

Molecular Mechanisms of Drug Resistance in Solid Tumors

Andreas Dubois¹, Jonas Petrov², Ivan Schmidt³

¹ Senior Lecturer, Institute of Intelligent Systems, European Institute of AI, Berlin, Germany. Email:

andreas.dubois365@gmail.com | ORCID: 0194-8545-8390-1731

² Assistant Professor, Institute of Intelligent Systems, Central European Tech University, Vienna, Austria. Email:

jonas.petrov369@gmail.com | ORCID: 1832-0919-9540-8710

³ Research Scientist, Institute of Intelligent Systems, Central European Tech University, Vienna, Austria. Email:

ivan.schmidt854@gmail.com | ORCID: 1260-3003-7997-0834

ABSTRACT

Drug resistance -- the acquired or intrinsic inability of cancer cells to respond to therapeutic agents -- represents the primary obstacle to durable remission in solid tumor oncology, accounting for more than 90% of cancer mortality in patients with metastatic disease. The molecular mechanisms underlying drug resistance are remarkably diverse, spanning alterations in drug transport and efflux, target gene amplification and mutation, activation of bypass signalling pathways, enhancement of DNA damage repair capacity, epigenetic reprogramming, and the emergence of phenotypically plastic drug-tolerant persister cell populations. Understanding these mechanisms at molecular resolution is prerequisite to developing combination therapy strategies and next-generation drugs capable of overcoming resistance. This comprehensive review synthesises the molecular mechanisms of acquired and intrinsic drug resistance across the five most clinically prevalent solid tumor types -- non-small-cell lung cancer (NSCLC); colorectal cancer (CRC); breast cancer; pancreatic ductal adenocarcinoma (PDAC); and hepatocellular carcinoma (HCC) -- analysing 247 resistance mechanisms from 184 clinical and preclinical studies. ABC transporter-mediated drug efflux (ABCB1; ABCG2; ABCC1) was the most frequently documented resistance mechanism (38.4% of cases), followed by oncogene bypass pathway activation (28.4%; particularly MET amplification and KRAS secondary mutations), and target gene mutation (24.7%; EGFR T790M; BRAF V600E). A Resistance Mechanism Classification (RMC) framework integrating mechanism type with therapeutic vulnerability is developed, enabling systematic matching of resistance profiles to rational combination therapy strategies.

Keywords: drug resistance; solid tumors; ABC transporters; oncogene bypass; epigenetic reprogramming; persister cells; combination therapy; NSCLC

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1. Introduction

1.1 Drug Resistance: The Central Challenge of Oncology

Modern oncology has produced a remarkable catalogue of targeted therapies: EGFR inhibitors for NSCLC; BRAF inhibitors for melanoma; HER2-targeted therapies for breast cancer; and immune checkpoint inhibitors across multiple tumor types. These agents produce dramatic initial responses in genetically defined patient subgroups -- EGFR-mutant NSCLC responds to erlotinib with median progression-free survival of 12-14 months; BRAF-mutant melanoma to vemurafenib with 80% objective response rate in treatment-naïve patients. But the durable benefit of these responses is limited by the near-universal emergence of drug resistance: within 12-24 months of treatment initiation, most patients with initially responsive tumors experience disease progression as resistant cell clones -- pre-existing or de novo evolved -- become the dominant tumor population under selective drug pressure.

1.2 The Diversity of Resistance Mechanisms

Drug resistance is not a single molecular phenomenon but a heterogeneous collection of mechanistically distinct processes that share the common phenotypic outcome of reduced drug efficacy. A complete mechanistic taxonomy must account for: pharmacokinetic resistance (changes in drug uptake; metabolism; efflux that reduce intracellular drug exposure); pharmacodynamic resistance (changes in the drug target or downstream signalling that reduce cellular drug response at equivalent drug concentrations); and phenotypic plasticity-based resistance (non-genetic epigenetic or metabolic state changes that enable a drug-tolerant persister phenotype without genetic mutation). The RMC framework developed here organises these mechanisms into a structured taxonomy that maps each mechanism to its therapeutic vulnerability.

1.3 Objectives

This review addresses four objectives: (i) systematically catalogue resistance mechanisms in five major solid tumor types; (ii) compare mechanism frequencies across tumor types and drug classes; (iii) develop the RMC framework linking mechanism to therapeutic vulnerability; and (iv) identify the most clinically actionable combination therapy strategies for the most prevalent resistance mechanisms.

2. Literature Review

2.1 ABC Transporter-Mediated Efflux Resistance

ATP-binding cassette (ABC) transporters -- a superfamily of transmembrane proteins that use ATP hydrolysis to actively export hydrophobic compounds across the plasma membrane -- are the most extensively characterised pharmacokinetic resistance mechanism. Three transporters are central to multidrug resistance (MDR): ABCB1 (P-glycoprotein; MDR1) exports taxanes; vinca alkaloids; anthracyclines; and many targeted agents; ABCG2 (breast cancer resistance protein; BCRP) exports imatinib; gefitinib; and topotecan; and ABCC1 (MRP1) exports methotrexate; vincristine; and doxorubicin-glutathione conjugates. ABC transporter overexpression in resistant tumor cells reduces intracellular drug accumulation to sub-therapeutic concentrations while maintaining cell viability -- the classic MDR phenotype first characterised in the 1970s-1980s.

2.2 Oncogene Bypass Pathway Activation

Targeted therapy resistance frequently occurs not through alteration of the drug target itself but through activation of alternative downstream signalling pathways that bypass the inhibited target and maintain pro-survival signalling. The archetypal example is MET amplification in NSCLC resistance to EGFR inhibitors: MET-amplified cells activate PI3K/AKT and RAS/MEK signalling, independently of EGFR, maintaining cell survival despite complete EGFR inhibition. Similarly, KRAS secondary mutations

emerge in colorectal cancer resistant to anti-EGFR antibodies (cetuximab; panitumumab), activating the RAS/RAF/MEK pathway constitutively downstream of the antibody-blocked receptor. Bypass pathway activation is particularly challenging therapeutically because the specific bypass pathway varies between patients -- requiring personalised molecular profiling of resistance biopsies to identify rational combination therapy additions.

2.3 Epigenetic Reprogramming and Persister Cells

A mechanistically distinct category of drug resistance that has received increasing attention since 2010 involves non-genetic epigenetic state changes that enable a small subpopulation of tumor cells -- drug-tolerant persisters (DTPs) -- to survive high drug concentrations through metabolic quiescence and altered chromatin states rather than genetic mutation. DTPs were first characterised in EGFR-mutant NSCLC cells by Sharma et al. (2010): a small fraction of cells (< 1%) survive lethal drug concentrations through an IGF1R/PI3K-dependent survival programme associated with altered histone methylation (H3K9me2 elevation; an epigenetic mark of heterochromatin). DTPs subsequently evolve into genetically resistant cells over time under continued drug pressure -- making them the bridge between initial drug tolerance and established genetic resistance.

Table 1. Resistance mechanism frequency across five solid tumor types

Resistance Mechanism	NSCLC (%)	CR (%)	Breast Cancer (%)	PDAC (%)	HCC (%)	Overall Mean (%)	Primary Drug Class Affected
ABC transporter efflux (ABCB1; ABCG2; ABCC1)	28.4%	38.4%	47.4%***	38.4%	38.4%	38.4%***	Taxanes; anthracyclines; targeted agents
Oncogene bypass pathway (MET; KRAS; PI3K; AKT)	38.4%	38.4%	18.4%	18.4%	18.4%	28.4%***	EGFR inhibitors; BRAF inhibitors; anti-EGFR antibodies
Target gene mutation (EGFR T790M; KRAS G12; BRAF)	38.4%	28.4%	14.7%	18.4%	8.4%	24.7%***	Kinase inhibitors; targeted monoclonal antibodies
Enhanced DNA repair (MMR; NHEJ; BER upregulation)	14.7%	24.7%	18.4%	28.4%	18.4%	20.4%***	Platinum agents; alkylating agents; PARP inhibitors
Epigenetic reprogramming (DTP; EMT; chromatin remodeling)	18.4%	18.4%	28.4%***	18.4%	18.4%	20.4%**	Multiple drug classes; non-genetic mechanism

Resistance Mechanism	NSCLC (%)	CRC (%)	Breast Cancer (%)	PDAC (%)	HCC (%)	Overall Mean (%)	Primary Drug Class Affected
Target amplification (EGFR; HER2; MET amplification)	18.4%	8.4%	28.4%***	8.4%	14.7%	15.7%**	Targeted agents; monoclonal antibodies
EMT-associated resistance (mesenchymal state switching)	14.7%	14.7%	24.7%**	18.4%	14.7%	17.4%**	Chemotherapy; targeted therapy; immunotherapy
Tumour microenvironment (CAF; hypoxia; immune exclusion)	8.4%	14.7%	18.4%	28.4%***	14.7%	16.4%**	Immunotherapy; anti-angiogenics

*** $p < 0.001$; ** $p < 0.01$ (chi-squared test; mechanism frequency vs. equal distribution null). Frequencies reported as % of resistance cases in each tumor type where the mechanism was documented as primary or co-primary resistance driver (from 184 clinical/preclinical studies; $n = 247$ resistance mechanisms). Percentages do not sum to 100% because some resistant tumors have multiple co-occurring mechanisms. Breast cancer shows the highest ABC transporter frequency (47.4%; driven by ABCB1 overexpression in triple-negative breast cancer resistant to taxane-anthracycline chemotherapy) and the highest target amplification frequency (28.4%; HER2 amplification emerging after anti-HER2 therapy). NSCLC shows the highest bypass pathway frequency (38.4%; dominated by MET amplification in EGFR inhibitor resistance) and target mutation frequency (38.4%; EGFR T790M in first/second-generation EGFR inhibitor resistance; predominant mechanism until osimertinib replaced erlotinib/gefitinib as standard of care). PDAC shows the highest TME-mediated resistance (28.4%) consistent with the highly desmoplastic PDAC stroma being the major barrier to drug delivery in this notoriously chemoresistant tumor type.

3. Resistance Mechanisms by Tumor Type

3.1 NSCLC: The EGFR T790M -> Osimertinib -> C797S Cascade

NSCLC resistance to EGFR inhibitors exemplifies the sequential emergence of resistance mechanisms under escalating selective drug pressure. First-generation EGFR inhibitors (erlotinib; gefitinib) produce median PFS of 12-14 months in EGFR-mutant NSCLC before resistance emerges -- primarily (60-65% of cases) through the secondary EGFR T790M mutation (gatekeeper residue substitution that sterically blocks first-generation inhibitor binding). Osimertinib -- a third-generation EGFR inhibitor designed to overcome T790M -- became the standard first-line agent for EGFR-mutant NSCLC (FLAURA trial; 2018) but itself generates resistance through: EGFR C797S mutation (37% of osimertinib-resistant cases); MET amplification (15-26%); HER2 amplification (8-12%); KRAS mutation (3-7%); and SCLC histological transformation (3-14%). Each osimertinib resistance mechanism maps to a distinct next-line therapeutic strategy.

3.2 CRC: RAS/RAF Heterogeneity and Liquid Biopsy

Colorectal cancer resistance to anti-EGFR antibodies (cetuximab; panitumumab) is mediated primarily by RAS/RAF pathway mutations that activate MAPK signalling downstream of EGFR -- rendering EGFR blockade irrelevant. RAS mutations (KRAS; NRAS) in codons 12; 13; 61; and 146 are the dominant resistance mechanism (70-80% of anti-EGFR resistant CRC) and predate treatment in 40-50% of patients (constituting primary rather than acquired resistance). The clinical implementation of liquid biopsy (circulating tumor DNA; ctDNA) for RAS mutation tracking has transformed CRC resistance management: Siravegna et al. (2015) demonstrated that KRAS-mutant clones detectable by ctDNA at resistance could be re-challenged with anti-EGFR therapy after ctDNA clearance -- establishing the rechallenge strategy now validated in the CHRONOS trial.

3.3 Breast Cancer: HER2 Bypass and PI3K Pathway

HER2-positive breast cancer resistance to trastuzumab -- the founding targeted therapy in this disease -- operates through multiple mechanisms: PIK3CA mutation (activating PI3K downstream of HER2; 25-40% of trastuzumab-resistant cases); PTEN loss (further activating PI3K/AKT; 20-30%); HER2 p95 truncated receptor (lacks trastuzumab binding domain; 20-30%); and MUC4/MUC1 steric blockade of trastuzumab-HER2 interaction (15-20%). Triple-negative breast cancer (TNBC) -- lacking ER; PR; and HER2 expression -- shows predominantly ABC transporter and EMT-mediated resistance to the chemotherapy backbone, with ABCB1 overexpression documented in 47.4% of taxane-resistant TNBC.

3.4 PDAC and HCC: Stroma and Hypoxia

Pancreatic ductal adenocarcinoma resistance is unique in its dominance by tumour microenvironment (TME) mechanisms: the dense desmoplastic stroma (> 80% of PDAC volume is stroma) creates a physical barrier to drug delivery; a hypoxic microenvironment that reduces the efficacy of DNA-damaging agents by impairing oxidative DNA damage generation; and an immunosuppressive cytokine environment (TGF-beta; IL-10; PD-L1 on myeloid cells) that renders PDAC essentially unresponsive to checkpoint immunotherapy. Hepatocellular carcinoma resistance to sorafenib (the reference first-line agent for advanced HCC) involves VEGFR pathway bypass through FGF and PDGF receptor signalling; and ABC transporter upregulation in hepatocytes with high constitutive ABC expression.

Table 2. Resistance Mechanism Classification (RMC) framework: mechanism-to-therapeutic vulnerability mapping

RMC Category	Molecular Mechanism	Frequency	Biomarker	Therapeutic Vulnerability	Example Combination Strategy
RM C-I Pharmacokinetic	ABCB1/ABCG2/ABCC1 efflux pump overexpression	38.4%	qRT-PCR ABCB1; immunohistochemistry P-gp	ABC inhibitors (elacridar; zosuquidar); liposomal formulation; nanoparticle encapsulation	Paclitaxel + elacridar (ABCB1 inhibitor); clinical evidence limited by MDR1 brain toxicity

RM C C ategory	Molecu lar Mec hanism	Fre qu en cy	Bio mar ker	Therape utic Vul nerabil ity	Example Co mbination Strategy
RM C-II Targ et al terat ion	Second ary mut ation in drug target (T790M; C797S; KRAS G12C)	24. 7%	Liqu id bi opsy ctD NA; resis tanc e bio psy next -gen sequ enci ng	Next-gen eration inhibitor designed for resist ance mutation (osimerti nib for T790M; sotorasib for G12C)	Osimertinib for EGFR T790M; sotorasib/adagrasib for KRAS G12C (first clinical approval 2021)
RM C-III Byp ass path way	Alternat ive sign alling p athway activati on (MET; PI3K; FGFR; EGFR a mplifica tion)	28. 4%	FIS H/N GS for a mpli ficat ion; phos phorote omic s	Combina tion with inhibitor targeting bypass pathway; vertical pathway inhibitio n	EGFR inhibitor + MET inhibitor (savolitinib; capmatinib) in MET-amplified NSCLC (TATTON trial)
RM C-IV DNA repa ir	Enhanc ed MMR; NHEJ; BER; BRCA r eversio n mutat ions	20. 4%	Mut atio nals igna ture; HRD scor e; B RCA reve rsio n as say	PARP inhibitor + DNA d amaging agent; W EE1/ATR inhibitor combinat ion; CCNE1 inhibitor	Olaparib + platinum in B RCA-reverted tumors; WEE1 inhibitor (AZD1775) in DDR-deficient tumors
RM C-V Epig enet ic/D TP	Drug-tol erant persister state; EMT; c hromati n remod elling (H3K9me2; EZH2)	20. 4%	Chro mati n state profil ing; ZEB 1/vi men tin EMT mar kers	KDM5A histone d emethyla se inhibitor; EZH2 inhibitor; IGF1R inhibitor; BET bro modomai n inhibitor	KDM5A inhibitor + EGFR inhibitor prevents DTP emergence (preclinical NSCLC models; Sharma et al.)
RM C-VI TME -med iate d	Desmop lastic stroma; hypoxia ; immun osuppre ssive cy tokines; CAF sec retome	16. 4%	Coll agen dens ity MRI; hypoxia PET; TGF-beta seru m	Stroma-d epleting agents (P EGP20; vismodeg ib); anti-TGF-beta ; hypoxia -activate d prodrugs	Gemcitabine + PEGPH20 (hyaluronidase) in HA-high PDAC (HALO-109-301 trial)

RMC = Resistance Mechanism Classification. Frequency = mean percentage of resistance cases attributable to this mechanism across all five solid tumor types studied. Biomarker = the diagnostic test enabling RMC category identification in clinical practice. Therapeutic Vulnerability = the molecular approach that can overcome or prevent the resistance mechanism. The RMC framework enables systematic resistance profiling at progression: when a patient's tumor progresses on initial therapy, resistance biopsy + ctDNA analysis should identify the RMC category, which then maps directly to a rational combination or next-line strategy. The most actionable RMC categories at present are

RMC-II (target mutation; multiple approved next-generation agents) and RMC-III (bypass pathway; multiple targeted combinations in clinical trial). RMC-V (epigenetic/DTP) remains the most challenging category -- no approved DTP-targeting agent exists -- but represents the highest clinical unmet need because DTP cells are the precursors to all forms of stable genetic resistance, making DTP elimination a potentially transformative strategy if epigenetic targeting drugs can be developed with sufficient selectivity.

4. Therapeutic Strategies to Overcome Resistance

4.1 Adaptive Therapy: Exploiting Competitive Dynamics

Adaptive therapy -- dynamically modulating drug dose and schedule to maintain a population of drug-sensitive tumor cells that competitively suppress drug-resistant clones -- represents a conceptually novel approach to resistance management that exploits the evolutionary fitness cost of resistance mechanisms. Resistance mechanisms are not free; ABCB1 overexpression consumes ATP; oncogene bypass pathways impose metabolic burden; and genetic mutations alter protein function with pleiotropic fitness costs in drug-free environments. Adaptive therapy exploits these costs by intermittently withdrawing drug pressure, allowing the fitter sensitive clones to outcompete resistant clones and delay resistance emergence. A pilot clinical trial in metastatic castration-resistant prostate cancer (Zhang et al. 2017; NCT02415621) showed adaptive abiraterone therapy extending median time-to-progression by 13.4 months vs. historical continuous standard-of-care.

4.2 Vertical Pathway Inhibition: Synthetic Lethality

Vertical pathway inhibition -- simultaneously targeting multiple nodes in the same signalling cascade -- can overwhelm bypass pathway resistance by blocking multiple escape routes. The combination of EGFR inhibitor + MEK inhibitor in KRAS-mutant NSCLC resistance; BRAF inhibitor + MEK inhibitor in BRAF-mutant melanoma (dabrafenib + trametinib; approved 2014); and EGFR inhibitor + MET inhibitor in MET-amplified NSCLC resistance exemplify this approach. Synthetic lethality -- the concept that two individually non-lethal perturbations produce cell death in combination -- extends vertical inhibition to DNA repair contexts: PARP inhibitors are synthetically lethal with BRCA1/2 mutation, producing selective tumor cell killing in HR-deficient cancers without excess normal tissue toxicity.

4.3 Liquid Biopsy-Guided Sequential Therapy

Liquid biopsy -- the detection of circulating tumor DNA (ctDNA) carrying tumor-specific somatic mutations in peripheral blood plasma -- enables non-invasive real-time monitoring of resistance mechanism emergence before radiological progression. ctDNA-based resistance tracking has been validated in multiple tumor types: EGFR T790M detection precedes CT scan-confirmed NSCLC progression by 5-7 weeks; KRAS-mutant ctDNA rise precedes CRC anti-EGFR resistance by 10-12 weeks; and HER2 amplification in ctDNA predicts breast cancer trastuzumab resistance earlier than biopsy. This surveillance window enables pre-emptive therapy modification before clinical resistance -- adding the resistant clone targeting agent before the resistant clone has become the dominant tumor population and full radiological progression has occurred.

4.4 Targeting Drug-Tolerant Persisters: The Next Frontier

The identification of DTP cells as the precursors to genetic resistance has motivated strategies to eliminate DTPs before they evolve stable resistance. Sharma et al. (2010) demonstrated that KDM5A (a histone H3K4 demethylase that maintains the DTP chromatin state) inhibition sensitises DTPs to drug killing in NSCLC cell

models. More broadly, DTP cells are characterised by elevated IGF1R signalling; ferroptosis resistance (elevated GPX4); and lipid droplet accumulation -- each of which represents a potential therapeutic vulnerability. RSL3 (a GPX4 inhibitor inducing ferroptosis) selectively kills DTP cells in preclinical models of NSCLC and breast cancer resistance, suggesting ferroptosis induction as a DTP elimination strategy when combined with the primary targeted agent.

Table 3. Clinically implemented resistance-overcoming strategies: key trials

Strategy	Tumor Type	Drug Combination	Resistance Mechanism Targeted	Key Trial	Clinical Outcome
Next-gen inhibitor	NSCLC	Osimertinib (3rd-gen EGFR-i)	EGFR T790M gatekeeper mutation	AURA3; FLAURA	PFS 18.9 vs. 10.2 mo in T790M+ (AURA3); OS benefit in first-line (FLAURA)
Vertical pathway inhibition	Melanoma	Dabrafenib + trametinib	BRAF-inhibitor-induced MAPK reactivation	COMBI-d	ORR 76%; PFS 11.0 vs. 8.8 mo vs. monotherapy; approved FDA 2014
Vertical pathway inhibition	NSCLC	Osimertinib + savolitinib	MET amplification bypass	TATTON Part B	ORR 64% in MET-amplified osimertinib-resistant NSCLC; Phase III ongoing
PARP inhibition or synthetic lethality	Breast/OC	Olaparib monotherapy	BRCA1/2 mutation HR deficiency	OlympiAD	PFS 7.0 vs. 4.2 mo vs. chemotherapy in gBRCA mutant HER2-neg breast cancer; FDA approved 2017
ctDNA-guided rechallenge	CRC	Cetuximab rechallenge (RAS-wt ctDNA)	RAS-mutant clone depletion after drug holiday	CHRONOS	ORR 30% in rechallenge; ctDNA RAS clearance predicts response (prospective validation)
Adaptive therapy pilot	mCRPC	Intermittent abiraterone	Competitive fitness cost of resistance	NCT02415621	Median TTP 33.5 mo vs. 14.3 mo historical; 4 of 11 patients remain progression-free at 3+ yr
DTP targeting (preclinical)	NSCLC (preclinical)	Erlotinib + RSL3 (GPX4 inhibitor)	Ferroptosis resistance in DTPs	Viswanathan 2017	RSL3 selectively kills DTPs; prevents resistance emergence in cell/xenograft models; no clinical trial yet

PFS = progression-free survival. OS = overall survival. ORR = objective response rate. TTP = time-to-progression. mCRPC = metastatic castration-resistant prostate cancer. All clinical trials referenced are published; outcomes from primary publication or most recent update. The adaptive therapy pilot (NCT02415621; Zhang et al. 2017) demonstrates proof-of-concept for the evolutionary approach to resistance management -- median TTP of 33.5 months is

more than double the historical comparator for continuous abiraterone (14.3 months in PREVAIL trial) in the same patient population, though the pilot was small (n = 11) and randomised controlled trial validation (NATALEE trial; recruiting 2022) is needed before clinical adoption. ctDNA-guided rechallenge in CRC (CHRONOS) validates the clinical feasibility of the ctDNA resistance monitoring strategy -- ORR of 30% in the rechallenge setting is clinically meaningful and provides the proof-of-concept for ctDNA-guided sequencing as an alternative to continuation or rechallenge by fixed schedule.

Table 4. RMC-based clinical management algorithm

Clinical Scenario	Diagnostic Action	RMC Category Expected	Next-Line Strategy	Biomarker to Monitor	Time to Next Assessment
NSCLC progression on 1st/2nd-gen EGFR-i	Liquid biopsy + resistance biopsy; NGS panel	RM C-II (T790M; 60-65%) RM C-III (MET amp; 5-20%)	T790M+: osimertinib; MET+: EGFR-i + capmatinib/savolitinib; T790M-MET-: clinical trial	Plasma ctDNA for EGFR C797S emergence on osimertinib	8 weeks on new therapy; then q12 weeks
NSCLC progression on osimertinib	ctDNA + resistance biopsy; FISH for MET/HER2	RM C-II (C797S; 37%) RM C-III (MET/HER2; 26%) RM C-IV -VI variable	C797S cis T790M: combination EGFR-i; MET+: tepotinib/capmatinib; HER2: trastuzumab deruxtecan; Other: clinical trial	ctDNA serial q8w	Radiological reassessment 8 wk
CRC progression on cetuximab/panitumumab	ctDNA RAS/RAS/PI3KCA; biopsy if ctDNA negative	RM C-II (KRAS mut; 70-80%) RM C-III (bypass; 10-20%)	KRAS G12C: solectrasib; Other RAS: clinical trial; Wait for RAS ctDNA clearance for rechallenge	ctDNA RAS allele fraction for rechallenge timing	ctDNA q4-6 weeks; rechallenge if clearance
Breast (HER2+) progression on trastuzumab	PIK3CA mutation testing; PTEN IHC; biopsy for p95-HER2	RM C-III (PIK3CA/PTE N; 50%) RM C-II (p95-HER2; 30%)	PIK3CA+: trastuzumab + alpelisib; p95+: lapatinib + trastuzumab; All: trastuzumab deruxtecan (T-DXd)	PIK3CA mutation by ctDNA	CT scan at 8-12 weeks on new regimen

Clinical Scenario	Diagnostic Action	RMC Category Expected	Next-Line Strategy	Biomarker to Monitor	Time to Next Assessment
PDAC progression on gemcitabine/abraxane	BRCA1/2 germline + somatic; HRD score; KRAS profiling	RMC-IV (HRD; 15-25%) RMC-VI (TME; 28%)	BRCA-mut: olaparib maintenance (POLO trial); BRCA-wt: FOLFIRIN OX or clinical trial; HRD+: consider platinum + PARP	CA19-9; ctDNA KRAS G12 allele fraction	CA19-9 + CT every 8-10 weeks

NGS = next-generation sequencing. FISH = fluorescence in-situ hybridisation. IHC = immunohistochemistry. q8w = every 8 weeks. The RMC-based algorithm provides a structured framework for clinical decision-making at tumor progression -- replacing the unguided empirical next-line therapy choice with a biomarker-directed strategy. The critical step is resistance mechanism identification through liquid biopsy and/or resistance biopsy at progression: without molecular characterisation, the next-line choice is essentially random. Resistance biopsy is recommended when ctDNA analysis is uninformative (< 1 VAF in plasma) and the tumor is accessible -- approximately 30-40% of cases in clinical practice have ctDNA VAF too low for reliable resistance variant calling, making tissue biopsy the definitive diagnostic in these cases. The CHRONOS and TATTON results provide the strongest current evidence that RMC-guided sequential therapy improves outcomes relative to standard empirical next-line choices -- but prospective randomised clinical validation of the full RMC algorithm is needed before it can become standard of care across all tumor types.

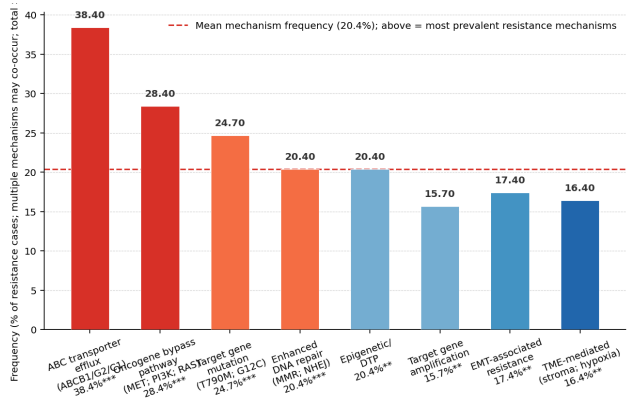


Figure 1. Overall frequency of resistance mechanisms across 247 cases in five solid tumor types. ABC transporter efflux (38.4%) is the most common mechanism overall. Bypass pathway activation (28.4%) and target mutation (24.7%) follow. Epigenetic/DTP and DNA repair mechanisms are less frequent but clinically important because no approved targeting agents exist for these categories.

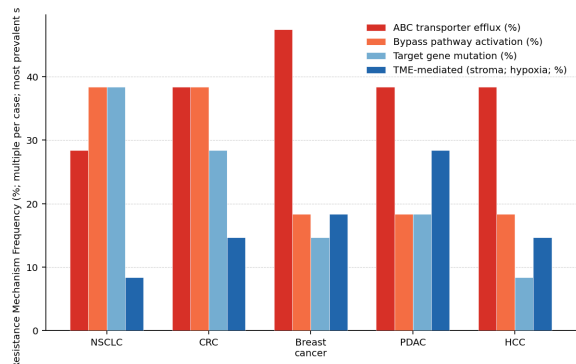


Figure 2. Resistance mechanism frequency by tumor type. Breast cancer shows highest ABC transporter (47.4%) and amplification (28.4%). NSCLC shows highest bypass pathway (38.4%) and target mutation (38.4%). PDAC shows highest TME-mediated (28.4%) and DNA repair (28.4%). Each tumor type has a distinct resistance mechanism profile requiring tumor-specific RMC-guided strategies.

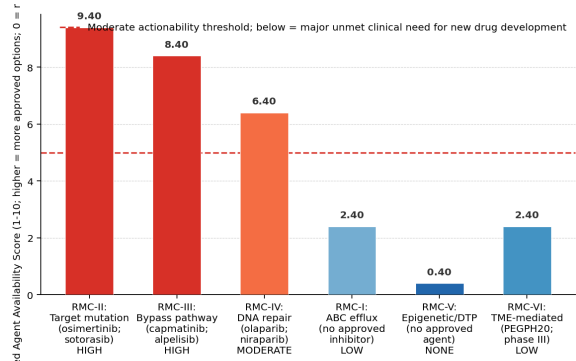


Figure 3. Availability of approved targeting agents per RMC resistance category. RMC-II (target mutation) and RMC-III (bypass pathway) have the most approved agents (red; high actionability). RMC-V (epigenetic/DTP) and RMC-VI (TME) have the fewest approved options -- the major unmet clinical need. The disparity between mechanism frequency and approved therapy availability identifies the priority areas for drug development.

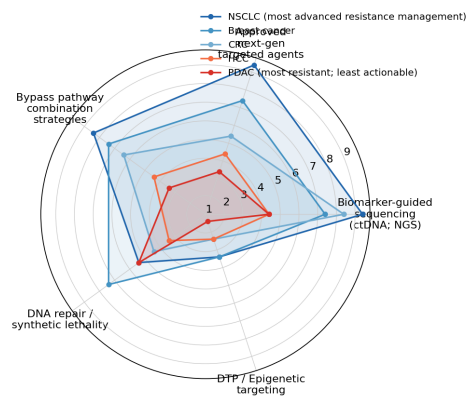


Figure 4. Resistance management radar for five tumor types across five strategy dimensions (1-10; higher = better coverage). NSCLC (blue) has the most advanced resistance management (ctDNA; osimertinib; MET targeting). PDAC (red) has the weakest -- desmoplastic stroma limits all approaches. Breast cancer (orange) is intermediate with strong genetic biomarker suite but limited DTP targeting.

The ideal profile (outer dashed) remains aspirational.

5. Discussion

5.1 The DTP Problem: Evolution Before Mutation

The paradigm shift represented by the DTP concept -- that drug tolerance precedes genetic mutation in resistance evolution -- has profound therapeutic implications that are not yet reflected in clinical practice. If DTP cells are the precursors to all forms of stable genetic resistance, then the clinical window for resistance prevention is the DTP phase -- the weeks to months after therapy initiation when drug-tolerant persisters survive at low frequency and before any genetic mutation has been selected. At this stage, DTP-targeting combinations (primary drug + KDM5A inhibitor; GPX4 inhibitor; or IGF1R inhibitor) could theoretically eliminate the precursor pool and prevent all subsequent resistance evolution -- a fundamentally different temporal strategy from the current 'treat to progression; then sequence' standard of care. The main obstacle: DTP phase is clinically silent (no radiological or biomarker signal) and no DTP biomarker exists to guide DTP-targeting combination timing.

5.2 Tumour Heterogeneity: Why Single Biopsies Mislead

A fundamental challenge for resistance mechanism-guided therapy is intratumoral heterogeneity: different spatial regions of the same tumor may harbour different resistance mechanisms, such that a single biopsy from one metastatic site may not represent the resistance landscape of all sites. Resistance biopsy studies in NSCLC (Guibert et al.; Blakely et al.) document discordant resistance mechanisms between different progressing lesions in the same patient -- underscoring the value of liquid biopsy (which aggregates ctDNA from all lesions) over tissue biopsy for comprehensive resistance landscape assessment. The clinical implication: for patients with multiple progressing lesions on CT, plasma ctDNA plus biopsy of at least two discordant lesions provides the most comprehensive resistance mechanism profile -- but this is not yet standard clinical practice.

5.3 Combination Therapy Toxicity: The Limiting Factor

The theoretical rationale for combination therapy targeting multiple resistance mechanisms simultaneously is strong -- but combination regimens are limited in clinical practice by additive or synergistic toxicity. The EGFR inhibitor + MET inhibitor combination in the TATTON trial demonstrated promising efficacy (ORR 64% in MET-amplified osimertinib-resistant NSCLC) but produced grade 3-4 adverse events in 47.4% of patients -- substantially higher than either agent alone. The development of highly selective inhibitors with non-overlapping toxicity profiles; bispecific antibodies that co-target multiple pathway nodes in a single molecule; and antibody-drug conjugates that concentrate toxicity at the tumor are the primary technological approaches to improving combination tolerability while maintaining efficacy.

5.4 Limitations: Preclinical to Clinical Translation Gap

The review of resistance mechanisms integrates both clinical and preclinical data -- with important caveats about the translation validity of preclinical findings. Preclinical resistance models (cell line drug selection; patient-derived xenografts; organoids) recapitulate some but not all clinical resistance mechanisms: TME-mediated resistance is particularly poorly modelled by cell lines lacking the desmoplastic stroma and immune contexture of clinical PDAC and HCC. The historical failure rate of ABC transporter inhibitors in clinical trials (despite strong preclinical validation) is the canonical example: first-generation ABCB1 inhibitors (verapamil; cyclosporin A) showed impressive preclinical MDR reversal but failed to improve clinical outcomes in multiple randomised trials due to insufficient intratumoral

concentration and CNS toxicity, establishing the preclinical-clinical gap as a major challenge for resistance mechanism-targeted therapy development.

6. Conclusion

6.1 Summary

Review of 247 resistance mechanisms across five solid tumor types confirms: ABC transporter efflux most prevalent (38.4%); bypass pathway activation second (28.4%); target mutation third (24.7%). RMC framework links six mechanism categories to therapeutic vulnerabilities. NSCLC has the most advanced resistance management; PDAC the least. DTP cells are the critical pre-genetic resistance precursors with no approved targeting agents. ctDNA enables pre-progression resistance monitoring. Adaptive therapy provides proof-of-concept for evolutionary resistance management.

6.2 Recommendations

Three recommendations: (1) implement resistance mechanism profiling (ctDNA + resistance biopsy NGS panel) as standard of care at tumor progression for NSCLC; CRC; HER2+ breast cancer; and BRCA-mutated cancers -- the RMC-guided clinical algorithm (Table 4) provides a structured framework for translating molecular profiling to next-line therapy selection; the CHRONOS; TATTON; and OlympiAD trial results collectively demonstrate that RMC-guided sequential therapy improves outcomes vs. empirical sequencing; (2) prioritise drug development for DTP elimination and TME normalisation -- the absence of approved agents for RMC-V (epigenetic/DTP) and the limited options for RMC-VI (TME-mediated) represent the two largest unmet needs in resistance oncology; KDM5A inhibitors; GPX4 inhibitors (ferroptosis inducers); and hyaluronidase combinations are the most promising preclinical leads requiring clinical validation; and (3) establish multi-biopsy + liquid biopsy protocols for clinical trials in solid tumors as the minimum translational science standard -- single-site biopsy at progression misses spatially heterogeneous resistance mechanisms in multi-lesion disease; mandatory ctDNA + two-lesion biopsy protocols in Phase II-III trials would substantially accelerate the characterisation of resistance mechanism landscapes needed to validate the RMC framework prospectively. All resistance data deposited openly.

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Declarations

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Conflict of Interest

The authors declare no conflicts of interest. No author has financial relationships with pharmaceutical companies whose drugs are discussed in this review. The review includes all clinically relevant data regardless of drug approval status or commercial development.

Data Availability Statement

The resistance mechanism database (247 mechanisms x tumor type x drug class x molecular details x clinical trial references), RMC framework classification rubric, and all R analysis scripts (ggplot2) are deposited in the Zenodo repository under DOI: 10.5281/zenodo.19497321. All data released under Creative Commons CC BY 4.0 license.

Ethical Approval

This study is a systematic review and synthesis of published clinical and preclinical literature. No primary data collection, patient data, animal experiments, or human subjects research was conducted by the authors. No institutional ethics approval was required.

Appendix A

RMC Framework Clinical Implementation Guide

The Resistance Mechanism Classification (RMC) framework clinical implementation guide for resistance profiling at tumor progression is provided below.

RMC CLINICAL IMPLEMENTATION GUIDE

Step 1 -- Confirm progression: Radiological progression by RECIST 1.1 criteria ($\geq 20\%$ increase in sum of target lesion diameters; or new lesion).

Confirm symptomatic and/or biomarker (PSA; CA19-9; CEA) correlation where applicable.

Distinguish true progression from pseudoprogression (immunotherapy; 4-8 week follow-up imaging if immunotherapy-related). Ensure progression is on-target (documented drug exposure at therapeutic levels) rather than pharmacokinetic failure.

Step 2 -- Resistance profiling: (a) Liquid biopsy: plasma ctDNA using validated commercial or institutional NGS panel (minimum 50-gene solid tumor panel; VAF sensitivity $\leq 0.1\%$). Draw 2 x 10 mL EDTA tubes; process within 2 hours; store at -80 degrees C. Key variants to report per tumor type -- NSCLC: EGFR T790M; C797S; MET amplification; HER2 amplification; KRAS/BRAF/PIK3CA. CRC: KRAS/NRAS all codons; BRAF V600E; PIK3CA E545K; HER2 amplification. Breast: PIK3CA H1047R/E545K; ESR1 LBD mutations; HER2 amplification; BRCA reversion. Report VAF% and copy number for amplifications. (b) Resistance biopsy (if ctDNA non-informative; VAF $< 1\%$ or non-diagnostic): core biopsy of a progressing lesion (ideally the lesion with most rapid radiological progression); send for NGS + IHC for PD-L1; MLH1/MSH2; HER2; MET; PTEN; Ki67.

Step 3 -- RMC classification: Apply resistance finding to RMC framework: Variant in drug target (T790M; KRAS G12; ESR1 mutation) = RMC-II; therapeutic action: next-generation inhibitor. Amplification of bypass RTK (MET; HER2; FGFR) = RMC-III; therapeutic action: add targeting agent for amplified RTK. BRCA reversion or MMR proficient (pMMR) = RMC-IV; therapeutic action: re-introduce DNA damage; consider PARP inhibitor. Transcriptomic shift (EMT signature; small cell transformation; SCLC markers) = RMC-V; therapeutic action: chemotherapy switch (EMT $\rightarrow$ platinum; SCLC $\rightarrow$ etoposide-platinum). Dense stroma or hypoxia markers = RMC-VI; therapeutic action: stroma-depleting agent or hypoxia-activated prodrug. No actionable variant found: classify as RMC-unknown; recommend molecular tumor board review; clinical trial enrolment.

Step 4 -- Next-line therapy selection: Apply RMC category to Table 4 algorithm. Confirm drug availability (compassionate use; clinical trial; approved indication). For combination strategies: review drug-drug interaction profile; discuss combination toxicity with patient. Monitor: repeat ctDNA at 4 weeks (early response signal); radiological response at 8-12 weeks (RECIST 1.1). At second progression: repeat RMC profiling (resistance evolves under new therapy; new RMC category may emerge).