2025 ASCO ANNUAL MEETING

# Initial Phase 1 Dose Escalation Data for Emiltatug Ledadotin (Emi-Le), a Novel B7-H4-Directed Dolasynthen Antibody-Drug Conjugate

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# Declaration of Interest


## Erika Hamilton, MD

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**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

# Summary

- B7-H4 is a transmembrane protein highly expressed in a range of solid tumors, including breast cancer (BC), ovarian cancer (OC), endometrial cancer (EC), and adenoid cystic carcinoma type 1 (ACC-I)
- Emi-Le is a B7-H4-directed Dolasynthen ADC with a proprietary auristatin F-HPA microtubule inhibitor payload designed with controlled bystander effect (different from MMAE, MMAF and topo-1)
- Preliminary data from the dose escalation portion of the ongoing Phase 1 trial in patients with TNBC, HR+/HER2- BC, OC, EC, and ACC-I demonstrates clinical activity and tolerability in the locally advanced/metastatic setting
  - In the intermediate dose range (38.1-67.4 mg/m$^2$), 31% ORR in evaluable patients with high B7-H4 expression; 44% ORR in evaluable B7-H4 high patients with ≤4 prior lines of therapy*
  - Preliminary evidence of encouraging anti-tumor activity in patients with ACC-I, 56% ORR (uPR+cPR)
- Further clinical development is ongoing (NCT05377996)

*Data cut: March 8, 2025

# Unmet Medical Need in B7-H4 Expressing Tumors

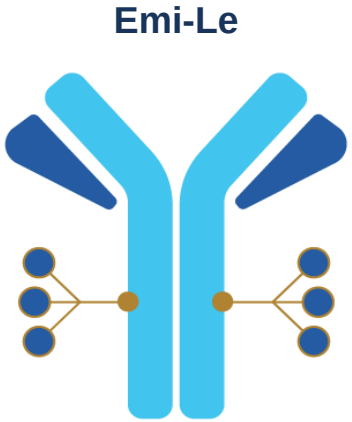
- **B7-H4 is a transmembrane protein highly expressed in a range of solid tumors**, including breast cancer, ovarian cancer, endometrial cancer, and ACC-I[1]
- **B7-H4 has been shown to be a negative prognostic factor** across various tumors[2,3]
- **Unmet medical need persists** across these multiple tumor types:
  - **Clinical outcomes with current standard of care therapies remain limited in treatment refractory setting**:
    - TNBC (topo-1 naïve): ORR ~5%, PFS ~7 weeks; OS ~6.7 months[4]
    - HR+/HER2- metastatic BC (post CDK4/6; topo-1 naive): ORR ~20%, PFS ~5 months, OS ~18 months[5,6,7,8,9]
    - Endometrial cancer: ORR ~15%, PFS ~4 months, OS ~12 months[10]
    - Ovarian cancer (platinum-resistant): ORR 10-15%, PFS ~2-4 months, OS ~12 months[11]
    - ACC-I: No FDA approved therapy, PFS ~2-3 months, OS ~2-3 years[12,13,14,15]

1. Sachdev et al. ASCO 2019; 2. Wang et al., Cancer Cell Int., 2018; 3. Song et al., Oncotarget. 2016; 4. Bardia et al. NEJM 2021 based on ASCENT clinical trial control arm in topo-1 naive; 5. Rugo et al. J Clin Oncol 2022; 6. Rugo et al. Lancet 2023; 7. Bardia et al. J Clin Oncol 2025; 8. Dato-DXd prescribing information; 9. Modi et al. NEJM 2022; 10. Makker et al. NEJM 2022; 11. Laurent et al., J Clin Oncol. 2023; 12. Ferrarotto et al., Clin Can Res. 2020; 13. de Sousa Clin Can Res. 2023; 14. Hanna et al., Cancer Res Commun. 2023; 15. Ferrarotto et al., Abs 903P, ESMO 2023

BC, breast cancer; ORR, overall response rate; OS, overall survival; PFS, progression free survival; TNBC, triple-negative breast cancer; topo-1, topoisomerase-1 inhibitor

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

- 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; drug-to-antibody ratio (DAR) 6
  - 2 FDA Fast Track designations
    - Advanced or metastatic recurrent TNBC
    - Advanced or metastatic HER-2 low / HER-2 negative breast cancer post-topo-1 ADC (including TNBC and HR+ breast cancers who have received or are ineligible for endocrine therapy)




ADC, antibody drug conjugate; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; TNBC, triple-negative breast cancer; topo-1, topoisomerase-1 inhibitor

# Phase 1 Dose Escalation and Expansion Clinical Trial

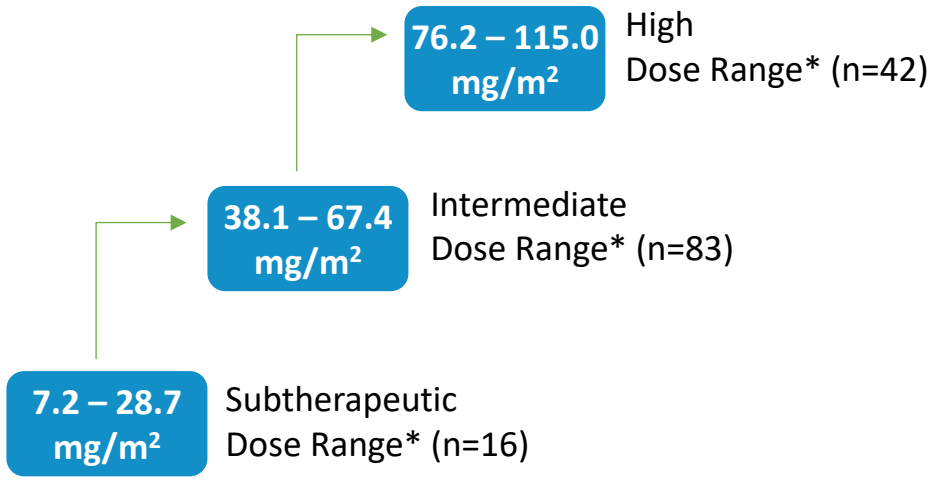
## Dose Escalation and Backfill Cohorts

**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 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**
**44.5 mg/m² on D1/8 of the 1st 4-week cycle followed by 80 mg/m² Q4W**

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

**Presented here are interim results from the Phase 1 dose escalation/backfill cohorts**

* Including a broad range of doses and multiple dosing schedules. All patients enrolled in US

ACC-1, adenoid cystic carcinoma – type 1; ADA, anti-drug antibody; ADC, antibody-drug conjugate; ASCO/CAP, American Society of Clinical Oncology and the College of American Pathologists; C1, cycle 1; D1/D8, administered on days 1 and 8 of the cycle; DCR, disease control rate; DOR, duration of response; ER-, estrogen receptor negative; HER2-, human epidermal growth factor receptor 2 negative; HR+/HER2- BC, hormone-receptor-positive, human epidermal growth factor receptor 2 negative breast cancer; IHC, immunohistochemistry; ISH, in situ hybridization; mg/m², milligrams per meter squared; ORR, overall response rate; PK, pharmacokinetics; PR-, progesterone receptor negative; 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

## Dose Escalation/Backfill Patients Across all Doses

| | TNBC (N=63) | HR+/HER2- MBC (N=37) | Ovarian (N=14) | Endometrial (N=14) | ACC-I (N=13) | Total (N=141) |
|---|---|---|---|---|---|---|
| **Median age** | 48 | 62 | 61 | 65.5 | 52 | 55 |
| **ECOG PS, n(%)** | | | | | | |
| **0** | 30 (47.6%) | 13 (35.1%) | 5 (35.7%) | 9 (64.3%) | 9 (69.2%) | 66 (46.8%) |
| **1** | 33 (52.4%) | 24 (64.9%) | 9 (64.3%) | 5 (35.7%) | 4 (30.8%) | 75 (53.2%) |
| **Median prior lines of therapy (range)** | 5 (2-9) | 7 (2-15) | 5 (2-11) | 3 (1-4) | 1 (0-3) | 4 (0-15) |
| **Prior Topo-1 ADCs received, n (%)** | | | | | | |
| **Prior trastuzumab deruxtecan** | 21 (33.3%) | 15 (40.5%) | 0 | 0 | 0 | 36 (25.5%) |
| **Prior sacituzumab govitecan** | 54 (85.7%) | 15 (40.5%) | 0 | 0 | 1 (7.7%) | 70 (49.6%) |
| **Prior both** | 17 (27.0%) | 10 (27.0%) | 0 | 0 | 0 | 27 (19.1%) |
| **Prior either** | 58 (92.1%) | 20 (54.1%) | 0 | 0 | 1 (7.7%) | 79 (56.0%) |
| **B7-H4 Expression[1], n (%)** | | | | | | |
| **TPS Known** | 53 (84.1%) | 31 (83.8%) | 13 (92.9%) | 14 (100%) | 5 (38.5%) | 116 (82.3%) |
| **High (TPS ≥70)** | 24 (45.3%) | 8 (25.8%) | 7 (53.8%) | 5 (35.7%) | 4 (80.0%) | 48 (41.4%) |
| **Low (TPS <70)** | 29 (54.8%) | 23 (74.2%) | 6 (46.2%) | 9 (64.3%) | 1 (20.0%) | 68 (58.6%) |
| **TPS Unknown** | 10 (15.9%) | 6 (16.2%) | 1 (7.1%) | 0 | 8 (61.5%) | 25 (17.7%) |

- 92.1% of patients with TNBC treated with ≥1 prior topo-1 ADC
- Across all patients, 41.4% determined to be B7-H4 high, based on a preliminary 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; MBC, metastatic breast cancer TNBC, triple-negative breast cancer; topo-1, topoisomerase-1 inhibitor

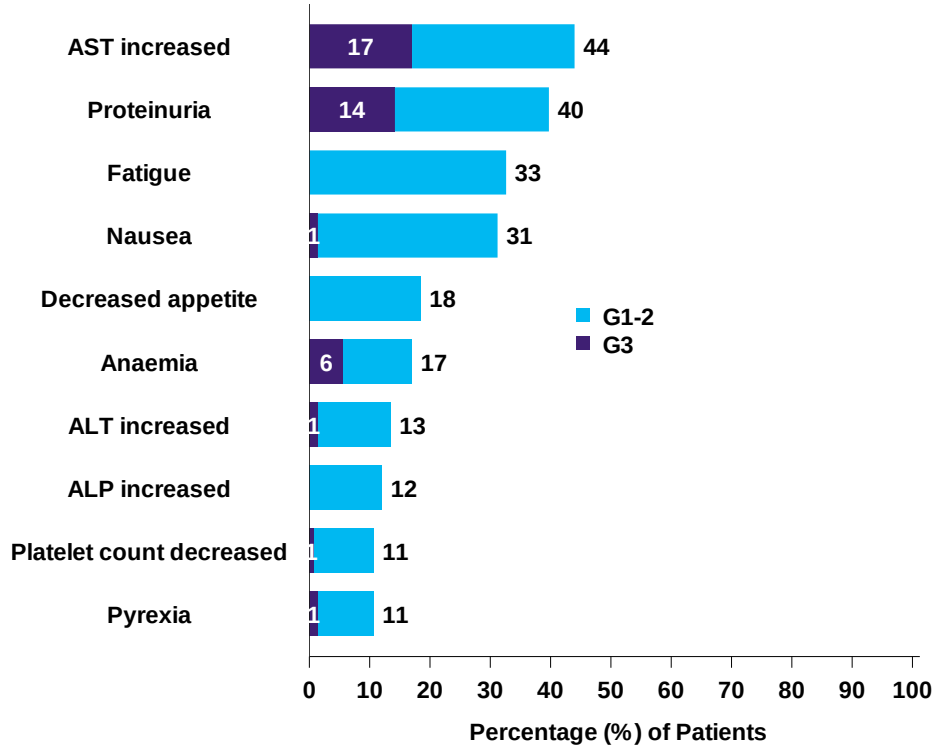
# Safety Summary

## Dose Escalation/Backfill Patients Across all Doses (N=141)

| | Total (N=141) |
|---|---|
| Any treatment related adverse event (TRAE) | 117 (83.0%) |
| Grade 3 TRAE | 52 (36.9%) |
| Treatment-related serious adverse event (SAE) | 8 (5.7%) |
| TRAE leading to treatment discontinuation | 5 (3.5%) |
| TRAE leading to dose reduction | 23 (16.3%) |
| TRAE leading to dose delay | 33 (23.4%) |
| TRAE leading to death | 0 |

- Most common TRAEs were transient AST increase, generally asymptomatic and reversible proteinuria, generally low-grade fatigue and nausea
- Reasons for discontinuation: proteinuria (G3), infusion related reaction (G3), nephrotic syndrome in the presence of gout flare (G3), cystitis hemorrhagic (G2), pain in extremity (G2)
- No dose-limiting treatment-related neuropathy, neutropenia, ocular toxicity, ILD, or thrombocytopenia observed in this data set

**TRAEs Observed in ≥10% of patients**



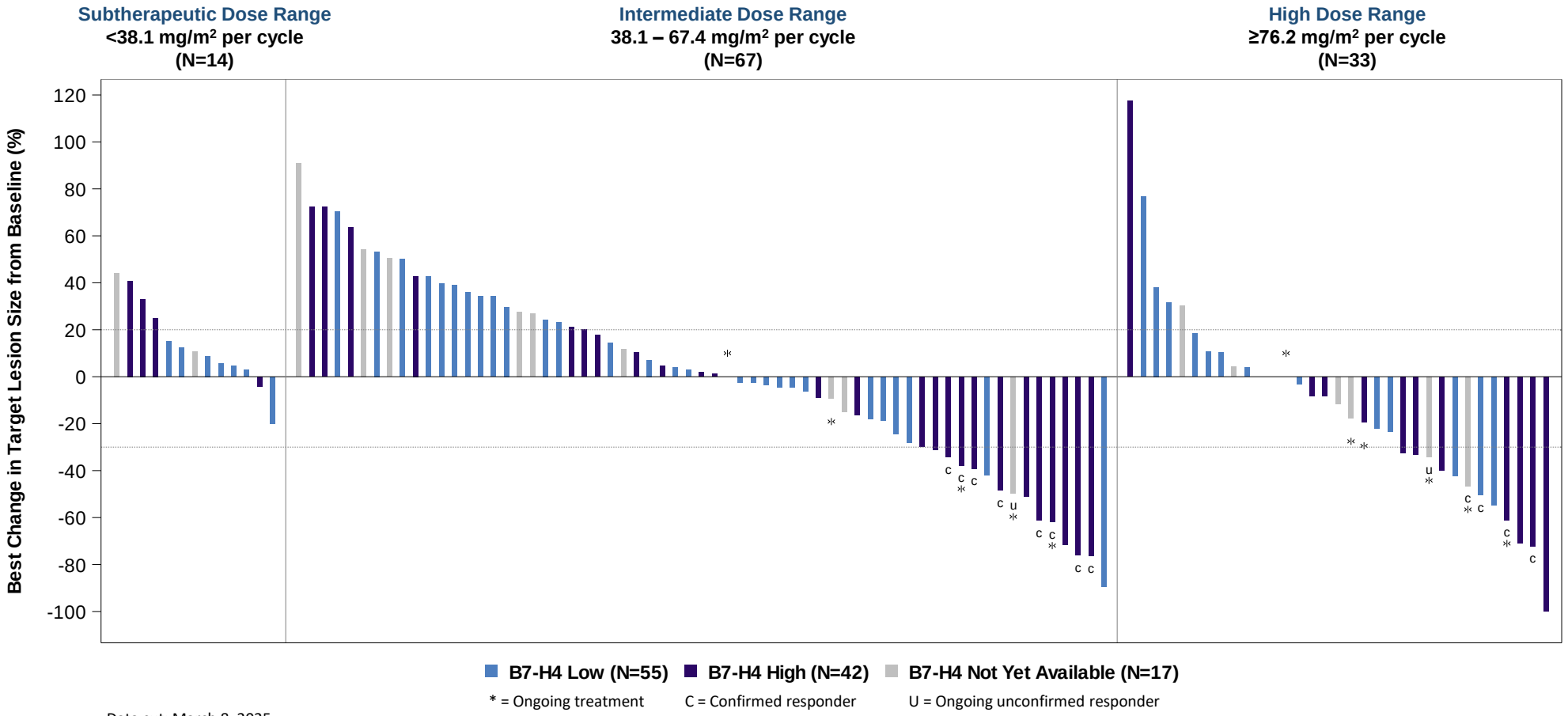

Data cut: March 8, 2025

AST increases were transient, increasing by Day 8 and returning to baseline or G1 by subsequent dose.

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

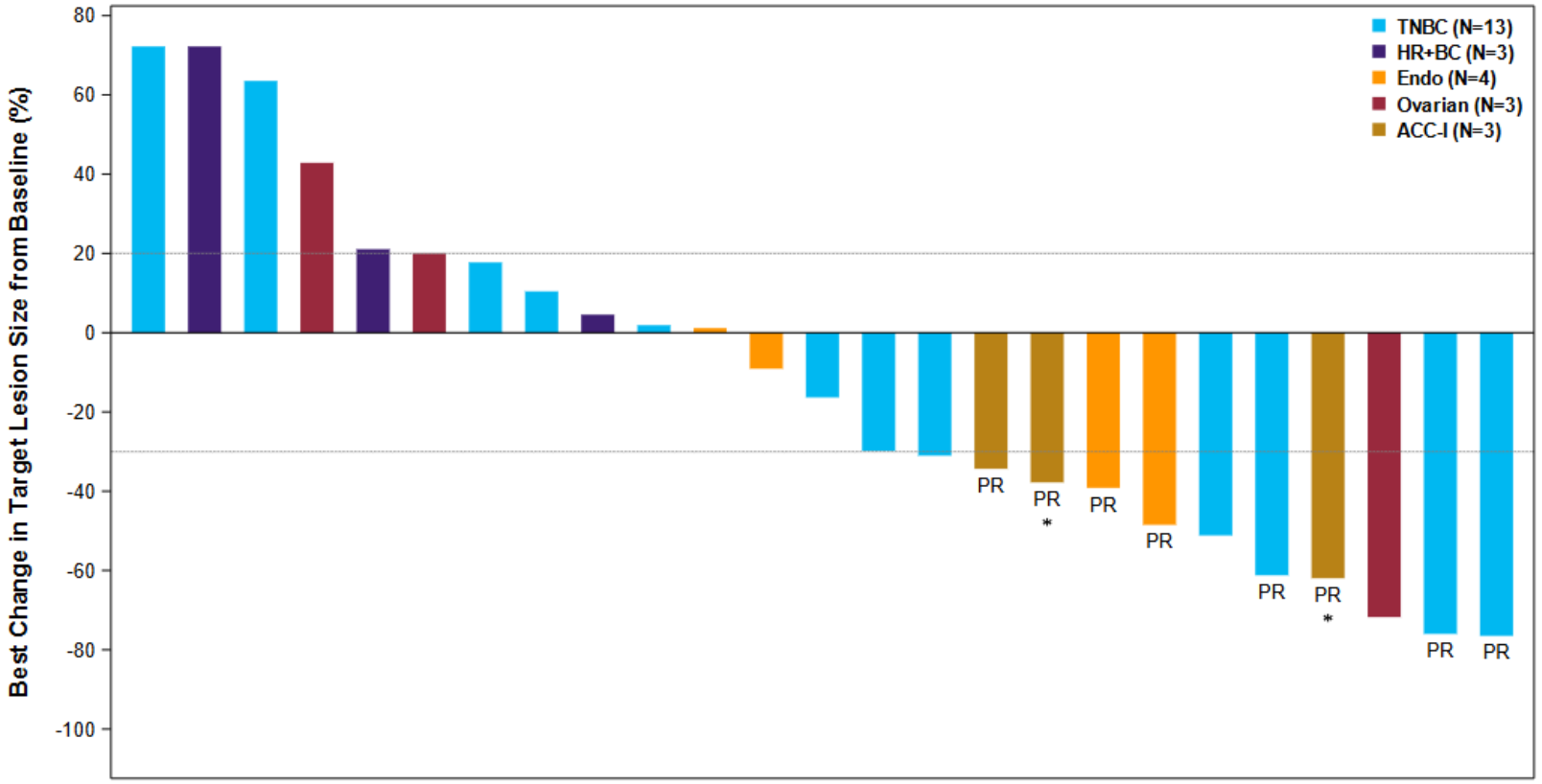
## Clinical Activity Appears to be Correlated with Both Dose and B7-H4 Expression




Data cut: March 8, 2025

Evaluable population (N=114) consists of patients with measurable disease at baseline and at least one post-baseline scan. Of the 141 patients in the safety population, 11 did not have measurable disease at baseline or were ongoing without a post-baseline scan, and 16 discontinued prior to first scan (including 1 B7-H4 high ovarian cancer patient in the Intermediate Dose Range and 1 B7-H4 high TNBC patient in the High Dose Range). Missing from waterfall but included in the evaluable population (N=114) are 5 patients with progressive disease as best response who had a post-treatment scan but not post-baseline measurement of their target lesion.

# Clinical Activity in B7-H4 High Evaluable Patients Across All Tumor Types in the Intermediate Dose Range (38.1-67.4 mg/m²)




* = Ongoing treatment

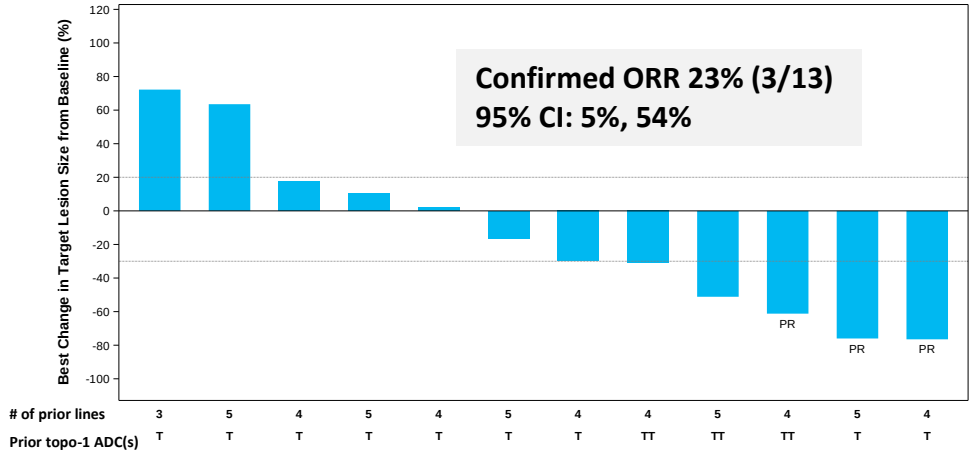
- 31% (8/26) ORR (95% CI: 14%, 52%)
  - TNBC: ORR 23% (3/13)
  - Endometrial: ORR 50% (2/4)
- 44% (7/16) ORR (95% CI: 20%, 70%) in patients with ≤4 prior lines of therapy
- No confirmed responses observed in B7-H4 low patients

Data cut: March 8, 2025

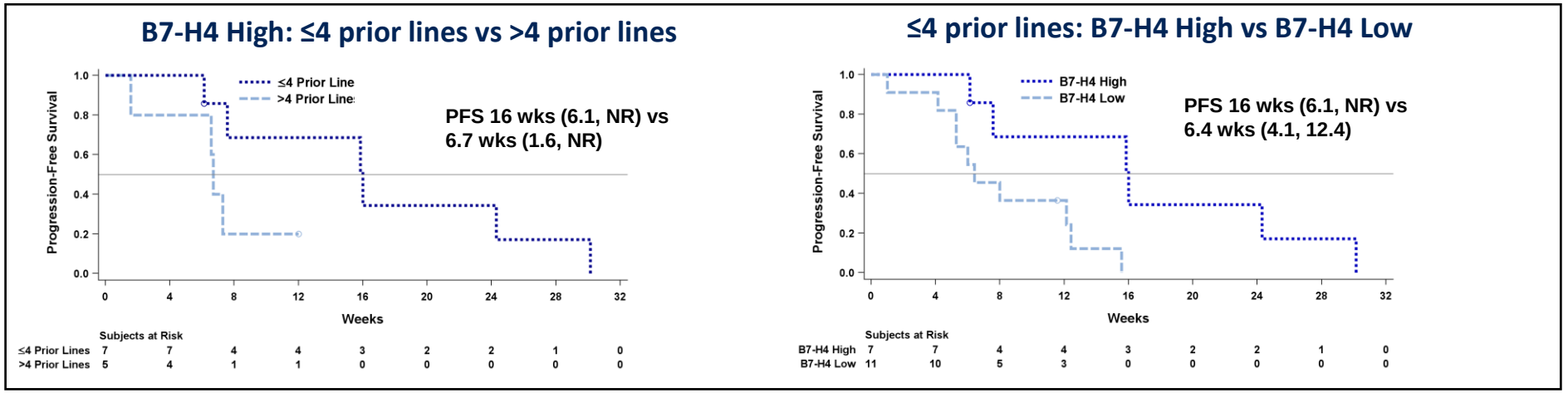
Evaluable population (N=26) defined as patients with measurable disease at baseline and at least one post-baseline scan. Missing from waterfall, but included in response rate denominator, is one TNBC patient with 8 prior lines and progressive disease as best response who had a post-treatment scan but not post-baseline measurement of their target lesion

# Clinical Activity in Evaluable Patients with TNBC

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




**Preliminary PFS**




T = Previously treated with one topoisomerase-1 inhibitor ADC; TT = Previously treated with more than one topoisomerase-1 inhibitor ADC

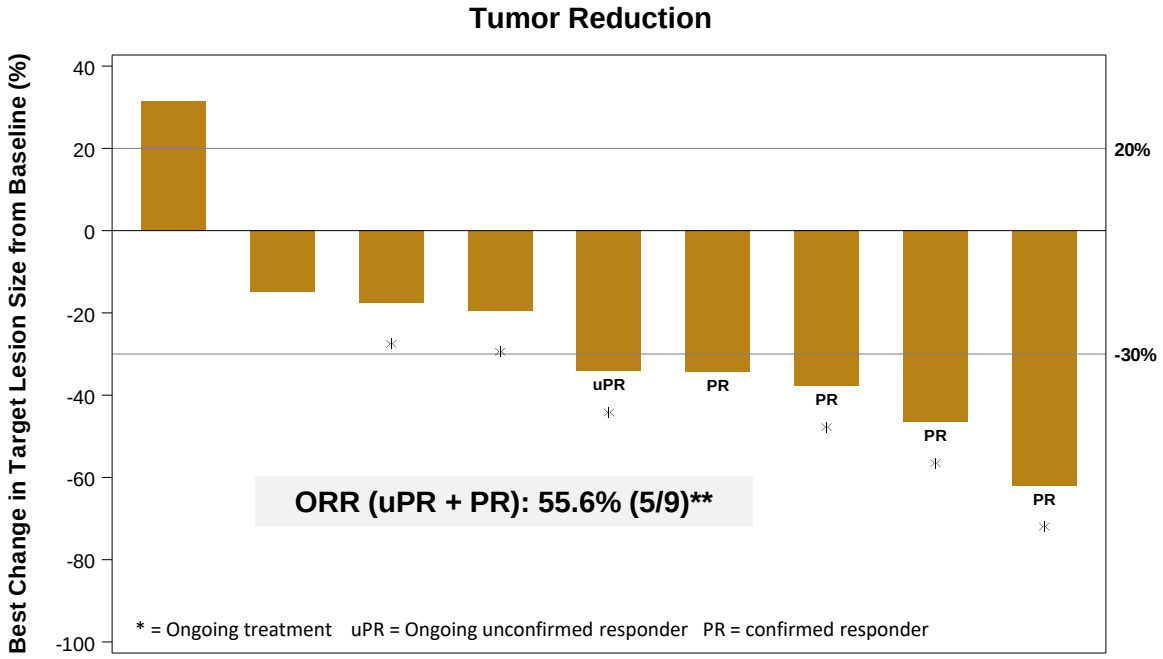
Data cut: March 8, 2025; Evaluable population defined as patients with measurable disease at baseline and at least one post-baseline scan. One patient did not have target lesions identified at baseline and is therefore not included in waterfall. Missing from waterfall, but included in response rate denominator, 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. 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; ORR, overall response rate;PFS, progression free survival; TNBC, triple-negative breast cancer

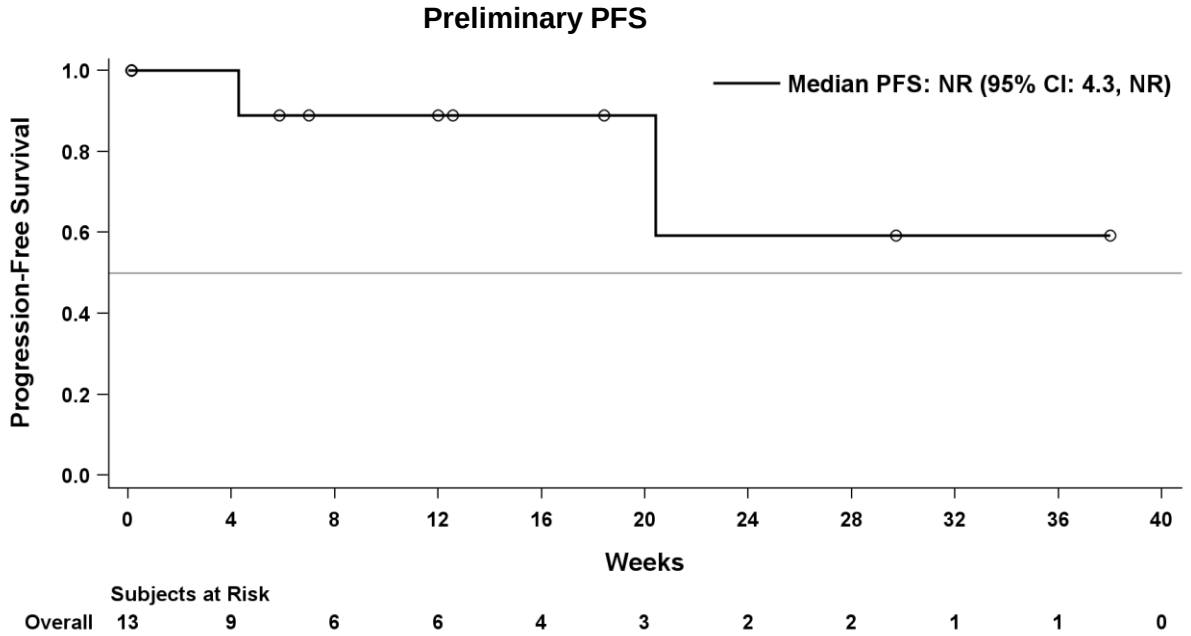


PRESENTED BY: Erika Hamilton, MD

# Clinical Activity in Evaluable Patients with Adenoid Cystic Carcinoma Type 1 (ACC-I), All Doses, Unselected for B7-H4 Expression




**Includes one uPR, which was confirmed after the data cutoff



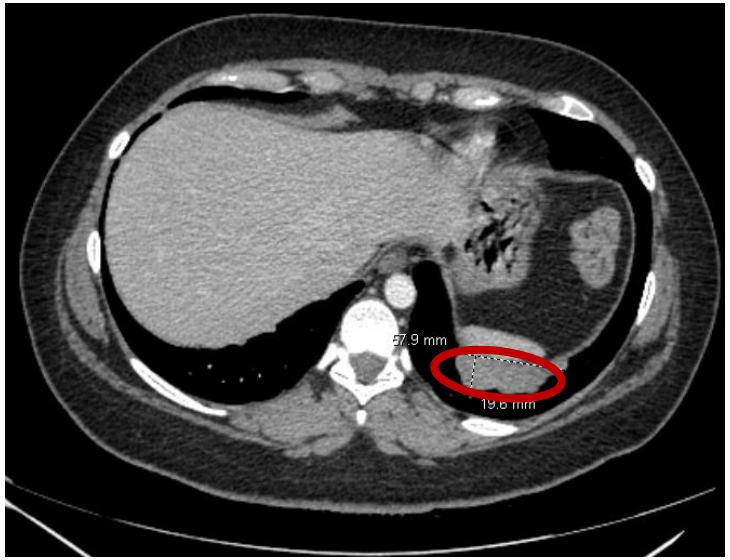

Data cut: March 8, 2025

At data cut, 4 patients were ongoing in treatment, but did not have their first scan yet. Patients are excluded from waterfall and are censored at study day 1 in PFS plot

NR, not reached; ORR, overall response rate; PFS, progression free survival

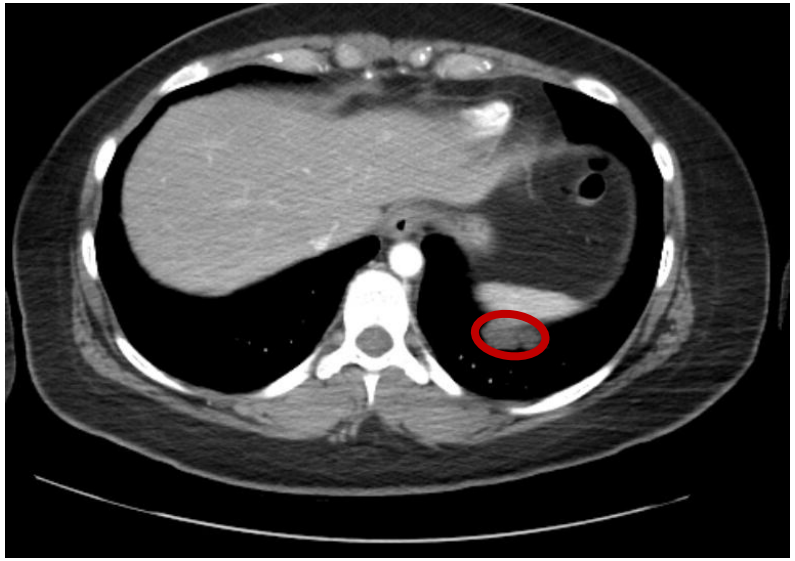
# ACC-I Patient Case*

Baseline




Left posterior lung base pleural nodularity measures 5.8 x 2.0 cm

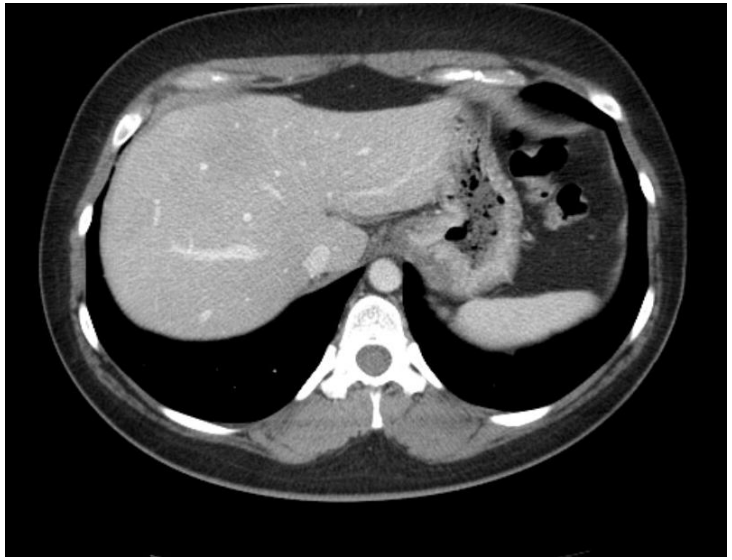
Cycle 2 Day 15



Left posterior lung base pleural nodularity measures 3.9 x 1.7 cm

Post Cycle 5

(post Mar 08 data cut)



No measurable disease in the chest

*Patient included in data presented on previous slide

# Conclusion

- Emi-Le is a B7-H4-directed Dolasynthen auristatin-F HPA ADC
- Preliminary data from the dose escalation portion of the ongoing Phase 1 trial suggest encouraging clinical activity and tolerability in the locally advanced/metastatic setting
  - In the intermediate dose range (38.1-67.4 mg/m$^2$), 31% ORR in evaluable patients with B7-H4 high expression; 44% ORR in evaluable B7-H4 high patients with ≤4 prior lines of therapy
  - In TNBC, Emi-Le exhibits promising preliminary anti-tumor activity, PFS and OS in patients with high B7-H4 expression who had previously received at least one topo-1 ADC; more favorable outcomes in patients with high B7-H4 expression and ≤4 prior lines of therapy in the locally advanced/metastatic setting
  - Evidence of encouraging preliminary anti-tumor activity and PFS in patients with ACC-I, 56% ORR (uPR + cPR)
- Further clinical development is ongoing in the dose expansion portion of the trial evaluating 2 doses in patients with locally advanced/metastatic TNBC who have received 1-4 prior lines of locally advanced/metastatic therapy, including at least one prior topo-1 ADC:
    - 67.4 mg/m$^2$ Q4W
    - 44.5 mg/m$^2$ on days 1 and 8 of the first 4-week cycle, followed by 80 mg/m$^2$ Q4W

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