

A Phase 1 Trial of TRU-016, an anti-CD37 Small Modular Immunopharmaceutical (SMIP™) in Relapsed and Refractory CLL

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Introduction

Therapy for chronic lymphocytic leukemia (CLL), the most common form of leukemia in the Western hemisphere, has improved dramatically with the development of monoclonal antibodies. However, this approach has been limited by lack of effectiveness in high risk genetic patients (rituximab) or significant immunosuppression leading to risk of infection (alemtuzumab). TRU-016 is a novel small modular immunopharmaceutical (SMIP™) directed against CD37 for use in B-cell malignancies.

CD37 as a Protein Therapeutic Target

CD37 is a member of the transmembrane 4 (tetraspanin) superfamily. It is a 40-54 kDa molecule with two extracellular surface domains expressed on mature B-lymphocytes, and transformed mature B-cell leukemia and lymphoma. It forms complexes with integrins, MHC class II molecules, co-stimulatory molecules, and other tetraspanins. However, its function in B-cells is not well defined.

TRU-016: CD37 Small Modular Immunopharmaceutical (SMIP)

A SMIP is a novel class of biologic agents specific for cell-surface antigen CD37. The Fc region interacts with FcR, facilitating SMIP-dependent cellular cytotoxicity (SDCC). *In vivo* it forms a dimer with a molecular weight of 105 kDa. TRU-016 was selected for development based on its ability to mediate apoptosis and SDCC.

Herein we describe the early results of a Phase I study evaluating TRU-016 in relapsed, refractory CLL/SLL including patients with high risk genomic features. Preliminary results suggest that this agent leads to decreases in lymphocytosis, lymphadenopathy, and organomegaly even in heavily pretreated patients or those with high risk cytogenetics, and support further Phase II single agent studies as well as incorporation into combination regimens with agents that have demonstrated synergy *in vitro*.

Methods

Patients: 26 patients with relapsed/refractory CLL/SLL were enrolled on this study. The median age was 65 (range 47-83). There were 14 male and 11 female patients. The median number of prior therapies was 6 (range 1-15). Twenty patients were Rai stage 3 or 4. Ten patients had deletion 17p13.1, six patients had deletion 11q22-23, and one patient had both.

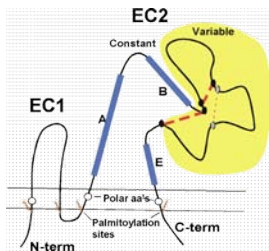
Inclusion Criteria:

- Relapsed CLL/SLL after treatment with at least 1 fludarabine-containing regimen
- At least 1 of the following:
 - Progressive lymph node enlargement or splenomegaly
 - Anemia or thrombocytopenia due to marrow involvement
 - Unintentional weight loss > 10% over the preceding 6 month period
 - Progressive lymphocytosis with increase > 50% over 2 month period or anticipated doubling time < 6 months
 - Fever or night sweats without infection
- Age ≥ 18 years
- ECOG performance status ≤ 2
- Life expectancy ≥ 3 months
- Normal renal and hepatic function
- ANC > 500/mm³
- Platelets > 30,000/mm³
- No previous anticancer therapy or surgery within 30 days
- Written informed consent

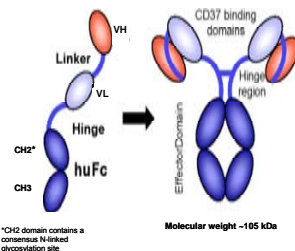
Exclusion Criteria:

- Therapy with rituximab within 30 days of enrollment or alemtuzumab within 12 weeks of enrollment
- 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
- Pregnant or breast feeding

CD37



TRU-016



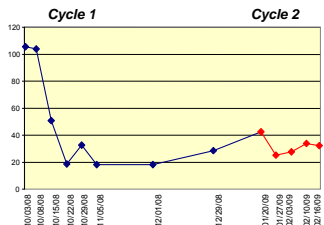
Study Design

- Traditional phase I study using 3 + 3 design
- 2 dosing strategies based upon previous studies showing rapid clearance of antibodies in CLL:
 - Once weekly for 4 weeks
 - Three times weekly for week 1 then once weekly in weeks 2-4
- Patients may receive up to 2 additional cycles if clinical benefit observed with first cycle

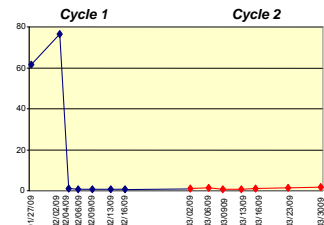
Dose Escalation Cohorts

Dose Level	Dose (mg/kg)
1	0.03
2	0.1
3	0.3
4	1
5	3
6	6
7	3 mg/kg TIW
8	10
9	15
10	20
11	6 mg/kg TIW
12	10 mg/kg TIW
13	15 mg/kg TIW
14	20 mg/kg TIW

PT 10004 Lymphocyte Response: 1.0 mg/kg weekly



PT 10006 Lymphocyte Response: 3 mg/kg TIW week 1 then q wk



Patient Characteristics

- Average of 6.5 prior regimens
- Average of 3 anti-CD20 containing regimens
- 24 patients with genomic data:
 - 10 with 17p deletion
 - 6 with 11q deletion
 - 1 with both

Patient Responses

- Clinical activity has been observed at low doses in every cohort beyond cohort 2
- Patients have experienced
 - Reductions in lymphadenopathy; up to 39% by CT
 - Reduction in splenomegaly
 - Reduction in peripheral lymphocytosis
 - Improvement in pre-treatment cytopenias
- 2 patients with leukemia cutis had complete or partial clearance of skin lesions

Reduction in Lymphocytosis

- Mean reduction in ALC, all patients: 61%
- Median reduction in ALC, all patients: 67%
- Mean reduction in ALC, cohort 3 or later: 76%
- Median reduction in ALC, cohort 3 or later: 71%
- Mean reduction in ALC, Lymphs >10,000: 78%
- Median reduction in ALC, Lymphs >10,000: 84%

Toxicities

- The maximum tolerated dose has not yet been reached.
- Most adverse events have been grades 1 and 2
- Dose limiting toxicities:
 - Sepsis resulting in death (n = 1), dose level 10 mg/kg, unrelated to study drug
 - ITP (n = 1), dose level 3 mg/kg
 - Grade 4 neutropenia (n = 1), dose level 6 mg/kg
- Some patients have experienced infusional toxicities similar to other monoclonal antibody therapies

Conclusions

- TRU-016 is a novel, clinically active biologic agent for the treatment of highly refractory B-cell CLL/SLL
- Toxicities have been manageable at dose levels evaluated to date
- Most toxicities have been hematological
- Full assessment of clinical activity and NCI96 responses at higher doses will require additional follow-up
- Phase 2 study will further evaluate efficacy in both refractory and also less heavily pre-treated patient group
- Future combination studies planned in with agents that have demonstrated synergy *in vitro*

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