CANOA 2025

Come definire la malattia triplo negativa?

Davide Massa -
Università degli Studi di Padova

Disclosure

- Travel Expenses: Eli Lilly, Pfizer
- Scientific Collaborative Board: GSK

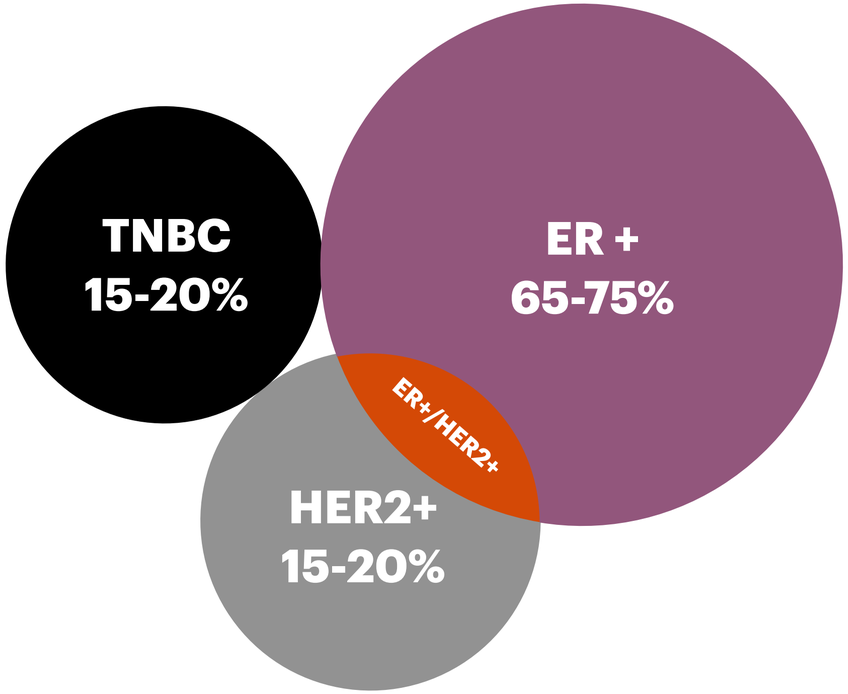
Outline

1. **TNBC**: a pragmatic **category**
2. **TNBC?**: Molecular and Immune **heterogeneity**
3. Challenging TNBC perimeter: **ER-low/HER2-low**
4. **Moving forward**

Defining TNBC

A leftover category of tumors lacking druggable targets

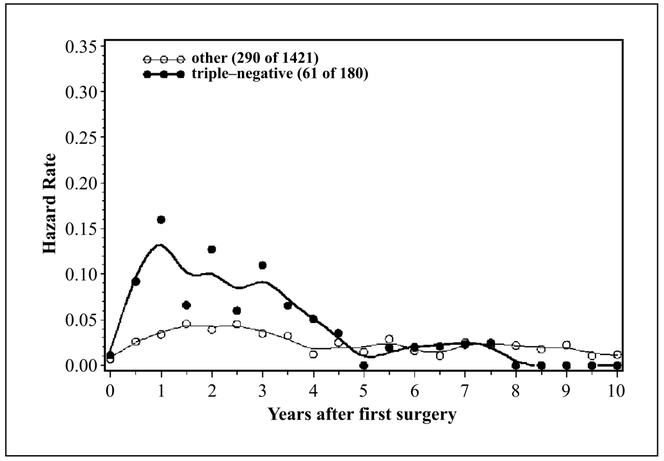
- TNBC is a heterogeneous disease pathologically **defined by what it is not:** a tumor lacking the expression on IHC of the three most commonly targeted biomarkers in the treatment of BC: **ER, PgR, HER2**

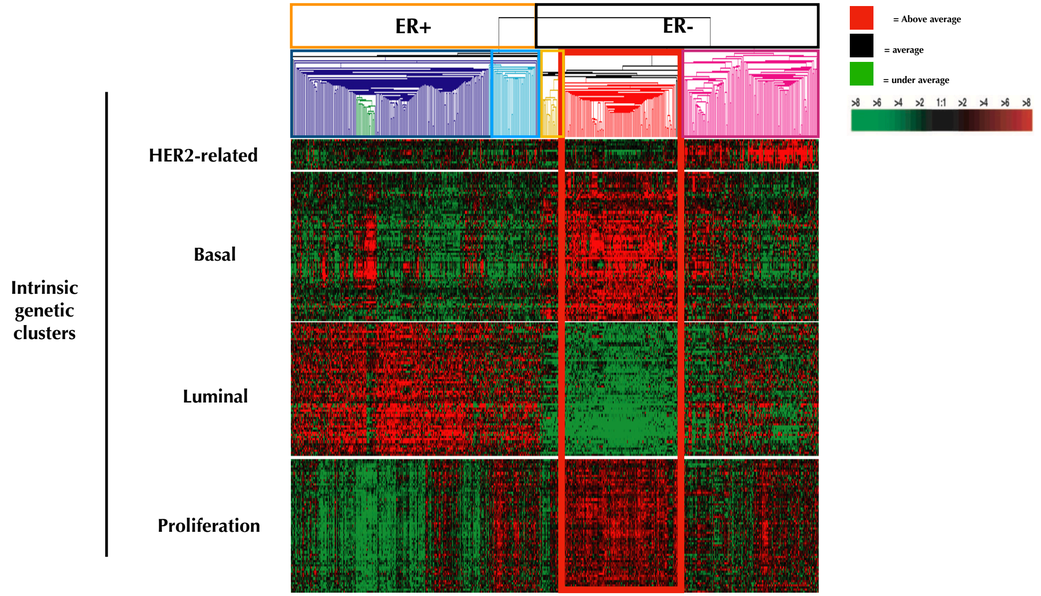


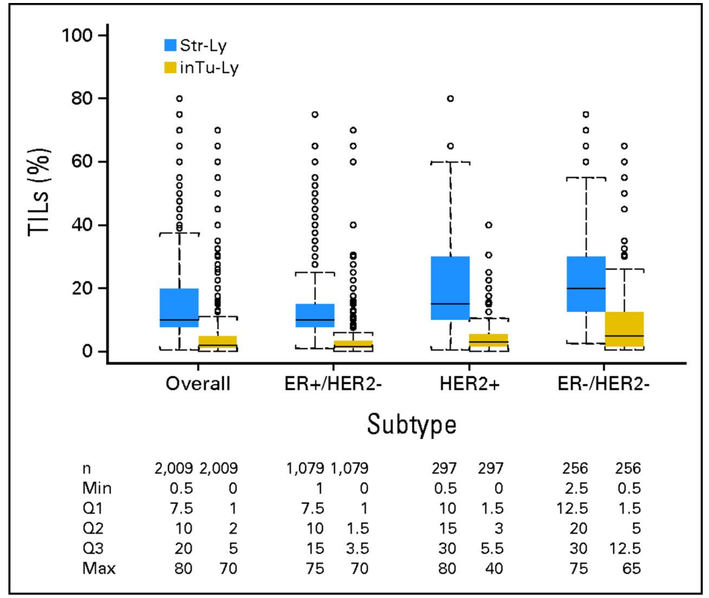
TNBC by classical IHC definition

Shared clinical, molecular, and immune features

- **Young age**
- **High grade, high ki67**
- **Poor prognosis**: High rate of early recurrence (Peak risk of recurrence at 1-3 y); High rate of distant recurrence (+Visceral); Rapid progression from distant recurrence to death
- Molecular features: **Basal molecular profile**
- Immune features: High density of **Tumor infiltrating lymphocytes**, which are prognostic



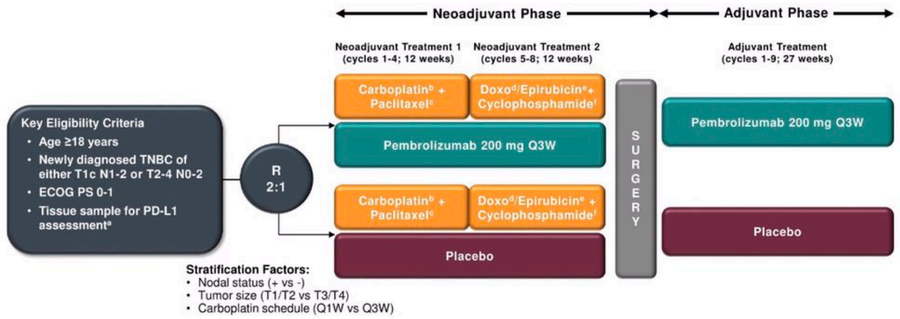




Dent et al. CCR 2007; Perou C et al, Nature 2000; Loi JCO 2013; Loi Jco 2019; Denkert et al. Lancet 2018

TNBC: CT and ICI sensitivity

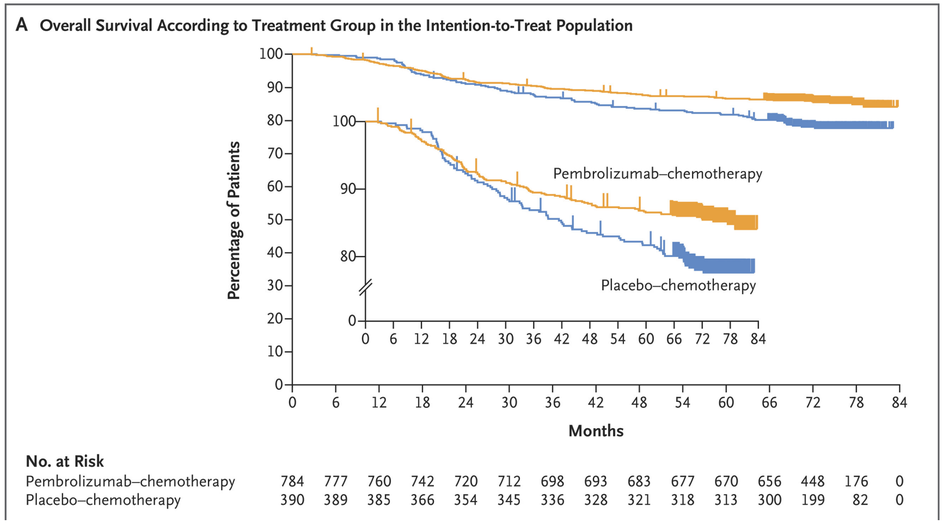
Neoadjuvant Pembrolizumab + CT



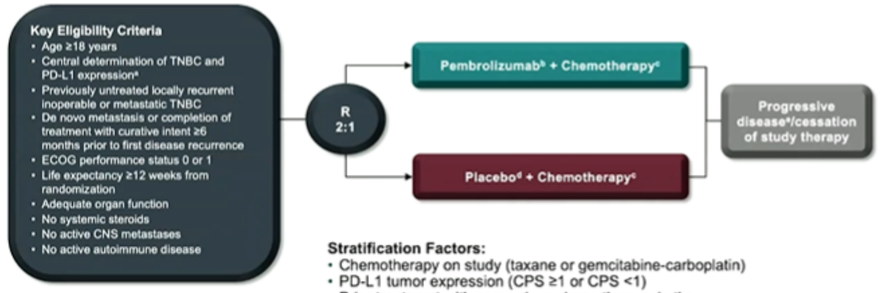
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

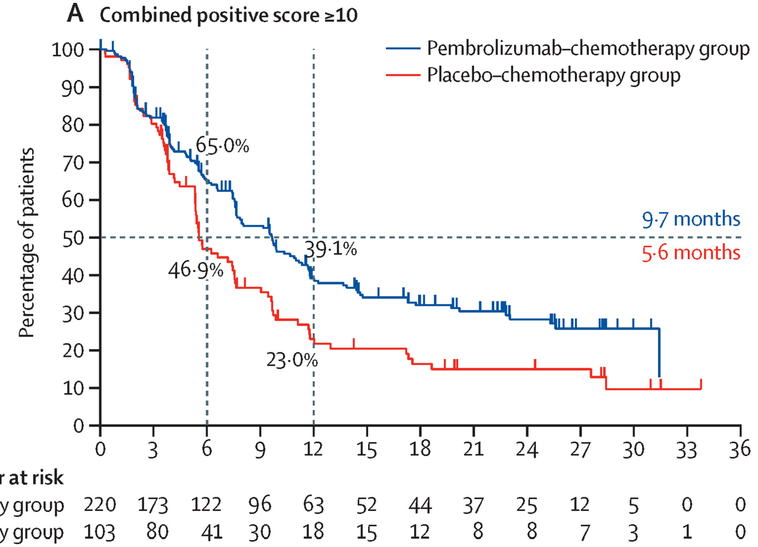
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 Q1W.
[c]Paclitaxel dose was 80 mg/m² Q1W.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.



1st line Pembrolizumab + CT





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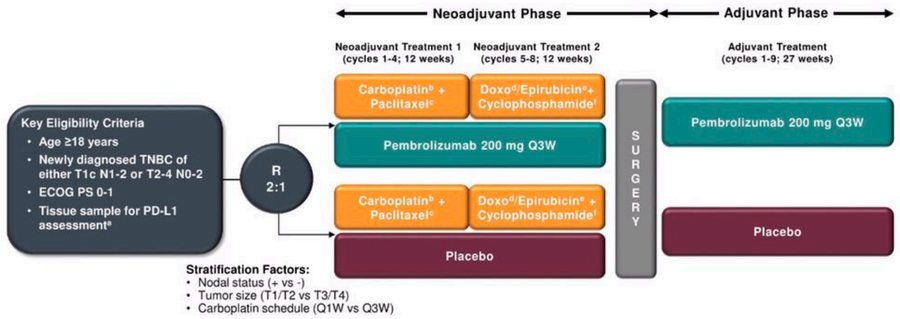

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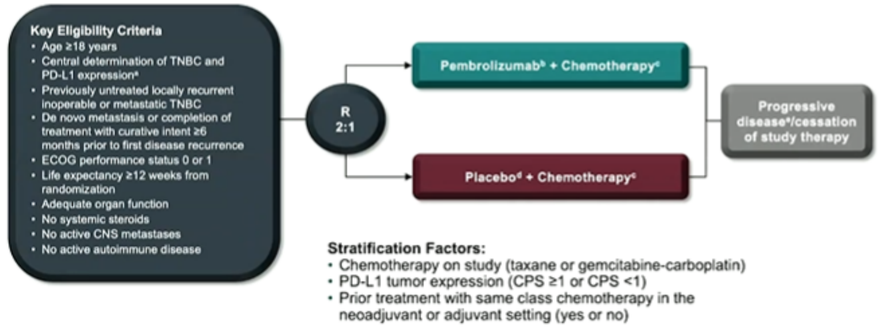
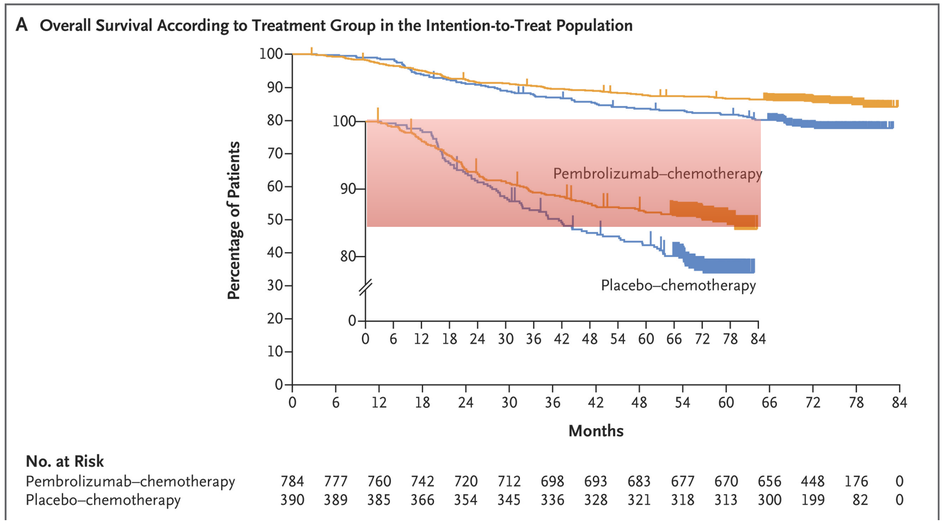
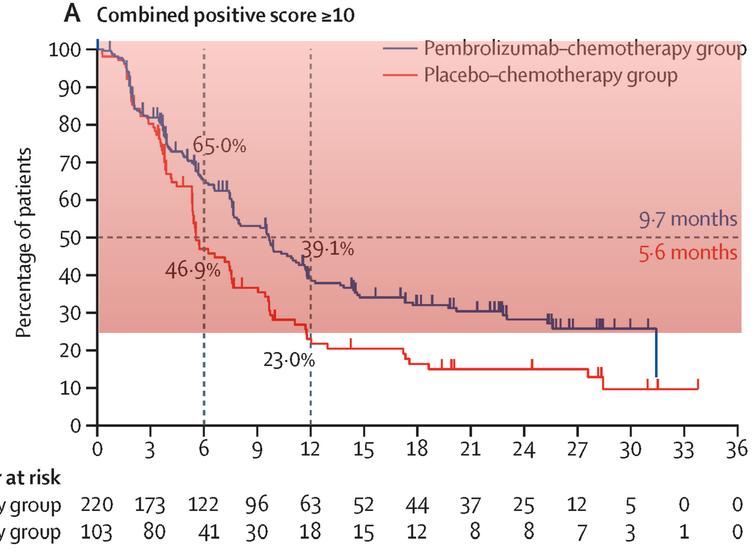




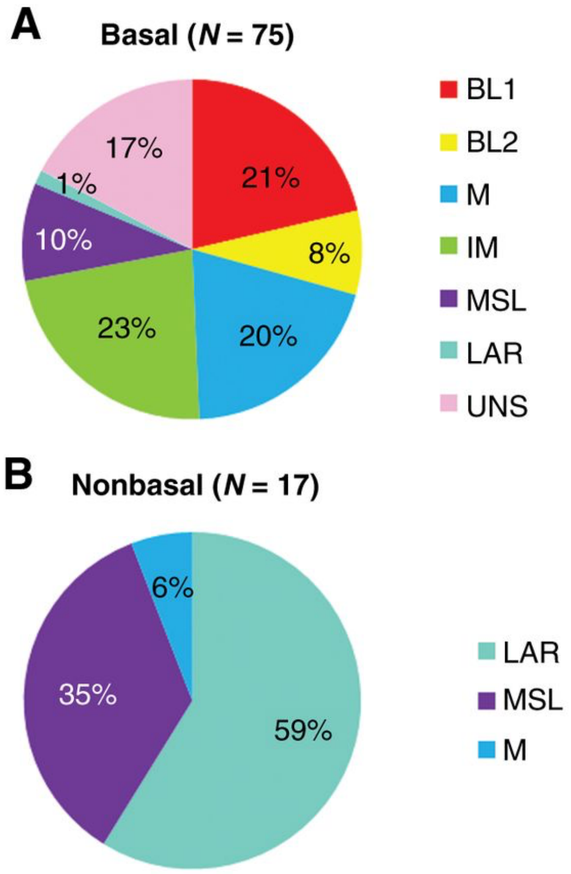
Non responders



TNBC: an heterogeneous entity

Gene-expression, Immune features

GE-based subtypes



H. Masuda et al. CCR 2013; Bereche et al. JNCI 2020; Y. Bereche et al. Annals 2018 ; Gruosso et al. JCI 2019;

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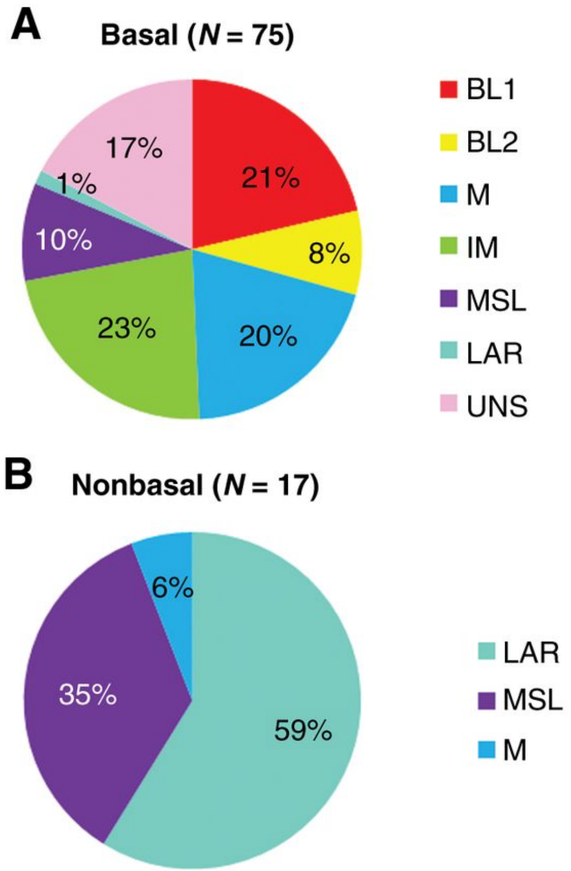
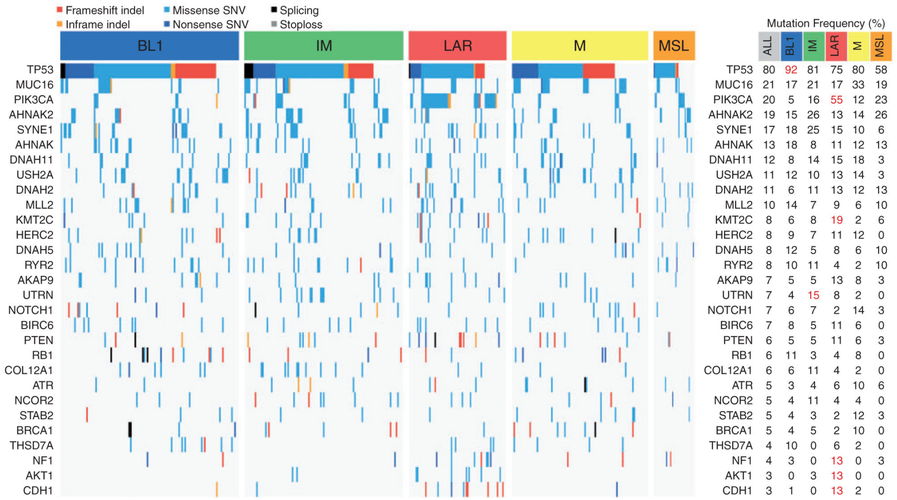


Mutational landscape in GE-based subtypes



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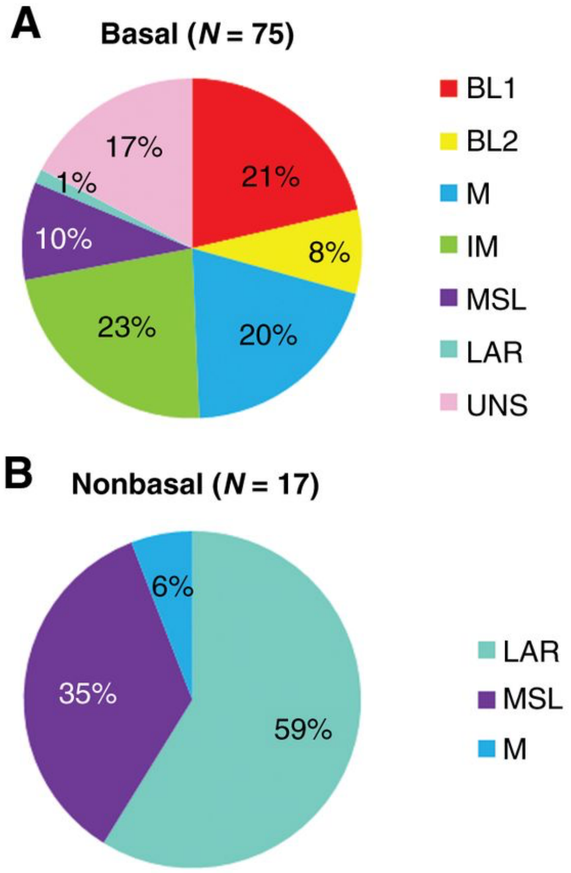

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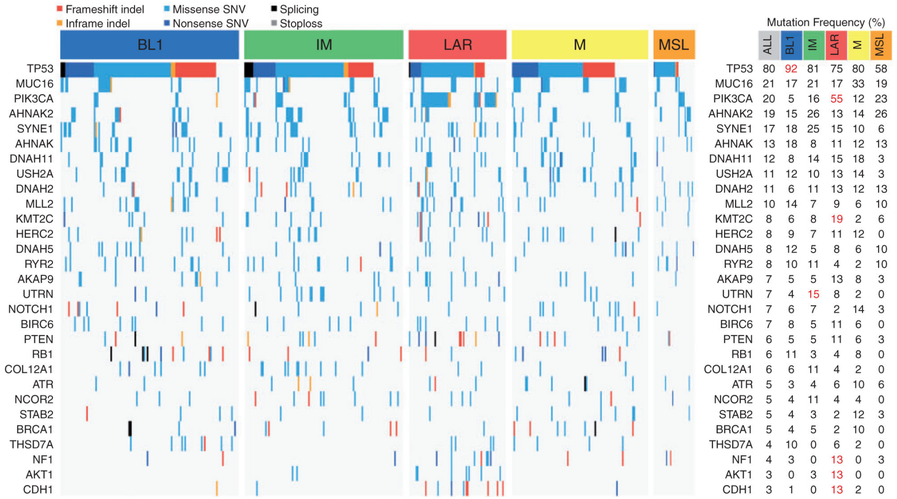
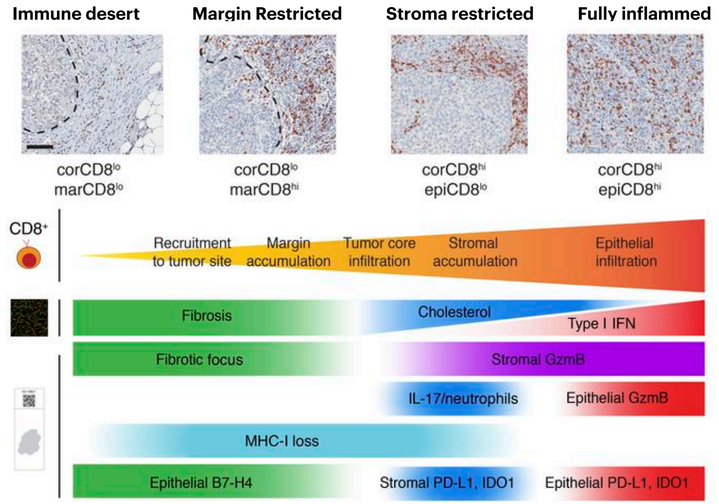


Immune features



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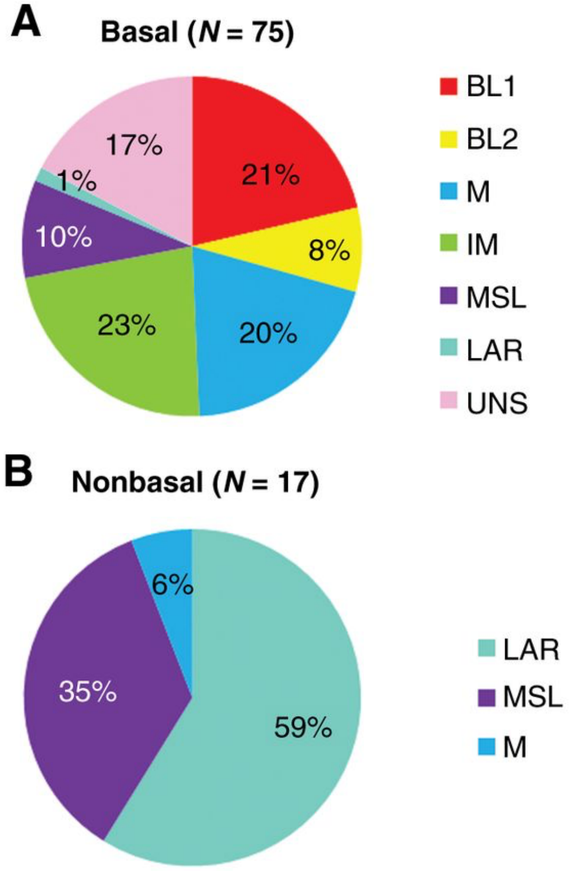

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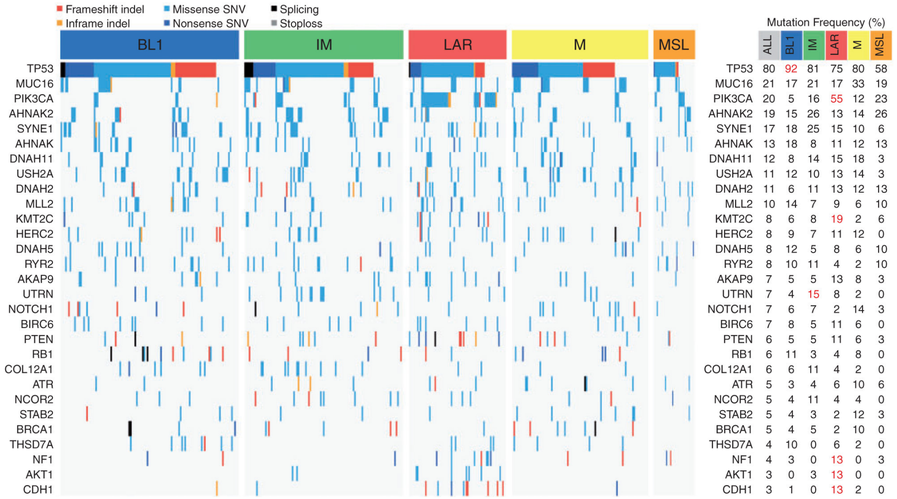
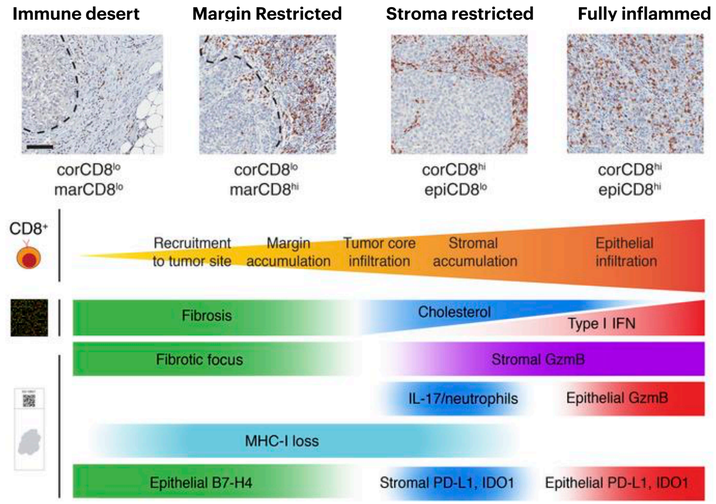


Immune features



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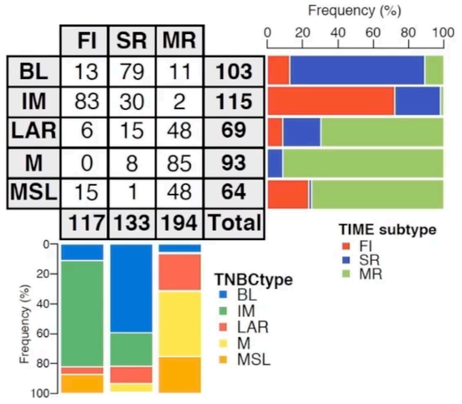

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High internal-heterogeneity

Challenging TNBC perimeter: ER-low

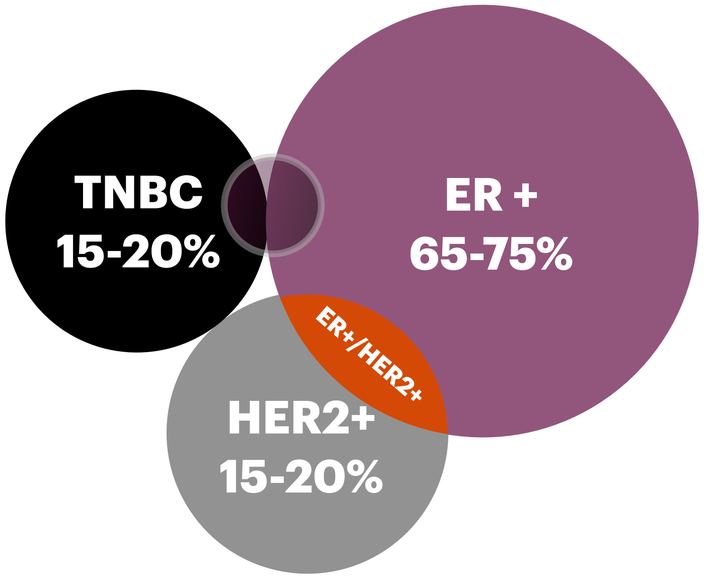
A case study of the limitations of our rigid IHC-Based Definition of TNBC

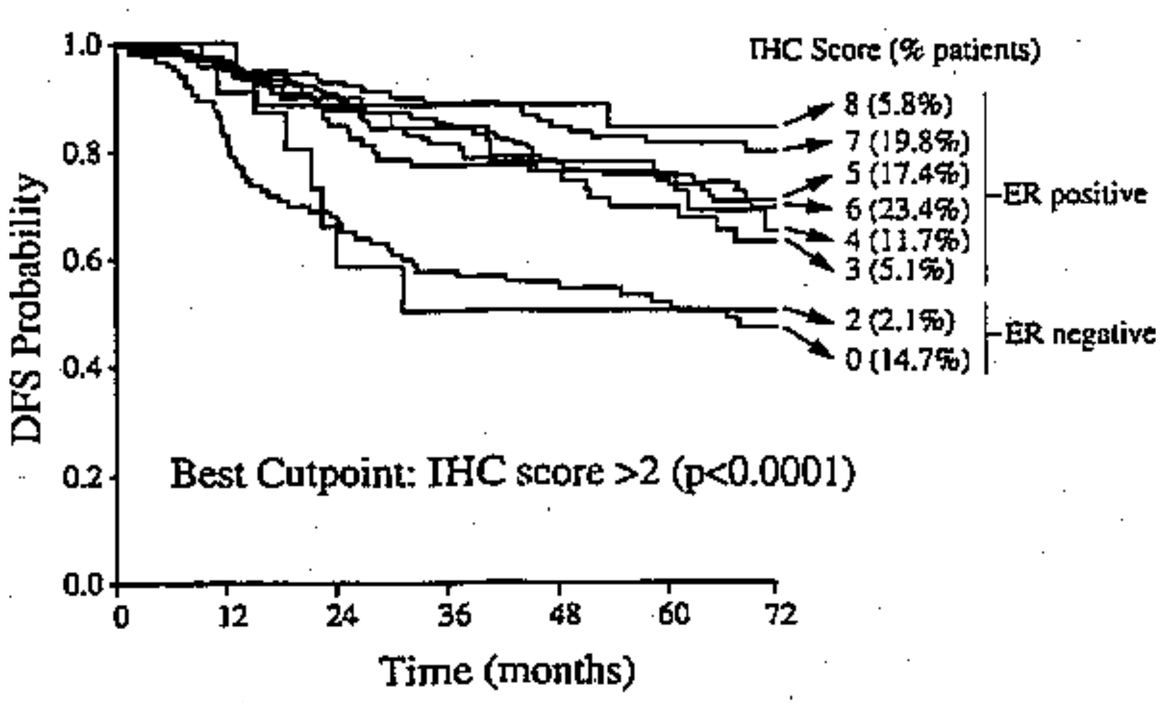
Blurred ER-Boundaries

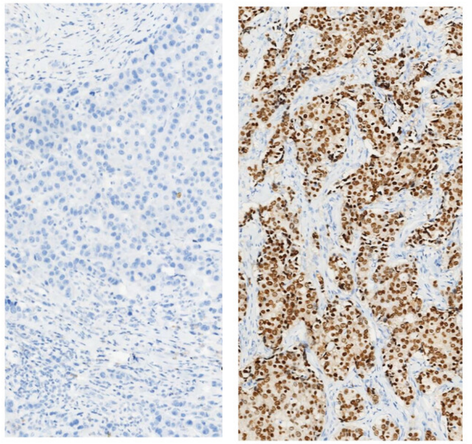
High internal-heterogeneity

Challenging TNBC definition

ER ≥1%: a conservative threshold







Harvey JM et al. J Clin Oncol. 1999

Early stage ER-low and TNBC: Prognosis

ER-low: a challenge to our rigid definition of TNBC

3055 HER2- BC pts who received NACT (MDACT cohort):[1]

- ER <1% 30.5%
- ER 1-9% 5.6%
- ER ≥10% 63.9%

2765 HER2- BC pts who received NACT (GBG trials):[2]

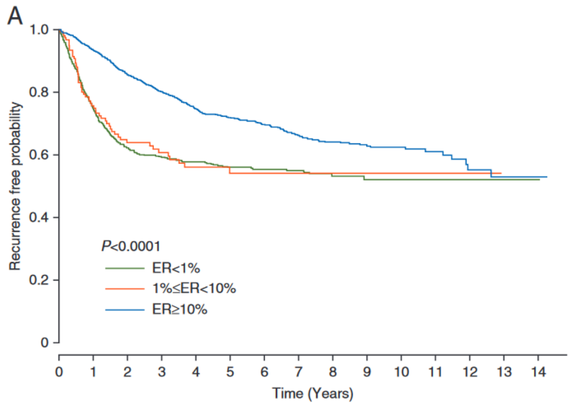
- ER <1% 32.6%
- ER 1-9% 3.4%
- ER ≥10% 64%

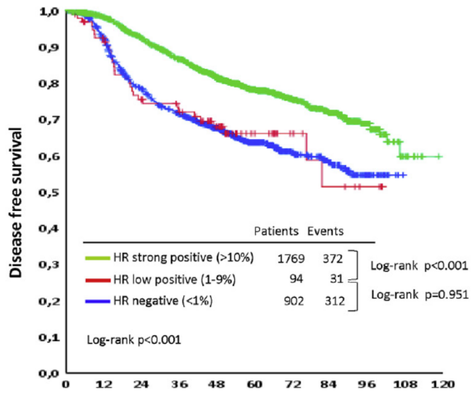
826 HER2- and ER<10% pts who received NACT and/or adj therapy[3]

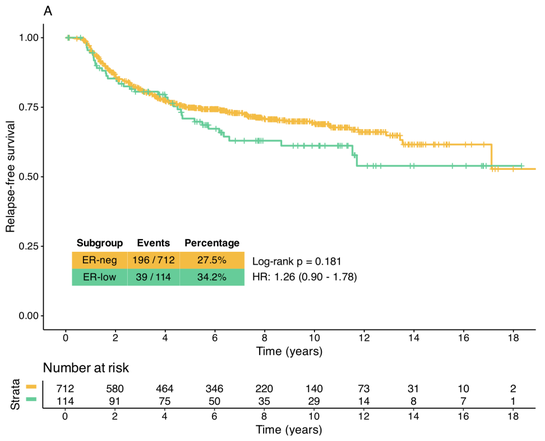
- ER <1% 86%
- ER 1-9% 14%

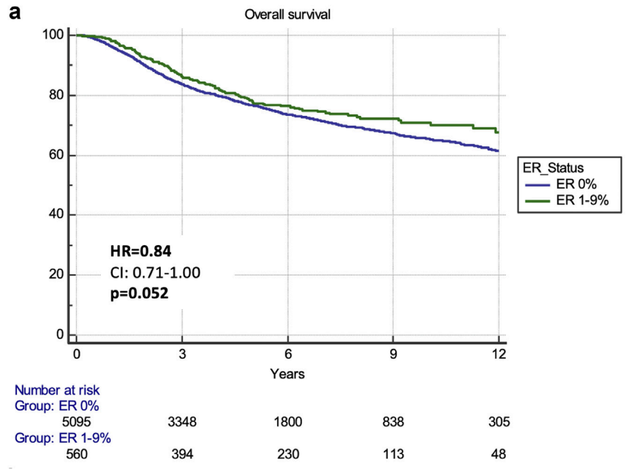
5665 HER2- and ER<10% BC pts who received NACT and/or adj therapy (Sweden cohort):[4]

- ER <1% 90.1%
- ER 1-9% 9.9%





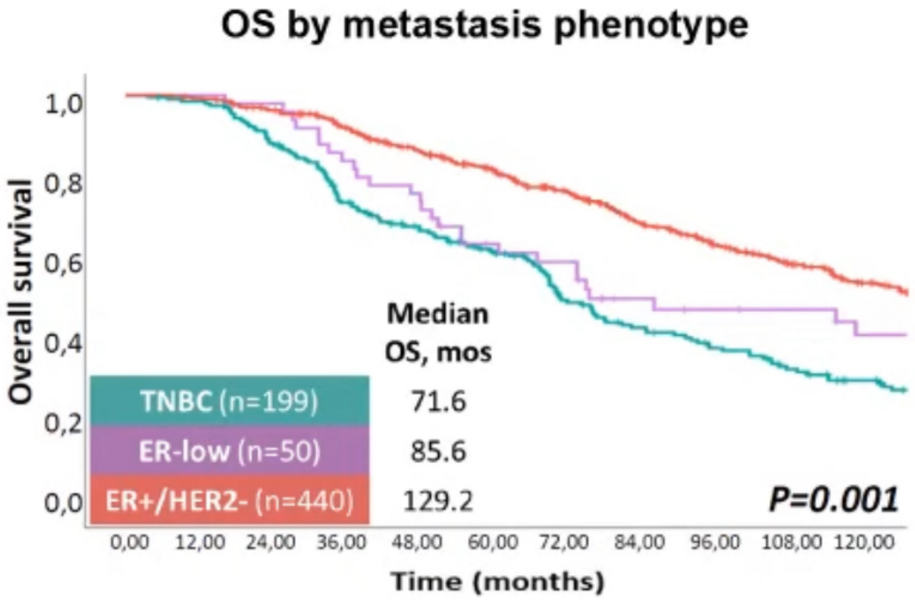


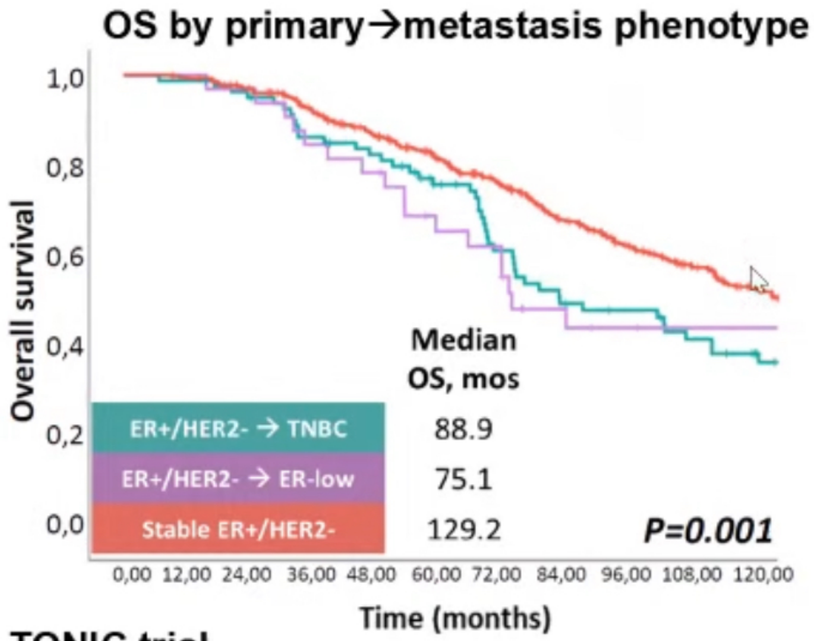


1. Fujii T, *et al.*, Ann Oncol 2017; 28(10):2420-2428. 2. Eur J Cancer 2021,148, Villegas SL, *et al.* 3. Massa D. Et al JNCI 2024. 4. Balazs A. Lancet 2024

Metastatic ER-low and TNBC: Prognosis

ER-low: a challenge to our rigid definition of TNBC





Outcomes of patients in the TONIC trial

CBR

	TNBC (n=95)	ER-low (n=15)	P-value
Yes	21 (22.1%)	3 (20.0%)	1

PFS

	TNBC (n=95)	ER-low (n=15)	P-value
Median, mos	1.9	1.7	0.7

OS

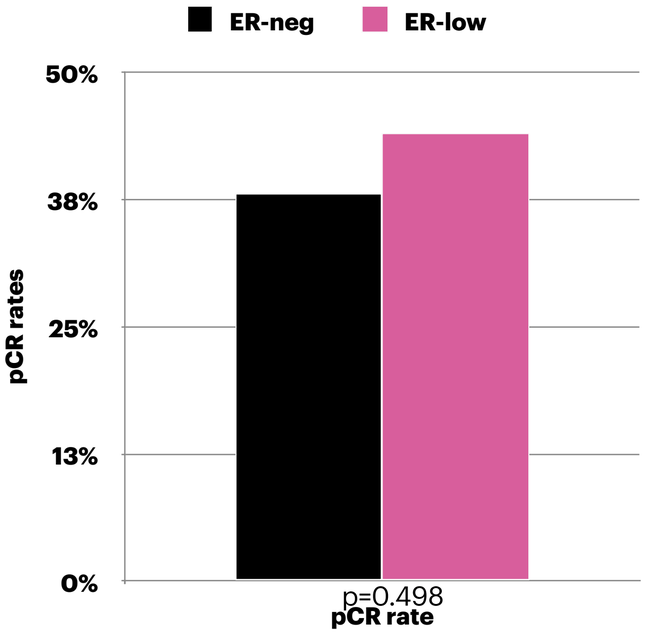
	TNBC (n=95)	ER-low (n=15)	P-value
Median, mos	8.6	5.3	0.3

Miglietta et al. ASCO 2024, Under-review

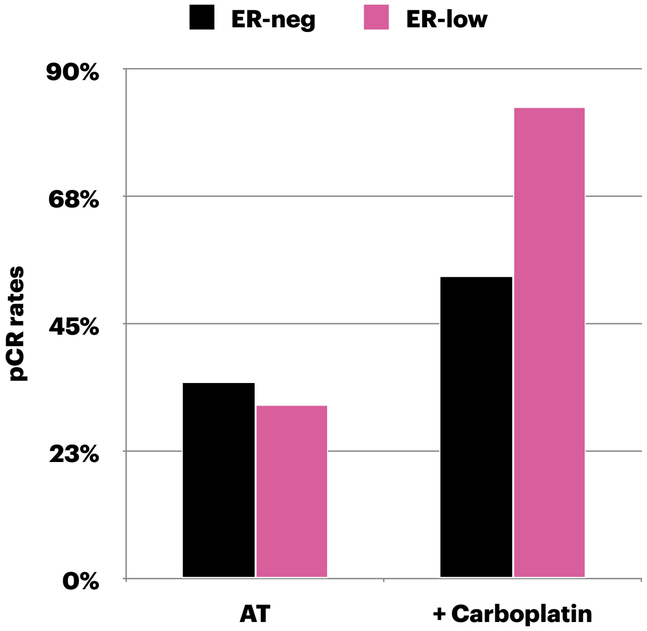
ER-low and Response to CT

ER-low and ER-neg tumors have similar response rates to NACT

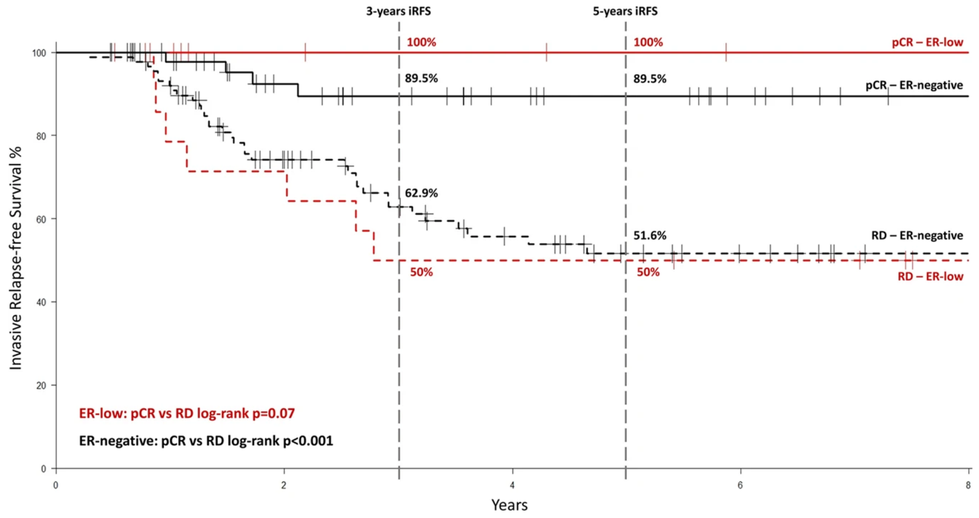
Similar pCR rate to TNBC



Similar increase in pCR-rate +Carboplatin



Prognostic effect of pCR



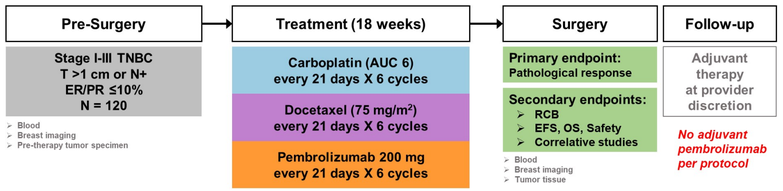
Paakkola et al. ESMO Open 2021; Dieci MV. Et al. BJC 2022; Dieci MV NPJ 2021

ER-low and Response to Immunotherapy

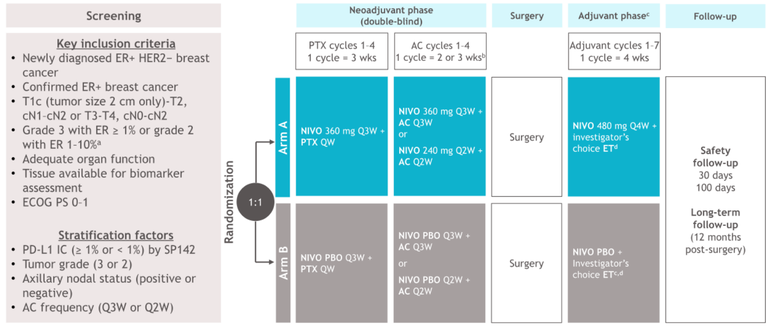
TNBC trial

HR+ trials

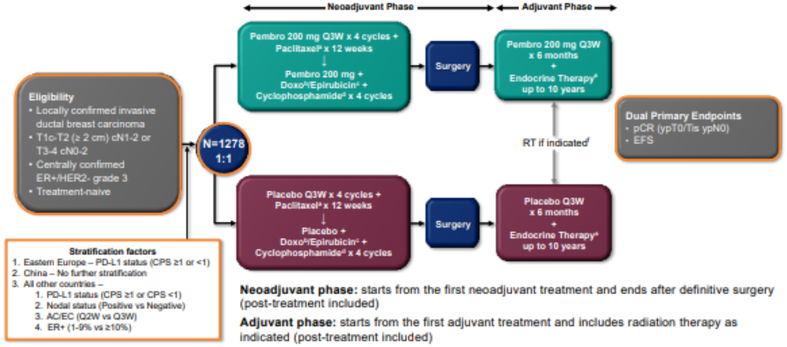
NEOPACT



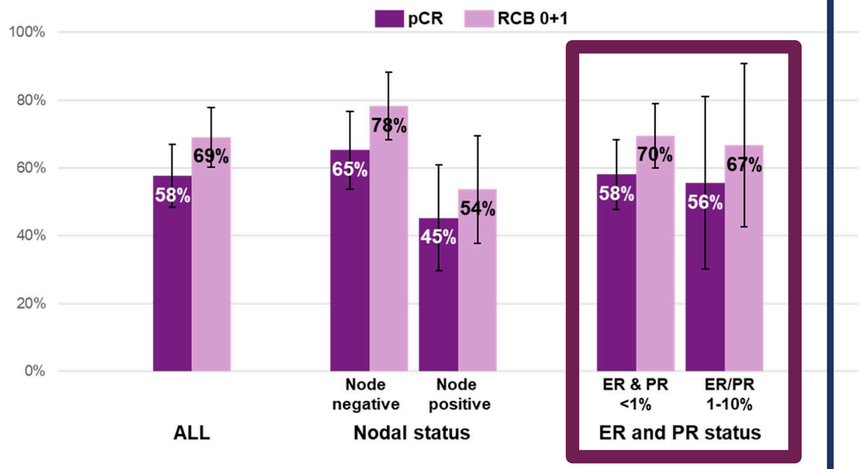
CheckMate 7FL trial



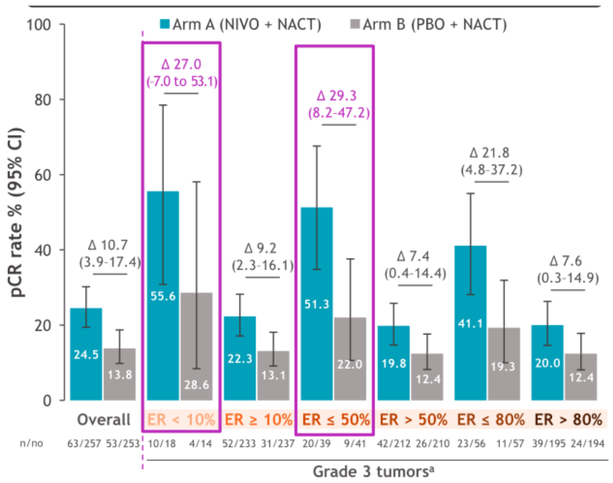
KEYNOTE-756 trial



A pCR by ER status (ER-neg vs low)



pCR by ER status (ER-pos vs low)



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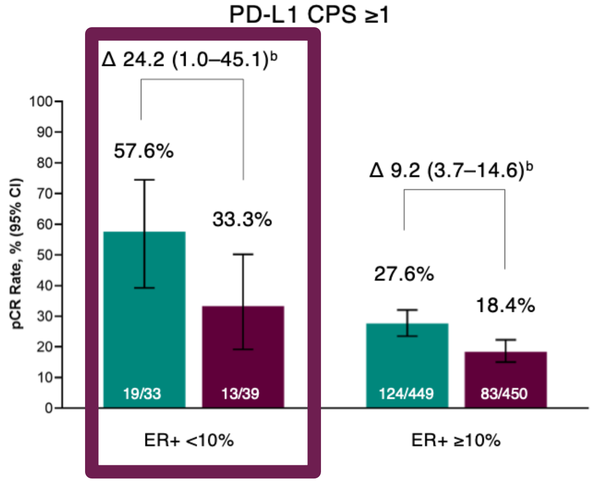


Loi S et al, ESMO 2023. Loi S et al, SABCS 2023. Cardoso F et al, ESMO 2023. O'Shaughnessy J et al, SABCS 2023; Sharma et al. JAMA Oncology 2023

ER-low: Transcriptomic profile

ERlow and TNBC have similar transcriptomic profile

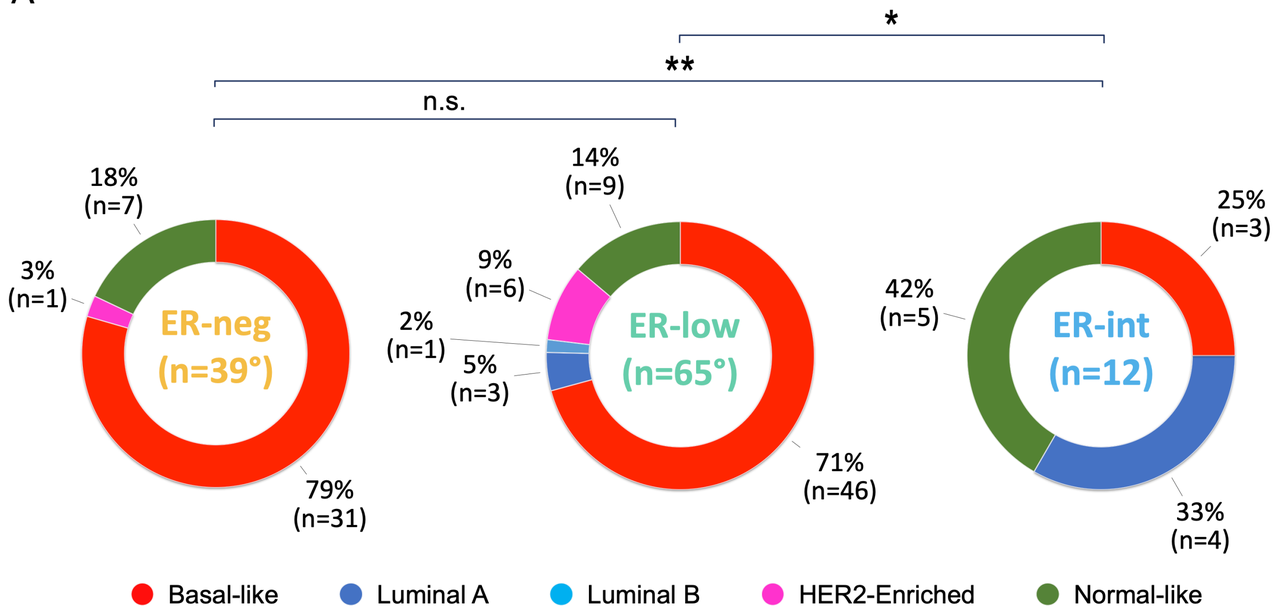
OXFORD

JNCI: Journal of the National Cancer Institute, 2024, **116(12)**, 1914–1927
https://doi.org/10.1093/jnci/djae178
Advance Access Publication Date: July 31, 2024
Article

Immune and gene-expression profiling in estrogen receptor low and negative early breast cancer

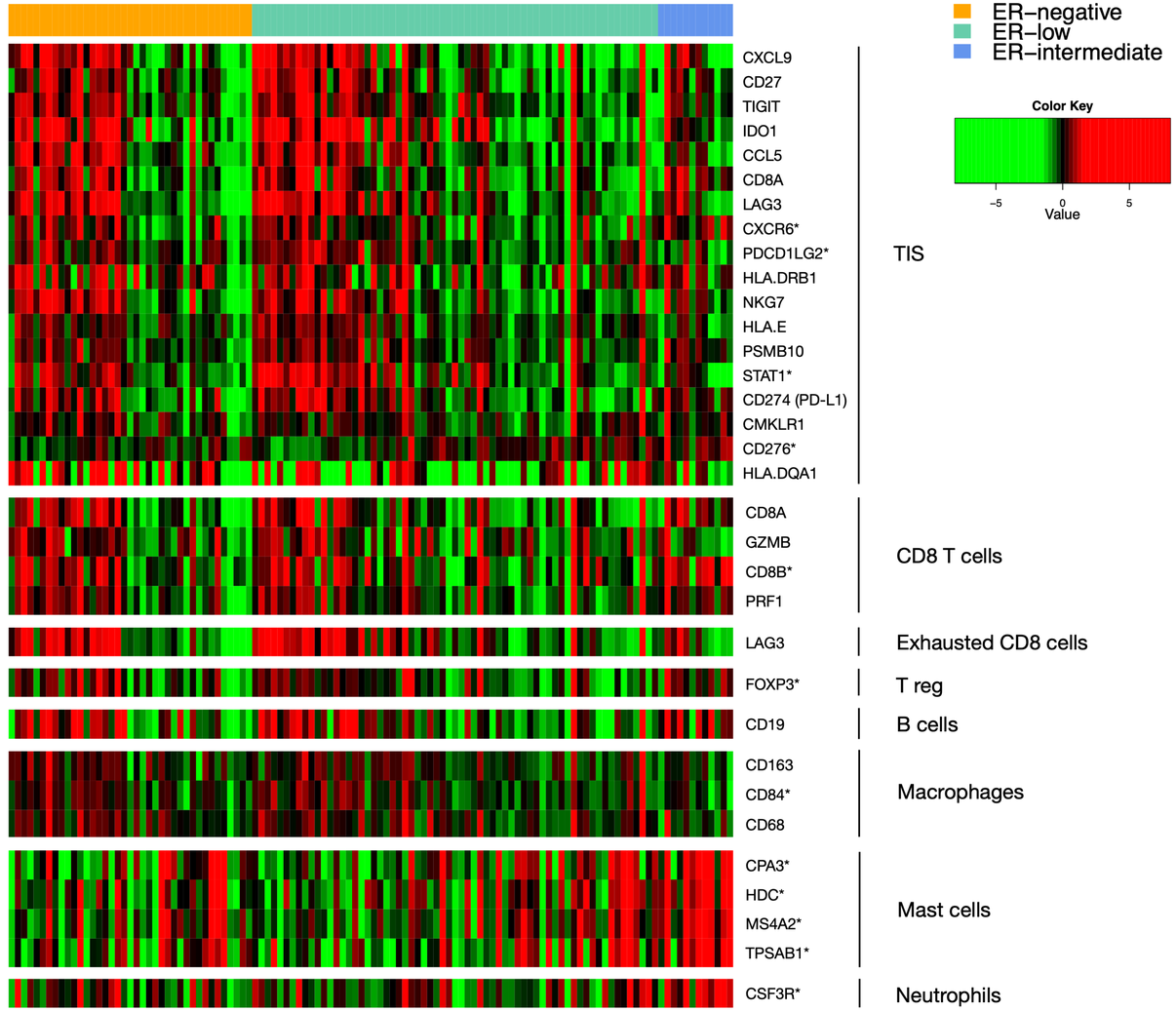
Davide Massa, MD,[1,2] Claudio Vernieri, PhD,[3,4] Lorenzo Nicolè, PhD,[5] Carmen Criscitiello, PhD,[6,7] Florence Boissière-Michot, PhD,[8] Séverine Guiu, PhD,[9,10] Angélique Bobrie, PhD,[9,10] Gaia Griguolo, MD,[1,2,*] Federica Miglietta, PhD,[1,2] Andrea Vingiani, MD,[6,11] Riccardo Lobefaro, MD,[3] Beatrice Taurelli Salimbeni, MD,[7] Claudia Pinato, PhD,[12] Francesca Schiavi, PhD,[12] Silvia Brich, PhD,[11] Carlo Pescia, MD,[13] Nicola Fusco, MD,[6,13] Giancarlo Pruneri, PhD,[6,11] Matteo Fassan, PhD,[14,15] Giuseppe Curigliano, PhD,[6,7] Valentina Guarneri, PhD,[1,2] William Jacot, PhD,[8,9,10] Maria Vittoria Dieci, MD[1,2]

A



°matched for age, histotype and stage

B



Massa D. Et al JNCI 2024

ER-low immune microenviornment

ER-low and TNBC tumors have similar immune features

OXFORD

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Article

Immune and gene-expression profiling in estrogen receptor low and negative early breast cancer

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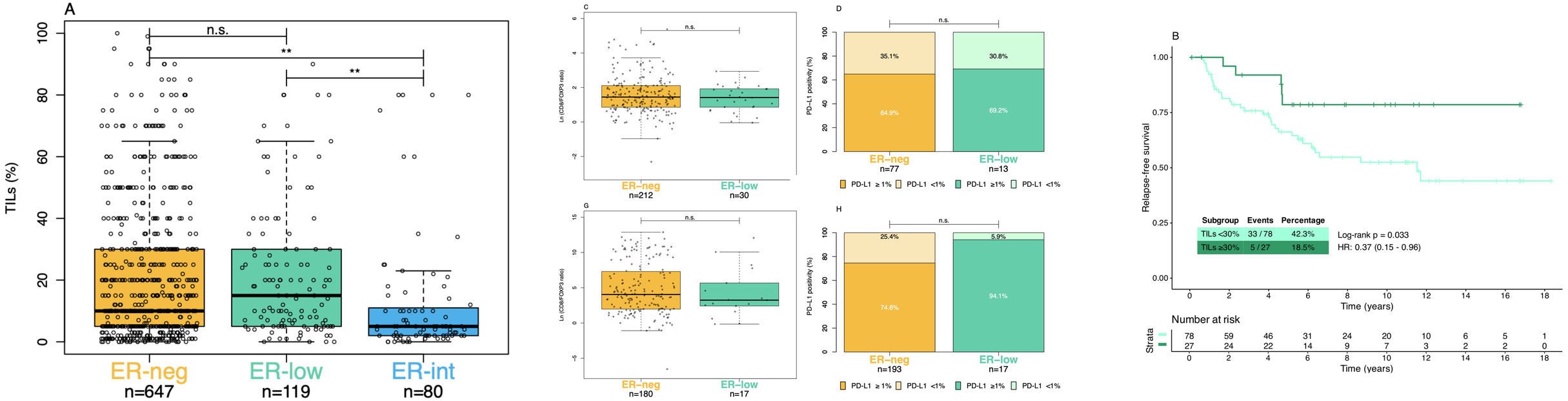


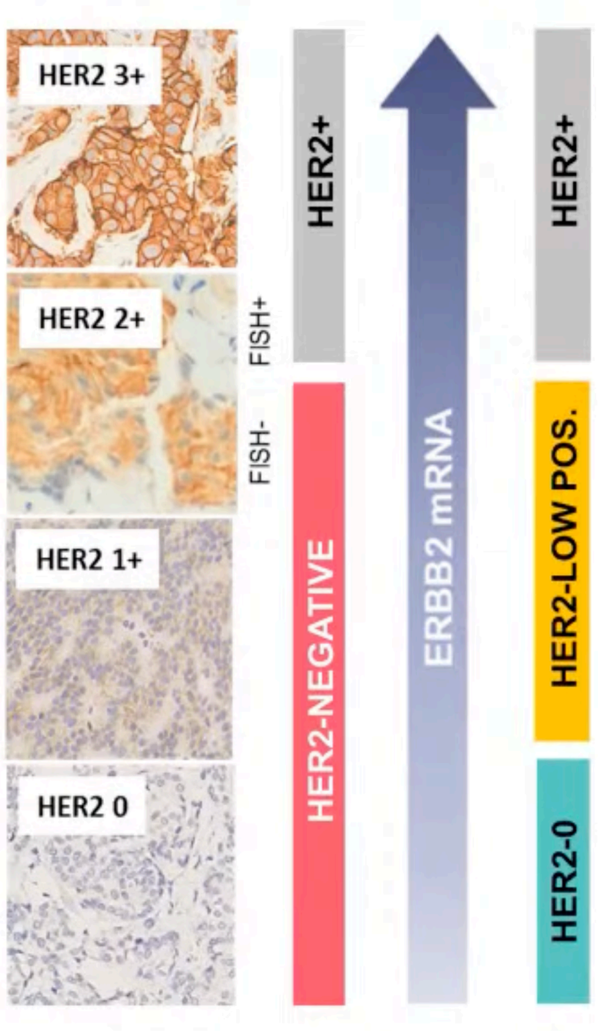
D. Massa et al JNCI 2024

Challenging TNBC perimeter: HER2-low

Still a leftover category of tumors lacking druggable targets?

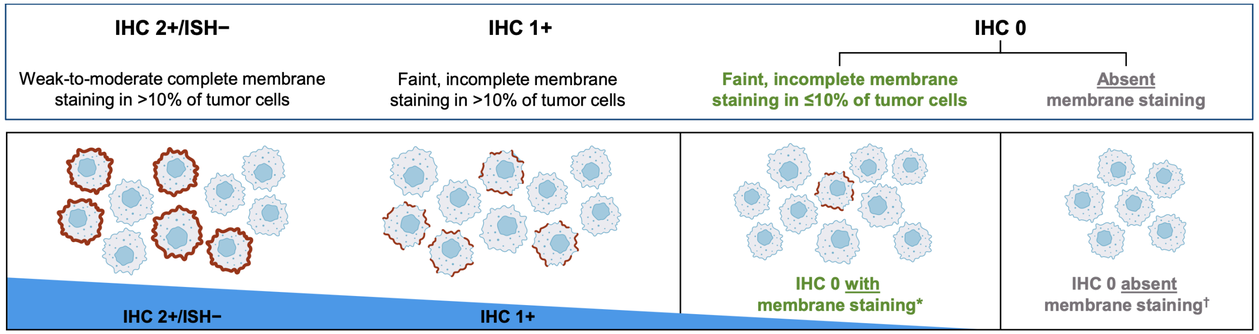
HER2-low and ADCs

HER2-low: Not a separate entity, but a new target



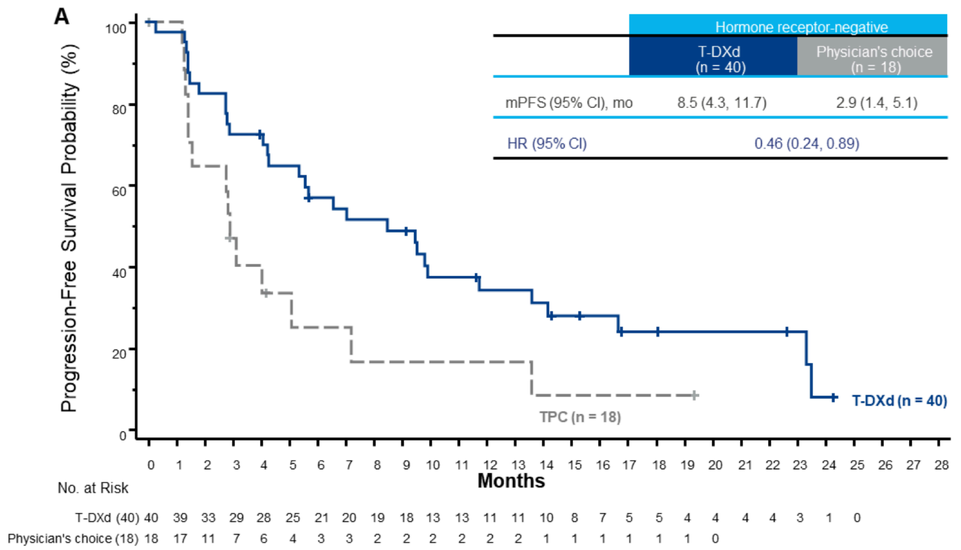
Miglietta F. et al. NPJ.

HER2



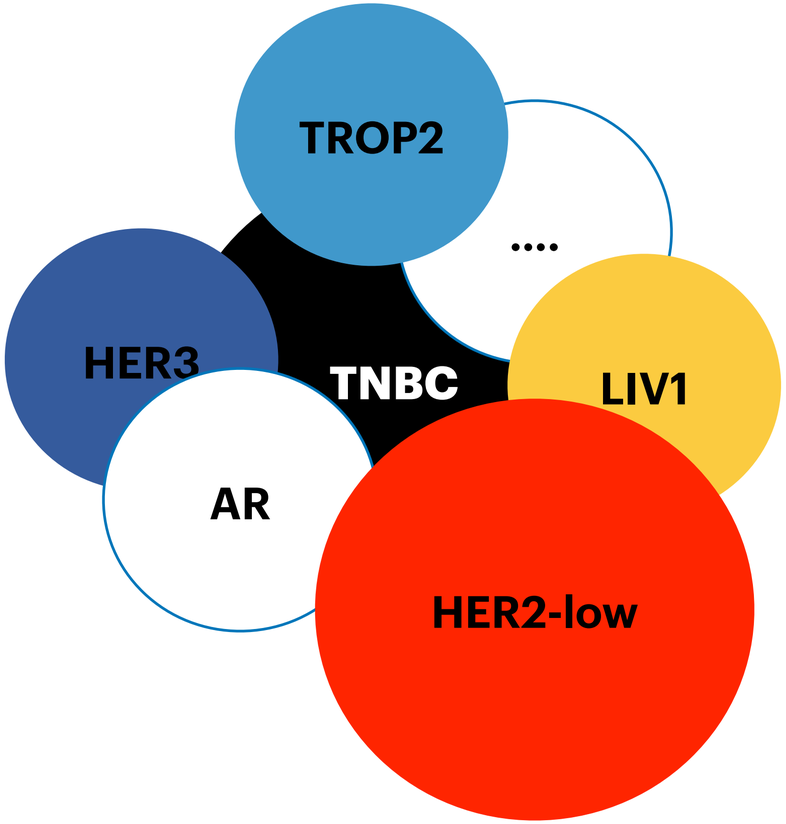
HER2-low **HER2-ultra low**

DB-04

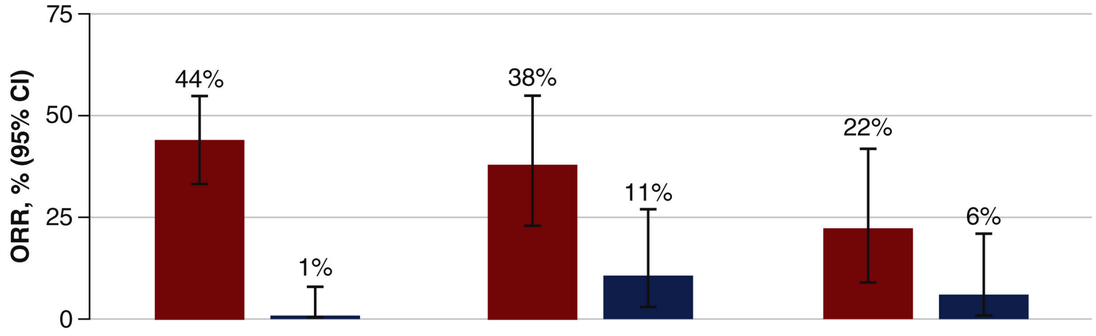


ADCs: blurring TNBC definition

Still a leftover category of tumors <u>lacking druggable targets?</u>

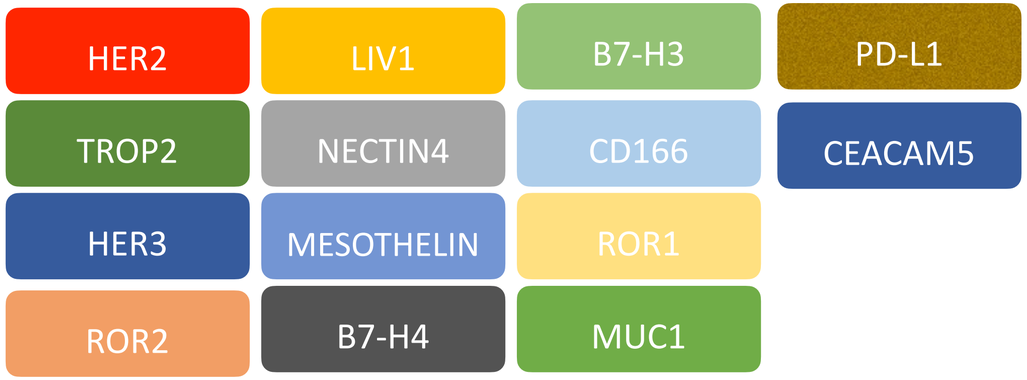


TROP2



	Trop-2 high H-score: >200-300 (*n* = 157)		Trop-2 medium H-score: 100-200 (*n* = 74)		Trop-2 low H-score: 0 to <100 (*n* = 59)	
	SG (*n* = 85)	TPC (*n* = 72)	SG (*n* = 39)	TPC (*n* = 35)	SG (*n* = 27)	TPC (*n* = 32)
ORR, % (*n*)	44 (37)	1 (1)	38 (15)	11 (4)	22 (6)	6 (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

And more..



Moving Forward: short term

Rethinking TNBC definition

Step 1: Recognizing ER-low

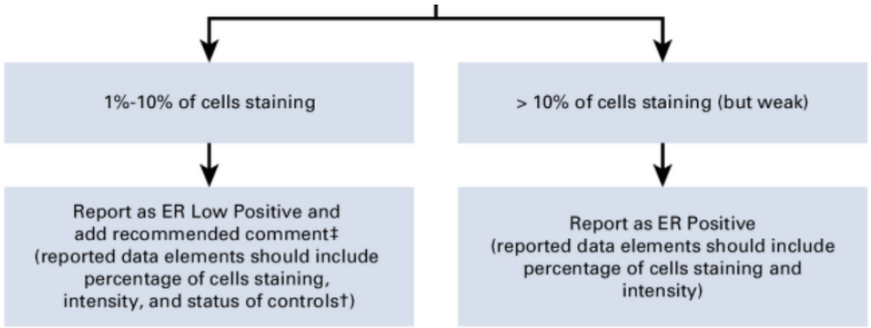
ASCO/CAP 2020 Guideline Update

2020

ASCO special articles

Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update

Kimberly H. Allison, MD[1]; M. Elizabeth H. Hammond, MD[2]; Mitchell Dowsett, PhD[3]; Shannon E. McKernin[4]; Lisa A. Carey, MD[5]; Patrick L. Fitzgibbons, MD[6]; Daniel F. Hayes, MD[7]; Sunil R. Lakhani, MD[8,9]; Mariana Chavez-MacGregor, MSc[10]; Jane Perlmutter, PhD[11]; Charles M. Perou, PhD[5]; Meredith M. Regan, ScD[12]; David L. Rimm, MD, PhD[13]; W. Fraser Symmans, MD[10]; Emina E. Torlakovic, MD, PhD[14,15]; Leticia Varella, MD[16]; Giuseppe Viale, MD[17,18]; Tracey F. Weisberg, MD[19]; Lisa M. McShane, PhD[20]; and Antonio C. Wolff, MD[21]



2024

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

S. Loibl[1,2], F. André[3], T. Bachelot[4], C. H. Barrios[5], J. Bergh[6], H. J. Burstein[7], M. J. Cardoso[8,9], L. A. Carey[10], S. Dawood[11], L. Del Mastro[12,13], C. Denkert[14], E. M. Fallenberg[15], P. A. Francis[16], H. Gamal-Eldin[17], K. Gelmon[18], C. E. Geyer[19], M. Gnant[20], V. Guarneri[21,22], S. Gupta[23], S. B. Kim[24], D. Krug[25], M. Martin[26], I. Meattini[27,28], M. Morrow[29], W. Janni[30], S. Paluch-Shimon[31], A. Partridge[7], P. Poortmans[32,33], L. Pusztai[34], M. M. Regan[35], J. Sparano[36], T. Spanic[37], S. Swain[38], S. Tjulandin[39], M. Toi[40], D. Trapani[7], A. Tutt[41,42], B. Xu[43], G. Curigliano[44,45] & N. Harbeck[46], on behalf of the ESMO Guidelines Committee*

TNBC

- HER2-negative tumours with 1%-9% ER and/or PgR expression (ER-/PgR-low) are a heterogenous group, some of which behave biologically similarly to TNBCs; therapeutic strategies should be adjusted to this specific situation since this might lead to a higher response to ChT and to reduced efficacy of ET compared with classical HR-positive breast cancer [II, B].

Step 2: Including ER-low tumors in TNBC trials

Rething rigid TNBC definition to reflect biology while remaining clinically practical

ER-low pts should have access to treatments and trials for TNBC

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Optimizing choices and sequences in the diagnostic-therapeutic landscape of advanced triple-negative breast cancer: An Italian consensus paper and critical review

F. Miglietta [a,b], A. Fabi [c], D. Generali [d,e], M.V. Dieci [a,b], G. Arpino [f], G. Bianchini [g,h], S. Cinieri [i], P. F. Conte [j], G. Curigliano [k,l], M. De Laurentiis [m], L. Del Mastro [n,o], S. De Placido [f], A. Gennari [p], F. Puglisi [q,r], A. Zambelli [s,t], F. Perrone [u], V. Guarneri [a,b,*]

- Patients with tumors exhibiting low levels of ER expression (1–9 %) should be considered as TN and should therefore be granted access to drugs developed/registered for TN mBC

  Consensus reached (agreement level = 95.66 %).

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)☆

F. Cardoso[1*], S. Paluch-Shimon[2], E. Senkus[3], G. Curigliano[4], M. S. Aapro[5], F. André[6], C. H. Barrios[7], J. Bergh[8], G. S. Bhattacharyya[9], L. Biganzoli[10], F. Boyle[11], M.-J. Cardoso[1,12], L. A. Carey[13], J. Cortés[14,15], N. S. El Saghir[16], M. Elzayat[17], A. Eniu[18], L. Fallowfield[19], P. A. Francis[20], K. Gelmon[21], J. Gligorov[22], R. Haidinger[23], N. Harbeck[24], X. Hu[25], B. Kaufman[26], R. Kaur[27], B. E. Kiely[28], S.-B. Kim[29], N. U. Lin[30], S. A. Mertz[31], S. Neciosup[32], B. V. Offersen[33], S. Ohno[34], O. Pagani[35], A. Prat[36,37,38], F. Penault-Llorca[39,40], H. S. Rugo[41], G. W. Sledge[42], C. Thomssen[43], D. A. Vorobiof[44], T. Wiseman[45], B. Xu[46], L. Norton[47], A. Costa[48,49] & E. P. Winer[30]

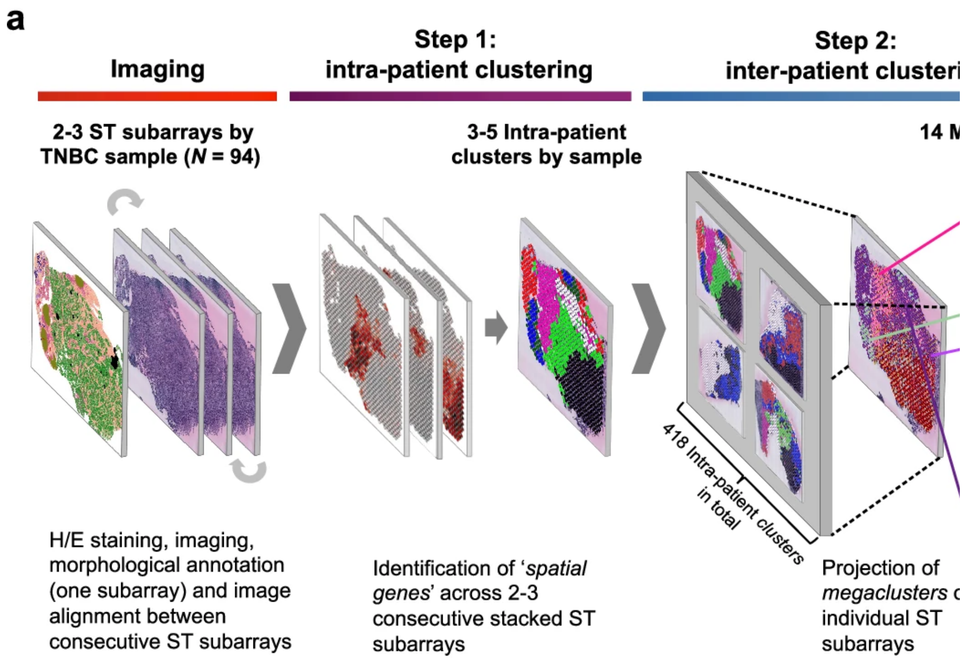
Guideline statement	LoE/GoR	Consensus
Patients with low (1%-10%) ER-positive (and PgR-positive), HER2-negative ABC should not be considered for ET exclusively.	III/B	95%
Patients with low (1%-10%) ER-positive (and PgR-positive), HER2-negative ABC can be considered as patients with triple-negative ABC for clinical trials.		

Moving Forward: long term

Beyond IHC

Beyond IHC

Spatial Transcriptomics and Clusters



- Group similar spots in each tumor based on spatially resolved gene expression
- Each group = a local biological neighborhood : immune-rich, proliferative, stromal, etc. E.g a city park full of people; industrial zones

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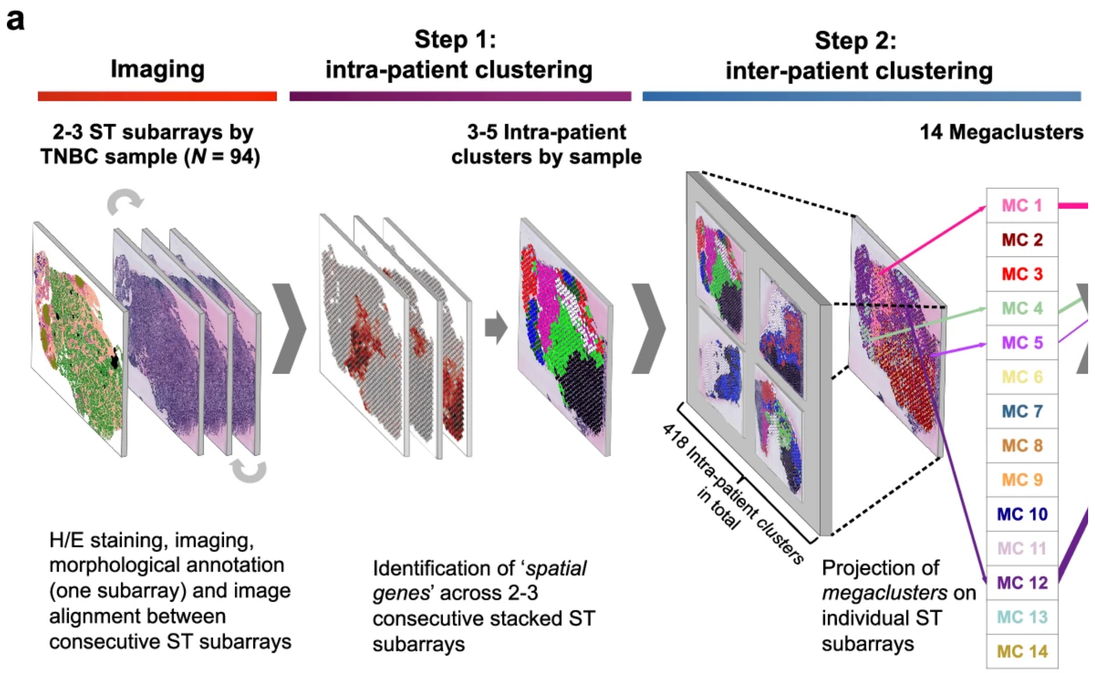
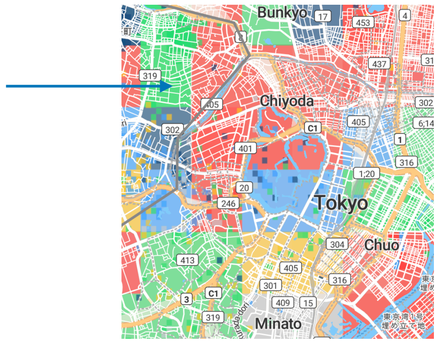
Beyond IHC

Spatial Transcriptomics and Clusters

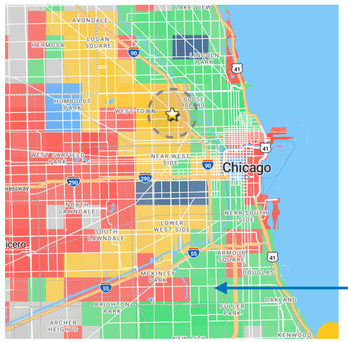


- Group similar spots in each tumor based on spatially resolved gene expression
- Each group = a local biological neighborhood : immune-rich, proliferative, stromal, etc. E.g a city park full of people; industrial zones
- Group similar clusters across tumors into **megaclusters (MCs): MC9: immune-rich parks with simlar features across cities; MC7: industrial zones near commercial areas**

Tokyo



Chicago



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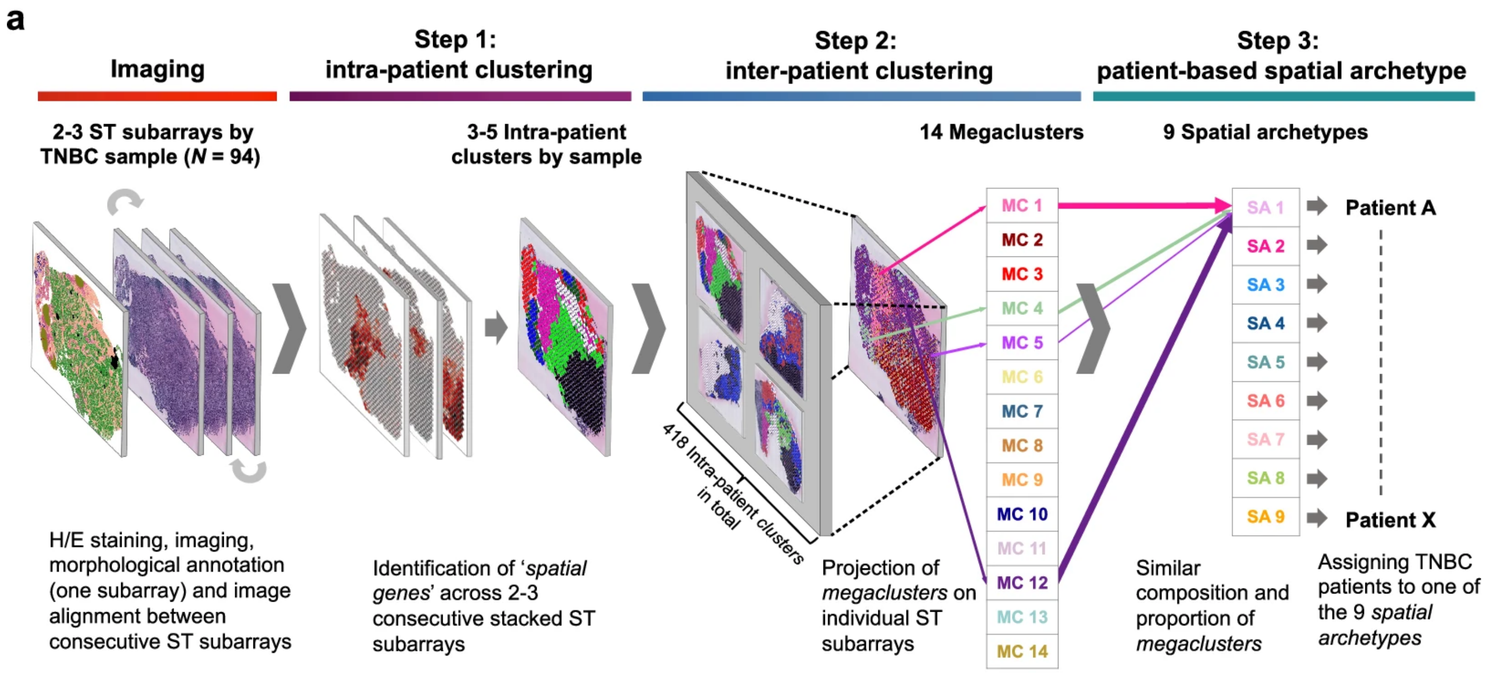
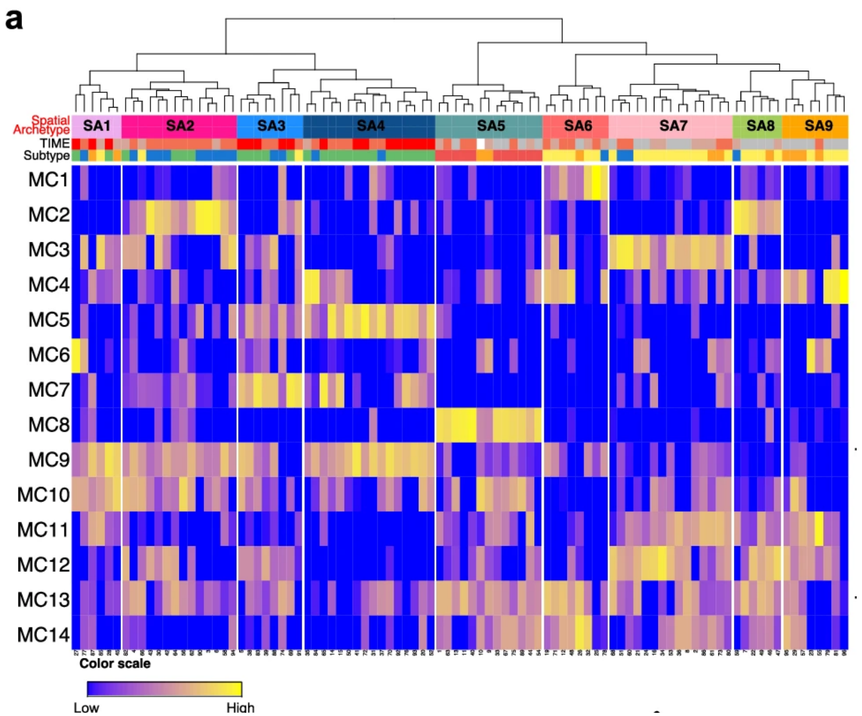
Beyond IHC

Lehmann subtypes as simplifications that mask spatial heterogeneity





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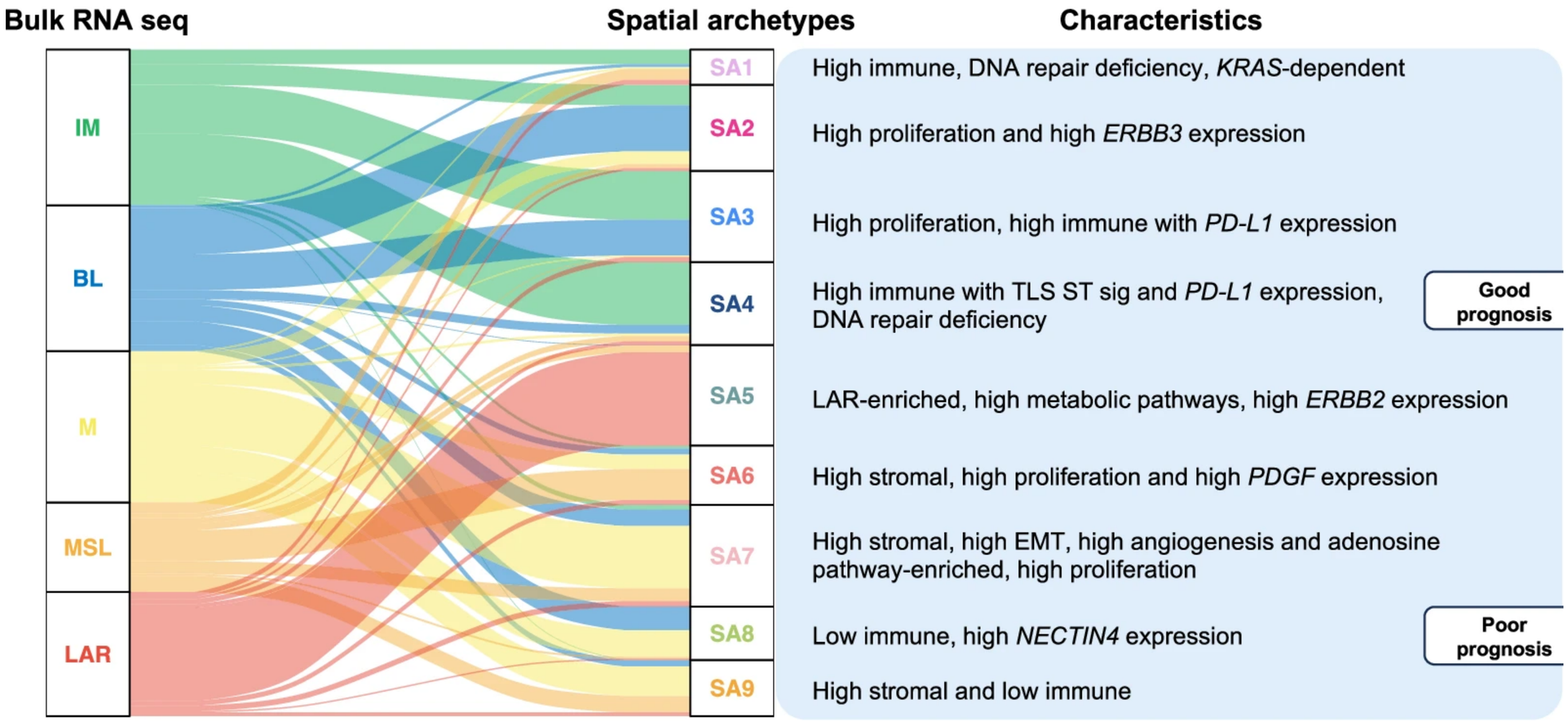
- Each tumor is a mosaic of MCs
- Group tumors (cities) by their MC composition → 9 Spatial Archetypes
- e.g: London and New-York: mostly industrial/commercial buildings near a few parks; Verona and Padova: residential areas, industrial buildings in the outer zone

Spatial Archetypes: common characteristics

Classifying tumors not just by surface markers, but by the biology of their ecosystem

TNBC, as defined by IHC, is only the surface:

- Spatial and functional classifications that reflect tumor ecosystems—not just receptor status



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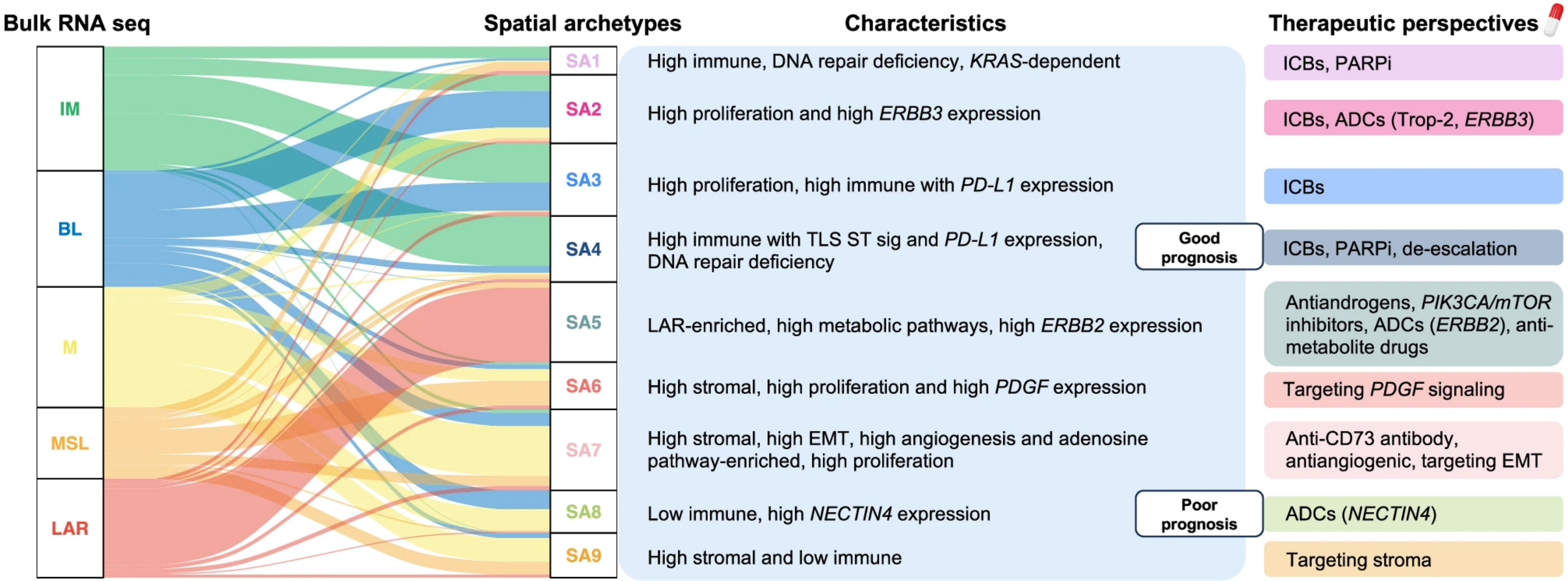
Spatial Archetypes: Clinically actionable TNBC subgroups

Classifying tumors not just by surface markers, but by the biology of their ecosystem

TNBC, as defined by IHC, is only the surface:

- Spatial and functional classifications that reflect tumor ecosystems—not just receptor status



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Conclusion: rethinking TNBC

1. TNBC was born out of **clinical necessity**, not biological logic:
→ A pragmatic category defined by the **absence of biomarkers.**

2. Apparent homogeneity masked **profound heterogeneity:**
→ Shared phenotype, but **diverse molecular and immune landscapes**.

3. ER-low tumors expose the cracks in **rigid IHC-based definitions:**
→ Clinically and biologically closer to TNBC than to luminal tumors.

4. HER2-low: ADC are further blurring the boundaries of TNBC definition

5. Beyond IHC, toward biology-driven classifications (spatial, transcriptomic)?

To improve patient care and research precision, TNBC must be redefined not just by what it's missing, but by what it is.