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

Abstract 189

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

Francine Foss, MD

Professor of Medicine, Hematology and Stem Cell Therapy

Yale University School of Medicine

New Haven, CT 06517

Disclosures

- Consultant/Advisor for Kyowa Kirin, and Secura Bio.
- Grant/Research Support from Astex Pharmaceuticals, and Daiichi-Sankyo

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.

Introduction

- Relapsed or refractory CTCL is an incurable disease

- Denileukin diftitox (Dd) is a recombinant fusion protein of diphtheria toxin and human interleukin-2

- Dd was approved in the US from 1999-2014 for the treatment of patients with relapsed/refractory CTCL

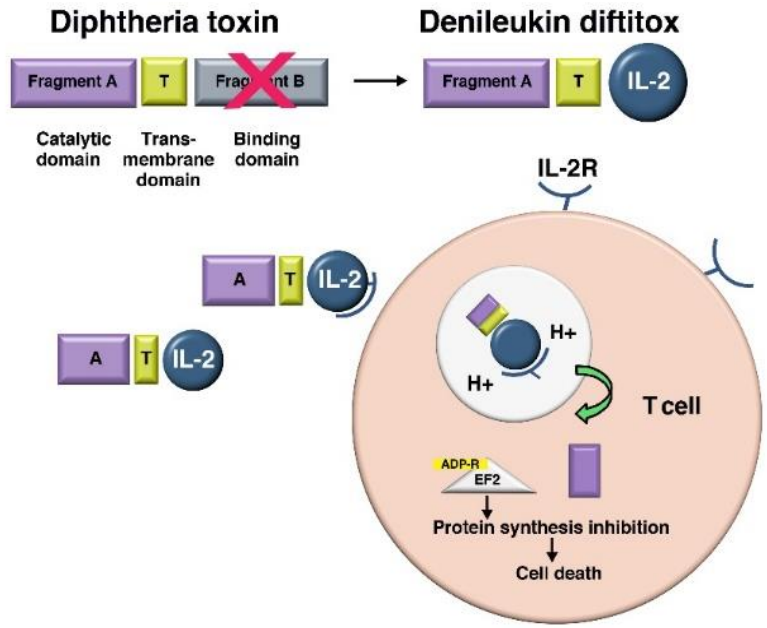
- It was voluntarily taken off the market in 2014 due to manufacturing issues

- E7777 is a reformulated version with ~1.5-2 times greater specific bioactivity in non-clinical assays and is considered a new drug entity by the FDA

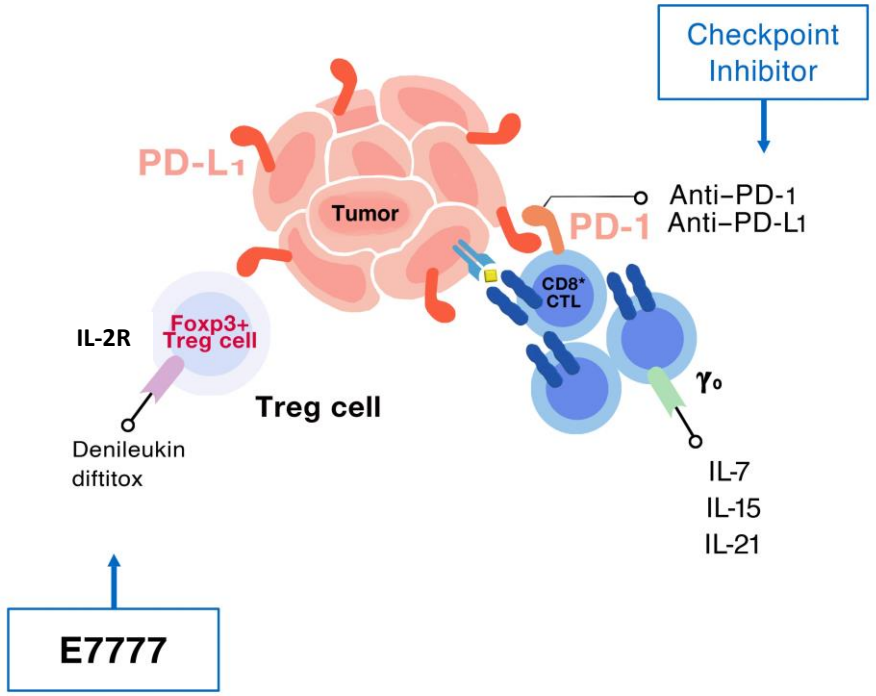
How it works: Novel immunotherapy with differentiated MOA

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*

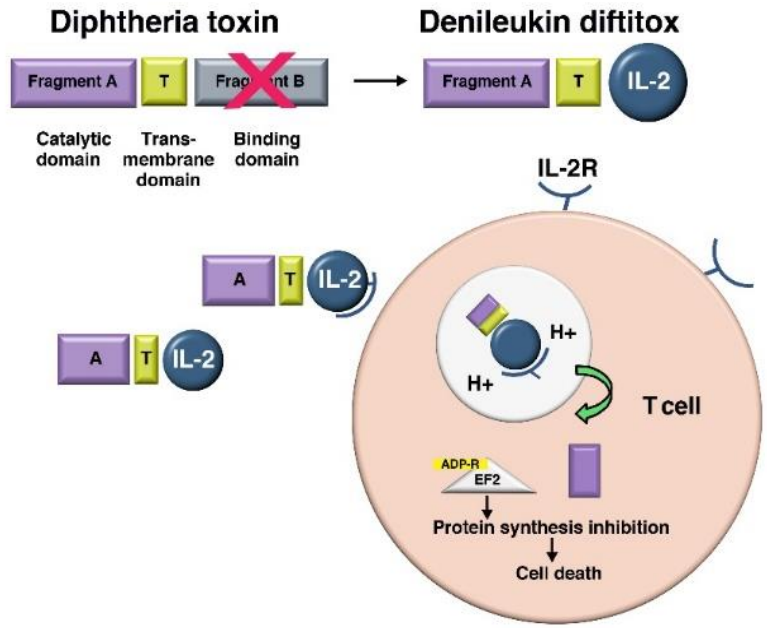


Mahdi, et al. Targeting regulatory T cells by E7777 enhances CD8 T-cell–mediated anti-tumor activity and extends survival benefit of anti-PD-1 in solid tumor models. Front Immunol. 2023; 14: 1268979

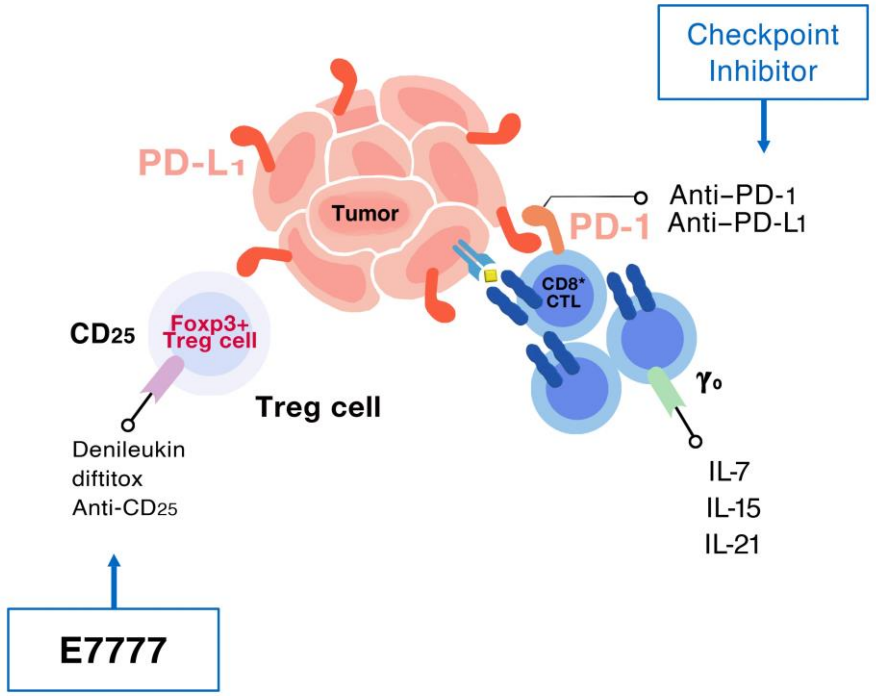
How it works: Novel immunotherapy with differentiated MOA

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*



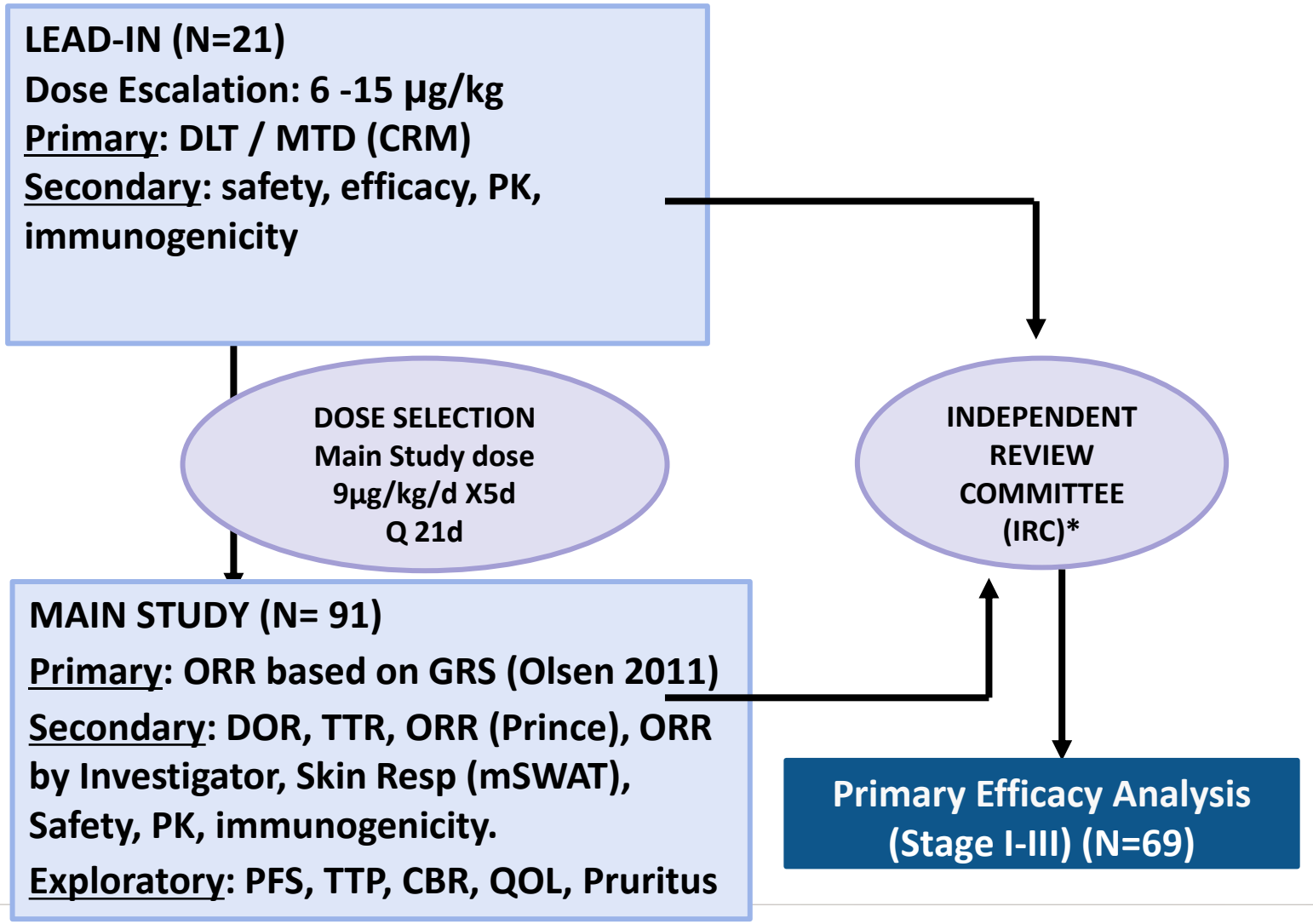
Woodall-Jappe M, et al. E7777 (denileukin diftitox) enhances anti-tumor activity and significantly extends survival benefit of anti-PD-1 in syngeneic solid tumor models (Poster 894). Society for Immunotherapy of Cancer's (SITC) Virtual Conference, 09-14 November 2020.

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.

E7777-Study 302 - Objectives

- **Primary Objective**
  - To demonstrate efficacy in recurrent or persistent Stage I - III CTCL as assessed by ORR; Objective Response defined as CRs plus PRs, per ISCL/EORTC Global Response Score (Olsen 2011)[1]

- **Secondary objectives**
  - To determine DOR, TTR, skin response, duration of skin response, time to skin response, and ORR using alternate criteria (Prince, 2010)[2]
  - To evaluate safety and tolerability in all subjects
  - To evaluate safety and tolerability in Stage I-III Main Study subjects plus Stage I-III subjects from Lead-In 9 µg/kg combined
  - Exploratory objectives included progression-free survival (PFS), time to progression (TTP), pruritus improvement, and quality of life assessment

1. Olsen, et al. J Clin Oncol 2011; 29: 2598-2607.IRC: Primary Endpoint, Investigator: Secondary Endpoint
2. Prince, et al. J Clin Oncol 2010; 28: 1870-1877. IRC: Secondary Endpoint

Statistical Analyses

- **Two-sided 95% confidence interval (CI) is calculated using Clopper-Pearson method for binary endpoints including:**
  - ORR per Olsen criteria (2011) by IRC, Investigator, and Prince assessment
  - Skin response (based on mSWAT) per Olsen criteria (2011)
  - As per FDA guidance, *E7777 would be considered efficacious and demonstrate clinical benefit if the lower limit of the 2-sided 95% exact confidence interval (CI) of the observed ORR exceeds 25.0%, as determined by the Independent Review Committee (IRC)*

- **Kaplan-Meier method is used for time-to-event endpoints including:**
  - Duration of Response (DOR) in subjects with confirmed response
  - Time-to-Response (TTR) in subjects with confirmed response
  - Progression-Free Survival (PFS)

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)

Treatment Disposition (n=69)

Category	E7777 9 µg/kg (N = 69) n (%)
Treatment Ongoing at Data Cutoff Date	2 (2.9)
Completed 8 cycles per Protocol	12 (17.4)
Discontinued Treatment	55 (79.7)
Progression	28 (40)
Adverse Event	7 (10.1)
Subject Choice	7 (10.1)
Administrative/Other	19 (27)
Withdrawal of Consent	6 (8.7)
Completed Treatment or Discontinued Treatment but on Survival Follow-Up at Data Cutoff	5 (7.2)

Disease progression: was confirmed by Global Response Score (Olsen [2011]) …or…

Clinical progression: was progression that was not confirmed by GRS (eg, worsening of symptoms without progression by GRS, or increase in the thickness of skin lesions that was not captured by the mSWAT score)

Primary Efficacy Outcome

- **The main efficacy outcome measure was objective response rate (ORR), *as assessed by an Independent Review Committee (IRC) using Olsen (2011) criteria***
- **The ORR was 25/69 (36.2%),** 95% exact CI: (25.0%, 48.7%)

	Independent (IRC) Primary Efficacy Analysis Set (N = 69)	**Investigator Stage I-III Efficacy Analysis Set (N = 71)***
Best Overall Response Based on GRS, n (%)		
Complete Response (CR)	6 (8.7)	6 (8.5)
Partial Response (PR)	19 (27.5)	24 (33.8)
Stable Disease (SD)	36 (52.2)	33 (46.5)
Progressive Disease (PD)	3 (4.3)	4 (5.6)
Unknown	5 (7.2)	4 (5.6)
Objective Response Rate (CR + PR), n (%)	**25 (36.2)**	**30 (42.3)**
95% CI	(25.0, 48.7)	(30.6, 54.6)

**Two subjects were classified as having visceral disease (Stage IV) at baseline by the IRC which was discordant to initial investigator assessment*

Overall Response in Skin by mSWAT

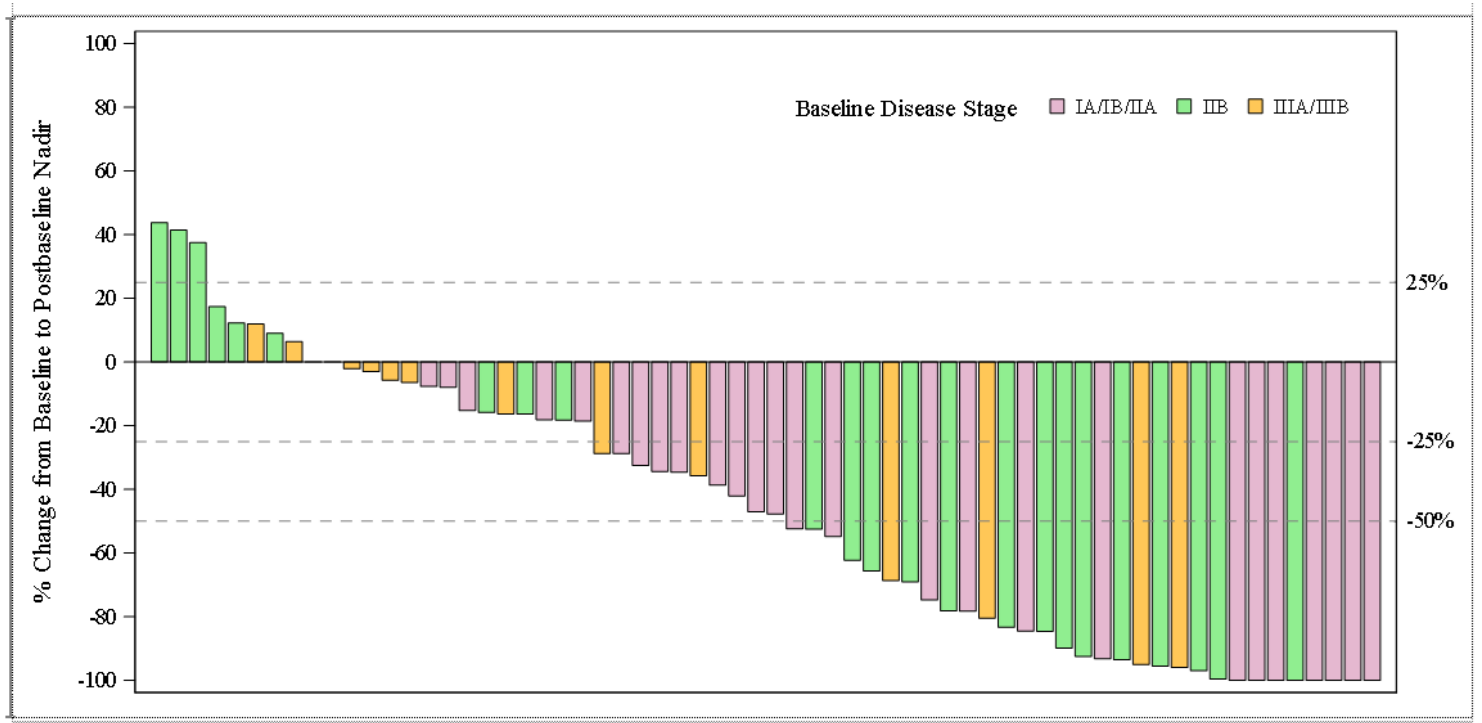
Of 64 evaluable subjects, 54 (84.4%) had a decrease in skin tumor burden

31 (48.4%) had a maximum decrease from baseline of ≥50%

8 of 64 subjects (12.5%) achieved a CR

Skin burden reductions were achieved across all stages

Waterfall Plot for Skin Tumor Burden (mSWAT Score) by IRC per Olsen 2011



This plot represents each subject's percent change in mSWAT score from baseline to postbaseline nadir.
Out of 69 subjects, 64 subjects who have baseline and at least one postbaseline mSWAT scores are included.
mSWAT = modified Severity Weighted Assessment Tool.

Summary of Tumor Response

by Baseline CTCL Stage per IRC (Olsen)

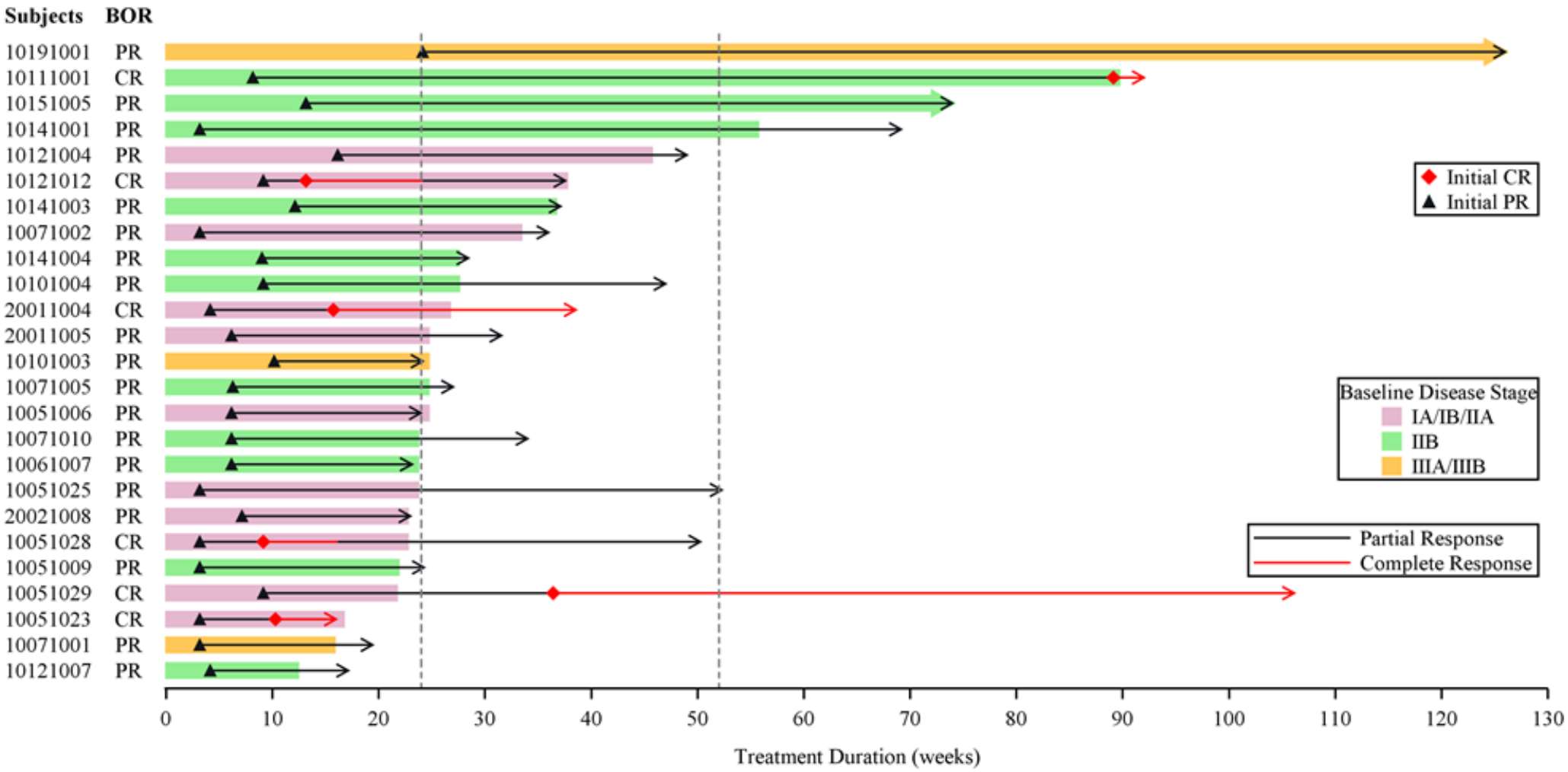
Primary Efficacy Analysis Set (n=69)	CTCL Disease Stage at Study Entry		
	IA/IB/IIA (N = 30)	**IIB (N = 24)**	**IIIA/IIIB (N = 15)**
Best Overall Response Based on GRS, n (%)			
Complete Response (CR)	5 (16.7)	1 (4.2)	0 (0.0)
Partial Response (PR)	6 (20.0)	10 (41.7)	3 (20.0)
Stable Disease (SD)	17 (56.7)	9 (37.5)	10 (66.7)
Progressive Disease (PD)	0 (0.0)	3 (12.5)	0 (0.0)
Unknown	2 (6.7)	1 (4.2)	2 (13.3)
Objective Response Rate (CR + PR), n (%)	**11 (36.7)**	**11 (45.8)**	**3 (20.0)**
95% CI	(19.9, 56.1)	(25.6, 67.2)	(4.3, 48.1)
Clinical Benefit Rate (CR + PR + Durable SD*), n (%)	**18 (60.0)**	**13 (54.2)**	**3 (20.0)**
95% CI	(40.6, 77.3)	(32.8, 74.4)	(4.3, 48.1)

Duration of Response

- **Observed median DOR was 6.47 months**

- **13/25 (52%) of responders had duration of response ≥ 6 months**
- **5/25 (20%) had duration of response ≥ 12 months**

Swimmer Plot per IRC n=25 (Olsen, 2011)



Characteristics of Responders

	IRC Assessment (N = 69)	Inv. Assessment (N = 71)
Time to Response (months)		
Subjects with Objective Response (n)	25	30
Median (Min,max)	1.41 (0.7, 5.6)	1.41 (0.7, 9.5)
No. Subjects with Time to First Objective Response Occurring after No. of Treatment Cycles Indicated, n (%)		
1	9 (36.0)	10 (33.3)
2	8 (32.0)	11 (36.7)
3	4 (16.0)	3 (10.0)
≥ 4	4 (15.0)	6 (20.0)
Clinical Benefit Rate (CR + PR + Durable SD*), n (%)	**34 (49.3)**	**38 (53.5)**
95% CI	(37.0, 61.6)	(41.3, 65.5)

Patients receiving any of the following agents (romidepsin, brentuximab, or mogamulizumab) had a similar ORR by IRC compared to patients who did not receive these agents.

E7777 Administration and Treatment Duration

Category	Stage I-III Safety Set E7777 9 µg/kg (N = 69) n (%)
Cumulative No. of Cycles Received, n (%)	
Median	**6.0**
Range in cycles (Min, Max)	1, 42
1 - 4	29 (42.0)
5 - 8	21 (30.4)
≥ 9	19 (27.5)
≥ 16	4 (5.8)
Overall Number of Infusions per Cycle	
Median	4.88

Overview of Treatment-Emergent AEs

Category	E7777 9 µg/kg (N = 69)
Subjects with Any TEAE	68 (98.6)
Subjects with Any TEAE with Worst CTCAE Grade of	
≥ 3	30 (43.5)
3	27 (39.1)
4	3 (4.3)
5	0 (0.0)
Subjects with Any Serious TEAE	26 (37.7)
Fatal Serious TEAE	0 (0.0)
Non-fatal Serious TEAE	26 (37.7)
Subjects with Any TEAE Leading to Drug Adjustment	29 (42.0)
Study Drug Discontinuation	8 (11.6)
Study Drug Dose Reduction	3 (4.3)
Study Drug Interruption	26 (37.7)

TEAEs in ≥ 15%, Overall and ≥ Gr 3 (n=69)

Preferred Term	Any Grade	Grade ≥3
Subjects with Any TEAE	68 (98.6)	30 (43.5)
Nausea	30 (43.5)	1 (1.4)
Fatigue	22 (31.9)	0 (0.0)
Alanine aminotransferase increased	19 (27.5)	6 (8.7)
Chills	19 (27.5)	1 (1.4)
Peripheral edema	19 (27.5)	1 (1.4)
Aspartate aminotransferase increased	18 (26.1)	3 (4.3)
Infusion related reaction	17 (24.6)	4 (5.8)
Headache	16 (23.2)	0 (0.0)
Diarrhea	13 (18.8)	0 (0.0)
Pruritus	13 (18.8)	4 (5.8)
Capillary leak syndrome*	12 (17.4)	4 (5.8)
Pyrexia	11 (15.9)	1 (1.4)
Hypoalbuminemia	10 (14.5)	0 (0.0)
Decreased appetite	9 (13.0)	1 (1.4)
Constipation	8 (11.6)	0 (0.0)

* Capillary leak syndrome is defined as a single preferred term or at least 2 of the following symptoms: hypotension, edema, or serum albumin < 3.0 g/dL within a cycle.

Conclusions

- Relapsed or refractory CTCL represents an incurable orphan disease
- E7777 targets the IL-2 receptor (on malignant T-cells and Tregs)
- E7777 at a dose of 9 mcg/kg/day x 5 days every 3 weeks was associated with an ORR of 36.2% per IRC (42.3% by investigator assessment)
- Observed median response duration was 6.4 months
- No new safety signals (compared to prior studies); no cumulative toxicity
- Adverse events of special interest (AESI) (i.e., CLS, acute infusion reactions, vision impairment, elevated LFTs) were primarily limited to Cycles 1,2
- E7777 would potentially fulfill a serious unmet medical need (if approved) for relapsed/refractory CTCL patients

Acknowledgements

- ***We thank the patients, their families and caregivers who participated in this clinical trial***
- ***Study investigators and sites***

- Oleg Akilov MD PhD, Univ of Pittsburgh; Pamela Allen MD, Emory University; Fernando Cabanillas MD, Univ of Puerto Rico; Nam Dang MD PhD, Univ Florida; Madeleine Duvic MD, MD Anderson Cancer Center; Tatyana Feldman MD, Hackensack Univ Med Ctr; David Fisher MD, Dana Farber Cancer Institute; Francine Foss MD, Yale University; Larisa Geskin MD, Columbia University; James Grichnik MD PhD, Univ South Florida; Auris Huen MD, MD Anderson Cancer Center; Youn Kim MD, Stanford University; Timothy Kuzel MD, Rush University; Lauren Pinter-Brown MD, Univ California Irvine; H. Miles Prince MD PhD, Peter MacCallum Cancer Center, Melbourne; Christiane Querfeld MD PhD, City of Hope; Lucia Seminario-Vidal MD, University of South Florida; Lubomir Sokol MD PhD, H. Lee Moffitt Cancer & Research Institute; Jillian Wells, MD, Westmead Hospital, Sydney; Henry Wong MD PhD, Univ of Arkansas; Costas Yannakou MBBS, Epworth Healthcare, Melbourne

This study was funded by Citius Pharma, Inc

The authors would also like to thank Wenyin Lin, Ruth Dixon, and Eleanor Parico-Esguerra, for their valuable contributions toward this work

Thank you!

City of Hope®

International Society for Cutaneous Lymphomas
ISCL