Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC)

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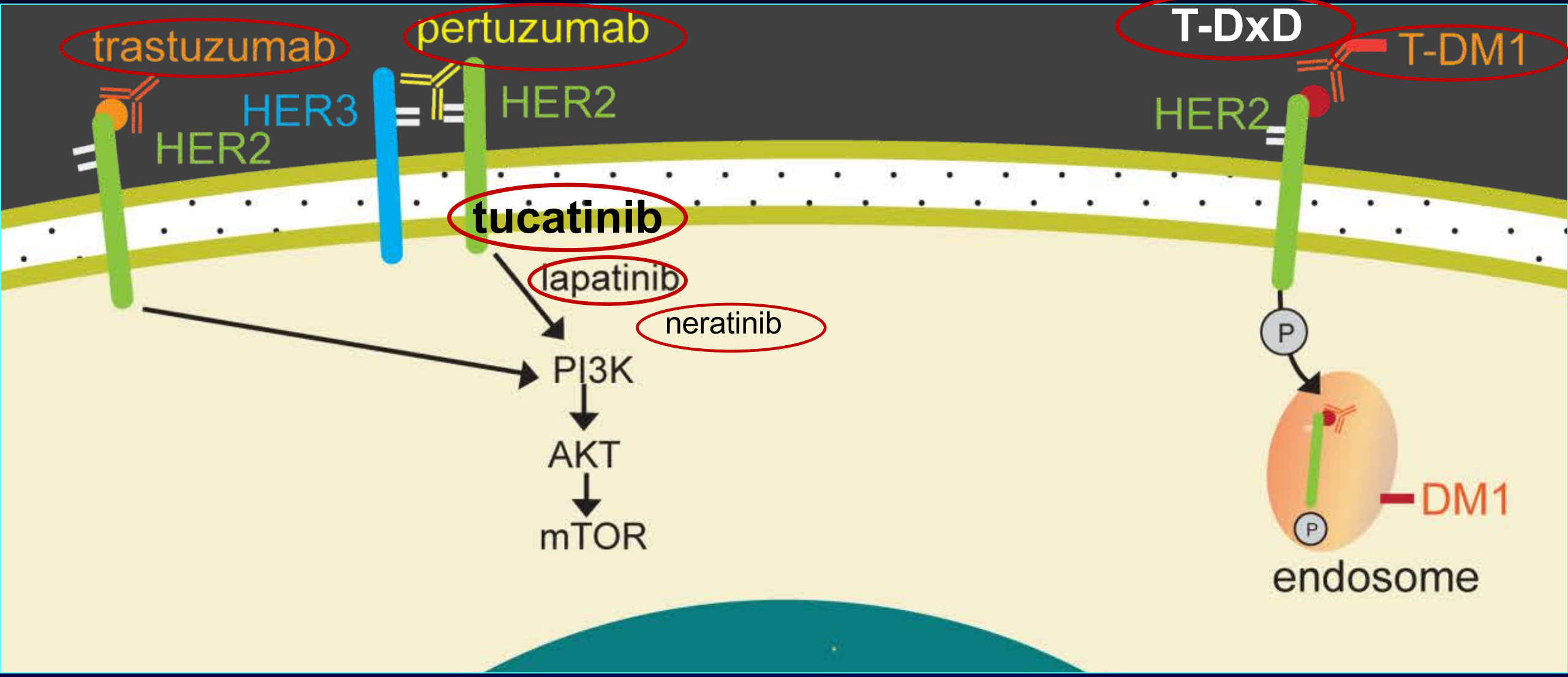
Professor of Medicine

2020: 7 FDA APPROVED HER2-DIRECTED THERAPIES



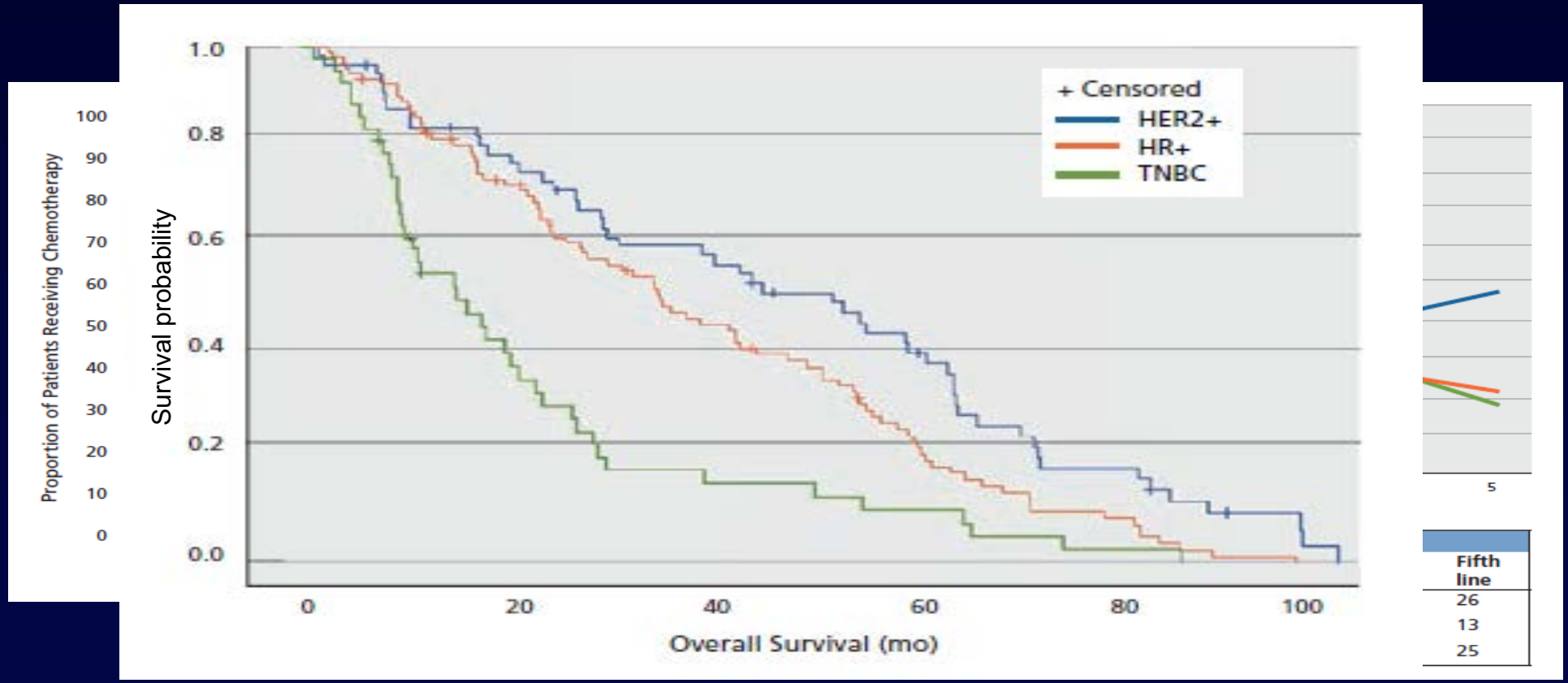
T-DM1, trastuzumab emtansine

Gajria D, et al. *Expert Rev Anticancer Ther*. 2011;11:263-275.

Courtesy of Sara Hurvitz, MD

After THP and T-DM1, then what?

Number of Lines and Median Duration of Chemotherapy by Subtype (n=199)



<u>Multiple</u> lines of therapy available & appropriate as long as patient has reasonable performance status & willing to receive therapy

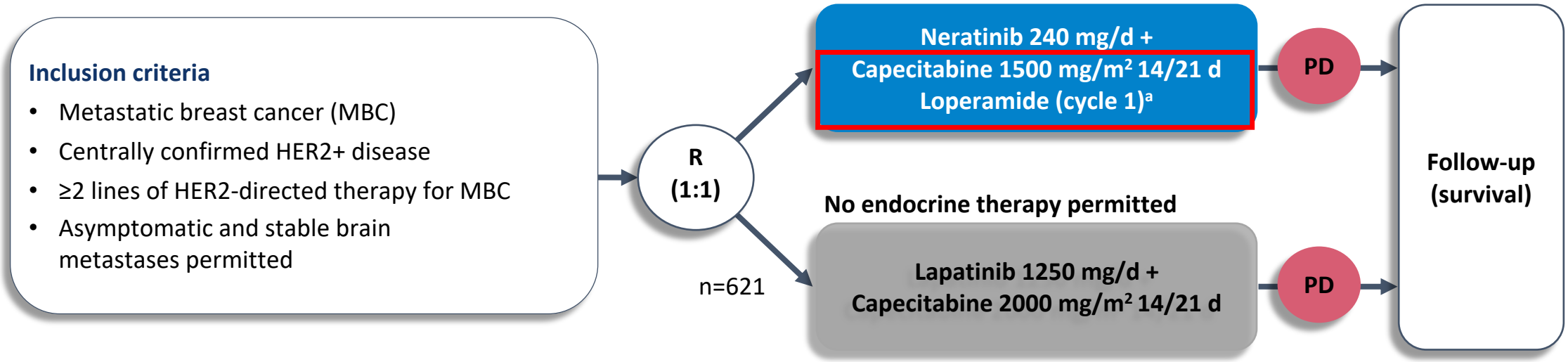
Seah et al, JNCCN 2014; 12:71

Courtesy of Sara Hurvitz, MD

Newly Approved Therapy: Tyrosine Kinase Inhibitor

Neratinib + Capecitabine

NALA Phase III trial of neratinib: study design



Stratification variables

- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints

- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

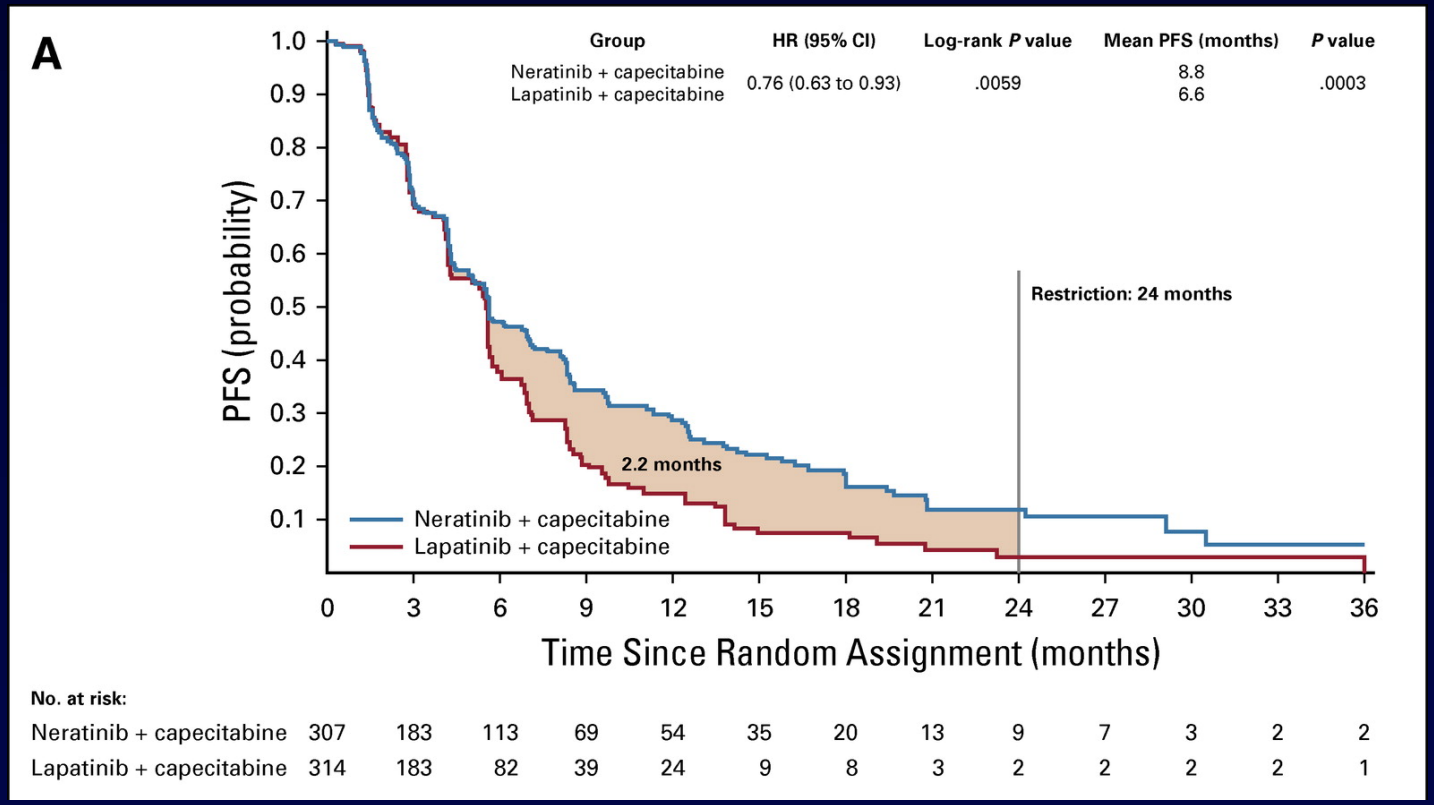
Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

Saura C, et al. ASCO Annual Meeting 2019;*Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) Abs 1002

Courtesy of Sara Hurvitz, MD

NALA Results

- PFS (by restricted means analysis at 24 mos)
  - 8.8 mos (neratinib) vs. 6.6 mos (lapatinib) p=0.003
- Cumulative incidence intervention CNS mets
  - 22.8% (neratinib) vs 29.2% (lapatinib); p=0.043
- Grade 3/4 diarrhea
  - 24% (neratinib) vs. 13% (lapatinib)



Saura C, et al. *Journal of Clinical Oncology* 2020:38(27):3138-3149.

Courtesy of Sara Hurvitz, MD

CONTROL: Incidence of Treatment-Emergent Diarrhea by Worst Grade in ADJUVANT setting

	LOP (n=137)	LOP + budesonide (n=64)	LOP + colestipol (n=136)	LOP prn + colestipol (n=104)	LOP prn + neratinib dose escalation (n=60)
Treatment-emergent diarrhea incidence, N (%)					
No diarrhea	28 (20)	9 (14)	23 (17)	5 (5)	2 (3)
Gr 1	33 (24)	16 (25)	38 (28)	33 (32)	24 (40)
Gr 2	34 (25)	21 (33)	47 (35)	31 (30)	25 (42)
Gr 3	42 (31)	18 (28)	28 (21)	35 (34)	9 (15)
Gr 4	0	0	0	0	0

Budesonide 9 mg qd; colestipol 2g BID;
loperamide escalation: 120 mg x 7d →160 mg x 7 d then 240 mg

Courtesy of Sara Hurvitz, MD

Chan A, et al. Presented at the 2019 San Antonio Breast Cancer Symposium. Abstract #P5-14-03.

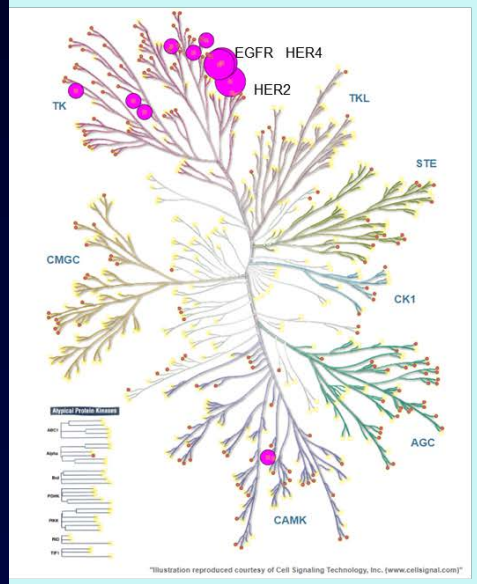
Neratinib Approval - 2.25.2020

Neratinib approved in combination with capecitabine for adult patients with advanced or metastatic HER2-positive breast cancer *who have received two or more prior anti-HER2 based regimens in the metastatic setting*.

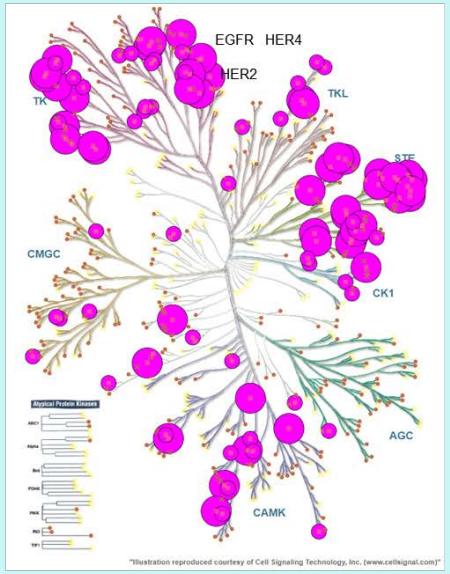
Neratinib PI.

Courtesy of Sara Hurvitz, MD

Tucatinib: HER2 Selective Kinase Inhibitor



Tucatinib



Neratinib

- IC50 < 1uM (large circle)
- 1uM < IC50 < 10uM (medium circle)
- IC50 > 10uM (small circle)

Kinome scan data from the Library of Integrated Network-based Cellular Signatures (https://lincs.hms.harvard.edu/kinomescan/)

- Kinome analysis shows limited activity in a panel of 237 protein kinases at 1 or 10 μM
  - Activity is restricted to HER2 related kinases EGFR and HER4
- Tucatinib is selective for HER2 vs. EGFR in biochemical assays

Compound	Biochemical Selectivity (Kinase Assays)	
	HER2 IC_{50} (nM)	EGFR IC_{50} (nM)
Tucatinib	6.9	449
Neratinib	5.6	1.8
Lapatinib	109	48

- *Lapatinib and neratinib inhibit EGFR and HER2 with similar potencies*

- Less EGFR-associated toxicity than other HER2-targeted TKIs
- CNS penetration
- Well tolerated and active in combinations (eg, with T-DM1, capecitabine, or trastuzumab)

Agent	Cellular Selectivity, IC_{50} (nM)	
	HER2	EGFR
Tucatinib	8	4000
Neratinib	7	8
Lapatinib	49	31

Courtesy of Sara Hurvitz, MD

HER2CLIMB Trial Design

Key Eligibility Criteria

- Measurable or non-measurable HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG 0, 1
- Brain MRI at baseline
  - No evidence of brain metastases, or
  - Untreated, previously treated stable, or previously treated progressing, brain metastases not needing immediate local therapy

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
Treatment (21-day cycle)

Tucatinib 300 mg PO BID +
Trastuzumab 6 mg/Kg Q3W (loading dose 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

Placebo + Trastuzumab + Capecitabine
Treatment (21-day cycle)

Placebo (Pbo) +
Trastuzumab 6 mg/Kg Q3W (loading dose 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

*Stratification Factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region of world (US or Canada or rest of world)

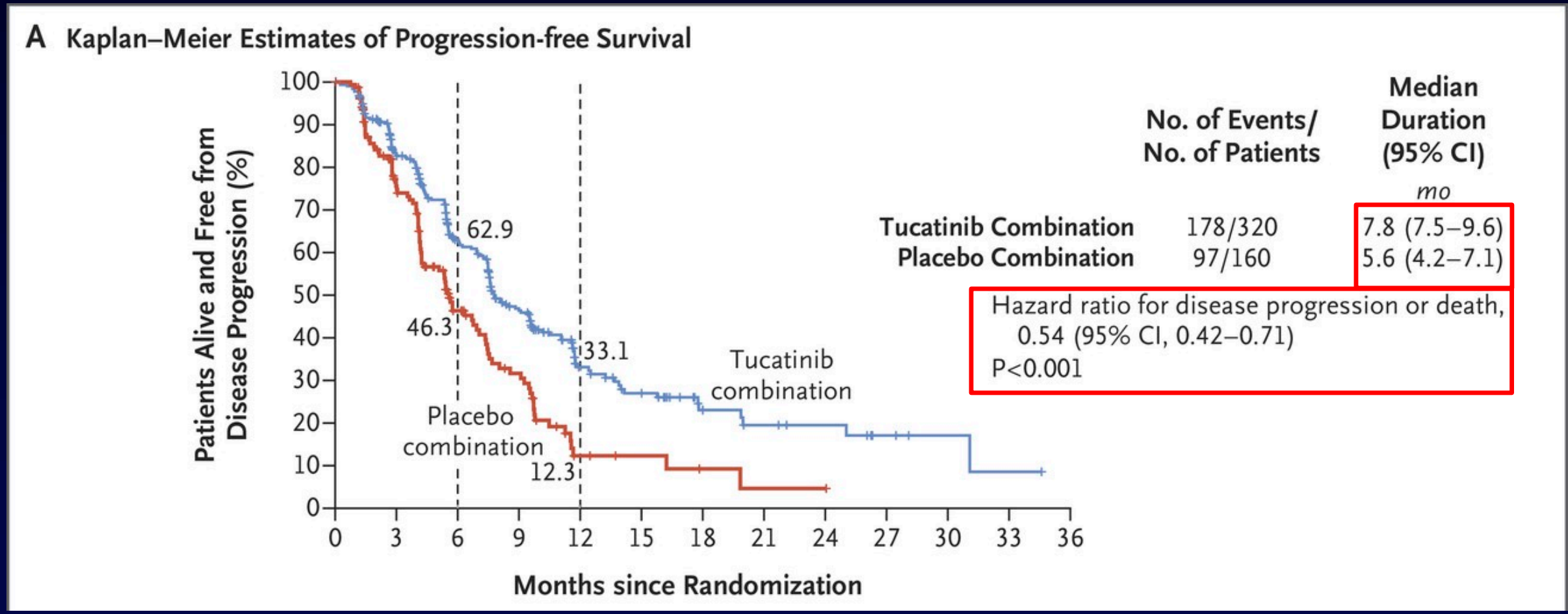
Baseline Characteristics of Note

- **60% HR positive**
- **48% CNS Metastases**
- **36% de novo metastatic breast cancer**
- **Median 3 prior lines of therapy in metastatic setting (range 1-14)**

Courtesy of Sara Hurvitz, MD

https://clinicaltrials.gov/ct2/show/NCT02614794

Progression-free Survival



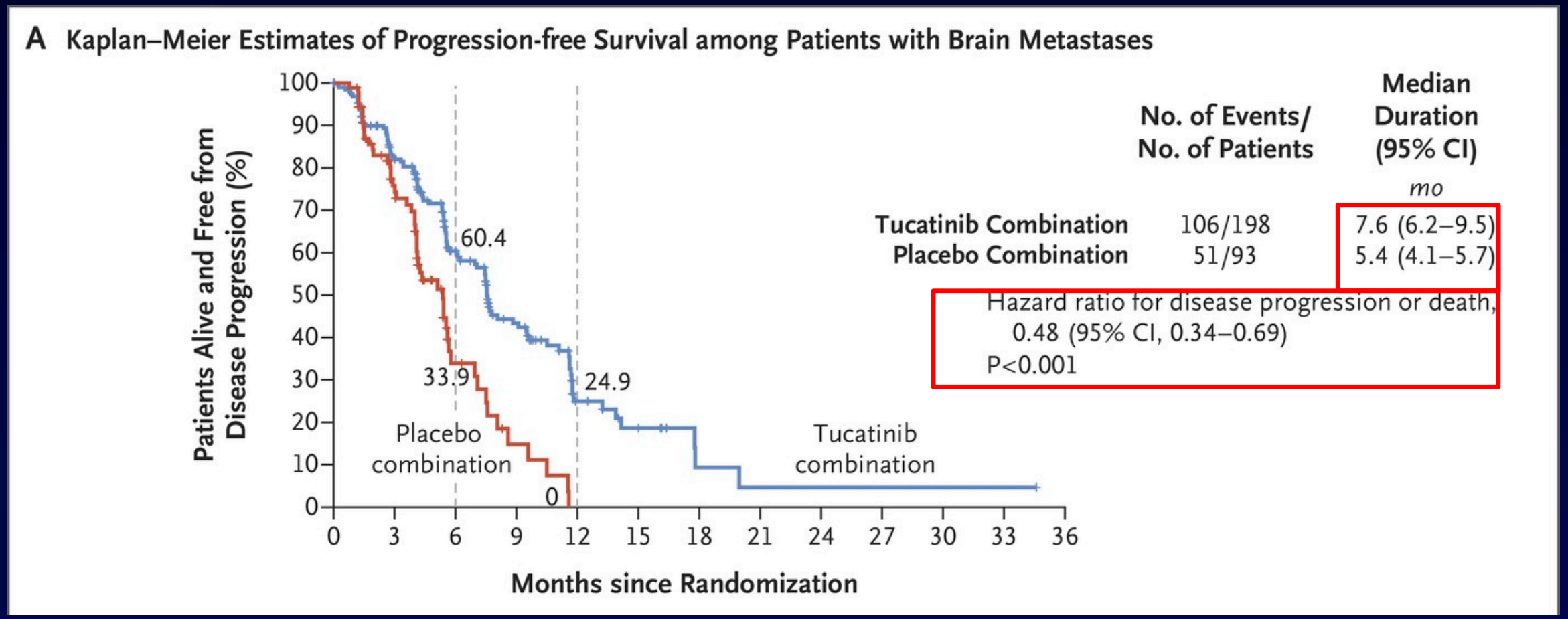
- ORR: 41% (tucatinib) vs. 23% (placebo)

The NEW ENGLAND JOURNAL of MEDICINE

RK Murthy et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914609

Courtesy of Sara Hurvitz, MD

Progression-free Survival among the Patients with Brain Metastases



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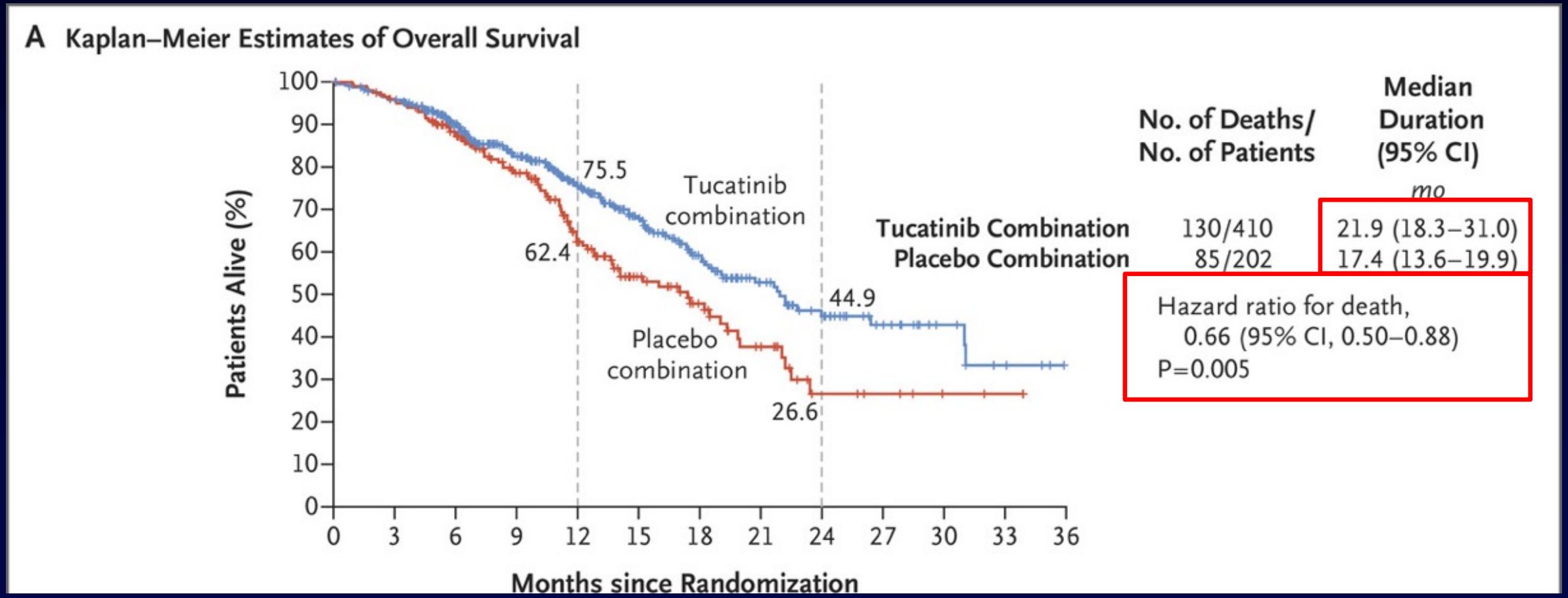
RK Murthy et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914609

Courtesy of Sara Hurvitz, MD

Overall Survival in the Total Population



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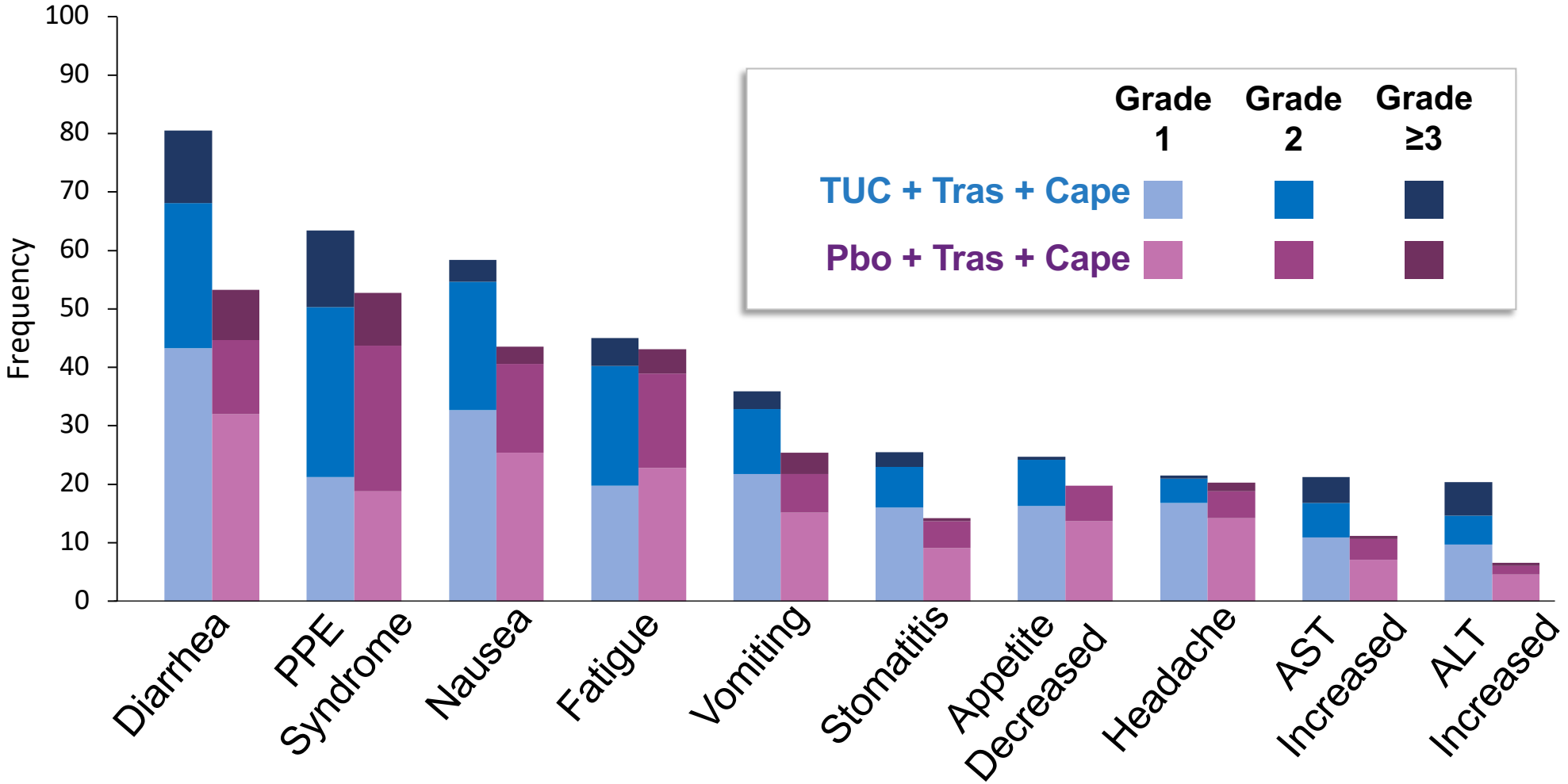
RK Murthy et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914609

Courtesy of Sara Hurvitz, MD

Most Common Adverse Events (≥20% in the Tucatinib Arm)



PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

Courtesy of Sara Hurvitz, MD

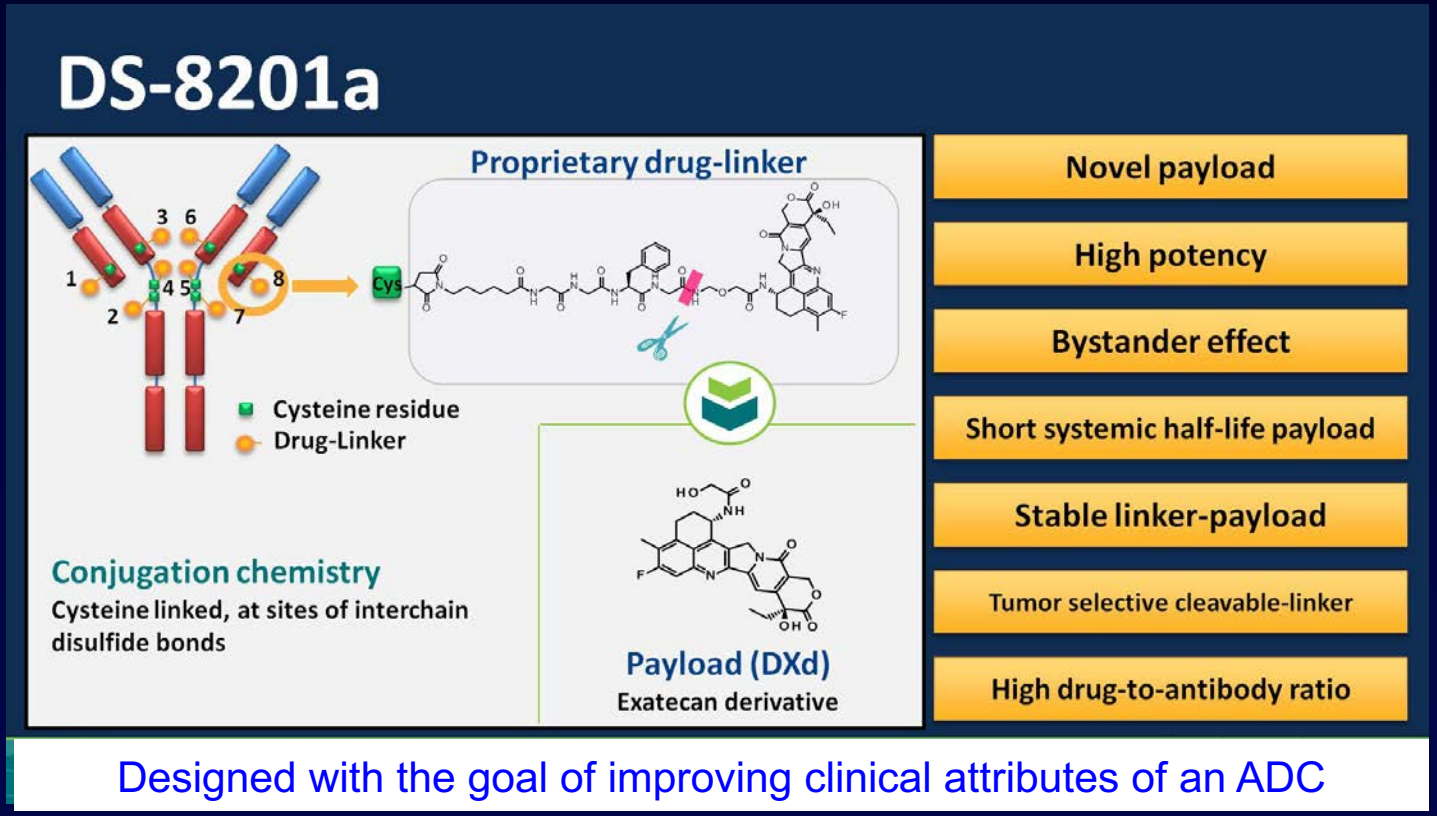
Tucatinib Approval

On April 17, 2020, the FDA approved tucatinib in combination with trastuzumab/capecitabine for treatment of advanced, unresectable or metastatic HER2+ BC, including patients with brain metastases, who have received ≥ 1 previous HER2-targeted therapy in the metastatic setting

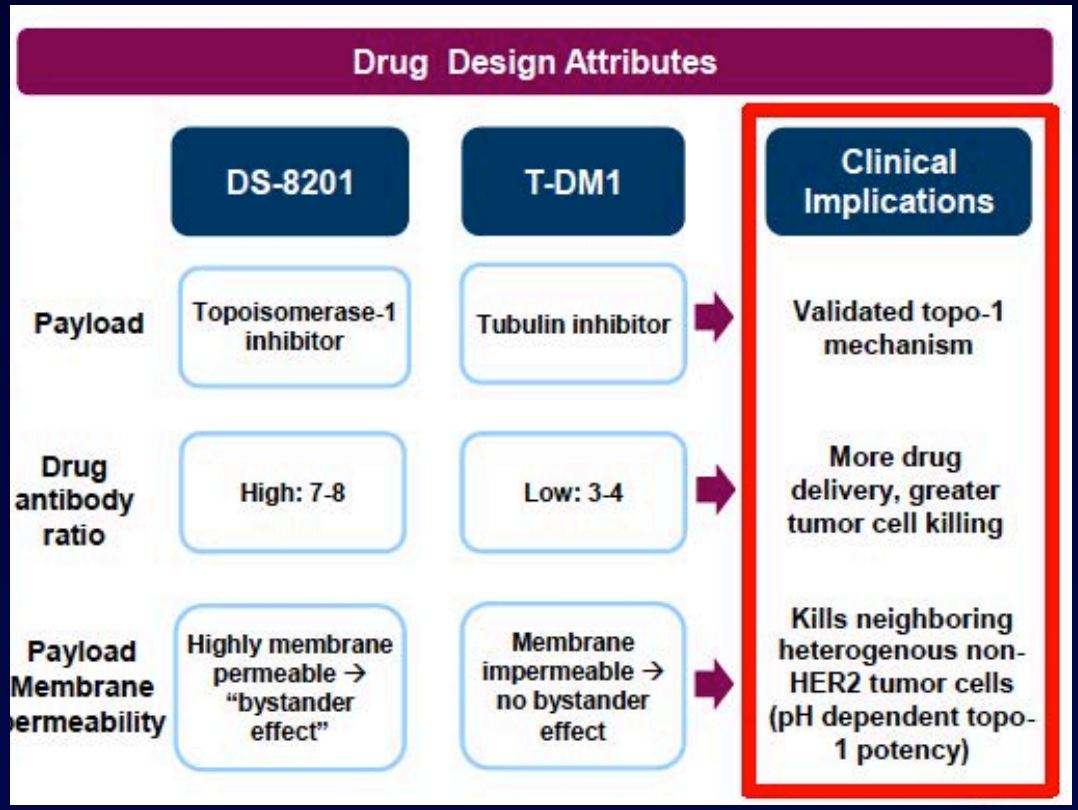
Tucatinib PI.

Courtesy of Sara Hurvitz, MD

Trastuzumab Deruxtecan (DS-8201a): Structure and Mechanism of Action



Designed with the goal of improving clinical attributes of an ADC



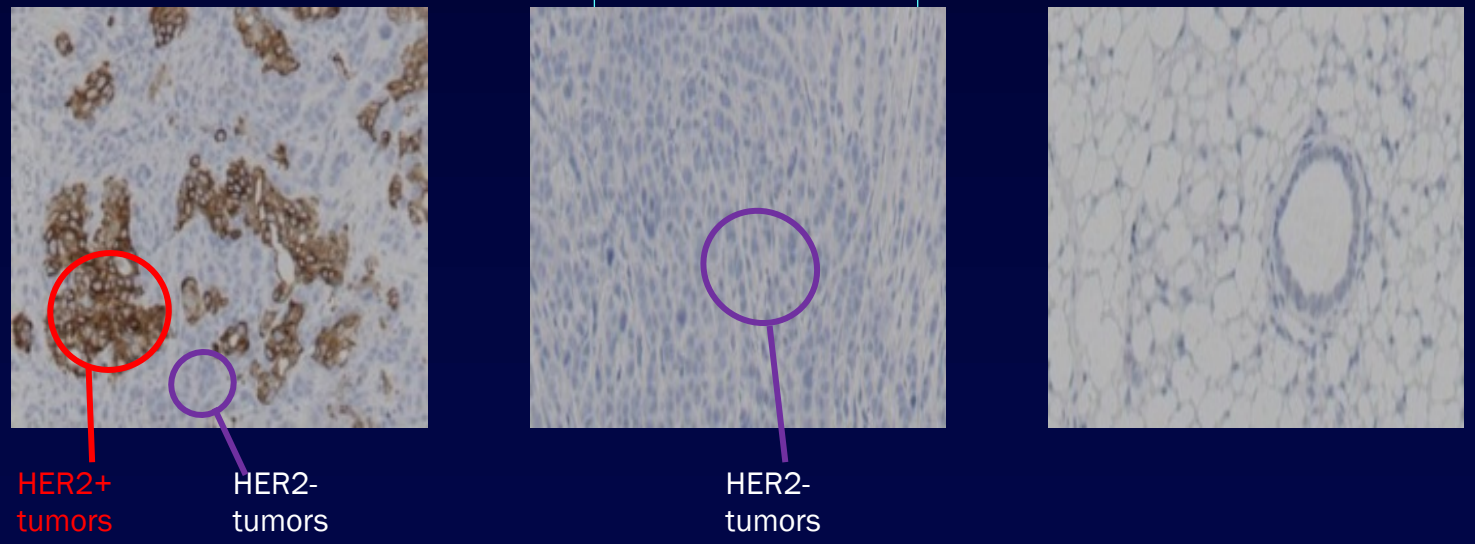
Doi et al. *J Clin Oncol*. 2017;35. DOI: 10.1200/JCO.2017.35.15_suppl.108

Courtesy of Sara Hurvitz, MD

Bystander effect of T-DXd

Bystander effect (Preclinical, after 14 day treatment)

Control	T-DM1, 10 mg/kg	DS-8201a, 3.0 mg/kg
Co-culture of HER2+ and HER2- tumors in vivo	*Activity against HER2+ tumors only*	*Activity against HER2+ and HER2- tumors*



DS-8201a: Ability to kill neighboring tumor cells

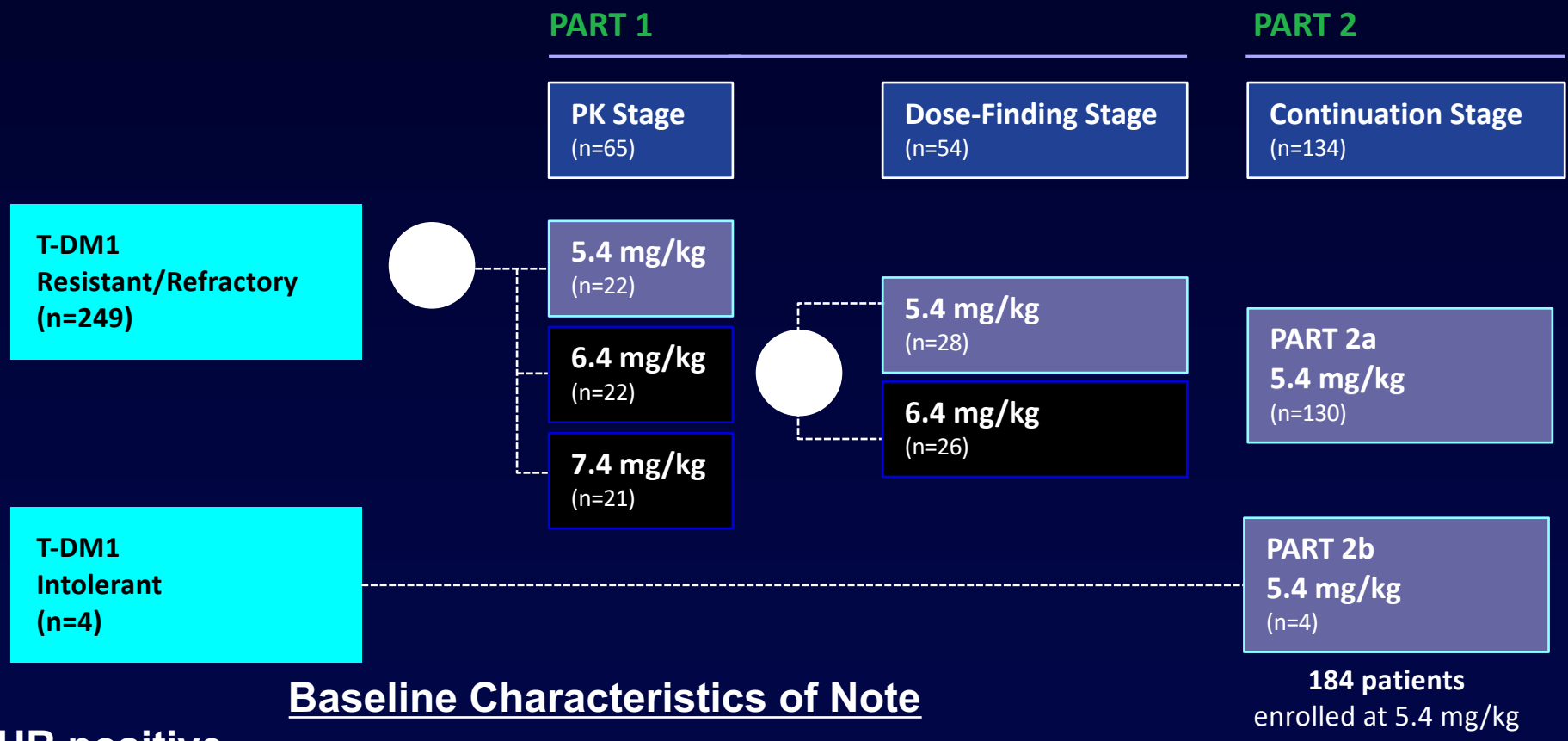
Ogitani-Y *et al.*, Cancer Science 2016; 107:1039–1046

Courtesy of Sara Hurvitz, MD

DESTINY-Breast01 Study Design:
An Open-Label, Multicenter, Phase 2 Study

Population

- ≥18 years of age
- Unresectable and/or metastatic BC
- HER2-positive (centrally confirmed on archival tissue)
- Prior T-DM1
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed

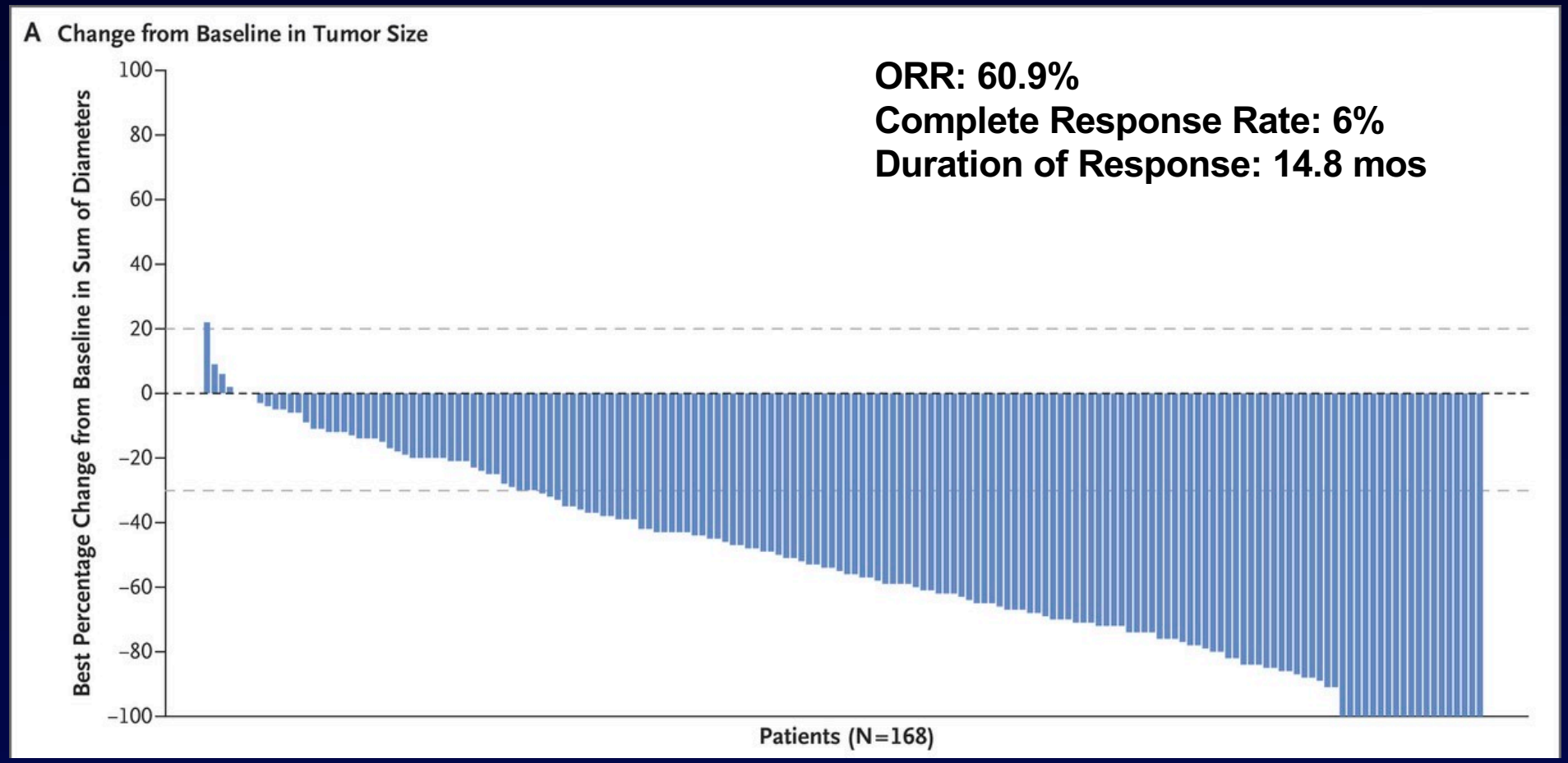


Baseline Characteristics of Note

- **53% HR positive**
- **HER2 IHC 3+ 84%; 1+/2+ (FISH+) 16%**
- **92% visceral disease; 13% h/o brain metastases**
- **Median 6 prior lines of therapy (range 2-27)**

Courtesy of Sara Hurvitz, MD

Response to Trastuzumab Deruxtecan, According to Tumor Size and Subgroup Analyses.

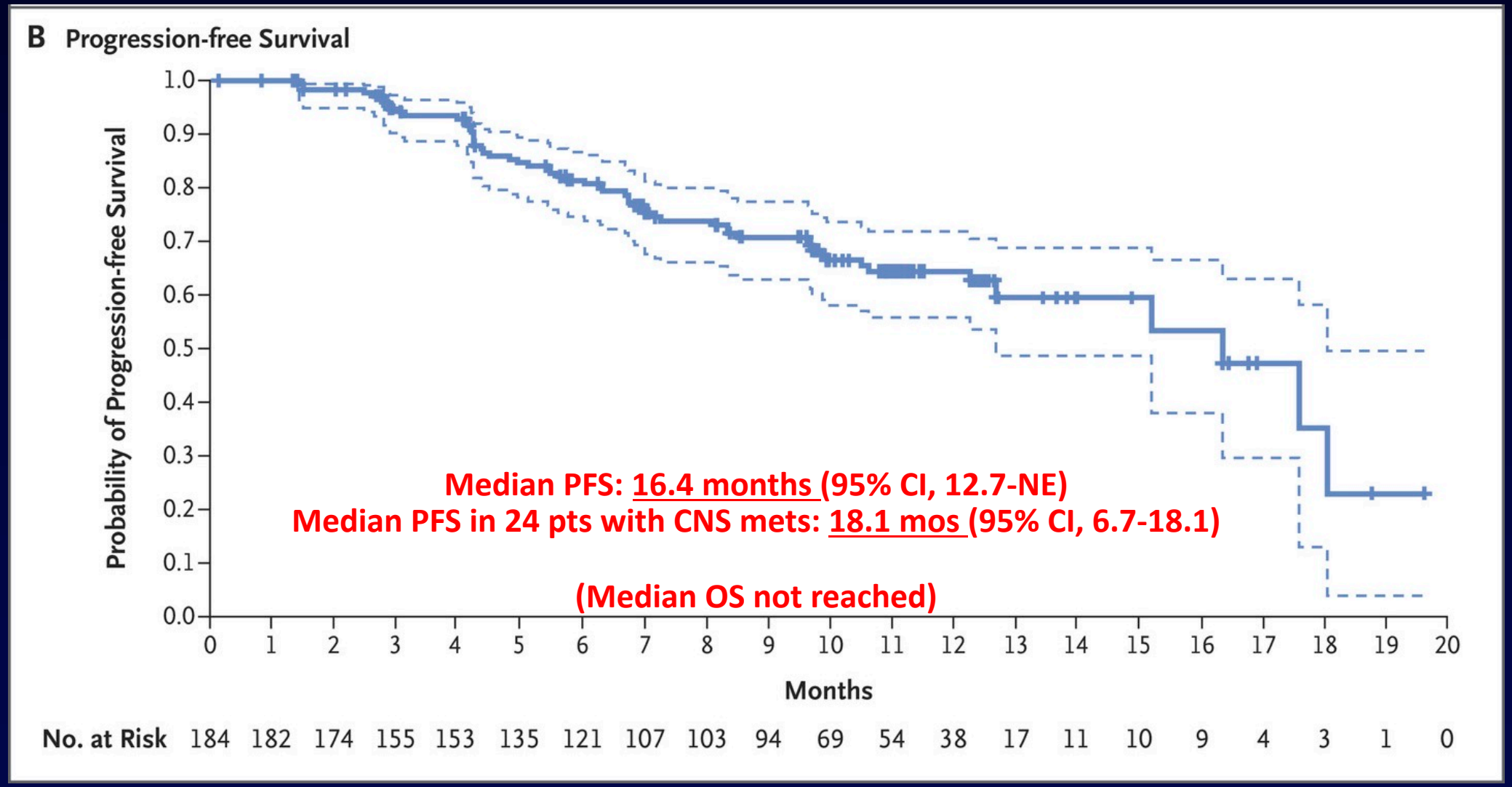


The NEW ENGLAND JOURNAL of MEDICINE

S Modi et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914510

Courtesy of Sara Hurvitz, MD

Kaplan–Meier Analysis of Progression-free Survival.



S Modi et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914510

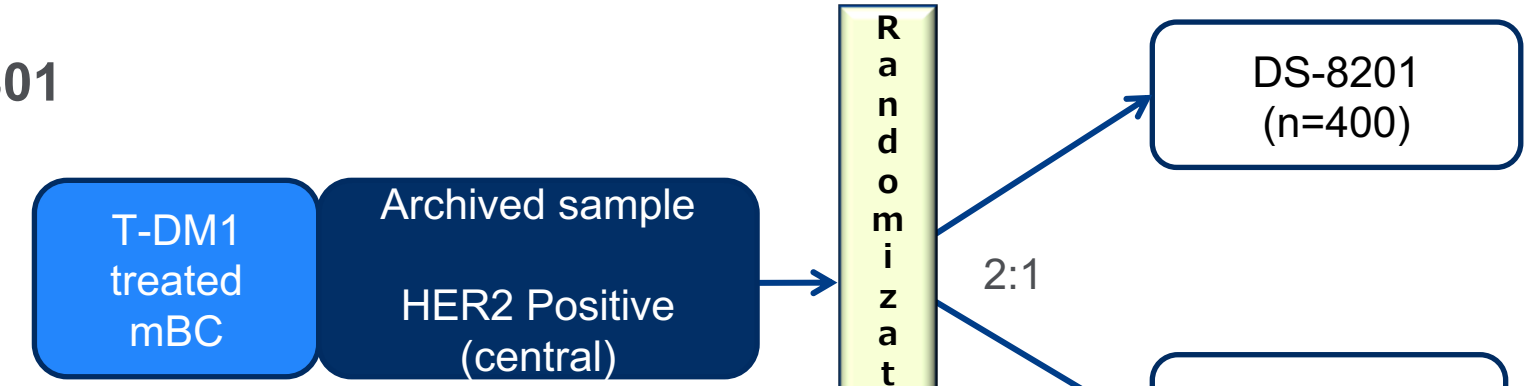
Courtesy of Sara Hurvitz, MD

The NEW ENGLAND JOURNAL of MEDICINE

DESTINY-Breast02 and -Breast03: U301 & U302

Ph III HER2+ mBC Trial Designs

U301



*trastuzumab + capecitabine or lapatinib + capecitabine

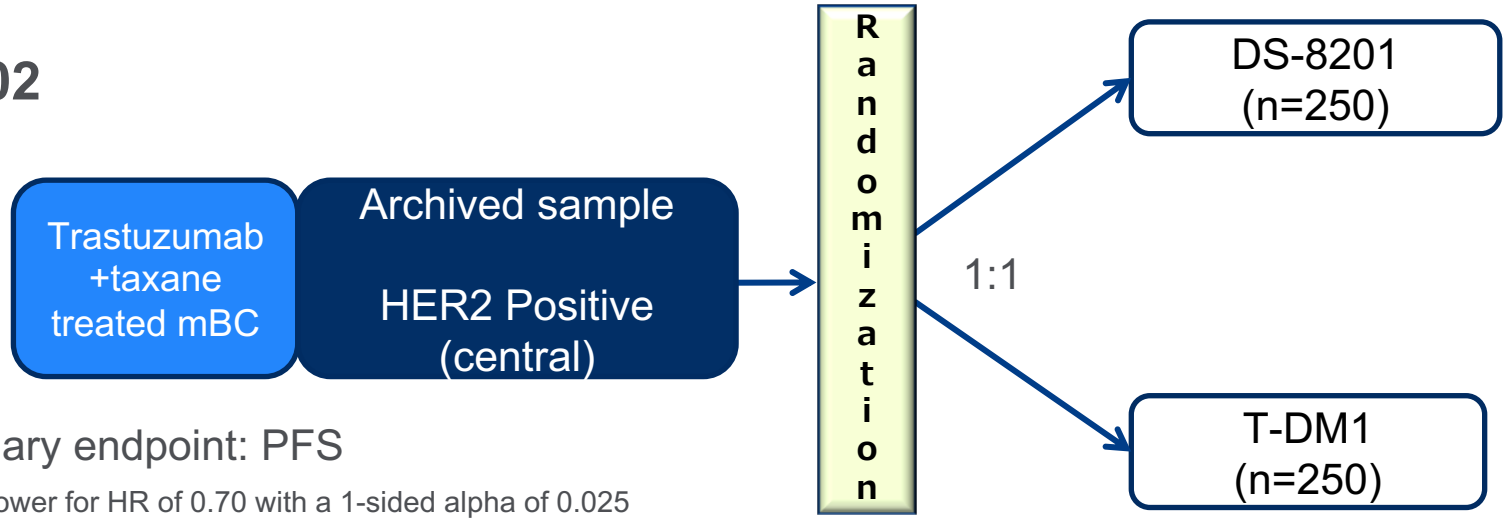
Primary endpoints: PFS

PFS: 90% power for HR of 0.70 in PFS with a 1-sided alpha of 0.025

OS: 80% power for HR of 0.75 with a 1-sided alpha of 0.025

PFS will be tested first, if positive, OS will be tested at the same alpha level. There is a planned OS interim analysis at the same time when PFS primary analysis is performed.

U302

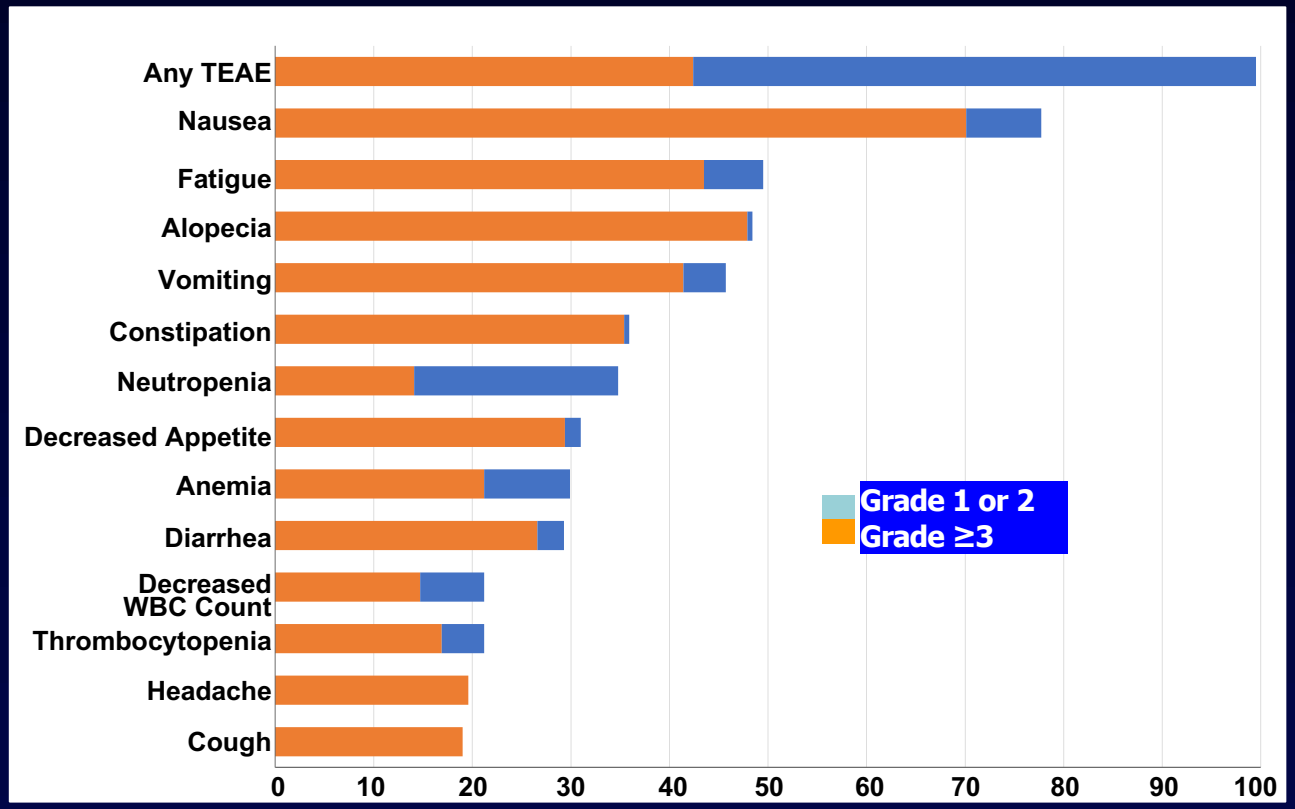


Primary endpoint: PFS

90% power for HR of 0.70 with a 1-sided alpha of 0.025

Courtesy of Sara Hurvitz, MD

TDxD: Treatment-Emergent Adverse Events (in >15% of Patients)



Interstitial Lung Disease

Median time from the first infusion of T-DXd to onset of ILD was 27.6 weeks (range, 6-76 weeks)

	Patients who received T-DXd 5.4 mg/kg (N=184)					
Preferred Term, n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade/ Total**
Interstitial lung disease[a]	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**

- Serious TEAEs, 22.8% (drug related, 12.5%)
- TEAEs associated with discontinuation, 15.2% (drug related, 14.7%); **the majority were due to pneumonitis/ILD (8.7%)**
- 9 (4.9%) TEAE-associated deaths

Courtesy of Sara Hurvitz, MD

Modi S, et al. *N Engl J Med.* 2020;382:610-621.

Pneumonitis-associated with DS-8201a

ILD in Phase 1/2 studies[1]

	All-grade	Grade 5
All subjects N=665	9.9%	0.8%
Breast cancer, any dose N=510	10.6%	0.8%
Breast cancer, 5.4 mg/kg N=269	5.6%	0.4%

Conclusions

- **Higher likelihood of developing ILD associated with[1]:**
  - **Higher dose (≥6.4 mg/kg)**
  - **Japanese origin:** *Japanese patients 49% of N=665 sample*
  - **Number of prior therapies:** *Many patients in Phase1/2 have multiple prior lines of therapy*
- **Median 149 days (~6 months) to onset[1] allows for monitoring & intervention**
- **Education and guidelines implementation underway**

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Source: [1]Powell et al, SABCS 2018; Poster #P6-17-06, Abstract #979

Courtesy of Sara Hurvitz, MD

Management of Interstitial Lung Disease in Clinical Studies of Trastuzumab Deruxtecan

Monitor

Suspected ILD

Interrupt drug

Rule out ILD if the patient exhibits:

- Radiographic changes suggesting ILD
- Acute onset of new/worsening pulmonary or related symptoms (eg, cough, dyspnea, fever)

Confirm

Assessments should include:

- High-resolution CT
- Pulmonologist consultation and, if indicated, ID consultation
- Blood culture and CBC; other blood tests as needed
- Consider bronchoscopy and BAL if indicated and feasible
- PFTs and pulse oximetry
- Arterial blood gasses, if indicated
- As soon as ILD suspected, collect 1 blood sample for PK assessment, if feasible

All ILD events should be followed until resolution and after drug discontinuation.

Manage

Hold drug for any ILD events independent of grade

- **Grade 1:** Hold until fully resolved, then:
  - *If resolved ≤ 28 d from onset:* maintain dose
  - *If resolved > 28 d after onset:* reduce dose by 1 level
  - *If grade 1 ILD occurs beyond cycle Day 22 and has not resolved within 49 d from last infusion:* discontinue drug
- **Grades 2-4:** permanently discontinue treatment and follow toxicity management guidelines for trastuzumab deruxtecan

Fam-trastuzumab deruxtecan-nxki PI.

Courtesy of Sara Hurvitz, MD

FDA Accelerated Approval 12.20.2019

fam-trastuzumab deruxtecan-nxki approved for patients with unresectable or metastatic HER2-positive breast cancer *who have received two or more prior anti-HER2-based regimens in the metastatic setting*.

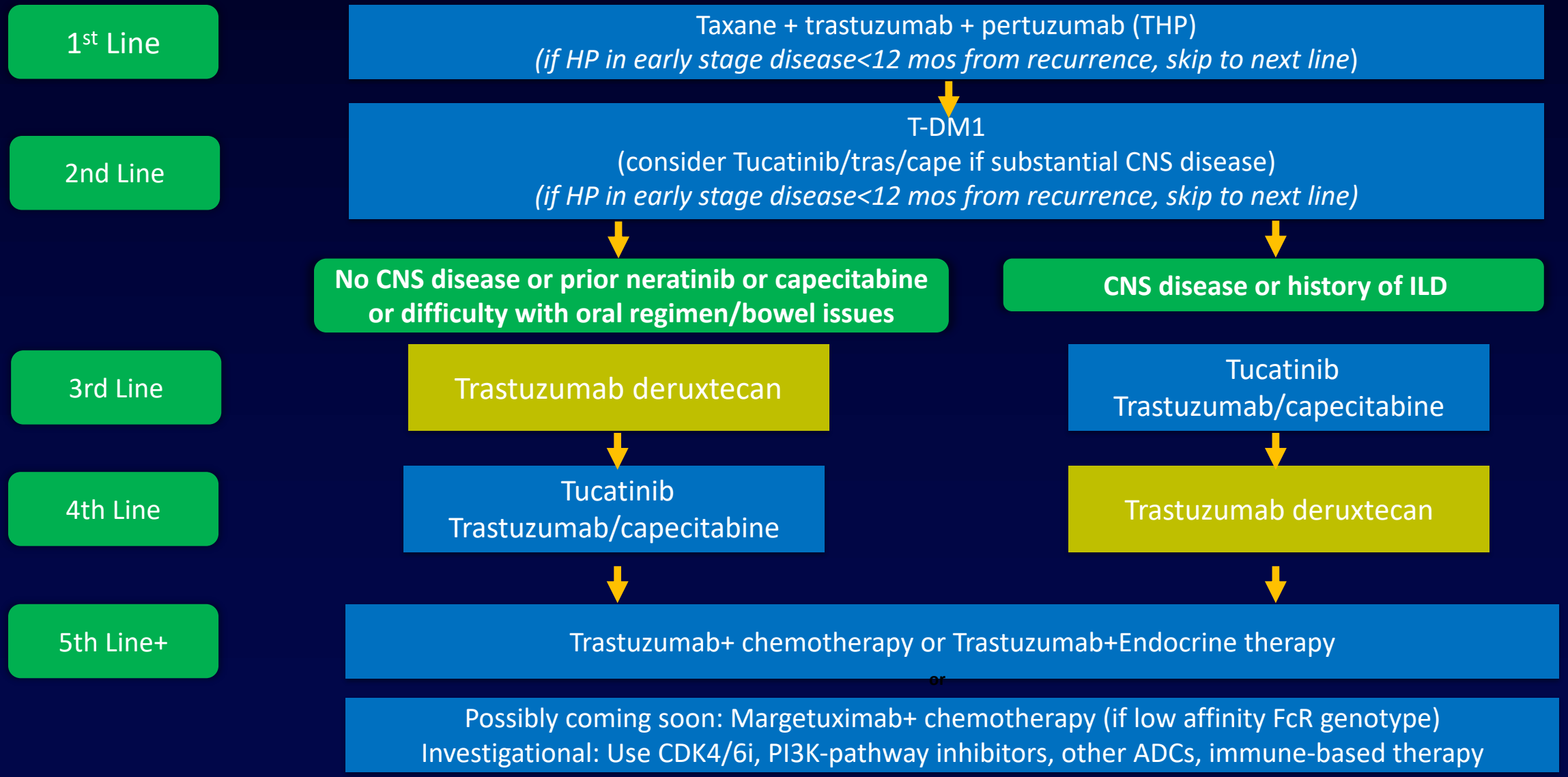
Courtesy of Sara Hurvitz, MD

How to Best Sequence New ≥3rd-Line Agents?

	Trastuzumab Deruxtecan	**Tucatinib + Tras/Cape**	**Neratinib + Capecitabine**
PROS	Very high ORR	OS and PFS benefit	PFS benefit
	Durable benefit Long PFS	Activity in both treated and progressive brain mets	Delays time to CNS Rx
	Activity maintained in pts with treated brain mets	Manageable toxicity profile	
CONS	ILD is serious potential risk	Absolute PFS benefit modest	Serious diarrhea is common
	No data on efficacy in progressive brain mets		Benefit modest

Courtesy of Sara Hurvitz, MD

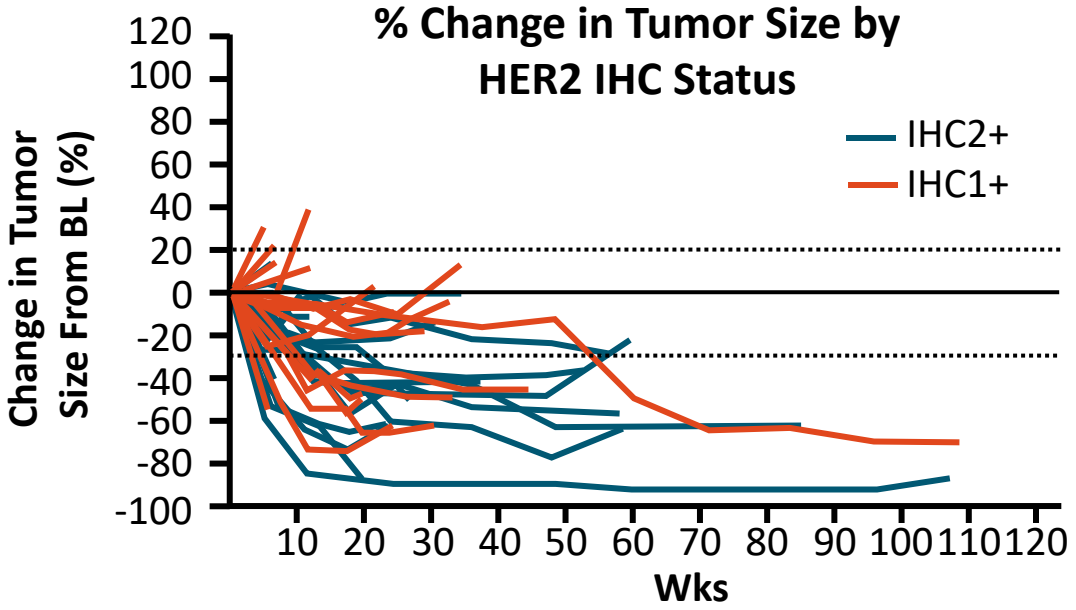
Approach to Therapy for Metastatic HER2+ Disease: Move to Personalization

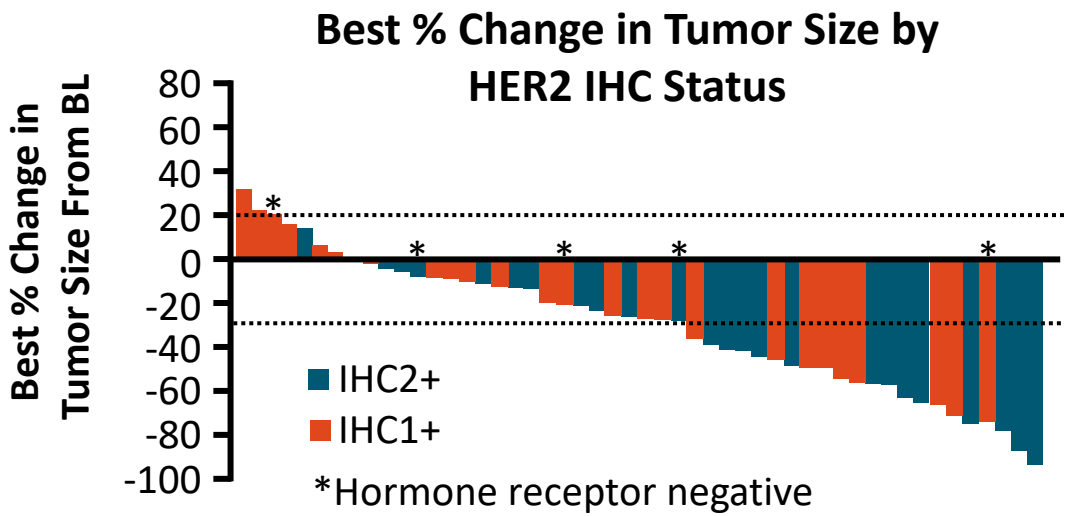


Courtesy of/adapted from Ian Krop

Courtesy of Sara Hurvitz, MD

HER2-Low MBC: Use of trastuzumab deruxtecan??





Line at 20% indicates PD; line at -30% indicates PR.

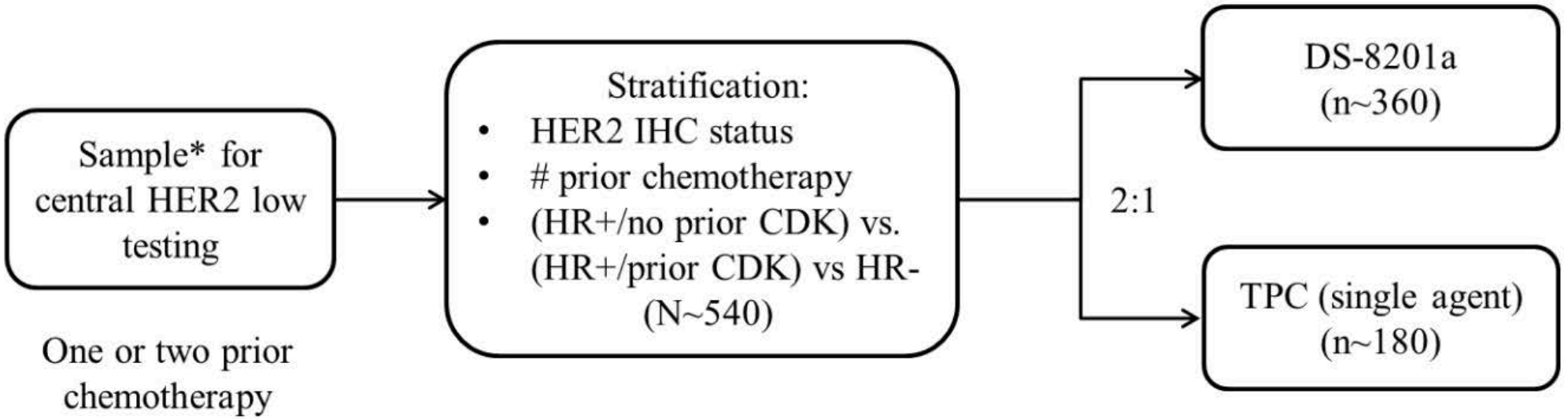
Efficacy in HER2-Low MBC	Confirmed ORR, %	Median DoR, Mos	Median PFS, Mos
All (N = 51)	44.2	9.4	7.6
IHC 2+ (n = 24)	**54.5**	11.0	**13.6**
IHC 1+ (n = 27)	**33.3**	7.9	**5.7**
HR+ (n = 45)	47.4	11.0	7.9
Prior CDK4/6 inhibitor (n = 15)	33.3	NR	7.1

Modi. SABCS 2018. Abstr P6-17-02.

Courtesy of Sara Hurvitz, MD

Slide credit: clinicaloptions.com

DESTINY-Breast04
HER2 Low (1+ or 2+ IHC)



CDK = cyclin-dependent kinase, HER2 = human epidermal growth factor receptor 2, IHC = immunohistochemistry, TPC = treatment of physician's choice.

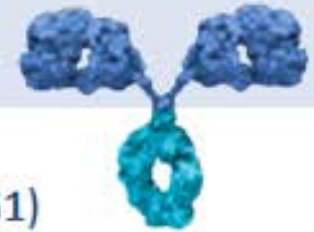
https://clinicaltrials.gov/ct2/show/NCT03734029

Courtesy of Sara Hurvitz, MD

Margetuximab: Fc-engineered to Activate Immune Responses

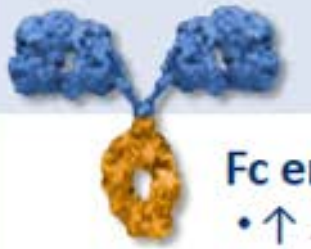
Trastuzumab

Fab:
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival



Fc:
- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

Margetuximab[1,2]



Fab:
- Same specificity and affinity
- Similarly disrupts signaling

Fc engineering:
- ↑ Affinity for activating FcγRIIIA (**CD16A**)
- ↓ Affinity for inhibitory FcγRIIB (**CD32B**)

Margetuximab Binding to FcγR Variants:

Receptor Type	Receptor	Allelic Variant	Relative Fc Binding	Affinity Fold-Change
Activating	CD16A	158F	Lower	6.6x ↑
		158V	Higher	4.7x ↑
	CD32A	131R	Lower	6.1x ↓
		131H	Higher	↔
Inhibitory	CD32B	232I/T	Equivalent	8.4x ↓

1. Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123. 2. Stavenhagen JB, et al. *Cancer Res*. 2007;67(18):8882-8890.

Courtesy of Sara Hurvitz, MD

Planned* Exploratory PFS Analyses by FcγR Genotypes (CBA)

Margetuximab benefit appears to be increased in low-affinity CD16A-158F allele carriers

		Median PFS (95% CI), Months		HR by Unstratified Cox Model	95% CI	Unstratified Log-Rank *P* Value
		Margetuximab + Chemotherapy	Trastuzumab + Chemotherapy			
	All patients	5.8 (5.52–6.97)	4.9 (4.17–5.59)	0.78	(0.61–0.99)	0.044
Activating function	CD16A/F carrier (FV or FF), n=437	6.9 (5.55–8.15)	5.1 (4.14–5.59)	0.68	(0.52–0.90)	0.005
	CD16A/FF, n=192	8.2 (5.52–10.51)	5.6 (4.50–8.31)	0.69	(0.46–1.05)	0.080
	CD16A/FV, n=245	6.3 (5.52–7.23)	4.3 (4.01–5.59)	0.71	(0.50–1.01)	0.055
	CD16A/VV, n=69	4.8 (2.46–5.65)	5.6 (2.86–11.04)	1.78	(0.87–3.62)	0.110
	CD32A/RR, n=122	5.7 (4.80–10.55)	5.5 (2.76–8.21)	0.69	(0.41–1.17)	0.166
	CD32A/RH, n=247	6.9 (5.55–8.15)	5.6 (4.17–6.67)	0.74	(0.52–1.06)	0.102
	CD32A/HH, n=137	5.6 (3.29–8.28)	4.1 (2.79–5.59)	0.80	(0.49–1.30)	0.365
Inhibitory function	CD32B/II†, n=380	5.8 (5.55–7.66)	5.5 (4.17–5.65)	0.85	(0.64–1.13)	0.265
	CD32B/IT†, n=117	6.0 (4.14–NA)	5.5 (2.79–7.16)	0.63	(0.36–1.10)	0.098

*Non-alpha allocating, exploratory analysis.

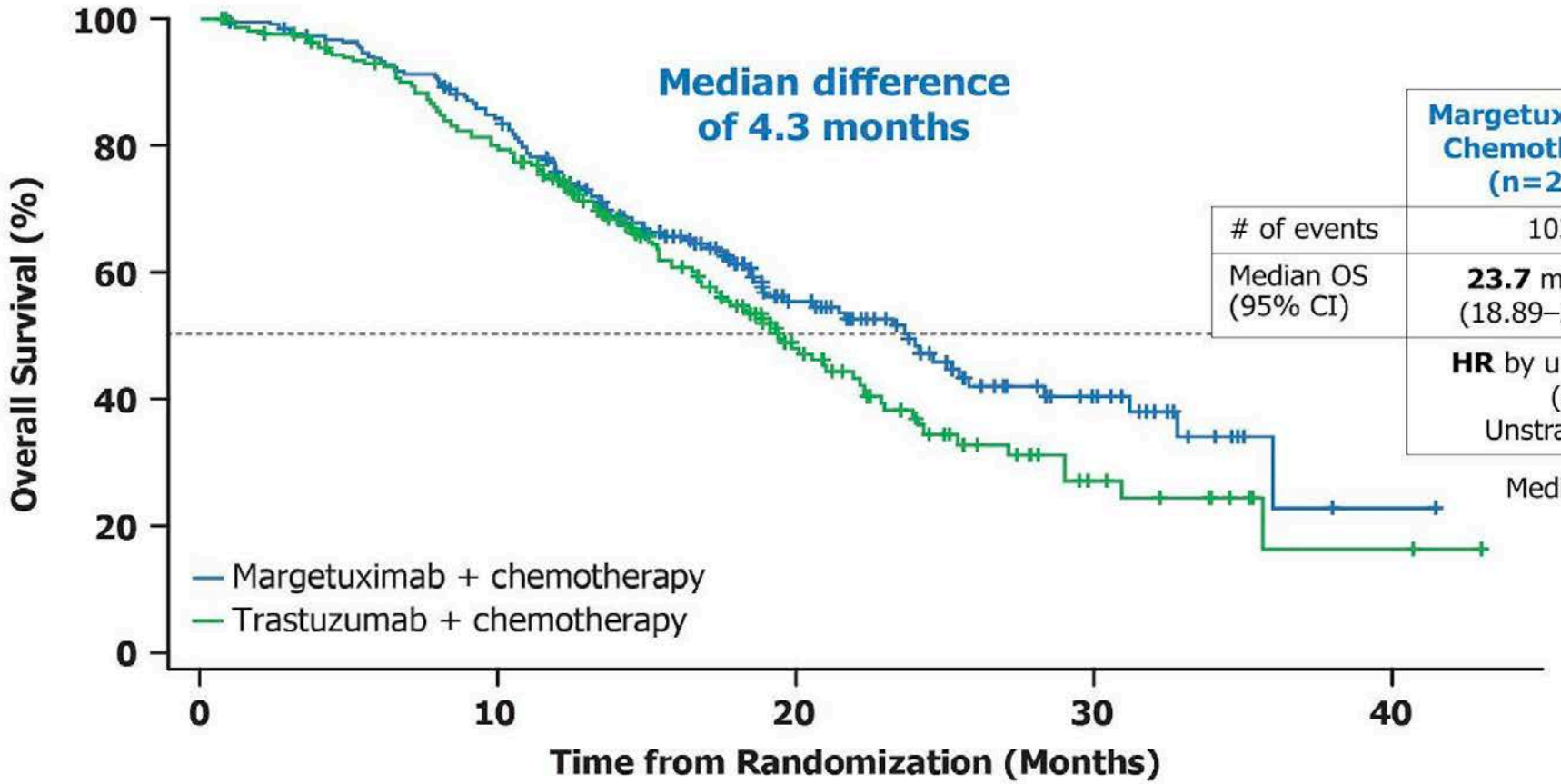
†CD32B/TT not included on forest plot because n=9 is too small (5 on margetuximab, 4 on trastuzumab) to make analysis meaningful.

Courtesy of Sara Hurvitz, MD

Prespecified OS in CD16A-158F carriers

[1]Sep-2019 Cutoff

CD16A-158F Carriers, FF or FV, n=437 of 506 (86%) genotyped



	Margetuximab + Chemotherapy (n=221)	Trastuzumab + Chemotherapy (n=216)
# of events	103	114
Median OS (95% CI)	**23.7** months (18.89–28.32)	**19.4** months (16.85–22.28)
HR by unstratified Cox model, **0.79** (95% CI, 0.61–1.04) Unstratified log-rank ***P*=0.087**		

Median follow-up: 15.6 months

Margetuximab	221	219	212	204	196	181	157	135	111	91	68	55	42	31	27	19	13	8	2	1	1	0
Trastuzumab	216	210	201	192	176	165	145	123	98	81	57	43	30	21	16	11	9	6	2	2	2	1	0

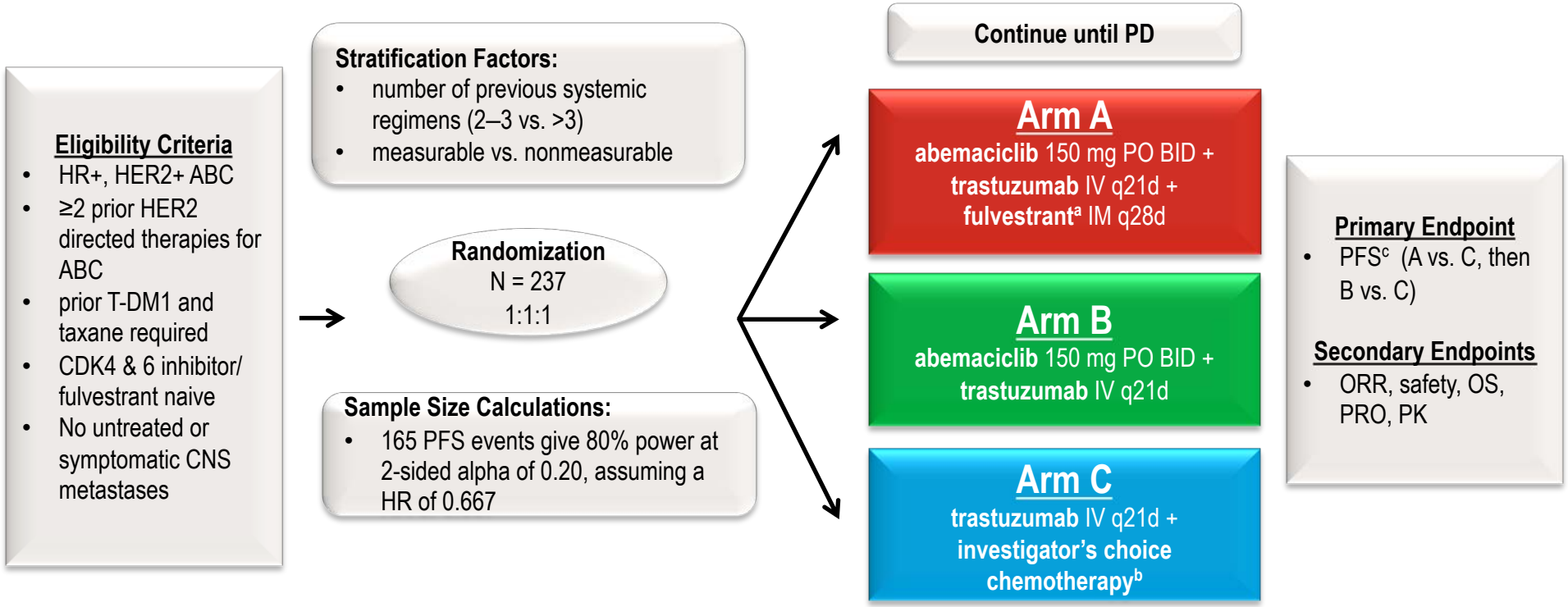
Courtesy of Sara Hurvitz, MD

Additional HER2 Targeting ADCs in Breast Cancer

Drug Name	Clinical Trials	Setting
A166	Phase 1/2: NCT03602079	HER2+ locally advanced/metastatic solid tumors that did not respond or stopped responding to approved therapies
ALT-P7 (HM2-MMAE)	Phase 2: NCT03281824	HER2+ metastatic breast cancer patients who have progressed on previous trastuzumab-based therapy
ARX788	Phase 1: NCT02512237 Phase 1: NCT03255070	HER2+ advanced cancers
DHES0815A (anti-HER2/PBD-MA)	Phase 1: NCT03451162	HER2+ breast cancer
MEDI4276	Phase 1: NCT02576548	HER2+ advanced solid tumors
RC48	Phase 1b/2: NCT03052634 Phase 2: NCT03500380	HER2+ advanced breast cancer
SYD985 ([vic-]trastuzumab duocarmazine)	Phase 3: TULIP; NCT03262935	HER2+ unresectable locally advanced or metastatic breast cancer vs. physician's choice
XMT-1522 (TAK-522)	Phase 1: NCT02952729	HER2+ advanced breast cancer and other advanced tumors

Courtesy of Sara Hurvitz, MD

CDK4/6 inhibitor for HER2+/HR+ breast cancer: monarcHER STUDY DESIGN



Abbreviations: ABC = advanced breast cancer, HR+ = hormone receptor-positive, HER2(+) = human epidermal growth factor receptor-2 (positive), n = number of patients, PD = progressive disease, BID= twice daily, q21d= every 21 days, PFS = Progression Free Survival, ORR = Objective Response Rate, OS = Overall Survival, PRO = Patient Reported Outcomes, PK = pharmacokinetics

[a]Dosing per fulvestrant label

[b]Standard-of-care single-agent chemotherapy should include approved drug in breast cancer.

[c]investigator assessed

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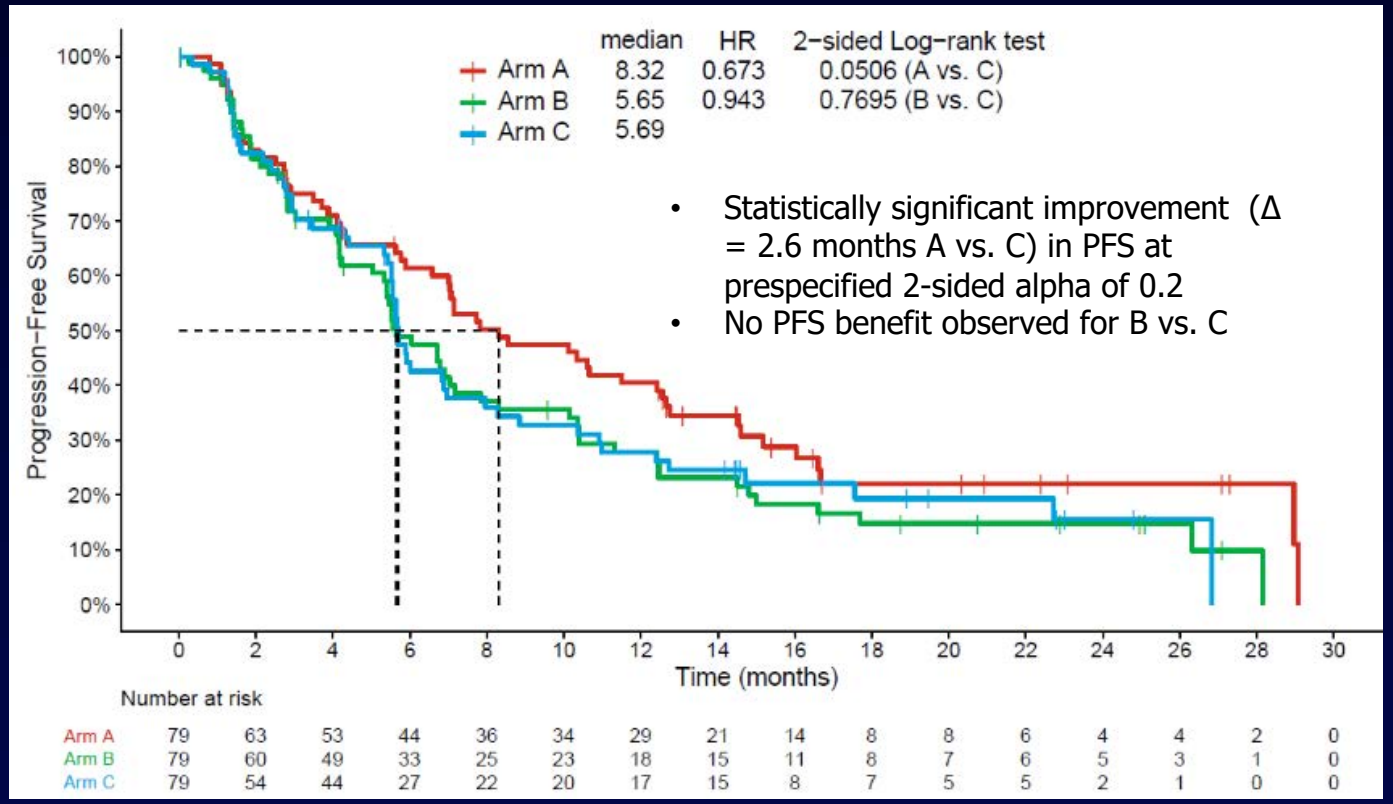
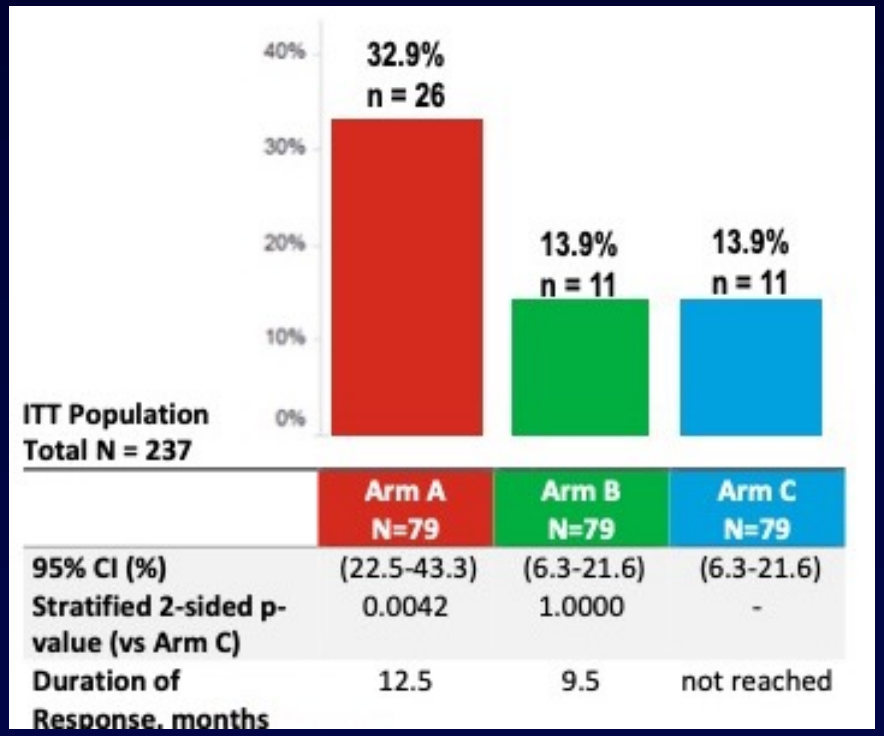
Phase II monarchHER: PFS and ORR



- Statistically significant improvement (Δ = 2.6 months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

OBJECTIVE RESPONSE RATE



	Arm A N=79	Arm B N=79	Arm C N=79
95% CI (%)	(22.5-43.3)	(6.3-21.6)	(6.3-21.6)
Stratified 2-sided p-value (vs Arm C)	0.0042	1.0000	-
Duration of Response, months	12.5	9.5	not reached

- Arm A= abemaciclib + trastuzumab + fulvestrant
- Arm B= abemaciclib + trastuzumab
- Arm C= trastuzumab + chemotherapy

Tolaney S, et al. *Ann Oncol.* 2019;30(suppl_5):v851-v934.

Courtesy of Sara Hurvitz, MD

Summary

- VERY exciting time for novel therapies to treat HER2+ metastatic breast cancer
- 3 new approvals in the last year (tucatinib, trastuzumab deruxtecan, neratinib)
- Many novel agents being evaluated:
  - Margetuximab may be next approval?
  - Other ADCs
  - Novel antibodies
  - CDK4/6 inhibitors
  - Immune therapy

Courtesy of Sara Hurvitz, MD

CASE 1: A patient with HER2-positive breast cancer who received trastuzumab deruxtecan

50 y.o. female diagnosed 2002 with stage III ER+ HER2+ BC, s/p TCH, lumpectomy with residual disease, tamoxifen. 2 years later metastases to spine. Treated with trastuzumab/endocrine therapy, lapatinib/trastuzumab/endocrine therapy; vinorelbine/trastuzumab/pertuzumab; T-DM1, went on HER2CLIMB trial of trastuzumab/capecitabine +/- tucatinib; I thought she was getting tucatinib because she had rash, SBO, colitis, dose reduced tucatinib (or placebo), ultimately taken off study for PD 14 mos after enrolling (Later found out she was on placebo arm!). Placed on study of trastuzumab deruxtecan 9/2018. Still on study with disease control (cycle 37 now). Tolerating well but significant hair thinning. Nausea much better than at beginning of study.

Courtesy of Sara Hurvitz, MD

CASE 2: A patient with HER2-positive breast cancer who received tucatinib (?)

65 yo woman diagnosed with right breast calcs 2015 s/p incisional biopsy showing DCIS, mastectomy revealing multifocal invasive ductal carcinoma (1,2,4,4,4,5 mm) from DCIS. T1a(m) N0(i-). ER 95%, PR neg, HER2 3+. Received APT regimen 2015-2016. Started AI 2016. Diagnosed with metastatic breast cancer 4 years later in 2020. Liver biopsy revealed metastatic ductal carcinoma ER (1-2+) 5-10%, PR 0%, HER2 2+ by IHC, positive by FISH (copy 11.45, ratio 4.98). Signed consent for a trial evaluating T-DM1 +/- tucatinib (unknown if she is on tucatinib). Tolerating GREAT but third cycle delayed 3 weeks due to grade 3 ALT/AST elevation. Post-cycle 3 scans showing disease shrinkage (near PR)

Courtesy of Sara Hurvitz, MD

CASE 3: A patient with HER2-positive breast cancer who received neratinib

61 yo female diagnosed with stage III ER/PR+ HER2+ left BC 1999 s/p ddAC-T, high dose chemo → ASCT, RT, tamoxifen. Four years later (2003) metastatic recurrence to lungs. ER+PR- HER2+. Treated with AI, trastuzumab/cape, tras/vinorelbine, gemcitabine/trastuzumab, fulvestrant/tras, CMF, T-DM1, trastuzumab/lapatinib, eribulin/tras, THP, Palbociclib/trastuzumab/letrozole, tucatinib/cape/tras compassionate use (brain mets), then at PD, took neratinib/taxane and response only lasted 3 months before progression—underscoring fact that there is likely cross-resistance with TKI's. Passed in 2020 after 17 years with MBC.

Courtesy of Sara Hurvitz, MD

Thank you!