ESMO DEEP DIVE:
BREAST CANCER

METASTATIC TRIPLE NEGATIVE BREAST CANCER

Peter Schmid, *Chair*

Barts Cancer Institute
London

ESMO WEBINAR SERIES

ESMO

PROGRAMME AND SPEAKERS

9 October 2024

5 min	**Welcome and introduction** Peter Schmid
15 min	**What to do with early relapsers? Current concepts and ongoing research** Rebecca Dent
15 min	**Where are we heading with ADCs? Ongoing research and future directions** Sara Tolaney
15 min	**Is there more to come from immunotherapy?** Giampaolo Bianchini
15 min	**QnA and Discussion** All speakers

Peter Schmid
Chair
Barts Cancer Institute
London

Rebecca Dent
Speaker
National Cancer Center
Singapore

Sara Tolaney
Speaker
Dana-Farber Cancer
Institute

Giampaolo Bianchini
Speaker
Vita-Salute San Raffaele
University, IRCCS San
Raffaele Hospital

LEARNING OBJECTIVES

- To acquire a deeper understanding of the clinical course of breast cancer.
- To understand biological hypotheses on classification and risk stratification, ongoing/required research in therapeutics and knowledge of use of omics technologies for biomarker-enabled precision medicine for breast cancer.
- To develop skills and abilities for critical analysis, interpretation of research data and therapeutic strategies.
- To become better equipped for informed, innovative thinking and engagement in ongoing or new research projects.

ESMO DEEP DIVE: BREAST CANCER

THANK YOU FOR YOUR ATTENTION

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ESMO DEEP DIVE:
BREAST CANCER

WHAT TO DO WITH EARLY RELAPSERS?

Current Concepts and Ongoing Research

Prof Rebecca Dent, MD, FRCP (Canada)

Senior Consultant, National Cancer Center Singapore

Duke-NUS Medical School

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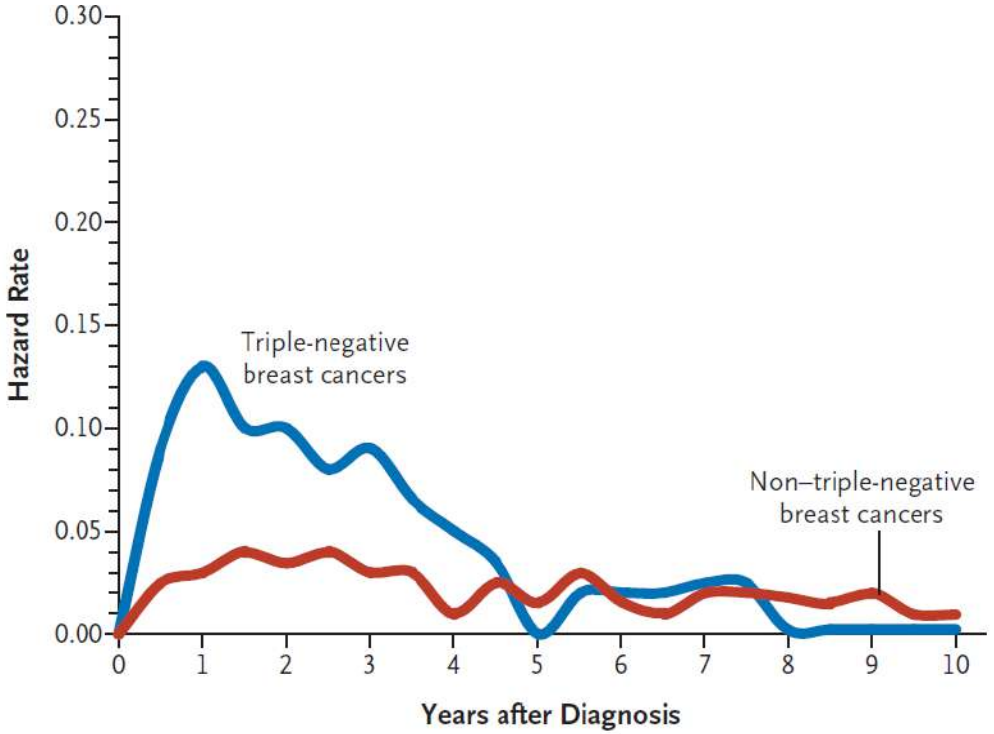
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Natural History

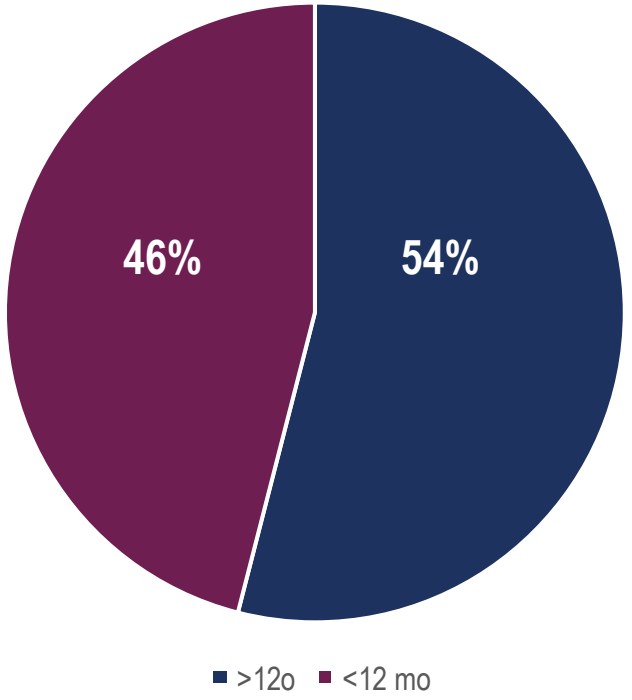
TNBC ASSOCIATED WITH EARLY RELAPSE

Time to Distant Recurrence



The mean time to distant recurrence is approximately 2.4 years for TNBC compared with 4.4 years for ER+ patients

Late vs Early Recurrence after Early Stage TNBC

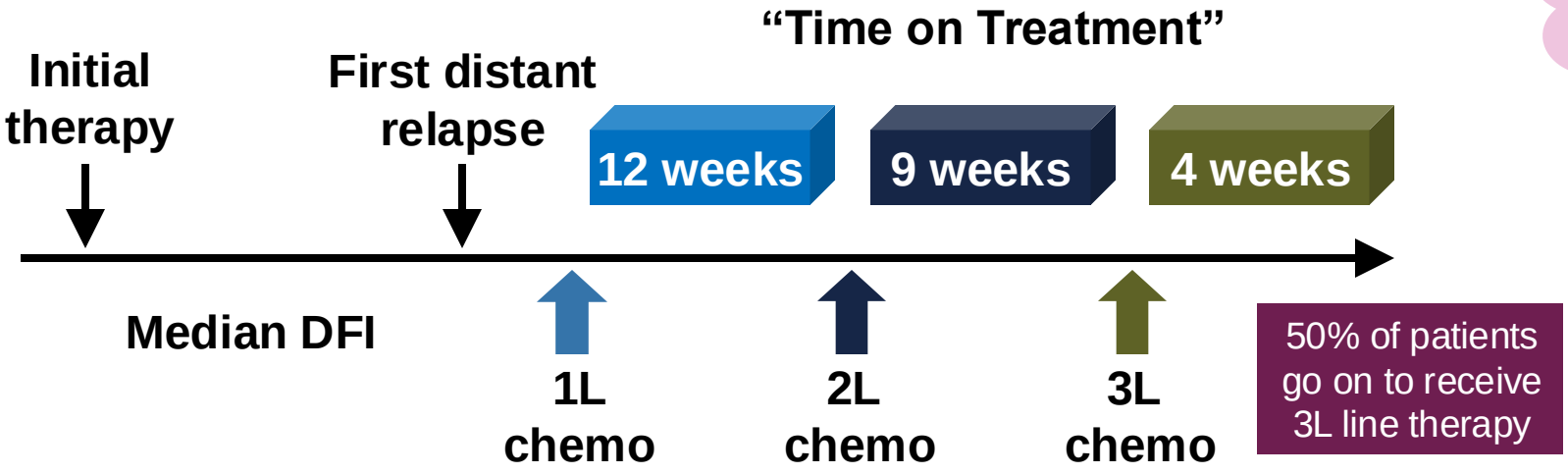


Grinda T et al, Eur J Cancer 2023

1. Dent R, et al. *Clin Cancer Res*. 2007;13:4429-4434; 2. Gaedcke J, et al. *Mod Pathol.* 2007;20(8):864-870; 3. Foulkes WD, et al. *N Engl J Med*. 2010;363(20):1938-1948; 4. Nofech-Mozes, et al. *Breast Cancer Res Treat.* 2009;118:131-137.

THE MAJOR PROBLEM OF TUMOUR RESISTANCE TO THERAPY

Critical to Bring in Palliative Care early

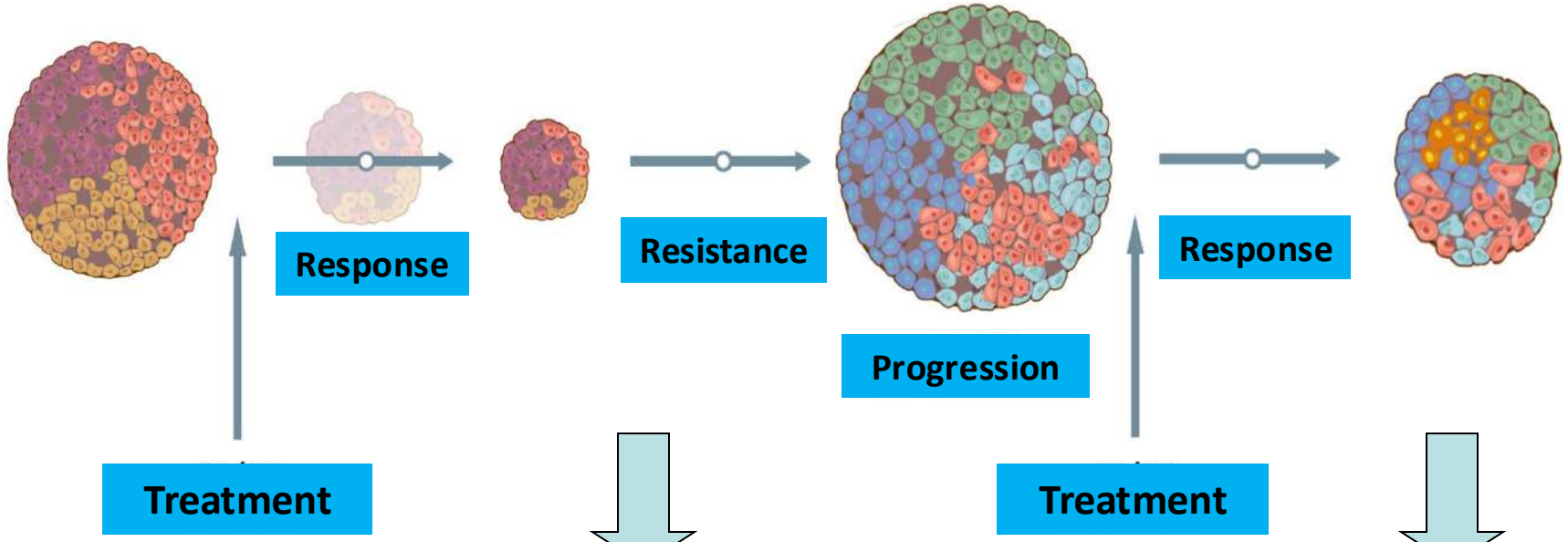


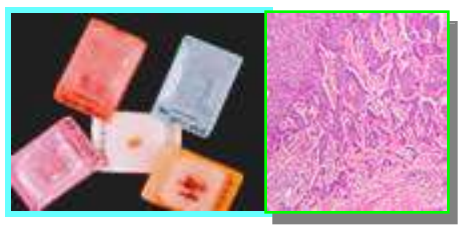
Patients with TN disease receive fewer treatments and stay on each treatment regimen for a shorter interval

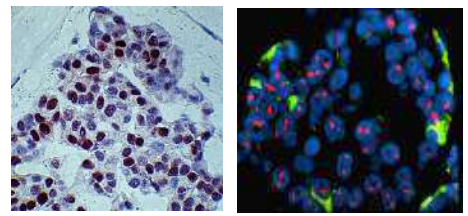
Kassam F …Dent R et al. Clin Breast Cancer 2009

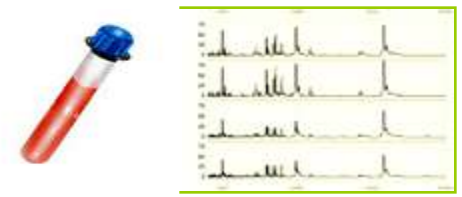
Simple then complex biology

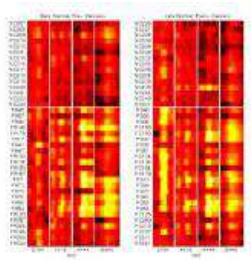
The Major Problem Of TUMOR RESISTANCE TO THERAPY

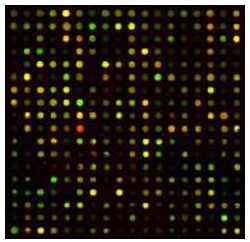


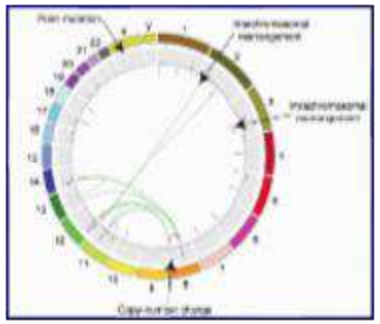






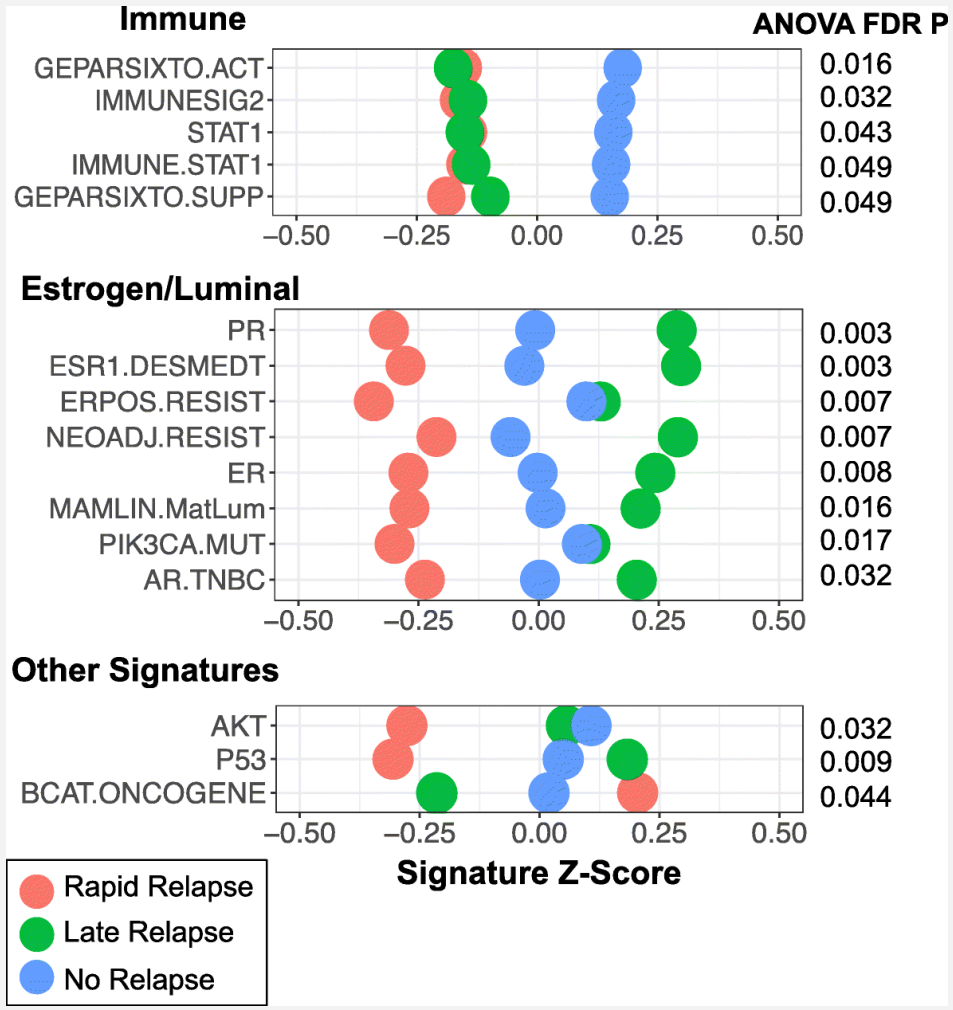




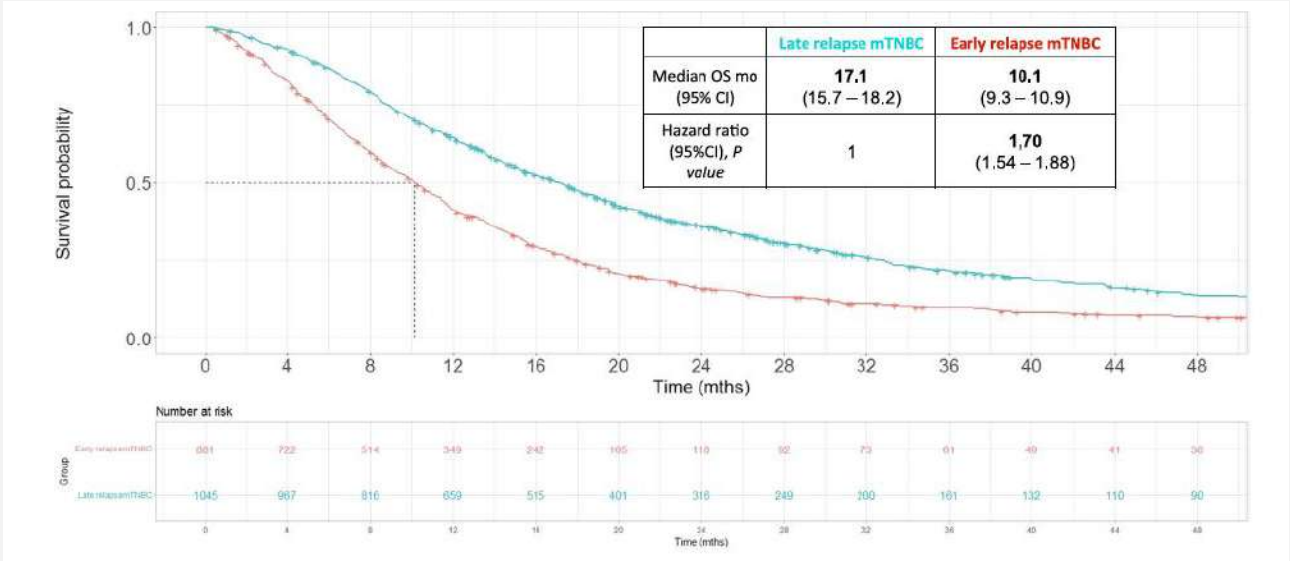


J. Ribeiro & F. Cardoso

EARLY RELAPSE AFTER TNBC: BIOLOGICALLY DISTINCT AND ASSOCIATED WITH WORSE OUTCOMES



Poor Overall Survival for Early Relapsers



Grinda T et al, Eur J Cancer 2023

PFS ~3 mo
OS ~10 mo

Trial exclusion

- Early relapsing TNBC is a biologically and clinically distinct entity[3]:
  - Aggressive, intrinsically resistant to standard therapies[4]
  - More common in younger patients with large primary tumours without *BRCA* alterations[1,2]
- Most trials exclude these patients, posing a real challenge in clinical practice

[1]Grinda T, et al. Eur J Cancer 2023; [2]Kim H, et al. Cancers (Basel) 2021;
[3]Zhang Y, et al. BMC Cancer 2021; [4]Karaayvaz M, et al. Nat Commun 2018

EARLY RELAPSERS OFTEN EXCLUDED FROM FIRST LINE TNBC TRIALS

	IMP130	KN355	ASCENT-03	ASCENT-04	CAPITELLO-290	TROPION-Breast02	TROPION-Breast05
DFI	≥12m	≥6m (21% of randomized pts had DFI 6-12m)	DFI ≥6m	DFI ≥6m	DFI ≥6m (no cap)	Cap for DFI ≤12m 20% of randomized pts	DFI ≥6m Cap for DFI 6-12m 20% of randomized pts
COMMENTS	Did *not* allow any DFI < 12m	Did *not* allow DFI ≤6m	Does *not* allow DFI ≤6m; no known cap on DFI 6-12m	Does *not* allow DFI ≤6m; no known cap on DFI 6-12m	Does *not* allow DFI ≤6m	Allows any DFI *(within cap)*	Does *not* allow DFI ≤6m

*DFI -time between completion of treatment with curative intent (either date of primary breast tumour surgery or date of last dose of systemic anticancer therapy (not including endocrine therapy), whichever occurred last) and the first documented local or distant disease recurrence (either by biopsy or imaging).

Slide courtesy of Sara M. Tolaney, MD, MPH

IMpassion132 – first trial specifically for early relapsing TNBC

- Double-blind placebo-controlled randomised phase 3 trial

- **Unresectable locally advanced/ metastatic TNBC**
- **Prior anthracycline and taxane for early TNBC**
- **Disease progression <12 months after last treatment with curative intent for early TNBC** [a]
- **No prior chemotherapy for advanced TNBC**
- **Known PD-L1 status (SP142)**

R 1:1

Carboplatin/gemcitabine or capecitabine[b] + atezolizumab 1200 mg q3w

Carboplatin/gemcitabine or capecitabine[b] + placebo q3w

Treatment continued until disease progression or unacceptable toxicity

Primary endpoint:

- OS (hierarchical testing: PD-L1+ TNBC[c] then, if positive, modified ITT population[d])

Dent R et al. Annals of Oncology 2024

Baseline Characteristics

Population with PD-L1+ TNBC

Characteristic	Placebo + CT (n=177)	Atezolizumab + CT (n=177)
Median (range) age, years	48 (25–83)	48 (23–77)
ECOG performance status 0, n (%)	101 (57)	110 (62)
Prior platinum, n (%)	32 (18)	31 (18)
Prior capecitabine, n (%)	47 (27)	52 (29)
DFI <6 months, n (%)	123 (69)	117 (66)
Lung and/or liver metastases, n (%)	110 (62)	106 (60)
Chosen CT: carboplatin/gemcitabine, n (%)	130 (73)	130 (73)
Chosen CT: capecitabine, n (%)	47 (27)	47 (27)

DFI = disease-free interval; ECOG = Eastern Cooperative Oncology Group

Dent R et al. Annals of Oncology 2024

CAN IMMUNOTHERAPY WORK IN PATIENTS WITH TNBC WHO EXPERIENCE EARLY RELAPSE?

IMPASSION132

- Unresectable locally advanced/ metastatic TNBC
- Prior anthracycline and taxane for early TNBC
- Disease progression <12 months after last treatment with curative intent for early TNBC [a]
- No prior chemotherapy for advanced TNBC
- Known PD-L1 status (SP142)

R 1:1

Carboplatin/gemcitabine or capecitabine[b] + atezolizumab 1200 mg q3w

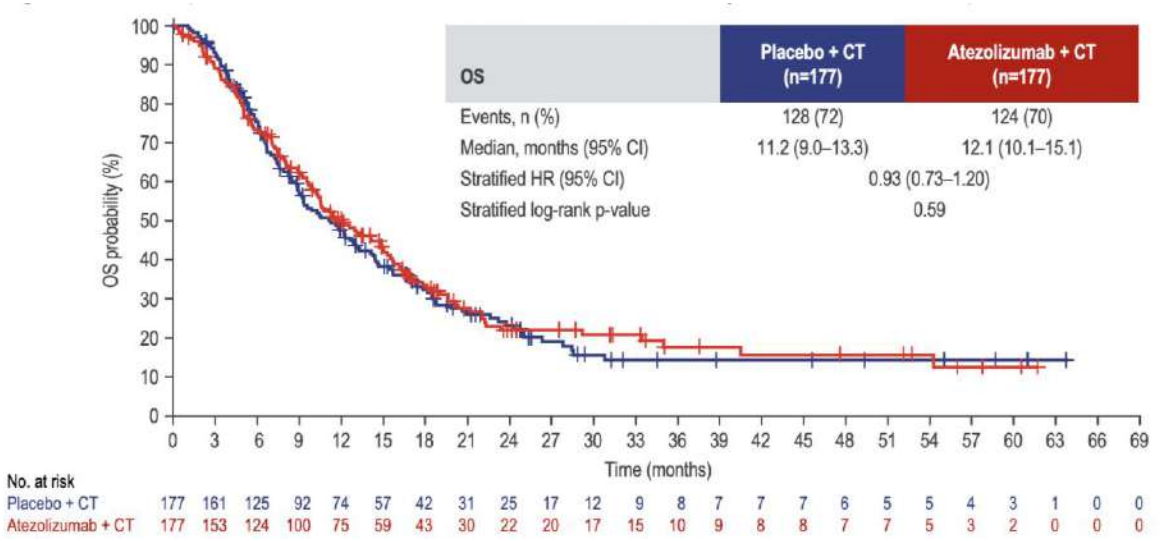
Carboplatin/gemcitabine or capecitabine[b] + placebo q3w

Treatment continued until disease progression or unacceptable toxicity

Stratification factors:
- Visceral (lung and/or liver) metastases
- CT backbone
- PD-L1 status (during all-comer enrolment)

Primary endpoint:
- OS (hierarchical testing: PD-L1+ TNBC[c] then, if positive, modified ITT population[d])

No improvement in OS in PD-L1+ TNBC



OS	Placebo + CT (n=177)	Atezolizumab + CT (n=177)
Events, n (%)	128 (72)	124 (70)
Median, months (95% CI)	11.2 (9.0–13.3)	12.1 (10.1–15.1)
Stratified HR (95% CI)	0.93 (0.73–1.20)	
Stratified log-rank p-value	0.59	

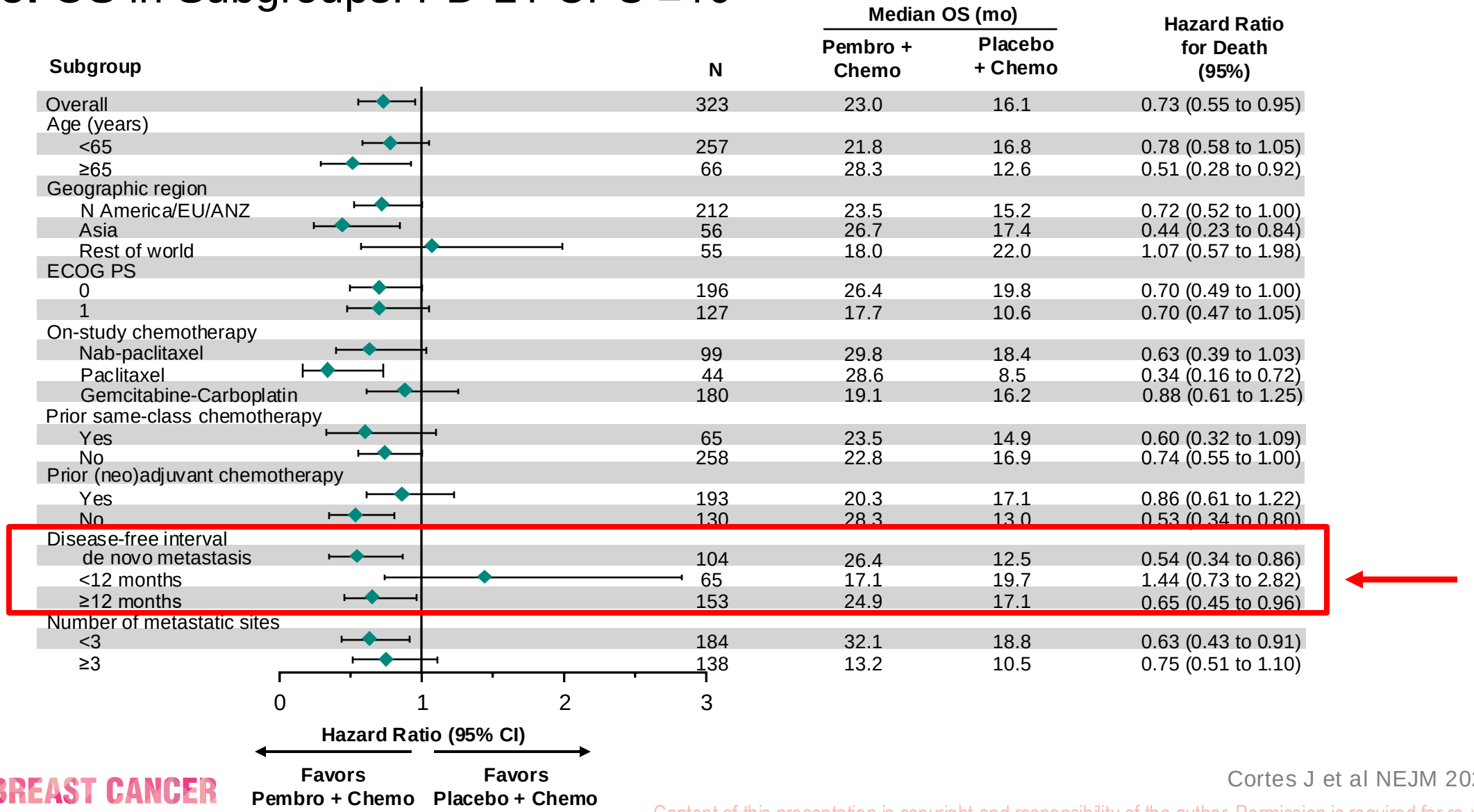
- 68% DFI<6mo
- 73% recv'd carbo/gem

Poor Outcomes:
PFS ~4 mo | OS ~12 mo

Dent R et al. Annals of Oncology 2024

NO BENEFIT TO PEMBROLIZUMAB SEEN IN KN355 FOR PTS WITH DFI <6-12 MO

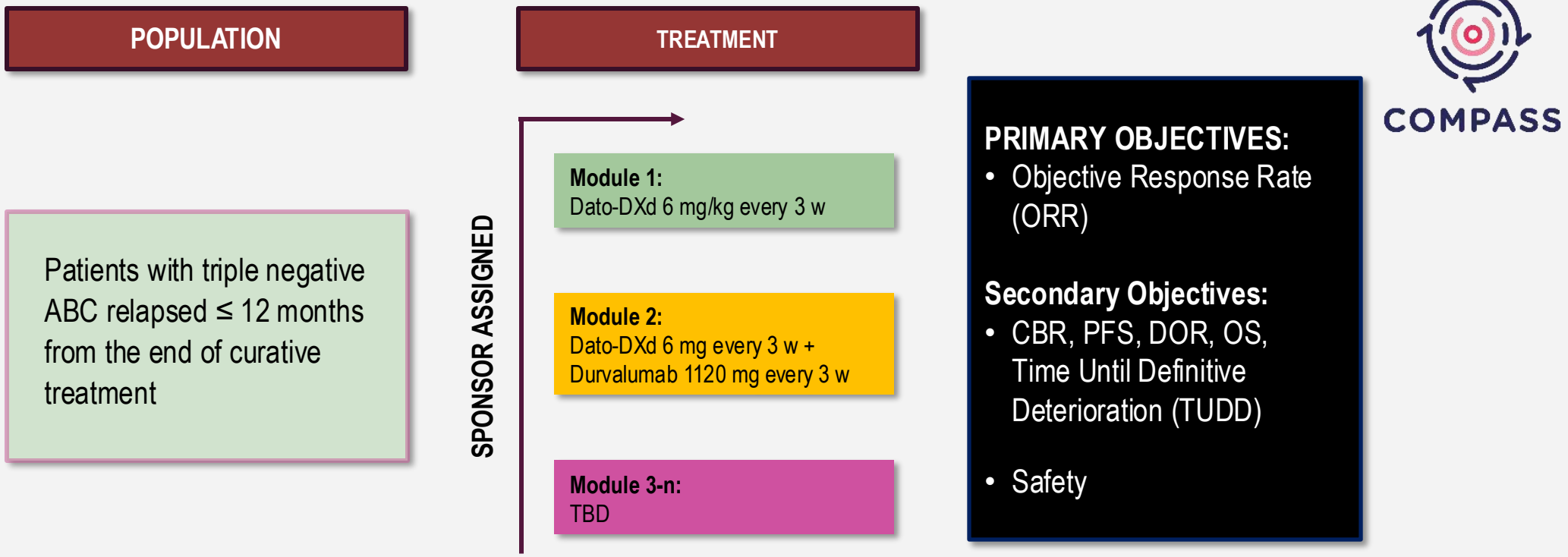
KN355: OS in Subgroups: PD-L1 CPS ≥10



Subgroup	N	Median OS (mo) Pembro + Chemo	Median OS (mo) Placebo + Chemo	Hazard Ratio for Death (95%)
Overall	323	23.0	16.1	0.73 (0.55 to 0.95)
Age (years)				
<65	257	21.8	16.8	0.78 (0.58 to 1.05)
≥65	66	28.3	12.6	0.51 (0.28 to 0.92)
Geographic region				
N America/EU/ANZ	212	23.5	15.2	0.72 (0.52 to 1.00)
Asia	56	26.7	17.4	0.44 (0.23 to 0.84)
Rest of world	55	18.0	22.0	1.07 (0.57 to 1.98)
ECOG PS				
0	196	26.4	19.8	0.70 (0.49 to 1.00)
1	127	17.7	10.6	0.70 (0.47 to 1.05)
On-study chemotherapy				
Nab-paclitaxel	99	29.8	18.4	0.63 (0.39 to 1.03)
Paclitaxel	44	28.6	8.5	0.34 (0.16 to 0.72)
Gemcitabine-Carboplatin	180	19.1	16.2	0.88 (0.61 to 1.25)
Prior same-class chemotherapy				
Yes	65	23.5	14.9	0.60 (0.32 to 1.09)
No	258	22.8	16.9	0.74 (0.55 to 1.00)
Prior (neo)adjuvant chemotherapy				
Yes	193	20.3	17.1	0.86 (0.61 to 1.22)
No	130	28.3	13.0	0.53 (0.34 to 0.80)
Disease-free interval				
de novo metastasis	104	26.4	12.5	0.54 (0.34 to 0.86)
<12 months	65	17.1	19.7	1.44 (0.73 to 2.82)
≥12 months	153	24.9	17.1	0.65 (0.45 to 0.96)
Number of metastatic sites				
<3	184	32.1	18.8	0.63 (0.43 to 0.91)
≥3	138	13.2	10.5	0.75 (0.51 to 1.10)

Cortes J et al NEJM 2022

COMPASS: PLATFORM TRIAL FOR TNBC WITH EARLY RELAPSE

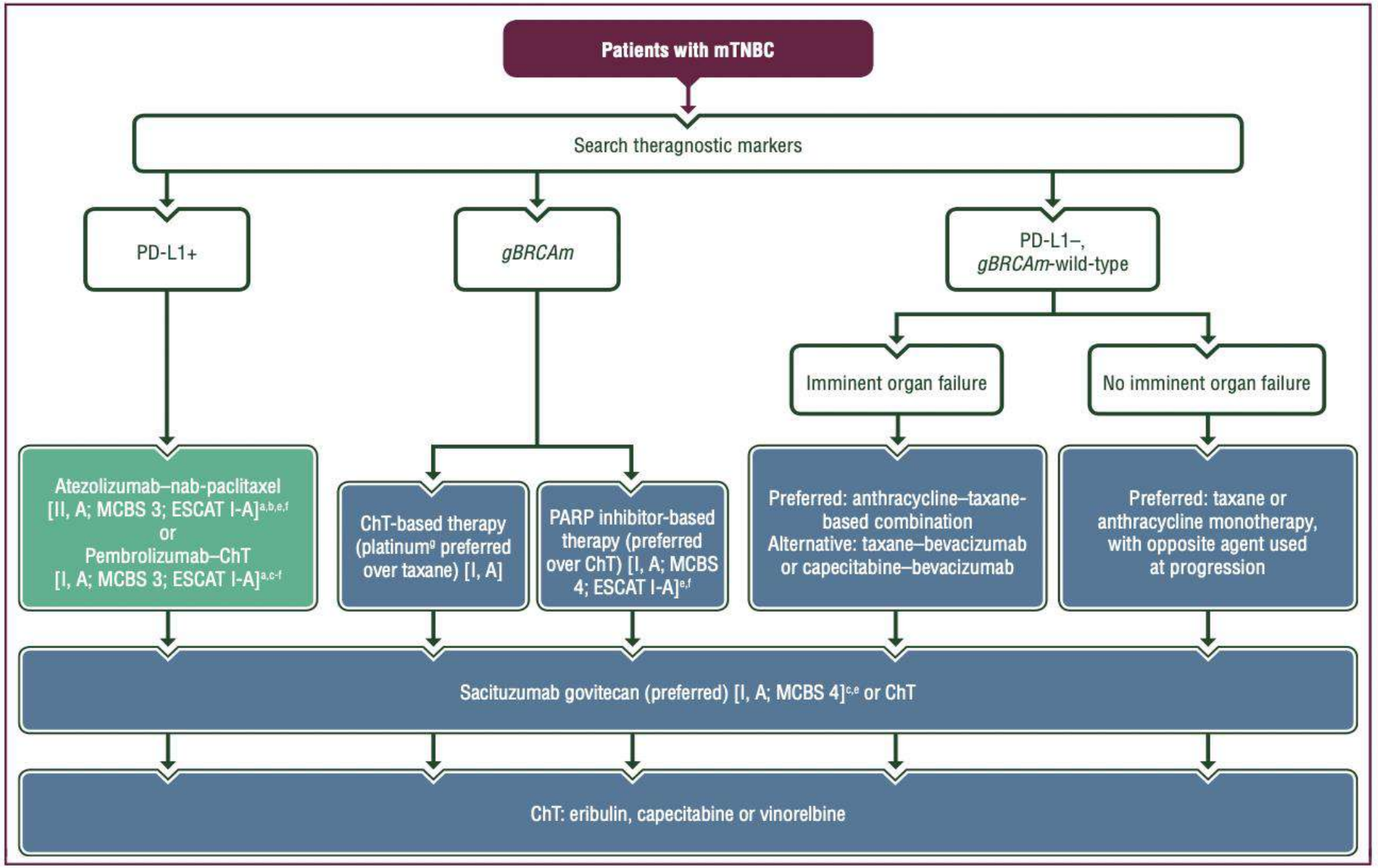


A phase Ib/II, open-label, modular, dose-finding and dose-expansion study to explore safety, tolerability, pharmacokinetics, and anti-tumor activity of novel therapeutics in patients with early relapsed metastatic triple-negative breast cancer

ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer☆

A. Gennari[1], F. André[2], C. H. Barrios[3], J. Cortés[4,5,6,7], E. de Azambuja[8], A. DeMichele[9], R. Dent[10], D. Fenlon[11], J. Gligorov[12], S. A. Hurvitz[13,14], S.-A. Im[15], D. Krug[16], W. G. Kunz[17], S. Loi[18], F. Penault-Llorca[19], J. Ricke[2,17], M. Robson[20], H. S. Rugo[21], C. Saura[22], P. Schmid[23], C. F. Singer[24], T. Spanic[25], S. M. Tolaney[26], N. C. Turner[27], G. Curigliano[28], S. Loibl[29], S. Paluch-Shimon[30] & N. Harbeck[31], on behalf of the ESMO Guidelines Committee*

Does not include relapses < 12 mo



Annals of Oncology 2021

KEY POINTS IN METASTATIC TNBC

- Not all Metastatic TNBC created equal
  - ✓ Histology (ie. metaplastic TNBC)
  - ✓ ”De Novo” vs. ”Early Relapsing” vs. “Heavily-Pretreated”

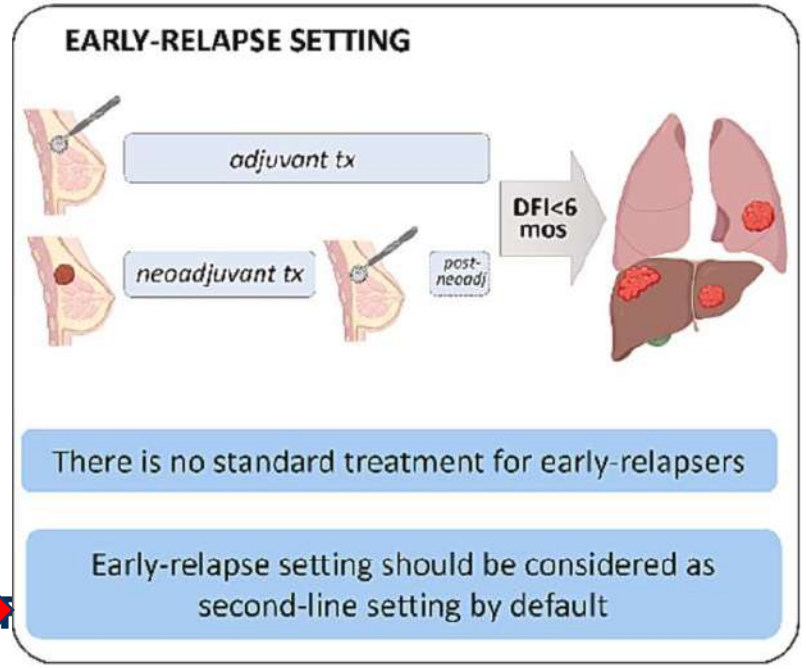
- Current era “early relapsing” patients are effectively also “heavily pre-treated” as have received multi combination agent anthracycline/taxane/platinum-based chemotherapy with checkpoint inhibition, and sometimes post-operative capecitabine (or olaparib) + checkpoint inhibition

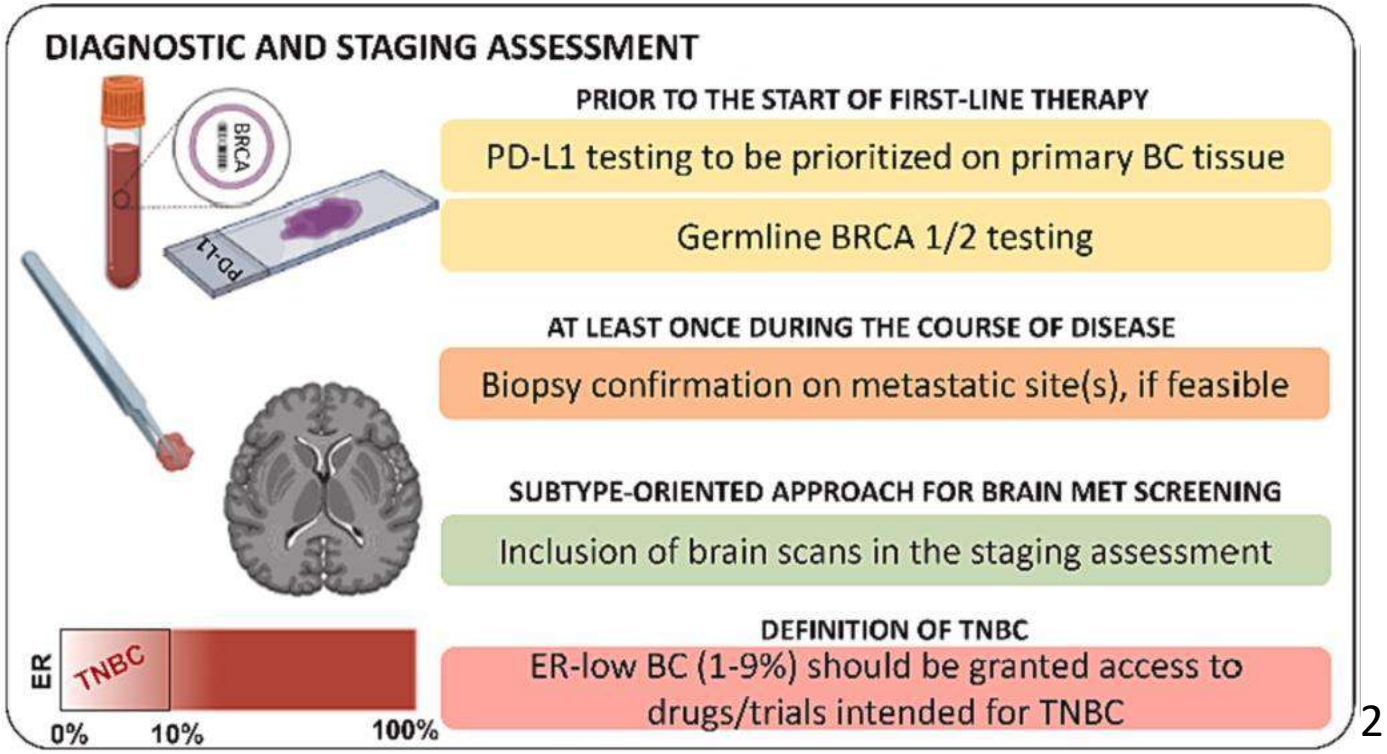
TREATING TNBC ON MONDAY MORNING

Optimizing choices and sequences in the diagnostic-therapeutic landscape of advanced triple-negative breast cancer: An Italian consensus paper and critical review

F. Miglietta [a,b], A. Fabi [c], D. Generali [d,e], M.V. Dieci [a,b], G. Arpino [f], G. Bianchini [g,h], S. Cinieri [i], P. F. Conte [j], G. Curigliano [k,l], M. De Laurentis [m], L. Del Mastro [n,o], S. De Placido [f], A. Gennari [p], F. Puglisi [q,r], A. Zambelli [s,t], F. Perrone [u], V. Guarneri [a,b,*]

Cancer Treatment Reviews 2023



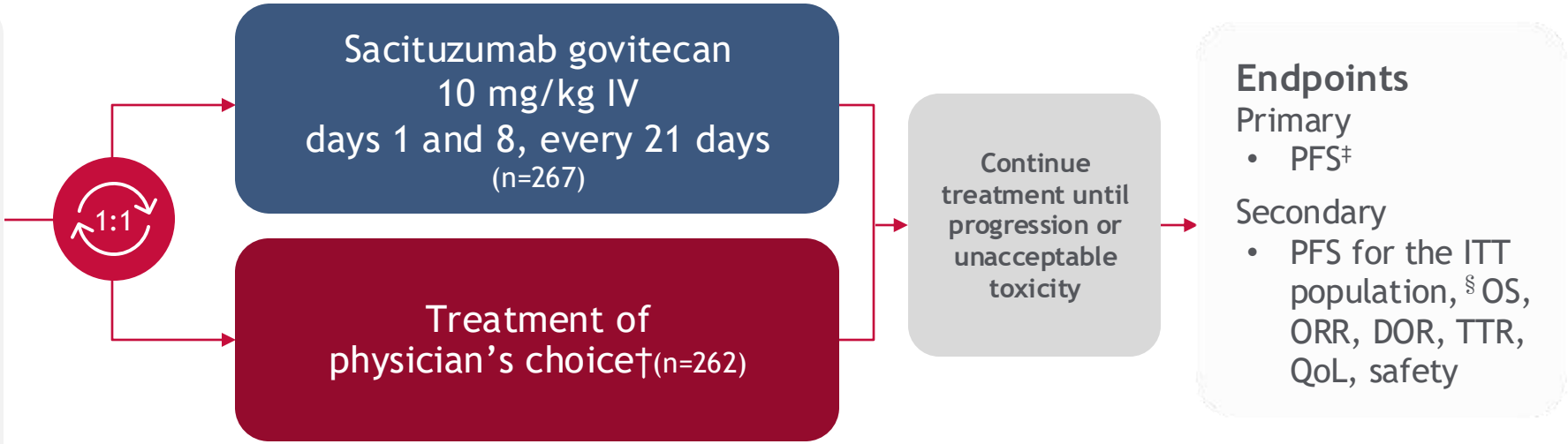


ASCENT: A phase 3 confirmatory study of sacituzumab govitecan in 2L and later mTNBC[1-3*]

Metastatic TNBC

- ≥2 chemotherapies - one of which could be in neo/adjuvant setting provided progression occurred within a 12-months period
- Patients with stable brain metastasis were allowed

(N=529)



Stratification factors

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

NCT02574455

*ASCENT was an international, Phase 3, multicentre, open-label, randomised trial of patients with unresectable locally advanced or metastatic TNBC (N=529). †Treatment of physician's choice: eribulin, vinorelbine, gemcitabine, or capecitabine; ‡PFS measured by an independent centralised and blinded group of radiology experts who assessed tumour response using RECIST 1.1 criteria in patients without brain metastasis; §The full population or intention-to-treat population includes all randomised patients (with and without brain metastases).

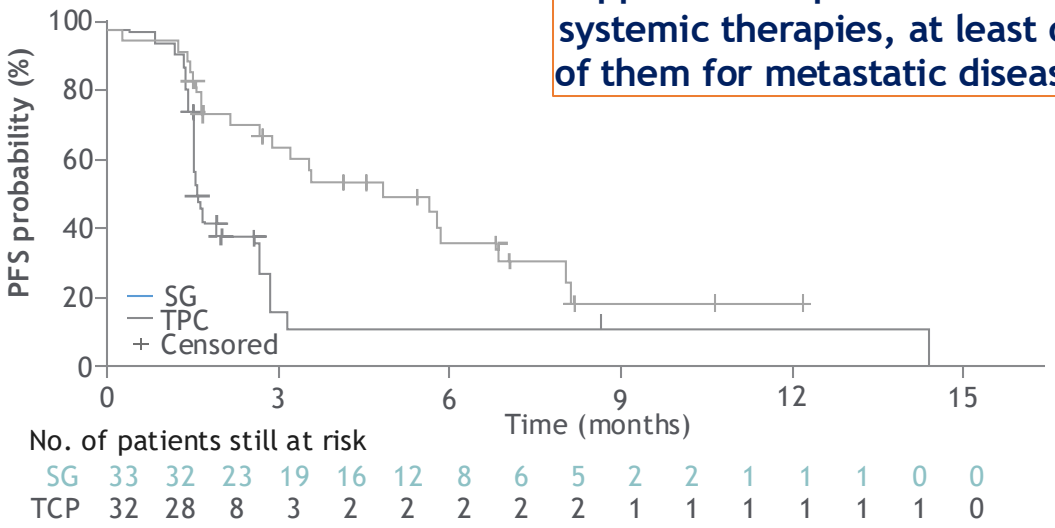
DOR, duration of response; IV, intravenous; ITT, intention-to-treat; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumours; TNBC, triple-negative breast cancer; TTR, time to response; QoL, quality of life.

1. Bardia A, et al. *N Engl J Med.* 2021;384(16):1529-1541; 2. Bardia A, et al. ESMO 2020. Abstract LBA17; 3. ClinicalTrials.gov website. Available at: https://clinicaltrials.gov/ct2/show/NCT02574455. Accessed March 2022.

ASCENT: In patients with 2L mTNBC, PFS and OS improvement was consistent with the overall study population

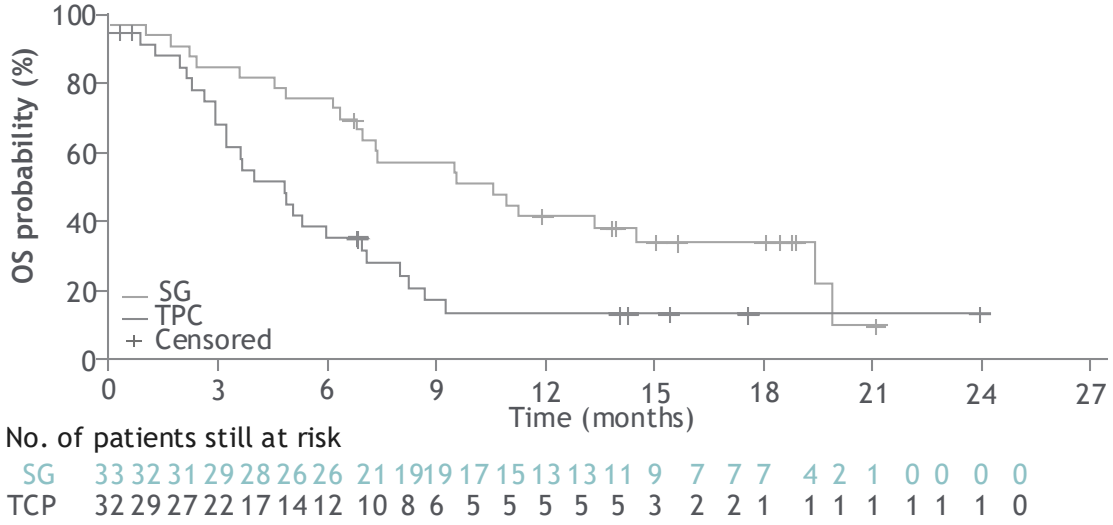
Progression-free survival

Approved for patients with ≥2 systemic therapies, at least one of them for metastatic disease*,†



BICR Analysis	SG (n=33)	TPC (n=32)
No. of events	21	23
Median PFS – mo (95%) CI	5.7 (2.6–8.1)	1.5 (1.4–2.6)
HR (95% CI)	0.41 (0.22–0.76)	

Overall survival

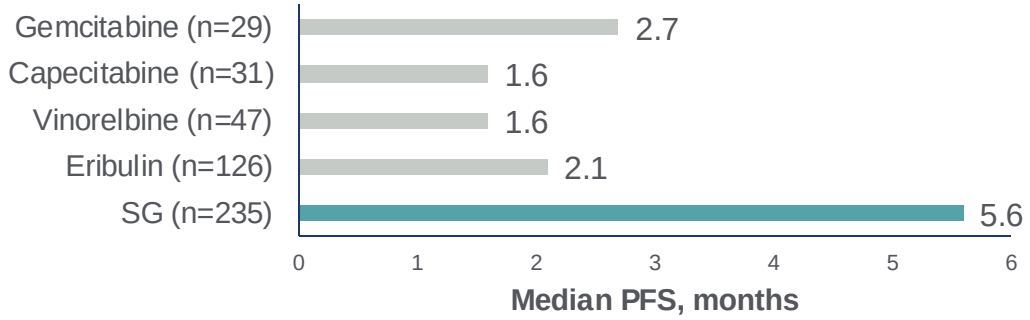


BICR Analysis	SG (n=33)	TPC (n=32)
No. of events	22	24
Median OS—mo. (95% CI)	10.9 (6.9–19.5)	4.9 (3.1–7.1)
HR (95% CI)	**0.51** (0.28–0.91)	

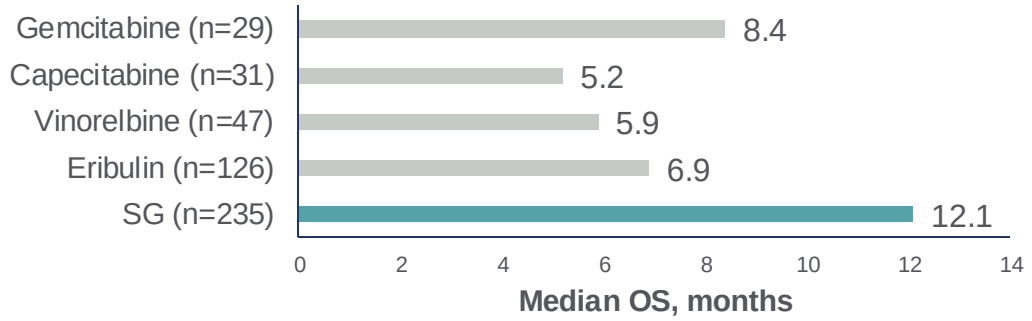
Carey LA, et al. NPJ Breast Cancer. 2022;8(1):72.

ASCENT: Assessment of SG vs TPC, by Agent

PFS in ASCENT



OS in ASCENT



	Sacituzumab Govitecan (n=235)	TPC (n=233)			
		Eribulin (n=126)	Vinorelbine (n=47)	Gemcitabine (n=29)	Capecitabine (n=31)
ORR	35%	5%	4%	3%	6%

The efficacy benefit observed with SG was retained when evaluating each TPC chemotherapy agent individually

CBR, clinical benefit rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

O'Shaughnessy J, et al. ASCO 2021 (Poster 1077)

Trastuzumab Deruxtecan vs Chemotherapy in Previously Treated HER2-low BC

Clinical Trial Design (Phase III- Destiny-Breast04)

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

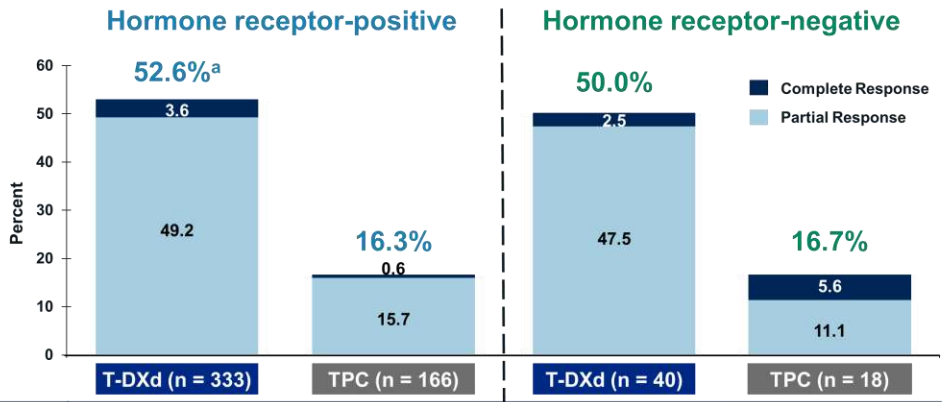
HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

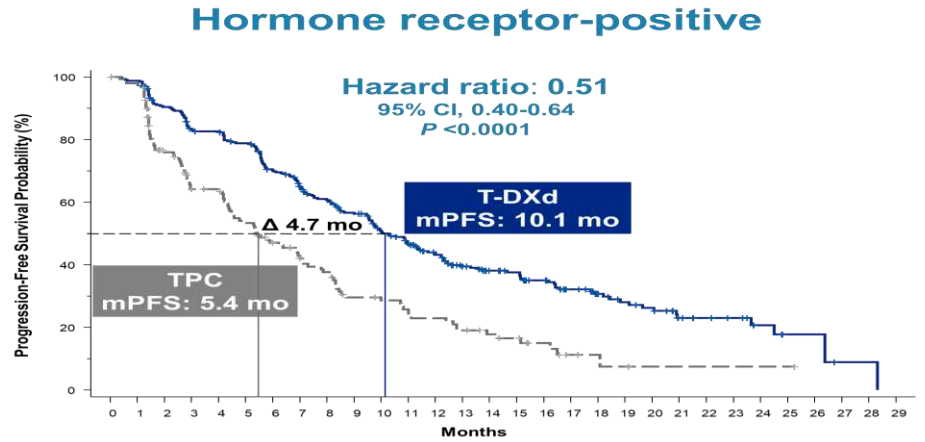
Key secondary endpoints[d]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

ORR

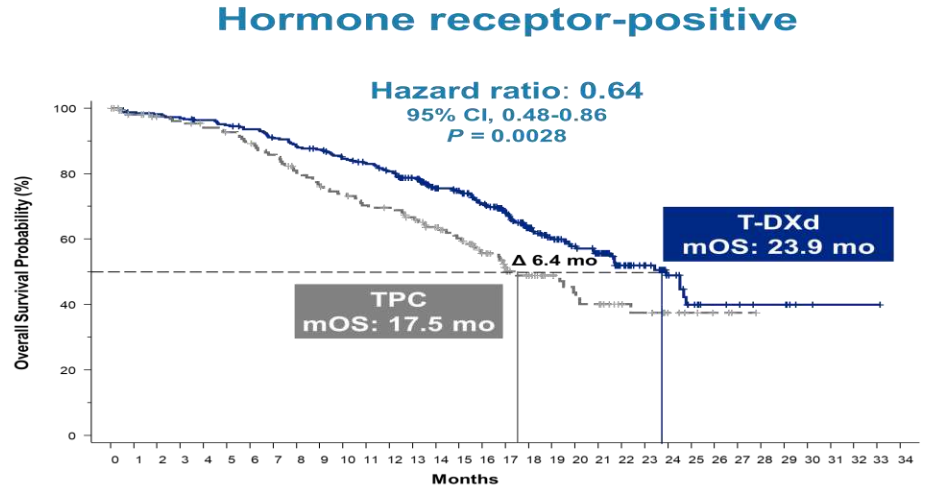


	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive Disease, %	7.8	21.1	12.5	33.3
Not Evaluable, %	4.2	12.7	7.5	5.6
Clinical Benefit Rate[b], %	71.2	34.3	62.5	27.8
Duration of Response, months	10.7	6.8	8.6	4.9

PFS



OS

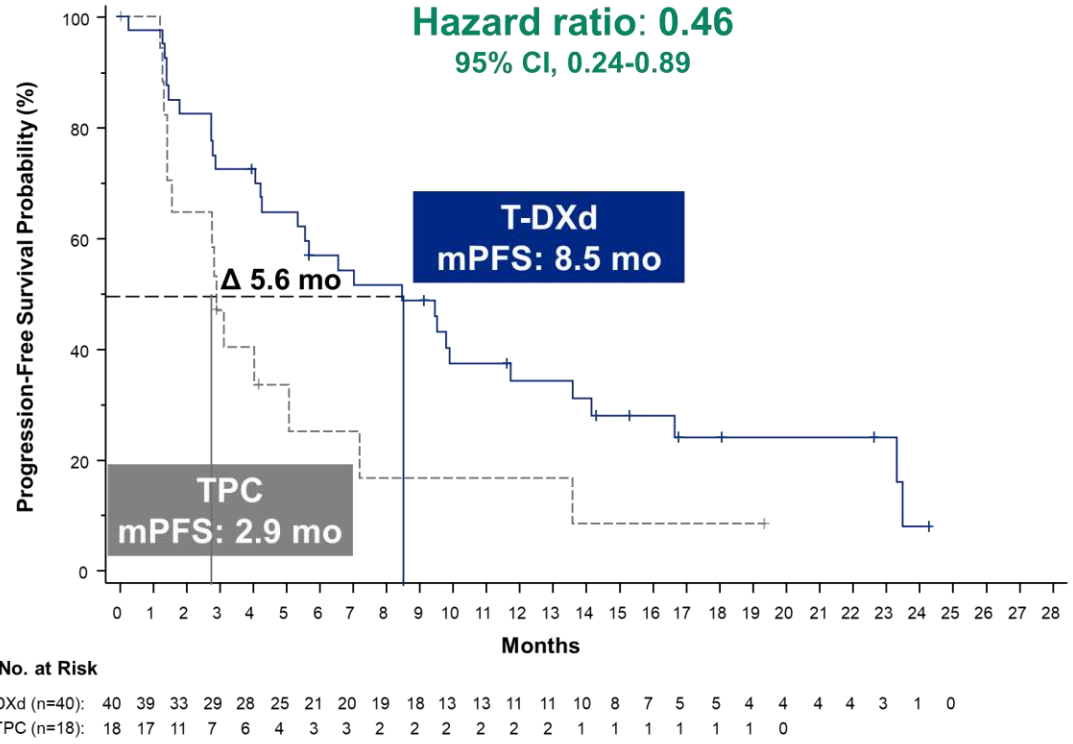


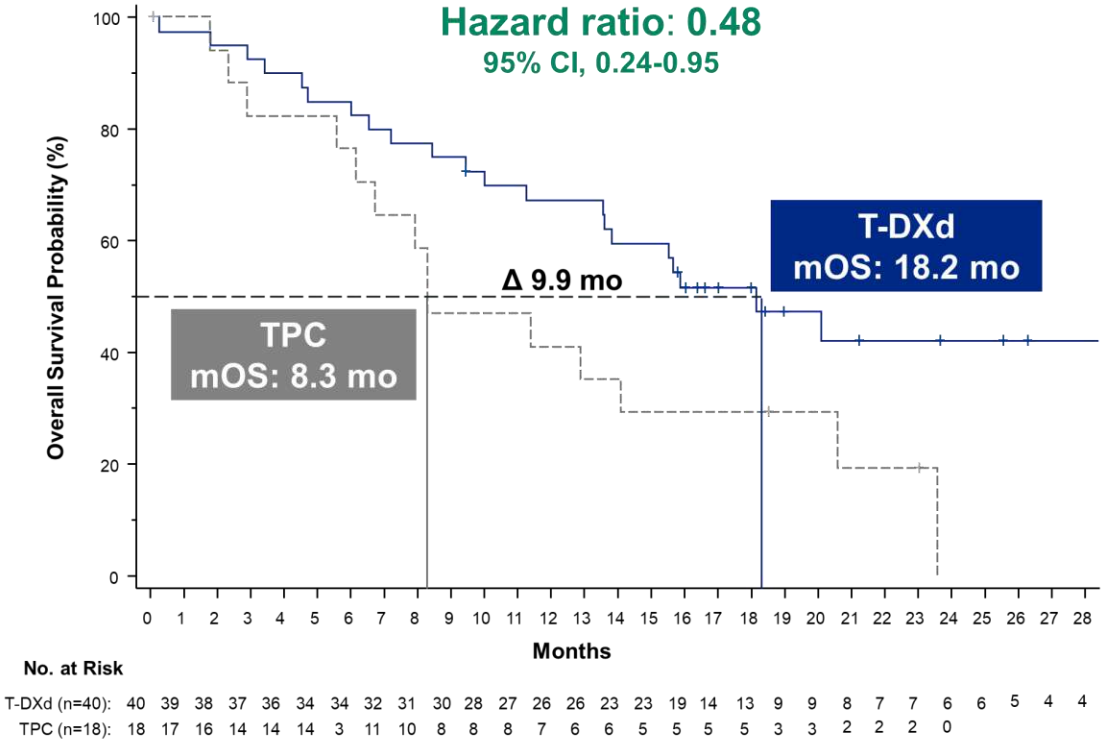
Modi S, et al. ASCO 2022

- Review protocol – were TNBC pts included if < 12 mo (ie. 2nd line)

Trastuzumab Deruxtecan vs Chemotherapy in Previously Treated HER2-low BC
TNBC & Low HER2 (exploratory analysis)

Hormone receptor-negative

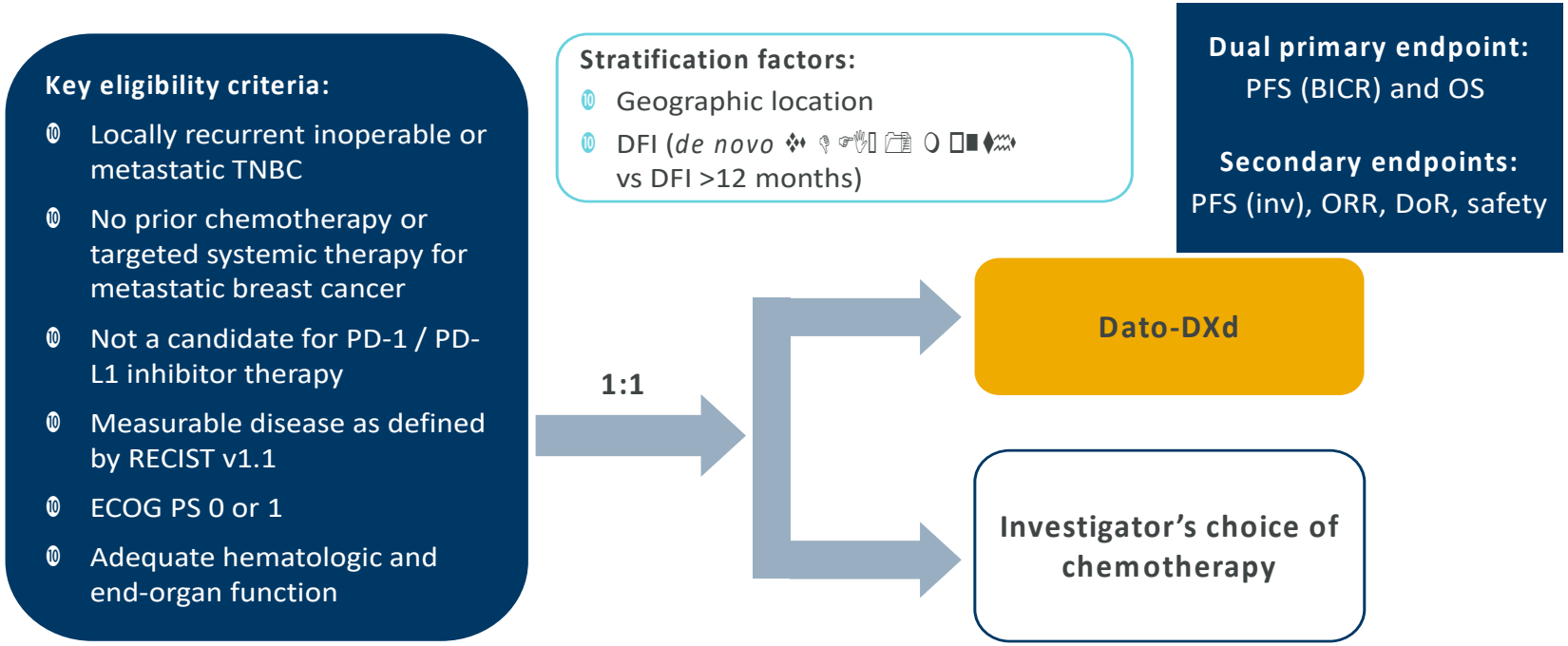




Modi S, et al. ASCO 2022

Ongoing Phase 3 Clinical Trials with Dato-DXd in 1L

TROPION-Breast02[1]



- 1st line therapy for TNBC
- PD-L1 negative

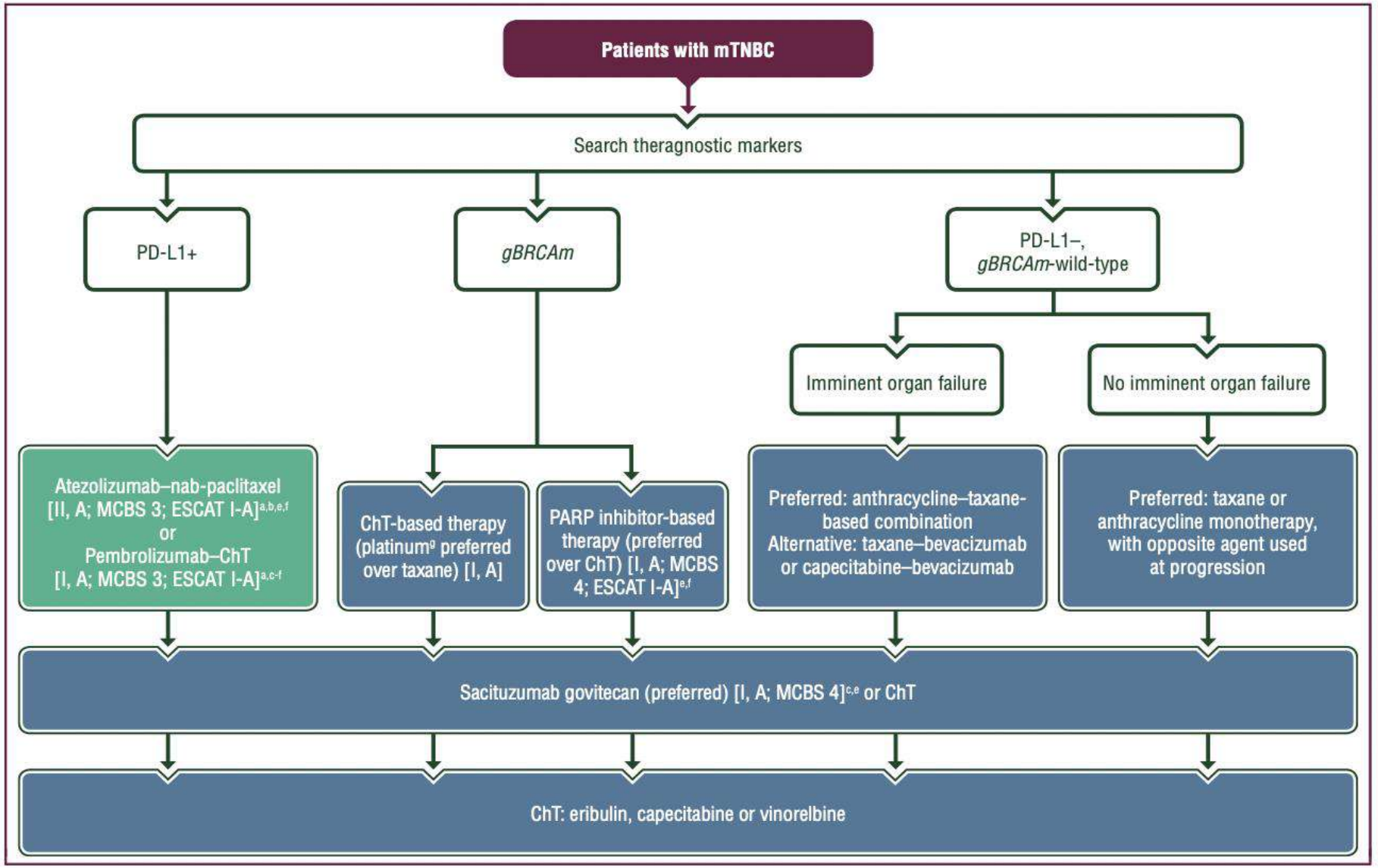
1. https://clinicaltrials.gov/study/NCT05374512

Dent et al. Future Oncology 2024

ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer☆

A. Gennari[1], F. André[2], C. H. Barrios[3], J. Cortés[4,5,6,7], E. de Azambuja[8], A. DeMichele[9], R. Dent[10], D. Fenlon[11], J. Gligorov[12], S. A. Hurvitz[13,14], S.-A. Im[15], D. Krug[16], W. G. Kunz[17], S. Loi[18], F. Penault-Llorca[19], J. Ricke[2,17], M. Robson[20], H. S. Rugo[21], C. Saura[22], P. Schmid[23], C. F. Singer[24], T. Spanic[25], S. M. Tolaney[26], N. C. Turner[27], G. Curigliano[28], S. Loibl[29], S. Paluch-Shimon[30] & N. Harbeck[31], on behalf of the ESMO Guidelines Committee*

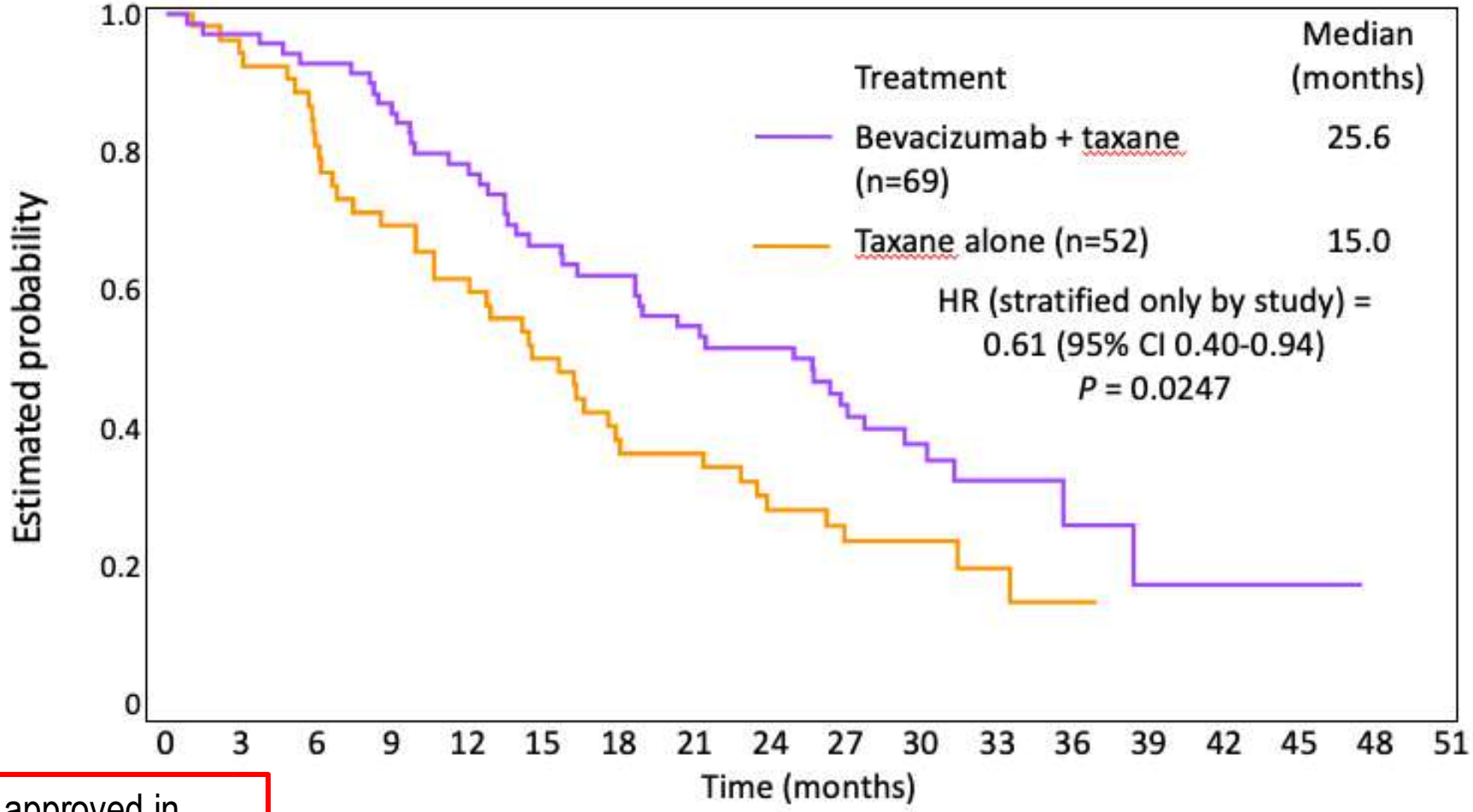
Trials used to make recommendations did not include pts < 12mo DFI



Annals of Oncology 2021

TAXANE ± BEVACIZUMAB: OS (TAXANE-PRETREATED HR-) N.B. SUBGROUP ANALYSIS UNPLANNED

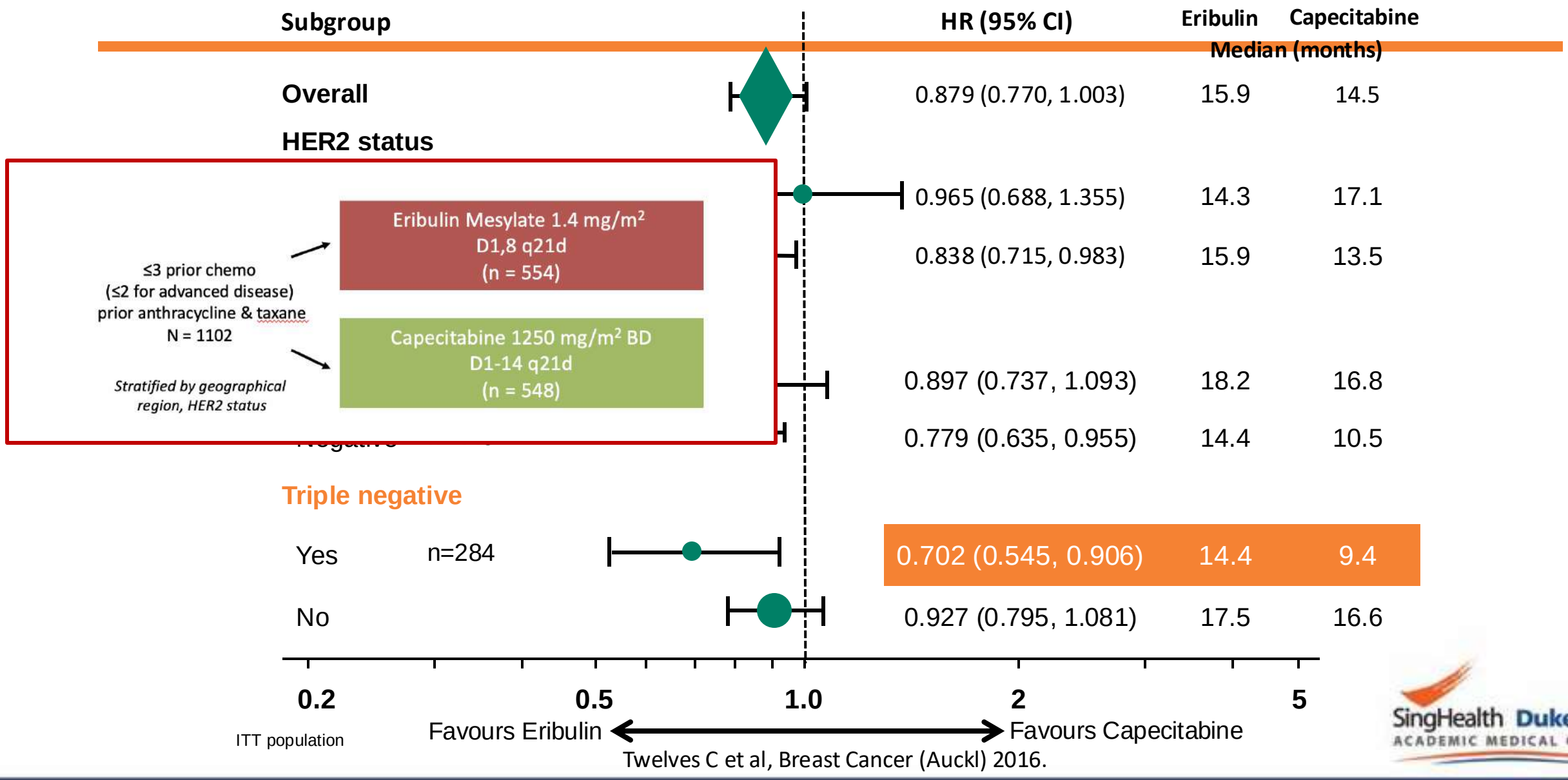
ESMO-MCBS v1.1 score: 2



AVAB00092e. Miles DW et al, ESMO 2010

Bevacizumab not approved in USA and other parts of the world

Study 301: Eribulin vs Capecitabine



Twelves C et al, Breast Cancer (Auckl) 2016.

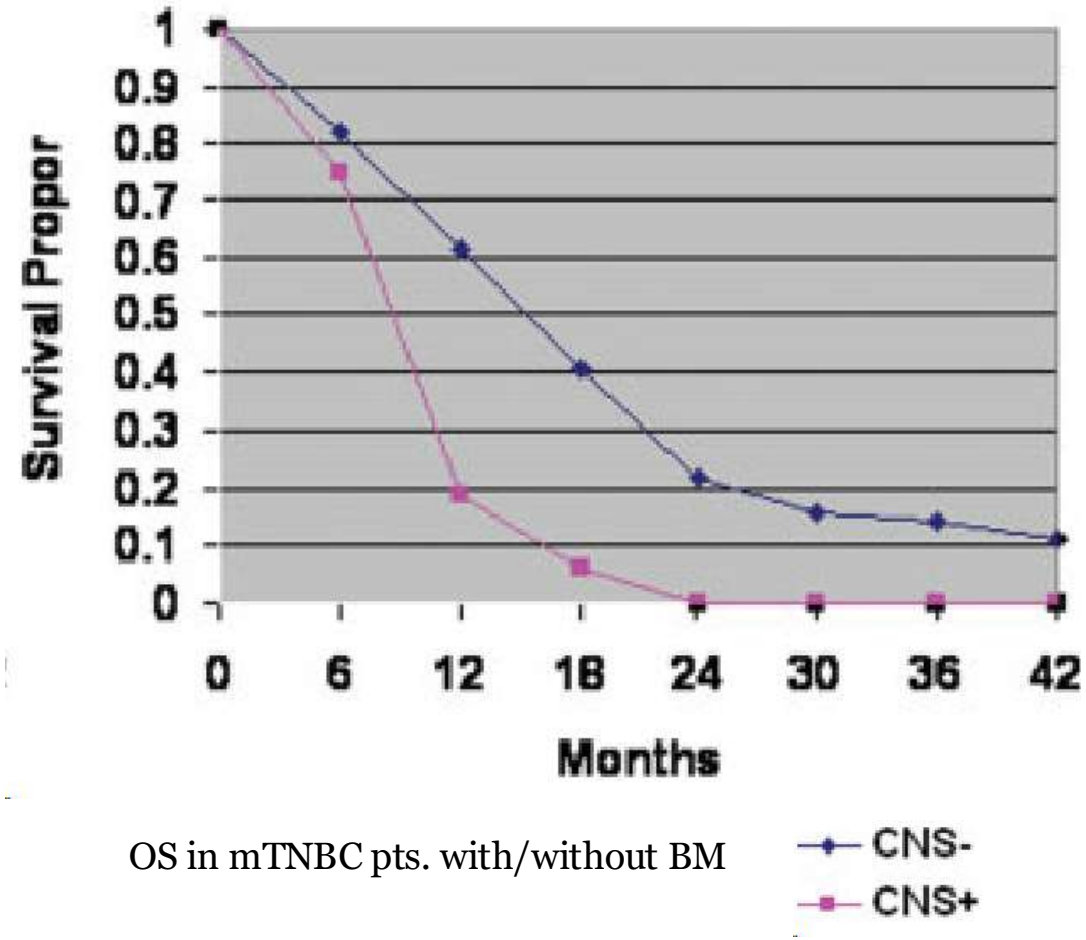
30

CNS METASTASES AND TNBC

Special Considerations

Incidence of BM in metastatic TNBC resembles metastatic HER2-positive BC[1]
Shorter BMFS[2]
Higher rate of LMD
Different progression patterns:
- HER2-positive mBC: stable extracranial disease at brain metastases diagnosis common
- SD/PR: 50%[3]
- mTNBC: parallel progression of extra- and intracranial disease

Poor prognosis of mTNBC with BM[4]



OS in mTNBC pts. with/without BM

1 Bansal R et al. Clin Breast Cancer 2023;23:825-831.; 2 Berghoff A et al. Br J Cancer 2012;106;440-446.; 3 Bendell JC et al. Cancer 2003;97:2972-2977.; 4 Lin NU et al. Cancer 2008;113:2638-2645

Subgroup Analysis of Patients With Brain Metastases From the Phase 3 ASCENT Study of Sacituzumab Govitecan Versus Chemotherapy in Metastatic Triple-Negative Breast Cancer

Dieras et al.

Table 4: Progression-Free Survival

	Brain Metastases-Positive (N=61)	
BICR Analysis	**SG (n=32)**	**TPC (n=29)**
No. of events	24	21
Median PFS—mo (95% CI)	2.8 (1.5-3.9)	1.6 (1.3-2.9)
HR (95% CI)	0.65 (0.35-1.22)	

Table 5: Overall Survival

	Brain Metastases-Positive (N=61)	
	SG (n=32)	**TPC (n=29)**
No. of events	24	21
Median OS—mo (95% CI)	6.8 (4.7-14.1)	7.5 (4.7-11.1)
HR (95% CI)	0.87 (0.47-1.63)	

Modest benefit in PFS
No benefit in OS in CNS +

(small numbers)

Brenner et al. San Antonio Breast Cancer Symposium®, December 8-11, 2020

Evidence of deficient DNA repair in breast cancer brain metastases

RESEARCH ARTICLE Open Access

A *BRCA1* deficient-like signature is enriched in breast cancer brain metastases and predicts DNA damage-induced poly (ADP-ribose) polymerase inhibitor sensitivity

Ryan P McMullin[1,2,3], Ben S Wittner[2,4], Chuanwei Yang[1,2,3], Benjamin R Denton-Schneider[1], Daniel Hicks[1], Raj Singavarapu[1], Sharon Moulis[1,2,3], Jeongeun Lee[1,2,3], Mohammad R Akbari[5], Steven A Narod[5], Kenneth D Aldape[6], Patricia S Steeg[7], Sridhar Ramaswamy[2,4] and Dennis C Sgroi[1,2,3*]

Annals of Oncology 29: 1948–1954, 2018
doi:10.1093/annonc/mdy216
Published online 18 June 2018

Annals of Oncology 2018, 29: 1948-1954

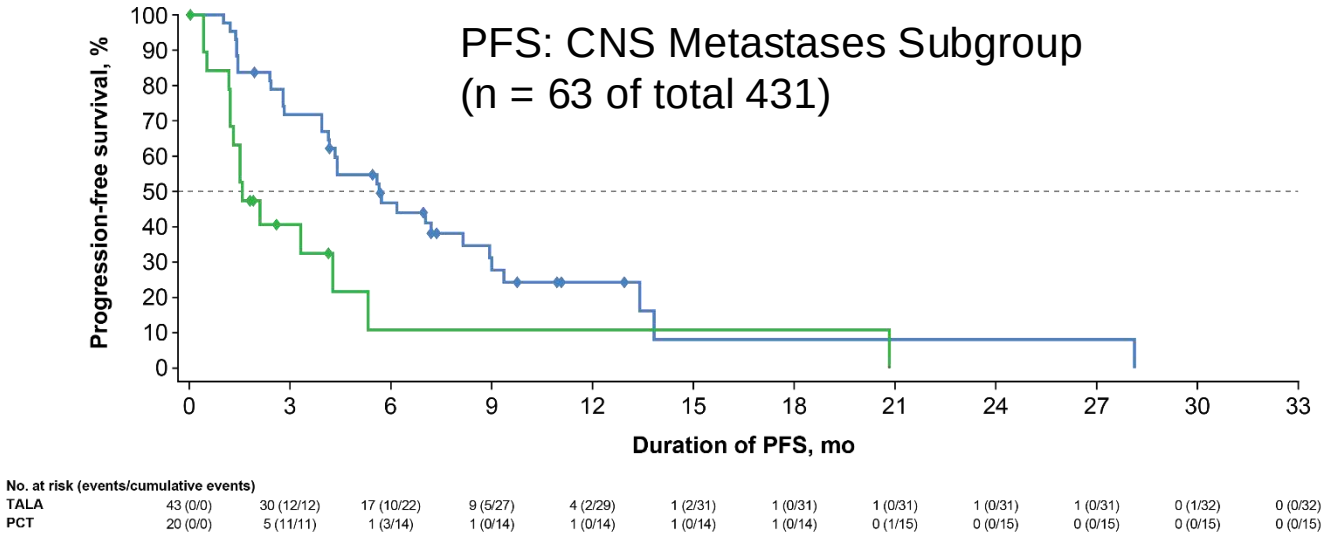
BCRT 2014, 16:R25

Breast cancer brain metastases show increased levels of genomic aberration-based homologous recombination deficiency scores relative to their corresponding primary tumors

M. Diossy[1], L. Reiniger[2,3], Z. Sztupinszki[1,4], M. Krzystanek[1], K. M. Timms[5], C. Neff[5], C. Solimeno[5], D. Pruss[5], A. C. Eklund[1], E. Tóth[6], O. Kiss[6], O. Rusz[7], G. Cserni[7,8], T. Zombori[7], B. Székely[9,10], J. Tímár[9], I. Csabai[11] & Z. Szallasi[1,3,12*]

ESMO DEEP DIVE: BREAST CANCER

Talazoparib vs. MD Choice yields PFS advantage in *BRCA*-associated brain metastases

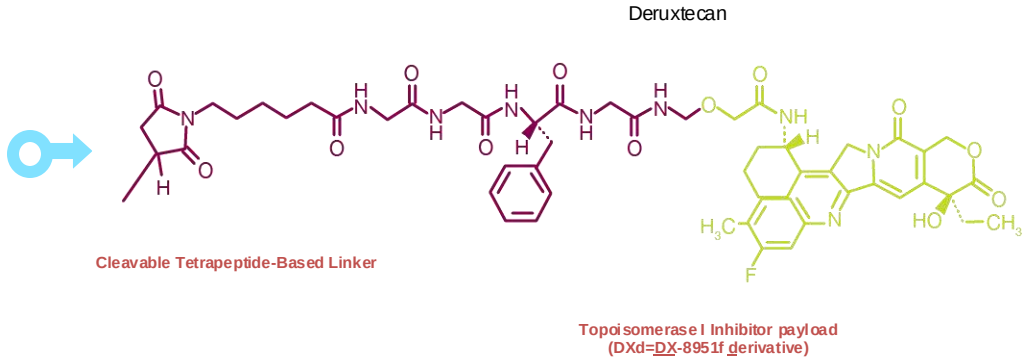


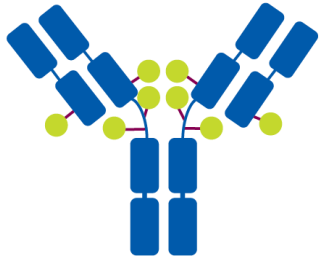
(Compared to 8.6 vs. 5.6 mos PFS for total study population)

	TALA (n = 43)	Overall PCT (n = 20)
Events, no. (%)	32 (74%)	15 (75%)
Median, mo (95% CI)	**5.7 (4.1, 8.1)**	**1.6 (1.2, 4.3)**
	Hazard ratio, 0.32, 95% CI, 0.15, 0.68 ***P* = .0016**	

J. Litton SABCS 2017

TUXEDO-2: TNBC and BRAIN METS





- Histologically confirmed triple-negative breast cancer
- Radiologically documented metastatic disease
- Newly diagnosed brain metastases or brain metastases progressing after prior local therapy
- Measurable disease (RANO-BM criteria)
- No indication for immediate local treatment
- Leptomeningeal disease allowed
- KPS ≥70%, ECOG ≤2
- Indication for systemic therapy
- Minimum of one prior line of chemotherapy for early or advanced disease
- Prior treatment with IOs, PARPi and/or TROP-2 directed compounds allowed
- Life expectancy of at least 3 months
- Age >18 years
- LVEF ≥50%

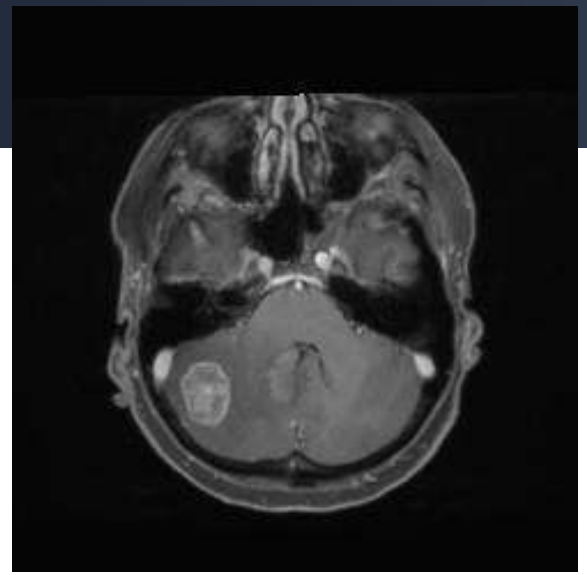
→ Datopotamab-deruxtecan (6.0 mg/kg i.v. once every three weeks) → Treatment until progression, unacceptable toxicity or withdrawal for any reason → Futher treatment according to local standard

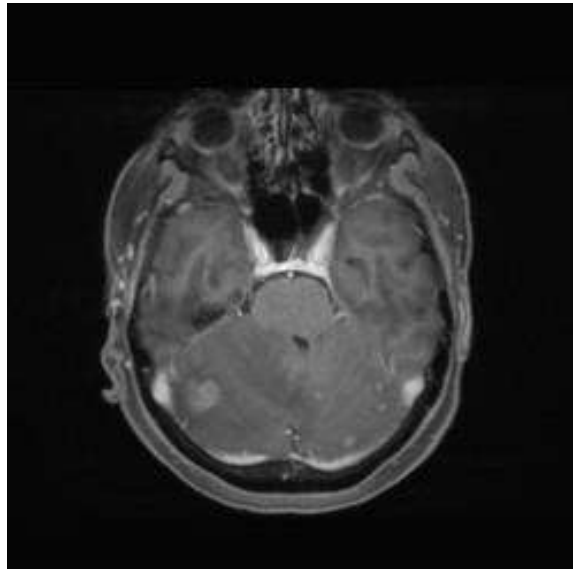
Safety FU four weeks after EOT

Survival FU at 6, 12, and 18 months

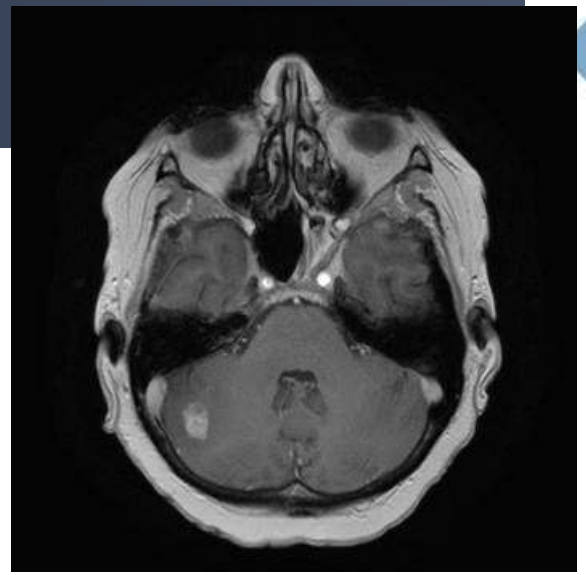
- Single-arm phase II
- Simon Optimal Two Stage Design
- Dato-DXd in pts. with triple-negative breast cancer active BM

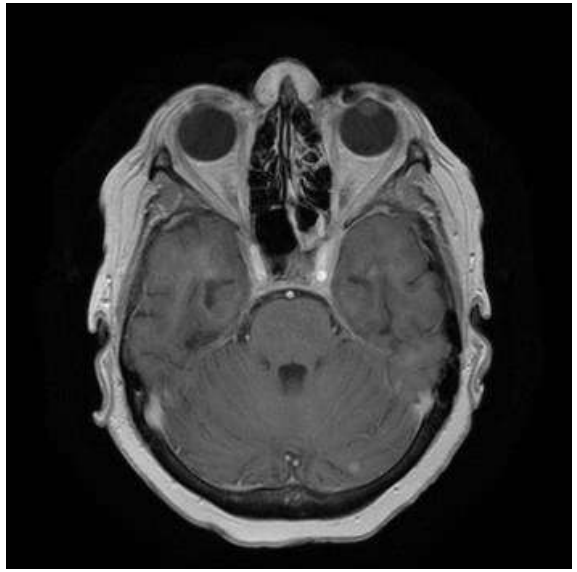
Slide courtesy Rupert Bartsch





Dato-DXd

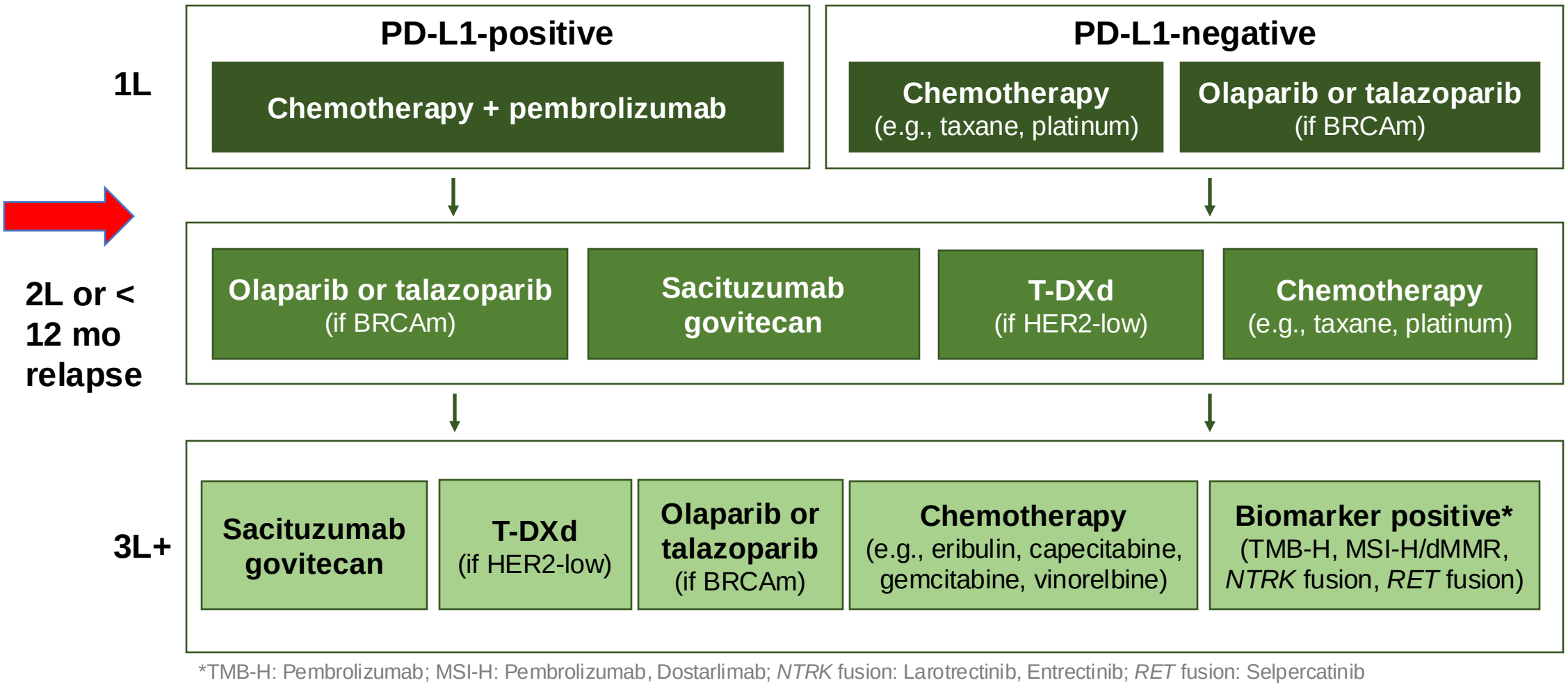




Baseline

Post cycle 4

Treatment Algorithm for Metastatic TNBC



*TMB-H: Pembrolizumab; MSI-H: Pembrolizumab, Dostarlimab; *NTRK* fusion: Larotrectinib, Entrectinib; *RET* fusion: Selpercatinib

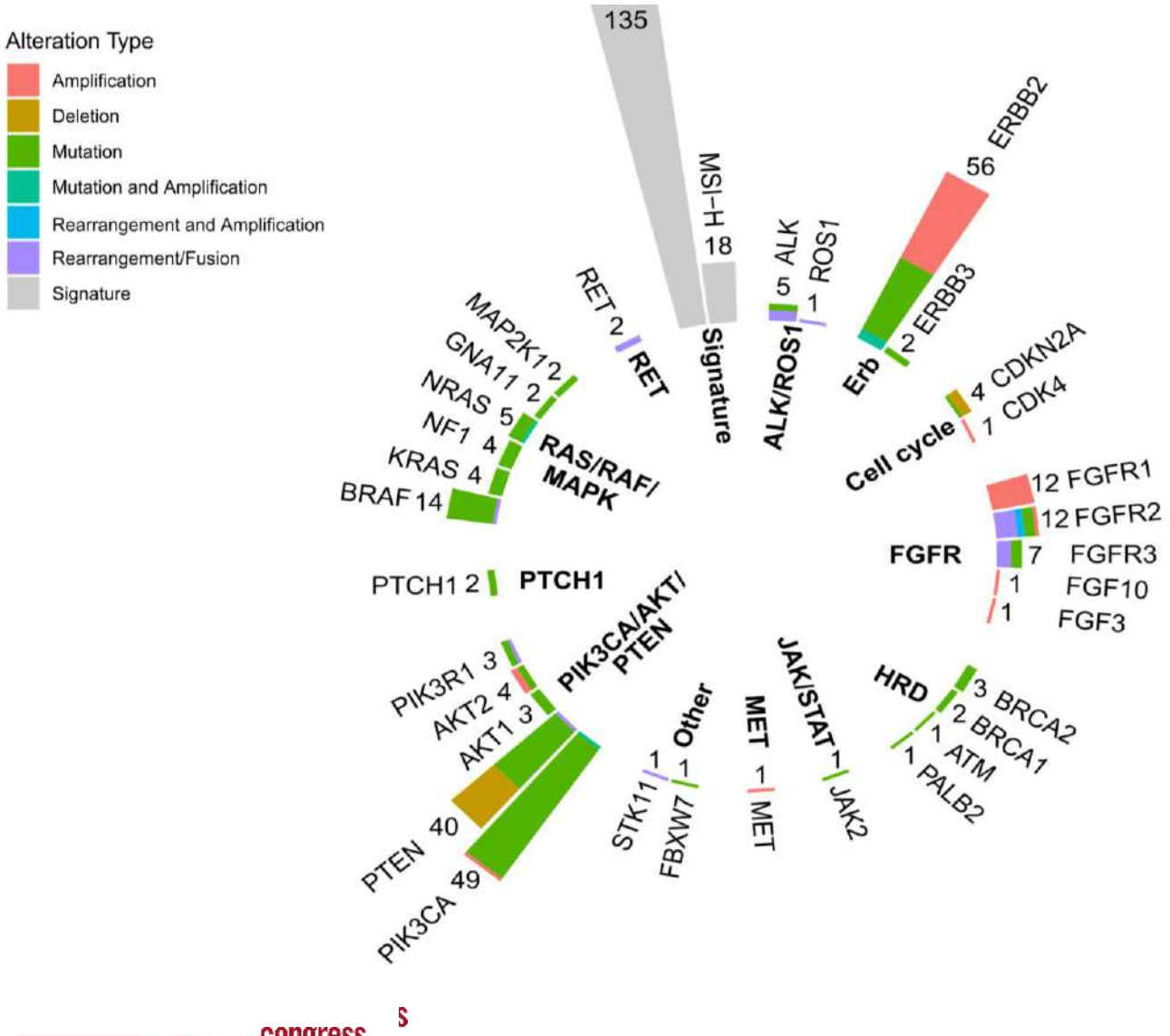
Consider NGS at time of metastatic diagnosis especially for clinical trial eligibility

Slide courtesy of Ana C. Garrido-Castro, M.D.

Next Generation of therapies

Will they address biological bottlenecks?

The ROME trial: genomic alterations in ITT population



Alteration group	Therapy assigned	n
ALK/ROS1	Alectinib	4
	Entrectinib	2
Cell cycle	Palbociclib	5
Erb	TDM1	31
	Pertuzumab + Trastuzumab	12
	Trastuzumab + Lapatinib	11
	Pertuzumab + TDM1	2
	TDM1 + Atezolizumab	1
	Trastuzumab + Everolimus	1
FGFR	Pemigatinib	33
HRD	Talazoparib	7
JAK/STAT	Itacitinib	1
MET	Tepotinib	1
Other	Everolimus	2
PIK3CA/AKT/PTEN	Ipatasertib	66
	Atezolizumab + Ipatasertib	24
	Alpelisib	6
	Everolimus	3
PTCH1	Vismodegib	2
RAS/RAF/MAPK	Vemurafenib + Cobimetinib	16
	Cobimetinib	14
	Cobimetinib + Atezolizumab	1
RET	Pralsetinib	1
	Selpercatinib	1
Signature	Ipilimumab + Nivolumab	148
	Nivolumab	5

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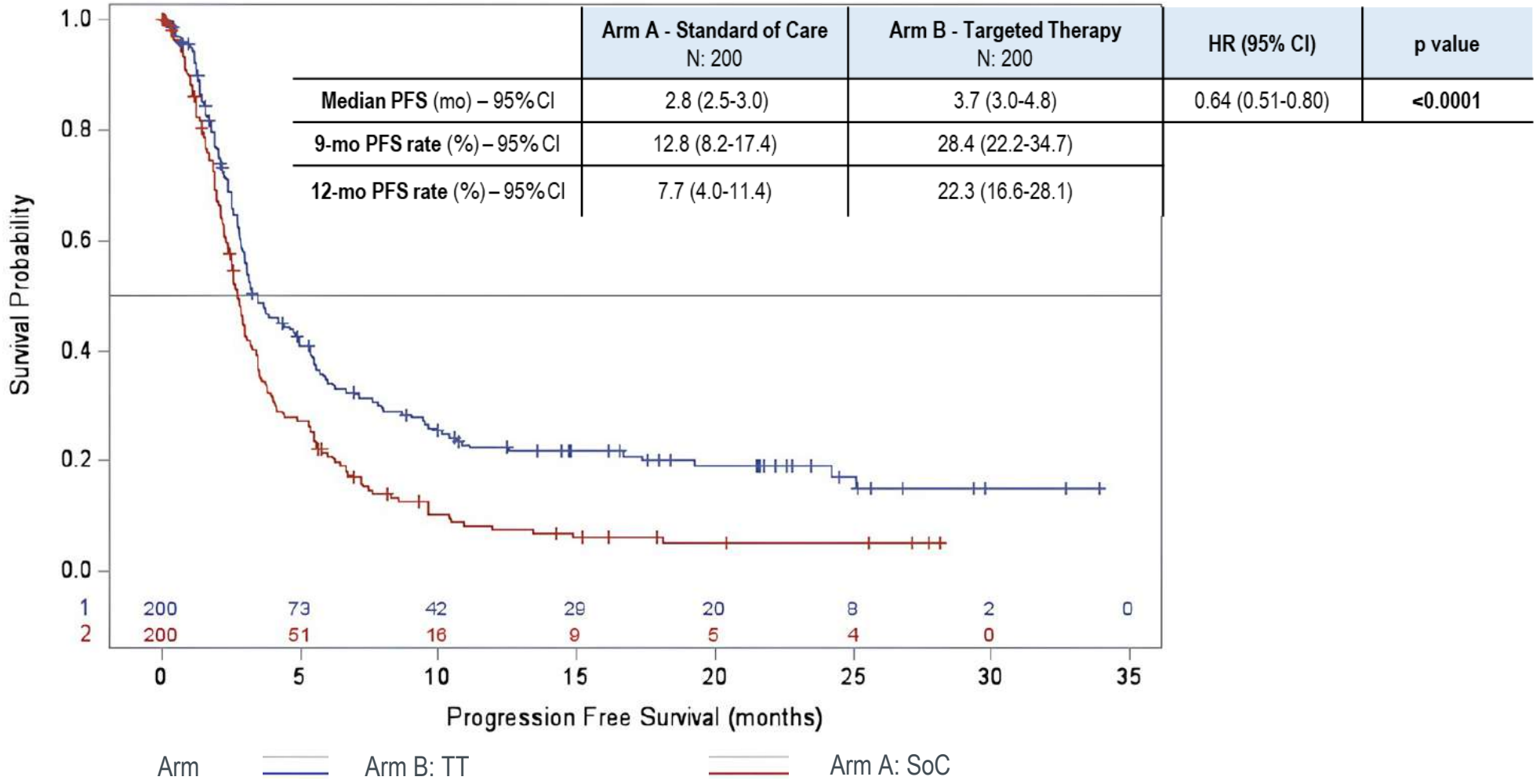
Secondary endpoint: PFS in ITT population

	Arm A - Standard of Care N: 200	Arm B - Targeted Therapy N: 200	HR (95% CI)	p value
Median PFS (mo) – 95% CI	2.8 (2.5-3.0)	3.7 (3.0-4.8)	0.64 (0.51-0.80)	**<0.0001**
9-mo PFS rate (%) – 95% CI	12.8 (8.2-17.4)	28.4 (22.2-34.7)		
12-mo PFS rate (%) – 95% CI	7.7 (4.0-11.4)	22.3 (16.6-28.1)		



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UNANSWERED QUESTIONS

- Any role in re-challenging with immune checkpoint inhibition if PD-L1 + on repeat biopsy?
  - Unlikely unless combining with ADC or other combination (currently only part of clinical trial)
- Any role in re-challenging with PARP inhibitor if already received in adjuvant setting?
  - Unlikely, likely has developed secondary mutations (ie. reversion mutations)
- Given high rate of CNS metastases and some suggestion of newer generation of ADCs having CNS penetration, should we screen all high risk TNBC with CNS imaging? (feasibility trials ongoing)

PALLIATIVE CARE RESOURCES AND SUPPORT AT END OF LIFE

WHO and ASCO recommend comprehensive palliative care programs to improve QOL for cancer patients

Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial

Camilla Zimmermann, Nadia Swami, Monika Krzyzanowska, Breffni Hannon, Natasha Leighl, Amit Oza, Malcolm Moore, Anne Rydall, Gary Rodin, Ian Tannock, Allan Donner, Christopher Lo

Ferrell et al., JCO, 2017; Zimmerman et al., Lancet, 2014

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Giuseppe Curigliano
Hope Rugo
Barbara Pistilli
Peter Schmid
Paolo Tarantino
Sara Tolaney

ESMO DEEP DIVE: BREAST CANCER

Thank you

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ESMO WEBINAR SERIES

ESMO DEEP DIVE:
BREAST CANCER

WHERE ARE WE HEADING WITH ANTIBODY DRUG CONJUGATES?

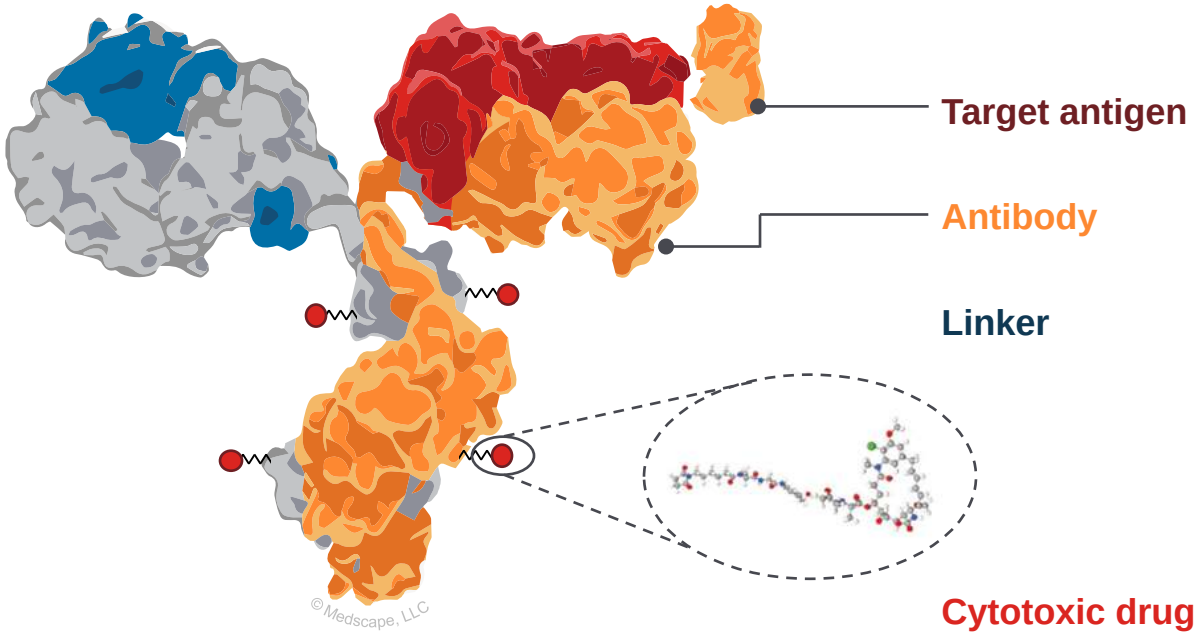
ONGOING RESEARCH AND FUTURE DIRECTIONS

Sara M. Tolaney, MD, MPH

Dana-Farber Cancer Institute

ESMO WEBINAR SERIES

Core Structure of an ADC



Key Functions

- Recognition of target cancer cells
- Guidance system for cytotoxic drugs
- Bridge between antibody and drugs to control release of drugs inside cancer cells
- Warhead for killing cancer cells

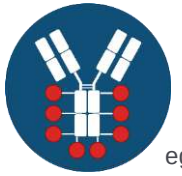
Fu Z, et al. Signal Transduct Target Ther. 2022;7:93.

ADCs: Past, Present, Future

eg, T-DM1

First-Generation ADCs

- Noncleavable linkers
- Moderate activity
- Little activity in tumors with low or heterogenous target expression



eg, T-DXd

Second-Generation ADCs

- Improved antibody binding
- Use of more potent payloads
- Higher DAR
- "Bystander effect", with activity against tumors with low or heterogenous target expression

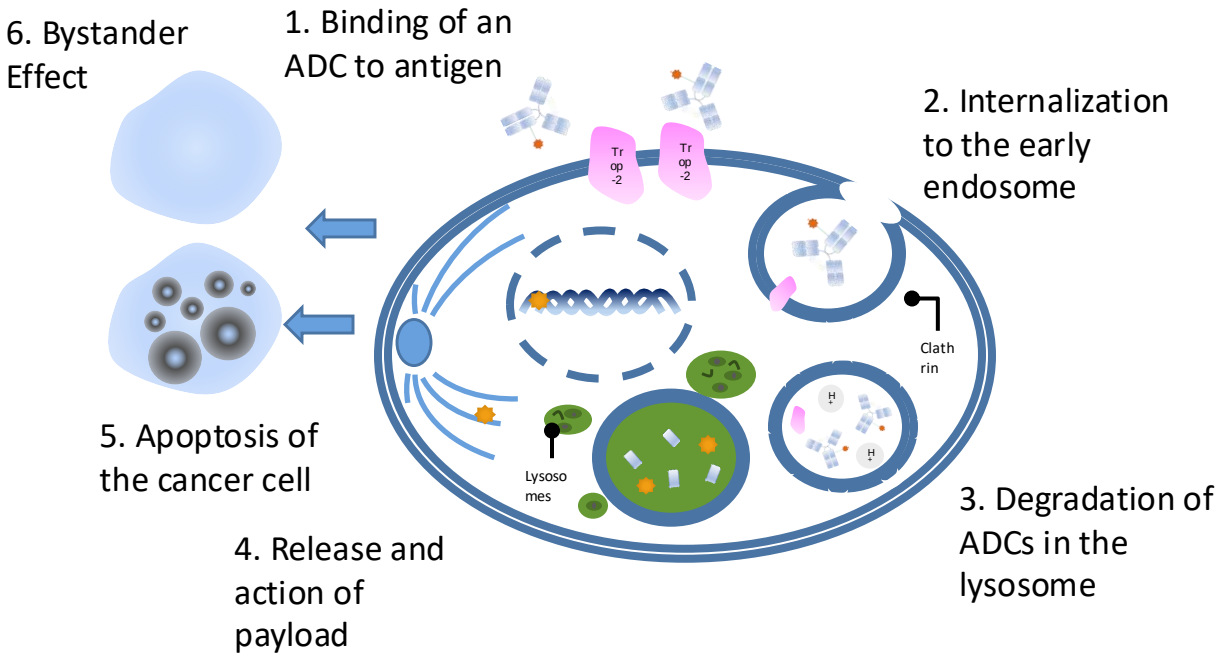
Next-Generation ADCs

- Better optimization of antibody, linkers, and conjugation chemistry
- Biparatopic antibodies
- Multiple payloads
- Innovative payloads (eg, ISACs)

ISAC, immune-stimulating antibody conjugate; T-DM1, trastuzumab emtansine.

Tarantino P, et al. CA Cancer J Clin. 2022;72:165-182; Beck A, et al. Nat Rev Drug Discov. 2017;16:315-337; Hafeez U, et al. Molecules. 2020;25:4764.

Selective delivery of toxic payload

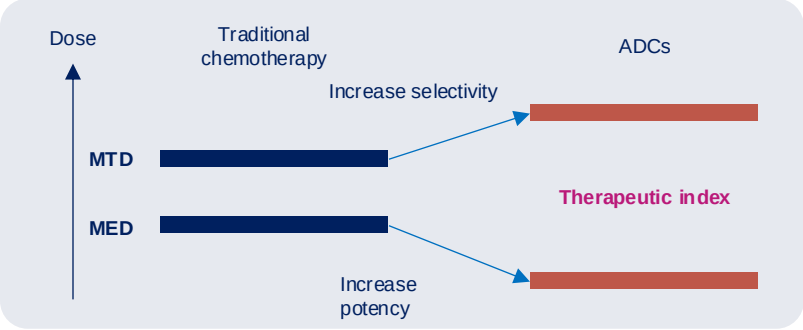


Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

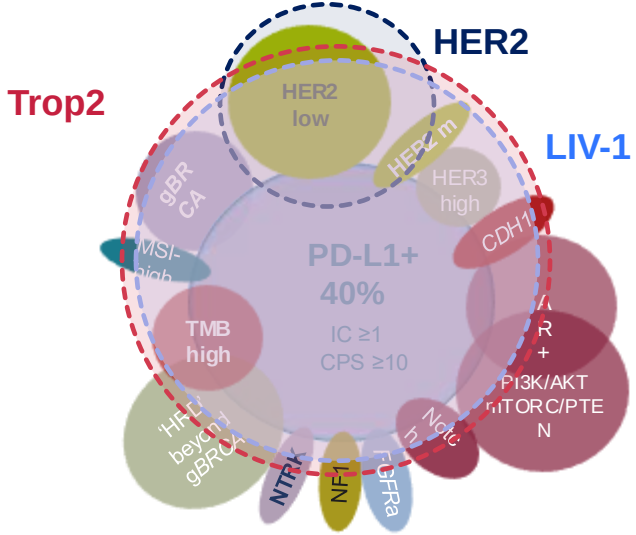
Can we address the limitations of cytotoxic chemotherapy with ADCs?

Limitations of cytotoxic therapy[1,2]

- Lack of tumour specificity
- Dose-limiting toxicity via systemic exposure of normal cells to cytotoxic agents
- Narrow therapeutic index
- ADCs were designed to have an expanded therapeutic index



ADCs: efficient and specific drug delivery to antigen-expressing tumour cells[3]



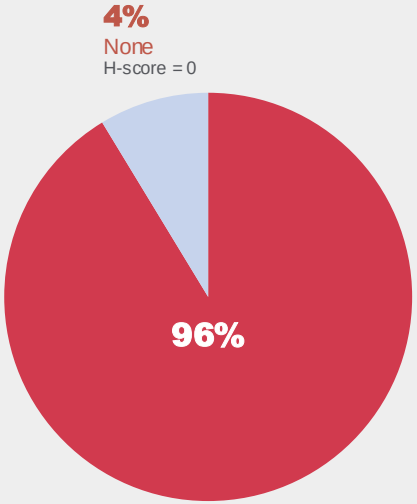
ADC, antibody-drug conjugate; AR+, androgen receptor positive; CDH1 m, pathogenic mutation in CDH1 gene; CPS, combined positive score; ERBB2 m, pathogenic mutation in ERBB2 gene; FGFR a, activating alteration of FGFR1/2/3; gBRCA, germline mutation in BRCA1 or BRCA2 gene; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HRD, homologous recombination deficiency; IC, immune cells; mTORC, mammalian target of rapamycin complex 1; MED, minimum effective dose; MSI, microsatellite instability; MTD, maximum tolerated dose; NF1 m, pathogenic mutation in NF1 gene; NTRK r, rearrangement of NTRK1, NTRK2 or NTRK3 gene; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinases; PTEN, phosphatase and tensin homologs; TMB, tumour mutation burden; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen 2.

1. LoRusso PM, et al. *Clin Cancer Res*. 2011;17(20):6437–6447; 2. Nakada T, et al. *Chem Pharm Bull*. 2019;67(3):173–185. 3. Punie K, ESMO 2021 Presentation (Gilead Symposium).

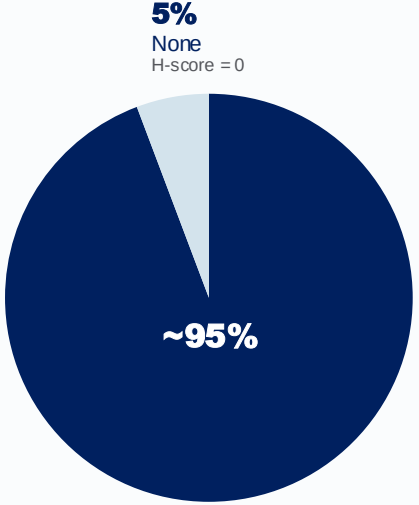
High Trop-2 Expression in mTNBC and HR+/HER2- mBC[1-3]

Trop-2 is expressed in **96% of patients with mTNBC[1-2]** and approximately **95% of patients with HR+/HER2- mBC[3]**

Trop-2 Expression in Patients with mTNBC (N=290)*,†[1-2]



Trop-2 Expression in Patients with HR+/HER2- mBC (N=238)‡§[3]



High Trop-2 expression rates suggest that **pre-therapy biomarker assessment is not required[1-3].**

*Trop-2 expression was determined on primary or metastatic archival tumour tissue; †Trop-2 expression was measured using a validated IHC assay in a central laboratory. ‡Trop-2 expression was determined on primary or metastatic archival tumour tissue; §membrane Trop-2 expression was assessed by a validated research IHC assay at a CAP/CLIA central laboratory. HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; H-score, histochemical score; IHC, immunohistochemistry; mBC, metastatic breast cancer; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen-2. 1. Hurvitz SA, et al. SABCS [virtual meeting]. 2020 (oral presentation GS3-06); 2. Bardia A, et al. *Ann Oncol*. 2021;32(9):1148–1156; 3. Rugo HS, et al. SABCS 2022. Oral presentation GS1-11.

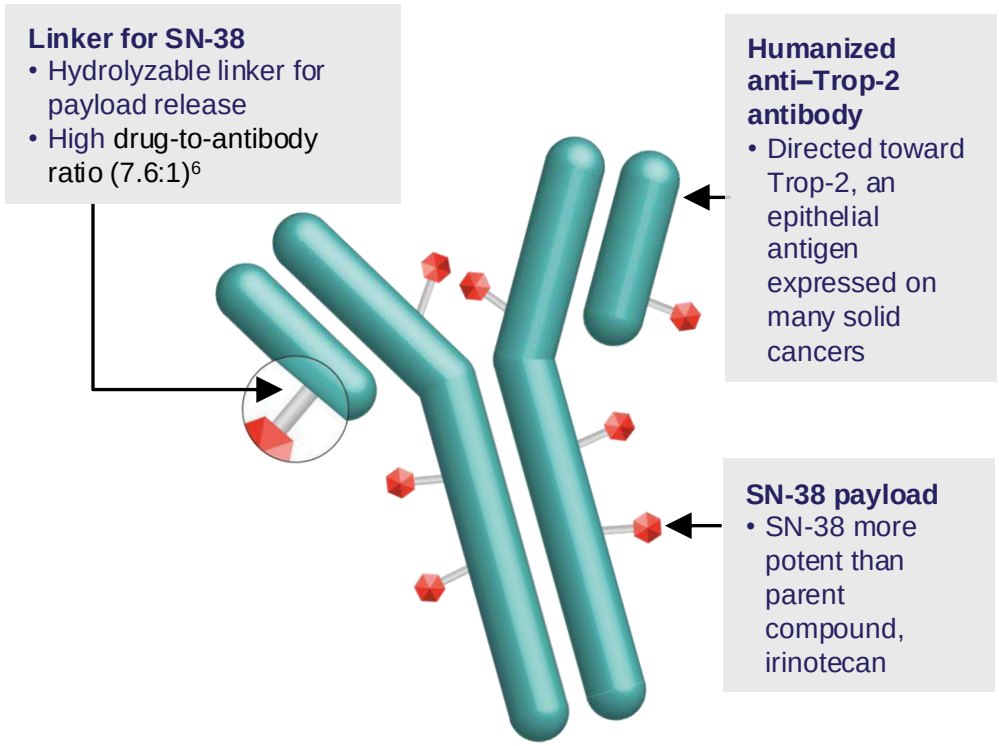
TROP2-directed ADCs

	Sacituzumab govitecan (IMMU-132)	Datopotamab deruxtecan (DS-1062a)	Sacituzumab tirumotecan (MK-2870)
Antibody	hRS7 Humanized IgG1 mAb	MAAP-9001a Humanized IgG1 mAb	hRS7 Humanized IgG1 mAb
Payload	SN38 (DNA Topoisomerase I inhibitor)	DXd (DNA Topoisomerase I inhibitor)	KL610023 (DNA Topoisomerase I inhibitor)
Linker cleavage	Enzymatic and pH-dependent	Enzymatic	Enzymatic and pH-dependent
Bystander effect	Yes	Yes	Yes
DAR	7.6	4	7.4
Half-life	11-14h	~5 days	57h
Dosing	D1, D8 of Q3W schedule	Q3W	Q2W

Sands J et al. ASCO 2018; Okajima D et al. ASCO 2018; Bardia A et al. ESMO Breast Cancer 2021; Cheng Y et al. Front Oncol 2022.

Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed ADC

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC and fast-track designation in metastatic urothelial cancer[7]



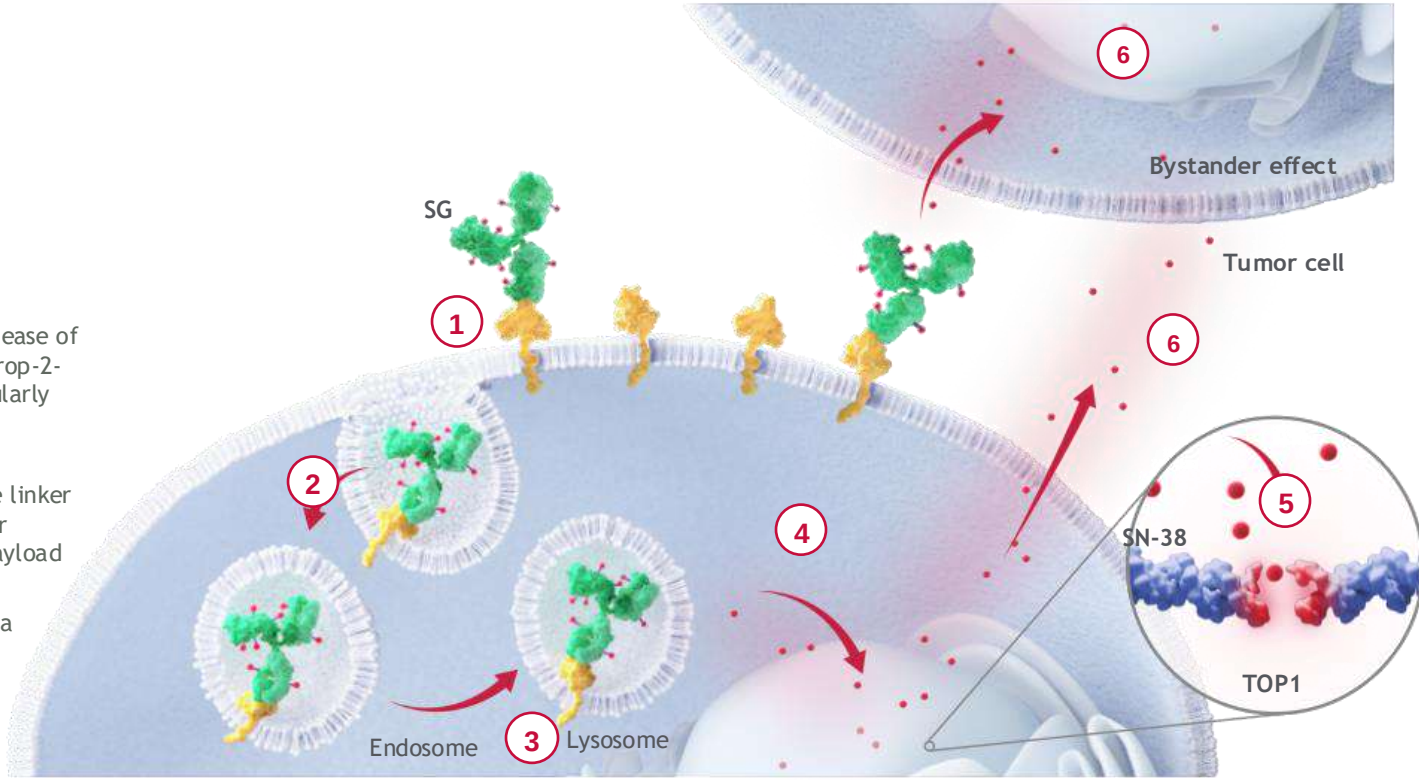
ADC, antibody–drug conjugate; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Vidula N et al. *J Clin Oncol.* 2017;35:15(suppl):Abstract 1075. 2. Ambrogi et al. *PLoS One.* 2014;9(5):e96993. 3. Goldenberg DM et al. *Expert Opin Biol Ther.* 2020 Aug;20(8):871-885. 4. Nagayama A et al. *Ther Adv Med Oncol.* 2020;12:1758835920915980. 5. Cardillo TM et al. *Bioconjugate Chem.* 2015;26:919-931. 6. Goldenberg DM et al. *Oncotarget.* 2015;6:22496-224512. 7. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020.

SG Is a First-in-Class Trop-2-Directed ADC That Concentrates SN-38 Payload Intracellularly and in the Surrounding Tumor Microenvironment

1) Binding
2) Internalization
3) Intracellular trafficking
4) Lysosomal degradation
5) Cell cytotoxicity
6) Bystander effect

- Rapid internalization and efficient release of the SN-38 payload intracellularly in Trop-2-expressing cancer cells and extracellularly into the surrounding tumor microenvironment[1-3]
- Before internalization of the ADC, the linker can be cleaved at the pH of the tumor microenvironment, releasing SN-38 payload outside the targeted tumor cell[2,3]
- DNA damage to the targeted cell and a bystander effect on adjacent tumor cells that may not express Trop-2[2]



[a]Adapted from Rugo HS, et al.[2]

ADC, antibody–drug conjugate; DNA, deoxyribonucleic acid; SG, sacituzumab govitecan; TOP1, topoisomerase I; Trop-2, trophoblast cell-surface antigen 2.

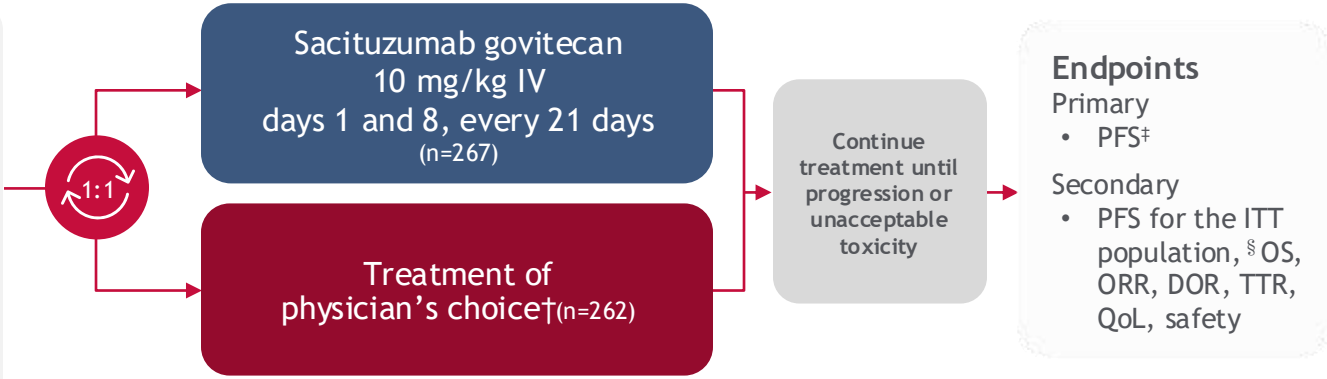
1. Goldenberg DM, et al. *Oncotarget.* 2015;6:22496-22512; 2. Rugo HS, et al. *Future Oncol.* 2020;16:705-715; 3. Kopp A, et al. *Mol Cancer Ther.* 2023;22:102-111.

ASCENT: A phase 3 confirmatory study of sacituzumab govitecan in 2L and later mTNBC[1-3*]

Metastatic TNBC

- ≥2 chemotherapies - one of which could be in neo/adjuvant setting provided progression occurred within a 12-months period
- Patients with stable brain metastasis were allowed

(N=529)



Stratification factors

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

NCT02574455

*ASCENT was an international, Phase 3, multicentre, open-label, randomised trial of patients with unresectable locally advanced or metastatic TNBC (N=529). †Treatment of physician's choice: eribulin, vinorelbine, gemcitabine, or capecitabine; ‡PFS measured by an independent centralised and blinded group of radiology experts who assessed tumour response using RECIST 1.1 criteria in patients without brain metastasis; §The full population or intention-to-treat population includes all randomised patients (with and without brain metastases).

DOR, duration of response; IV, intravenous; ITT, intention-to-treat; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumours; TNBC, triple-negative breast cancer; TTR, time to response; QoL, quality of life.

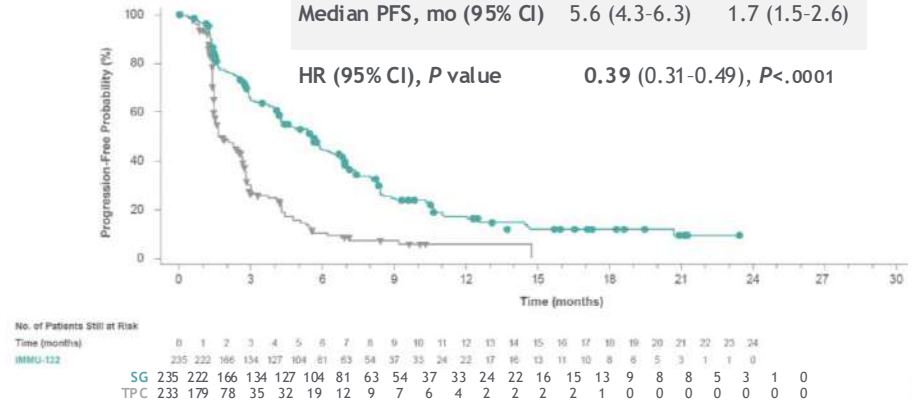
1. Bardia A, et al. *N Engl J Med*. 2021;384(16):1529-1541; 2. Bardia A, et al. ESMO 2020. Abstract LBA17; 3. ClinicalTrials.gov website. Available at: https://clinicaltrials.gov/ct2/show/NCT02574455. Accessed March 2022.

ASCENT: Statistically significant and clinically meaningful improvement in PFS and OS (BMNeg Population)

The ASCENT trial demonstrated statistically significant improvement in PFS and OS over single-agent chemotherapy in the primary study population

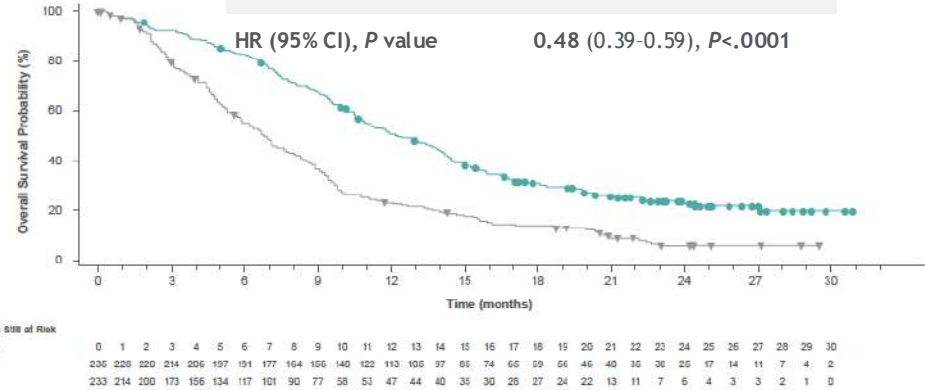
Progression-free survival (BICR Analysis)

BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	167	150
Median PFS, mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P* value	**0.39** (0.31-0.49), ***P*<.0001**	



Overall survival

	SG (n=235)	TPC (n=233)
No. of events	173	199
Median OS, mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P* value	**0.48** (0.39-0.59), ***P*<.0001**	



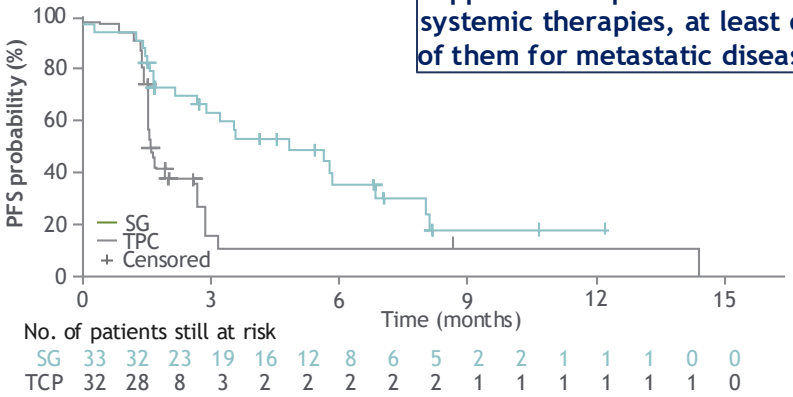
- Analysis based on final database lock confirmed the improvement in clinical outcomes over TPC:
  - Median PFS of 5.6 vs 1.7 months (HR 0.39, P<0.0001)
  - Median OS of 12.1 vs 6.7 months (HR 0.48, P<0.0001)
  - **OS rate at 24 months of 22.4% (95% CI, 16.8-28.5) vs 5.2% (95% CI, 2.5-9.4)**

1. Bardia A, et al. J Clin Oncol. 2022;40(suppl 16):1071

ASCENT: In patients with 2L mTNBC, PFS and OS improvement was consistent with the overall study population

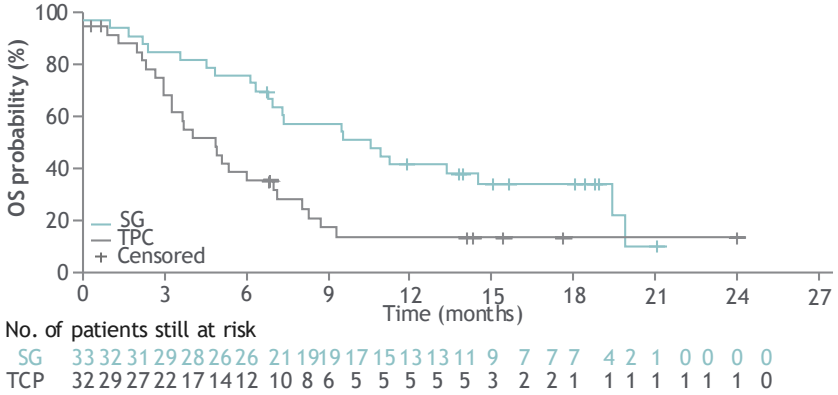
Progression-free survival

Approved for patients with ≥2 systemic therapies, at least one of them for metastatic disease*,†



BICR Analysis	SG (n=33)	TPC (n=32)
No. of events	21	23
Median PFS - mo (95% CI	5.7 (2.6-8.1)	1.5 (1.4-2.6)
HR (95% CI)	0.41 (0.22-0.76)	

Overall survival



BICR Analysis	SG (n=33)	TPC (n=32)
No. of events	22	24
Median OS—mo. (95% CI)	10.9 (6.9-19.5)	4.9 (3.1-7.1)
HR (95% CI)	**0.51** (0.28-0.91)	

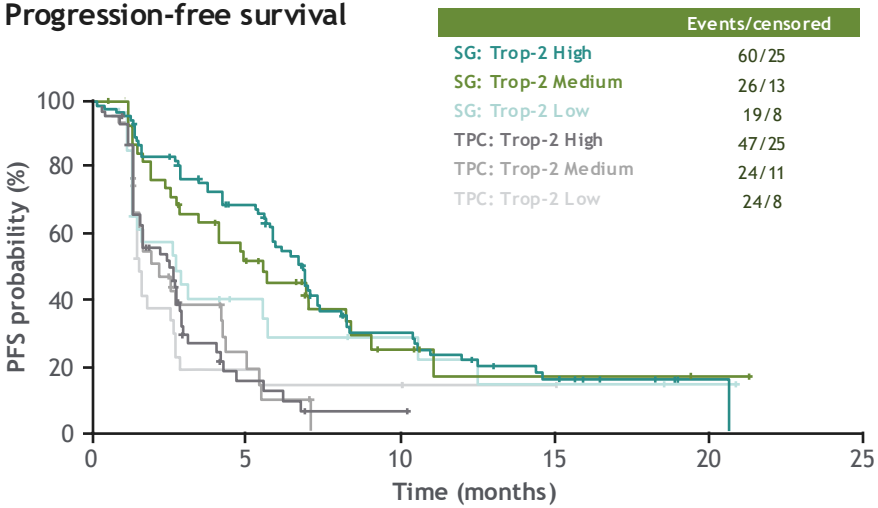
†sacituzumab govitecanSummary of Product Characteristics. Gilead Sciences Ireland UC. https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf

Assessed by independent central review in the brain-metastasis-negative population who recurred ≤12 months after (neo)adjuvant chemotherapy and received one line of therapy in the metastatic setting prior to study enrolment. BICR, blind independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

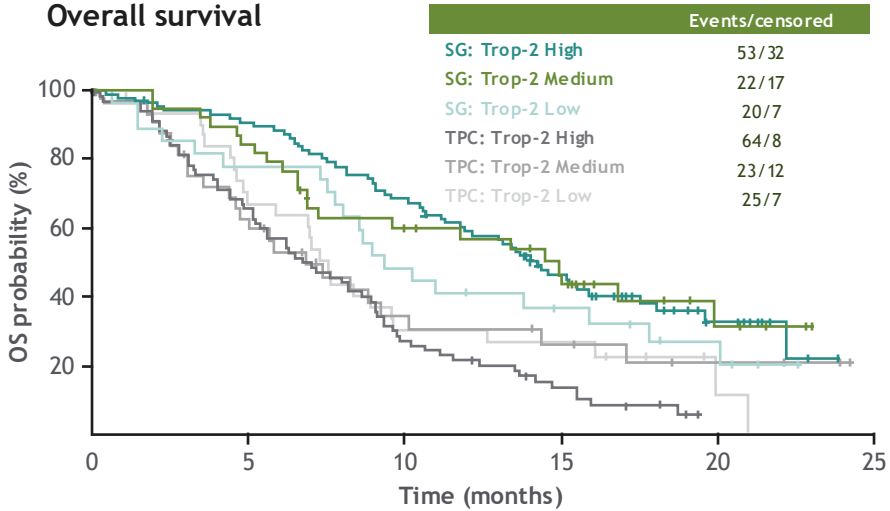
1. Carey LA, et al. NPJ Breast Cancer. 2022;8(1):72.

Clinical benefit with SG vs TPC is irrespective of level of Trop-2 expression, in previously treated mTNBC

Progression-free survival



Overall survival

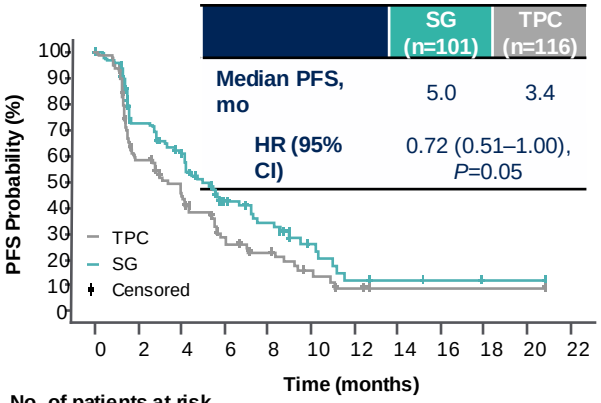


	Trop-2 High; H-score: 200-300		Trop-2 Medium; H-score: 100-200		Trop-2 Low; H-score: <100	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
Median PFS, mo (95% CI)	6.9 (5.8-7.4)	2.5 (1.5-2.9)	5.6 (2.9-8.2)	2.2 (1.4-4.3)	2.7 (1.4-5.8)	1.6 (1.4-2.7)
Median OS, mo (95% CI)	14.2 (11.3-17.5)	6.9 (5.3-8.9)	14.9 (6.9-NE)	6.9 (4.6-10.1)	9.3 (7.5-17.8)	7.6 (5.0-9.6)

Assessed in brain-metastases-negative population. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring.
H-score, histochemical score; NE, not estimable; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen-2.
1. Hurvitz SA, et al. Oral presentation. SABCS [Virtual meeting] 2020. (Abstract GS3-06).

SG Improved PFS vs TPC in HER2 IHC0 and HER2-Low Groups, Consistent with Outcomes in the ITT Population

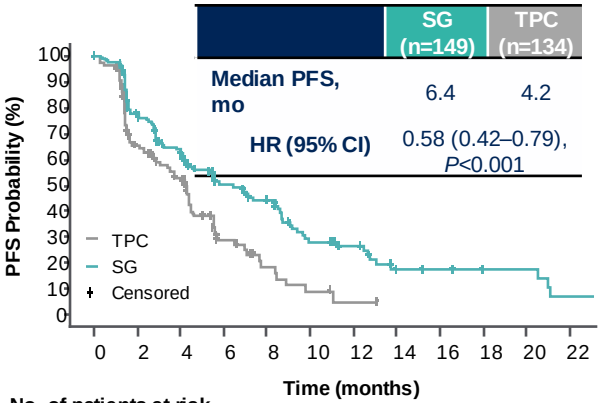
HER2 IHC0



No. of patients at risk

TPC	116	53	39	20	14	7	3	1	1	1	1	0
SG	101	64	50	27	20	9	4	3	2	1	1	0

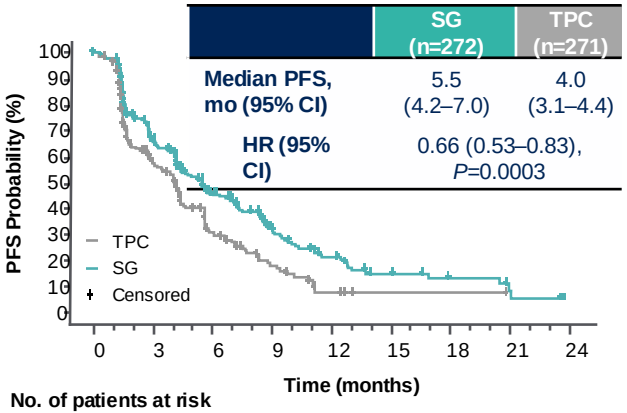
HER2-Low[a]



No. of patients at risk

TPC	134	65	43	16	8	4	1	0	0	0	0	0
SG	149	99	77	50	38	22	16	8	7	5	5	2

ITT[1]



No. of patients at risk

TPC	271	105	41	17	4	1	1	0	
SG	272	148	82	44	22	12	6	3	0

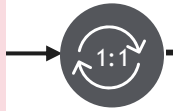
- Within the HER2-Low population, median PFS with SG vs TPC for the IHC1+ and IHC2+ subgroups was 7.0 vs 4.3 (HR, 0.57) and 5.6 vs 4.0 (HR, 0.58) months, respectively
- Median PFS in a sensitivity analysis of the HER2-Low subgroup did not show any differences compared with the ITT population

[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unavailable.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo H, et al. *J Clin Oncol*. 2022. In press.

ASCENT 03: Sacituzumab govitecan vs TPC (Gem + carbo, paclitaxel, Nab-paclitaxel) in 1L PD-L1– mTNBC, NCT05382299

1L mTNBC PD-L1–

- Previously untreated, inoperable, locally advanced, or metastatic TNBC
- PD-L1– tumors (CPS <10, IHC 22C3 assay) OR PD-L1+ tumors (CPS ≥10, IHC 22C3 assay) if treated with anti-PD-(L)1 agent in the curative setting
- ≥6 months since treatment in curative setting
- Prior anti-PD-(L)1 agent allowed in the curative setting
- PD-L1 and TNBC status centrally confirmed



N=540
(≤25% *de novo*)

Sacituzumab govitecan
10 mg/kg IV on days 1 and 8 of 21-day cycles

TPC chemotherapy
Gem + carbo: gem 1000 mg/m^2 with carbo AUC 2 IV on days 1 and 8 of 21-day cycles
Paclitaxel: 90 mg/m^2 IV on days 1, 8, and 15 of 28-day cycles
Nab-paclitaxel: 100 mg/m^2 IV on days 1, 8, and 15 of 28-day cycles

Treated until BICR-confirmed progression or unacceptable toxicity

Crossover to SG allowed after BICR-verified disease progression

Long-term follow-up

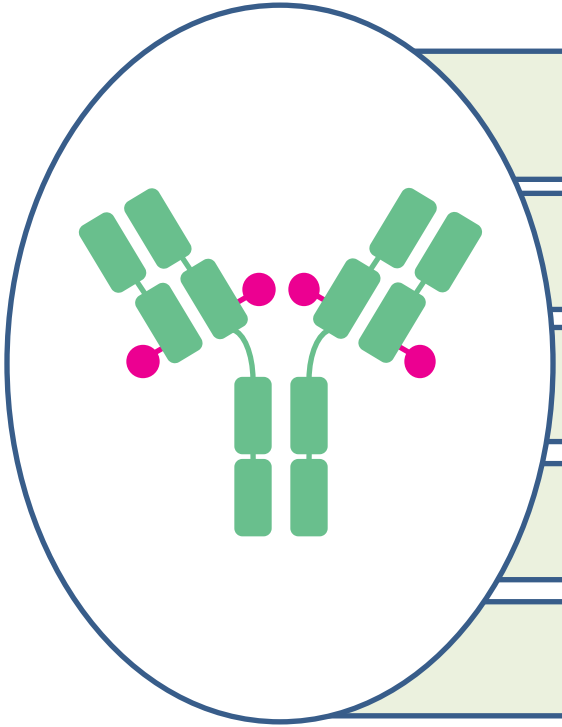
Stratification Factors:

- *De novo* vs recurrent disease within 6-12 months of treatment in the curative setting vs recurrent disease >12 months after treatment in the curative setting
- Geographic region

BICR, blinded independent central review; CPS, combined positive score; IHC, immunohistochemistry; mTNBC, metastatic triple negative breast cancer; PD-L1, programmed death ligand 1; R, randomized; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

1. EU Clinical trial register: EudraCT: 2021-005743-79. https://www.clinicaltrialsregister.eu/ctr-search/search/ Accessed April 2022.

Datopotamab Deruxtecan (Dato-DXd): TROP2 ADC IN DEVELOPMENT

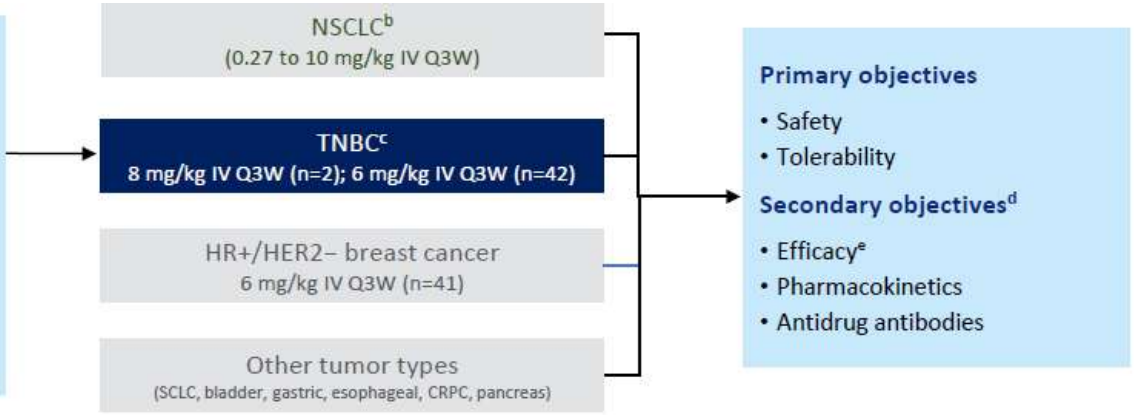


- Circulating free payload is negligible due to high stability of the linker, thereby limiting systemic exposure or nontargeted delivery of the payload[1]
- High-potency membrane-permeable payload (DXd) that requires TROP2-mediated internalization for release[2]
- DS-1062 has a DAR of 4 for optimized therapeutic index[2]
- DS-1062 has a substantially **longer half-life** than SG (≈ 5 days vs 11-14 hours), enabling a more optimal dosing regimen[3]
- SG's DLT is neutropenia, while DS-1062's DLTs are maculopapular rash and stomatitis/mucosal inflammation[4-6]

Dato-DXd in Advanced TNBC
TROPION-PanTumor01 Study

Study Design

- Advanced/unresectable or metastatic HR−/HER2− (IHC 0/1+ or IHC2+/ISH-) breast cancer
- Relapsed or progressed after local standard treatments
- Unselected for TROP2 expression[a]
- Age ≥18 years (US) or ≥20 years (Japan)
- ECOG PS 0-1
- Measurable disease per RECIST 1.1
- Stable, treated brain metastases allowed



Bardia A, et al. SABCS 2022. P6-10-03.

TROPION-PanTumor01 Study: Dato-DXd
Efficacy

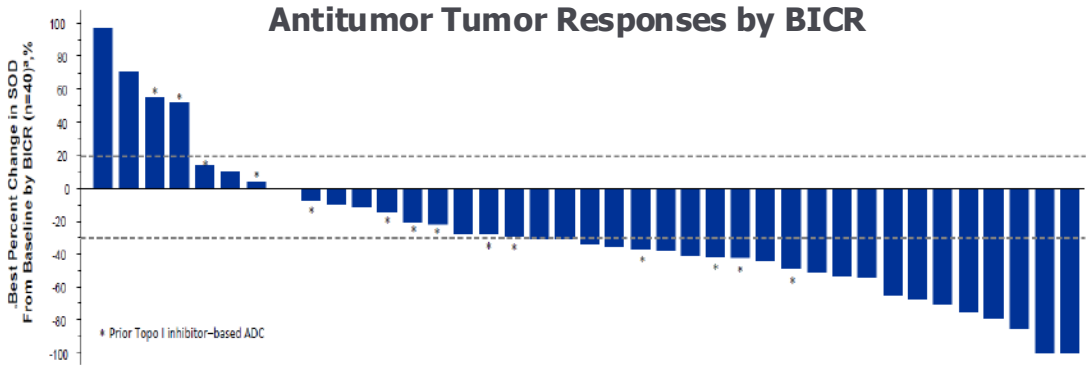
ORR by BICR:
- All patients: **32%**
- Topo I inhibitor-naive patients: **44%**

mDOR: 16.8 months in both groups

mPFS:
- All patients: 4.4 months
- Topo I inhibitor-naive patients: 7.3 months

mOS:
- All patients: 13.5 months
- Topo I inhibitor-naive patients: 14.3 months

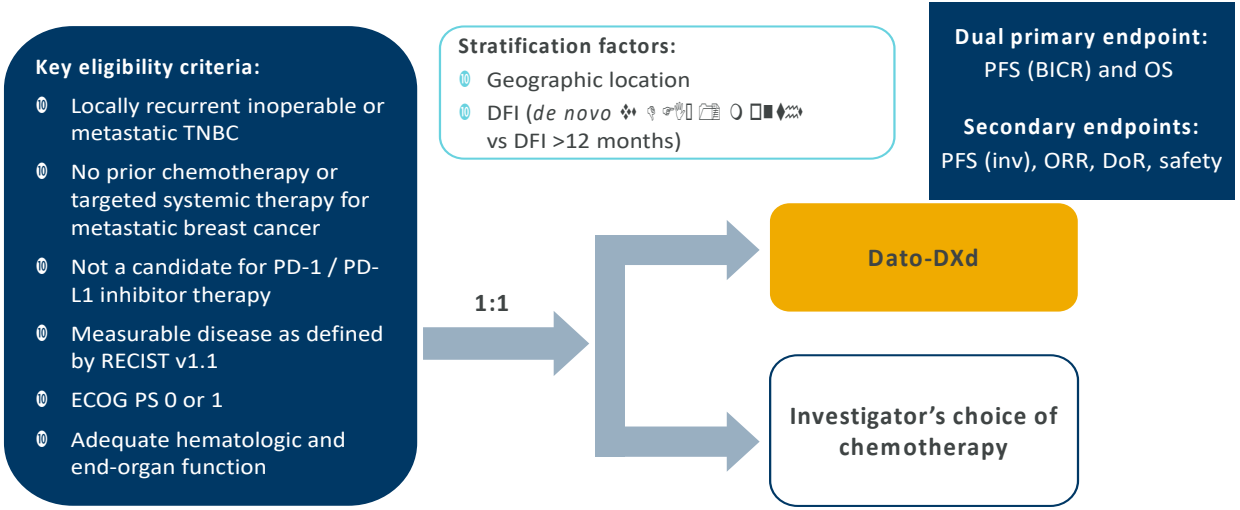
AEs:Most common TEAEs: stomatitis (73%), nausea (66%), vomiting (39%)



Bardia A, et al. SABCS 2022. P6-10-03.

Ongoing Phase 3 Clinical Trials with Dato-DXd in 1L

TROPION-Breast02[1]



- 1st line therapy for TNBC
- PD-L1 negative

1. https://clinicaltrials.gov/study/NCT05374512

Design of Sacituzumab Tirumotecan (sac-TMT)

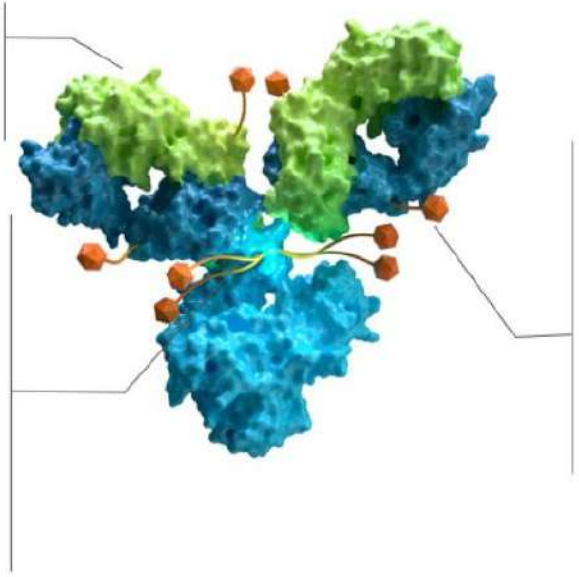
Sac-TMT is a TROP2 ADC developed with a proprietary Kthiol (pyrimidine-thiol) linker conjugated to a novel topoisomerase I inhibitor at DAR 7.4. The features of sac-TMT lead to release of the payload both in the tumor microenvironment (TME) and inside tumor cells, achieving a balance between safety and efficacy.

Antibody

- hRS7, a recombinant humanized anti-TROP2 antibody with high affinity

Linker

- **Kthiol conjugation:** irreversible coupling to improve stability of ADC
- **Payload release:** intracellular cleavage and extracellular hydrolysis in TME
- **Balanced stability:** balance between efficacy and safety to expand therapeutic window

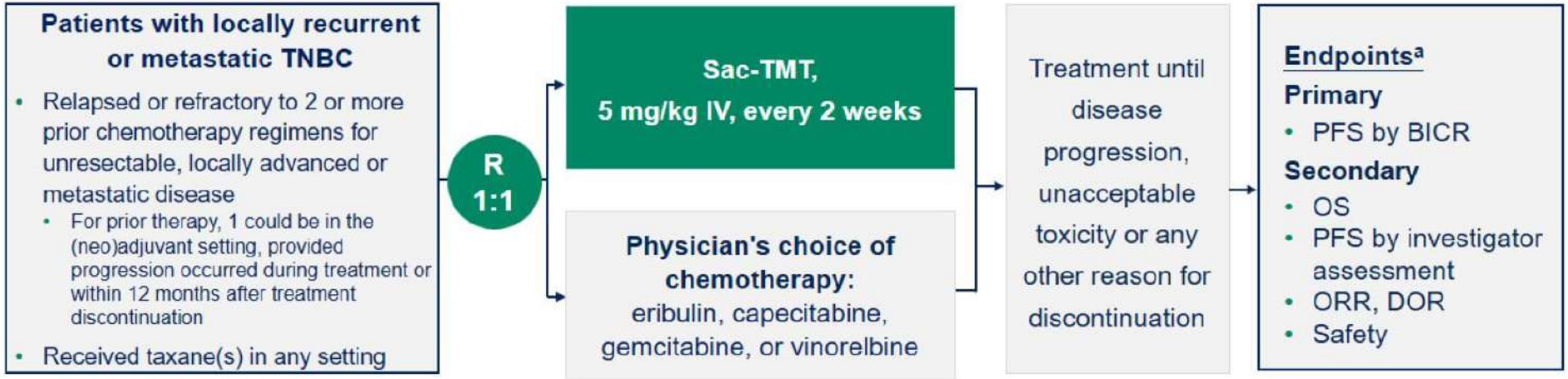


Payload

- **Novel topo I inhibitor** (a belotecan derivative), highly active
- Average **DAR: 7.4** (range: 7–8)
- **Bystander effect**
- Methylsulfonyl derivatization enhances linker stability and toxin permeability

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; TME, tumor microenvironment; TROP2, trophoblast cell surface antigen 2.

OptiTROP-Breast01: Randomized, Controlled, Open-Label Phase III Study (NCT05347134)



Stratification factors

- Line of prior therapy (2–3 vs >3)
- Presence of liver metastases (yes vs no)

Tumor assessment

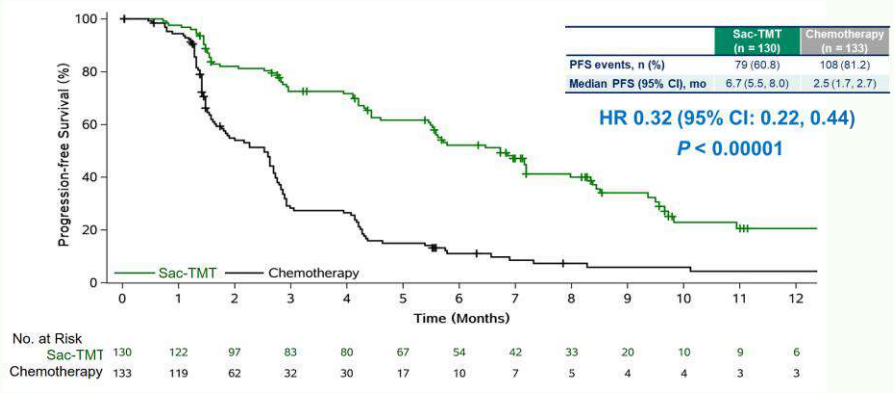
- Every 6 weeks for the first year and every 12 weeks afterward.

[a]Tumor response was assessed using RECIST version 1.1.

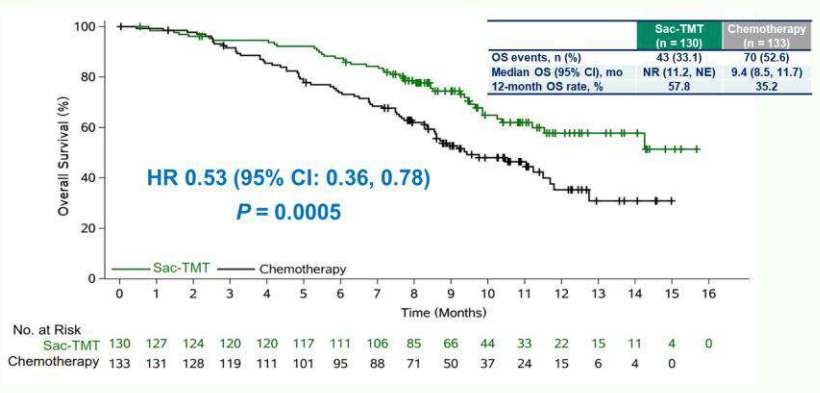
BICR, blinded independent central review; DOR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer.

OptiTROP-Breast01: Sac-TMT vs TPC in 2L+ mTNBC

PFS

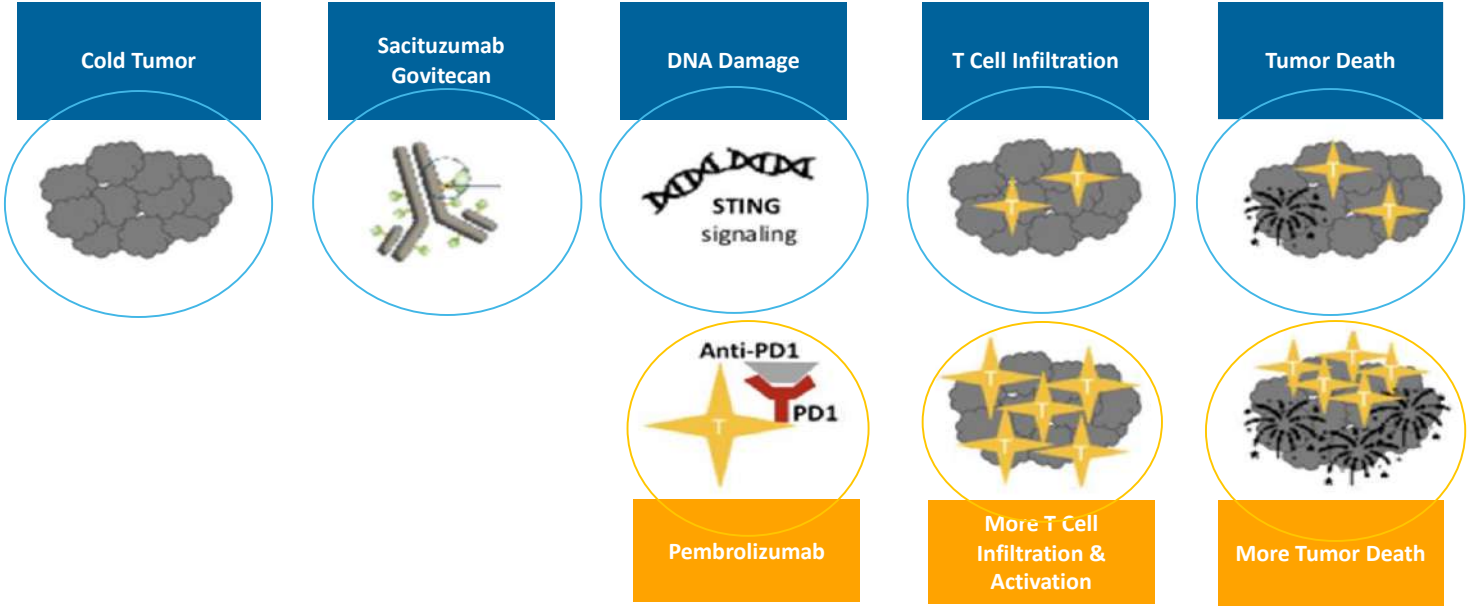


OS



Fan Y et al. ASCO 2024.Zu B et al. J Clin Oncol. 2024;42(16_suppl).

Can we combine ADCs with checkpoint inhibition?

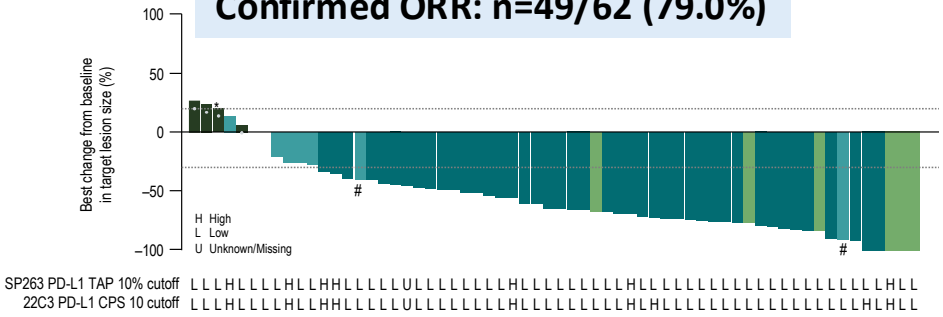


Slide courtesy of S. Tolaney

BEGONIA: ADC + ICI in 1L mTNBC

Dato-DXd + Durvalumab in mTNBC

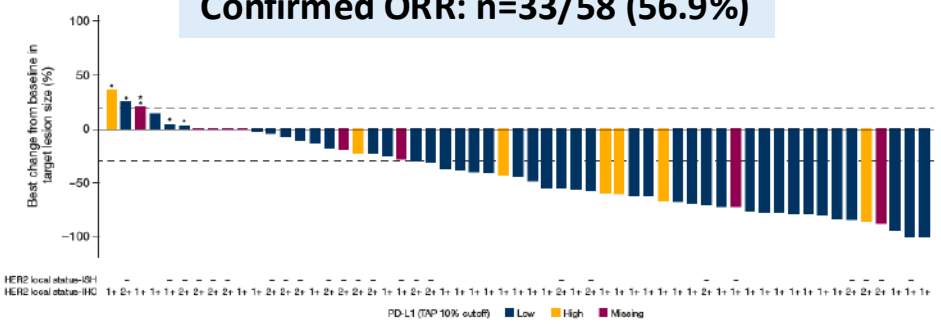
Confirmed ORR: n=49/62 (79.0%)



- Responses observed regardless of PD-L1
- No DLTs
- TRAE ILD/pneumonitis: G1, n=1; G2, n=2
- Stomatitis: most common AE leading to dose reduction (n=11)

T-DXd + Durvalumab in HER2-low mTNBC

Confirmed ORR: n=33/58 (56.9%)



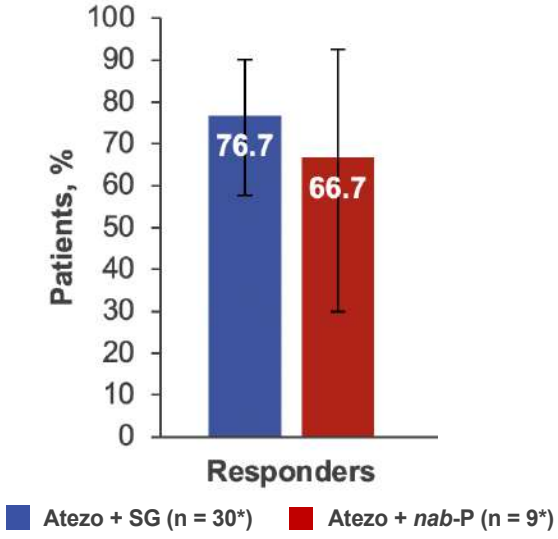
- Responses regardless of PD-L1 or HER2-low category
- No DLTs
- TRAE ILD/pneumonitis: G1, n=3; G2, n=3; G3, n=1, G5, n=1 (COVID-associated pneumonitis)

Schmid P et al. ESMO 2023; Schmid P et al. SABCS 2022.

MORPHEUS: SG + ICI in 1L mTNBC

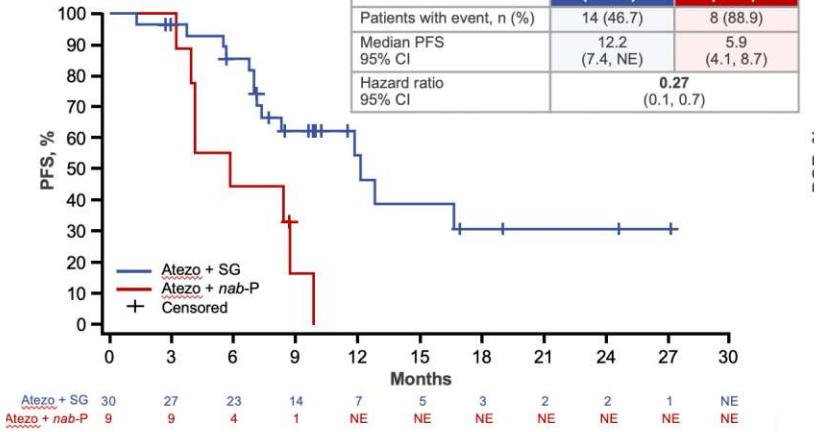
SG + Atezolizumab in 1L PD-L1+ mTNBC

Confirmed ORR = 76.7% (17% CR)



Median PFS: 12.2 mo

	Atezo + SG (n = 30)*	Atezo + *nab*-P (n = 9)*
Patients with event, n (%)	14 (46.7)	8 (88.9)
Median PFS 95% CI	12.2 (7.4, NE)	5.9 (4.1, 8.7)
Hazard ratio 95% CI	0.27 (0.1, 0.7)	

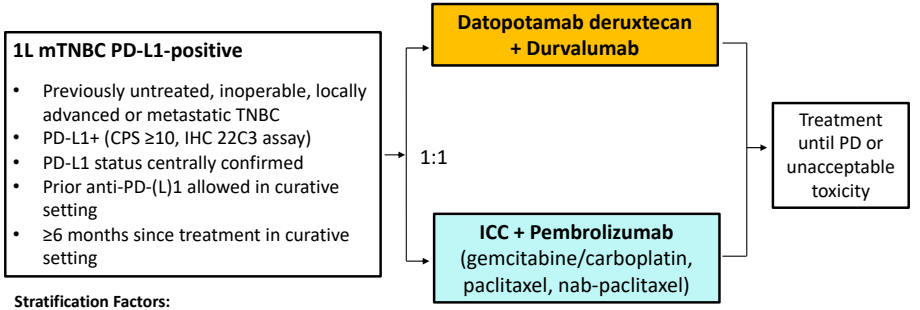


PFS data were immature at this analysis

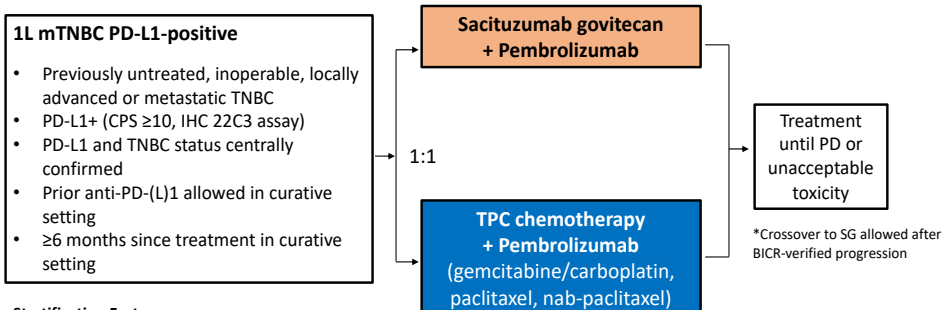
Schmid P et al. ESMO Breast 2024.

ADC + ICI in 1L PD-L1+ mTNBC

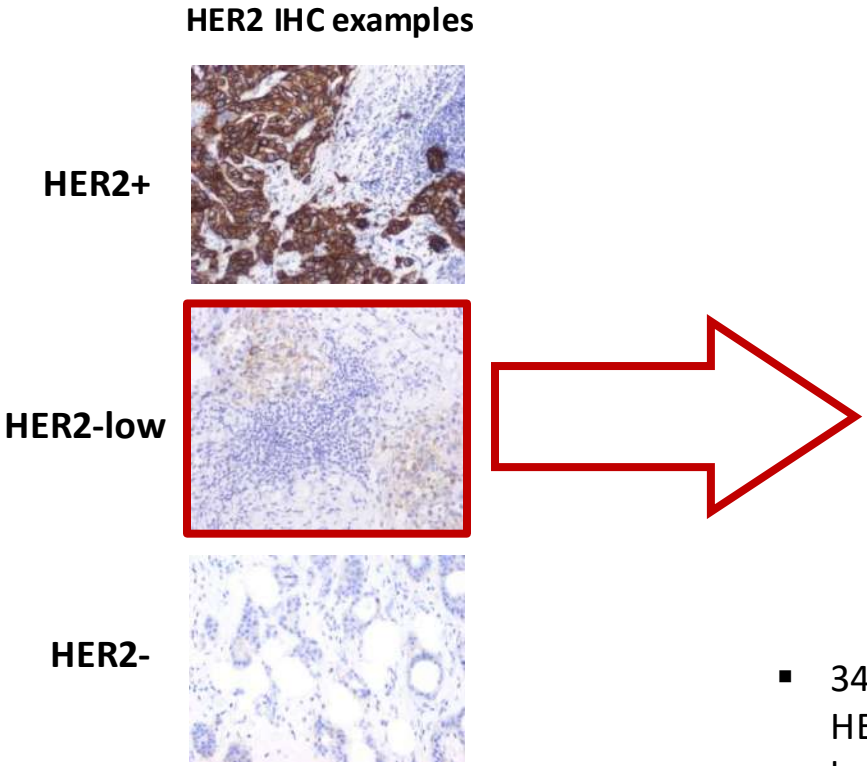
TROPION-Breast05: Dato-DXd + Durvalumab vs. TPC + Pembrolizumab in 1L PD-L1+ mTNBC

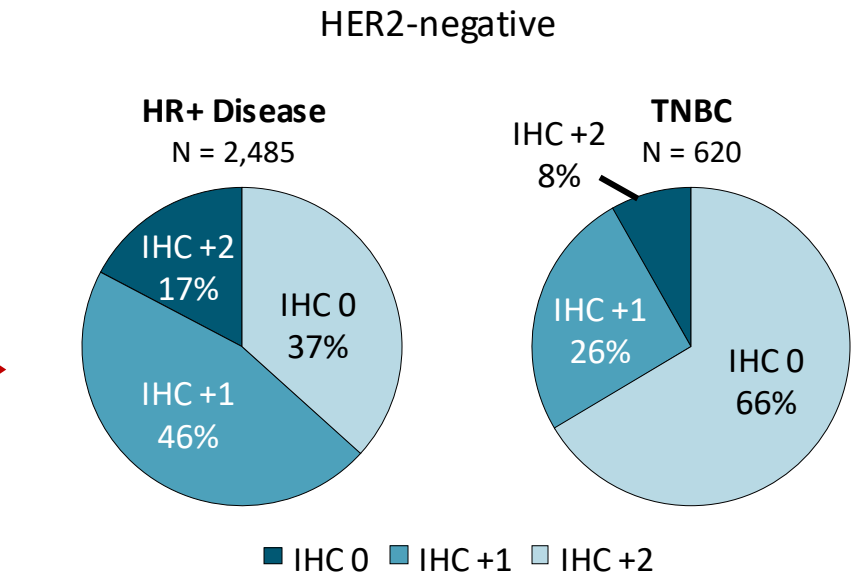


ASCENT-04: Sacituzumab govitecan + Pembrolizumab vs. TPC + Pembrolizumab in 1L PD-L1+ mTNBC



Prevalence of HER2-low by HR-status



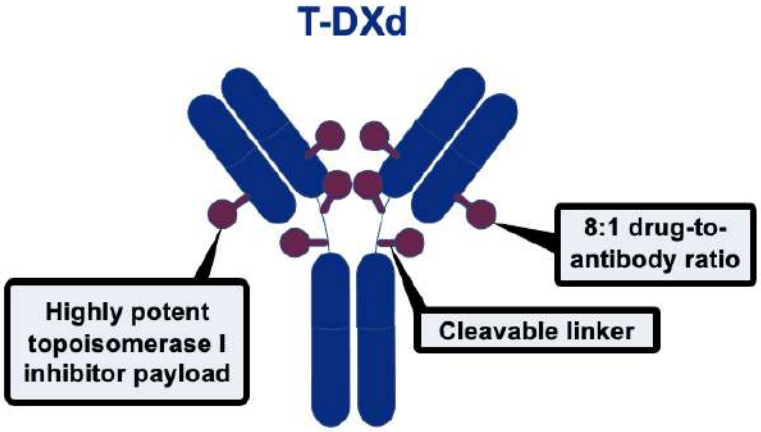


- 34% to 63% of breast cancer patients considered HER2-negative under current guidelines express low levels of HER2

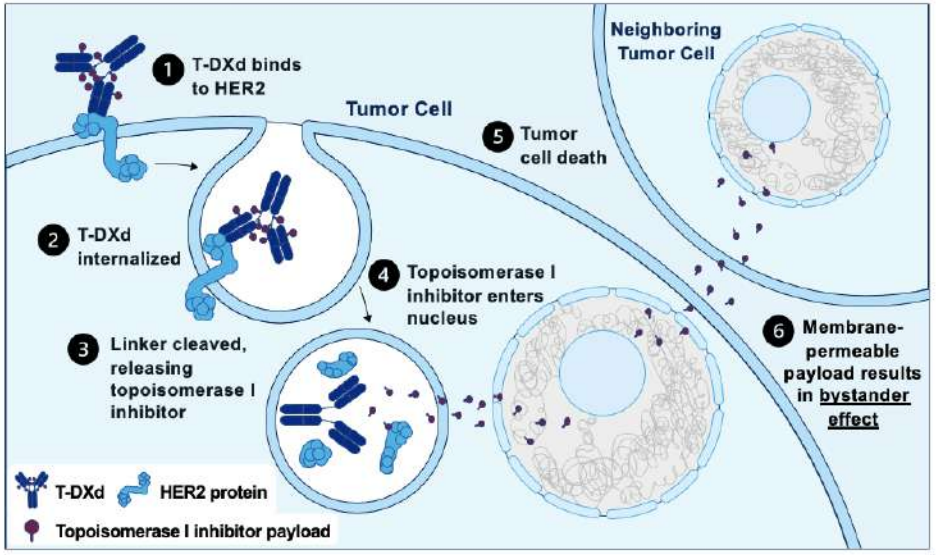
Schettini. ESMO Breast Cancer Virtual Meeting 2020. Abstr 23P. Slide courtesy of Aleix Prat.

Trastuzumab Deruxtecan (T-DXd)

STRUCTURE AND MECHANISM OF ACTION



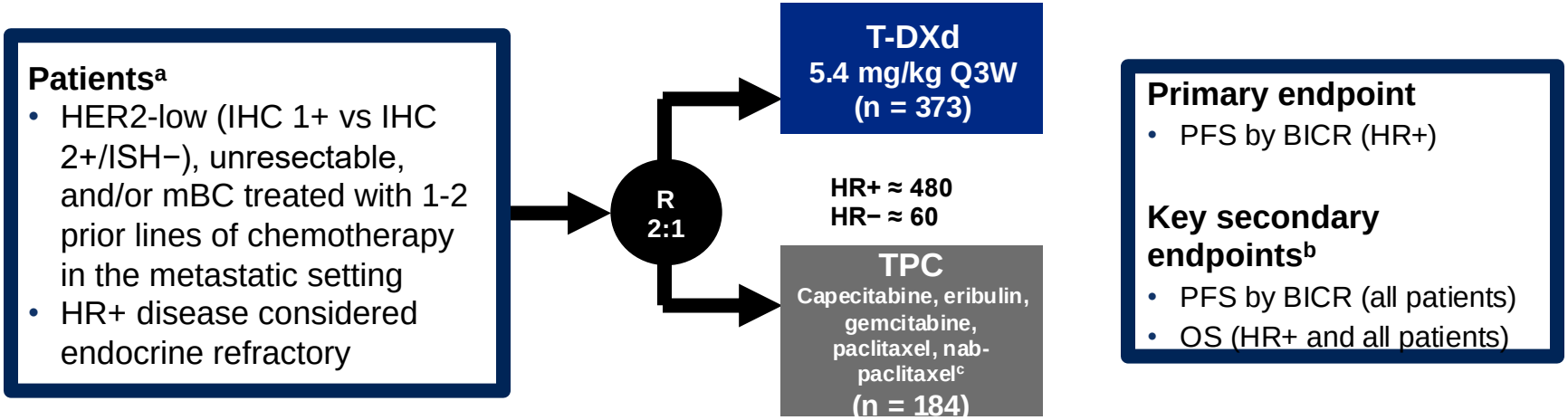
Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect



Modi S, et al. ASCO Annual Meeting 2022

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)



Stratification factors

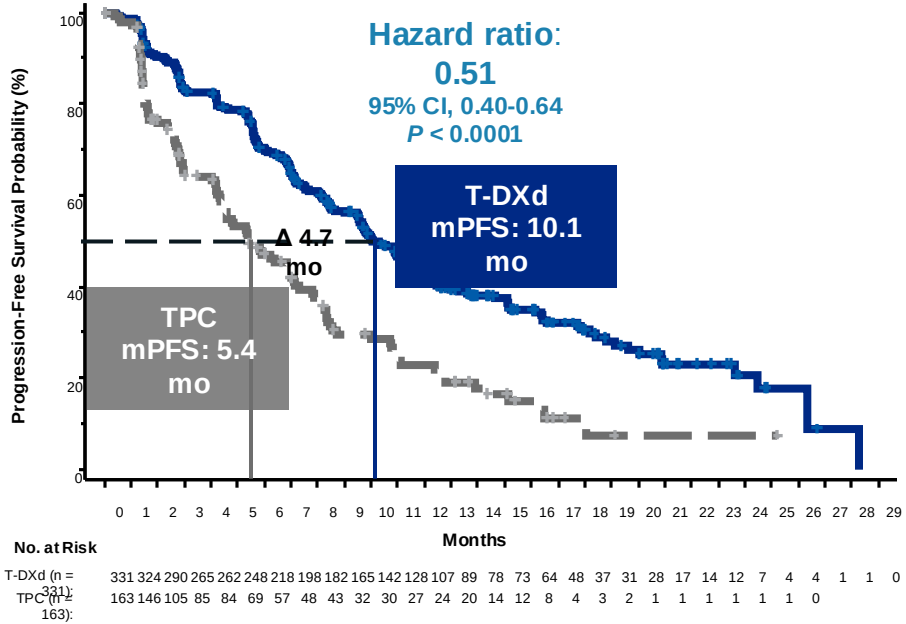
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

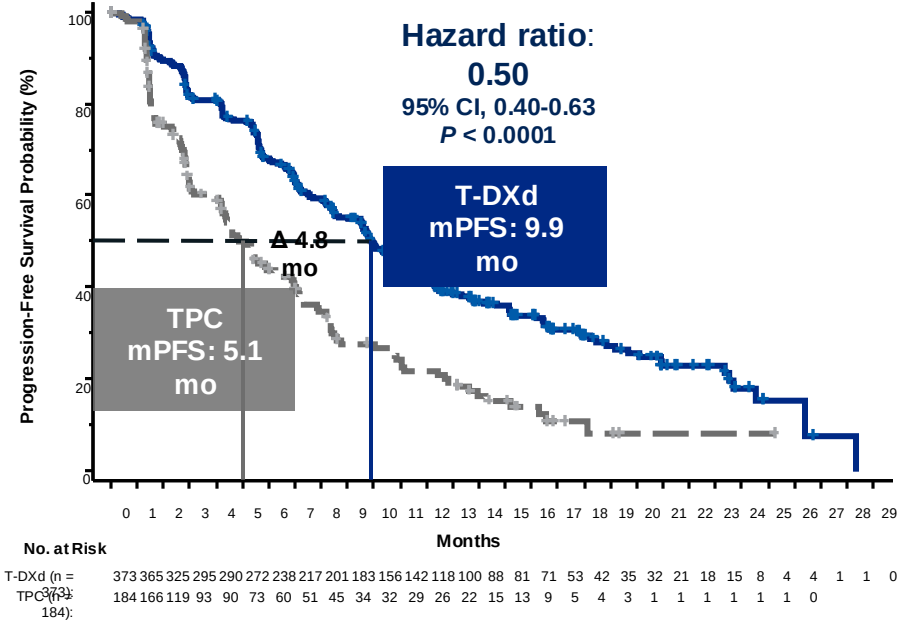
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

DB04- PFS in HR+ and All Patients

Hormone receptor–positive



All patients

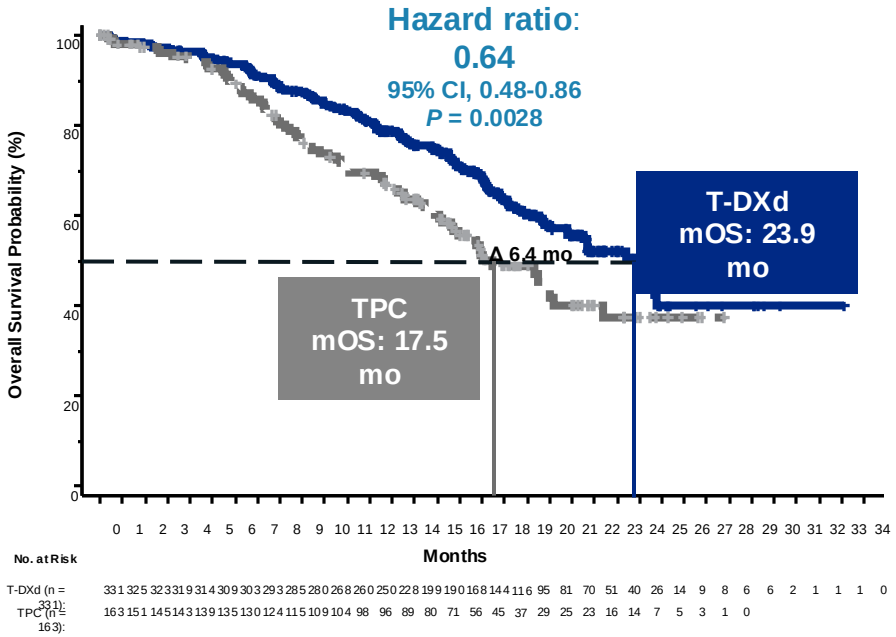


PFS by blinded independent central review.

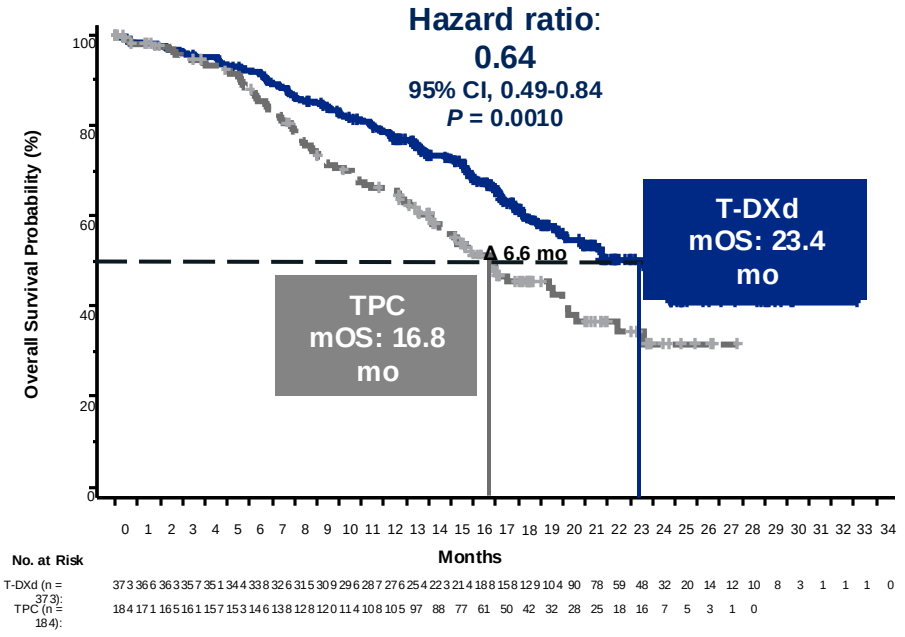
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

DB04- OS in HR+ and All Patients

Hormone receptor–positive



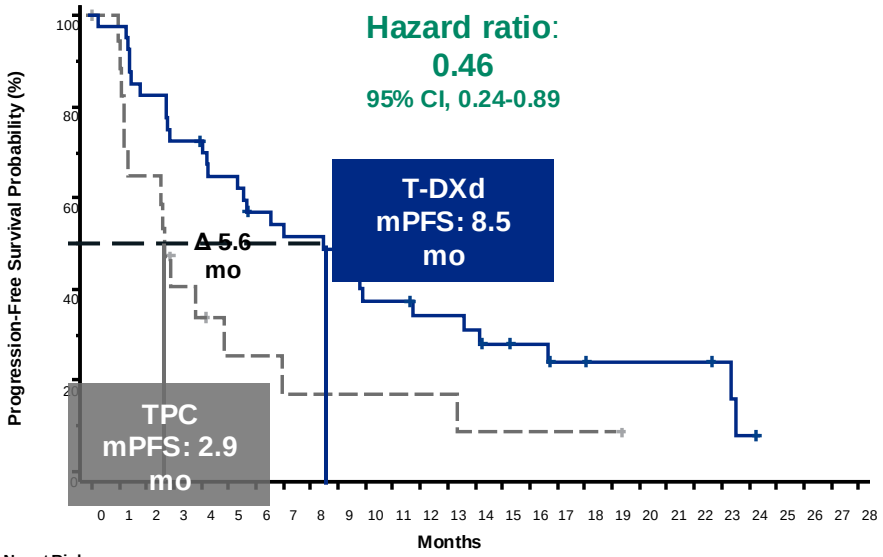
All patients



HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS and OS in HR− (Exploratory Endpoints)

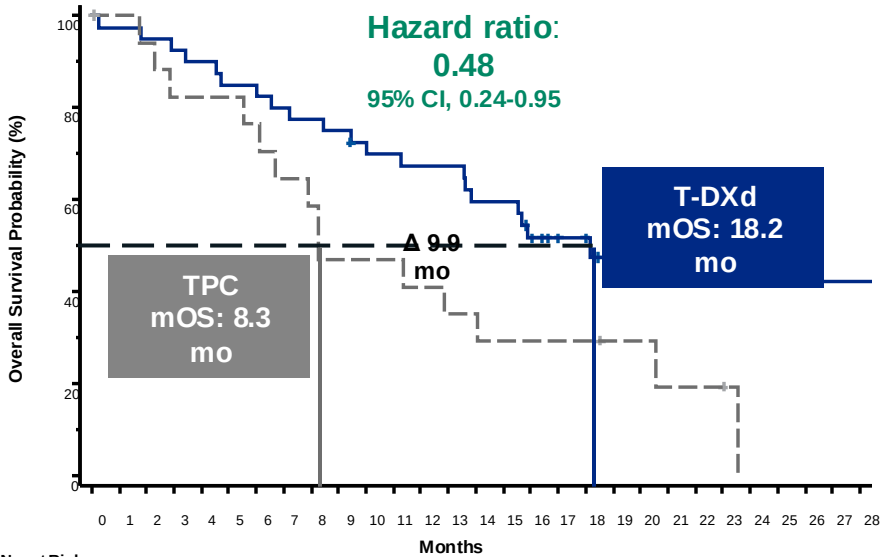
PFS



No. at Risk

T-DXd (n = 40):	40	39	33	29	28	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	3	1	0
TPC (n = 18):	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	0				

OS

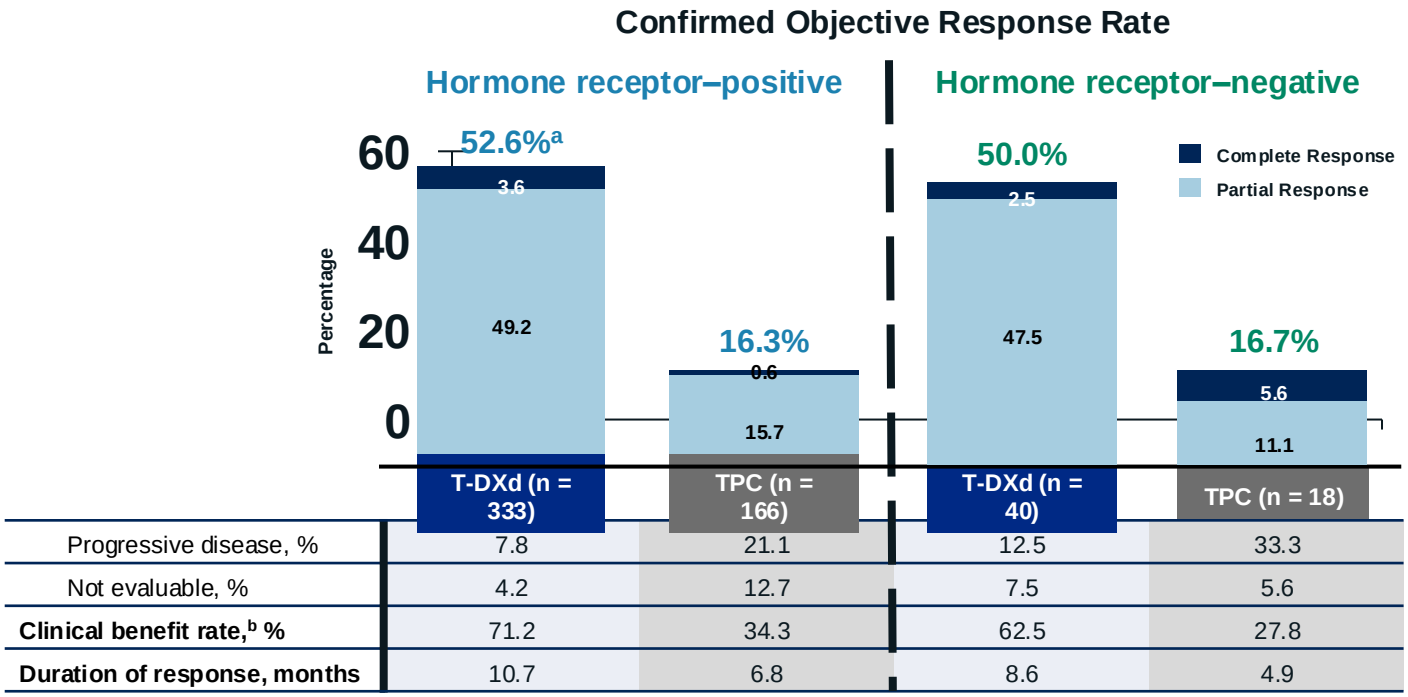


No. at Risk

T-DXd (n = 40):	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n = 18):	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based on data from the electronic data capturecorrected for misstratification.

Confirmed ORR



	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

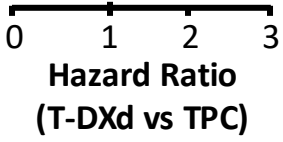
Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded independent central review.

Determining HER2-Low Status: Biopsy Considerations

- HER2-low status changes over time
- **Which timepoint** and **what type of biopsy** should be used to define a tumor as HER2 low?
- DESTINY-Breast04 required "adequate archived or recent tumor-biopsy specimens"
  - Excluded: fine-needle aspirates, other cytologic specimens, decalcified bone metastases
- In DESTINY-Breast04, T-DXd had consistent efficacy regardless of tumor sample characteristics

DESTINY-Breast04: Median PFS by Tumor Sample Characteristics

Subgroup	mPFS, Mo T-DXd	mPFS, Mo TPC	Hazard Ratio (95% CI)
Tumor Location			
Primary (n = 196)	9.6	4.2	0.47 (0.32-0.70)
Metastases (n = 359)	10.9	5.4	0.50 (0.38-0.66)
Specimen Type			
Biopsy (n = 448)	10.9	5.3	0.46 (0.35-0.59)
Excision/resection (n = 108)	7.5	3.0	0.57 (0.33-1.0)
Archival tissue (n = 482)	10.3	5.3	0.48 (0.37-0.61)
Newly obtained tissue (n = 75)	9.7	4.8	0.57 (0.30-1.1)
Specimen Collection Date	7.0	6.8	0.78 (0.24-2.54)
2013 and earlier (n = 29)	11.4	4.3	0.44 (0.28-0.70)
2014-2018 (n = 175)	9.8	5.1	0.49 (0.37-0.66)
2019 or later (n = 310)	6.6	2.8	0.54 (0.20-1.4)
Missing (n = 43)			



Practical Definition of HER2 Low
A *HER2*-nonamplified tumor showing HER2-low expression on any prior specimen in course of disease

Miglietta. NPJ Breast Cancer. 2021;7:137.
Modi. NEJM. 2022;387:9.
Prat. SABCS 2022. Abstr HER2-18.

T-DXd: Benefit even in HER2 0 DAISY TRIAL

	Total	Cohort 1 (HER2 over-expressing)	Cohort 2 (HER2 low-expressing)	Cohort 3 (HER2 non-detected)
BOR confirmed n / N [95%CI]	86 / 177 (48.6%) [41.0; 56.2]	48 / 68 (70.6%) [58.3; 81.0]	27 / 72 (37.5%) [26.4; 49.7]	11 / 37 (29.7%) [15.9; 47.0]
Median DOR (months) [95%CI]	8.5 [6.5; 9.8]	9.7 [6.8; 13]	7.6 [4.2; 9.2]	6.8 [2.8; Not reached]
Median PFS (months) [95%CI]	7.0 [6.0; 8.7]	11.1 [8.5; 14.4]	6.7 [4.4; 8.3]	4.2 [2.0; 5.7]

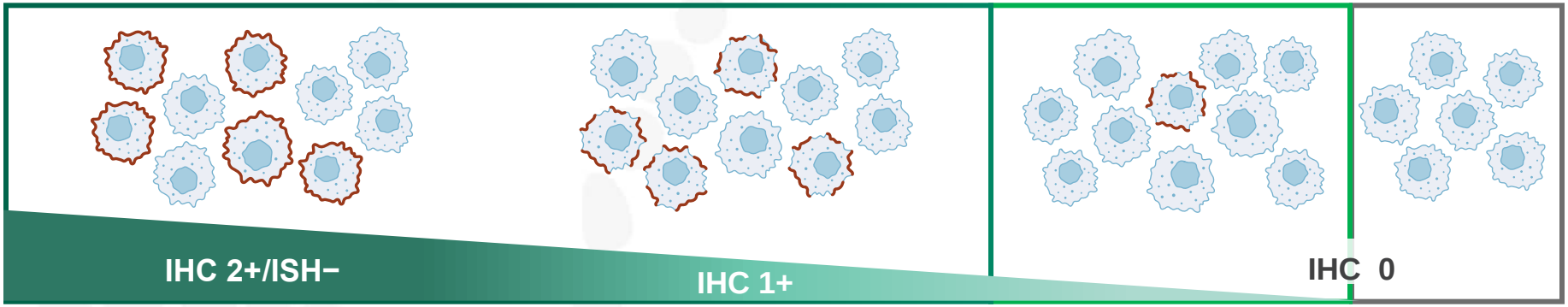
Decreasing ORR by degree of HER2 expression

Dieras V et al, SABCS 2021

What about HER2-ultralow in mTNBC?

HER2-low
~60–65%[2,3]

HER2-ultralow
~20–25%[2–4]



IHC 2+/ISH−	IHC 1+	IHC 0	
Weak-to-moderate complete membrane staining in >10% tumor cells	Faint, incomplete membrane staining in >10% tumor cells	**Faint, incomplete membrane staining in ≤10% tumor cells**	Absent / no observable membrane staining

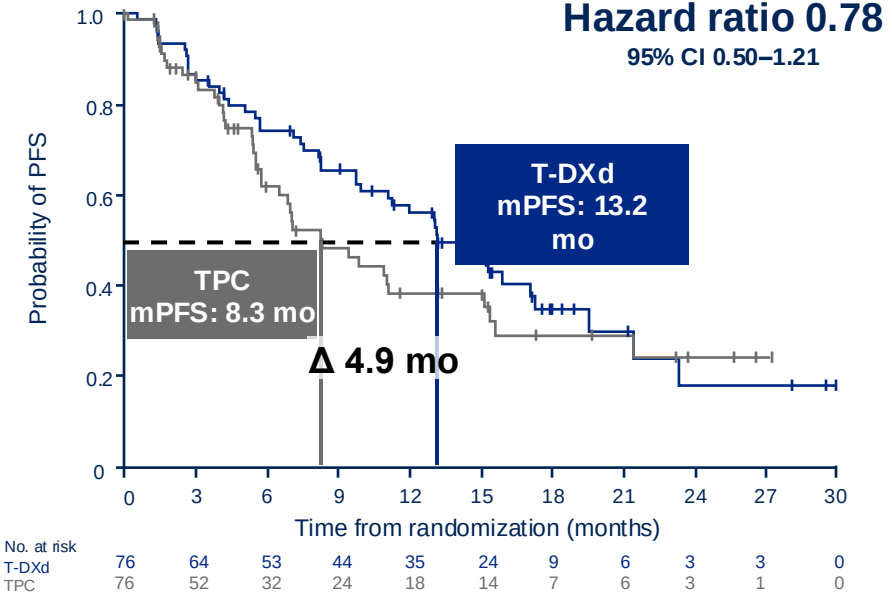
Patients with a HER2-low classification at any stage of the disease may be considered eligible for T-DXd

HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry.
Curigliano G, et al. Presented at ASCO Breast Annual Meeting 2024, 31 May–4 June. Chicago, IL. Abstract #LBA1000.

DB06 Demonstrated benefit for TDXd in HR+ HER2-ultralow

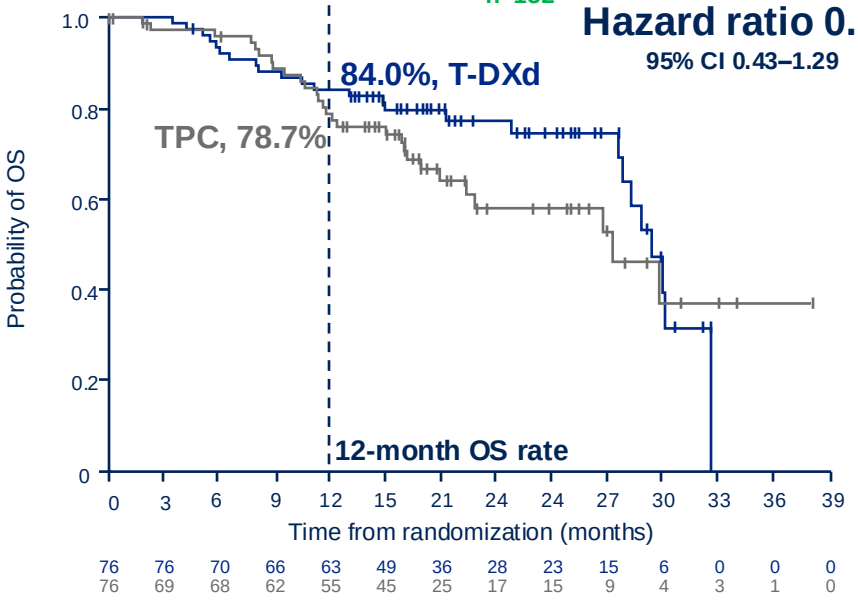
PFS (BICR)

n=152



OS*

n=152



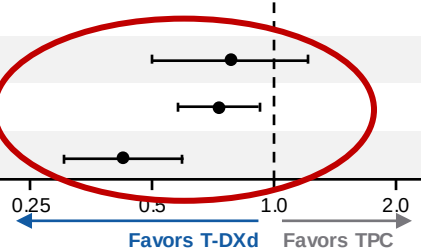
PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Curigliano G et al. *ASCO 2024*

PFS (BICR) in ITT by tumor sample characteristics and IHC score in DB06– NEED DATA IN TNBC

Subgroup	Number of events / patients (%)		Median, months (95% CI)		Hazard ratio (95% CI)
	T-DXd	TPC	T-DXd	TPC	
HER2-low (primary endpoint)	225/359 (62.7)	232/354 (65.5)	13.2 (11.4, 15.2)	8.1 (7.0, 9.0)	0.62 (0.51, 0.74)
ITT (ie HER2-low and HER2-ultralow) (secondary endpoint)	269/436 (61.7)	271/430 (63.0)	13.2 (12.0, 15.2)	8.1 (7.0, 9.0)	0.63 (0.53, 0.75)
Tumor location*					
Primary	55/93 (59.1)	63/99 (63.6)	14.9 (9.8, 19.4)	7.9 (5.8, 9.7)	0.55 (0.38, 0.80)
Metastatic	214/343 (62.4)	208/331 (62.8)	13.2 (12.0, 15.2)	8.1 (7.0, 9.5)	0.66 (0.55, 0.80)
Specimen collection type					
Biopsy	232/375 (61.9)	249/389 (64.0)	13.1 (11.3, 15.2)	8.1 (6.9, 9.3)	0.63 (0.53, 0.76)
Excision/resection	37/61 (60.7)	22/41 (53.7)	16.4 (9.7, 19.5)	8.3 (6.9, 18.1)	0.62 (0.36, 1.08)
HER2 IHC expression					
IHC 0 with membrane staining	44/76 (57.9)	39/76 (51.3)	13.2 (9.8, 17.3)	8.3 (5.8, 15.2)	0.78 (0.50, 1.21)
IHC 1+	157/239 (65.7)	150/234 (64.1)	13.1 (11.0, 15.2)	8.2 (7.1, 9.8)	0.73 (0.59, 0.92)
IHC 2+/ISH−	65/117 (55.6)	80/118 (67.8)	15.2 (12.2, 21.4)	7.0 (6.2, 8.4)	0.43 (0.31, 0.60)



*Primary tumor samples were breast or regional lymph node samples obtained from patients who had confirmed metastatic disease (ie in the metastatic setting)
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH−, in situ hybridization–negative; ITT, intent-to-treat; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Viale G et al, ESMO 2024

DESTINY-Breast15 Study Design (NCT05950945)

Patient Population

- **All Patients:**
  - mBC
  - HER2 status
    - IHC 0
    - HER2-low: IHC 1+; IHC 2+/ISH–
  - Up to 2 pLOT in metastatic setting
  - Inclusion to ensure ethnic diverse population
- **HR+ (Early Progressors) = Cohort 3**
  - Recurrent disease <2 years from initiation of adjuvant endocrine therapy **OR**
  - Progression within 12 months of completion of adjuvant CDK4/6i
  - Progression within the first 12 months of CDK4/6i in the first line metastatic setting
- **HR–**
  - 2 pLOT capped at 25% of cohort and only allowed if one of the lines included SG

Cohort 1: HR-/HER2-low mBC (n = 100)

Cohort 2: HR-/HER2 IHC0 mBC (n = 50)

Cohort 3: HR+/HER2-low mBC (n = 50)

Cohort 4: HR+/HER2 IHC0 mBC (n = 50)

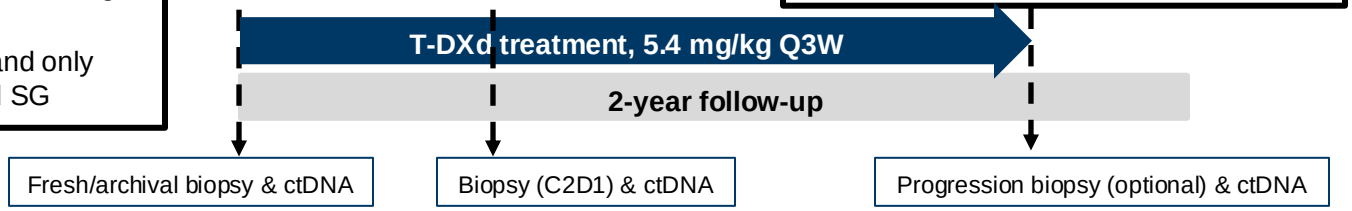
Primary Endpoint: TTNT

Key Secondary: rwPFS

Secondary Endpoints:
- TTD
- QoL/PROs
- Tolerability
- ORR

Exploratory Endpoints: pathology/ translational research plan

Descriptive stats of primary endpoint for FAS in subgroups:
- Brain mets
- Prior IO use
- Prior sacituzumab govitecan
- Bone metastases only



ctDNA, circulating tumor deoxyribonucleic acid; FAS, full analysis set; ISH, in situ hybridization; IO, immuno-oncology; ORR, objective response rate; pLOT, prior line of therapy; PROs, patient-reported outcomes; Q3W, every 3 weeks; QoL, quality of life; rwPFS, real-world progression-free survival; SG, sacituzumab govitecan; TTD, time to treatment discontinuation; TTNT, time to next treatment.

Toxicity Profiles Differ Across ADCs

	Trastuzumab deruxtecan		Datopotamab deruxtecan		Sacituzumab govitecan[a]		Sacituzumab tirumotecan	
Adverse Event	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Neutropenia	33.2	13.7	11.1	1.1	70.1	50.7	74	32
Anemia	33.2	8.1	11.1	1.1	34.0	6.3	80	28
Thrombocytopenia	23.7	5.1	-	-	6.3	0.4	41	12
Nausea	73.0	4.6	51.1	1.4	55.2	1.1	35	0
Vomiting	34.0	1.3	19.7	1.1	19.0	0.4	-	-
Diarrhea	22.4	1.1	-	-	56.7	9.3	-	-
Fatigue	47.7*	7.5*	23.6	1.7	37.7	5.6	-	-
Alopecia	37.7	N/A	36.4	N/A	45.9	N/A	-	-
Stomatitis	-	-	50.0	6.4	-	-	44	9
Dry eye	-	-	21.7	0.6	-	-	0.8	-
ILD/pneumonitis	12.1	2.2	2.5	0.6	0	0	0.8	-

N/A, not applicable; "-", not reported. *Includes fatigue, asthenia and malaise. [a] In ASCENT: pneumonitis, any grade (0.4%), grade ≥3 (0.4%); stomatitis, any grade (10.1%), grade ≥3 (0.8%).

Modi S et al. N Engl J Med 2022;387:9-20; Bardia A et al. ESMO 2023; Rugo HS et al. J Clin Oncol 2022;40(29):3365-76; Rugo HS et al. Lancet 2023;402(10411):1423-33; Bardia A et al. N Engl J Med 2021;384:1529-41; Fan Y et al. ASCO 2024.

Toxicity Profiles Differ Across ADCs

	Trastuzumab deruxtecan (DESTINY-Breast04)		Datopotamab deruxtecan (TROPION-Breast01)		Sacituzumab govitecan[a] (TROPiCS-02)		Sacituzumab tirumotecan (OptiTROP-Breast01)	
Adverse Event	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Neutropenia	33.2	13.7	11.1	1.1	**70.1**	**50.7**	**74**	**32**
Anemia	33.2	8.1	11.1	1.1	34.0	6.3	80	28
Thrombocytopenia	**23.7**	**5.1**	-	-	6.3	0.4	**41**	**12**
Nausea	73.0	4.6	51.1	1.4	55.2	1.1	35	0
Vomiting	34.0	1.3	19.7	1.1	19.0	0.4	-	-
Diarrhea	22.4	1.1	-	-	56.7	9.3	-	-
Fatigue	47.7*	7.5*	23.6	1.7	37.7	5.6	-	-
Alopecia	37.7	N/A	36.4	N/A	45.9	N/A	-	-
Stomatitis	-	-	50.0	6.4	-	-	44	9
Dry eye	-	-	21.7	0.6	-	-	0.8	-
ILD/pneumonitis	12.1	2.2	2.5	0.6	0	0	0.8	-

Abbreviations: "-", not reported. *Included fatigue, asthenia and malaise. [a] In ASCENT: pneumonitis, any grade (0.4%), grade ≥3 (0.4%); stomatitis, any grade (0.1%), grade ≥3 (0.8%).

Modi S et al. N Engl J Med 2022;387:9-20; Bardia A et al. ESMO 2023; Rugo HS et al. J Clin Oncol 2022;40(29):3365-76; Rugo HS et al. Lancet 2023;402(10411):1423-33; Bardia A et al. N Engl J Med 2021;384:1529-41; Fan Y et al. ASCO 2024.

Toxicity Profiles Differ Across ADCs

	Trastuzumab deruxtecan (DESTINY-Breast04)		Datopotamab deruxtecan (TROPION-Breast01)		Sacituzumab govitecan[a] (TROPiCS-02)		Sacituzumab tirumotecan (OptiTROP-Breast01)	
Adverse Event	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Neutropenia	33.2	13.7	11.1	1.1	70.1	50.7	74	32
Anemia	33.2	8.1	11.1	1.1	34.0	6.3	80	28
Thrombocytopenia	23.7	5.1	-	-	6.3	0.4	41	12
Nausea	**73.0**	**4.6**	51.1	1.4	55.2	1.1	35	0
Vomiting	**34.0**	**1.3**	19.7	1.1	19.0	0.4	-	-
Diarrhea	22.4	1.1	-	-	**56.7**	**9.3**	-	-
Fatigue	47.7*	7.5*	23.6	1.7	37.7	5.6	-	-
Alopecia	37.7	N/A	36.4	N/A	45.9	N/A	-	-
Stomatitis	-	-	50.0	6.4	-	-	44	9
Dry eye	-	-	21.7	0.6	-	-	0.8	-
ILD/pneumonitis	12.1	2.2	2.5	0.6	0	0	0.8	-

Abbreviations: "-", not reported. *Included fatigue, asthenia and malaise. [a] In ASCENT: pneumonitis, any grade (0.4%), grade ≥3 (0.4%); stomatitis, any grade (0.1%), grade ≥3 (0.8%).

Modi S et al. N Engl J Med 2022;387:9-20; Bardia A et al. ESMO 2023; Rugo HS et al. J Clin Oncol 2022;40(29):3365-76; Rugo HS et al. Lancet 2023;402(10411):1423-33; Bardia A et al. N Engl J Med 2021;384:1529-41; Fan Y et al. ASCO 2024.

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Neutropenia	33.2	13.7	11.1	1.1	70.1	50.7	74	32
Anemia	33.2	8.1	11.1	1.1	34.0	6.3	80	28
Thrombocytopenia	23.7	5.1	-	-	6.3	0.4	41	12
Nausea	73.0	4.6	51.1	1.4	55.2	1.1	35	0
Vomiting	34.0	1.3	19.7	1.1	19.0	0.4	-	-
Diarrhea	22.4	1.1	-	-	56.7	9.3	-	-
Fatigue	47.7*	7.5*	23.6	1.7	37.7	5.6	-	-
Alopecia	37.7	N/A	36.4	N/A	45.9	N/A	-	-
Stomatitis	-	-	**50.0**	**6.4**	-	-	**44**	**9**
Dry eye	-	-	**21.7**	**0.6**	-	-	0.8	-
ILD/pneumonitis	**12.1**	**2.2**	2.5	0.6	0	0	0.8	-

Abbreviations: "-", not reported. *Included fatigue, asthenia and malaise. [a] In ASCENT: pneumonitis, any grade (0.4%), grade ≥3 (0.4%); stomatitis, any grade (0.1%), grade ≥3 (0.8%).

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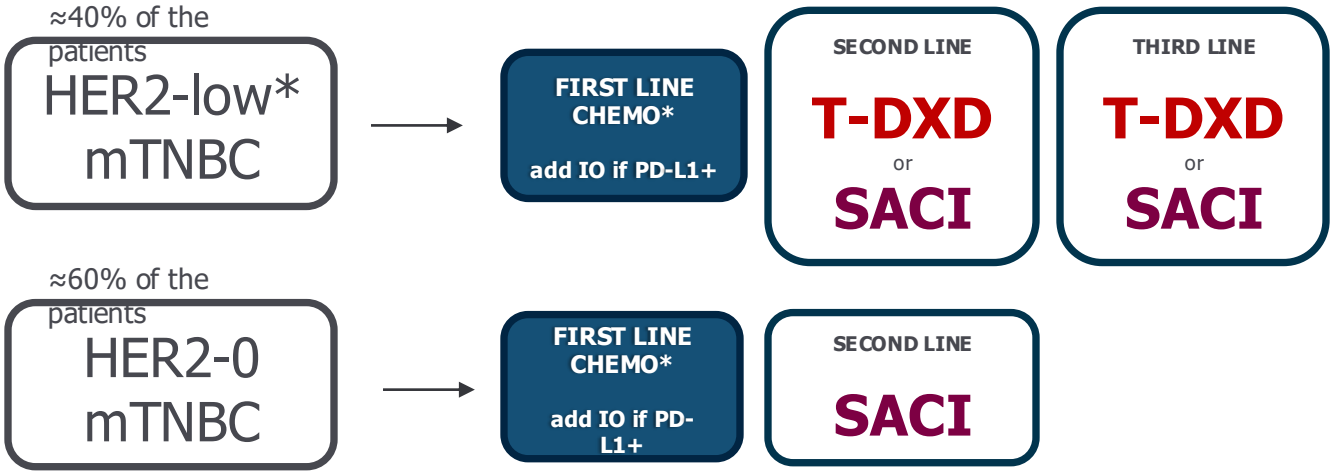
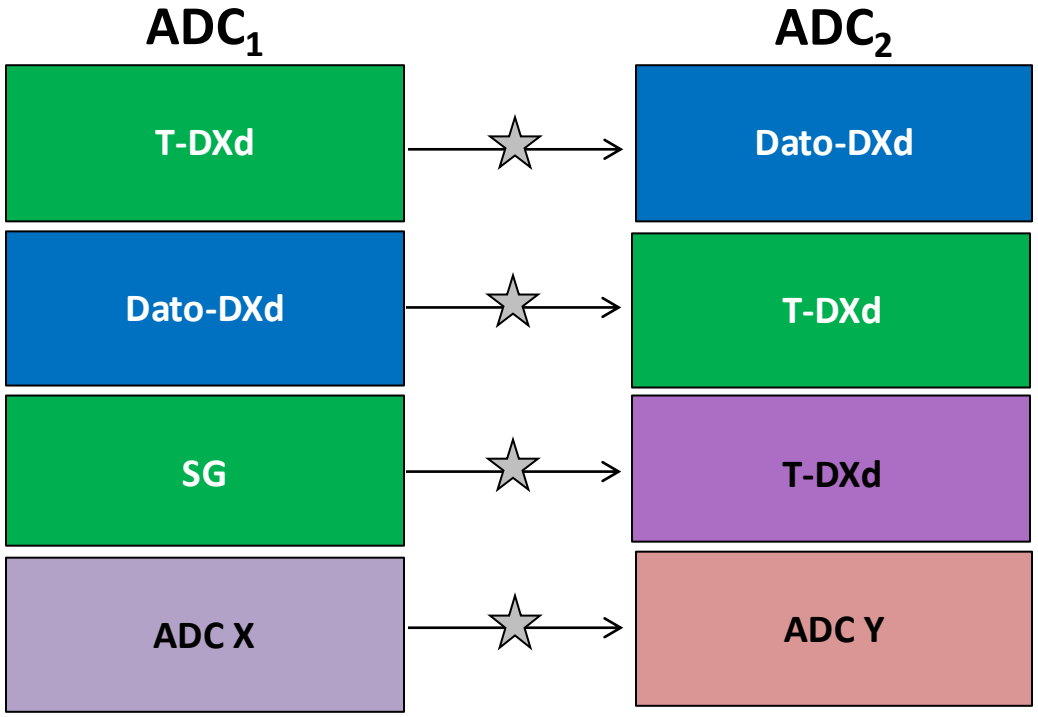
Dana-Farber Cancer Institute | Brigham and Women's Hospital | Harvard Medical School

Treatment of mTNBC with ADCs



*PARP inhibitors can be considered in the first through third line setting for BRCAm patients

Critical Question: How will ADCs work in sequence?

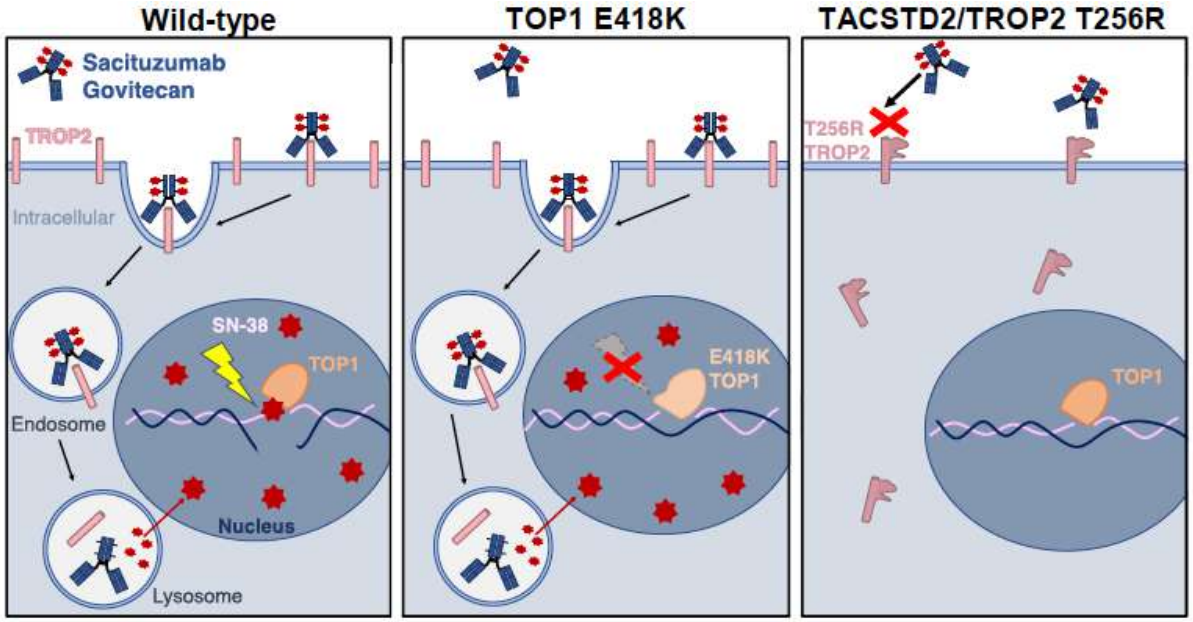


Retrospective studies evaluating ADC sequencing

	Population	ADC 1	ADC 2	
Abelman[1]	N=68 HR+: 44%, TNBC 56% Prior lines of tx: 3 to 7	mTTP: 5.4 mos	mTTP: 2.5 mos	TOP1 variant may drive resistance
Raghavendra[2]	N=33 Subtype data not available	PFS: SG = 4.6 mos PFS: TDxd = 7.6 mos	PFS SG → TDxd: 5.5 mos PFS TDxd → SG: 2.4 mos	Suggest superiority of T-Dxd but HR status is unknown
Huppert[3]	N=84 HR+/HER2low: 67% HR-/HER2low: 33% Prior lines of tx: 2 to 4.5	TTNT SG → TDxd: • HR+ = 8 mos • HR- = 7.8 mos TTNT TDxd → SG: • HR+ = 5.5 mos • HR- = undetermined	TTNT SG → TDxd: • HR+ = 3.7mos • HR- = 2.8 mos TTNT TDxd → SG: • HR+ = 2.7 mos • HR- = undetermined	All HER2low expressing longer PFS with ADC1 than ADC2
Poumeaud[4]	N=179 HR+/HER2low: 69% HR-/HER2low: 31% Prior lines of tx: 3 to 5 Prior ADC use: 64% received SG as ADC1	mPFS = 4.5 mos mPFS HR+/HER2low = 2.7 mos (TDxd) mPFS HR-/HER2low = 4.9 mos (SG)	SG→TDxd PFS2 = 3.1 mos TDxd→SG PFS2 = 2.2 mos	In multivariate analysis SG→TDxd was associated with improved outcomes 50% primary resistance to ADC2

1. Abelman R, et al. Presented at SABCS 2023. Poster #PS08-03
2. Raghavendra AS, et al. Presented at SABCS 2023. Poster #PS08-01
3. Huppert L, et al. Presented at SABCS 2023. Poster #PS08-04
4. Poumeaud F, et al. Presented at SABCS 2023. Poster #PS08-02.

Mechanisms of resistance to ADC



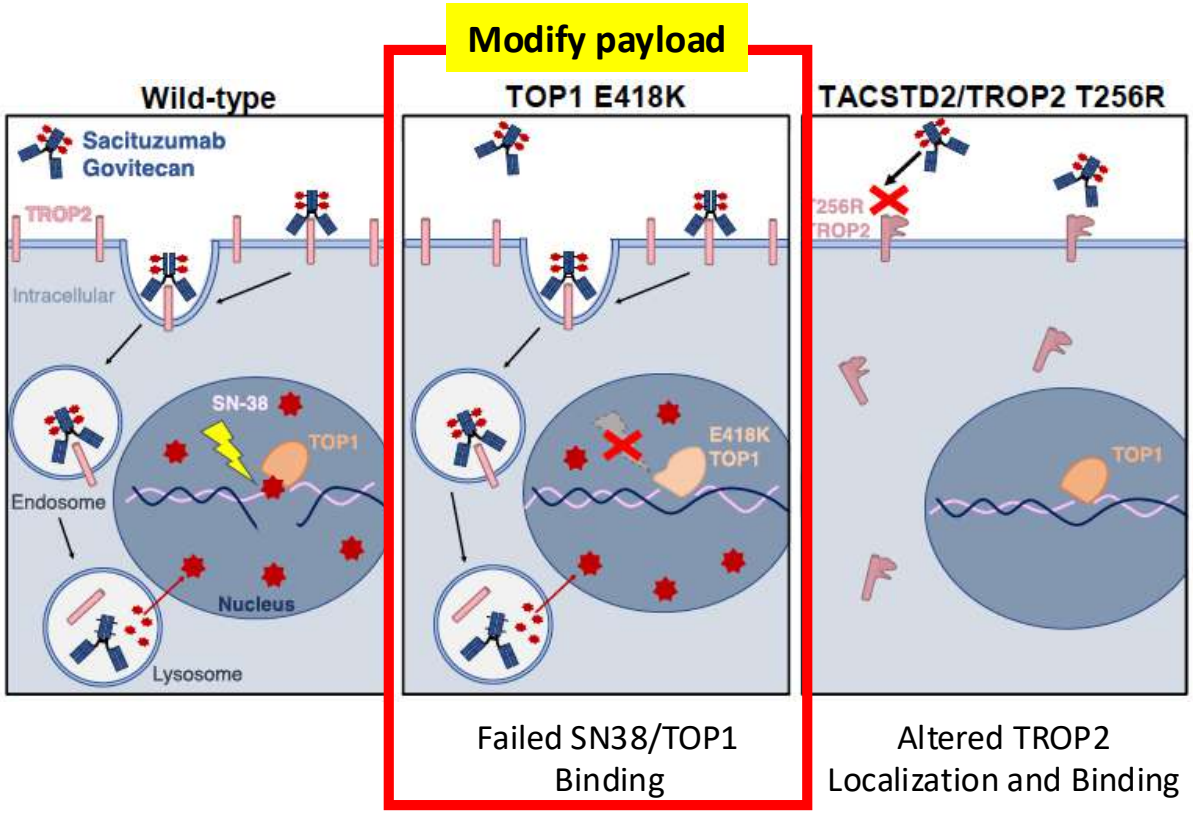
Failed SN38/TOP1 Binding

Altered TROP2 Localization and Binding

- Analysis of tumor tissue from 3 patients pre- and post Sacituzumab treatment
- Two acquired resistance mechanisms identified
  - Mutations in TOP1 leading to decreased binding of SN38 with topoisomerase I
  - Mutation in TROP2 leading to decreased binding of SG and decreased cell surface expression

Modified Coates et al. Cancer Discov 2021

Mechanisms of resistance to ADC



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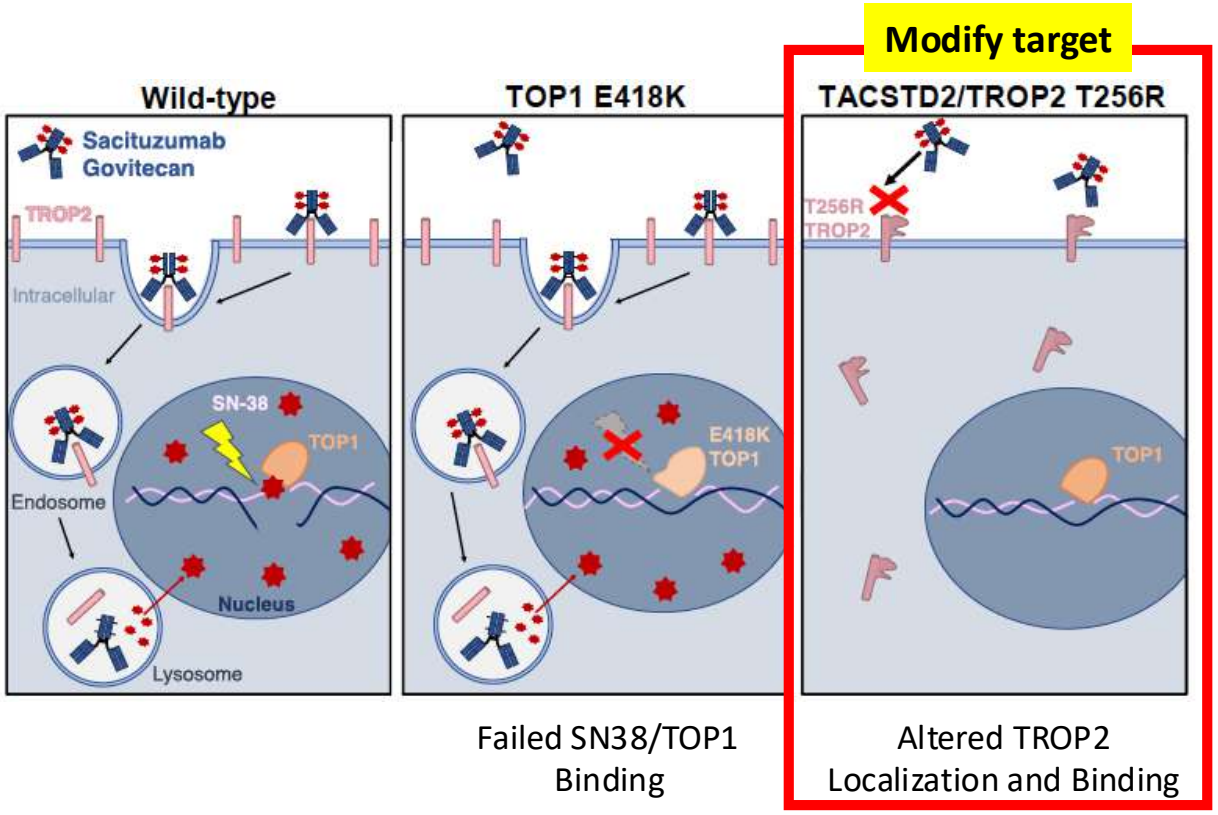
Modified Coates et al. Cancer Discov 2021

Mechanisms of resistance to ADC



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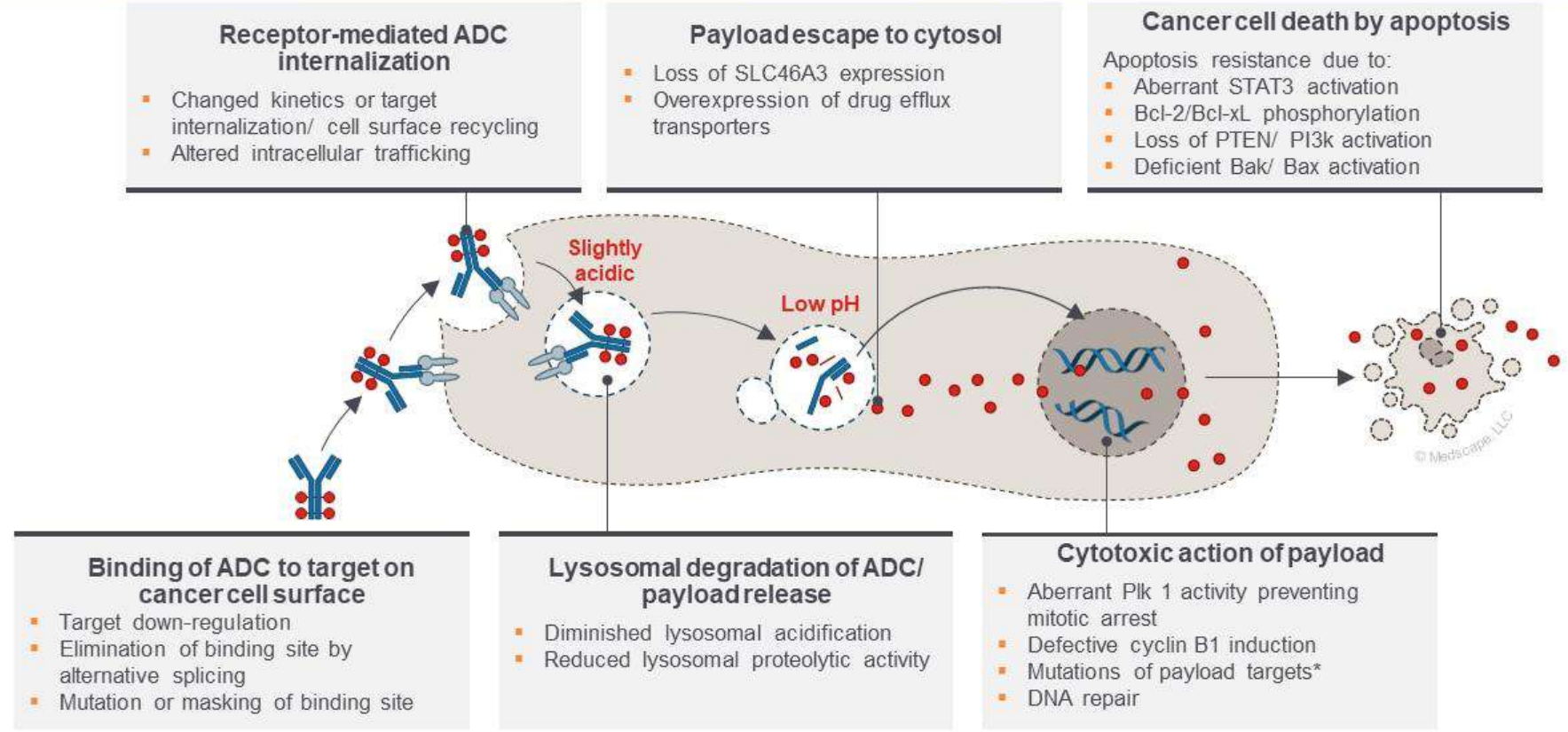
Modified Coates et al. Cancer Discov 2021

Mechanisms of resistance to ADC (0verview)



Collins DM, et al. Cancers (Basel) 2019

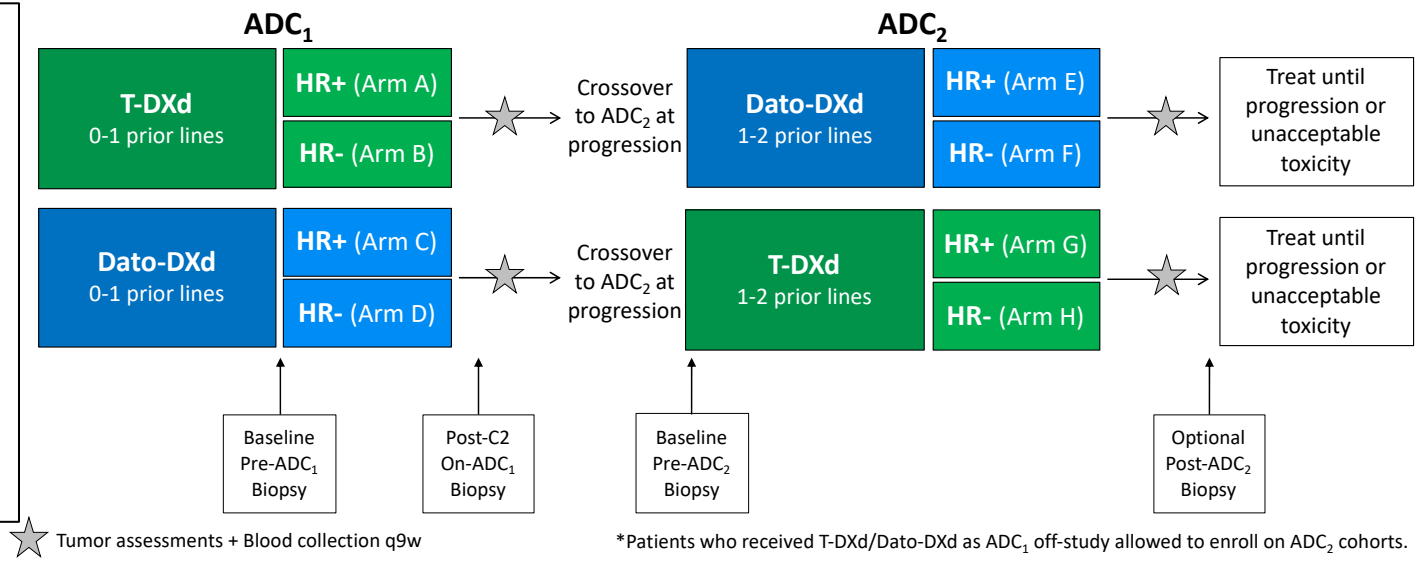
TReatment of ADC-Refractory Breast CancEr with Dato-**DXd** or T-**DXd:** TRADE-DXd

Primary endpoint (ADC_1, ADC_2): ORR
Secondary endpoints: PFS, OS, CBR, TTOR, DOR

Eligibility:

- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low breast cancer (any prior primary or metastatic tumor) defined as IHC 1+ or 2+/ISH non-amplified
- Most recent pathology: HER2 IHC 0 or HER2-low
- Measurable disease
- No prior topo-I inhibitor-based therapy

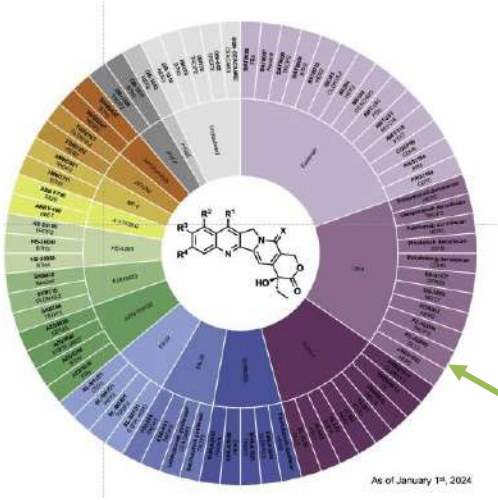
Allocation 1:1 to T-DXd or Dato-DXd as ADC_1



PI: A. Garrido-Castro

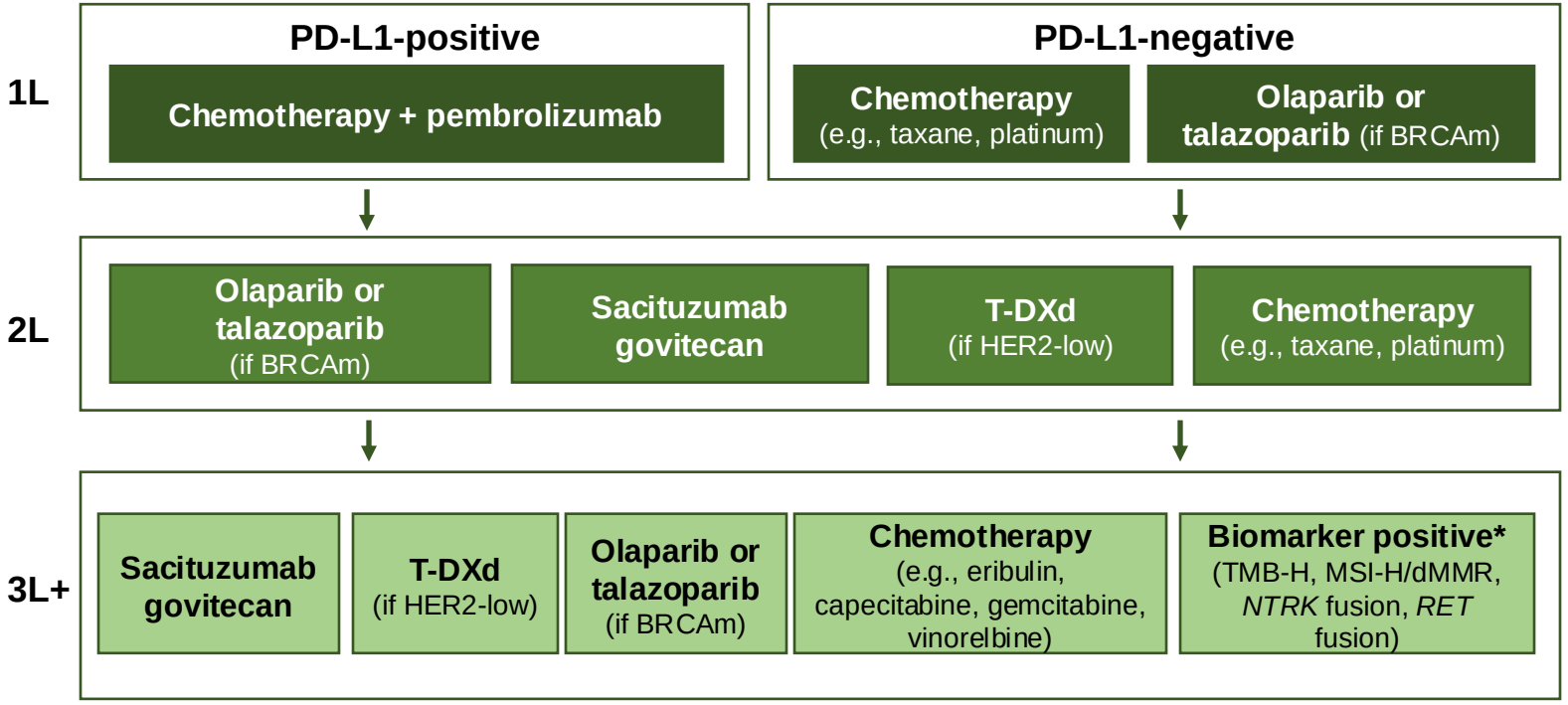
More ADCs to come: Payload differentiation for ADCs

	FDA approved	In development	Discontinued
Auristatin	**4**	**58**	**49**
Camptothecin	**2**	**83**	**2**
Maytansinoid	**2**	**7**	**32**
PBD	**1**	**6**	**26**
Calicheamicin	**2**	**None**	**4**
Tubulysin		7	3
Eribulin		5	None
Undisclosed		4	2
TLR		3	3
Duocarmycin		2	3
STING		2	None
Glucocorticoid		1	2
Amanitine		1	1
Hemiasterlin		1	1
KSP inhibitor	None	1	None
PROTAC		1	None
Anthracycline			5
DNA-damaging agent			4
Vinca alkaloid			3
Antimetabolite		None	2
BCL-XL			2
Antibiotic			1
Docetaxel			1



Colombo R., Tarantino P et al. submitted

Treatment Algorithm for Metastatic TNBC



*TMB-H: Pembrolizumab; MSI-H: Pembrolizumab, Dostarlimab; *NTRK* fusion: Larotrectinib, Entrectinib; *RET* fusion: Selpercatinib

Slide courtesy of Ana C. Garrido-Castro, M.D.

ESMO DEEP DIVE:
BREAST CANCER

IS THERE MORE TO COME FROM IMMUNOTHERAPY?

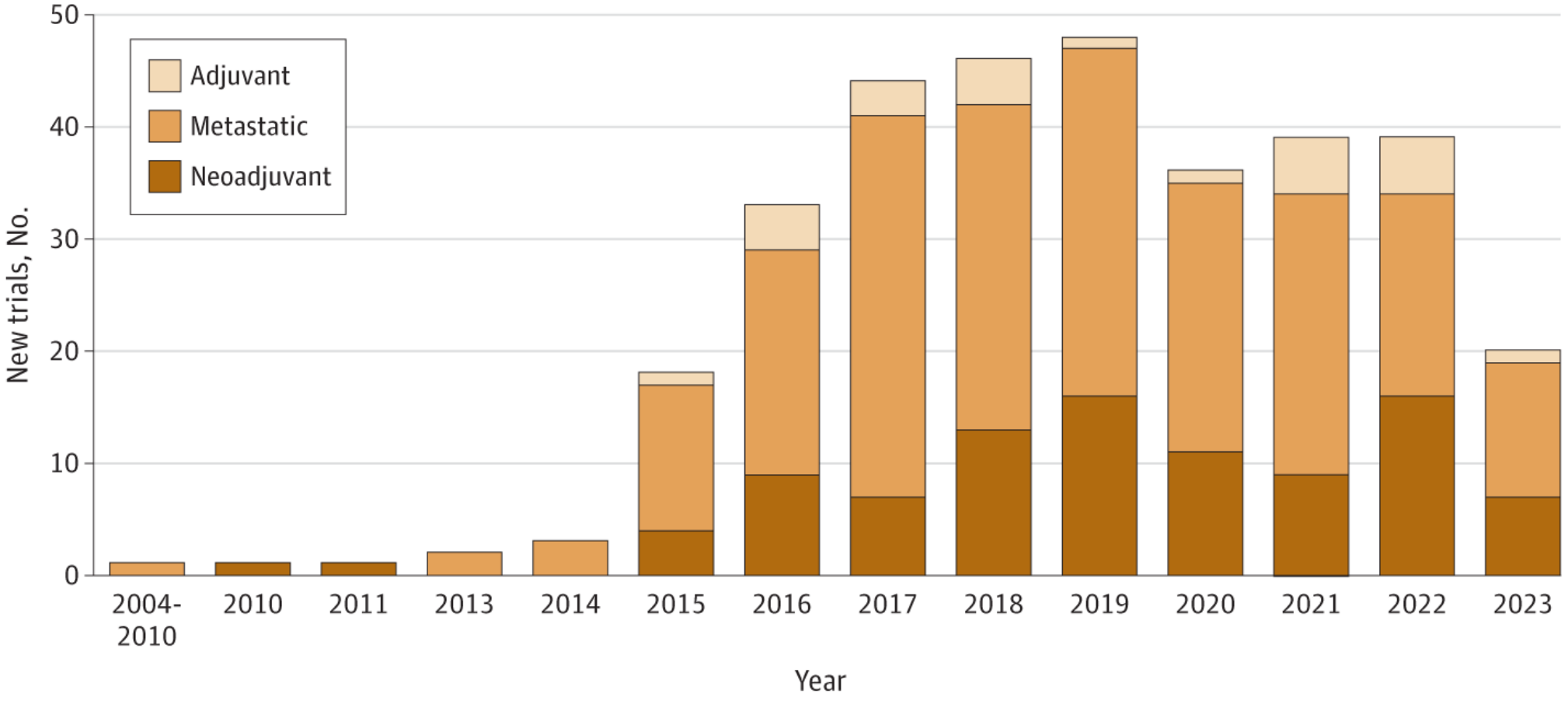
Giampaolo Bianchini
Head Breast Cancer Group - IRCCS Ospedale San Raffaele
Associate Professor - Università Vita-Salute San Raffaele
Milan, Italy

DECLARATION OF INTERESTS

Personal fundings:
Consultancy: Roche, AstraZeneca, MSD, Daiichi Sankyo, Gilead, Seagen
Honoraria and/or Advisory Board: Roche, AstraZeneca, Daiichi Sankyo, Lilly, MSD, EISAI, Gilead, Seagen, Novartis, Pfizer, Menarini/Stemline, Exact Science, Agendia
Support for attending meetings and/or travel: Roche, Pfizer, MSD, Novartis, Daiichi Sankyo, AstraZeneca

Institutional fundings:
Research grant from Gilead

COMPLETED, ONGOING AND PLANNED TRIALS OF IMMUNOTHERAPIES IN PATIENTS WITH BREAST CANCER

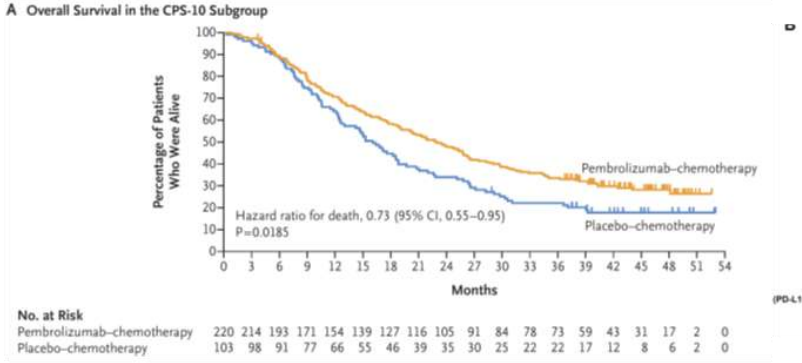


Mariani M JAMA Netw Open 2024

PRESENT: IMMUNOTHERAPY IN ADVANCED TNBC

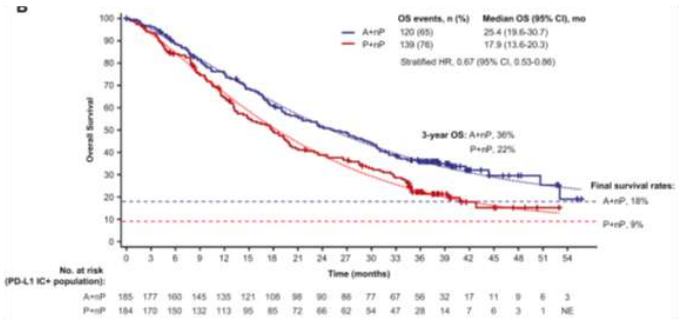
Advanced TNBC (1st line)
(only for "PD-L1" positive patients)

KEYNOTE 355
(CPS≥10, 22C3 Dako)



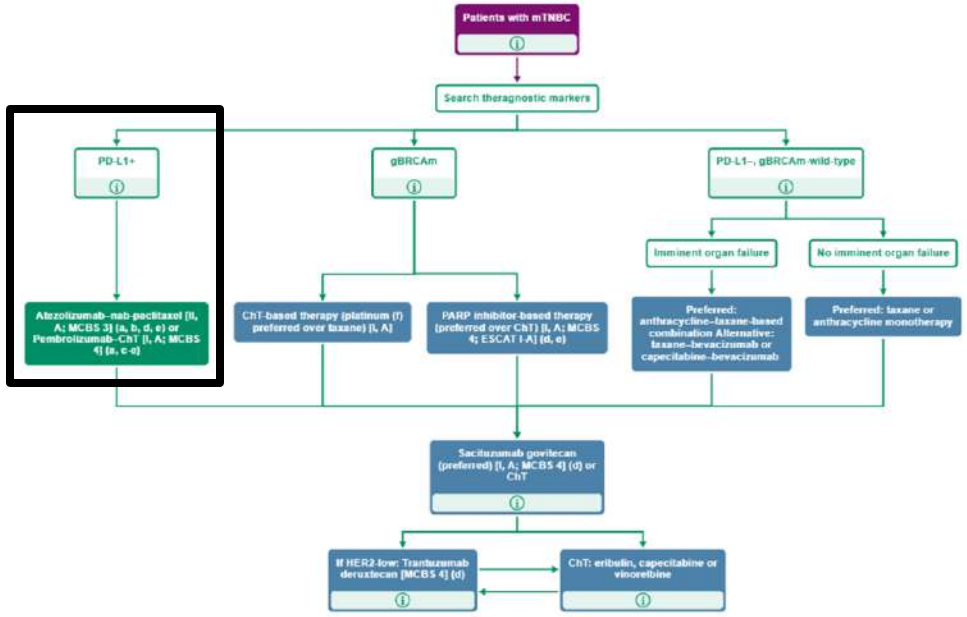
Cortes J NEJM 2022

IMpassion130
(IC≥1, SP142 Ventana)



Emens LA Ann Oncol 2021

ESMO guidelines
(Advanced TNBC)



G Curigliano, Living Guidelines, ESMO Breast 2023

Long-lasting benefit limited to few patients
ONLY in combination with few chemotherapies (taxanes and carbo/gem)
ONLY for 'PD-L1' positive tumors

PRESENT: IMMUNOTHERAPY IN ADVANCED TNBC

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(only for "PD-L1" positive patients)

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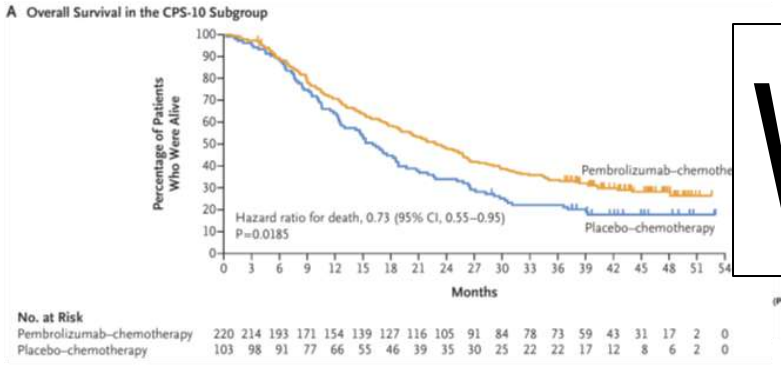

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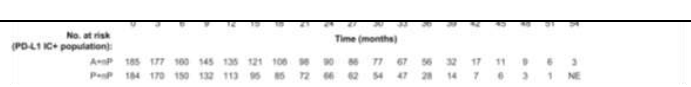
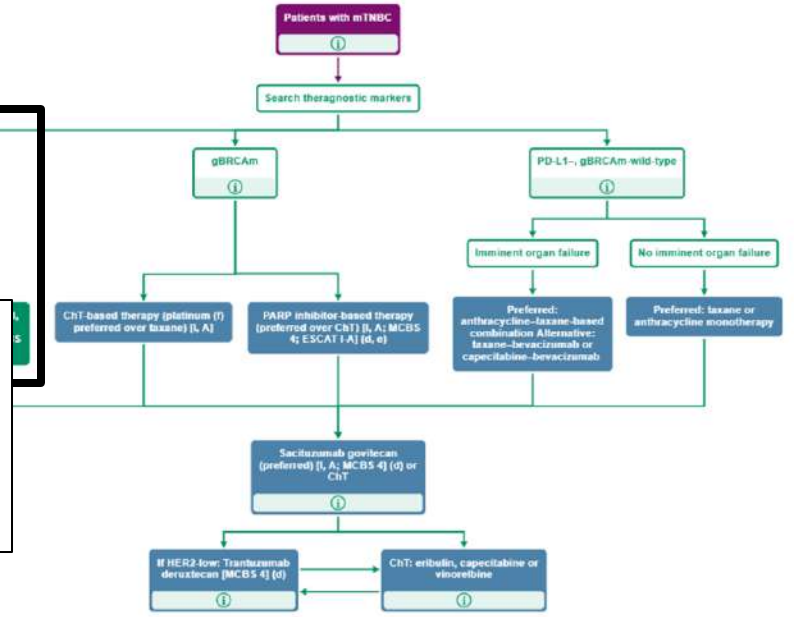


Emens LA Ann Oncol 2021

What's next?

ESMO guidelines
(Advanced TNBC)



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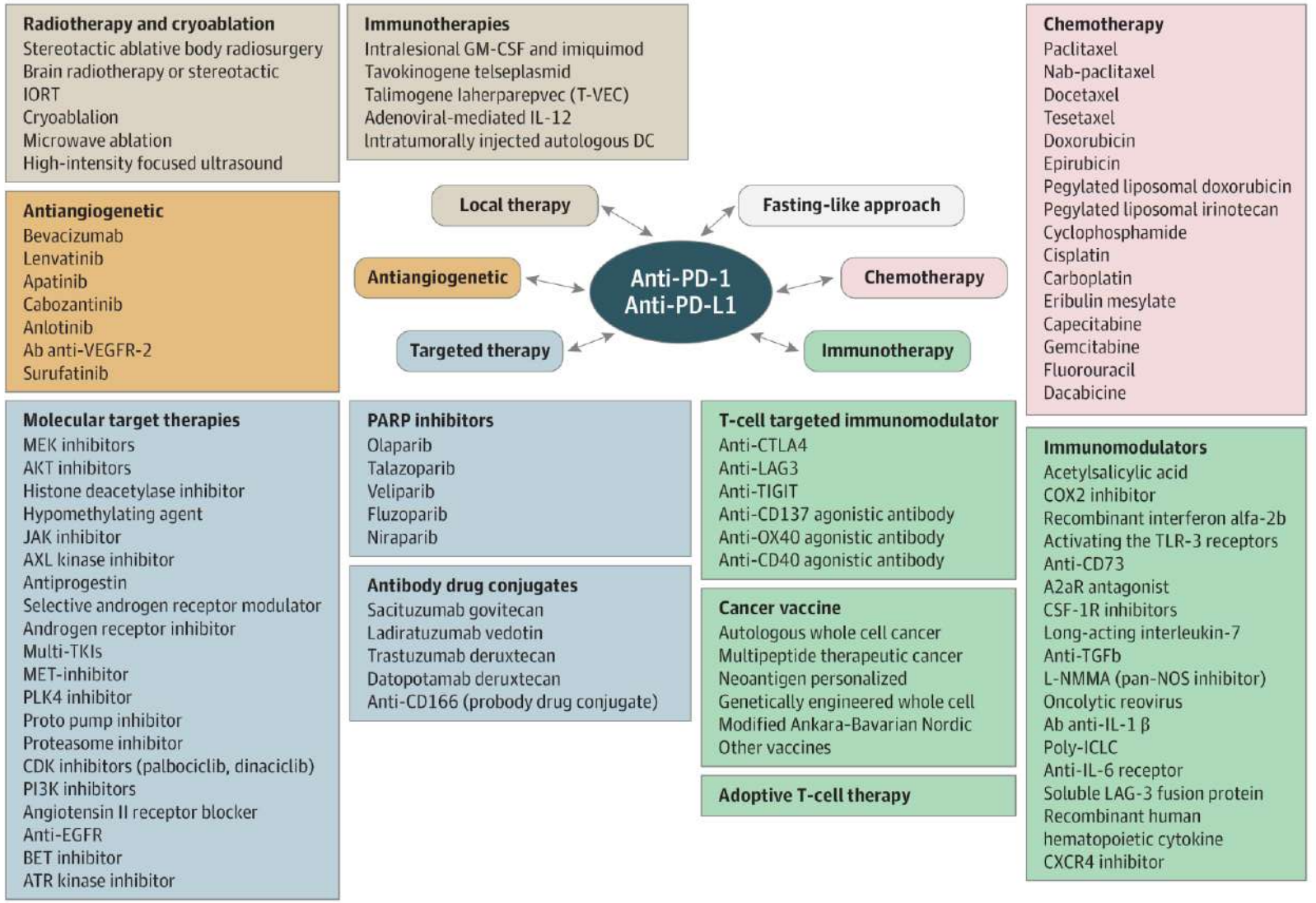
LANDSCAPE OF ANTI-PD-1/PD-L1 COMBINATION STRATEGIES IN TNBC



Bianchini G Nat Rev Clin Oncol 2022; Mariani M JAMA Netw Open 2024

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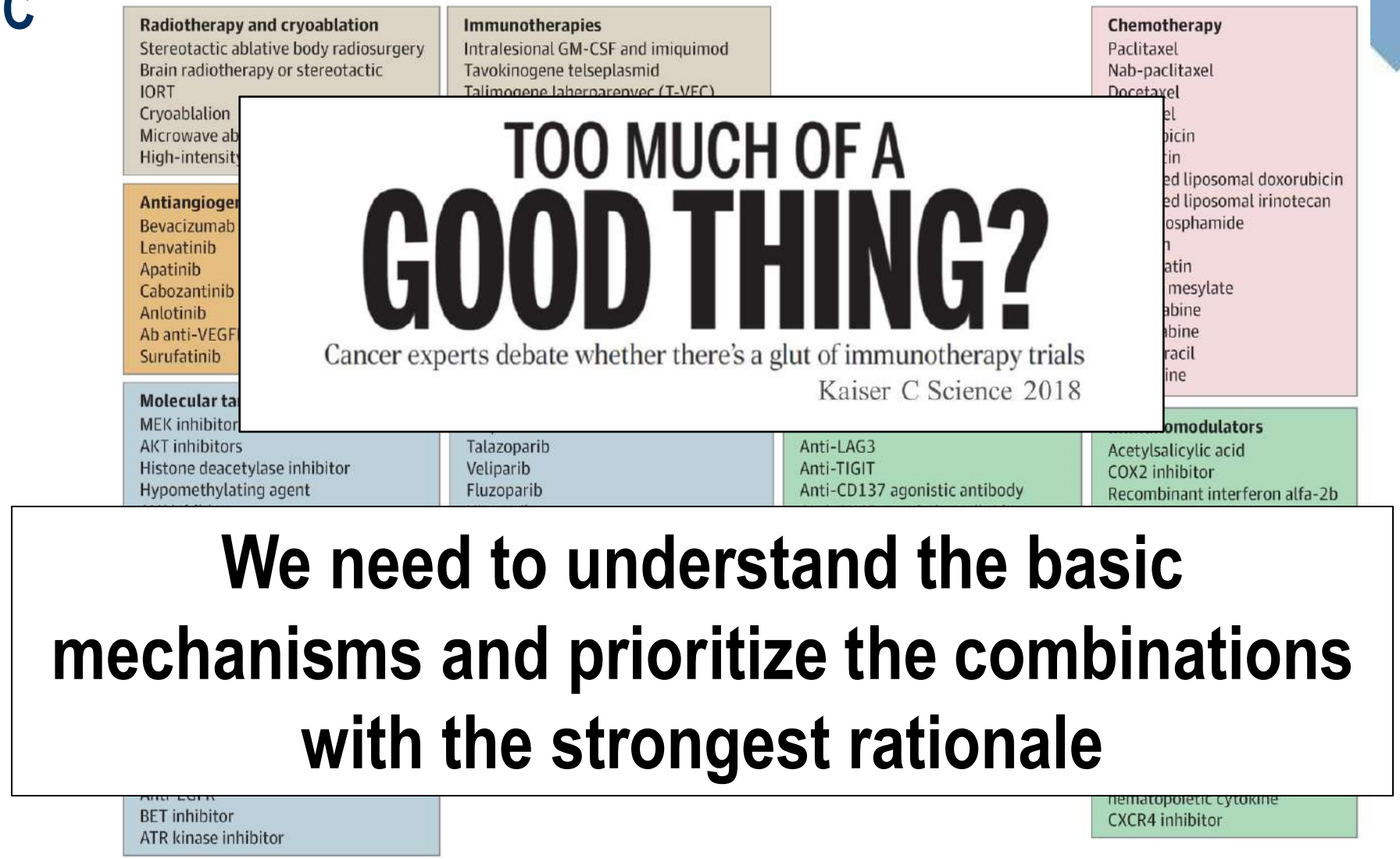
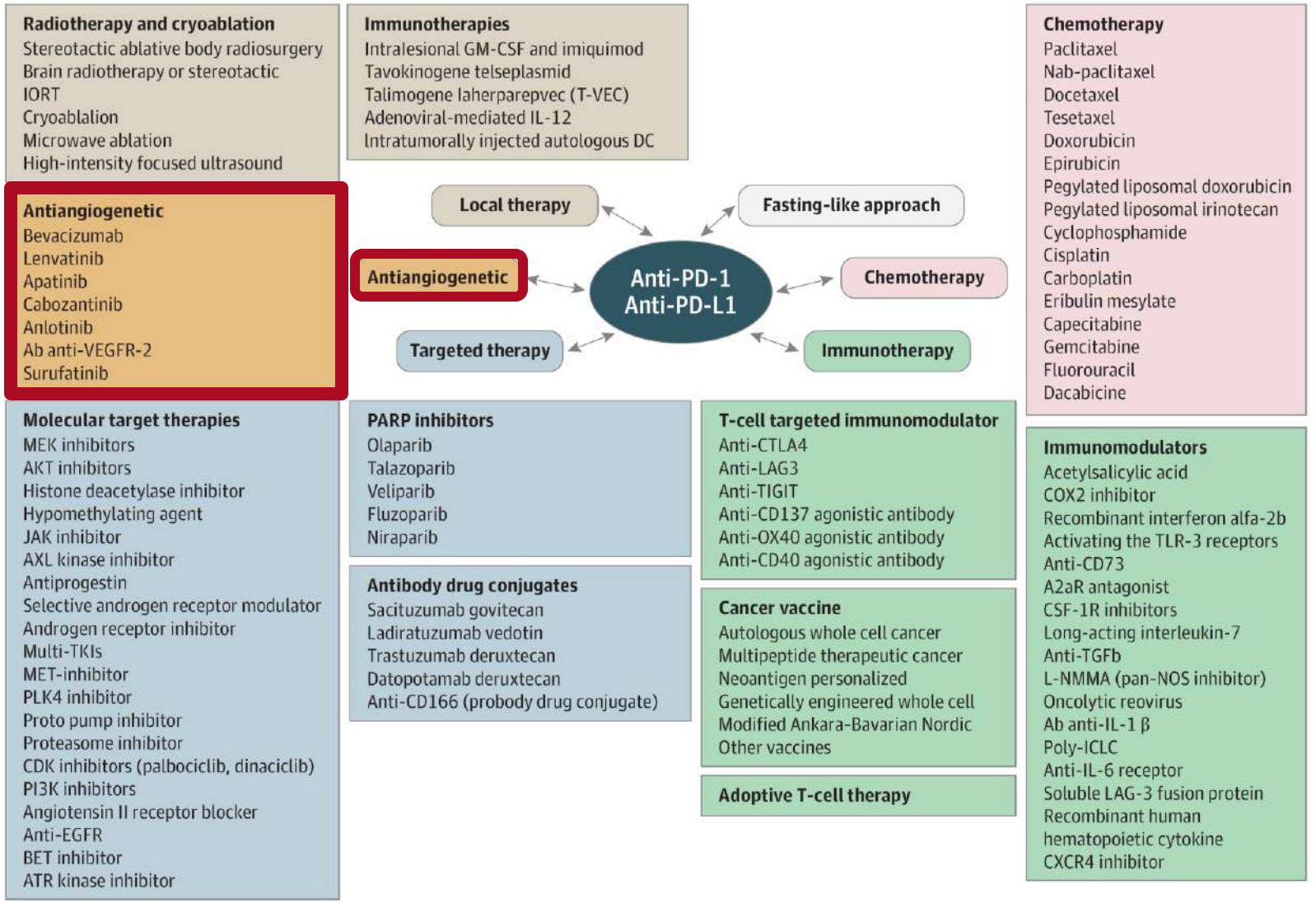


We need to understand the basic mechanisms and prioritize the combinations with the strongest rationale

Bianchini G Nat Rev Clin Oncol 2022; Mariani M JAMA Netw Open 2024

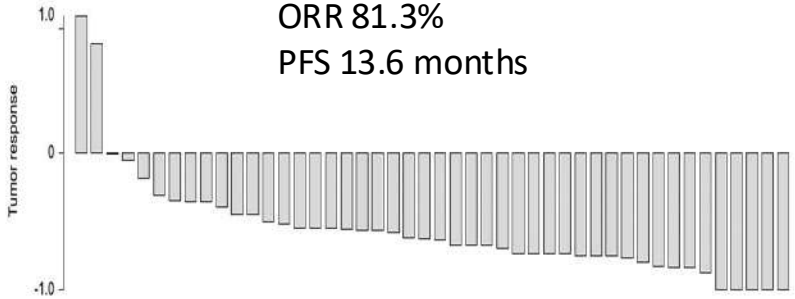
LANDSCAPE OF ANTI-PD-1/PD-L1 COMBINATION STRATEGIES IN TNBC



Bianchini G Nat Rev Clin Oncol 2022; Mariani M JAMA Netw Open 2024

ANTIANGIOGENIC AND ICI IN ADVANCED TNBC

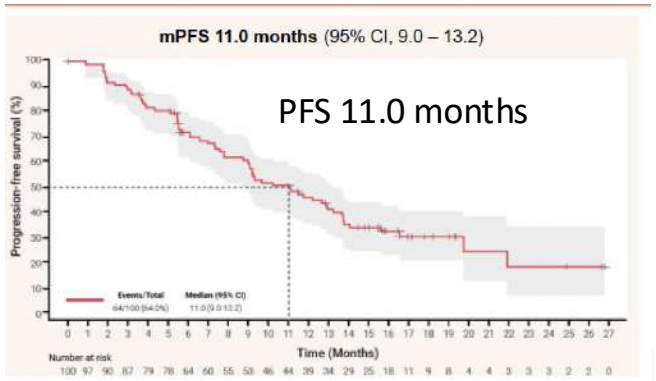
FUTURE-C-Plus
(Camrelizumab, Famitinib and Nab-Paclitaxel)



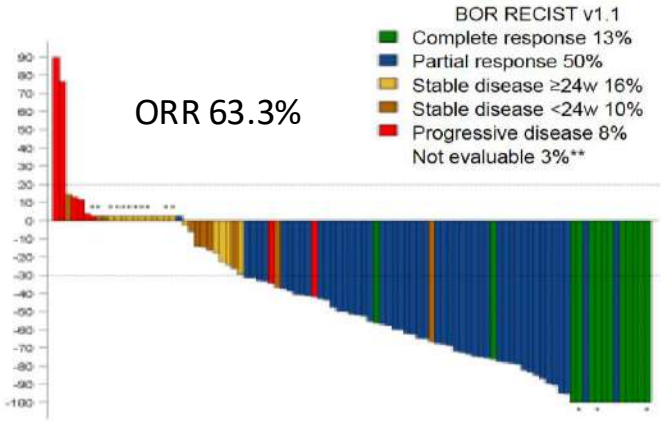
ORR 81.3%
PFS 13.6 months

Wu SY Molecular cancer 2022; Chen L Clin Cancer Res 2022

ATRACTINIB trial
(Atezolizumab, bevacizumab, paclitaxel)



PFS 11.0 months



ORR 63.3%

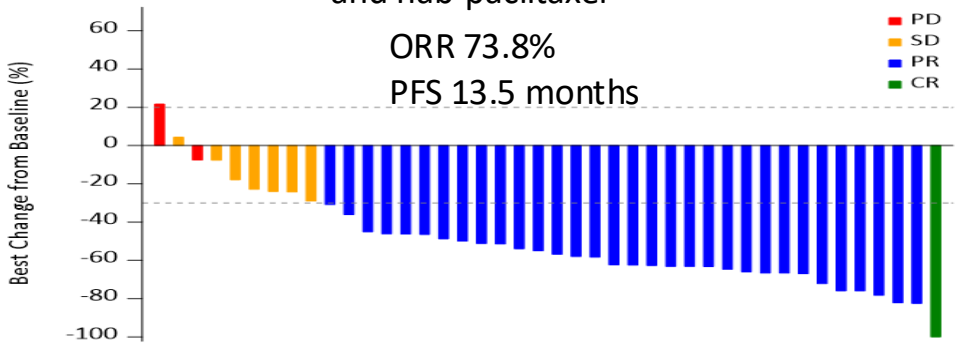
Gion M SABCS 2023

Ivonescimab (anti-PD-1 x VEGF-A Bispecific Ab)
and nab-paclitaxel/paclitaxel

ORR 72.4%
PFS 9.3 months

Ouyang Q ESMO 2024

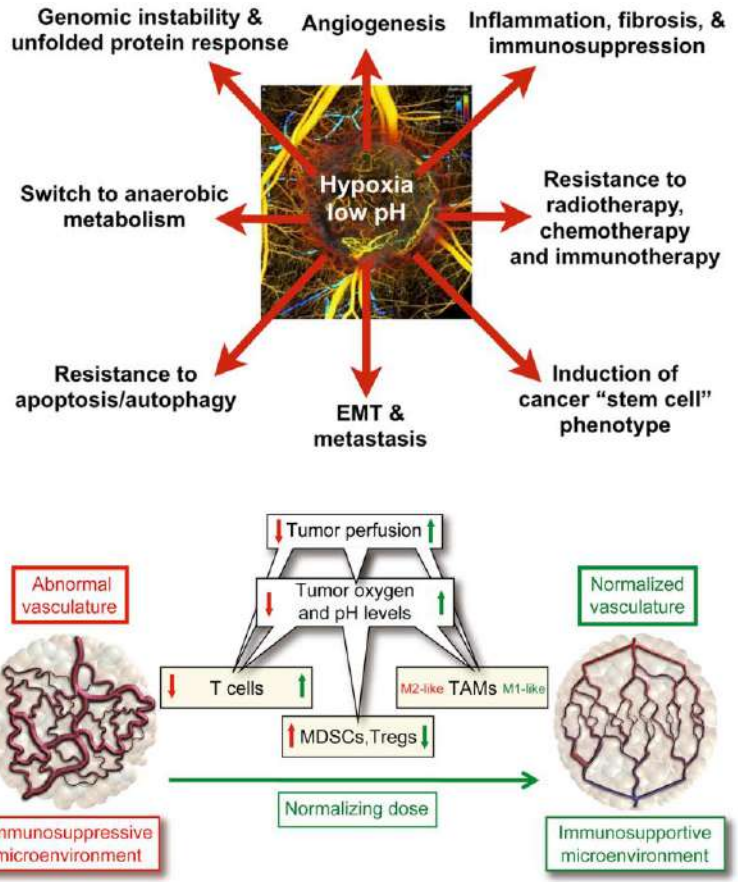
PM8002/BNT327 (anti-PD-L1 x VEGF-A Bispecific Ab)
and nab-paclitaxel



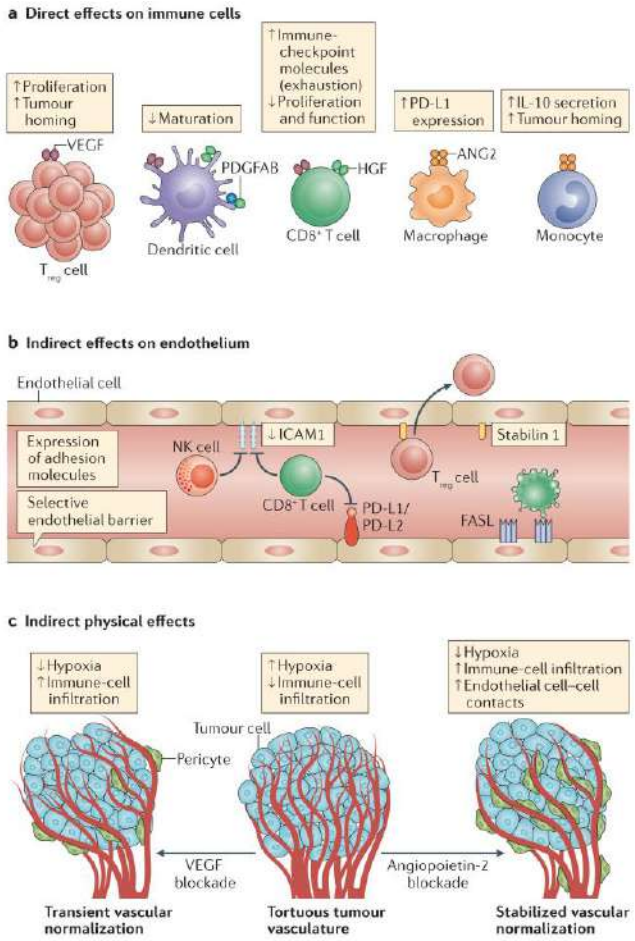
ORR 73.8%
PFS 13.5 months

Wu J ESMO 2024

ANTIANGIOGENESIS REVISITED: FROM STARVING TUMORS TO IMPROVING IMMUNOTHERAPY OUTCOMES

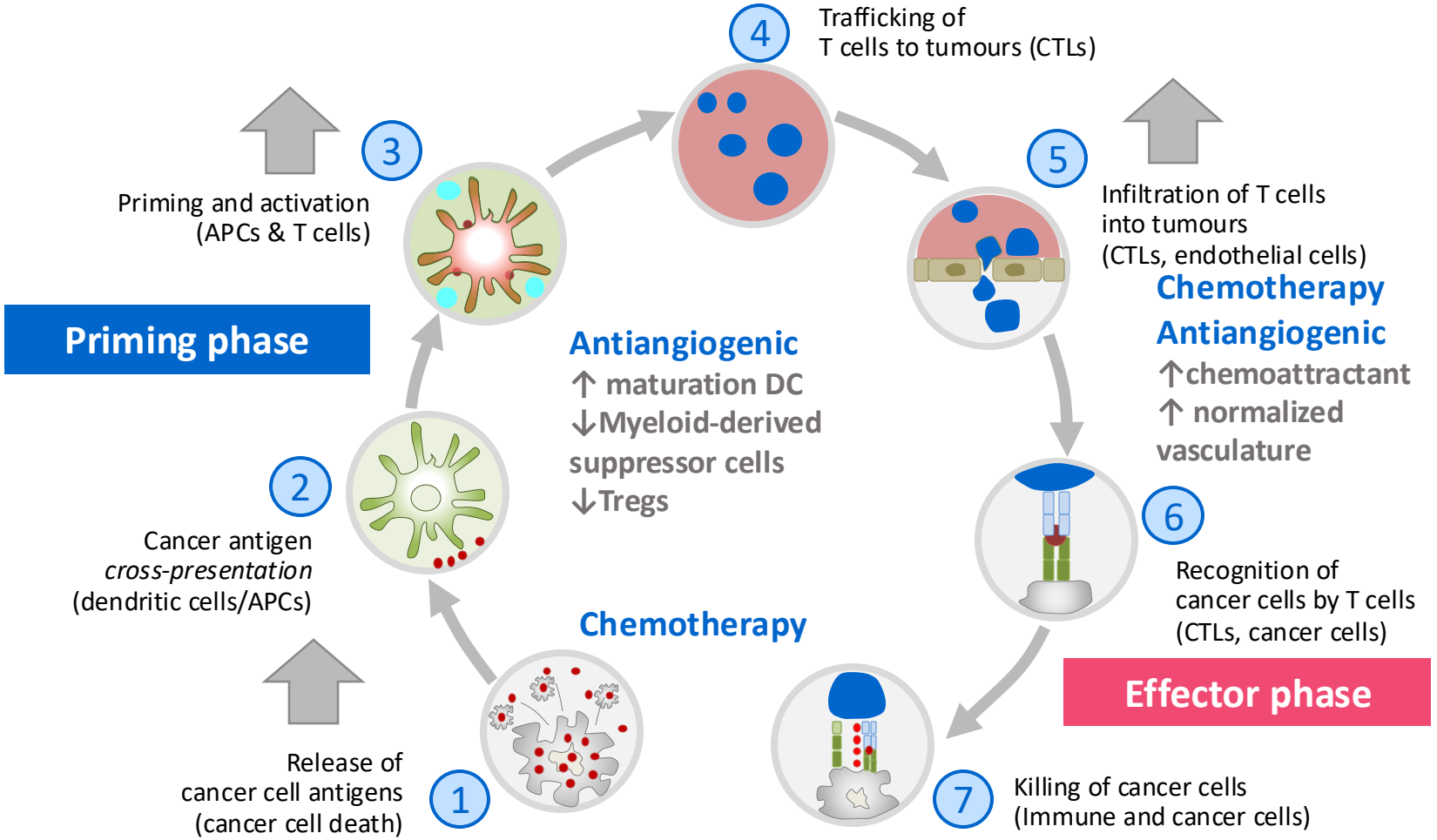


Jain Rakesh K Cancer Cell 2014



Khan KA Nat Rev Clin Oncol 2018

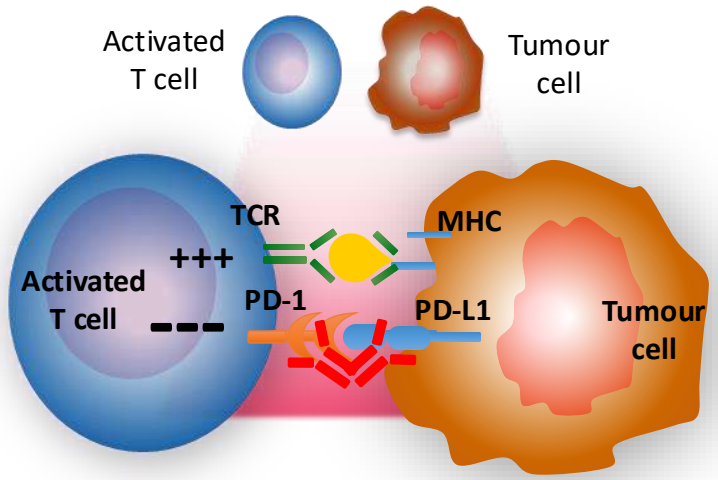
RATIONALE FOR ICI/ANTIANGIOGENIC/CHEMOTHERAPY COMBINATIONS



PD-1/PD-L1 pathway is a key mechanism of immune resistance

Effector phase

TUMOUR MICROENVIRONMENT



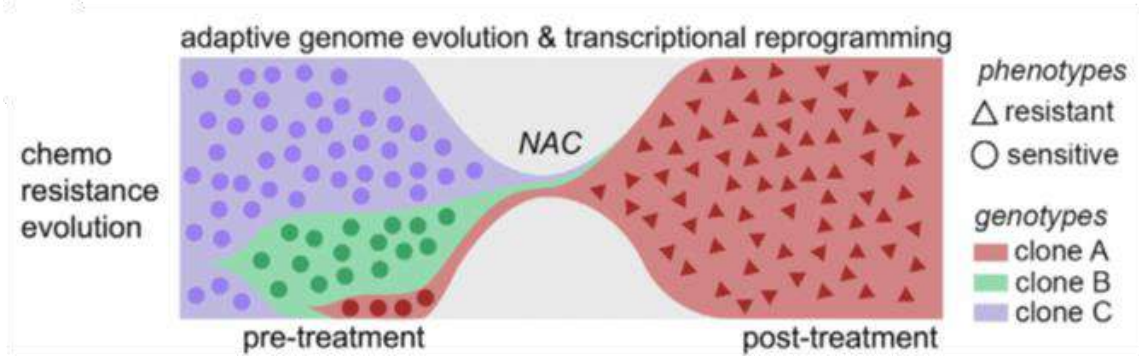
Anti-PD1/Anti-PD-L1

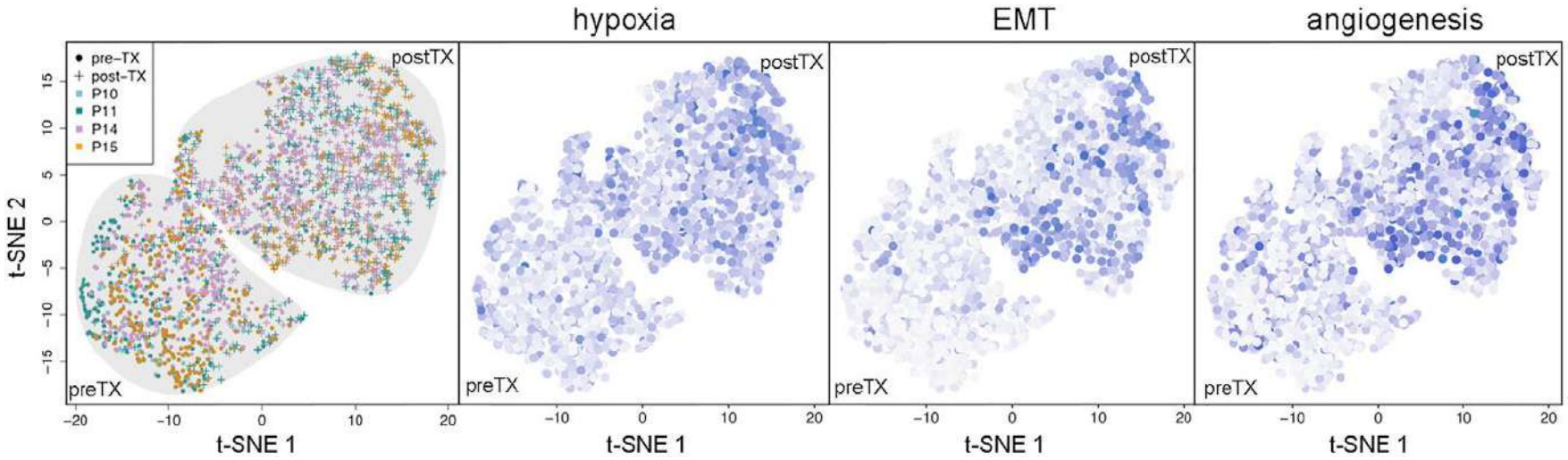
Anti-PD1/PD-L1 restores anti-tumour T-cell activity by targeting PD-L1 on tumour cells and tumour-infiltrating immune cells

APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte;
PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.

Adapted from Chen DS Immunity 2013

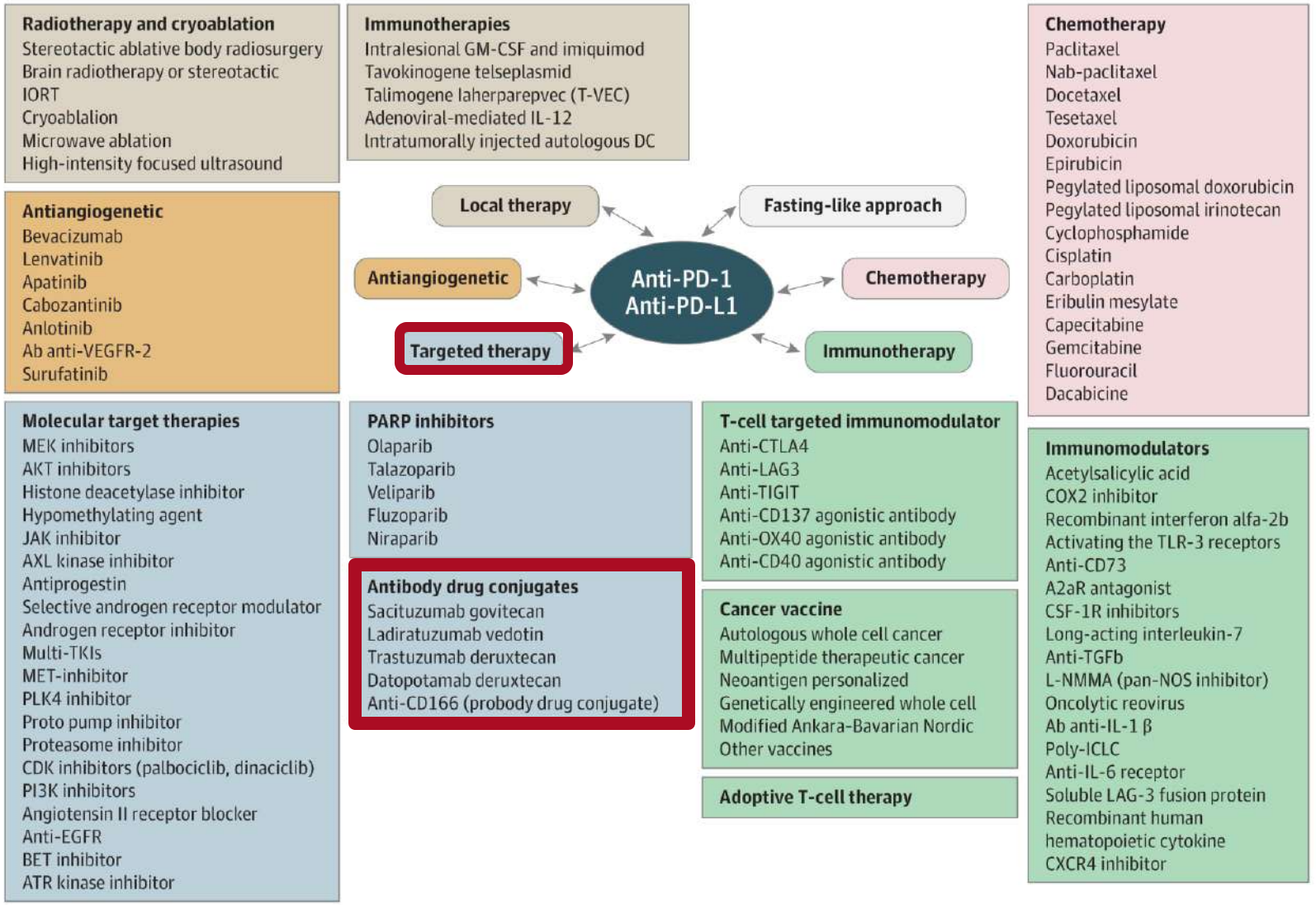
CHEMOTHERAPY INDUCED TRANSCRIPTIONAL REPROGRAMMING OF RESISTANT SIGNATURES INCLUDING ANGIOGENESIS, EMT AND HYPOXIA





Kim C Cell 2018

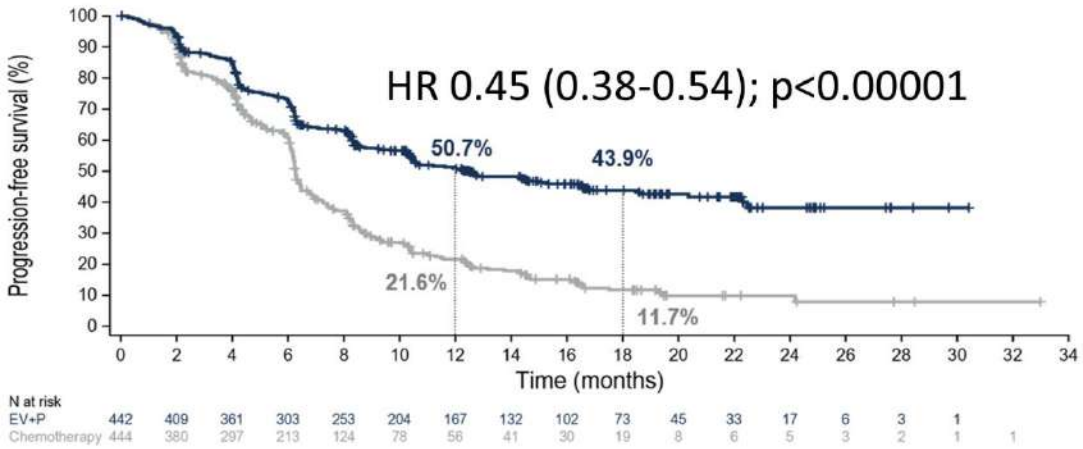
LANDSCAPE OF ANTI-PD-1/PD-L1 COMBINATION STRATEGIES IN TNBC

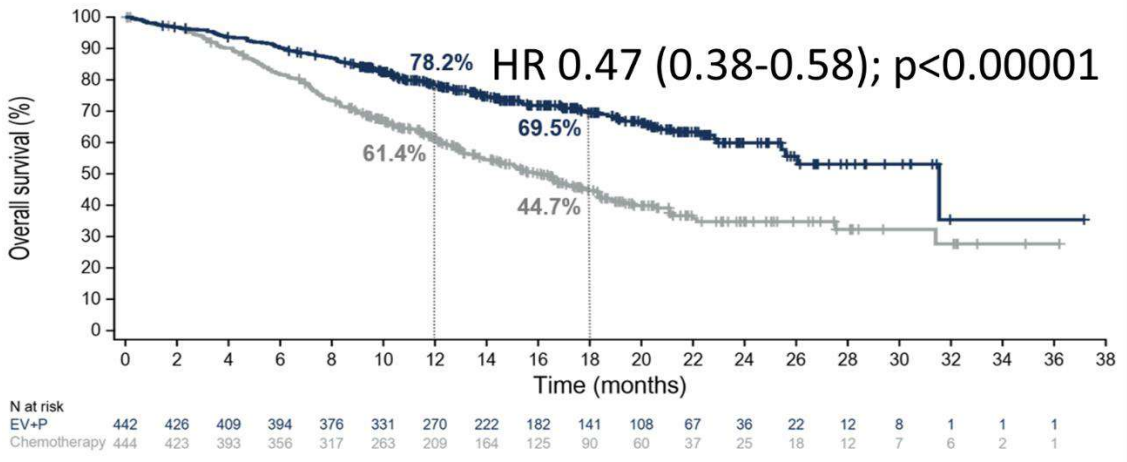


Bianchini G Nat Rev Clin Oncol 2022; Mariani M JAMA Netw Open 2024

SYNERIGISTIC EFFECT OF ADCs - ICIs COMBINATIONS

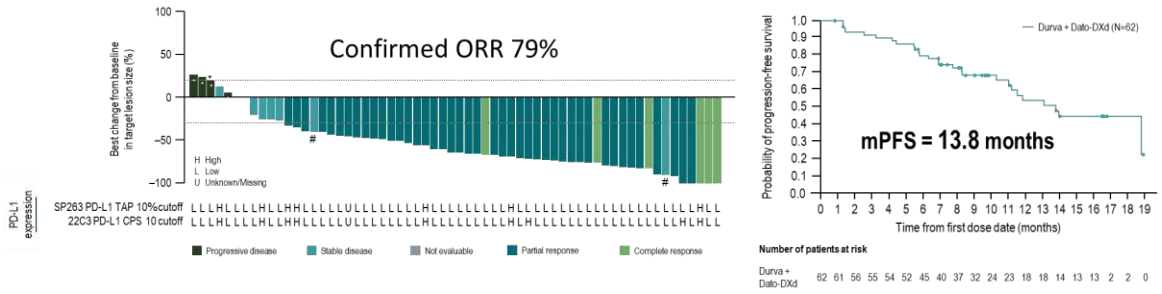
Enfortunab Vendotin + **Pembro** (mUC)





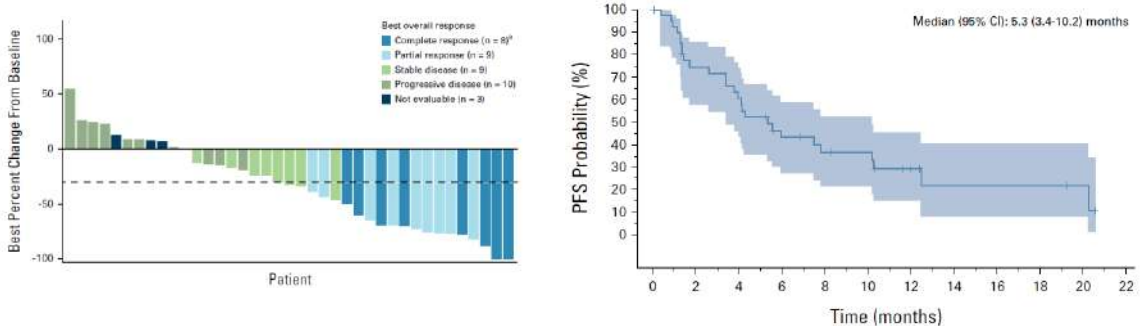
Powles T ESMO 2023; Powels T NEJM 2023

Datopotamab Deruxtecan + **Durva** (mTNBC)



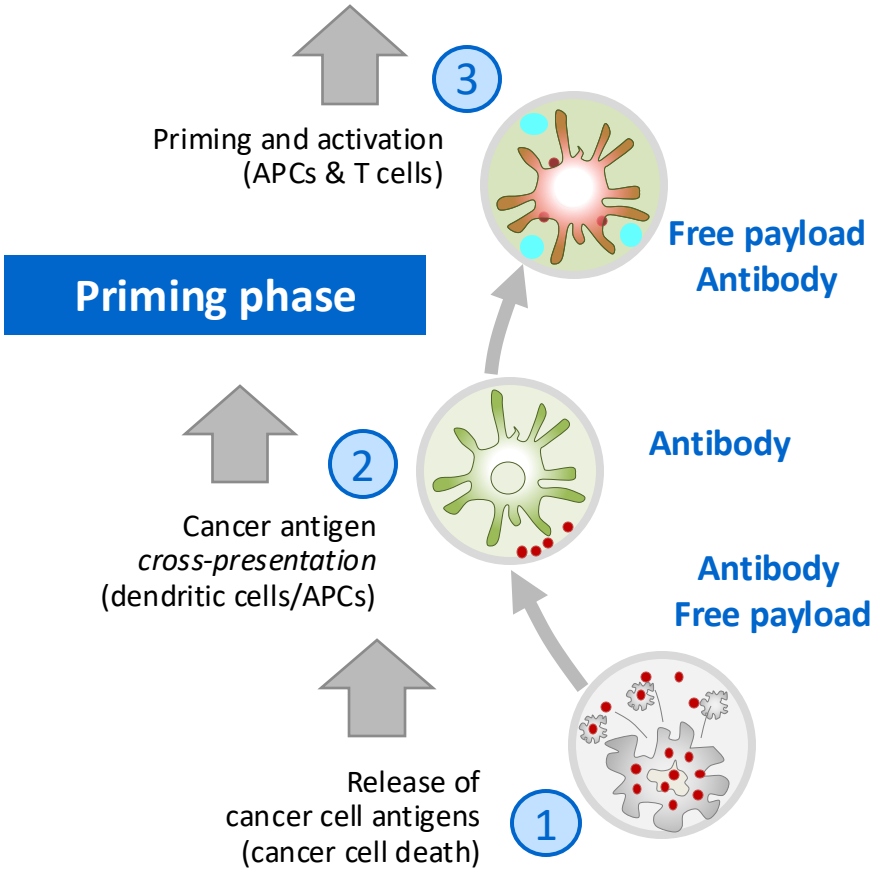
Schmid P ESMO 2023

Sacituzumab Govitecan + **Pembro** (mUC)

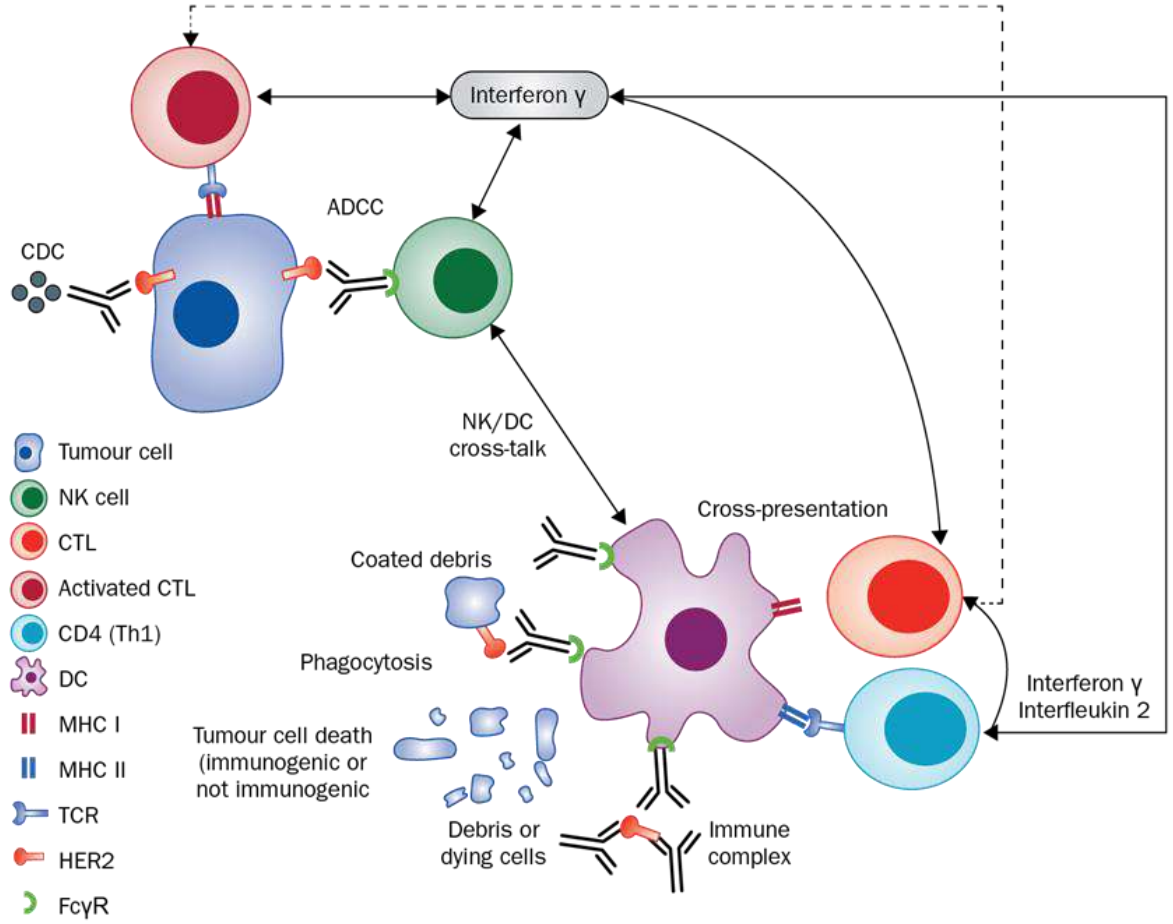


Grivas P JCO 2024

STRONG RATIONALE FOR ICIs/ADCs COMBINATIONS



APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.



Bianchini G Lancet Oncol 2014

Adapted from Chen DS & Mellman I. *Immunity* 2013

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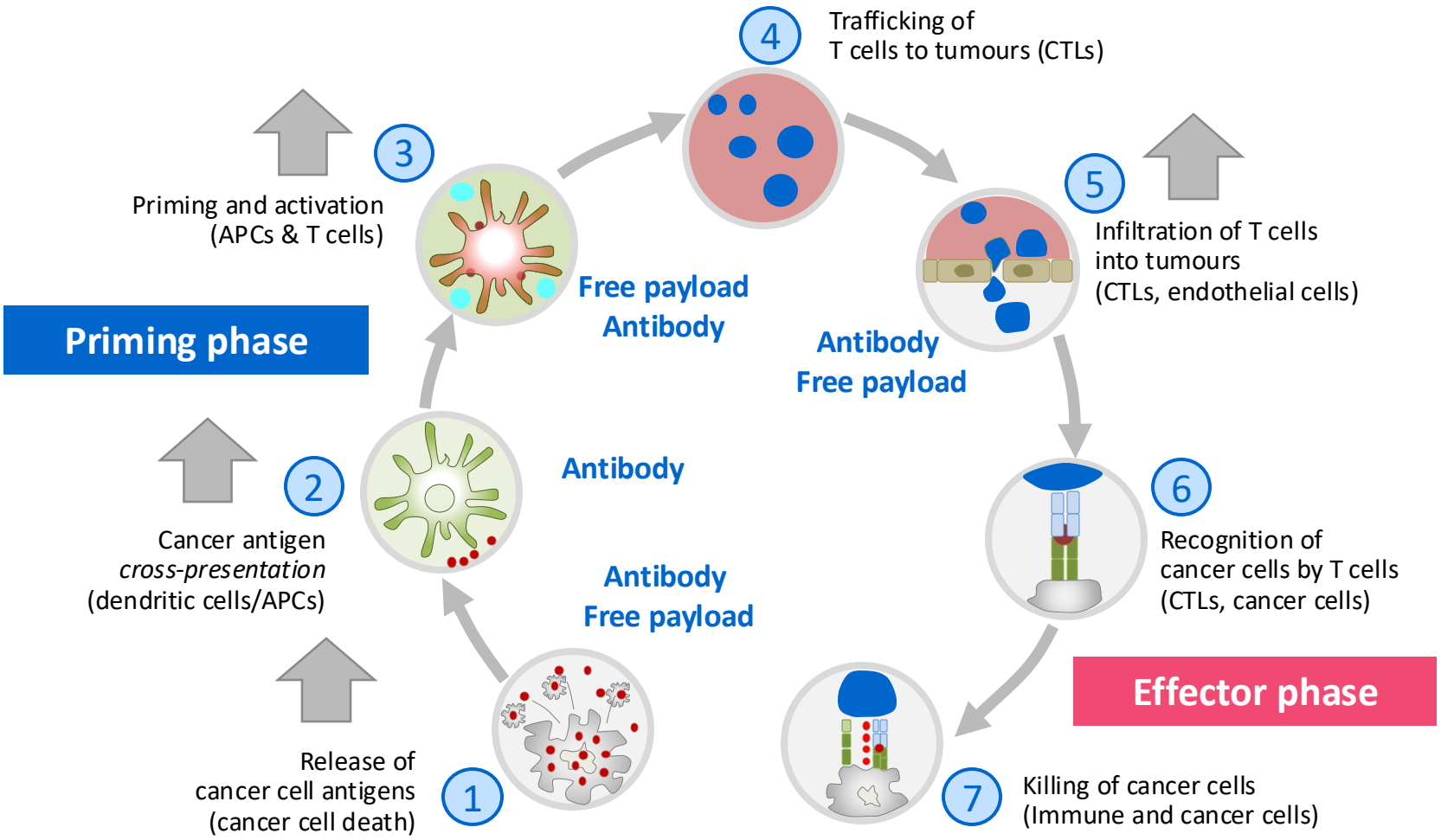

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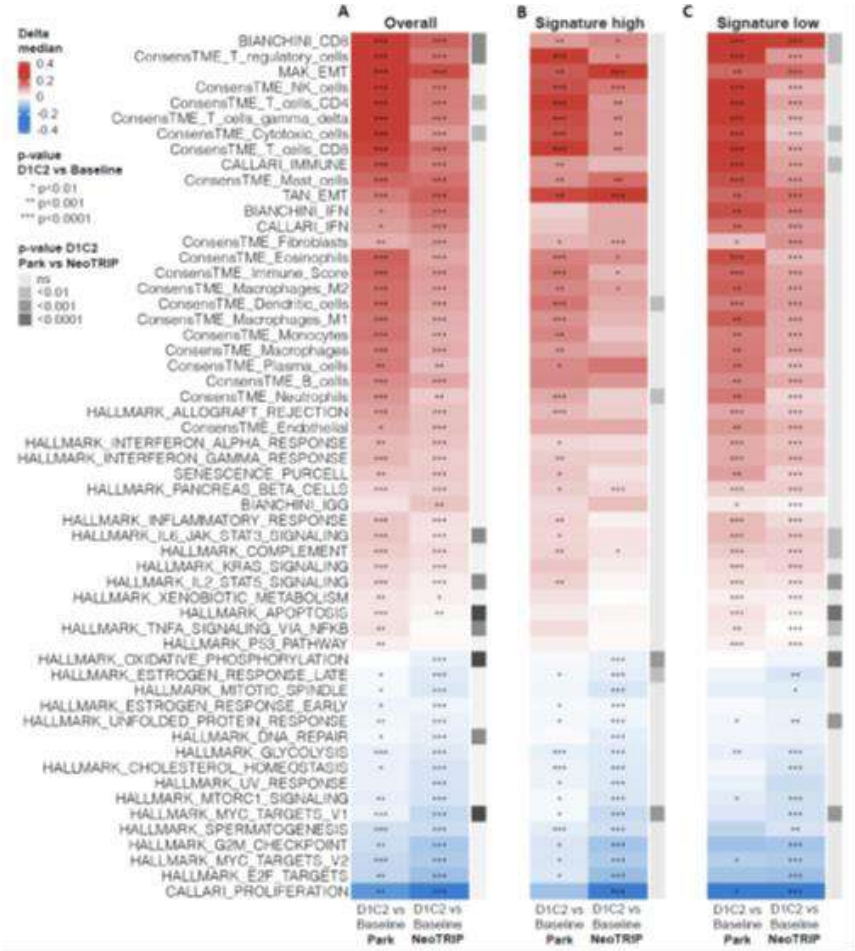
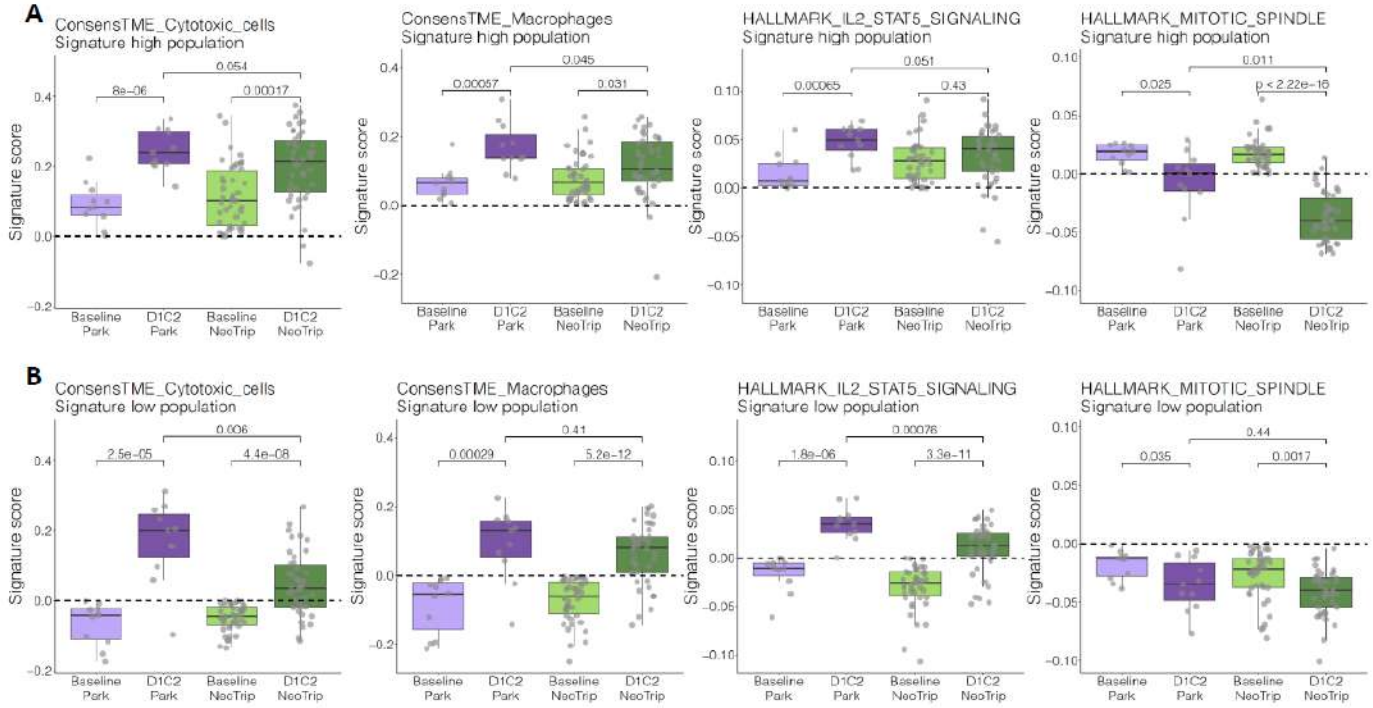
Adapted from Chen DS & Mellman I. *Immunity* 2013; Bianchini G *Lancet Oncol* 2014; Herbst R *Nature* 2014

Benefit from ICI in ‘PD-L1 negative’ aTNBC?

ANTHRACYCLINE ELICIT A STRONGER IMMUNOMODULATORY EFFECT IN “IMMUNE LOW” (PD-L1 NEG) TUMORS





Barreca M SABCS 2021 (Poster Discussion)

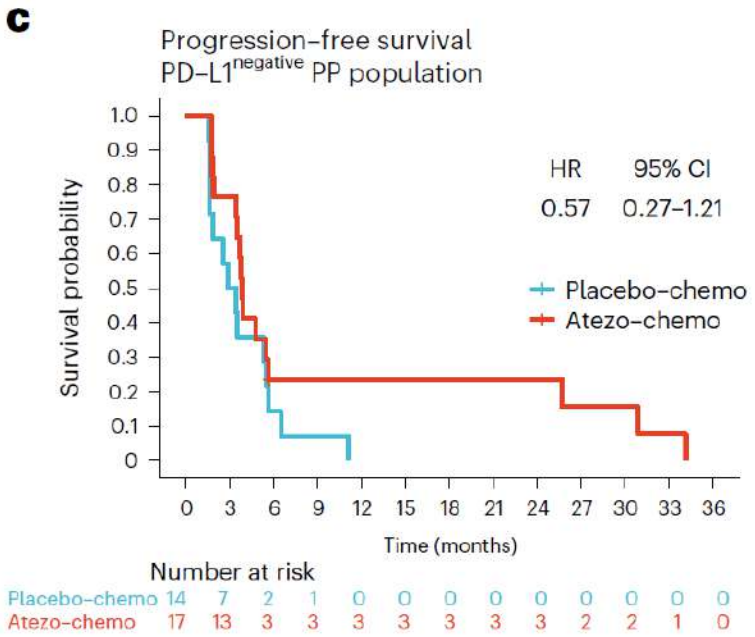
POSSIBLE BENEFIT FROM ATEZOLIZUMAB COMBINED TO ANTHRACYCLINES IN PD-L1 NEG METASTATIC TNBC

nature medicine

Article https://doi.org/10.1038/s41591-022-02126-1

Atezolizumab plus anthracycline-based chemotherapy in metastatic triple-negative breast cancer: the randomized, double-blind phase 2b ALICE trial

PD–L1 status			
Positive	21	10	0.63 (0.28 – 1.43)
Negative	19	17	0.55 (0.27 – 1.14)



Røssevold AH Nature Med 2022

POSSIBLE BENEFIT FROM ATEZOLIZUMAB COMBINED TO ANTHRACYCLINES IN PD-L1 NEG METASTATIC TNBC

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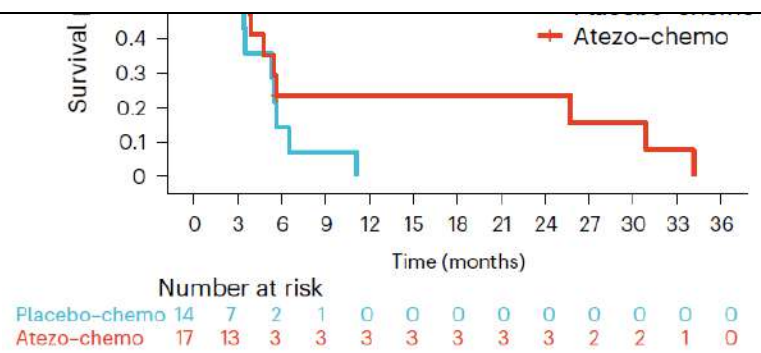
nature medicine

Article

Atezolizumab
chemotherapy
breast cancer:
phase 2b ALIC

Promising results from ICI combinations with ADCs and antiangiogenic

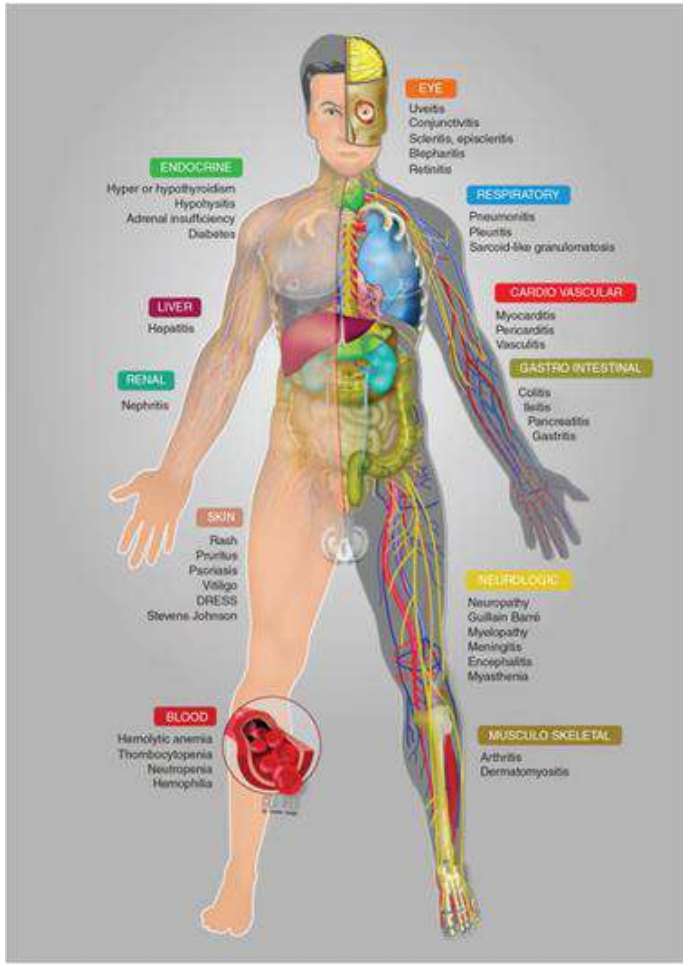


Røssevold AH Nature Med 2022

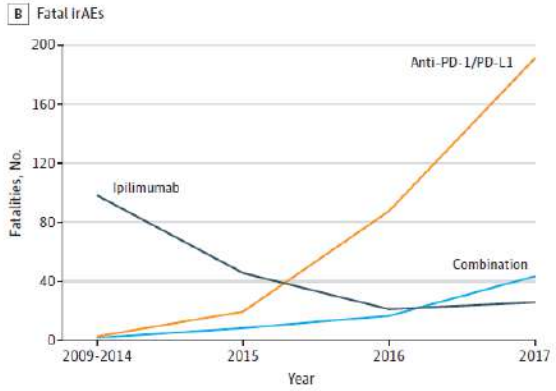
Urgent need, but great opportunity and promise

Precision Immunology

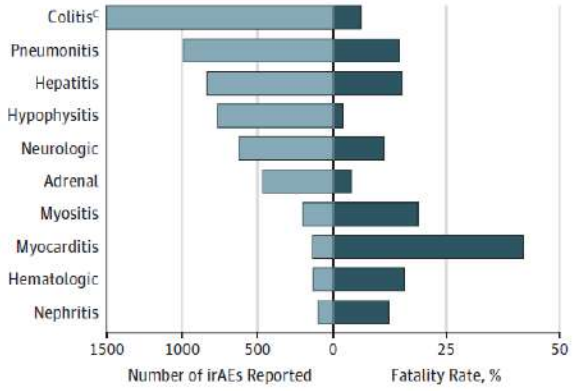
THE ACHILLES' HEEL OF IMMUNOTHERAPY AND IMMUNOTHERAPY COMBINATIONS



Fatal irAEs



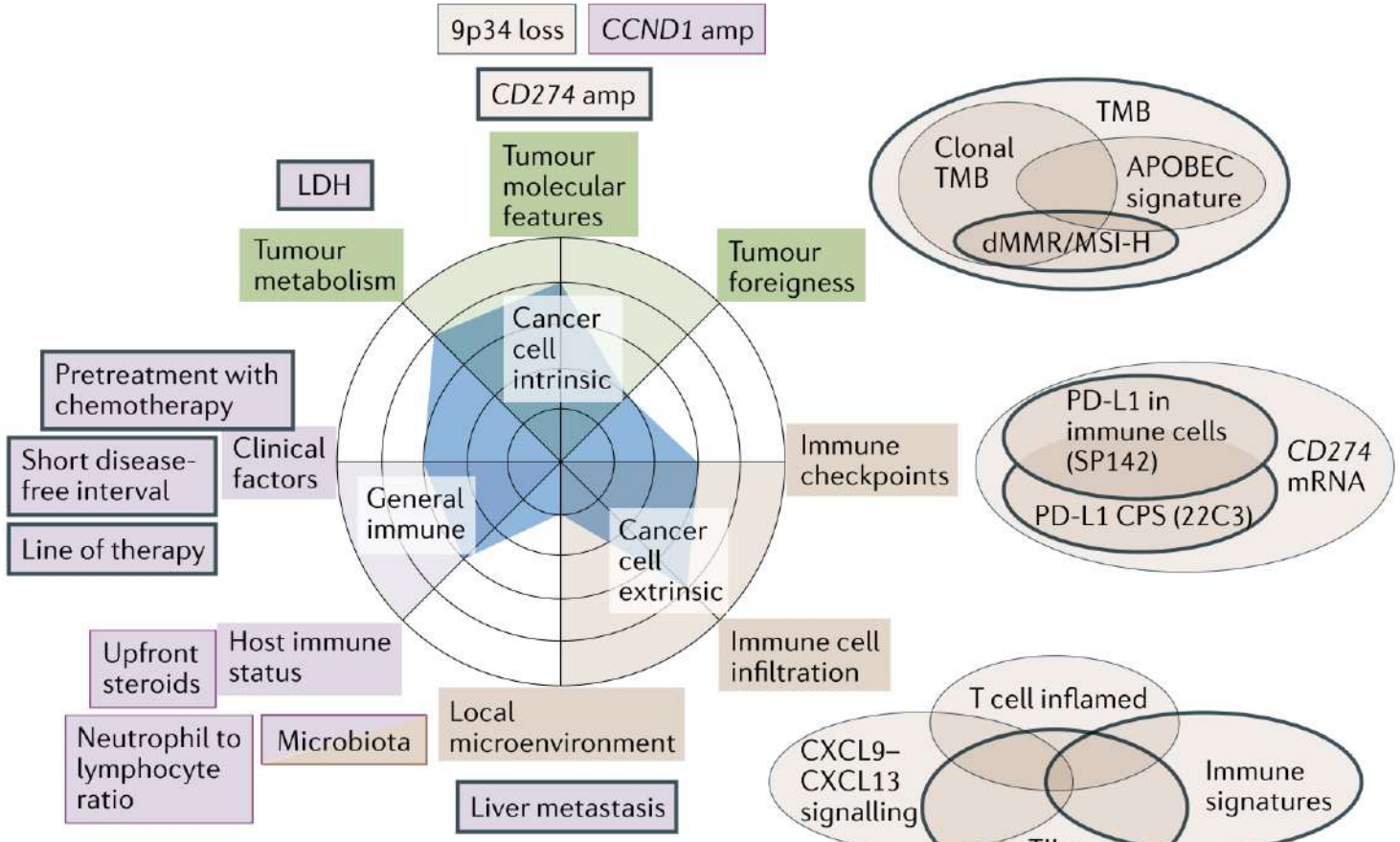
Cases and fatality rates



Fatal irAEs: rare but real

Champiat et al Ann Oncol 2016; Wang et al, JAMA Oncology 2018; Bianchini G ESMO Breast 2023

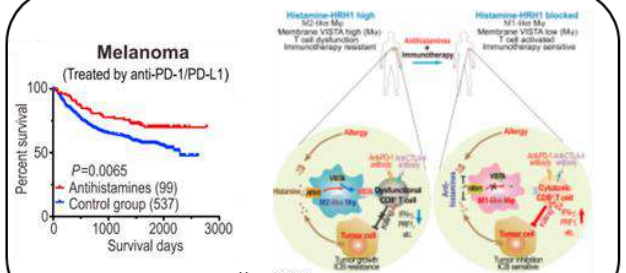
MISSED OPPORTUNITIES FOR PRECISION IMMUNOLOGY: TAILORING IMMUNOTHERAPY ON INDIVIDUAL CANCER IMMUNOGRAM



Bianchini G Nat Rev Clin Oncol 2022
Licata L The Breast 2023

Expanding the concept of immune combinations

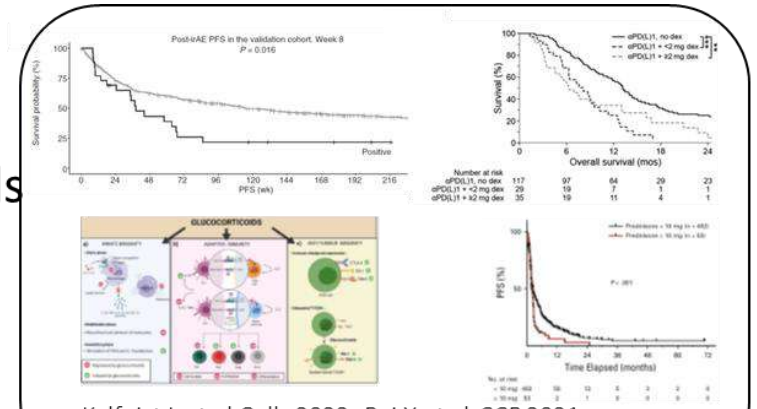
UNINTENDED AND UNDER-RECOGNIZED IMMUNE-MODULATORS



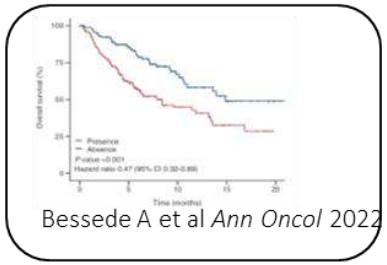
Li H et Cancer Cell 2022

H1-antihistamine

Corticosteroids



Kalfeist L et al Cells 2022; Bai X et al *CCR* 2021;
Iorgulescu JB et al *CCR* 2020; Arbour KC et *JCO* 2018



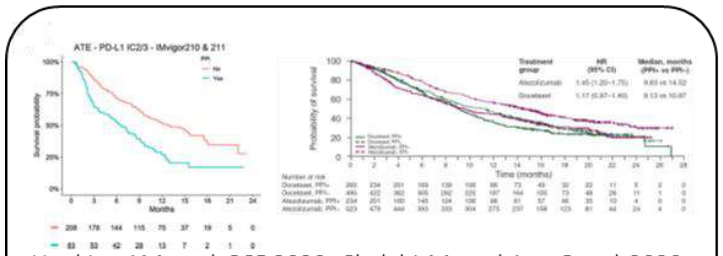
Bessede A et al *Ann Oncol* 2022

Acetaminophen

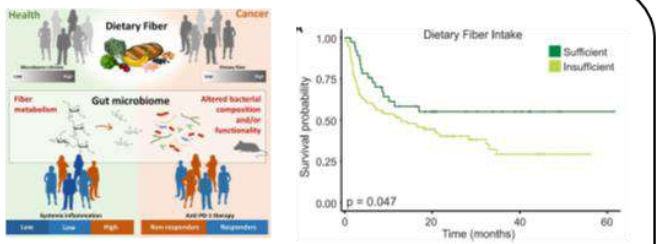
Proton pump inhibitors

Dietary change

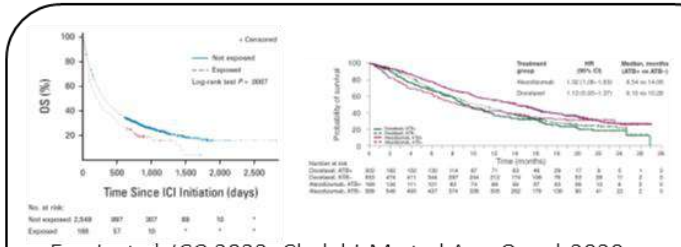
Antibiotics



Hopkins AM et al *CCR* 2020; Chalabi M et al Ann Oncol 2020



Matson V *Cancer Cell* 2022; Spencer Christine N et al Science 2021



Eng L et al *JCO* 2023; Chalabi M et al Ann Oncol 2020;
Li H et Cancer Cell 2022

Taking into account the host

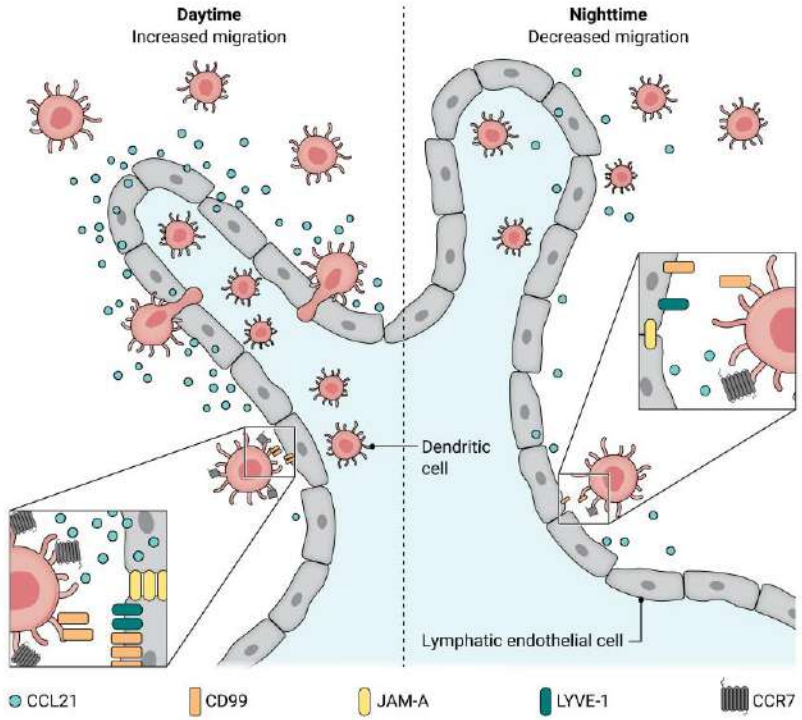
CLINICAL IMPLICATIONS OF THE CIRCADIAN CONTROL OF THE IMMUNE SYSTEM

SCIENCE IMMUNOLOGY | REVIEW

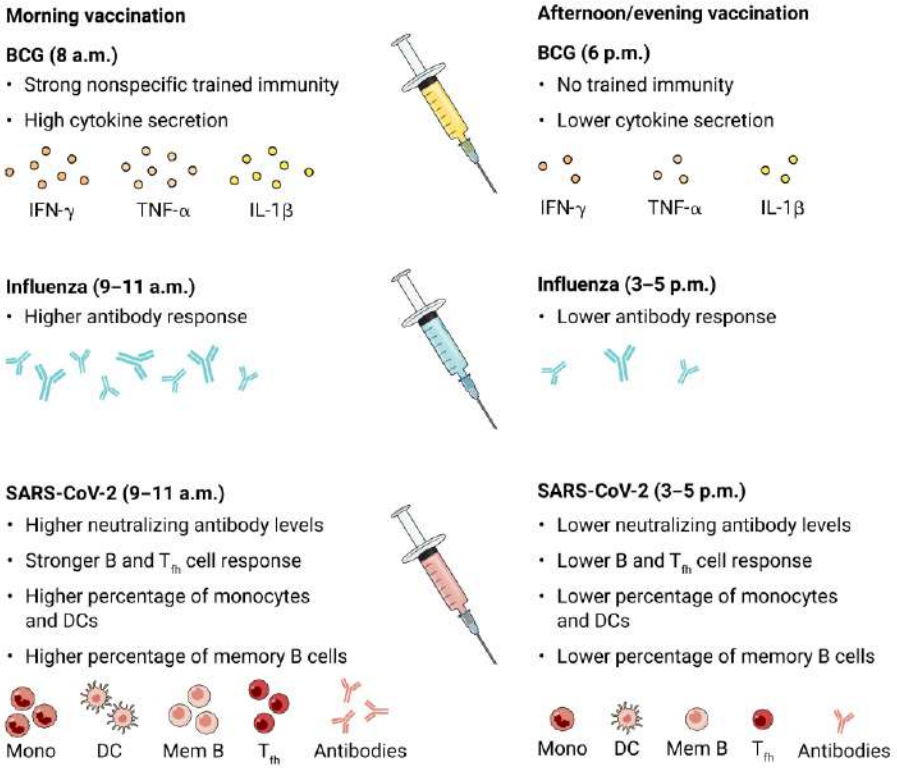
IMMUNE REGULATION

The circadian immune system

Chen Wang[1]†, Lydia Kay Lutes[1]†, Coline Barnoud[1], Christoph Scheiermann[1,2]*



Benefits of morning vaccination

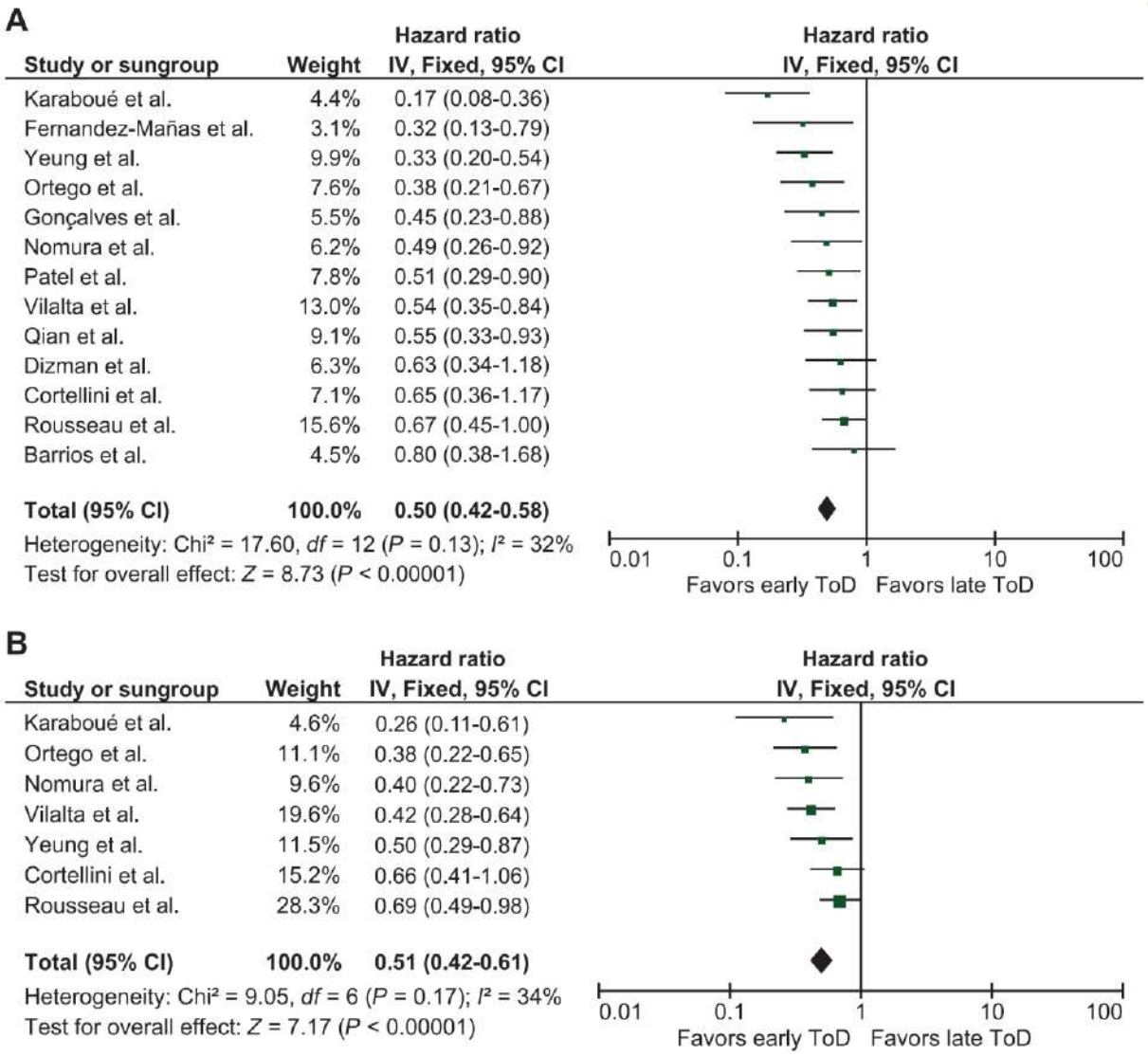


- The quantity and function of tumor-infiltrating T cells are time-of-day dependent
- Rhythmic tumor infiltration of T cells depends on the endothelial circadian clock

Wang C Science Immunology 2022; Wang C Cell 2024

CLINICAL IMPACT OF IMMUNOTHERAPY-INFUSION TIME OF DAY: HOST MATTER

Morning administrations of ICIs is better



Landré T ESMO Open 2024

What's next?
Looking outside breast immuno-oncology

TUMOR VACCINES: THE LONG PATH FROM FAILURE TO SUCCESS

1990 to 2014
"Breast Cancer" & "Vaccine"
(ClinicalTrials.Gov)

172 trials

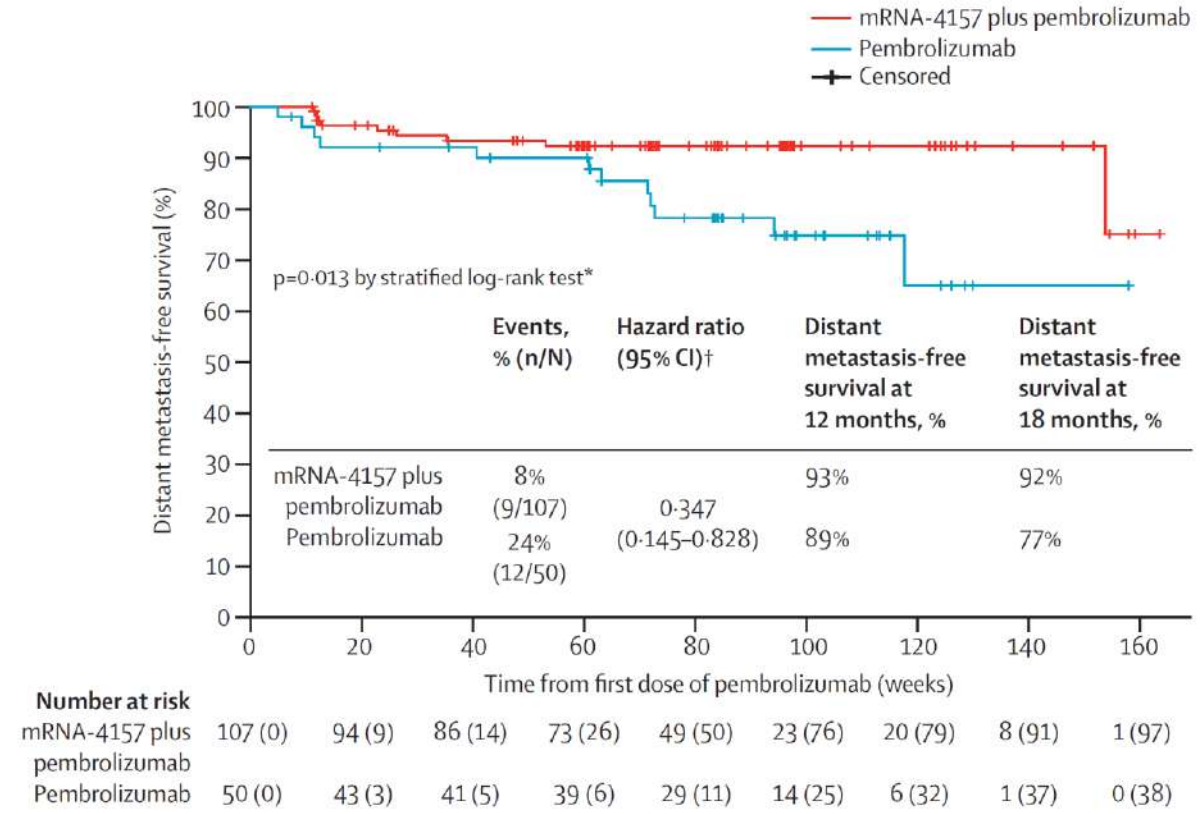
Failure

PERSONALISED mRNA THERAPEUTIC VACCINE

V940 vaccine (mRNA-4157)

It is a **personalised mRNA therapeutic created on demand** and encoding up to 34 neoantigens present in each patient's tumour

KEYNOTE-942



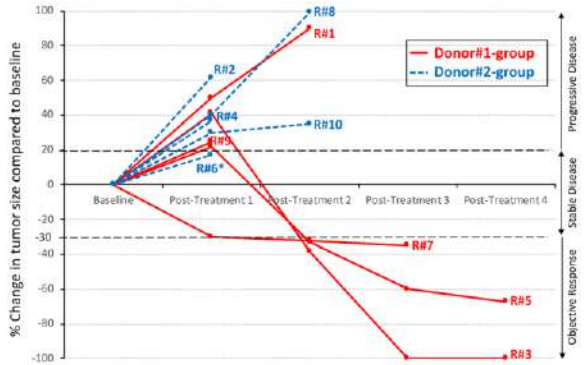
	Events, % (n/N)	Hazard ratio (95% CI)†	Distant metastasis-free survival at 12 months, %	Distant metastasis-free survival at 18 months, %
mRNA-4157 plus pembrolizumab	8% (9/107)	0·347 (0·145–0·828)	93%	92%
Pembrolizumab	24% (12/50)		89%	77%

Number at risk									
mRNA-4157 plus pembrolizumab	107 (0)	94 (9)	86 (14)	73 (26)	49 (50)	23 (76)	20 (79)	8 (91)	1 (97)
Pembrolizumab	50 (0)	43 (3)	41 (5)	39 (6)	29 (11)	14 (25)	6 (32)	1 (37)	0 (38)

Weber JS Lancet 2024

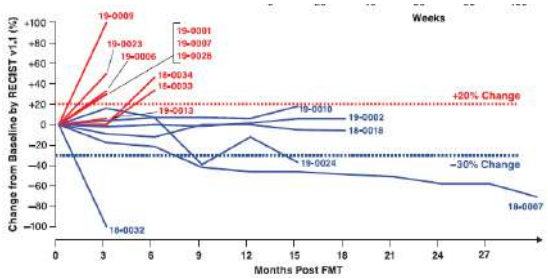
FECAL MICROBIOTA TRANSPLANTATION (FMT) PLUS ICI

Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients



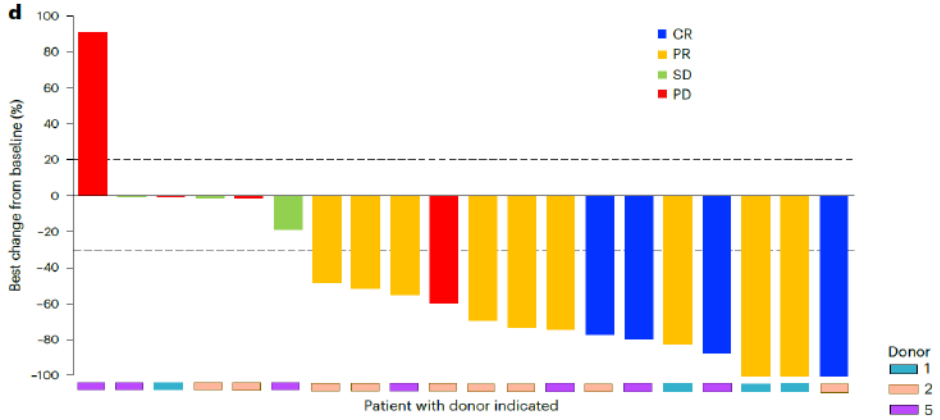
Baruch EN *Science* 2020

Fecal microbiota transplant overcomes resistance to anti–PD-1 therapy in melanoma patients



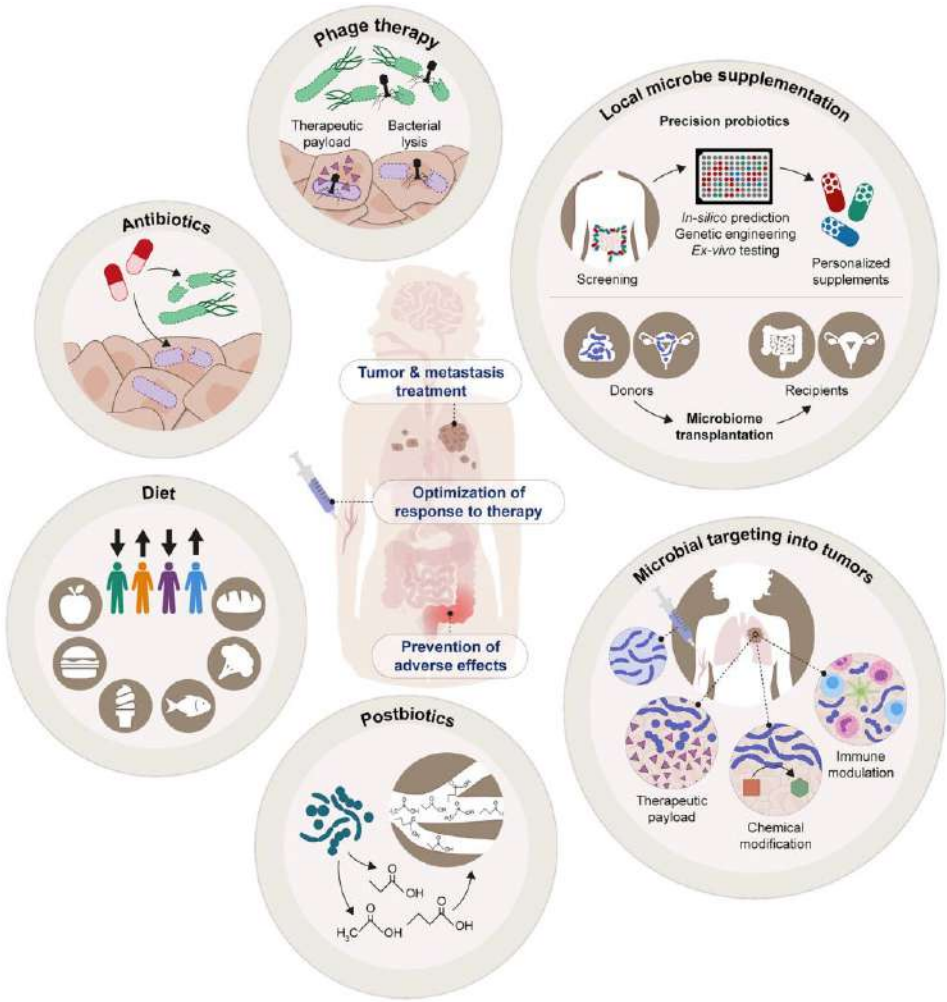
Davar D Science 2021

Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial



Routry B Nature Medicine 2023

MICROBIOME MODULATION IN CANCER TREATMENT BEYOND FMT

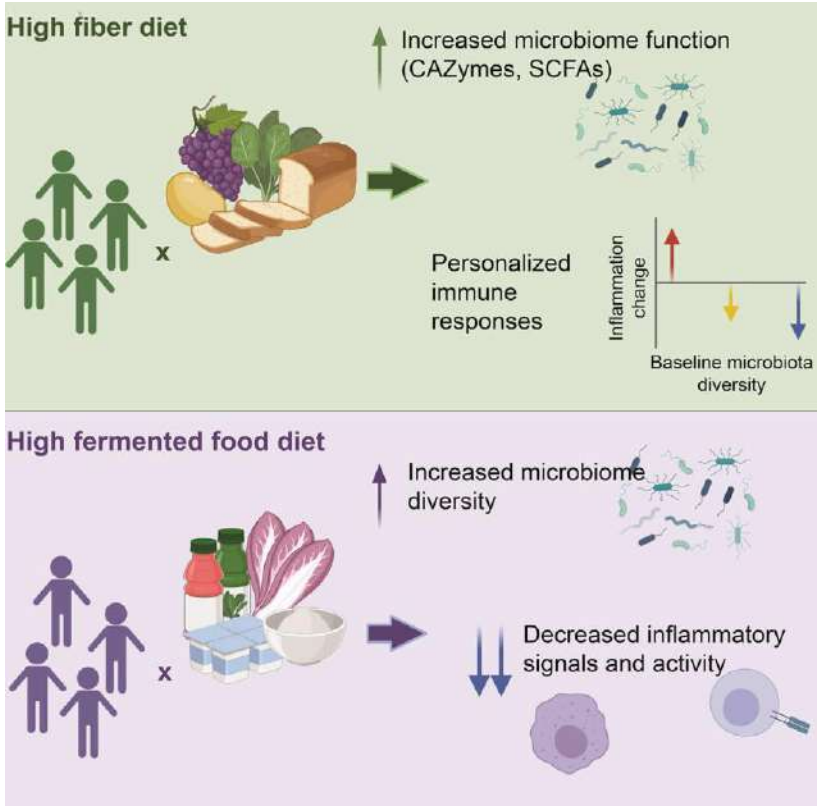


Several modalities potentially enabling rational microbiome manipulation contributing to cancer treatment

Cullin N Cancer Cell 2021

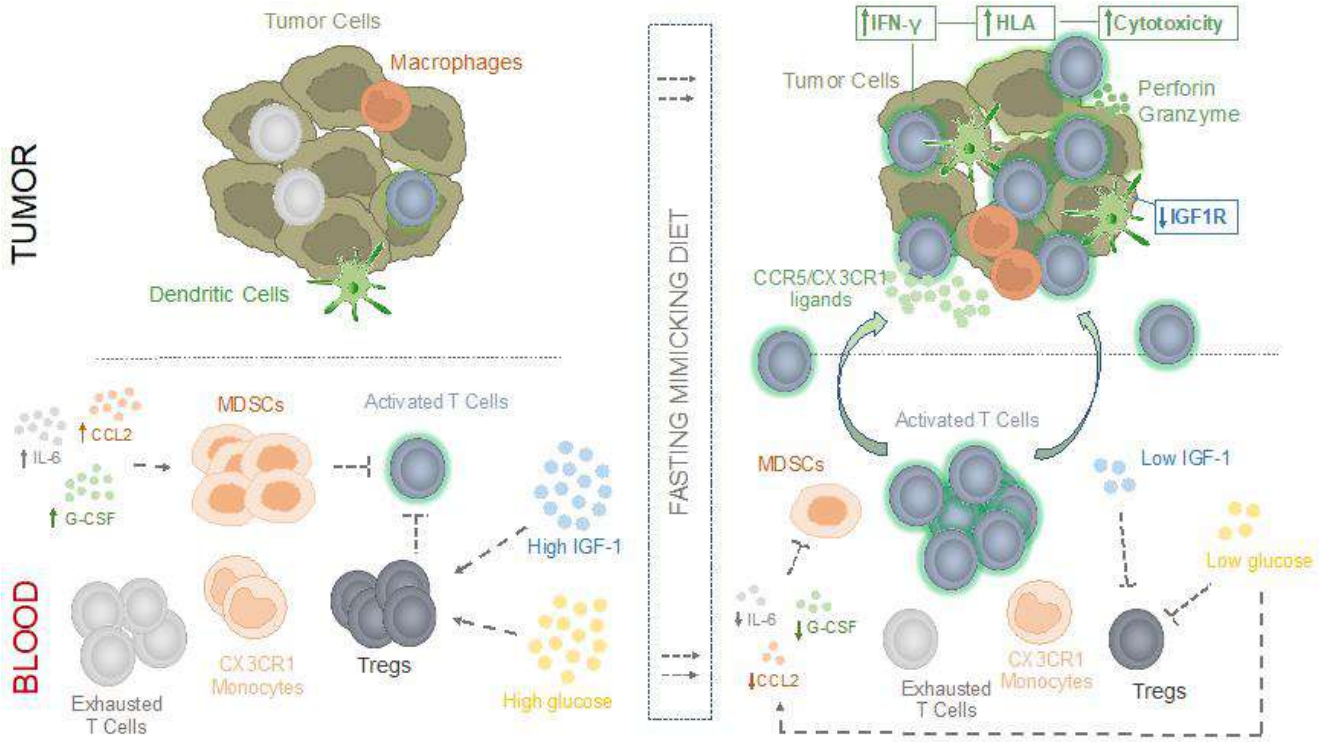
DIET AS THERAPEUTIC INTERVENTION

Gut-microbiota-targeted diets modulate human immune status



Wastyk HC Cell 2021

Fasting-Mimicking Diet reshapes metabolism and antitumor immunity



Vernieri C Cancer Discovery 2022

KEY ELEMENTS TO SUCCEED IN IMPROVING

- Develop a deep understanding of tumor-immune interactions and their relationship with the host
- Define the mechanisms of action for immune combinations and prioritize their clinical development based on strong scientific rationale
- Realize the promises and opportunities of precision immunology
- Apply lessons learned from the broader field of immuno-oncology

ESMO DEEP DIVE: BREAST CANCER

Thank you

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esmo@esmo.org

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