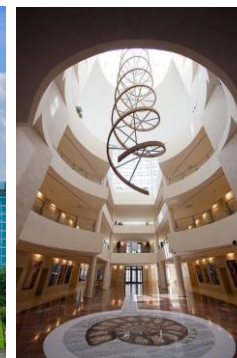


TROP-2 ADC: targeting metastatic breast cancer

Giampaolo Bianchini MD

Associate Professor - *Università Vita-Salute San Raffaele*
Head Breast Cancer Group
Head translational and clinical immunotherapy research
IRCCS Ospedale San Raffaele
Milan, Italy

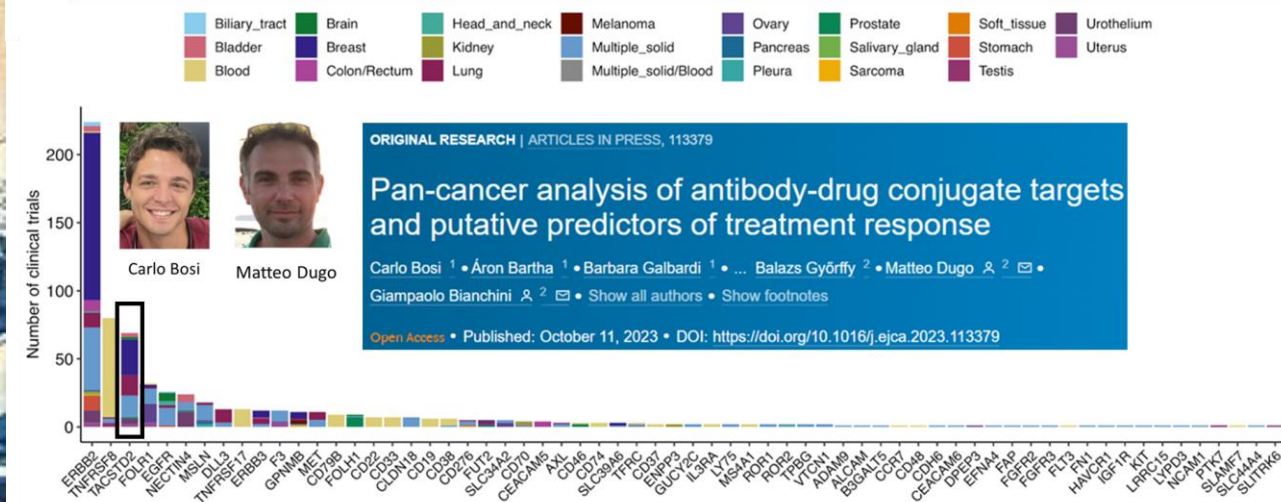
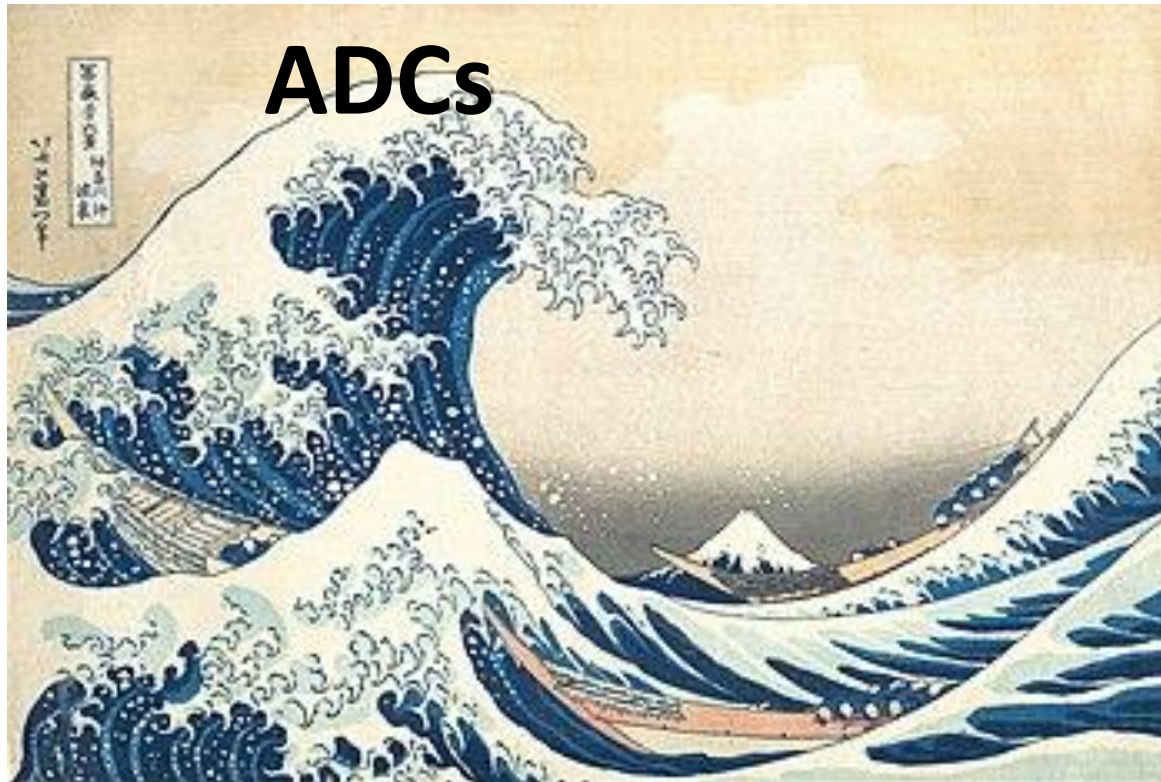


UniSR
Università Vita-Salute
San Raffaele

Disclosures

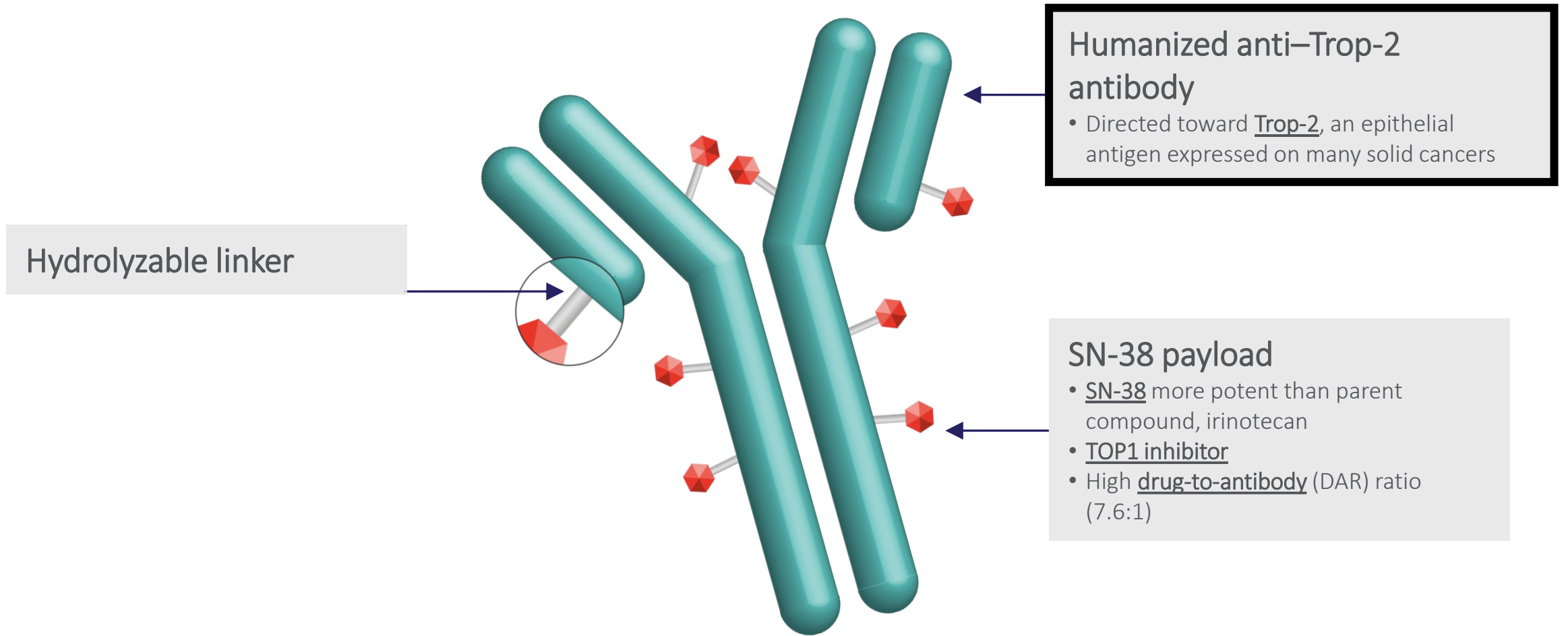
Honoraria for consultancy/advisory role/speaker fee from Gilead, Roche, AstraZeneca, Daichii Sankyo, Eisai, Exact Science, Eli Lilly, MSD, Novartis, Pfizer, Sanofi, Seagen, Menarini/Stemline, Helsin and Agendia

ADCs: the new revolutionary wave in oncology

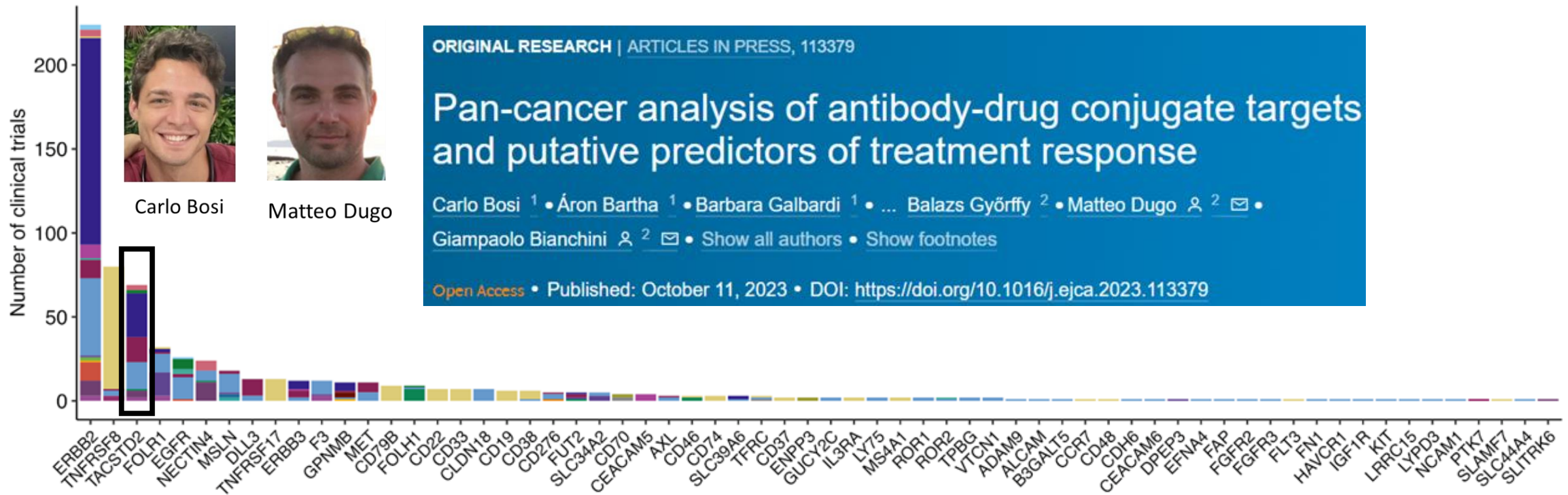
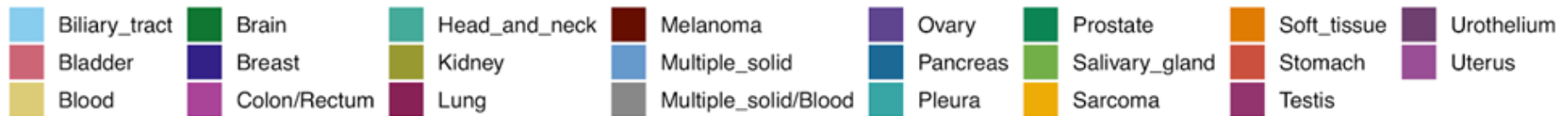


Bosi C, et al. Eur J Cancer. 2023 Dec;195:113379.

Sacituzumab Govitecan: what unique?



Trop-2 is one of the most attractive target for ADCs

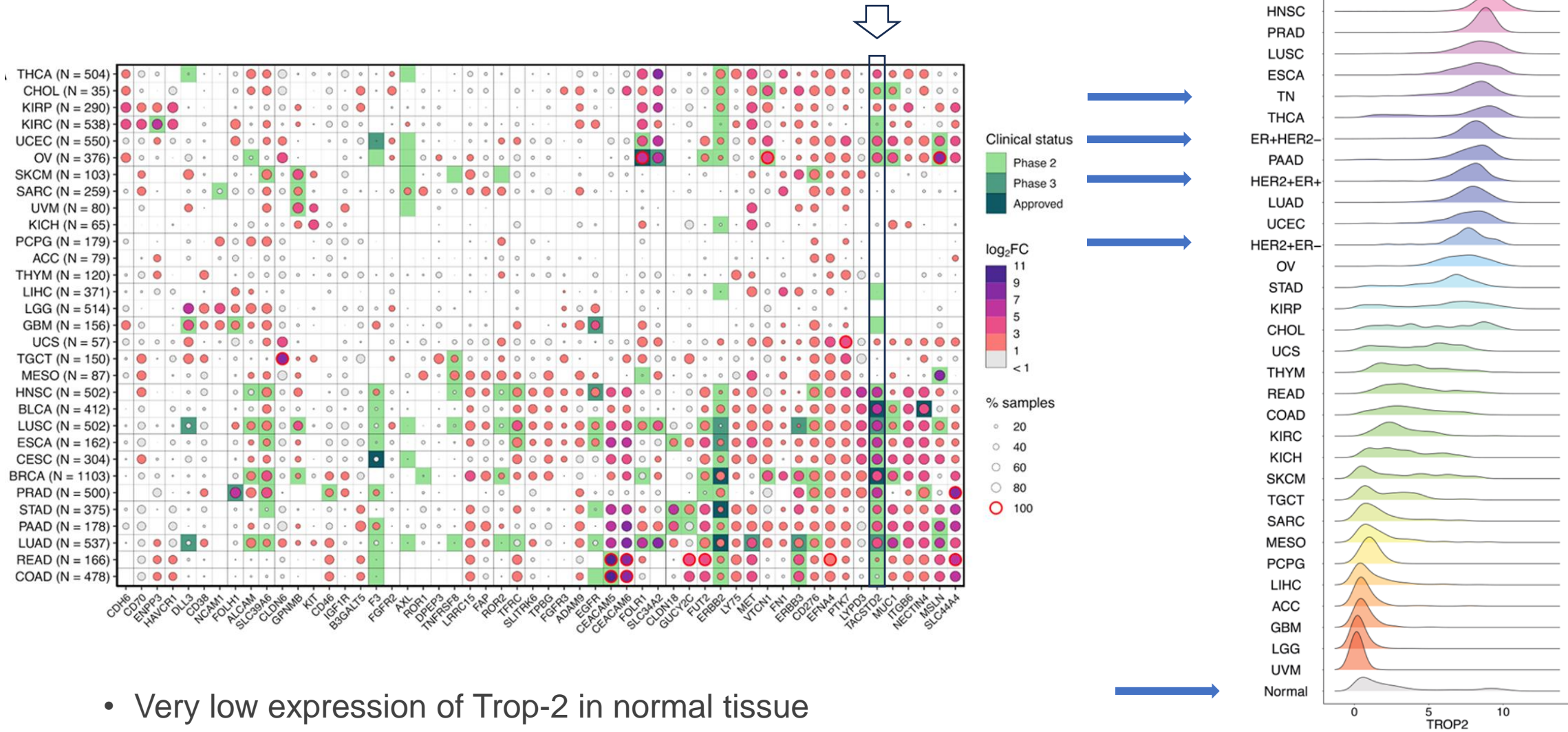


Carlo Bosi



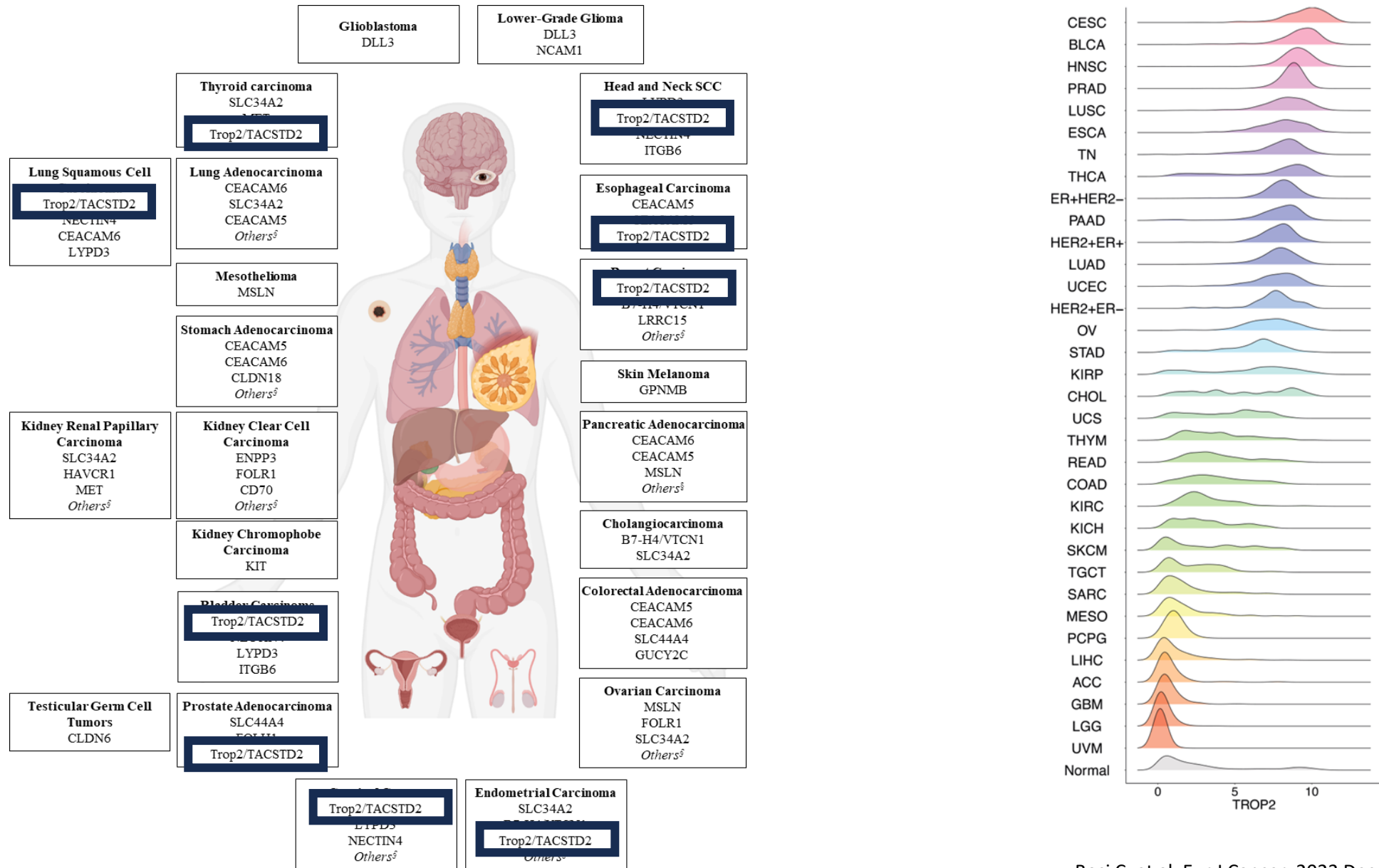
Matteo Dugo

Trop-2 is one of the most attractive target for ADCs

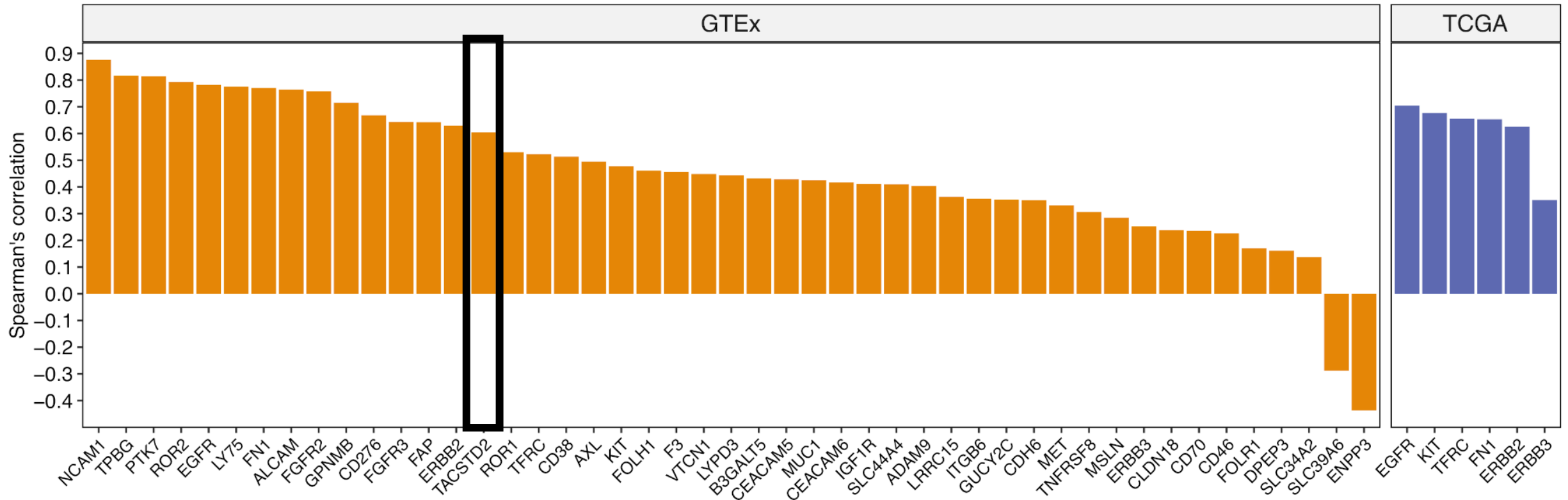


- Very low expression of Trop-2 in normal tissue
- Trop-2 is highly expressed in all breast cancer subtypes

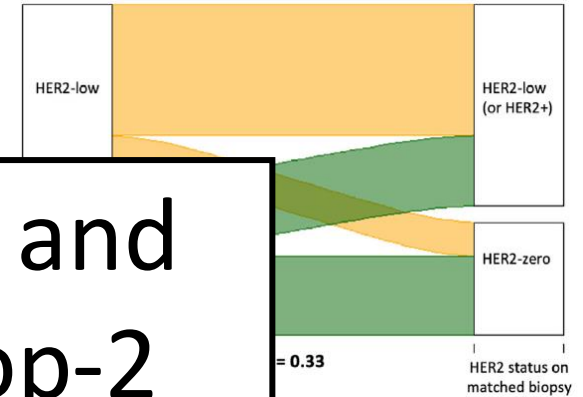
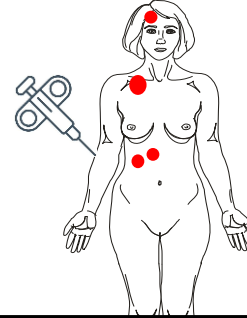
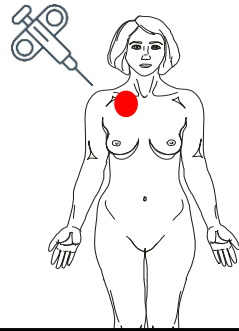
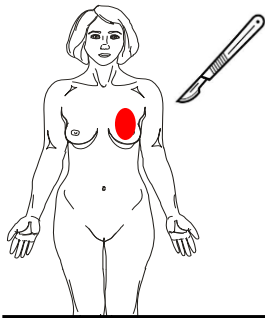
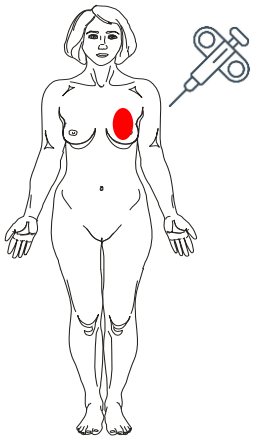
Trop-2 is one of the most attractive target for ADCs



Correlations between mRNA counts and protein levels of ADC targets

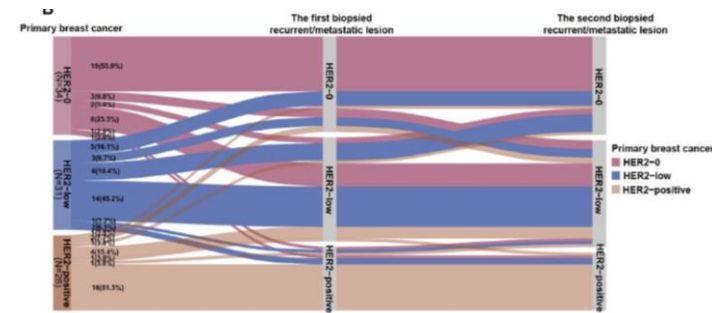
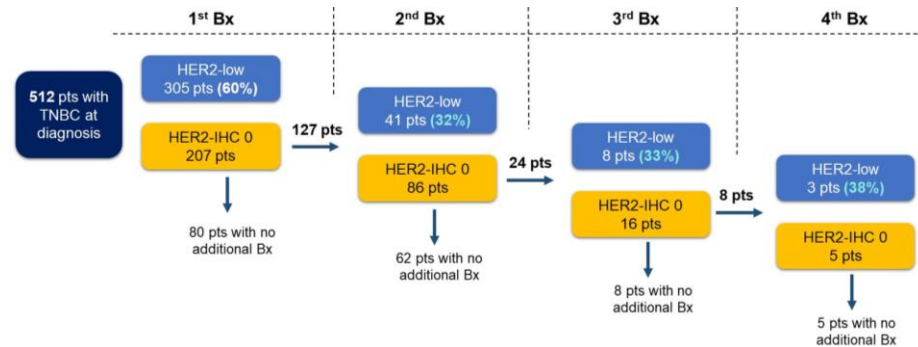
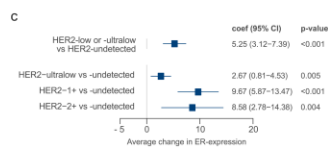
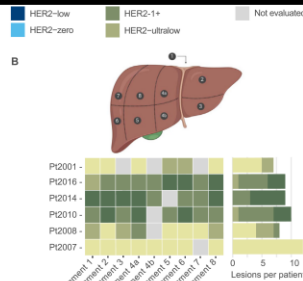
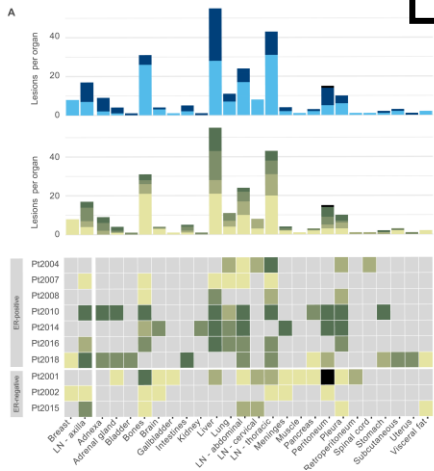


Spatial and temporal heterogeneity of HER2 by IHC



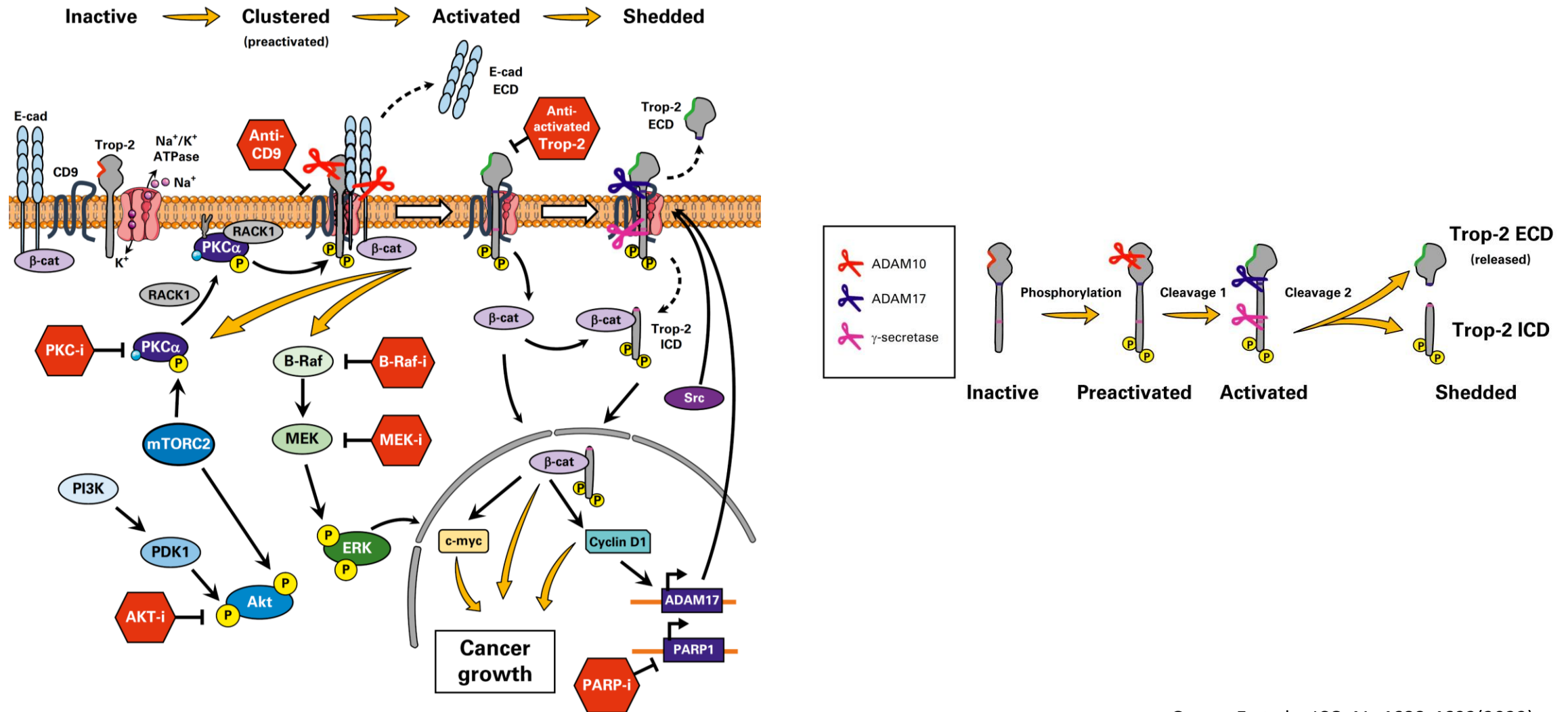
Few information about spatial and temporal heterogeneity of Trop-2

Core biopsy → Su

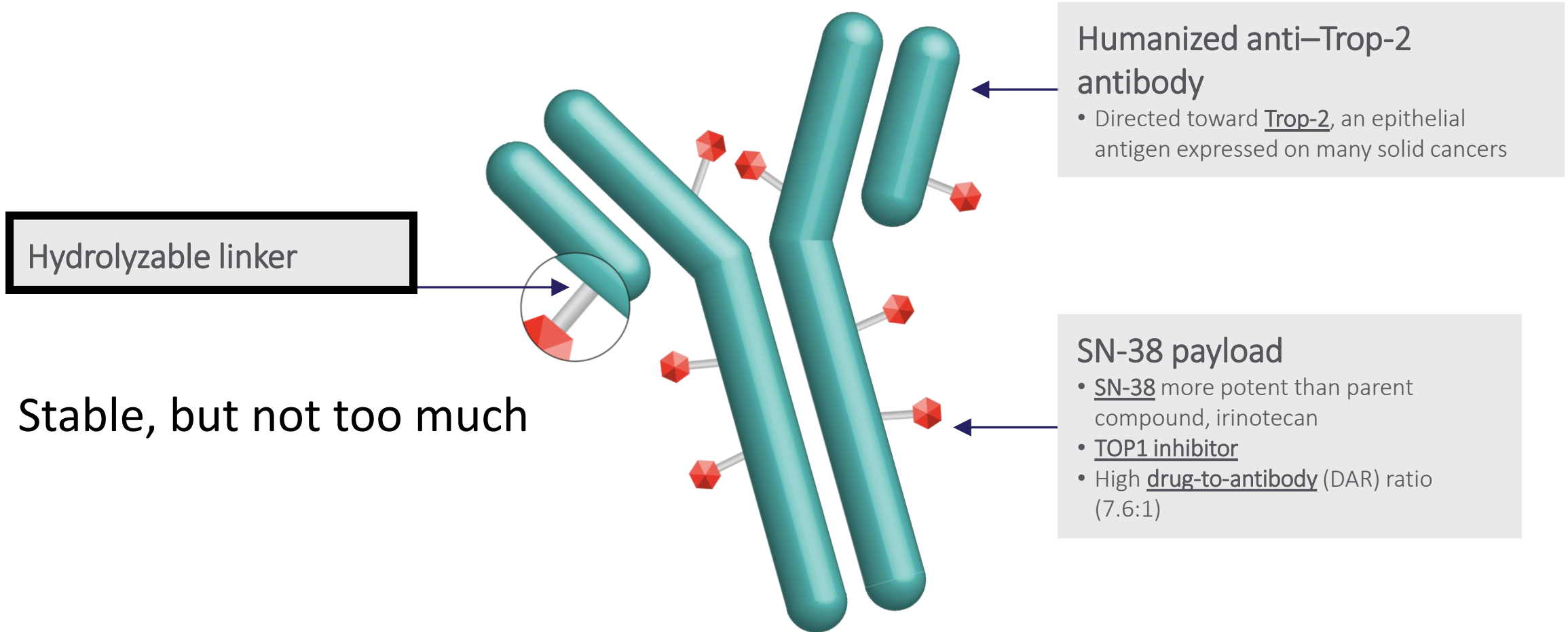


Bar Y ASCO 2022; Zhang J ASCO 2022; Tarantino P EJC 2022; Geukens T EJC 2023

Sequential activation of Trop-2 by proteolysis



Sacituzumab Govitecan: what unique?



Perez EA, et al. Breast Cancer Res Treat. 2010;121:261-271

Challenging the current dogma



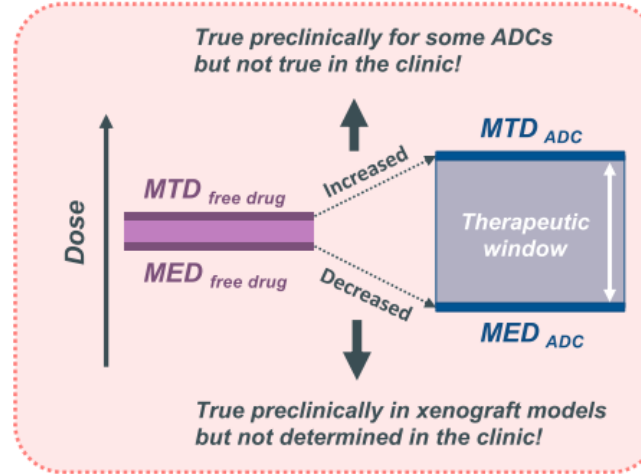
Commentary The therapeutic window of antibody drug conjugates: A dogma in need of revision

Raffaele Colombo^{1,*} and Jamie R. Rich^{1,*}
¹ADC Therapeutic Development, Zymeworks Inc., Vancouver, BC, Canada
 *Correspondence: raffaele.colombo@zymeworks.com (R.C.), jamie.rich@zymeworks.com (J.R.R.)
<https://doi.org/10.1016/j.ccell.2022.09.016>

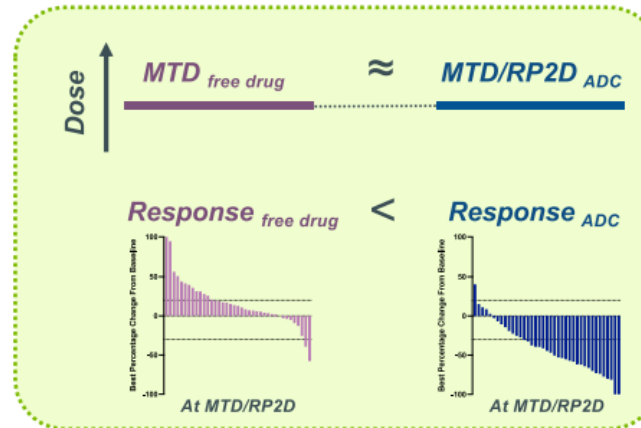
Part of the activity of the ADCs is associate to the free payload release (which contribute to the bystander effect)

A Current and revised views of ADC therapeutic window

Current representation not supported by clinical data

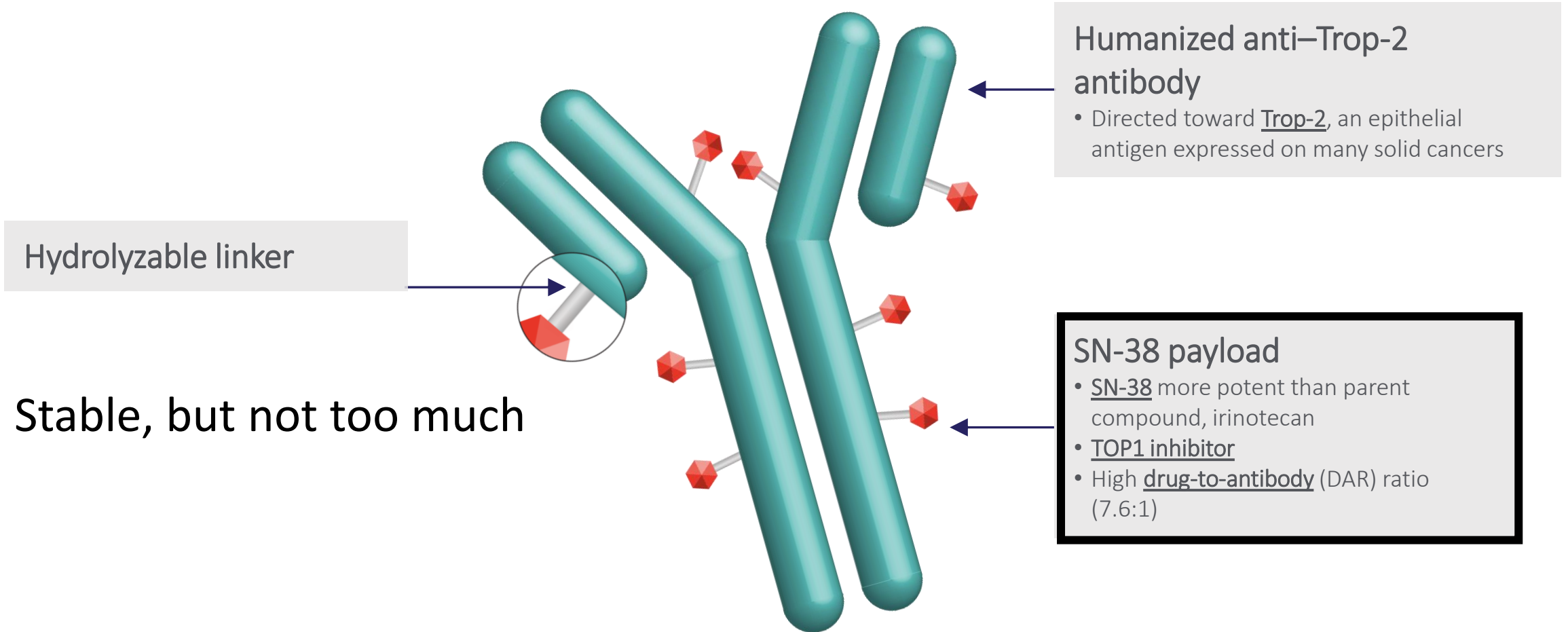


Revised representation based on emerging clinical data



Configuration	Antibody moiety	Linker	Site specific	Dose regimen	ADC or 50%	Cytotoxin Content (mg/kg)
DM1	Lys	MCC	non-oligo	3.5 N	Q3W	Maytansine
DM1	Lys	MCC	non-oligo	3.5 N	Q3W	Kadcyla
DM4	Lys	SPDB	deulfide	3.9 N	Q3W	Debio 1562
DM4	Lys	SPDB	deulfide	3.9 N	Q3W	IMG853
DM4	Lys	SPDB	deulfide	3.9 N	Q3W	CX-2009
DM4	Lys	SPDB	deulfide	3.9 N	Q2W	SAR408701
DM4	Lys	SPDB	deulfide	3.7 N	Q3W	OBT076
DM4	Lys	SPDB	deulfide	3.7 N	Q3W	TRPH-22
RED-108	IgY	non-oligo	2	Y	Q3W	
MMAE	Cys	MC	VCII	4 N	Q3W	Dolastatin 10
MMAE	Cys	MC	VCII	4 N	Q3W	TZT-1027
MMAE	Cys	MC	VCII	4 N	Q3W	Adcetris
MMAE	Cys	MC	VCII	4 N	Q3W	Polivy (DLBCL)
MMAE	Cys	MC	VCII	4 N	Q3W	Polivy (CLL)
MMAE	Cys	MC	VCII	4 N	Q3W	Polivy (NHL)
MMAE	Cys	MC	VCII	3.8 N	Q3W	Padcev
MMAE	Cys	MC	VCII	4 N	Q3W	Tivdak
MMAE	Cys	MC	VCII	4 N	Q2W	Aldixi (BC)
MMAE	Cys	MC	VCII	4 N	Q2W	Aldixi (GC)
MMAE	Cys	MC	VCII	3.1 N	Q3W	ABBV-399
MMAE	Cys	MC	VCII	3.1 N	Q2W	ABBV-399
MMAE	Cys	MC	VCII	4 N	Q3W	SGN-LIV1A
MMAE	Cys	MC	VCII	4 N	Q3W	SGN-LIV1A
MMAE	Cys	MC	VCII	4 N	Q3W	MK-2140
MMAE	Cys	MC	VCII	4 N	Q3W	MRG001
MMAE	Cys	MC	VCII	4 N	Q3W	MRG002
MMAE	Cys	MC	VCII	4 N	Q3W	MRG003
MMAE	Cys	MC	VCII	4 N	Q2W	BA3011
MMAE	Cys	MC	VCII	4 N	Q2W	BA3021
MMAE	Cys	MC	VCII	4 N	Q3W	FOR46
MMAE	Cys	MC	VCII	4 N	Q3W	OB99
MMAE	Cys	MC	VCII	2 N	Q3W	CX-2029
MMAE	Cys	MC	VCII	2 Y	Q3W	ALY77
Duo-5	Lys	non-oligo	VCII	2 Y	Q3W	A166
MMAF	Cys	MC	non-oligo	4 N	Q3W	Benrep
AS289	pAF	hydrolyzable	non-oligo	2 Y	Q4W	ARX788
Aur0101	Cys	MC	VCII	4 N	Q3W	ABBV-647
AF-HPA	Cys	MP	ester	10 N	Q3W	XMT-1536
DXd	Cys	MC	GGFG	8 N	Q3W	Trinotecan
DXd	Cys	MC	GGFG	8 N	Q3W	Trinotecan
DXd	Cys	MC	GGFG	8 N	Q3W	Topotecan
DXd	Cys	MC	GGFG	8 N	Q3W	Topotecan
DXd	Cys	MC	GGFG	8 N	Q3W	Topotecan
DXd	Cys	MC	GGFG	8 N	Q3W	Belotecan
DXd	Cys	MC	GGFG	8 N	Q3W	Exatecan
DXd	Cys	MC	GGFG	8 N	Q3W	Enheru (BC, LC)
DXd	Cys	MC	GGFG	8 N	Q3W	Enheru (GC)
DXd	Cys	MC	GGFG	8 N	Q3W	HER3-DXd
DXd	Cys	MC	GGFG	8 N	Q3W	Dato-DXd
DXd	Cys	MC	GGFG	8 N	Q3W	BTH3-DXd
DXd	Cys	MC	GGFG	8 N	Q3W	CDH6-DXd
SN-38	Cys	MCC	carbonyl	7.6 N	Q2W	Trodelvy
SN-38	Cys	peroxide	carbonyl	7.4 N	Q2W	SKB264
SJG-136	Cys	MP	VA	2.3 N	Q3W	SJG-136
SJG-136	Cys	MP	VA	2.3 N	Q3W	SJG-136
SJG-136	Cys	MP	VA	2.3 N	Q3W	SJG-136
SG3199	Cys	MP	VA	2.3 N	Q3W	Zynlonta
SG3199	Cys	MP	VA	2.3 N	Q3W	ADCT-301 (HL)
SG3199	Cys	MP	VA	2.3 N	Q3W	ADCT-301 (NHL)
DGN549	Cys	MEIN	AA	2 Y	Q3W	MGN632
Pibrozolesin	Cys	MC	VCII	4 N	Q3W	Pibrozolesin
Pibrozolesin	Cys	MC	VCII	4 N	Q3W	Pibrozolesin
DUBA	Cys	MEIO	VCII	2.8 N	Q3W	Carzolesin
DUBA	Cys	MEIO	VCII	2.7 N	Q3W	SYD985
DUBA	Cys	MEIO	VCII	2.7 N	Q3W	MGC018
Halaven	Cys	MC	VCII	4 N	Q3W	Halaven
Halaven	Cys	MC	VCII	4 N	Q3W	Halaven
Halaven	Cys	MC	VCII	4 N	Q3W	Halaven
Eribulin	Cys	MEIO	VCII	4 N	Q3W	MORAB-202
HTI-286	pAMF	DBCO	VCII	4 Y	Q3W	HTI-286
E7974	pAMF	DBCO	VCII	4 Y	Q3W	E7974
SC239	pAMF	DBCO	VCII	4 Y	Q3W	STRO-002

Sacituzumab Govitecan: what unique?

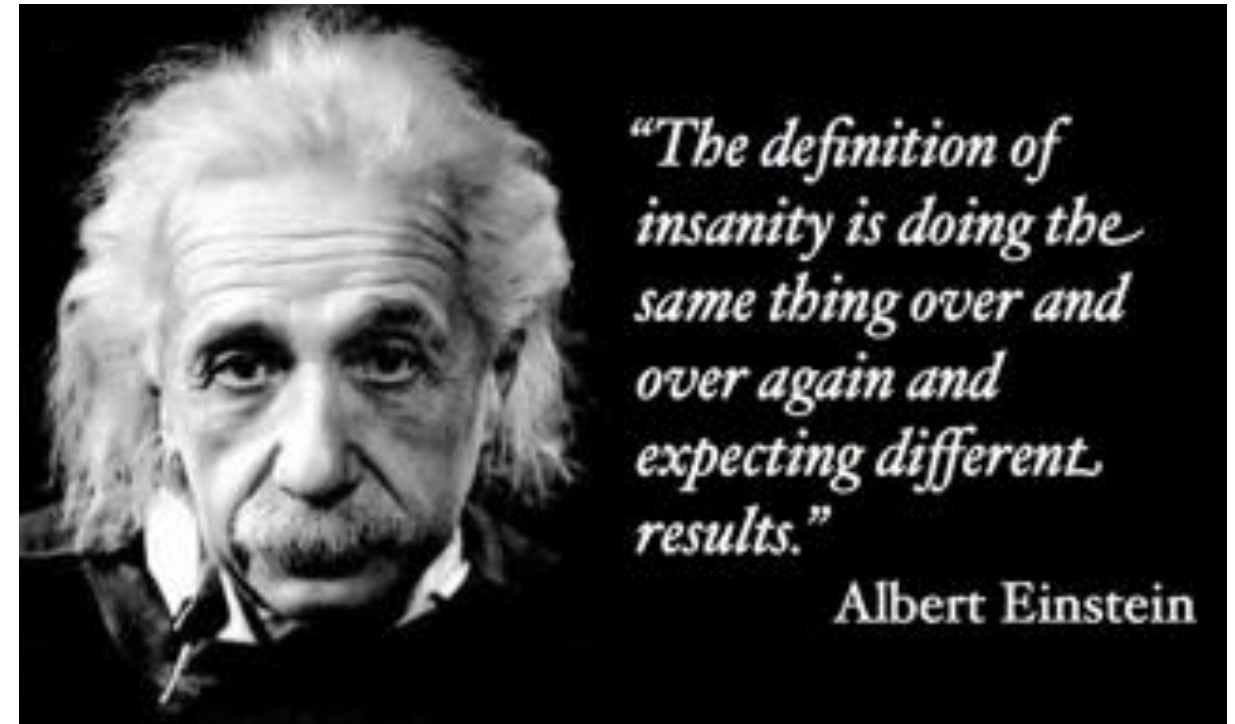
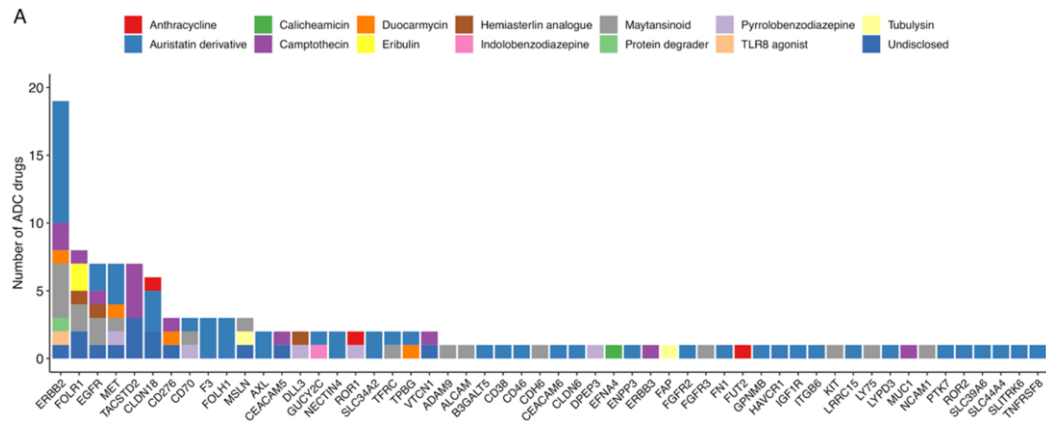


Perez EA, et al. Breast Cancer Res Treat. 2010;121:261-271

Payload optimization

Camptothecin-based topoisomerase I inhibitors have stood out as one of the most promising payload classes for ADCs

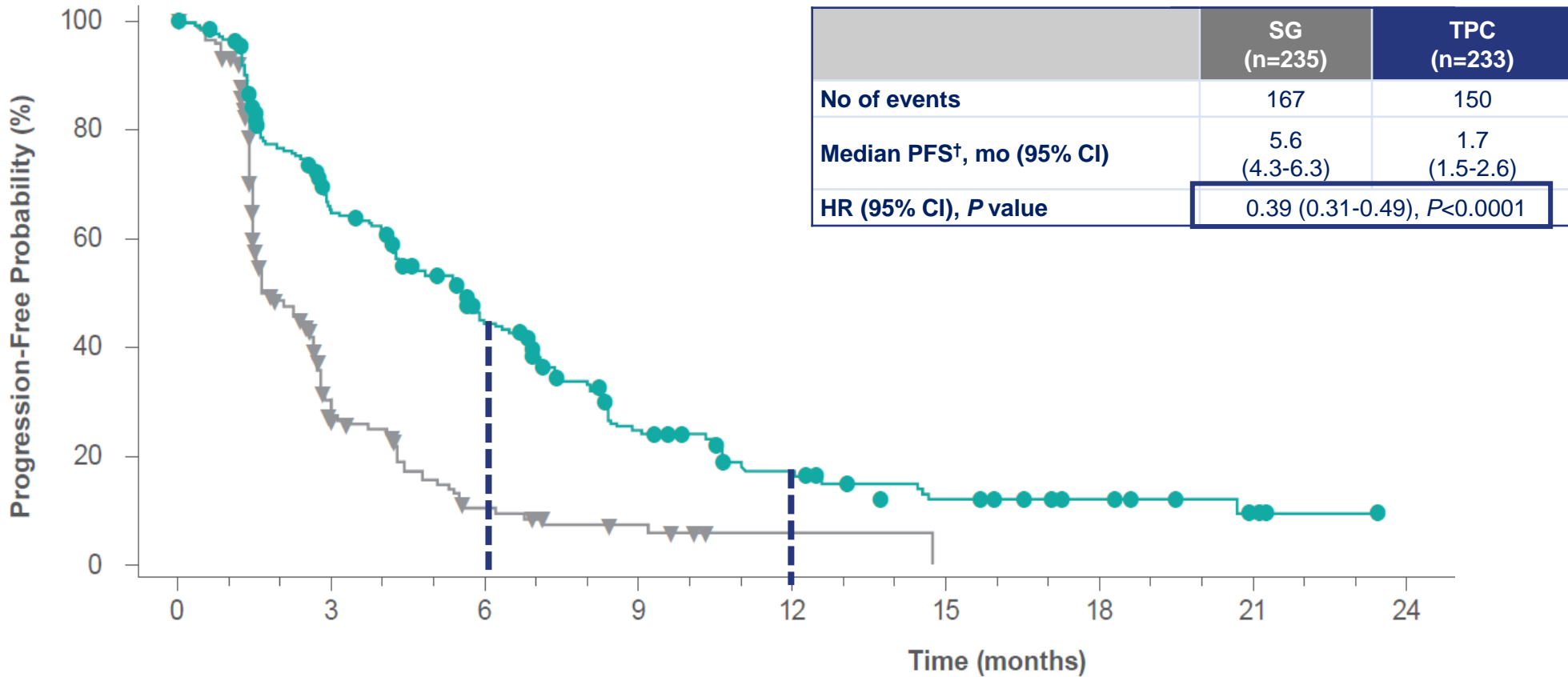
Non-cross-resistant



Sacituzumab Govitecan
Lessons from clinical implementation

**Did SG keep his
promises?**

ASCENT: Progression-Free Survival



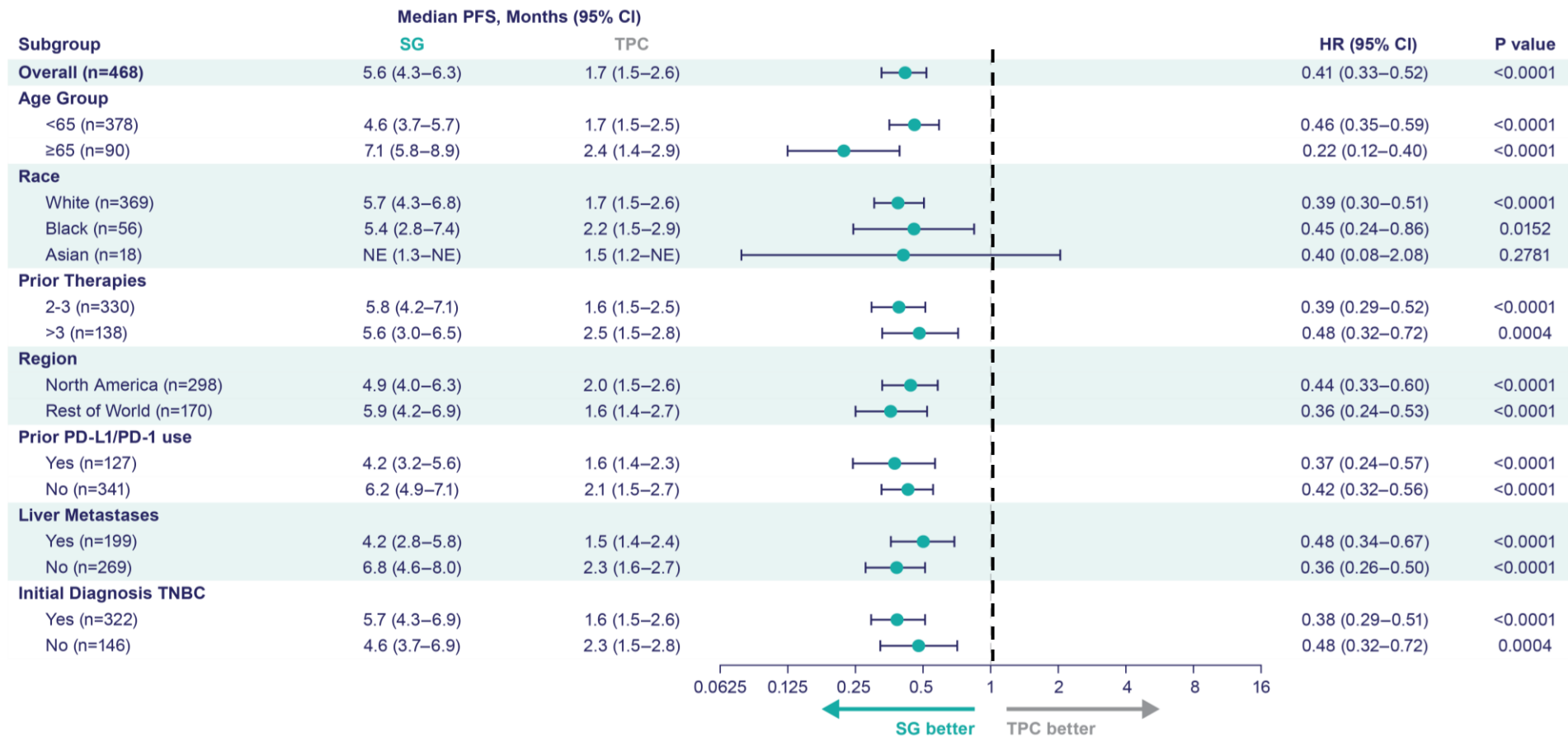
No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
SG	235	222	166	134	127	104	81	63	54	37	33	24	22	17	16	13	11	10	8	6	5	3	1	1	0
TPC	233	178	77	34	31	18	11	8	6	5	3	1	1	1	0	0	0	0	0	0	0	0	0	0	0

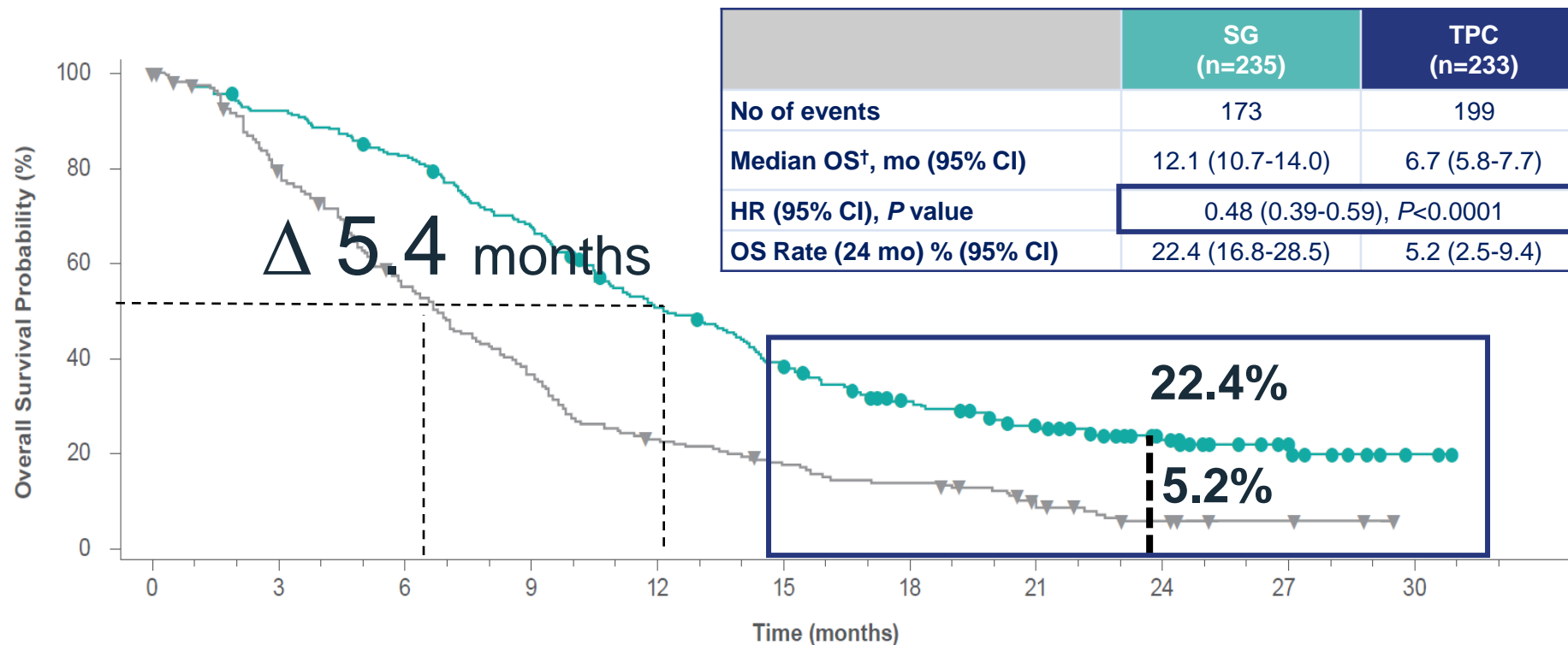
Bardia A, et al. Presented at ASCO 2022 (abstract ID #1071)

ASCENT: Progression-Free Survival by Subgroup

HR < 0.5 in all subgroups



Unprecedented Overall Survival benefit



No. of Patients Still at Risk

Time (months)

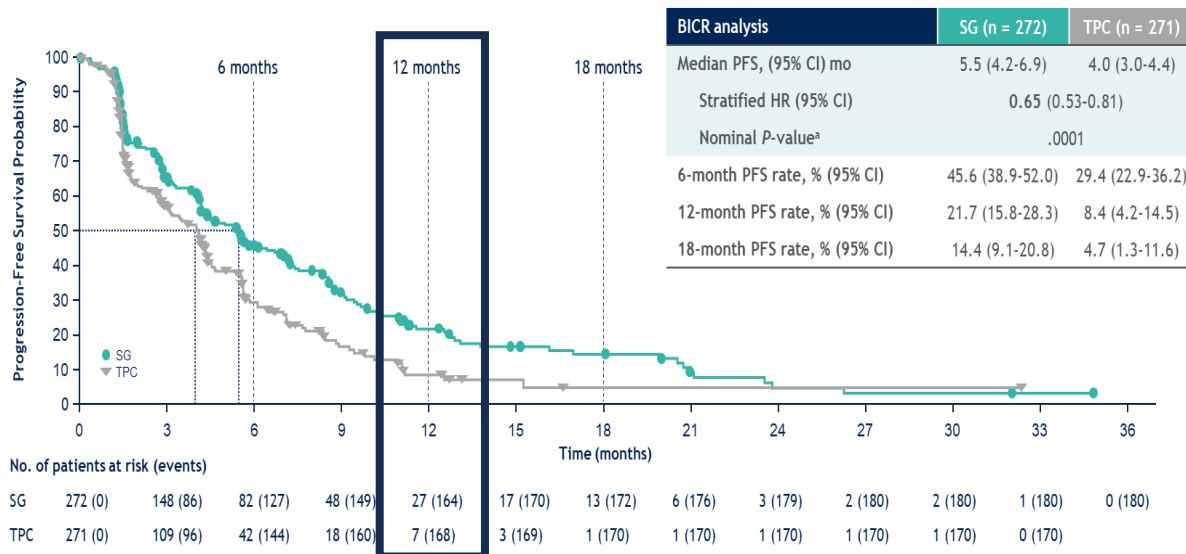
SG

TPC

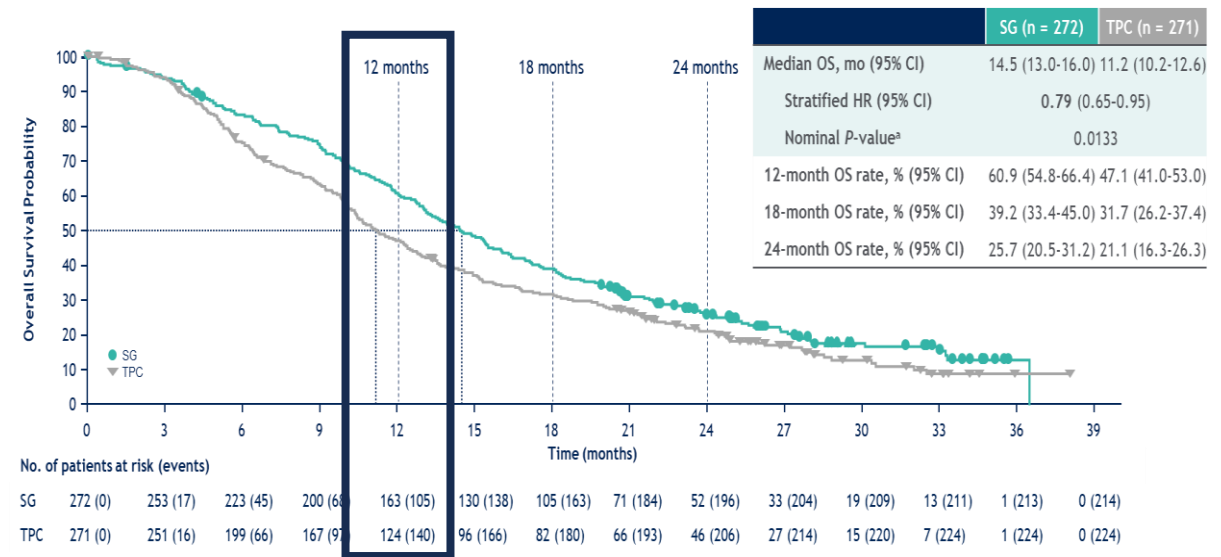
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
235	228	220	214	206	197	191	177	164	156	140	122	113	105	97	85	74	65	59	56	46	40	35	30	25	17	14	11	7	4	2
233	214	200	173	156	134	117	101	90	77	58	53	47	44	40	35	30	28	27	24	22	13	11	7	6	4	3	3	2	1	0

TROPiCS-02 Final Analysis: Progression-Free and Overall Survival

Progression-Free Survival



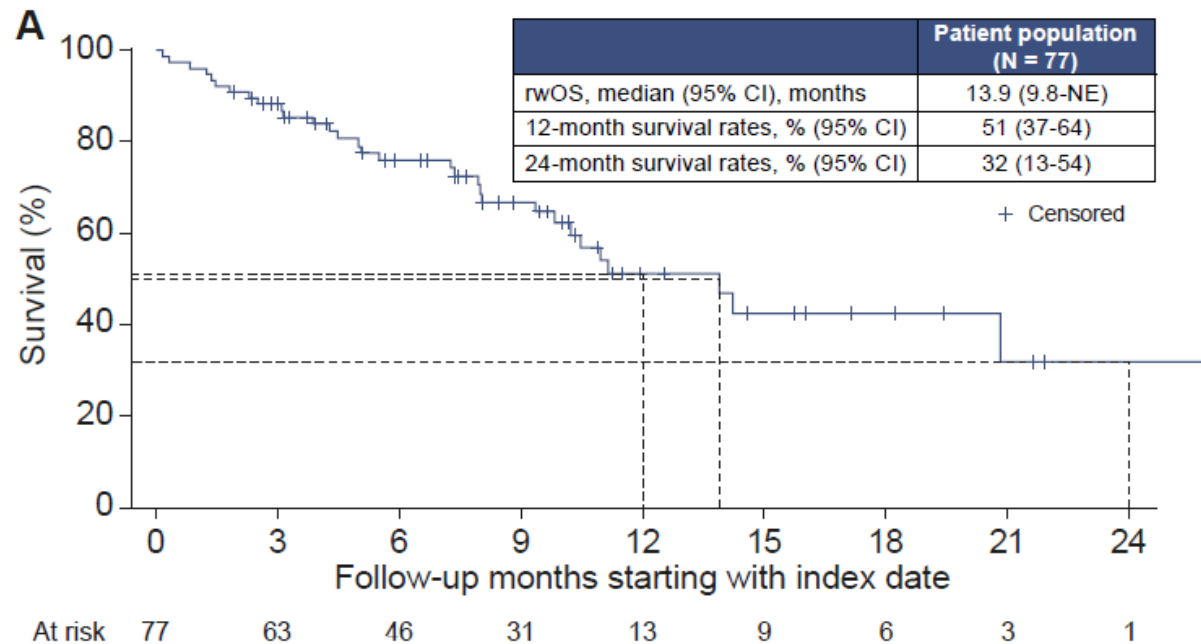
Overall Survival



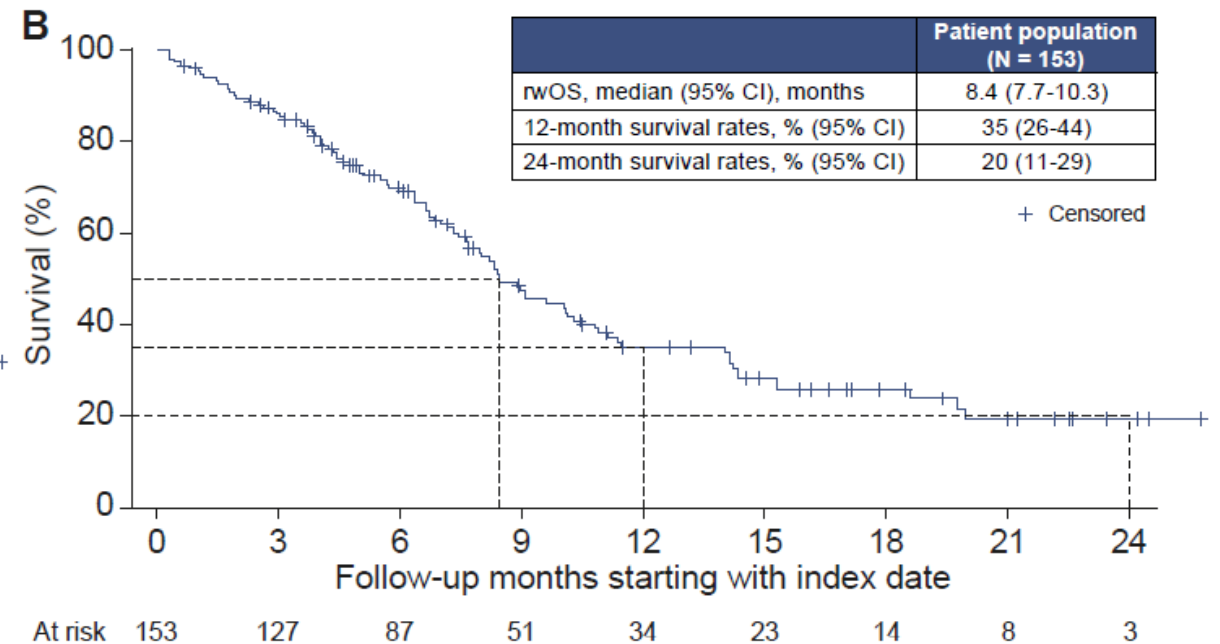
SG Real-world clinical outcomes

Real-world OS in patients with mTNBC treated with SG in 2L (A) and 3L+^a (B)

2L



3L+



^aIndex date as start date.

Dashed lines indicate 12-month and 24-month survival rates and median rwOS. 2L, second line; 3L+, third line or later; CI, confidence interval; IQR, interquartile range; LoT, line of therapy; mTNBC, metastatic triple-negative breast cancer; NE, not estimable; rwPFS, real-world progression free survival; rwOS, real-world overall survival; SG, sacituzumab govitecan; TTNTD, time to next treatment or death.

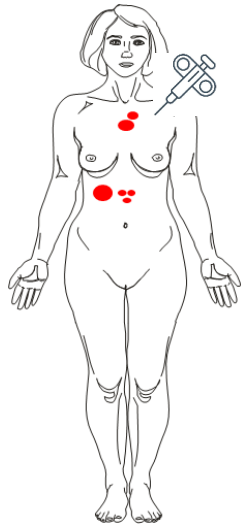
1. Kalinsky K, et al. Presented at ESMO 2023. Poster #FPN393P.

SG in monoterapia e indicato per il trattamento di pazienti adulti con cancro della mammella triplo-negativo metastatico (metastatic triple-negative breast cancer, mTNBC) o non resecabile che abbiano ricevuto in precedenza almeno due terapie sistemiche, almeno una delle quali per la malattia avanzata.² Per maggiori informazioni sulla rimborsabilità del farmaco, consultare il Riassunto delle Caratteristiche del Prodotto.

Material destinado a profissionais da saúde prescritor ou dispensador.

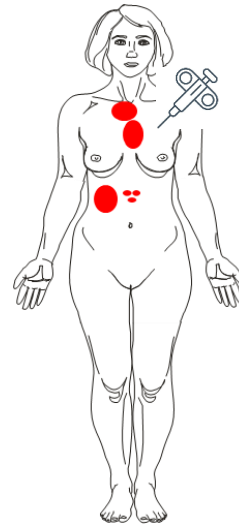
Any subgroup of special interest?

Implications of “re-biopsy” in HER2+ and ER+/HER2- aBC



Biopsy
ER+/HER2-
HER2+

Past

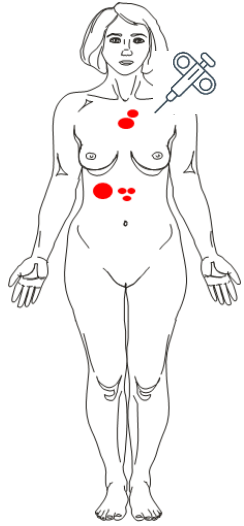


Biopsy
TNBC

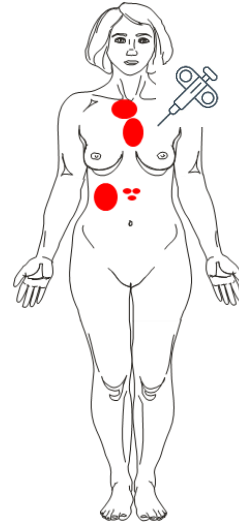


Implications of “re-biopsy” in HER2+ and ER+/HER2- aBC

Past



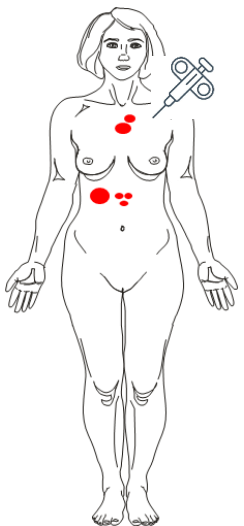
Biopsy
ER+/HER2-
HER2+



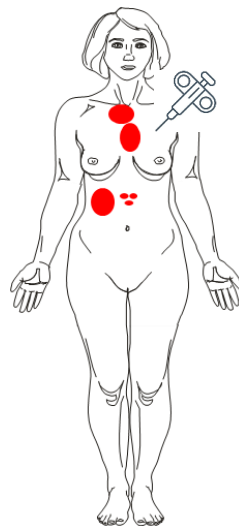
Biopsy
TNBC



post-ASCENT



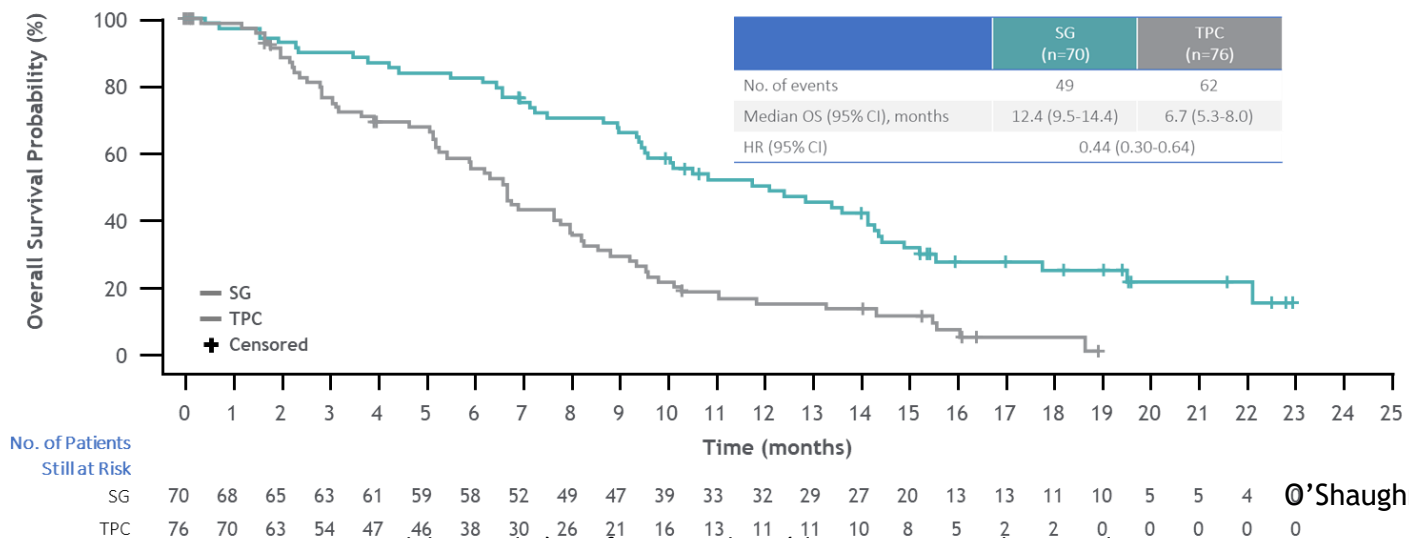
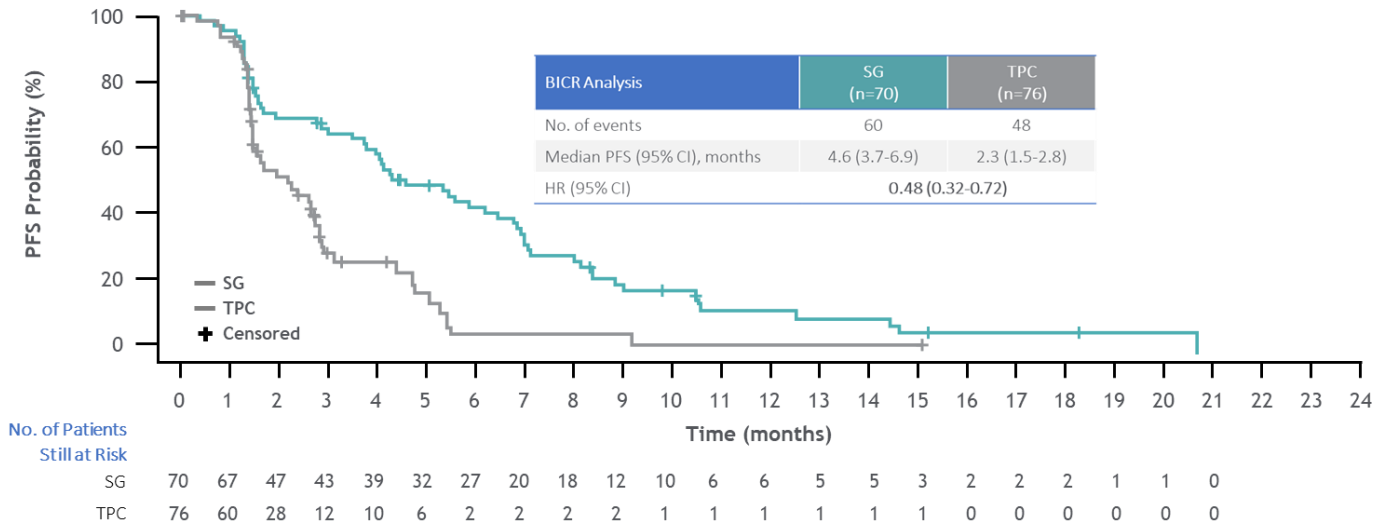
Biopsy
ER+/HER2-
HER2+



Biopsy
TNBC



PFS and OS benefit in pts without TNBC at initial diagnosis

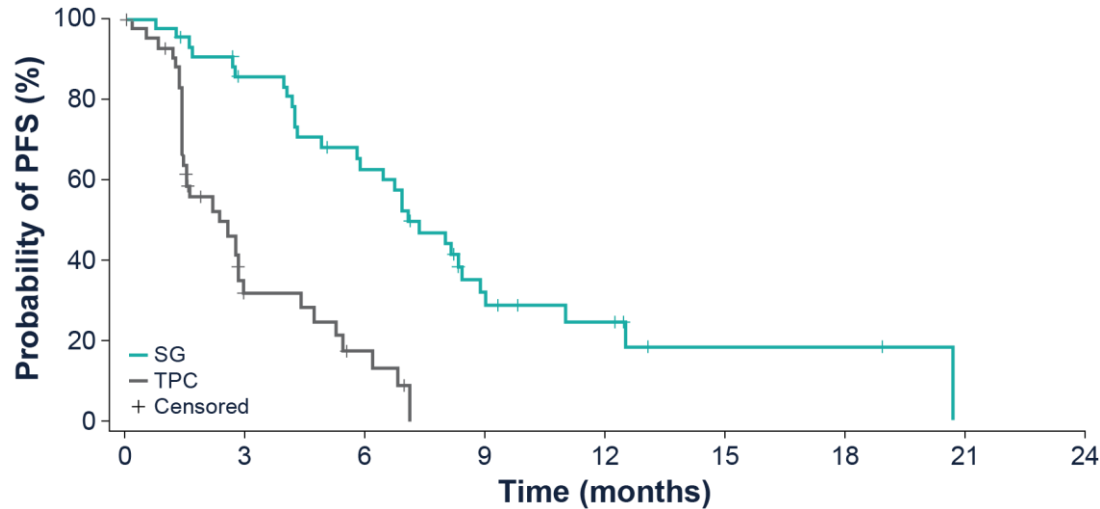


Is older age an issue?

Patients aged ≥ 65 Years

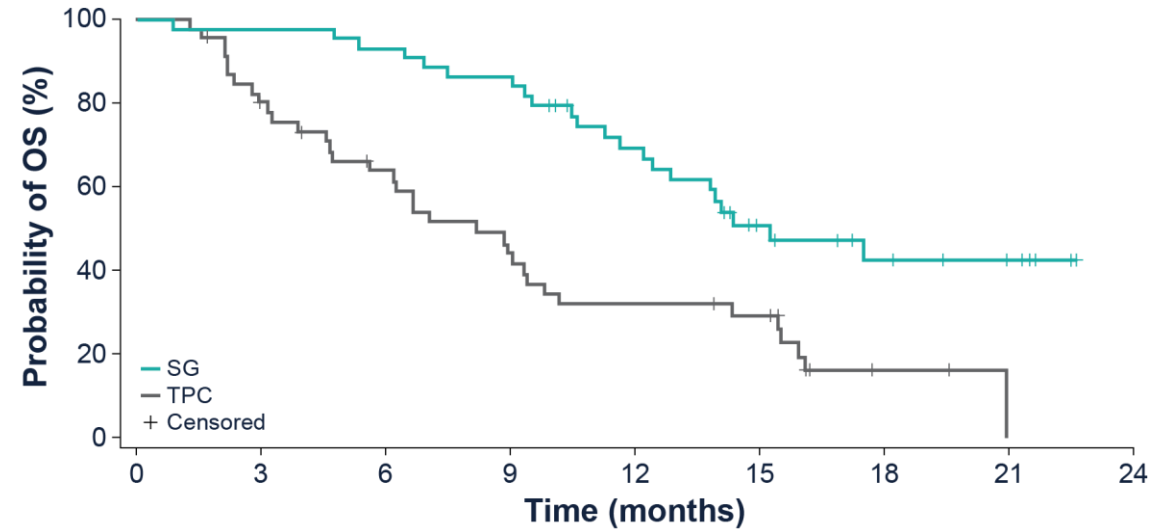
PFS BICR Analysis	≥ 65 y	
	SG (n=44)	TPC (n=46)
No. of events	30	33
Median PFS—mo. (95% CI)	7.1 (5.8-8.9)	2.4 (1.4-2.9)
HR (95% CI), <i>P</i> value	0.22 (0.12-0.40), <i>P</i> <0.0001	

	≥ 65 y	
	SG (n=44)	TPC (n=46)
No. of events	22	35
Median OS—mo. (95% CI)	15.3 (12.4-NE)	8.2 (5.6-9.8)
HR (95% CI), <i>P</i> value	0.37 (0.22-0.64), <i>P</i> =0.0003	



No. of Patients Still at Risk

	0	3	6	9	12	15	18	21	24												
SG	44	43	38	34	33	27	24	20	17	10	7	7	6	3	2	2	2	2	1	1	0
TPC	46	39	19	9	9	7	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0



No. of Patients Still at Risk

	0	3	6	9	12	15	18	21	24															
SG	44	43	43	43	43	42	41	39	38	38	33	29	27	24	22	14	12	11	9	8	7	6	2	0
TPC	46	46	43	35	31	28	26	22	21	18	14	13	13	13	12	11	6	3	2	2	1	0	0	0

Is older age an issue?

Event, n (%)	SG (n=258)		TPC (n=224)	
	<65 y (n=209)	≥65 y (n=49)	<65 y (n=176)	≥65 y (n=48)
Any TEAE*	208 (99.5)	49 (100)	171 (97)	48 (100)
Grade ≥3	153 (73)	33 (67)	115 (65)	30 (63)
Leading to dose reduction	39 (19)	17 (35)	43 (24)	16 (33)
Leading to study drug discontinuation	11 (5)	1 (2)	11 (6)	1 (2)
Any TRAE	204 (98)	48 (98)	152 (86)	40 (83)
Grade ≥3	135 (65)	31 (63)	79 (45)	26 (54)
Leading to dose reduction	39 (19)	17 (35)	41 (23)	16 (33)
Leading to study drug discontinuation	4 (2)	1 (2)	6 (3)	0
Leading to death	0	0	1 (1)	0

Rates of AEs were similar for patients aged ≥75 years as observed in patients aged ≥65 years

TEAE is defined as an AE with start date on or after the date of first dose of study treatment and up to 30 days after date of last dose of study treatment.

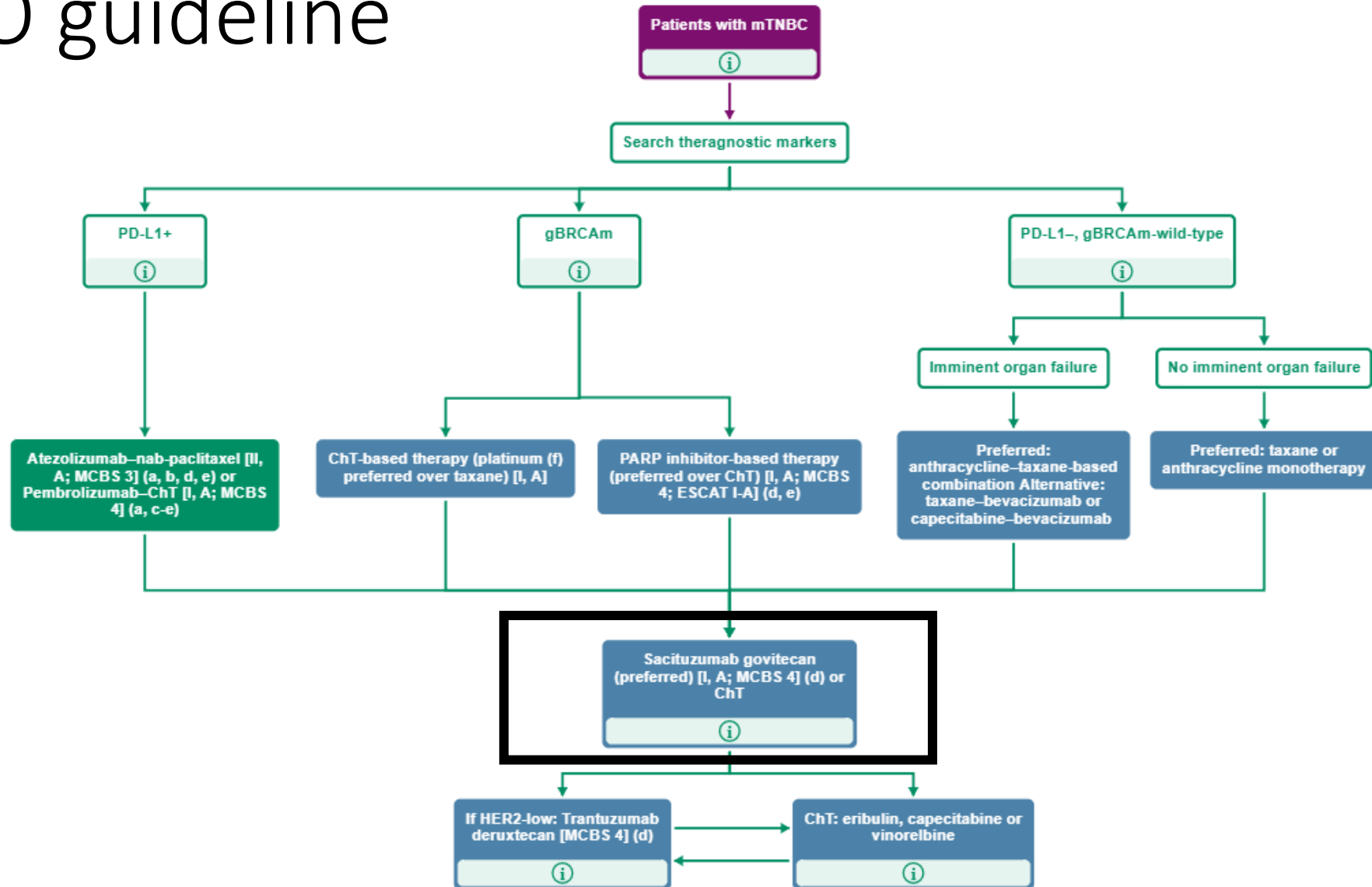
*Patients may report more than 1 event per preferred term. AEs were coded using MedDRA v22.1 and were counted once for each preferred term. AE severity was graded per NCI CTCAE v4.03.

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology for AEs; SG, sacituzumab govitecan; TEAE, treatment-emergent AE;

TPC, treatment of physician's choice; TRAE, treatment-related AE.

Positioning of SG in the TNBC therapeutic algorithm

ESMO guideline



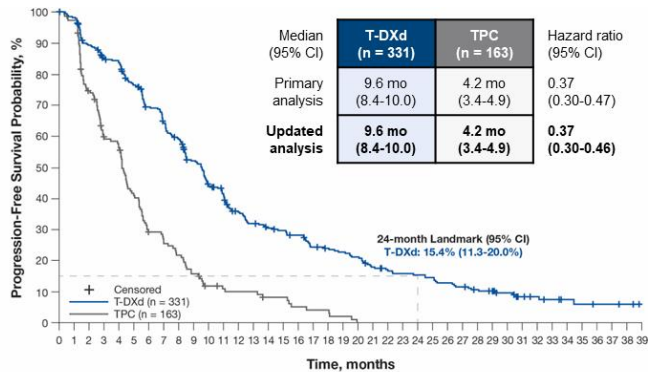
Sustained remarkable OS benefit from T-DXd in HER2-low

The consistent results across all endpoints (ORR, mDoR, PFS, and OS) establish the role of T-DXd in TN HER2-low mBC



Patients still at risk:

T-DXd (n = 331) 331 305 303 317 313 307 302 292 294 278 267 254 250 243 230 220 225 212 199 188 183 176 168 155 147 136 124 106 91 72 56 54 46 42 34 25 17 11 7 5 4 3 2 1 1 0
 TPC (n = 163) 163 155 143 142 138 134 129 123 114 108 103 97 96 91 87 82 75 71 65 64 58 55 50 47 43 43 42 35 31 25 15 13 11 11 9 7 5 2 2 1 0

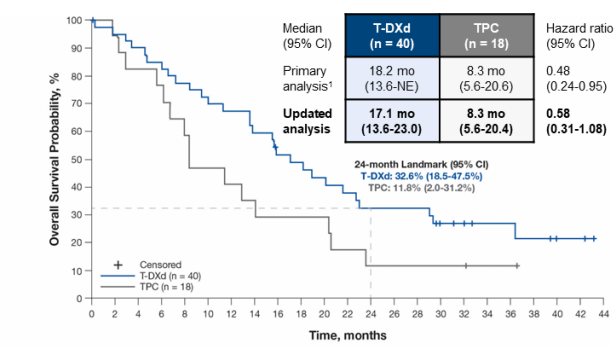


Patients still at risk:

T-DXd (n = 331) 331 323 290 272 267 241 215 198 181 154 129 119 98 88 82 74 74 63 60 57 53 44 40 37 36 34 30 27 23 21 16 11 9 7 5 4 3 3 2 0
 TPC (n = 163) 163 143 127 83 76 38 34 29 21 14 12 11 9 8 5 4 4 2 0

OS

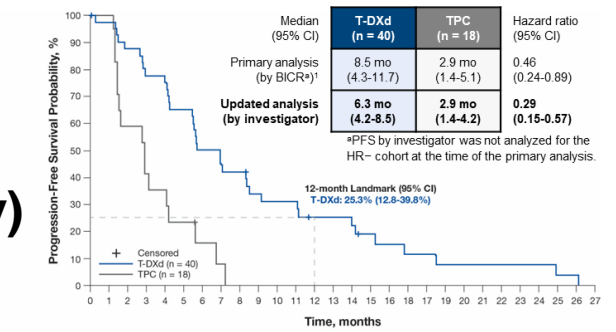
HR-



Patients still at risk:

T-DXd (n = 40) 40 38 36 34 31 28 23 19 18 16 14 12 12 8 7 5 5 4 2 2 0
 TPC (n = 18) 18 16 14 13 10 8 7 6 5 5 3 2 2 2 2 1 1 0 0 0 0

PFS(inv)



Patients still at risk:

T-DXd (n = 40) 40 39 35 31 30 26 19 17 12 11 11 8 7 5 4 3 3 2 2 2 2 2 1 1 0
 TPC (n = 18) 18 17 10 7 6 4 2 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0

32-month median follow-up

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Material destinado à profissionais da saúde prescritor ou dispensador. Bianchini G. Annals of Oncology (2023) 34 (suppl_2).

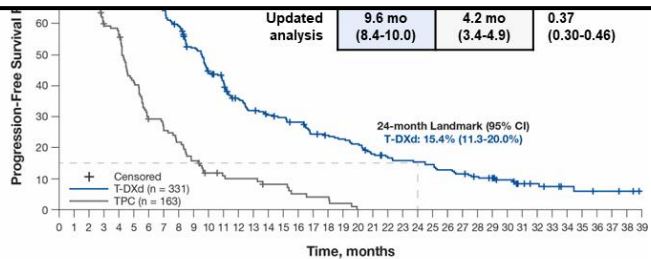
Sustained remarkable OS benefit from T-DXd in HER2-low

The consistent results across all endpoints (ORR, mDoR, PFS, and OS) establish the role of T-DXd in TN HER2-low mBC

Current limitations

- Exploratory analysis
- Only 58 patients

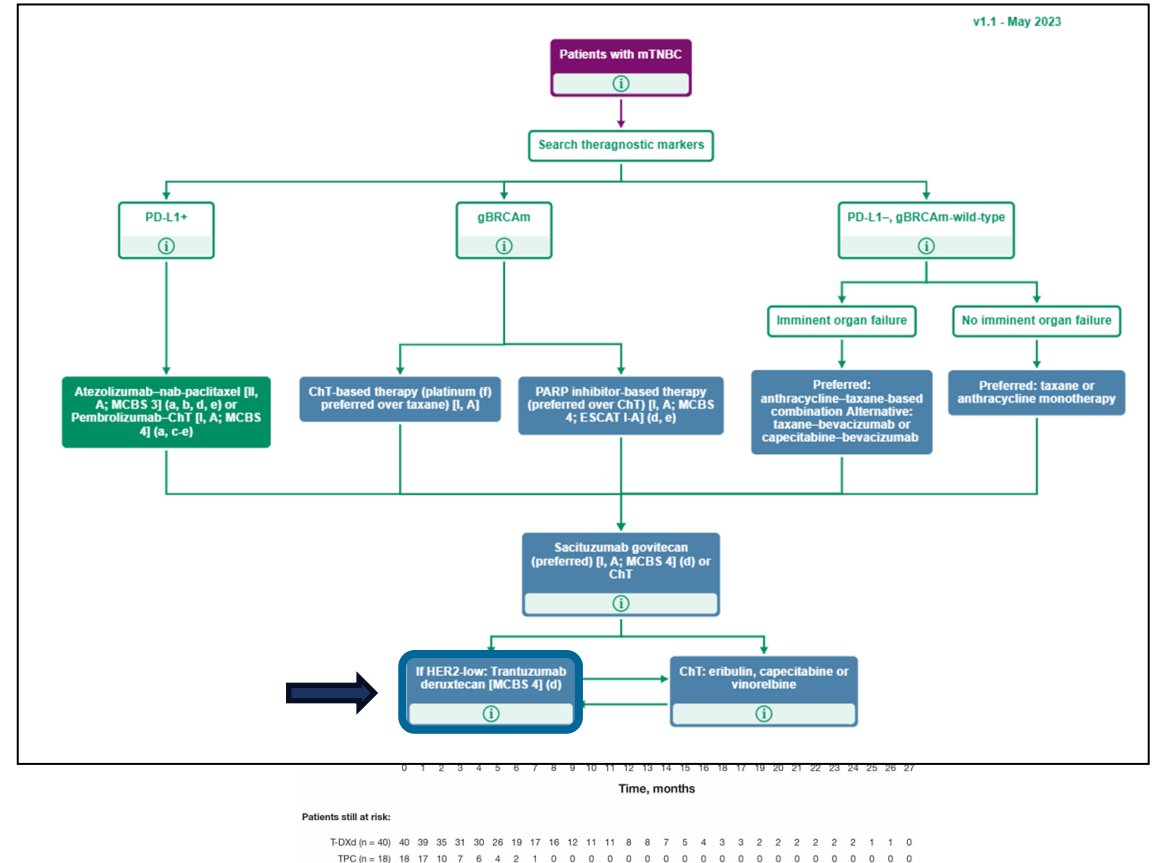
PFS(inv)



Patients still at risk:

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	
T-DXd (n = 331)	331	323	290	252	207	241	215	188	161	154	129	119	98	88	82	79	74	63	60	57	43	40	37	36	34	30	27	23	21	16	11	9	7	5	4	3	2	0			
TPC (n = 163)	163	143	107	80	76	36	34	29	21	14	12	11	9	8	5	4	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TNBC



32-month median follow-up

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Treatment after neoadjuvant KEYNOTE 522 regimen

What about re-challenge with ICI?

High Risk
TNBC



Carbo/tax → A(E)C
Pembro

Surgery (RD)

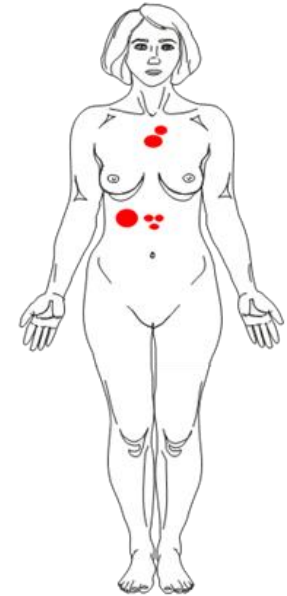


Pembro

(more than 12 months)



Re-challenge with
ICIs?

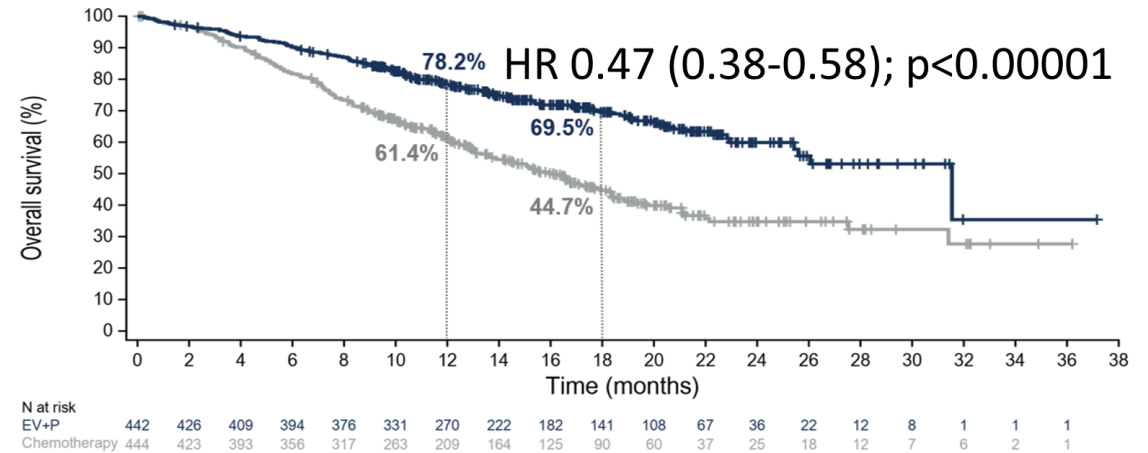
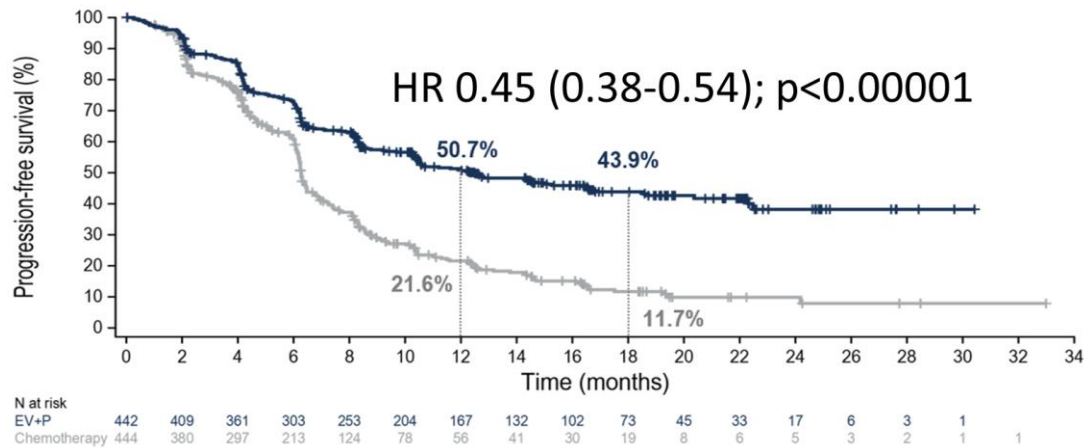


High priority for clinical trials

Targeting mechanism
of “immune resistance”

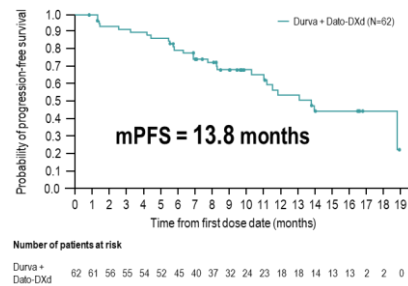
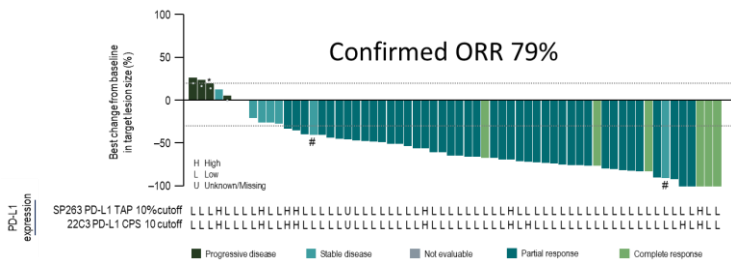
Synerigstic effect of ADC - ICIs combination

Enfortunab Vendotin + Pembro (mUC)



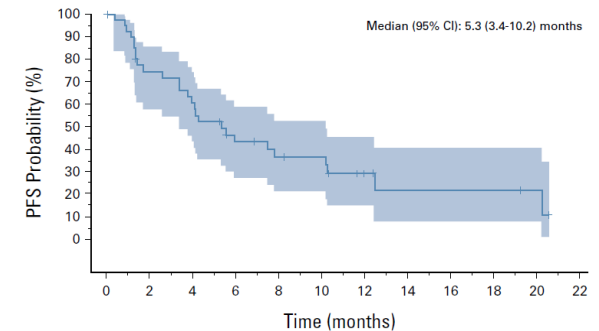
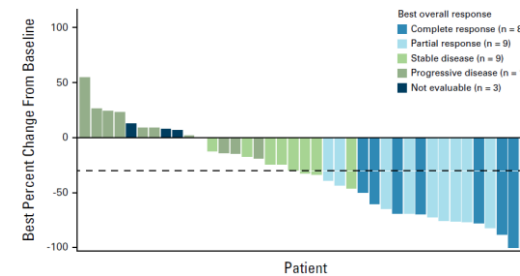
Powles T . Annals of Oncology (2023) 34 (suppl_2): S1281-S1282.

Datopotamab Deruxtecan + Durva (mTNBC)



Schmid P. Annals of Oncology (2023) 34 (suppl_2): S334-S390.ESMO 2023

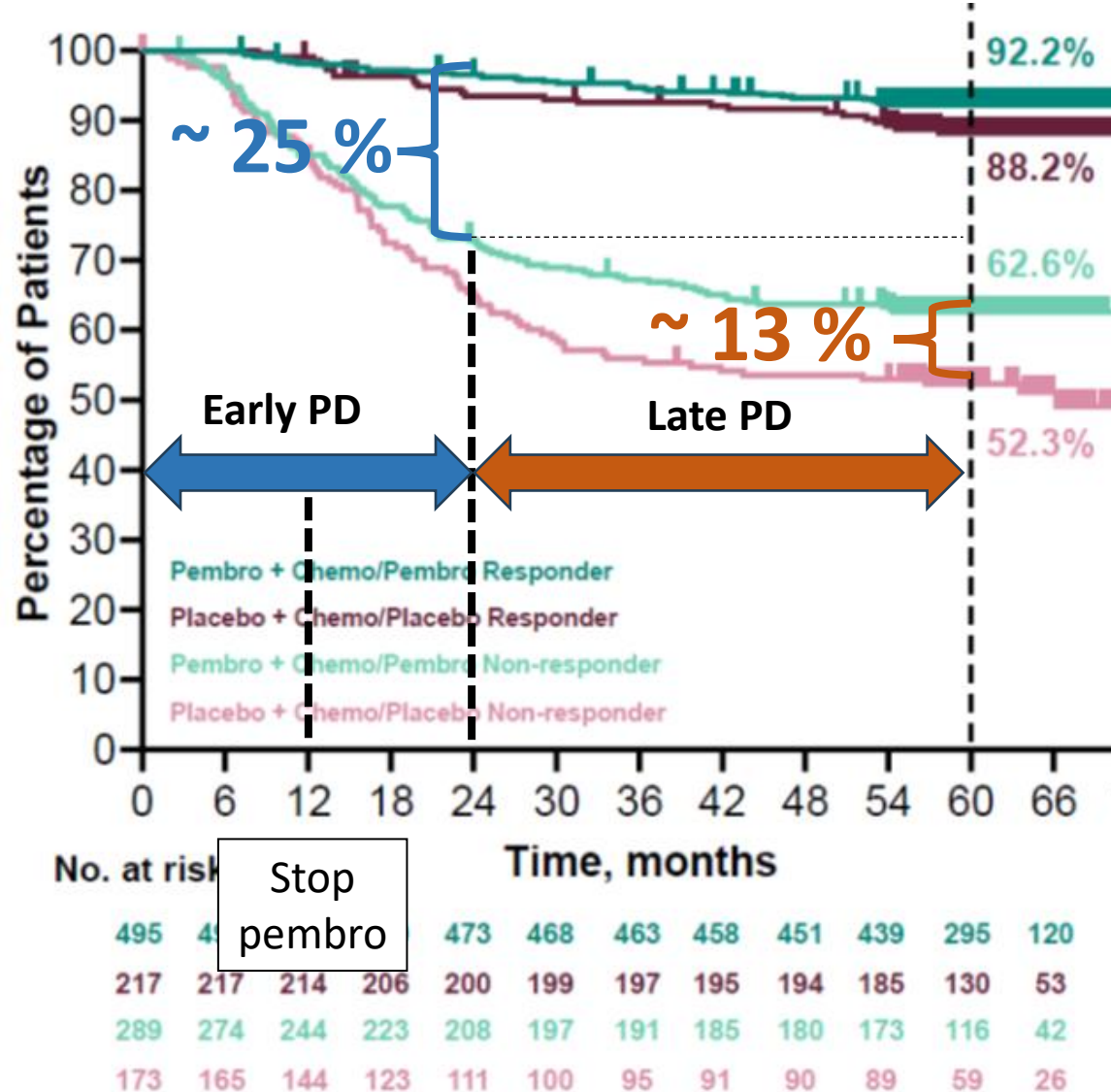
Sacituzumab Govitecan + Pembro (mUC)



Grivas P, et al. TROPHY-U-01 Cohort 3. J Clin Oncol. 2024

Early progression (within 12 months)

Neoadjuvant
KEYNOTE-522
regimen



Early progression (within 12 months)

6 months

12 months

Neoadjuvant
KEYNOTE-522
regimen

High priority for clinical trials

SG or T-DXd (if HER2low)
(eribulin)

If PD-L1+

SG (+/- pembro)
Pembro/Nab?
Pembro/Cerbo/Gem?

If PD-L1-

SG
(eribulin)

Safety and optimal management of SG in clinical practice

ASCENT: AEs observed in > 20% 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

- AEs leading to treatment discontinuation were low for SG and TPC: 4.7% and 5.4%

Importance of the right dose

Table 3. Efficacy outcomes for patients with dose reductions or interruptions (brain metastasis-negative population).

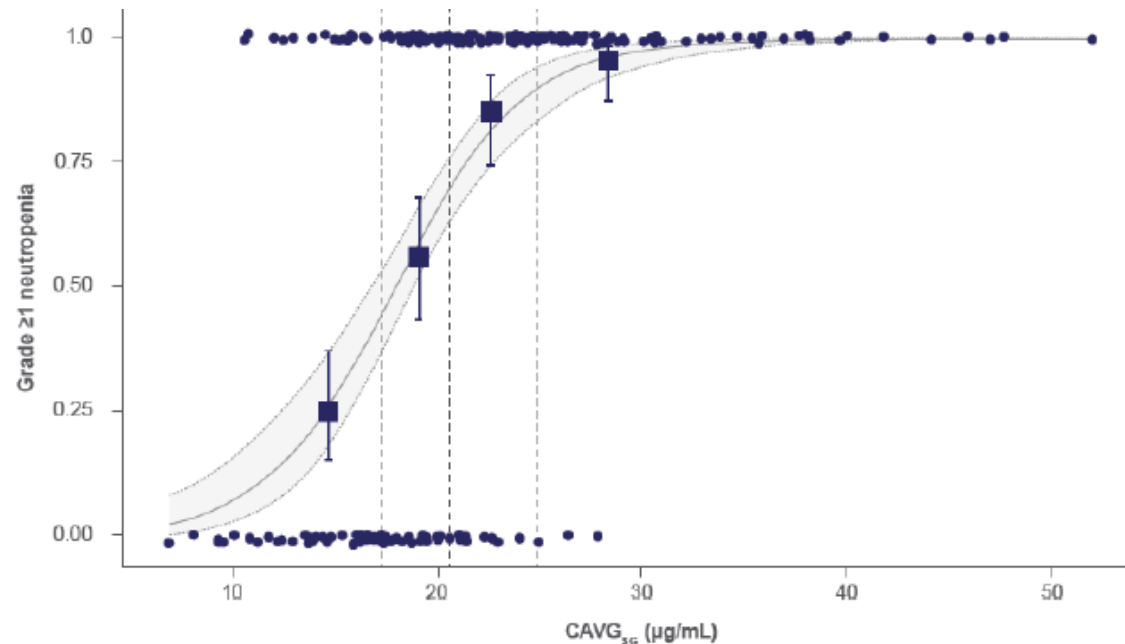
Outcome	Overall BMNeg population		Dose reductions		No dose reductions		Dose interruptions		No dose interruptions	
	SG (n = 235)	TPC (n = 233)	SG (n = 62)	TPC (n = 52)	SG (n = 173)	TPC (n = 181)	SG (n = 144)	TPC (n = 78)	SG (n = 91)	TPC (n = 155)
ORR (BICR), n (%)	82 (35)	11 (5)	29 (47)	7 (13)	53 (31)	4 (2)	56 (39)	5 (6)	26 (29)	6 (4)
CBR (BICR), n (%)	105 (45)	20 (9)	37 (60)	11 (21)	68 (39)	9 (5)	71 (49)	12 (15)	34 (37)	8 (5)
Best overall response, n (%)										
CR	10 (4)	2 (1)	5 (8)	1 (2)	5 (3)	1 (1)	7 (5)	0	3 (3)	2 (1)
PR	72 (31)	9 (4)	24 (39)	6 (12)	48 (28)	3 (2)	49 (34)	5 (6)	23 (25)	4 (3)
Median PFS (BICR), mo (95% CI)	5.6 (4.3–6.3)	1.7 (1.5–2.6)	8.3 (5.4–10.3)	2.9 (2.7–4.3)	4.6 (3.5–5.7)	1.5 (1.4–1.7)	5.7 (4.3–7.0)	2.7 (1.7–3.0)	4.2 (2.9–6.8)	1.6 (1.5–2.2)

Dose reduction = efficacy → Starting with a lower dose will not significantly impact efficacy
Dose interruptions

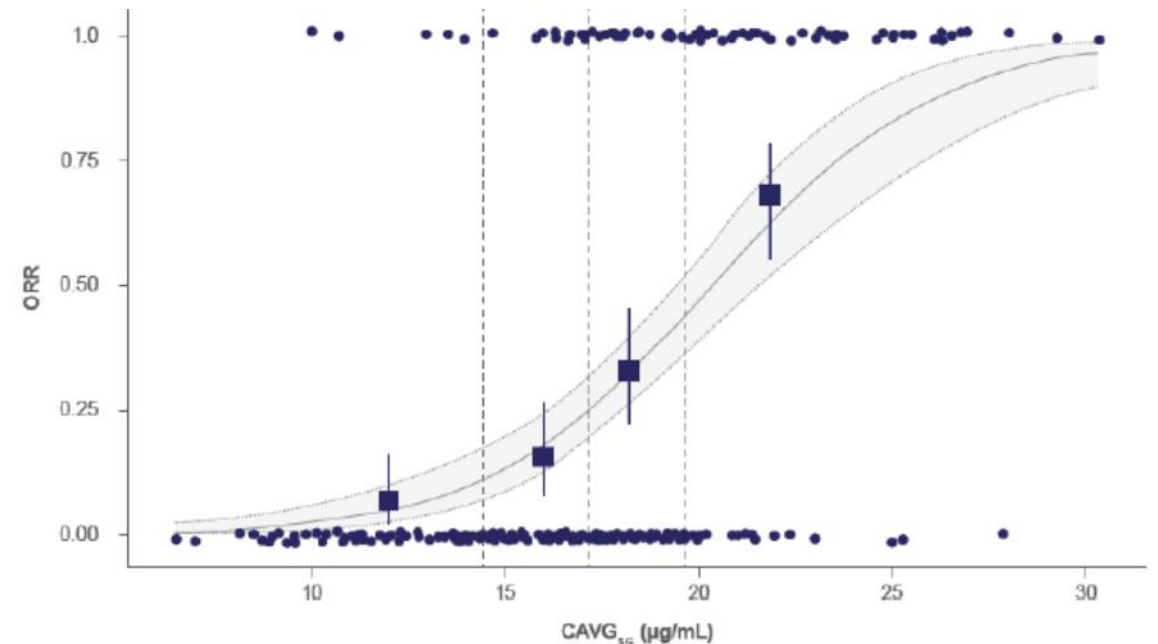
Very common and dangerous misinterpretation

Observed proportion and predicted probability of ORR vs CAVGSG and Grade ≥ 1 Neutropenia

Grade ≥ 1 Neutropenia vs CAVSG

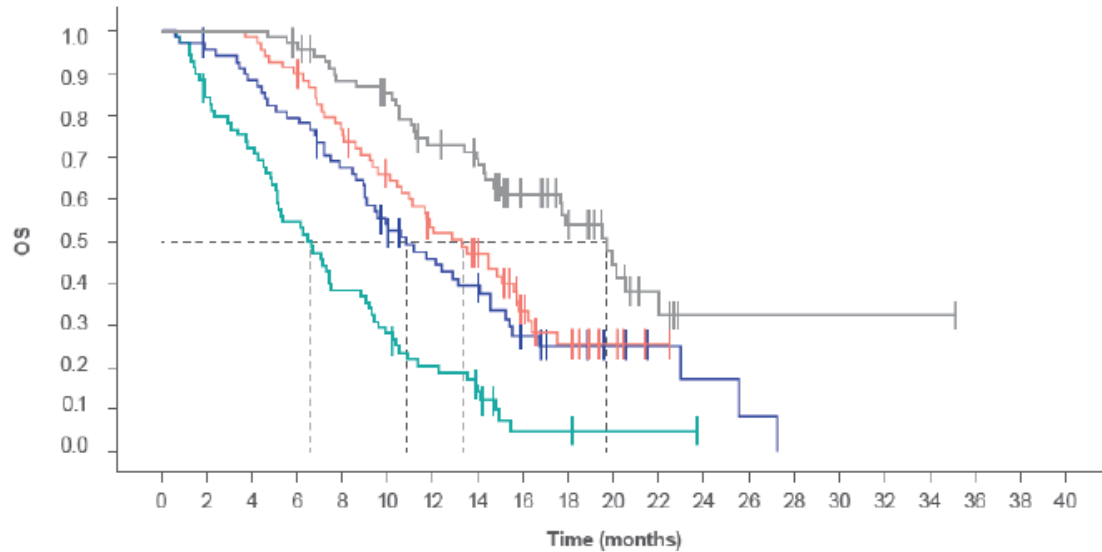


ORR vs CAVSG



Kaplan-Meier Curve of OS and PFS stratified by $CAVG_{tAB}$

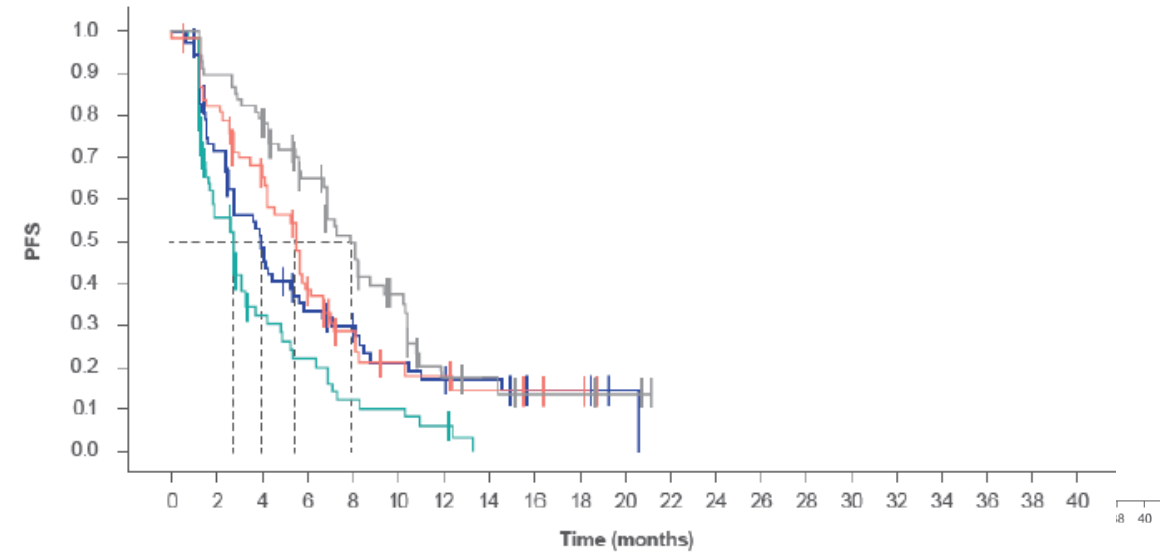
OS



Number at Risk

CAVG _{tAB}	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	
1st Quartile	69	58	49	37	26	19	13	8	2	2	1	1	0	0	0	0	0	0	0	0	0	0
2nd Quartile	69	65	60	54	45	35	28	24	13	9	6	3	2	1	0	0	0	0	0	0	0	0
3rd Quartile	69	69	68	62	52	42	33	27	14	9	4	1	0	0	0	0	0	0	0	0	0	0
4th Quartile	70	70	70	67	59	55	46	41	30	22	14	7	1	1	1	1	1	1	0	0	0	0

PFS



Number at Risk

CAVG _{tAB}	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	
1st Quartile	68	34	16	11	6	5	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2nd Quartile	69	47	33	19	15	10	8	7	3	3	1	0	0	0	0	0	0	0	0	0	0	0
3rd Quartile	69	54	42	21	12	7	6	4	3	2	0	0	0	0	0	0	0	0	0	0	0	0
4th Quartile	69	61	54	37	25	16	6	5	3	3	2	0	0	0	0	0	0	0	0	0	0	0

Dashed lines in C and D indicate median OS and PFS, respectively, for each quartile.
 $CAVG_{tAB}$, average concentration of Total Antibody; OS, overall survival; PFS, progression-free survival.

Optimal dose management: key messages

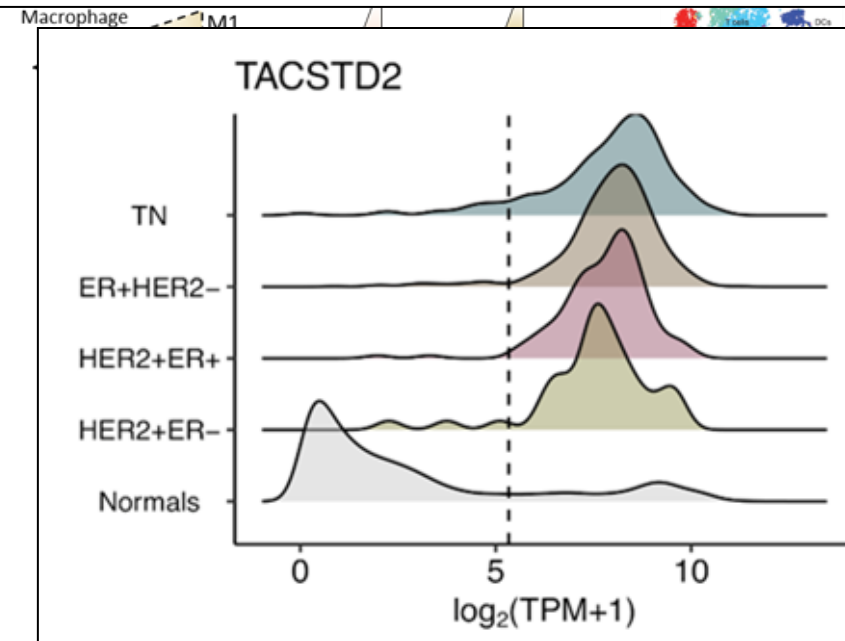
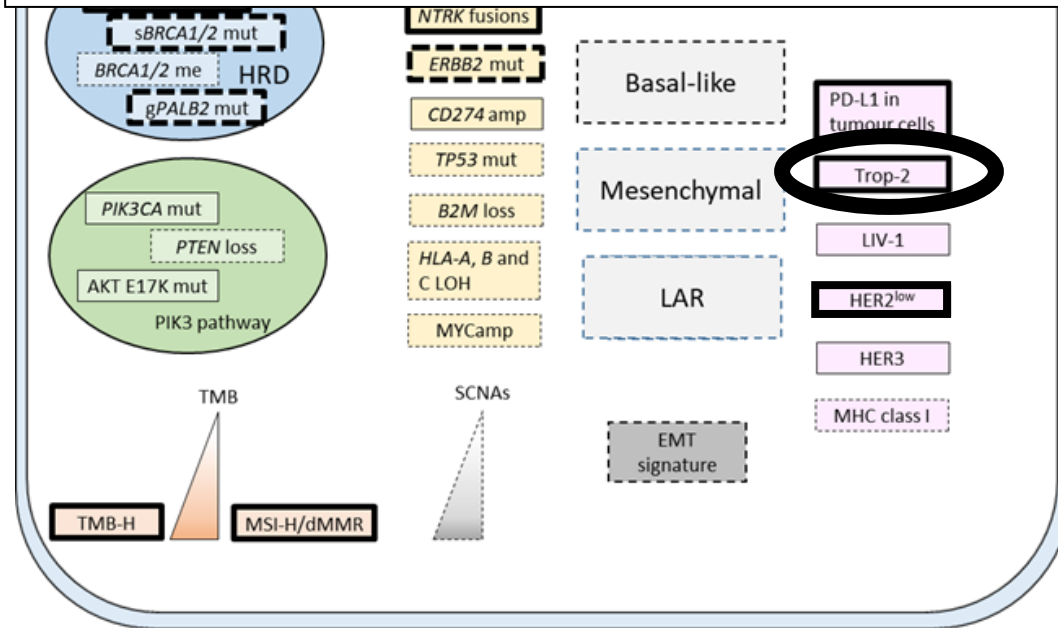
- **REDUCE the dose** in case of adverse events as indicated and needed. This will not impact efficacy
- **DO NOT REDUCE the dose** only because you are afraid of potential side effect. An arbitrarily administered lower dose is less effective

Trop-2 expression: is it relevant?

Cancer-cell intrinsic

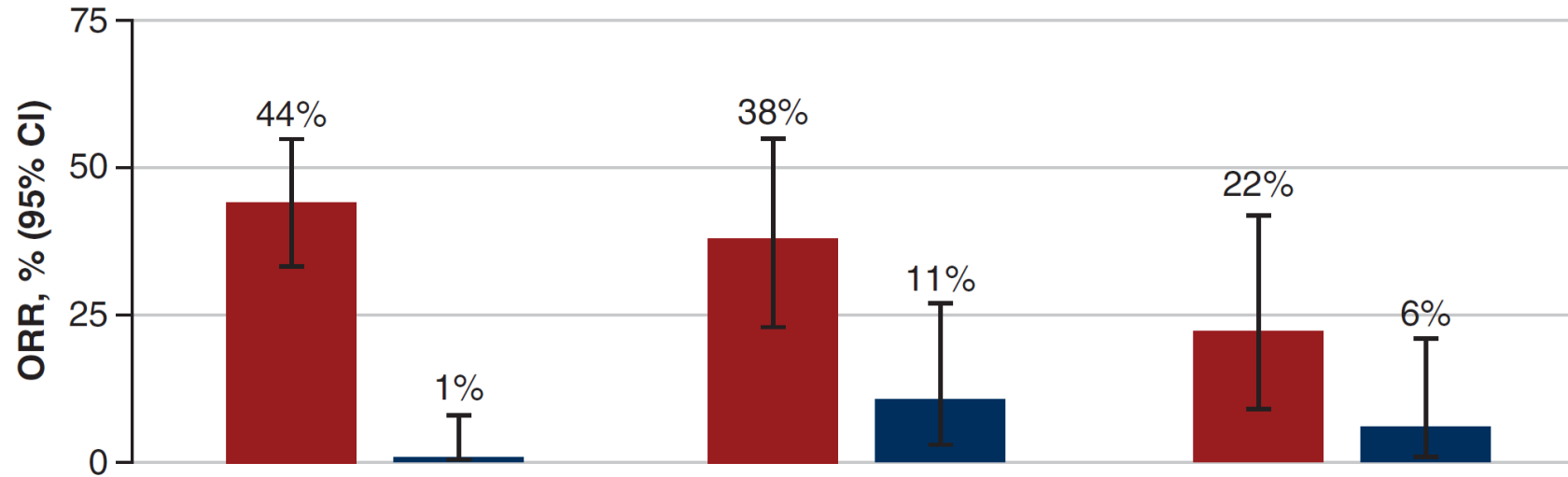
Cancer-cell extrinsic (TME)

Does level of Trop-2 expression matter?



Established relevant therapeutic targets
 Likely relevant therapeutic targets
 Possibly relevant therapeutic targets
 Therapeutic targets of uncertain significance

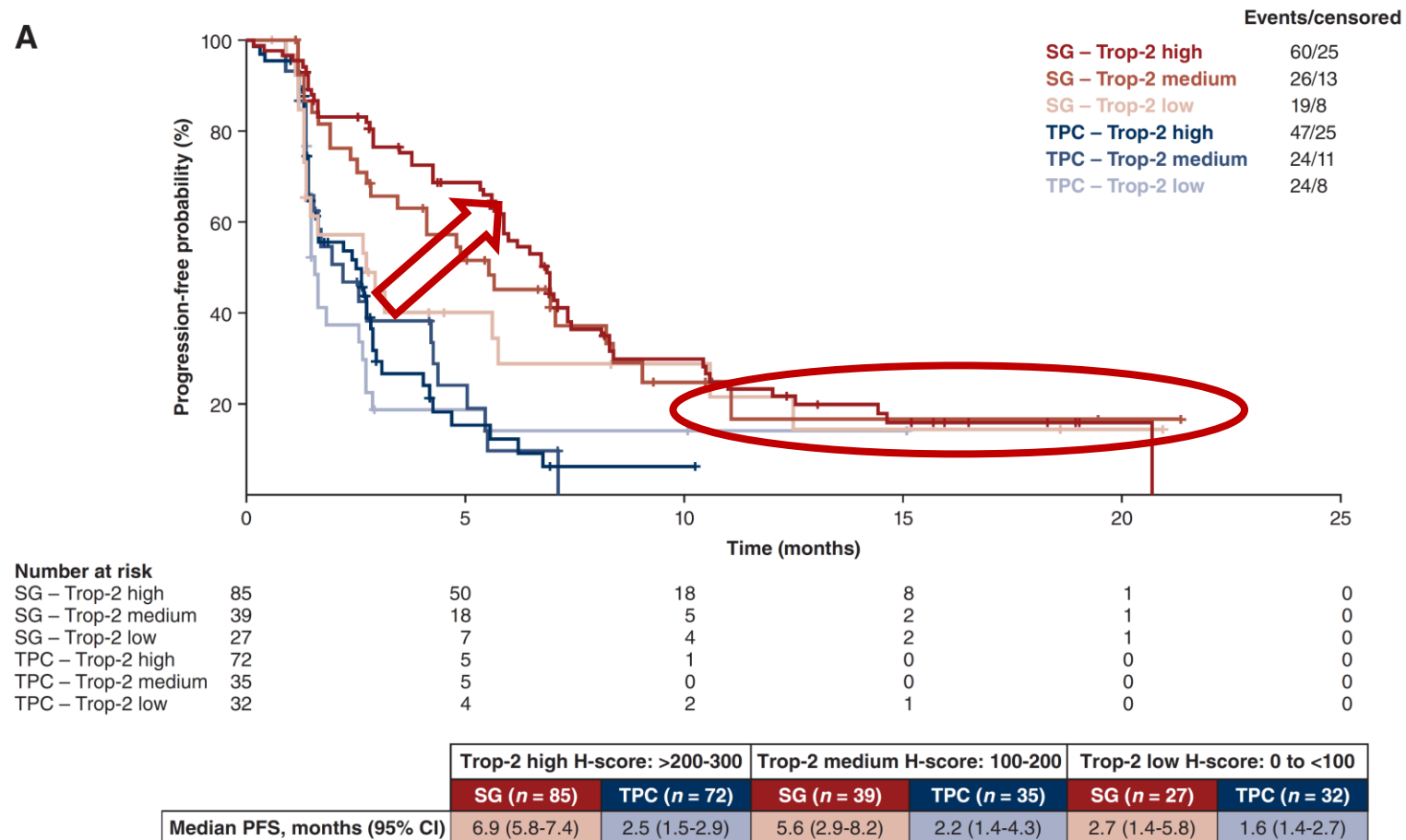
ORR by Trop-2 expression



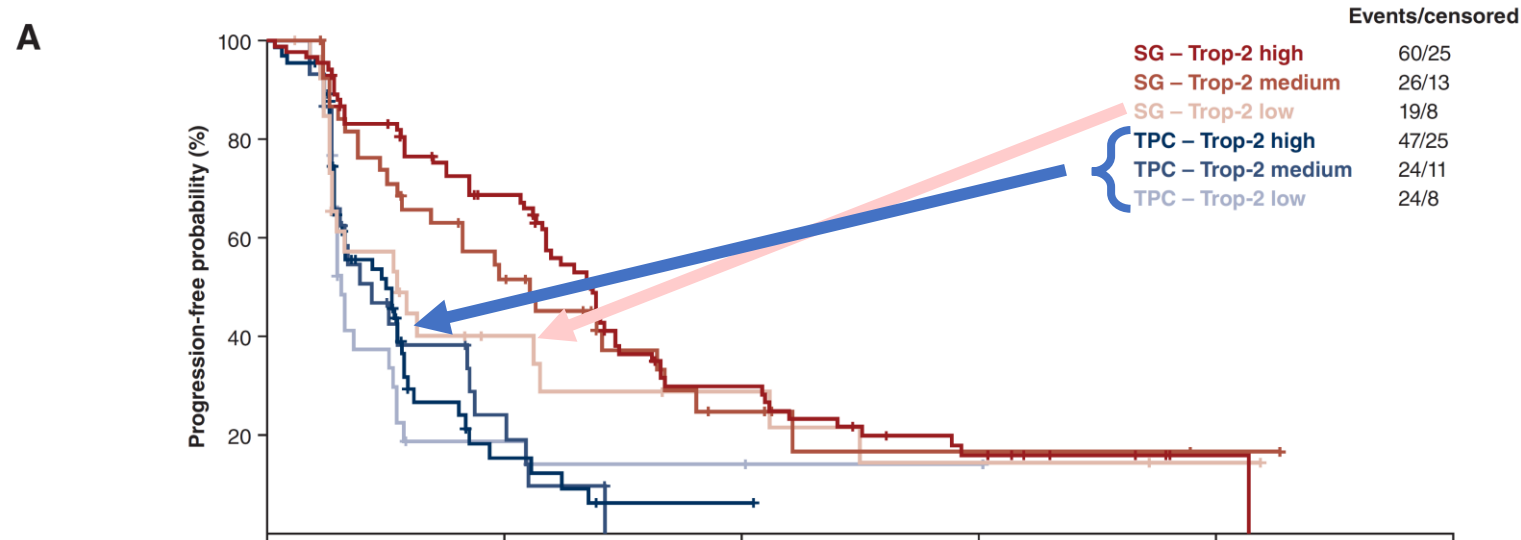
	Trop-2 high H-score: >200-300 (n = 157)		Trop-2 medium H-score: 100-200 (n = 74)		Trop-2 low H-score: 0 to <100 (n = 59)	
	SG (n = 85)	TPC (n = 72)	SG (n = 39)	TPC (n = 35)	SG (n = 27)	TPC (n = 32)
ORR, % (n)	44 (37)	1 (1)	38 (15)	11 (4)	22 (6)	6 (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

	SG (n = 235)	TPC (n = 233)
Trop-2 expression, n (%)	151 (64)	139 (60)
(High) H-score >200-300	85/151 (56)	72/139 (52)
(Medium) H-score 100-200	39/151 (26)	35/139 (25)
(Low) H-score 0 to <100 ^a	27/151 (18)	32/139 (23)

PFS by Trop-2 expression



PFS by Trop-2 expression



Target matter: Trop-2 expression might be associated with the magnitude of benefit, but it is not clinical useful to select patients potentially candidate to SG)

Median PFS, months (95% CI)	6.9 (5.8-7.4)	2.5 (1.5-2.9)	5.6 (2.9-8.2)	2.2 (1.4-4.3)	2.7 (1.4-5.8)	1.6 (1.4-2.7)

Sacituzumab Govitecan in RWD

Conclusions

- Benefit from Sacituzumab Govitecan in TNBC is transformative and unprecedented (more than 50% reduction of risk of death)
- SG represents a new gold standard and should be used as soon as possible according to regulatory approvals and reimbursement rules
- SG has a manageable safety profile, but optimal management is needed and dose reduction and dose administration should be appropriate as indicated by the clinical trials



Wave

The best is yet to come



Acknowledgements



UniSR

Università Vita-Salute
San Raffaele



I.R.C.C.S. Ospedale
San Raffaele



FONDAZIONE AIRC PER LA RICERCA SUL CANCRO

IRCCS Ospedale San Raffaele

Matteo Dugo

Barbara Galbardi

Luca Licata

Giulia Viale

Marta Piras

Lorenzo Sica

Alessia Rognone

Stefania Zambelli

Patrizia Zucchinelli

Alberta Locatelli

Lucia Viganò

Università Vita-Salute San Raffaele

Carlo Bosi

Giulia Notini

Matteo M. Naldini

Marco Mariani

Fondazione Michelangelo

Luca Gianni

Pinuccia Valagussa

Maurizio Callari

Marco Barreca

Cambridge University

H. Raza Ali

Ciccy Wang

Yale University

Lajos Pusztai

Istituto Europeo di Oncologia/UNIMI

Giuseppe Curigliano

Carmen Criscitiello

Semmelweis University

Balázs Győrffy (co-last author)

Áron Bartha (co-first author)



FONDAZIONE MICHELANGELO
avanzamento dello studio e cura dei tumori