

Anaplastic Large-Cell Lymphoma

ALK positive

Morphology · Molecular pathogenesis · Diagnosis

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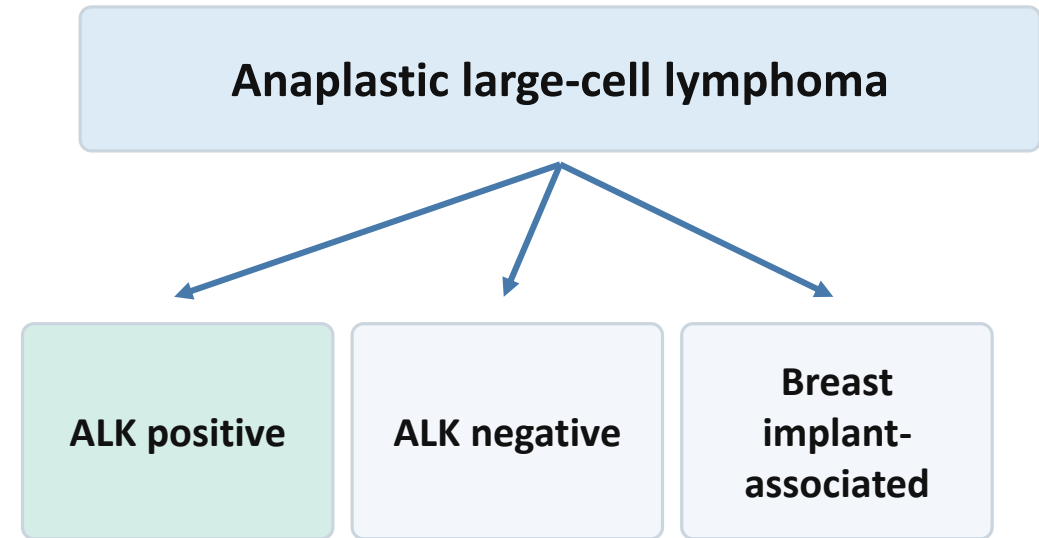
What should a pathologist be able to explain?

- Place ALK-positive ALCL within mature T-cell lymphomas
- Connect ALK fusion signaling with the neoplastic phenotype
- Recognize hallmark cells and the sinusoidal growth pattern
- Apply a lineage-conscious diagnostic approach

Classification: A mature T-cell neoplasm

- WHO-HAEM5 retains ALK-positive ALCL as a distinct entity
- The broader ALCL family contains several clinically distinct disorders
- Morphologic overlap does not establish identical biology

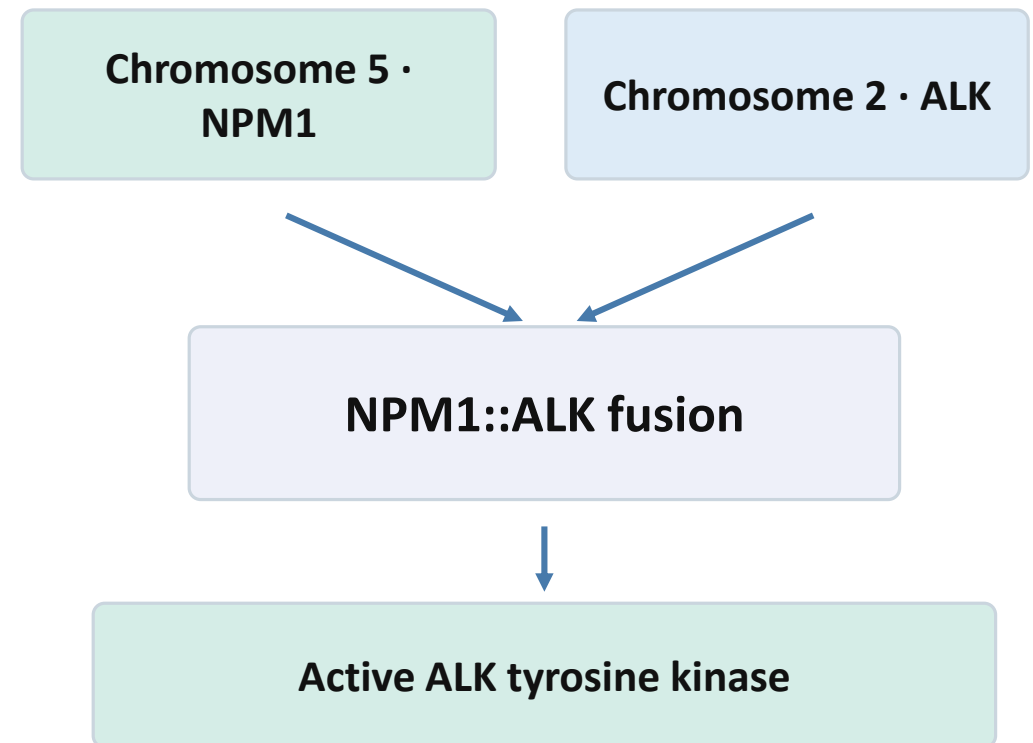
Classification schematic



The defining molecular event

- A rearrangement disrupts ALK at chromosome 2p23
- The fusion gene encodes an abnormal ALK tyrosine kinase
- Constitutive kinase activity is the central oncogenic feature

Schematic



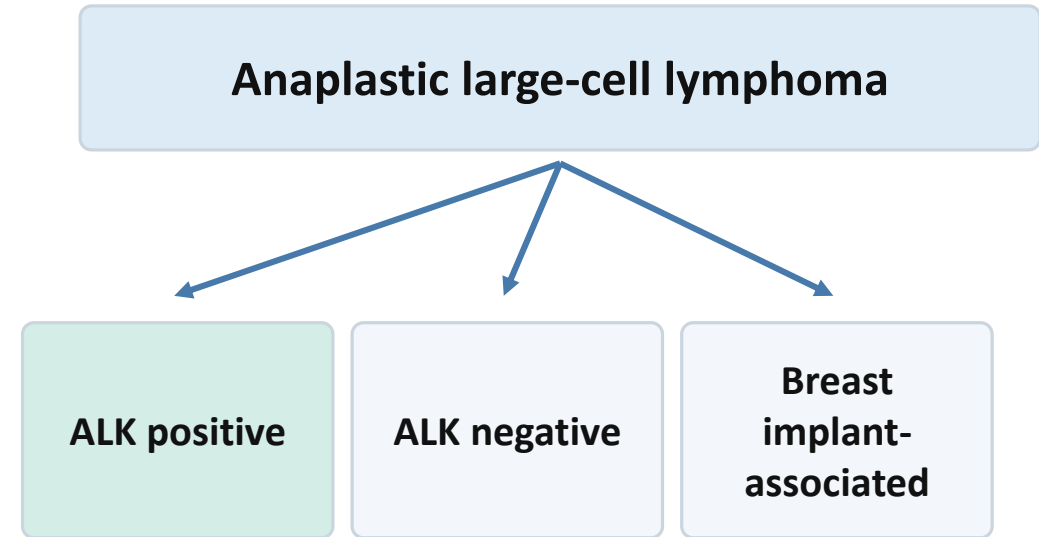
What ALK positivity does—and does not—mean

- ALK positivity is a disease-defining result in the correct context
- ALK expression alone does not establish T-cell lineage
- Morphology and a complementary immunophenotypic panel remain essential

Systemic ALCL is not a single molecular disease

- ALK-positive ALCL: ALK rearranged, often younger patients
- ALK-negative ALCL: Morphologic overlap, distinct genetic landscape
- Breast implant-associated ALCL: Separate clinical entity, generally ALK negative

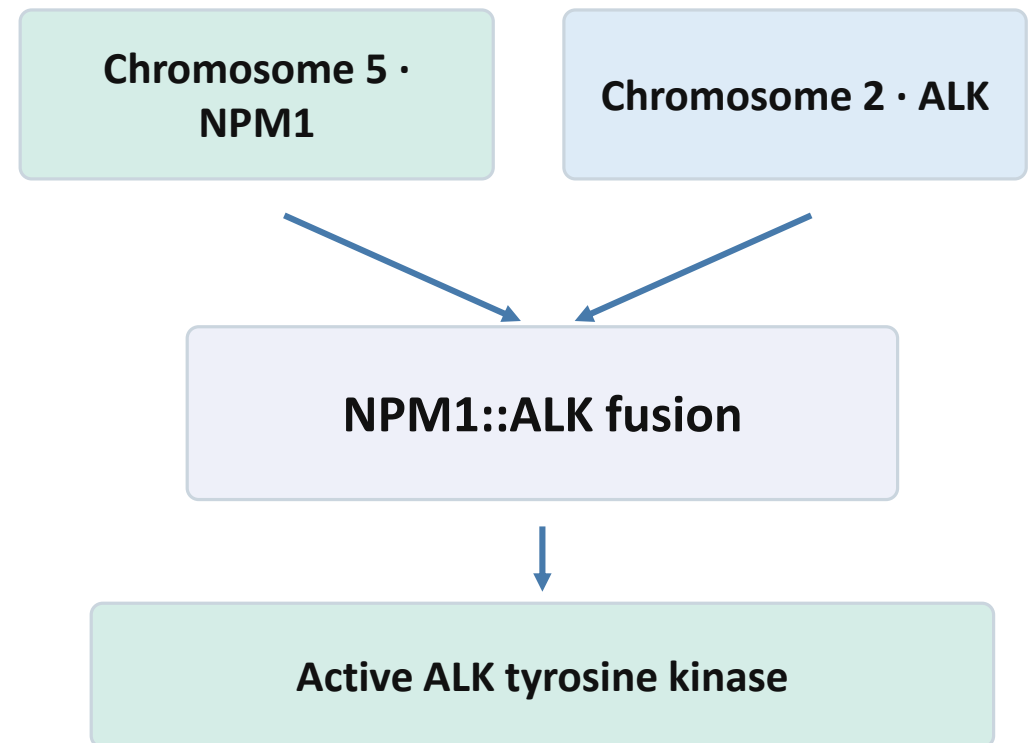
Classification schematic



The usual translocation: T(2;5)

- The recurrent t(2;5)(p23;q35) joins NPM1 and ALK
- NPM1::ALK is a constitutively activated fusion tyrosine kinase
- Other ALK fusion partners also occur

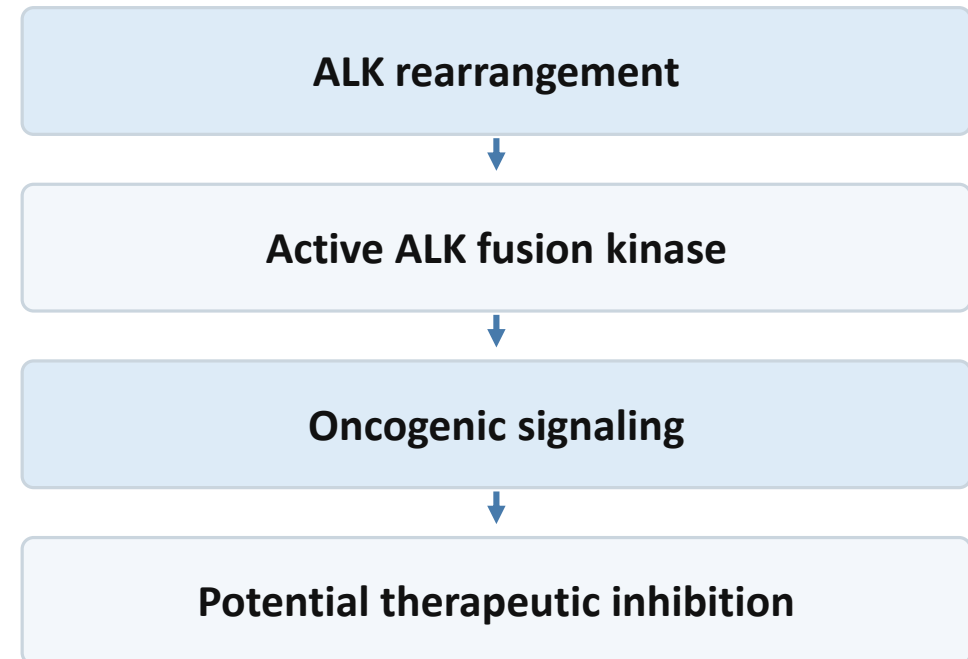
Schematic



How fusion changes normal signaling

- A fusion partner supplies aberrant kinase activation
- The fusion is expressed in a cellular compartment where ALK is normally absent
- Proliferation and survival signaling proceed without ordinary receptor control

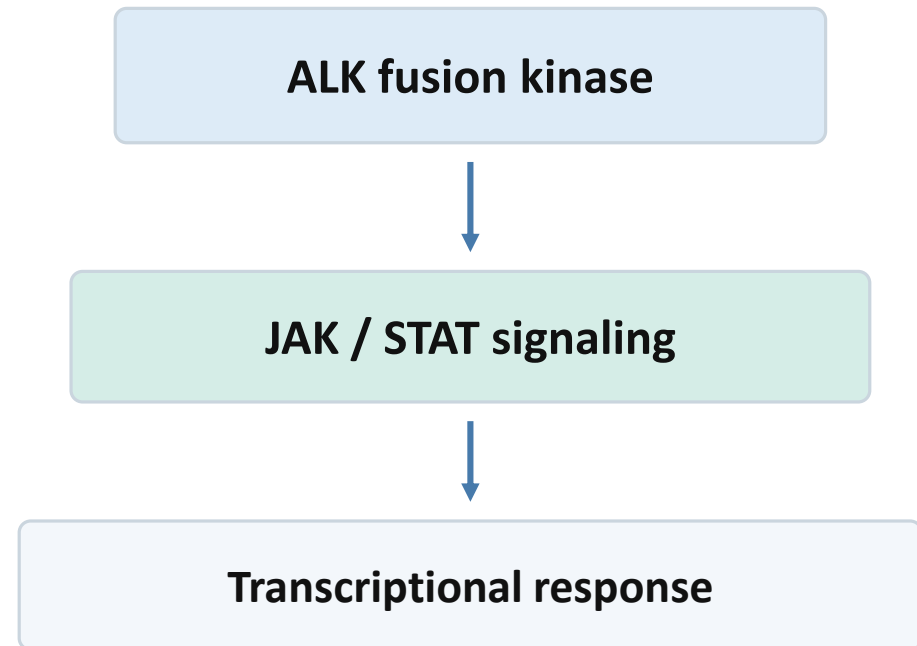
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Oncogenic signaling: JAK/STAT3 axis

- ALK signaling engages the JAK/STAT signaling network
- STAT3-dependent transcription contributes to malignant-cell survival
- The diagram depicts a simplified relationship, not a complete interactome

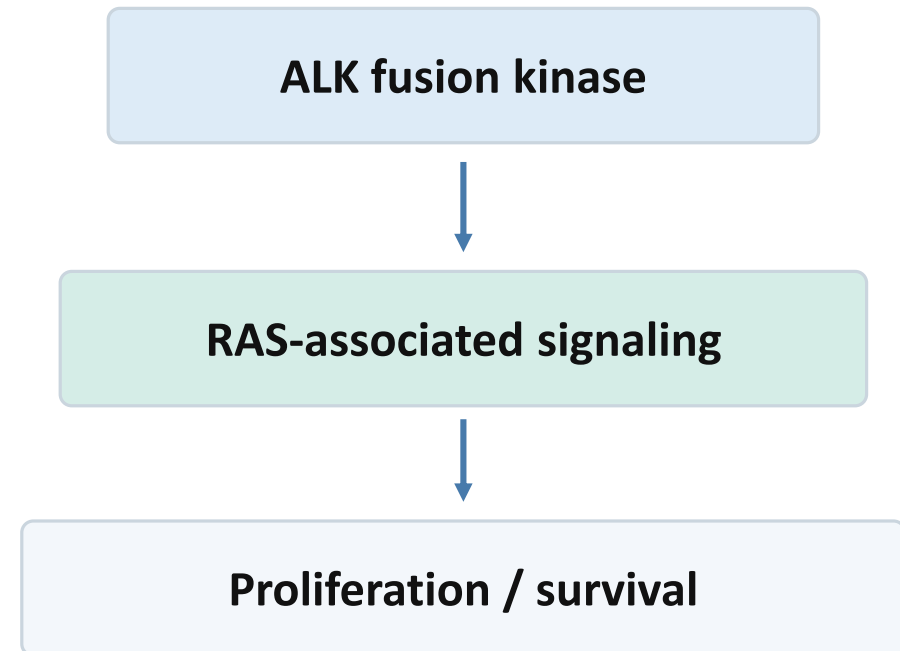
Simplified signaling scheme



Oncogenic signaling: RAS pathway

- Constitutively active ALK can drive RAS-related signaling
- Growth and proliferation become uncoupled from normal regulation
- The textbook places RAS signaling among the principal downstream routes

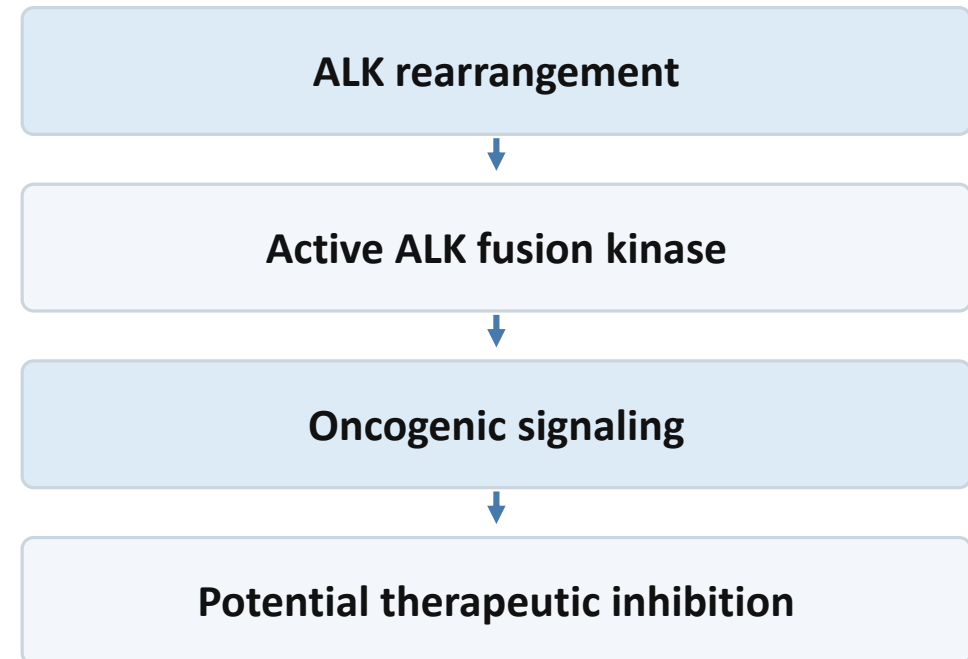
Simplified signaling scheme



The kinase is a diagnostic and therapeutic target

- Fusion-derived ALK is present in tumor cells rather than ordinary lymphocytes
- Tumor-cell ALK can be demonstrated by immunohistochemistry
- ALK blockade can exploit dependence on abnormal kinase activity

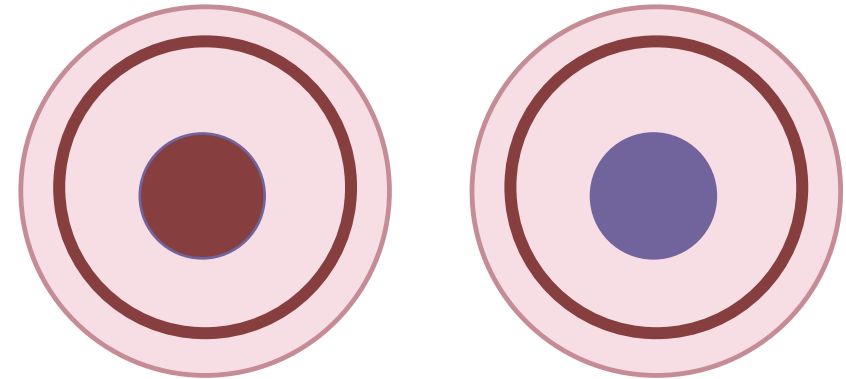
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ALK IHC provides a molecular surrogate

- ALK is not normally expressed in lymphocytes
- Positive tumor-cell staining strongly supports an ALK rearrangement
- Interpret unusual patterns with tumor morphology and lineage markers

Native schematic · subcellular staining patterns



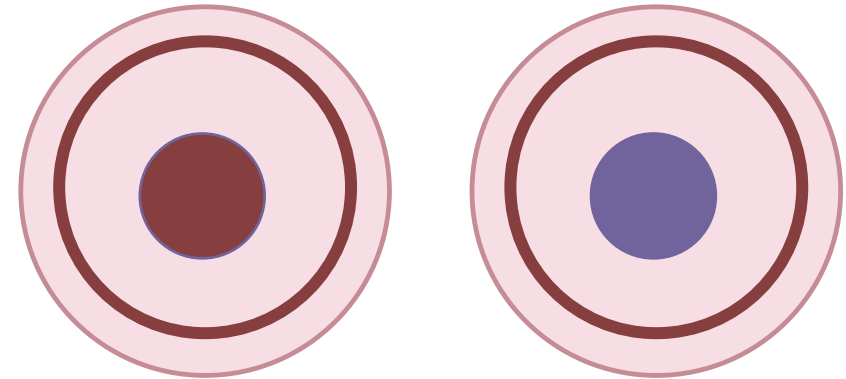
ALK: Cytoplasmic ± nuclear pattern

NPM1::ALK often nuclear + cytoplasmic

Fusion partner influences ALK localization

- NPM1::ALK usually yields nuclear and cytoplasmic staining
- Several alternative fusions yield predominantly cytoplasmic staining
- Staining distribution can suggest—but not definitively identify—the partner

Native schematic · subcellular staining patterns



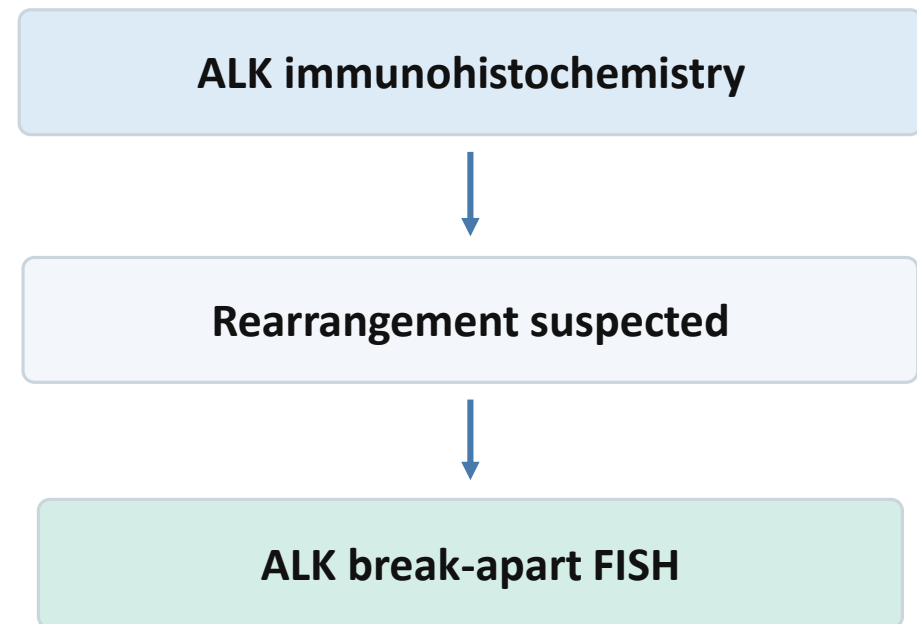
ALK: Cytoplasmic ± nuclear pattern

NPM1::ALK often nuclear + cytoplasmic

Testing molecular identity when necessary

- ALK IHC is an efficient initial method
- ALK break-apart FISH can document rearrangement in ambiguous cases
- Targeted fusion assays may identify a partner when clinically useful

Diagnostic tests answer different questions

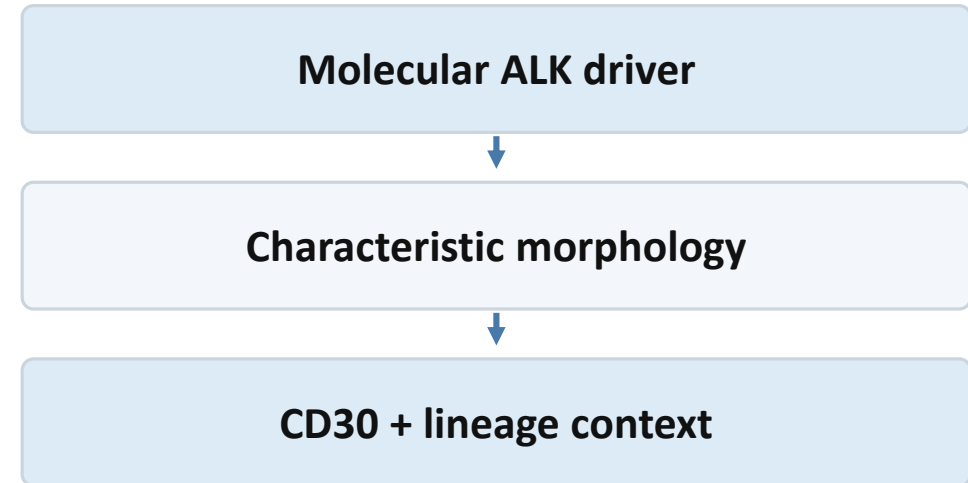


Molecular confirmation, if required

How molecular and tissue findings integrate

- ALK rearrangement identifies the driver
- Hallmark-cell morphology defines a recognizable appearance
- CD30 and a broad lineage panel establish the diagnostic context

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Typical age distribution

- ALK-positive cases preferentially affect children and young adults
- Age is a clue, not a stand-alone diagnostic criterion
- Older patients can still have ALK-positive ALCL

Children / young adults

Characteristic tendency — not an exclusion rule

Anatomical distribution

- Lymph nodes are often involved in systemic disease
- Extranodal soft-tissue involvement is frequent
- Site alone cannot distinguish ALCL from another large-cell malignancy

Sites are clinical, not diagnostic, evidence

Lymph node

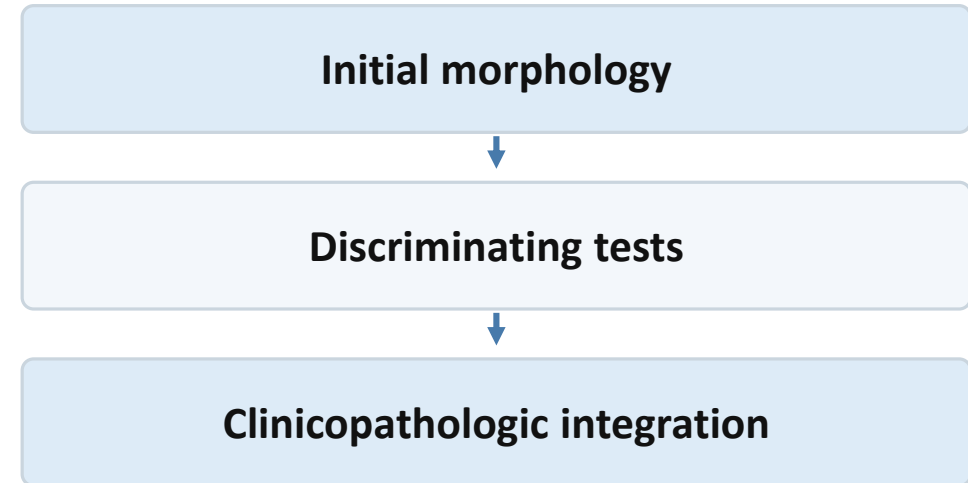
Extranodal soft tissue

Other systemic sites possible

Clinical appearance can be nonspecific

- Lymphadenopathy or an extranodal mass may prompt biopsy
- Constitutional symptoms occur in systemic lymphomas
- Diagnostic confirmation is tissue-based, not clinical alone

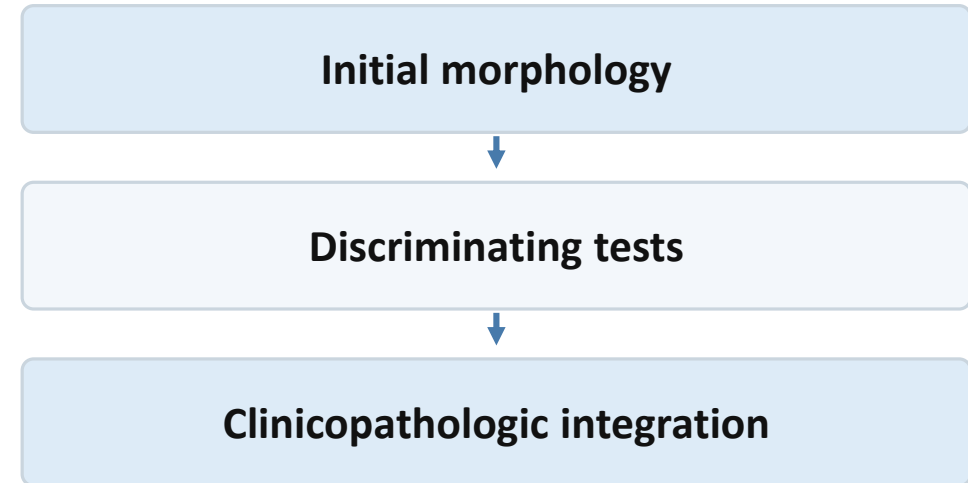
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Clinical question: Node or soft-tissue mass?

- The initial differential spans lymphoma, carcinoma and other tumors
- Perivascular or sinusoidal clusters can appear cohesive
- Lineage-specific tests become critical when morphology is deceptive

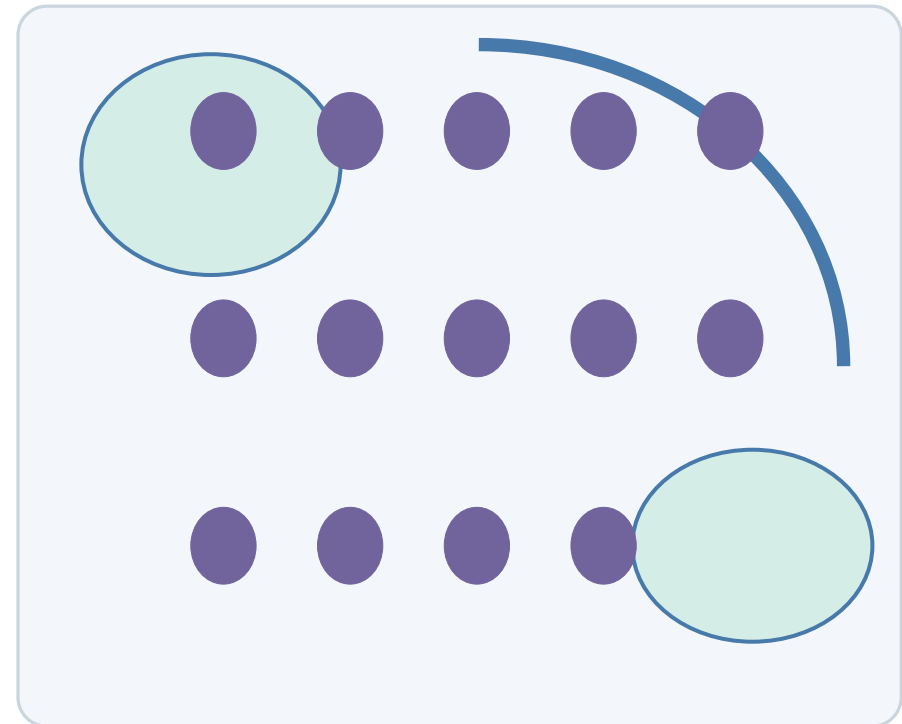
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Nodal effacement is an architectural clue

- Diffuse infiltration may replace normal lymph-node compartments
- Residual follicles or sinuses may be partly retained
- Architectural interpretation requires low-power examination

Schematic · not H&E microscopy

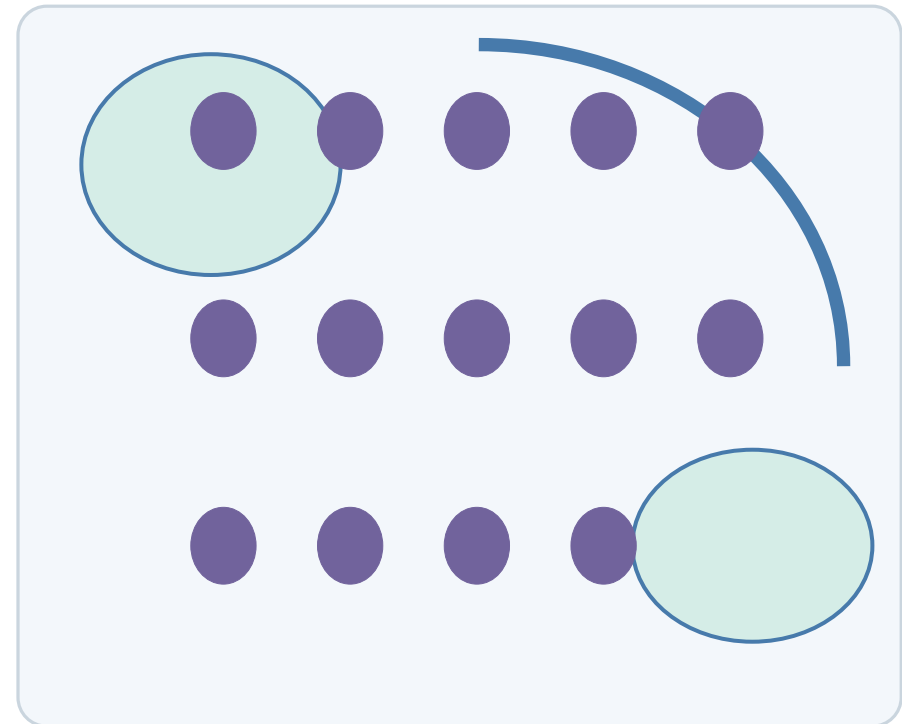


Neoplastic cells within sinuses

Sinusoidal distribution can resemble metastasis

- Tumor cells may fill lymph-node sinuses
- Large cells can be arranged in cohesive-looking groups
- Cytokeratin and lymphoid markers resolve a common diagnostic trap

Schematic · not H&E microscopy

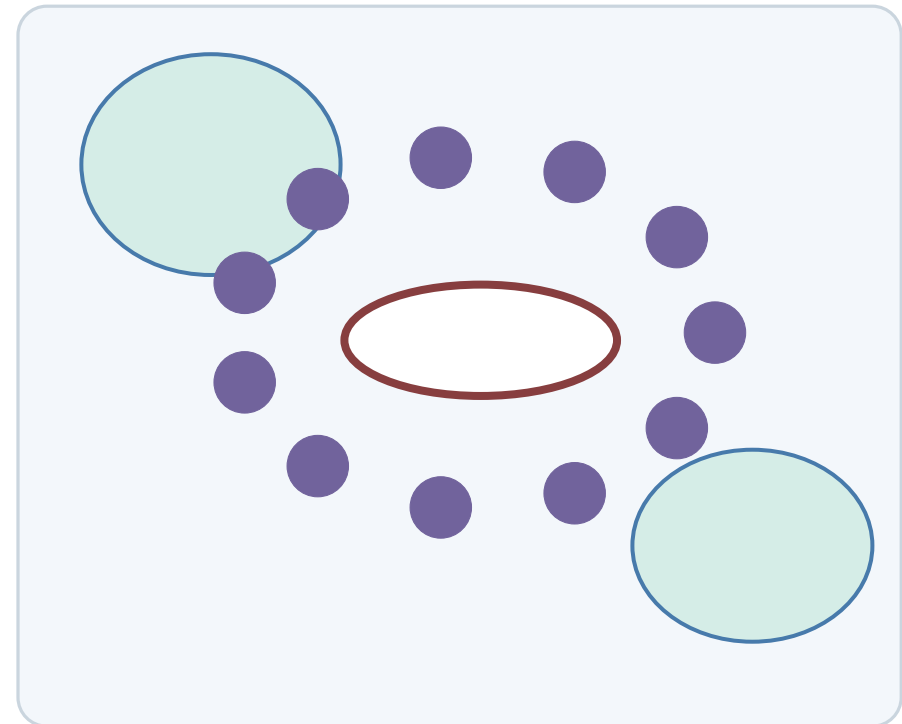


Neoplastic cells within sinuses

Perivascular growth is another recognizable pattern

- Neoplastic cells may aggregate around venules
- Perivascular foci can be found even when the dominant field is mixed
- Search these zones for diagnostically useful hallmark cells

Schematic · not H&E microscopy

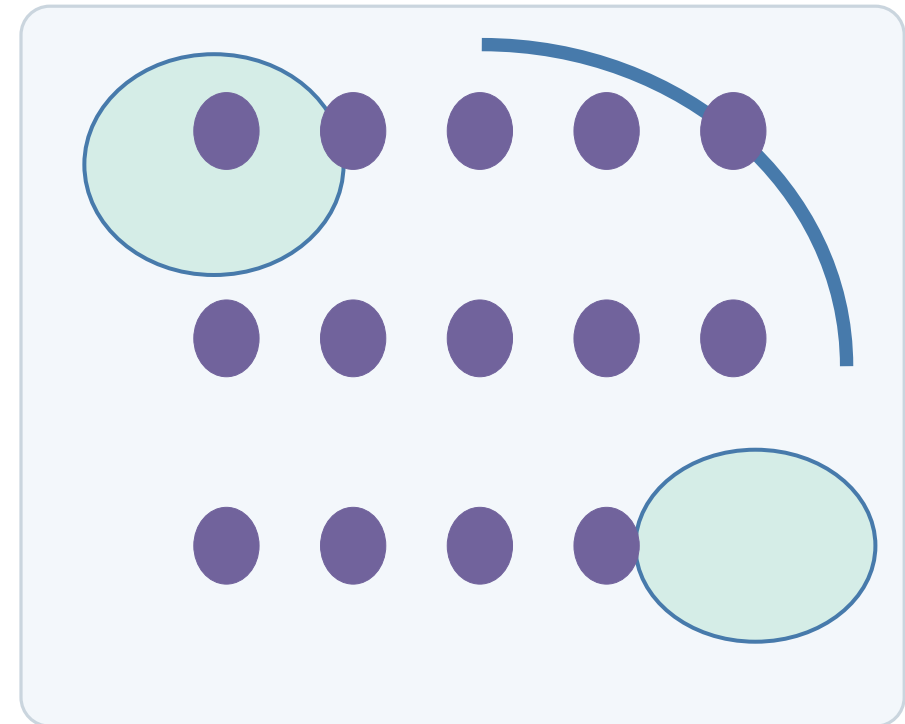


Tumor around venule

Why carcinoma may be suspected

- Large epithelioid cells may create a cohesive appearance
- Sinus infiltration resembles some metastatic carcinomas
- ALK-positive ALCL usually lacks convincing epithelial lineage markers

Schematic · not H&E microscopy

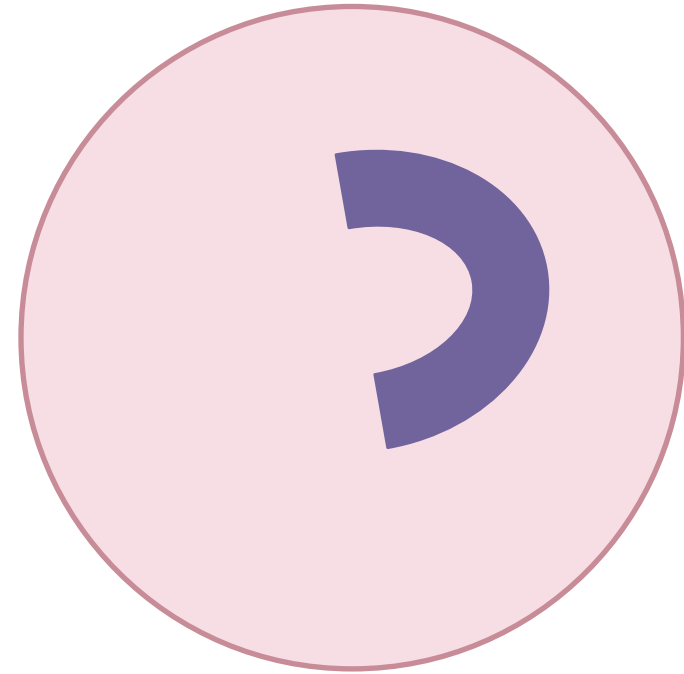


Neoplastic cells within sinuses

Hallmark cell: The essential cytology

- Large cell with ample cytoplasm
- Eccentric, horseshoe-shaped or kidney-shaped nucleus
- The distinctive shape is helpful, but not individually specific

Schematic · not a specimen



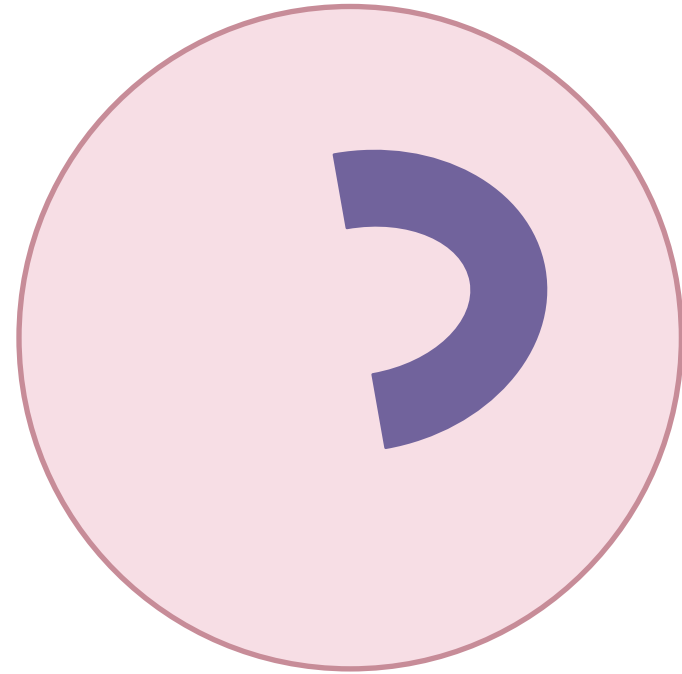
Abundant cytoplasm

Eccentric reniform / horseshoe nucleus

Nuclear contour is more useful than cell size

- Hallmark nuclei may be reniform, horseshoe-shaped or embryoid
- Variable atypia and multinucleation can coexist
- Look for recurring characteristic cells across fields

Schematic · not a specimen



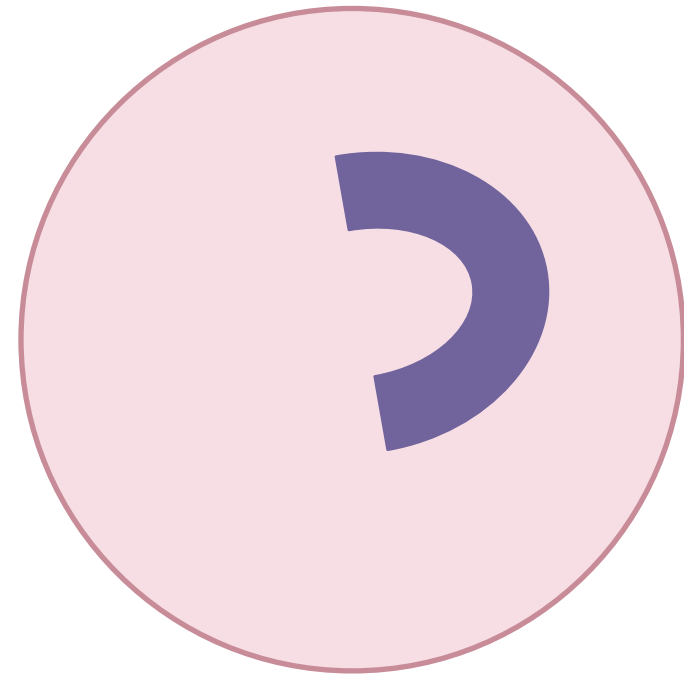
Abundant cytoplasm

Eccentric reniform / horseshoe nucleus

Cytoplasmic volume and perinuclear zone

- The cytoplasm is often abundant and variably eosinophilic
- A perinuclear pale or eosinophilic Golgi region may be conspicuous
- This feature helps explain the distribution of CD30 staining

Schematic · not a specimen



Abundant cytoplasm

Eccentric reniform / horseshoe nucleus

The common histologic pattern

- Sheets of medium-to-large pleomorphic anaplastic cells
- Hallmark cells are readily identifiable
- High-grade cytology coexists with a molecularly defined entity

The small-cell pattern is a diagnostic challenge

- Smaller atypical lymphoid cells may dominate the infiltrate
- Larger hallmark cells may be sparse or perivascular
- ALK can highlight cells when CD30 is concentrated in large elements

Lymphohistiocytic pattern: A masked tumor

- Reactive histiocytes can obscure neoplastic cells
- Scattered atypical cells may be difficult to recognize on H&E
- ALK and CD30 stains assist localization of the tumor population

Hodgkin-like morphology can mislead

- Tumor cells may resemble Hodgkin/Reed–Sternberg variants
- An inflammatory or sclerotic background may complicate classification
- ALK testing and a complete phenotype prevent misassignment

Variation occurs within the same tumor

- Distinct histologic patterns may coexist in one case
- A small biopsy can overrepresent one component
- Immunophenotypic interpretation must consider the sampled architecture

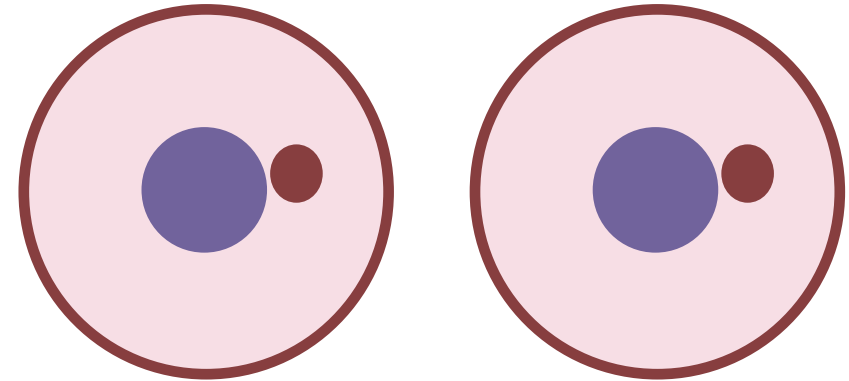
Morphologic patterns: Comparative view

Pattern	Dominant appearance	Diagnostic reminder
Common	Large pleomorphic cells	Hallmark nuclei conspicuous
Small cell	Mostly smaller tumor cells	ALK may show broad involvement
Lymphohistiocytic	Many reactive histiocytes	Tumor may be obscured
Hodgkin-like	HSR-like cells / background	Exclude classical Hodgkin

CD30: A central phenotypic feature

- ALCL is characterized by strong CD30 expression in large neoplastic cells
- Membranous and perinuclear Golgi staining is characteristic
- CD30 alone is insufficiently specific for the diagnosis

Native schematic · subcellular staining patterns

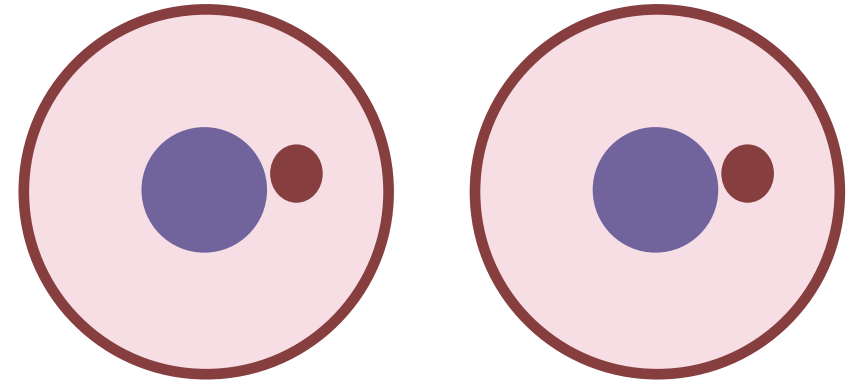


CD30: Membrane + perinuclear Golgi zone

CD30 distribution matters

- Golgi-associated accentuation provides a recognizable staining signature
- In small-cell variants, smaller tumor cells may stain less intensely
- An apparently focal stain must be interpreted against ALK and morphology

Native schematic · subcellular staining patterns

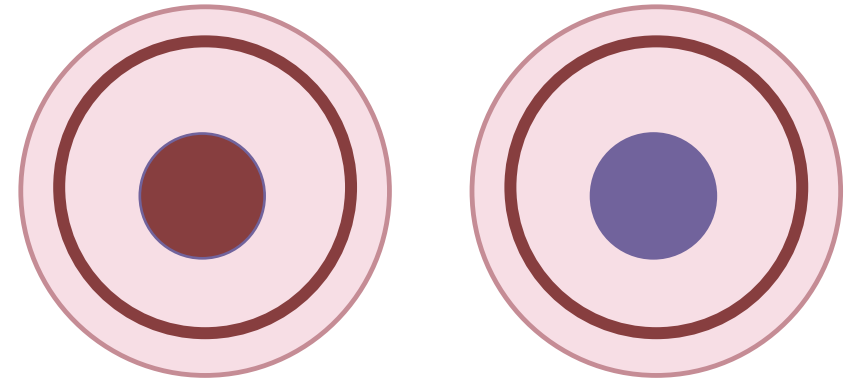


CD30: Membrane + perinuclear Golgi zone

ALK: The decisive companion to CD30

- ALK expression is expected in ALK-positive ALCL
- Both staining intensity and cellular location are informative
- Confirm that stained cells are the neoplastic population

Native schematic · subcellular staining patterns



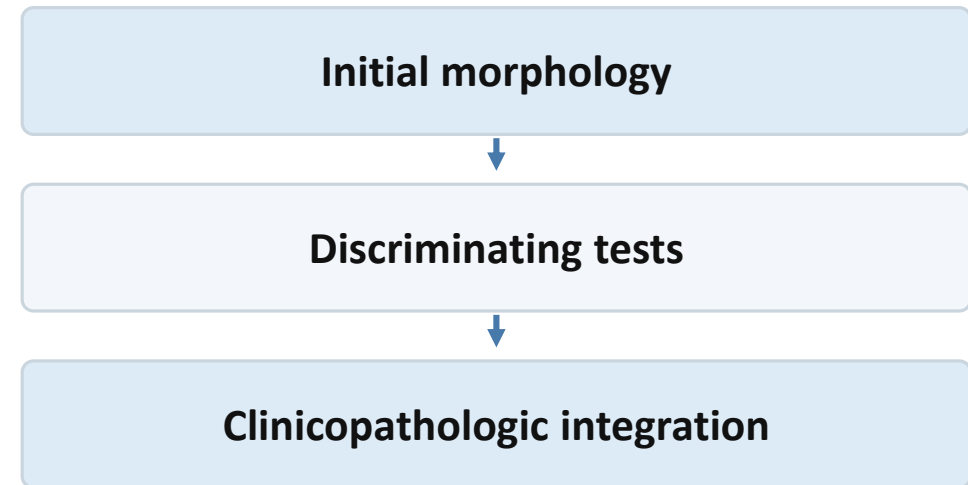
ALK: Cytoplasmic ± nuclear pattern

NPM1::ALK often nuclear + cytoplasmic

T-lineage markers may be absent

- CD3, CD5 and CD7 may be lost in tumor cells
- Some cases show a “null” immunophenotype despite T-cell origin
- A negative CD3 stain does not exclude ALK-positive ALCL

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Cytotoxic and activation phenotype

- Cytotoxic proteins such as TIA1 and granzyme B can be expressed
- EMA is often present; CD4 may also be expressed
- None replaces ALK/CD30 plus lineage and morphology assessment

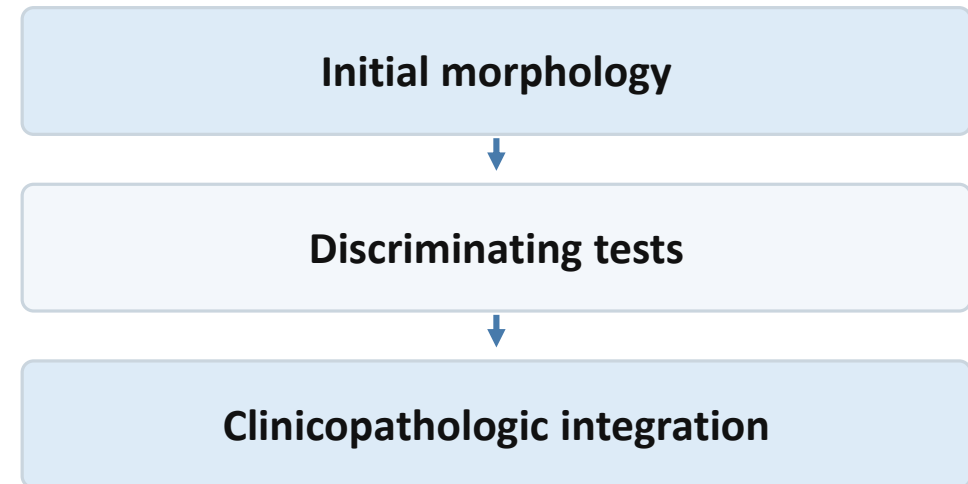
Practical initial immunohistochemical panel

Diagnostic question	Stain / assay	Caution
ALCL phenotype	CD30, ALK	Not independently specific
T-cell identity	CD2, CD3, CD5, CD7	Antigen loss possible
B-cell mimic	CD20, PAX5	Check plasmacytic markers
Carcinoma mimic	Broad cytokeratin	Interpret phenotype in context

Interpret a discordant panel deliberately

- ALK and CD30 positivity is compelling but not sufficient in isolation
- Review stain distribution, controls and viable tumor areas
- Expand testing for epithelial, B-cell or histiocytic mimics as indicated

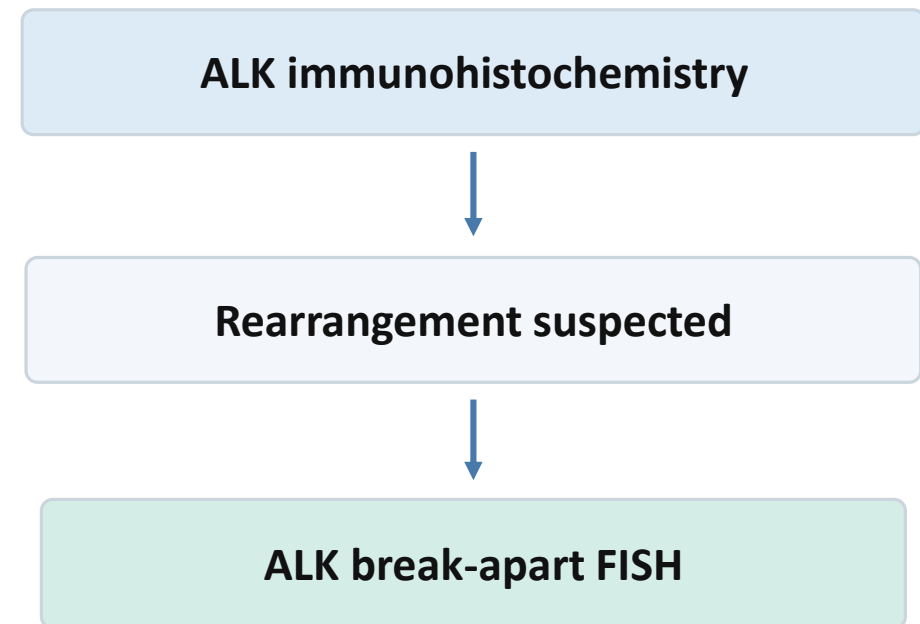
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FISH confirms ALK locus disruption

- A break-apart assay can show an ALK rearrangement
- FISH supports genetics; It does not by itself prove T-cell lineage
- A fusion-specific assay can add information beyond a break-apart result

Diagnostic tests answer different questions

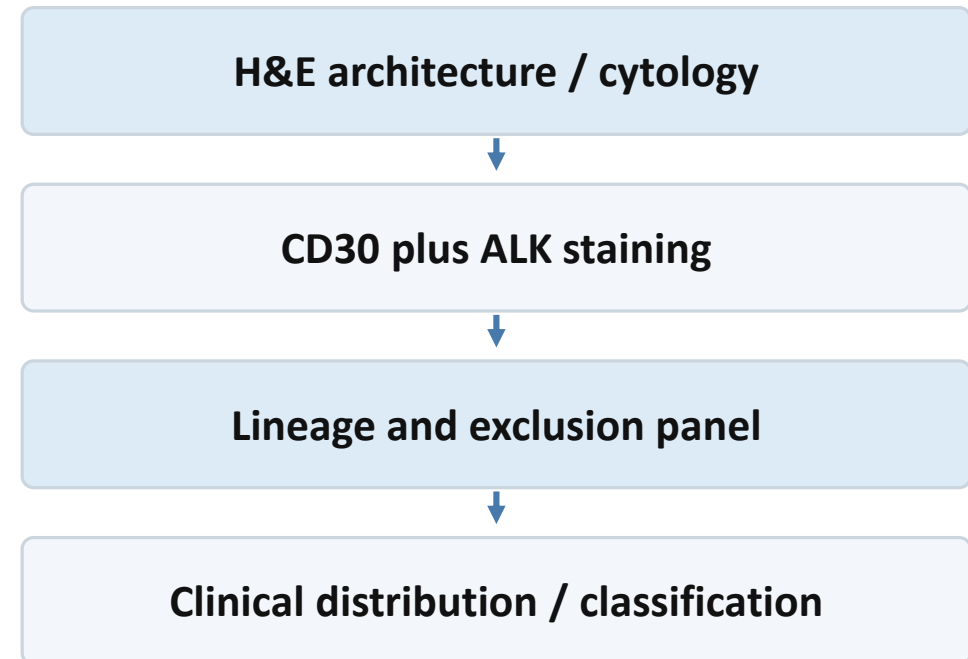


Molecular confirmation, if required

The diagnostic sequence

- Start with architecture and cytology on H&E
- Establish strong CD30 expression and tumor-cell ALK positivity
- Confirm a compatible mature T-cell phenotype and exclude mimics

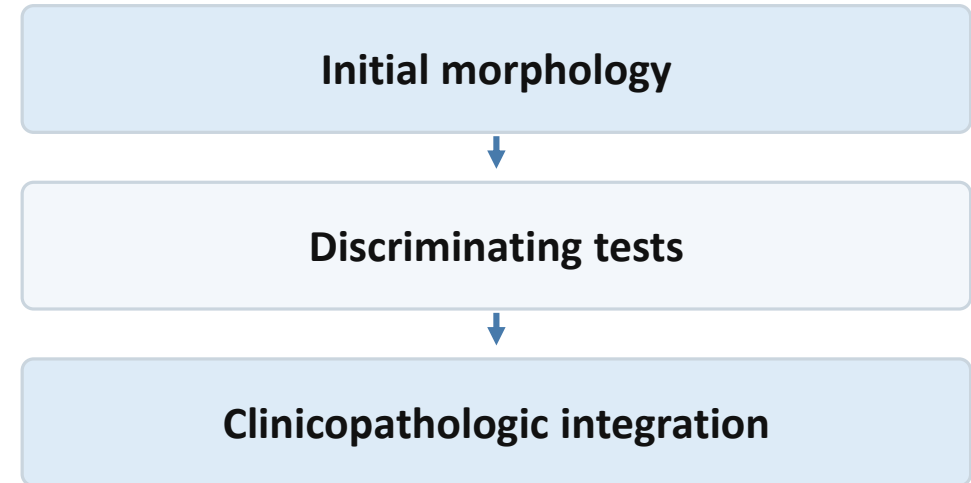
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Biopsy quality determines diagnostic confidence

- Preserve architecture when feasible
- Avoid relying on a tiny reactive-looking area in heterogeneous disease
- Interpret stains alongside adjacent H&E and clinical distribution

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Differential 1: Metastatic carcinoma

- Shared clues: Large cells, sinusoidal distribution, cohesive clusters
- Favor ALCL: Hallmark nuclei with CD30 and tumor-cell ALK
- Epithelial lineage markers help adjudicate a carcinoma mimic

Feature	ALK+ ALCL	Carcinoma
Growth	May be sinusoidal	May colonize sinuses
Morphology	Hallmark cells possible	Epithelial differentiation
ALK / CD30	Usually coexpressed	Not a defining pair
Cytokeratin	Typically absent	Supports epithelial lineage

Differential 2: Classical Hodgkin lymphoma

- Both can contain bizarre large cells and CD30 positivity
- Classical Hodgkin lymphoma typically lacks ALK expression
- A broader B-cell/Hodgkin phenotype and architecture resolve overlap

Feature	ALK+ ALCL	Classical Hodgkin
CD30	Strong	Usually strong
ALK	Positive	Usually negative
Cells	Hallmark cells	Hodgkin / RS cells
Workup	T/cytotoxic phenotype	Hodgkin / B-cell panel

Differential 3: ALK-positive large B-cell lymphoma

- Both diseases may stain for ALK
- ALK-positive large B-cell lymphoma usually has plasmablastic differentiation
- CD30 is usually absent; B/plasma-cell markers and light chains assist

Feature	ALK+ ALCL	ALK+ large B-cell
ALK	Positive	Positive
CD30	Characteristically strong	Usually negative
Lineage	Mature T-cell	B / plasma-cell
Phenotype	Aberrant T markers	CD138, light chains

Differential 4: PTCL, NOS

- A CD30-positive peripheral T-cell lymphoma is not automatically ALCL
- Characteristic morphology and ALK status are discriminating
- PTCL, NOS remains an exclusionary category after classification workup

Feature	ALK+ ALCL	PTCL, NOS
ALK fusion	Defining	Absent by definition
CD30	Strong in large tumor cells	Variable
Cells	Hallmark morphology	Variable pleomorphism
Diagnosis	Distinct entity	Diagnosis of exclusion

Differential 5: Systemic ALK-negative ALCL

- Both systemic groups are typically CD30 positive
- An ALK rearrangement defines the positive subtype
- Age and prognosis differ at population level; Histology overlaps

Feature	ALK+ ALCL	ALK- ALCL
ALK protein	Expressed	Absent
CD30	Strong	Strong
Age	Often younger	Often older
Outcome	Generally more favorable	Generally less favorable

Differential 6: Primary cutaneous ALCL

- A skin-limited tumor requires clinical distribution and staging context
- Primary cutaneous ALCL is usually ALK negative
- A tumor in skin may represent secondary involvement by systemic disease

Feature	Systemic ALCL	Primary cutaneous ALCL
Distribution	Nodal / extranodal	Skin-limited at diagnosis
ALK	Positive in target topic	Usually negative
CD30	Strong	Strong
Needed	Systemic assessment	Skin / staging context

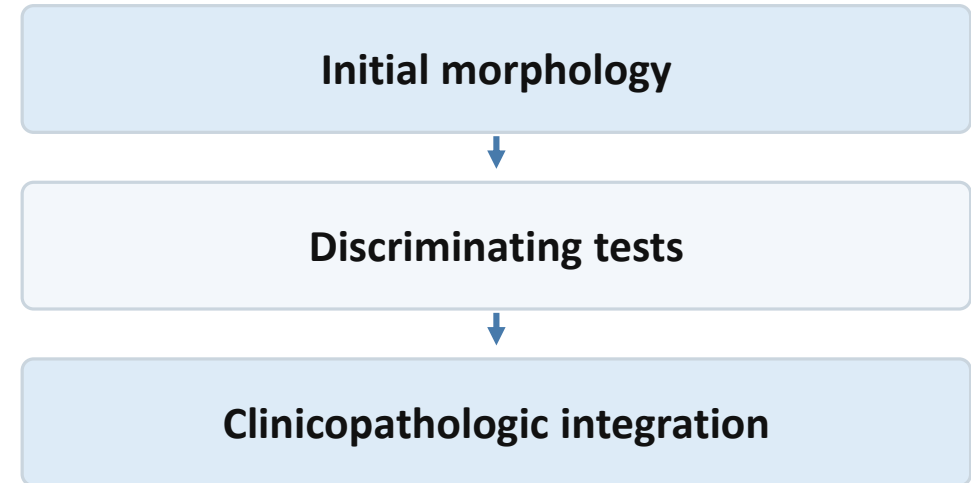
Breast implant-associated ALCL is separate

- Usually presents in relation to an implant capsule or effusion
- This entity is generally ALK negative and CD30 positive
- Do not classify a capsule-based lesion as ordinary systemic ALCL without history

When TCR clonality is informative

- Can support T-cell derivation in phenotypically ambiguous cases
- Does not establish ALCL subtype by itself
- Apparent clonality must be interpreted with assay limitations

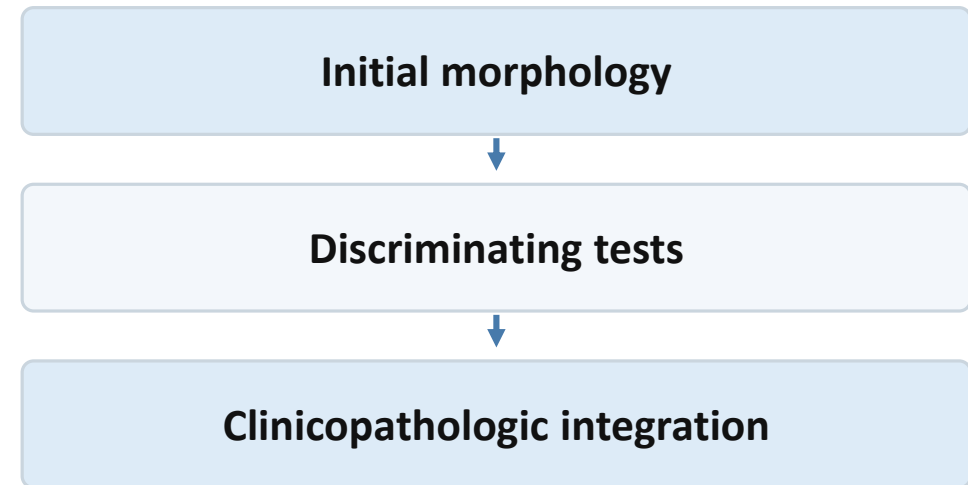
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Problem-solving when the phenotype is sparse

- Verify ALK staining in viable morphologically atypical cells
- Look for a CD30-rich hallmark-cell component
- Use molecular assays and broad lineage markers if needed

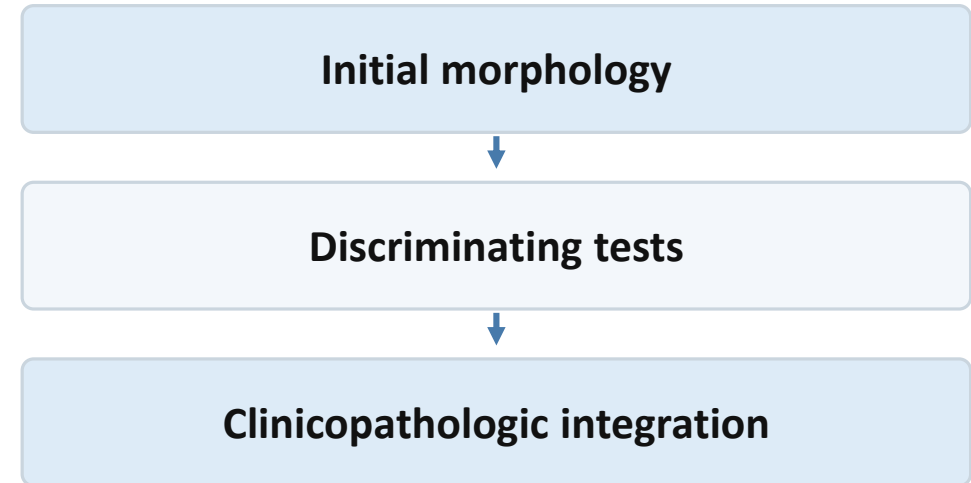
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Reporting: Communicate diagnostic certainty

- Name the entity as ALK-positive anaplastic large-cell lymphoma
- Record ALK/CD30 patterns and the relevant lineage results
- Mention unresolved mimics or confirmatory molecular work, if applicable

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Prognosis contrasts with other aggressive T-cell tumors

- ALK-positive ALCL as having a relatively favorable outlook
- Its younger age distribution is part of the clinical context
- Subtype and clinical stage still matter to individual prognosis

Robbins treatment-outcome statement

- Textbook reports a 75%–80% cure rate with chemotherapy
- This is a summarized textbook estimate, not a patient-specific prediction
- Clinical series and treatment eras vary;
Avoid using it as a universal cutoff

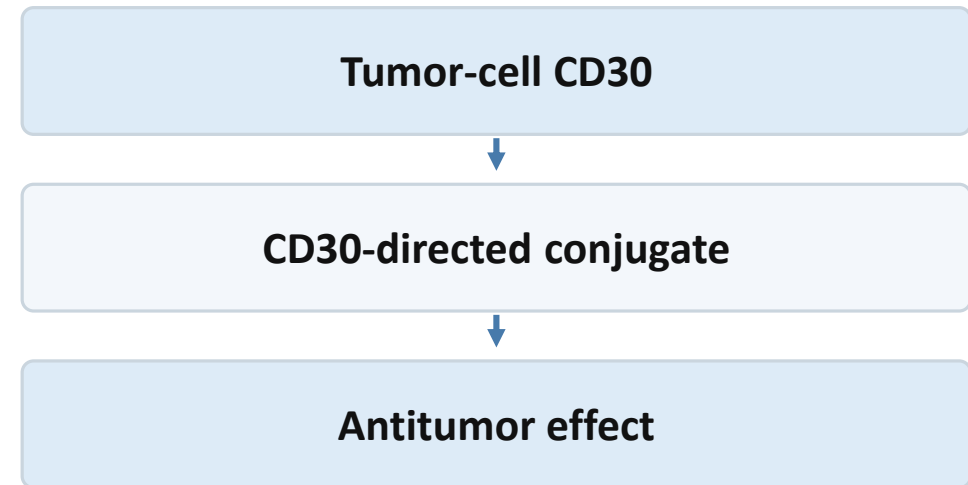
75%–80%

Textbook-reported chemotherapy cure rate

CD30 also creates a therapeutic opportunity

- CD30 is an antigenic target of antibody–drug conjugates
- The antigen can be expressed across different CD30-positive lymphomas
- Clinical treatment selection depends on setting and current protocols

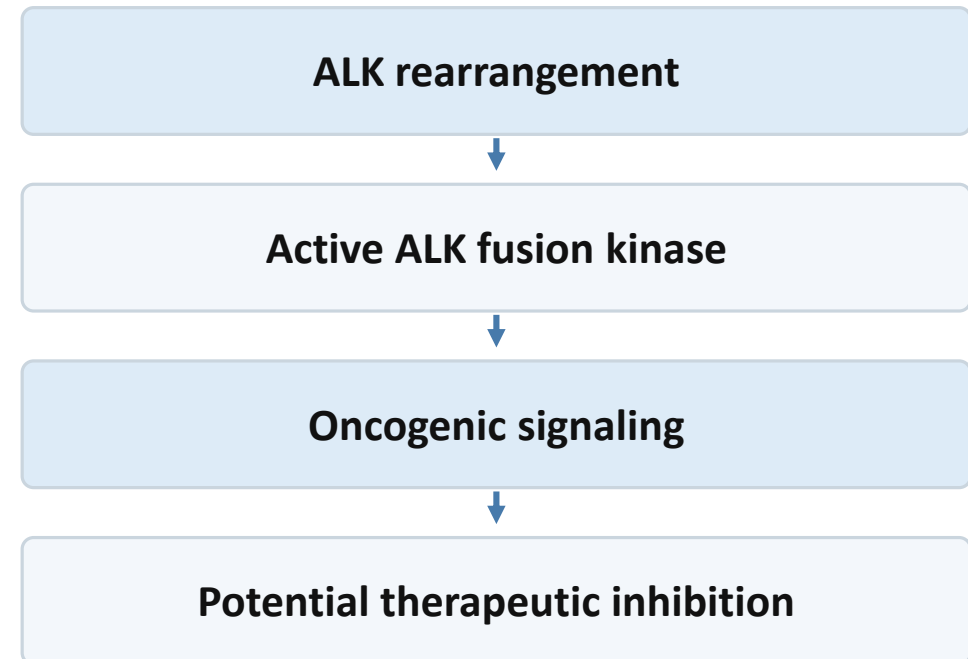
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ALK inhibitors exploit driver dependence

- ALK-targeted agents can elicit responses in refractory disease
- The rationale follows directly from constitutive fusion kinase signaling
- Response does not make a diagnostic lineage assessment optional

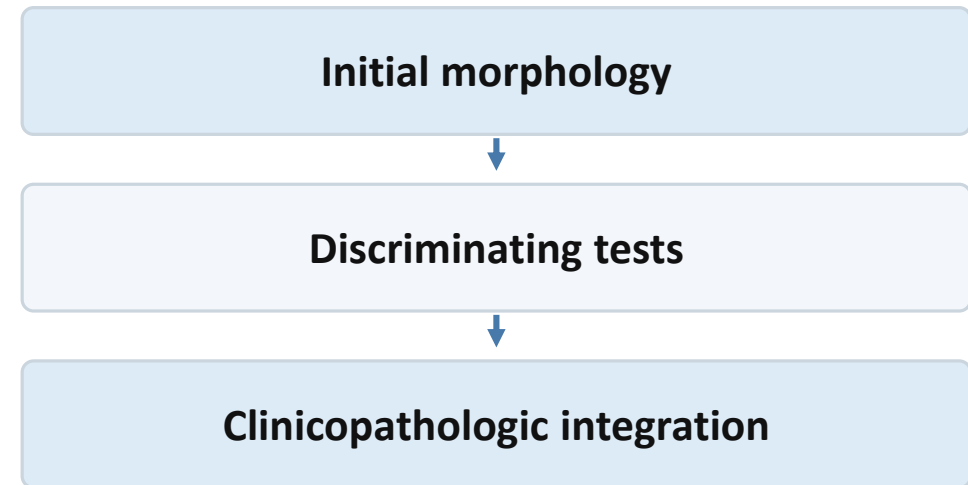
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Treatment history can change immunostains

- CD30 expression may change following CD30-targeted therapy
- Rebiopsy and current staining should be interpreted in therapeutic context
- Compare with the pretreatment specimen where available

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Case 1: Younger patient with adenopathy

Illustrative teaching case — not a clinical specimen

- A 19-year-old has enlarged cervical nodes and a soft-tissue lesion
- Biopsy: Large pleomorphic cells with horseshoe-shaped nuclei
- Tumor cells: CD30 positive and ALK positive; CD3 largely absent

Case 1: Construct the reasoning

Illustrative teaching case — not a clinical specimen

- The molecularly defined entity is ALK-positive ALCL
- Loss of CD3 is compatible with an aberrant T-cell phenotype
- A carcinoma mimic should be excluded if the tumor appears cohesive

Case 2: A carcinoma-like sinusoidal infiltrate

Illustrative teaching case — not a clinical specimen

- Lymph-node sinuses are packed with large cohesive-looking cells
- Cell nuclei are kidney-shaped in a subset
- CD30 and ALK are strongly expressed; Broad cytokeratins negative

Case 2: Identify the decisive evidence

Illustrative teaching case — not a clinical specimen

- Sinusoidal location alone does not make a carcinoma
- Hallmark morphology plus CD30/ALK supports ALCL
- Negative epithelial markers further weaken the carcinoma hypothesis

Case 3: Sparse hallmark cells

Illustrative teaching case — not a clinical specimen

- An atypical infiltrate consists mostly of small cells and histiocytes
- Only rare cells display reniform nuclei and strong CD30
- ALK stains a much wider neoplastic population

Case 3: Avoid false reassurance

Illustrative teaching case — not a clinical specimen

- This pattern is compatible with a variant ALK-positive ALCL
- A small-cell or lymphohistiocytic component can mask disease
- Review ALK-rich regions and correlate with the architecture

Case 4: ALK-positive does not equal ALCL

Illustrative teaching case — not a clinical specimen

- Large ALK-positive tumor cells lack CD30
- CD138 and plasmacytic markers are expressed
- Strong light-chain restriction favors a B-lineage process

Case 4: Choose the correct branch

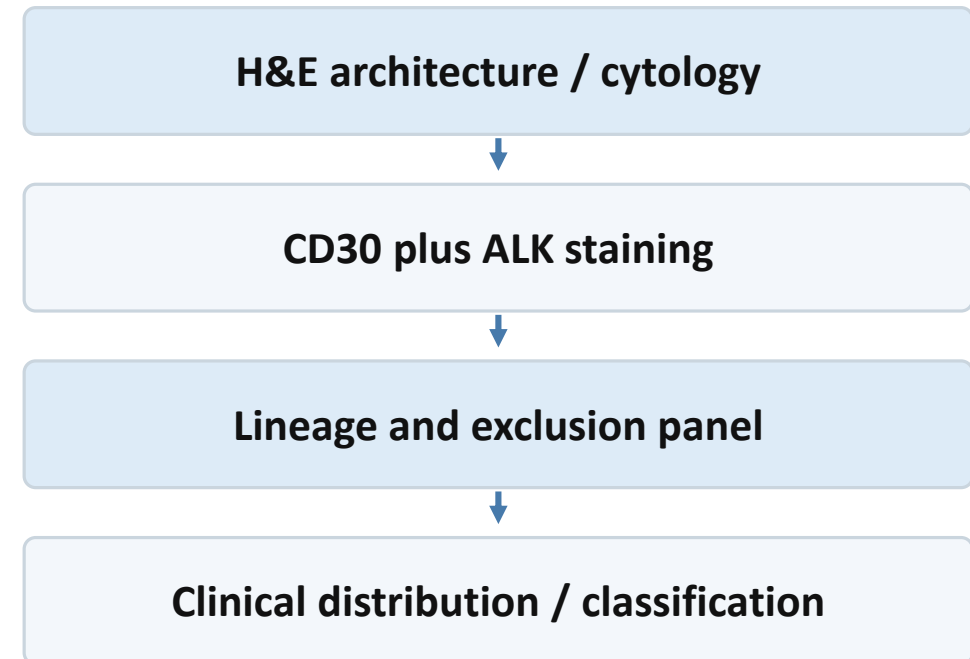
Illustrative teaching case — not a clinical specimen

- Consider ALK-positive large B-cell lymphoma
- Do not override the lineage phenotype based only on ALK
- Expand B-cell/plasma-cell workup as indicated

Integrated diagnostic decision tree

- Morphology → CD30/ALK → lineage → clinical localization
- No single stain solves every large-cell differential
- Classify only after ruling out the best-supported mimics

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Five findings worth retaining

- ALK rearrangement drives constitutive kinase signaling
- Hallmark nuclei and sinusoidal growth are characteristic
- Strong tumor-cell CD30 plus ALK anchors the phenotype
- T-cell markers may be lost; Assess alternate lineages
- Outcome is often favorable relative to ALK-negative disease

Selected references and source boundaries

- Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed., ch. 13
- Amador & Feldman, Am J Clin Pathol 2021: diagnostic approach
- Ferry et al., J Hematol Oncol 2024: WHO/ICC classification
- Additional source details and provenance are retained in speaker notes