Phase I/II Study of Umbralisib (TGR-1202) in Combination with Ublituximab (TG-1101) and Pembrolizumab in Patients with Relapsed/Refractory CLL and Richter's Transformation

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Background / Rationale: PD-1/PD-L1 axis

- ***Pre-clinical data supports a major role for the PD-1 and PD-L1/PD-L2 axis in mediating immune evasion in CLL:***
  - **T-cells**: PD-1 expression is significantly higher in CLL patients with increased memory and terminally differentiated cells
  - **CLL**: Higher levels of PD-L1 / PD-L2 and can inhibit T-cell proliferation and induce T-regs
  - **Microenvironment**: Within lymph node proliferation centers, PD-1+ T-cells are in close contact with PD-L1+ CLL cells
  - **TCL-1 mouse model:** Anti-PD-L1 treatment prevents aberrant T-cell subset distributions, PD-1 expression, and restores T-cell effector functions

- ***Disconnect between promising preclinical data and clinical data with anti-PD-1 monotherapy:***

Study	Efficacy
CLL (Mayo), n=16	ORR 0%, PFS 2.4 months, OS 11.2 months
RT (Mayo), n=9	ORR 44%, PFS 5.4 months, OS 10.7 months
Real world data (OSU) n=10	90% failure rate in RT, OS 2 months

Grzywnowicz et al., PLOS 2012
Brusa et al., Haem 2012
Palma et al., Haem 2017
Ringelstein-Harlev et al. Blood 2014
Ding et al., Blood 2017
Rogers et al., BJH 2018

Background / Rationale: PI3K inhibition

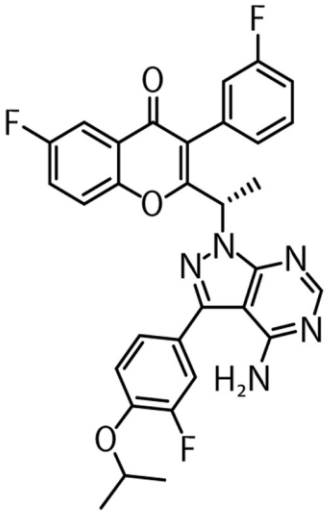
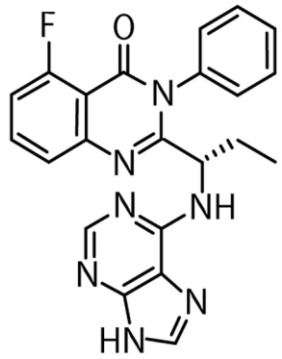
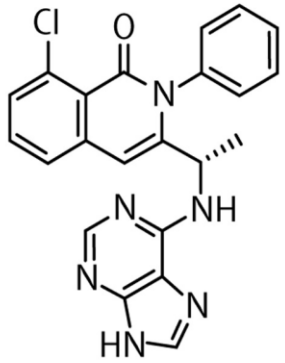
- ***PI3Kδ inhibition is hypothesized to increase innate / adaptive cell-mediated immune responses***

- ***PI3Kδ inhibition + PD-1 blockade:***
  - A key interaction exists between **PI3K signaling** and **immune checkpoint surveillance** by which **inhibition of PI3Kδ decreases PD-L1 tumor expression**, suggesting potential synergistic activity between agents that block PD-L1/PD-1 and PI3Kδ

- ***Striking a balance between dampening immune evasion and increasing immune mediated AEs:***
  - AEs observed with all PI3Kδ inhibitors may be caused by inhibition of T-regs and T-cell mediated immune effects
  - Selection of a PI3Kδ inhibitor to pair with a PD-1 inhibitor should consider its clinical activity, immune mediated toxicity profile, and effect on T-cell subsets

Umbralisib + Ublituximab ("U2")

- **Umbralisib**: Next generation PI3Kδ inhibitor, with a unique structure and improved tolerability[1]
  - Improved selectivity to PI3Kδ isoform
  - Inhibition of CK1ε
    - Potential regulator of Treg count and function
  - Ongoing long-term safety analyses demonstrate low rates of immune-mediated toxicity[2]
  - Oral – once daily administration
  - Phase 2/3 dose: 800 mg QD
- **Ublituximab**: glycoengineered anti-CD20 monoclonal antibody
  - Enhanced ADCC compared to rituximab

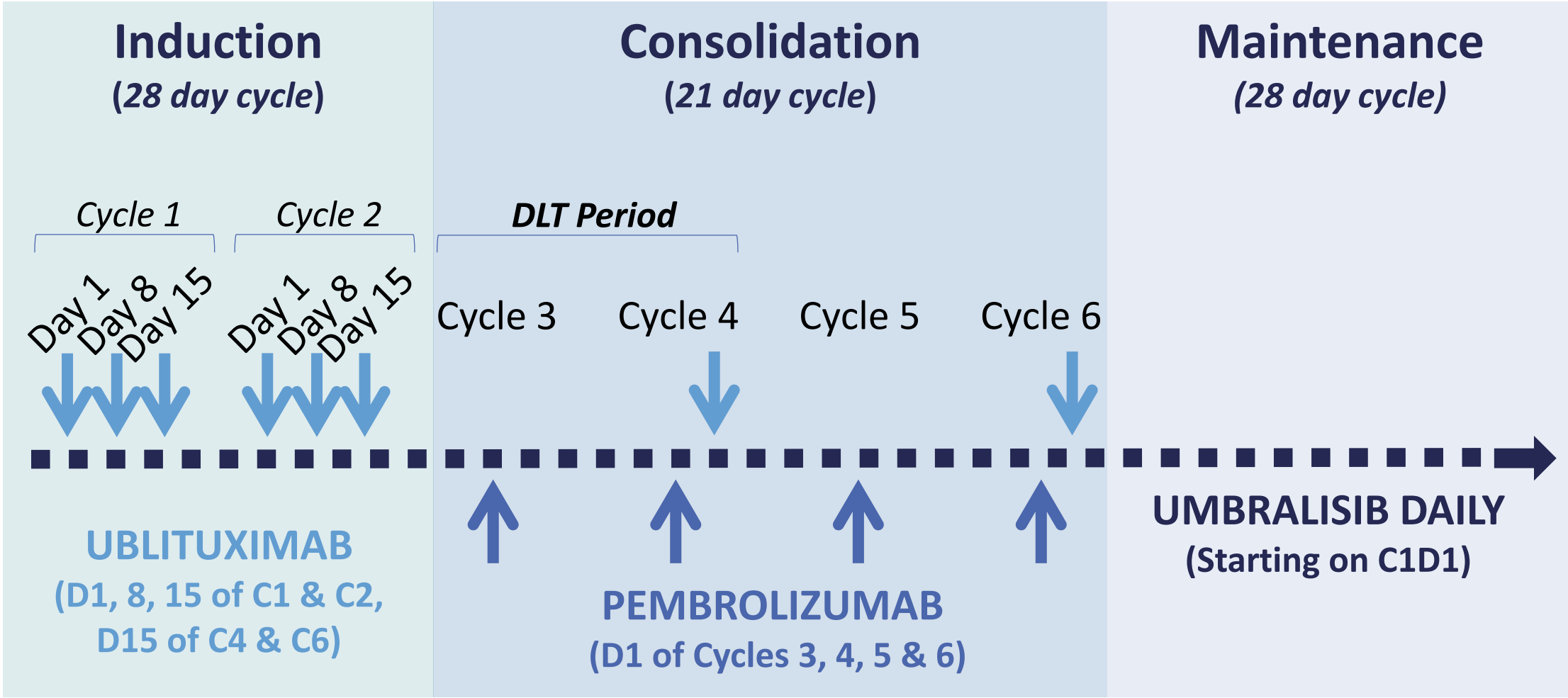
	Umbralisib	Idelalisib	Duvelisib
			
Isoform		**K_d (nM)**	
PI3Kα	>10 000	600	40
PI3Kβ	>10 000	19	0·89
PI3Kγ	1400	9·1	0·21
PI3Kδ	6·2	1·2	0·047
CK1ε	180	>30 000	>30 000

[1]Burris et al., Lancet Oncology 2018; [2]Davids et al., EHA 2018

Study Hypothesis & Rationale

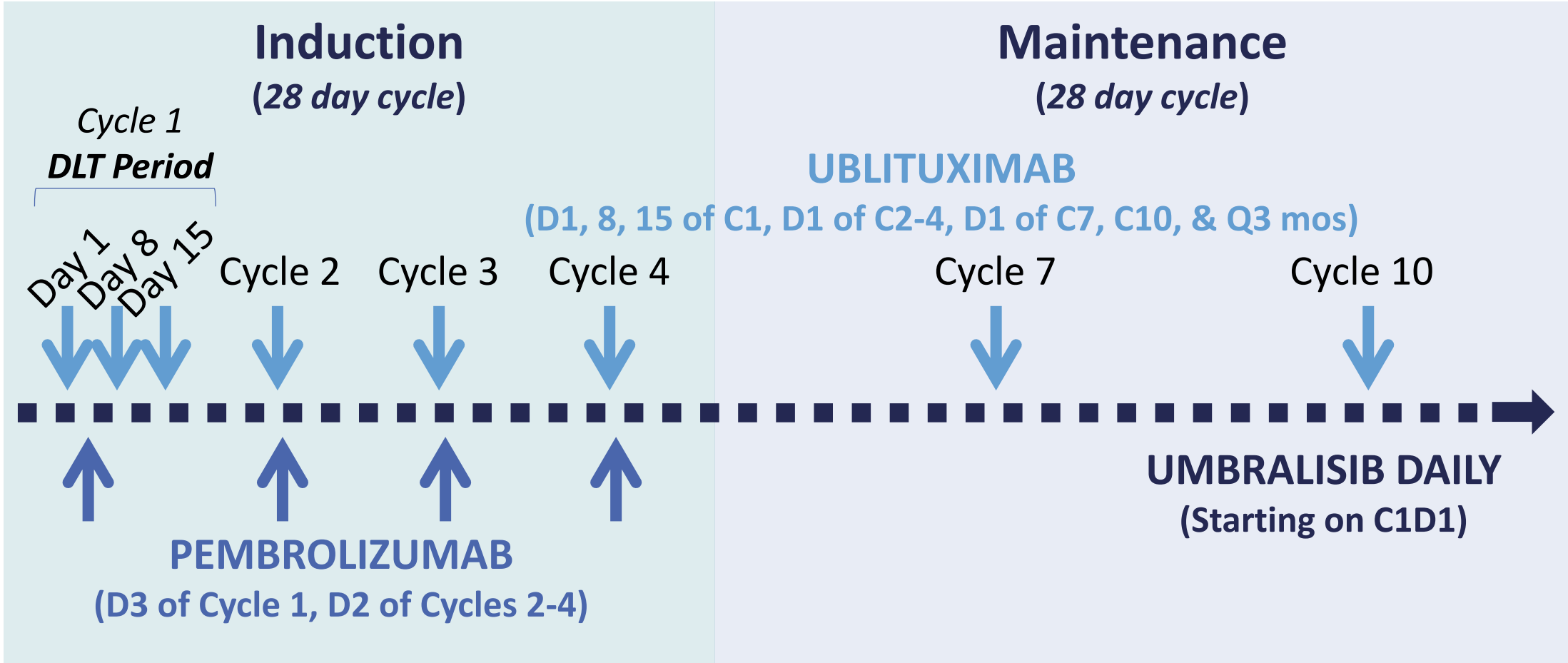
- Umbralisib was selected due to **preclinical data** showing minimal effect on T-regs and **clinical experience** showing favorable toxicity profile with minimal (but not absent) autoimmune toxicities
- **Study design:** Phase I/II dose-escalation (3+3 design), multicenter study to assess the safety & efficacy of U2 + pembro in patients with R/R CLL and RT (NCT02535286)
  - **Cohort 1: Pembo 100 mg**
  - **Cohort 2: Pembro 200 mg**
- **Correlative studies:** Peripheral blood and/or bone marrow samples were collected at screening, month 2, and month 6

Study Design: Treatment Schedule for CLL



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

Study Design: Treatment Schedule for RT



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

Study Objectives and Key Eligibility

- **Primary Objective**
  - To determine the safety of U2 + pembro in CLL and RT patients
- **Secondary Objectives**
  - To evaluate efficacy (ORR, PFS) – iwCLL (2008) & Cheson (2007)
  - To describe the immunophenotypic profiles of B and T cells
- **Key Eligibility**
  - CLL: progressed on at least one prior therapy
    - Mid-study amendment required CLL pts to be BTK refractory (PD within 6 mos of prior BTK)
  - RT: chemo-immunotherapy refractory or not eligible for high-dose chemo
  - 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

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.

Disposition and Safety

Enrollment by Cohort

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

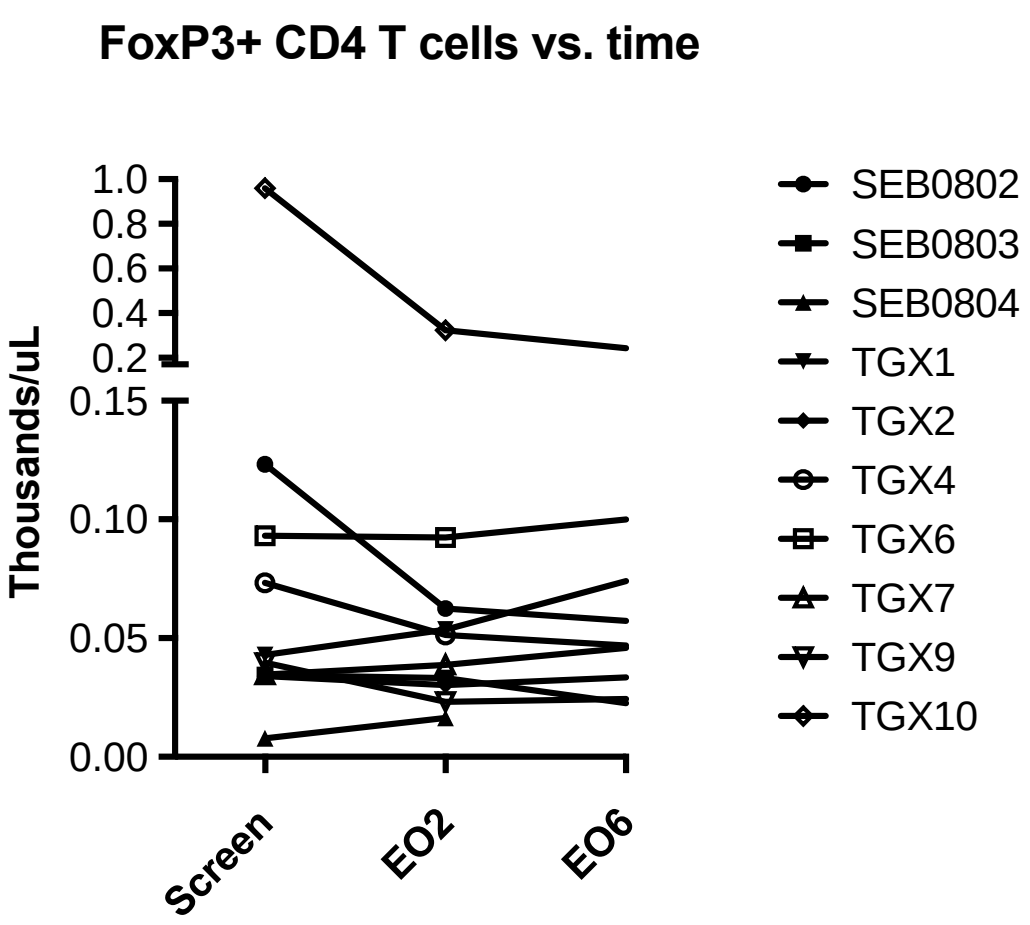
- 1 DLT at 200 mg pembro dose (transient elevated LFT - resolved); MTD not reached
- Grade 3/4 LFT elevations occurred in 4 patients (20%)
- No Grade 3/4 diarrhea and no events of colitis observed
- No Grade 3/4 pembro associated autoimmune events
- Median follow-up for all subjects: 11 mos (23 mos for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

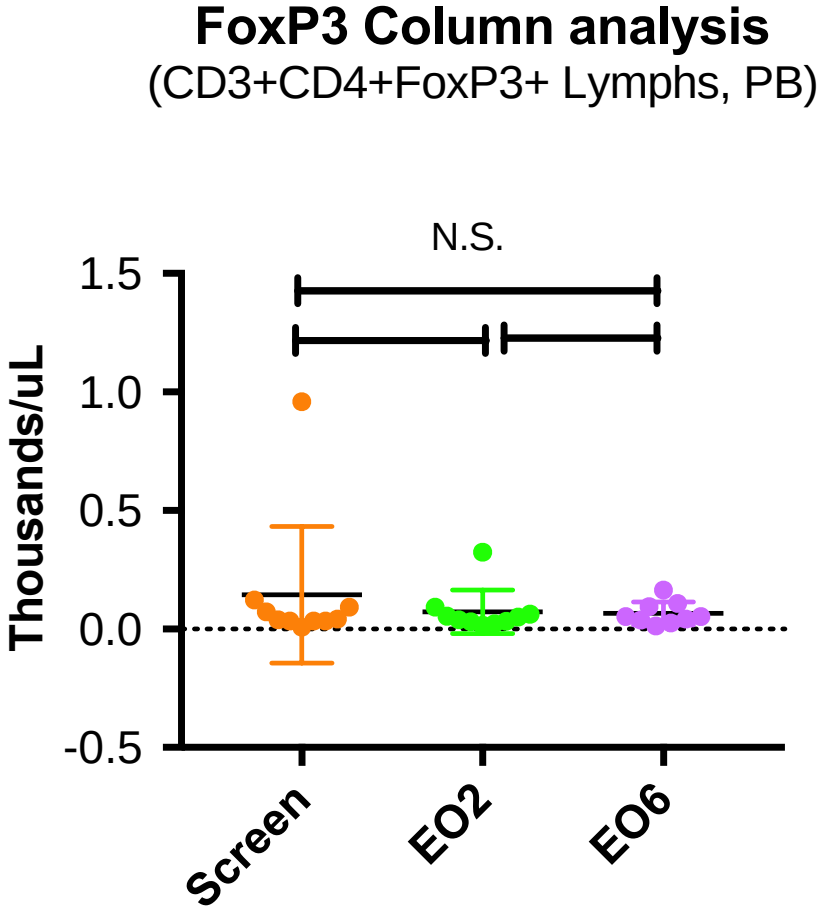
Adverse Events for (All Causality) >20% (N=20)

	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%		

Correlatives: T-reg population

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

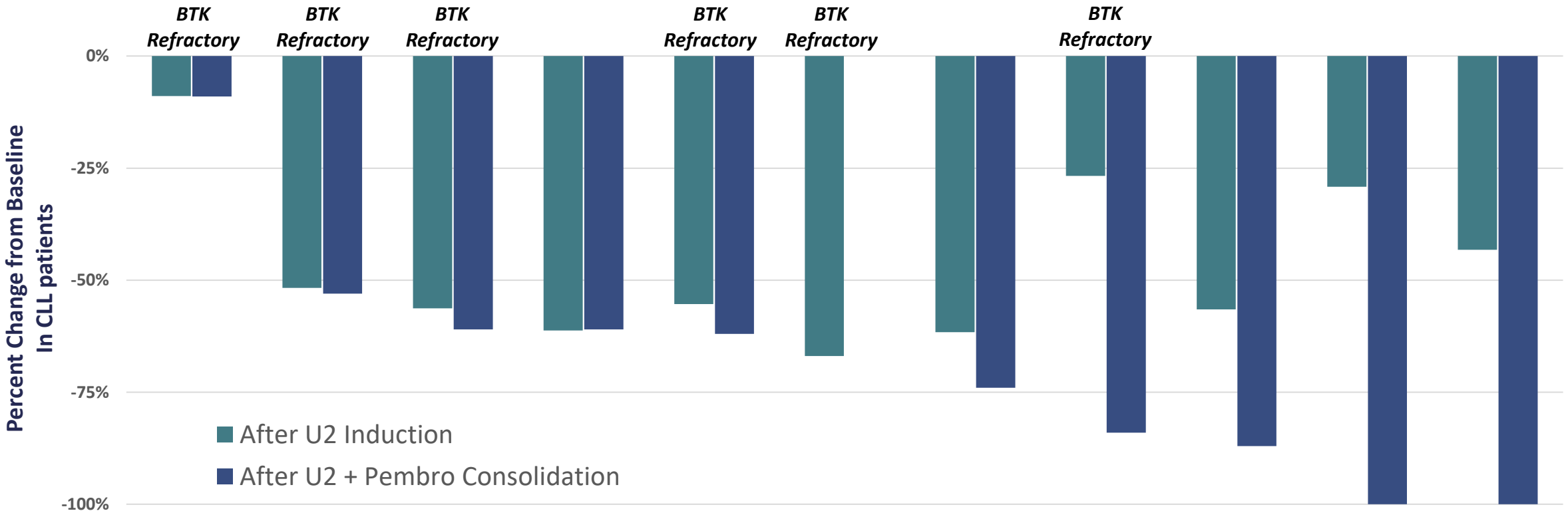




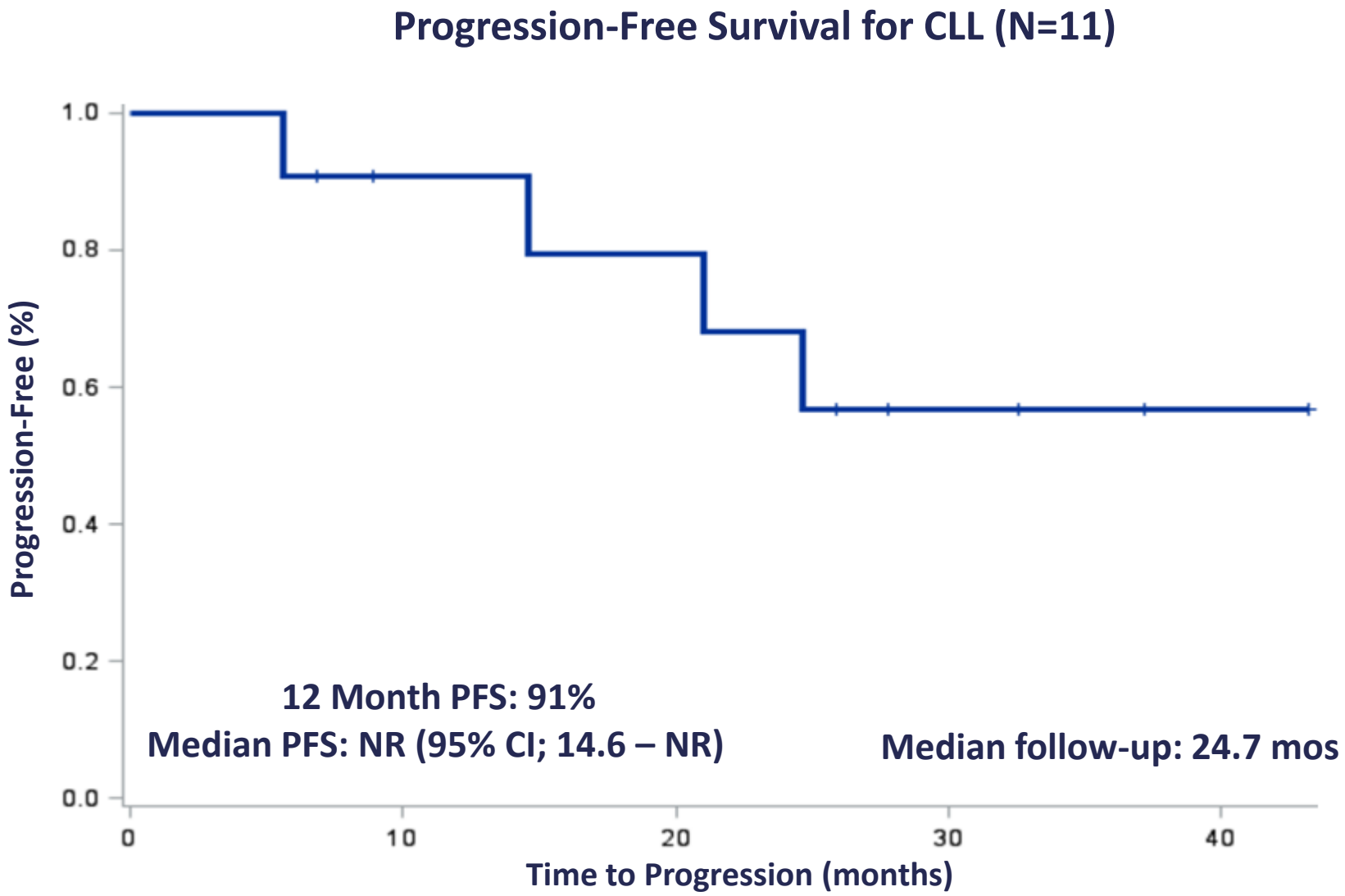
Efficacy: ORR in CLL

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

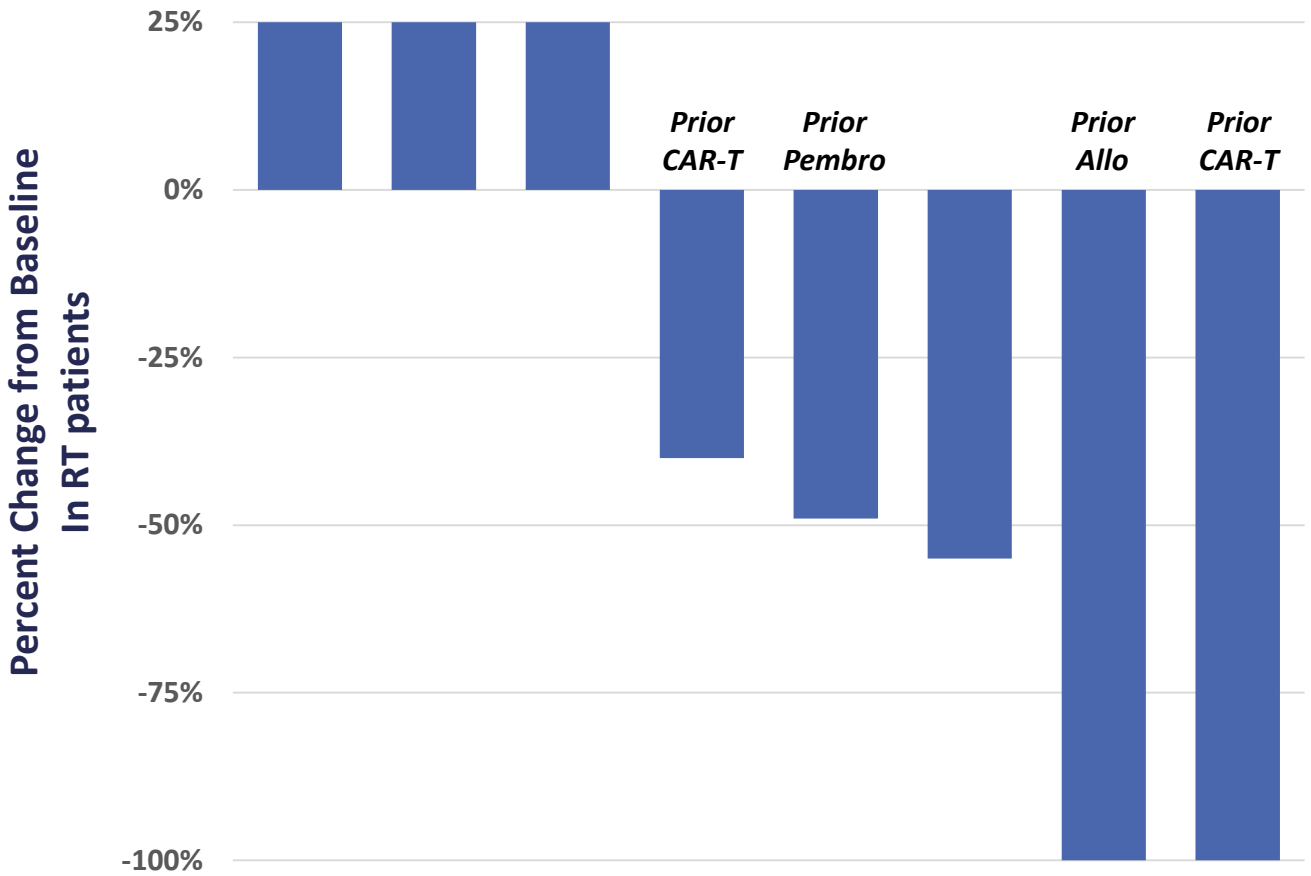
- BTK Refractory CLL
  - **ORR: 83% (5/6)**
  - 80% of BTK Refractory responders (4/5) achieved response after U2 Induction, prior to addition of pembro



Efficacy: PFS for the CLL Subjects



Efficacy: ORR in Richter's



- Heavily refractory Richter's
  - 7/8 BTK Refractory
  - Durable responses observed

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

RT Patient 1: Case Study

- 73 yo Male
- Cytogenetics: 17p/11q del
- Prior Treatment History for CLL:
  - **2010**: FCR
  - **2014**: BR
  - **2014**: Ibrutinib
  - **2015**: Idelalisib + rituximab
  - **2015**: CD19 - CAR-T
  - **2017**: Ibrutinib again for 4 mos… progressed with Richter's
- Prior Treatment for RT:
  - **Oct 2017**: CD19 CAR-T → ibrutinib
  - Not eligible for HD chemotherapy

Started U2 + Pembro

Cohort 1 - 100 mg

- **End of Cycle 2**: 76%↓ - PR
- **End of Cycle 5**: Complete Response
  - **PET-negative** by Lugano Criteria (Cheson 2014)
- Tolerated U2 + Pembro well
  - 1 G3/4 AE: neutropenia
  - Umbralisib held for 4 days, G-CSF initiated and recovered. Resumed full dose umbralisib

<u>Subject remained in CR for 12 months</u>

RT Patient 2: Case Study

- 62 yo Male
- Prior Treatment History for CLL:
  - **2008**: PCR
  - **2011**: BR
  - **2013**: FCR
  - **2013**: Ofatumumab + Fludara + Cyclophosphamide
  - **2014**: Alemtuzumab
  - **2014**: Allo Transplant
- Prior Treatment for RT:
  - **Nov 2014**: R-CHOP + Ibrutinib
    - PD while on Ibrutinib in 2017
    - Target Lesion SPD = 45 cm

Started U2 + Pembro

Cohort 1 - 100 mg

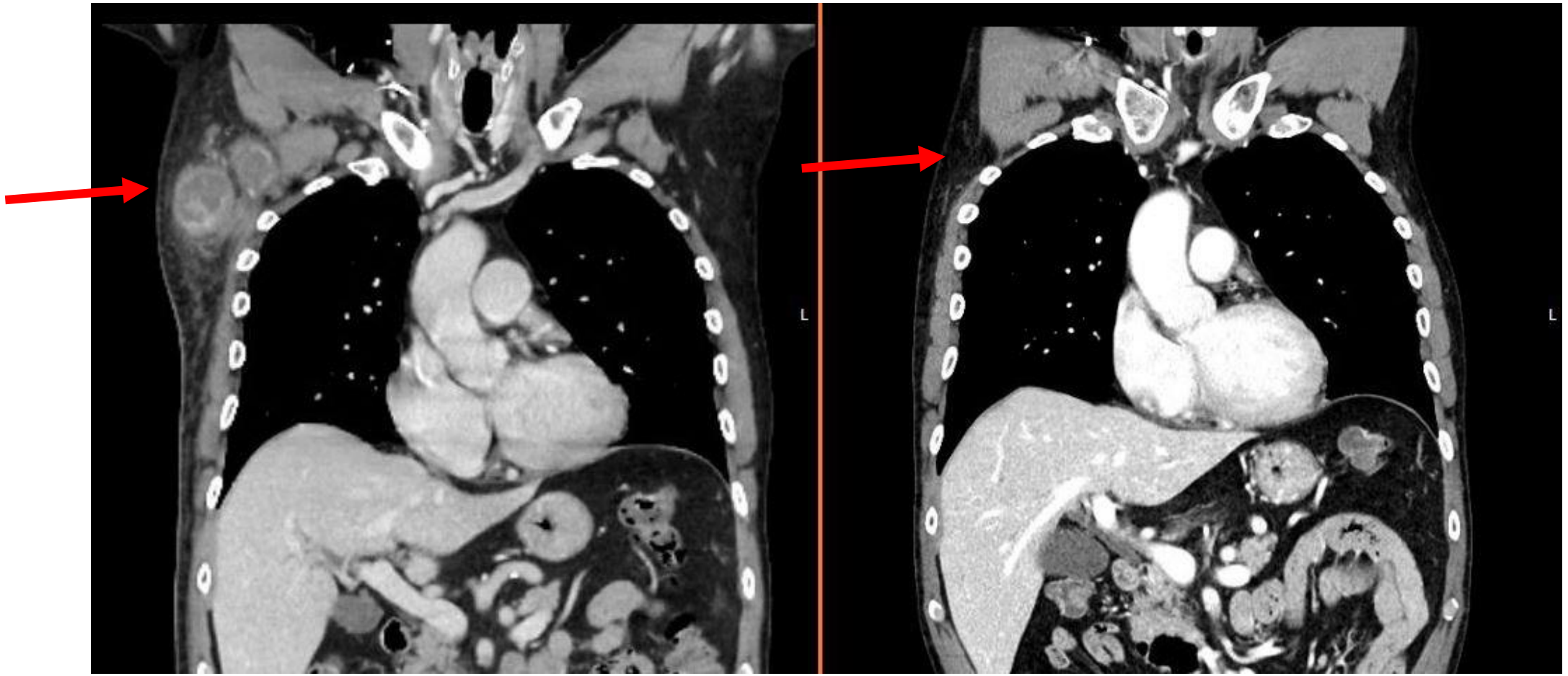
- **End of Cycle 2**: 76%↓ - PR
- **End of Cycle 5**: 78%↓ - PR
- **End of Cycle 8**: Complete Response
  - **PET-negative** by Lugano Criteria (Cheson 2014)
- Tolerated U2 + Pembro well
  - 1 G3 event of Hypophosphatemia (possible related)
  - 1 G3 event of Hyperglycemia (not related)
  - No umbralisib dose modifications required

Subject remains on study in CR now 20+ mos

RT Patient 2: Case Study CR (cont'd)

Baseline CT

End of Cycle 8 CT



Subject remains in Complete Response now 20+ mos on trial

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 amendment underway to replace pembro with novel anti-PD-L1 (TG-1501)

Acknowledgements

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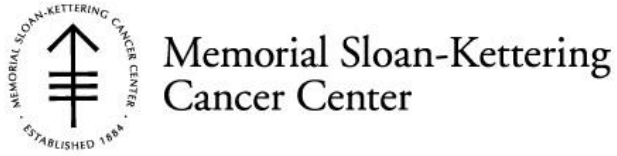
- Participating Centers:



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