

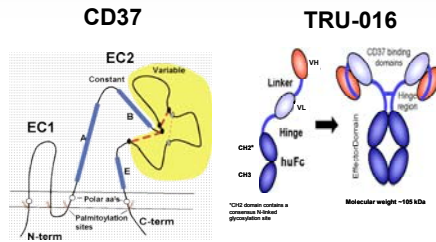
# A Phase 1 trial of TRU-016, an anti-CD37 Small Modular Immunopharmaceutical (SMIP™) protein in relapsed and refractory CLL: Early promising clinical activity

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## Background

CD37 is a tetraspanin family member expressed predominantly on normal and transformed B-cells across a wide range of maturational stages. TRU-016 is a novel humanized anti-CD37 SMIP protein. Pre-clinical studies have demonstrated CD37 SMIP protein mediates significantly greater direct killing of CLL cells than rituximab that is dependent upon tyrosine phosphorylation changes at 65 and 50-55 kD. TRU-016 also mediates greater NK cell mediated killing of CLL cells as compared to either alemtuzumab or rituximab. A phase I study with TRU-016 was initiated based upon these data.



## Study Design

- First in human, Phase 1 study using 3 + 3 dose escalation design in subjects with relapsed or refractory CLL
- Based on previous studies showing rapid clearance of antibodies in CLL, two dosing strategies were evaluated:
  - Once weekly for 4 weeks
  - Three times the first week then once weekly for 3 weeks
- Patients may receive up to 2 additional cycles if clinical benefit observed with first cycle

## Eligibility

### Inclusion Criteria:

- Relapsed or refractory CLL/SLL after treatment with at least one fludarabine-containing regimen
- Active disease requiring treatment
- Age  $\geq$  18 years
- ECOG PS  $\leq$  2
- Creatinine, Total Bilirubin, SGOT, SGPT  $\leq$  2 x ULN
- ANC  $>$  500/mm<sup>3</sup>
- Platelets  $>$  30,000/mm<sup>3</sup>
- No previous anticancer therapy or surgery within 30 days
- Written informed consent

### Exclusion Criteria:

- Rituximab within 30 days or alemtuzumab within 12 weeks of enrollment; other protein therapeutic or investigational therapy within 30 days
- Concurrent malignancy (except non-melanomatous skin cancer) that limits survival to  $<$  2 years
- Active infection requiring systemic therapy
- Positive serology for HIV, HCV or HBsAg/HBcAb
- Pregnant or breast feeding
- Significant concurrent medical diseases

## Patient Demographics

33 Evaluable patients		N (%)
Age, mean		64 years
< 70 yrs		24 (73)
$\geq$ 70 yrs		9 (27)
Gender: F/M		14 (42) / 19 (58)
CLL/SLL		29 (88) / 4 (12)
Duration of Diagnosis, mean		8.8 years
ECOG	0, 1, 2	10 (30), 20 (61), 2 (6)
Rai Stage	0, I&II, III&IV	1 (3), 9 (27), 23(70)
Hgb < 11 gm/dL		21 (64)
ANC < 1.5 (10 <sup>9</sup> /L)		8 (24)
Platelets < 100 (10 <sup>3</sup> /L)		14 (42)
Deletion 17p13		12 (36)
Deletion 11q22-23		6 (18)
Both		2 (6)
None		6 (18)
Other (trisomy 12, deletion 13q14)		7 (21)

## Results

### Planned Dose Levels and Enrollment to Date

Cohort	Dose (mg/kg)	# Enrolled	Entered Cycle 2	Entered Cycle 3
1	0.03	1	-	-
2	0.1	1	-	-
3	0.3	1	-	-
4	1	3	1	0
5	3	4	3	2
6	6	7	2	2
7	3 mg/kg TIW	8	3	1
8	10	5	4	4
11	6 mg/kg TIW	3	3	2
12	10 mg/kg TIW			

### Dose Response in Evaluable Patients:

#### Reduction in Lymphadenopathy by CT Scan

Dose Cohort	N	Mean	Median
1 mg/kg	3	14%	5%
3 mg/kg	2	30%	30%
6 mg/kg	3	53%	35%
TIW Load			
3 mg/kg	5	30%	40%

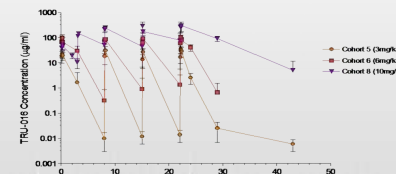
### Dose Response in Evaluable Patients: Reduction in

#### Peripheral Absolute Lymphocyte Count (ALC)

Dose Cohort	N	Normalization of ALC <sup>1</sup> N (%)	Median Reduction <sup>2</sup>	Mean Reduction <sup>2</sup>	Best Response <sup>3</sup>
1 mg/kg	3	0/3 (0%)	67%	67%	0
3 mg/kg	4	0/4 (0%)	78%	79%	0
6 mg/kg	4	1/4 (25%)	85%	85%	1 PR
10 mg/kg	5	4/5 (80%)	95%	82%	2 PR
3 mg/kg TIW	4	1/4 (25%)	49%	52%	1 PR
6 mg/kg TIW	4	1/1 (100%)	77%	77%	1 PR

<sup>1</sup> = Only patients with elevated peripheral ALC at Day 1 compared to count at end of treatment (C1, 2, or 3)  
<sup>2</sup> = Only patients with elevated peripheral ALC at Day 1 compared to Day 29  
<sup>3</sup> = Best response as reported by investigator for all patients in cohort; 2 month confirmation pending

### Mean TRU-016 Serum Concentration vs. Time



## Toxicities

Dose Limiting Toxicity	Grade	Related (Y/N)	Cohort (Dose)	History
neutropenia	4	Y	6 (6 mg/kg)	Marrow disease
idiopathic thrombocytopenia purpura	4	Y	7 (3 mg/kg TIW)	Prior episode 6 months earlier
septic shock - death	5	N	8 (10 mg/kg)	Lymphocyte # doubled in past 30 days

Serious Adverse Event	Grade	Related (Y/N)	Cohort
Pneumonia	2	N	1
Pyrexia	2	N	1
Neutropenia	4	Y	6
ITP	4	Y	7
GI hemorrhage	3	N	7
Dyspnea	2	N	7
Squamous cell carcinoma	3	N	7
Herpes zoster	2	Y	7
Septic shock	5	N	8
Febrile neutropenia	3	Y	8
Pneumonia	3	Y	8
Infusion related reaction	3	Y	11
Chest pain	3	N	11
Asthma	3	N	11

## Conclusions

- Interim data from 33 CLL and SLL patients treated with TRU-016 demonstrated a manageable safety profile.
- No consistent DLT pattern has emerged to prevent dose escalation and the MTD has yet to be established. Protocol amended to increase dose.
- Preliminary efficacy data demonstrate dose dependent reductions in peripheral lymphocytosis and objective responses in the higher dose cohorts
- These results support the further evaluation of TRU-016 in this population