Triple-Negative Breast Cancer: Pathologic and Molecular Features

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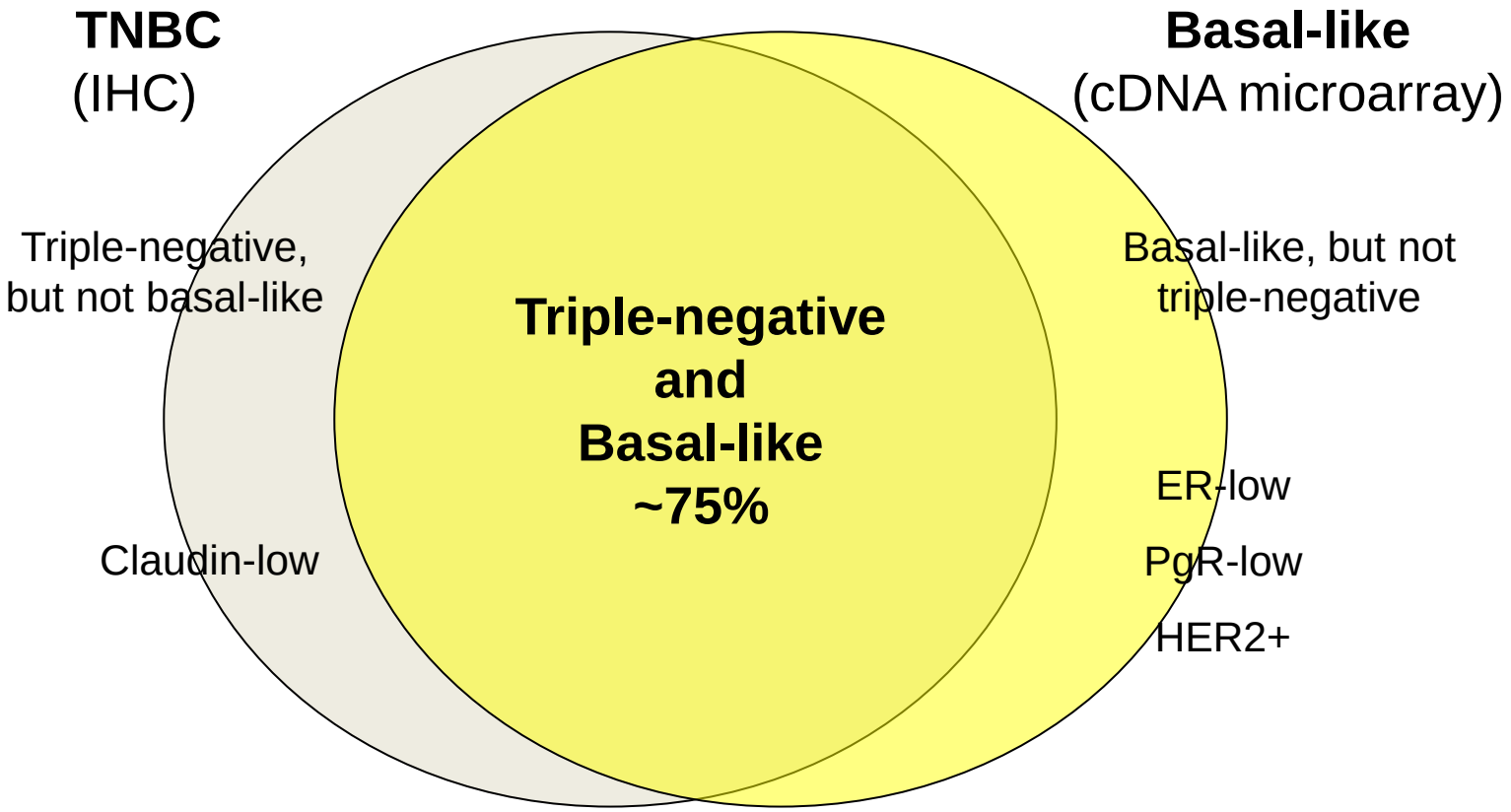
Triple-negative breast cancers

- Definition
- Histologic and clinical features
- Molecular phenotypes
  - Basal-like
  - Claudin-low
  - HER2-enriched

Triple negative breast cancer

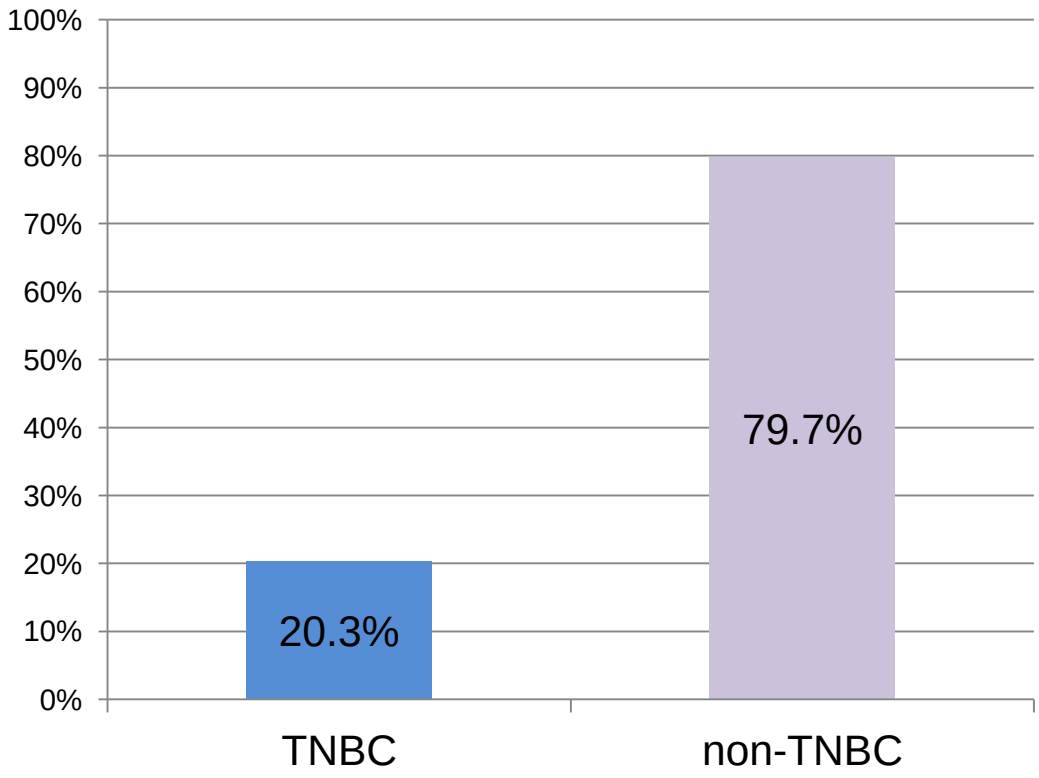
- ER-negative, PR-negative & HER2-negative
- 10~20% of all breast cancers
  - ✓ Depending on the thresholds used to define ER/PR positivity and the methods for HER2 assessment
- Clinical implications
  - ✓ Lack of tailored therapy (hormone therapy, HER2-targeted therapy)
  - ✓ Overlap profiles with basal-like cancers

TNBC VS Basal-like



Incidence of TN cancers in Korean breast cancer patients (n=1,198)

Unpublished data

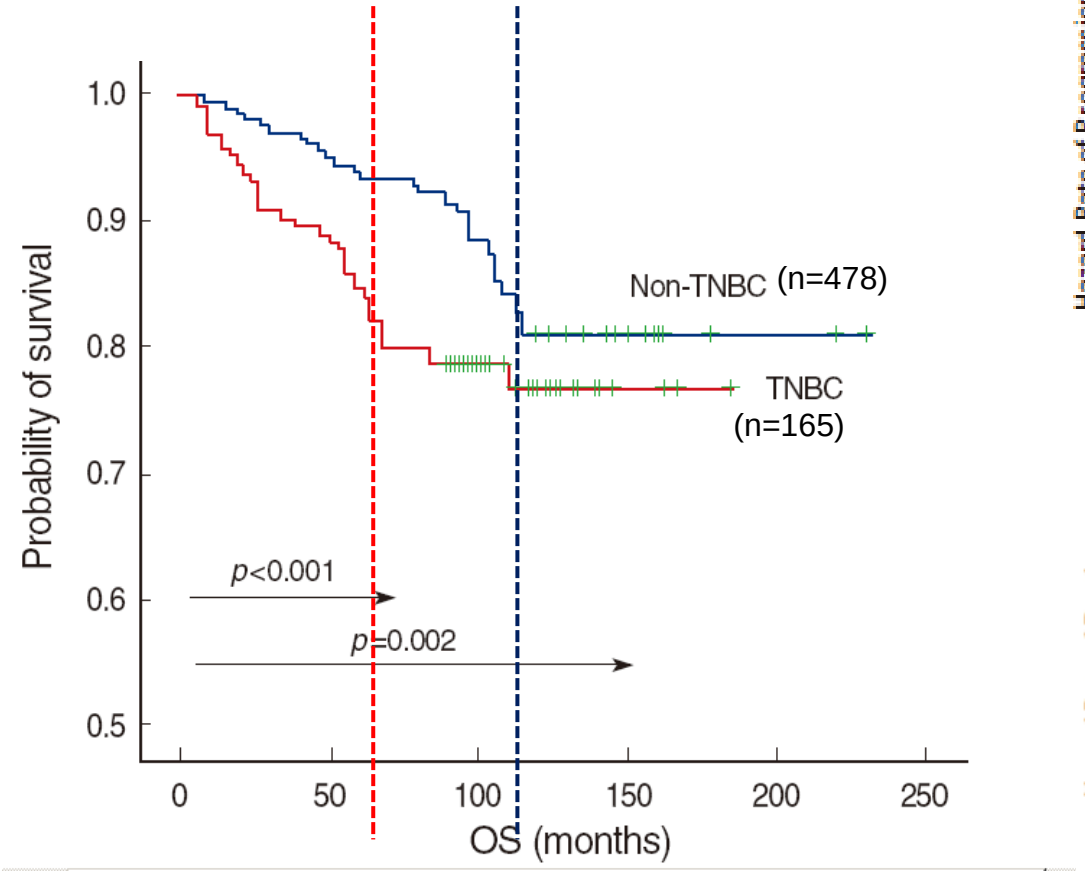


ER(SP1), AS>2
PR(1E2), AS> 2
HER2, SISH positive

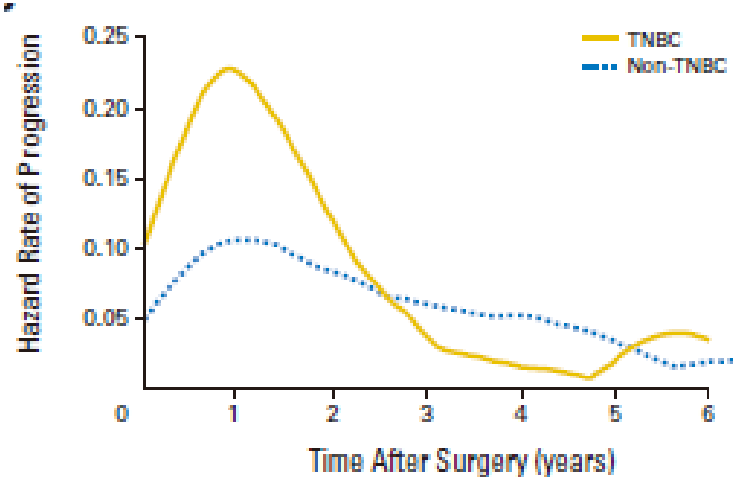
Clinical features of TNBC

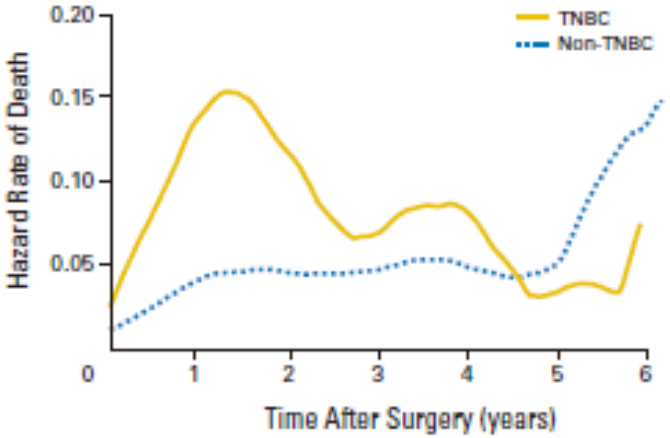
- More prevalent in
  - ✓ Younger patients (< 50 years)
  - ✓ African-American women
  - ✓ *BRCA1* mutation carriers
- More aggressive than non-TNBC
  - ✓ High risk of early relapse(1^{st} ~3^{rd} years)
  - ✓ Majority of deaths in the first 5 years
- Pattern of metastatic spread
  - ✓ Favor a hematogeneous spread (lungs, brain)
  - ✓ Less frequently metastasize to axillary nodes and bone

Survival of TNBC



Bae et al. J Breast Cancer 2009;12:4-13





J Clin Oncol 2008;26:1275-81

pCR to neoadjuvant chemotherapy

		pCR(%)		
Regimens	No	TNBC	Non-TNBC	p
FAC/FEC/AC (n=308)	308	20	5	0.001
TFAC/TFEC (n=588)	588	28	17	0.072
Single agent taxane (n=58)	58	12	2	0.82
Other (n=164)	164	14	7	0.33
Total (n=1,118)	1118	22	11	0.034

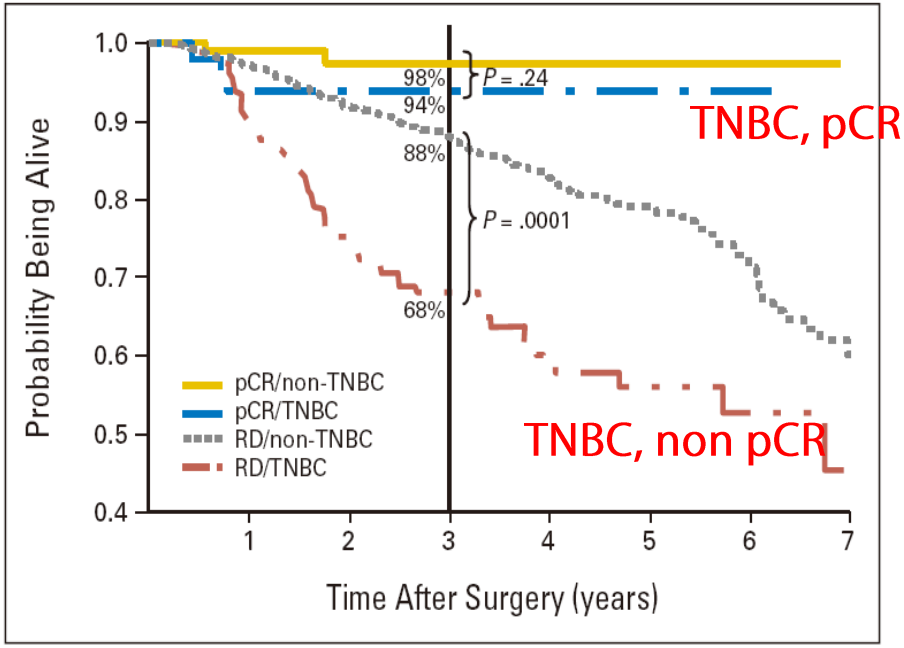
J Clin Oncol 2008;26:1275-81

Molecular classification	No	pCR (%)	
Luminal A/B subtype	30	7	
Normal breast like	10	0	
HER2+	20	45	
Basal subtype	22	45	p<0.001

Clin Cancer Res 2005;11:5678-85

Survival of TNBC according to pCR

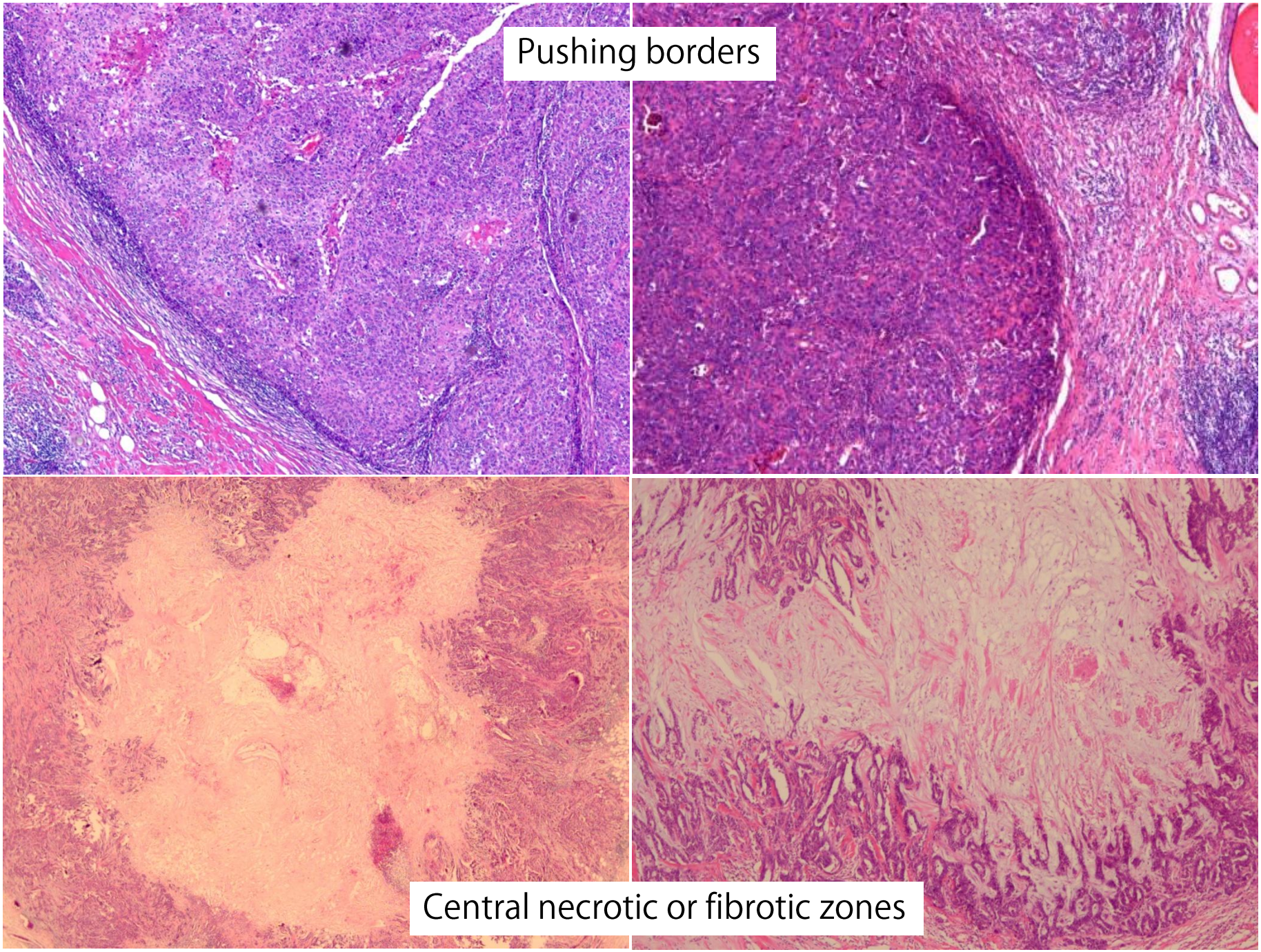
- High pCR rates after anthracycline or platinum-based neoadjuvant chemotherapy
  - ✓ Patients with pCR have excellent prognosis
  - ✓ Patients with residual disease have a dismal outcome

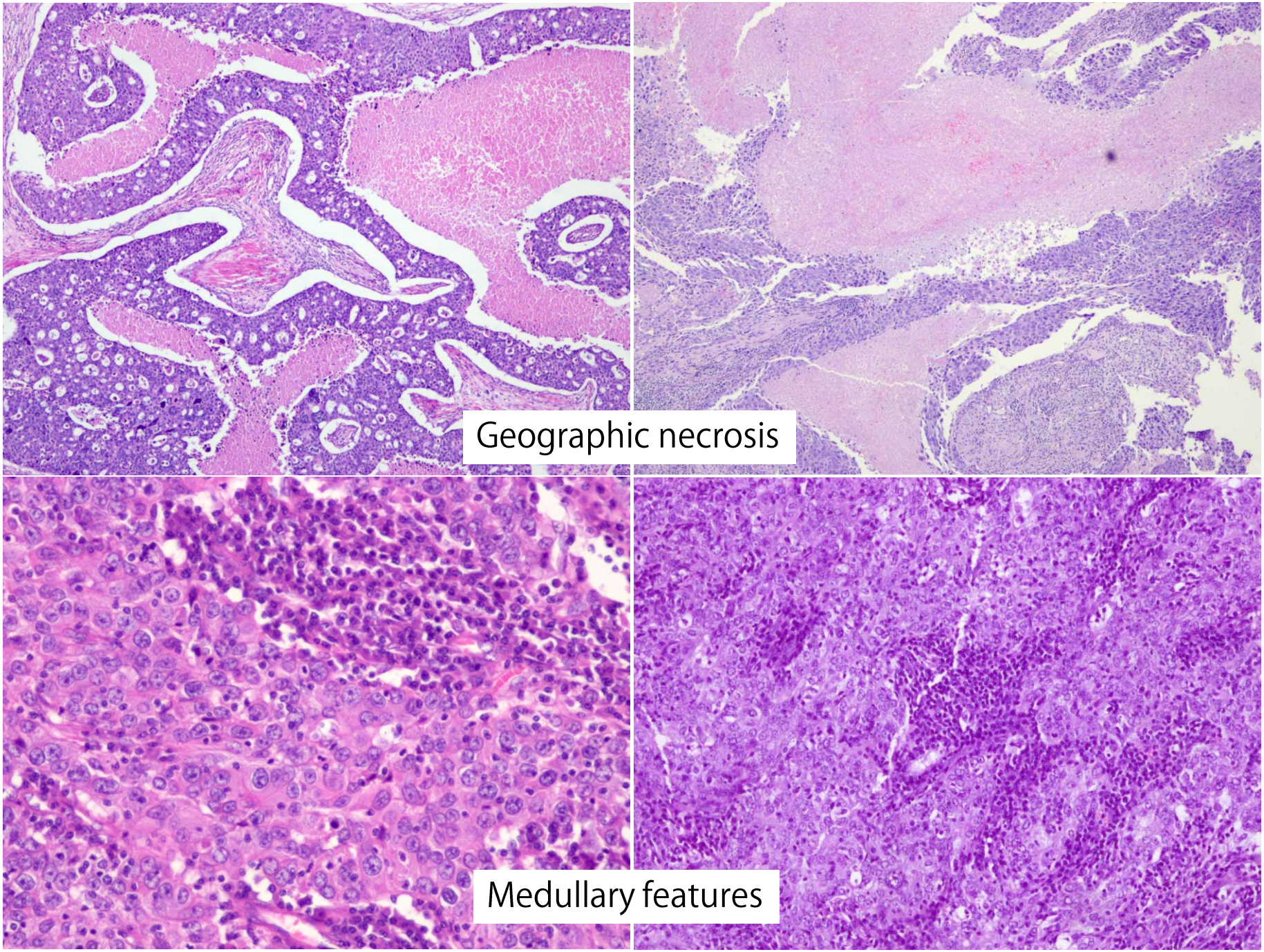


J Clin Oncol 2008;26:1275-81

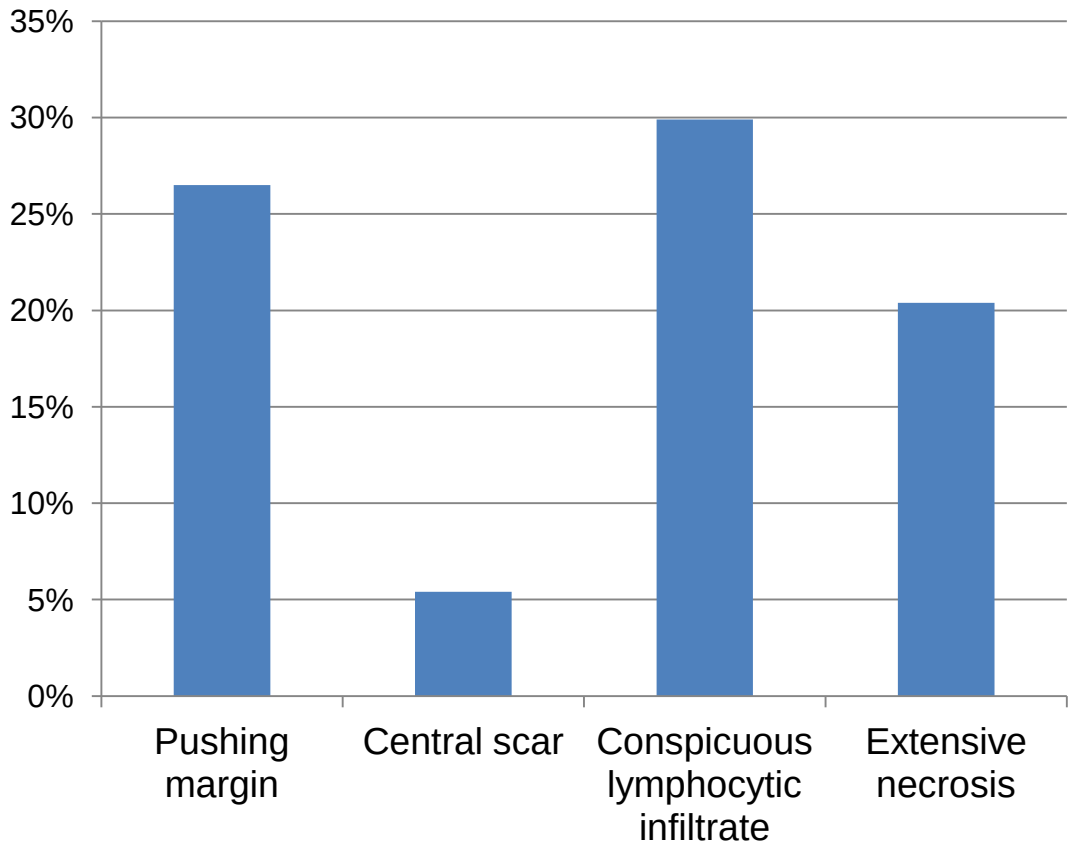
Morphologic features of TNBC

- High histological grade
- High mitotic index
- Central necrotic or fibrotic zones
- Pushing borders
- Conspicuous lymphocytic infiltrate
- Typical/atypical medullary features
- Presence of metaplastic elements
  - ✓ Squamous cells
  - ✓ Spindle cells


Pushing borders
Central necrotic or fibrotic zones


Geographic necrosis
Medullary features

Incidence of characteristic morphologies in TNBCs (n=147)



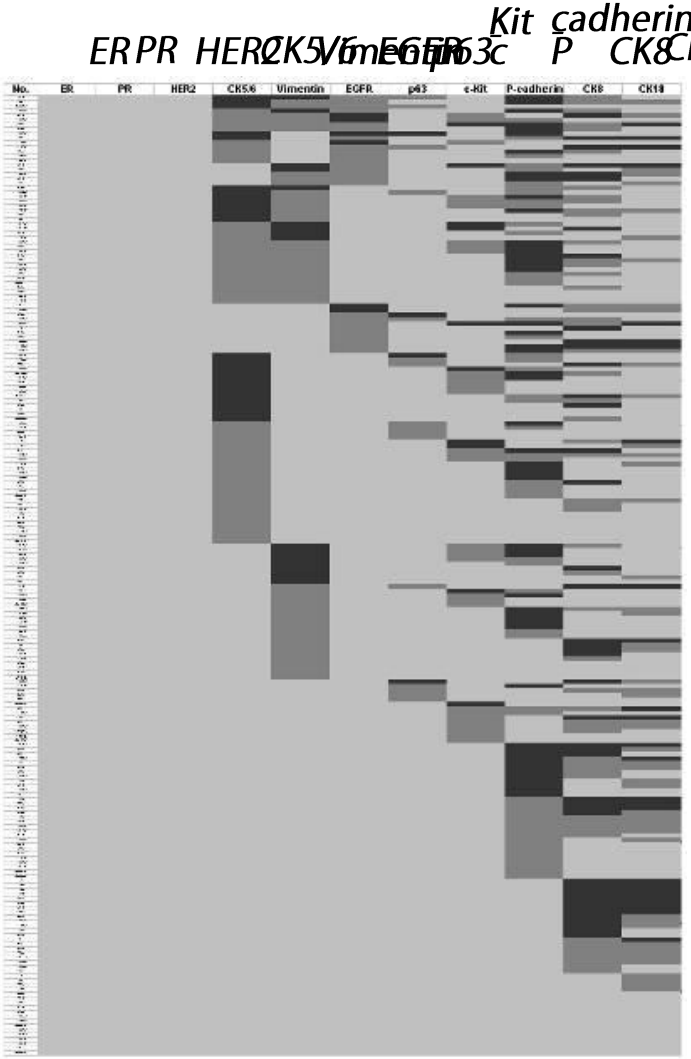
Bae et al. 2008 USCAP abstract #80

Histologic types of TNBC

- High grade tumors
  - ✓ Invasive ductal, NOS, grade 3
  - ✓ (Atypical) Medullary
  - ✓ Metaplastic
  - ✓ Apocrine
- Low grade tumors
  - ✓ Secretory
  - ✓ Adenoid cystic
- Myoepithelial

Heterogeneity of immunophenotype in TNBC

(n=212)



Conclusion: IHC profiles do not define robust clusters within TN breast cancers

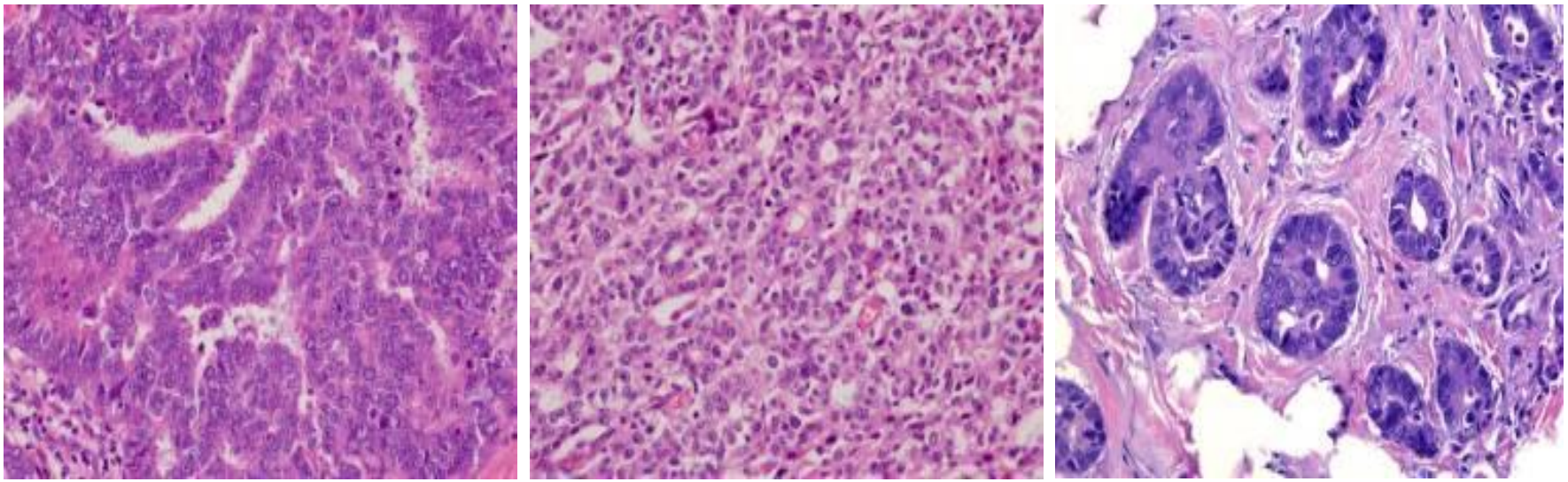
Focal: <70% cells positive

Diffuse: ≥70% cells positive

Bae et al. 2008 USCAP abstract #80

Comparison of morphology among cases with similar IHC expression

No.	ER	PR	HER2	CK5/6	Vim	EGFR	p63	c-Kit	P-cad	CK8	CK18
34											
109											
199											



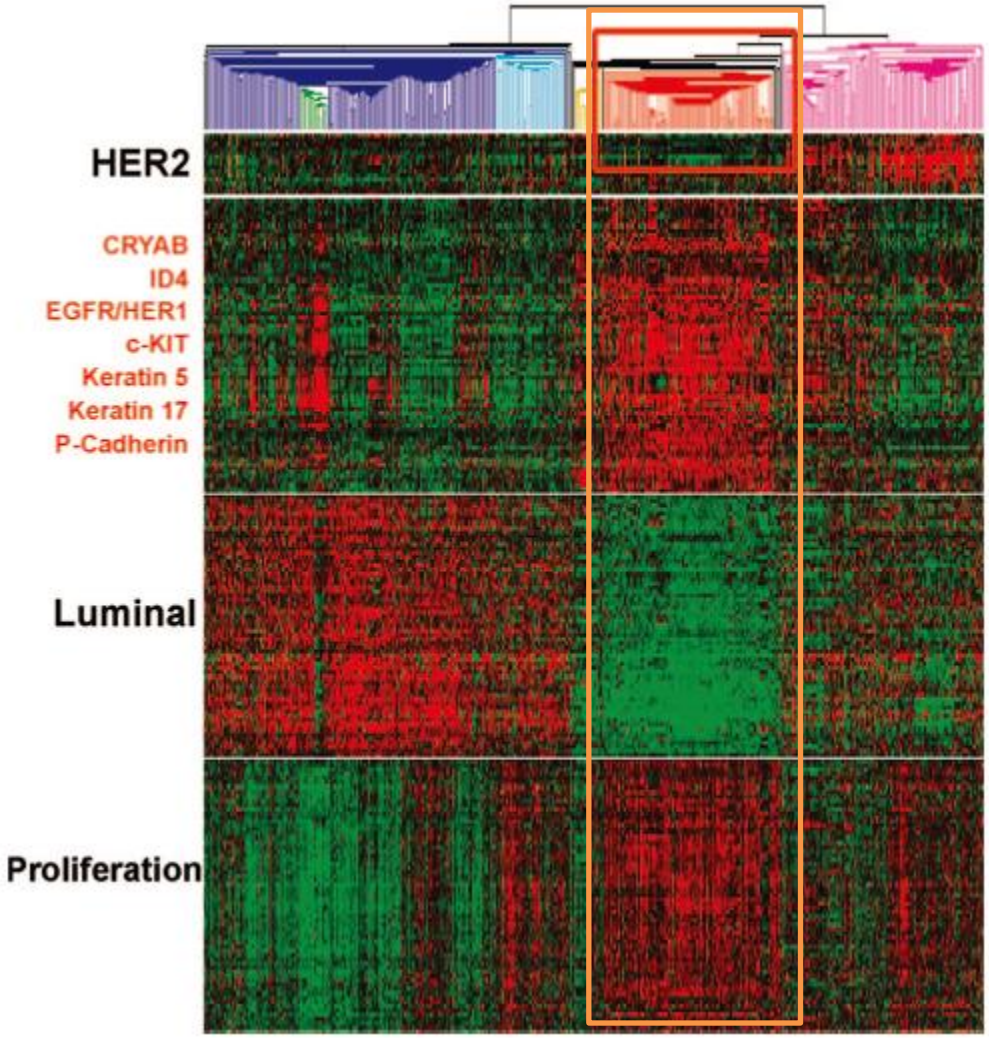
Comparison of morphologic phenotype for three cases showing coexpression of CK5/6 and c-Kit

Bae et al. 2008 USCAP abstract #80

Molecular subtypes of TNBC

Subtypes	Frequency	Characteristics
Basal-like	39-54%	Expression of basal CKs, share common expression profile with BRCA1 related tumors
Claudin-low	25-39%	Expression of stem cell and mesenchymal associated genes
HER2-enriched	7-14%	Overexpression of HERs but lack of HER2 gene amplification
Luminal B	4-7%	Low level expression of luminal markers and luminal associated genes
Luminal A	4-5%	High level expression of luminal markers and luminal associated genes
Apocrine	~5%	Expression of androgen receptor pathway genes

Basal-like breast cancer



- p53 mutated in > 50%
- Highly proliferative (RB loss)
- BRCA1-associated
- Genetic instability

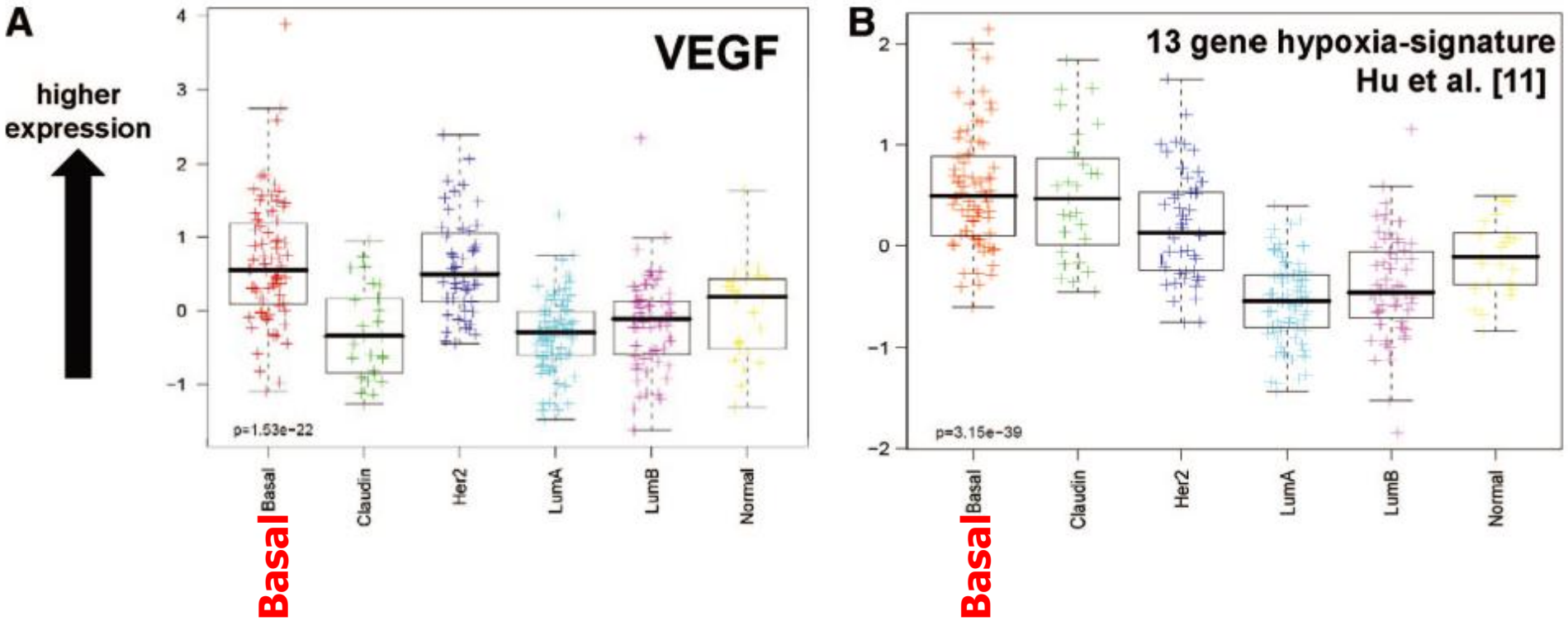
Perou, Oncologists 2011;16(suppl1):61-70

Basal-like breast cancer and BRCA1 phenotype

	Basal-like and TN	Cancers arising in BRCA1 mutation carriers
BRCA1 dysfunction	BRCA1 promoter hypermethylation/ BRCA1 downregulation by ID4 overexpression	BRCA1 gene mutation
ER & PR-negative	√	√
HER2-negative	√	√
High grade	√	√
Pushing border	√	√
Lymphocytic infiltrate	√	√
p53 mutation	√	√

Oncogene 2006;25:5846-53

BRCA1 dysfunction appears to be one of the drivers of basal-like breast cancers and of a subgroup of triple-negative cancers



Perou, Oncologists 2011;16(suppl1):61-70

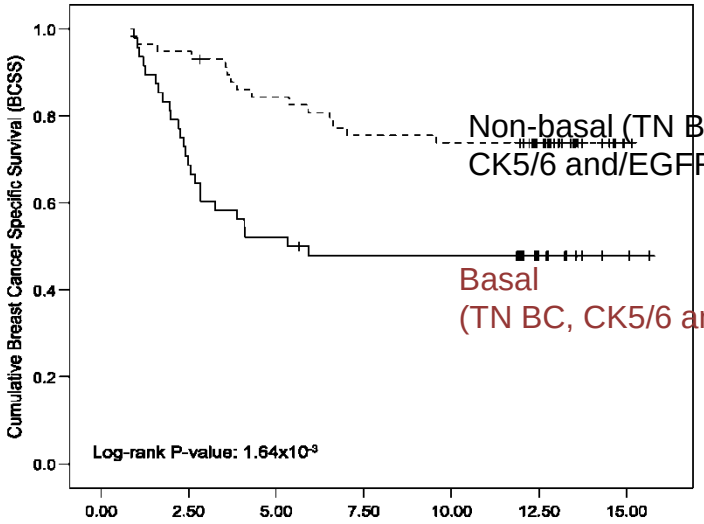
Immunohistochemical surrogates for BLBC

- Triple negative phenotype
- ER-HER2 negative (double negative)
- Expression of one or more basal cytokeratins (CK5,6,17)
- Lack of expression of ER and HER2 with expression of CK5/6 and/or EGFR

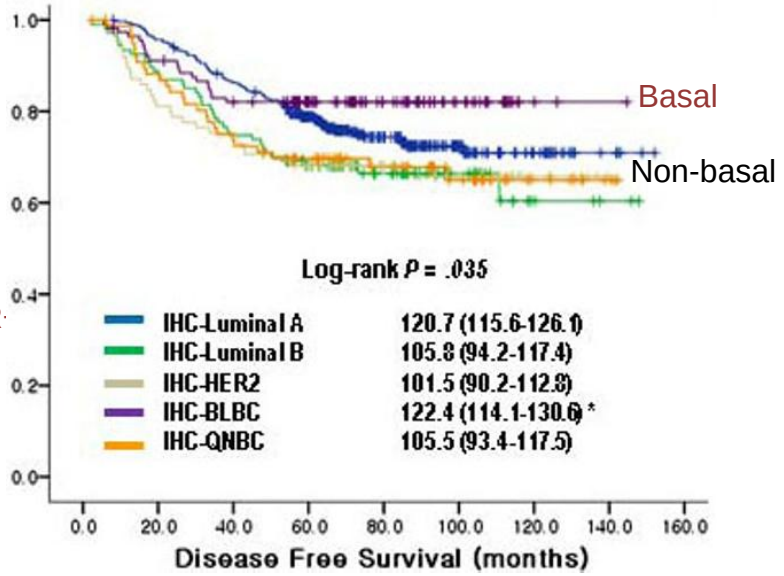
- There is no internationally accepted definition or consensus for BLBCs

Prognosis of TNBC according to basal phenotype

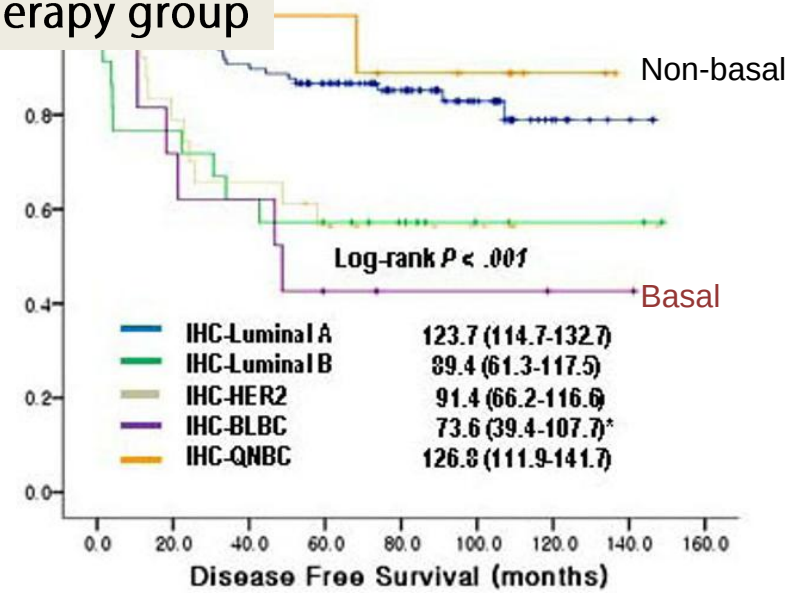
With chemotherapy group



Clin Cancer Res 2008;14:1368-76



Without chemotherapy group

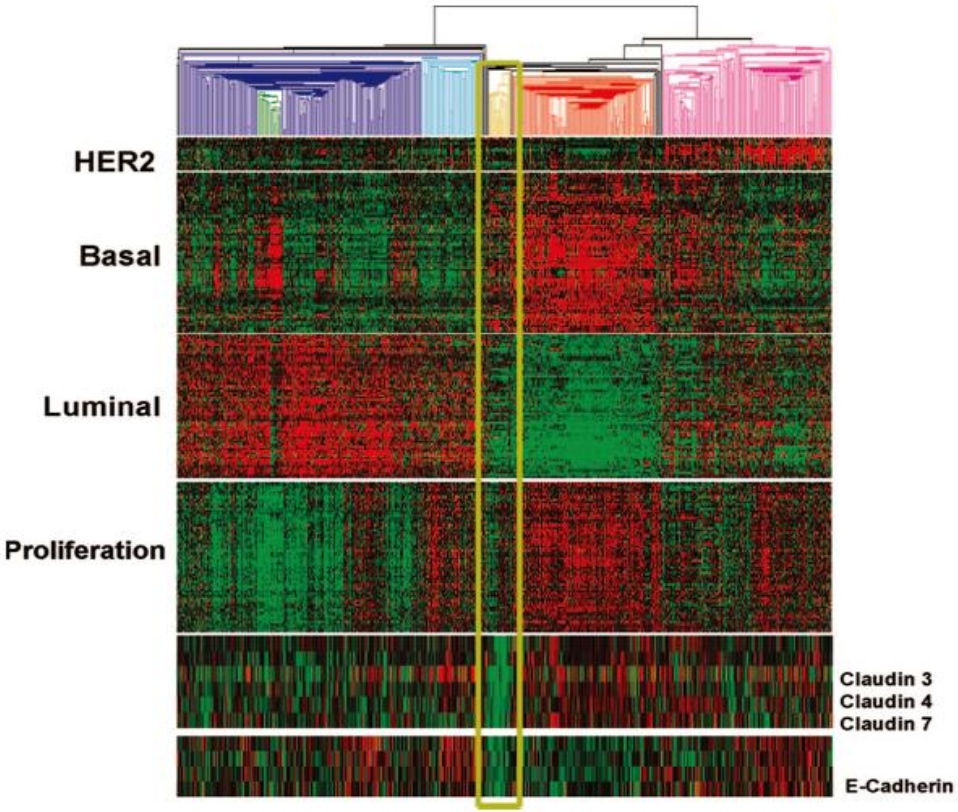


Survival in BLBC

	HR(95% CI)	p	HR(95% CI)	p
Adjuvant CTx		0.028		0.011
Not done	1		1	
Done	0.34 (0.12-0.88)		0.22 (0.08-0.59)	

Claudin-low subtype

- 5-10% of breast cancers
- Lack of/low expression of claudins,-3, -4, -7 and E-cadherin
- Stem cell and epithelial-to-mesenchymal transition features
- Poor prognosis as seen in luminal B, HER2-enriched and basal-like subtype



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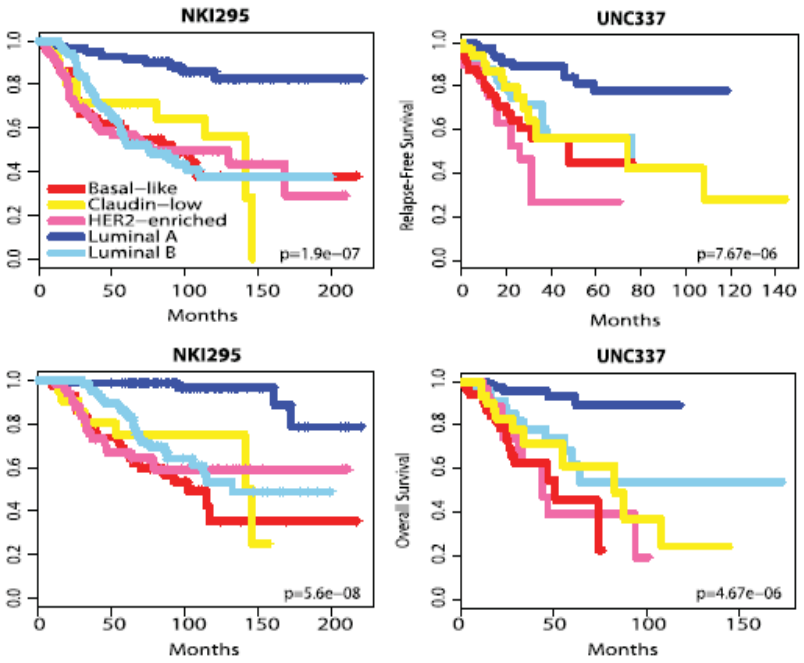
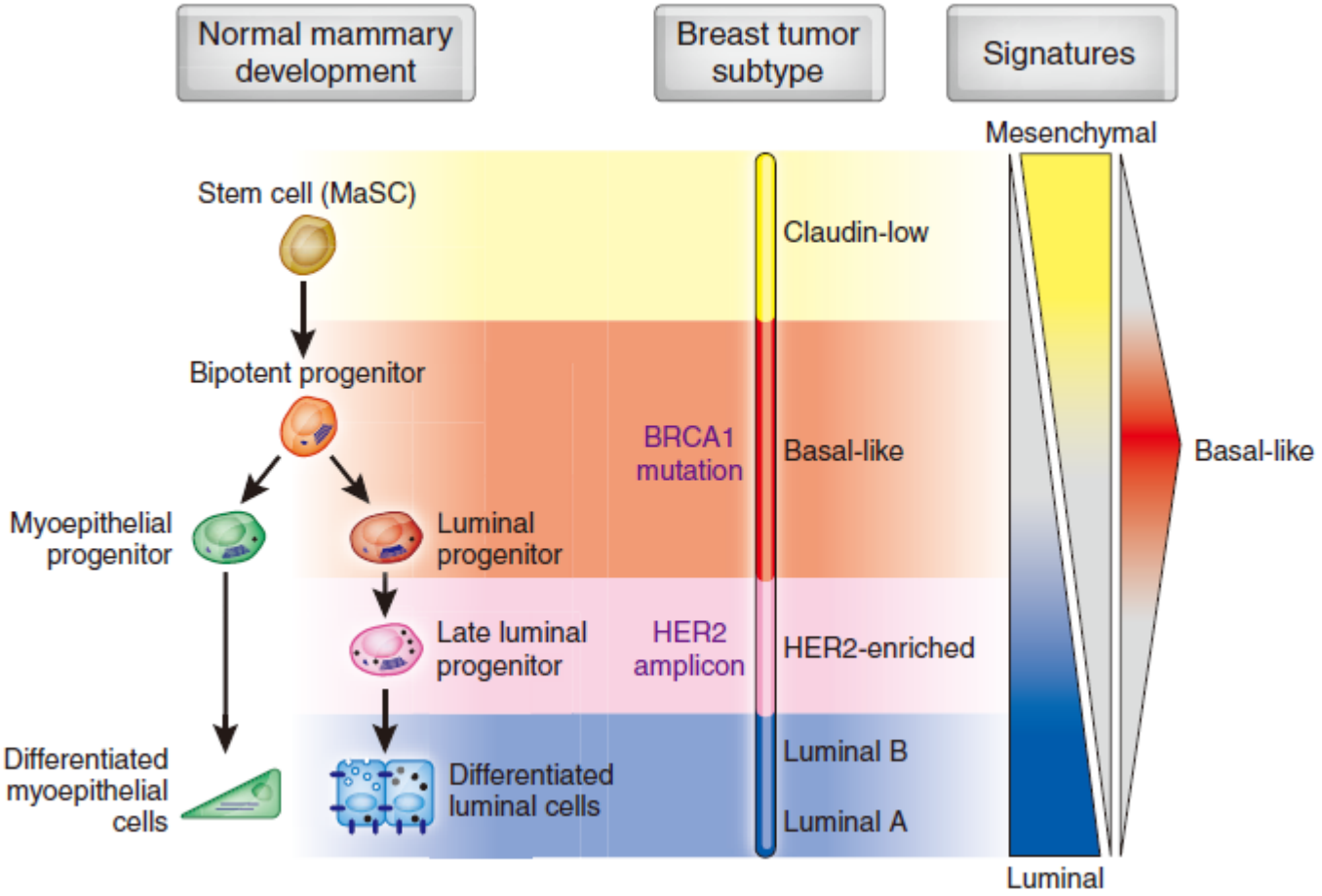


Prat et al. Breast Cancer Research 2010, 12:R68



Prat & Perou, Nature Med 2009;15:842-4

- Basal-like breast cancers may originate from luminal progenitors rather than basal/myoepithelial cells of the breast
- Histogenesis and differentiation are two distinct processes although often mistakenly used as synonyms

Summary

- TNBC is a heterogeneous entity, and can be classified into several biologically distinct subtypes
- In the absence of therapy, patients with TNBC have a poor prognosis
- TNBC does benefit from chemotherapy, but better treatment options are needed.
- PARP inhibitor, antiangiogenesis therapy and therapies targeting cancer stem cells may have an important impact in TNBC patients