Practical Guidance for the Community Oncologist

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

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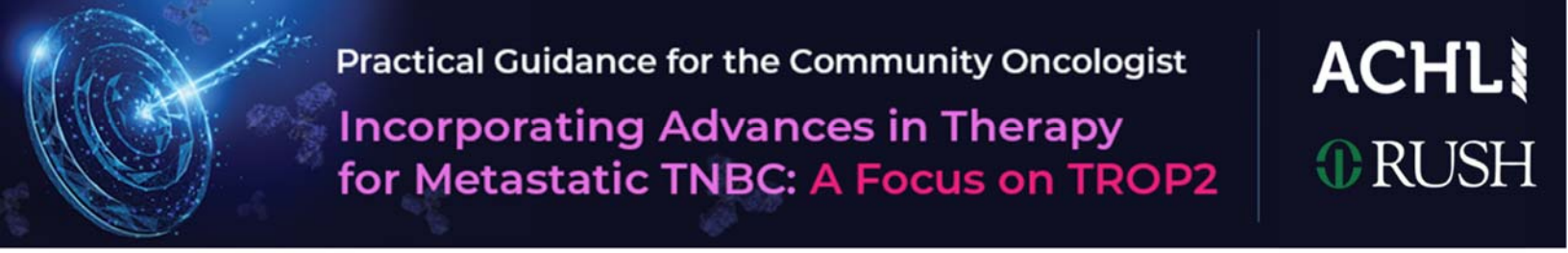

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Tuesday, October 18, 2022
11:00 AM – 12:00 PM (CT)

Ascension
50 Medical Park East Drive; Suite 254
Birmingham, AL 35235

Faculty:
Sara Hurvitz, MD, FACP
Professor of Medicine
University of California, Los Angeles (UCLA)
Co-Director, Santa Monica-UCLA Outpatient Oncology Practice
Medical Director, Clinical Research Unit
Jonsson Comprehensive Cancer Center at UCLA
Director of Breast Oncology
Simms/Mann UCLA Center for Integrative Oncology
Los Angeles, CA

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Please note: Presentation slides may not reflect printed slides.

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.

Statement of Need

This activity aims to help oncologists/hematologists, oncology nurses, and others involved on the multidisciplinary TNBC team to understand the latest roles and clinical evidence with the new and emerging TROP2-targeted treatments. Following this activity, clinicians will also be better able to incorporate TROP-2-targeted ADCs into appropriate TNBC treatment plans.

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

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Agenda

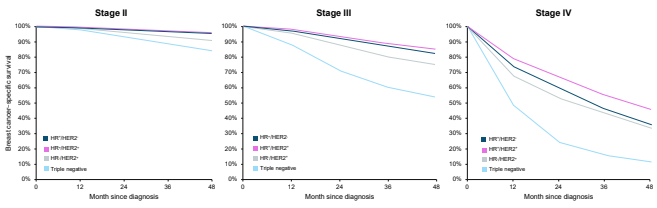
Presentation
TNBC Challenges
The ABCs of ADCs
TROP2 as a Target in TNBC
Additional ADCs in TNBC
Strategies to Incorporate Anti-TROP2 ADCs Into Treatment Paradigms
Case-Based Discussion
Q&A

Ihdwxuhv#ri#Wulsoh0Qhjdwlyh#Euhdvw#Fdqfhu

- 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.

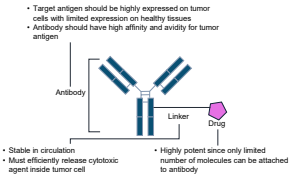
PD-L1 Testing

- 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.

Mechanism of Action of ADCs



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.

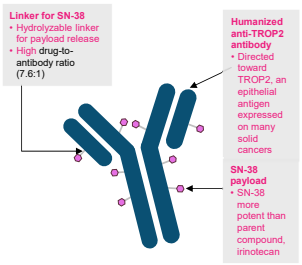
TROP2

- 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.

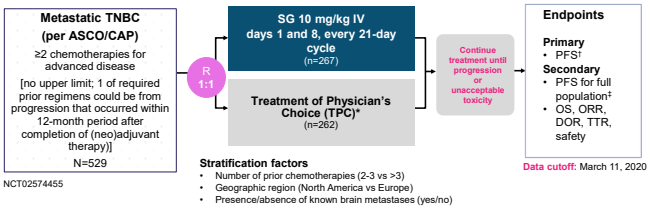
Sacituzumab Govitecan (SG) Is a First-in-Class TROP2–Directed ADC

- 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)

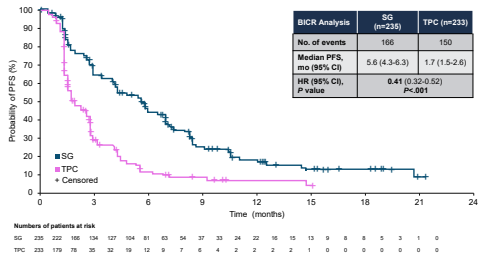
Data cutoff: March 11, 2020

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)

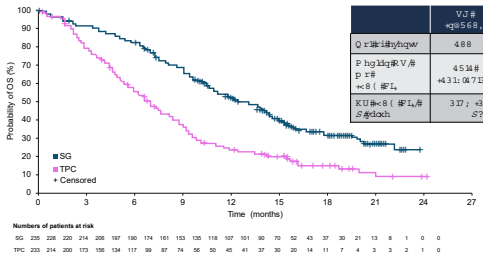


BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS, mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P* value	0.41 (0.32-0.52) *P*<.001	

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



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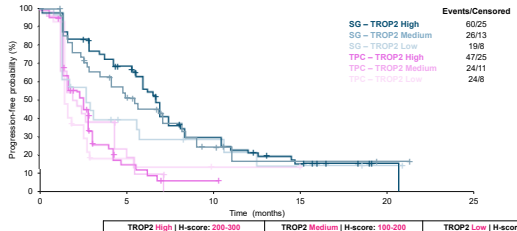
Assessed by independent central review in brain metastases–negative population.

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

TRAE		SG (n=258) All Grade (%)	SG (n=258) Grade 3 (%)	SG (n=258) Grade 4 (%)	TPC (n=224) All Grade (%)	TPC (n=224) Grade 3 (%)	TPC (n=224) 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.

ASCENT: Post-Progression Therapy Outcomes in mTNBC

- 222/267 (83%) pts randomized to receive SG discontinued SG due to PD
  - Median age: 53 years (range, 27-82)
  - Median number of prior anticancer regimens: 4
  - Known germline *BRCA*1/2 mutations: 7%
- Pts received SG for a median duration of 4.2 months (range, 0.0-18.7)
- Following SG discontinuation, post-progression therapy received by 73% (n=163) of pts
  - Common post-SG therapies included eribulin (N=70; 32%), carboplatin (N=34; 15%), capecitabine (N=34; 15%), and atezolizumab, (N=15; 7%)
- Median time to receipt of post-progression therapy: 5.4 months (range, 1.0-19.8)

PD = progressive disease; SG = sacituzumab govitecan

Cortés J et al. Post-progression therapy outcomes in patients (pts) from the phase 3 ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC). [abstract]. In: SABCS. 2021 Dec 10; San Antonio, TX. Abstract PS-16-15.

ASCENT: Post-Progression Therapy Outcomes in mTNBC

- Median OS in pts who received any post PD treatment vs those who did not receive post PD treatment following SG:
  - 13.4 vs 7.3 months (HR, 0.46; 95% CI, 0.32-0.67; *P*<0.0001) from time of randomization
  - 7.9 vs 2.0 months (HR, 0.14; 95% CI, 0.09-0.22; *P*<0.0001) from end of SG treatment

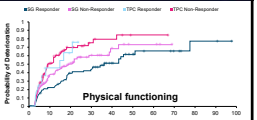
Agent	Median OS from Time of Randomization	Median OS From End of SG Treatment
Eribulin	14.1 (95% CI, 10.9-14.9)	8.4 (95% CI, 6.8-9.2)
Carboplatin	13.6 (95% CI, 10.6-15.9)	8.9 (95% CI, 6.7-10.8)
Atezolizumab	16.5 (95% CI, 8.7 to not evaluable)	8.6 (95% CI, 4.3 to not evaluable)
Capecitabine	14.9 (95% CI, 10.9-16.8)	8.9 (95% CI, 6.6-10.3)

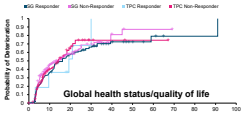
Cortés J et al. Post-progression therapy outcomes in patients (pts) from the phase 3 ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC). [abstract]. In: SABCS. 2021 Dec 10; San Antonio, TX. Abstract PS-16-15.

ASCENT: Quality of Life

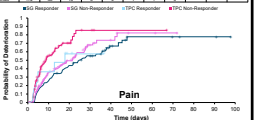
- HRQoL was assessed using EORTC QLQ-C30
- 5 domains were assessed at baseline and day 1 of each cycle: global health status/quality of life (QoL), physical functioning, role functioning, pain, and fatigue
- For all domains except diarrhea, SG responders had longer TTD than SG non-responders

Compared to TPC responders, SG responders had more prolonged TTD for almost all domains, except diarrhea, emotional functioning, fatigue & N/V



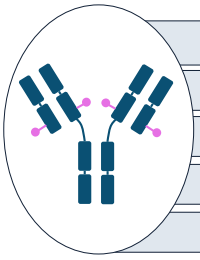


EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; N/V = nausea/vomiting; TPC = treatment of physician's choice; TTD = time to first deterioration



Loibl S et al. Assessment of health-related quality of life by clinical response from the phase 3 ASCENT study in metastatic triple negative breast cancer (mTNBC). [abstract]. In: SABCS. 2021 Dec 10; San Antonio, TX. Abstract PS-16-01.

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§

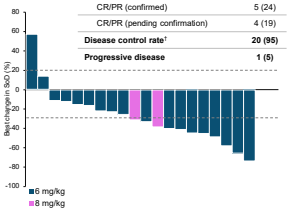
Q3W = every 3 weeks

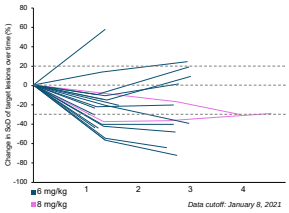
*Estrogen receptor positivity <1%; †Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression; ‡HR+ cohort is currently open for enrollment at 6 mg/kg; §Progression includes progressive disease per RECIST 1.1 and clinical progression.

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.

TROPION-PanTumor01: Dato-DXd TNBC Cohort (April 6, 2021 Update)

- 43 patients with TNBC received ≥1 dose of Dato-DXd:
  - 27 patients (63%) continuing
  - 16 patients (37%) discontinuing treatment (due to disease progression)
- Median age was 53 years (range, 32-82 years)
  - 41 patients (95%) received ≥2 prior lines of therapy
  - 19 patients (44%) received prior immunotherapy
  - 7 (16%) received prior sacituzumab govitecan
- Median duration of treatment: 2.8 months (range, 0.7-6.9 months)
  - Median follow-up 3.9 months (range, 0.3-9.2 months)
- Among 38 patients evaluable for response:
  - ORR by BICR: 39% (15 partial responses [PR]), with 12 confirmed and 3 pending confirmation
  - Disease control rate: 84% (32/38)
  - Median time to response: 1.35 months (1.2-3.2 months) for 12 confirmed PRs

Krop I et al. Datopotamab deruxtecan in advanced/metastatic HER2- breast cancer: Results from the phase 1 TROPION-PanTumor01 study. [abstract] In: SABCS; 2021 Dec 7; San Antonio. Abstract GS1-05.

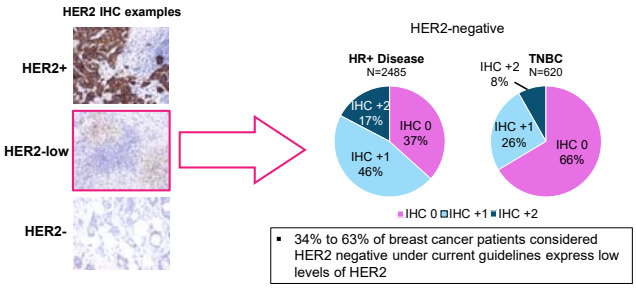
NRG

TROPION-PanTumor01: Dato-DXd TNBC Cohort (April 6, 2021 Update)

- All-cause treatment-emergent adverse events (TEAEs; any grade, grade ≥3) were observed in 95% and 35% of patients, respectively; 2 events were grade 4 and 0 grade 5.
- The most common TEAEs (any grade [≥30%], grade ≥3) included nausea (58%, 0%), stomatitis (53%, 9%), alopecia (35%, N/A), vomiting (35%, 2%), and fatigue (33%, 7%).

Krop I et al. Datopotamab deruxtecan in advanced/metastatic HER2- breast cancer: Results from the phase 1 TROPION-PanTumor01 study. [abstract] In: SABCS; 2021 Dec 7; San Antonio. Abstract GS1-05.

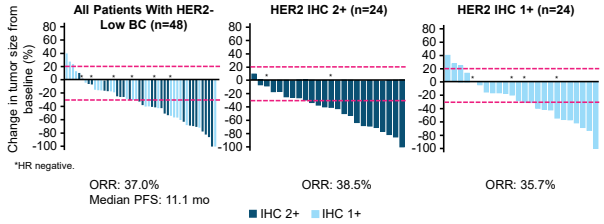
Prevalence of HER2-low by HR Status



- 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



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

Women and men with unresectable and/or metastatic HER2-low breast cancer; progression on endocrine therapy, 1-2 prior lines chemotherapy; no prior HER2 positivity (IHC3+ or ISH+) (planned N=540)

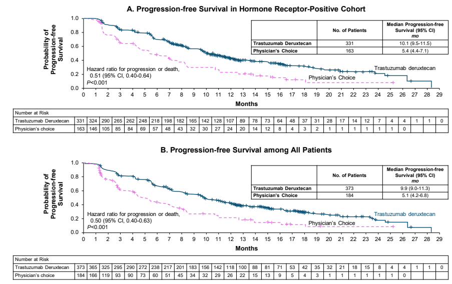
→ **Trastuzumab deruxtecan** 5.4 mg/kg on Days 1 and 8 (*21-day cycles*)

→ **Chemotherapy*** — *Investigator's choice of capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel.

- 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.

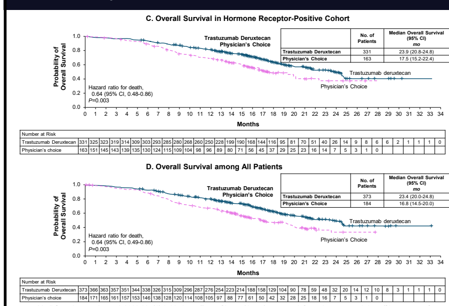
DESTINY-Breast04: Trastuzumab Deruxtecan vs Chemotherapy in Previously Treated HER2-low BC



A. Progression-free Survival in Hormone Receptor-Positive Cohort
Probability of Progression-free Survival
No. of Patients
Median Progression-free Survival (95% CI) mo
Trastuzumab Deruxtecan 331 10.1 (9.5-11.5)
Physician's Choice 163 5.4 (4.4-7.1)
Hazard ratio for progression or death, 0.51 (95% CI, 0.40-0.64)
P<0.001
Trastuzumab deruxtecan
Physician's Choice
Months
Number at Risk
B. Progression-free Survival among All Patients
Probability of Progression-free Survival
Trastuzumab Deruxtecan 373 9.9 (9.0-11.3)
Physician's Choice 184 5.1 (4.2-6.8)
Hazard ratio for progression or death, 0.50 (95% CI, 0.40-0.63)
P<0.001
Months
Number at Risk

Modi S et al. *N Engl J Med*. 2022;387(1):9-20.

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

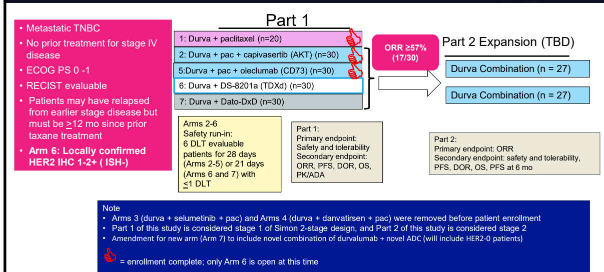


C. Overall Survival in Hormone Receptor-Positive Cohort
Probability of Overall Survival
No. of Patients
Median Overall Survival (95% CI) mo
Trastuzumab Deruxtecan 331 23.9 (20.8-24.8)
Physician's Choice 163 17.5 (15.2-22.4)
Hazard ratio for death, 0.64 (95% CI, 0.48-0.86)
P=0.003
Months
Number at Risk
D. Overall Survival among All Patients
Trastuzumab Deruxtecan 373 23.4 (20.0-24.8)
Physician's Choice 184 16.8 (14.5-20.0)
Hazard ratio for death, 0.64 (95% CI, 0.49-0.86)
P=0.003
Months
Number at Risk

On August 5, 2022, the FDA approved trastuzumab deruxtecan to treat patients with unresectable or metastatic HER2-low breast cancer

Modi S et al. *N Engl J Med*. 2022;387(1):9-20.; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-her2-low-breast-cancer. Accessed August 8, 2022.

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-)
Part 1
1: Durva + paclitaxel (n=20)
2: Durva + pac + capivasertib (AKT) (n=30)
5:Durva + pac + oleclumab (CD73) (n=30)
6: Durva + DS-8201a (TDXd) (n=30)
7: Durva + Dato-DxD (n=30)
ORR ≥57% (17/30)
Part 2 Expansion (TBD)
Durva Combination (n = 27)
Durva Combination (n = 27)
Arms 2-6
Safety run-in:
6 DLT evaluable patients for 28 days (Arms 2-5) or 21 days (Arms 6 and 7) with ≤1 DLT
Part 1:
Primary endpoint:
Safety and tolerability
Secondary endpoint:
ORR, PFS, DOR, OS, PK/ADA
Part 2:
Primary endpoint: ORR
Secondary endpoint: safety and tolerability, PFS, DOR, OS, PFS at 6 mo

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)

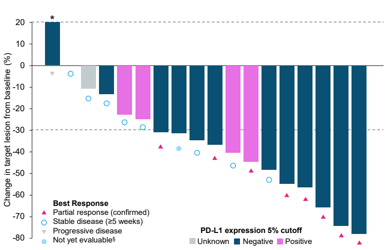
= enrollment complete; only Arm 6 is open at this time

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



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?

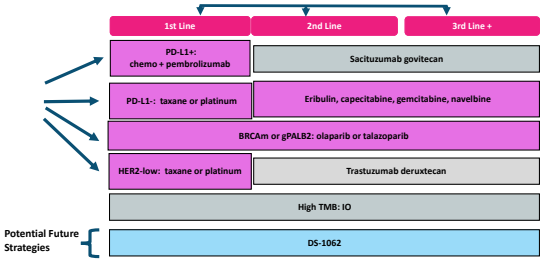
CI = confidence interval; D = durvalumab; ORR = overall response rate; TDxd = trastuzumab deruxtecan

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

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 August 10, 2022. 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 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		Other Recommended Regimens	Useful in Certain Circumstances

• Anthracyclines
  • Doxorubicin
  • Liposomal doxorubicin
• Taxanes
  • Paclitaxel
• Antimetabolites
  • Capecitabine
  • Gemcitabine
• Microtubule inhibitors
  • Vinorelbine
  • Eribulin
• Sacituzumab govitecan (for TNBC [category 1]) or HR+/HER2-
	• For HER2 IHC 1+ or 2+/ISH negative:
	  • Trastuzumab deruxtecan (category 1)
	• 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
		• Cyclophosphamide
		• Docetaxel
		• Albumin-bound paclitaxel
		• Epirubicin
		• Ixabepilone
			• 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 August 8, 2022.

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

Systemic therapy → Continue therapy until progression or unacceptable toxicity → Alternative systemic therapy → Most patients will be candidates for multiple lines of systemic therapy to palliate advanced breast cancer. At each reassessment, clinicians should assess value of ongoing treatment, risks and benefits of an additional line of systemic therapy, patient performance status, and patient preferences through a shared decision-making process → Consider no further cytotoxic therapy and continue supportive care (See NCCN Guideline for Palliative Care) and NCCN Guidelines for Supportive Care

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed August 8, 2022.

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

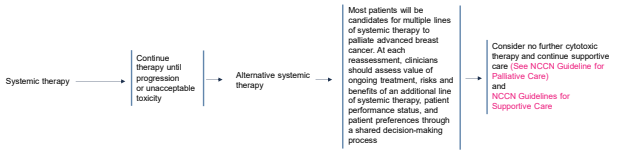
HER2 Negative

Preferred Regimens		Other Recommended Regimens	Useful in Certain Circumstances

• Anthracyclines
  • Doxorubicin
  • Liposomal doxorubicin
• Taxanes
  • Paclitaxel
• Antimetabolites
  • Capecitabine
  • Gemcitabine
• Microtubule inhibitors
  • Vinorelbine
  • Eribulin
• Sacituzumab govitecan (for TNBC [category 1]) or HR+/HER2-
	• For HER2 IHC 1+ or 2+/ISH negative:
	  • Trastuzumab deruxtecan (category 1)
	• 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
		• Cyclophosphamide
		• Docetaxel
		• Albumin-bound paclitaxel
		• Epirubicin
		• Ixabepilone
			• 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 August 8, 2022.

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 August 8, 2022.

How to Receive Credit

To receive credit:

1. Go to www.ACHLcme.org
2. Click on "Use Certificate Code"
3. Enter the Certificate Code: **XXXXX**
4. Complete the posttest and evaluation, and your certificate will be immediately available to you

Participants will receive an automated certificate. You may print or save this record for your files. It will also be sent to you via email to the address provided in your profile on www.ACHLcme.org. There is no fee to participate in the activity or for the generation of the certificate.

Inquiries may be directed to ACHL at (877) 444-8435, ext. 160.

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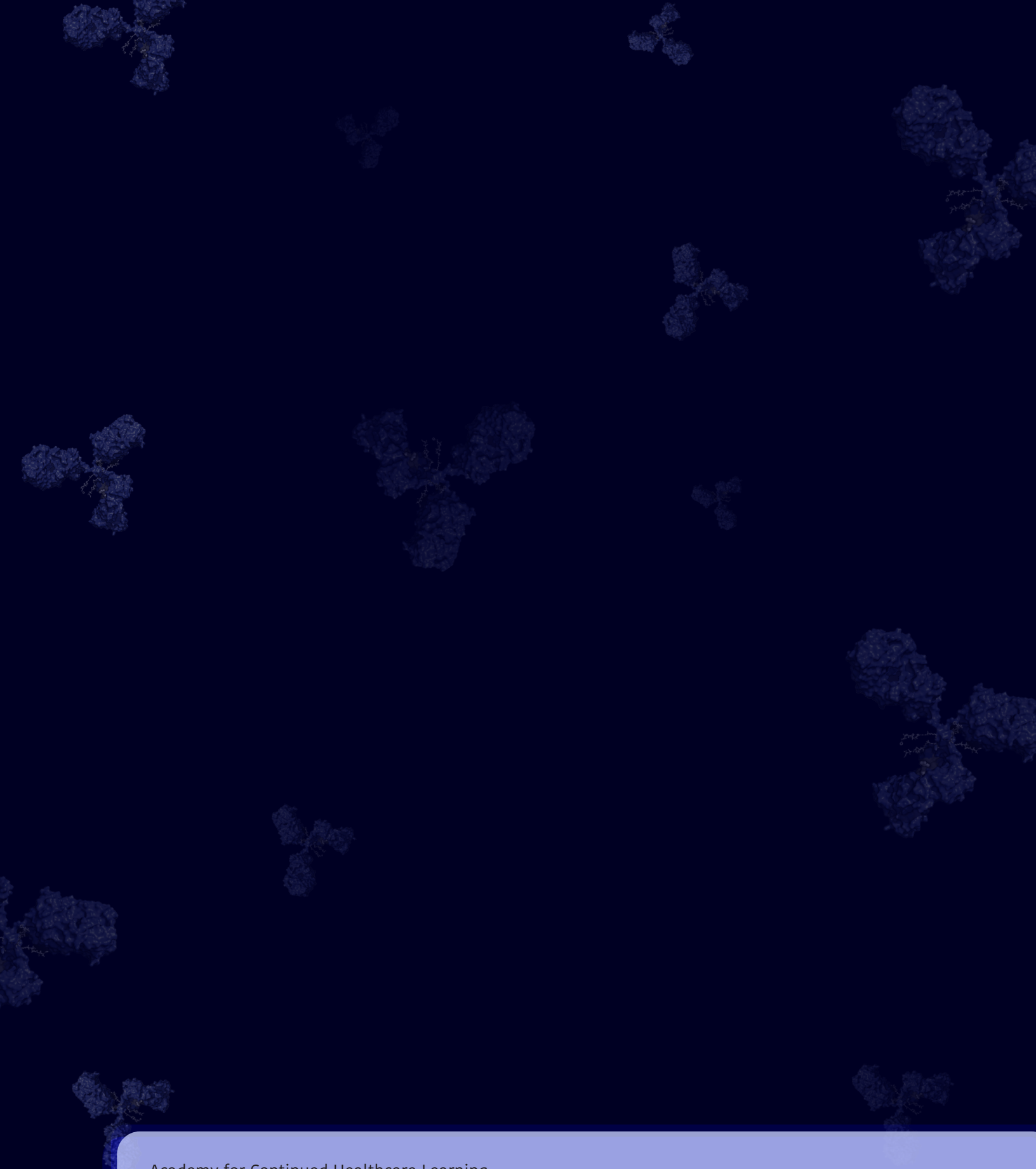

Academy for Continued Healthcare Learning
230 W. Monroe, Suite 2300
Chicago, Illinois 60606
Ph (877) 444-8435