HER Family Transmembrane Proteins and Breast Cancer: An old story turns a new corner
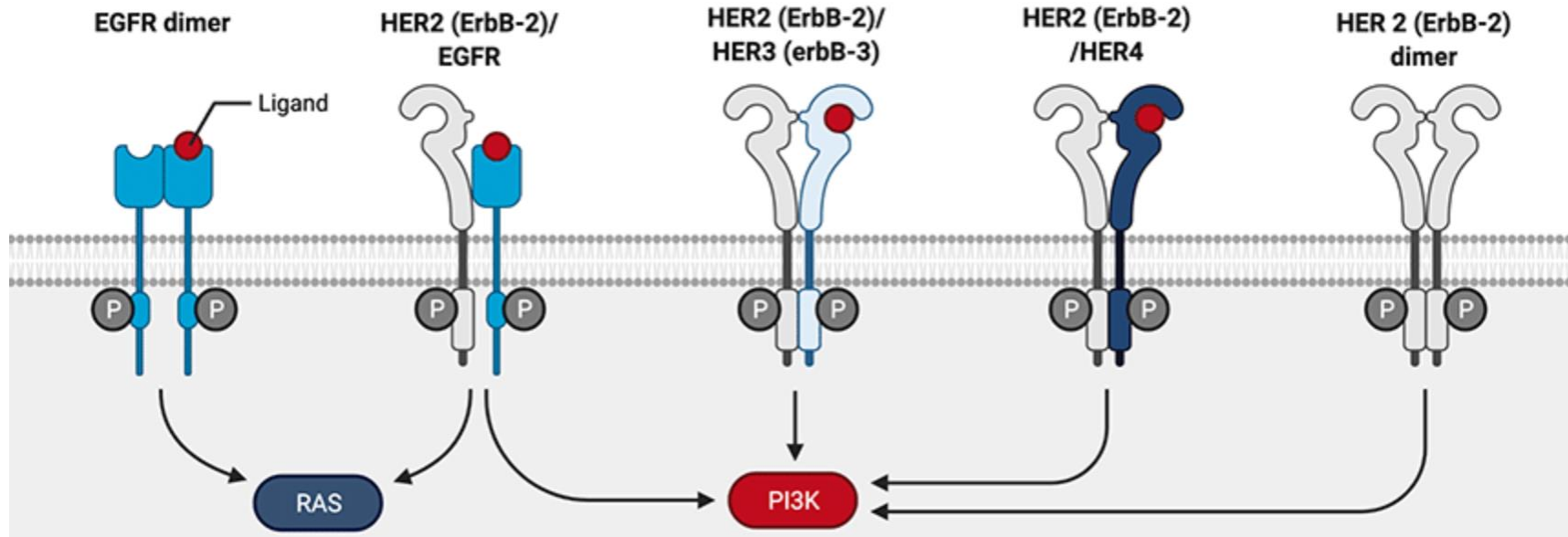
V.K. Gadi, MD PhD
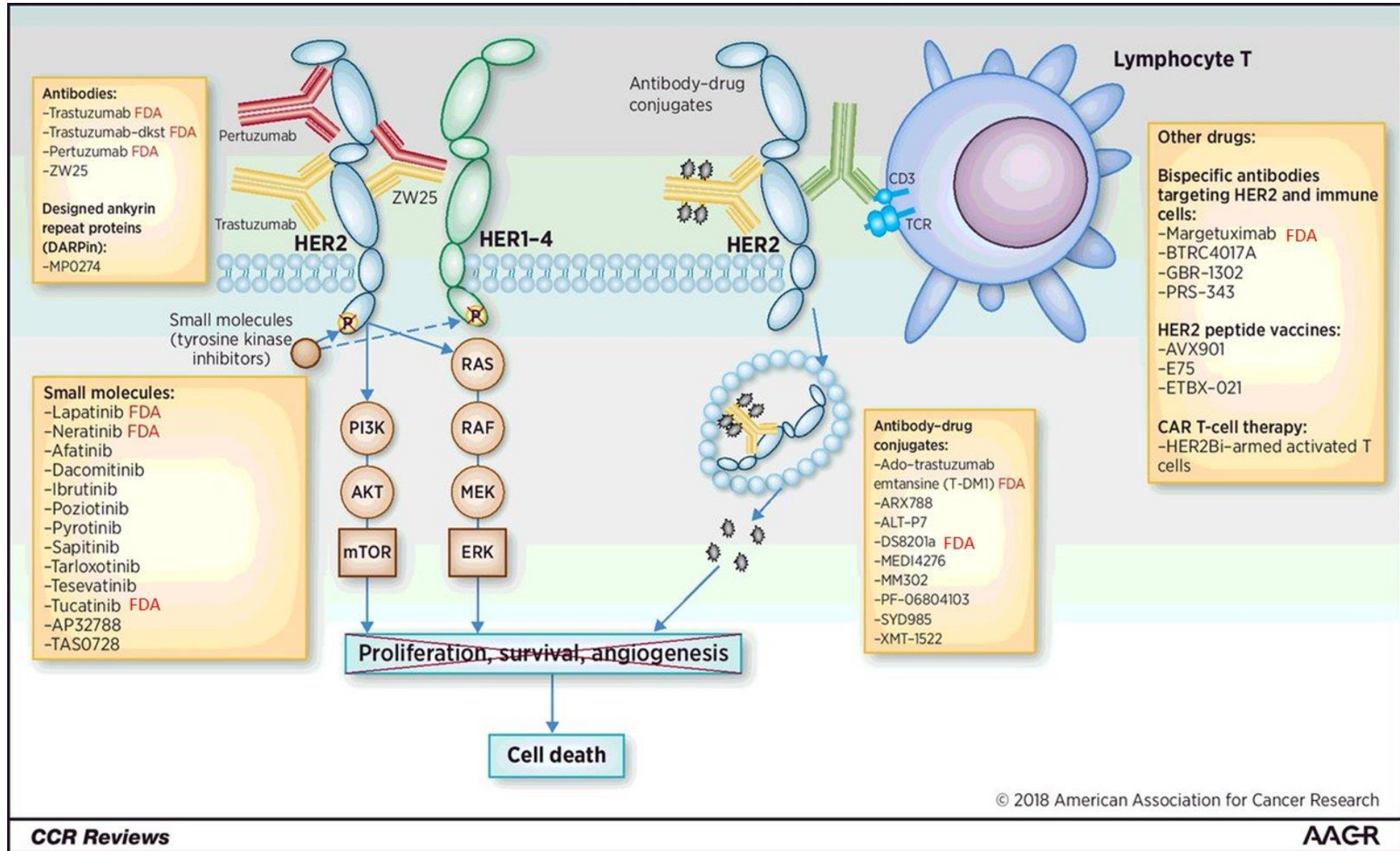
Deputy Director, U of Illinois Cancer Center

October 19, 2024
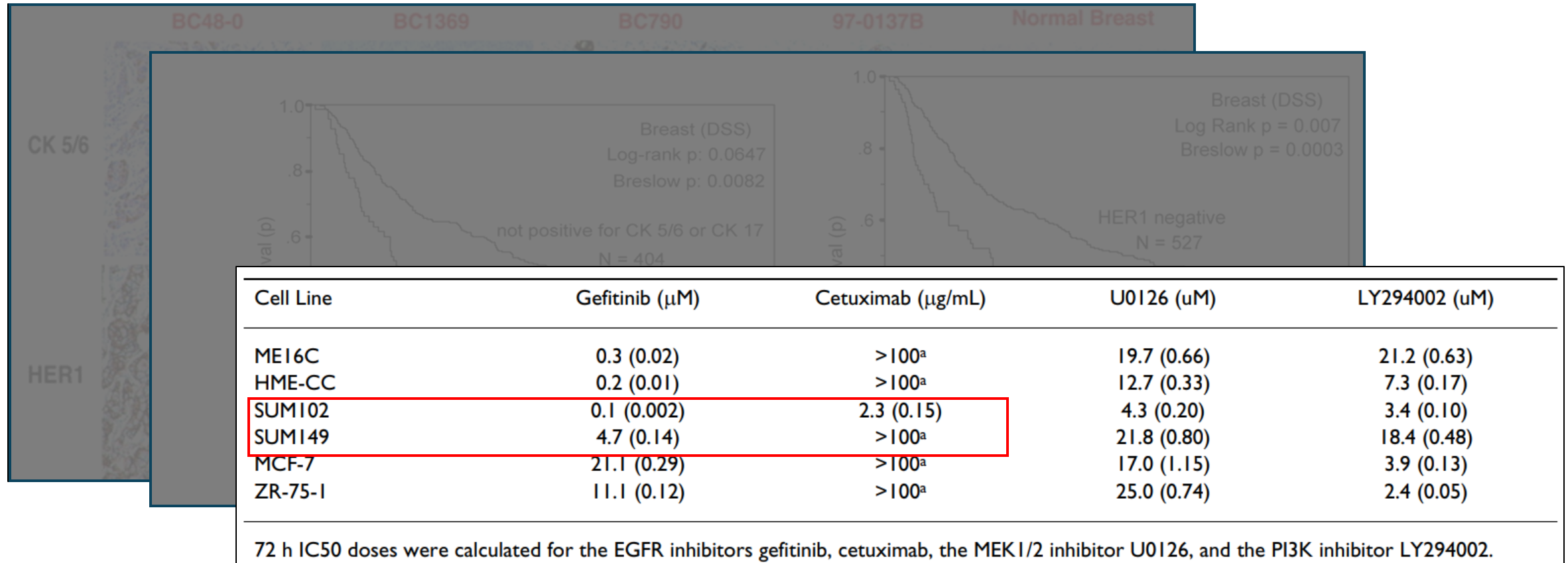
6th Annual
BREAST CANCER SYMPOSIUM
YESTERDAY, TODAY AND TOMORROW

OCTOBER 18- 20, 2024
HUDSON HALL
HUDSON, NY

PROGRAM DIRECTOR
Maria Theodoulou, MD
Breast Cancer Medicine
New York Oncology Hematology
Albany, NY

Modern *EGFR* Family

Antibodies:
–Trastuzumab FDA
–Trastuzumab-dkst FDA
–Pertuzumab FDA
–ZW25

Designed ankyrin repeat proteins (DARPin):
–MPO274

Small molecules:
–Lapatinib FDA
–Neratinib FDA
–Afatinib
–Dacomitinib
–Ibrutinib
–Poziotinib
–Pyrotinib
–Sapitinib
–Tarloxotinib
–Tesevatinib
–Tucatinib FDA
–AP32788
–TAS0728

Antibody–drug conjugates:
–Ado-trastuzumab emtansine (T-DM1) FDA
–ARX788
–ALT-P7
–DS8201a FDA
–MEDI4276
–MM302
–PF–06804103
–SYD985
–XMT–1522

Other drugs:

Bispecific antibodies targeting HER2 and immune cells:
–Margetuximab FDA
–BTRC4017A
–GBR–1302
–PRS–343

HER2 peptide vaccines:
–AVX901
–E75
–ETBX–021

CAR T-cell therapy:
–HER2Bi–armed activated T cells

Pertuzumab
Trastuzumab
ZW25
HER2
HER1–4
HER2
Lymphocyte T
CD3
TCR
Antibody-drug conjugates
Small molecules (tyrosine kinase inhibitors)

PI3K
AKT
mTOR

RAS
RAF
MEK
ERK

Proliferation, survival, angiogenesis

Cell death

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EGFR lessons

EGFR in TNBC

Cell Line	Gefitinib (μM)	Cetuximab (μg/mL)	U0126 (uM)	LY294002 (uM)
ME16C	0.3 (0.02)	>100[a]	19.7 (0.66)	21.2 (0.63)
HME-CC	0.2 (0.01)	>100[a]	12.7 (0.33)	7.3 (0.17)
SUM102	0.1 (0.002)	2.3 (0.15)	4.3 (0.20)	3.4 (0.10)
SUM149	4.7 (0.14)	>100[a]	21.8 (0.80)	18.4 (0.48)
MCF-7	21.1 (0.29)	>100[a]	17.0 (1.15)	3.9 (0.13)
ZR-75-1	11.1 (0.12)	>100[a]	25.0 (0.74)	2.4 (0.05)

72 h IC50 doses were calculated for the EGFR inhibitors gefitinib, cetuximab, the MEK1/2 inhibitor U0126, and the PI3K inhibitor LY294002.

Nielson, *Clin Cancer Res* 2004
Hoadley, *BMC Genomics* 2007

TBCRC 001: Randomized Phase II Study of Cetuximab in Combination With Carboplatin in Stage IV Triple-Negative Breast Cancer
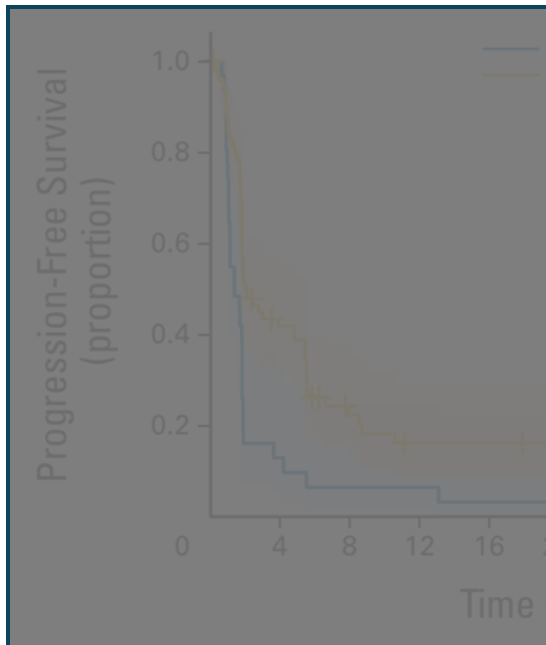
Response	Arm 1 (n = 31) C Only No.	%	Arm 1B (n = 25) C + Cb† No.	%	Arm 2 (n = 71) C + Cb No.	%	C + Cb* (n = 51) Basal-Like Tumors‡ No.	%
CR	0	0	0	0	1	1	1	2
PR	2	6	4	16	11	16	7	14
SD	3	10	7	28	15	21	8	16
> 6 months	1	3	3	12	10	14	7	14
PD	26	84	12	48	38	54	32	63
NE	0	0	2	8	6	8	3	6

Carey, *JCO* 2012

Non-canonical HER2 targeting

Hey VK, can I ask you about a patient?

- Dr. WG: I have a patient, pretty fit, with ER+ Her2- disease with metastatic disease first in the bones but now with liver involvement. She's been through endocrine therapy but blew threw it and now on cape but looking like she's progressing. I sent the liver for Oncoplex (NGS panel), and EK [lab med] says she's got a HER2 mutation – V777L. Do I try to give her a TKI like neratinib?

- Me: Yes, and with trastuzumab and fulvestrant…

- WG: Great. Can you help me get it?

- Me: Yes!

HER kinase inhibition in patients with HER2- and HER3-mutant cancers

Hyman, *Nature* 2019
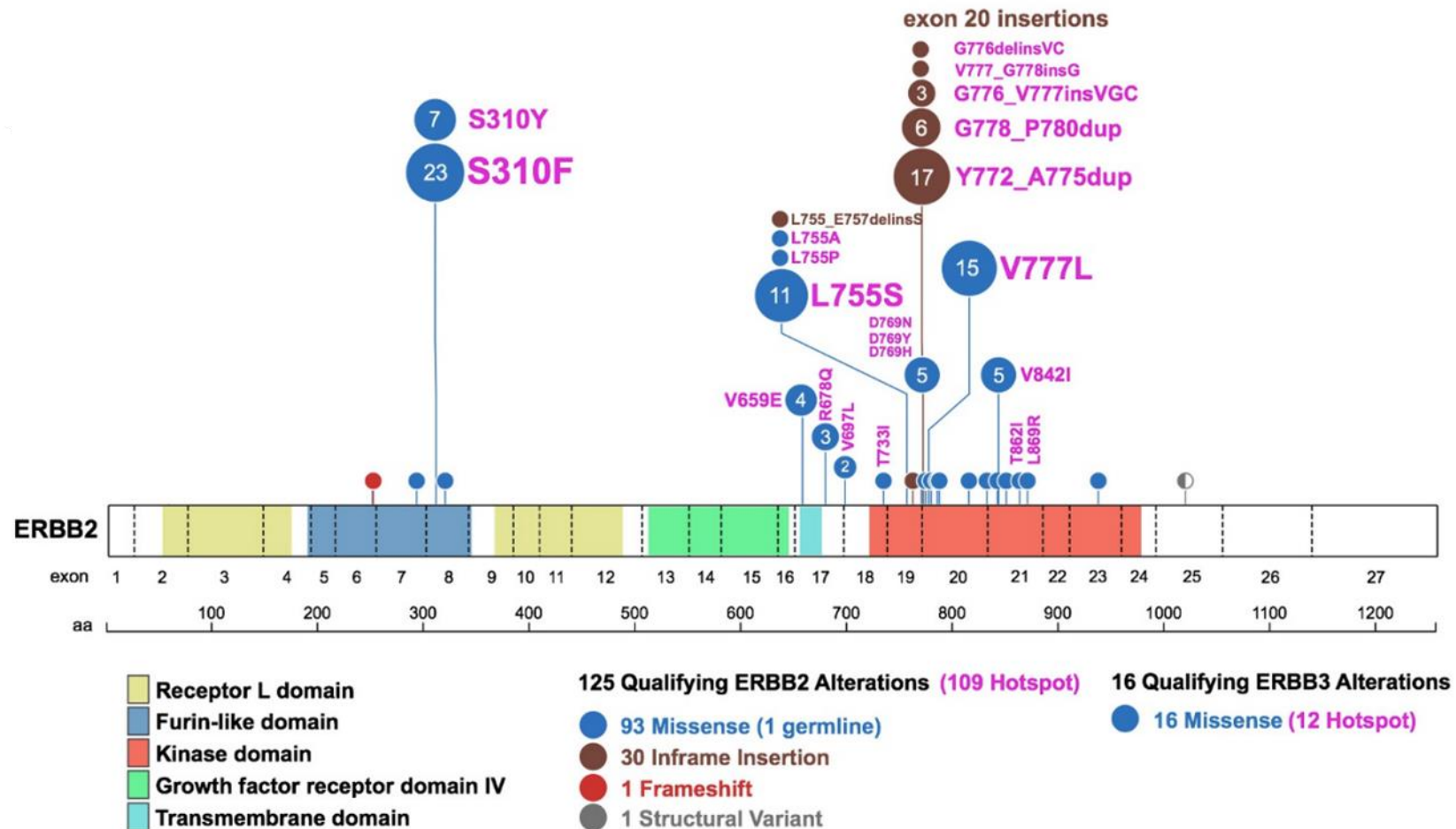
Patient characteristic	HER2 mutant (n=125)	HER3 mutant (n=16)	Total (n=141)
Age, years			
Median (range)	61 (30–83)	66 (39–82)	61 (30–83)
<65 years, n (%)	81 (64.8)	7 (43.8)	88 (62.4)
≥65 years, n (%)	44 (35.2)	9 (56.3)	53 (37.6)
Sex, n (%)			
Female	80 (64.0)	12 (75.0)	92 (65.2)
Male	45 (36.0)	4 (25.0)	49 (34.8)
ECOG performance status, n (%)			
0	37 (29.6)	1 (6.3)	38 (27.0)
1	83 (66.4)	12 (75.0)	95 (67.4)
2	5 (4.0)	3 (18.8)	8 (5.7)
Previous systemic treatment lines, n (%)			
Any	121 (96.8)	16 (100)	137 (97.2)
1	33 (26.4)	1 (6.3)	34 (24.1)
2	30 (24.0)	11 (68.8)	41 (29.1)
≥3	58 (46.4)	4 (25.0)	62 (44.0)
Median time from metastasis to enrolment, years (range)	1.02 (0.0–15.0)	1.13 (0.3–4.5)	1.03 (0.0–15.0)
Tumour type, n (%)			
Lung	26 (20.8)	0 (0)	26 (18.4)
Breast	25 (20.0)	0 (0)	25 (17.7)
Bladder	16 (12.8)	2 (12.5)	18 (12.8)
Colorectal	12 (9.6)	5 (31.3)	17 (12.1)
Biliary tract	9 (7.2)	2 (12.5)	11 (7.8)
Endometrial	7 (5.6)	1 (6.3)	8 (5.7)
Cervical	5 (4.0)	0 (0)	5 (3.5)
Gastroesophageal	5 (4.0)	2 (12.5)	7 (5.0)
Ovarian	4 (3.2)	1 (6.3)	5 (3.5)
Other	16 (12.8)	3 (18.8)	19 (13.5)
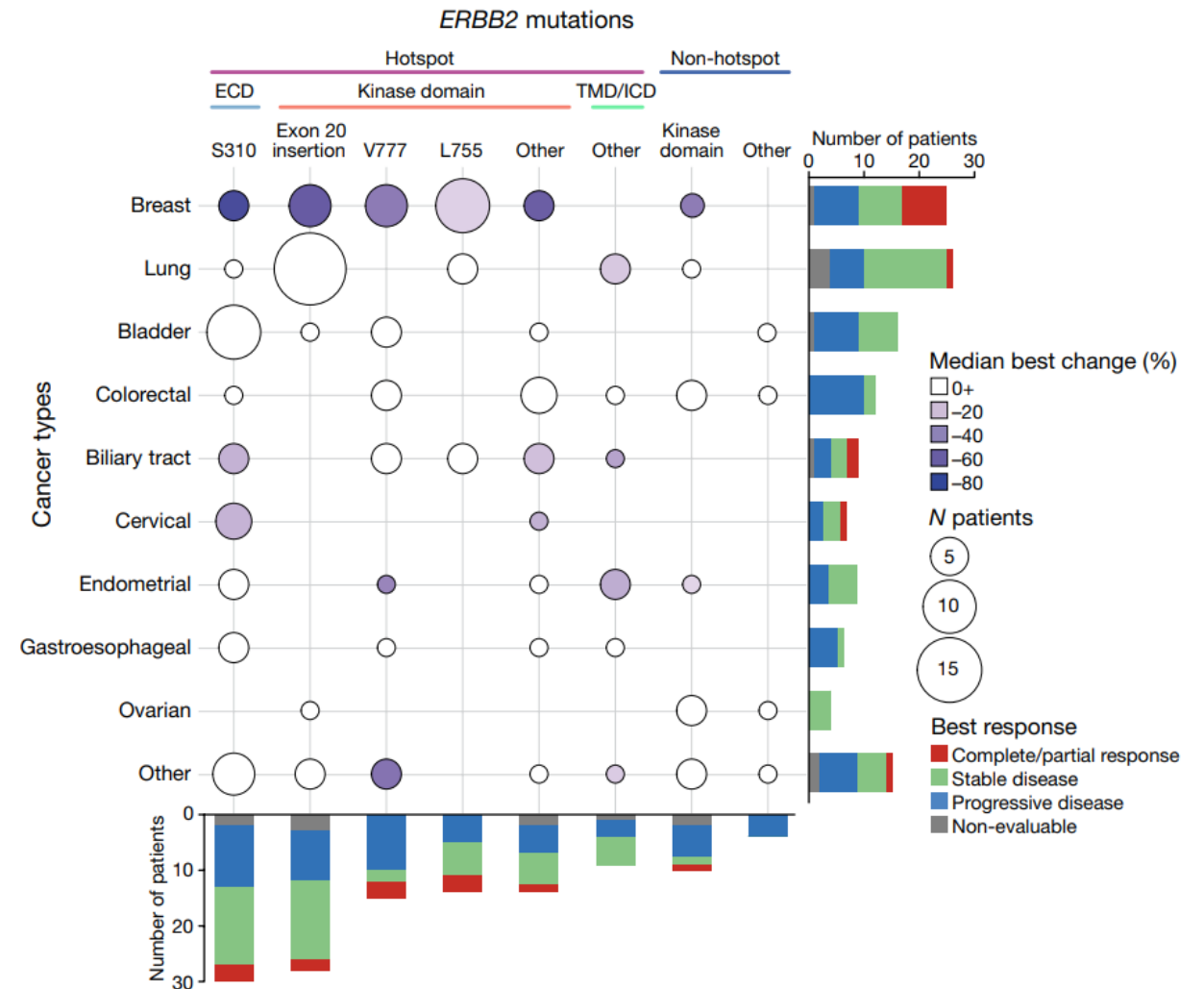
Efficacy and genomic analysis of *HER2*-mutant, metastatic triple-negative breast cancer treated with neratinib alone or in combination with trastuzumab in the phase 2 SUMMIT basket trial

Abstract #1094
Poster board #72

Komal Jhaveri,[1] Sara A. Hurvitz,[2] Adam Brufsky,[3] Ron Bose,[4] Maria de Miguel,[5] Ella Evron,[6] Nisha Unni,[7] Sonya Reid,[8] David Quinn,[9] Devalingam Mahalingam,[10] Cristina Saura,[11] José Angel García-Sáenz,[12] Alejandro Martinez-Bueno,[13] Angel Guerrero,[14] Christelle de la Fouchardière,[15] Hans Wildiers,[16] Georg Bischof,[17] Judith Bebchuk,[17] Lisa D. Eli,[17] David Solit[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [3]University of Pittsburgh, Pittsburgh, PA, USA; [4]Washington University School of Medicine, Saint Louis, MO, USA; [5]The Royal Marsden NHS Foundation Trust, Sutton, UK; [6]Kaplan Hospital, Rehovot, Israel; [7]UT Southwestern Medical Center, Dallas, TX, USA; [8]Vanderbilt University Medical Center, Nashville, TN, USA; [9]USC Keck School of Medicine, Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [10]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; [11]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [12]Instituto de Investigacion Sanitaria Hospital Clinico San Carlos (IdISSC), Madrid, Spain; [13]Pangaea Biotech, USP, Dexeus University Institute, Barcelona, Spain; [14]Instituto Valenciano de Oncologia, GEICAM Breast Cancer Group, Valencia, Spain; [15]Centre Léon Bérard, Lyon Cedex, France; [16]U. Z. Gasthuisberg, Leuven, Belgium; [17]Puma Biotechnology, Inc, Los Angeles, CA, USA

**Figure 1. SUMMIT study design: triple-negative *HER2*-mutant MBC cohorts**

Parameter	Neratinib (n=10)	Neratinib + Trastuzumab (n=17)
Objective response (confirmed PR or CR)[a], n (%)		
CR	1 (10.0)	2 (11.8)
PR	3 (30.0)	4 (23.5)
Objective response rate, % (95% CI)	40.0 (12.2–73.8)	35.3 (14.2–61.7)
Best overall response (confirmed or unconfirmed PR or CR), n (%)		
CR	1 (10.0)	2 (11.8)
PR	4 (40.0)	5 (29.4)
Best overall response rate (95% CI)	50.0 (18.7–81.3)	41.2 (18.4–67.1)
Median duration of response[b], months (95% CI)	3.78 (3.75–3.88)	6.14 (4.17–9.49)
Clinical benefit rate, %[c] (95% CI)	40.0 (12.2–73.8)	47.1 (23.0–72.2)
CR	1 (10.0)	2 (11.8)
PR	3 (30.0)	4 (23.5)
SD ≥24 weeks	0	2 (11.8)
Median PFS[b], months (95% CI)	2.89 (0.95–5.52)	6.24 (2.10–8.18)

Jhaveri, ASCO 2024

What about HER3?

Patritumab Deruxtecan (HER3-DXd), a Human Epidermal Growth Factor Receptor 3−Directed Antibody-Drug Conjugate, in Patients With Previously Treated Human Epidermal Growth Factor Receptor 3−Expressing Metastatic Breast Cancer: A Multicenter, Phase I/II Trial

Krop, *JCO* 2023
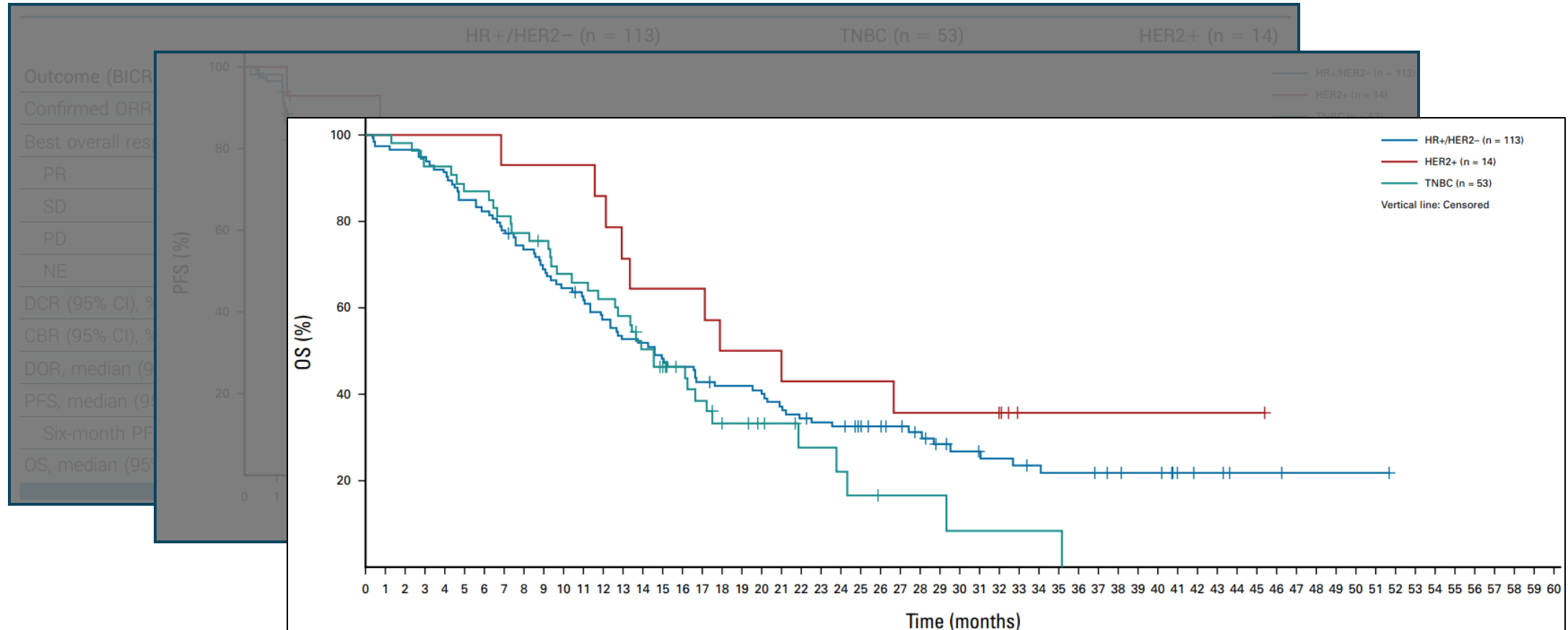
Targetable *ERBB2* mutation status is an independent marker of adverse prognosis in estrogen receptor positive, *ERBB2* non-amplified primary lobular breast carcinoma: a retrospective in silico analysis of public datasets
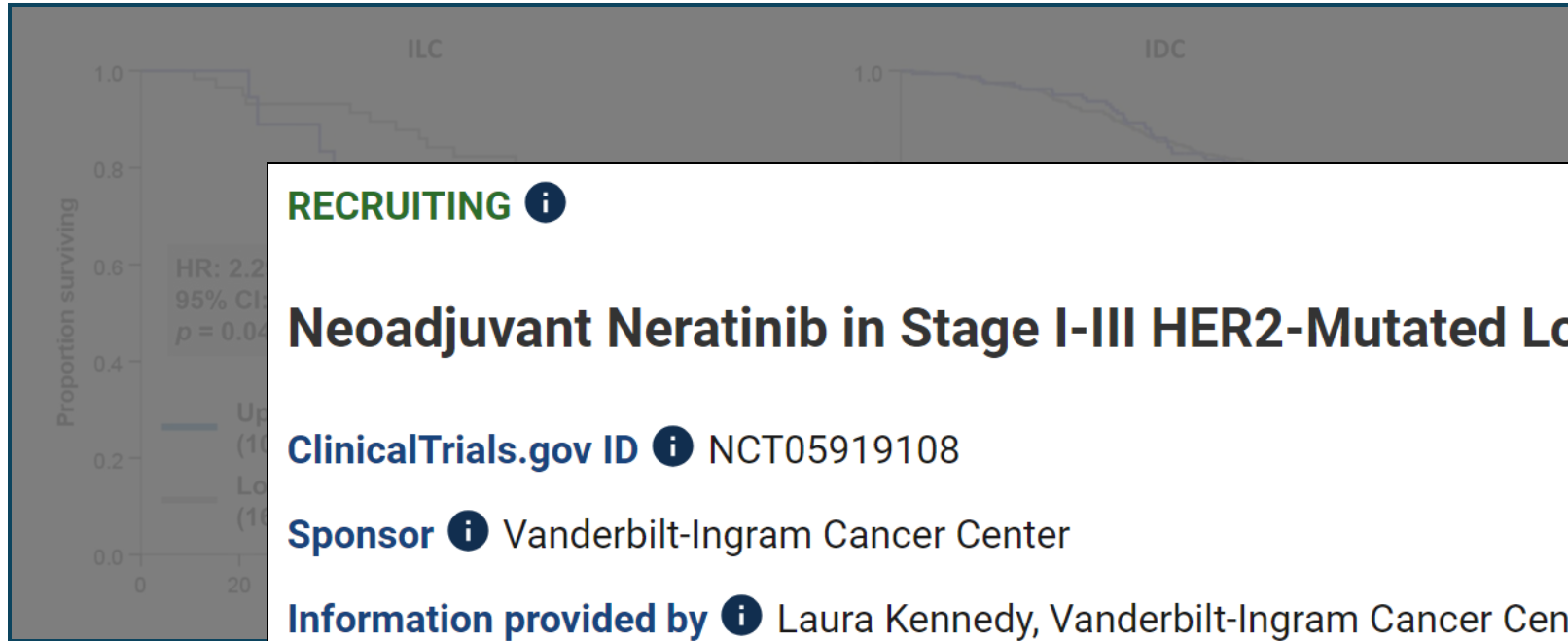
RECRUITING ⓘ

Neoadjuvant Neratinib in Stage I-III HER2-Mutated Lobular Breast Cancers

**ClinicalTrials.gov ID** ⓘ NCT05919108

Sponsor ⓘ Vanderbilt-Ingram Cancer Center

Information provided by ⓘ Laura Kennedy, Vanderbilt-Ingram Cancer Center (Responsible Party)

Last Update Posted ⓘ 2024-06-13

Kurozumi, *Breast Cancer Research* 2020
Kennedy and Arteaga, clinicaltrials.gov

ERBB3 Overexpression is Enriched in Diverse Patient Populations with Castration-sensitive Prostate Cancer and is Associated with a Unique AR Activity Signature

Vellky J, *Clin Cancer Res* 2024
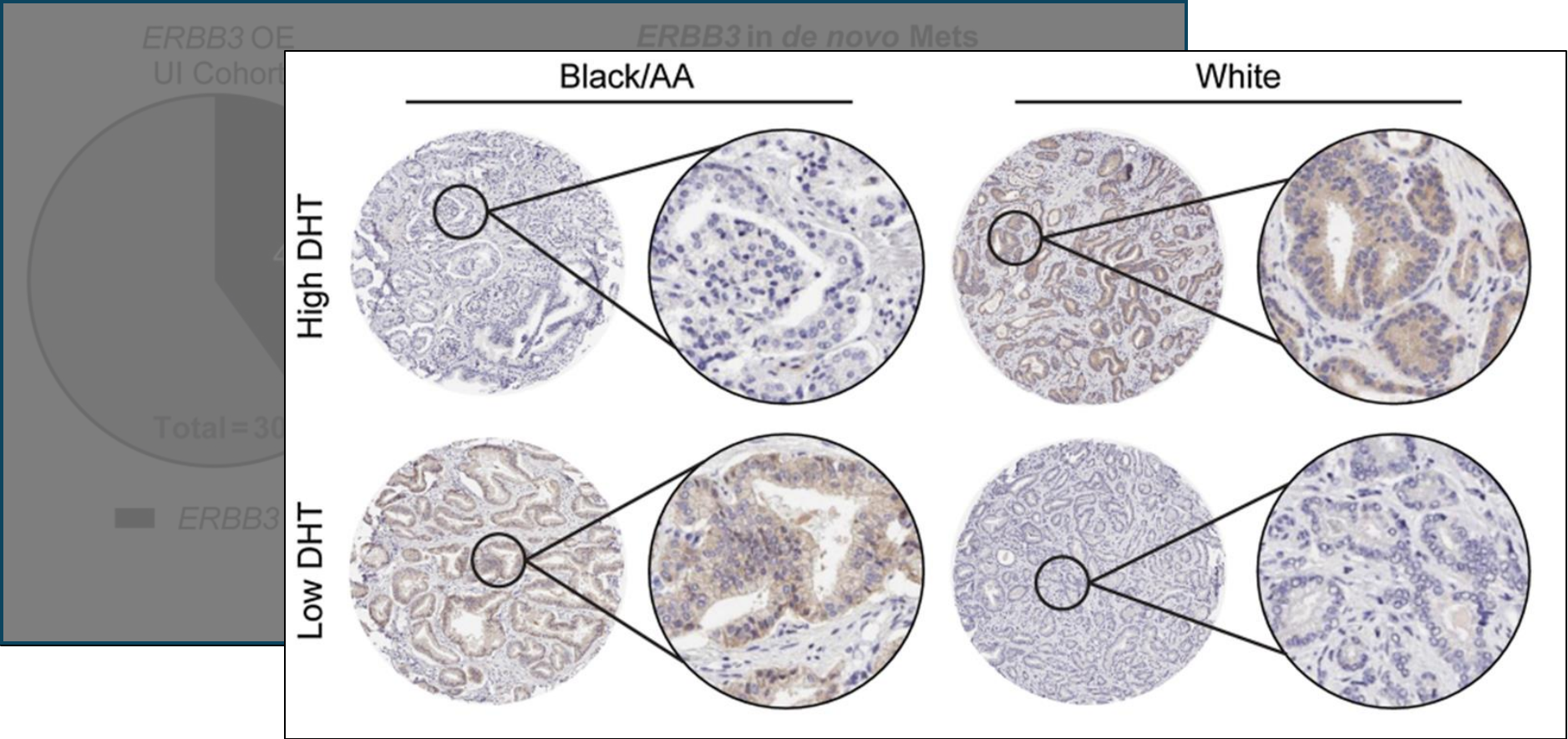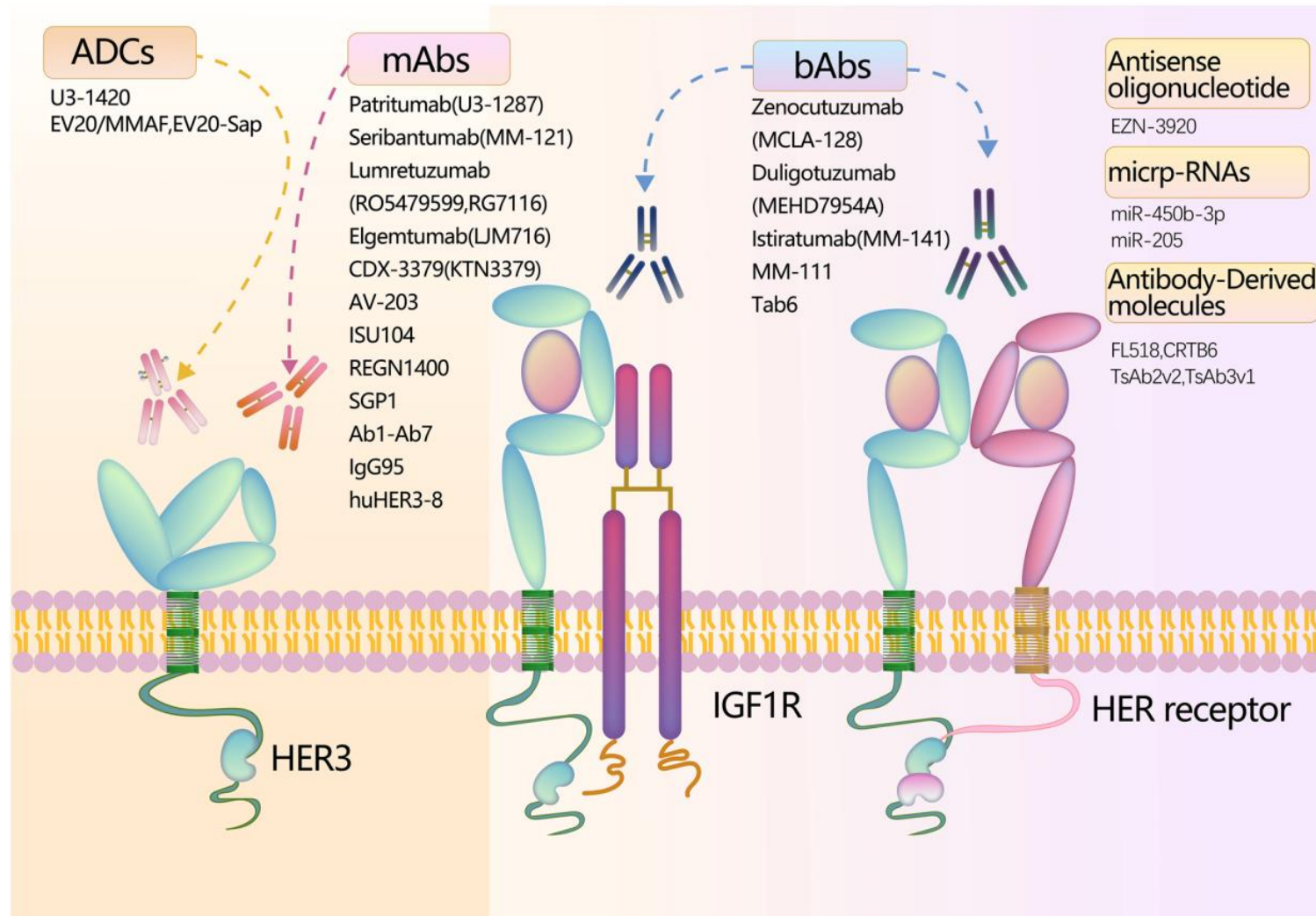
HER: The other siblings and cousins

HER2 is the paradigm

- Should we revisit EGFR with available better tools?

- HER2 as a lead footed driver

- HER3
    - Not just a target for ADC
    - Some real biology worth exploring