Phase I Trial of Siplizumab in CD-2 Positive Lymphoproliferative Disease

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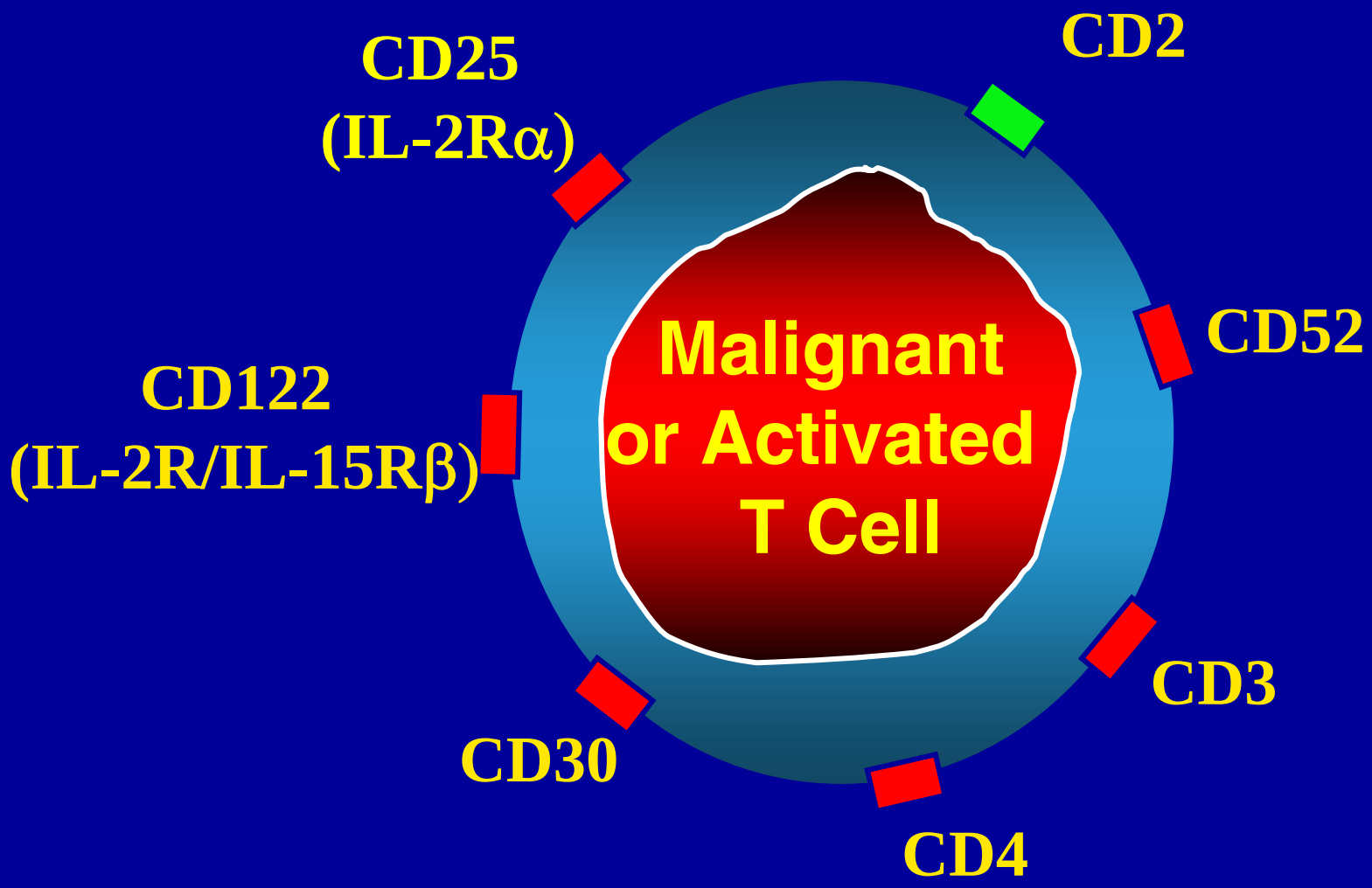
Target for Receptor-directed Therapy



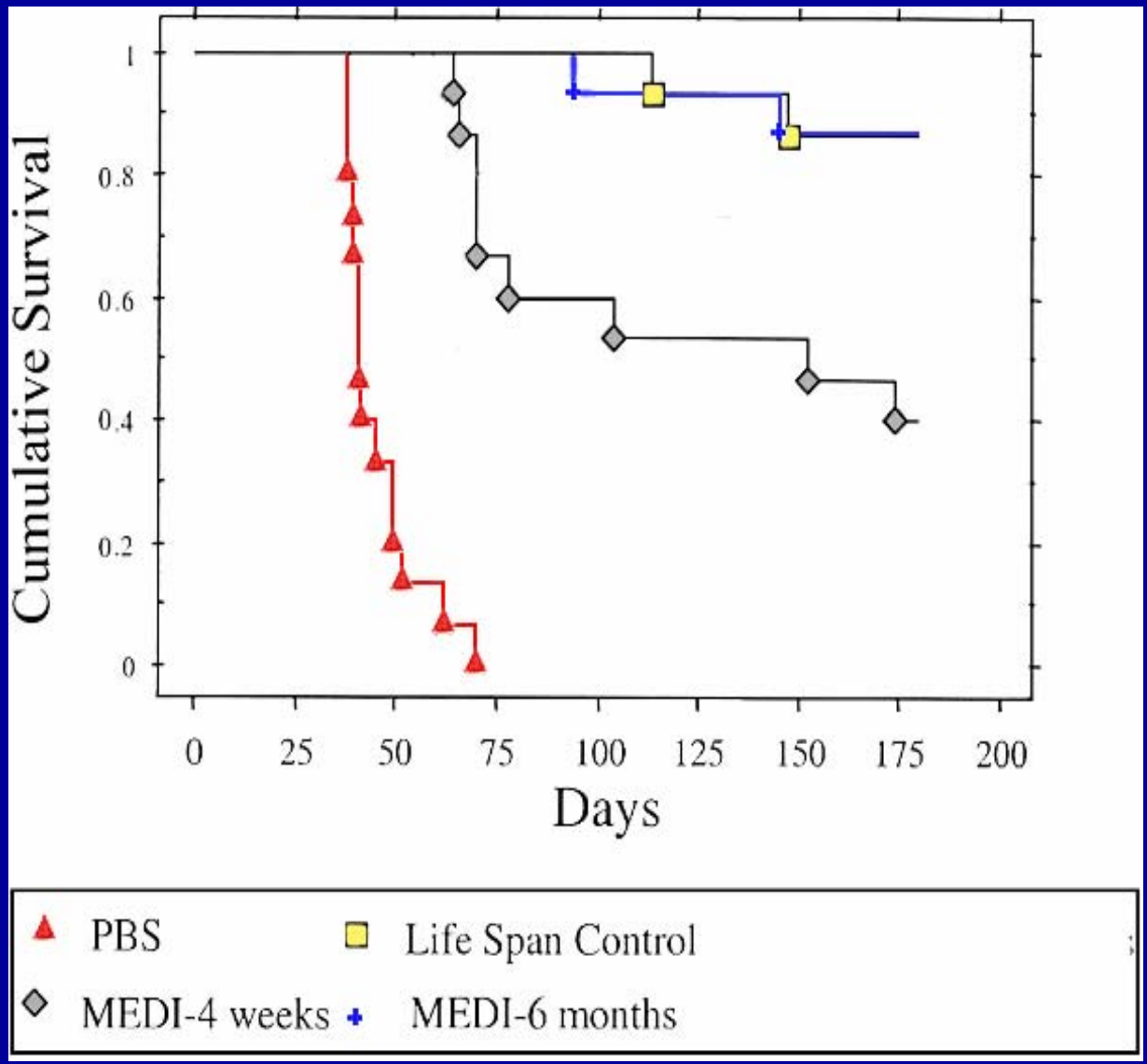
CD2

- Sheep red blood cell receptor
- Binds to LFA3
- Highly expressed on T and NK cells

Background

- Siplizumab is a humanized IgG1 kappa class monoclonal antibody that binds to the CD2 receptor on human T- and NK-cells.
- In an animal model of adult T-cell leukemia/lymphoma (ATL)-fifty percent of animals survived tumor challenge after 4 weeks of siplizumab treatment and the life-span of tumor bearing animals treated for six months was equivalent to that of animals not challenged with tumors.

Preclinical Studies of MEDI-507 in ATL Model



Zhang, Blood 102:284-8, 2003

Primary Objectives

- Determine the maximum tolerated dose (MTD) of MEDI-507 administered to patients with CD2-positive lymphoproliferative disorders.
- Determine the safety and tolerability of MEDI-507 in this patient population.

Secondary Objectives

- Estimate the time course of MEDI-507 saturation of CD2 binding sites in peripheral blood and tumor aspirates.
- Determine the serum pharmacokinetics of MEDI-507.
- Estimate the time course of T-cell and NK-cell depletion after MEDI-507.
- Estimate the time course of T-cell and NK-cell recovery after MEDI-507.
- Explore the antitumor activity of MEDI-507 with regard to response rate, time to progression, and overall survival.

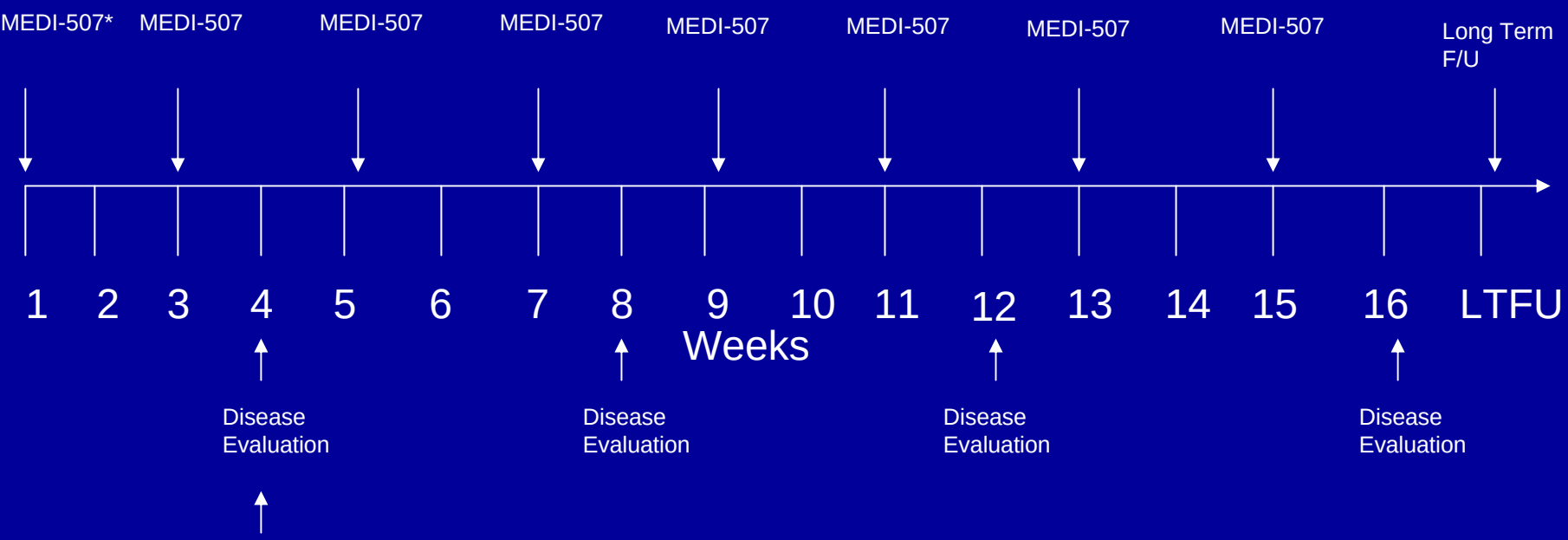
Additional Inclusion Criteria

- Cells must express CD2. At least 30% of cells must be CD2 positive by immunohistochemistry for the patient to be eligible for the study.
- Measurable or evaluable disease
- KPS ≥70%, life expectancy of at least 2 months
- Adequate hematologic, renal and hepatic function
- ≥18 years of age

Exclusion Criteria

- Known history of CNS disease
- Concurrent anti-cancer therapy
- Prior history of adverse events related to previously administered monoclonal antibody
- Active infection requiring systemic therapy
- CMV positive or HIV positive
- Hepatitis B surface antigen positive or antibodies to Hepatitis C virus

Treatment Schema



*MEDI-507 received over 2-3 consecutive days per week (depending on cohort), every other week for 16 weeks or until PD, toxicity, or other reasons for withdrawal. If pts have a positive response after 8 treatment weeks, dosing can continue until PD, toxicity, or other reasons for withdrawal.

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Dose-escalation scheme

	MEDI-507 Doses (mg/kg)[b]		
	Day 1 Dosing	**Day 2 Dosing**	**Day 3 Dosing**
Cohort 1[a]	0.2	0.2	—
Cohort 2	0.2	0.2	0.2
Cohort 3[a]	0.4	0.4	—
Cohort 4	0.4	0.4	0.4
Cohort 5	0.4	0.8	1.2
Cohort 6	0.4	1.2	1.8
Cohort 7	0.4	1.8	2.6

[a] Patients in Cohorts 1 and 3 will receive MEDI-507 on 2 consecutive days each treatment week, e.g., Monday and Tuesday. Patients in the remaining cohorts will receive MEDI-507 on 3 consecutive days each treatment week, e.g., Monday, Tuesday, and Wednesday.

[b] MEDI-507 will be administered every other week for 16 weeks or until unacceptable toxicity, documentation of disease progression, or other reasons for patient withdrawal, whichever comes first. If pts have a positive response after 8 treatment weeks, dosing can continue until PD, toxicity, or other reasons for withdrawal.

Premedication

- 30-90 minutes before each MEDI-507 infusion orally
  - Acetaminophen 650 mg
  - Diphenhydramine 25-50 mg
- Grade 2 chills occurred in most patients with first dose of MEDI-507 in dose levels 1 and 2
  - Meperidine 25 mg IV at the start of MEDI-507 infusion

Infection Prophylaxis

- ValAcyclovir 500 mg daily
- Fluconazole 200 mg daily
- Sulfamethoxazole/Trimethoprim

  800 mg/160 mg Twice daily three times weekly

Patient Characteristics (N=19)

Age-median range	49 (34-74)
Gender	
Male	12
Female	7
Karnosfky Performance Status	
100	1
90	17
80	1
Leukemia/Lymphoma Types	
Adult T-Cell Leukemia/Lymphoma	9
Large Granular Lymphocyte Leukemia	5
Cutaneous T-Cell Lymphoma	4
Peripheral T-Cell Lymphoma	1
Median number of prior regimens	1 (0-3)
Prior Therapy	
Chemotherapy	10
Radiotherapy	2
Monoclonal Antibodies	6
Other (PUVA, pamidronate)	7

Dose Escalation and Courses

Dose	Median no. of Courses (range)
.4 mg /kg	2 (2-3)
.6 mg/kg	4 (2-5)
.8 mg/kg	8 (2-8)
1.2 mg/kg	7 (1-8)
2.4 mg/kg	6 (5-8)
3.4 mg/kg	4 (1-7) currently ongoing

Siplizumab-related adverse events (NCI Version 3.0) N=12*

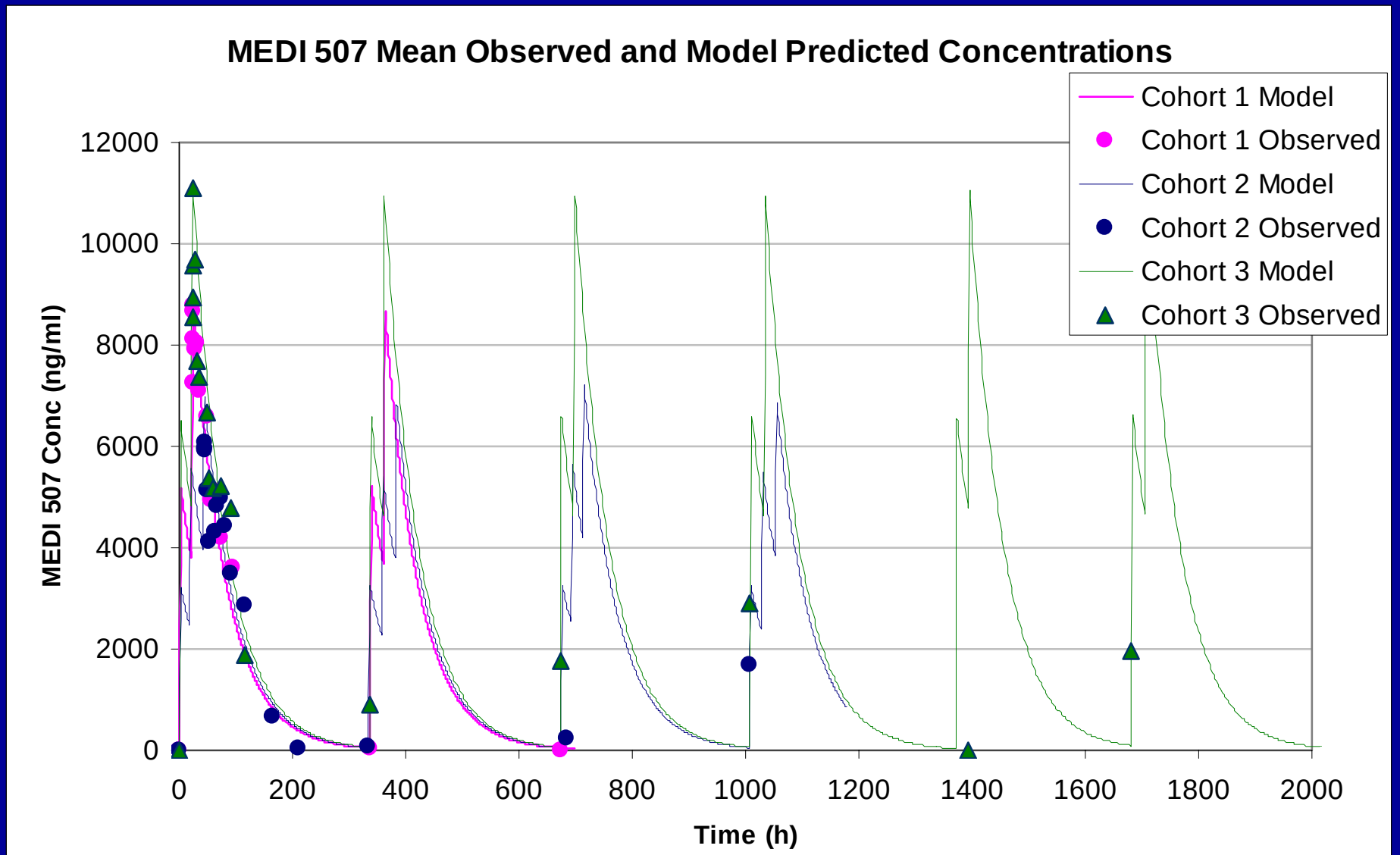
Event	Grade 1	Grade 2	Grade 3	Grade 4
Lymphopenia	-	-	4	5
WBCs, decreased	1	1	4	2
Pyrexia	6	1	-	-
Infusional Reaction	-	6	-	-
Chills	2	3	-	-
Thrombocytopenia	2	-	2	-
SGOT, increased	4	-	-	-
CMV Antigenemia	2	2	-	-
Fatigue	2	1	-	-
Neutropenia	1	1	-	1
Myalgia	2	-	-	-
Hypotension	2	-	-	-
Hemoglobin, decreased	-	1	1	-
SGPT, increased	2	-	-	-
Hypoalbuminemia	2	-	-	-
Headache	2	-	-	-
Amylase , increased	-	-	1	-
Bilirubin, increased	-	-	1	-
Alkaline Phosphatase, increased	-	-	1	-

*Events considered related occurring in ≥ 2 patients(any grade) or ≥ 1 patient (grade 3 or greater) up to the 1.2 mg/kg dose level

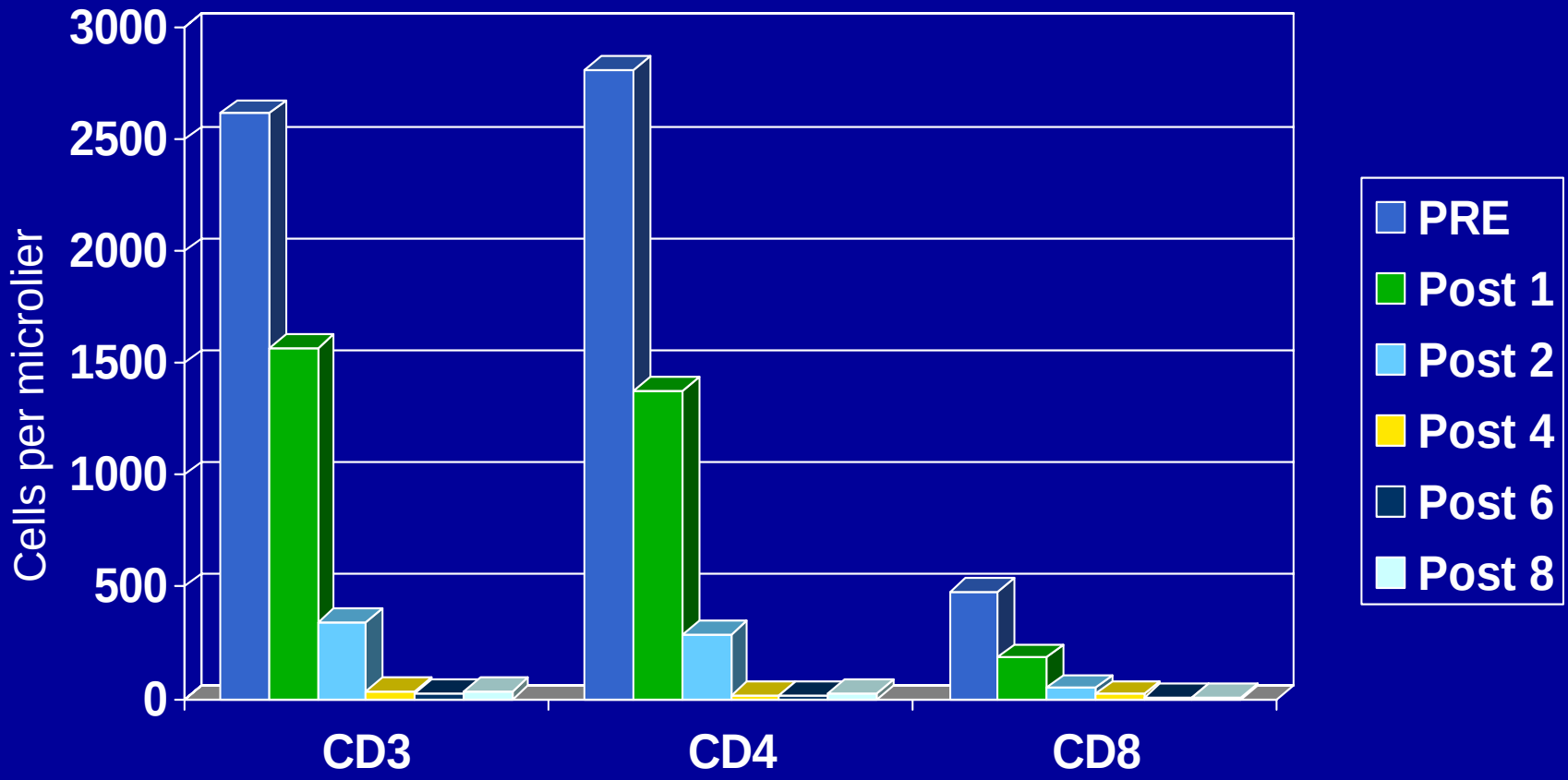
Geometric Mean (CV%) Pharmacokinetic Parameters of Siplizumab (N=9)

Cohort	Dose mg/kg	Week	Tmax (h)*	Cmax ng/ml	Half life h
1	0.4	1	3.8 (3.3 - 10.7)	9099 (8)	34 (11)
2	0.6	1	3.9 (3.8 - 5.1)	6240 (20)	32 (32)
3	0.8	1	3.9 (3.8 - 4.0)	10981 (19)	64 (73)

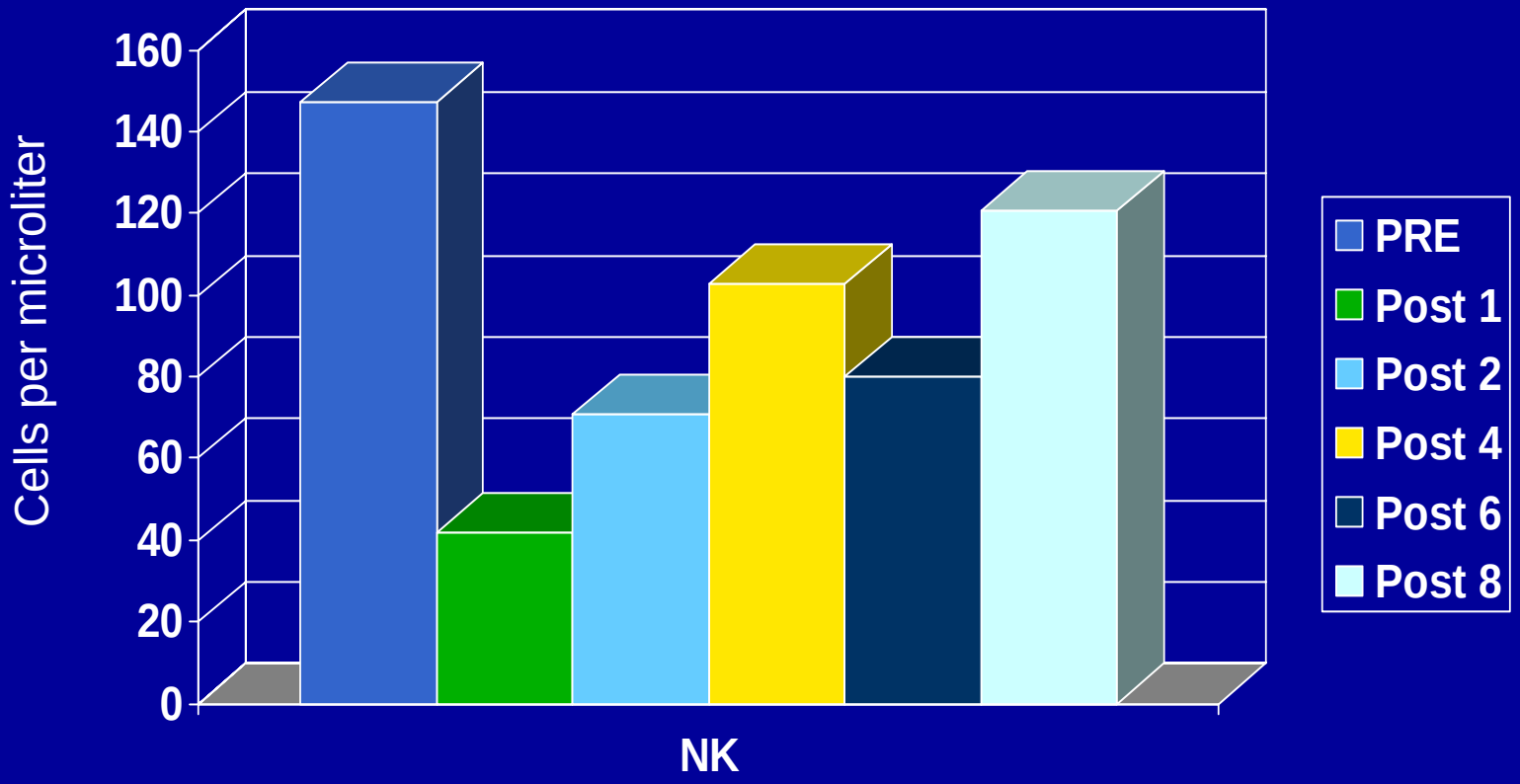
***median (range)**


MEDI 507 Mean Observed and Model Predicted Concentrations
Cohort 1 Model
Cohort 1 Observed
Cohort 2 Model
Cohort 2 Observed
Cohort 3 Model
Cohort 3 Observed
MEDI 507 Conc (ng/ml)
12000
10000
8000
6000
4000
2000
0
0
200
400
600
800
1000
1200
1400
1600
1800
2000
Time (h)

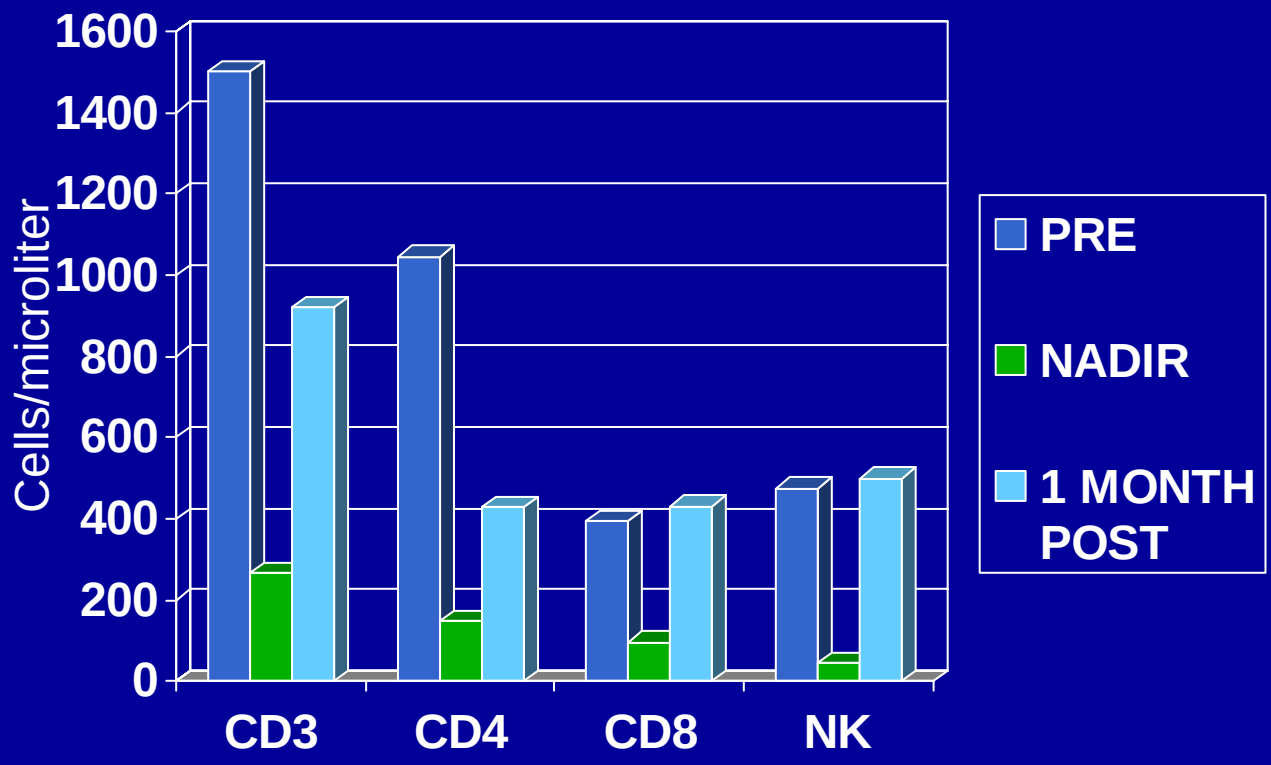
Depletion of T cells post MEDI-507 Dose Level 3



Depletion of NK cells post MEDI-507 Dose Level 3



Recovery of T and NK cells post MEDI-507

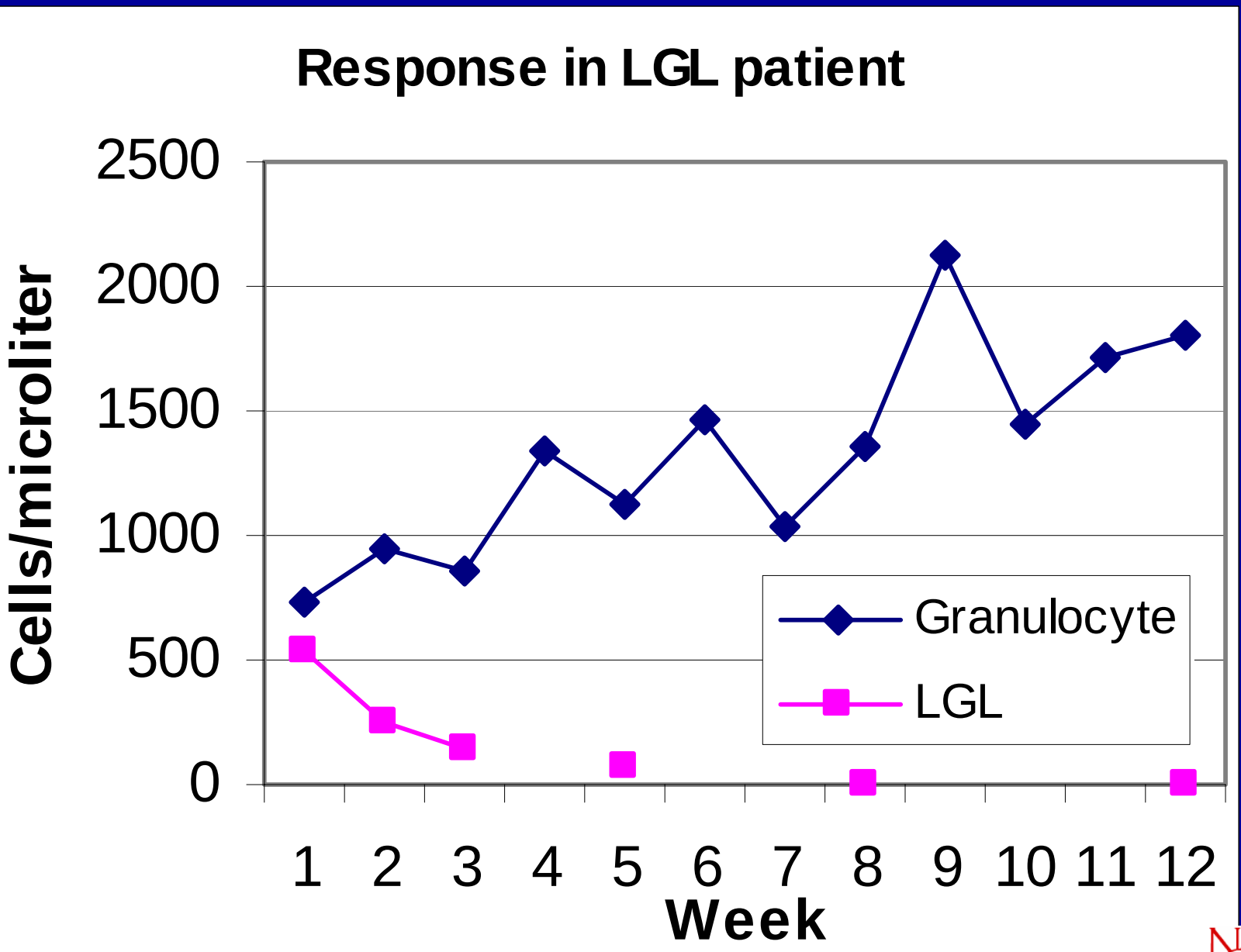


CMV Reactivation

- 8 patients had CMV reactivation (5 ATL, 1 LGL, 2 CTCL)
- CMV reactivation is considered one or more instances of CMV antigen positivity any time during treatment

Summary of Response by Dose Level (N=19)

Clinical Response	.4 mg/kg	.6 mg/kg	.8 mg/kg	1.2 mg/kg	2.4 mg/kg	3.4 mg/kg
Progressive Disease	2	2	1	2	2	2
Stable Disease	-	-	-	2	1	1 (treatment ongoing)
Objective Response	Improvement in neutrophil response to G-CSF ; minor response-had to discontinue due to CMV antigenemia	Partial remission in an ATL patient after 2 courses; had to d/c due to CMV antigenemia	1 LGL patient has achieved a complete pathologic remission (still in CR 6 months after therapy); 1 ATL patient achieved a PR in peripheral blood, lymph nodes and skin			


Response in LGL patient
Cells/microliter
2500
2000
1500
1000
500
0
1 2 3 4 5 6 7 8 9 10 11 12
Week
Granulocyte
LGL

Summary of Results

- The preliminary data show that 19 patients have received a median of 5 courses of siplizumab over 6 dose levels ranging from 0.4 to 3.4 mg/kg every other week.

- The majority of adverse events have been mild, Grade 1 or 2, and the MTD has not been reached.

- Infusional reactions have been Grade 1 or 2 and have been confined to the first treatment day of each cycle for the majority of patients. Premedication with meperidine prevented or ameliorated the infusional reaction.

Summary of Results (cont'd)

- No serious adverse event have led to discontinuation. 3 patients experienced serious adverse events (line sepsis, fever and neutropenia, catheter-related infection). These events were judged to be unrelated to siplizumab by the investigator.
- 4 patients had to discontinue siplizumab prematurely due to adverse events (3 with CMV antigenemia, 1 with polymyalgia rheumatica). The protocol has been amended to allow for treatment of CMV antigenemia.
- No immunogenicity has been detected up to the 1.2 mg/kg dose level.

Conclusions

- MEDI-507 has been well tolerated
  - Up to Grade 2 infusional reactions confined to the first treatment day up to 3.4 mg/kg IV every 14 days for the majority of patients
- The MTD has not been reached and accrual is ongoing
- Transient T cell depletion has been noted in all patients

Conclusions (cont'd)

- Dose proportional pharmacokinetic parameters up to a dose level of .8 mg/kg
- Confirmed responses have been observed suggesting potential clinical activity

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