

Management of Breast Cancer

Pathology-guided local and systemic treatment

Control local disease

Treat systemic risk

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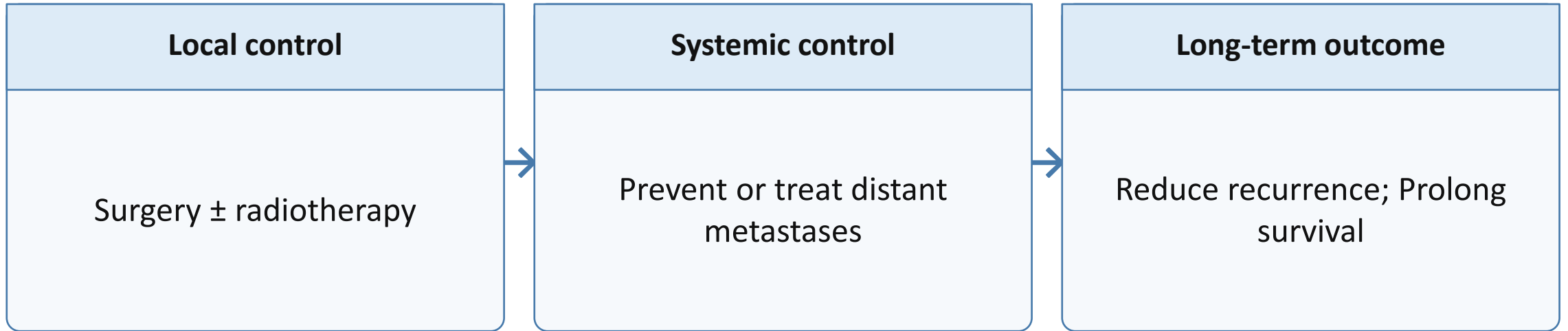
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Learning outcomes

- Distinguish local control from treatment of occult or established systemic disease.
- Explain why stage, grade, proliferation, and ER/PR/HER2 status change treatment selection.
- Connect companion assays with endocrine, HER2-directed, DNA-repair, PI3K, and immune-based therapy.
- Interpret neoadjuvant response and integrate pathology into multidisciplinary decisions.

Two complementary goals of treatment



Effective management addresses both the primary region and clinically occult or evident distant disease.

SCHEMATIC

Local therapy and systemic therapy treat different risks

LOCAL THERAPY

Targets tumor in breast and regional field

Breast-conserving surgery / mastectomy;
Radiotherapy

SYSTEMIC THERAPY

Targets disseminated cancer cells or
micrometastases

Endocrine therapy, chemotherapy, and
molecularly targeted treatment

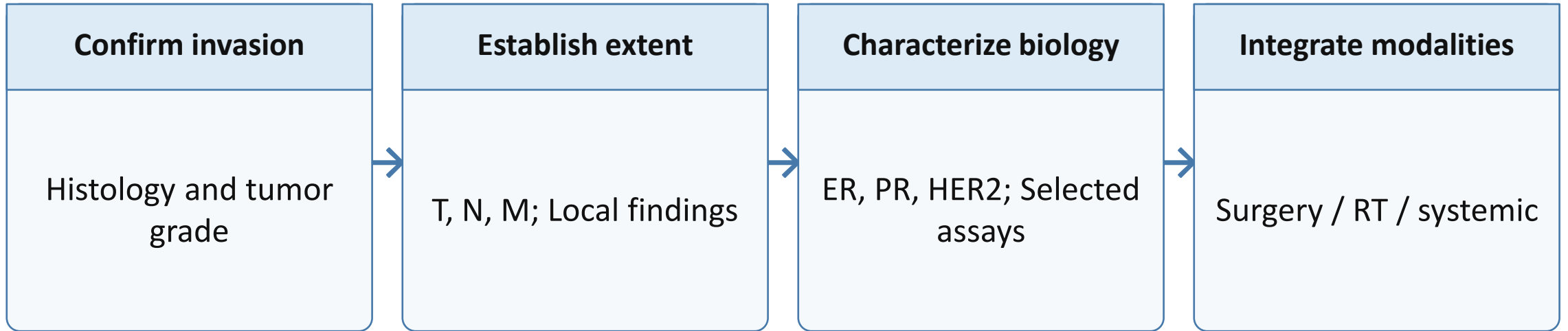
Both may be necessary because excision of the primary tumor does not exclude distant spread.

Extent and biology are independent treatment dimensions

EXTENT / STAGE	BIOLOGY / PHENOTYPE
Tumor size and regional lymph nodes	Histologic grade and proliferation
Distant metastatic disease	ER, PR, and HER2 expression
Skin or chest wall involvement	Actionable molecular alterations

A tumor can be anatomically limited yet biologically aggressive, or extensive but endocrine-responsive.

Clinical treatment framework



Treatment is chosen by combining pathology with anatomic staging and clinical presentation.

SCHEMATIC

Three practical clinical biomarker groups

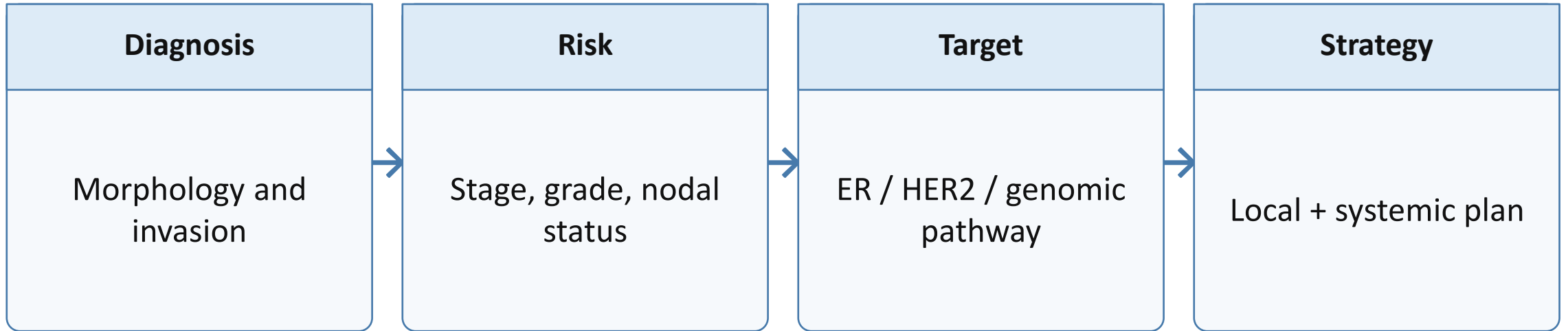
LUMINAL	HER2-POSITIVE	TRIPLE-NEGATIVE
ER-positive / usually HER2-negative	HER2 overexpression or amplification	ER-, PR-, HER2-negative
Endocrine sensitivity is central	Candidate for HER2-directed treatment	Endocrine and conventional HER2 targets absent

Clinical biomarker grouping is useful but does not encompass all molecular heterogeneity.

The pathology report drives a treatment discussion

- Confirm in situ versus invasive carcinoma, histologic subtype, and grade.
- Document primary tumor extent, margins, nodal findings, and lymphovascular invasion when assessed.
- Provide validated ER/PR/HER2 results and selected molecular findings.
- Separate findings that estimate prognosis from those that predict response to a treatment.

An integrated decision chain



There is no single universal treatment for every biologic subtype.

SCHEMATIC

Anatomic staging describes where disease has spread

- The AJCC eighth-edition anatomic framework uses tumor (T), regional nodes (N), and metastases (M).
- Stage 0 includes ductal carcinoma in situ; Distant metastasis defines stage IV.
- Skin/chest wall infiltration and inflammatory carcinoma alter the assessment of local extent.
- Anatomic stage and prognosis are related but not interchangeable.

Prognostic stage incorporates tumor biology

ANATOMIC COMPONENT	BIOLOGIC MODIFIERS
Primary tumor characteristics (T)	Histologic grade
Regional nodes (N)	ER and PR expression
Distant metastases (M)	HER2; Selected gene assays

The AJCC 8th-edition staging framework; This lecture does not substitute for an updated staging manual.

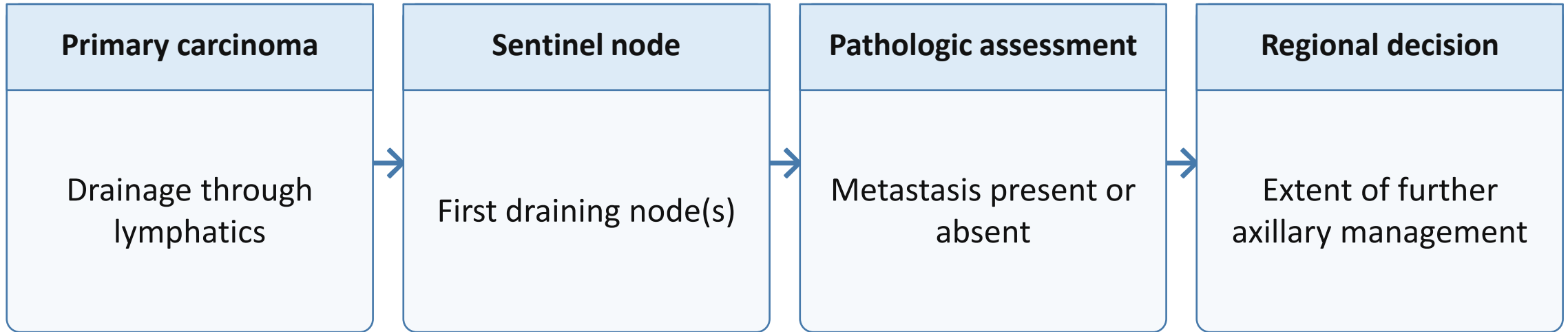
Distant spread dominates prognosis

- Distant metastasis is the strongest adverse prognostic feature.
- Once distant disease is established, cure is uncommon according to the textbook.
- Long remissions and meaningful palliation are possible in some endocrine-responsive and HER2-positive tumors.
- Systemic treatment intent differs between occult metastatic risk and established metastatic disease.

Regional nodal status is crucial before distant spread

- Axillary lymph-node status strongly predicts outcome in nonmetastatic invasive cancer.
- Clinical palpation alone can produce false-positive and false-negative assessments.
- Histological examination improves accuracy, including detection of small metastatic deposits.
- Nodal assessment helps define risk but does not itself specify a molecular treatment target.

Sentinel-node mapping limits unnecessary dissection



Negative sentinel node findings can help avoid morbidity from extensive axillary surgery in appropriately selected patients.

Primary tumor morphology retains treatment relevance

- Tumor size and direct extension inform local extent and resection planning.
- Higher histologic grade is associated with poorer prognosis within stage groups.
- Lymphovascular invasion signals greater likelihood of recurrence.
- Special histologic types may affect expectations of behavior and treatment response.

Prognostic versus predictive biomarkers

PROGNOSTIC

Estimates natural history or outcomes

Examples: M status, nodal burden, grade, lymphovascular invasion

PREDICTIVE

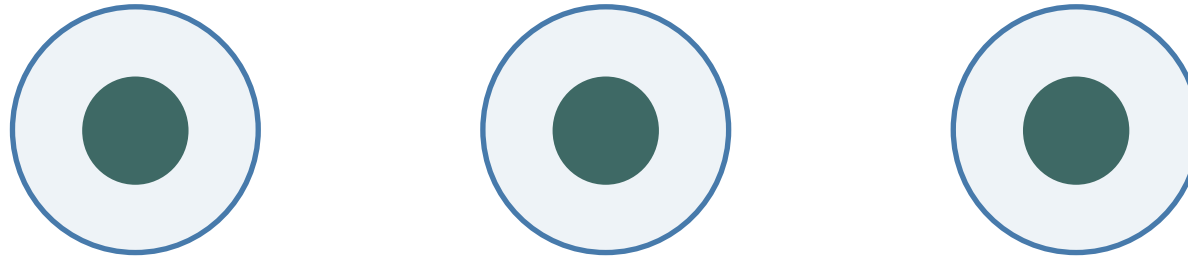
Estimates response to a specified intervention

Examples: ER for endocrine treatment; HER2 for HER2 blockade

Some measurements (such as ER, HER2, and proliferation) provide both kinds of information.

ER immunohistochemistry identifies endocrine sensitivity

- Assay: Nuclear estrogen receptor (ER) immunostaining in carcinoma cells.
- ER positivity as nuclear expression in $\geq 1\%$ of tumor cells.
- “Low-positive” ER (1%–10%) carries different biology and outcomes from strongly ER-expressing disease.

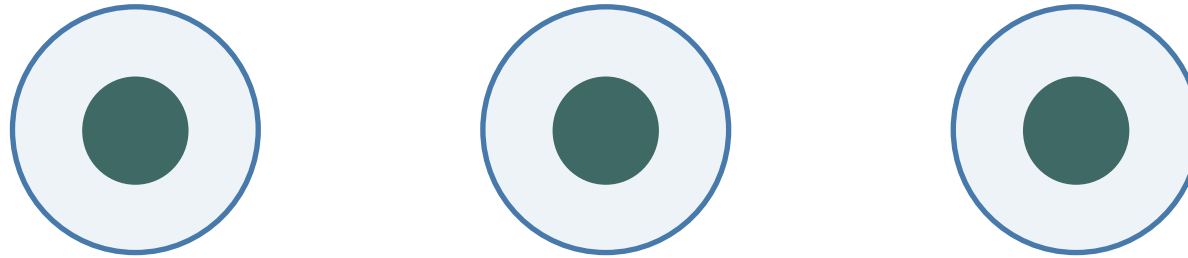


Nuclear localization

SIMPLIFIED ASSAY SCHEMATIC — NOT MICROSCOPY

PR expression refines luminal interpretation

- PR is assessed by nuclear immunohistochemistry and often accompanies ER positivity.
- PR positivity as staining in $\geq 1\%$ of tumor cells.
- Within ER-positive carcinoma, lower PR expression is associated with worse outcomes than strongly coexpressed ER and PR.

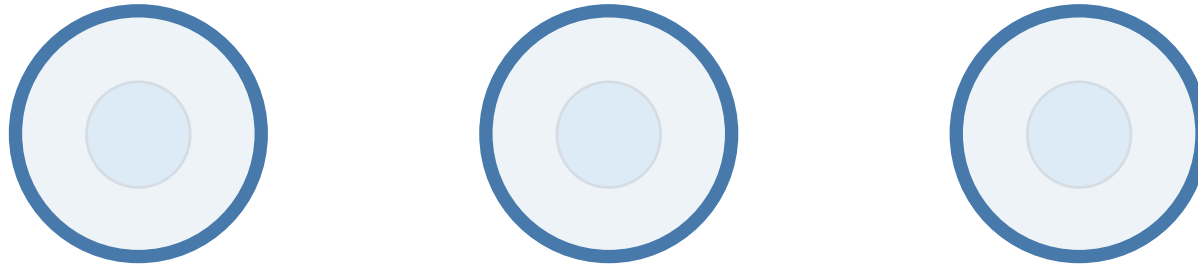


Nuclear localization

SIMPLIFIED ASSAY SCHEMATIC — NOT MICROSCOPY

HER2 identifies a targetable receptor axis

- HER2 protein expression is assessed by membrane IHC; Gene amplification can be assessed by ISH.
- Overexpression commonly reflects HER2 gene amplification.
- The result is predictive of response to HER2-directed agents and is also prognostically relevant.



Membrane localization

SIMPLIFIED ASSAY SCHEMATIC — NOT MICROSCOPY

Proliferation and gene-expression assays refine risk

- Ki-67 reflects tumor proliferation, but its use must be interpreted in context.
- Gene-expression signatures frequently emphasize proliferation-related transcripts.
- Their central clinical role is to identify selected endocrine-responsive cancers unlikely to benefit meaningfully from chemotherapy.
- Gene-expression subtype labels are not identical to routine clinical ER/HER2 groups.

Treatment planning is risk–benefit integration

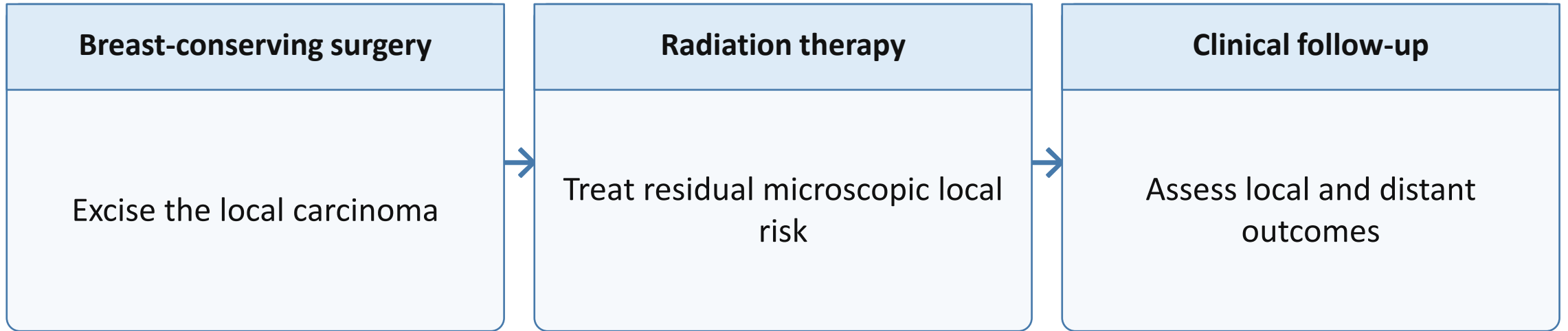
Selection is driven by both predicted benefit and disease burden.

- Histology and biomarkers stratify probable sensitivity.
- Tumor and nodal stage quantify the burden requiring local and systemic control.
- Therapy can be delivered before or after surgery depending on subtype, stage, and presentation.

Breast-conserving treatment is common

- In many patients, local control is achieved by breast-conserving surgery combined with radiotherapy.
- Preservation of breast tissue and elimination of local tumor deposits are compatible goals.
- The modality choice depends on local extent and clinical circumstances.
- Local treatment does not replace systemic therapy when distant recurrence risk is substantial.

Breast conservation uses complementary interventions



Surgery plus radiotherapy as a principal local-control strategy.

SCHEMATIC

Mastectomy is not routinely required for every cancer

- Robbins reserves mastectomy mainly for locally advanced disease or selected patients at high risk of a second primary cancer.
- A patient at elevated risk may elect mastectomy to reduce the risk of subsequent cancer.
- Mastectomy does not automatically eliminate the risk of distant recurrence.
- Decisions remain individualized rather than dictated by histologic name alone.

Locally advanced disease challenges local control

- Skin or chest-wall invasion is a marker of locally advanced tumor.
- Inflammatory carcinoma is associated with dermal lymphovascular tumor involvement.
- Large and invasive tumors may be difficult to control by excision alone.
- Stage and presentation influence the sequencing of systemic and local modalities.

Breast conservation versus mastectomy

BREAST CONSERVATION

Appropriate in many patients

Usually paired with radiation therapy

Preserves breast tissue

MASTECTOMY

Consider for locally advanced disease

Can be a choice in high-risk patients

Does not itself treat occult distant disease

No universal rule for individual operative eligibility is specified in the supplied source.

Why systemic therapy accompanies local treatment

- Some carcinomas disseminate before metastases become clinically evident.
- Systemic therapy treats known or presumed distant microscopic disease.
- It may also reduce the likelihood of local recurrence.
- Treatment selection therefore cannot rest on the success of surgery alone.

Adjuvant and neoadjuvant describe timing

ADJUVANT

Systemic treatment after primary surgery

Addresses recurrence risk after local excision

Benefit judged by biology and disease burden

NEOADJUVANT

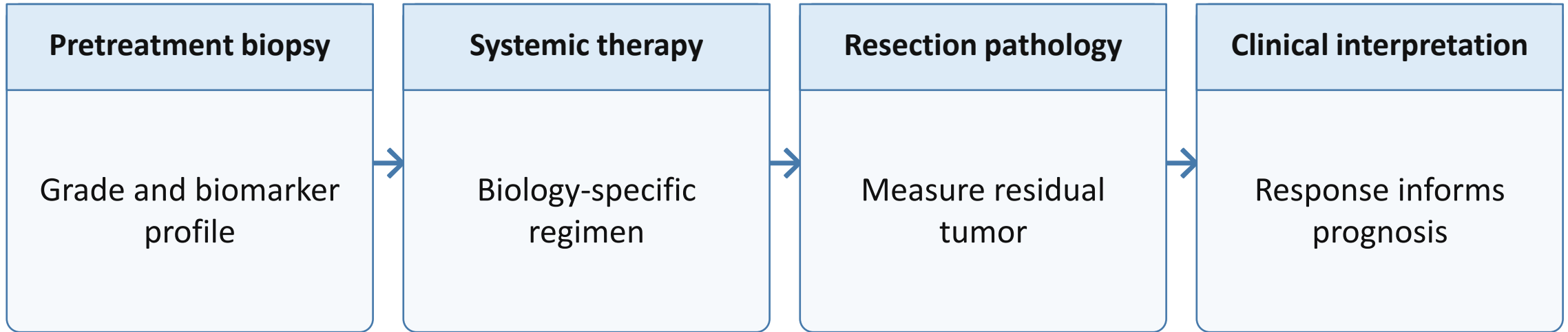
Systemic treatment before definitive surgery

Permits observation of tumor response

Timing depends on stage, subtype, and presentation

These are timing strategies, not separate drug classes.

Neoadjuvant treatment creates an in vivo response test



Response is a particularly informative prognostic indicator for HER2-positive and triple-negative carcinoma.

SCHEMATIC

Pathologic complete response has subtype dependence

- Pathologic complete response (pCR) denotes absence of residual invasive carcinoma under the relevant pathology definition.
- Strong pCR responses to chemotherapy with HER2-positive and triple-negative cancers.
- Response to neoadjuvant therapy is a strong prognostic factor in these groups.
- The same prognostic inference is less reliable for most luminal cancers.

Chemotherapy benefit varies by proliferation

- Cytotoxic chemotherapy is emphasized for highly proliferative cancers.
- High proliferation may occur in more than one clinical molecular subtype.
- Tumor burden and patient presentation contribute to the decision and timing.
- Avoid treating “breast cancer” as a single chemotherapy-sensitive disease.

Luminal A and high-proliferation disease differ

MINIMALLY PROLIFERATIVE LUMINAL A

Strong endocrine sensitivity

Low expected chemotherapy benefit

Consider how a genomic assay may refine risk

HIGHLY PROLIFERATIVE CARCINOMA

Greater rationale for cytotoxic chemotherapy

May occur across clinical molecular groups

Subtype-specific targeted therapy can coexist

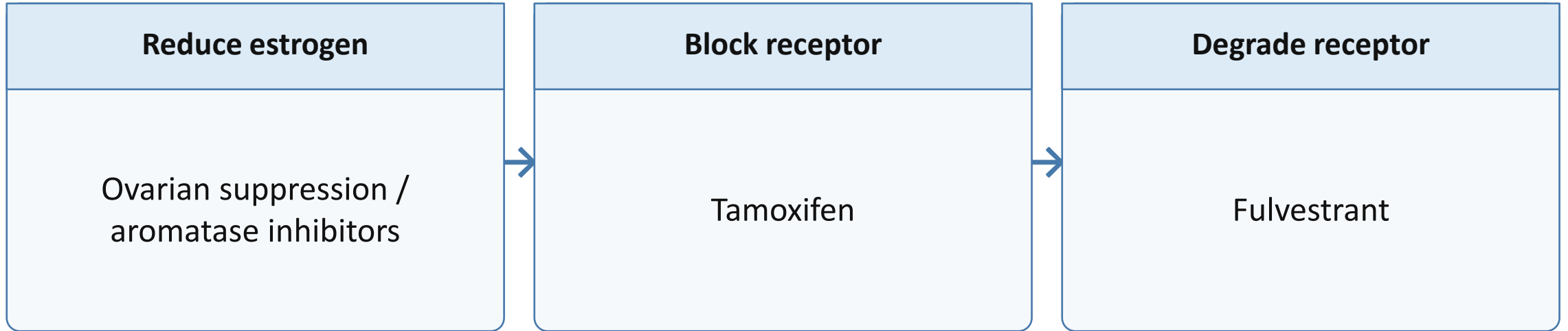
Avoid inferring drug efficacy from ER status alone.

Endocrine therapy is central to many luminal cancers

The treatment exploits estrogen-dependent growth rather than indiscriminate cytotoxic injury.

- ER nuclear staining provides an essential companion diagnostic.
- Agents can reduce estrogen supply, block receptor signaling, or degrade ER.
- Treatment is particularly important in endocrine-responsive, low-proliferation disease.

Three endocrine strategies



These distinct mechanisms converge on lowering estrogen receptor–mediated growth signaling.

SCHEMATIC

Estrogen deprivation removes an upstream stimulus

- Oophorectomy or ovarian suppression reduces ovarian estrogen stimulation in appropriate patients.
- Aromatase inhibitors such as letrozole reduce estrogen biosynthesis.
- Both are listed among endocrine approaches Table 23.7.
- Hormonal milieu and clinical setting determine which approach is suitable.

Tamoxifen acts at the estrogen receptor

- Tamoxifen is listed as an ER-blocking treatment.
- Target presence is established by ER immunohistochemistry.
- This strategy directly limits estrogen receptor signaling rather than acting as standard cytotoxic chemotherapy.
- ER-negative tumors generally lack the corresponding target.

Fulvestrant promotes ER degradation

- Fulvestrant is presented as a receptor-degrading endocrine treatment.
- Reducing functional ER addresses a different intervention point from lowering estrogen availability.
- Receptor biology and acquired resistance affect therapeutic selection.
- Management of metastatic resistance also requires molecular reassessment when indicated.

Endocrine treatment: Cytostatic versus cytotoxic

CYTOSTATIC EFFECT

Restrains proliferation driven by ER signaling

May achieve disease control without direct bulk cytotoxicity

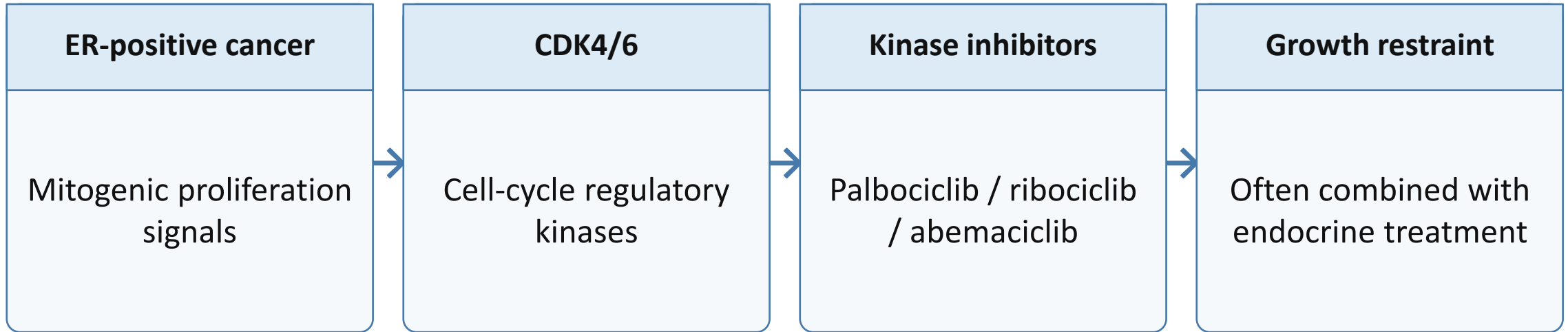
CYTOTOXIC EFFECT

Damages or kills malignant cells

More relevant to chemotherapy and some antibody–drug conjugates

Robbins explicitly characterizes endocrine treatment as effective cytostatic—not cytotoxic—therapy for ER-positive cancer.

CDK4/6 inhibition restrains cell-cycle progression



CDK4/6 inhibition in ER-positive cancer, usually with an aromatase inhibitor.

SCHEMATIC

Interpreting Ki-67 in a CDK4/6 discussion

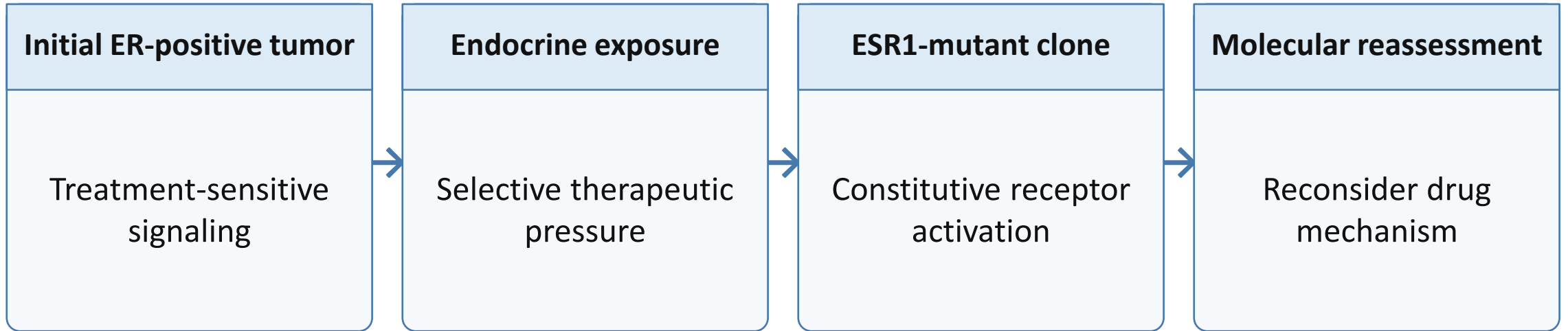
- Ki-67 IHC estimates proliferative activity, an important tumor-biologic feature.
- Robbins Table 23.7 lists Ki-67 under companion assays for CDK4/6 inhibitors.
- Ki-67 should not be presented as a universally sufficient standalone eligibility test.
- Interpret proliferation alongside receptor status, stage, and clinical context.

Endocrine resistance can have a molecular mechanism

ESR1 mutations may produce ligand-independent ER activation.

- ESR1 alterations in endocrine-resistant metastatic ER-positive breast cancer.
- Testing at relapse or progression on endocrine treatment can guide therapeutic decisions.
- A tumor may retain an ER-driven phenotype while losing sensitivity to earlier endocrine strategies.

A luminal cancer can evolve under endocrine therapy



Conceptual illustration of one documented resistance pathway; It does not represent every resistant carcinoma.

SCHEMATIC

Genomic assays can reduce unnecessary chemotherapy

- Selected mRNA-expression profiles identify lower-risk, endocrine-responsive cancers.
- Their principal value is to help recognize patients who are unlikely to gain appreciably from chemotherapy.
- Results supplement—not replace—histology, stage, and ER/HER2 testing.
- Assay utility is context-dependent; The textbook does not mandate use in every patient.

HER2-targeted therapy is a biomarker–drug match

HER2 protein overexpression or genomic amplification identifies a therapeutically actionable driver.

- Pathology establishes receptor status by IHC and appropriate molecular assays.
- Antibodies, antibody–drug conjugates, and kinase inhibitors act at different therapeutic levels.
- Targeted therapy can be integrated with systemic cytotoxic treatment.

HER2-targeted approaches

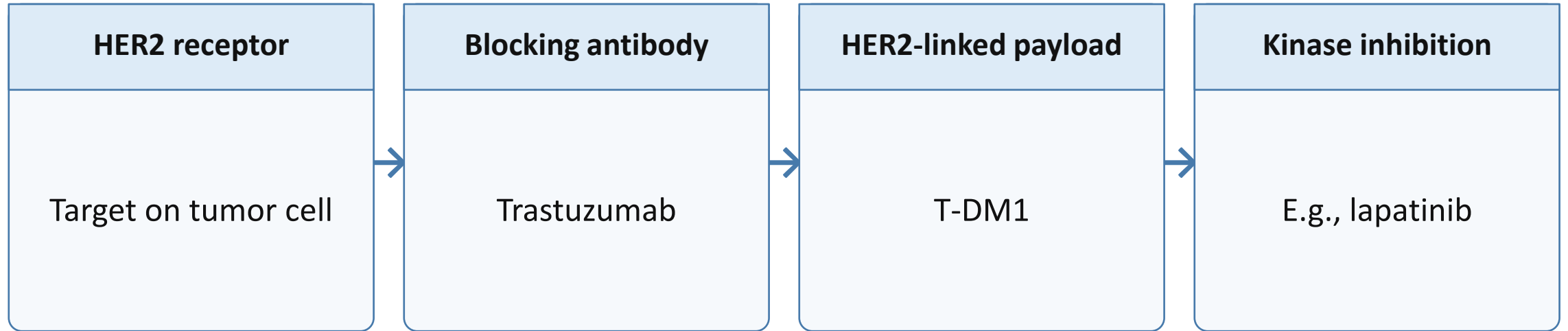


Table 23.7 lists antibodies, antibody–drug conjugates, and tyrosine kinase inhibitors as therapeutic classes.

SCHEMATIC

Trastuzumab targets HER2-positive carcinoma

- Trastuzumab is a monoclonal antibody directed at HER2.
- Its rationale depends on target expression/amplification in tumor cells.
- HER2-targeted treatment is not interchangeable with endocrine therapy.
- HER2 status must be reliably measured and interpreted before selecting this class.

T-DM1 links a HER2 antibody to cytotoxic therapy

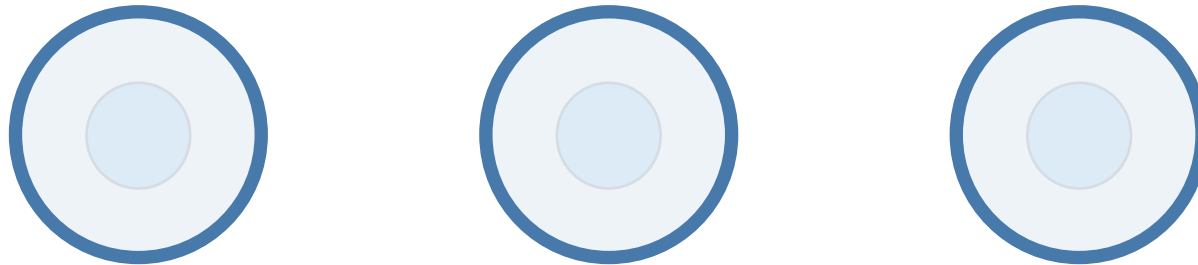
- T-DM1 (trastuzumab emtansine) is an antibody–drug conjugate.
- The antibody delivers a cytotoxic payload to cells selected by HER2-directed binding.
- It combines target recognition with a cytotoxic treatment mechanism.
- HER2 assessment remains central to this approach.

Tyrosine kinase inhibition targets HER2 signaling

- Lapatinib as a HER2-associated tyrosine kinase inhibitor.
- The target is receptor-associated growth signaling rather than circulating estrogen.
- Molecular selection remains essential because the pathway is not uniform across tumors.
- Specific drug choices and regimens require clinical guideline verification beyond the textbook.

HER2 testing connects morphology with treatment

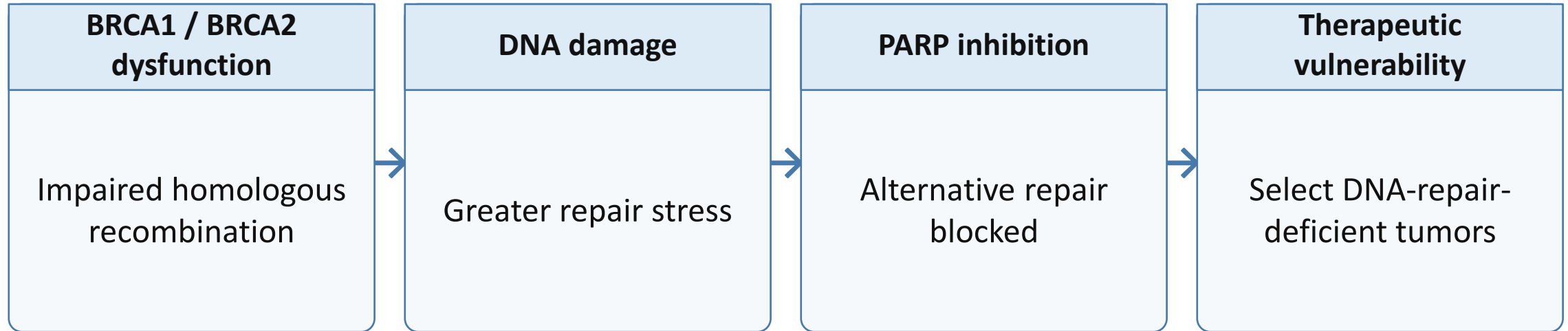
- HER2 IHC assesses membrane protein expression.
- In situ hybridization (ISH) evaluates HER2 amplification when indicated.
- Robbins also lists DNA sequencing for HER2 mutations in relevant contexts.



Membrane localization

SIMPLIFIED ASSAY SCHEMATIC — NOT MICROSCOPY

Homologous recombination deficiency creates vulnerability



Schematic summary of the homologous-recombination repair / PARP rationale in Table 23.7.

SCHEMATIC

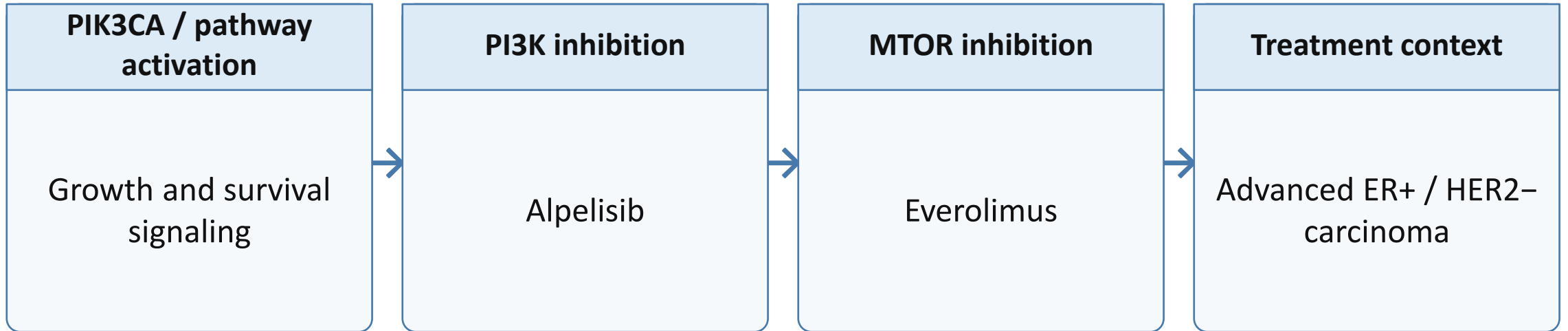
BRCA alterations act as predictive biomarkers

- Germline BRCA1 or BRCA2 pathogenic variants identify a recognized PARP-inhibitor-responsive group.
- DNA sequencing as the companion approach.
- Other mechanisms of homologous recombination deficiency may be relevant but are less conclusively established in the text.
- Do not equate every triple-negative tumor with BRCA-deficient disease.

PARP inhibition exploits altered repair capacity

- Olaparib is the PARP inhibitor example given by Robbins.
- The therapeutic idea depends on susceptibility created by homologous recombination repair defects.
- This is a genetically informed treatment strategy rather than a therapy for all breast cancers.
- Clinical eligibility must be determined by the relevant treatment setting and validated genomic findings.

PI3K–AKT–mTOR is another therapeutic pathway



Selected advanced luminal cancers and the predictive value of PIK3CA mutation for PI3K-directed therapy.

SCHEMATIC

PIK3CA testing is a drug-selection tool

- Activating PIK3CA mutation is a companion marker for PI3K inhibition.
- Sequencing can identify the actionable alteration.
- PI3K-pathway changes are common but not every alteration necessarily predicts the same drug response.
- The context highlighted is advanced ER-positive, HER2-negative carcinoma.

MTOR and PI3K inhibitors act at distinct nodes

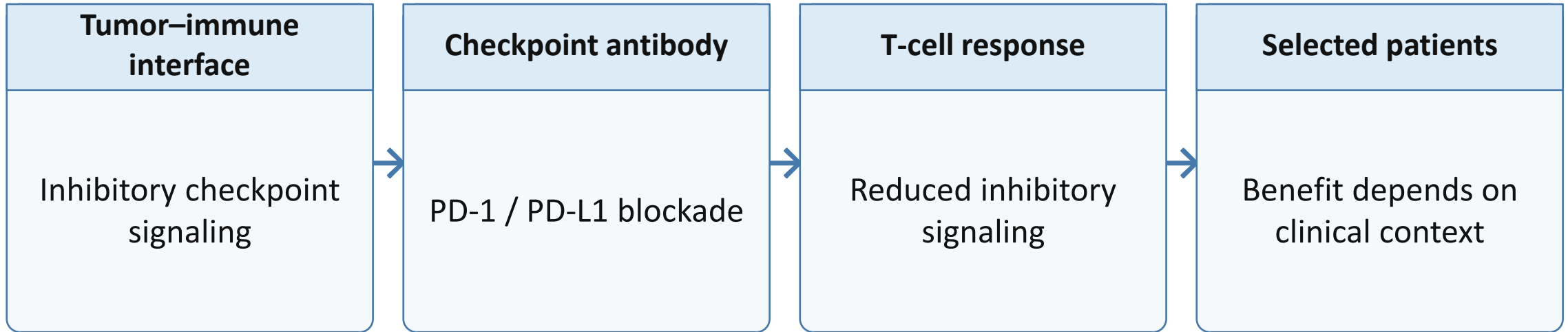
- Everolimus inhibits mTOR signaling.
- Alpelisib is a PI3K-targeted inhibitor.
- Both are pathway-oriented, but target and biomarker logic must not be conflated.
- Clinical selection depends on molecular results and the therapy setting.

Immunotherapy depends on tumor–immune context

Checkpoint blockade is relevant in selected high-grade, ER-negative cancers.

- Checkpoint proteins include PD-1/PD-L1 and CTLA-4.
- Immune biomarkers as predictors only in defined settings.
- Immune therapy is not a default treatment for every ER-negative tumor.

Checkpoint inhibition releases an immune brake



Illustrative mechanism; The specific example drugs and permitted indications are context dependent.

SCHEMATIC

Immune biomarkers have different meanings

- PD-L1 immunohistochemistry is one companion assay.
- Tumor mutational burden (TMB) may inform immunotherapy eligibility in particular settings.
- Mismatch repair deficiency (MMRD) or microsatellite instability (MSI) is rare in breast cancer but may be actionable.
- Do not treat PD-L1, TMB, and MMRD as interchangeable measurements.

Tumor-infiltrating lymphocytes carry response information

- TILs are mononuclear inflammatory cells in tumor and associated stroma.
- Prominent TILs with better prognosis and response to neoadjuvant chemotherapy in TNBC and HER2-positive cancers.
- This is biologic context, not a substitute for validated receptor testing.
- Pathologists should distinguish an immune infiltrate from an immune-drug companion assay.

TROP2 can carry a cytotoxic payload

- TROP2 is a cell-surface glycoprotein expressed by many triple-negative carcinomas.
- Sacituzumab govitecan is the TROP2-directed antibody–drug conjugate example.
- The payload is cytotoxic while antibody binding provides target-oriented delivery.
- Optimal response-predictive assays remain under investigation.

Antibody blockade versus antibody–drug conjugate

BLOCKING ANTIBODY

Binds target receptor / signaling protein

Example: Trastuzumab against HER2

ANTIBODY–DRUG CONJUGATE

Antibody guides attached cytotoxic payload

Examples: T-DM1 (HER2); Sacituzumab
govitecan (TROP2)

Similar antibody architecture does not imply the same mode of action.

Biomarker-to-treatment matrix

Tumor finding	Therapeutic class	Companion evidence
ER nuclear expression	Endocrine therapy	ER IHC
HER2 overexpression / amplification	HER2-directed agents	HER2 IHC / ISH
Germline BRCA1/2 alteration	PARP inhibitor	Validated germline DNA testing
PIK3CA activating alteration	PI3K inhibitor	Validated mutation assay
Selected immune phenotype	Checkpoint inhibitor	Context-specific PD-L1 / TMB / MMRD

Case 1 · ER-positive, low-proliferation cancer

HYPOTHETICAL TEACHING CASE

A resected invasive carcinoma has strong nuclear ER expression, is HER2-negative, and has low proliferation.

REASONING

- Classify this as an endocrine-responsive phenotype; Stage and nodal findings still determine recurrence risk.

INTERPRETATION

Endocrine therapy and a potentially limited contribution from chemotherapy in minimally proliferative luminal cancers.

Case 2 · Highly proliferative luminal carcinoma

HYPOTHETICAL TEACHING CASE

An invasive carcinoma expresses ER but shows higher proliferation and adverse histologic features.

REASONING

- ER positivity alone does not eliminate the rationale for cytotoxic chemotherapy.

INTERPRETATION

Assess extent, grade, nodal status, and potential genomic risk information alongside endocrine sensitivity.

Case 3 · HER2-positive carcinoma after neoadjuvant treatment

HYPOTHETICAL TEACHING CASE

A core biopsy shows invasive, HER2-positive carcinoma. Systemic therapy precedes surgery.

REASONING

- A carefully documented pathology assessment of residual disease is needed after treatment.

INTERPRETATION

Neoadjuvant response conveys prognostic information in HER2-positive disease; HER2-directed therapy rests on verified target status.

Case 4 · Triple-negative tumor with inherited DNA-repair defect

HYPOTHETICAL TEACHING CASE

An invasive tumor lacks ER, PR, and HER2; Germline testing identifies a BRCA1 alteration.

REASONING

- The clinical phenotype and the germline predictive biomarker answer different questions.

INTERPRETATION

High proliferation supports chemotherapy consideration; BRCA-associated repair deficiency provides rationale for PARP-targeted treatment in appropriate contexts.

Case 5 · Endocrine-treated disease progresses

HYPOTHETICAL TEACHING CASE

A previously endocrine-responsive metastatic ER-positive cancer progresses during hormone-directed treatment.

REASONING

- Progression may reflect acquired resistance; ESR1 mutation testing is one documented strategy.

INTERPRETATION

Molecular reassessment can change treatment selection even when the original biopsy established ER positivity.

Case 6 · Locally advanced breast cancer

HYPOTHETICAL TEACHING CASE

A primary carcinoma clinically involves skin and regional nodes, with no distant metastasis documented in the scenario.

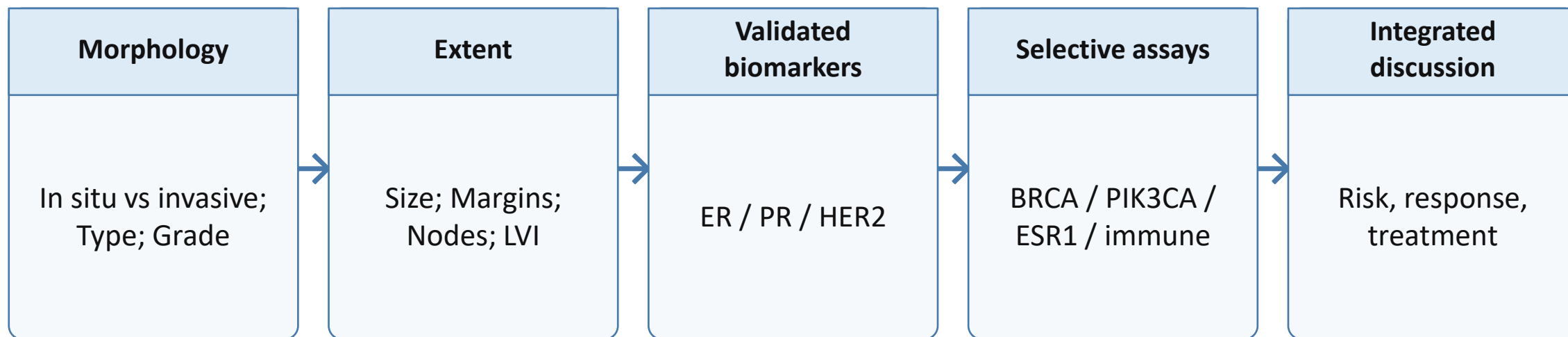
REASONING

- Local therapy is challenging, and the order of treatment depends on subtype, stage, and presentation.

INTERPRETATION

Integrate systemic treatment planning with local modalities rather than relying on an excision-only strategy.

Pathology-to-therapy sign-out checklist



Report only examinations actually performed; Results require appropriate methods and interpretation.

SCHEMATIC

Limitations of source-based treatment teaching

SUPPORTED BY ROBBINS

Conceptual goals and modalities

Biology-driven treatment classes

Examples of drug targets and assays

NOT ESTABLISHED HERE

Current drug approvals in every region

Patient-specific regimen, dosing or sequencing

Complete 2026 guideline eligibility rules

Therapy tables are educational; Institutional protocols and current oncology guidelines determine actual prescribing.

Three durable principles

**Control the breast and regional disease; Treat systemic risk;
Target the biology.**

- Disease extent determines anatomic risk and feasibility of local treatment.
- ER, HER2, DNA-repair, PI3K, and selected immune markers can predict treatment sensitivity.
- Response to neoadjuvant treatment adds prognostic information, especially in HER2-positive and triple-negative carcinomas.

Core reference and interpretation boundaries

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 23, The Breast: Invasive Carcinoma of the Breast (pp. 954–967).
- Management of Breast Cancer (pp. 965–966); Table 23.7, Targeted Treatment of Breast Cancer (p. 966).
- Prognostic and Predictive Factors; Breast Cancer Staging; Tables 23.5–23.6 (pp. 964–965).
- Treatment examples reflect the supplied textbook rather than a separately verified, contemporary prescribing guideline.