City of Hope

International Society for Cutaneous Lymphomas ISCL

5TH World Congress of Cutaneous Lymphomas

Enhancing the Ability to Diagnose, Interpret and Apply Best Treatment Options for Cutaneous Lymphomas

Therapeutics/Preclinical Studies

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

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Disclosures

- Consultant and Honorarium for Kyowa Kirin, Mallinckrodt Pharmaceuticals, MundiPharma, and Takeda Pharmaceuticals.
- On the Speakers Bureau for Mallinckrodt Pharmaceuticals, and Takeda Pharmaceuticals.

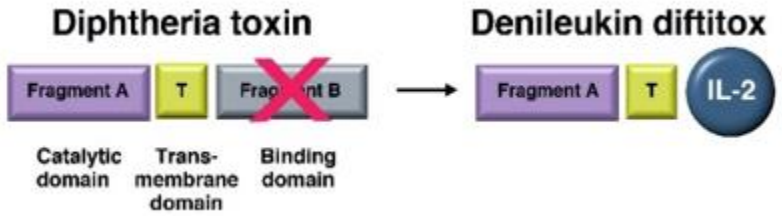
This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of denileukin diftitox will be addressed.

Introduction



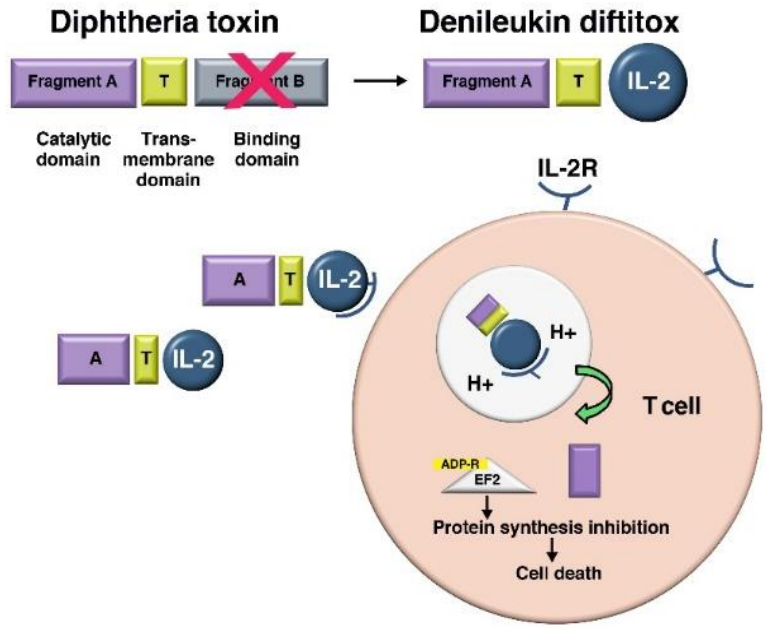
- Denileukin diftitox (Dd), a recombinant fusion protein composed of diphtheria toxin fragments and human interleukin-2 was approved
- marketed in the US from 1999-2014 for the treatment of relapsed/refractory CTCL
- Manufacturing improvements (to decrease the presence of misfolded and aggregated proteins) resulted in a new, more bioactive formulation[1], E7777
    - E7777 has ~1.5-2 times greater specific bioactivity in non-clinical assays compared with this.
    - considered a new drug by the FDA requiring a new registrational clinical trial
- 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 – clinical results presented at this meeting
    - Efficacy and Safety of E7777 (improved purity Denileukin diftitox) in Patients with Relapsed or Refractory Cutaneous T-cell Lymphoma: Results from Pivotal Study 302

1. Prince, et al. J Clin Oncol 2010; 28: 1870-1877. IRC: Secondary Endpoint

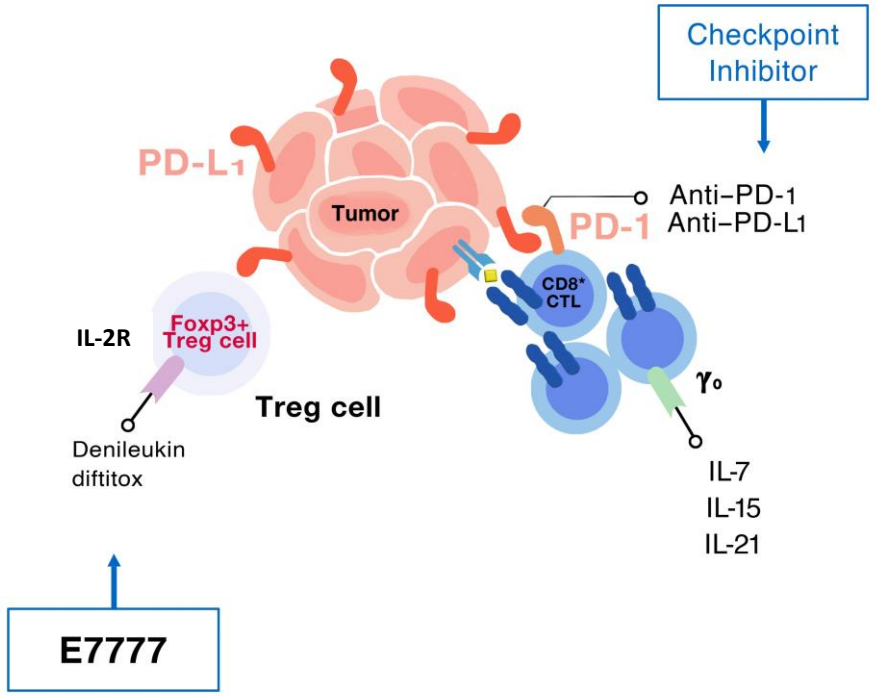
How it works: Novel immunotherapy with differentiated MOA

E7777 is an engineered IL-2-diphtheria toxin fusion protein with a differentiated mechanism of action supporting two therapeutic effects

Binds to IL-2 receptor to kill tumor cells directly



Eliminates Immunosuppressive Tregs*



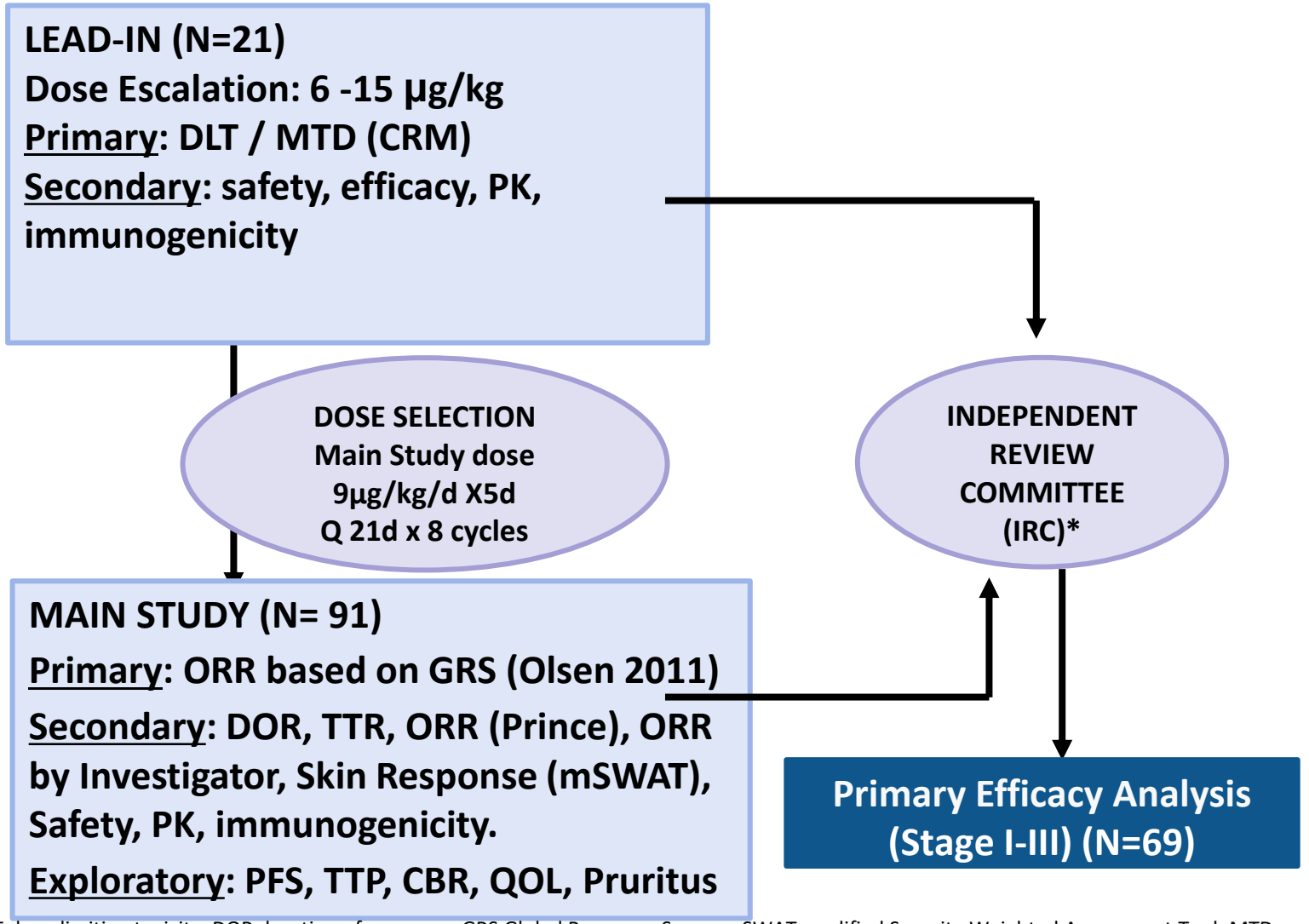
Mahdi, et al. Targeting regulatory T cells by E7777 enhances CD8 T-cell–mediated anti-tumor activity and extends survival benefit of anti-PD-1 in solid tumor models. Front Immunol. 2023; 14: 1268979

Multi-center open label single arm registrational trial of E7777 in relapsed/refractory CTCL

Study 302 (NCT01871727

STUDY POPULATION N=112*

- Age ≥ 18
- Recurrent or Persistent CTCL (MF or SS) Stage I-IV
- CD25+ Tumor
- ≥ 1 prior CTCL therapy
- No prior denileukin diftitox
- ECOG 0-2
- Adequate organ function



* Stage IV patients were enrolled but not included in primary efficacy analysis, in order to match Study 11 that led to its full approval. Investigator-assessed response data was also collected.

CBR clinical benefit rate; CRM continual reassessment method; DLT dose-limiting toxicity; DOR duration of response; GRS Global Response Score; mSWAT modified Severity Weighted Assessment Tool; MTD maximum tolerated dose; ORR objective response rate; PK pharmacokinetic(s); QoL Quality of Life; TTP time to progression; TTR time to response

Safety and tolerability assessment

- Evaluation of safety included:
  - incidence and severity of treatment-emergent AEs (TEAEs), and
  - adverse events of special interest (AESIs)
    - *capillary leak syndrome (CLS)*,*
    - *infusion reaction*,*
    - *visual impairment*,*
    - *hepatotoxicity*

**these three AEs were listed as Box warnings in the label*

Patient Demographics

Primary Efficacy Analysis Set (n=69)

Category	E7777 9 µg/kg (N = 69), n (%)
Age (years)	
n	69
Median (range)	**64.0 (28-87)**
Age Group (years), n (%)	
< 65 years	35 (50.7)
≥ 65 years	34 (49.3)
Sex, n (%)	
Male	45 (65.2)
Female	24 (34.8)
Race, n (%)	
White	50 (72.5)
Black or African American	13 (18.8)
Asian or Other	5 (7.2)
Missing	1 (1.4)

CTCL Type	E7777 9 µg/kg (N = 69), n (%)
Mycosis Fungoides	66 (95.7)
Sezary Syndrome	3 (4.3)
CTCL Disease Stage	
IA	5 (7.2)
IB-IIA	25 (23.2)
IIB	24 (34.8)
IIIA	8 (11.6)
IIIB	7 (10.1)
Prior Therapies (median =4)	
1-2	13 (18)
3-4	26 (24)
5-7	18 (26)
8+	12(17)

Primary Efficacy Outcome

- **Primary Efficacy Assessment [Stage I-III; n=69]*:**
  - median age was 64 years
  - 66 patients had Mycosis Fungoides and 3 had Sezary Syndrome
  - 39 (57%) had disease of stage IIb or higher
  - median number of E7777 cycles received was 6 (range 1 to 42)
  - The median number of infusions per cycle was 4.88
  - **ORR** (95% CI) by IRC, was **36.2%** (25.0%, 48.7%),
  - CR: 8.7%

*Full detailed efficacy data is being presented as an oral presentation at this meeting

Overall TEAEs

- 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 adverse events (≥ 5%) were capillary leak syndrome (10%) and infusion reactions (9%)
- Overall, the mean numbers of TEAEs per subject were higher in the first 1 to 2 treatment cycles
- Most patients [92.8%] had at least 1 AESI (mostly Grade 1/2)
- 22 patients (31.9%) experienced AESIs that were Grade ≥3; (11.6%) had drug discontinuation; (4.3%) had drug dose reduction, and (37.7%) had drug dose interruption

Overview of Treatment-Emergent Adverse Events of Special Interest (AESI)

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)
Hypersensitivity	47 (68.1)	9 (13.0)
Infection	8 (11.6)	8 (11.6)
Rash	12 (17.4)	2 (2.9)
Thrombotic event	1 (1.4)	0 (0.0)

Capillary leak syndrome was defined as a single preferred term and/or any 2 preferred terms that are related to edema, hypotension, and decreased albumin within a cycle; hypersensitivity may have overlapping preferred terms based on their definition, but the occurrence was differentiated by the number of days from the receipt of the study drug: plus 5 days from each dose

Capillary Leak Syndrome (CLS)

- Fourteen patients (20.3%) had CLS. CLS was defined as the occurrence of at least 2 of the following: hypotension, edema, or serum albumin < 3.0 g/dL
- CLS was 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

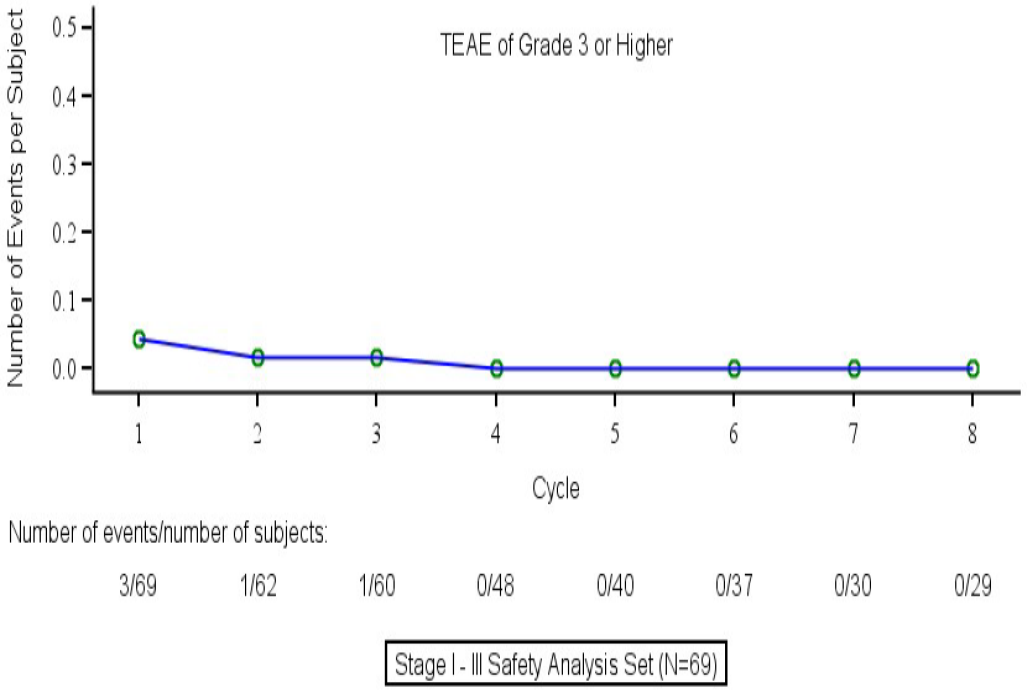


Figure 1: Number of Treatment-Emergent Capillary Leak Syndrome Adverse Events per Subject by Cycle

Infusion Reactions

- Fifty-one patients (73.9%) had an AESI related to infusion reaction
    - Grade 1 in 43.5%,
    - Grade 2 in 26.1%
    - Grade 3 in 4.3%.
- One patient (1.4%) had study drug discontinuation, and (11.6%) had either study drug dose reduction or interruption. In the event of infusion-related reactions, systemic corticosteroids could be added to premedication for subsequent E7777 infusion

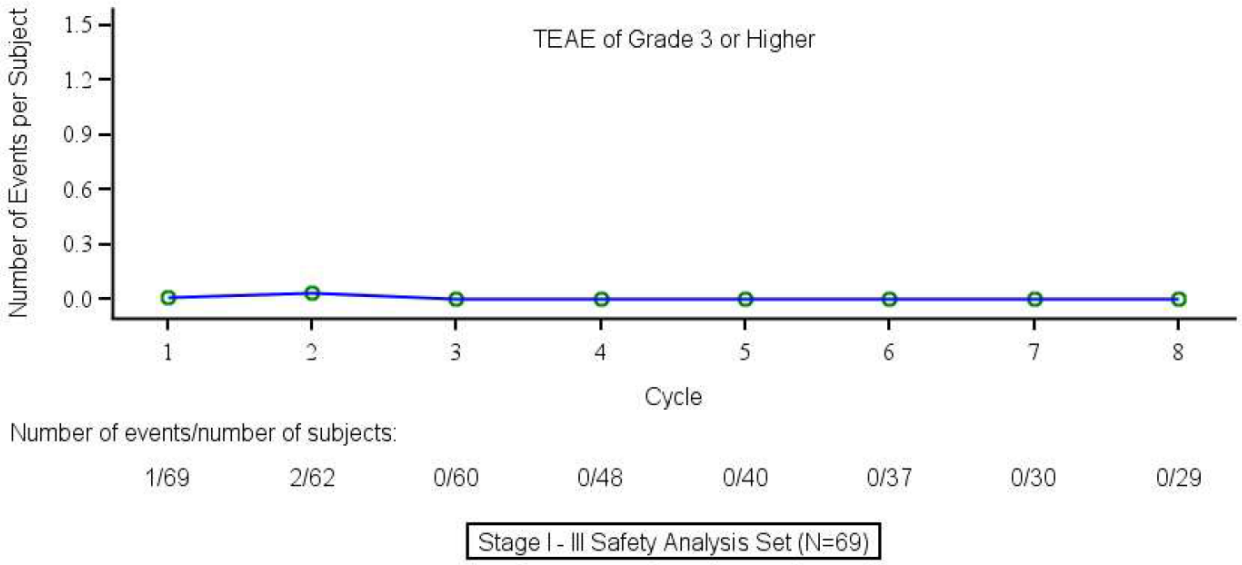


Figure 2: Number of Treatment-Emergent Infusion Reaction Adverse Events per Subject by Cycle

Visual Impairment

- 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

Hepatotoxicity

- Twenty-five patients (36.2%) had AESI related to hepatoxicity. The TEAEs were
  - 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

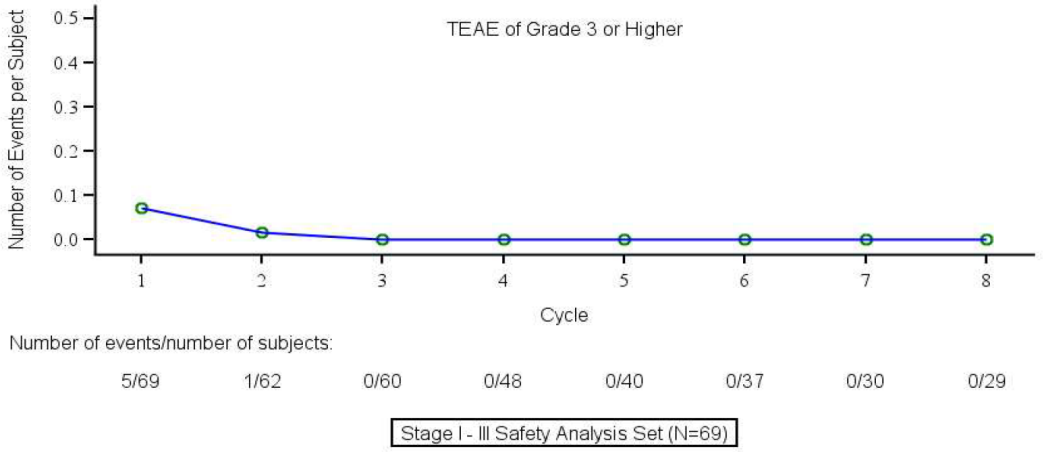


Figure 3: Number of Treatment-Emergent Alanine Aminotransferase Increased Adverse Events per Subject by Cycle

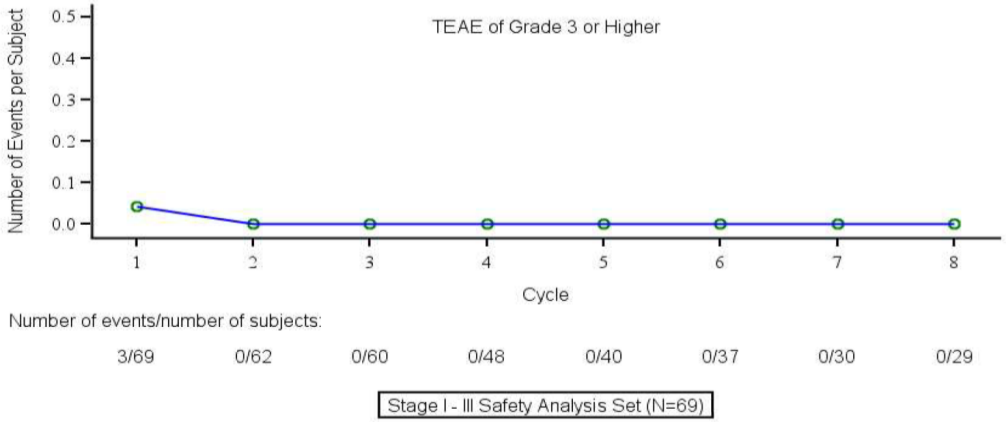


Figure 4: Number of Treatment-Emergent Aspartate Aminotransferase Increased Adverse Events per Subject by Cycle

Conclusions

- No new safety signals were observed with E7777 when compared to the safety profile of denileukin diftitox
- There is no evidence of cumulative toxicity; most patients had at least 1 TEAE (primarily Grade 1 or 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 cycles 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

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Thank you!

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