Safety and Tolerability of E7777 (improved purity Denileukin diftitox [ONTAK]) in Patients with Relapsed or Refractory Cutaneous T-cell Lymphoma: Results from Pivotal Study 302

Miles Prince1, MD, FRCPA, Larisa J Geskin2, MD, Oleg E Akilov3, MD, Ph.D, Timothy M. Kuzel4, MD, FACP, Christiane Querfeld5, MD, Ph.D., Chean Eng Ooi6, Ph.D., Dongyuan Xing6, Ph.D., Nicholas Sauter6, MD, Preeti Singh7, MD, Myron Czuczman7, MD, Francine Foss8, MD

1Department of Haematology, Peter MacCallum Cancer Centre, Melbourne, Australia 2Department of Dermatology, Columbia University Medical Center, NY; 3Cutaneous Lymphoma Program, University of Pittsburgh, Pittsburgh, PA; 4Department of Medicine, Division Hematology/Oncology/Cell Therapy, Rush University Medical Center, Chicago, IL 5 Department of Dermatology, City of Hope Comprehensive Cancer Center, Duarte, CA; 6Eisai Inc., Nutley, NJ;7Citius Pharmaceuticals, Cranford, NJ; 8Yale Cancer Center, Yale Medical Group, New Haven, CT

INTRODUCTION

- Denileukin diftitox (Dd), a recombinant fusion protein composed of diphtheria toxin fragments and human interleukin-2 was approved and marketed (as ONTAK) in the US from 1999-2014 for the treatment of relapsed/refractory CTCL.
- Manufacturing improvements (to decrease the presence of misfolded and aggregated proteins) resulted in a new, more bioactive formulation, E7777.
- E7777 has ~1.5-2 times greater specific bioactivity in non-clinical assays compared with ONTAK and it is considered a new drug by the FDA requiring a new registrational clinical trial.
- E7777 directly targets both malignant T-cells and immunosuppressive Tregs via binding to the IL-2 receptor on these cells
- Study 302 (NCT01871727) is a multicenter, open-label, single-arm registrational trial in which the primary efficacy and safety of E7777 were assessed. Here, we report the safety results of E7777.

METHOD

- E7777 was given at 9 mcg/kg/day for 5 days every 21 days up to 8 cycles; premeds included acetaminophen, diphenhydramine, antiemetics, and 250-500cc saline IV pre- and post-E7777; steroids added only in case of infusion reaction
- Key inclusion/exclusion criteria included histopathologic diagnosis of CTCL (MF or SS); Stages I to IV; ≥ 1 prior CTCL therapy; ECOG performance status 0 or 1; CD25 assay-positive tumor; no prior exposure to ONTAK.
- Study accrued Stage I-IV (n=112) and here we present Stage I-III 9 ug/kg dose (n=69) which is primary efficacy analysis set. Evaluation of safety included incidence and severity of treatment-emergent AEs (TEAEs), and adverse events of special interest (AESIs).
- Key AESIs include capillary leak syndrome (CLS), infusion reaction, visual impairment (these three AEs were listed as Box warnings in the ONTAK label); and hepatotoxicity

RESULTS

- The Primary Efficacy endpoint [Stage I-III; n=69], ORR (95% CI) by IRC, was 36.2% (95% CI: 25.0%, 48.7%), with 8.7% achieving a complete response; detailed efficacy data is being presented as an oral presentation at this meeting:
  Publication #618; Session 624 on Sunday, Dec 11, 2022 at 5:45 pm
- In the Primary Efficacy Analysis Set patients with I-III disease (n=69), the median age was 64 years and the median number of E7777 cycles received was 6 (range 1 to 42); 66 patients had mycosis fungoides and 3 had Sezary syndrome, and 39 (57%) had disease of stage IIb or worse; patients were heavily pretreated with a median of 4 prior therapies.
- The most common TEAEs were: nausea (43.5%); fatigue (31.9%); and increased ALT, chills, and peripheral edema (27.5%) each
  - Thirty patients (43.5%) had a Grade ≥3 TEAE (90% Grade 3; 10% Grade 4)).
  - The most common serious AEs (≥ 5%) were capillary leak syndrome (10%) and infusion reactions (9%).
  - Mean numbers of TEAEs per subject were higher in the first 1 to 2 treatment cycles.
- Most patients [92.8%] had at least 1 TEAE (mostly Grade 1/2).
- 22 patients (31.9%) experienced AEs that were Grade ≥3; (11.6%) had drug discontinuation; (4.3%) had drug dose reduction, and (37.7%) had drug dose interruption.
- Fourteen patients (20.3%) had CLS (defined as the occurrence of at least 2 of the following: hypotension, edema, or serum albumin < 3.0 g/dL)
  - Grade 1 in 2.9%, Grade 2 in 11.6%, Grade 3 in 4.3%, and Grade 4 in 1.4%.
  - Nine patients (13.0%) underwent drug modification: (4.3%) discontinued E7777; and (10.1%) had either dose reduction or temporary dose interruption.
  - CLS typically occurred in the first 1/2 cycles
- Risk/severity of CLS was mitigated by fluid management; confirmation of serum albumin levels (≥ 3.0 g/dl); close monitoring of weight, edema, and BP; early drug interruption; and rapid initiation of diuretic therapy on recovery.
- Fifty-one patients (73.9%) had an AESI related to infusion reaction.
  - Grade 1 in 43.5%, Grade 2 in 26.1%, and Grade 3 in 4.3%.
  - One patient (1.4%) had study drug discontinuation, and (11.6%) had either study drug dose reduction or interruption; systemic corticosteroids may be added to premedication for subsequent E7777 infusions.
- Nine patients (13.0%) had an event related to visual impairment; all were AEs of blurred vision, which was Grade 1 in 11.6% and Grade 2 in 1.4%; no Grades 3, 4, or 5. One patient (1.0%) had drug interruption; no events led to study drug dose reduction
- Twenty-five patients (36.2%) had AESI related to hepatoxicity
  - Grade 1 in 17.4%, Grade 2 in 7.2%, Grade 3 in 11.6%, and no Grade 4/5
  - Majority of hepatic adverse events were elevations in transaminases that occurred within the first or second cycle, resolved without medical intervention, and did not require treatment discontinuation

Table 1: Overview of Treatment-Emergent Adverse Events of Special Interest for E7777

AESI Preferred Term	E7777 9 µg/kg (N=69) n (%)	
	Any Grade	Grade ≥3
Capillary leak syndrome	14 (20.3)	4 (5.8)
Infusion Reaction	51 (73.9)	3 (4.3)
Visual Impairment	9 (13.0)	0 (0.0)
Hepatotoxicity	25 (36.2)	8 (11.6)

Figure 1: Capillary Leak syndrome occurrence over the treatment period

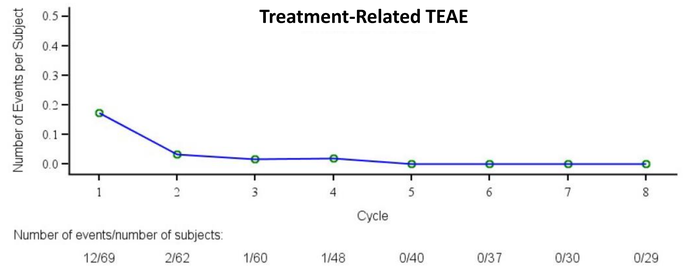
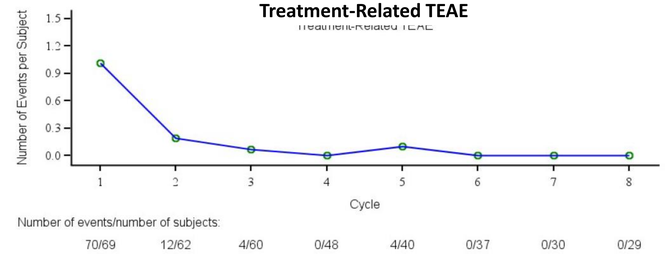


Figure 2: Infusion reaction occurrence over the treatment period



CONCLUSIONS

- No new safety signals were observed with E7777 when compared to the safety profile of ONTAK.
- There is no evidence of cumulative toxicity. Most patients had at least 1 TEAE which were mostly Grade 1/2.
- Specific AESIs: CLS, infusion reactions, and visual impairment (prior ONTAK Box warnings) were mostly Grade 1/2 and effectively managed.
- AESIs mostly occurred in cycle 1 and 2
- Overall, E7777 was well-tolerated with the use of pre-medications, close patient monitoring, and prompt initiation of supportive measures and drug management.

ACKNOWLEDGEMENTS

This study was funded by Citius Pharma Inc. The authors would like to thank the patients, their families and caregivers, and all investigators involved in this study.