2025 ESMO BREAST CANCER
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Clinical Activity of Emiltatug Ledadotin (Emi-Le), a B7-H4-Directed ADC, in Patients with TNBC who Received at Least One Prior Topoisomerase-1 Inhibitor (Topo-1) ADC

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Mini-Oral Session 1; Abs 298MO

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Declaration of Interests

Erika Hamilton, MD

Director, Breast Cancer Research Program
Chair, Breast Executive Committee
Sarah Cannon Research Institute, Nashville, TN

Consulting Advisory Role (to institution only):

Accutar Biotechnology, Arvinas, AstraZeneca, BeiGene, Circle Pharma, Daiichi Sankyo, Entos, Gilead Sciences, Halda Therapeutics, Incyclix Bio, IQVIA, Janssen, Jazz Pharmaceuticals, Jefferies LLC, Johnson and Johnson, Lilly, Medical Pharma Services, Mersana, Novartis, Pfizer, Pyxis Oncology, Roche/Genentech, Samsung Bioepis, Shorla Pharma, Stemline Therapeutics, Tempus Labs, Zentalis Pharmaceuticals

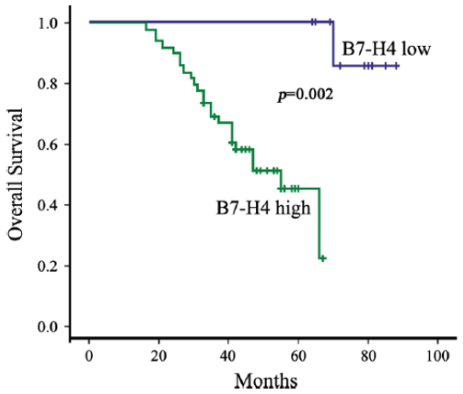
Contracted Research/Grant (to institution only):

Abbvie, Acerta Pharma, Accutar Biotechnology, ADC Therapeutics, AKESOBIO Australia, Amgen, Aravive, ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, BeiGene, Black Diamond, Bliss BioPharmaceuticals , Boehringer Ingelheim, Bristol-Myers Squibb, Cascadian Therapeutics, Clovis, Compugen, Context Therapeutics , Cullinan, Curis, CytomX, Daiichi Sankyo, Dana Farber Cancer Inst, Dantari, Deciphera, Duality Biologics, eFFECTOR Therapeutics, Eisai, Ellipses Pharma, Elucida Oncology, EMD Serono, Fochon Pharmaceuticals, FujiFilm, G1 Therapeutics, Gilead Sciences, H3 Biomedicine, Harpoon, Hutchinson MediPharma, Immunogen, Immunomedics, Incyte, Infinity Pharmaceuticals , Inspirna, InventisBio, Jacobio, Karyopharm, K-Group Beta, Kind Pharmaceuticals , Leap Therapeutics, Lilly, Loxo Oncology, Lycera, Mabspace Biosciences, Macrogenics, MedImmune, Mersana, Merus, Millennium, Molecular Templates, Myriad Genetic Laboratories, Novartis, Nucana, Olema, OncoMed, Oncothyreon , ORIC Pharmaceuticals, Orinove, Orum Therapeutics, Pfizer, PharmaMar, Pieris Pharmaceuticals , Pionyr Immunotherapeutics, Plexxikon, Prelude Therapeutics, Profound Bio, Radius Health, Regeneron, Relay Therapeutics, Repertoire Immune Medicine, Rgenix, Roche/Genentech, SeaGen, Sermonix Pharmaceuticals, Shattuck Labs, Silverback Therapeutics, StemCentRx, Stemline Therapeutics, Sutro, Syndax, Syros, Taiho, TapImmune, Tesaro, Tolmar, Torque Therapeutics, Treadwell Therapeutics, Verastem, Zenith Epigenetics, Zymeworks

Emiltatug Ledadotin (Emi-Le; XMT-1660): A B7-H4-Directed Dolasynthen Auristatin F-HPA ADC

- **High unmet medical need in relapsed/refractory TNBC following treatment with a topo-1 ADC**
  - Standard of care single-agent chemotherapy has limited efficacy: ORR ~5%, PFS ~7 weeks, OS ~6.7 months[1,2]
  - Real-world data suggest limited activity for a second topo-1 ADC in this population[3,4]
- **Response rate tends to diminish with increasing lines of treatment**
  - In the ASCENT trial, sacituzumab govitecan ORR was 35% in overall population compared to 23% in patients with greater than 3 prior lines[1]
- **B7-H4 is a clinically validated target** and **a negative prognostic factor in patients with TNBC**[5]; highly expressed in a range of solid tumors, including breast cancers, with limited expression in healthy tissue[6]
- **Emi-Le is a B7-H4-directed ADC with a proprietary auristatin F-HPA microtubule inhibitor payload** designed with controlled bystander effect (different from MMAE, MMAF and topo-1)
  - Novel ADC design; site-specific bioconjugation; target-optimized DAR 6
  - 2 FDA Fast Track designations, including in post-topo-1 ADC HER2- breast cancer

TNBC Overall Survival by B7-H4 Expression[5]



1. Bardia et al. *NEJM* 2021; 2. Based on ASCENT clinical trial control arm in topo-1 naive; Bardia et al. *NEJM* 2021; 3. Colombo et al., Cancer Discovery. 2024; 4. Huppert et al. NPJ Breast Cancer 2025. 5. Wang et al., Cancer Cell Int., 2018; 6. Sachdev et al. ASCO 2019

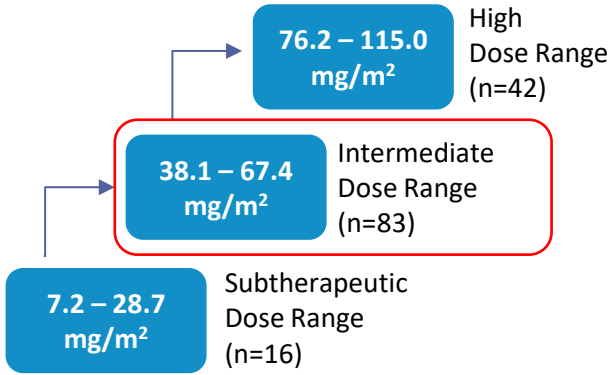
ADC, antibody-drug conjugate; auristatin F-HPA, auristatin F hydroxypropyl amide; DAR, drug-to-antibody ratio; ORR, objective response rate per RECIST version 1.1; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; TNBC, triple-negative breast cancer; PFS, progression-free survival; topo-1; topoisomerase-1 inhibitor

Phase 1 Dose Escalation and Expansion Trial

Dose Escalation and Backfill Cohorts

Key Enrollment Criteria:

- Patients ≥18 years old
- ECOG PS 0-1
- Advanced/metastatic TNBC, HR+/HER2- BC, EC, OC, ACC-I
- Progressed after available standard of care therapy
- B7-H4 expression assessed retrospectively based on fresh or archived tissue
- In parallel with DES, backfill cohorts enrolling additional participants at multiple dose levels
- Data from both DES and backfill cohorts will be utilized to determine the RP2D



Primary Endpoints: MTD, safety and tolerability
Secondary Endpoints: ORR, DOR, DCR, PK, ADA

Dose Expansion : TNBC

Key Enrollment Criteria:

- Advanced or metastatic TNBC
- 1-4 prior lines of treatment in a locally advanced or metastatic setting, including at least one prior topo-1 ADC
- Patients stratified by B7-H4 expression

Dose A
67.4 mg/m² Q4W

Dose B
C1: 44.5 mg/m² D1/8 followed by 80 mg/m² Q4W thereafter

Primary Endpoints: Safety, tolerability and preliminary antitumor activity
Secondary Endpoints: PK and ADA

- Across all tumor types, in evaluable B7-H4 high patients treated in the intermediate dose range (38.1-67.4 mg/m2) the ORR was 31%
- Presented here are interim results from the dose escalation portion of the ongoing Phase 1 trial of Emi-Le in the TNBC dose escalation/backfill cohorts dosed in the intermediate dose range (38.1-67.4 mg/m²)

Data cut: March 8, 2025

ACC-1, adenoid cystic carcinoma – type 1; ADA, anti-drug antibody; ADC, antibody-drug conjugate; C1, cycle 1; C2, cycle 2; D1/8, on day 1 and day 8 of a 28 day cycle; DES, dose escalation study; DCR, disease control rate; DOR, duration of response; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2-, human epidermal growth factor receptor 2 negative; HR+/HER2- BC, hormone-receptor-positive, human epidermal growth factor receptor 2 negative breast cancer; mg/m², milligrams per meter squared; MTD, maximum tolerated dose; OC, ovarian cancer; ORR, overall response rate; PK, pharmacokinetics; Q4W, dosing every four weeks; RP2D, recommended phase 2 dose; TNBC, triple-negative breast cancer; topo-1, topoisomerase-1 inhibitor

Patient Demographics and Disease Characteristics

Patients with TNBC Treated in the Intermediate Dose Range (38.1-67.4 mg/m^2)

	TNBC (N=44)
Median age	49.5
Median prior lines in locally advanced/ metastatic setting (range)	4 (1-9)
Prior Topo-1 ADCs received, n (%)	
Prior trastuzumab deruxtecan	14 (31.8%)
Prior sacituzumab govitecan	38 (86.4%)
Prior both	11 (25.0%)
Prior either	41 (93.2%)
B7-H4 expression[1], n (%)	
TPS status known	36 (81.8%)
High (TPS ≥70)	14 (38.9%)
Low (TPS <70)	22 (61.1%)
TPS not yet determined	8 (18.2%)

- Heavily pretreated patient population
- 93.2% previously treated with at least one prior topo-1 ADC
- 38.9% determined to be B7-H4 high, based on a TPS cutoff of ≥70%

Data cut: March 8, 2025

1. Archival or fresh tissue evaluated retrospectively by IHC for B7-H4 expression with a preliminary high cut off set at Tumor Proportion Score (TPS)≥70

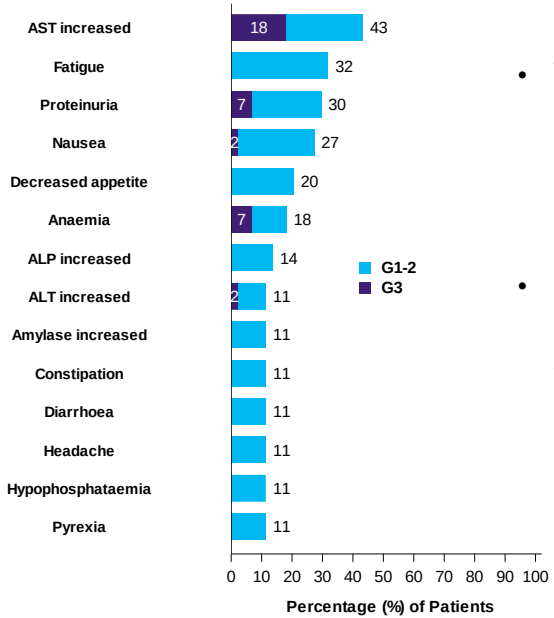
ADC, antibody-drug conjugate; IHC, immunohistochemistry; TNBC, triple-negative breast cancer; topo-1, topoisomerase-1 inhibitor

Safety Summary

Patients with TNBC Treated in the Intermediate Dose Range (38.1-67.4 mg/m^2)

Patients with:	(N=44)
Any treatment related adverse event (TRAE)	34 (77.3%)
Grade 3 TRAE	16 (36.4%)
Treatment-related serious adverse event (SAE)	3 (6.8%)
TRAE leading to treatment discontinuation	2 (4.5%)
TRAE leading to dose reduction	4 (9.1%)
TRAE leading to dose delay	3 (6.8%)
TRAE leading to death	0

TRAEs Observed in ≥10% of patients



- TRAEs leading to treatment discontinuation: nephrotic syndrome in patient with concurrent gout flare (n=1), pain in extremity (n=1)
- No dose-limiting treatment-related neuropathy, neutropenia, ocular toxicity, ILD, or thrombocytopenia

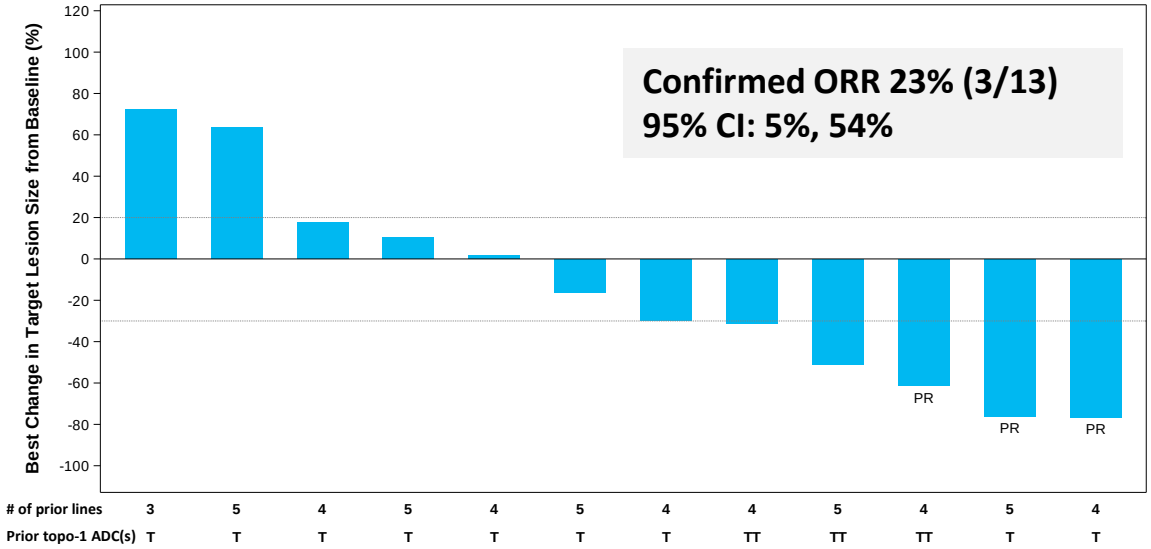
Data cut: March 8, 2025

AST increase were transient, increasing by Day 8 and returning to baseline or G1 by subsequent dose. Proteinuria was generally asymptomatic and reversible

ALP, alkaline phosphatase; ALT, alanine transaminase; AST aspartate aminotransferase; G, grade; ILD, interstitial lung disease; SAE, serious adverse event; TNBC, triple-negative breast cancer; TRAE, treatment-related adverse event

Clinical Activity in Evaluable Patients With B7-H4 High TNBC

Intermediate Dose Range (38.1-67.4 mg/m^2)



- Heavily pre-treated patient population
- All received at least one prior topo-1 ADC
- In patients with ≤4 prior lines in locally advanced/metastatic setting, ORR 29% (2/7)
- No confirmed responses observed in B7-H4 low patients

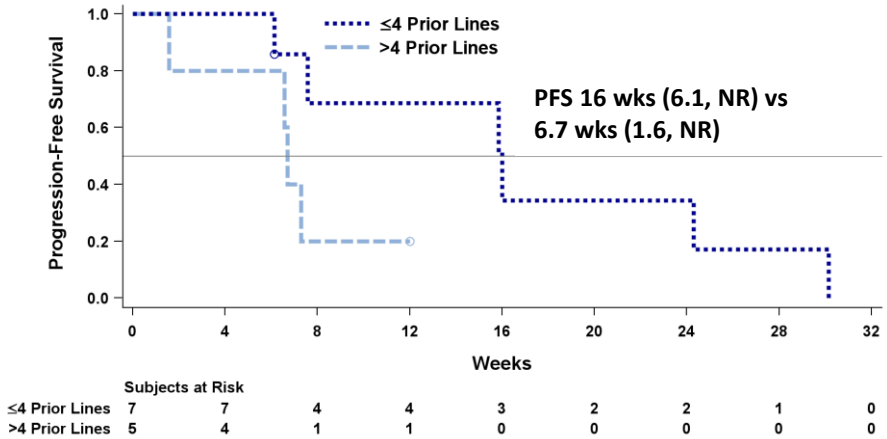
Data cut: March 8, 2025
T = Previously treated with one topoisomerase-1 inhibitor ADC
TT = Previously treated with more than one topoisomerase-1 inhibitor ADC
Evaluable population defined as patients with measurable disease at baseline and at least one post-baseline scan. One patient did not have target lesions identified at baseline and is therefore not included. Missing from waterfall, but included in response rate denominator, is one TNBC patient with 8 prior lines, including topo-1 ADC and progressive disease as best response who had a post-treatment scan but not post-baseline measurement of their target lesion

ADC, antibody-drug conjugate; CI, confidence interval; ORR, overall response rate; TNBC, triple-negative breast cancer; topo-1, topoisomerase-1 inhibitor

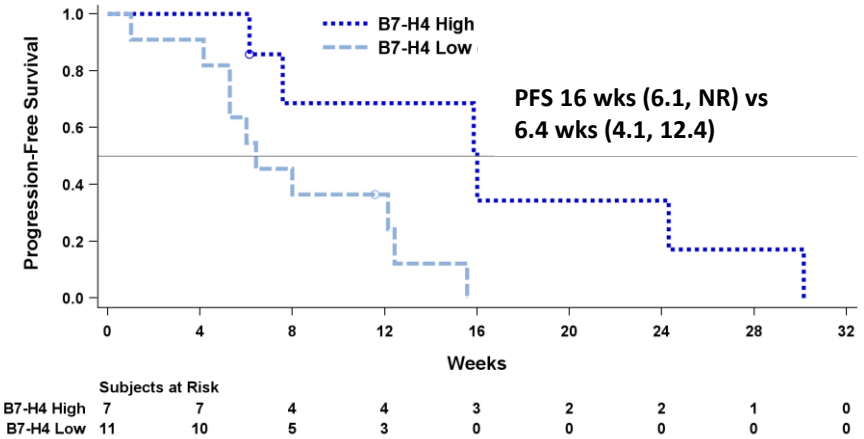
Preliminary Progression-Free Survival in Patients with TNBC

Intermediate Dose Range (38.1-67.4 mg/m^2)

B7-H4 High TNBC
≤4 prior lines vs >4 prior lines



Patients with TNBC, ≤4 prior lines of therapy
B7-H4 High vs B7-H4 Low

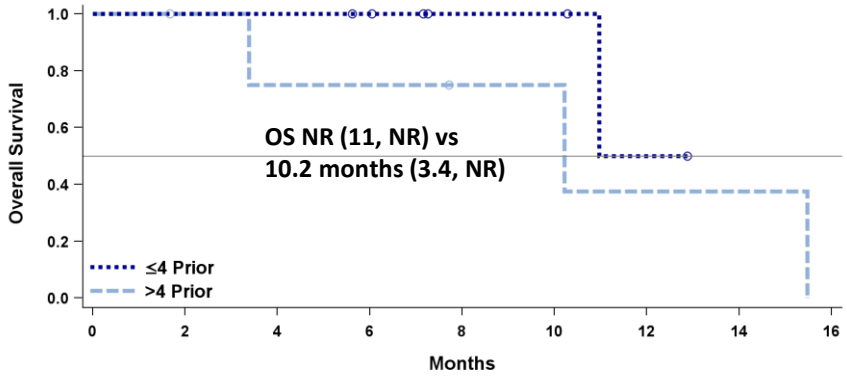


Data cut: March 8, 2025
One B7-H4 High patient with 5 prior lines had an unknown number of prior lines in the locally advanced or metastatic setting
CI, confidence interval; NR, not reached; PFS, progression free survival; TNBC, triple-negative breast cancer

Preliminary Overall Survival in Patients with TNBC

Intermediate Dose Range (38.1-67.4 mg/m^2)

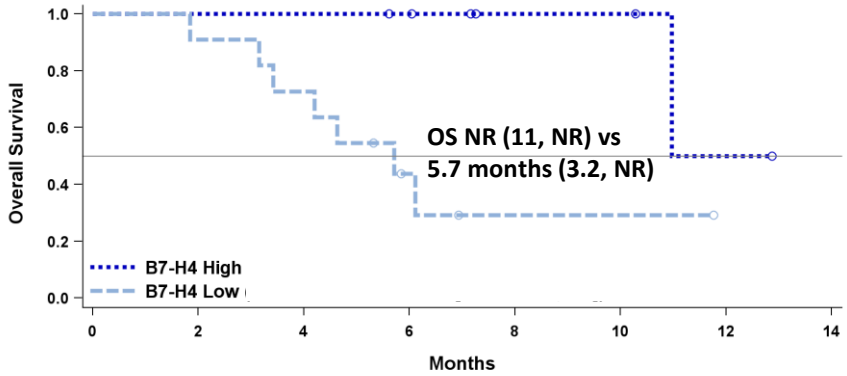
B7-H4 High TNBC
≤4 prior lines vs >4 prior lines



Subjects at Risk

≤4 Prior Lines	7	7	7	6	3	3	1	0	0
>4 Prior Lines	5	4	3	3	2	2	1	1	0

Patients with TNBC, ≤4 prior lines of therapy
B7-H4 High vs B7-H4 Low



Subjects at Risk

B7-H4 High	7	7	7	6	3	3	1	0	
B7-H4 Low	11	10	8	3	1	1	0	0	

Data cut: March 8, 2025
One B7-H4 High patient with 5 prior lines had an unknown number of prior lines in the locally advanced or metastatic setting
CI, confidence interval; NR, not reached; OS, overall survival; TNBC, triple-negative breast cancer

Conclusion

- High unmet medical need in patients with locally advanced/metastatic TNBC following treatment with a topo-1 ADC
- Preliminary data from the dose escalation/backfill cohorts of the ongoing Phase 1 trial suggest that Emi-Le has encouraging clinical activity and tolerability in a heavily pretreated TNBC population who had previously received a topo-1 ADC
    - 23% ORR in evaluable patients with B7-H4 high at the intermediate dose range; 29% ORR in patients with ≤4 prior lines in locally advanced/metastatic setting
    - Encouraging preliminary PFS and OS. More favorable outcomes in patients who had received ≤4 prior lines of treatment
- Further clinical development of Emi-Le is ongoing in the dose expansion portion of the Phase 1 trial in patients with locally advanced/metastatic TNBC who have received 1-4 prior lines of metastatic therapy, including at least one prior topo-1 ADC, across two dose cohorts:
    - 67.4 mg/m^2 Q4W
    - 44.5 mg/m^2 D1/D8 followed by 80 mg/m^2 Q4W starting at cycle 2

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Thank you to the patients and their families participating in this study and to my fellow investigators and their research staff

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