Eline Naert / Dienst Medische Oncologie

Advanced HER2-positive breast cancer: Treatment algorithm anno 2022

BSMO meeting
04/02/2022

UZ GENT
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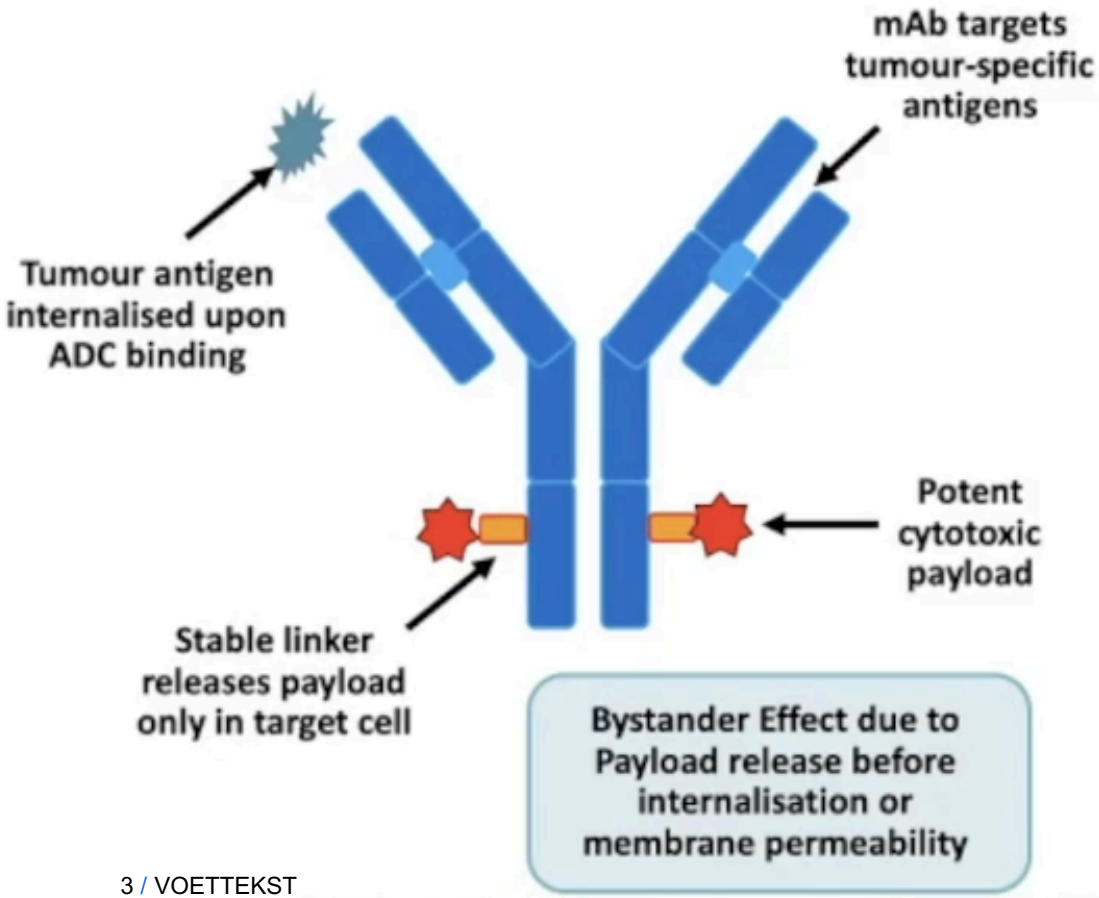
Content

- **The march of T-DXD and tucatinib**
- Who are the new kids on the block?
- Triple positive mBC
- Brain metastases
- Superresponders
- Guidelines and summary

HER2-targeting Antibody Drug Conjugates (ADCs)



ADC Attributes	T-DM1[3-5]	T-DXd[1-4,a]
Payload MoA	Anti-microtubule	Topoisomerase I inhibitor
Drug-to-antibody ratio	~3.5:1	~8:1
Tumor-selective cleavable linker?	No	Yes
Evidence of bystander anti-tumor effect?	No	Yes

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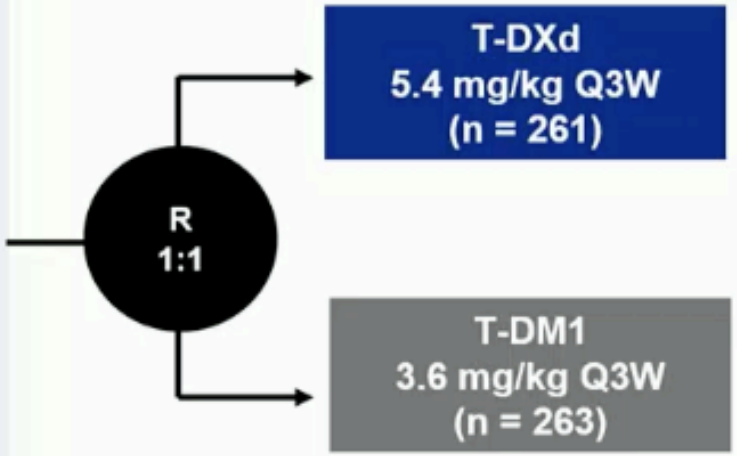
DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

An open-label, multicenter study (NCT03529110)

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

2021 ESMO congress

BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Ph3, phase 3; Q3W, every 3 weeks.
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

Prior Therapies

	T-DXd (n = 261)	T-DM1 (n = 263)
Prior Treatment for mBC, n (%)		
No	21 (8.0)	29 (11.0)
Yes	240 (92.0)	234 (89.0)
Prior lines of therapy in the metastatic setting (includes rapid progressors as one line of treatment)[a], n (%)		
0	2 (0.8)	3 (1.1)
1	130 (49.8)	123 (46.8)
2	56 (21.5)	65 (24.7)
3	35 (13.4)	35 (13.3)
4	15 (5.7)	19 (7.2)
≥5	23 (8.8)	18 (6.8)
Prior cancer therapy[b], %		
Trastuzumab	99.6	99.6
Pertuzumab	62.1	60.1
Other anti-HER2		
Anti-HER2 TKI	16.1	13.7
Other anti-HER2 antibody or ADC	0.8	1.1

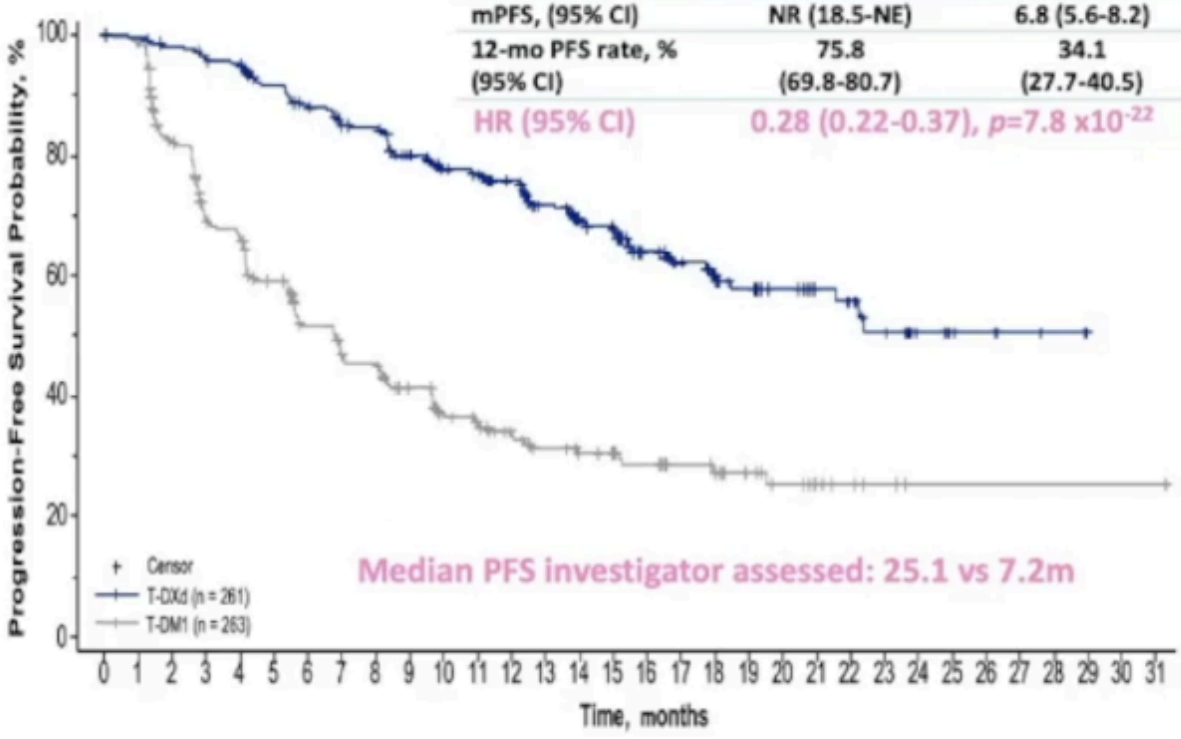
TKI, tyrosine-kinase inhibitor.
[a]Rapid progressors defined as progression within 6 mo of (neo)adjuvant therapy) or 12 mo if regimen contained pertuzumab. Line of therapy does not include endocrine therapy. [b]All patients received at least 1 prior cancer therapy. One patient with prior T-DM1 treatment was enrolled in error in the T-DXd arm.

San Antonio Breast Cancer Symposium®, December 7-10, 2021

T-DXd vs T-DM1: Progression-free Survival

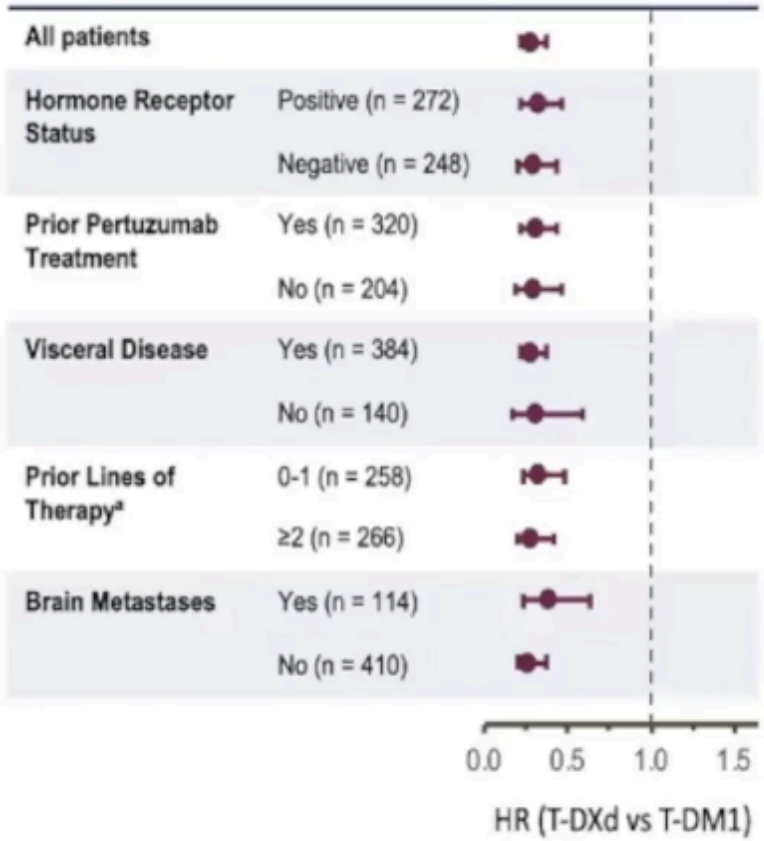
Primary Endpoint: PFS by BICR

	T-DXd	T-DM1
mPFS, (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37), p=7.8 x10^{-22}	



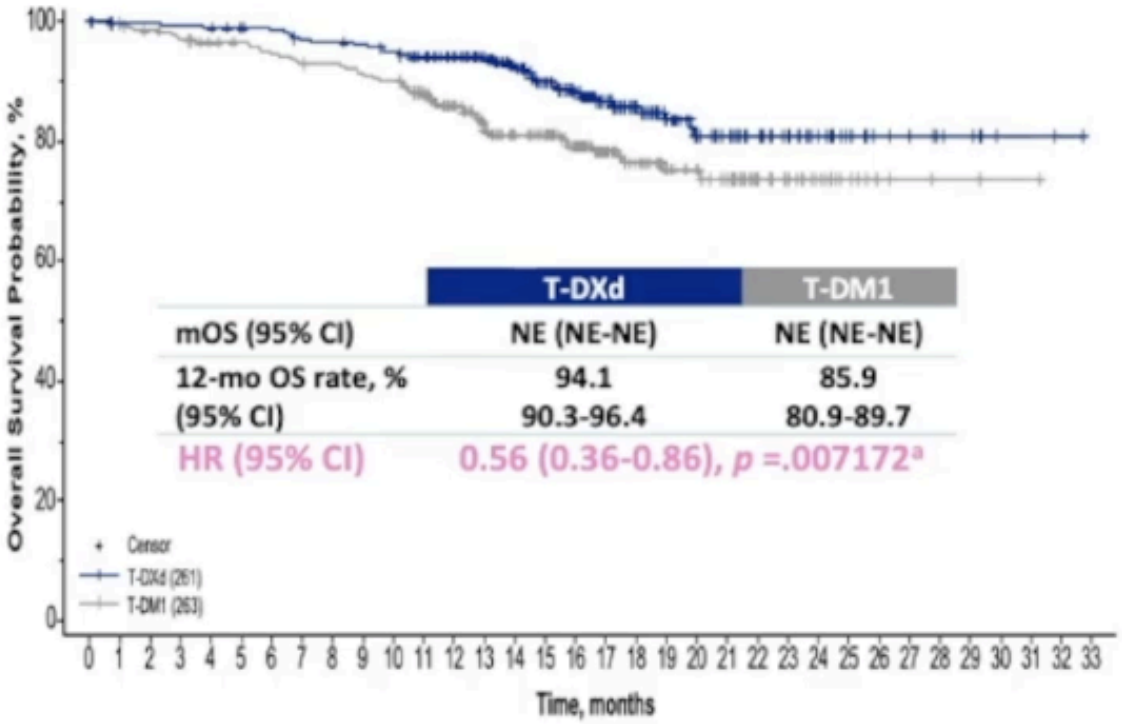
Median PFS investigator assessed: 25.1 vs 7.2m

PFS in Subgroups



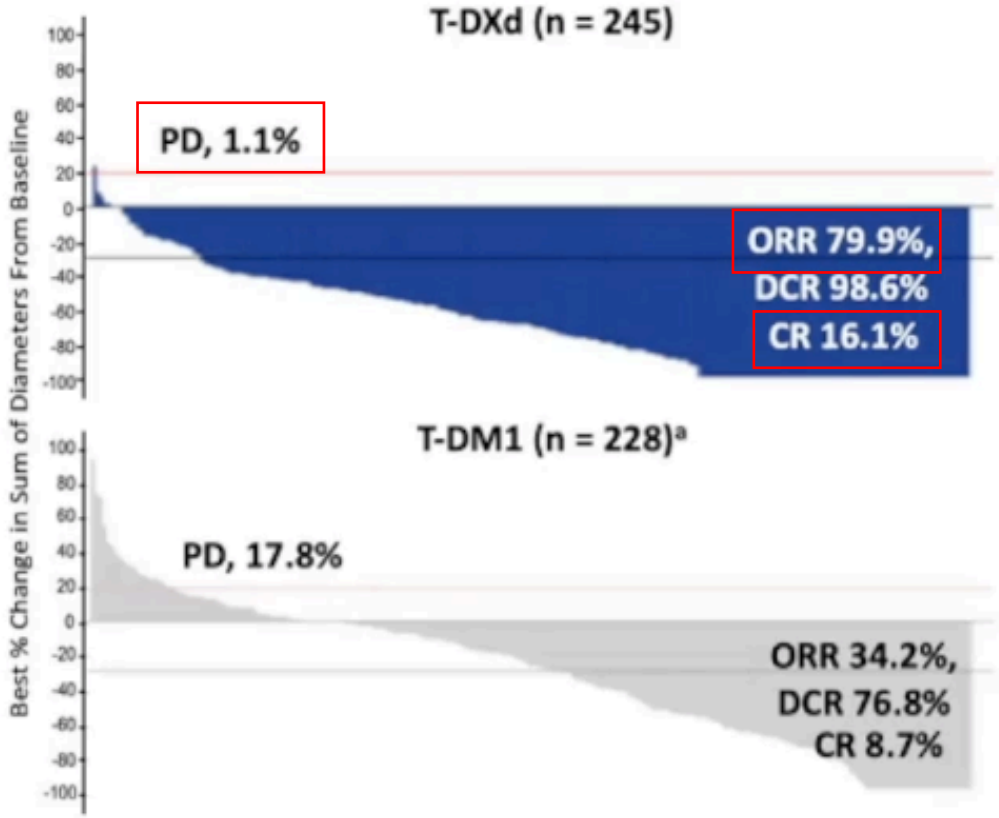
T-DXd vs T-DM1: Overall Survival & Response

Overall Survival



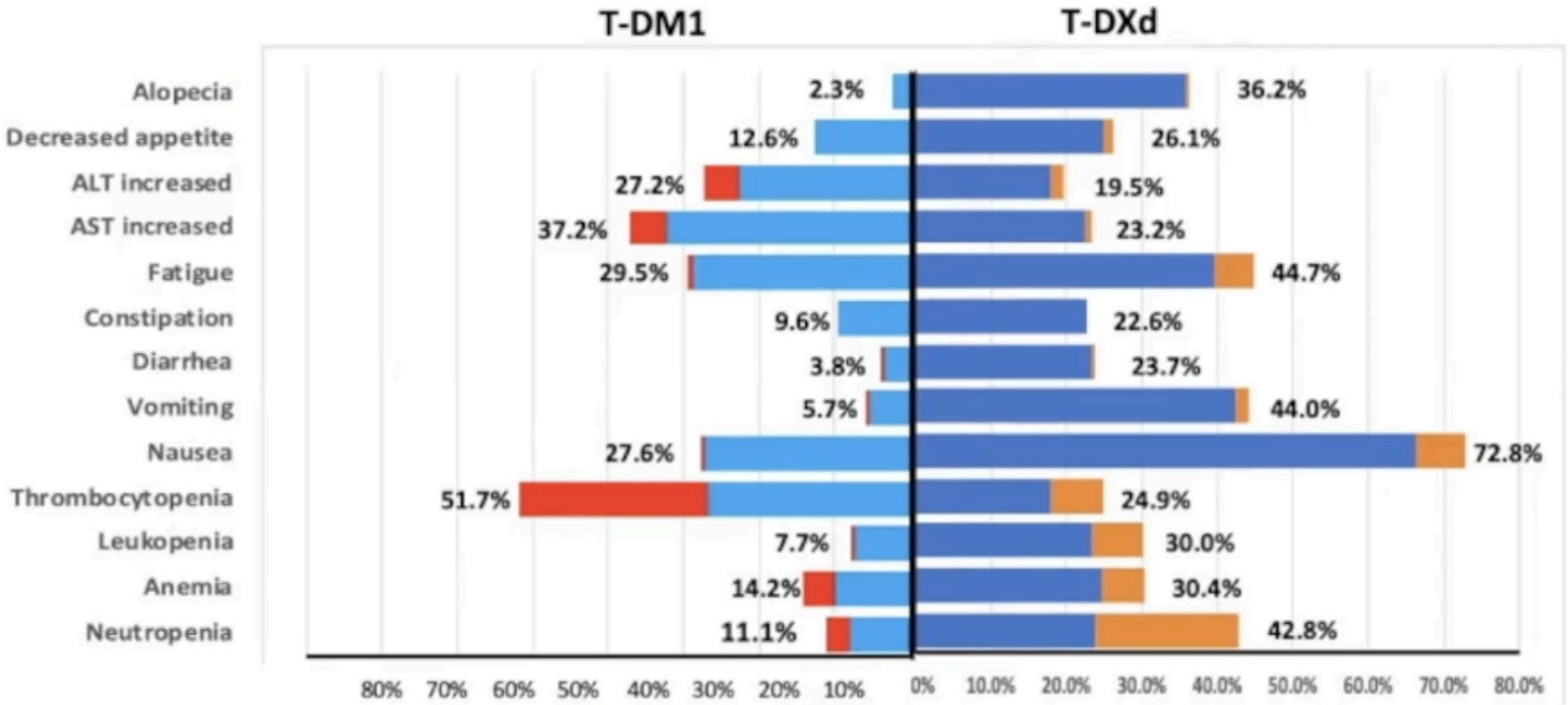
	T-DXd	T-DM1
mOS (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 90.3-96.4	85.9 80.9-89.7
HR (95% CI)	0.56 (0.36-0.86), *p* =.007172[a]	

Response Rate



Cortes, ESMO 2021

T-DXd versus T-DM1: Safety



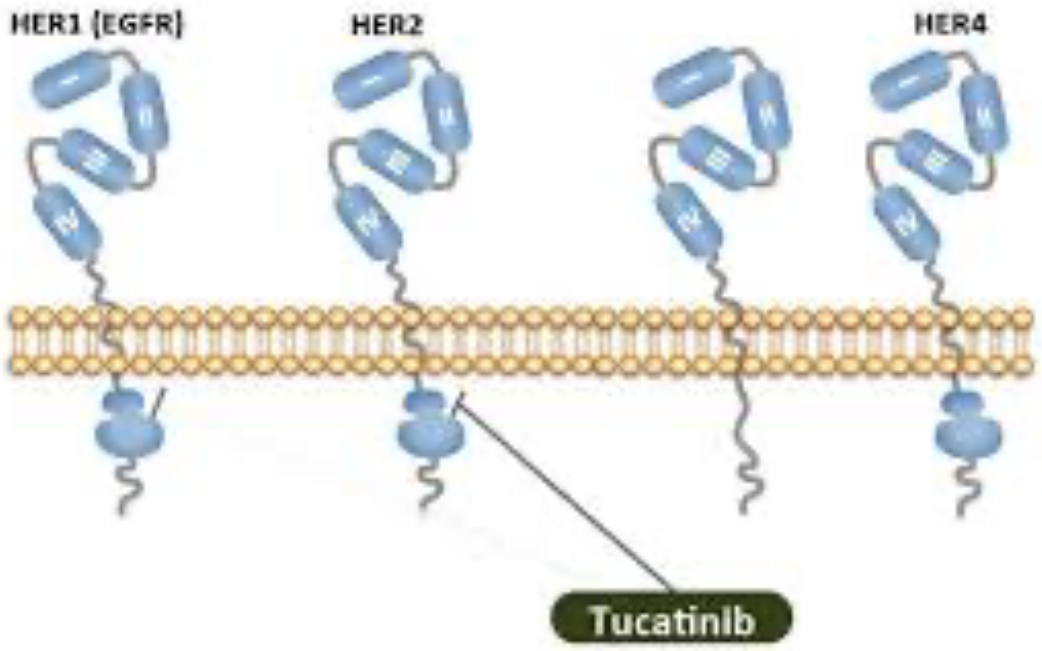
Adjudicated as drug-related ILD/pneumonitis[a], n (%)

	n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
	T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
	T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

No difference between Asia (10.9%) and non-Asia (10.0%) regions in ILD/pneumonitis rates, with no grade 4 or 5 events

Tucatinib is an oral TKI that is highly selective for the kinase domain of HER2 with minimal inhibition of EGFR.

- In cell signaling assays, tucatinib exhibits greater than >1000-fold selectivity for HER2 relative to EGFR in vitro.
- Inhibition of EGFR has not been shown to enhance efficacy of HER2 blockade.



Her 2 Climb: Design

- **Key Eligibility Criteria**
- HER2+ MBC
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- CNS metastases
  - Treated, stable
  - Untreated, not needing immediate local therapy
  - Previously treated, progressing

R 2:1

N = 410

Tucatinib + trastuzumab + capecitabine
(21-day cycle)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1,000 mg/m^2 PO BID (days 1-14)

N = 202

Placebo + trastuzumab + capecitabine
(21-day cycle)

Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1,000 mg/m^2 PO BID (days 1-14)

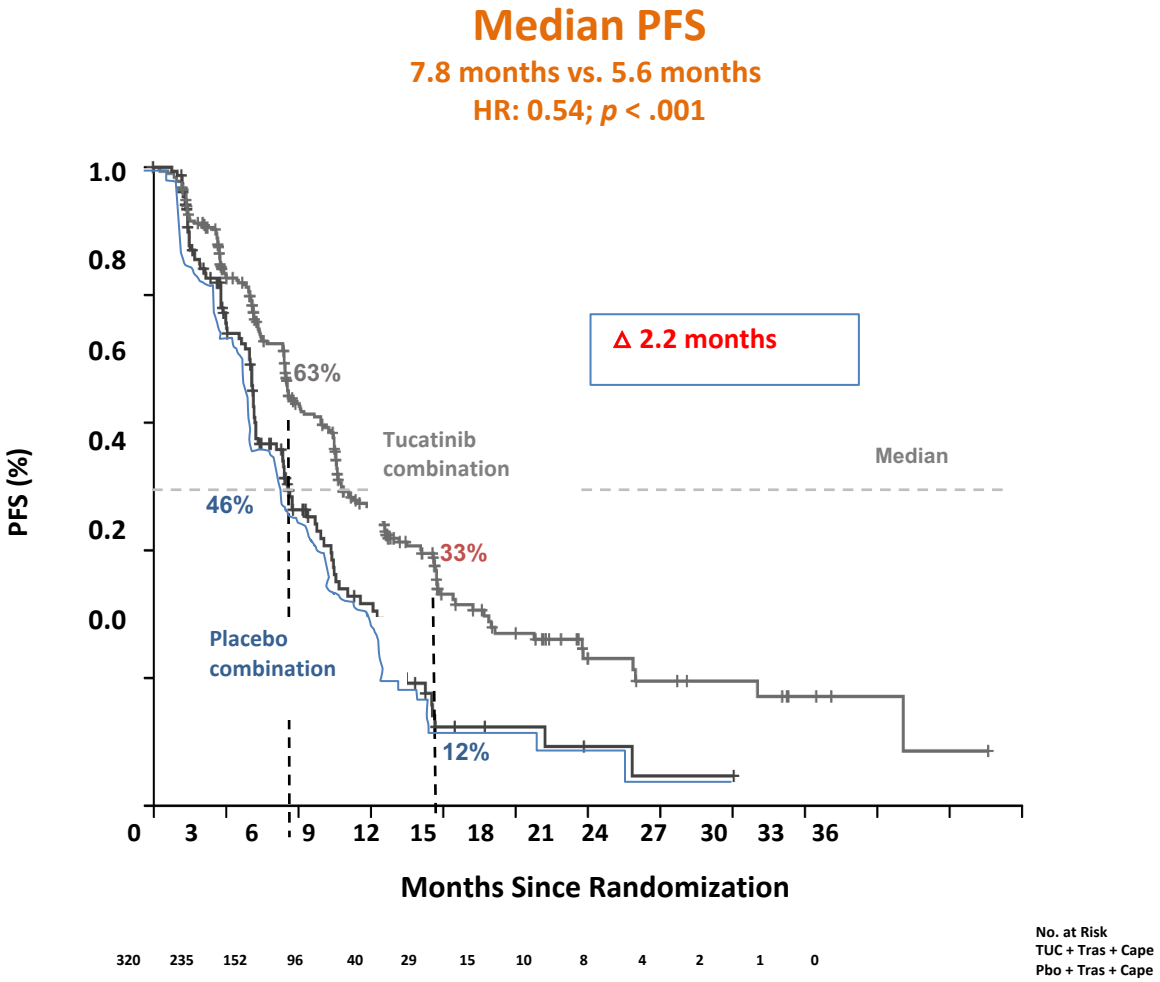
- Primary endpoint: investigator-assessed PFS (RECIST v 1.1)
- Key secondary endpoints: OS, investigator-assessed ORR (RECIST v 1.1)

Her 2 Climb: Patient characteristics

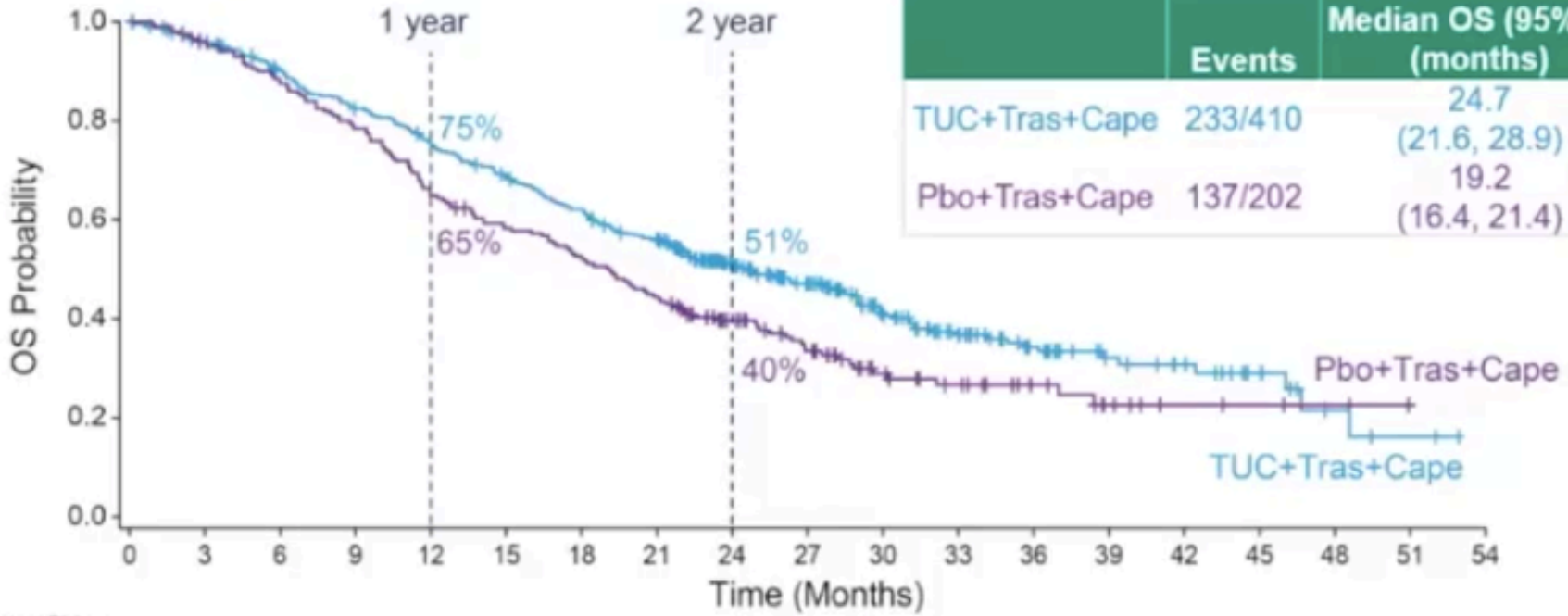
Characteristic, n (%)		Total Population, N=612	
		TUC+Tras+Cape n=410	Pbo+Tras+Cape n=202
Female		407 (99)	200 (99)
Age (years), median (range)		55.0 (22, 80)	54.0 (25, 82)
ECOG performance status	0	204 (50)	94 (47)
	1	206 (50)	108 (54)
Stage IV at initial diagnosis		143 (35)	77 (39)
Hormone receptor status	ER and/or PR-positive	243 (60)	127 (63)
	ER and PR-negative	161 (40)	75 (37)
Prior lines of therapy, median (range)	Overall	4.0 (2, 14)	4.0 (2,17)
	Metastatic setting	3.0 (1, 14)	3.0 (1, 13)
Presence/history of brain metastases		198 (48)	93 (46)
Treated, stable		118 (59.6)	55 (59.1)
Untreated		44 (22.2)	22 (23.7)
Treated, progressing		36 (18.2)	16 (17.2)

Baseline characteristics were balanced between endpoint populations and treatment arms

Her 2 Climb: Results



Overall Survival Benefit with Tucatinib Regimen Is Consistent with the Primary Analysis



	Events	Median OS (95% CI) (months)	HR (95% CI)	P Value
TUC+Tras+Cape	233/410	24.7 (21.6, 28.9)	0.73 (0.59, 0.90)	0.004
Pbo+Tras+Cape	137/202	19.2 (16.4, 21.4)		

Subjects at Risk

TUC+Cape+Trap	410	387	356	325	295	268	241	214	153	122	81	56	38	24	19	11	4	2	0
Pbo+Cape+Trap	202	191	174	156	129	114	103	87	63	47	28	21	14	8	4	3	2	0	0

Median overall study follow-up: 29.6 months

- OS benefit with tucatinib was consistent across prespecified patient subgroups.
- Sensitivity analyses accounting for cross-over showed consistent results with ITT analysis.

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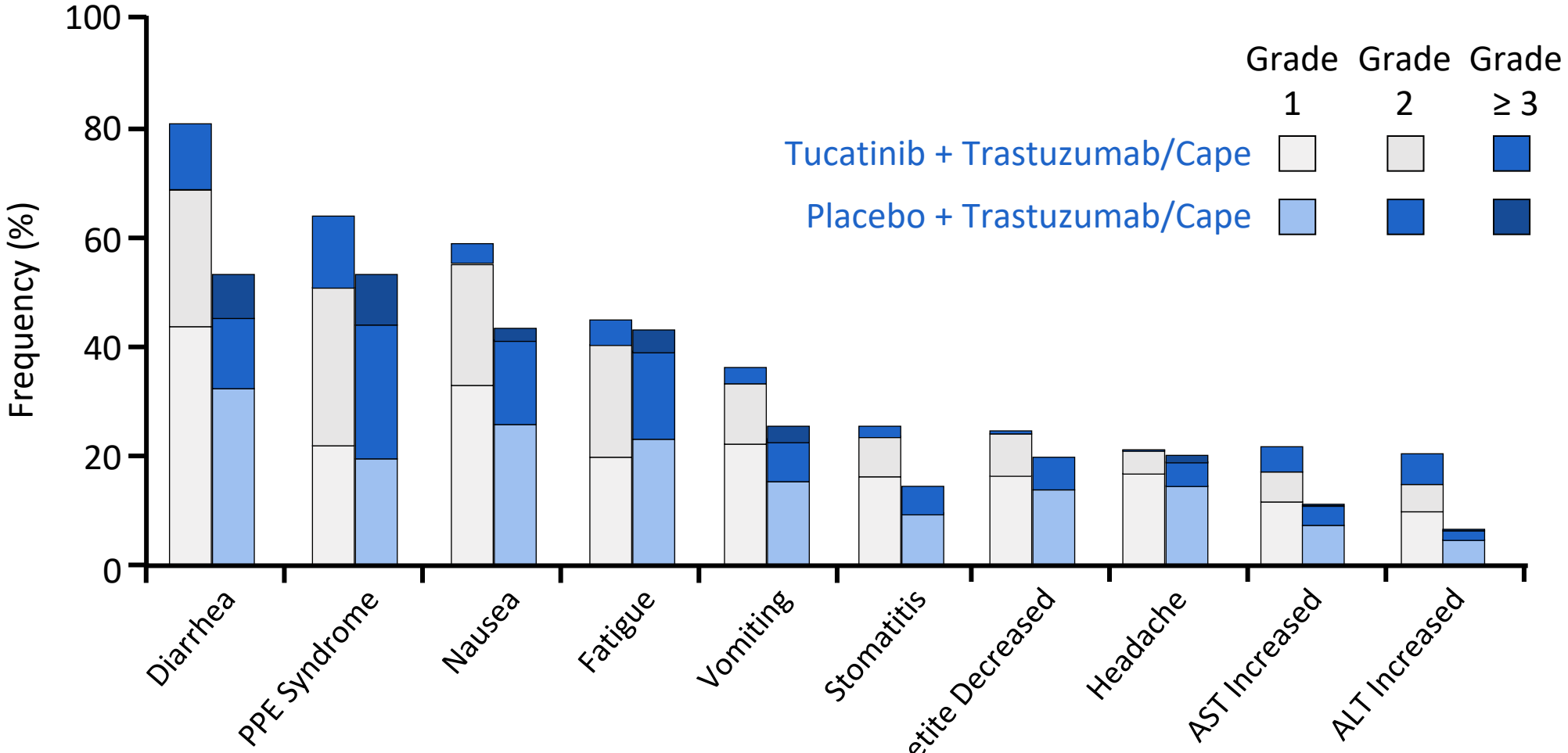
HER2CLIMB: Most Common Adverse Events



Treatment discontinuation tucatinib: 5,7%
Treatment discontinuation capecitabine: 9,8%

Slide credit: clinicaloptions.com

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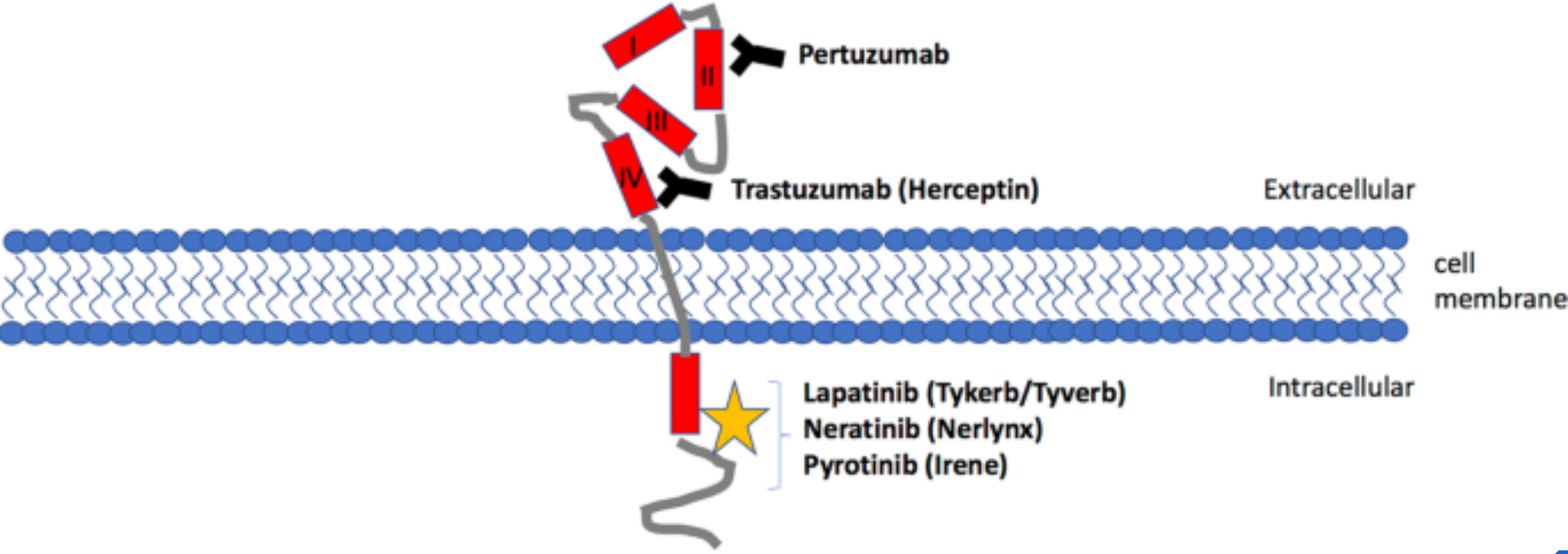
Pyrotinib


I
II
III
IV
Pertuzumab
Trastuzumab (Herceptin)
Extracellular
cell membrane
Intracellular
Lapatinib (Tykerb/Tyverb)
Neratinib (Nerlynx)
Pyrotinib (Irene)

New HER2-TKIs: Pyrotinib

- HER2+
- Prior Tr
  + Taxan
- Max 2 l

Stratific

- HR (pos
- 1/2L ver

1L 39

Binghe Xu, SABCS 2021

PHOEBE: Adverse events grade 3 and more

Events, n (%)	Pyrotinib arm (n=134)	Lapatinib arm (n=132)
Diarrhea	41 (30.6%)	11 (8.3%)
Hand-foot syndrome	22 (16.4%)	20 (15.2%)
Vomiting	8 (6.0%)	1 (0.8%)
White blood cell count decreased	8 (6.0%)	0
Neutrophil count decreased	7 (5.2%)	4 (3.0%)
Hypertriglyceridaemia	7 (5.2%)	4 (3.0%)
Hypokalaemia	4 (3.0%)	1 (0.8%)
Alanine aminotransferase increased	3 (2.2%)	1 (0.8%)
Lymphocyte count decreased	3 (2.2%)	0

Dose reduction: 47%
Treatment discontinuation: 1,5%
Treatment interruption: 61%

SYD 985

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SYD985 (HER2-ADC) in HER2+ MBC

TULIP Trial

- HER2+ MBC
- ≥2L or T-DM1 for MBC
- Stable brain metastases allowed

R 2:1

n = 291 → **SYD985 treatment 1.2 mg/kg IV Q3W**

n = 146 → **Physician's choice treatment (TPC)**

Stratification factors:

- Region (EU+Singapore vs N America)
- No of prior lines for MBC (1-2 vs >2)
- Prior pertuzumab (yes vs no)

Primary endpoint: PFS (BICR)

Physician's choice:

- Lapatinib + Capecitabine
- Trastuzumab + Capecitabine
- Trastuzumab + Vinorelbine
- Trastuzumab + Eribulin

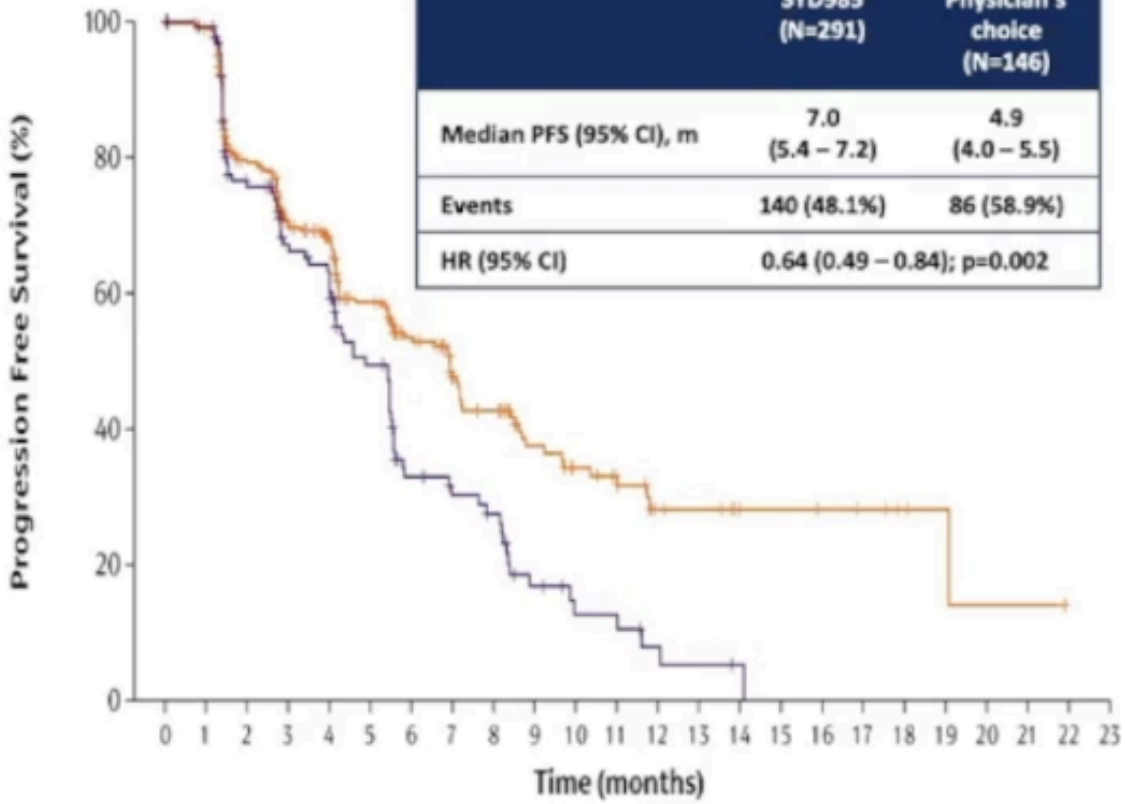
SYD985

ADC Attributes	SYD985
Payload MoA	Alkylater duocarmycin (DUBA)
Drug-to-antibody ratio	~2.4-2.8 : 1
Evidence of bystander anti-tumor effect?	Yes

Saura, ESMO 2021

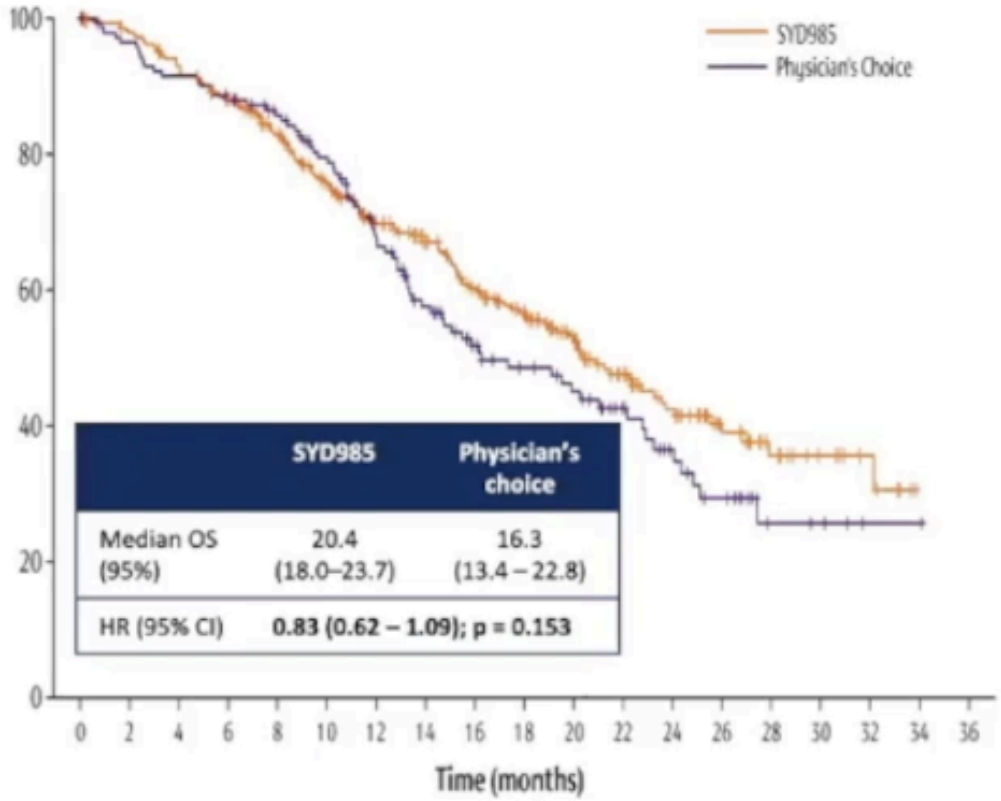
SYD985 (Tulip Trial): PFS & Overall Survival

Primary Endpoint: PFS by BICR



	SYD985 (N=291)	Physician's choice (N=146)
Median PFS (95% CI), m	7.0 (5.4 – 7.2)	4.9 (4.0 – 5.5)
Events	140 (48.1%)	86 (58.9%)
HR (95% CI)	0.64 (0.49 – 0.84); p=0.002	

Overall Survival



	SYD985	Physician's choice
Median OS (95%)	20.4 (18.0–23.7)	16.3 (13.4 – 22.8)
HR (95% CI)	0.83 (0.62 – 1.09); p = 0.153	

Saura, ESMO 2021

SYD985 (Tulip Trial): Safety

Eye toxicity: 78.1% SYD985 (TPC 29.2%)
- **Grade ≥ 3 for 21.2%**
- **Discontinuation 20.8%**
- **Dose modifications in 22.9%**

Risk mitigation strategy in trial:
Prophylactic lubricating eye drops, regular eye exams by ophthalmologist, G3+ keratitis stop treatment, G3 conjunctivitis delay treatment until reduced to G2

Number of patients with By Preferred Term	SYD985 (n=288)		Physician's choice (n=137)	
	All Grades	>=grade 3	All Grades	>=grade 3
At least one TEAE	278 (96.5%)	152 (52.8%)	132 (96.4%)	66 (48.2%)
Conjunctivitis	110 (38.2%)	16 (5.6%)	3 (2.2%)	0
Keratitis	110 (38.2%)	35 (12.2%)	11 (8.0%)	0
Fatigue	96 (33.3%)	9 (3.1%)	41 (29.9%)	2 (1.5%)
Dry eye	87 (30.2%)	12 (4.2%)	14 (10.2%)	0
Nausea	73 (25.3%)	3 (1.0%)	43 (31.4%)	0
Alopecia	62 (21.5%)	1 (0.3%)	16 (11.7%)	0
Decreased appetite	61 (21.2%)	0	15 (10.9%)	0
Diarrhea	60 (20.8%)	3 (1.0%)	49 (35.8%)	3 (2.2%)
Asthenia	58 (20.1%)	5 (1.7%)	23 (16.8%)	1 (0.7%)
Constipation	57 (19.8%)	0	24 (17.5%)	0
Lacrimation increased	53 (18.4%)	0	2 (1.5%)	0
Cough	48 (16.7%)	1 (0.3%)	14 (10.2%)	0
Vomiting	36 (12.5%)	1 (0.3%)	23 (16.8%)	1 (0.7%)
Neutropenia	31 (10.8%)	14 (4.9%)	33 (24.1%)	25 (18.2%)
Pneumonitis	19 (6.6%)	6 (2.1%)	0	0
Interstitial lung disease	3 (1.0%)	1 (0.3%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	2 (0.7%)	1 (0.3%)	32 (23.4%)	5 (3.6%)

Saura, ESMO 2021

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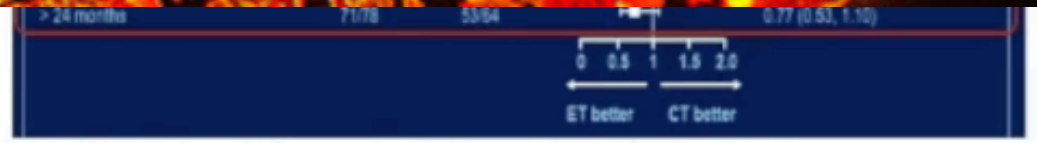
1L HER2 combination: Endocrine or Chemo backbone?

- HR+ H
- DFI >1

Stratifi
- Prior ET
- De novo



Zhong Yu Yuan, ASCO 2021

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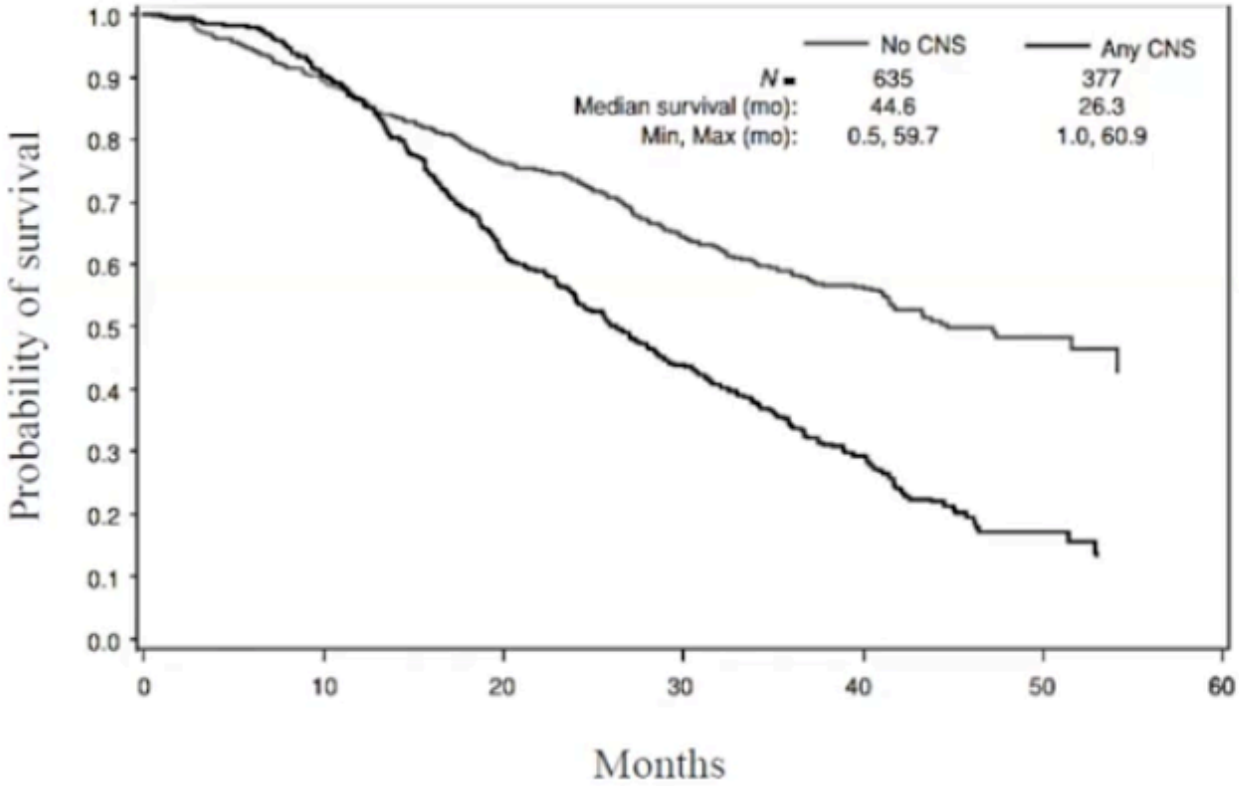
Brain Metastases -> Poor Prognosis

In the prospective "registHER" study, women with HER2+ MBC who developed CNS metastases had adverse outcomes.

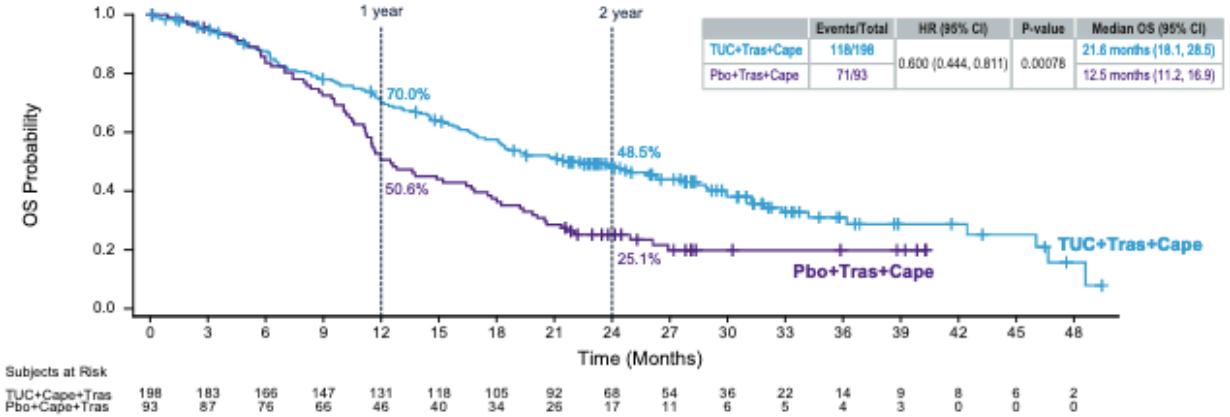
Kaplan-Meier survival cures for HER2+ MBC patients with and without BrM [Brufsky 2011]



Brufsky AM et al, Clin Cancer Res, 2011

Her 2 Climb – updated results

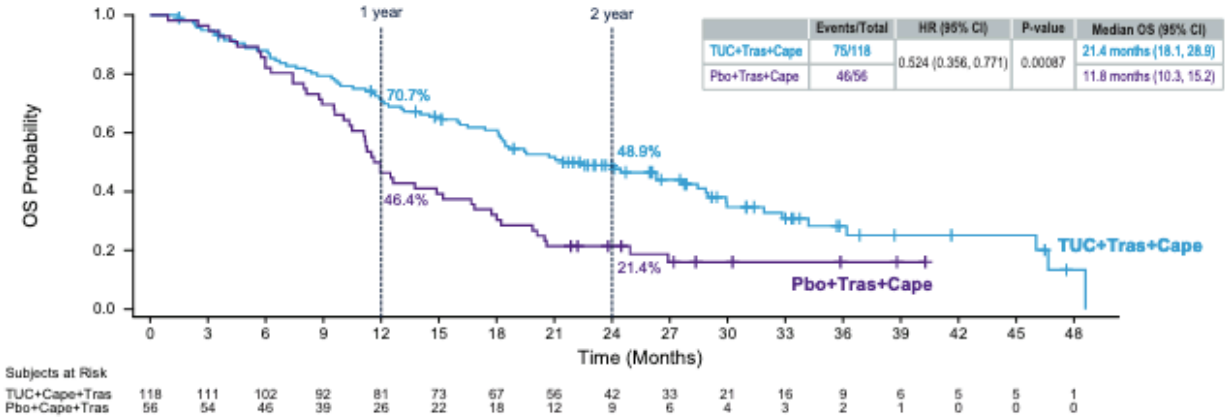
OS for All Patients with Brain Metastases



	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	118/198	0.600 (0.444, 0.811)	0.00078	21.6 months (18.1, 28.5)
Pbo+Tras+Cape	71/93			12.5 months (11.2, 16.9)

- OS benefit with tucatinib was improved with additional follow-up. Median OS was 9.1 months longer in the tucatinib arm compared with the control arm in all patients with brain metastases.
  - Previously reported, median OS was 6.1 months longer in tucatinib arm compared with control arm in all patients with brain metastases (18.1 vs 12.0 months)[4]

OS for Patients with Active Brain Metastases



	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	75/118	0.524 (0.356, 0.771)	0.00087	21.4 months (18.1, 28.9)
Pbo+Tras+Cape	46/56			11.8 months (10.3, 15.2)

- Median OS was 9.6 months longer in the tucatinib arm compared with the control arm in patients with active brain metastases.

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DESTINY-Breast 03:

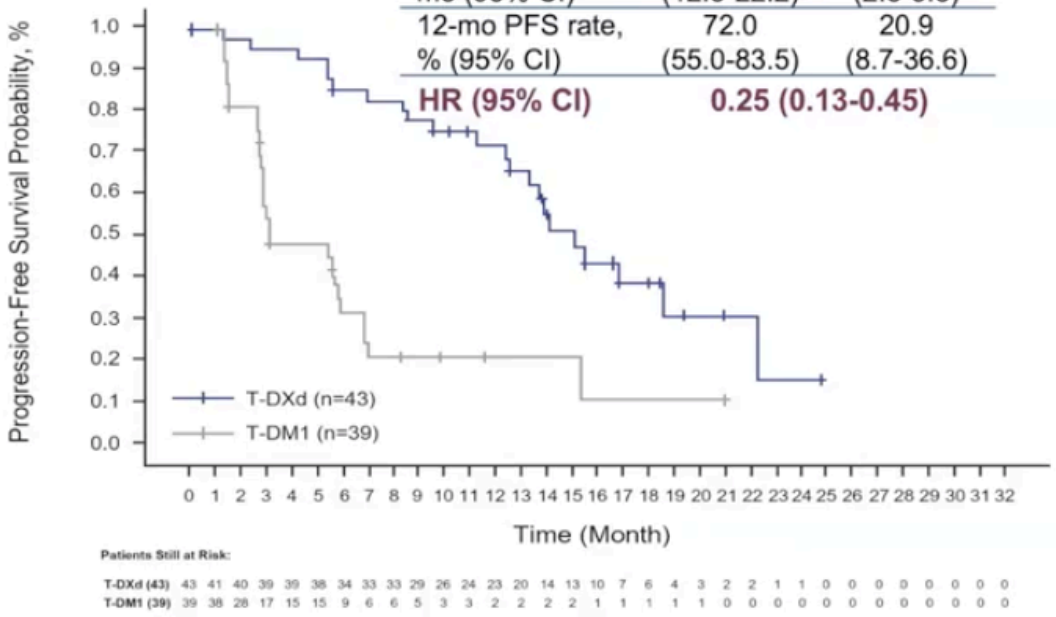
Baseline Characteristics and Prior Therapies

	T-DXd n = 261	T-DM1 n = 263
Age, median (range), years	54.3 (27.9-83.1)	54.2 (20.2-83.0)
Female, n (%)	260 (99.6)	262 (99.6)
Region, n (%)		
Europe	54 (20.7)	50 (19.0)
Asia	149 (57.1)	160 (60.8)
North America	17 (6.5)	17 (6.5)
Rest of world	41 (15.7)	36 (13.7)
HER2 status (IHC[a]), n (%)		
3+	234 (89.7)	232 (88.2)
2+ (ISH amplified)	25 (9.6)	30 (11.4)
1+ | Not evaluable	1 (0.4) | 1 (0.4)	0 | 1 (0.4)
ECOG PS, n (%)		
0 | 1	154 (59.0) | 106 (40.6)	175 (66.5) | 87 (33.1)
Hormone receptor, n (%)		
Positive | Negative	131 (50.2) | 130 (49.8)	134 (51.0) | 129 (49.0)
History of BM, n (%)		
Yes | No	62 (23.8) | 199 (76.2)	52 (19.8) | 211 (80.2)
BM at baseline,[b] n (%)		
Yes | No	43 (16.5) | 218 (83.5)	39 (14.8) | 224 (85.2)
Visceral disease, n (%)		
Yes | No	184 (70.5) | 77 (29.5)	185 (70.3) | 78 (29.7)
Prior treatment for mBC, n (%)	240 (92.0)	234 (89.0)
Prior lines of therapy in the metastatic setting,[c] n (%)		
0-1 | ≥2	132 (50.6) | 129 (49.4)	126 (47.9) | 137 (52.1)
Prior cancer therapy,[d] n (%)		
Trastuzumab	260 (99.6)	262 (99.6)
Pertuzumab	162 (62.1)	158 (60.1)

Destiny Breast 03

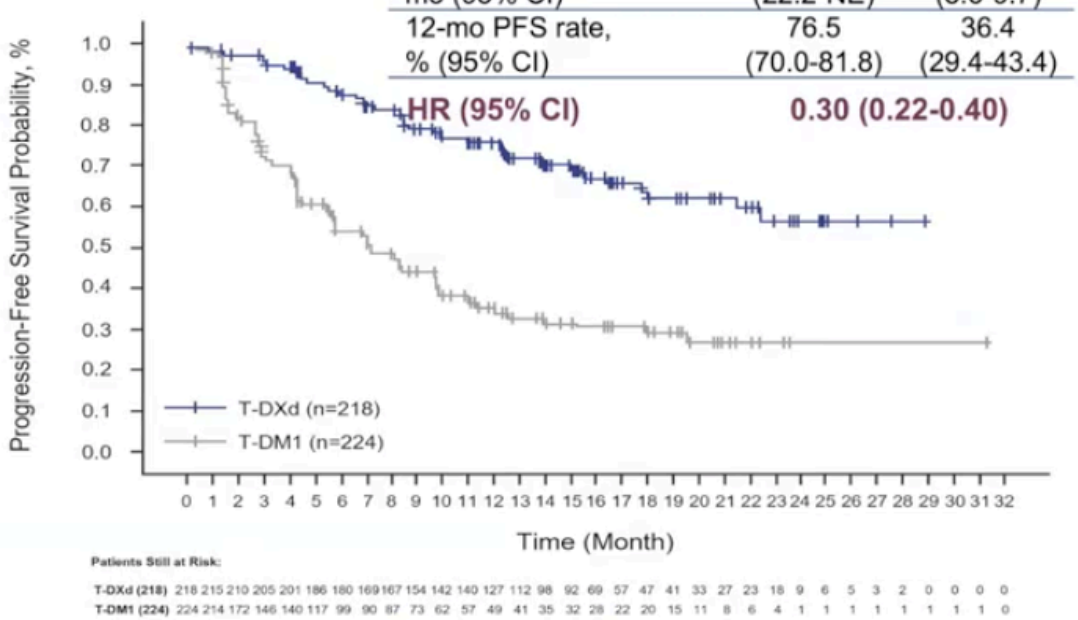
Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	15.0 (12.5-22.2)	3.0 (2.8-5.8)
12-mo PFS rate, % (95% CI)	72.0 (55.0-83.5)	20.9 (8.7-36.6)
HR (95% CI)	0.25 (0.13-0.45)	



No Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	NE (22.2-NE)	7.1 (5.6-9.7)
12-mo PFS rate, % (95% CI)	76.5 (70.0-81.8)	36.4 (29.4-43.4)
HR (95% CI)	0.30 (0.22-0.40)	



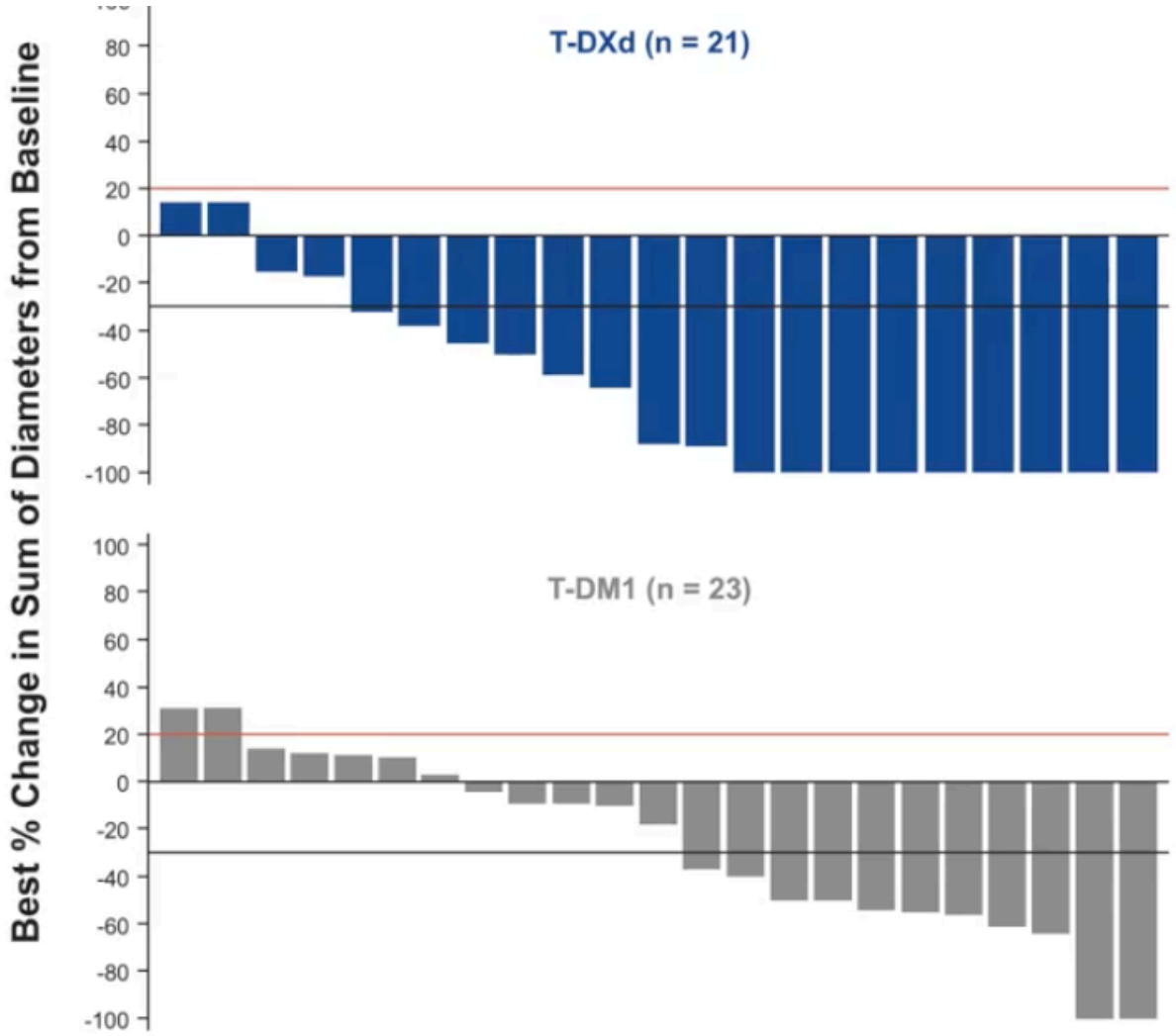
At data cutoff, in patients with BM at baseline, PD was observed:

- In 21/43 treated with T-DXd versus 27/39 with T-DM1
  - In the brain in 9/21 treated with T-DXd versus 11/27 with T-DM1

At data cutoff, in patients without BM at baseline, PD was observed:

- In 63/218 treated with T-DXd versus 128/224 with T-DM1
  - In the brain in 4/63 treated with T-DXd versus 1/128 with T-DM1

mPFS, median progression-free survival; PD, progressive disease; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

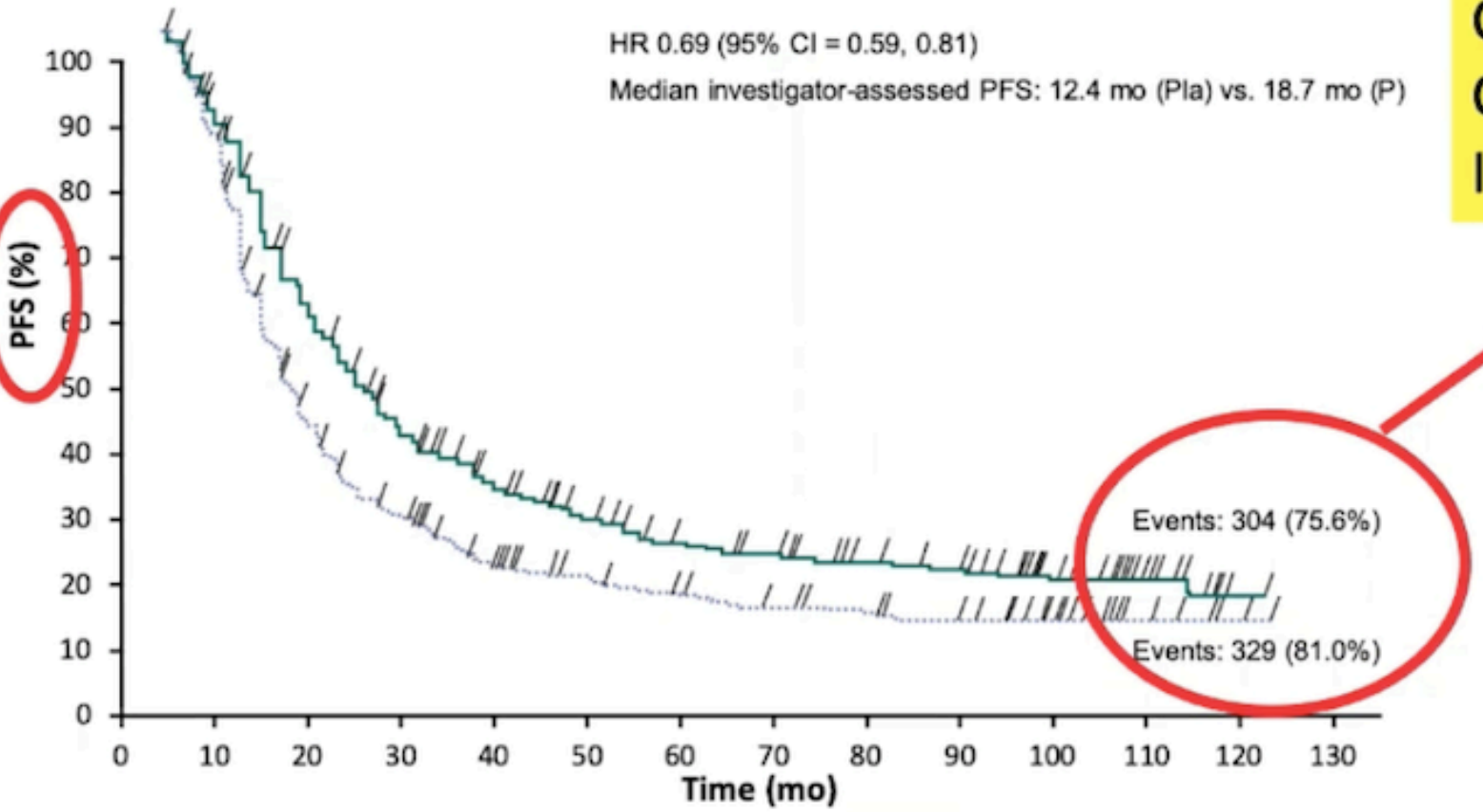


	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/Non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not Evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)
Subjects with Objective Response of CR or PR, n	23	12

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

Content

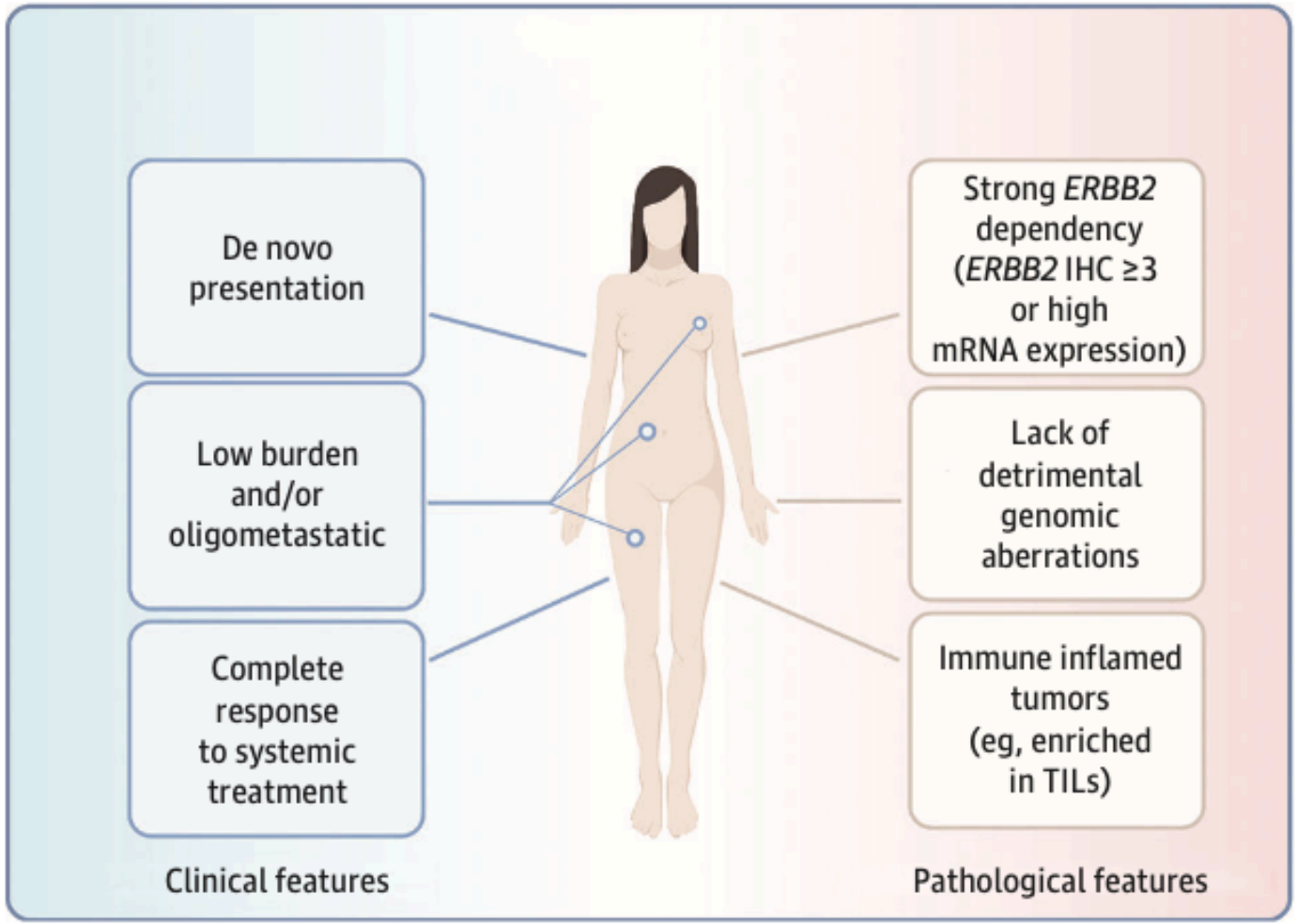
- The march of T-DxD and tucatinib
- Who are the new kids on the block?
- Triple positive mBC
- Brain metastases
- **Superresponders**
- Guidelines and summary



Are some of these patients cured?
Could they discontinue therapy?
Could we raise the tail even further?
Is it time to aim for cure?

Swain et al. *ASCO.* 2019.
Wong et al. *The Oncologist.* 2019.

Long-term responses



Content

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1st line

Trastuzumab + Pertuzumab + Taxane

Destiny Breast 09
Her2 Climb 05
NRG-BR004

2nd line

Trastuzumab Deruxtecan

Her2 Climb 04

3rd line

Tucatinib + Trastuzumab + Capecitabine	T-DM1

4th line

Tucatinib + Trastuzumab + Capecitabine	T-DM1

5th line

Neratinib + Capecitabine	Lapatinib + Capecitabine	Trastuzumab + chemotherapy	Margetuximab + chemotherapy	...

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[h]

HER2-Positive			
Setting	**Regimen**	**NCCN Category of Preference**	**NCCN Category of Evidence**
First line[i]	Pertuzumab + trastuzumab + docetaxel[k]	Preferred Regimen	1
	Pertuzumab + trastuzumab + paclitaxel[k]	Preferred Regimen	2A
Second line[j]	Fam-trastuzumab deruxtecan-nxki[j,l,m]	Preferred Regimen	1
	Ado-trastuzumab emtansine (T-DM1)[j]	Other Recommended Regimen	2A
Third line and beyond (optimal sequence is not known)	Tucatinib + trastuzumab + capecitabine[k,n]	Other Recommended Regimen[n]	1
	Trastuzumab + docetaxel or vinorelbine[k,o]	Other Recommended Regimen	2A
	Trastuzumab + paclitaxel ± carboplatin[k,o]	Other Recommended Regimen	2A
	Capecitabine + trastuzumab or lapatinib[k,o]	Other Recommended Regimen	2A
	Trastuzumab + lapatinib[k,o] (without cytotoxic therapy)	Other Recommended Regimen	2A
	Trastuzumab + other agents[k,o,p,q]	Other Recommended Regimen	2A
	Neratinib + capecitabine[o]	Other Recommended Regimen	2A
	Margetuximab-cmkb + chemotherapy[o] (capecitabine, eribulin, gemcitabine, or vinorelbine)	Other Recommended Regimen	2A
Additional targeted therapy options (See BINV-R)			

[j] Regimens may also be used as an option for third-line and beyond; the optimal sequence for third-line therapy and beyond is not known.

[k] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

[l] Fam-trastuzumab deruxtecan-nxki may be considered in the first-line setting as an option for select patients (ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens]).

[m] Fam-trastuzumab deruxtecan-nxki is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).

[n] Tucatinib + trastuzumab + capecitabine is preferred in patients with both systemic and CNS progression in the third-line setting and beyond; and it may be given in the second-line setting.

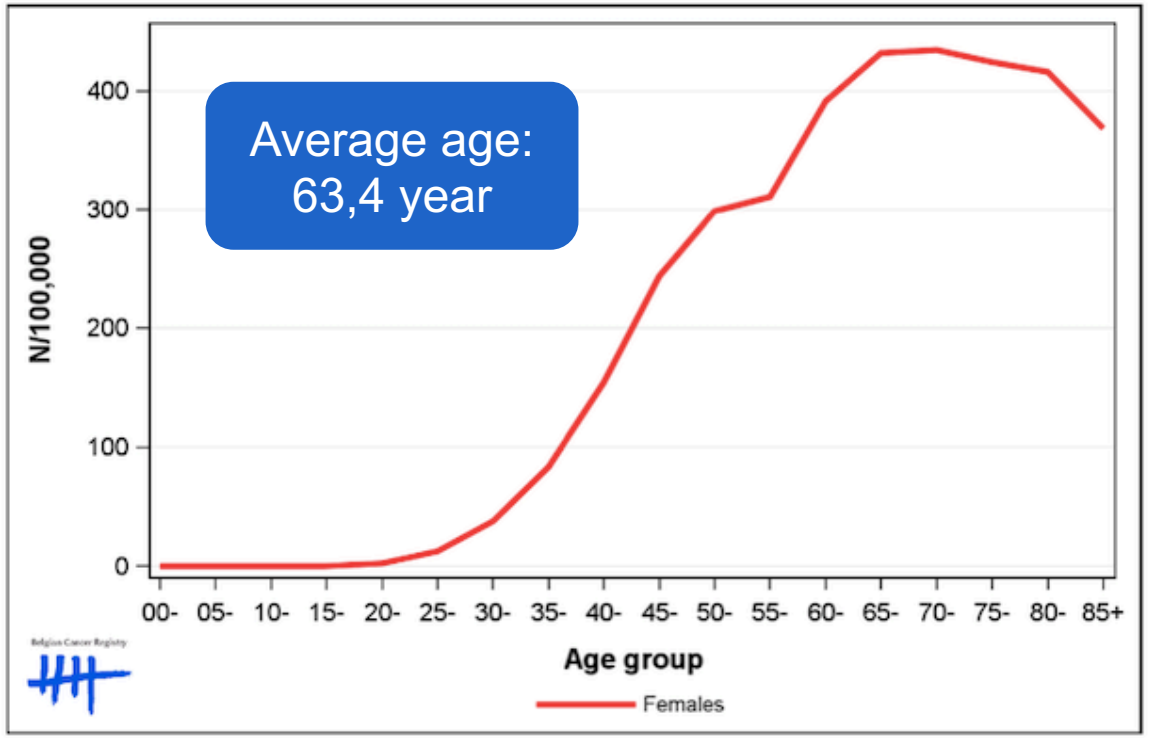
Pending questions…

1/ Should we screen every patient with brain MRIs?

2/ How should we position tucatinib and T-Dxd to each other?

	Tucatinib = Tukysa	Trastuzumab Deruxtecan = Enhertu
Phase	III	III
Trial name	Her 2 Climb	Destiny Breast 03
Population	N = 612 (max 82 y)	N = 524 (max 83 y)
Investigator arm	Tucatinib + capecitabine/T	Trastuzumab Deruxtecan
Comparator arm	Placebo + capecitabine/T	T-DM1
Median prior lines	3 (1-14)	1 (0-NA)
Prior T+P	100%	62%
CNS effect?	Yes	Yes
ORR benefit?	Yes	Yes
PFS benefit?	Yes	Yes
OS benefit?	Yes	NA
AEs of interest	Diarrhea Grade 3 13%	ILD, alopecia
FDA approval	04/2020	12/2019
EMA approval	02/2021	01/2021

3/ What about th



	Tucatinib = Tukysa	Trastuzumab Deruxtecan = Enhertu	Neratini = Nerlyn			
Phase	III	III	III			
Trial name	Her 2 Climb	Destiny Breast 03	NALA			
Population	N = 612	N = 524	N = 621	N = 536	N = 267	N = 437
Median age (max)	55 (82)	54 (83)	55 (63)	55 (86)	50 (69)	56 (84)
Investigator arm	Tucatinib + capecitabine/T	Trastuzumab Deruxtecan	Neratinib + capecitabine	Margetuximab + chemo	Pyrotinib + capecitabine	SYD 985
Comparator arm	Placebo + capecitabine/T	T-DM1	Lapatinib + capecitabine	Trastuzumab + chemo	Lapatinib + capecitabine	TPC
AEs of interest	Diarrhea Grade 3 13%	ILD, alopecia	Diarrhea Grade 3 24%	IRR	Diarrhea Grade 3 31%, HFS	Conjunctivitis/ keratitis

Take home messages HER2+ mBC

1/ T-DxD is the new 2nd line SOC

2/ Trastuzumab + ET in 1st line for triple + mBC
is a reasonable alternative to trastuzumab + chemo in patients that are not candidates for chemotherapy

3/ T-DxD and tucatinib are both active against brain metastases

4/ mOS reaching 57 months in the latest update of the CLEOPATRA trial
Acknowledgement of a subset of patients with an extremely good prognosis!!

NAERT ELINE
Adjunct Kliniekhoofd
Medische Oncologie
Eline.naert@uzgent.be

Universitair Ziekenhuis Gent
C. Heymanslaan 10 | B 9000 Gent
T +32 (0)9 332 21 11
E info@uzgent.be

www.uzgent.be
Volg ons op

UZ GENT
UNIVERSITEIT GENT