. Critically, the specificity and rapidity of mutation detection by plasma NGS enables expedited therapeutic switching without the morbidity of repeat tissue sampling (Merker *et al.*, 2018).

Rational vertical and horizontal combinatorial approaches

Combinatorial strategies targeting oncogenic signalling at multiple nodes are designed to suppress the clonal selection of resistant subpopulations. Vertical cotargeting within a single pathway such as BRAF + MEK + EGFR inhibition in BRAF V600E CRC (BEACON trial; mOS 9.3 vs. 5.9 months; HR 0.60; p<0.001) (Kopetz *et al.*, 2019) and horizontal

cotargeting of parallel survival pathways such as EGFR + MET bispecific antibody plus chemotherapy (MARIPOSA-2) (Passaro *et al.*, 2023) are proving clinically tractable. In breast cancer, vertical PI3K inhibition added to CDK4/6 + endocrine therapy (INAVO120) achieved an unprecedented mPFS of 15.0 months (Jhaveri *et al.*, 2024), while horizontal CDK2 inhibition added to CDK4/6 inhibitor backbone is under evaluation to overcome Cyclin E-driven resistance (Pandey *et al.*, 2019).

Liquid biopsy-guided adaptive therapy

Circulating tumour DNA (ctDNA) analysis enables non-invasive, real-time genomic monitoring of resistance evolution, facilitating early detection of emergent resistance clones weeks to months before radiological progression (Merker *et al.*, 2018). The AURA3 trial demonstrated 93% concordance of plasma EGFR T790M detection with tissue biopsy, validating the plasma-first rebiopsy strategy that has since become standard practice (Mok *et al.*, 2015). The ctDNA-DYNAMIC trial demonstrated that ctDNA-guided adjuvant chemotherapy decisions in stage II colon cancer maintained DFS non-inferiority while sparing ~50% of patients unnecessary chemotherapy (HR 1.06; 90% CI 0.70–1.62) (Tie *et al.*, 2022). Multianalyte liquid biopsy platforms integrating ctDNA with circulating tumour cells (CTCs), cell-free RNA, and methylation profiling represent the next generation of resistance-monitoring tools (Ignatiadis *et al.*, 2021).

Artificial intelligence and machine learning in therapeutic optimisation

Artificial intelligence (AI) and machine learning (ML) are increasingly applied to predict drug resistance, identify synthetic lethality interactions, and optimise therapeutic sequencing (Sammut *et al.*, 2022). Deep-learning-based protein structure prediction, exemplified by AlphaFold, has opened the way to structure-guided design of small molecules against previously intractable targets such as KRAS (Jumper *et al.*, 2021). Deep learning models trained on multi-omic data (genomics, transcriptomics, proteomics) have demonstrated superior predictive accuracy for clinical response compared with single-omics approaches in preclinical validation studies (Sammut *et al.*, 2022). AI-driven 'molecular tumour boards' integrating genomic reports, treatment history, and clinical trial databases in real time are transitioning from experimental to routine clinical implementation at major cancer centres (Kurnit *et al.*, 2017) (Table 3).

Emerging Frontiers in Molecular Targeted Oncology

Tumour-agnostic targeting and basket trial design

A paradigmatic shift in oncology is the adoption of tumour-agnostic therapeutic indications, wherein drug approval is predicated on the molecular alteration rather than the tissue of origin. Larotrectinib a selective pan-TRK inhibitor received the first-ever tumour-agnostic FDA approval based on an ORR of 75% (95% CI 63–84%) across 17 cancer types harbouring NTRK gene fusions, with a durable 12-month response duration in 71% of responders (Drilon *et al.*, 2018). Pembrolizumab has received tumour-agnostic approvals for MSI-H/dMMR tumours (KEYNOTE-158; ORR 34.3%) and TMB-high tumours (≥10 mut/Mb; ORR 29%) (Marabelle *et al.*, 2020). This paradigm demands comprehensive molecular profiling at diagnosis ideally by comprehensive genomic profiling (CGP) panels covering all FDA-actionable alterations and challenges the histology-centric design of clinical trials and reimbursement frameworks (Schwaederle *et al.*, 2016).

Antibody-drug conjugates: Next-generation platform

ADCs represent a rapidly maturing therapeutic platform that combines the selectivity of tumour antigen-targeting monoclonal antibodies with the cytotoxic potency of chemotherapy payloads delivered intracellularly via cleavable linker chemistry. T-DXd achieves a drug-to-antibody ratio (DAR) of 8 substantially higher than first-generation ADCs enabling a 'bystander killing effect' in adjacent HER2-negative cells via a membrane-permeable DXd payload (Modi *et al.*, 2022; Ogitani *et al.*, 2016). Beyond breast cancer, T-DXd is approved in HER2-amplified gastric cancer, HER2-mutated NSCLC, and HER2-expressing CRC. Sacituzumab govitecan (Trop-2 targeting, SN-38 payload) demonstrated mPFS of 5.6 vs. 1.7 months in metastatic TNBC (ASCENT trial; HR 0.41) (Bardia *et al.*, 2021). More than 80 ADCs are in active clinical development across oncology.

Table 3: *Selected phase II/III clinical trials of combination strategies to overcome resistance.*

Trial (Phase)	Cancer Type	Combination Strategy	Population	Primary Outcome	Status	Ref.
BEACON CRC (Phase III)	BRAF V600E CRC	Encorafenib + Binimetinib + Cetuximab vs. Irinotecan+Cetuximab	Prior chemo (2nd/3rd line)	mOS 9.3 vs. 5.9 mo; HR 0.60; p<0.001	FDA-approved 2020	Kopetz *et al.*, 2019
MARIPOSA-2 (Phase III)	EGFR-mutant NSCLC	Amivantamab + Chemo ± Lazertinib vs. Chemo alone	Post-osimertinib progression	mPFS 6.3 vs. 4.2 mo; HR 0.48; p<0.001	FDA-approved 2024	Passaro *et al.*, 2023
MARIPOSA (Phase III)	EGFR-mutant NSCLC	Amivantamab + Lazertinib vs. Osimertinib	1st-line EGFR-mutant (exon 19 del/ L858R)	mPFS 23.7 vs. 16.6 mo; HR 0.70; p<0.001	FDA-approved 2024	Cho *et al.*, 2024
FLAURA2 (Phase III)	EGFR-mutant NSCLC	Osimertinib + Platinum-doublet chemo vs. Osimertinib alone	1st-line EGFR-mutant	mPFS 25.5 vs. 16.7 mo; HR 0.62; p<0.001	Approved (FDA/EMA 2024)	Planchard *et al.*, 2023
INAVO120 (Phase III)	PIK3CA-mutant HR+/ HER2- BC	Inavolisib + Palbociclib + Fulvestrant vs. Placebo + Palbo + Fulvestrant	Post-aromatase inhibitor (1st line)	mPFS 15.0 vs. 7.3 mo; HR 0.43; p<0.001	FDA-approved 2024	Jhaveri *et al.*, 2024
MONALEESA-3 (Phase III)	HR+/HER2- BC	Ribociclib + Fulvestrant vs. Placebo + Fulvestrant	Post-endocrine therapy (1st/2nd line)	mOS 53.7 vs. 41.5 mo; HR 0.73; p=0.004	FDA-approved 2017	Slamon *et al.*, 2020
KRYSTAL-10 (Phase III)	KRAS G12C CRC	Adagrasib + Cetuximab vs. Chemo (FOLFIRI ± bevacizumab)	2nd-line KRAS G12C-mutant CRC	mPFS 5.6 vs. 2.2 mo; HR 0.44; ORR 34% vs. 2%	FDA-approved 2024	Wainberg *et al.*, 2024
POLO (Phase III)	BRCA1/2-mutant PDAC	Olaparib maintenance vs. Placebo	Post-platinum 1st-line (no progression)	mPFS 7.4 vs. 3.8 mo; HR 0.53; p=0.004	FDA-approved 2019	Golan *et al.*, 2019
DESTINY-Breast04 (Phase III)	HER2-low BC	Trastuzumab Deruxtecan (T-DXd) vs. Physician's choice chemo	HR+/HER2-low (IHC1+ or 2+/ISH-)	mPFS 9.9 vs. 5.1 mo; HR 0.50; p<0.001 (HR+ cohort)	FDA-approved 2022	Modi *et al.*, 2022
ASCEMBL (Phase III)	CML (≥2 prior TKIs)	Asciminib vs. Bosutinib	CML-CP after ≥2 prior TKIs	MMR at 24 wks: 25.5% vs. 13.2%; OR 2.27; p=0.029	FDA-approved 2021	Rea *et al.*, 2021

Abbreviations: CRC, colorectal cancer; NSCLC, non-small-cell lung cancer; BC, breast cancer; PDAC, pancreatic ductal adenocarcinoma; HR+, hormone receptor-positive; HER2, human epidermal growth factor receptor 2; CML, chronic myeloid leukaemia; CML-CP, CML chronic phase; T-DXd, trastuzumab deruxtecan; IHC, immunohistochemistry; ISH, in situ ybridization; MMR, major molecular response; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; mo, months; wks, weeks; HR, hazard ratio; OR, odds ratio; chemo, chemotherapy; palbo, palbociclib.

PROTAC-mediated targeted protein degradation

PROTACs (Proteolysis-Targeting Chimaeras) represent a mechanistically distinct approach that redirects the endogenous ubiquitin-proteasome system (UPS) to degrade a target protein of interest, rather than merely inhibiting its catalytic activity (Bekes *et al.*, 2022). By engaging the target protein with one moiety and recruiting an E3 ubiquitin ligase (e.g., CRBN or VHL) with another, PROTACs catalytically degrade the target protein in a sub-stoichiometric manner, achieving sustained suppression that circumvents resistance mechanisms dependent on mutations within the drug-binding domain (Bekes *et al.*, 2022; Ahamed *et al.*, 2026). Clinical-stage PROTACs include ARV-471 (PROTAC targeting ER+ breast cancer; mPFS 5.7 months in VERITAC-2 trial) (Hamilton *et al.*, 2024), ARV-766 (AR PROTAC in mCRPC), and multiple BRD4/KRAS PROTAC candidates in Phase I.

Synthetic lethality: Expanding beyond PARP inhibition

The success of PARP inhibitors in BRCA-deficient cancers has catalysed systematic exploration of synthetic lethal interactions across the broader DNA damage response (DDR) network (Lord and Ashworth, 2017). ATR kinase inhibitors (ceralasertib, elimusertib) exploit ATM loss or replication stress to selectively induce lethal replication catastrophe in cancer cells, with ceralasertib + olaparib demonstrating ORR of 47% in ATM-deficient advanced cancers

(Yap *et al.*, 2021). WEE1 kinase inhibitors (adavosertib, ZN-c3) abrogate the S/G2 checkpoint in TP53-mutant tumours, forcing mitotic entry with unrepaired DNA (Leijen *et al.*, 2016). The MTAP deletion present in ~15% of all solid tumours and creating synthetic lethality with PRMT5 inhibition via substrate competition represents a potentially pan-cancer actionable vulnerability currently targeted by AMG193 and PRT811 in early-phase trials (Mavrakis *et al.*, 2016) (Table 4).

Table 4: *Promising next-generation molecular targets under active clinical investigation.*

Target / pathway	Alteration/ Context	Candidate agent(s)	Cancer type	Mechanism	Phase	Ref.
KRAS G12D/ G12V	Point mutation codon 12 (non-G12C; undruggable until 2023)	MRTX1133; RMC-9805; RM-018	PDAC, CRC, NSCLC	Non-covalent KRAS G12D inhibitor; pan-KRAS (tri-complex)	Phase I/II (2024)	Wang *et al.*, 2022
SOS1 (RAS GEF)	RAS/MAPK hyperactivation (pan-KRAS context)	BI-1701963 + Trametinib; BBO-8520	KRAS-mutant pan-cancer	SOS1 allosteric inhibitor → RAS-GEF disruption	Phase I/II	Hofmann *et al.*, 2022
SHP2 (PTPN11)	RAS/MAPK feed-forward loop (KRAS co-dependency)	TNO155 + Ribociclib; RMC-4630 + Cobimetinib	KRAS-mutant pan-cancer	SHP2 allosteric inhibitor → RAS pathway suppression	Phase I/II	Hofmann *et al.*, 2022
ATR kinase	ATM loss; replication stress (HRR-deficient tumours)	Ceralasertib + Olaparib; Elimusertib + Chemo	ATM-deleted tumours; TNBC; NSCLC	ATR inhibition → replication catastrophe (synthetic lethality)	Phase I/II	Yap *et al.*, 2021
WEE1 kinase	TP53 mutation; replication stress (pan-cancer)	Adavosertib; ZN-c3; IZN-1042	Ovarian, NSCLC, AML	S/G2 checkpoint abrogation → premature mitosis	Phase I–III	Leijen *et al.*, 2016
PRMT5 (methyltransferase)	MTAP deletion (~15% of all solid tumours)	AMG193; PRT811; SCI-ON-03	GBM, PDAC, NSCLC (MTAP-deleted)	Synthetic lethality via MTA accumulation → PRMT5 inhibition	Phase I (2023–2024)	Mavrakis *et al.*, 2016
MCL-1 (anti-apoptotic)	BCL-2 family dysregulation; MMp53 co-alteration	AMG176; AZD5991; AZD0466 (MCL-1+BCL-xL)	Haematological malignancies; TNBC	BH3-mimetic MCL-1 inhibition → mitochondrial apoptosis	Phase I/II	Kotschy *et al.*, 2016
CDK2	Cyclin E amplification (post-CDK4/6i resistance)	Milciclib; PF-07104091; BLU-222	HR+ Breast Cancer (post CDK4/6 inhibitor)	Selective CDK2 inhibitor → block Cyclin E-driven bypass	Phase I/II	Pandey *et al.*, 2019
FGFR2/3	FGFR2 fusion (CCA); FGFR3 mut/fusion (bladder)	Pemigatinib; Infigratinib; Erdafitinib; Futibatinib	CCA; Urothelial carcinoma	Pan-FGFR or selective irreversible TKI	Approved + Phase III	Meric-Bernstam *et al.*, 2022
RET fusion/ mutation	RET fusion (NSCLC, PTC); RET M918T (MTC)	Selpercatinib; Pralsetinib	NSCLC; MTC; PTC	Highly selective RET TKI (spares VEGFR2, avoids oedema)	Approved (FDA 2020)	Wirth *et al.*, 2020

Abbreviations: PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small-cell lung cancer; CRC, colorectal cancer; GBM, glioblastoma multiforme; AML, acute myeloid leukaemia; TNBC, triple-negative breast cancer; CCA, cholangiocarcinoma; MTC, medullary thyroid cancer; PTC, papillary thyroid cancer; HR+, hormone receptor-positive; DDR, DNA damage response; GEF, guanine-exchange factor; MTA, methylthioadenosine; MTAP, methylthioadenosine phosphorylase; HRR, homologous recombination repair; BH3, BCL-2 homology 3; VEGFR2, vascular endothelial growth factor receptor 2.

Discussion

The present review synthesises the expansive and rapidly evolving landscape of molecular targeted therapy in human oncology, charting the transformation from empirical cytotoxic chemotherapy to mechanism-informed, biomarker-directed precision medicine. The cumulative clinical evidence unambiguously demonstrates that molecularly selected targeted therapy achieves superior ORRs and PFS compared

with conventional therapy in biomarker-positive populations superiority that has translated into OS benefits in landmark trials including IRIS (CML) (Druker *et al.*, 2006), CLEOPATRA (HER2+ breast cancer) (Swain *et al.*, 2020), COMBI-d (BRAF V600E melanoma) (Robert *et al.*, 2019), MONALEESA-3 (HR+ breast cancer) (Slamon *et al.*, 2020), and BEACON-CRC (Kopetz *et al.*, 2019).

A critical and recurring theme throughout this review is the biological inevitability of acquired resistance. The multiple converging mechanisms delineated in Section 3 on-target mutations, bypass signalling, downstream reactivation, phenotypic transformation, and epigenetic reprogramming collectively underscore the remarkable adaptive plasticity of malignant cells under selective therapeutic pressure (Vasan *et al.*, 2019; Boumahdi and de Sauvage, 2020; Holohan *et al.*, 2013). The heterogeneous clonal architecture of tumours, predetermining the pre-existence of minor resistant subclones that expand upon drug selection, has been rigorously characterised by single-cell DNA and RNA sequencing studies (Maynard *et al.*, 2020). This insight argues strongly against targeting single molecular nodes in isolation and reinforces the rationale for rational upfront combination strategies, as exemplified by the MARIPOSA and FLAURA2 trials in EGFR-mutated NSCLC (Planchard *et al.*, 2023; Cho *et al.*, 2024).

The emergence of tumour-agnostic approvals represents a conceptual evolution that challenges histocentric cancer classification and validates the primacy of molecular over anatomical taxonomy (Drilon *et al.*, 2018; Marabelle *et al.*, 2020; Schwaederle *et al.*, 2016). This paradigm will intensify clinical demand for comprehensive genomic profiling at diagnosis, necessitating equitable access to NGS technology globally a major health system and health economics challenge, particularly in low- and middle-income countries where the majority of the global cancer burden resides (Sung *et al.*, 2021). The rapid clinical translation of PROTACs, ADCs with novel payloads, synthetic lethality exploiters (ATR/WEE1/PRMT5 inhibitors), and pan-KRAS inhibitors collectively signals that the druggable oncoproteome continues to expand substantially (Bekes *et al.*, 2022; Mavrakis *et al.*, 2016; Wang *et al.*, 2022). The integration of AI-driven multi-omic analysis with ctDNA-based longitudinal monitoring holds the greatest promise for real-time adaptive therapeutic orchestration a framework in which treatment decisions are continuously informed by evolving tumour genomic dynamics rather than fixed at the time of diagnosis (Merker *et al.*, 2018; Sammut *et al.*, 2022; Kurnit *et al.*, 2017; Khamis *et al.*, 2026). Several limitations of the current review merit acknowledgement. The predominantly retrospective and mechanistic nature of resistance studies largely conducted in selected academic cohorts with comprehensive molecular profiling may not reflect the full complexity of resistance biology in unselected clinical populations. Furthermore, the majority of resistance data derive from NSCLC and breast cancer, with substantially less clinical evidence available for rarer tumour types despite their often higher proportional frequencies of actionable alterations. Publication bias towards positive trials and early-phase results may overestimate the therapeutic benefit of emerging agents. Lastly, the rapid pace of approvals with several agents receiving accelerated approval on single-arm phase II data necessitates cautious interpretation pending confirmatory randomised trial results.

Conclusion

Molecular targeted therapy has irrevocably transformed oncology, converting several historically incurable malignancies CML, BRAF-mutated melanoma, EGFR-mutated NSCLC, HER2-amplified breast cancer into conditions compatible with prolonged high-quality survival or, in CML, potential functional cure. The breadth of actionable oncogenic alterations continues to expand, with emerging targets including KRAS G12D, PRMT5, MCL-1, SOS1, and WEE1 enriching the therapeutic armamentarium and extending precision oncology to previously intractable cancer types. Overcoming acquired resistance the defining challenge of targeted oncology requires a multipronged strategy encompassing next-generation inhibitor development, rational vertical and horizontal combination regimens, liquid biopsy-guided adaptive therapy, and AI-assisted molecular tumour board integration. The future of precision oncology lies in the convergence of multi-omic tumour characterisation, longitudinal resistance monitoring, and intelligent therapeutic orchestration a vision that is rapidly transitioning from experimental promise to clinical reality.

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Novelty Statement

Much of the existing literature on molecular targeted therapy is organised around a single tumour type or a single mechanistic class of agent, which tends to obscure the recurring biological logic that governs both response and relapse across cancers with entirely different tissues of origin. The present review departs from that convention by adopting a pan-cancer, mechanism-first architecture: Rather than surveying oncology drug classes tumour by tumour, it constructs a unified taxonomy of acquired resistance on-target mutation, bypass-pathway activation, downstream reactivation, phenotypic lineage switching, epigenetic persistence, and microenvironment-mediated protection and then maps landmark clinical trial evidence onto that taxonomy rather than the reverse.

Author's Contribution

Duha Mudher Abbas, as the sole author of this review, was responsible for the entirety of the work: conceptualisation of the pan-cancer, resistance-centred framework; the literature search and screening across PubMed, Embase, and ClinicalTrials.gov; critical appraisal and synthesis of the primary trial and mechanistic literature; drafting of the original manuscript; design of the figures and summary tables; and the review, editing, and final approval of the submitted version. The author takes full responsibility for the integrity of the work and for ensuring that questions relating to the accuracy of any part of it are appropriately investigated and resolved.

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Conflict of interest
The authors have declared no conflict of interest.

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