CHALLENGING CASES

Triple Negative Breast Cancer Report

Prepared by: Cornerstone Specialty Network

Challenging Cases conducted: September 29, October 14, November 4, November 7, November 12, November 17, December 1, December 3, December 12, December 15

Participating Practices

Challenging Cases in… Breast Cancer

Program conducted:

September–December 2025

Note: Aggregated results and high-level summary based on 8 practices and 2 Live Regional Exchange meetings (89 HCPs) and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated. Clinical data, NCCN Guidelines, and FDA approvals current at time of presentation.

Report completed: Dec 23, 2025

• Utah Cancer Specialists (n=7)	September 29, 2025
• Cancer Center of Kansas (n=6)	October 14, 2025
• Atlantic Health Systems (n=9)	November 4, 2025
• Live Regional Exchange Phoenix (n=12)	November 7, 2025
• Fort Wayne Hematology & Oncology (n=8)	November 12, 2025
• Georgia Cancer Specialists #1 (n=8)	November 17, 2025
• Highlands Oncology (n=5)	December 1, 2025
• Northwestern Medicine (n=11)	December 3, 2025
• Live Regional Exchange Austin (n=12)	December 12, 2025
• Georgia Cancer Specialists #2 (n=11)	December 15, 2025

Overall Program Impact and Future Considerations

Community oncologists favor chemo-immunotherapy for front-line PD-L1 positive TNBC and routinely reassess HER2 IHC status to guide and expand treatment options in the 2L setting; sequencing of ADCs is primarily based on efficacy with limited impact of NCCN Guidelines and sacituzumab govitecan (SG) is often used post fam-trastuzumab deruxtecan (T-DXd); high level of comfort with managing side effect profile of SG through modified dosing schedules and use of prophylactic or reactive G-CSFs; T-DXd viewed favorably and as a potential new 1L standard of care

- **Front-line strategy:** Chemo-immunotherapy is standard of care for PD-L1–positive TNBC, with clinicians sometimes seeking higher CPS scores for IO eligibility, while chemo-IO rechallenge after early recurrence is avoided in favor of ADCs due to limited benefit and toxicity concerns
- **HER2 assessment:** Repeat biopsies at diagnosis and progression are routinely done to identify HER2-positivity for expanded treatment options based on tissue accessibility; NCCN Guidelines can influence but not dictate decisions
- **ADC choice:** Sacituzumab govitecan (SG) is preferred for HER2- (IHC 0), ER/PR-negative disease; fam-trastuzumab deruxtecan (T-DXd) is preferred for (HER2-low) TNBC; general comfort and experience managing side effect profile of both SG (prophylactic or reactive G-CSF) and T-DXd (ILD screening scans)
- **Sequencing:** T-DXd is often sequenced prior to SG due to greater efficacy; however, sequential ADC use is approached with caution due to lack of clinical data or real-world evidence
- **Future direction: I**ncreasingly crowded space with multiple ADCs alone or in combination with immunotherapies varying for the 1L setting in TNBC, with first to approval likely to gain greatest traction while familiarity will increase uptake over more recent approvals
- ***Recommended actions:*** *Increase educational initiatives emphasizing T-DXd efficacy data and side effect management through Challenging Cases; initiate real-world evidence trials (CSN Clinical Investigations) to support optimal sequencing of prior ADCs before T-DXd to promote earlier adoption; proactively engage community oncologists through advisory boards to raise awareness of key T-DXd data and clinical trial results prior to approval to maximize uptake and clinical impact*

Challenging Cases in…

Breast Cancer

Triple Negative Breast Cancer

Patient Case: metastatic disease

- *Diagnostic and therapeutic considerations in the 1L and 2L setting for advanced disease*

- *What role do ADCs play in the management of patients with triple negative breast cancer?*

    - *How to sequence to optimize patient outcomes?*
    - *Impact of NCCN Guidelines?*
    - *Impact of adverse events, monitoring and management?*

Initial Case Presentation

Patient Data

- ***44-year-old female***
- ECOG PS: 1
- Fatigue, bruising sensation in the breast and lump on self exam

Diagnostics

- **Mammogram, x-ray, biopsy:**
  - HER2: IHC 1+
  - ER negative
  - PR negative
  - PD-L1: CPS 30
  - BRCA: negative

Metastatic diagnosis

- **Site of mets:** *Lymph node and Lungs*

What initial metastatic treatment do you recommend?

CPS = combined positive score

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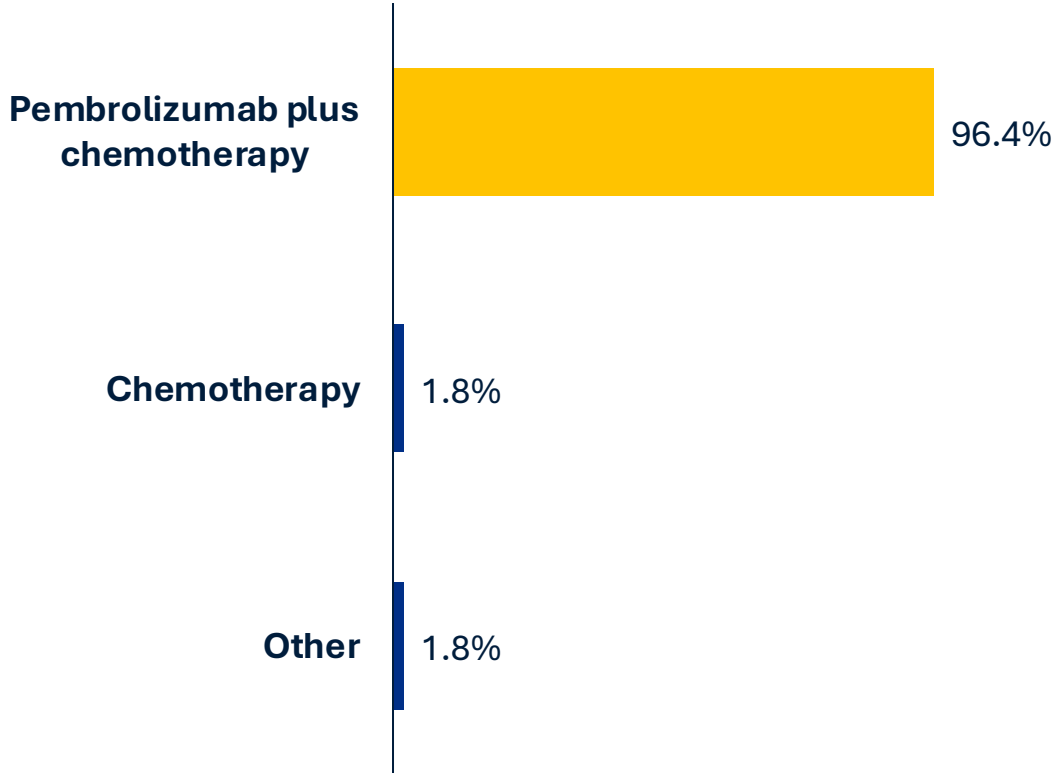
ARS Results from HCP Participants

What initial metastatic treatment do you recommend if HER2 IHC 1+, ER negative, PR negative, PD-L1 CPS 30, and BRCA negative (no prior neo/adjuvant treatment)?



Answered: 55

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

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
See BINV-Q (1) for Considerations for systemic therapy.		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	PD-L1 CPS ≥10[g] regardless of germline *BRCA* mutation status[b]	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[i] (category 1, preferred)
	PD-L1 CPS <10[g] and no germline *BRCA1/2* mutation[b]	Systemic chemotherapy BINV-Q (5)
	PD-L1 CPS <10[g] and germline *BRCA1/2* mutation[b]	• PARPi (olaparib, talazoparib) (category 1, preferred) • Platinum (cisplatin or carboplatin) (category 1, preferred)

What chemotherapy agents do you typically recommend?

Systemic Chemotherapy
BINV-Q (5)

Systemic Chemotherapy for HR-Positive or -Negative and HER2-Negative[a]		
See BINV-Q (1) for Considerations for systemic chemotherapy. Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel • Anti-metabolites ▸ Capecitabine ▸ Gemcitabine • Microtubule inhibitors ▸ Vinorelbine ▸ Eribulin	• 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

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KEY RECAP

KEYNOTE-355

Phase 3 trial that led to the approval of pembrolizumab added to chemotherapy as first-line for mTNBC

Study Design: Randomized, double-blind, multicenter phase III trial

Stratified by chemotherapy (taxane vs gem/carbo); PD-L1 tumor expression (CPS > 1 vs < 1); previous Tx with same class of chemotherapy for EBC (Y vs N)

Adult patients with previously untreated locally recurrent inoperable or metastatic TNBC completed curative intent Tx ≥ 6 mos before first recurrence (N = 847)

Pembrolizumab + chemotherapy* (n = 566)

- Pembrolizumab 200 mg IV Q3W

Until progression, toxicity, or completion of 35 cycles of pembrolizumab/placebo

Placebo + chemotherapy* (n = 281)

*Investigator's choice of chemotherapy was permitted:

- Nab-paclitaxel 100 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- Paclitaxel 90 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- Gem 1000 mg/m^2 + carbo AUC 2 on Days 1, 8 of 21-day cycle

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

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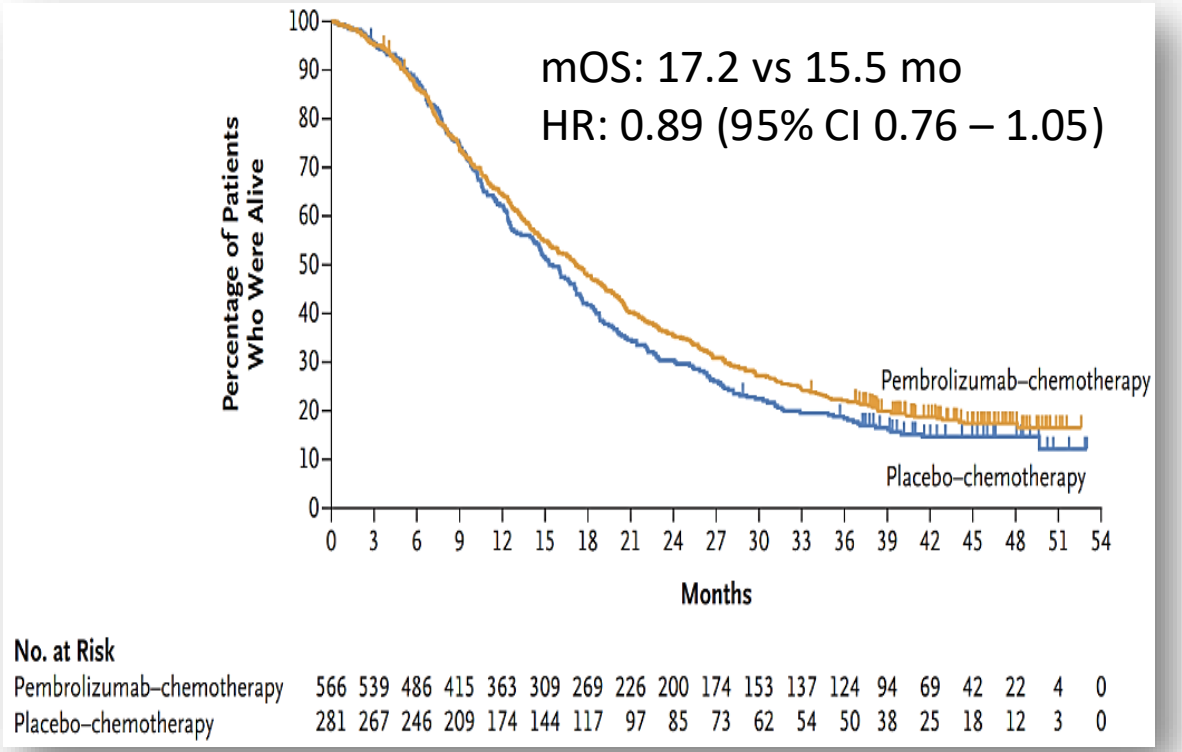
N Engl J Med 2022;387:217-26

KEY RECAP

KEYNOTE-355

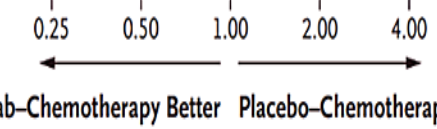
Phase 3 trial that led to the approval of pembrolizumab added to chemotherapy as first-line for mTNBC

Overall Survival in the Intention-to-Treat Population



Evidence for PD-L1 CPS cutoff of 10 selected by NCCN and the FDA for the approval

Subgroup	No. of Patients	Median Overall Survival: Pembrolizumab–chemotherapy (mo)	Median Overall Survival: Placebo–chemotherapy (mo)	Hazard Ratio for Death (95% CI)
Overall	847	17.2	15.5	0.89 (0.76–1.05)
PD-L1 CPS cutoff of 1				
CPS ≥1	636	17.6	16.0	0.86 (0.72–1.04)
CPS <1	211	16.2	14.7	0.97 (0.72–1.32)
PD-L1 CPS cutoff of 10				
CPS ≥10	323	23.0	16.1	0.71 (0.54–0.93)
CPS <10	524	14.7	15.2	1.04 (0.85–1.26)
PD-L1 CPS cutoff of 20				
CPS ≥20	204	24.0	15.6	0.72 (0.51–1.01)
CPS <20	643	15.9	15.5	0.96 (0.80–1.14)



N Engl J Med 2022;387:217-26

Management of TNBC mBC in the context of (neo)adjuvant therapy

Neoadjuvant approach

- Pembrolizumab with chemotherapy if T>2cm or node + (Keynote-522)
- Anthracyclines and Carbo? (both part of the Keynote-522)

Post-neoadjuvant approach

- ***What if no pCR?***
  - Continue Pembrolizumab (consider other chemo such as capecitabine, or PARP1i)
- ***What if pathologic CR?***
  - Continue Pembrolizumab?
    - No additional pembrolizumab after surgery is being evaluated

How would your treatment decision change if the patient had been diagnosed with earlier stage disease and previously treated based on Keynote-522?

Carbo/Taxol/Pembro followed by Doxo/Cytoxan

How do you view continuing IO therapy versus switching to chemotherapy or an ADC?

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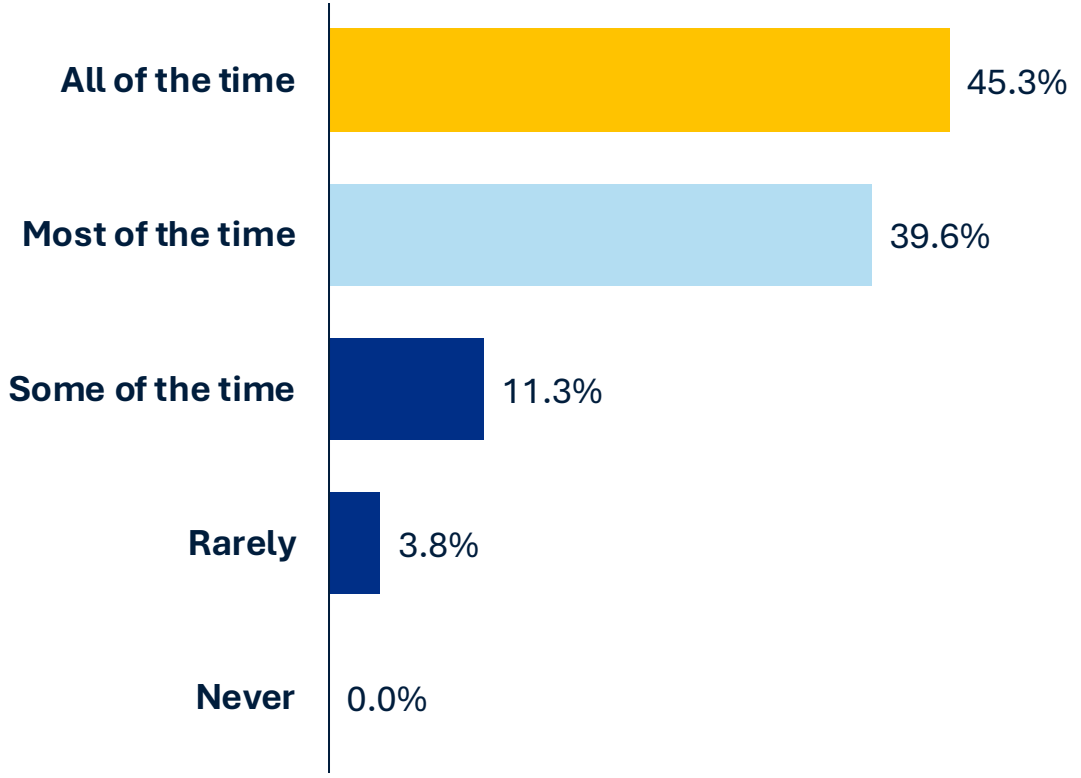
ARS Results from HCP Participants

Do you test or retest for HER2 status on tumor progression?



Answered: 53

Historically TNBC vs targeting ‘low’ and ‘ultralow’ HER2-expressing tumors in mBC[1]

TNBC: ASCENT Trial
At least two prior therapies, one in the metastatic setting

HER2 IHC categories within HR+, HER2-negative mBC (per ASCO/CAP[2]):

IHC 2+/ISH−	IHC 1+	IHC 0+	IHC 0
Weak-to-moderate complete membrane staining in >10% of tumor cells	Faint, incomplete membrane staining in >10% of tumor cells	**Faint, incomplete membrane staining in ≤10% of tumor cells**	**Absent membrane staining**

HER2-low/ultralow: DESTINY-Breast04, at least one prior chemo in the metastatic setting or recurrence during or within 6 months
DESTINY-Breast06, no prior chemo in metastatic setting

1. Curigliano G et al. Presented at: ASCO Annual Meeting; May 31 – June 4, 2024; Chicago, IL. Presentation LBA1000; 2. Wolff AC, et al. *J Clin Oncol*. 2023;41:3867–3872

Annals of Oncology (2024) 35 (suppl_2): 1-72. 10.1016/annonc/annonc1623

Management of TNBC tumor progression while on Pembro + Chemotherapy

Patient Data

- ***44-year-old female***
- ECOG PS: 1

- HER2 IHC 1+
- ER negative
- PR negative
- PD-L1 CPS 30
- BRCA negative

Progression

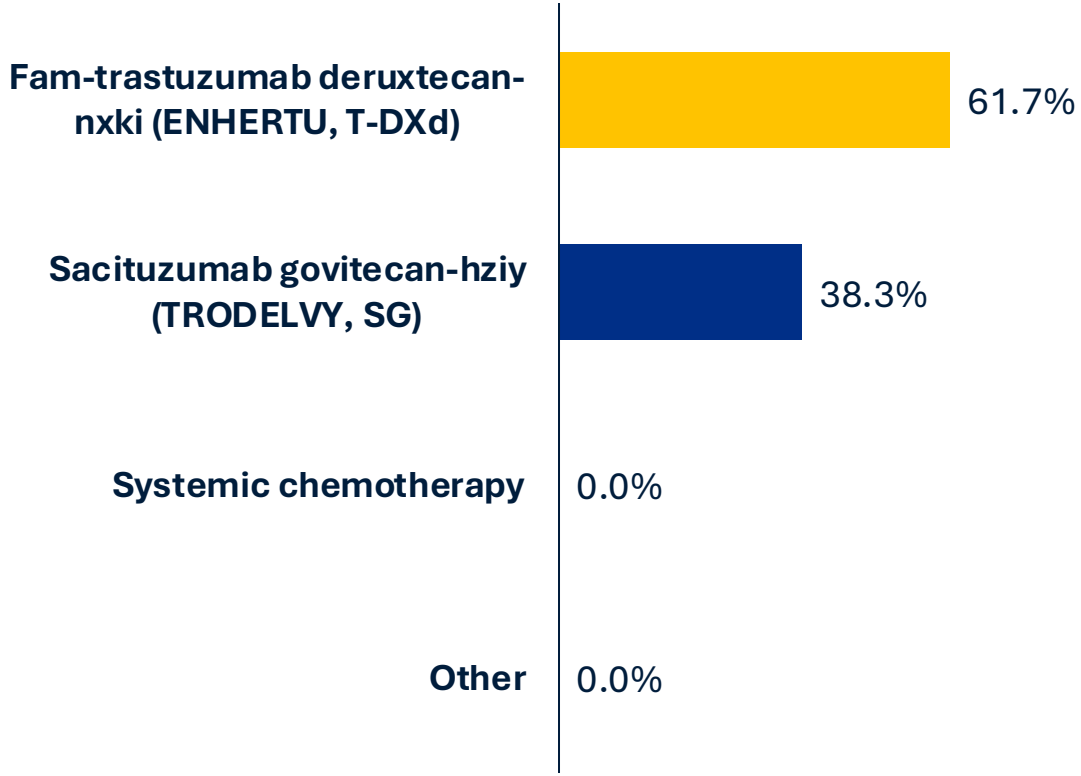
- **New liver metastases**
- **After a partial response that had been achieved while on Pembrolizumab plus chemotherapy after 11 months**

What treatment do you recommend next?

CPS = combined positive score

ARS Results from HCP Participants

What treatment do you recommend next, i.e., as second line therapy (tumor HER2 1+, PD-L1+, ER/PR negative)?



Answered: 60

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2025
Invasive Breast Cancer

NCCN Guidelines Index
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SYSTEMIC THERAPY FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
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	PD-L1 CPS <10[g] and germline *BRCA1/2* mutation[b]	• PARPi (olaparib, talazoparib) (category 1, preferred) • Platinum (cisplatin or carboplatin) (category 1, preferred)
Second Line	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib) (category 1, preferred)
	Any	Sacituzumab govitecan[l] (category 1, preferred)
		Systemic chemotherapy BINV-Q (5) or targeted agents BINV-Q (7)
	No germline *BRCA1/2* mutation[b] and HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[k] (other recommended regimen)

Do NCCN Guidelines influence your treatment decision in the second line setting?

How do you view the category 1, preferred recommendation in the second line setting?

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Two phase 3 studies evaluating ADCs in the refractory setting: Only *TNBC*

	ASCENT (SG)	DESTINY-Breast04 (T-DXd)	
Indication	**April 7, 2021:** for 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**.	**August 5, 2022:** for adult patients with **unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer** who have received **a prior chemotherapy** in the metastatic setting or developed **disease recurrence during or within six months** of completing adjuvant chemotherapy.	
Study Design	**SG vs TPC** **mTNBC** **HER2 IHC 0 (n=293); HER2-low (n=122)** **≥ 2 prior standard chemotherapy regimens (≥ 1 in the metastatic setting; 13% had 1 prior line)**	**T-DXd vs TPC** **HR-, HER2-low** **HER2 IHC 1+ (n=33) or IHC 2+/ISH- (n=30)** **1-2 lines of chemotherapy**	**T-DXd vs TPC** **HR+, HER2-low** **IHC 1+ (n=288) or IHC 2+/ISH- (n=206)** **1-2 lines of chemotherapy**
N	**(ITT population*)** **267** / **262**	**N with HR- tumor, R 2:1** **40** / **18**	**N with HR+ tumor, R2:1** 331 / 163
Median PFS, mo	**4.8** / **1.7** HR **0.41** (0.33-0.52); P<0.0001 **IHC 0: 4.3; IHC1+/2+: 6.2** / **IHC 0: 1.6; IHC1+/2+: 2.9**	**8.5** / **2.9** HR **0.46** (0.24-0.89)	10.1 / 5.4 HR **0.51** (0.40-0.64) *P* < 0.0001
Median OS, mo	**11.8** / **6.9** HR **0.51** (0.42-0.63); P<0.0001 **IHC 0: 11.7; IHC1+/2+: 13.4** / **IHC 0: 5.9; IHC1+/2+: 8.7**	**18.2** / **8.3** HR **0.48** (0.24-0.95)	23.9 / 17.5 HR **0.64** (0.48-0.86) *P* = 0.0028
ORR, %	**31%** / **4%** **IHC 0: 31%; IHC1+/2+: 32%** / **IHC 0: 4%; IHC1+/2+: 8%**	**50.0%** / **16.7%**	52.9% / 16.6%

*In the ITT population, 78% of the ITT population were HER2-evaluable by IHC (SG, n = 211; TPC, n = 204); overall, 71% were HER2 IHC0 and 29% were HER2-low

Modi et al., N Engl J Med. 2022 Jul 7;387(1):9-20.

TPC: treatment of physician's choice

J Clin Oncol 42:1738-1744

Highlights of Prescribing Information

	ENHERTU® (fam-trastuzumab deruxtecan-nxki)	TRODELVY® (sacituzumab govitecan-hziy)
Black box warnings	**Interstitial Lung Disease** **Embryo-fetal toxicity**	**Neutropenia** (***Primary prophylaxis with G-CSF is recommended for all patients at increased risk of febrile neutropenia***) **Diarrhea**
Contraindications	None	Severe hypersensitivity reaction
Warnings And Precautions	• Neutropenia • Left Ventricular Dysfunction	• Hypersensitivity and Infusion-Related Reactions • Nausea/Vomiting • Patients with Reduced UGT1A1 Activity • Embryo-Fetal Toxicity
Adverse reactions	**(>20%)** Decreased white blood cell count, nausea, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, fatigue, decreased platelet count, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, vomiting, alopecia, constipation, decreased blood potassium, decreased appetite, diarrhea, and musculoskeletal pain.	**(>25%)** Decreased leukocyte count, decreased neutrophil count, decreased hemoglobin, diarrhea, nausea, decreased lymphocyte count, fatigue, alopecia, constipation, increased glucose, decreased albumin, vomiting, decreased appetite, decreased creatinine clearance, increased alkaline phosphatase, decreased magnesium, decreased potassium, and decreased sodium.
Drug Interactions	---	UGT1A1 inhibitors or inducers
Specific Populations	Avoid in: Lactation, Females and Males of Reproductive Potential	Avoid in: Lactation Advise patients of potential risk to a fetus and to use effective contraception

https://daiichisankyo.us/prescribing-information-portlet/getPIContent?productName=Enhertu&inline=true

https://www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.pdf

How do potential adverse events influence your treatment decision between ADCs in 2L TNBC?

How do you manage febrile neutropenia? Prophylaxis G-CSF for all? (part of label)

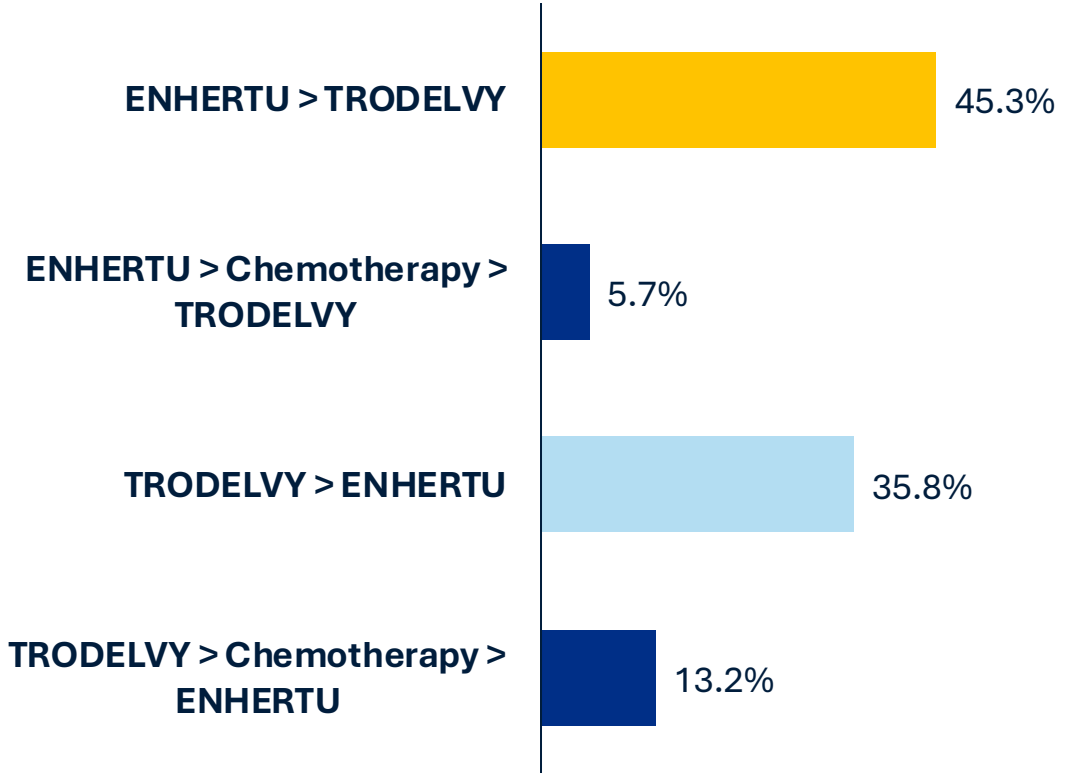
Do you order screening scans for ILD?

Do you dose reduce or take pts off treatment?

Differential cost of care?

ARS Results from HCP Participants

What is your current preferred order for sequencing ADCs in Triple Negative Breast Cancer when you decide to recommend an ADC --- in the context of single agent chemotherapy?



Answered: 53

Recent potentially practice changing data in 2025

KEY DATA: ASCO 2025

ASCENT-04: Sacituzumab Govitecan + Pembrolizumab in 1L setting for patient with PD-L1–Positive Advanced TNBC

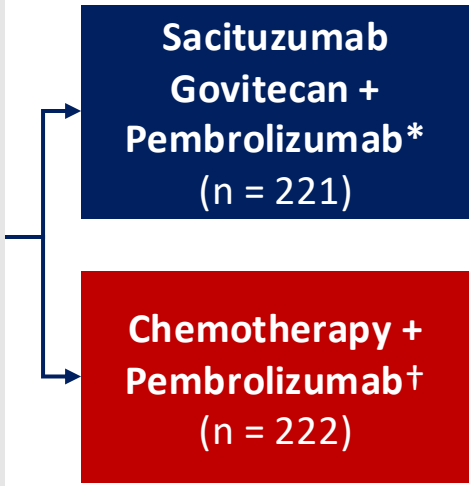
Not yet FDA approved

Study Design: Global, multicenter, randomized, phase III trial

Stratified by curative treatment-free interval (de novo vs recurrence within 6-12 mo vs recurrence in >12 mo); region (US/Canada/W Europe vs RoW); prior anti–PD-1/PD-L1 (yes vs no)

- Previously untreated, locally advanced unresectable or metastatic TNBC
- PD-L1 positive (CPS ≥10 using 22C3 assay)
- ≥6 mo since curative treatment (prior anti–PD-1/PD-L1 therapy allowed)

(N = 443)



Treatment continued until BICR-verified disease progression or unacceptable toxicity

Crossover to 2L SG permitted upon progression

Note: (96 / 119 pts (81%) received SG monotherapy)

*SG 10 mg/kg IV D1, 8 + Pembro 200 mg D1 of 21-day cycle.

†Paclitaxel 90 mg/m^2 or nab-paclitaxel 100 mg/m^2 D1, 8, 15 of 28-day cycle or gemcitabine 1000 mg/m^2 + carboplatin AUC 2 D1, 8 of 21-day cycle; Pembro 200 mg D1 of 21-day cycle.

Primary endpoint: PFS by BICR

Secondary endpoints: OS and ORR by BICR (hierarchical testing), DoR by BICR, safety, QoL

Select Baseline Characteristics

Characteristic, n (%)	SG + Pembro (n = 221)	CT + Pembro (n = 222)
ECOG PS, n (%)		
• 0	156 (71)	154 (69)
• ≥1	65 (29)	67 (30)*
Curative tx-free interval		
• De novo	75 (34)	75 (34)
• Recurrence 6-12 mo	40 (18)	40 (18)
• Recurrence >12 mo	106 (48)	107 (48)
Metastatic sites		
• Lymph node	159 (72)	154 (69)
• Lung	111 (50)	95 (43)
• Bone	61 (28)	45 (20)
• Liver	55 (25)	57 (26)
• Brain	8 (4)	6 (3)
• Other	81 (37)	71 (32)
Prior anti–PD-1/PD-L1 therapy	9 (4)	11 (5)
CT selected†		
• Taxane	116 (52)	114 (51)
• Gem/carbo	105 (48)	108 (49)

Note: Treatment arms were consistent for age, sex, race, geographical region

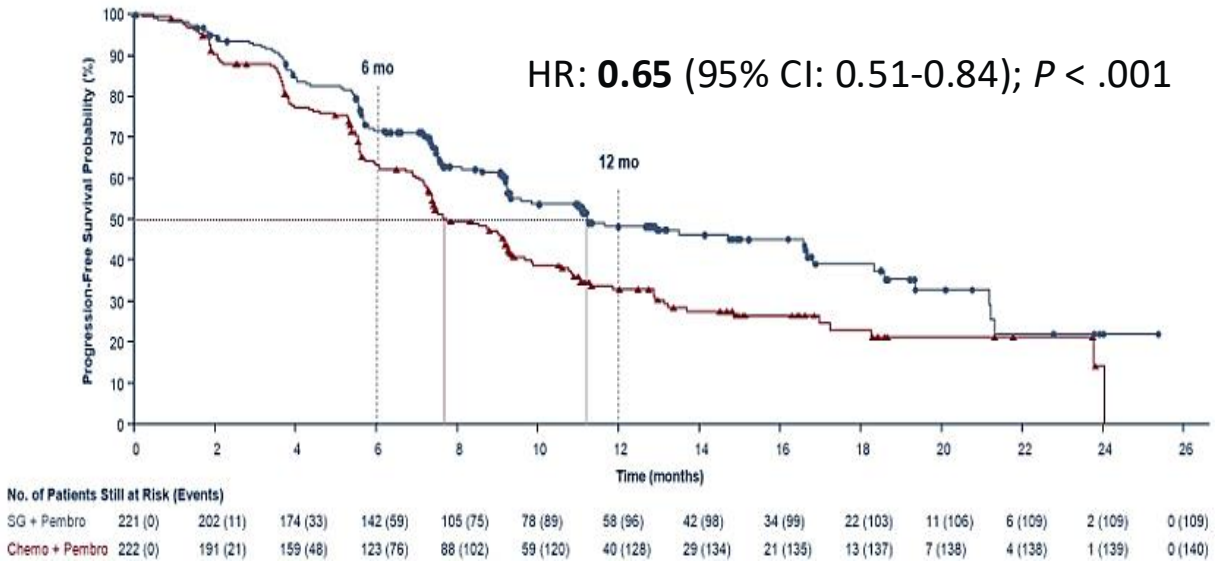
*1 patient had ECOG PS ≥2. †CT was selected prior to randomization; 2 randomized patients did not receive tx.

KEY DATA: ASCO 2025

ASCENT-04: Sacituzumab Govitecan + Pembrolizumab in 1L setting for patient with PD-L1–Positive Advanced TNBC

Not yet FDA approved

Primary Endpoint: PFS by BICR (ITT population)



	SG + Pembro (n = 221)	CT + Pembro (n = 222)
Events, n	109	140
Median PFS, mo (95% CI)	**11.2** (9.3-16.7)	**7.8** (7.3-9.3)
6-mo PFS, % (95% CI)	72% (65-77)	63% (56-69)
12-mo PFS, % (95% CI)	48% (41-56)	33% (26-40)

Median follow-up: 14.0 mo (range: 0.1-28.6)

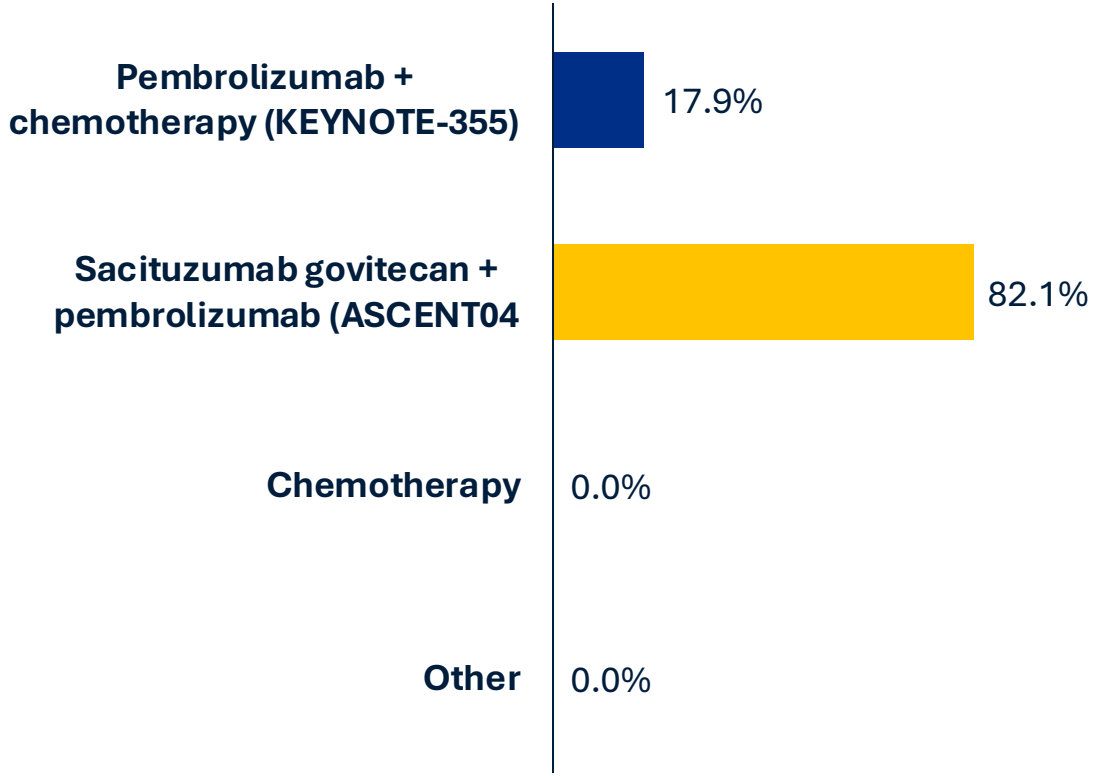
PFS by subgroup analysis

	SG + Pembro		CT + Pembro		HR (95% CI)
	n	Median PFS, Mo (95% CI)	n	Median PFS, Mo (95% CI)	
Age					
• <65 yr	163	11.3 (9.3-16.8)	165	7.5 (7.0-9.2)	0.61 (0.45-0.82)
• ≥65 yr	58	11.1 (7.5-NR)	57	9.3 (7.3-13.2)	0.85 (0.52-1.39)
ECOG PS					
• 0	158	12.9 (9.3-16.8)	154	8.7 (7.3-9.9)	0.65 (0.48-0.88)
• ≥1	65	9.2 (7.5-18.3)	67	7.5 (5.6-9.3)	0.66 (0.43-1.03)
Geographic region					
• US/Canada/W Europe	85	11.7 (7.5-19.4)	85	7.4 (5.7-9.9)	0.65 (0.43-0.98)
• Rest of World	136	11.2 (9.3-16.7)	137	8.4 (7.4-9.3)	0.66 (0.48-0.91)
Curative tx-free interval					
• De novo	75	8.1 (7.3-18.6)	75	7.7 (6.1-11.9)	0.89 (0.59-1.34)
• Recurrence 6-12 mo	40	9.9 (5.7-16.8)	40	7.2 (4.4-9.1)	0.62 (0.36-1.08)
• Recurrence ≥12 mo	106	16.6 (11.0-NR)	107	8.7 (7.3-10.8)	0.52 (0.35-0.76)
Prior (neo)adjuvant anti–PD-1/PD-L1 therapy					
• Yes*	9	7.5 (0.9-NR)	11	6.6 (2.1-NR)	1.08 (0.31-3.75)
• No	212	11.7 (9.3-16.8)	211	7.8 (7.4-9.3)	0.65 (0.50-0.84)
CT selected prior to randomization					
• Taxane	116	11.1 (8.6-16.7)	114	9.2 (7.2-12.9)	0.82 (0.58-1.17)
• Gem/carbo	105	11.3 (9.2-21.2)	108	7.4 (6.9-9.0)	0.52 (0.36-0.75)

*Small numbers of patients received prior anti-PD-L1 data

ARS Results from HCP Participants

What would be your preference for 1L HR-, HER2-, PD-L1+ (TNBC) if the ASCENT04 regimen is approved by the FDA?



Answered: 56

Key Data ESMO 2025

BEGONIA: Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as 1L treatment for mTNBC: Final results from the phase Ib/II BEGONIA study

Not yet FDA approved

- Dato-DXd 6 mg/kg IV every 3 weeks (q3w) + Durvalumab 1120 mg IV q3w, until disease progression or unacceptable toxicity.
- Primary endpoints: safety and tolerability
- Secondary endpoints: confirmed objective response rate (cORR), duration of response (DoR), and progression-free survival (PFS) (per RECIST v1.1).

Arm 7 (regardless of PD-L1), n=62:

- Confirmed ORR: 79.0% (95% CI 66.8–88.3)
- Median DoR: 17.6 months (95% CI 10.5–27.3)
- Median PFS: 14.0 months (95% CI 11.0–21.1)

Arm 8 (PD-L1–high tumors), n=33:

- Confirmed ORR: 81.8% (95% CI 64.5–93.0)
- Median DoR and PFS: immature

TROPION-Breast05 will assess the potential role of Dato-DXd with or without durvalumab in patients with PD-L1-high advanced or metastatic TNBC

ESMO 2025: Abst #555MO

First line single agent ADCs for TNBC: non-PD-L1 +

New Data ESMO 2025 (Oct 2025)	**TROPION-Breast02 (N=644)**	**ASCENT-03 (N=558)**
Study Design	Locally recurrent unresectable or metastatic TNBC patients who are not candidates for IO (tumors PD-L1-ve, previous IO in adjuvant setting, or no access to IO), no prior chemo or targeted therapy, ECOG PS0 or 1 (no crossover)	Locally advanced, inoperable or metastatic TNBC patients who are PD-L1-ve or treated with IO in early setting (crossover)
Efficacy	**Dato-DXd** (n=323) vs *ICC (n=321)	**SG** (n=279) vs ‡Chemotherapy (n=279)
• **mPFS (mo)**	10.8 vs 5.7 (HR=0.57)	9.7 vs 6.9 (HR=0.62)
• **mOS (mo)**	23.7 vs 18.7 (HR=0.79)	21.5 vs 20.2 (data not mature)
• **ORR**	62.5% vs 29.3%	48% vs 46%
• **mDOR (mo)**	12.3 vs 7.1	12.2 vs 7.2
Safety	**Dato-DXd** (n=319)	**SG** (n=275)
• **Grade ≥3 TRAEs**	33% vs 29%	61% vs 53%
	European Society for Medical Oncology (ESMO) Congress; 2025; LBA21.	European Society for Medical Oncology (ESMO) Congress; 2025; LBA20
	*Investigators choice chemotherapy: Paclitaxel, nab-paclitaxel, capecitabine, carboplatin, eribulin mesylate/eribulin	‡ Chemotherapy: Paclitaxel, nab-paclitaxel, gemcitabine + carboplatin

For Ascent03 and TROPION-Breast02 only 5% of patients had prior neoadjuvant IO therapy
Waiting on data for subgroup analysis for patients with prior neoadjuvant IO therapy

If ASCENT03 or TROPION-Breast02 are approved by the FDA – what would be your preference for patients with first-line metastatic TNBC who are not candidates for PD-1/PD-L1 inhibitors?

Key Takeaways

Triple Negative Breast Cancer

Patient Case: Advanced disease, untreated

- 1st-line has been chemo + pembro if PD-L1 +ve (KEYNOTE-355), now new data from ASCENT 04 (SG + pembro) will be an option (when FDA approved)
  - Data at ESMO 2025 with SG alone for PD-L1 -ve (ASCENT03)
  - Data at ESMO 2025 with Dato-DXd for PD-L1 -ve (TROPION-Breast02)
- 2nd-line consideration of what ADC to use, impact of subsetting TNBC based on HER2 low and ultralow for decision making
  - Sacituzumab govitecan: good activity across HER2-negativity, heavily pre-treated patients with improved OS over std chemotherapy (ASCENT)
  - Trastuzumab deruxtecan: good activity in HER2-low/ultralow patients with HR+ or HR- disease (DESTINY-Breast04)
- Side effect profile and prophylaxis management (neutropenia and ILD) may impact decision making in the 2L setting