



Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Clinically Relevant Biomarkers and the Tumor Immune Microenvironment

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#LearnACI

Disclosures

- Royalty: Springer/Demos Publishing – Textbooks
- Consulting Fees: Bristol-Myers Squibb; Roche Diagnostics
- Contracted Research: Bristol-Myers Squibb
- I will be discussing non-FDA approved indications during my presentation.

Outline

1. Biomarker testing for advanced/metastatic triple negative breast carcinoma (TNBC)
2. Biomarker testing for early-stage TNBC
3. Tumor infiltrating lymphocytes (TILs): An emerging biomarker

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Biomarker Testing for Immunotherapy in Advanced/Metastatic TNBC

- PD-L1
- Tumor mutation burden (TMB)
- Microsatellite instability (MSI)/mismatch repair deficiency (dMMR)

PD-L1 in Advanced/Metastatic TNBC

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^a lymphocytes and plasma cells, located in tumor-associated stroma

PD-L1 in Advanced/Metastatic TNBC

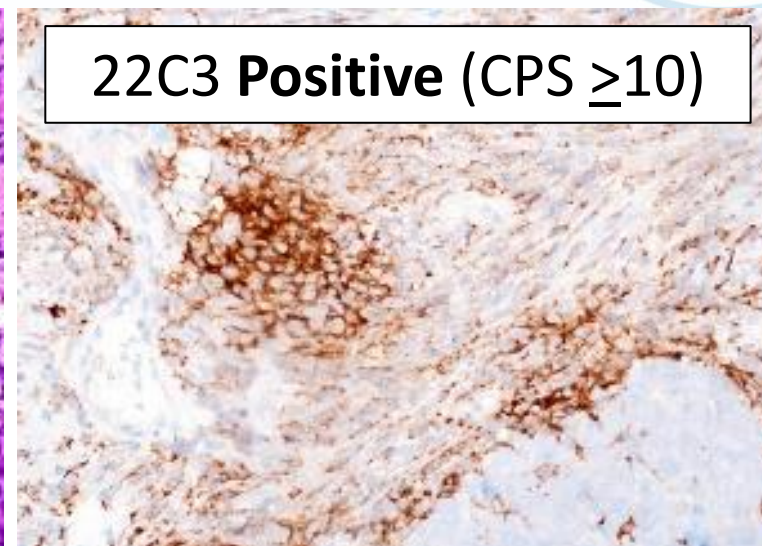
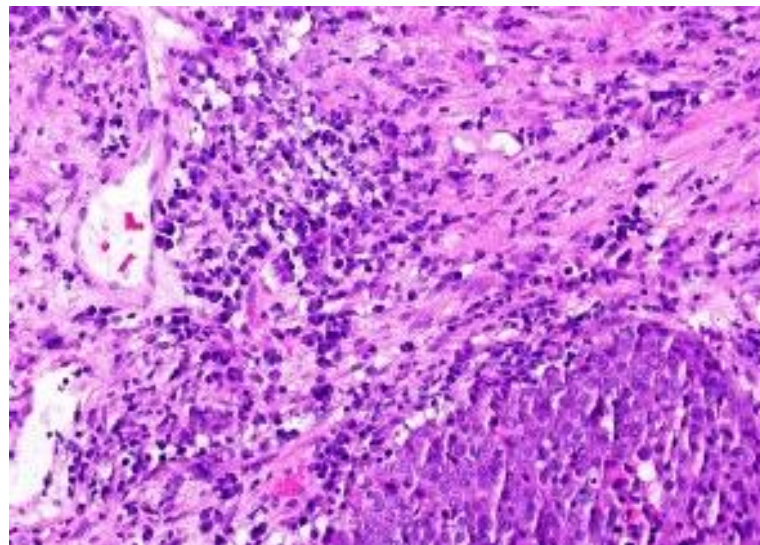
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PD-L1 IHC with the 22C3 assay

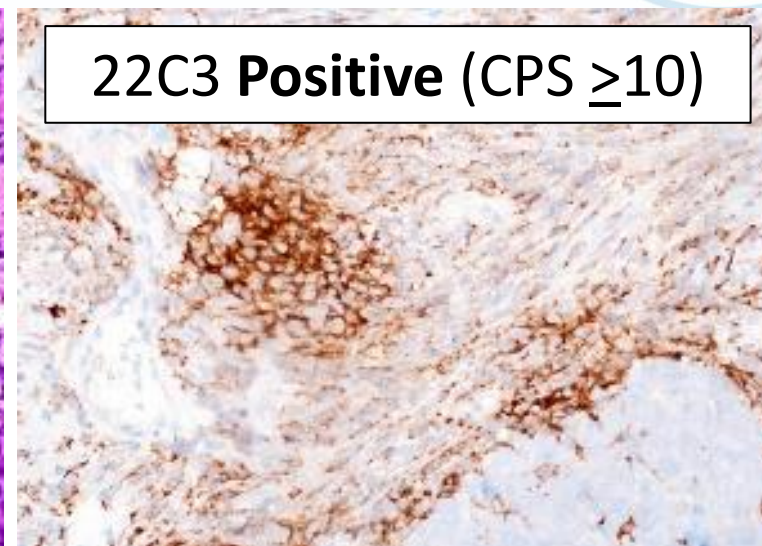
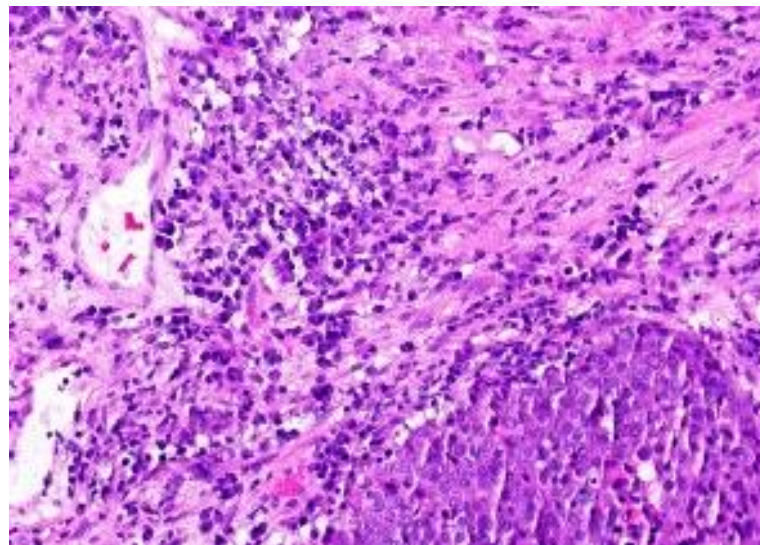
PD-L1 IHC with the 22C3 assay

Locally
advanced
TNBC

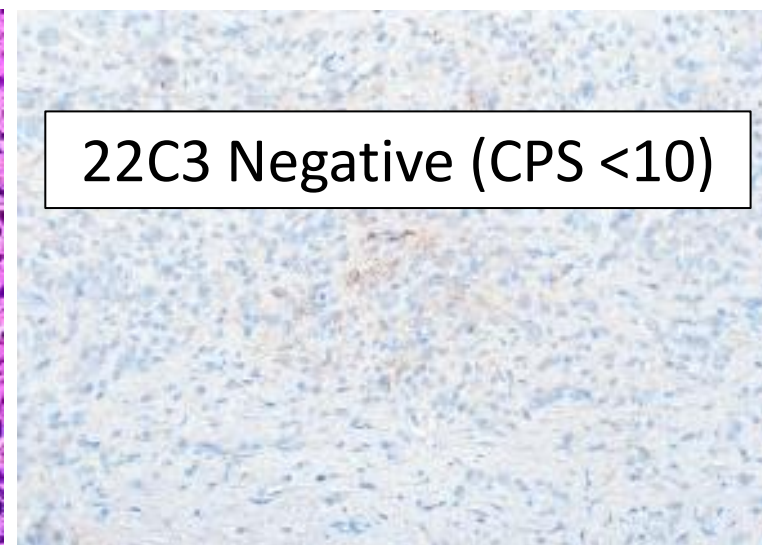
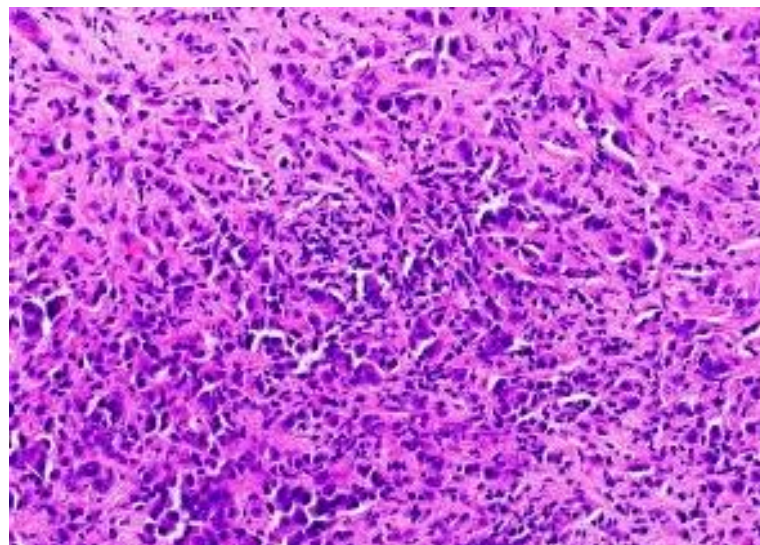


PD-L1 IHC with the 22C3 assay

Locally
advanced
TNBC



Metastatic
TNBC to
chest wall



A word on atezolizumab and the SP142 assay in advanced/metastatic TNBC

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^a metastases to the liver are often non-inflamed

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- When considering metastatic sites to test for PD-L1, it is preferable to prioritize extrahepatic^a sites or the primary tumor, if available
- PD-L1 testing should not be performed on fine needle aspirate cell-block specimens or decalcified bone

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Measures of Genomic Instability in Advanced/Metastatic TNBC

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^a TMB-high \geq 10 mutations per megabase

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~5% breast cancers

Result of genomic instability

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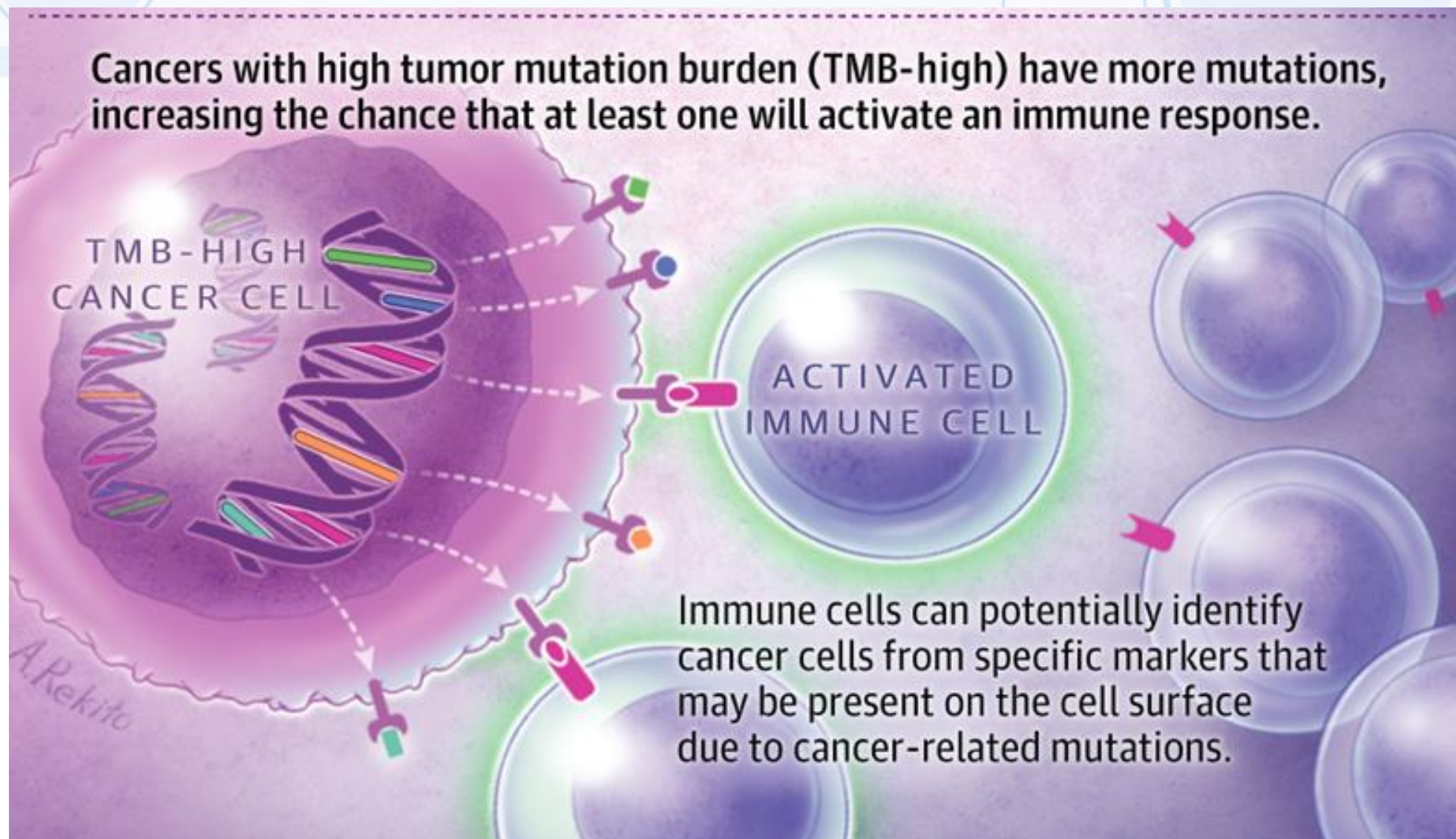
- Microsatellite instability (MSI)-high status

~2% breast cancers

- Mismatch repair protein deficiency (dMMR)

Causes of genomic instability

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Immune Checkpoint Inhibition for TMB-high, MSI-high, and dMMR Solid Tumors

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- Single-agent pembrolizumab is approved for patients with TMB-high, MSI-high or dMMR advanced solid tumors, irrespective of histology
- First *tumor agnostic* approval of immunotherapy (ie, approval for advanced solid tumors of any primary site)
- Accelerated approval for single-agent dostarlimab for dMMR advanced solid tumors, irrespective of histology (2021)

Assays to Determine TMB, MSI, and MMR Status

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 - The FoundationOneCDx assay (Foundation Medicine, Inc.) is FDA-approved as a companion diagnostic assay for TMB
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- dMMR is determined by mismatch repair protein IHC
 - The Ventana MMR RxDx Panel was granted FDA approval as a companion diagnostic to determine MMR status for use of dostarlimab

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Biomarkers for Immunotherapy in Early-stage TNBC

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- None at this time!

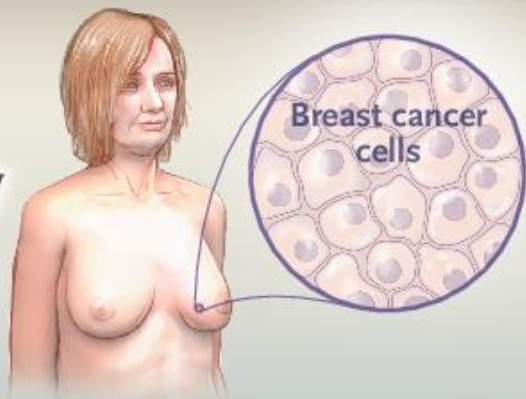
Pembrolizumab for Triple-Negative Breast Cancer

RANDOMIZED, DOUBLE-BLIND, PHASE 3 TRIAL

1174

Patients

with previously
untreated
triple-negative
breast cancer



Neoadjuvant

Pembrolizumab

+ chemotherapy,

followed by surgery
and adjuvant pembrolizumab
~~+ chemotherapy~~

(N=784)

Neoadjuvant

Placebo

+ chemotherapy,

followed by surgery
and adjuvant placebo
~~+ chemotherapy~~

(N=390)

**Pathological complete
response at time of surgery**

64.8%

51.2%

Difference, 13.6 percentage points; 95% CI, 5.4–21.8; P<0.001

N Engl J Med 2020; 382:810-21, visual abstract

Higher %pCR, event-free survival, and overall survival
IRRESPECTIVE of PD-L1 status

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Tumor infiltrative lymphocytes (TILs)

- An emerging prognostic biomarker in early breast cancer

Tumor infiltrative lymphocytes (TILs)

- Stromal TILs in primary tumors is prognostic in early TNBC and HER2+ breast cancer

Tumor infiltrative lymphocytes (TILs)

- Stromal TILs in primary tumors is prognostic in early TNBC and HER2+ breast cancer
- TILs have not been validated to direct clinical decision-making for chemotherapy or immunotherapy

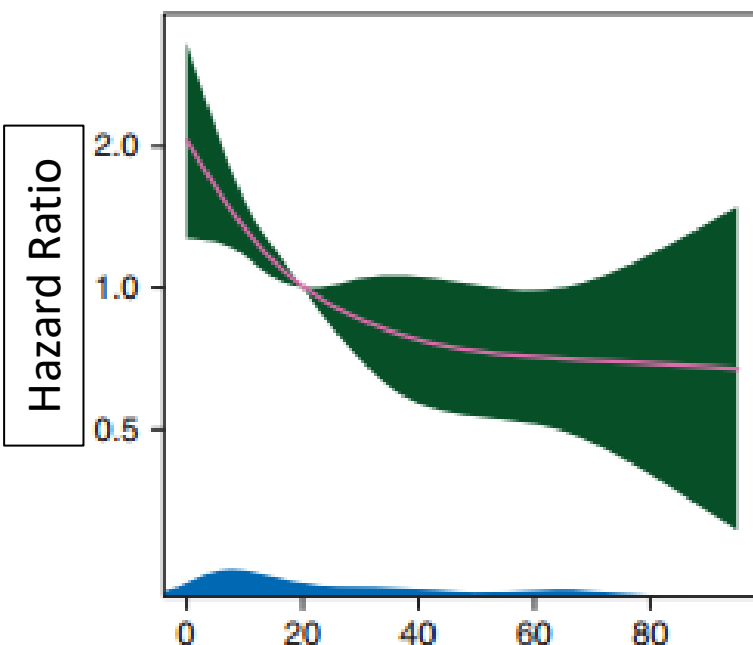
Clinical validity of tumor-infiltrating lymphocytes analysis in patients with triple-negative breast cancer

G. Pruneri^{1,6,†*}, A. Vingiani^{2,6,†}, V. Bagnardi^{3,7}, N. Rotmensch³, A. De Rose², A. Palazzo⁴, A. M. Colleoni⁴, A. Goldhirsch^{5,8} & G. Viale^{2,6}

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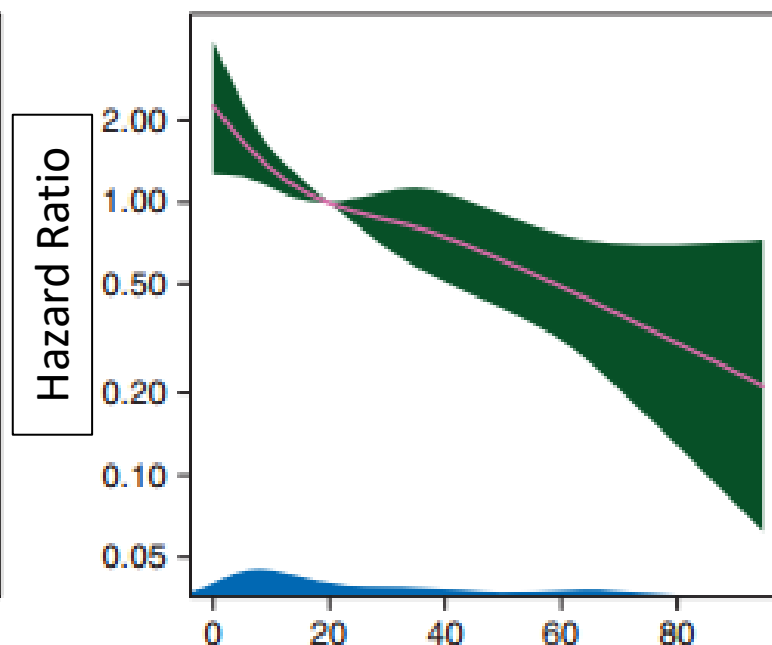
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Disease free survival



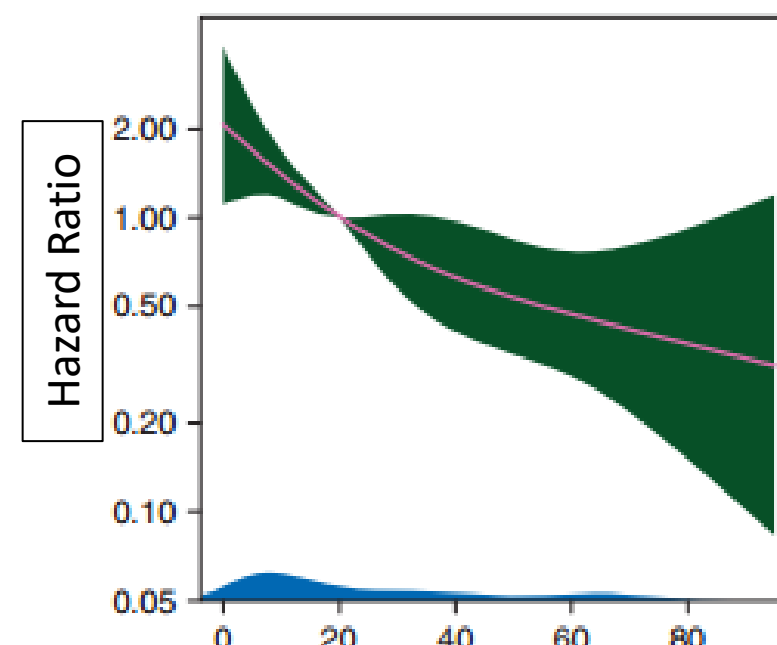
Increasing TILs →

Distant-disease free survival



Increasing TILs →

Overall survival



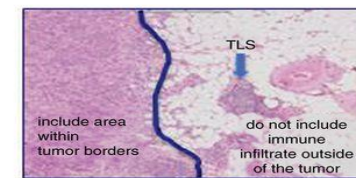
Increasing TILs →

Standardized approach for TILs evaluation in breast cancer.

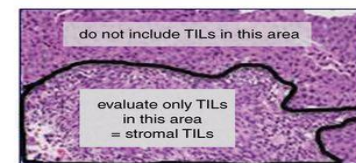


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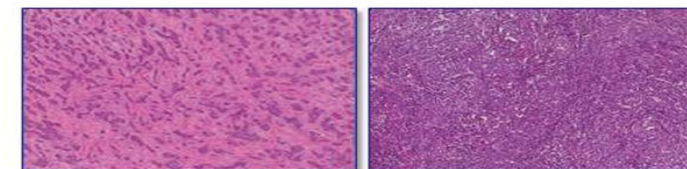
Step 1: Select tumor area



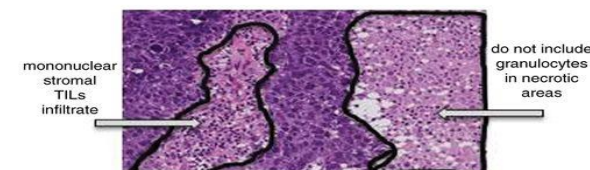
Step 2: Define stromal area



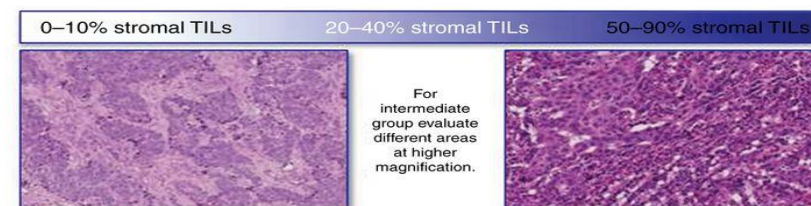
Step 3: Scan at low magnification



Step 4: Determine type of inflammatory infiltrate



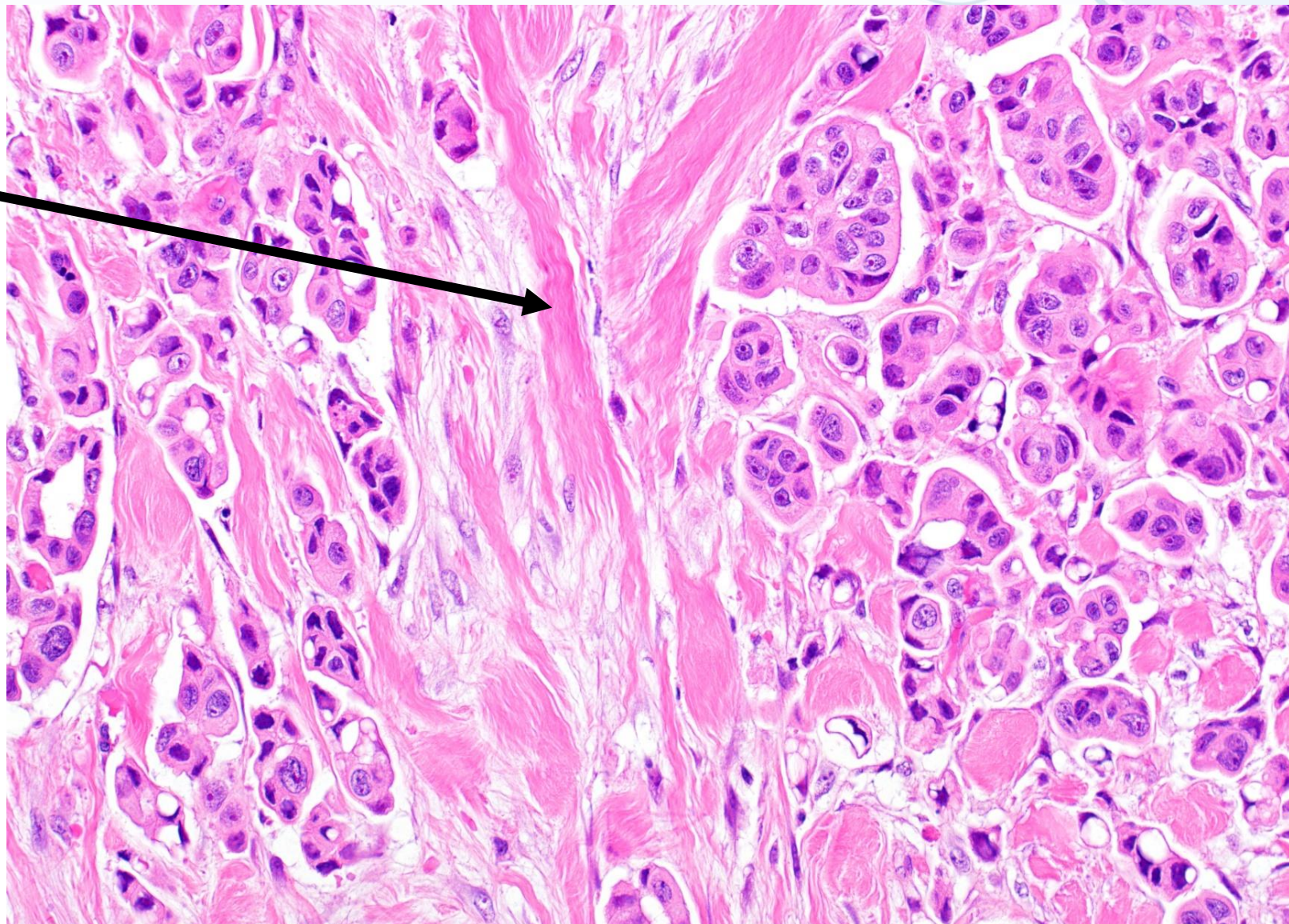
Step 5: Assess the percentage of stromal TILs (examples of percentages shown in figure 4)



R. Salgado et al. Ann Oncol 2015;26:259-271

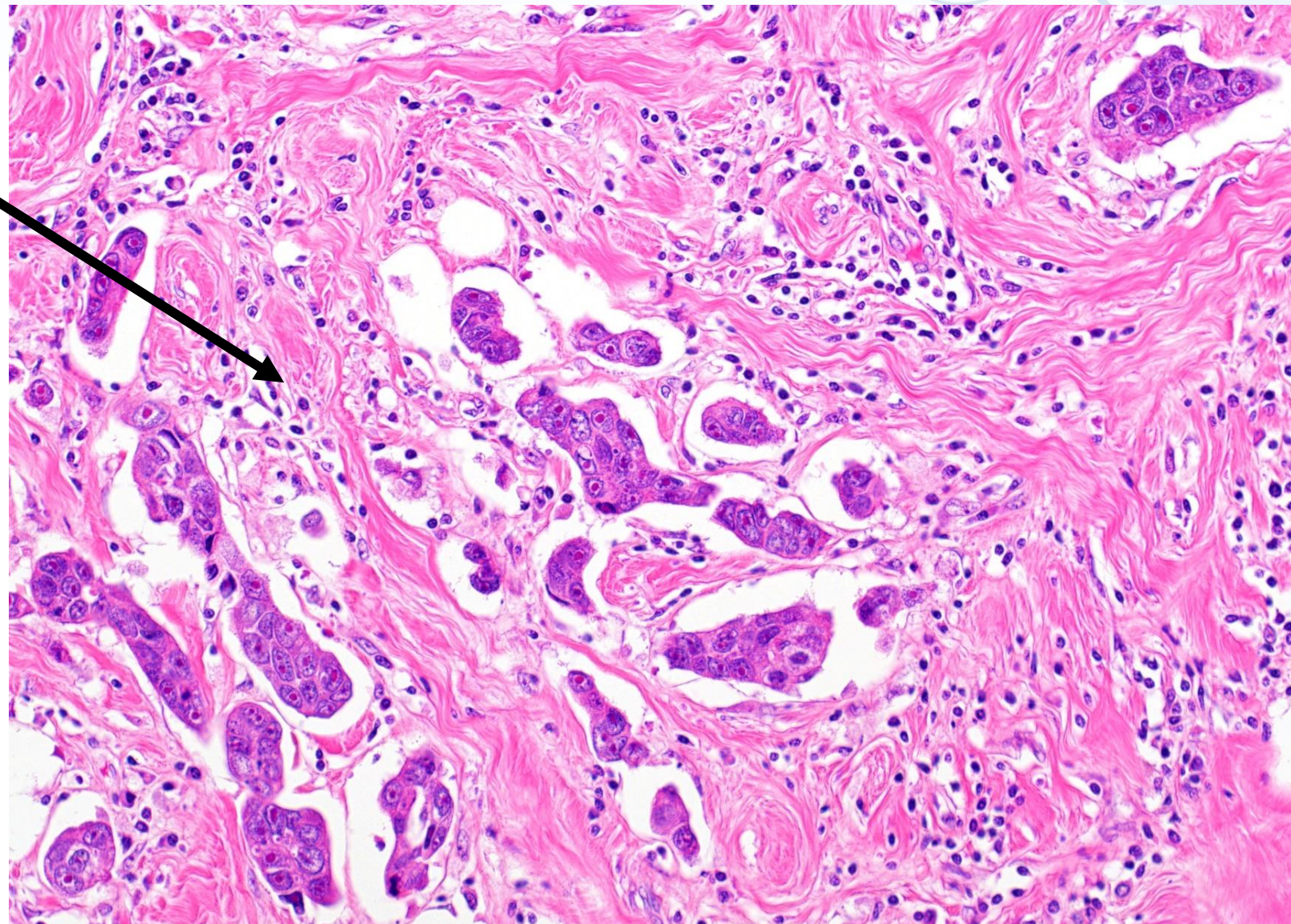
Micropapillary breast carcinoma with minimal (1%) TILs

NO Lymphocytes in
cancer stromal space



Micropapillary breast carcinoma with moderate (30%) TILs

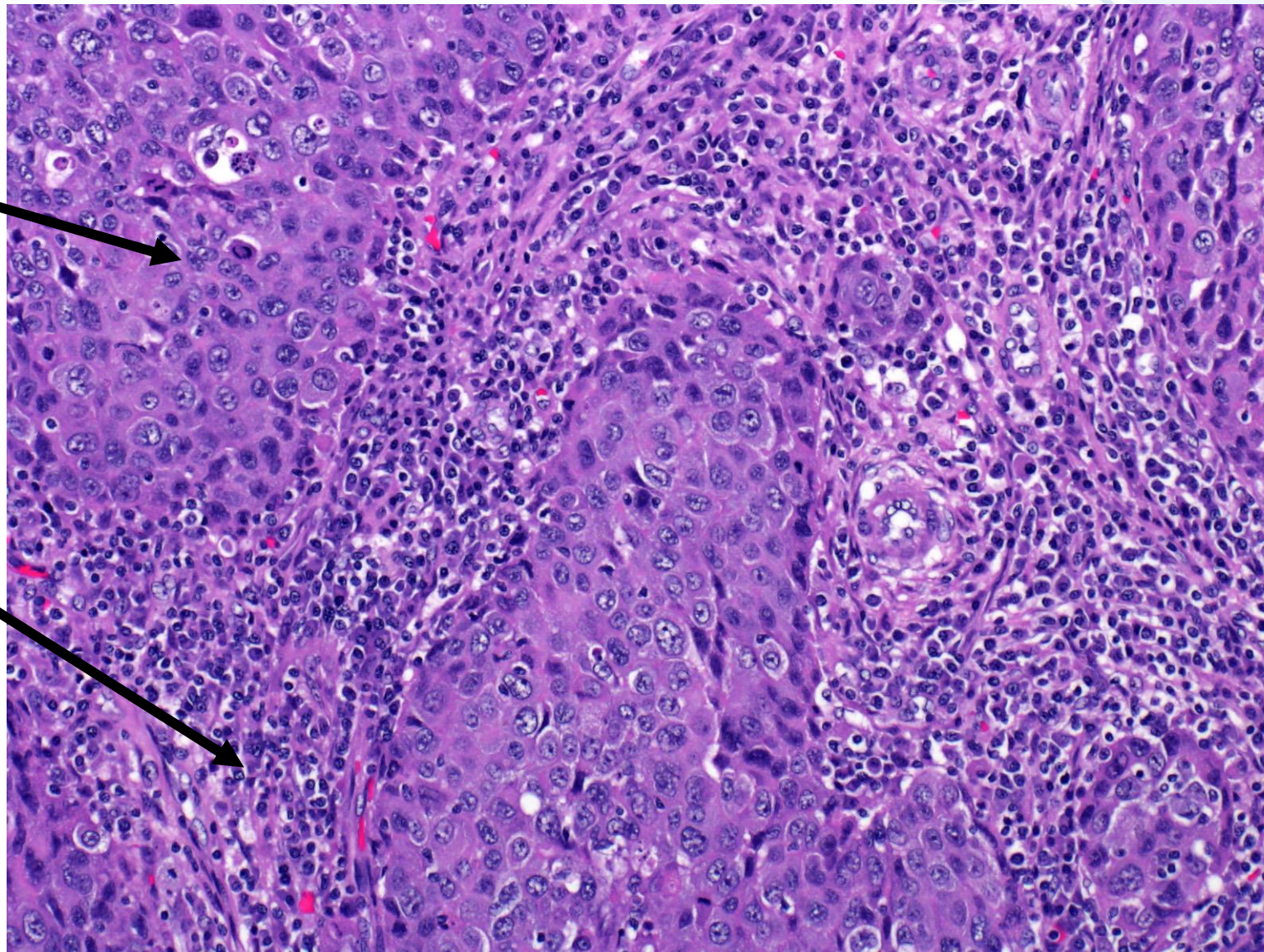
Lymphocytes in cancer
stromal space



HER2+ carcinoma with brisk (90%) TILs

Cancer cell
nest

Lymphocytes in cancer
stromal space

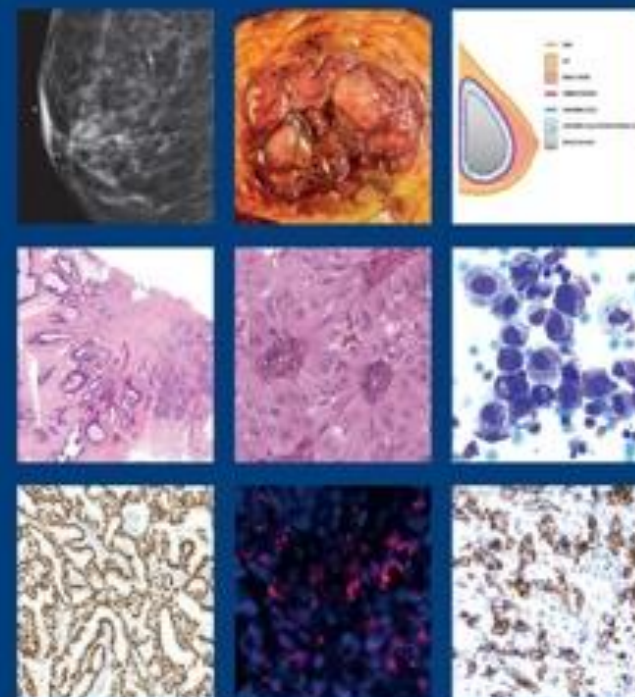


TILs in the WHO Classification of Breast Tumours, 5th Ed. (2019)

WHO Classification of Tumours • 5th Edition

Breast Tumours

Edited by the WHO Classification of Tumours Editorial Board



TILs in the WHO Classification of Breast Tumours, 5th Ed. (2019)

- TILs recognized as a prognostic biomarker in early stage TNBC
- But, there is still a need for society-level guidelines and training



Summary

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- PD-L1 and TMB are predictive biomarkers for immunotherapy in advanced/metastatic TNBC

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- Currently no predictive immune biomarkers for early-stage TNBC

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- PD-L1 and TMB are predictive biomarkers for immunotherapy in advanced/metastatic TNBC
- Currently no predictive immune biomarkers for early-stage TNBC
- TILs are a favorable prognostic biomarker in early TNBC, but are not ready for clinical decision making