San Antonio Breast Cancer Symposium 2022

TRIO-US B-12 TALENT: Neoadjuvant trastuzumab deruxtecan (T-DXd) with or without anastrozole for HER2-low, HR+ early-stage breast cancer

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Disclosures

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Sara A. Hurvitz	Stock and Other Ownership Interests	Ideal Implant (spouse)
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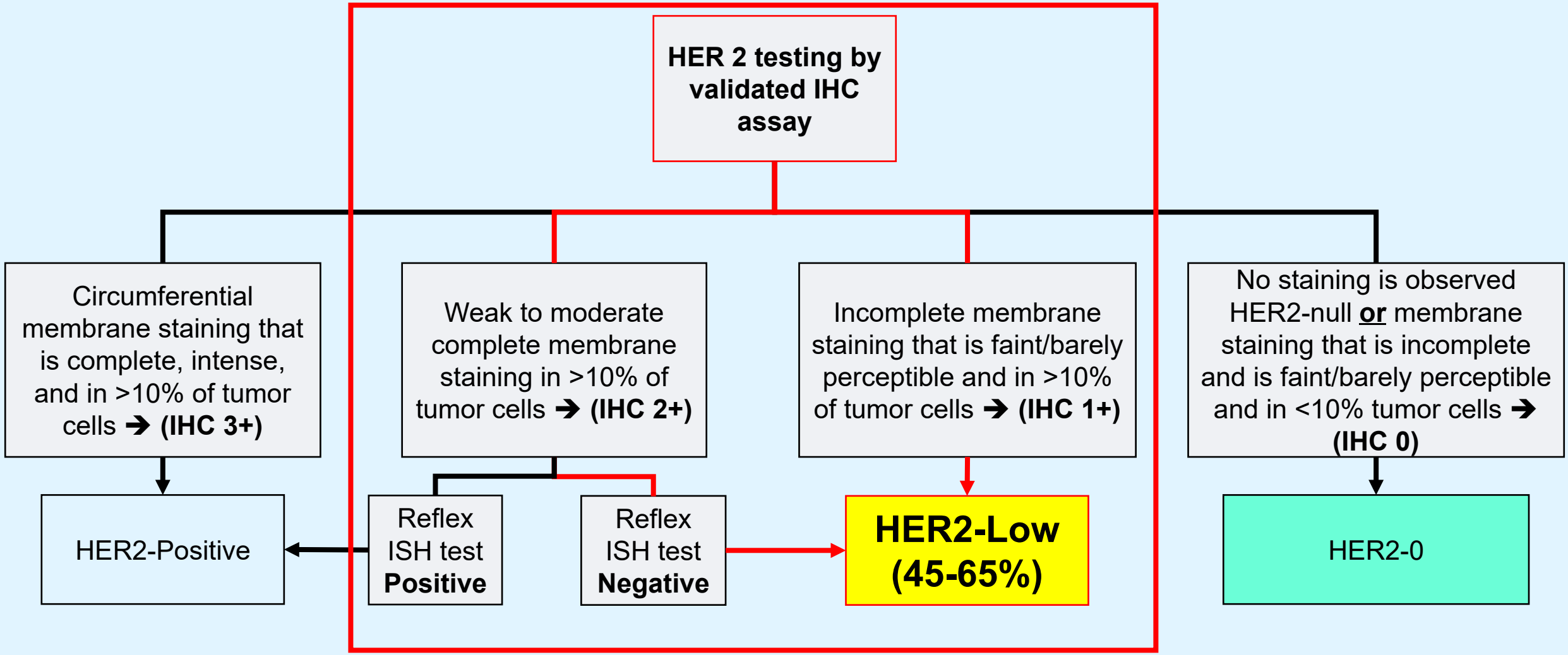
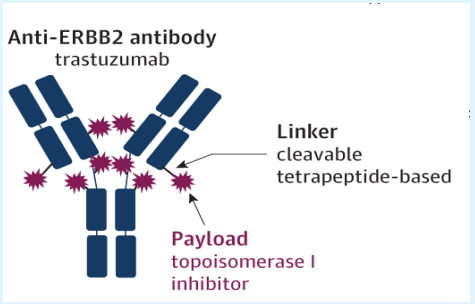
HER2-Low Breast Cancer: Current Definition (operational)

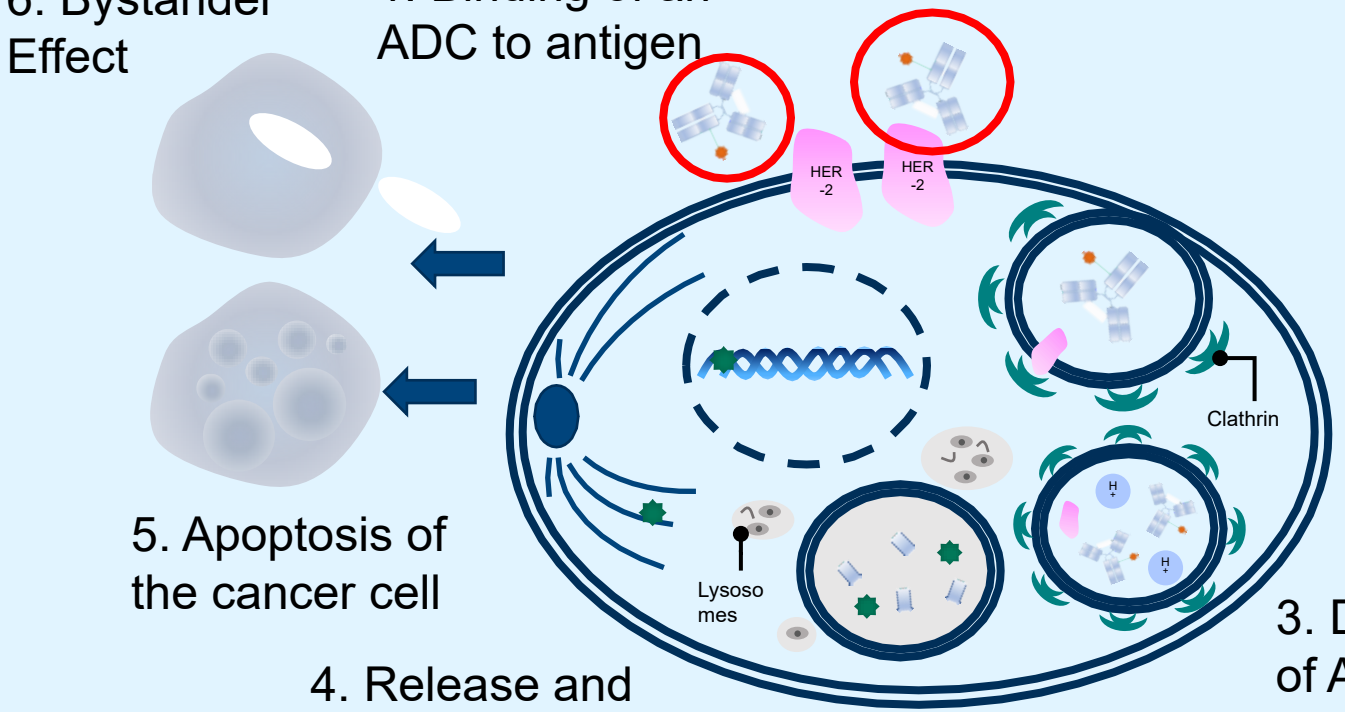


Adapted from: Prat A et al. JAMA Oncol. 2022

Antibody-Drug Conjugates (ADCs): Selective Delivery of Toxic Payload

Trastuzumab Deruxtecan (T-DXd)





Adapted from: Prat A et al. JAMA Oncol. 2022;
Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

HER2-Low Breast Cancer: Trastuzumab Deruxtecan (T-DXd)

- T-DXd has demonstrated impressive efficacy in metastatic HER2-low breast cancer [1], however, efficacy in localized HER2 low breast cancer not known
- Neoadjuvant anthracycline-taxane based combination chemotherapy is often utilized to treat high-risk localized Hormone Receptor positive (HR+) breast cancer, however, it is associated with:
  - pathologic complete response rates (5-8%) [2], slightly lower in HER2 low [3,4]
  - radiological response rate (~ 50%) [2]
  - dose reductions and/or interruptions (25-40%) [2,5]
  - significant toxicity (myelosuppression, neuropathy, cardiomyopathy, leukemia risk) [2,5]

- We designed an investigator-initiated clinical trial to evaluate efficacy of T-DXd for patients with localized HR+/HER2-low breast cancer
- Given the cross-talk between ER and HER2, we also evaluated whether addition of endocrine therapy would improve efficacy of T-DXd in this setting

[4]Modi S et al. NEJM 2022, [2]Spring L et al. JAMA Oncol. 2016; [3]Denkert C et al. Lancet Oncol 2021; [4]Tarantino P et al. JAMA Oncol ; [5]Cottu P et al. Ann Oncol. 2018

TRIO-US B-12 (TALENT): Study Design

Study Population:
- Hormone Receptor +
- HER2-low (by local and/or central review)
- Stage II-III operable
- Men or Pre-/Post-menopausal women

stratified by HER2 expression level (1+ or 2+ by IHC) and menopausal status (pre or post)

Arm A (N=29): T-DXd 5.4mg/kg

Treatment: 6 or 8 cycles* + EOT

Arm B (N=29): T-DXd 5.4mg/kg + anastrozole (+GnRH analog for men/premenopausal women)

Surgery**

**After surgery, adjuvant therapy as per discretion of treating provider.

Tissue acquisition from archival tissue or biopsy at baseline and biopsy between C1D17-C1D21, and tissue at time of surgical resection

All tissue collected for study: pathology centrally reviewed

* Originally, 6 cycles of treatment were given but in 02/2022, an amendment increased the number of treatment cycles from 6 to 8 cycles

Study Objectives & Statistical Considerations

- Primary Objective:
  - Evaluate pathologic complete response (pCR) rate in breast and lymph nodes (ypT0/is ypTN0; residual cancer burden index, RCBi = 0)

- Secondary Objectives:
  - Objective response rate
  - Tumor biomarkers including change in HER2
  - Safety

- Simon's minimax two-stage study design:
  - 58 participants randomly assigned 1:1 to one of two treatment arms
  - no formal statistical comparison between the arms
  - pCR ≤ 5% as statistical benchmark

Consort Diagram

Enrollment from 09/2020 – 10/2022

Assessed for eligibility (N=69)

- Excluded (N=11)
  - Ineligible (N=7)
  - Declined to participate (N=4)

Randomized (N=58)

Randomized to Arm A (N=29)

- Completed 6 cycles (N=14)
- Completed 8 cycles (N=7)
- Receiving therapy (N=4)
- Off study prior to completing protocol-specified therapy (N=4) [A]

Randomized to Arm B (N=29)

- Completed 6 cycles (N=13)
- Completed 8 cycles (N=8)
- Receiving therapy (N=5)
- Off study prior to completing protocol-specified therapy (N=3) [B]

[A] 2 pts withdrew consent,1 pt expired (death due to myocardial infarction after severe GI toxicity), and 1 met discontinuation criteria (Gr. 4 hypokalemia)
[B] 3 pts met discontinuation criteria (1 Gr. 4 hypokalemia, 1 small bowel obstruction leading to dose hold for > 49 days, and 1 progressive disease)

Baseline Characteristics

Participant Characteristics	Treatment Arm	
	Arm A (N=29)	Arm B (N=29)
Median Age (Range)	59 (33 - 87)	55 (32 - 83)
Menopausal Status		
Post- (2 men in Arm A)	17 (60.7%)	17 (58.6%)
Baseline HER2 Expression (from Central Review)*		
0	2 (6.9%)	2 (6.9%)
1+	22 (75.9%)	25 (86.2%)
2+	4 (13.8%)	2 (6.9%)
1+ & 2+**	1 (3.4%)	0 (0.0%)
Histology		
Invasive Ductal	25 (86.2%)	26 (89.7%)
Invasive Lobular	4 (13.8%)	3 (10.3%)***
Baseline Hormone Receptor Status		
ER+ and PR+	24 (82.8%)	26 (89.7%)
Lymph node Status		
Node positive	15 (51.7%)	16 (55.2%)
Stage		
IIA	8 (27.6%)	11 (37.9%)
IIB	13 (44.8%)	15 (51.7%)
IIIA	7 (24.1%)	3 (10.3%)
IIIB	1 (3.4%)	0 (0.0%)

* Patients were eligible if HER2 IHC was 1+ or 2+ by local **or** central review **1 multicentric lesion ***1 mixed ductal/lobular

Baseline Characteristics

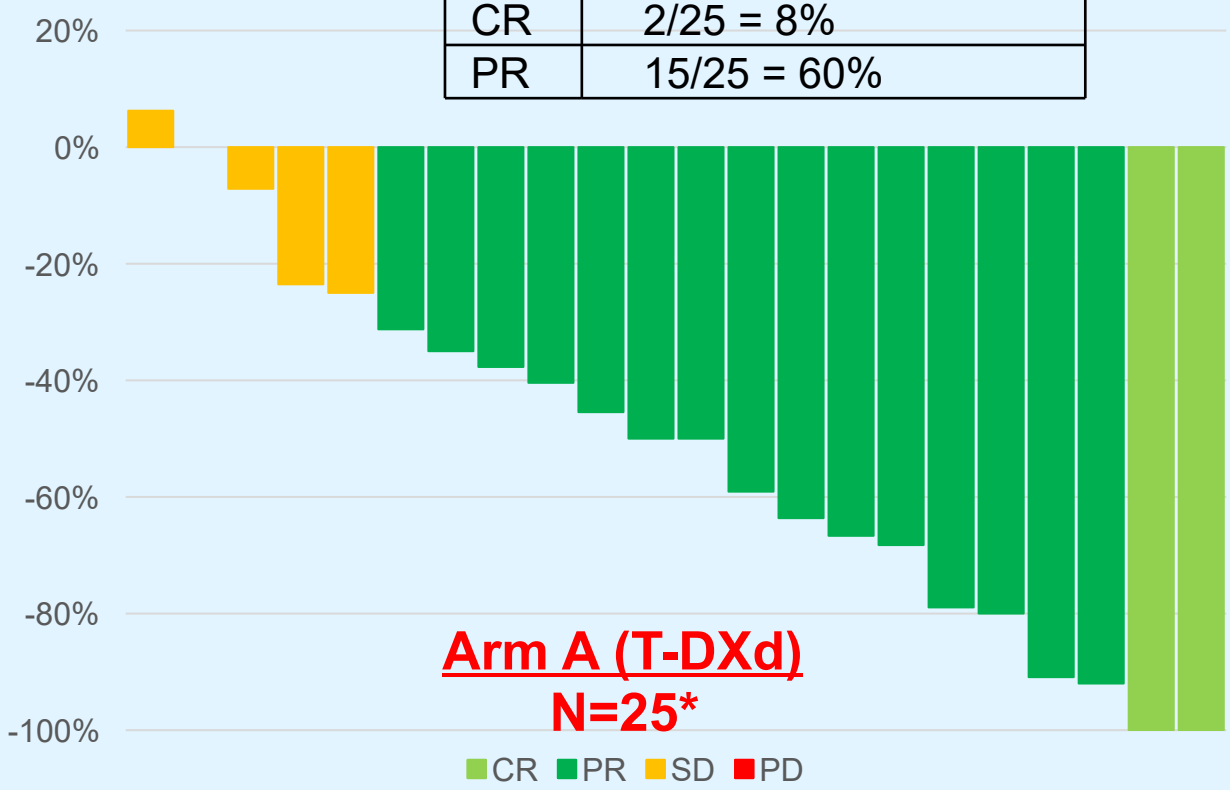
Participant Characteristics	Treatment Arm	
	Arm A (N=29)	Arm B (N=29)
Baseline Ki67 Scores (Central Review)		
<10%	1 (3.4%)	0 (0.0%)
≥10% and <30%	12 (41.4%)	10 (34.5%)
≥30%	16 (55.2%)	19 (65.5%)
Tumor Grade		
Grade 1	4 (13.8%)	1 (3.4%)
Grade 2	14 (48.3%)	16 (55.2%)
Grade 3	11 (37.9%) [A]	11 (37.9%)[B]
Not reported	0 (0.0%)	1 (3.4%)

4 patients had HER2 IHC 1+ by local assessment which was determined as IHC 0 by central assessment

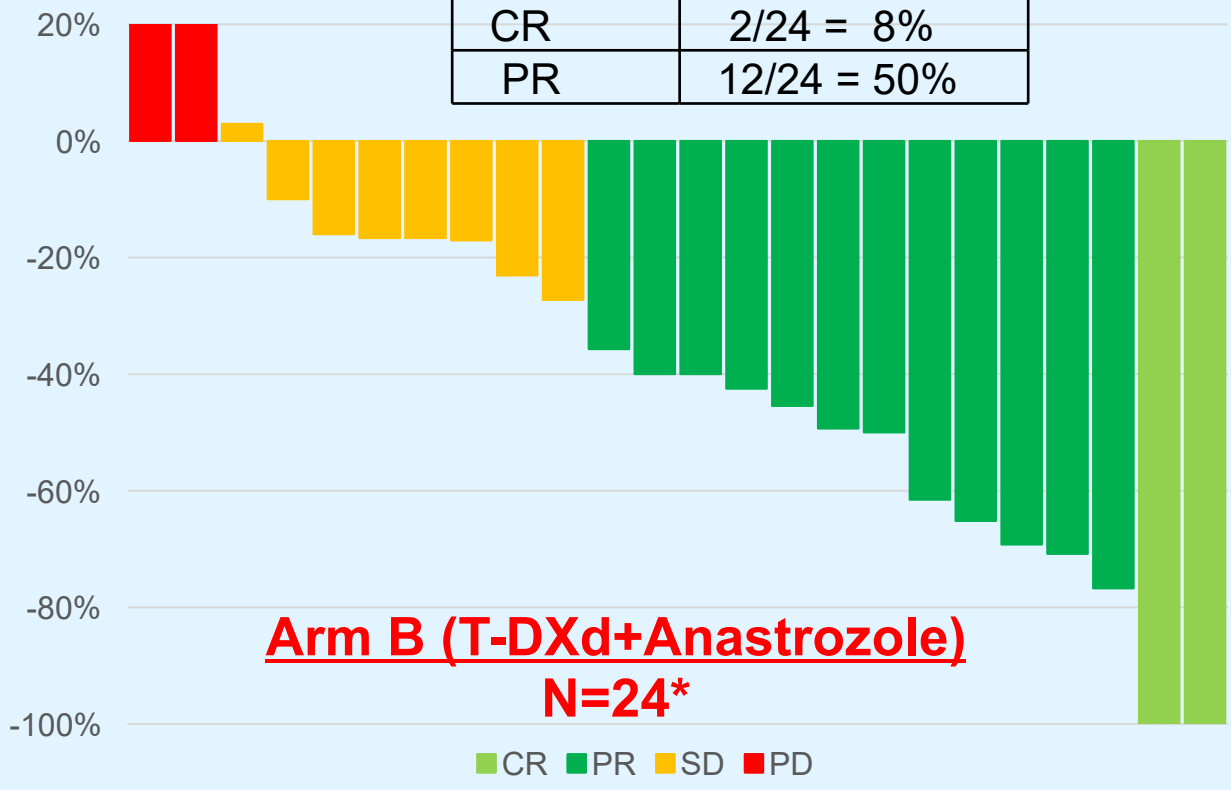
[A] 1 patient with single lesion and multiple grades (2 & 3) included in Grade 3 only
[B] 2 patients with 2 masses and multiple grades (2 & 3) included in Grade 3 only

Objective Response Rate with T-DXd (based on imaging)

Arm A	
ORR	17/25 = 68%
CR	2/25 = 8%
PR	15/25 = 60%



Arm B	
ORR	14/24 = 58%
CR	2/24 = 8%
PR	12/24 = 50%

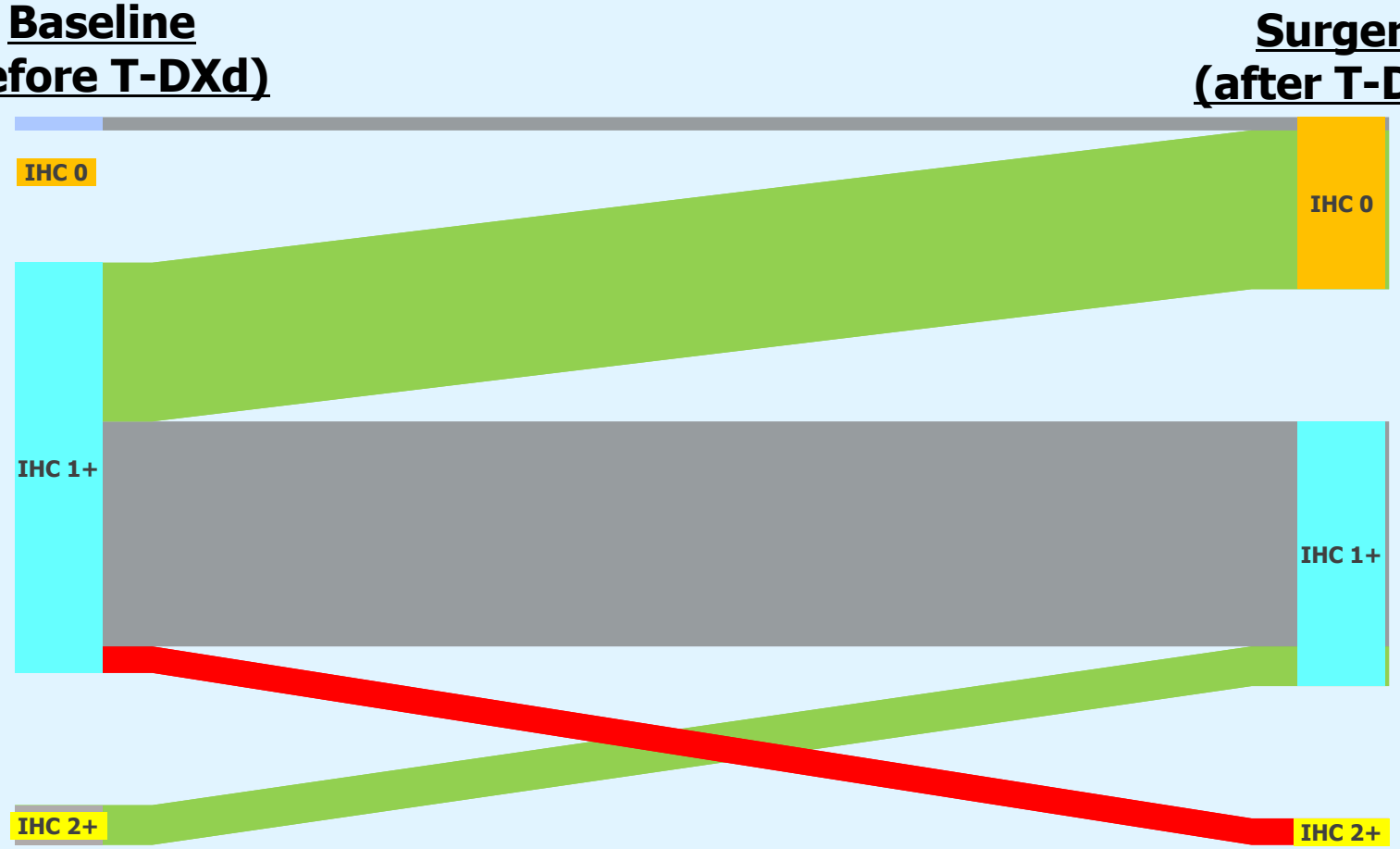


Waterfall plot with bars representing change in tumor size after treatment with T-DXd, compared to baseline, as per RECIST v1.1. Intention to treat population for ORR includes all who received at least 1 cycle of protocol therapy, data cutoff 11/25/2022.

- 4 patients still on treatment; 3 patients did have imaging (treatment discontinued prematurely), but included in intention to treat (ITT) denominator for ORR analysis per protocol

* 5 patients still on treatment

HER2 IHC Change from Baseline to Surgery with T-DXd (central review)



49% (17/35) had change in HER2 IHC after T-DXd treatment

Of those who had change, majority (88%) had decrease in HER2 IHC expression

Green: IHC staining of HER2 decreased from baseline to surgery
Gray: IHC staining of HER2 remained stable from baseline to surgery
Red: IHC staining of HER2 increased from baseline to surgery

Note: The observed change in IHC immunostaining may not accurately reflect changes in HER2 protein expression in carcinoma cells

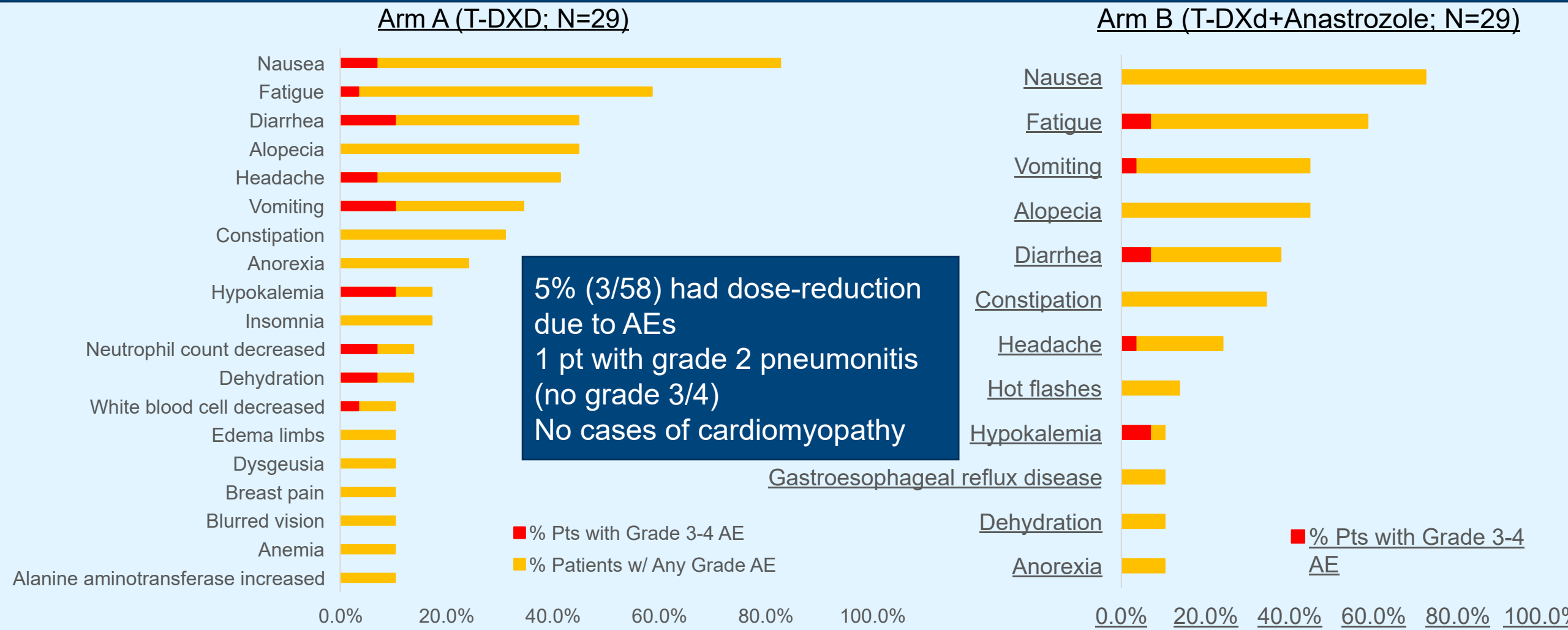
Residual Cancer Burden after T-DXd (by arm, cycles and stage)

Cycles	Stage at Baseline	Arm A (T-DXd) N=22*				Arm B (T-DXd+Anastrozole) N=20**			
		RCB-0	RCB-I	RCB-II	RCB-III	RCB-0	RCB-I	RCB-II	RCB-III
6 Cycles	Stage IIA	0	1 (5%)	2 (9%)	0	0	1 (5%)	6 (30%)	0
	Stage IIB	0	1 (5%)	4 (18%)	2 (9%)	0	0	3 (15%)	1 (5%)
	Stage IIIA	0	0	1 (5%)	2 (9%)	0	0	1 (5%)	1 (5%)
	Stage IIIB	0	0	1 (5%)	0	0	0	0	0
8 Cycles	Stage IIA	0	0	2 (9%)	0	0	1 (5%)	1 (5%)	0
	Stage IIB	0	0	1 (5%)	1 (5%)	0	0	2 (10%)	0
	Stage IIIA	1 (5%)	0	0	0	0	1 (5%)	0	0
	Stage IIIB	0	0	0	0	0	0	0	0

As of data cutoff 11/25/2022: surgical outcomes pending for 24% (7/29) patients being treated in Arm A and 31% (9/29) in Arm B.

- *4 pts discontinued early Arm A **3 pts discontinued early (included in denominator for intention to treat analysis) Arm B
- RCBi = Residual cancer burden index; RCB 0 = pCR; Histology or IHC Status did not appear to be associated with RCB response

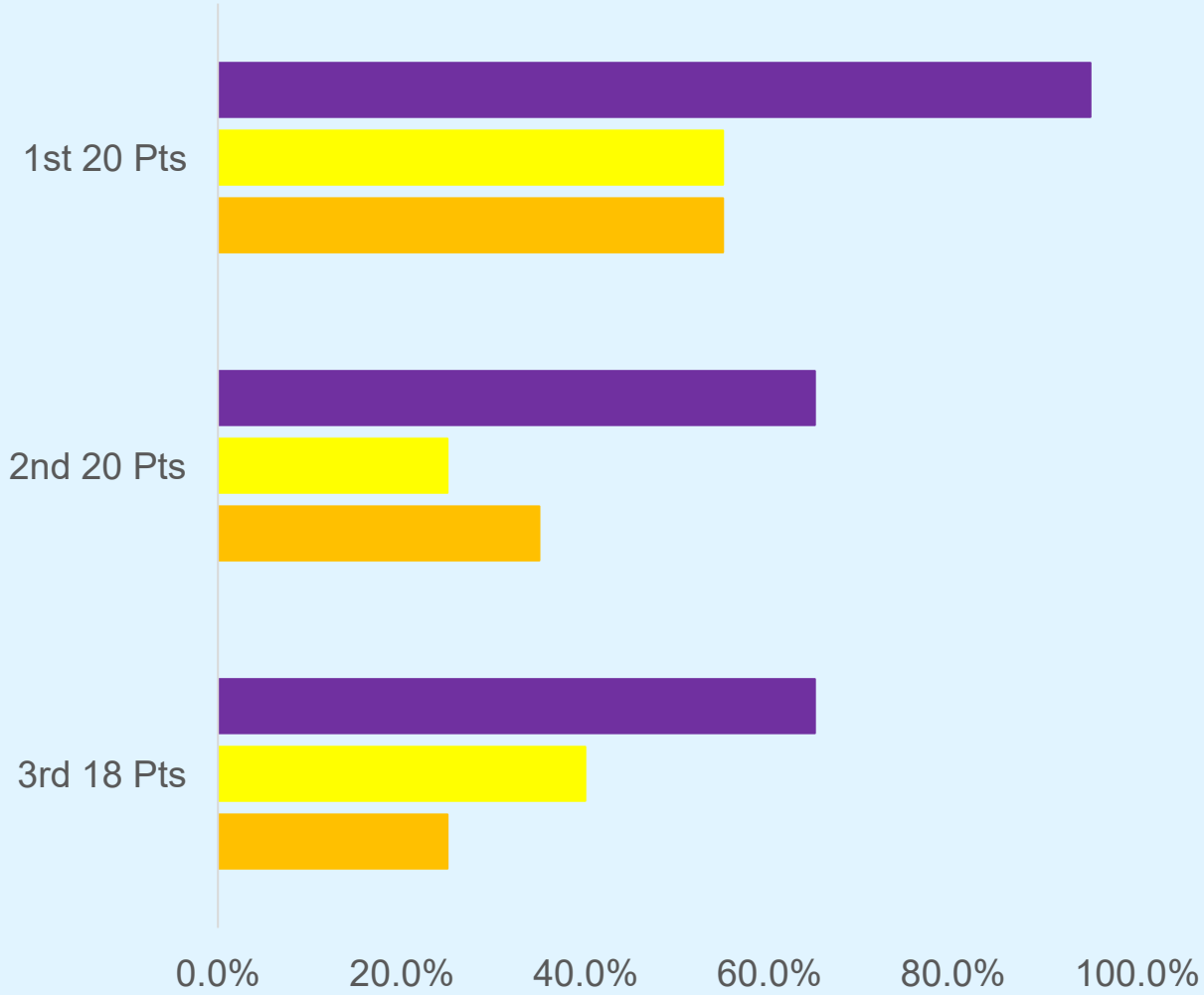
Adverse Effects (T-DXd Related, ≥ 10%)



As of data cutoff 11/25/2022, includes all participants who received at least 1 dose of study treatment; AEs in 3 or more patients. 3 patients discontinued due to AEs.

1 death due to myocardial infarction after severe GI toxicity, possibly related.

T-DXd Related Gastrointestinal AEs: Change over time from study initiation



Incidence of GI AEs appeared to decrease over time, possibly due to better supportive therapy

As of data cutoff 11/25/2022, includes all participants who received at least 1 dose of study treatment, AE = Adverse Effect, GI = Gastrointestinal.

Conclusions

- Neoadjuvant Trastuzumab deruxtecan (T-DXd) demonstrated preliminary evidence of clinical activity in HER2 low, HR+ localized breast cancer with a toxicity profile consistent with previous reports:
  - ORR: 68% (T-DXd alone, Arm A); 58% (T-DXd with anastrozole, Arm B)
  - RCB 0/1 rate: 15% (both arms); surgical outcomes pending (24% in arm A; 31% in Arm B)
  - Nausea most common AE; 1 case of grade 2 pneumonitis; dose reductions due to AEs: 5%
- Addition of endocrine therapy to T-DXd did not appear to enhance efficacy, but caution needs to be exerted in strong conclusions given small numbers
- Dynamic changes in HER2 tissue expression noted after treatment with T-DXd
- Study provides rich platform for translational research to evaluate more sensitive methods of HER2 detection, develop predictive biomarkers, and understand mechanisms of resistance in residual disease to guide future therapeutic strategies, including combination therapy

This is the first report of neoadjuvant T-DXd for pts with HR+, HER2-low breast cancer and provides groundwork for future studies with antibody-drug conjugates for patients with early-stage breast cancer

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Thank you