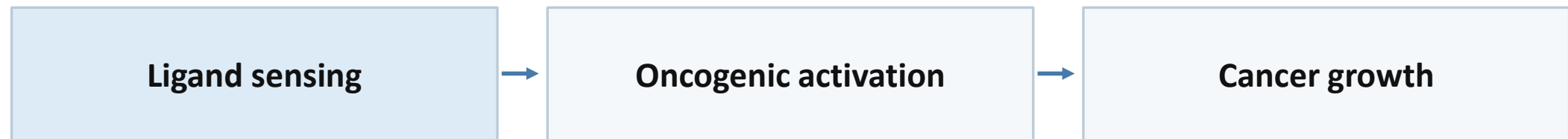


Growth Factor Receptors

Receptor tyrosine kinase activation, oncogenic alterations and therapeutic resistance



Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

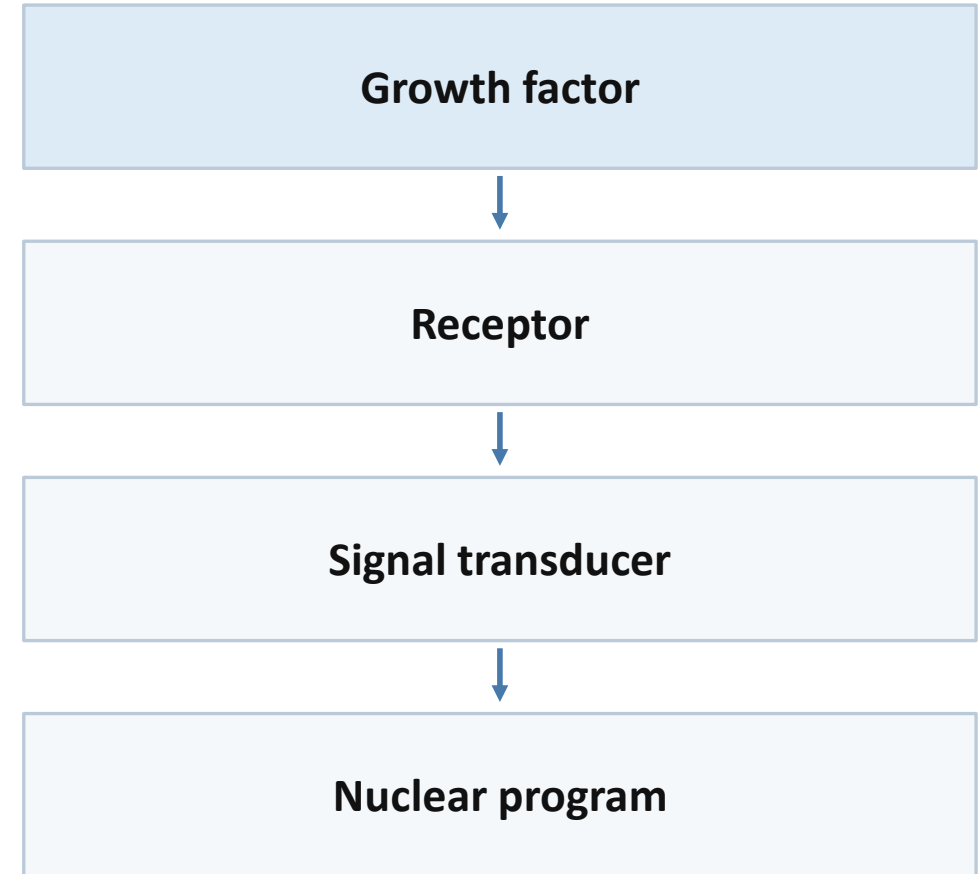
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Learning outcomes

- Explain how a normal receptor tyrosine kinase converts ligand binding into a transient signal.
- Distinguish point mutation, gene amplification, and rearrangement as RTK oncogenic mechanisms.
- Link specific receptor lesions to the example tumors and targeted-therapy implications.
- Explain why receptor-directed therapy can select resistant tumor subclones.

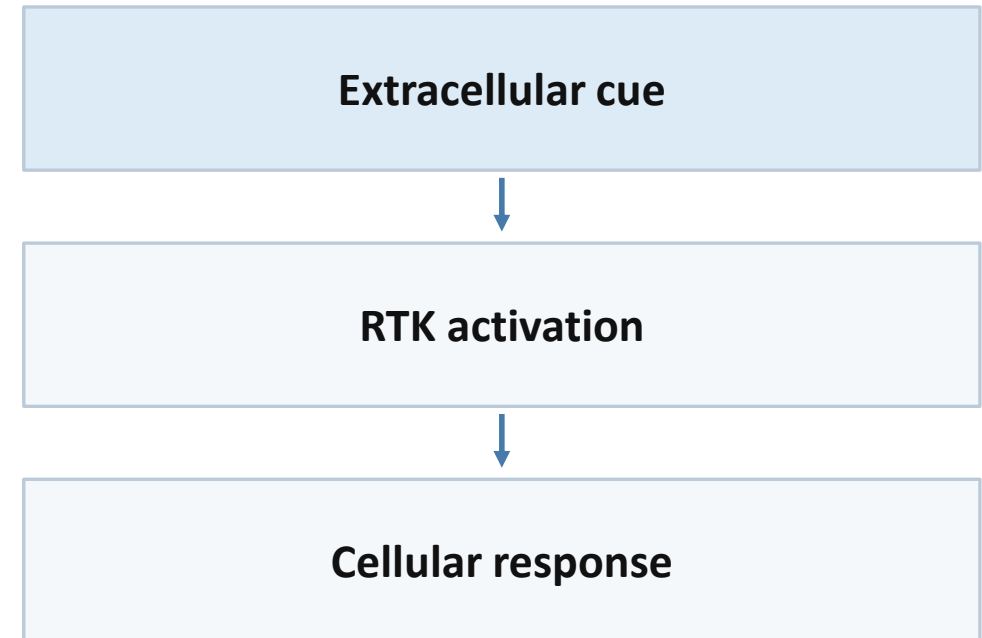
Receptors are one class of proto-oncogene products

- Proto-oncogenes encode growth factors, receptors, signal transducers, transcription factors, or cell-cycle regulators.
- Receptor oncogenes act near the cell surface, upstream of intracellular growth programs.
- Gain of receptor activity reduces dependence on normal extracellular control.



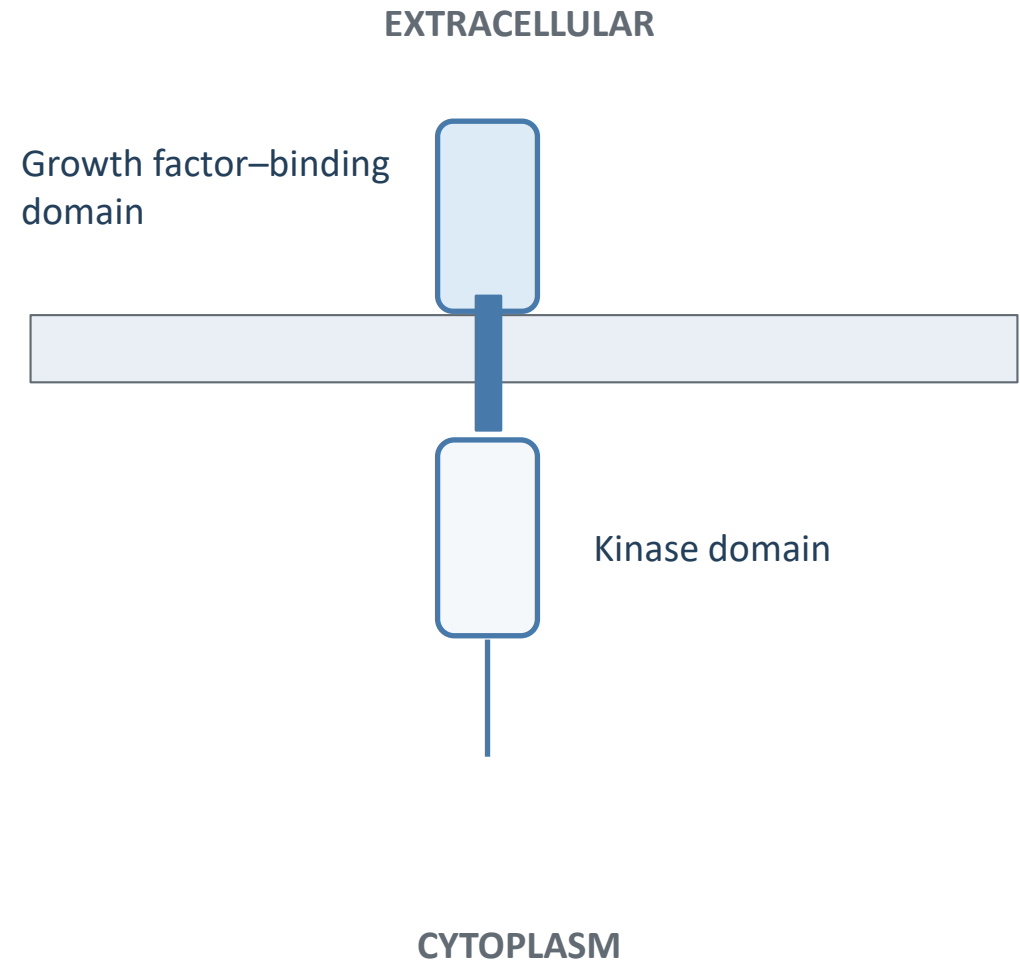
Why receptor tyrosine kinases matter in cancer

- Many oncogenes encode growth factor receptors.
- Receptor tyrosine kinases (RTKs) are among the most important growth factor receptors in oncogenesis.
- The same signaling machinery ordinarily supports regulated cell proliferation and survival.



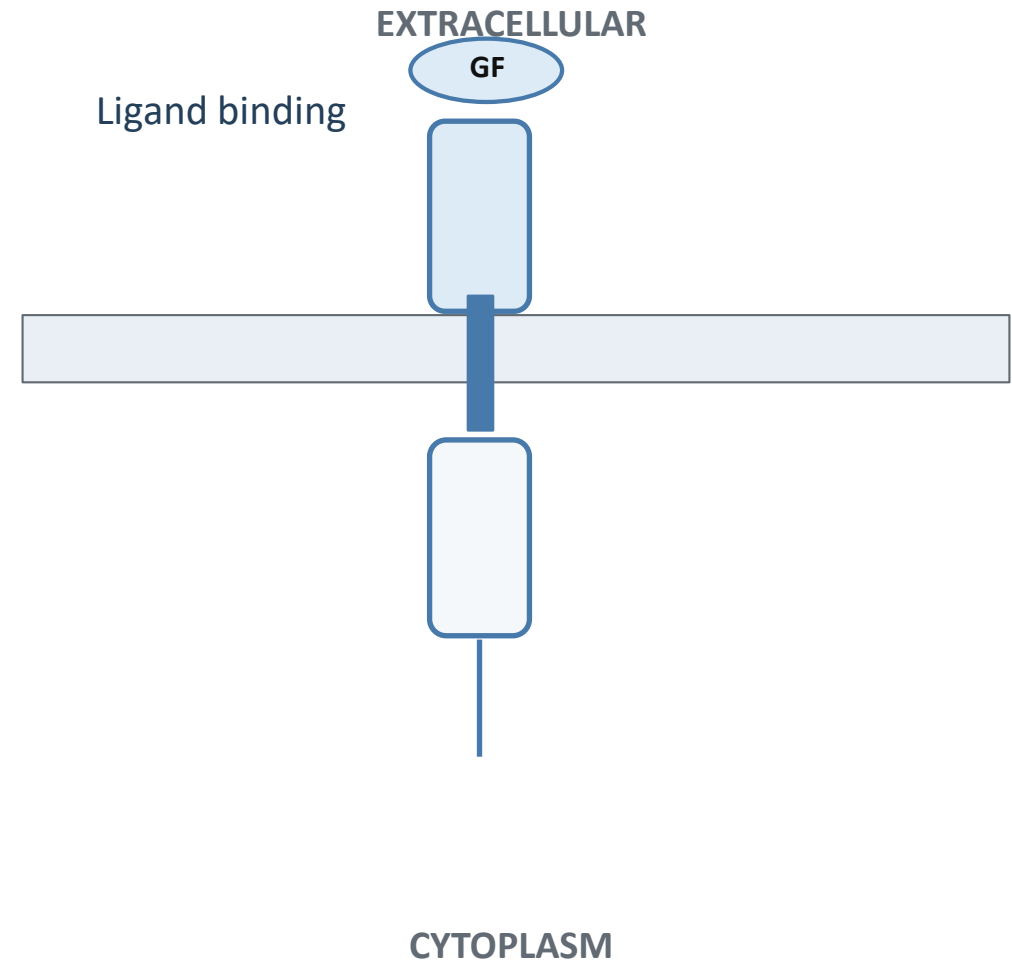
An RTK crosses the plasma membrane

- Extracellular domain recognizes a specific growth factor.
- Cytoplasmic domain contains tyrosine kinase activity.
- The receptor links an external ligand to intracellular signaling machinery.



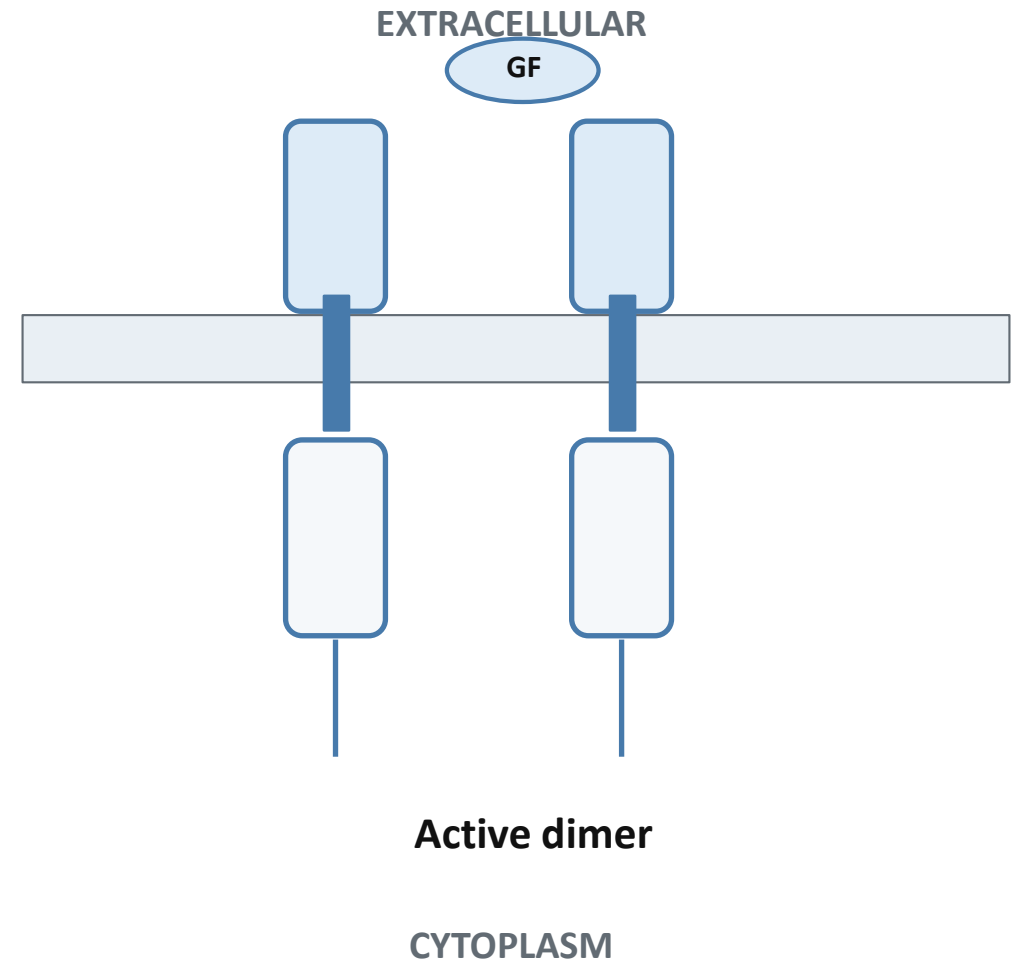
Ligand binding begins a normal RTK signal

- Activation normally begins with a matching growth factor binding its receptor.
- Receptor engagement triggers a conformational change.
- The signal is ligand-dependent in its physiologic state.



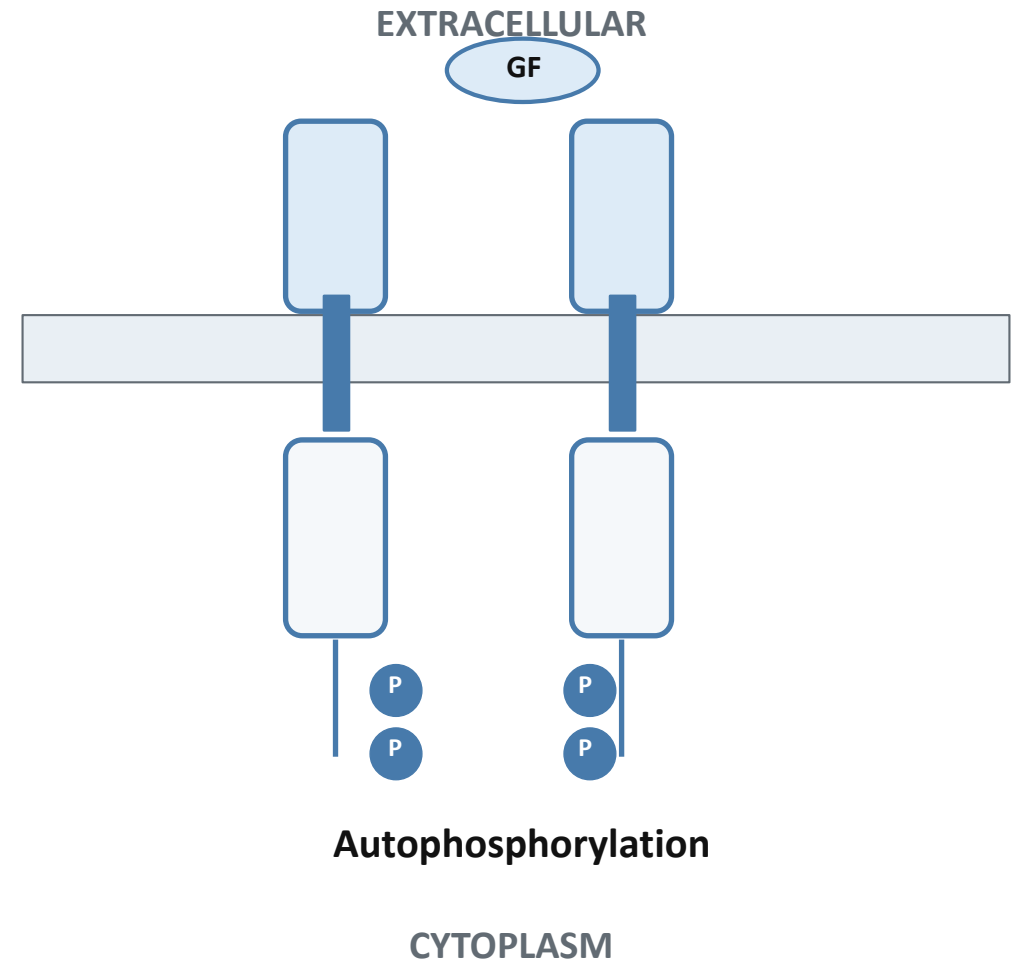
Ligand engagement favors the active dimer

- Activated receptors adopt an active dimeric state.
- Dimer formation places intracellular kinase domains in an activation-competent arrangement.
- Dimerization is a key step between ligand recognition and signaling.



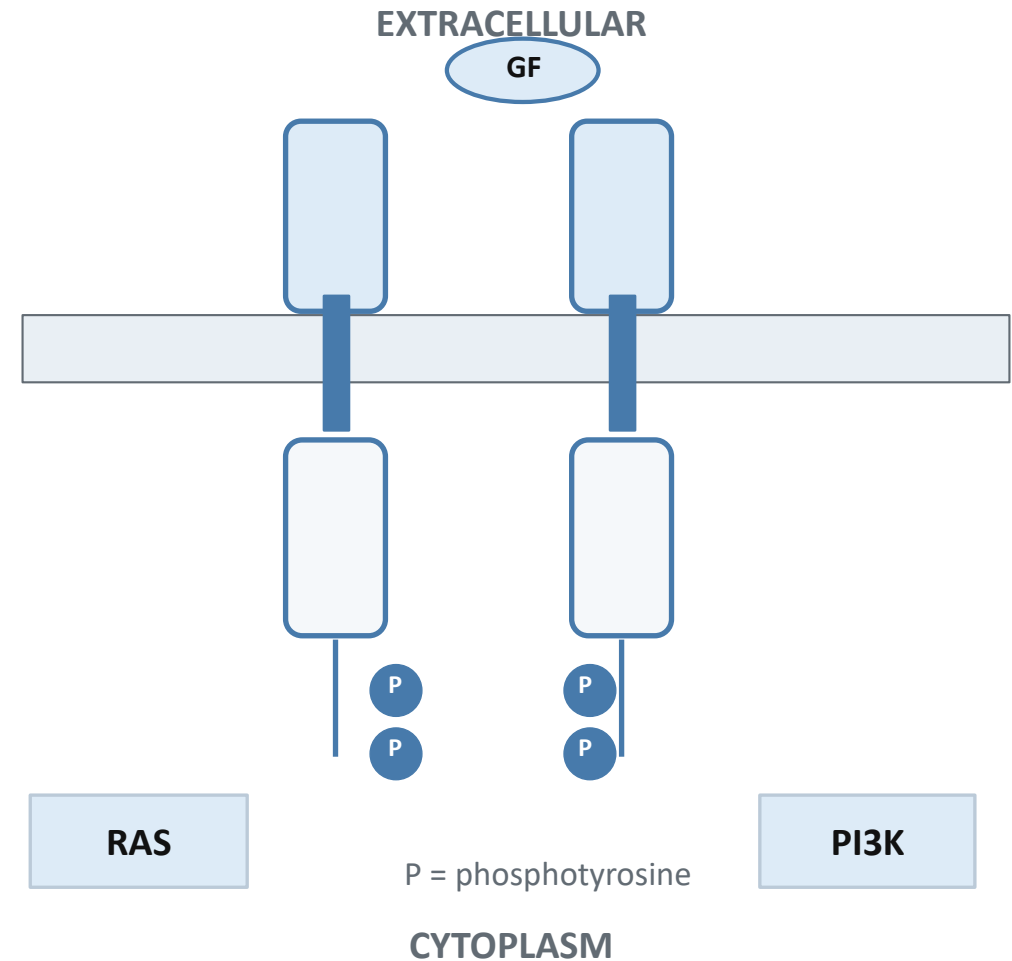
Autophosphorylation creates signaling sites

- Activated RTKs phosphorylate tyrosine residues on intracellular receptor tails.
- Phosphotyrosines form molecular recruitment sites for downstream proteins.
- Kinase activation is therefore coupled to assembly of a signaling complex.



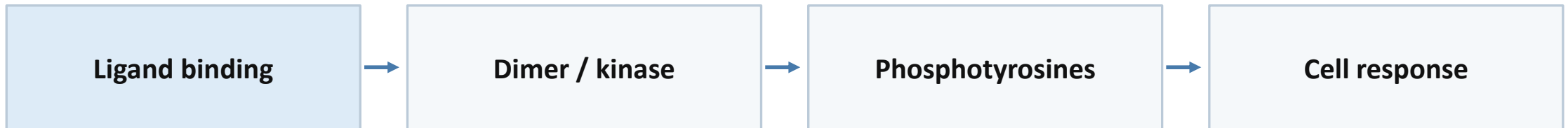
Phosphorylated tails recruit signaling proteins

- RAS-linked signaling molecules and PI3K-associated signaling are recruited downstream.
- Receptor phosphorylation creates docking sites rather than directly entering the nucleus.
- The signal is propagated through additional cytoplasmic components.



The normal signaling sequence is ordered

- Ligand recognition precedes the active receptor conformation.
- Tyrosine phosphorylation precedes recruitment of downstream proteins.
- Downstream signals ultimately regulate transcription and cell-cycle entry.



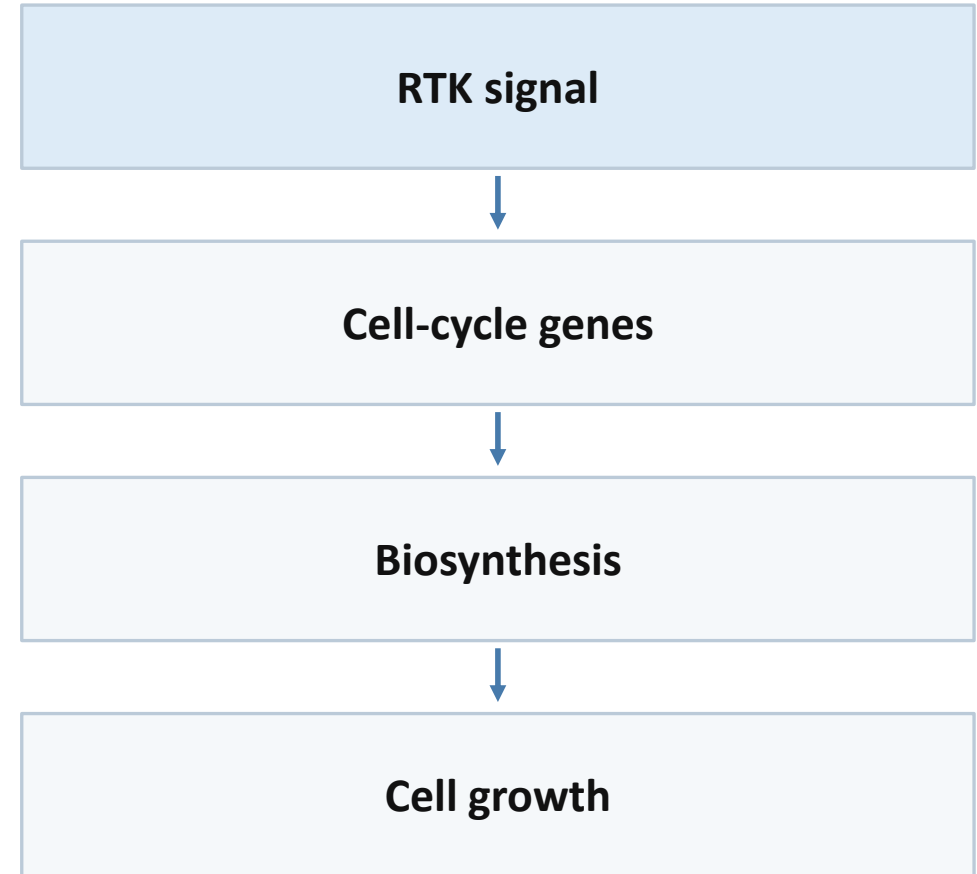
RTK activation is normally transient

Physiologic activation depends on an external growth factor.

Normal receptor	Oncogenic receptor
Requires ligand to activate	Can be active without ligand
Transient activation	Persistent kinase activity
External growth control	Relative autonomy from external cues

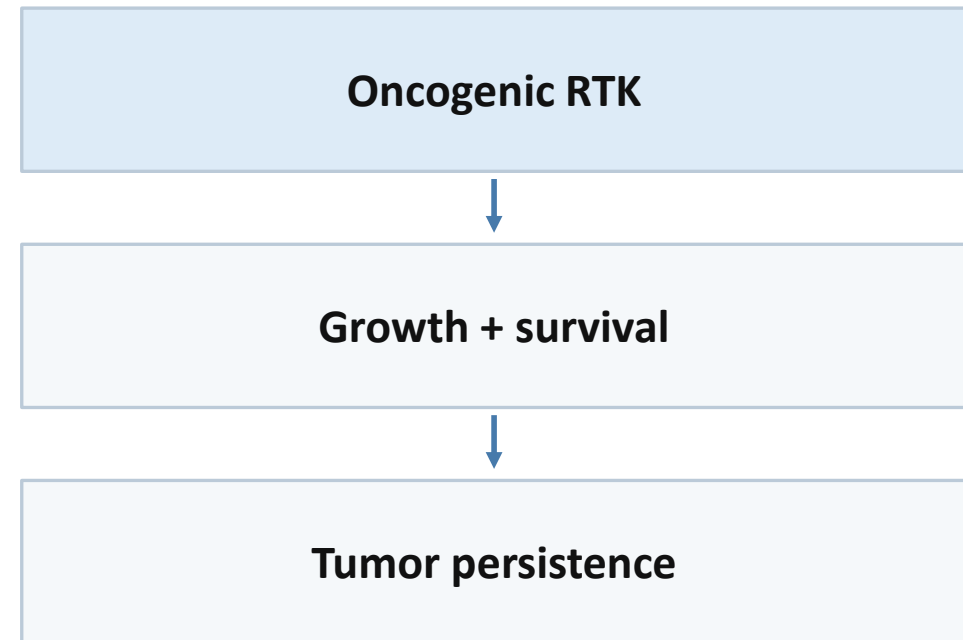
Mitogenic signaling needs more than DNA replication

- Normal growth signaling promotes cell-cycle entry and progression.
- Growth also requires synthesis of membranes, proteins, and other macromolecules.
- The associated program coordinates biosynthesis and cell survival.



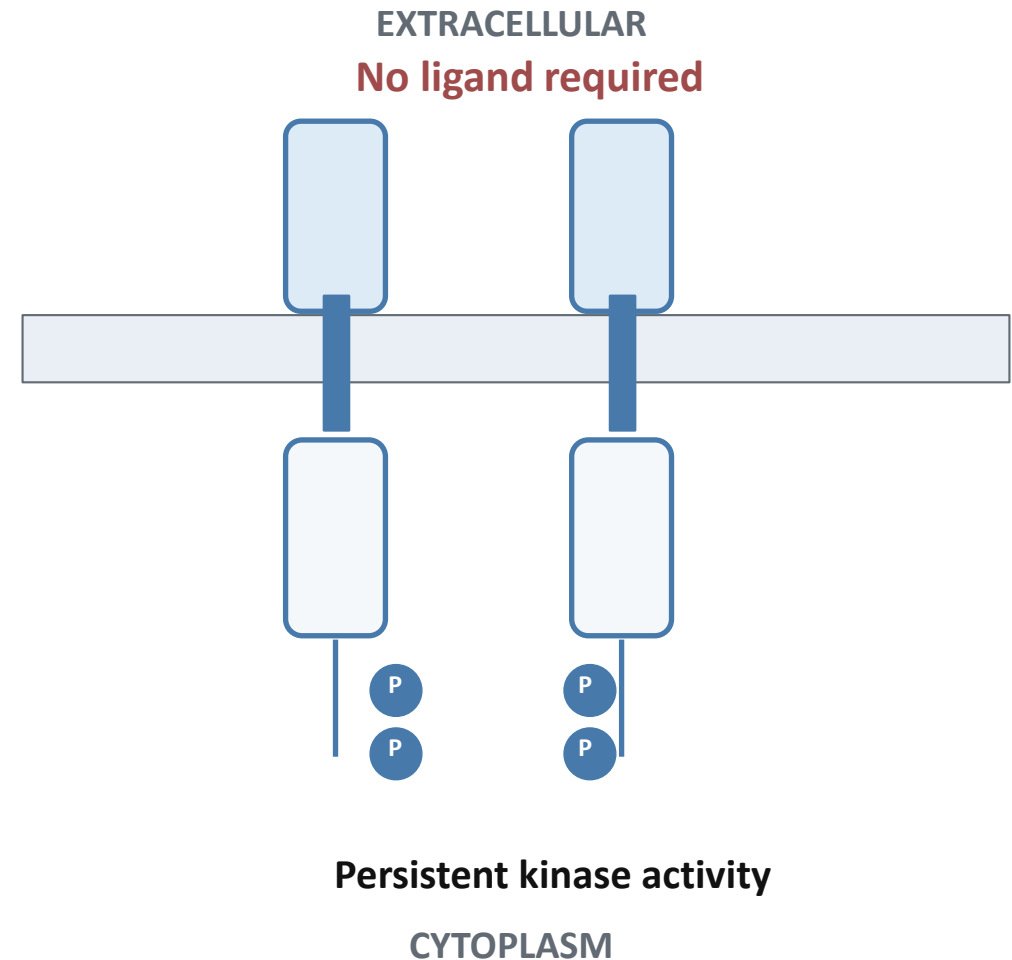
RTK signaling can also support survival

- Growth signaling can augment cell survival, not simply accelerate division.
- Consequently, inhibiting a driver RTK may trigger apoptosis.
- This dual effect helps explain tumor regression following effective therapy.



An oncogenic RTK can signal without ligand

- Activating genetic lesions generate constitutive tyrosine kinase activity.
- Mitogenic signals continue even without growth factor.
- The receptor becomes an oncoprotein rather than a physiologically regulated switch.



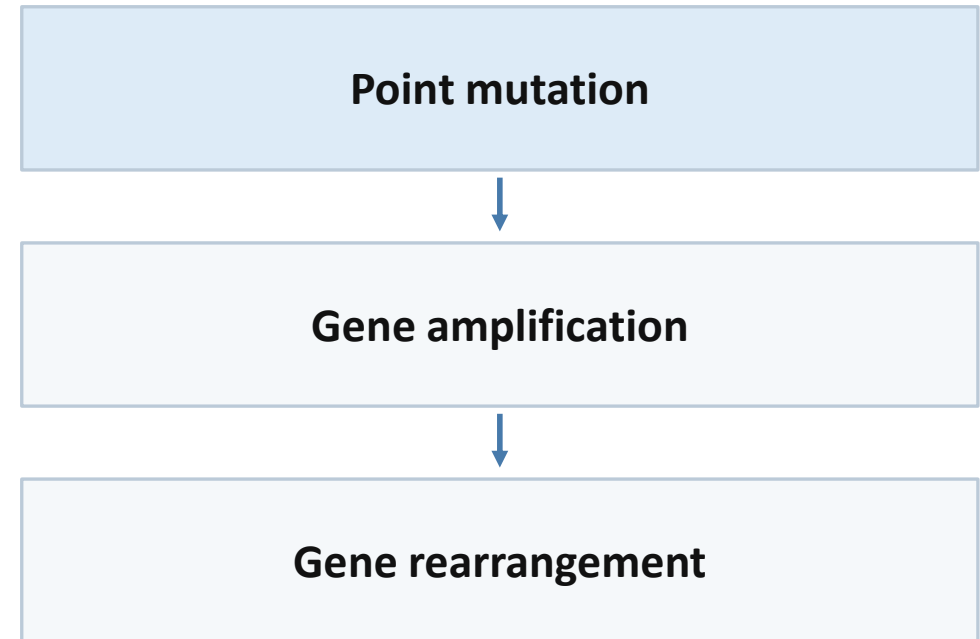
Constitutive signaling removes a normal dependency

Normal RTKs couple signal strength to the availability of growth factor.

Normal control	Tumor-associated escape
Ligand needed for activation	Ligand-independent activity
Short-lived activation	Persistent downstream signaling
Proliferation responds to cues	Proliferation can become autonomous

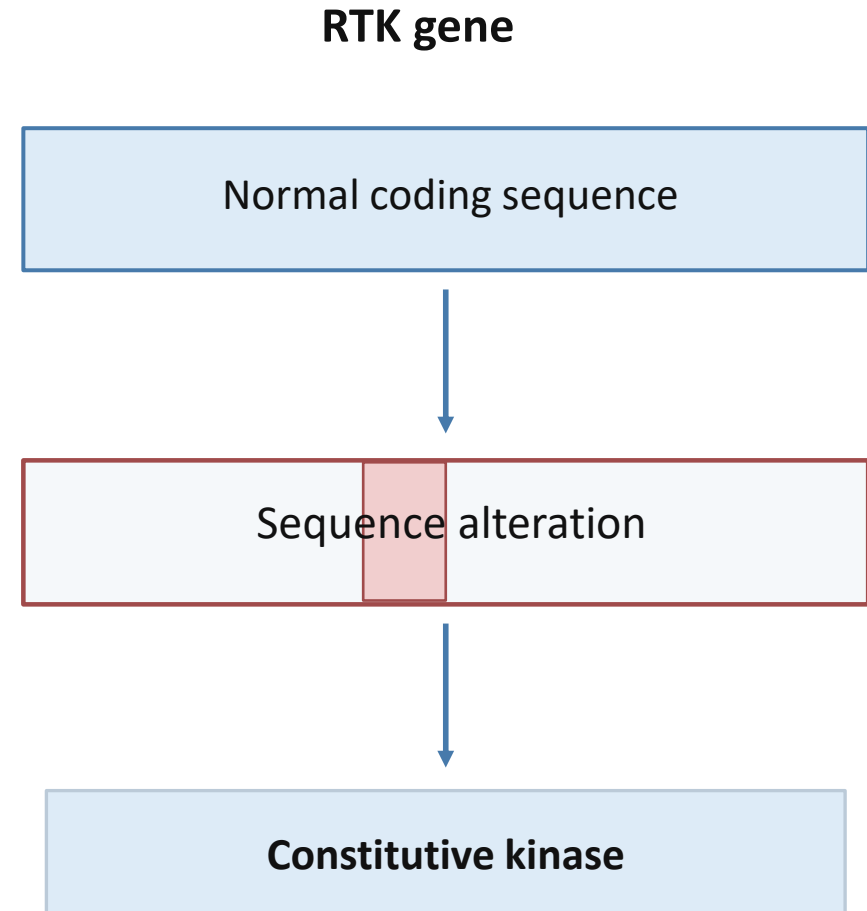
Three genomic routes converge on RTK activation

- Point mutation: Alters receptor function.
- Amplification: Increases copy number and receptor abundance.
- Rearrangement: Can create an oncogenic fusion kinase.



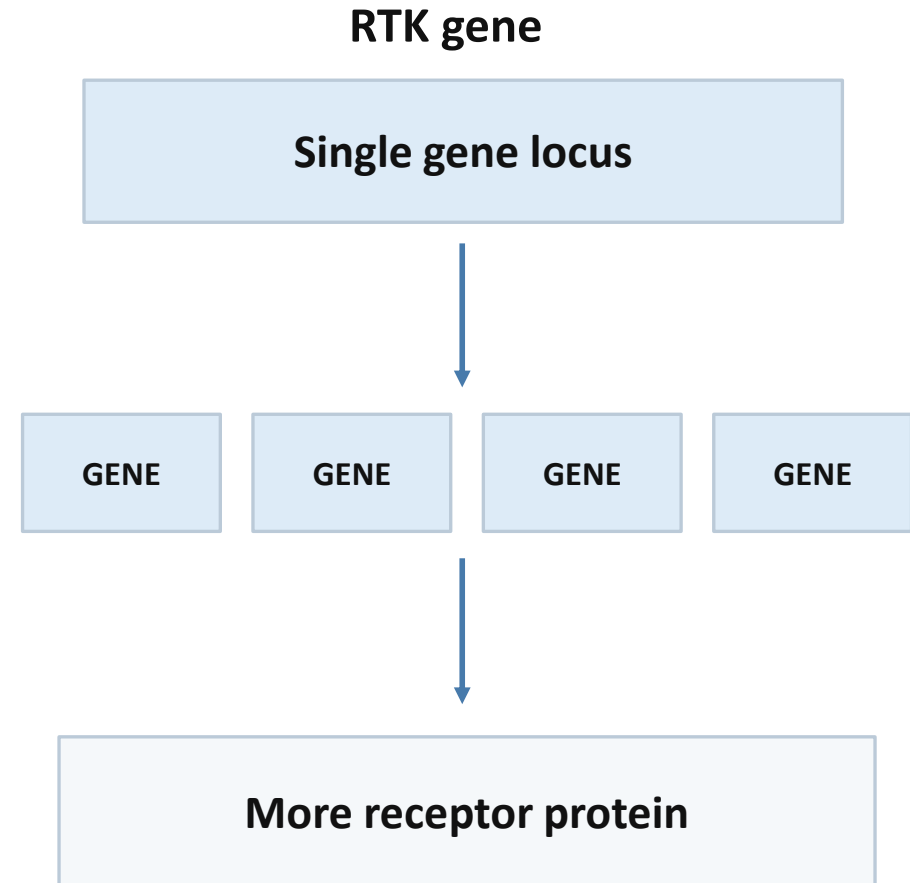
Point mutations can activate the receptor kinase

- A nucleotide-level alteration can increase receptor activity.
- An activated kinase can signal without normal ligand control.
- Examples: ERBB1 in lung adenocarcinoma and KIT in gastrointestinal stromal tumors.



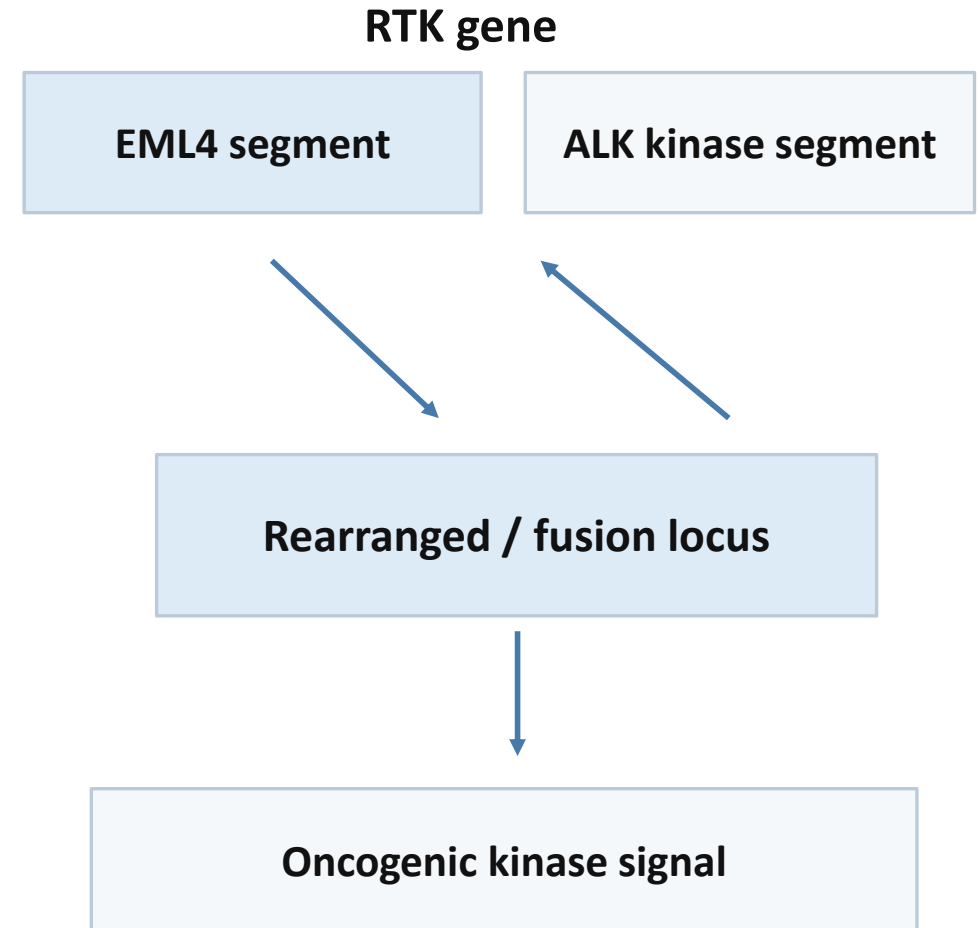
Gene amplification raises receptor abundance

- Additional gene copies can drive marked receptor overexpression.
- , ERBB2 amplification is the canonical breast carcinoma example.
- Excess HER2 is associated with constitutive tyrosine kinase activity.



Rearrangement can generate a fusion oncoprotein

- Chromosomal rearrangement can join portions of different genes.
- Fusion can retain an active kinase component while changing normal regulation.
- The EML4::ALK fusion in lung adenocarcinoma is a central example.

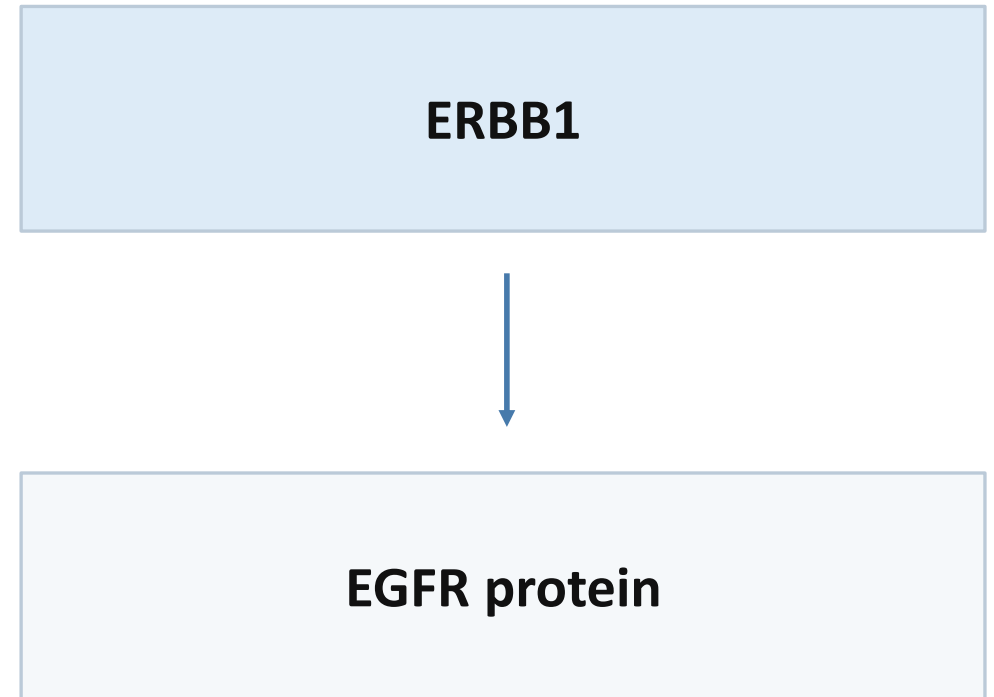


Mechanism should not be confused with tumor type

Genetic event	Receptor example	Tumor association
Point mutation	ERBB1 / EGFR	Lung adenocarcinoma
Gene amplification	ERBB2 / HER2	Breast carcinoma
Gene rearrangement	EML4::ALK	Lung adenocarcinoma

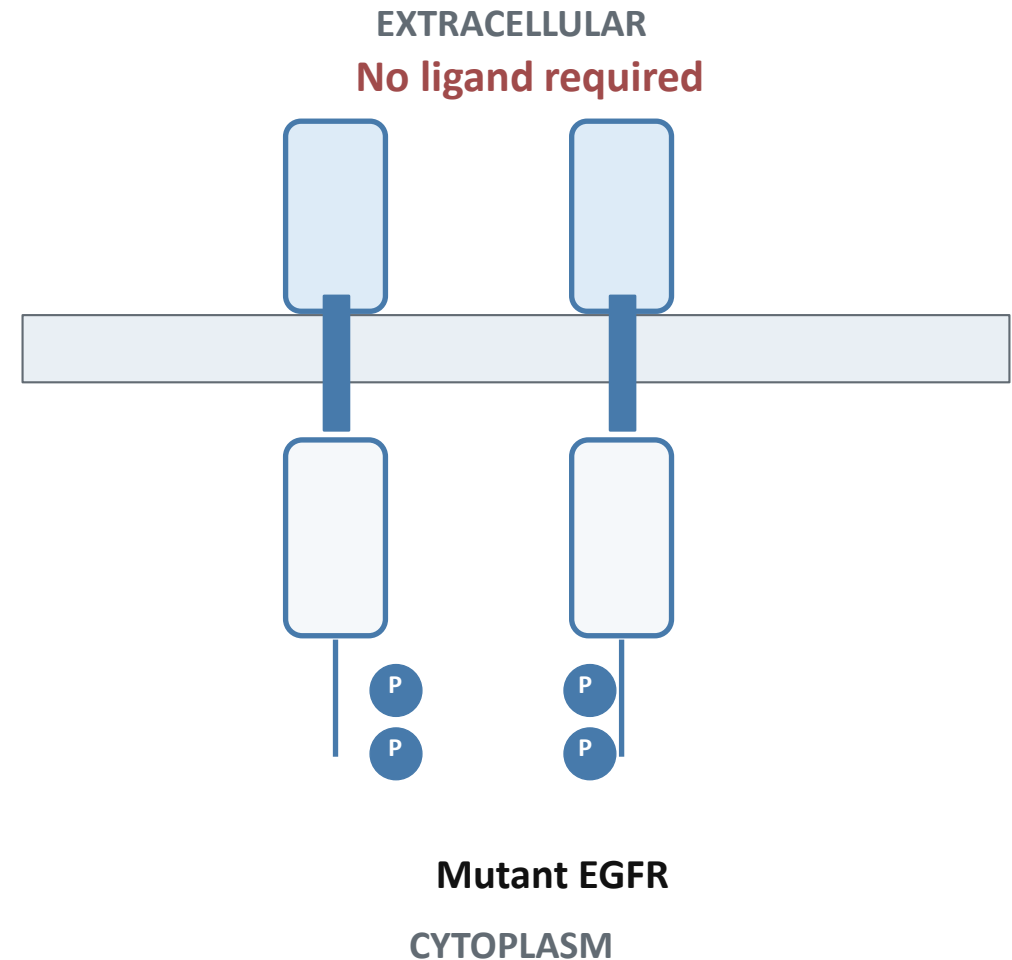
EGFR is encoded by ERBB1

- ERBB1 is the proto-oncogene name; EGFR is its receptor product.
- EGFR belongs to the receptor tyrosine kinase family.
- Oncogenic EGFR activity derives from activating ERBB1 mutations in the highlighted lung subset.



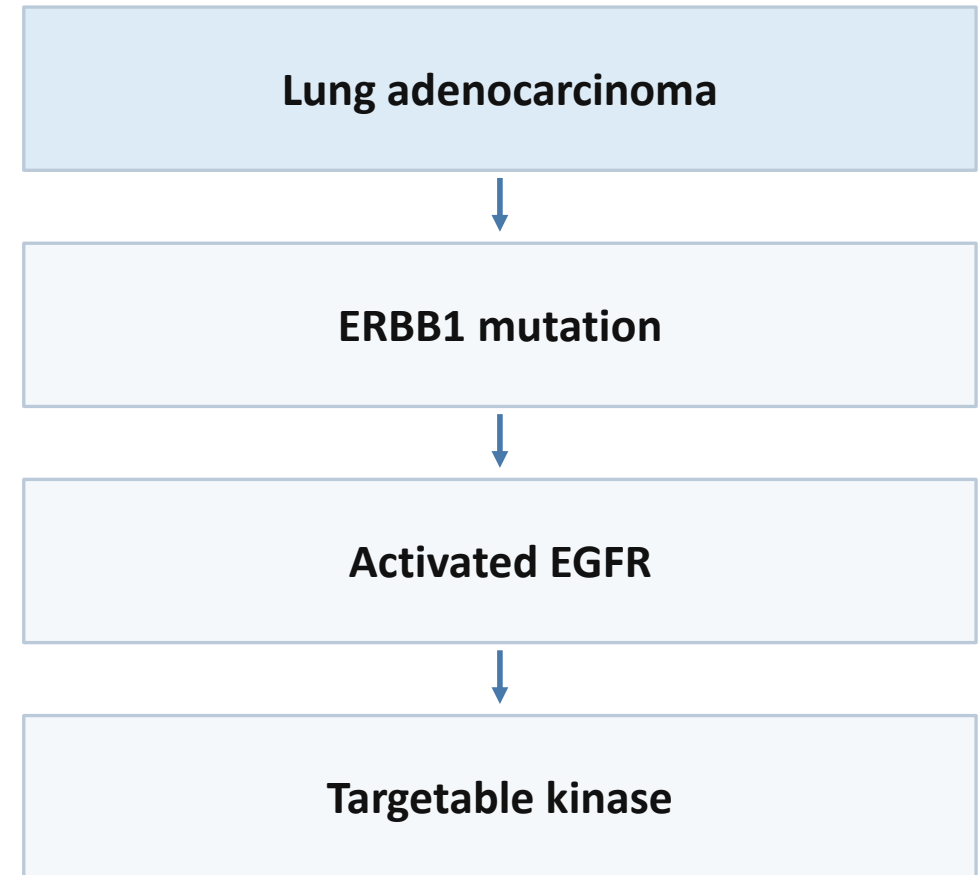
Mutant EGFR bypasses ligand dependence

- Several different ERBB1 point mutations can activate the EGFR kinase.
- These lesions are associated with persistent downstream growth signals.
- No single universal EGFR mutation is specified in the source passage.



EGFR-mutant lung adenocarcinoma is a molecular subset

- Only a subset of lung adenocarcinomas harbor the highlighted ERBB1 mutations.
- This is a molecular mechanism, not a distinct histologic morphology established by the source excerpt.
- Genotype helps explain why selected tumors respond to EGFR-directed inhibition.



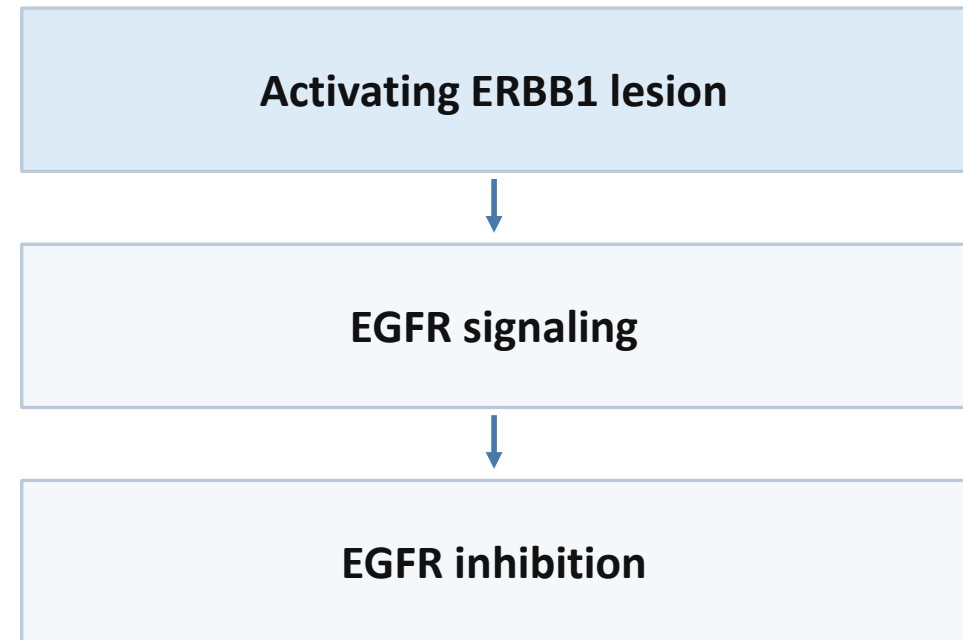
A receptor mutation is not the same as excess ligand

Autocrine growth factor production increases availability of an extracellular stimulus.

Autocrine ligand loop	Mutant receptor
Cell provides its own ligand	Receptor kinase is activated genetically
Ligand–receptor interaction remains relevant	Ligand may no longer be required
Example: PDGF / PDGFR in gliomas	Example: mutant EGFR in lung cancer

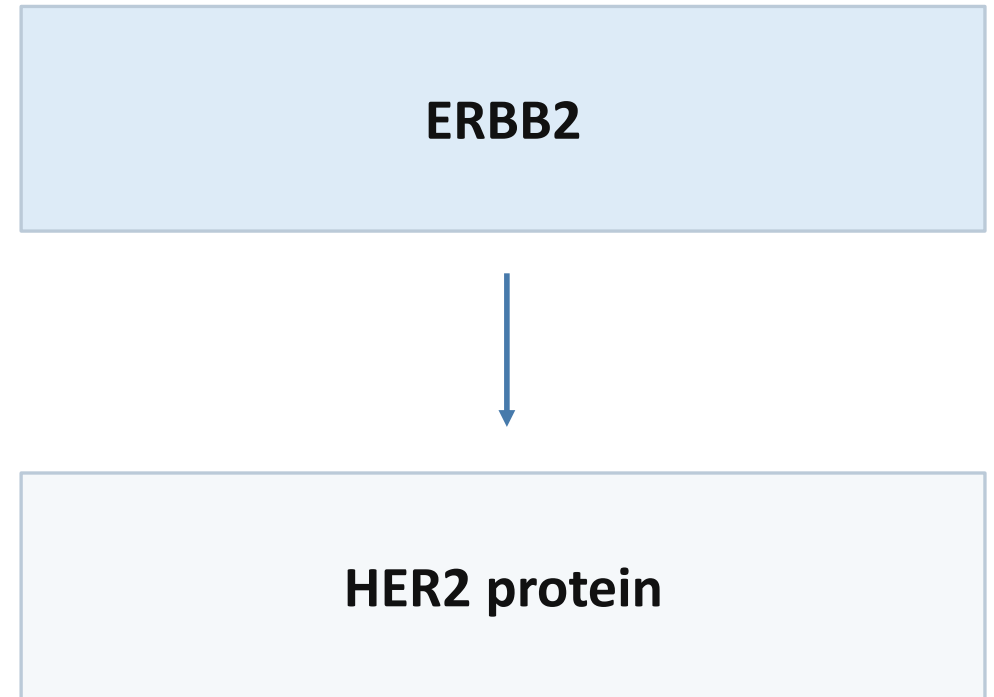
The EGFR target is the altered kinase

- EGFR-directed inhibitors suppress kinase signaling in susceptible EGFR-mutant lung adenocarcinomas.
- Responses establish that the mutant pathway can be functionally important to tumor survival.
- The therapeutic principle is pathway dependency, not guaranteed cure.



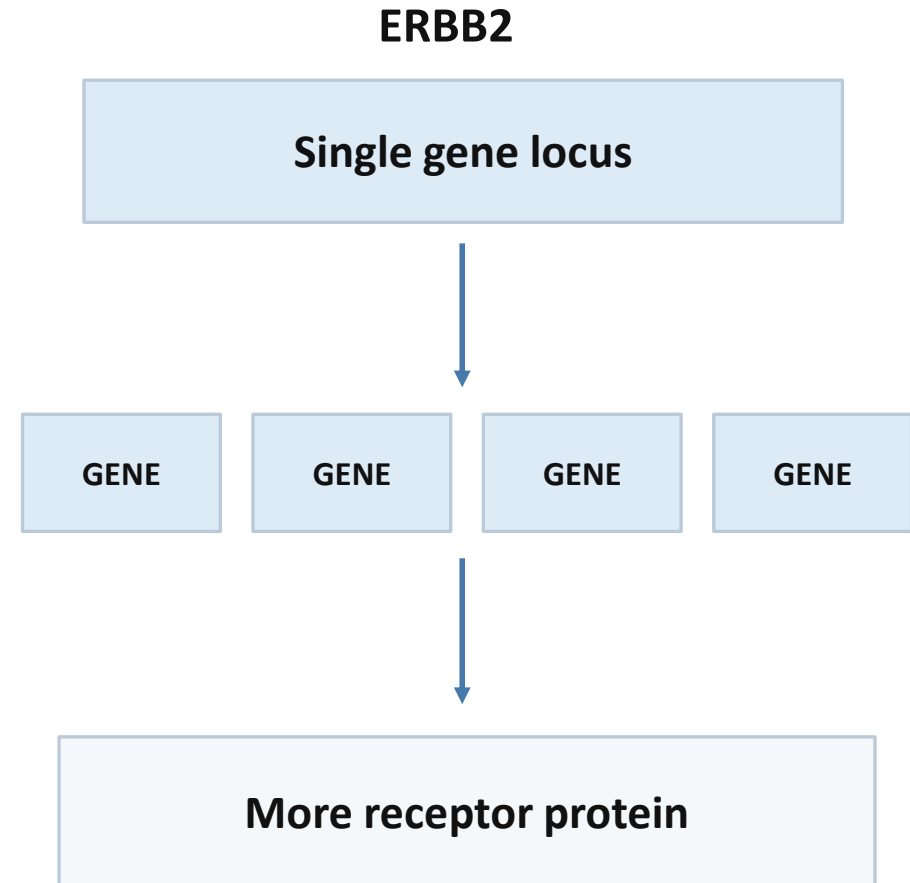
HER2 is encoded by ERBB2

- ERBB2 is a distinct receptor tyrosine kinase gene within the ERBB family.
- Its protein product is HER2.
- ERBB2 amplification rather than point mutation in selected breast carcinomas.



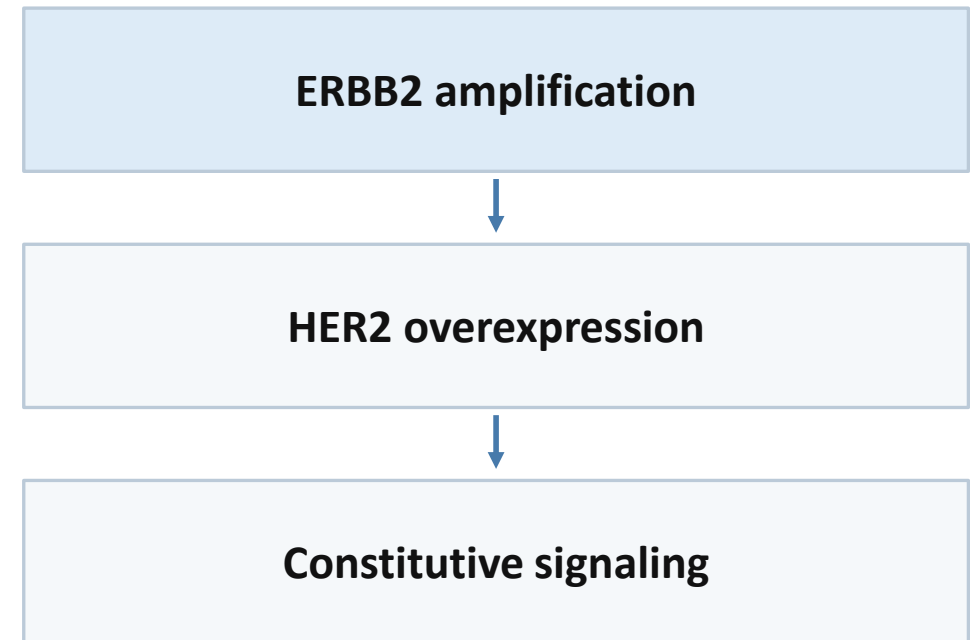
ERBB2 amplification changes gene dosage

- More copies of ERBB2 can produce more HER2 receptor protein.
- The source connects receptor overexpression to persistent kinase activity.
- Gene dosage and receptor activation are mechanistically linked in this example.



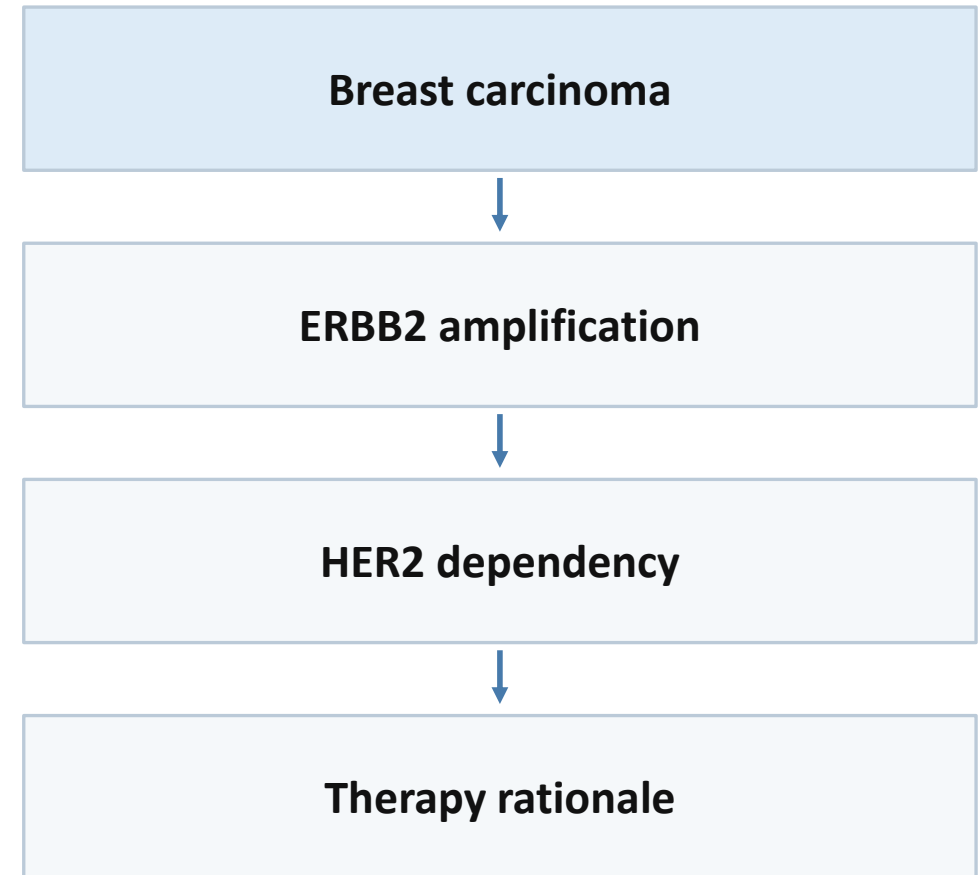
HER2 overexpression is biologically consequential

- Excess HER2 is associated with constitutive tyrosine kinase signaling.
- Such signaling supports cell proliferation and survival.
- The same pathway is a rationale for HER2-directed agents.



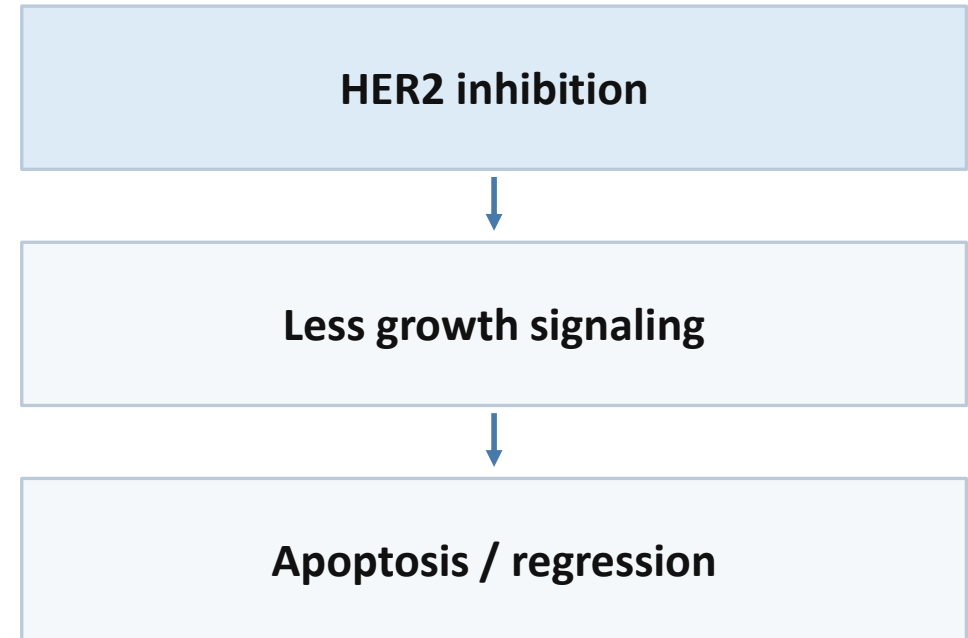
ERBB2 amplification occurs in certain breast cancers

- The textbook does not state that all breast carcinomas amplify ERBB2.
- This lesion defines a biologically significant subgroup.
- An amplified oncogenic driver can create vulnerability to HER2 inhibition.



HER2 inhibition can induce tumor regression

- Antibodies and other HER2-inhibiting agents can produce clinical responses.
- Growth arrest alone does not explain the observed activity.
- Apoptosis after blockade illustrates the survival contribution of RTK signaling.



EGFR and HER2 illustrate different oncogenic routes

Feature	EGFR example	HER2 example
Gene	ERBB1	ERBB2
Dominant lesion described	Activating point mutation	Amplification
Illustrative tumor	Lung adenocarcinoma	Breast carcinoma
Targeted therapy concept	EGFR inhibition	HER2 inhibition

ALK is another receptor tyrosine kinase oncogene

- ALK is a receptor tyrosine kinase gene.
- Rearrangements as a common ALK oncogenic mechanism.
- In a different tumor context, activating ALK point mutations also occur.

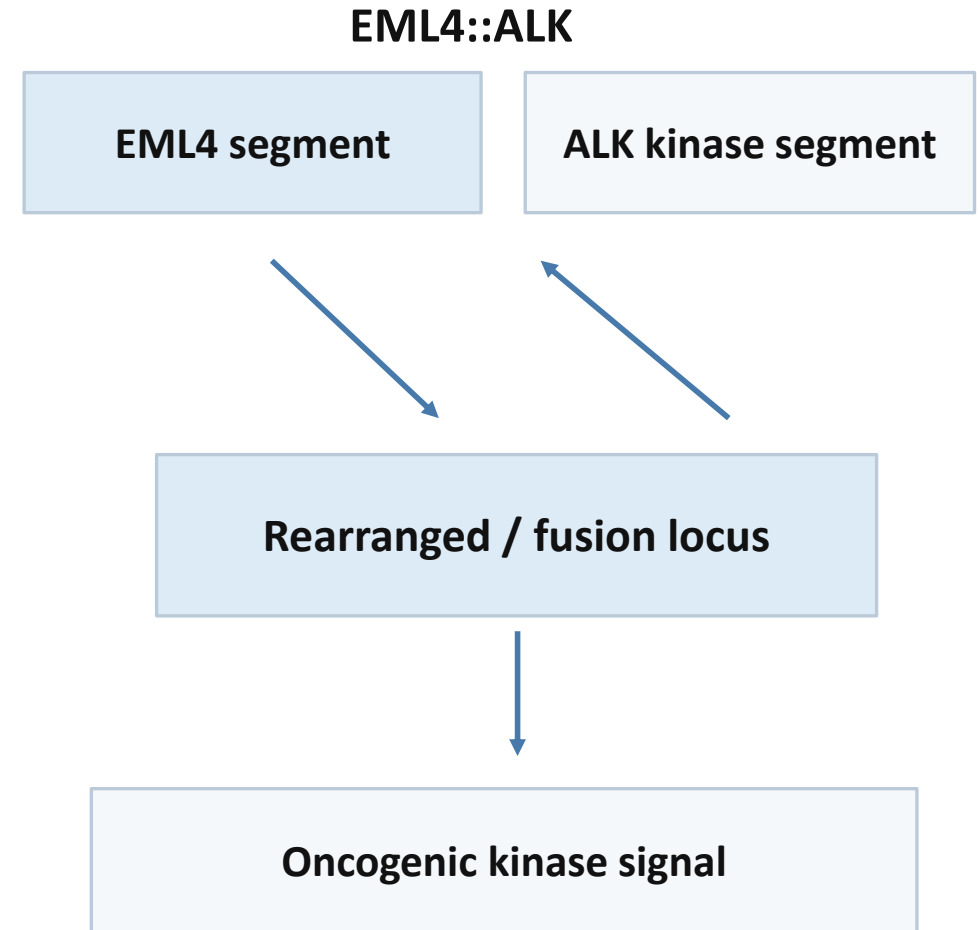
ALK rearrangement



ALK point mutation

EML4::ALK arises from a chromosome 5 rearrangement

- A deletion on chromosome 5 joining segments of EML4 and ALK.
- The fusion gene produces an EML4–ALK chimeric protein.
- The resulting protein has constitutive tyrosine kinase activity.



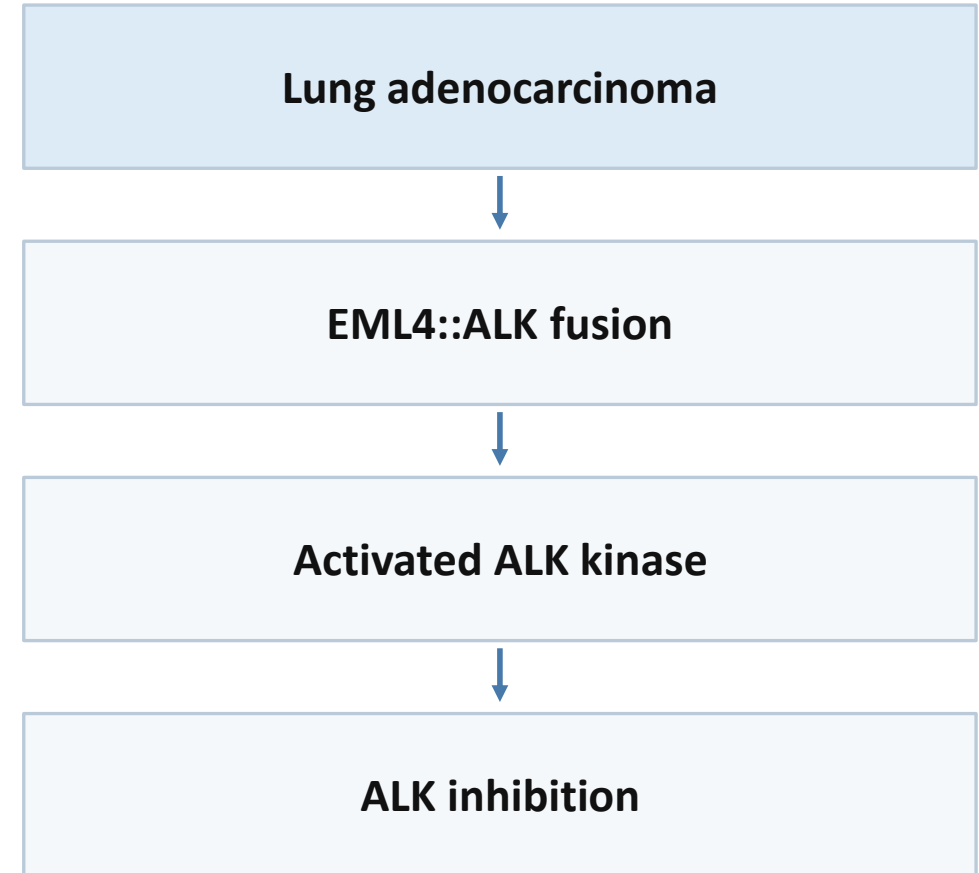
A fusion kinase differs from a full-length RTK

The genomic fusion modifies the native gene context.

Native ALK receptor	EML4–ALK fusion product
Encoded by the ALK gene	Encoded by a rearranged fusion gene
Growth-factor receptor context	Chimeric kinase context
Normally controlled signaling	Constitutive kinase activity

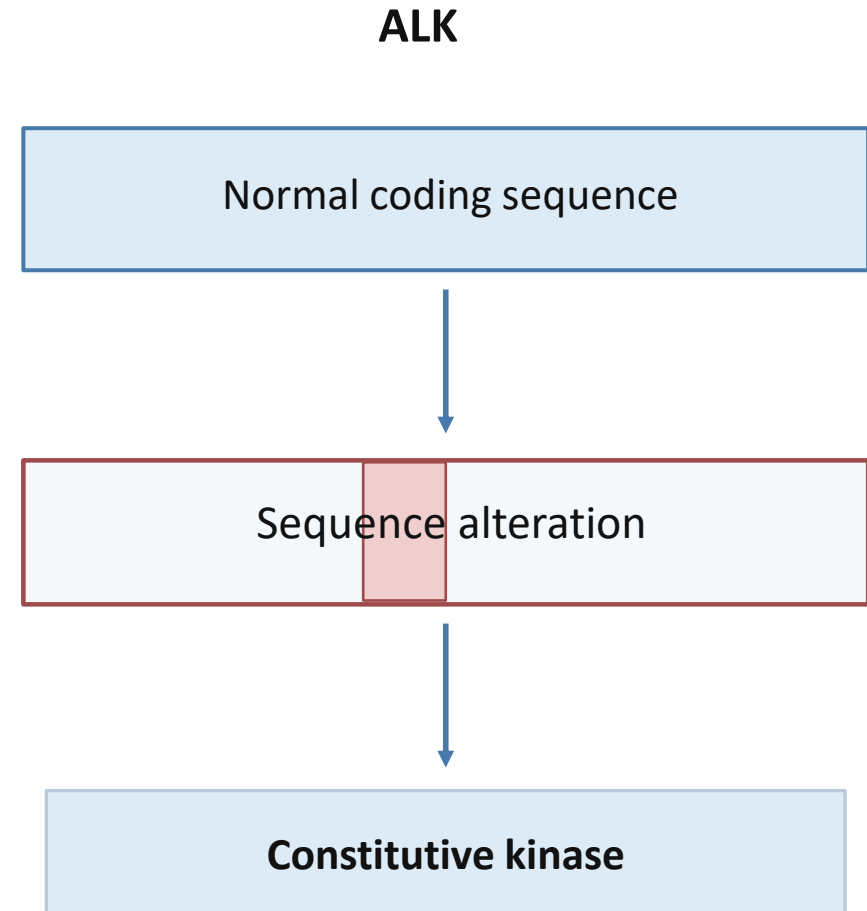
EML4::ALK identifies a lung cancer subgroup

- An ALK fusion occurs in a subset of lung adenocarcinomas.
- The fusion is a molecular driver with constitutive kinase activity.
- ALK inhibitors can yield responses in tumors harboring the relevant fusion.



ALK point mutations are relevant to neuroblastoma

- Activating ALK point mutations also act as oncogenic events.
- A subset of neuroblastomas.
- Thus, the same kinase gene can be activated through distinct alterations in different tumors.



The oncogenic lesion can depend on cellular context

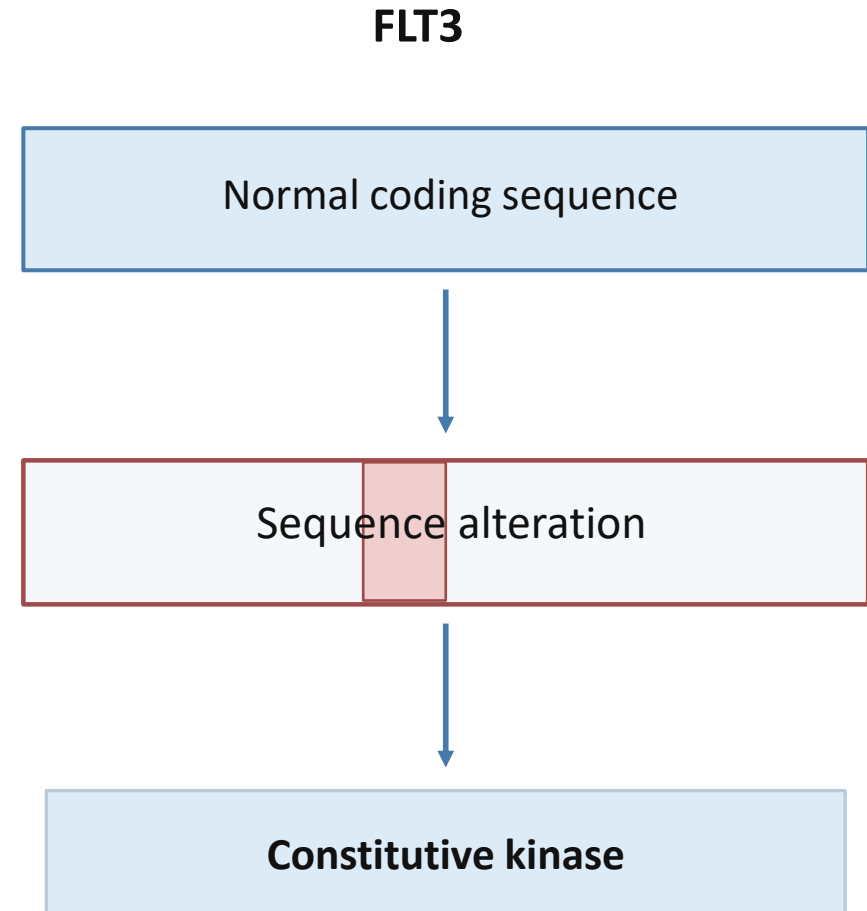
ALK alteration	Example tumor	Molecular consequence
Rearrangement / fusion	Lung adenocarcinoma	Constitutive fusion kinase
Rearrangement / translocation	Certain lymphomas	Constitutive ALK signaling
Activating point mutation	Neuroblastoma	Activated ALK kinase

Other receptor genes broaden the oncogene spectrum

Receptor gene	Activation reported in Table 7.5	Example tumor
FLT3	Point mutation or small duplications	Leukemia
RET	Point mutation	MEN 2A / MEN 2B; familial medullary thyroid carcinoma
PDGFRB	Amplification or translocation	Gliomas; leukemias
KIT	Point mutation	Gastrointestinal stromal tumors

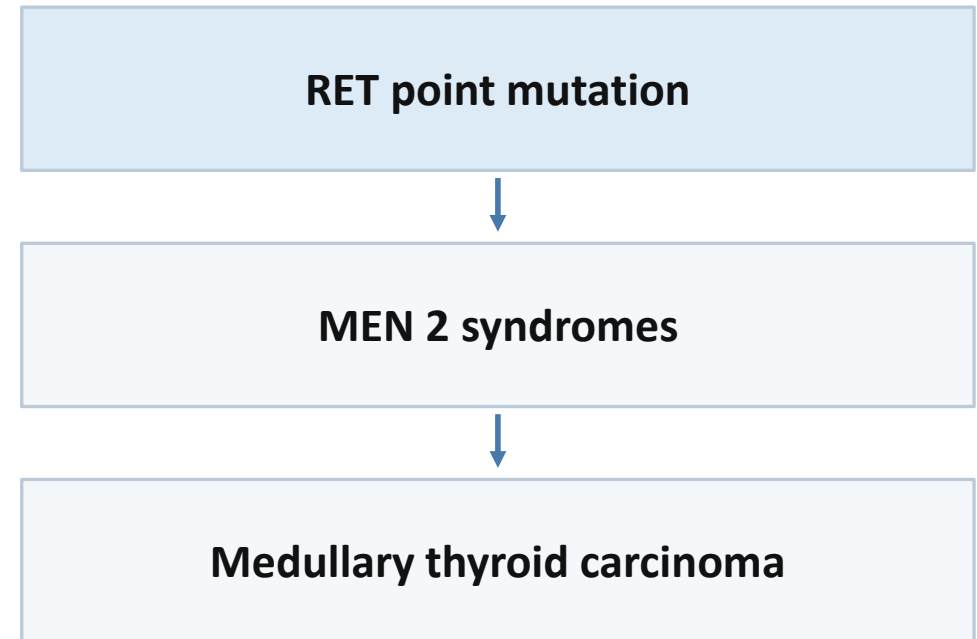
FLT3: Small sequence alterations can activate a kinase

- FLT3 encodes a receptor tyrosine kinase.
- Oncogenic alterations include point mutation or small duplications.
- Table 7.5 associates these lesions with leukemia.



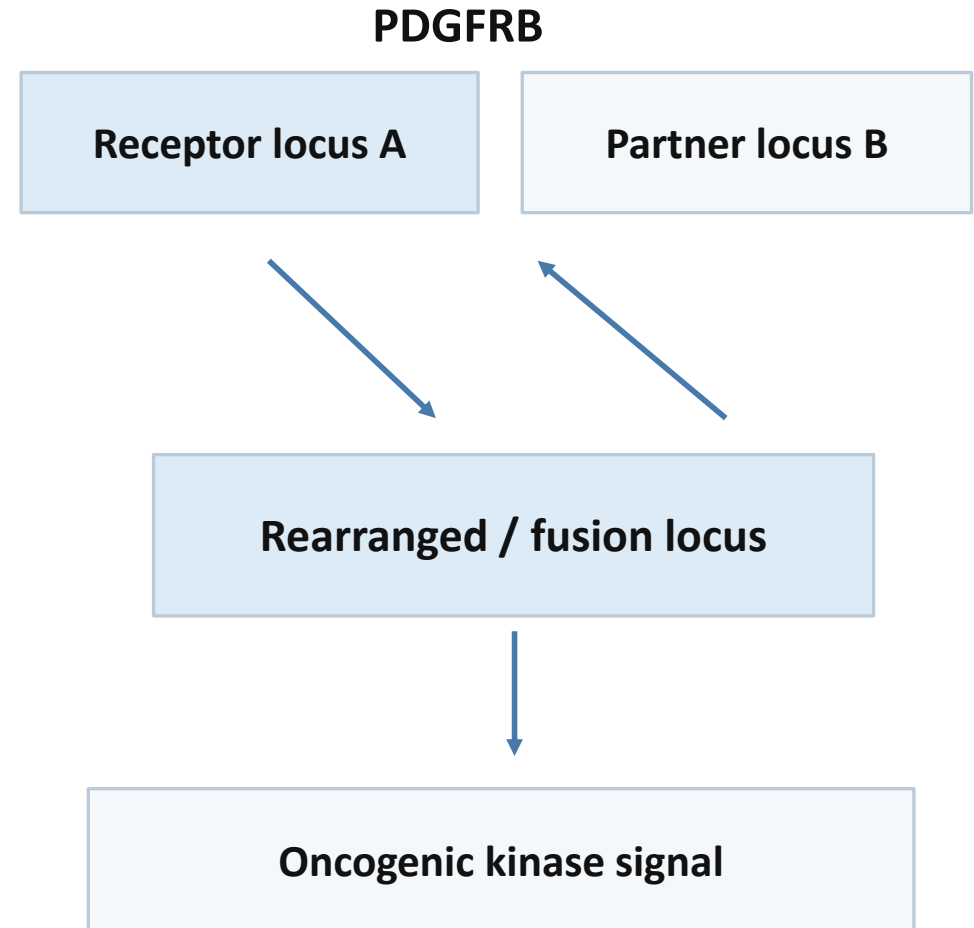
RET: Point mutations in hereditary endocrine tumors

- RET encodes a neurotrophic factor receptor tyrosine kinase.
- RET point mutations with MEN 2A, MEN 2B, and familial medullary thyroid carcinoma.
- This is an example of a receptor oncogene implicated in inherited cancer syndromes.



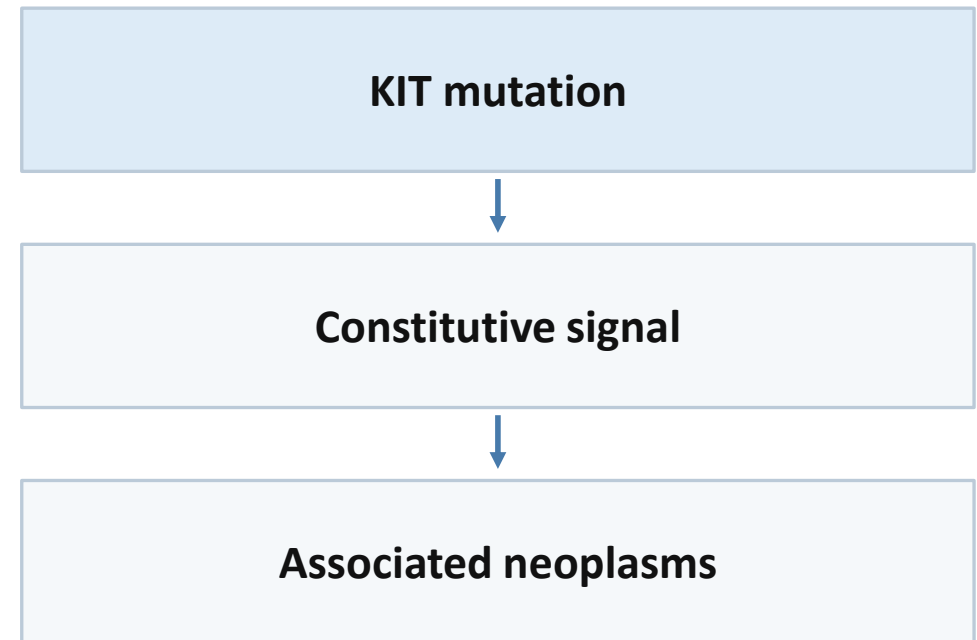
PDGFRB: Amplification and translocation

- PDGFRB encodes a platelet-derived growth factor receptor.
- Its oncogenic modes in the source table include amplification and translocation.
- The associated disease examples are gliomas and leukemias.



KIT: Activating receptor point mutations

- KIT encodes the receptor for KIT ligand.
- Point mutation is the activation mechanism shown in the source table.
- Gastrointestinal stromal tumors, seminomas, and leukemias are listed associations.

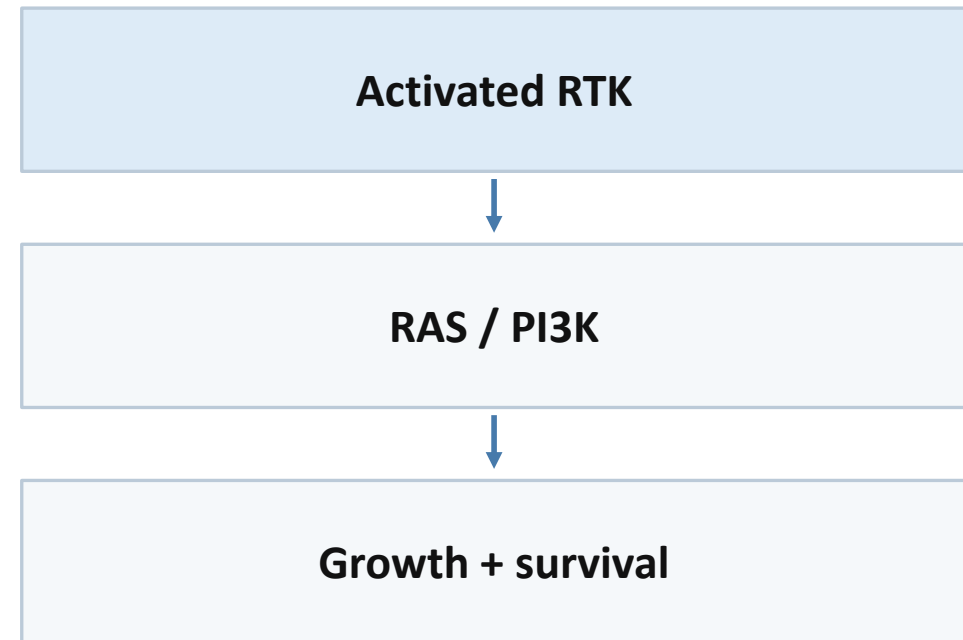


An alteration–tumor matrix prevents overgeneralization

Gene	Mutation	Amplification	Rearrangement
ERBB1	Yes (lung)	Not listed	Not listed
ERBB2	Not highlighted	Yes (breast)	Not listed
ALK	Yes (neuroblastoma)	Not listed	Yes (lung; lymphoma)
PDGFRB	Not listed	Yes	Yes
KIT	Yes	Not listed	Not listed

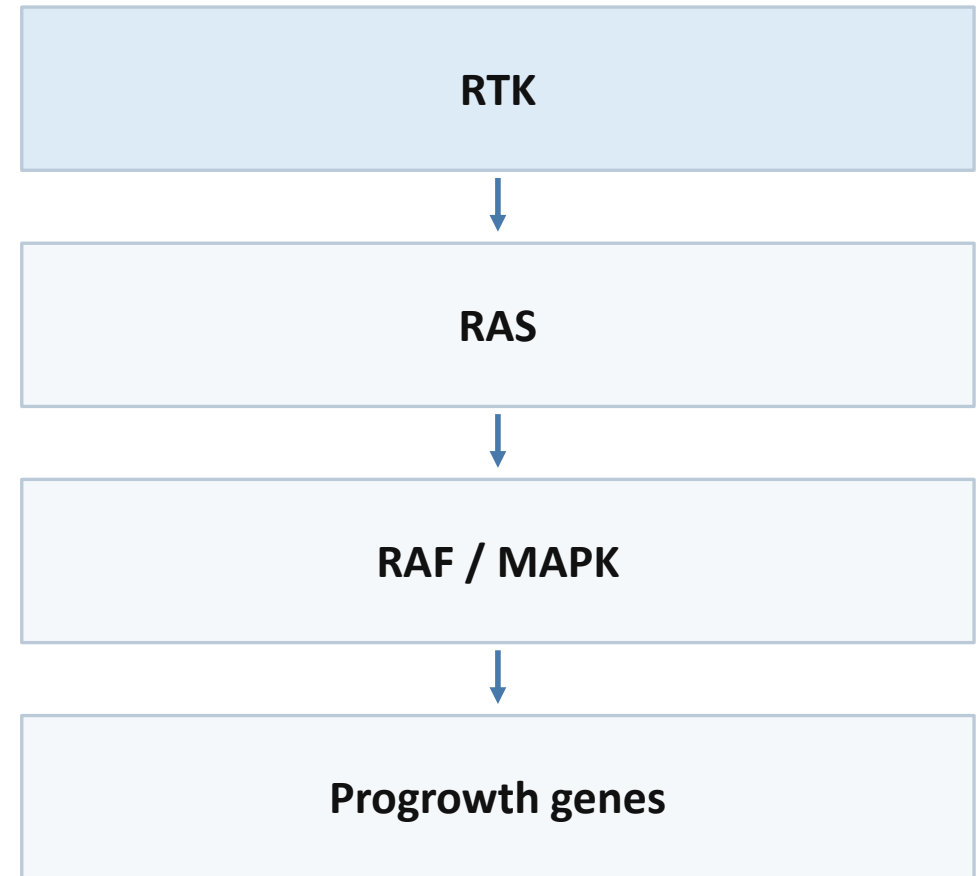
Activated RTKs converge on cytoplasmic effectors

- Autophosphorylated receptors recruit proteins connected to RAS and PI3K signaling.
- Different RTK oncogenes can converge on shared downstream growth programs.
- The cellular consequence depends on receptor context and its downstream signaling.



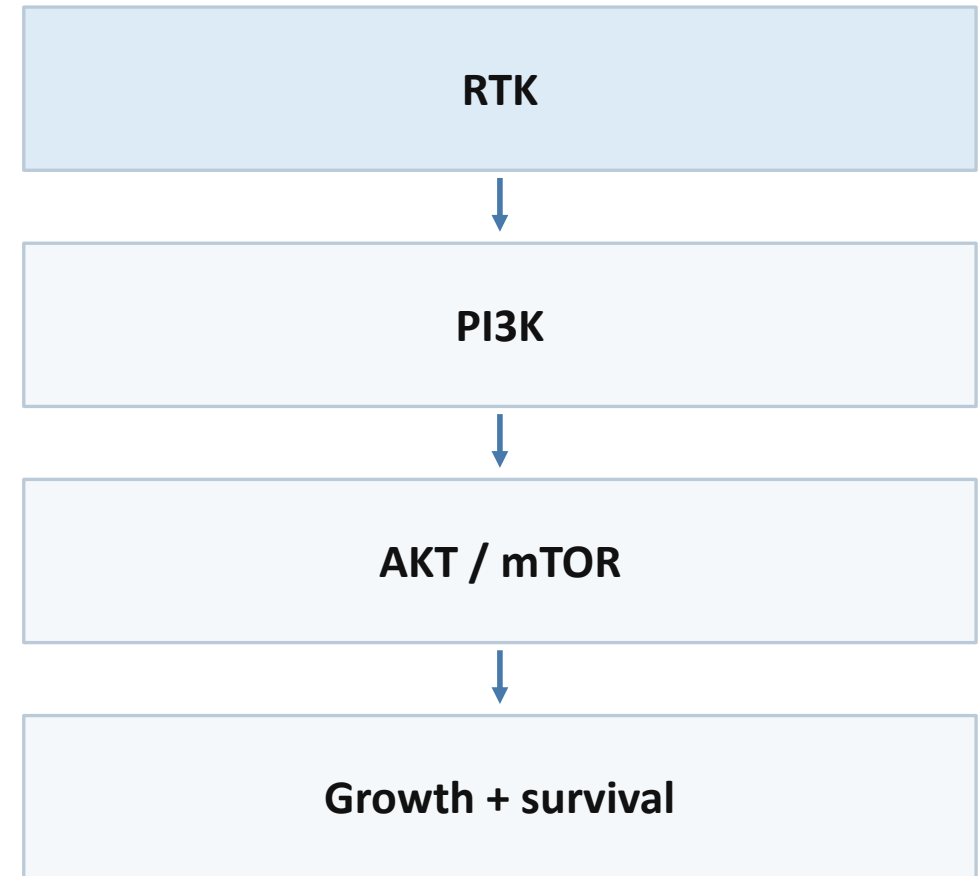
RAS links receptors to mitogenic signaling

- The adjacent Robbins section places RAS immediately downstream of activated RTKs.
- RAS conveys signals toward the RAF–MAPK arm.
- This pathway is one route to transcription of progrowth genes.



PI3K links receptor signals to growth and survival

- PI3K is recruited in RTK signaling and feeds into AKT-associated pathways.
- This arm supports growth-related biosynthesis and cell survival.
- Its outputs help explain the consequences of RTK blockade.



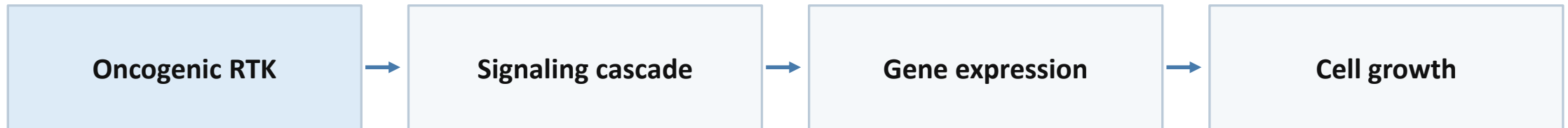
Two major downstream arms have distinct emphases

RTK signaling can stimulate RAS–MAPK and PI3K–AKT signaling.

RAS → RAF → MAPK	PI3K → AKT / mTOR
Progrowth transcriptional signaling	Growth-related metabolism and synthesis
Cell-cycle progression	Cell survival and growth
Both can respond to activated RTKs	Both can respond to activated RTKs

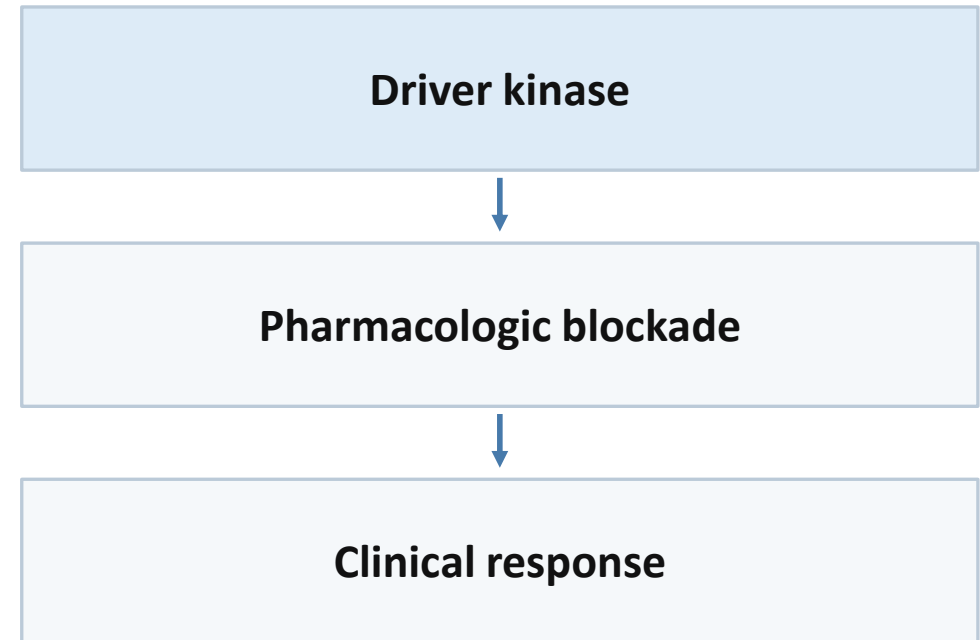
Receptor oncogenes sit upstream of transcriptional change

- Constitutive kinase activity initiates repeated cytoplasmic signaling.
- Signal cascades alter transcriptional programs.
- Proliferation and survival follow from the combined cell-state changes.



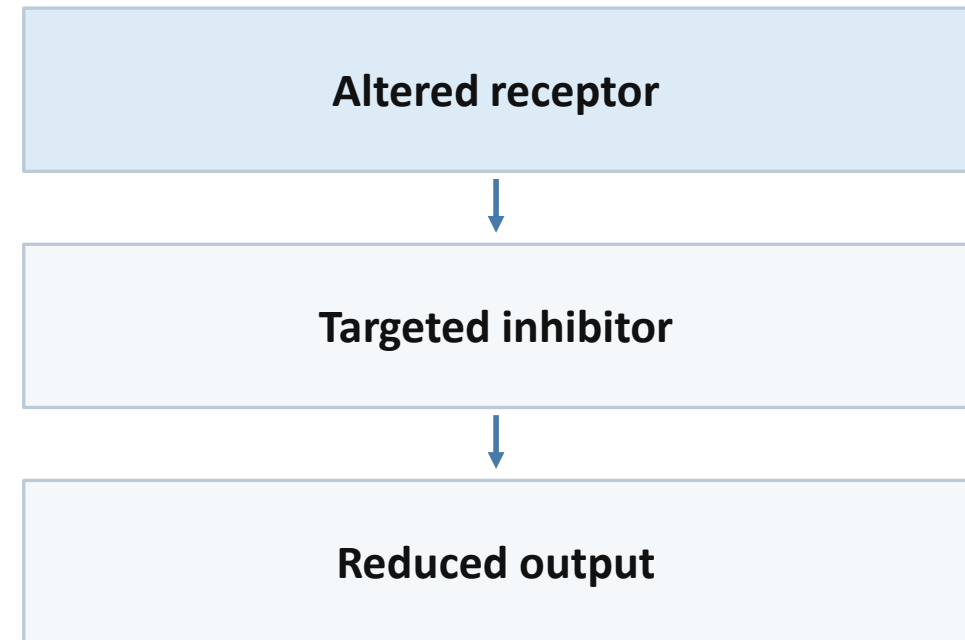
Targeted therapy tests driver dependency

- If a cancer depends on a constitutively active kinase, inhibiting it may suppress tumor growth.
- Responses to EGFR, HER2, and ALK inhibitors support the causal importance of those receptors.
- Drug response is functional evidence; It does not imply permanent tumor eradication.



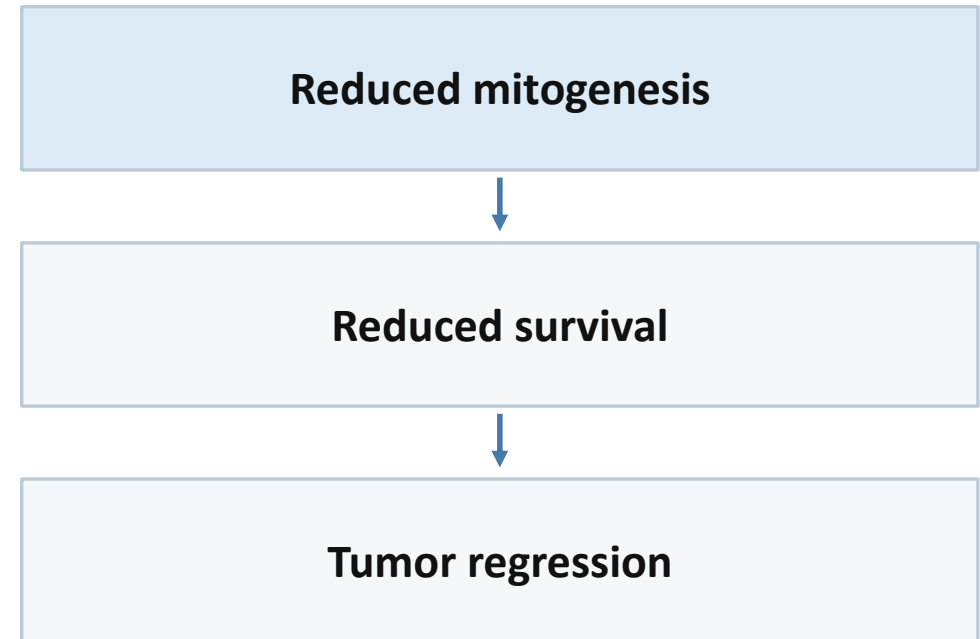
The therapeutic intervention can act at the receptor

- HER2-targeting antibodies and drugs interfere with HER2 activity.
- EGFR inhibitors target activated EGFR signaling in appropriately altered lung cancers.
- ALK inhibitors suppress ALK signaling in tumors with the relevant fusion.



Blocking a driver RTK may induce apoptosis

- Receptor signaling normally supports survival as well as division.
- Suppression of an essential oncogenic RTK can remove survival signals.
- Tumor regression can therefore follow cell death, not merely slower proliferation.



Therapeutic response is not equivalent to cure

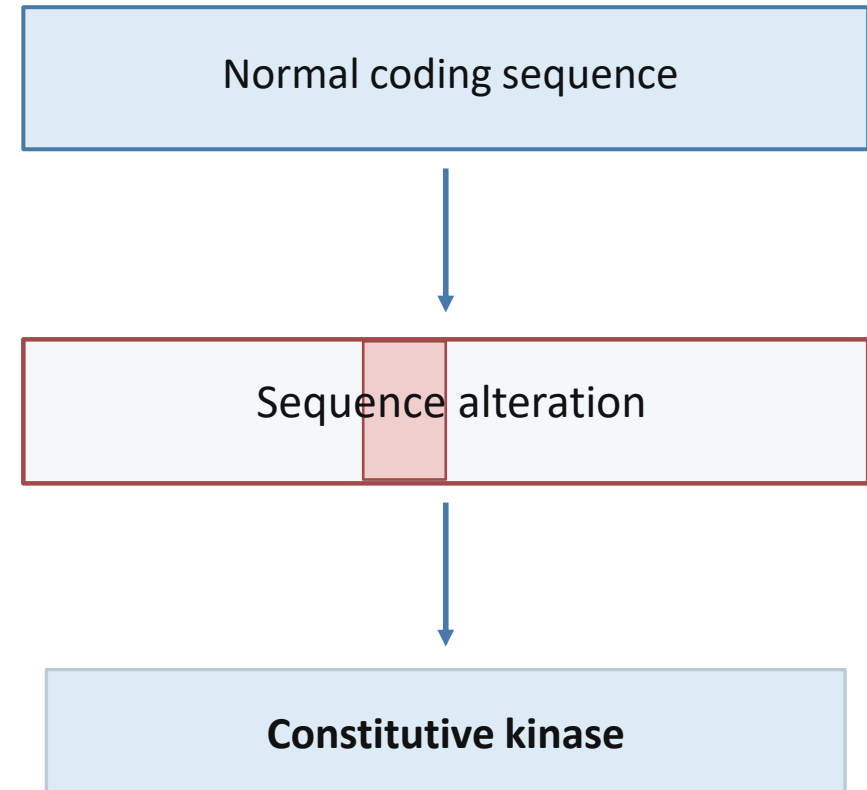
Inhibitors can elicit major responses in selected receptor-driven tumors.

Initial dependency	Escape under treatment
Dominant clone relies on RTK	Surviving subclone bypasses inhibition
Kinase inhibitor blocks key signal	Acquired alterations restore growth
Tumor shrinks	Resistant disease may emerge

An EGFR alteration can obstruct drug binding

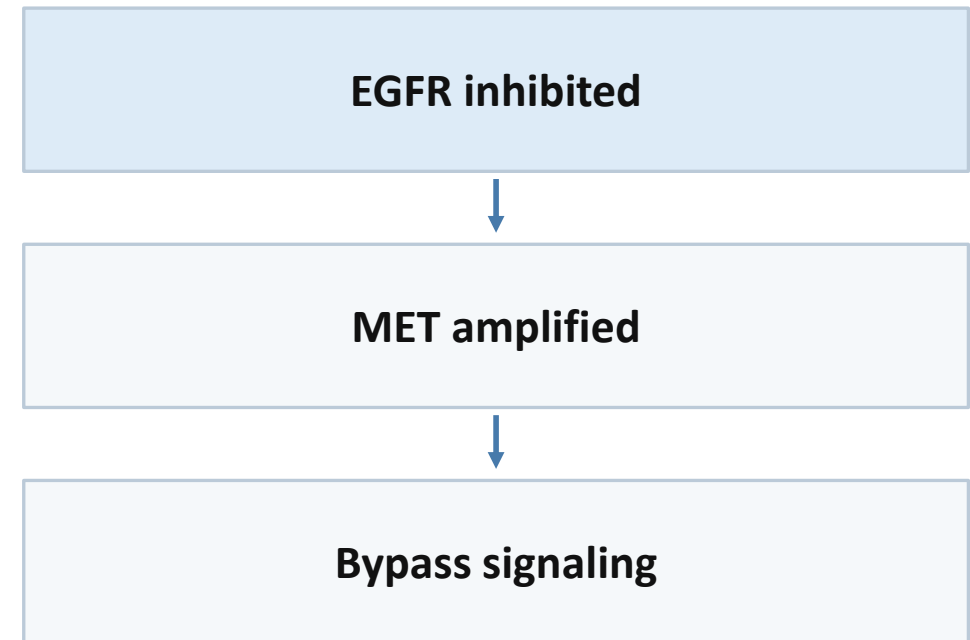
- Lung cancers may acquire further EGFR mutations during EGFR inhibitor treatment.
- Some such alterations prevent the inhibitor from binding effectively.
- An active pathway can persist despite drug exposure.

EGFR resistance



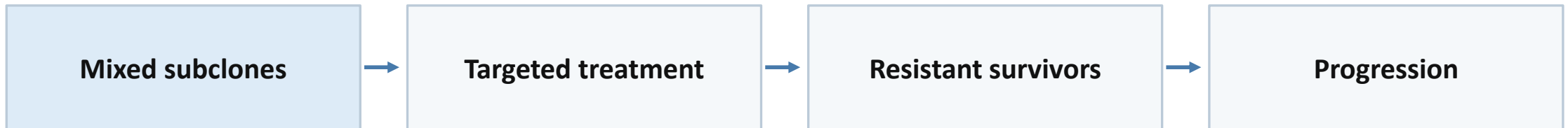
MET amplification provides an alternative signaling route

- MET encodes another receptor tyrosine kinase.
- Amplification of MET is a resistance mechanism described for EGFR-inhibited lung cancers.
- An alternative driver can bypass the inhibited EGFR pathway.



Tumor heterogeneity makes resistance plausible

- Tumors may contain genetically distinct subclones.
- Treatment suppresses susceptible cells but favors survival of resistant populations.
- The surviving population can repopulate the tumor.



Two resistance routes are mechanistically distinct

Mechanism	Molecular example	Why the inhibitor fails
On-target alteration	Further EGFR mutation	Drug cannot bind the altered target
Bypass activation	MET gene amplification	Alternative RTK supports signaling
General principle	Subclonal diversity	Drug selects a non-susceptible cell population

Genetic mechanism is not identical to receptor abundance

ERBB2 amplification predicts increased gene dosage and receptor overexpression in the source example.

Mutation	Amplification / fusion
Changes protein function	Changes dosage or gene architecture
EGFR and KIT examples	HER2 dosage; ALK fusion examples
Requires genotype-aware interpretation	Requires mechanism-aware interpretation

Clinicopathologic interpretation must remain specific

Tumor context	Molecular finding	Supported inference
Lung adenocarcinoma	Activating ERBB1 mutation	EGFR-driven signaling may be targetable
Breast carcinoma	ERBB2 amplification	HER2 overexpression may confer therapeutic vulnerability
Lung adenocarcinoma	EML4::ALK fusion	Constitutive ALK kinase is a therapeutic target

Case: An EGFR-driven lung adenocarcinoma

Hypothetical teaching case

- Hypothetical lung adenocarcinoma carries an activating ERBB1 mutation.
- Predict persistent kinase signaling even without an external EGFR ligand.
- EGFR inhibition may suppress both proliferation and survival; Resistance can later emerge.

What makes the receptor oncogenic?

Constitutive tyrosine kinase activation caused by an ERBB1 mutation.

Case: A HER2-amplified breast carcinoma

Hypothetical teaching case

- Hypothetical breast carcinoma demonstrates ERBB2 amplification.
- Gene amplification increases HER2 abundance and oncogenic signaling.
- HER2-directed inhibition is mechanistically appropriate for the illustrated lesion.

Which genetic route is present?

Copy-number amplification, rather than the ERBB1 point-mutation example.

Case: An ALK fusion in lung adenocarcinoma

Hypothetical teaching case

- Hypothetical lung adenocarcinoma harbors EML4::ALK.
- The rearrangement produces a chimeric protein with constitutive ALK kinase activity.
- This is mechanistically different from ordinary ligand-driven receptor dimerization.

What is the oncogenic protein?

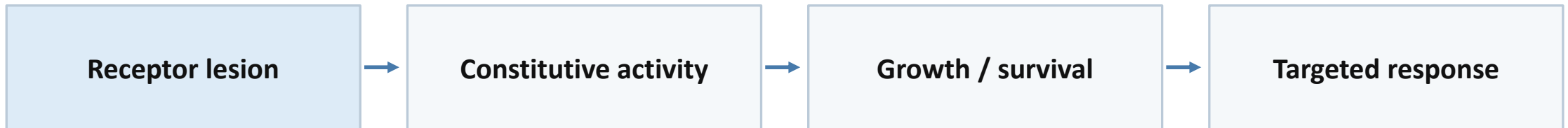
A constitutively active EML4–ALK fusion kinase.

Classify the receptor oncogene mechanism

Alteration	Molecular event	Most direct result
ERBB1 activating mutation	Point mutation	Ligand-independent EGFR kinase
ERBB2 amplification	Increased copy number	HER2 overexpression / activity
EML4::ALK fusion	Gene rearrangement	Constitutive chimeric ALK kinase
MET amplification on therapy	Bypass resistance	Reactivated downstream signaling

A mechanistic approach to receptor-driven neoplasia

- Identify the receptor gene and its specific alteration.
- Infer how the lesion changes kinase regulation.
- Link the resulting signal to proliferation, survival, and possible treatment dependence.



Core synthesis: Oncogenic RTKs

- Normal RTKs transmit transient ligand-triggered signals by dimerization and tyrosine phosphorylation.
- Point mutations, amplification, and rearrangements can create persistent receptor-kinase activity.
- EGFR, HER2, and ALK illustrate lesion-specific tumor associations and therapeutic vulnerabilities.
- Resistant subclones can escape via target mutation or alternative kinase activation.

Source and teaching references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 7, Neoplasia, pp. 252–254.
- Growth Factor Receptors: textbook narrative and Table 7.5 (source transcript in supplied project files).
- Limited contextual material: Oncoproteins and Cell Growth; Growth Factors; and the opening of Downstream Components of the RTK Signaling Pathway.
- All pathway figures in this lecture are original editable schematics, not reproduced textbook figures.