

# Phase 1 study of an anti-CD30 Fc engineered humanized monoclonal antibody in Hodgkin lymphoma (HL) or anaplastic large cell lymphoma (ALCL) patients: safety, pharmacokinetics (PK), immunogenicity and efficacy

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## Background

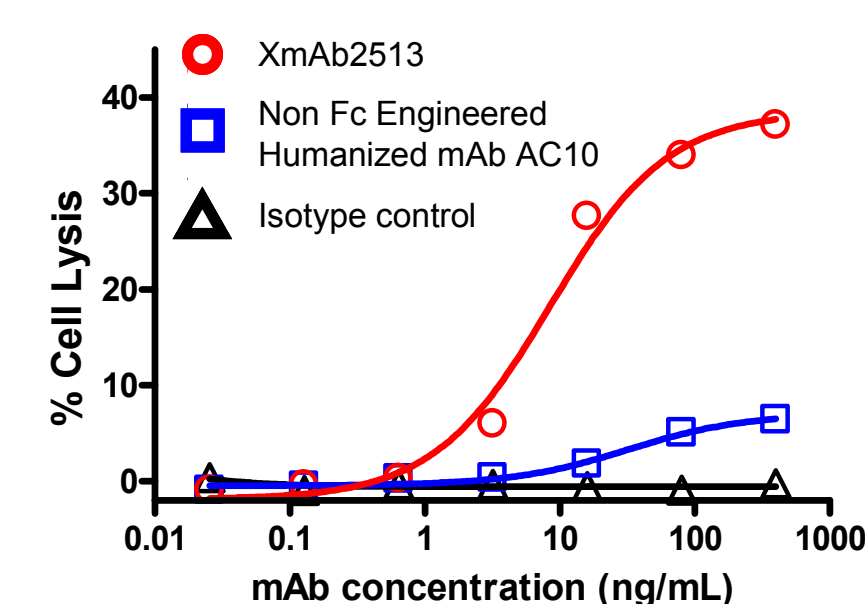
### CD30 Antigen

- CD30 expressed on Reed Sternberg cells in Hodgkin's Lymphoma & anaplastic T cell lymphoma cells
- Soluble CD30 associated with poor prognosis in HL
- Binding of antibody to CD30 antigen blocks ligand binding that may drive cell proliferation
- mAbs targeting cell surface markers (e.g., rituximab) have been successful in lymphoma and other diseases

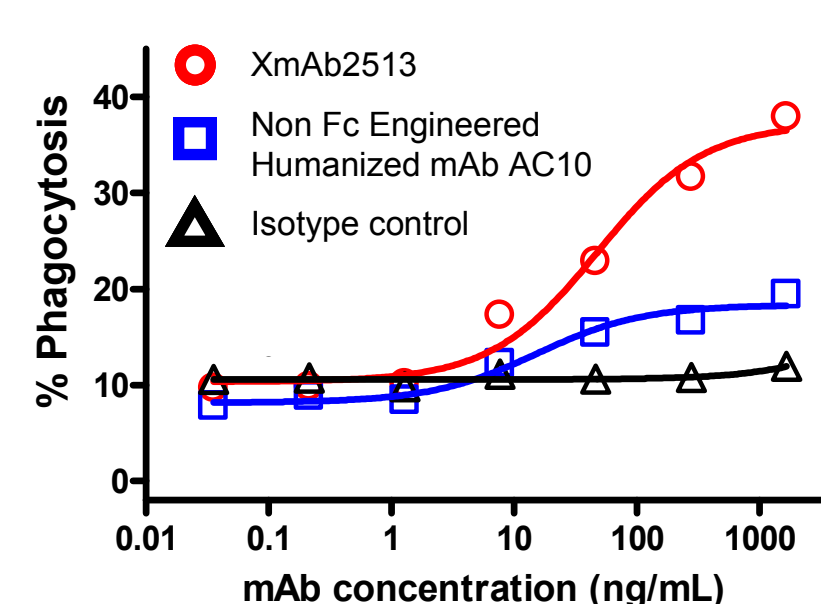
### XmAb2513

- Humanized version of the murine mAb AC10 (anti-human CD30)
- XmAb Fc region engineered for high affinity Fcγ receptor binding
- Has improved effector functions: Antibody dependent cell-mediated cytotoxicity (ADCC) / phagocytosis (ADCP)
- Does not exhibit complement dependent cytotoxicity (CDC)

### XmAb2513 has improved ADCC



### XmAb2513 has improved ADCP



ADCC activity of XmAb2513 and control mAbs using human PBMC effector cells and CD30+ L540 target cells

ADCP activity of XmAb2513 and control mAbs using cultured primary human macrophages and CD30+ L540 target cells

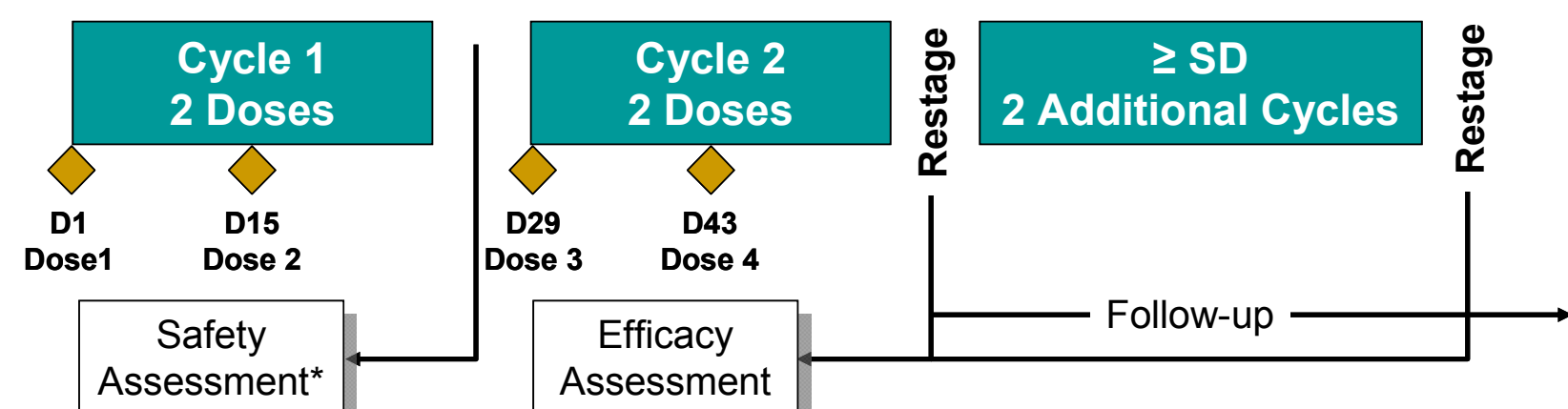
## Study Description

### Objectives

- Establish the **maximum tolerated dose (MTD)** and / or recommended dose(s) for further study
- Determine the **safety** and **tolerability** profile of every other week (QOW) iv dosing of XmAb2513
- Characterize the **PK** and **immunogenicity** of every other week dosing of XmAb2513
- Evaluate **preliminary antitumor activity**

### Dose Escalation Design

- Six dose levels: 0.3, 1.0, 3.0, 6.0, 9.0, or 12 mg/kg; 2 hour IV infusion every other week
- Treatment duration up to 16 weeks (max 8 doses)
- Accelerated (single pt / cohort) and standard dose (3 + 3) escalation design (no intra-patient dose escalation)
- Dose escalation will be allowed following review of pertinent safety data for all patient(s) through day 28.
- Patients without sufficient safety data may be replaced
- Expanded cohort of 6 to 12 additional patients at the recommended Phase 2 dose



\* For decision to open next cohort to enrollment

### Safety Assessment: informs escalation to next cohort at end of Cycle 1

- DLT during Cycle 1 triggers expansion of cohort to six patients
- DLT = any "related" Grade ≥ 3 AE (by NCI CTCAE, V 3.0) with the exceptions:
  - Decreased platelet count (Grade 3 or 4) if recovery to 50,000/mm<sup>3</sup> occurs within 14 days in the absence of platelet transfusion or bleeding
  - Neutropenia (Grade 3 or 4) if recovery to 1000/mm<sup>3</sup> occurs within 14 days in the absence of fever or infection
- MTD reached when 2 / 6 patients experience DLT

### Efficacy Assessment: Post-Cycle 2 (by IWG Criteria<sup>†</sup>)

- SD or better allowed to receive an additional 2 cycles
- Final cohort may be expanded to an additional 12 patients to explore efficacy

## Study Design (cont'd)

### Selection Criteria

- Relapsed or refractory CD30-positive HL or ALCL who met the following inclusion criteria enrolled in this study:
  - Age ≥18
  - Measurable disease (i.e., lesions ≥ 1cm)
  - ECOG performance status 0 or 1
  - Adequate organ function
  - No limit to prior number of therapies
    - Must have received two or more prior therapeutic regimens (one of which should include hematopoietic cell transplant)
    - Prior autologous or allogeneic stem cell transplant allowed
    - Prior Anti-CD30 therapy allowed

### Patient Demographics and Disease Characteristics

	XmAb2513-01 Dose Cohort (mg/kg)						Total (N=17)
	0.3 (N=3)	1.0 (N=1)	3.0 (N=6)	6.0 (N=3)	9.0 (N=3)	12.0 (N=1)	
<b>Diagnosis</b>							
HL	3 (100%)	1 (100%)	6 (100%)	3 (100%)	3 (100%)	1 (100%)	17 (100%)
ALCL	0	0	0	0	0	0	0
Median Age (years) (range)	30 (28 – 42)	44 (N/A)	32 (26 – 50)	33 (26 – 45)	24 (20 – 41)	28 (N/A)	32 (20 – 50)
Gender (% Male)	100%	100%	67%	100%	33%	0	71%
<b>ECOG PS</b>							
0	1 (33%)	0	4 (67%)	1 (33%)	3 (100%)	1 (100%)	9 (53%)
1	1 (33%)	1 (100%)	2 (33%)	2 (67%)	0	0	7 (41%)
2*	1 (33%)	0	0	0	0	0	1 (6%)
<b>Prior Therapy</b>							
Median # Chemotherapies ‡ (range)	4 (2 – 5)	2 (N/A)	4 (1 – 5)	1 (1 – 4)	3 (1 – 3)	3 (N/A)	3 (1 – 5)
Radiation	2 (67%)	1 (100%)	4 (67%)	2 (67%)	2 (67%)	1 (100%)	12 (71%)
Autologous SCT	3 (100%)	1 (100%)	6 (100%)	2 (67%)	3 (100%)	1 (100%)	16 (94%)
Allogeneic SCT	1 (33%)	0	2 (33%)	1 (33%)	2 (67%)	1 (100%)	7 (41%)
Median Total # Treatments (range)	6 (6 – 8)	4 (N/A)	6 (2 – 12)	3 (2 – 10)	4 (2 – 5)	6 (N/A)	6 (2 – 12)

N/A = not applicable; SCT = stem cell transplant; UNK = unknown (results not yet entered)

\* Patient reclassified as PS 2 post-enrollment

‡ Excludes induction therapy for SCT

- Three patients enrolled in Cohort 1 (0.3 mg/kg) to ensure at least one evaluable for decision to open next cohort
- Cohort 3 (3.0 mg/kg) expanded to 6 patients due to Grade 3 thrombocytopenia considered "possibly related" to single XmAb2513 dose

## Safety

	XmAb2513-01 Dose Cohort (mg/kg)						Total (N=15)*
	0.3 (N=3)	1.0 (N=1)	3.0 (N=6)	6.0 (N=3)	9.0 (N=2)	12.0	
<b>Patients w/AE</b>	3 (100%)	1 (100%)	6 (100%)	2 (67%)	0		12 (80%)
<b>Patients w/related AE</b>	2 (67%)	1 (100%)	5 (83%)	2 (67%)	0		10 (67%)
<b>Patients w/Grade ≥ 3 AE ‡</b>	1 (33%)	0	2 (33%)	1 (33%)	0		4 (27%)
<b>Patients w/related Grade ≥ 3 AE</b>	0	0	1 (17%)	0	0		1 (7%)

AE = Adverse Event; SAE = Serious Adverse Event

\* Based on events reported as of 30-Apr-09

‡ NCI CTCAE V. 3.0

### Grade 3 / 4 AE's

- Cohort 1 (0.3 mg/kg)
  - Patient 004 – Grade 3 anemia; Grade 3 intermittent pyrexia (both unrelated)
- Cohort 3 (3.0 mg/kg)
  - Patient 007 – Grade 3 insomnia; Grade 3 nausea (both unrelated)
  - Patient 011 – Grade 3 thrombocytopenia (related); Grade 5 fungal pneumonia (unrelated)
- Cohort 4 (6.0 mg/kg)
  - Patient 016 – Grade 3 rigors; Grade 3 chills (both unrelated)

## Safety (cont'd)

### Most Common AE's (>10%)

	XmAb2513-01 Dose Cohort (mg/kg)						Total (N=15)*
	0.3 (N=3)	1.0 (N=1)	3.0 (N=6)	6.0 (N=3)	9.0 (N=2)	12.0	
<b>Patients w/AE</b>	3 (100%)	1 (100%)	6 (100%)	2 (67%)	0		12 (80%)
Nausea	1 (33%)	1 (100%)	1 (17%)	1 (33%)	0		4 (27%)
Chills	1 (33%)	0	0	2 (67%)	0		3 (20%)
Diarrhea	0	1 (100%)	1 (17%)	1 (33%)	0		3 (20%)
Fatigue	1 (33%)	1 (100%)	0	1 (33%)	0		3 (20%)
Infusion related reaction	1 (33%)	0	2 (33%)	0	0		3 (20%)
Pruritis	1 (33%)	1 (100%)	1 (17%)	0	0		3 (20%)
Rash	1 (33%)	1 (100%)	1 (17%)	0	0		3 (20%)
Anemia	1 (33%)	0	0	1 (33%)	0		2 (13%)
Arthralgia	2 (67%)	0	0	0	0		2 (13%)
Back pain	1 (33%)	0	0	1 (33%)	0		2 (13%)
Cough	0	0	2 (33%)	0	0		2 (13%)
Insomnia	1 (33%)	0	1 (17%)	0	0		2 (13%)
Peripheral edema	1 (33%)	0	0	1 (33%)	0		2 (13%)
Pyrexia	1 (33%)	0	1 (17%)	0	0		2 (13%)
Vomiting	0	1 (100%)	1 (17%)	0	0		2 (13%)

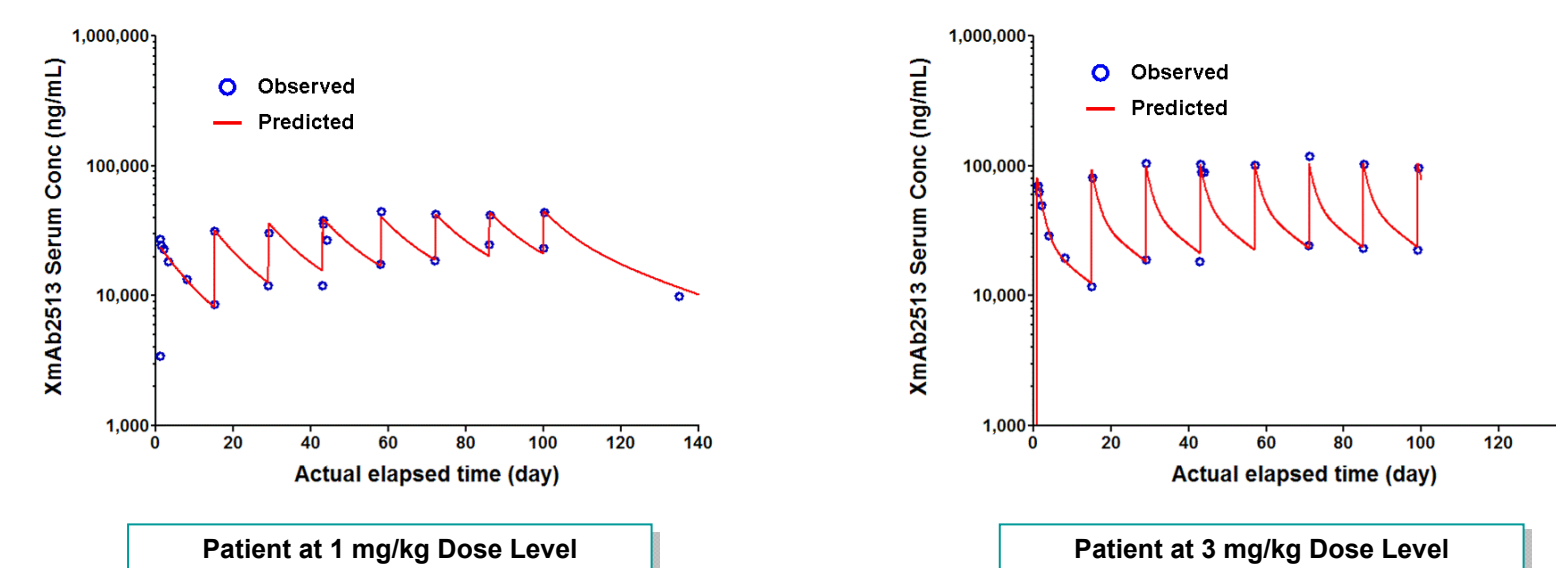
AE = Adverse Event

\* Based on events reported as of 30-Apr-09

### Summary

- XmAb2513's MTD has *not* been reached
- No immunogenicity detected by assessment for human antibodies to humanized antibodies (HAHA)
- Common AE's have been mild to moderate in severity
  - All AE's were assessed as Grade 1 or 2 except those listed below
- Grade ≥ 3 AE's
  - One related AE – thrombocytopenia in Cohort 3 (3.0 mg/kg)
    - Considered a DLT which led to Cohort expansion
    - Occurred in patient with 12 prior lines of therapy and history of GVHD and chronic immunosuppression after single infusion of XmAb2513
  - One fatal AE – occurred in same patient in Cohort 3
    - Patient hospitalized on Day 13 after first dose due to pneumonia / thrombocytopenia
    - Patient expired on Day 23 due to fungal pneumonia considered unrelated to study drug

## Pharmacokinetics



### Summary Results for First Dose Interval

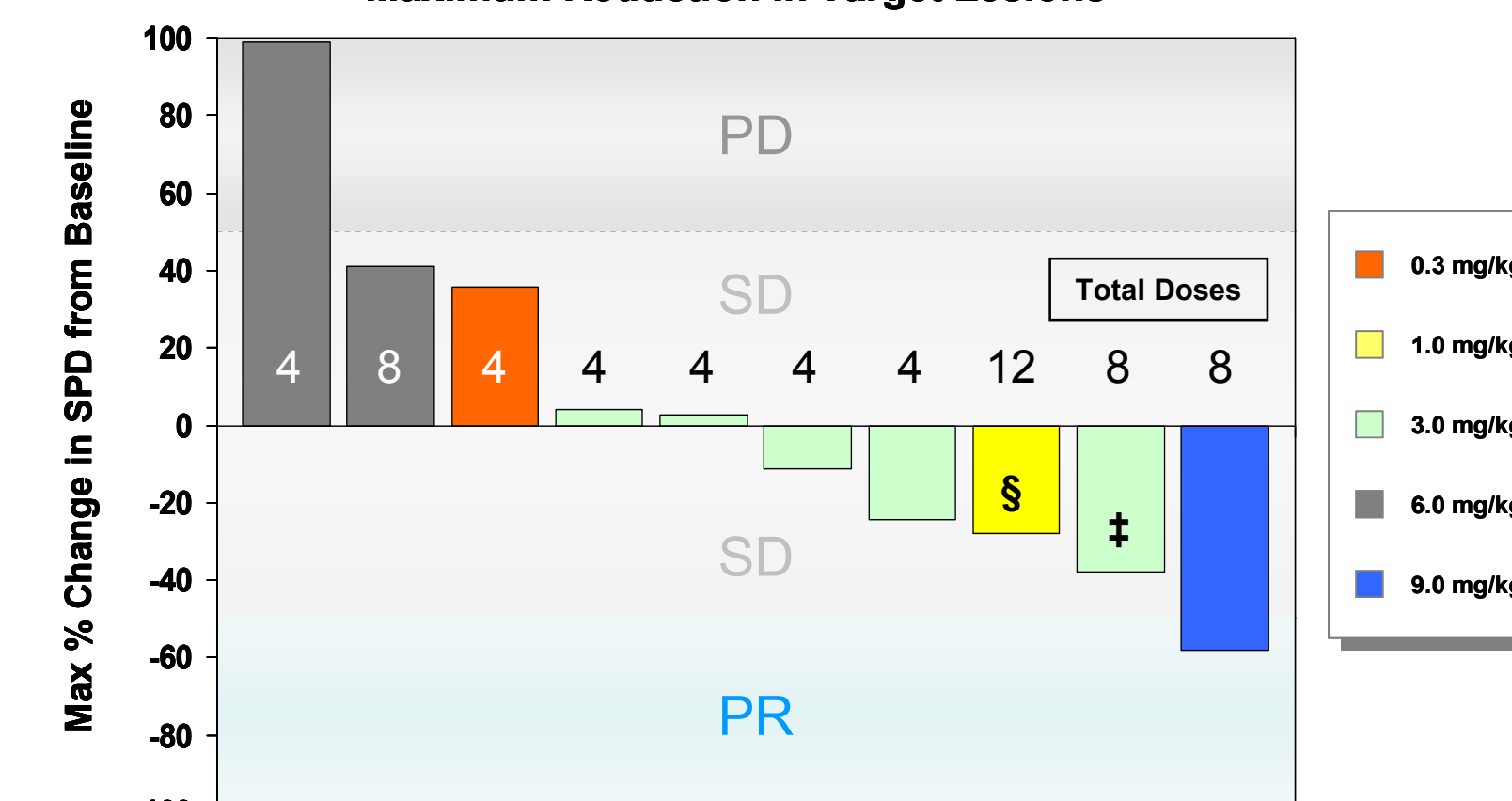
- XmAb2513 was non-linear across the 0.3 to 6.0 mg/kg dose levels
- Clearance showed decreased trend with increasing dose
- Half-life for the first dose interval was 6 to 10 days
- Distribution volume close to that of serum
- PK parameters computed either by non-compartment or 1- / 2-compartment methods were in close agreement

### Summary Results for Entire Dose Profile

- Half-life increased with repeat administration
- Steady-state trough levels reached after fourth dose administration (i.e. steady state requires > 2 cycles)
- Half-life data available for 1.0 and 3.0 mg/kg cohorts was 13 to 30 days

## Preliminary Efficacy (cont'd)

### Maximum Reduction in Target Lesions\*



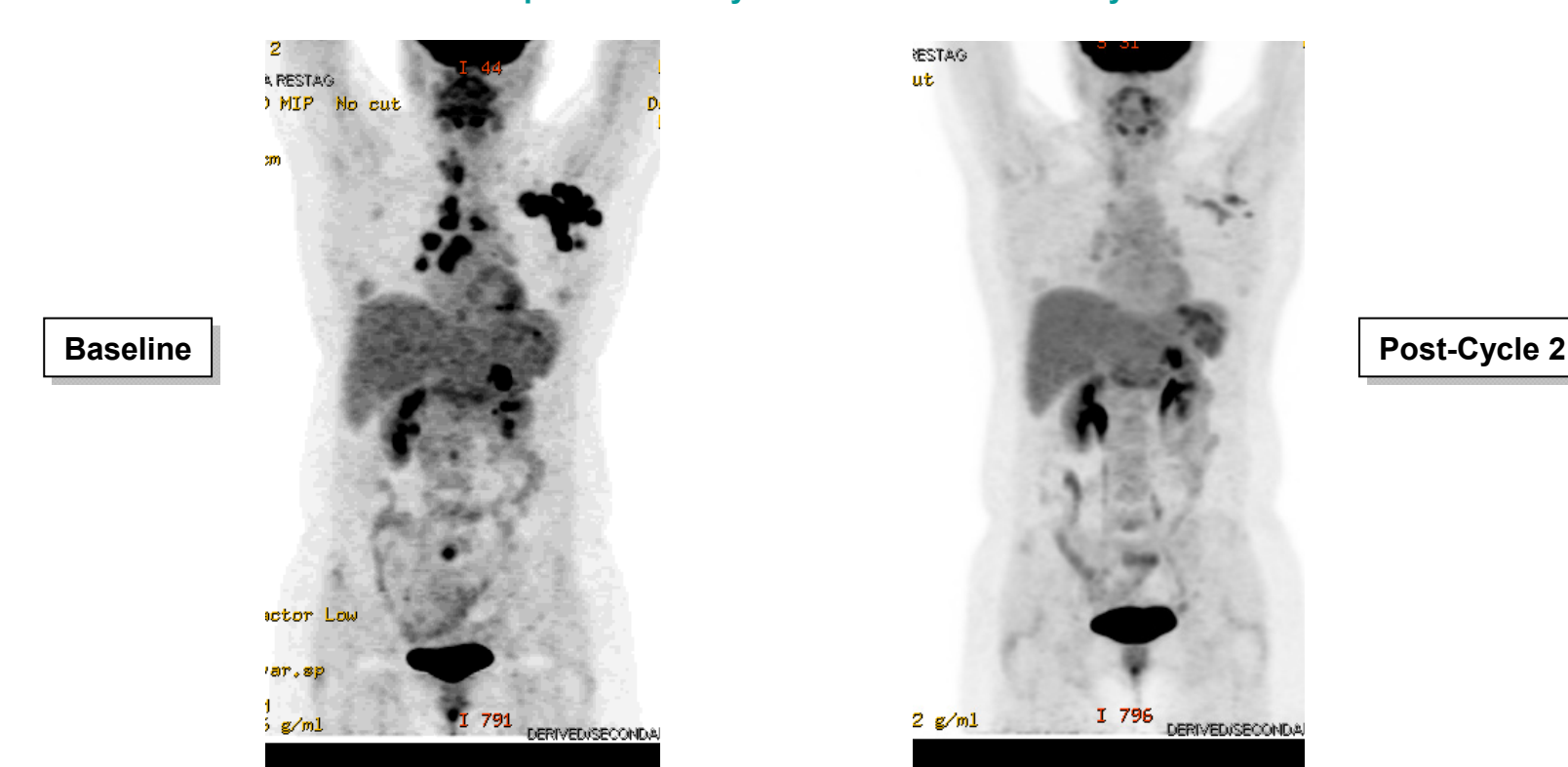
### Individual Patients

\* For patients with baseline measurements and at least one post-baseline tumor assessment

- Half of patients evaluable for efficacy have had reduction in sum of product diameters
- One patient with therapy extension (4 more doses) with SD (S)
- Substantive reduction (40%) in patient with prior anti-CD30 antibody therapy (‡)
- PR observed in first patient in Cohort 5 (9.0 mg/kg)

### Decreased FDG Avidity by PET

### Partial Response in a 40 y.o. Female with refractory HL



## Conclusions

### Population

- Significant prior therapy history (median 6 prior lines of therapy)

### MTD has not yet been reached

- Final cohort (12.0 mg/kg) may be expanded to explore efficacy

### Outpatient infusions of XmAb2513 have been well tolerated

- No immunogenicity detected by HAHA
- Majority of AE's mild to moderate in severity

### Pharmacokinetics

- Good agreement with model derived from cynomolgus monkey PK results
- Half-life for the first dose interval was 6 to 10 days; Half-life data available for 1.0 and 3.0 mg/kg cohorts was 13 to 30 days
- Steady-state trough levels reached after fourth dose administration (i.e. steady state requires > 2 cycles)

### Preliminary Efficacy

- Stable disease or better observed in more than half of patients evaluable for efficacy
  - Two SD patients were successfully treated in follow-up (40% tumor reduction in patient with prior anti-CD30 therapy)
  - One SD patient in observation only
- PR observed in first patient treated in Cohort 5 (9.0 mg/kg)
- Results pending for Cohort 6 (12.0 mg/kg)

### Results support further investigation as a single-agent in relapsed / refractory HL

### Safety profile also supports further investigation in combination with chemotherapy