Memorial Sloan Kettering Cancer Center

The International Academy of Pathology
Hong Kong Division

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Triple Negative Breast Carcinoma
Focus on Metaplastic Carcinoma

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Overview

- General Comments
- Focus on Metaplastic carcinoma
  - Morphology
  - Genomic alterations
  - Treatment and Prognosis

Triple negative breast carcinoma defined by exclusion

TNBC include all breast carcinoma that are:

- ER negative (<1% nuclear staining)
- PR negative (<1% nuclear staining)
- HER2 negative
  - HER2 IHC 0, 0+ or 1+
  - HER2 IHC 2+ (equivocal) *and* HER2 FISH not amplified

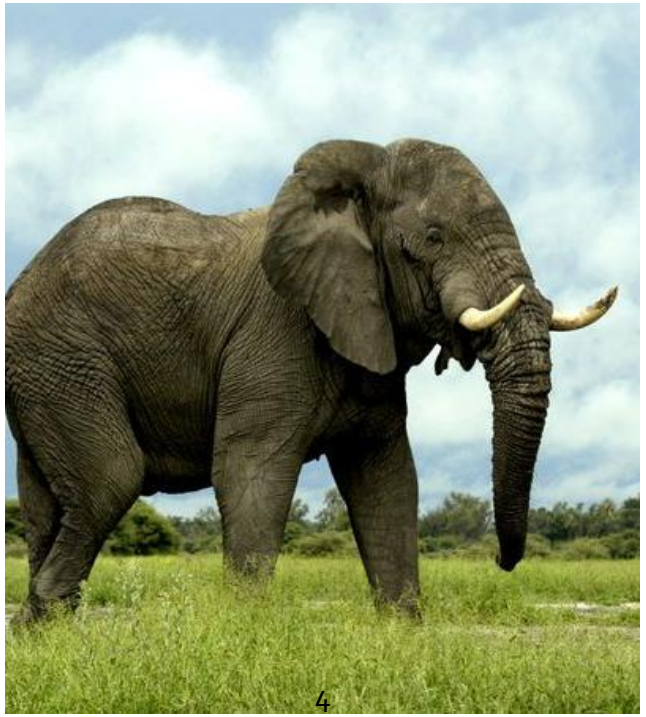
TNBC Defined by exclusion→not a specific entity

All these animals are

- Not carnivores
- Not insects
- Not fish… All very different









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ER, PR, HER2 status and histologic subtypes

Usually ER/PR(+) HER2(-)

- Invasive Lobular
- Tubular carcinoma
- Encapsulated papillary carcinoma
- Mucinous Carcinoma
- Invasive micropapillary
- Solid papillary, invasive
- Others

May be ER/PR(-) HER2(+)

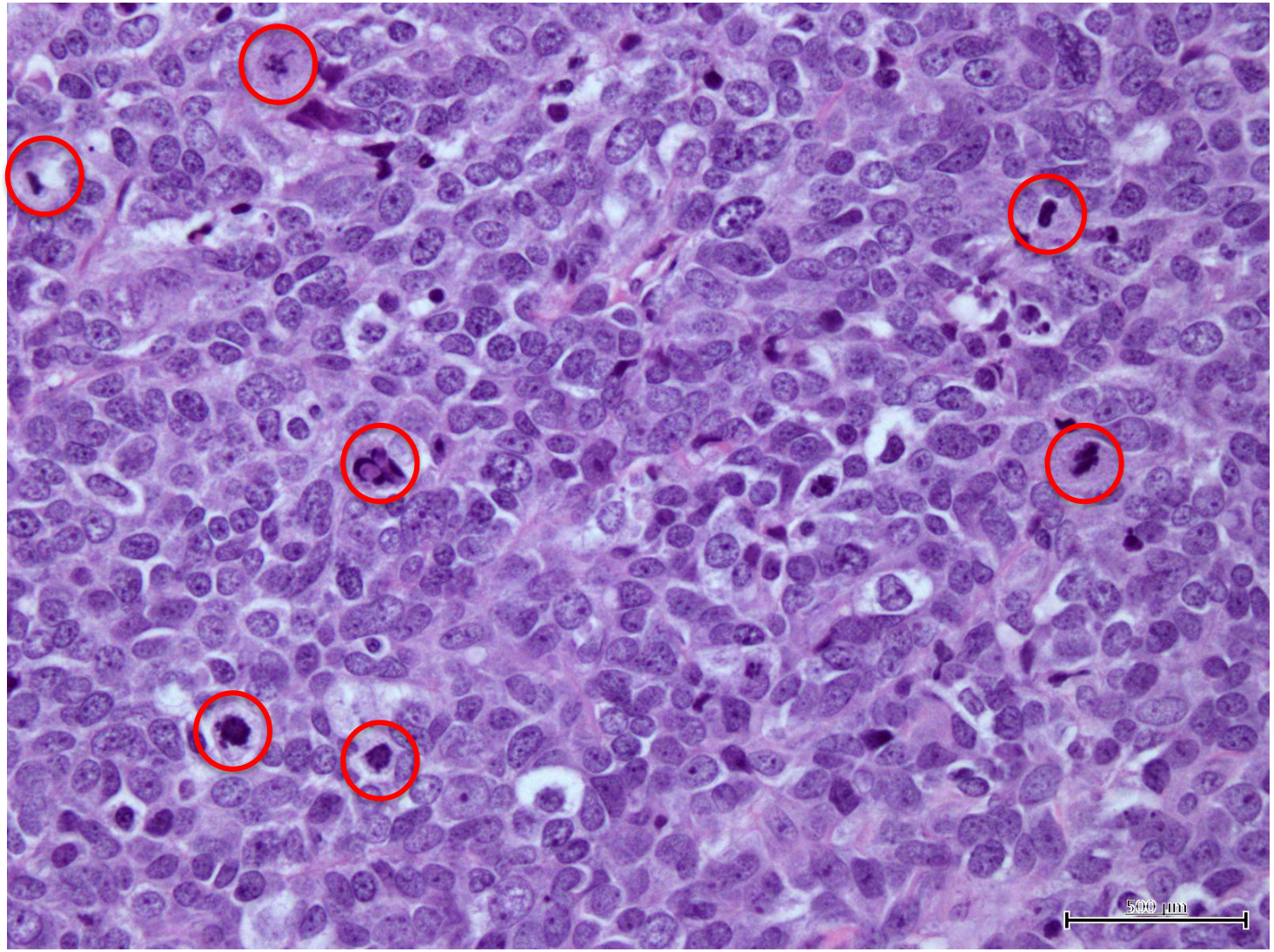
- IBC-NST, High grade
- Invasive apocrine High NG
- Others

Usually Triple Negative (TNBC)

- IBC-NST, high grade
- Metaplastic carcinoma
- Adenoid cystic carcinoma
- Secretory carcinoma (case)
- Invasive Apocrine
- Tall cell carcinoma with reverse polarity
- Acinic cell-like
- Mucoepidermoid
- Mucinous cystadenocarcinoma
- …

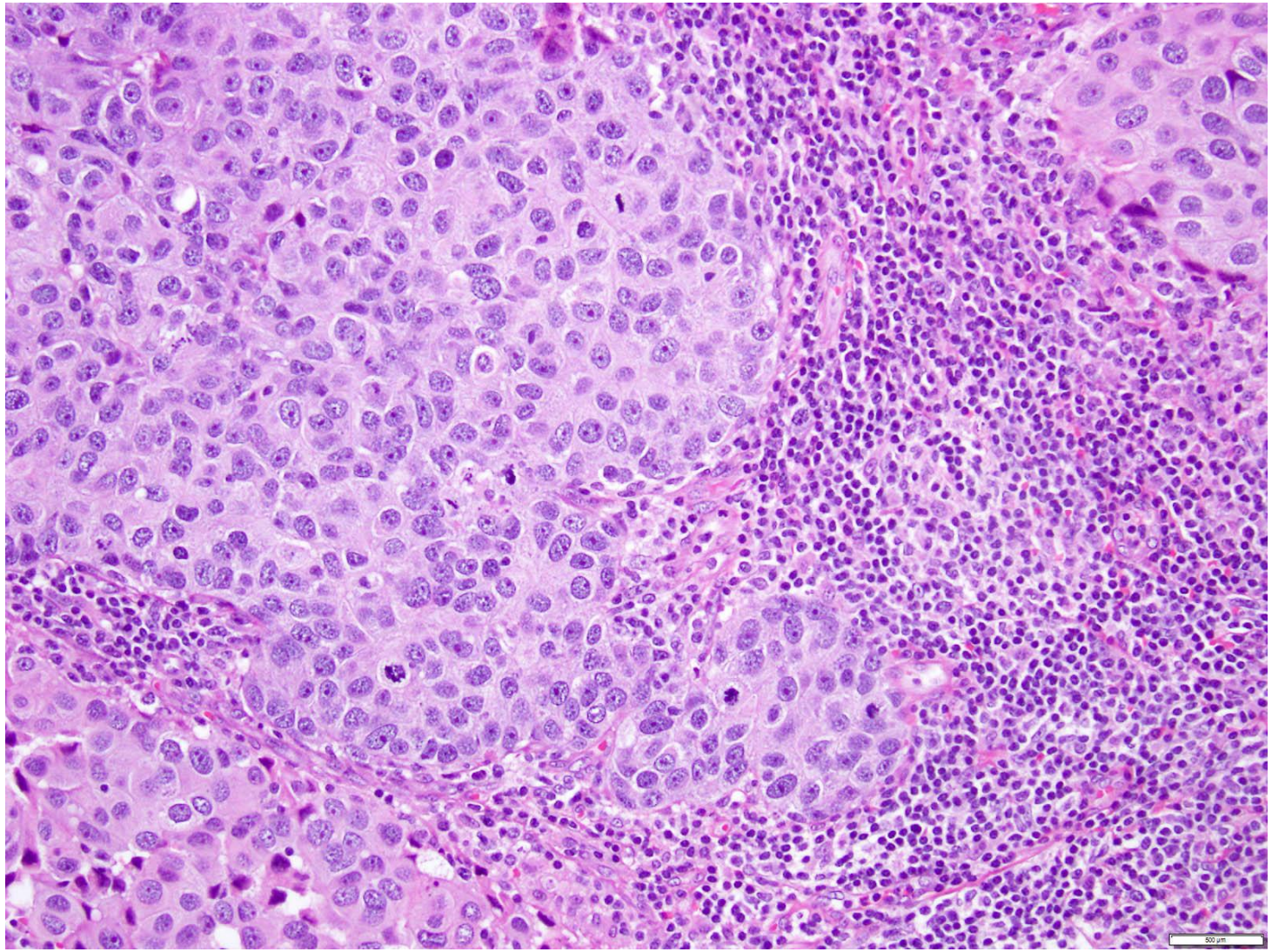
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Invasive carcinoma of no special type – most common TNBC



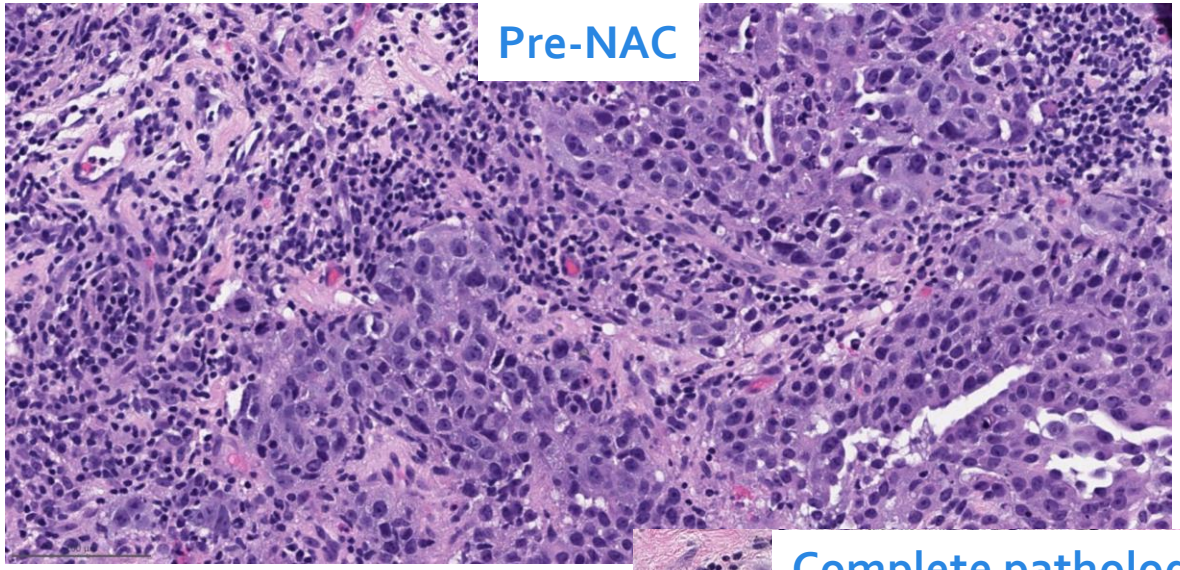
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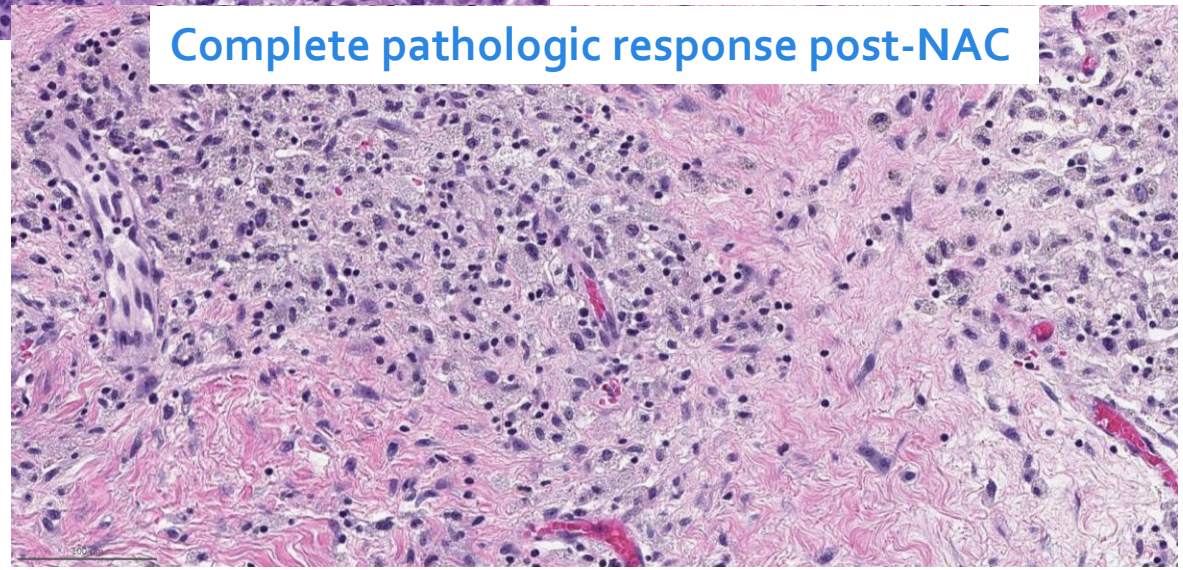
Tumor infiltrating lymphocytes (TILs)



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Increased TILs predicts response to neoadjuvant chemotherapy

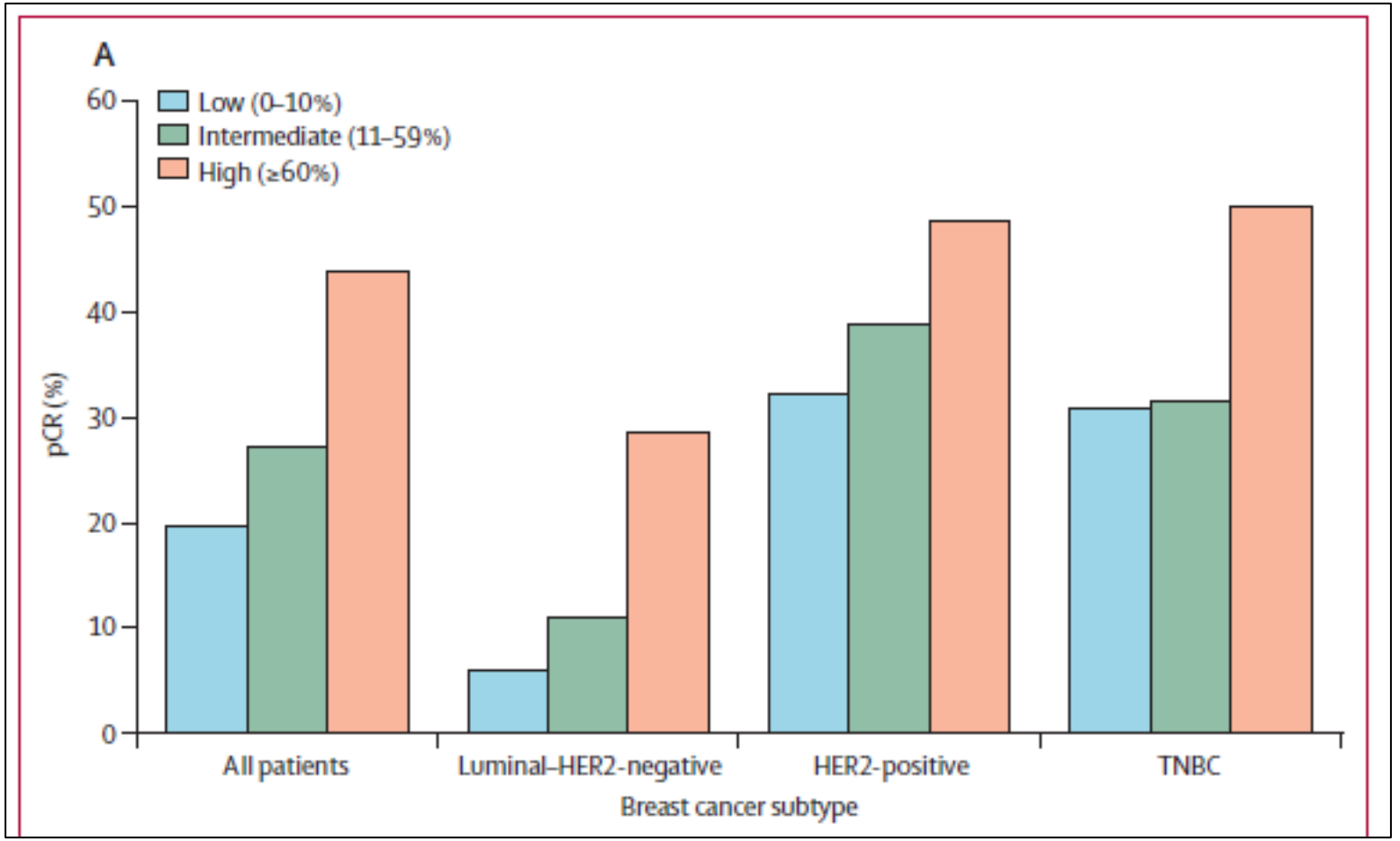




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Increased TIL predicts response to NAC in all subtypes

A pooled analysis of 3771 pts from 6 randomized trials shows higher pCR rates in BC with high TILs



Denkert C et al *Lancet Oncol*. 2018; 19:40-50.

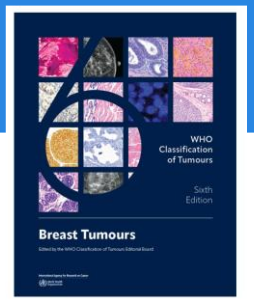
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Metaplastic carcinoma

different morphologic subtypes

Metaplastic Carcinoma



Metaplasia = transformation from one cell type into another

(from Greek verb μεταπλασειν = to transform, change)

Heterogeneous group of Invasive Breast Carcinomas characterized by differentiation of the neoplastic epithelium towards spindle, squamous cells and/or mesenchymal elements including, but not restricted to chondroid and osseous cells

Diagnosis requires evidence of epithelial differentiation by histopathological (+/-epithelial foci, +/- DCIS) and/ or immunohistochemical analysis

Clinical presentation and imaging findings

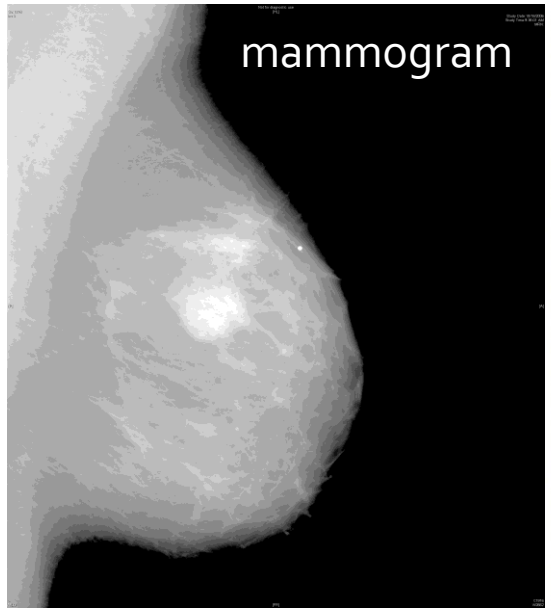
- Rare, 0.2–1% of all IBCs in women
- median age 63 years
- Clinical features similar to TNBC

  more likely to present at an advanced stage
- Palpable mass in ~85% cases
- Mass on U/S (100%) or

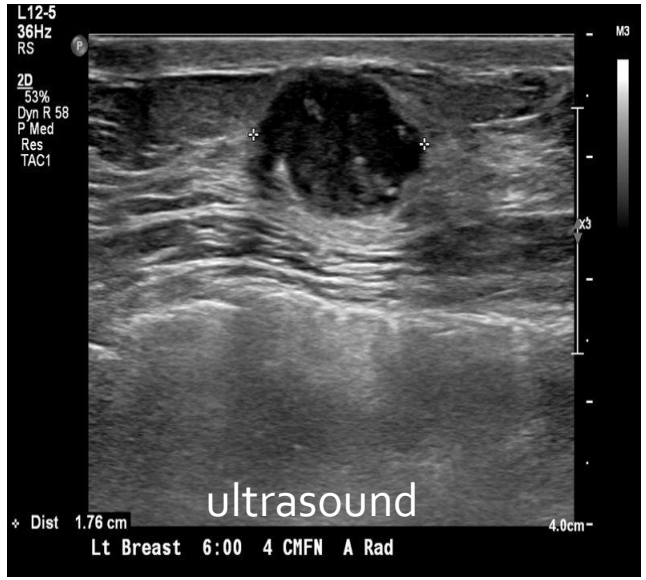
  mammography (78%)
- MicroCa^{2+} uncommon (17%)

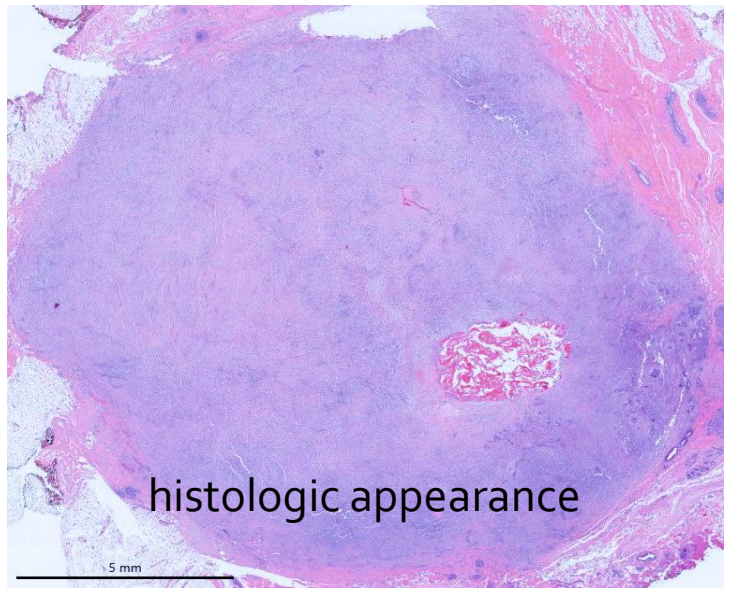
  - In DCIS

  - in osseous differentiation









Metaplastic Breast Carcinoma

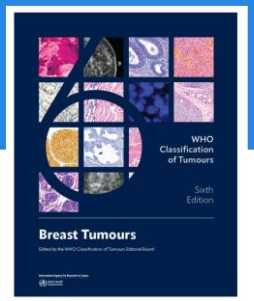
No minimum % of metaplastic component is required except:

Pure SCC: ≥90% squamous cells; Fibromatosis-like metaplastic carcinoma:>90% bland spindle cells

Any metaplastic component ≥10% should be mentioned in Dx

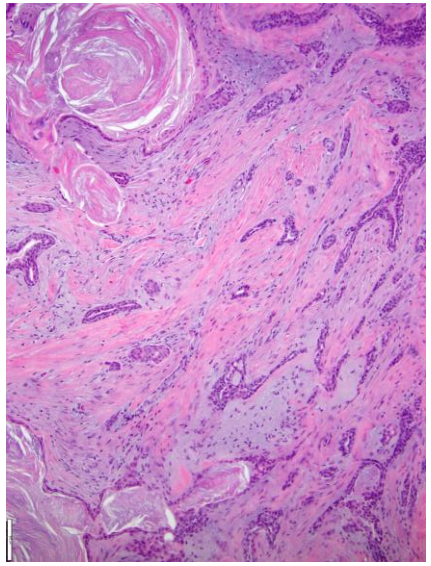
Epithelial metaplasia	Mesenchymal metaplasia
Squamous Pure: >90% tumor composed of squamous cells	**Chondroid, osteoid, rhabdoid, etc**
	Spindle cell
Mixed metaplastic carcinoma **(multiple morphologic components, i.e.: spindle, squamous, NST)** **Carcinomas with ≥3 metaplastic components are most aggressive** McCart-Reed et al. J Pathol. 2019 Feb;247(2):214-227	
Low grade adenosquamous	**Fibromatosis-like** >90% tumor composed of bland spindle cells

Metaplastic breast carcinoma

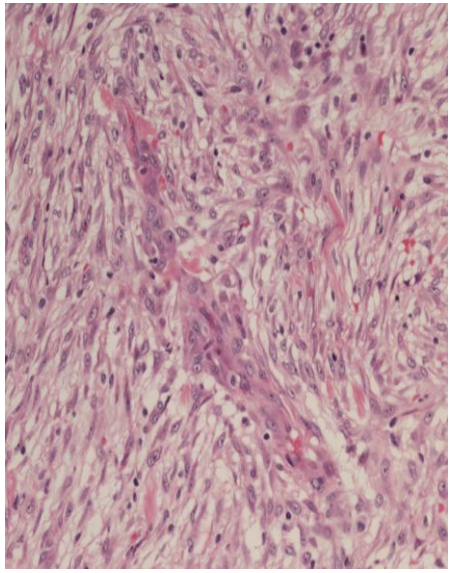


"Low" grade

Low grade adenosquamous

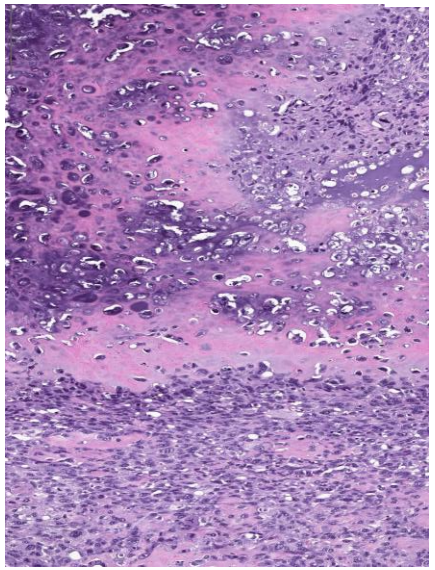


Fibromatosis-like

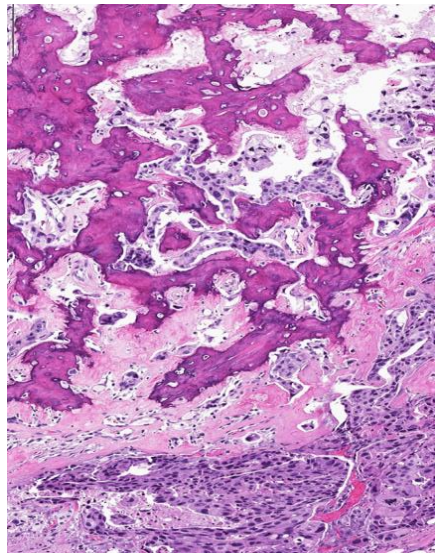


High grade

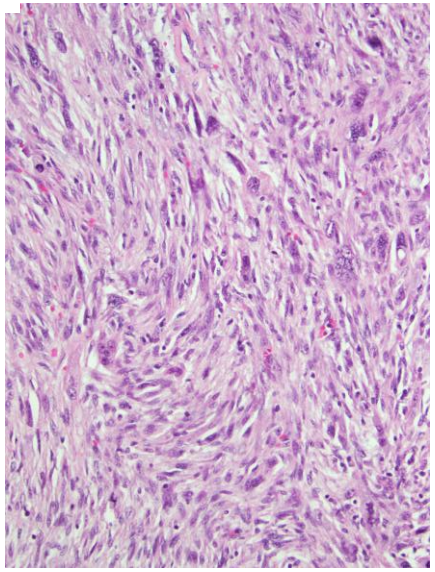
Myxochondroid

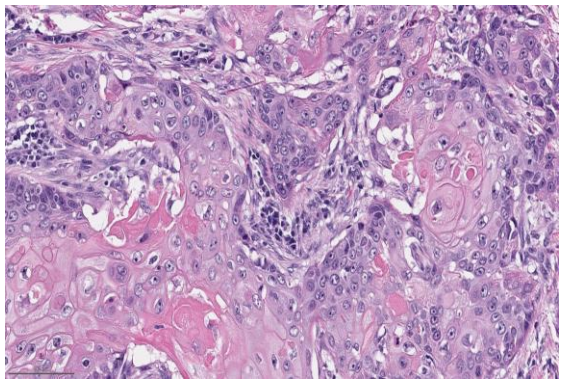


Osteosarcomatous

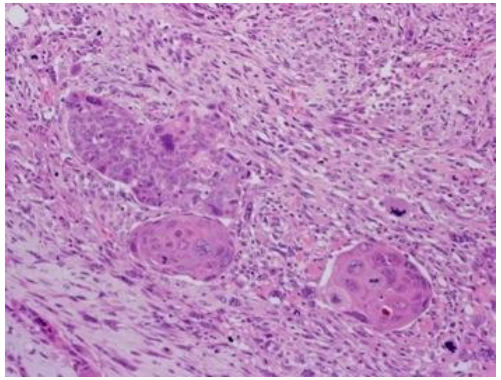


Spindle cell





Squamous



Mixed

Metaplastic Carcinoma – molecular alterations

- Genetic studies support a monoclonal origin of the various components
- No pathognomonic mutations or gene fusions have been identified
- Many molecular alterations have been reported

  TP53, *RB1*, chromatin-remodeling genes (*ARID1A* and *KMT2C*)

    TP53 mutations less frequent in spindle cell carcinoma and in low grade adenosquamous carcinoma than in other metaplastic carcinoma

  PI3K (*PIK3CA*, *PIK3R1*, and *PTEN*) pathway

  MAPK (*NF1*, *KRAS*, and *NRAS*) pathway

  WNT (*FAT1* and *CCN6* [*WISP3*]) pathway

  TERT promoter mutations identified in some fibromatosis-like metaplastic carcinoma

  EGFR overexpression/ mutations in squamous and spindle cell carcinoma, but no EGFR activating mutations

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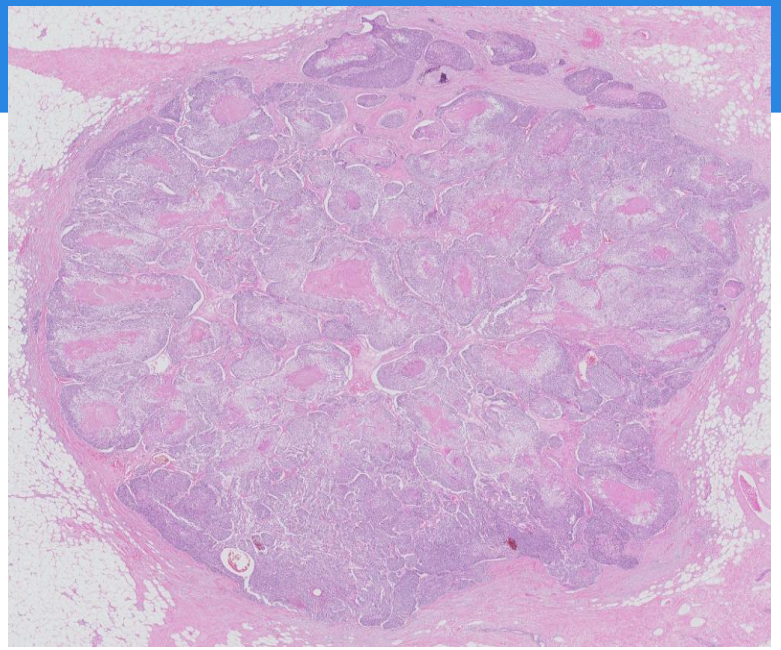
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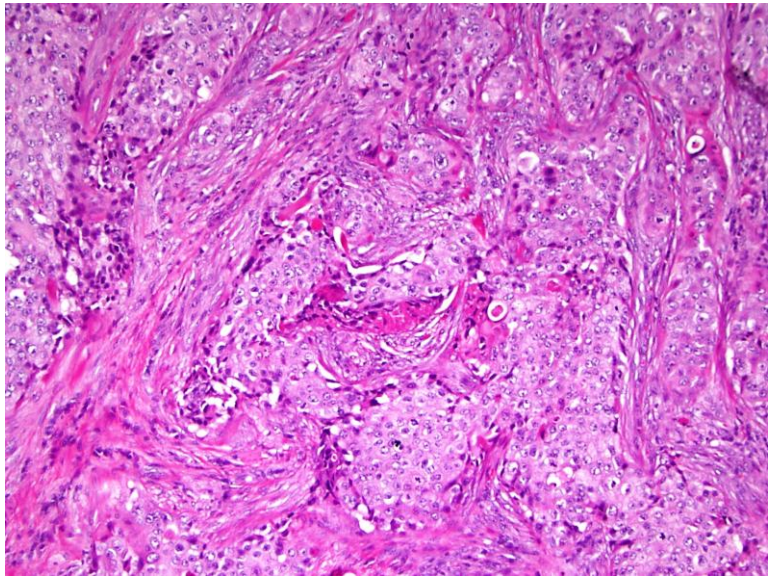
Metaplastic Carcinoma
Squamous cell carcinoma

Metaplastic squamous cell carcinoma (MSqCC)

- Pure MSqCC (>90% squamous) may present as a cystic mass
- Squamous cells: varying degrees of nuclear atypia, variable squamous differentiation
- A conspicuous stromal reaction and prominent inflammatory infiltrate are common
- MSqCC may be pure, or admixed with other carcinoma, usually spindle cell carcinoma, or IBC-NST.

- Diagnosis of primary breast MSqCC: need to rule out primary cutaneous SCC and metastatic SCC from other sites (e.g. lung and cervix)





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Squamous cell carcinoma (SCC): cutaneous vs mammary origin

Similar morphology and IHC

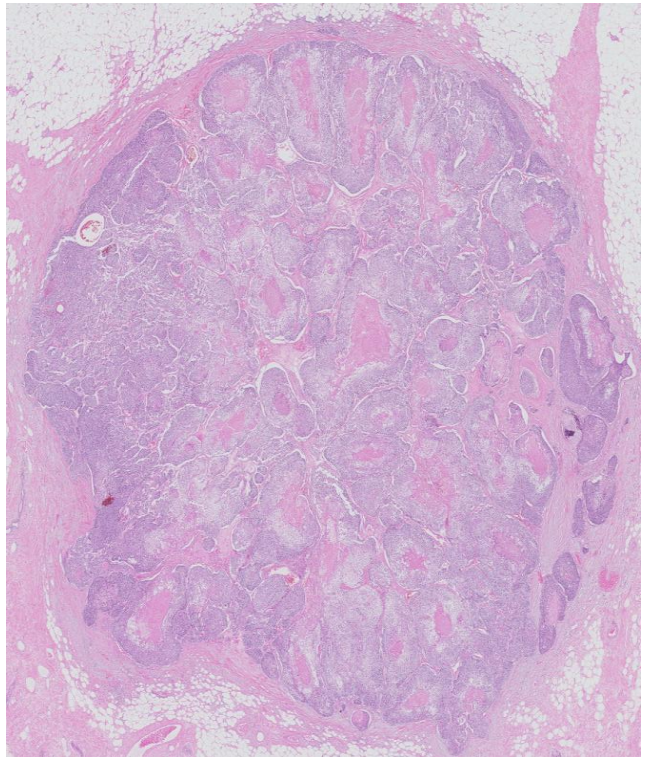
- CK5/6, p63/ p40, GATA3: usually diffusely positive
- ER and PR usually negative

Favor mammary origin

- Mass located predominantly in the breast
- DCIS and/ or invasive non-squamous component

Favor cutaneous origin

- History of an enlarging skin nodule/ lesion
- Carcinoma connects with epidermis/ SCC in situ in the epidermis
  skin ulceration common → limits assessment of SCC in situ
- *UV mutational signature (frequent C→T, and G→A substitutions)*



Differential DX Metaplastic breast SCC and Cutaneous SCC

Feature	Metaplastic breast SCC	Primary cutaneous SCC	P value
Age	64 y	63.5 y	
Size (cm)	35 5 (2.4-6)	1 cm (0.5-2)	
GATA3	10/12 (83%)	16/18 (89%)	NS
TRPS1	10/13 (77%)	6/18 (33%)	P=0.029
Sox10	4/13 (31%)	0/18 (0%)	P=0.0227
CK7	10/12 (83%)	3/18 (16%)	0.0005
PIK3CA/PIK3R1	11/14 (79%)	2/13 (15%)	P = 0.0040
NOTCH1	0/14 (0)	4/13 (31%)	P = 0.0407
Tumor Mutational Burden	2.6 m/Mb (2.5-4.0)	19.5 m/Mb (6.8-34.7)	P = 0.0002
UV-Mutation signature	0/13 (0)	9/13 (69%)	P = 0.0005

Rutland CD, Kingsley LG, Zdravkovic S, Vohra P, Chen YY, Krings G, Bean GR. Immunohistochemical and Molecular Features Distinguishing Metaplastic Breast Carcinoma With Squamous Differentiation From Cutaneous Squamous Cell Carcinoma. Am J Surg Pathol. 2026 Nov 1;50(11):1372-1387. PMID: 42682150

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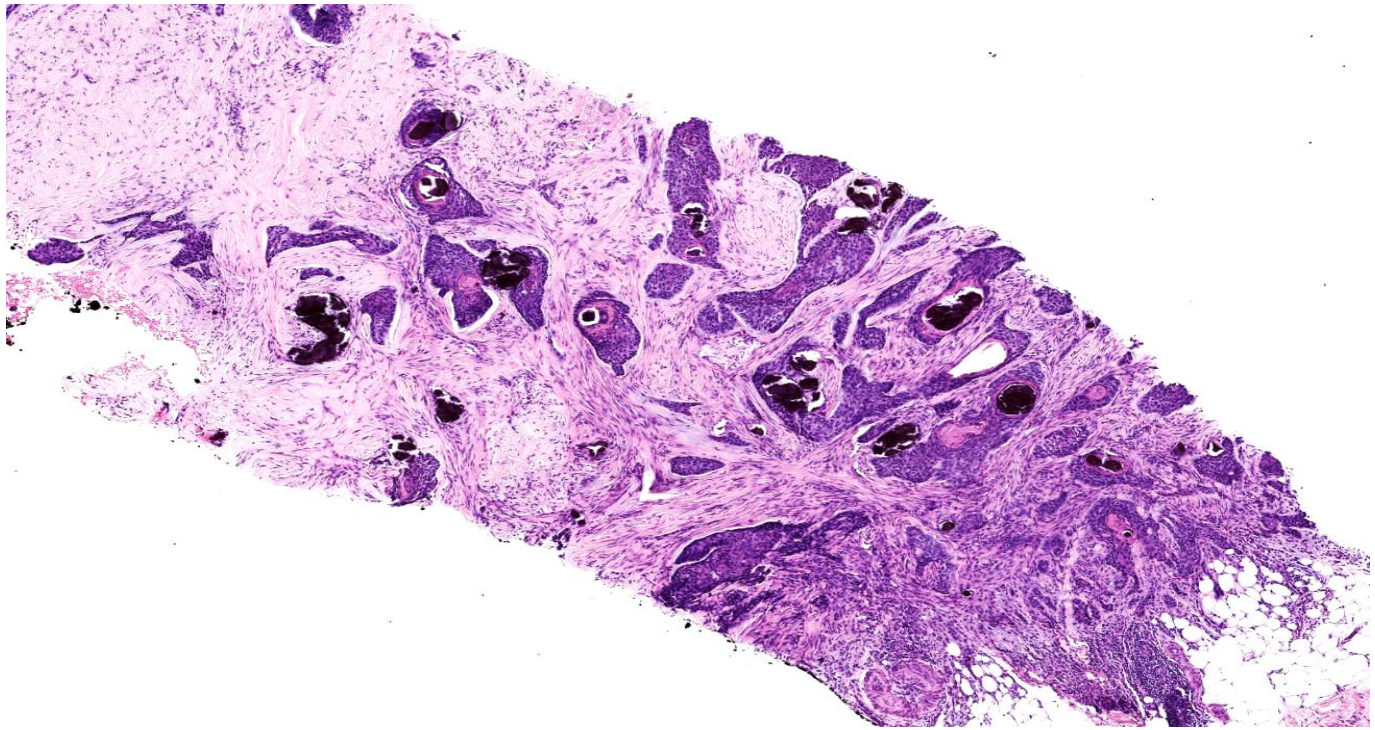
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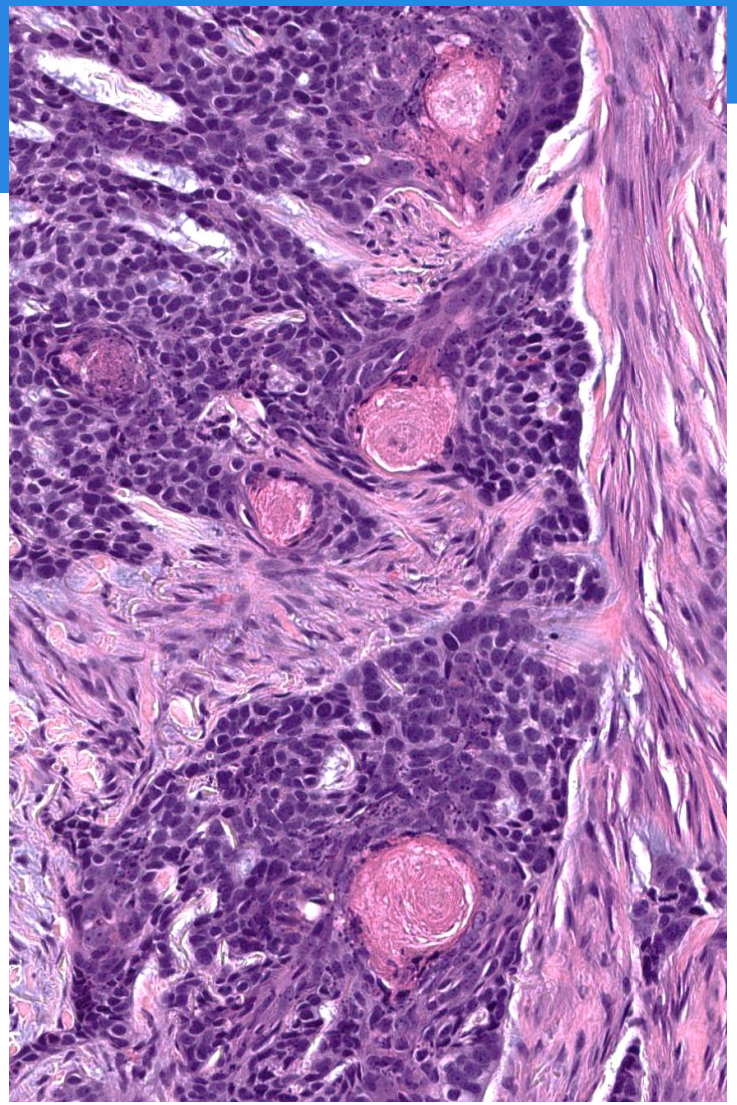
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Case: 50 yo Female
CNB left breast, medial (original dx)

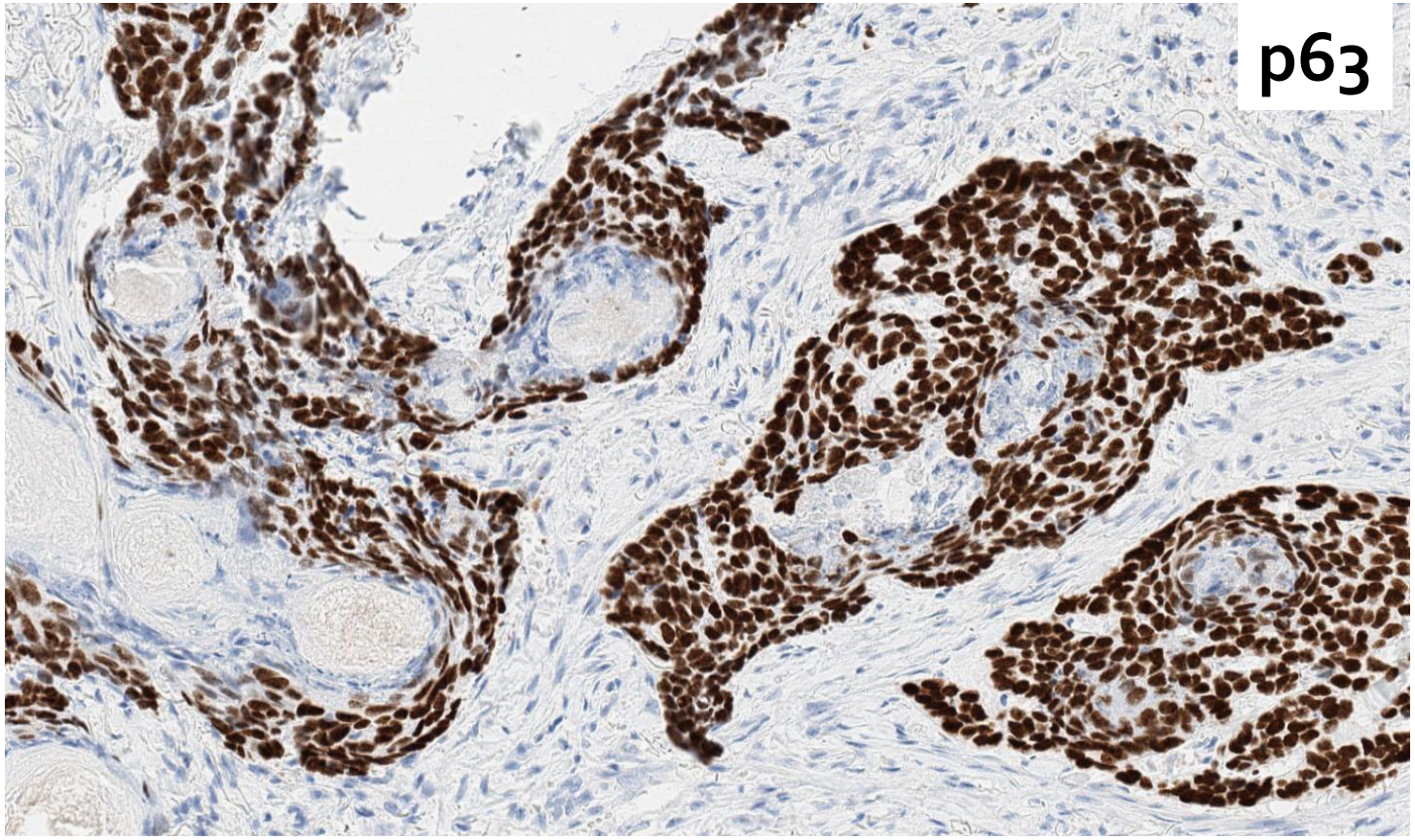
A. Breast, left, medial, core needle biopsy:
Invasive carcinoma with squamous features, at least 12 mm in linear extent,
Nottingham grade 2-3/3 (tubule 3, pleomorphism 2-3 mitoses 2).
Tumor infiltrating lymphocytes: Minimal.
Tumor biomarker:
Estrogen receptor: Negative (0)
Progesterone receptor: Negative (0)
HER-2/neu (by immunohistochemistry): Equivocal (2+)
Ki-67 proliferation index: 30-35%

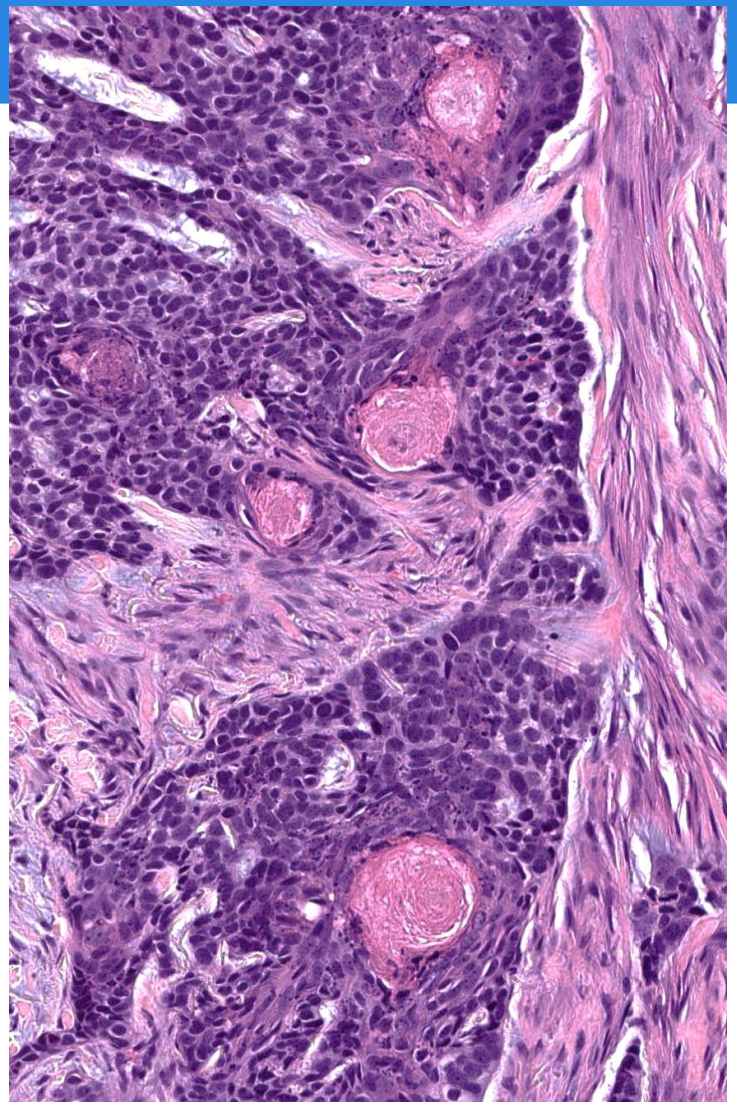




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p63(+) strong and diffuse





Usually primary MSqCC of the breast yields somewhat heterogeneous staining for p63

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NGS analysis (MSK-IMPACT)

Final DX: UV-signature supports primary cutaneous carcinoma

Note: Abundance of G>A, C>T, GG>AA and CC>TT transition mutations is suggestive of UV exposure induced mutagenesis

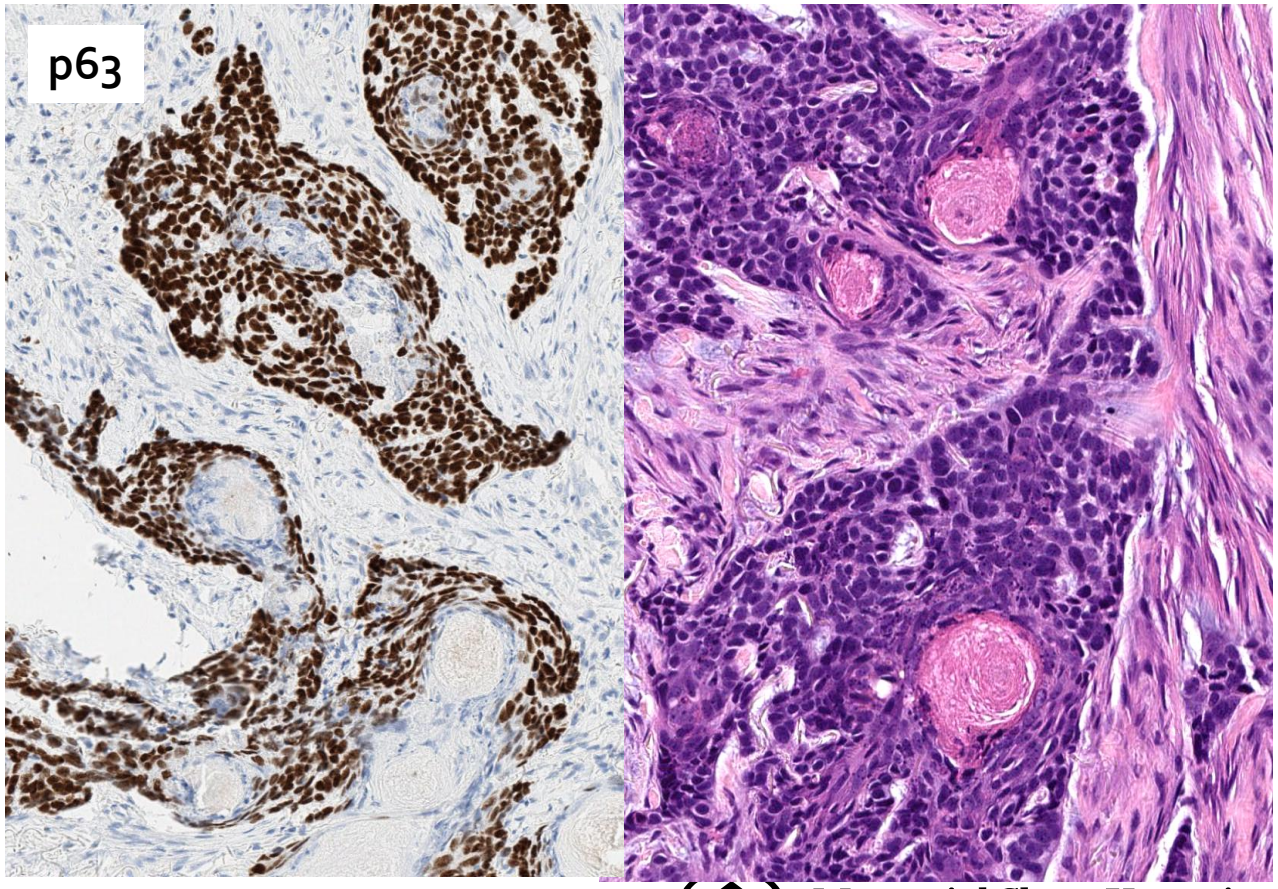
Summary: 79 mutations, no copy number alterations, 1 structural variant detected.

TUMOR MUTATION BURDEN: The estimated tumor mutation burden (TMB) for this sample is 65.1 mutations per megabase (mt/Mb).

POSITIVE FOR THE FOLLOWING SOMATIC ALTERATIONS:

1. TP53 (NM_000546) exon10 p.A347V (c.1040_1041delinsTT)
2. TP53 (NM_000546) exon6 p.R213* (c.637C>T)
3. TP53 (NM_000546) exon8 p.E285K (c.853G>A)
4. ABL1 (NM_005157) exon8 p.R457C (c.1369C>T)
5. ABL1 (NM_005157) exon11 p.P579S (c.1735C>T)
6. ABL1 (NM_005157) exon11 p.P650L (c.1949C>T)
7. ACVR1 (NM_001111067) exon5 p.T172I (c.515C>T)
8. AKT3 (NM_005465) exon6 p.D188N (c.562G>A)
9. ALK (NM_004304) exon9 p.G558E (c.1673G>A)
10. AMER1 (NM_152424) exon2 p.A840V (c.2519_2520delinsTT)
11. ARID1A (NM_006015) exon6 p.Q743* (c.2227C>T)

12…79. mutations in different genes, mostly G>A or C>T

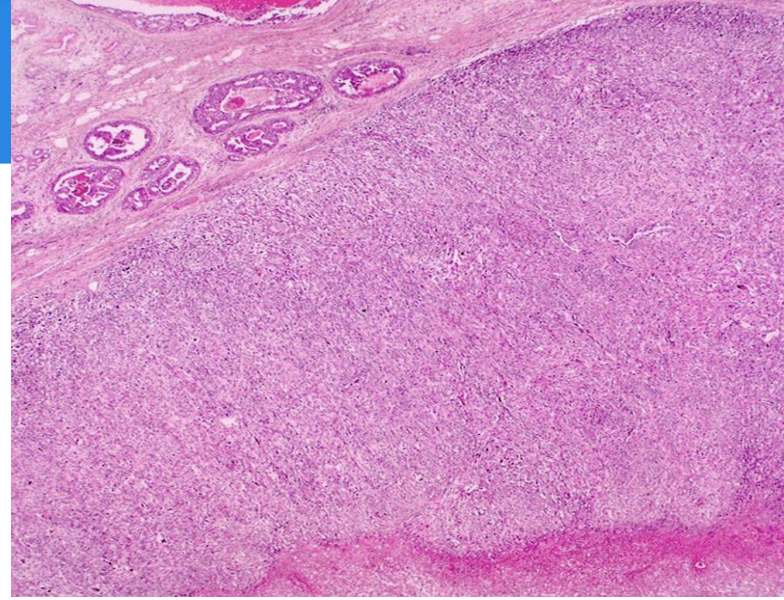


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Metaplastic Carcinoma
Spindle cell carcinoma

Metaplastic spindle cell carcinoma



- Spindle cells of moderate to high nuclear pleomorphism
- Fascicles, herringbone, storiform patterns etc
- +/- Inflammatory infiltrate
- +/- epithelioid and/or squamous foci
- The spindle cells have basal epithelial or myoepithelial differentiation (+/- staining for p63, CK5/6, CK14, calponin), possible overlap with malignant adenomyoepithelioma

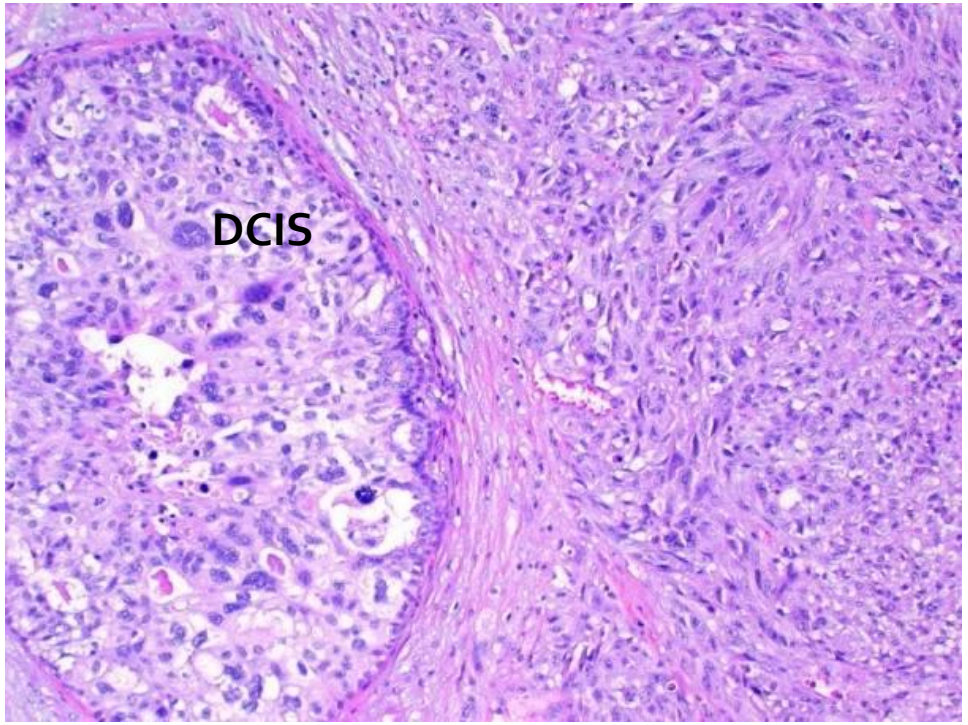
- *Fibromatosis-like metaplastic carcinoma (bland spindle cell proliferation) is a separate entity*

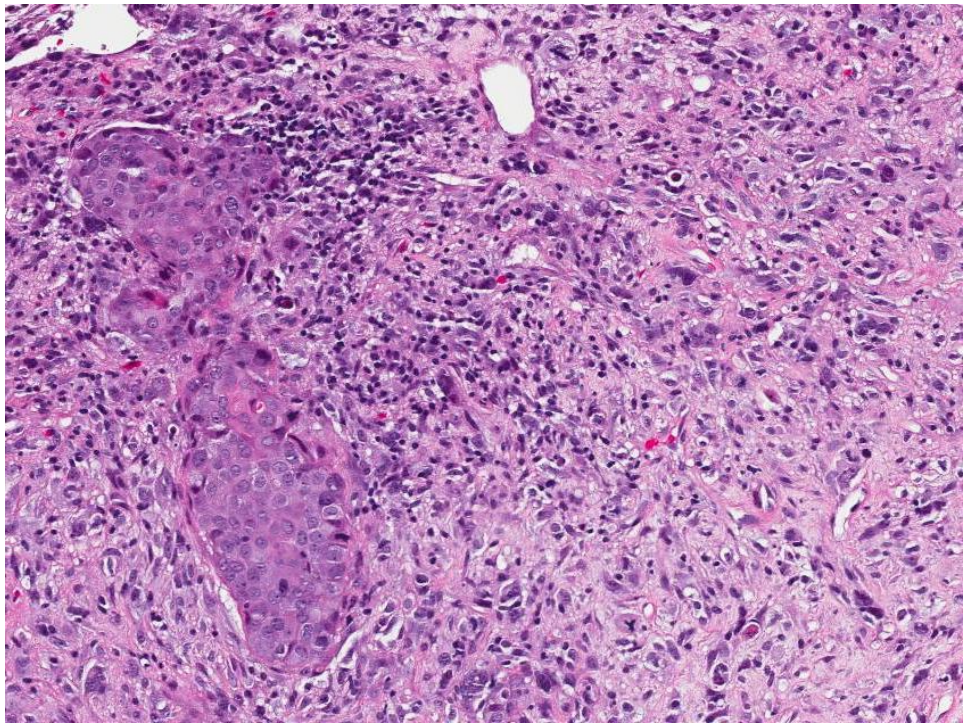
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Metaplastic Spindle Cell Carcinoma (MSpCC) Diagnostic Criteria

Diagnosis requires evidence of epithelial differentiation

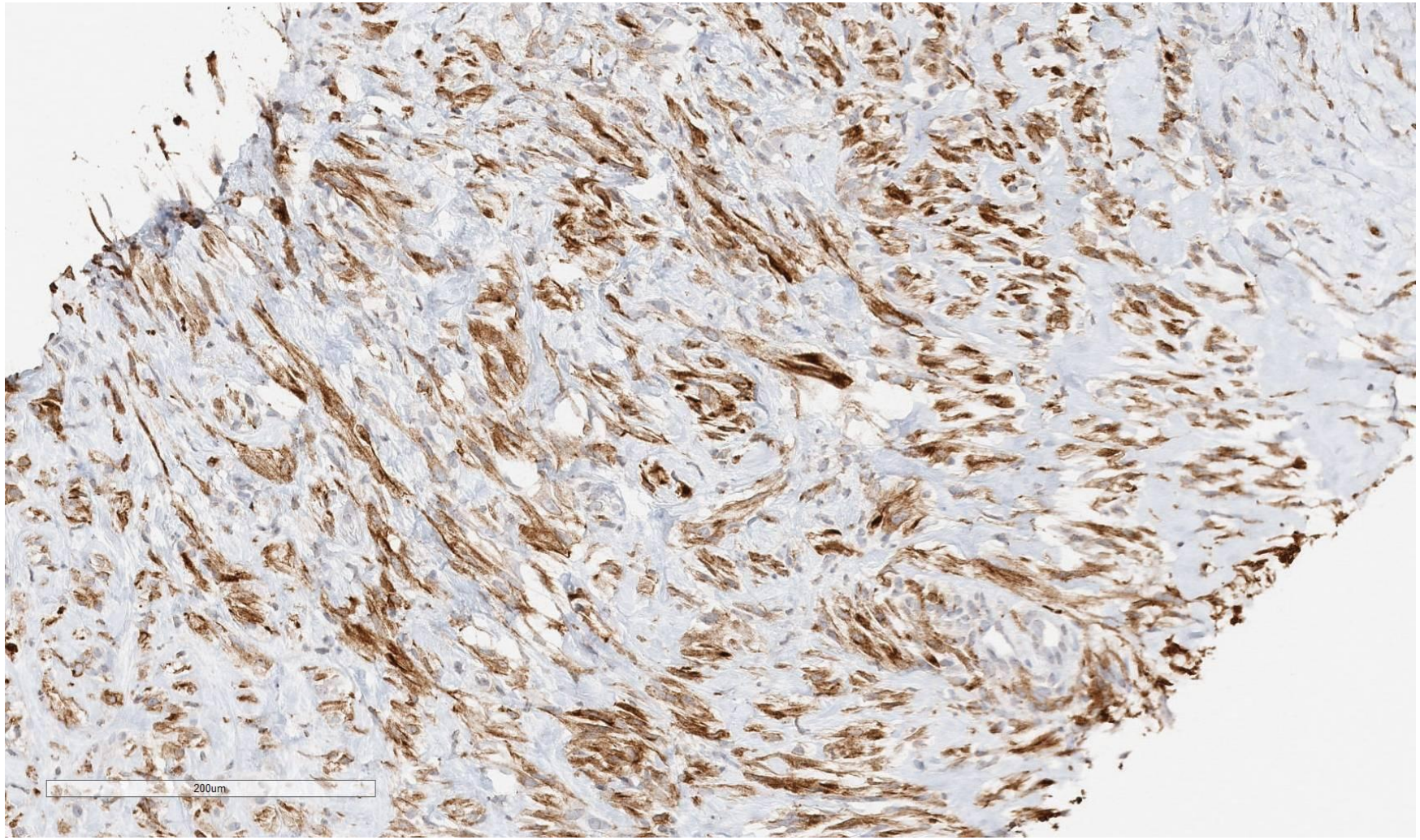
+/- IBC NST, +/-DCIS, or +/-cytokeratin (+)





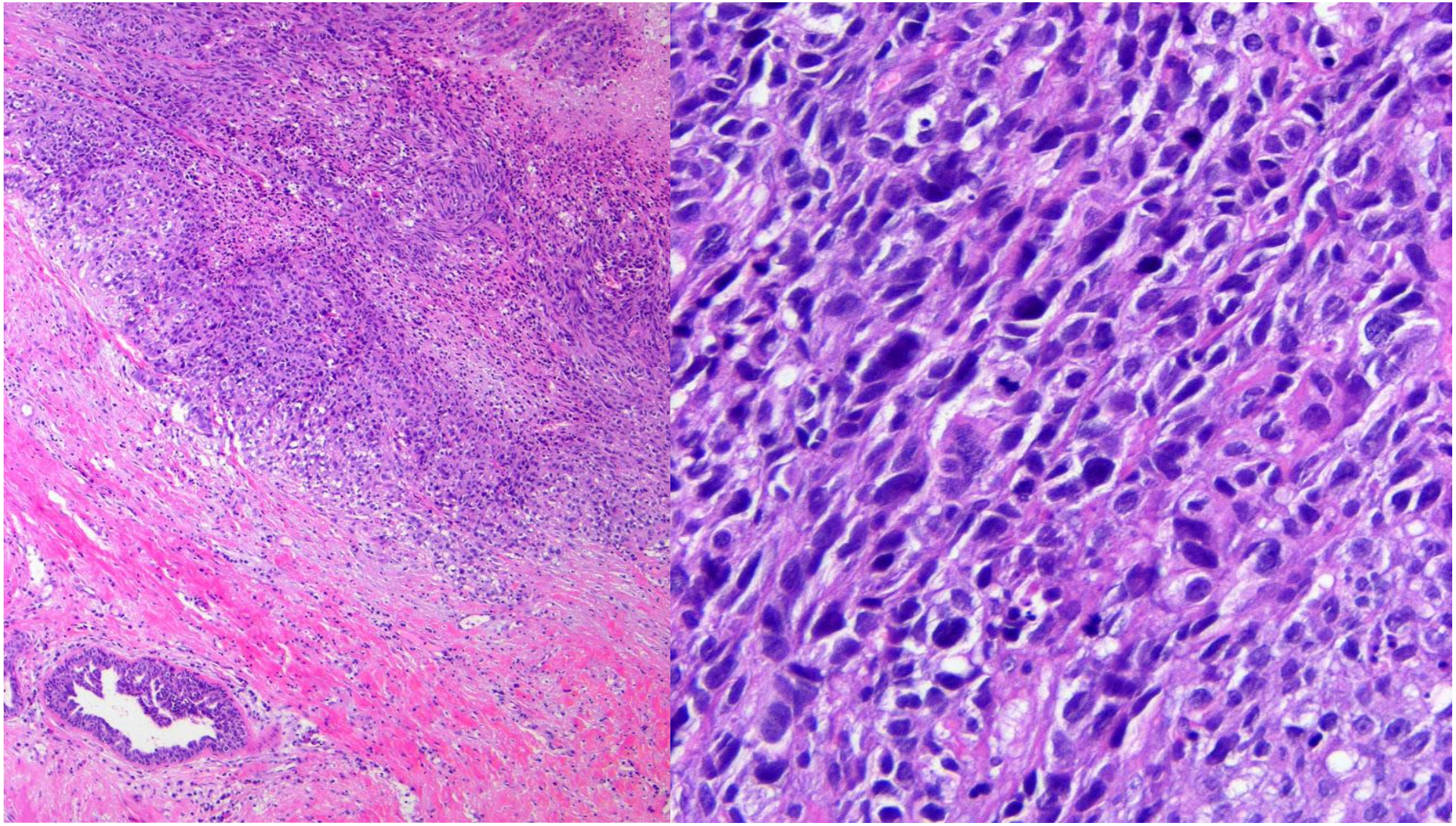
IHC evidence of epithelial differentiation

Use a panel of cytokeratins, especially high molecular weight cytokeratins



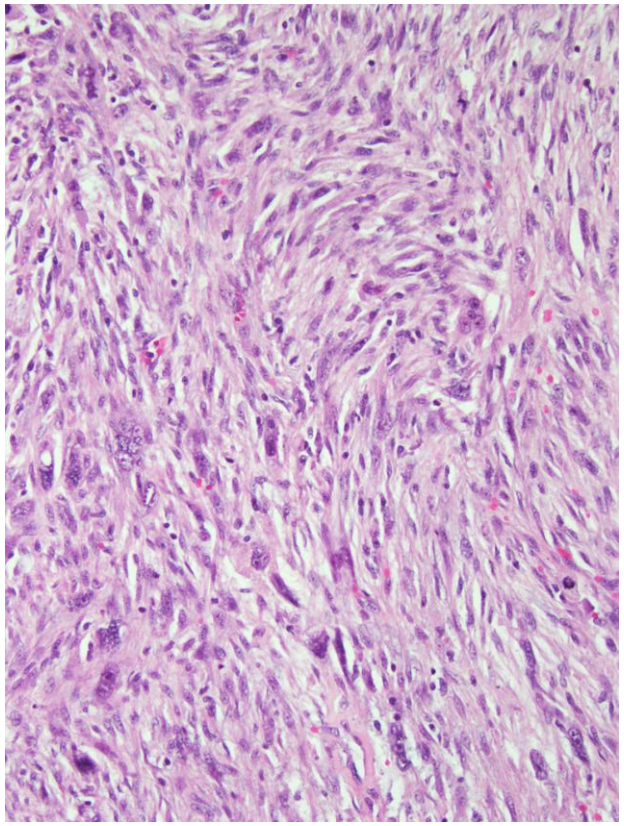
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Most MSpCC have sarcoma-like morphology

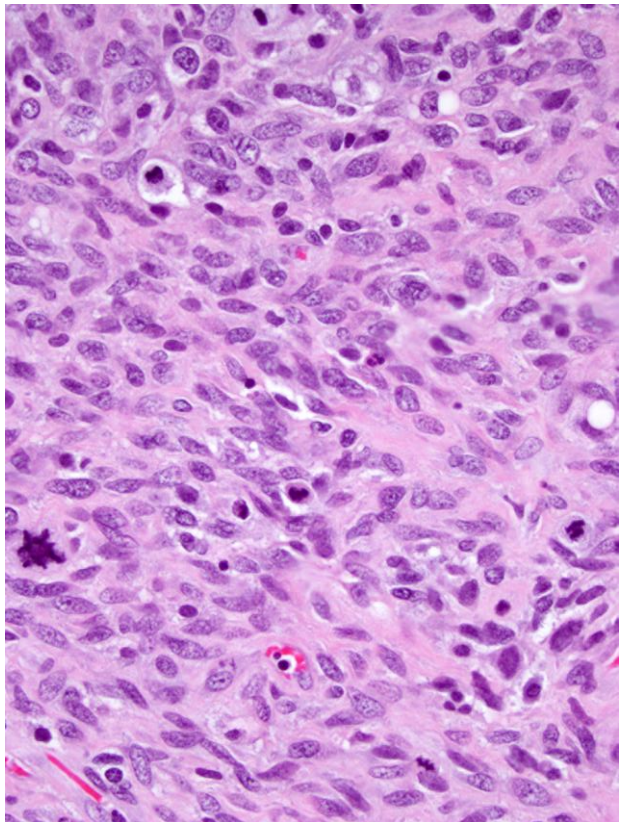


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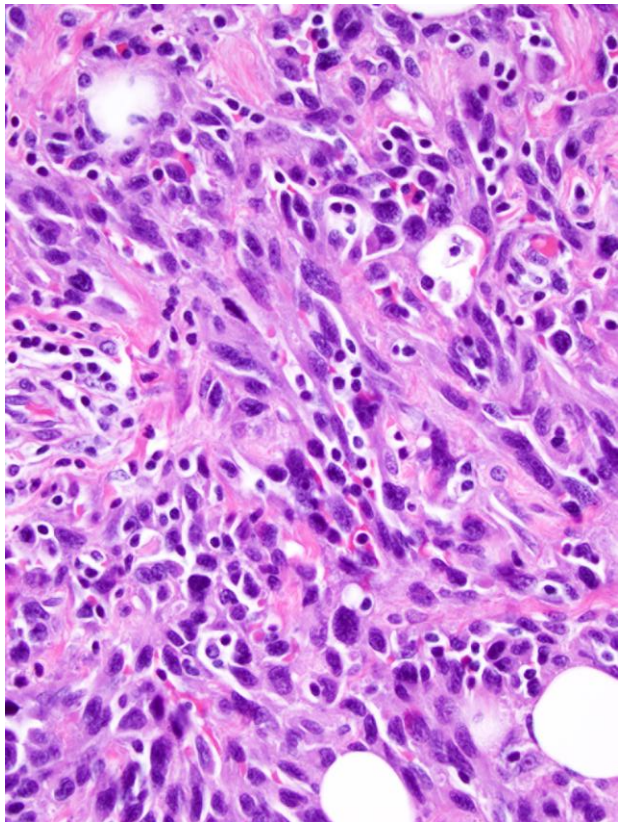
Differential diagnosis of metaplastic spindle cell carcinoma



Metaplastic
Spindle cell carcinoma



Malignant phyllodes tumor with sarcomatous overgrowth



Sarcoma

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MSpCC main Differential Dx : Malignant Phyllodes Tumor

- CKs and p63/p40 (myoepithelial/ squamous) often very focally and weakly positive
  - malignant PTs may show focal CK(+) and/or P63(+)
  - Ambiguous staining→ give a Differential Dx
  - Beware that (neo)adjuvant chemoTx for MSpCC, but not for malignant PT
- Rarely, no definitive DX can be rendered after review of the surgical specimen
  - These tumours are best considered as metaplastic carcinoma for management purpose.
- Next Generation Sequencing testing may be diagnostic
  - *MED12* exon 2 hotspot mutations are found in 30-60% of malignant PTs,
  - No *MED12* exon 2 hotspot mutations in metaplastic carcinomas

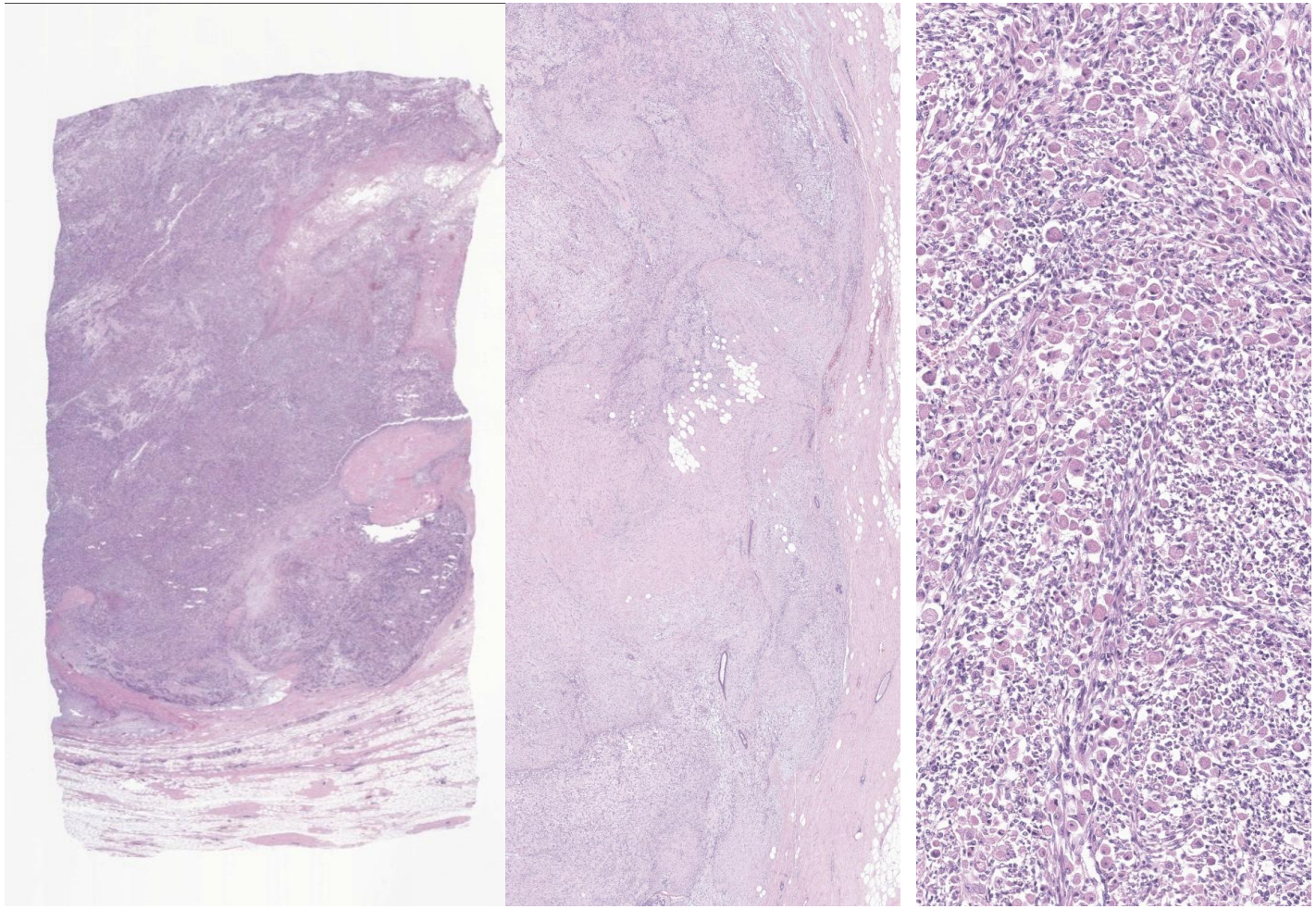
Malignant spindle cell neoplasm difficult to classify

Case Example

- High grade spindle cells
- +/- suggestion of leaf-like fronds/ FA
- No epithelial component
- Negative CKs and p63

Dx: High grade spindle cell neoplasm. Favor malignant PT, but cannot rule out Metaplastic Spindle Cell Carcinoma

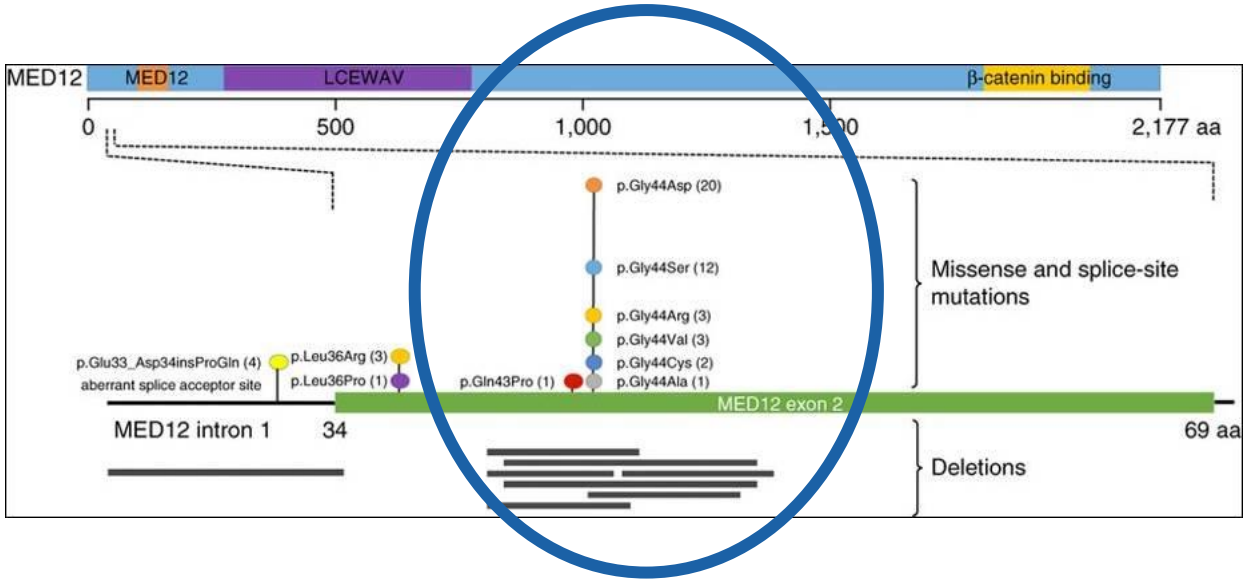
Molecular testing is suggested.



DDx Malignant spindle cell neoplasm
Molecular analysis *might* help

Hello Dr. Brogi,
I hope that this e-mail finds you well. I'm following up on the sarcomatoid breast case that came your way from RI a few months ago.

[redacted] testing was not definitive ("no reportable alterations with companion diagnostic claims"), though there was a med12 G44D substitution as well as several other alterations.



In the appropriate setting, the identification of MED12 exon 2 hotspot mutations supports the diagnosis of a FEL (malignant PT in this case)

MSpCC is a very aggressive tumor

Study	Davis (AJSP 2005)	Carter (AJSP 2006)
No. cases	22	29
Patient age (range)	60 years (32-79)	68 years (40-96)
Tumor size (range)	3.4 cm (1.5–8)	4 cm (1.5–15)
Sarcomatoid component	>95%	>80%
Nuclear grade	5 Intermediate 17 High	**7 Low** 9 Intermediate 13 High
Surgery	BCS 11/22; TM 11/22	No Data
Axillary LN(+)	1/17	1/20
Radiotherapy	12/22: BCS (3), TM(4), LR (5)	No Data
Adjuvant chemotherapy	21/22 (95%)	No Data
Median follow up	36 m (4-155); 21 patients	20 m (1-120); 24 patients
Local recurrence	10/21 (48%)	3/24 (13%)
Distant metastasis	9/21 (43%) (7 **lung**)	11/24 (46%) (7 **lung**)
Survival	DOD 6/21 (29%)	DOD 10/24 (42%)

Davis WG et al. Metaplastic sarcomatoid carcinoma of the breast with absent or minimal overt invasive carcinomatous component: a misnomer. AJSP 2005;29(11):1456-63 PMID: 16224212.

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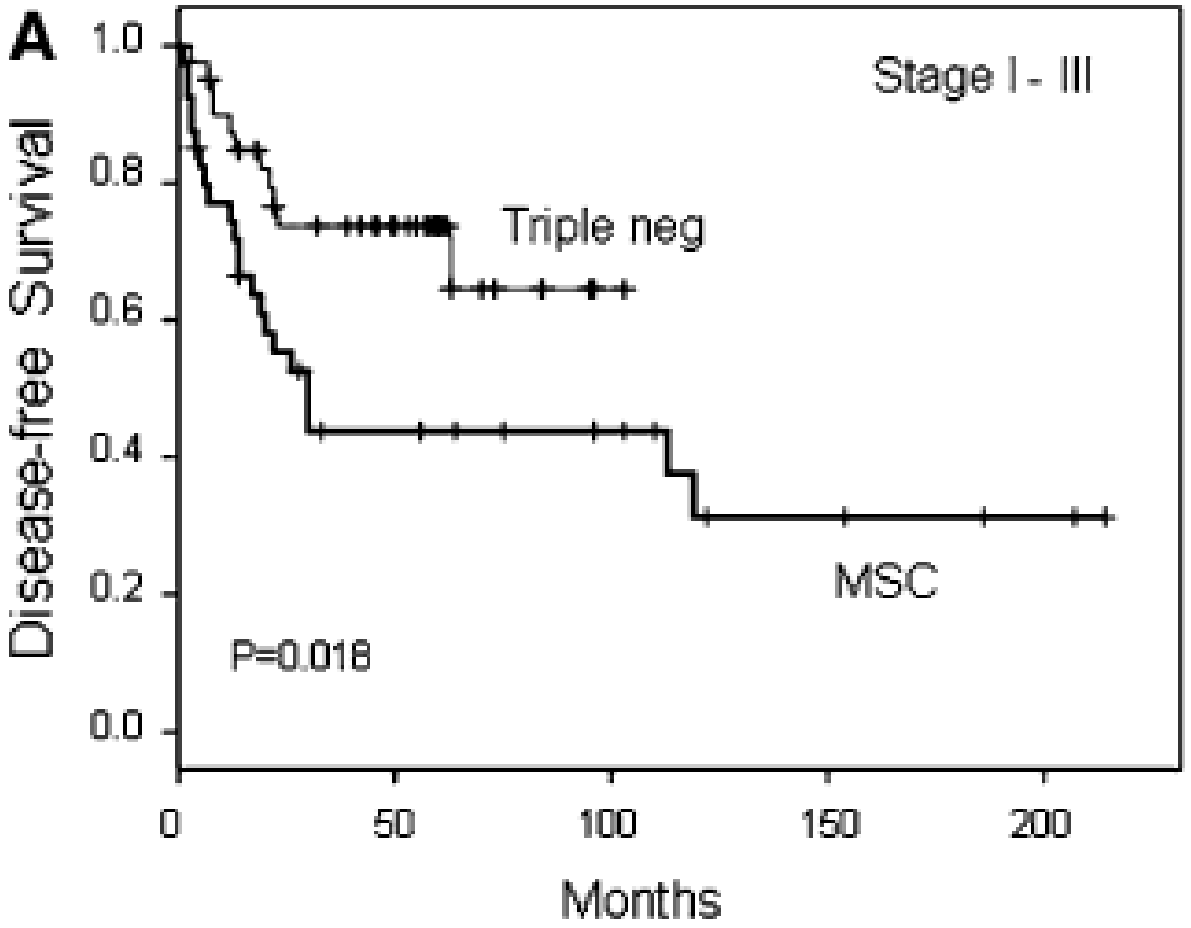
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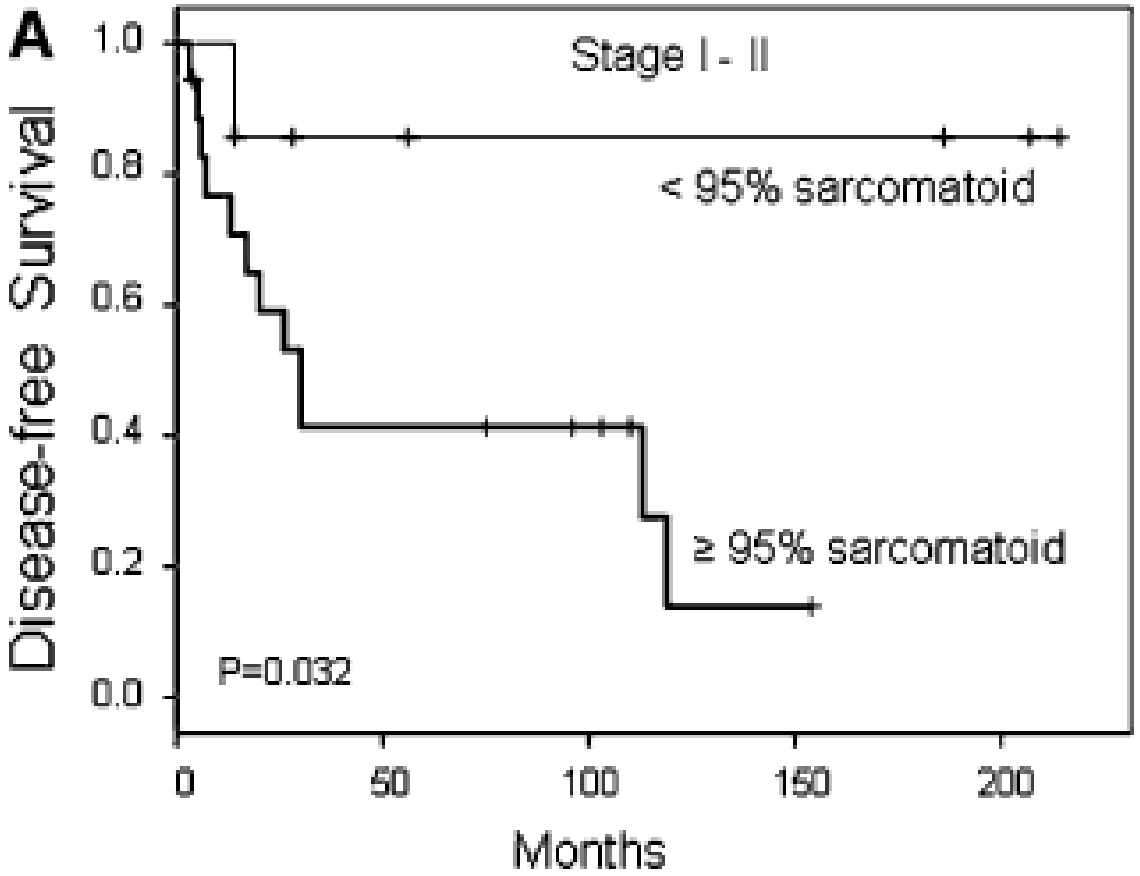
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MSpCC: more aggressive than all other TNBC
MSpCC with >95% sarcomatoid component most aggressive





Lester TR et al *Breast Cancer Res Treat*. 2012; 131:41-48

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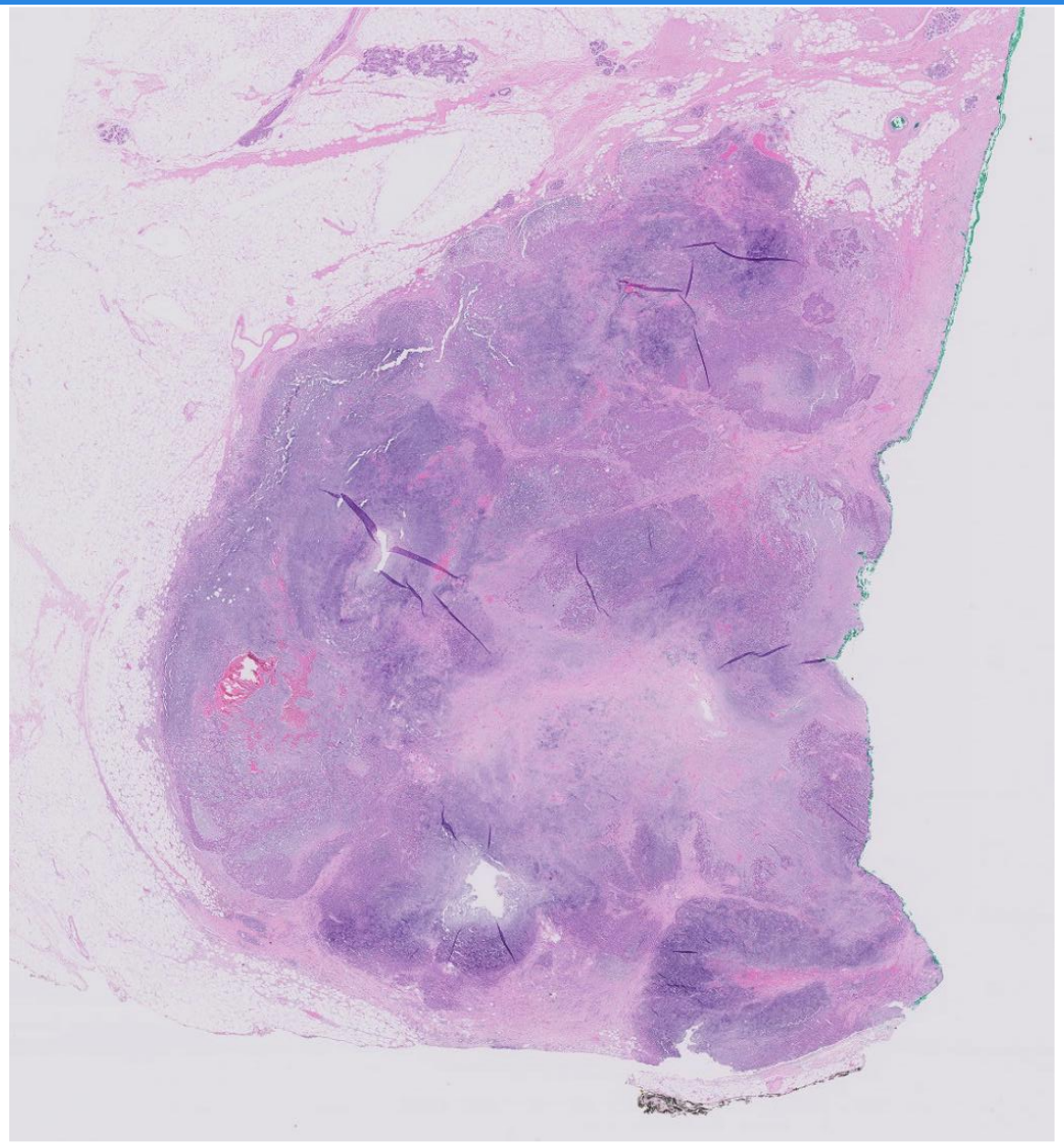
Metaplastic carcinoma

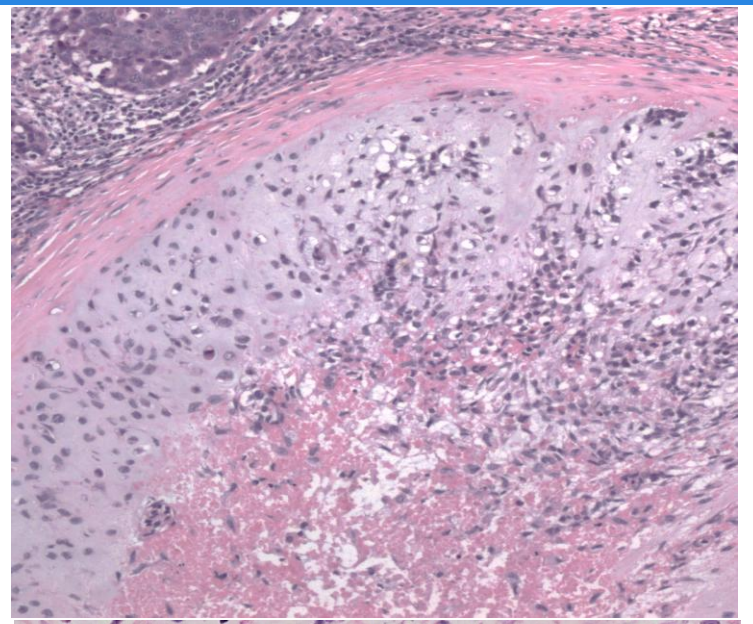
with heterologous mesenchymal differentiation / matrix production

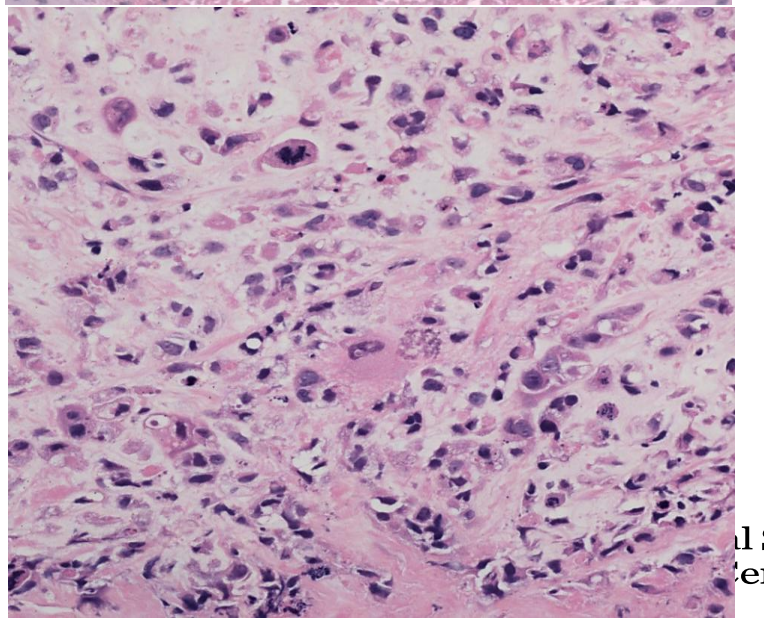
Metaplastic carcinoma with heterologous mesenchymal differentiation / matrix production

- Mesenchymal components (chondroid, osseous, rhabdomyoid, and occasionally neuroglial) and/ or Chondromyxoid matrix production.
- Some tumours may appear entirely mesenchymal.
- The mesenchymal components ranges from seemingly differentiated with minimal atypia to frankly malignant
- May be mixed with other metaplastic morphologies
- In the absence of epithelial elements or DCIS, IHC work-up for a broad range of CKs is required for accurate Dx.
- Differential DX includes malignant PT and primary and metastatic sarcomas.

Metaplastic carcinoma with heterologous mesenchymal differentiation / chondroid matrix production







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enter

77 patients with MPMPC and germline testing, treated at MSKCC 2000-2025

44 pure, 30 mixed (ductal 34%, squamous 7%)

- **Atypical MGA in 23% of cases**

20/75 patients received NAC: no pCR

median F/U: 58 months (range, 13–204)

- **12/72 pts (17%) local recurrence**
- **25/73 pts (35%) distant metastases**
- **20/73 (28%) pts died of disease**

Mack T. et al. Matrix-Producing Metaplastic Carcinoma of the Breast: Clinicopathologic, Germline, and Genomic Characterization of a Distinct Metaplastic Carcinoma Subtype – Breast Cancer Research (accepted for publication)

Metaplastic matrix-producing carcinoma (MPMPC) are a special type of metaplastic carcinoma, associated to Homologous Recombination Deficiency

77 patients with MPMPC and germline testing, treated at MSKCC 2000-2025

44 pure, 30 mixed (ductal 34%, squamous 7%)

- **Atypical MGA in 23% of cases**

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A comparator cohort of MC without matrix-production (non-MPMC) (n=43) was assembled for histologic, genomic, and hereditary predisposition analyses.

- **P53 alterations in 90% cases**
- **chromosome 8q gains in 48% cases**
- **enrichment of 8q-associated genes, including *MYC***
- **Compared with non-MPMC, MPMC demonstrated enrichment for**
  - **germline Pathogenic/Low Pathogenic Variants (32% vs. 7%; P=0.004),**
  - **HRD-associated germline P/LPVs (28% vs. 2%; P=0.004)**
  - **association with AMGA (23% vs. 0%; P=0.0005).**
- **Lower frequencies of *PIK3CA*, *TERT*, and *CDKN2A/B mutations compared to non-MPMPC***

Mack T. et al. Matrix-Producing Metaplastic Carcinoma of the Breast: Clinicopathologic, Germline, and Genomic Characterization of a Distinct Metaplastic Carcinoma Subtype – Breast Cancer Research (accepted for publication)

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Metaplastic Carcinoma

Low grade Adenosquamous(LG-ASC)

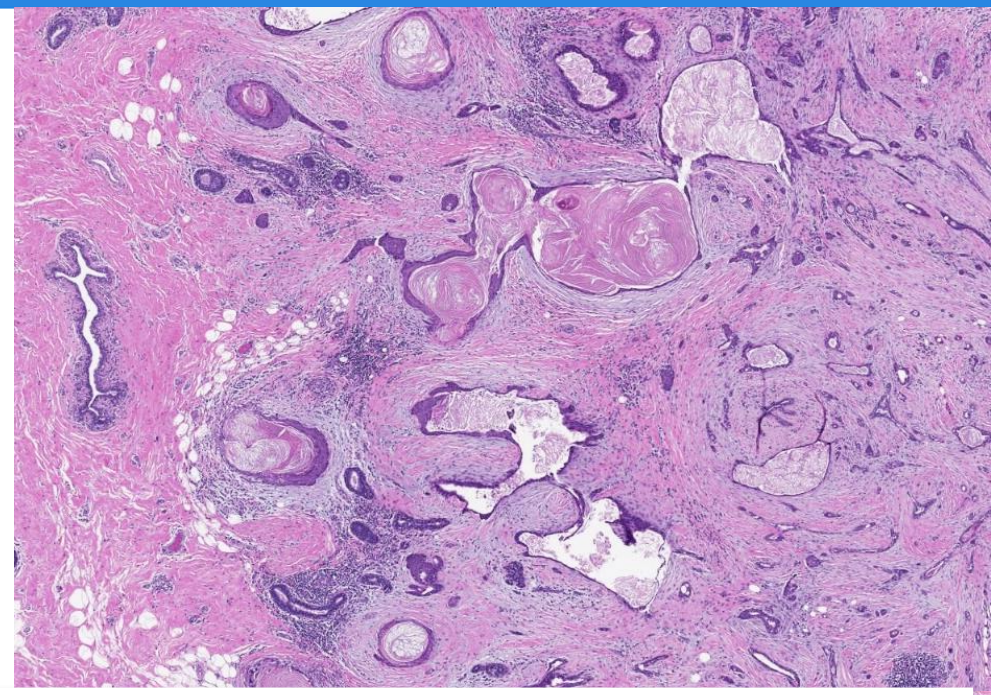
Low-grade adeosquamous carcinoma (LG-ASC)

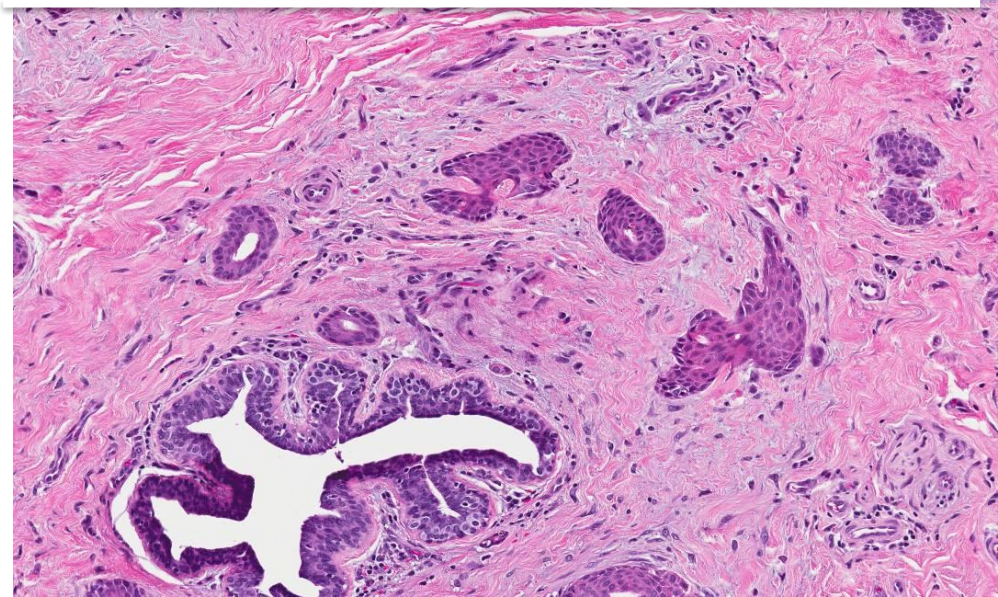
First described in 1987 by Dr. Rosen

Presentation: Rare; any age, often postmenopausal women
may occur in men

Location: Nipple/ retroareolar region most common site
but can arise anywhere in the breast
+/- associated sclerosing lesions
nipple adenoma, intraductal papilloma, adenomyoepithelioma, radial scar/ complex sclerosing lesion

Histology: Cells of glandular and squamous morphology
arranged in glands, tubules, solid nests
Low/ intermediate nuclear grade
Lamellar stroma + lymphocytes ("cannonball" pattern)
Usually ER, PR neg/ low and HER2 negative





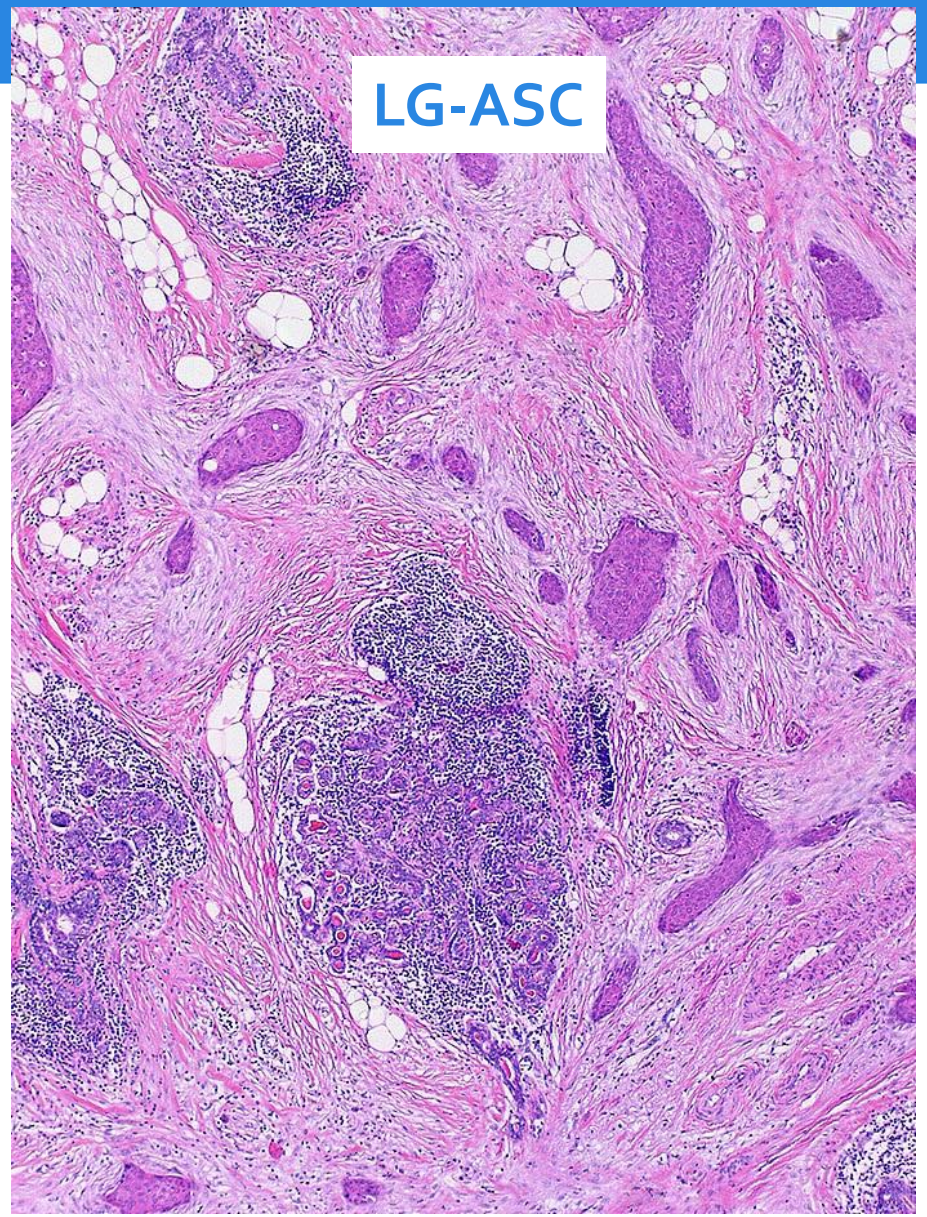
LG-ASC Differential Diagnosis

High grade lesions

- High grade adenosquamous carcinoma (malignant AME?)
- metaplastic mixed squamous and NST

Benign sclerosing lesions

- Syringomatous adenoma of the nipple
- Radial scar/ complex sclerosing lesion



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LG-ASC has relatively favorable prognosis

LN mets very uncommon
Local recurrence extremely rare

Historical series of 32 patients (1993)

- 5/25 (20%) local recurrences
  - including one that caused hemothorax→ patient death
- one patient with distant met
  - 8.4 cm BC and synchronous lung mass presumed to be metastatic BC

Van Hoeven and Rosen AJSP, 1993 (32 patients)

Contemporary series: No local recurrences or distant metastases

Tamminen A, et al. 2024;16(24):4246. (3 cases)
Lewis G, et al. Histopathology. 2023;83(2):252-263 (25 cases).
Bataillon G et al *Histopathology*. 2018; 73: 273-283 (13 cases)

High rate of *PIK3CA* mutations but no *TP53* mutation in LG-ASC

- Targeted sequencing found
  - *PIK3CA* mutation rate of 52% (11 of 21 cases)
  - No *TP53* mutation

Bataillon G et al *Histopathology.* 2018; 73: 273-283

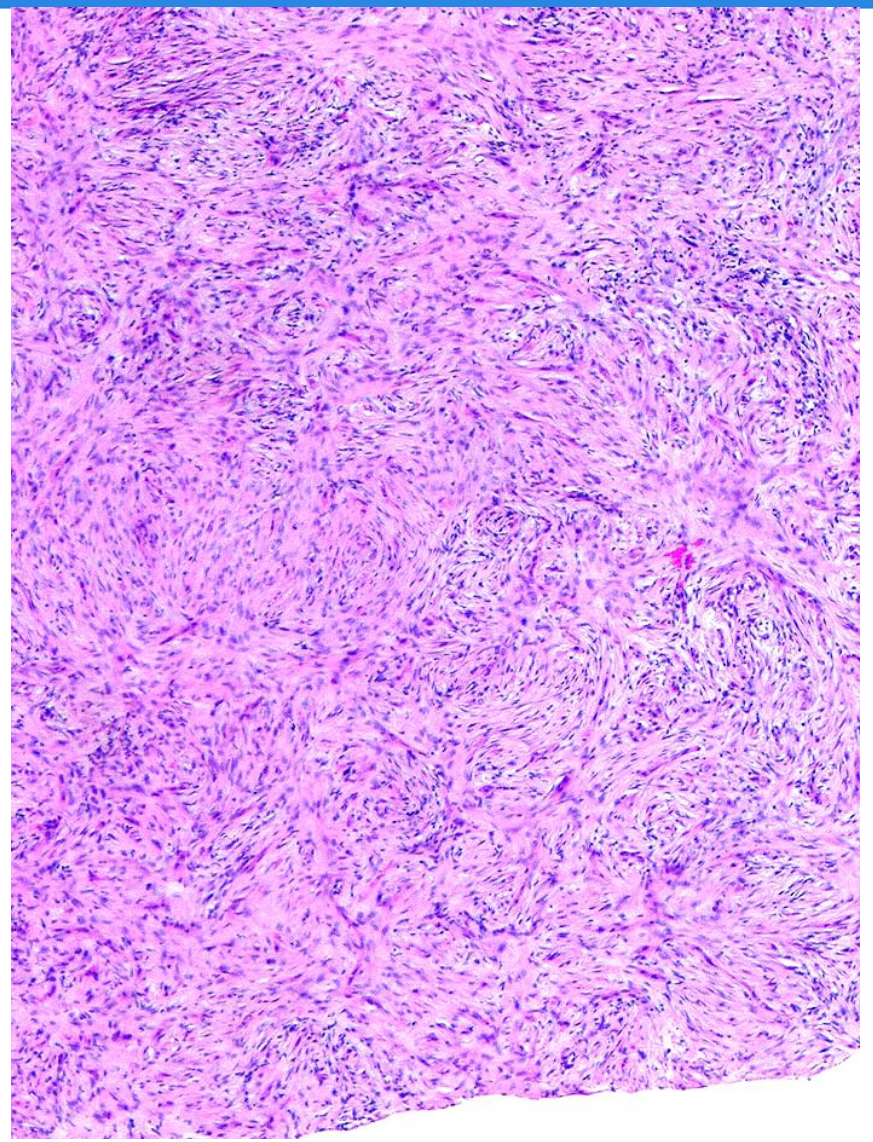
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Metaplastic Carcinoma
Fibromatosis-like

Fibromatosis-like metaplastic carcinoma

- > 90% composed of bland spindle cells
- no high nuclear grade component (invasive or in situ)
- Wavy interlacing fascicles, long fascicles with finger-like extensions infiltrating the adjacent breast parenchyma.
- Cords and clusters of plump spindled and more-epithelioid cells may be present.
- Focal squamous differentiation possible.
- Stroma has varying degrees of collagenization

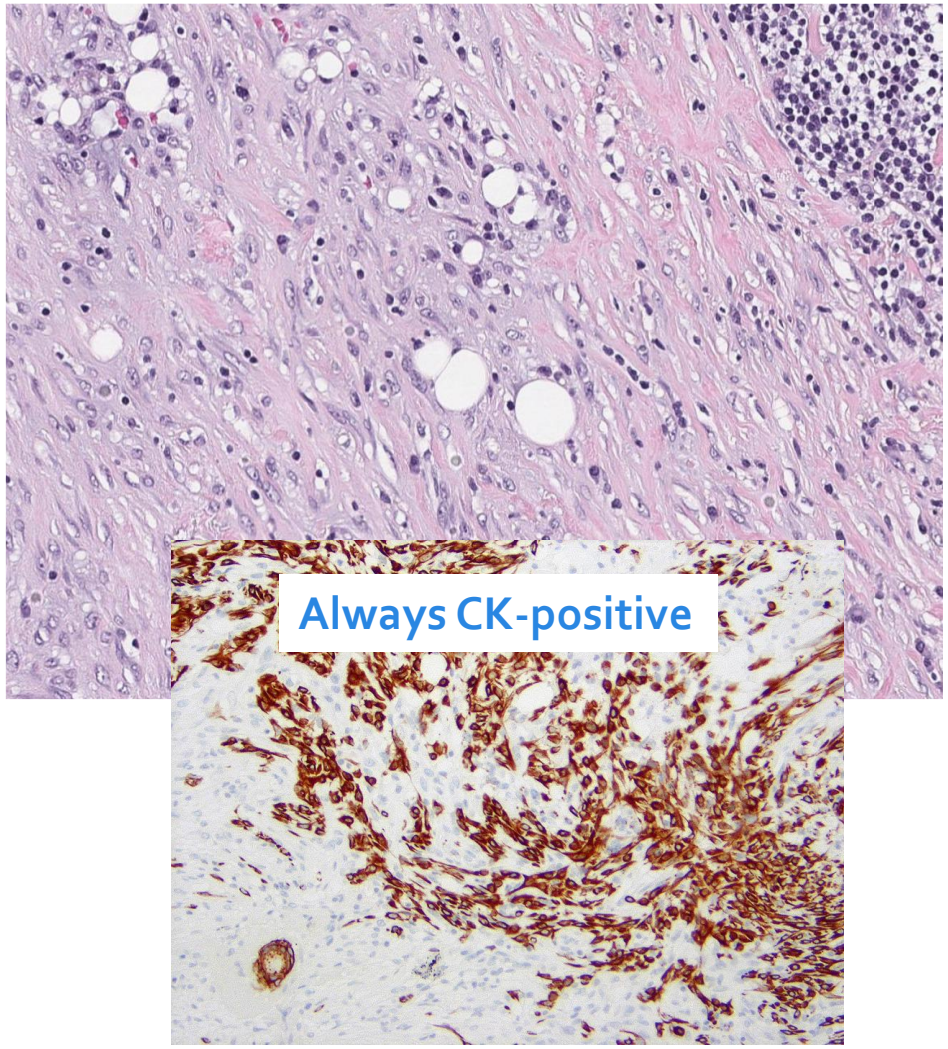
- Not to be confused with the more common high-grade spindle cell metaplastic carcinoma, that is very aggressive



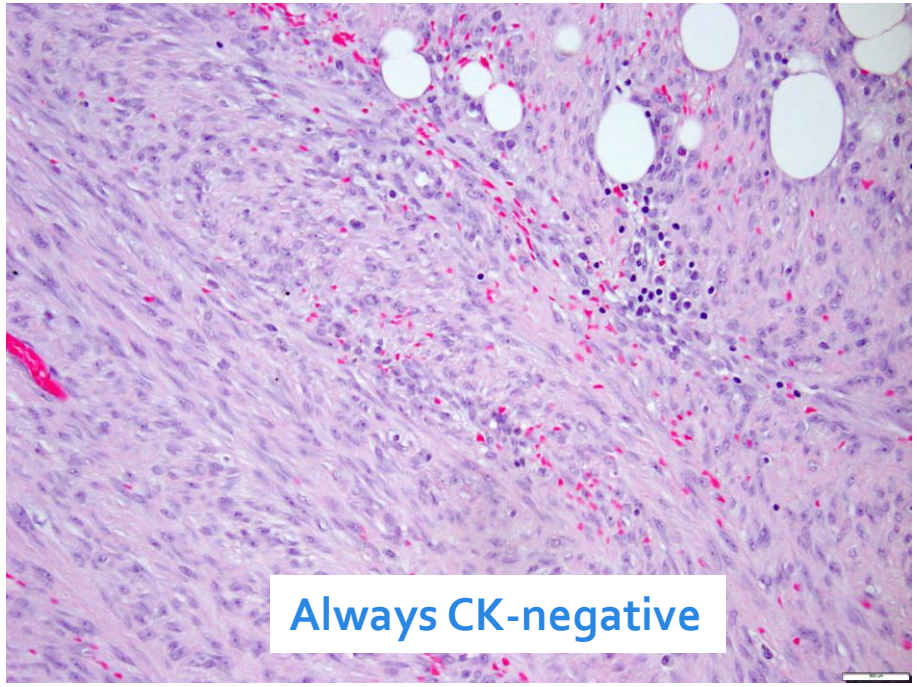
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Differential diagnosis

Fibromatosis-like metaplastic carcinoma



Fibromatosis



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Fibromatosis-like metaplastic carcinoma

- IHC: p63 and CKs (CK5/6, CK14, 34BE12, MNF116…) are always expressed
- Fibromatosis-like metaplastic carcinoma may show nuclear β-catenin, but is CK(+)

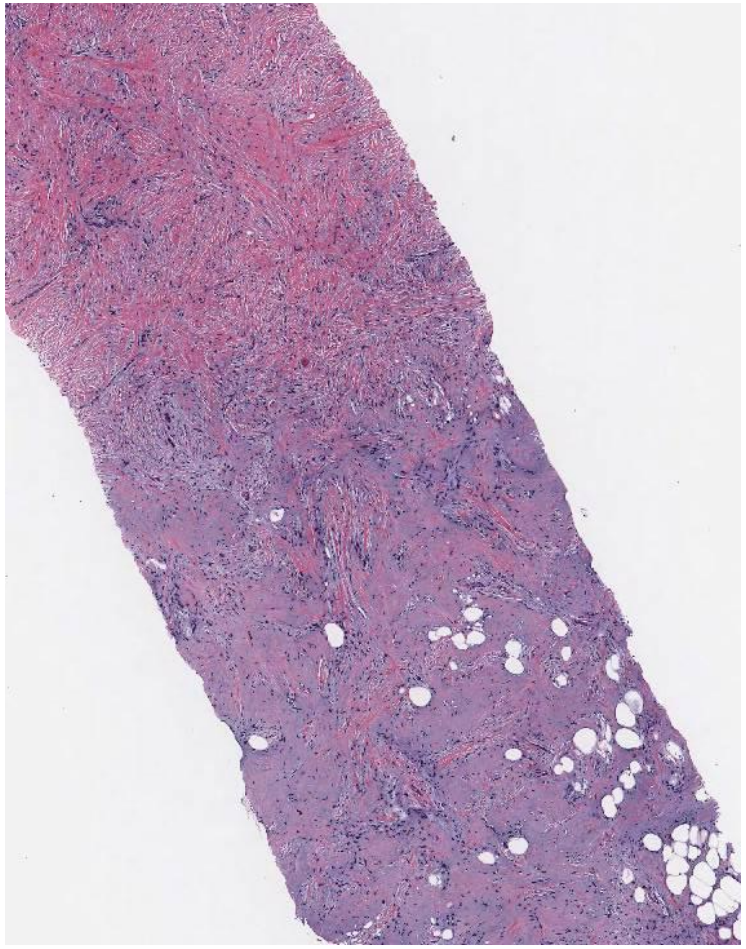
  Note: In general, nuclear β-catenin supports the diagnosis of fibromatosis

  However, in the breast, nuclear β-catenin is found also in:

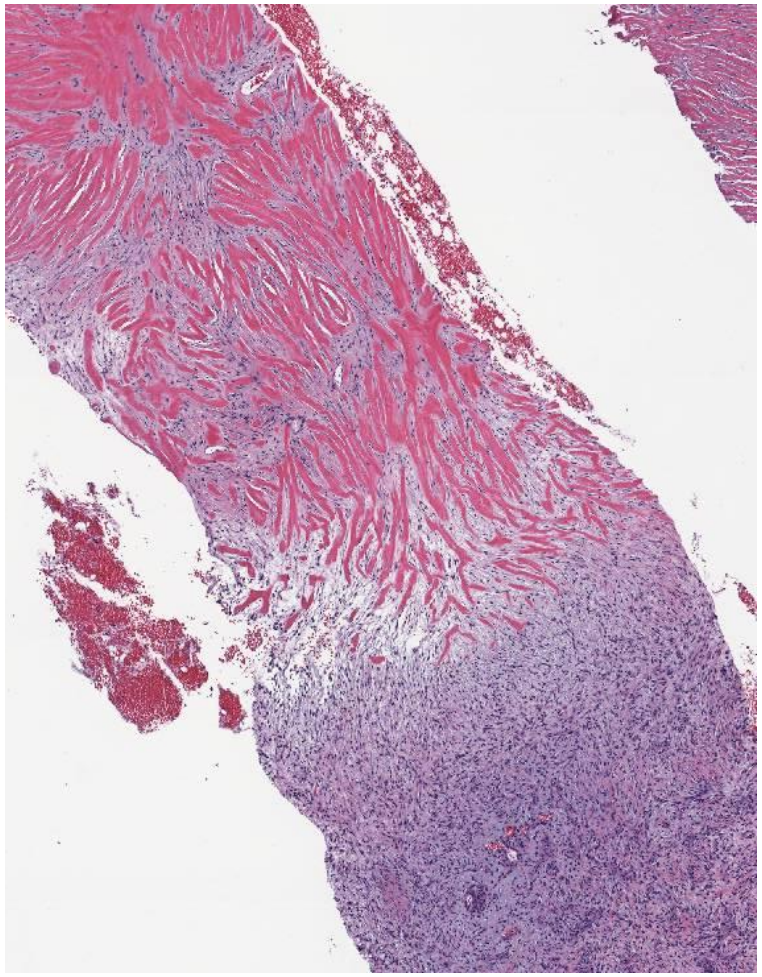
  – 23% metaplastic breast carcinomas (CK+ and p63+)
  – 94% benign phyllodes tumors (CD34+)
  – 57% malignant phyllodes tumors (CD34+/-)

- FL-MC has relatively "favorable" prognosis compared to other types of metaplastic carcinoma, but distant metastases may occur (lung>bone, etc)

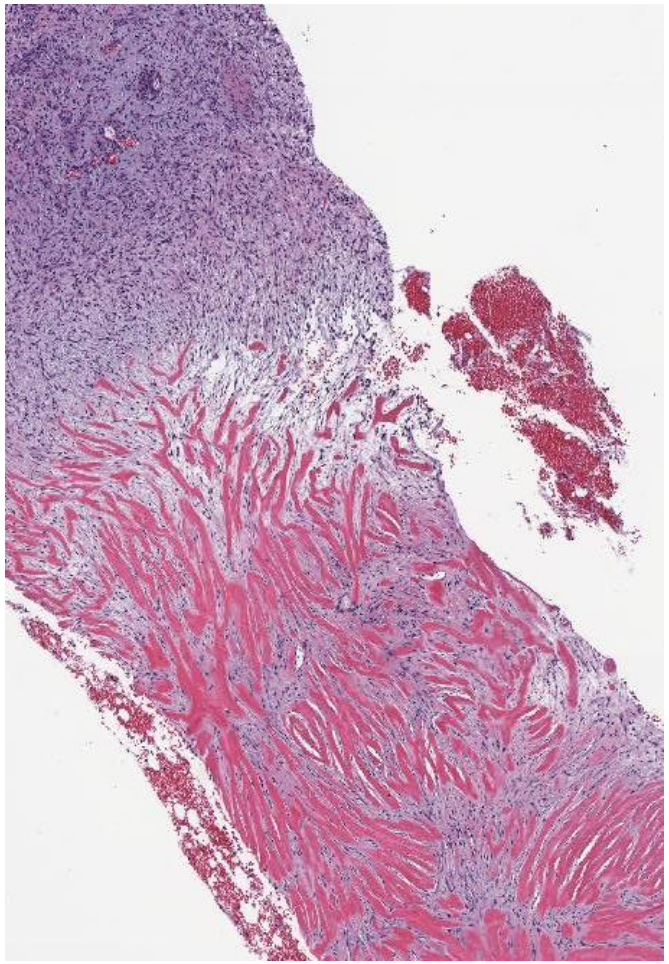
2014 CNB; CK7 neg
DX: fat necrosis

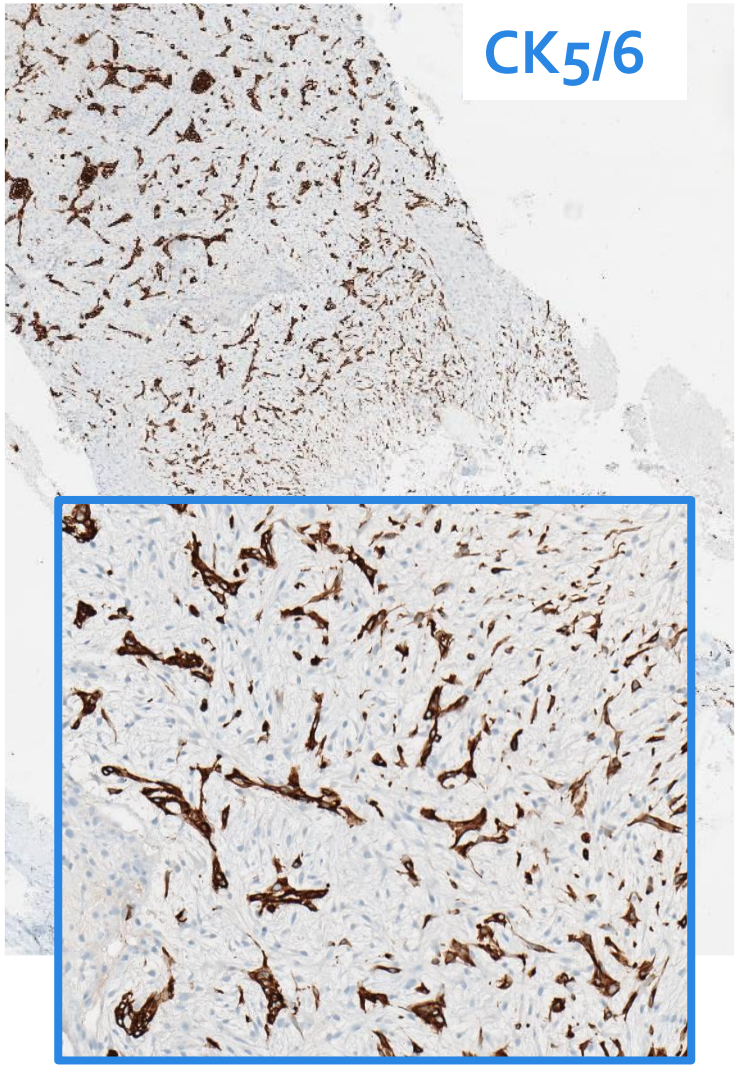


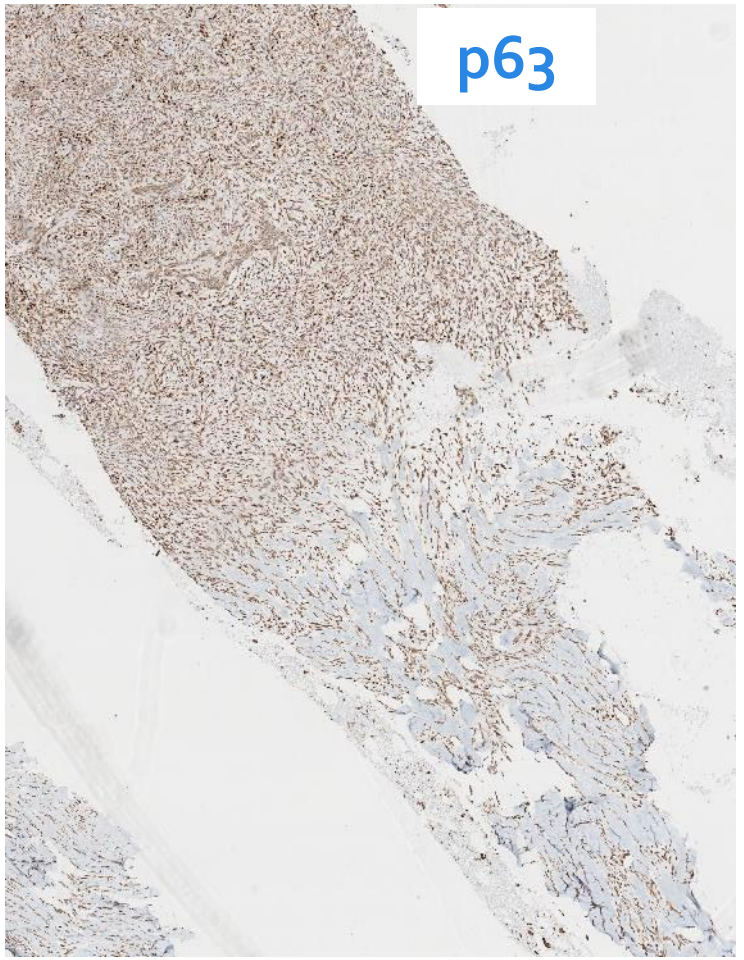
enlarging mass
2015 CNB



2015 Dx: "Fibromatosis-like" Metaplastic Carcinoma

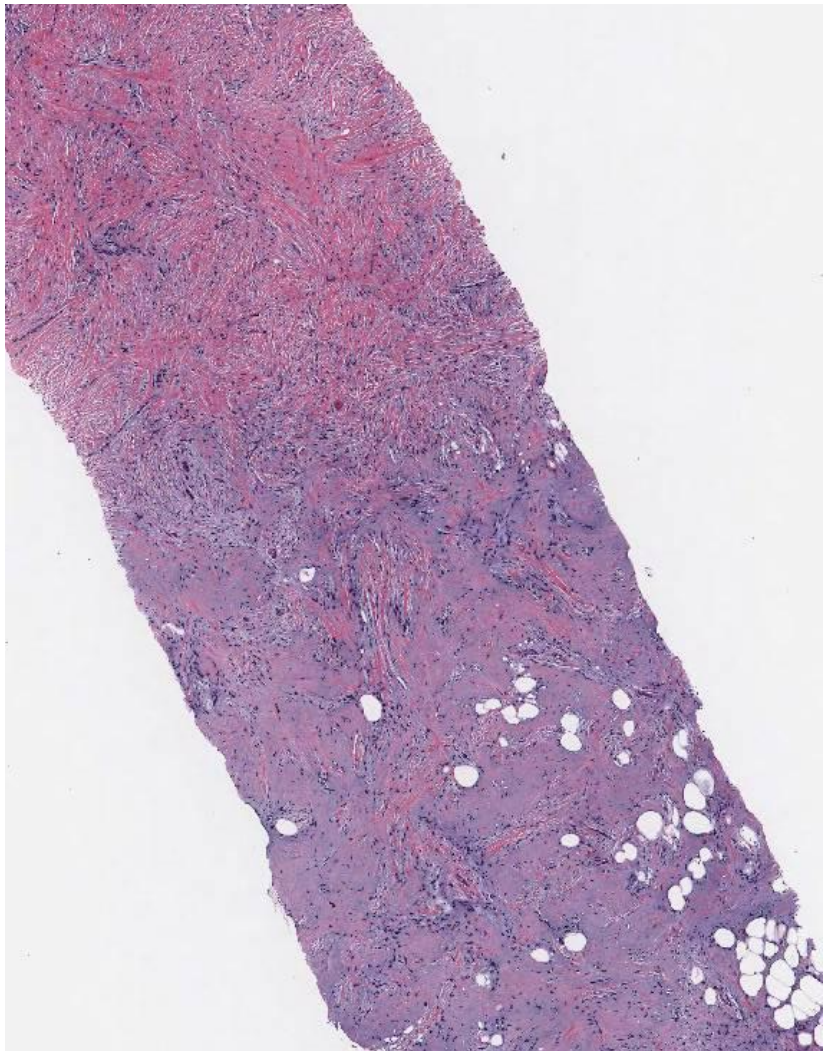




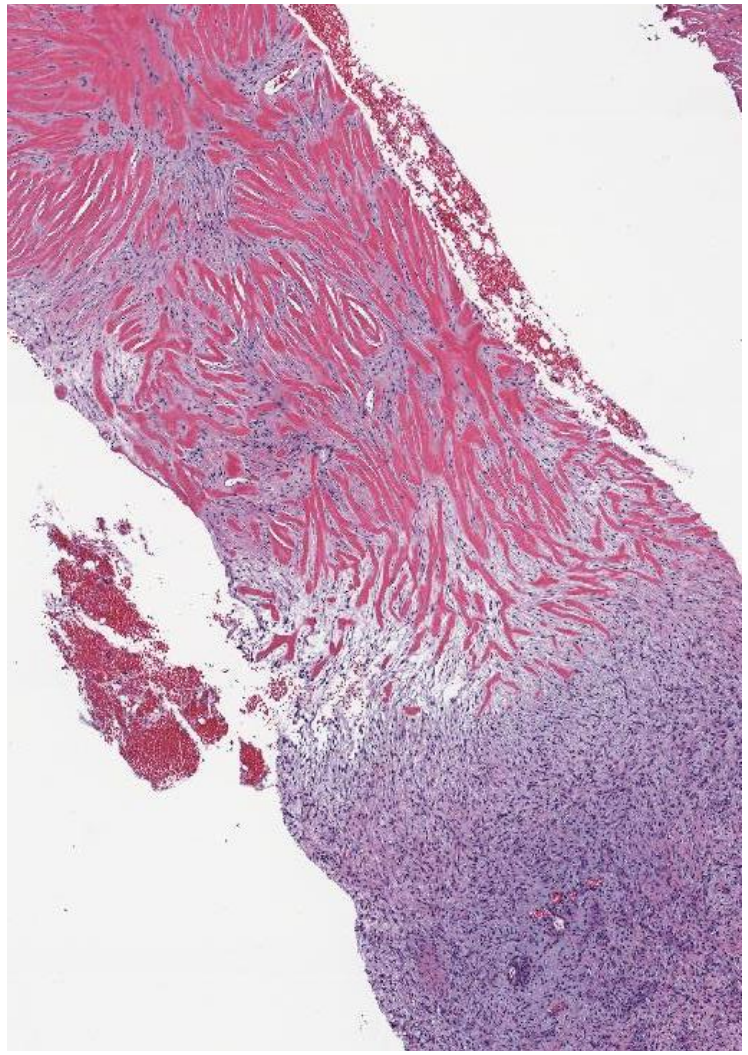


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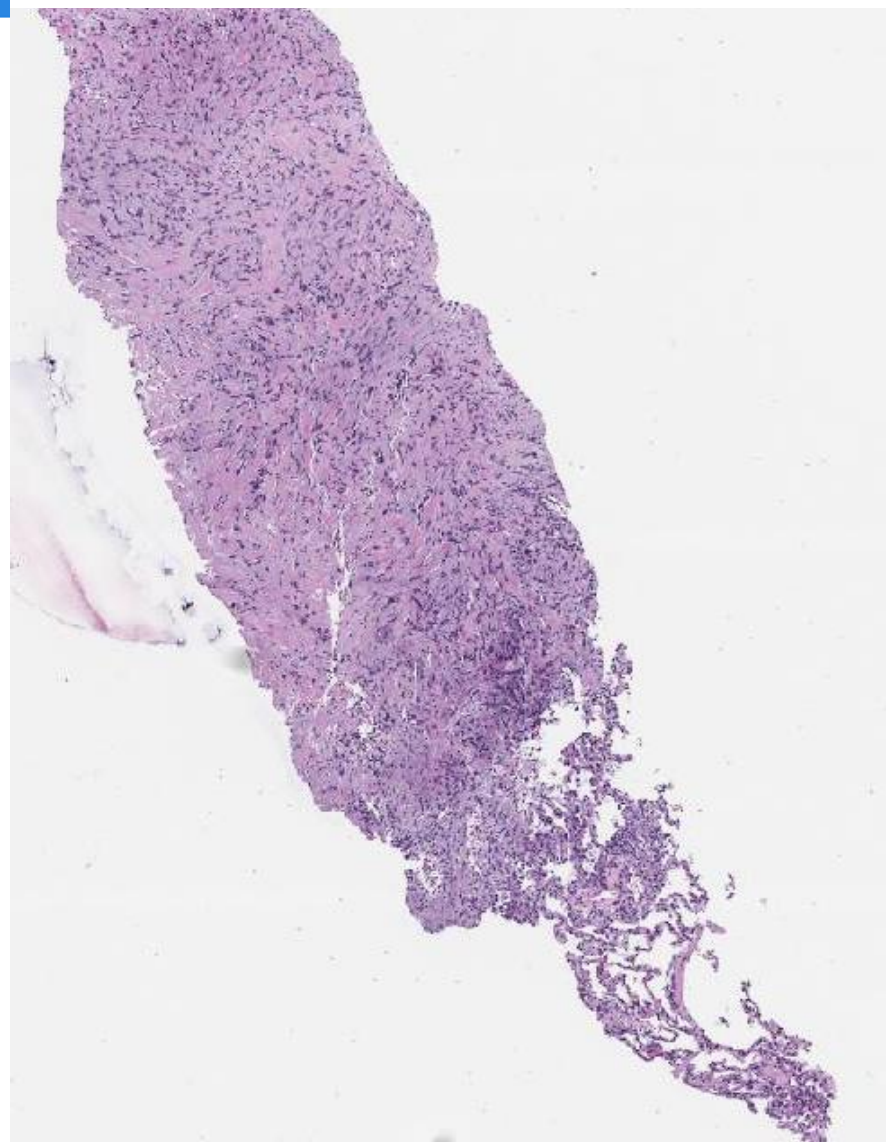
2014 breast



2015 breast



2016 lung metastasis



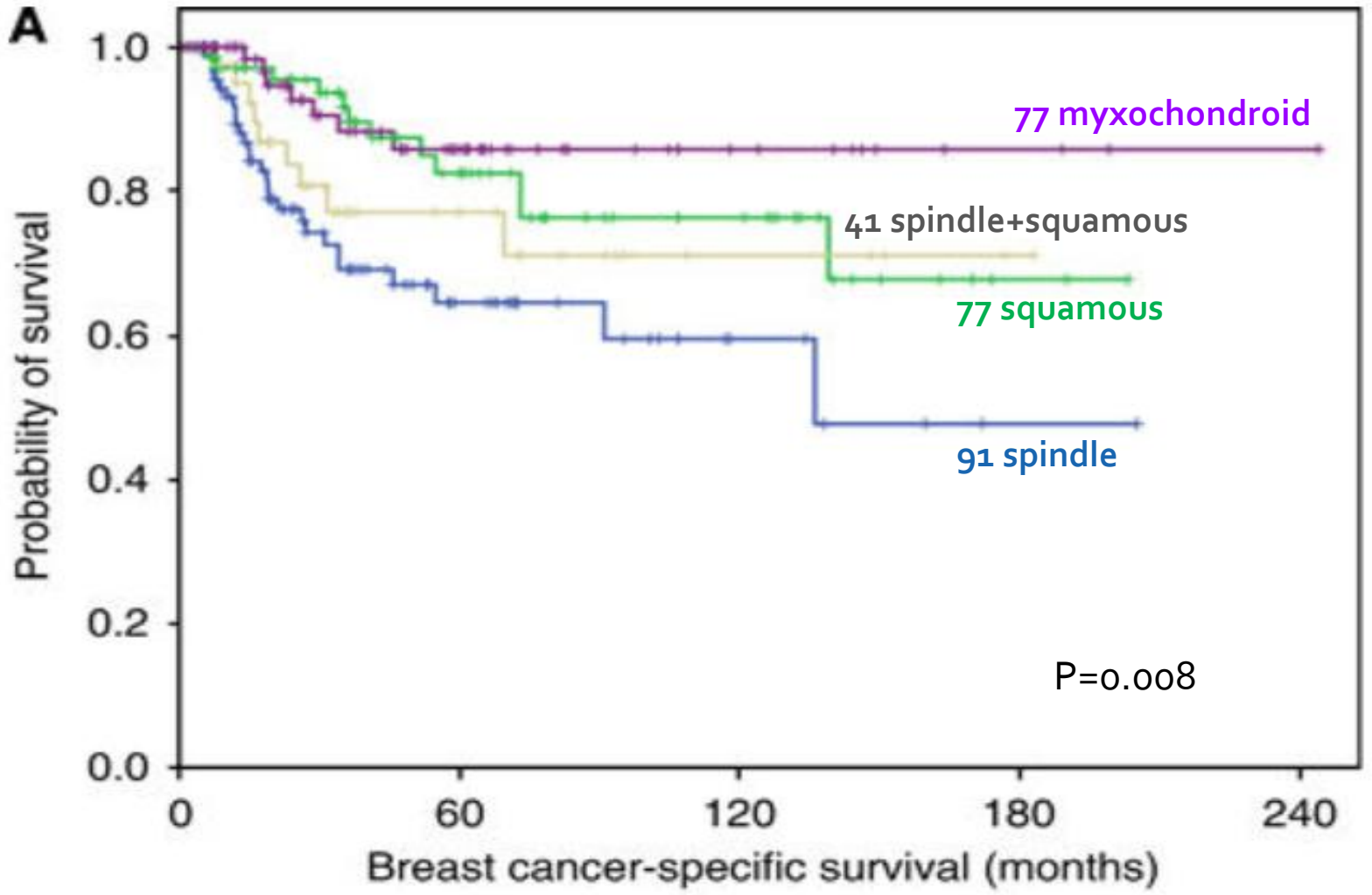
Some reports *of TERT* promoter mutations in fibromatosis-like metaplastic carcinoma with metastases

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Metaplastic Carcinoma
treatment and prognosis

Metaplastic carcinoma subtypes have different prognosis

Retrospective multicenter study

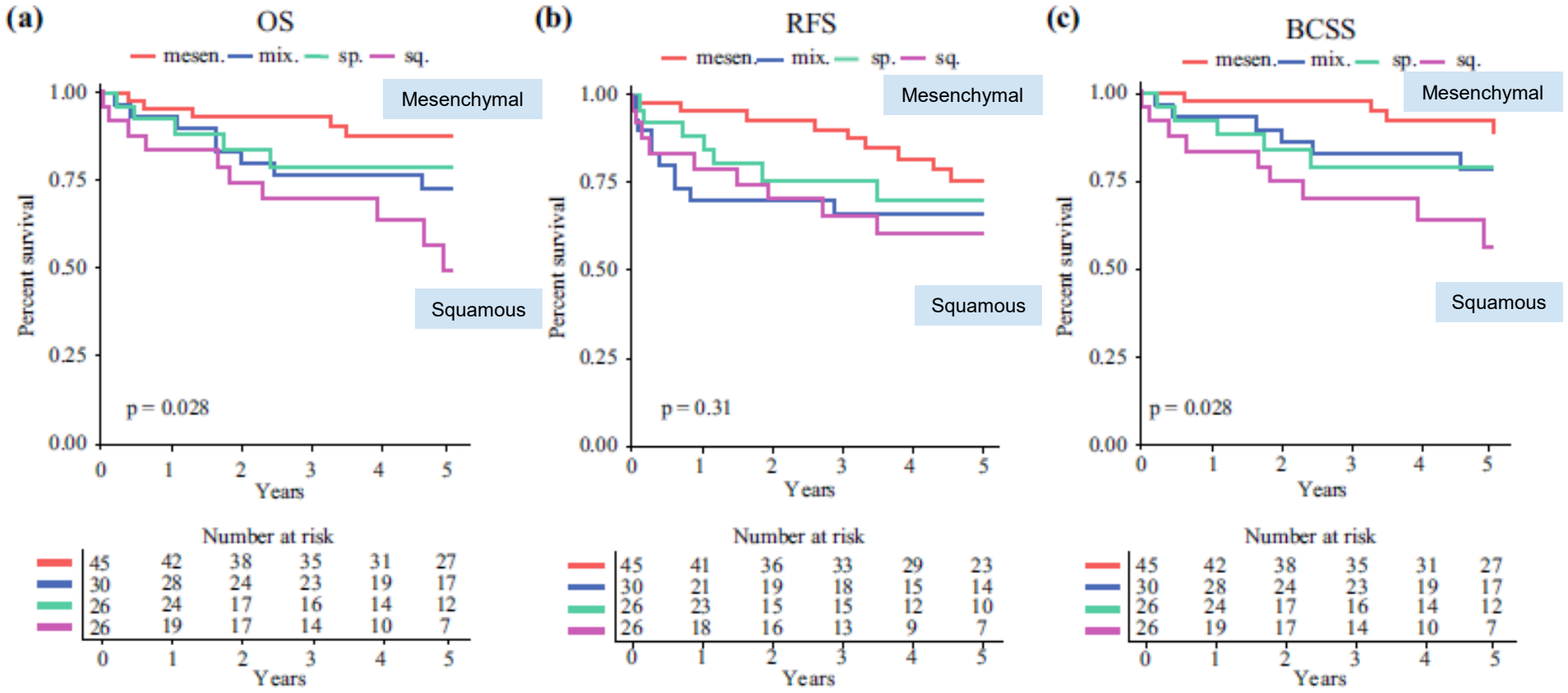


Rakha E et al *BJ cancer* 2015;112(2):283-9

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MBC prognosis based on subtype – MSK study

132 patients with metaplastic carcinoma treated @MSK between 1995-2017



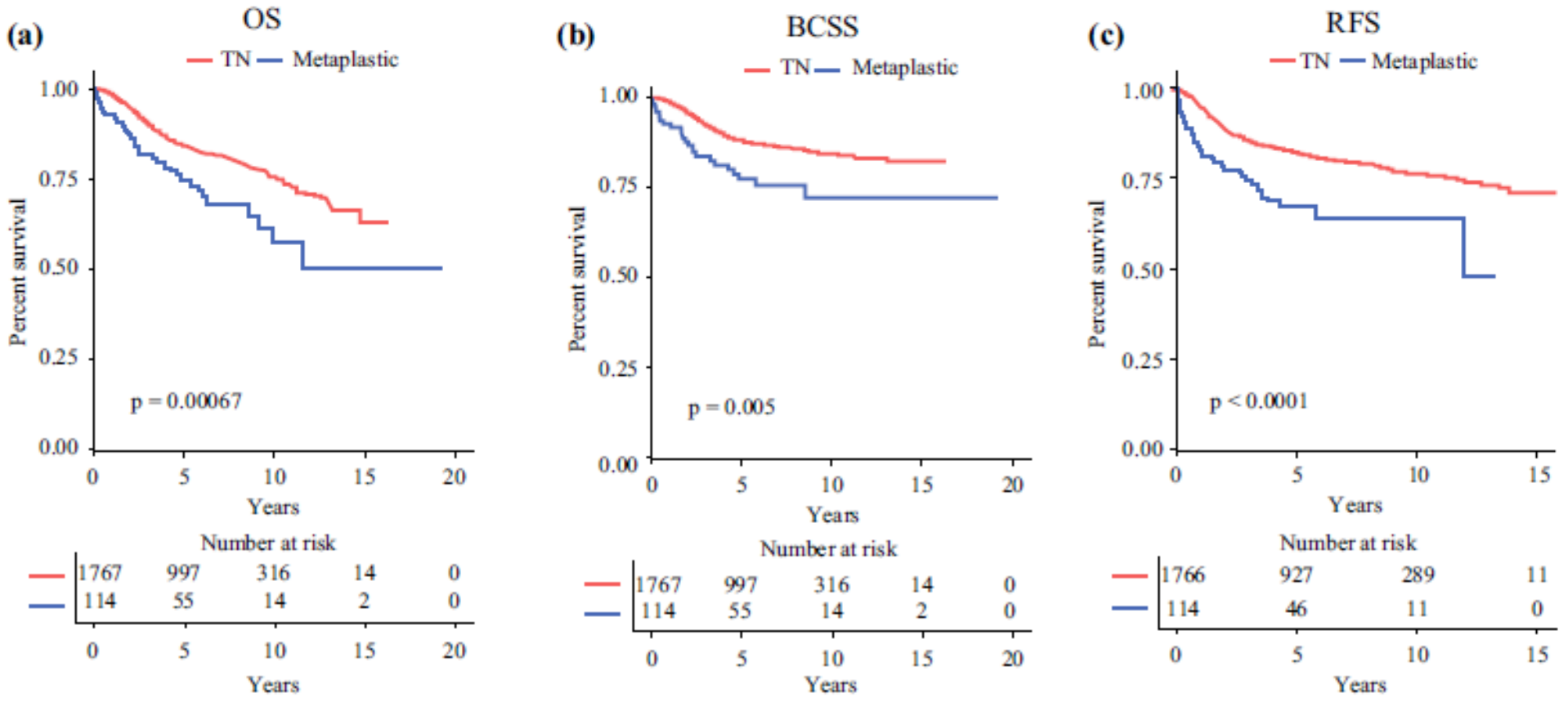
Tadros A.B, Ann Surg Oncol. 2021 28:4245-4253.

MBC prognosis compared to non-MBC TNBC

132 patients with metaplastic carcinoma treated @MSK between 1995-2017
compared to >1700 patients with non-metaplastic TNBC

Adjusted Mortality HR 1.9 (95%CI 1.3-2.8), p<0.001

Adjusted Recurrence HR 2.3 (95%CI 1.6-3.3), p<0.001



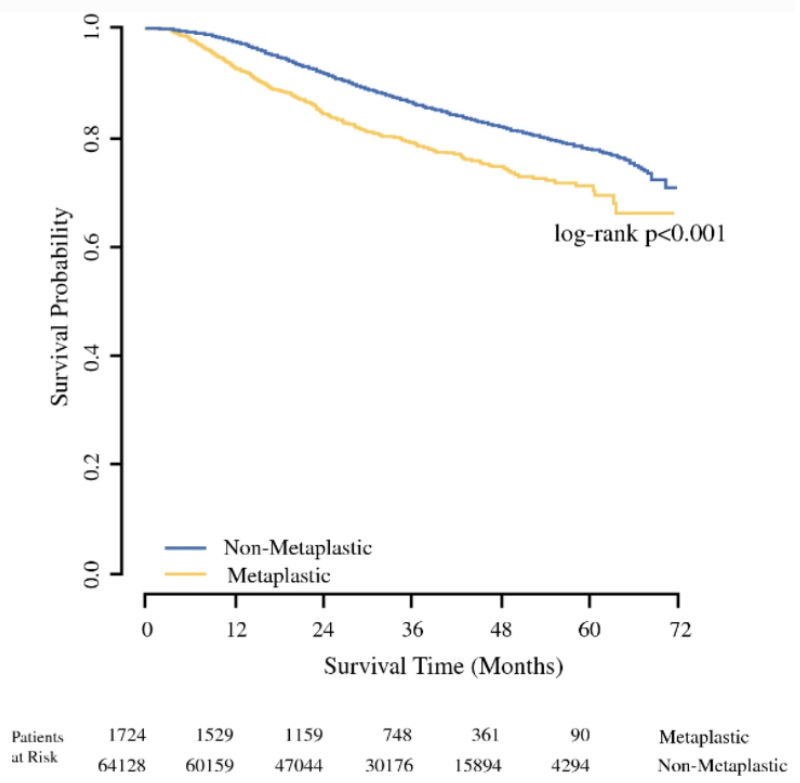
Tadros A.B, Ann Surg Oncol. 2021 28:4245-4253.

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Prognosis: metaplastic vs non-metaplastic TNBC

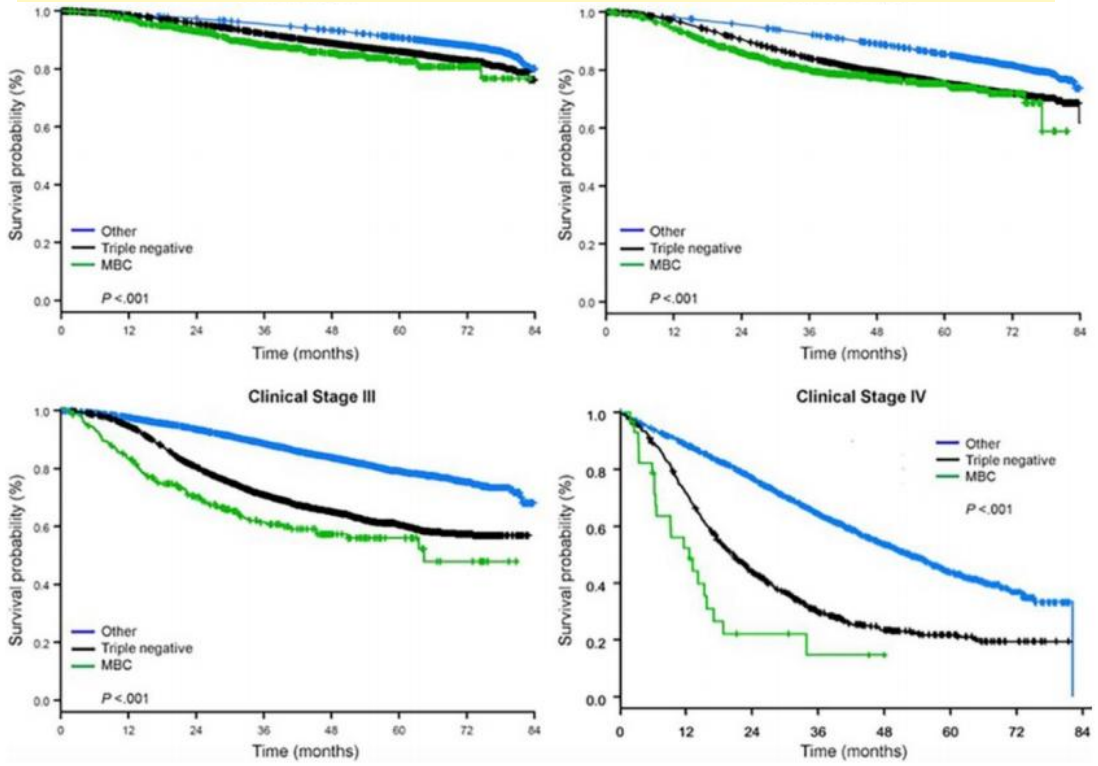
2010-2014 National Cancer Data Base

Metaplastic: Lower 5-Year Survival Rate
1700 Metaplastic: 71% (95%CI 68-74%)
64000 Non-Metaplastic TNBC: 78% (95%CI 77-78%)



Ong C.T, Ann Surg Oncol. 2018 Aug 25(8):2249-2260

Metaplastic: lower OS across all stages
2084 Metaplastic
55,998 non-metaplastic TNBC



Moreno A.C, Journal of Cancer, 2020; 11(6):1341-1350

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Metaplastic BC has limited response to NAC compared to TNBC

44 pts treated @MSK with NAC from 2002-2018

40 (91%) had T2-T3 tumors; 16 (36%) Bx-proven N(+)

All 44 patients received had ACT-based NAC

41 pts complete clinical-radiologic-pathologic post-NAC info

51% (21/41) Clinical or radiological response

22% (9/41) No clinical or radiological response

27% (11/41) Disease progression

3 pts progressed from eligible to ineligible for BCS

Overall pCR rate only 2% (1 myxochondroid)

For Reference
170 patients with TNBC
ACOSOG Z1071
Rates of TNBC pCR:
Breast 48% (81/170)
Axilla 49% (84/170)
Both 38% (65/170)

Boughey J.C, Ann Surg 2014, Oct; 260(4):608-14

Table 3. Rates of pathologic complete response in breast and lymph node stratified by histologic subtype of metaplastic carcinoma.

Metaplastic histologic subtype	Overall pCR (ypT0N0) *n* (%)	Breast pCR (ypT0) *n* (%)	Total ypN0 *n* (%)	Nodal pCR in cN +*n* (%)
All cases	1/44 (2%)	2/44 (5%)	26/44 (59%)	3/16 (19%)
Matrix-producing	1/19 (5%)	2/19 (11%)	13/19 (68%)	2/7 (29%)
Squamous cell carcinoma	0/12	0/12	5/12 (42%)	1/6 (17%)
Spindle cell carcinoma	0/6	0/6	5/6 (83%)	0/0
With mixed metaplastic elements	0/6	0/6	2/6 (33%)	0/3
No data	0/1	0/1	1/1 (100%)	0/0

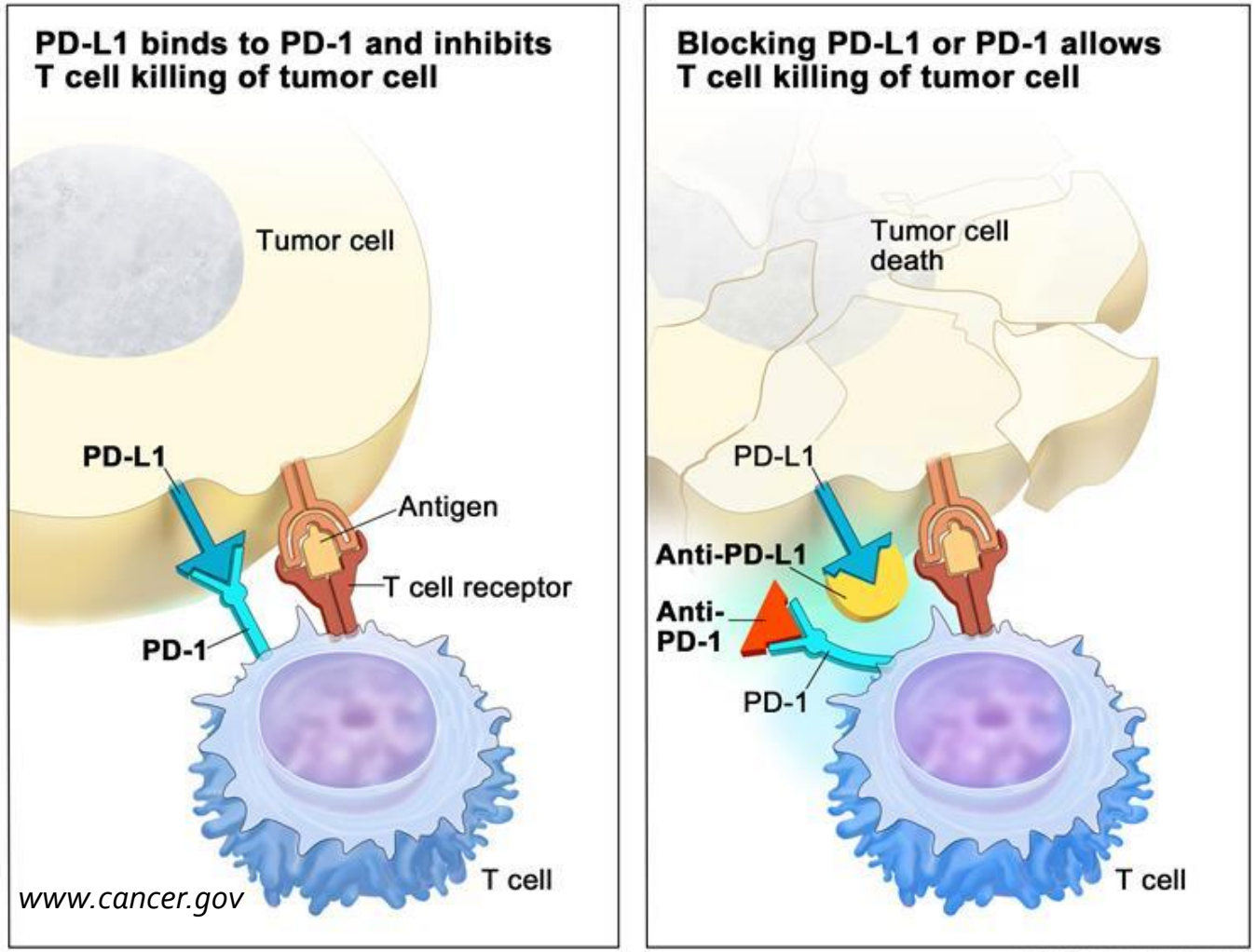
Wong W, NPJ Breast Cancer. 2021 Jul 22;7(1):96.

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Metaplastic Carcinoma
Immunotherapy and PDL1

Immunotherapy PD-L1



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Immunotherapy PD-L1

Atezolizumab (anti-PD-L1) IMpassion-130



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

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ABSTRACT

BACKGROUND
Unresectable locally advanced or metastatic triple-negative (hormone-receptor–negative and human epidermal growth factor receptor 2 [HER2]–negative) breast cancer is an aggressive disease with poor outcomes. Nanoparticle albumin-bound (nab)–paclitaxel may enhance the anticancer activity of atezolizumab.

METHODS
In this phase 3 trial, we randomly assigned (in a 1:1 ratio) patients with untreated metastatic triple-negative breast cancer to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel; patients continued the intervention until disease progression or an unacceptable level of toxic effects occurred. Stratification factors were the receipt or nonreceipt of neoadjuvant or adjuvant taxane therapy, the presence or absence of liver metastases at baseline, and programmed death ligand 1 (PD-L1) expression at baseline (positive vs. negative). The two primary end points were progression-free survival (in the intention-to-treat population and PD-L1–positive subgroup) and overall survival (tested in the intention-to-treat population; if the finding was significant, then it would be tested in the PD-L1–positive subgroup).

RESULTS
Each group included 451 patients (median follow-up, 12.9 months). In the intention-to-treat analysis, the median progression-free survival was 7.2 months with atezolizumab plus nab-paclitaxel, as compared with 5.5 months with placebo plus nab-paclitaxel (hazard ratio for progression or death, 0.80; 95% confidence interval [CI], 0.69 to 0.92; P=0.002); among patients with PD-L1–positive tumors, the median progression-free survival was 7.5 months and 5.0 months, respectively (hazard ratio, 0.62; 95% CI, 0.49 to 0.78; P<0.001). In the intention-to-treat analysis, the median overall survival was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (hazard ratio for death, 0.84; 95% CI, 0.69 to 1.02; P=0.08); among patients with PD-L1–positive tumors, the median overall survival was 25.0 months and 15.5 months, respectively (hazard ratio, 0.62; 95% CI, 0.45 to 0.86). No new adverse effects were identified. Adverse events that led to the discontinuation of any agent occurred in 15.9% of the patients who received atezolizumab plus nab-paclitaxel and in 8.2% of those who received placebo plus nab-paclitaxel.

CONCLUSIONS
Atezolizumab plus nab-paclitaxel prolonged progression-free survival among patients with metastatic triple-negative breast cancer in both the intention-to-treat population and the PD-L1–positive subgroup. Adverse events were consistent with the known safety profiles of each agent. (Funded by F. Hoffmann–La Roche/Genentech; IMpassion130 ClinicalTrials.gov number, NCT02425891.)

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*A complete list of the IMpassion130 trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

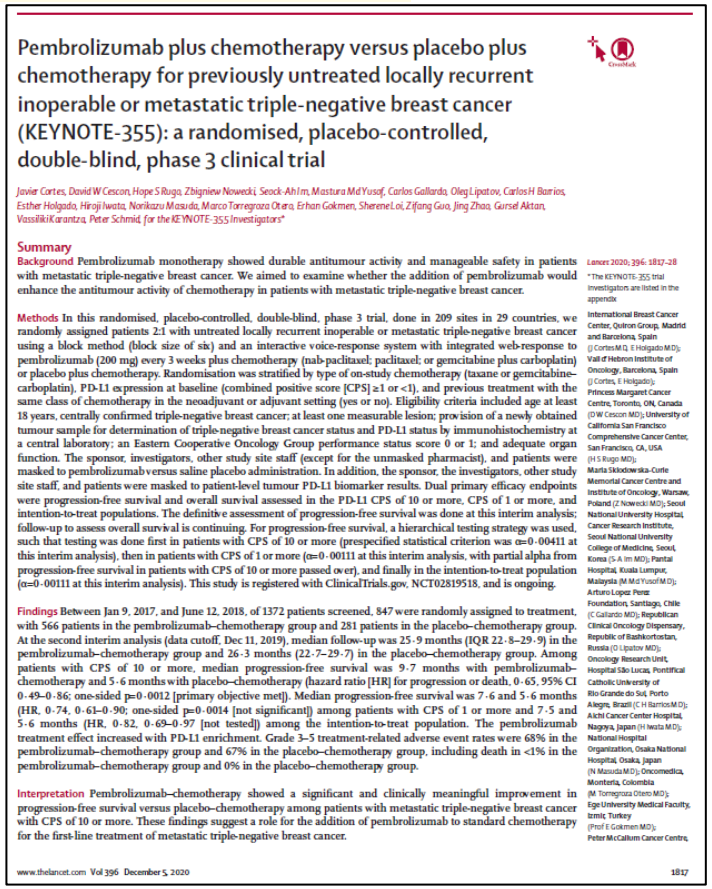
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SP142 antibody
Atezolizumab companion assay
Cutoff: >1% positive staining

Pembrolizumab (anti-PD1) KEYNOTE-355



Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial

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Summary

Background Pembrolizumab monotherapy showed durable antitumour activity and manageable safety in patients with metastatic triple-negative breast cancer. We aimed to examine whether the addition of pembrolizumab would enhance the antitumour activity of chemotherapy in patients with metastatic triple-negative breast cancer.

Methods In this randomised, placebo-controlled, double-blind, phase 3 trial, done in 209 sites in 29 countries, we randomly assigned patients 2:1 with untreated locally recurrent inoperable or metastatic triple-negative breast cancer using a block method (block size of six) and an interactive voice-response system with integrated web-response to pembrolizumab (200 mg) every 3 weeks plus chemotherapy (nab-paclitaxel; paclitaxel; or gemcitabine plus carboplatin) or placebo plus chemotherapy. Randomisation was stratified by type of on-study chemotherapy (taxane or gemcitabine–carboplatin), PD-L1 expression at baseline (combined positive score [CPS] ≥1 or <1), and previous treatment with the same class of chemotherapy in the neoadjuvant or adjuvant setting (yes or no). Eligibility criteria included age at least 18 years, centrally confirmed triple-negative breast cancer; at least one measurable lesion; provision of a newly obtained tumour sample for determination of triple-negative breast cancer status and PD-L1 status by immunohistochemistry at a central laboratory; an Eastern Cooperative Oncology Group performance status score 0 or 1; and adequate organ function. The sponsor, investigators, other study site staff (except for the unmasked pharmacist), and patients were masked to pembrolizumab versus saline placebo administration. In addition, the sponsor, the investigators, other study site staff, and patients were masked to patient-level tumour PD-L1 biomarker results. Dual primary efficacy endpoints were progression-free survival and overall survival assessed in the PD-L1 CPS of 10 or more, CPS of 1 or more, and intention-to-treat populations. The definitive assessment of progression-free survival was done at this interim analysis; follow-up to assess overall survival is continuing. For progression-free survival, a hierarchical testing strategy was used, such that testing was done first in patients with CPS of 10 or more (prespecified statistical criterion was α=0·00411 at this interim analysis), then in patients with CPS of 1 or more (α=0·00111 at this interim analysis, with partial alpha from progression-free survival in patients with CPS of 10 or more passed over), and finally in the intention-to-treat population (α=0·00111 at this interim analysis). This study is registered with ClinicalTrials.gov, NCT02819518, and is ongoing.

Findings Between Jan 9, 2017, and June 12, 2018, of 1372 patients screened, 847 were randomly assigned to treatment, with 566 patients in the pembrolizumab–chemotherapy group and 281 patients in the placebo–chemotherapy group. At the second interim analysis (data cutoff, Dec 11, 2019), median follow-up was 25·9 months (IQR 22·8–29·9) in the pembrolizumab–chemotherapy group and 26·3 months (22·7–29·7) in the placebo–chemotherapy group. Among patients with CPS of 10 or more, median progression-free survival was 9·7 months with pembrolizumab–chemotherapy and 5·6 months with placebo–chemotherapy (hazard ratio [HR] for progression or death, 0·65, 95% CI 0·49–0·86; one-sided p=0·0012 [primary objective met]). Median progression-free survival was 7·6 and 5·6 months (HR, 0·74, 0·61–0·90; one-sided p=0·0014 [not significant]) among patients with CPS of 1 or more and 7·5 and 5·6 months (HR, 0·82, 0·69–0·97 [not tested]) among the intention-to-treat population. The pembrolizumab treatment effect increased with PD-L1 enrichment. Grade 3–5 treatment-related adverse event rates were 68% in the pembrolizumab–chemotherapy group and 67% in the placebo–chemotherapy group, including death in <1% in the pembrolizumab–chemotherapy group and 0% in the placebo–chemotherapy group.

Interpretation Pembrolizumab–chemotherapy showed a significant and clinically meaningful improvement in progression-free survival versus placebo–chemotherapy among patients with metastatic triple-negative breast cancer with CPS of 10 or more. These findings suggest a role for the addition of pembrolizumab to standard chemotherapy for the first-line treatment of metastatic triple-negative breast cancer.

Lancet 2020; 396: 1817–28

*The KEYNOTE-355 trial investigators are listed in the appendix

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22C3 antibody
Pembrolizumab FDA-approved companion assay
CPS score cutoff >10%

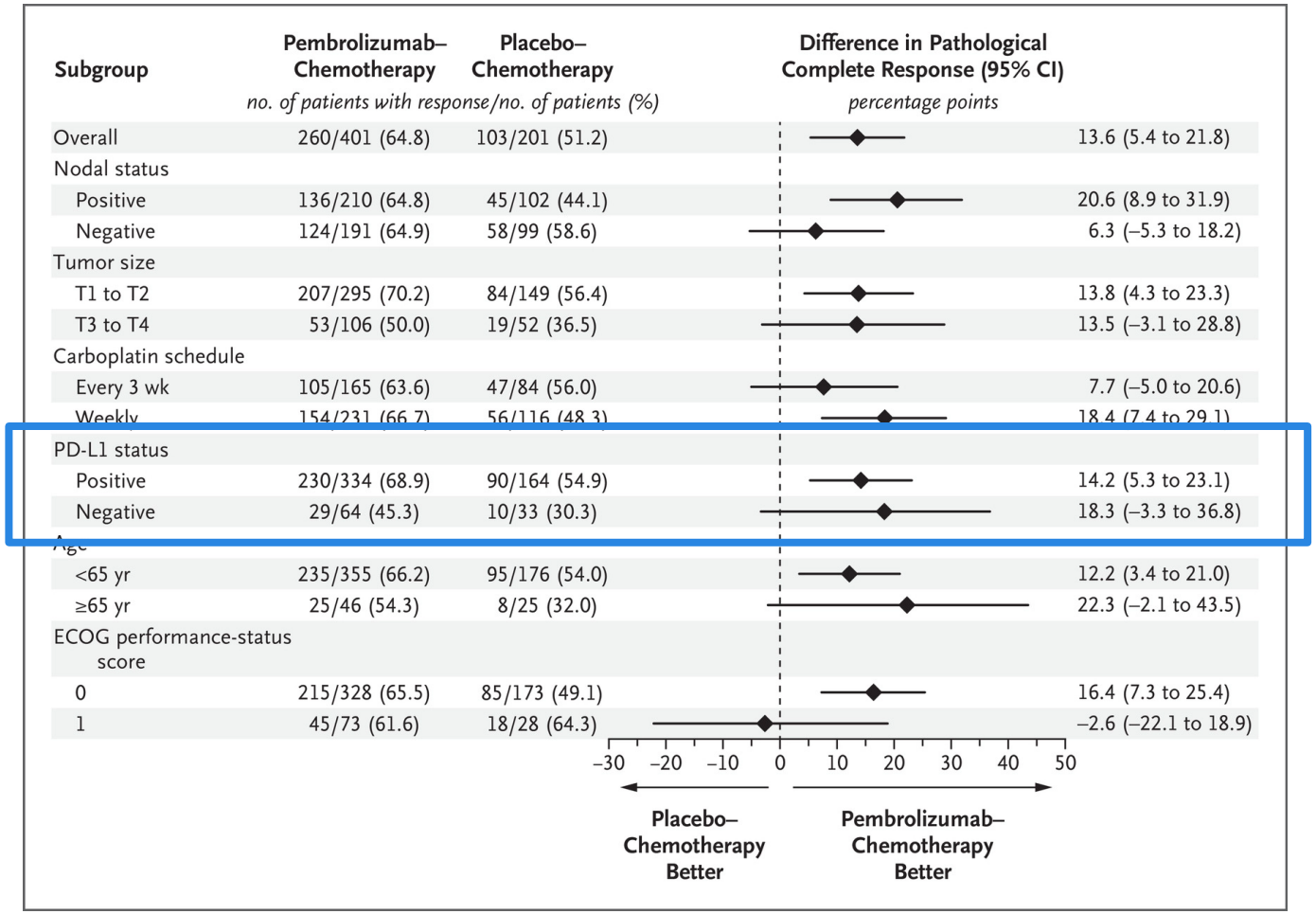
Combined Positive Score (CPS)

$$CPS = \frac{\text{\# PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# of viable tumor cells}} \times 100$$

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KEYNOTE-355: Higher response in PD-L1(+) TNBC

pCR in pts with TNBC treated with pembro-chemoTp was
68.9% in PD-L1(+) vs 45.3% in PD-L1(-)



Schmid P. N Engl J Med. 2020 382:810-821.

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PD-L1 in Metaplastic BC

PD-L1 expression higher in MBCs than other BC

Breast cancer subtype	PD-L1 status Cut-off ≥2+ intensity/≥5% tumour cells Negative	Positive	Total
Metaplastic carcinoma	39 (54%)	33 (46%)	72
TNBC-NOS	93 (91%)	9 (9%)	102
HER2-positive breast cancer	30 (94%)	2 (6%)	32
Hormone-positive breast carcinoma	79 (94%)	5 (6%)	84
Total	241 (83%)	49 (17%)	290

Joneja U, NPJ Breast Cancer. 2021 Jul 22;7(1):96.

Tumor Type	PDL1 (+)
Metaplastic	46%
TNBC	9%
ER-/ HER2+	6%
ER+/ HER2-	6%

Grabenstetter A. et al.
Am J Surg Pathol 2021;45:1274–1281

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Immunotherapy and Metaplastic BC: Reports of excellent response

Author, Year	Treatment setting	Subtype and staging	Chemotherapy regimens	Immunotherapy	Treatment response
Adams (2017)	Adjuvant	TNBC spindle cell, pT3N1a progressed to T4N1M1	(1) Adriamycin, cyclophosphamide (2) Doxorubicin, bevacizumab, everolimus then gemcitabine, carboplatin, IL-10	Nab-paclitaxel + pembrolizumab	9 weeks ulcerating wound healed and PET negative
Sayed (2019)	Adjuvant	TNBC squamous, cT4N1M0, ypT4N1aMx	(1) Neo-adjuvant 5-FU, Cytoxan, epirubin + docetaxel (2) Adjuvant capecitabine	Paclitaxel + durvalumab	Complete clinical response, NED on repeat imaging; continued response
Gorshein (2021)	Neo-adjuvant	TNBC, matrix-producing cT3NxM1		Pembrolizumab	Partial response at 1-year, s/p ALND, then 32 month follow up NED on imaging

Adams, S, NPJ Breast Cancer. March 29; 3, 8 (2017)
Gorshein, E, Case Rep Oncol. 2021:14:931-937
Sayed, A, Am J Case Rep. Nov 6; 30:1630-1635

Ongoing clinical trials for Metaplastic BC

Trial	Phase	Status
ARQule: ARQ751 (pan-AKT inhibitor) plus fulvestrant or paclitaxel compared to ARQ751 plus placebo in patients with breast or endometrial cancer harboring *PIK3CA*/AKT/PTEN mutations (NCT02761694)	1b	Ongoing
ARTEMIS: A clinical trial implementing diagnostic imaging + tumor genetic signature to predict sensitivity to standard-of-care versus personalized therapy. A non-randomized trial in which patients undergo baseline imaging and molecular testing of tumor biopsy. They receive standard anthracycline-based chemotherapy and undergo ultrasound imaging after cycles 2 and 4. After completing cycle 4 and obtaining molecular testing results, the patient may elect to continue standard chemotherapy or proceed to an experimental clinical trial designed to match tumor profile and TNBC subtype. Patients with tumors predicted to be resistant to standard chemotherapy are advised to participate in the experimental clinical trial (NCT02276443)	N/A	Ongoing
L-NMMA (pan-nitric oxide synthase) inhibitor plus docetaxel in refractory locally advanced or metastatic TNBC patients (NCT02834403)	1b/2	Ongoing
DART - Dual anti-CTLA4 and anti-PD1 blockade in rare tumors: Nivolumab (anti-CTLA4) antibody) plus ipilimumab (anti-PDL1 antibody) compared to nivolumab alone for patients with rare tumors, including MpBC (NCT02834013)	2	Ongoing
Pembrolizumab (anti-PD1 antibody) plus nab-paclitaxel for TNBC and HR+/HER2− breast cancer cohorts (NCT02752685)	2	Ongoing

Reddy, T.P, Breast Cancer Res. Nov 04; 22, 121(2020)

Metaplastic BC: Take home message

- **Heterogeneous morphology**
- **Worse prognosis than other TNBC stage-by-stage**

  Worst: spindle cell, squamous cell, mixed metaplastic

  Relatively better: metaplastic with heterologous mesenchymal elements / (myxochondroid)

  genetic evidence links metaplastic with heterologous mesenchymal elements to Homologous Recombination Deficiency → Olaparib treatment?

  – ***Fibromatosis-like: Locally aggressive, low metastatic potential***

  – ***Low Grade adenosquamous: Locally aggressive, questionable metastatic potential***

- **Very low (<5%) pCR rate after NAC, unlike other TNBC**
  – **disease progression in 27-40% cases**

- **High rate of PDL1(+) MBC**
  – **Immunotherapy may be beneficial**

Thank you for your attention



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