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Advances in Metastatic Triple Negative Breast Cancer: Immunotherapy, Antibody Drug Conjugates, and Beyond

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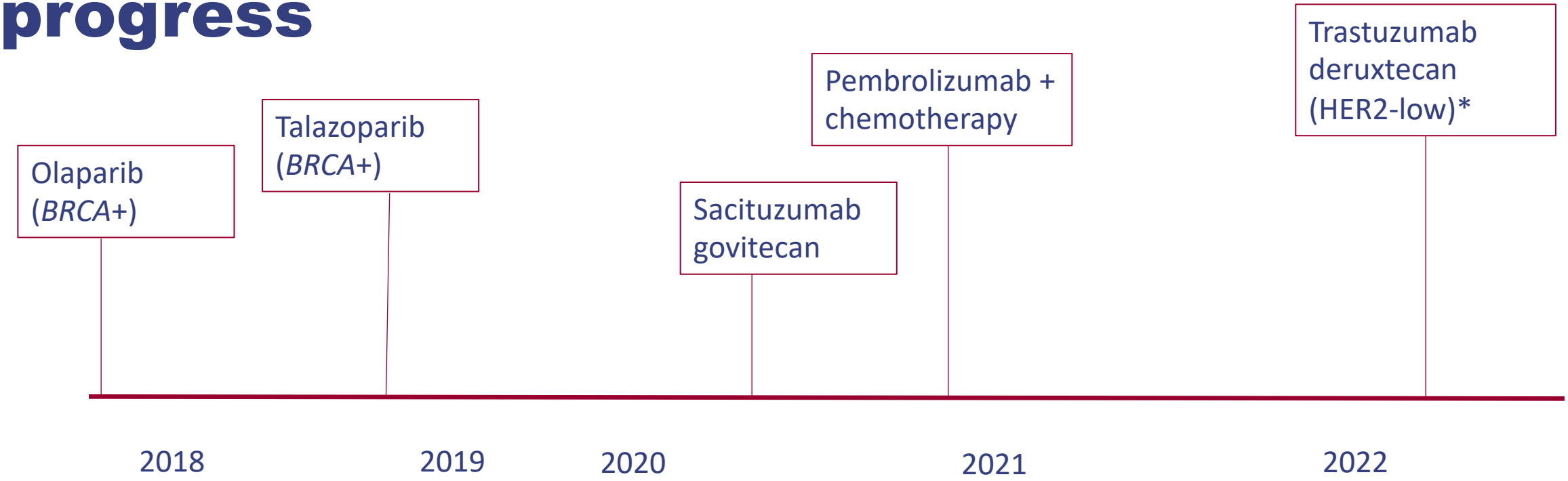
Triple negative breast cancer (TNBC)

- TNBC accounts for 20% of breast cancers worldwide
  - Almost 200,000 cases per year
- More commonly diagnosed in women younger than 40, disproportionately affects black women and carriers of *BRCA1* genetic mutations
- TNBC typically presents aggressively and has a poorer prognosis compared with other subtypes
  - 5-year survival for stage 4 disease = 12%
- Historically, given the absence of targeted therapy, the mainstay of treatment has been chemotherapy – but this is not enough

a. Gonzalez-Angulo AM, et al. *Clin Cancer Res.* 2011;17:1082-1089; b. Lin NU, et al. *Cancer*. 2012;118:5463-5472.

An area of great need…but, incredible progress



More exciting things to come:
-PARP inhibitors outside of the *BRCA*+ population
-New antibody-drug conjugates
-ADCs + IO (possibility of expanding IO to PDL1- patients?)

PARP inhibition

OlympiAD: Olaparib vs Chemotherapy

- Eligibility
  - Deleterious *BRCA* mutation
  - Advanced *ERBB2*- breast cancer
  - Up to 2 previous lines of chemotherapy for metastatic disease (platinum allowed if no POD during treatment)
- Primary Endpoint
  - Investigator-assessed PFS

Olaparib 300mg PO BID
(21-day cycle)

Physician's choice of:
Capecitabine
Vinorelbine
Eribulin

Stratification:
- Previous chemo for metastatic disease (y/n)
- HR status (+/-)
- Previous platinum-based therapy (y/n)

- Robson M, et al. *N Engl J Med.* 2017;377:523-533.

EMBRACA: Talazoparib vs Chemotherapy

- Eligibility
  - Deleterious *BRCA* mutation
  - Advanced *ERBB2*- breast cancer
  - Up to 2 previous lines of chemotherapy for metastatic disease
- Primary Endpoint
  - Investigator-assessed PFS

Talazoparib 1mg PO daily
(21-day cycle)

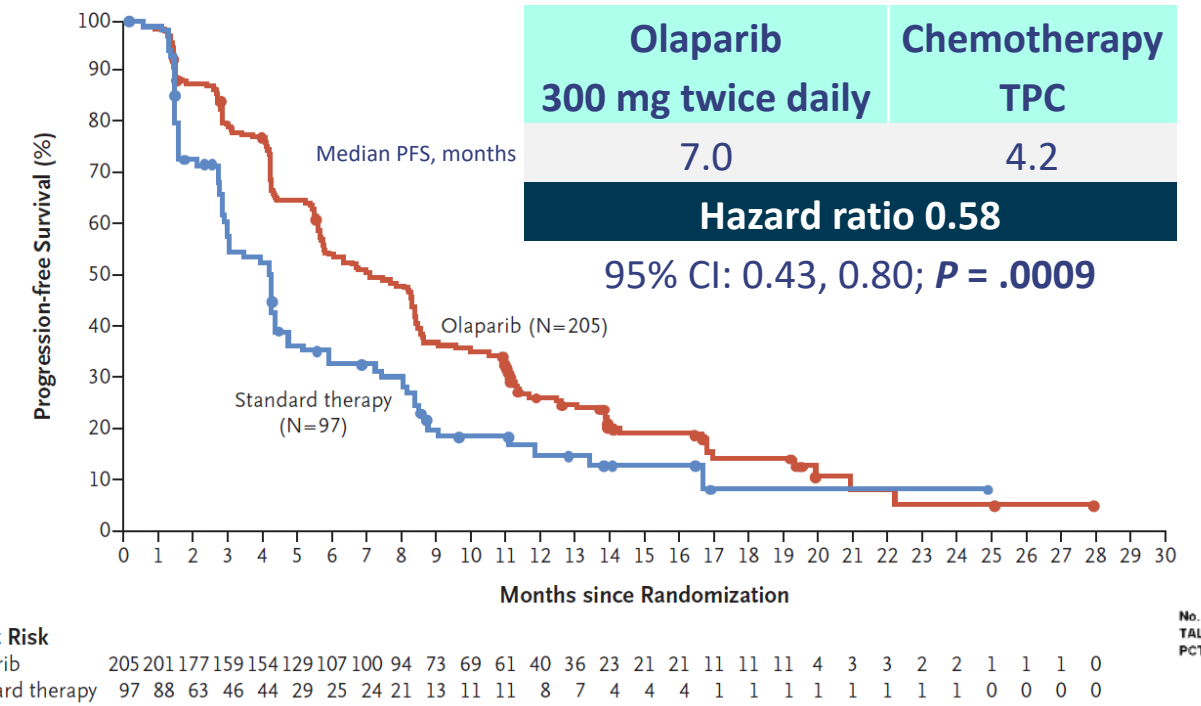
Physician's choice of:
Capecitabine
Vinorelbine
Eribulin
Gemcitabine
(21-day cycle)

Stratification:
-# of prior regimens (0 or >/ = 1)
-HR status (+/-)
-CNS mets (y/n)

- Litton JK, et al. *N Engl J Med*. 2018;379:753-763.

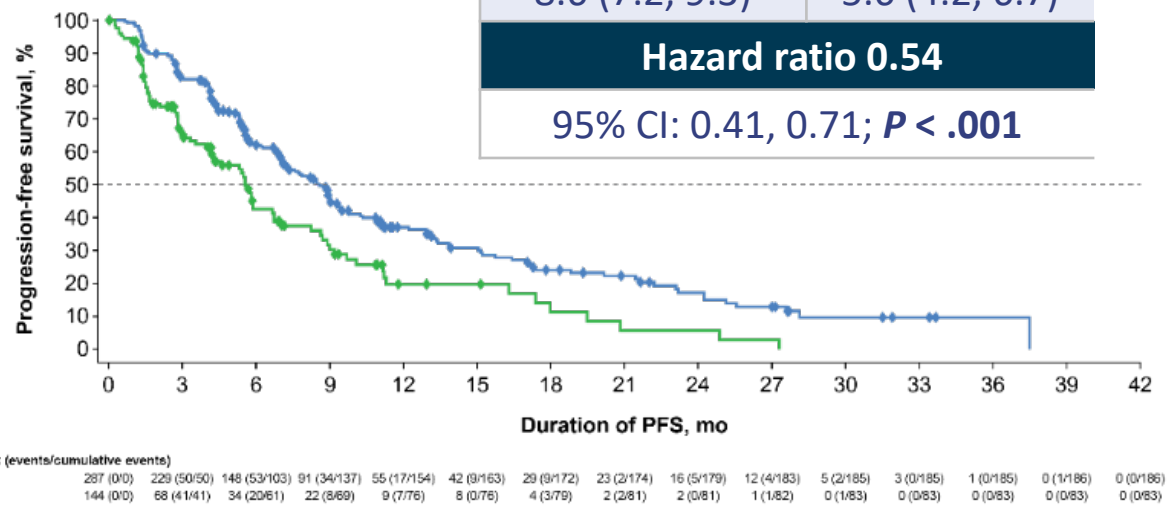
PARP Inhibitor Superior to Chemotherapy in *BRCA*mut MBC

OlympiAD[a]



Olaparib 300 mg twice daily	Chemotherapy TPC
7.0	4.2
Hazard ratio 0.58	
95% CI: 0.43, 0.80; ***P* = .0009**	

EMBRACA[b]



Talazoparib (n = 287)	Overall PCT (n = 144)
8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard ratio 0.54	
95% CI: 0.41, 0.71; ***P* < .001**	

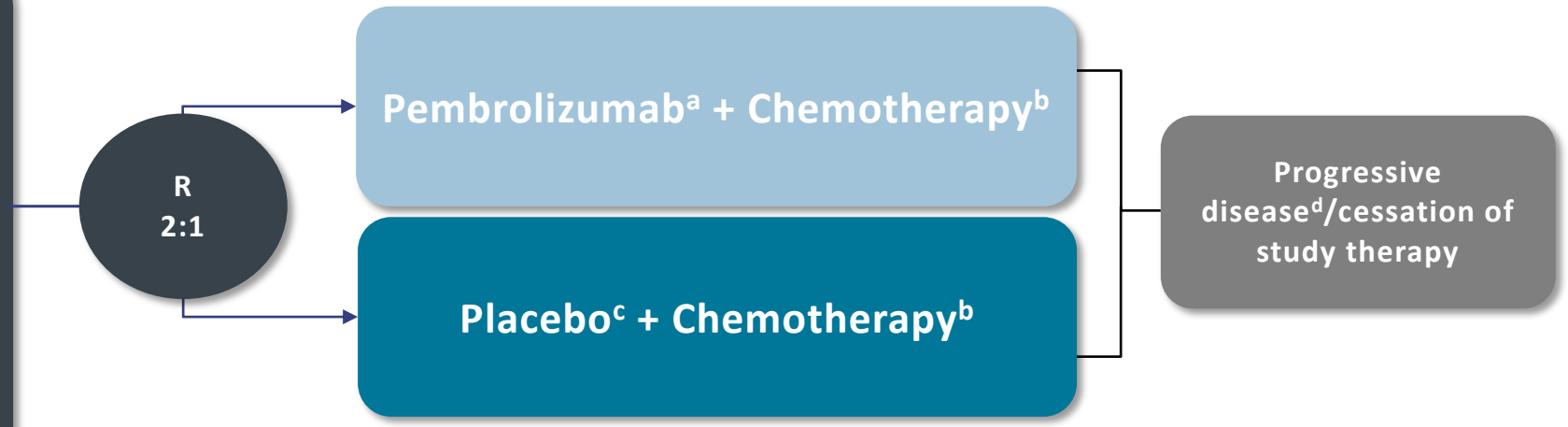
- a. Robson M, et al. *N Engl J Med.* 2017;377:523-533; b. Litton J, et al. *N Engl J Med.* 2018;379:753-763.

Immunotherapy

KEYNOTE-355: Pembrolizumab + Chemotherapy

Key Eligibility Criteria

- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease



Stratification Factors:

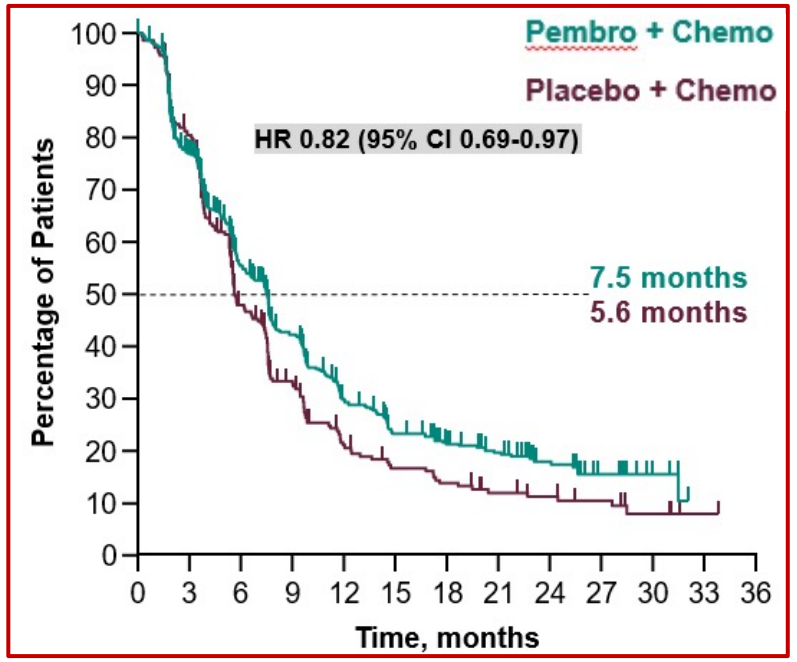
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days
[c]Normal saline
[d]Treatment may be continued until confirmation of progressive disease

- Cortes J, et al. ASCO 2020, Abs 1000.

Keynote-355: Progression-Free Survival

ITT

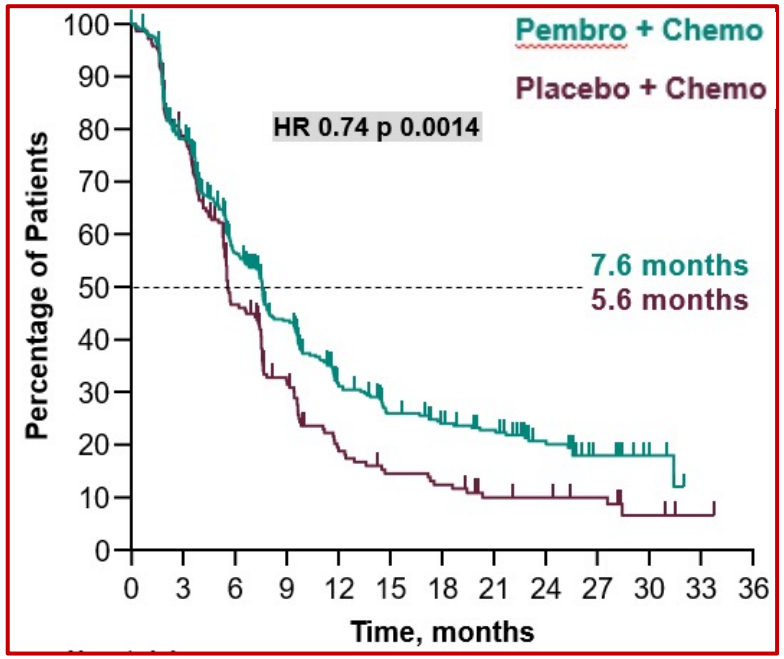


Statistical significance not tested due to prespecified hierarchical testing strategy

FDA approved 11/2020

PD-L1 CPS ≥1

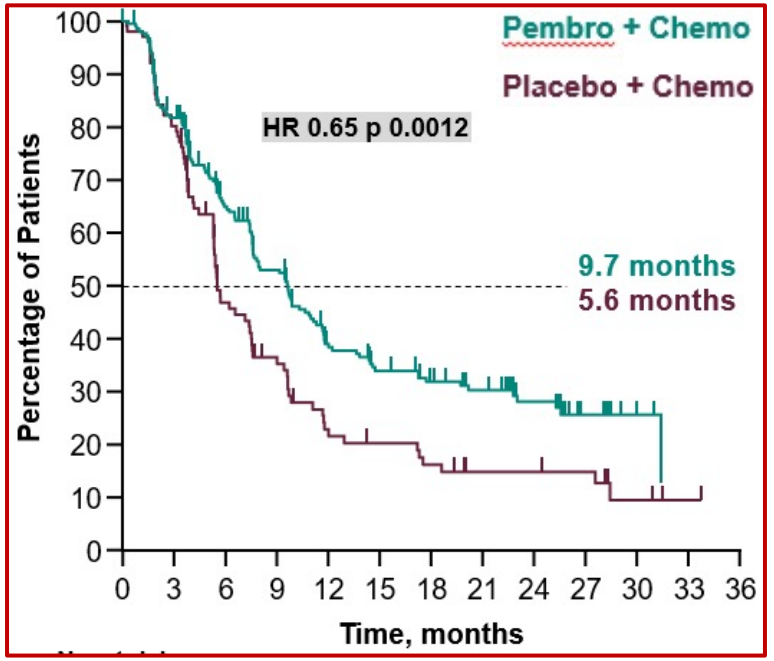
75% of pts



Prespecified *P* value boundary of 0.00111 not met

PD-L1 CPS ≥10

38% of pts



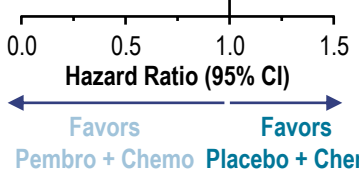
Prespecified *P* value boundary of 0.00411 met

- Cortes J, et al. *Lancet*. 2020;396:1817-1828.

Keynote-355: PFS Subgroup Analysis by On-Study Chemotherapy

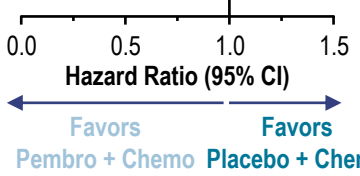
PD-L1 CPS ≥10

Subgroup	N	Median PFS (mo) Pembro + Chemo	Median PFS (mo) Placebo + Chemo	Hazard Ratio for Progression or Death (95% CI)
Overall	323	9.7	5.6	0.65 (0.49 to 0.86)
On-study chemotherapy				
Nab-Paclitaxel	99	9.9	5.5	0.57 (0.34 to 0.95)
Paclitaxel	44	9.6	3.6	0.33 (0.14 to 0.76)
Gemcitabine-Carboplatin	180	8.0	7.2	0.77 (0.53 to 1.11)



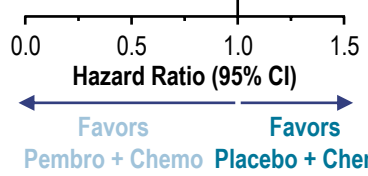
PD-L1 CPS ≥1

Subgroup	N	Median PFS (mo) Pembro + Chemo	Median PFS (mo) Placebo + Chemo	Hazard Ratio for Progression or Death (95% CI)
Overall	636	7.6	5.6	0.74 (0.61 to 0.90)
On-study chemotherapy				
Nab-Paclitaxel	204	6.3	5.3	0.66 (0.47 to 0.92)
Paclitaxel	84	9.4	3.8	0.46 (0.26 to 0.82)
Gemcitabine-Carboplatin	348	7.5	7.5	0.86 (0.66 to 1.11)



ITT

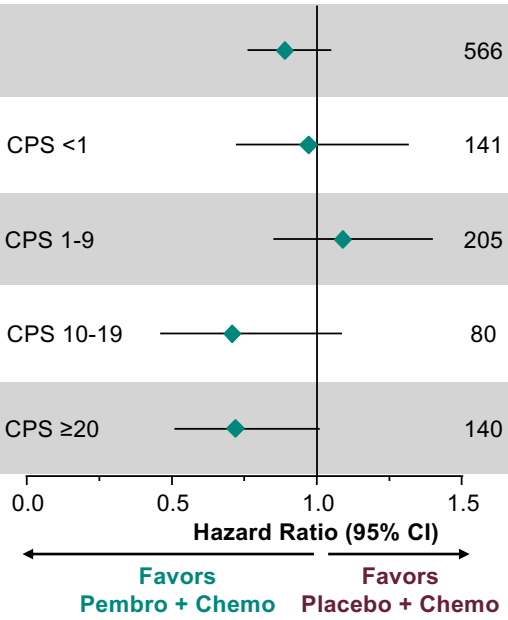
Subgroup	N	Median PFS (mo) Pembro- + Chemo	Median PFS (mo) Placebo + Chemo	Hazard Ratio for Progression or Death (95% CI)
Overall	847	7.5	5.6	0.82 (0.69 to 0.97)
On-study chemotherapy				
Nab-Paclitaxel	268	7.5	5.4	0.69 (0.51 to 0.93)
Paclitaxel	114	8.0	3.8	0.57 (0.35 to 0.93)
Gemcitabine-Carboplatin	465	7.4	7.4	0.93 (0.74 to 1.16)



- Slide adapted from Rugo H et al, SABCS 2020. GS3-01.

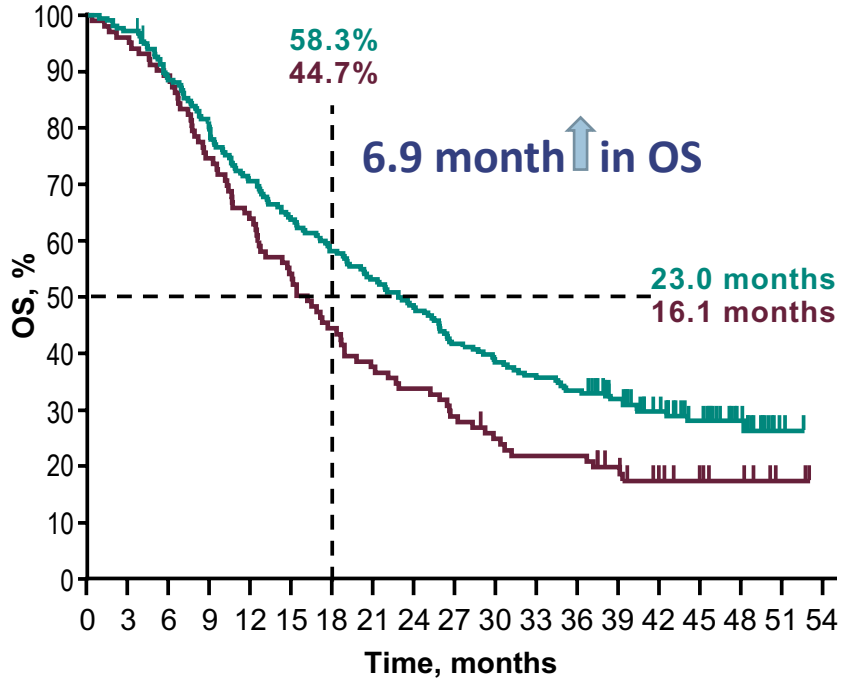
KEYNOTE 355 Overall Survival

Subgroup	Median OS (mo) Patients *n*	Pembro + Chemo	Patients *n*	Placebo + Chemo	Hazard Ratio (95% CI)
Overall	566	17.2	281	15.5	0.89 (0.76 to 1.05)
PD-L1 CPS <1	141	16.2	70	14.7	0.97 (0.72 to 1.32)
PD-L1 CPS 1-9	205	13.9	108	15.5	1.09 (0.85 to 1.40)
PD-L1 CPS 10-19	80	20.3	39	17.6	0.71 (0.46 to 1.09)
PD-L1 CPS ≥20	140	24.0	64	15.6	0.72 (0.51 to 1.01)



PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)	*P*-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093[a]
Placebo + Chemo	84/103	81.6%		



No. at risk

220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

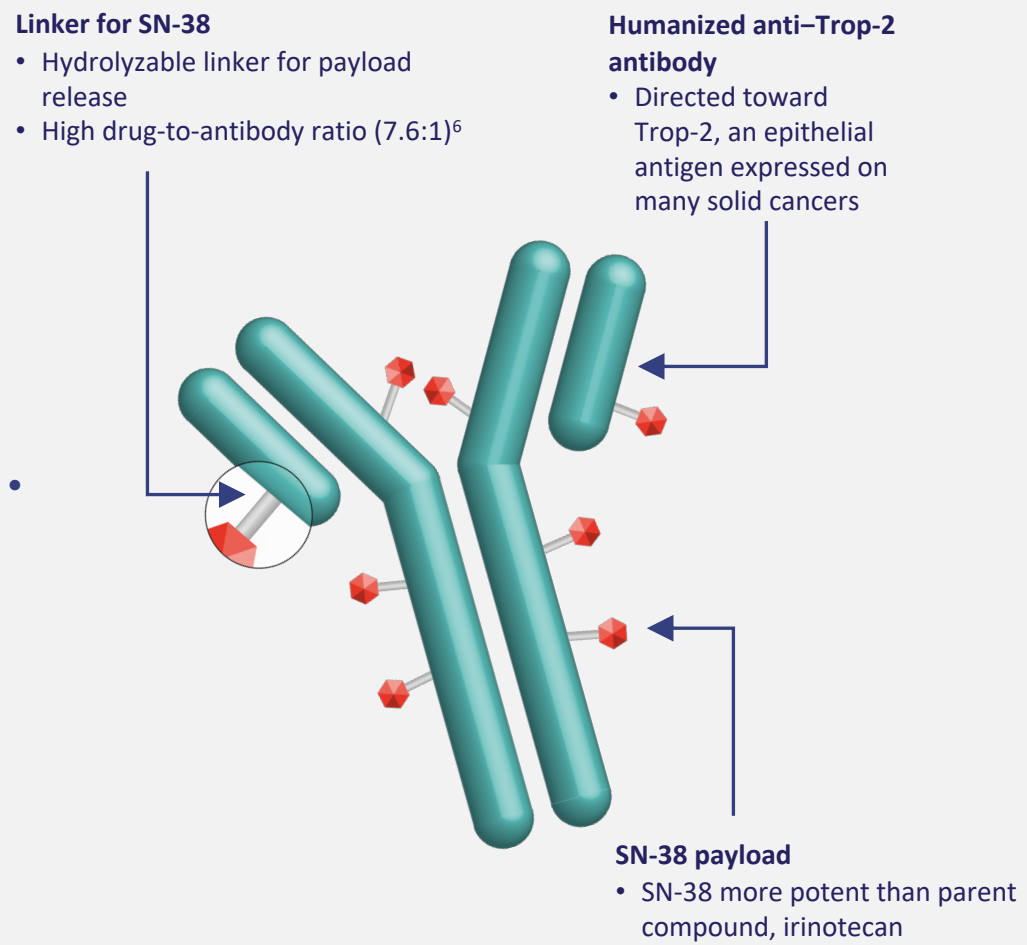
- For pembrolizumab + chemotherapy in mTNBC, CPS ≥10 is the best cut-off to define those expected to benefit, and this is the standard of care for mTNBC with CPS≥10

Cortes J, Cescon DW, Rugo HS et al. SABCS . 2021;GS1-02

Antibody-drug conjugates

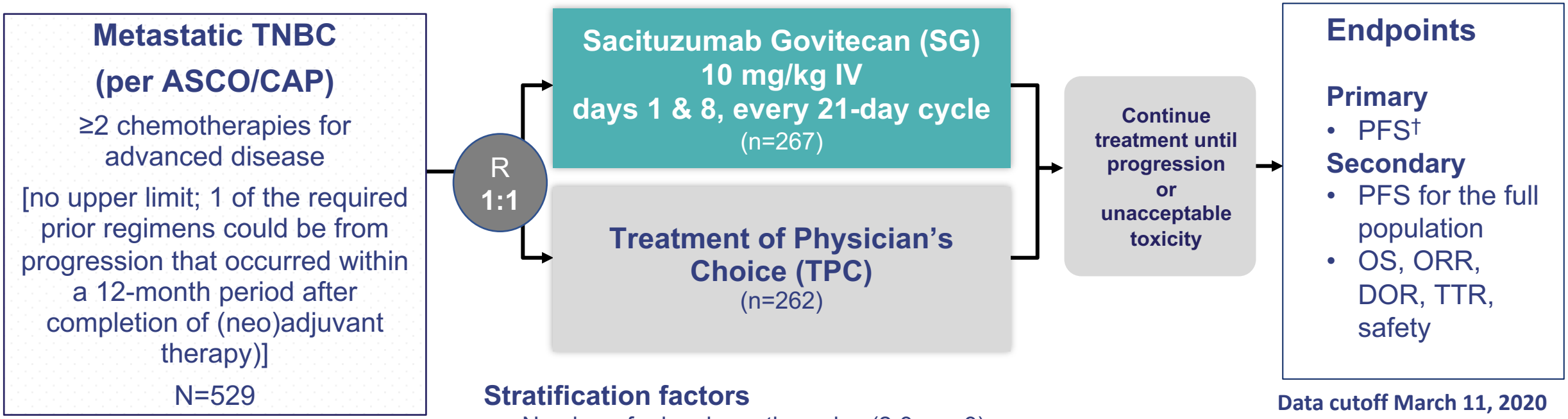
Sacituzumab Govitecan (SG)

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[a]
- Distinct features of SG:[b]
  - 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



a. Zaman S, et al. *Onco Targets Ther*. 2019;12:1781-1790); b. h. Bardia A, et al. *Annals of Oncology* (2020) 31 (suppl_4): S1142-S1215;

ASCENT: Sacituzumab Govitecan in Refractory/Relapsed mTNBC



Stratification factors

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

Data cutoff March 11, 2020

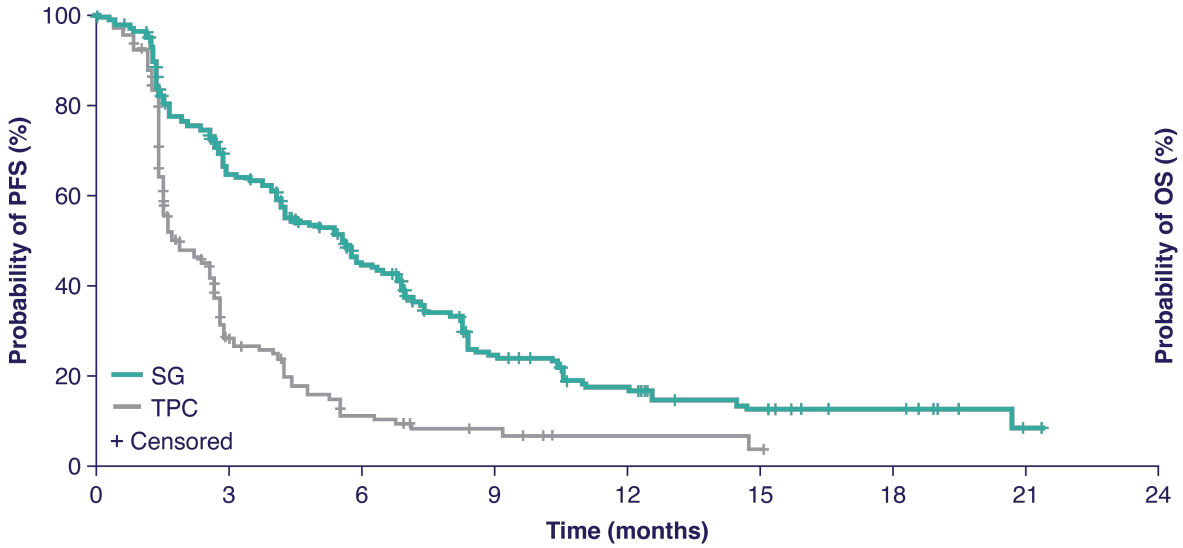
- **Primary results including PFS and OS**
- **ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation**

- Bardia A, et al. *Annals of Oncology* (2020) 31 (suppl_4): S1142-S1215.

ASCENT: Results

PFS

BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

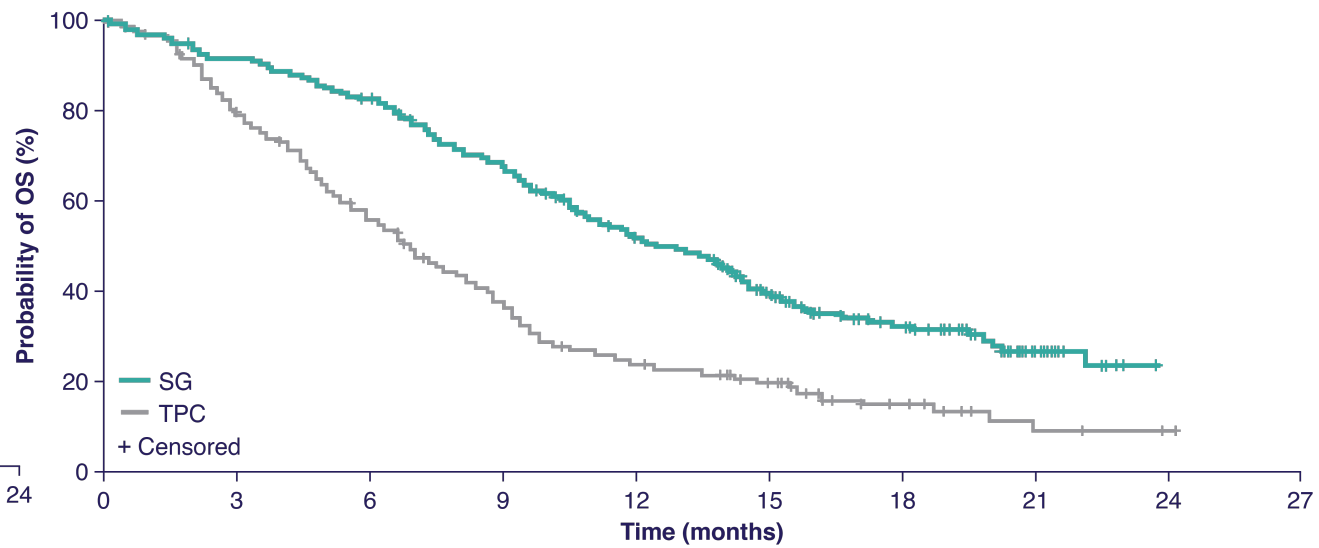


Number of patients at risk

SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

OS

	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

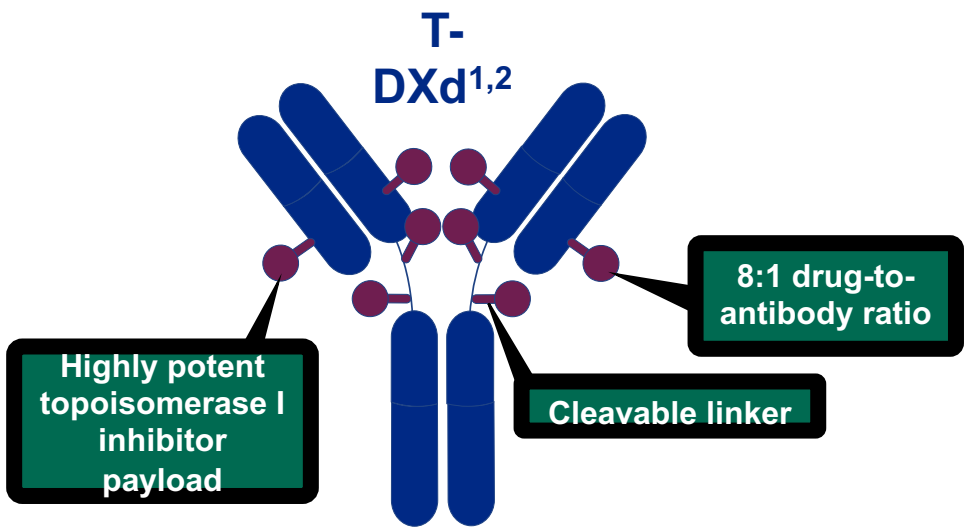


Number of patients at risk

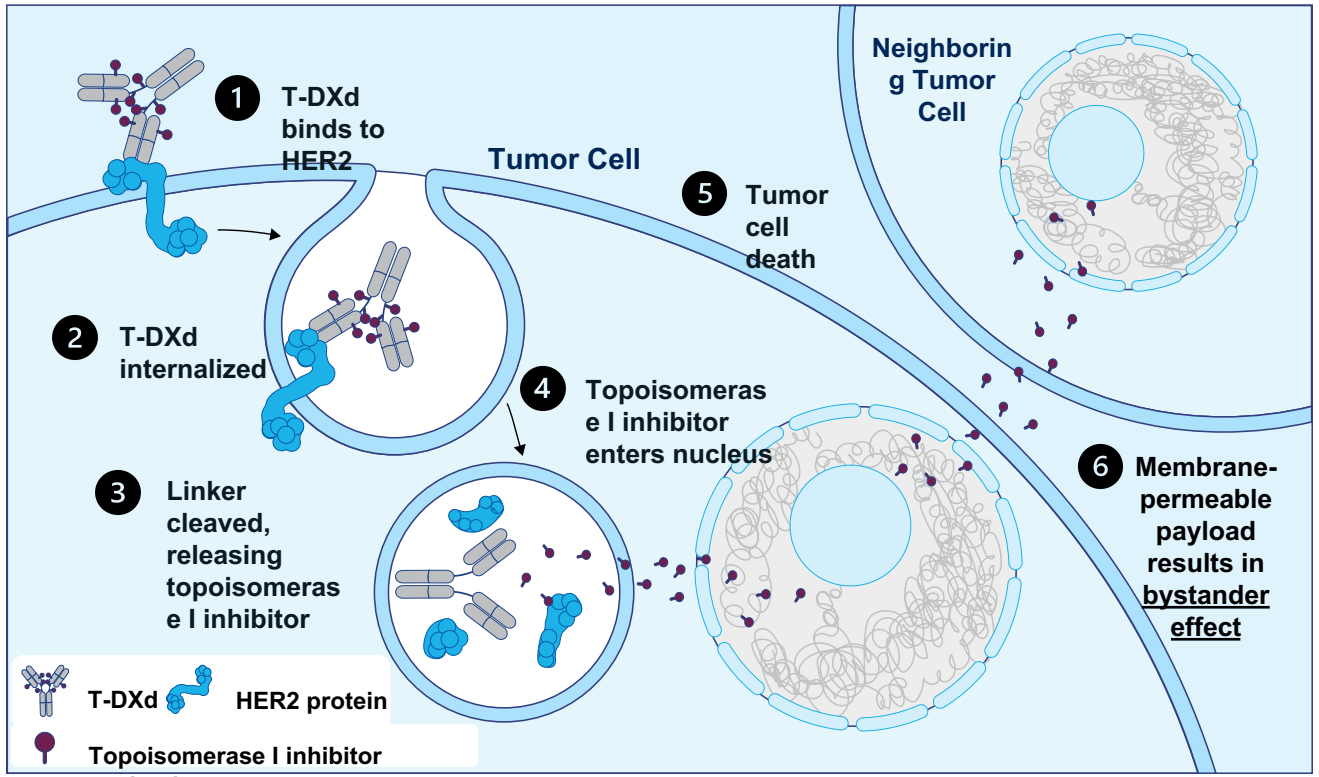
SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

- Bardia A, et al. *Annals of Oncology* (2020) 31 (suppl_4): S1142-S1215.

T-DXd MOA, Bystander Effect, and Rationale for Targeting HER2-low mBC



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[1,2]



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

- **Results from a phase 1b study have reported efficacy of T-DXd in heavily pretreated patients (N = 54) with HER2-low mBC, with a mPFS of 11.1 months and an ORR of 37.0%[3]**

HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

1. Nakada T, et al. *Chem Pharm Bull.* 2019;67:173-185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097-5108. 3. Modi S, et al. *J Clin Oncol.* 2020;38:1887-1896.

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

An open-label, multicenter study (NCT03734029)

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+)

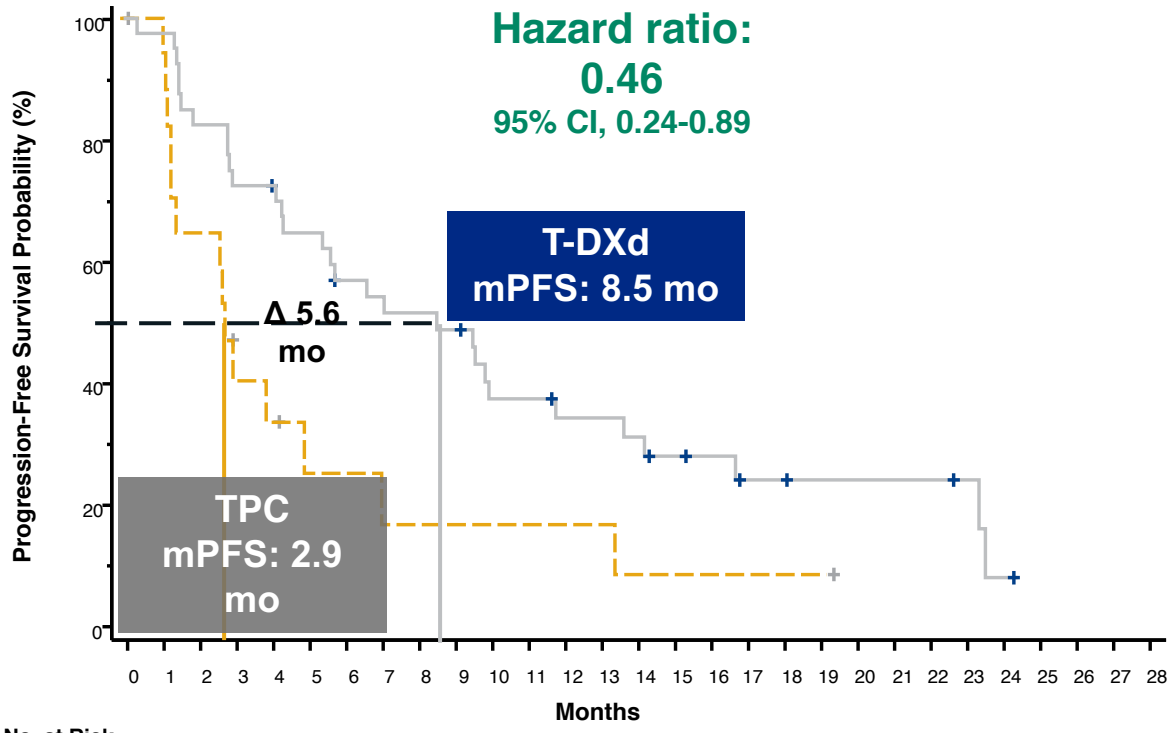
Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

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.

PFS and OS in HR− (Exploratory Endpoints)

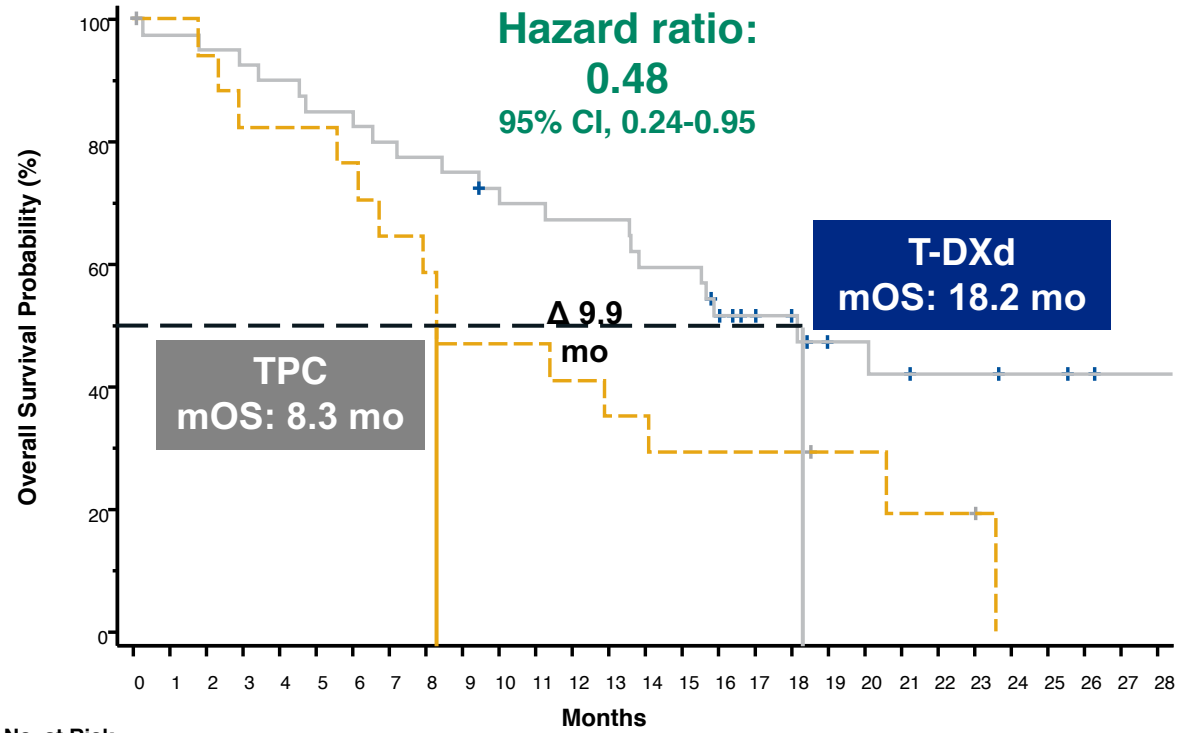
PFS



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	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

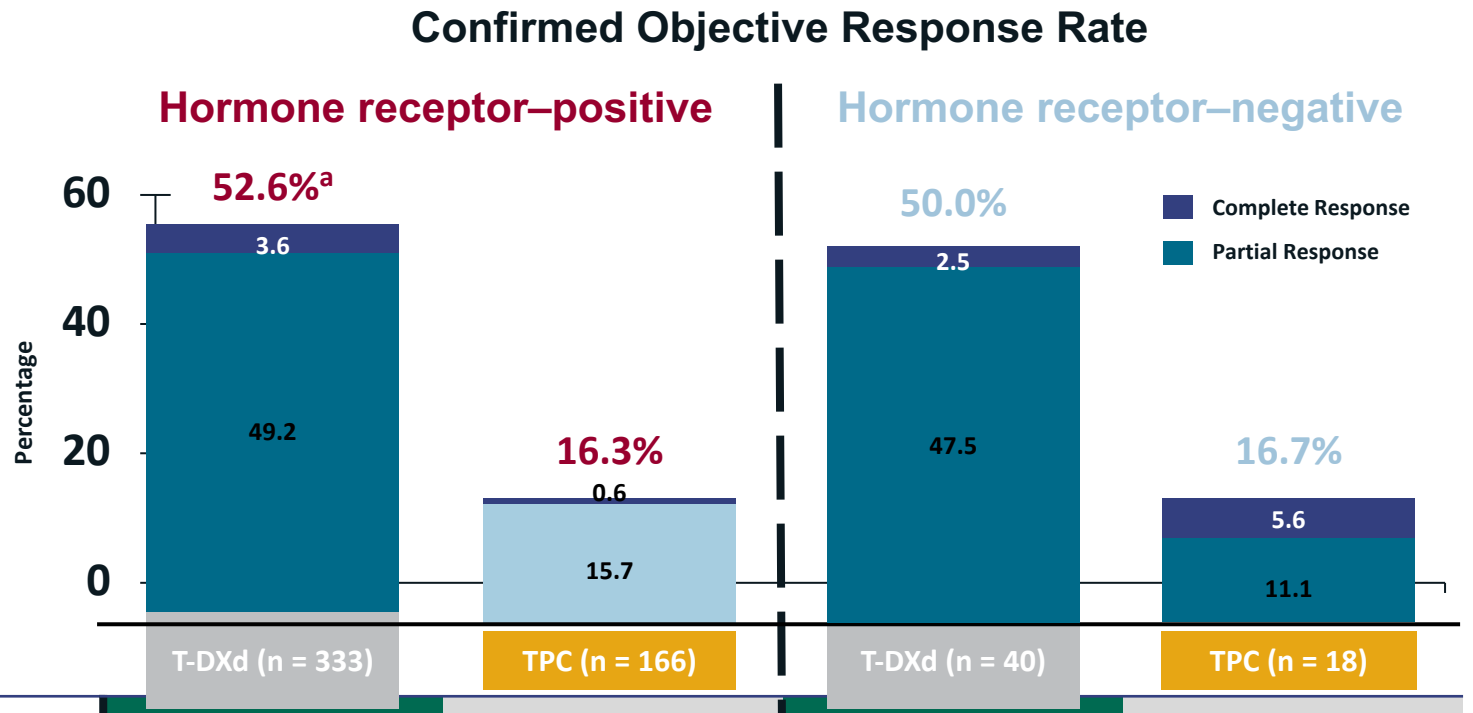


No. at Risk

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 capture corrected for misstratification.

Confirmed ORR



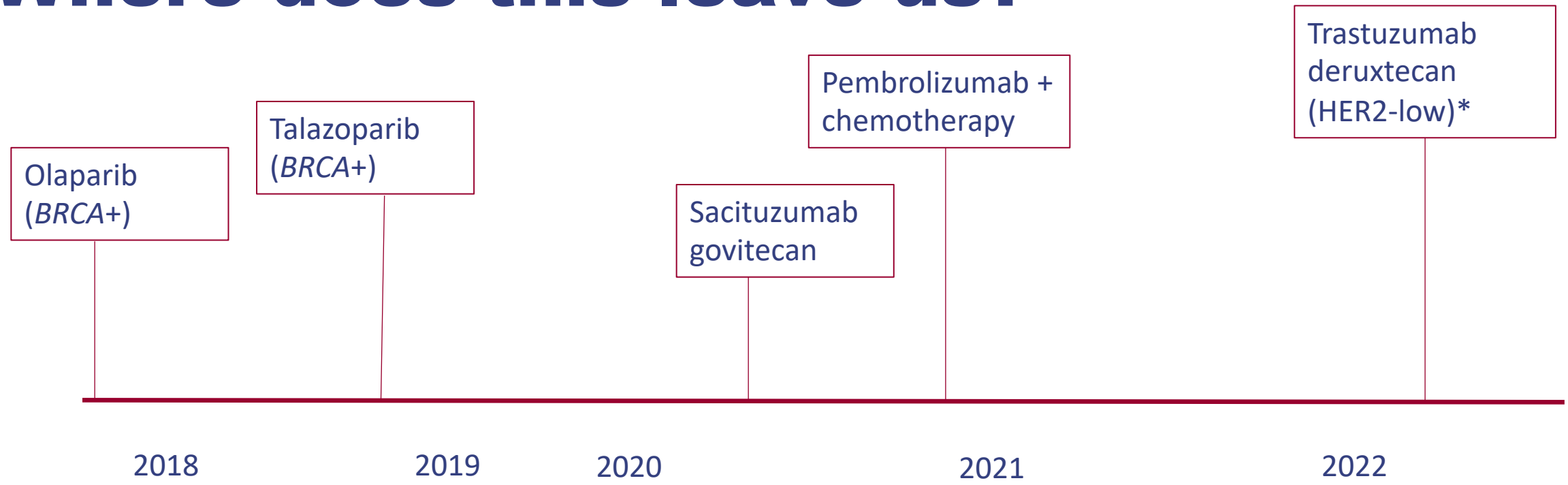
	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

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.

Where does this leave us?



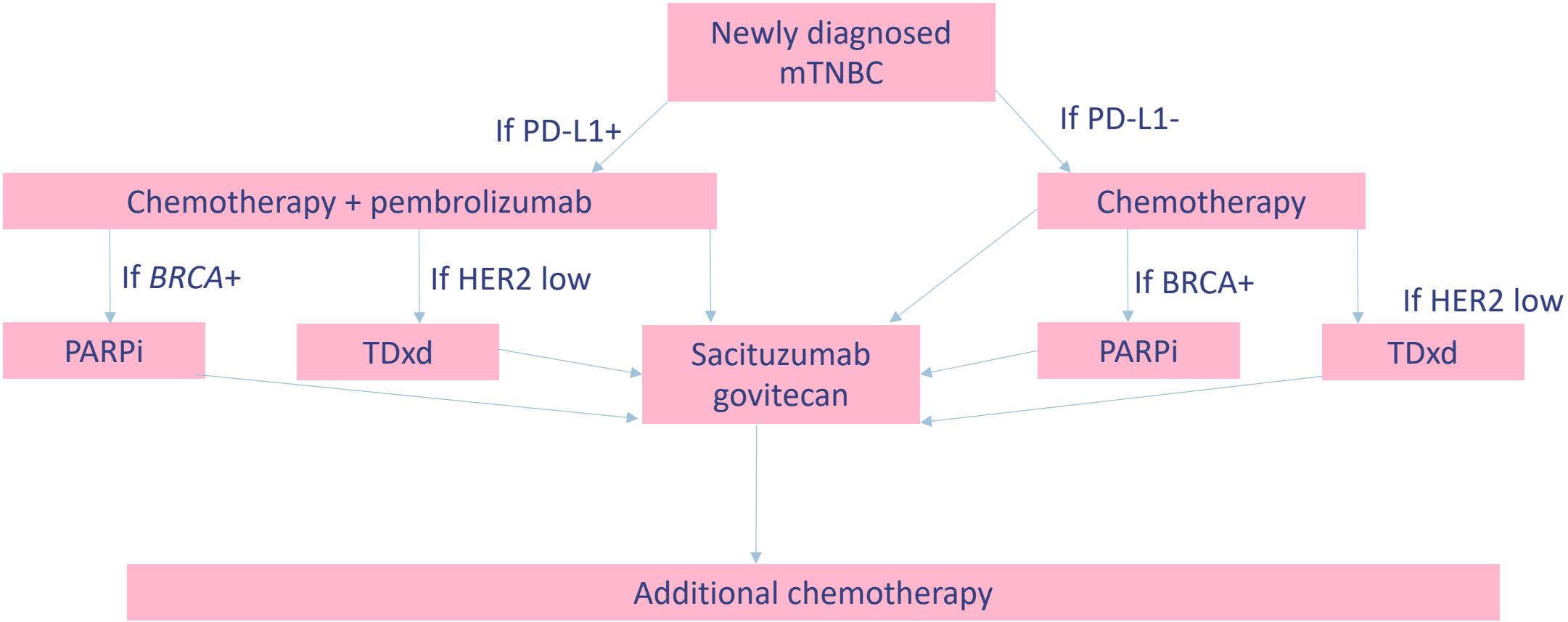
Case presentation

- 45F presents with a breast mass that is biopsied and found to be triple negative invasive ductal carcinoma (ER-PR- HER2 1+). During her workup, she is found to have a liver mass that is biopsied and is found to be metastatic breast cancer, also triple negative. PD-L1 CPS score is 13. Genetic testing is done and she is *BRCA* negative.

What would your recommendation be?

a) Initiate trastuzumab deruxtecan
b) Initiate taxane/pembrolizumab
c) Initiate olaparib
d) Initiate sacituzumab govitecan
e) Initiate a taxane

Treatment of metastatic TNBC



On the horizon

- PARP inhibitors outside of the *BRCA*+ population
- New antibody-drug conjugates
- ADCs + IO (possibility of expanding IO to PDL1- patients?)

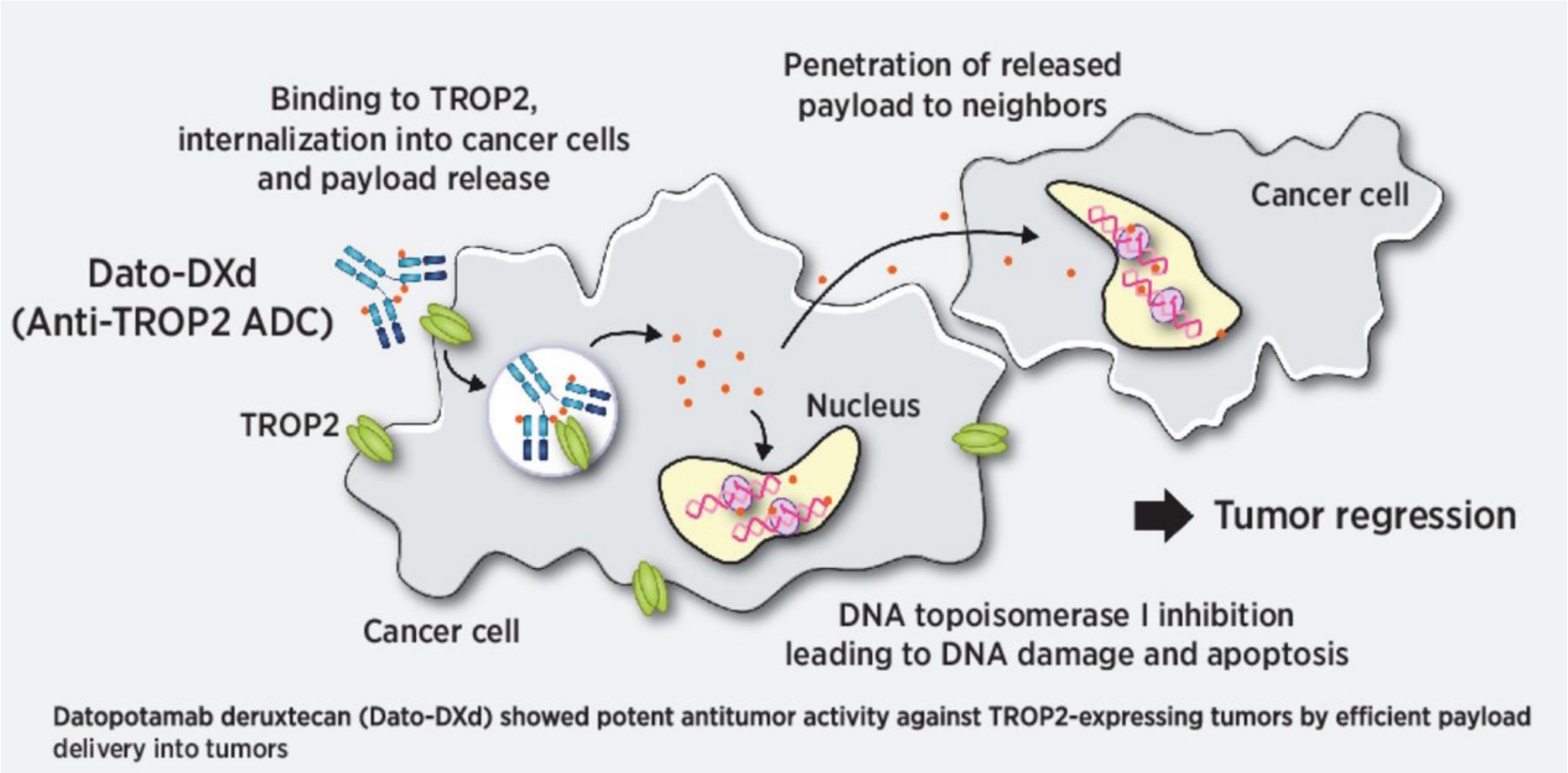
TBCRC 048: OLAPARIB EXPANDED Benefit in g*PALB2* + s*BRCA*

PALB2 N=13	sBRCA1/2 N=17	ATM & CHEK2** N=17
Germline: 9/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr Somatic: 0/2 – both SD* (limited assessments)	8/16 PR (50%)	0/13 germline 0/4 somatic

New cohorts are beginning for g*PALB2* and s*BRCA1/2* breast cancer

- Tung N, et al. *J Clin Oncol* 38: 2020 (suppl; abstr 1002).

Datopotamab deruxtecan (Dato-DXd, DS-1062a)



Datopotamab deruxtecan (Dato-DXd) showed potent antitumor activity against TROP2-expressing tumors by efficient payload delivery into tumors

TROPION-PanTumor01: Study Design

Phase 1 Trial: Datopotamab deruxtecan in advanced/metastatic HER2- breast cancer

- Relapsed/refractory advanced/metastatic solid tumors
- Unselected for TROP2 expression[a]
- Age ≥18 (US) or ≥20 (Japan) years
- ECOG PS 0-1
- Measurable disease per RECIST version 1.1
- Stable, treated brain metastases allowed

→ NSCLC[b] (0.27 to 10 mg/kg IV Q3W)

→ **TNBC[c] 8 mg/kg (n=2); 6 mg/kg (n=42)**

→ HR+/HER2− breast cancer[d]

→ Other tumor types (including SCLC, bladder, gastric, esophageal)

Primary objectives

- Safety
- Tolerability

Secondary objectives[e]

- Efficacy[f]
- Pharmacokinetics
- Antidrug antibodies

Data cutoff: July 30, 2021

ECOG PS, Eastern Cooperative Oncology Group performance status; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b] Results from the NSCLC cohort have been previously reported.[1,2] [c] Includes patients treated in the dose-escalation and dose-expansion portions. [d] Enrollment in the HR+/HER2− cohort is now complete and data will be forthcoming. [e] Exploratory objectives include analyses of biomarkers associated with response. [f] Response assessments are based on RECIST 1.1.

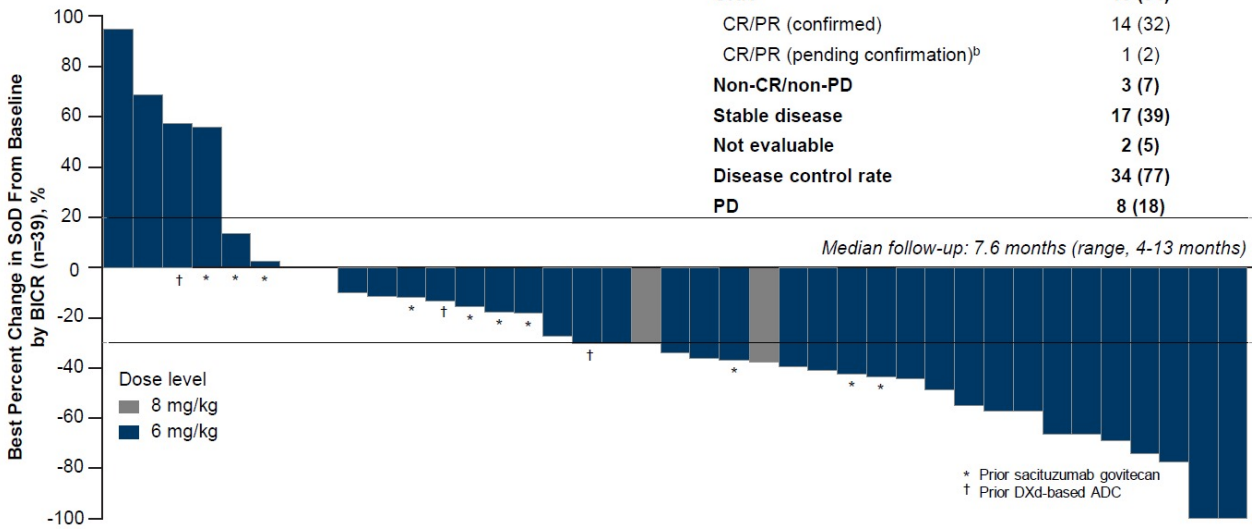
1. Garon E, et al. WCLC 2021. Abstract 156; 2. Meric-Bernstam F, et al. ASCO 2021.

Krop I, et al. Presented at: SABCS 2021. Abstract GS1-05.

TROPION-PanTumor01: Antitumor Responses by BICR

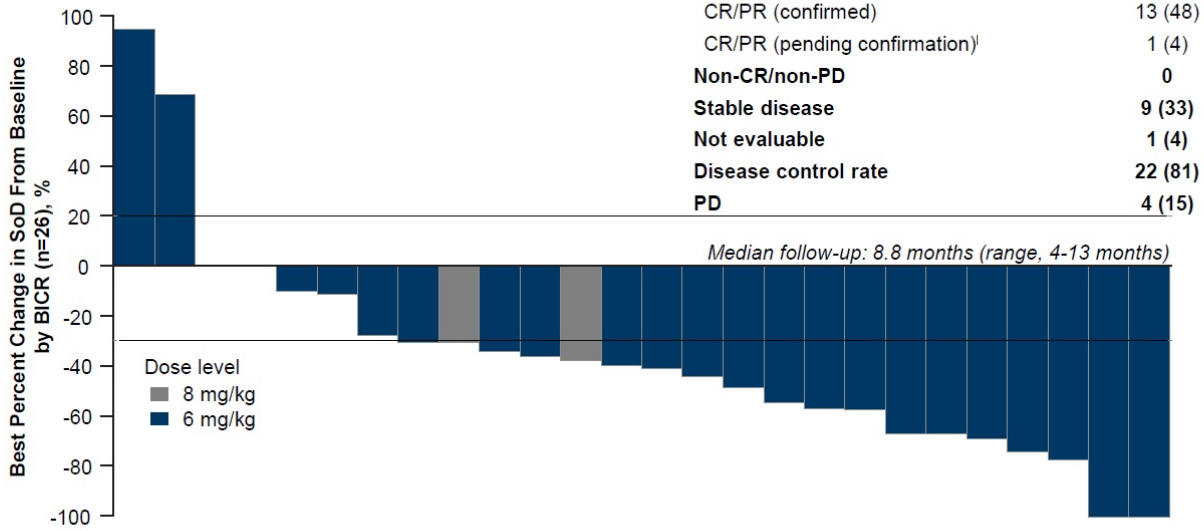
All Patients With TNBC

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



Patients With TNBC Without Prior Topo I Inhibitor-Based ADC

Patients, n (%)	SG/DXd Naive Patients (n = 27)
ORR	**14 (52)**
CR/PR (confirmed)	13 (48)
CR/PR (pending confirmation)[l]	1 (4)
Non-CR/non-PD	**0**
Stable disease	**9 (33)**
Not evaluable	**1 (4)**
Disease control rate	**22 (81)**
PD	**4 (15)**



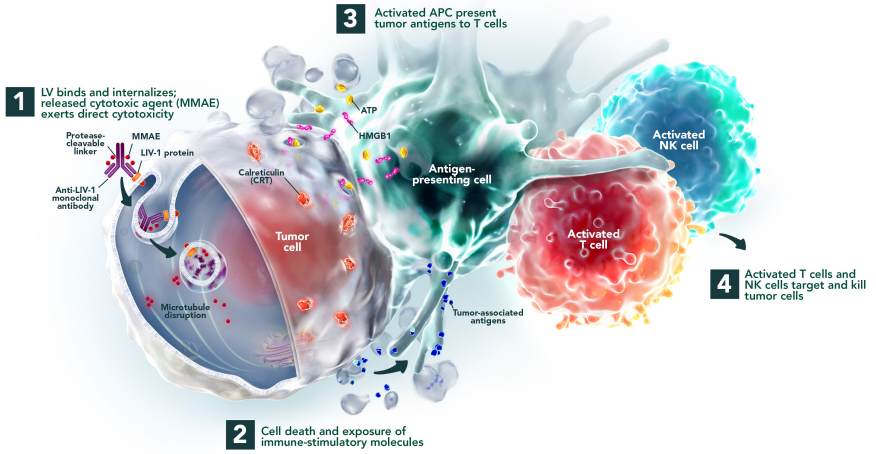
- Krop I, et al. Presented at: SABCS 2021. Abstract GS1-05.

Datopotamab: next steps

- Being studied as front-line therapy for mTNBC that is not PD-L1+ (against physician's choice chemotherapy) (TROPION-Breast 02)
- Being studied in combination with durvalumab for patients with triple negative breast cancer as one arm of BEGONIA
- Being studied for ER+ pretreated mBC (TROPION-Breast 01)

Ladiratuzumab vedotin (LV)

- LIV-1 is a transmembrane protein involved in the signaling pathway leading to epithelial-mesenchymal transition (EMT) and expression has been linked with malignant progression to metastasis in breast cancer[1,3]
- LIV-1 is expressed in ≥90% of all clinical subtypes of metastatic breast cancer tumors with low expression in normal tissues[4]
- LV is an ADC directed against LIV-1

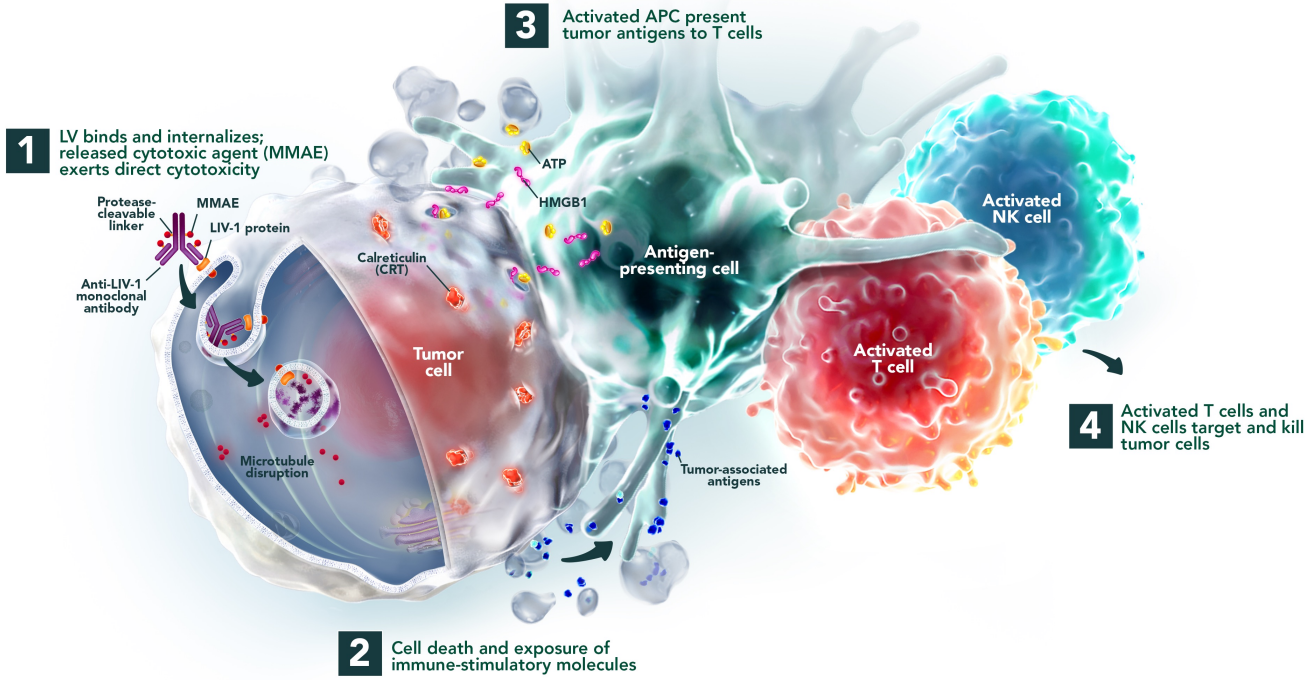


Ladiratuzumab vedotin is an investigational agents, and its safety and efficacy have not been established.

1. Lue H-W, et al. PLOS One. 2011;6(11):e27720.
2. Hogstrand C, et al. Biochem J. 2013;455:229-37.
3. Manning DL, et al. Eur J Cancer. 1994;30A(5):675-8.
4. Sussman D, et al. Mol Cancer Ther. 2014;13(12):2991-3000.

Jane Meisel. Phase 1b/2 Study of Ladiratuzumab Vedotin (LV) in Combination with Pembrolizumab for First-Line Treatment of Triple-Negative Breast Cancer (SGNLVA-002, Trial in Progress)

Rationale for Combining LV with Pembrolizumab



Ladiratuzumab vedotin is an investigational agents, and its safety and efficacy have not been established.

1. Cao A, et al. Cancer Res. 2018;78(13 Suppl):Abstract 2742.

Abbreviations:
LV, ladiratuzumab vedotin

Current Study Design

- SGNLVA-002 (NCT03310957) is an ongoing global single-arm, open-label, phase 1b/2 study of LV + pembrolizumab as 1L therapy for patients with unresectable locally advanced or mTNBC

- LV 1.5 mg/kg administered on Day 1 and Day 8 (off Day 15) of every 21-day cycle in combination with pembrolizumab administered on Day 1 of every cycle
  - Rationale for the combination: LV-induced immunogenic cell death elicits an inflammatory response, leading to enhanced antitumor immunity, antigen presentation, and tumor cell immune infiltration

- Eligible patients have metastatic TNBC, no prior cytotoxic treatment in the metastatic setting, tumor tissue PD-L1 CPS <10 using the PD-L1 IHC 22C3 clone, and at least 6 months since prior treatment with curative intent

Conclusions

- Triple negative breast cancer has come a long way in the past few years, with more breakthroughs on the way
- Many more options for patients, and options that offer more longevity as well as better quality of life
- The future: defining TNBC by what it is (g*BRCA*, HER2-low, PD-L1+, etc) rather than by what it is not!

Thank you!

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