Practical Guidance for the Community Oncologist

Incorporating Advances in Therapy for Metastatic TNBC: A Focus on TROP2

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Activity Description

Target Audience

This activity is intended for oncologists/hematologists, oncology nurses, and the multidisciplinary healthcare team who are involved in the care of patients with triple negative breast cancer.

Learning Objectives

Upon completion of this activity, participants will be able to:

- Discuss new and emerging targeted treatment approaches in the setting of TNBC
- Discuss the role of ADC therapies and TROP2 for TNBC
- Implement strategies to facilitate the use of novel and emerging therapies for TNBC in community-based settings

Support

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Hope Rugo, MD, FASCO (Chair) discloses that she has Research Grants from AstraZeneca, Ayala, Boehringer Ingelheim, Daiichi Sankyo, Gilead Sciences, Inc., Lilly, MacroGenics, Merck, Novartis, Pfizer, Polyphor, Roche, Seattle Genetics, Sermonix Pharmaceuticals, and is an Honorarium Recipient from Mylan, Napo Pharmaceuticals, Puma Biotechnology, Inc., and Samsung.

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Ruta Rao, MD (Faculty) discloses that she is a Consultant to Immunomedics and Merck.

Sara Tolaney, MD, MPH (Faculty) discloses that she receives:
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Agenda

Presentation
TNBC Challenges
The ABCs of ADCs
TROP2 as a Target in TNBC
Additional ADCs in TNBC
Strategies to Incorporate Anti-TROP2 ADCs Into Treatment Paradigms
Case-Based Discussion
Q&A

TNBC Challenges

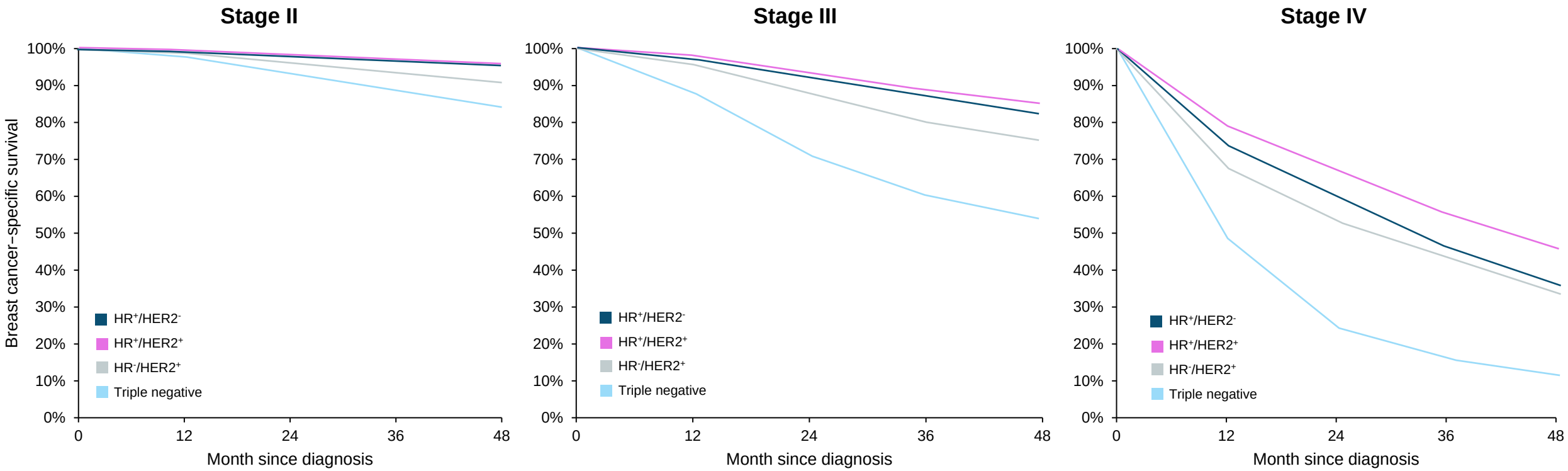
Features of Triple-Negative Breast Cancer

- 10%-15% of all breast cancers
- Defined by immunohistochemistry: not very sophisticated!
  - Lacks expression of ER, PR, and HER2
- Tends to be more aggressive
  - Higher grade
  - More responsive to chemotherapy
  - High relapse pattern in first 5 years
  - Sites of relapse (liver, CNS) different from ER-positive
  - Affected patients more often younger, Black
  - P53 mutations common
  - May be associated with *BRCA1* mutations and/or *BRCA* pathway dysfunction

CNS = central nervous system; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor

Liedtke C et al. *J Clin Oncol*. 2008;26(8):1275-81. Lin NU et al. *Cancer*. 2008;113(10):2638-45. Ahn SG et al. *J Breast Cancer*. 2016;19(3):223-30. Anders CK et al. *Clin Breast Cancer*. 2009;9(suppl 2):S73-81.

TNBC Is Associated With Shorter Overall Survival Compared With Other Subtypes Despite Anthracycline + Taxane Therapy



HR = hormone receptor; TNBC = triple-negative breast cancer

Howlader N et al. *Cancer Epidemiol Biomarkers Prev*. 2018;27(6):1-8. Bauer KR et al. *Cancer*. 2007;109(9):1721-8.

Options for TNBC: Preoperative/Adjuvant Therapy

PREOPERATIVE/ADJUVANT THERAPY REGIMENS

HER2 Negative

Preferred Regimens

- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)
- Olaparib, if germline *BRCA1/2* mutations
- High-risk TNBC: Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab
- TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy: Capecitabine

Useful in Certain Circumstances

- Dose-dense AC (doxorubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by weekly paclitaxel

Other Recommended Regimens

- AC followed by docetaxel every 3 weeks
- EC (epirubicin/cyclophosphamide)
- TAC (docetaxel/doxorubicin/cyclophosphamide)
- Select patients with TNBC in preoperative setting only
  - Weekly paclitaxel + carboplatin
  - Docetaxel + carboplatin

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 12, 2021.

Options for TNBC: Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease

Preferred Regimens

• Anthracyclines
  • Doxorubicin
  • Liposomal doxorubicin

• Taxanes   • Paclitaxel

• Antimetabolites
  • Capecitabine
  • Gemcitabine

• Microtubule inhibitors
  • Vinorelbine
  • Eribulin

• Sacituzumab govitecan-hziy (for TNBC)

Biomarkers Associated With FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents
Any	*BRCA 1* mutation *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib
TNBC	PD-L1 expression Threshold for positivity combined positive score ≥10	IHC	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib Entrectinib
Any	MSI-H/dMMR	IHC. PCR (tissue block)	Pembrolizumab Dostarlimab-gxly
Any	TMB-H (≥10 muts/mb)	NGS	Pembrolizumab

FISH = fluorescent in situ hybridization; IHC = immunohistochemistry; NGS = DNA sequencing by next-generation sequencing; PCR = polymerase chain reaction;; PD-L1 = programmed death-ligand 1

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 12, 2021.

PD-L1 Testing

- Detection by IHC
- Current NCCN guidelines
  - PD-L1 testing for pembrolizumab use: PD-L1 CPS ≥10 by 22C3 antibody

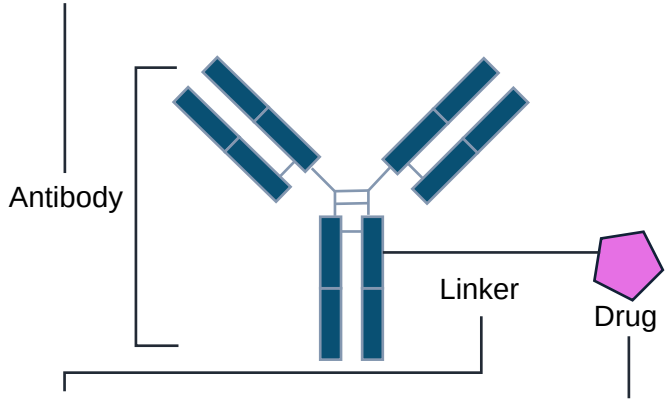
CPS = combined positive score; NCCN = National Comprehensive Cancer Network

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 12, 2021.

The ABCs of ADCs

Mechanism of Action of ADCs

- Target antigen should be highly expressed on tumor cells with limited expression on healthy tissues
- Antibody should have high affinity and avidity for tumor antigen



- Stable in circulation
- Must efficiently release cytotonic agent inside tumor cell

- Highly potent since only limited number of molecules can be attached to antibody

Ideal ADC has:

- Highly selective mAb for tumor-associated antigen that has restricted or no expression on normal (healthy) cells
- Potent cytotoxic agent (generally small molecule drug with high systemic toxicity) designed to induce target cell death after being internalized in tumor cell and released
- Linker that is stable in circulation, but releases cytotoxic agent in target cells

Mechanistically, ADCs exert their activity by:

1. Selective binding of antibody to tumor
2. Internalization
3. Lysosomal degradation
4. Release of cytotoxic payload → cytotoxic cell death

ADC = antibody-drug conjugate; mAb = monoclonal antibody

https://www.adcreview.com/the-review/antibody-drug-conjugates/what-are-antibody-drug-conjugates/. Accessed October 12, 2021.

TROP2 as a Target in TNBC

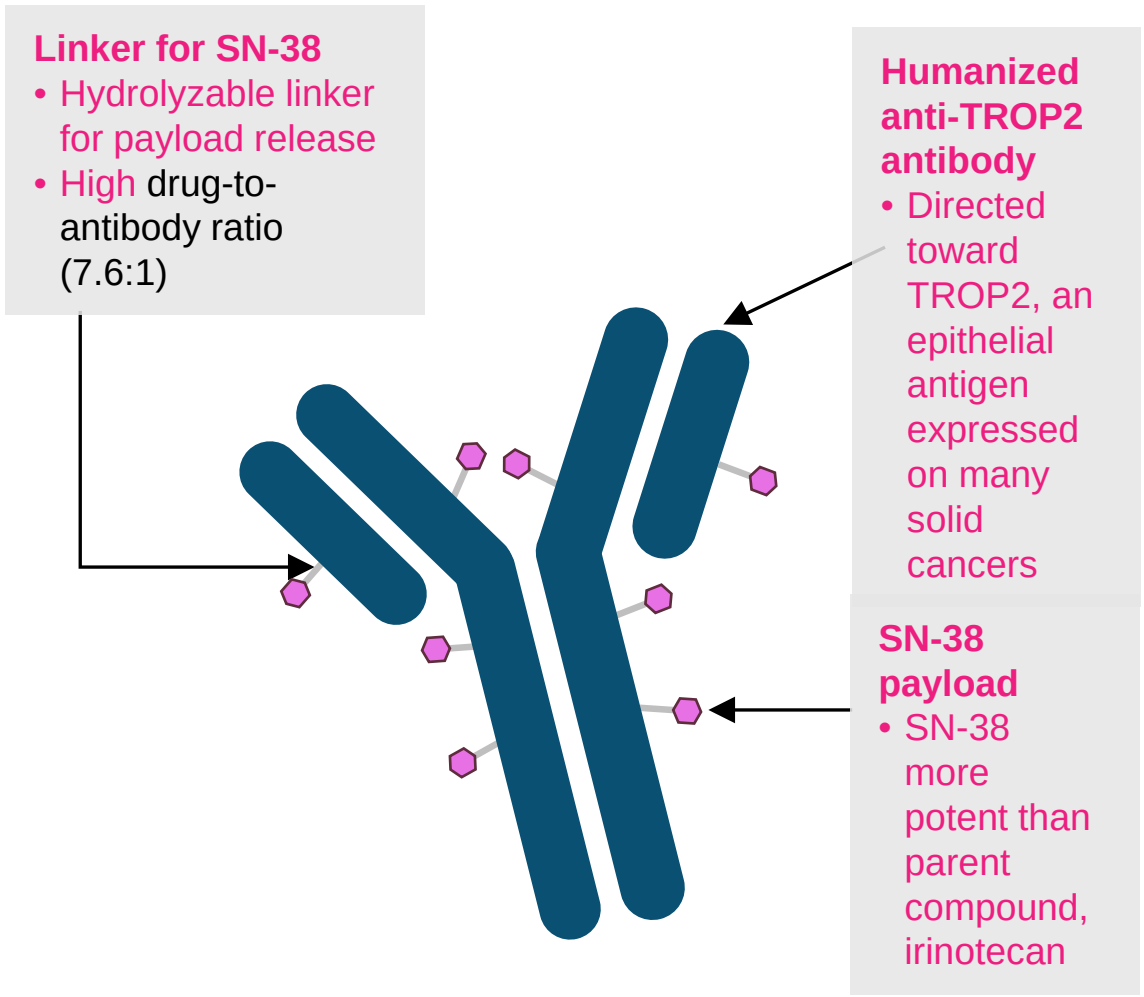
TROP2

- Trophoblast cell surface antigen 2 (TROP2)
- Glycoprotein that spans epithelial membrane surface
- Plays role in cell self-renewal, proliferation, and transformation
- Has essential role in embryonic development, placental tissue formation, embryo implantation, stem cell proliferation, and organ development
- Expressed in all subtypes of breast cancer
- Linked to poor prognosis in patients with breast cancer

https://www.onclive.com/view/role-of-trop-2-as-an-actionable-biomarker-in-solid-tumors. Accessed October 14, 2021. Vidula N et al. *J Clin Oncol*. 2017;35:15(suppl): Abstract 1075. Ambrogi F et al. *PLoS One*. 2014;9(5):e96993.

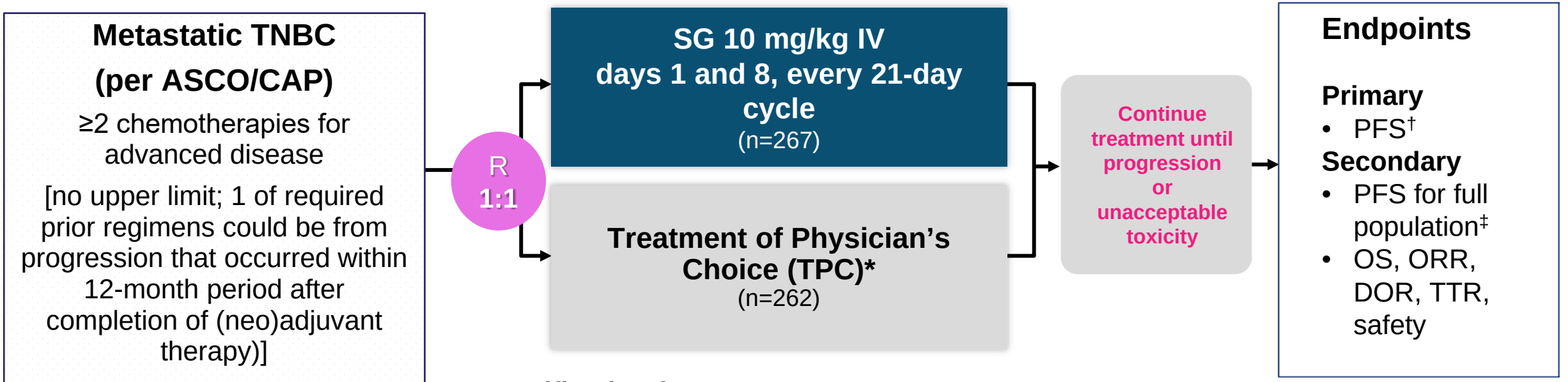
Sacituzumab Govitecan (SG) Is a First-in-Class TROP2–Directed ADC

- SG is distinct from other ADCs
  - Antibody highly specific for TROP2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for liberation of SN-38 from antibody
  - Hydrolysis of linker also releases SN-38 cytotoxic extracellularly in tumor microenvironment, providing bystander effect
- Granted regular approval April 2021 by FDA for metastatic TNBC
  - TROP2 testing not required



1. Goldenberg DM et al. *Expert Opin Biol Ther*. 2020;(8):871-85. 2. Nagayama A et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 3. Cardillo TM et al. *Bioconjugate Chem*. 2015;26(5):919-31. 4. Goldenberg DM et al. *Oncotarget*. 2015;6(26):22496-512. 5. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-sacituzumab-govitecan-triple-negative-breast-cancer. Accessed October 12, 2021.

ASCENT: Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC



NCT02574455

Stratification factors

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

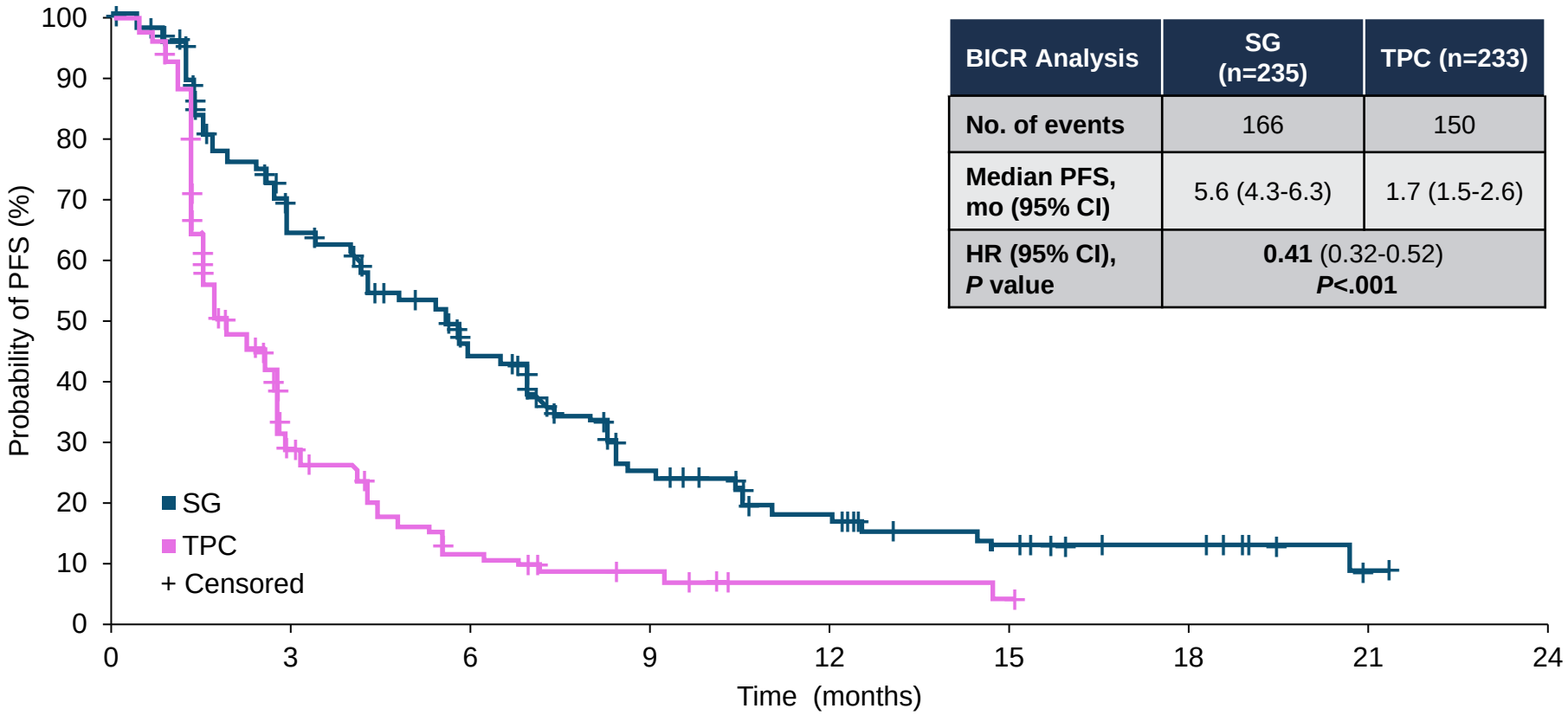
Data cutoff: March 11, 2020

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation.

*TPC = eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡Full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.
ASCO/CAP = American Society of Clinical Oncology/College of American Pathologists; DOR = duration of response; DSMC = Data Safety Monitoring Committee; IV = intravenous; MRI = magnetic resonance imaging; mTNBC = metastatic triple-negative breast cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R = randomization; RECIST = Response Evaluation Criteria in Solid Tumors; TTR = time to response.

Bardia A et al. *N Engl J Med*. 2021;384(16):1529-41.

ASCENT: Progression-Free Survival (BICR Analysis)



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*<.001**	

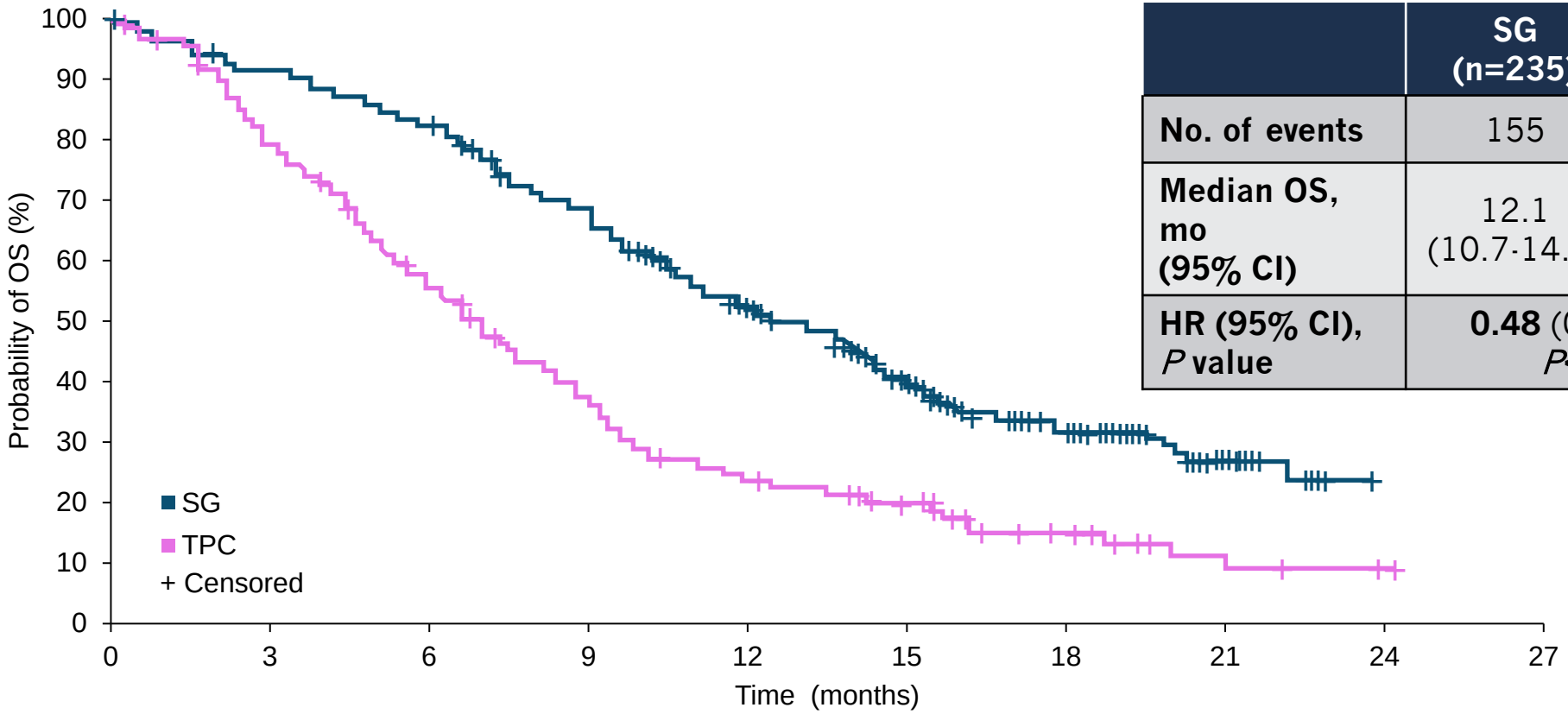
Numbers of patients at risk

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

Primary endpoint (PFS) assessed by independent central review in the brain metastases-negative population, as predefined in study protocol.
Secondary endpoint (PFS) assessed in full population (brain metastases–positive and –negative) and PFS benefit was consistent (HR=0.43 [0.35-0.54], P<.0001).
BICR = blind independent central review; CI = confidence interval; HR = hazard ratio

Bardia A et al. *N Engl J Med*. 2021;384(16):1529-41.

ASCENT: Overall Survival



	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** (0.33-0.59) ***P*<.001**	

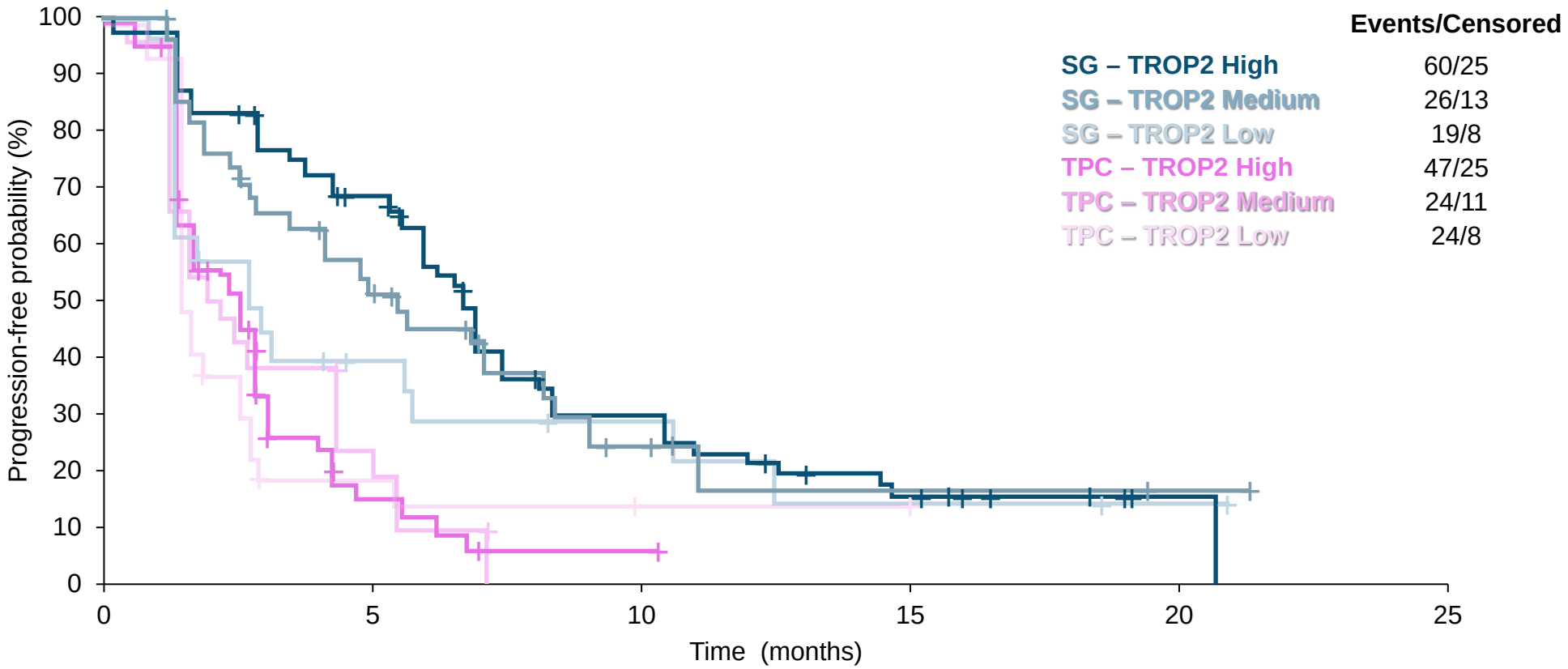
Numbers of patients at risk

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

Assessed by independent central review in brain metastases–negative population.

Bardia A et al. *N Engl J Med*. 2021;384(16):1529-41.

ASCENT: Progression-Free Survival by TROP2 Expression



	TROP2 High | H-score: 200-300		TROP2 Medium | H-score: 100-200		TROP2 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)

Assessed in brain metastases–negative population. TROP2 expression determined in archival samples by validated IHC assay and H-scoring.
H-score = histochemical score

Bardia A et al. *Ann Oncol*. 2021;32(9):1148-56.

ASCENT: Treatment-Related Adverse Events

- All grade: 98% of patients
- Grade 3/4: 64% of patients

		SG (n=258)			TPC (n=224)		
TRAE		**All Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hematologic	**Neutropenia**	**63**	**34**	**17**	**43**	**20**	**13**
	Anemia	**34**	**8**	**0**	**24**	**5**	**0**
	Leukopenia	16	9	1	11	4	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	**Diarrhea**	**59**	**10**	**0**	12	<1	0
	Nausea	**57**	**2**	**<1**	**26**	**<1**	**0**
	Vomiting	29	1	<1	10	<1	0
Other	**Fatigue**	**45**	**3**	**0**	**30**	**5**	**0**
	Alopecia	**46**	**0**	**0**	**16**	**0**	**0**

TRAE = treatment-related adverse event

Bardia A et al. *Ann Oncol*. 2021;32(9):1148-56.

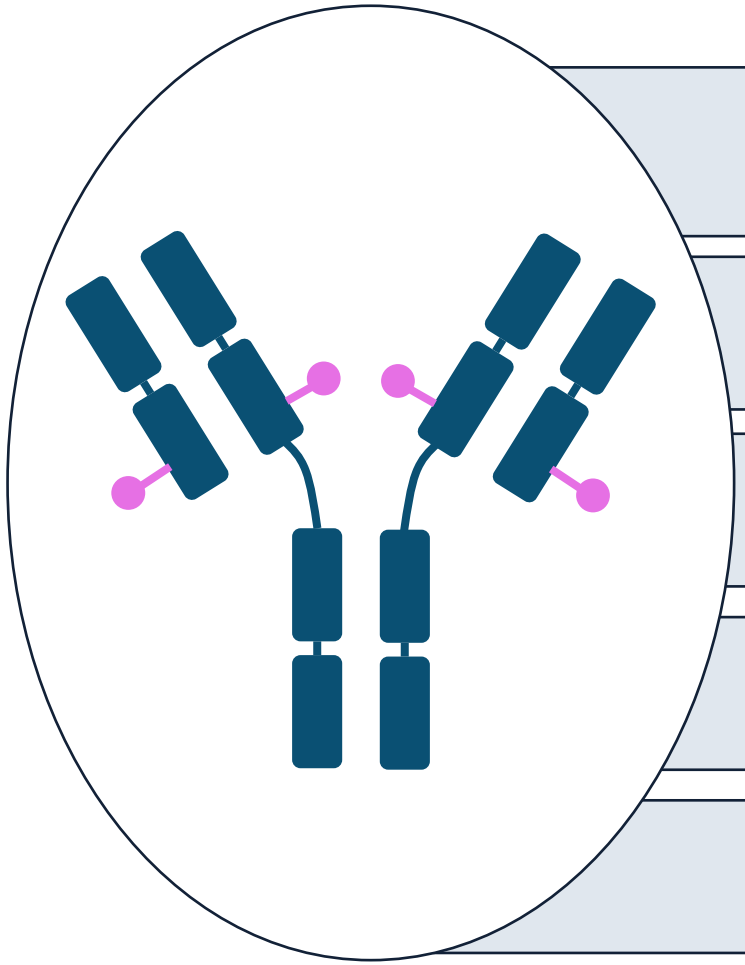
ASCENT: Treatment-Related Adverse Events (cont)

- Key grade ≥3 TRAEs (SG vs TPC)
  - Neutropenia (51% vs 33%)
  - Diarrhea (10% vs <1%)
  - Leukopenia (10% vs 5%)
  - Anemia (8% vs 5%)
  - Febrile neutropenia (6% vs 2%)
- G-CSF usage: 49% in SG arm vs 23% in TPC arm
- Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)

G-CSF = granulocyte-colony stimulating factor

Bardia A et al. *Ann Oncol*. 2021;32(9):1148-56.

Datopotamab Deruxtecan: TROP2 ADC in Development



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

DAR = drug-to-antibody ratio; DLT = drug-limiting toxicity

1. Goldenberg DM, et al. *Oncotarget.* 2015;6(26):22496-512. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22(20):5097-108. 3. Ocean AJ et al. *Cancer.* 2017;123(19):3843-54. 4. Bardia A, et al. *J Clin Oncol.* 2017;35(19):2141-8. 5. Lisberg AE et al. ASCO 2020; Abstract 9619. 6. Heist RS et al. WCLC 2019; Oral presentation.

TROPION-PanTumor01 (NCT03401385) – TNBC Cohort

Phase 1, First-in-human, Dose Escalation and Expansion Study

- Advanced/metastatic HR-/HER2-negative breast cancer (TNBC)*
- Relapsed/progressed on standard treatment
- Unselected for TROP2 expression†
- Measurable disease (per RECIST version 1.1)

→

Dato-DXd 6 mg/kg IV Q3W

2 patients received 8 mg/kg prior to selection of the 6-mg/kg dose for dose expansion

→

Primary objectives include:

- Safety, tolerability

Secondary objectives include:

- Efficacy, pharmacokinetics

Data cutoff January 8, 2021

- Current analysis includes 24 patients treated at the 6-mg/kg dose (n=22) and 8-mg/kg dose (n=2)‡
- Treatment ongoing in 18 patients (75%); 6 patients (25%) discontinued treatment, all due to disease progression§

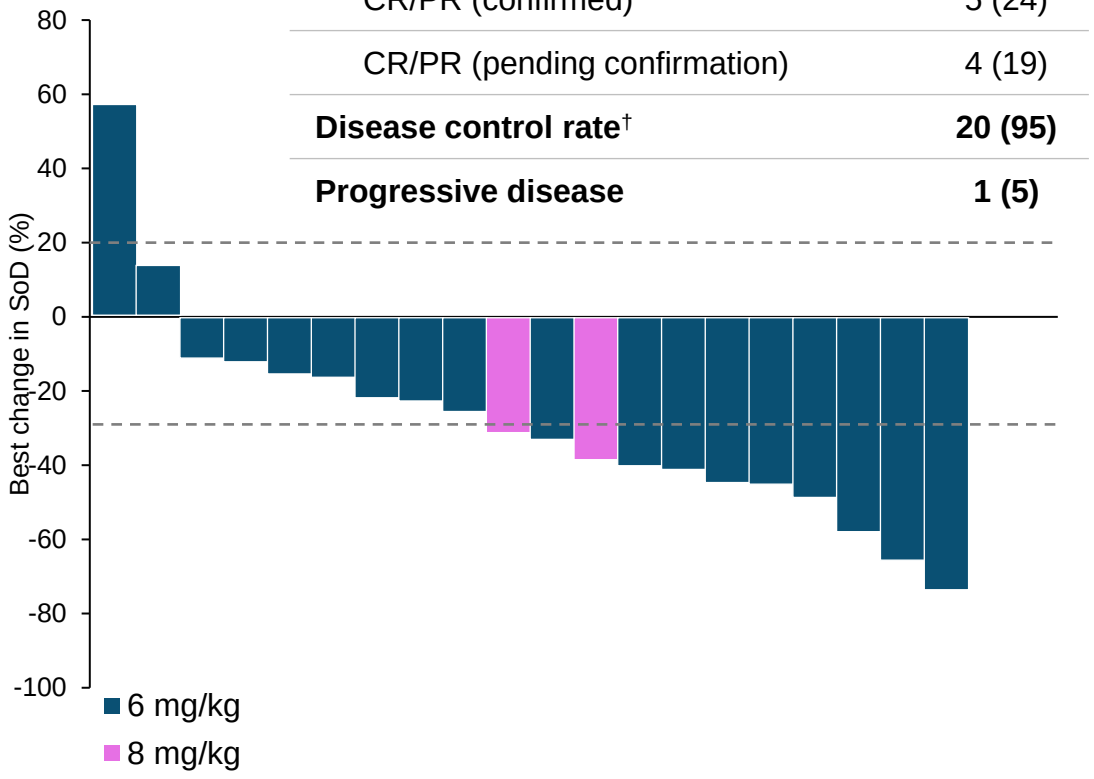
Q3W = every 3 weeks

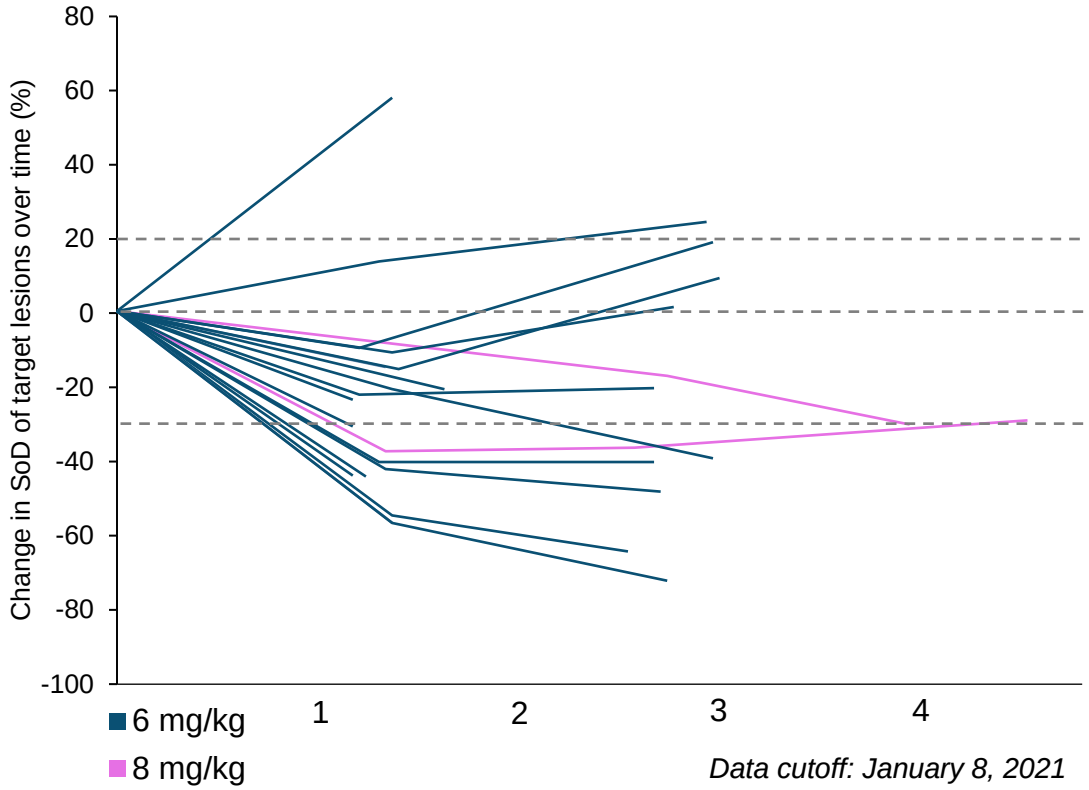
*Estrogen receptor positivity <1%; †Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression; ‡HR+ cohort is currently open for enrollment at 6 mg/kg; §Progression includes progressive disease per RECIST 1.1 and clinical progression.

https://clinicaltrials.gov/ct2/show/NCT03401385. Accessed October 12, 2021.

TROPION-PanTumor01: Dato-DXd TNBC Cohort

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





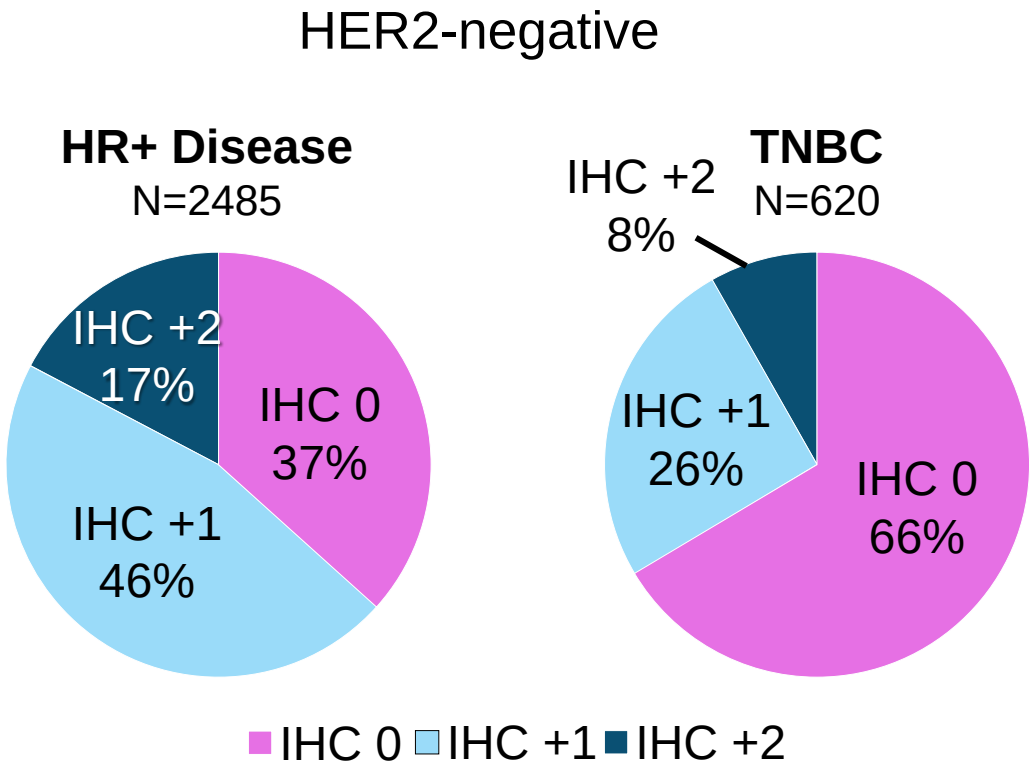
CR = complete response; PD = progressive disease; PR = partial response; SoD = sum of diameters

*Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. †Postbaseline tumor assessments were not yet available for 3 patients at data cutoff. One patient was not confirmed to have target lesion per BICR and therefore had best overall response of non-CR/non-PD; Includes patients with best overall response of CR, PR, stable disease, or non-CR/non-PD.

Bardia A et al. *Ann Oncol*. 2021;32(suppl 2):S60-78.

Additional ADCs in TNBC

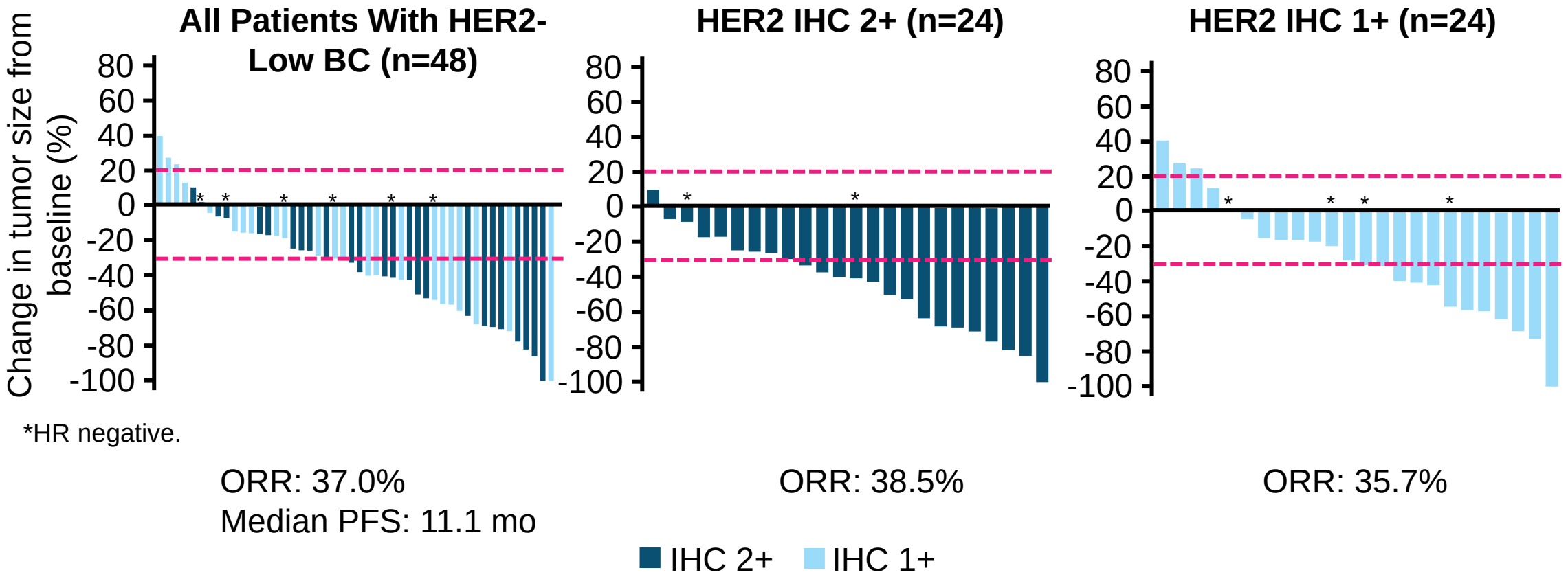
Prevalence of HER2-low by HR Status



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

Schettini F. ESMO Breast Cancer Virtual Meeting 2020; Abstract 23P. Slide courtesy of Aleix Prat, MD, PhD.

Phase 1b Trial: Trastuzumab Deruxtecan for Heavily Pretreated HER2-Low Advanced Breast Cancer



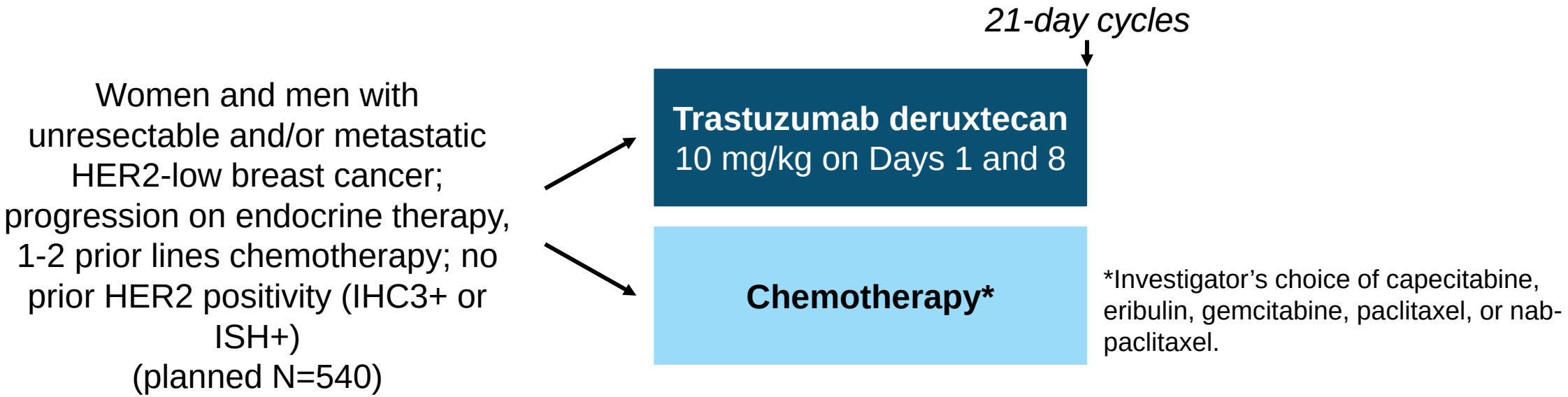
*HR negative.

BC = breast cancer

Modi S et al. *J Clin Oncol*. 2020;38(17):1887-96.

DESTINY-Breast04: Trastuzumab Deruxtecan vs Chemotherapy in Previously Treated HER2-low BC

- International, randomized, open-label phase 3 study



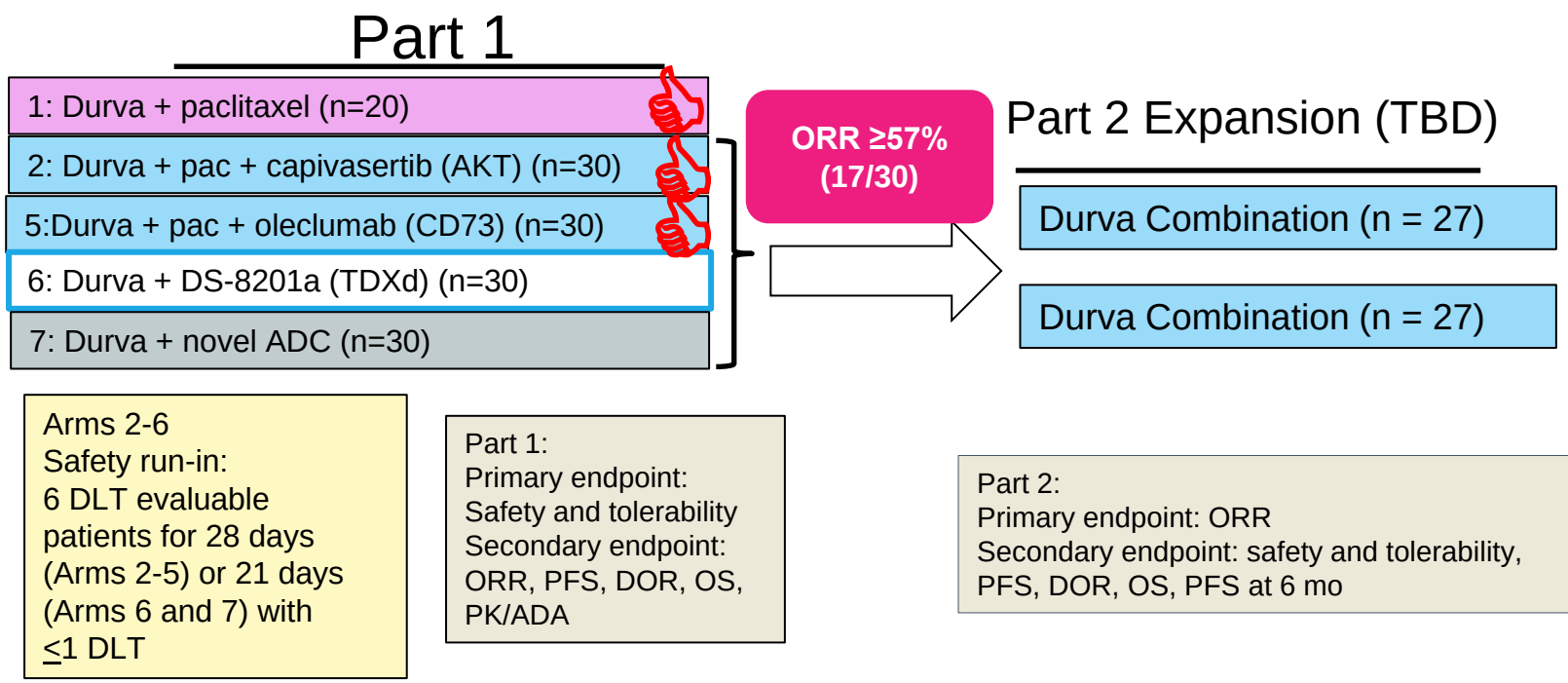
- Primary endpoints: PFS per BICR
- Secondary endpoints: OS, DOR, ORR, PFS per investigator

ISH = in situ hybridization

https://clinicaltrials.gov/ct2/show/NCT03734029. Accessed October 13, 2021.

BEGONIA Study Design: TDxd + Durvalumab for HER2-low TNBC

- Metastatic TNBC
- No prior treatment for stage IV disease
- ECOG PS 0 -1
- RECIST evaluable
- Patients may have relapsed from earlier stage disease but must be ≥12 mo since prior taxane treatment
- **Arm 6: Locally confirmed HER2 IHC 1-2+ (ISH-)**



Note
- Arms 3 (durva + selumetinib + pac) and Arms 4 (durva + danvatirsen + pac) were removed before patient enrollment
- Part 1 of this study is considered stage 1 of Simon 2-stage design, and Part 2 of this study is considered stage 2
- Amendment for new arm (Arm 7) to include novel combination of durvalumab + novel ADC (will include HER2-0 patients)

= enrollment complete; only Arm 6 is open at this time

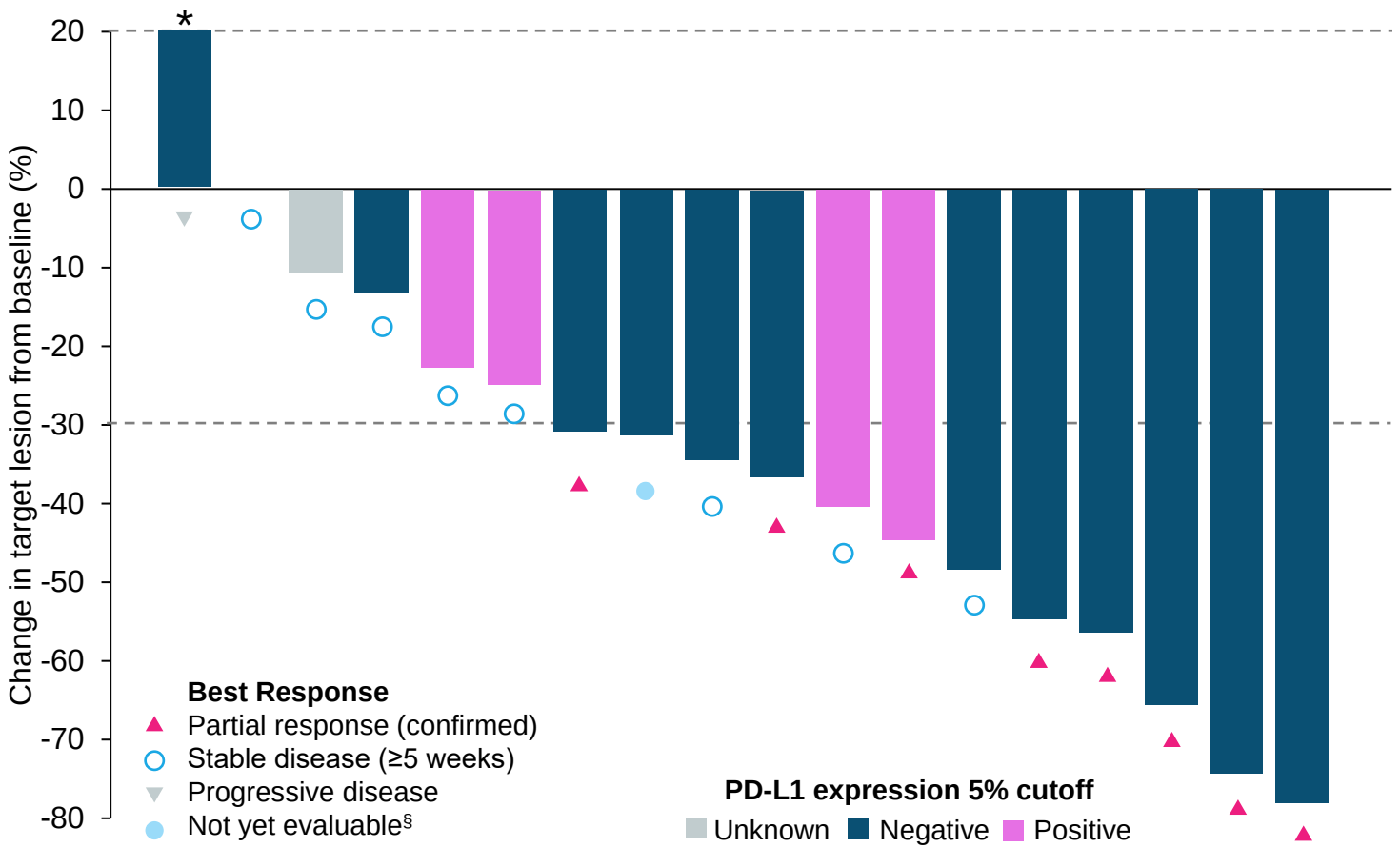
ADA = antidrug antibodies; durva = durvalumab; ECOG = Eastern Cooperative Oncology Group; pac = paclitaxel; PK = pharmacokinetics; TBD = to be determined; TDxd = trastuzumab deruxtecan

https://clinicaltrials.gov/ct2/show/NCT03742102. Accessed October 13, 2021.

TDxd+ Durvalumab: Efficacy

- Responses were observed in PD-L1–positive (confirmed ORR 1/1 [100%]) and PD-L1–negative (confirmed ORR 7/10 [70.0%]) groups

Parameter	D+TDXd
Patient who completed at least 1 on-treatment assessment, n	18
Response evaluable analysis set, n‡	12
Confirmed ORR, n (%) ‡ 95% CI Complete response, n Partial response, n	8/12 (66.7) 41.0, 86.7 0 8
Stable disease, n	8
Progressive disease, n	1



CI = confidence interval; D = durvalumab; ORR = overall response rate; TDxd = trastuzumab deruxtecan

Will there be a role for TDxd+ durvalumab in first-line HER2-low TNBC? Will activity be greater than TDxd alone, even in PD-L1–negative patients?

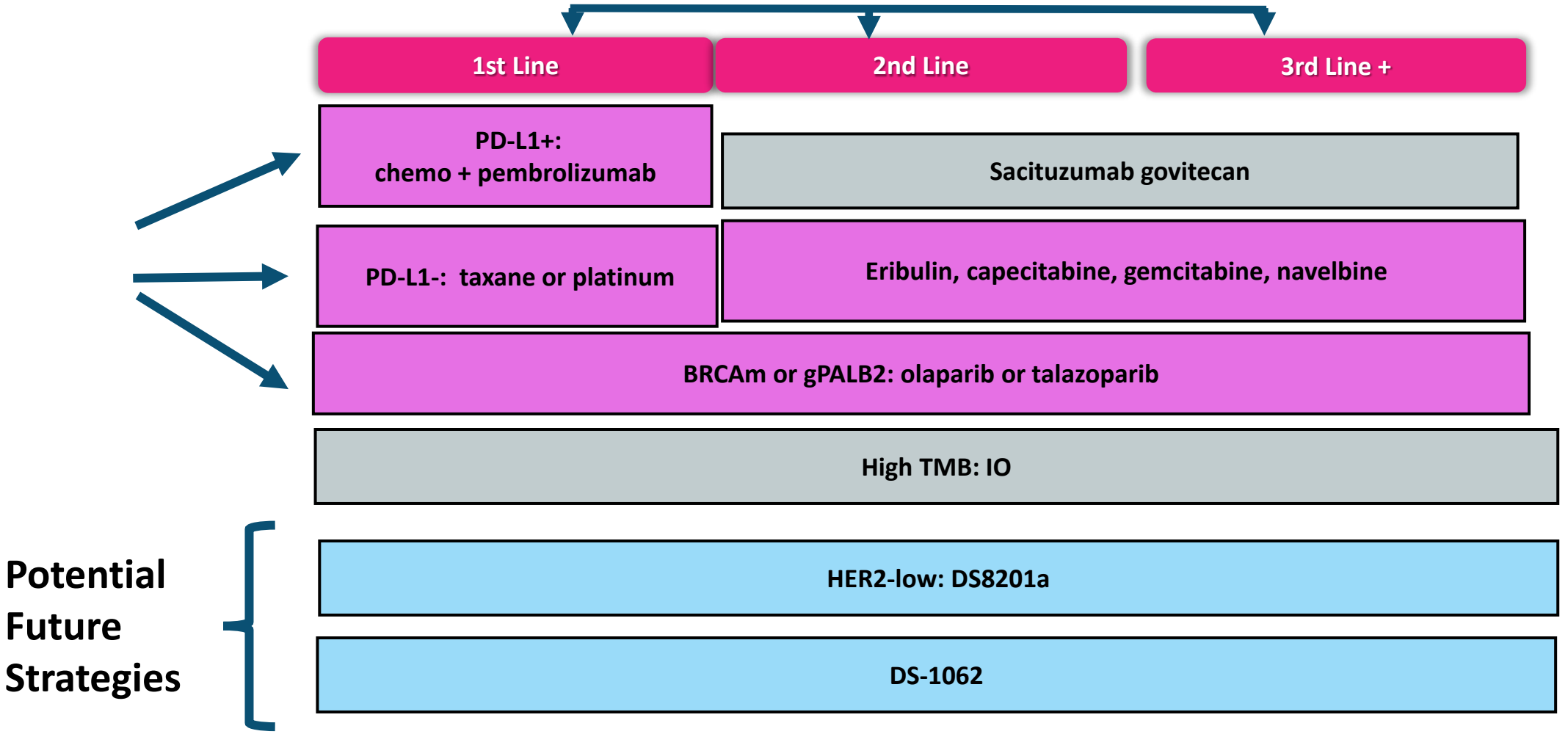
Schmid P et al. *J Clin Oncol*. 2021;39(suppl 15); Abstract 1023.

Additional Ongoing Clinical Trials

- Phase 2
  - Sacituzumab govitecan in localized TNBC (NeoStar)
    - https://www.clinicaltrials.gov/ct2/show/NCT04230109
  - Sacituzumab govitecan +/- pembrolizumab in metastatic TNBC
    - https://www.clinicaltrials.gov/ct2/show/NCT04468061
  - Sacituzumab govitecan in HER2-negative breast cancer and brain metastases
    - https://www.clinicaltrials.gov/ct2/show/NCT04647916

Strategies to Incorporate Anti-TROP2 ADCs Into Treatment Paradigms

Approach to Therapy for Metastatic TNBC+ Disease: Move to Personalization



IO = immunooncology agent; TMB = tumor mutational burden

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 13, 2021. Courtesy of Sara Tolaney, MD, MPH.

Common Anti-TROP2 ADC Adverse Events

- **Common AEs** (incidence ≥25%)
  - Neutropenia
  - Nausea
  - Diarrhea
  - Fatigue
  - Alopecia
  - Anemia
  - Vomiting
  - Constipation
  - Decreased appetite
  - Rash
  - Abdominal pain

AE = adverse event

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761115s000lbl.pdf. Accessed October 13, 2021.

Mitigating Anti-TROP2 ADC Adverse Events

- **Black box warnings: neutropenia and diarrhea**
  - **Severe or life-threatening neutropenia** may occur
    - Withhold SG for absolute neutrophil count below 1500/mm^3 or neutropenic fever
    - Monitor blood cell counts periodically during treatment
    - Consider G-CSF for secondary prophylaxis
    - Initiate anti-infective treatment in patients with febrile neutropenia without delay
  - **Severe diarrhea** may occur
    - Monitor patients with diarrhea and give fluid and electrolytes as needed
    - Administer atropine, if not contraindicated, for early diarrhea of any severity
    - At onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide
    - If severe diarrhea occurs, withhold SG until resolved to ≤ Grade 1 and reduce subsequent doses

G-CSF = granulocyte colony-stimulating factor

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761115s000lbl.pdf. Accessed October 13, 2021.

Additional Dose Modifications for Adverse Reactions With Anti-TROP2 ADCs

Adverse Reaction	Occurrence	Dose Modification
Severe neutropenia		
Grade 4 neutropenia ≥7 days OR Grade 3 febrile neutropenia (absolute neutrophil count <1000/mm^3 and fever ≥38.5°C) OR At time of scheduled treatment, Grades 3-4 neutropenia, which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction and administer G-CSF
	Second	50% dose reduction
	Third	Discontinue treatment
At time of scheduled treatment, Grades 3-4 neutropenia, which delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761115s000lbl.pdf. Accessed October 13, 2021.

Additional Dose Modifications for Adverse Reactions With Anti-TROP2 ADCs (cont)

Severe Nonneutropenic Toxicity		
Grade 4 nonhematologic toxicity of any duration OR Any Grades 3-4 nausea, vomiting, or diarrhea due to treatment that is not controlled with antiemetics and antidiarrheal agents OR Other Grades 3-4 nonhematologic toxicity persisting >48 hours despite optimal medical management OR At time of scheduled treatment, Grades 3-4 nonneutropenic hematologic or nonhematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
In the event of Grades 3-4 nonneutropenic hematologic or nonhematologic toxicity, which does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761115s000lbl.pdf. Accessed October 13, 2021.

Case-Based Discussion

Case 1: Wendy

Wendy is a 64-year-old woman with PD-L1–negative TNBC and a germline *BRCA* mutation who received adjuvant ACT chemotherapy and has experienced locally advanced tumor progression (supraclavicular recurrence) and then received PARP inhibition and developed further local progression.

- Aside from radiation therapy, what potential treatment options do we have to treat Wendy?
- Based on your treatment selection, what potential adverse events should you monitor for and counsel on?

ACT = doxorubicin + cyclophosphamide followed by paclitaxel; PARP = poly-ADP ribose polymerase

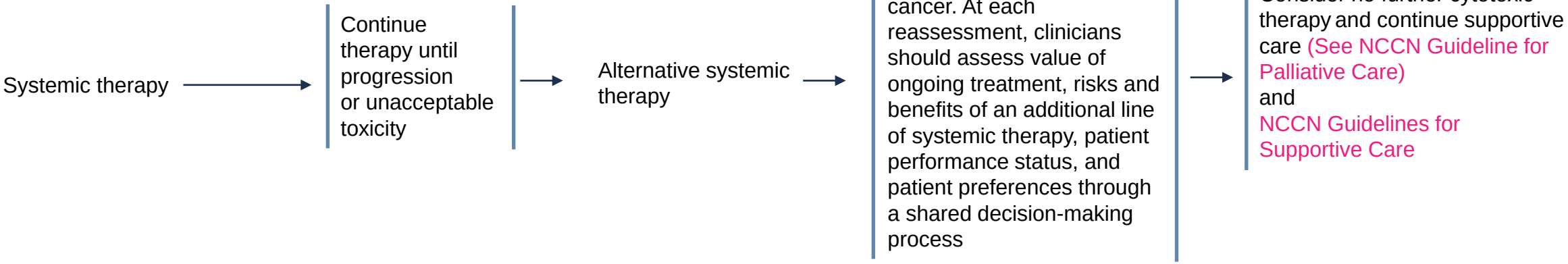
Systemic Regimens for Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease

HER2 Negative			

Preferred Regimens
• Anthracyclines
  • Doxorubicin
  • Liposomal doxorubicin
• Taxanes
  • Paclitaxel
• Antimetabolites
  • Capecitabine
  • Gemcitabine
• Microtubule inhibitors
  • Vinorelbine
  • Eribulin
• Sacituzumab govitecan (for TNBC)
	• For germline *BRCA1/2* mutations see additional targeted therapy options (BINV-R)
	• Platinum (for TNBC and germline *BRCA1/2* mutation)
	  • Carboplatin
	  • Cisplatin
	• For PD-L1–positive TNBC, see additional targeted therapy options
		Other Recommended Regimens
		• Cyclophosphamide
		• Docetaxel
		• Albumin-bound paclitaxel
		• Epirubicin
		• Ixabepilone
			Useful in Certain Circumstances
			• AC (doxorubicin/cyclophosphamide)
			• EC (epirubicin/cyclophosphamide)
			• CMF (cyclophosphamide/ methotrexate/fluorouracil)
			• Docetaxel/capecitabine
			• GT (gemcitabine/paclitaxel)
			• Gemcitabine/carboplatin
			• Paclitaxel/bevacizumab
			• Carboplatin + paclitaxel or albumin-bound paclitaxel

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 13, 2021.

Systemic Treatment of Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease: ER and/or PR Negative; HER2 Negative



https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 13, 2021.

Case 2: Brenda

Brenda is a 59-year-old woman who has metastatic TNBC. After initial first-line chemotherapy, she develops systemic progression and new brain metastases. Workup reveals that the brain metastases are not amenable to stereotactic radiosurgery.

- What potential options do we have to treat Brenda?
- What is the rationale for your choice of treatment?

Systemic Regimens for Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease

HER2 Negative			

Preferred Regimens
• Anthracyclines
  • Doxorubicin
  • Liposomal doxorubicin
• Taxanes
  • Paclitaxel
• Anti-metabolites
  • Capecitabine
  • Gemcitabine
• Microtubule inhibitors
  • Vinorelbine
  • Eribulin
• Sacituzumab govitecan (for TNBC)
	• For germline *BRCA 1/2* mutations see additional targeted therapy options (BINV-R)
	• Platinum (for TNBC and germline *BRCA1/2* mutation)
	  • Carboplatin
	  • Cisplatin
	• For PD-L1—positive TNBC see additional targeted therapy options (BINV-R)
		Other Recommended Regimens
		• Cyclophosphamide
		• Docetaxel
		• Albumin-bound paclitaxel
		• Epirubicin
		• Ixabepilone
			Useful in Certain Circumstances
			• AC (doxorubicin/cyclophosphamide)
			• EC (epirubicin/cyclophosphamide)
			• CMF (cyclophosphamide/ methotrexate/fluorouracil)
			• Docetaxel/capecitabine
			• GT (gemcitabine/paclitaxel)
			• Gemcitabine/carboplatin,
			• Paclitaxel/bevacizumab
			• Carboplatin + paclitaxel or albumin-bound paclitaxel

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 13, 2021.


Questions?

Q&A Discussion

Have you experienced issues with coverage for sacituzumab govitecan?

If you have experienced challenges with access, what have you done to help ensure eligible patients receive this medication?

Q&A Discussion

Do we know if datopotamab deruxtecan has longer lasting AEs compared to sacituzumab govitecan due to longer half-life?

Q&A Discussion

How does one select one chemotherapy regimen over another for TNBC?

Q&A Discussion

In the neoadjuvant setting, when using pembrolizumab, the trial used paclitaxel and carboplatin.

Is that something you are doing regularly, or in which patients would you use paclitaxel alone?

If using paclitaxel alone, are you still using pembrolizumab?

Q&A Discussion

Can you comment on if you are switching patients off of atezolizumab after the agent’s withdrawal?

Q&A Discussion

Would you combine capecitabine with pembrolizumab adjunctively in patients with TNBC with less than pathologic complete response after completing neoadjuvant?

Q&A Discussion

Have you heard when datopotamab deruxtecan may be available for patients with TNBC as well?

Q&A Discussion

On the same note of choosing therapy for TNBC, I’m curious about the diversity of treatment options for the “treatment of physician’s choice” arm in the sacituzumab govitecan trial.

Is this a common treatment arm in TNBC studies?

Are there subanalyses comparing what those physician’s choices were?

Please complete the post-test and evaluation.

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