

HER2

*Un paradigma
en evolución*

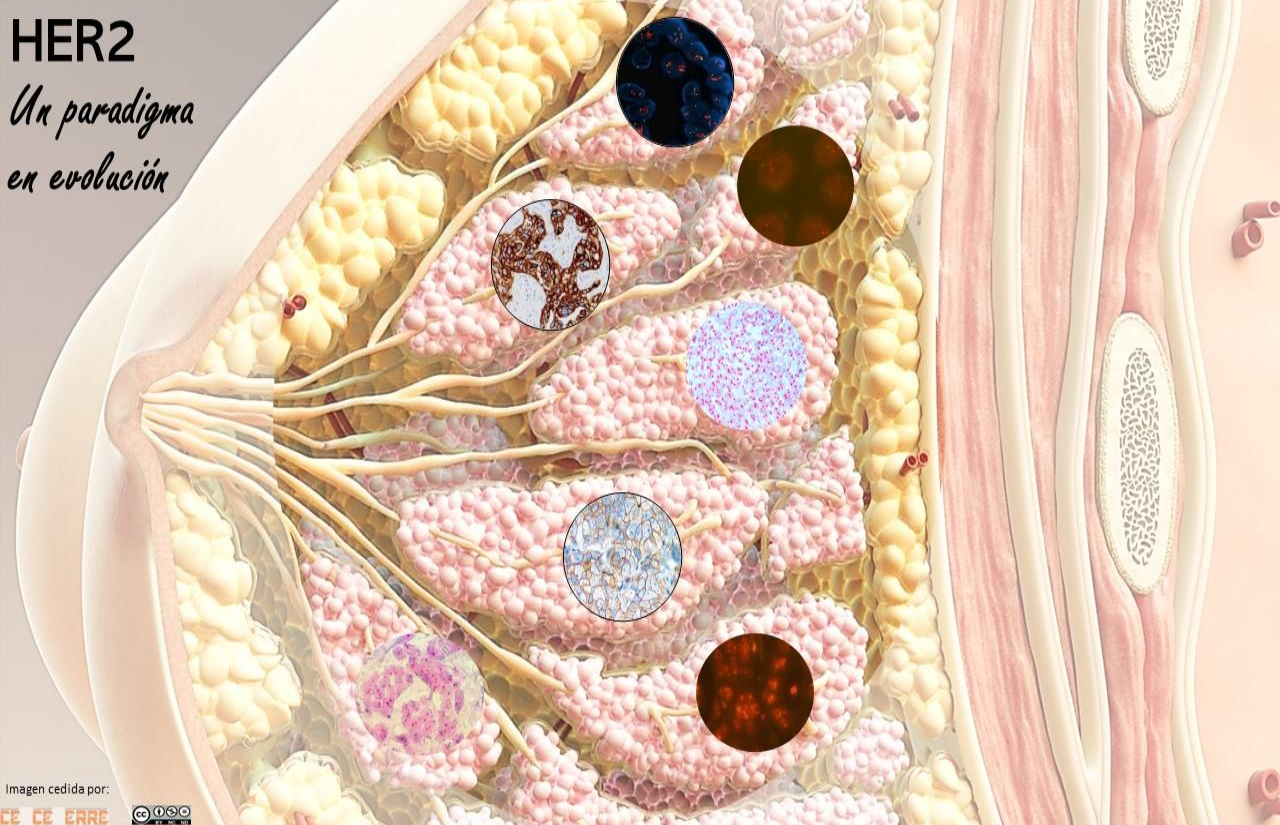


Imagen cedida por:

CE CE ERRE



Retos diagnósticos y terapéuticos: mirada hacia el futuro de la enfermedad HER2

Aleix Prat, MD PhD
Hospital Clinic de Barcelona
Oncología Médica

HER2 en cáncer de mama: un paradigma en evolución

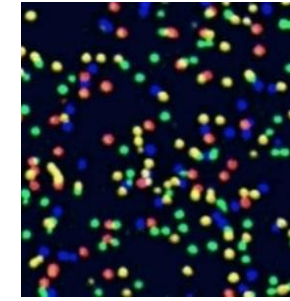
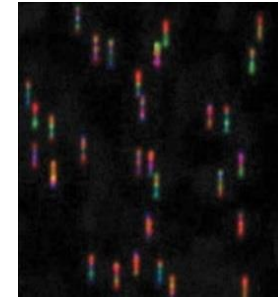
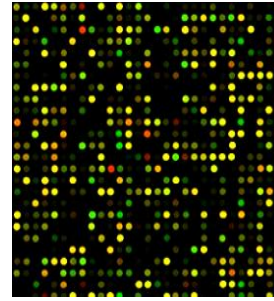
Retos diagnósticos y terapéuticos: mirada hacia el futuro de la enfermedad HER2

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Disclosures



Consultancy/speaker: Pfizer, Lilly, Novartis, Roche, Amgen, PUMA, Nanostring Technologies, Seattle Genetics, Daiichi-Sankyo, AstraZeneca, Guardant Health, Foundation Medicine

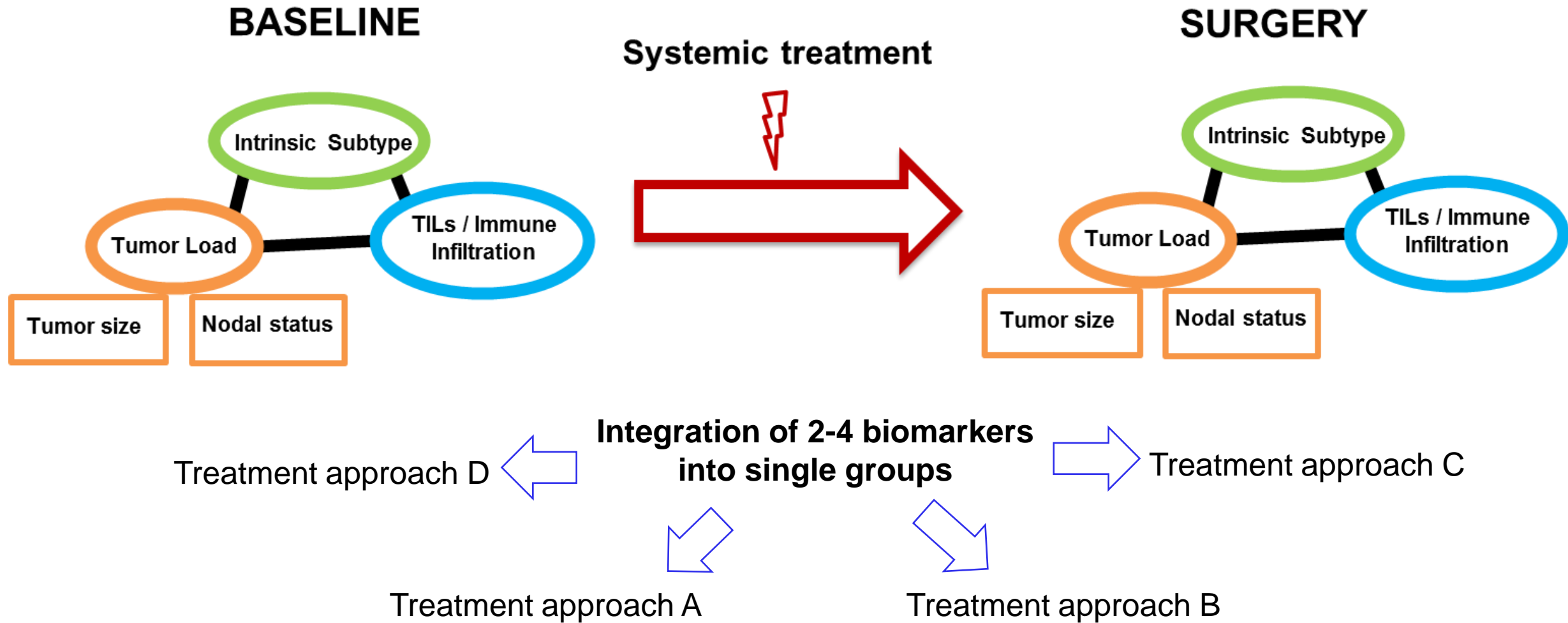
Research funding: Novartis, Roche, Nanostring Technologies, PUMA

Patents: ERBB2 (WO2018/103834A1), HER2DX (filed)

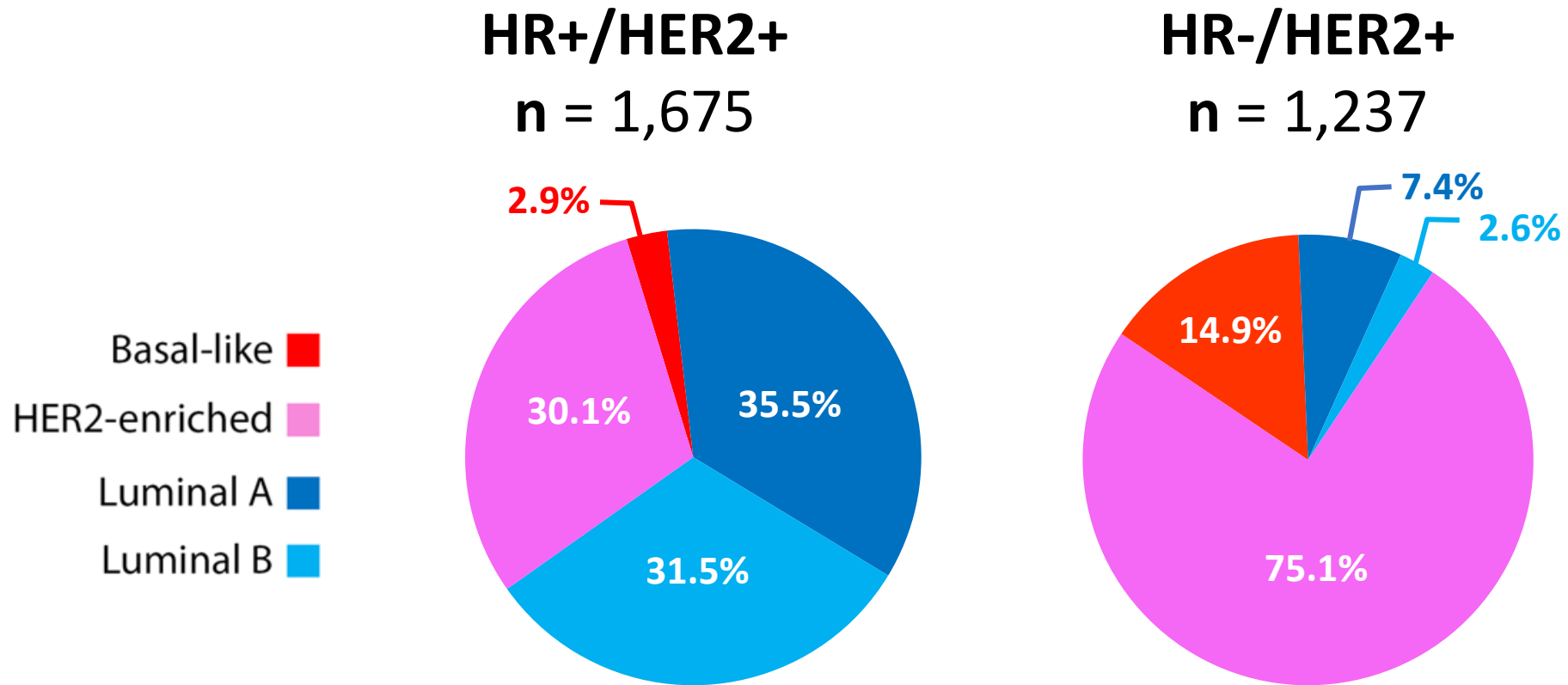
Scientific advisory board: Oncolytics Biotech

Founder: Reveal Genomics

Precision medicine in HER2+ disease



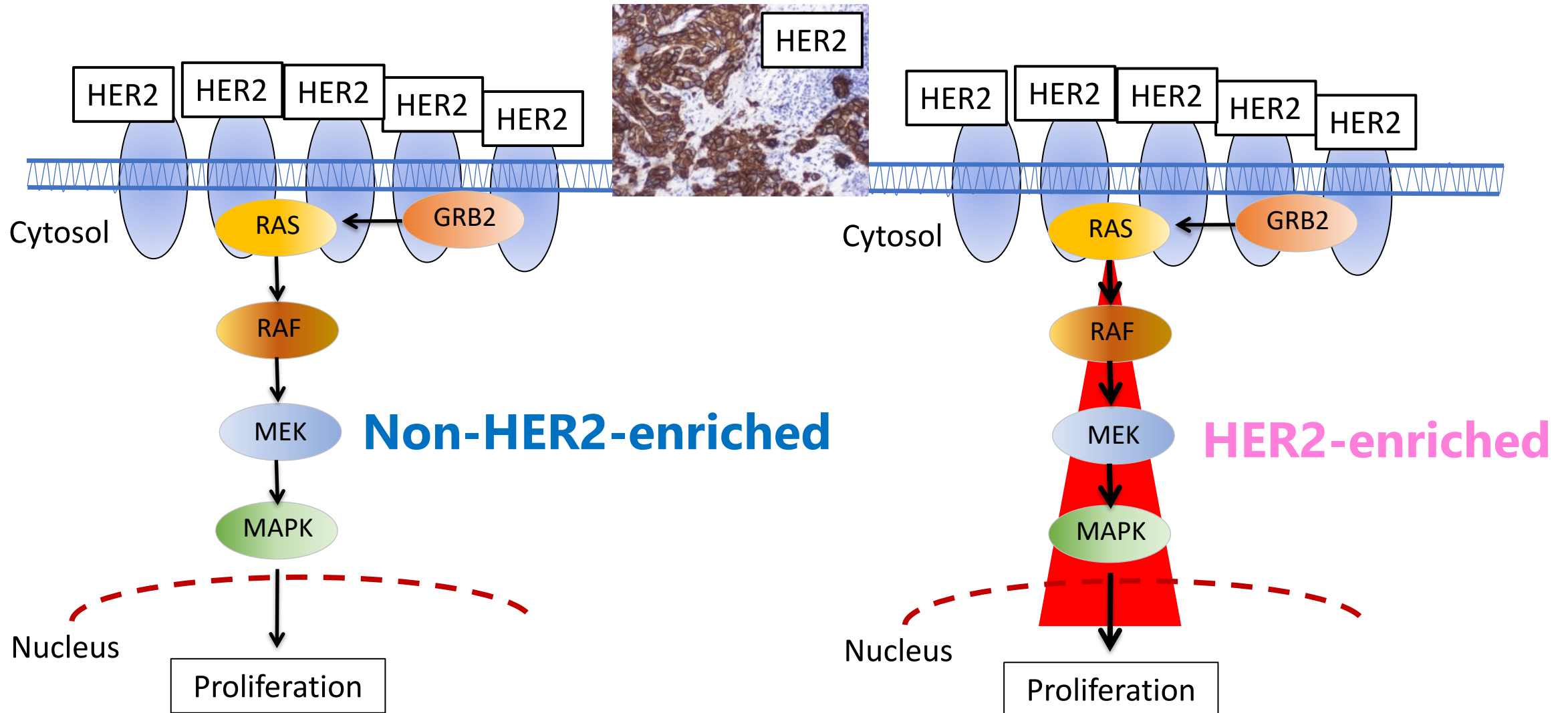
The intrinsic subtypes within HER2+ disease



HER2-E subtype represents 50-60% of all HER2+ tumors

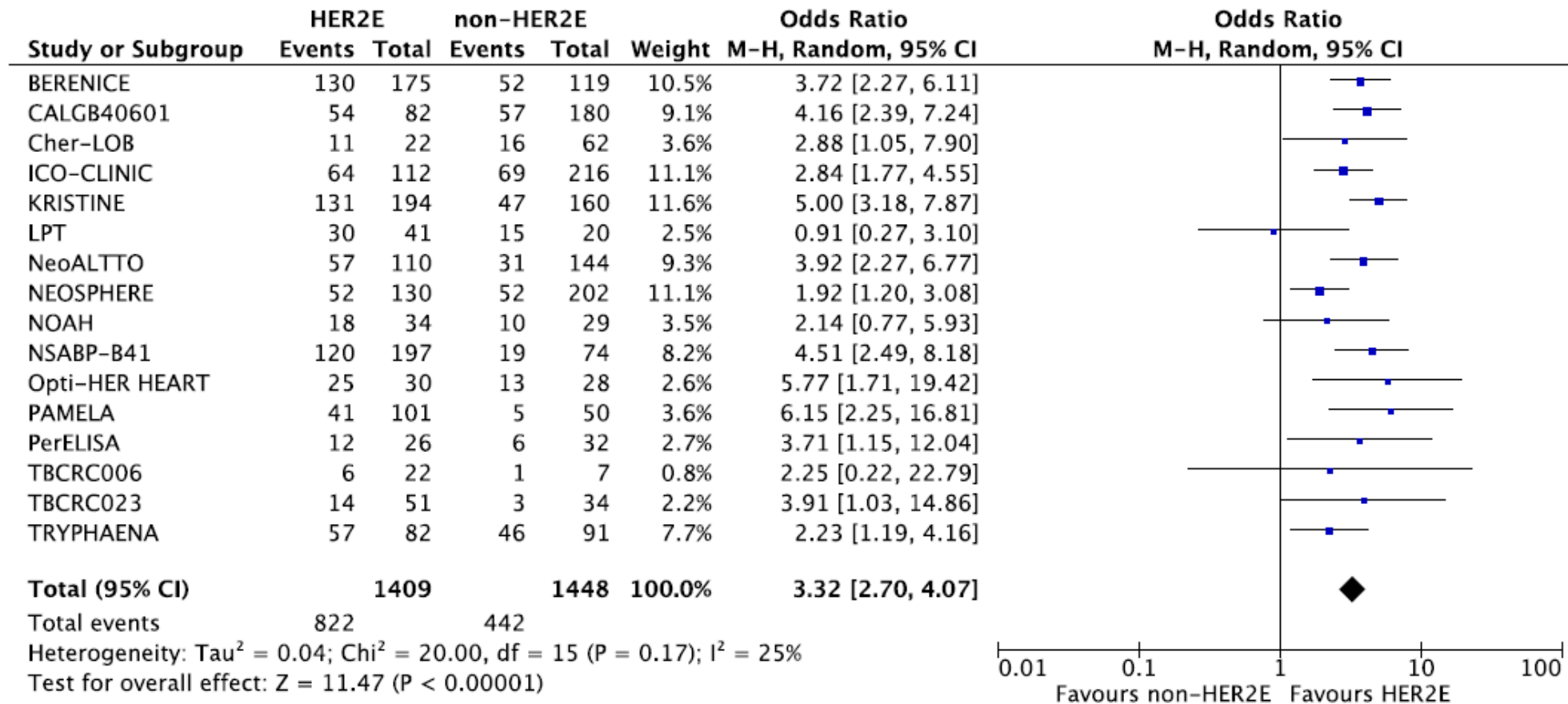
1. Cancer Genome Atlas Network Nature 2012; 490:61–70
2. Prat et al. J Natl Cancer Inst. 2014;106 (8)
3. Cejalvo et al. Cancer Treat Rev 2018
4. Cejalvo JM, et al. Ann Oncol. 2017 vol 28 suppl 5

HER2 signaling pathway in HER2+ breast cancer



HER2-E vs. pCR in HER2+ disease: a systematic review and meta-analysis

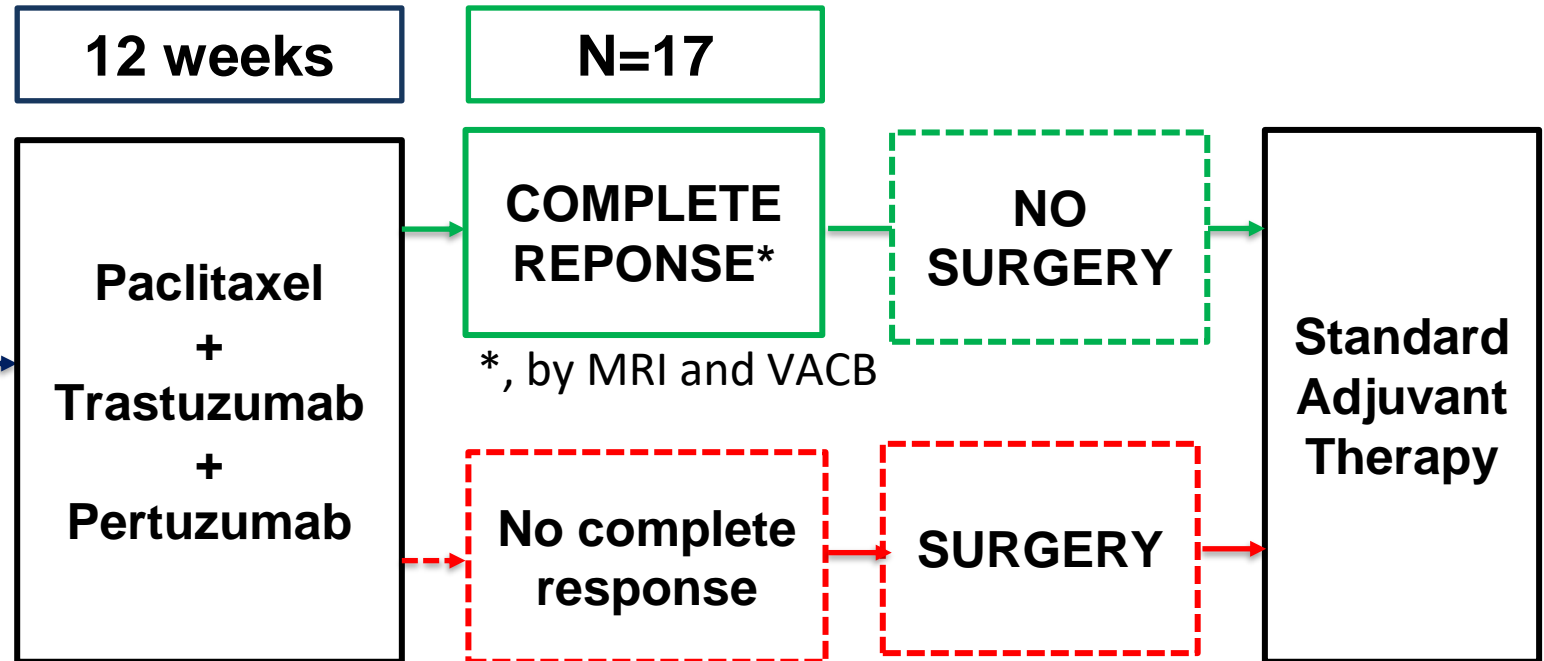
N=2,857 across 16 studies



Omission of surgery in stage I HER2+ and PAM50 HER2-E/ERBB2-high



HER2+
PAM50 HER2-E
ERBB2high
Unifocal lesion
cT1 (≤ 2 cm)
cN0



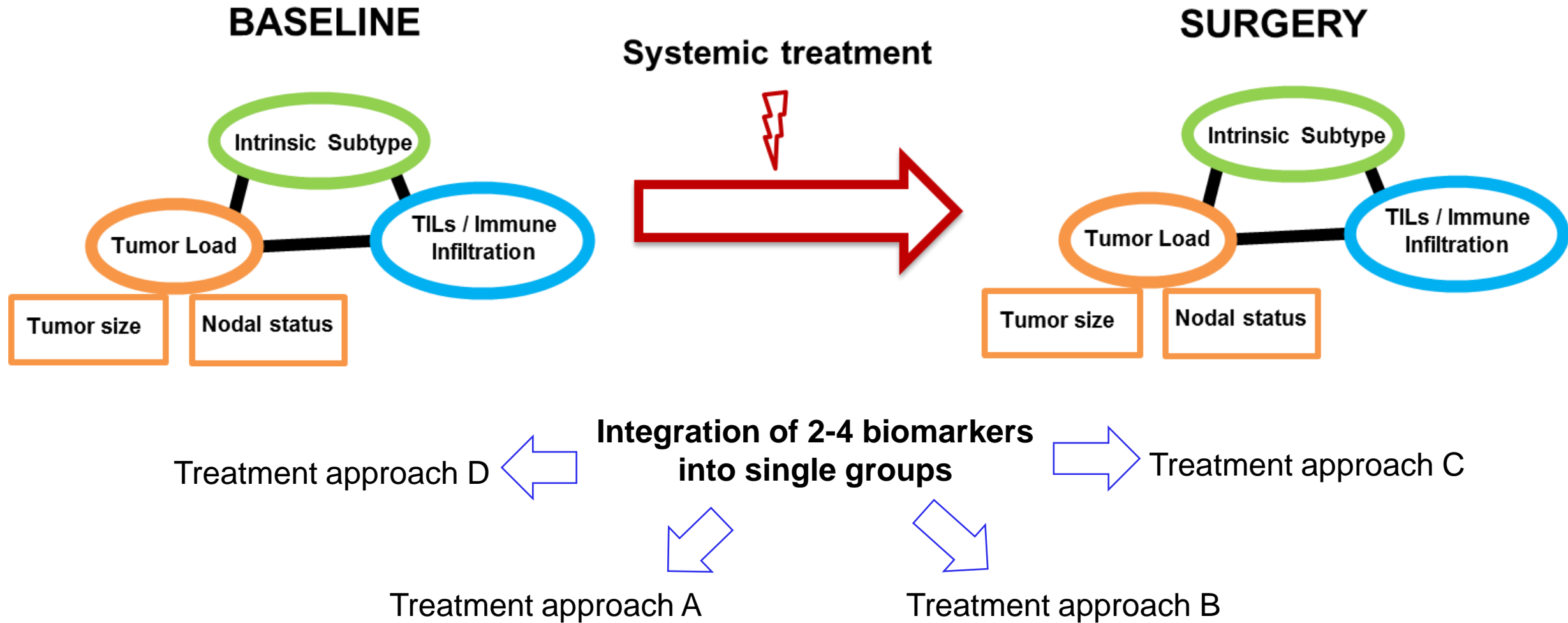
ClinicalTrials.gov Identifier: NCT04578106
PIs: Dr. Pascual and Dr. Prat

Primary endpoint



LR-iDFS at 3 years

Precision medicine in HER2+ disease

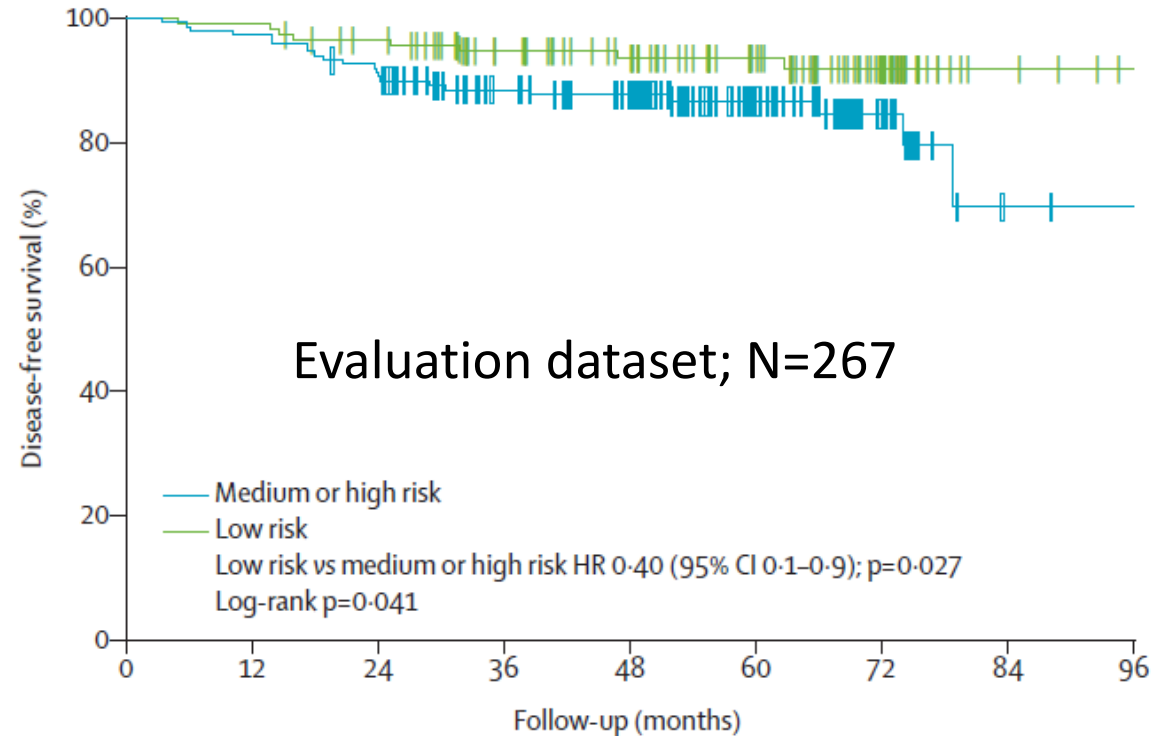
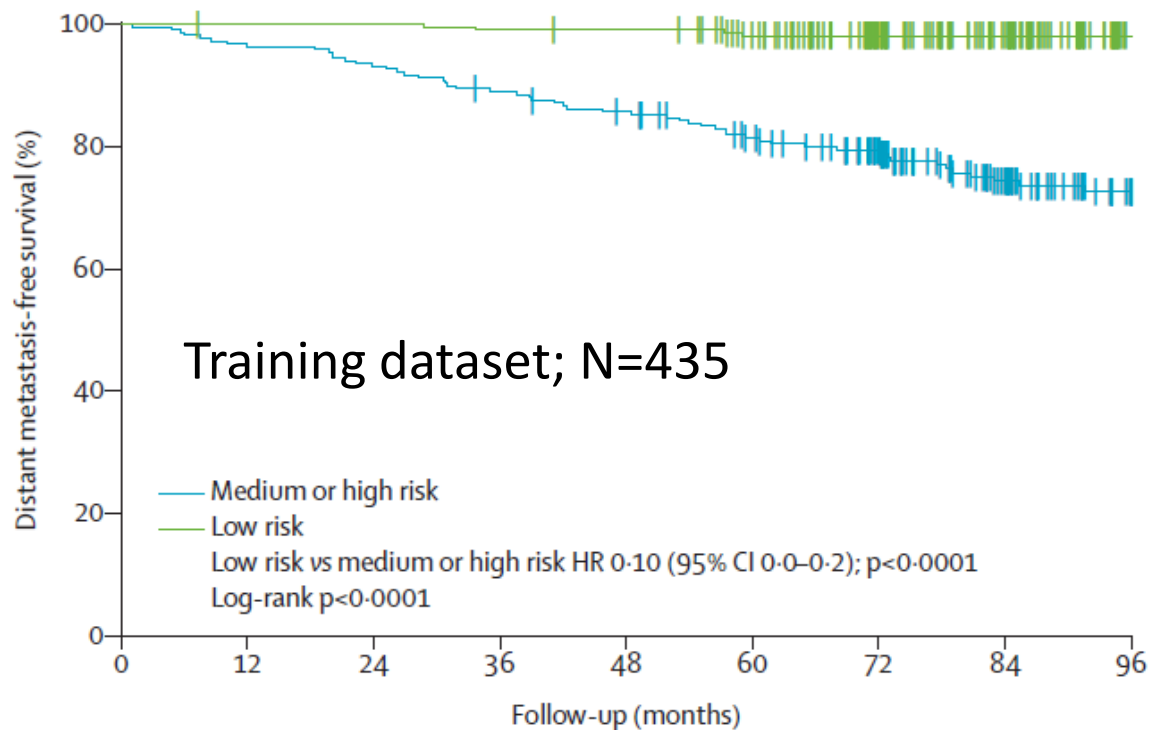


A multivariable prognostic score to guide systemic therapy in early-stage HER2+ breast cancer

THE LANCET Oncology

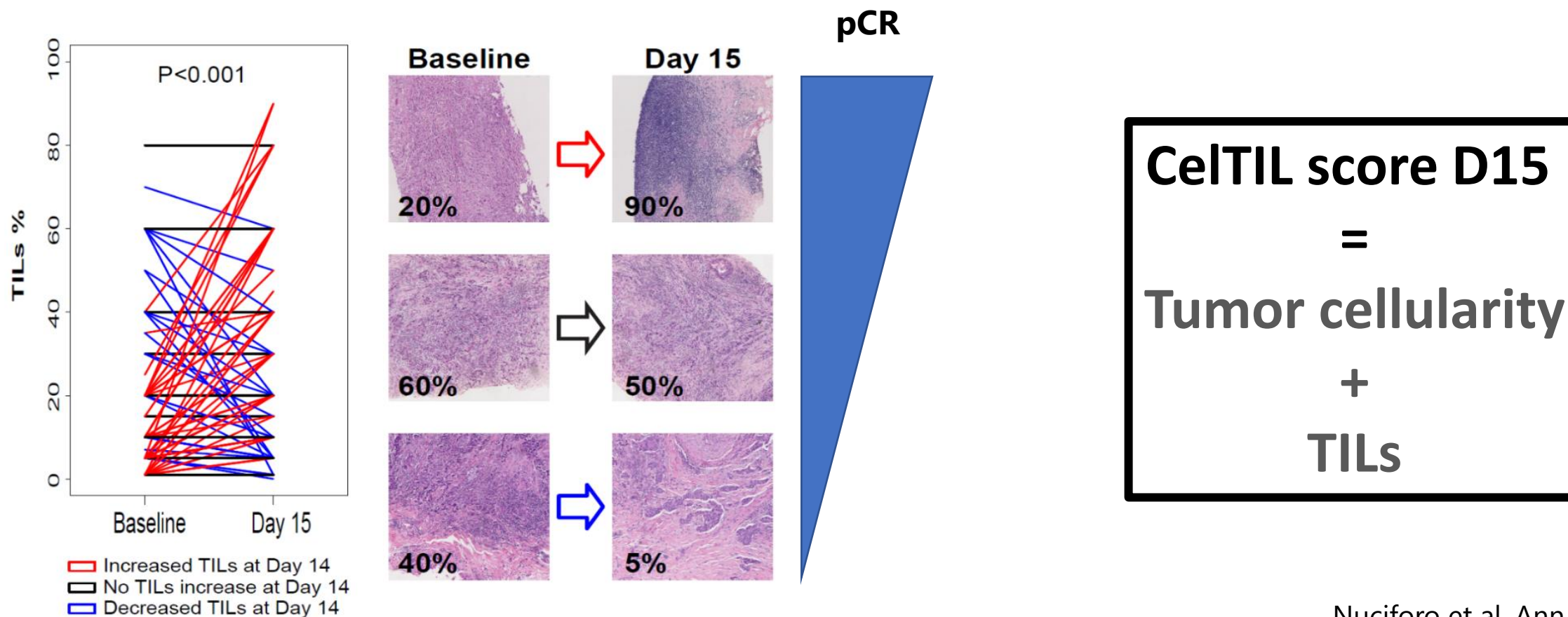
- **HER2DX** integrates clinical, genomic and TILs to predict prognosis
- **HER2DX** as a continuous variable was significantly associated with DMFS/DFS
- **HER2DX** was not associated with pCR

HER2DX
17 variables
into 1 score



Early changes in TILs and tumor cellularity in HER2+ BC

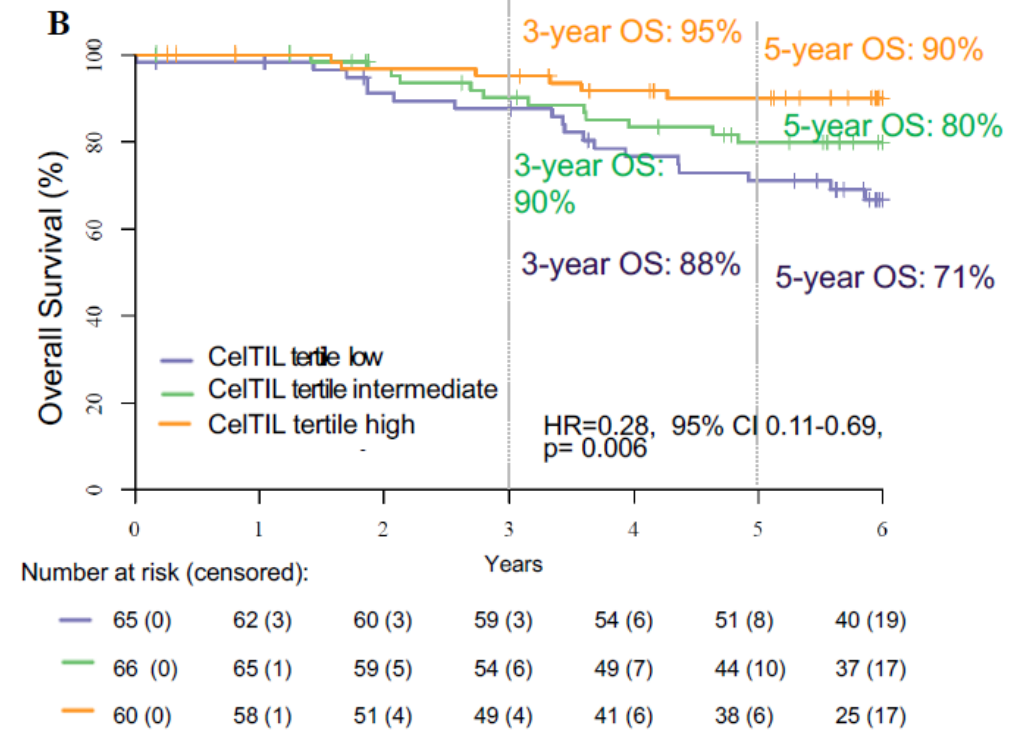
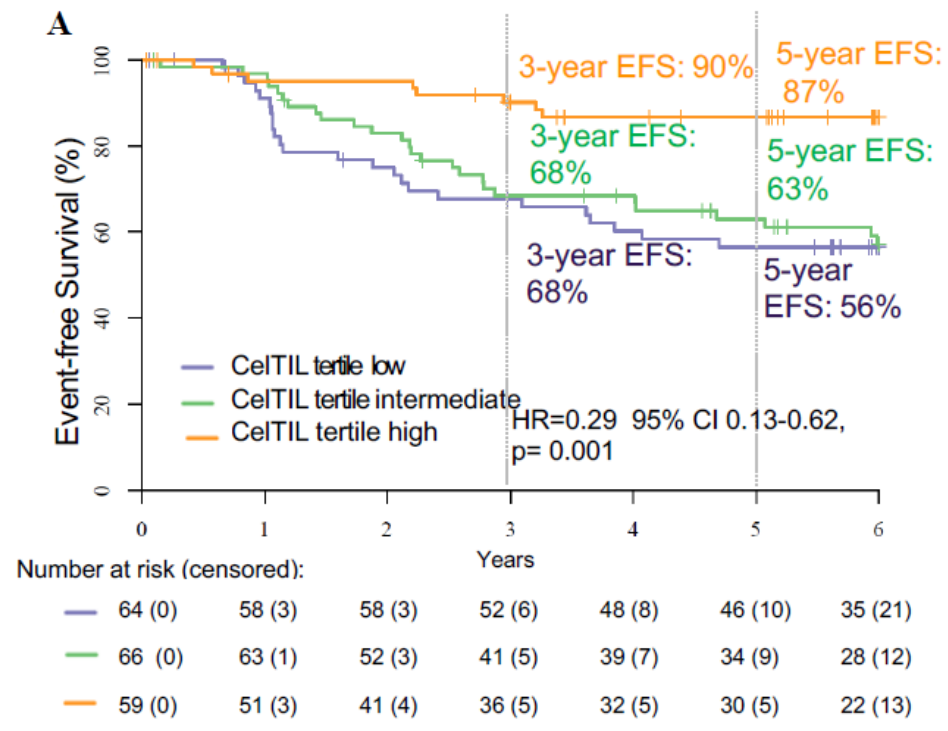
Retrospective Analysis from PAMELA trial (n=134/151)
Lapatinib + Trastuzumab (+ ET if HR+) for 18 weeks



CeTIL score and long-term survival outcome in the neoALTT0 trial (trastuzumab-based arms)

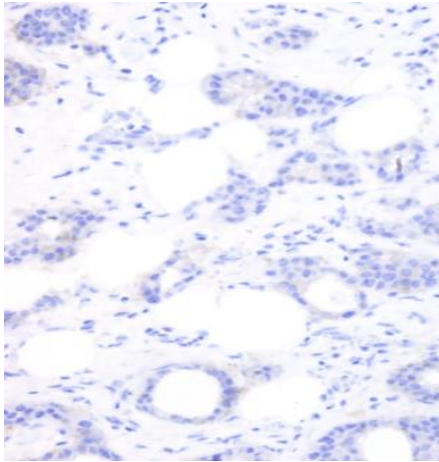
CeTIL at week 2
 2 variables → 1 score

- **CeTIL** as a continuous variable was significantly associated with pCR, EFS/OS
- **CeTIL** provides additional information beyond main clinical-pathological variables and pCR/RD
- **CeTIL** requires an on-treatment biopsy

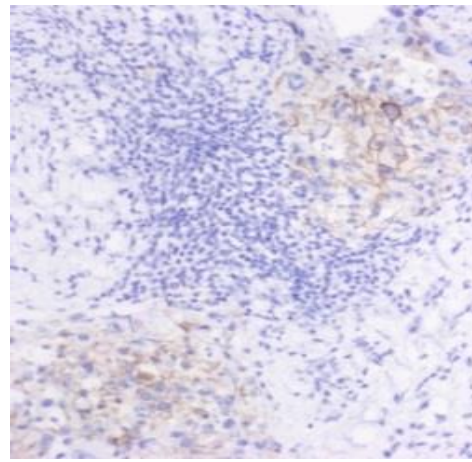


Continuous expression of HER2

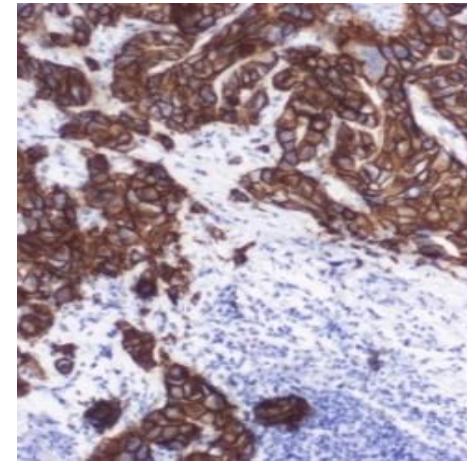
HER2 0



HER2-low



HER2+



HER2 protein
HER2 mRNA

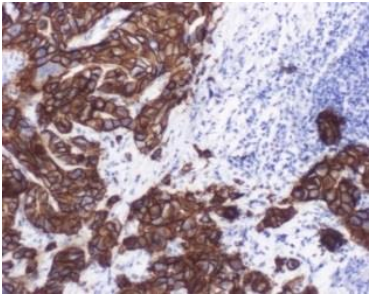
Images courtesy Aleix Prat, MD, PhD

IHC, immunohistochemistry.

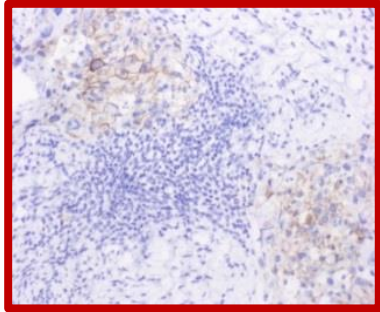
Continuous expression of HER2

HER2 IHC examples

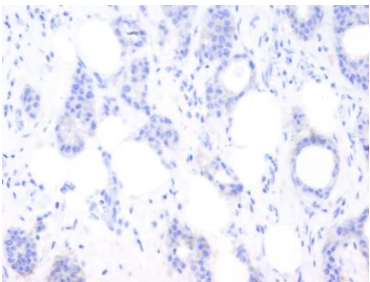
HER2+



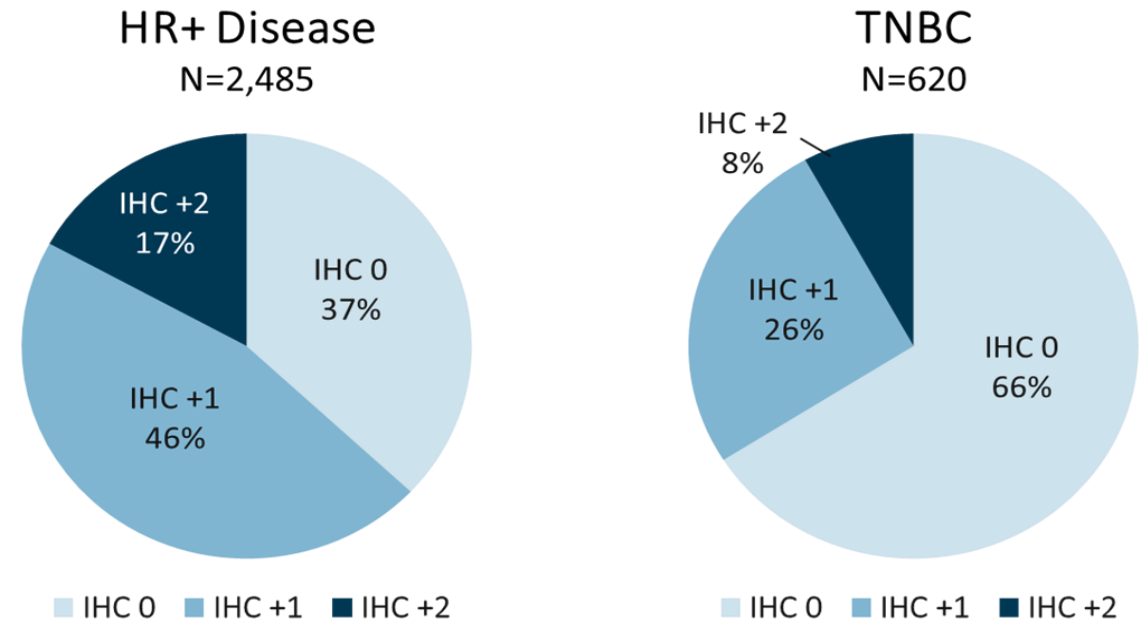
HER2-low



HER2-



HER2-negative

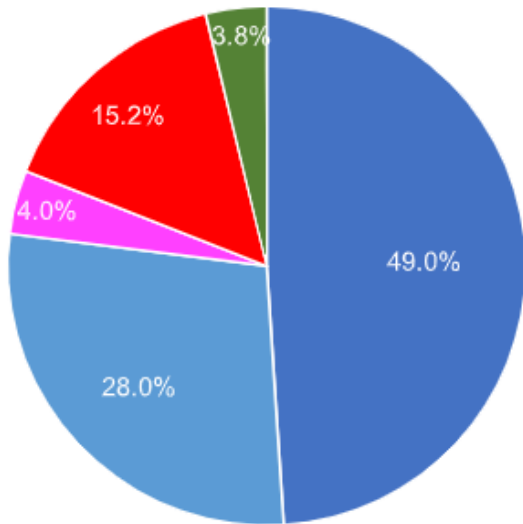


Schettini F et al. ESMO Breast 2020 (Poster #23P)

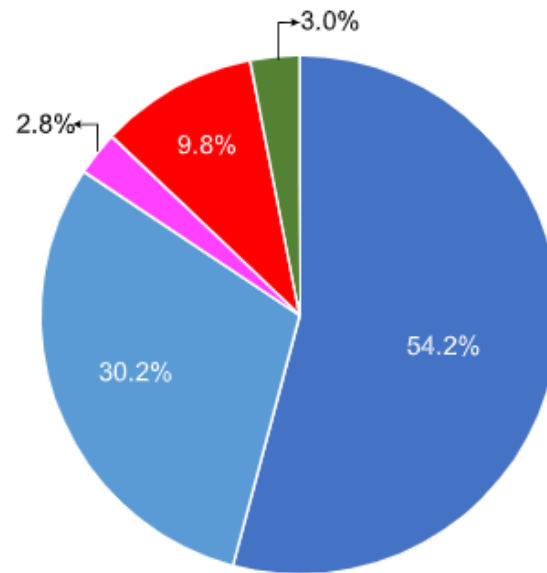
34-63% of HER2-negative breast cancer expresses HER2

The intrinsic subtypes in HER2-low and HER2+ breast cancer

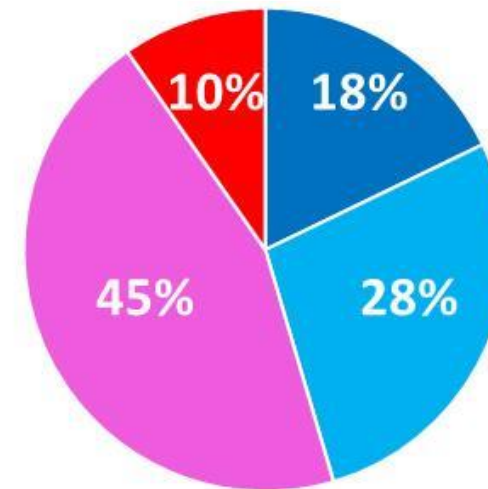
HER2 1+
(N=673)



HER2 2+/ISH-neg
(N=701)



HER2+
(N=1217)



Schettini et al. NPJ Breast 2021

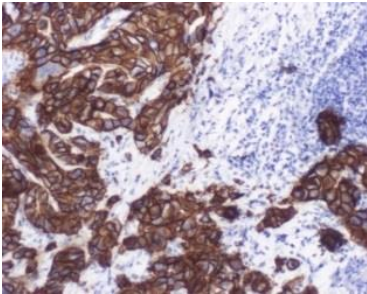
TCGA Nature 2012; Prat CCR 2014; Prat JNCI 2014;
Ferrari Nat Com 2015; Carey JCO 2016; Fumagalli JAMA Oncol 2016

■ Luminal A ■ Luminal B ■ HER2-enriched ■ Basal-like ■ Normal-like

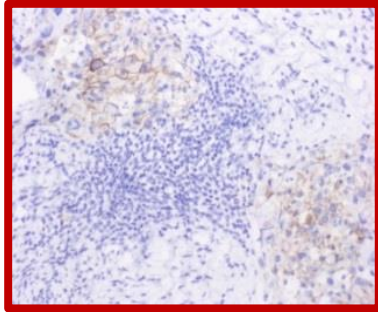
Continuous expression of HER2

HER2 IHC examples

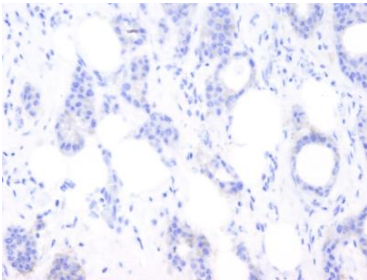
HER2+



HER2-low



HER2-



100 HER2 IHC cases vs. 4 pathologists

Kappa scores:

HER2 0: 0.82 (almost perfect agreement)

HER2 1+: 0.67 (substantial agreement)

HER2 2+: 0.736 (substantial agreement)

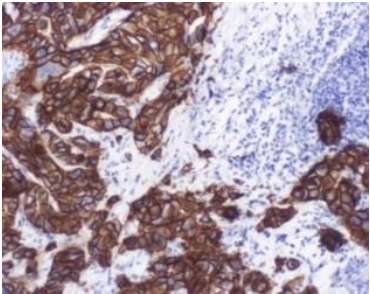
HER2 3+: 0.92 (almost perfect agreement)

High inter-pathologist discordance rate for HER2-low disease

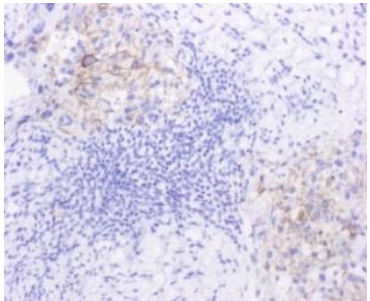
Continuous expression of HER2

HER2 IHC examples

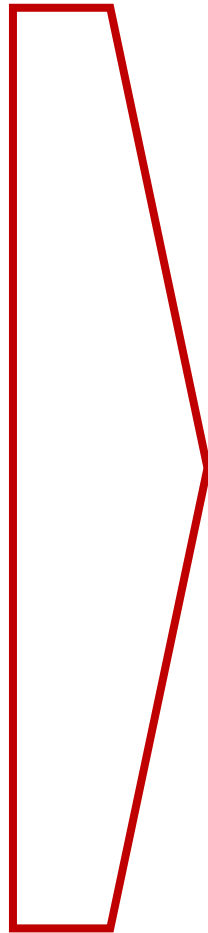
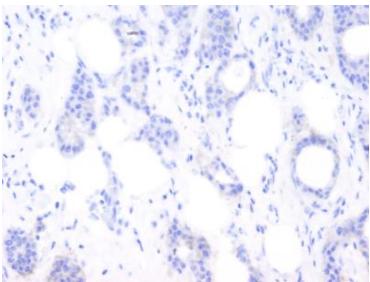
HER2+



HER2-low



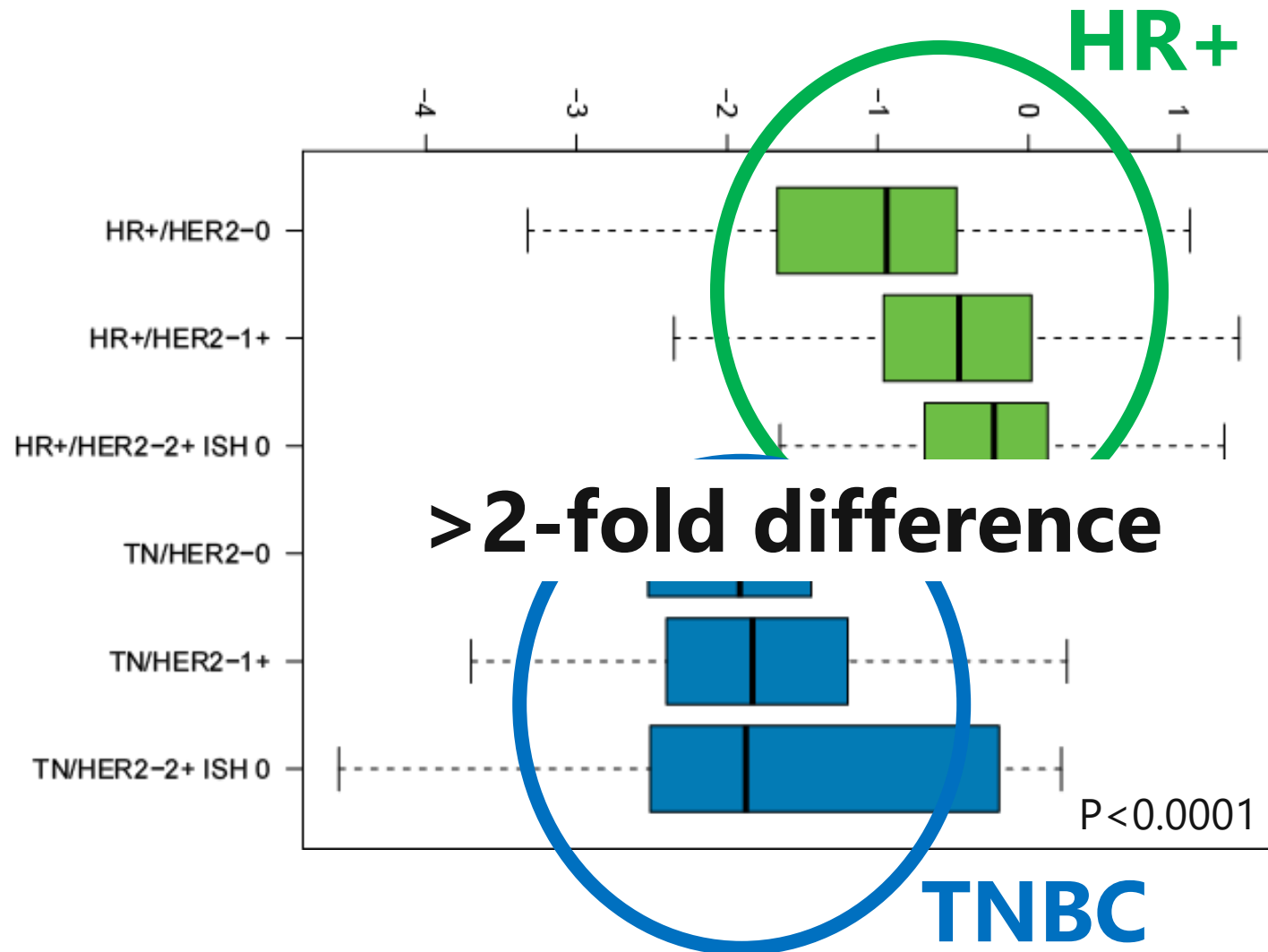
HER2-



HER2 protein
HER2 mRNA



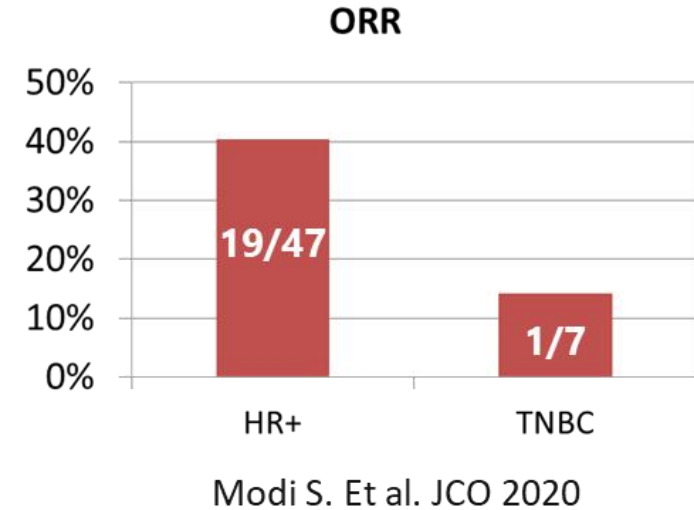
ERBB2 mRNA expression based on HR status



© original reports

Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low-Expressing Advanced Breast Cancer: Results From a Phase Ib Study

Shanu Modi, MD¹; Haeseong Park, MD, MPH²; Rashmi K. Murthy, MD, MBE³; Hiroji Iwata, PhD, MD⁴; Kenji Tamura, MD, PhD⁵; Junji Tsurutani, MD, PhD⁶; Alvaro Moreno-Aspitia, PhD⁷; Toshihiko Doi, MD, PhD⁸; Yasuaki Sagara, MD⁹; Charles Redfern, MD¹⁰; Ian E. Krop, MD, PhD¹¹; Caleb Lee, MD, PhD¹²; Yoshihiko Fujisaki, MS¹³; Masahiro Sugihara, PhD¹³; Lin Zhang, MD, PhD¹²; Javad Shahidi, MD¹²; and Shunji Takahashi, MD¹⁴



Schettini et al. NPJ Breast 2021

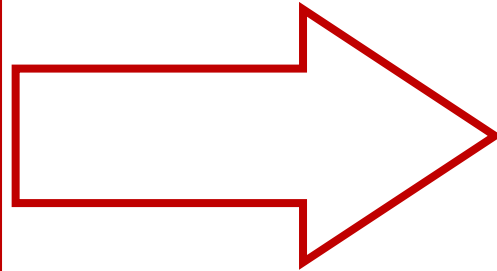
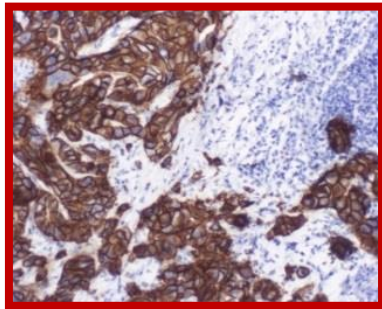
Continuous expression of HER2 in breast cancer



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HER2 IHC examples

HER2+



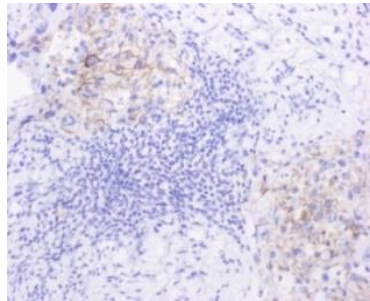
HER2-Enriched Subtype and ERBB2 Expression in HER2-Positive Breast Cancer Treated with Dual HER2 Blockade

Aleix Prat, Tomás Pascual, Carmine De Angelis, Carolina Gutierrez, Antonio Llombart-Cussac, Tao Wang, Javier Cortés, Brent Rexer, Laia Paré, Andres Forero, Antonio C. Wolff, Serafín Morales, Barbara Adamo, Fara Brasó-Maristany, Maria Vidal, Jamunarani Veeraraghavan, Ian Krop, Patricia Galván, Anne C. Pavlick, Begoña Bermejo, Miguel Izquierdo, Vanessa Rodrik-Outmezguine, Jorge S. Reis-Filho, Susan G. Hilsenbeck, Mafalda Oliveira, Maria Vittoria Dieci, Gaia Griguolo, Roberta Fasani, Paolo Nuciforo, Joel S. Parker, PierFranco Conte, Rachel Schiff, Valentina Guarneri, C. Kent Osborne, Mothaffar F. Rimawi

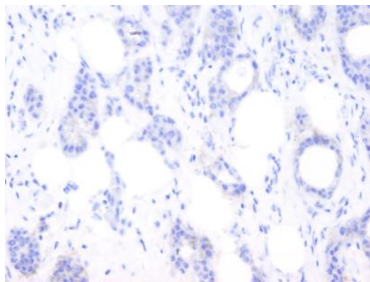
doi: [10.1093/jnci/djz042](https://doi.org/10.1093/jnci/djz042)

Published: 30 April 2019

HER2-low

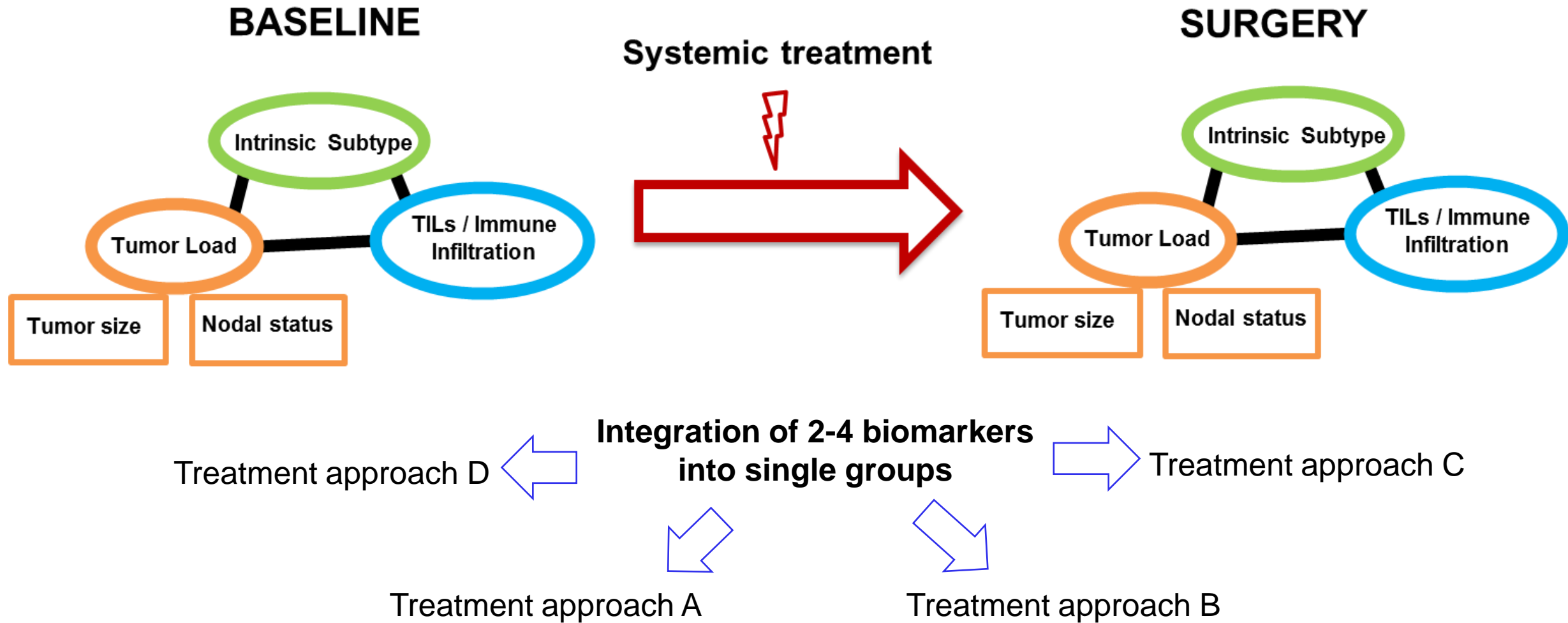


HER2-



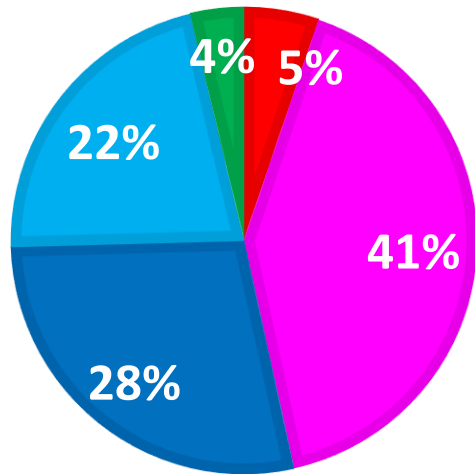
FISH, Fluorescence In Situ Hybridization; FFPE, formalin-fixed paraffin-embedded IHC, immunohistochemistry;

Precision medicine in HER2+ disease

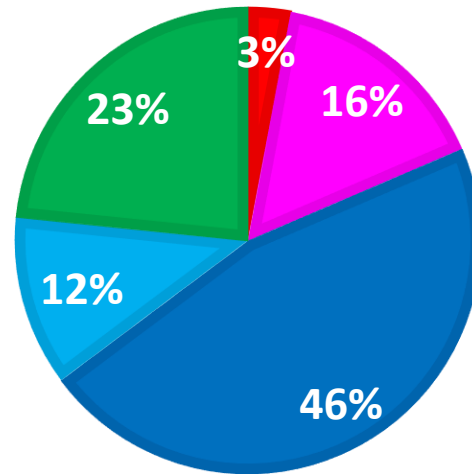


The composition of intrinsic tumor subtypes after neoadjuvant anti-HER2-based treatment

BASELINE (N=810)



SURGERY (N=372)



■ Basal ■ Her2 ■ Luminal A ■ Luminal B ■ Normal

Bianchini G, *et al.* ESMO 2018.
Gavilá J, *et al.* BMC Med 2018
Pernas S, *et al.* Front Oncol 2017
Carey L, *et al.* JCO 2017

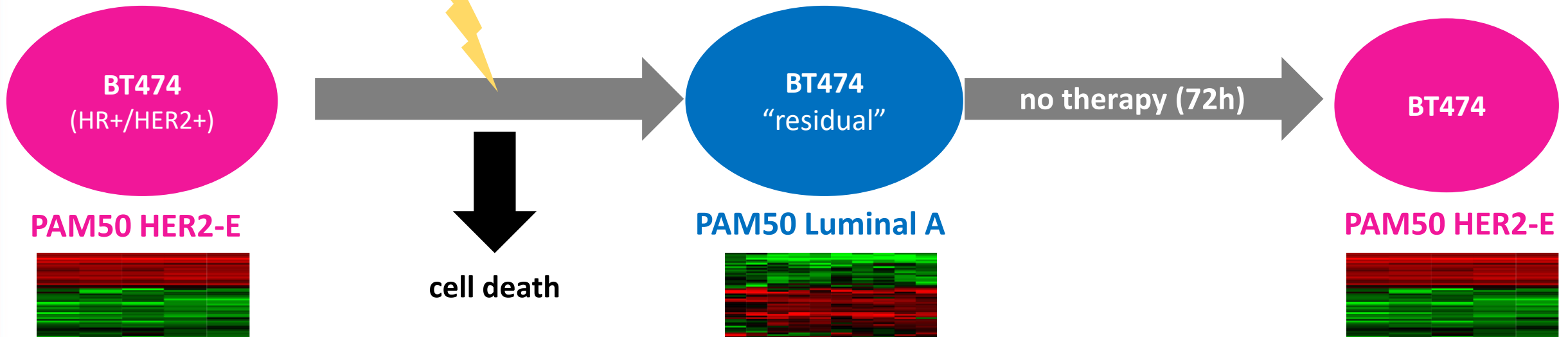
Residual tumors following anti-HER2-therapy are mostly Luminal A

Phenotypic changes of HER2-positive breast cancer during and after dual HER2 blockade

Fara Brasó-Maristany^{1,2}, Gaia Griguolo^{1,2,3,4}, Tomás Pascual^{1,2,5}, Laia Paré⁵, Paolo Nuciforo^{6,7}, Antonio Llombart-Cussac⁸, Begoña Bermejo⁹, Mafalda Oliveira^{6,7}, Serafín Morales¹⁰, Noelia Martínez¹¹, María Vidal^{1,2,5}, Barbara Adamo^{1,2}, Olga Martínez^{1,2}, Sonia Pernas^{5,12}, Rafael López¹³, Montserrat Muñoz^{1,2}, Núria Chic^{1,2}, Patricia Galván^{1,2}, Isabel Garau¹⁴, Luis Manso¹⁵, Jesús Alarcón¹⁶, Eduardo Martínez¹⁷, Sara Gregorio¹⁸, Roger R. Gomis¹⁸, Patricia Villagrasa⁵, Javier Cortés^{7,19}, Eva Ciruelos^{5,15} & Aleix Prat^{1,2,5*}

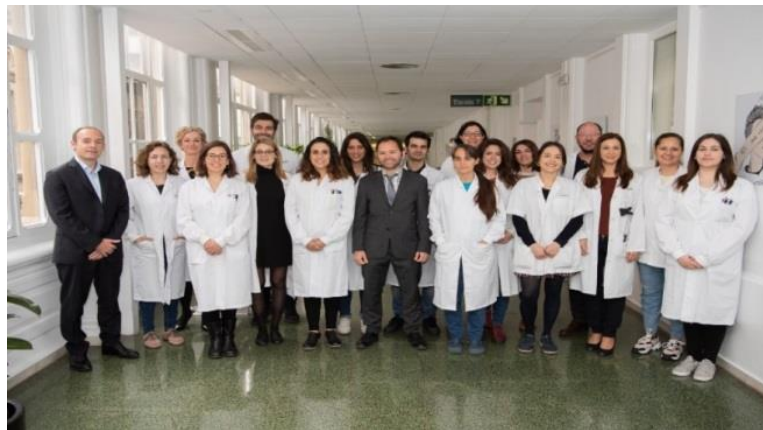
Subtype changes in HER2+ preclinical models

anti-HER2 therapy
(single or dual blockade)



Take-home messages

- HER2-E subtype within HER2+ disease is a biomarker of anti-HER2 sensitivity, chemosensitivity and endocrine-resistance.
- In terms of prognosis, HER2-E and Basal-like HER2+ tumors have a poor outcome.
- HER2DX might allow to better identify patients for de-escalation and escalation of systemic therapy.
- ERBB2 mRNA provides additional value beyond HER2 IHC and subtype.
- HER2-low disease is frequent but it is not reproducible and deserves attention.
- Subtype can change after neoadjuvant therapy. The clinical implications of this are unknown today.



Funders



H2020: Grant agreement No. 847912



Collaborators



SHAPING THE FUTURE OF CANCER RESEARCH



Dr. Perou
Dr. Carey



Dr. Perrone
Dr. Tonini



Dr. Ciruelos
Dr. Manso



Dr. Taberero
Dr. Saura
Dr. Oliveira
Dr. Balmaña



Dr. Turner
Dr. Johnston

Thank you