Phase I/II triple therapy study of umbralisib and ublituximab ("U2") combined with checkpoint inhibition in patients with rel/ref CLL and Richter's transformation

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Background / Rationale

- Pre-clinical data supports a major role for the PD-1 and PD-L1/PD-L2 axis in mediating immune evasion in CLL, however, there is a disconnect between promising preclinical data and clinical data with anti-PD-1 monotherapy

Study	Efficacy
CLL[1], n=16	ORR 0%, PFS 2.4 mos, OS 11.2 mos
RT[1], n=9	ORR 44%, PFS 5.4 mos, OS 10.7 mos
Real world RT[2], n=10	90% failure rate in RT, OS 2 mos

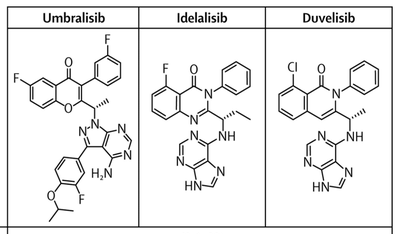
[1]Ding et al., Blood 2017; [2]Rogers et al., BJH 2018

- A key interaction exists between PI3K signaling and immune checkpoint surveillance by which inhibition of PI3K decreases PD-L1 tumor expression, suggesting potential synergistic activity with PD-1 + PI3K blockade

Umbralisib

- Umbralisib (TGR-1202) is a next generation PI3Kδ inhibitor, with a unique structure and activity profile, including:
  - A differentiated safety profile from other PI3Kδ inhibitors;
  - Oral, once-daily (QD) dosing;
  - Inhibition of casein kinase-1 epsilon (CK-1ε), a protein which may inhibit regulatory T-cell function

Comparison of Structure and Kinase Inhibition Profile[1]



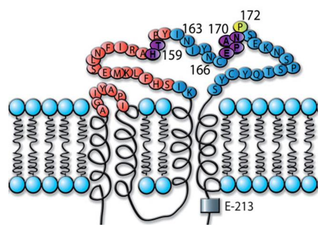
Isoform	K_d (nM)		
PI3Kα	>10,000	600	40
PI3Kβ	>10,000	19	0.89
PI3Kγ	1400	9.1	0.21
PI3Kδ	6.2	1.2	0.047
CK1ε	180	>30,000	>30,000

[1]Burris et al., Lancet Oncology 2018

Ublituximab

- Ublituximab is a novel, glycoengineered, chimeric monoclonal antibody targeting a unique epitope on the CD20 antigen, and demonstrating greater ADCC activity than rituximab and ofatumumab
- Ublituximab is currently in Phase 3 development in combination with umbralisib for patients with CLL and NHL

Ublituximab Binding Epitope



Red: Amino acids contributing to ofatumumab binding
Yellow: Amino acids essential for rituximab, but not ofatumumab binding
Purple: Core amino acids of ublituximab epitope

Study Design

- Phase I/II dose-escalation (3+3 design), multicenter study to assess the safety and efficacy of pembrolizumab in combination with umbralisib and ublituximab (U2) in pts with relapsed or refractory CLL and RT (NCT02535286)
- Correlative studies: Peripheral blood and/or bone marrow samples were collected at screening, month 2 and month 6

Study Objectives

Primary Objective
- To determine the safety of U2 + pembro in CLL and RT pts

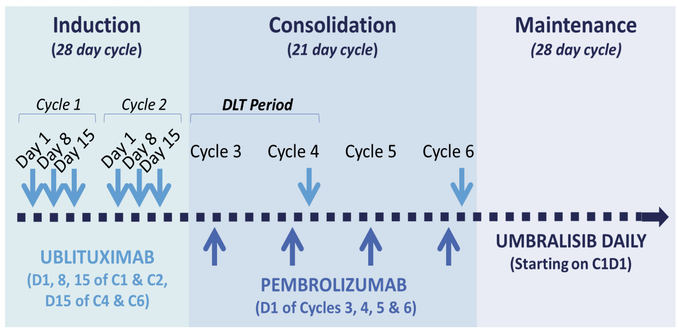
Secondary Objectives
- To evaluate efficacy
- To describe the immunophenotypic and cytokine profiles of B and T cells in subjects

Key Eligibility Criteria

- CLL or RT pts who have progressed on at least one prior therapy
  - Mid-study amendment required CLL pts to be BTK refractory (progression on or within 6 mos of prior BTK) and RT pts to be chemo-immunotherapy refractory or not eligible for high-dose chemotherapy
- No limit on # of prior therapy treatment regimens
- ANC > 750/µL, platelet count > 40,000/µL
- Prior exposure to PD-1 or PI3K inhibitor was not an exclusion

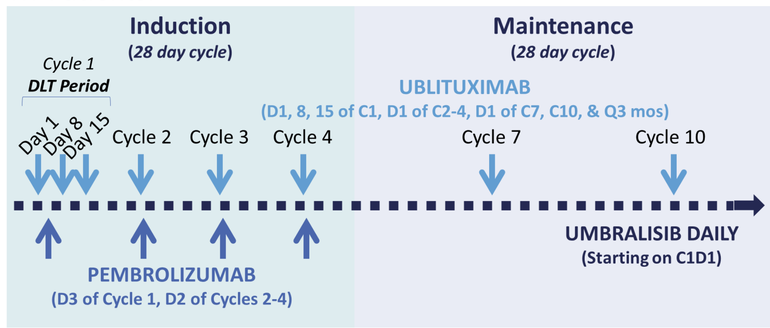
Treatment Schedule

CLL Patients:



Efficacy assessed at the end of Cycles 2, 6 & 12. After Month 12, efficacy is assessed per investigator discretion.

RT Patients:



Efficacy assessed at the end of Cycles 2 & 4 and Q3 cycles thereafter until Month 12. After Month 12, efficacy assessed per investigator discretion.

Dose Escalation Schema:

Cohort	Ublituximab	Umbralisib	Pembro
1	900 mg	800 mg	100 mg
2	900 mg	800 mg	200 mg

Results

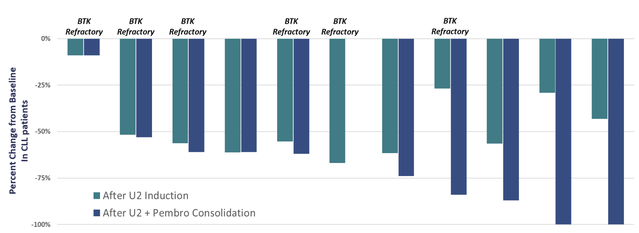
Demographics

Chronic Lymphocytic Leukemia	
Evaluable for Safety & Efficacy, n	11
Median Age, years (range)	70 (60 - 81)
Male/Female	7 / 4
ECOG, 0/1/2	5 / 6 / 0
Prior Therapy Regimens, median (range)	1 (1 – 4)
Prior BTK (ibrutinib or acalabrutinib), n (%)	7 (64%)
Refractory to prior BTK	6/7 (86%)
Refractory to immediate prior therapy, n (%)	8 (73%)
At least 1 high risk feature (del17p, del11q, TP53mut, NOTCH1mut or Complex karyotype)	8 (73%)
≥2 high risk features	6 (55%)
17p del/TP53 mutated, n (%)	3 (27%)
Complex Karyotype, n (%)	5 (45%)
NOTCH1/ATM/SF3B1mut, n (%)	5 (45%)
IGHV Unmutated, n (%)	5 (45%)
Bulky Disease, n (%)	7 (64%)

Richter's Transformation	
Evaluable for Safety, n	9
Evaluable for Efficacy†, n	8
Median Age, years (range)	66 (53 - 73)
Male/Female	6 / 3
ECOG, 0/1/2	3 / 5 / 1
Prior Therapy Regimens, median (range)	5 (1 – 9)
Prior ibrutinib	8 (89%)
Refractory to prior ibrutinib	8/8 (100%)
Prior Chemo Regimen	9 (100%)
Prior idelalisib + rituximab	2 (22%)
Prior venetoclax	3 (33%)
Prior CAR-T / Allo Transplant	3 (33%)
Refractory to immediate prior therapy	8 (89%)
Bulky Disease, n (%)	8 (89%)

†1 RT patient not evaluable – treated on CLL regimen.

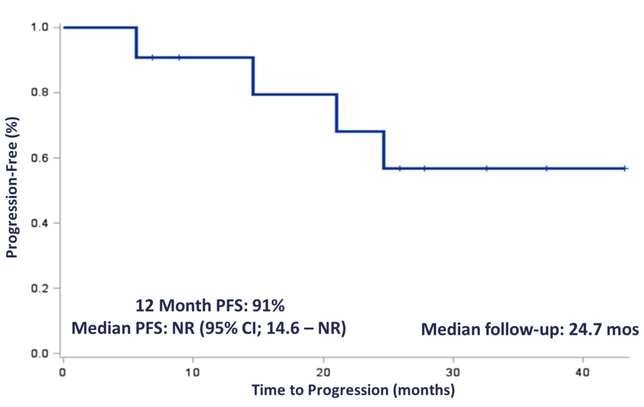
Efficacy: CLL



BTK Refractory CLL
- **ORR: 83% (5/6)**
- 80% of BTK Refractory responders (4/5) achieved response after U2 Induction, prior to addition of pembro

Group	N	CR N (%)	PR N (%)	SD N (%)	ORR N (%)
CLL	11	1 (9%)	9 (82%)	1 (9%)	10 (91%)

Progression-Free Survival for CLL (N=11)



Safety and Disposition

All Causality Adverse Events In > 20% of Patients (n=11)	All Grades		Grade 3/4	
	N	%	N	%
Neutropenia	13	65%	8	40%
Fatigue	11	55%	1	5%
Cough	10	50%		
Diarrhea	10	50%		
Pyrexia	10	50%		
Infusion related reaction	9	45%		
Nausea	9	45%	1	5%
Chills	8	40%		
Headache	8	40%		
Thrombocytopenia	8	40%	3	15%
Decreased appetite	7	35%		
Nasal congestion	7	35%		
Blood Alk Phos increased	6	30%		
Peripheral Edema	6	30%		
Anemia	5	25%	1	5%
Dizziness	5	25%		
Insomnia	5	25%		
Myalgia	5	25%		
Oral candidiasis	5	25%		
Vomiting	5	25%		

- 1 DLT at 200 mg pembro dose (transient elevated LFT - resolved); MTD not reached
- Grade 3/4 LFT elevations occurred in 4 patients (20%)
- No Grade 3/4 diarrhea and no events of colitis observed
- No Grade 3/4 pembro associated autoimmune events
- Median follow-up for all subjects: 11 mos (23 mos for CLL cohort)
- No patients had their pembro dose reduced while 3 patients had their umbralisib dose reduced (asthenia/fatigue, headache, neutropenia)

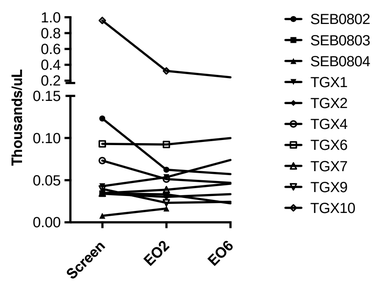
Enrollment by Cohort:

Pembro Dose	CLL	RT	Total
100 mg	5	4	9
200 mg	6	5	11

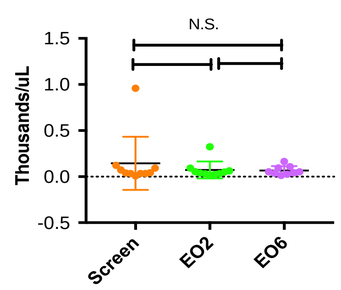
Correlatives: T-reg population

Circulating FoxP3+ CD4+ T cell levels do not change significantly in CLL study patients

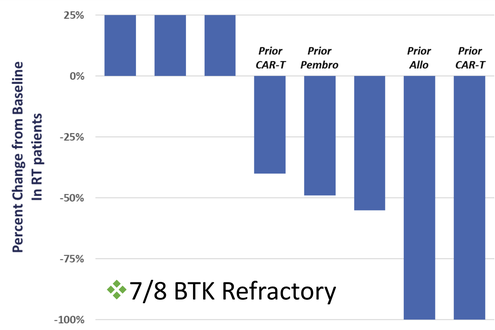
FoxP3+ CD4 Cells vs. Time



FoxP3 Column Analysis
(CD3+CD4+FoxP3+ Lymphs, PB)



Efficacy: Richter's Transformation



Group	N	CR N (%)	PR N (%)	SD N (%)	ORR N (%)
RT	8	2 (25%)	1 (12.5%)	2 (25%)	3 (38%)

Spotlight: Patient Case

U2 + Pembro: Cohort 1 - 100 mg

- Six prior lines of tx, including allo transplant
- Complete Response by end of Cycle 8
- Tolerated combination well
  - 1 G3 event of Hypophosphatemia (possible related)
  - 1 G3 event of Hyperglycemia (not related)
  - No umbralisib dose modifications required
- Subject remains on study in CR now 20+ mos

Conclusions

- **Triplet combination of umbralisib + ublituximab ("U2") + pembrolizumab was well tolerated**
  - Immune mediated toxicities were not increased above what would be expected with either umbralisib or pembrolizumab alone
- **Responses were durable in BTK refractory, high-risk pts, including two durable CRs in RT pts**
  - Data suggest that CLL pts who achieve less than CR with a checkpoint inhibitor-containing regimen can achieve durable remissions and that time-limited schedules should be explored
- **Maintenance of T-regs throughout therapy may explain limited autoimmune sequelae**
- **Enrollment is ongoing in both the CLL (BTK refractory only) and RT cohorts**
  - Protocol now amended to replace pembro with novel anti-PD-L1, cosibelimab (TG-1501)

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