Triple Negative Breast Cancer Update:
From Immunotherapy to Antibody-drug Conjugates

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Disclosures

- Grant/Research Support from Imugene, and Merck.
- Consultant for Gilead Sciences and Novartis.
- On the Speakers Bureau for AstraZeneca, Daiichi-Sankyo, Eisai, Gilead Sciences, and Merck.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Outline

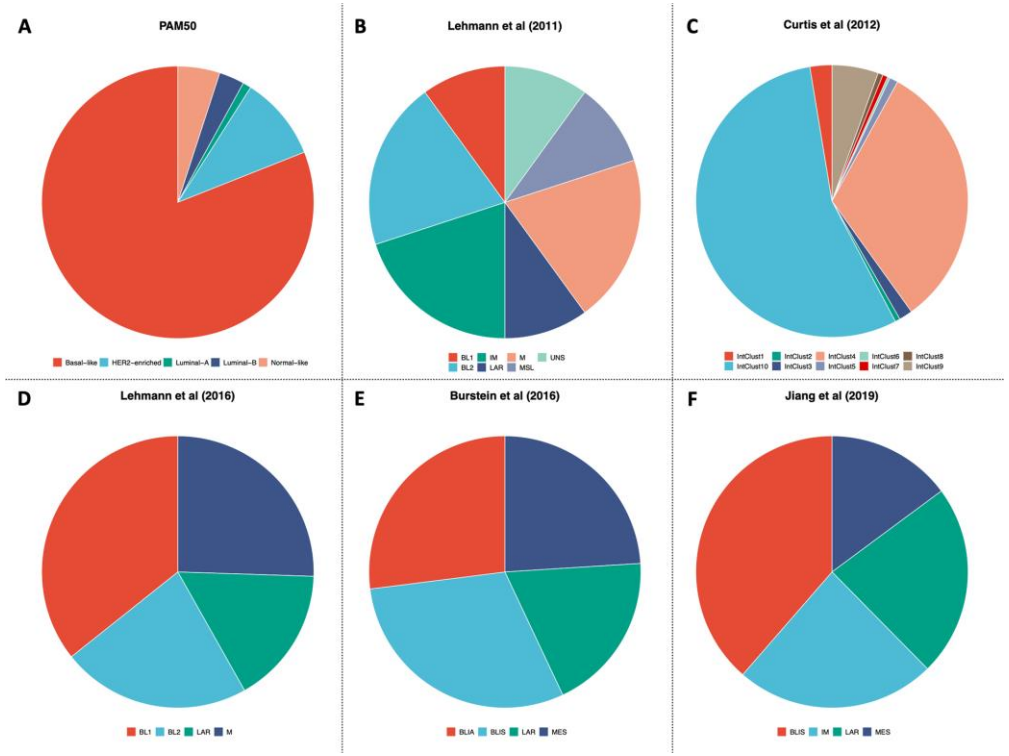
- Overview of triple negative breast cancer (TNBC)
- Role of Immune Checkpoint Inhibitors
- Role of PARP inhibitors
- Antibody Drug Conjugates (ADC)
- HER2 low BC
- Other emerging therapy: AR, AKT inhibitor

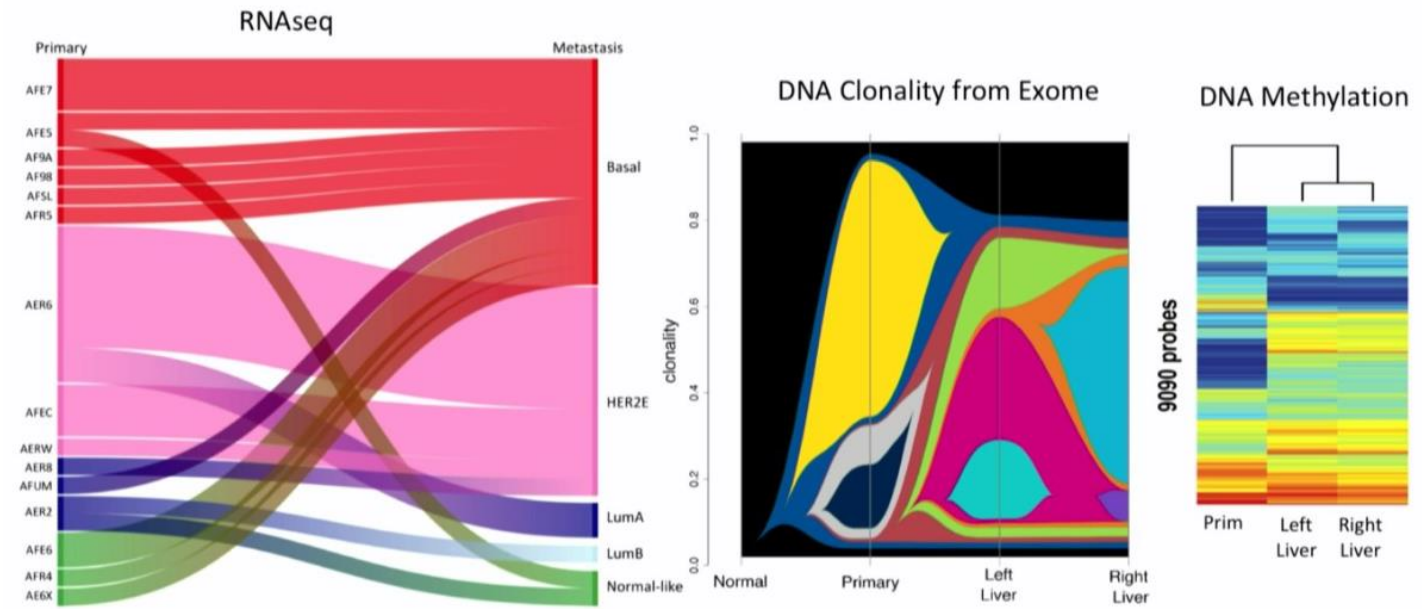
Triple Negative Breast Cancer (TNBC)

- Defined by lack of ER/PR/HER2 receptors
- 15 -20% of all invasive breast cancers
- More common in younger women, AA and Hispanic ethnicity
- Most common type seen in women with BRCA
- Significantly more aggressive: visceral and brain metastasis
- Lack of effective therapy
- Medium survival in mTNBC:
  - OS 15-18 month
  - 5y OS 12% per SEER database

Hartman AR et al Cancer 2012
Dent R et al Clin Cancer Res 2007
Bianchini et al Nature Review 2016

TNBC Tumor Biology: Molecular Heterogeneity and Tumor Evolution

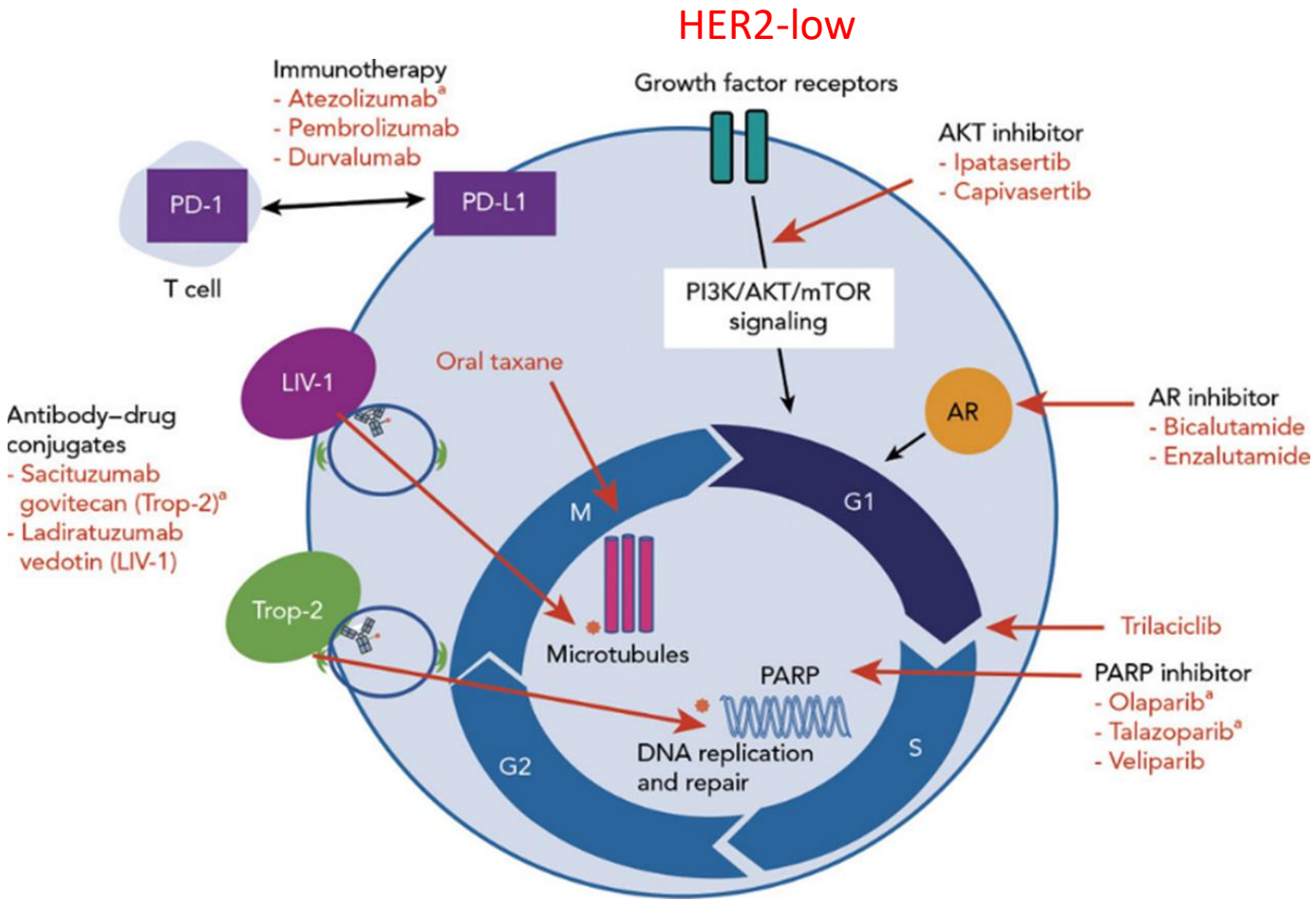




Adrian Lee SABCS 2019

Marra et al NPJ Breast 2020

Targets for mTNBC Therapy



PARP inhibitor + ICI

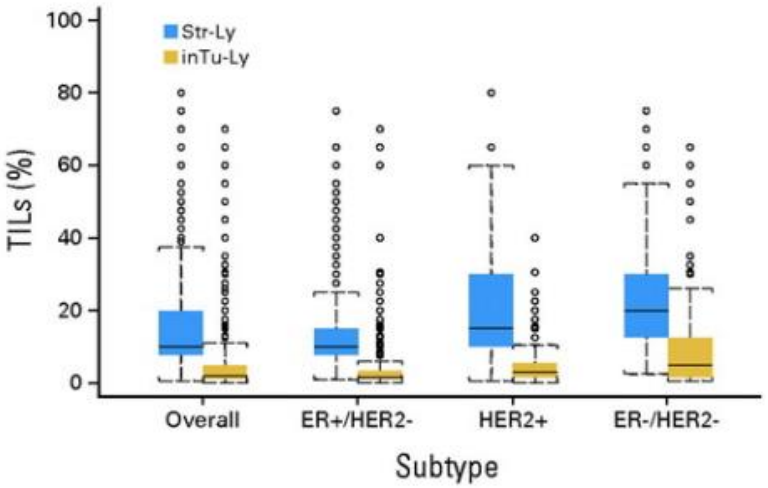
Vidula JNCCN 2020

Overview of mTNBC Treatment

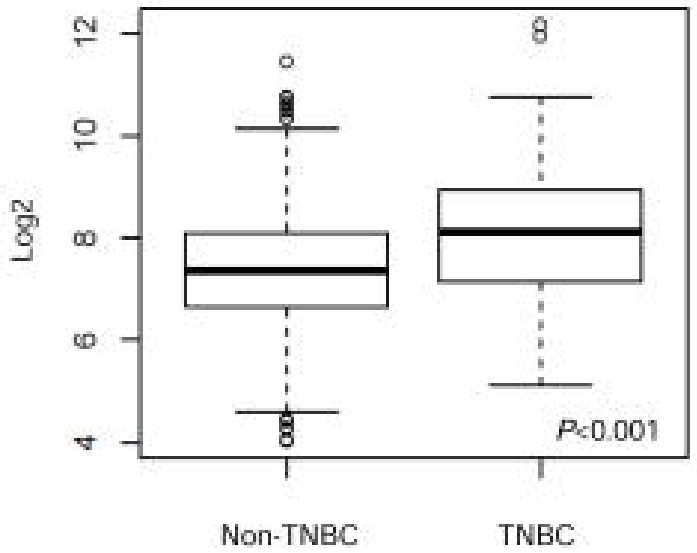
- NCCN recommends either **anthracyclines or taxanes** as preferred first-line options for patients who did not receive these agents previously
- Pembrolizumab for **PD-L1+TNBC (22C3 Ab) in 1L**
- PARP inhibitors for DNA Repair Defect in **2L+**
- Trop-2-targeted ADC, sacituzumab govitecan, is approved **2+L setting**
- **Tumor Agnostic approval of pembrolizumab**: In patients with high levels of microsatellite instability (MSI), deficient mismatch repair (dMMR), or high tumor mutational burden (TMB), pembrolizumab is approved as monotherapy

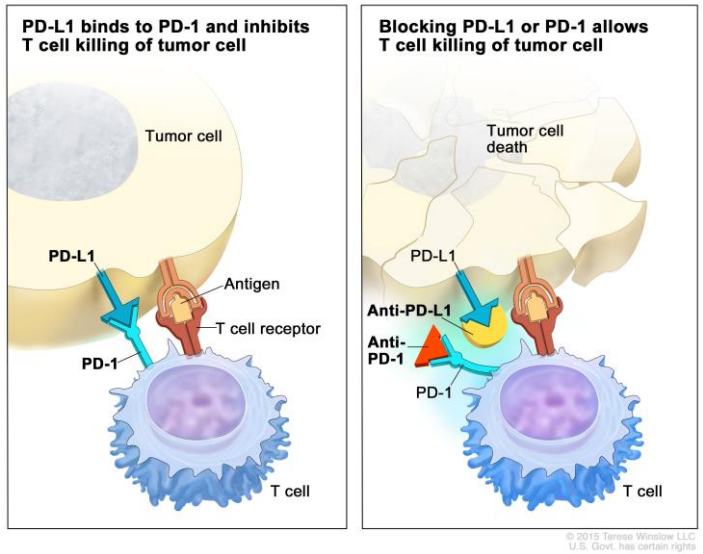
TNBC: more immuno-responsive

Tumor Infiltrating Lymphocytes[1]



PD-L1 Expression[2]





Loi. JCO. 2013
Mittendorf. Cancer Immunol Res. 2014
Cancer.gov

IMpassion130: Atezolizumab 1st line TNBC

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + nab-P arm:
Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

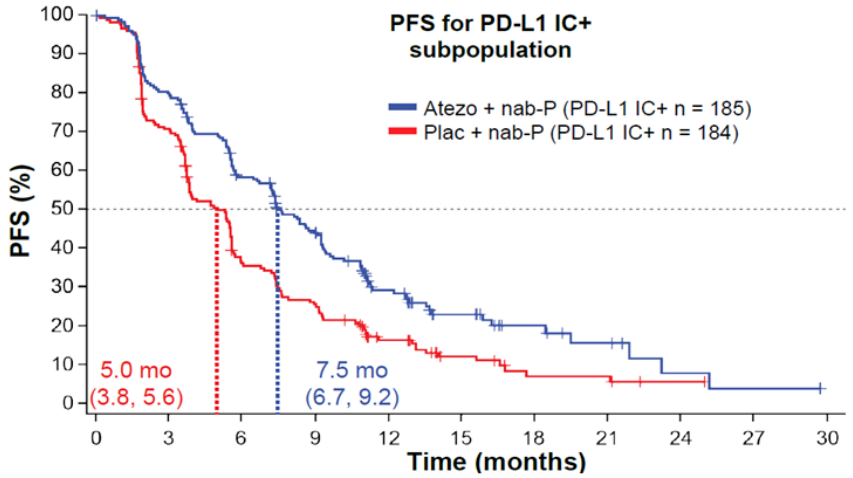
+ *nab*-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

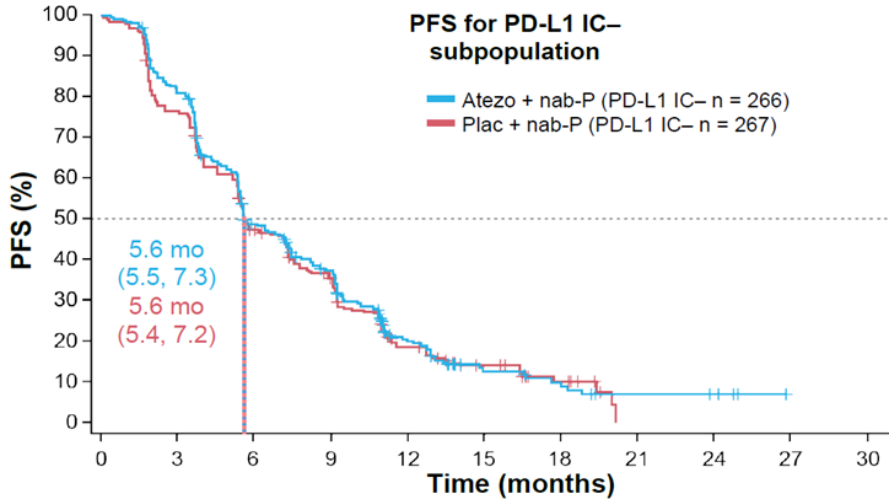
Plac + nab-P arm:
Placebo IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

RECIST v1.1
PD or toxicity



- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated



N=451 each arm

SP142 PD-L1 : 41% PD-L1+ (≥ 1 % IC).

Schmid P et ESMO 2018

IMpassion131: Atezolizumab+ Paclitaxel 1st line TNBC

- Metastatic or unresectable locally advanced TNBC
- No prior chemotherapy or targeted therapy for advanced TNBC
- Previous eBC treatment completed ≥12 months before randomisation
- Taxane eligible
- Measurable disease
- ECOG PS 0/1

R
2:1

Atezolizumab 840 mg d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

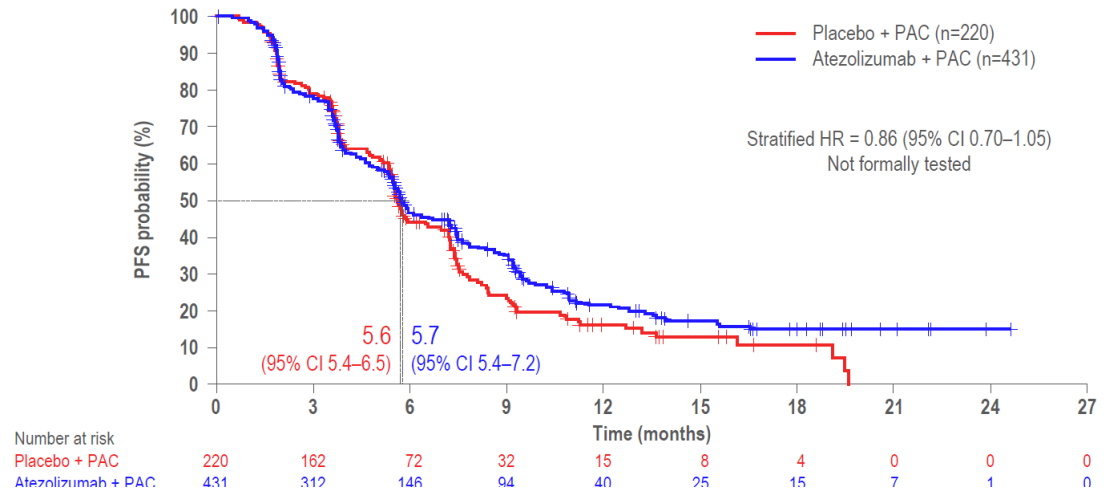
8–10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

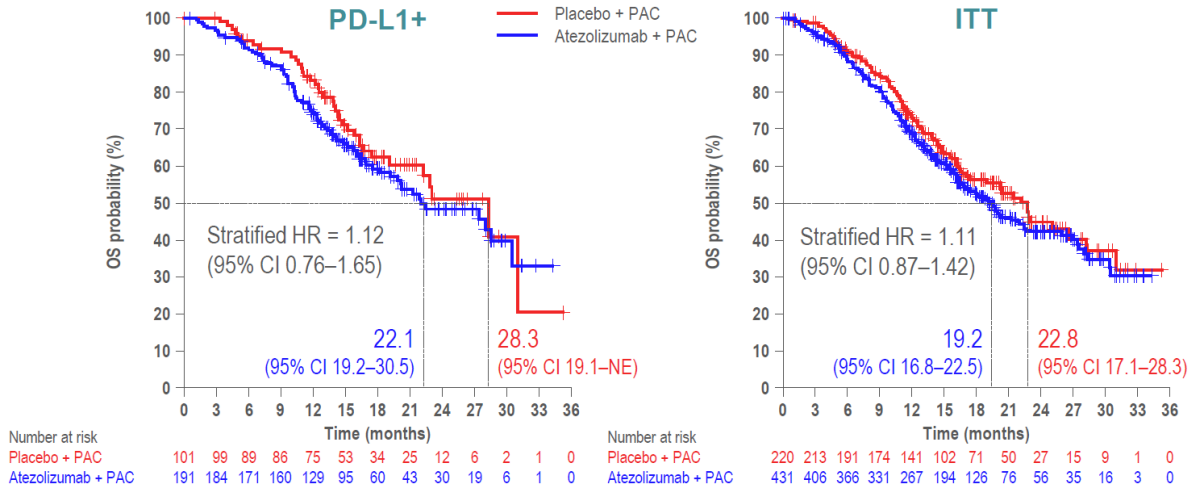
Placebo d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

Stratification:
- Prior taxane (yes vs no)
- Tumour PD-L1 status (IC <1% vs ≥1%)[a]
- Liver metastases (yes vs no)
- Geographical region (N America vs W Europe/Australia vs E Europe/Asia Pacific vs S America)

Primary endpoint: PFS (investigator assessed)
Secondary endpoints include:
- OS, ORR, PFS (IRC assessed)
- PROs
- Safety
- Translational research

[a]PD-L1 IC: area of PD-L1-stained tumour-infiltrating ICs as a percentage of tumour area by VENTANA SP142 immunohistochemistry assay. eBC = early breast cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; IC = immune cell; IRC = independent review committee; ORR = objective response rate; PRO = patient-reported outcome; q28d = every 28 days; R = randomisation





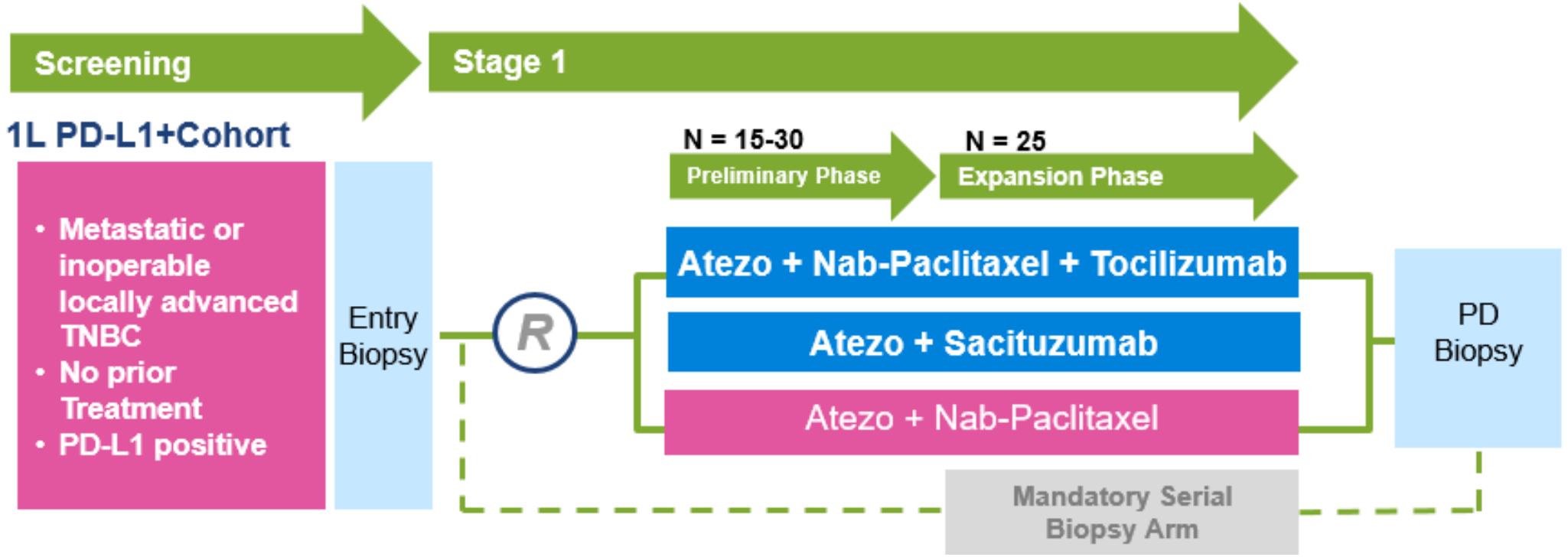
Median duration of follow-up: 14.5 months (placebo + PAC) vs 14.1 months (atezolizumab + PAC) in the ITT population

- The primary objective of IMpassion131 was not met: addition of atezolizumab to paclitaxel did not significantly improve PFS in patients with PD-L1-positive metastatic TNBC
- There was no evidence of an OS benefit (secondary endpoint) with the addition of atezolizumab to paclitaxel
- Potential reasons for the contrast with the benefit seen in IMpassion130 requires further exploration

City of Hope

Miles D ESMO 2020

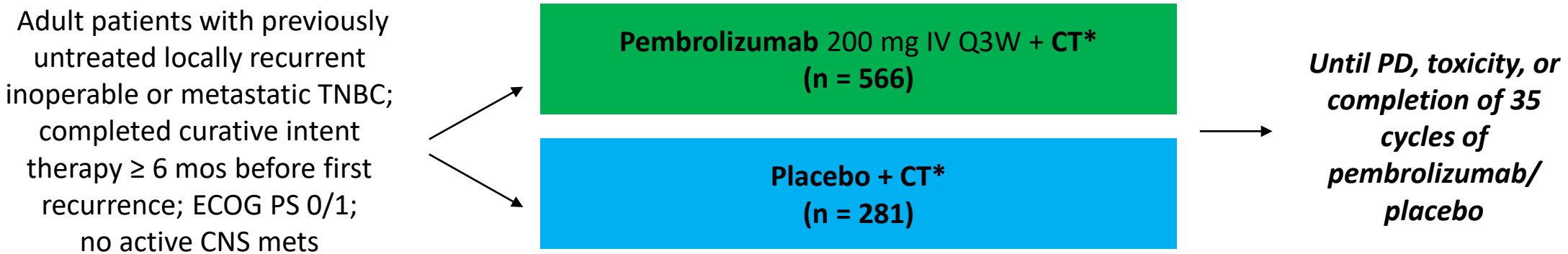
Morpheus TNBC



KEYNOTE-355: Study Design

- Randomized, double-blind, multicenter phase III trial
  - Current analysis reports PFS by CT regimen and key secondary endpoints

Stratified by CT (taxane vs gemcitabine/carboplatin); PD-L1 tumor expression (CPS > 1 vs < 1); previous Tx with same class of CT for EBC (yes vs no)



*Investigator's choice of CT was permitted: nab-paclitaxel 100 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle; paclitaxel 90 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle; or gemcitabine 1000 mg/m^2 + carboplatin AUC 2 on Days 1, 8 of 21-day cycle

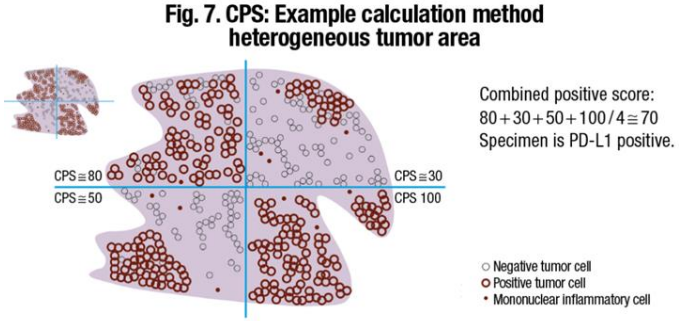
- Primary endpoints: PFS and OS (in PD-L1 CPS ≥ 10, PD-L1 CPS ≥ 1, and ITT)
- Secondary endpoints: ORR, DoR, DCR, safety

Rugo. SABCS 2020. Abstr GS3-01.

KEYNOTE-355: Pembrolizumab in 1st Line metastatic TNBC:

- First-line pembrolizumab + CT improved PFS in patients with PD-L1 positive (CPS ≥ 10) metastatic TNBC: 9.7 vs 5.6 mo in PD-L1>10% goup

PFS	Pembrolizumab + CT	Placebo + CT	HR (95% CI)
PD-L1 CPS ≥10	(n = 220)	(n = 103)	
▪ Median PFS, mo	9.7	5.6	0.66 (0.50-0.88)
▪ 12-mo PFS, %	39.1	23.0	
PD-L1 CPS ≥1	(n = 425)	(n = 211)	
▪ Median PFS, mo	7.6	5.6	0.75 (0.62-0.91)
▪ 12-mo PFS, %	31.7	19.4	
ITT population	(n = 566)	(n = 281)	
▪ Median PFS, mo	7.5	5.6	0.82 (0.70-0.98)
▪ 12-mo PFS, %	29.3	20.8	



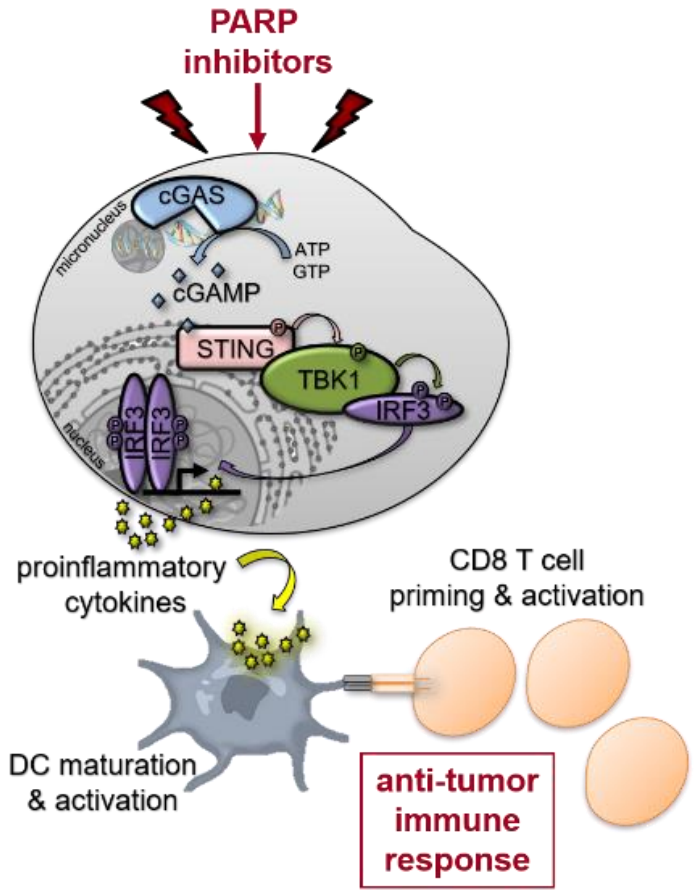
- OS update : Pembro plus chemo significantly prolonged OS and PFS in patients with PD-L1–positive (CPS ≥10) metastatic TNBC
  - Median OS with PD-L1 CPS ≥10: 23.0 mo vs 16.1 mo without pembrolizumab
  - Median PFS with PD-L1 CPS ≥10: 9.7 mo vs 5.6 mo without pembrolizumab

Rugo ESMO 2021

PARP Inhibitors May Activate Immune Responses

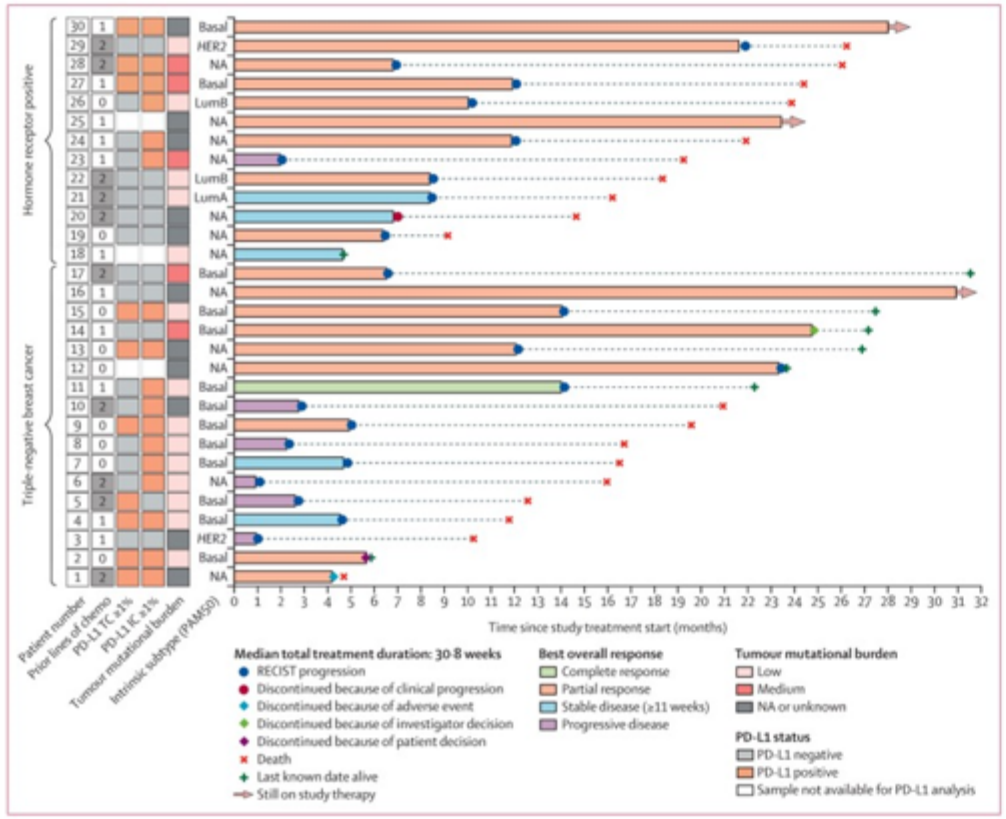
- PARP inhibitors may activate the cGAS/STING (stimulator of interferon genes) pathway
  - ↑ proinflammatory cytokines
  - ↑ Ag presentation
  - ↑ PD-L1 expression

- PARPi + ICI synergistic

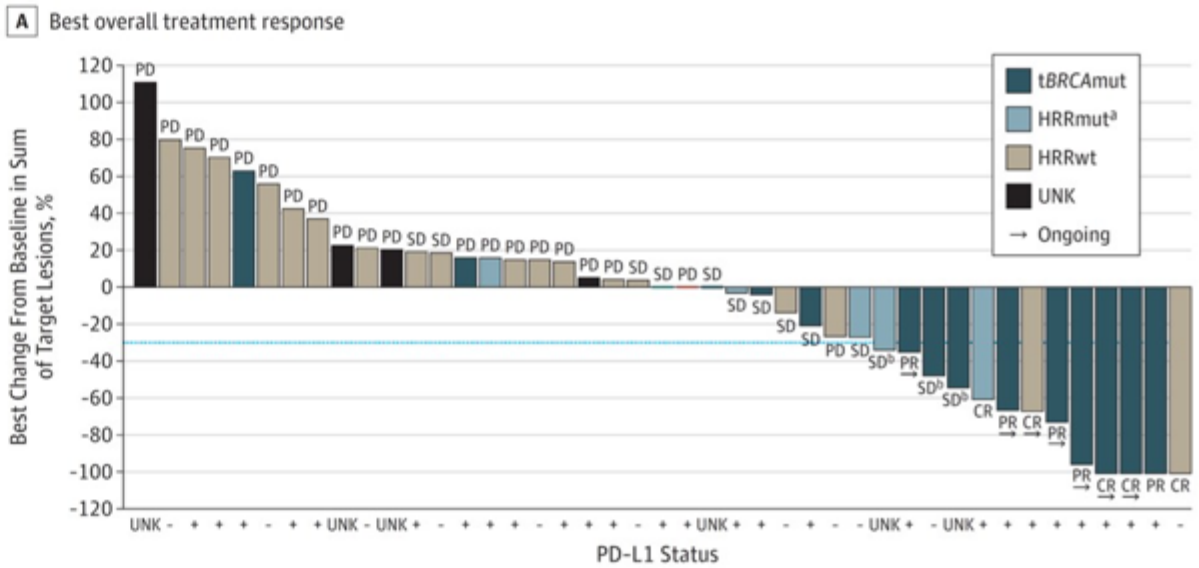


Huang J et al. Biochem Biophys Res Commun 2015
Jiao S et al. Clin Cancer Res 2017
Sato H et al. Nat Commun 2017
Pantelidou C et al. Cancer Discov 2019

Combination of PARPi and Immune Checkpoint inhibitor



Combination of ***olaparib*** and ***durvalumab*** (MEDIOLA trial) showed promising antitumor activity in patients with germline BRCA-mutated metastatic breast cancer



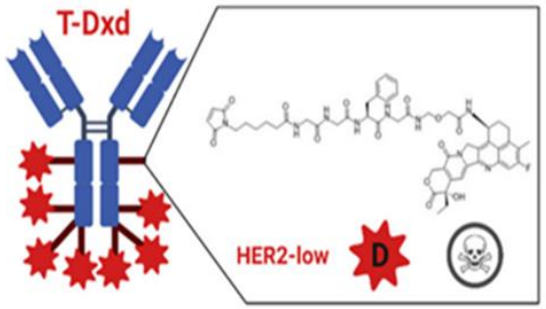
Combination ***niraparib*** plus ***pembrolizumab*** (TOPACIO trial) provides promising antitumor activity in patients with advanced or metastatic TNBC, with numerically higher response rates in those with tumor *BRCA* mutations

City of Hope.

Domchek SM et al Lancet 2020
Vinayak et al JAMA Oncology 2019

Novel ADCs in TNBC

- Trastuzumab Deruxtecan (T-DXd)
- Trop2 ADC:
  - Sacituzumab Govitecan (SG)
  - Datopotamab Deruxtecan (Dato-Dxd)
- HER3 ADC (Patritumab)



Target Antigen: HER2 (trastuzumab vehicle)

mAb isotype: IgG1

Linker type: cleavable

Payload (class): Dxd (Camptothecin)

Payload action: Topoisomerase-1 inhibitor

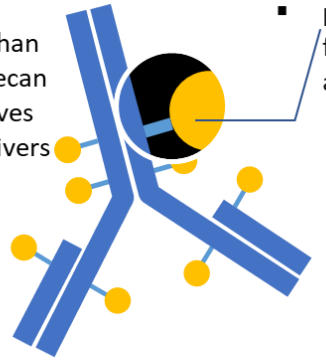
DAR: 8

Linker for SN-38

- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid release of payload at or inside tumor

SN-38 Payload

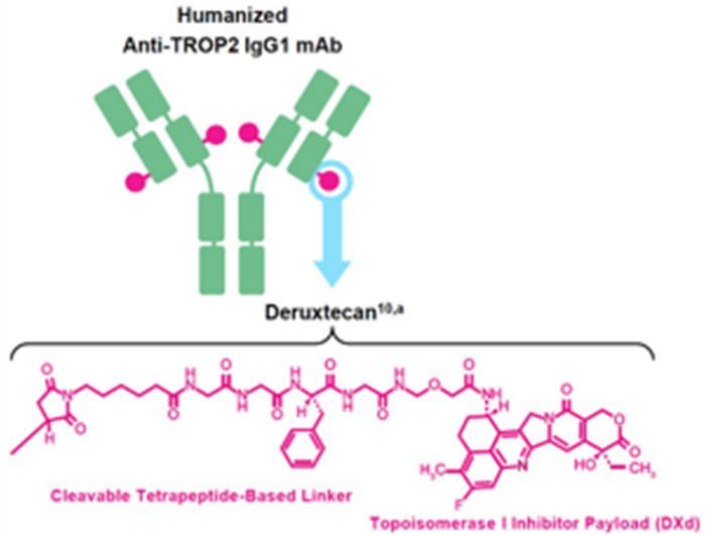
- Delivers 136-fold more than parent compound irinotecan
- Unique chemistry improves solubility, selectively delivers SN-38 to tumor



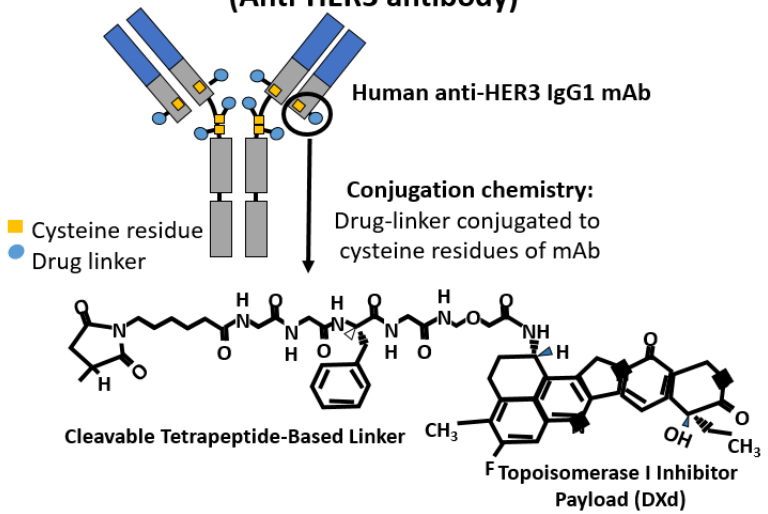
Humanized Anti-TROP2 Antibody

- Antibody type: hRS7 IgG1κ

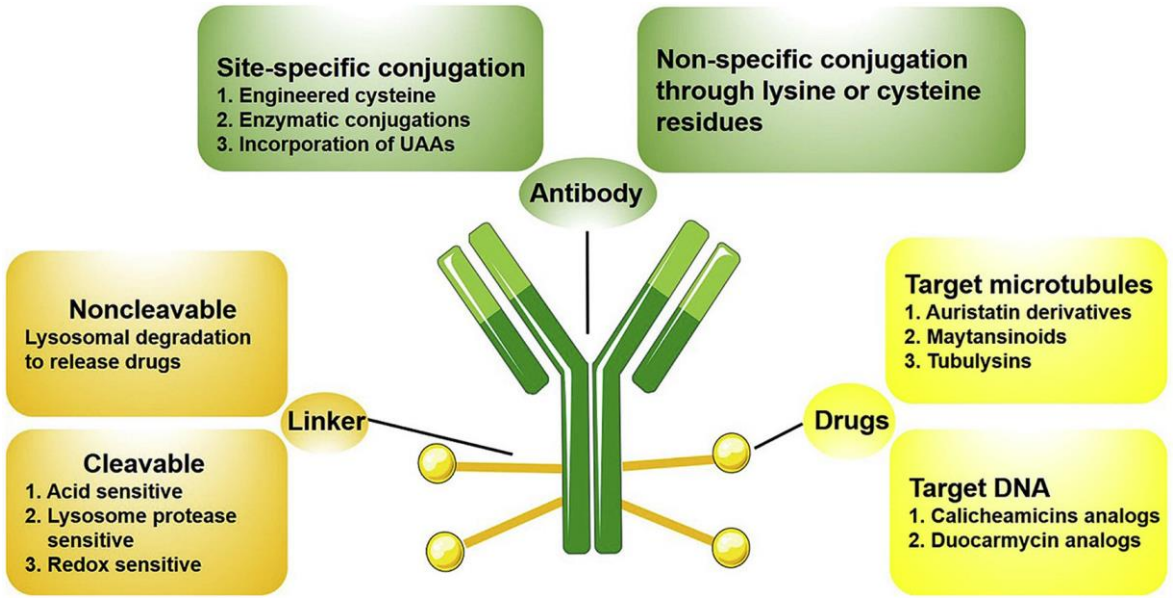
Datopotamab Deruxtecan

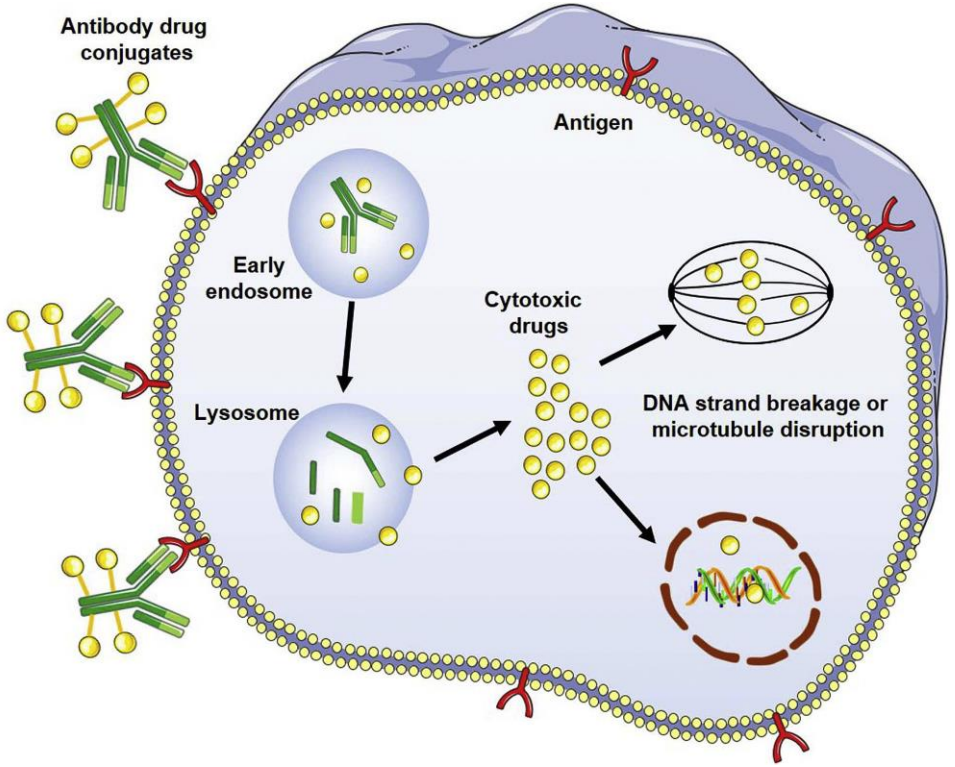


Patritumab Deruxtecan (Anti-HER3 antibody)



Antibody Drug Conjugates

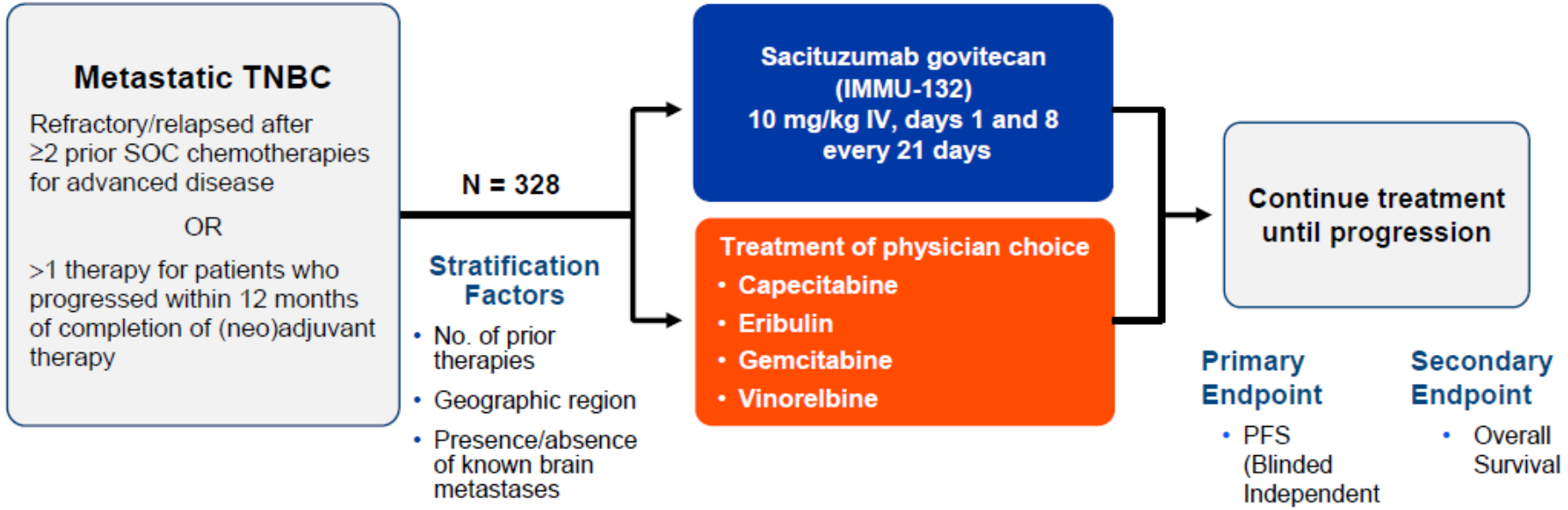




- Ado-trastuzumab emtansine (T-DM1)
- Fam-trastuzumab deruxtecan (DS-8201)
- Sacituzumab govitecan (IMMU-132)
- Patritumab

Zhao et al Acta Pharmaceutica Sinica B 2020

Phase III ASCENT Trial

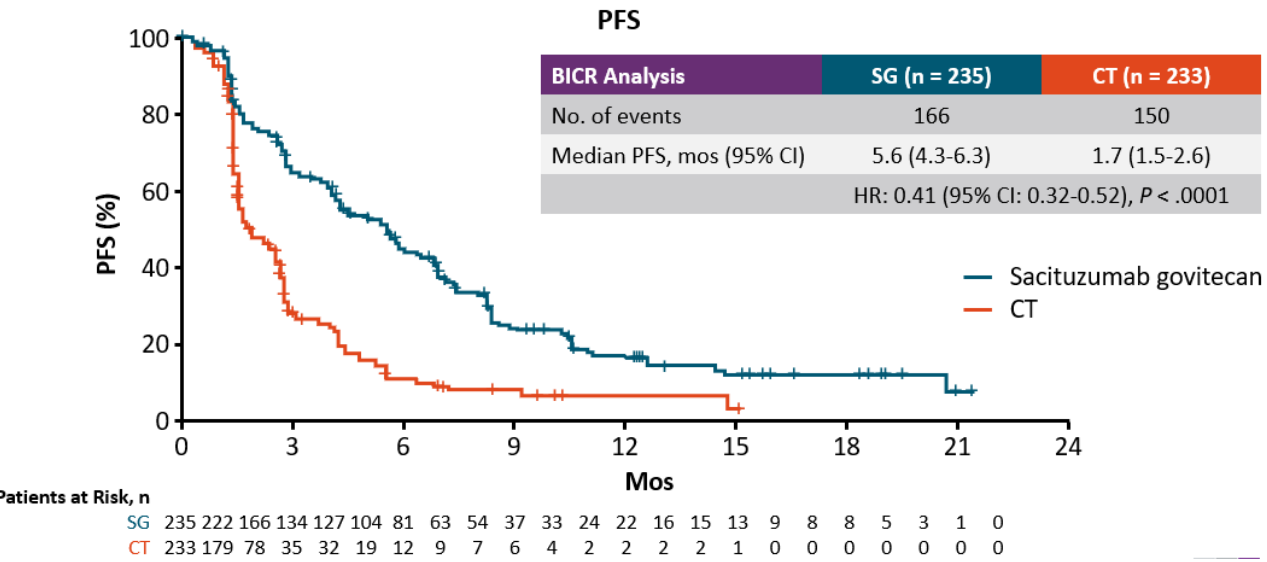


- Clinical trials number: NCT02574455

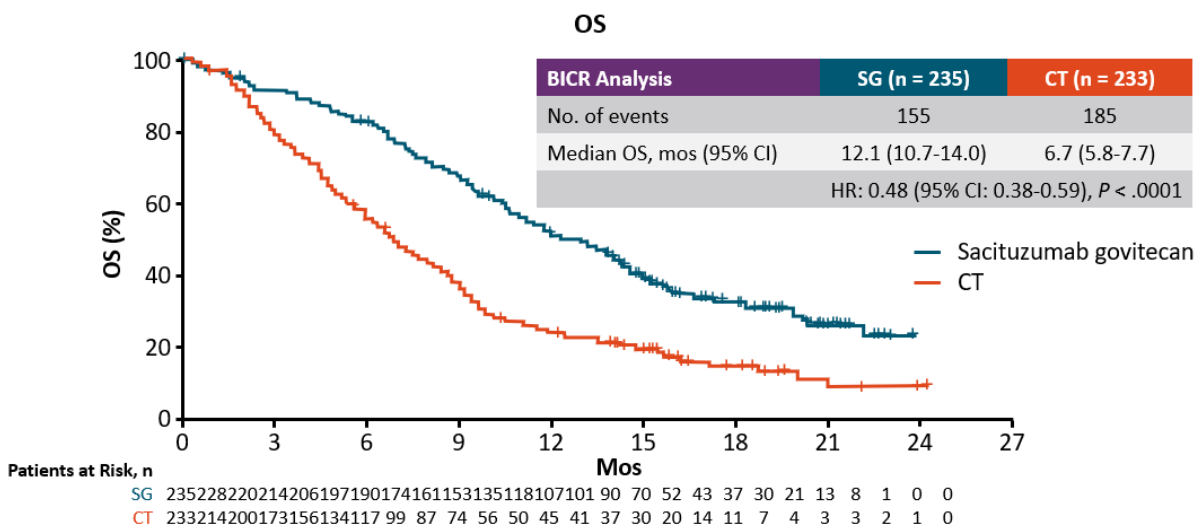
	Sacituzumab Govitecan (n = 235)		Physician's Choice CT (n = 233)
ORR, n (%)	82 (35)		11 (5)
P value		< .0001	
CR, n (%)	10 (4)		2 (1)
PR, n (%)	72 (31)		9 (4)
CBR, n (%)	105 (45)		20 (9)
P value		< .0001	
Median DOR, mos	6.3		3.6
P value		.057	

Bardia et al ESMO 2020

Phase III ASCENT Trial



BICR Analysis	SG (n = 235)	CT (n = 233)
No. of events	166	150
Median PFS, mos (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
	HR: 0.41 (95% CI: 0.32-0.52), *P* < .0001	



BICR Analysis	SG (n = 235)	CT (n = 233)
No. of events	155	185
Median OS, mos (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
	HR: 0.48 (95% CI: 0.38-0.59), *P* < .0001	

PFS was 5.6 months (95% confidence interval [CI], 4.3 to 6.3; 166 events) with sacituzumab govitecan and 1.7 months with chemo

The median overall survival was 12.1 months (95% CI, 10.7 to 14.0) with sacituzumab govitecan and 6.7 months (95% CI, 5.8 to 7.7) with chemotherapy (hazard ratio for death, 0.48; 95% CI, 0.38 to 0.59; P<0.001).

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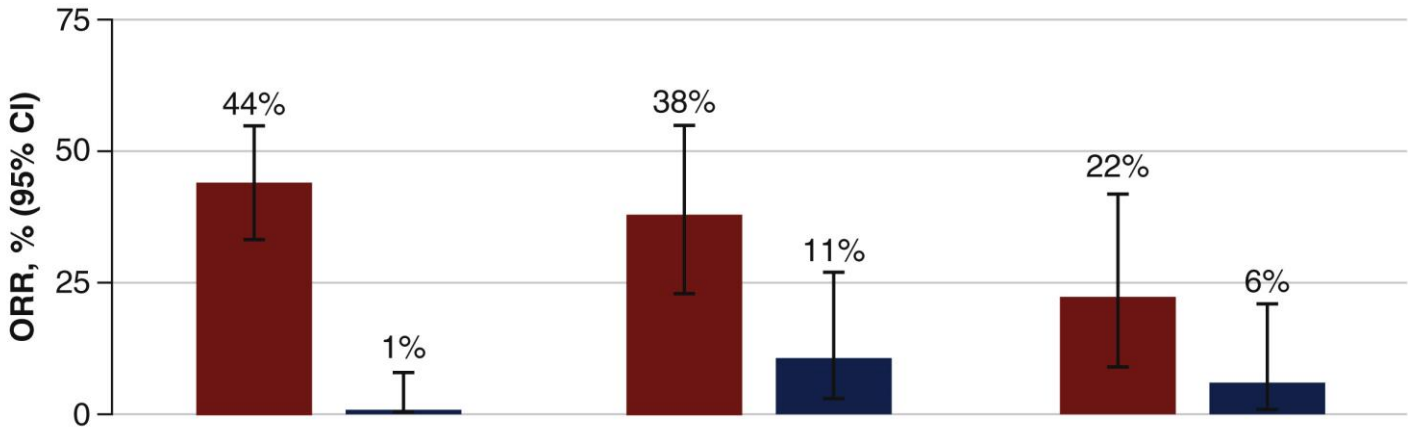
Bardia et al ESMO 2020

ORR by TROP-2 IHC Expression in ASCENT Study of Sacituzumab



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

Bardia. Ann Oncol. 2021;32:1148.

ASCENT 04: PD-L1+ TNBC, 1st line

1L mTNBC PD-L1+

(per ASCO/CAP)

- Previously untreated, inoperable, locally advanced OR metastatic
- PD-L1+ by PD-L1 IHC 22C3 (CPS ≥ 10)
- ≥ 6 months since treatment in curative setting.
- PD-L1 and TNBC status must be centrally confirmed

N=570. No more than 25% de novo.

R 1:1

Arm A: Sacituzumab Govitecan (SG) 10 mg/kg IV days 1 & 8, every 21-day cycle and pembrolizumab 200 mg on Day 1 of 21-day cycles

Arm B: Treatment of Physician's Choice (TPC)* and pembrolizumab 200 mg

Continue treatment until BICR-confirmed disease progression or unacceptable toxicity

Long-term Follow-up

Crossover to SG in eligible patients allowed after BICR-confirmed disease progression

Stratification factors

- De novo versus recurrent disease within 6 to 12 months of treatment in the curative setting versus recurrent disease occurring > 12 months of treatment in the curative setting
- Geographic region (North America vs Rest of World)
- Prior exposure to anti-PD-(L)1 therapy (yes/no)

Endpoints

Primary

- PFS in ITT population†

Secondary

- OS, ORR, DOR, TTR, PROs, safety

*TPC: gemcitabine 1000 mg/m2 plus carboplatin AUC 2 on Days 1 and 8 of a 21-day cycle, or paclitaxel 90 mg/m2 on Days 1, 8, and 15 of a 28-day cycle, or nab-Paclitaxel 100 mg/m2 on Days 1, 8, and 15 of a 28-day cycle.

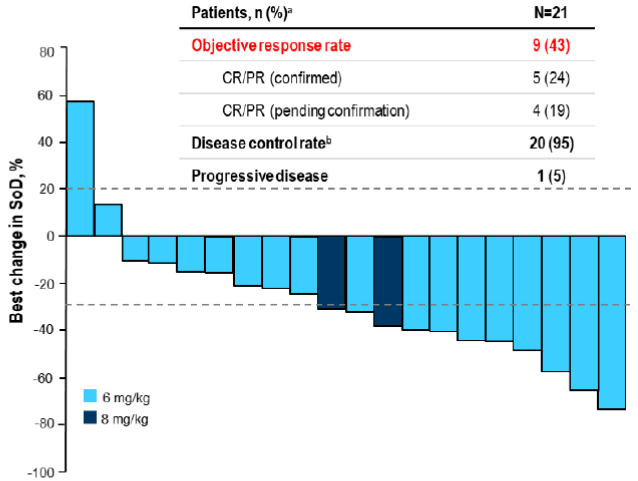
†PFS measured by blinded independent central review who will assess tumor response using RECIST 1.1 criteria. BICR=blinded independent central review CPS=combined positive score; DOR=duration of response; IV,=intravenous; ITT=intent to treat; mTNBC=metastatic triple-negative breast cancer; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; PRO=patient-reported outcomes; R=randomization; RECIST=Response Evaluation Criteria in Solid Tumors; TTR: time to response

Dato-DXd: TROPION-PanTumor01

Phase 1 Study of Dato-DXd

- Patients aged ≥18 (US) or 20 (Japan) with **metastatic/unresectable advanced solid tumors and**
  - **Relapsed from/refractory to standard treatment (or for which no standard treatment is available)**
  - ECOG PS 0-1
  - Measurable disease per RECIST v1.1
- **Unselected for TROP2 expression**
  - Pretreatment tumor tissue required for retrospective analysis of TROP2 expression

- **TNBC enrollment completed:**
  - 8.0 mg/kg: 2 patients
  - 6.0 mg/kg: 42 patients
- **HR-positive/HER2-negative BC enrollment ongoing**
  - 6.0 mg/kg: target is 40 patients

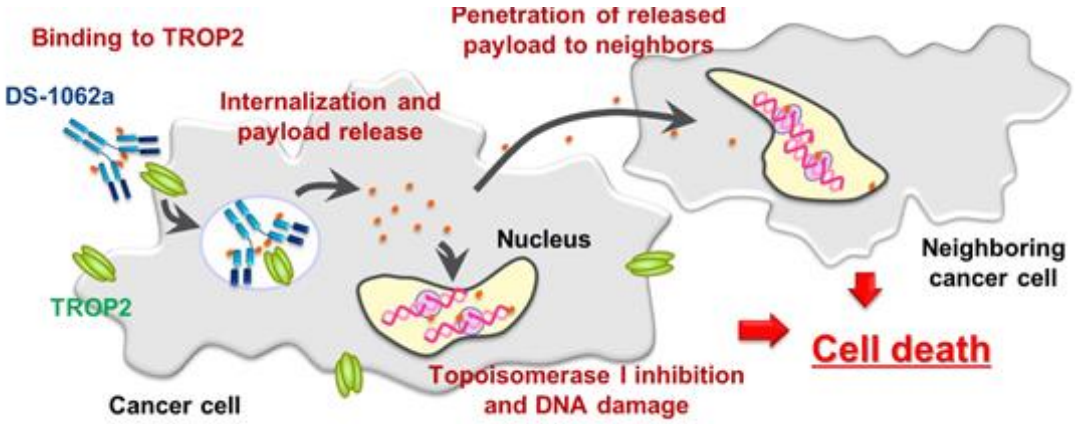


Patients, n (%)[a]	N=21
Objective response rate	9 (43)
CR/PR (confirmed)	5 (24)
CR/PR (pending confirmation)	4 (19)
Disease control rate[b]	20 (95)
Progressive disease	1 (5)

N= 21
ORR 43%
DCR 95%

- **8.0 mg/kg is determined as the MTD**
- **6.0 mg/kg is the recommended Ph3 dose (Lower rates of AEs and severe AEs; similar efficacy as for 8mg/kg)**

ECOG, Eastern Cooperative Oncology Group; MTD, maximum tolerated dose; NSCLC, non–small cell lung cancer; PS, performance status; RDE, recommended do
RECIST, Response Evaluation Criteria in Solid Tumors; TROP2, trophoblast cell-surface protein 2; US, United States.



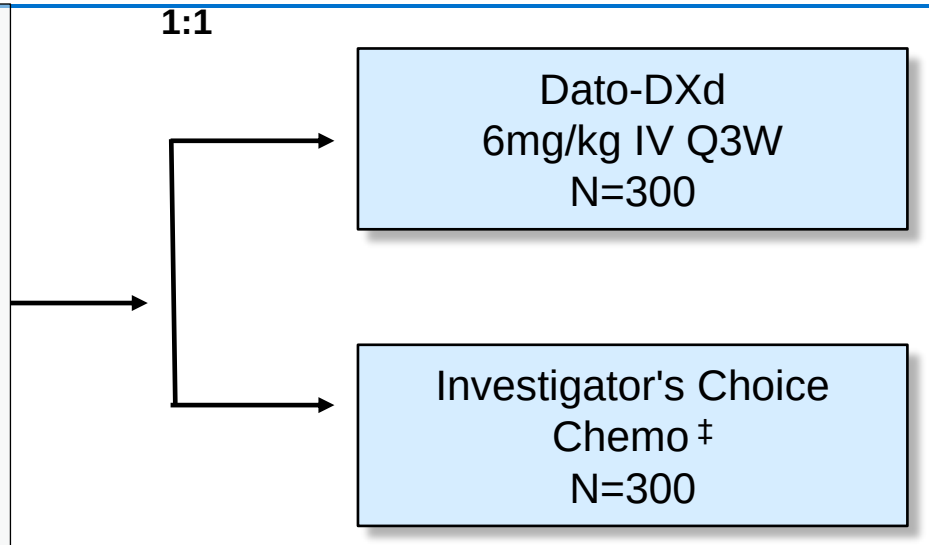
City of Hope.

Bardia et al ESMO Breast Cancer irtual Congress 2021

TROPIONBreast02

Key Eligibility Criteria

- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not candidate for PD-1/PD-L1 inhibitor therapy †
- Measurable disease as defined by RECIST v1.1
- Mandatory tumor sample ≤ 3 months old*
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function



Dual primary endpoints
PFS (BICR), OS

Secondary endpoints
PFS (inv), ORR, DoR, TTD, DCR, PRO, Safety, Tolerability, PK, and Immunogenicity

Exploratory endpoints
TROP2, PD-L1

Stratification factors:

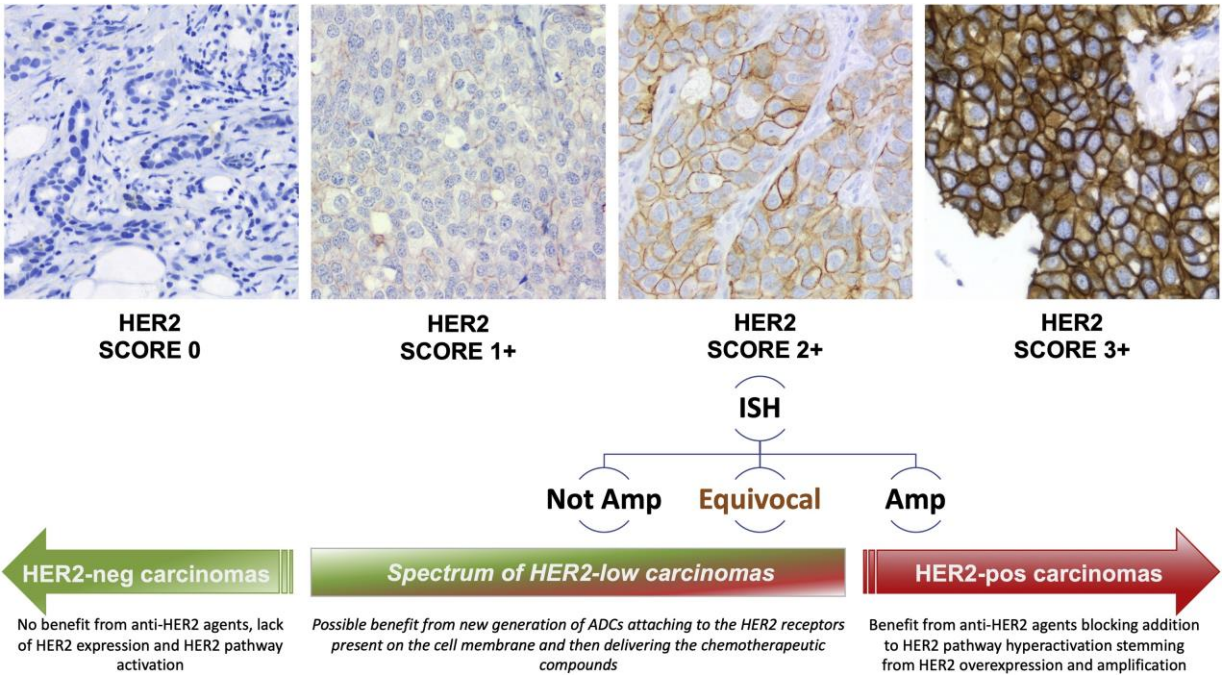
- Geographic location (US/Canada/EU vs rest of world)
- DFI** (de novo vs prior DFI≤12 mo vs prior DFI>12 mo)
- PD-L1 status (positive vs negative)

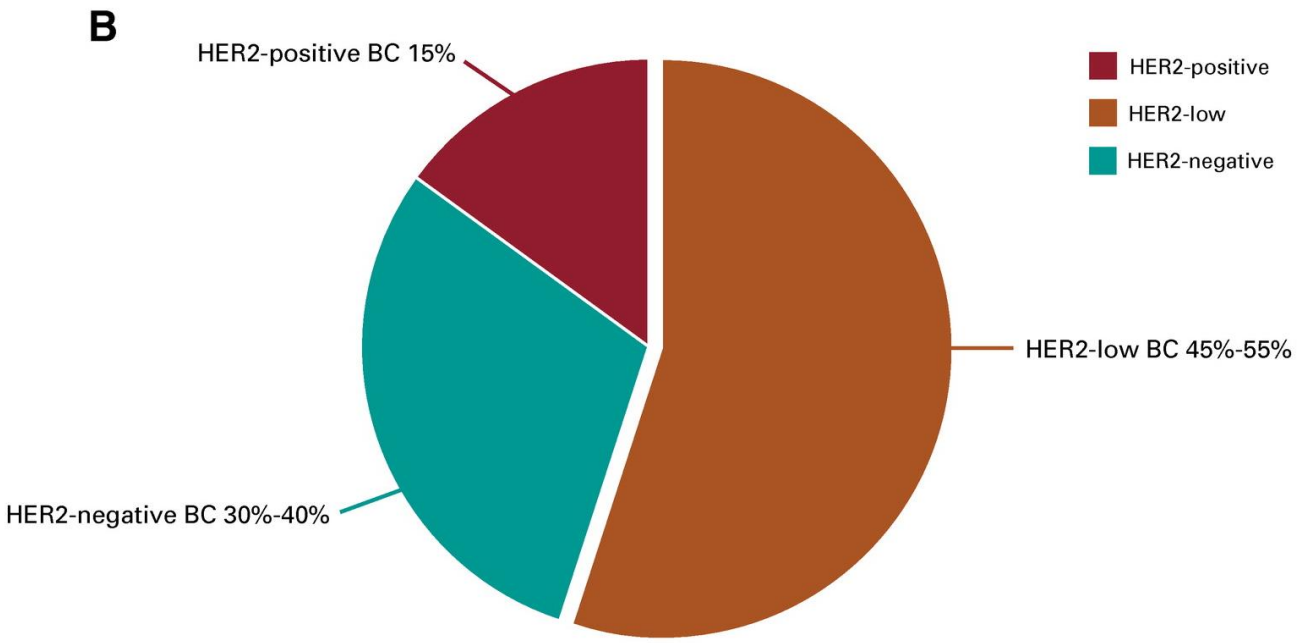
Response assessment: Scan Q6W for 48 weeks, then Q9W thereafter *until RECIST1.1 disease progression (as assessed by Investigator), regardless of study intervention discontinuation or start of subsequent anticancer therapy. Following disease progression, 1 additional follow-up scan should be performed as per Imaging schedule (i.e., either 6 weeks or 9 weeks later).*

Ongoing trials for ADCs in mTNBC

Register number (target accrual, N)	Design; arms and regimen	Study population	Primary outcome	Status
SGN-LIV1A				
NCT03310957 *N* = 122	Phase I/II, single arm; SGN-LIV1A plus pembrolizumab	Metastatic TNBC	ORR, incidence of AEs and DLT	Accruing
NCT01969643 *N* = 418	Phase I dose escalation and dose expansion; different cohorts will receive SGN-LIV1A monotherapy or in combination with trastuzumab	Metastatic TNBC and HER2-positive	Incidence of AEs	Accruing
Morpheus-TNBC NCT03424005 *N* = 280	Phase Ib/II, open label, randomizing to several cohorts, including one of atezolizumab plus sacituzumab govitecan	Metastatic TNBC	ORR, frequency of AEs	Accruing
Trastuzumab duocarmazine				
TULIP NCT03262935 *N* = 436	Phase III; open label, randomizing to one of two arms: trastuzumab duocarmazine vs. TPC	HER2-positive, refractory to at least two lines of CT for MBC	PFS	Completed; results pending
NCT04235101 *N* = 436	Phase I, single arm; trastuzumab duocarmazine plus niraparib	HER2-positive or HER2-low tumors for which no standard therapy exists	Frequency of AEs	Accruing
NCT04602117 *N* = 27	Phase I, single arm; trastuzumab duocarmazine plus paclitaxel	HER2-positive or HER2-low tumors for which no standard therapy exists	Frequency of AEs	Not recruiting yet
Disitamab vedotin (RC48-ADC)				
NCT04400695 *N* = 366	Phase III; open label, randomizing to one of two arms: trastuzumab duocarmazine vs. TPC	HER2-low breast cancer; one to two prior lines of treatment in the advanced setting. Prior treatment with anthracyclines	To assess efficacy (PFS) of ADC vs. control arm	Not recruiting yet
NCT03500380 *N* = 228	Randomized phase II (vs. lapatinib plus capecitabine)	HER2-positive breast cancer; prior treatment with trastuzumab; one to two prior lines of treatment in the advanced setting	To assess efficacy (PFS) of ADC vs. control arm	Accruing; no results to date

HER2 low tumor: 1+ or 2+ by IHC, ISH neg

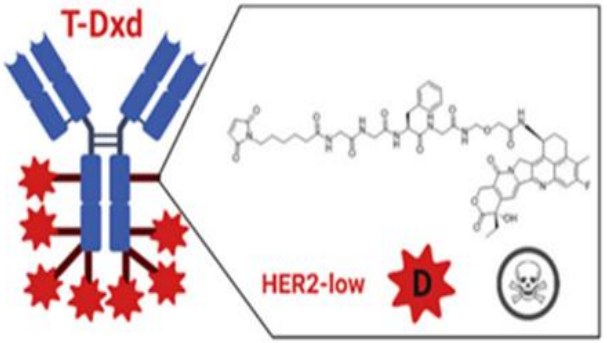




- HER2-low tumor accounts for approx. 45-55% of all MBCs, 60% of HR+HER- MBC ; **30% of TNBCs**

Marchio et al Seminars in Cancer Biology 2021
Tarantino et al JCO 2020
Agostinetto et al Cancers 2021

Trastuzumab Deruxtecan (T-DXd) Phase Ib Study (N=51): HER2-Low Tumors



Target Antigen: HER2 (trastuzumab vehicle)

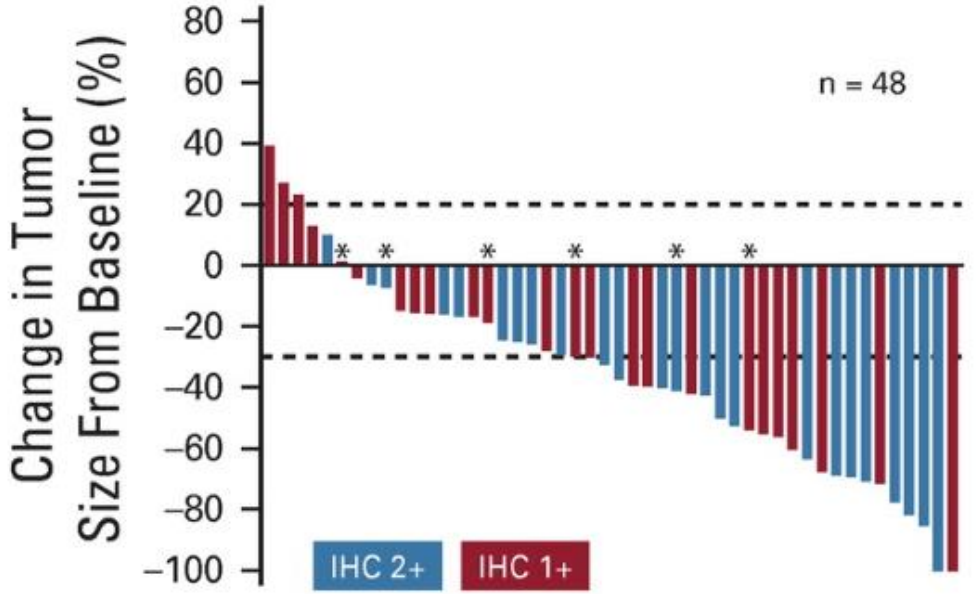
mAb isotype: IgG1

Linker type: cleavable

Payload (class): Dxd (Camptothecin)

Payload action: Topoisomerase-1 inhibitor

DAR: 8



T-Dxd showed efficacy in HER-low tumor

- ORR of 44%
- DCR of 85%
- PFS 12.9 mon

	Confirmed ORR, % (n)	mDoR, mo	mPFS, mo
All (N = 51)	44.2 (43)	9.4	7.6
IHC 2+ (n = 24)	54.5 (22)	11.0	13.6
IHC 1+ (n = 27)	33.3 (21)	7.9	5.7
HR+ (n = 45)	47.4 (38)	11.0	7.9
Prior CDK4/6 inhibitor (n = 15)	33.3 (12)	NR	7.1

Modi. SABCS 2018. P6-17.02.
Modi. J Clin Oncol. 2020;38:1887
Marchio et al Seminars in Cancer Biology 2021

DESTINY-Breast04: Phase III Study of Trastuzumab Deruxtecan (T-DXd) vs TPC for HER2-Low MBC

- HER2-low (IHC1+ or IHC2+/ISH-) MBC
- 1-2 prior chemo in the metastatic setting or recurrence ≤6 mo after adjuvant CT;
- ≥1 ET if HR-positive;
- Treated, stable brain metastases eligible

(N = 557)

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

Treatment of physician's choice
(n = 184)

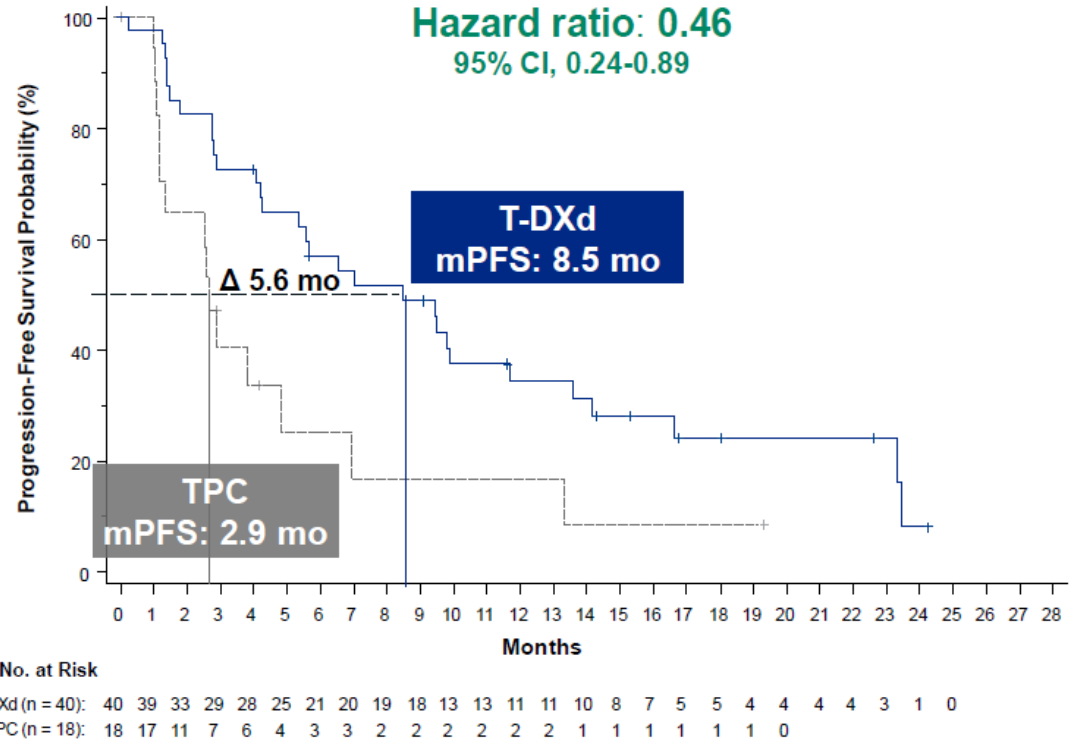
*TPC: capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel.

DB04 established HER2-low MBC as a new targetable population

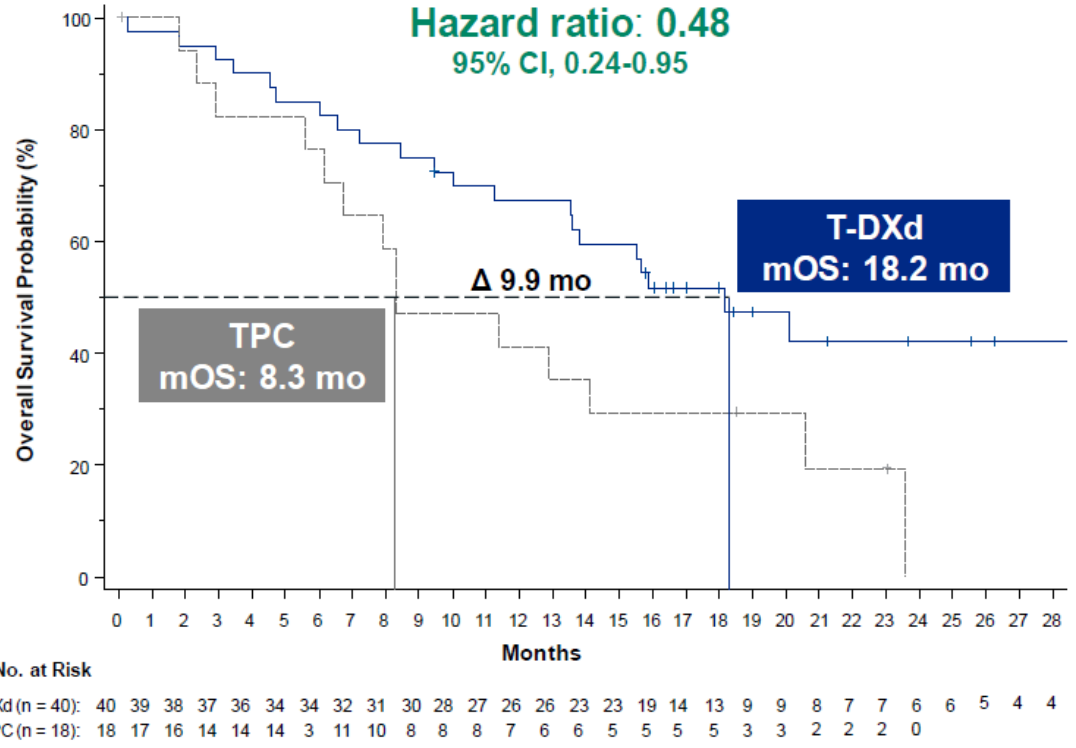
Modi. ASCO 2022. LBA3. Modi. N Eng J Med. 2022

DB04: PFS and OS in HR- (TNBC, N=58): Exploratory Endpoints

PFS

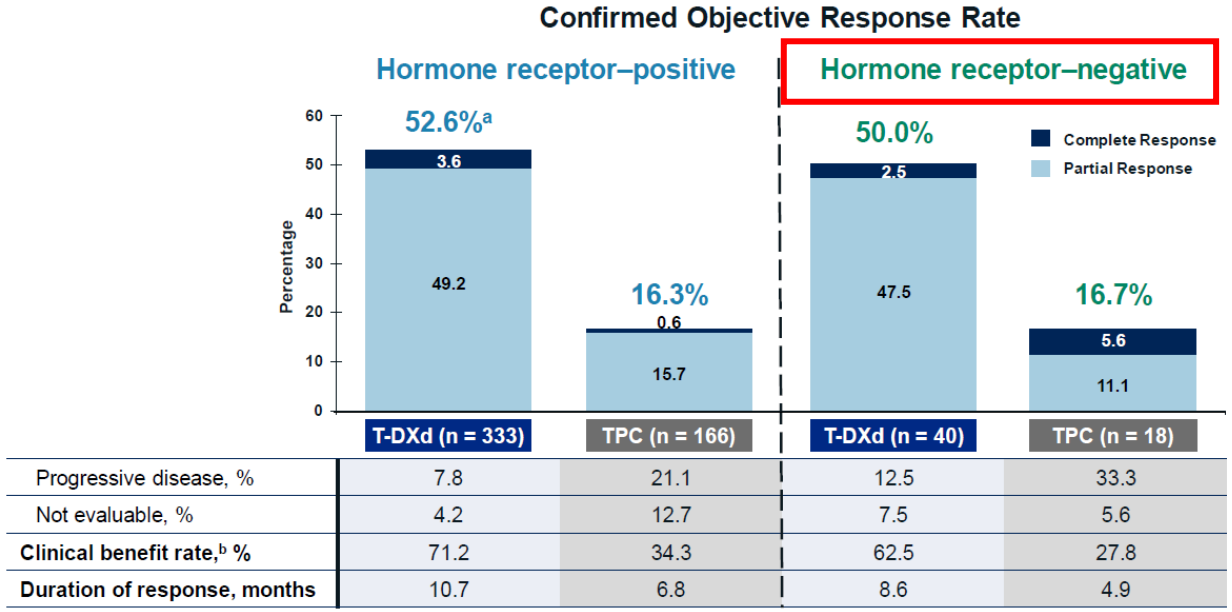


OS

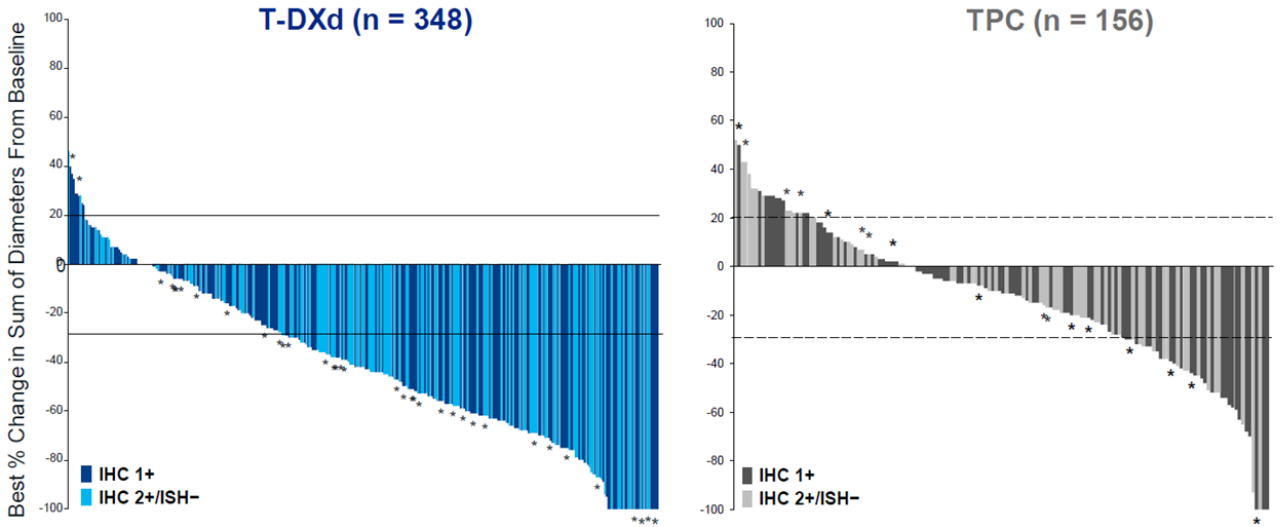


Modi. ASCO 2022. Abstr LBA3. Modi. NEJM. 2022

DB04: Confirmed ORR in HR+ and TNBC



	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



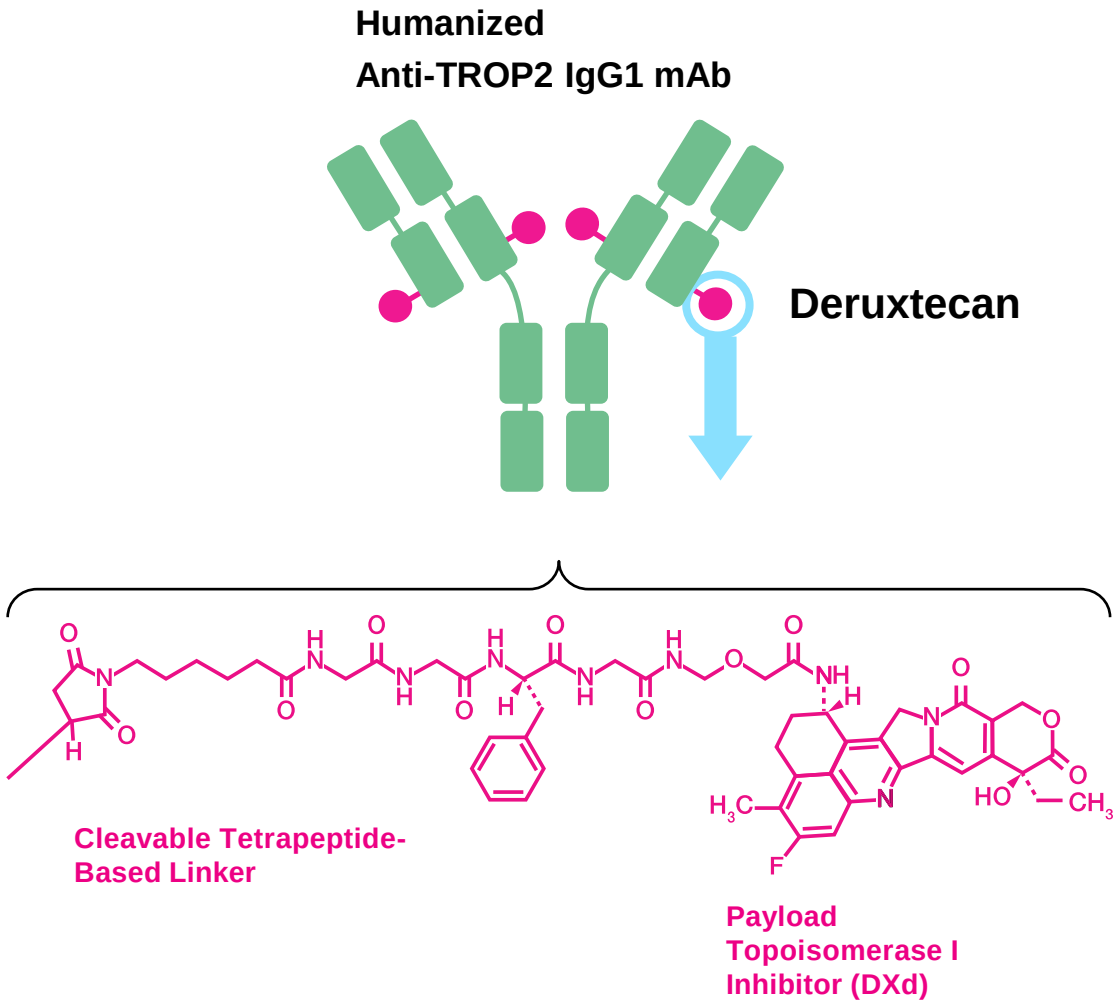
- DB04 TNBC cohort showed impressive ORR, PFS and OS data
- Limited number of patient, N=58 only
- 8/9/22 FDA approval of T-DXd in HER2 low

Modi. ASCO 2022. Abstr LBA3. Modi. NEJM. 2022

Dato-TXd

Dato-DXd is a TROP2-directed ADC designed with 3 components[1]:

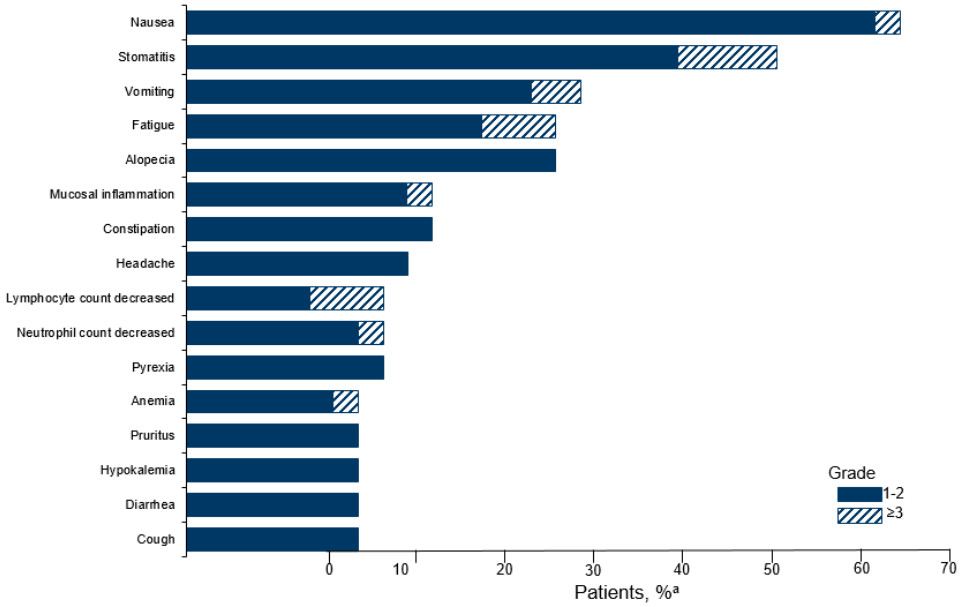
- **Antibody part**: humanized anti-TROP2 IgG1 mAb
- **Cytotoxic part**: topoisomerase I inhibitor payload (Exatecan derivative, DXd); drug-to-antibody ratio ~4:1
- **Linker**: tetrapeptide-based cleavable linker



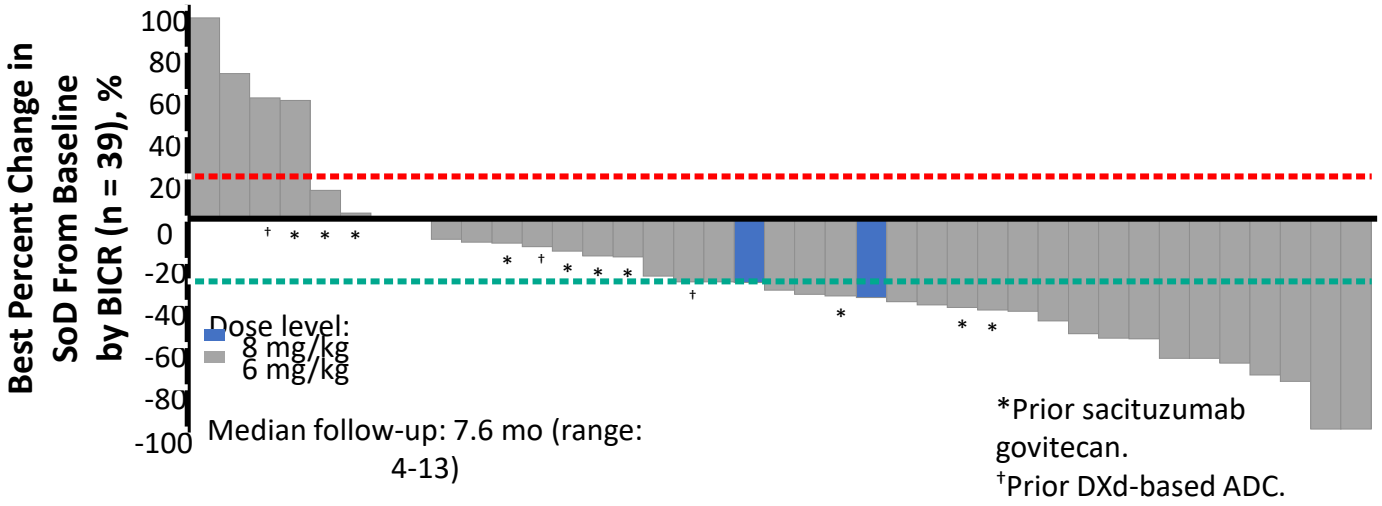
Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185

TROPION-PanTumor01 Trial of Dato-DXd, ADC Targeting TROP2: TNBC Cohort

Patients, n (%)	All Patients (N = 44)
ORR	15 (34)
▪ CR/PR (confirmed)	14 (32)
▪ CR/PR (pending confirmation)	1 (2)
▪ Non-CR/non-PD	3 (7)
▪ Stable disease	17 (39)
▪ Not evaluable	2 (5)
▪ Disease control rate	34 (77)
▪ PD	8 (18)



ILD, interstitial lung disease.
[a] n=44 patients.



- Most common adverse events observed were nausea and stomatitis (predominantly grade 1-2)
- Low frequency of hematologic toxicity and diarrhea
- No cases adjudicated as drug-related ILD

Confirmatory trial: Phase III TROPIONBreast02: DatoDxd vs TPC in TNBC

Krop. SABCS 2021. Abstr GS1-05.

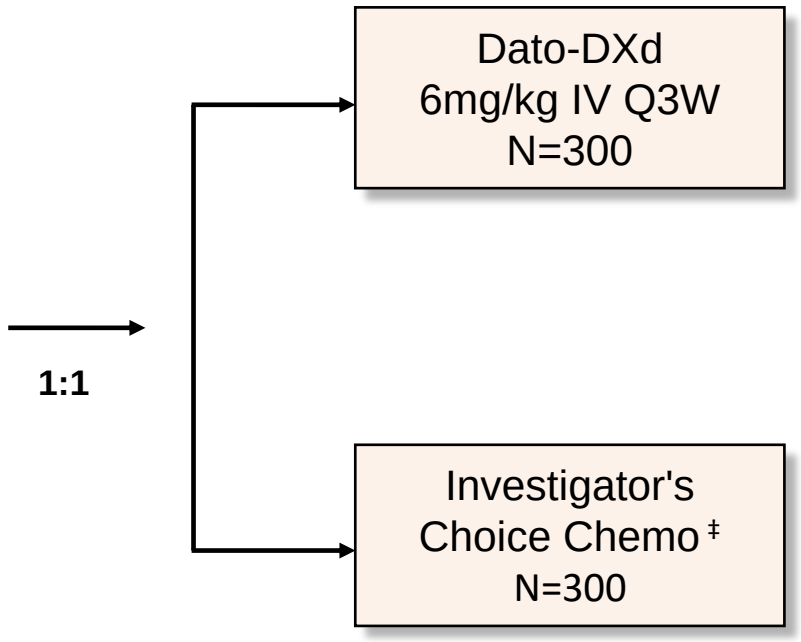
TropionBreast02: Dato-TXd vs TPC in 1st line mTNBC

Key Eligibility Criteria

- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy for metastatic breast cancer
- Not candidate for PD-1/PD-L1 inhibitor therapy †
- Measurable disease as defined by RECIST v1.1
- Mandatory tumor sample ≤ 3 months old*
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function

Stratification factors:

- Geographic location (US/Canada/EU vs rest of world)
- DFI** (de novo vs prior DFI≤12 mo vs prior DFI>12 mo)
- PD-L1 status (positive vs negative)



Dual primary endpoints
PFS (BICR), OS

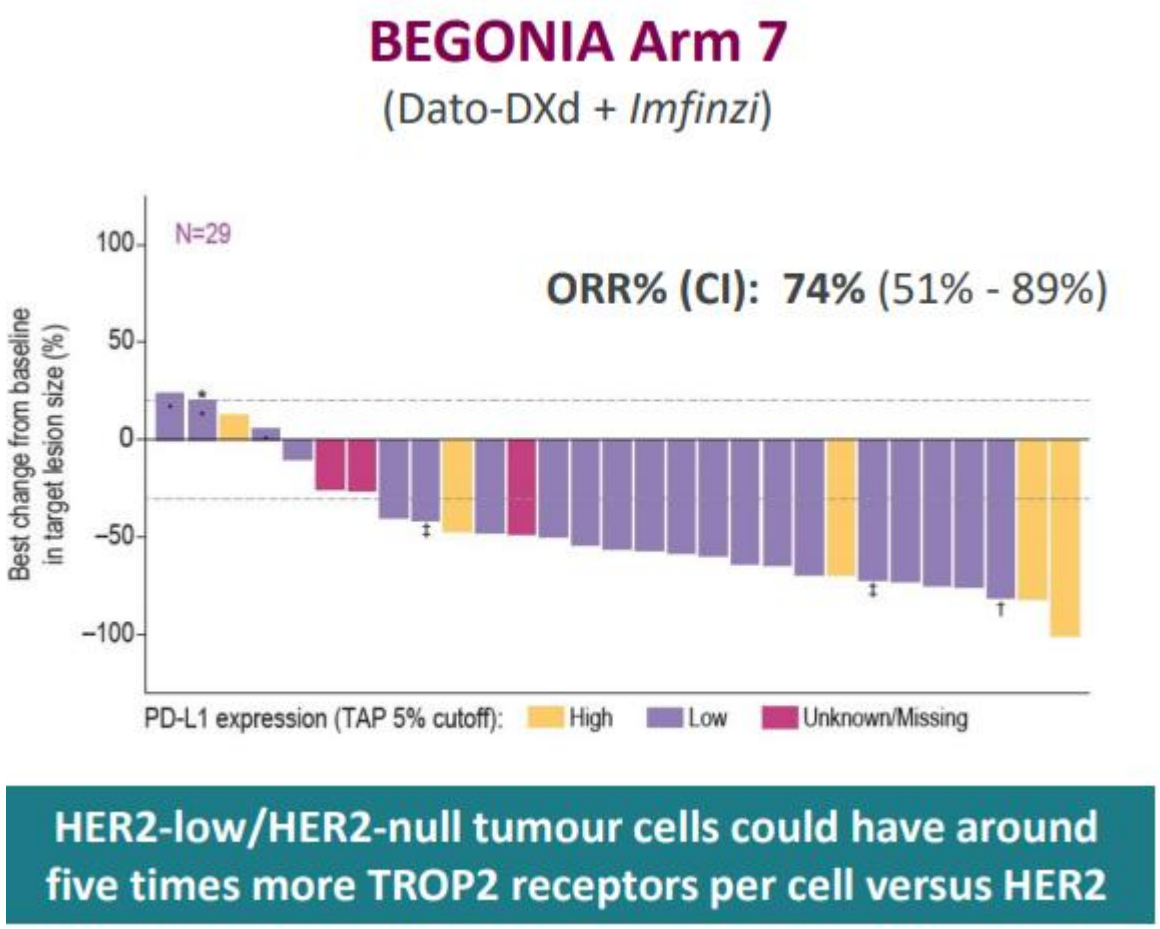
Secondary endpoints
PFS (inv), ORR, DoR, TTD, DCR, PRO, Safety, Tolerability, PK, and Immunogenicity

Exploratory endpoints
TROP2, PD-L1

Response assessment: Scan Q6W for 48 weeks, then Q9W thereafter *until RECIST1.1 disease progression*

† PD-L1 negative, previous PD-1/PD-L1 inhibitor therapy for early-stage breast cancer, comorbidities precluding PD-1/PD-L1 inhibitor therapy, or PD-L1 positive with no access to pembrolizumab (no regulatory approval in country); ‡ If no prior taxane or DFI >12 months, paclitaxel or nab-paclitaxel; If prior taxane and DFI ≤ 12 months: capecitabine, carboplatin, or eribulin; *An archival tumour specimen obtained before the diagnosis of locally recurrent inoperable or metastatic breast cancer may be submitted on a case-by-case basis, pending approval by the Global Study Team; ** DFI: time between completion of treatment with curative intent (either date of primary breast tumour surgery or date of last dose of systemic anti-cancer therapy [not including endocrine therapy], whichever occurred last) and the first documented local or distant disease recurrence (either by biopsy or imaging)

Dato-DXd + Durvalumab as first line TNBC therapy



N = 27, medial follow-up of 3.9 months (range, 2-6)

ORR 74% (95% CI, 54%-89%) , 1 CR and 67% PR irrespective of PD-L1 expression.

Preliminary results of BEGONIA show that datopotamab deruxtecan plus durvalumab demonstrated a robust response rate in first-line locally advanced or metastatic TNBC in a biomarker-unselected population

Schmit P ESMO Breast 2022

Patritumab Deruxtecan in HER3+ MBC: U31402-A-J101 Study

- HER3 overexpressed in 30-50% BC
- HER2-DXd, DAR8
-
- HER3 + defined by IHC 2+ or 3+, over 25% membrane positivity for DE/DF cohort; over 10% for DEXP cohort

KEY ELIGIBILITY CRITERIA

- Advanced/unresectable or metastatic breast cancer
- HER3-positive[a]

DF & DEXP (HR+/HER2−)

- ≥2 and ≤6 lines of prior chemotherapy; ≥2 for advanced disease

DEXP (TNBC)

- 1 to 2 prior chemotherapy regimens for advanced disease

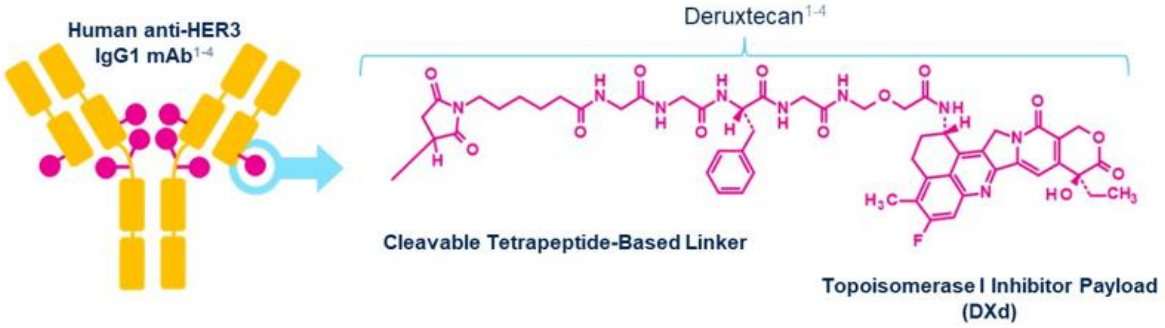
Dose Escalation (DE)[b] Any BC Subtype	Dose Finding (DF) Any BC Subtype	Dose Expansion (DEXP)
8.0 mg/kg IV Q3W n=6		HER3-High[c]: HR+/HER2− 6.4 mg/kg IV Q3W (n=31); 4.8 mg/kg IV Q3W (n=33); TNBC 6.4 mg/kg IV Q3W (n=31)
6.4 mg/kg IV Q3W n=15		
4.8 mg/kg IV Q3W n=15		
3.2 mg/kg IV Q3W n=3	3.2→4.8→6.4 mg/kg Q3W then 6.4 mg/kg Q3W (n=12)	HER3-Low[c]: HR+/HER2− 6.4 mg/kg IV Q3W (n=21)
1.6 mg/kg IV Q3W n=3	4.2 mg/kg IV Q2W × 3 cycles then 6.4 mg/kg IV Q3W (n=12)	

Data for all 3 phases were pooled

- **Efficacy** is reported by BC subtype: HR+/HER2− (n=113), TNBC (n=53), and HER2+ (n=14)
- **Safety** is reported for patients who received HER3-DXd 4.8 mg/kg (n=48), 6.4 mg/kg (n=98), and all patients (N=182[d])

DE, dose escalation; DEXP, dose expansion; DF, dose finding; EWOC, escalation with overdose control; HR, hormone receptor; IHC, immunohistochemistry; mCRM, modified continuous reassessment method; Q2W, once every 2 weeks; Q3W, once every 3 weeks; TNBC, triple-negative breast cancer.

[a] HER3 status was determined by IHC in archival tumor tissue (pre-treatment samples [<6 months prior to HER3-DXd treatment] were used for screening when archival tissue was not available); HER3-positive was defined as IHC 2+ and IHC 3+ for DE/DF cohorts and as ≥25% membrane positivity at 10x for DEXP cohorts. [b] Guided by mCRM with EWOC. [c] HER3-high was defined as ≥75% membrane positivity at 10x; HER3- des two patients with unknown BC subtype.



Ian E. Krop ASCO 2022

Patient Characteristics

		HR+/HER2− (n=113) HER3-High and -Low[a]	TNBC (n=53) HER3-High[a]	HER2+ (n=14) HER3-High[a]
Median age (range), years		55.0 (30-83)	59.0 (30-81)	58.0 (37-70)
Country, %	Japan	70.8	86.8	100.0
	USA	29.2	13.2	0.0
ECOG PS, %	0	75.4	62.3	85.7
	1	24.6	37.7	14.3
HER2 status, %[b]	HER2-zero	34.5	35.8	0.0
	HER2-low	51.3	54.7	0.0
	HER2+	0.0	0.0	100.0
	HER2 IHC 2+ (ISH unknown)	11.5	9.4	0.0
	Unknown	2.7	0.0	0.0
Presence of metastasis (BICR), %	Lung and/or Liver	90.3	64.2	85.7
	Lung	43.4	47.2	42.9
	Liver	75.2	34.0	57.1
	Brain[c]	10.6	9.4	28.6
	Bone	60.2	35.8	50.0
Median sum of diameters (BICR; range), mm		54.0 (10, 182)	44.4 (11, 186)	44.6 (17, 85)
Median number of prior cancer regimens (range), n	All regimens	7.0 (2-14)	3.0 (1-13)	6.5 (2-11)
	In advanced setting	6.0 (2-13)	2.0 (1-13)	5.5 (2-11)
	CT in advanced setting	3.0 (1-7)	2.0 (1-6)	4.0 (2-8)

Patients with HER3-expressing metastatic BC with poor prognostic characteristics were heavily pretreated.

BICR, blinded independent central review; CT, chemotherapy; DE/DF, dose escalation/dose finding; ECOG PS, Eastern Cooperative Oncology Group performance status; ISH, in situ hybridization.
[a] HER3-high was defined as ≥75% membrane positivity at 10x; HER3-low was defined as ≥25% and <75% membrane positivity at 10x. In DE/DF cohorts, IHC 2+ and 3+ were considered HER3-high. [b] HER2 status (based on medical records) was defined as: HER2-zero, IHC 0; HER2-low, IHC 1+ or 2+ (ISH−); HER2+, IHC 2+ (ISH+), IHC 3+. [c] Patients with clinically active brain metastases were excluded.

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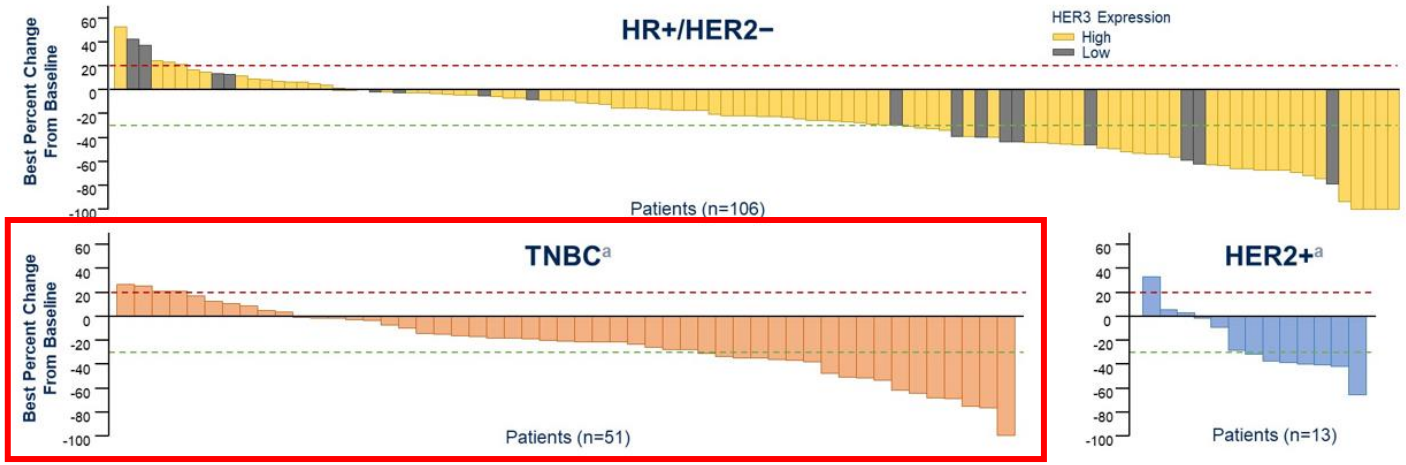
Clinical Efficacy



HER3-DXd induced a clinically meaningful decrease in tumor size by BICR in most patients across BC subtypes.[b]

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

- HER3-DXd demonstrated durable antitumor activity across BC subtypes

- TNBC cohort: N=53, ORR 22.6%, DOR 5.9 mo, PFS 5.5 mon

Efficacy in TNBC is encouraging.
Confirmatory data needed

- Toxicities:
  - TEAE associated with treatment discon 9.9%
    - Pneumonitis N=6
    - Disease progression N=2
    - Decreased LVEF N=1
    - ILD N=1
  - ILD 6.6%, mostly G1-2, 1 G5 ILD (0.5%)

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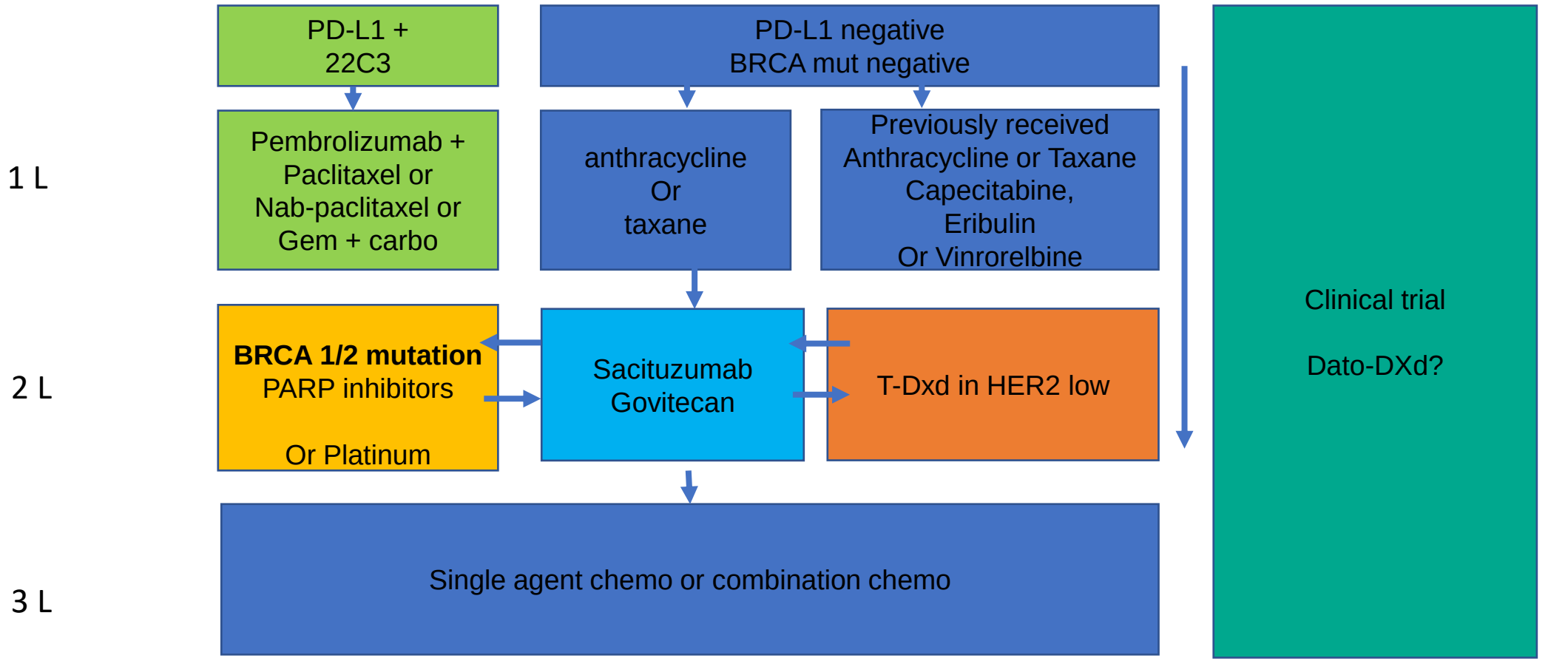
ADCs to Target MBC: Ongoing studies

Drug	Target	Selected Ongoing Trials in MBC
Ado-trastuzumab emtansine (T-DM1)*	HER2	NCT04457596, NCT03975647 NCT04873362, NCT04740918
Trastuzumab deruxtecan (DS-8201a, T-DXd)*	HER2	NCT04784715, NCT04494425, NCT04739761, NCT04622319
Disitamab (RC-48)	HER2	Pending
Trastuzumab duocarmazine (SYD985)	HER2	NCT04602117, NCT01042379
Patritumab deruxtecan (U3-1402, HER3-DXd)	HER3	NCT04699630, NCT04610528
Sacituzumab govitecan (IMMU-132)*	TROP-2	NCT04230109, NCT04647916, NCT04595565, NCT04468061
Datopotamab deruxtecan (DS-1062)	TROP-2	NCT05104866, NCT03401385
Ladiratuzumab vedotin (SGN-LIV1a)	LIV-1	NCT01969643, NCT03310957

Trials of ADC+ immune checkpoint inhibitor in TNBC

Trial	Antibody-Drug Conjugate	Immune Checkpoint Inhibior
SGNLVA-001	Ladiratuzumab Vedotin	Pembrolizumab
ASCENT-03	Sacituzumab Govitecan	
Saci-IO	Sacituzumab Govitecan	
Morpheus-TNBC	Sacituzumab Govitecan	Atezolizumab
InCITe	Sacituzumab Govitecan	Avelumab
DESTINY-Breast08	T-DXd	Durvalumab
NTC04596150	CX-2009 (CD166-directed probody DC)	CX-072 (PD-L1 IO)

mTNBC- Treatment Algorithm



ADCs Sequencing?

Conclusion: We are making progress!!

- Triple Negative Breast Cancer (TNBC) is molecularly complex with tumor heterogeneity and clonal evolution
- Immune checkpoint inhibitor (ICI) has been approved for treatment of metastatic TNBC, and shown promising efficacy in early stage TNBC
- PARP inhibitors will continue to play important role in BRCA 1/2 mutated TNBC, PARPi+ ICI may show promising synergy in both gBRCA WT vs mutant pt
- AR targeted therapy had modest efficacy in AR+ TNBC
- AKT inhibitors: ipatasertib failed to show efficacy in phase III trials. Other AKT inhibitors on active trial.
- Antibody drug conjugates targeting a variety of receptors representing promising new treatments in breast cancer therapy
- HER-2 low tumor represent 40% of TNBC and T-DXd is FDA approved for treatment of HER2 low BC
- HER-2 low status does not impact response to eribulin or SG
- Novel immune stimulation strategies are actively developed