

BiRAGAS.

Oncology Pathway Atlas

Failed therapies and mechanisms of resistance, illustrated

209 cited pathway figures across 27 cancer types

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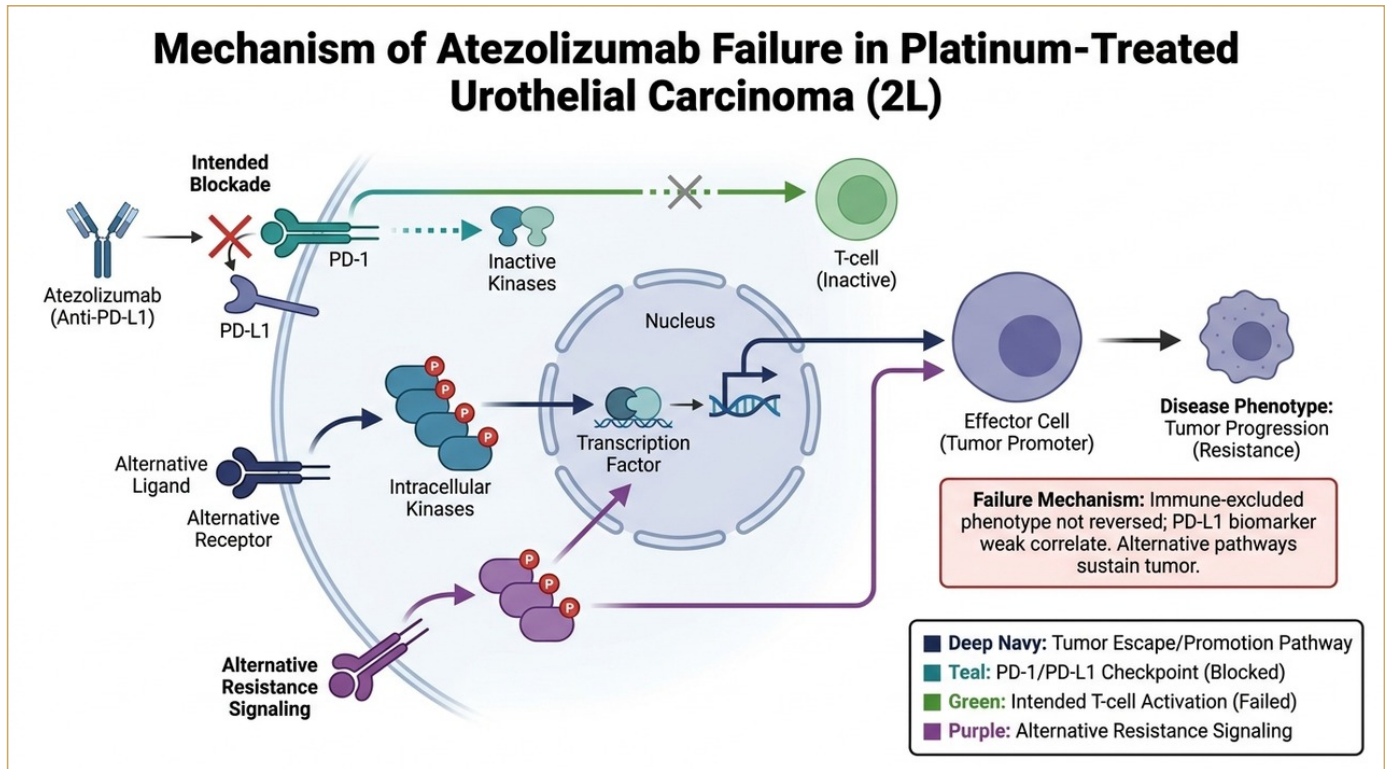
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Atezolizumab

Platinum-treated locally advanced/metastatic urothelial carcinoma (2L)



Indication: Platinum-treated locally advanced/metastatic urothelial carcinoma (2L)

Resistance / failure mechanism:

PD-L1 IHC selection failed to enrich for benefit; biomarker was a weak correlate, and the immune-excluded/depleted phenotype in the selected subgroup was not reversed by PD-L1 blockade.

BiRAGAS pattern P3 · population-dilution

Citation: Powles T et al. Lancet 2018;391:748-757. PMID 29268948

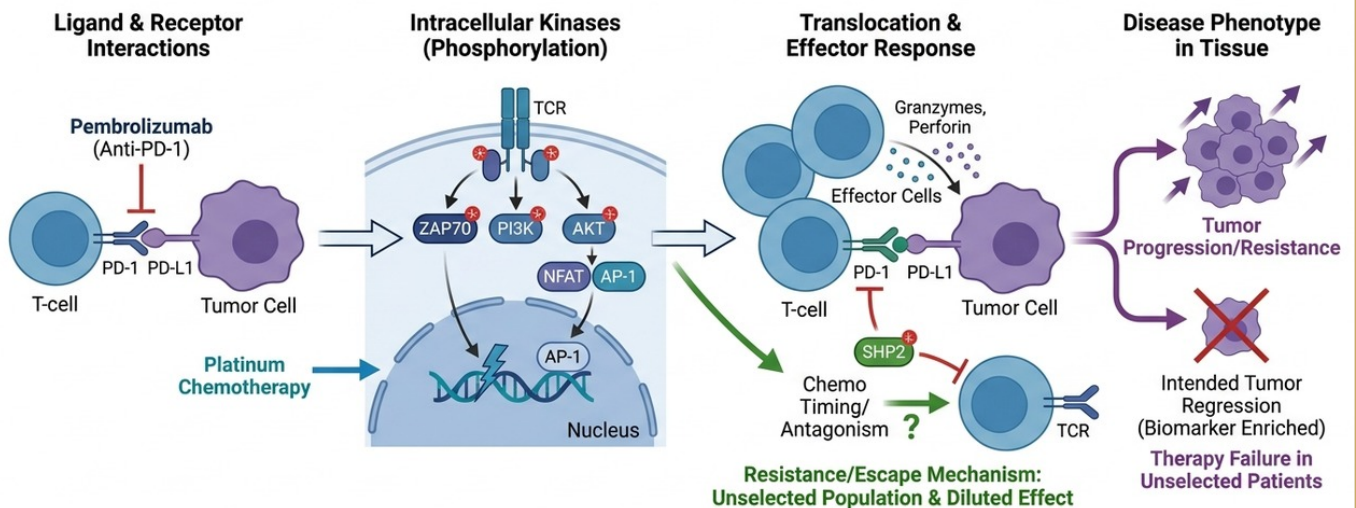
ClinicalTrials.gov: [NCT02302807](https://clinicaltrials.gov/ct2/show/study/NCT02302807)

Pembrolizumab +/- platinum chemotherapy

Advanced/unresectable urothelial carcinoma (first-line)

Mechanism of Therapy Failure in Advanced Urothelial Carcinoma (First-Line)

Deep Navy: Anti-PD-1 Pathway
Teal: Platinum Chemotherapy Action
Green: Resistance/Escapes Mechanism
Purple: Tumor Cell Signaling & Phenotype



Indication: Advanced/unresectable urothelial carcinoma (first-line)

Resistance / failure mechanism:

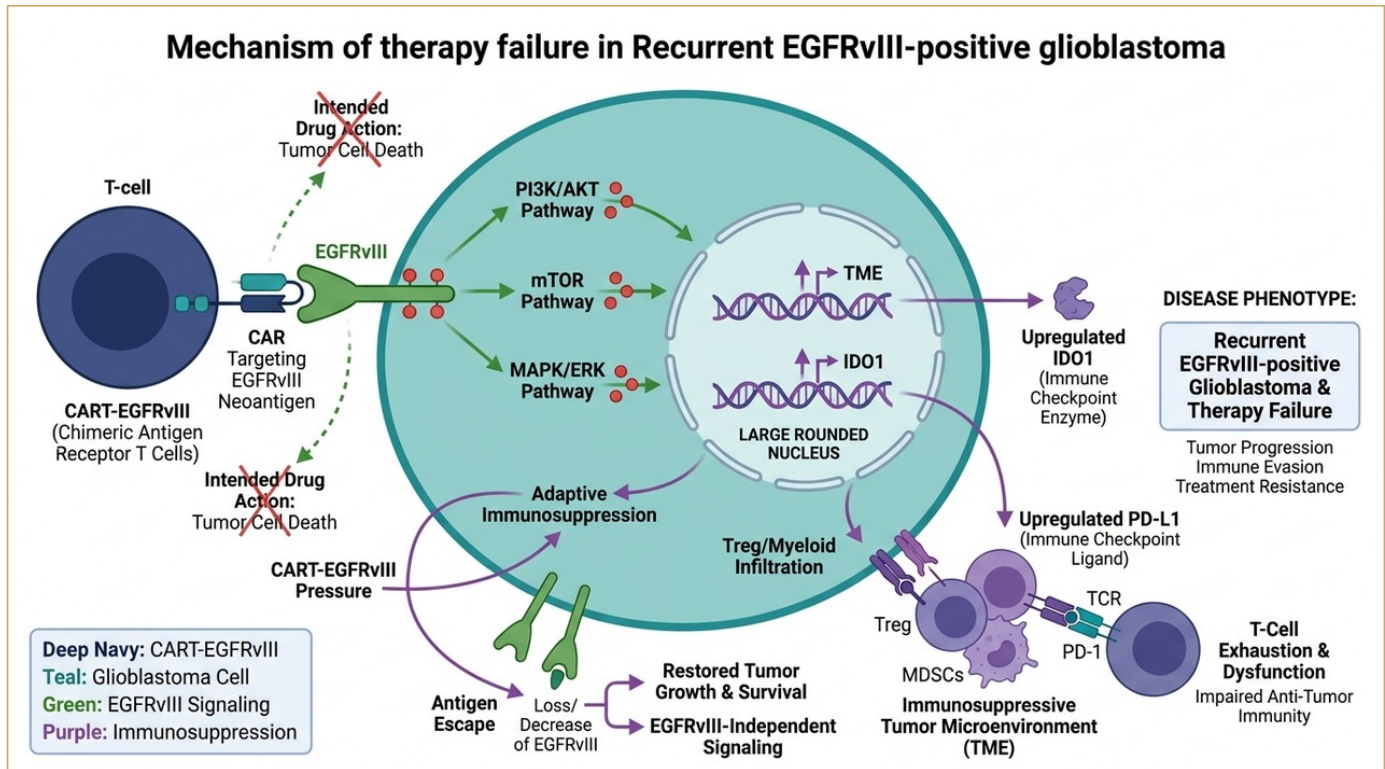
Adding PD-1 blockade to chemotherapy without biomarker enrichment provided no additive benefit; antagonism/timing and unselected population diluted effect.

BiRAGAS pattern P6 · combination-no-rationale

Citation: Powles T et al. Lancet Oncol 2021;22:931-945. PMID 34051178

ClinicalTrials.gov: [NCT02853305](https://clinicaltrials.gov/ct2/show/study/NCT02853305)

Recurrent EGFRvIII-positive glioblastoma



Indication: Recurrent EGFRvIII-positive glioblastoma

Resistance / failure mechanism:

Antigen escape (loss/decrease of EGFRvIII after CAR-T pressure) plus adaptive immunosuppression in the TME (upregulated IDO1, PD-L1, Treg/myeloid infiltration).

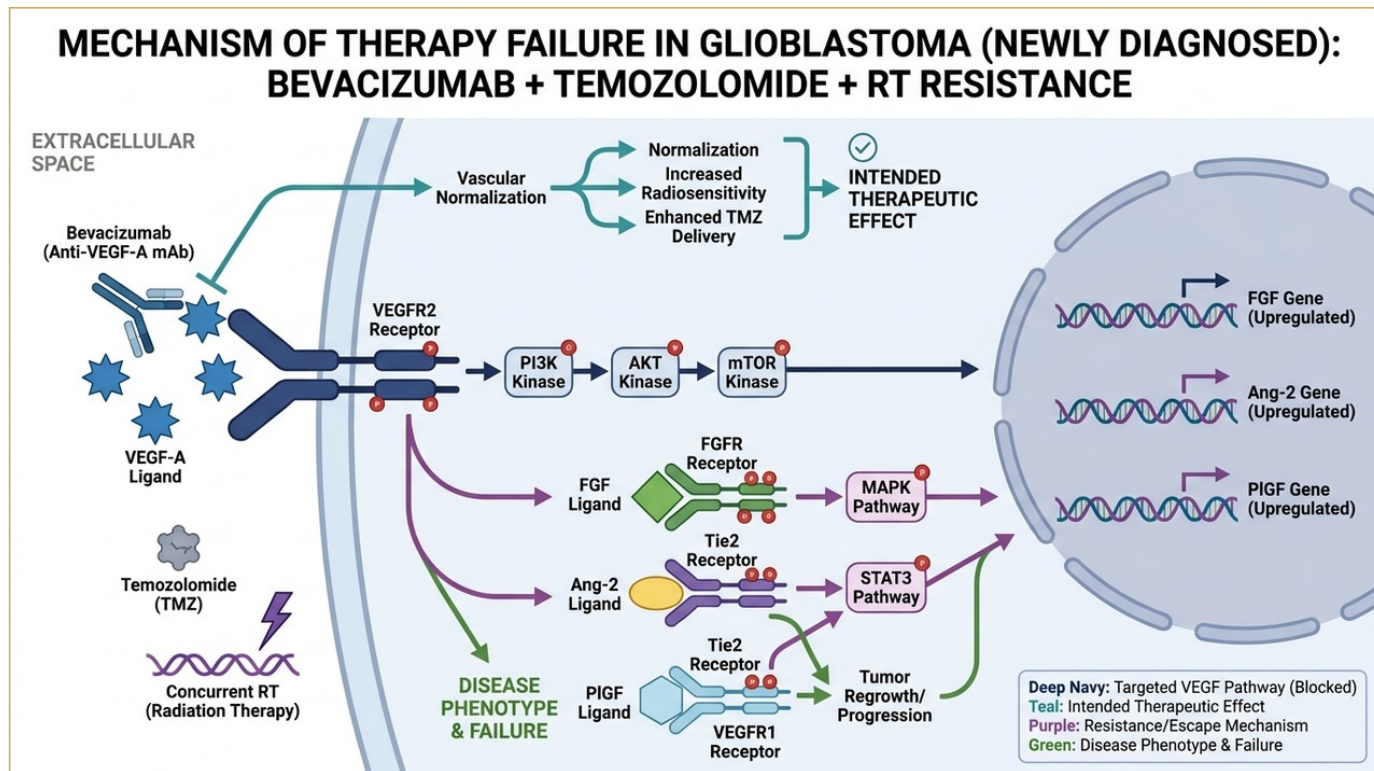
BiRAGAS pattern P7 · antigen-escape

Citation: O'Rourke DM et al. Sci Transl Med 2017;9:eaad0984. PMID 28724573

ClinicalTrials.gov: NCT02209376

Bevacizumab + temozolomide + concurrent RT

Glioblastoma (newly diagnosed)



Indication: Glioblastoma (newly diagnosed)

Resistance / failure mechanism:

VEGF blockade evasion via alternative pro-angiogenic factors (FGF, Ang-2, PlGF) and vessel co-option; pseudoresponse

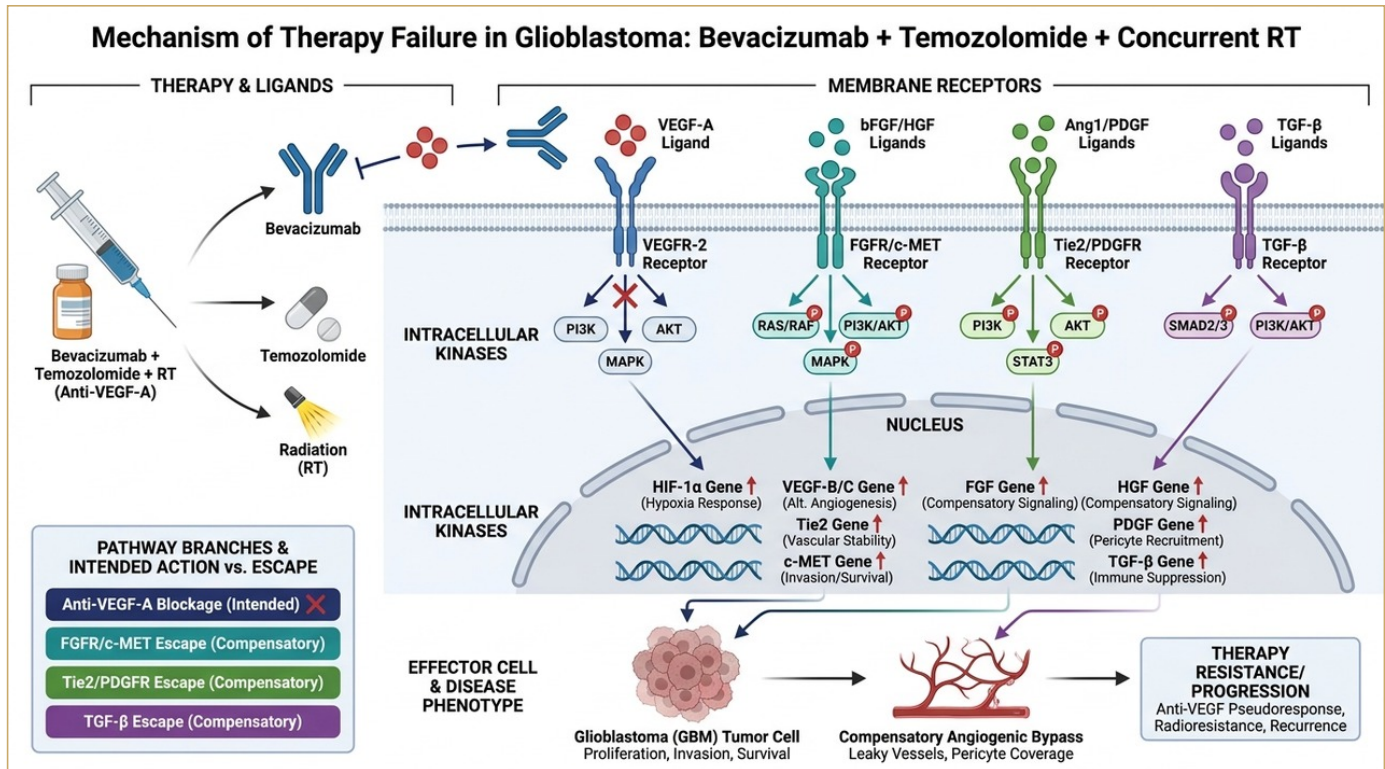
BiRAGAS pattern P2 · bypass/parallel-pathway

Citation: Gilbert MR et al. N Engl J Med 2014;370:699-708, PMID 24552317

ClinicalTrials.gov: [NCT00884741](https://clinicaltrials.gov/ct2/show/study/NCT00884741)

Bevacizumab + temozolomide + concurrent RT

Glioblastoma (newly diagnosed)



Indication: Glioblastoma (newly diagnosed)

Resistance / failure mechanism:

Compensatory angiogenic bypass; anti-VEGF pseudoresponse; anti-angiogenesis does not durably reverse GBM radioresistance

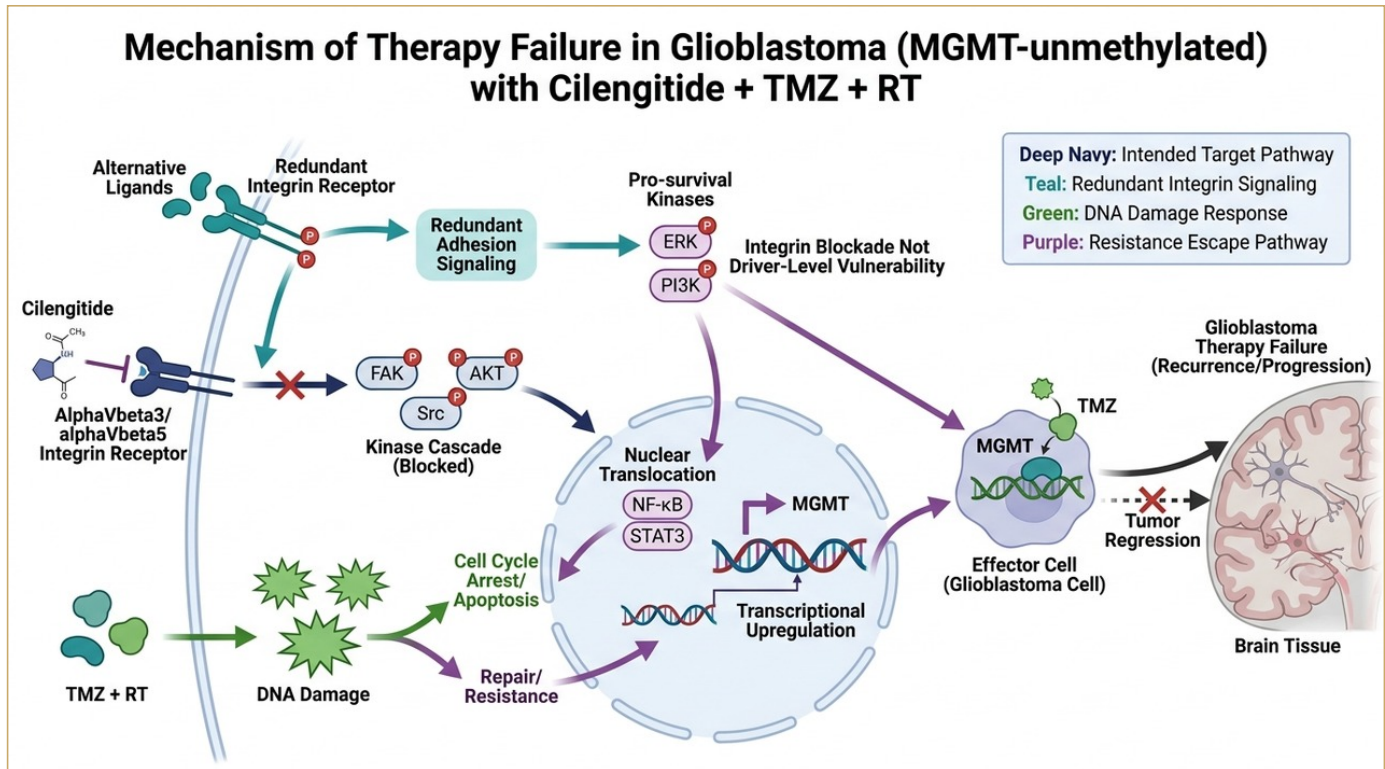
BiRAGAS pattern P2 · bypass/parallel-pathway

Citation: Chinot OL et al. N Engl J Med 2014;370:709-722, PMID 24552318

ClinicalTrials.gov: NCT00943826

Cilengitide + TMZ + RT

Glioblastoma (newly diagnosed, MGMT-unmethylated)



Indication: Glioblastoma (newly diagnosed, MGMT-unmethylated)

Resistance / failure mechanism:

Redundant integrin/adhesion signaling; integrin blockade not a driver-level vulnerability

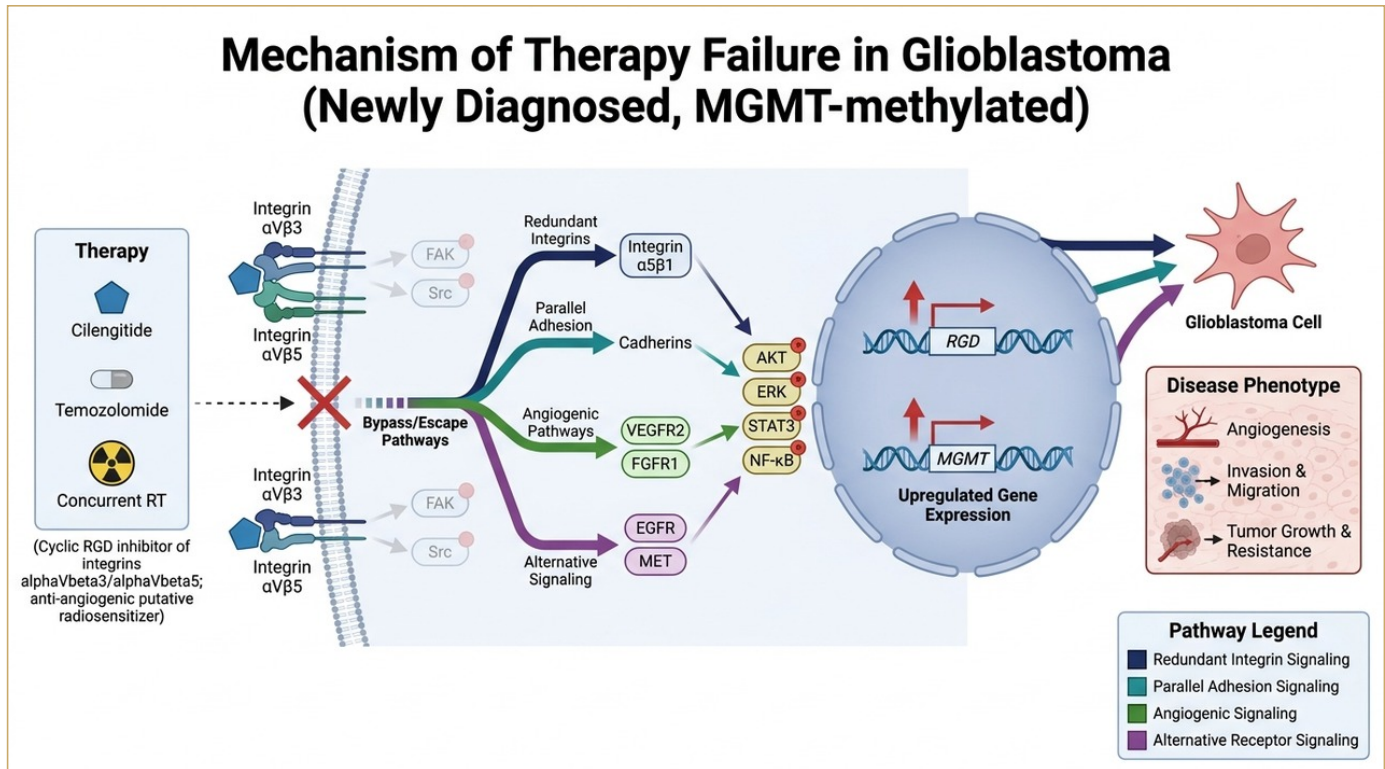
BiRAGAS pattern P2 · pathway-redundancy

Citation: Nabors LB et al. Neuro Oncol 2015;17:708-717, PMID 25762461

ClinicalTrials.gov: [NCT00813943](https://clinicaltrials.gov/ct2/show/study/NCT00813943)

Cilengitide + temozolomide + concurrent RT

Glioblastoma (newly diagnosed, MGMT-methylated)



Indication: Glioblastoma (newly diagnosed, MGMT-methylated)

Resistance / failure mechanism:

Integrin alphaVbeta3/5 blockade bypassed by redundant integrins and parallel adhesion/angiogenic pathways

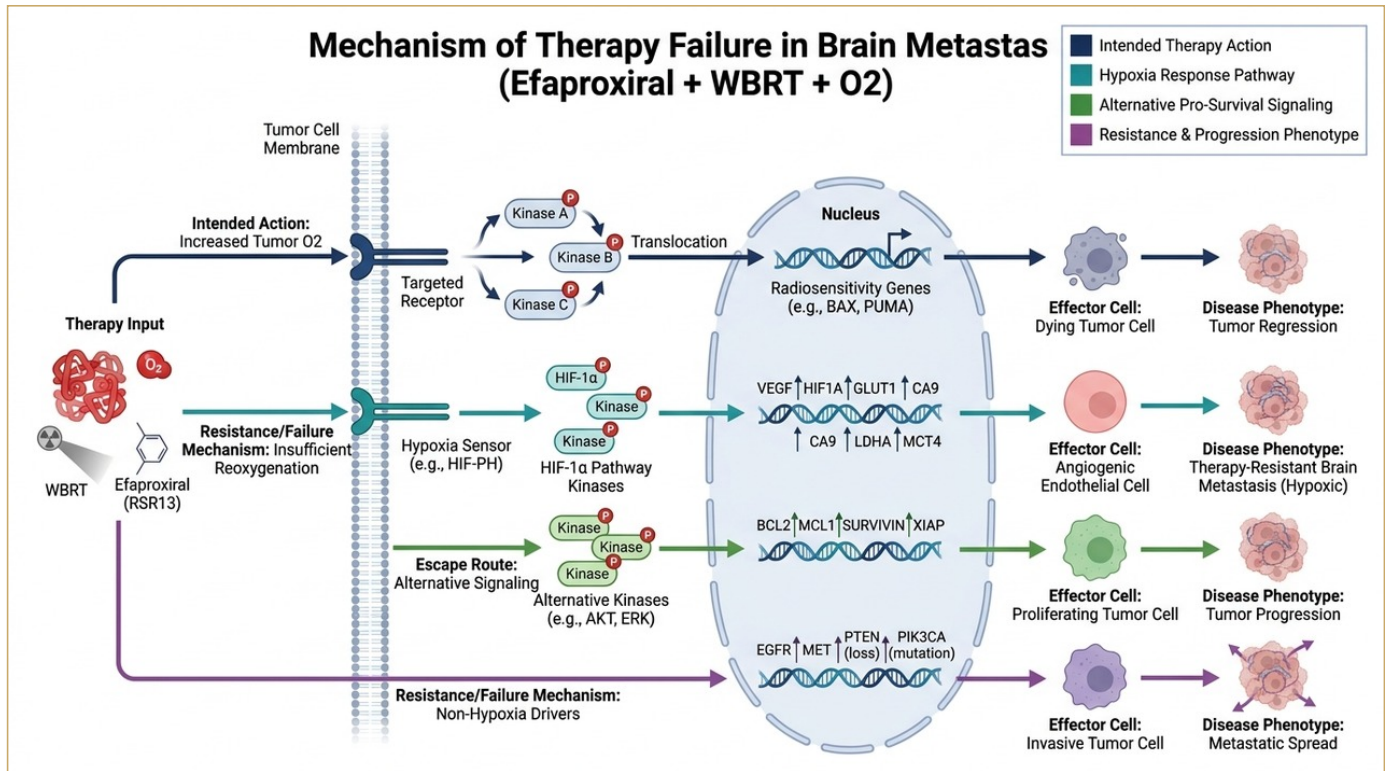
BiRAGAS pattern P2 · pathway-redundancy

Citation: Stupp R et al. Lancet Oncol 2014;15:1100-1108, PMID 25163906

ClinicalTrials.gov: [NCT00689221](https://clinicaltrials.gov/ct2/show/study/NCT00689221)

Efaproxiral (RSR13) + WBRT + O2

Brain metastases (mixed solid tumors)



Indication: Brain metastases (mixed solid tumors)

Resistance / failure mechanism:

Reoxygenation insufficient; subgroup benefit not reproducible; hypoxia not the dominant radioresistance driver in most brain mets

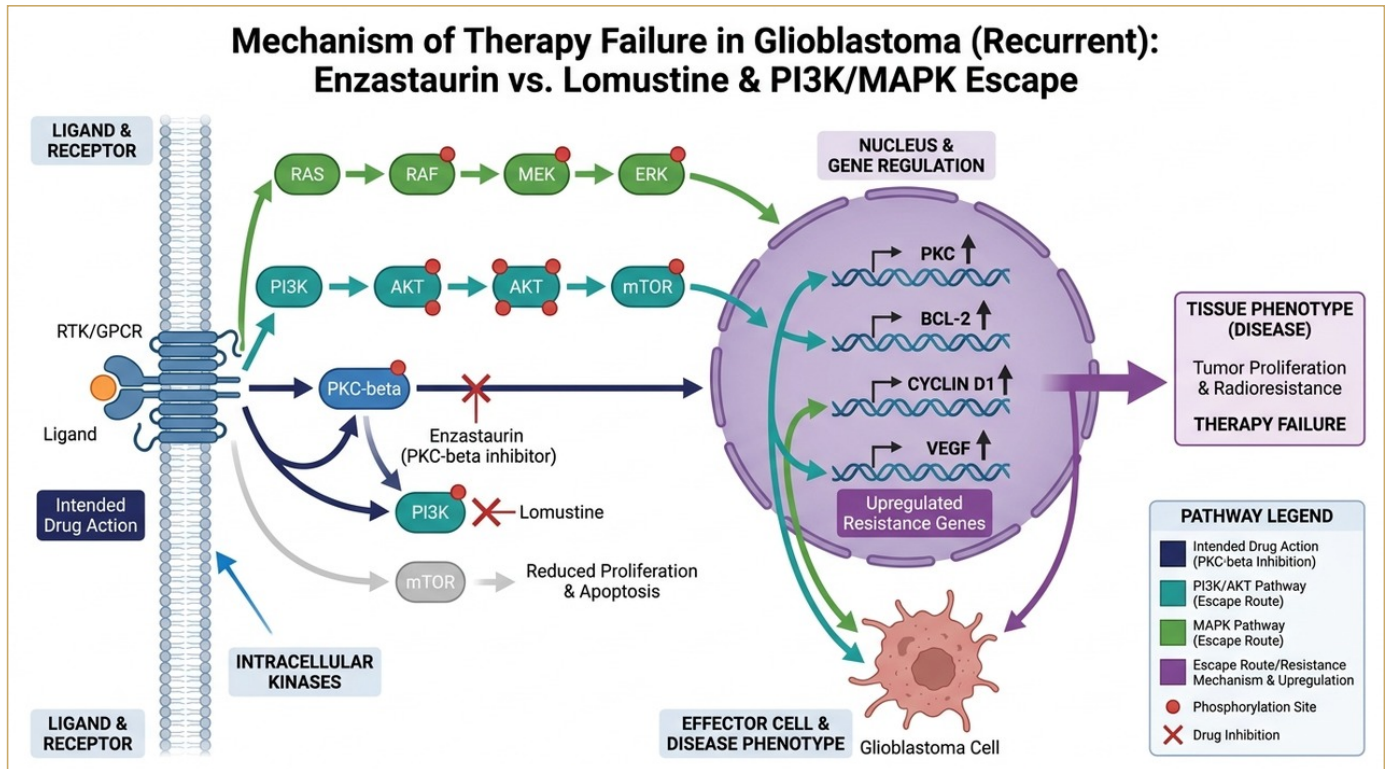
BiRAGAS pattern P1 · correlate-not-driver

Citation: Suh JH et al. J Clin Oncol 2006;24:106-114, PMID 16314623

[ClinicalTrials.gov: NCT00083304](https://clinicaltrials.gov/ct2/show/study/NCT00083304)

Enzastaurin (oral PKC-beta inhibitor) vs lomustine

Glioblastoma (recurrent)



Indication: Glioblastoma (recurrent)

Resistance / failure mechanism:

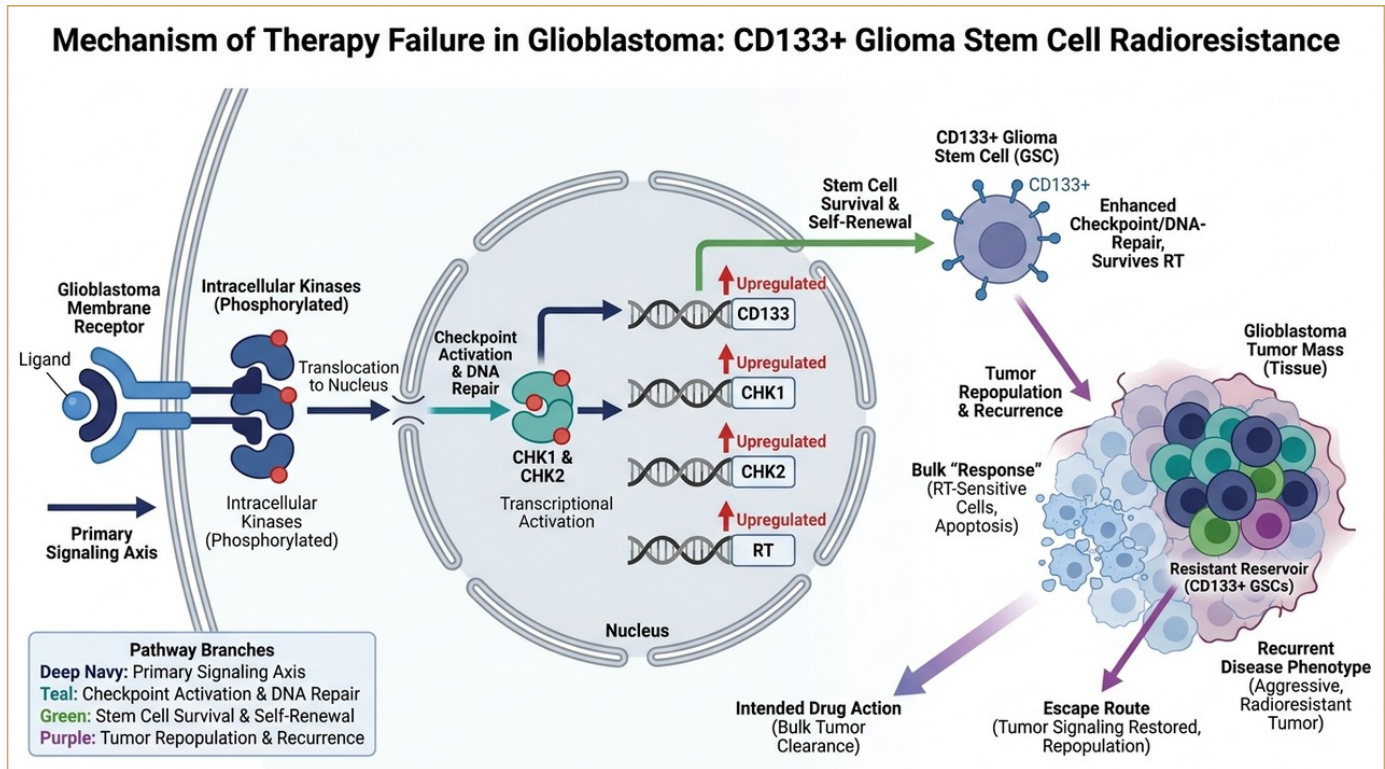
PKC-beta not a non-redundant driver; parallel PI3K/MAPK signaling maintains proliferation and radioresistance

BiRAGAS pattern P2 · bypass/parallel-pathway

Citation: Wick W et al. J Clin Oncol 2010;28:1168-1174, PMID 20124186

N/A, radioresistance mechanism (cancer stem cells)

Glioblastoma (mechanism)



Indication: Glioblastoma (mechanism)

Resistance / failure mechanism:

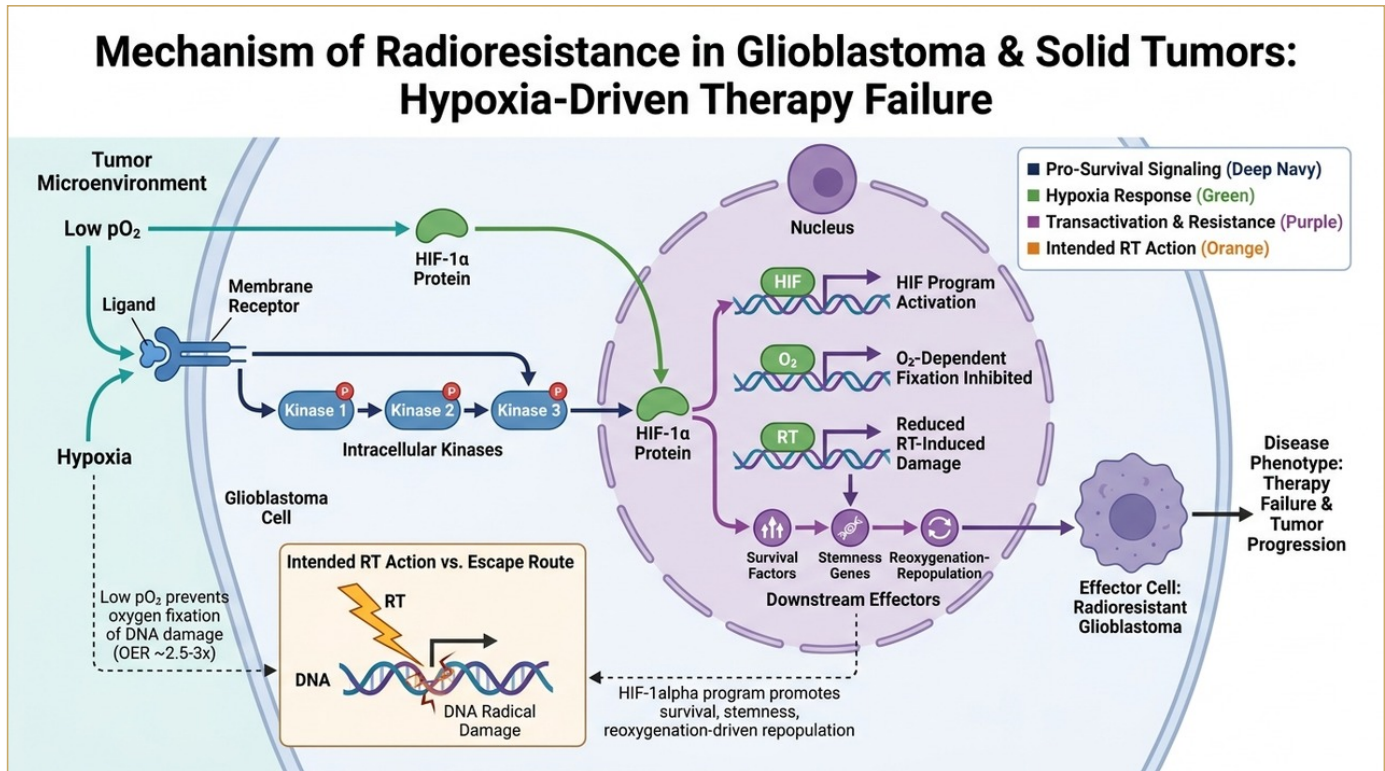
Stem-cell subpopulation with enhanced checkpoint/DNA-repair survives and repopulates (bulk 'response' masks resistant reservoir)

BiRAGAS pattern P3 · population-dilution

Citation: Bao S et al. Nature 2006;444:756-760, PMID 17051156

N/A, radioresistance mechanism (tumor hypoxia / HIF-1alpha)

Glioblastoma / solid tumors (mechanism)



Indication: Glioblastoma / solid tumors (mechanism)

Resistance / failure mechanism:

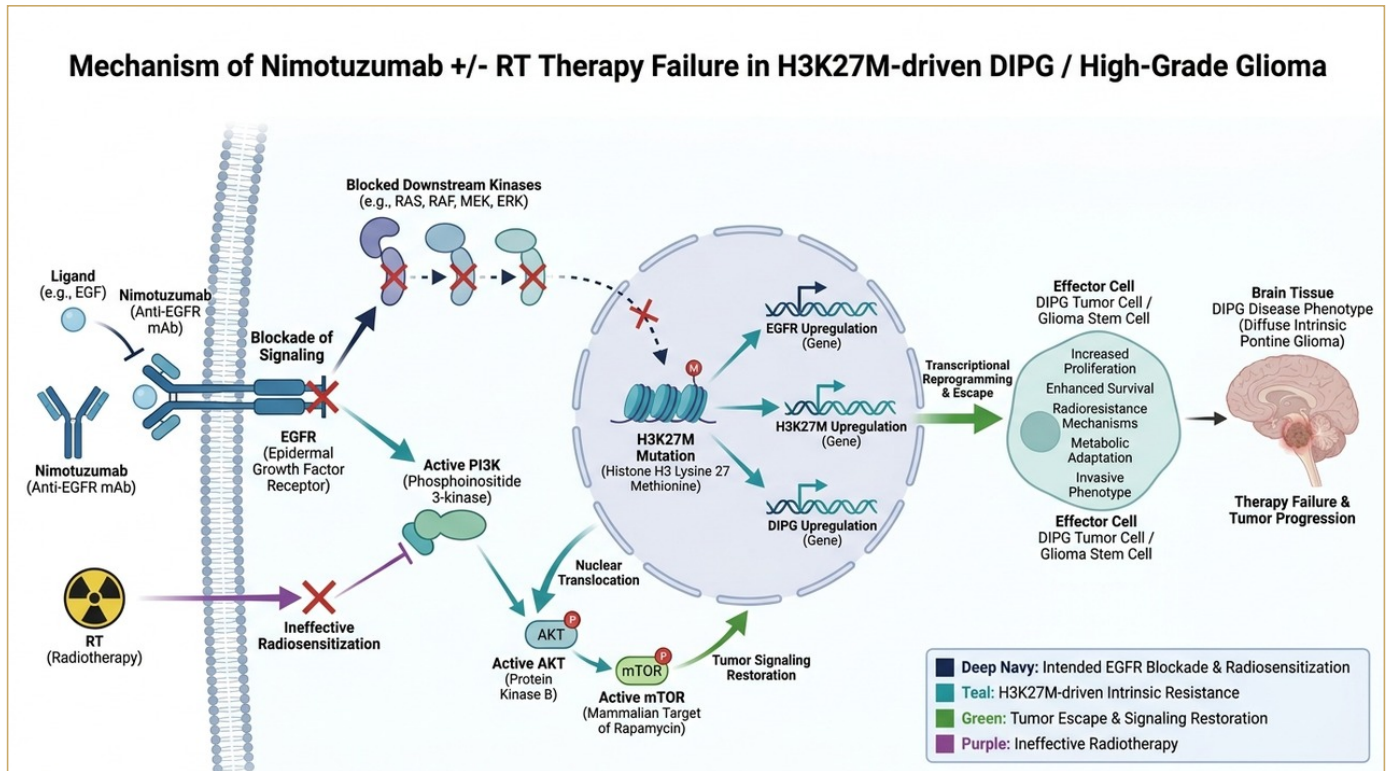
Low pO_2 prevents oxygen fixation of DNA damage; HIF-1 α program promotes survival, stemness, reoxygenation-driven repopulation

BiRAGAS pattern P4 · TME/immune-exclusion

Citation: Brown JM, Wilson WR. Nat Rev Cancer 2004;4:437-447, PMID 15170446

Nimotuzumab +/- RT

DIPG / high-grade glioma (pediatric)



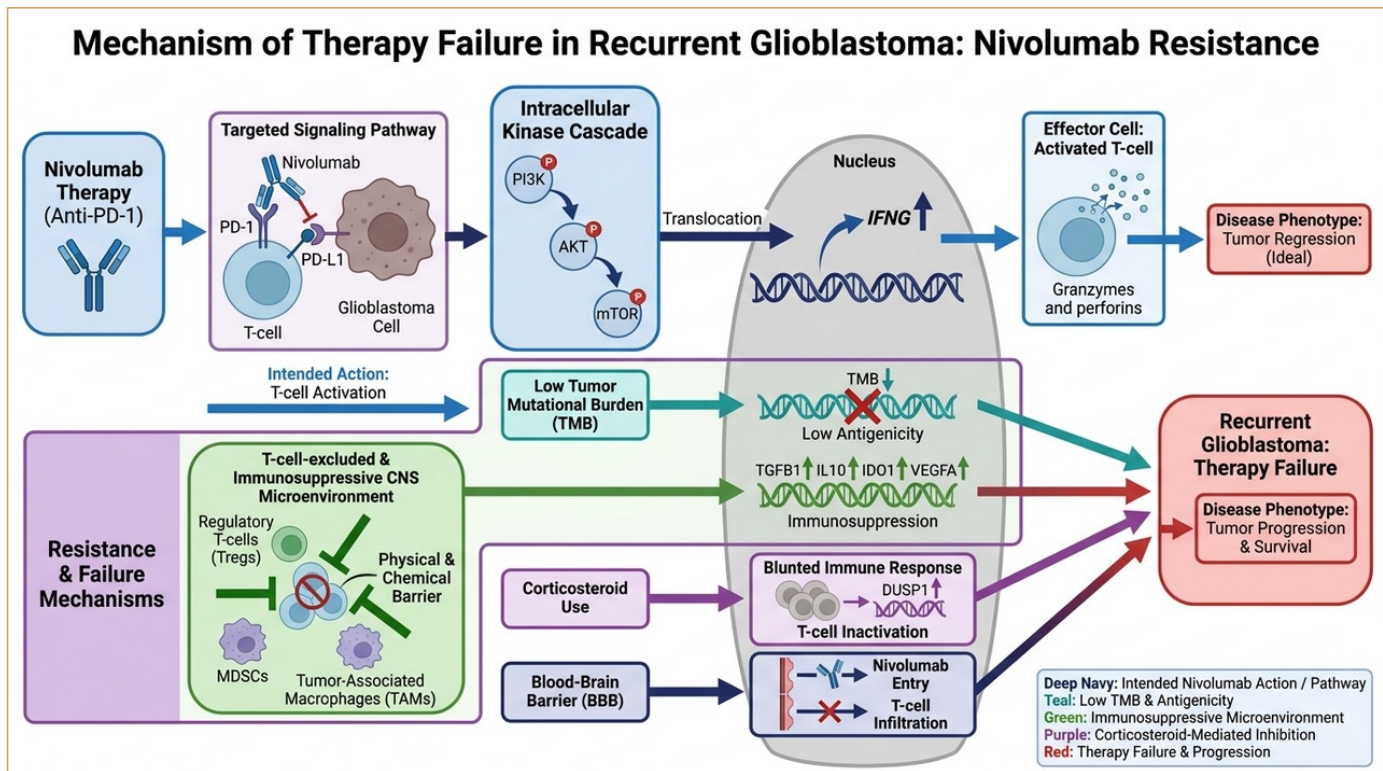
Indication: DIPG / high-grade glioma (pediatric)

Resistance / failure mechanism:

EGFR not the driver in H3K27M-driven DIPG; antibody radiosensitization ineffective against intrinsic radioresistance

BiRAGAS pattern P1 · correlate-not-driver

Citation: Bartels U et al. J Neurooncol 2014;120:341-347, PMID 25073688



Indication: Recurrent glioblastoma

Resistance / failure mechanism:

Low TMB, T-cell-excluded and profoundly immunosuppressive CNS microenvironment; corticosteroid use and blood-brain barrier further blunt immune response.

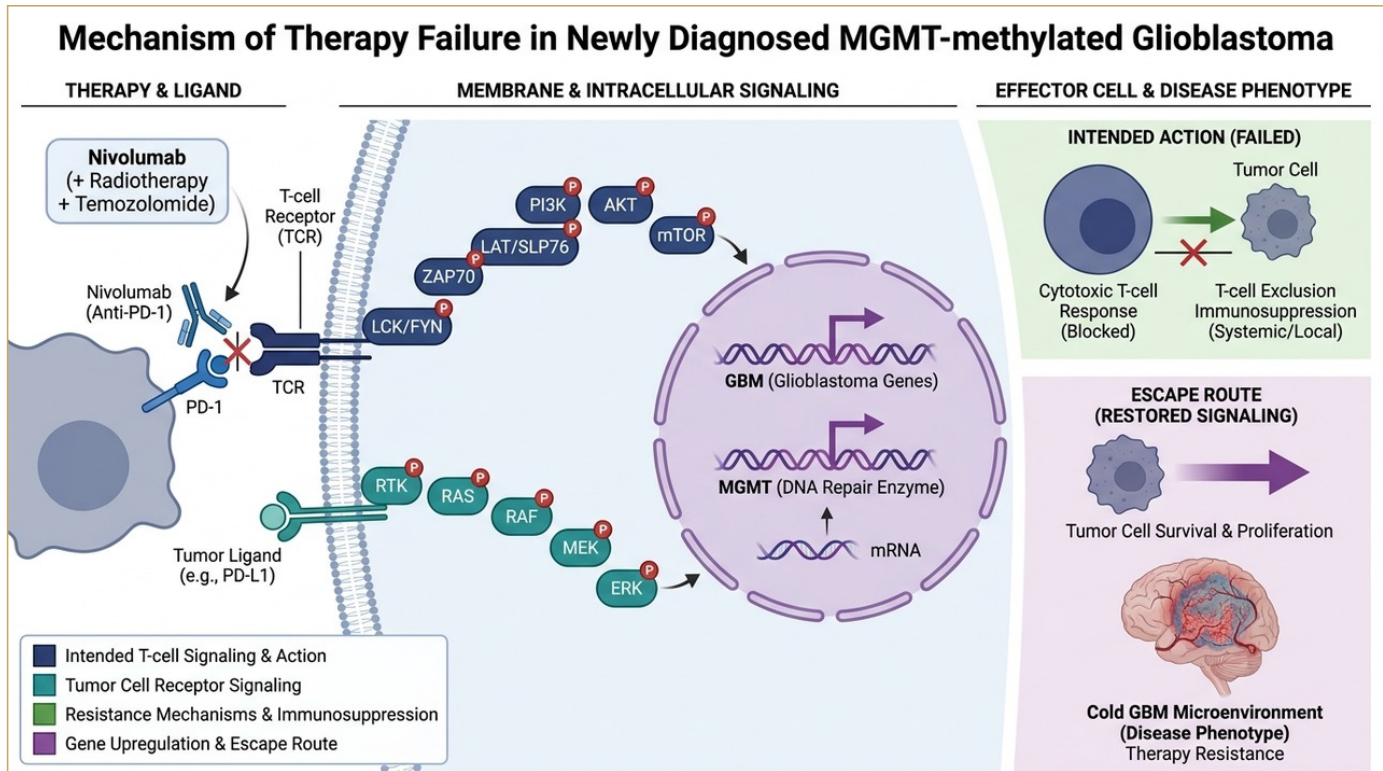
BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Reardon DA et al. JAMA Oncol 2020;6:1003-1010. PMID 32437507

ClinicalTrials.gov: NCT02017717

Nivolumab (+ radiotherapy + temozolomide)

Newly diagnosed MGMT-methylated glioblastoma



Indication: Newly diagnosed MGMT-methylated glioblastoma

Resistance / failure mechanism:

Cold GBM microenvironment plus systemic/local immunosuppression; PD-1 blockade added without a rational combination to overcome T-cell exclusion.

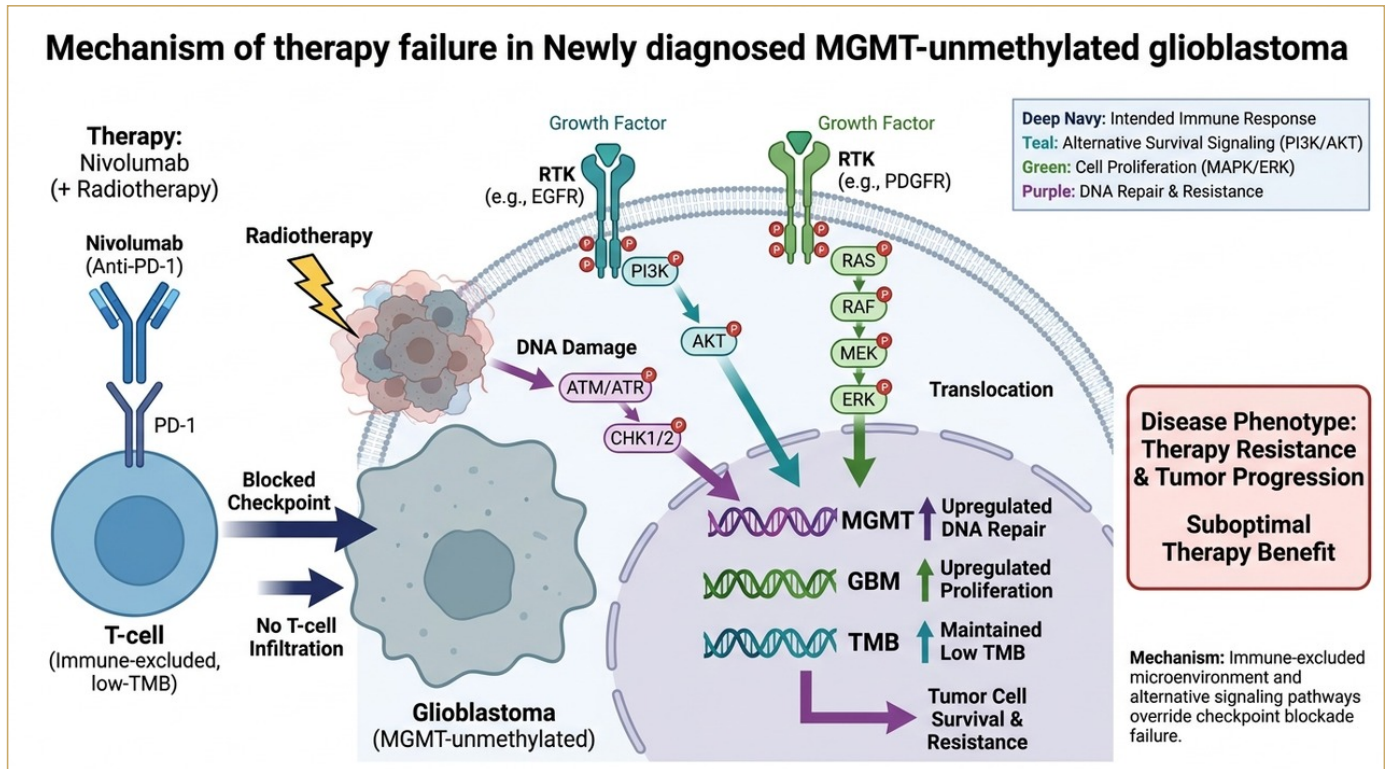
BiRAGAS pattern P6 · TME/immune-exclusion

Citation: Lim M et al. Neuro-Oncol 2022;24:1935-1949. PMID (verify, unresolved)

[ClinicalTrials.gov: NCT02667587](https://clinicaltrials.gov/ct2/show/study/NCT02667587)

Nivolumab (+ radiotherapy)

Newly diagnosed MGMT-unmethylated glioblastoma



Indication: Newly diagnosed MGMT-unmethylated glioblastoma

Resistance / failure mechanism:

Immune-excluded, low-TMB GBM; substituting an inactive checkpoint agent for effective chemotherapy removed benefit.

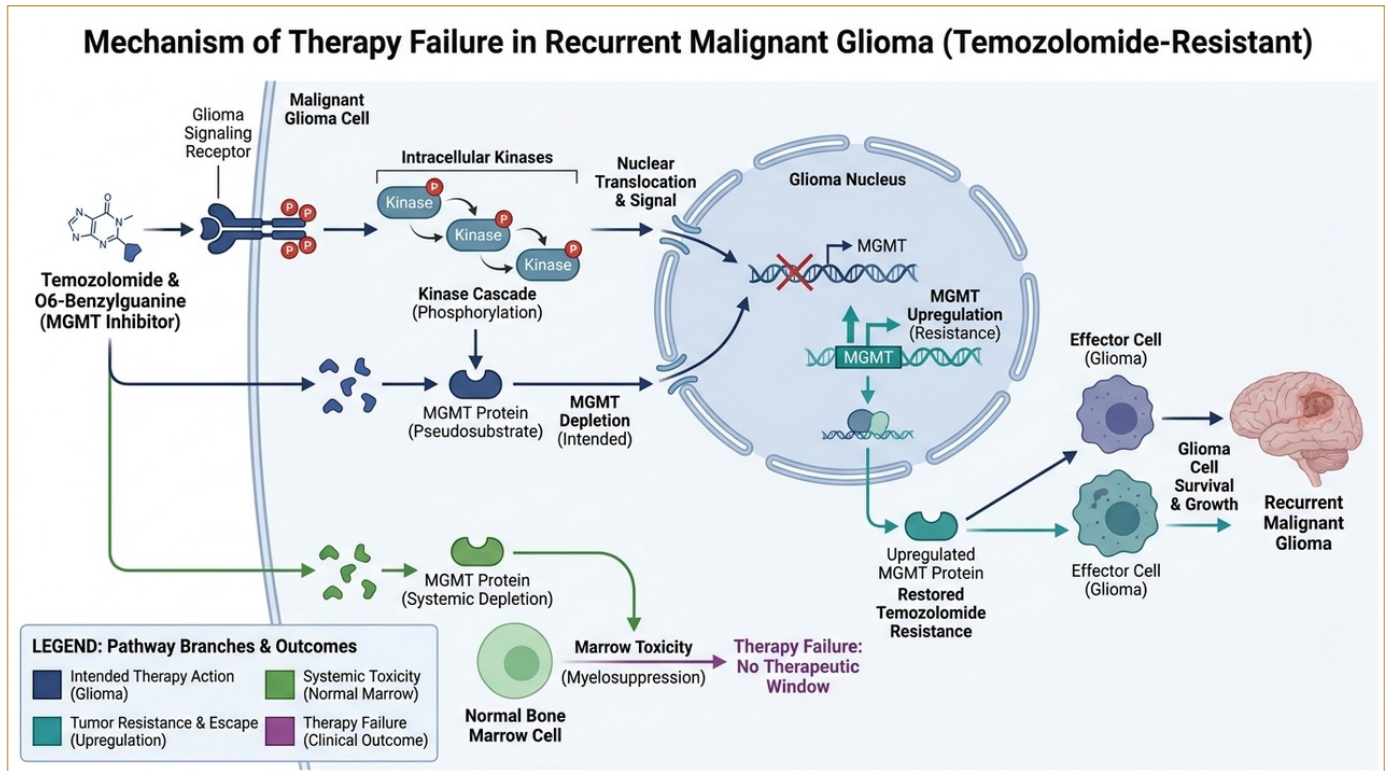
BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Omuro A et al. Neuro-Oncol 2023;25:123-134. PMID (verify, unresolved)

ClinicalTrials.gov: [NCT02617589](https://clinicaltrials.gov/ct2/show/study/NCT02617589)

O6-benzylguanine (MGMT inhibitor) added to temozolomide

Recurrent malignant glioma (temozolomide-resistant)



Indication: Recurrent malignant glioma (temozolomide-resistant)

Resistance / failure mechanism:

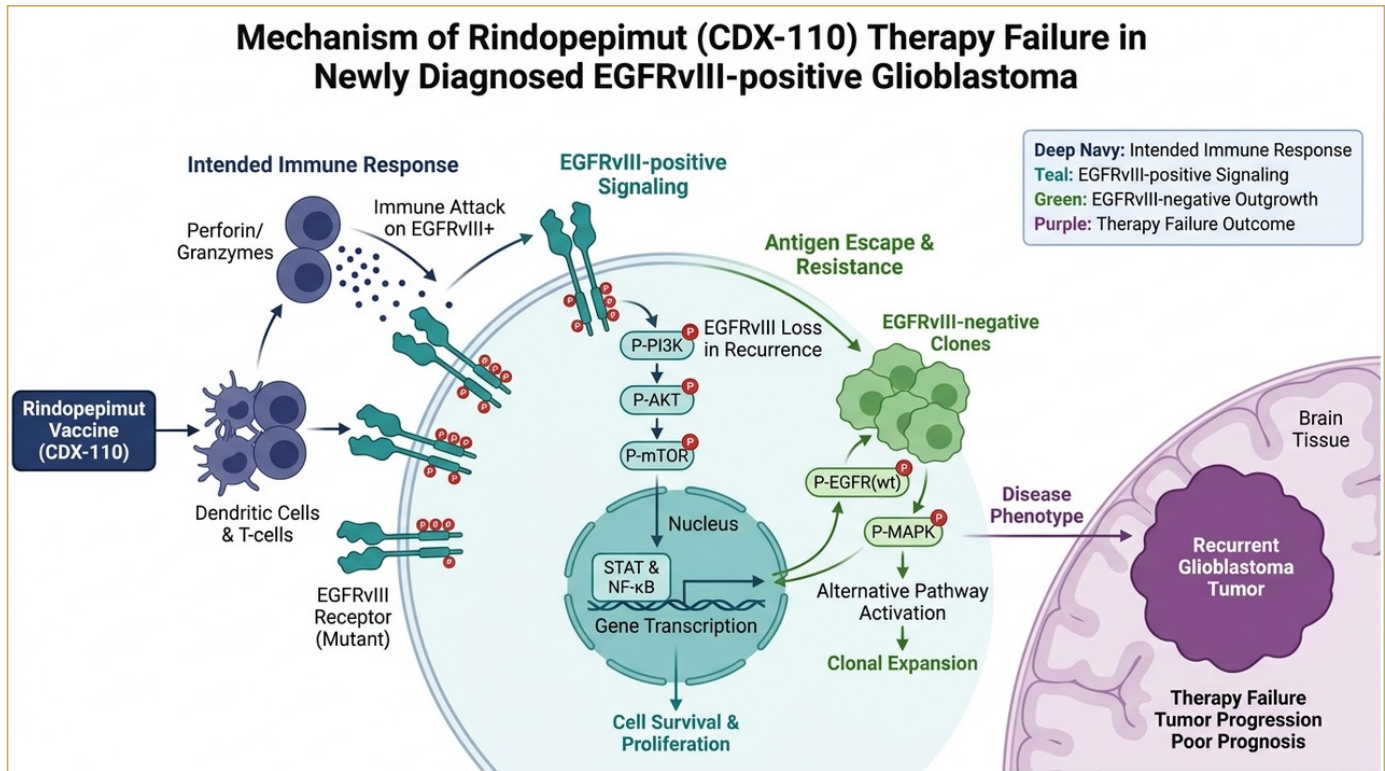
Systemic MGMT depletion sensitized normal marrow as much as tumor (on-mechanism toxicity), preventing a therapeutic window for reversing MGMT-mediated resistance

BiRAGAS pattern P6 · on-mechanism-toxicity

Citation: Quinn JA et al. J Clin Oncol 2009;27(8):1262-1267. PMID 19204199

Rindopepimut (CDX-110, EGFRvIII peptide-KLH vaccine)

Newly diagnosed EGFRvIII-positive glioblastoma



Indication: Newly diagnosed EGFRvIII-positive glioblastoma

Resistance / failure mechanism:

Antigen escape: EGFRvIII is heterogeneously/clonally expressed and was lost in ~60% of recurrences (including many control tumors), so targeting it drove outgrowth of EGFRvIII-negative clones.

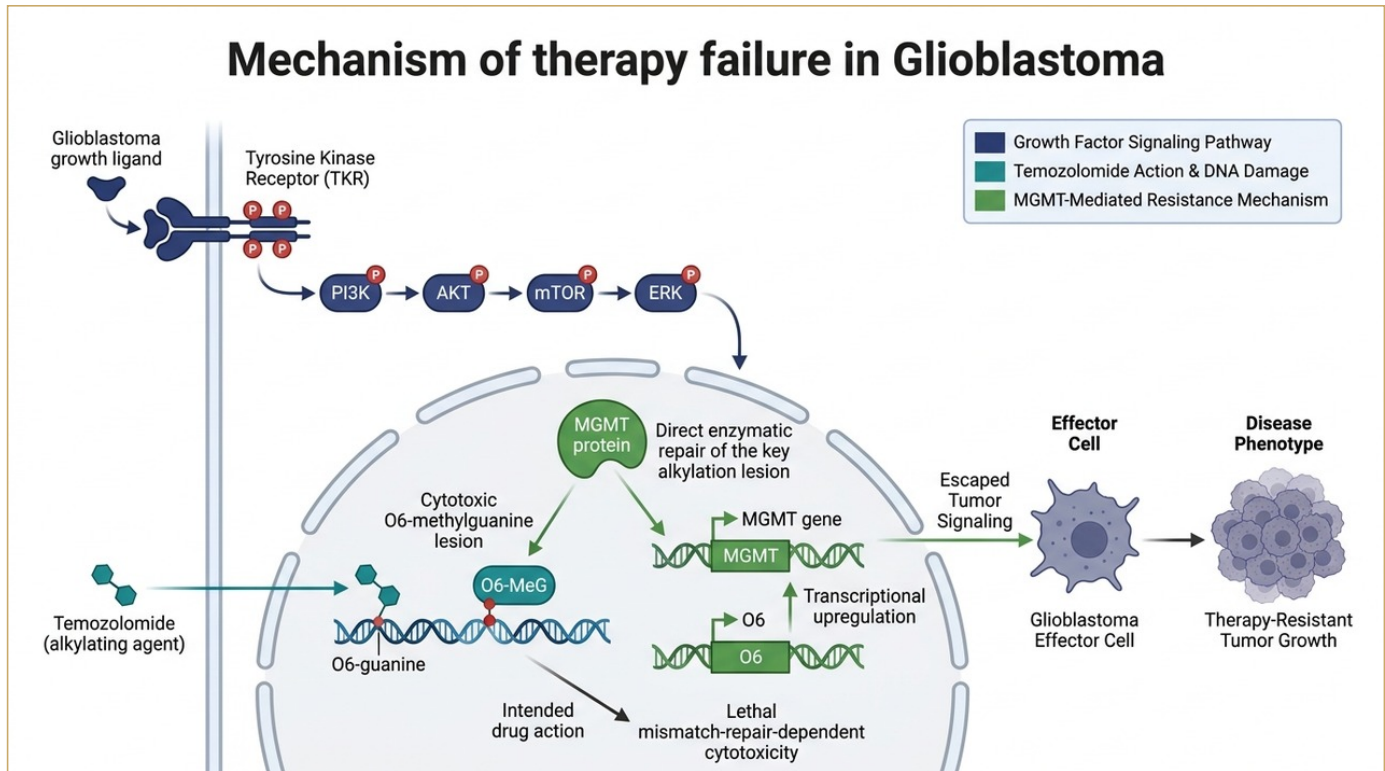
BiRAGAS pattern P1 · antigen-escape

Citation: Weller M et al. Lancet Oncol 2017;18:1373-1385. PMID 28844499

ClinicalTrials.gov: [NCT01480479](https://clinicaltrials.gov/ct2/show/study/NCT01480479)

Temozolomide (alkylating agent)

Glioblastoma



Indication: Glioblastoma

Resistance / failure mechanism:

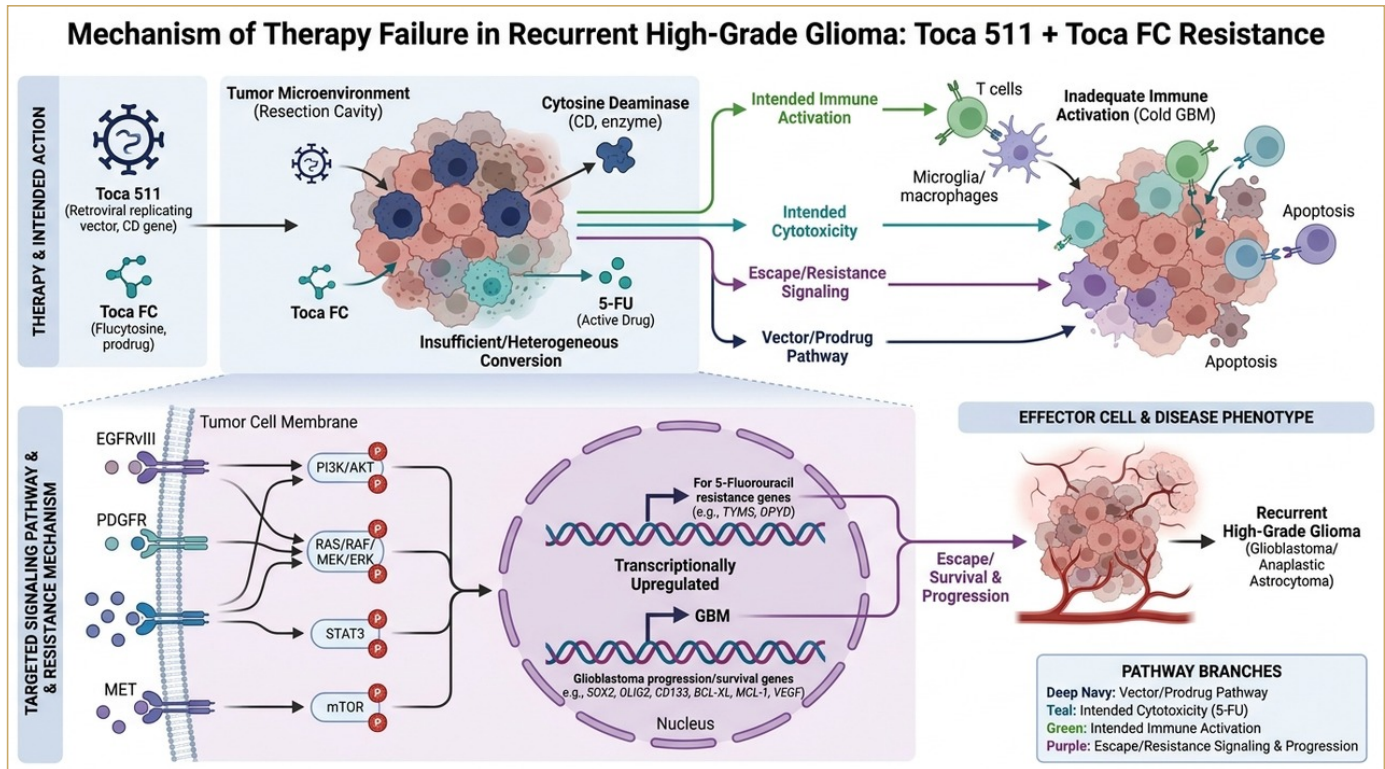
Direct enzymatic repair of the key alkylation lesion by MGMT prevents lethal mismatch-repair-dependent cytotoxicity

BiRAGAS pattern P1 · DNA-repair/apoptosis-evasion

Citation: Hegi ME et al. N Engl J Med 2005;352(10):997-1003. PMID 15758010

Vocimagene amiretrorepvec (Toca 511) + Toca FC (flucytosine)

Recurrent high-grade glioma (glioblastoma/anaplastic astrocytoma) at resection



Indication: Recurrent high-grade glioma (glioblastoma/anaplastic astrocytoma) at resection

Resistance / failure mechanism:

Insufficient/heterogeneous vector spread and prodrug conversion in a bulky immunosuppressed CNS tumor; immune activation inadequate against cold GBM.

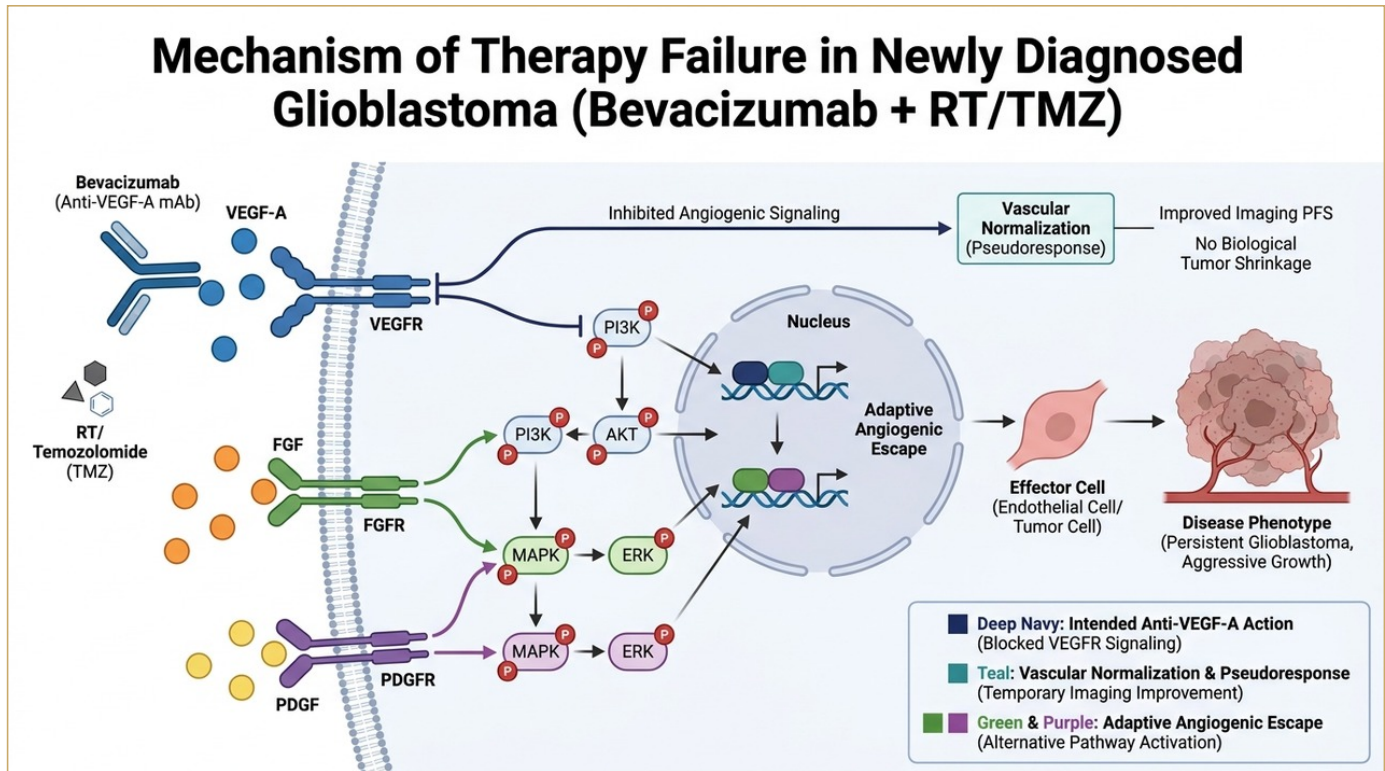
BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Cloughesy TF et al. JAMA Oncol 2020 (Toca 5). PMID (verify, unresolved)

ClinicalTrials.gov: [NCT02414165](https://clinicaltrials.gov/ct2/show/study/NCT02414165)

bevacizumab + RT/temozolomide

Glioblastoma (newly diagnosed)



Indication: Glioblastoma (newly diagnosed)

Resistance / failure mechanism:

Vascular normalization/pseudoresponse improves imaging PFS without altering tumor biology; adaptive angiogenic escape

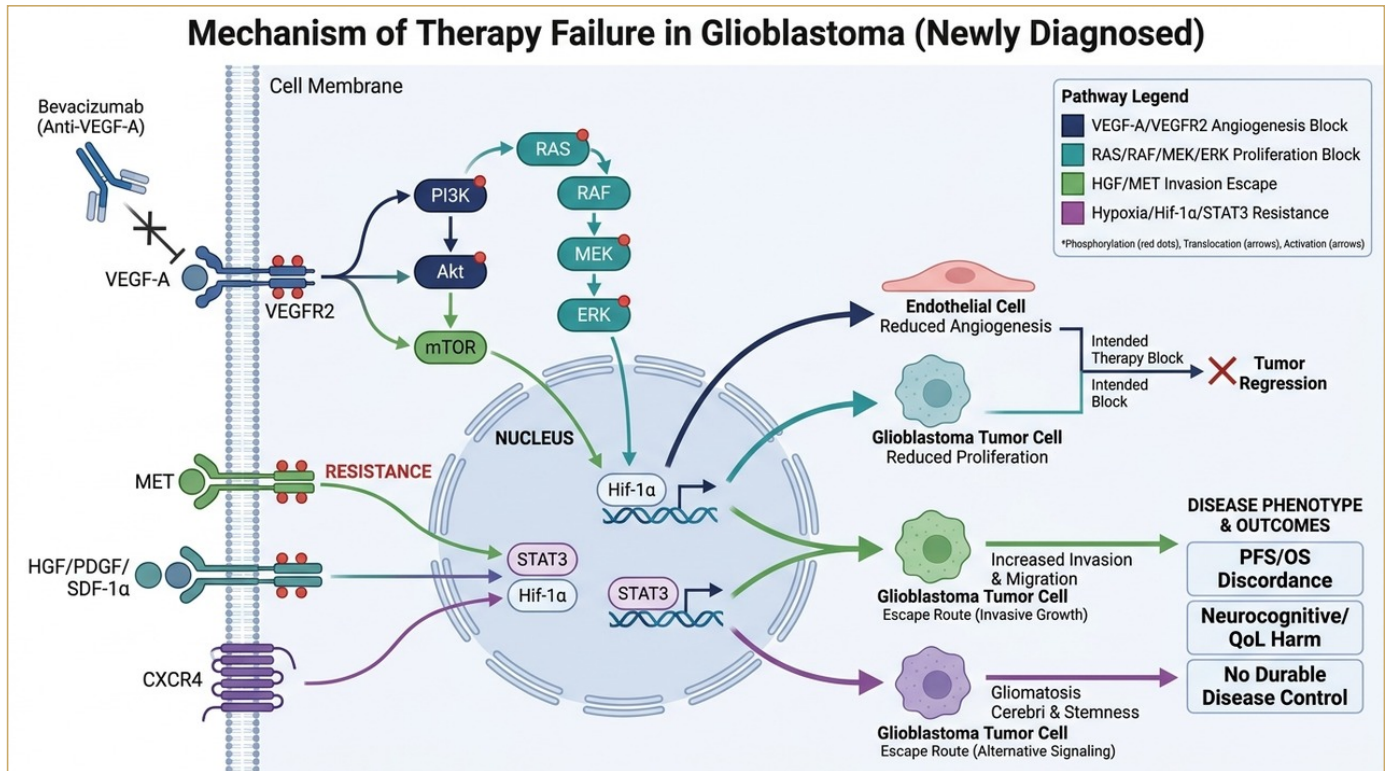
BiRAGAS pattern P5 · correlate-not-driver

Citation: Chinot OL et al. N Engl J Med 2014;370:709-722, PMID 24552317

[ClinicalTrials.gov: NCT00943826](https://clinicaltrials.gov/ct2/show/study/NCT00943826)

bevacizumab + RT/temozolomide

Glioblastoma (newly diagnosed)



Indication: Glioblastoma (newly diagnosed)

Resistance / failure mechanism:

PFS/OS discordance plus on-mechanism neurocognitive/QoL harm; no durable disease control

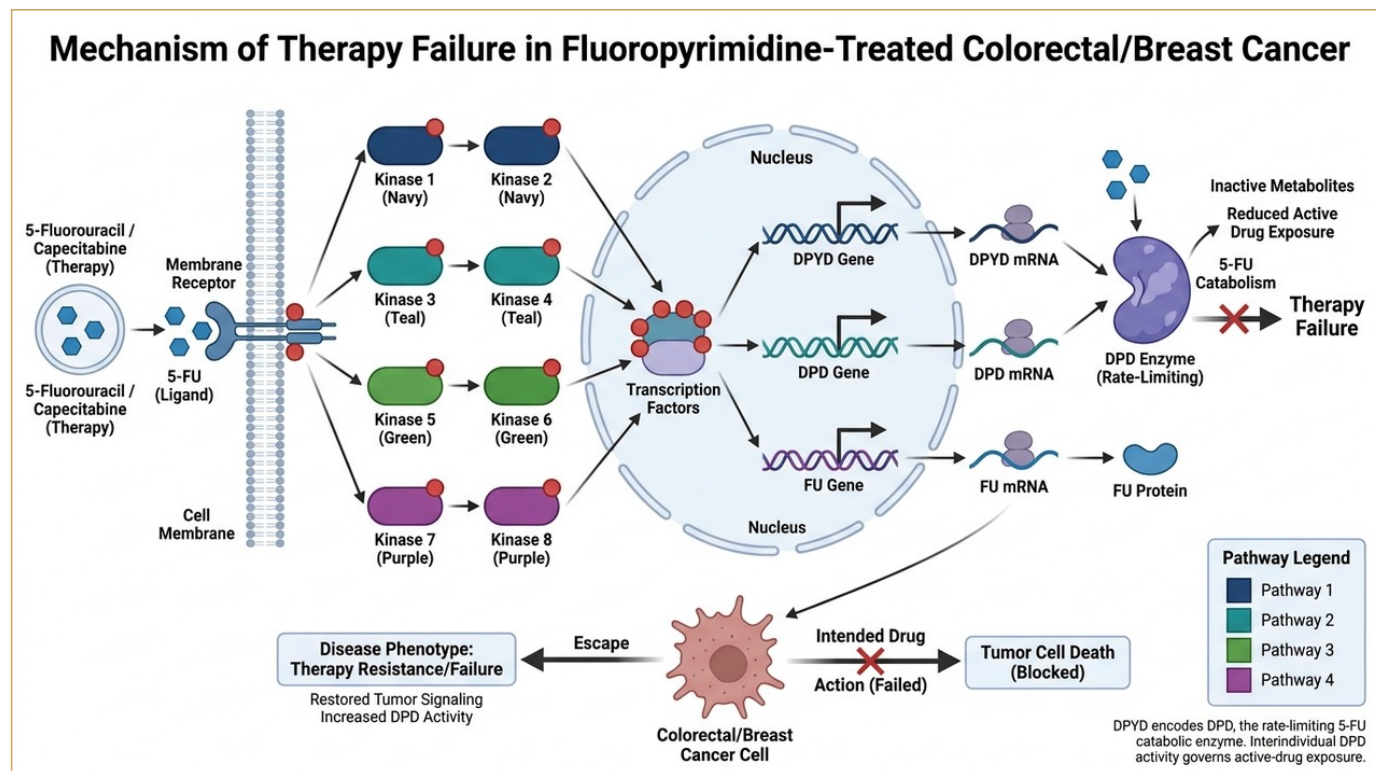
BiRAGAS pattern P5 · on-mechanism-toxicity

Citation: Gilbert MR et al. N Engl J Med 2014;370:699-708, PMID 24552318

[ClinicalTrials.gov: NCT00884741](https://clinicaltrials.gov/ct2/show/study/NCT00884741)

5-Fluorouracil / capecitabine (DPYD pharmacogenomics)

Colorectal / breast (fluoropyrimidine-treated)



Indication: Colorectal / breast (fluoropyrimidine-treated)

Resistance / failure mechanism:

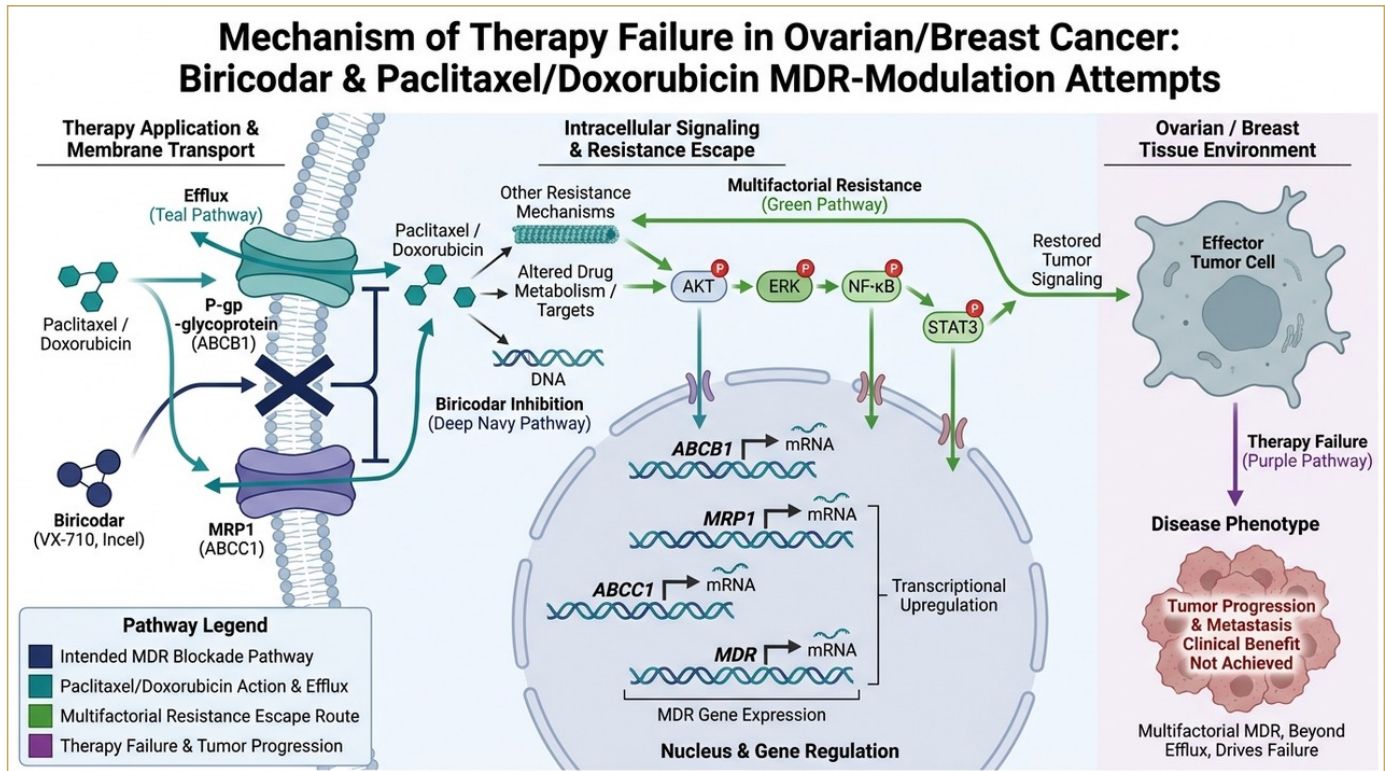
Interindividual DPD activity governs active-drug exposure; a metabolism/pharmacogenomic determinant of both resistance and toxicity

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Amstutz U et al. Clin Pharmacol Ther 2018;103(2):210-216 (CPIC DPYD guideline). PMID 29152729

Biricodar (VX-710, Incel) added to paclitaxel or doxorubicin

Ovarian / breast (MDR-modulation attempts)



Indication: Ovarian / breast (MDR-modulation attempts)

Resistance / failure mechanism:

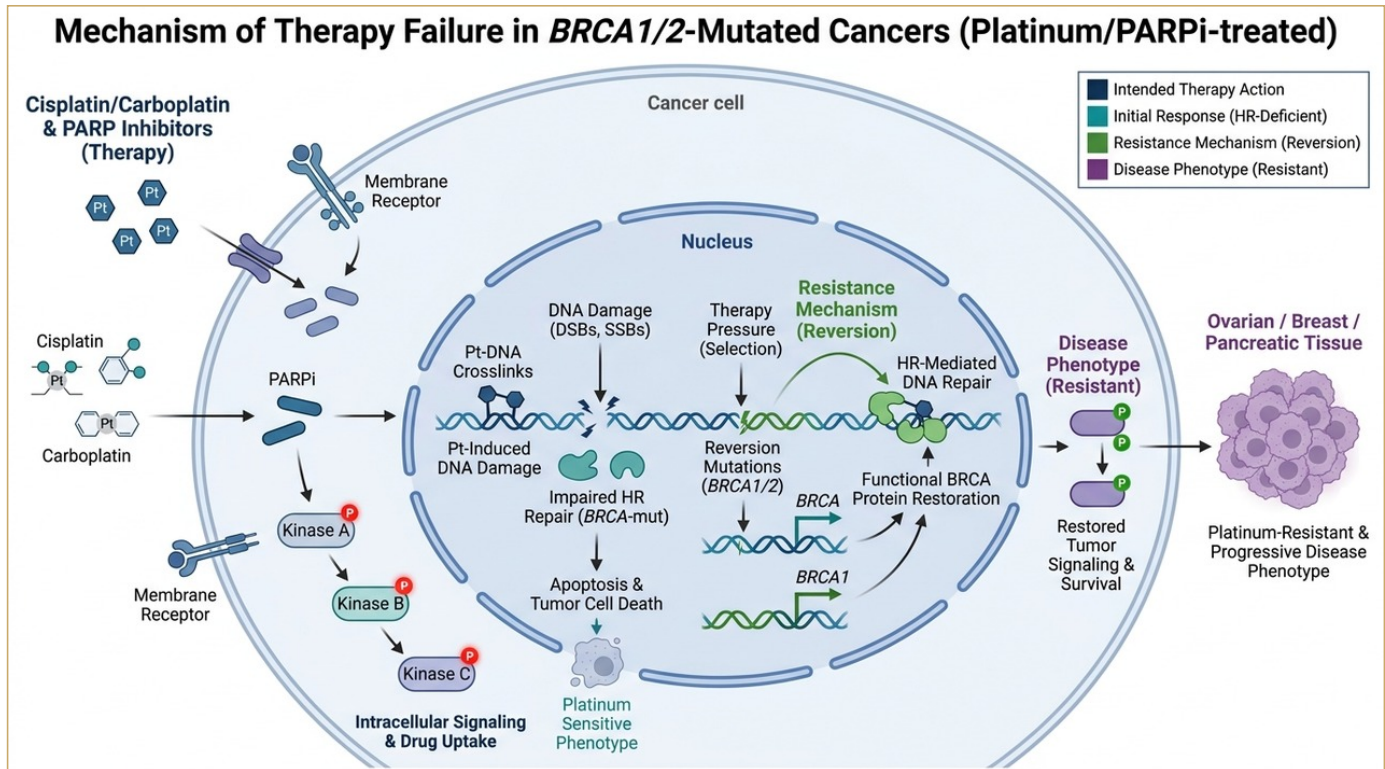
Dual-transporter blockade did not translate to clinical benefit because MDR in these tumors is multifactorial beyond efflux

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Verify (Vertex VX-710/biricodar early-phase reports; e.g., Rowinsky EK et al. J Clin Oncol 1998;16:2964-2976. PMID 9738565)

Cisplatin / carboplatin (and cross-resistant PARP inhibitors)

BRCA1/2-mutated ovarian / breast / pancreatic (platinum-treated)



Indication: BRCA1/2-mutated ovarian / breast / pancreatic (platinum-treated)

Resistance / failure mechanism:

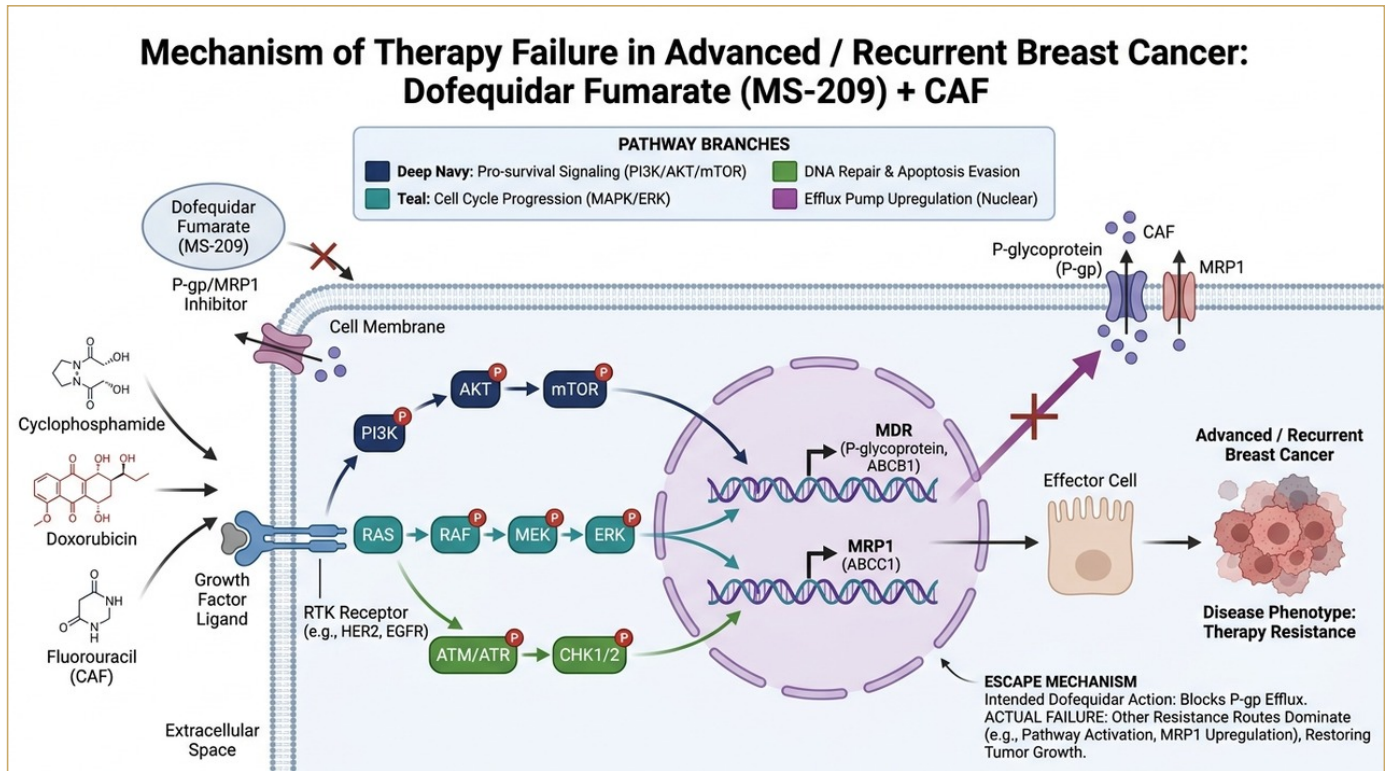
Reversion mutations restore functional BRCA protein and HR-mediated repair of Pt-DNA crosslinks; on-target restoration of DNA-repair capacity

BiRAGAS pattern P1 · DNA-repair/apoptosis-evasion

Citation: Sakai W et al. Nature 2008;451(7182):1116-1120. PMID 18264087

Dofequidar fumarate (MS-209) added to cyclophosphamide/doxorubicin/fluorouracil

Advanced / recurrent breast cancer



Indication: Advanced / recurrent breast cancer

Resistance / failure mechanism:

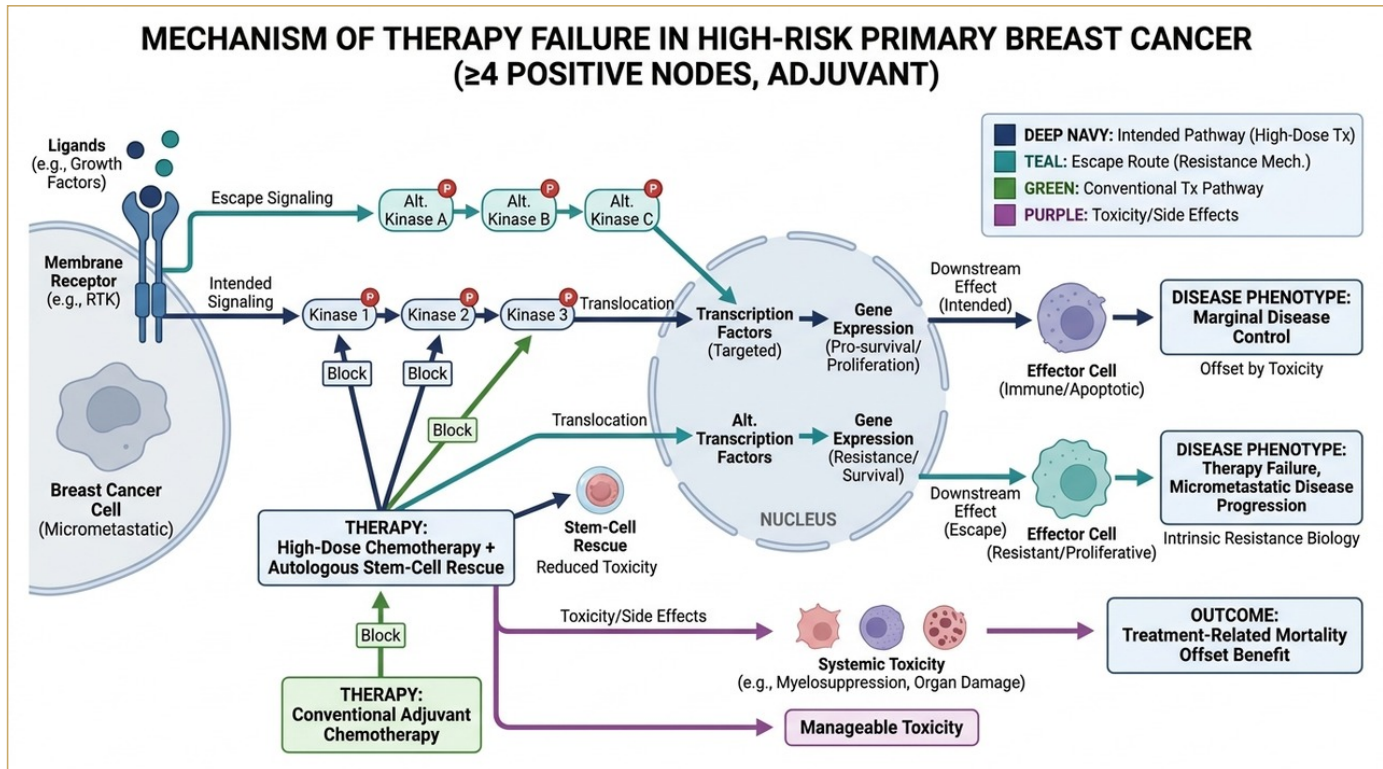
Efflux modulation benefits only the subset whose resistance is actually P-gp-driven; in unselected patients other resistance routes dominate, diluting effect

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Saeki T et al. J Clin Oncol 2007;25(4):411-417. PMID 17179098

High-dose alkylating chemotherapy + autologous stem-cell rescue vs convent

High-risk primary breast cancer (≥ 4 positive nodes, adjuvant)



Indication: High-risk primary breast cancer (≥ 4 positive nodes, adjuvant)

Resistance / failure mechanism:

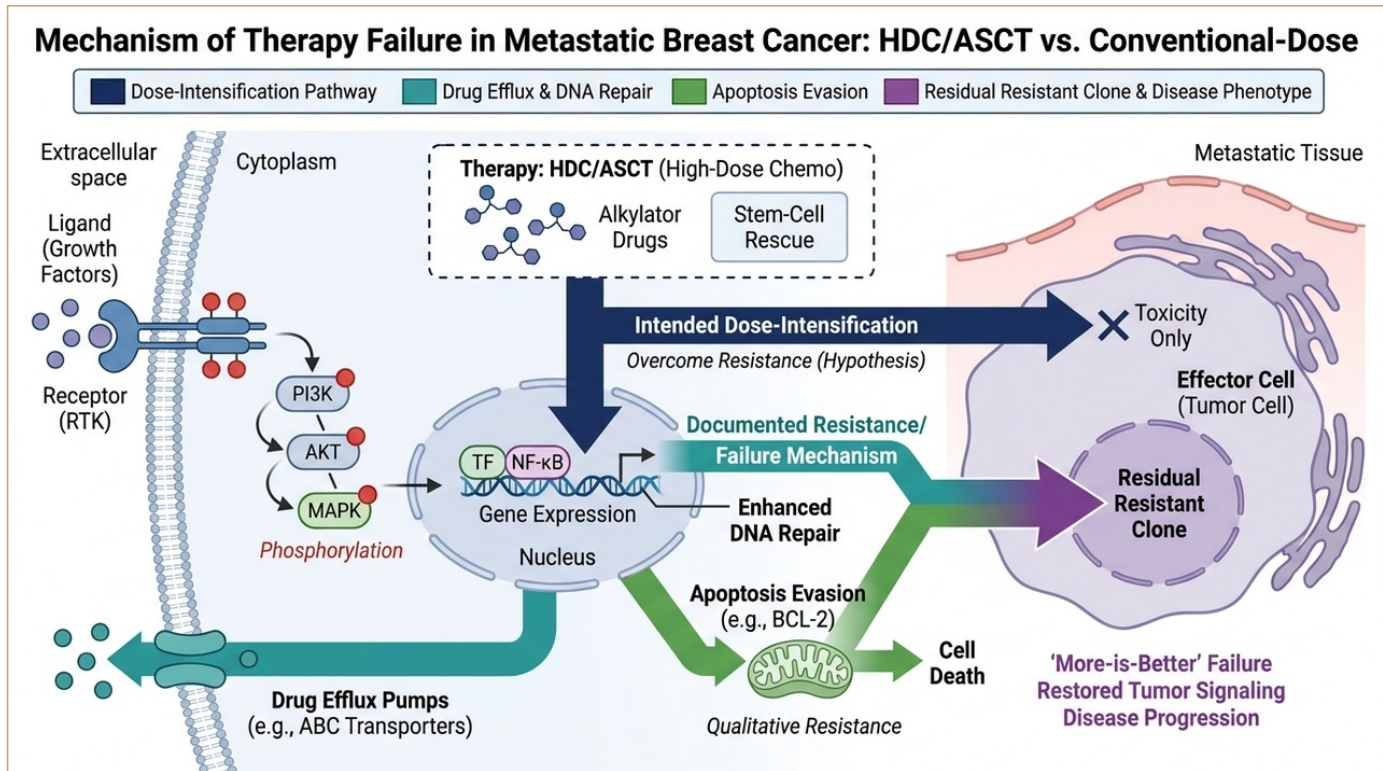
Dose escalation does not overcome intrinsic resistance biology in the surviving micrometastatic population; toxicity/treatment-related mortality offset marginal disease control

BiRAGAS pattern P6 · combination-no-rationale

Citation: Rodenhuis S et al. N Engl J Med 2003;349(1):7-16. PMID 12840087

High-dose chemotherapy with autologous hematopoietic stem-cell transplant

Metastatic breast cancer



Indication: Metastatic breast cancer

Resistance / failure mechanism:

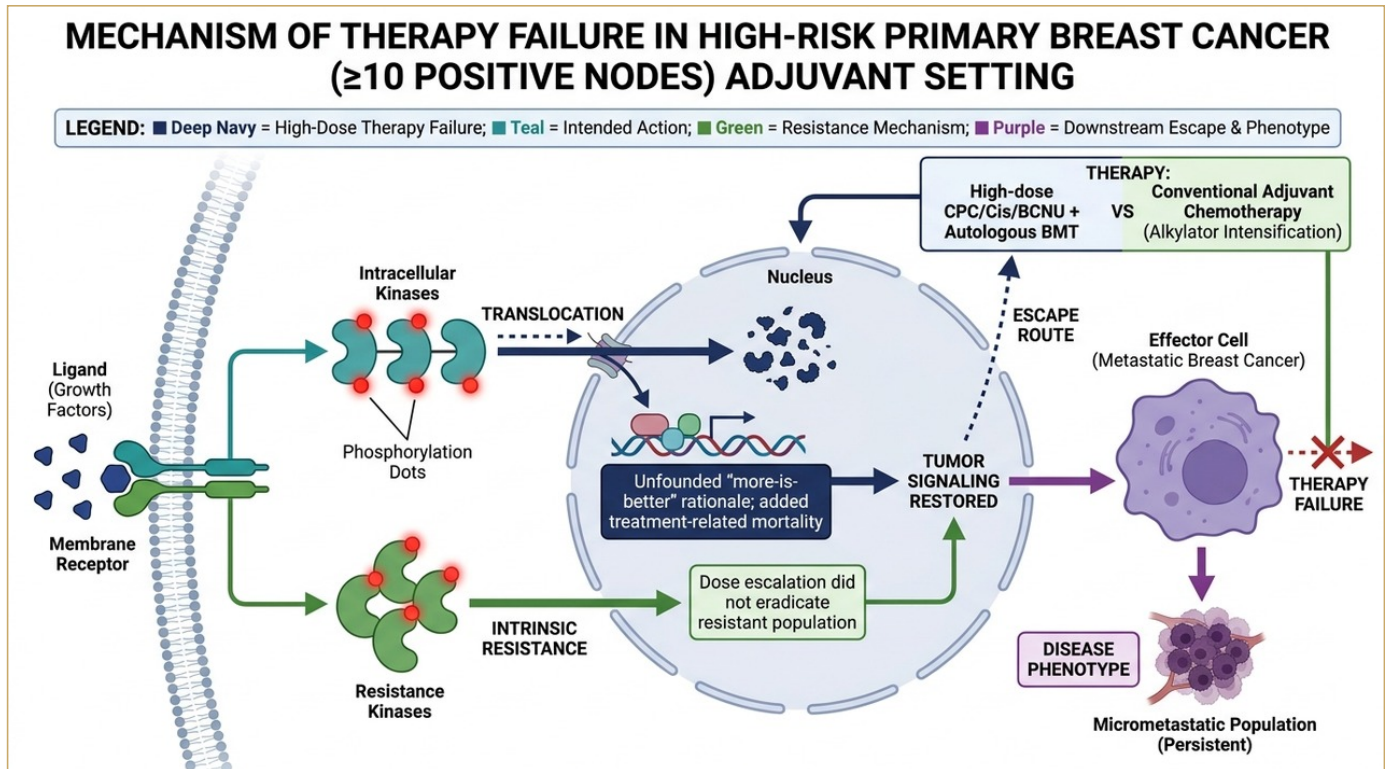
'More-is-better' intensification without a mechanistic rationale for the residual resistant clone; drug resistance is qualitative (efflux, DNA repair, apoptosis evasion) not simply dose-surmountable, so marrow rescue only added toxicity

BiRAGAS pattern P6 · combination-no-rationale

Citation: Stadtmauer EA et al. N Engl J Med 2000;342(15):1069-1076. PMID 10760307

High-dose cyclophosphamide/cisplatin/carmustine + autologous BMT vs conven

High-risk primary breast cancer (≥ 10 positive nodes, adjuvant)



Indication: High-risk primary breast cancer (≥ 10 positive nodes, adjuvant)

Resistance / failure mechanism:

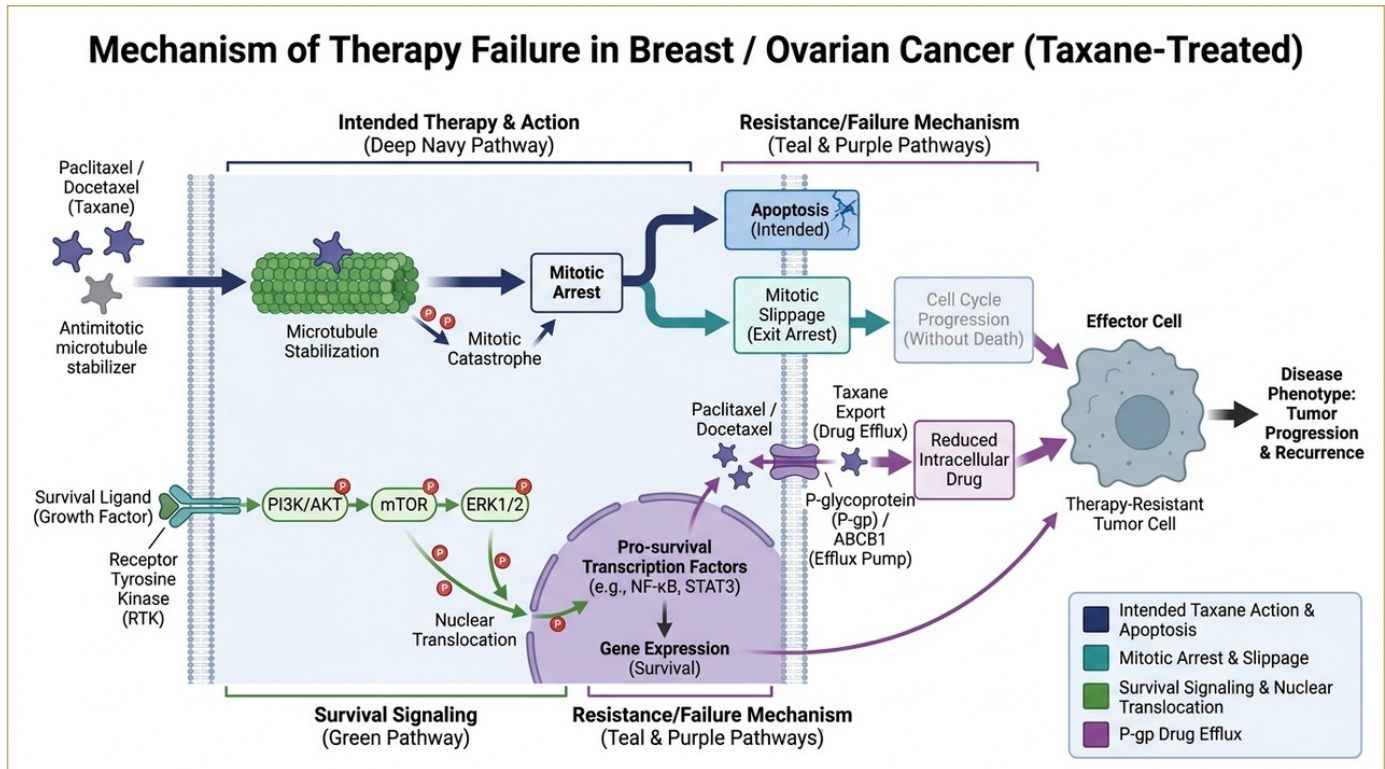
Dose escalation did not eradicate the intrinsically resistant micrometastatic population; added treatment-related mortality; unfounded 'more-is-better' rationale

BiRAGAS pattern P6 · combination-no-rationale

Citation: Peters WP et al. J Clin Oncol 2005;23(10):2191-2200. PMID 15767638

Paclitaxel / docetaxel

Breast / ovarian (taxane-treated)



Indication: Breast / ovarian (taxane-treated)

Resistance / failure mechanism:

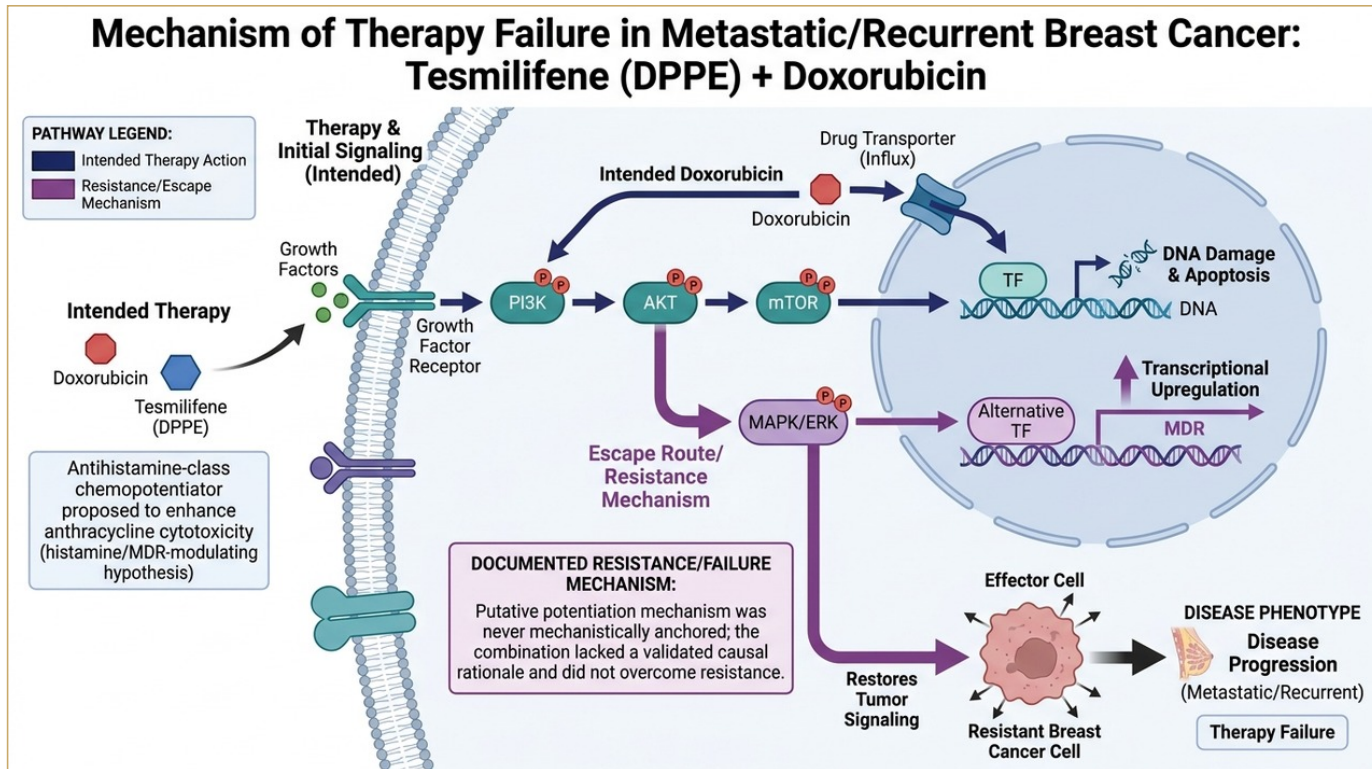
Cells exit mitotic arrest without death (slippage) and/or export drug via P-gp, escaping taxane-induced apoptosis

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Orr GA et al. Oncogene 2003;22(47):7280-7295. PMID 14576838

Tesmilifene (DPPE) added to doxorubicin

Metastatic / recurrent breast cancer



Indication: Metastatic / recurrent breast cancer

Resistance / failure mechanism:

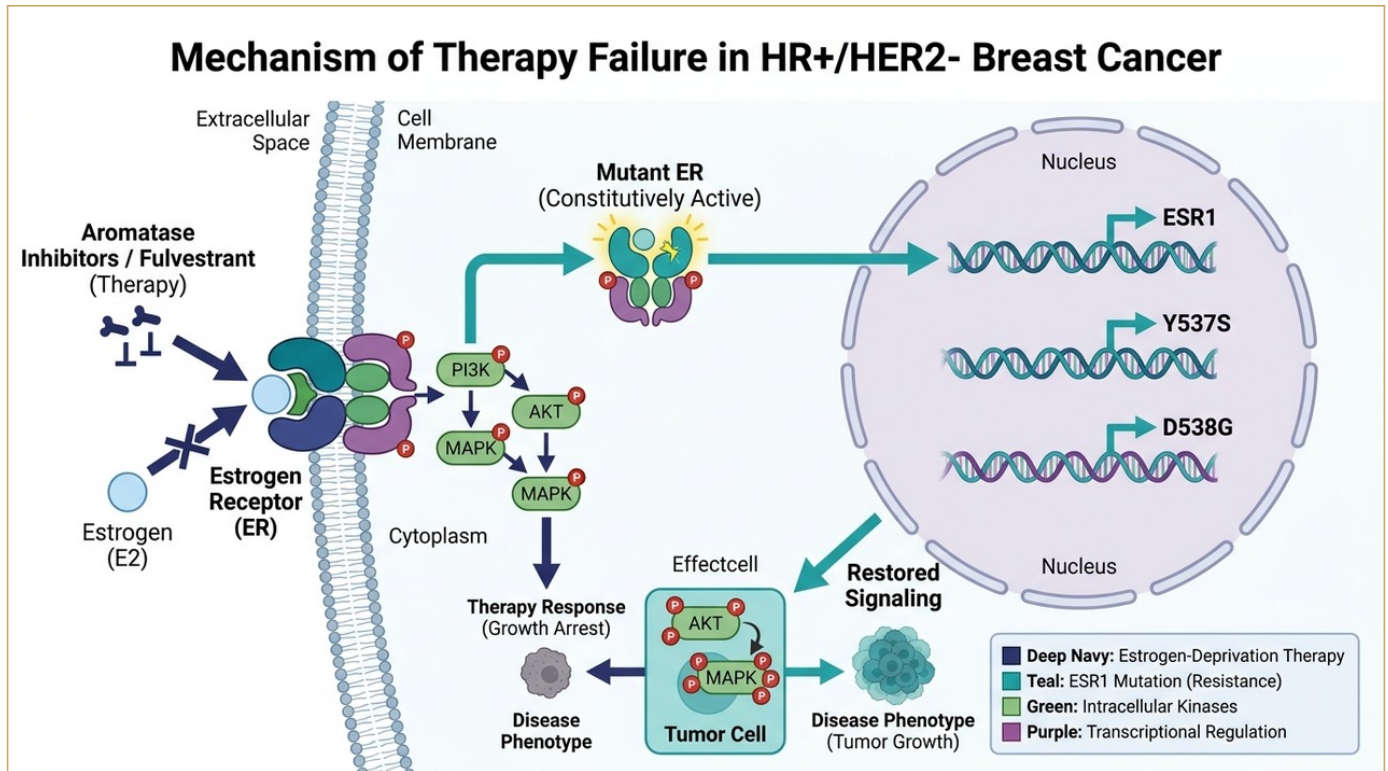
Putative potentiation mechanism was never mechanistically anchored; the combination lacked a validated causal rationale and did not overcome resistance

BiRAGAS pattern P6 · combination-no-rationale

Citation: Reyno L et al. J Clin Oncol 2004;22(2):269-276. PMID 14722036

aromatase inhibitors / fulvestrant

HR+/HER2- breast cancer



Indication: HR+/HER2- breast cancer

Resistance / failure mechanism:

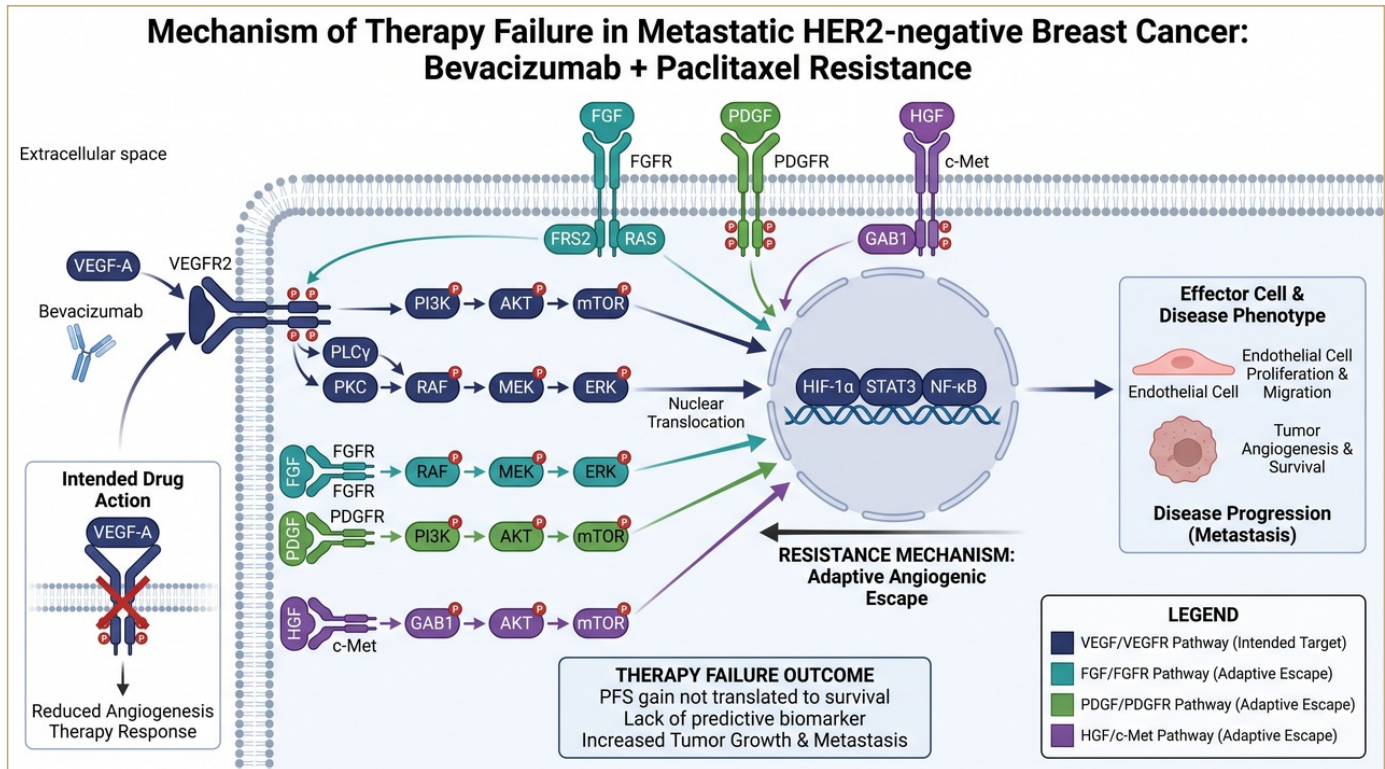
ESR1 Y537S / D538G render estrogen receptor constitutively active (ligand-independent), bypassing estrogen deprivation

BiRAGAS pattern P7 · target-mutation

Citation: Toy W et al. Nat Genet 2013;45:1439-1445, PMID 24185512; Robinson DR et al. Nat Genet 2013;45:1446-1451, PMID 24185510

bevacizumab + paclitaxel

Metastatic breast cancer (HER2-negative)



Indication: Metastatic breast cancer (HER2-negative)

Resistance / failure mechanism:

PFS gain not translated to survival; adaptive angiogenic escape and lack of predictive biomarker

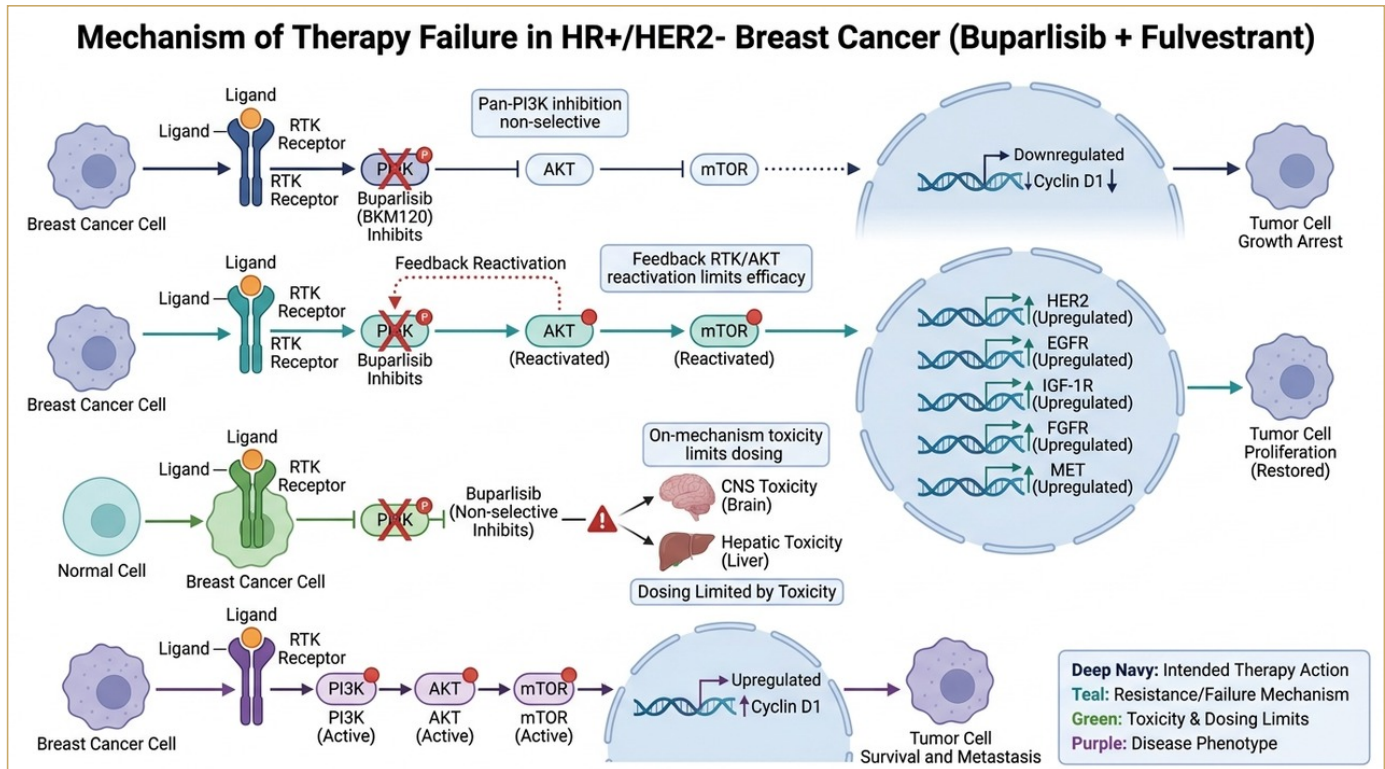
BiRAGAS pattern P5 · correlate-not-driver

Citation: Miller K et al. N Engl J Med 2007;357:2666-2676, PMID 18160686

ClinicalTrials.gov: NCT00028990

buparlisib (BKM120) + fulvestrant

HR+/HER2- breast cancer



Indication: HR+/HER2- breast cancer

Resistance / failure mechanism:

Pan-PI3K inhibition non-selective, on-mechanism CNS/hepatic toxicity limits dosing; feedback RTK/AKT reactivation limits efficacy

BiRAGAS pattern P4 · on-mechanism-toxicity

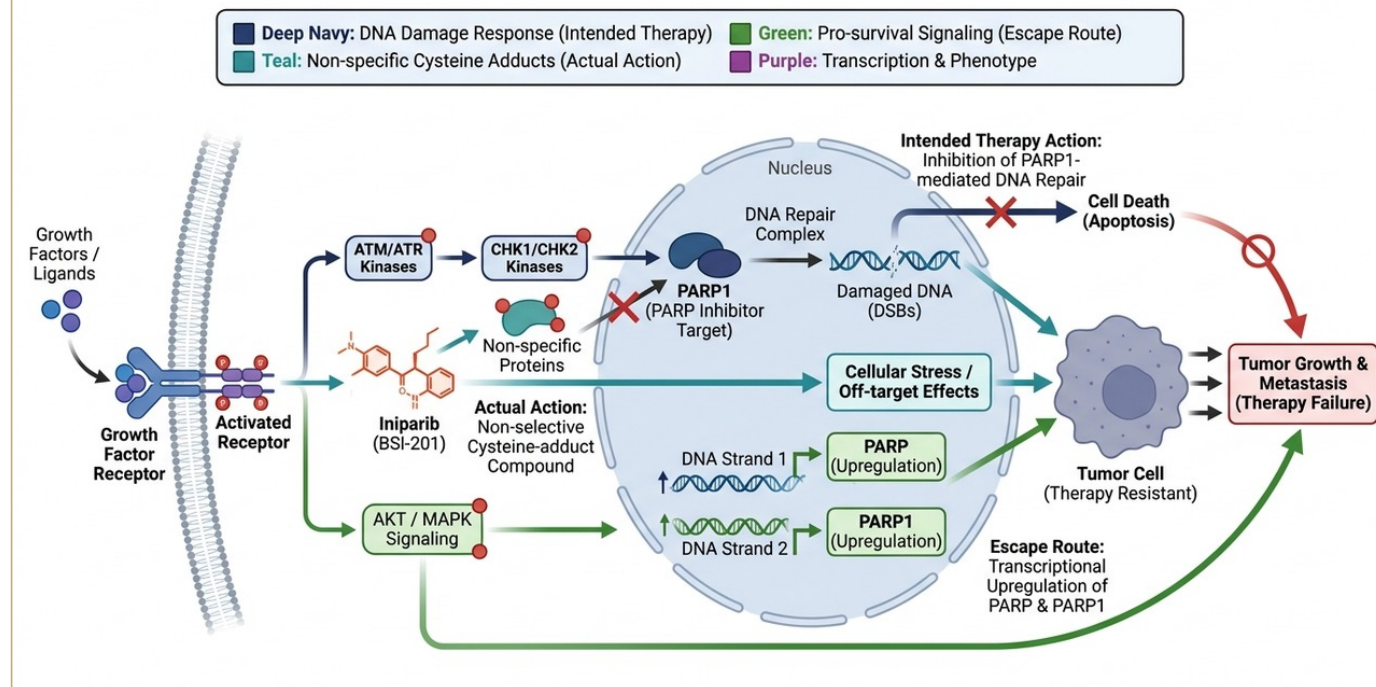
Citation: Di Leo A et al. Lancet Oncol 2018;19:87-100, PMID 29804902

ClinicalTrials.gov: NCT01633060

iniparib (BSI-201) + gemcitabine/carboplatin

Triple-negative breast cancer (metastatic)

Mechanism of therapy failure in Triple-negative breast cancer (metastatic)



Indication: Triple-negative breast cancer (metastatic)

Resistance / failure mechanism:

Iniparib is not a true PARP inhibitor (non-selective cysteine-adduct compound); the presumed mechanism never existed

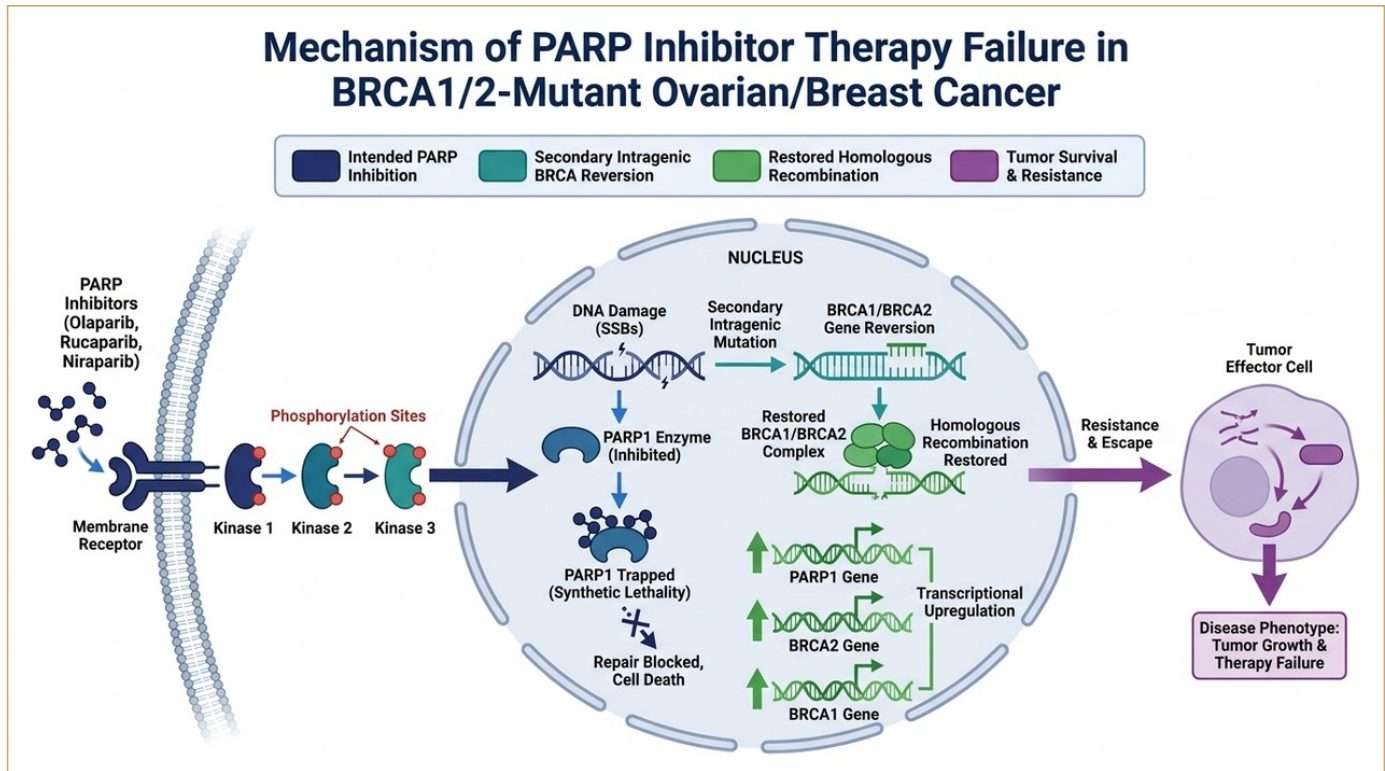
BiRAGAS pattern P1 · correlate-not-driver

Citation: O'Shaughnessy J et al. J Clin Oncol 2014;32:3840-3847, PMID 25185099; Patel AG et al. Clin Cancer Res 2012, PMID 22496272

[ClinicalTrials.gov: NCT00938652](https://clinicaltrials.gov/ct2/show/study/NCT00938652)

olaparib / rucaparib / niraparib

Ovarian / breast (BRCA1/2-mutant)



Indication: Ovarian / breast (BRCA1/2-mutant)

Resistance / failure mechanism:

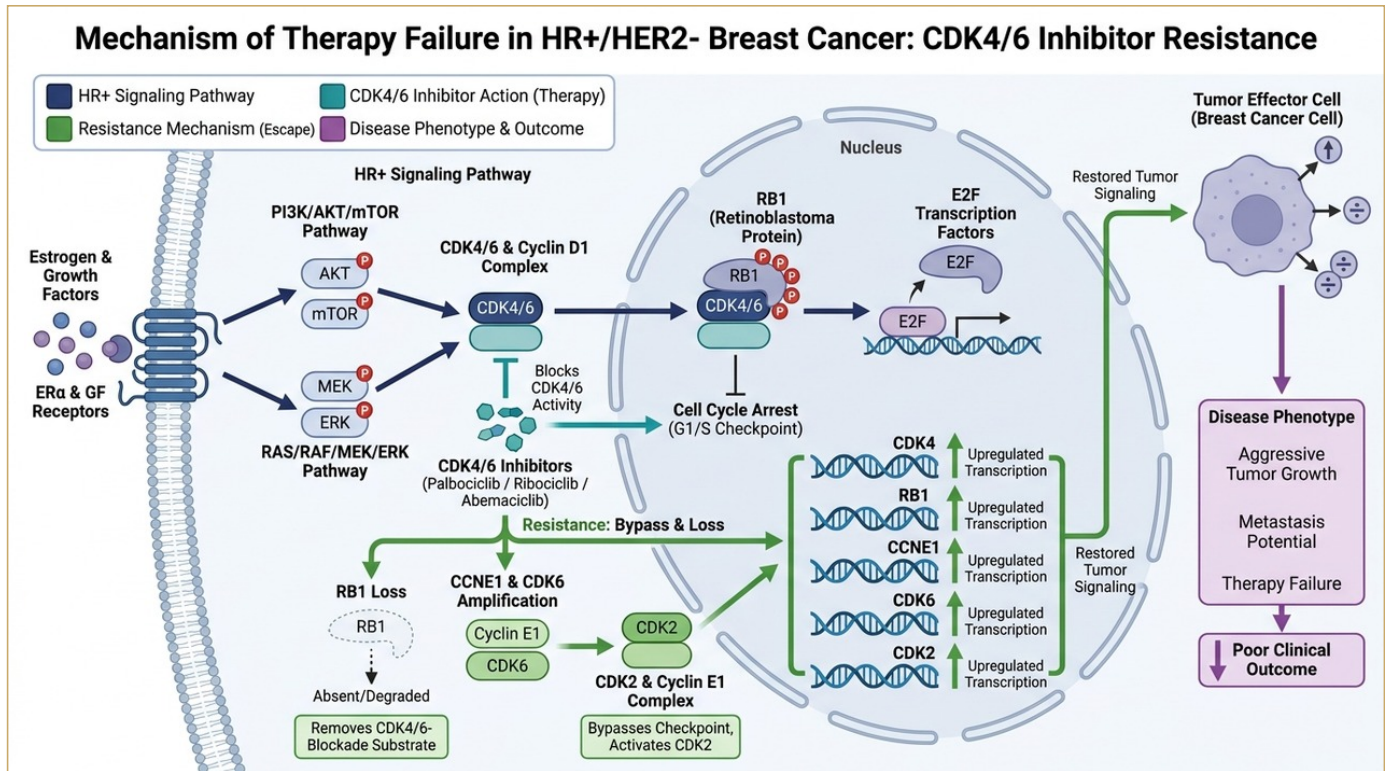
Secondary intragenic BRCA2/BRCA1 mutations restore open reading frame and homologous recombination, re-establishing DNA repair

BiRAGAS pattern P2 · DNA-repair/apoptosis-evasion

Citation: Sakai W et al. Nature 2008;451:1116-1120, PMID 18264087

palbociclib / ribociclib / abemaciclib (+ endocrine)

HR+/HER2- breast cancer



Indication: HR+/HER2- breast cancer

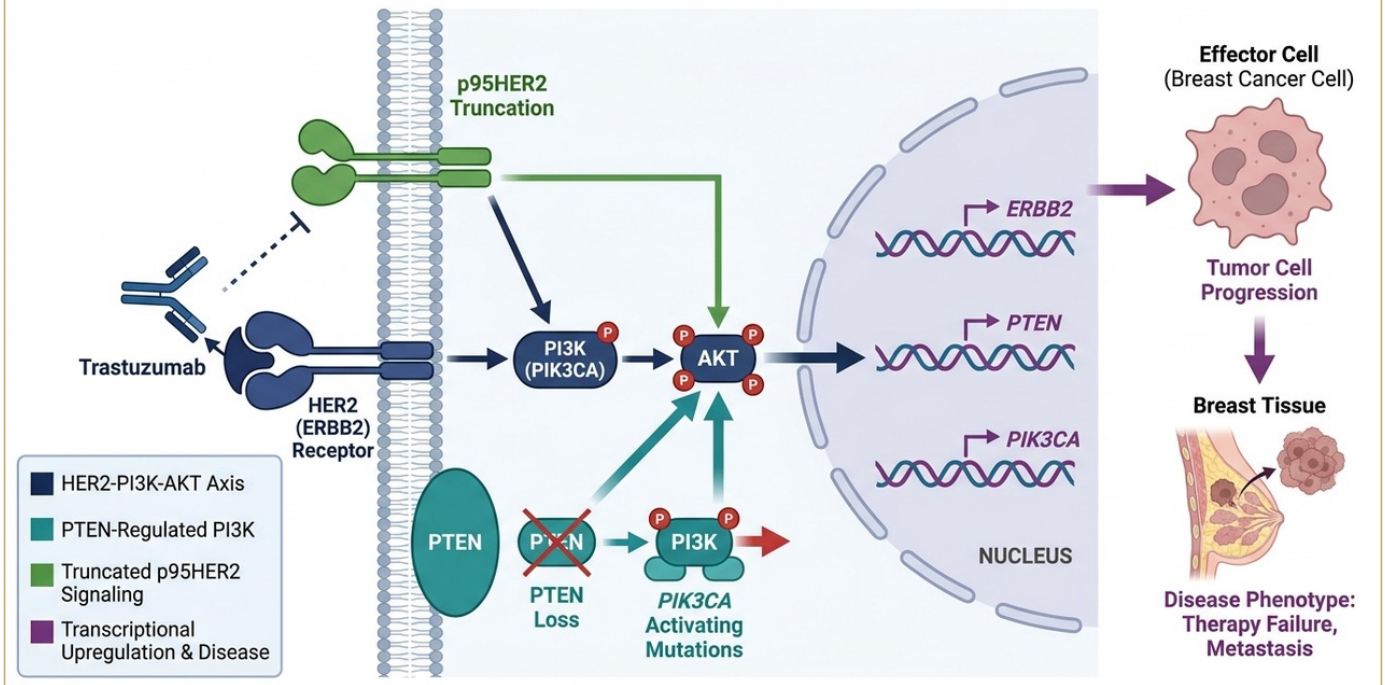
Resistance / failure mechanism:

RB1 loss removes CDK4/6-blockade substrate; CCNE1/CDK6 amplification and CDK2 activation bypass the checkpoint

BiRAGAS pattern P2 · bypass/parallel-pathway

Citation: Condorelli R et al. Ann Oncol 2018;29:640-645, PMID 29236940; O'Leary B et al. Cancer Discov 2018

Mechanism of Therapy Failure in HER2+ Breast Cancer: Trastuzumab Resistance



Indication: HER2+ breast cancer

Resistance / failure mechanism:

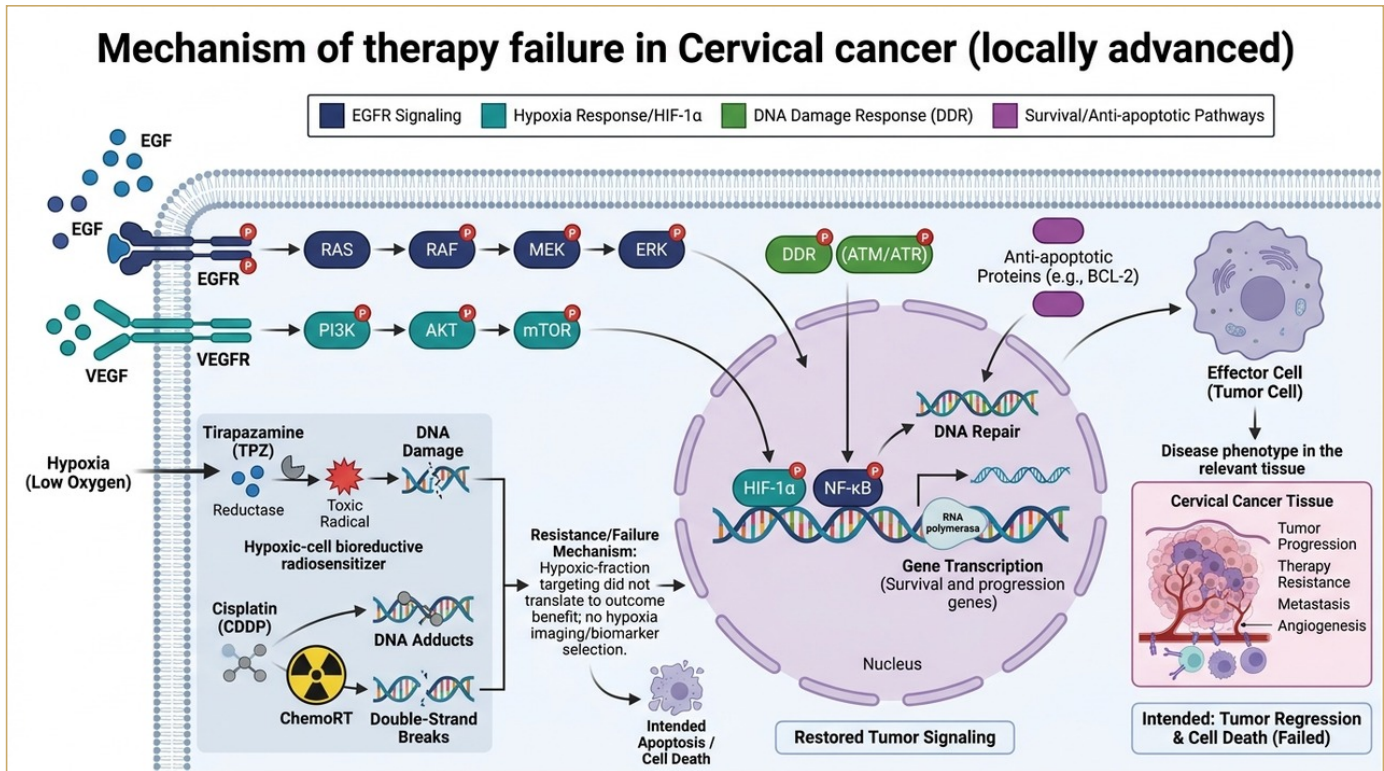
PTEN loss / PIK3CA activating mutations sustain PI3K/AKT downstream of HER2; p95HER2 truncation lacks trastuzumab epitope

BiRAGAS pattern P2 · bypass/parallel-pathway

Citation: Nagata Y et al. Cancer Cell 2004;6:117-127, PMID 15324695

Tirapazamine + cisplatin + chemoRT

Cervical cancer (locally advanced)



Indication: Cervical cancer (locally advanced)

Resistance / failure mechanism:

Hypoxic-fraction targeting did not translate to outcome benefit; no hypoxia imaging/biomarker selection

BiRAGAS pattern P4 · TME/immune-exclusion

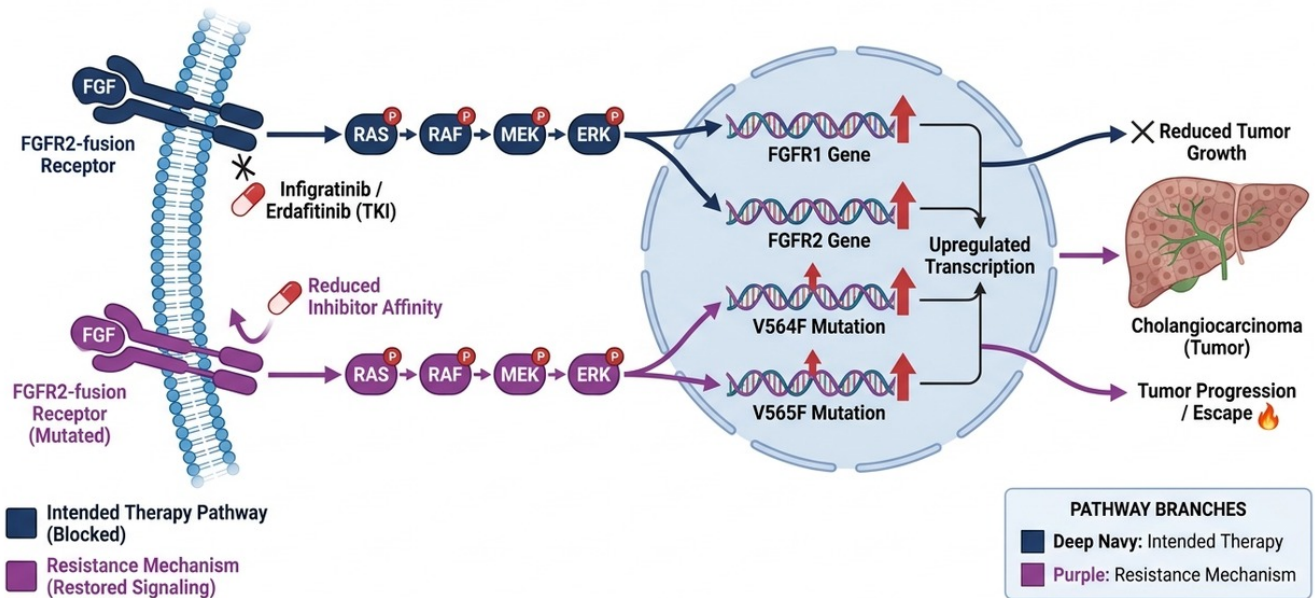
Citation: DiSilvestro PA et al. J Clin Oncol 2014;32:458-464, PMID 24395863

ClinicalTrials.gov: NCT00098995

infigratinib (BGJ398) / erdafitinib

Cholangiocarcinoma (FGFR2-fusion)

Mechanism of Therapy Failure in Cholangiocarcinoma (FGFR2-fusion)



Indication: Cholangiocarcinoma (FGFR2-fusion)

Resistance / failure mechanism:

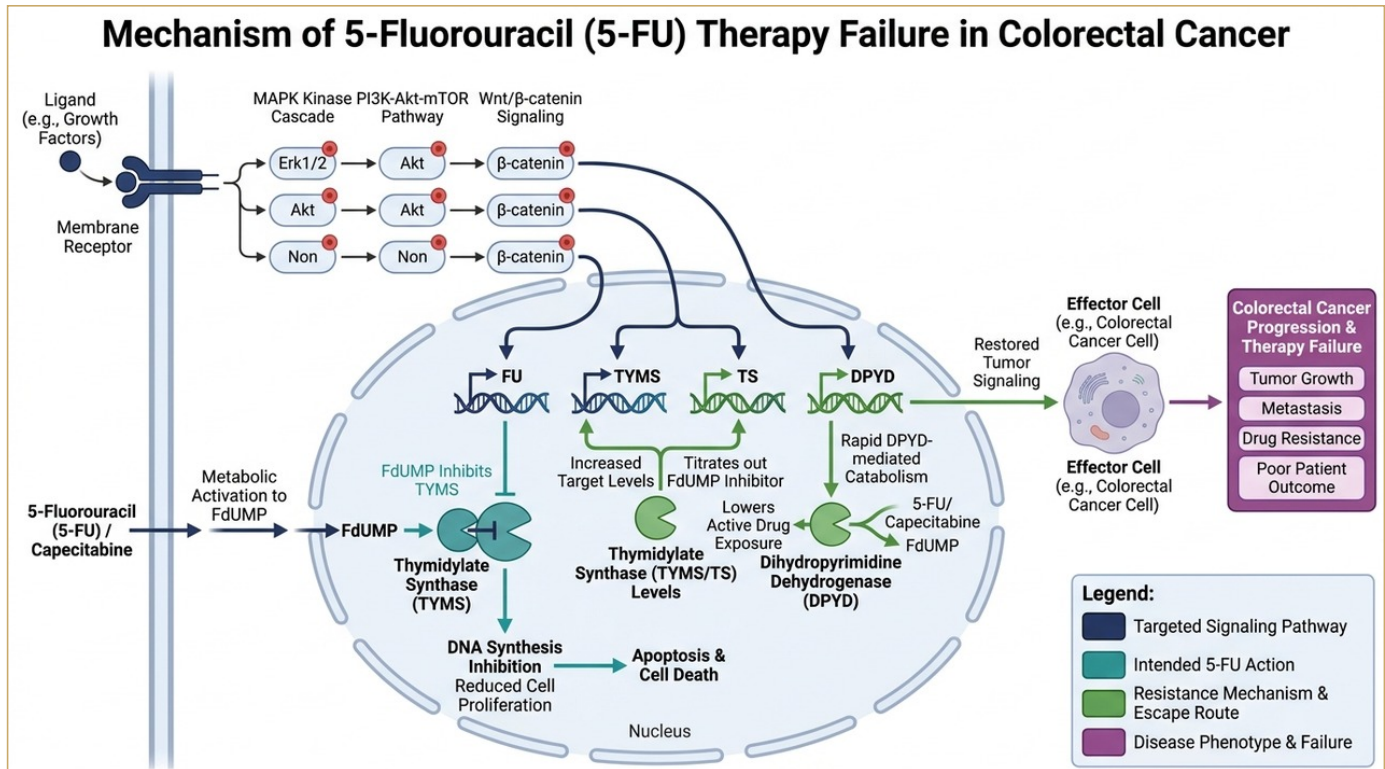
FGFR2 gatekeeper (V564F/V565F) and molecular-brake/activation-loop mutations reduce inhibitor affinity; polyclonal on-target escape

BiRAGAS pattern P7 · target-mutation

Citation: Goyal L et al. Cancer Discov 2017;7:252-263, PMID 28034880

5-Fluorouracil (5-FU) / capecitabine

Colorectal cancer



Indication: Colorectal cancer

Resistance / failure mechanism:

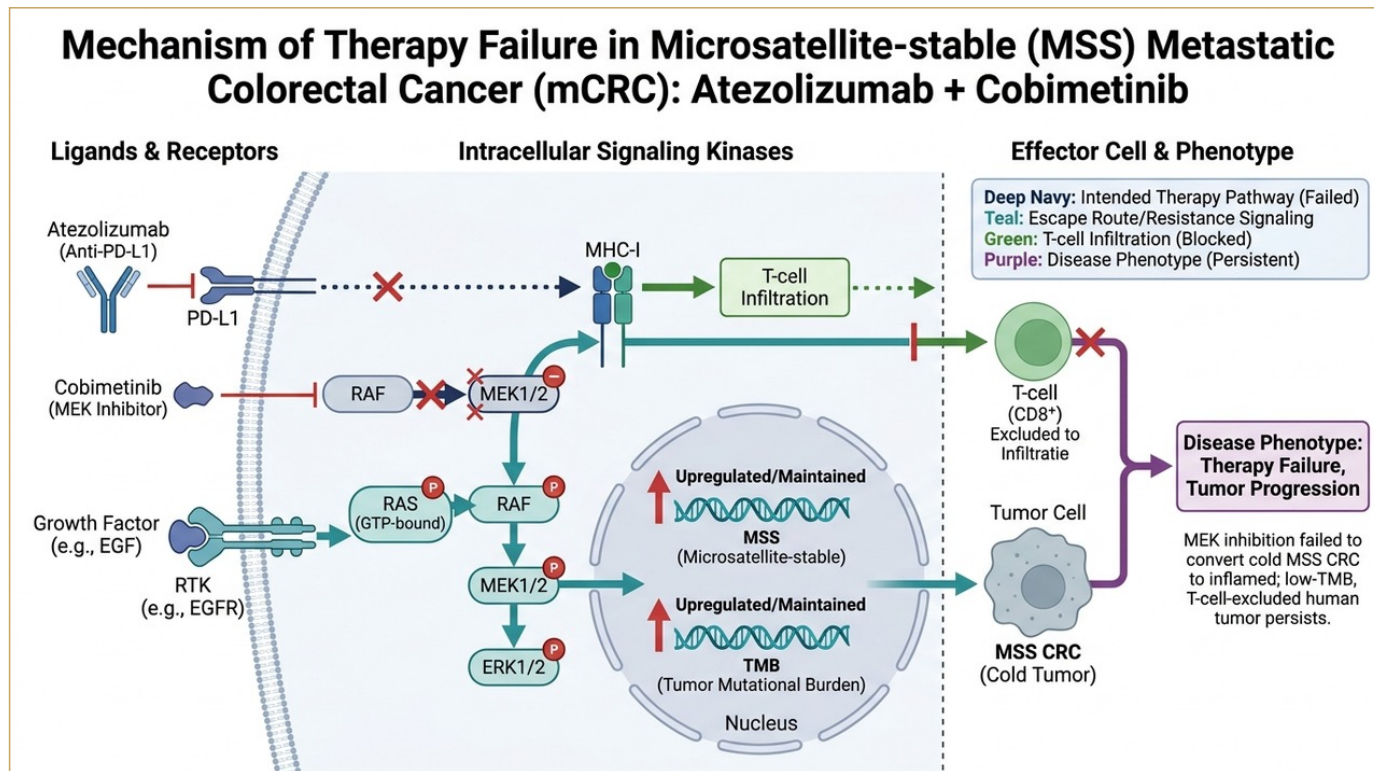
Increased target (TS) levels titrate out the inhibitor; rapid DPYD-mediated catabolism lowers active-drug exposure

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Longley DB, Harkin DP, Johnston PG. Nat Rev Cancer 2003;3(5):330-338. PMID 12724731

Atezolizumab + cobimetinib

Microsatellite-stable metastatic colorectal cancer



Indication: Microsatellite-stable metastatic colorectal cancer

Resistance / failure mechanism:

MEK inhibition did not convert cold MSS CRC to inflamed in patients; combination rationale from preclinical models failed to translate to a low-TMB, T-cell-excluded human tumor.

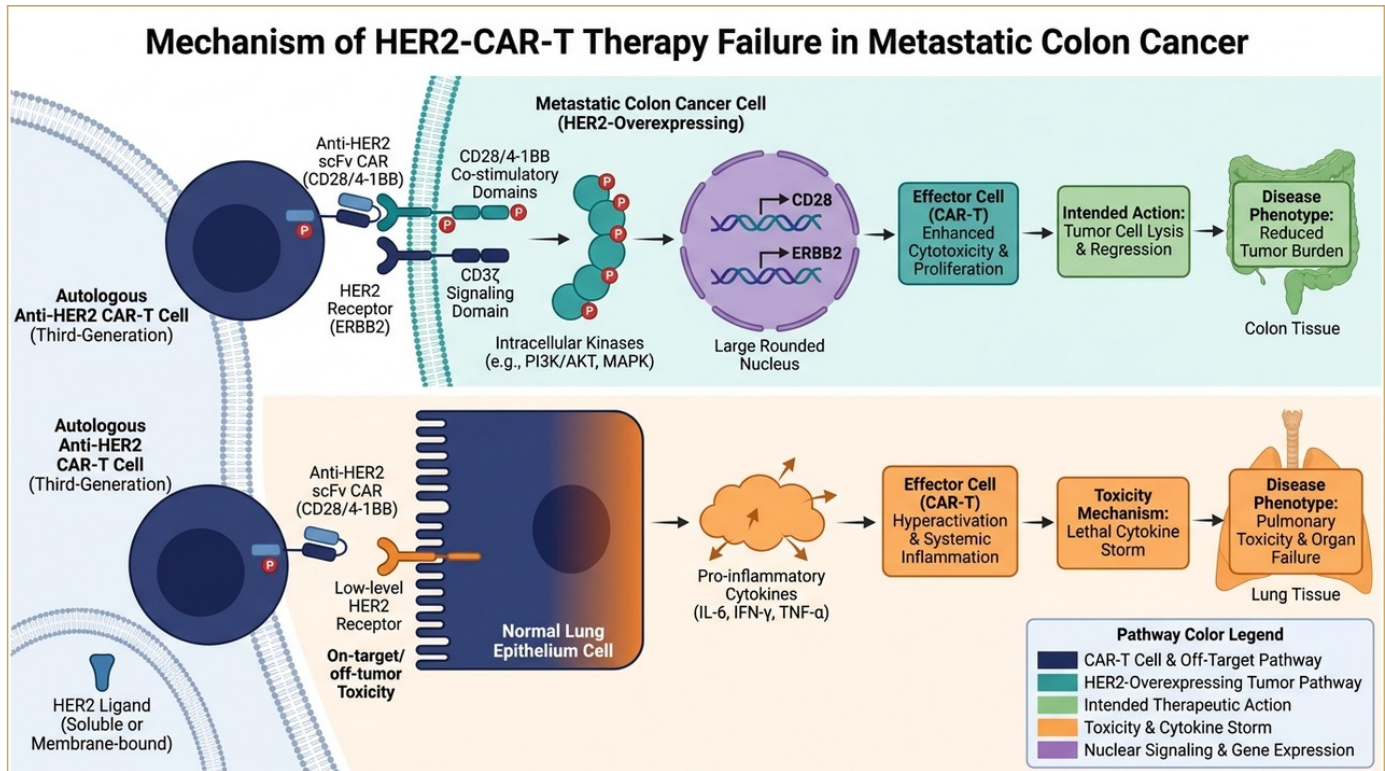
BiRAGAS pattern P6 · combination-no-rationale

Citation: Eng C et al. Lancet Oncol 2019;20:849-861. PMID 31003911

ClinicalTrials.gov: [NCT02788279](https://clinicaltrials.gov/ct2/show/study/NCT02788279)

Autologous anti-HER2 (trastuzumab-based scFv) third-generation CAR-T cells

Metastatic colon cancer (HER2/ERBB2-overexpressing)



Indication: Metastatic colon cancer (HER2/ERBB2-overexpressing)

Resistance / failure mechanism:

On-target/off-tumor toxicity: low-level HER2 on normal lung epithelium recognized by high-avidity CAR-T, triggering lethal cytokine storm rather than tumor resistance per se.

BiRAGAS pattern P4 · on-mechanism-toxicity

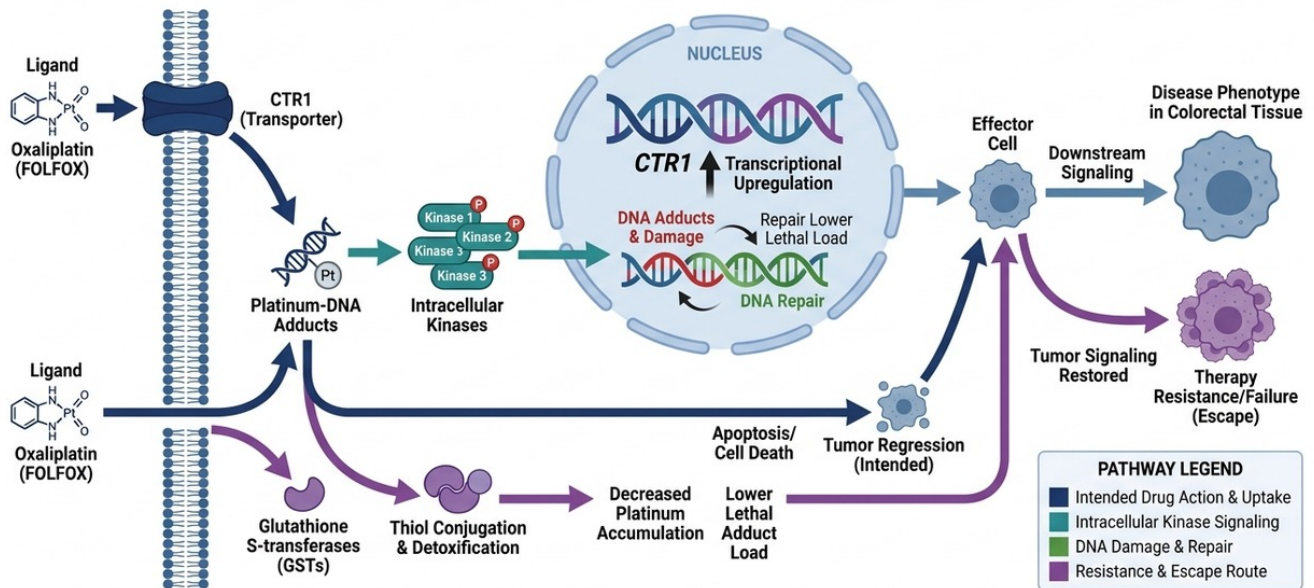
Citation: Morgan RA et al. Mol Ther 2010;18:843-851. PMID 20179677

Oxaliplatin (FOLFOX)

Colorectal cancer (oxaliplatin-treated)

Mechanism of Therapy Failure in Colorectal Cancer (Oxaliplatin-treated)

Intended drug action vs. resistance escape route via decreased accumulation and thiol conjugation



Indication: Colorectal cancer (oxaliplatin-treated)

Resistance / failure mechanism:

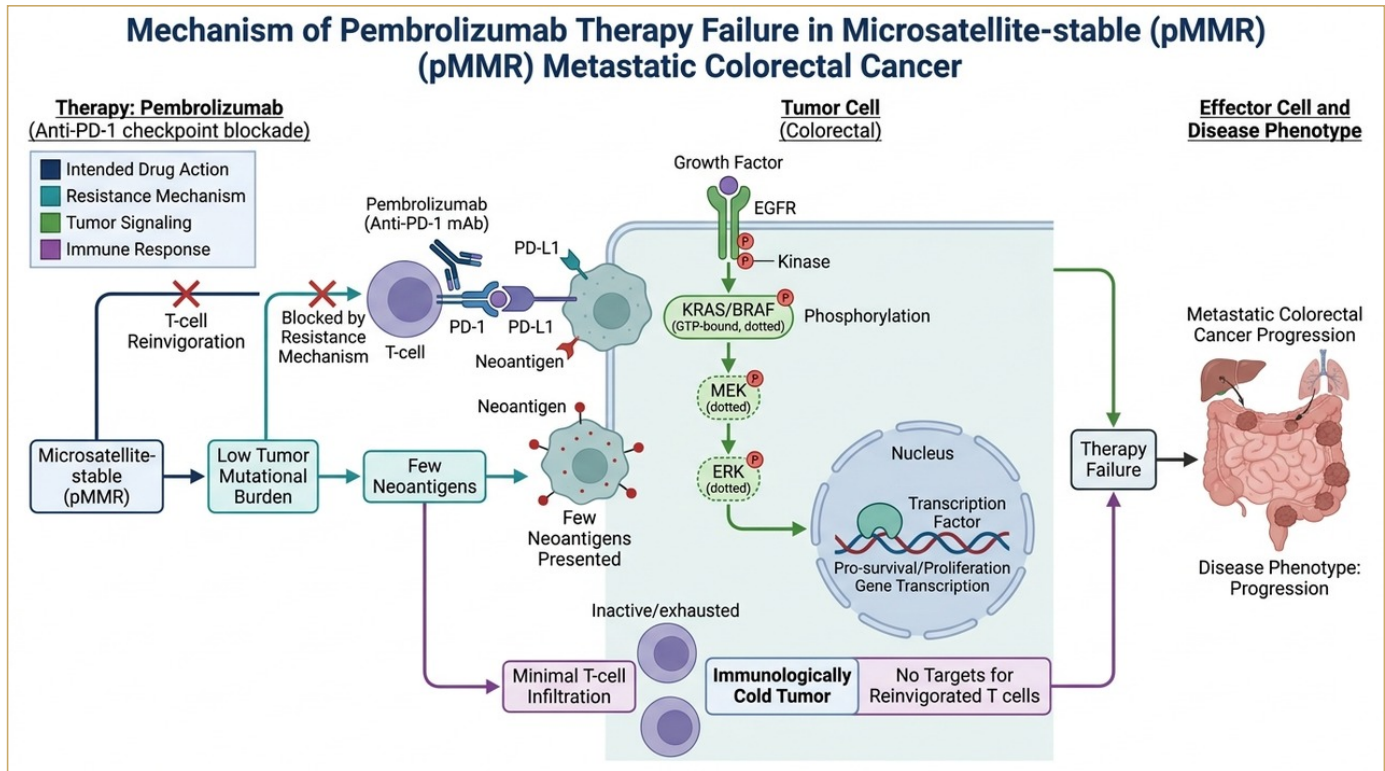
Decreased platinum accumulation plus thiol conjugation and repair lower lethal DNA-adduct load

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Martinez-Balibrea E et al. Mol Cancer Ther 2015;14(8):1767-1776. PMID 26184483

Pembrolizumab

Microsatellite-stable (pMMR) metastatic colorectal cancer



Indication: Microsatellite-stable (pMMR) metastatic colorectal cancer

Resistance / failure mechanism:

Low tumor mutational burden → few neoantigens, minimal T-cell infiltration; immunologically cold tumor without targets for reinvigorated T cells.

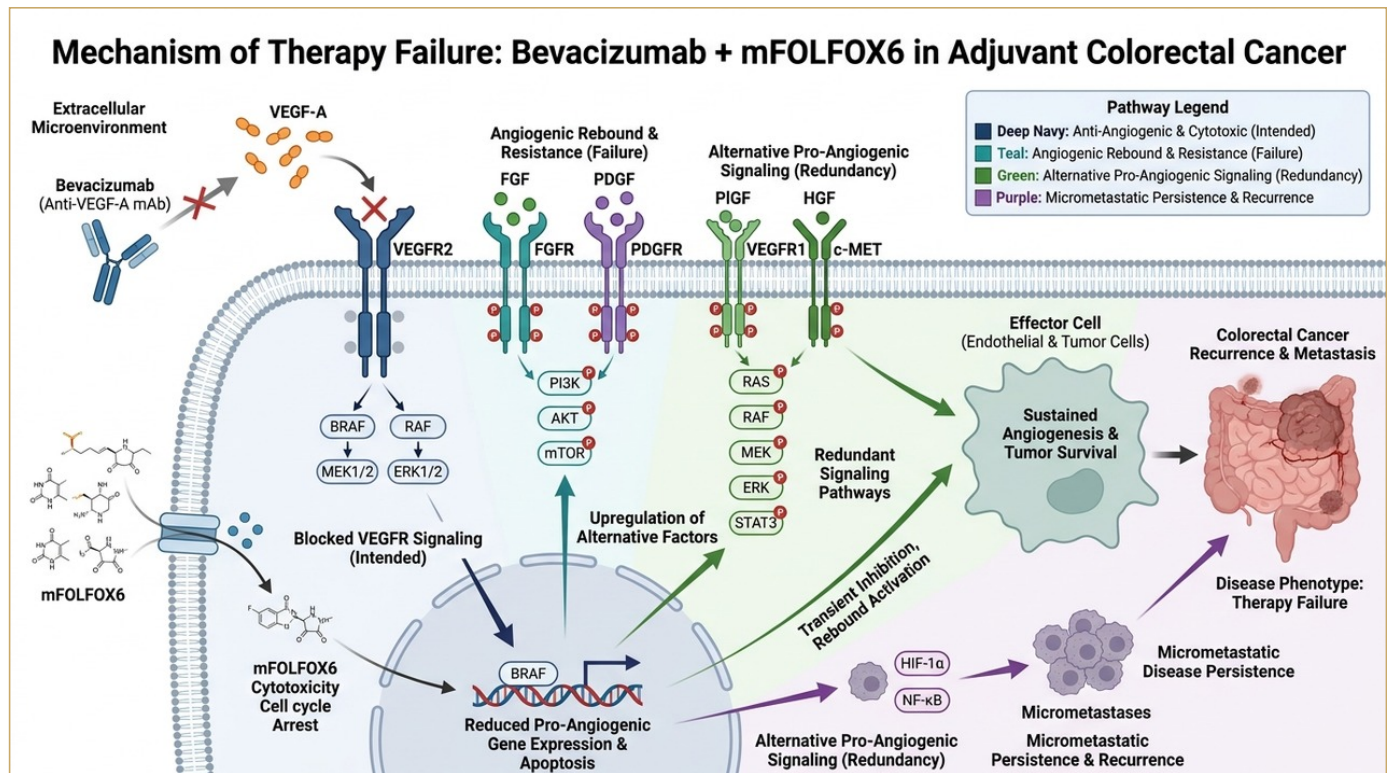
BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Le DT et al. N Engl J Med 2015;372:2509-2520. PMID 26028255

ClinicalTrials.gov: [NCT01876511](https://clinicaltrials.gov/ct2/show/study/NCT01876511)

bevacizumab + mFOLFOX6

Colorectal (adjuvant, stage II/III)



Indication: Colorectal (adjuvant, stage II/III)

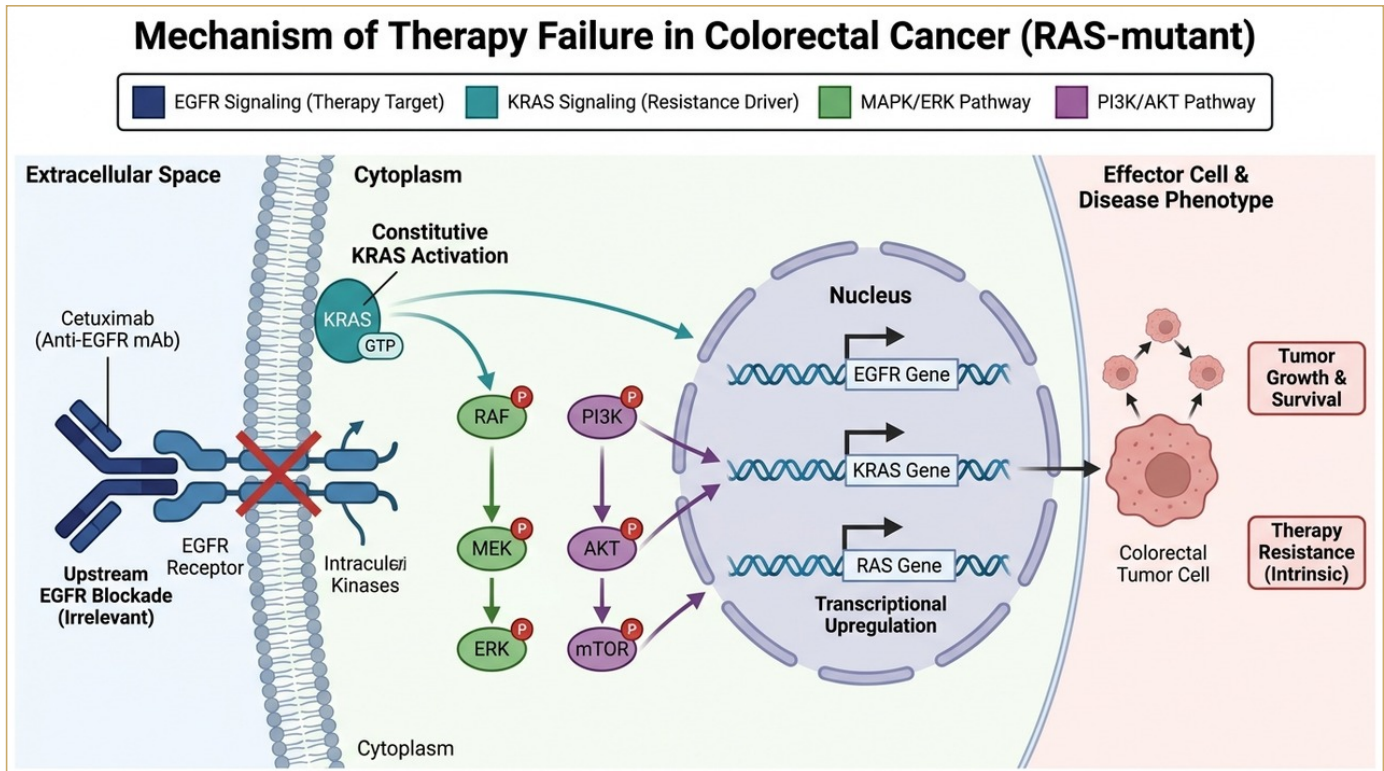
Resistance / failure mechanism:

Transient anti-angiogenic effect only during dosing; VEGF blockade does not eradicate micrometastatic disease (angiogenic rebound/redundancy)

BiRAGAS pattern P1 · bypass/parallel-pathway

Citation: Allegra CJ et al. J Clin Oncol 2011;29:11-16, PMID 20940184

ClinicalTrials.gov: [NCT00096278](https://clinicaltrials.gov/ct2/show/study/NCT00096278)



Indication: Colorectal (RAS-mutant)

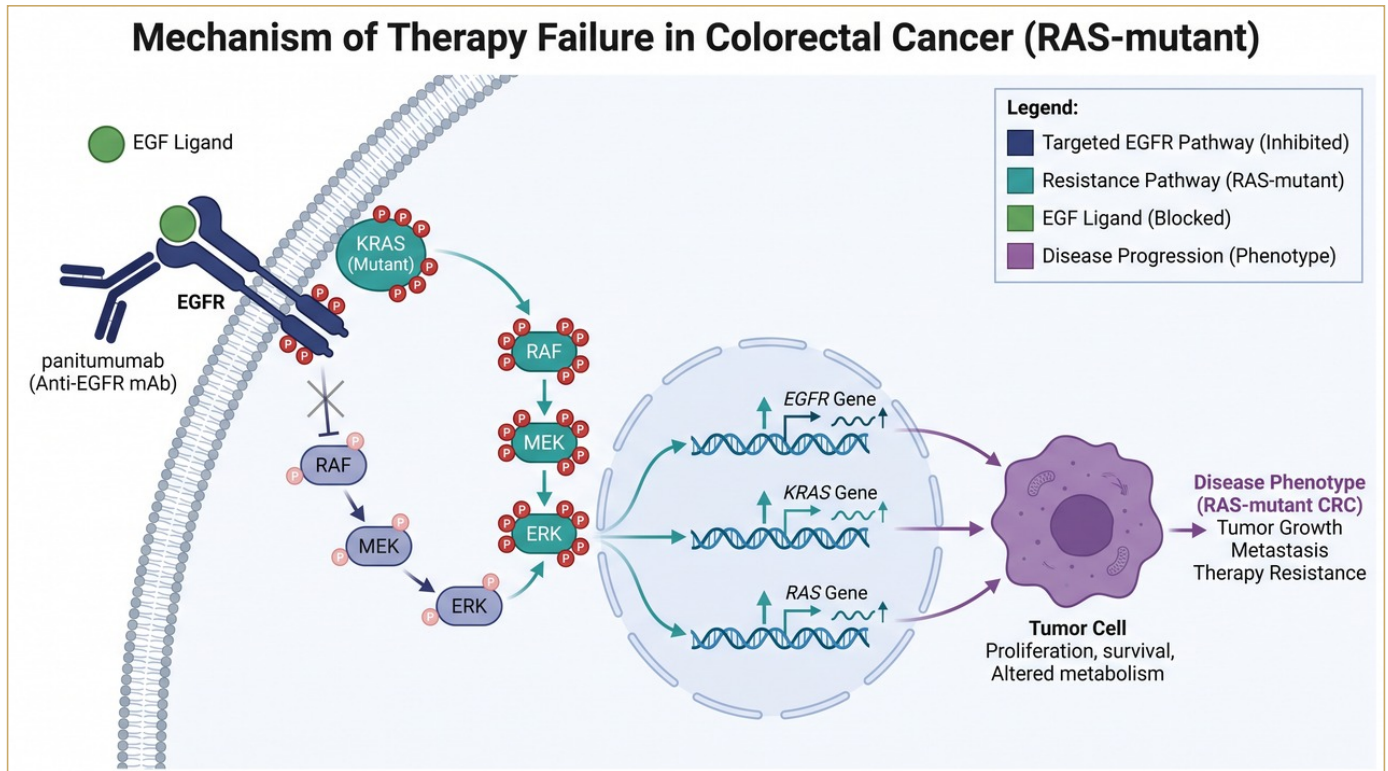
Resistance / failure mechanism:

Constitutive downstream KRAS activation makes upstream EGFR blockade irrelevant (intrinsic resistance)

BiRAGAS pattern P3 · bypass/parallel-pathway

Citation: Karapetis CS et al. N Engl J Med 2008;359:1757-1765, PMID 18946061

[ClinicalTrials.gov: NCT00079066](https://clinicaltrials.gov/ct2/show/study/NCT00079066)



Indication: Colorectal (RAS-mutant)

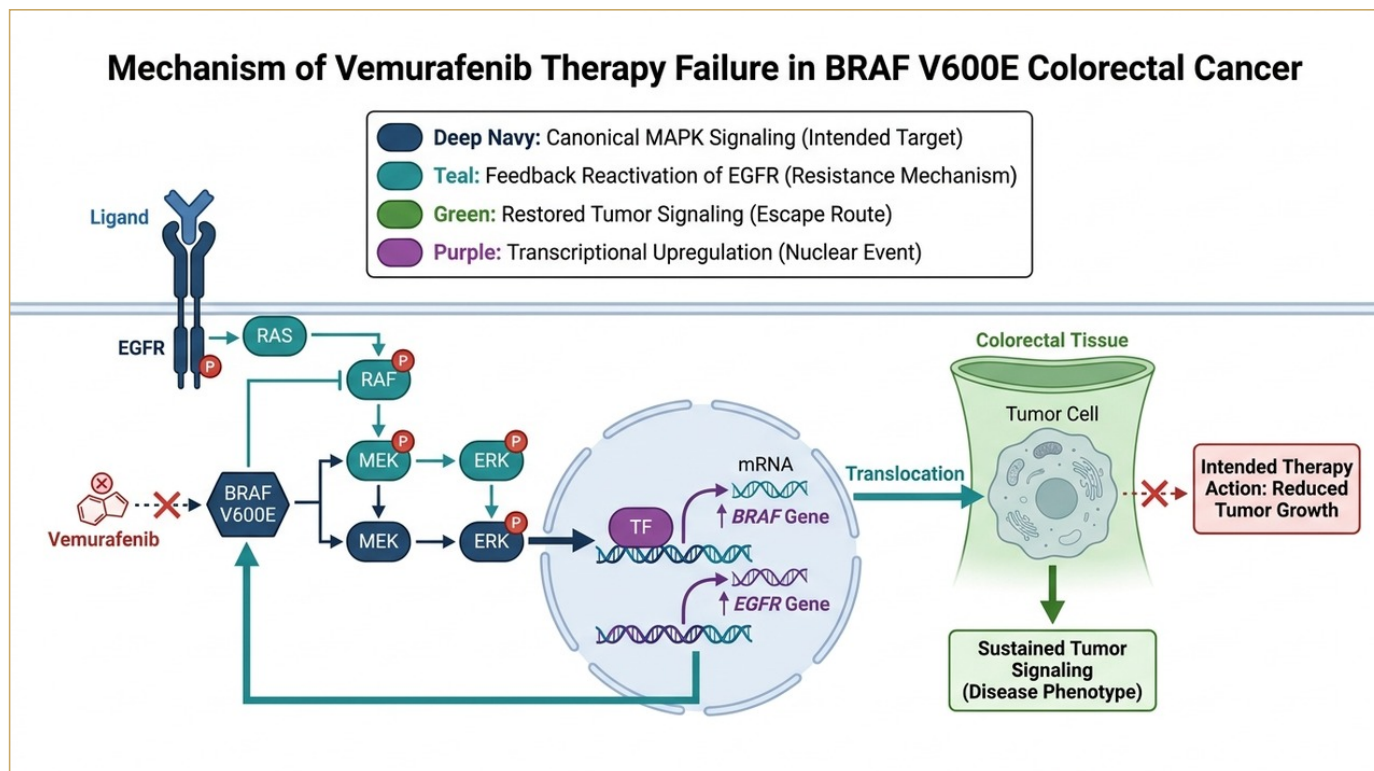
Resistance / failure mechanism:

Downstream KRAS mutation uncouples response from EGFR inhibition

BiRAGAS pattern P3 · bypass/parallel-pathway

Citation: Amado RG et al. J Clin Oncol 2008;26:1626-1634, PMID 18316791

[ClinicalTrials.gov: NCT00113763](https://clinicaltrials.gov/ct2/show/study/NCT00113763)



Indication: Colorectal (BRAF V600E)

Resistance / failure mechanism:

BRAF inhibition triggers rapid feedback reactivation of EGFR (high basal EGFR in colon epithelium) restoring MAPK signaling

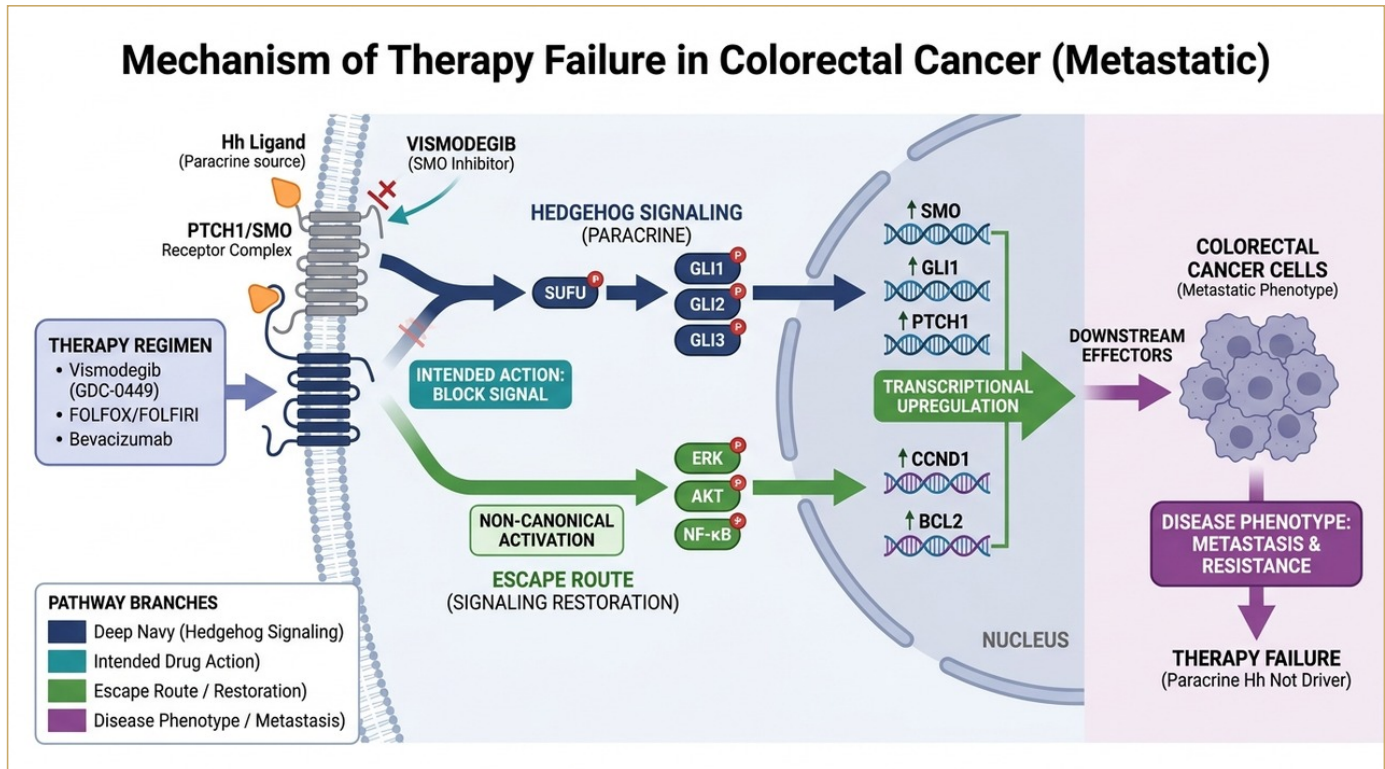
BiRAGAS pattern P2 · feedback-reactivation

Citation: Prahallad A et al. Nature 2012;483:100-103, PMID 22281684; Kopetz S et al. J Clin Oncol 2015;33:4032-4038, PMID 26460303

ClinicalTrials.gov: [NCT01524978](https://clinicaltrials.gov/ct2/show/study/NCT01524978)

vismodegib (GDC-0449) + FOLFOX/FOLFIRI + bevacizumab

Colorectal cancer (metastatic)



Indication: Colorectal cancer (metastatic)

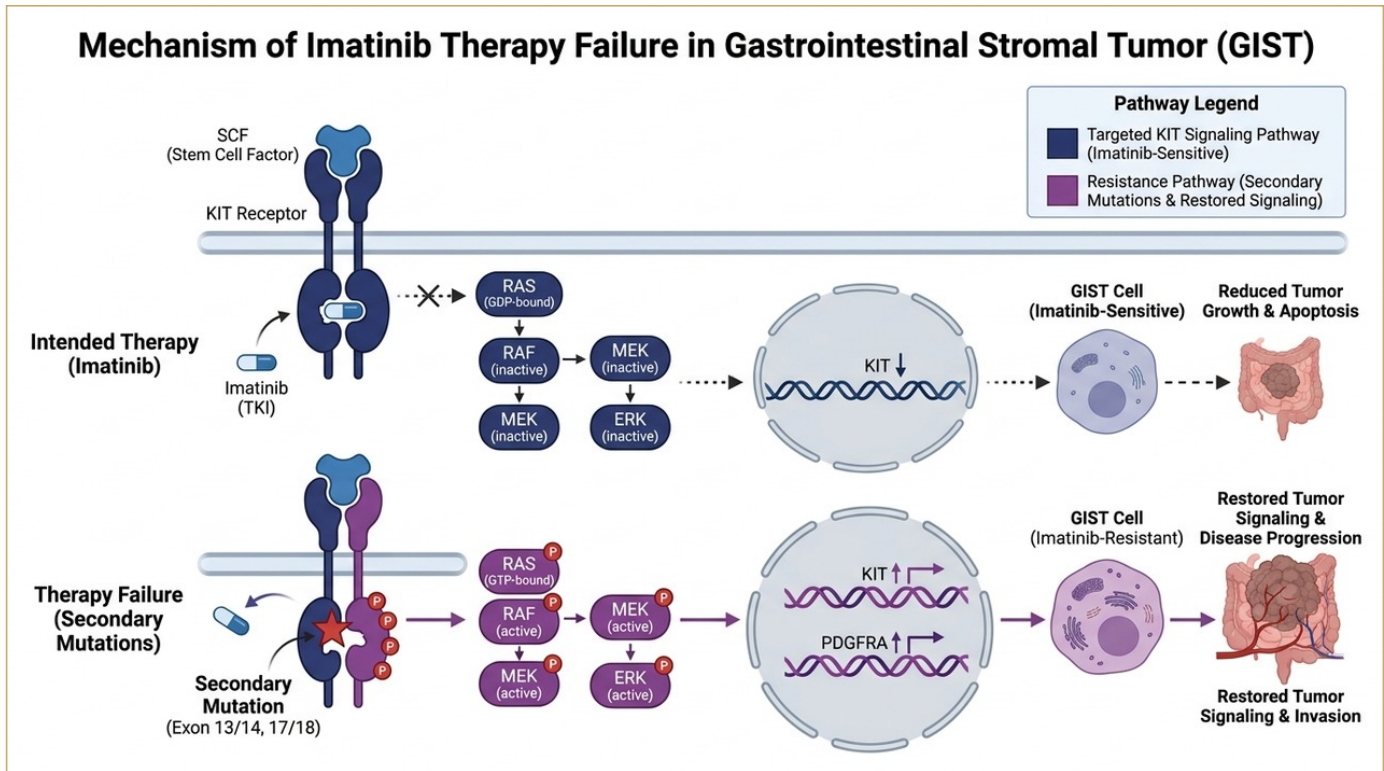
Resistance / failure mechanism:

Hedgehog signaling not a driver in colorectal carcinoma (paracrine/correlative only)

BiRAGAS pattern P6 · correlate-not-driver

Citation: Berlin J et al. Clin Cancer Res 2013;19:258-267, PMID 23172884

ClinicalTrials.gov: [NCT00636610](https://clinicaltrials.gov/ct2/show/study/NCT00636610)



Indication: Gastrointestinal stromal tumor (GIST)

Resistance / failure mechanism:

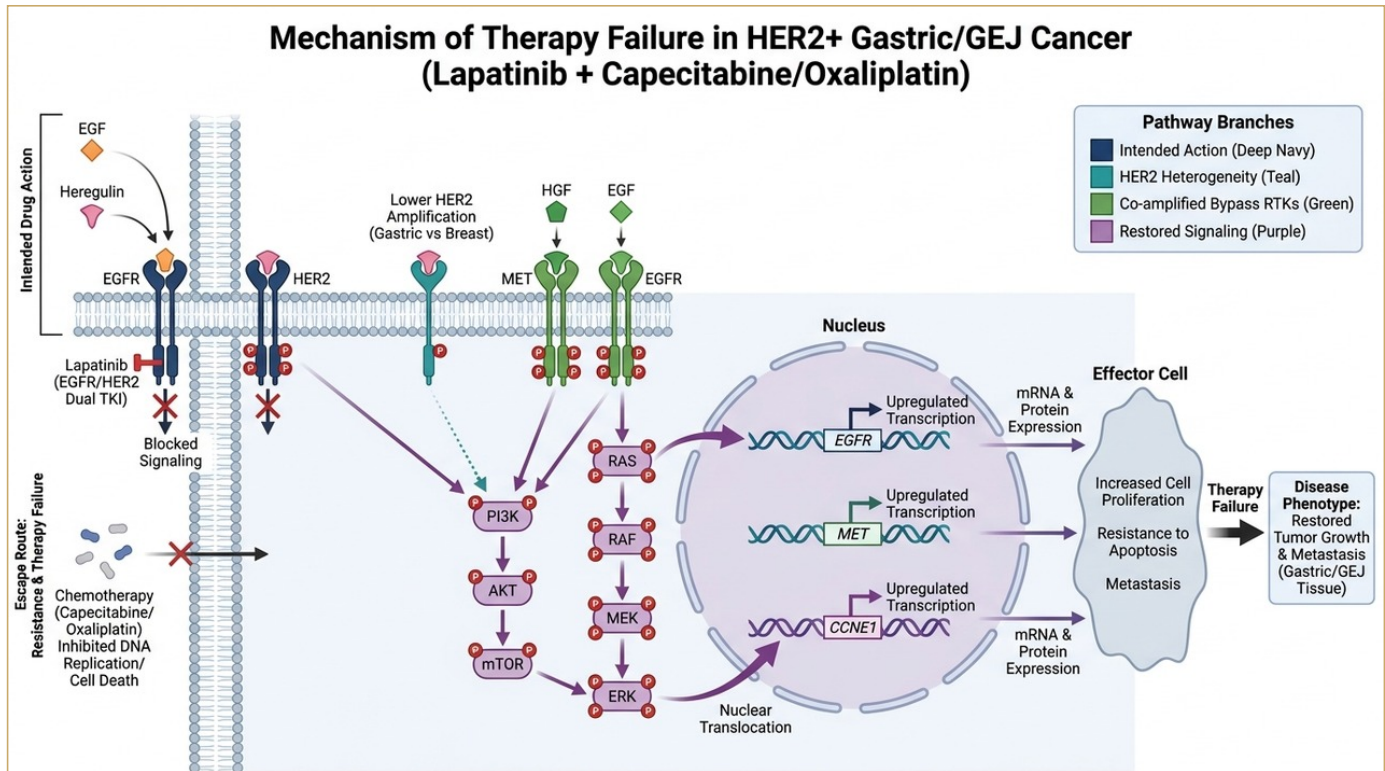
Secondary KIT mutations in ATP-binding pocket (exon 13/14) or activation loop (exon 17/18) restore kinase activity; polyclonal across lesions

BiRAGAS pattern P7 · target-mutation

Citation: Heinrich MC et al. J Clin Oncol 2006;24:4764-4774, PMID 16954519; Antonescu CR et al. Clin Cancer Res 2005

lapatinib + capecitabine/oxaliplatin

HER2+ gastric/GEJ cancer



Indication: HER2+ gastric/GEJ cancer

Resistance / failure mechanism:

HER2 heterogeneity/lower amplification in gastric vs breast; co-amplified bypass RTKs (MET, EGFR, CCNE1) blunt HER2 dependence

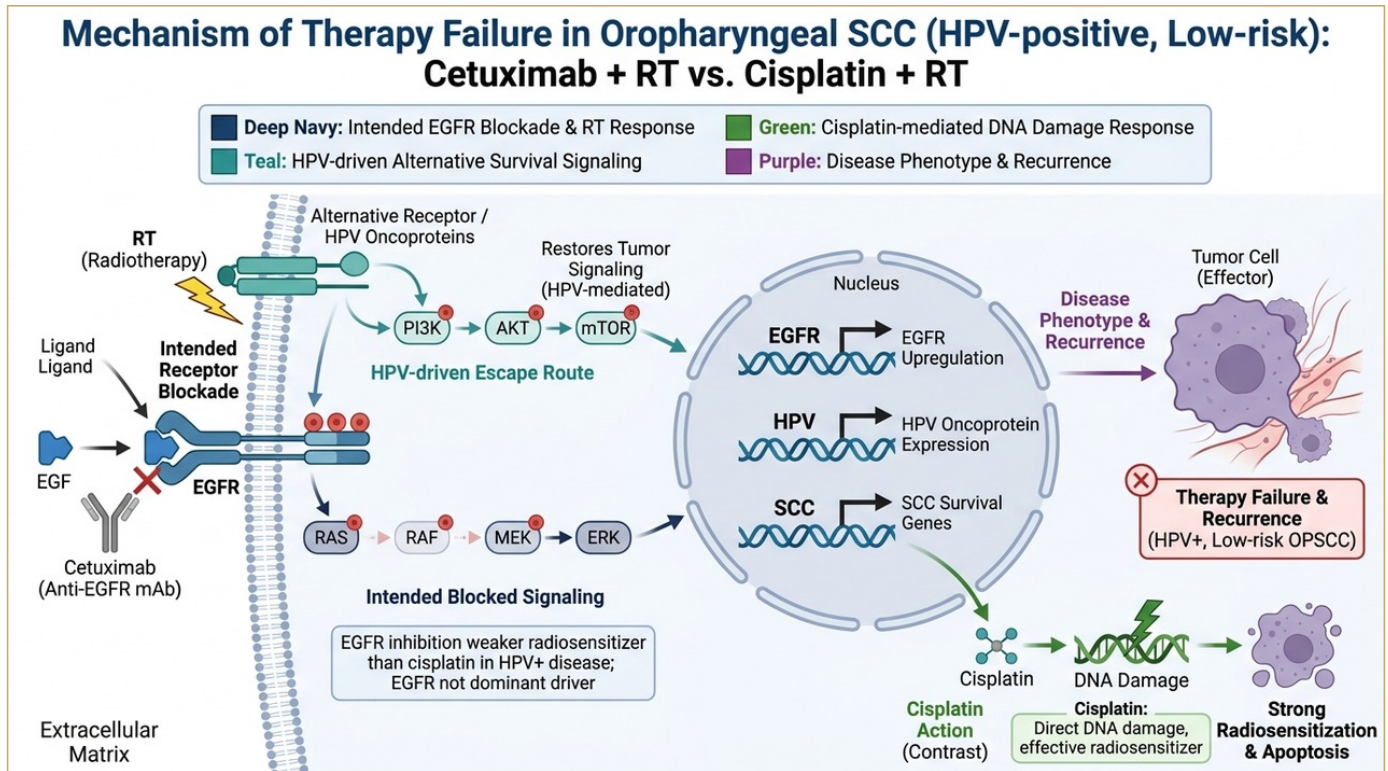
BiRAGAS pattern P3 · pathway-redundancy

Citation: Hecht JR et al. J Clin Oncol 2016;34:443-451, PMID 26628478

ClinicalTrials.gov: [NCT00680901](https://clinicaltrials.gov/ct2/show/study/NCT00680901)

Cetuximab + RT (de-escalation vs cisplatin + RT)

Oropharyngeal SCC (HPV-positive, low-risk)



Indication: Oropharyngeal SCC (HPV-positive, low-risk)

Resistance / failure mechanism:

EGFR inhibition a weaker radiosensitizer than cisplatin in HPV+ disease; EGFR not the dominant survival driver

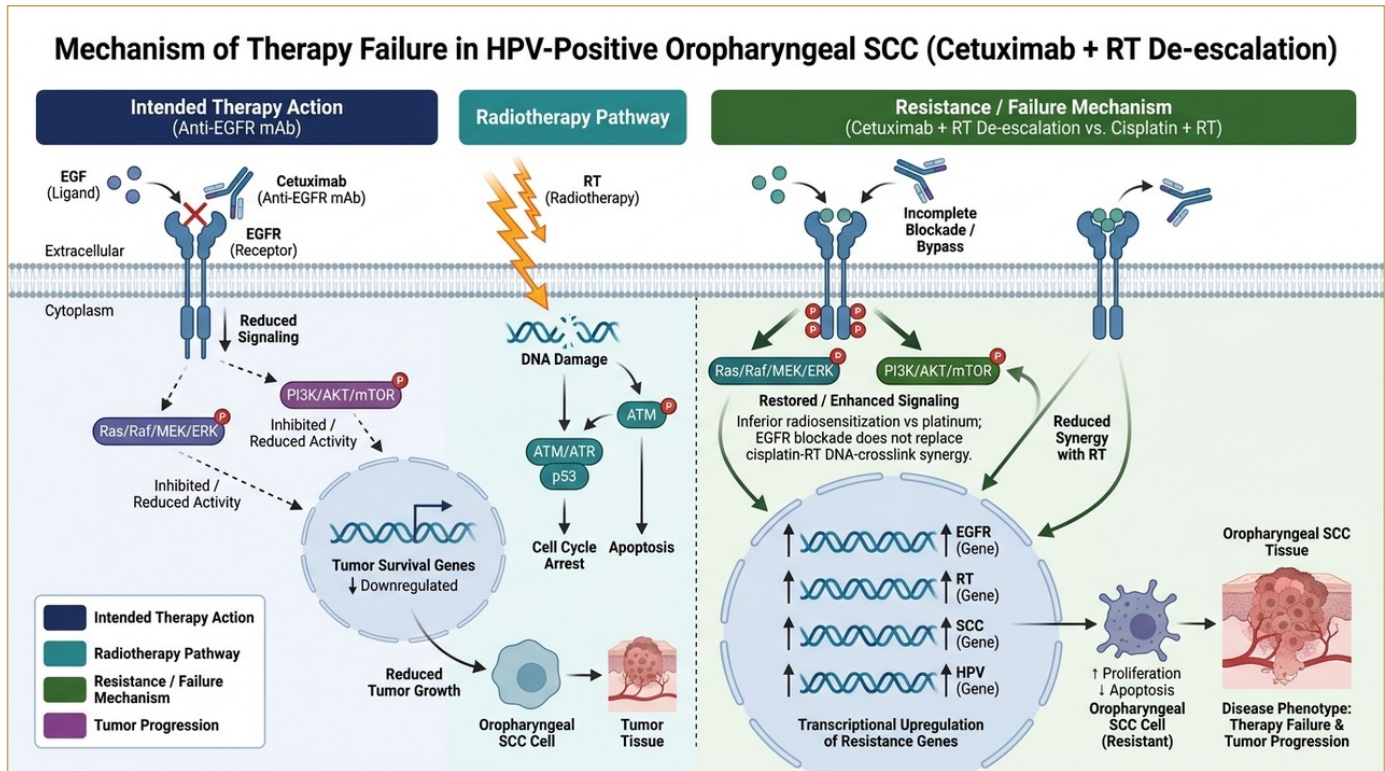
BiRAGAS pattern P6 · combination-no-rationale

Citation: Gillison ML et al. Lancet 2019;393:40-50, PMID 30449625

ClinicalTrials.gov: NCT01302834

Cetuximab + RT (de-escalation vs cisplatin + RT)

Oropharyngeal SCC (HPV-positive, low-risk)



Indication: Oropharyngeal SCC (HPV-positive, low-risk)

Resistance / failure mechanism:

Inferior radiosensitization vs platinum; EGFR blockade does not replace cisplatin-RT DNA-crosslink synergy

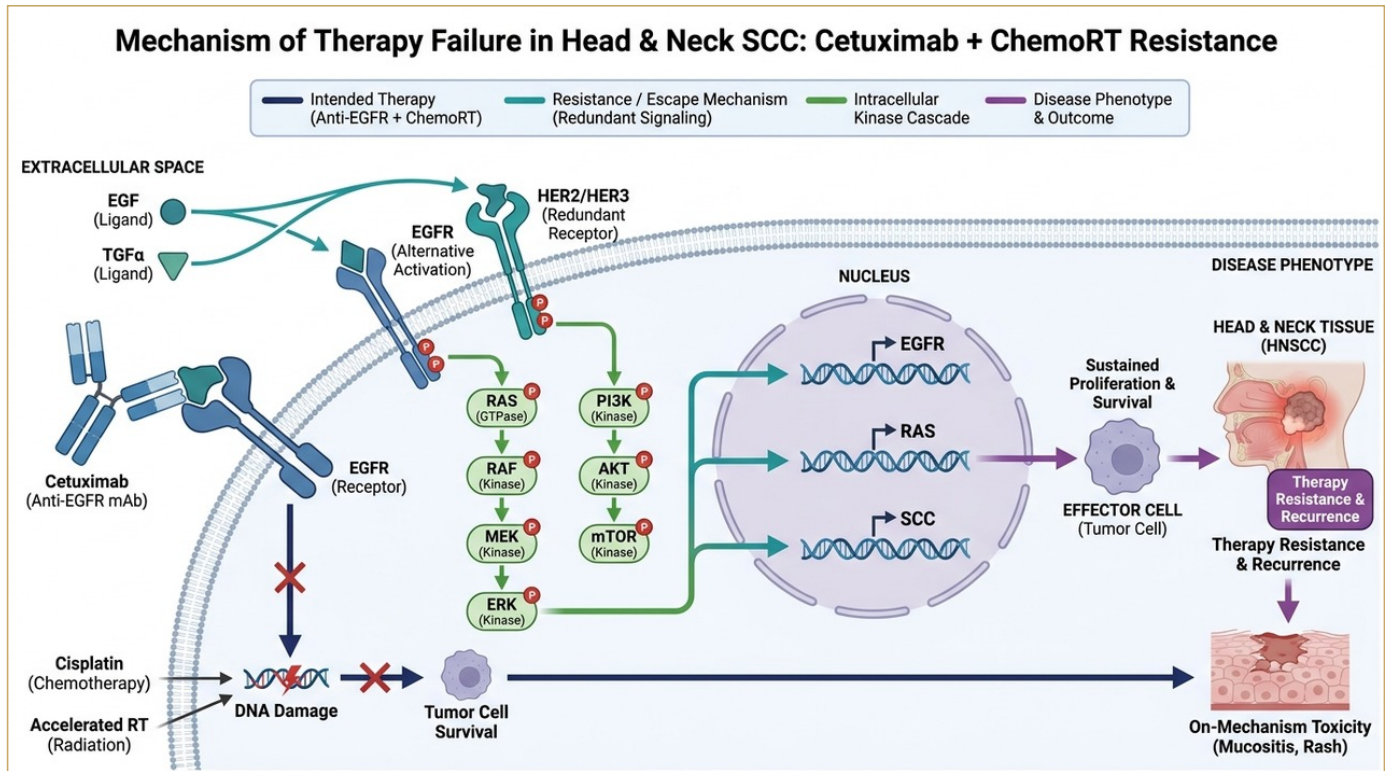
BiRAGAS pattern P6 · combination-no-rationale

Citation: Mehanna H et al. Lancet 2019;393:51-60, PMID 30449623

ClinicalTrials.gov: [NCT01874171](https://clinicaltrials.gov/ct2/show/study/NCT01874171)

Cetuximab added to cisplatin + accelerated RT

Head and neck SCC (locally advanced)



Indication: Head and neck SCC (locally advanced)

Resistance / failure mechanism:

Redundant EGFR downstream signaling (RAS/PI3K) already engaged; on-mechanism toxicity without efficacy gain

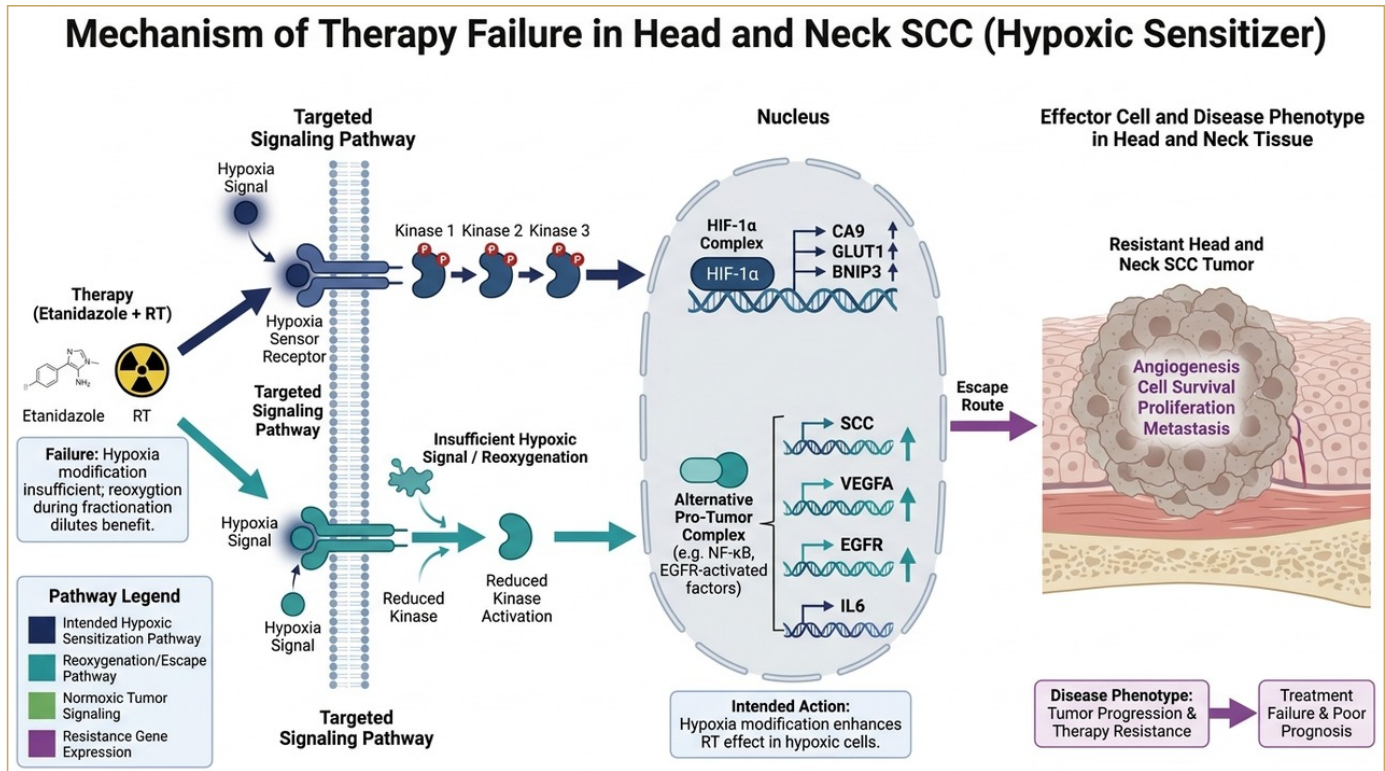
BiRAGAS pattern P2 · pathway-redundancy

Citation: Ang KK et al. J Clin Oncol 2014;32:2940-2950, PMID 25154822

ClinicalTrials.gov: [NCT00265941](https://clinicaltrials.gov/ct2/show/study/NCT00265941)

Etanidazole + RT

Head and neck SCC (hypoxic sensitizer)



Indication: Head and neck SCC (hypoxic sensitizer)

Resistance / failure mechanism:

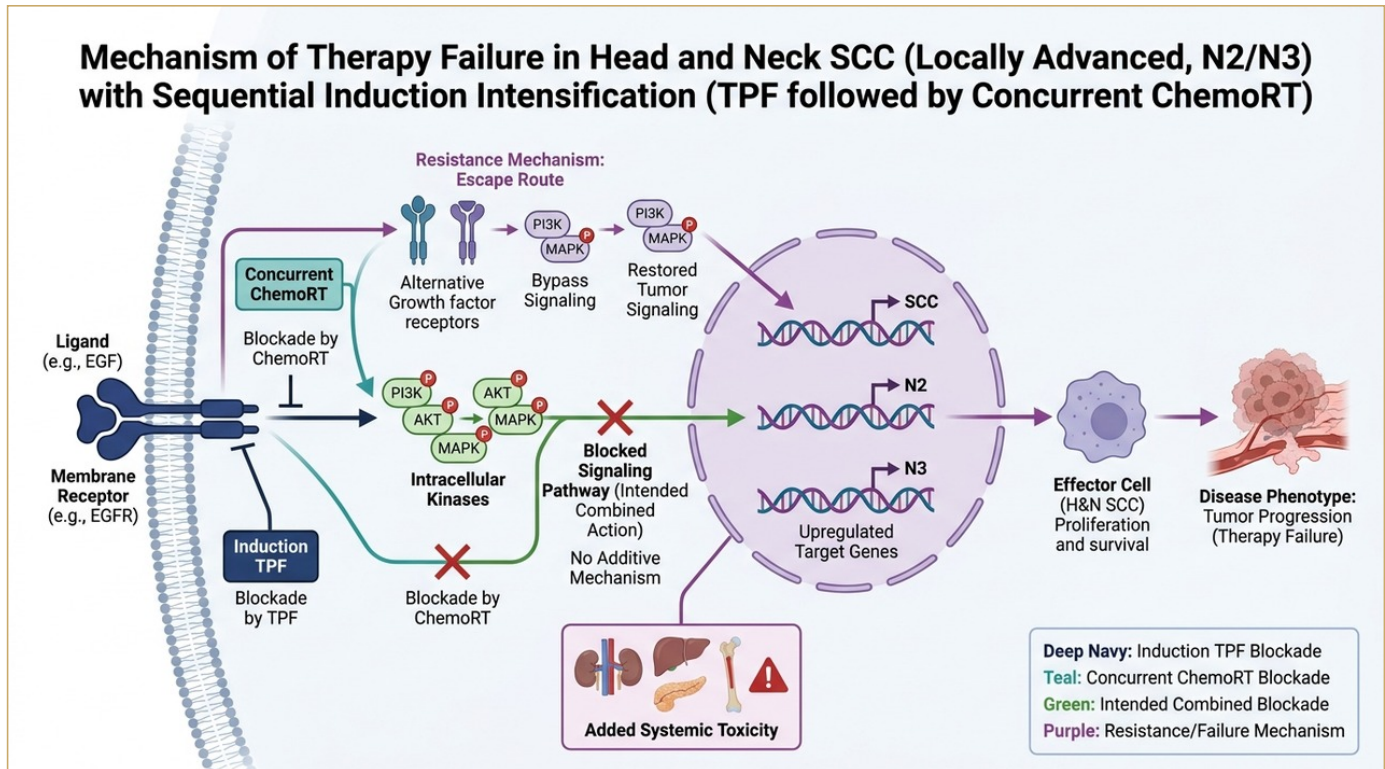
Hypoxia modification insufficient without patient selection; reoxygenation during fractionation dilutes benefit

BiRAGAS pattern P4 · TME/immune-exclusion

Citation: Lee DJ et al. Int J Radiat Oncol Biol Phys 1995;32:567-576, PMID 7790243

Induction TPF before concurrent chemoRT

Head and neck SCC (locally advanced, N2/N3)



Indication: Head and neck SCC (locally advanced, N2/N3)

Resistance / failure mechanism:

No additive mechanism over definitive chemoRT; added systemic toxicity

BiRAGAS pattern P6 · combination-no-rationale

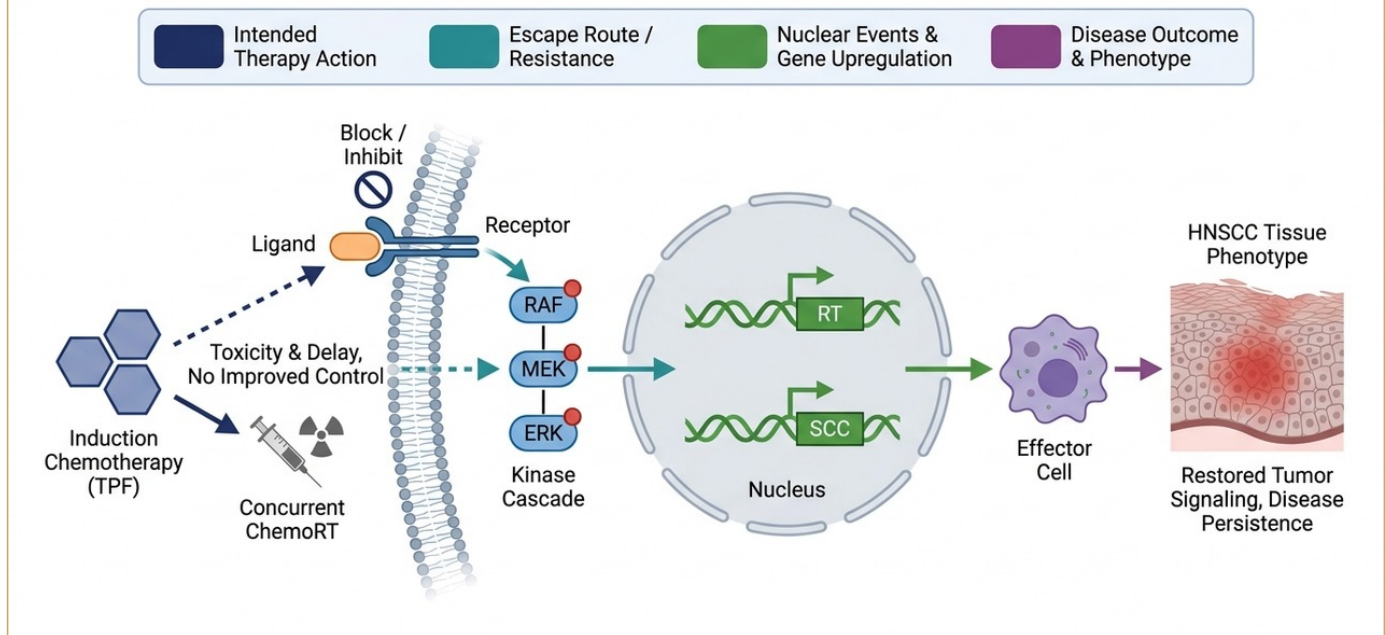
Citation: Cohen EEW et al. J Clin Oncol 2014;32:2735-2743, PMID 25049329

ClinicalTrials.gov: [NCT00117572](https://clinicaltrials.gov/ct2/show/study/NCT00117572)

Induction chemotherapy (TPF) before concurrent chemoRT

Head and neck SCC (locally advanced)

Mechanism of Therapy Failure in Locally Advanced Head and Neck SCC (HNSCC) with Sequential Intensification



Indication: Head and neck SCC (locally advanced)

Resistance / failure mechanism:

Induction intensification adds toxicity/delay without improving the RT-controlled locoregional compartment

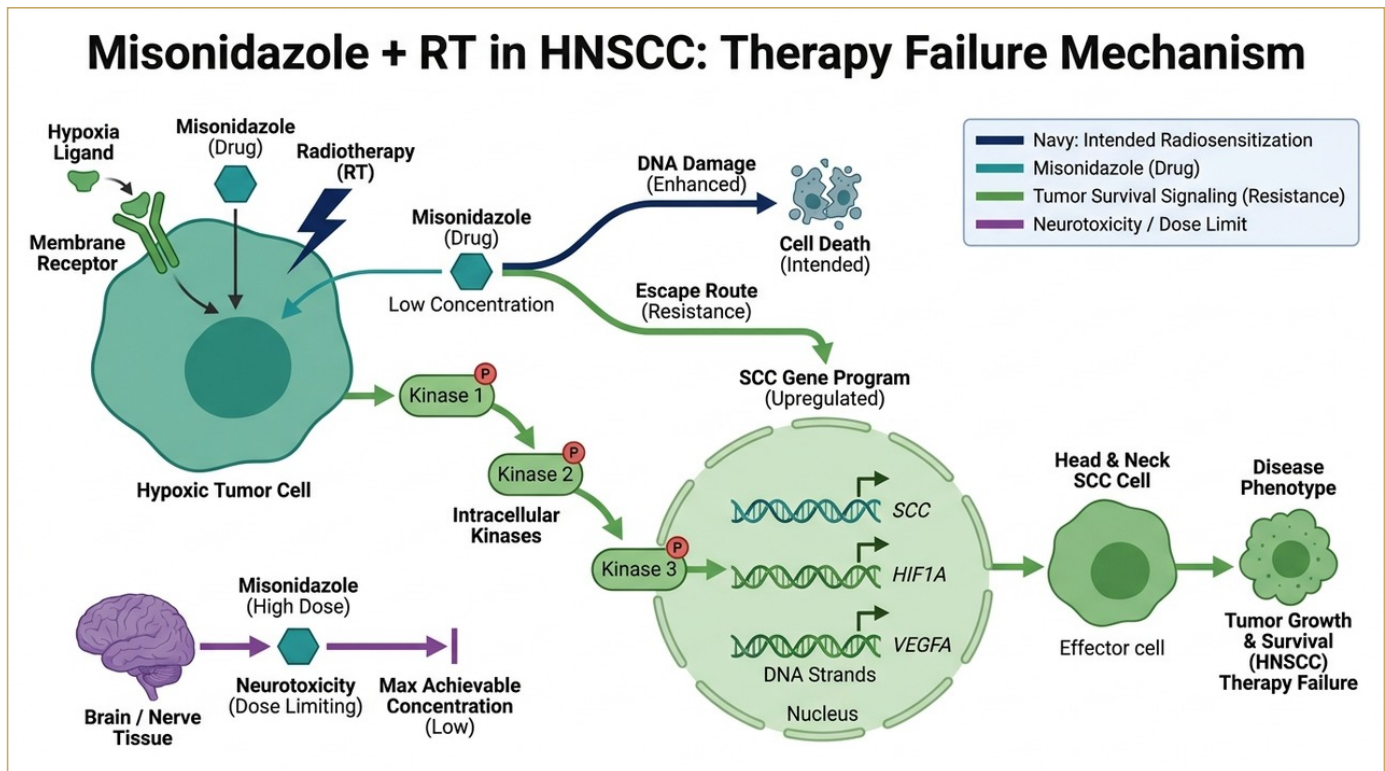
BiRAGAS pattern P6 · combination-no-rationale

Citation: Haddad R et al. Lancet Oncol 2013;14:257-264, PMID 23474112

[ClinicalTrials.gov: NCT00095875](https://clinicaltrials.gov/ct2/show/study/NCT00095875)

Misonidazole + RT

Head and neck SCC / multiple solid tumors (historical hypoxic sensitizer)



Indication: Head and neck SCC / multiple solid tumors (historical hypoxic sensitizer)

Resistance / failure mechanism:

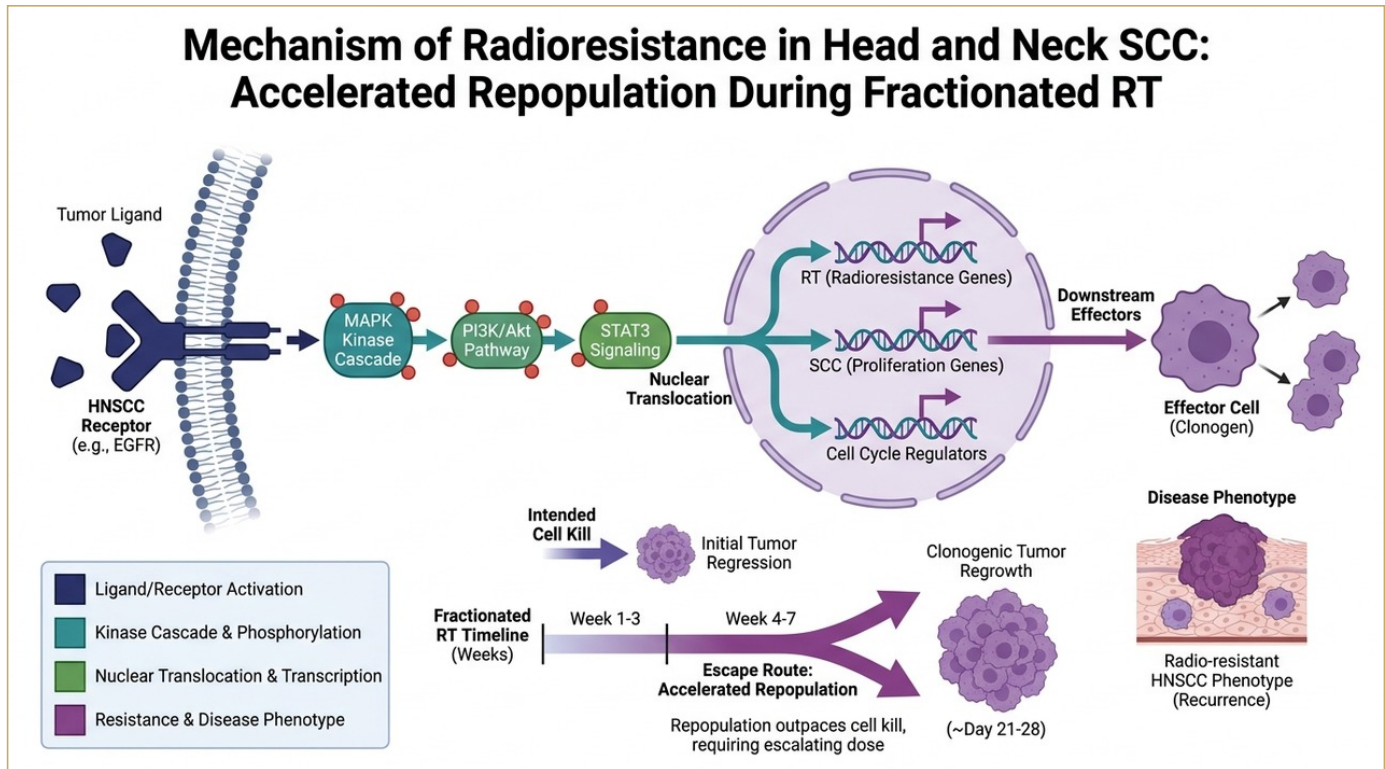
Neurotoxicity capped achievable drug concentration below radiosensitizing threshold (on-mechanism toxicity); unselected patients

BiRAGAS pattern P5 · on-mechanism-toxicity

Citation: Overgaard J. J Clin Oncol 2007;25:4066-4074 (meta-analysis), PMID 17827455

N/A, radioresistance mechanism (accelerated repopulation)

Head and neck SCC (mechanism)



Indication: Head and neck SCC (mechanism)

Resistance / failure mechanism:

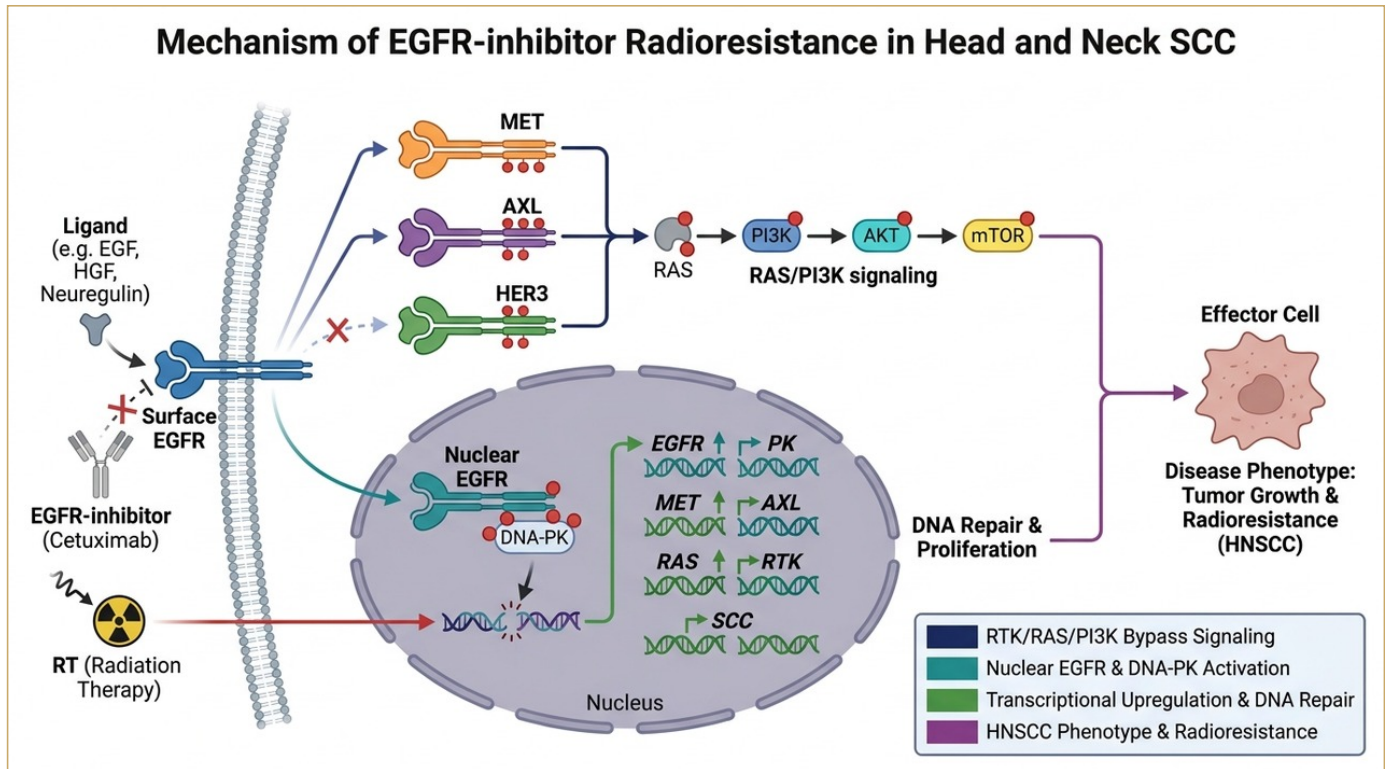
Repopulation of clonogenic tumor cells during protracted fractionation outpaces cell kill (temporal escape)

BiRAGAS pattern P3 · population-dilution

Citation: Withers HR, Taylor JM, Maciejewski B. Acta Oncol 1988;27:131-146, PMID 3390344

N/A, resistance mechanism to cetuximab/EGFR-inhibitor + RT

Head and neck SCC (EGFR-inhibitor radioresistance mechanism)



Indication: Head and neck SCC (EGFR-inhibitor radioresistance mechanism)

Resistance / failure mechanism:

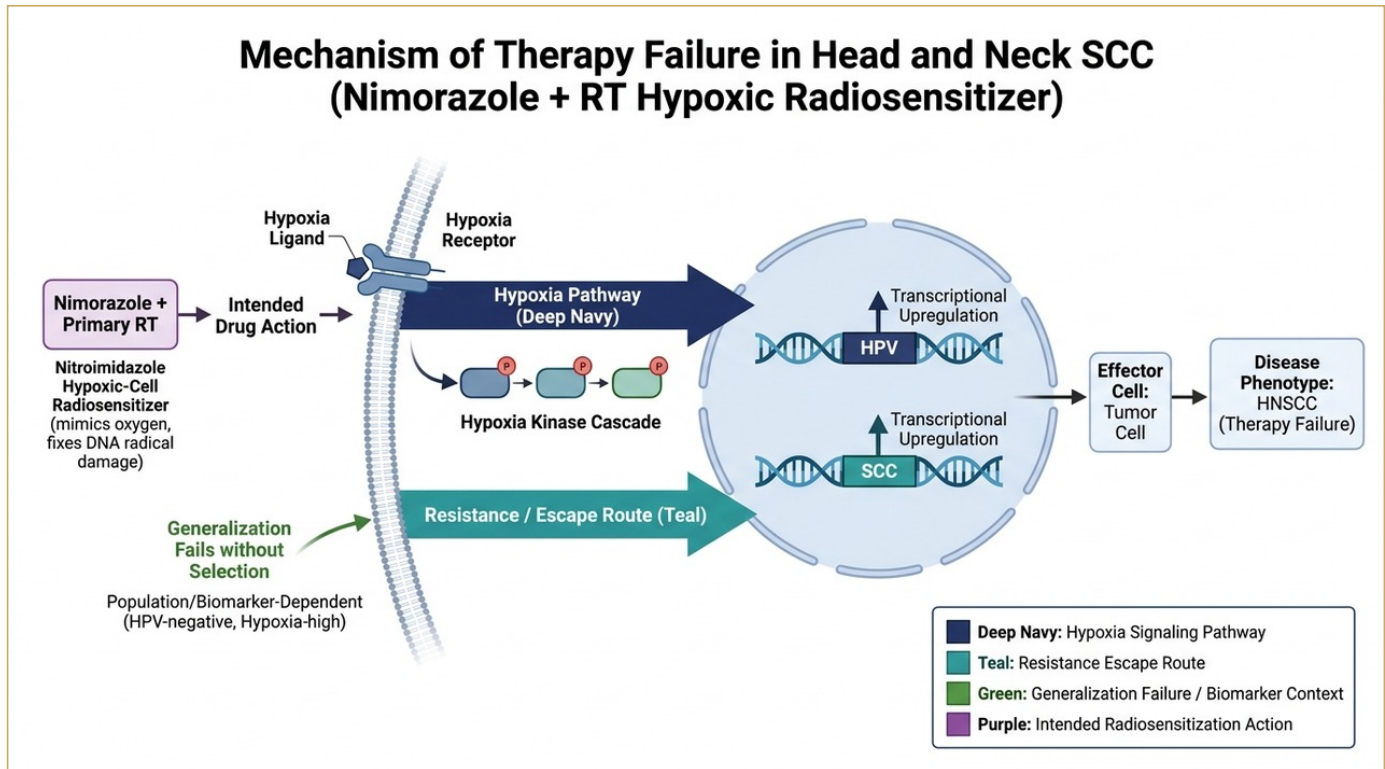
Nuclear EGFR translocation activates DNA-PK repair; parallel RTK (MET, AXL, HER3) and RAS/PI3K bypass sustain repair despite surface-EGFR blockade

BiRAGAS pattern P2 · bypass/parallel-pathway

Citation: Bonner JA et al. N Engl J Med 2006;354:567-578; Rodemann HP mechanism reviews, PMID 16467544

Nimorazole + primary RT (hypoxic radiosensitizer), context entry

Head and neck SCC (hypoxic modification, regionally positive context)



Indication: Head and neck SCC (hypoxic modification, regionally positive context)

Resistance / failure mechanism:

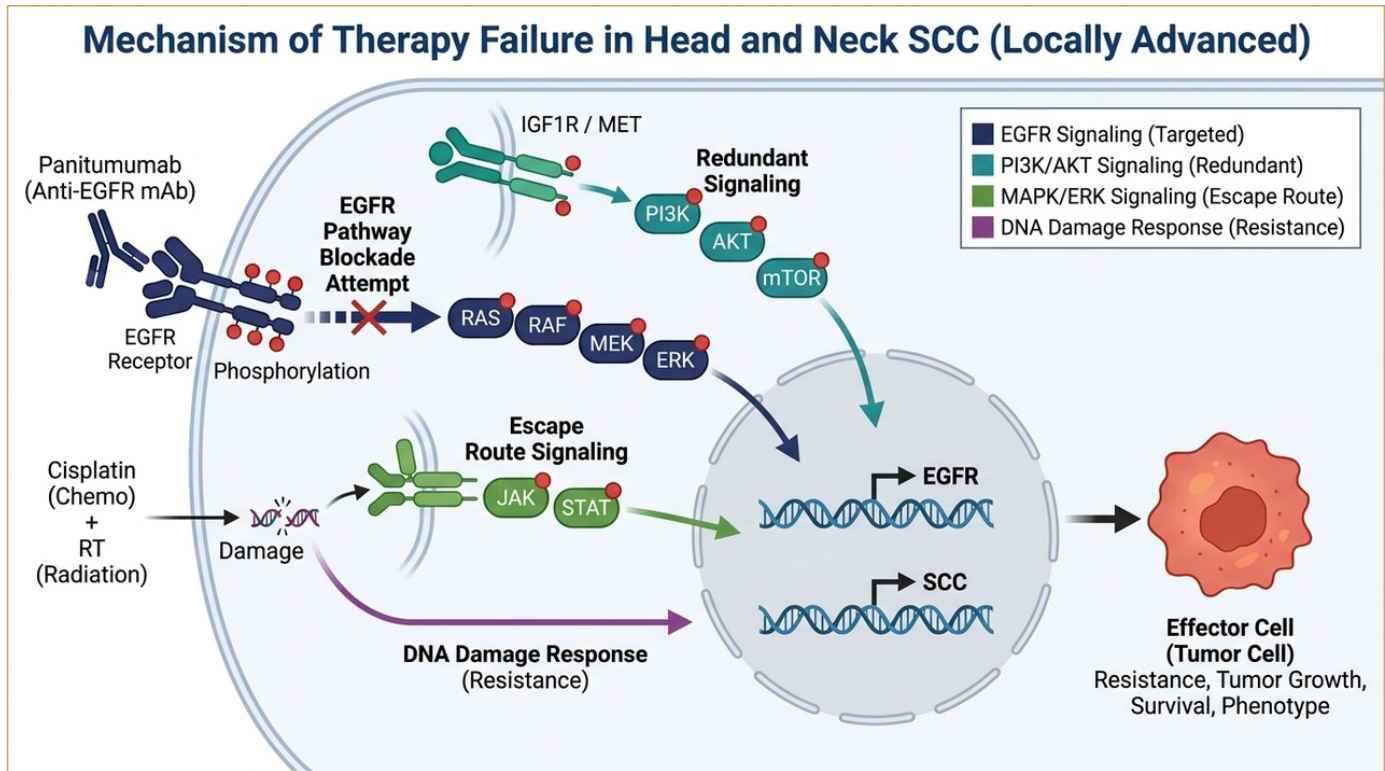
Hypoxic radiosensitization benefit is population/biomarker-dependent (HPV-negative, hypoxia-high); generalization fails without hypoxia-signature selection

BiRAGAS pattern P1 · correlate-not-driver

Citation: Overgaard J et al. Radiother Oncol 1998;46:135-146, PMID 9510041

Panitumumab + chemoRT / + RT

Head and neck SCC (locally advanced)



Indication: Head and neck SCC (locally advanced)

Resistance / failure mechanism:

EGFR blockade cannot replace platinum radiosensitization; redundant downstream signaling

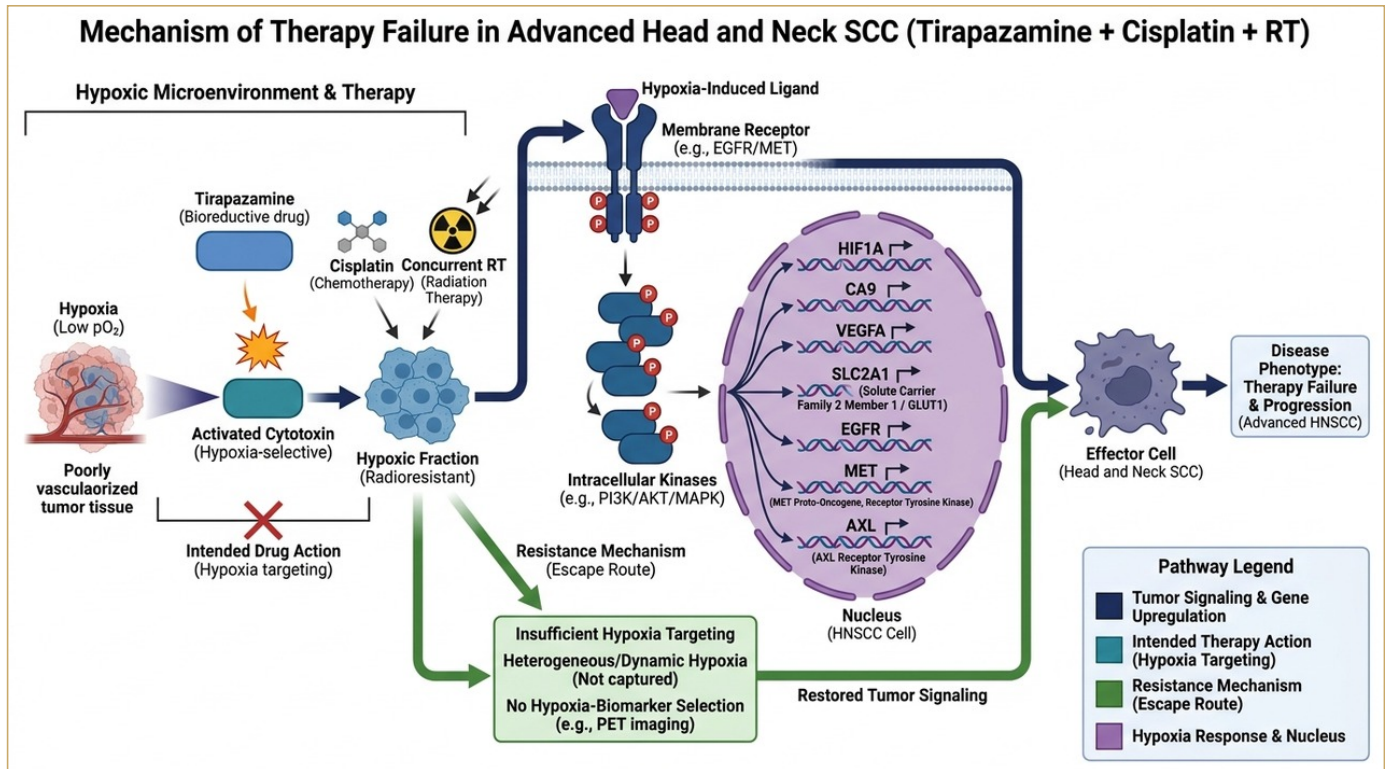
BiRAGAS pattern P6 · combination-no-rationale

Citation: Mesia R et al. Lancet Oncol 2015;16:208-220, PMID 25596660

ClinicalTrials.gov: [NCT00500760](https://clinicaltrials.gov/ct2/show/study/NCT00500760)

Tirapazamine + cisplatin + concurrent RT (vs cisplatin-RT)

Head and neck SCC (advanced)



Indication: Head and neck SCC (advanced)

Resistance / failure mechanism:

Hypoxia targeting insufficient; heterogeneous/dynamic hypoxia not captured, no hypoxia-biomarker selection

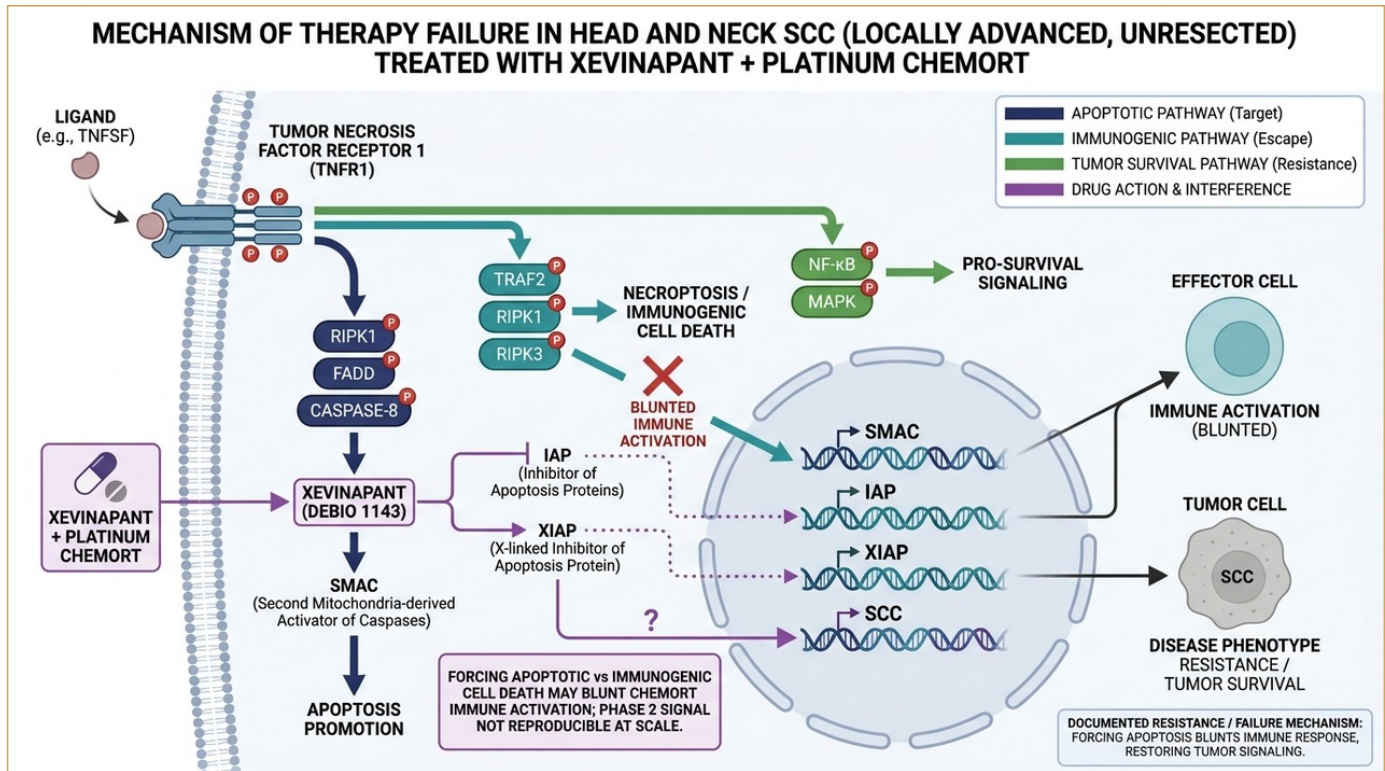
BiRAGAS pattern P4 · TME/immune-exclusion

Citation: Rischin D et al. J Clin Oncol 2010;28:2989-2995, PMID 20479425

ClinicalTrials.gov: [NCT00094081](https://clinicaltrials.gov/ct2/show/study/NCT00094081)

Xevinapant (Debio 1143) + platinum chemoRT

Head and neck SCC (locally advanced, unresected)



Indication: Head and neck SCC (locally advanced, unresected)

Resistance / failure mechanism:

Forcing apoptotic vs immunogenic cell death may blunt chemoRT immune activation; Phase 2 signal not reproducible at scale

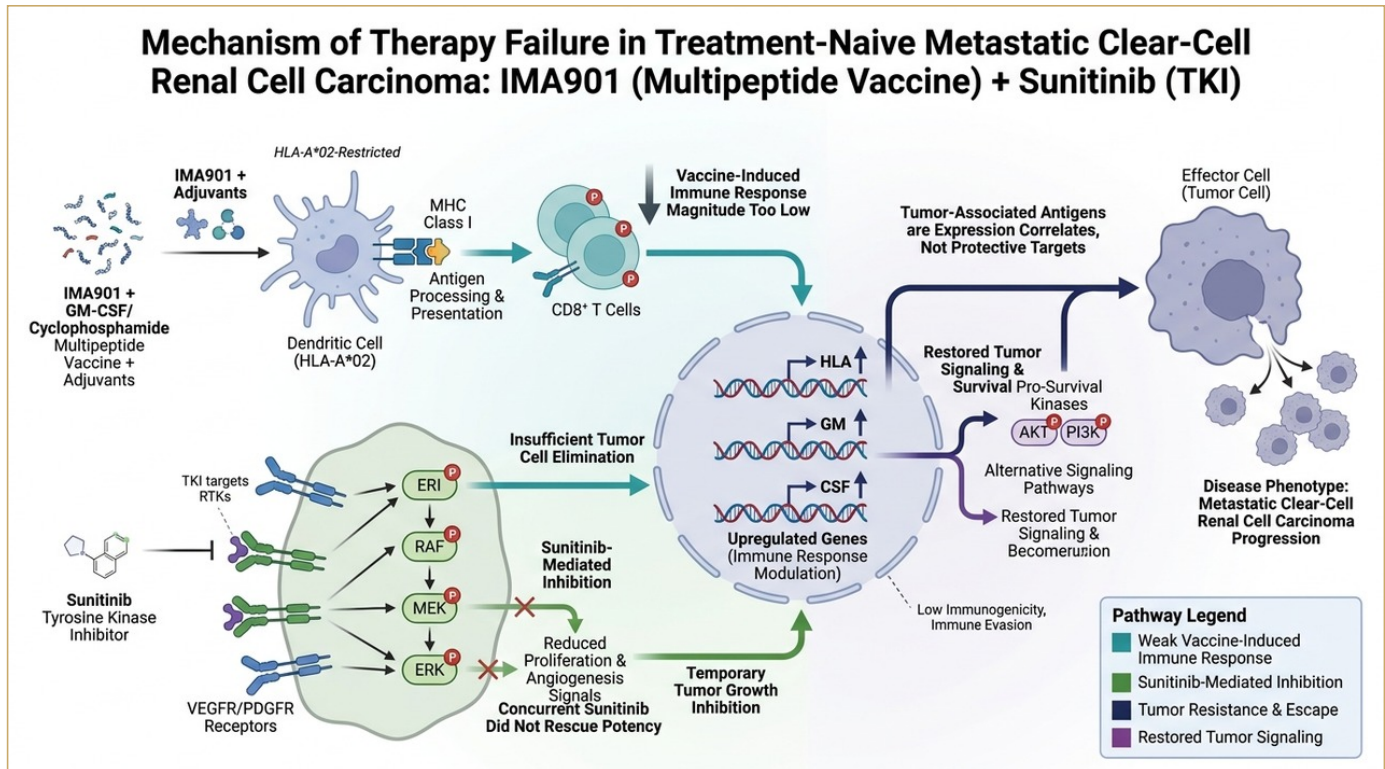
BiRAGAS pattern P6 · DNA-repair/apoptosis-evasion

Citation: Bourhis J et al. J Clin Oncol 2025; ClinicalTrials.gov NCT04459715

ClinicalTrials.gov: NCT04459715

IMA901 (multipeptide tumor-associated-antigen vaccine) + sunitinib

Treatment-naïve metastatic clear-cell renal cell carcinoma



Indication: Treatment-naïve metastatic clear-cell renal cell carcinoma

Resistance / failure mechanism:

Vaccine-induced immune-response magnitude was too low to matter; tumor-associated (self) antigens were correlates of expression, not protective targets, and concurrent sunitinib did not rescue potency.

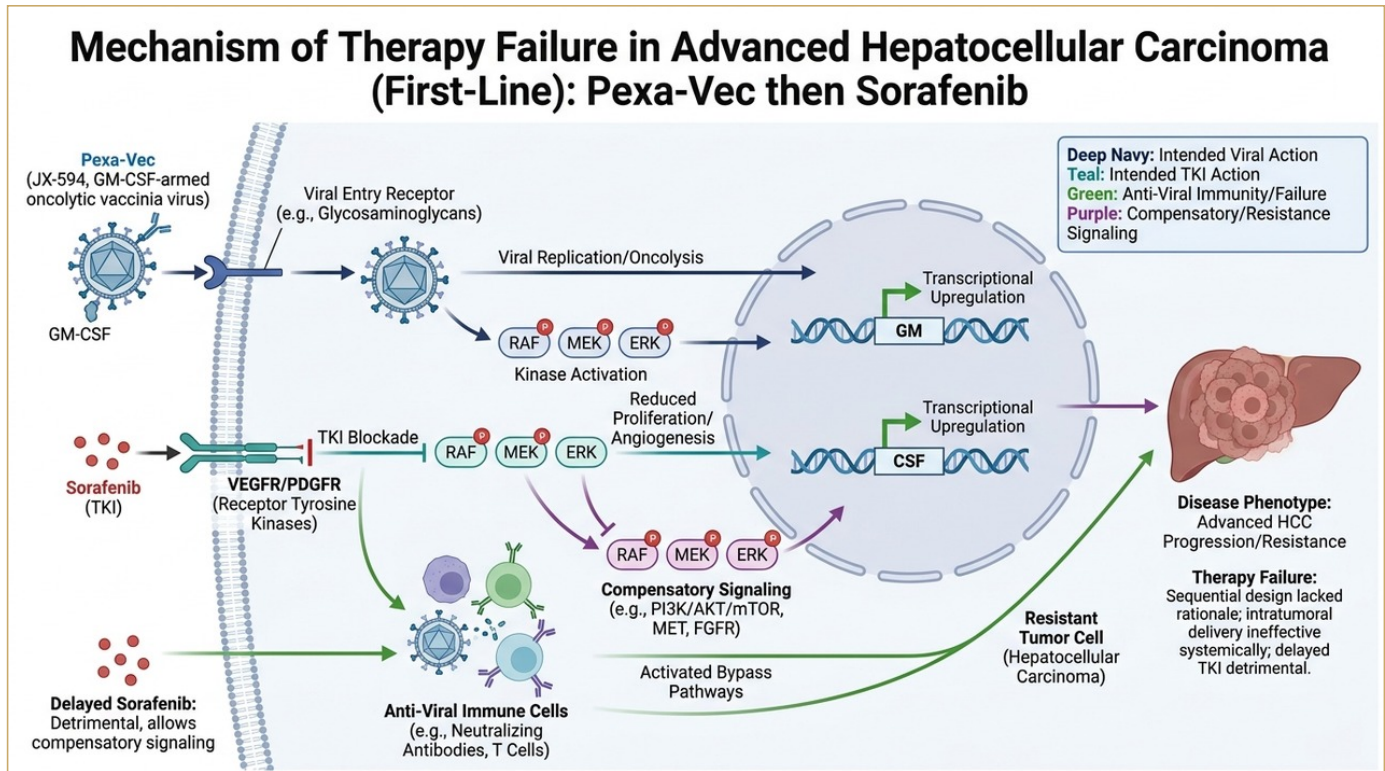
BiRAGAS pattern P3 · correlate-not-driver

Citation: Rini BI et al. Lancet Oncol 2016;17:1599-1611. PMID 27720136

ClinicalTrials.gov: [NCT01265901](https://clinicaltrials.gov/ct2/show/study/NCT01265901)

Pexa-Vec (pexastimogene devacirepvec / JX-594) then sorafenib

Advanced hepatocellular carcinoma (first-line)



Indication: Advanced hepatocellular carcinoma (first-line)

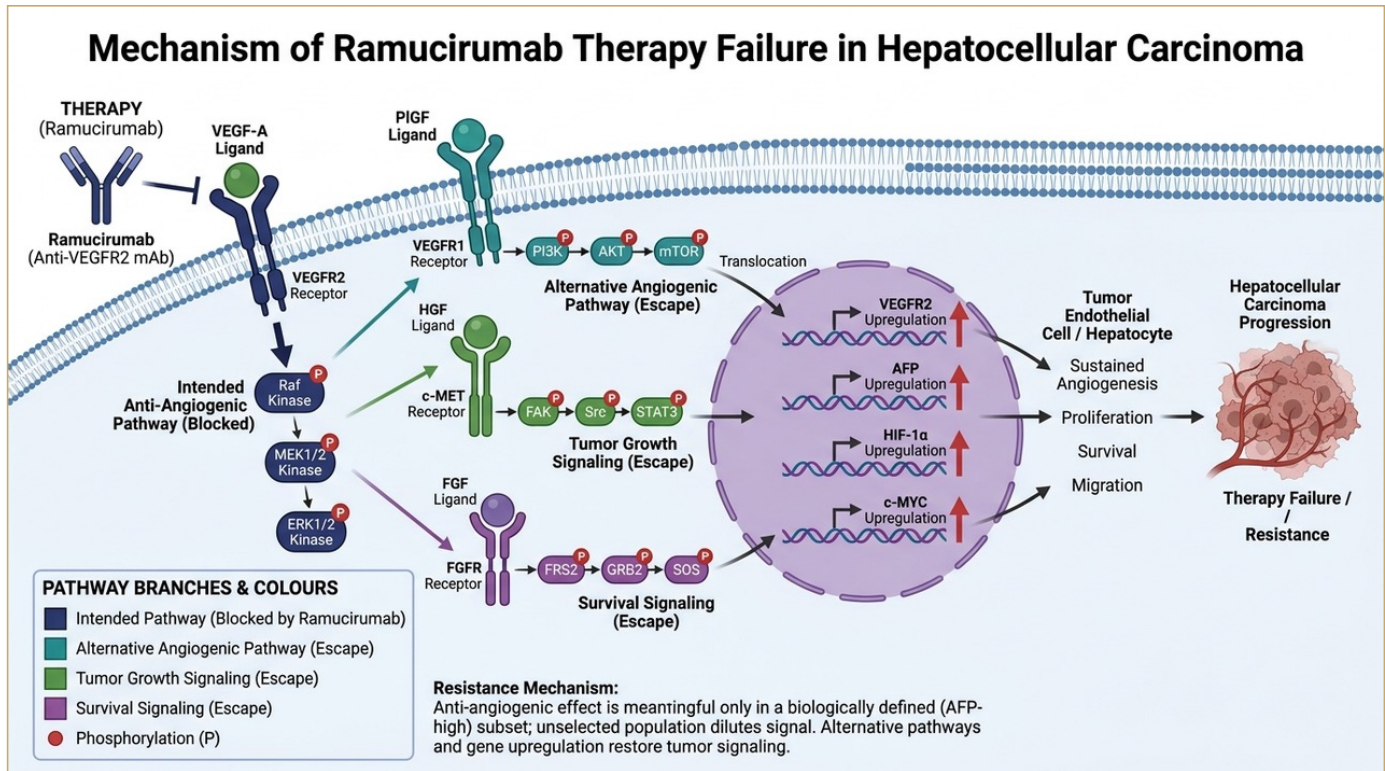
Resistance / failure mechanism:

Sequential oncolytic-virus-then-TKI design lacked rationale; intratumoral virus delivery/anti-viral immunity did not translate to systemic tumor control, and delaying effective sorafenib was detrimental.

BiRAGAS pattern P6 · combination-no-rationale

Citation: Abou-Alfa GK et al. Liver Cancer 2024;13:256-264. PMID 38756145

ClinicalTrials.gov: [NCT02562755](https://clinicaltrials.gov/ct2/show/study/NCT02562755)



Indication: Hepatocellular carcinoma

Resistance / failure mechanism:

Anti-angiogenic effect meaningful only in a biologically defined (AFP-high) subset, unselected population dilutes signal

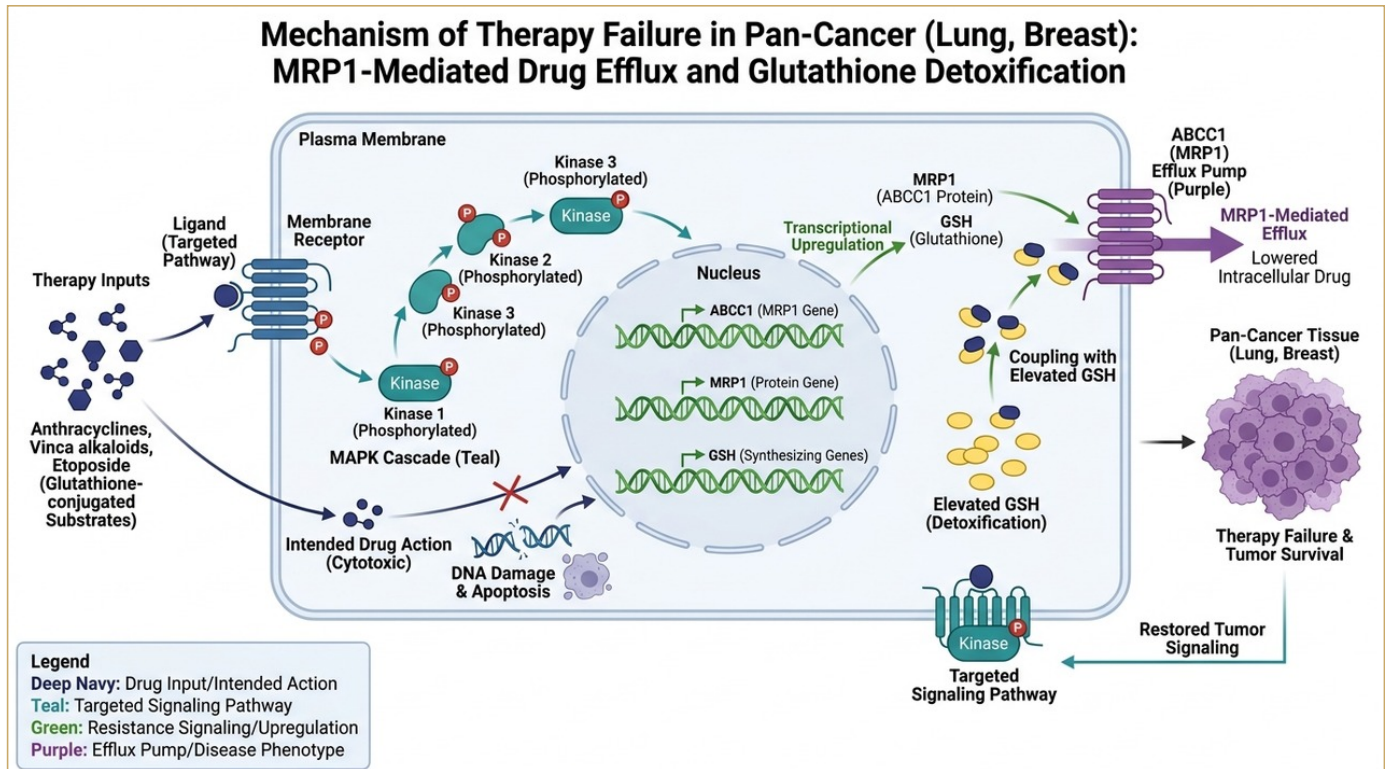
BiRAGAS pattern P3 · population-dilution

Citation: Zhu AX et al. Lancet Oncol 2015;16:859-870, PMID 25795410

ClinicalTrials.gov: [NCT01140347](https://clinicaltrials.gov/ct2/show/study/NCT01140347)

Anthracyclines, vinca alkaloids, etoposide (glutathione-conjugated substrates)

Pan-cancer (lung, breast)



Indication: Pan-cancer (lung, breast)

Resistance / failure mechanism:

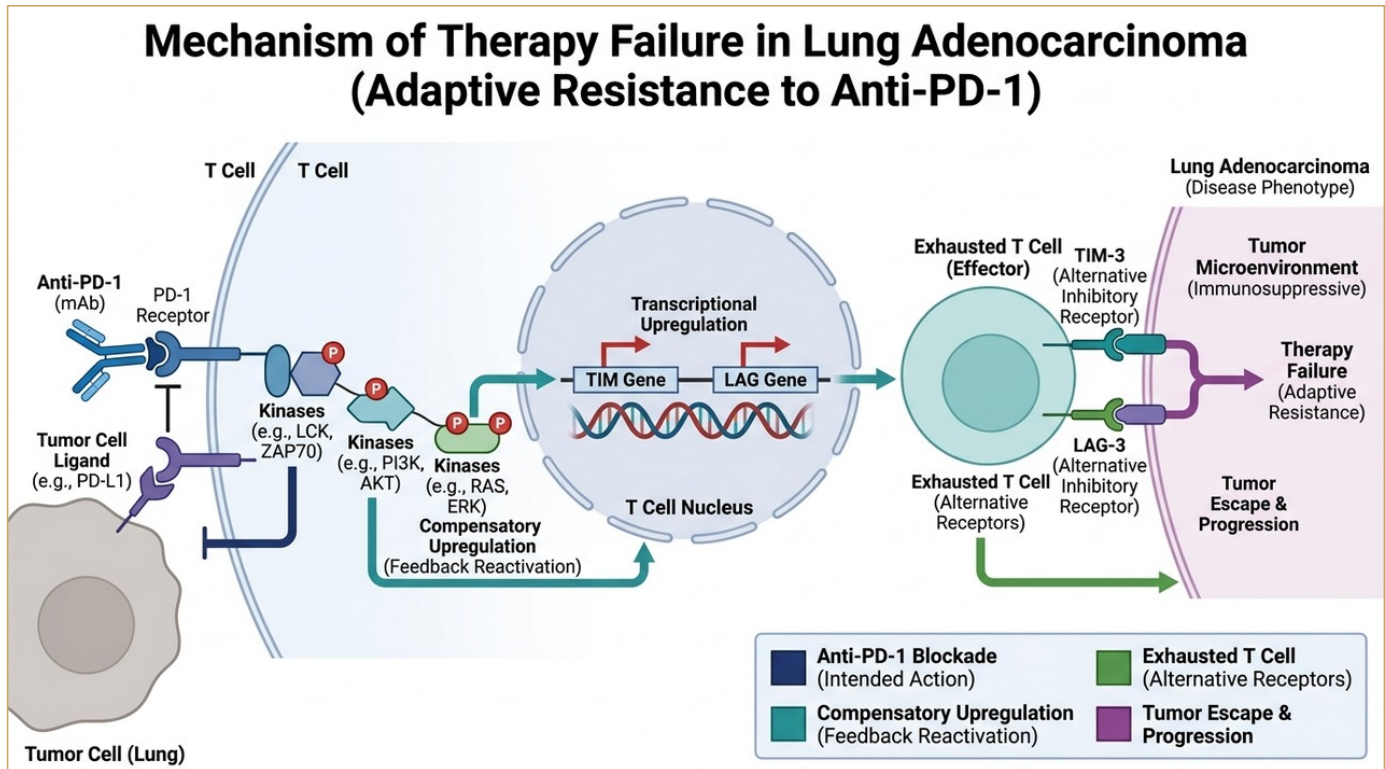
MRP1-mediated efflux of glutathione conjugates lowers intracellular drug; couples with elevated GSH detoxification

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Cole SPC. Annu Rev Pharmacol Toxicol 2014;54:95-117. PMID 24050699

Anti-PD-1

Lung adenocarcinoma (adaptive resistance to anti-PD-1)



Indication: Lung adenocarcinoma (adaptive resistance to anti-PD-1)

Resistance / failure mechanism:

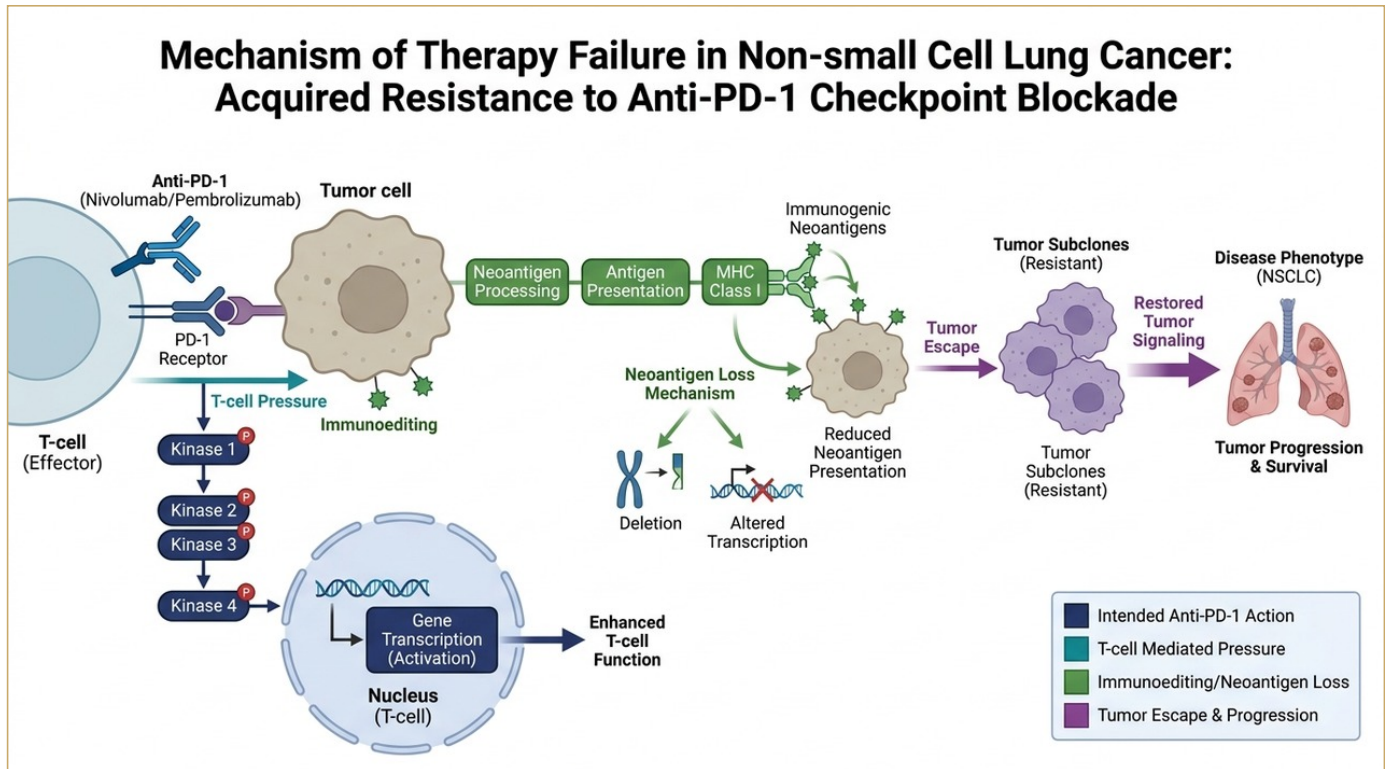
Feedback reactivation of immunosuppression: compensatory upregulation of alternative inhibitory receptors (TIM-3, later LAG-3) on exhausted T cells re-establishes suppression after PD-1 blockade.

BiRAGAS pattern P2 · feedback-reactivation

Citation: Koyama S et al. Nat Commun 2016;7:10501. PMID 26883990

Anti-PD-1 (nivolumab/pembrolizumab)

Non-small cell lung cancer (acquired resistance to anti-PD-1)



Indication: Non-small cell lung cancer (acquired resistance to anti-PD-1)

Resistance / failure mechanism:

Immunoediting: T-cell pressure selects for outgrowth of tumor subclones that have lost immunogenic neoantigens (via deletion or altered transcription), collapsing the target repertoire.

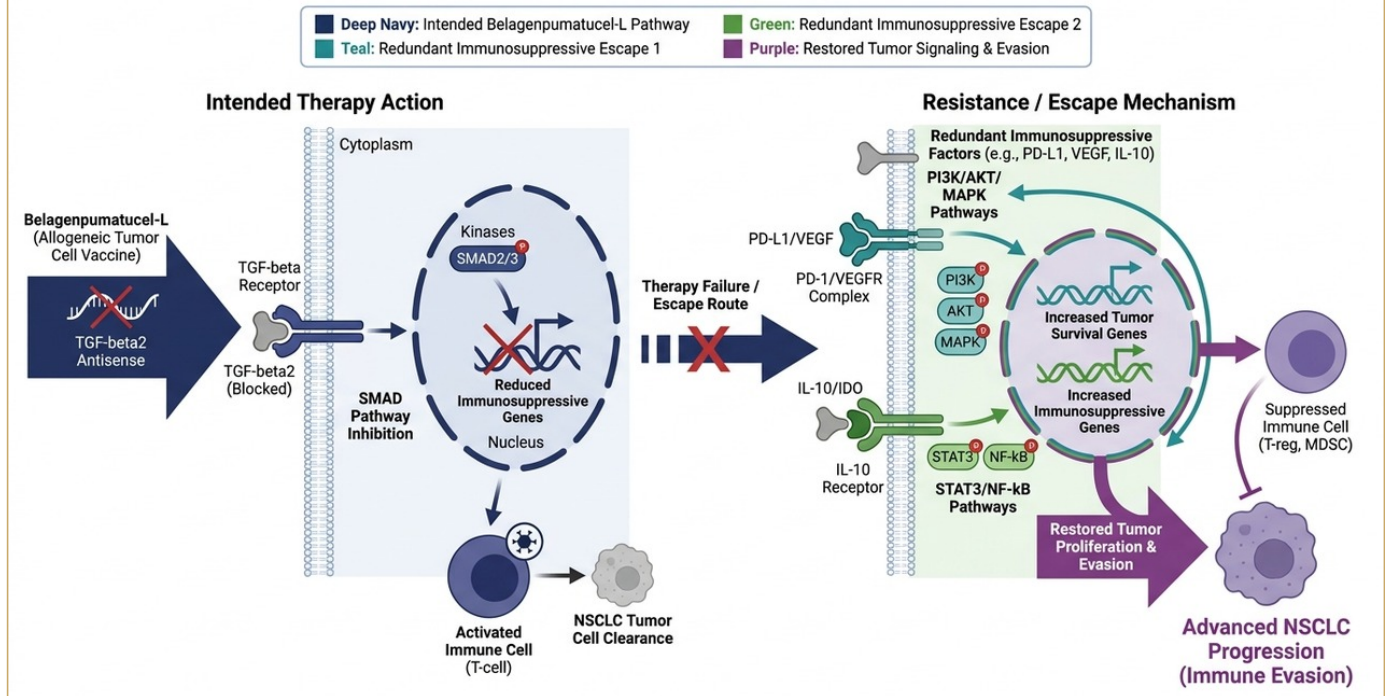
BiRAGAS pattern P2 · antigen-escape

Citation: Anagnostou V et al. Cancer Discov 2017;7:264-276. PMID 28031159

Belagenpumatucel-L (Lucanix, TGF-beta2-antisense allogeneic tumor cell vac

Advanced non-small cell lung cancer (maintenance after front-line chemo)

Mechanism of Belagenpumatucel-L Therapy Failure in Advanced NSCLC



Indication: Advanced non-small cell lung cancer (maintenance after front-line chemo)

Resistance / failure mechanism:

Whole-cell vaccine failed to overcome NSCLC immune evasion; TGF-beta2 knockdown alone insufficient against redundant immunosuppressive pathways.

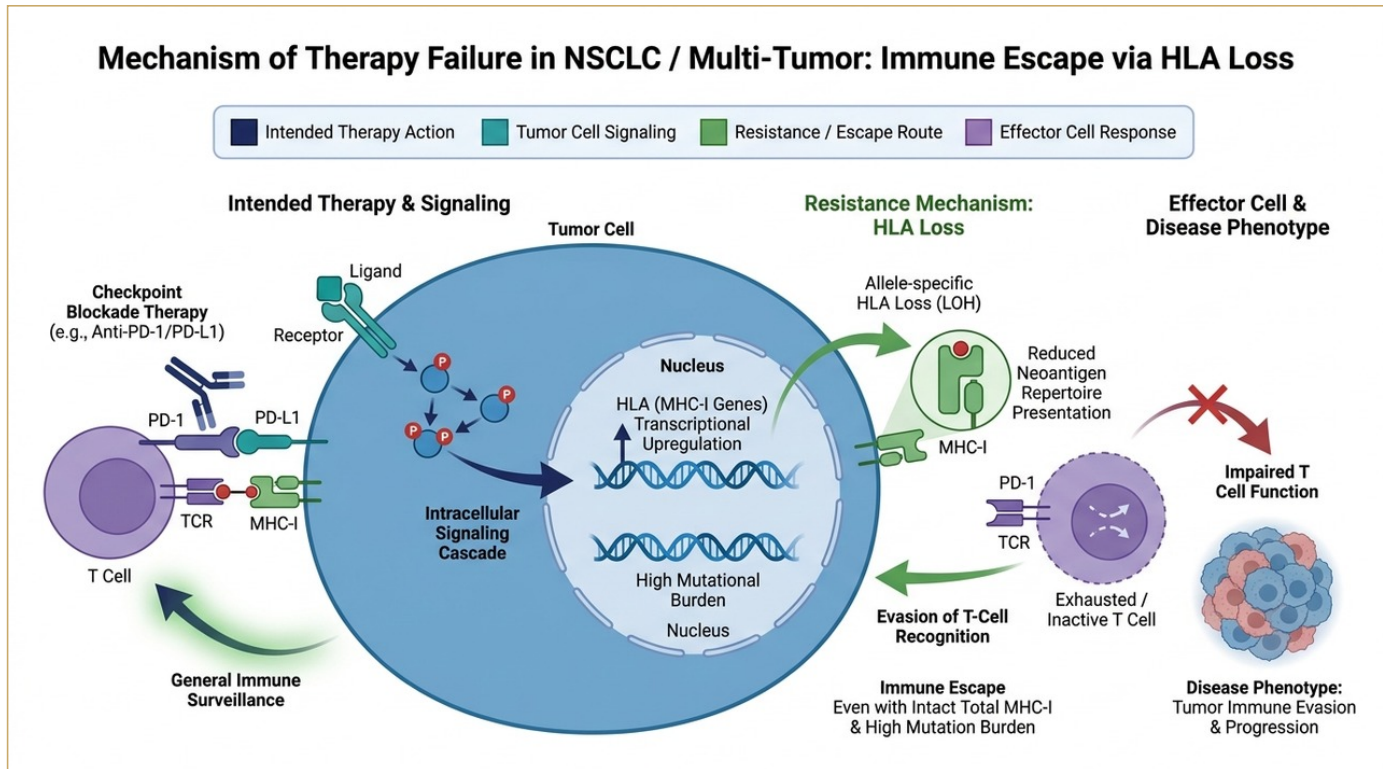
BiRAGAS pattern P3 · correlate-not-driver

Citation: Giaccone G et al. Eur J Cancer 2015;51:2321-2329. PMID 26283035

ClinicalTrials.gov: [NCT00676507](https://clinicaltrials.gov/ct2/show/study/NCT00676507)

Checkpoint blockade / general immune surveillance

Non-small cell lung cancer / multi-tumor (immune escape via HLA loss)



Indication: Non-small cell lung cancer / multi-tumor (immune escape via HLA loss)

Resistance / failure mechanism:

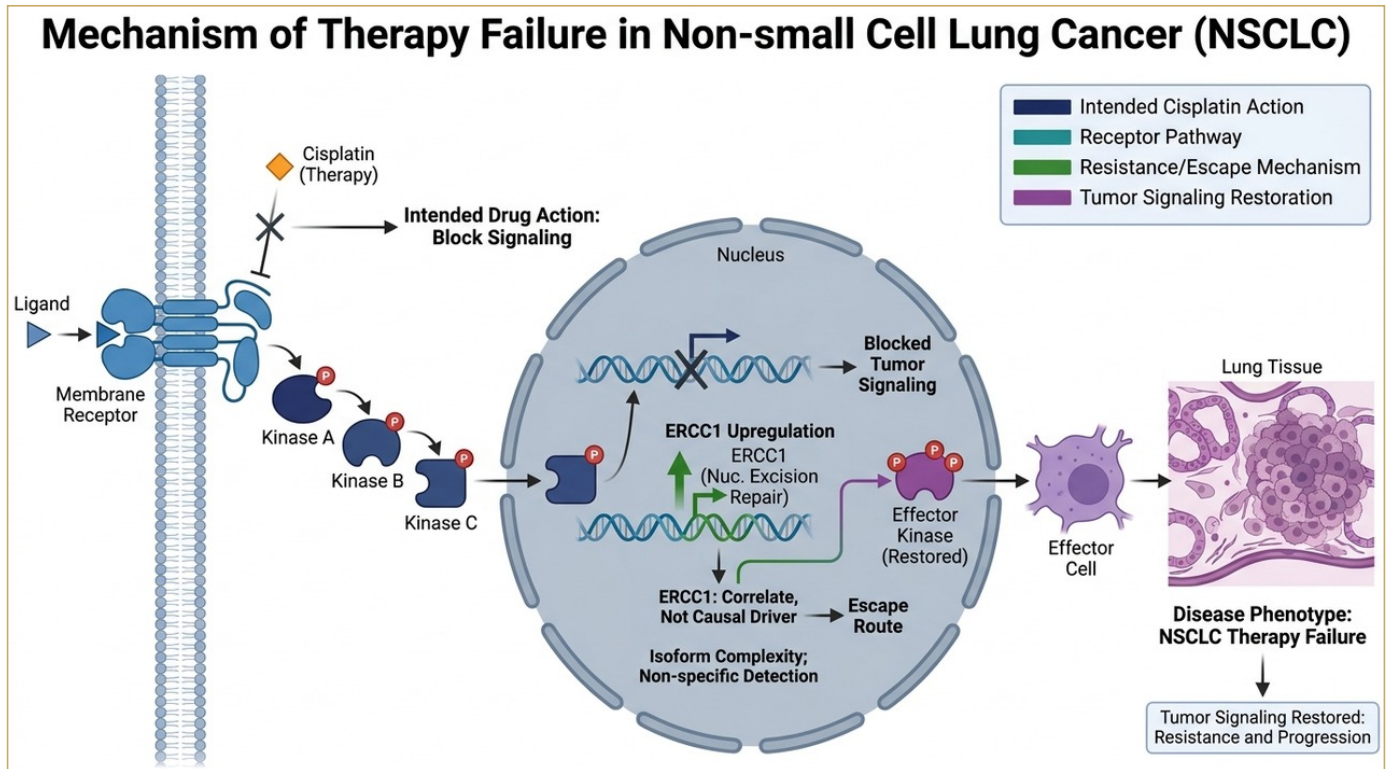
Allele-specific HLA loss reduces the neoantigen repertoire presentable to T cells, allowing immune evasion even with intact total MHC-I and high mutational burden.

BiRAGAS pattern P2 · antigen-escape

Citation: McGranahan N et al. Cell 2017;171:1259-1271. PMID 29107330

Cisplatin (ERCC1-guided/customized platinum therapy)

Non-small cell lung cancer



Indication: Non-small cell lung cancer

Resistance / failure mechanism:

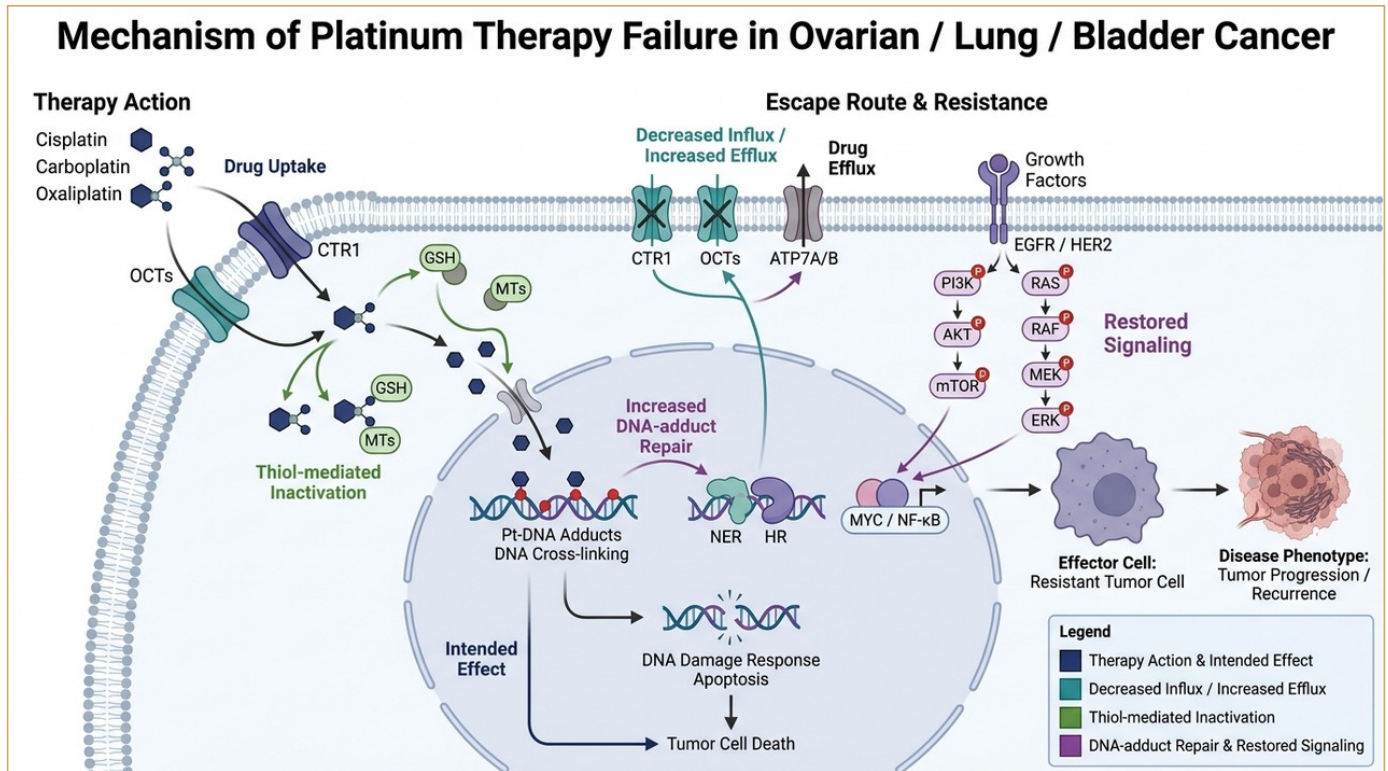
ERCC1 was a correlate, not a clinically actionable causal driver; isoform complexity and non-specific detection invalidated it as a resistance readout to guide therapy

BiRAGAS pattern P1 · correlate-not-driver

Citation: Friboulet L et al. N Engl J Med 2013;368(12):1101-1110. PMID 23514287

Cisplatin / carboplatin / oxaliplatin

Ovarian / lung / bladder (platinum-treated)



Indication: Ovarian / lung / bladder (platinum-treated)

Resistance / failure mechanism:

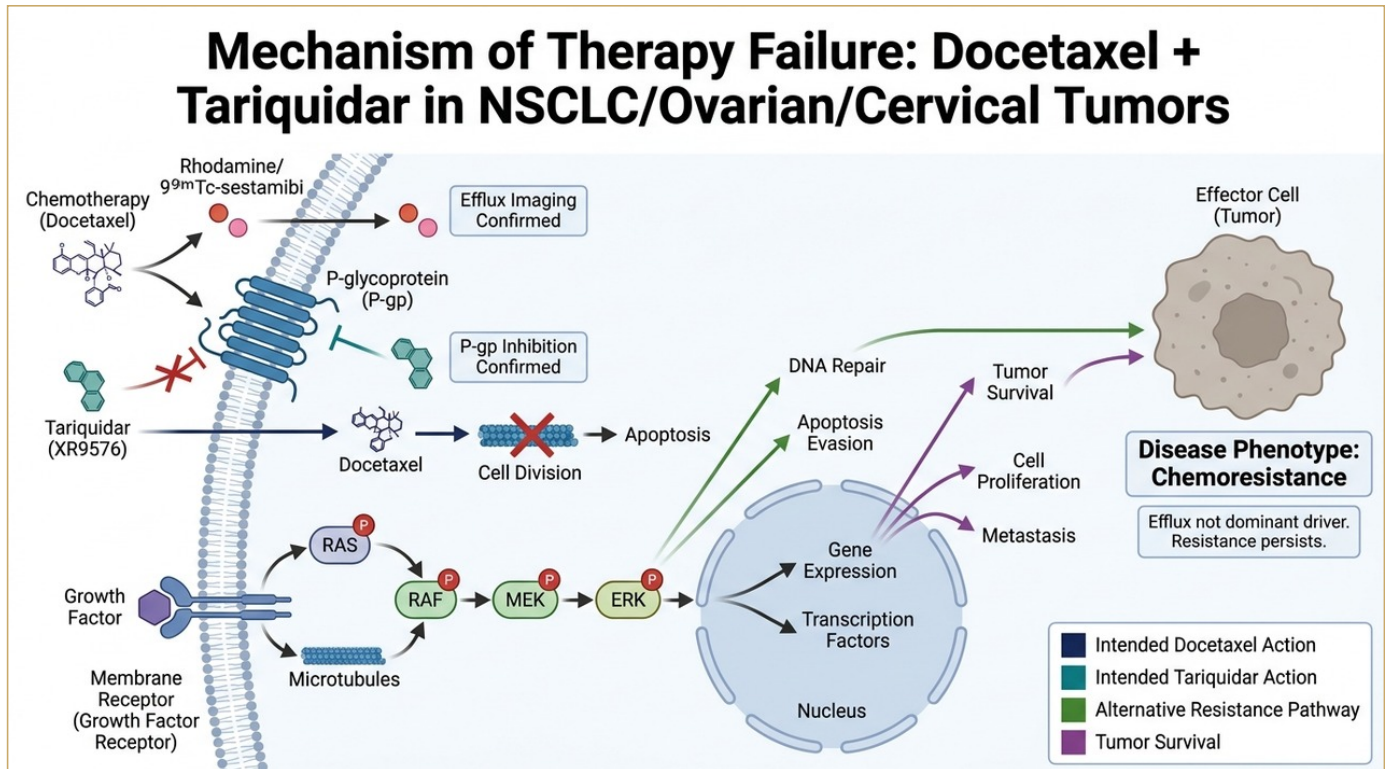
Multifactorial: decreased drug influx and increased efflux, thiol-mediated inactivation, and increased DNA-adduct repair reduce lethal lesion burden

BiRAGAS pattern P1 · DNA-repair/apoptosis-evasion

Citation: Galluzzi L et al. Oncogene 2012;31(15):1869-1883. PMID 22182883

Docetaxel + tariquidar (XR9576) pharmacodynamic modulation

Non-small cell lung / ovarian / cervical



Indication: Non-small cell lung / ovarian / cervical

Resistance / failure mechanism:

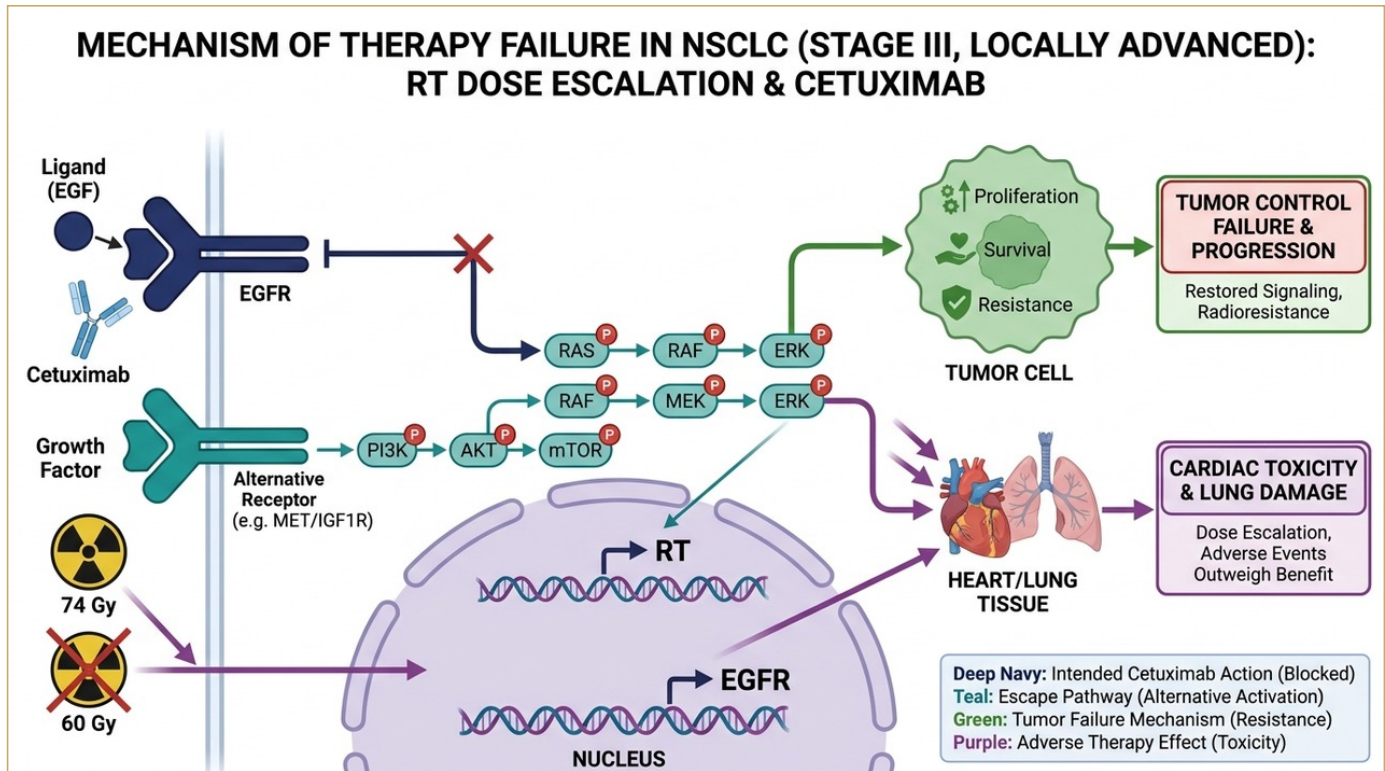
Demonstrated pharmacologic P-gp inhibition did not overcome tumor chemoresistance, indicating efflux is not the dominant resistance driver in these solid tumors

BiRAGAS pattern P1 · correlate-not-driver

Citation: Kelly RJ et al. Clin Cancer Res 2011;17(3):569-580. PMID 21081657

Dose-escalated RT (74 Gy vs 60 Gy) +/- cetuximab + carbo/paclitaxel

NSCLC (locally advanced, stage III)



Indication: NSCLC (locally advanced, stage III)

Resistance / failure mechanism:

Dose escalation increased heart/lung dose (cardiac toxicity) outweighing tumor control; EGFR blockade redundant

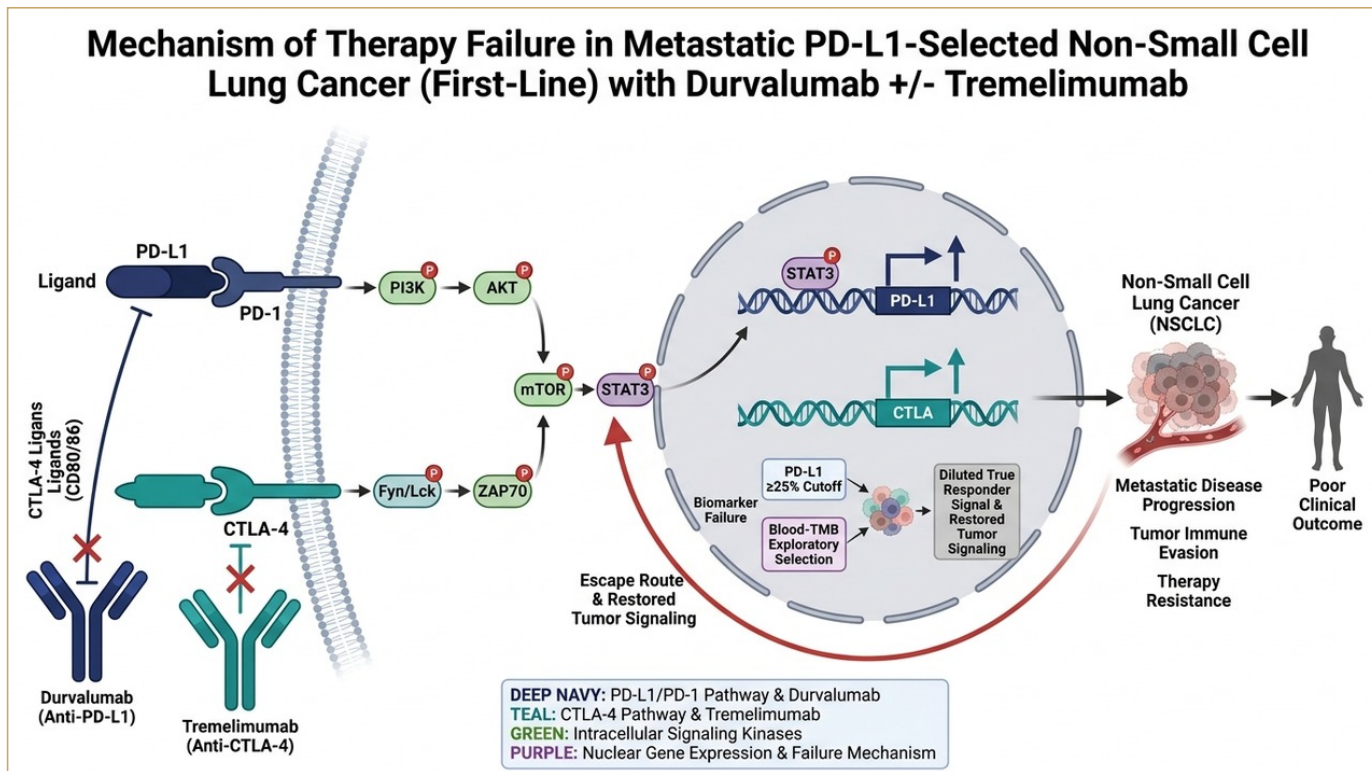
BiRAGAS pattern P4 · on-mechanism-toxicity

Citation: Bradley JD et al. Lancet Oncol 2015;16:187-199, PMID 25601342

ClinicalTrials.gov: [NCT00533949](https://clinicaltrials.gov/ct2/show/study/NCT00533949)

Durvalumab +/- tremelimumab

Untreated metastatic/PD-L1-selected non-small cell lung cancer (first-line)



Indication: Untreated metastatic/PD-L1-selected non-small cell lung cancer (first-line)

Resistance / failure mechanism:

PD-L1 $\geq 25\%$ cutoff and blood-TMB exploratory selection failed to identify the benefiting population; the chosen biomarker threshold diluted any true responder signal.

BiRAGAS pattern P3 · population-dilution

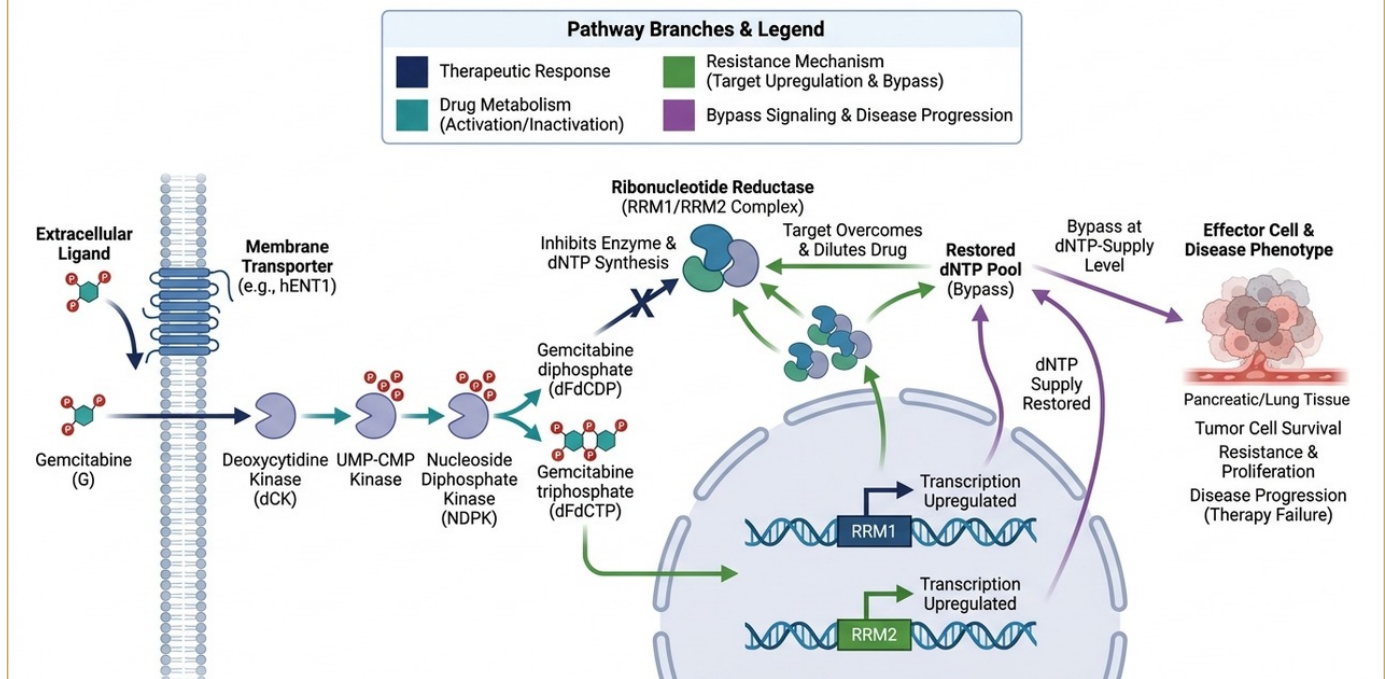
Citation: Rizvi NA et al. JAMA Oncol 2020;6:661-674. PMID 32271377

ClinicalTrials.gov: NCT02453282

Gemcitabine

Pancreatic / lung (gemcitabine-treated)

Mechanism of Gemcitabine Therapy Failure in Pancreatic / Lung Cancer (Gemcitabine-treated)



Indication: Pancreatic / lung (gemcitabine-treated)

Resistance / failure mechanism:

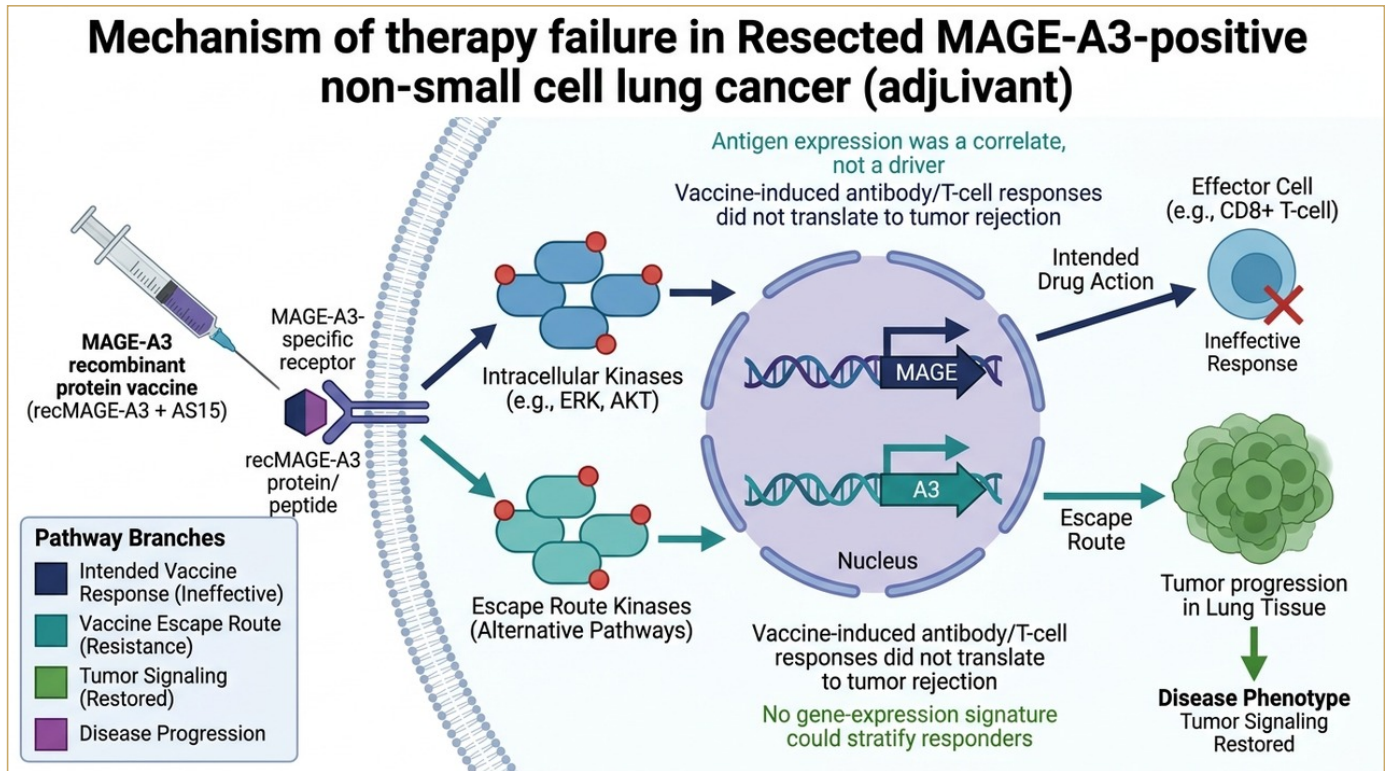
Target (ribonucleotide reductase) upregulation overcomes enzyme inhibition and dilutes drug incorporation; on-mechanism/bypass at the dNTP-supply level

BiRAGAS pattern P2 · pathway-redundancy

Citation: Bepler G et al. J Clin Oncol 2006;24(29):4731-4737. PMID 16966686

MAGE-A3 recombinant protein vaccine (recMAGE-A3 + AS15)

Resected MAGE-A3-positive non-small cell lung cancer (adjuvant)



Indication: Resected MAGE-A3-positive non-small cell lung cancer (adjuvant)

Resistance / failure mechanism:

Antigen expression was a correlate, not a driver; vaccine-induced antibody/T-cell responses did not translate to tumor rejection, and no gene-expression signature could stratify responders.

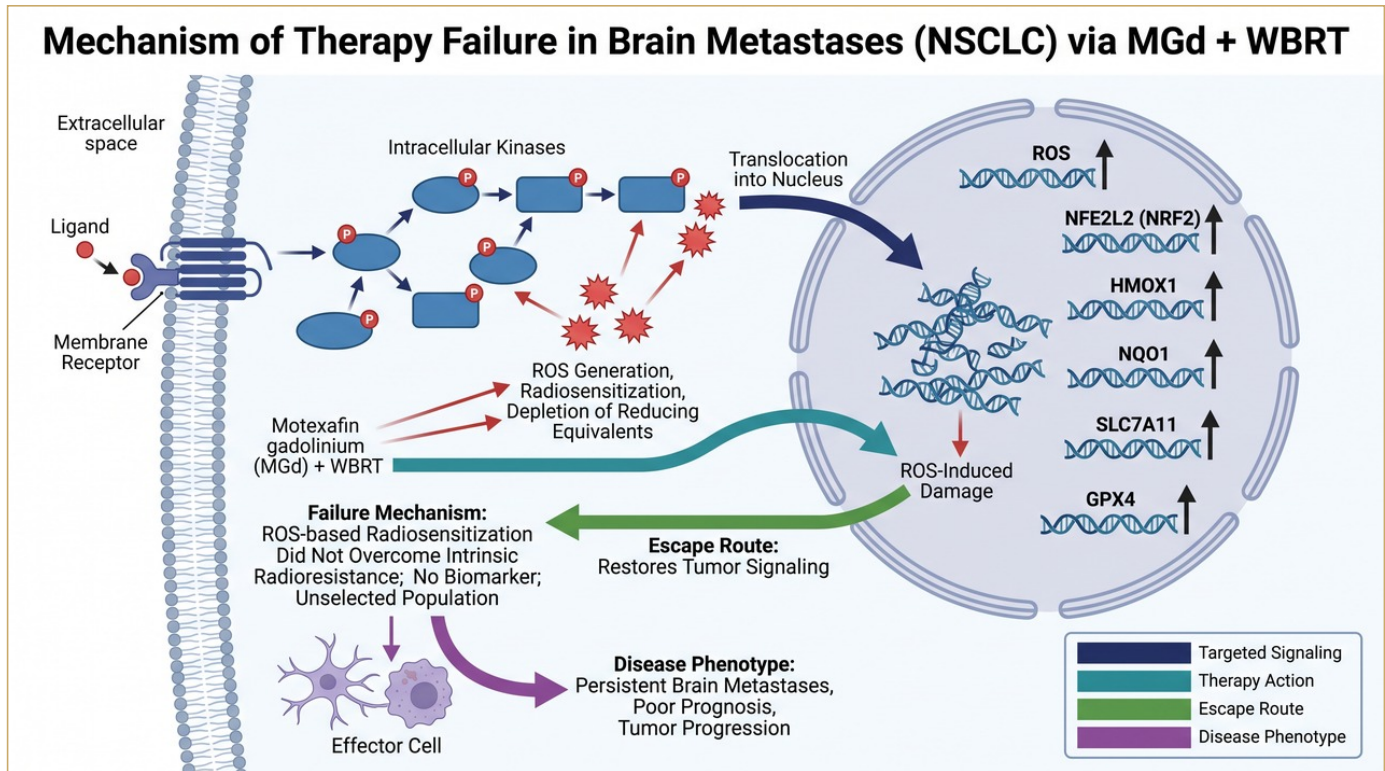
BiRAGAS pattern P1 · correlate-not-driver

Citation: Vansteenkiste JF et al. Lancet Oncol 2016;17:822-835. PMID 26765324

[ClinicalTrials.gov: NCT00480025](https://clinicaltrials.gov/ct2/show/study/NCT00480025)

Motexafin gadolinium (MGd) + WBRT

Brain metastases (predominantly NSCLC)



Indication: Brain metastases (predominantly NSCLC)

Resistance / failure mechanism:

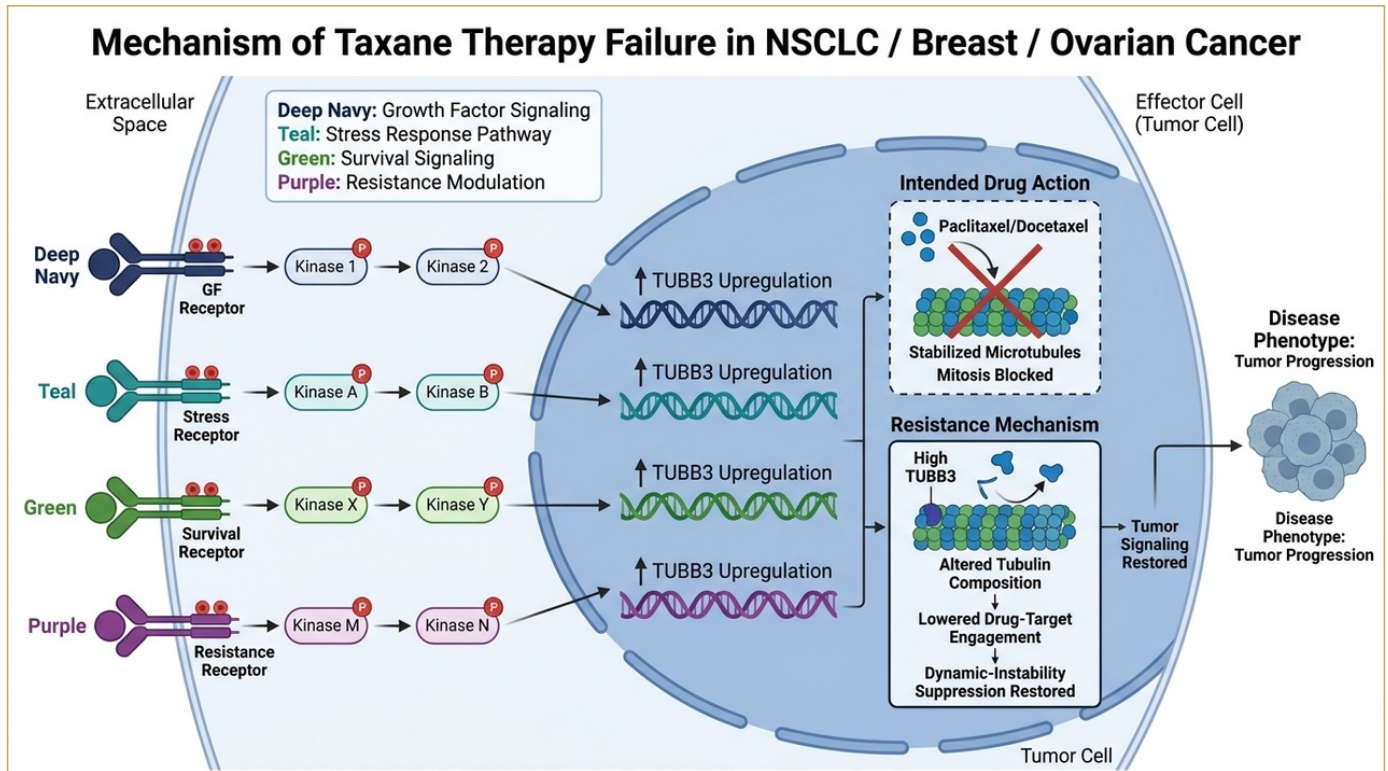
ROS-based radiosensitization did not overcome intrinsic radioresistance/repair; unselected population, no predictive biomarker

BiRAGAS pattern P1 · correlate-not-driver

Citation: Mehta MP et al. J Clin Oncol 2003;21:2529-2536, PMID 12829672

Paclitaxel / docetaxel

Non-small cell lung cancer / breast / ovarian



Indication: Non-small cell lung cancer / breast / ovarian

Resistance / failure mechanism:

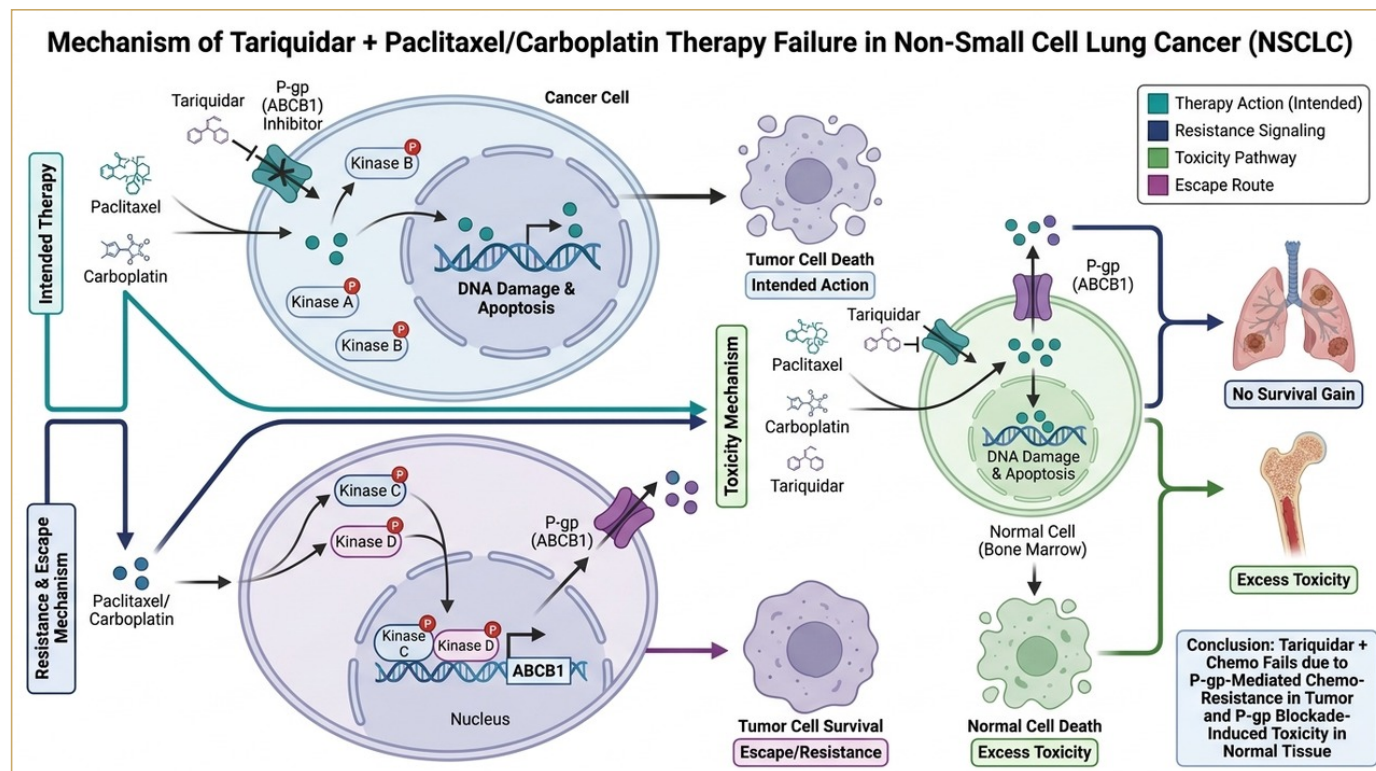
Altered tubulin isotype composition (high TUBB3) lowers drug-target engagement and dynamic-instability suppression; on-target structural resistance

BiRAGAS pattern P1 · target-mutation

Citation: Kavallaris M. Nat Rev Cancer 2010;10(3):194-204. PMID 20147901

Tariquidar (XR9576) added to paclitaxel + carboplatin

Non-small cell lung cancer (advanced, first-line)



Indication: Non-small cell lung cancer (advanced, first-line)

Resistance / failure mechanism:

Potent P-gp blockade increased chemotherapy exposure in normal tissues (bone marrow), producing excess toxicity in a chemo-naïve lung population without a survival gain

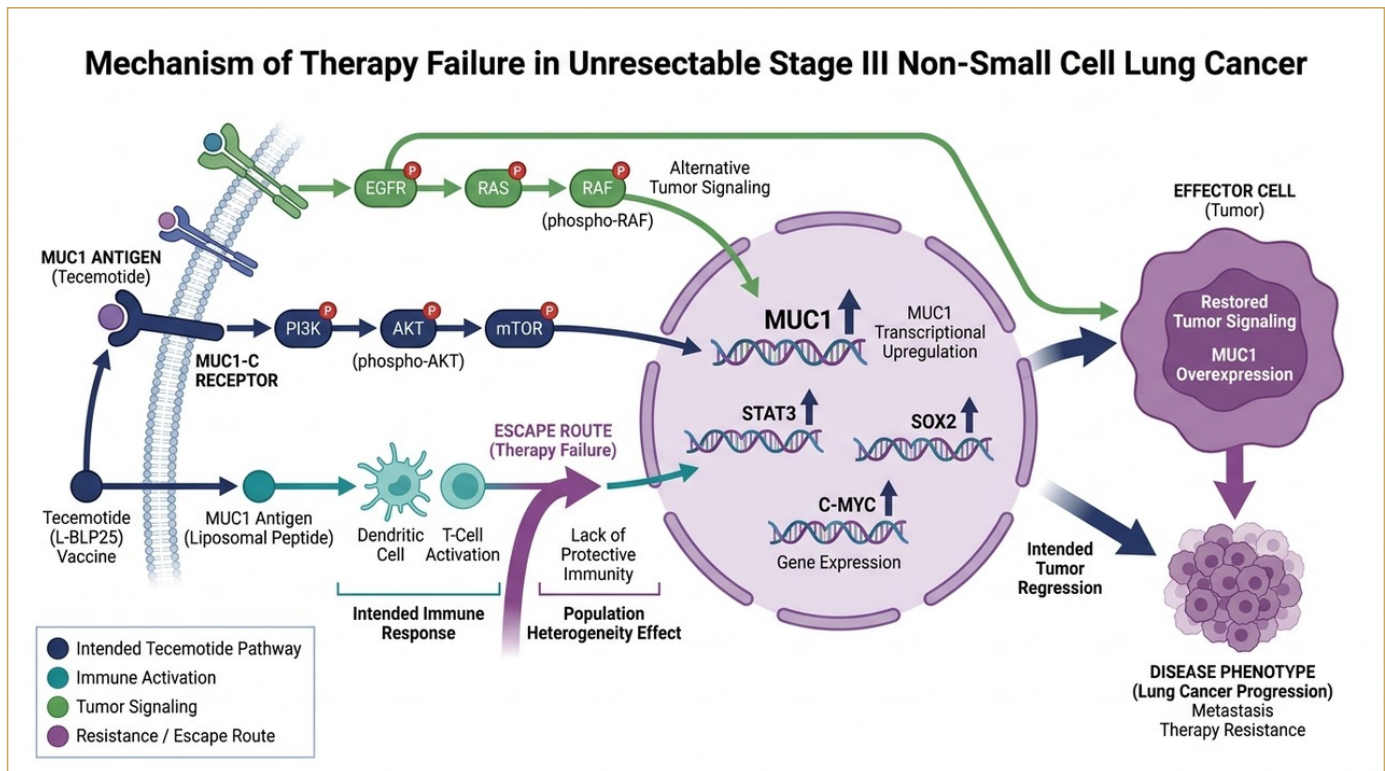
BiRAGAS pattern P6 · on-mechanism-toxicity

Citation: ClinicalTrials.gov NCT00042302 (terminated); Kelly RJ et al. Clin Cancer Res 2011;17(3):569-580. PMID 21081657

ClinicalTrials.gov: NCT00042302

Tecemotide (L-BLP25 / Stimuvax)

Unresectable stage III non-small cell lung cancer



Indication: Unresectable stage III non-small cell lung cancer

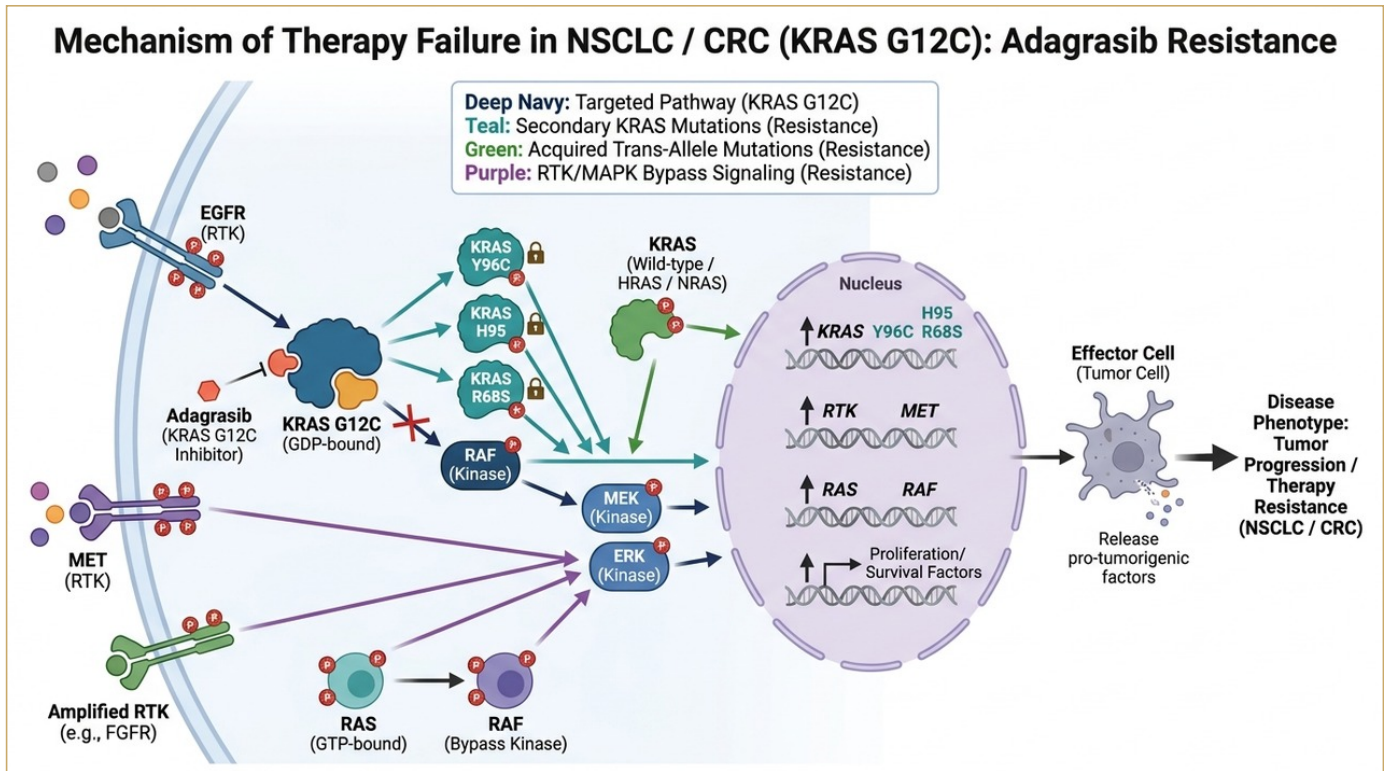
Resistance / failure mechanism:

MUC1 vaccination did not induce protective immunity in the overall population; apparent subgroup effect reflects population heterogeneity rather than a validated driver.

BiRAGAS pattern P3 · correlate-not-driver

Citation: Butts C et al. Lancet Oncol 2014;15:59-68. PMID 24525013

[ClinicalTrials.gov: NCT00409188](https://clinicaltrials.gov/ct2/show/study/NCT00409188)



Indication: NSCLC / CRC (KRAS G12C)

Resistance / failure mechanism:

Secondary KRAS pocket mutations (Y96C, H95, R68S), acquired trans-allele KRAS mutations, and RTK/MAPK bypass (MET amp, RAS/RAF/MEK, EGFR)

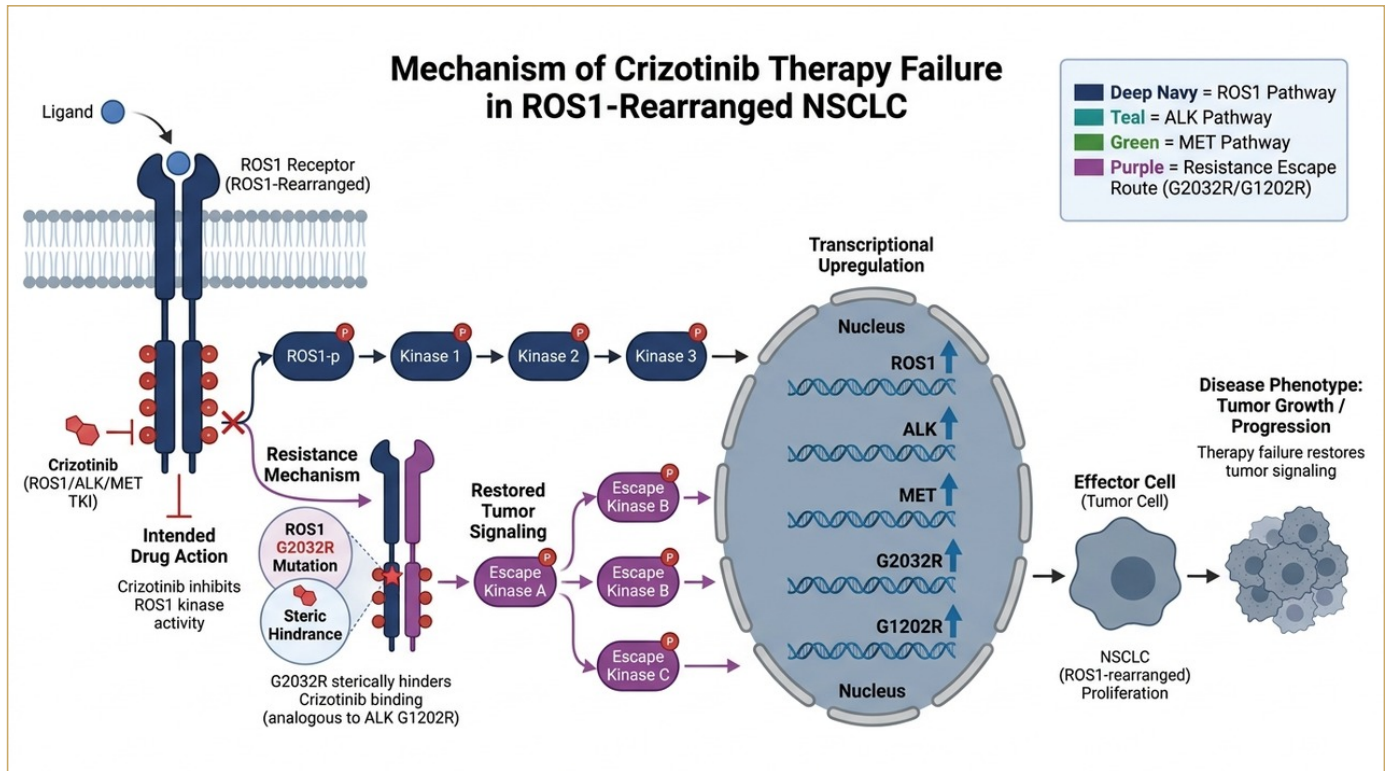
BiRAGAS pattern P7 · bypass/parallel-pathway

Citation: Awad MM et al. N Engl J Med 2021;384:2382-2393, PMID 34161704

[ClinicalTrials.gov: NCT03785249](https://clinicaltrials.gov/ct2/show/study/NCT03785249)

crizotinib

NSCLC (ROS1-rearranged)



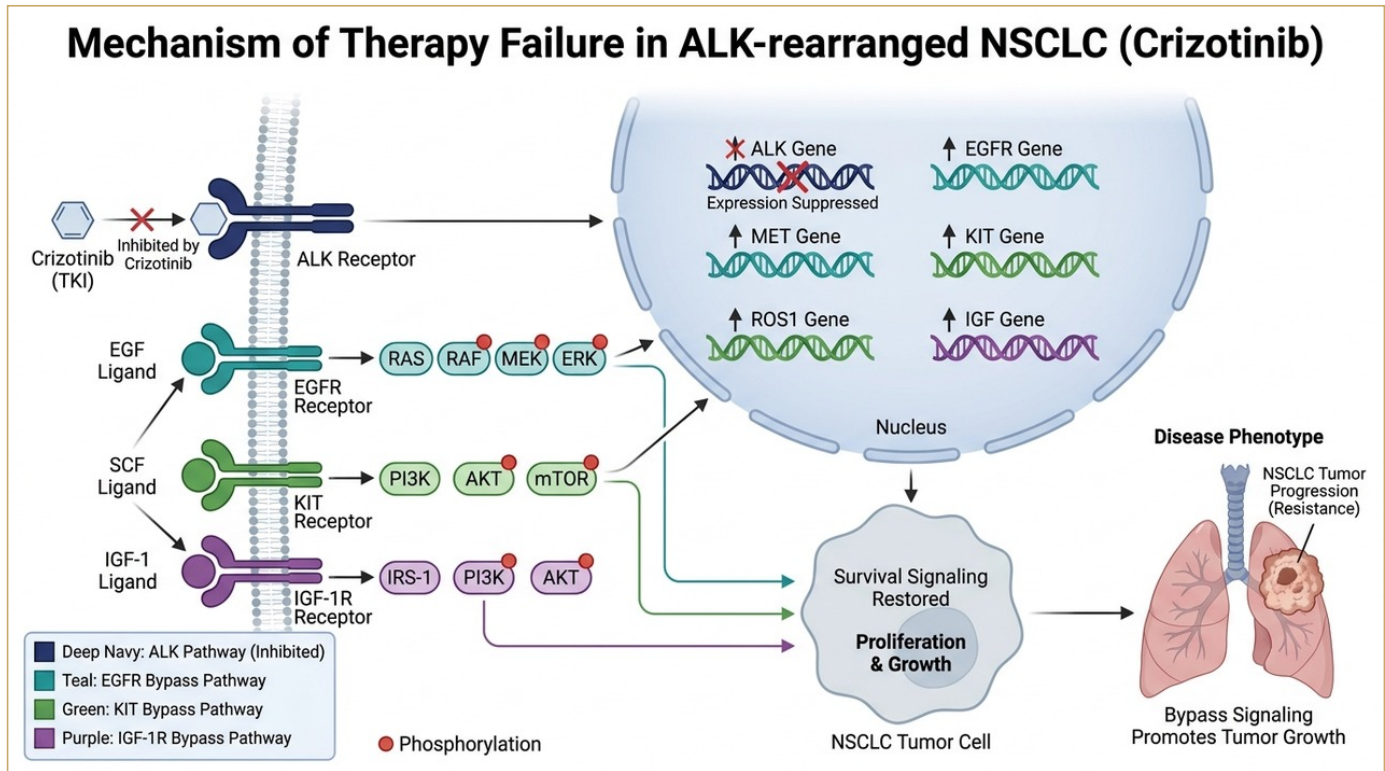
Indication: NSCLC (ROS1-rearranged)

Resistance / failure mechanism:

ROS1 G2032R sterically hinders crizotinib binding (analogous to ALK G1202R)

BiRAGAS pattern P7 · target-mutation

Citation: Awad MM et al. N Engl J Med 2013;368:2395-2401, PMID 23724914



Indication: NSCLC (ALK-rearranged)

Resistance / failure mechanism:

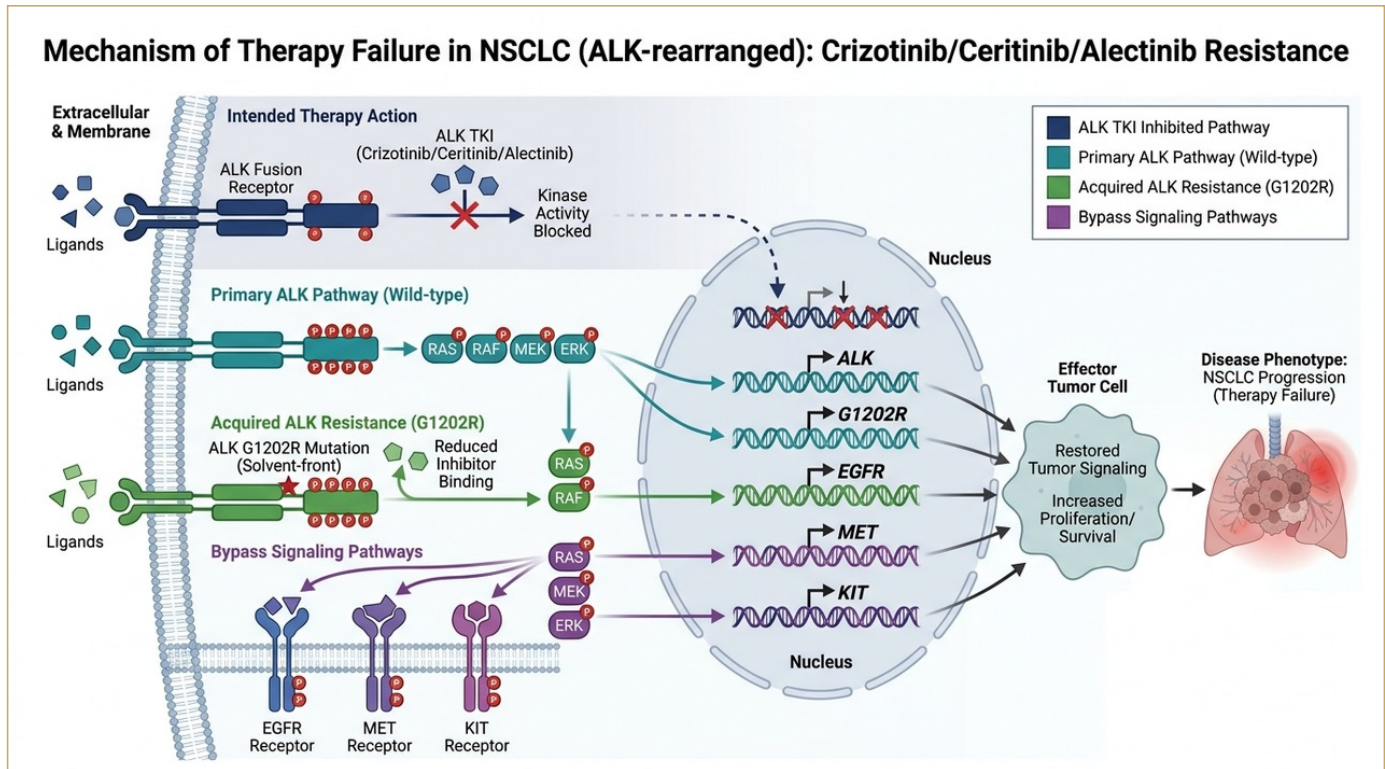
Bypass signaling via EGFR, KIT, or IGF-1R activation maintains downstream survival independent of ALK inhibition

BiRAGAS pattern P2 · bypass/parallel-pathway

Citation: Katayama R et al. Sci Transl Med 2012;4:120ra17, PMID 22277784

crizotinib / ceritinib / alectinib

NSCLC (ALK-rearranged)



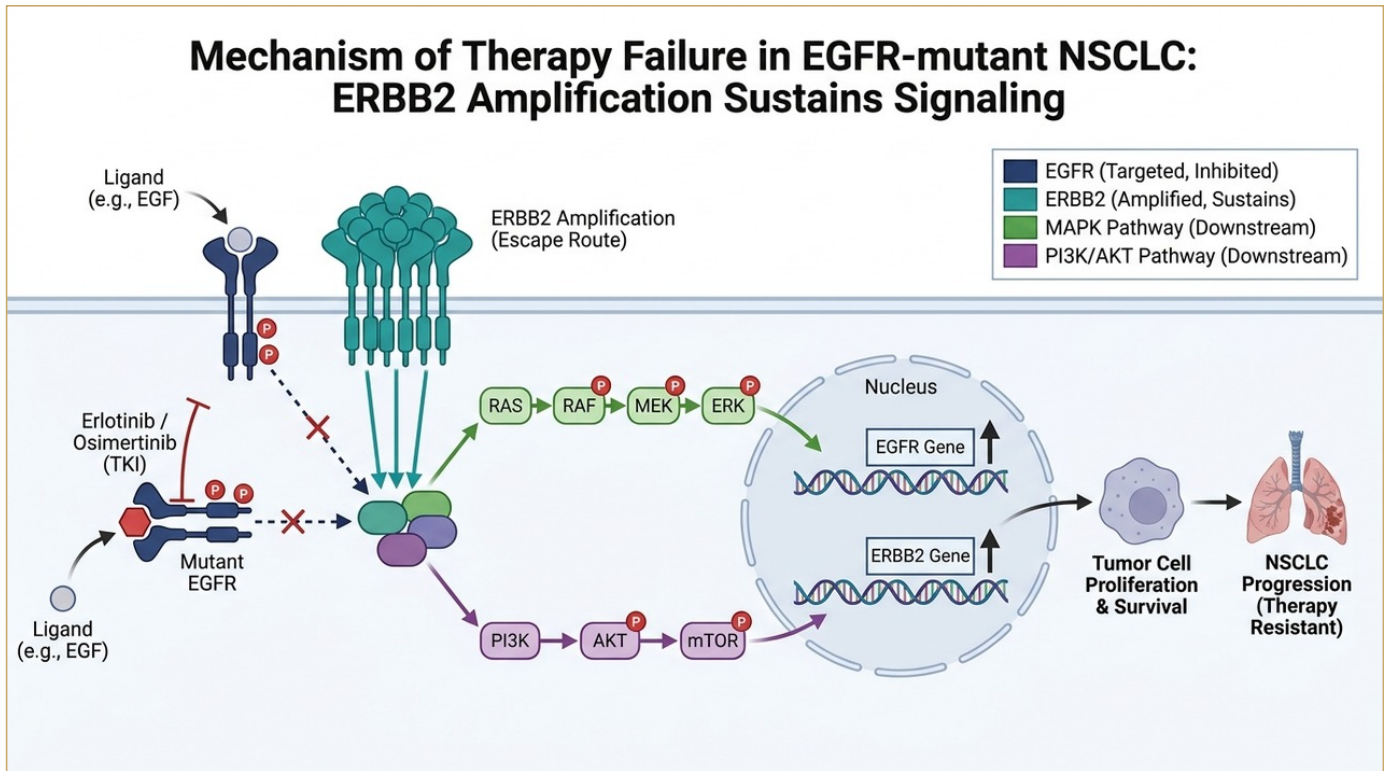
Indication: NSCLC (ALK-rearranged)

Resistance / failure mechanism:

ALK G1202R solvent-front substitution reduces inhibitor binding; bypass via EGFR/MET/KIT in others

BiRAGAS pattern P7 · target-mutation

Citation: Gainor JF et al. Cancer Discov 2016;6:1118-1133, PMID 27432227



Indication: NSCLC (EGFR-mutant)

Resistance / failure mechanism:

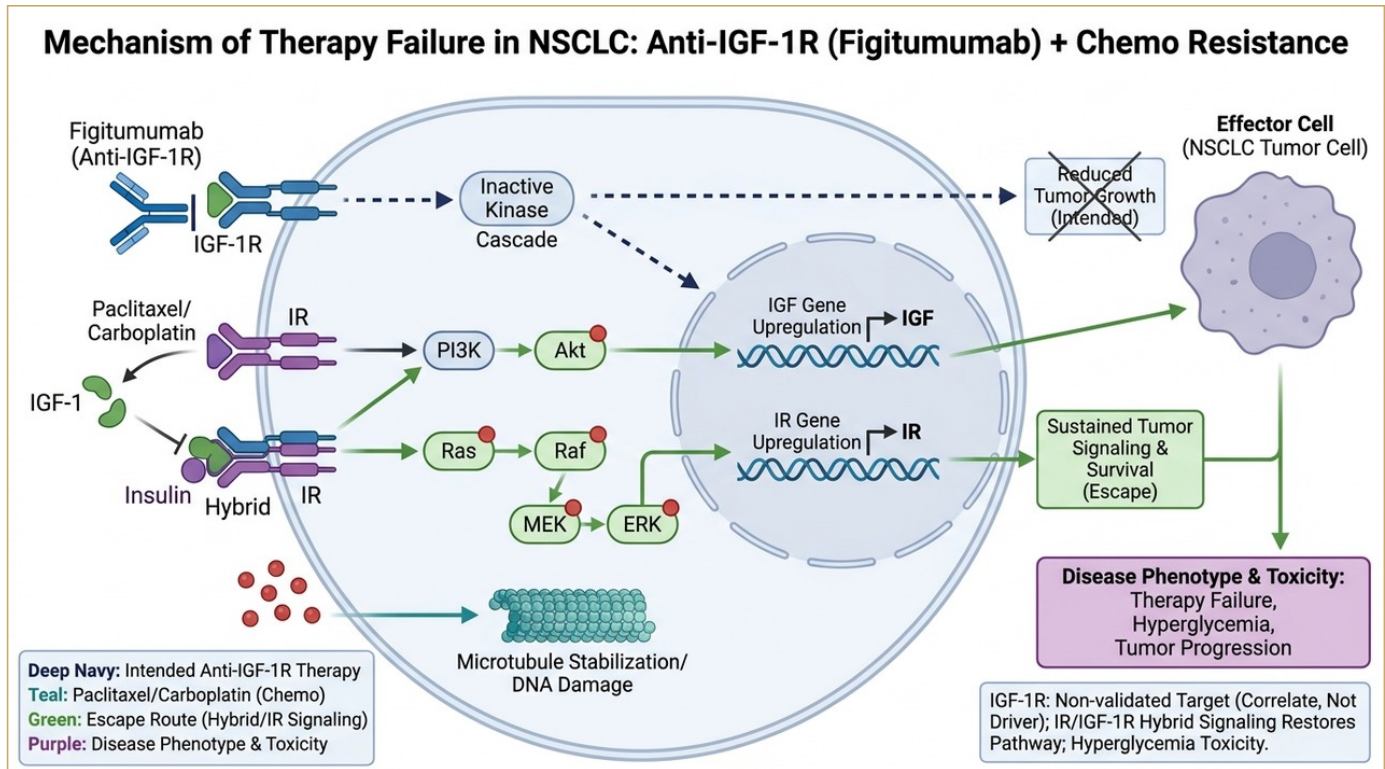
ERBB2 amplification sustains downstream signaling independent of EGFR inhibition

BiRAGAS pattern P2 · bypass/parallel-pathway

Citation: Takezawa K et al. Cancer Discov 2012;2:922-933, PMID 22956644

figitumumab (CP-751,871) + paclitaxel/carboplatin

NSCLC (non-adenocarcinoma)



Indication: NSCLC (non-adenocarcinoma)

Resistance / failure mechanism:

IGF-1R a non-validated target (correlate, not driver); IR/IGF-1R hybrid signaling and hyperglycemia toxicity

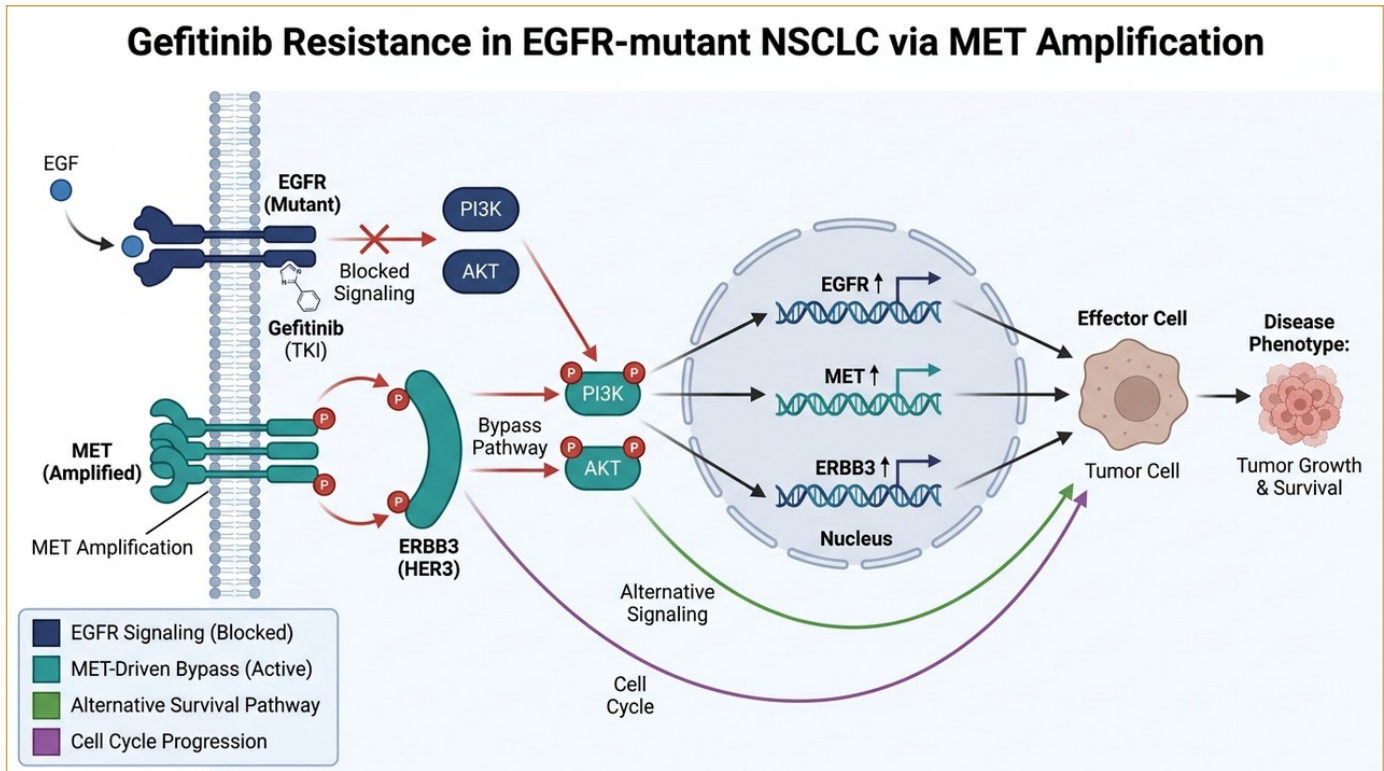
BiRAGAS pattern P1 · correlate-not-driver

Citation: Langer CJ et al. J Clin Oncol 2014;32:2059-2066, PMID 24888810

ClinicalTrials.gov: [NCT00596830](https://clinicaltrials.gov/ct2/show/study/NCT00596830)

gefitinib

NSCLC (EGFR-mutant)



Indication: NSCLC (EGFR-mutant)

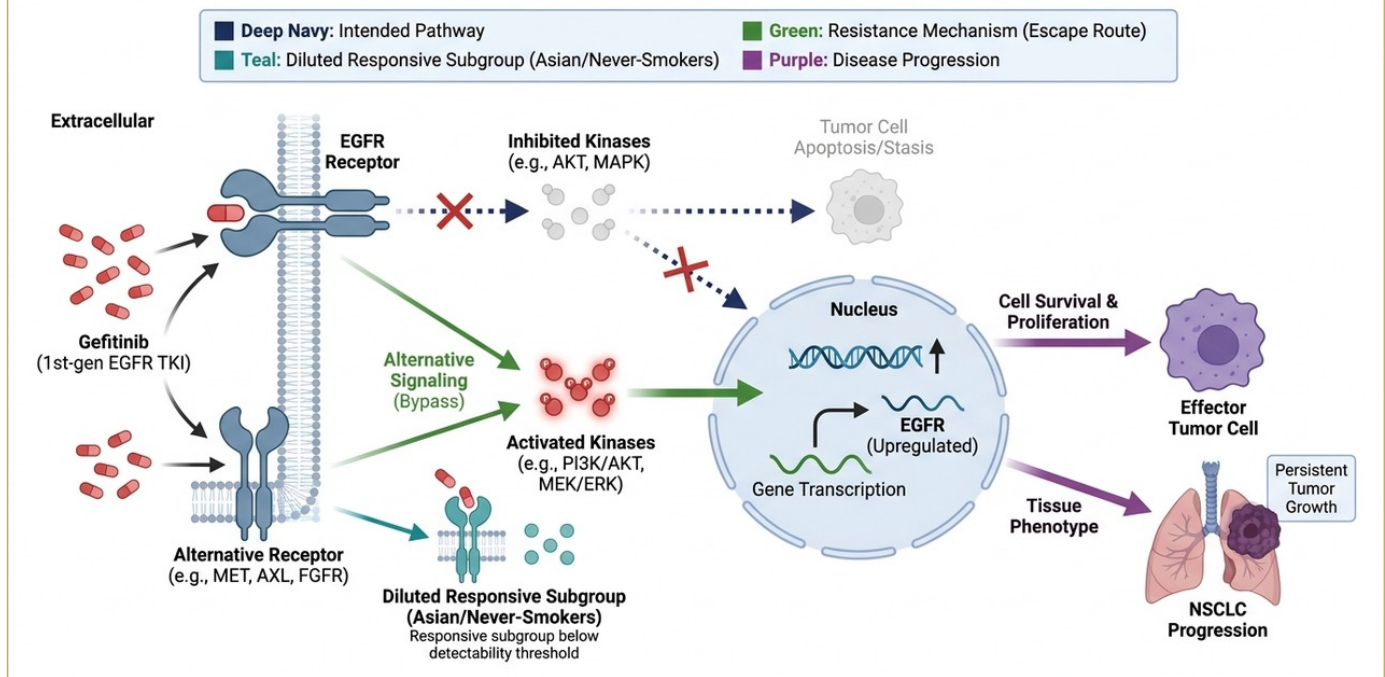
Resistance / failure mechanism:

MET amplification reactivates PI3K/AKT via ERBB3 (HER3), bypassing EGFR blockade

BiRAGAS pattern P2 · bypass/parallel-pathway

Citation: Engelman JA et al. Science 2007;316:1039-1043, PMID 17463250

Mechanism of Therapy Failure in NSCLC (Molecularly Unselected) - Gefitinib Resistance



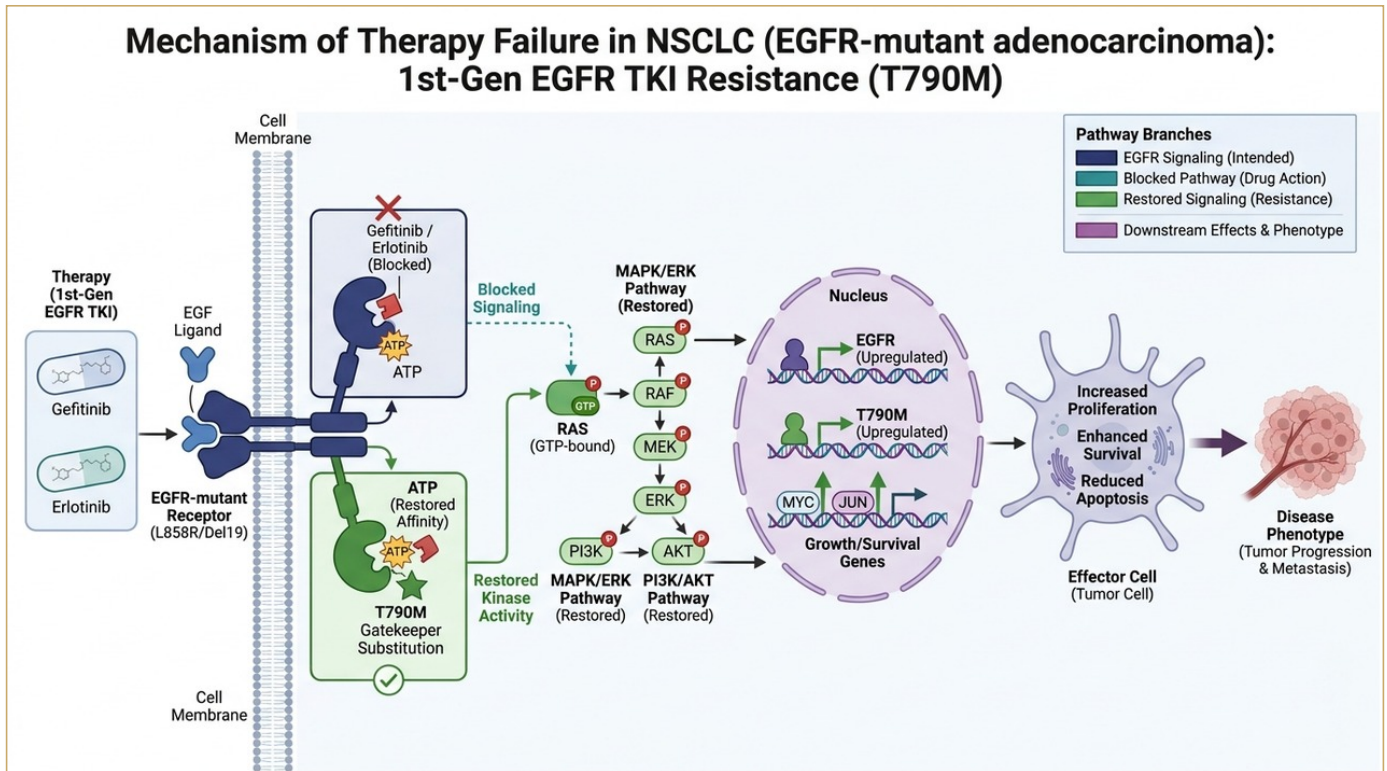
Indication: NSCLC (molecularly unselected)

Resistance / failure mechanism:

Population not enriched for EGFR mutations, responsive subgroup (never-smokers, Asian) diluted below detectability

BiRAGAS pattern P3 · population-dilution

Citation: Thatcher N et al. Lancet 2005;366:1527-1537, PMID 16257339



Indication: NSCLC (EGFR-mutant adenocarcinoma)

Resistance / failure mechanism:

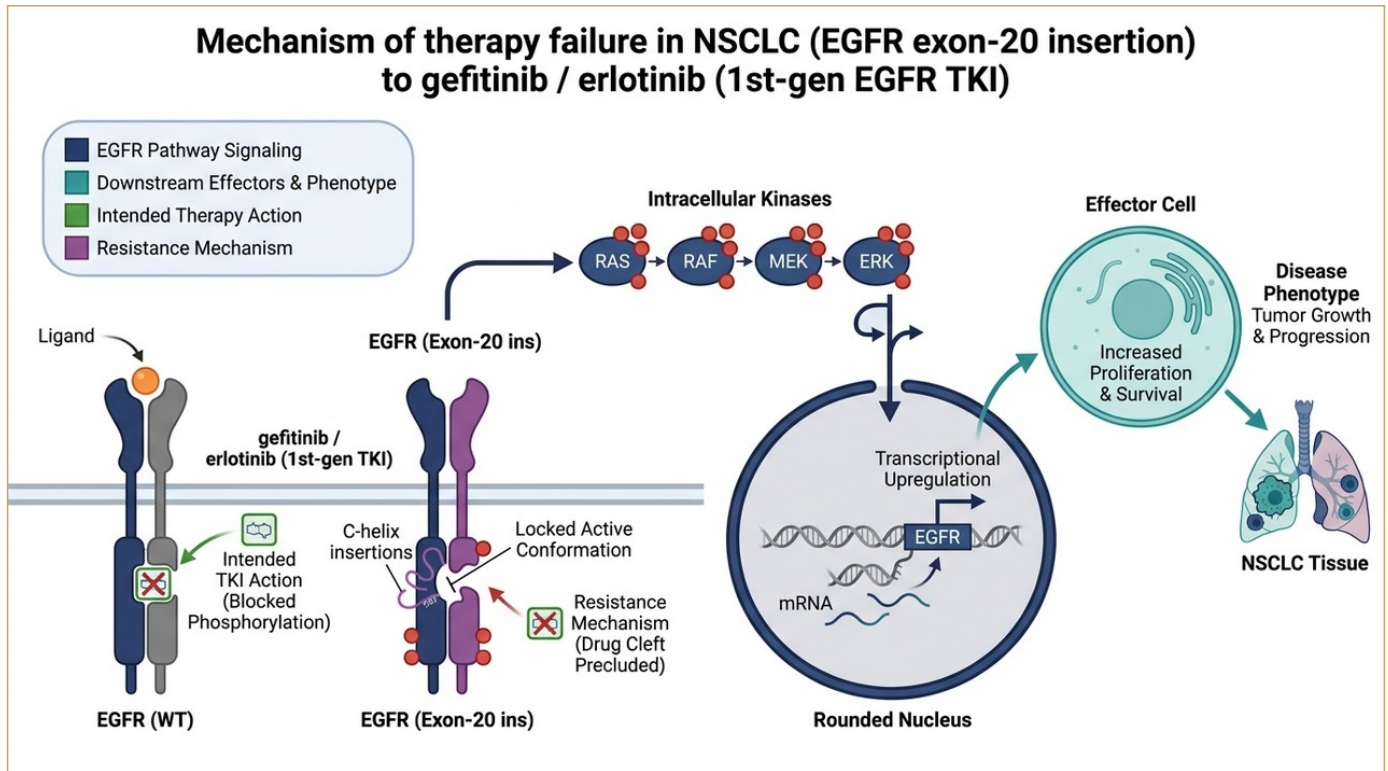
EGFR T790M gatekeeper substitution restores ATP affinity and sterically blocks drug binding

BiRAGAS pattern P7 · target-mutation

Citation: Kobayashi S et al. N Engl J Med 2005;352:786-792, PMID 15737014; Pao W et al. PLoS Med 2005;2:e73

gefitinib / erlotinib

NSCLC (EGFR exon-20 insertion)



Indication: NSCLC (EGFR exon-20 insertion)

Resistance / failure mechanism:

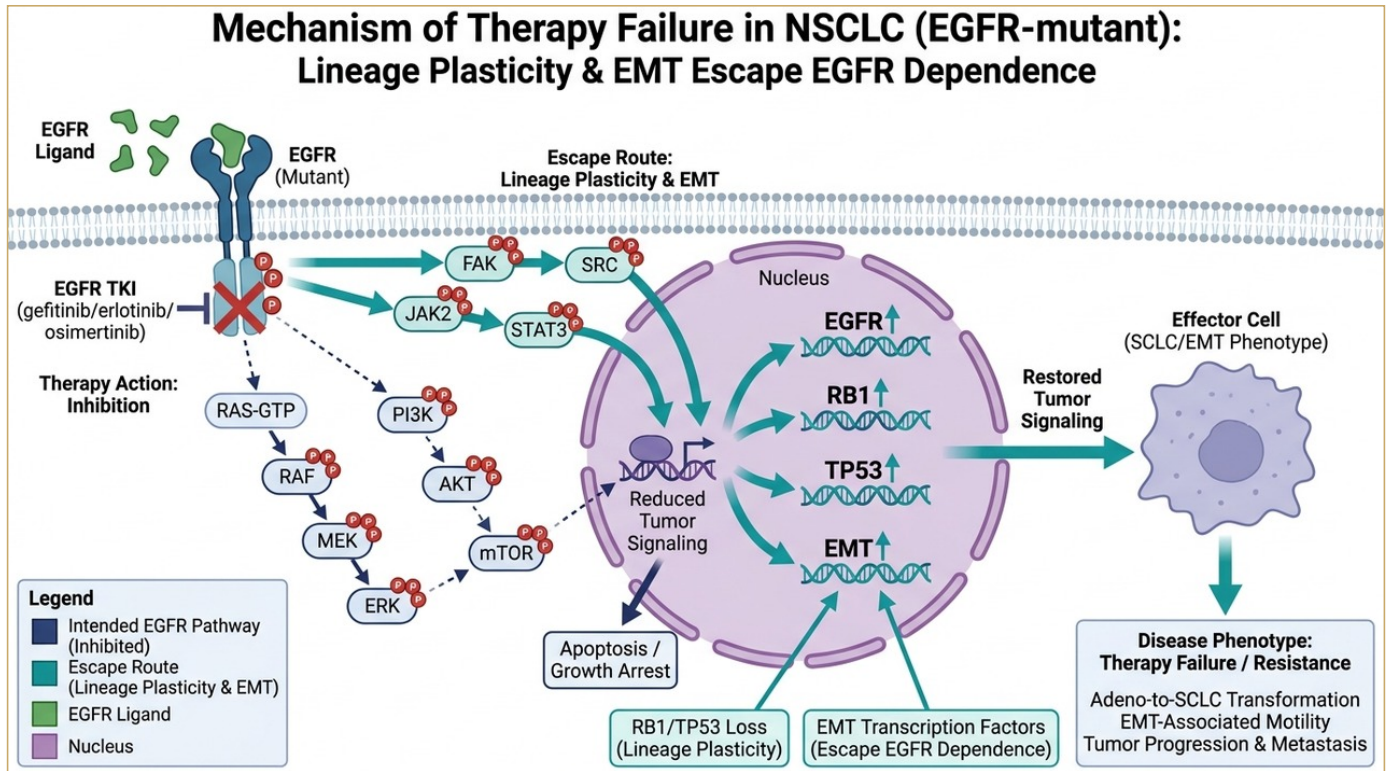
C-helix insertions constrain the ATP pocket into active conformation without enlarging the drug cleft, precluding TKI binding

BiRAGAS pattern P7 · target-mutation

Citation: Yasuda H et al. Sci Transl Med 2013;5:216ra177, PMID 24353160

gefitinib / erlotinib / osimertinib

NSCLC (EGFR-mutant)



Indication: NSCLC (EGFR-mutant)

Resistance / failure mechanism:

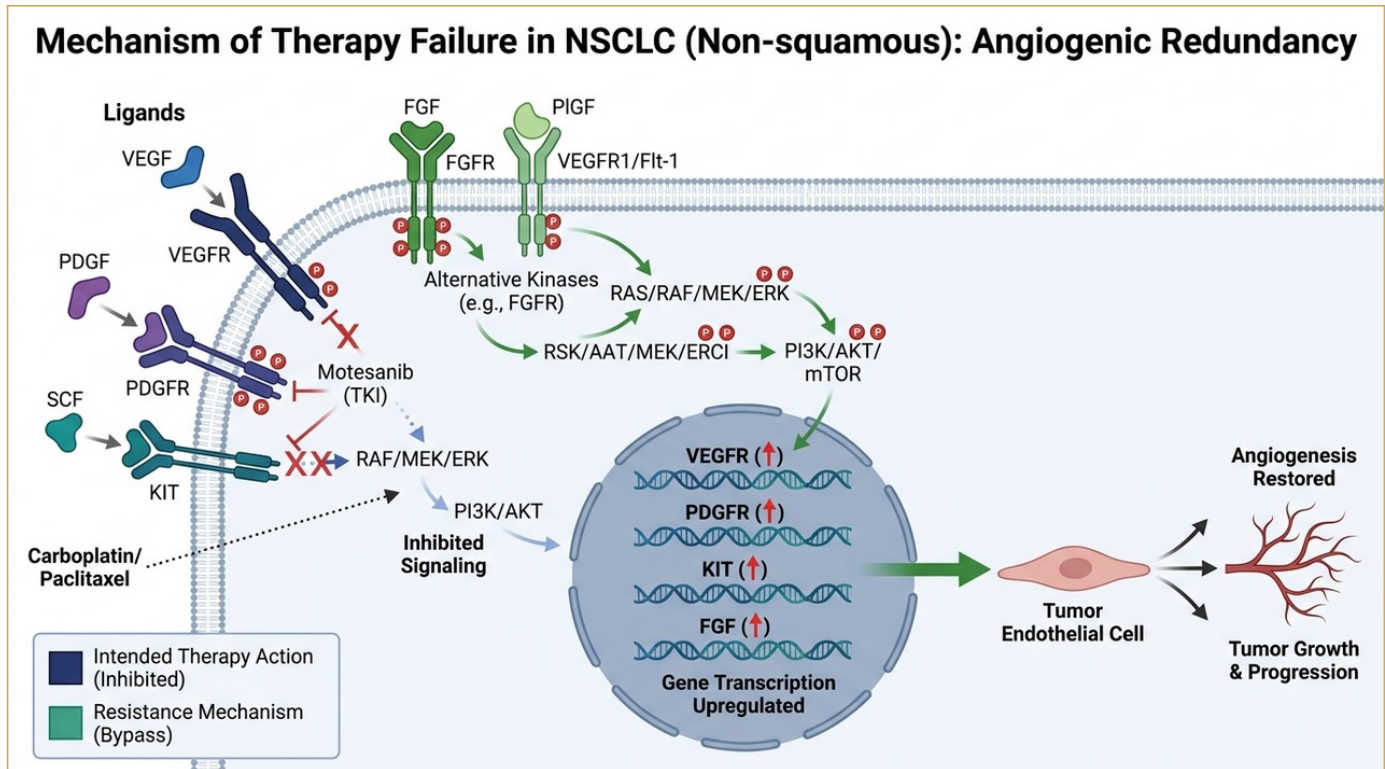
Lineage plasticity: adeno-to-SCLC transformation (RB1/TP53 loss) and EMT escape EGFR dependence

BiRAGAS pattern P2 · lineage-plasticity/transformation

Citation: Sequist LV et al. Sci Transl Med 2011;3:75ra26, PMID 21430269

motesanib + carboplatin/paclitaxel

NSCLC (non-squamous)



Indication: NSCLC (non-squamous)

Resistance / failure mechanism:

Angiogenic redundancy, blocking VEGFR alone bypassed by alternative pro-angiogenic ligands (FGF, PIGF)

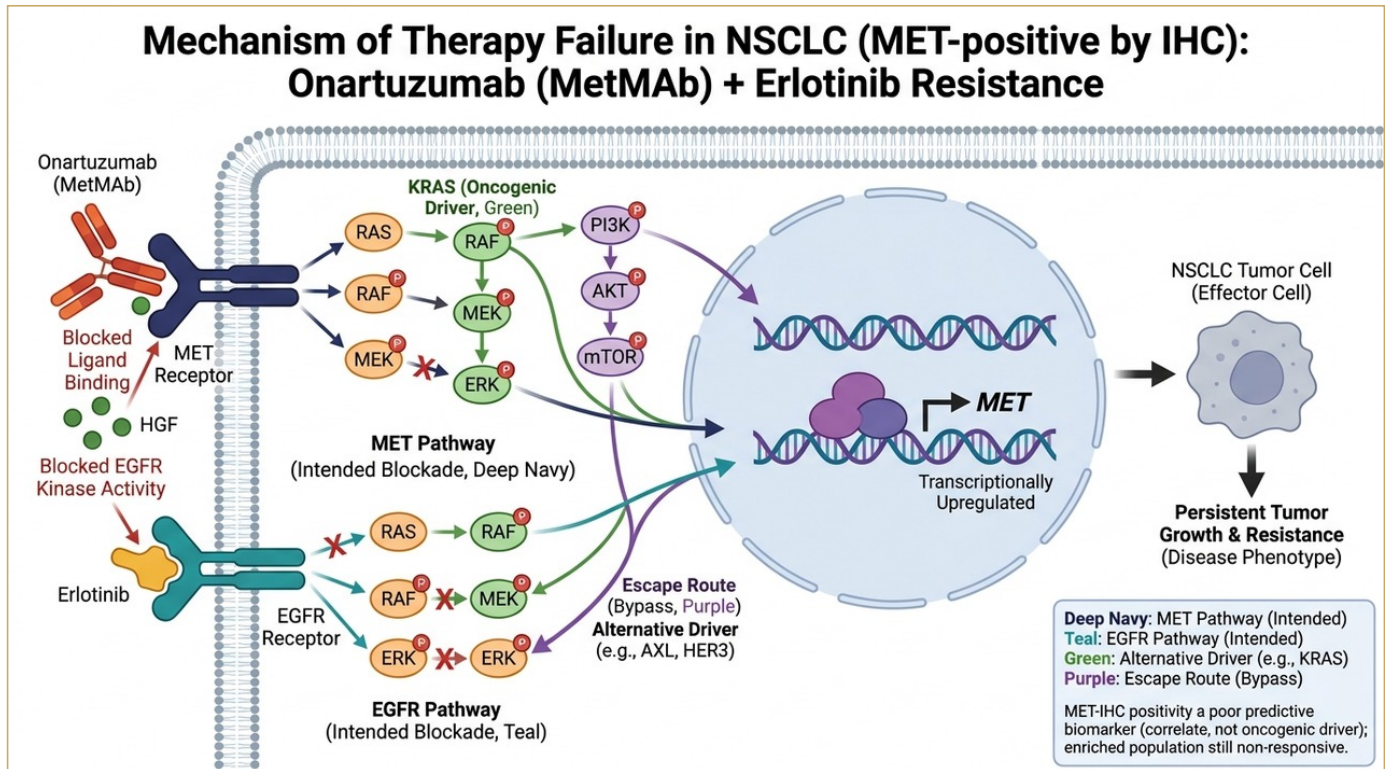
BiRAGAS pattern P2 · pathway-redundancy

Citation: Scagliotti GV et al. J Clin Oncol 2012;30:2829-2836, PMID 22753918

[ClinicalTrials.gov: NCT00460317](https://clinicaltrials.gov/ct2/show/study/NCT00460317)

onartuzumab (MetMab) + erlotinib

NSCLC (MET-positive by IHC)



Indication: NSCLC (MET-positive by IHC)

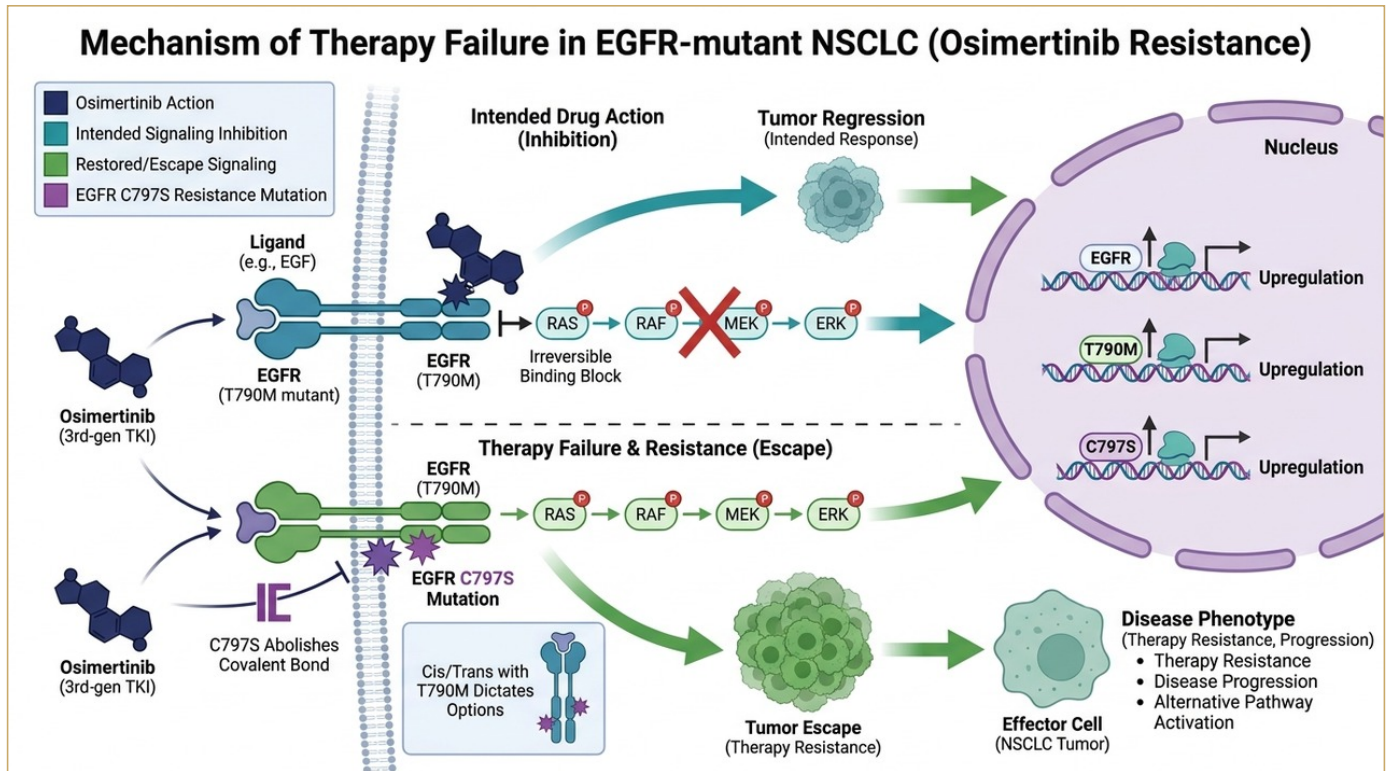
Resistance / failure mechanism:

MET-IHC positivity a poor predictive biomarker (correlate, not oncogenic driver); enriched population still non-responsive

BiRAGAS pattern P1 · correlate-not-driver

Citation: Spigel DR et al. J Clin Oncol 2017;35:412-420, PMID 27937096

[ClinicalTrials.gov: NCT01456325](https://clinicaltrials.gov/ct2/show/study/NCT01456325)



Indication: NSCLC (EGFR-mutant)

Resistance / failure mechanism:

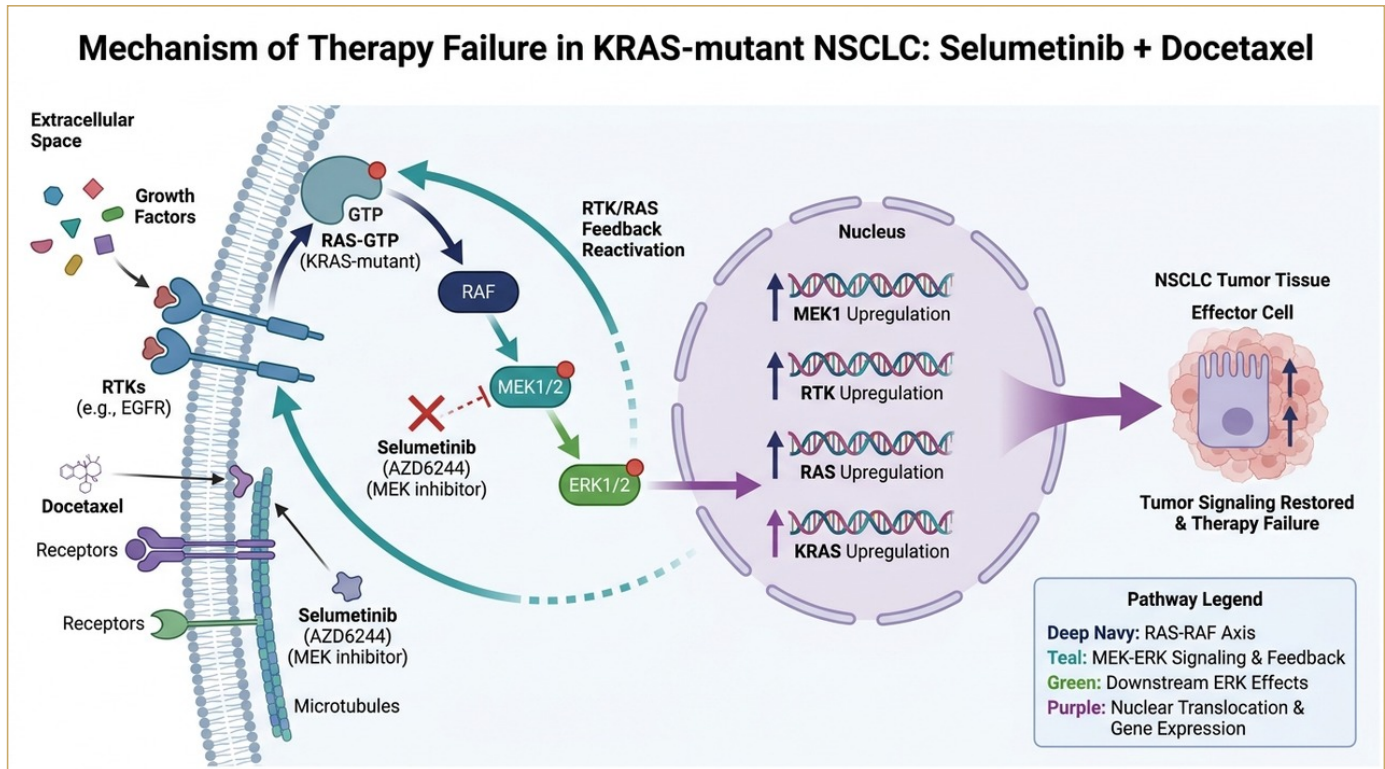
EGFR C797S abolishes covalent cysteine bond required by osimertinib; cis/trans with T790M dictates options

BiRAGAS pattern P7 · target-mutation

Citation: Thress KS et al. Nat Med 2015;21:560-562, PMID 25939061

selumetinib (AZD6244) + docetaxel

NSCLC (KRAS-mutant)



Indication: NSCLC (KRAS-mutant)

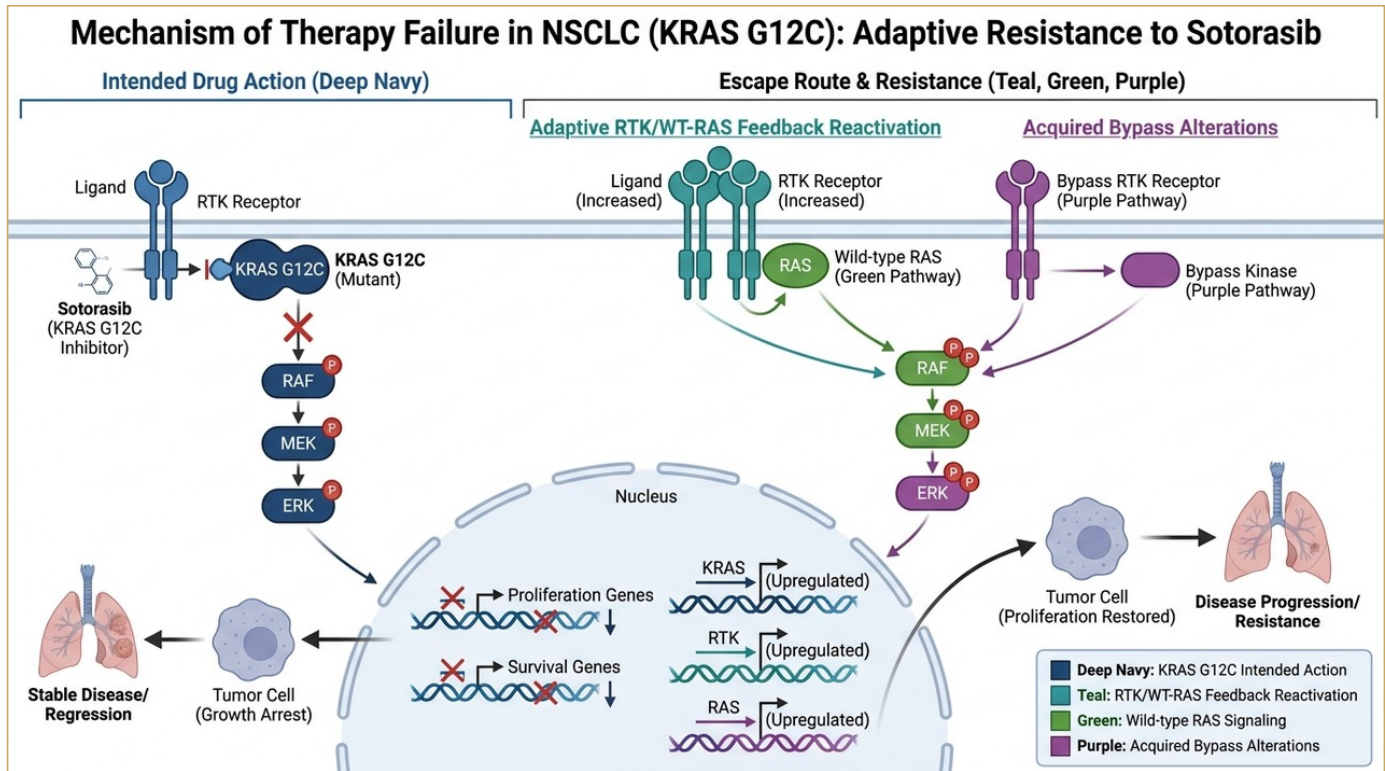
Resistance / failure mechanism:

MEK inhibition alone triggers RTK/RAS feedback reactivation of ERK; KRAS status insufficient to confer MEK dependence

BiRAGAS pattern P2 · feedback-reactivation

Citation: Janne PA et al. JAMA 2017;317:1844-1853, PMID 28492898

[ClinicalTrials.gov: NCT01933932](https://clinicaltrials.gov/ct2/show/study/NCT01933932)



Indication: NSCLC (KRAS G12C)

Resistance / failure mechanism:

Adaptive RTK/wild-type-RAS feedback reactivation and acquired bypass alterations blunt durability

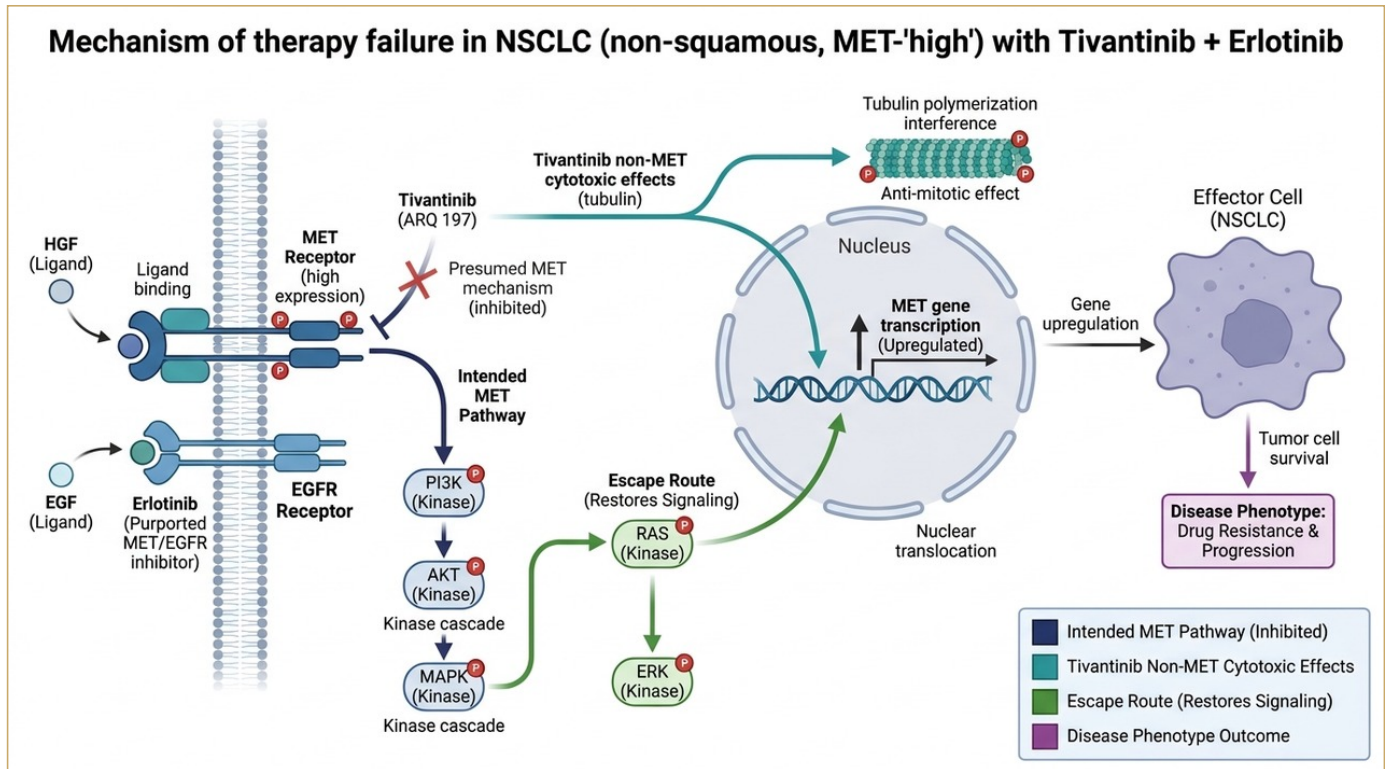
BiRAGAS pattern P2 · feedback-reactivation

Citation: de Langen AJ et al. Lancet 2023;401:733-746, PMID 36764316

ClinicalTrials.gov: NCT04303780

tivantinib (ARQ 197) + erlotinib

NSCLC (non-squamous, MET-'high')



Indication: NSCLC (non-squamous, MET-'high')

Resistance / failure mechanism:

Tivantinib acts largely via non-MET cytotoxic (tubulin/anti-mitotic) effects, the presumed MET mechanism was not operative

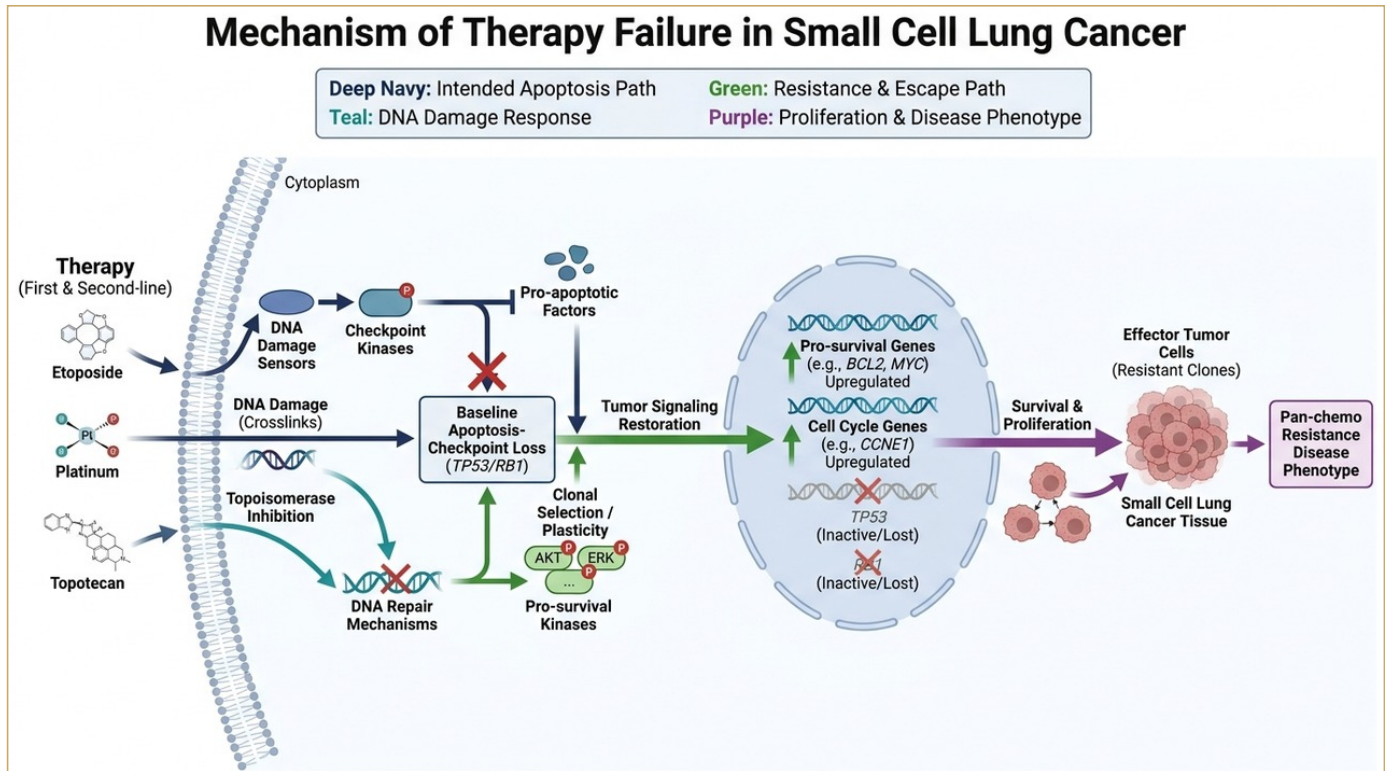
BiRAGAS pattern P1 · correlate-not-driver

Citation: Scagliotti G et al. J Clin Oncol 2015;33:2667-2674, PMID 26134280

ClinicalTrials.gov: [NCT01244191](https://clinicaltrials.gov/ct2/show/study/NCT01244191)

Etoposide + platinum (first-line), topotecan (second-line)

Small cell lung cancer



Indication: Small cell lung cancer

Resistance / failure mechanism:

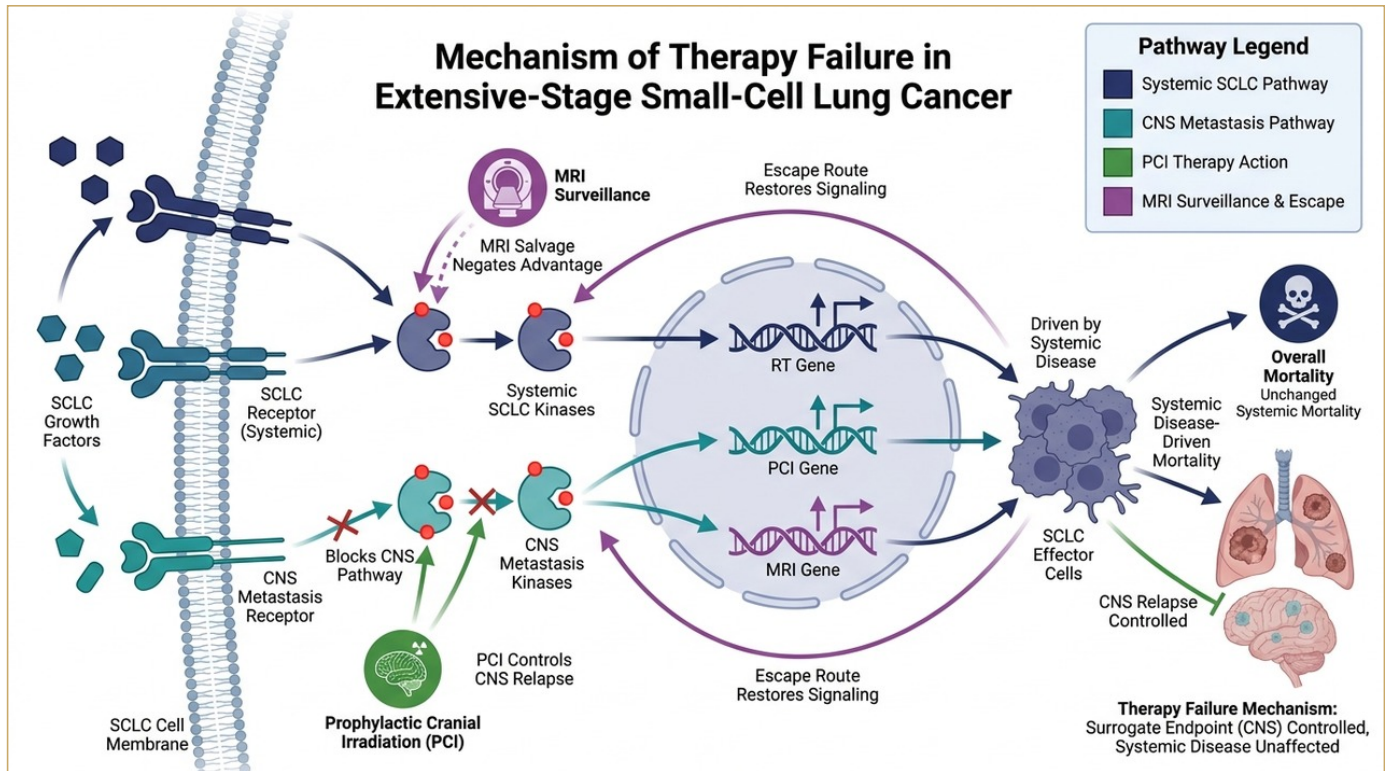
Baseline apoptosis-checkpoint loss (TP53/RB1) plus selection/plasticity of surviving clones yields swift pan-chemo resistance

BiRAGAS pattern P1 · DNA-repair/apoptosis-evasion

Citation: George J et al. Nature 2015;524(7563):47-53. PMID 26168399

Prophylactic cranial irradiation (PCI) vs MRI surveillance

Small-cell lung cancer (extensive-stage)



Indication: Small-cell lung cancer (extensive-stage)

Resistance / failure mechanism:

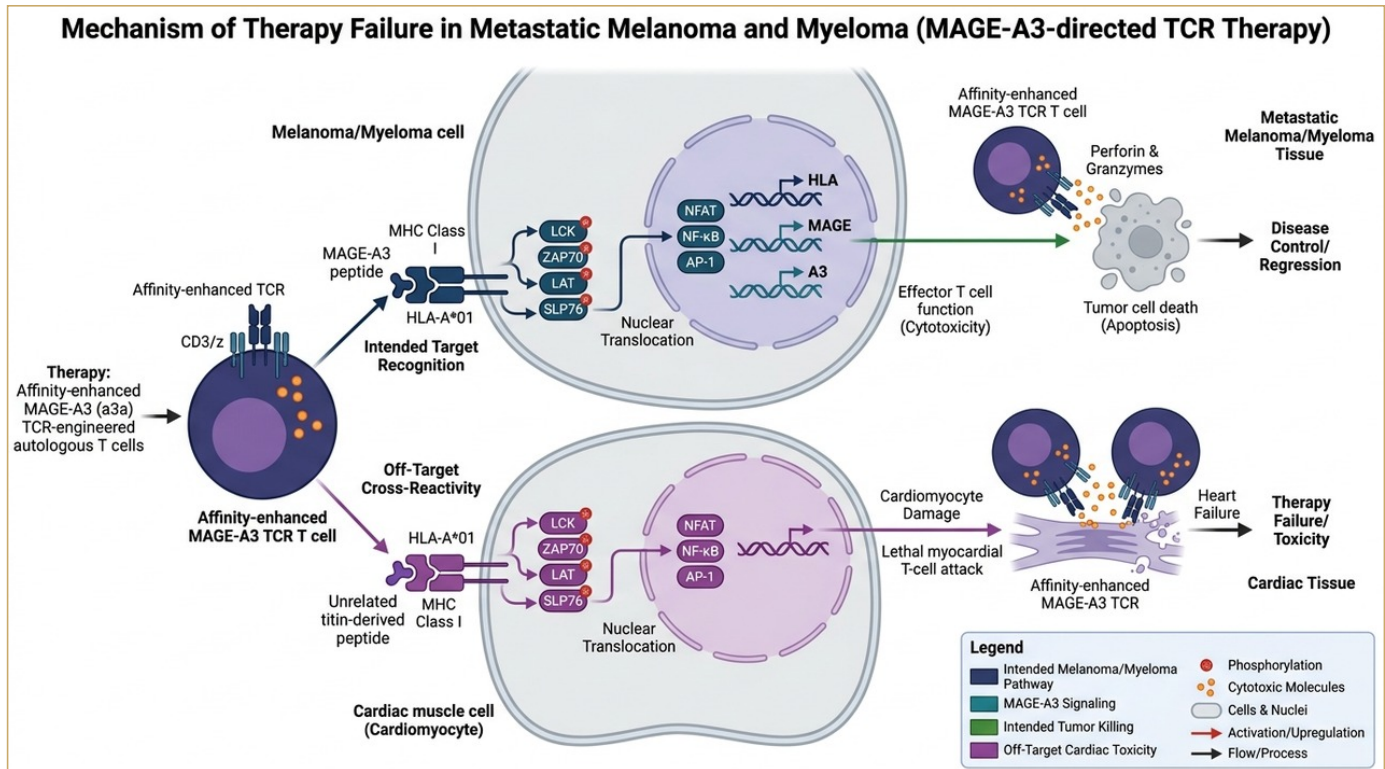
PCI controls a surrogate (CNS relapse) without altering systemic disease-driven mortality; MRI salvage negates advantage

BiRAGAS pattern P1 · correlate-not-driver

Citation: Takahashi T et al. Lancet Oncol 2017;18:663-671, PMID 28343976

Affinity-enhanced MAGE-A3 (a3a) TCR-engineered autologous T cells

Metastatic melanoma and myeloma (MAGE-A3-directed TCR therapy)



Indication: Metastatic melanoma and myeloma (MAGE-A3-directed TCR therapy)

Resistance / failure mechanism:

On-target/off-tumor cross-reactivity: affinity-enhanced TCR recognized an unrelated titin-derived peptide in cardiac muscle, causing lethal myocardial T-cell attack.

BiRAGAS pattern P4 · on-mechanism-toxicity

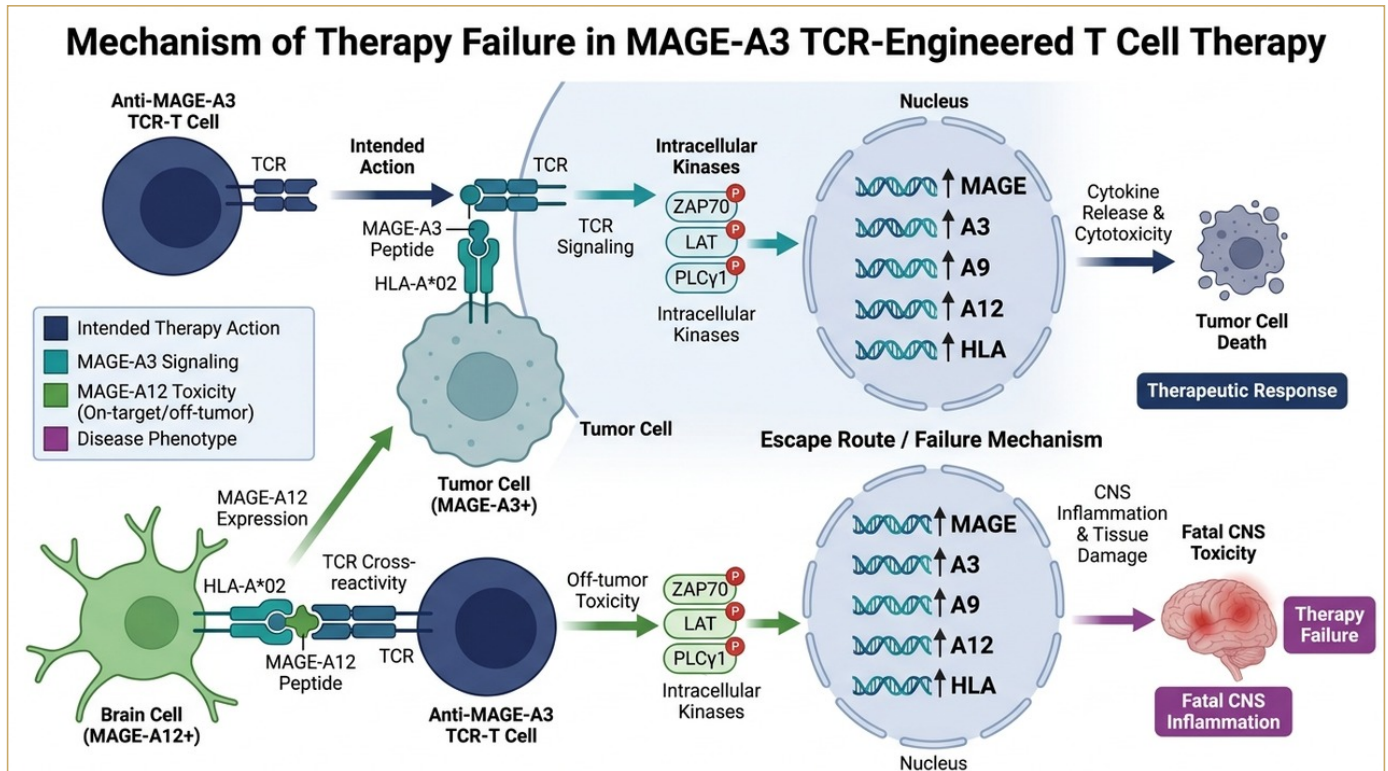
Citation: Linette GP et al. Blood 2013;122:863-871. PMID 23770775; Cameron BJ et al. Sci Transl Med 2013;5:197ra103.

PMID 23926201

ClinicalTrials.gov: NCT01350401

Anti-MAGE-A3 (a3a) TCR-engineered autologous T cells (HLA-A*02-restricted)

Metastatic melanoma / synovial sarcoma / esophageal (MAGE-A3 TCR, HLA-A*02)



Indication: Metastatic melanoma / synovial sarcoma / esophageal (MAGE-A3 TCR, HLA-A*02)

Resistance / failure mechanism:

On-target/off-tumor toxicity: unexpected MAGE-A12 expression in human brain recognized by the TCR, causing fatal CNS inflammation.

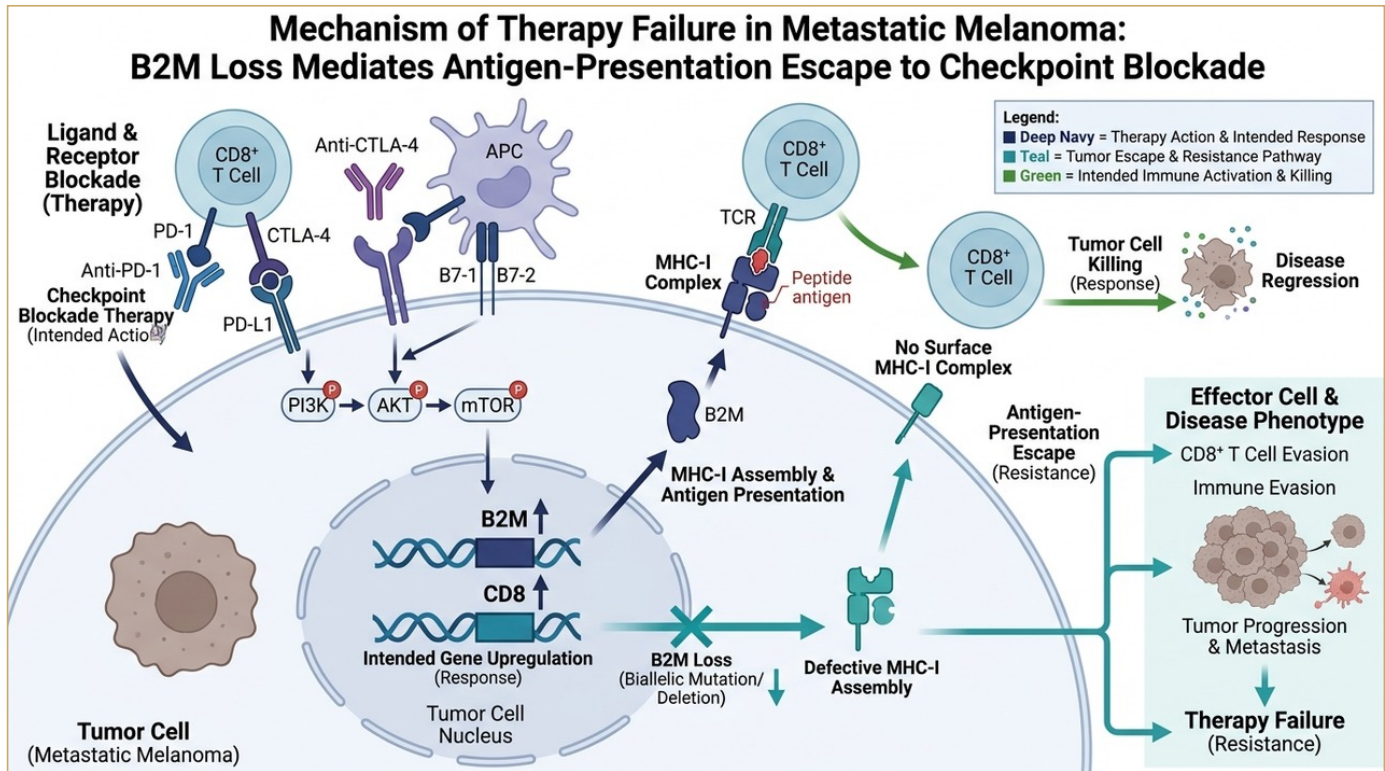
BiRAGAS pattern P4 · on-mechanism-toxicity

Citation: Morgan RA et al. J Immunother 2013;36:133-151. PMID 23377668

ClinicalTrials.gov: [NCT01273181](https://clinicaltrials.gov/ct2/show/study/NCT01273181)

Anti-PD-1 / anti-CTLA-4

Metastatic melanoma (resistance to checkpoint blockade)



Indication: Metastatic melanoma (resistance to checkpoint blockade)

Resistance / failure mechanism:

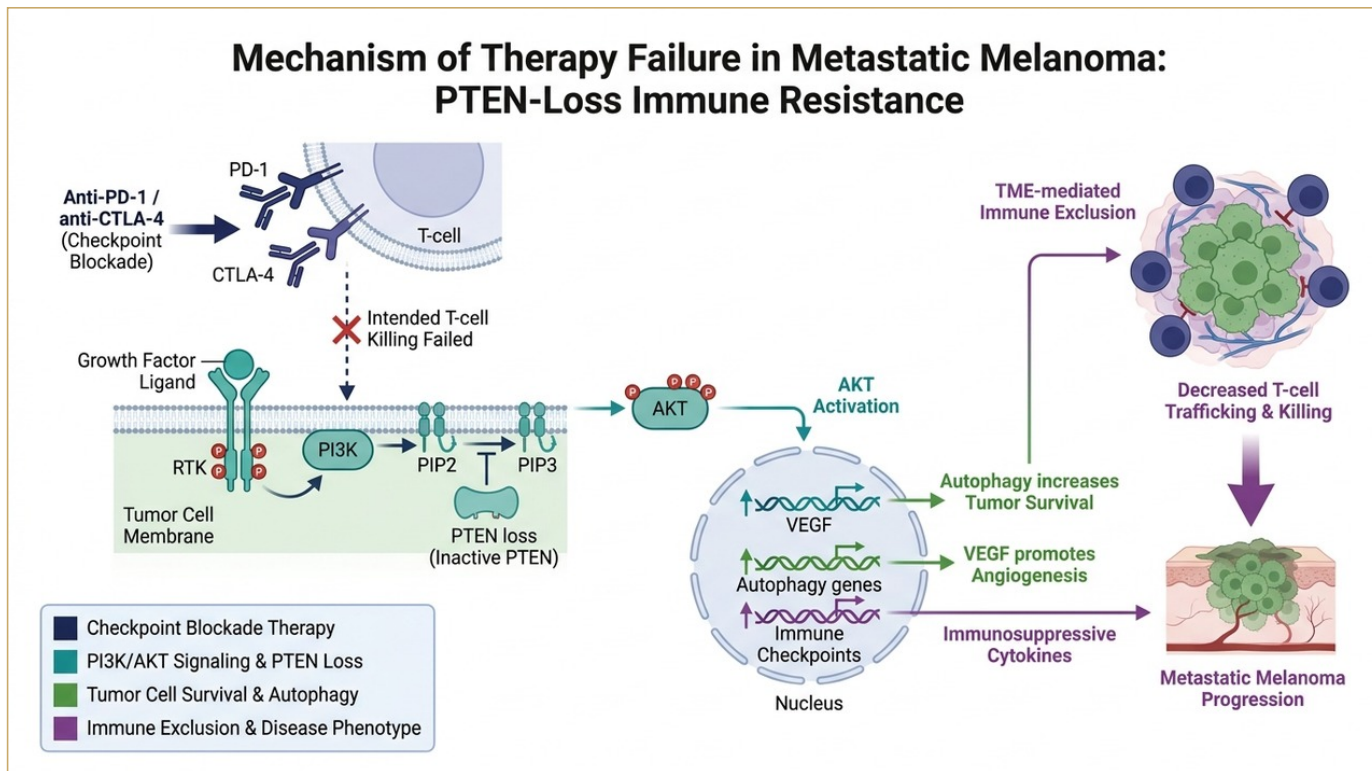
B2M loss (biallelic mutation/deletion) eliminates surface MHC-I assembly, so tumor cells cannot present antigen to CD8 T cells -> antigen-presentation escape.

BiRAGAS pattern P2 · antigen-escape

Citation: Sade-Feldman M et al. Nat Commun 2017;8:1136. PMID 29070816

Anti-PD-1 / anti-CTLA-4

Metastatic melanoma (PTEN-loss immune resistance)



Indication: Metastatic melanoma (PTEN-loss immune resistance)

Resistance / failure mechanism:

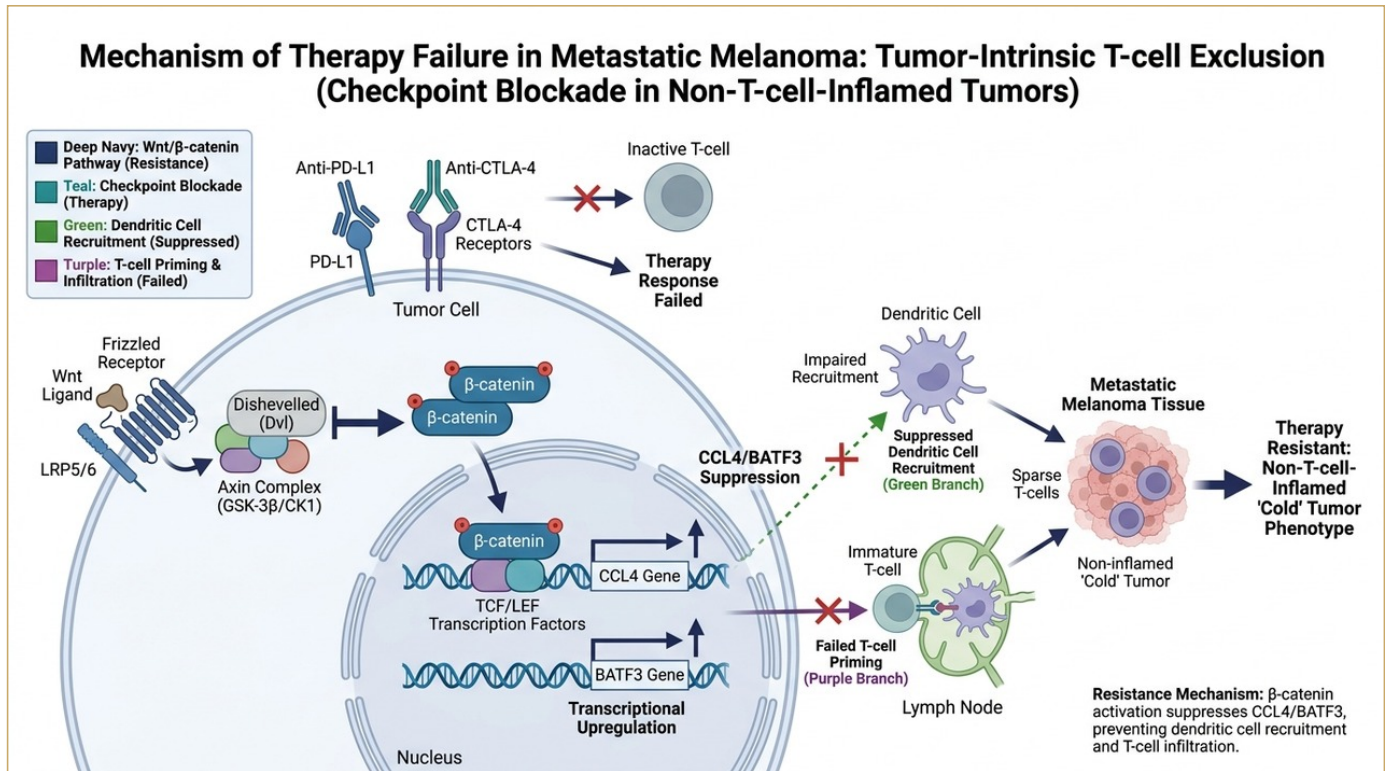
PTEN loss/PI3K-AKT activation increases immunosuppressive cytokines (VEGF) and autophagy, decreasing T-cell trafficking and killing -> TME-mediated immune exclusion.

BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Peng W et al. Cancer Discov 2016;6:202-216. PMID 26645196

Anti-PD-L1 / anti-CTLA-4 (mechanistic + correlative)

Metastatic melanoma (tumor-intrinsic T-cell exclusion)



Indication: Metastatic melanoma (tumor-intrinsic T-cell exclusion)

Resistance / failure mechanism:

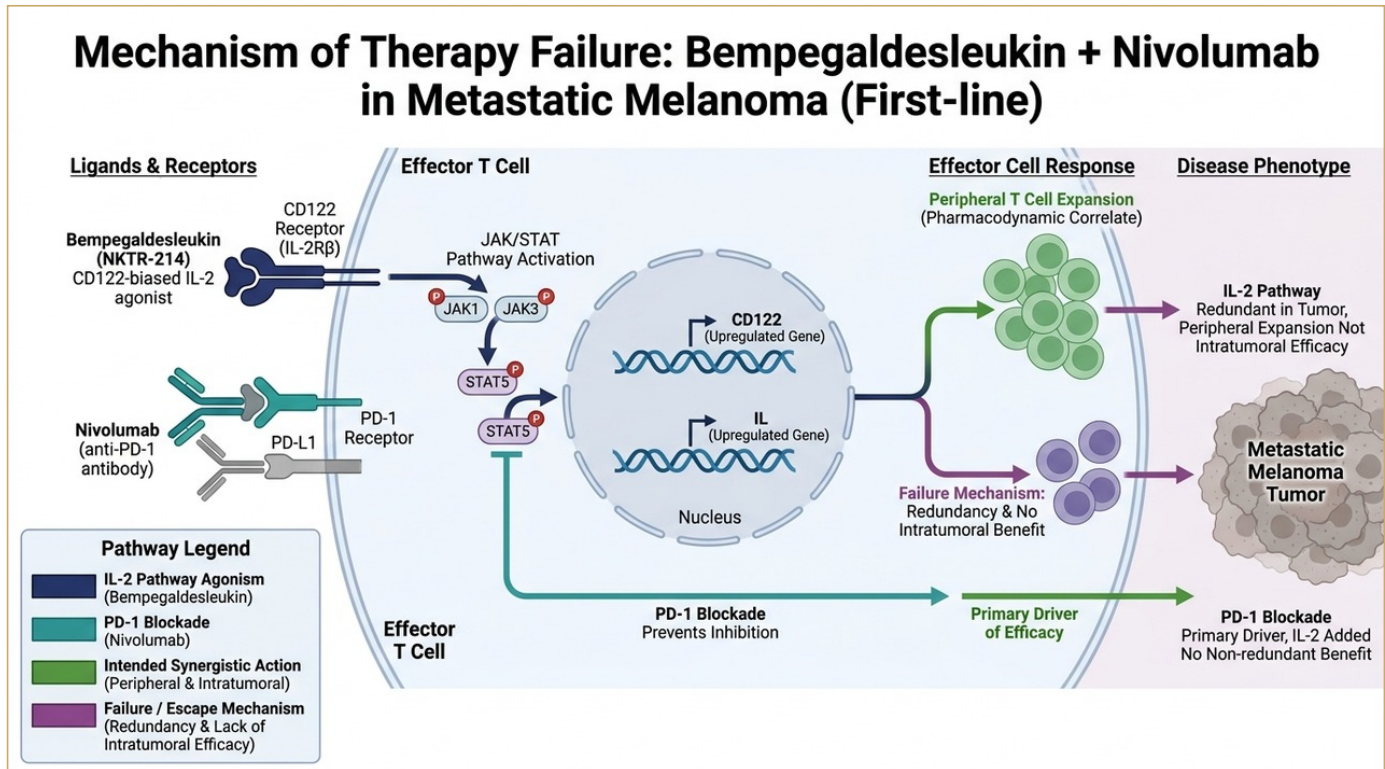
Beta-catenin activation suppresses CCL4/BATF3 dendritic-cell recruitment, preventing T-cell priming and infiltration -> non-inflamed 'cold' tumor unresponsive to checkpoint therapy.

BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Spranger S et al. Nature 2015;523:231-235. PMID 25970248

Bempegaldesleukin (NKTR-214) + nivolumab

Metastatic melanoma (first-line)



Indication: Metastatic melanoma (first-line)

Resistance / failure mechanism:

IL-2-pathway agonism did not add non-redundant benefit to PD-1 blockade; expanded peripheral T cells were a pharmacodynamic correlate that did not convert to intratumoral efficacy.

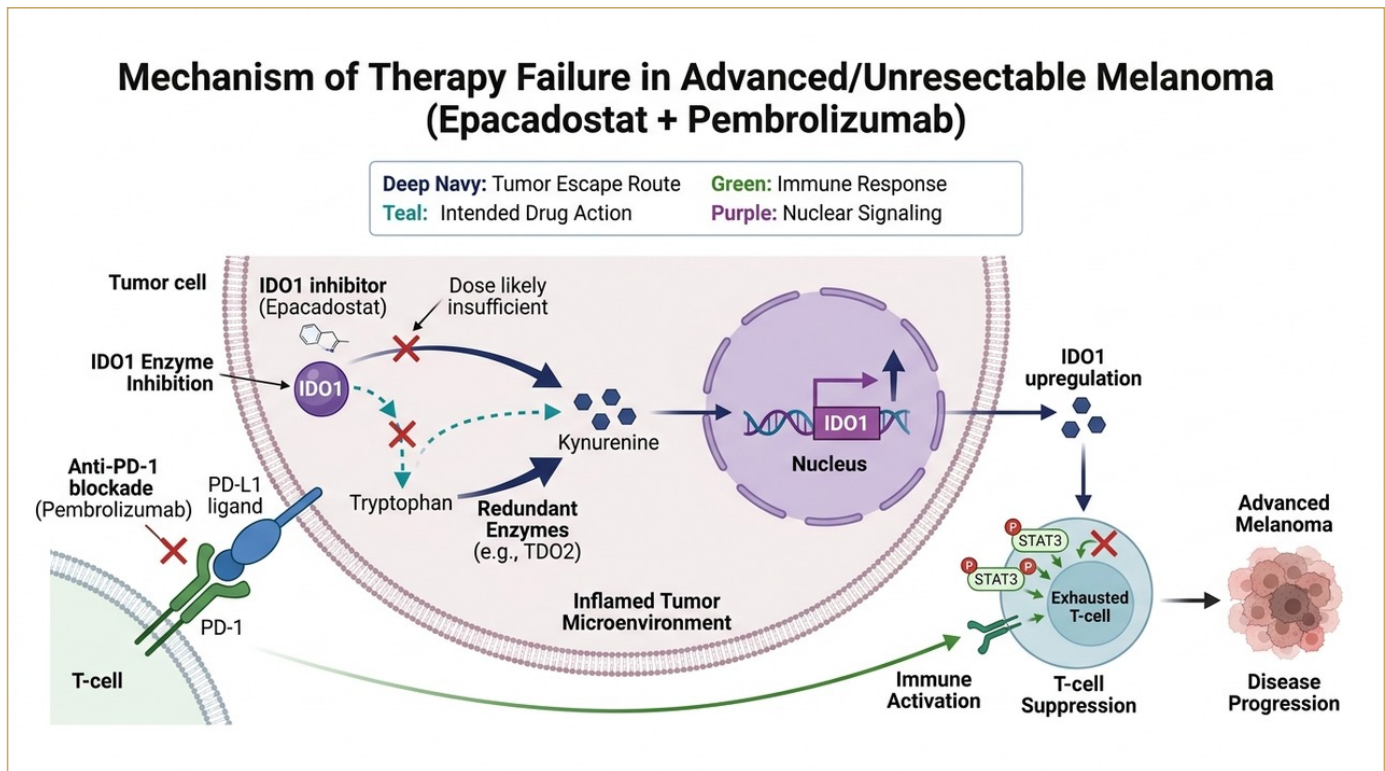
BiRAGAS pattern P6 · combination-no-rationale

Citation: Diab A et al. (PIVOT IO-001) J Clin Oncol 2023. PMID (verify, unresolved)

[ClinicalTrials.gov: NCT03635983](https://clinicaltrials.gov/ct2/show/study/NCT03635983)

Epacadostat + pembrolizumab

Advanced/unresectable melanoma (first-line)



Indication: Advanced/unresectable melanoma (first-line)

Resistance / failure mechanism:

IDO1 was a correlate of an inflamed tumor rather than a non-redundant driver of resistance; dose likely insufficient and kynurenine pathway redundant, so IDO1 inhibition added no benefit.

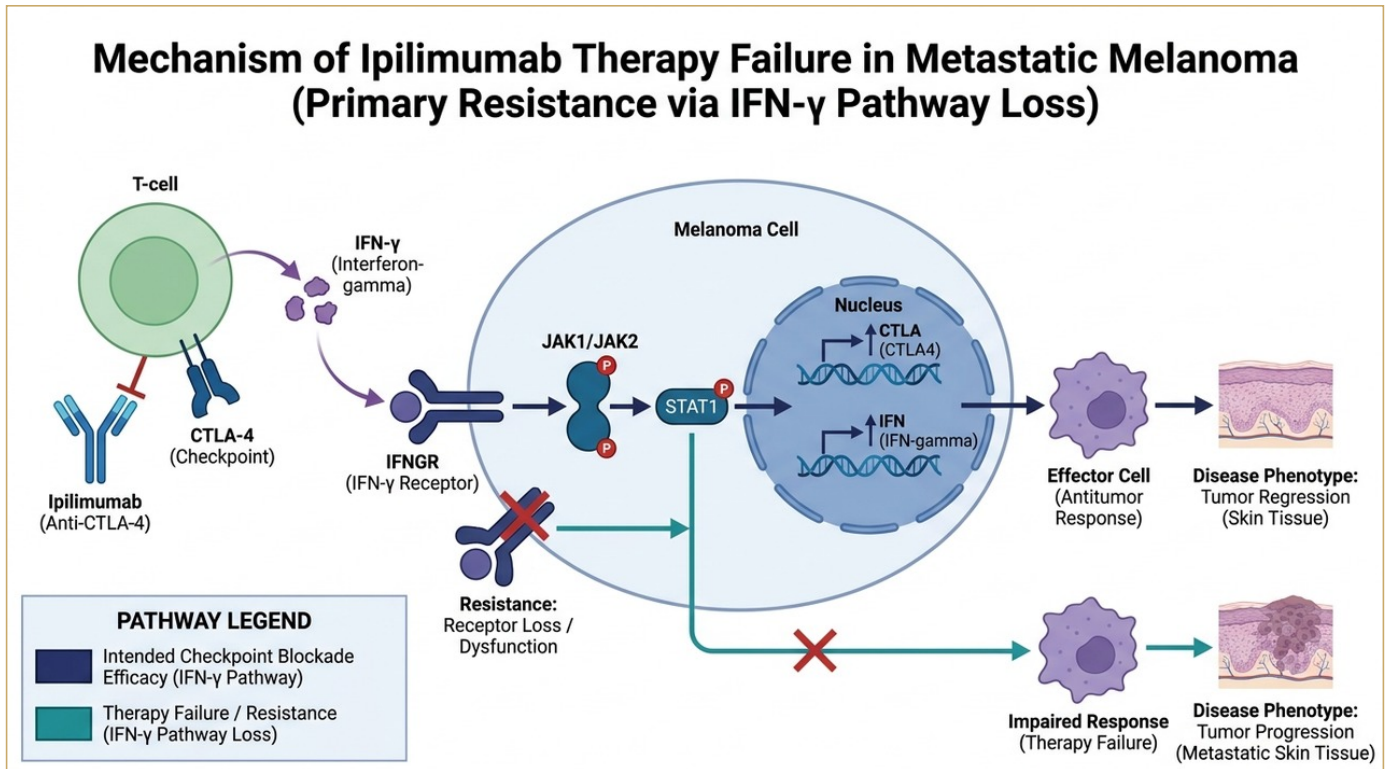
BiRAGAS pattern P6 · combination-no-rationale

Citation: Long GV et al. Lancet Oncol 2019;20:1083-1097. PMID 31221619

[ClinicalTrials.gov: NCT02752074](https://clinicaltrials.gov/ct2/show/study/NCT02752074)

Ipilimumab

Metastatic melanoma (primary resistance to anti-CTLA-4)



Indication: Metastatic melanoma (primary resistance to anti-CTLA-4)

Resistance / failure mechanism:

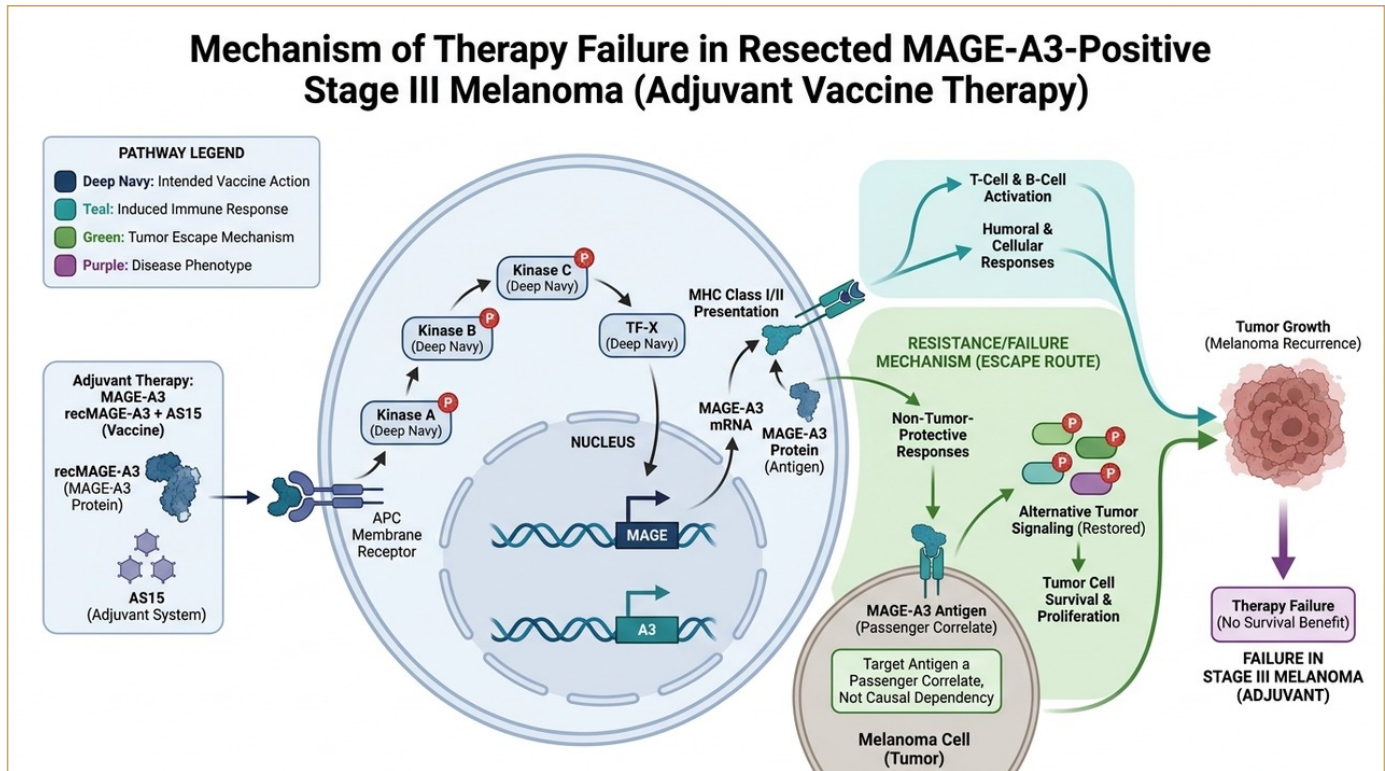
Loss of interferon-gamma receptor/downstream signaling impairs tumor response to T-cell-derived IFN-gamma, blunting the antiproliferative and antigen-presentation effects required for checkpoint efficacy.

BiRAGAS pattern P2 · target-mutation

Citation: Gao J et al. Cell 2016;167:397-404. PMID 27716510

MAGE-A3 recombinant protein vaccine (recMAGE-A3 + AS15)

Resected MAGE-A3-positive stage III melanoma (adjuvant)



Indication: Resected MAGE-A3-positive stage III melanoma (adjuvant)

Resistance / failure mechanism:

MAGE-A3 vaccination generated humoral/cellular responses that were not tumor-protective; target antigen a passenger correlate rather than a causal dependency.

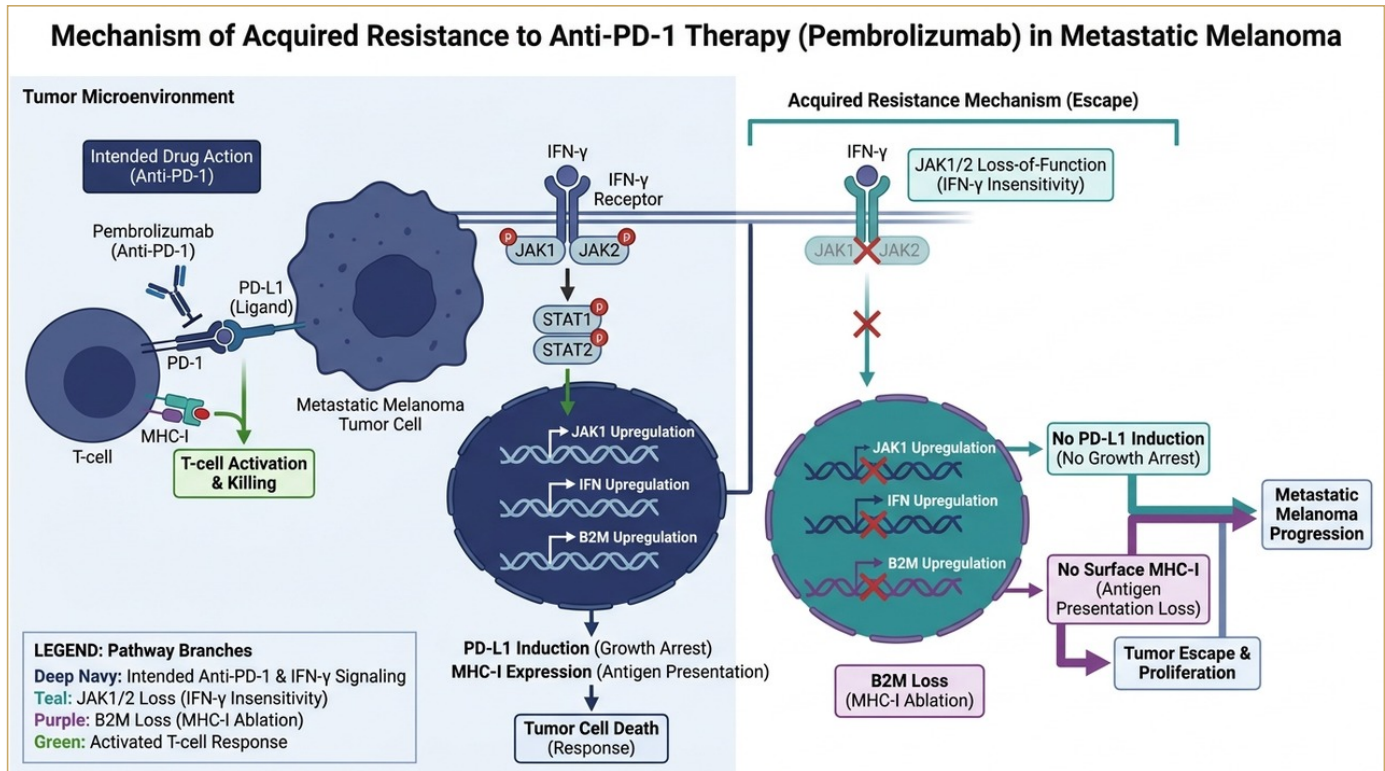
BiRAGAS pattern P1 · correlate-not-driver

Citation: Dreno B et al. Lancet Oncol 2018;19:916-929. PMID 30078459

ClinicalTrials.gov: [NCT00796445](https://clinicaltrials.gov/ct2/show/study/NCT00796445)

Pembrolizumab

Metastatic melanoma (acquired resistance to anti-PD-1)



Indication: Metastatic melanoma (acquired resistance to anti-PD-1)

Resistance / failure mechanism:

JAK1/2 loss-of-function abolishes IFN-gamma sensitivity (no PD-L1 induction, no growth arrest); B2M loss ablates surface MHC-I -> combined interferon-insensitivity and antigen-presentation loss.

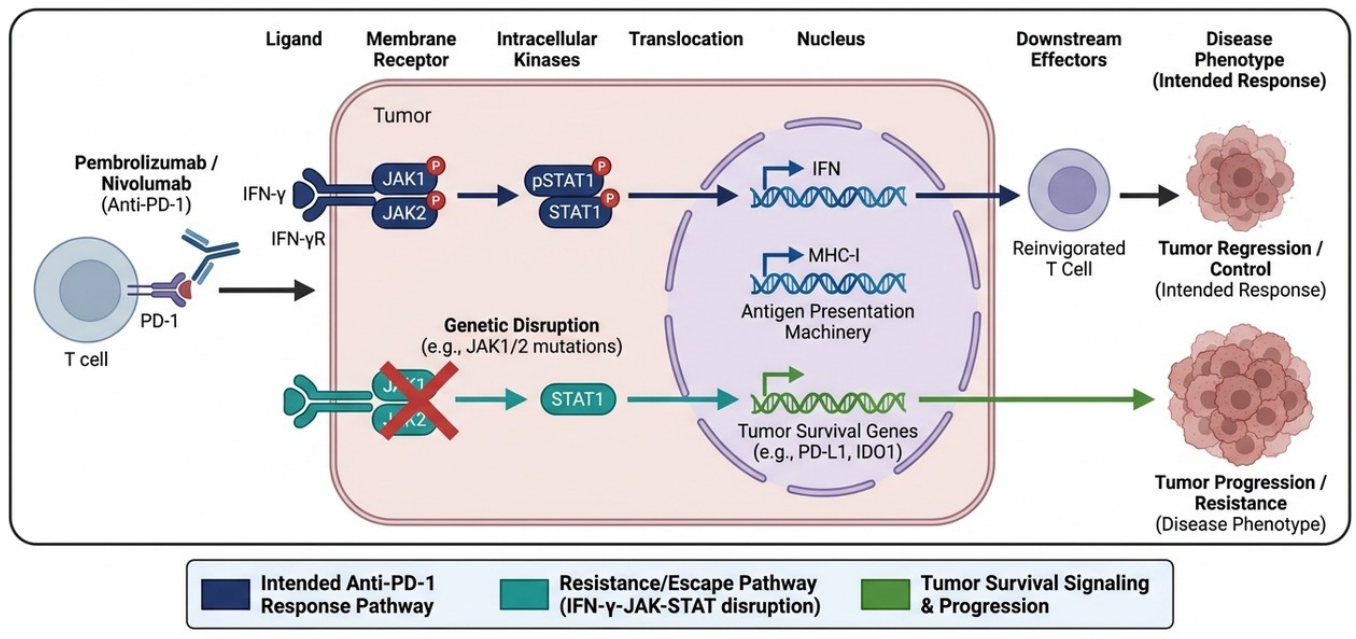
BiRAGAS pattern P2 · target-mutation

Citation: Zaretsky JM et al. N Engl J Med 2016;375:819-829. PMID 27433843

Pembrolizumab / nivolumab

Metastatic melanoma (primary resistance to anti-PD-1)

Mechanism of Therapy Failure in Metastatic Melanoma (Primary Resistance to Anti-PD-1 Checkpoint Blockade)



Indication: Metastatic melanoma (primary resistance to anti-PD-1)

Resistance / failure mechanism:

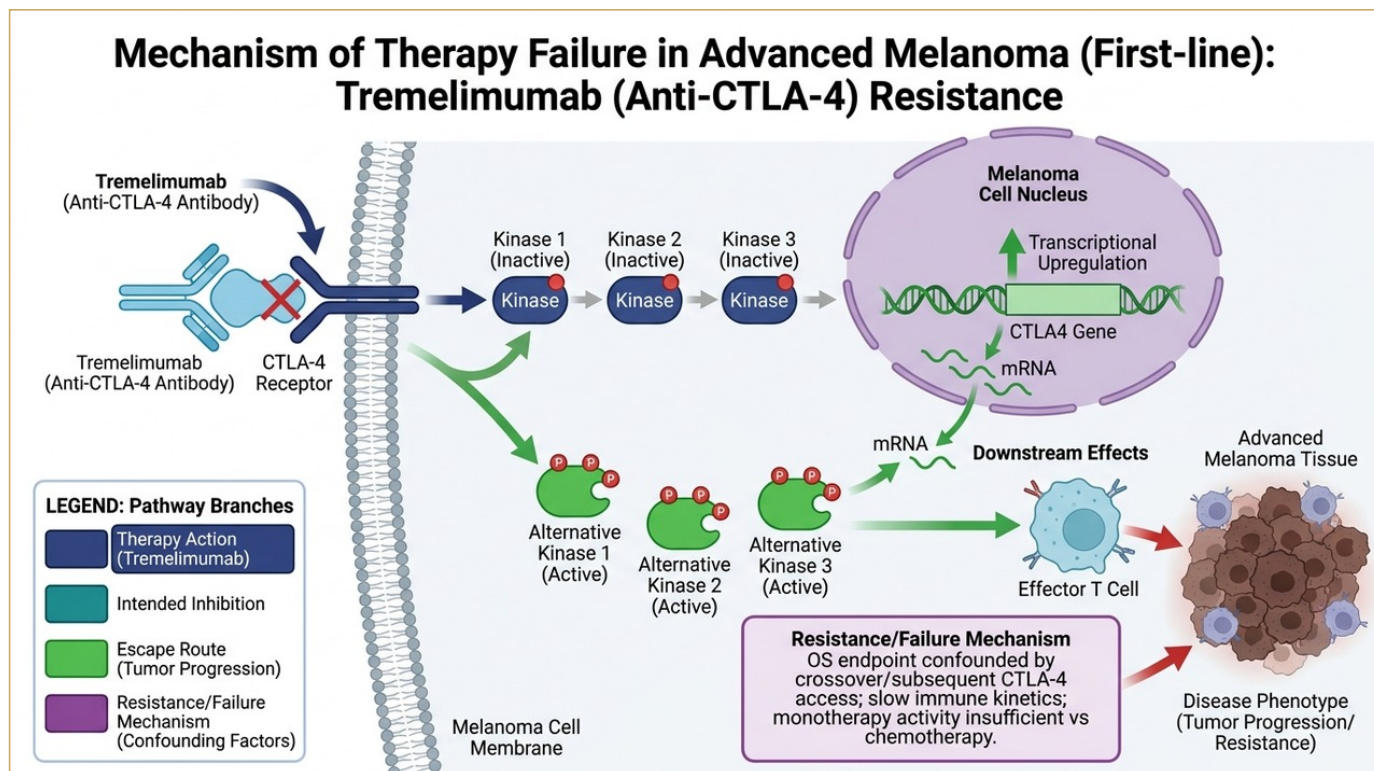
Genetic disruption of the IFN-gamma-JAK-STAT signaling axis renders tumor cells insensitive to interferon-mediated antiproliferative and antigen-presentation effects of reinvigorated T cells.

BiRAGAS pattern P2 · target-mutation

Citation: Shin DS et al. Cancer Discov 2017;7:188-201. PMID 27903500

Tremelimumab

Advanced melanoma (first-line)



Indication: Advanced melanoma (first-line)

Resistance / failure mechanism:

OS endpoint confounded by crossover/subsequent CTLA-4 access and slow immune kinetics; monotherapy CTLA-4 activity insufficient vs chemotherapy comparator.

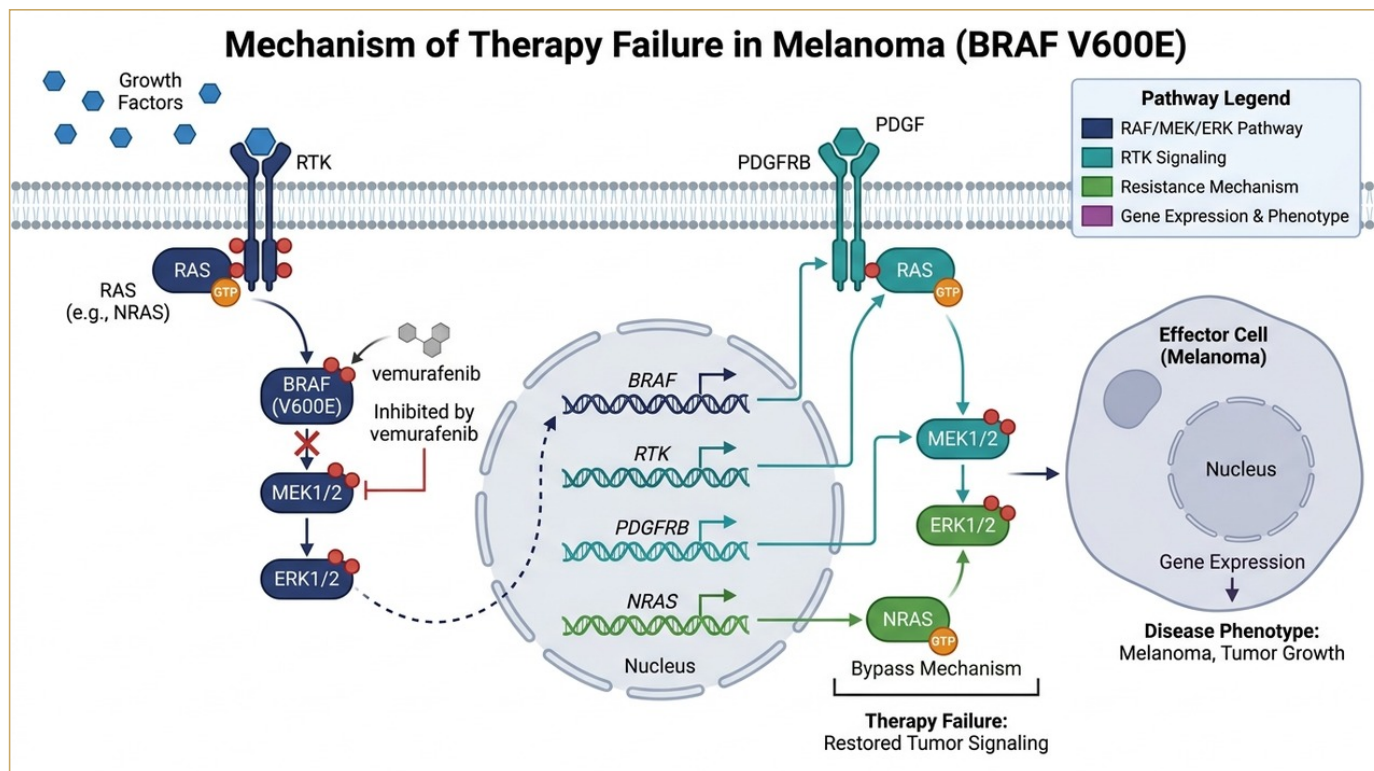
BiRAGAS pattern P5 · correlate-not-driver

Citation: Ribas A et al. J Clin Oncol 2013;31:616-622. PMID 23295794

[ClinicalTrials.gov: NCT00257205](https://clinicaltrials.gov/ct2/show/study/NCT00257205)

vemurafenib

Melanoma (BRAF V600E)



Indication: Melanoma (BRAF V600E)

Resistance / failure mechanism:

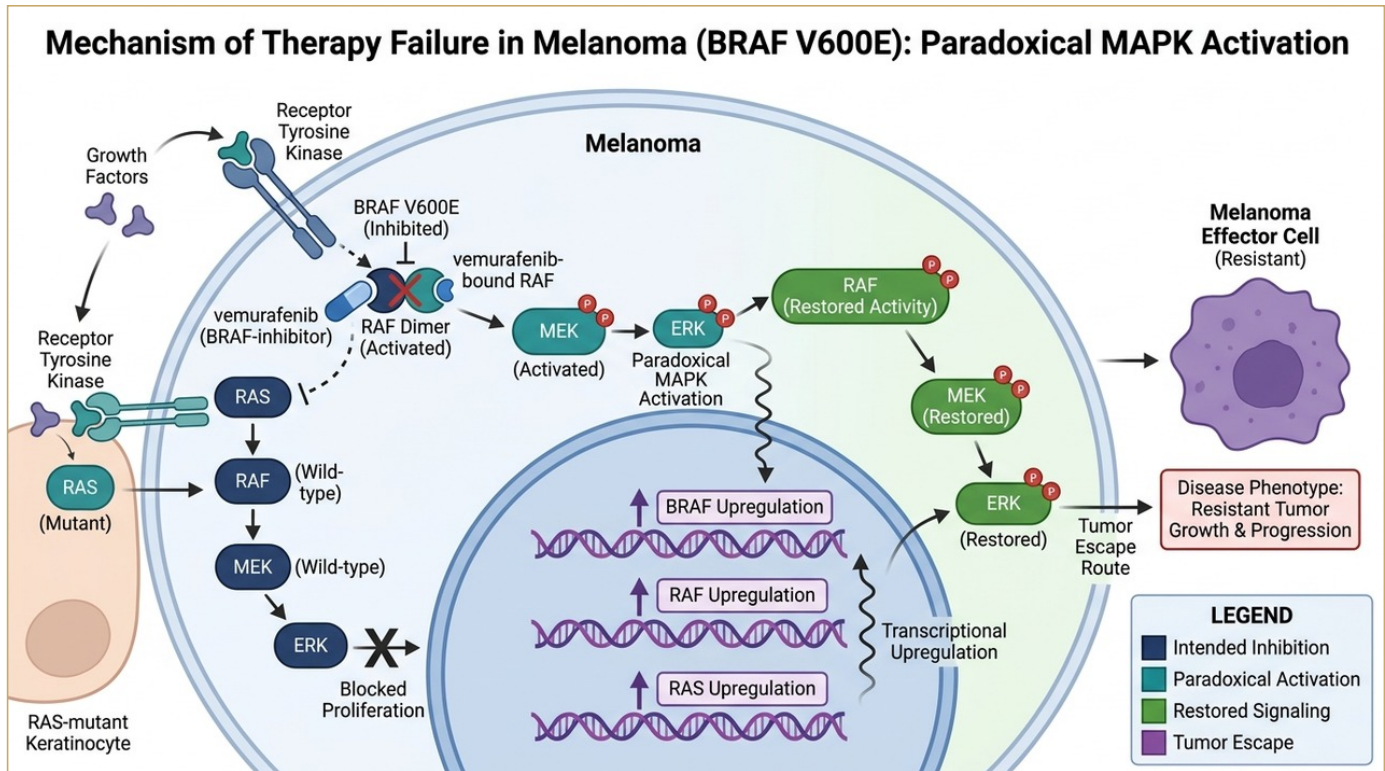
RTK upregulation (PDGFRB) or NRAS mutation reactivates MEK/ERK, bypassing BRAF inhibition

BiRAGAS pattern P2 · bypass/parallel-pathway

Citation: Nazarian R et al. Nature 2010;468:973-977, PMID 21107323

vemurafenib (BRAF-inhibitor monotherapy)

Melanoma (BRAF V600E)



Indication: Melanoma (BRAF V600E)

Resistance / failure mechanism:

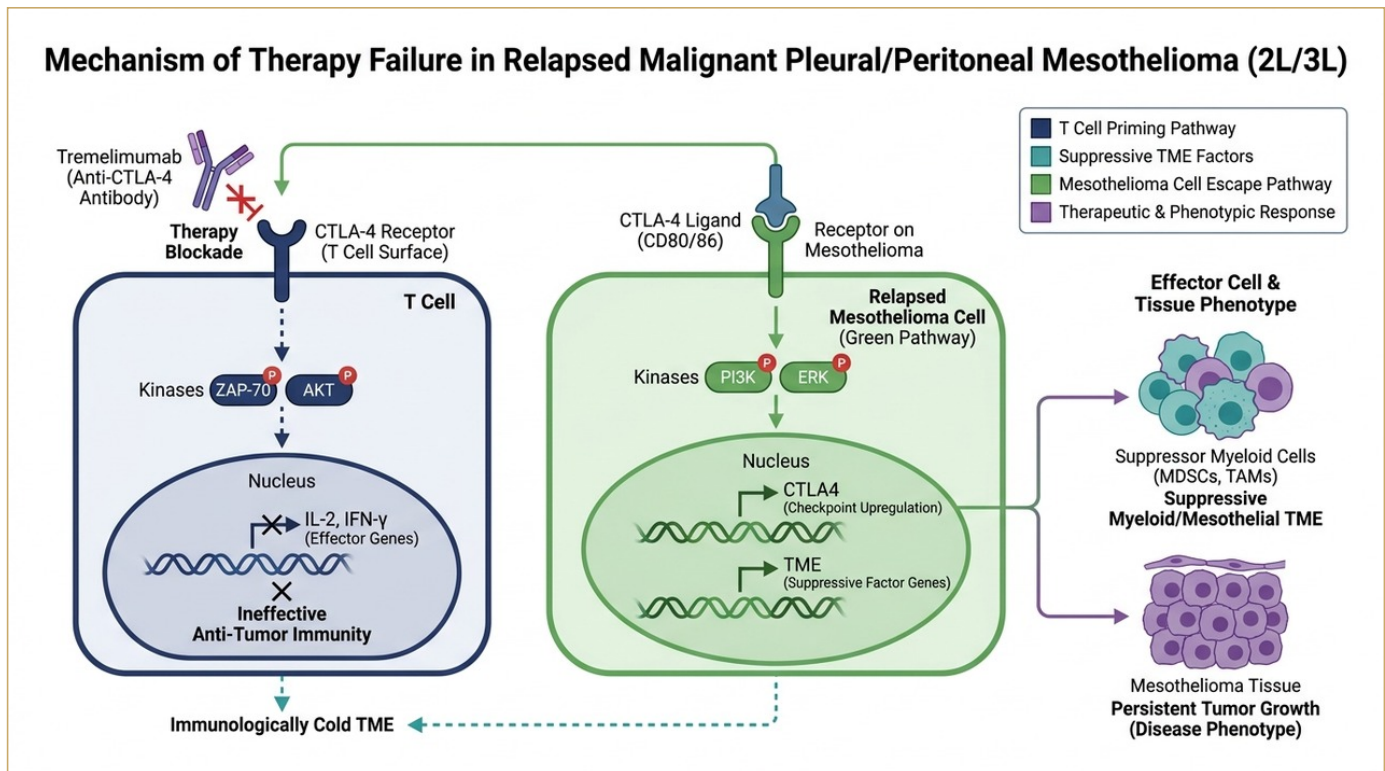
Paradoxical MAPK activation: BRAF inhibitor drives RAF dimerization and ERK signaling in RAS-mutant keratinocytes, rationale for adding MEK inhibitor

BiRAGAS pattern P4 · on-mechanism-toxicity

Citation: Su F et al. N Engl J Med 2012;366:207-215, PMID 22256804

Tremelimumab

Relapsed malignant pleural/peritoneal mesothelioma (2L/3L)



Indication: Relapsed malignant pleural/peritoneal mesothelioma (2L/3L)

Resistance / failure mechanism:

Mesothelioma is immunologically cold with a suppressive myeloid/mesothelial TME; single-agent CTLA-4 blockade could not generate effective anti-tumor immunity.

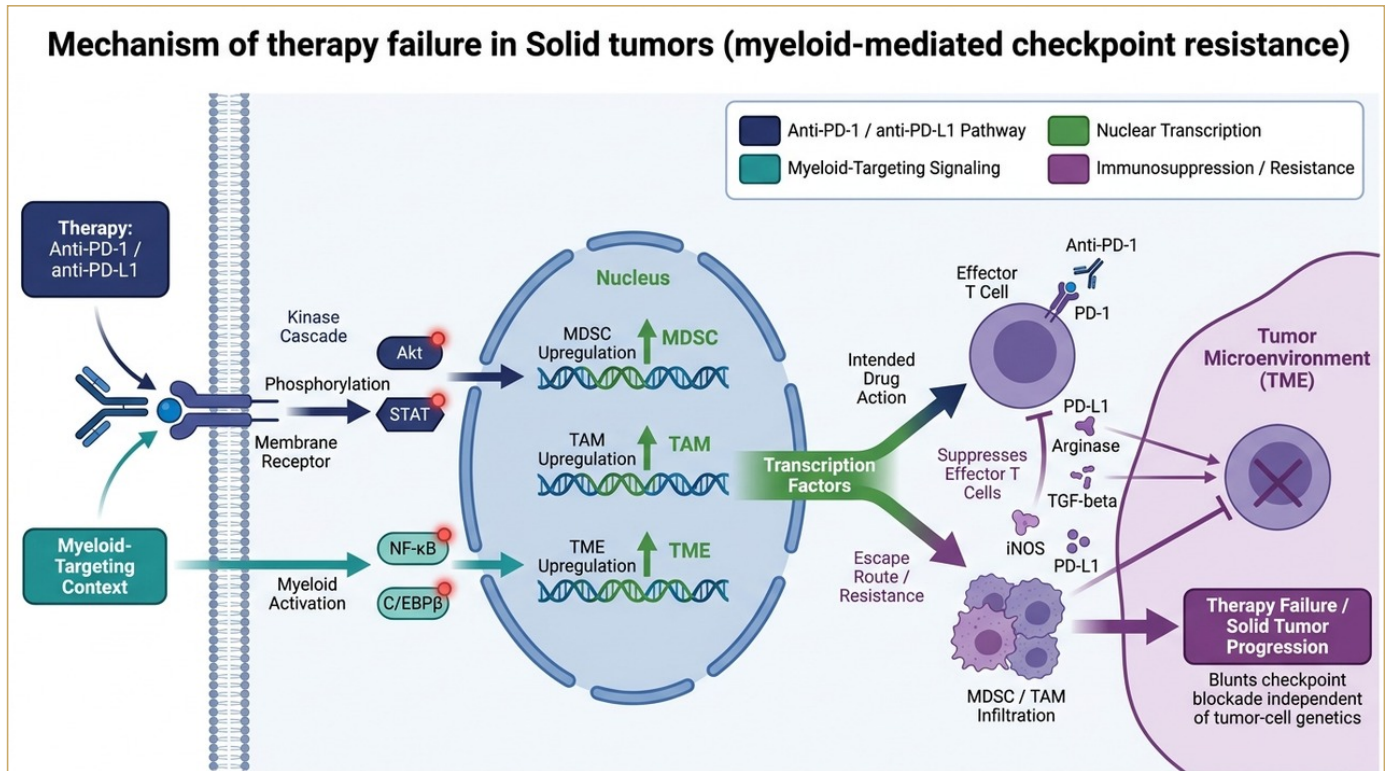
BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Maio M et al. Lancet Oncol 2017;18:1261-1273. PMID 28729154

[ClinicalTrials.gov: NCT01843374](https://clinicaltrials.gov/ct2/show/study/NCT01843374)

Anti-PD-1 / anti-PD-L1 (with myeloid-targeting context)

Solid tumors (myeloid-mediated checkpoint resistance)



Indication: Solid tumors (myeloid-mediated checkpoint resistance)

Resistance / failure mechanism:

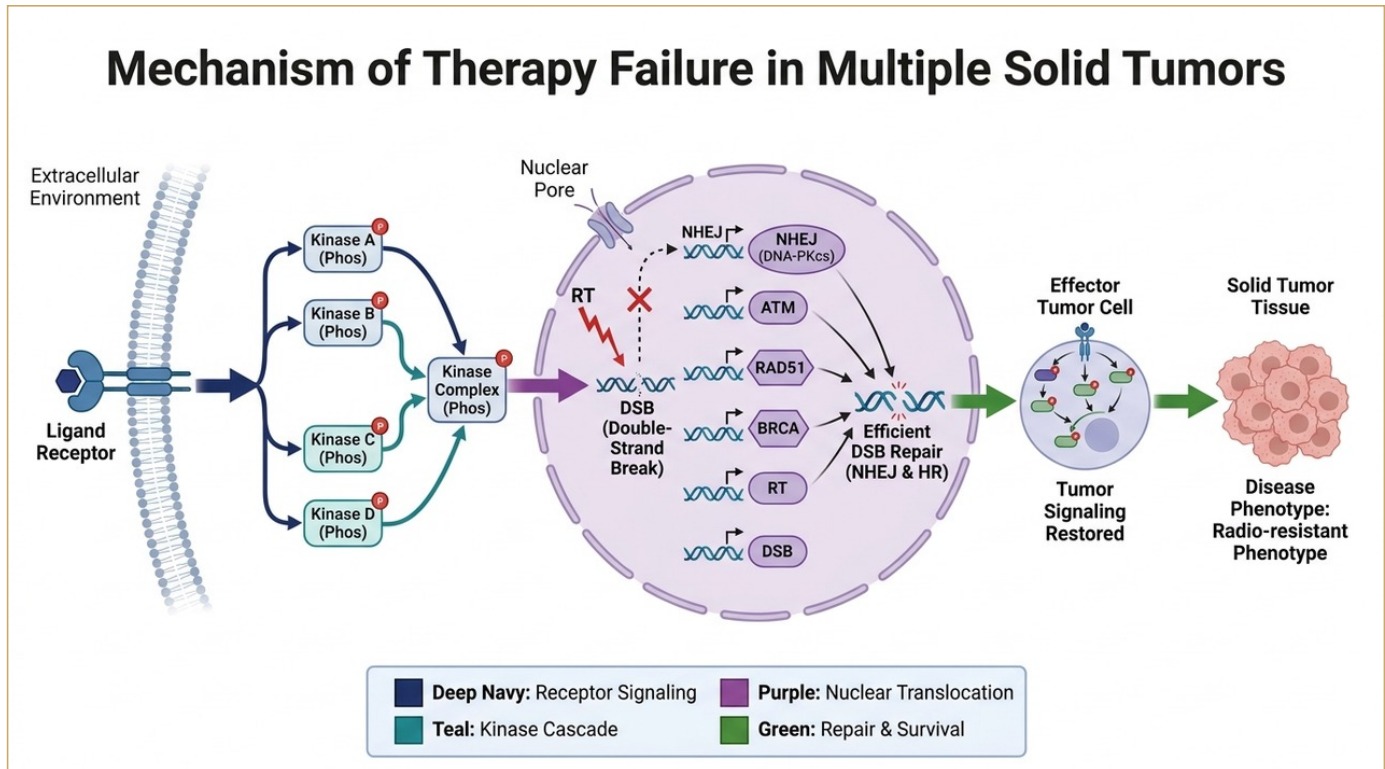
MDSC/tumor-associated-macrophage infiltration suppresses effector T cells (arginase, iNOS, TGF-beta, PD-L1), producing a suppressive TME that blunts checkpoint blockade independent of tumor-cell genetics.

BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Highfill SL et al. Sci Transl Med 2014;6:237ra67. PMID 24848257

N/A, radioresistance mechanism (DSB-repair upregulation)

Multiple solid tumors (mechanism)



Indication: Multiple solid tumors (mechanism)

Resistance / failure mechanism:

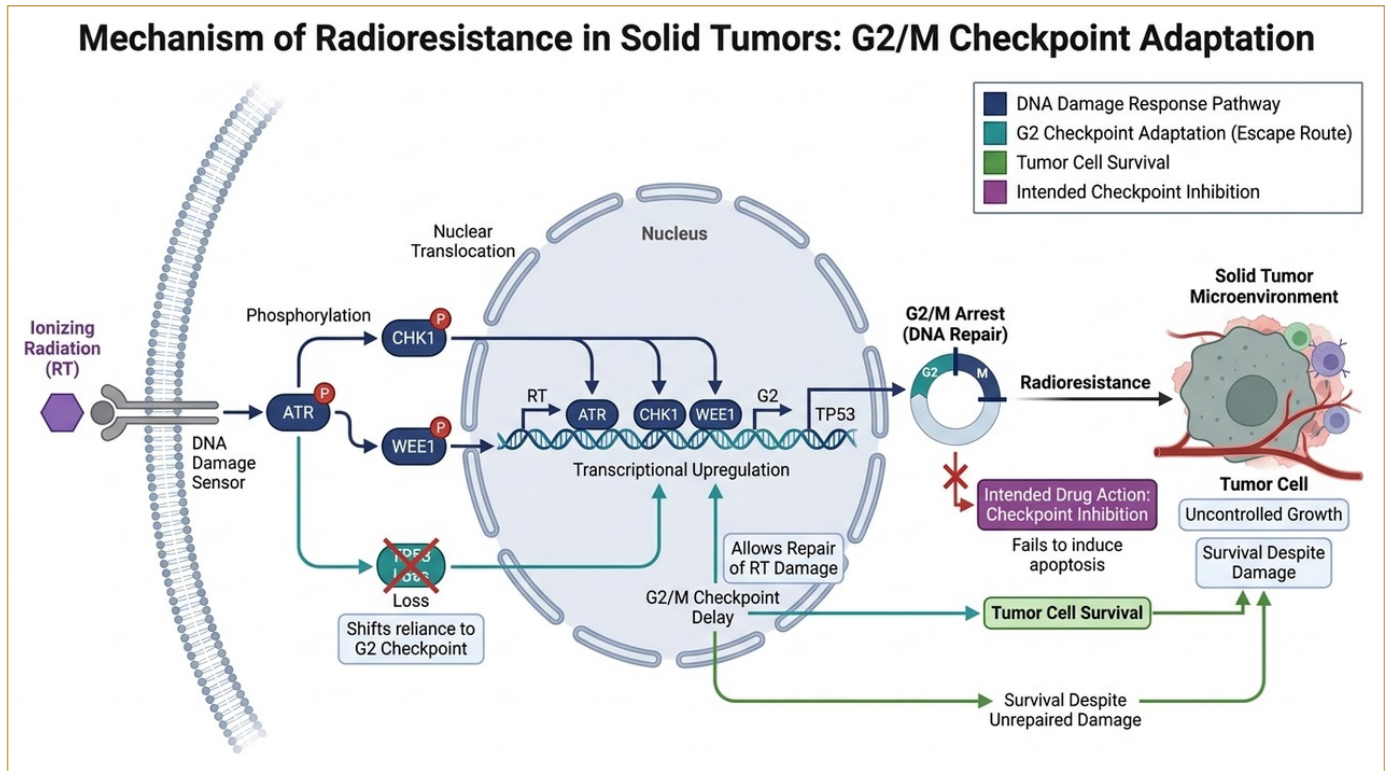
Efficient DSB repair removes the lethal lesions RT depends on; DNA-PKcs/ATM hyperactivation correlates with clinical radioresistance

BiRAGAS pattern P6 · DNA-repair/apoptosis-evasion

Citation: Goldstein M, Kastan MB. Annu Rev Med 2015;66:129-143, PMID 25423595

N/A, radioresistance mechanism (cell-cycle checkpoint adaptation, CHK1/WEE

Multiple solid tumors (mechanism)



Indication: Multiple solid tumors (mechanism)

Resistance / failure mechanism:

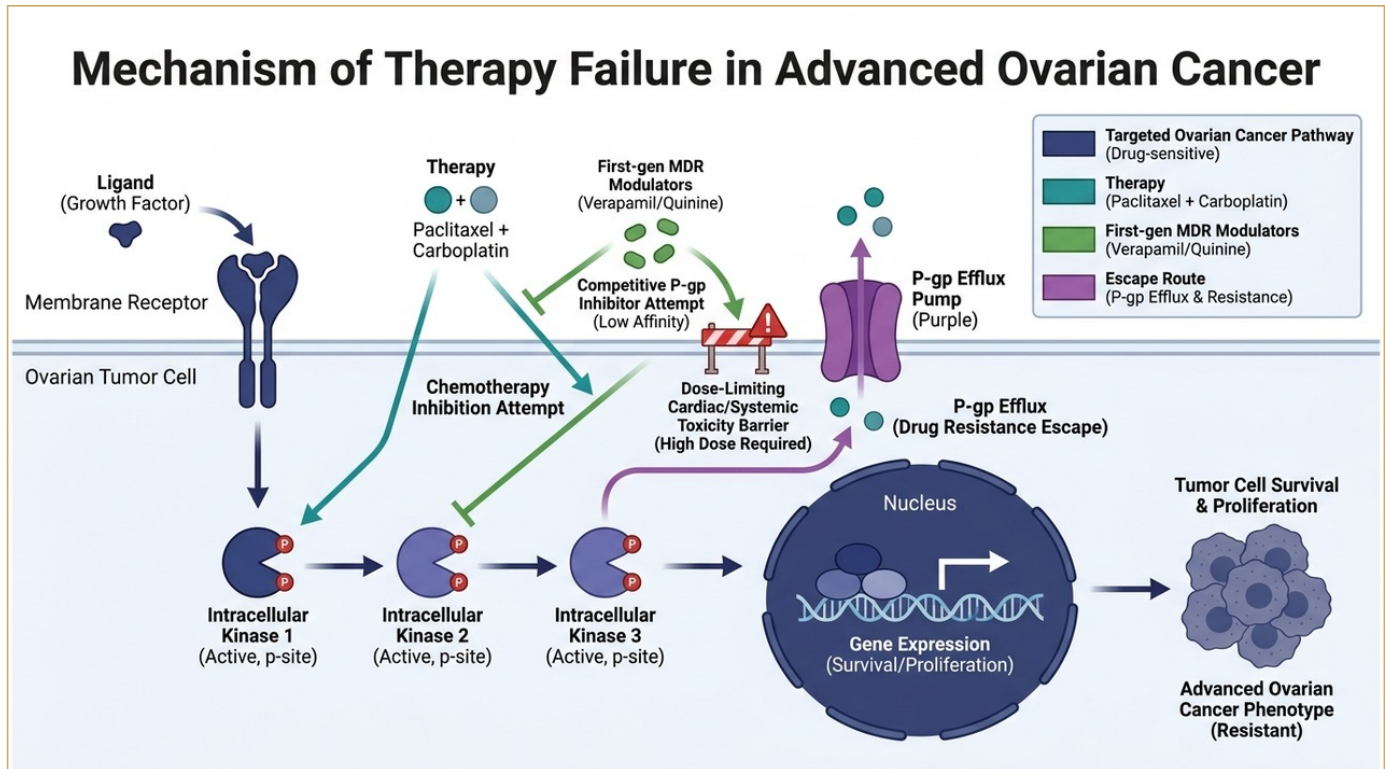
G2/M checkpoint delay allows repair of RT damage; TP53 loss shifts reliance to G2 checkpoint, enabling survival despite unrepaired damage

BiRAGAS pattern P6 · feedback-reactivation

Citation: Morgan MA, Lawrence TS. Clin Cancer Res 2015;21:2898-2904, PMID 26133775

Paclitaxel + carboplatin +/- first-generation MDR modulators (verapamil/qu) Advanced ovarian cancer

Advanced ovarian cancer



Indication: Advanced ovarian cancer

Resistance / failure mechanism:

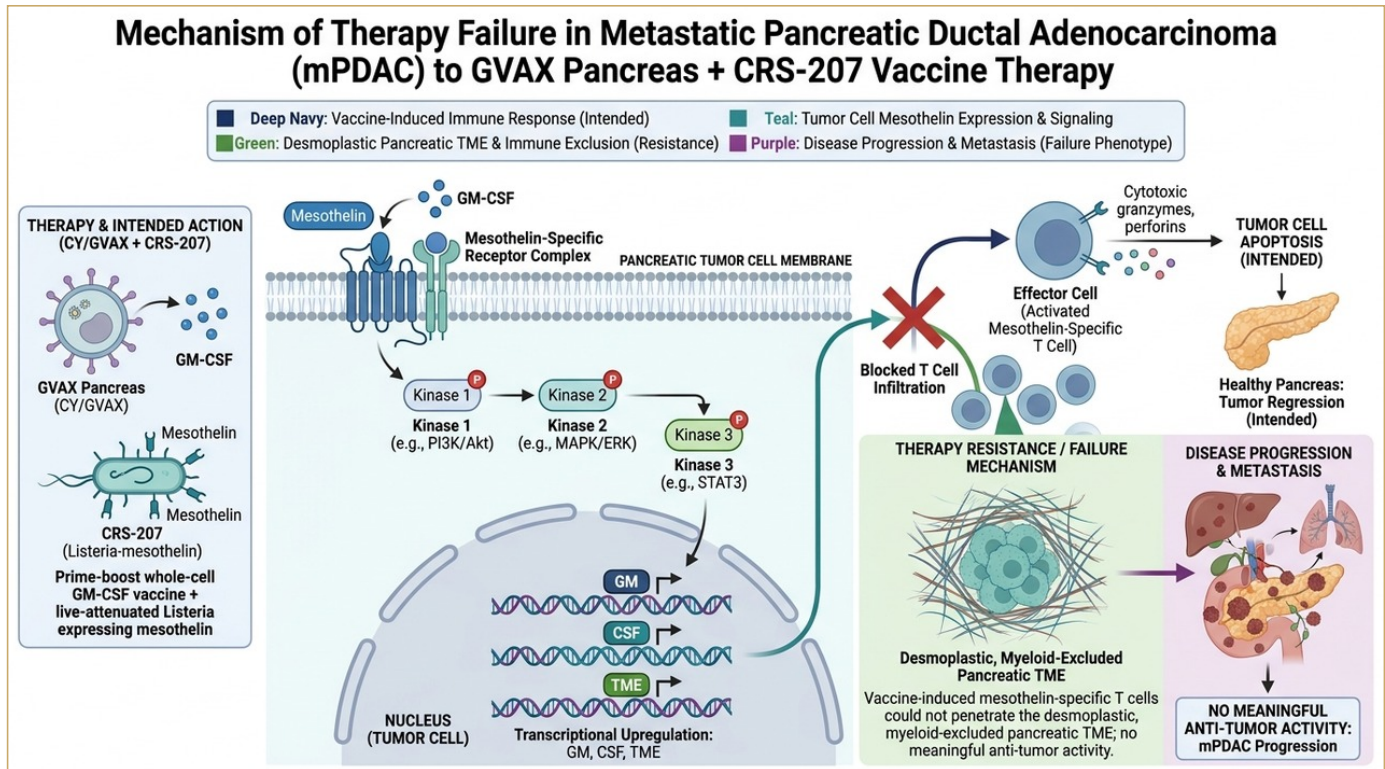
Low modulator affinity forced doses causing dose-limiting cardiac/systemic toxicity before achieving P-gp inhibition; on-mechanism toxicity barrier

BiRAGAS pattern P6 · on-mechanism-toxicity

Citation: Ozols RF et al. J Clin Oncol 1987;5(4):641-647 (verapamil modulation). PMID 3549931

GVAX pancreas (CY/GVAX) + CRS-207 (Listeria-mesothelin)

Metastatic pancreatic ductal adenocarcinoma



Indication: Metastatic pancreatic ductal adenocarcinoma

Resistance / failure mechanism:

Vaccine-induced mesothelin-specific T cells could not penetrate the desmoplastic, myeloid-excluded pancreatic TME; no meaningful anti-tumor activity.

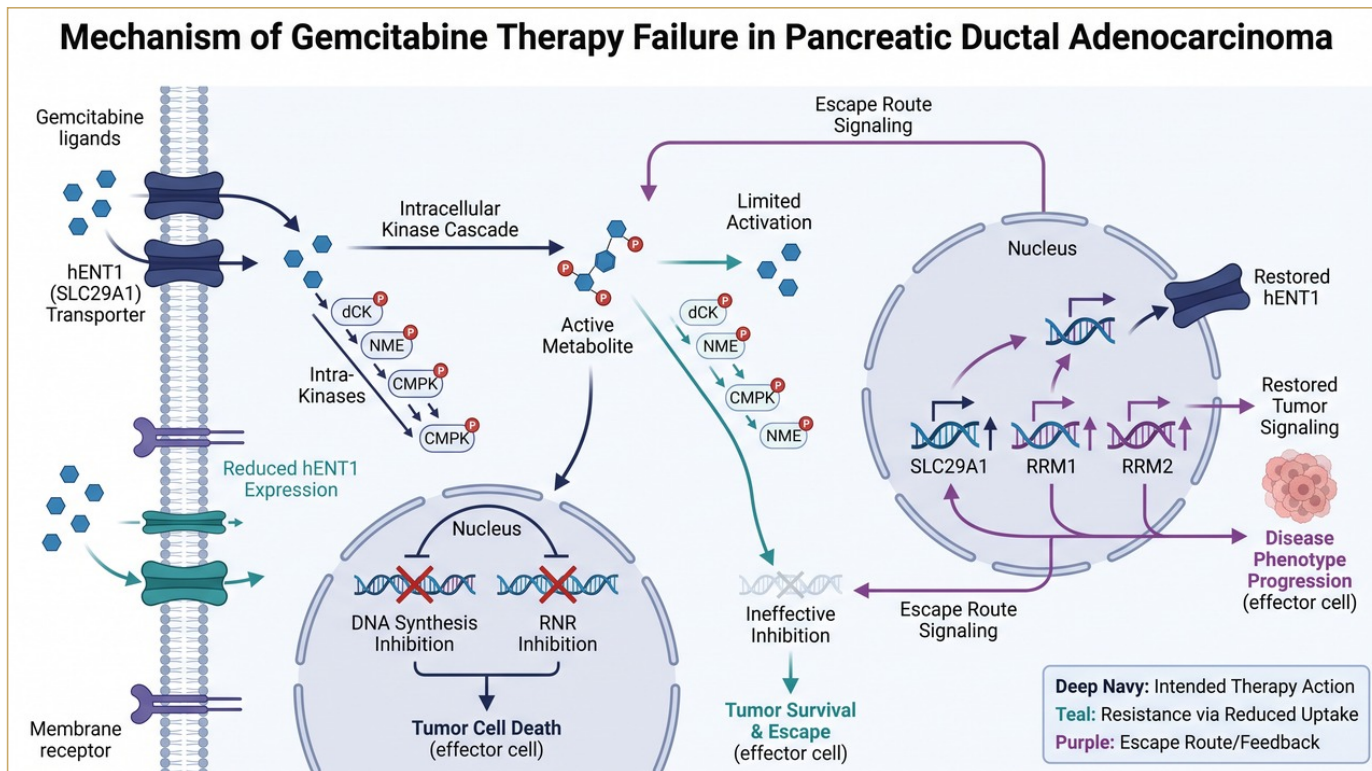
BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Le DT et al. (ECLIPSE) Clin Cancer Res 2019. PMID (verify, unresolved)

[ClinicalTrials.gov: NCT02004262](https://clinicaltrials.gov/ct2/show/study/NCT02004262)

Gemcitabine

Pancreatic ductal adenocarcinoma



Indication: Pancreatic ductal adenocarcinoma

Resistance / failure mechanism:

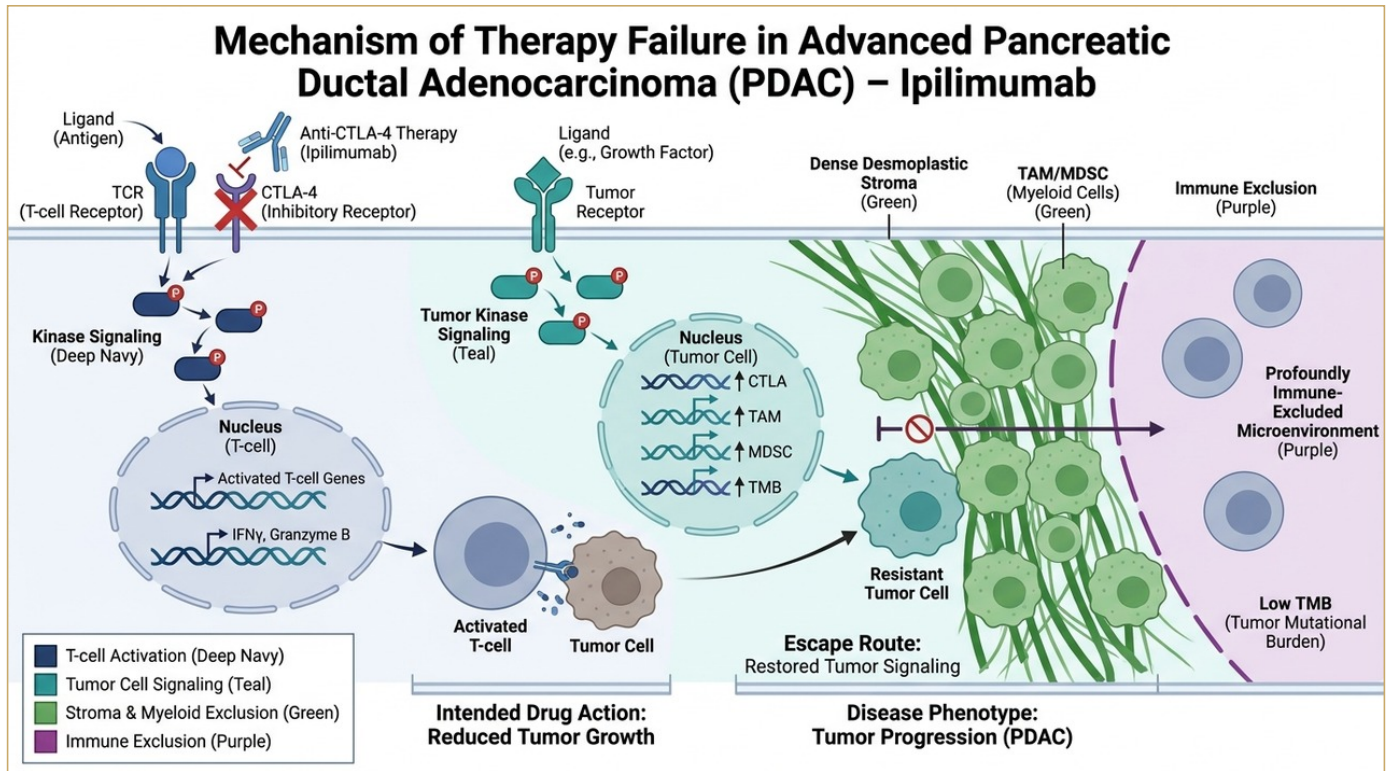
Loss of hENT1-mediated influx limits intracellular drug and activation; reduced-accumulation resistance

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Mini E et al. Ann Oncol 2006;17(Suppl 5):v7-v12. PMID 16807468

Ipilimumab

Advanced pancreatic ductal adenocarcinoma



Indication: Advanced pancreatic ductal adenocarcinoma

Resistance / failure mechanism:

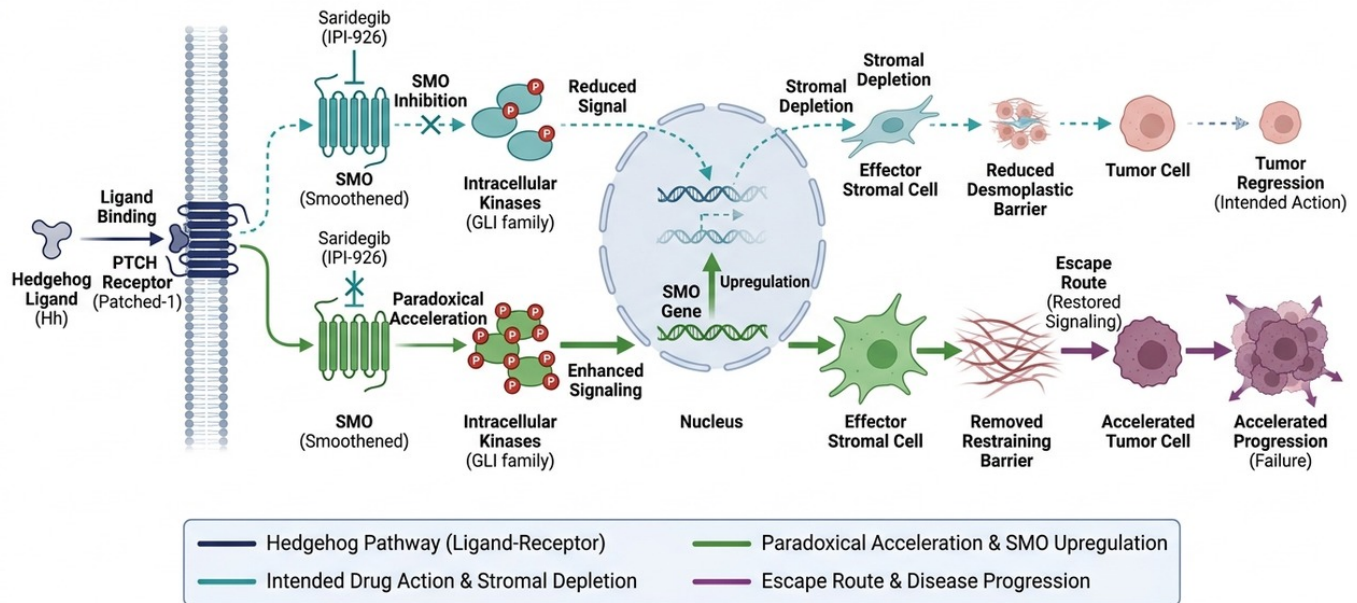
Dense desmoplastic/fibrotic stroma with myeloid (TAM/MDSC) exclusion of T cells, low TMB; profoundly immune-excluded microenvironment.

BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Royal RE et al. J Immunother 2010;33:828-833. PMID 20842054

ClinicalTrials.gov: [NCT00112580](https://clinicaltrials.gov/ct2/show/study/NCT00112580)

Mechanism of Therapy Failure in Pancreatic Adenocarcinoma: Saridegib (IPI-926) + Gemcitabine (Hedgehog/SMO Inhibitor Strategy)



Indication: Pancreatic adenocarcinoma

Resistance / failure mechanism:

Stromal/Hedgehog depletion removed a restraining desmoplastic barrier, paradoxically accelerating progression

BiRAGAS pattern P6 · TME/immune-exclusion

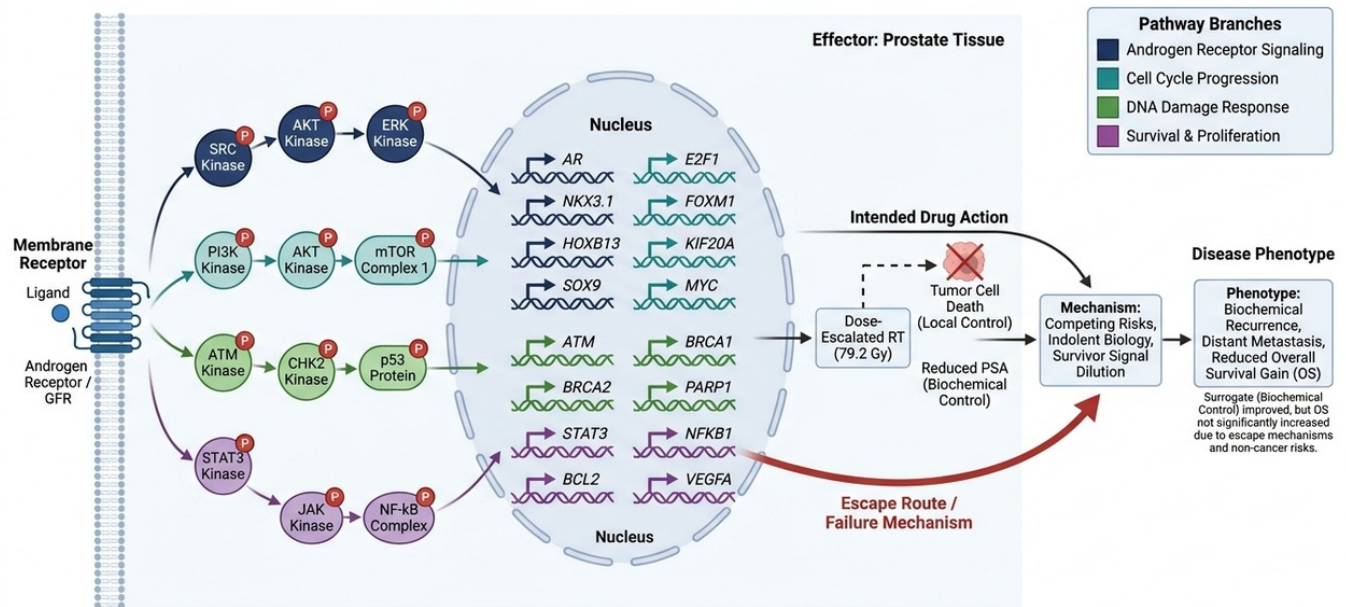
Citation: Infinity halt (2012); Rhim AD et al. Cancer Cell 2014 / Ozdemir BC et al. Cancer Cell 2014

ClinicalTrials.gov: [NCT01130142](https://clinicaltrials.gov/ct2/show/study/NCT01130142)

Dose-escalated RT (79.2 Gy vs 70.2 Gy)

Prostate cancer (localized, intermediate-risk)

Mechanism of Therapy Failure in Prostate Cancer (Intermediate-Risk) - Dose-Escalated RT (79.2 Gy vs 70.2 Gy)



Indication: Prostate cancer (localized, intermediate-risk)

Resistance / failure mechanism:

Surrogate (biochemical control) improved without OS gain; competing risks and indolent biology dilute survival signal

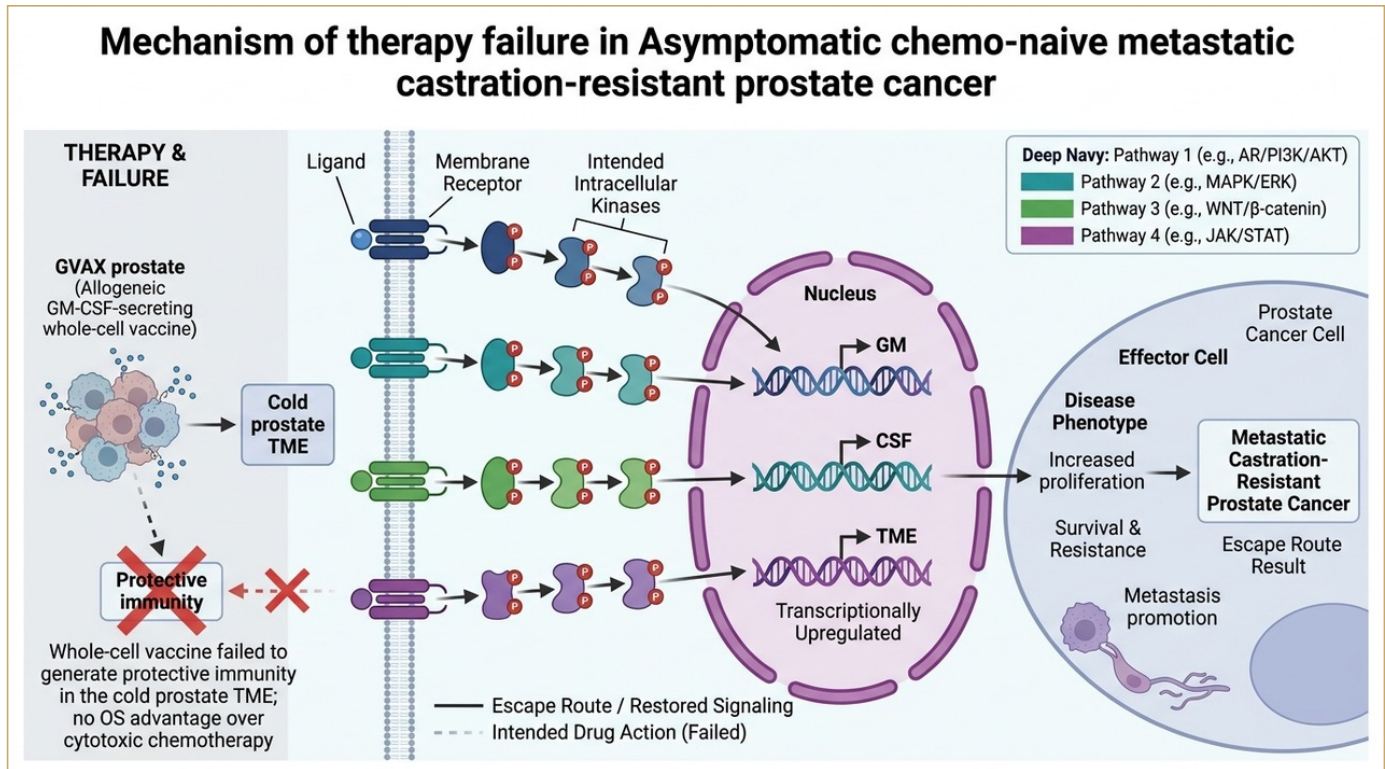
BiRAGAS pattern P1 · correlate-not-driver

Citation: Michalski JM et al. JAMA Oncol 2018;4:e180039, PMID 29543933

ClinicalTrials.gov: NCT00033631

GVAX prostate (allogeneic GM-CSF-secreting whole-cell vaccine)

Asymptomatic chemo-naïve metastatic castration-resistant prostate cancer



Indication: Asymptomatic chemo-naïve metastatic castration-resistant prostate cancer

Resistance / failure mechanism:

Whole-cell vaccine failed to generate protective immunity in the cold prostate TME; no OS advantage over cytotoxic chemotherapy.

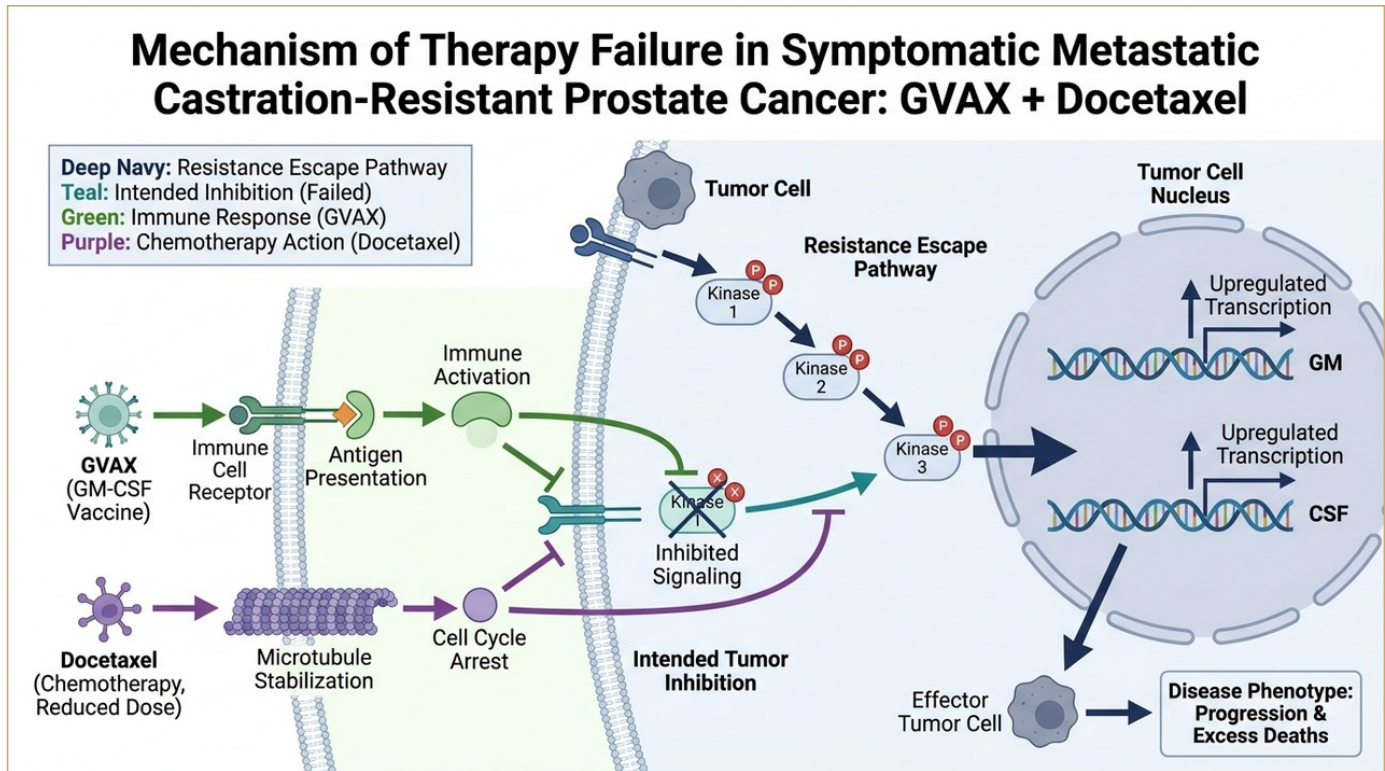
BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Cell Genesys VITAL-1 termination (2008); reviewed in Madan RA & Gulley JL, Curr Opin Urol 2011. PMID (verify, unresolved)

ClinicalTrials.gov: NCT00089856

GVAX prostate + docetaxel

Symptomatic metastatic castration-resistant prostate cancer



Indication: Symptomatic metastatic castration-resistant prostate cancer

Resistance / failure mechanism:

Empiric vaccine+chemotherapy combination lacked mechanistic rationale; docetaxel dose reduction in the combination arm plus excess deaths signaled net harm.

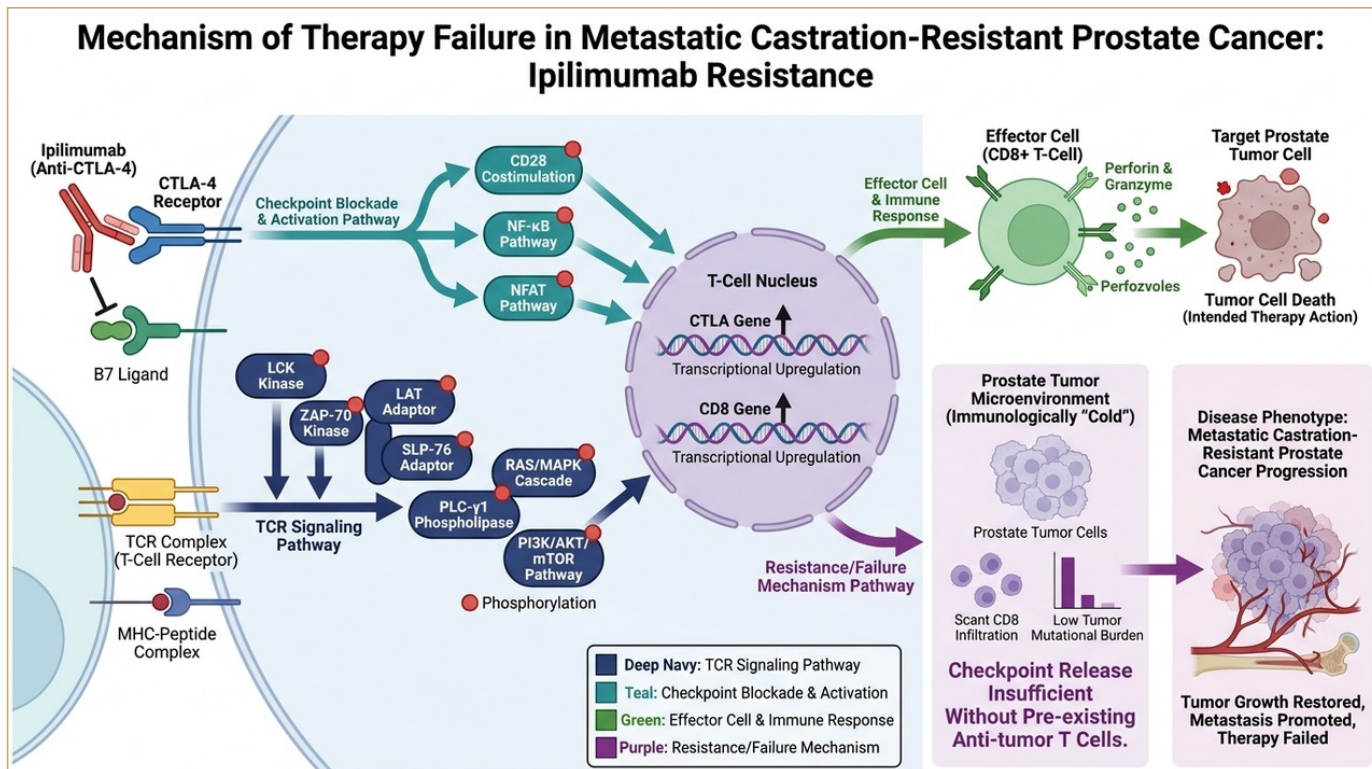
BiRAGAS pattern P6 · combination-no-rationale

Citation: Cell Genesys VITAL-2 termination (2008); Small EJ et al. reviewed in Drake CG, Nat Rev Immunol 2010. PMID (verify, unresolved)

[ClinicalTrials.gov: NCT00133224](https://clinicaltrials.gov/ct2/show/study/NCT00133224)

Ipilimumab

Metastatic castration-resistant prostate cancer



Indication: Metastatic castration-resistant prostate cancer

Resistance / failure mechanism:

Immunologically 'cold', T-cell-excluded prostate tumor microenvironment with low tumor mutational burden and scant CD8 infiltration; checkpoint release insufficient without pre-existing anti-tumor T cells.

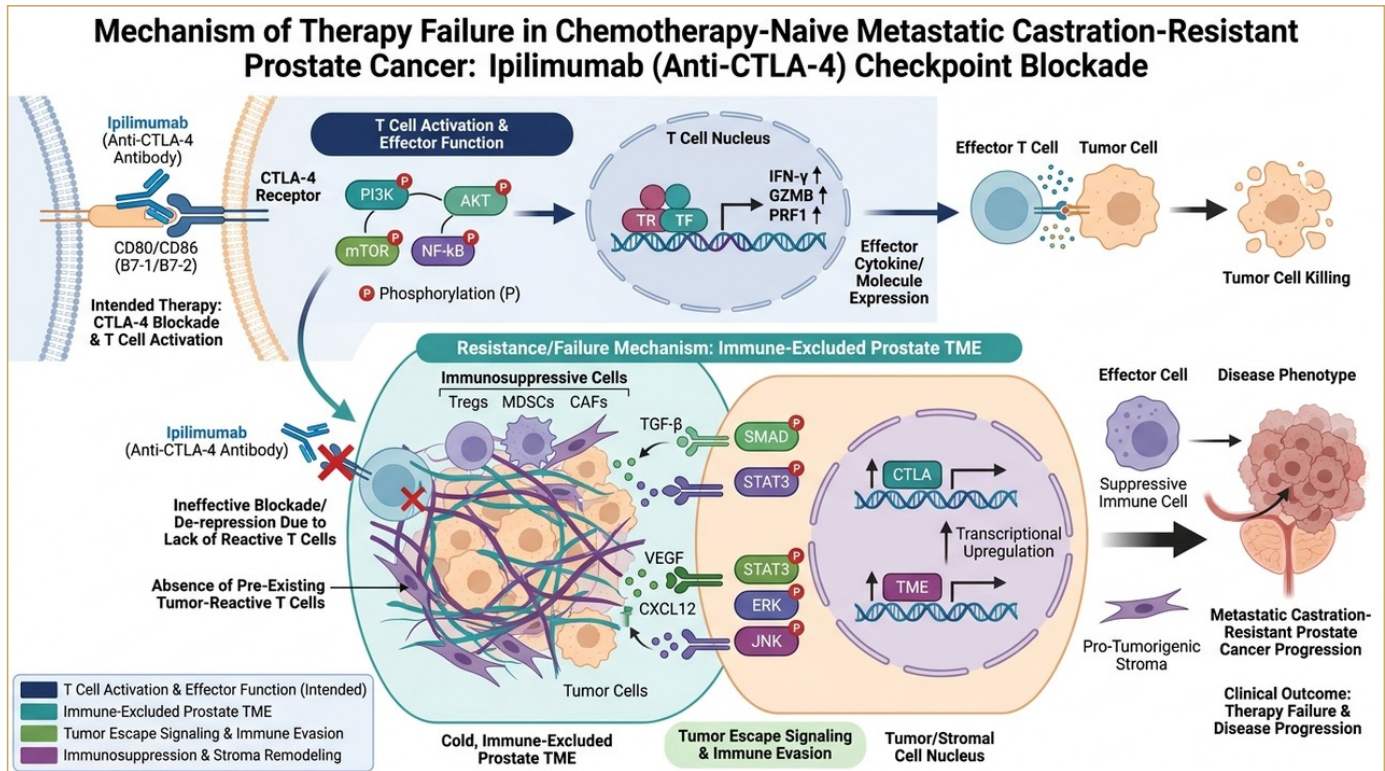
BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Kwon EM et al. Lancet Oncol 2014;15:700-712. PMID 24831977

ClinicalTrials.gov: [NCT00861614](https://clinicaltrials.gov/ct2/show/study/NCT00861614)

Ipilimumab

Chemotherapy-naive metastatic castration-resistant prostate cancer



Indication: Chemotherapy-naive metastatic castration-resistant prostate cancer

Resistance / failure mechanism:

Same cold, immune-excluded prostate TME; absence of pre-existing tumor-reactive T cells to be de-repressed by CTLA-4 blockade.

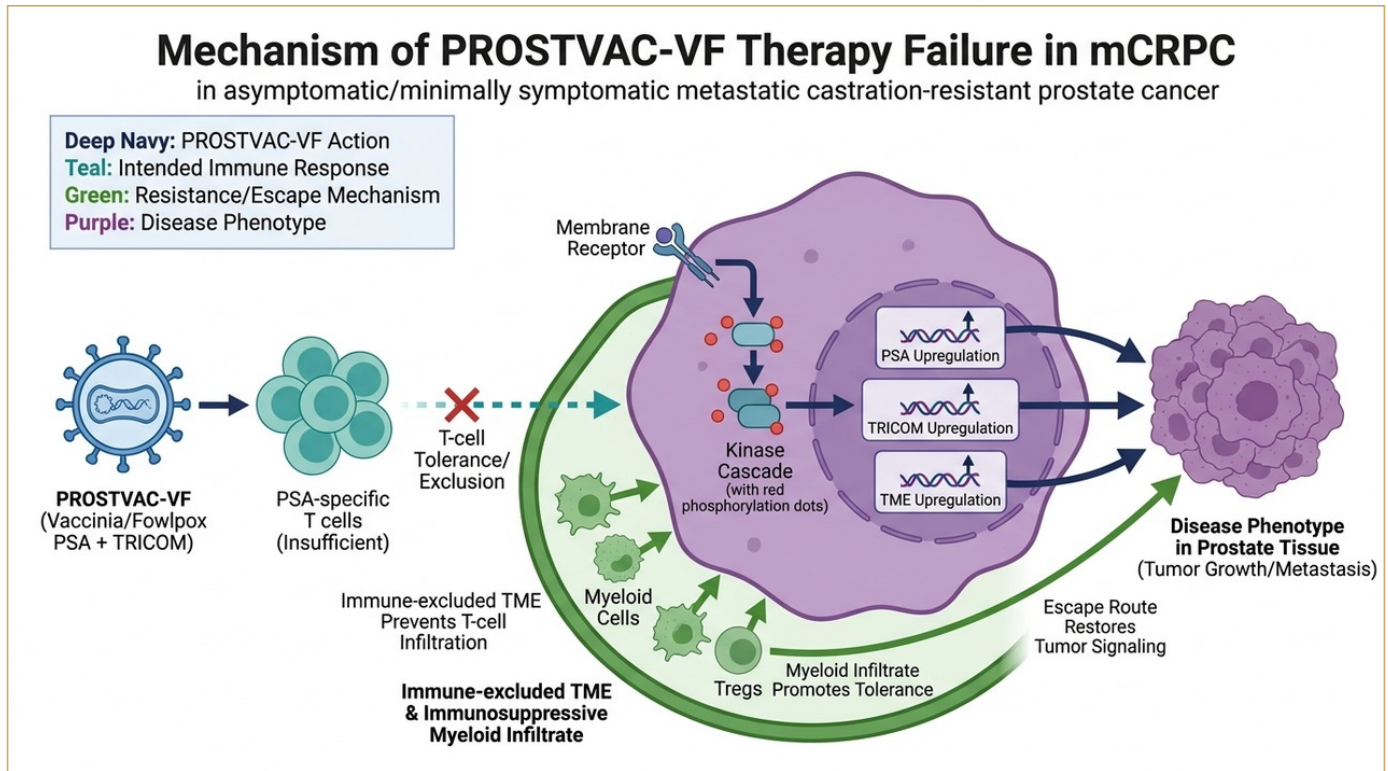
BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Beer TM et al. J Clin Oncol 2017;35:40-47. PMID 27918725

ClinicalTrials.gov: [NCT01057810](https://clinicaltrials.gov/ct2/show/study/NCT01057810)

PROSTVAC-VF (rilimogene, PSA-targeted poxviral vaccine)

Asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer



Indication: Asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer

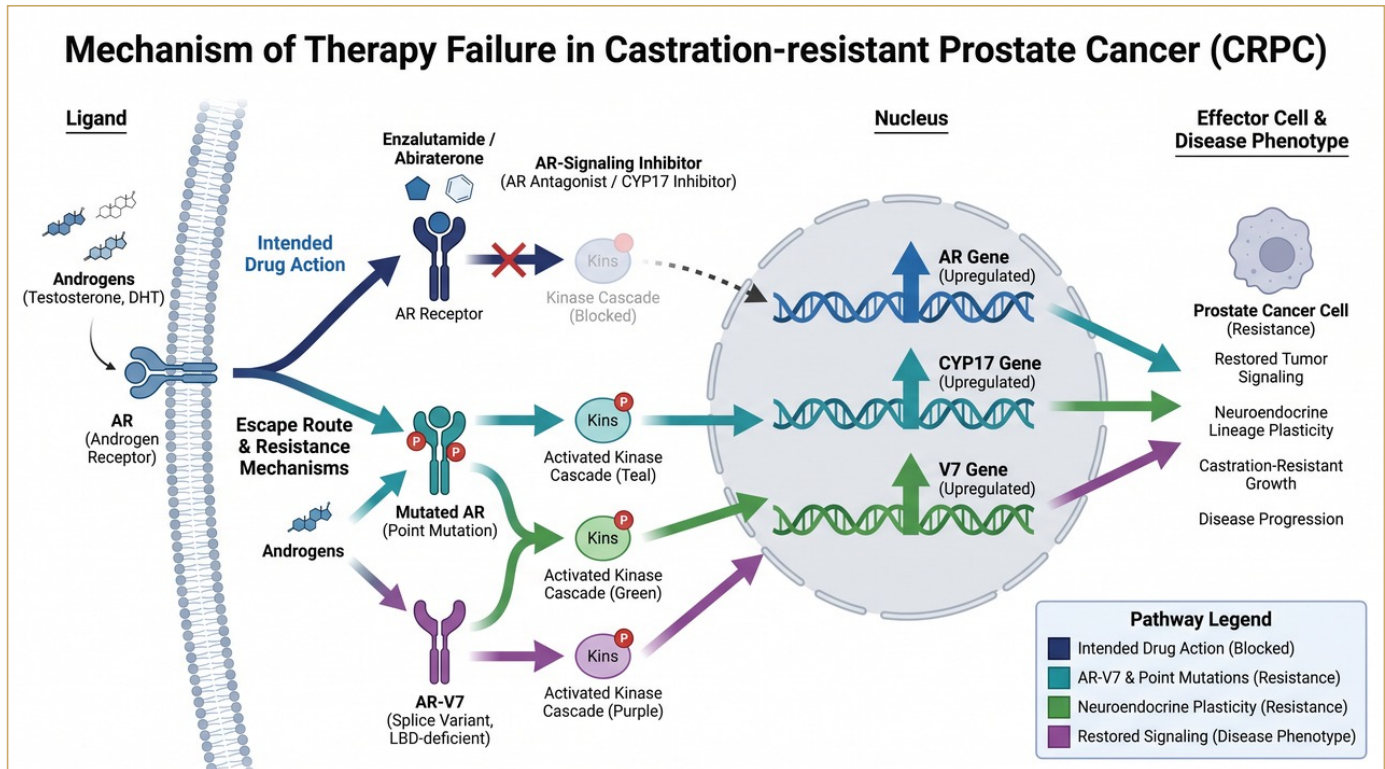
Resistance / failure mechanism:

Immune-excluded prostate TME and immunosuppressive myeloid infiltrate; vaccine-induced PSA-specific T cells insufficient to overcome tolerance, despite an earlier phase 2 OS signal that did not replicate.

BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Gulley JL et al. J Clin Oncol 2019;37:1051-1061. PMID 30521405

[ClinicalTrials.gov: NCT01322490](https://clinicaltrials.gov/ct2/show/study/NCT01322490)



Indication: Castration-resistant prostate cancer

Resistance / failure mechanism:

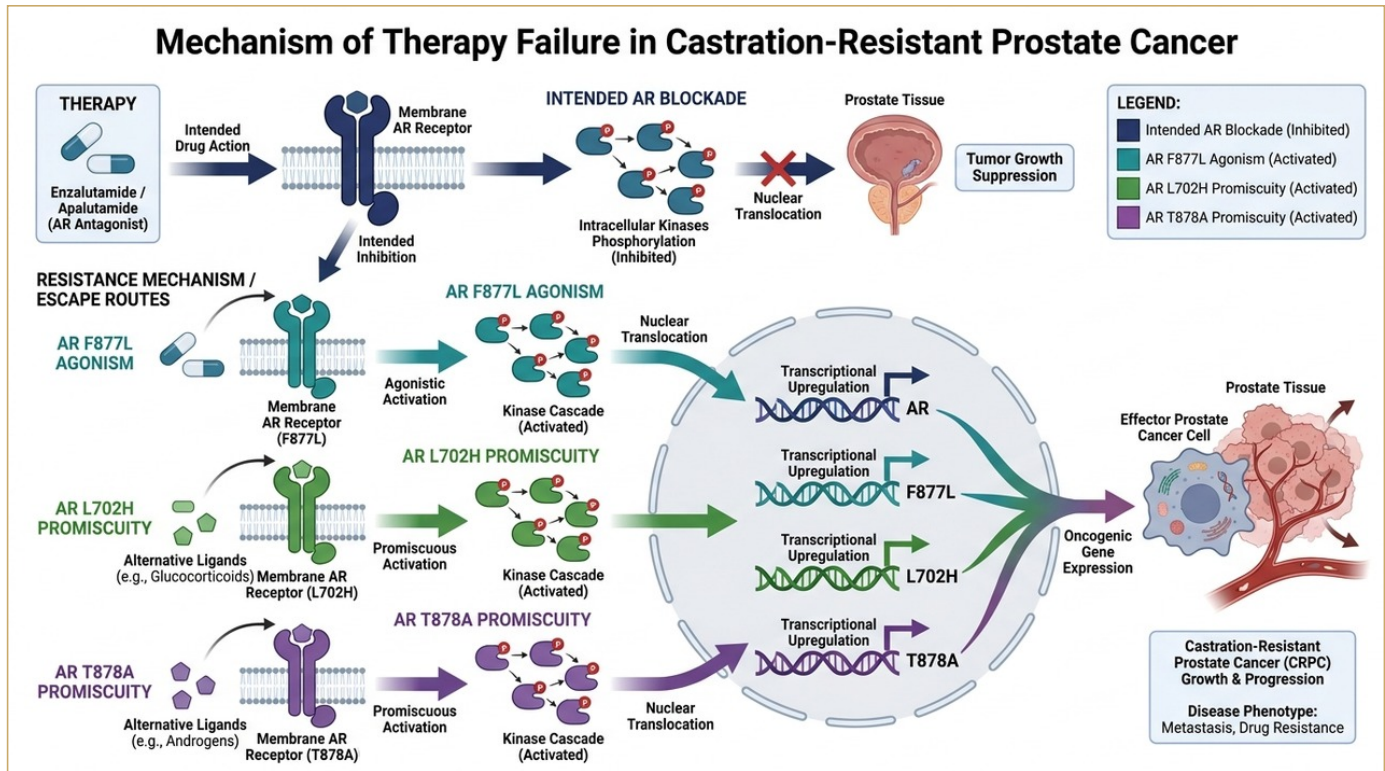
AR-V7 splice variant lacks the ligand-binding domain (constitutively active, drug-insensitive); AR point mutations and neuroendocrine lineage plasticity

BiRAGAS pattern P2 · lineage-plasticity/transformation

Citation: Antonarakis ES et al. N Engl J Med 2014;371:1028-1038, PMID 25184630

enzalutamide / apalutamide

Castration-resistant prostate cancer



Indication: Castration-resistant prostate cancer

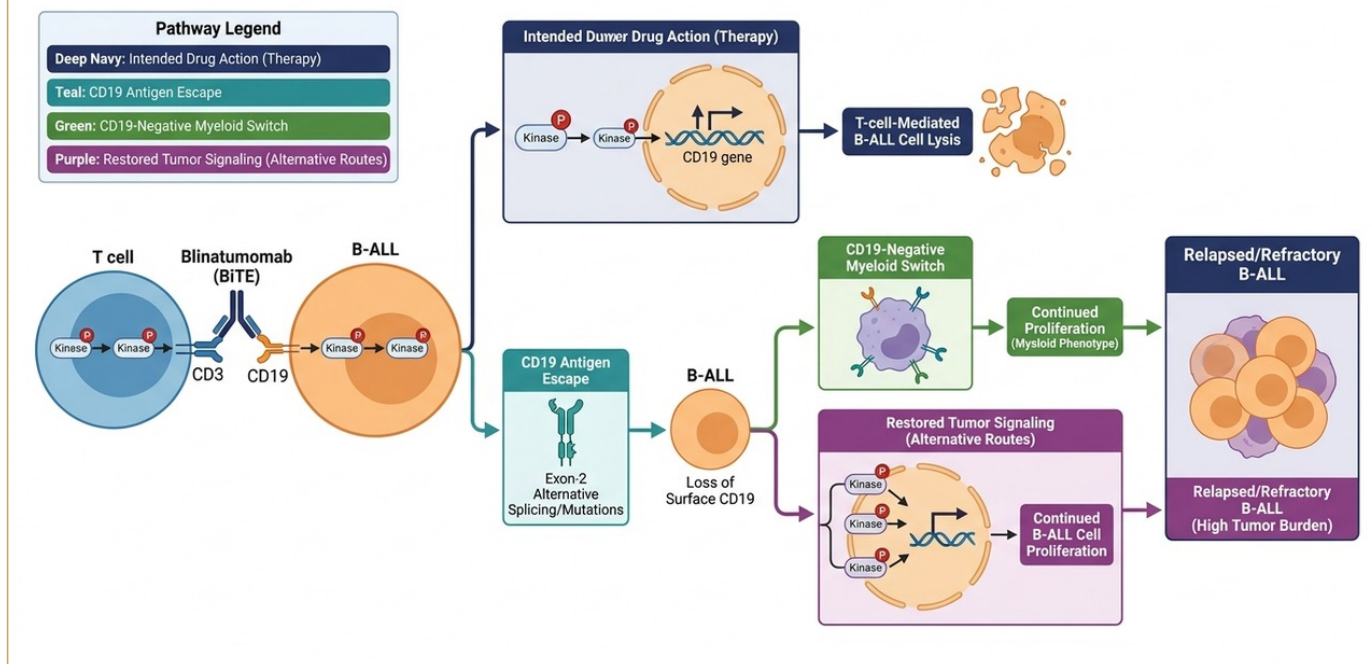
Resistance / failure mechanism:

AR F877L confers enzalutamide/apalutamide agonism; AR L702H and T878A broaden ligand promiscuity

BiRAGAS pattern P7 · target-mutation

Citation: Joseph JD et al. Cancer Discov 2013;3:1020-1029, PMID 23779130

Mechanism of Therapy Failure in B-ALL: Blinatumomab Resistance



Indication: B-ALL

Resistance / failure mechanism:

CD19 antigen escape: exon-2 alternative splicing, frameshift/missense CD19 mutations and loss of surface CD19; also CD19-negative myeloid lineage switch

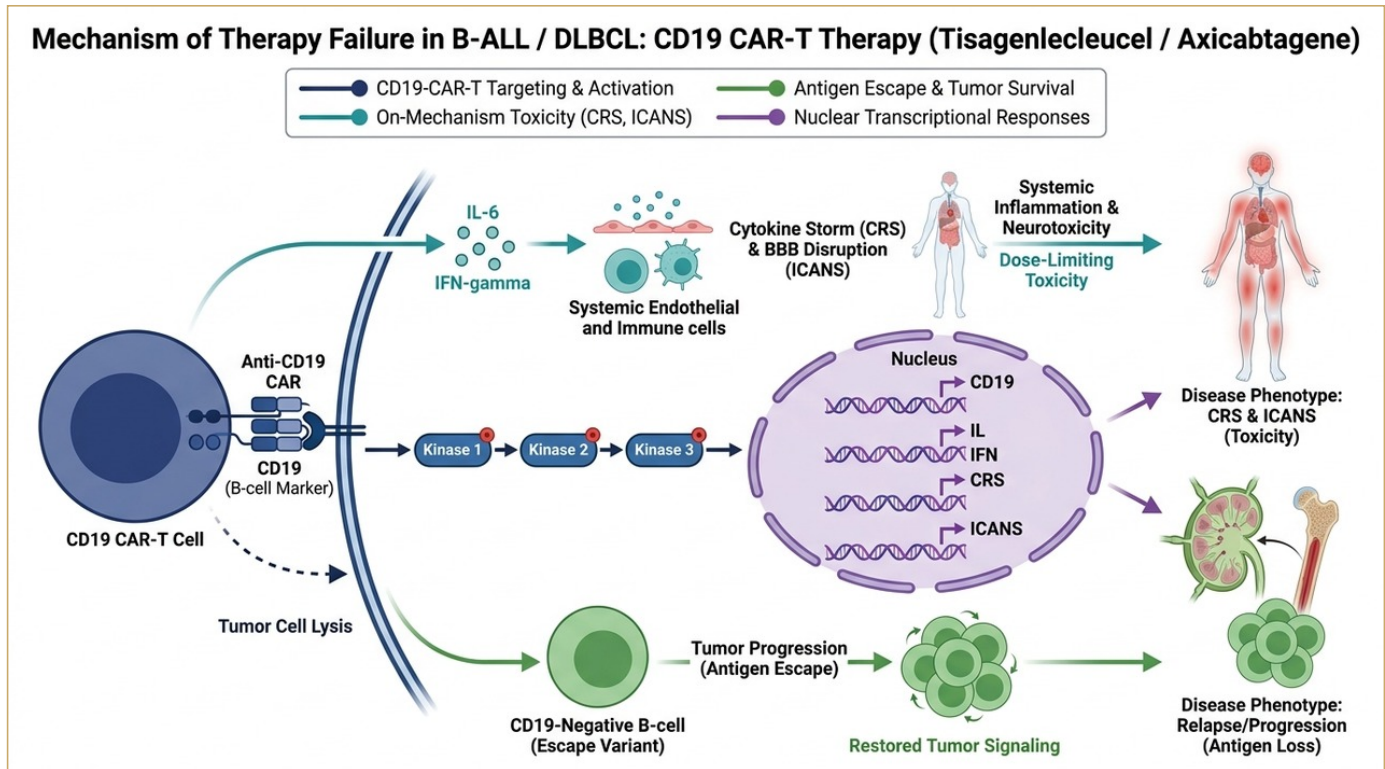
BiRAGAS pattern P7 · antigen-escape

Citation: Kantarjian H et al. N Engl J Med 2017;376:836-847 (TOWER, PMID 28249141)

ClinicalTrials.gov: [NCT02013167](https://clinicaltrials.gov/ct2/show/study/NCT02013167)

CD19 CAR-T (tisagenlecleucel / axicabtagene)

B-ALL / DLBCL



Indication: B-ALL / DLBCL

Resistance / failure mechanism:

On-mechanism toxicity: massive T-cell activation triggers an IL-6/IFN-gamma cytokine storm (CRS) and blood-brain-barrier disruption (ICANS); dose-limiting rather than an efficacy-resistance mechanism

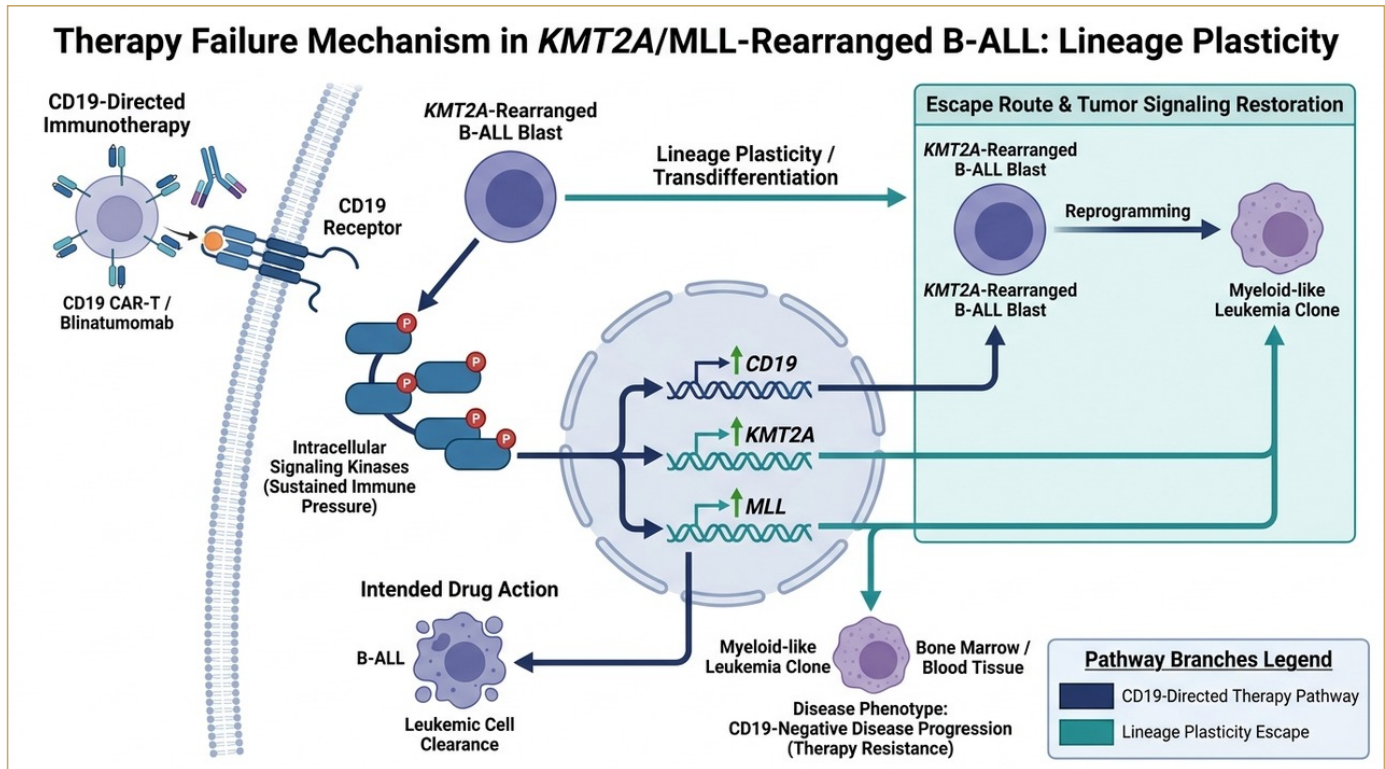
BiRAGAS pattern P4 · on-mechanism-toxicity

Citation: Maude SL et al. N Engl J Med 2018;378:439-448 (ELIANA); Neelapu SS et al. 2017 (ZUMA-1)

ClinicalTrials.gov: [NCT02435849](https://clinicaltrials.gov/ct2/show/study/NCT02435849)

CD19 CAR-T / blinatumomab (CD19-directed immunotherapy)

B-ALL (KMT2A/MLL-rearranged)



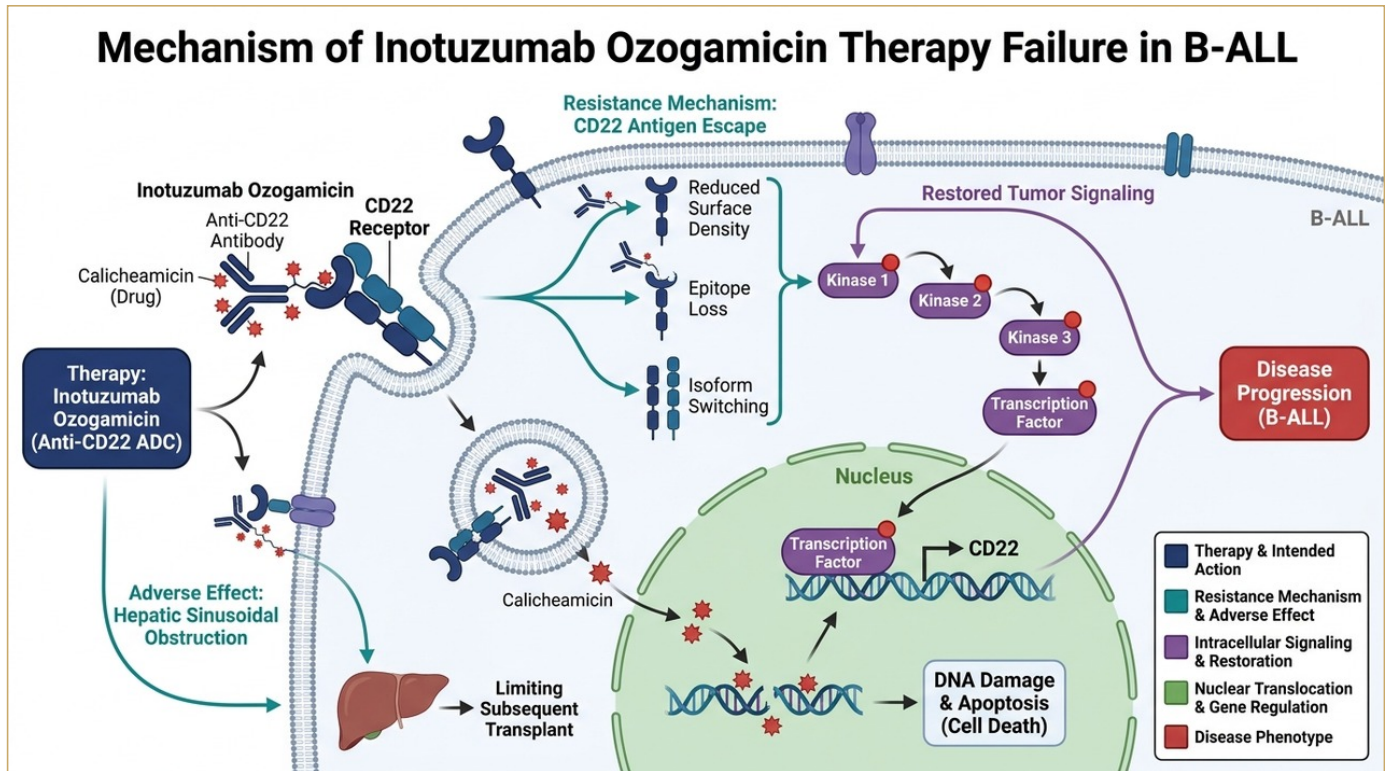
Indication: B-ALL (*KMT2A*/MLL-rearranged)

Resistance / failure mechanism:

Lineage plasticity/transdifferentiation: *KMT2A*-rearranged blasts reprogram from lymphoid to myeloid, escaping CD19-directed therapy while retaining the leukemic clone

BiRAGAS pattern P2 · lineage-plasticity/transformation

Citation: Gardner R et al. Blood 2016;127:2406-2410 (PMID 26907630); Jacoby E et al. Nat Commun 2016;7:12320



Indication: B-ALL

Resistance / failure mechanism:

CD22 antigen escape (reduced surface density, epitope loss, isoform switching); plus on-mechanism hepatic sinusoidal obstruction limiting subsequent transplant

BiRAGAS pattern P7 · antigen-escape

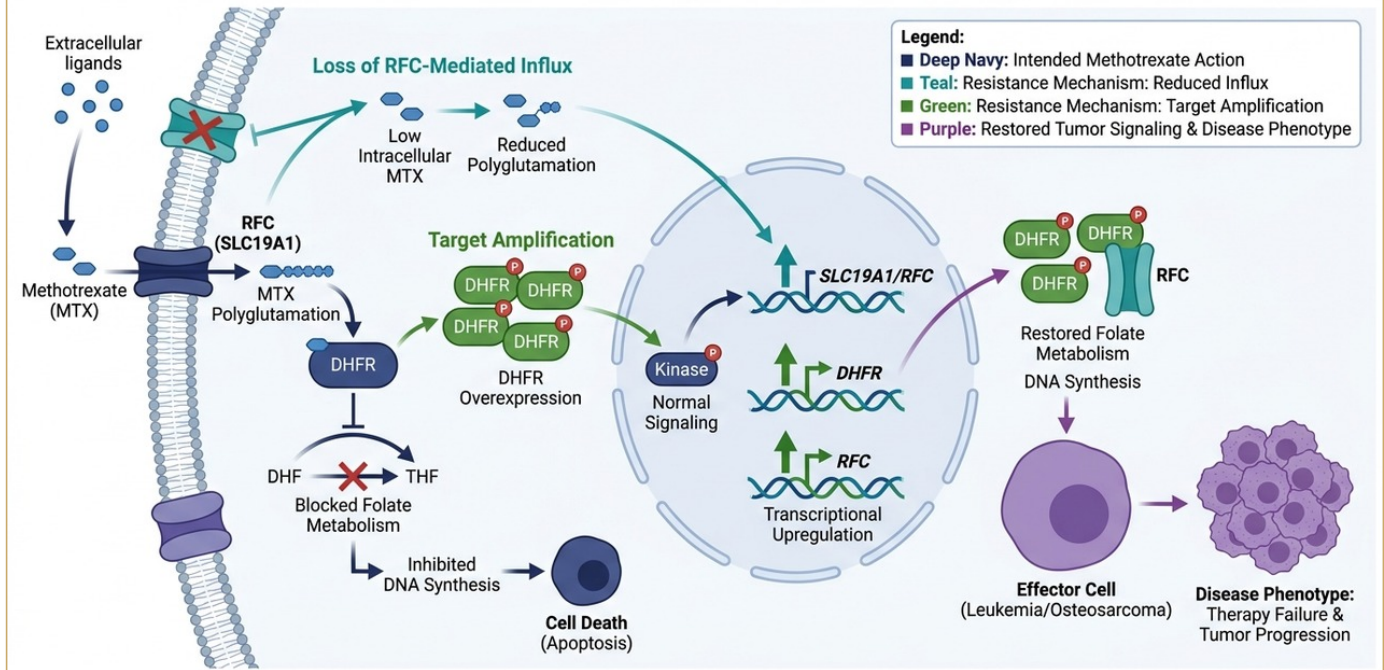
Citation: Kantarjian HM et al. N Engl J Med 2016;375:740-753 (INO-VATE, PMID 27292104)

ClinicalTrials.gov: [NCT01564784](https://clinicaltrials.gov/ct2/show/study/NCT01564784)

Methotrexate

Acute lymphoblastic leukemia / osteosarcoma

Mechanism of Therapy Failure in Acute Lymphoblastic Leukemia / Osteosarcoma: Methotrexate Resistance



Indication: Acute lymphoblastic leukemia / osteosarcoma

Resistance / failure mechanism:

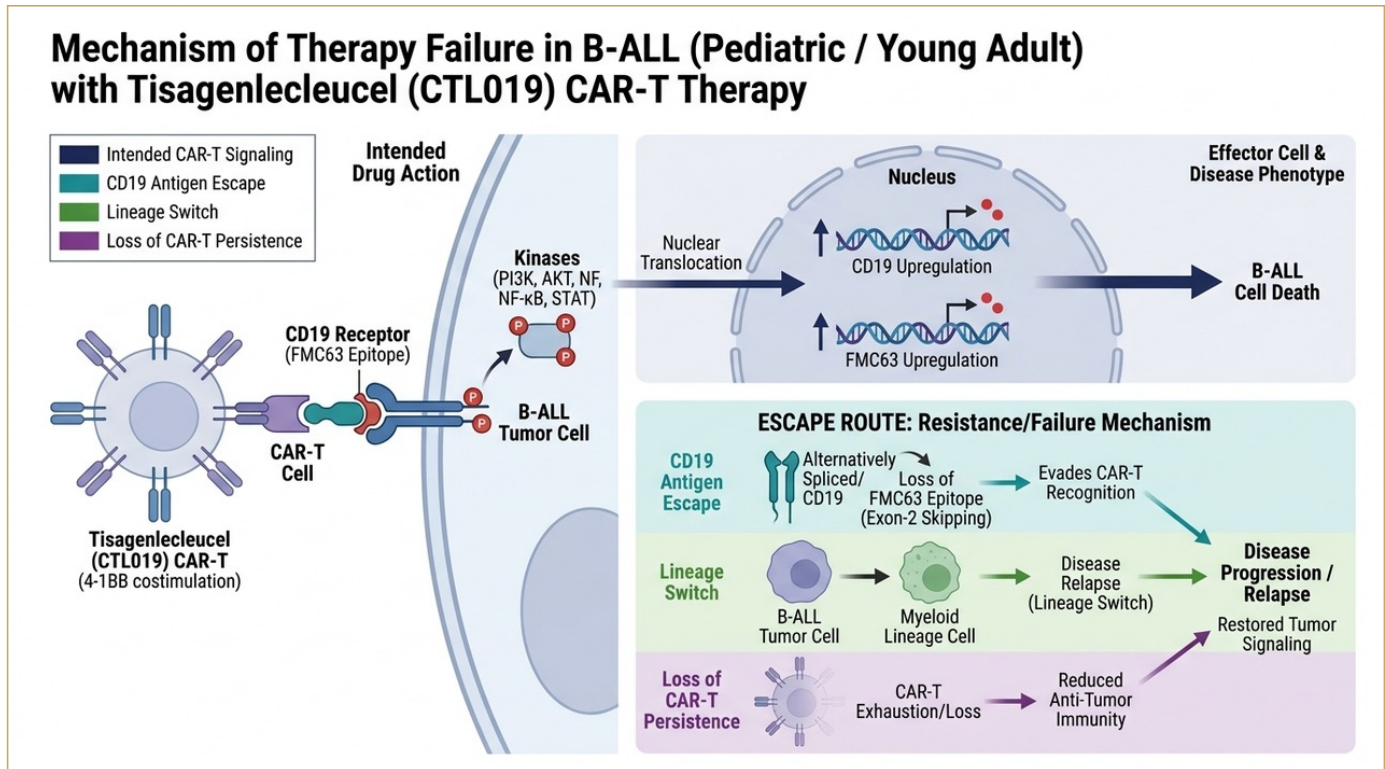
Target amplification raises DHFR above inhibitable levels; loss of RFC-mediated influx lowers intracellular drug and polyglutamation

BiRAGAS pattern P1 · target-mutation

Citation: Zhao R, Goldman ID. Oncogene 2003;22(47):7431-7457. PMID 14576851

Tisagenlecleucel (CTL019)

B-ALL (pediatric / young adult)



Indication: B-ALL (pediatric / young adult)

Resistance / failure mechanism:

CD19 antigen escape via alternatively spliced/mutated CD19 (loss of the FMC63 epitope, exon-2 skipping) and lineage switch; also loss of CAR-T persistence

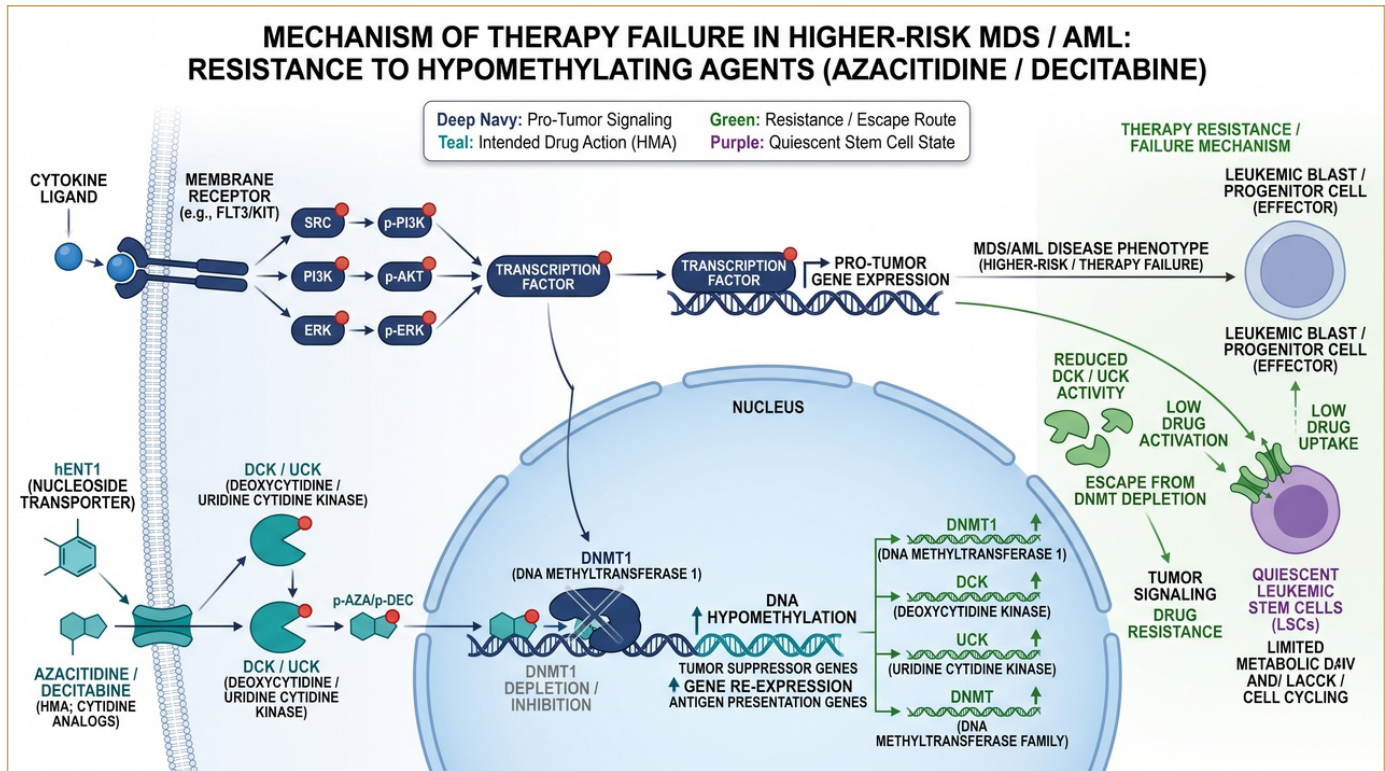
BiRAGAS pattern P7 · antigen-escape

Citation: Sotillo E et al. Cancer Discov 2015;5:1282-1295 (PMID 26516035); Maude SL et al. N Engl J Med 2018 (ELIANA)

ClinicalTrials.gov: [NCT02435849](https://clinicaltrials.gov/ct2/show/study/NCT02435849)

Azacitidine / Decitabine

MDS (higher-risk) / AML



Indication: MDS (higher-risk) / AML

Resistance / failure mechanism:

Pharmacologic/metabolic: reduced drug activation and incorporation via low deoxycytidine kinase (DCK)/UCK, reduced nucleoside transporter (hENT1) uptake, and quiescent stem cells that escape S-phase-dependent DNMT depletion.

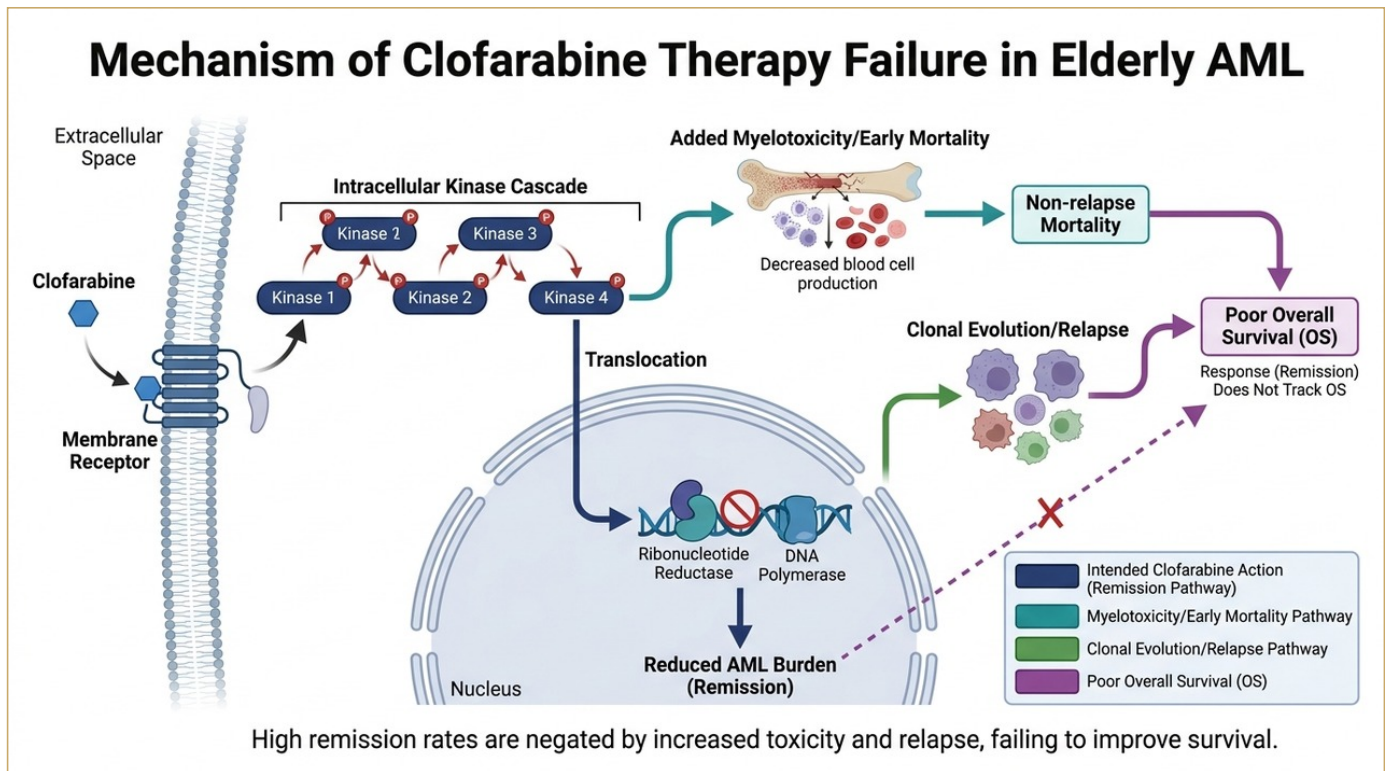
BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Stomper J et al. Leukemia 2021 (HMA resistance mechanisms review); Qin T et al. Blood 2009 (DCK); PMID (verify, unresolved)

ClinicalTrials.gov: [NCT00071799](https://clinicaltrials.gov/ct2/show/study/NCT00071799)

Clofarabine

AML (newly diagnosed, elderly)



Indication: AML (newly diagnosed, elderly)

Resistance / failure mechanism:

Higher remission rates did not convert to survival because added myelotoxicity/early mortality (and relapse) negated the response advantage, response was a surrogate that did not track OS.

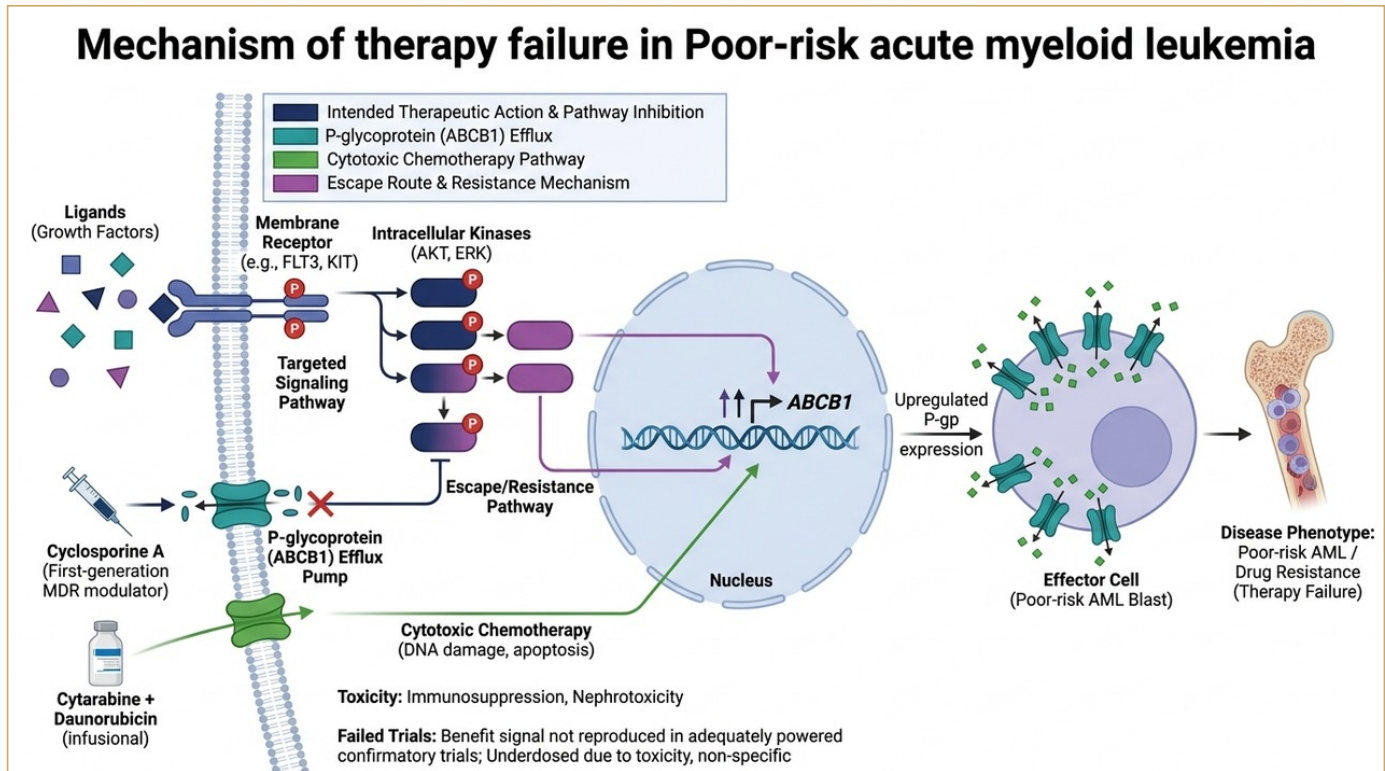
BiRAGAS pattern P5 · correlate-not-driver

Citation: Faderl S et al. Blood 2012;120(23):4534-6 (CLASSIC I); PMID (verify, unresolved)

ClinicalTrials.gov: [NCT00317642](https://clinicaltrials.gov/ct2/show/study/NCT00317642)

Cyclosporine A (first-generation MDR modulator) added to cytarabine + daun

Poor-risk acute myeloid leukemia



Indication: Poor-risk acute myeloid leukemia

Resistance / failure mechanism:

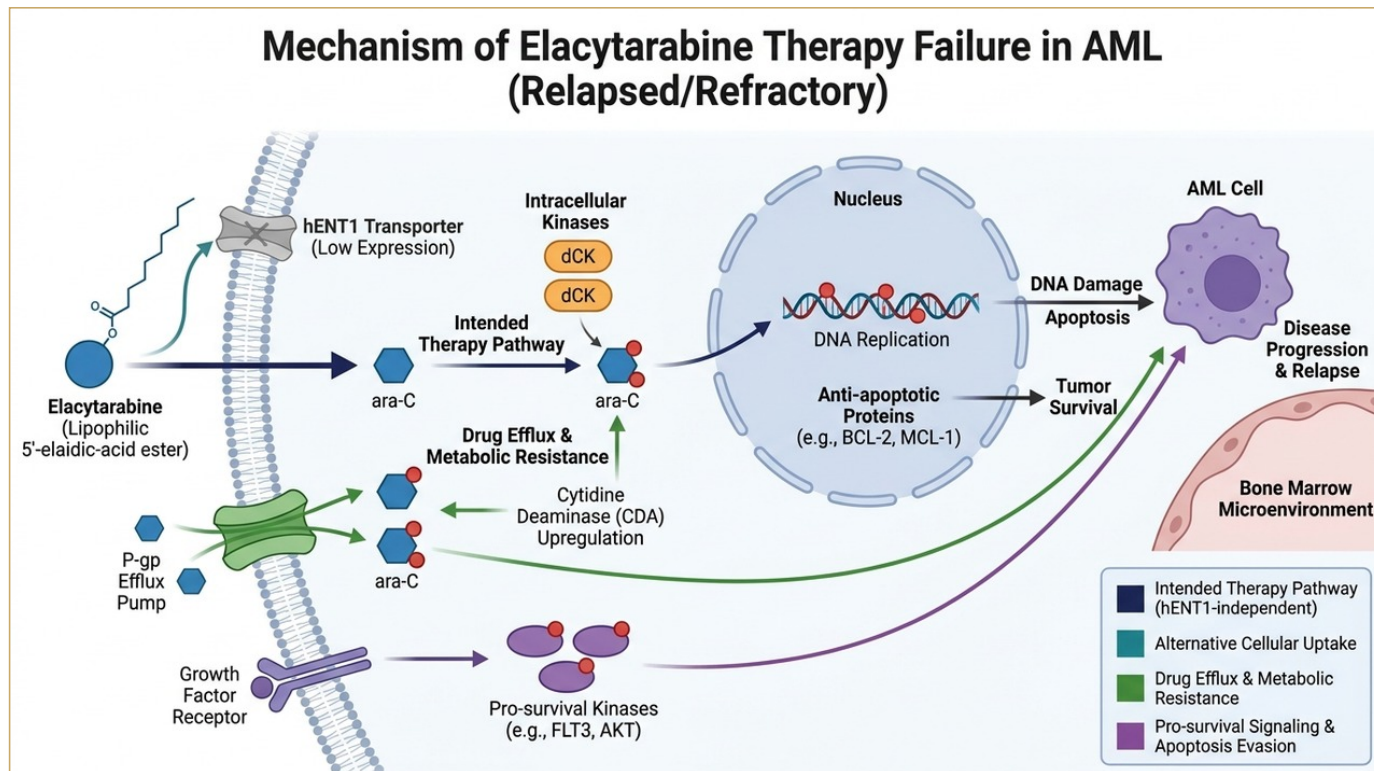
First-gen modulators were underdosed due to their own toxicity (immunosuppression, nephrotoxicity) and non-specific; benefit signal not reproduced in adequately powered confirmatory trials

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: List AF et al. Blood 2001;98(12):3212-3220. PMID 11719356

Elacytarabine

AML (relapsed/refractory)



Indication: AML (relapsed/refractory)

Resistance / failure mechanism:

Rationale was to bypass low hENT1 transporter expression (a proposed cytarabine-resistance mechanism), but hENT1-independent delivery did not translate to benefit, the transporter was a correlate, not the limiting driver of ara-C resistance.

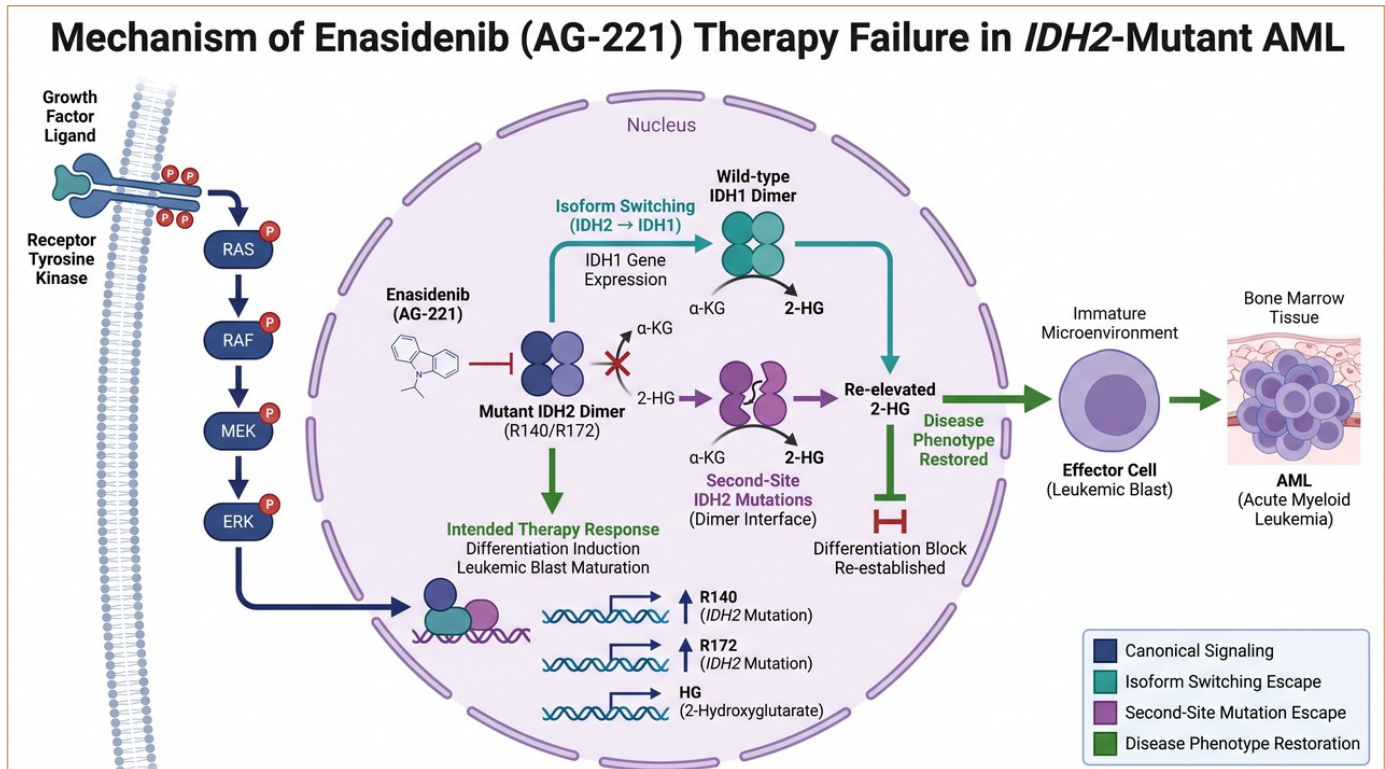
BiRAGAS pattern P1 · pharmacologic/efflux-metabolism

Citation: Roboz GJ et al. J Clin Oncol 2014;32(18):1919-26 (CLAVELA). PMID 24841975

ClinicalTrials.gov: [NCT01147939](https://clinicaltrials.gov/ct2/show/study/NCT01147939)

Enasidenib (AG-221)

AML (IDH2-mutant)



Indication: AML (IDH2-mutant)

Resistance / failure mechanism:

Isoform switching (IDH2→IDH1) and trans/second-site IDH2 mutations at the dimer interface re-elevate 2-HG; differentiation block re-established despite on-target drug.

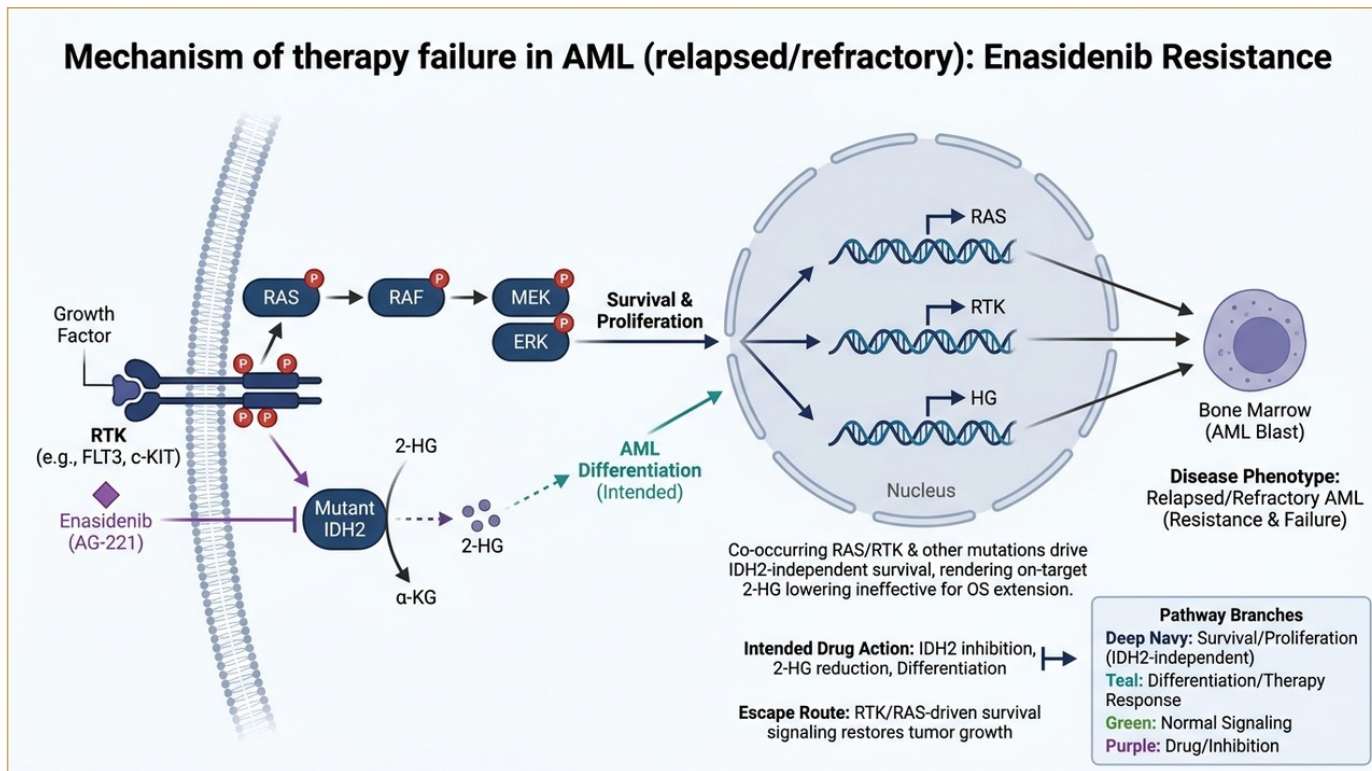
BiRAGAS pattern P7 · target-mutation

Citation: Intlekofer AM et al. Nature 2018;559:125-129 (acquired resistance via IDH2 dimer-interface mutations), PMID 29950729

ClinicalTrials.gov: [NCT01915498](https://clinicaltrials.gov/ct2/show/study/NCT01915498)

Enasidenib (AG-221)

AML (relapsed/refractory)



Indication: AML (relapsed/refractory)

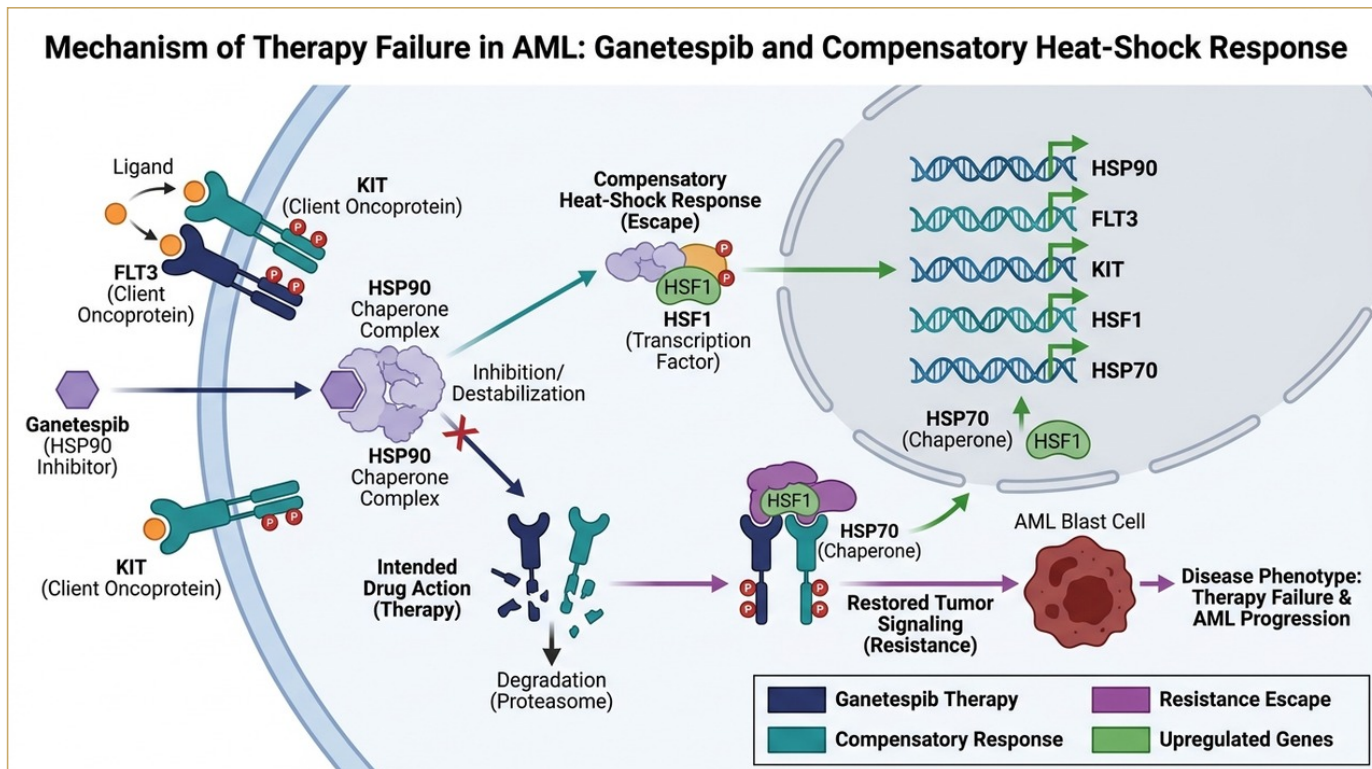
Resistance / failure mechanism:

Single-agent differentiation therapy in heavily pretreated, clonally heterogeneous R/R AML: co-occurring RAS/RTK and other mutations drive IDH2-independent survival, so on-target 2-HG lowering did not extend OS.

BiRAGAS pattern P3 · bypass/parallel-pathway

Citation: de Botton S et al. Blood 2023 (IDHENTIFY); ClinicalTrials.gov NCT02577406 (PMID (verify, unresolved))

ClinicalTrials.gov: [NCT02577406](https://clinicaltrials.gov/ct2/show/study/NCT02577406)



Indication: AML

Resistance / failure mechanism:

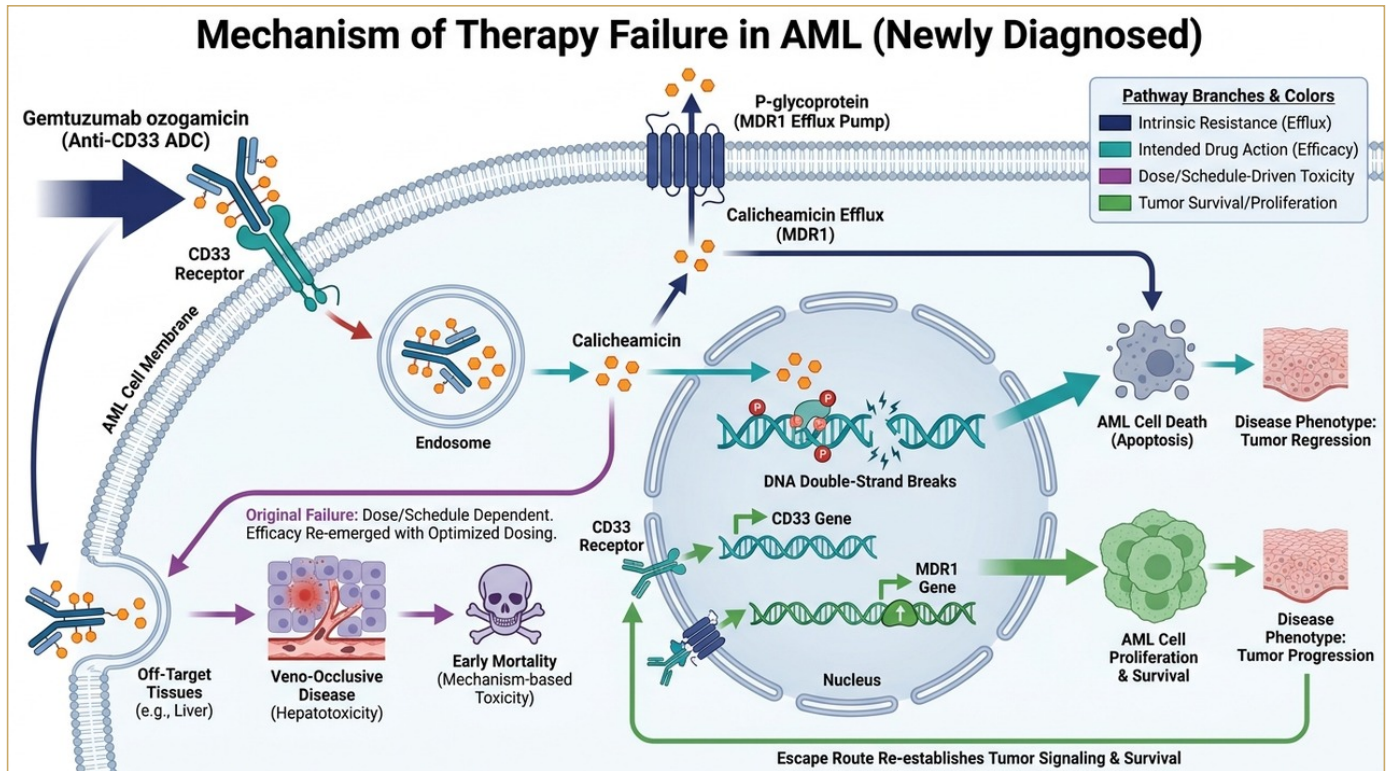
HSP90 blockade triggers compensatory heat-shock response (HSF1/HSP70 induction) that re-stabilizes clients; broad chaperone targeting lacked a stratified oncogenic-addiction rationale in AML.

BiRAGAS pattern P2 · feedback-reactivation

Citation: Ganetespiib (STA-9090) early-phase AML program (Synta Pharmaceuticals); no pivotal Phase-3 publication, program-level entry, exact NCT/PMID not established

Gemtuzumab ozogamicin

AML (newly diagnosed)



Indication: AML (newly diagnosed)

Resistance / failure mechanism:

Original failure was dose/schedule-driven hepatotoxicity (veno-occlusive disease) and early mortality (mechanism-based toxicity); efficacy re-emerged once dosing was optimized. Intrinsic resistance also linked to P-glycoprotein/MDR1 efflux of calicheamicin.

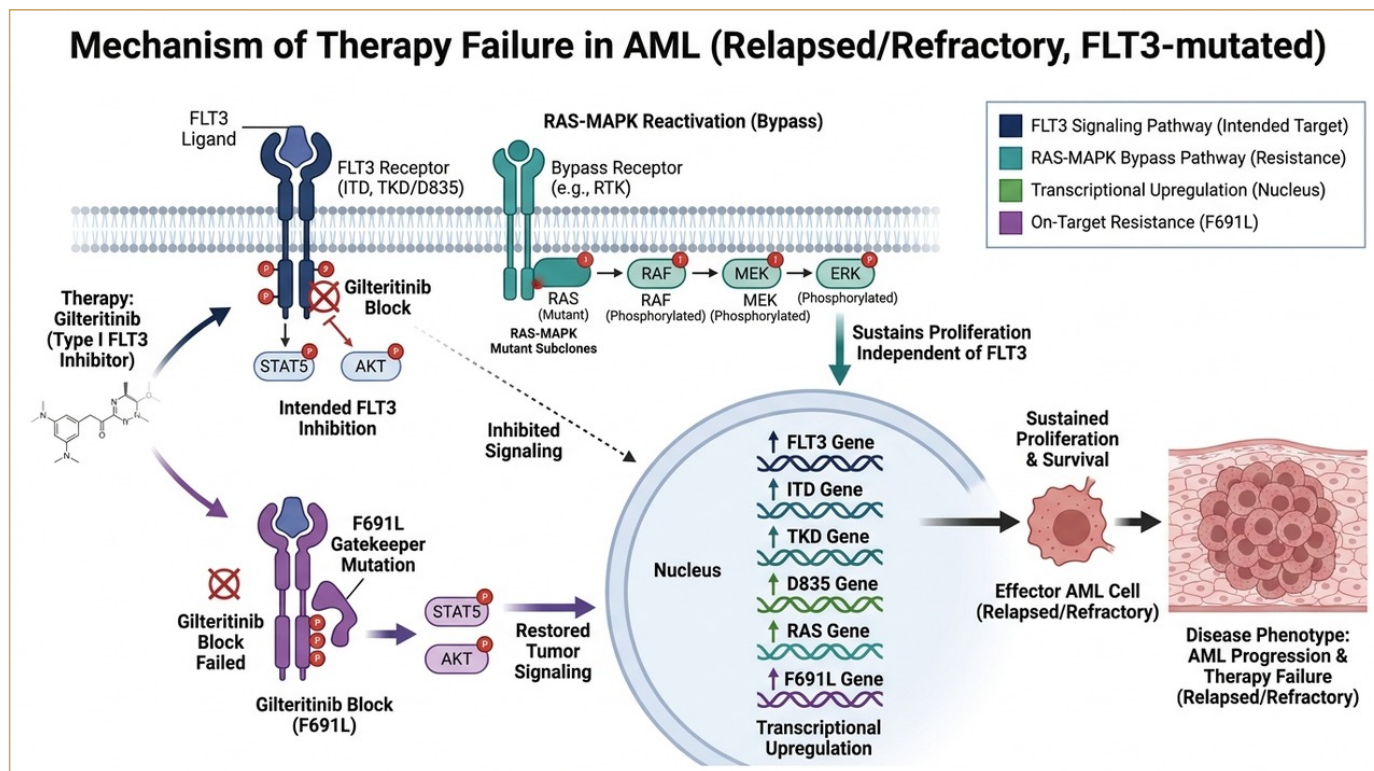
BiRAGAS pattern P4 · on-mechanism-toxicity

Citation: Petersdorf SH et al. Blood 2013;121(24):4854-60 (S0106). PMID 23321251

ClinicalTrials.gov: [NCT00085709](https://clinicaltrials.gov/ct2/show/study/NCT00085709)

Gilteritinib

AML (relapsed/refractory, FLT3-mutated)



Indication: AML (relapsed/refractory, FLT3-mutated)

Resistance / failure mechanism:

Bypass/parallel-pathway reactivation: outgrowth of RAS-MAPK-mutant subclones sustains proliferation independent of FLT3 inhibition, plus on-target F691L gatekeeper mutation.

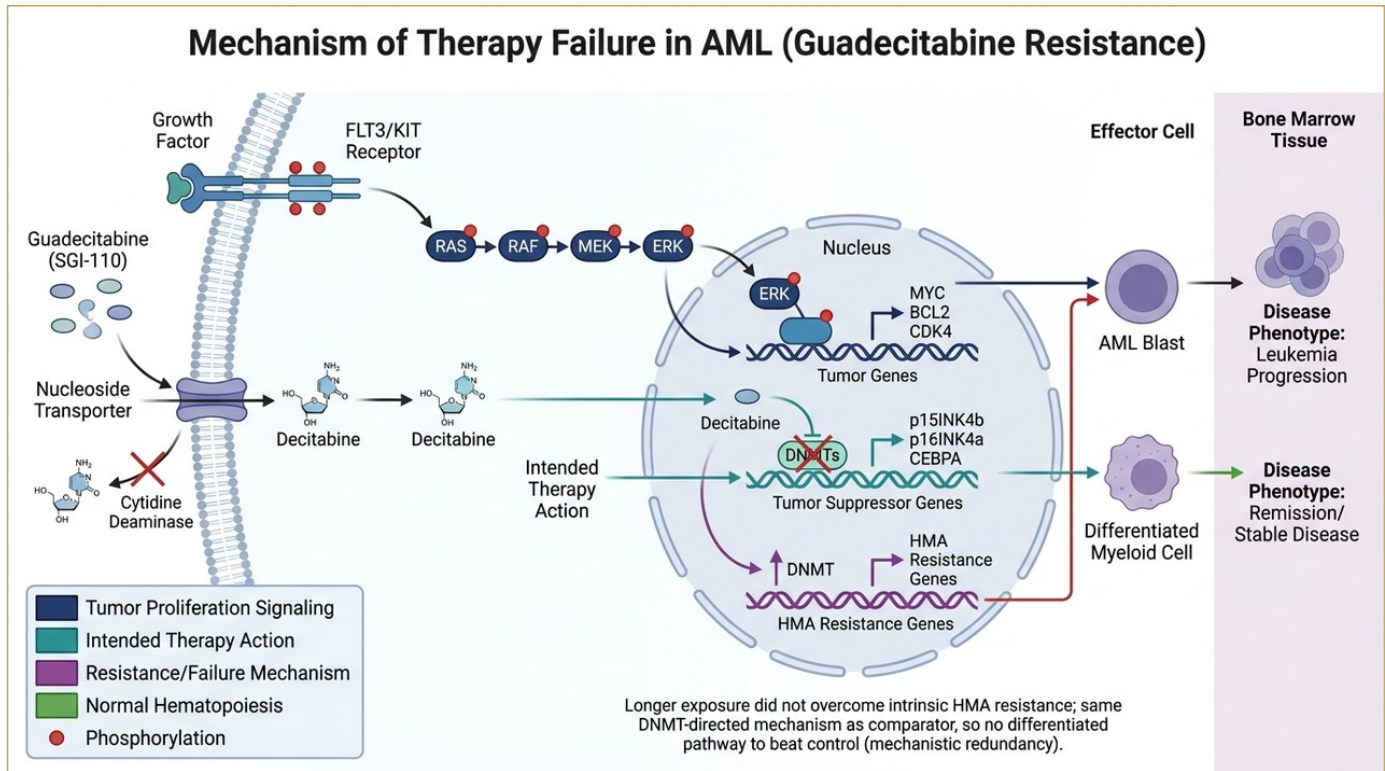
BiRAGAS pattern P2 · bypass/parallel-pathway

Citation: McMahon CM et al. Cancer Discov 2019;9(8):1050-1063. PMID 31048320

ClinicalTrials.gov: [NCT02421939](https://clinicaltrials.gov/ct2/show/study/NCT02421939)

Guadecitabine (SGI-110)

AML (newly diagnosed, unfit for intensive induction)



Indication: AML (newly diagnosed, unfit for intensive induction)

Resistance / failure mechanism:

Longer decitabine exposure did not overcome intrinsic HMA resistance; the same DNMT-directed mechanism as the comparator, so no differentiated pathway to beat control (mechanistic redundancy vs standard HMAs).

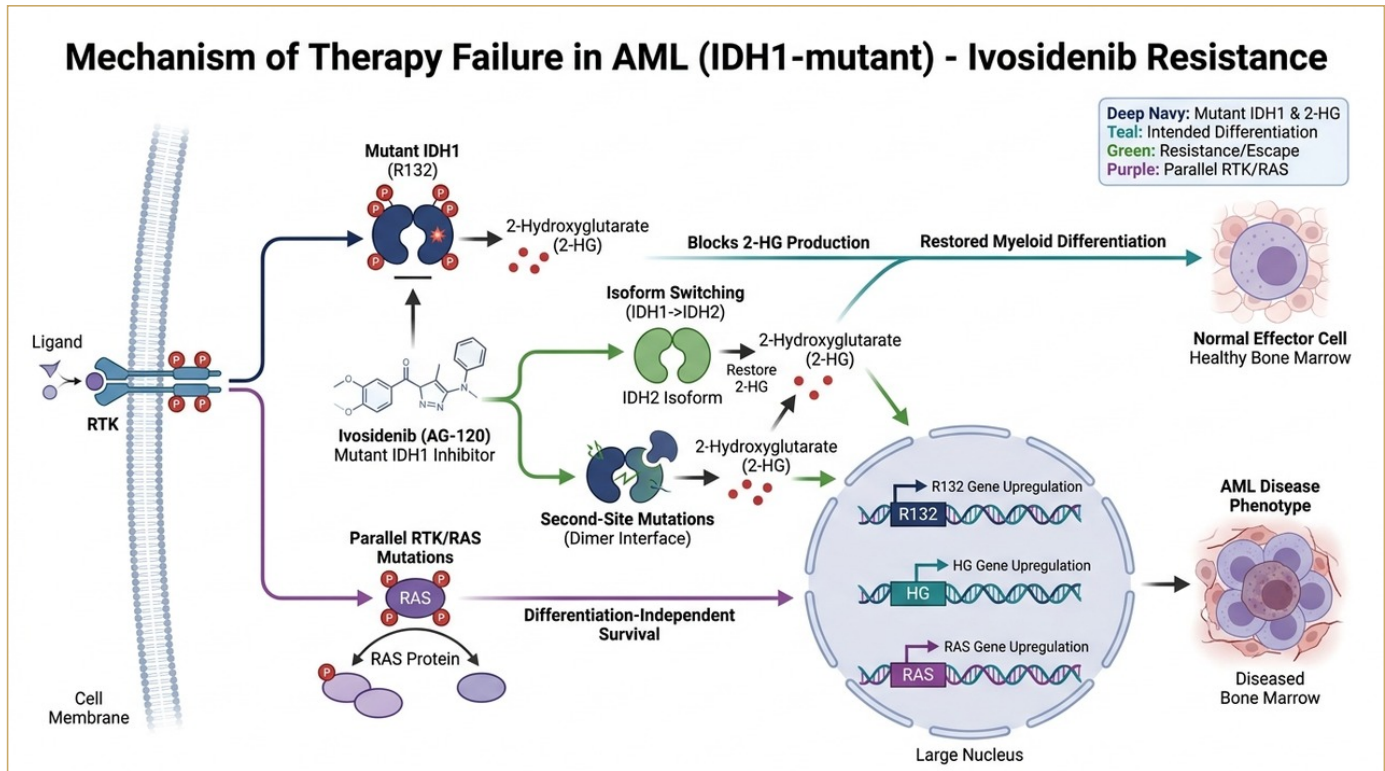
BiRAGAS pattern P2 · pathway-redundancy

Citation: Fenaux P et al. Lancet Haematol 2023 (ASTRAL-1); ClinicalTrials.gov NCT02348489 (PMID (verify, unresolved))

ClinicalTrials.gov: [NCT02348489](https://clinicaltrials.gov/ct2/show/study/NCT02348489)

Ivosidenib (AG-120)

AML (IDH1-mutant)



Indication: AML (IDH1-mutant)

Resistance / failure mechanism:

Isoform switching (IDH1→IDH2) and second-site mutations at the drug-binding dimer interface restore 2-HG production; parallel receptor-tyrosine-kinase/RAS mutations provide differentiation-independent survival.

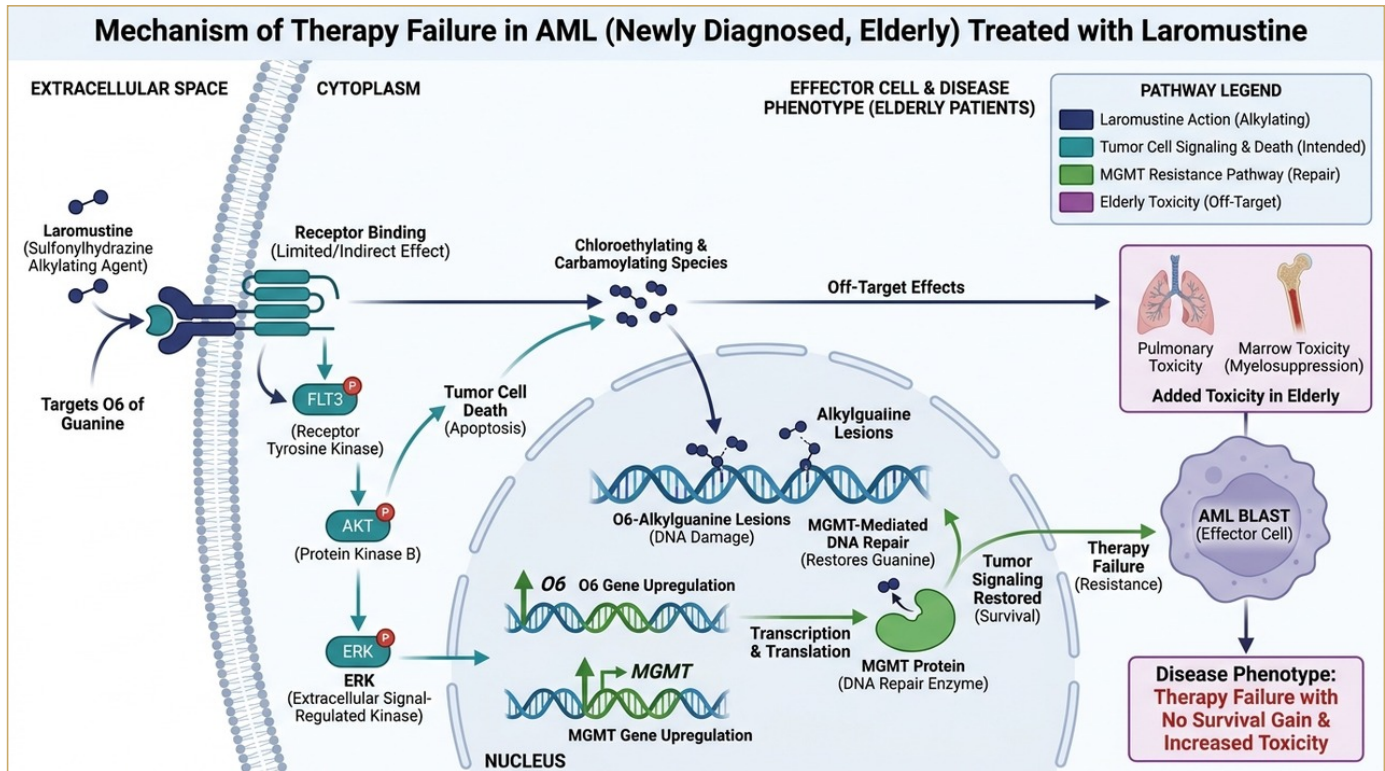
BiRAGAS pattern P7 · bypass/parallel-pathway

Citation: Intlekofer AM et al. Nature 2018;559:125-129 (acquired resistance via IDH2 dimer-interface mutations), PMID 29950729

ClinicalTrials.gov: [NCT02074839](https://clinicaltrials.gov/ct2/show/study/NCT02074839)

Laromustine (cloretazine, VNP40101M)

AML (newly diagnosed, elderly)



Indication: AML (newly diagnosed, elderly)

Resistance / failure mechanism:

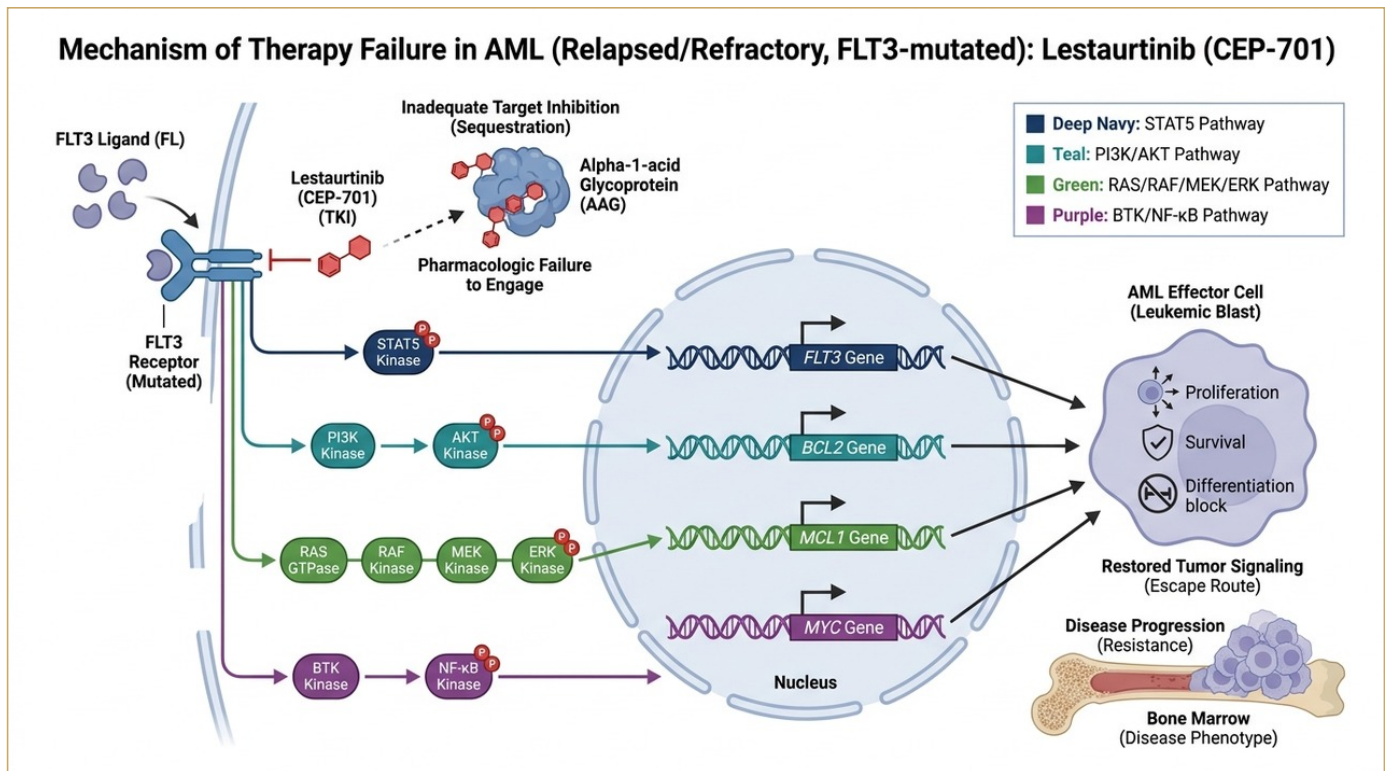
Alkylator activity counteracted by MGMT-mediated DNA-repair of O6-alkylguanine lesions; added pulmonary/marrow toxicity in elderly patients with no offsetting survival gain.

BiRAGAS pattern P4 · DNA-repair/apoptosis-evasion

Citation: Schiller GJ et al. J Clin Oncol 2010 (laromustine elderly AML); PMID 20026800

Lestaurtinib (CEP-701)

AML (relapsed/refractory, FLT3-mutated)



Indication: AML (relapsed/refractory, FLT3-mutated)

Resistance / failure mechanism:

Inadequate/inconsistent target inhibition (high plasma protein binding, alpha-1-acid glycoprotein sequestration) meant FLT3 was rarely fully suppressed in vivo, pharmacologic failure to engage the driver.

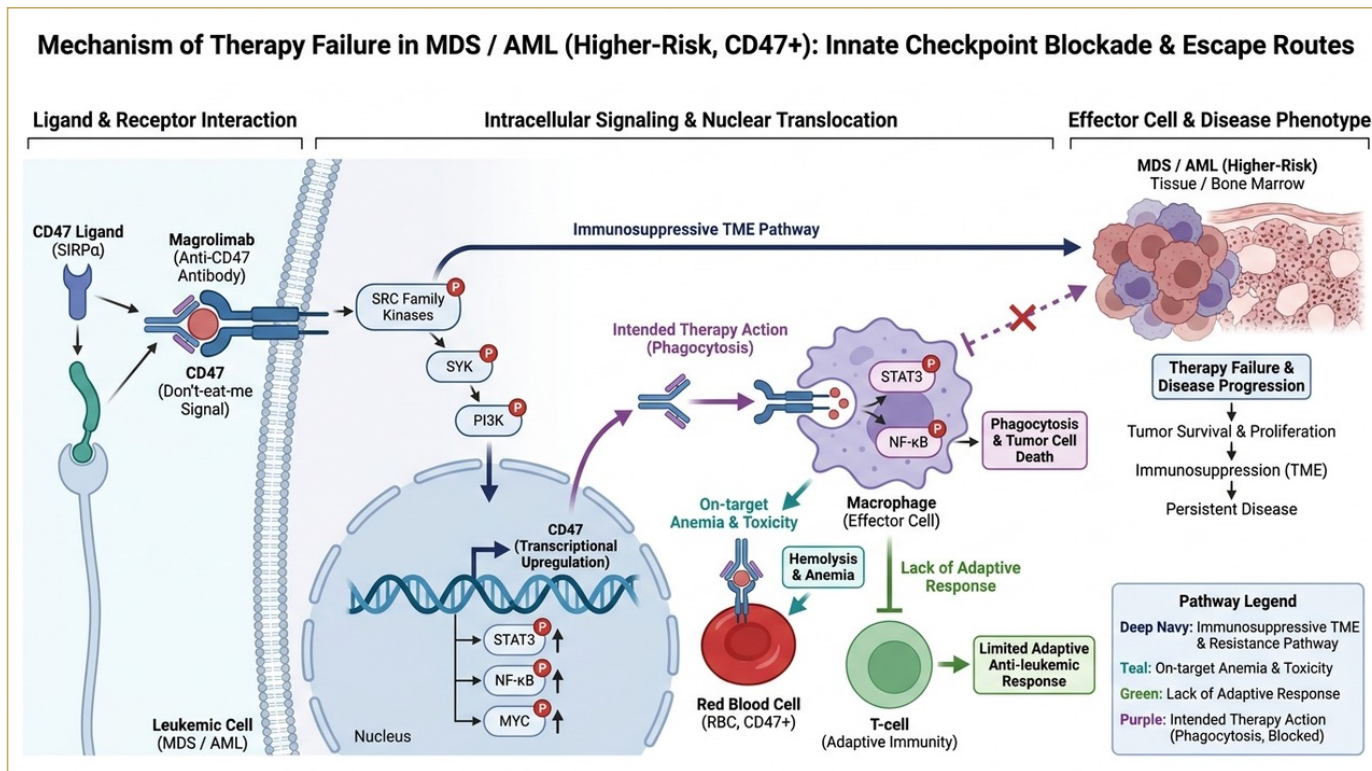
BiRAGAS pattern P4 · pharmacologic/efflux-metabolism

Citation: Levis M et al. Blood 2011;117(12):3294-301. PMID 21653326

ClinicalTrials.gov: [NCT00079482](https://clinicaltrials.gov/ct2/show/study/NCT00079482)

Magrolimab

MDS / AML (higher-risk, CD47+)



Indication: MDS / AML (higher-risk, CD47+)

Resistance / failure mechanism:

Innate immune checkpoint blockade did not overcome the immunosuppressive AML/MDS microenvironment; on-target anemia (CD47 on RBCs) and lack of adaptive anti-leukemic response limited efficacy.

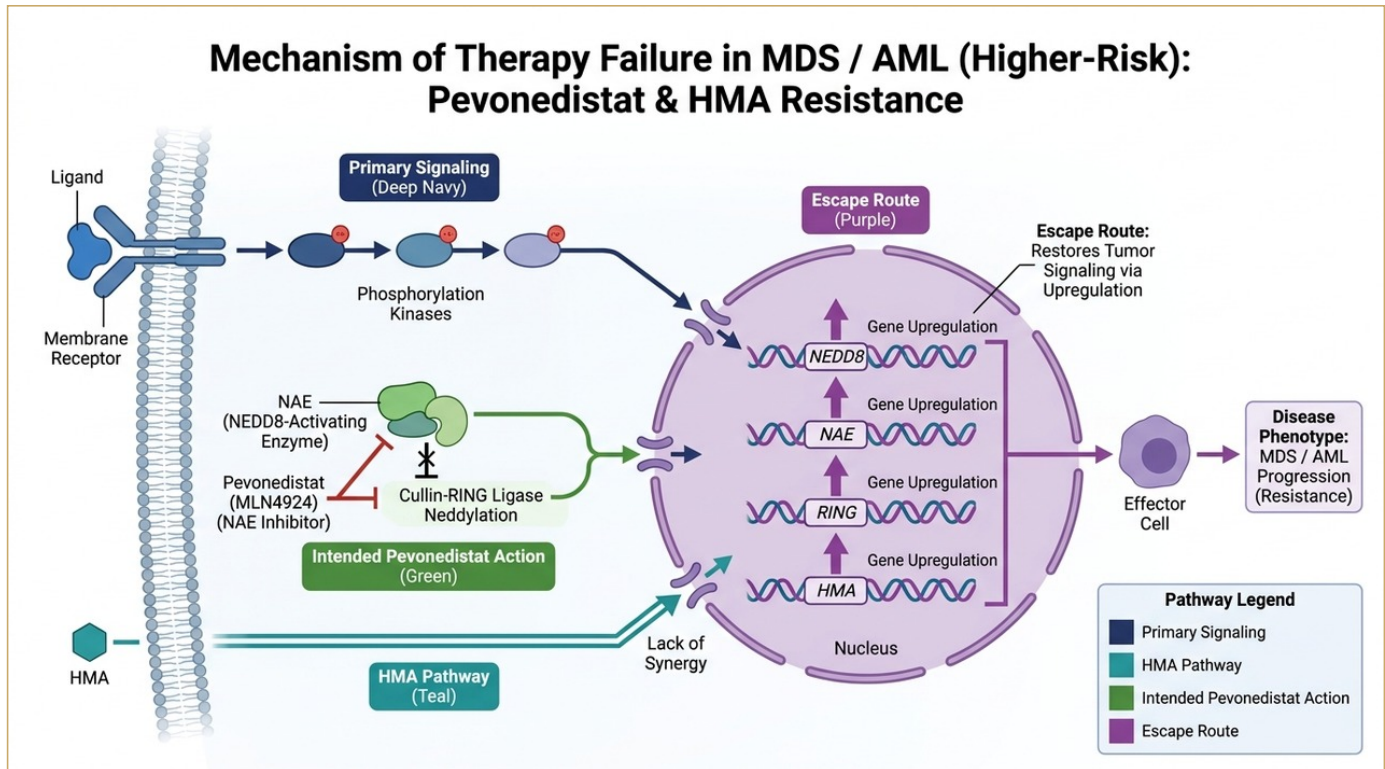
BiRAGAS pattern P3 · TME/immune-exclusion

Citation: Gilead Sciences press releases 2023-2024; ClinicalTrials.gov NCT04313881 (ENHANCE)

ClinicalTrials.gov: [NCT04313881](https://clinicaltrials.gov/ct2/show/study/NCT04313881)

Pevonedistat (MLN4924)

MDS / AML (higher-risk)



Indication: MDS / AML (higher-risk)

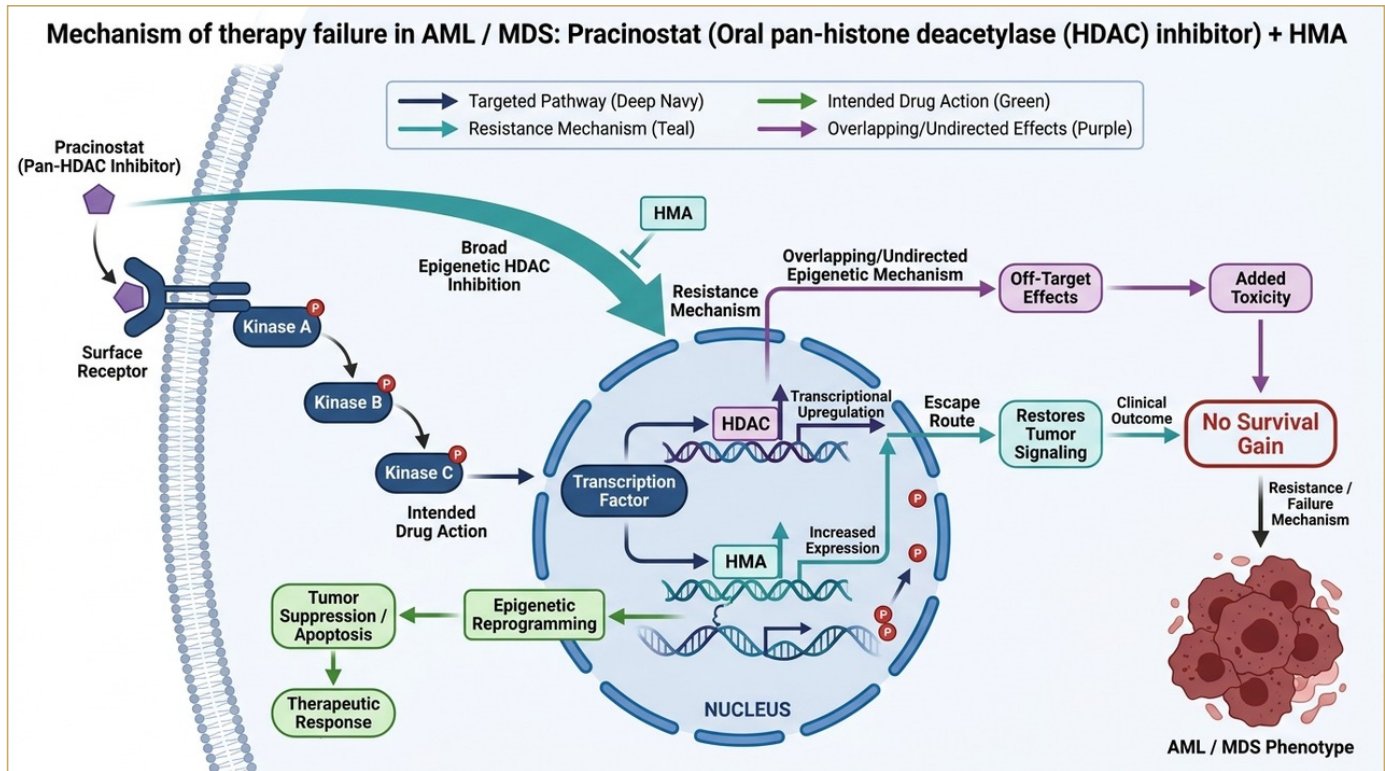
Resistance / failure mechanism:

Adding NAE inhibition to an HMA lacked a biomarker-defined dependency; the two agents did not synergize on a shared, validated resistance node in the trial population.

BiRAGAS pattern P6 · combination-no-rationale

Citation: Sekeres MA et al. (PANTHER Phase 3, 2023); ClinicalTrials.gov NCT03268954 (PMID (verify, unresolved))

ClinicalTrials.gov: [NCT03268954](https://clinicaltrials.gov/ct2/show/study/NCT03268954)



Indication: AML / MDS

Resistance / failure mechanism:

Broad epigenetic HDAC inhibition added to an HMA without a predictive biomarker; overlapping/undirected epigenetic mechanism plus added toxicity yielded no survival gain.

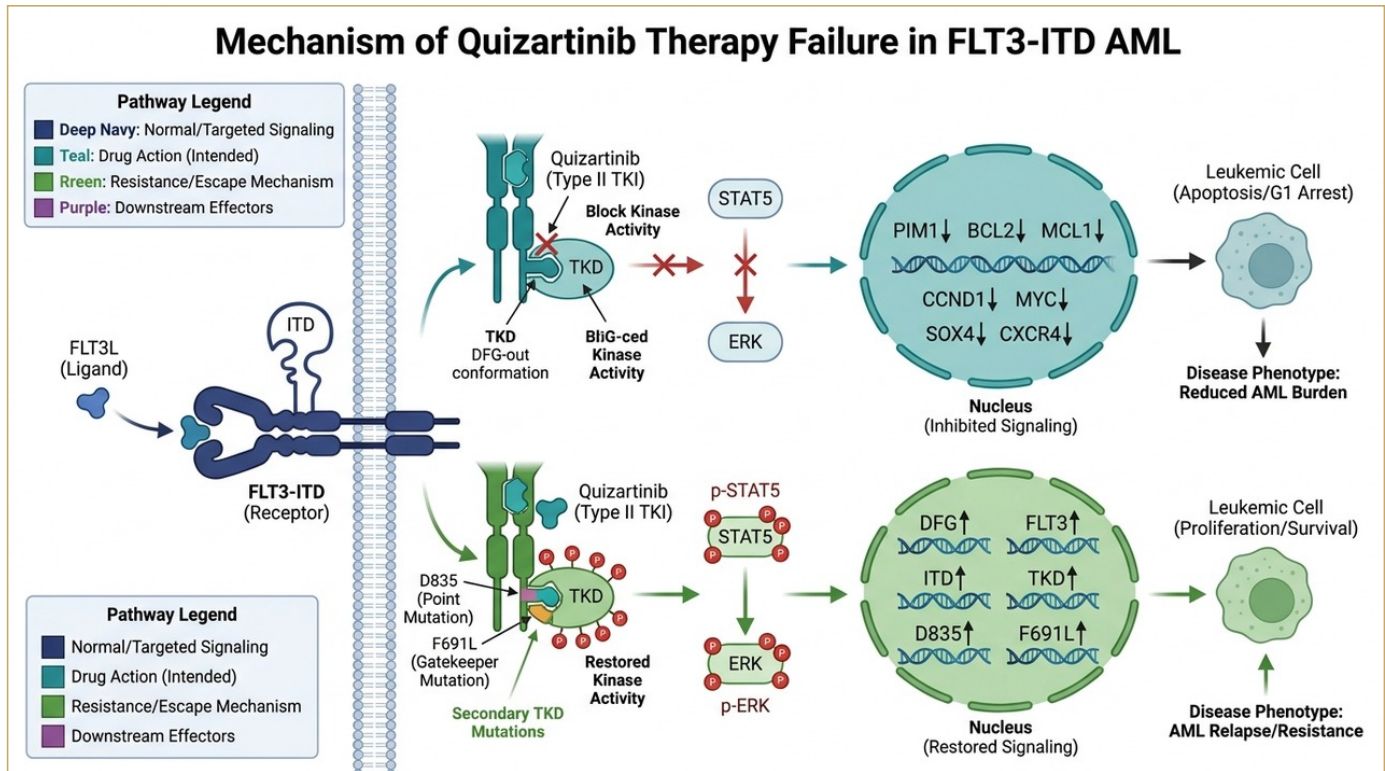
BiRAGAS pattern P6 · combination-no-rationale

Citation: Helsinn/MEI Pharma announcement 2020; ClinicalTrials.gov NCT03151408 (PMID (verify, unresolved))

ClinicalTrials.gov: [NCT03151408](https://clinicaltrials.gov/ct2/show/study/NCT03151408)

Quizartinib

AML (relapsed/refractory, FLT3-ITD)



Indication: AML (relapsed/refractory, FLT3-ITD)

Resistance / failure mechanism:

Secondary FLT3-TKD point mutations (D835, F691L gatekeeper) restore kinase activity in the ITD-mutant clone despite continued drug (classic on-mechanism target-mutation escape).

BiRAGAS pattern P7 · target-mutation

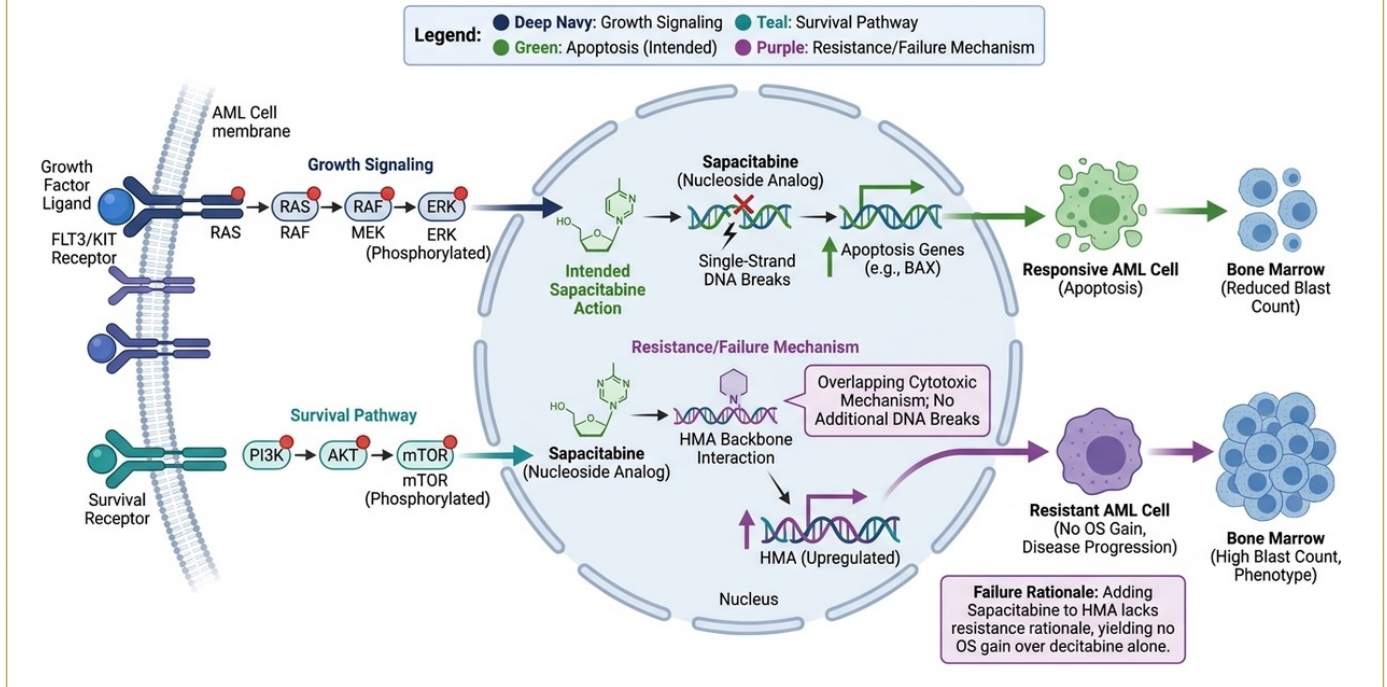
Citation: Smith CC et al. Nature 2012;485(7397):260-3. PMID 22504184

ClinicalTrials.gov: [NCT02039726](https://clinicaltrials.gov/ct2/show/study/NCT02039726)

Sapacitabine

AML (newly diagnosed, elderly ≥ 70)

Mechanism of Therapy Failure in AML (Elderly ≥ 70 , Sapacitabine Treatment)



Indication: AML (newly diagnosed, elderly ≥ 70)

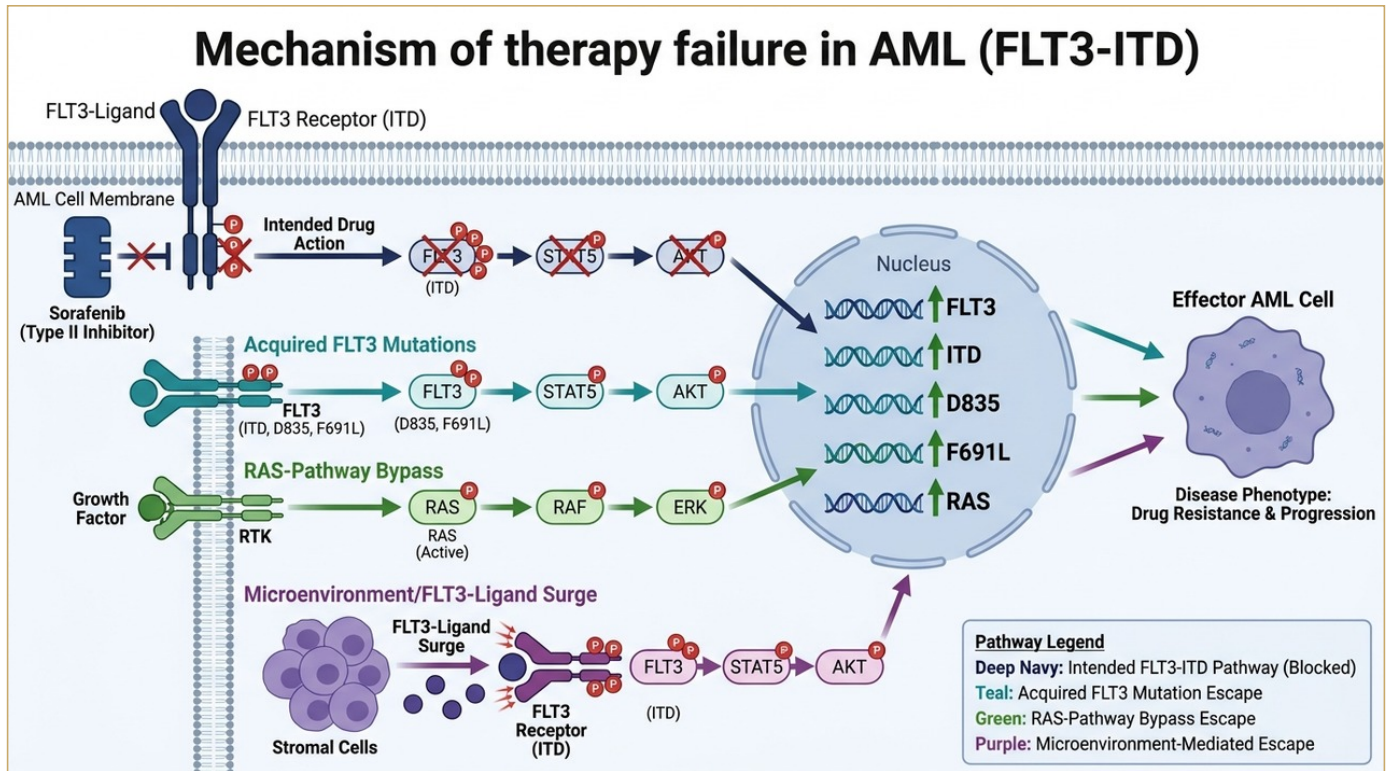
Resistance / failure mechanism:

Adding a second cytotoxic nucleoside to an HMA backbone lacked a resistance-directed rationale; overlapping cytotoxic mechanism yielded no OS gain over decitabine alone.

BiRAGAS pattern P6 · combination-no-rationale

Citation: Kantarjian HM et al. Cancer 2021;127(23):4421-4431 (SEAMLESS). PMID 34424530

ClinicalTrials.gov: [NCT01303796](https://clinicaltrials.gov/ct2/show/study/NCT01303796)



Indication: AML (FLT3-ITD)

Resistance / failure mechanism:

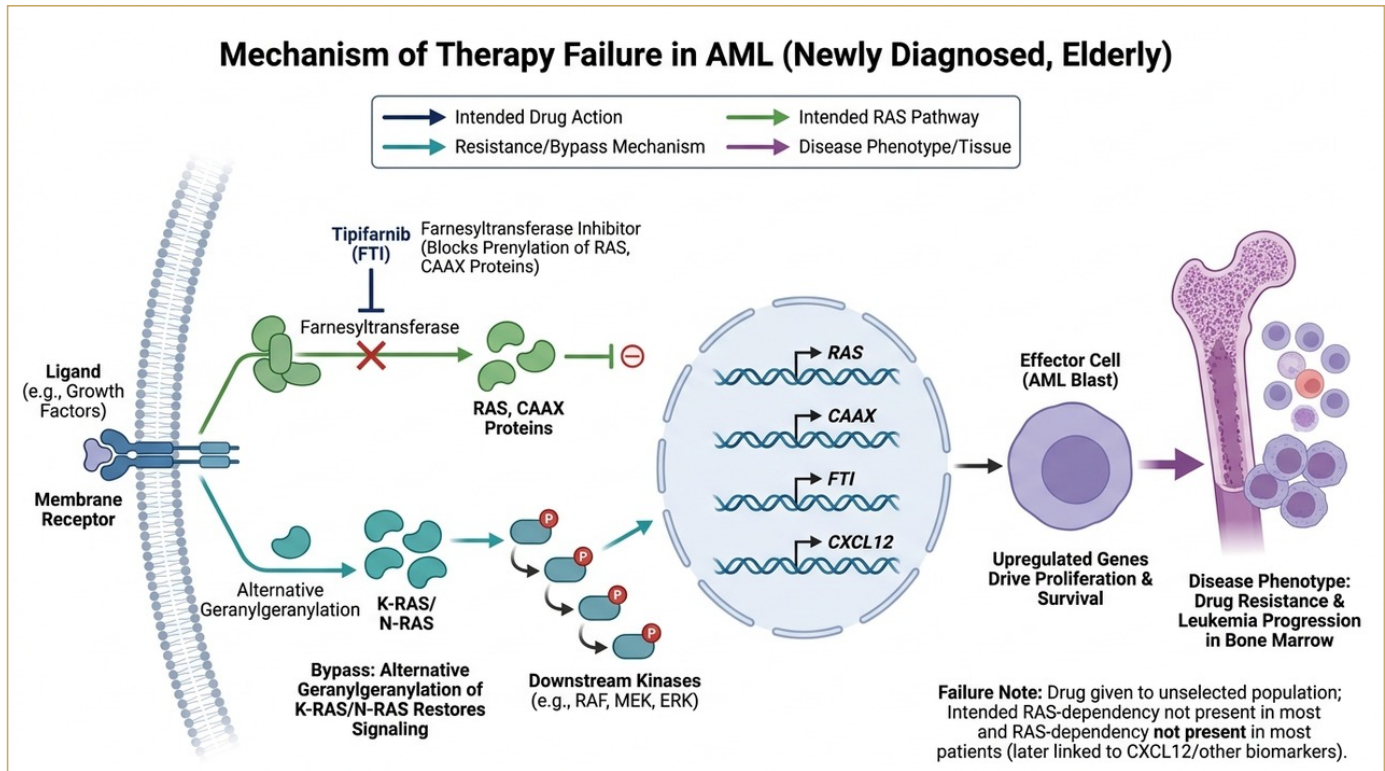
Acquired FLT3 activation-loop/gatekeeper (D835, F691L) mutations plus RAS-pathway bypass; also microenvironment/FLT3-ligand surges blunt type-II inhibitor efficacy.

BiRAGAS pattern P7 · target-mutation

Citation: Man CH et al. Blood 2012;119(22):5133-43 (sorafenib FLT3-ITD resistance); PMID 22368270

Tipifarnib

AML (newly diagnosed, elderly)



Indication: AML (newly diagnosed, elderly)

Resistance / failure mechanism:

FTI blockade is bypassed by alternative geranylgeranylation of K-RAS/N-RAS, and the drug was given to a molecularly unselected population (later work pointed to CXCL12/other biomarkers), so the intended RAS-pathway dependency was not present in most patients.

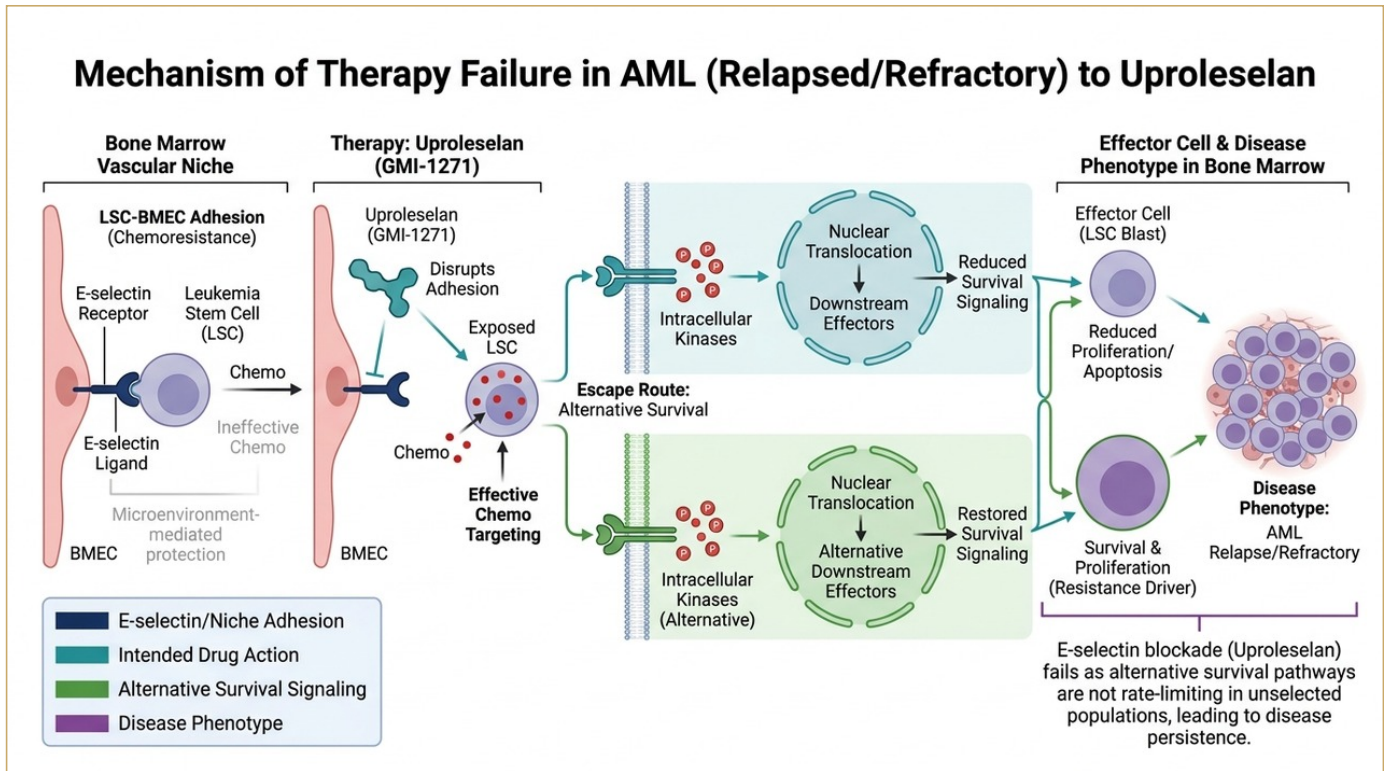
BiRAGAS pattern P3 · bypass/parallel-pathway

Citation: Harousseau JL et al. Blood 2009;114(6):1166-73. PMID 19168783

Uproleselan (GMI-1271)

AML (relapsed/refractory)

Mechanism of Therapy Failure in AML (Relapsed/Refractory) to Uproleselan



Indication: AML (relapsed/refractory)

Resistance / failure mechanism:

The E-selectin/niche-adhesion axis, though a real chemoresistance mechanism preclinically, was not the rate-limiting driver of survival in the biomarker-unselected trial population.

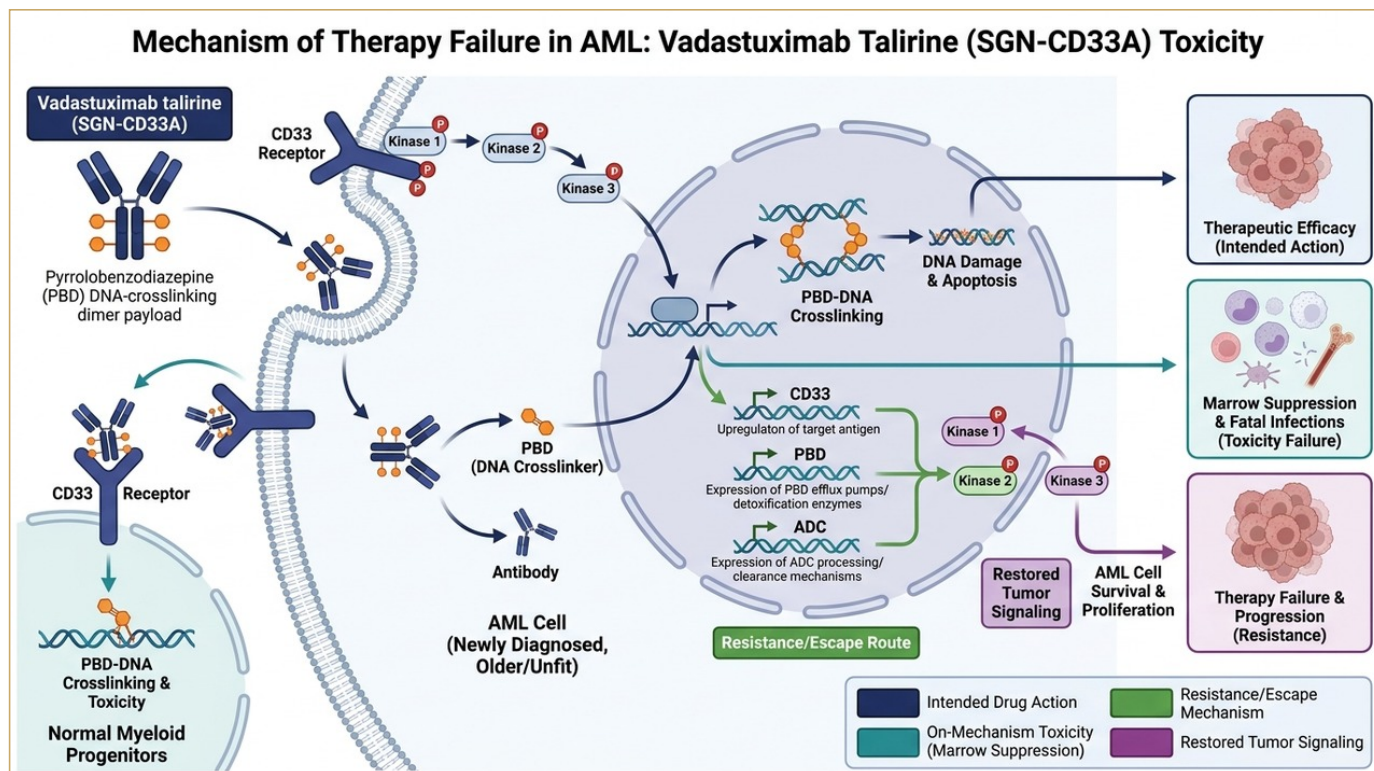
BiRAGAS pattern P1 · TME/immune-exclusion

Citation: GlycoMimetics Phase 3 top-line 2024; ClinicalTrials.gov NCT03616470 (PMID (verify, unresolved))

ClinicalTrials.gov: [NCT03616470](https://clinicaltrials.gov/ct2/show/study/NCT03616470)

Vadastuximab talirine (SGN-CD33A)

AML (newly diagnosed, older/unfit)



Indication: AML (newly diagnosed, older/unfit)

Resistance / failure mechanism:

On-mechanism ADC/PBD toxicity, CD33 is expressed on normal myeloid progenitors, so target-mediated marrow suppression plus DNA-crosslink toxicity drove fatal infections rather than an efficacy failure.

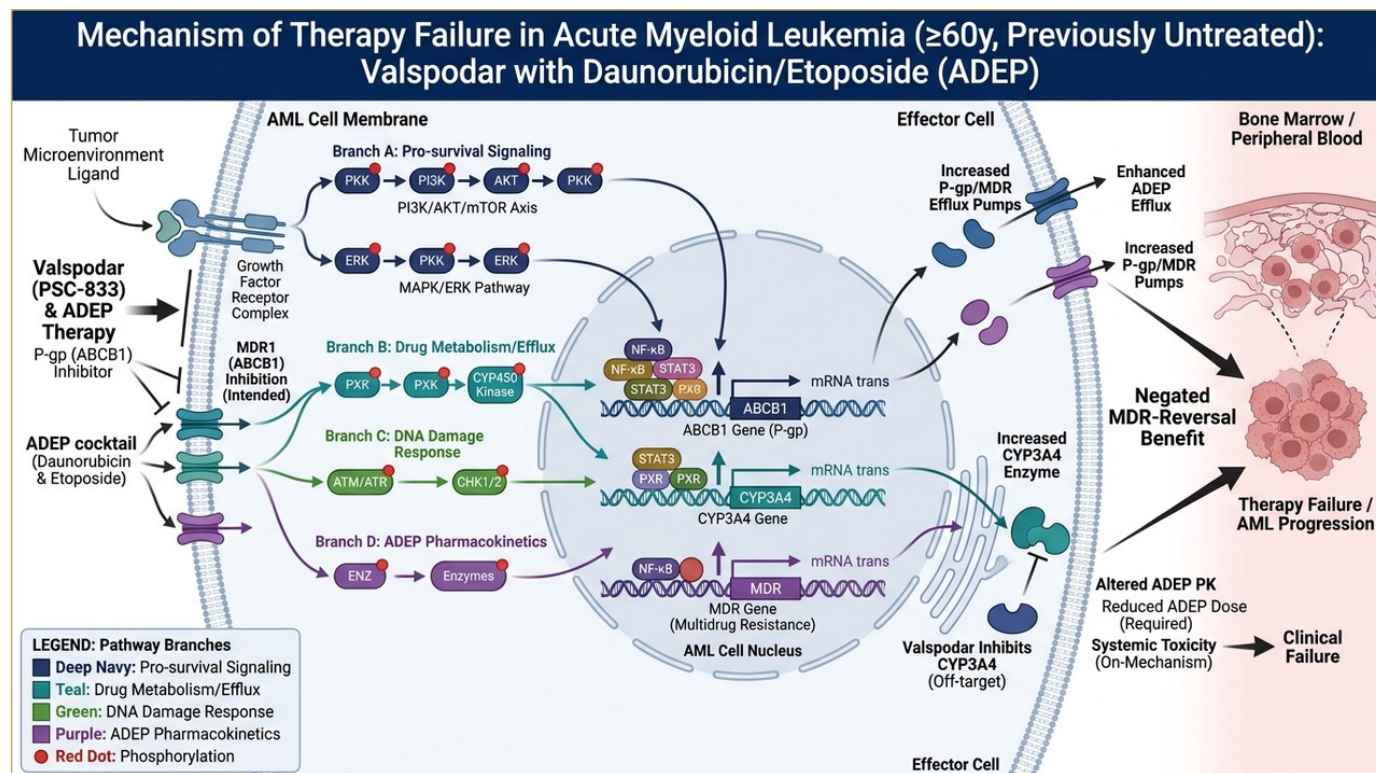
BiRAGAS pattern P4 · on-mechanism-toxicity

Citation: Seattle Genetics announcement; ASH Clinical News 2017; ClinicalTrials.gov NCT02785900 (PMID (verify, unresolved))

ClinicalTrials.gov: [NCT02785900](https://clinicaltrials.gov/ct2/show/study/NCT02785900)

Valspodar (PSC-833) added to daunorubicin/etoposide (ADEP)

Acute myeloid leukemia (>=60y, previously untreated)



Indication: Acute myeloid leukemia (>=60y, previously untreated)

Resistance / failure mechanism:

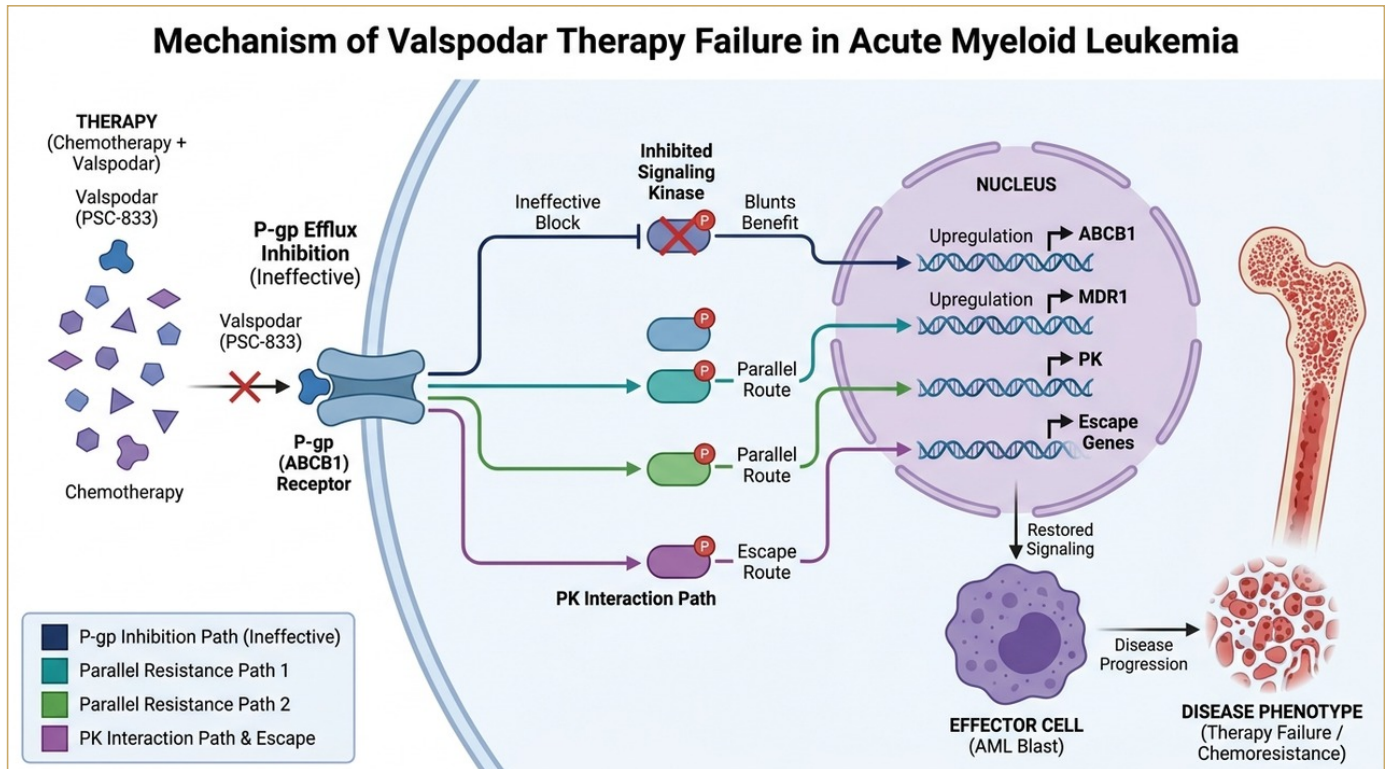
Valspodar inhibits CYP3A4, altering pharmacokinetics of co-administered cytotoxics and requiring dose reduction, causing on-mechanism toxicity that negated any MDR-reversal benefit

BiRAGAS pattern P6 · on-mechanism-toxicity

Citation: Baer MR et al. Blood 2002;100(4):1224-1232. PMID 12149202

Valspodar (PSC-833) added to induction/consolidation chemotherapy

Acute myeloid leukemia (<60y, newly diagnosed)



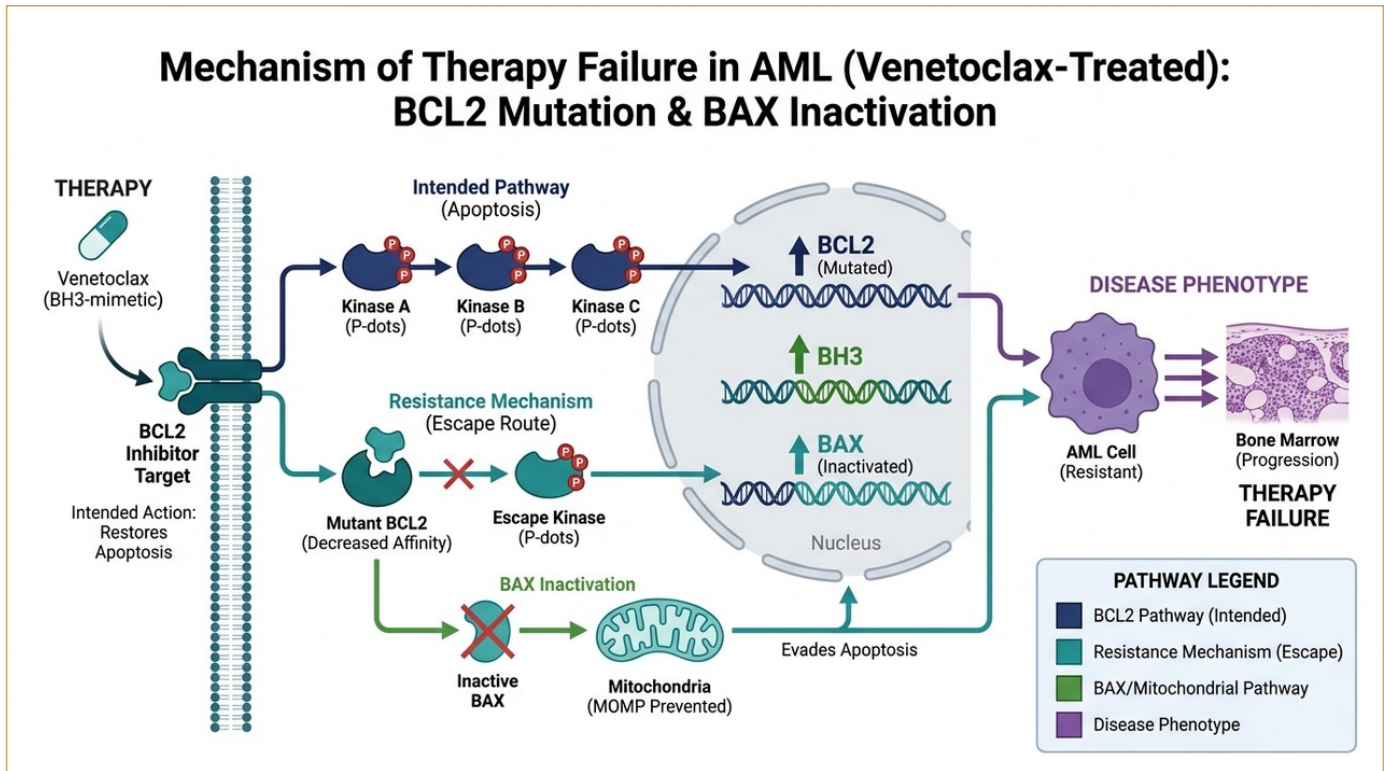
Indication: Acute myeloid leukemia (<60y, newly diagnosed)

Resistance / failure mechanism:

P-gp inhibition alone does not overcome AML chemoresistance; efflux is one of several parallel resistance routes and PK interactions blunt benefit

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Kolitz JE et al. Blood 2010;116(9):1413-1421. PMID 20522709



Indication: AML (venetoclax-treated)

Resistance / failure mechanism:

On-target BCL2 mutations decrease drug affinity; BAX inactivation prevents mitochondrial outer-membrane permeabilization, evading BH3-mimetic-induced apoptosis.

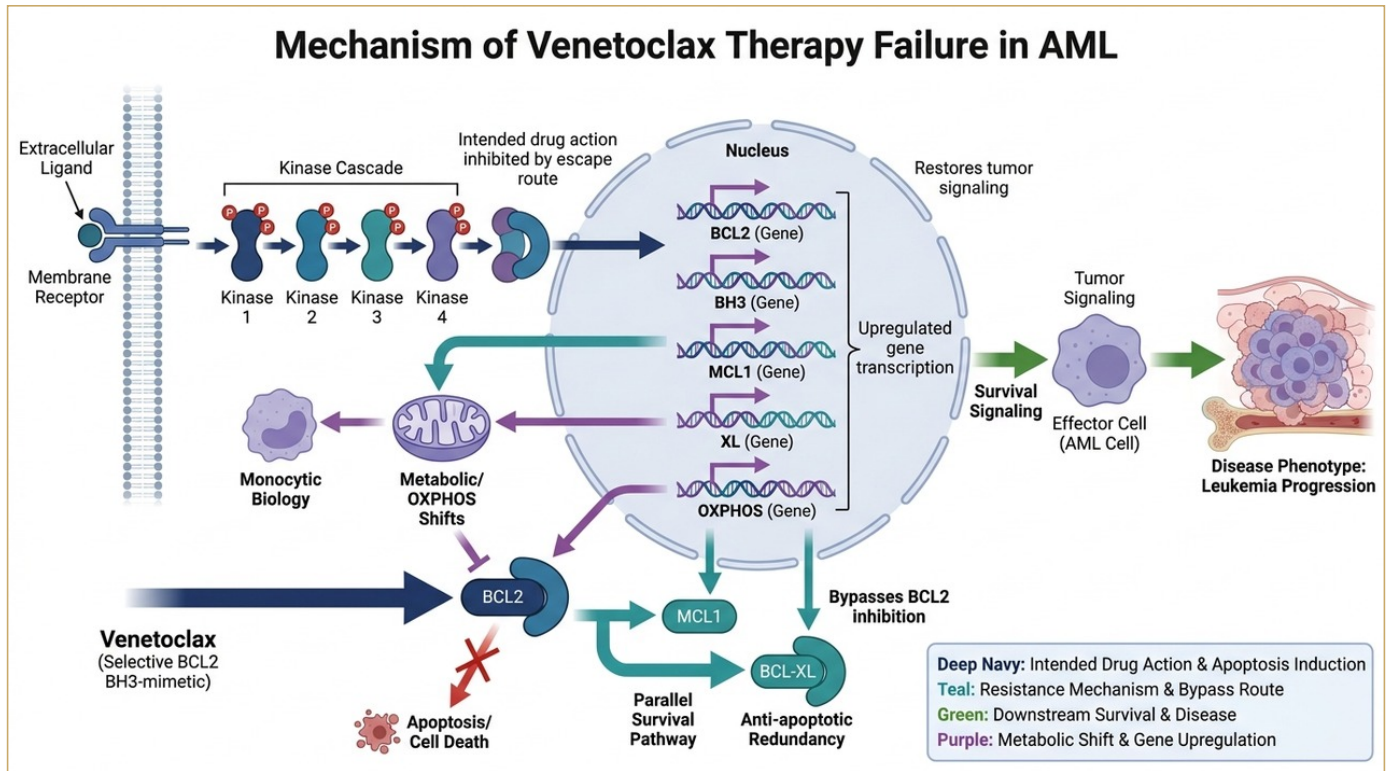
BiRAGAS pattern P7 · target-mutation

Citation: Blomberg P et al. Cancer Discov 2019;9(3):342-353 (BCL2 G101V); PMID 30514704

[ClinicalTrials.gov: NCT02993523](https://clinicaltrials.gov/ct2/show/study/NCT02993523)

Venetoclax

AML (venetoclax-treated)



Indication: AML (venetoclax-treated)

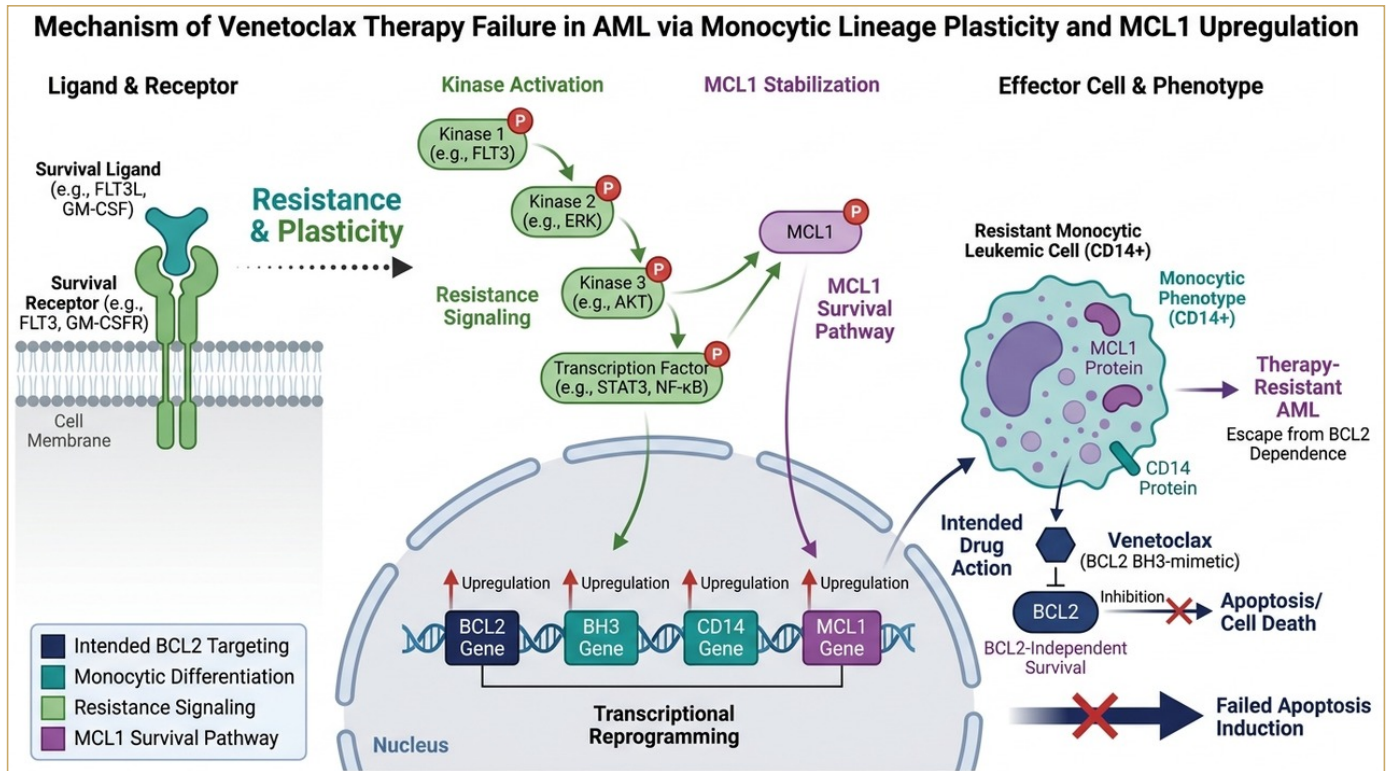
Resistance / failure mechanism:

Anti-apoptotic redundancy: MCL1 (and BCL-XL) upregulation, often driven by metabolic/OXPHOS shifts and monocytic biology, provides a parallel survival pathway bypassing BCL2 inhibition.

BiRAGAS pattern P2 · pathway-redundancy

Citation: Ramsey HE et al. Cancer Discov 2018;8(12):1566-1581 (MCL1 in venetoclax resistance); PMID (verify, unresolved)

ClinicalTrials.gov: [NCT02993523](https://clinicaltrials.gov/ct2/show/study/NCT02993523)



Indication: AML (venetoclax-treated)

Resistance / failure mechanism:

Lineage plasticity / differentiation state: monocytic (CD14+) leukemic cells lose BCL2 dependence and rely on MCL1, so venetoclax selects for or drives a resistant monocytic phenotype.

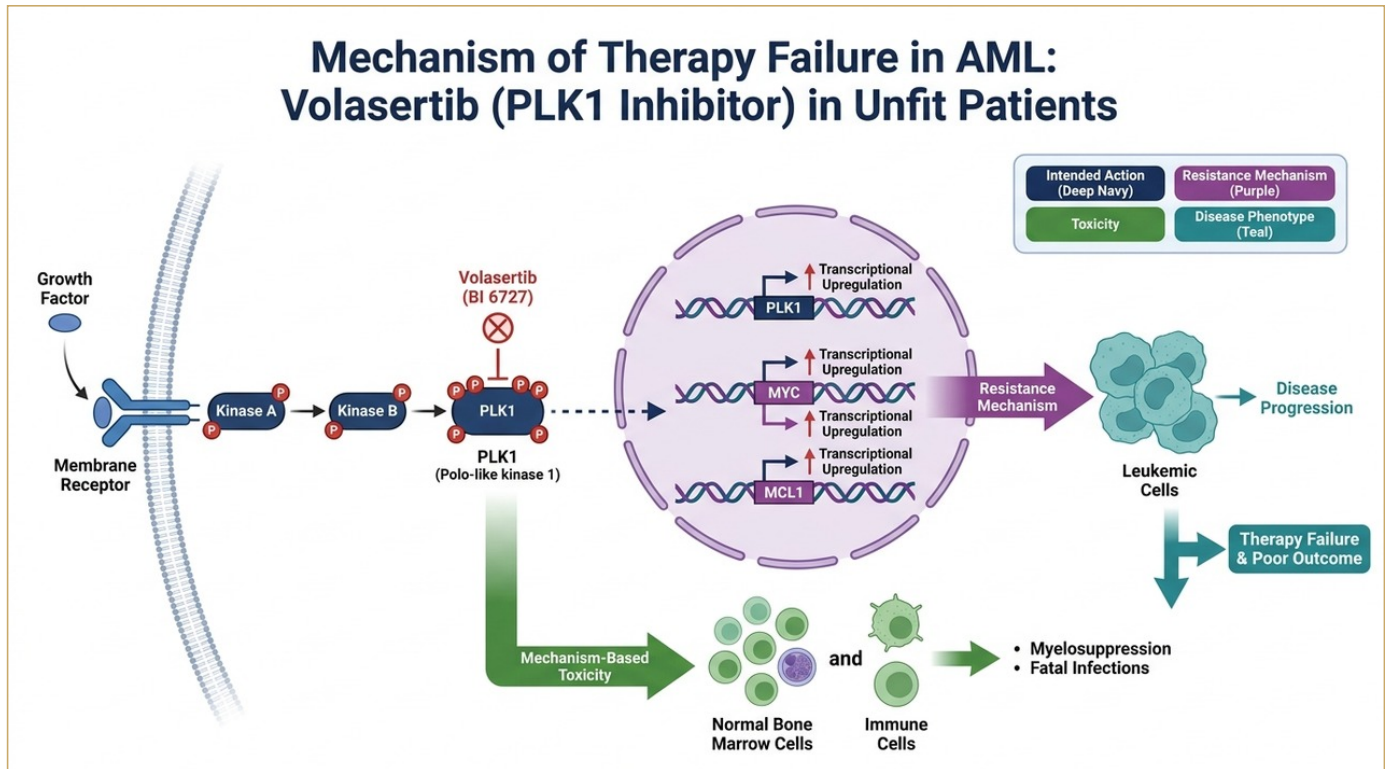
BiRAGAS pattern P2 · lineage-plasticity/transformation

Citation: Pei S et al. Cancer Discov 2020;10(4):536-551 (monocytic venetoclax resistance). PMID 31974170

ClinicalTrials.gov: [NCT02993523](https://clinicaltrials.gov/ct2/show/study/NCT02993523)

Volasertib (BI 6727)

AML (newly diagnosed, older/unfit)



Indication: AML (newly diagnosed, older/unfit)

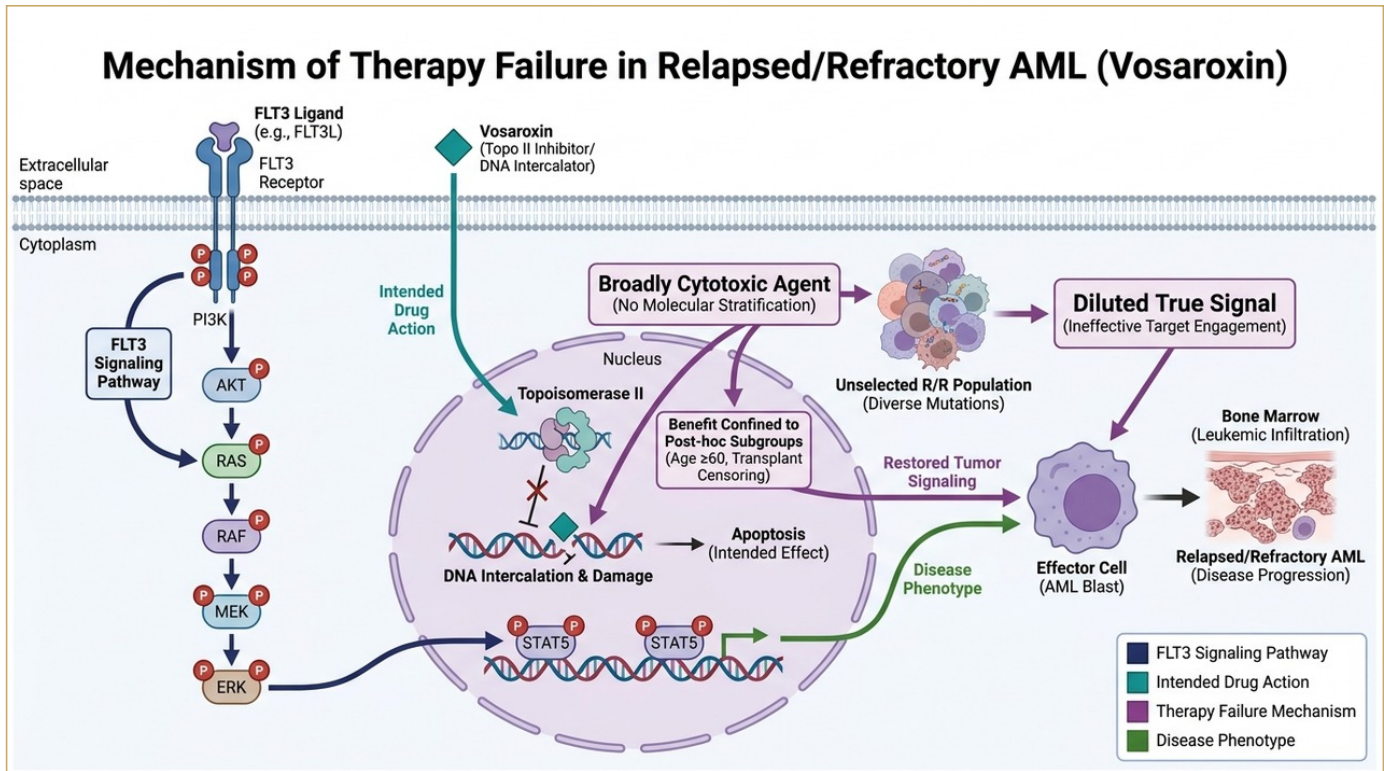
Resistance / failure mechanism:

Anti-mitotic PLK1 inhibition is not tumor-selective; added myelosuppression/fatal infections outweighed any leukemic-cell effect (mechanism-based toxicity in an unfit population).

BiRAGAS pattern P4 · on-mechanism-toxicity

Citation: Doehner H et al. Blood 2021;138(2):145-158 (Adjunctive Volasertib Phase 3). PMID 34350385

ClinicalTrials.gov: [NCT01721876](https://clinicaltrials.gov/ct2/show/study/NCT01721876)



Indication: AML (relapsed/refractory)

Resistance / failure mechanism:

Broadly cytotoxic DNA-damaging agent added to cytarabine with no molecularly stratified target; benefit confined to post-hoc subgroups (age ≥60, censoring for transplant), consistent with an unselected R/R population diluting any true signal.

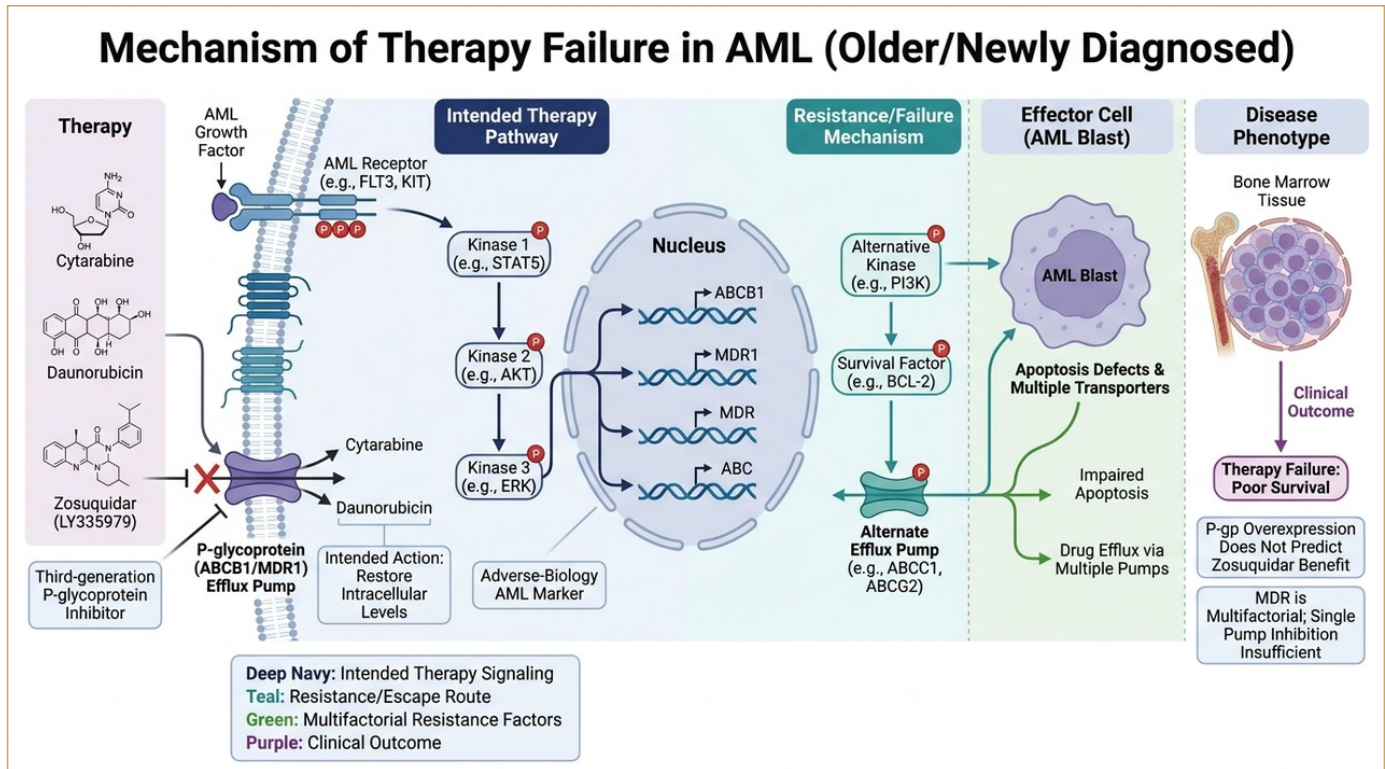
BiRAGAS pattern P3 · population-dilution

Citation: Ravandi F et al. Lancet Oncol 2015;16(9):1025-36. PMID 26234174

ClinicalTrials.gov: [NCT01191801](https://clinicaltrials.gov/ct2/show/study/NCT01191801)

Zosuquidar (LY335979) added to cytarabine + daunorubicin

Acute myeloid leukemia (older/newly diagnosed)



Indication: Acute myeloid leukemia (older/newly diagnosed)

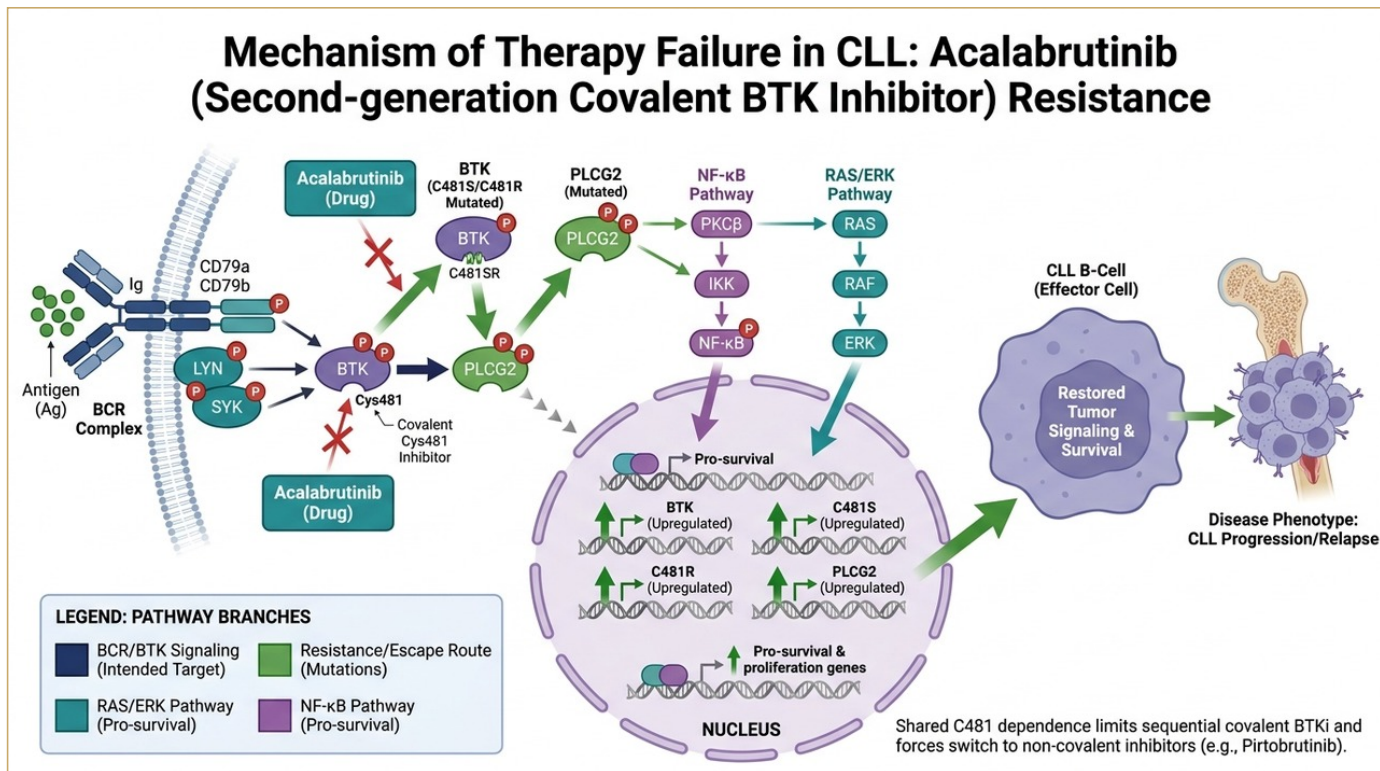
Resistance / failure mechanism:

P-gp overexpression is a marker of adverse-biology AML but pharmacologic pump inhibition did not translate to survival; MDR is multifactorial (multiple ABC transporters, apoptosis defects), so blocking one efflux pump is insufficient

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Cripe LD et al. Blood 2010;116(20):4077-4085. PMID 20716770

ClinicalTrials.gov: NCT00046930



Indication: CLL

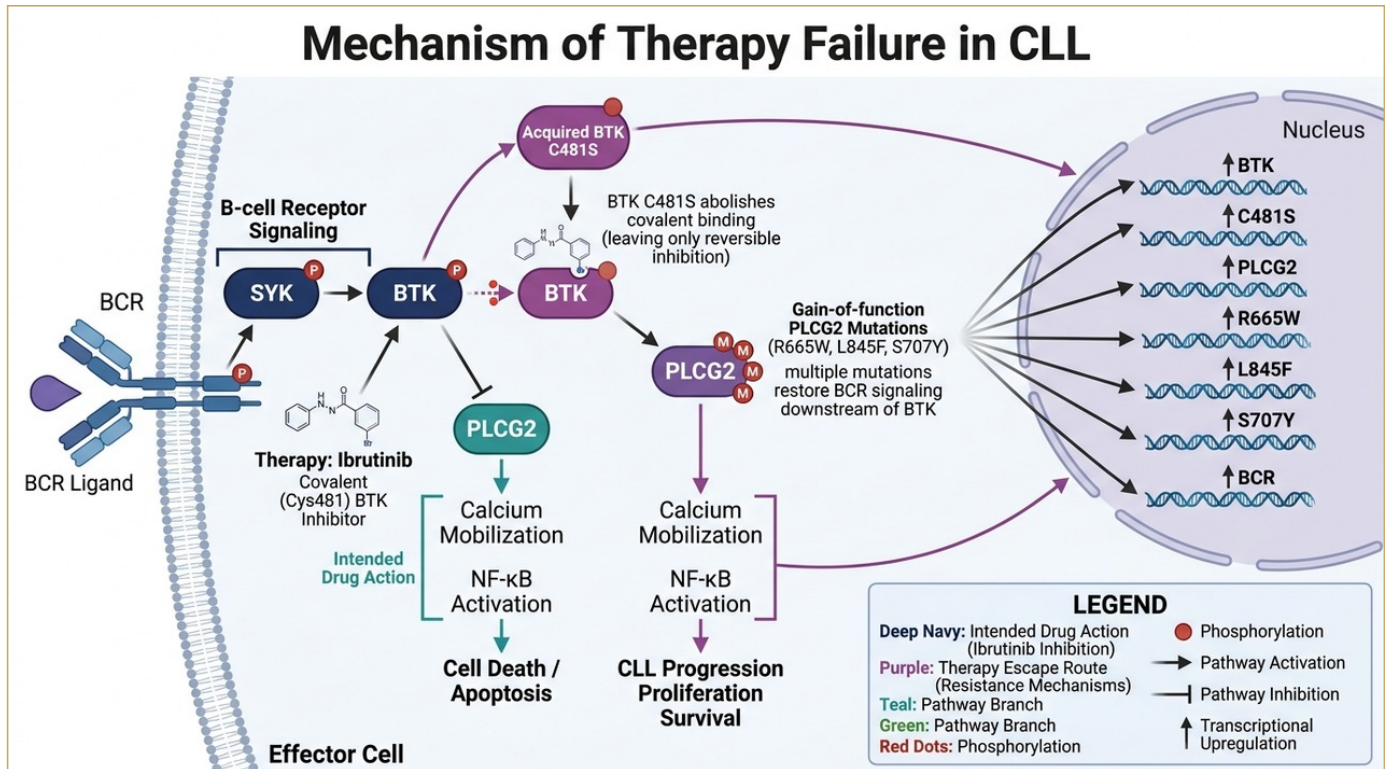
Resistance / failure mechanism:

BTK C481S/C481R and PLCG2 mutations; shared Cys481 dependence limits sequential covalent BTKi and forces switch to non-covalent inhibitors (e.g., pirtobrutinib)

BiRAGAS pattern P7 · target-mutation

Citation: Woyach JA et al. resistance analyses; Sharman JP et al. ELEVATE-TN, Lancet 2020 (PMID (verify, unresolved))

[ClinicalTrials.gov: NCT02475681](https://clinicaltrials.gov/ct2/show/study/NCT02475681)



Indication: CLL

Resistance / failure mechanism:

Acquired BTK C481S abolishes covalent binding (leaving only reversible inhibition); gain-of-function PLCG2 mutations (R665W, L845F, S707Y) restore BCR signaling downstream of BTK

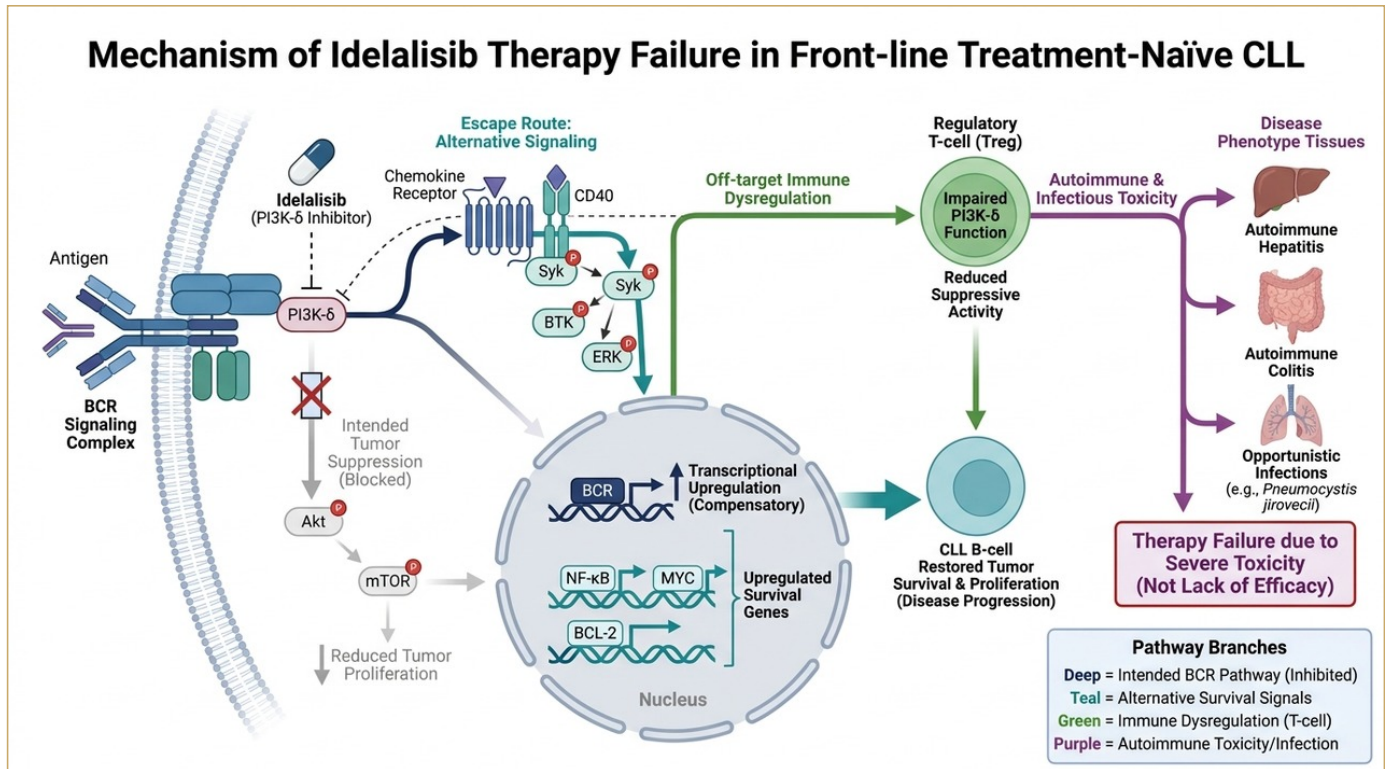
BiRAGAS pattern P7 · target-mutation

Citation: Woyach JA et al. N Engl J Med 2014;370:2286-2294 (PMID 24869598)

ClinicalTrials.gov: [NCT01578707](https://clinicaltrials.gov/ct2/show/study/NCT01578707)

Idelalisib (combination front-line)

CLL (treatment-naïve, front-line)



Indication: CLL (treatment-naïve, front-line)

Resistance / failure mechanism:

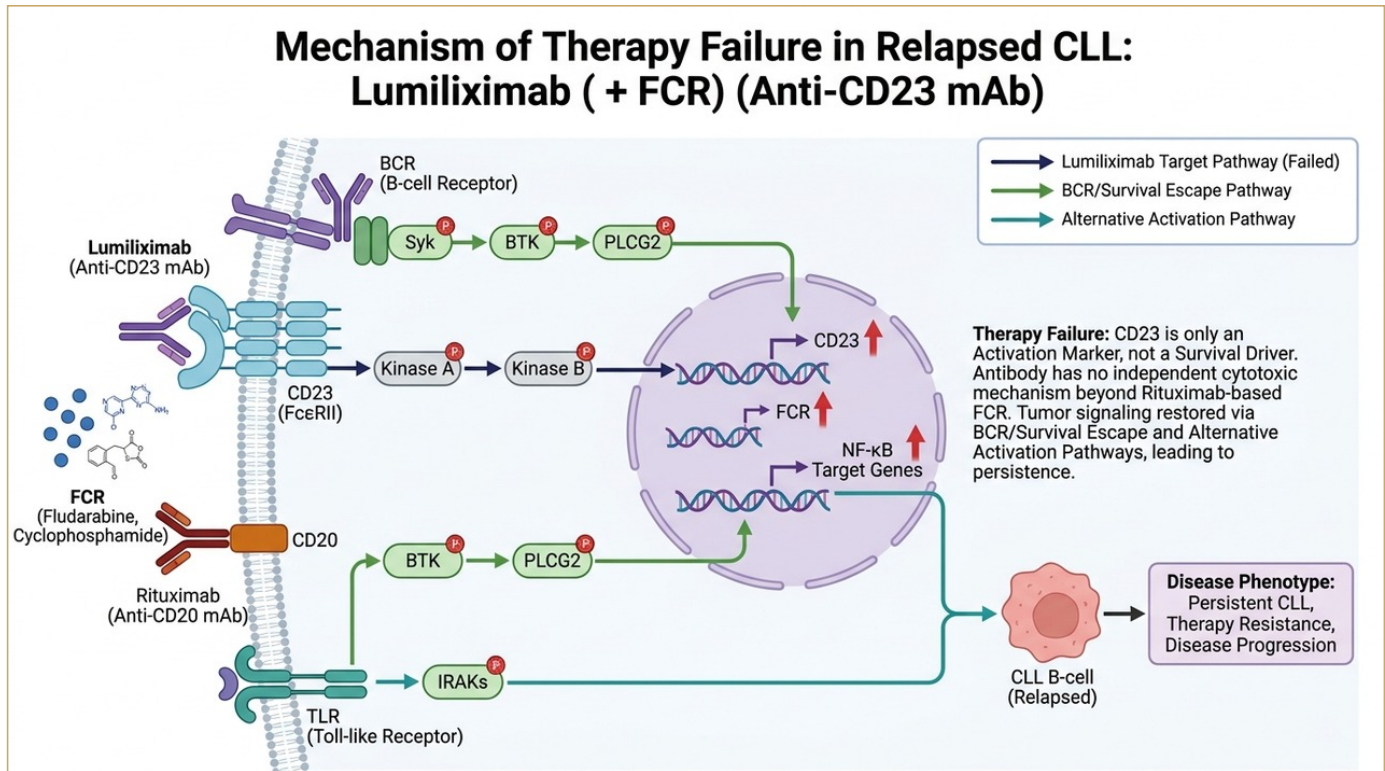
On-mechanism/off-target immune dysregulation: PI3K-delta blockade impairs regulatory T-cell function, driving autoimmune hepatitis/colitis and opportunistic infection; toxicity, not lack of efficacy, drove failure

BiRAGAS pattern P4 · on-mechanism-toxicity

Citation: Lampson BL et al. Blood 2016;128:195-203 (PMID 27247136)

Lumiliximab (+ FCR)

CLL (relapsed)



Indication: CLL (relapsed)

Resistance / failure mechanism:

CD23 is an activation-marker correlate, not a survival driver in CLL; the antibody added no independent cytotoxic mechanism beyond rituximab-based FCR

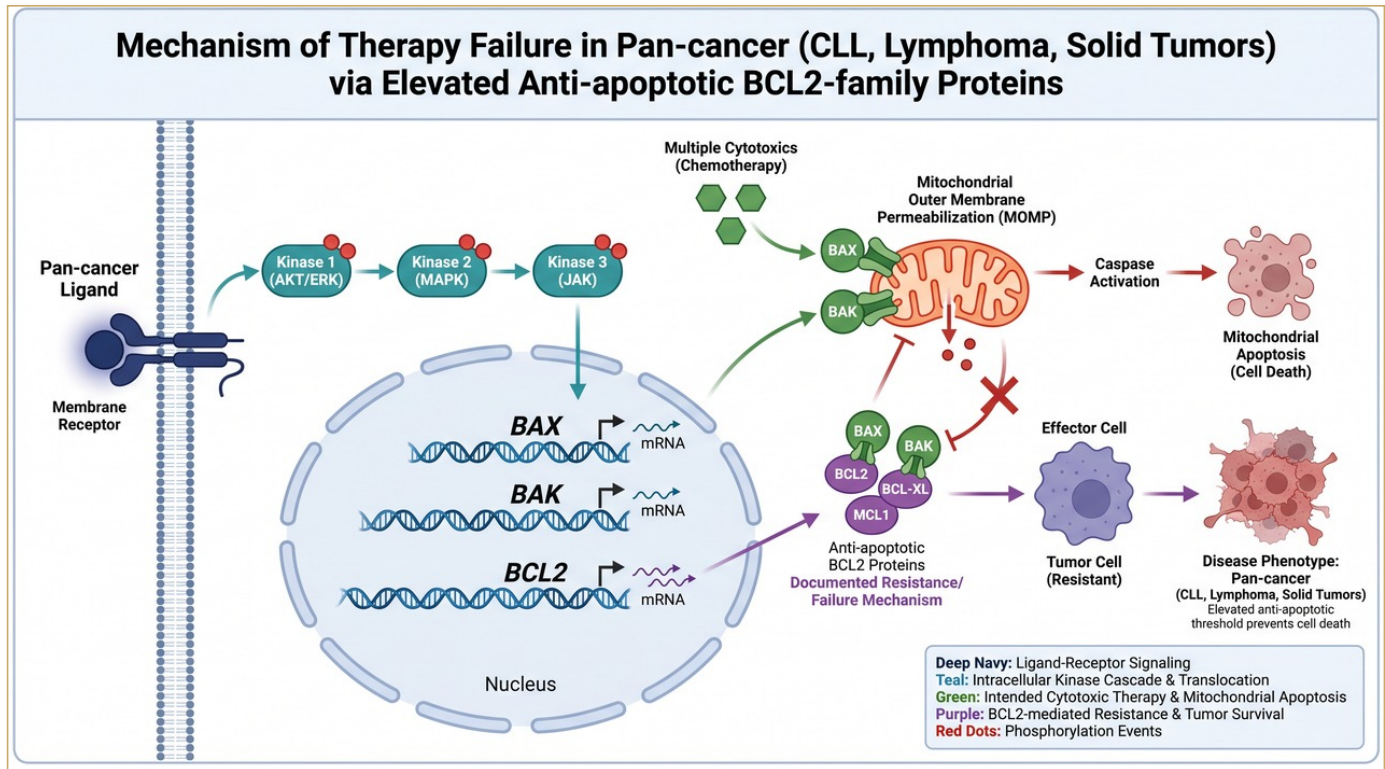
BiRAGAS pattern P1 · correlate-not-driver

Citation: Awan FT et al. Leuk Lymphoma 2014 (LUCID/152CL201), PMID 25130401; ClinicalTrials.gov NCT00391066

[ClinicalTrials.gov: NCT00391066](https://clinicaltrials.gov/ct2/show/study/NCT00391066)

Multiple cytotoxics dependent on intrinsic (mitochondrial) apoptosis

Pan-cancer (CLL, lymphoma, solid)



Indication: Pan-cancer (CLL, lymphoma, solid)

Resistance / failure mechanism:

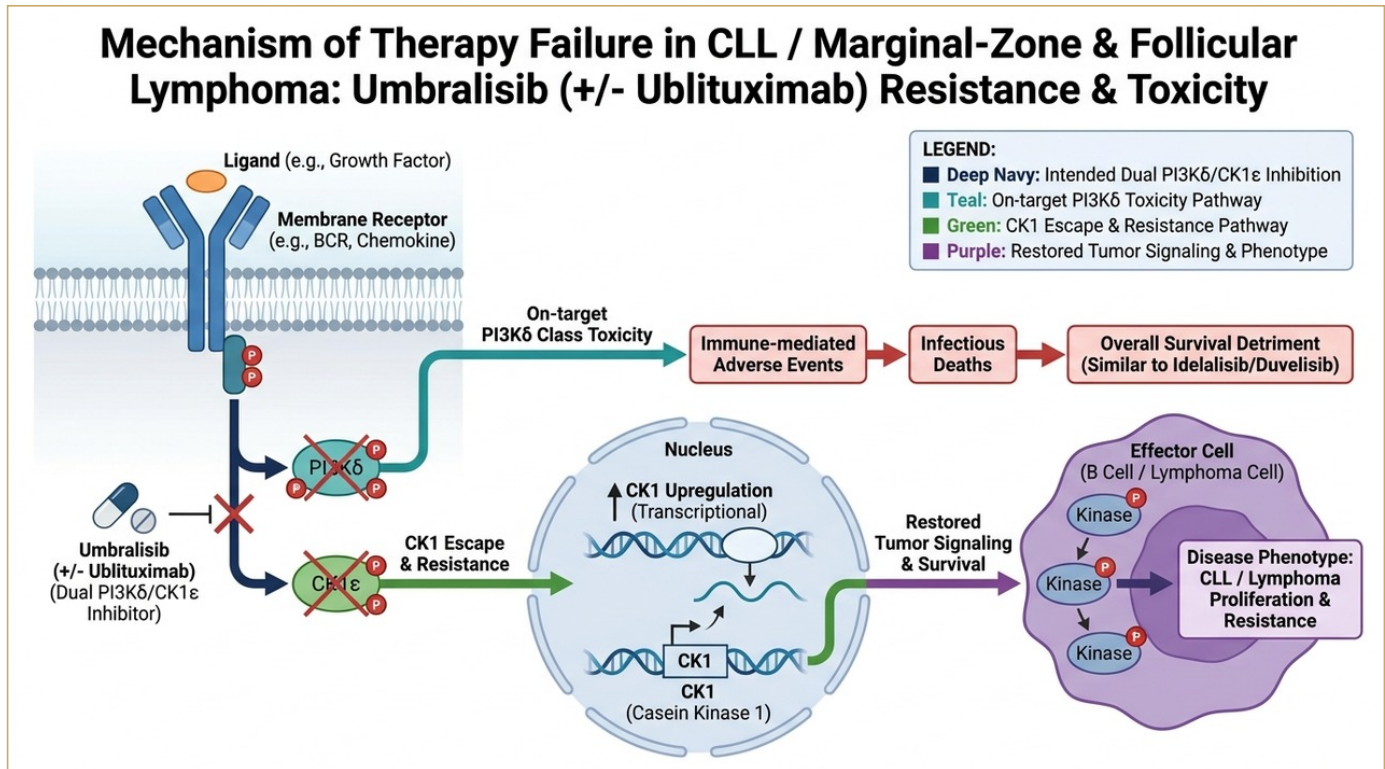
Elevated anti-apoptotic BCL2-family proteins raise the apoptotic threshold so cytotoxic damage fails to trigger cell death

BiRAGAS pattern P1 · DNA-repair/apoptosis-evasion

Citation: Adams JM, Cory S. Oncogene 2007;26(9):1324-1337. PMID 17322918

Umbralisib (+/- ublituximab)

CLL / marginal-zone & follicular lymphoma



Indication: CLL / marginal-zone & follicular lymphoma

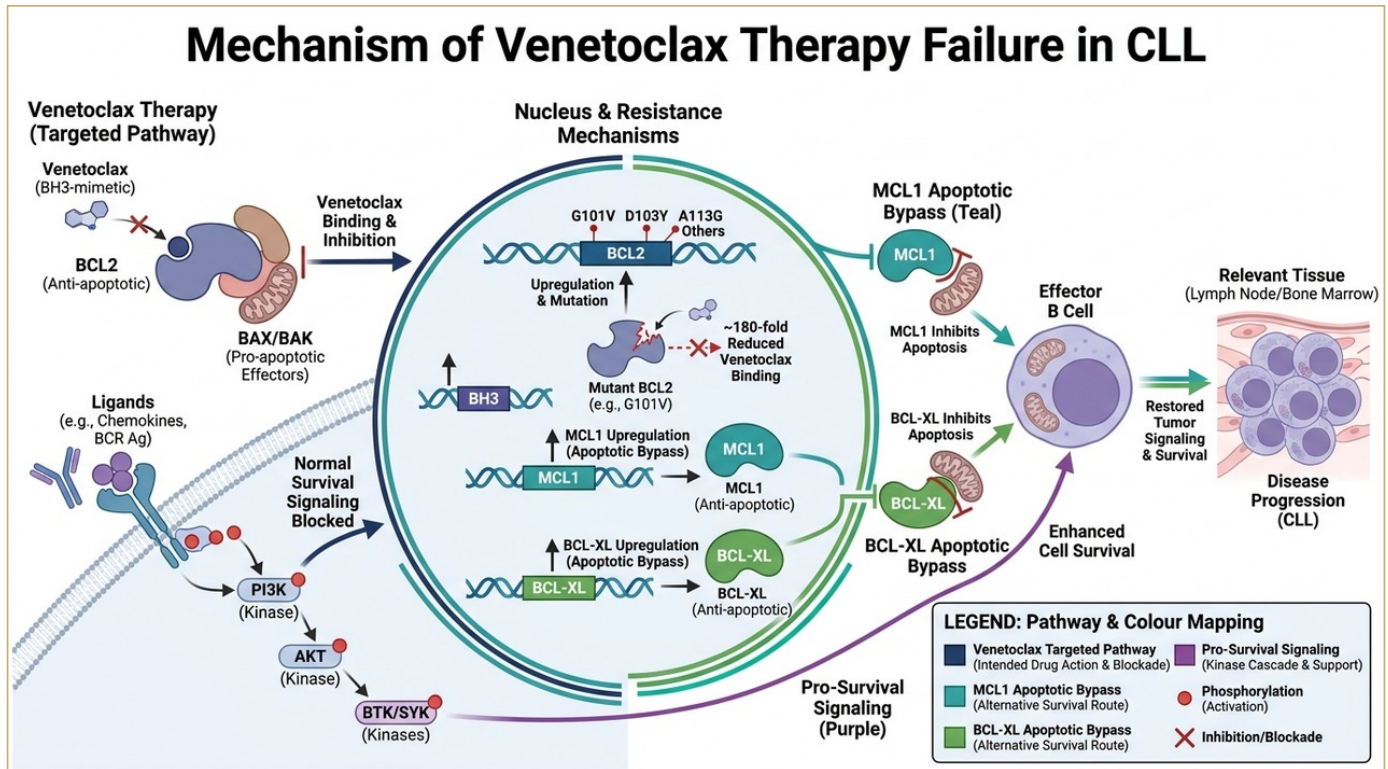
Resistance / failure mechanism:

On-mechanism PI3K-delta class toxicity (immune-mediated and infectious deaths) producing an overall-survival detriment; the same class liability seen with idelalisib/duvelisib

BiRAGAS pattern P4 · on-mechanism-toxicity

Citation: Gribben JG et al. UNITY-CLL; FDA/TG Therapeutics withdrawal 2022 (PMID (verify, unresolved))

[ClinicalTrials.gov: NCT02612311](https://clinicaltrials.gov/ct2/show/study/NCT02612311)



Indication: CLL

Resistance / failure mechanism:

Acquired BCL2 G101V (and D103Y, A113G, others) reduces venetoclax binding ~180-fold; parallel upregulation of MCL1/BCL-XL provides an apoptotic bypass

BiRAGAS pattern P7 · target-mutation

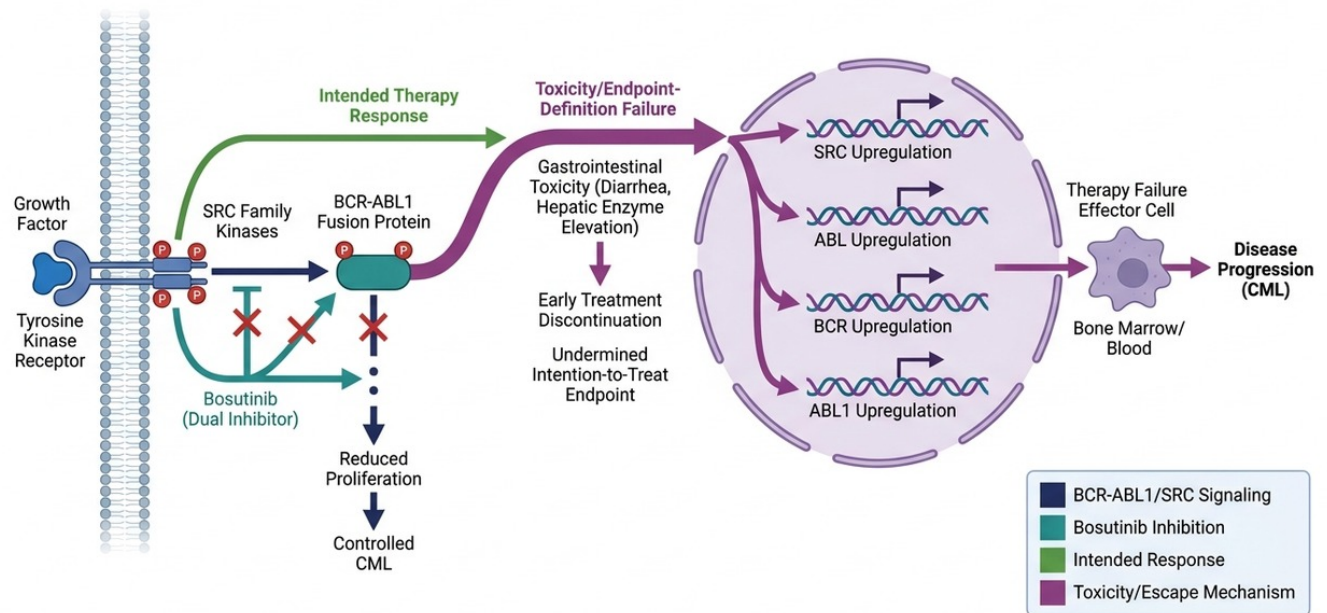
Citation: Blomberg P et al. Cancer Discov 2019;9:342-353 (PMID 30514704)

ClinicalTrials.gov: [NCT02005471](https://clinicaltrials.gov/ct2/show/study/NCT02005471)

Bosutinib

CML (chronic phase, frontline)

Mechanism of Bosutinib Therapy Failure in Chronic Phase CML (Frontline)



Indication: CML (chronic phase, frontline)

Resistance / failure mechanism:

On-mechanism gastrointestinal toxicity (diarrhea, hepatic enzyme elevation) caused early treatment discontinuation, undermining the strict intention-to-treat endpoint, a toxicity/endpoint-definition failure, not loss of anti-leukemic potency.

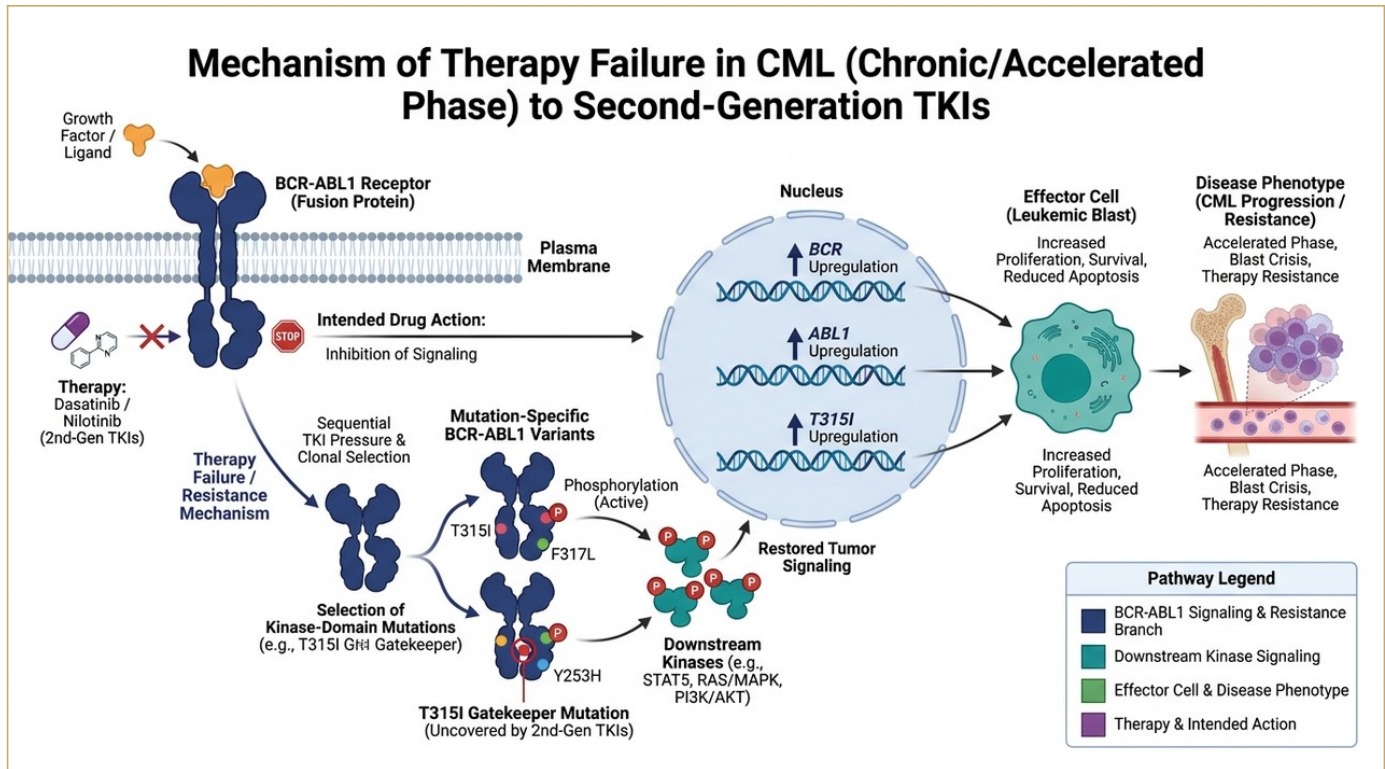
BiRAGAS pattern P5 · on-mechanism-toxicity

Citation: Cortes JE et al. J Clin Oncol 2012;30(28):3486-92 (BELA). PMID 22949154

ClinicalTrials.gov: [NCT00574873](https://clinicaltrials.gov/ct2/show/study/NCT00574873)

Dasatinib / Nilotinib (2nd-generation TKIs)

CML (chronic/accelerated phase)



Indication: CML (chronic/accelerated phase)

Resistance / failure mechanism:

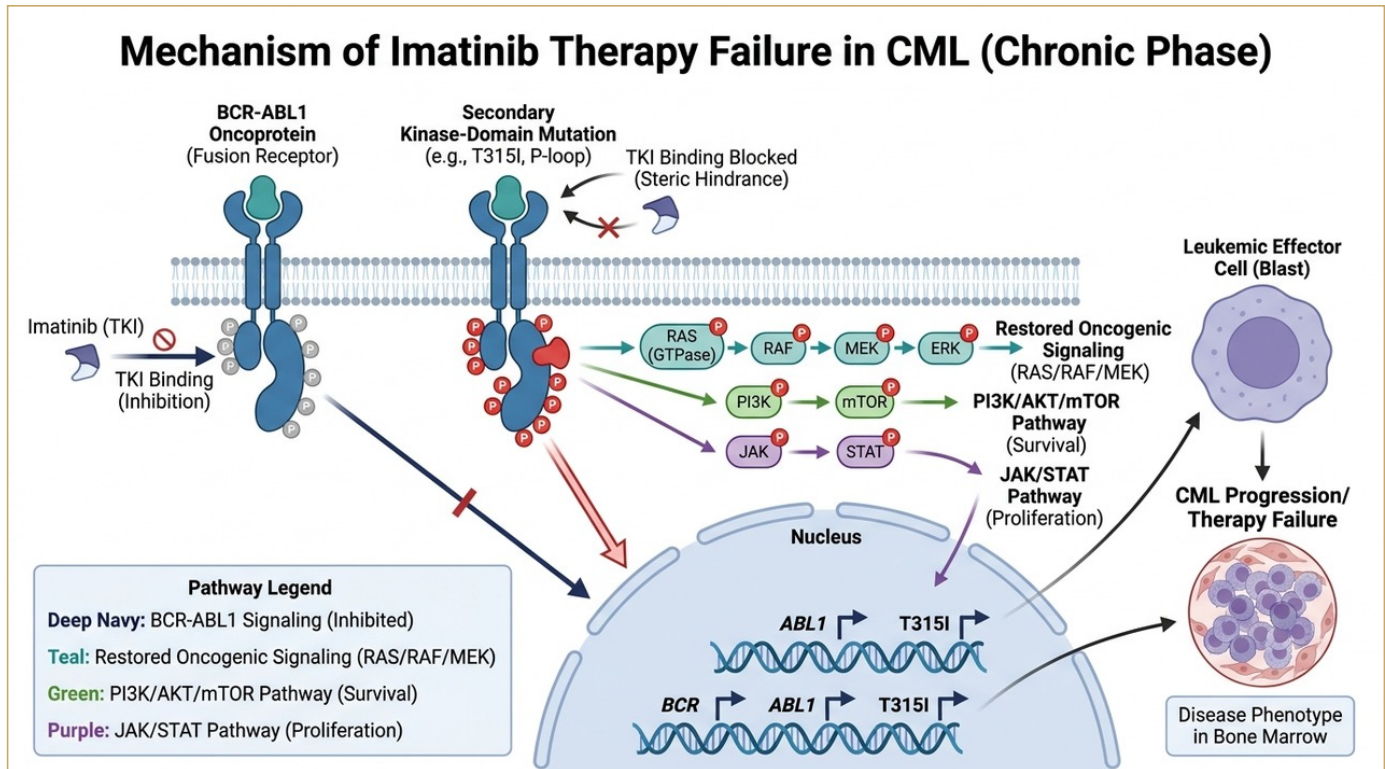
Selection of mutation-specific BCR-ABL1 kinase-domain variants and stepwise compound mutations under sequential TKI pressure; T315I gatekeeper remains uncovered until ponatinib/asciminib.

BiRAGAS pattern P7 · target-mutation

Citation: Soverini S et al. Blood 2011;118(5):1208-15 (BCR-ABL1 KD mutations); PMID 21562040

Imatinib

CML (chronic phase)



Indication: CML (chronic phase)

Resistance / failure mechanism:

Secondary BCR-ABL1 kinase-domain mutations (>100 described; T315I gatekeeper, P-loop mutations) sterically block or reduce TKI binding while preserving oncogenic kinase activity.

BiRAGAS pattern P7 · target-mutation

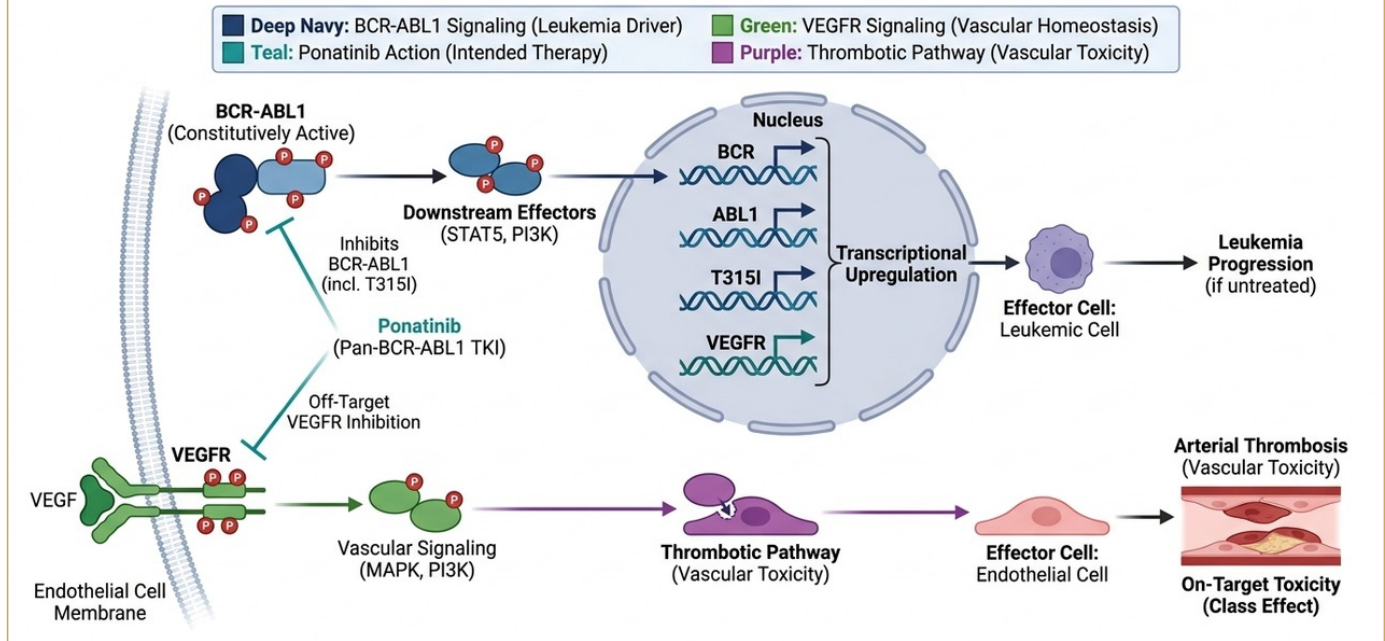
Citation: Gorre ME et al. Science 2001;293(5531):876-80. PMID 11423618

ClinicalTrials.gov: [NCT00006343](https://clinicaltrials.gov/ct2/show/study/NCT00006343)

Ponatinib

CML / Ph+ ALL (resistant/intolerant, incl T315I)

Mechanism of Ponatinib Therapy Failure in CML/Ph+ ALL due to On-Target Vascular Toxicity



Indication: CML / Ph+ ALL (resistant/intolerant, incl T315I)

Resistance / failure mechanism:

On-mechanism vascular toxicity: potent multi-kinase (incl VEGFR) inhibition and endothelial effects cause arterial thrombosis, a class/target-linked harm rather than loss of anti-leukemic efficacy.

BiRAGAS pattern P4 · on-mechanism-toxicity

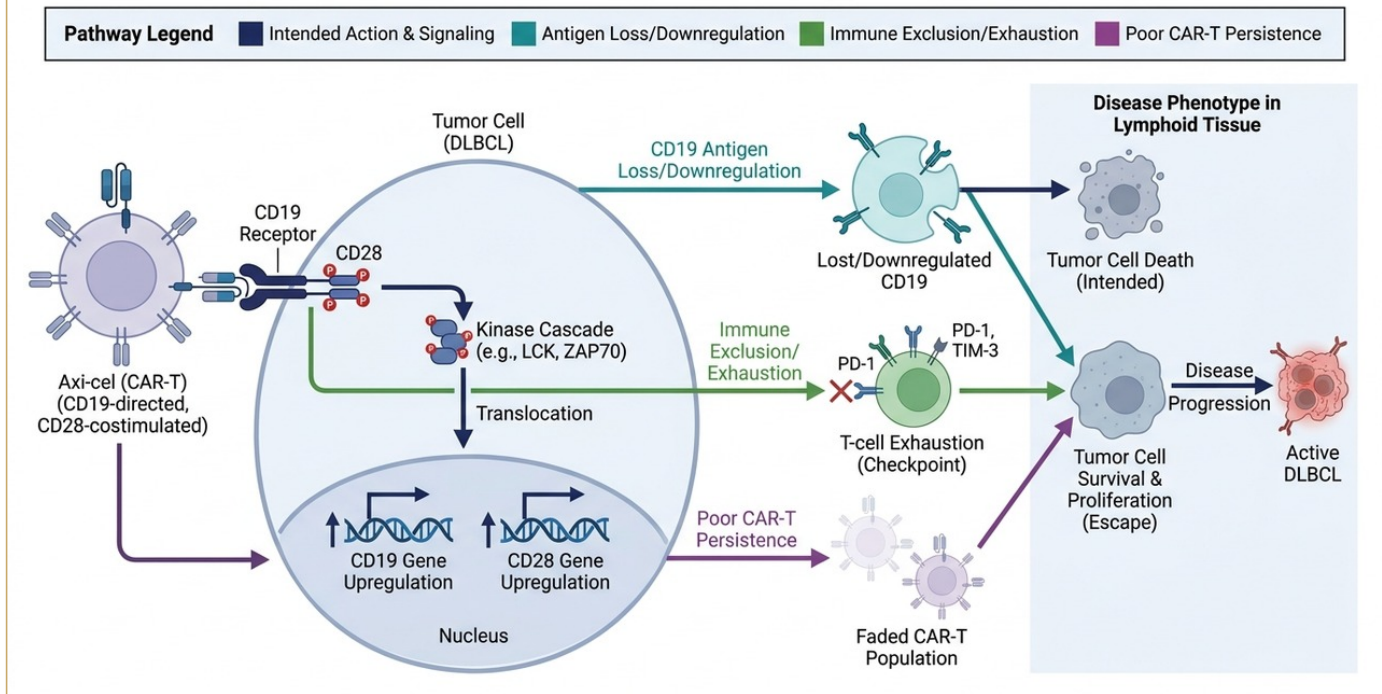
Citation: Cortes JE et al. N Engl J Med 2013;369(19):1783-96 (PACE). PMID 24180494

ClinicalTrials.gov: [NCT01207440](https://clinicaltrials.gov/ct2/show/study/NCT01207440)

Axicabtagene ciloleucel (axi-cel)

DLBCL / large B-cell lymphoma

Mechanism of Therapy Failure in DLBCL / Large B-Cell Lymphoma: Axi-cel Resistance



Indication: DLBCL / large B-cell lymphoma

Resistance / failure mechanism:

CD19 antigen loss/downregulation; immune exclusion via impaired antigen presentation and T-cell exhaustion; poor CAR-T persistence

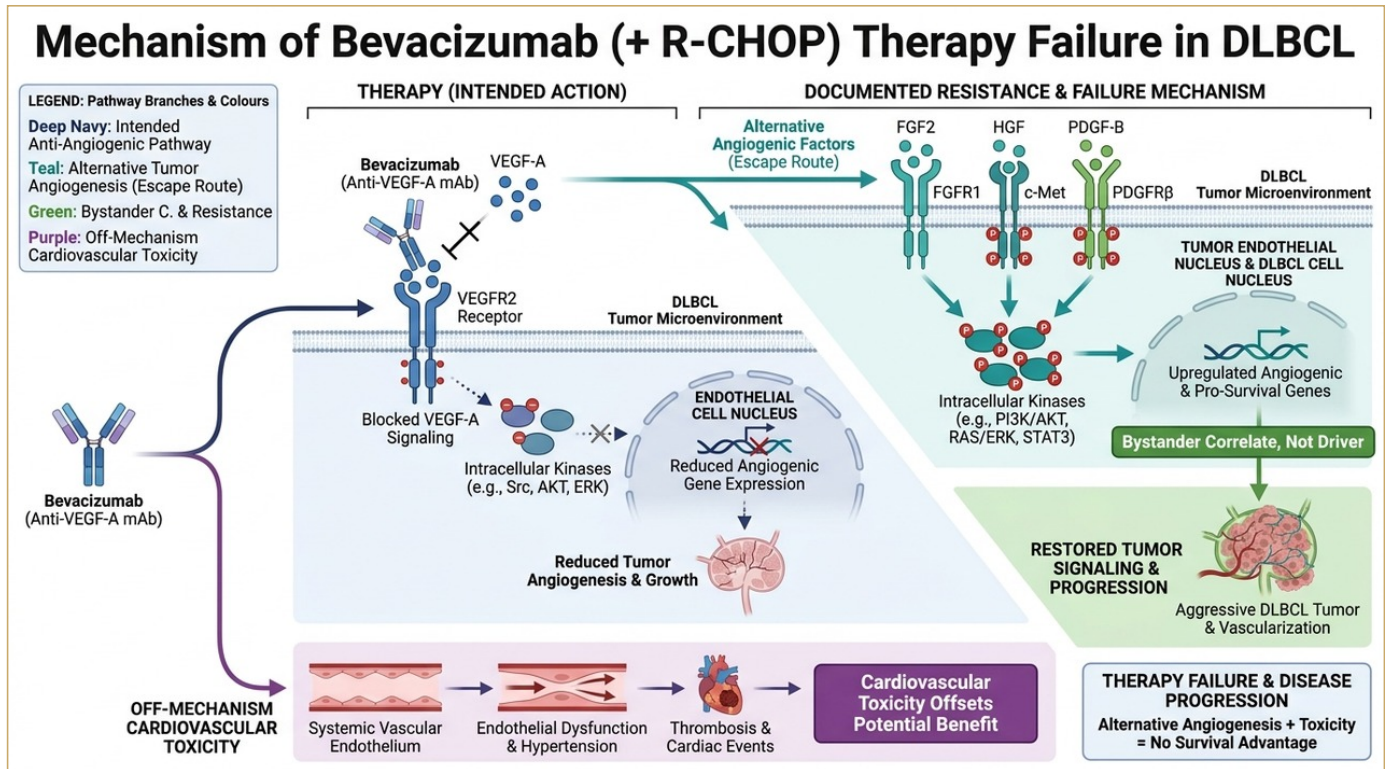
BiRAGAS pattern P7 · antigen-escape

Citation: Neelapu SS et al. N Engl J Med 2017;377:2531-2544 (ZUMA-1, PMID 29226797)

ClinicalTrials.gov: [NCT02348216](https://clinicaltrials.gov/ct2/show/study/NCT02348216)

Bevacizumab (+ R-CHOP)

DLBCL



Indication: DLBCL

Resistance / failure mechanism:

Tumor angiogenesis is a bystander correlate in DLBCL rather than a driver; anti-VEGF added on-mechanism cardiovascular toxicity that offset any potential benefit

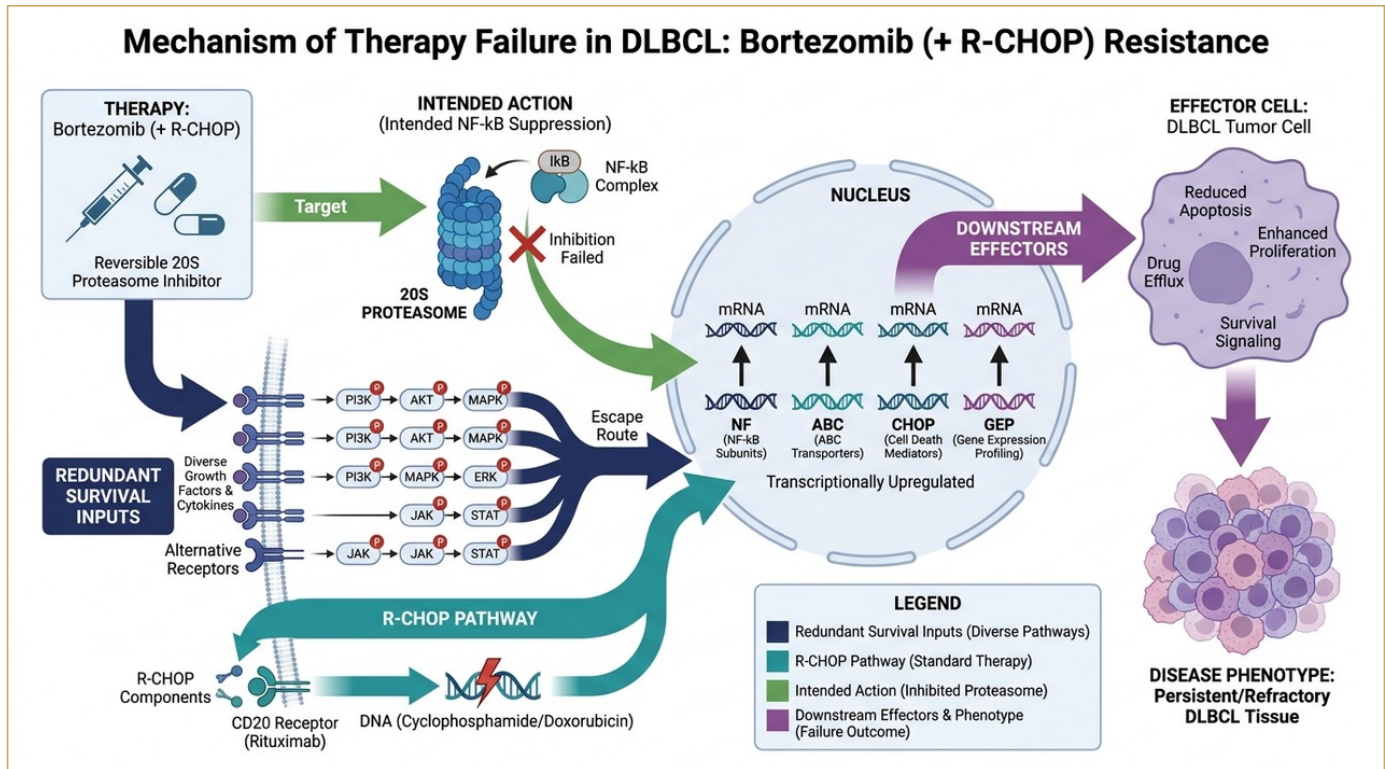
BiRAGAS pattern P1 · correlate-not-driver

Citation: Seymour JF et al. J Clin Oncol 2014;32:3986-3992 (PMID (verify, unresolved))

ClinicalTrials.gov: [NCT00486759](https://clinicaltrials.gov/ct2/show/study/NCT00486759)

Bortezomib (+ R-CHOP)

DLBCL



Indication: DLBCL

Resistance / failure mechanism:

NF-kB is one of several redundant survival inputs, so proteasome inhibition adds little on top of R-CHOP; GEP subgroup benefit surfaced only with long follow-up, i.e., the unselected primary population diluted the effect

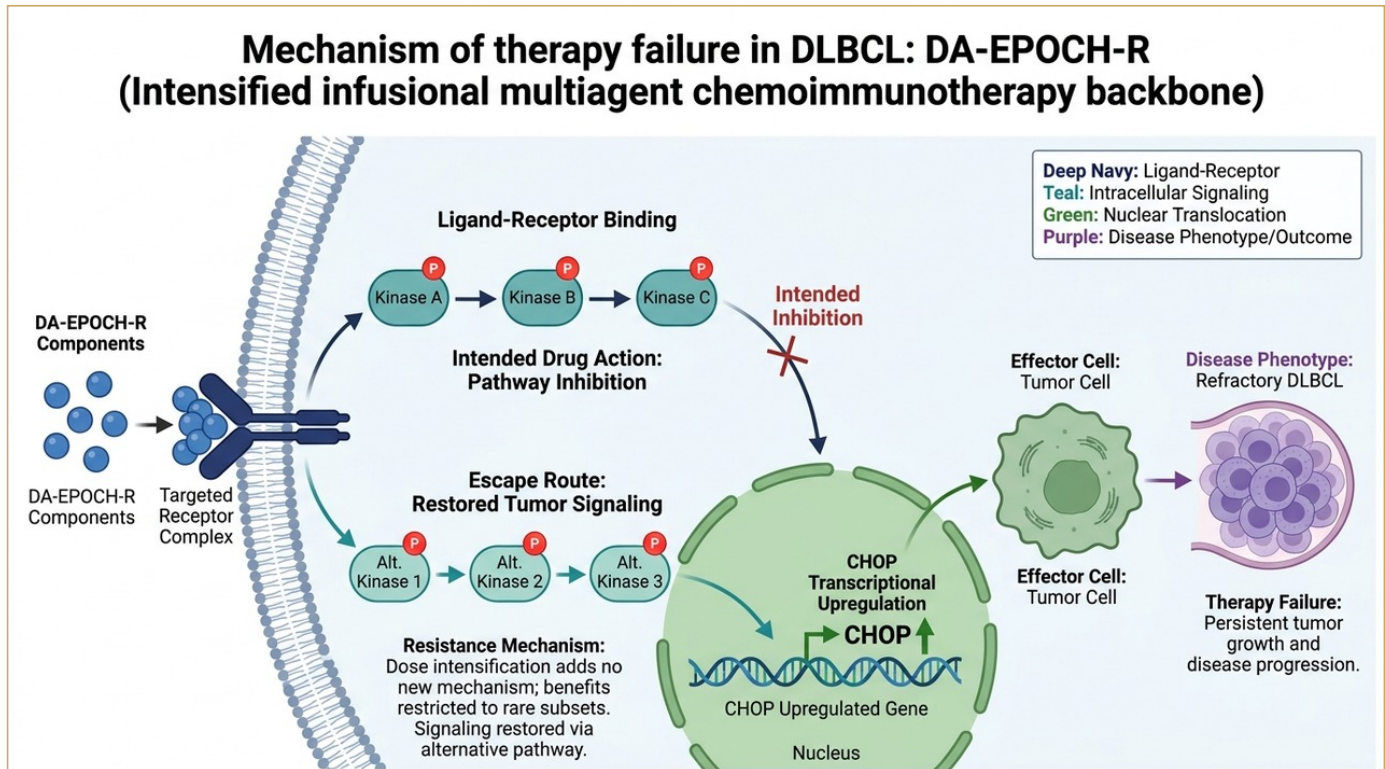
BiRAGAS pattern P3 · population-dilution

Citation: Davies A et al. Lancet Oncol 2019;20:649-662 (PMID 30948276)

ClinicalTrials.gov: NCT01324596

DA-EPOCH-R (dose-adjusted infusional)

DLBCL



Indication: DLBCL

Resistance / failure mechanism:

Dose intensification adds no new mechanism over R-CHOP for unselected DLBCL; any benefit is restricted to rare high-grade/double-hit subsets not enriched in this population

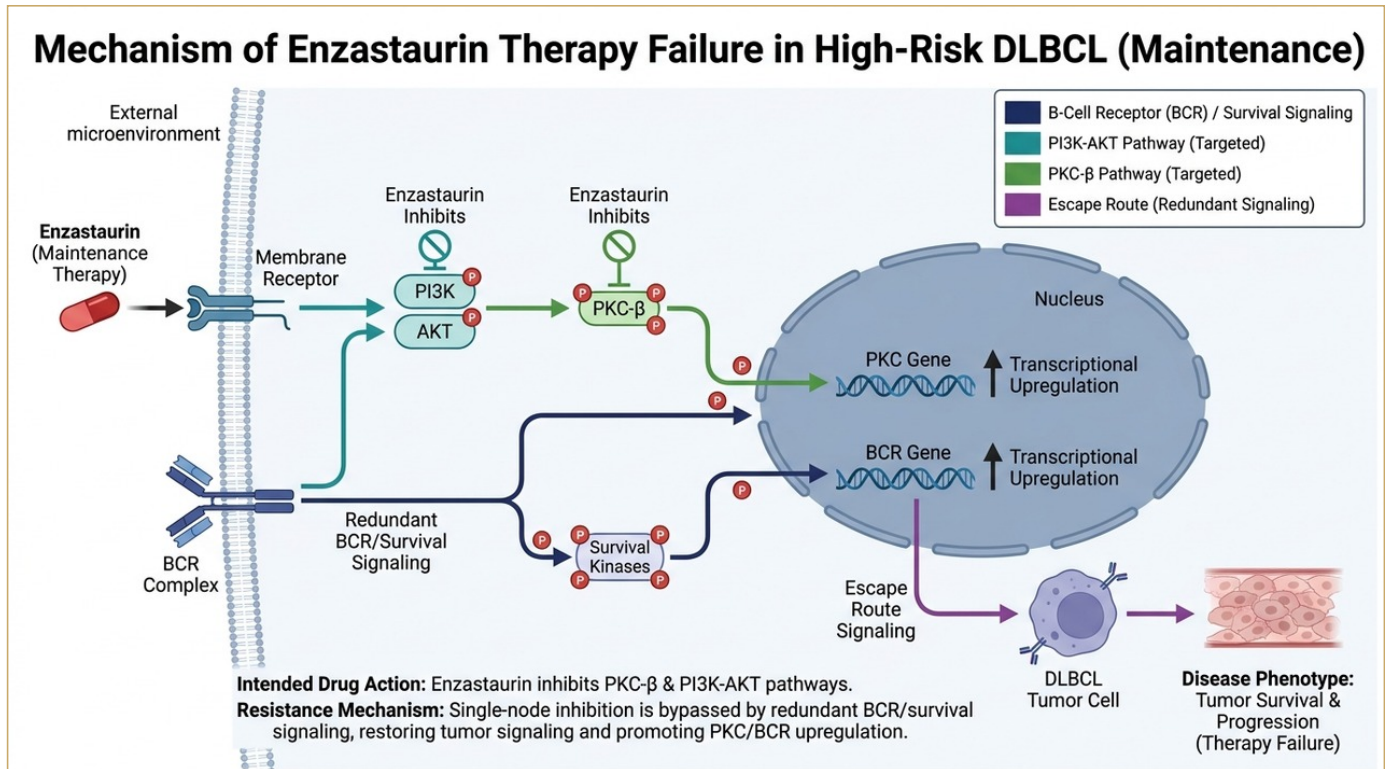
BiRAGAS pattern P3 · population-dilution

Citation: Bartlett NL et al. J Clin Oncol 2019;37:1790-1799 (PMID 30939090)

[ClinicalTrials.gov: NCT00118209](https://clinicaltrials.gov/ct2/show/study/NCT00118209)

Enzastaurin (maintenance)

DLBCL (high-risk, maintenance)



Indication: DLBCL (high-risk, maintenance)

Resistance / failure mechanism:

PKC-beta expression is a prognostic correlate, not a causal dependency in minimal residual DLBCL; single-node inhibition is bypassed by redundant BCR/survival signaling

BiRAGAS pattern P1 · correlate-not-driver

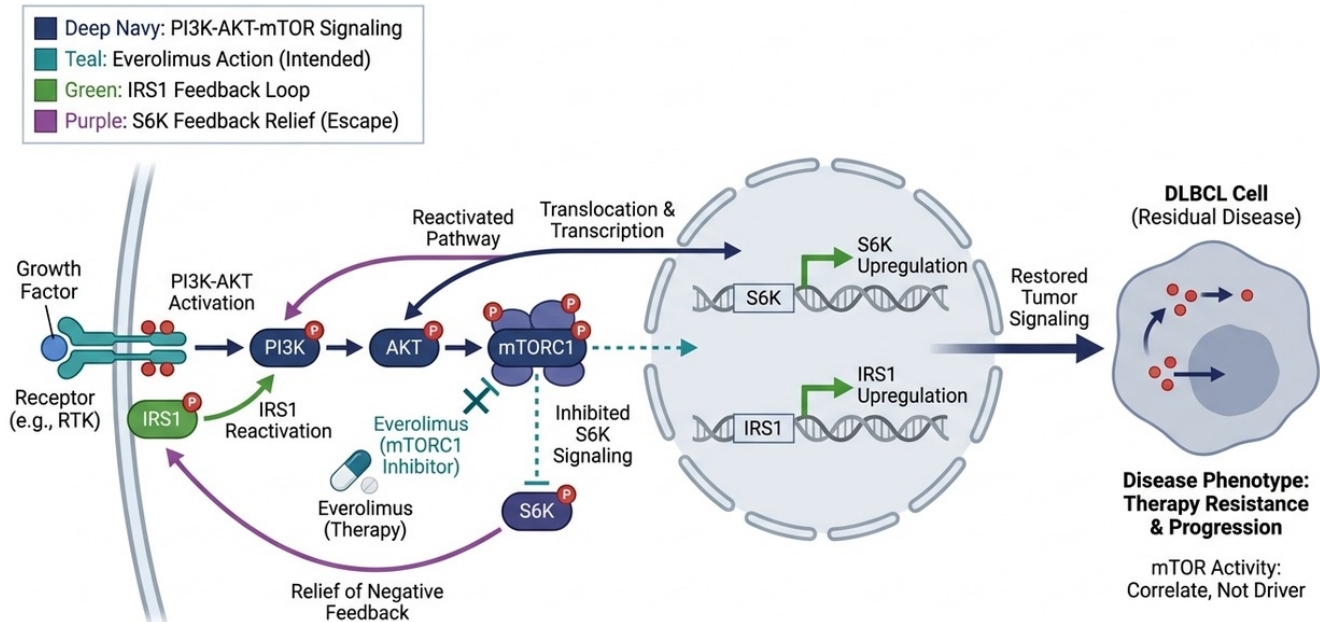
Citation: Crump M et al. J Clin Oncol 2016;34:2484-2492

[ClinicalTrials.gov: NCT00332202](https://clinicaltrials.gov/ct2/show/study/NCT00332202)

Everolimus (adjuvant maintenance)

DLBCL (high-risk, adjuvant maintenance)

Mechanism of Therapy Failure in DLBCL (High-Risk, Adjuvant Maintenance)



Indication: DLBCL (high-risk, adjuvant maintenance)

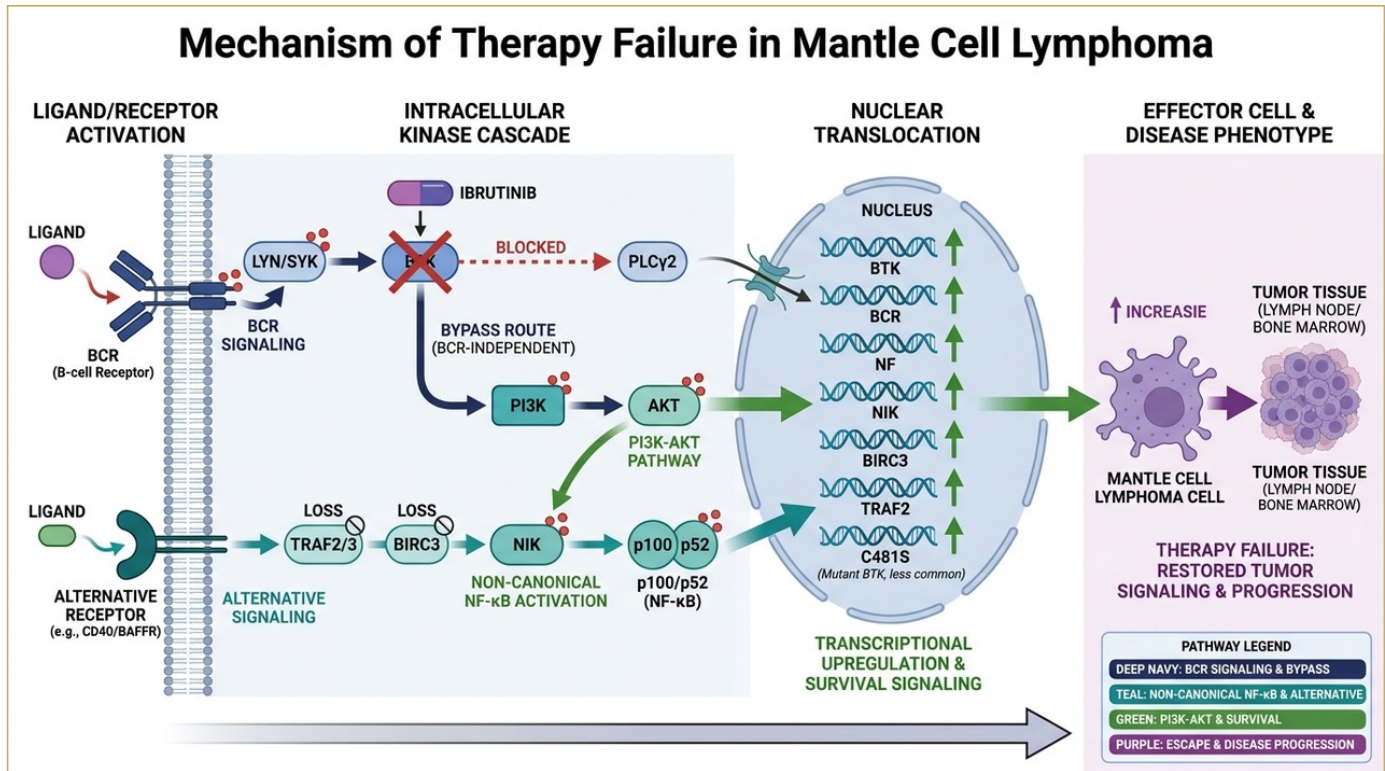
Resistance / failure mechanism:

mTORC1 blockade relieves S6K-IRS1 negative feedback, reactivating PI3K-AKT; mTOR activity is a correlate rather than a validated causal driver of residual DLBCL

BiRAGAS pattern P2 · feedback-reactivation

Citation: Witzig TE et al. Ann Oncol 2018;29:707-714

[ClinicalTrials.gov: NCT00790036](https://clinicaltrials.gov/ct2/show/study/NCT00790036)



Indication: Mantle cell lymphoma

Resistance / failure mechanism:

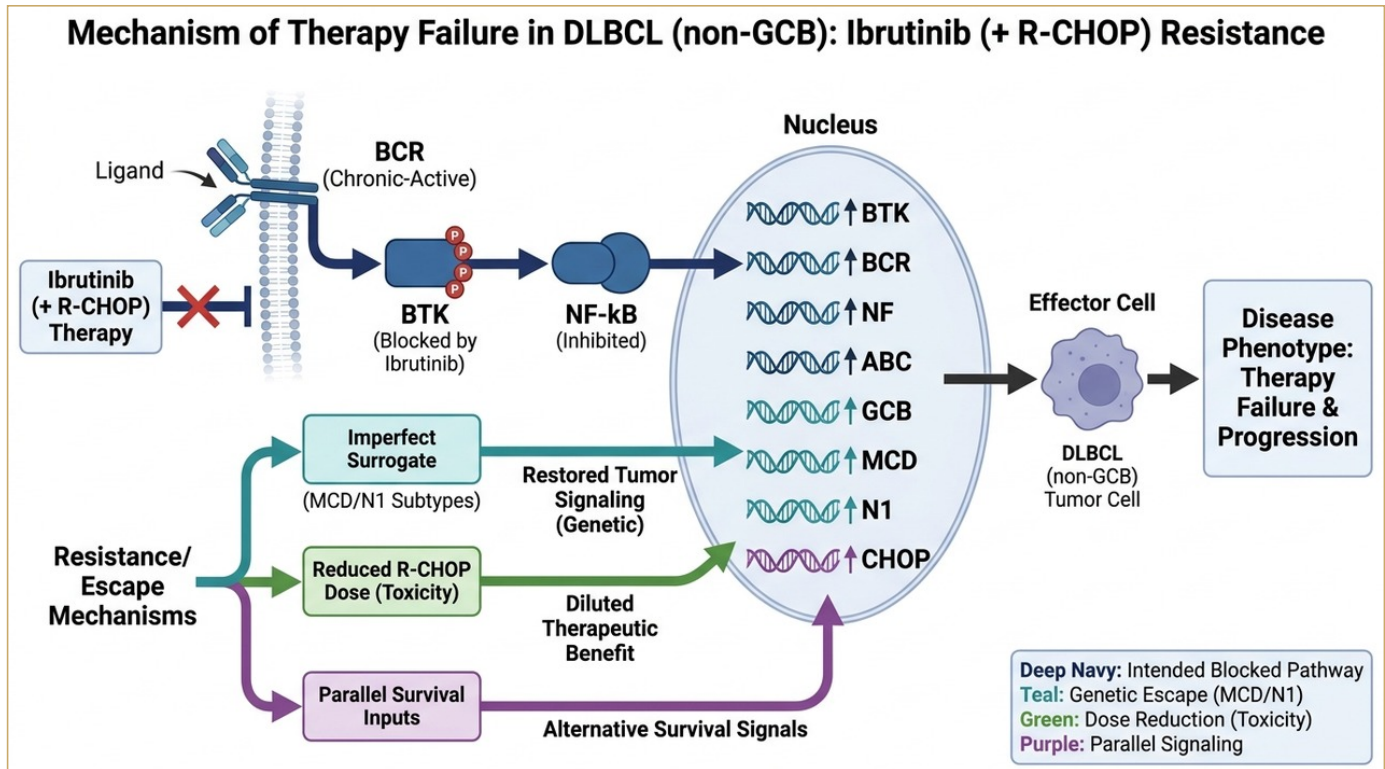
Bypass of BTK via alternative/non-canonical NF-κB activation (NIK, BIRC3 or TRAF2/3 loss) and PI3K-AKT; less commonly BTK C481S; survival becomes BCR-independent

BiRAGAS pattern P2 · bypass/parallel-pathway

Citation: Rahal R et al. Nat Med 2014;20:87-92 (PMID 24362935); Chiron D et al. Cancer Discov 2014;4:1022-1035

Ibrutinib (+ R-CHOP)

DLBCL (non-GCB)



Indication: DLBCL (non-GCB)

Resistance / failure mechanism:

Non-GCB IHC is an imperfect surrogate for BCR-addicted genetic subtypes (MCD/N1); older patients could not tolerate full-dose R-CHOP so on-mechanism toxicity diluted any benefit; BTK is one of several parallel survival inputs

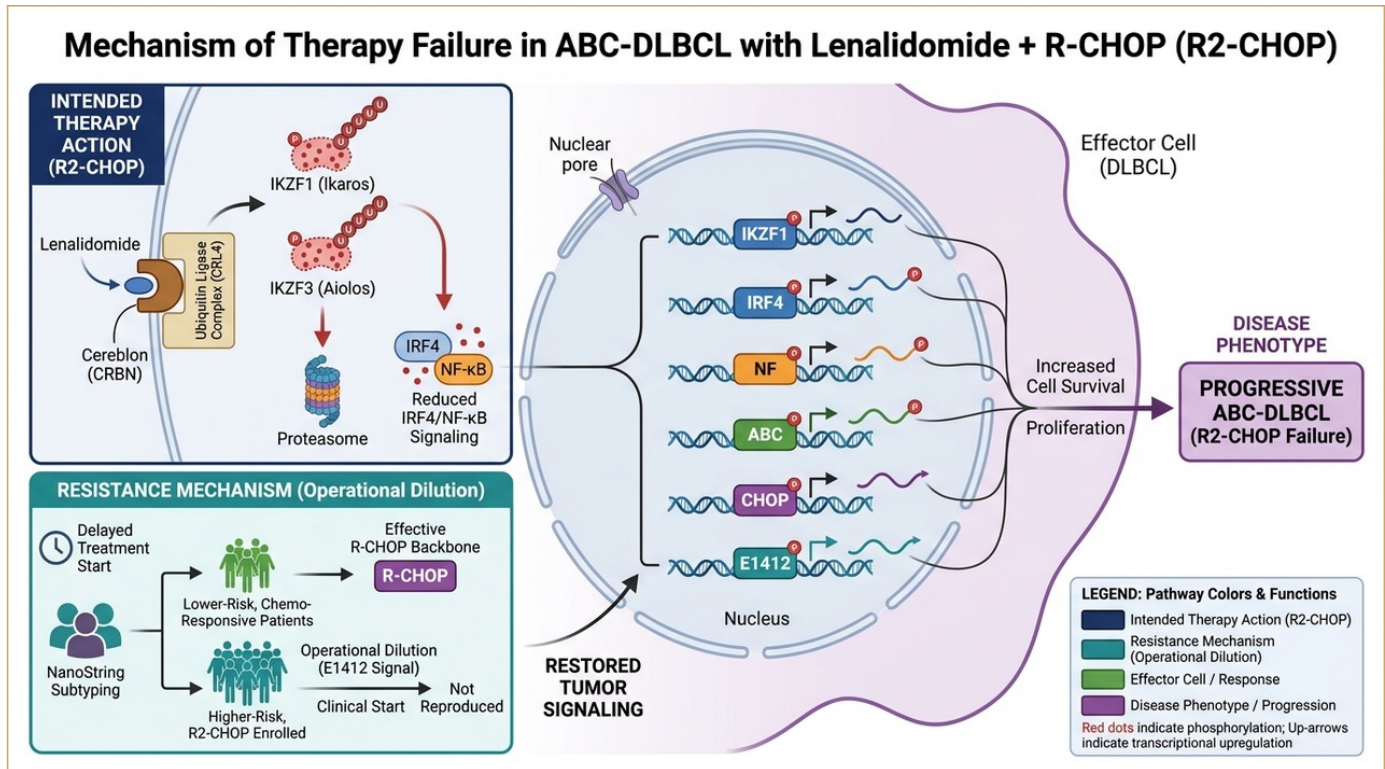
BiRAGAS pattern P3 · population-dilution

Citation: Younes A et al. J Clin Oncol 2019;37:1285-1295 (PMID 30901302)

ClinicalTrials.gov: [NCT01855750](https://clinicaltrials.gov/ct2/show/study/NCT01855750)

Lenalidomide (+ R-CHOP; R2-CHOP)

DLBCL (ABC / activated B-cell)



Indication: DLBCL (ABC / activated B-cell)

Resistance / failure mechanism:

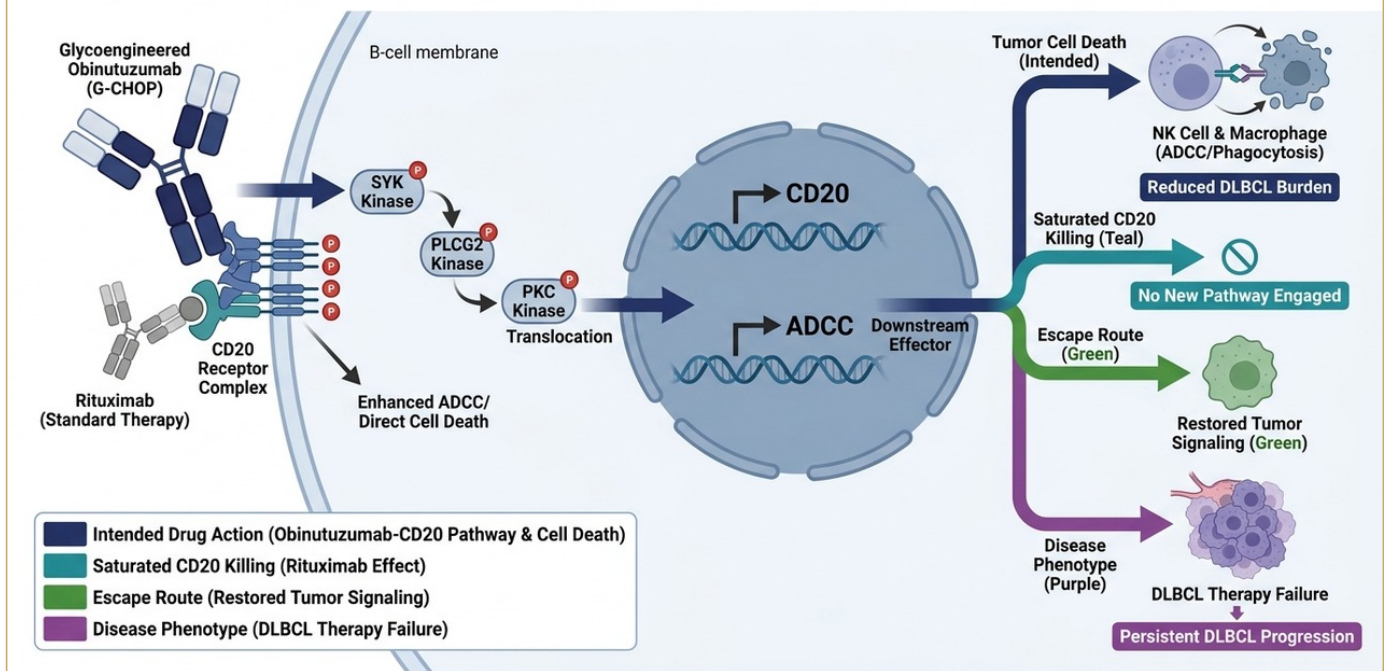
Operational population dilution: mandatory NanoString subtyping delayed treatment start and enrolled lower-risk, chemo-responsive patients, leaving little margin over an effective R-CHOP backbone; the earlier E1412 signal (clinical start) was not reproduced

BiRAGAS pattern P3 · population-dilution

Citation: Nowakowski GS et al. J Clin Oncol 2021;39:1317-1328 (PMID 33621109)

ClinicalTrials.gov: [NCT02285062](https://clinicaltrials.gov/ct2/show/study/NCT02285062)

Mechanism of Therapy Failure in DLBCL: Obinutuzumab (G-CHOP) Resistance



Indication: DLBCL

Resistance / failure mechanism:

Swapping to a higher-ADCC anti-CD20 is a redundant mechanism; CD20-directed killing is already saturated by rituximab, so no new pathway is engaged

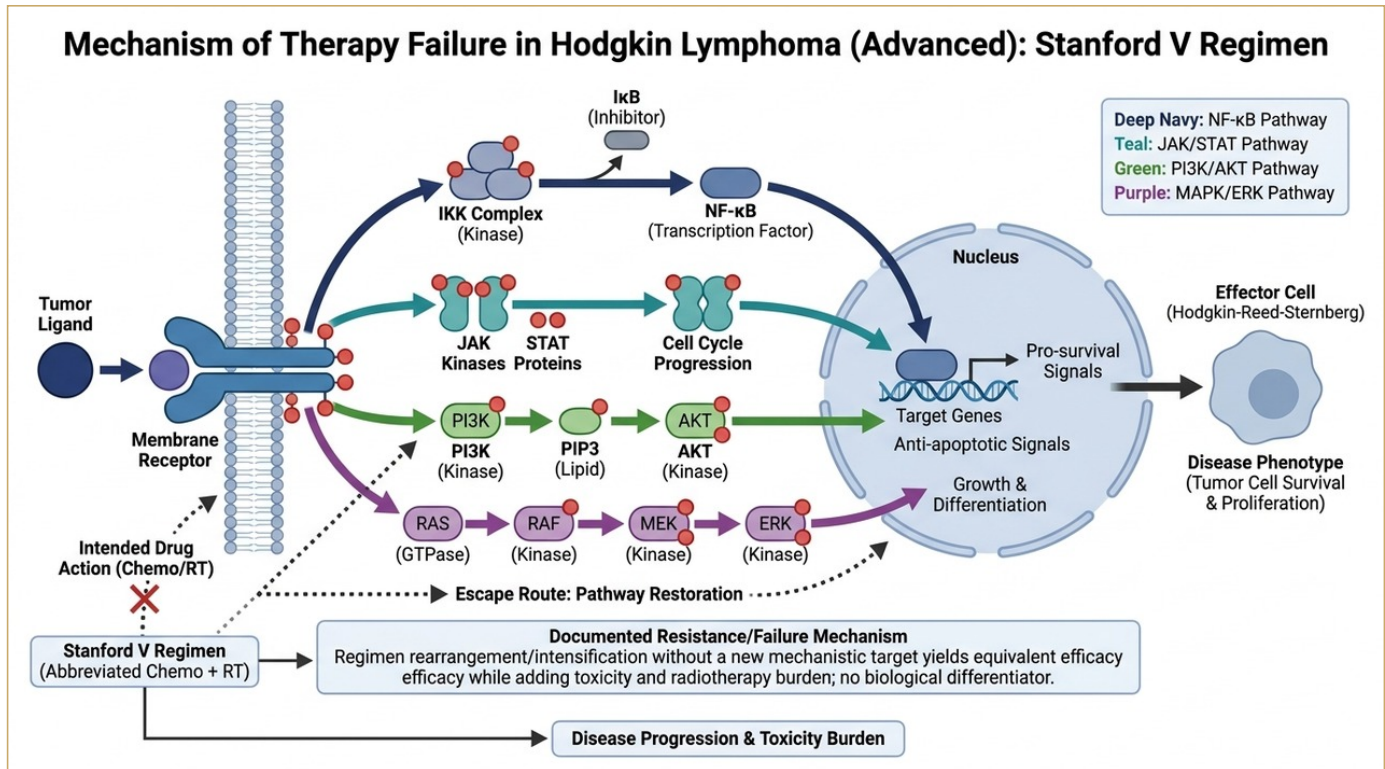
BiRAGAS pattern P2 · pathway-redundancy

Citation: Vitolo U et al. J Clin Oncol 2017;35:3529-3537 (PMID 28779999)

[ClinicalTrials.gov: NCT01287741](https://clinicaltrials.gov/ct2/show/study/NCT01287741)

Stanford V regimen

Hodgkin lymphoma (advanced)



Indication: Hodgkin lymphoma (advanced)

Resistance / failure mechanism:

Regimen rearrangement/intensification without a new mechanistic target yields equivalent efficacy while adding toxicity and radiotherapy burden; no biological differentiator

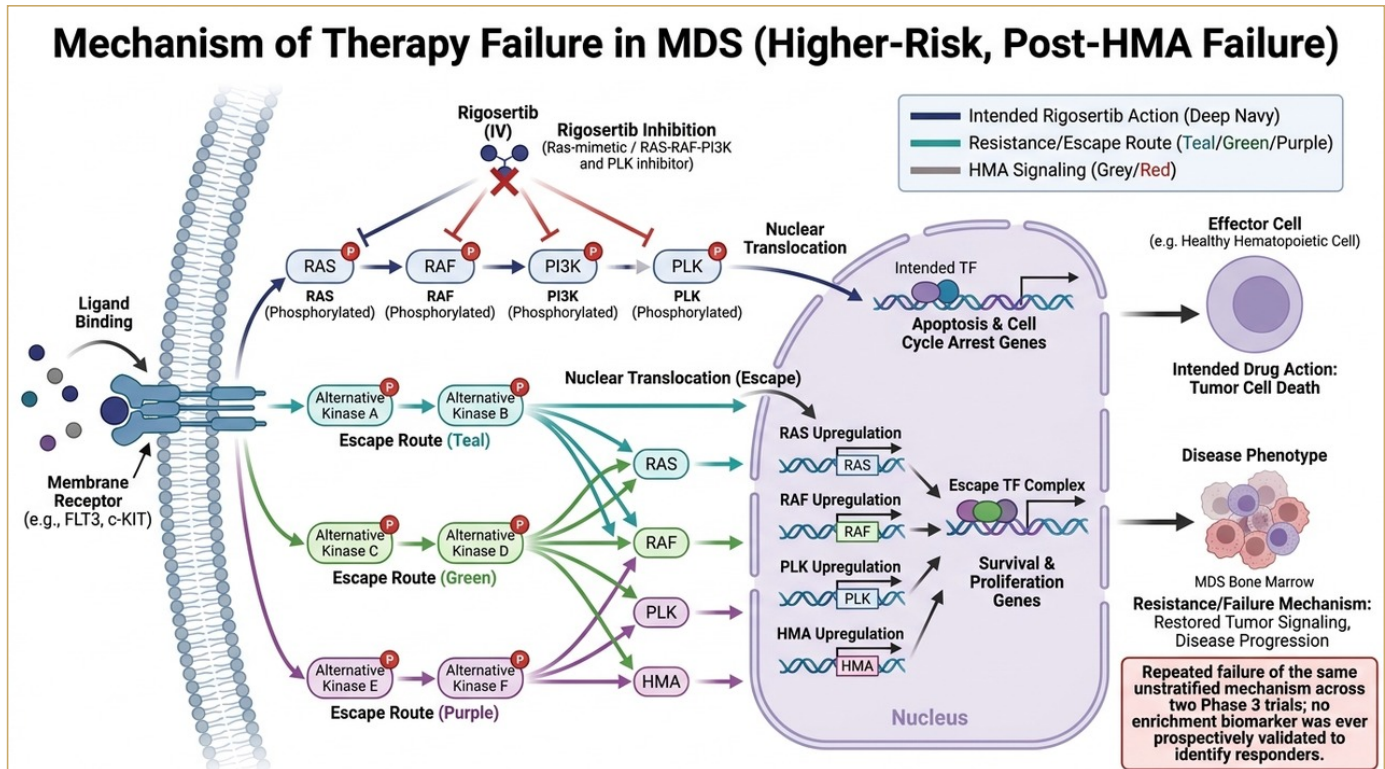
BiRAGAS pattern P2 · pathway-redundancy

Citation: Gordon LI et al. J Clin Oncol 2013;31:684-691 (PMID 23182987)

ClinicalTrials.gov: [NCT00003389](https://clinicaltrials.gov/ct2/show/study/NCT00003389)

Rigosertib (IV)

MDS (higher-risk, post-HMA failure)



Indication: MDS (higher-risk, post-HMA failure)

Resistance / failure mechanism:

Repeated failure of the same unstratified mechanism across two Phase 3 trials; no enrichment biomarker was ever prospectively validated to identify responders.

BiRAGAS pattern P1 · correlate-not-driver

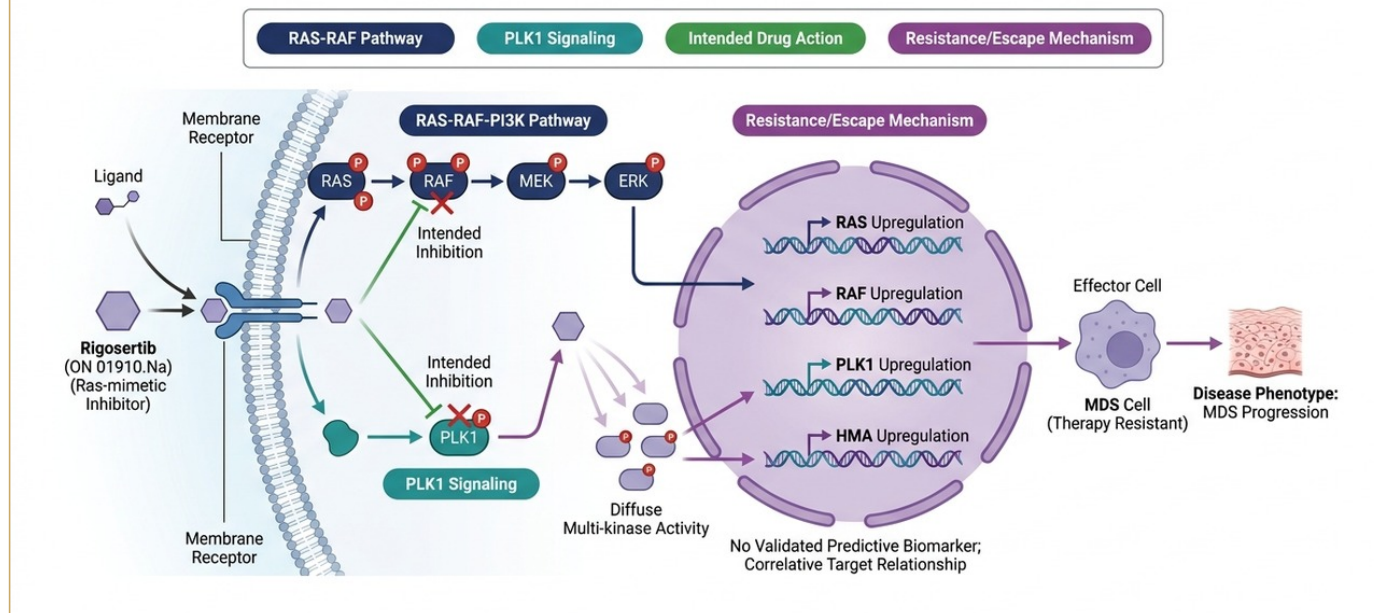
Citation: INSPIRE Phase 3 (ASH 2020 / Onconova); ClinicalTrials.gov NCT02562443 (PMID (verify, unresolved))

ClinicalTrials.gov: [NCT02562443](https://clinicaltrials.gov/ct2/show/study/NCT02562443)

Rigosertib (ON 01910.Na)

MDS (higher-risk, post-HMA failure)

Mechanism of Therapy Failure in MDS (Higher-Risk, Post-HMA Failure) with Rigosertib



Indication: MDS (higher-risk, post-HMA failure)

Resistance / failure mechanism:

Diffuse multi-kinase/Ras-mimetic mechanism without a validated predictive biomarker; any activity concentrated in an unplanned subgroup, indicating the target relationship was correlative rather than a stratified driver.

BiRAGAS pattern P1 · correlate-not-driver

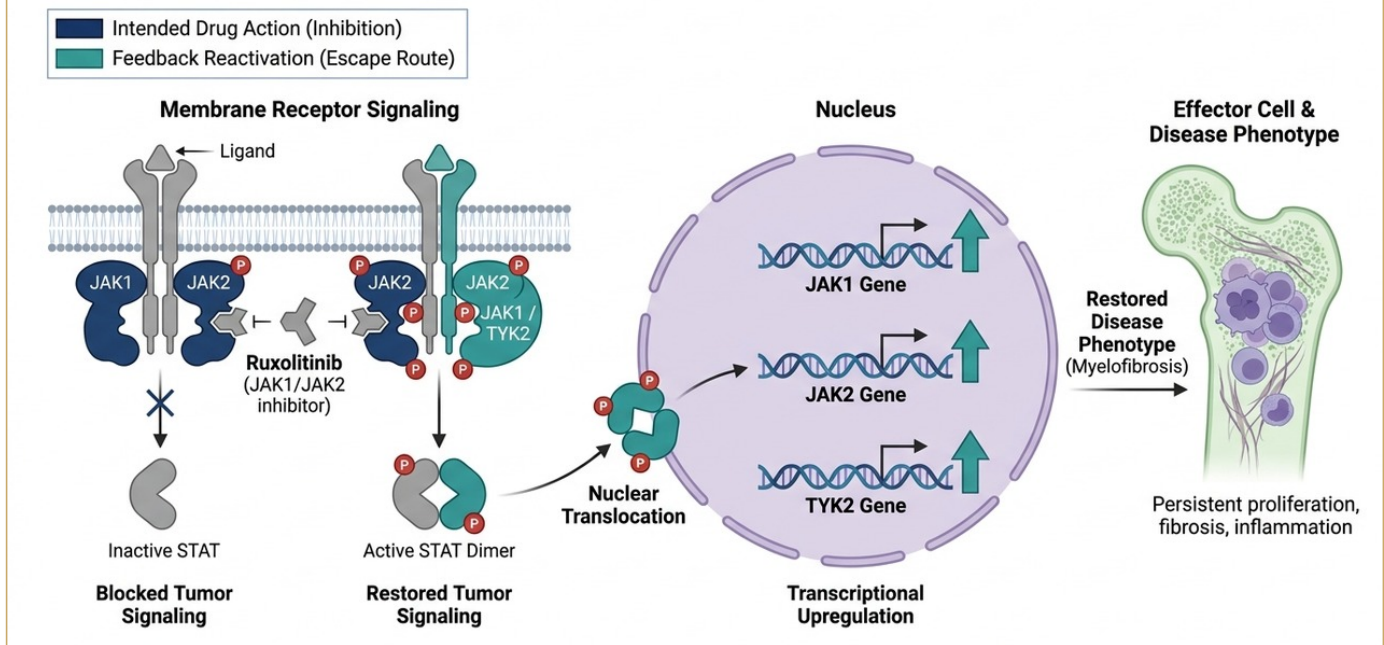
Citation: Garcia-Manero G et al. Lancet Oncol 2016;17(4):496-508. PMID 26968357

[ClinicalTrials.gov: NCT01241500](https://clinicaltrials.gov/ct2/show/study/NCT01241500)

Ruxolitinib

Myelofibrosis / MPN (JAK2-driven)

Mechanism of Therapy Failure in Myelofibrosis / MPN (JAK2-driven): Ruxolitinib Resistance via Feedback Reactivation



Indication: Myelofibrosis / MPN (JAK2-driven)

Resistance / failure mechanism:

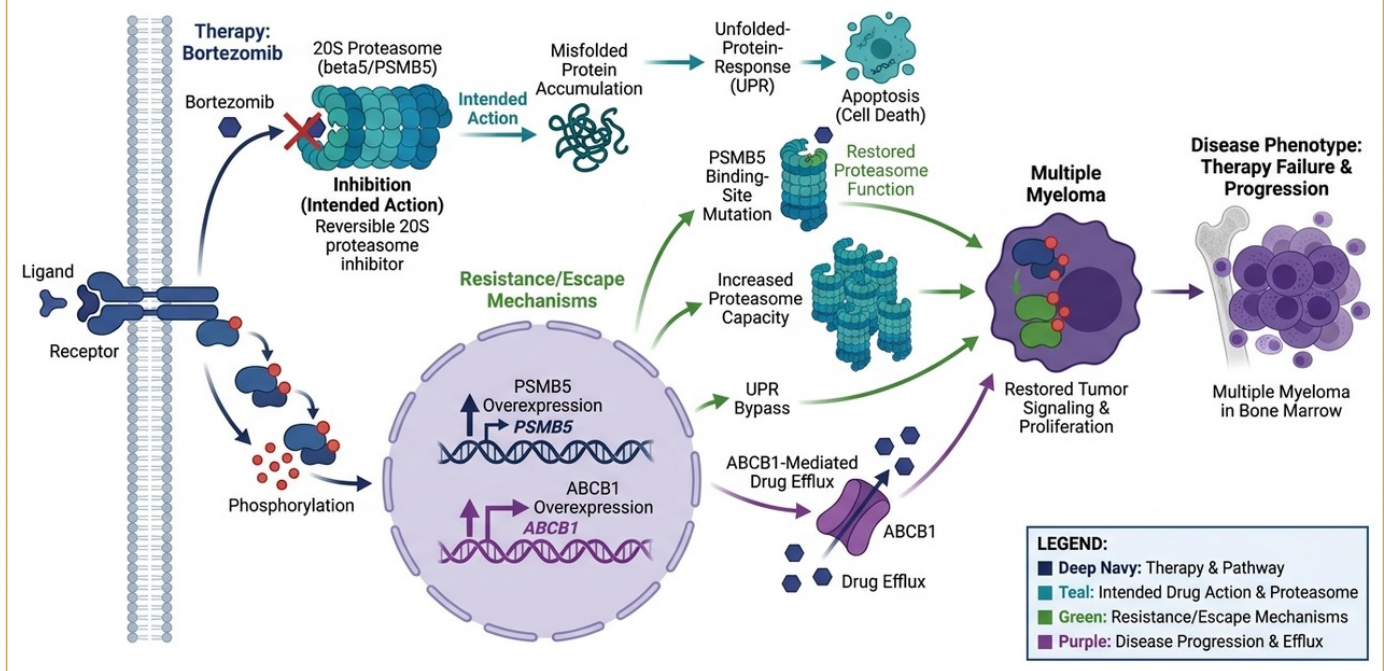
Feedback reactivation: JAK2 transactivation through heterodimerization with JAK1/TYK2 restores STAT signaling despite continued inhibitor (type-I inhibitor persistence), rather than a JAK2 gatekeeper mutation.

BiRAGAS pattern P2 · feedback-reactivation

Citation: Koppikar P et al. Nature 2012;489(7414):155-9. PMID 22820254

ClinicalTrials.gov: [NCT00952289](https://clinicaltrials.gov/ct2/show/study/NCT00952289)

Mechanism of Bortezomib Therapy Failure in Multiple Myeloma



Indication: Multiple myeloma

Resistance / failure mechanism:

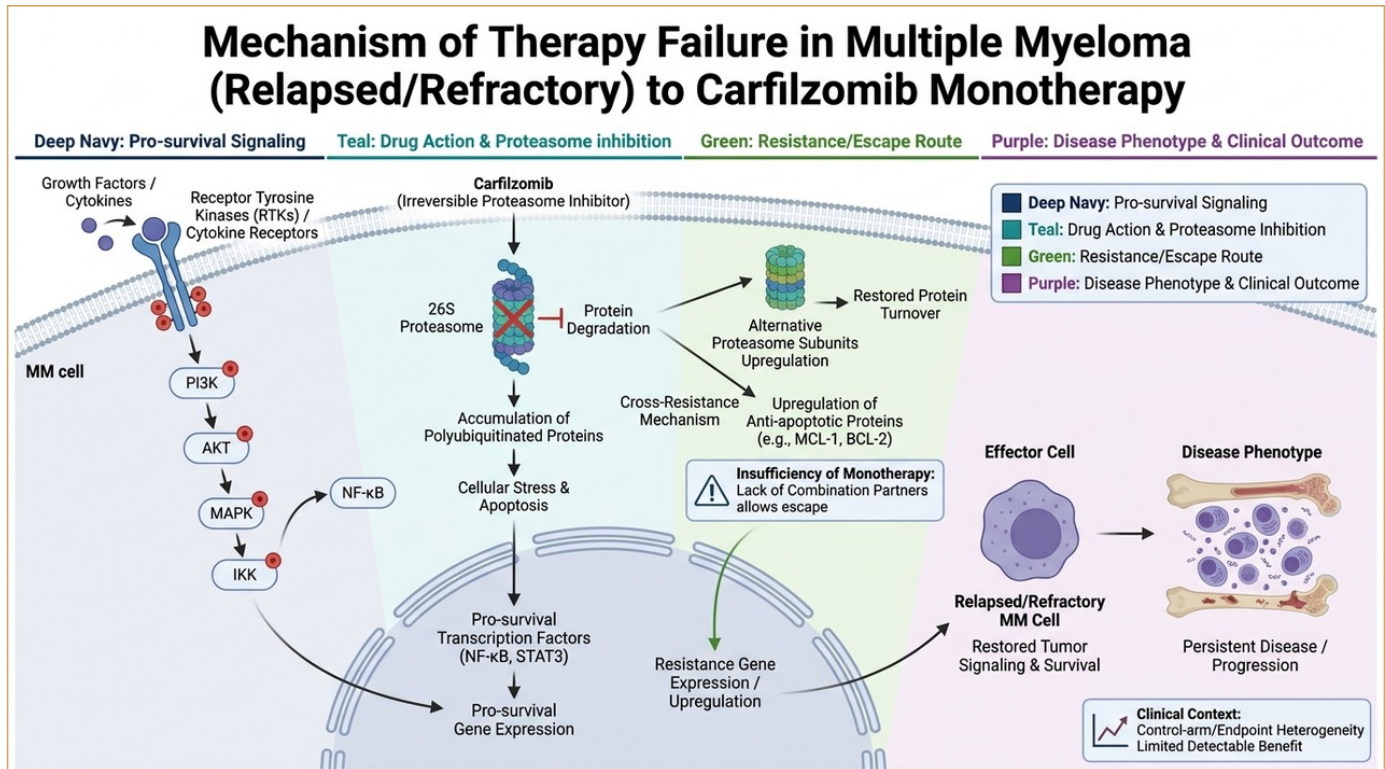
PSMB5 binding-site mutations and PSMB5 overexpression, upregulation of proteasome subunits, unfolded-protein-response bypass, and ABCB1-mediated drug efflux

BiRAGAS pattern P7 · target-mutation

Citation: Oerlemans R et al. Blood 2008;112:2489-2499 (PMID 18541827)

Carfilzomib (monotherapy)

Multiple myeloma (relapsed/refractory)



Indication: Multiple myeloma (relapsed/refractory)

Resistance / failure mechanism:

Cross-resistance in a proteasome-inhibitor-refractory population plus insufficiency of monotherapy without combination partners; control-arm/endpoint heterogeneity also limited detectable benefit

BiRAGAS pattern P3 · pharmacologic/efflux-metabolism

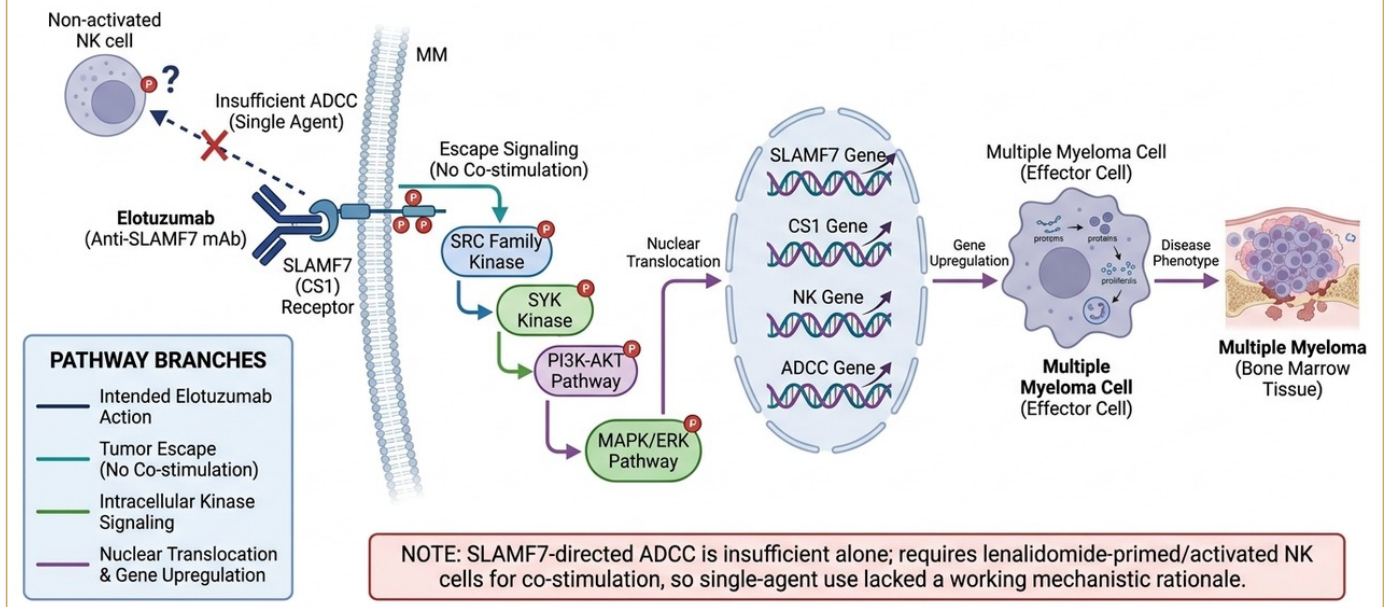
Citation: Hajek R et al. FOCUS trial, Leukemia 2017;31:107-114 (PMID (verify, unresolved))

ClinicalTrials.gov: [NCT01302392](https://clinicaltrials.gov/ct2/show/study/NCT01302392)

Elotuzumab (single agent)

Multiple myeloma

Mechanism of Therapy Failure in Multiple Myeloma: Single-Agent Elotuzumab



Indication: Multiple myeloma

Resistance / failure mechanism:

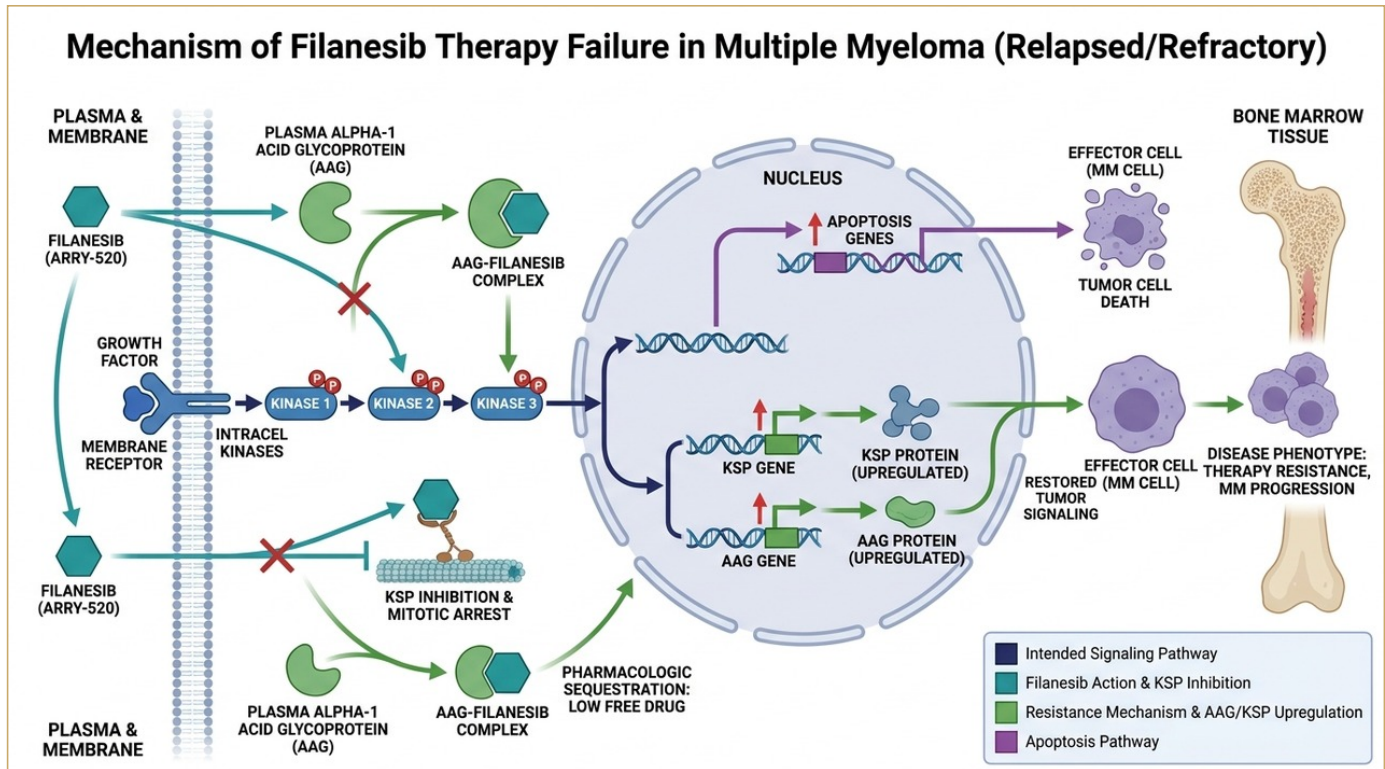
SLAMF7-directed ADCC is insufficient alone; requires lenalidomide-primed/activated NK cells for co-stimulation, so single-agent use lacked a working mechanistic rationale

BiRAGAS pattern P6 · combination-no-rationale

Citation: Zonder JA et al. Blood 2012;120:552-559, PMID 22184404

Filanesib (ARRY-520)

Multiple myeloma (relapsed/refractory)



Indication: Multiple myeloma (relapsed/refractory)

Resistance / failure mechanism:

Pharmacologic sequestration: high plasma alpha-1 acid glycoprotein (AAG) binds filanesib and lowers free drug, so only AAG-low patients respond; efficacy gated by a pharmacologic biomarker not used to select the broad population

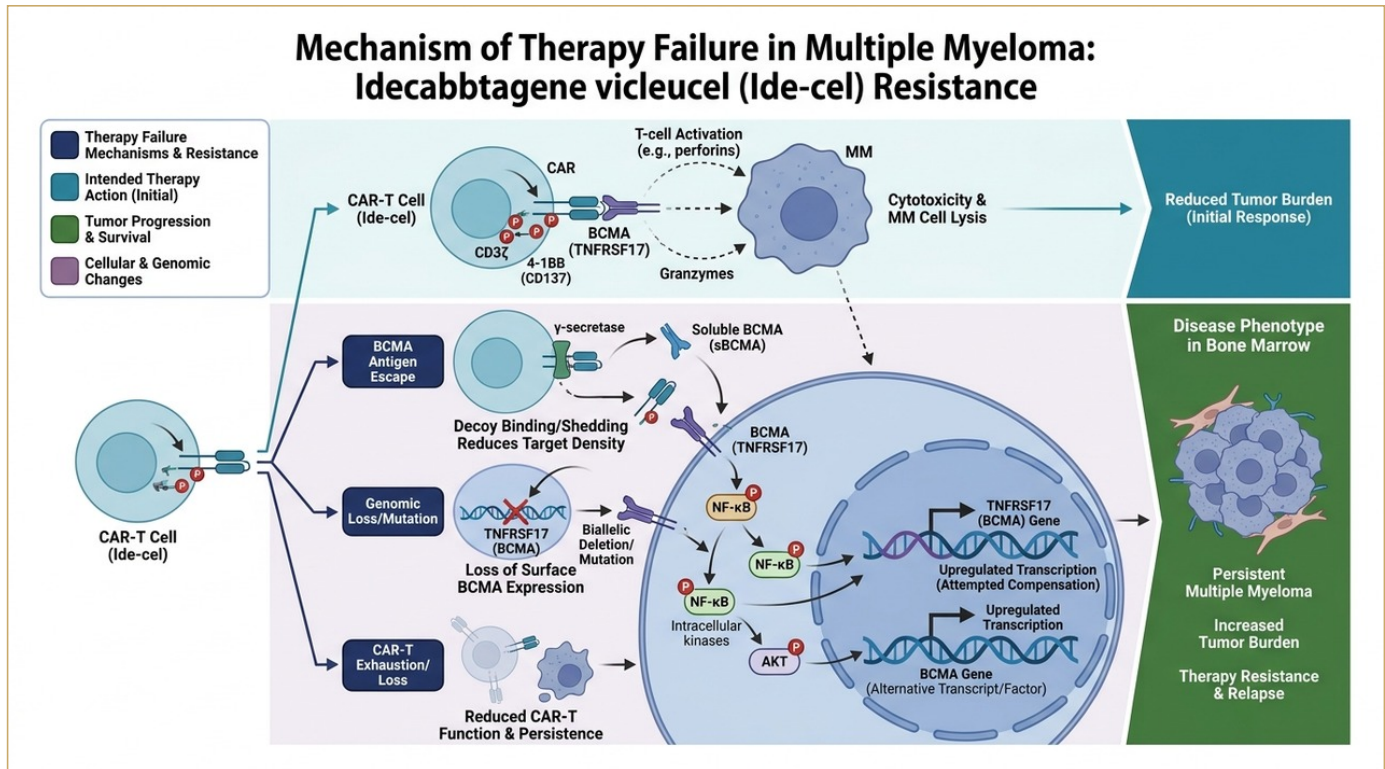
BiRAGAS pattern P3 · pharmacologic/efflux-metabolism

Citation: Shah JJ et al. Br J Haematol 2017;179:257-267 (PMID 28817190)

ClinicalTrials.gov: [NCT00821249](https://clinicaltrials.gov/ct2/show/study/NCT00821249)

Idecabtagene vicleucel (ide-cel)

Multiple myeloma



Indication: Multiple myeloma

Resistance / failure mechanism:

BCMA antigen escape via biallelic TNFRSF17 (BCMA) deletion/mutation and gamma-secretase-mediated BCMA shedding (soluble BCMA) reducing target density; also CAR-T exhaustion/loss

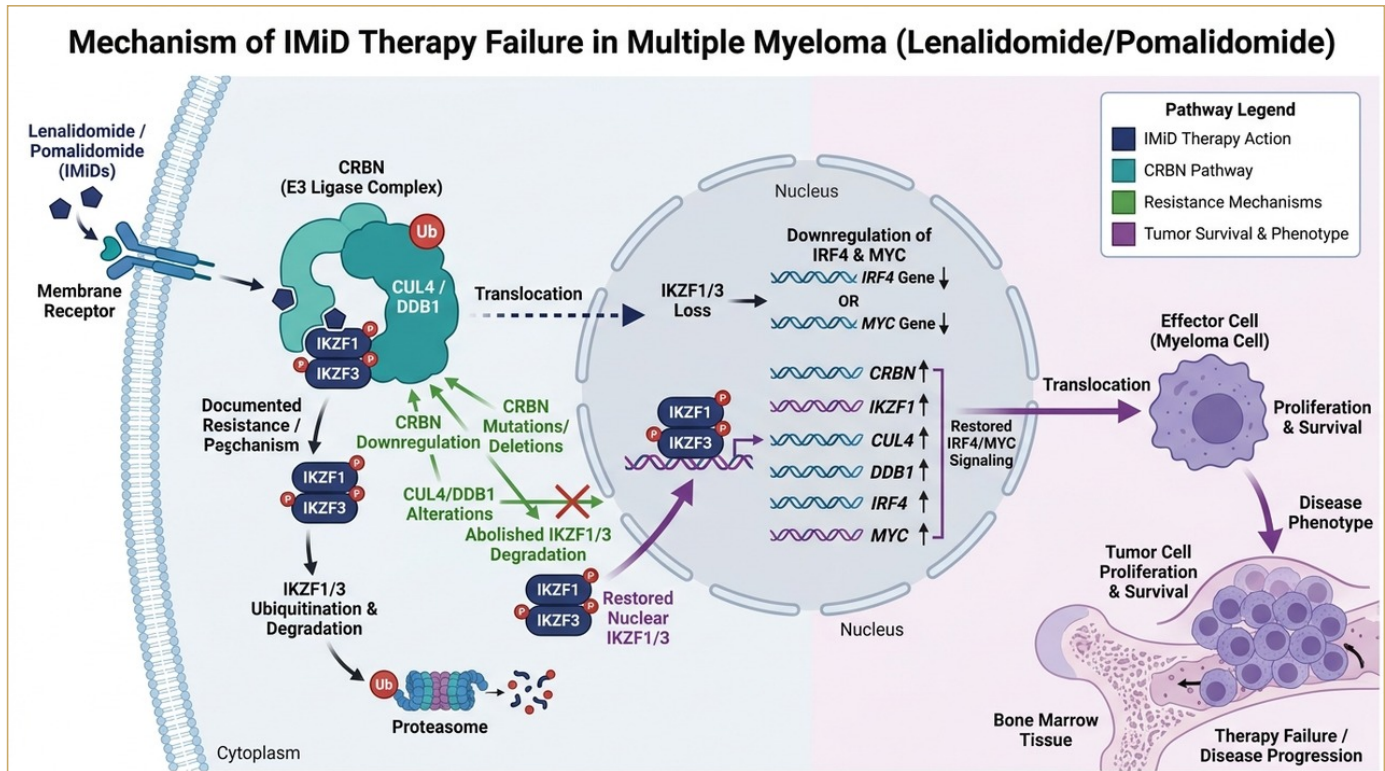
BiRAGAS pattern P7 · antigen-escape

Citation: Munshi NC et al. N Engl J Med 2021;384:705-716 (KarMMa); Da Via MC et al. Nat Med 2021;27:616-619

ClinicalTrials.gov: [NCT03361748](https://clinicaltrials.gov/ct2/show/study/NCT03361748)

Lenalidomide / pomalidomide (IMiDs)

Multiple myeloma



Indication: Multiple myeloma

Resistance / failure mechanism:

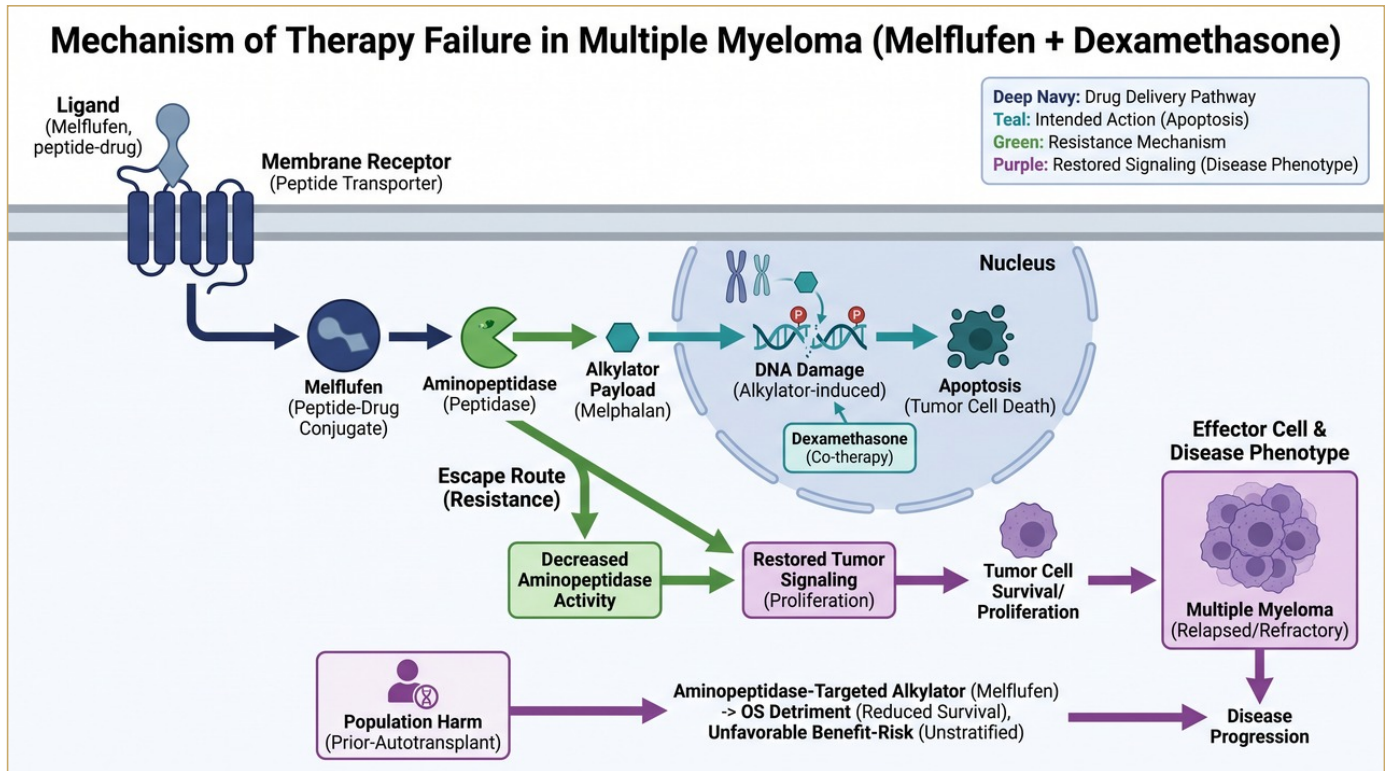
CRBN downregulation, loss-of-function CRBN mutations/deletions, and CRBN-pathway (CUL4/DDB1) alterations abolish IKZF1/3 degradation, restoring IRF4/MYC

BiRAGAS pattern P7 · target-mutation

Citation: Zhu YX et al. Blood 2011;118:4771-4779 (PMID 21860026); Kortum KM et al. Blood 2016

Melflufen (melphalan flufenamide) + dexamethasone

Multiple myeloma (relapsed/refractory)



Indication: Multiple myeloma (relapsed/refractory)

Resistance / failure mechanism:

Population harm: the aminopeptidase-targeted alkylator conferred an OS detriment in prior-autotransplant patients, an unfavorable benefit-risk in an unstratified population

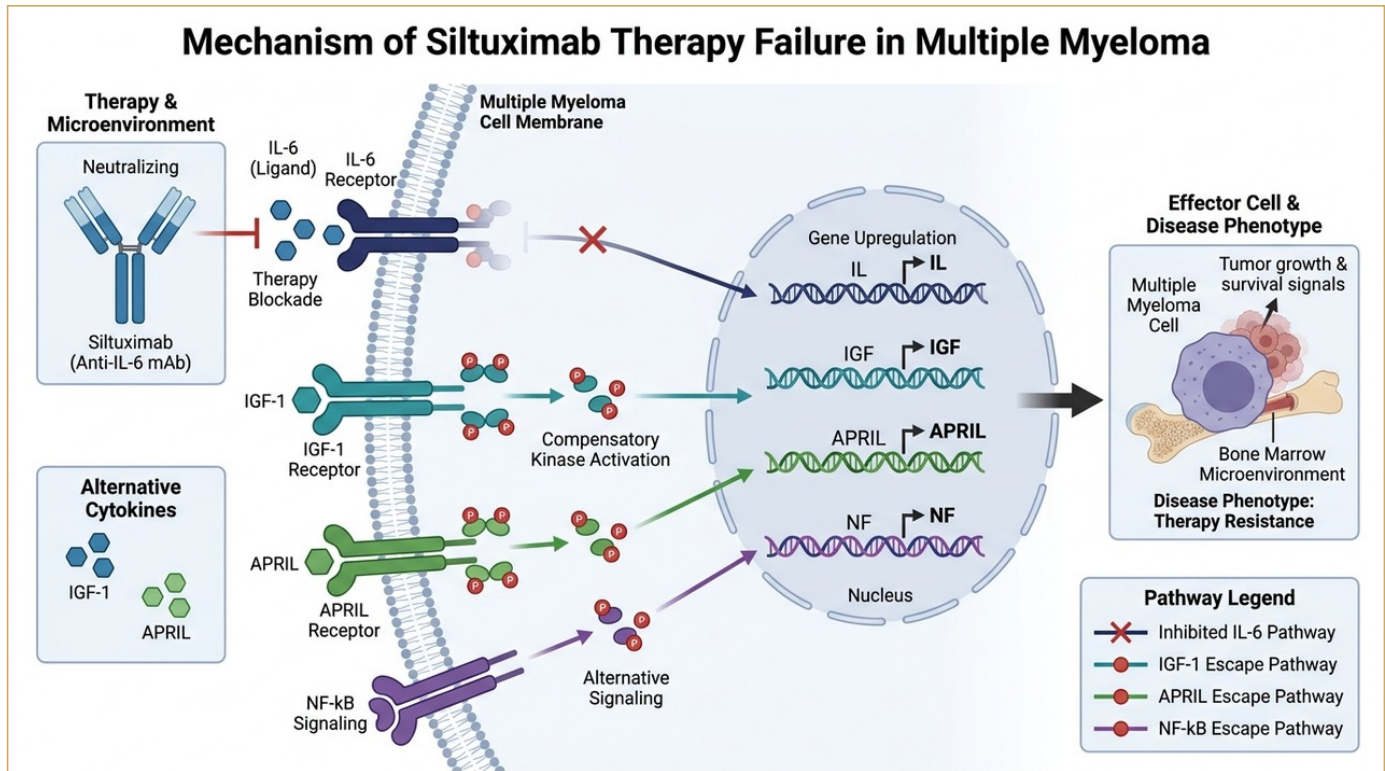
BiRAGAS pattern P3 · population-dilution

Citation: Schjesvold FH et al. Lancet Haematol 2022;9:e98-e110 (OCEAN, PMID 35032434)

ClinicalTrials.gov: [NCT03151811](https://clinicaltrials.gov/ct2/show/study/NCT03151811)

Siltuximab (+ bortezomib; or + VMP)

Multiple myeloma



Indication: Multiple myeloma

Resistance / failure mechanism:

IL-6 is a supportive microenvironmental correlate, not a non-redundant survival driver; blockade is compensated by alternative cytokines (IGF-1, APRIL) and NF-kB signaling

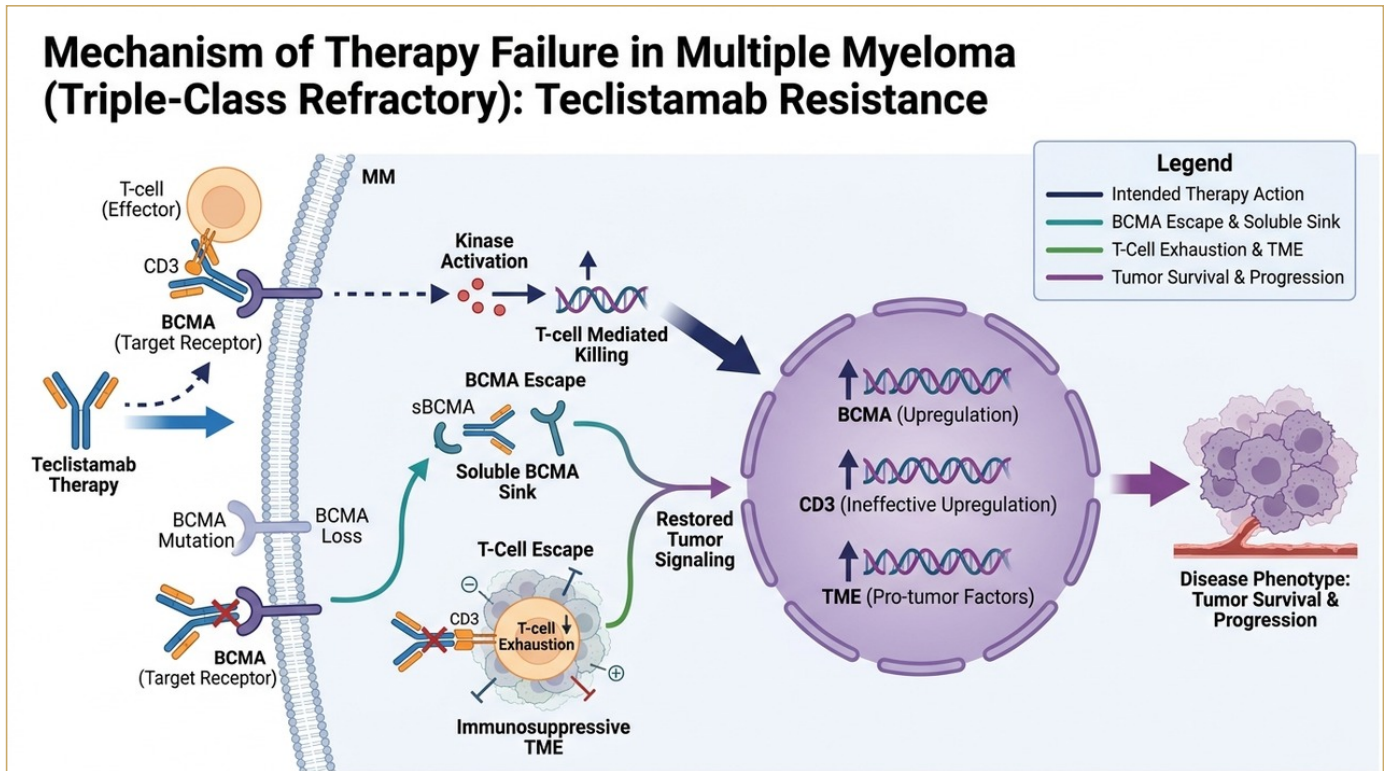
BiRAGAS pattern P1 · correlate-not-driver

Citation: Orłowski RZ et al. Am J Hematol 2015;90:42-49 (PMID 25294016); San-Miguel J et al. Blood 2014;123:4136 (PMID 24833354)

ClinicalTrials.gov: NCT00401843

Teclistamab

Multiple myeloma (triple-class refractory)



Indication: Multiple myeloma (triple-class refractory)

Resistance / failure mechanism:

BCMA loss/mutation and soluble-BCMA sink reduce target engagement; T-cell exhaustion and an immunosuppressive TME blunt bispecific efficacy

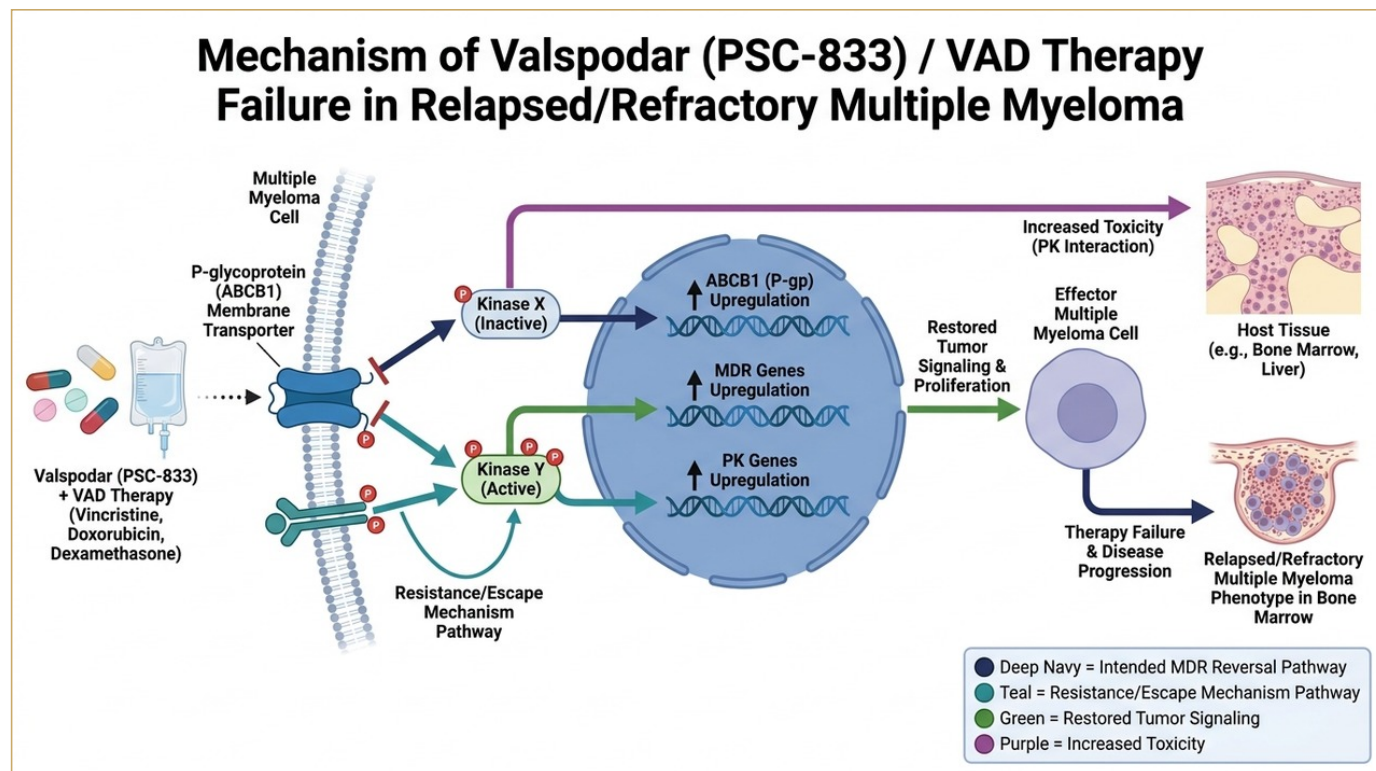
BiRAGAS pattern P7 · antigen-escape

Citation: Moreau P et al. N Engl J Med 2022;387:495-505 (MajesteC-1, PMID 35661166); Lee H et al. Nat Med 2023 (BCMA escape)

[ClinicalTrials.gov: NCT04557098](https://clinicaltrials.gov/ct2/show/study/NCT04557098)

Valspodar (PSC-833) added to vincristine/doxorubicin/dexamethasone (valspo

Multiple myeloma (relapsed/refractory)



Indication: Multiple myeloma (relapsed/refractory)

Resistance / failure mechanism:

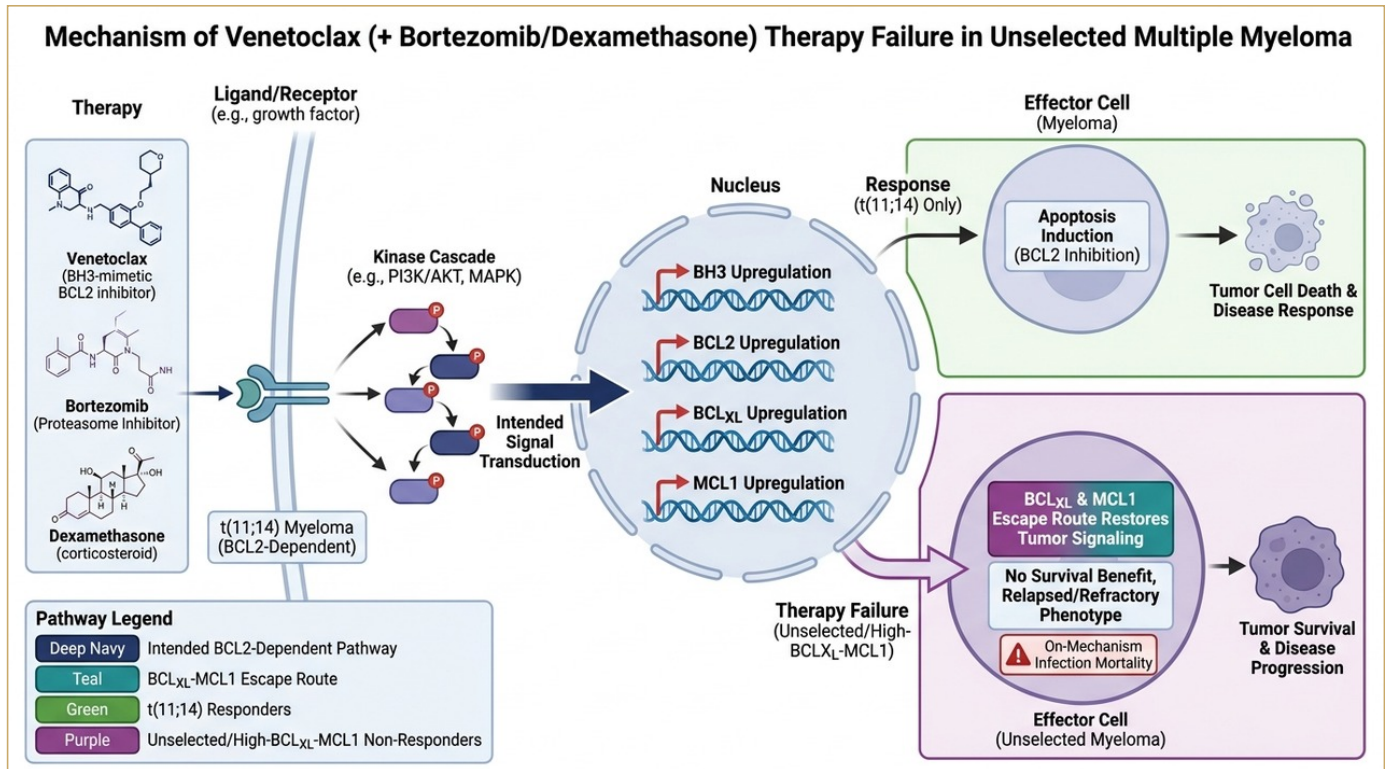
MDR reversal via P-gp inhibition failed to improve response; increased toxicity from PK interaction offset any efflux benefit

BiRAGAS pattern P6 · on-mechanism-toxicity

Citation: Friedenberg WR et al. Cancer 2006;106(4):830-838. PMID 16419071

Venetoclax (+ bortezomib/dexamethasone)

Multiple myeloma (relapsed/refractory, unselected)



Indication: Multiple myeloma (relapsed/refractory, unselected)

Resistance / failure mechanism:

Population mismatch: only BCL2-dependent myeloma (t(11;14)) responds, while unselected/high-BCLXL-MCL1 disease derives no survival benefit and suffers on-mechanism infection mortality; canonical unstratified-population failure

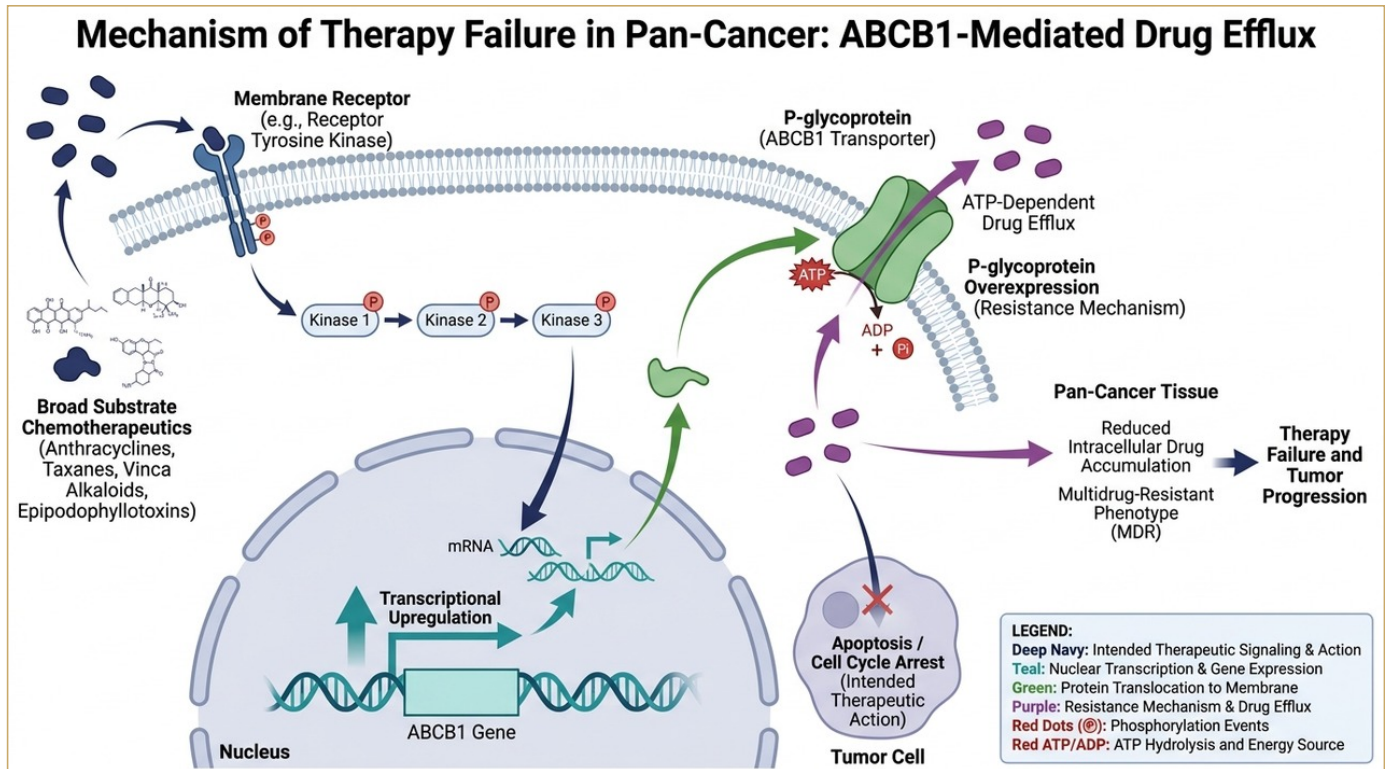
BiRAGAS pattern P3 · population-dilution

Citation: Kumar S et al. Lancet Oncol 2020;21:1630-1642 (PMID 33129376)

ClinicalTrials.gov: [NCT02755597](https://clinicaltrials.gov/ct2/show/study/NCT02755597)

Broad substrate chemotherapeutics (anthracyclines, taxanes, vinca alkaloid

Pan-cancer



Indication: Pan-cancer

Resistance / failure mechanism:

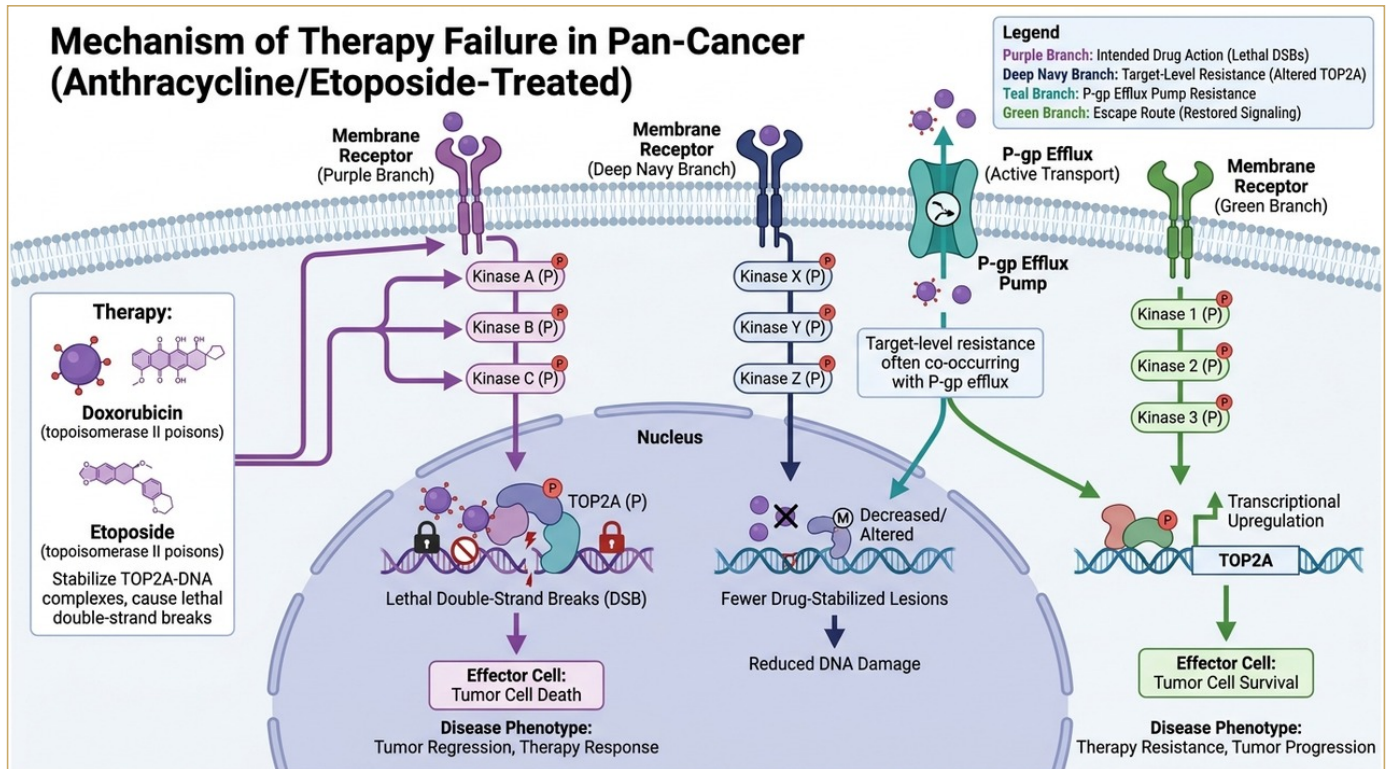
ATP-dependent drug efflux by P-glycoprotein reduces intracellular drug accumulation; overexpression selected during treatment produces classic multidrug-resistant phenotype

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Gottesman MM, Fojo T, Bates SE. Nat Rev Cancer 2002;2(1):48-58. PMID 11902585

Doxorubicin / etoposide (topoisomerase II poisons)

Pan-cancer (anthracycline/etoposide-treated)



Indication: Pan-cancer (anthracycline/etoposide-treated)

Resistance / failure mechanism:

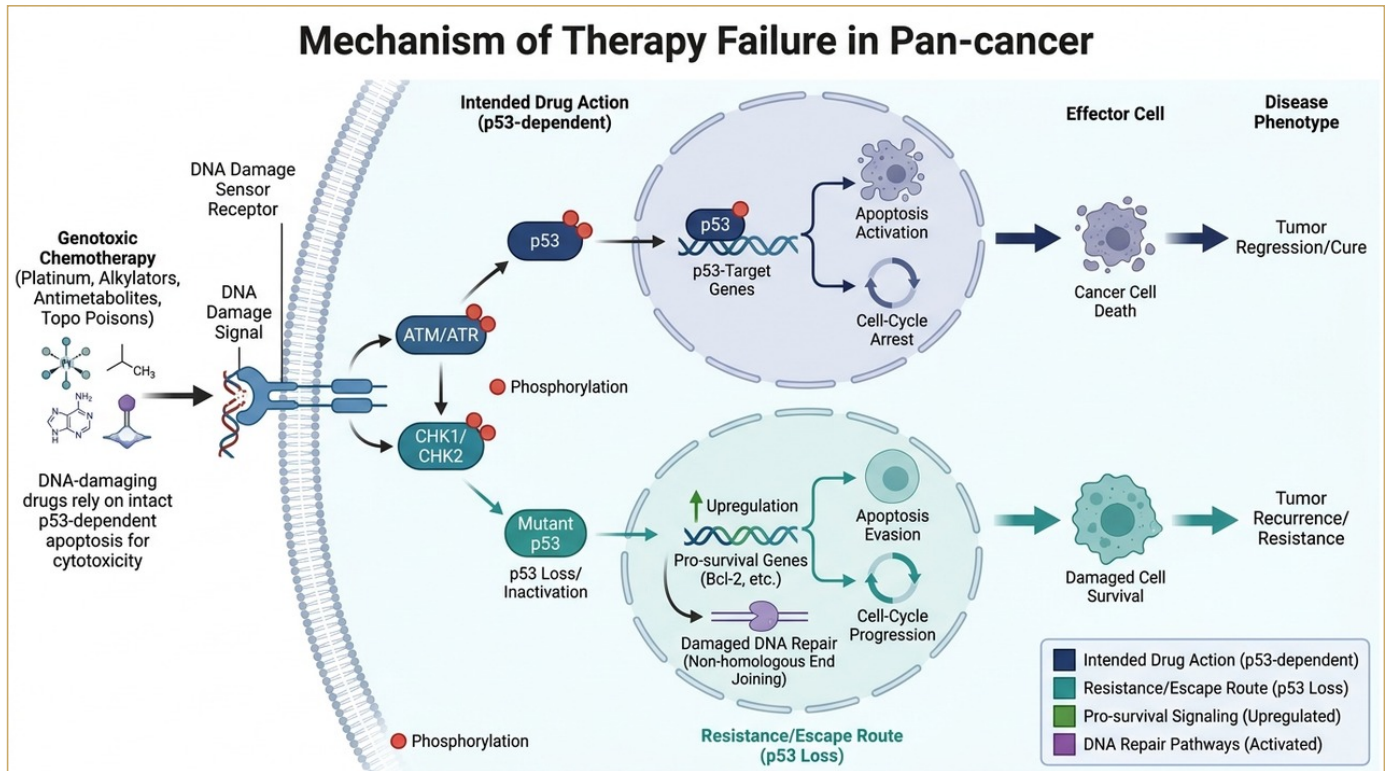
Decreased/alterd target enzyme yields fewer drug-stabilized DNA lesions; target-level resistance often co-occurring with P-gp efflux

BiRAGAS pattern P1 · target-mutation

Citation: Nitiss JL. Nat Rev Cancer 2009;9(5):338-350. PMID 19377506

Genotoxic chemotherapy (platinum, alkylators, antimetabolites, topo poison

Pan-cancer



Indication: Pan-cancer

Resistance / failure mechanism:

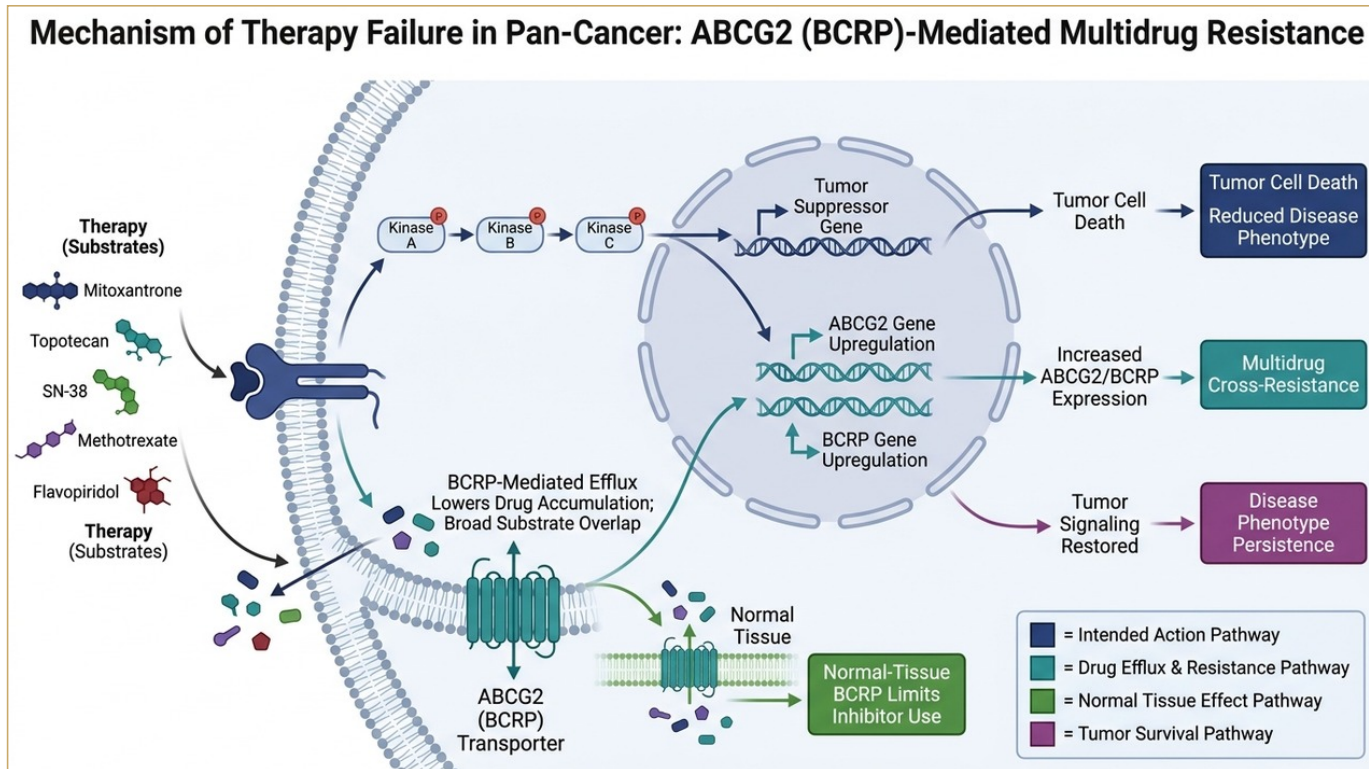
Loss of p53-mediated apoptosis/cell-cycle-checkpoint response allows damaged cells to survive genotoxic therapy

BiRAGAS pattern P1 · DNA-repair/apoptosis-evasion

Citation: Lowe SW et al. Science 1994;266(5186):807-810. PMID 7973635

Mitoxantrone, topotecan, SN-38 (irinotecan active metabolite), methotrexat

Pan-cancer



Indication: Pan-cancer

Resistance / failure mechanism:

BCRP-mediated efflux lowers drug accumulation; broad substrate overlap gives multidrug cross-resistance, and normal-tissue BCRP limits inhibitor use

BiRAGAS pattern P5 · pharmacologic/efflux-metabolism

Citation: Robey RW et al. Nat Rev Cancer 2018;18(7):452-464. PMID 30115934