Abstract 2564: Depletion of T-regulatory cells by denileukin diftitox-cxdl (E7777) in combination with pembrolizumab in relapsed/refractory (r/r) gynecologic malignancies: Phase I study results

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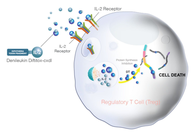
Background

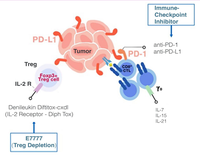
- Immunotherapies such as PD-1 checkpoint inhibitors have revolutionized how we manage oncology patients, contributing to an overall increase of life expectancy across multiple tumors.
- However, responses by single-agent checkpoint inhibitors remain limited, due to the complexities of the tumor microenvironment and dynamic immune system.
- Denileukin diftitox-cxdl (E7777 or LYMPHIR) is an IL-2 receptor-directed immunotoxin indicated for the treatment adult patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy[1]

Denileukin diftitox-cxdl (E7777) is an engineered IL-2-diphtheria toxin fusion protein with two proposed mechanisms of action through IL-2 receptor targeting

E7777 binds to the IL-2 receptor, internalizes, and exerts cytotoxic activity to tumor cells directly[2]



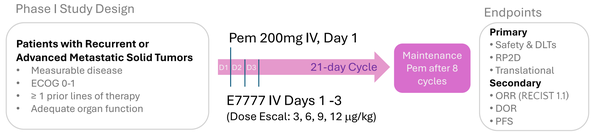
E7777 transiently eliminates immunosuppressive Treg cells, unleashing potent host immune responses[2]



- Published data demonstrated that the combination of E7777 (transient Treg depletion) + anti-PD-1 therapy resulted in synergistic activity in murine models.[5]
- In this study , we explore the combination of two distinct immunomodulatory agents (pembrolizumab and E7777) to determine their safety and tolerability in patients with recurrent or advanced solid tumors (focused on gynecologic neoplasms).

Methodology

Phase I Study Design



This is an open-label phase I/II study (NCT05200559), investigating the safety and efficacy of a combined regimen of the immune-checkpoint inhibitor pembrolizumab (Pem) with the T-regulatory cell depleting agent denileukin diftitox-cxdl (provided by Citius Oncology, Inc). The TITE-CRM method of dose assignment will be used, which will improve the quality of the assessment of potential toxicities better than the 3+3 method, and facilitate the evaluation of efficacy.

Patients diagnosed with recurrent or metastatic solid tumors in the 2L+ setting will receive E7777 given in 4 dose levels (DL) (iv 3-12 mcg/kg day 1-3) combined with pembrolizumab (iv 200 mg day 1) on a 21-day cycle for 8 cycles followed by maintenance pembrolizumab monotherapy. Dose limiting toxicities (DLT) were measured during cycle 1 (21 days) using CTCAE v5 criteria. Efficacy in terms of ORR were measured using RECIST 1.1 criteria.

Participants will be treated until disease progression or unacceptable toxicities and/or DLTs.

Safety will be evaluated in terms of dose-limiting toxicities and the frequency and severity of immune and non-immune mediated treatment-emergent adverse events (TEAEs).

Patient Characteristics

Number of Pts (ITT)		N=25
Median age (range)		64y (43, 88)
Sex		96% female
Race		88% white
Prior therapies, median (range)		5 (1-14)
Pts with prior anti-PD-1/L1		14 pts
Histology %	Endometrial	40%
	Ovarian	36%
	Other	24%
Stage at Diagnosis	Stage I	28%
	Stage II	4 %
	Stage III	24 %
	Stage IV	44 %
# Pts by Dose Level (DL)	DL1	4 pts
	DL2	2 pts
	DL3	6 pts
	DL4	13 pts

Safety: Reported Adverse Events

Safety Summary: E7777 + Pem

DLTs	Of the 24/25 pts evaluable for DLTs, only 1 case of reversible Gr 3 capillary leak syndrome (CLS) was seen at DL4, related to symptoms of dyspnea and edema
SAEs	A total of 16 serious adverse events (7 pts total) were associated with the E7777 + Pem treatment at DL4 (no Gr 4). These included GI related AEs (nausea, vomiting, and abdominal pain)
MTD	Maximum tolerated dose was not achieved
RP2D	Requires translational data assessment
irAEs	Limited immune-related AEs (≥ Gr 3) have been documented with this novel combination
Anemia	84% of patients experienced Gr 1-2 anemia

AEs by dose level (any attribution)	DL1	DL2	DL3	DL4	Total
Total #pts that experienced at least one AE	4	2	6	13	25
Total #pts that experienced at least one SAE	2	0	4	11	17
Total #pts at risk	4	2	6	13	25

Most Common Adverse Event (All grades ≥ 10 pts)	Total
Anemia	21
Fatigue	19
Chills	17
Hypoalbuminemia	15
Hypokalemia	15
Hypomagnesemia	15
Hyponatremia	15
Anorexia	14
Diarrhea	14
Nausea	14
Lymphocyte count decreased	13
Hyperglycemia	12
Vomiting	12
Alkaline phosphatase increased	11
Blood LDH increased	11

TRAE (SAEs)	Total	Dose Levels DL1-3	Dose Levels DL4	Grade Gr 3	Grade Gr 4
Hypoalbuminemia*	3	0	3	0	0
Nausea	2	0	2	2	0
Vomiting	2	0	2	2	0
Abdominal pain	1	0	1	1	0
Acute kidney injury	1	0	1	1	0
Bronchospasm	1	0	1	1	0
Diarrhea	1	0	1	1	0
Dyspnea	1	0	1	1	0
Generalized edema	1	0	1	1	0
Gen. muscle weakness	1	0	1	1	0
Hallucinations	1	0	1	1	0
Hyponatremia	1	0	1	1	0
Total	16	0	16	13	0

* All events were grade 2

Conclusions

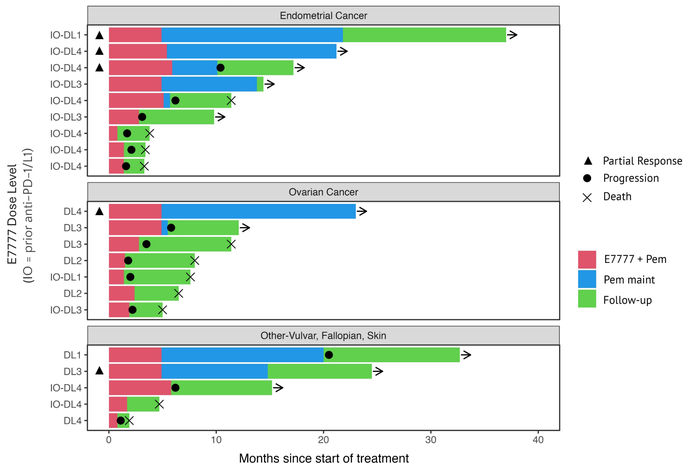
Denileukin diftitox-cxdl (E7777) + Pembrolizumab, in patients with advanced or refractory GYN tumors, was well tolerated and demonstrated promising durable efficacy, including in the prior-IO setting

- Treg depletion by E7777 plus PD-1 inhibition by Pem was overall well tolerated; there was one reversible DLT, no new safety signals or unexpected irAEs were reported
- mPFS of 20.5 mo (6.5. –NA) was demonstrated for the 10 pts (48%) who achieved a clinical benefit in this heavily pre-treated population
- Given the lack of effective salvage treatments for these patients, in particular in those that have failed prior immune-checkpoint inhibition, the novel combination of denileukin diftitox-cxdl plus pembrolizumab provides a potential viable therapeutic option.

Results: Responses & Clinical Benefit

Duration of Treatment and Individual Response:

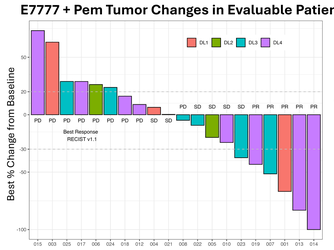
Denileukin Diftitox-cxdl (E7777) + Pembrolizumab Evaluable Patients (n=21)



IO = designates patients who had received prior anti-PD-1/L1; DL = dose levels

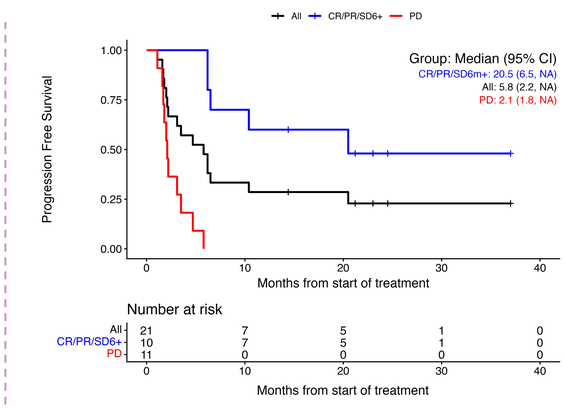
- ORR = 24%, from 21 evaluable pts across different tumors (5 PRs).
- **Pts with endometrial cancer that had prior IO exposure experienced a 33% ORR (including 1 pt with a > 3y response).**
- 10 (48%) of evaluable pts achieved a clinical benefit (CR, PR or SD ≥ 6 mo).
- median DOR - only 1 of the 5 PRs had progressed at time of analysis, therefore, the mDOR has not been reached. The current duration of response times (time since PR was achieved) is 4.2-35 months with a median of 21.1 months.

E7777 + Pem Tumor Changes in Evaluable Patients



- Responses were seen across all E7777 DLs, with the more pronounced changes from baseline observed at DL4. No responses were reported in 8 stage IV pts.

mPFS for Denileukin Diftitox-cxdl + Pembrolizumab



- The Kaplan-Meier median progression-free survival (mPFS) was 5.8 mo (2.2, NA) for the 21 evaluable pts
- mPFS of 20.5 mo (6.5, NA) was seen for the 10 pts (48%) who achieved a clinical benefit
- 5 patients had a PFS of > 20 months including 1 patient with > 30 months PFS

Future Directions

- A phase II expansion study is planned to test the benefit of this E7777 + Pem in different GYN tumors and settings (e.g. less heavily pre-treated or prior-IO).
- Given the lack of therapeutic options for endometrial cancer patients after immune-checkpoint inhibition therapy, we seek to explore this regimen's early signal in this patient population
- Ongoing translational studies are exploring the impact of this therapy on Tregs, host immuno-effector cells, and tumor microenvironment (TME); these studies may indicate possible biomarkers or other factors that may be associated with increased efficacy that can be tested in the planned Phase II study.

References: 1. LYMPHIR, Prescribing Information, Citius Pharma, Inc 2024; 2. Lansigan, F., et al. Cancer Manag Res, 2010. **2**: p. 53-9.; 3. Kaminetzky, D. and K.B. Hymes, Biologics, 2008. **2**(4): p. 717-24.; 4.Tsuneoka M, et al., J Biol Chem, 1993. 268(35): p. 26461-5.; 5. Schuster M, et al., Scientific Reports, 2017. 7(1): p. 613; **6**. Maiden, H., el al. Frontiers in Immunology, 2023

Terms and abbreviations (alphabetical): AE (Adverse Event), Clinical benefit (Pts who achieved a CR, PR or durable stable disease of ≥ 6 mo), DL (Dose Level), DLT (Dose Limiting Toxicities), IO (immuno-oncology treatment), irAEs (immune-related adverse events), TRAE (treatment-related adverse event) ITT (intent to treat), PR (partial response, documented following 3rd cycle of combination Tx), ORR (overall response rate), Patients (pts), PR (partial response) PD (progression of disease), SD (stable disease), SD6 (stable disease ≥ 6 mo), PFS (progression-free survival)

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