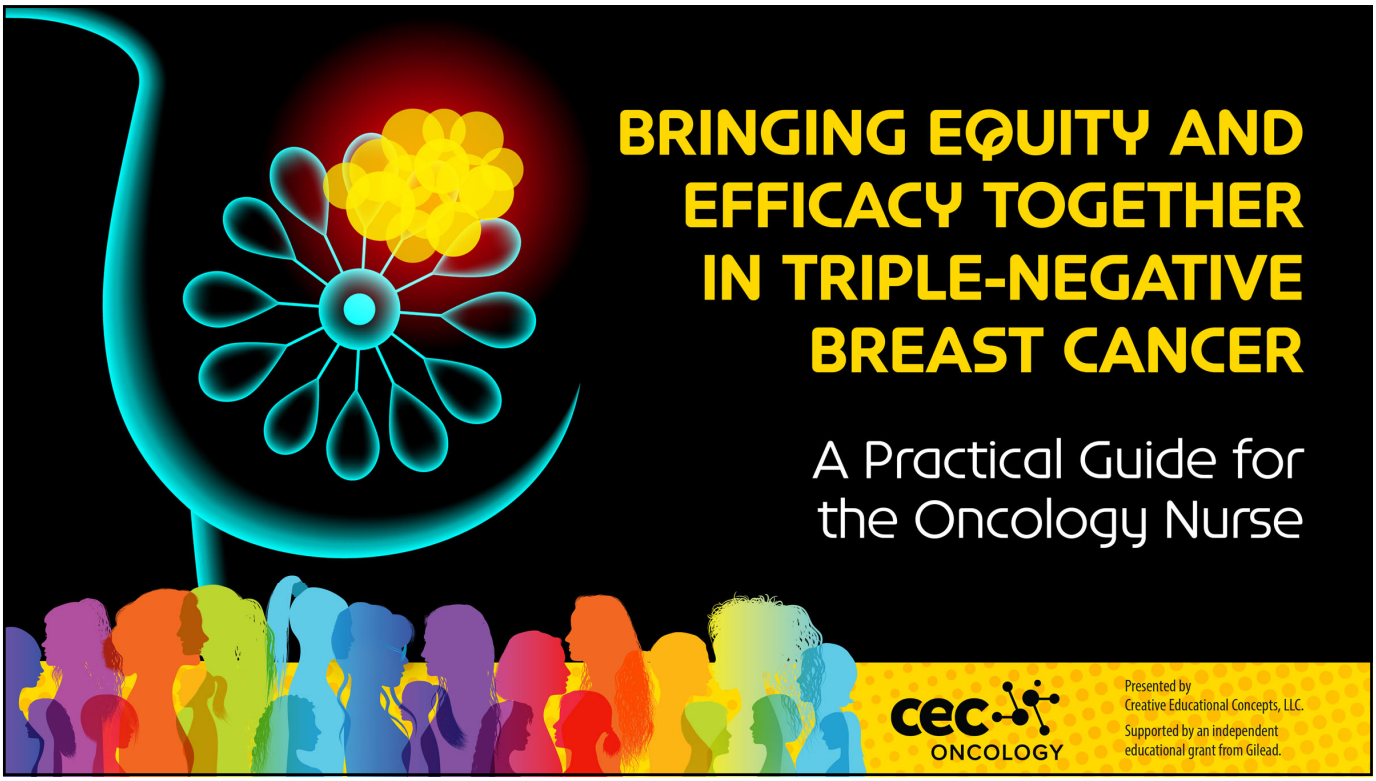


Thank You

Presented by Creative Educational Concepts

cec HEALTHCARE EDUCATION

Supported through an independent educational grant from Gilead

Learning Objectives

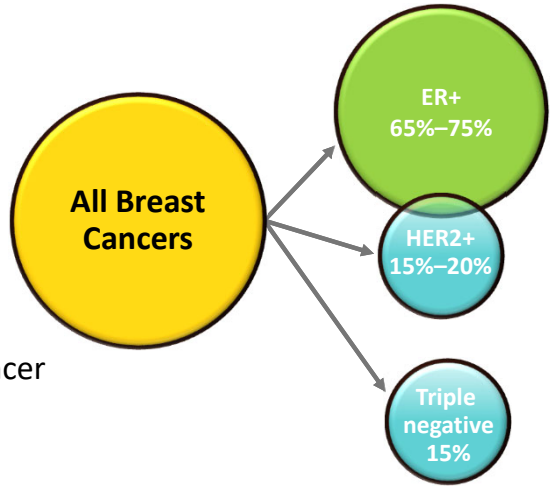
- Discuss the multifaceted etiology of the racial disparity observed in triple-negative breast cancer (TNBC), with a focus on both biologic and non-biologic factors, and identify tangible strategies oncology nurses can employ to promote equitable care and outcomes for all patients.
- Review antibody-drug conjugate (ADC) structure, mechanism of action, and real-world clinical considerations, with a particular focus on toxicity management, for oncology nurses who care for TNBC patients receiving ADCs.
- Examine completed, ongoing, and planned clinical trial data for ADCs as part of the evolving and expanding TNBC treatment calculus, including recent FDA approvals and updated guideline recommendations.
- Using a patient case-driven approach, design evidence-based treatment plans for patients with TNBC, with an emphasis on the placement of novel therapies in the shifting TNBC treatment calculus, strategies for anticipating, recognizing, and treating adverse events, and effectively integrating socioeconomic and other non-biologic factors into equitable cancer care.

Delineating the Disparity in TNBC

A Renewed Outlook on an Established Problem

Triple-negative Breast Cancer (TNBC)
Epidemiology and Clinical Gravity

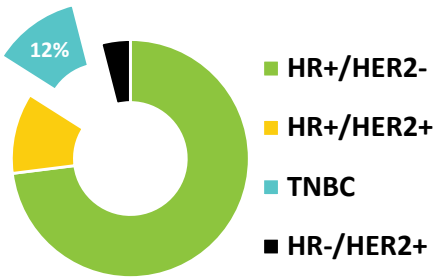
- TNBC lacks estrogen and progesterone hormone receptors (ER and PR), and does not exhibit overexpression of human epidermal growth factor receptor 2 (HER2)
- TNBC accounts for ~15% of breast cancers
- More common in
  - Young women
  - Individuals of African and Hispanic heritage
  - *BRCA1* germline mutations
- Poorer overall survival vs other forms of breast cancer (median OS = ~18 months)
- More aggressive disease course
  - Higher risk of both local and distant recurrence
- Historically, limited treatment options



TNBC, triple-negative breast cancer.

Saha P, Nanda R. *Ther Adv Med Oncol.* 2016; Lebert JM, et al. *Curr Oncol.* 2018.

Triple-negative Breast Cancer (TNBC)
Epidemiology and Racial Disparity



77%
5-year survival for TNBC in ALL comers

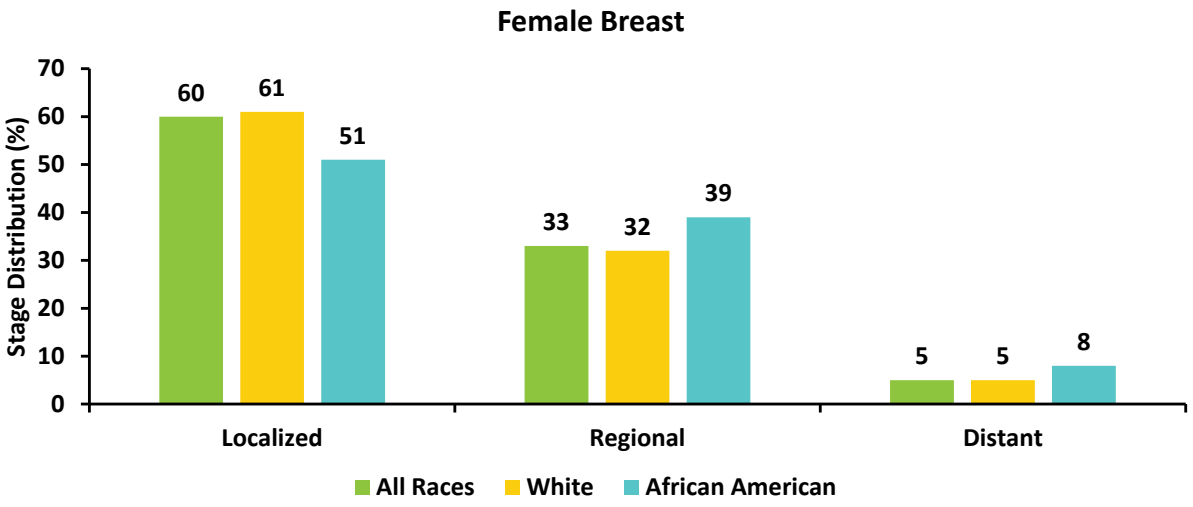
73%
5-year survival for TNBC in NH Black women

- **Higher probability of developing TNBC**
  - 12.1/100,000 for NH White women
  - 22.8/100,000 for Black women
  - NH Black women have higher incidence rates than NH White women before the age of 40, when most TNBC is diagnosed, and this does not seem to be related to socioeconomic risk
- **Higher probability of dying of TNBC**
  - Studies suggest West African heritage is associated with inherited susceptibility for TNBC
  - NH Black women are likely to be diagnosed at more advanced stages than NH White women
  - NH Black women have a 12% higher 5-year mortality than NH White women, even when age and clinical factors are adjusted; however, this difference is resolved when factors relating to access-to-care are adjusted for

NH, non-Hispanic.

https://www.cancer.org/cancer/breast-cancer/about/types-of-breast-cancer/triple-negative.html; Wang F, et al. *Cancer Res.* 2021; Prakash O, et al. *Front Public Health.* 2020; Hossain F, et al. *Front Public Health.* 2019; https://seer.cancer.gov/statfacts/html/breast-subtypes.html.

Delineating the Disparity
Stage at Diagnosis

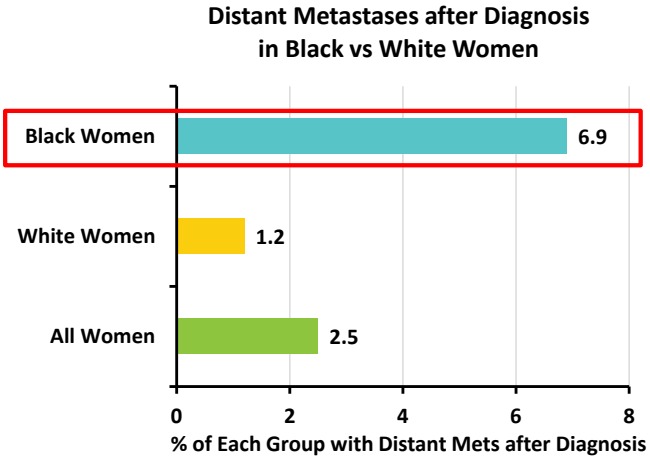


Esnaola NF. *ASCO*. 2021. Oral Session; Siegel R, et al. *CA Cancer Clin J.* 2011.

Delineating the Disparity
Rate of Distant Metastases

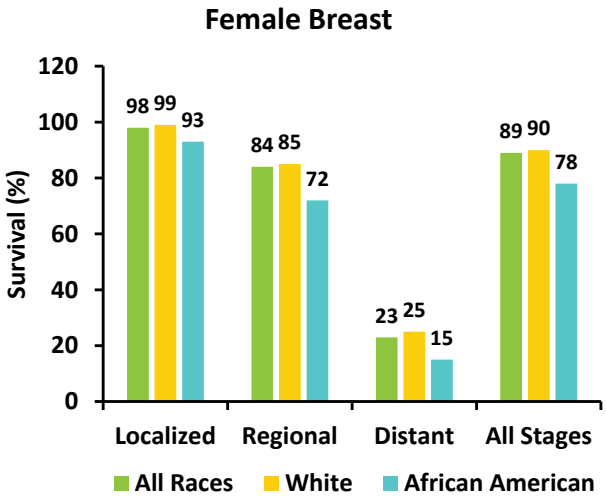
Even with statistical adjustment for later stage diagnosis, Black women still exhibit nearly a **6-fold higher rate** of distant metastases vs White women.

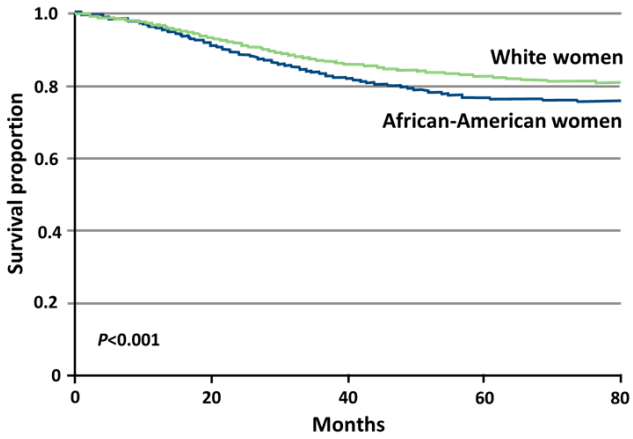
Baseline Characteristics at Diagnosis			
	Black Women	White Women	*P*-value
N (%)	101 (22.9%)	340 (77.1%)	
Median age (SD)	55.9 (12.37)	57.5 (11.9)	0.218
Stage I	59 (58.4%)	284 (83.5%)	<0.0001
Stage II	29 (28.7%)	45 (13.2%)	
Stage III	10 (9.9%)	10 (2.9%)	
Stage IV	3 (3.0%)	1 (0.3%)	



Blanter J, et al. *ASCO*. 2021. Abstract 1084.

Delineating the Disparity
Survival





Cho B, et al. *JAMA Oncol.* 2021; Esnaola NF. *ASCO*. 2021. Oral Session; Siegel R, et al. *CA Cancer Clin J.* 2011.

Factors That Contribute to Health Inequity

Socioeconomic Factors

- Poverty
- Financial toxicity of care
- Lack of healthcare access

Biological Factors

- Genomic mutations including *BRCA1*
- Population genetics and inherited susceptibility
- Obesity and comorbidities (HTN, diabetes)

Bias-driven Factors

- Systemic bias
- Implicit bias
- Previous patient discrimination

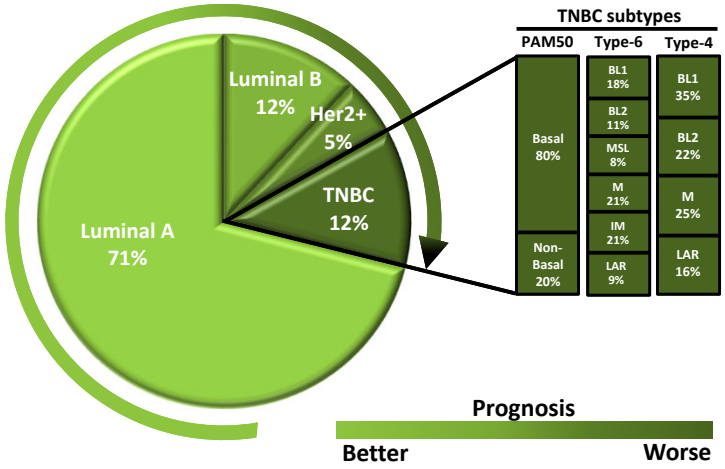
Historical Factors

- Cultural practices
- Mistrust in the medical community
- Lack of access to clinical trials

Wang F, et al. *Cancer Res.* 2021; Prakash O, et al. *Front Public Health.* 2020; Hossain F, et al. *Front Public Health.* 2019; Newman LA, Kaljee LM. *JAMA Surg.* 2017; Penner LA, et al *J Clin Oncol.* 2016; Penner LA, et al. *Soc Sci Med.* 2017.

The Intrinsic Heterogeneity of TNBC
Challenge and Opportunity

- Traditional chemotherapy has long been the primary treatment modality for TNBC
- The search for actionable treatment targets has revealed TNBC as a condition with immense molecular heterogeneity



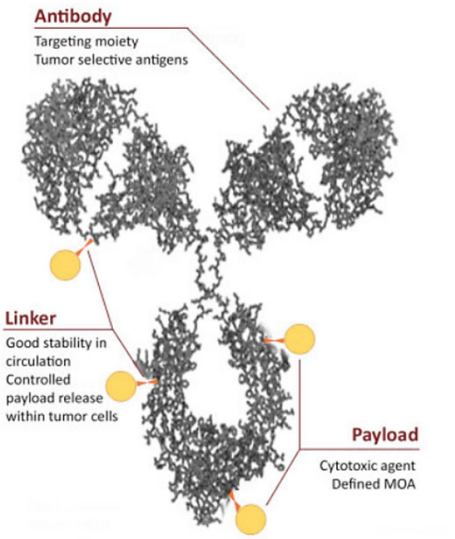
Gatti V, et al. *Int J Mol Sci.* 2019; Bianchini G, et al. *Nat Rev Clin Oncol.* 2016.

Demystifying Antibody-drug Conjugates (ADCs)

Structure, Mechanism, and Evidentiary Base

Demystifying ADCs
Structure

- Empirically, ADCs are composed of 3 components
  - Antibody targeted to a tumor antigen
  - Cytotoxic payload
  - Cleavable linker (linking antibody to payload)



Birrer MJ, et al. *J Natl Cancer Inst*. 2019.

Demystifying ADCs
Mechanism

Though complex, the MOA of ADCs can be distilled into 4 basic steps:

I. Antibody finds and binds target antigen on cancer cell

II. Drug-antigen complex is taken up into the cell via receptor-mediated endocytosis

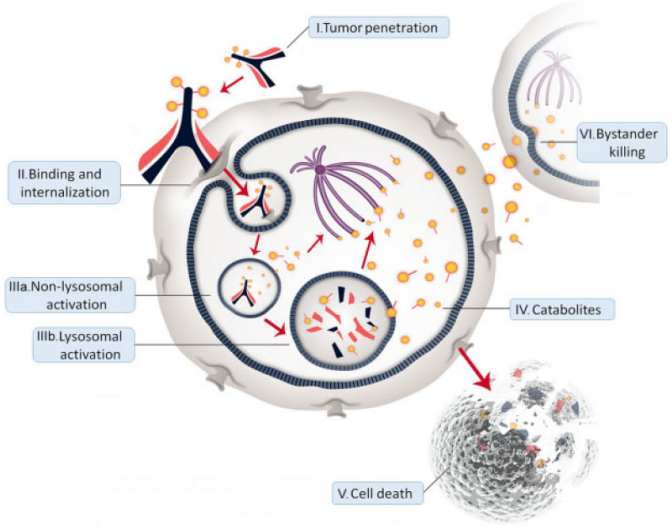
III. Linker is cleaved, releasing the payload

IV. Payload is released into cytoplasm and exerts cytotoxic effect, leading to cancer cell death via:

a) Bystander effect

b) ADCC

c) CDC



Nagayama A, et al. *Ther Adv Med Oncol.* 2020; Birrer MJ, et al. *J Natl Cancer Inst*. 2019.

NCCN Guidelines for TNBC Treatment
The Emergence of ADCs

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Invasive Breast Cancer

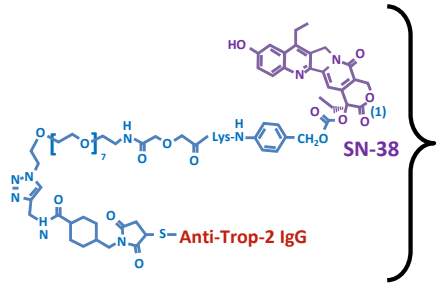
NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a,b,c]

HER2-Negative			
Preferred Regimens		**Other Recommended Regimens[i]**	**Useful in Certain Circumstances[i]**
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel • Anti-metabolites ▸ Capecitabine ▸ Gemcitabine • Microtubule inhibitors ▸ Vinorelbine ▸ Eribulin • Sacituzumab govitecan-hziy (for TNBC [category 1] or HR+/HER2-)[d]	• For HER2 IHC 1+ or 2+/ISH negative: ▸ Fam-trastuzumab deruxtecan-nxki[e,f] (category 1) • For germline *BRCA1/2* mutations[g] see additional targeted therapy options (BINV-R)[h] • Platinum (for TNBC and germline *BRCA1/2* mutation)[g] ▸ Carboplatin ▸ Cisplatin • For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[h]	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Carboplatin + paclitaxel or albumin-bound paclitaxel

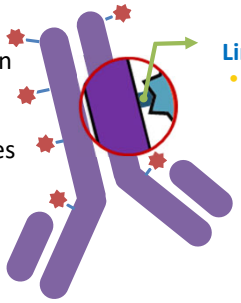
NCCN Clinical Practice Guidelines. *Breast Cancer*. Version 4.2022.

Sacituzumab Govitecan (IMMU-132)
Trop-2–targeted Antibody-drug Conjugate



Humanized RS7 Antibody
- Targets Trop-2, an antigen expressed in many epithelial cancers, including mTNBC (88%)

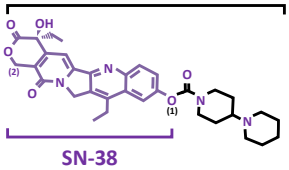
SN-38 Payload
- Targets 136-fold more than parent compound irinotecan
- Unique chemistry improves solubility, ***selectively delivers SN-38 to tumor***



Linker for SN-38
- High drug-to-antibody ratio (7.6:1)

Irinotecan (Topoisomerase Inhibitor)

Irinotecan

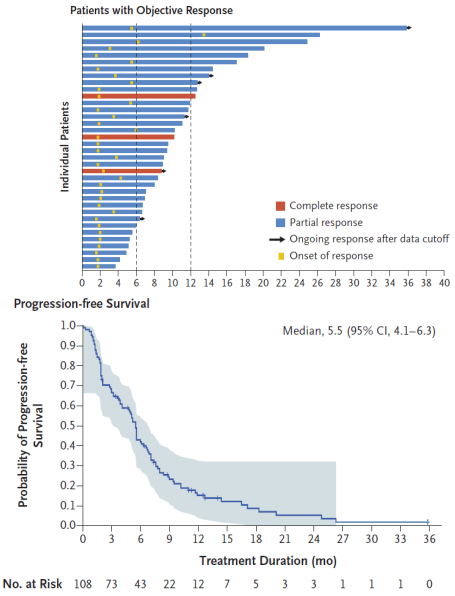


SN-38

Bystander effect: In acidic tumor microenvironment, SN-38 is released from anti–Trop-2 antibody, thereby diffusing into neighboring Trop-2–negative cells

Khoury K, et al. *ASCO*. 2019. Abstract e14651; Bardia A, et al. *J Clin Oncol*. 2017.

Sacituzumab Govitecan in mTNBC
Clinical Trial Evidentiary Base



- Phase I/II trial (NCT01631552) enrolled 108 patients with TNBC
  - At least 2 prior systemic therapies
- Sacituzumab govitecan achieved robust, durable, and clinically meaningful responses
  - ORR = 33.3% (with 3 CRs)
  - Median DOR = 7.7 months
  - mPFS = 5.5 months
  - OS = 13.0 months
- Led to **accelerated approval in April 2020** and **initiation of confirmatory phase III trial (ASCENT)**

Bardia A, et al. *N Engl J Med*. 2019.

ASCENT
Sacituzumab Govitecan vs Single-agent CT in Metastatic TNBC after ≥2 Previous CT Regimens

- Randomized, open-label phase III trial

Patients with mTNBC and ≥2 prior CT (no upper limit); 1 line could include PD within 12 months of (neo)adjuvant therapy (N=529)

21-day cycles

Sacituzumab govitecan
10 mg/kg IV on Days 1 and 8
(n=267)

Physician's choice single-agent CT*
(n=262)

*Eribulin, vinorelbine, gemcitabine, or capecitabine

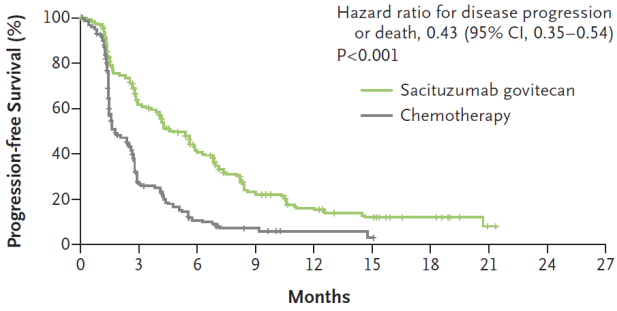
- **Primary endpoint:** PFS in patients without brain metastases
- **Secondary endpoints:** PFS (full population), OS, ORR, DoR, TTR, safety

- **Trial halted early based on efficacy** per unanimous independent DSMC recommendation

Bardia A, et al. *N Engl J Med*. 2021.

ASCENT
Progression-free Survival (PFS) in the Full Population

	No. of Patients	No. of Events	Median Progression-free Survival
			mo (95% CI)
Sacituzumab Govitecan	267	190	4.8 (4.1–5.8)
Chemotherapy	262	171	1.7 (1.5–2.5)

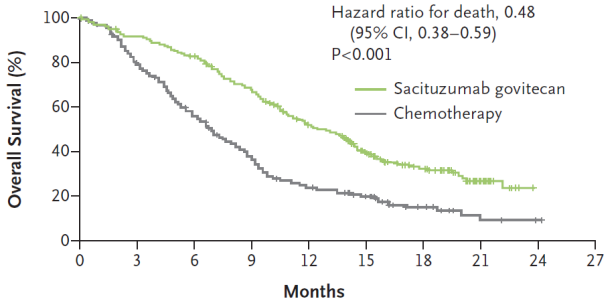


No. at Risk								
Sacituzumab govitecan	267	145	82	38	23	14	8	1
Chemotherapy	262	41	13	6	2	1	0	0

Bardia A, et al. *N Engl J Med*. 2021.

ASCENT
Overall Survival (OS) among Patients without Brain Metastases

	No. of Patients	No. of Events	Median Overall Survival
			mo (95% CI)
Sacituzumab Govitecan	235	155	12.1 (10.7–14.0)
Chemotherapy	233	185	6.7 (5.8–7.7)



No. at Risk									
Sacituzumab govitecan	235	214	190	153	107	70	37	13	0
Chemotherapy	233	173	117	74	45	30	11	3	1

Bardia A, et al. *N Engl J Med*. 2021.

FDA U.S. FOOD & DRUG ADMINISTRATION

April 13, 2021

Sacituzumab govitecan receives **full FDA approval** for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.

FDA Prescribing Information.

Sacituzumab Govitecan
Important Updates from ASCO 2021

- **Abstract 1080**—ASCENT subanalysis: SG in patients with prior neoadjuvant/adjuvant chemotherapy
  - Recurrence within 12 months of neo/adjuvant treatment, then 1 line of prior therapy in metastatic setting
  - SG achieved PFS and OS benefits over TPC with statistical significance
  - Supports use of SG in **earlier lines of therapy** (2nd-line metastatic)
- **Abstract 1077**—ASCENT subanalysis: SG vs TPC, by individual chemo agent
  - SG efficacy benefit was retained vs each individual chemotherapeutic
- **Other ongoing trials**
  - NeoSTAR (*data at ASCO 2022*), SACI-IO TNBC, SEASTAR, Morpheus-TNBC

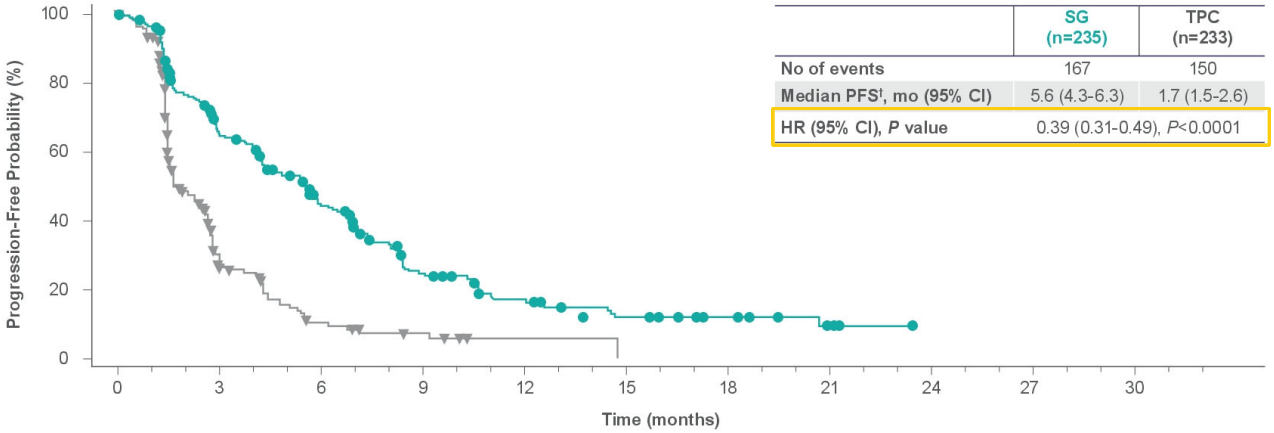
ClinicalTrials.gov; Carey L, et al. *ASCO*. 2021. Abstract 1080; O'Shaughnessy J, et al. *ASCO*. 2021. Abstract 1077.

Sacituzumab Govitecan
Important Updates from ASCO 2022

- **Abstract 1071**—ASCENT final data analysis
  - Final database lock for the trial was February 25, 2021
  - At final analysis, SG achieved the following vs. TPC (single-agent chemo) :
    - **Median progression-free survival:** 5.6 vs. 1.7 months (*P*<0.0001)
    - **Overall survival rate (at 24 months):** 22.4% vs. 5.2% (median OS = 12.1 vs. 6.7 months; *P*<0.0001)
    - **Health-related quality of life (hrQoL):** Improvement with SG vs. TPC across all five focus domains
    - **Safety profile was manageable, D/C rate similar to TPC, with no new signals observed**
  - *Final analysis confirms earlier results of superior survival and improved quality of life with SG vs. TPC in 2L+ mTNBC, with manageable safety*
- **Abstract e13068**—A systematic review of SG in TNBC
  - Review of evidentiary base from inception of SG up until January 2022 revealed clinically meaningful ORR across all data analyses in TNBC
- **Abstract 512**—Results from NeoSTAR
  - SG demonstrated notable single agent efficacy in neoadjuvant setting for TNBC (pCR rate = 30%)
- **Abstract 1076**—SG exposure-response analysis in mTNBC
  - Confirmed FDA-approved 10 mg/kg dosing regimen as optimally safe and effective in the metastatic setting
- **TROPiCs-02**—Moving SG into the HR+/HER2- mBC setting
  - SG achieved statistically significant and clinically meaningful PFS benefit over single-agent chemo; improvements also seen in OS and CBR

ClinicalTrials.gov; Bardia A, et al. *ASCO*. 2022. Abstract 1071; Khalid F, et al. ASCO. 2022. Abstract e13068; Spring L, et al. *ASCO*. 2022. Abstract 512; Singh I, et al. *ASCO* 2022. Abstract 1076; Rugo H, et al. *ASCO*. 2022. Abstract LBA1001.

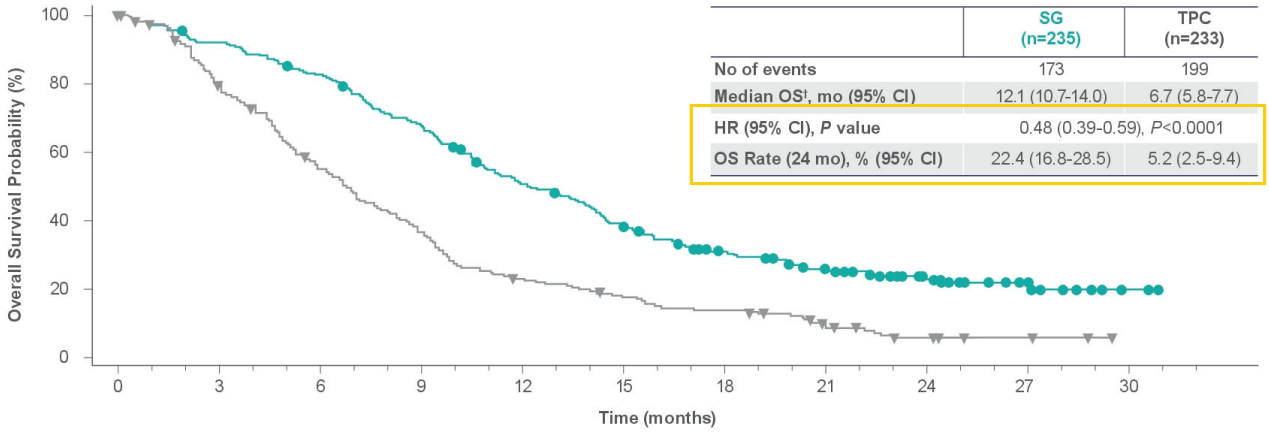
ASCENT
Final Data Analysis from ASCO 2022—PFS



	SG (n=235)	TPC (n=233)
No of events	167	150
Median PFS[†], mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P* value	0.39 (0.31-0.49), *P*<0.0001	

Bardia A, et al. *ASCO*. 2022. Abstract 1071.

ASCENT
Final Data Analysis from ASCO 2022—OS



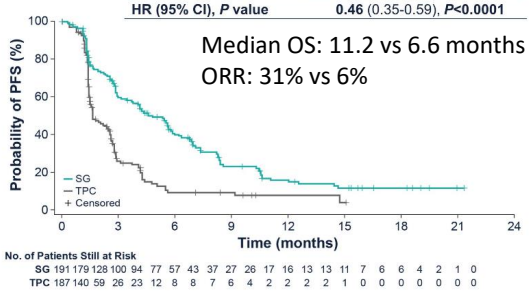
	SG (n=235)	TPC (n=233)
No of events	173	199
Median OS†, mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P* value	0.48 (0.39-0.59), *P*<0.0001	
OS Rate (24 mo), % (95% CI)	22.4 (16.8-28.5)	5.2 (2.5-9.4)

Bardia A, et al. *ASCO*. 2022. Abstract 1071.

ASCENT
Outcomes by Age: <65 vs ≥65 Years

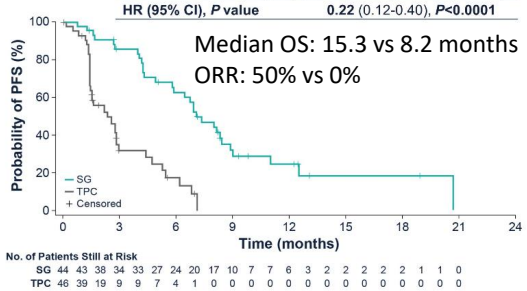
PFS BICR Analysis	<65 y SG (n=191)	<65 y TPC (n=187)
No. of events	136	117
Median PFS—mo (95% CI)	4.6 (3.7-5.7)	1.7 (1.5-2.5)
HR (95% CI), *P* value	0.46 (0.35-0.59), *P*<0.0001	

Median OS: 11.2 vs 6.6 months
ORR: 31% vs 6%



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

Median OS: 15.3 vs 8.2 months
ORR: 50% vs 0%



- Dose reductions: more frequent in patients ≥65 years old vs <65 years old
- No treatment-related deaths
- TRAE rates were similar for patients ≥75 years vs patients ≥65 years
  - Neutropenia and diarrhea most common

Kalinsky K, et al. *ASCO*. 2021. Abstract 1011.

Sacituzumab Govitecan
Practical Nursing Pearls

- Sacituzumab govitecan is the only ADC to obtain FDA approval for TNBC to-date
- Recommended dosing regimen: 10 mg/kg IV once weekly
  - Days 1 and 8 of continuous 21-day treatment cycle until progression or toxicity
- **Key toxicity considerations**
  - Black box warnings for neutropenia and diarrhea
  - Premeds for infusion reactions and CINV are recommended
    - Infusion reaction premed options: antipyretics, H1/H2 blockers, +/- corticosteroids if patient has a documented history of infusion reaction
    - CINV premed options: 2 or 3-drug combo, incorporating dexamethasone +/- 5HT3-receptor antagonist or an NK_1 receptor antagonist (may also include other agents, as needed)
  - N/V, infusion hypersensitivity, fatigue, alopecia, embryo-fetal toxicity
- Notable drug-drug interactions: UGT1A1 inhibitors or inducers

FDA Prescribing Information.

Sacituzumab Govitecan
Practical Nursing Pearls

Adverse Reaction	Occurrence	Dose Modification
Severe Neutropenia		
Grade 4 neutropenia ≥7 days OR Grade 3 febrile neutropenia (absolute neutrophil count <1,000/mm^3 and fever ≥38.5°C) OR At time of scheduled treatment, Grade 3–4 neutropenia that delays dosing by 2–3 weeks for recovery to ≤Grade 1	First	25% dose reduction and administer granulocyte-colony stimulating factor (G-CSF)
	Second	50% dose reduction
	Third	Discontinue treatment
At time of scheduled treatment, Grade 3–4 neutropenia that delays dosing beyond 3 weeks for recovery to ≤Grade 1	First	Discontinue treatment
Severe Non-neutropenic Toxicity		
Grade 4 non-hematologic toxicity of any duration OR Any Grade 3–4 nausea, vomiting, or diarrhea due to treatment that is not controlled with antiemetics and antidiarrheal agents OR Other Grade 3–4 non-hematologic toxicity persisting >48 hours despite optimal medical management OR At time of scheduled treatment, Grade 3–4 non-neutropenic hematologic or non-hematologic toxicity that delays dose by 2–3 weeks for recovery to ≤Grade 1	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
In the event of Grade 3–4 non-neutropenic hematologic or non-hematologic toxicity that does not recover to ≤Grade 1 within 3 weeks	First	Discontinue treatment

FDA Prescribing Information.

Sacituzumab Govitecan
Practical Nursing Pearls

How do I properly grade my patient's treatment-related diarrhea?

Grade 1
- Increase of <4 stool per day vs baseline; mild increase in ostomy output

Grade 2
- Increase of 4–6 stools per day vs baseline; moderate increase in ostomy output
- Poses limitations to instrumental ADLs

Grade 3
- Increase of ≥7 stools per day vs baseline; severe increase in ostomy output
- Poses limitations to self-care ADLs
- Hospitalization indicated

Grade 4
- Life-threatening consequences (i.e., dehydration/fluid status, severe electrolyte imbalances, etc.)
- Urgent and immediate intervention indicated

National Cancer Institute (NCI). CTCAE. Version 5.0. 2017.

Sacituzumab Govitecan
Practical Nursing Pearls

- Evidence-based diarrhea management protocol
  - If patient has Grade 3–4 diarrhea, withhold treatment until symptoms resolve to ≤Grade 1
  - If Grade 1 or 2, do the following at onset of diarrhea
    - Evaluate for infectious causes
    - If infectious etiology is negative, initiate loperamide 4 mg initial dose followed by 2 mg per diarrhea episode (16 mg max daily dose)
    - D/C loperamide 12 hours after diarrhea has resolved
    - Consider other supportive measures, as needed
  - If hypercholinergic response is suspected (excessive cramping, salivation, and/or unresolved diarrhea), consider atropine as a pre-medication on a prospective basis

FDA Prescribing Information.

HRQoL in the ASCENT Study
Primary HRQoL Domains

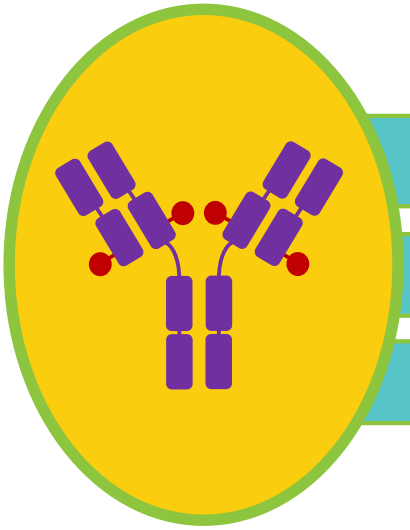
	LS Mean Change from Baseline (95% CI)			Noninferiority Margin (MID) [5]
	SG (N=236)	TPC (N=183)	SG Minus TPC	
Global health status/QoL	0.66 (-2.21, 3.53)	-3.42 (-6.77, -0.08)	4.08 (0.82, 7.35)	-4
Physical functioning	1.31 (-1.38, 3.99)	-4.39 (-7.52, -1.26)	5.69 (2.63, 8.76)	-5
Role functioning	-2.24 (-6.13, 1.65)	-7.83 (-12.41, -3.25)	5.59 (1.13, 10.05)	-6
Fatigue	1.97 (-1.20, 5.13)	7.13 (3.40, 10.87)	-5.17 (-8.81, -1.52)	+5
Pain	-8.93 (-12.57, -5.30)	-1.89 (-6.18, 2.40)	-7.04 (-11.24, -2.85)	+6

Red: SG superior to TPC

- For primary HRQoL domains, SG showed greater improvements than TPC
- SG had greater N/V/D than TPC but did not impact QoL
- SG significantly prolonged time to first deterioration in HRQoL
- SG significantly shortened time to improvement in physical functioning and pain

Loibl S, et al. *ESMO*. 2021. Abstract 257P.

Datopotamab Deruxtecan (Dato-DXd, DS-1062)
TROP2 ADC in Development



Circulating free payload is negligible due to high stability of the linker, thereby limiting systemic exposure or nontargeted delivery of the payload[1]

DS-1062 has a substantially **longer half-life** than SG (≈5 days vs 11–14 hours), enabling a more optimal dosing regimen[3]

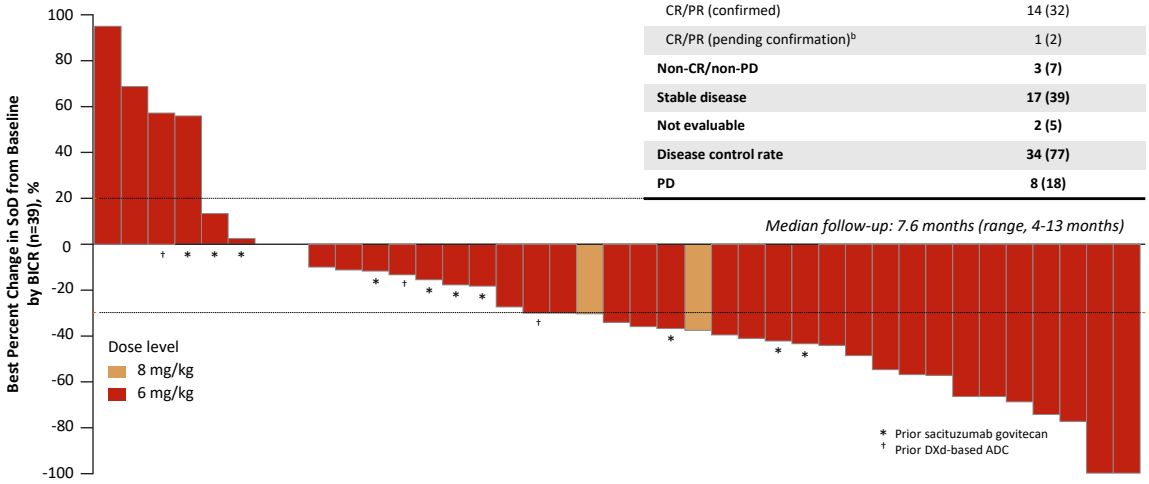
SG's dose-limiting toxicities (DLTs) are neutropenia and diarrhea, while DS-1062's DLTs are maculopapular rash and stomatitis/mucosal inflammation[4,5]

[1]Goldenberg DM, et al. *Oncotarget*. 2015; [2]Ogitani Y, et al. *Clin Cancer Res.* 2016; [3]Ocean AJ, et al. *Cancer*. 2017; [4]Bardia A, et al. *J Clin Oncol.* 2017; [5]Lisberg AE, et al. 2020 ASCO Virtual Scientific Program. Abstract 9619.

Antitumor Responses by BICR

All Patients with TNBC

Patients, n (%)[a]	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)**



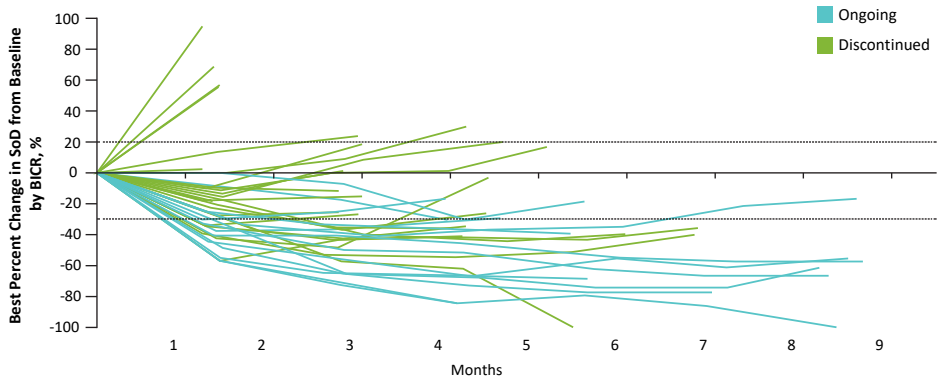
[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. Postbaseline tumor assessments were not yet available for 2 patients at the data cutoff. Three patients were not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD.
[b] Includes patients with an unconfirmed response but are ongoing treatment.

Data cutoff: July 30, 2021

BICR, blinded independent central review; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SoD, sum of diameters.

Krop I, et al. 2021 *SABCS*. Oral Presentation GS1-05.

Duration of Disease Control in Patients with TNBC

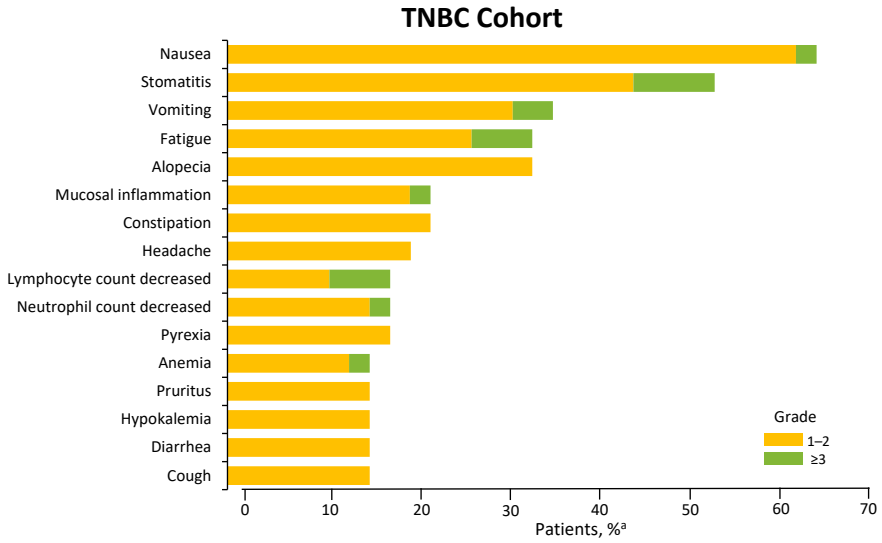


- The median duration of response was not reached (range, 2.7–7.4+ months), with the majority of responses ongoing at the data cutoff

Data cutoff: July 30, 2021

Krop I, et al. 2021 *SABCS*. Oral Presentation GS1-05.

Treatment-emergent Adverse Events in ≥15% of 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

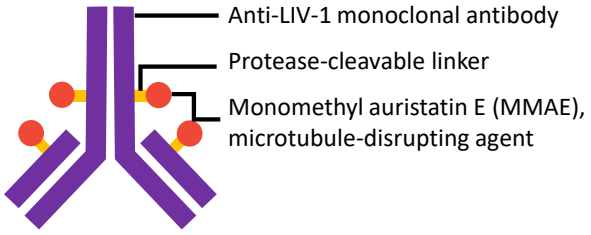
ILD, interstitial lung disease.
[a] n=44 patients.

Data cutoff: July 30, 2021

Krop I, et al. 2021 *SABCS*. Oral Presentation GS1-05.

Phase I Study
SGN-LIV1A (Ladiratuzumab Vedotin) in Heavily Pretreated mTNBC and HR+/HER2- MBC

- SGN-LIV1A
  - Humanized Ab that targets the LIV-1 zinc transporter
  - Conjugated to microtubule-disrupting agent monomethyl auristatin E (MMAE)
- 614 MBC tumor samples evaluated
  - 90% positive for LIV-1 expression
  - Moderate-to-high LIV-1 expression in 68% of mTNBC samples



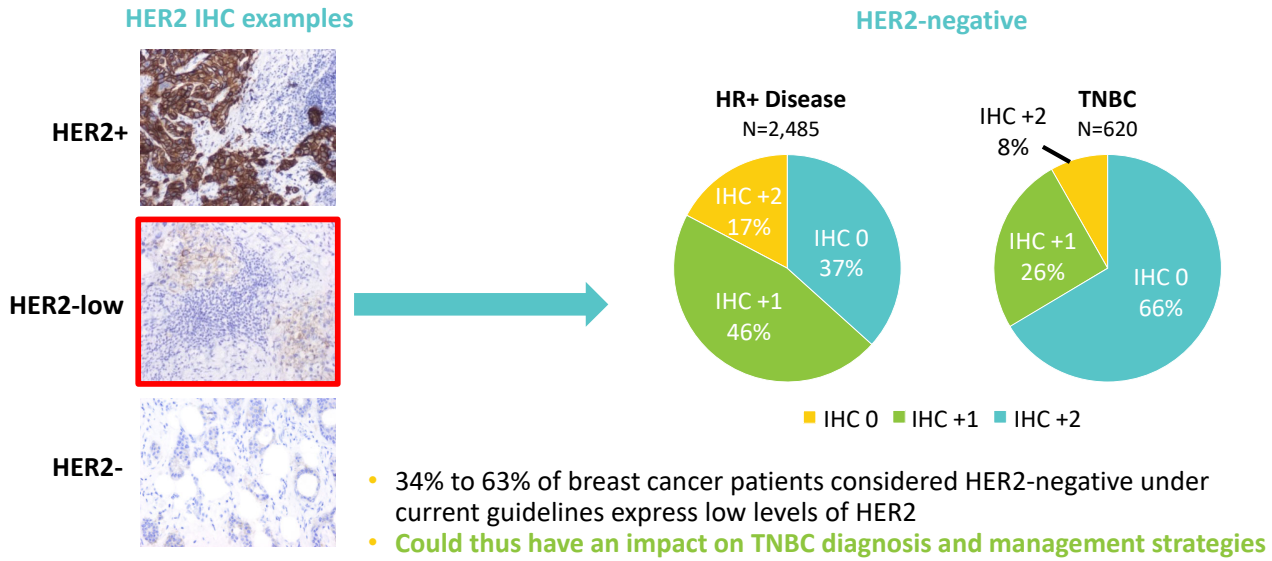
Nagayama A, et al. *Ther Adv Med Oncol*. 2020; Modi S, et al. *SABCS*. 2017. Abstract PD3-14; ClinicalTrials.gov.

Phase I Study of Ladiratuzumab Vedotin in Heavily Pretreated mTNBC
Efficacy and Safety Outcomes

- Efficacy in all mTNBC (n=60): ORR, 25%
- Toxicities: alopecia, neutropenia, nausea, AST ↑, neuropathy
- Ongoing trials
  - Phase I expansion (NCT01969643)
  - Phase I/II trial of SGN-LIV1A + pembrolizumab (NCT03310957)
    - Global enrollment ongoing and study design presented at ASCO 2022
  - Phase II neoadjuvant I-SPY 2 trial (NCT01042379)

Modi S, et al. *SABCS*. 2017. Abstract PD3-14; Meisel JL, et al. *ASCO*. 2022. Abstract TPS1127; ClinicalTrials.gov.

A New Realm in TNBC
Prevalence of "HER2-low" Disease

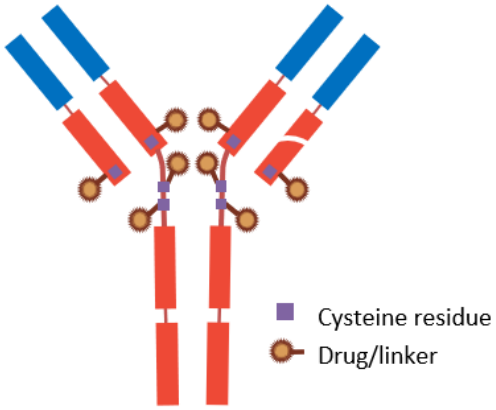


- 34% to 63% of breast cancer patients considered HER2-negative under current guidelines express low levels of HER2
- **Could thus have an impact on TNBC diagnosis and management strategies**

Schettini F, et al. *ESMO*. 2020. Abstract 23P; Slide courtesy of Aleix Prat.

Trastuzumab Deruxtecan (DS-8201/T-DXd)
ADC Targeting HER2

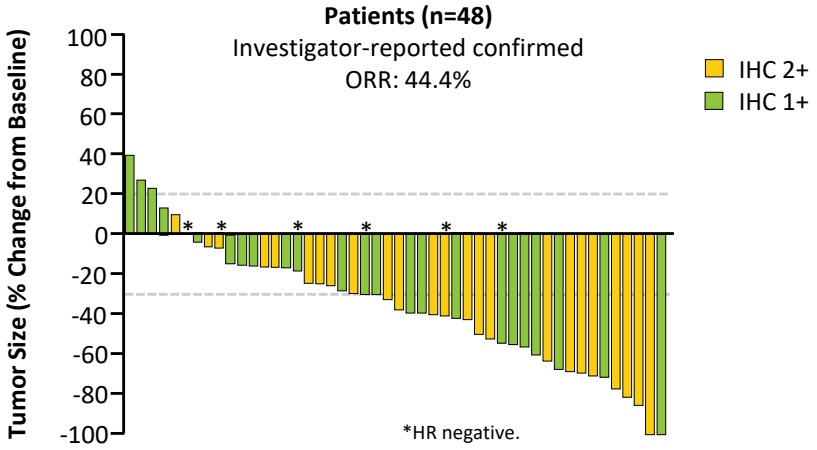
- FDA approved for HER2+ metastatic breast therapies in the metastatic setting
- Stable linker-payload
- Bystander killing effect
- **Black box warnings**
  - **Interstitial lung disease**
  - **Embryo-fetal toxicity**



Topoisomerase I inhibitor (DXd) payload
(exatecan derivative)

Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019; Trail PA, et al. *Pharmacol Ther*. 2018; Ogitani Y, et al. *Cancer Sci*. 2016; FDA Prescribing Information.

Phase Ib Trial of T-DXd in HER2-low Tumors
Cohort with Advanced Breast Cancer

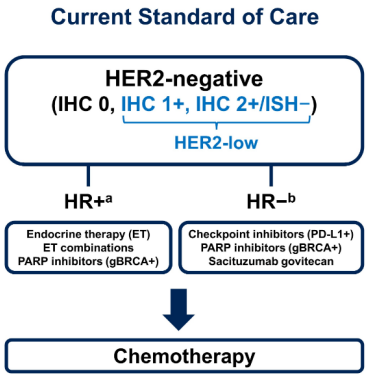


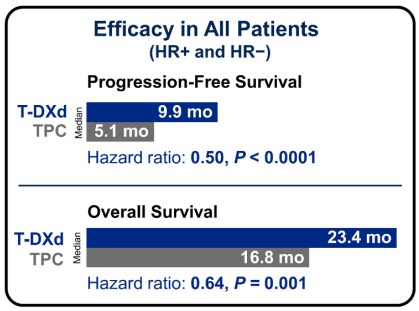
- DESTINY-Breast04 (NCT03734029): ongoing phase III trial comparing T-DXd vs physician's choice CT in HER2-low unresectable/metastatic breast cancer

Modi S, et al. *J Clin Oncol*. 2020; ClinicalTrials.gov.

DESTINY-Breast04—ASCO 2022
Practice-changing Power in HER2-low mBC

- 'HER2-low' status defined as IHC 1+ and IHC 2+/ISH-
- At the ASCO 2022 data readout, DESTINY-Breast04 established HER2-low as a new targetable patient population, representing therapeutic progress for ~50% of patients with mBC
- ***T-DXd achieved statistically significant and clinically meaningful improvement in this nascent treatment setting, constituting a new standard of care in HR+/HER2-low mBC***



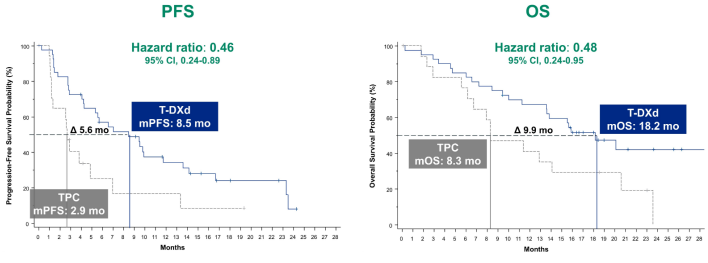


Modi S, et al. *ASCO*. 2022. Abstract LBA3.

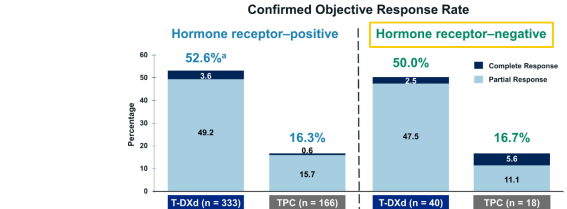
DESTINY-Breast04—ASCO 2022
Practice-changing Power in HER2-low mBC

- 58 patients with TNBC were included in the study
  - 40% with 1 prior line of chemotherapy; 60% with 2 prior lines
- Though efficacy analyses were exploratory for this population, both PFS and OS endpoints were robust and clinically meaningful

PFS and OS in HR− (Exploratory Endpoints)



Confirmed ORR

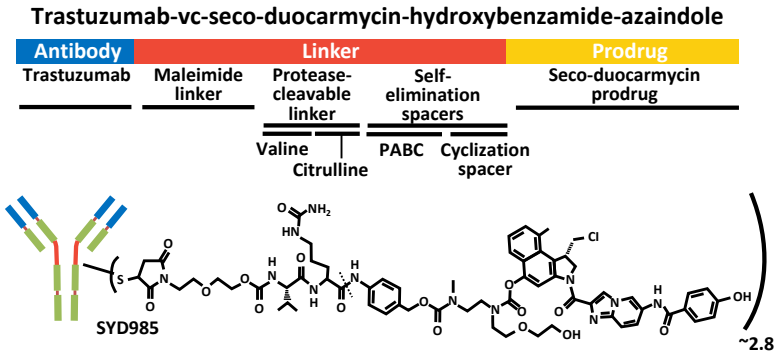


	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Modi S, et al. *ASCO*. 2022. Abstract LBA3.

HER2-directed ADC
Trastuzumab Duocarmazine (SYD985)

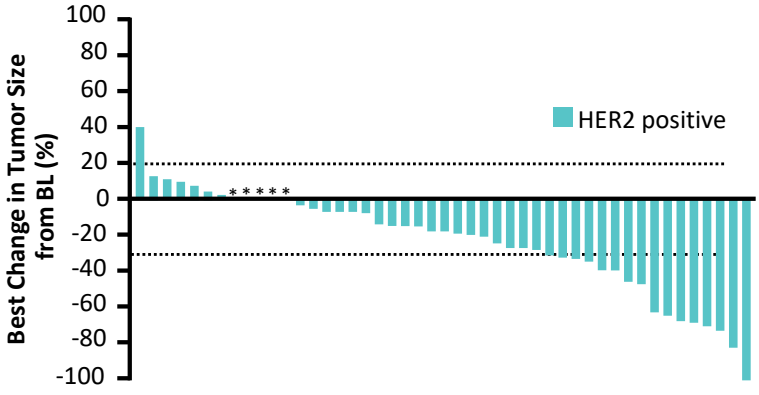
- HER2 antibody with same amino acid sequence as trastuzumab
- Proteolytic cleavage of linker in tumor microenvironment leads to activation of prodrug payload
- Active toxin (DUBA) alkylates DNA, kills dividing and nondividing cells
- Bystander killing effect



Dokter W, et al. *Mol Cancer Ther*. 2014; Elgersma RC, et al. *Mol Pharm*. 2015.

Efficacy of Trastuzumab Duocarmazine in Locally Advanced or Metastatic BC
Phase I Results

Change in Tumor Size in HER2+ BC (n=48)*
Best % Change in Tumor Size by HER2 IHC Status

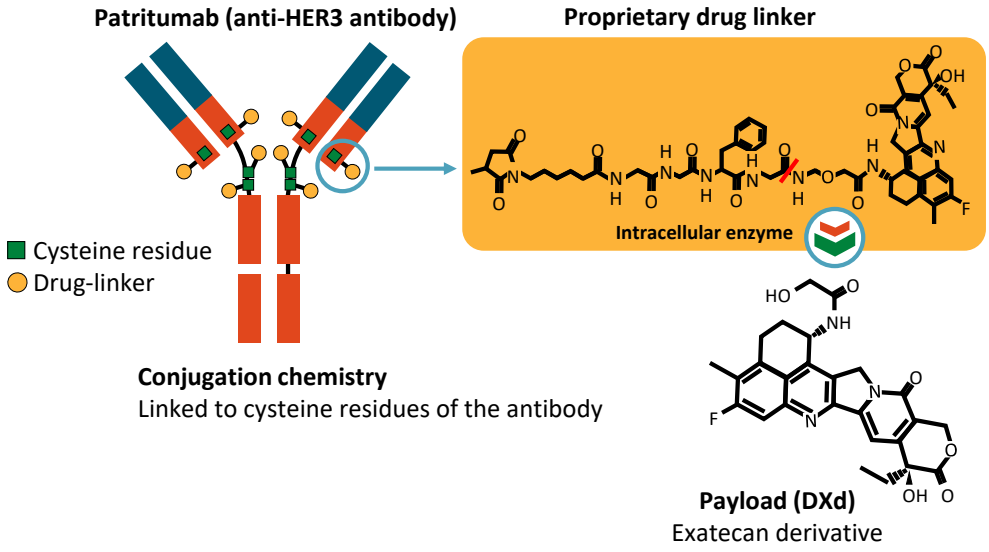


*Dose-expansion phase; n=5 patients with 0% best percentage change.

- ORR in HER2+ (n=48): 33%
  - HER2 low/ER- (n=15): 40%
  - HER2 low/ER+ (n=32): 27%
- **Ocular toxicity** and **fatigue** most frequently reported TRAEs

Banerji U, et al. *Lancet Oncol*. 2019.

Patritumab Deruxtecan (U3-1402)
Novel Anti-HER3 ADC



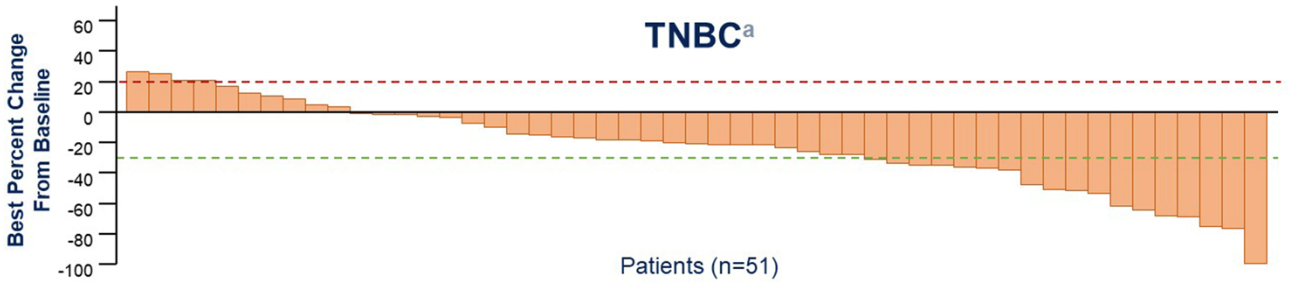
Kogawa T, et al. *ASCO*. 2018. Abstract 2512.

Patritumab Deruxtecan in HER3-overexpressing MBC
Phase I/II Trial Results

- HER3 expression found in multiple tumor types
  - **Breast,** melanoma, ovarian, bladder, prostate cancer, NSCLC, etc.
- Patritumab deruxtecan in phase I/II of HER3+ MBC (N=42)
  - Median 6 prior lines of therapy
  - All subtypes (HER2+/HR+/**TNBC**)
  - ORR 43%, mPFS ~8 months
  - 33.3% of patients experienced serious TRAEs
    - Thrombocytopenia (35.7%)
    - Neutropenia (28.6%)
    - Leukopenia (21.4%)

Lyu H, et al. *Acta Pharm Sin B*. 2018; Yonemori. *ESMO*. 2019. Abstract 261.

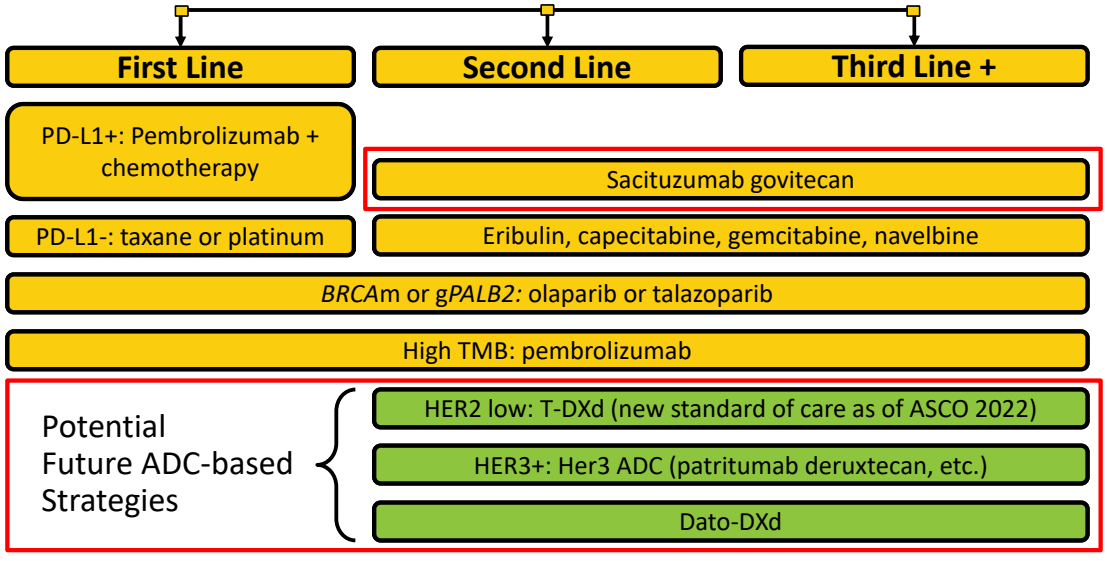
Patritumab Deruxtecan in HER3-overexpressing MBC
Phase I/II Trial Results



- At data cutoff (median 31.9 months), HER3-DXd demonstrated durable antitumor activity across all studied BC subtypes
  - TNBC (n=53)
  - HR+/HER2- (n=113)
  - HER2+ (n=14)
- All patients (N=182)
  - **ORR 28.6%, DOR 7.0 months**
- TNBC cohort (n=53)
  - **ORR 22.6%, DOR 5.9 months**

Krop I, et al. *ASCO.* 2022. Abstract 1002.

Evidence-based Management of mTNBC
Evolving Placement of ADCs in the Paradigm



NCCN Clinical Practice Guidelines. *Breast Cancer*. Version 4.2022.

Closing the TNBC Outcomes Chasm

Nursing Perspectives on Novel Therapeutics and Patient-centered Care

Patient Case: RH

RH is a 56-year-old Black female diagnosed with ER-, PR-, HER2- (triple-negative) breast cancer (TNBC) who is treated with neoadjuvant dose-dense doxorubicin, cyclophosphamide → paclitaxel (dd AC→T). She presents to the clinic 18 months later with fatigue. Routine blood work reveals ALT and AST 2x ULN.

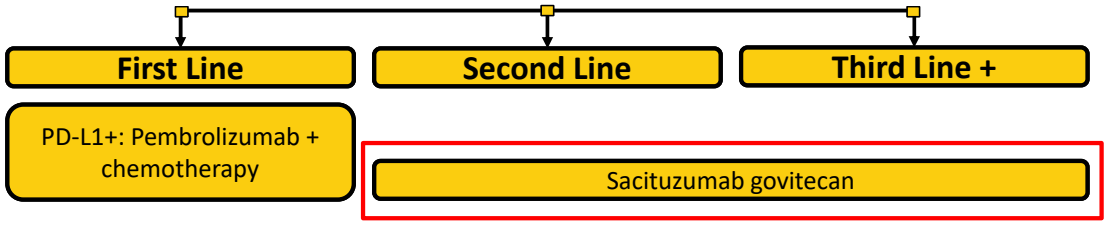
- CT reveals one liver and one lung lesion
- Biopsy of the liver lesion confirms metastatic TNBC
- No brain lesions on MRI
- Liver, kidney, and bone marrow function are adequate for chemotherapy
- Genetic testing with an appropriate panel reveals no detectable mutations
- PD-L1+ (CPS ≥10)

Patient Case: RH

RH is started on a frontline combination of pembrolizumab + chemotherapy (gemcitabine/carboplatin) per evidence-based guidelines. She achieves a partial response that lasts for 7 months. At that time, she returns to your clinic, again reporting fatigue. Blood work reveals ALT and AST are now 3x ULN.

- CT reveals a new liver lesion, confirming disease progression
- Liver, kidney, and bone marrow function remain sufficient for chemotherapy treatment

Patient Case: RH



NCCN Clinical Practice Guidelines. *Breast Cancer*. Version 3.2022.

Patient Case: RH

RH is started on sacituzumab govitecan 10 mg/kg, administered on days 1 and 8 of a 21-day treatment cycle. She receives 3 complete cycles and is about to start a 4th cycle when she tells you she is having diarrhea. She describes the diarrhea as follows:

- Non-urgent
- 3–5 times daily (an increase of 2–4 daily BMs vs normal)
- Not currently symptomatic, but "inconvenient and bothersome"
  - Modest impact on ADLs
- Stool studies reveal no infectious etiology

Patient Case: RH

- **Grade 1**
  - Increase of <4 stool per day vs baseline; mild increase in ostomy output
- **If Grade 1 or 2, at onset of diarrhea**
  - Evaluate for infectious causes
  - If infectious etiology is negative, initiate loperamide 4 mg initial dose followed by 2 mg per diarrhea episode (16 mg max daily dose)
  - D/C loperamide 12 hours after diarrhea has resolved
  - Consider other supportive measures, as needed

National Cancer Institute (NCI). CTCAE. Version 5.0. 2017; FDA Prescribing Information.

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Bardia A, Mayer IA, Vahdat LT, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. *N Engl J Med.* 2019;380(8):741–751.

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Carey LA, Loirat D, Punie K, et al. Assessment of sacituzumab govitecan (SG) in patients with prior neoadjuvant/adjuvant chemotherapy in the phase 3 ASCENT study in metastatic triple-negative breast cancer (mTNBC). Abstract 1080. Presented at: 2021 ASCO Annual Meeting (virtual); June 4–8, 2021.

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Kalinsky K, Oliveira M, Traina TA, et al. Outcomes in patients (pts) aged ≥65 years in the phase 3 ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC). Abstract 1011. Presented at: 2021 ASCO Annual Meeting (virtual); June 4–8, 2021.

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