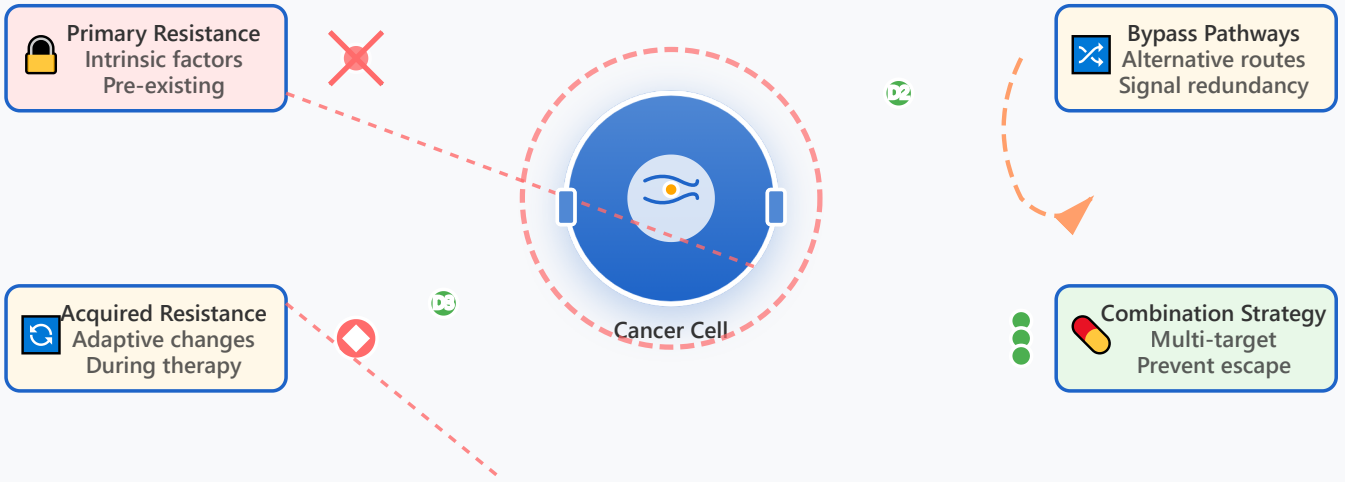
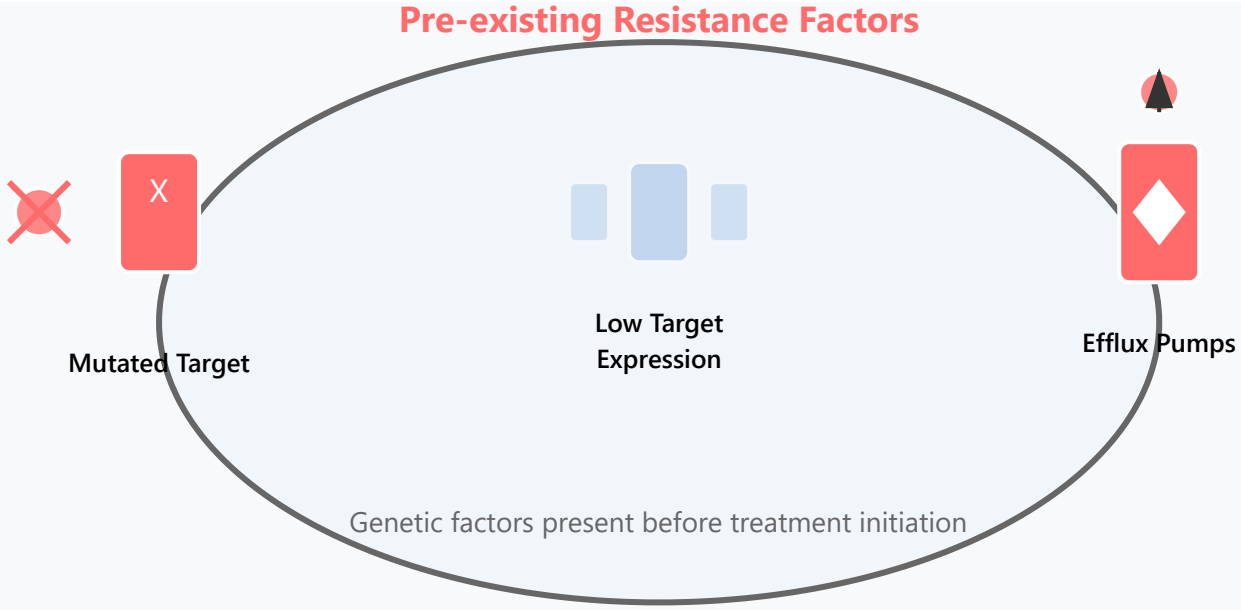
Resistance Mechanisms



Monitoring Approaches: Serial biopsies and liquid biopsy track resistance evolution

Primary (Intrinsic) Resistance



Key Characteristics

- Pre-existing in tumor cells before treatment
- Germline or somatic mutations present at diagnosis
- Tumor heterogeneity with resistant subclones
- Immediate treatment failure or minimal response

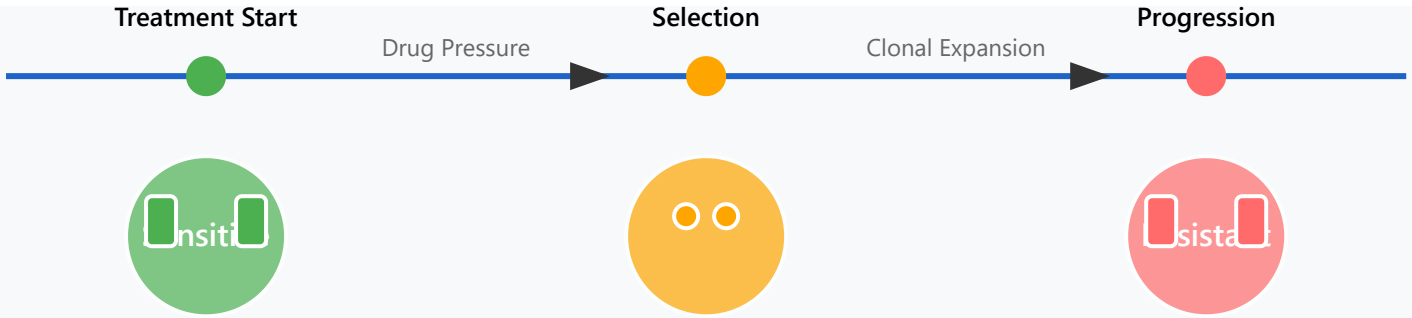
Mechanisms

- Target gene mutations preventing drug binding
- Low or absent target protein expression
- High expression of drug efflux transporters
- Pre-existing bypass pathway activation

Clinical Example

EGFR-mutant NSCLC with T790M: Approximately 60% of EGFR-mutant non-small cell lung cancers that develop resistance to first-generation EGFR TKIs (erlotinib, gefitinib) harbor the T790M gatekeeper mutation, which increases ATP affinity and prevents drug binding.

Acquired Resistance



Adaptive Mechanisms During Therapy

Secondary Mutations

Target alterations
Downstream changes

Gene Amplification

MET amplification
HER2 amplification

Phenotypic Changes

EMT transition
Histologic shifts

Key Characteristics

- Develops during treatment exposure
- Initial response followed by progression
- Clonal selection under drug pressure
- Time to resistance: months to years

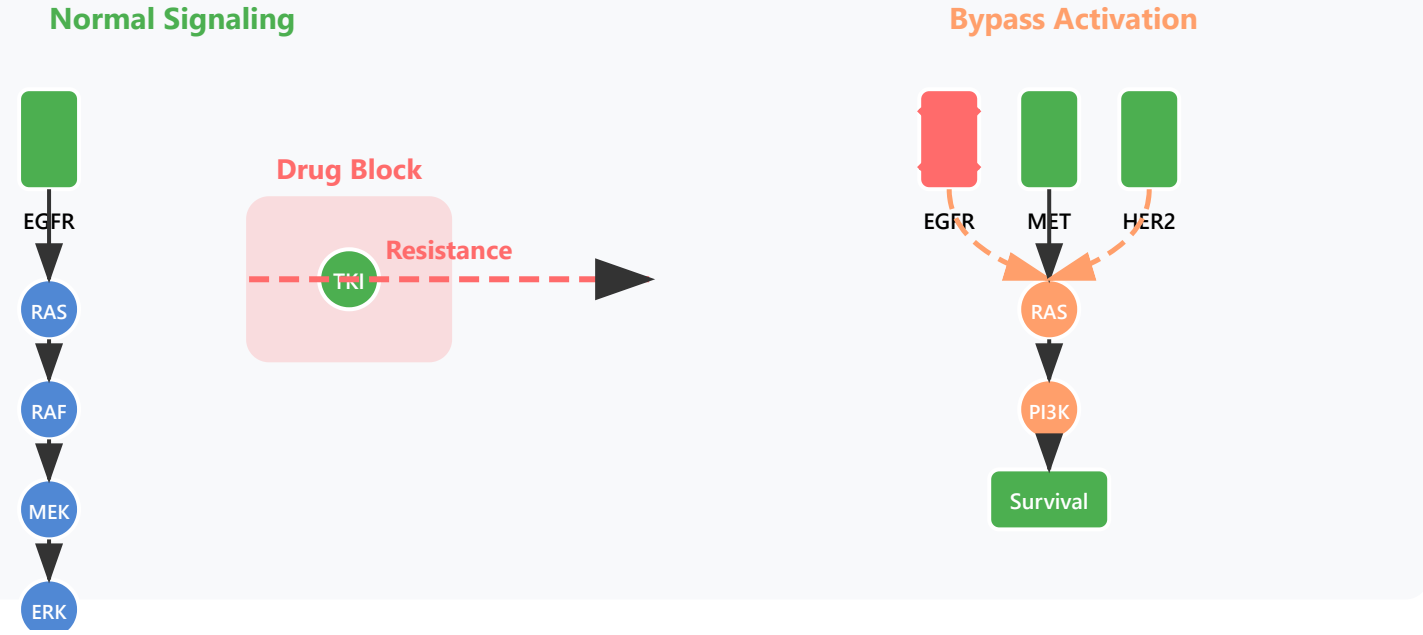
Common Mechanisms

- On-target: Secondary mutations in target gene
- Off-target: Parallel pathway activation
- Drug metabolism: Increased efflux, decreased uptake
- Histologic transformation: SCLC conversion

Clinical Example

Osimertinib Resistance in EGFR T790M+ NSCLC: C797S mutation emerges in approximately 15-30% of patients treated with osimertinib (third-generation EGFR TKI), preventing covalent drug binding. MET amplification accounts for another 15-20% of resistance mechanisms.

Bypass Pathway Activation



Key Characteristics

- Alternative pathways maintain signaling output
- Signal redundancy overcomes single-target inhibition
- Can be pre-existing or acquired during treatment
- Often involves parallel RTK activation

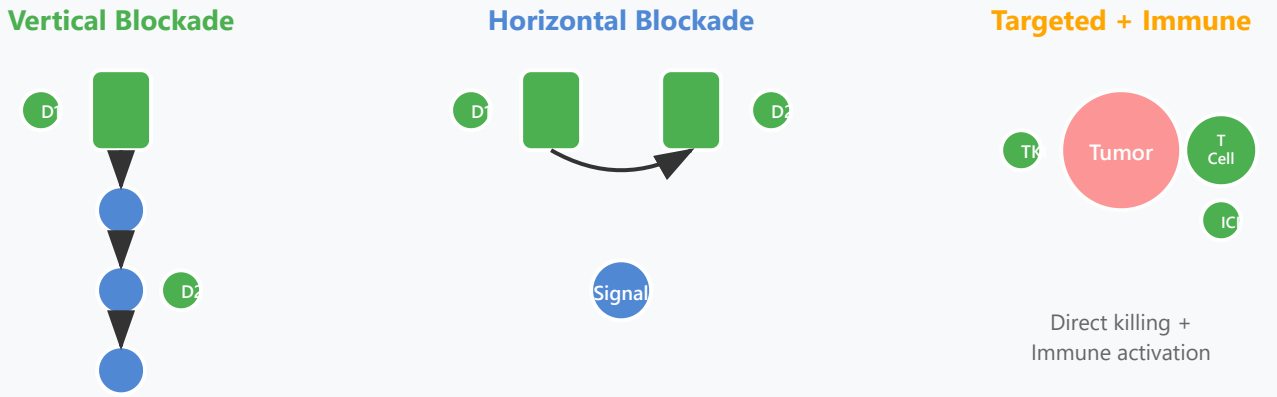
Common Bypass Routes

- MET amplification bypassing EGFR inhibition
- HER2/HER3 activation maintaining PI3K signaling
- IGF-1R upregulation in hormone receptor+ breast cancer
- PIK3CA mutations activating downstream signaling

Clinical Example

MET Amplification in EGFR-mutant NSCLC: MET gene amplification occurs in 5-15% of patients with acquired resistance to EGFR TKIs. MET activation maintains downstream PI3K/AKT and MAPK signaling despite EGFR inhibition. Combination of EGFR and MET inhibitors shows clinical benefit in this subset.

Combination Therapy Strategies



Benefits of Combination Therapy

- Delay or prevent resistance emergence
- Target multiple resistance mechanisms
- Deeper responses
- Synergistic efficacy
- Address tumor heterogeneity

Combination Approaches

- Vertical: Target multiple nodes in same pathway
- Horizontal: Inhibit parallel signaling pathways
- Targeted + Chemo: Overcome different resistance types
- Targeted + Immune: Direct + immune-mediated killing

Clinical Considerations

- Increased toxicity requiring dose adjustments
- Cost and access considerations
- Biomarker-driven selection of combinations
- Sequential vs. concurrent administration

Clinical Example

Dabrafenib + Trametinib in BRAF V600E Melanoma: Combined BRAF and MEK inhibition (vertical blockade) significantly improves progression-free survival compared to BRAF inhibitor alone (11 vs 7 months median PFS). The combination delays resistance by preventing feedback reactivation of the MAPK pathway and reduces paradoxical MAPK activation.

Resistance Mechanisms: Summary & Clinical Impact

Primary Resistance

- **Timing:** Present before treatment
- **Frequency:** 20-30% of patients
- **Strategy:** Upfront biomarker testing, alternative therapies

Acquired Resistance

- **Timing:** Develops during therapy
- **Frequency:** Nearly universal (6-24 months)
- **Strategy:** Resistance profiling, sequential therapies

Bypass Pathways

- **Mechanism:** Alternative signaling activation
- **Frequency:** 15-25% of resistance cases
- **Strategy:** Horizontal combination therapy

Combination Strategy

- **Goal:** Prevent/delay resistance
- **Approaches:** Vertical, horizontal, multi-modal
- **Challenge:** Toxicity management

Clinical Decision Framework

Initial Assessment	Monitoring	Progression Strategy
• Comprehensive genomic profiling	• Serial liquid biopsy (ctDNA)	• Re-biopsy for mechanism
• Tumor heterogeneity evaluation	• Radiologic response tracking	• Mechanism-directed therapy
• Baseline resistance screening	• Resistance biomarker surveillance	• Clinical trial consideration

Key Takeaway: Understanding resistance mechanisms guides rational therapy selection, optimal sequencing strategies, and novel combination approaches to improve patient outcomes in targeted cancer therapy.