



Dealing with heterogeneity of triple negative breast cancer: From luminal androgen receptor to mesenchymal stem like subtype

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Disclosures

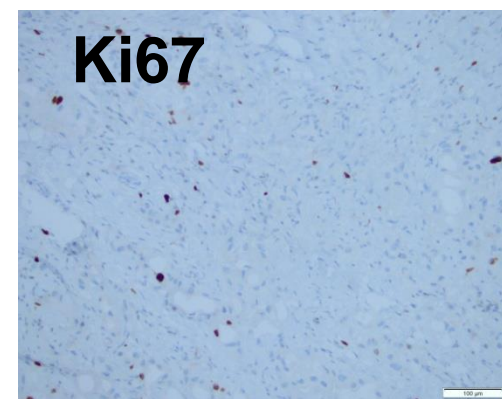
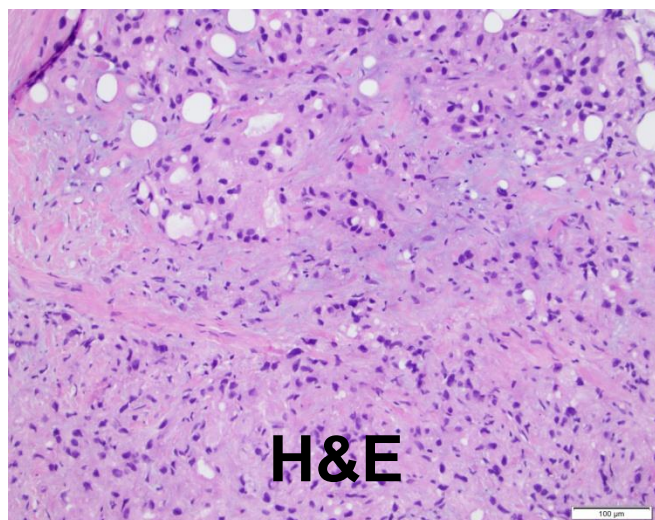
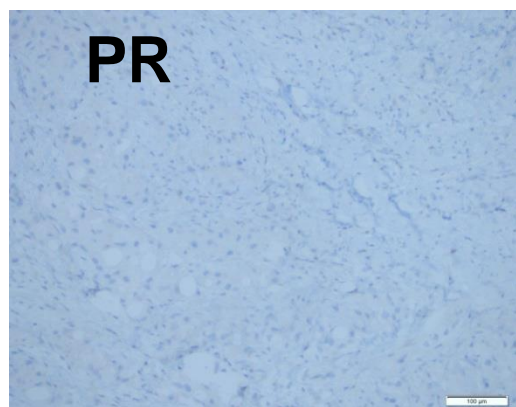
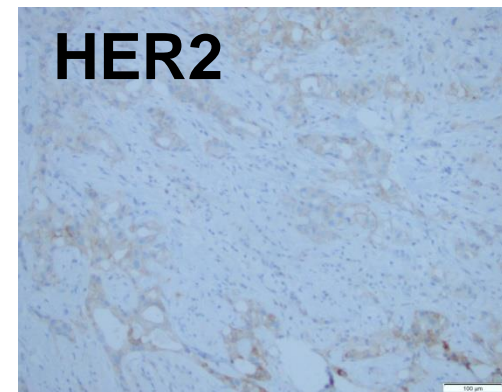
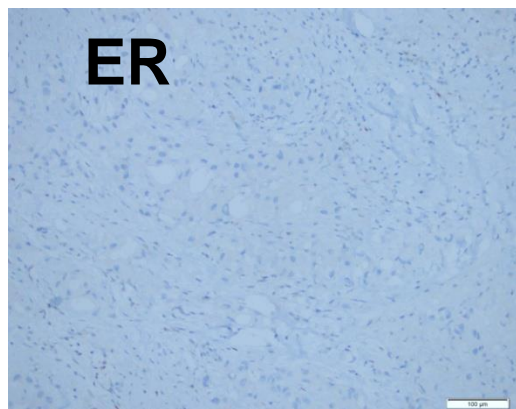
- Advisor
 - Roche, Celgene
- Honoraria
 - Roche, Novartis, Celgene, Eisai

Case Presentation

- 60 year-old postmenopausal woman
 - ~15 mm, grade 2, apocrine, ER neg, PR neg, HER2-neg
- No metastases observed
- Treated with lumpectomy + SLNB
 - 18 mm, grade 2, apocrine carcinoma of the breast, triple negative, Ki 67 11%
 - 1 +(IHQ)/2 LN

Stage pT1cN0(i+)M0

Case Presentation



Case Presentation

- How to treat this patient?
 - Chemotherapy?
 - Radiation therapy only?
- No data about chemotherapy benefit in this tumor type, but...
 - Triple negative
 - But Ki67 11%

Case Presentation

- MammaPrint®...

1

Your SYMPHONY Results

MammaPrint® Results

High Risk of Recurrence

Low Risk of Recurrence

Your Tumor is
High Risk

TargetPrint® Results
quantitative mRNA gene expression

ER Negative

-1.0

0.0

1.0

PR Negative

-1.0

0.0

1.0

HER2 Negative

-1.0

0.0

1.0

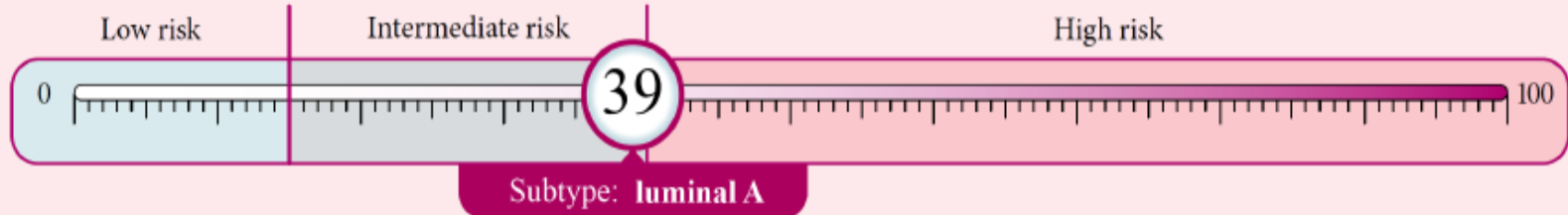
Blueprint™ Subtype when combined with
MammaPrint®

High Risk Luminal

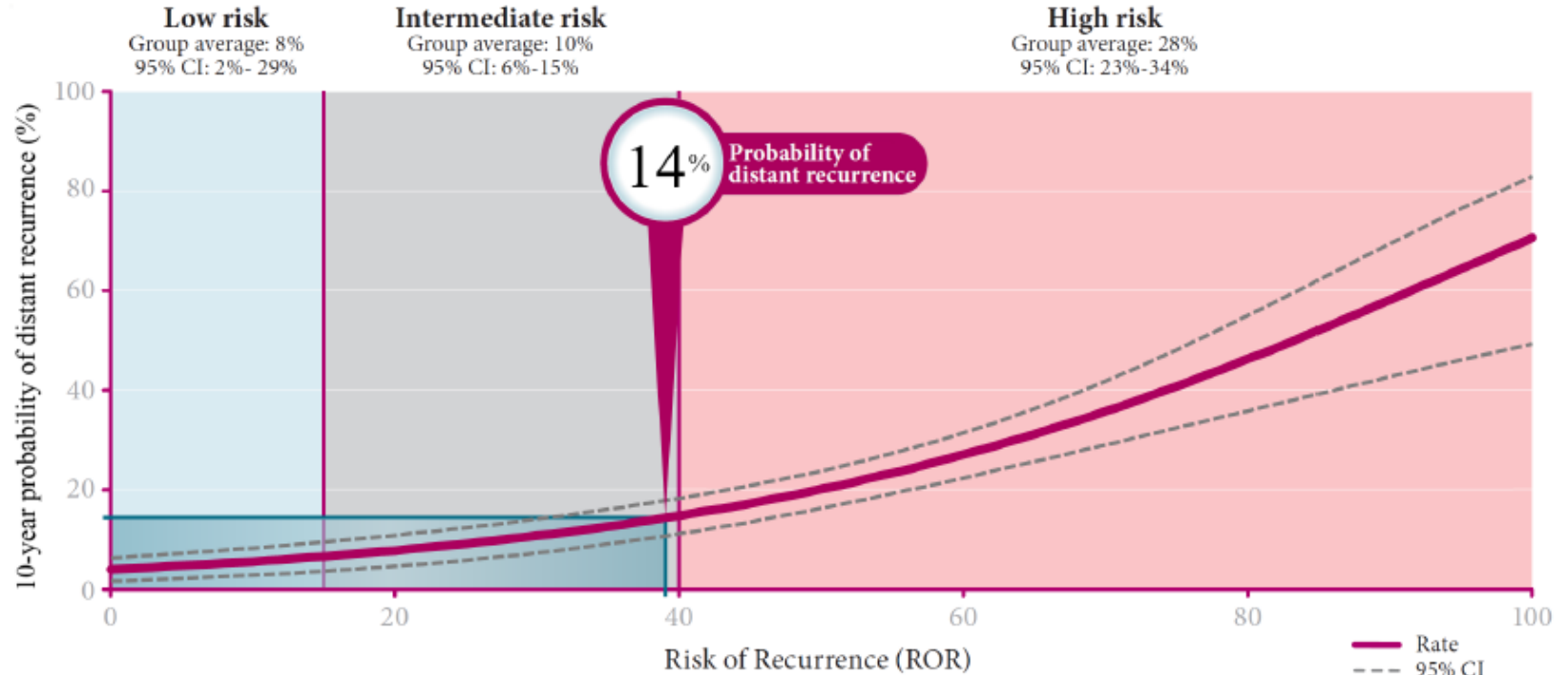
Case Presentation

- Prosigna®

Risk of Recurrence*:



* The ROR ranges from 0 through 100 and correlates with the probability of distant recurrence (DR) in the tested patient population. The risk classification is provided to guide the interpretation of the ROR using cutoffs related to clinical outcome.

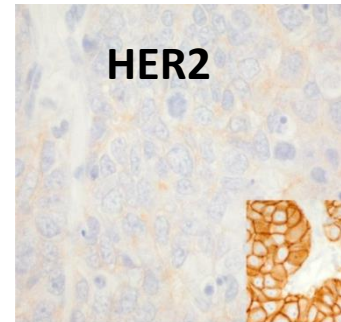
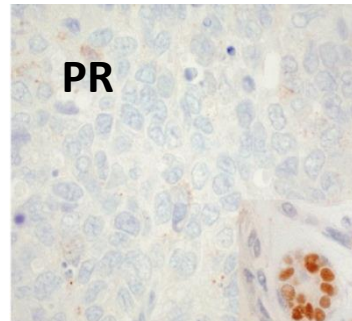
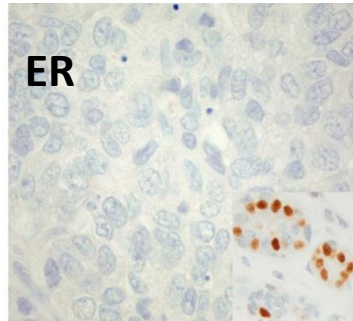


Case Presentation

- TC X 4
- Radiation Therapy
- 20 m after diagnosis
 - CEA: 8 CA 15.3: 60
 - Bone metastases
 - Mediastinal lymph nodes

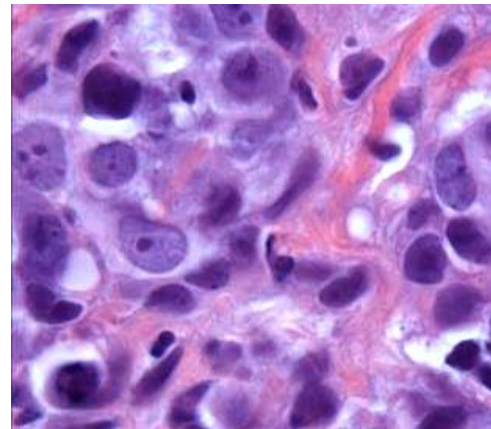
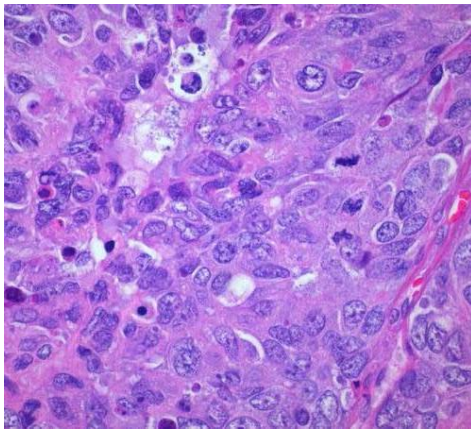
“Triple Negative” Breast Cancer

Immunohistochemistry



- ER and PR <1% nuclear
- HER2 “negative”: IHC 0 or 1+ staining or 2+ IHC staining with negative FISH

Histology



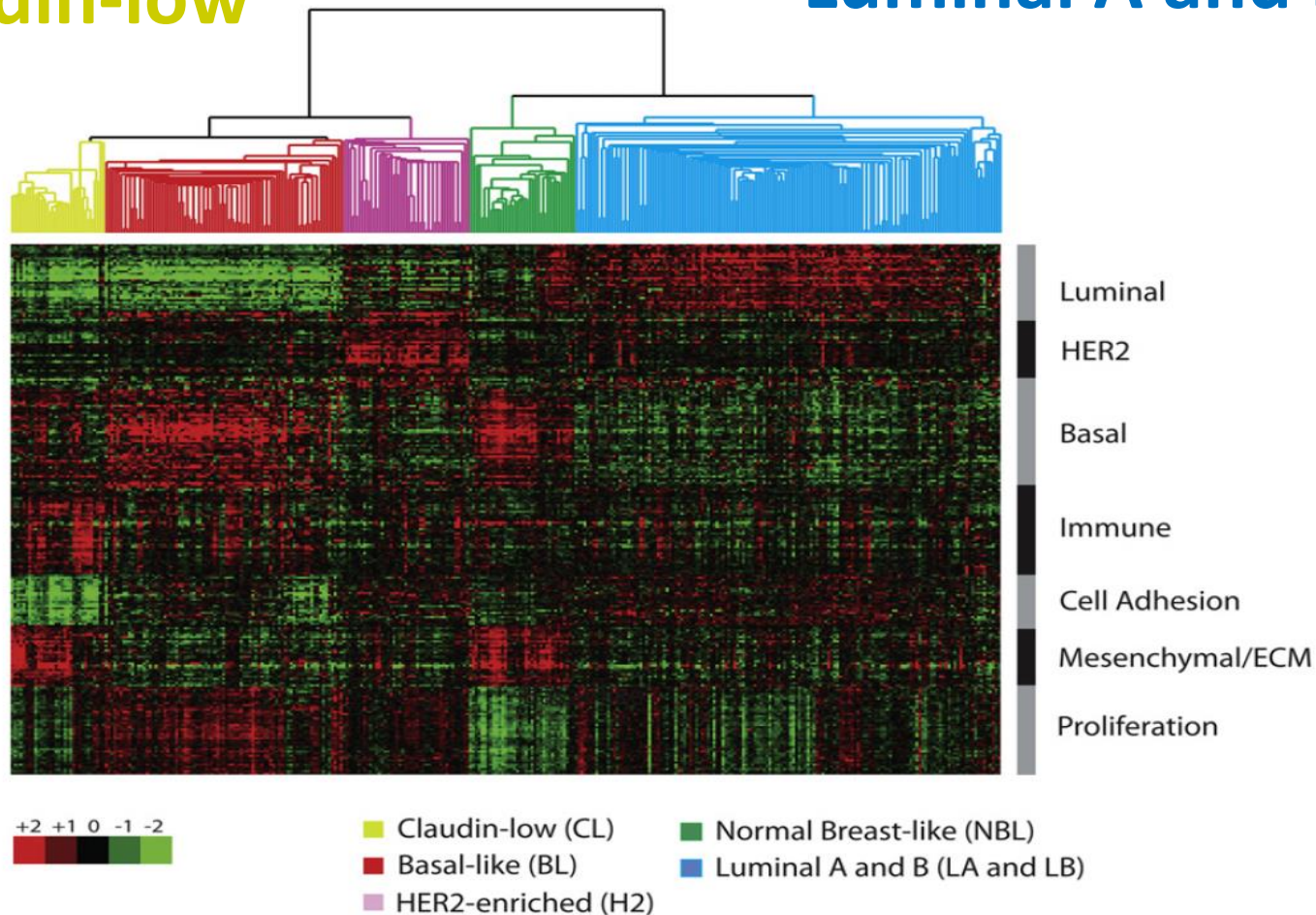
- High grade ductal

What is 'Standard Therapy' For TNBC?

- No specific systemic regimen guidelines exist
- Little data on which to base decisions
- Few historical controls making it challenging to design clinical trials for this subgroup

Deconstructing the molecular portraits of breast cancer

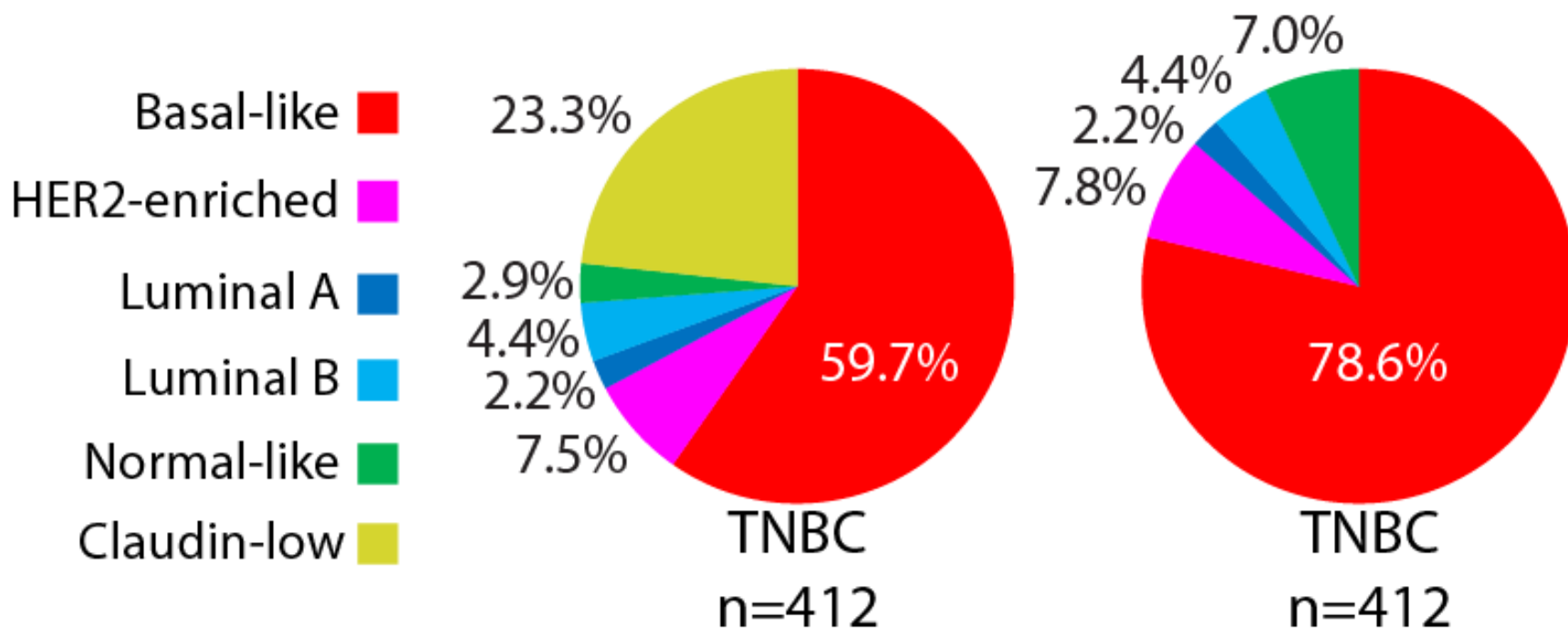
Basal-like
Claudin-low **HER2-enriched** **Normal-like**
Luminal A and B



Molecular Characterization of Basal-Like and Non-Basal-Like Triple-Negative Breast Cancer

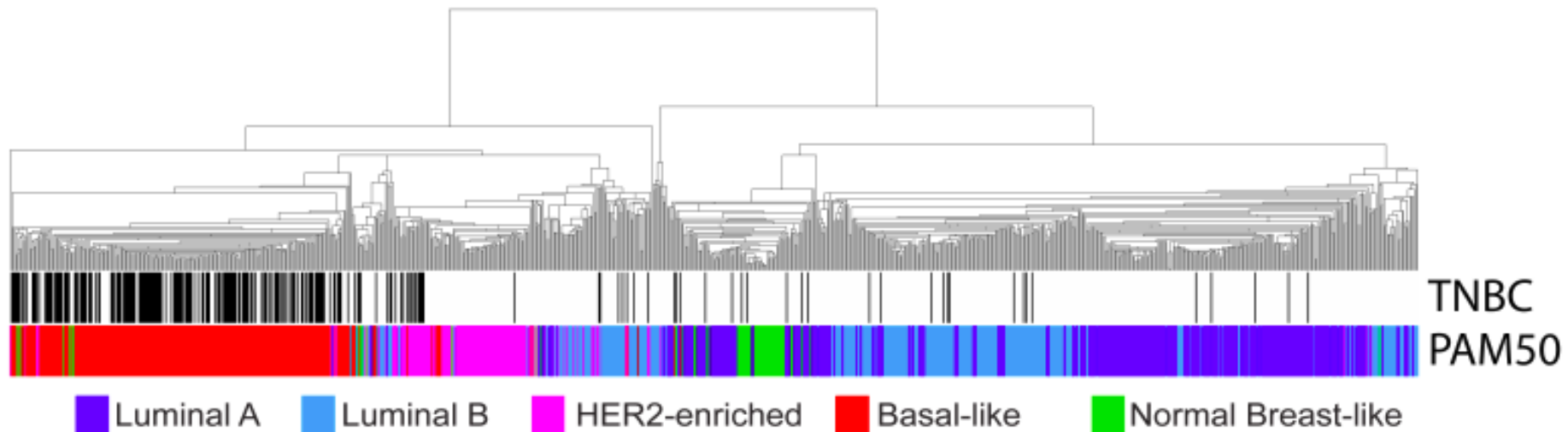
ALEX PRAT,^{a,b,c} BARBARA ADAMO,^{b,c} MAGGIE C.U. CHEANG,^d CAREY K. ANDERS,^d LISA A. CAREY,^d CHARLES M. PEROU^{d,e,f}

^aTranslational Genomics Unit, ^bBreast Cancer Unit, and ^cMedical Oncology Department, Vall d'Hebron Institute of Oncology, Barcelona, Spain; ^dLineberger Comprehensive Cancer Center, ^eDepartment of Genetics, and ^fDepartment of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, North Carolina, USA



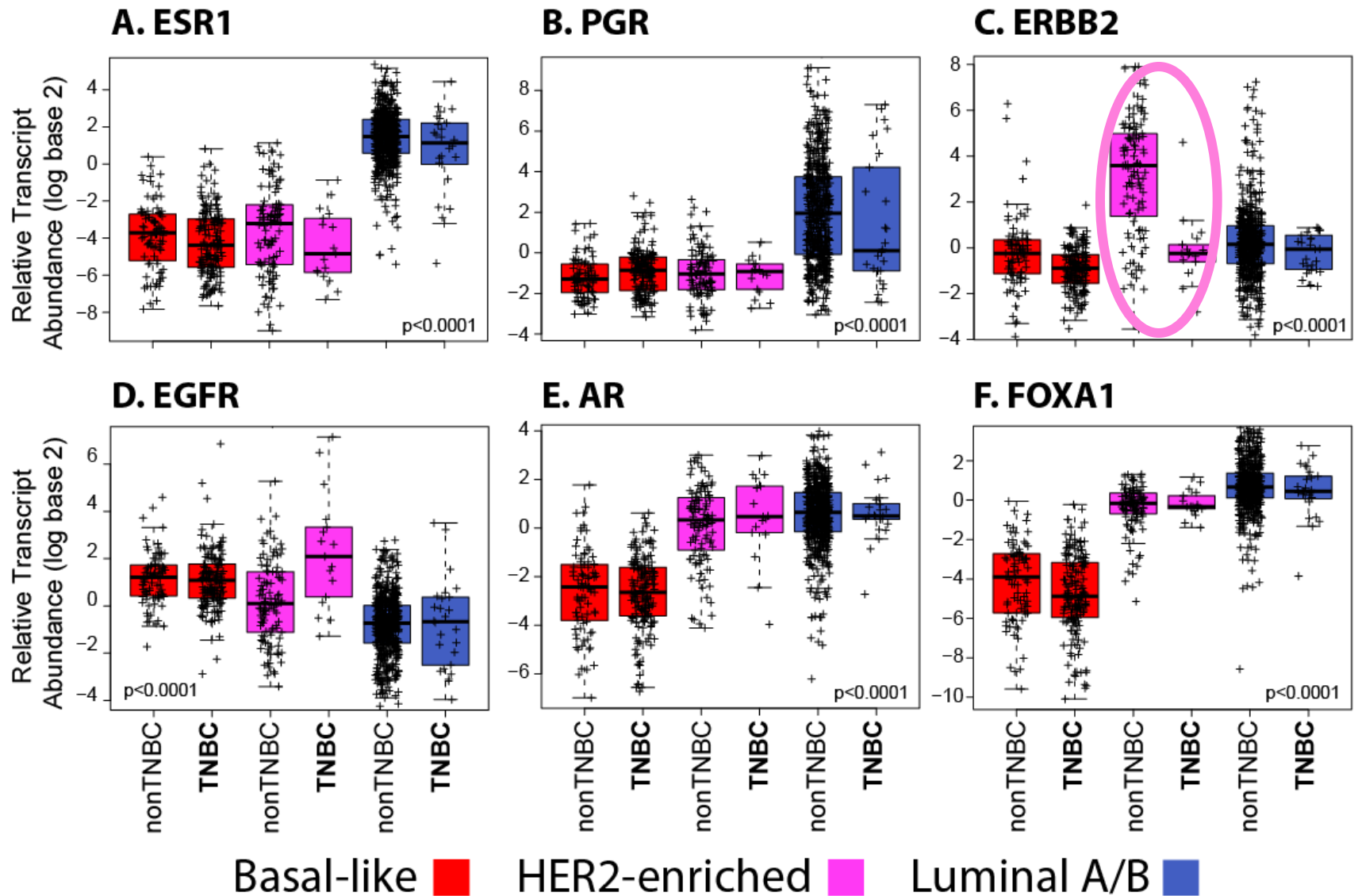
What do TNBCs that are nonBasal-like look like?

- Hierarchical clustering of 1,005 tumors from a combined data set using the available PAM50 genes.

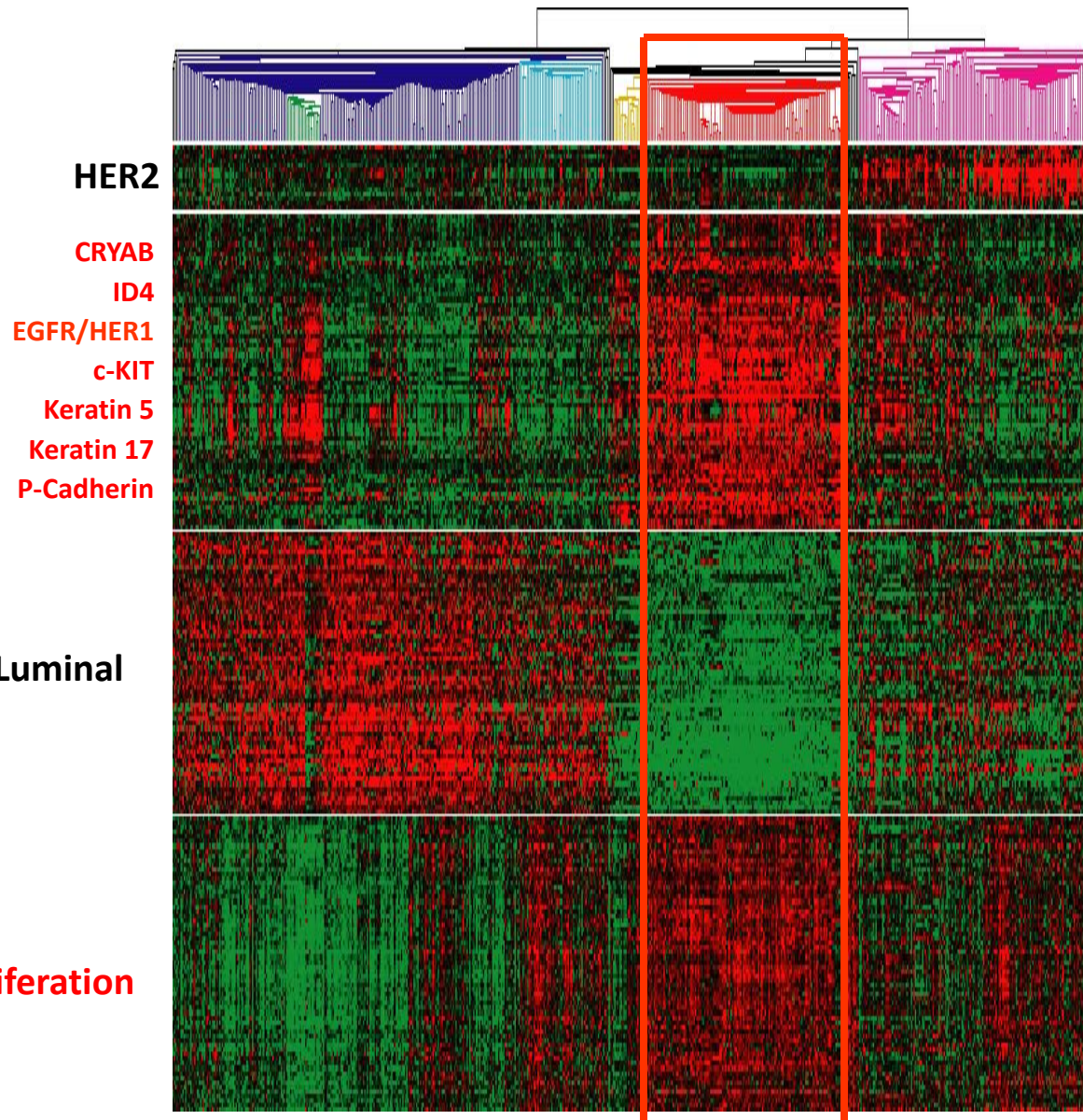


- TN tumors that are **HER2-enriched** have similar gene expression patterns as nonTN that are **HER2-enriched**.
- TN tumors that are **Luminal A/B** have similar gene expression patterns as nonTN that are **Luminal A/B**.

What do TNBCs that are nonBasal-like look like?

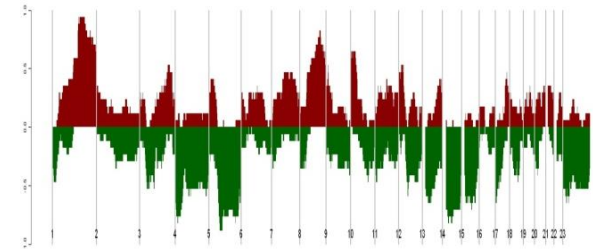


Basal-like subtype

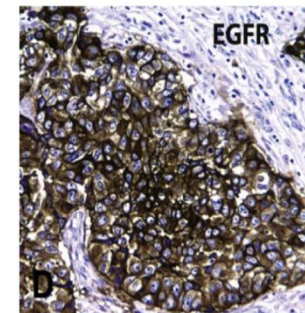


Data Highlights

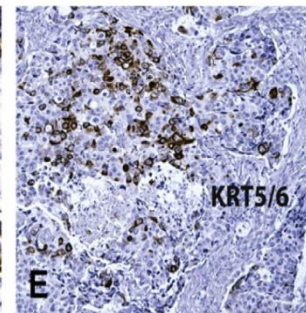
1. 10-25% of all tumors.
2. Risks factors: multiparity
2. Highly proliferative (RB-loss).
3. TP53 mutations: 80%
4. PIK3CA: 9%.
4. BRCA1-associated.
5. High CNA.
6. Distinct cell type of origin or developmental stage of arrest.



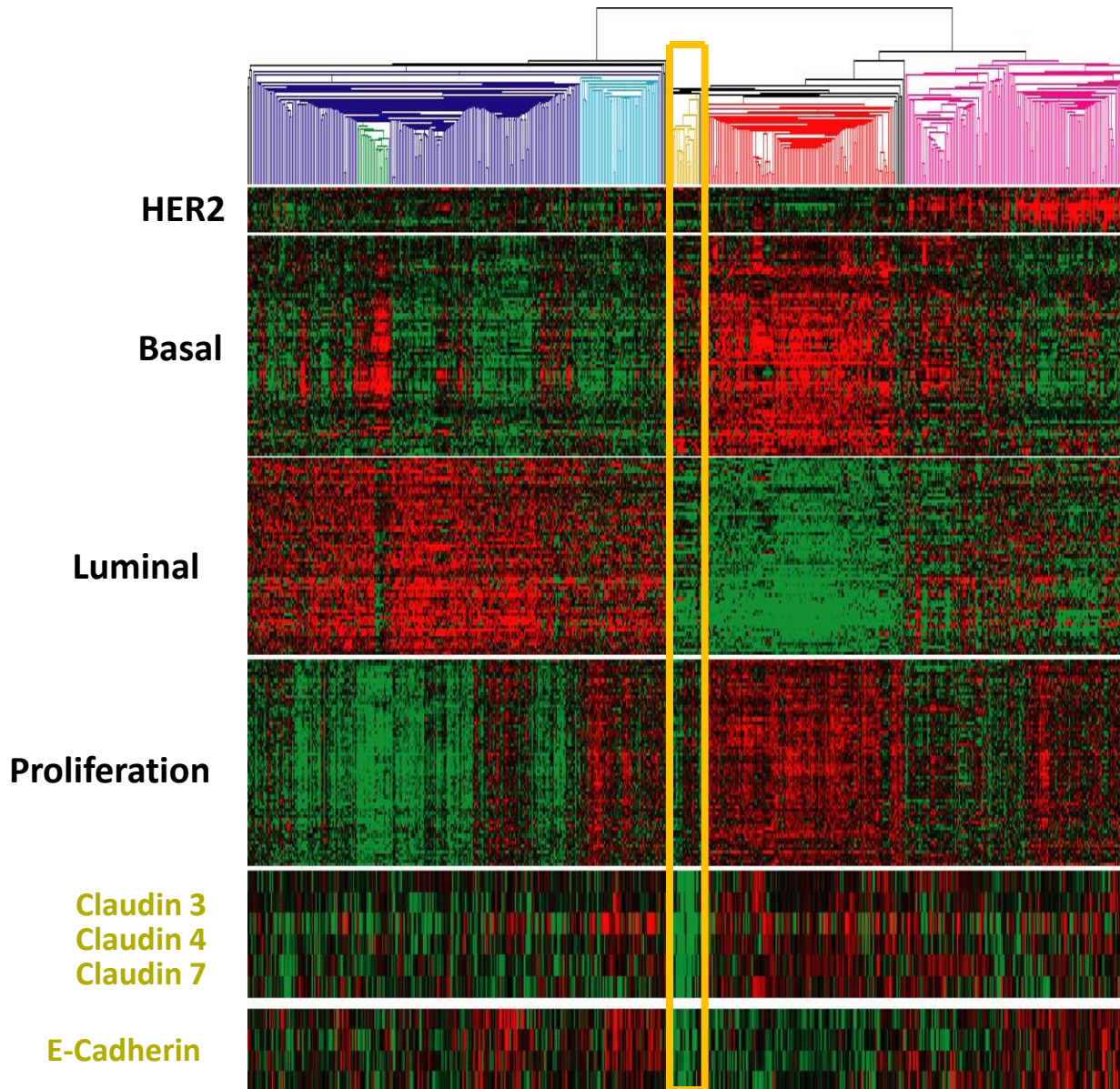
EGFR



Keratin 5/6



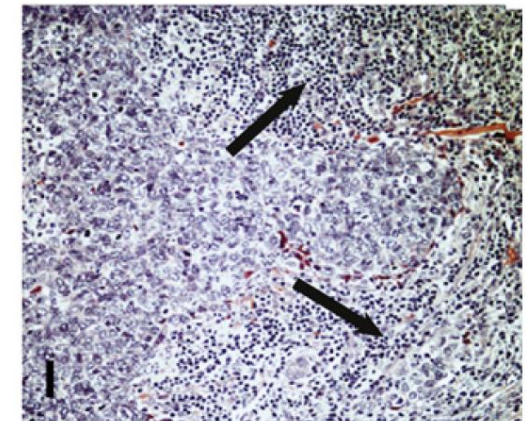
Claudin-low subtype



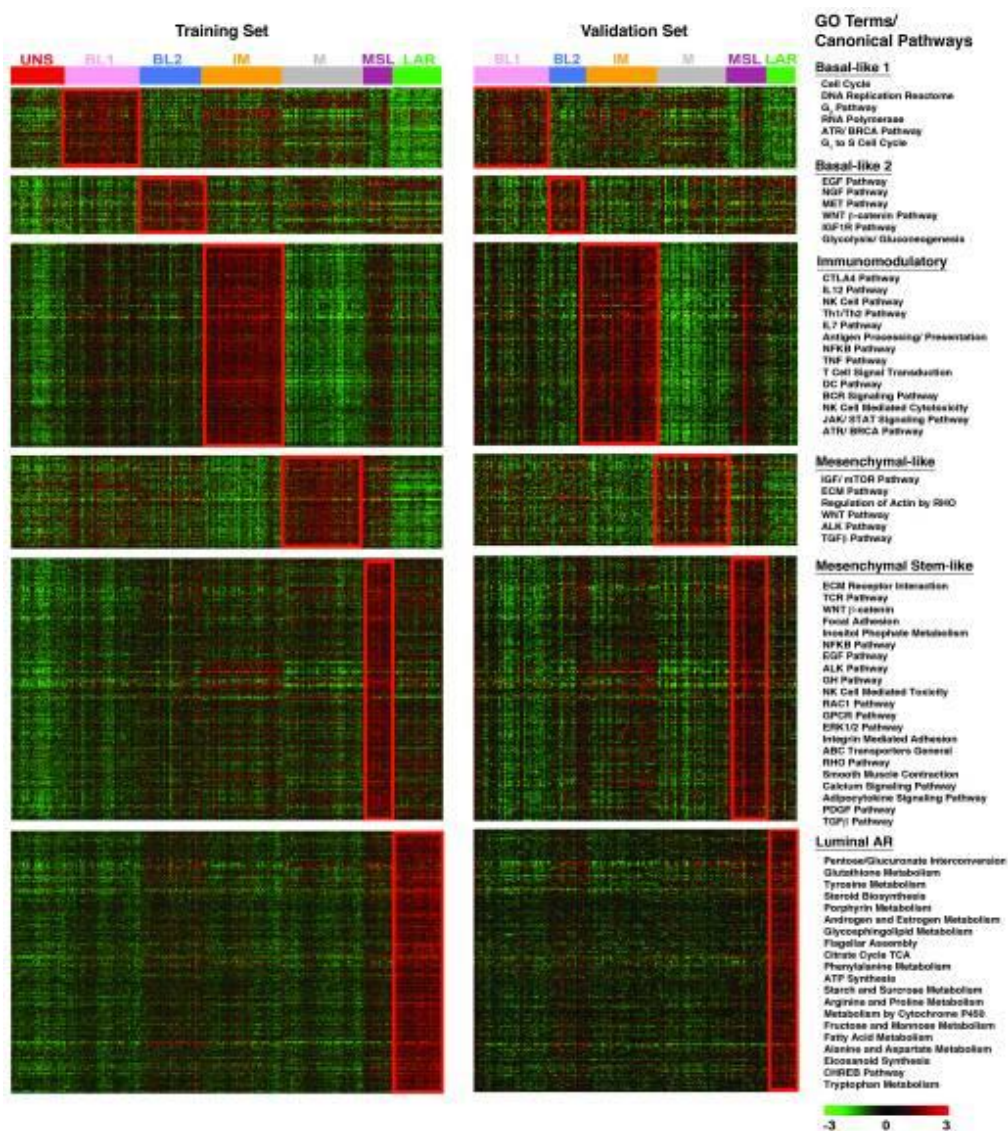
Data Highlights

1. 5-10% of tumors.
2. Typically TNBCs.
3. Low expression of cell-cell junction proteins.
4. Stem cell + EMT (mesenchymal) features.
5. Lymphocyte infiltrates.
6. Metaplastic.
7. Distinct cell type of origin or developmental stage of arrest.

Immune infiltrate



Identification of Human TNBC Subtypes



Basal-like 1: Cell cycle, DNA repair and proliferation genes

Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

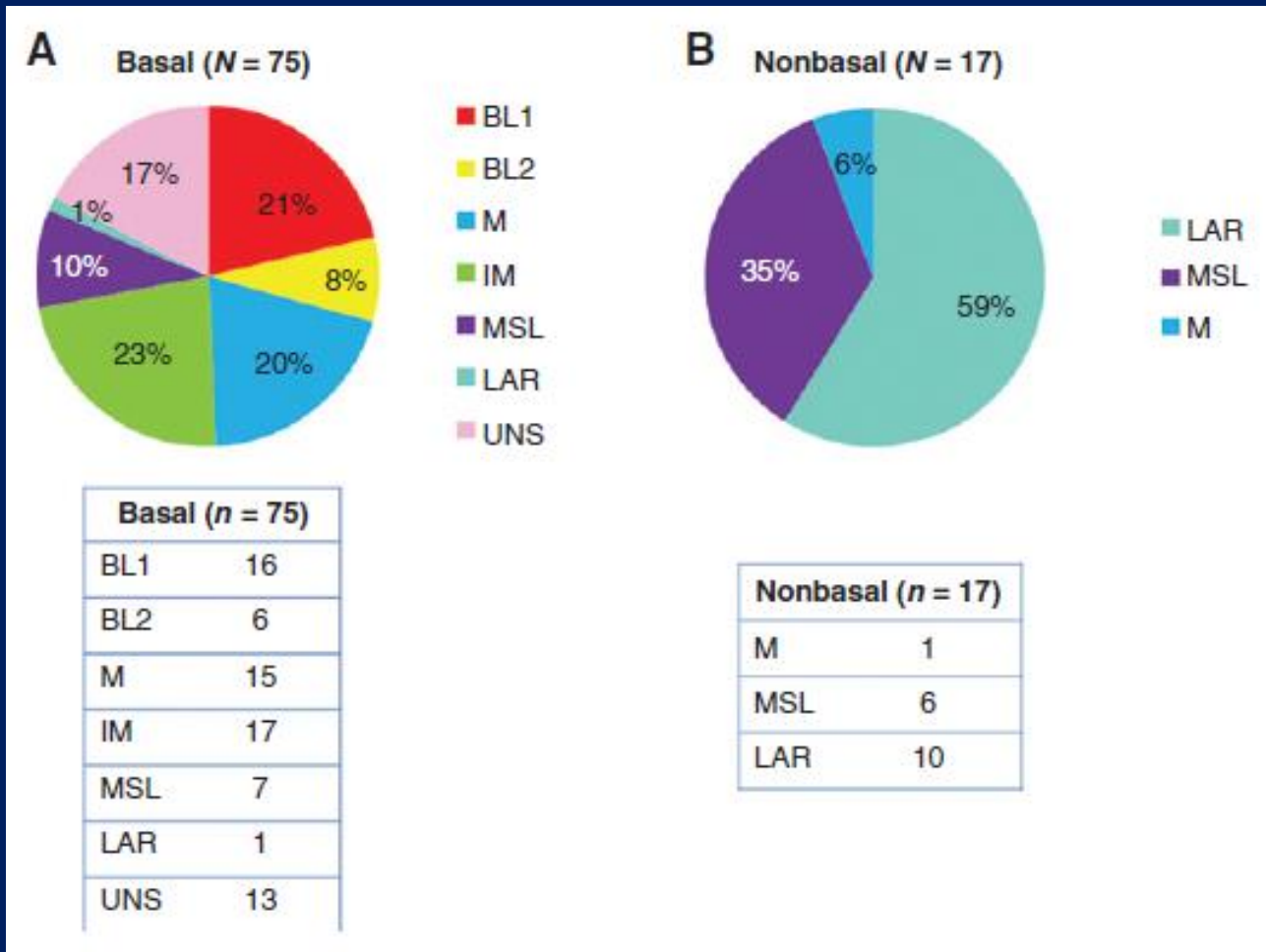
IM: Immune cell processes (medullary breast cancer)

M: Cell motility and differentiation, EMT processes

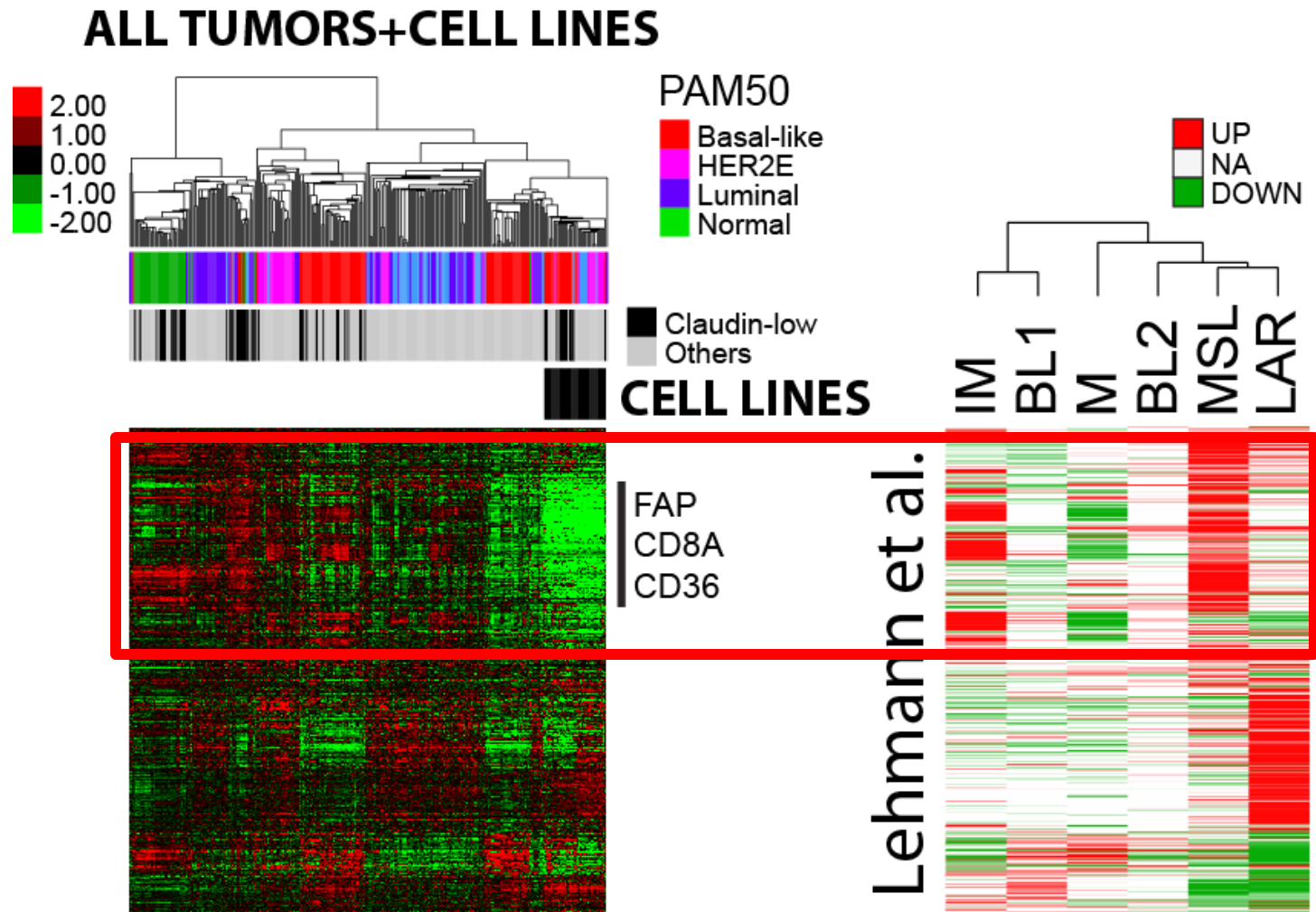
MSL: Similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

LAR: Androgen receptor and downstream genes, luminal features

PAM50 versus 7-TN subtype Classifications



IM and MSL subtypes are mostly defined by genes coming from non-tumor cells



Clinical Cancer Research



Differential Response to Neoadjuvant Chemotherapy Among 7 Triple-Negative Breast Cancer Molecular Subtypes

Hiroko Masuda, Keith A. Baggerly, Ying Wang, et al.

Clin Cancer Res 2013;19:5533-5540. Published OnlineFirst August 15, 2013.

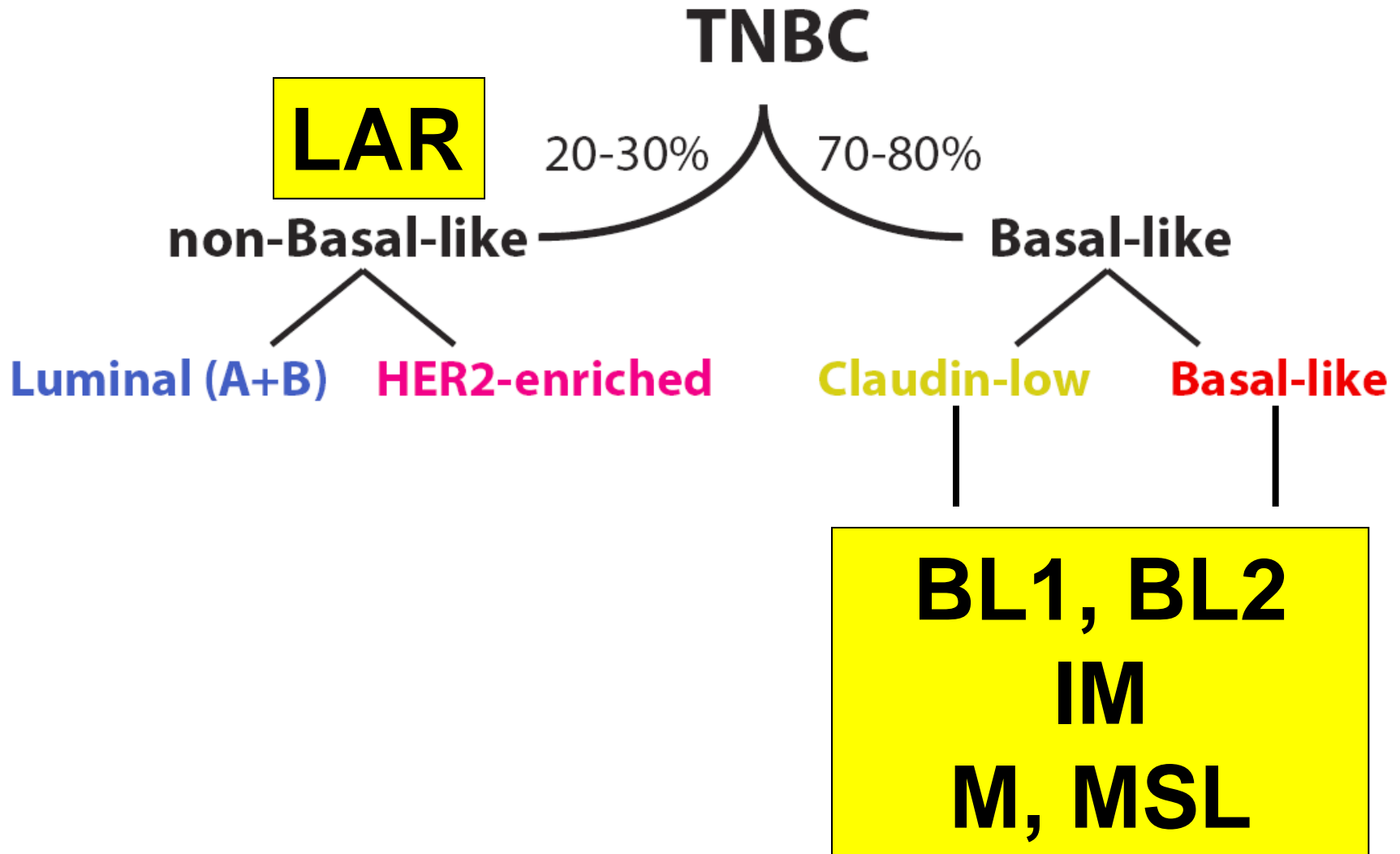
	pCR	Non-pCR	pCR rate	95% Confidence interval	P
BL1	11	10	0.52	0.31–0.73	P = 0.043
BL2	0	8	0.00	0.00–0.00	
M	8	18	0.31	0.13–0.48	
IM	8	19	0.30	0.12–0.46	
MSL	3	10	0.23	0.001–0.45	
LAR	2	18	0.10	0.03–0.23	
UNS	5	10	0.33	0.09–0.57	

NOTE: Likelihood ratio test: adjusting clinical features: age, clinical stage, nuclear grade, and treatment type. TNBC subtype was an independent predictor of pCR status ($P = 0.022$).

TNBC ≠ Basal-like, and Basal-like ≠ TNBC

- Within TNBC, ALL the intrinsic subtypes can be identified in different proportions, although Basal-like tumors predominate.
 - *Most TNBC Luminals have similar gene expression patterns as HR+ Luminal tumors.*
 - *Most TNBC HER2-E have similar gene expression patterns as HER2+ HER2-E tumors, except for lack of amplification/overexpression of ERBB2/GRB7 amplicon.*
 - *Most TNBCs that are not Basal-like are likely to benefit from other targeted and/or chemo agents than TNBC that are Basal-like.*
- Lehmann et al. 7-TNBC classification represents a distinct approach for classifying TNBC:
 - Mixed tumor and microenvironment features.
 - Has been associated with multi-agent chemotherapy response: BL1 vs. BL2, BL1 vs. LAR.

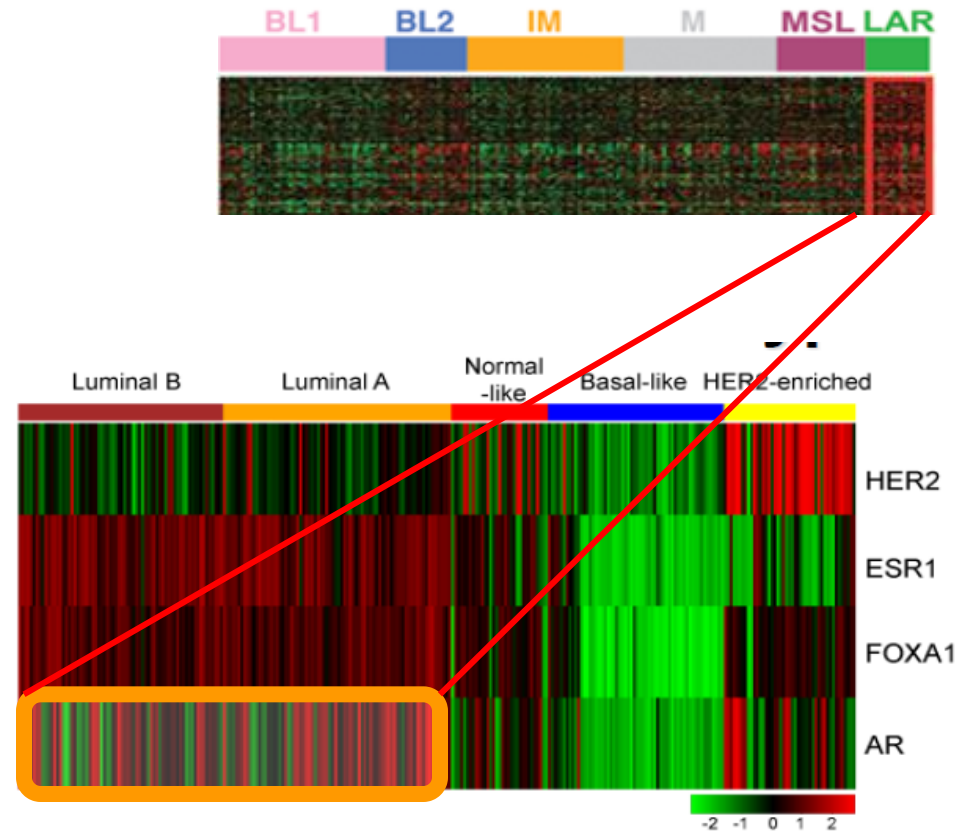
How could TNBCs be stratified?



LAR

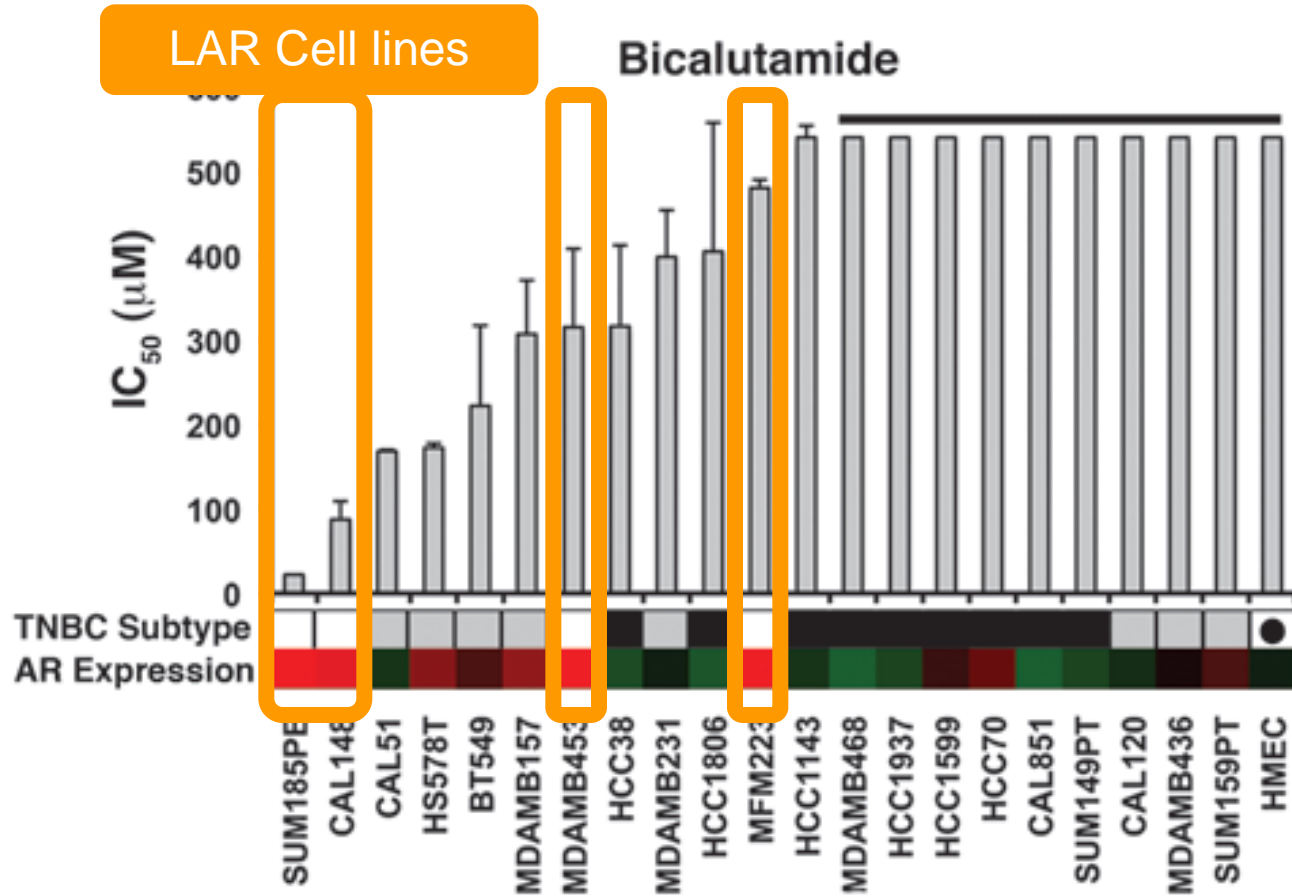
- Triple negative breast cancer is comprised of 6 molecularly distinct subtypes

- 10% are “Luminal AR” (LAR)
- LAR express higher levels of AR mRNA vs other TNBC subtypes
- LAR breast cancers are heavily enriched in hormonally-regulated pathways
- Luminal AR is more closely related to hormone receptor positive breast cancer (Luminal A and B) than to other subtypes



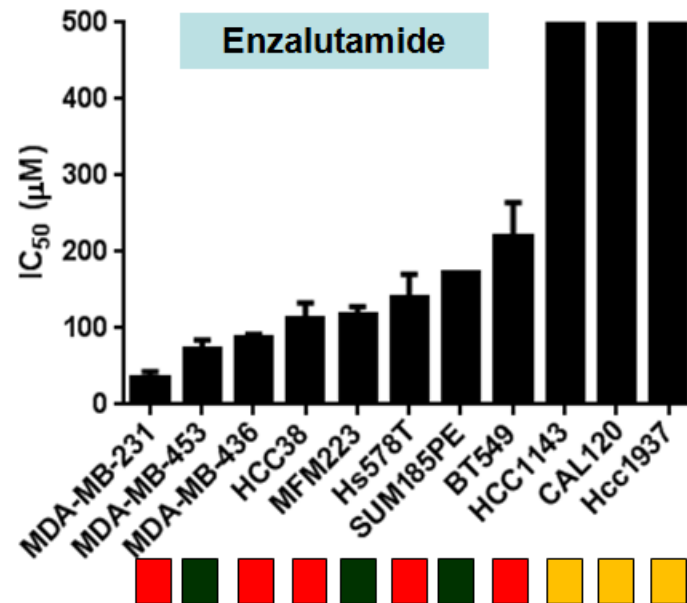
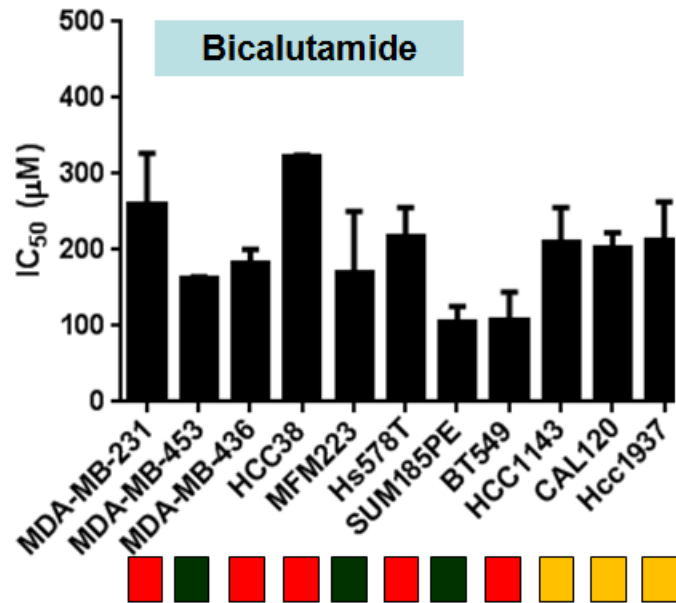
BL= Basal Like, IM = Immunomodulatory,
ML= Mesenchymal-Like, MSL= Mesenchymal Stem-like, **LAR = Luminal AR**

LAR



- All LAR cell lines had some response to bicalutamide
- Not all of “AR+” cell lines were LAR (40%)
- The majority (70%) of “AR+” cell lines responded to bicalutamide

LAR



■ LAR
 ■ AR+ Non-LAR
 ■ AR-

LAR

Phase II Trial of Bicalutamide in Patients with Androgen Receptor Positive, Hormone Receptor Negative Metastatic Breast Cancer

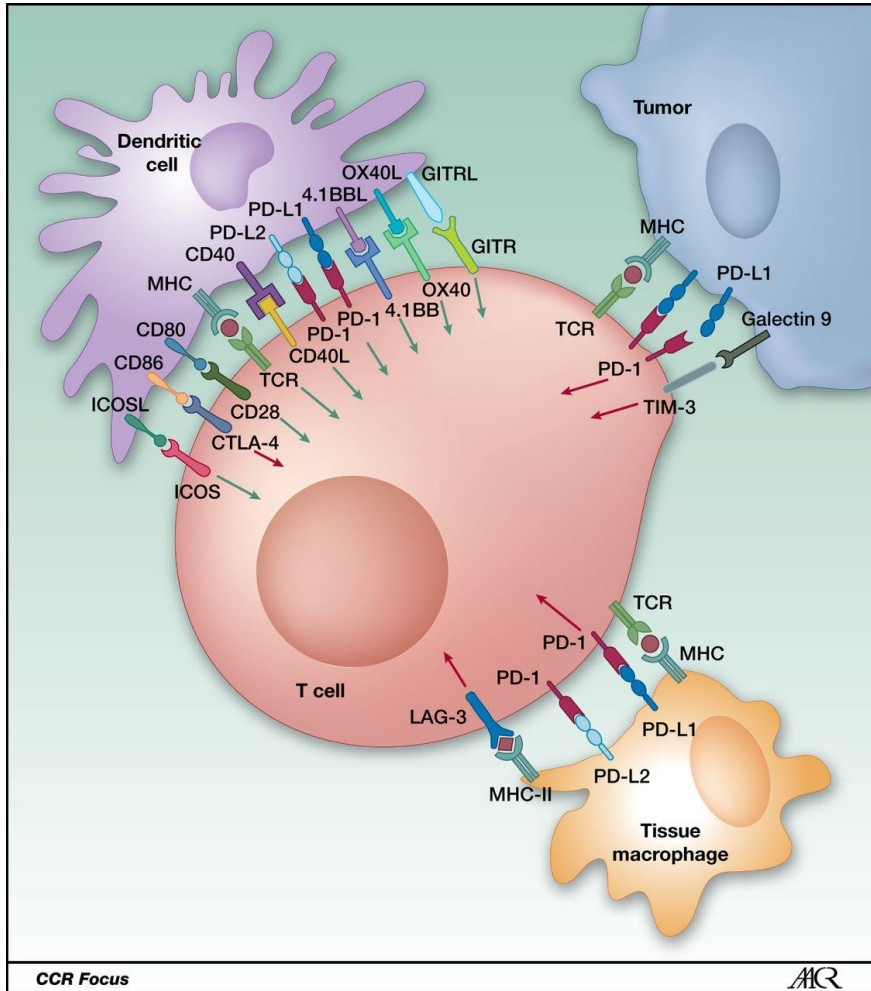
Ayca Gucaip, Sara Tolaney, Steven J. Isakoff, et al.

Clin Cancer Res Published OnlineFirst August 21, 2013.

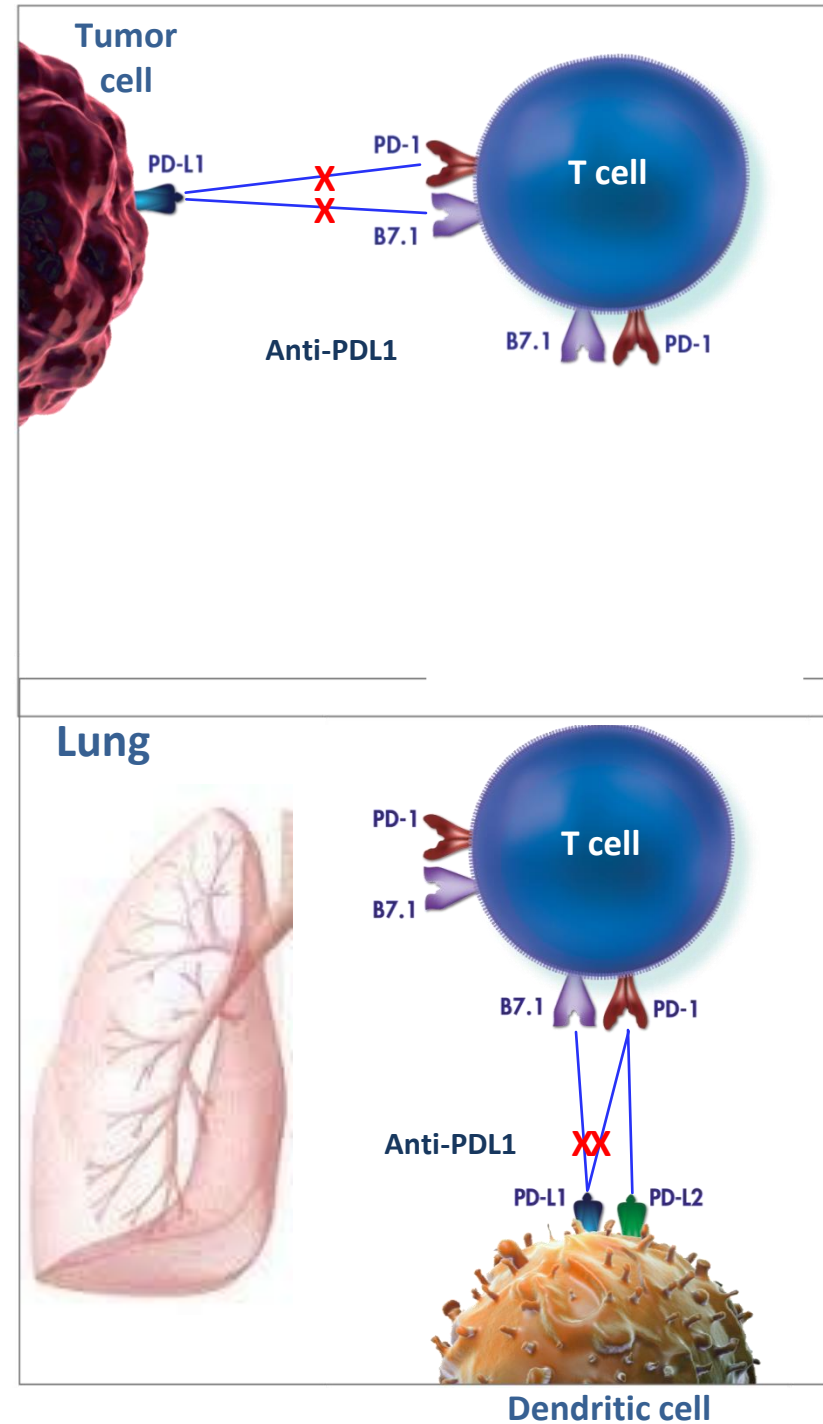
Table 2.

Pts with clinical benefit on bicalutamide	AR%	ER%	PgR%	HER2	Site of Testing	Site of Mets	Prior Therapy LABC/ MBC	DOR on Prior Therapy (weeks)	DOR on bicalutamide (weeks)
1	10-20	1	0	Neg	1 ⁰	LN	0	NA	231+
#2	>80	3	0	Neg	Met	GI	0	NA	54
#3	>80	0	0	-/+	1 ⁰	Breast LN	1	NR	25
#4	>90	0	0	Neg	1 ⁰	LN Bone	1	158	35
#5	>50	0	0	Neg	1 ⁰	LN Bone	1	15	43+

IM

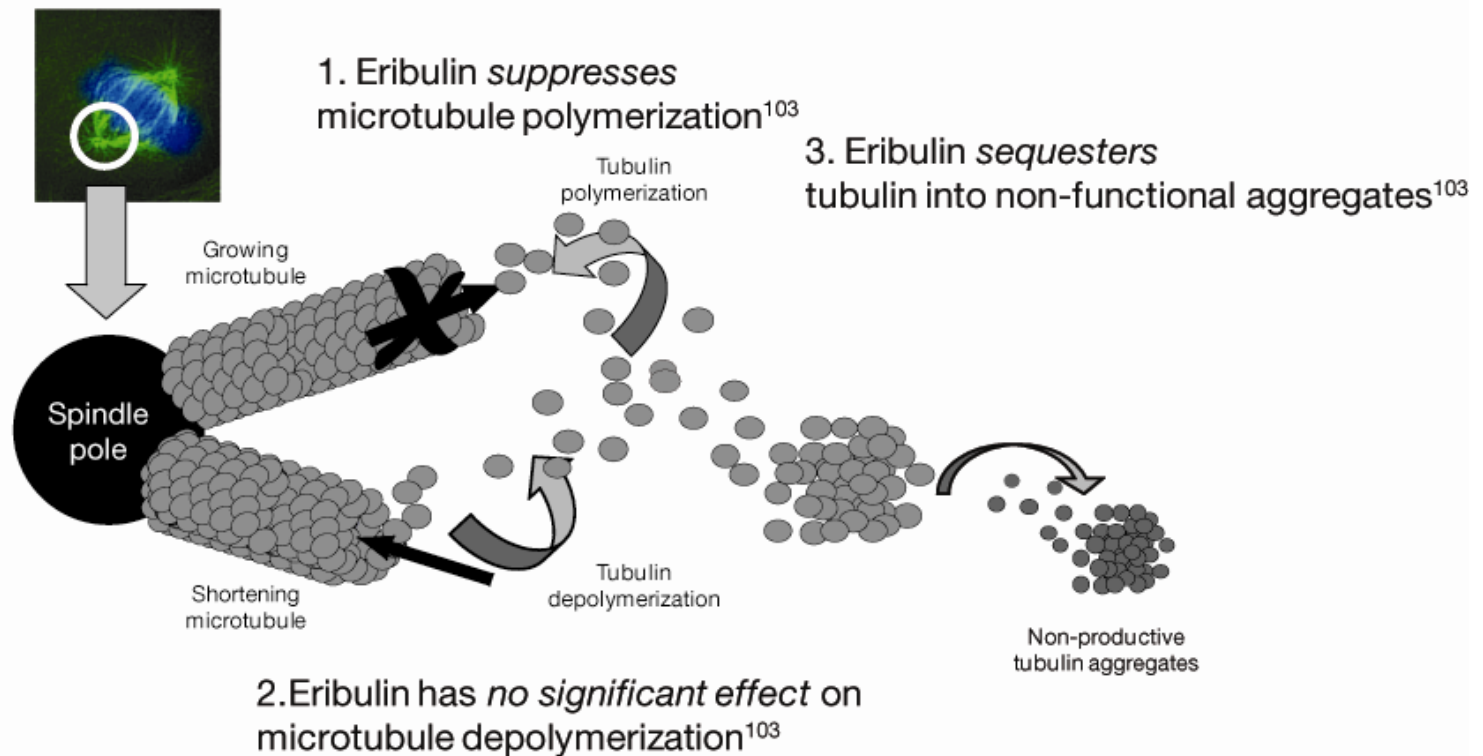


Akbari O, et al. Mucosal Immunol. 2010;
 Matsumoto K, et al. Biochem Biophys Res Commun. 2008;
 Chen, et al. Immunity, 2013



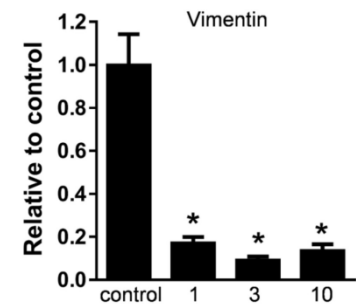
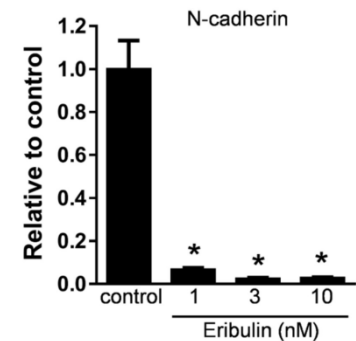
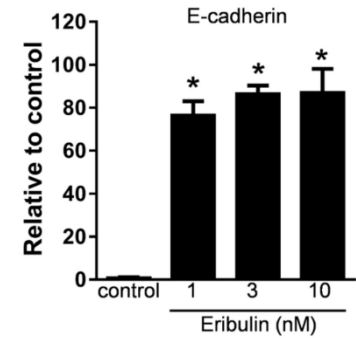
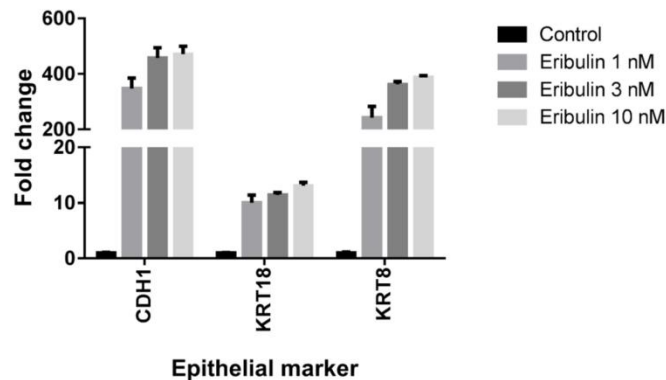
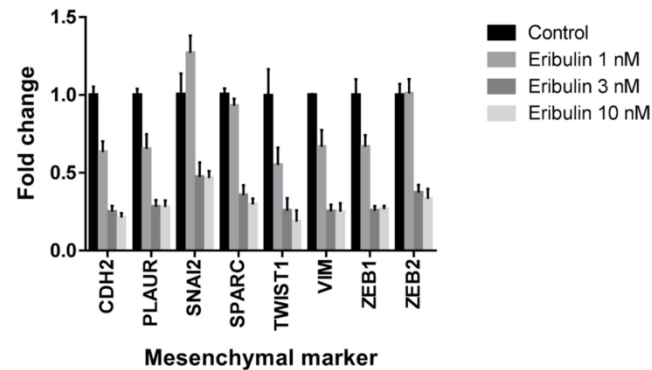
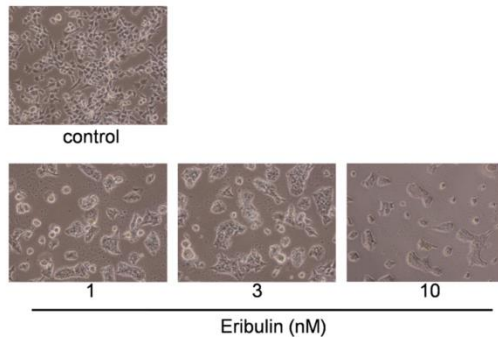
ML, MSL "

Eribulin Mesylate (E7389): A Novel Tubulin Targeted Agent



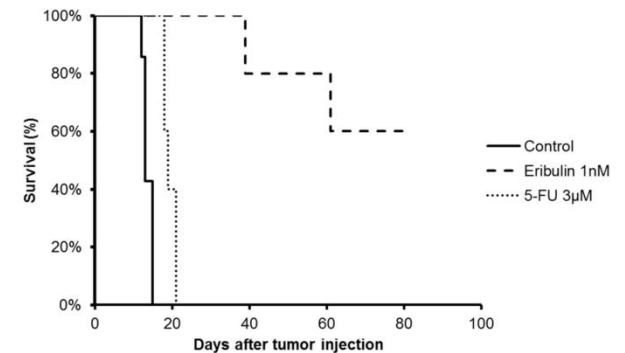
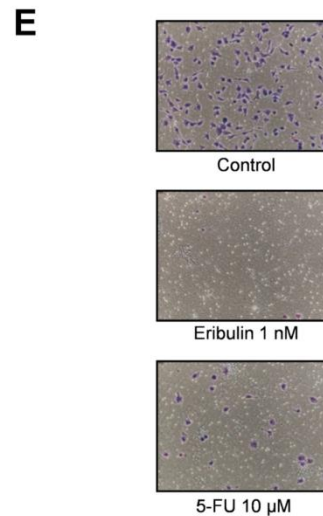
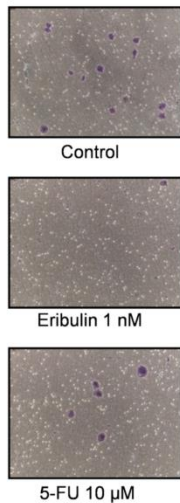
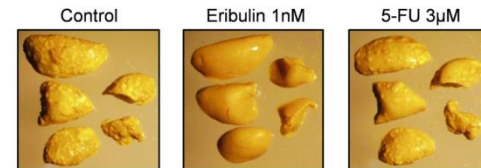
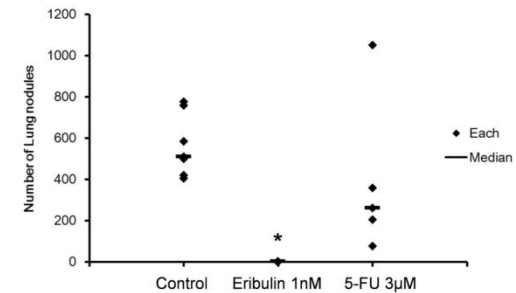
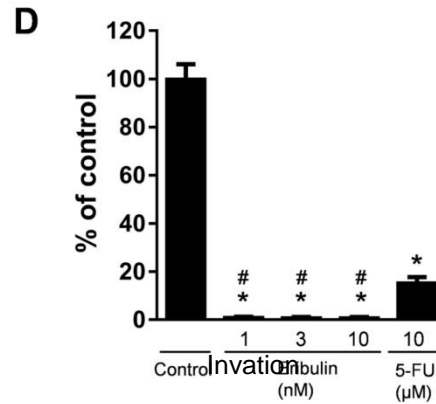
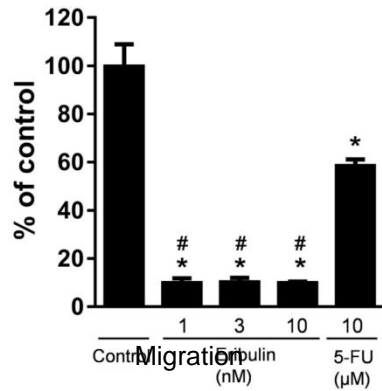
ML, MSL

Eribulin Mesylate (E7389): EMT to MET phenoype



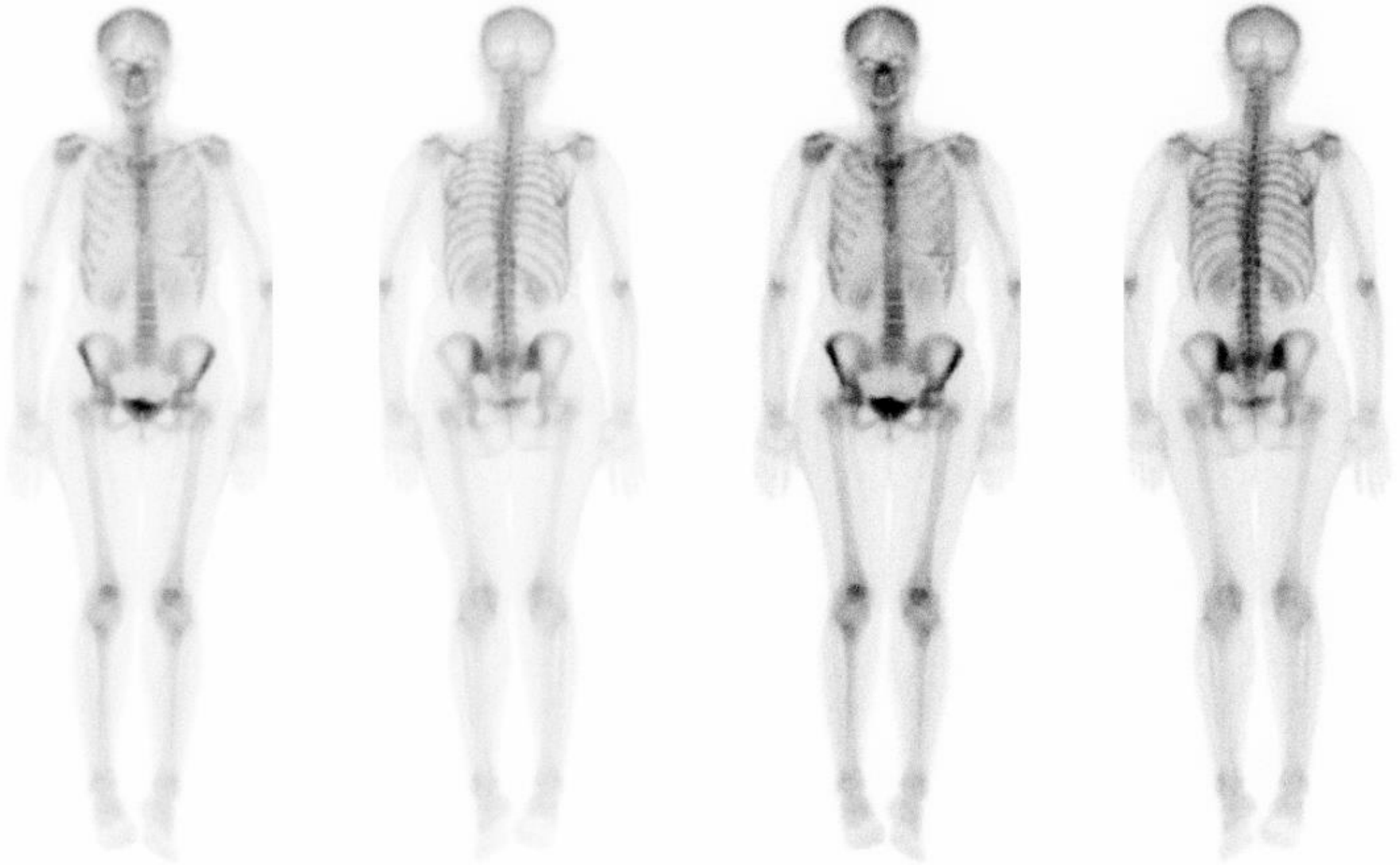
ML, MSL

Eribulin Mesylate (E7389): EMT to MET phenoype



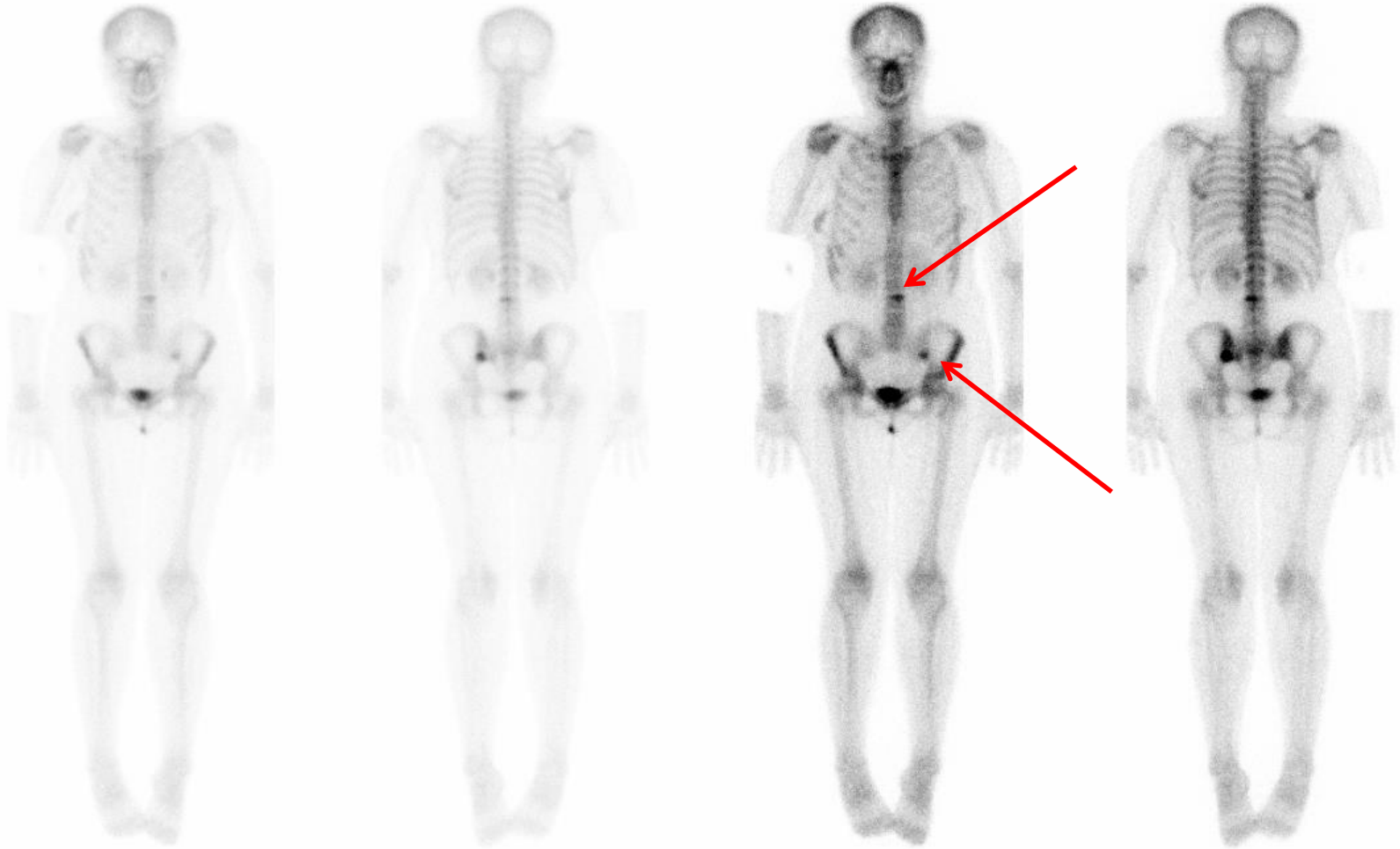
Coming back to our patient...

Coming back to our patient...



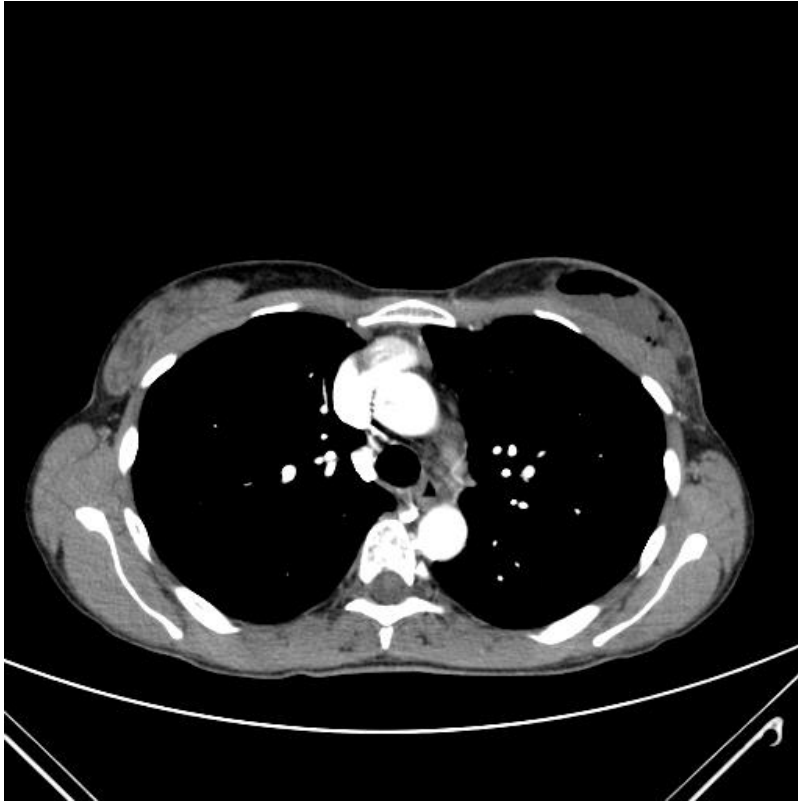
Jan 2012

Coming back to our patient...

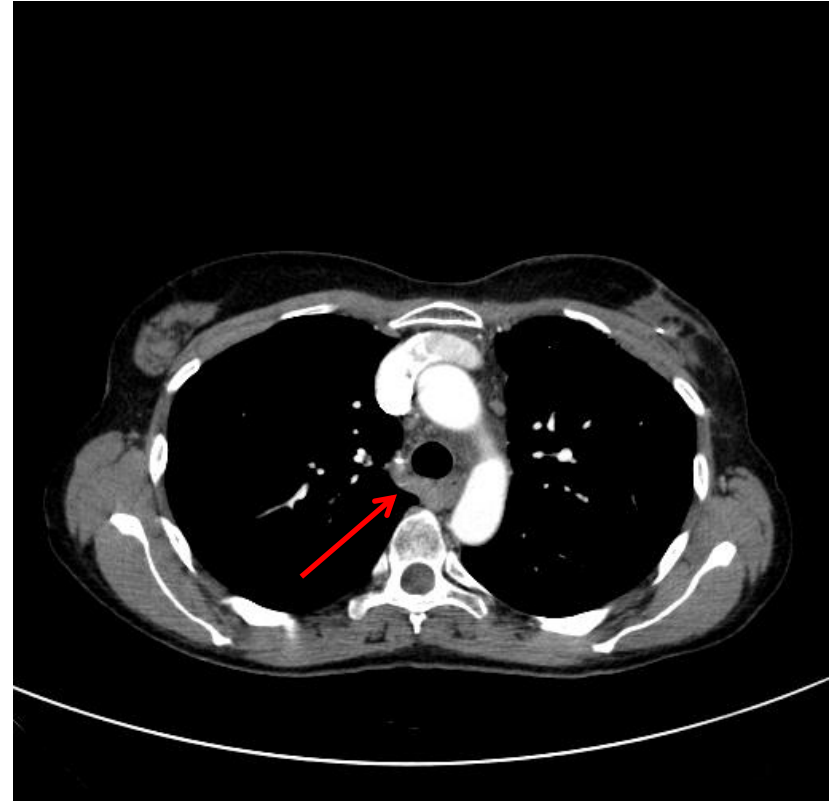


Sep 2013

Coming back to our patient...

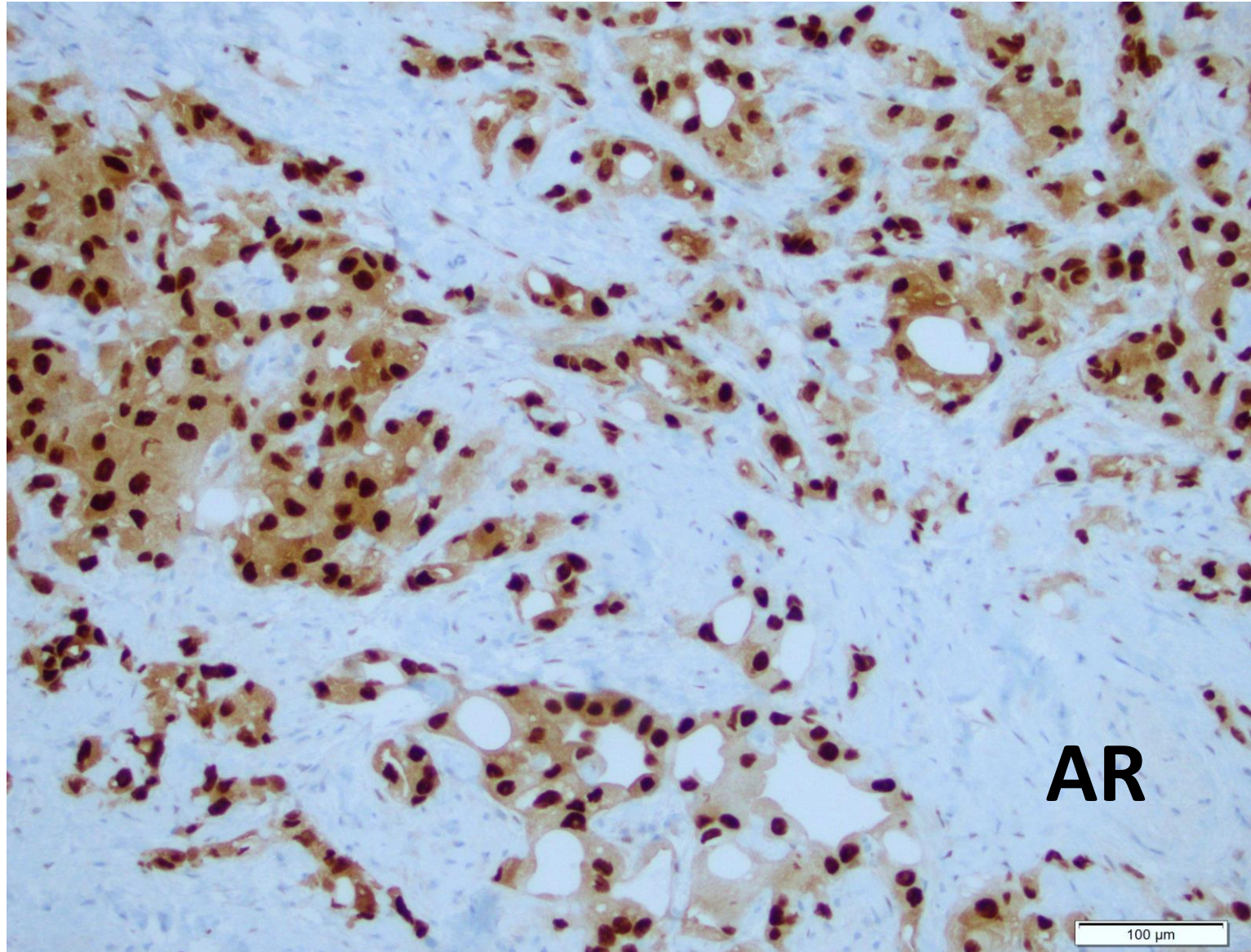


Jan 2012



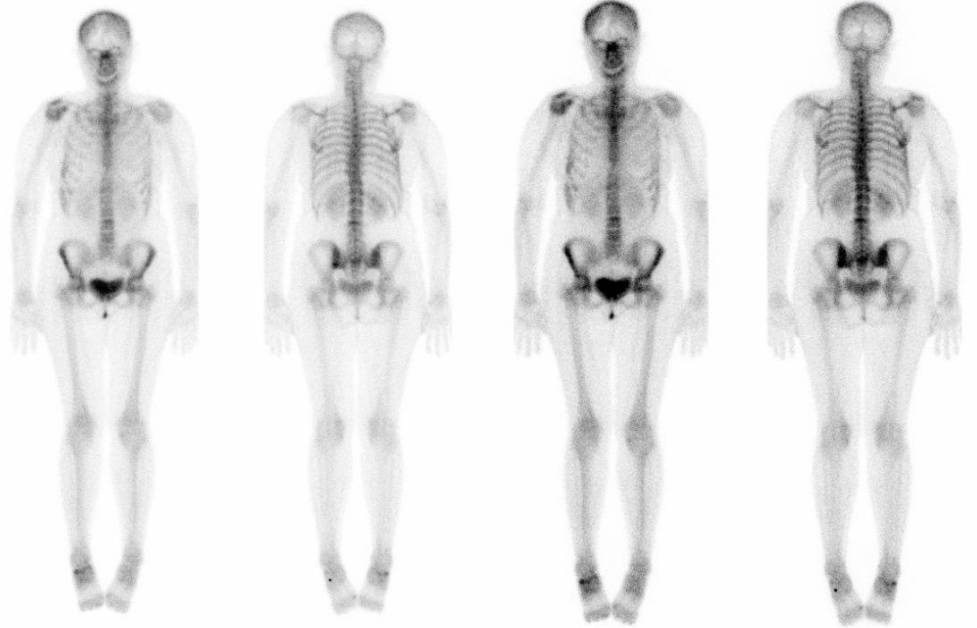
Sep 2013

Coming back to our patient...



Case Presentation

- She refused chemotherapy
- Bicalutamide was offered...



Sep 2014

TNBC Subtypes: (Some) Research Strategies

**Basal-like 1: Cell cycle,
DNA repair and
proliferation genes**



PARPi, \pm DNA damaging agents
homologous recombination
deficiency assay (BRCA-1 ness)

**Basal-like 2: Growth factor
signaling (EGFR, MET, Wnt,
IGF1R)**



EGFR (cetuximab, lapatinib)
Self-renewal pathways (stem cell)
Wnt
Notch (PF03084014, AACR 2012)

**IM: Immune cell
processes (medullary
breast cancer)**



Immune check point
PD1/PDL1, CTLA4
Vaccines: MUC1, NYO-ESO1

**M: Cell motility and
differentiation, EMT
processes**

**MSL: Similar to M but
growth factor signaling, low
levels of proliferation genes
(metaplastic cancers)**

(eribulin?) Plus
PI3Ki, RAS/MEK/Erk,
MET, PTEN
etc, etc

**LAR: Androgen receptor
and downstream genes,
luminal features**



Agents targeting androgen receptor
(enzalutamide, bicalutamide, etc)



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Aleix Prat
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