

Anticorpos Conjugados à Droga em Câncer de Mama Triplo Negativo

Debora de Melo Gagliato

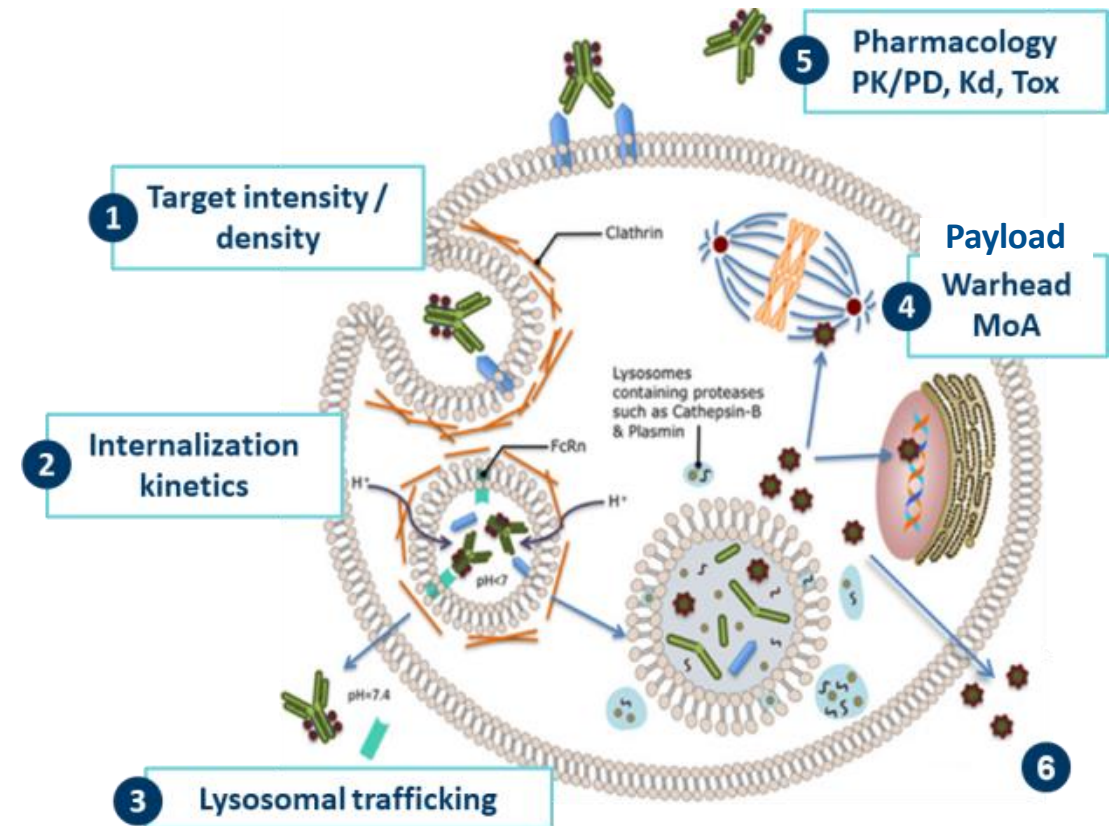
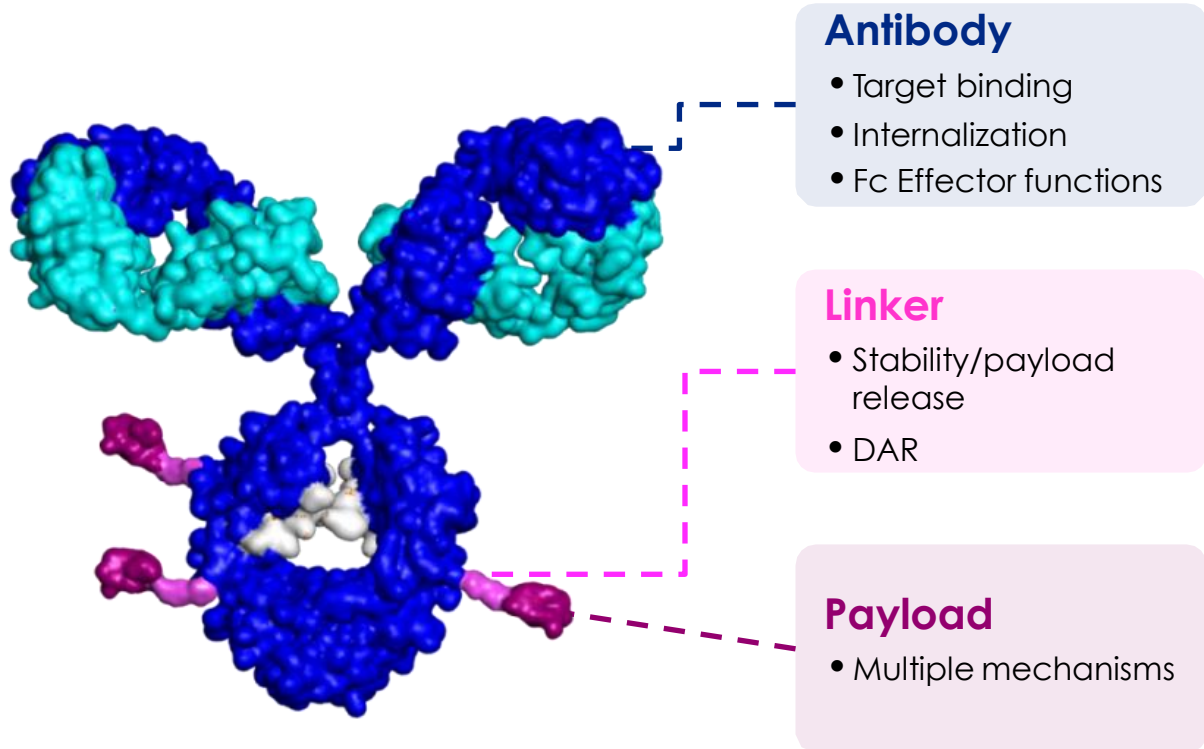
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the University of Texas



A Beneficência
Portuguesa
de São Paulo

Anatomy and Mechanism of action of ADCs

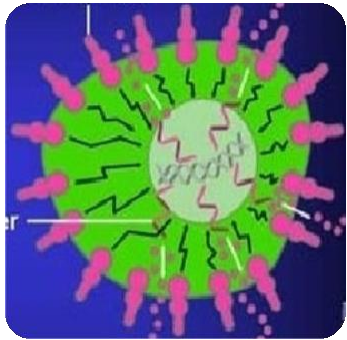
Antibody Drug Conjugate



Considerations for choosing optimal ADC targets

1

Surface protein density



- High target density for solid tumors

HER2: $1.2 \times 10^5 - 200,000$ ¹

FOLR: 300,000²

TROP2: 250,000³

- Lineage-restricted targets for heme

¹ <https://doi.org/10.1373/clinchem.2017.274266>

² Yao, X et al. Int J Cancer. 2013 December 15; 133(12): 2925–2933

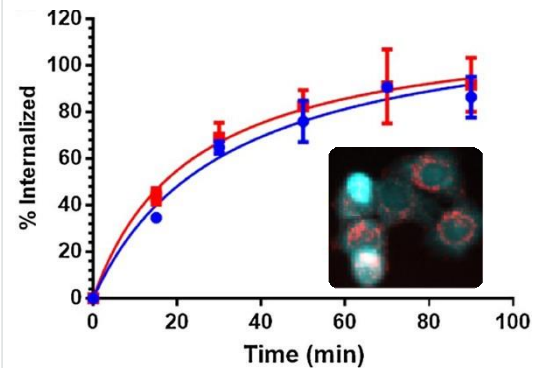
³ Cell Signaling Tech. surface proteomics database, patient samples

2

Internalization

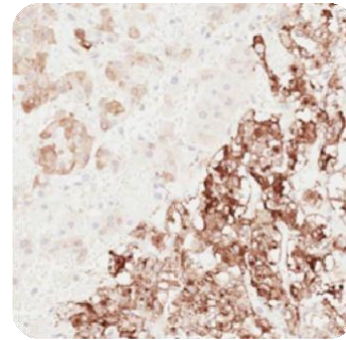


Efficient internalization

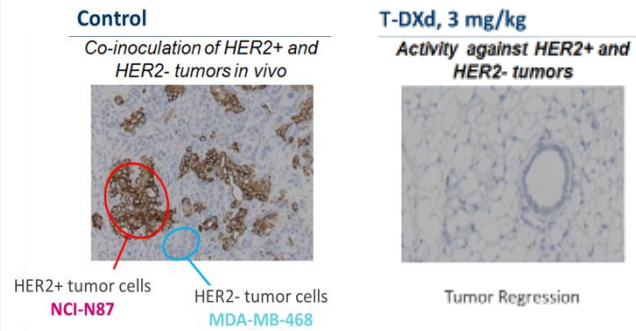


3

Heterogeneity of expression



Overcome with bystander activity



Ogitani Y et al. 2016. Cancer Science 1077: 1039-1046

4

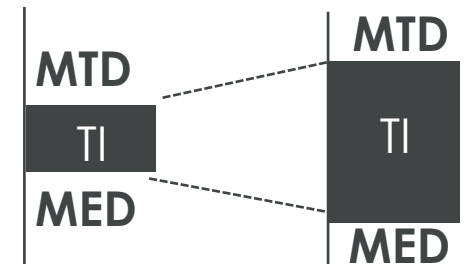
Normal tissue expression



Tolerated with lower potency payloads / DAR

High potency payload / DAR

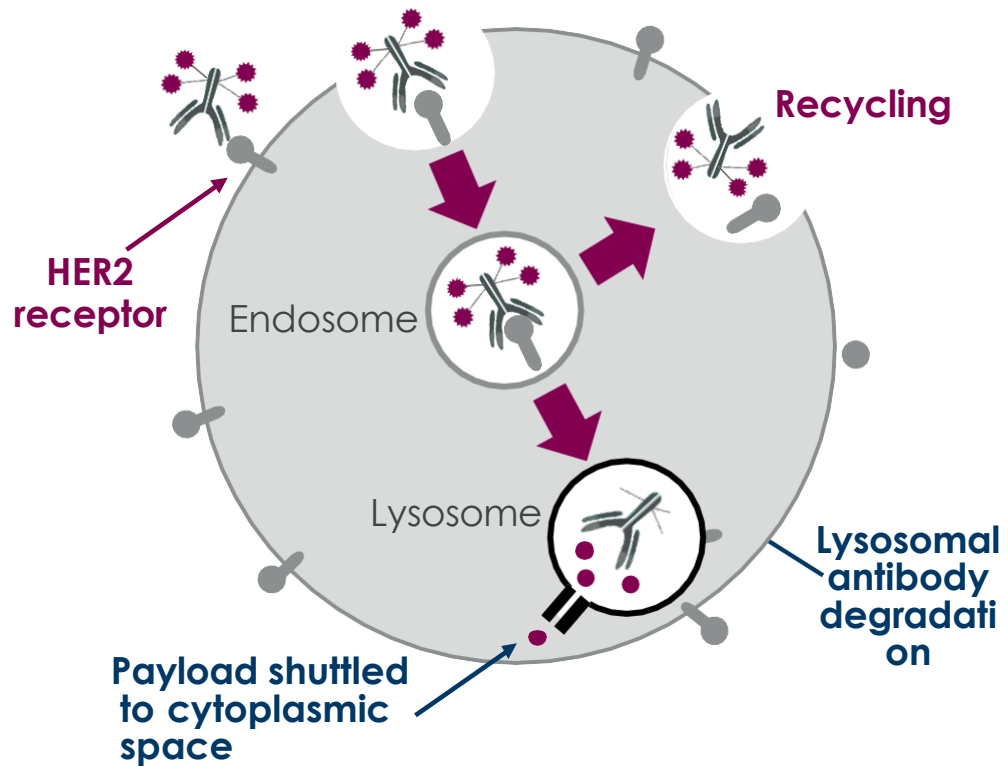
Low potency payload / DAR



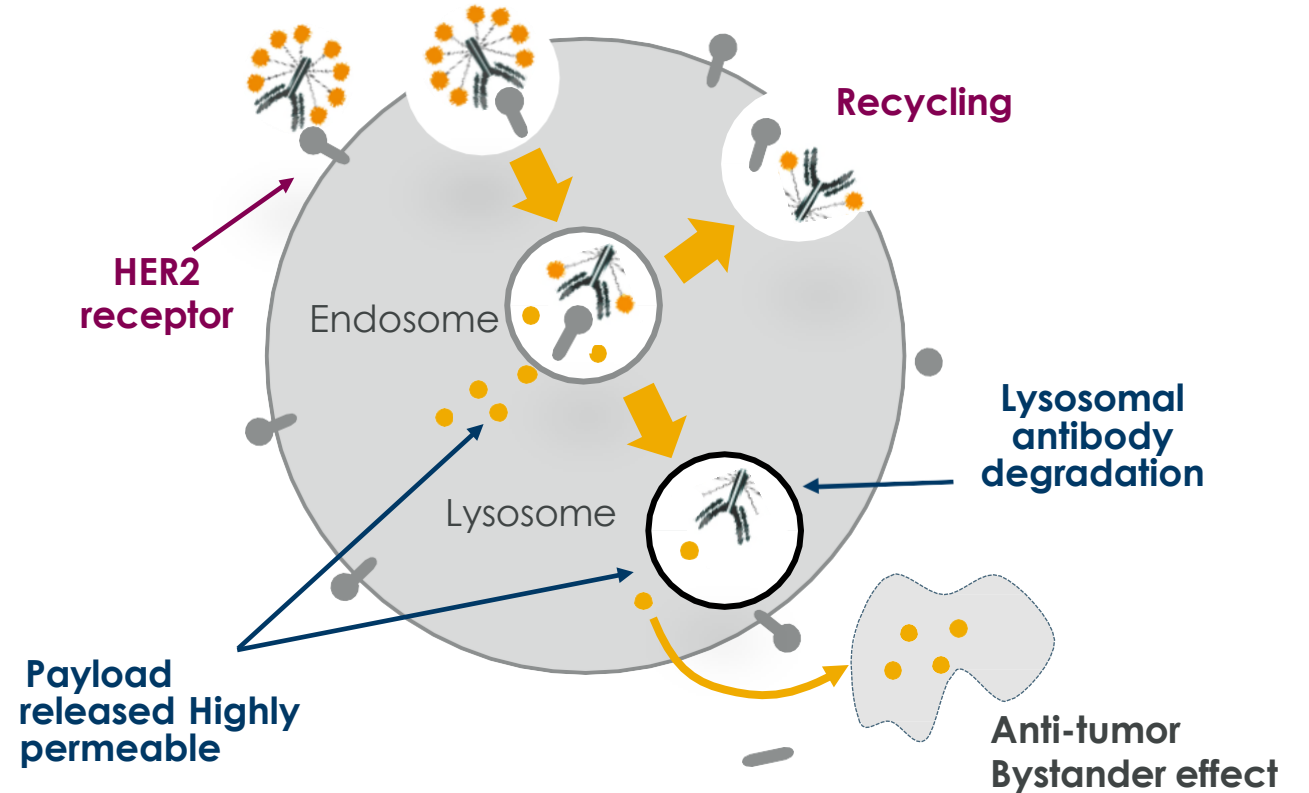
Novo ADC (T-DXd) versus T-DM1

Unlike T-DM1, T-DXd is cleaved by cathepsin in endosomes and is highly permeable

T-DM1: non-cleavable linker¹⁻³



T-DXd: cleavable linker¹⁻³

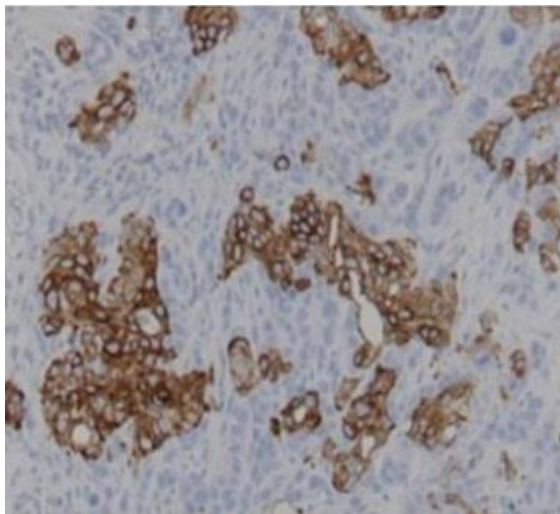


Bystander effect dos ADCs em neoplasias heterogêneas

In vivo bystander effect of DS-8201a vs T-DM1 after 14 days of treatment

Control

Co-culture of HER2+ and
HER2- tumors in vivo

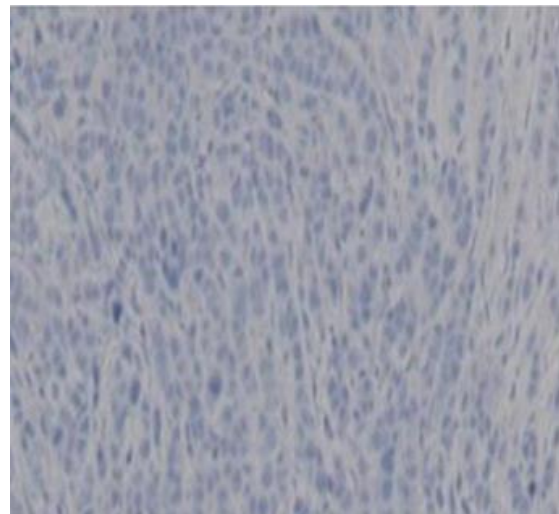


HER2+
cells NCI-
N87

HER2-
cells
MDA-MB-468

T-DM1, 10 mg/kg

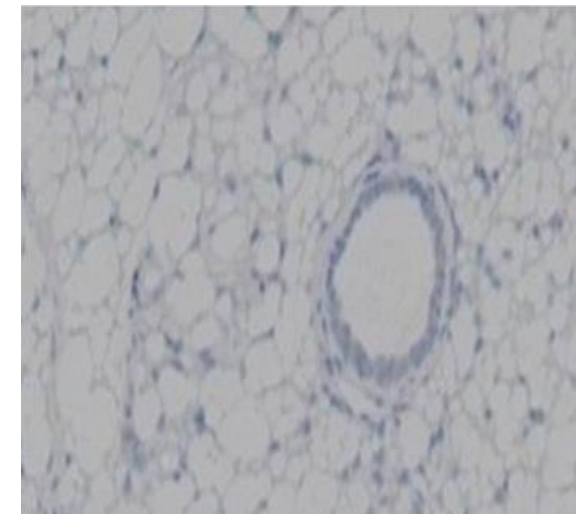
HER2- cells still persist



HER2-
cells
MDA-MB-468

DS-8201a, 3.0 mg/kg

Both HER2+ and HER2-
are impacted



Tumor regression

T-DM1 e heterogeneidade tumoral

Definição de heterogeneidade de HER2

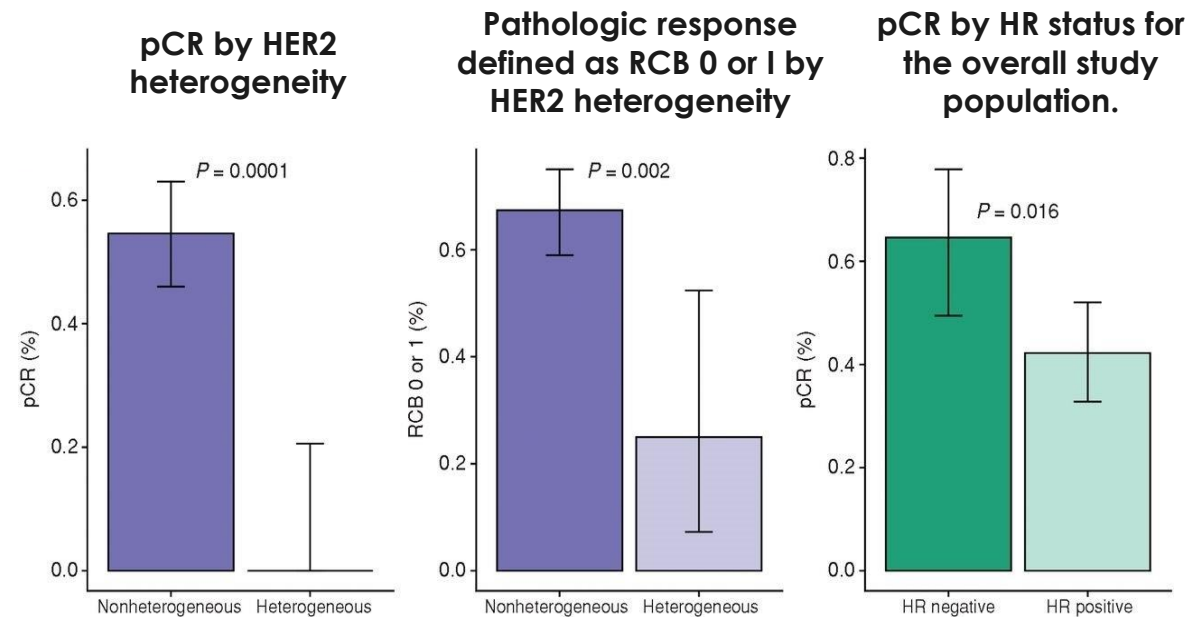
- Área com amplificação de ERBB2 em > 5% mas < 50% das células tumorais

OU

- Área HER2 negativa detectadas por FISH

T-DM1 showed pathological complete responses only in tumors with homogeneous HER2 expression

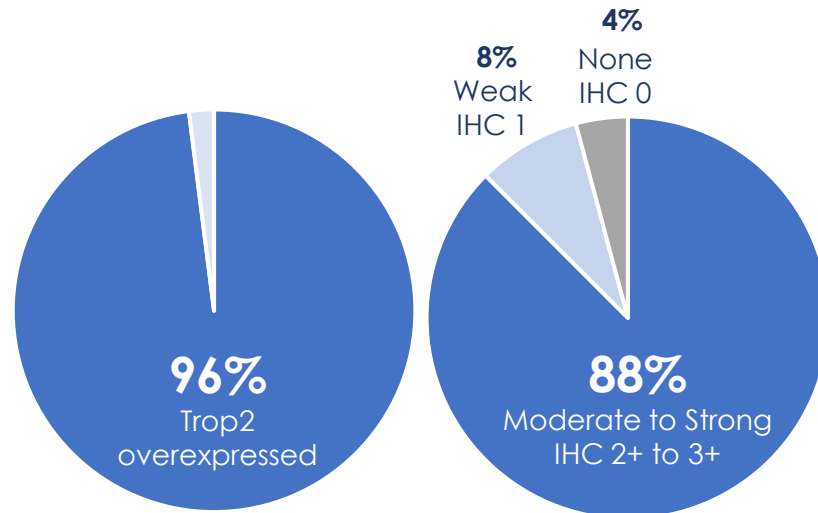
T-DM1 IS ONLY EFFICACIOUS IN HOMOGENEOUS TUMORS



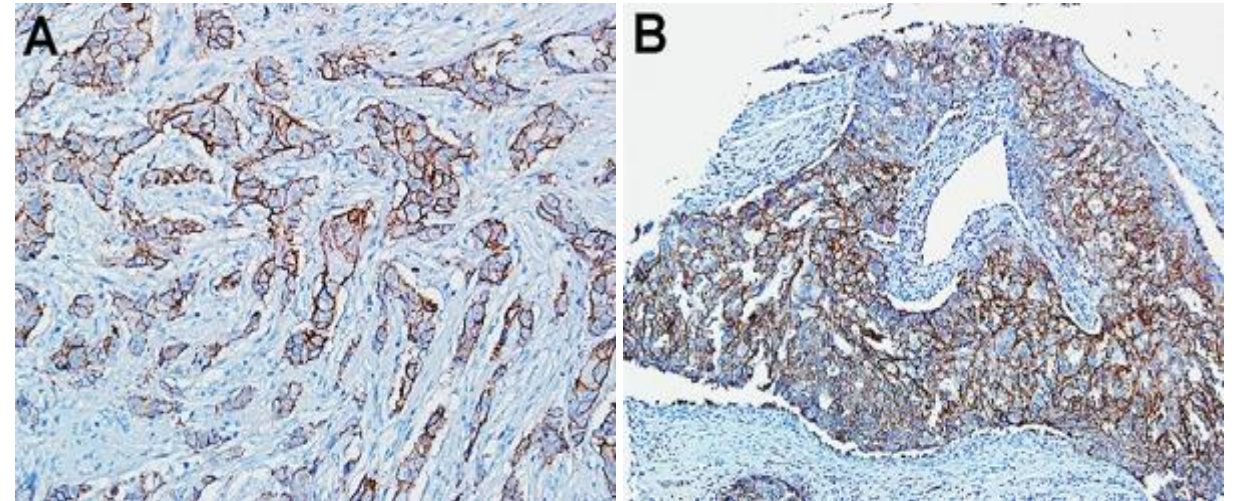
ADCs anti Trop 2 Sacituzumabe Govitecan

Superexpressão de Trop-2 em CMTN

Trop-2 Expression in Patients with TNBC (n=48)^{1,a,b}



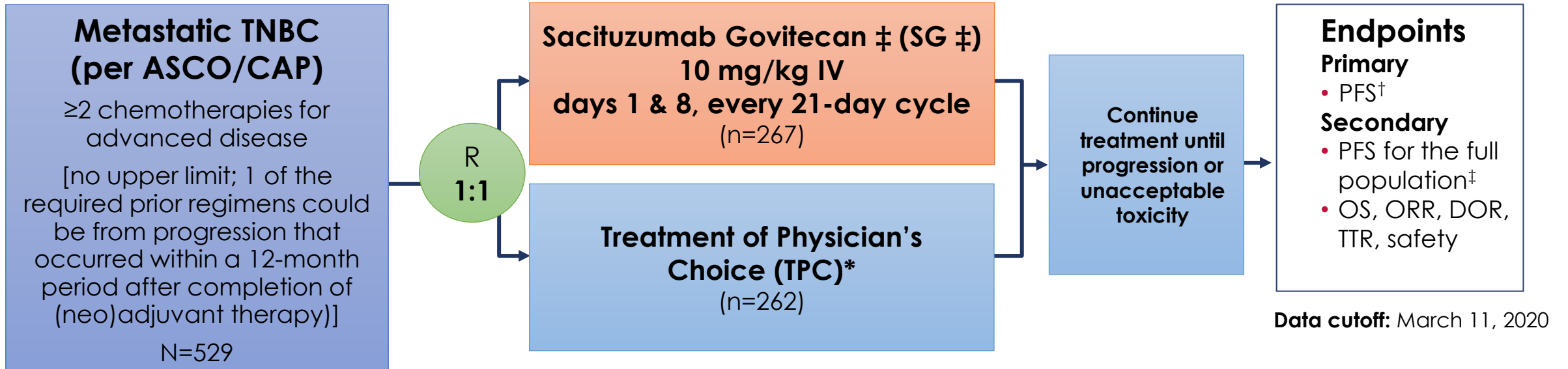
Strong (3+) Trop-2 expression in two TNBC specimens within a tumor microarray²



High Trop-2 overexpression rate with predominantly moderate to strong intensity of IHC staining suggests that pretherapy biomarker assessment for TNBC patient selection is not required.¹

^a immunohistochemistry (IHC) scores of archival samples from SG \pm -treated patients: A total of 48 patients had archival tumors (60% primary tumors, 40% miscellaneous metastases) evaluated for Trop-2 expression by IHC; ^bIHC scoring was based on staining intensity of >10% of the tumor cells within the specimen: strong (3+), moderate (2+), weak (1+), or absent (negative). If <10% of the tumor cells were positive, sample was scored as negative, irrespective of score. IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen-2; UC, urothelial cancer.

ASCENT: Study Design



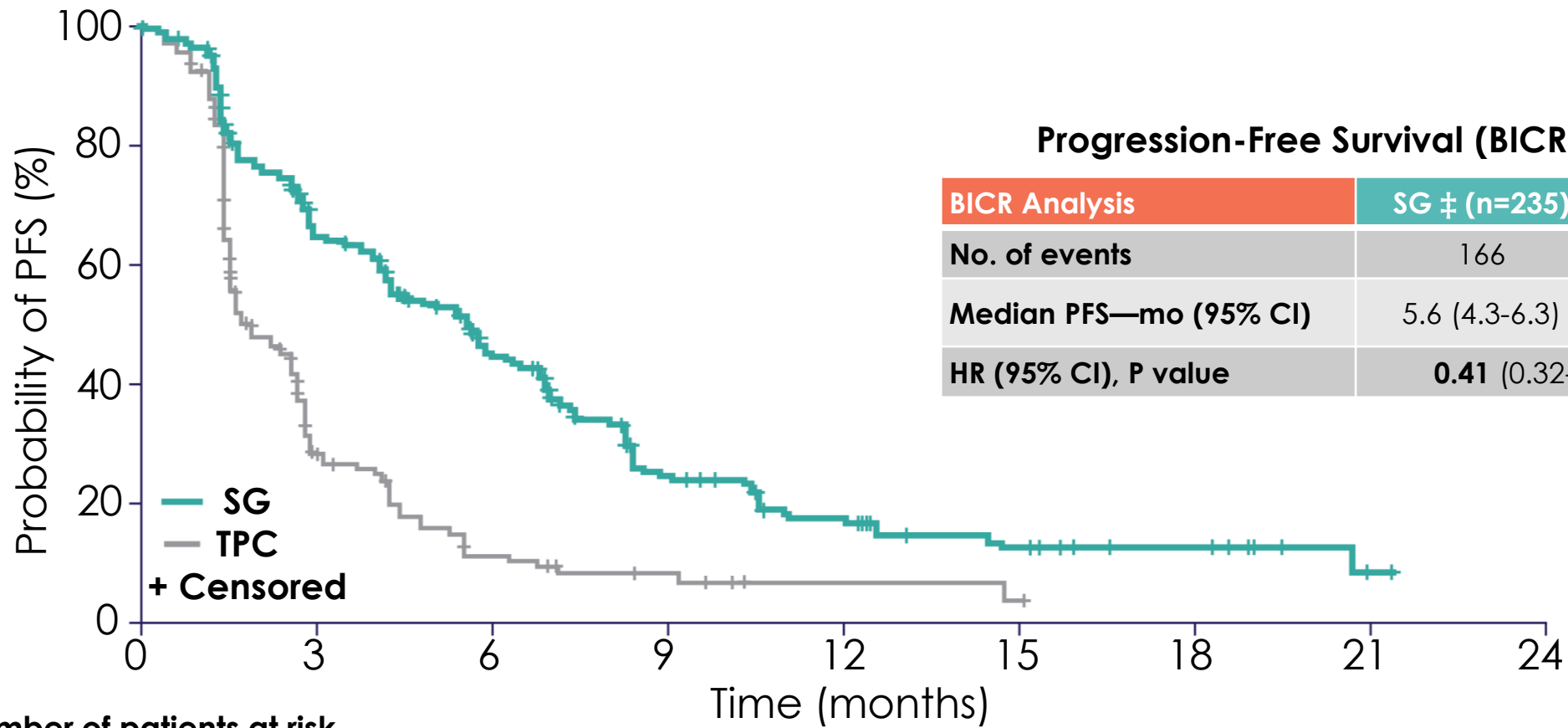
NCT02574455

Stratification factors

- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

**Eribulin, vinorelbine, gemcitabine, or capecitabine*

Progression-Free Survival

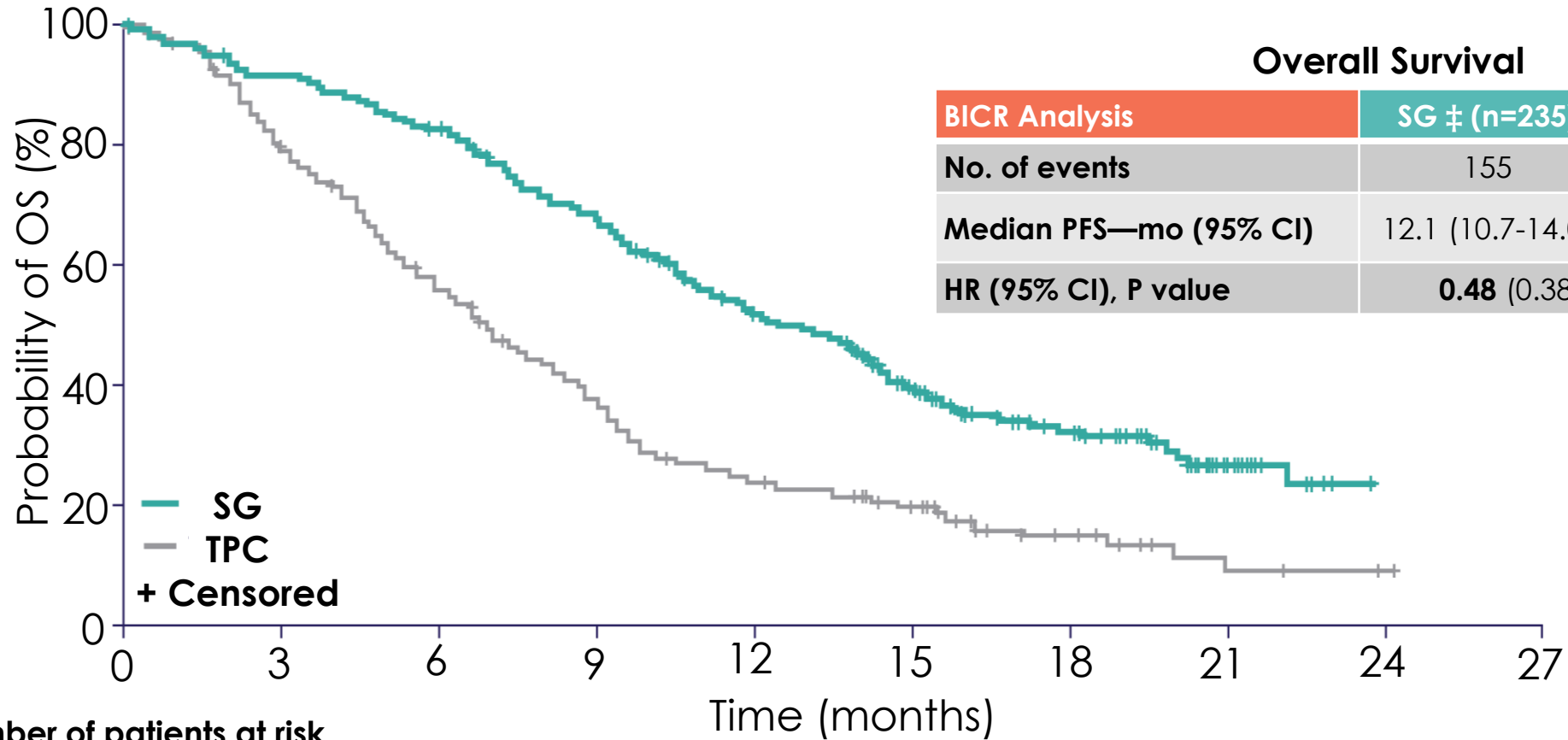


Number of patients at risk

SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	179	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

ADC, antibody-drug conjugate; BICR, blinded independent central review; HR, hazard ratio; mTNBC, metastatic triple-negative breast cancer; PFS, progression-free survival; SG ‡, Sacituzumab Govitecan ‡; TPC, treatment of physician's choice; Trop-2, trophoblast cell-surface antigen 2.

Overall Survival

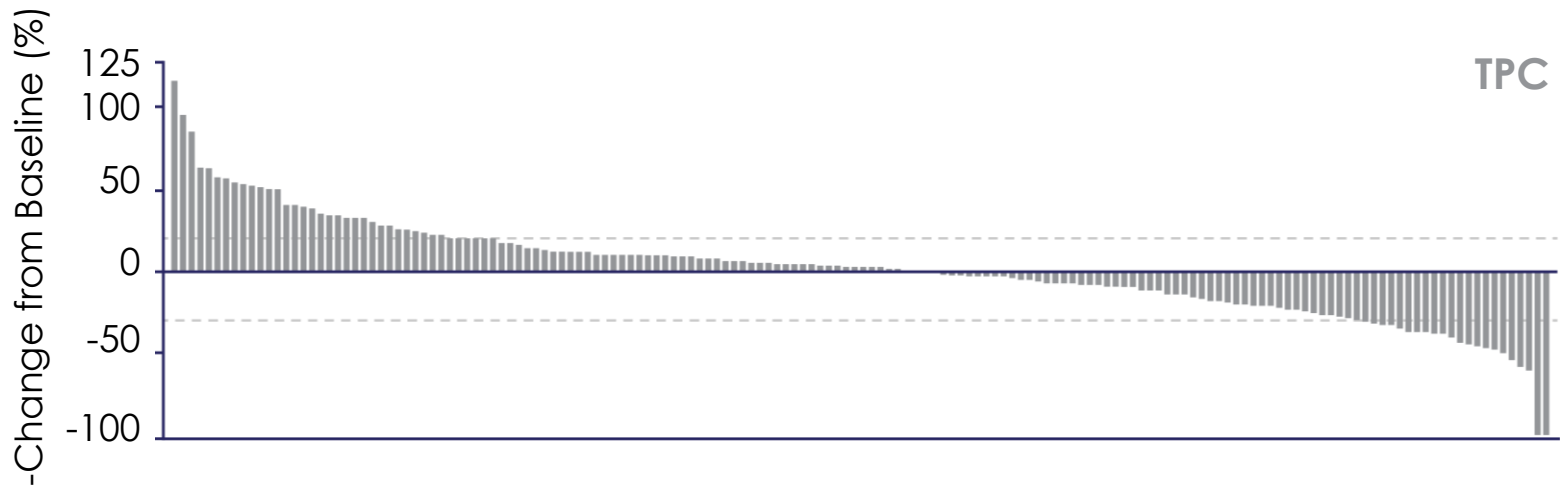
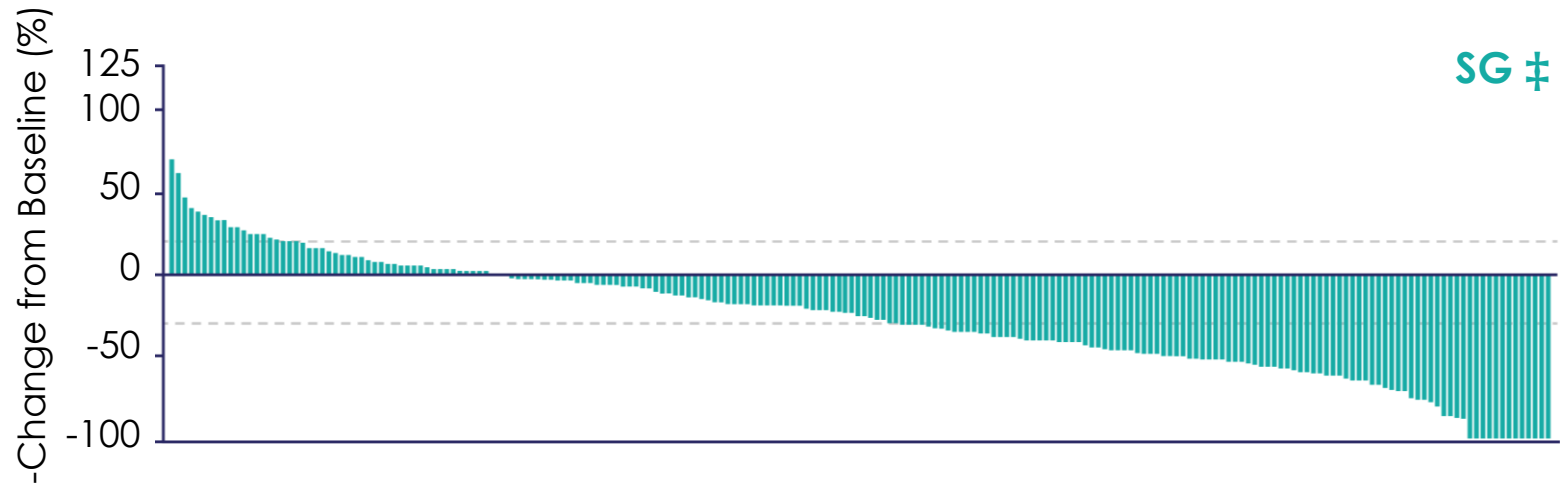


Number of patients at risk

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

HR, hazard ratio; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SG ‡, Sacituzumab Govitecan ‡; TPC, treatment of physician's choice; Trop-2, trophoblast cell-surface antigen 2.

Overall Response Rate



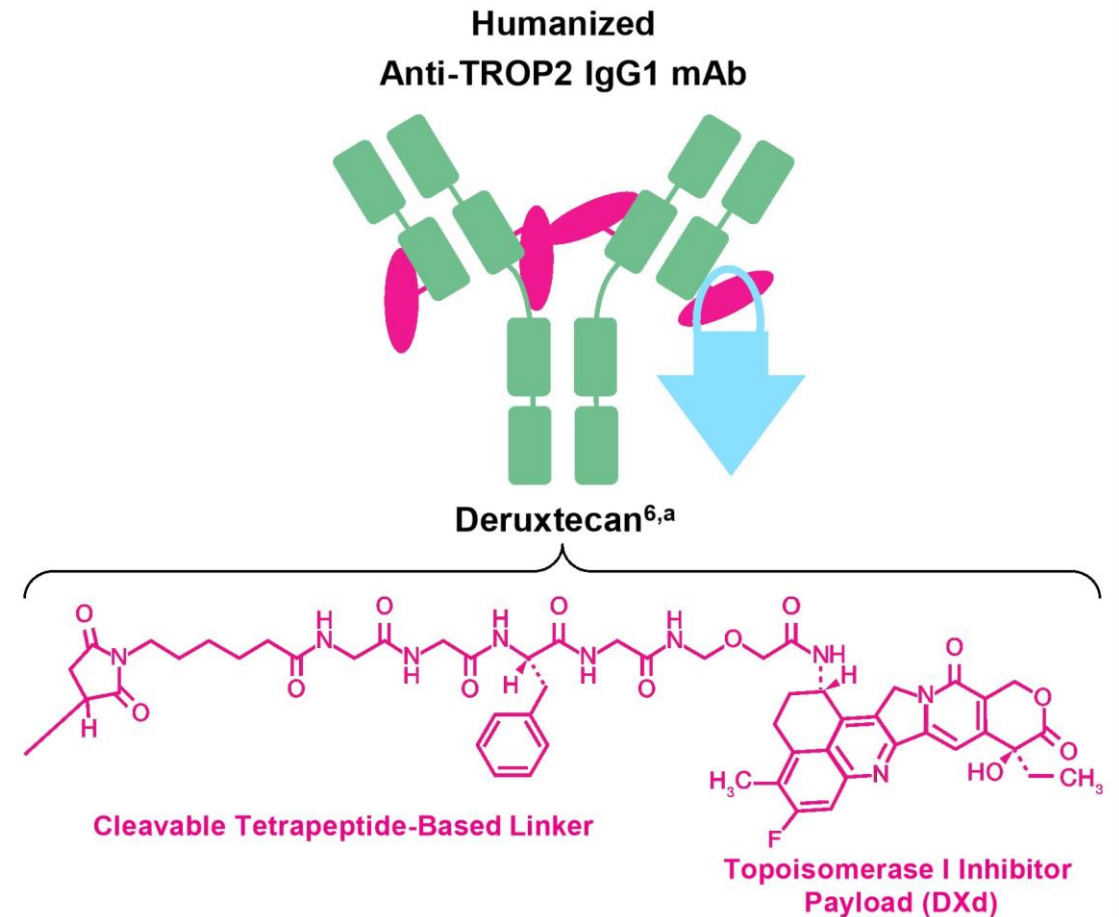
	SG ‡ (n=235)	TPC (n=233)
ORR—no. (%)	82 (35)	11 (5)
P-value	<0.0001	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	105 (45)	20 (9)
P-value	<0.0001	
Median DOR —mo (95%CI)	6.3 (5.5–9.0)	3.6 (2.8–NE)
P-value	0.057	

BICR, blind independent central review; CBR, clinical benefit rate (CR + PR + SD \geq 6 mo); CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response; SG ‡, Sacituzumab Govitecan ‡; TPC, treatment of physician's choice; TTR, time to response.

ADCs anti Trop 2 Datopotamabe Govitecan

Datopotamab Deruxtecan: Trop-2 Directed ADC

- Dato-DXd is a differentiated TROP2-directed ADC designed with 3 components^{2,3}:
 - A humanized anti-TROP2 IgG1⁴ mAb
 - A topoisomerase I inhibitor payload (exatecan derivative, DXd)
 - A tetrapeptide-based cleavable linker
- 6 mg/kg has been selected as the dose for expansion into Other advanced tumor types

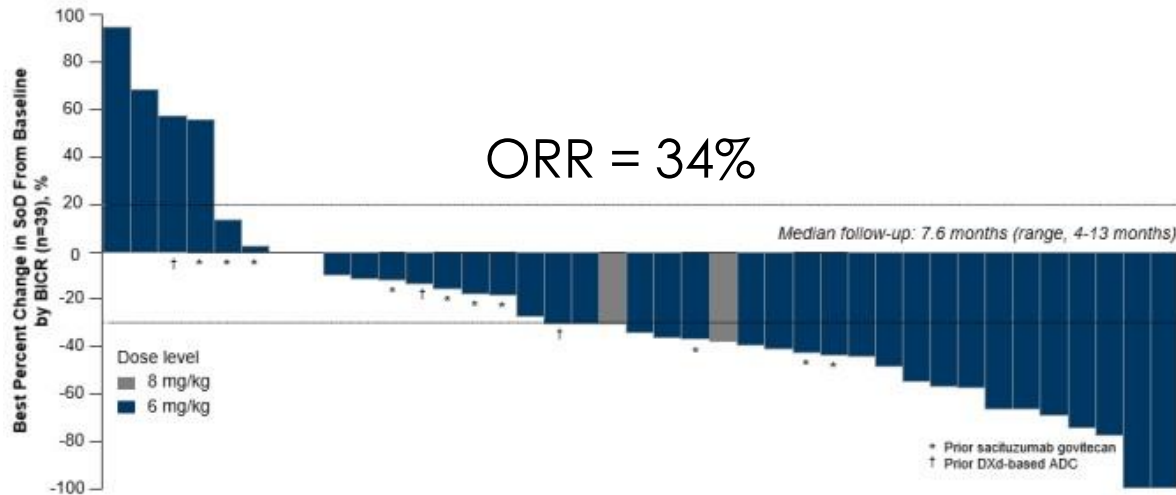


ADC, antibody drug conjugate; AE, adverse event; IgG1, immunoglobulin G1; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; TNBC, triple negative breast cancer; TROP2, trophoblast cell surface antigen.

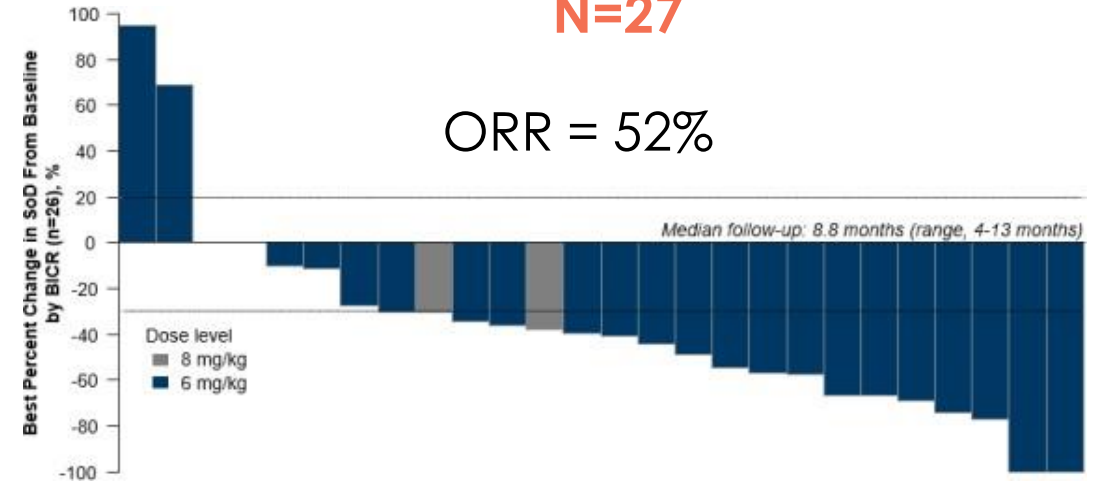
^aActual drug positions may vary

TROPION-PanTumor01: Datopotamab in TNBC Cohort

All patients



Patients without prior Topo I inhibitor-based ADC N=27



Median prior lines of therapy = 3
Prior Topo1 inhibitor-based ADC = 30%

^a Includes response evaluable patients who had ≥ 1 postbaseline tumor assessment or discontinued treatment. Postbaseline tumor assessments were not yet available for 2 patients at the data cutoff. Three patients were not confirmed to have a target lesion per BICR and, therefore, had a best overall response of non-CR/non-PD.

^b Includes patients with an unconfirmed response but are ongoing treatment.

TROP2 ADC Trials: 1st Line mTNBC

ASCENT-03

Study Population 1L mTNBC

- Previously untreated locally advanced, unresectable, or metastatic TNBC
- PD-L1- by 22C3 CPS < 10 or PD-L1+ by 22C3 CPS ≥ 10 in patients previously treated with na aPD-(L)1 agente the curative setting
- ≥ 6 months since treatment in the curative setting

N = 540

1:1 randomization

Continue treatment until BICR-verified disease progression or unacceptable toxicity

Sacituzumab Govitecan
10 mg/kg IV
Day 1 and Day 8 of 21-day cycle

TPC*

- Gemcitabine 1000 mg/m² with carboplatin AUC 2 IV na Days 1 and 8 of 21-day cycle
- Paclitaxel 90 mg/m² IV on Days 1, 8, and 15 of 28-day cycle
- Nab-Paclitaxel 100 mg/m² IV on Days 1, 8, and 15 of 28-day cycle

*Crossover to SG in eligible patients allowed after BICR-verified disease progression.

Endpoints

Primary

- PFS[†]

Secondary

- OS
- ORR[†]
- DOR[†]
- TTR[†]
- PROs
- Safety

[†] By BICR using RECIST v1.1

TROPION B-02

Un-treated mTNBC
Not eligible for PD-1/PD-L1 Tx
N=600

1:1

R

DATO-DXd

Investigator's choice
Pacl/nab-pacl, Cape, carbo, eribulin

Dual Primary Endpoints: PFS/OS

TROP2 ADC Trials: 1st Line mTNBC, PDL1+

ASCENT-04

Study Population 1L metastatic TNBC

- Previously untreated locally advanced, unresectable, or metastatic TNBC
- PD-L1- by 22C3 CPS ≥ 10
- ≥ 6 months since treatment in the curative setting
- Prior aPD-(L)1 use allowed in the curative setting
- PD-L1 and TNBC status centrally confirmed

N = 440

1:1 randomization

Arm A*:
Pembrolizumab 200 mg IV on Day 1 of 21-day cycle+
Sacituzumab govitecan 10 mg/kg IV on Days 1 and 8 of 21-day cycle

Arm B TPC^{a,b}:
Pembrolizumab 200 mg IV on Day 1 of 21-Day cycle + 1 of the following:
• Gemcitabine 1000 mg/m² with carboplatin AUC 2 IV on Days 1 and 8 of 21-day cycle
• Paclitaxel 90 mg/m² IV on Days 1, 8, and 15 of 28-day cycle
• Nab-Paclitaxel 100 mg/m² IV on Days 1, 8, and 15 of 28-day cycle

^aMaximum 35 cycles of pembrolizumab (Arm A) or TPC (Arm B)
^bCrossover to SG in eligible patients allowed after BICR-verified disease progression.

Endpoints

Primary

- PFS^c

Secondary

- OS
- ORR^c
- DOR^c
- TTR^c
- PROs
- Safety

^cBy BICR using RECIST v1.1

TROPION B-05

Phase 3 Dato-DXd + Durvalumab in 1L PD-L1+ mTNBC

Key Eligibility Criteria

- Previously untreated metastatic or locally advanced inoperable TNBC
- Measurable disease as defined by RECIST v1.1
- Adequate ECOG, hematologic and end-organ function
- PD-L1+ (TAP ≥ 10% IHC SP263)
- No active brain metastases
- DFI ≥ 6 mo since treatment in curative setting
- Prior PD-1/PD-L1 treatment for early stage TNBC allowed

N ~550

1:1

Dato-DXd** + Durvalumab

Chemotherapy** + Pembrolizumab

Primary endpoint

- PFS (BICR)

Secondary endpoints

- OS, PFS (inv) ORR, DoR, TTD, DCR, PRO, Safety, Tolerability, PK, and immunogenicity

Exploratory endpoint

- TROP2

ADCs anti HER2

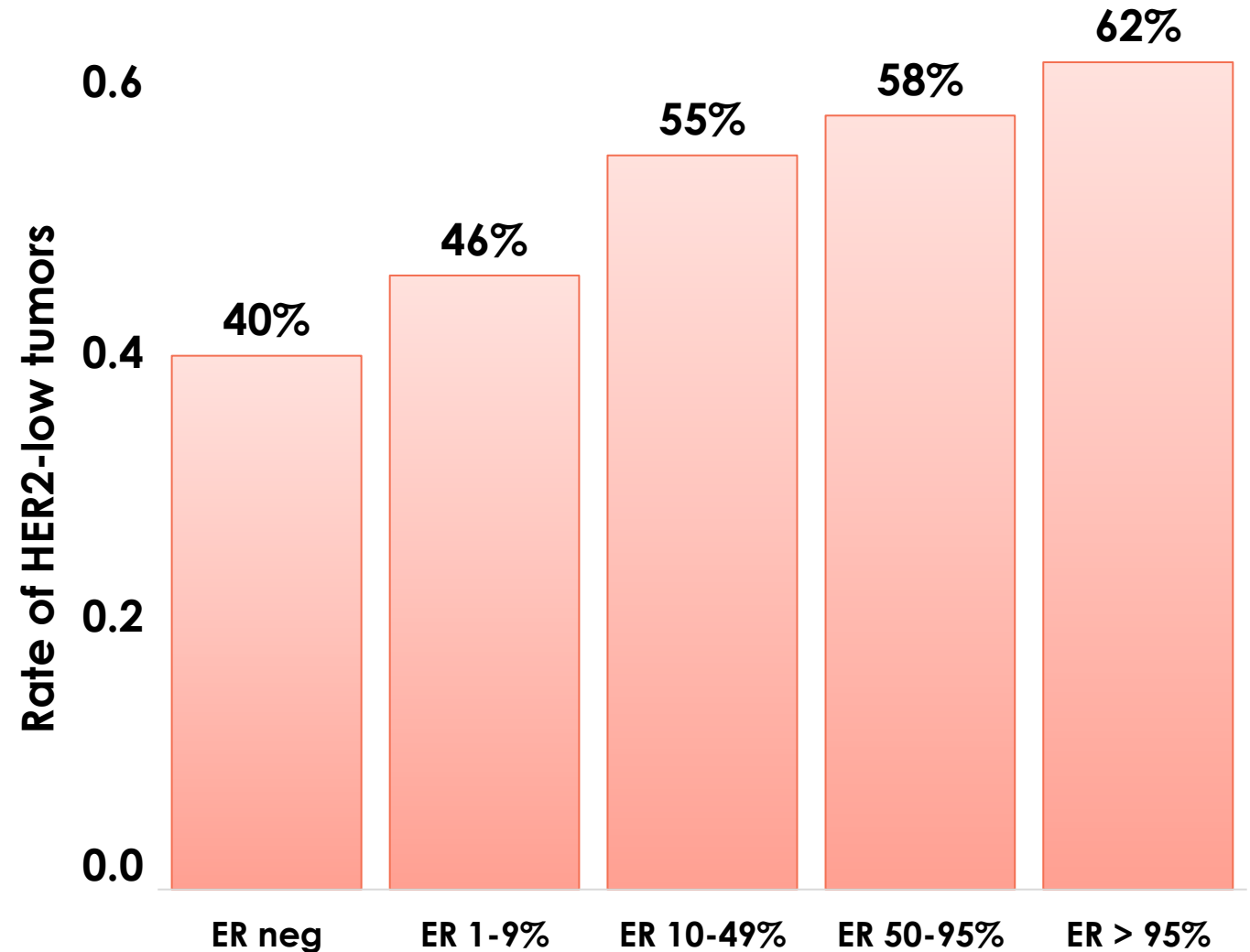
Trastuzumabe Deruxtecan

Prevalência de HER2 low de acordo com expressão de ER

The **rate of HER2-low tumors** increased progressively with the increase of ER expression

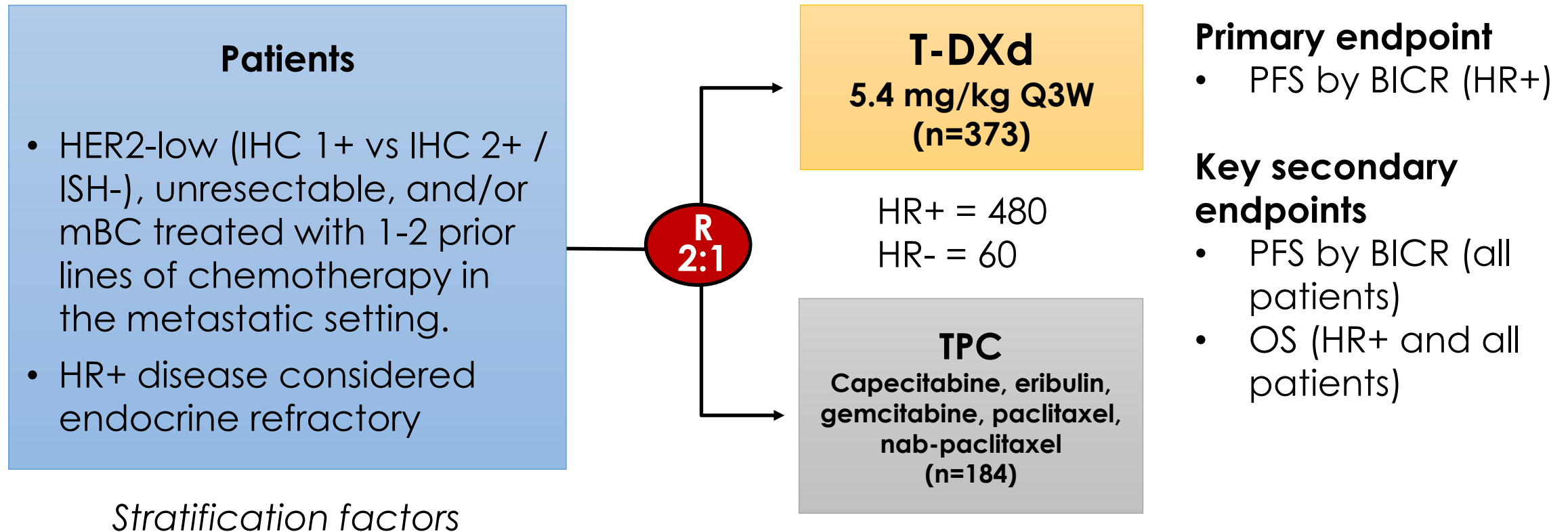
- ER-negative: **40%**
- ER-low (ER 1-9%): **46%**
- ER-moderate (ER 10-49%): **55%**
- ER-high (ER 50-95%): **58%**
- ER-very high (>95%): **62%**

ER estrogen receptor



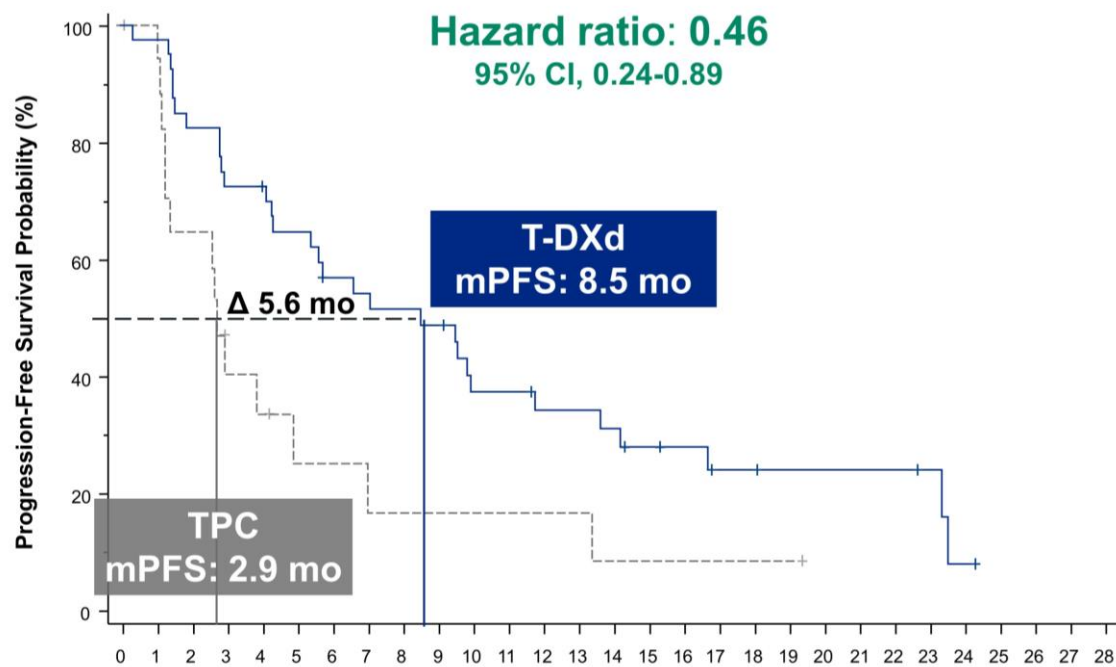
DESTINY Breast 04

An open-label, multicenter study (NCT03734029)

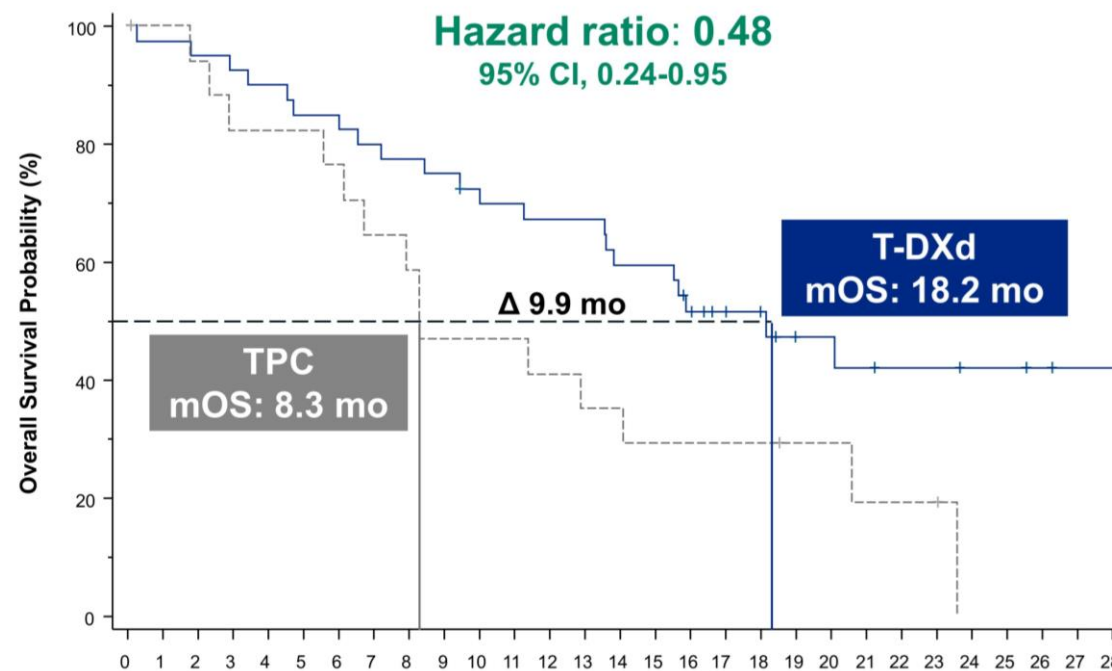


SLP e SG na População Receptor Hormonal Negativo

PFS

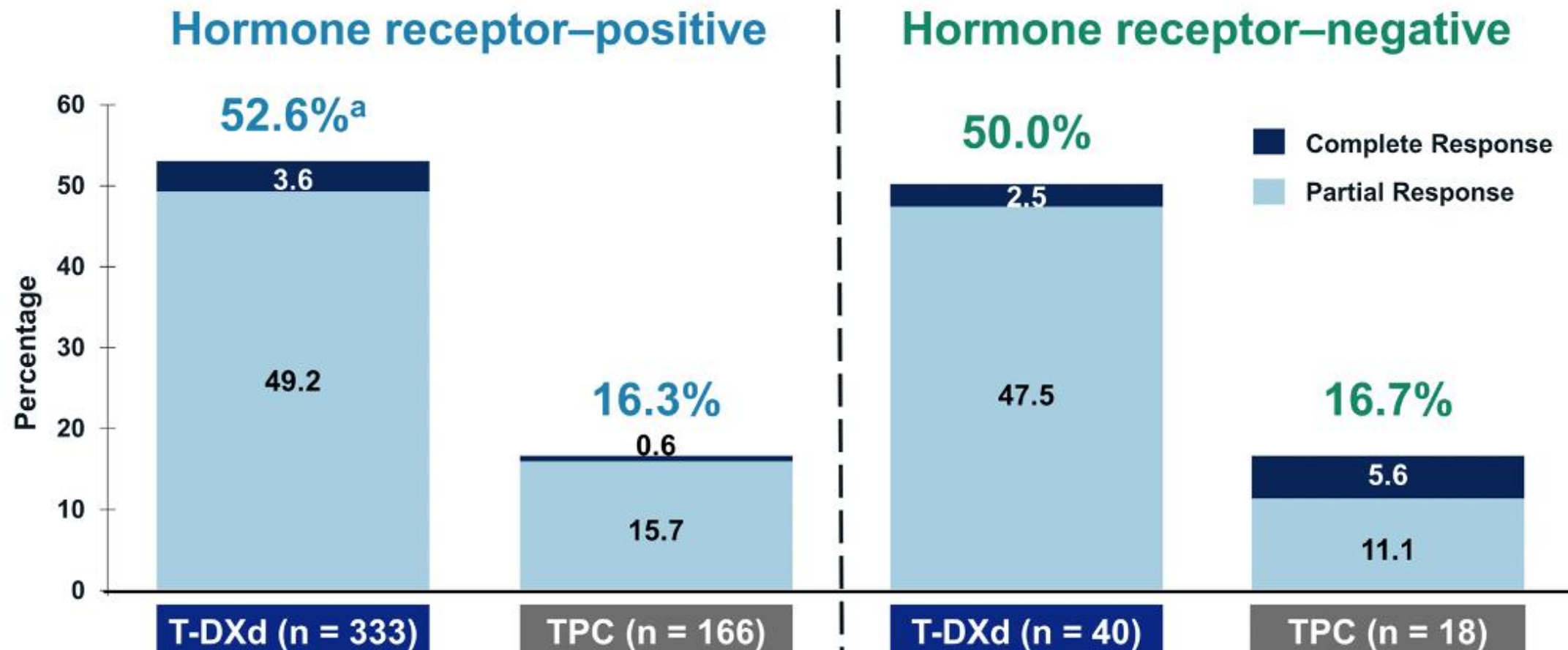


OS



DB 04 Taxa de Resposta Objetiva

Confirmed Objective Response Rate



**Qual será o melhor ADC
em TNBC ?**

BEGONIA Study

- Metastatic or inoperable locally advanced TNBC
- 1L metastatic setting
- ≥ 12 months since prior taxane therapy

Arm 6: **PD11-08**

Unresectable, HR-, HER2 low breast cancer
[IHC2+/ISH-, IHC 1+/ISH-, IHC 1+/ISH untested]

Durvalumab 1120mg q3 weeks

Trastuzumab deruxtecan 5.4mg/kg q3 weeks



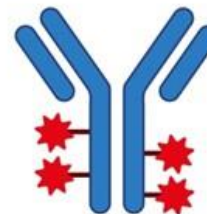
Antibody-Drug Conjugate
HER2 antibody + Topo1
inhibitor payload

Arm 7: **PD11-09**

Unresectable, HR-, HER2- breast cancer

Durvalumab 1120mg q3 weeks

Datopotamab deruxetecan 6mg/kg q3 weeks



Antibody-Drug Conjugate
TROP-2 antibody + Topo1
inhibitor payload

BEGONIA Study

TNBC Her2 Low: Trastuzumabe Deruxtecan+Durvalumabe

Confirmed ORR = 33 (56.9%)

- Complete Response = 1
- Partial Response = 32

Median PFS, months = 12.6 months

TNBC: Dato Deruxtecan +Durvalumabe

Confirmed ORR = 39 (73.6%)

- Complete Response = 4
- Partial Response = 35

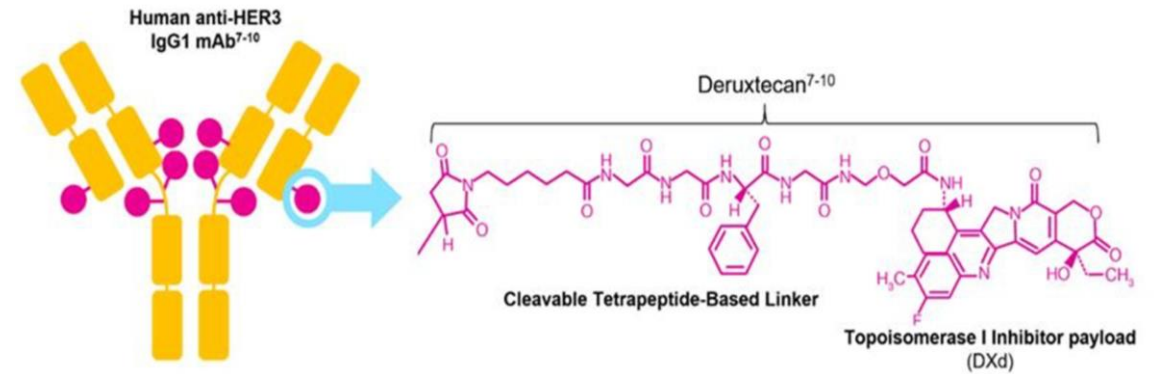
Durable Responses with 82% ongoing at data cutoff (median follow-up time 7.2 months)

**ADC anti HER3
Patritumabe Deruxtecan**

Patritumabe Deruxtecan

- HER3 is overexpressed in MBC and has been associated with poor clinical outcomes¹⁻⁵
- Patritumab deruxtecan (HER3-DXd; U3-1402) is a novel investigation ADC directed Against HER3 that has 3 components:
 - A fully anti-HER3 IgG1 monoclonal antibody (patritumab)
 - A topoisomerase I inhibitor payload, na exatecan derivate
 - A tetrapeptide-based cleavable linker
- Safety and preliminar antitumor activity of DXd were previously reported in this ongoing, phase 1/2 clinical trial (NCT02980341/JapicCTI-163401)⁶

Structure of HER3-DXd (Antibody-Drug Conjugate)



- Humanized anti-HER3 mAB
- Topoisomerase 1 inhibitor, exatecan derivative
- Tetrapeptide-based cleavable linker

1. Mishra R, et al. Oncol ver. 2018;12(1)355; 2. gala K, et al. Clin Cancer Res. 2014;20(6):1410-1416; 3. Mota JM, et al. Oncotarget. 2017;8(51):89284-89306; 4. Mijoo K, et al. Oncotarget. 2014;5(21):10222-10236. 5. Fontanini G, et al. Clin Cancer res. 1998;4(1):241-249; 6. Masuda N, et al. SABCS 2018. Poster PD1-03

HER3 Amplification in solid tumors

High HER3 expression measured by immunohistochemistry has been observed in several studies:

Tumor type	% high HER3 expression. By IHC
Pancreatic	41
Breast	43
Colorectal	17
Gastric	59
Melanoma	65
Ovary	53
Head and neck	9
Cervix	56

Clinical Activity of HER3-DXd Across BC subtypes

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)	30.1 (21.8 – 39.4)	22.6 (12.3 – 36.2)	42.9 (17.7 – 71.1)
Best overall response, %			
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-months 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

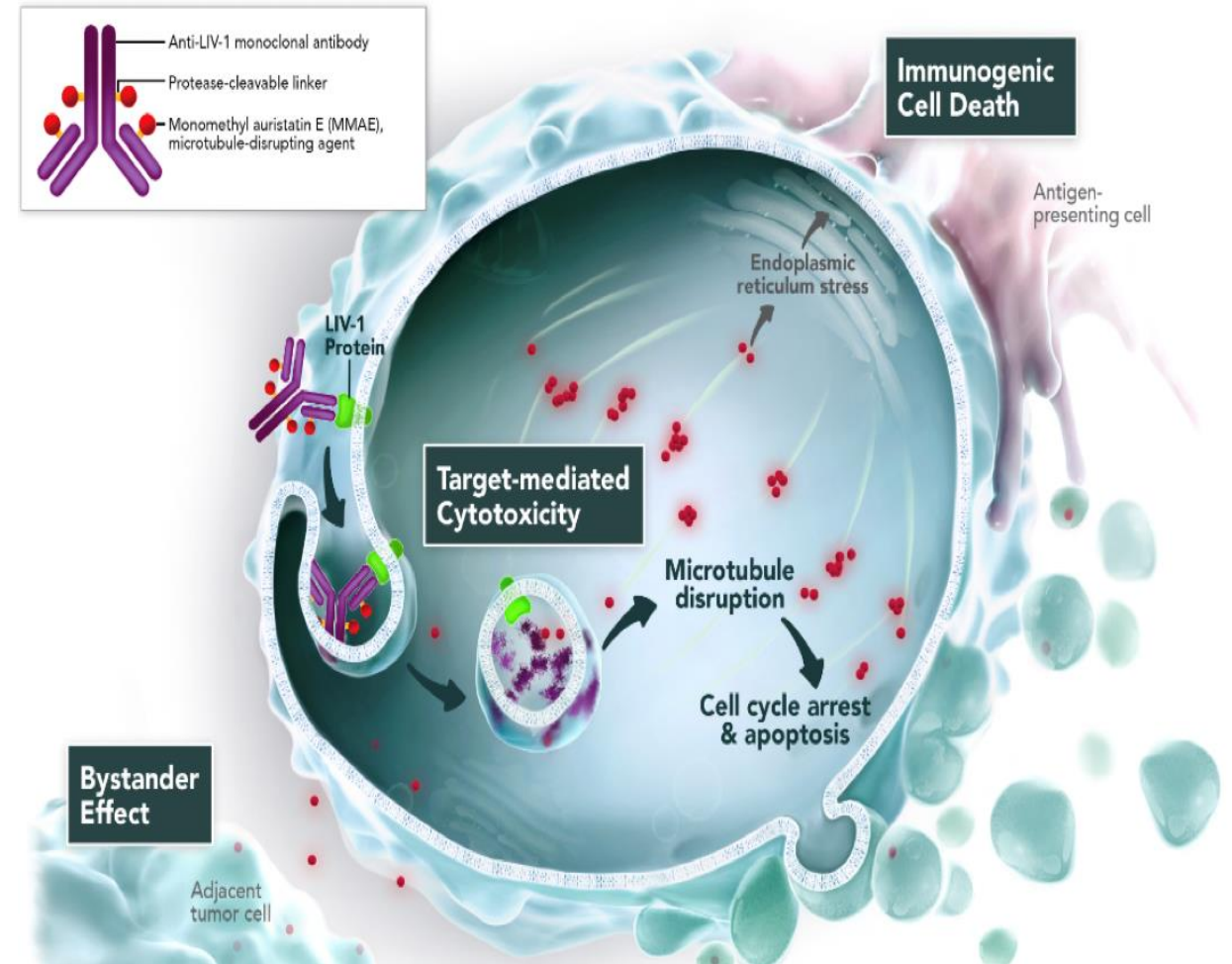
Confirmed ORR for all patients (N = 182), 28.6% (95% CI, 22.1% - 35.7%); median DOR, 7.0 mo (95% CI, 5.5 – 8.5 months)

TNBC 1 to 2 lines of chemotherapy in previous lines of therapy

ADC Anti Liv1 Ladiratumumabe Vedotina

Ladiratumumab Vedotin (LV)

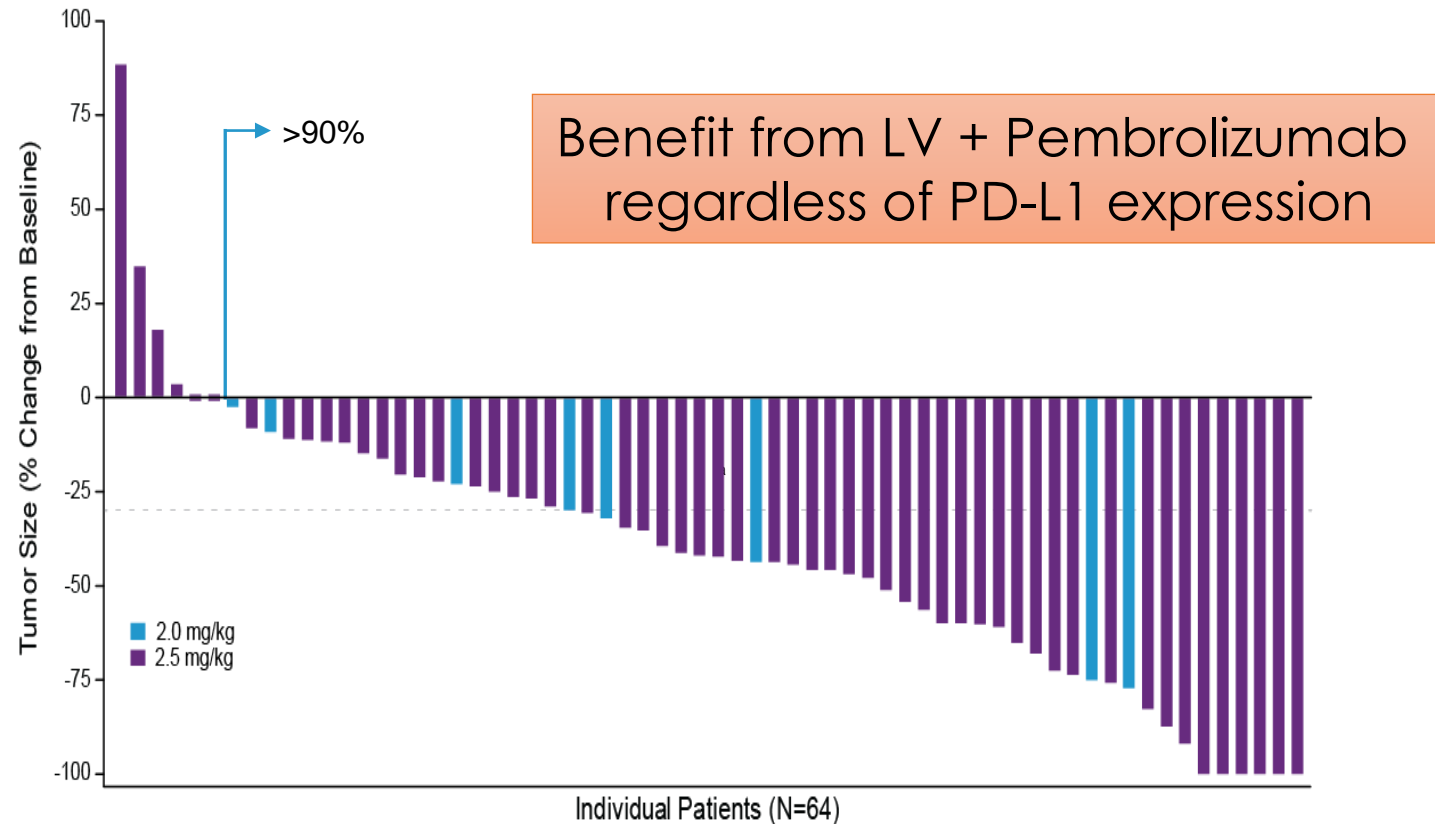
- LV
 - Humanized IgG1 ADC
- Selectively binds to cells expressing LIV-1 (90%+ MBCs)
 - Conjugated to monomethyl auristatin E (MMAE)
- LV-mediated delivery of MMAE drives antitumor activity through
 - Cytotoxic cell killing
 - Inducing Immunogenic Cell Death



LV + Pembrolizumab

First line metastatic TNBC

> 90% of subjects achieved tumor reduction



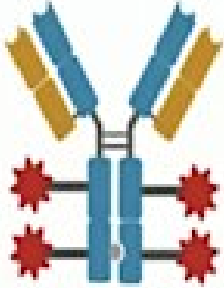

- The efficacy evaluable population includes all treated subjects with at least one evaluable post-baseline assessment according to RECIST v1.1 or who had discontinued from the study (N=69).
- Of the efficacy evaluable population, 5 subjects did not have evaluable response assessments before study discontinuation.

Futuro do Tratamento com ADCs

ADCs with novel Targets in Development for BC

ADC	Target	Payload	Treatment	Phase, NCTID
Ladiratuzumab vedotin (SGN-LIV1a)	LIV1	MMAE	Monotx SGN-LIV1a+atezo SGN-LIV1a+pembro	Ph 1, NCT01969643 Ph 1/2, NCT03424005 Ph 1/2, NCT03310957
Enfortumab vedotin	Nectin-4	MMAE	Monotx	Ph 2, NCT04225117
CX2009	CD166	DM4	Monotx and combination	Ph 2, NCT04596150
Patritumab deruxtecan (U3-1402)	HER3	DXd	Monotx	Ph 1/2, NCT02980341
BA3021-001 (CAB-ROR2 ADC)	ROR2	Undisclosed	Monotx Monotx and PD-L1 inhibitor	Ph 1/2, NCT03504488
Zilovertamab vedotin (VLS-101/MK-2140)	ROR1	MMAE	Monotx	Ph 2, NCT04504916
DS-7300	B7-H3	DXd	Monotx	Phase 1, NCT04145622
AZD8205 XMT-1660	B7-H4	Top1i Microtubule inhibitor	Monotx	Phase 1, NCT05123482 Phase 1, NCT05377996

Next Generation ADCs

	Type	Key characteristics	Main properties	Some exemples
	Biparatropic-ADCs	mAb targeting 2 epitopes of the same antigen	Improved internalization Higher payload delivery	SW49 (Zw25-ADC targeting ECD2 and ECD4 on HER2)
	Bispecific-ADCs	mAb targeting 2 diferente antigens		MesobsFab (mesothelin and CD16) HER2-PRLR bispecific ADC
	Tumor-specifica activated probody-conjugates	Antibody activation in TME	Targeting “undruggable” targets	BA3021 CX2009
	Small molecule-drug conjugates	mAb replaced by small molecular-weight proteins	Greater and broader tumor tissue penetration	ANG1005 (a brain-penetrating peptide-taxol conjugate)

Non-tumor TARGET ANTIGENS

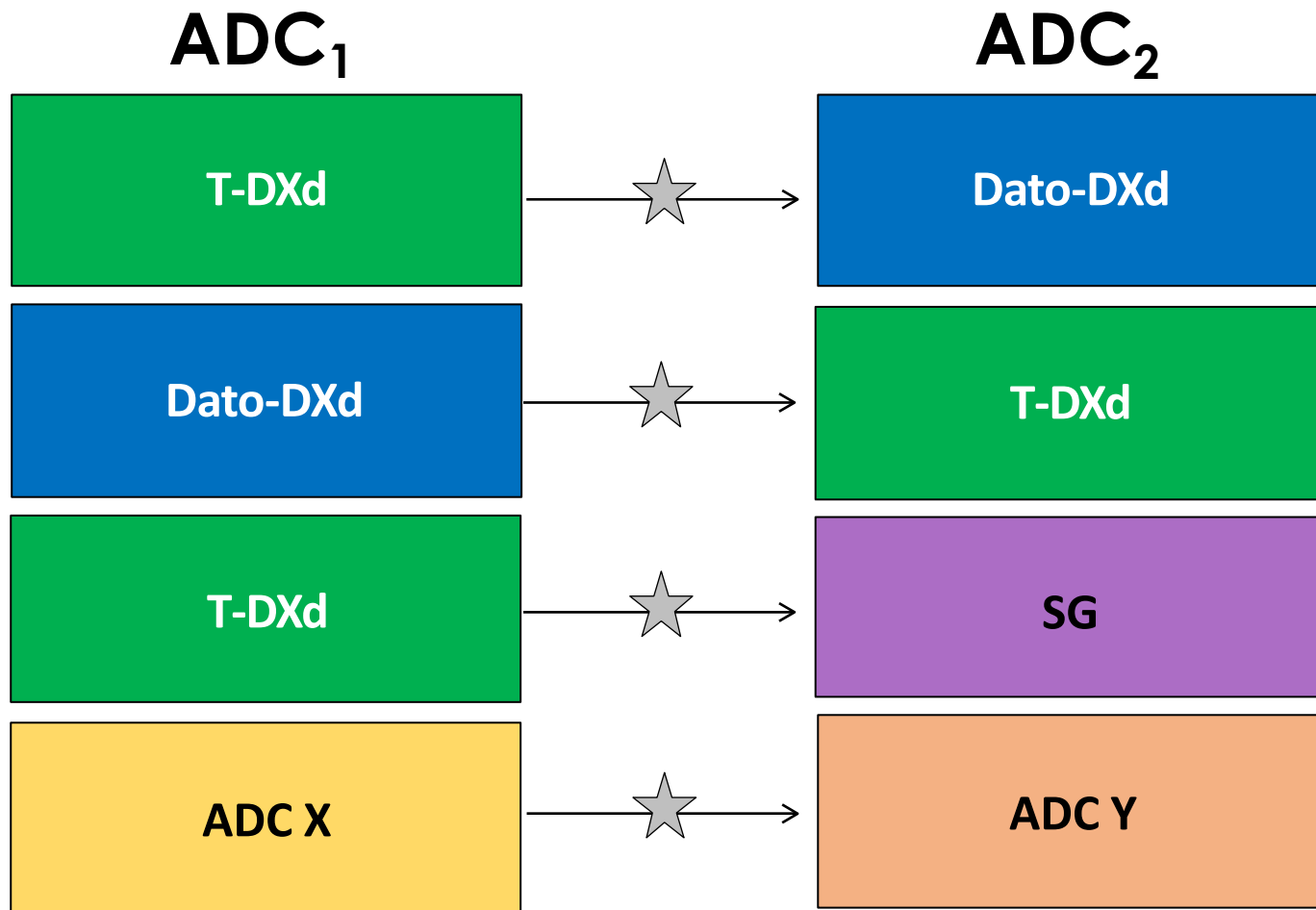
Type	Key characteristics	Main properties	Some exemples
Tumor-stroma antigens	Linker cleavage in the TME	Overcome barriers to tumor penetration	LRRC15 (ABBV-085)
Immune cells antigens		Reduce risk of developing drug resistance Increase imune response	B7-H3 (DS-7300, MGC018), CD25 (ADCT-301), PD-L1 (PD-L1-Dox)

Next Generation ADCs

Novel PAYLOADS

Type	Key characteristics	Main Properties	Some examples
Tumor-specific pathways	Tyrosinase-kinase inhibitors, apoptotic-pathway targeting agents	Reduce off-target toxicities	Inhibiting BCL-XL (ABBV-155)
Immunomodulatory payloads	Immune-stimulant molecules	Revert “cold” tumors into “hot” tumors	Chemokines, STING agonists, Toll-like receptor agonists
Radionuclide payloads	Radioactive payloads	Selectively deliver radioactive agents	90Y-FF-21101

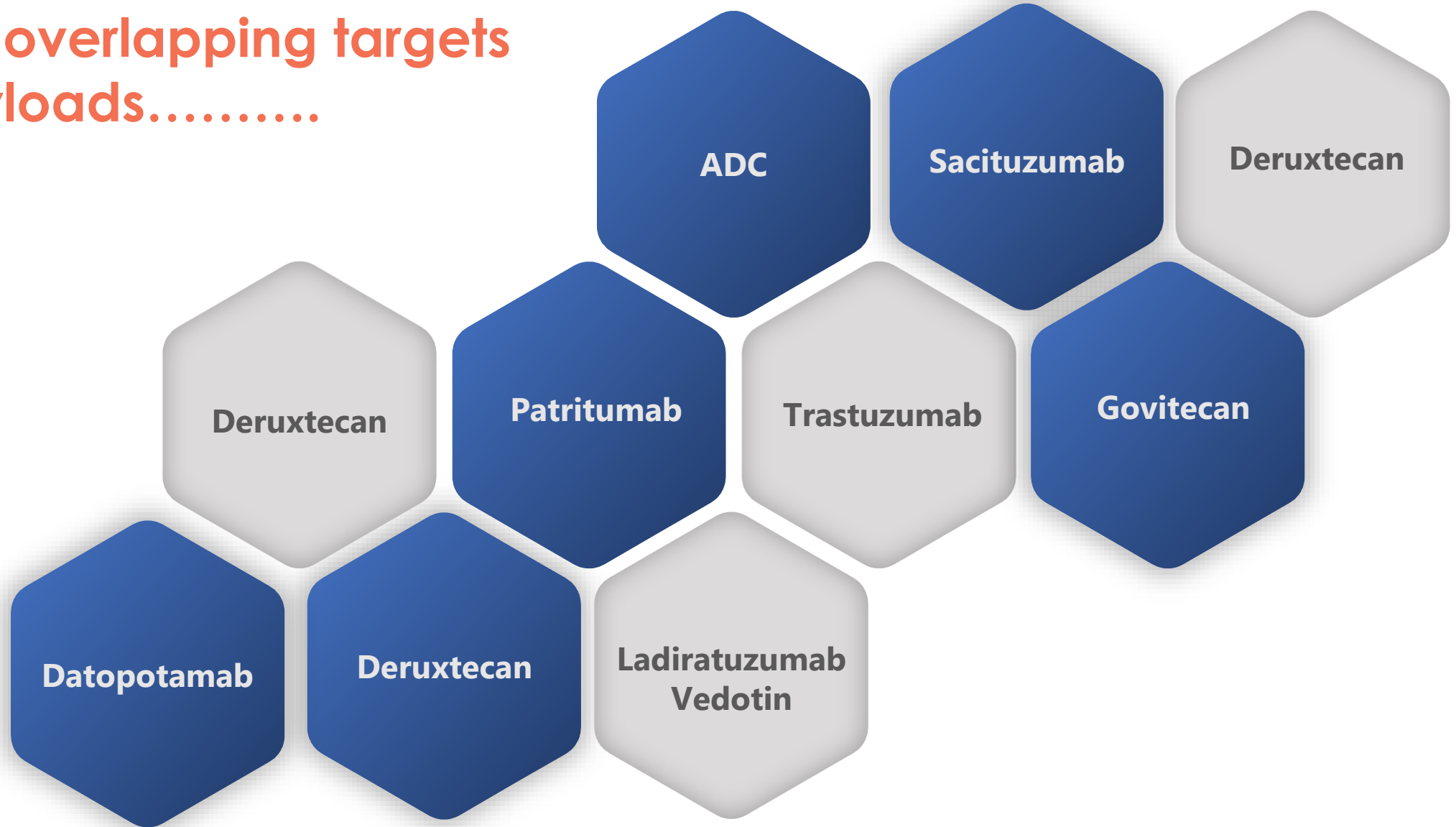
Will Need to Understand Sequencing of ADCs



Need comparison and sequencing studies

The Emerging Problems of Selection and Sequencing

Multiple overlapping targets and payloads.....



Conclusões

- Avanços tecnológicos nos trouxeram para a era da terapia com ADCs
- Possuem eficácia melhorada em relação à quimioterapia clássica
- Novos agentes têm aplicabilidade clínica mais ampla, com potenciais alvos únicos, prometendo mais progresso
- Para avançar no campo, precisamos de biomarcadores de resposta, testes de sequenciamento bem elaborados e uma compreensão da resistência para realmente "personalizar" terapia com ADCs

Obrigada

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A Beneficência
Portuguesa
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