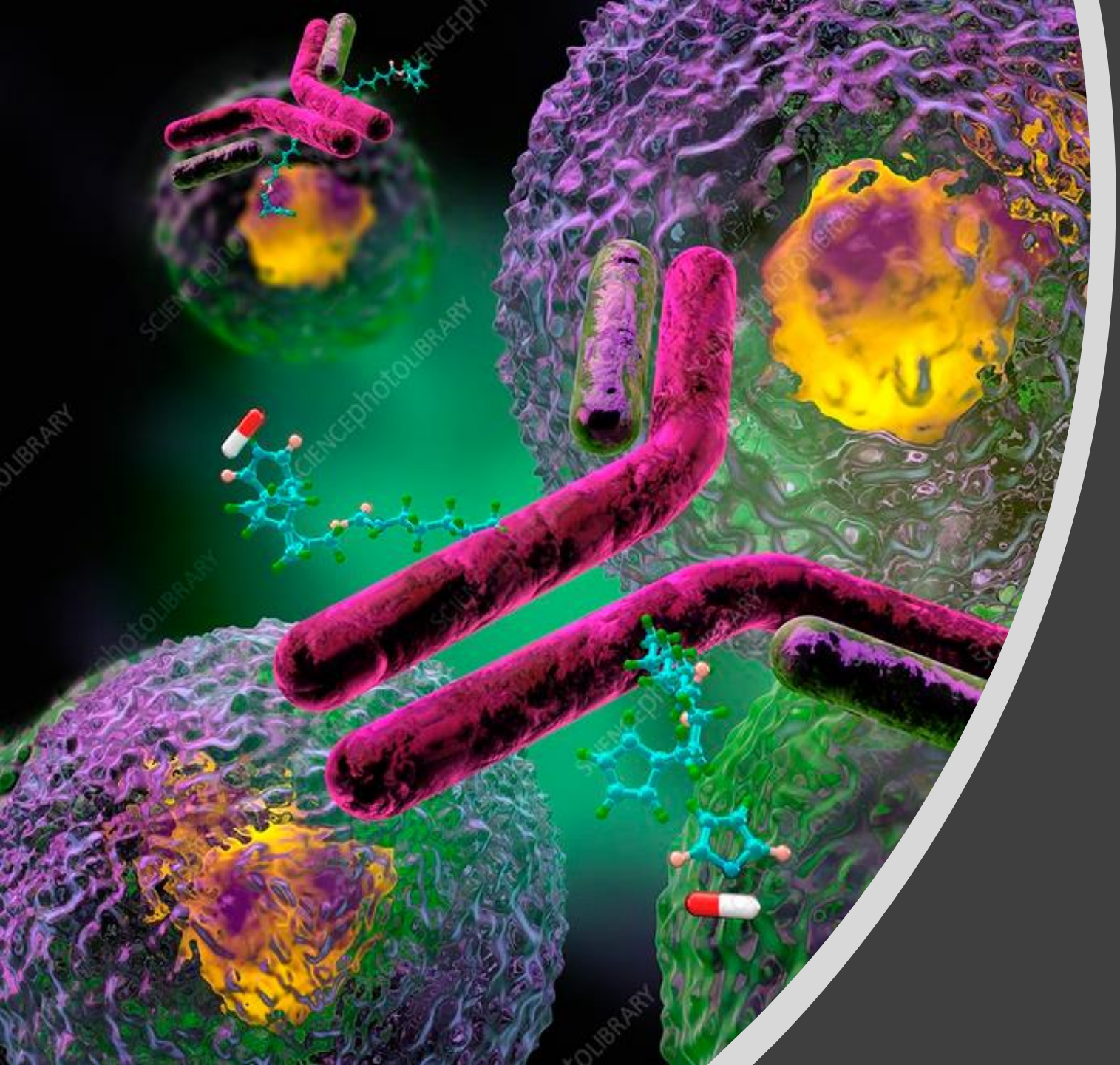


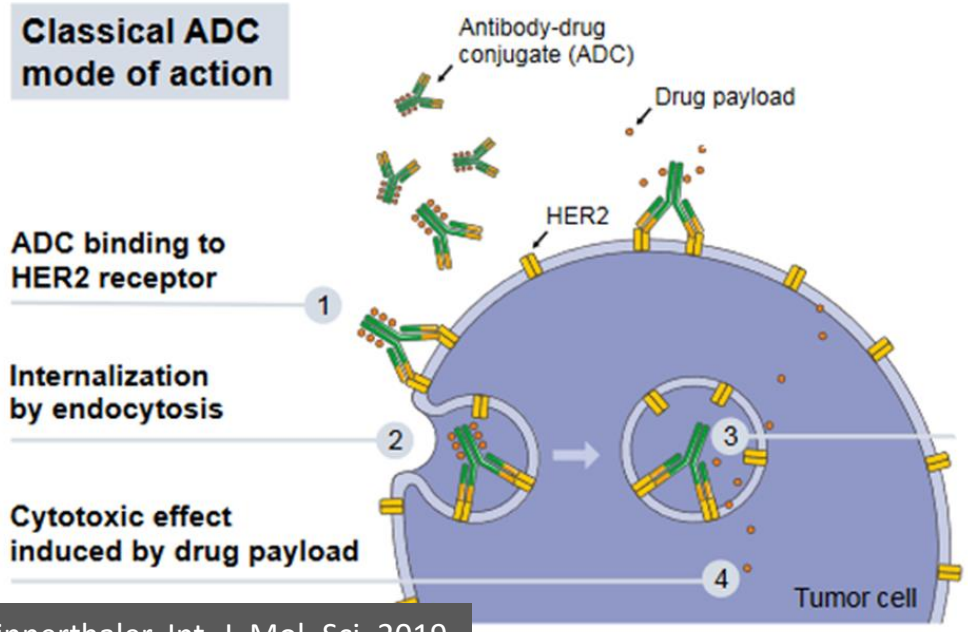
Antibody drug conjugates

Hvad betyder de nye ADC'er for behandlingen af brystkræft?

- HER2-targeterede ADC-er
  - TDM1 til HER2+
  - TDXd til HER2+ og HER2low
- TROP2-targeterede ADC-er
  - Sacituzumab Govitecan til TNBC og ER+ MBC
  - Datopotamab Deruxtecan – under udvikling – protokol i DK
- ADC-er under udvikling mod nye targets?
- Fremtiden

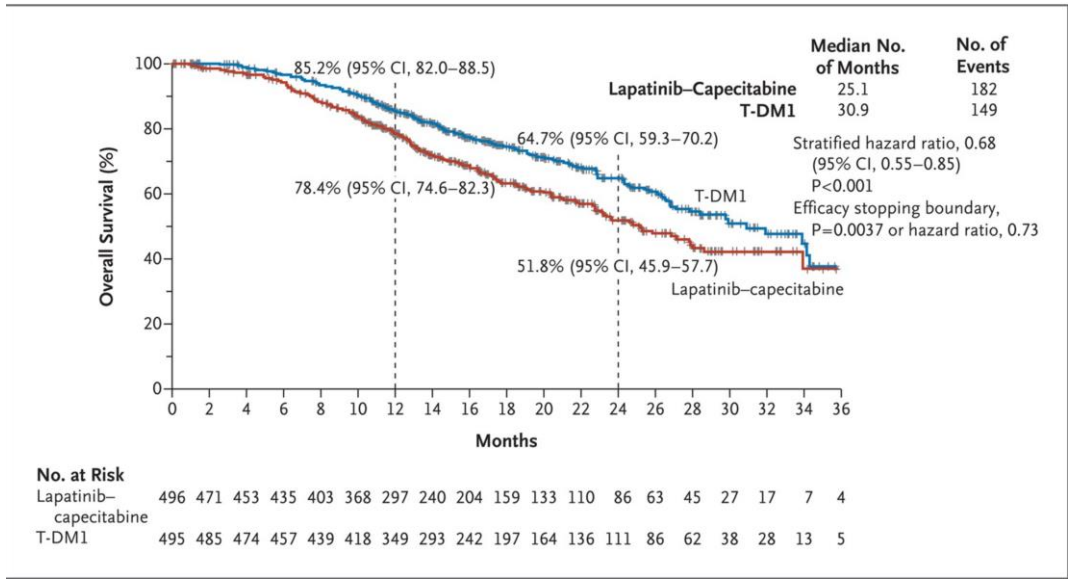
TDM1 (Trastuzumab Emtansine): Prototypen

Nakasa T Chem Pharm Bull 2019



Rinnerthaler, Int. J. Mol. Sci. 2019

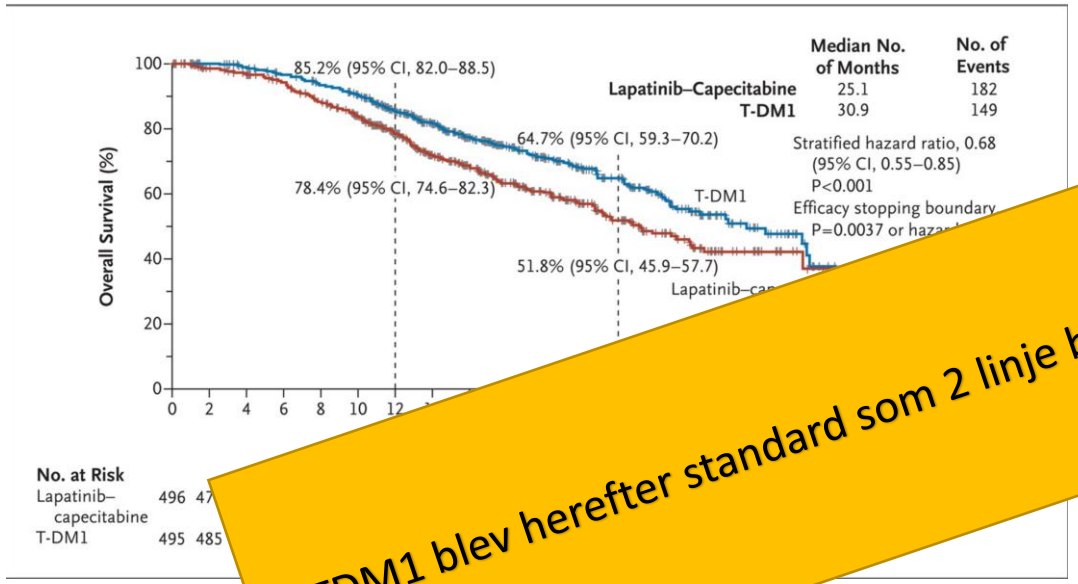
Emilia: TDM1 vs. lapatinib–capecitabine



	Cap + Lap (n=488)	T-DM1 (n=490)
All-grade AE, n (%)	477 (97.7)	470 (95.9)
Grade ≥3 AE, n (%)	278 (57.0)	200 (40.8)
AEs leading to treatment discontinuation (for any study drug), n (%)	52 (10.7)	29 (5.9)
AEs leading to death on treatment, n (%)[a]	5 (1.0)	1 (0.2)
Cardiac dysfunction AEs,[a] n (%)		
All grades	15 (3.1)	9 (1.8)
Grade 3	2 (0.4)	1 (0.2)
LVEF <50% and ≥15-point decrease from baseline, %[b]	7 (1.6)	8 (1.7)

N Engl J Med 2012; 367:1783-1791
DOI: 10.1056/NEJMoa1209124

Emilia: TDM1 vs. lapatinib–capecitabine



TDM1 blev herefter standard som 2 linje behandling til HER2-positiv mBC

	Cap + Lap (n=488)	T-DM1 (n=490)
All-	477 (97.7)	470 (95.9)
	278 (57.0)	200 (40.8)
tion	52 (10.7)	29 (5.9)
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LVEF <50% and ≥15-point decrease from baseline, %[b]	7 (1.6)	8 (1.7)

N Engl J Med 2012; 367:1783-1791
DOI: 10.1056/NEJMoa1209124

KATHERINE: T-DM1 superior to Trastuzumab for HER2+ Residual Disease

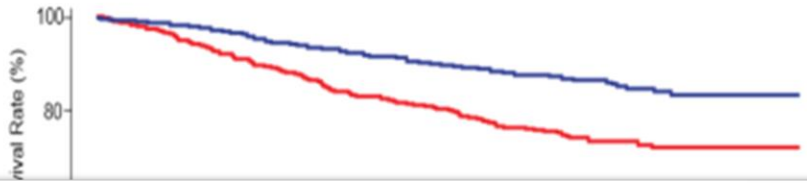
- Centrally confirmed HER2-positive breast cancer
- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Received neoadjuvant therapy consisting of
  - Minimum of 6 cycles of chemotherapy
  - Minimum of 9 weeks of taxane+ trastuzumab
- Pathologic residual invasive tumor in breast or axilla

R 1:1

N=1486

T-DM1
3.6 mg/kg IV Q3W
14 cycles

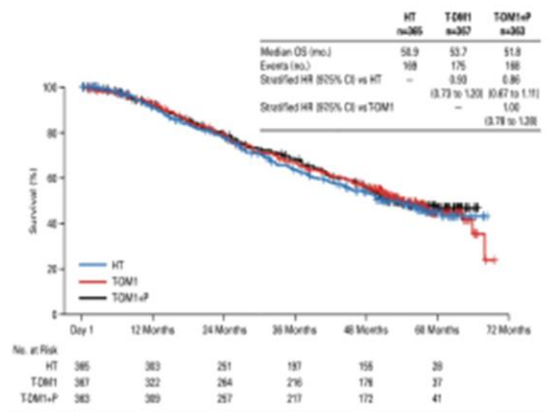
Trastuzumab
6 mg/kg IV Q3W
14 cycles



N Engl J Med 2019; 380:617-62

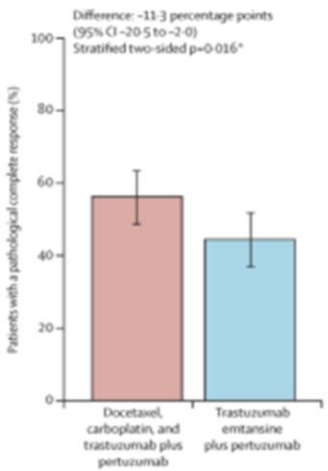
Marianne Trial: TDM1 not superior to TH

1. linje?

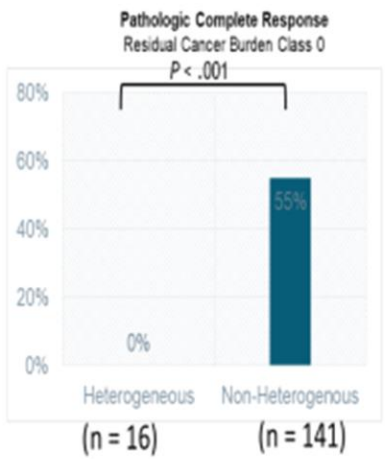


Kristine Trial: Chemo superior to TDM1 for pCR

Neo-adjuverende?



T-DM1+ P has no pCR benefit In heterogenous HER2+ EBC



Perez, E et al; Cancer 2019; Hurvitz S et al, Lancet 2018; Metzger Filho O, et al. J Clin Oncol. 2019;37(15_suppl):502-502.

KATHERINE: T-DM1 superior to Trastuzumab for HER2+ Residual Disease

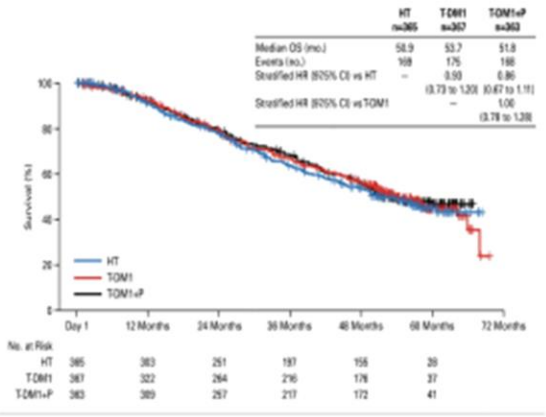
- Centrally confirmed HER2-positive breast cancer
- cT1-4/N0-3/M0 at presentation (cT1a-b/N0
- Received neoadjuvant therapy
  - Minimum
- Patho

TDM1 blev herefter standardbehandling til patienter med restsygdom efter neoadjuverende kemoter HER2-retttet behandling

N Engl J Med 2019; 380:617-62

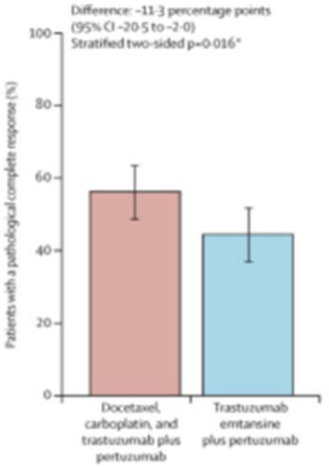
Marianne Trial: TDM1 not superior to TH

1. linje?

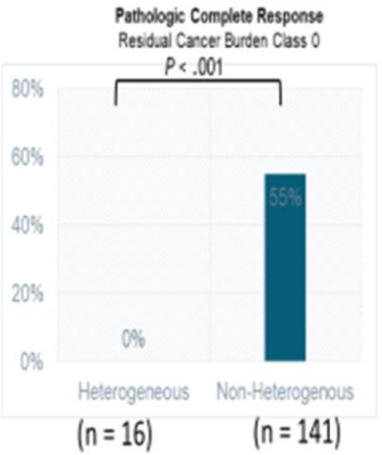


Kristine Trial: Chemo superior to TDM1 for pCR

Neo-adjuverende?



T-DM1+ P has no pCR benefit In heterogenous HER2+ EBC

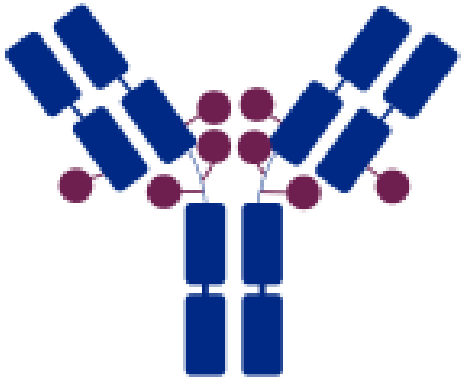


Perez, E et al; Cancer 2019; Hurvitz S et al, Lancet 2018; Metzger Filho O, et al. J Clin Oncol. 2019;37(15_suppl):502-502.

Trastuzumab Deruxtecan (T-DXd): Next Generation HER2 ADC

Characteristic Differences Between T-DXd and T-DM1

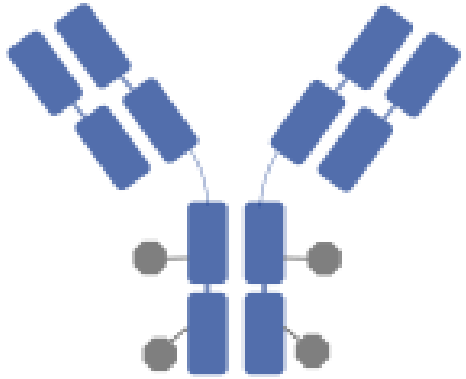
Trastuzumab deruxtecan (T-DXd)



HER2 Targeting ADCs with similar mAB Backbone

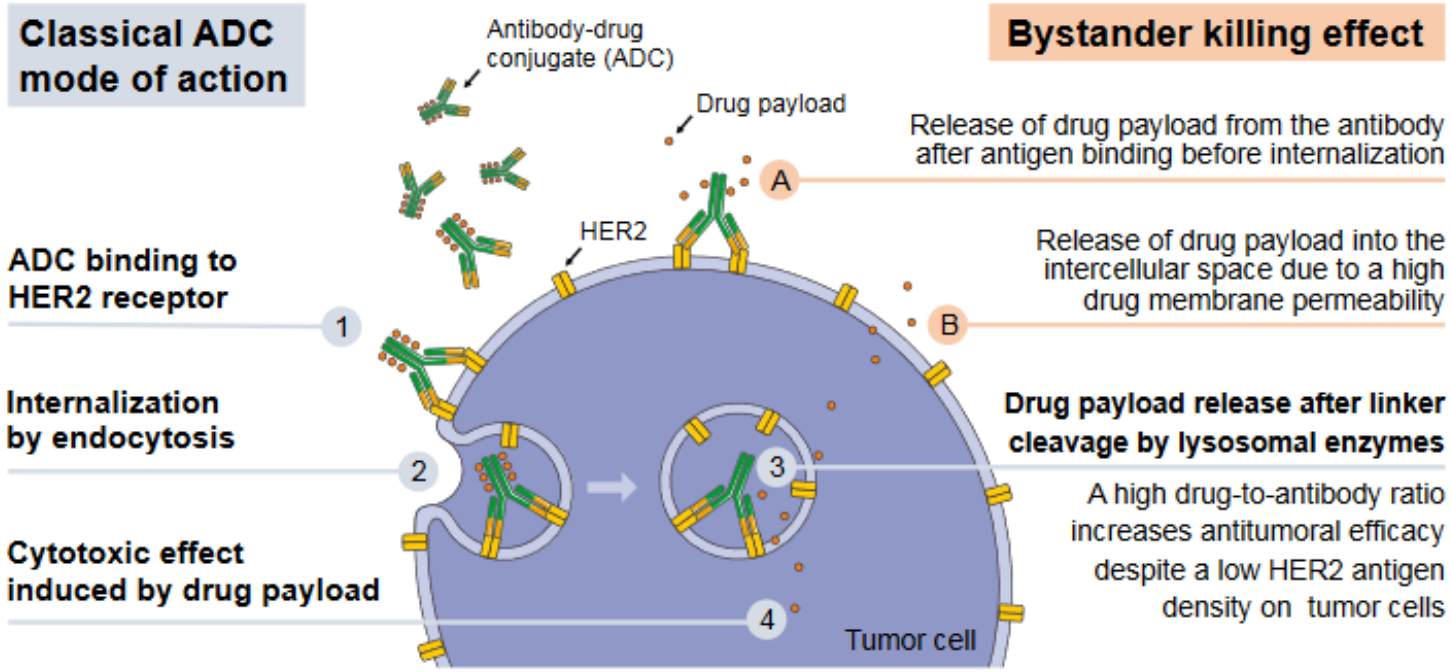
T-DXd	ADC Attributes	T-DM1
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)

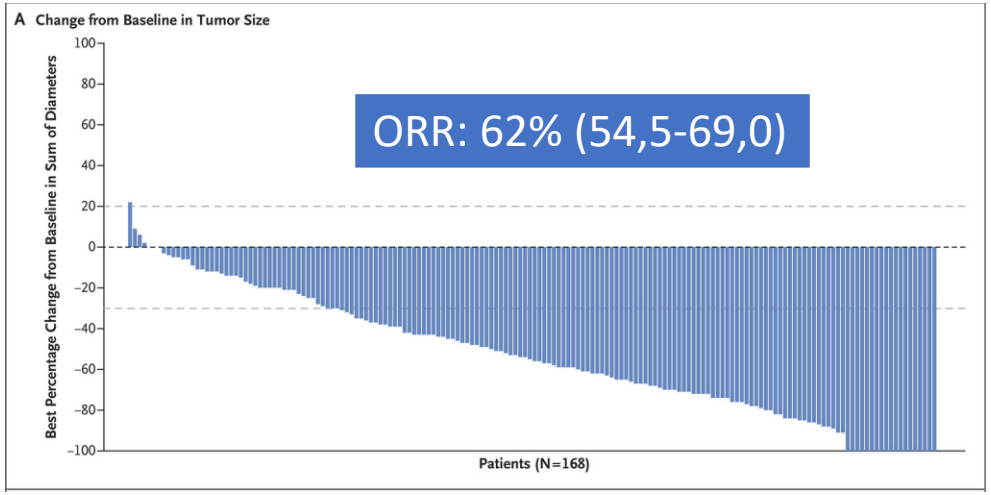


1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42. 4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res.* 2011;17:6437-47.

MOA
Rinnerthaler, Int. J. Mol. Sci. 2019



Destiny-01, fase II, mediant 6 tidligere behandlinger for HER2-positiv sygdom, alle TDM1



ORR: 62% (54,5-69,0)

ILD	N	%
G1	7	3.8
G2	16	8.7
G3	1	0.5
G4	0	0
G5	5	2.7

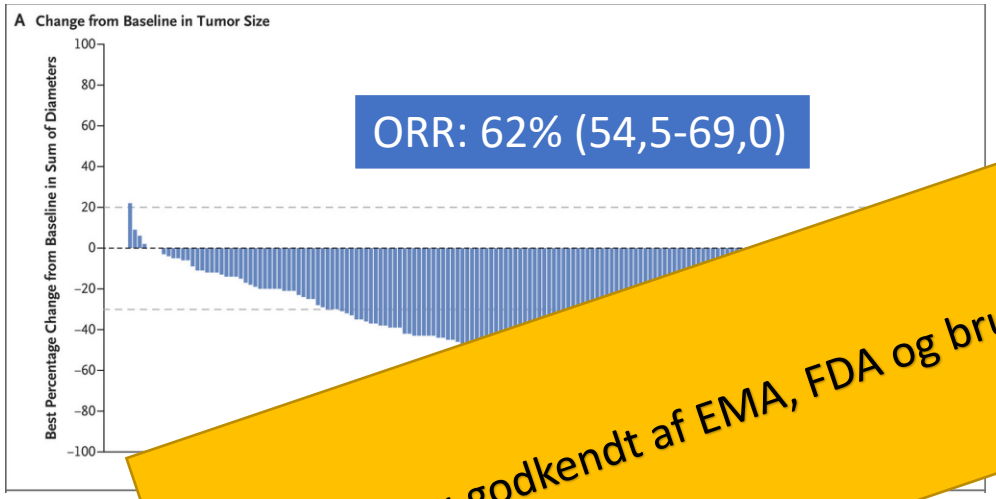
Efter 26.5 måneders follow-up

mPFS: 19.4 (95% CI, 14,1-25)
mOS: 29.1 (95% CI, 24.6-36.1)

Vs.

N Engl J Med 2020; 382:610-621 DOI: 10.1056/NEJMoa1914510,
Saura et al. ESMO 2021

Destiny-01, fase II, mediant 6 tidligere behandlinger for HER2-positiv sygdom, alle TDM1



ORR: 62% (54,5-69,0)

TDXD – nu godkendt af EMA, FDA og bruges som standard – fraset DK

ILD	N	%
		3.8
		8.7
	1	0.5
	0	0
G5	5	2.7

follow-up

FS: 19.4 (95% CI, 14,1-25)
mOS: 29.1 (95% CI, 24.6-36.1)

Vs.

N Engl J Med 2020; 382:610-621 DOI: 10.1056/NEJMoa1914510,
Saura et al. ESMO 2021

DESTINY-Breast02

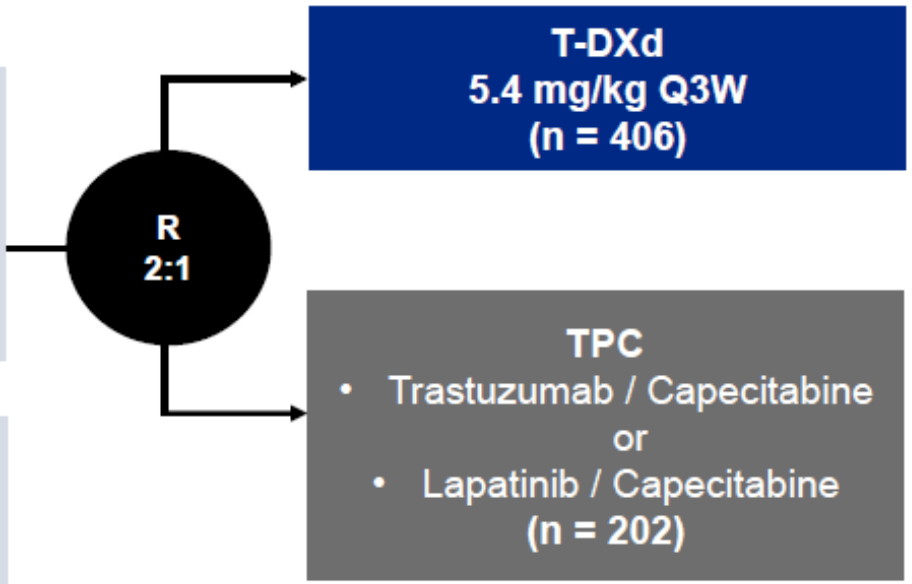
Randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]

- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- **Previously treated with T-DM1**

Stratification factors

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



Primary endpoint

- PFS (BICR[b])

Key secondary endpoint

- OS

Secondary endpoints

- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints

- CBR (BICR[b])
- PFS2[c] (investigator)

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:

- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

Prior therapy for MBC:

100% received prior trastuzumab

100% received prior T-DM1

78% received prior pertuzumab

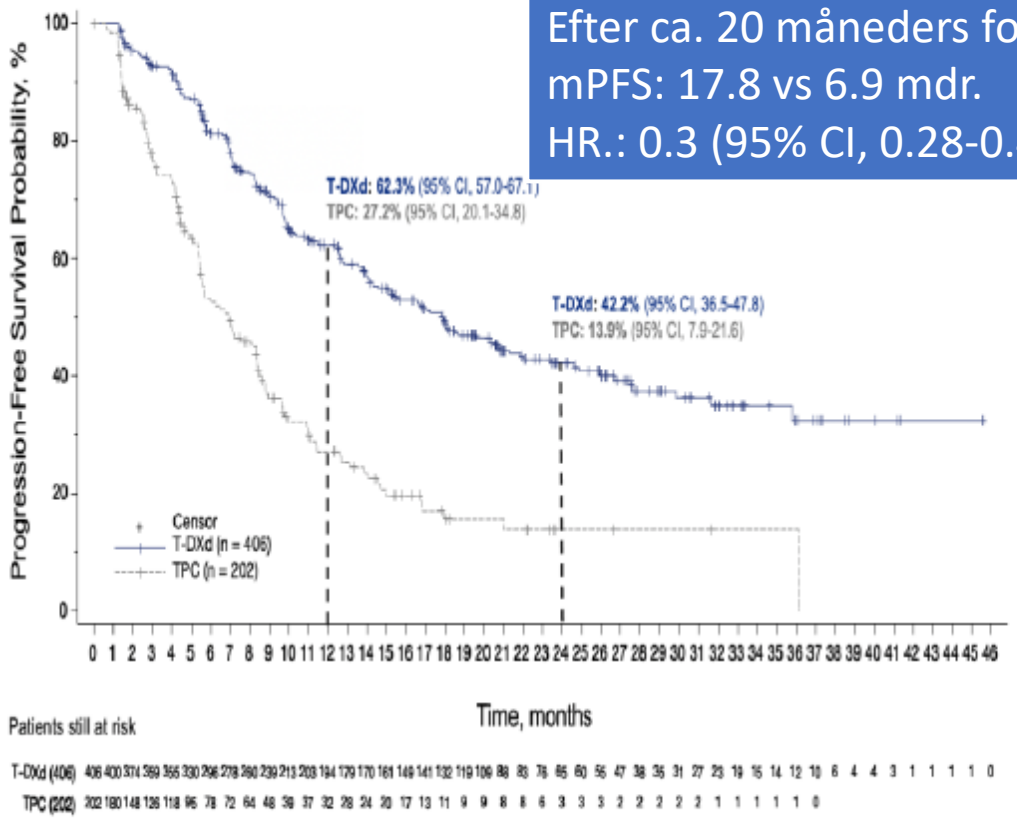
6% received HER2 TKI

Median lines of prior tx: 2

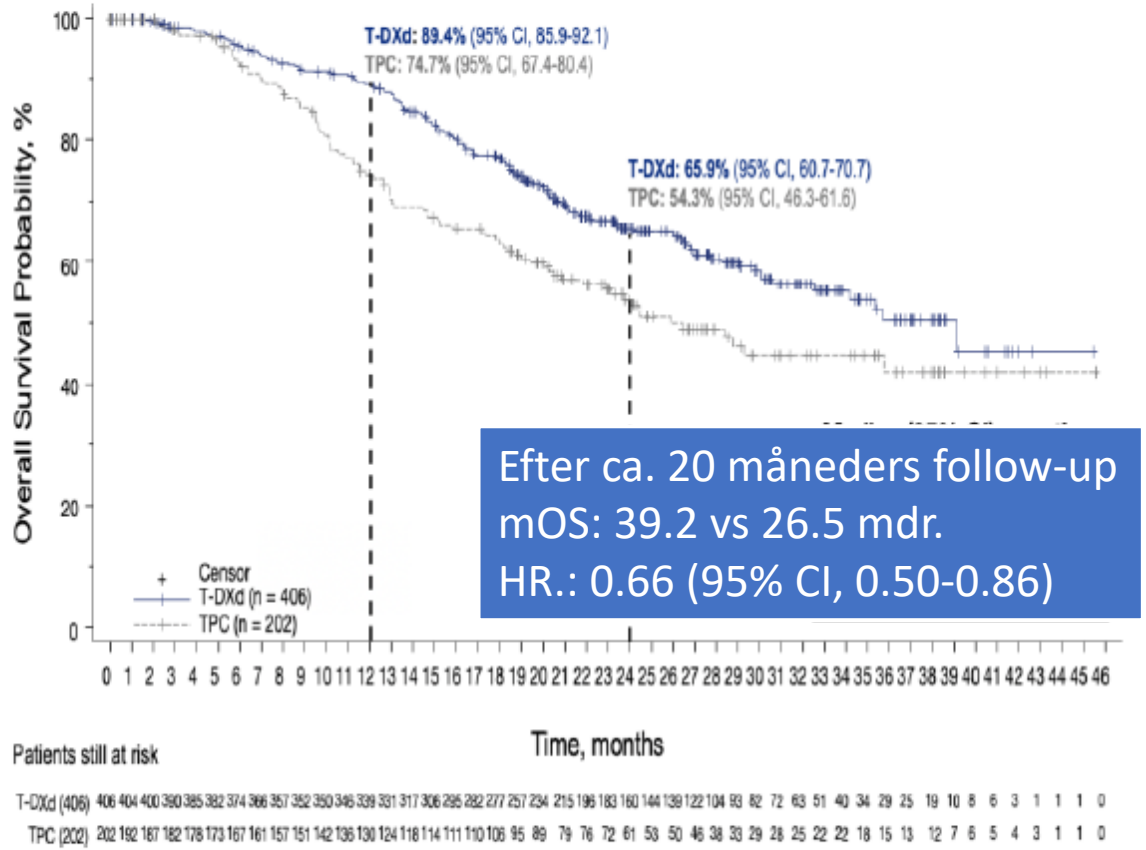
DESTINY-Breast02: Efficacy endpoints

Primary Endpoint: PFS by BICR

Efter ca. 20 måneders follow-up
mPFS: 17.8 vs 6.9 mdr.
HR.: 0.3 (95% CI, 0.28-0.45)



Key Secondary Endpoint: OS



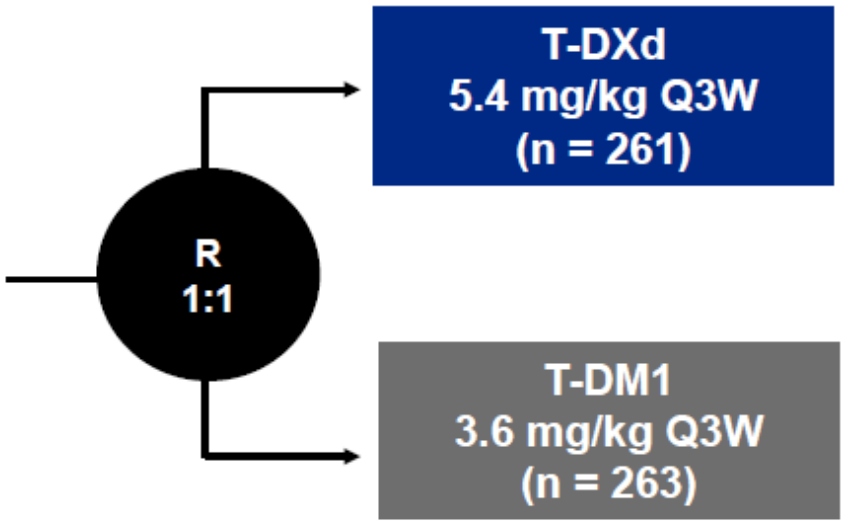
Efter ca. 20 måneders follow-up
mOS: 39.2 vs 26.5 mdr.
HR.: 0.66 (95% CI, 0.50-0.86)

Adjudicated as Drug-related ILD[a]						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
T-DXd (n = 404)	11 (2.7)	26 (6.4)	3 (0.7)	0	2 (0.5)	42 (10.4)
TPC (n = 195)	0	0	1 (0.5)	0	0	1 (0.5)

Krop I, SABC 2022

Destiny-03, fase III, 2 linje – alle tidl. behandlet med trastuzumab + taxan

Patients
- Unresectable or metastatic HER2-positive breast cancer
- **Previously treated with trastuzumab and taxane in advanced/metastatic setting**
- Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

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

Median study follow-up
- **T-DXd arm: 28.4 months (range, 0.0-46.9 months)**
- **T-DM1 arm: 26.5 months (range, 0.0-45.0 months)**

Prior therapy for MBC:
100% received prior trastuzumab
~60% received prior pertuzumab
~15% received other HER2 Tx
Median lines of prior tx: 2
One line of Tx: ~40%

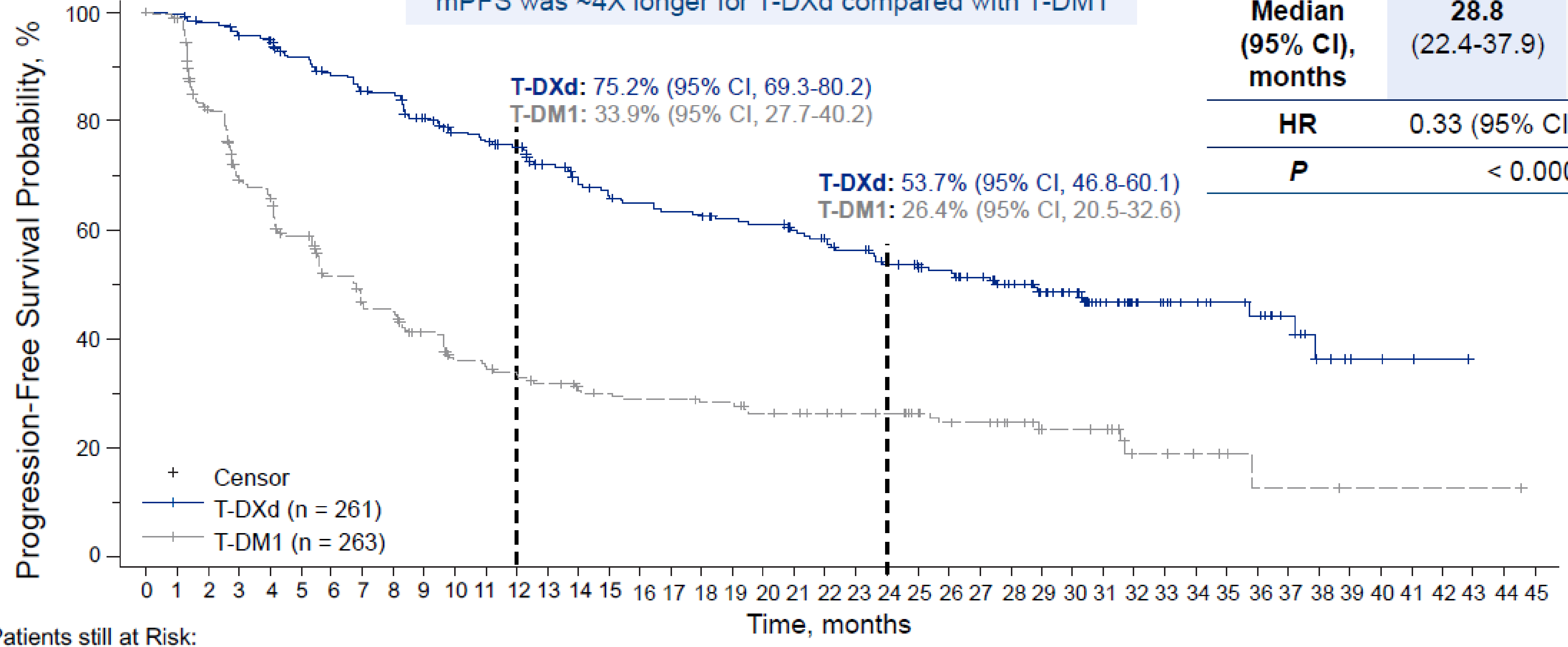
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

Hurvitz S, SABC 2022

Updated Primary Endpoint: PFS by BICR

mPFS was ~4X longer for T-DXd compared with T-DM1

	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	



Patients still at Risk:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
T-DXd	261	256	250	244	240	225	216	207	205	191	176	173	167	154	146	140	134	131	130	125	123	117	113
T-DM1	263	253	201	164	156	134	111	99	96	81	69	67	63	58	54	51	49	49	47	47	42	41	39

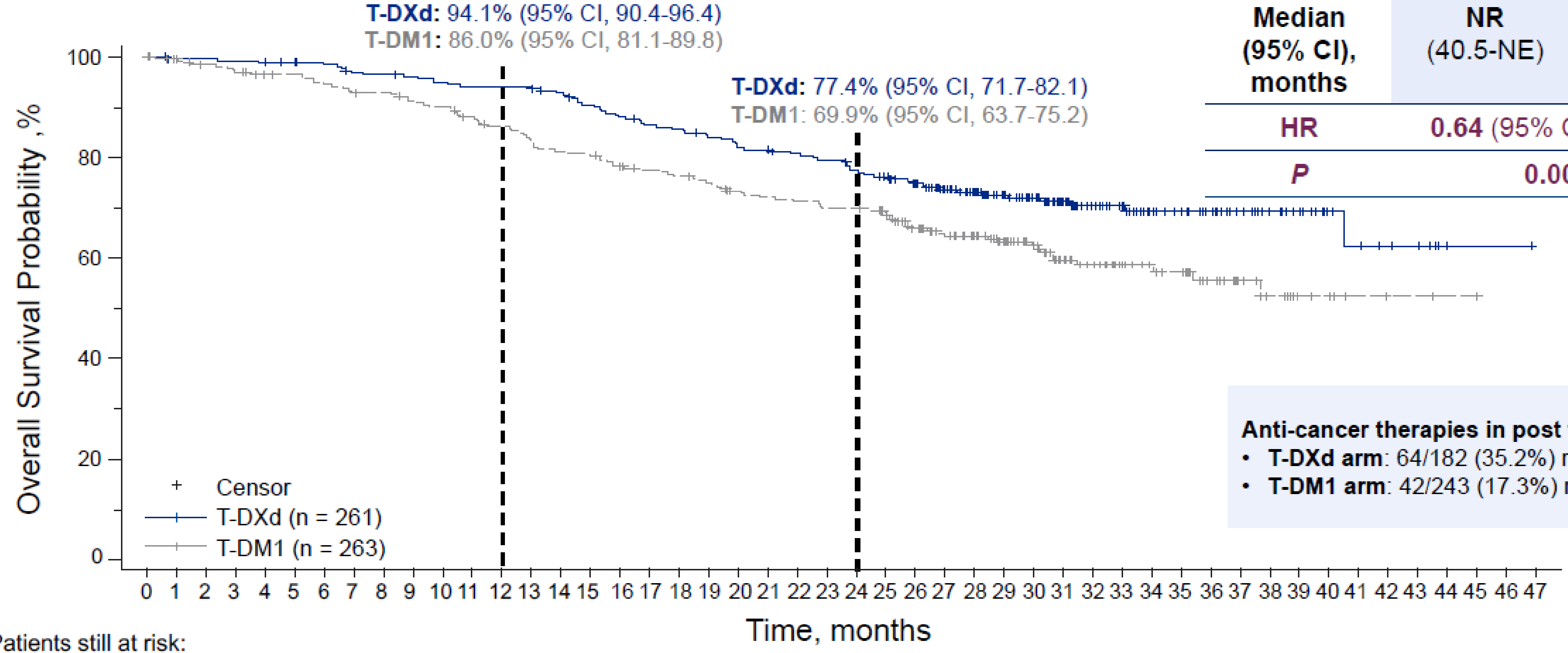
	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
T-DXd	107	99	96	90	82	73	64	55	41	32	28	23	20	18	13	7	5	4	2	1	0		
T-DM1	37	36	32	28	27	22	19	15	14	8	7	6	4	2	2	2	1	1	1	1	1	1	0

BICR, blinded independent central review; HR, hazard ratio; mo, month; mPFS, median progression-free survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Two-sided, from stratified log rank test. [b]Nominal *P* value.

Hurvitz S, SABC 2022

Key Secondary Endpoint: Overall Survival

	T-DXd	T-DM1
Median (95% CI), months	**NR** (40.5-NE)	**NR** (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**0.0037**[a,b]	



Anti-cancer therapies in post trial setting:
- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

Patients still at risk:

T-DXd 261 256 256 255 254 251 249 244 243 241 238 236 236 236 231 224 218 213 211 206 201 200 196 193 187 182 173 156 142 124 109 91 73 64 51 44 38 30 22 18 11 9 7 6 1 1 1 0

T-DM1 263 257 252 248 243 242 237 233 232 227 224 217 211 203 199 197 191 186 183 179 172 169 167 164 164 158 140 129 117 106 90 70 59 45 41 38 27 20 15 8 7 4 3 3 1 1 0

HR, hazard ratio; mOS, median overall survival; NE, not estimable; NR, not reached; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
There were 19 patients (7.3%) treated with T-DXd and 28 patients (10.6%) treated with T-DM1 who were lost to follow-up.
[a]The *P* value for overall survival crossed the prespecified boundary (*P* = 0.013) and was statistically significant. [b]Two-sided from stratified log-rank test.

Hurvitz S, SABC 2022

Confirmed ORR and Lung Safety Endpoints

	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal *P* value	< 0.0001	
CR, n (%)	55 (**21.1**)	25 (**9.5**)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)
CBR, n (%) [95% CI]	233 (89.3) [84.9-92.8]	122 (46.4) [40.2-52.6]
Nominal *P* value	< 0.0001	

Adjudicated Drug-Related Interstitial Lung Disease/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- With longer treatment exposure and follow-up, the ILD/pneumonitis rate increased from 10.5% in the PFS interim analysis[3] to 15.2%
  - There were 4 additional grade 1, 8 additional grade 2, and no additional grade 3 events
- There were no adjudicated drug-related grade 4 or 5 events

Destiny Breast 03 supports T-DXd as the superior HER2 ADC and the preferred 2nd line therapy for HER2+ MBC today

. Powell CA et al. *ESMO Open* 2022; 7(4): 100554. 3. Cortes J et al. *N Engl J Med.* 2022;386:1143-1154.

Hurvitz S, SABC 2022

Confirmed ORR and Lung Safety Endpoints

	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2
Nominal *P* value		
CR, n (%)		
PR, n (%)		
SD, n (%		
CBR,		
Nomi		

Adjudicated Drug

eumonitis

	rade 5	Any grade
	)	39 (15.2)
		8 (3.1)

posure and follow-up, the
rate increased from 10.5% in the PFS interim
to 15.2%

- There were 4 additional grade 1, 8 additional grade 2, and no additional grade 3 events
- There were no adjudicated drug-related grade 4 or 5 events

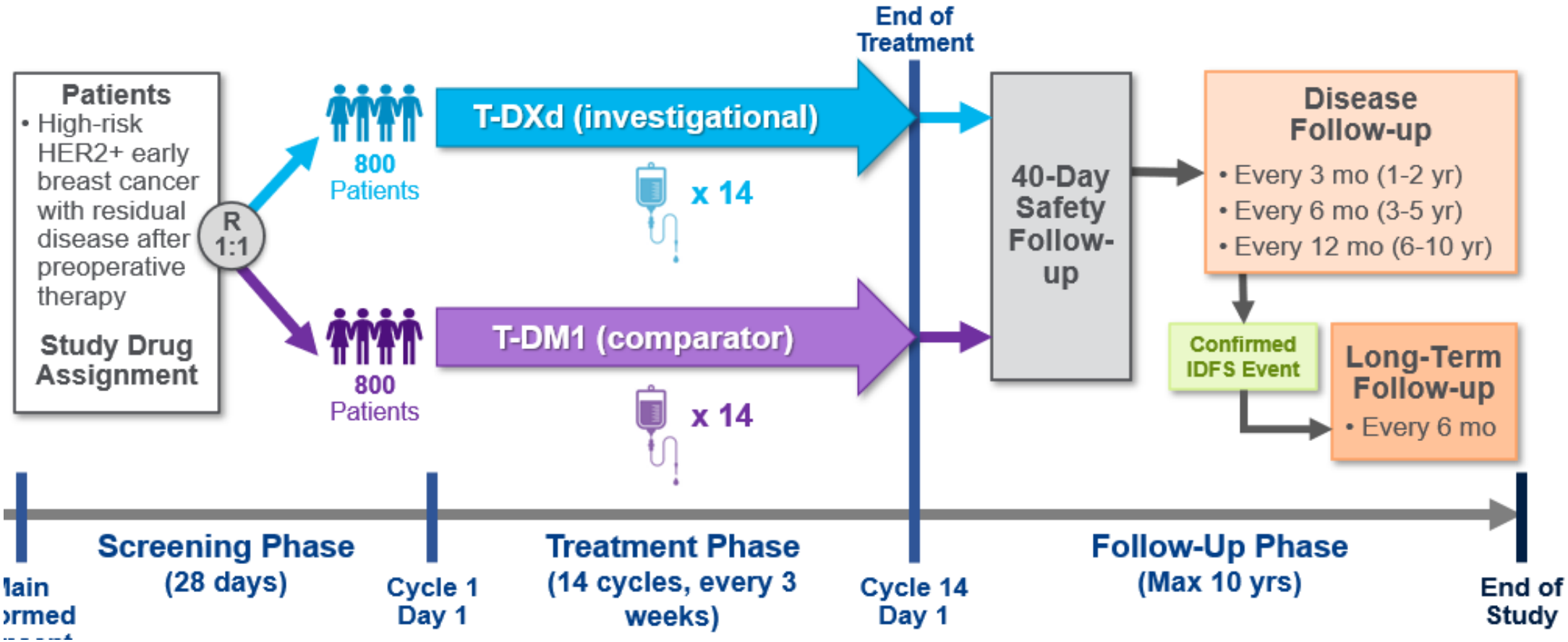
TDXD – nu (maj 22) godkendt af FDA og EMA (juni 22) som 2 linje behandling til HER2-positiv mBC
DK afventer….

Breast 03 supports T-DXd as the superior HER2 ADC and the preferred 2nd line therapy for HER2+ MBC today

. Powell CA et al. *ESMO Open* 2022; 7(4): 100554. 3. Cortes J et al. *N Engl J Med.* 2022;386:1143-1154.

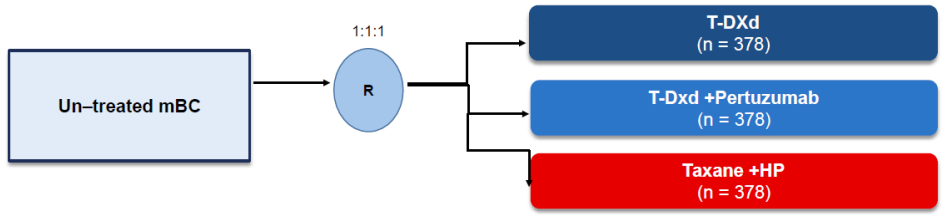
Hurvitz S, SABC 2022

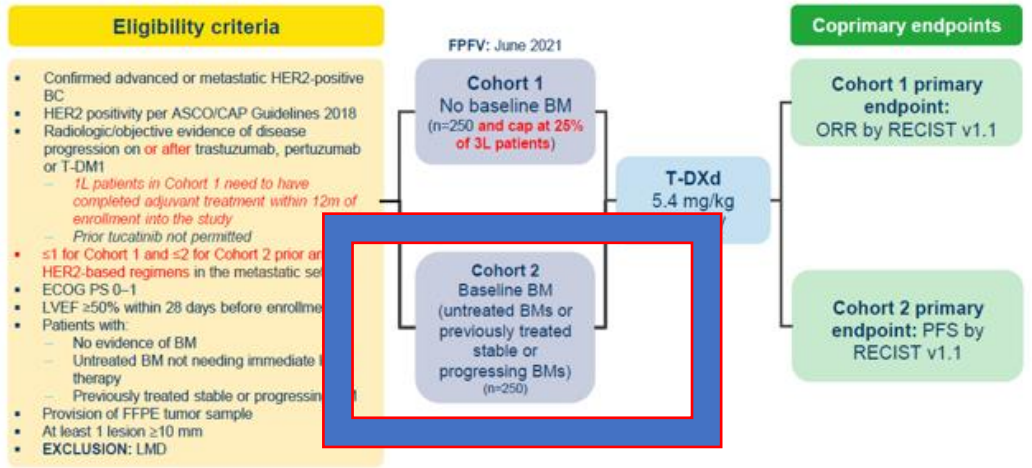
Destiny-05 Post-neoadjuvant til HER2-positive patienter, der efter NACT har residual sygdom



Destiny-09 og 12 – i Danmark

1 linje

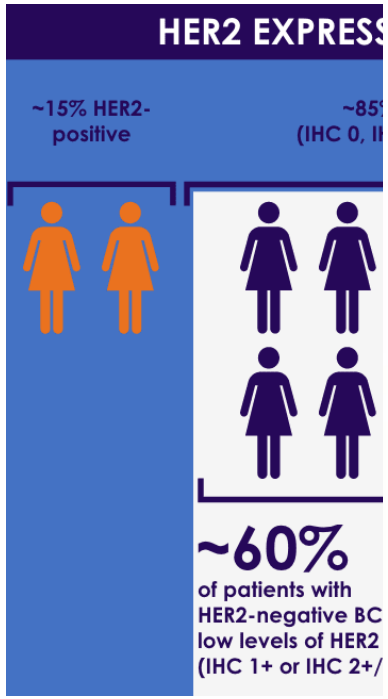


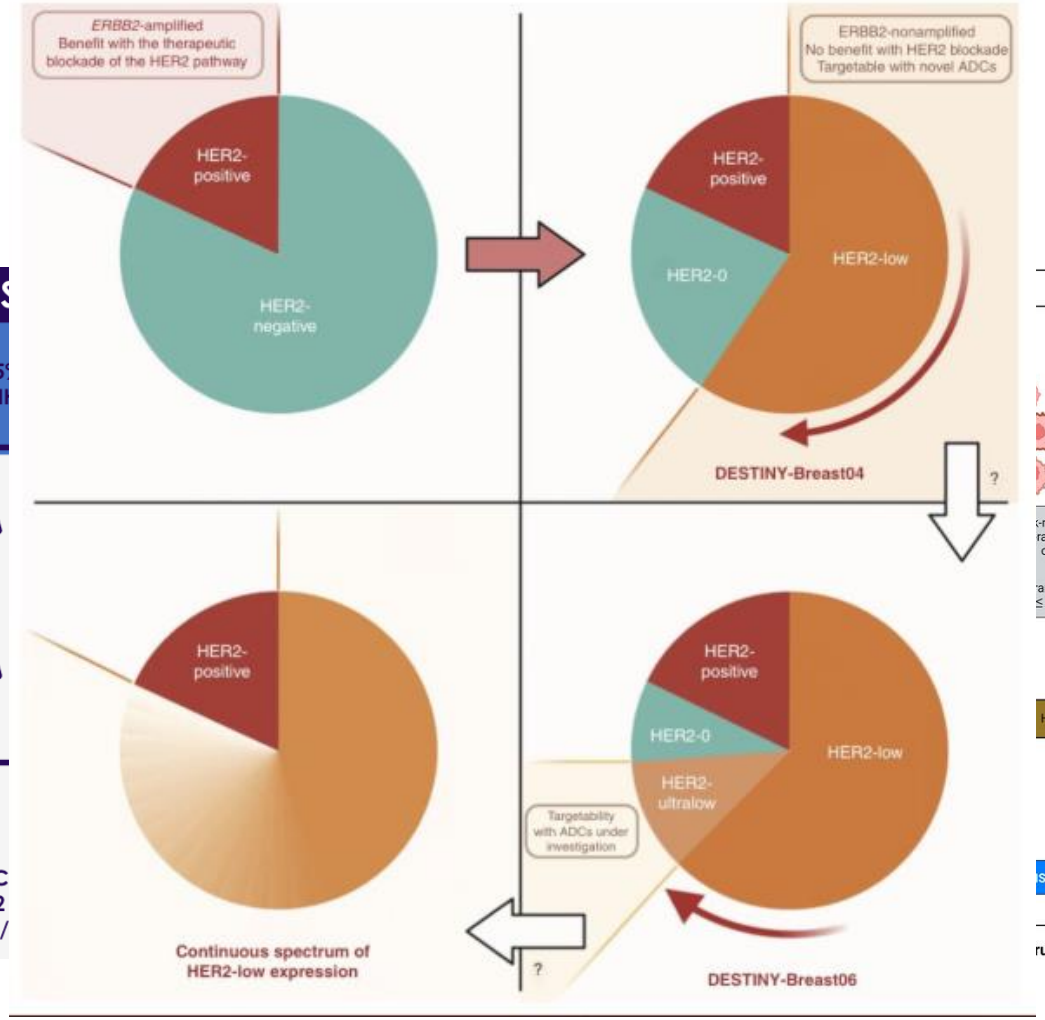


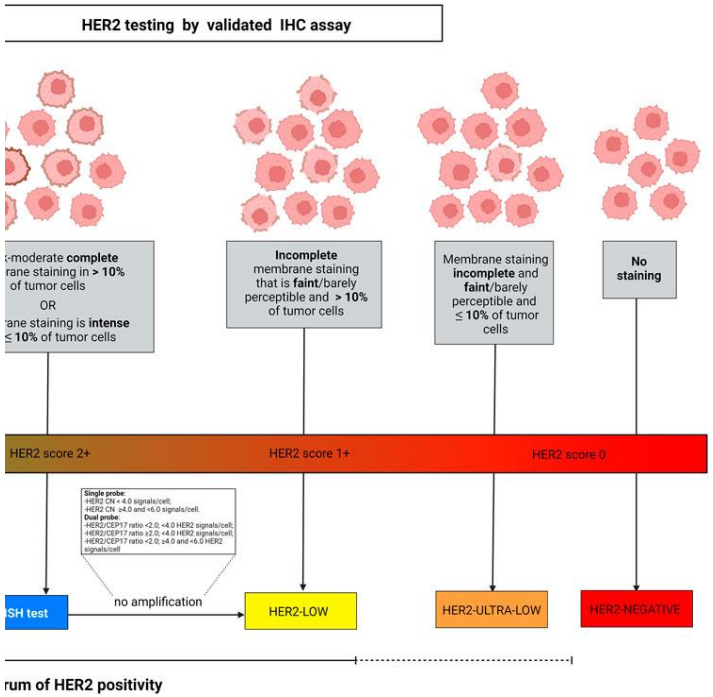
HER2-low

Et paradigmeskift

HER2-low

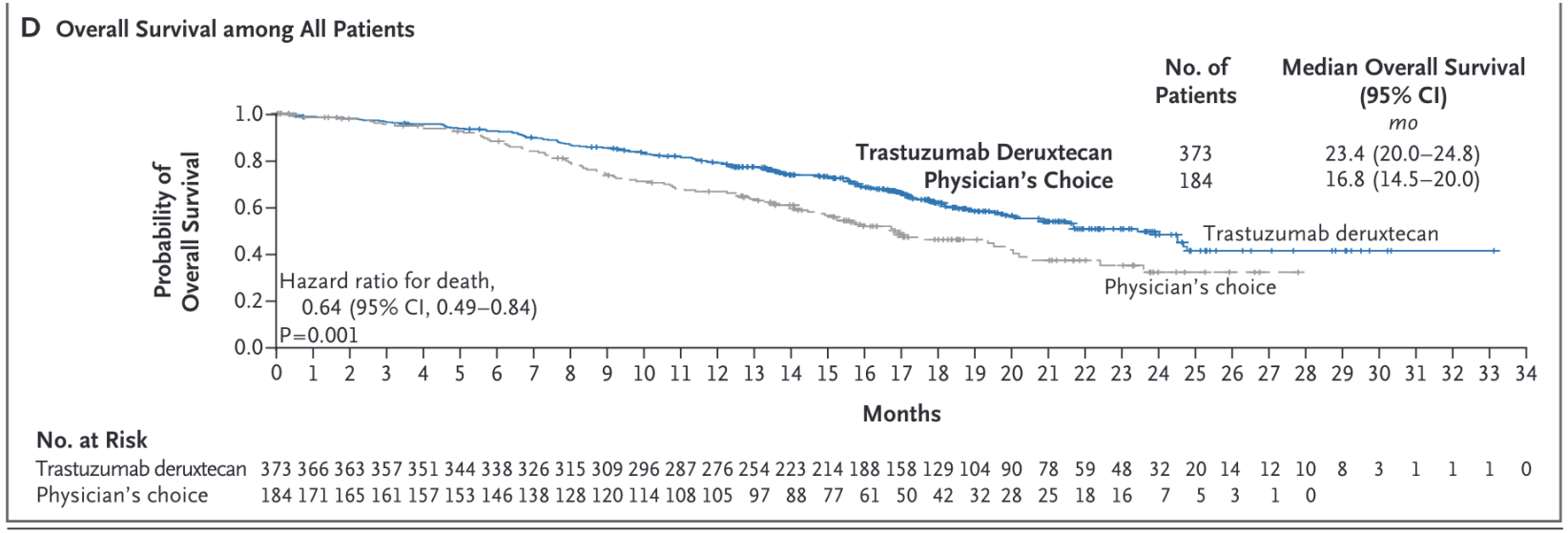

HER2 EXPRESS
~15% HER2-positive
~85%
(IHC 0, I
~60%
of patients with HER2-negative BC
low levels of HER2
(IHC 1+ or IHC 2+/


ERBB2-amplified
Benefit with the therapeutic blockade of the HER2 pathway
HER2-positive
HER2-negative
ERBB2-nonamplified
No benefit with HER2 blockade
Targetable with novel ADCs
HER2-positive
HER2-0
HER2-low
DESTINY-Breast04
?
HER2-positive
Continuous spectrum of HER2-low expression
HER2-positive
HER2-0
HER2-low
HER2-ultralow
Targetability with ADCs under investigation
?
DESTINY-Breast06


HER2 testing by validated IHC assay
Incomplete membrane staining that is faint/barely perceptible and > 10% of tumor cells
Membrane staining incomplete and faint/barely perceptible and ≤ 10% of tumor cells
No staining
HER2 score 2+
HER2 score 1+
HER2 score 0
no amplification
HER2-LOW
HER2-ULTRA-LOW
HER2-NEGATIVE

Destiny-04. Fase III forsøg til HER2-low patienter. TDXD vs. standard kemoterapi

N = 557, 89% ER+, 11% ER-
Ca. 70%, havde fået en CDK4/6-inhibitor
modtaget mediant 3 linjer behandling for metastatisk sygdom



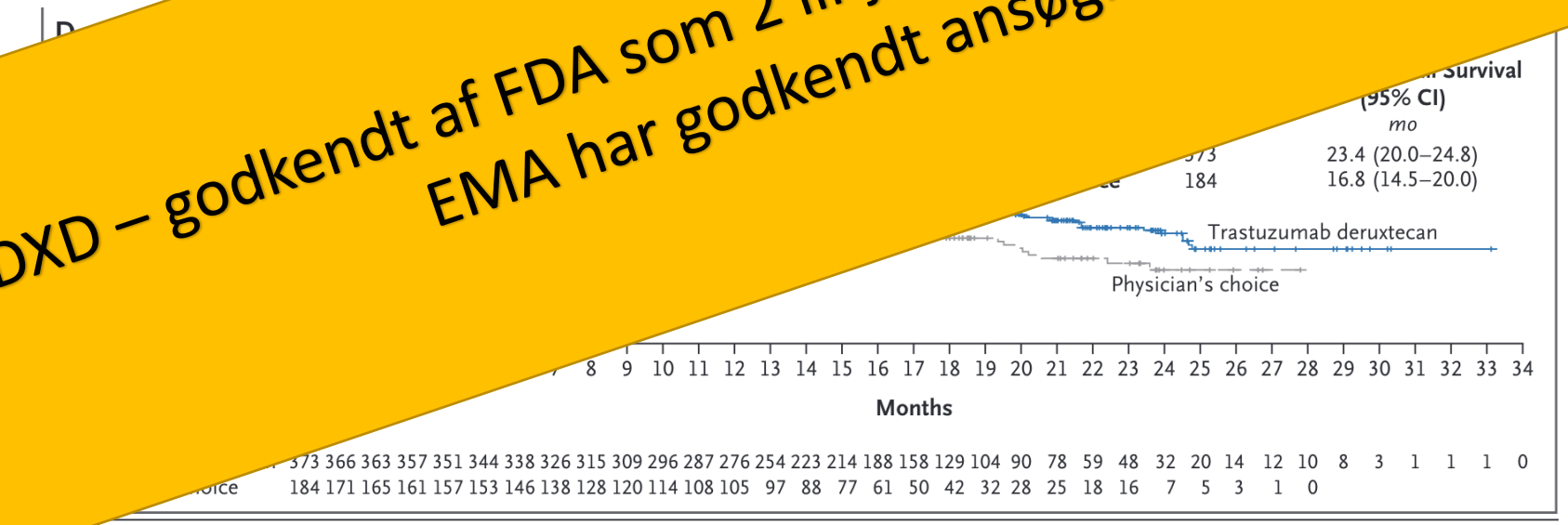
Modi S: DOI: 10.1056/NEJMoa2203690

Destiny-04. Fase III forsøg til HER2-low patienter. TDXD vs. standard kemot

N = 557, 89% ER+, 11% ER-

Ca. 70%, havde fået en CDK4/

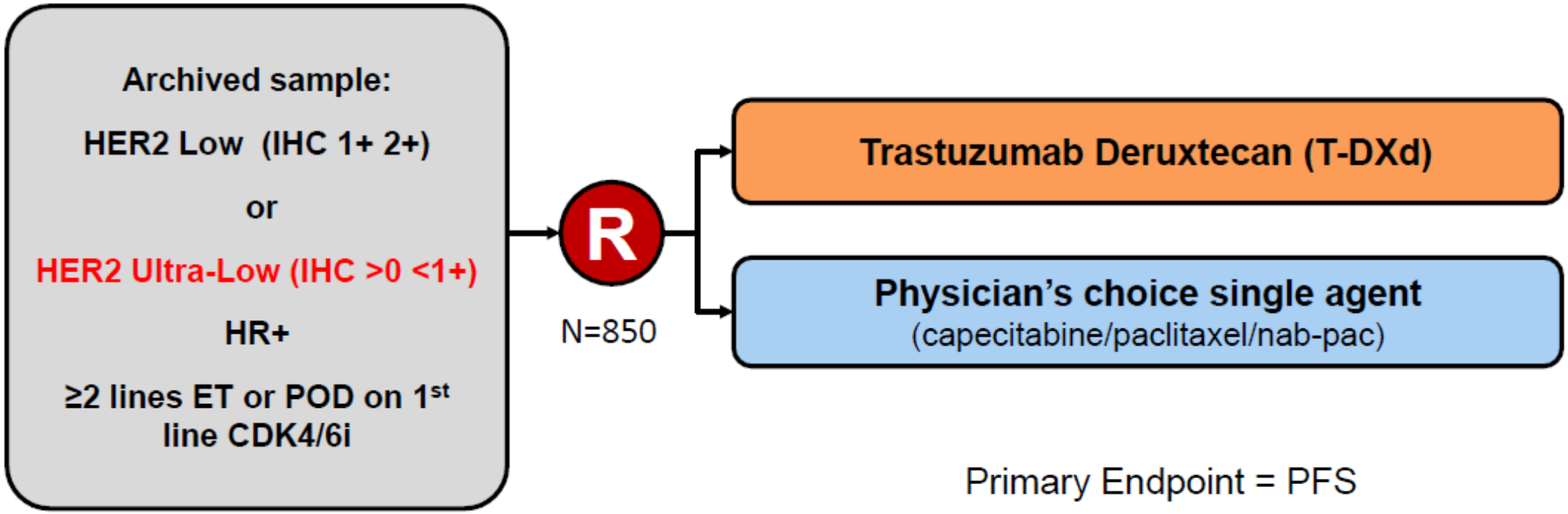
modtaget mediant 2



TDXD – godkendt af FDA som 2 linje behandling til HER2-low mBC
EMA har godkendt ansøgningen

Modi S: DOI: 10.1056/NEJMoa2203690

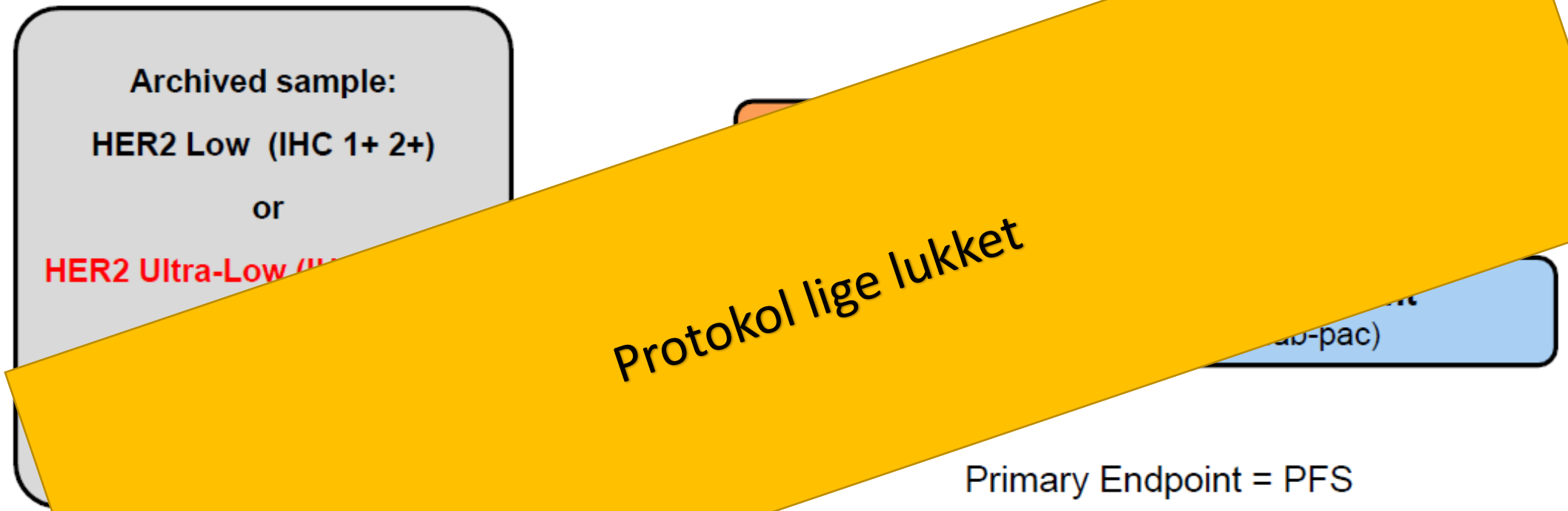
Destiny-06. Fase III forsøg til HER2-low el. 0 patienter. TDXD vs. standard kemoterapi



Primary Endpoint = PFS

ClinicalTrials.gov Identifier: NCT04494425

Destiny-06. Fase III forsøg til HER2-low el. 0 patienter. TDXD vs. standard kemot… i

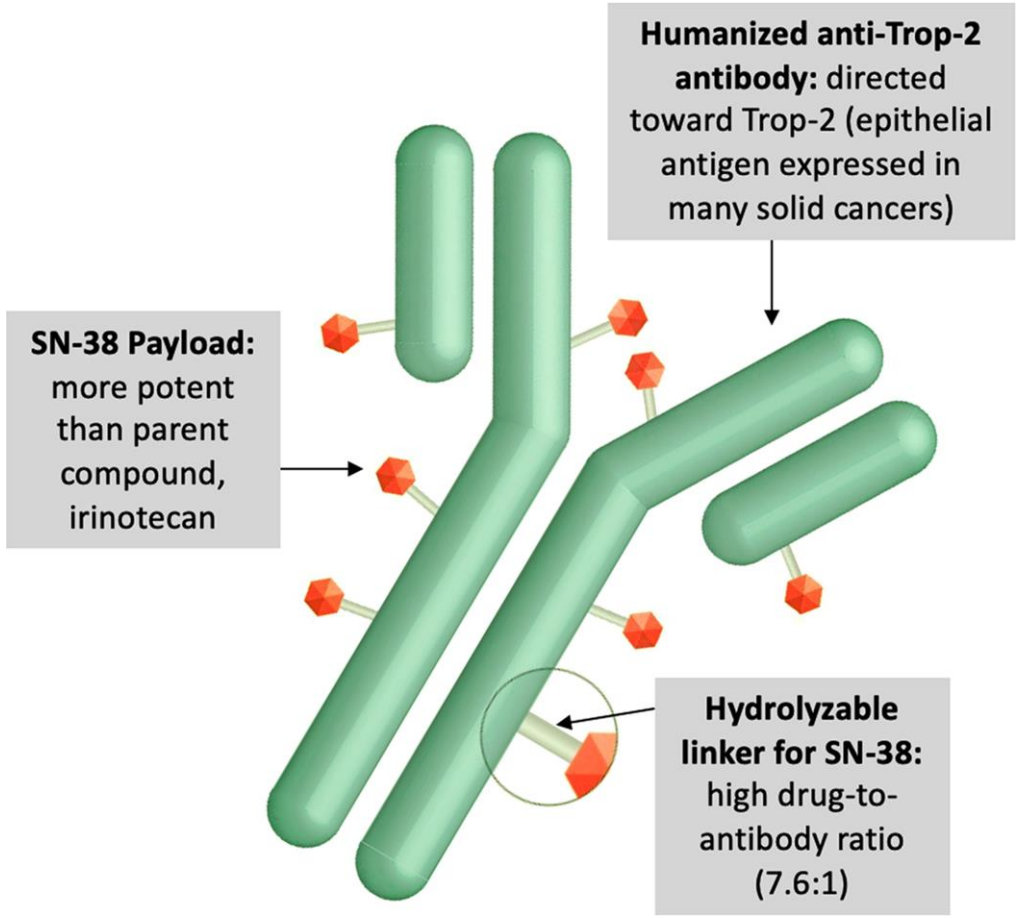


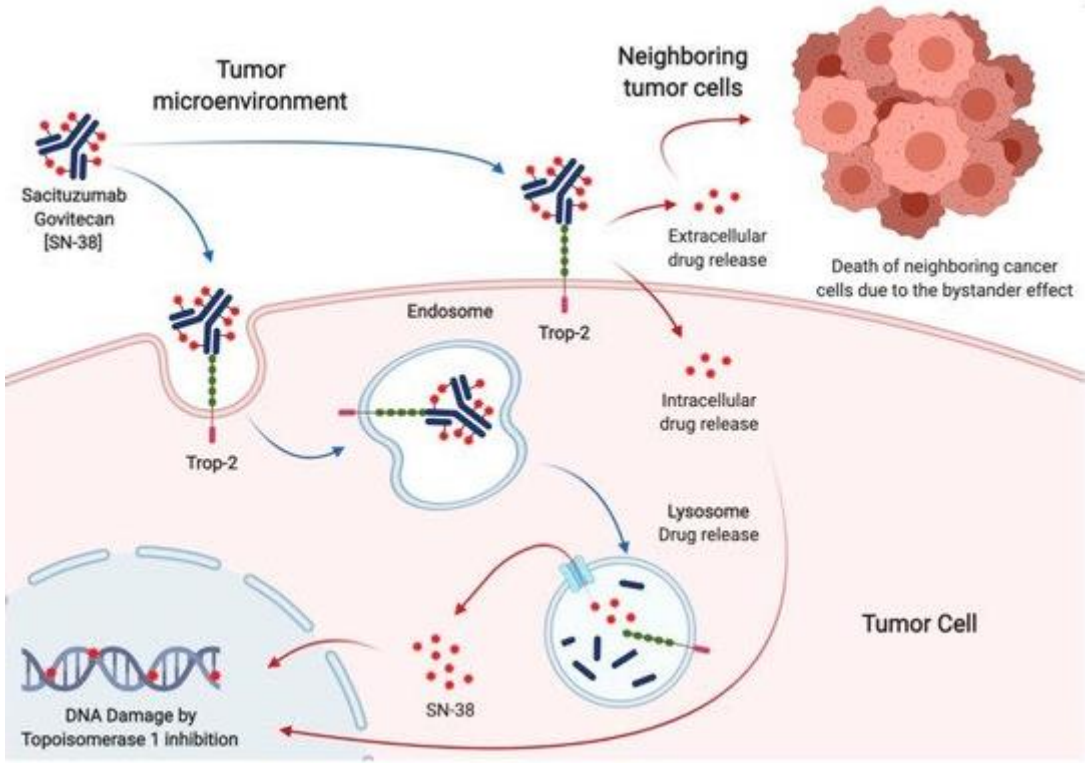
Protokol lige lukket

ClinicalTrials.gov Identifier: NCT04494425

TROP2-Targeteting ADCs

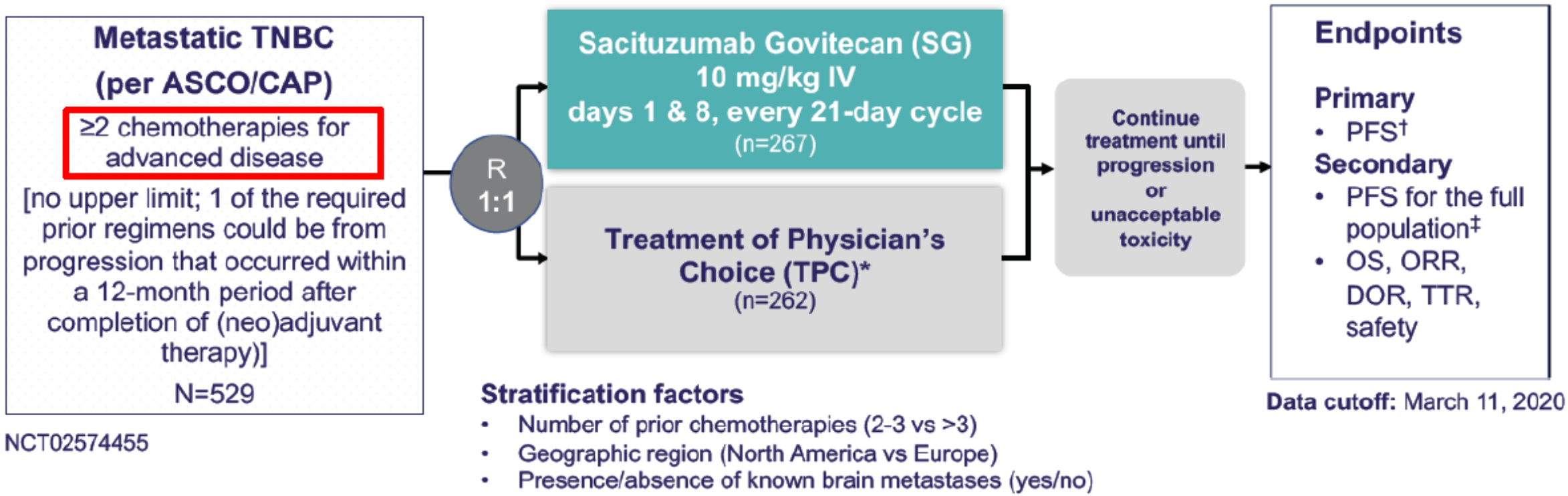
Sacituzumab Govitecan (sniger sig ind via tumor-associated calcium signal transducer 2)





The Oncologist, Volume: 26, Issue: 10, Pages: 827-834, First published: 27 June 2021, DOI: (10.1002/onco.13878)

Ascent. Fase III forsøg til ER-, HER2- mBC SG vs standard.

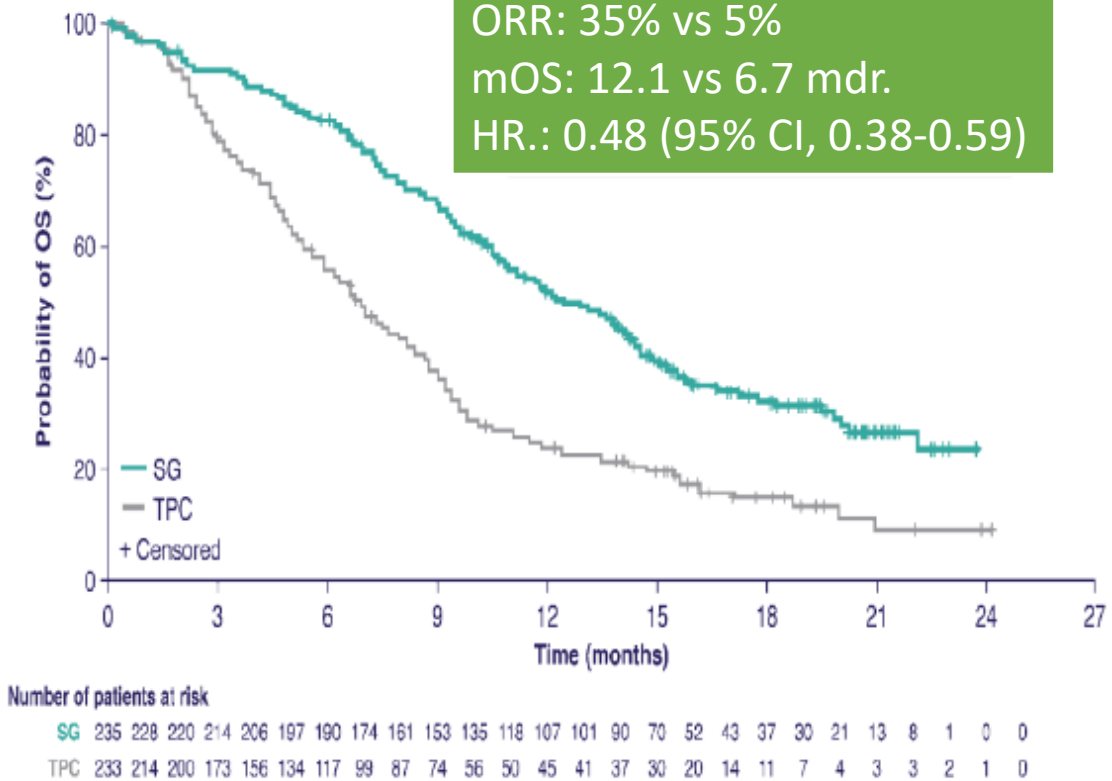


* TPC options: capecitabine, eribulin, gemcitabine, vinorelbine

Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541.

ASCENT: Sacituzumab Associated With 52% Increase in OS!

ORR: 35% vs 5%
mOS: 12.1 vs 6.7 mdr.
HR.: 0.48 (95% CI, 0.38-0.59)



Treatment-related discontinuation rates: Sacituzumab 4.7%, TPC 5.4%

TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

		SG (n=258)			TPC (n=224)		
	TRAE*	All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	Neutropenia†	63	46	17	43	27	13
	Anemia‡	34	8	0	24	5	0
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	Diarrhea	59	10	0	12	<1	0
	Nausea	57	2	<1	26	<1	0
	Vomiting	29	1	<1	10	<1	0
Other	Fatigue	45	3	0	30	5	0
	Alopecia	46	0	0	16	0	0

Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541.

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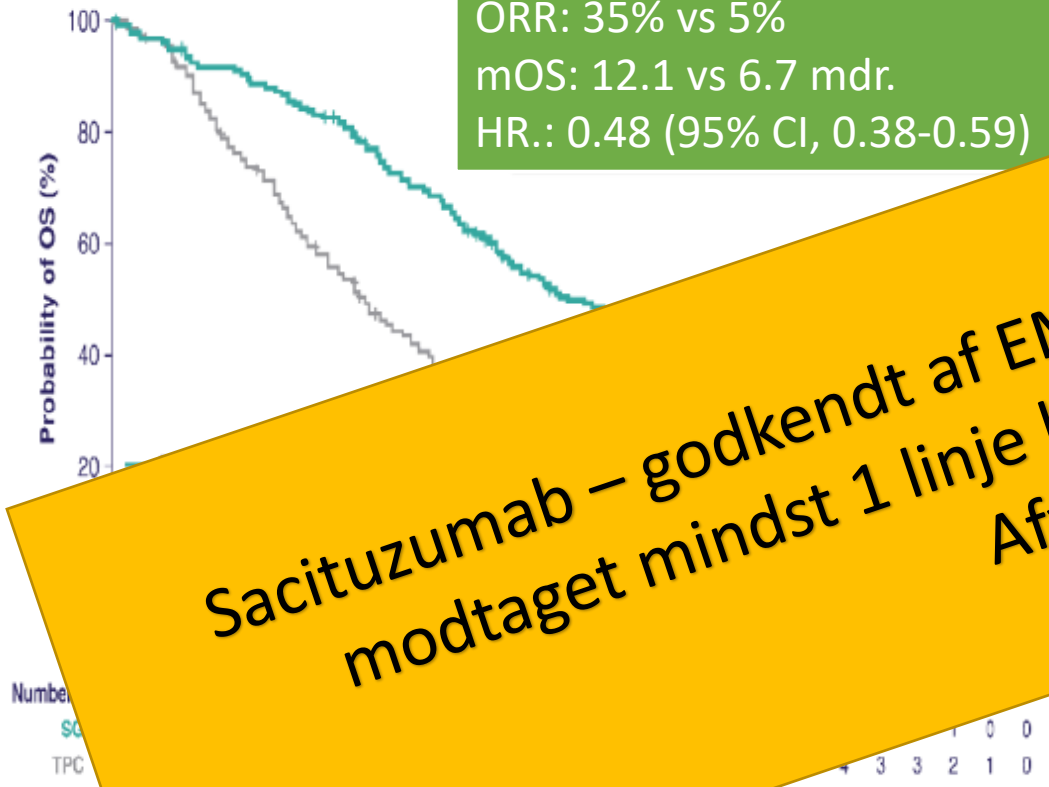


Sacituzumab – godkendt af EMA og FDA til patienter, der har modtaget mindst 1 linje behandling for deres mTNBC
Afvist i DK

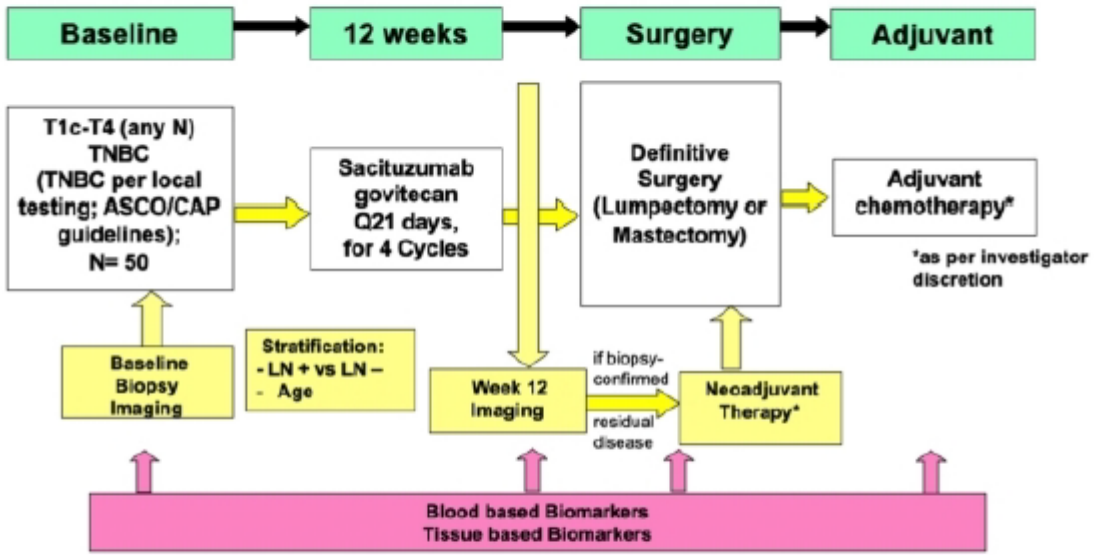
Treatment-related disc… …ab 4.7%, TPC 5.4%

TRAE… …f Patients)

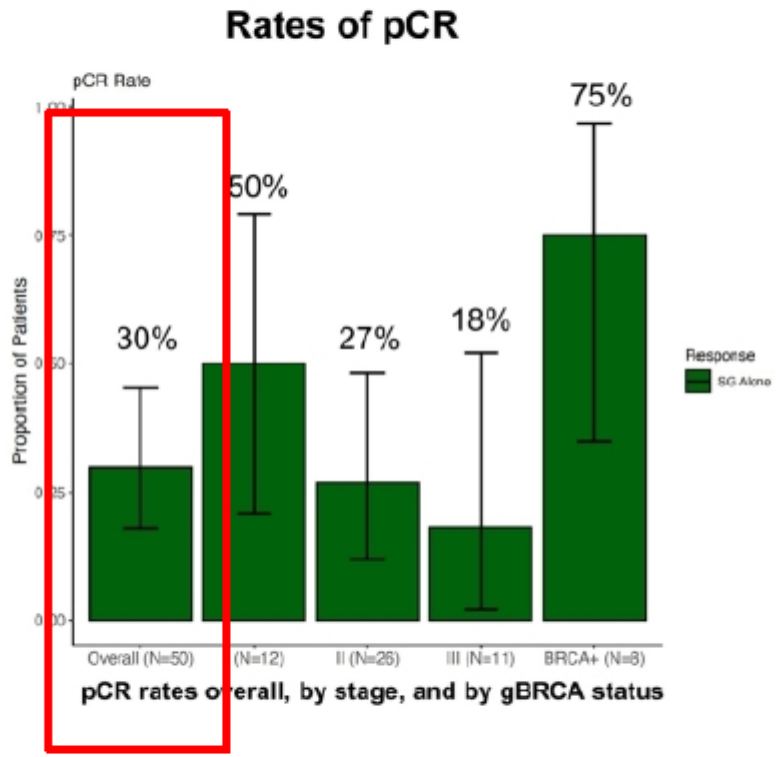
					TPC (n=224)	
					Grade 3, %	Grade 4, %
					27	13
				24	5	0
			1	11	5	1
		5	1	2	2	<1
		59	10	0	12	<1	0
	…usea	57	2	<1	26	<1	0
	Vomiting	29	1	<1	10	<1	0
Other	Fatigue	45	3	0	30	5	0
	Alopecia	46	0	0	16	0	0

Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541.

NeoSTAR Trial: neoadjuvant Sacituzumab for TNBC



N=50



Future plans: Consider optimal number of cycles and combinations

Spring L et al, ASCO 2022

TROPiCS02. Fase III forsøg til ER+, HER2- mBC SG vs standard.

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after:

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months

N=543

R
1:1

Sacituzumab govitecan
10 mg/kg IV
days 1 and 8, every 21 days
n=272

Treatment of physician's choice
(capecitabine, vinorelbine, gemcitabine or eribulin)
n=271

Endpoints

Primary
- PFS by BICR

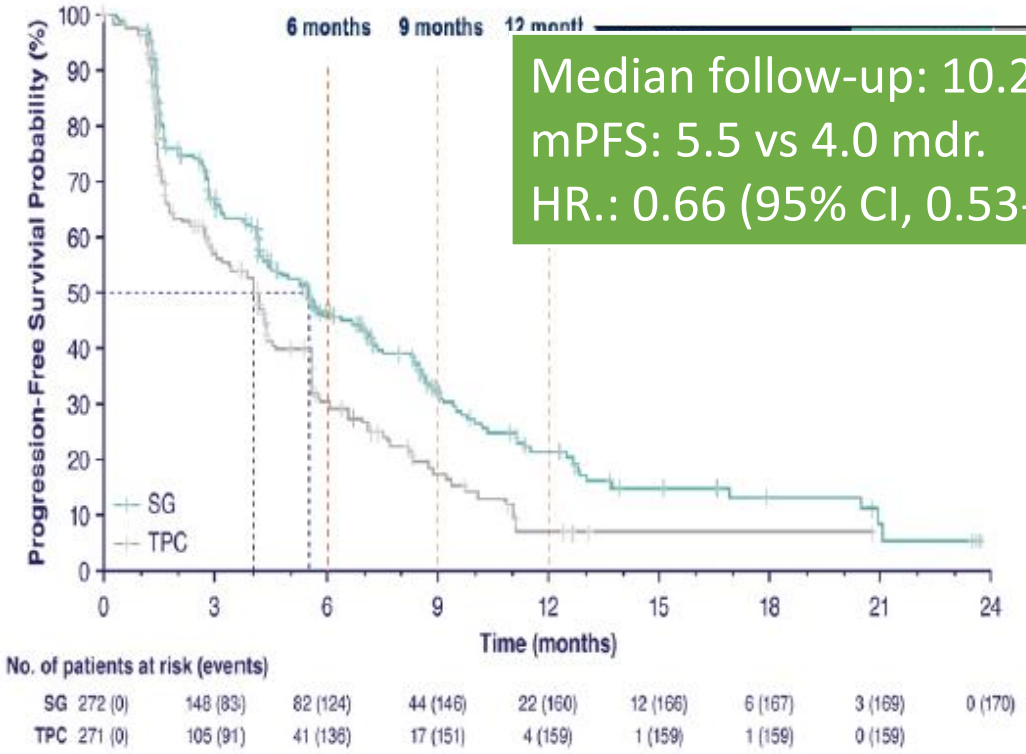
Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

Median prior lines of therapy = 3
All patients had prior CDK4/6i therapy

Rugo H et al, ESMO 2022

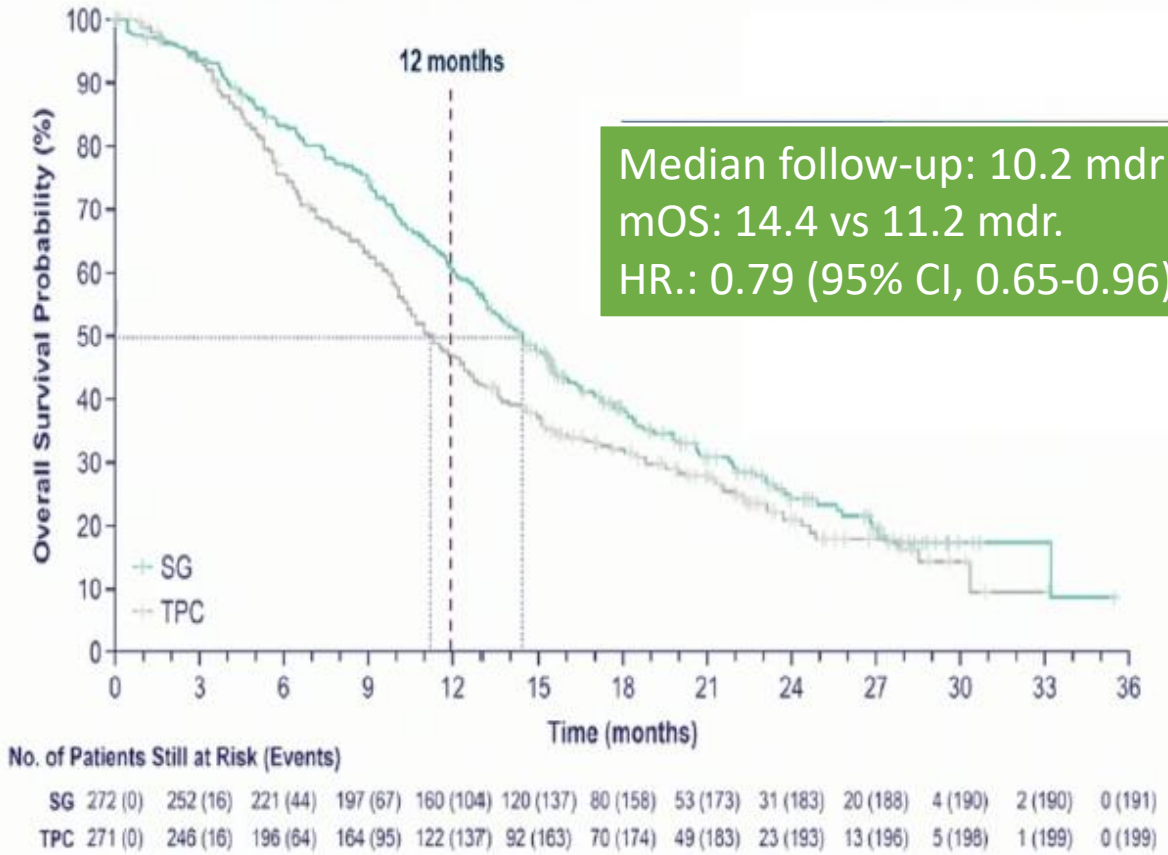
TROPiCS-02 Efficacy Endpoints

Progression Free Survival



Median follow-up: 10.2 mdr
mPFS: 5.5 vs 4.0 mdr.
HR.: 0.66 (95% CI, 0.53-0.83)

Overall Survival



Median follow-up: 10.2 mdr
mOS: 14.4 vs 11.2 mdr.
HR.: 0.79 (95% CI, 0.65-0.96)

Median follow-u
BICR, blinded independent central review; ITT, intent-to-treat; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

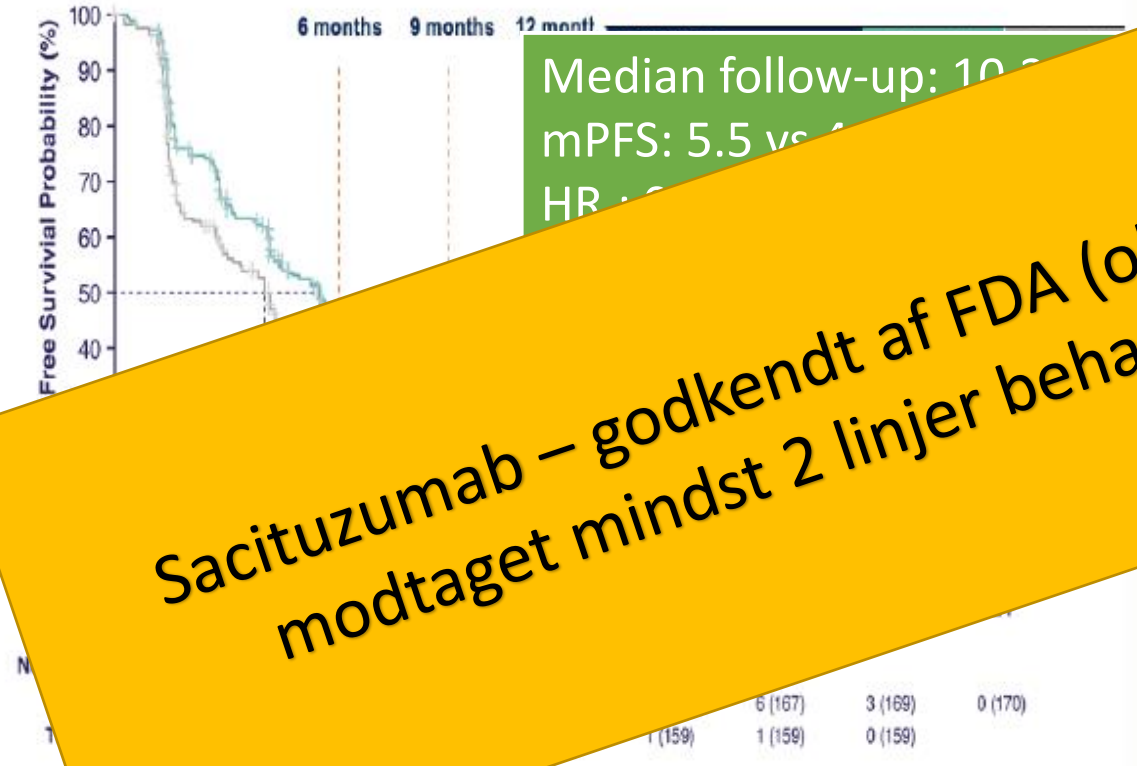
Rugo H et al, ESMO 2022

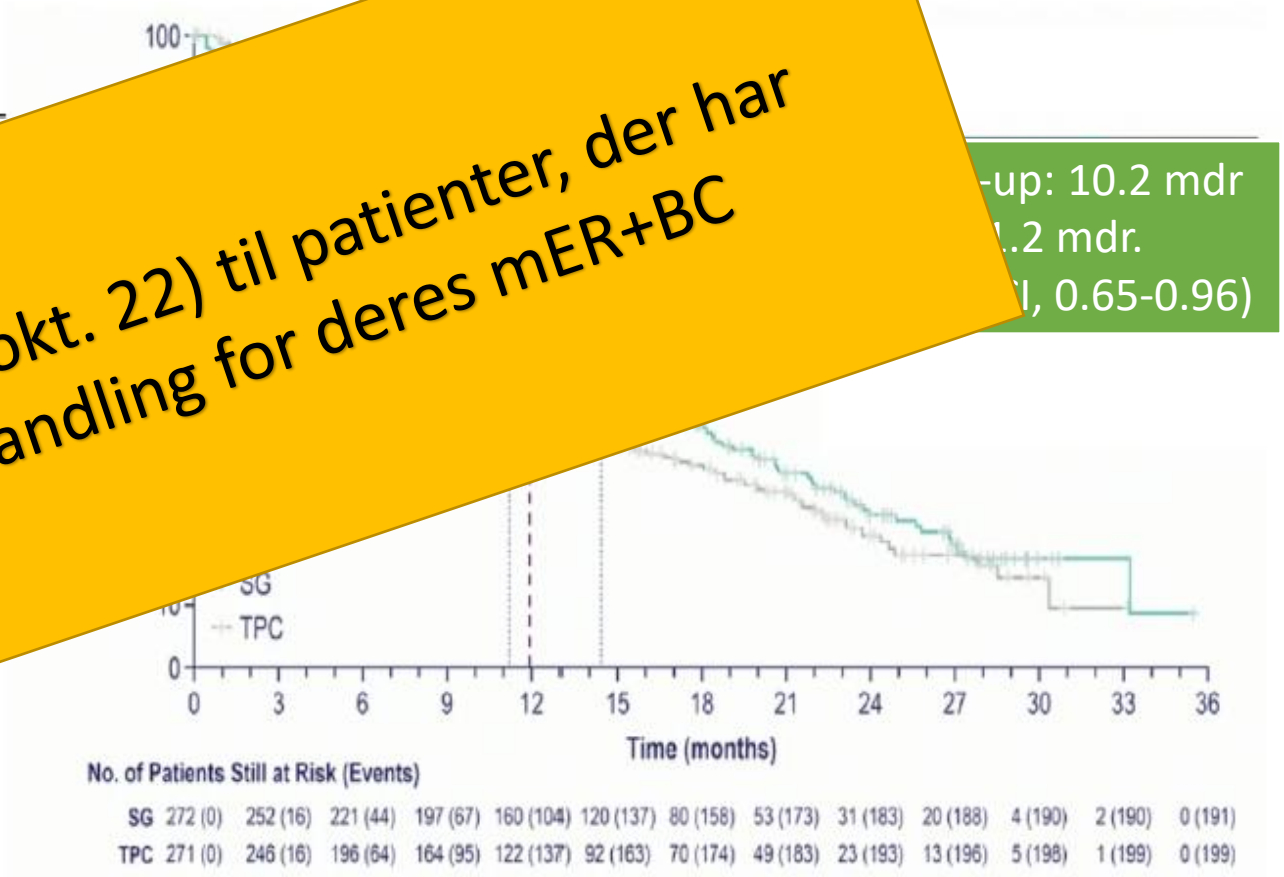
TROPiCS-02 Efficacy Endpoints

Progression Free Survival

Median follow-up: 10.2 mdr
mPFS: 5.5 vs 4.0 mdr.
HR: 0.66 (95% CI, 0.65-0.96)

Sacituzumab – godkendt af FDA (okt. 22) til patienter, der har modtaget mindst 2 linjer behandling for deres mER+BC



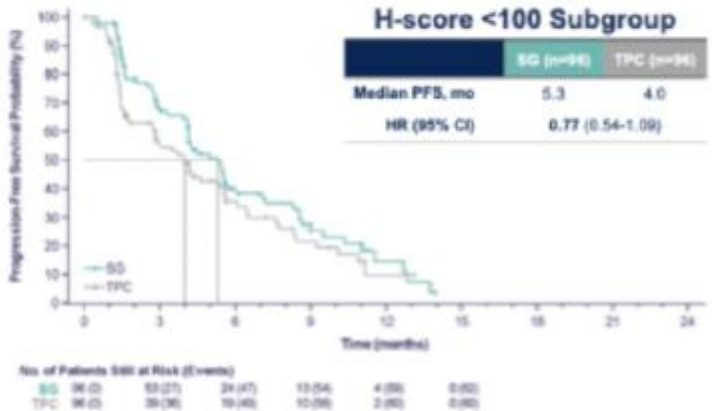


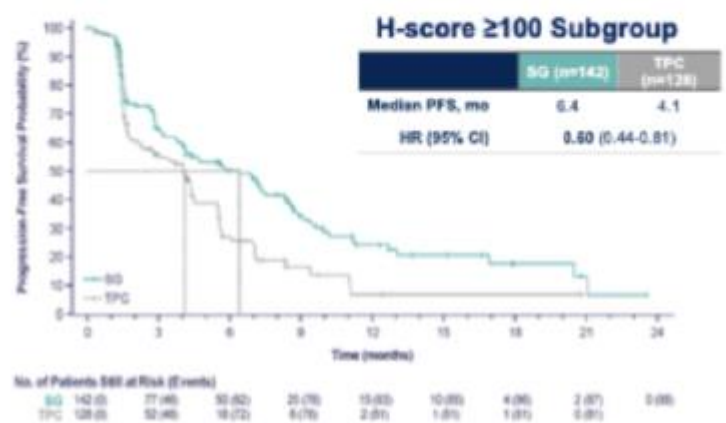
Median follow-u
BICR, blinded independent central review; ITT, intent-to-treat; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Rugo H et al, ESMO 2022

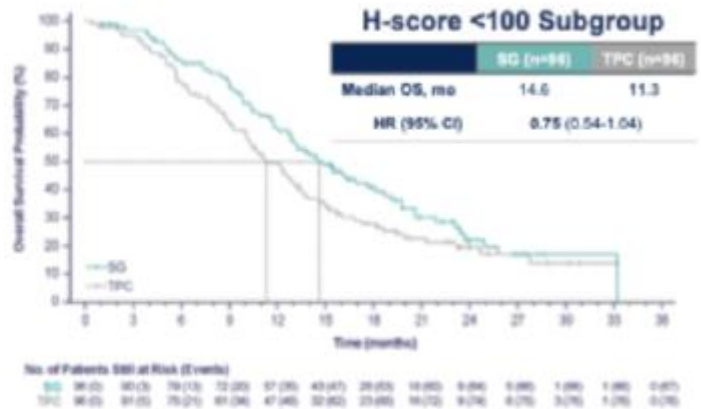
Sacituzumab improves PFS and OS across TROP-2 expression levels in TROPICS- O2

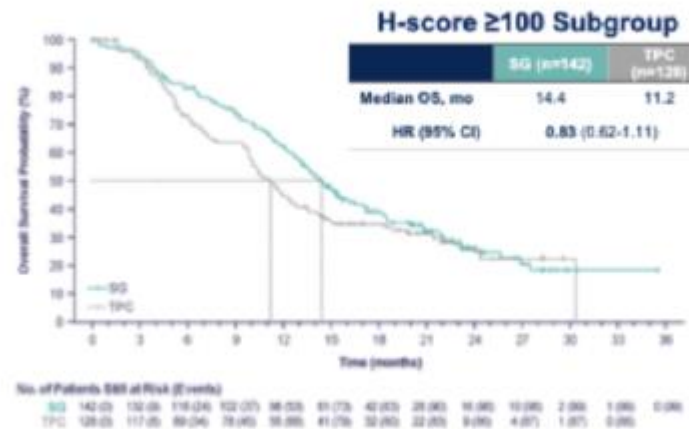
Progression Free Survival (PFS)





Overall Survival (OS)



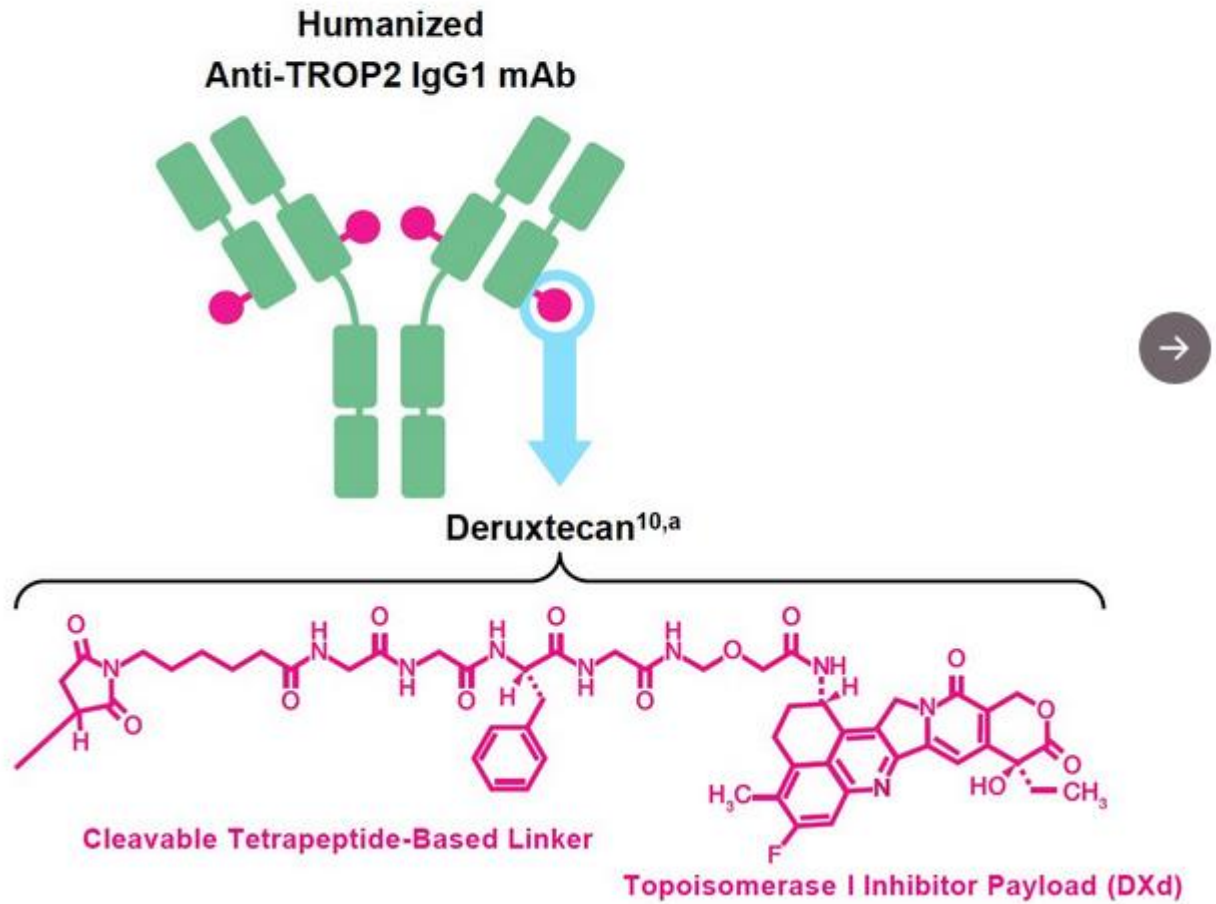


Rugo H et al, SABC 2022

Datopotamab Deruxtecan (Dato-DXd; DS-1062) and TROP2

Kombination af ”TDXD” og Trop2-targeteret antistof – den nye i klassen…

- Datopotamab deruxtecan (Dato-DXd; DS-1062) is a TROP2 directed ADC composed of 3 components[7,8]:
  - A humanized anti-TROP2 IgG1[9] mAb
  - A topoisomerase 1 inhibitor payload (exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker



TROP2 ADC til residual sygdom efter NACT

TROPION B-03

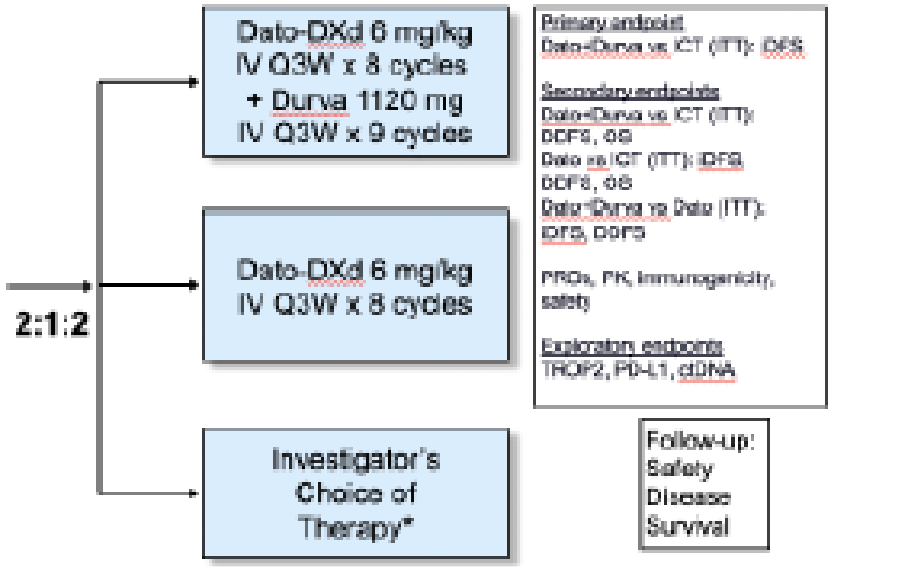
Phase 3 Dato-DXd +/- Durvalumab in Adjuvant Residual Disease TNBC

Key Eligibility Criteria

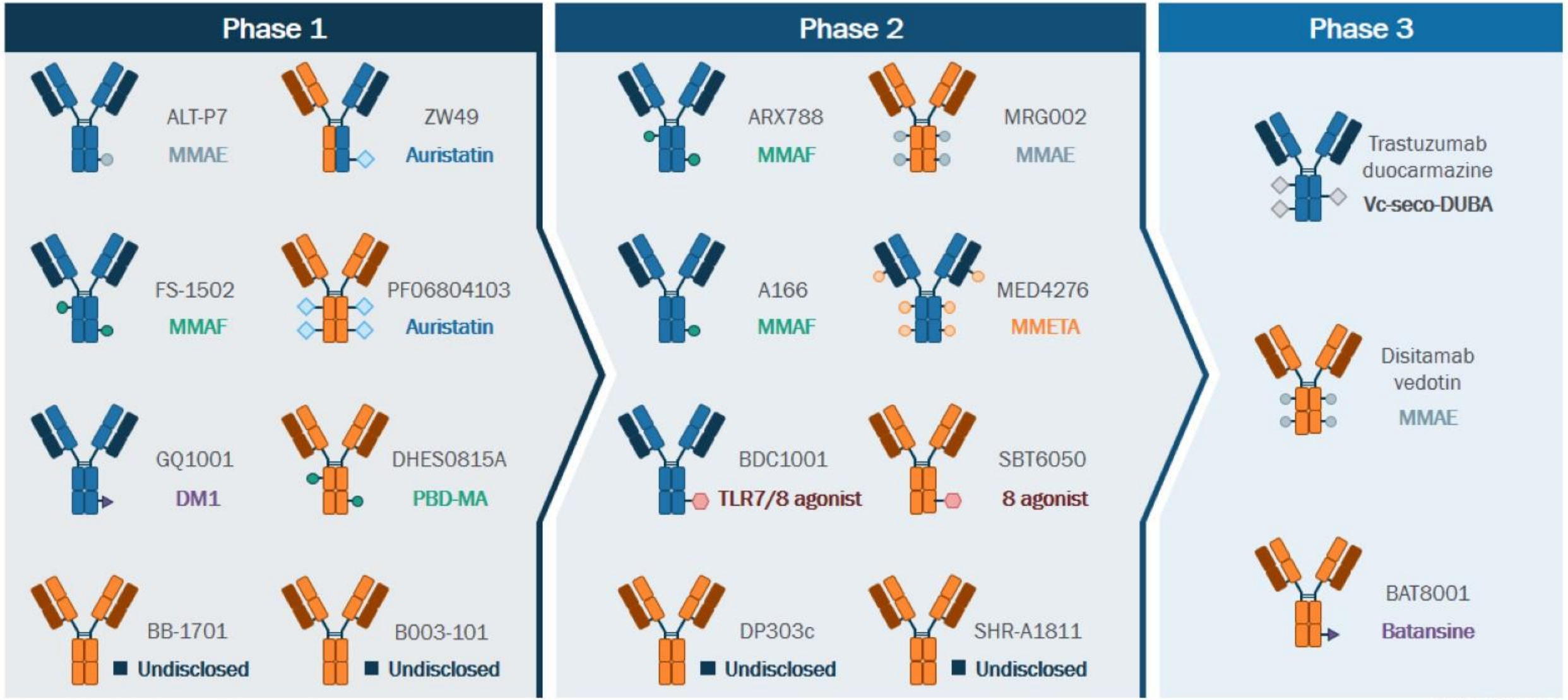
- Histologically confirmed invasive TNBC (ER<1%, PR<1%, HER2-negative)
- Completed at least 6 cycles of neoadjuvant therapy containing an anthracycline and/or a taxane with or without carboplatin, with or without pembrolizumab.
- Residual invasive disease after neoadjuvant therapy
- No evidence of loco-regional or distant relapse
- Radiotherapy delivered before the start of study treatment
- No adjuvant systemic therapy
- ECOG PS 0 or 1
- Adequate bone marrow reserve and organ function
- No known germline BRCA1 and BRCA2 mutation

Stratification factors:

- Prior neoadjuvant pembrolizumab (Yes vs No); cap No at 40%
- Residual disease (< 1 cm vs ≥ 1 cm); cap < 1 cm at 20%
- Prior neoadjuvant platinum chemotherapy (Yes vs No)



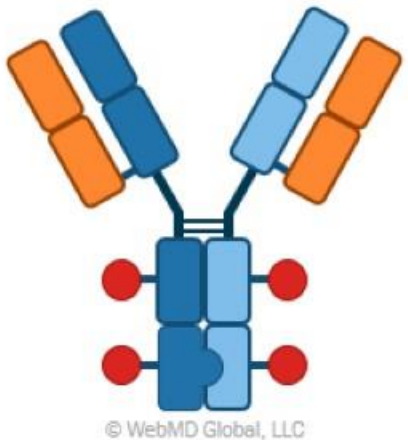
Novel Antibody-Drug Conjugates (cont)



Diaz-Rodriguez E, et al. Cancers 2022;14:154.

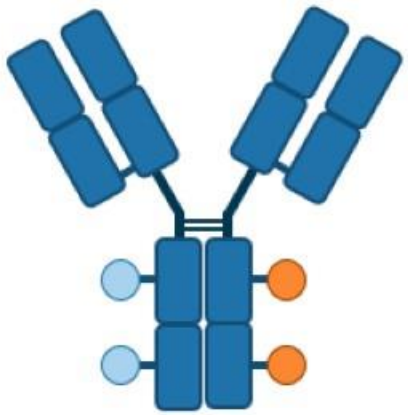
New Vehicles and Payloads

Bispecific ADCs[a,b]



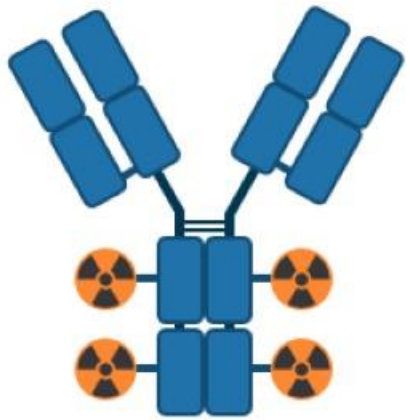
Encouraging response rate in highly pretreated patients with HER2+ solid tumors

Dual payload ADCs[c]



Solid activity in HER2+ breast cancer models when combining MMAE and MMAF payloads

Radionuclide/ IO ADCs[d,e]

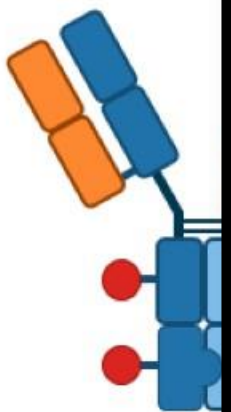


Early clinical activity observed in a phase 1 trial of a P-cadherin–targeted radioimmunotherapy with 90Y

a. Tarantino P, et al. CA Can J Clin 2022;72:165-182; b. Jhaveri K, et al. Ann Oncol. 2022;33(suppl 7):S197-S224, Abstract 460MO; c. Yamazaki CM, et al. Nat Commun. 2021;12:3528; d. Funase Y, et al. Nucl Med. 2021;62:232-239; e. Subbiah V, et al. Clin Cancer Res. 2020;26:5830-5842.

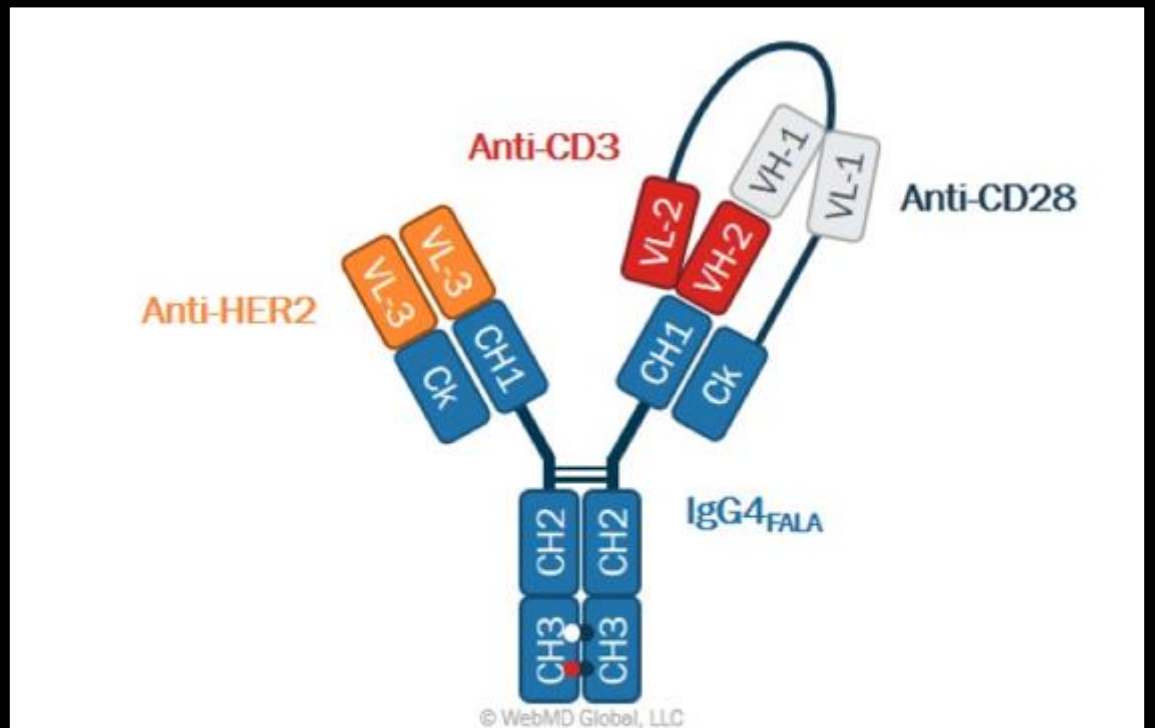
New Vehicles and Payloads

Bispecific



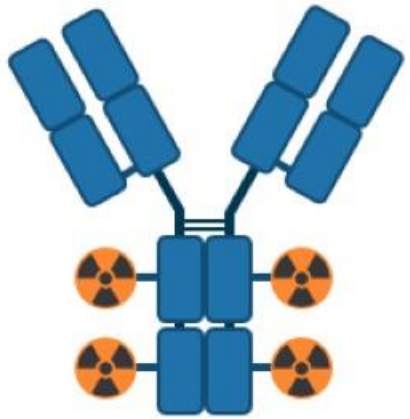
© WebMD G

Encouraging re
in highly pretre
with HER2+ s



Seung E, et al. Nature. 2022;603(7900):328-334.

Radionuclide/ IO ADCs[d,e]



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New Targets on the Horizon

HER3

NECTIN4

FRα

MESOTHELIN

MUC1

LIV1

B7H4

CEACAM

CD166

CD71

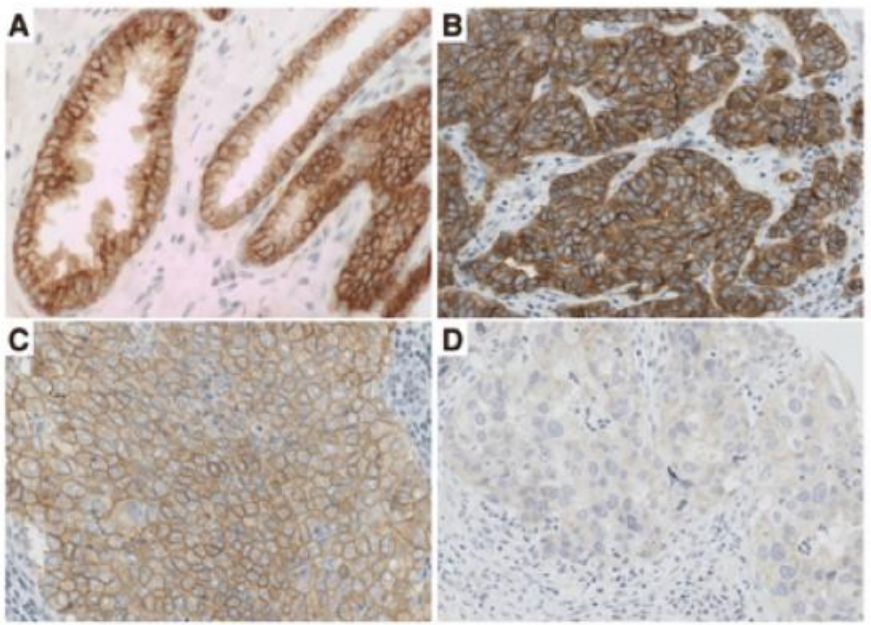
New Targets on the Horizon

HER3 | NECTIN4 | FRα | MESOTHELIN | MUC1

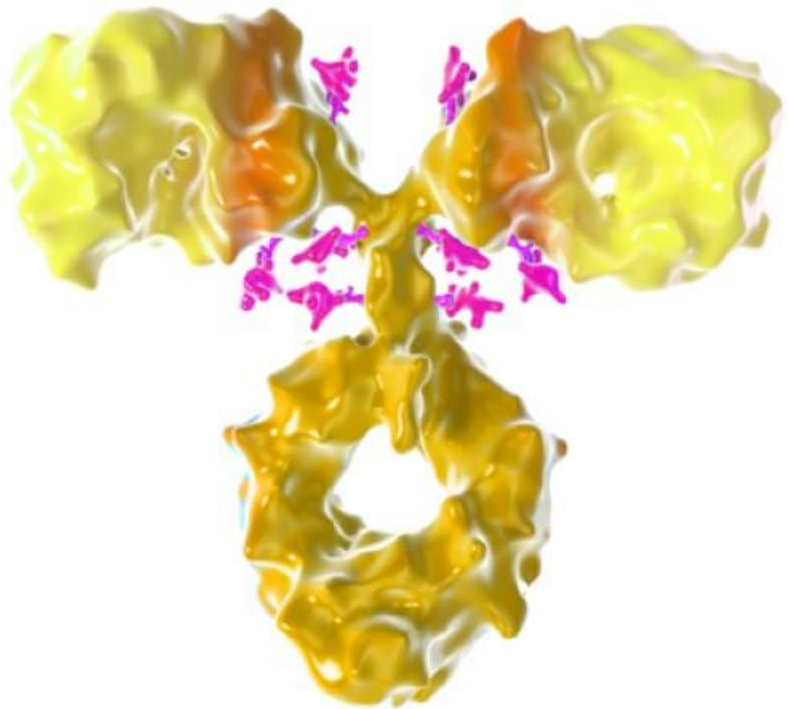
LIV1 | B7H4 | CEACAM | CD166 | CD71

HER3-DXd

HER3 is expressed in > 95% of breast cancers, with half showing a strong overexpression



Patritumab deruxtecan (U3-1402) is a novel ADC coupling an anti-HER3 mAb to DXd with a high DAR (8:1)



Luthala S. et al. BMC Cancer. 2018;18:1045.

HER3-DXd

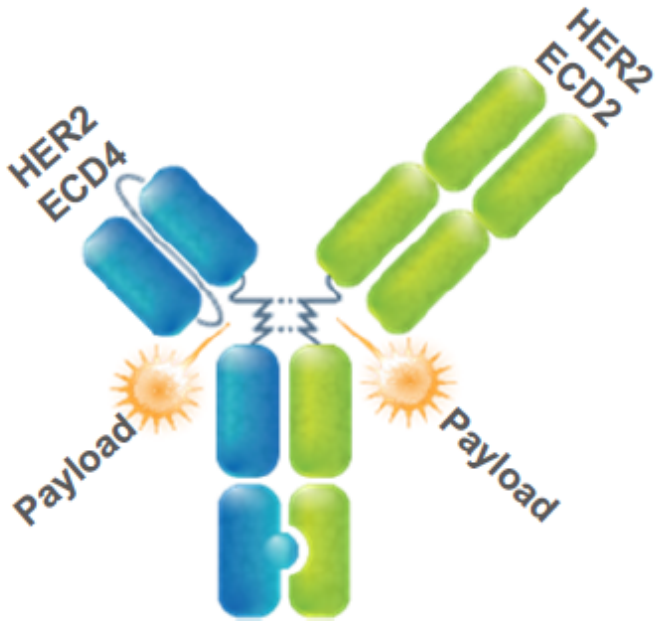
Outcomes (BICR per RECIST 1.1)	HR+/HER2− (n = 113) HER3-High and -Low	TNBC (n = 53) HER3-High	HER2+ (n = 14) HER3-High
Confirmed ORR, % (95% CI[a])	30.1 (21.8, 39.4)	22.6 (12.3, 36.2)	42.9 (17.7, 71.1)
Best overall response, %[b]			
PR	30.1	22.6	42.9
SD	50.4	56.6	50.0
PD	11.5	17.0	7.1
NE	8.0	3.8	0.0
DOR, median (95% CI), mo	7.2 (5.3, NE)	5.9 (3.0, 8.4)	8.3 (2.8, 26.4)
PFS, median (95% CI), mo	7.4 (4.7, 8.4)	5.5 (3.9, 6.8)	11.0 (4.4, 16.4)
6-month PFS rate, % (95% CI)	53.5 (43.4, 62.6)	38.2 (24.2, 52.0)	51.6 (22.1, 74.8)
OS, median (95% CI), mo	14.6 (11.3, 19.5)	14.6 (11.2, 17.2)	19.5 (12.2, NE)

HER3-DXd demonstrated durable antitumor activity across BC subtypes

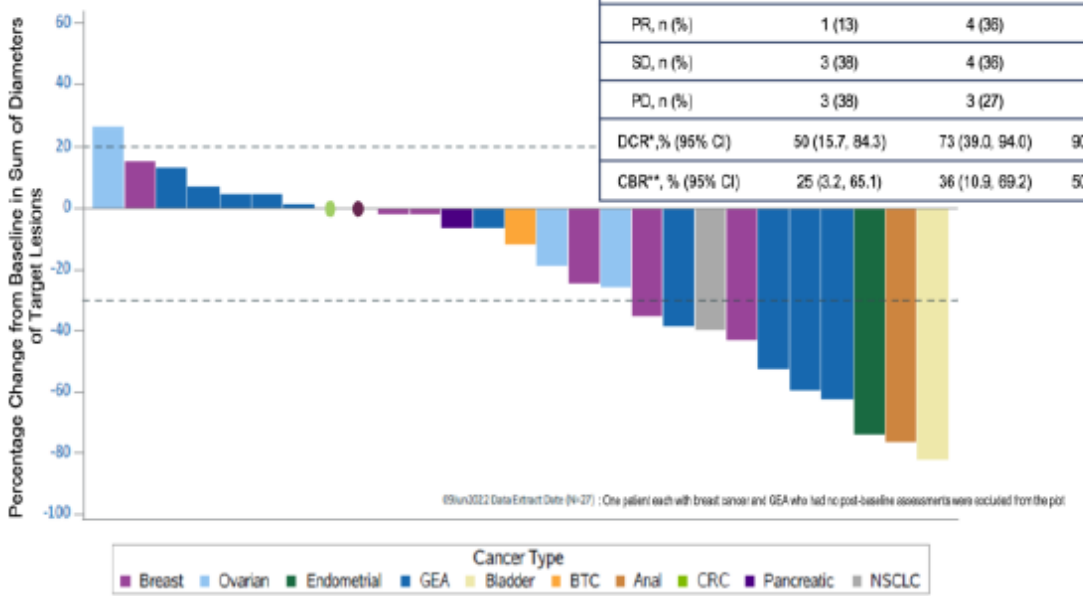
- Confirmed ORR for all patients (N = 182), 28.6% (95% CI, 22.1%, 35.7%); median DOR, 7.0 mo (95% CI, 5.5, 8.5 mo)

Krop I, et al. J Clin Oncol. 2022;40:(suppl 16): Abstract 1002.

Zanidatamab Zovodotin (ZW49): Anti-HER2 Bispecific ADC



	Breast (n=8)	GEA (n=11)	All Other (n=10)	Total (N=29)[a]
cORR, % (95% CI)	13 (0.3, 52.7)	36 (10.9, 69.2)	40 (12.2, 73.8)	31 (15.3, 50.8)
PR, n (%)	1 (13)	4 (36)	4 (40)	9 (31)
SD, n (%)	3 (38)	4 (36)	5 (50)	12 (41)
PD, n (%)	3 (38)	3 (27)	1 (10)	7 (24)
DCR*,% (95% CI)	50 (15.7, 84.3)	73 (39.0, 94.0)	90 (55.5, 99.7)	72 (52.8, 87.3)
CBR**, % (95% CI)	25 (3.2, 65.1)	36 (10.9, 69.2)	50 (18.7, 81.3)	38 (20.7, 57.7)

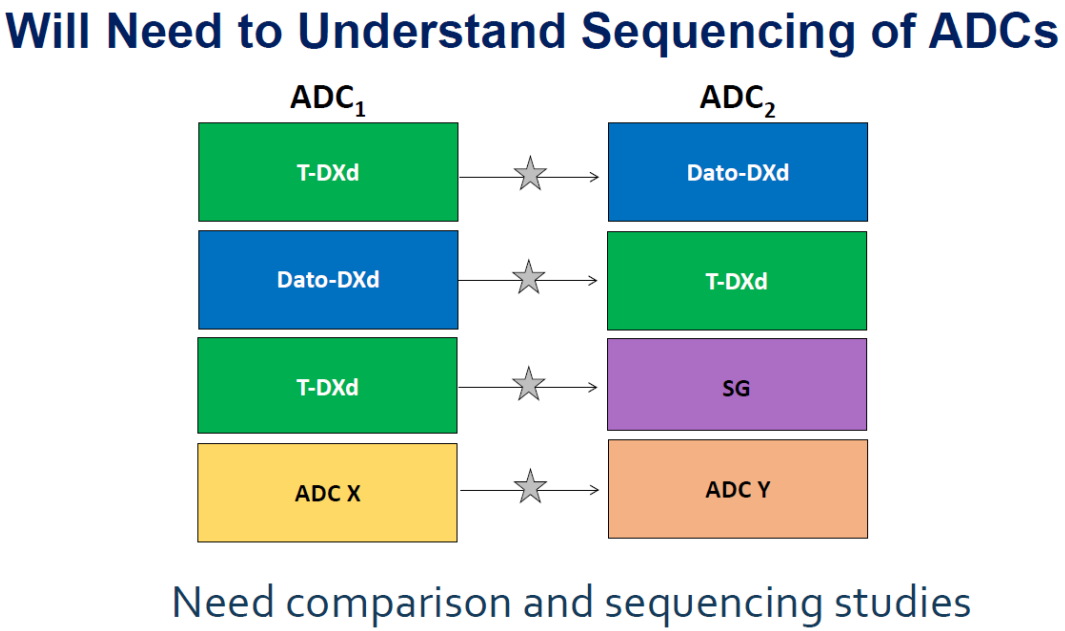


[a]One patient of the 30 treated at 2.5 mg/kg Q3W was HER2 negative per central review and not included. *DCR = CR, PR, or SD. **CBR = SD ≥ 24 weeks or best overall response of CR or PR.
BTC = biliary tract cancer; CBR = clinical benefit rate; cORR = confirmed objective response rate; CRC = colorectal cancer; DCR = disease control rate; DE = dose escalation; DX = dose expansion; GEA = gastroesophageal adenocarcinoma; NSCLC = non-small cell lung cancer; PD = progressive disease; PR = partial response; Q3W = once every 3 weeks; SD = stable disease

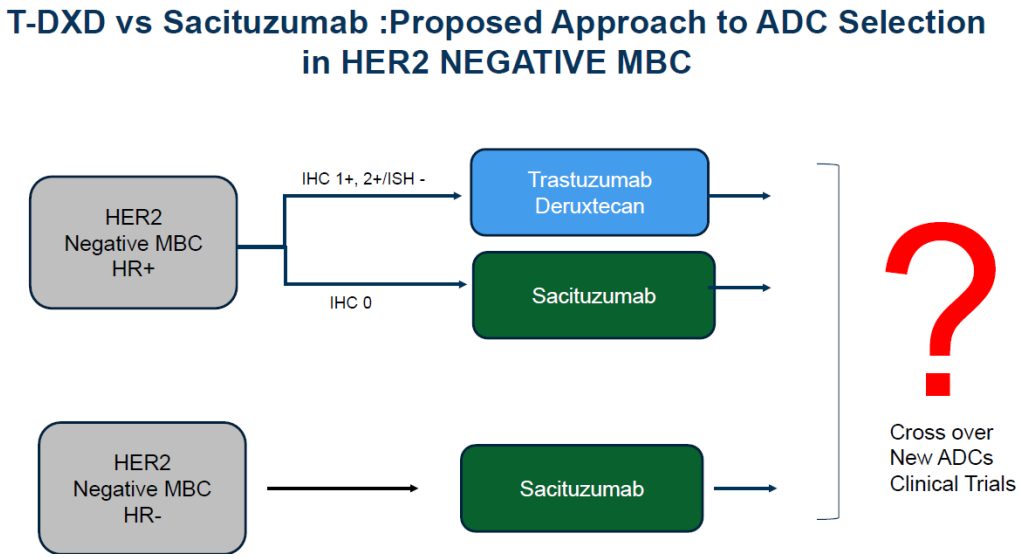
- Immunoglobulin 1-like antibody backbone directed against extracellular domain 4 (ECD4) & ECD2 of HER2
- Auristatin payload (tubulin targeting) covalently linked via a protease cleavable valine-citruline linker ; (DAR) = 2
- Antibody-induced internalization with increased toxin-mediated cytotoxicity and immunogenic cell death

Jhaveri K et al, ESMO 2022

Mange spørgsmål



Need comparison and sequencing studies



Opsamling

- Teknologiske fremskridt har bragt os ind i en spændende æra med ADC behandling
  - Næste generations lægemidler med forbedrede egenskaber har forbedret effektivitet
  - De nye lægemidler har bredere klinisk anvendelighed og har udvidet målgruppen

• Payload.: + parpi, immunterapi…

Targetmodulation med TKI-er eller statiner?

???

  - Biomarkører for respons
  - Vel-designede studier vedr. rækkefølge
  - Viden om resistensudvikling