Umbralisib as a backbone for combination therapy in CLL and lymphomas

The future of umbralisib

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NEW DRUGS IN HEMATOLOGY
BOLOGNA 2018

Disclosures

- Research
  - TG Therapeutics
  - Pharmacyclics
  - Abbvie
  - Johnson and Johnson
  - Acerta / AZ
  - Regeneron
  - DTRM BioPharma
  - Sunesis
  - Loxo
- Advisory / Consultancy
  - TG Therapeutics
  - Pharmacyclics
  - Abbvie
  - Johnson and Johnson
  - Acerta / AZ
  - DTRM BioPharma
  - Sunesis
  - Celgene

Umbralisib monotherapy…

- WELL TOLERATED
- ACTIVE IN CLL / lymphoid malignancies
- Minimal drug drug interactions
- AE profile distinct from other Pi3k delta inhibitors in terms of
  - Rate of discontinuation
  - Immune mediated toxicities
  - Even in kinase inhibitor intolerant patients and with long term follow up

Is umbralisib the ideal backbone for Pi3k inhibitor based combination therapies?

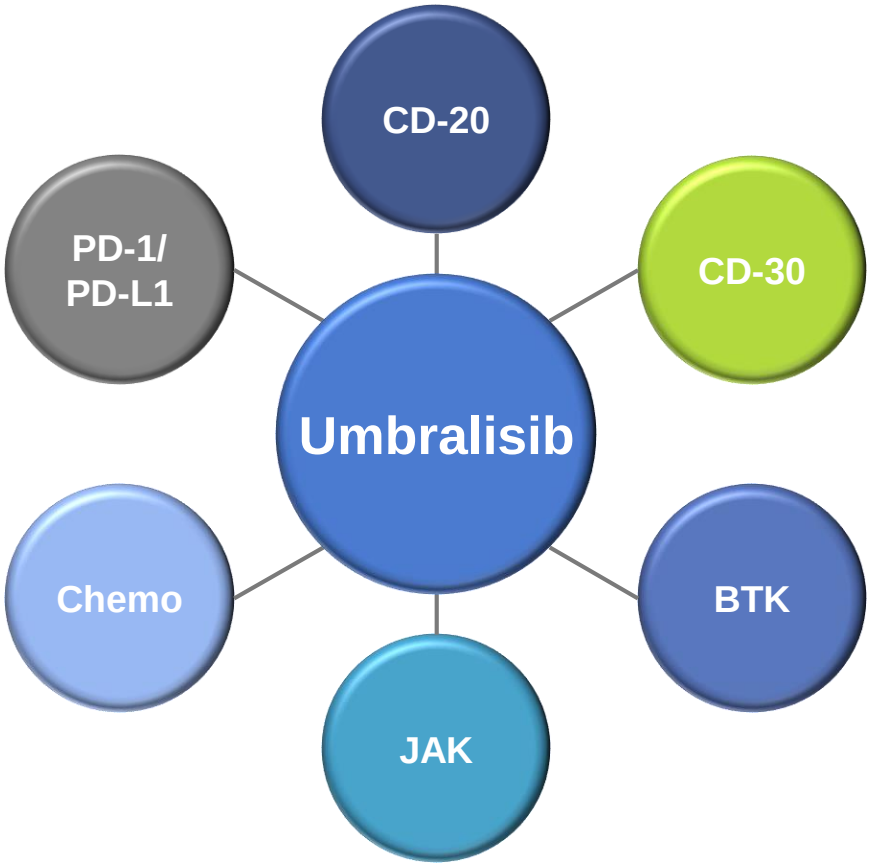
And where does this fit into the current space where ibrutinib and venetoclax are mainstays of therapy?

Proposed goals of novel agent combination therapy in CLL

- Improve **depth of response** over targeted agents monotherapies
- **Develop fixed duration** schedules over treat to progression approaches
- **Overcome poor risk features** of CLL where outcomes may be inferior with targeted agents as monotherapies (del17p, complex karyotype?)
- **Modify disease biology** – minimize resistance, transformation and secondary malignancies

Umbralisib in 2018 …

UMBRALISIB IN COMBINATION



Completed & Ongoing Combination Studies
Doublets
umbralisib + ublituximab
umbralisib + ibrutinib
umbralisib + brentuximab vedotin
umbralisib + ruxolitinib
Triplets
umbralisib + ublituximab + ibrutinib
umbralisib + obinutuzumab + Clb
umbralisib + ublituximab + pembrolizumab
umbralisib + ublituximab + bendamustine

Umbralisib + Ublituximab

Ublituximab + TGR-1202 Demonstrates Activity and a Favorable Safety Profile in Relapsed/Refractory B-Cell NHL and High-Risk CLL: Phase I Results

Matthew Lunning, DO[1], Julie Vose, MD[1], Nathan Fowler, MD[2], Loretta Nastoupil, MD[2], Jan A. Burger, MD[2], William G. Wierda, MD[2], Marshall T. Schreeder, MD[3], Tanya Siddiqi, MD[4], Christopher R. Flowers, MD[5], Jonathon B. Cohen, MD[5], Susan Blumel, RN, BSN[1], Myra Miguel, RN[2], Emily K. Pauli, PharmD[3], Kathy Cutter, RN[3], Christine McCarthy[4], Ryan Handy, BS[5], Peter Sportelli[6], Hari P. Miskin, MS[6], Michael S. Weiss[6] and Susan O'Brien, MD[7]

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Study Design

Study UTX-TGR-103 (NCT02006485) is a Ph I/Ib trial evaluating the combination of ublituximab + TGR-1202 in patients with relapsed or refractory NHL and CLL. The study is divided into two parts:

- **Phase I:** 3+3 Dose Escalation evaluating Cycle 1 DLTs (CLL & NHL separately)
- **Phase Ib:** Dose Expansion

Dose Escalation Schema:

Cohort	Ublituximab NHL Dose	Ublituximab CLL Dose	TGR Dose (QD)
1	900 mg	600 mg	800 mg
2	900 mg	600 mg	1200 mg
3	900 mg	900 mg	400 mg (micronized)
4	900 mg	900 mg	600 mg (micronized)
5	900 mg	900 mg	800 mg (micronized)
6	900 mg	900 mg	1000 mg (micronized)
7	900 mg	900 mg	1200 mg (micronized)
Expansion	*TGR-1202 at 800 mg, 1000 mg and 1200 mg micronized*		

Key Eligibility Criteria

- Confirmed B-cell non-Hodgkin lymphoma (NHL) or CLL/small lymphocytic lymphoma (SLL), and select other B-cell malignancies
- Relapsed after, or refractory to, at least 1 prior treatment regimen with no limit on prior therapies
- ECOG performance status ≤ 2
- Adequate organ system function: ANC ≥ 750/µL; platelets ≥ 50 K/µL *(ANC > 500/µL; platelets > 30 K/µL permitted with BM infiltration)*
- Patients with Richter's Transformation, or **refractory to prior PI3Kδ inhibitors or prior BTK inhibitors are eligible**.

Demographics

Evaluable for Safety (n)	71	
Evaluable for Efficacy† (n)	58	
Median Age, years (range)	65 (26 – 86)	
Male/Female	47/24	
Histology	**DLBCL**	24
	CLL/SLL	19
	FL	19
	MZL	6
	MCL	2
	Richter's	1
ECOG, 0/1/2	20/47/4	
Prior Therapy Regimens, median (range)	3 (1 – 10)	
Patients with ≥ 3 Prior Therapies (%)	61%	
Prior RTX Based Therapies, median (range)	3 (1 – 7)	
Refractory to Prior Therapy, n (%)	41 (58%)	

†13 Patients not evaluable (9 too early, 2 non-related AE, 1 removed per investigator discretion, 1 for SAE, 1 ineligible)

- Heavily pre-treated population with high-risk features, including 58% refractory to last treatment with multiple previous lines of rituximab (RTX) based therapy

Safety

All Causality AE's Occurring in ≥ 10% of Patients (n = 71)

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Nausea	33	46%	1	1%
Diarrhea	31	44%	2	3%
Fatigue	29	41%	2	3%
Neutropenia	21	30%	18	25%
Infusion related reaction	18	25%	1	1%
Vomiting	17	24%	-	-
Dyspnea	14	20%	2	3%
Back pain	13	18%	-	-
Dizziness	13	18%	-	-
Pyrexia	13	18%	2	3%
Decrease appetite	12	17%	-	-
Insomnia	12	17%	-	-
Sinusitis	11	15%	1	1%
Cough	10	14%	-	-
Anemia	9	13%	1	1%
Constipation	8	11%	-	-
Headache	8	11%	-	-
Vitamin D decrease	8	11%	-	-
Hypophosphatemia	7	10%	1	1%
Peripheral edema	7	10%	1	1%
Rash	7	10%	-	-

- Discontinuations due to AE: 8%
- Transaminitis: Grade 3/4 AST/ALT: 3%
- Dose reductions: 10%
- Addition of anti CD 20 did not seem to increase AEs monotherapy

Efficacy

Type	Patients Exposed to TGR-1202 Higher* Doses					
	Pts (n)	CR (n)	PR (n)	ORR n (%)	SD (n)	PD (n)
CLL/SLL	10	1	7	**8 (80%)**	2	-
DLBCL	16	3	2	**5 (31%)**	2	9
FL/MZL	17	4	8	**12 (71%)**	4	1
MCL	2	-	-	**0**	-	2
Richter's	1	-	1	**1 (100%)**	-	-
*Higher Dose = 1200 original formulation and 600 or > micronized						

- **CLL:** 75% of CLL patients had high-risk cytogenetics (17p and/or 11q del)
- **FL:** Patients were heavily pretreated with 75% of patients having been exposed to ≥ 3 prior therapies (range 1-9)
- **DLBCL:** 94% of DLBCL patients were refractory to prior regimen with 69% rituximab refractory, including one patient with triple hit lymphoma (BCL2, BCL6, and MYC rearrangements)

Conclusions

- Ublituximab in combination with TGR-1202 is well tolerated and highly active in a broad population of heavily pretreated and high-risk patients with NHL and CLL

- Discontinuations due to adverse events have been limited (8%) and the only Grade 3/4 AE reported in > 5% of patients was neutropenia

- Safety profile supports multi-drug regimens

U2 SELECTED FOR COMPARISON IN PHASE 3 STUDY IN CLL (R/R, front line)

Results are pending…

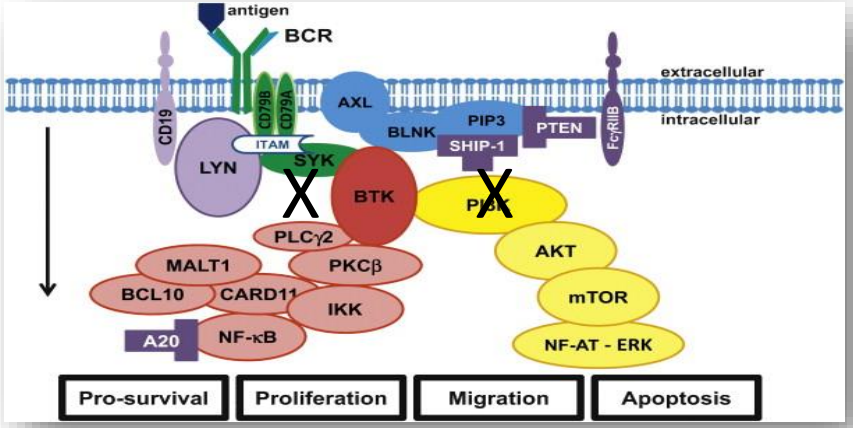
Study design very important as it contains novel agent (TGR 1202) monotherapy as a control arm!

Exploratory combinations with U2 backbone

+ Ibruntinib
+ Ibrutinib and Ublituximab
+ Pembroluzimab

UMBRALISIB PLUS IBRUTINIB

Updated Results of a Multicenter Phase I/IB Study of Umbralisib (TGR-1202) in Combination with Ibrutinib in Patients with Relapsed or Refractory MCL or CLL



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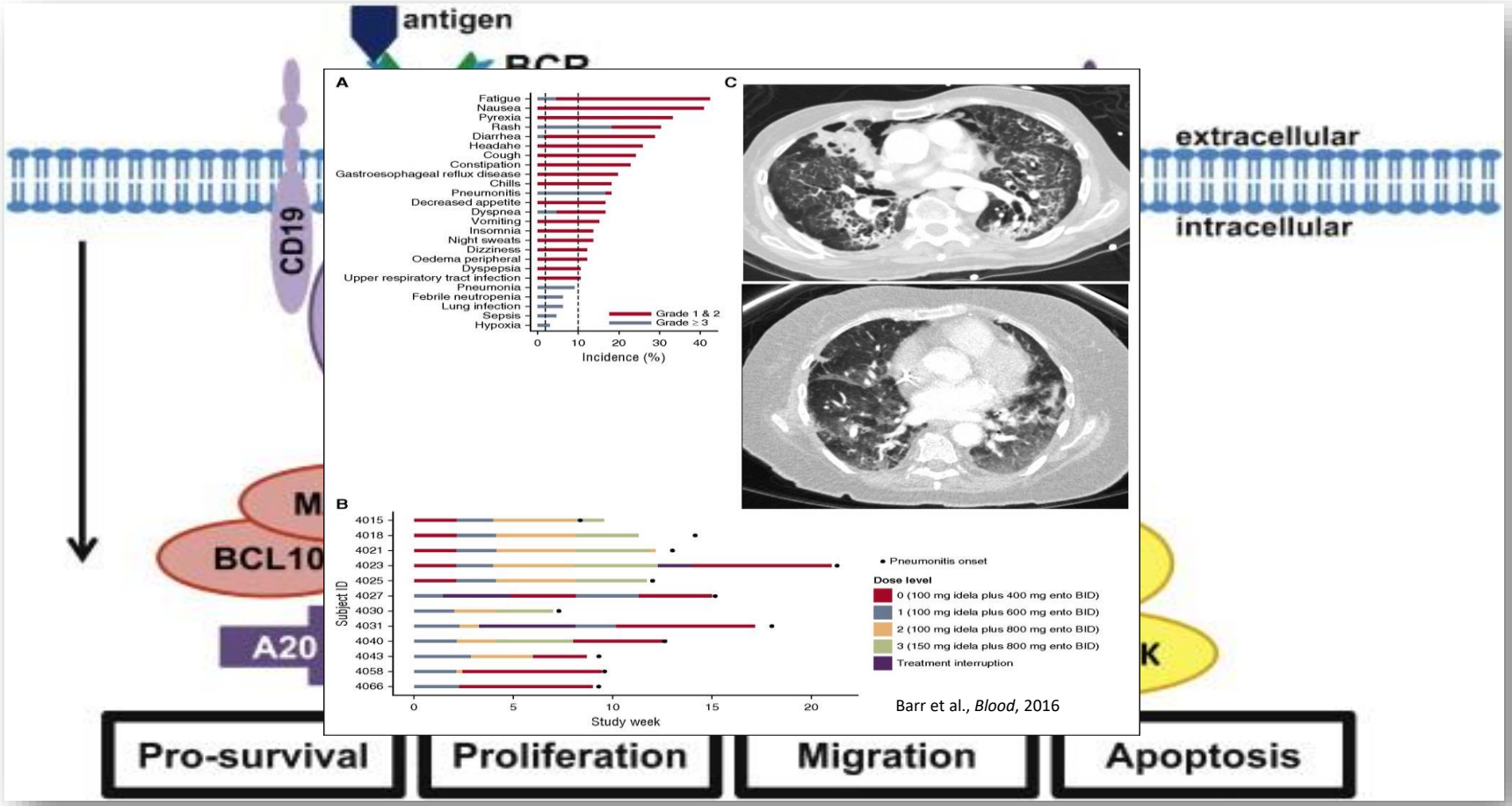
for the *Leukemia & Lymphoma Society Blood Cancer Research Partnership (LLS/BCRP)*

2017 ICML – Lugano, Switzerland – June 14, 2017

Background

Inhibiting multiple BCR pathway kinases may deepen and prolong response and overcome resistance mutations



Niemann et al., *Seminars in Cancer Biology*, 2013

Study Design

A phase I/Ib investigator-initiated multicenter trial of umbralisib (TGR-1202) + ibrutinib in R/R CLL and MCL

Endpoints

Primary:
- MTD, safety, and DLTs of TGR-1202 + ibrutinib

Secondary:
- Clinical response: ORR, CR, PR, PR-L, PFS, and remission duration
- Association of CLL prognostic factors with response

Exploratory:
- Association of novel prognostic factors such as BH3 profiling and somatic mutations with response

Key Eligibility Criteria

Inclusion:
- ≥1 prior standard therapy
- ANC ≥ 0.5 K/uL, platelets ≥ 30 K/uL
- Intact renal/hepatic function
- Ph I: pts with prior BTK/PI3Ki therapy were eligible

Exclusion:
- AutoSCT < 3 mo. or alloHCT < 12 mo. of study entry
- Active GVHD, immune suppression
- Active hepatitis, HIV, CNS involvement
- Require warfarin

Treatment Plan

- Parallel MCL/CLL arms, escalated independently
- TGR-1202: oral, daily (qam) and ibrutinib: oral, 420 mg daily for CLL, 560 mg daily for MCL (qpm)
- Both agents continued until time of progression or unacceptable toxicity
- Toxicity assessments by CTCAE v4.03, efficacy by 2008 IW-CLL or 2014 Lugano criteria (MCL)
- Phase Ib exp cohorts of 12 pts each in MCL/CLL

Dose Level	TGR-1202 Dose	Ibrutinib Dose CLL	Ibrutinib Dose MCL
1	400 mg	420 mg	560 mg
2	600 mg	420 mg	560 mg
3	800 mg	420 mg	560 mg
If > 2 DLTs in Cohort 1, 3- 6 pts will enroll in Cohort -1 as follows:			
-1	200 mg	420 mg	560 mg
If > 2 DLTs in Cohort –1, study will be terminated			

Results

Patient Characteristics (n=32)

	All (n=32)	MCL (n=14)	CLL (n=18)
Age, median (range)	67 (48-83)	67 (50-83)	67 (48-76)
Sex, male	20 (64.5%)	10 (77%)	10 (56%)
Prior therapy, median (range)	2 (1-6)	3 (2-5)	1.5 (1-6)
Prior autoSCT	4/32 (13%)	4/14 (29%)	0
Prior ibrutinib	4/32 (13%)	2/14 (14%)	2/18 (11%)
Prior PI3K inhibitor	4/32 (13%)	0%	4/18 (22%)
WBC (K/uL), median (range)	11.2 (3.9-338)	8.1 (4-338)	16.7 (3.9-116.8)
Hgb (g/dL), median (range)	11.7 (7.7-15.9)	12.4 (7.8-15.9)	11.2 (7.7-15.1)
Platelets (K/uL), median (range)	179 (45-316)	146 (75-290)	194 (45-316)
Beta-2M (mg/L), median (range)	4.1 (2.2-19.7)	4.2 (2.6-19.7)	4.1 (2.2-9.2)
Del(17p)			4/18 (22%)
Del(11q)			7/18 (39%)
Unmutated *IGHV*			12/18 (67%)
TP53 mutation			3/18 (17%)
NOTCH1 mutation			2 pts (limited testing)

Note: Three pts signed consent but never received study treatment due to not meeting eligibility criteria on C1D1, and are not included above or in subsequent analyses

Results

Additional Safety Analysis

CLL (n=18)

All grade non-heme toxicities in ≥20%*:

- Nausea: 39%, (33% Gr 1, 6% Gr2)
- Diarrhea: 28% (17% Gr 1, 11% Gr 2)
- Dizziness: 22% (all Gr 1)
- Fatigue: 22% (all Gr 1)

SAEs (in 1 patient each):

- Lipase elevation (Gr 3)
- Atrial fibrillation (Gr 3)
- Adrenal insufficiency (Gr 3)
- CNS aspergillus infection (Gr 3)
- Sudden death, uncertain cause (Gr 5)

Dose reduction:

- Ibrutinib: 3 patients (atrial fib, palpitations, vitreous hemorrhage)
- TGR-1202: 1 patient (diarrhea)

* Excludes asymptomatic , low-grade laboratory abnormalities

MCL (n=14)

All grade non-heme toxicities in ≥20%*:

- Fatigue: 43% (29% Gr 1, 14% Gr 2)
- Diarrhea: 36% (all Gr 1)
- Nausea: 36% (29% Gr 1, 7% Gr 2)
- Dizziness: 29% (all Gr 1)
- Anorexia: 20% (all Gr 1)
- Bruising: 21% (all Gr 1)
- Headache: 21% (all Gr 1)

SAEs:

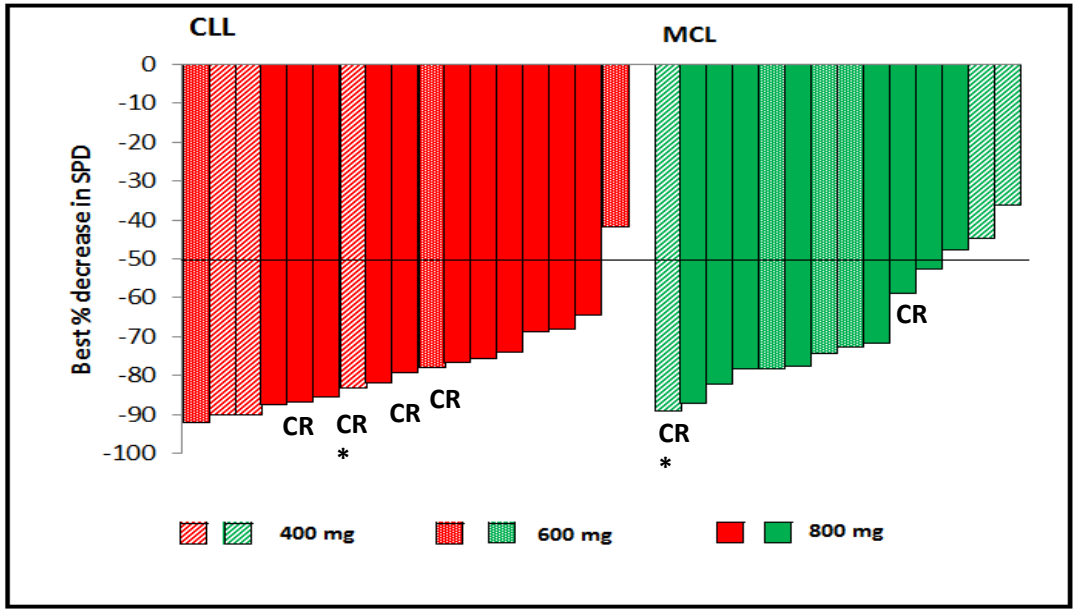
- Hypophosphatemia (n=2, both Gr 3)
- Lipase elevation (n=1, Gr 4)
- Atrial fibrillation (n=1, Gr 3)
- C. difficile infection (n=1, Gr 3)
- Influenza A infection (n=1, Gr 4)

Dose reduction:

- TGR-1202: 1 patient (dizziness)

Results

Updated Efficacy Analysis (n=31)



CLL (n=17)

- ORR: 16/17 (94%)
  - -PR or PR-L: 15/17 (88%)
  - -CR: 1/17 (6%), 3 other pts with radiographic CR
- All 3 pts with prior PI3Ki and 1 of the 2 pts with prior ibrutinib responded

MCL (n=14)

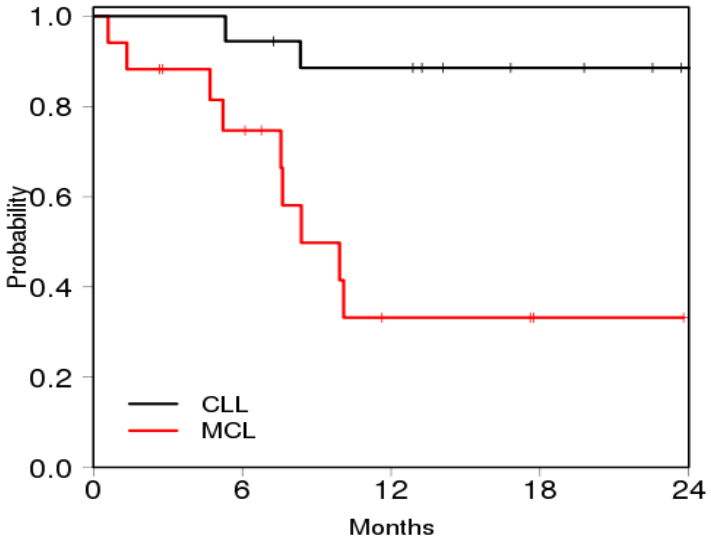
- ORR: 11/14 (79%)
- PR: 10/11 (71%)
- CR: 1/11 (9%), 1 other pt with radiographic CR
- Marked clinical benefit observed in 2 additional pts

*meets formal disease–specific criteria for CR

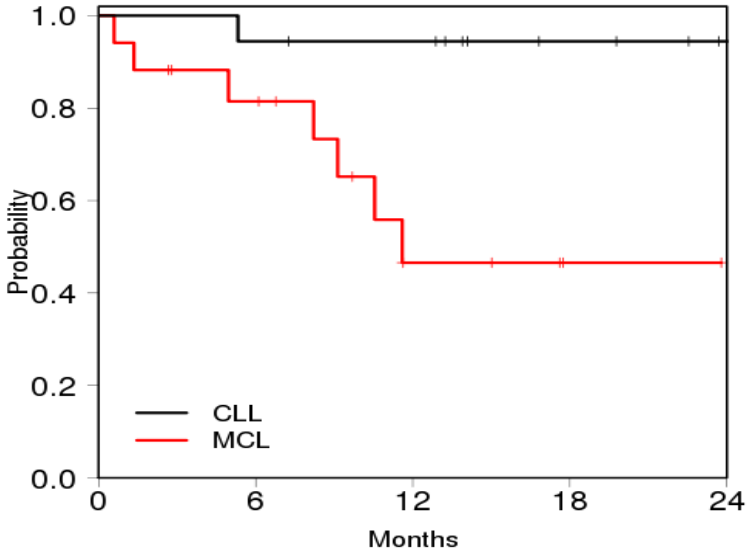
Results

Updated Efficacy Analysis (n=31)

PFS



OS



- Median follow-up time among survivors: 14 mo. (range 0.8-29.5)
- 1-year PFS for CLL is 88%, 1-year OS is 94%
- Median PFS and OS for MCL is 8.4 and 11.6 mo.
- 1 CLL pt has died due to progressive disease
- 6 MCL pts have died (5 due to PD, 1 due to tox from next therapy)

Well tolerated but

Not clear that the depth of response better than either agent alone…

U2 PLUS IBRUTINIB

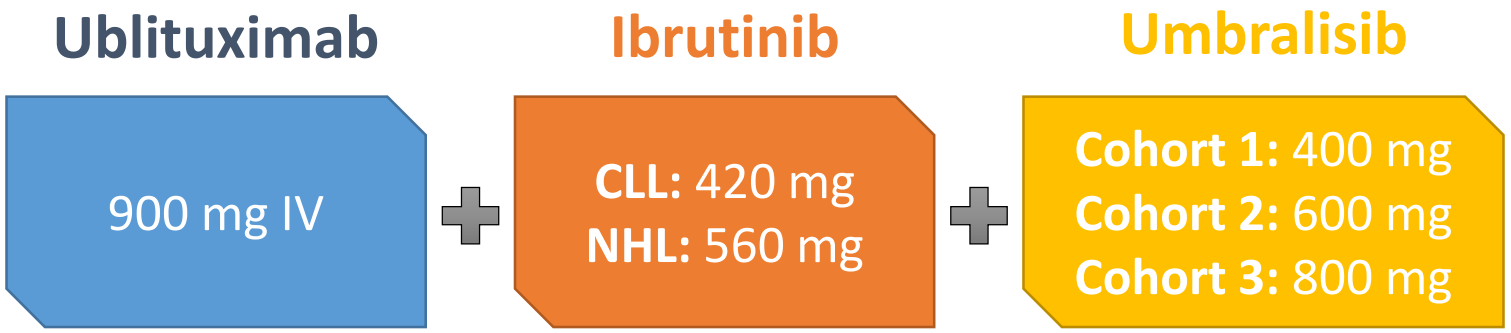
Tolerability and activity of chemo-free triplet combination of umbralisib (TGR-1202), ublituximab, and ibrutinib in patients with advanced CLL and NHL

Loretta Nastoupil, MD[1], Matthew A. Lunning, DO[2], Julie M. Vose, MD[2], Marshall T. Schreeder, MD[3], Tanya Siddiqi, MD[4], Christopher R. Flowers, MD[5], Jonathon B. Cohen, MD[5], Jan A. Burger, MD[1], William G. Wierda, MD[1], Susan O'Brien, MD[6], Peter Sportelli[7], Hari P. Miskin, MS[7], Michelle A. Purdom, RN, PhD[7], Michael S. Weiss[7] and Nathan H. Fowler, MD[1]

[1]MD Anderson Cancer Center, Houston, TX; [2]University of Nebraska Medical Center, Omaha, NE; [3]Clearview Cancer Institute, Huntsville, AL; [4]City of Hope National Medical Center, Duarte, CA; [5]Emory University/Winship Cancer Institute, Atlanta, GA; [6]University of California Irvine Cancer Center, Orange, CA; [7]TG Therapeutics, Inc., New York, NY

Presented at the 14th International Conference on Malignant Lymphoma
Lugano, Switzerland ● June 14 – 17, 2017

Study Design



- Enrolling patients with CLL (naïve & previously treated) and NHL (relapsed or refractory only)
- 3 + 3 dose escalation design (CLL and NHL independently)
- No limit on prior # of therapies
- ECOG Performance Status ≤ 2
- ANC ≥ 500/µL; platelets ≥ 30 K/µL
- Patients with Richter's Transformation, or refractory to prior PI3Kδ inhibitors or prior BTK inhibitors are eligible

Demographics

Evaluable for Safety (n)	38	
Evaluable for Efficacy† (n)	36	
Median Age, years (range)	65 (32 – 85)	
Male/Female	29/9	
Histology	CLL/SLL	20
	DLBCL	6
	FL	6
	MCL	4
	MZL	2
ECOG, 0/1/2	14/21/3	
Prior Therapy Regimens, median (range)	3 (0 – 6)	
Patients with ≥ 3 Prior Therapies, n (%)	21 (55%)	
Refractory to Prior Therapy, n (%)	13 (34%)	
Refractory to Rituximab, n (%)	15 (39%)	

†2 patients discontinued prior to first efficacy assessment (1 Pneumonia, 1 Investigator Discretion)

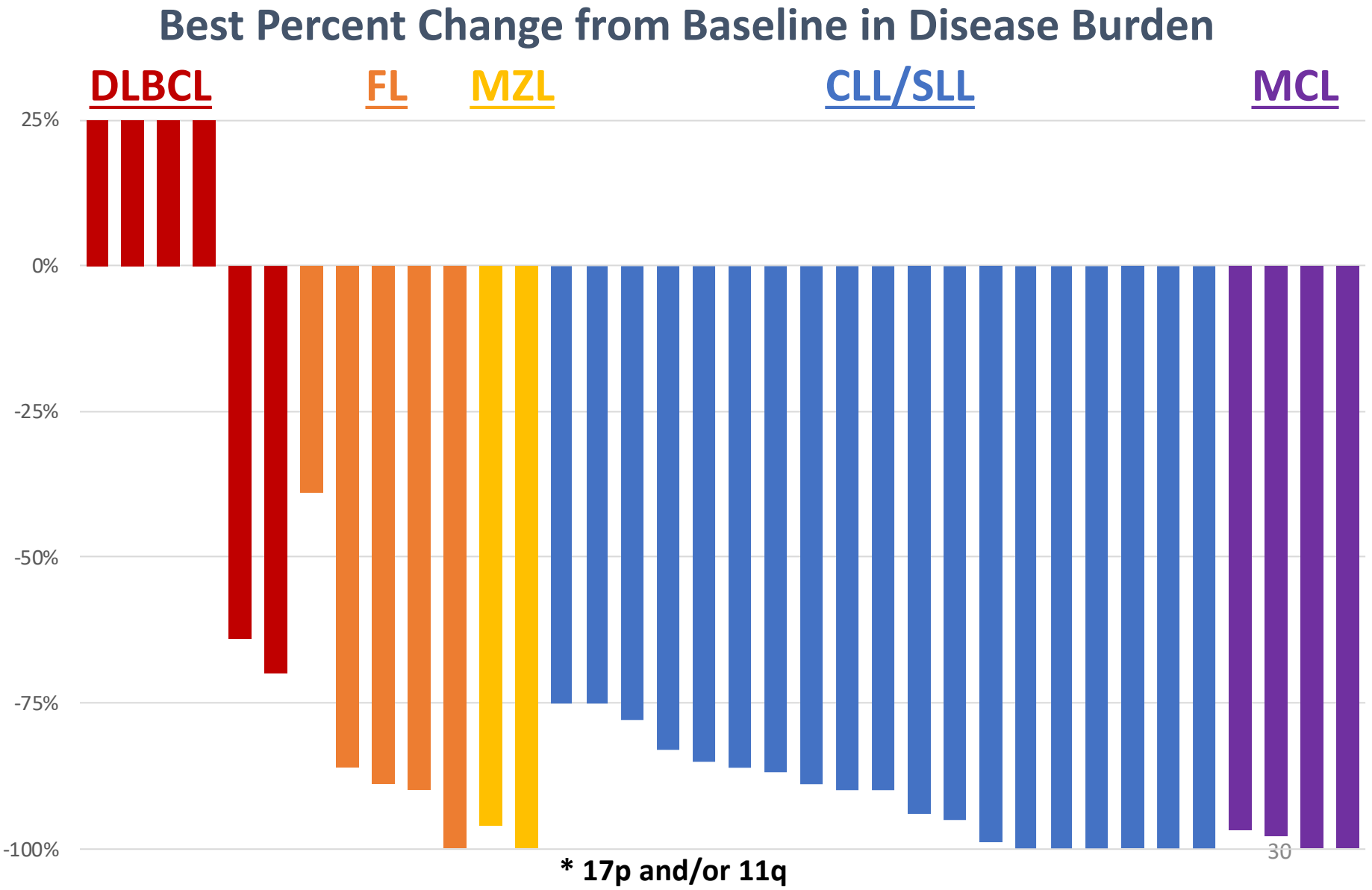
- 3 CLL patients were treatment naïve, all other patients were relapsed or refractory to prior therapy

Safety – Triplet combination well tolerated

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	18	47%	1	3%
Fatigue	18	47%	-	-
Dizziness	14	37%	1	3%
Insomnia	13	34%	-	-
Nausea	13	34%	-	-
Neutropenia	12	32%	7	18%
Cough	12	32%	-	-
Infusion related reaction	12	32%	-	-
Thrombocytopenia	11	29%	3	8%
Pyrexia	11	29%	1	3%
Rash	11	29%	1	3%
Anemia	10	26%	1	3%
Sinusitis	9	24%	-	-
Dyspnea	8	21%	1	3%
Stomatitis	8	21%	1	3%

- 1 DLT (reactivated varicella zoster) occurred CLL cohort level 1. No other DLT's were observed.
- Diarrhea majority Gr. 1 (32%) and Gr. 2 (13%), with no Gr. 4 event reported.
- Pneumonia (11% Gr. 3/4) and neutropenia were the only Gr. 3/4 AE's in >10% of patients
- Two patients discontinued due to an AE (sepsis and pneumonia)
- Median time on study 11.1 months (range 0.4 – 30+ months)

Waterfall Plot



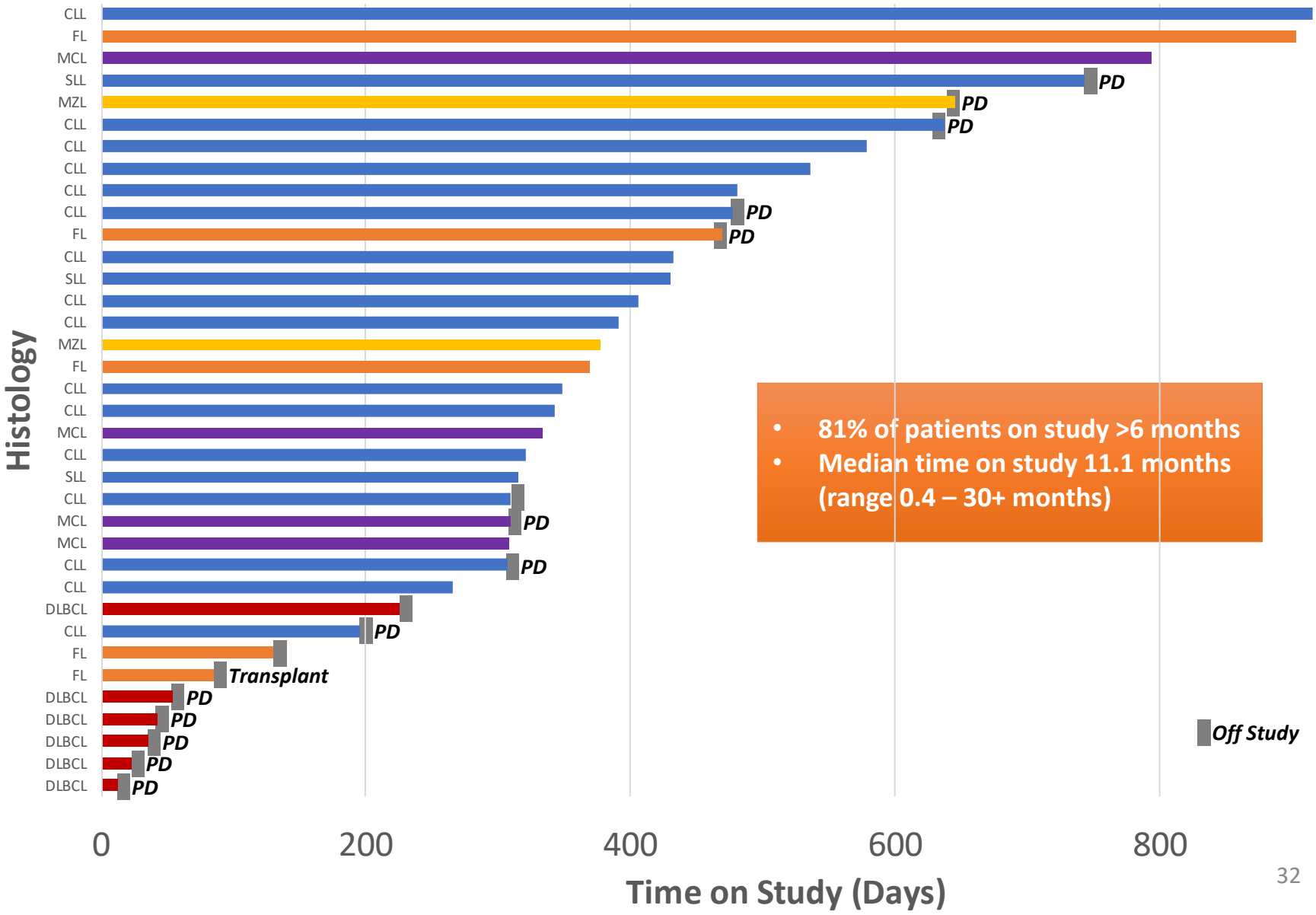
Overall Response Rate

Type	Pts (n)	CR† (n)	PR (n)	ORR n (%)	SD (n)	PD (n)
CLL/SLL	19	6	13	19 (100%)	-	-
MZL	2	1	1	2 (100%)	-	-
MCL	4	2	2	4 (100%)	-	-
FL	5	1	3	4 (80%)	1	-
DLBCL	6	-	1	1 (17%)	-	5
Total	**36**	**10**	**20**	**30 (83%)**	**1**	**5**

†CLL: 4/6 CR's pending bone marrow confirmation

- CLL
  - 8/16 (50%) had 17p and/or 11q deletion
  - 3 had a prior BTK and/or PI3Kδ inhibitor, including one patient refractory to both idelalisib and ibrutinib (ongoing CR, 1.5+ years)
- FL patients were heavily pretreated including 2 with prior ASCT, 1 refractory to prior ibrutinib, and 1 with 5 prior lines of rituximab based therapy
- DLBCL
  - Median of 4 prior therapies
  - 4/6 were of non-GCB subtype, including the sole responder

Time on Study



Triple combo did not seem to add toxicity to the BTK/Pi3K doublet

Higher rates of response as compared to doublet and more confirmed CRs

BUT

Still a treat to progression approach AND

No reported MRD data

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

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Presented at ASH 2017; Atlanta, GA

Mato AR, et al. *Blood.* 2017;130, (suppl 1; abstr 3010). Presented at: ASH Annual Meeting 2017 (poster).

Pembrolizumab: Background

- Data suggests that PD-1 and its ligands PD-L1/PD-L2 mediate immune evasion in CLL
  - Pembrolizumab (pembro) is ineffective as monotherapy in CLL (ORR 0%, median PFS 2.4 mo)[1], however responses have been observed in combination of ibrutinib/nivolumab[2]
- A key interaction exists between PI3K signaling and immune checkpoint surveillance by which inhibition of PI3K decreases PD-L1 tumor expression
  - Suggests that there may be synergistic activity between agents that block PD-1 and PI3K
- This study evaluated the safety and activity of umbralisib in combination with pembro and ublituximab in R/R CLL and RT, representing the first reported combination of a PD-1 inhibitor with a PI3Kδ inhibitor

Umbralisib-Ublituximab-Pembrolizumab: Study Design

- Phase I/II dose-escalation (3+3 design), multicenter study to assess the safety and efficacy of pembro in combination with umbralisib and UTX in R/R CLL and RT (NCT02535286)
- RT Cohort (U2 + 2 pembro dose cohorts)
- CLL Cohort (U2 + 2 pembro dose cohorts)
- DLT evaluation period:
  - CLL Cohort – Cycles 3 and 4
  - RT Cohort – Cycle 1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; R/R, relapsed/refractory; RT, Richter transformation; UTX, ublituximab.

Mato AR, et al. *Blood.* 2017;130, (suppl 1; abstr 3010). Presented at: ASH Annual Meeting 2017 (poster).

Umbralisib-Ublituximab-Pembrolizumab: Demographics

Evaluable for safety, n	11
Evaluable for efficacy*, n	10
Median age, years (range)	70 (60 – 81)
Male/Female, n	7 / 4
ECOG PS 0/1, n	6 / 5
Prior therapies, median (range)	2 (1 – 7)
17p del and *TP53* mutated, n (%)	2 (18%)
Complex karyotype, n (%)	5 (45%)
Notch 1, ATM mut, SF3B1 mut, n (%)	4 (36%)
Bulky disease, n (%)	7 (64%)
Prior BTKi, n (%)	7 (64%)
Refractory to prior BTKi, n (%)	6 (55%)
Median follow-up, mo (range)	7 (1 – 24)

*1 patient too early for response assessment.

BTKi, Bruton tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; mo, month(s); mut, mutation; n, number.

Mato AR, et al. *Blood.* 2017;130, (suppl 1; abstr 3010). Presented at: ASH Annual Meeting 2017 (poster).

Umbralisib-Ublituximab-Pembrolizumab: Safety

All Causality, All Grade AE's 20% or Grade 3/4 > 5% (N=11)

Cycle 3 – 6 for CLL, and Cycle ≥ 1 for RT	All Grades		Grade 3/4	
	n	%	n	%
Chills	5	45	-	-
Pyrexia	5	45	-	-
Neutropenia	4	36	3	27
Fatigue	4	36	1	9
Cough	4	36	-	-
Decreased Appetite	4	36	-	-
Headache	4	36	-	-
Leukopenia	3	27	1	9
Face Edema	3	27	-	-
Anemia	2	18	1	9
Nausea	2	18	1	9
Rash	2	18	1	9
Asthenia	1	9	1	9
Back pain	1	9	1	9

Laboratory Abnormality	All Grades		Grade 3/4	
	n	%	n	%
↑ Alkaline phosphatase	2	18	-	-
↑AST/ALT	1	9	1	9
↑ Cholesterol	1	9	1	9
↑ Triglycerides	1	9	1	9
Hypophosphatemia	1	9	1	9

- No colitis cases reported
- Of the 2 events of diarrhea
  - Grade 1, n=1
  - Grade 2,n=2
  - No Grade 3/4 diarrhea reported

ALT, alanine aminotransferase; AST, aspartate aminotransferase; n, number; RT, Richter transformation.

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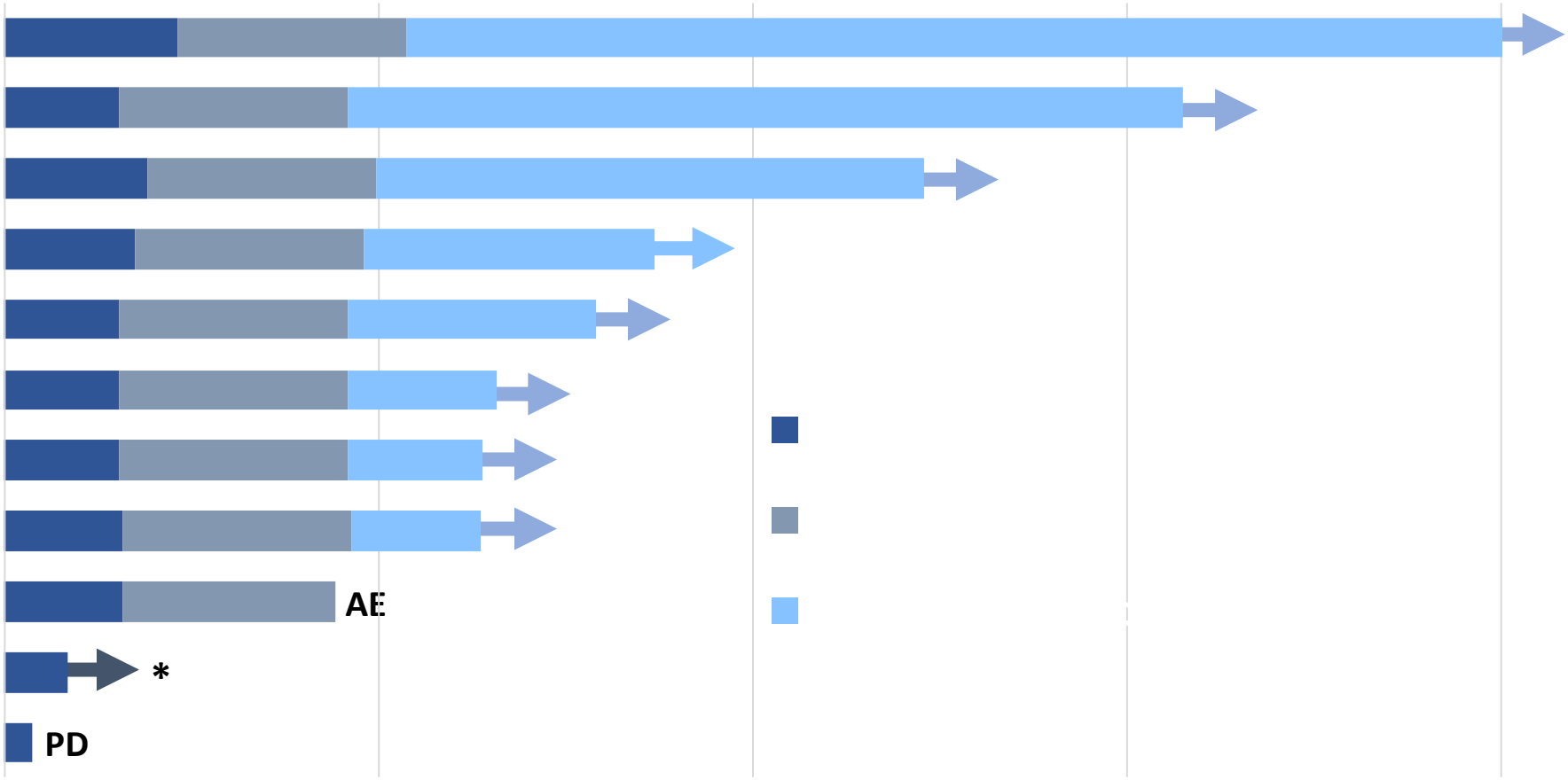
Efficacy of Umbralisib-Ublituximab-Pembrolizumab



Months Progression Free

*RT Case: 62 yo male; 7 prior lines of therapy, including HD chemo, R-CHOP, ASCT, and Ibrutinib (refractory). Initiated study in 10/2017. As of 12/2017, no significant AEs or lab abnormalities, with complete resolution of palpable LAD. Radiologic assessment pending.

ASCT, autologous hematopoietic stem cell transplantation; HD, high-dose; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RT, Richter transformation.

Mato AR, et al. *Blood.* 2017;130, (suppl 1; abstr 3010). Presented at: ASH Annual Meeting 2017 (poster).

Efficacy: Response Rates

- Evaluable CLL patients (n=9)
  - ORR CLL: 78% (all PR)
  - ORR BTKi refractory CLL: 75%
- Evaluable RT patients (n=2)
  - First RT patient was BTKi-refractory and initiated on the CLL dosing schedule, and experienced rapid progression
  - Schedule was later amended specifically for RT to start all agents in cycle 1
- Responses have been durable, with the first patient progression-free for >24 months

BTKi, Bruton tyrosine kinase inhibitor; RT, Richter transformation.

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Umbralisib-Ublituximab-Pembrolizumab Combination: Conclusions

- Umbralisib + Ublituximab (U2 regimen) + Pembrolizumab is the first study combining a PI3Kδ with a checkpoint inhibitor in CLL and RT patients
- MTD was not reached therefore primary endpoint was met
- Highly active triple combination in BTKi-refractory patient population warrants further evaluation
  - Enrollment continues specific to this population
  - Enrollment continues to RT patients

Clinical Experience with Umbralisib

- To date, 1000+ patients have been enrolled in a umbralisib trial with experience on drug ranging from 1 month to 5+ years.
- Multiple trials as a single agent or in combination with novel agents have been explored, as follows:

Phase	Study
I	Single Agent first in human in NHL and CLL
I/II	Combination with ublituximab in NHL and CLL
I/II	Combination with ublituximab and ibrutinib in NHL & CLL
I/II	Combination with ublituximab and bendamustine in NHL
I	Combination with ibrutinib in CLL and MCL
I	Combination with Obinutuzumab and Chlorambucil in CLL
I	Combination with Brentuximab in HD
I	Combination with ublituximab and pembrolizumab in CLL
I	Combination with Ruxolitinib in MF
II	Single agent TKI Intolerant in CLL
III	Single agent or combo with ublituximab in TN or R/R CLL
IIb	Single agent or combo with ublituximab (or benda) in NHL
I or II	Other trials as single agent or combinations in NHL or Solid Tumors

ASH 2017 Investigator Meeting, Data on file, TG Therapeutics

All current U2 combinations include treat to progression strategy

Proposed next steps as ublituximab heads towards the clinic…

- Needed - Data for time limited approaches with U2 (U2+V – 2 studies, 1 ongoing, 1 planned)
- Needed - Treatment decisions based on MRD status and depth of response
- Needed – Umbralisib combinations with other novel agents as the field evolves – venetoclax?, next generation BTK?, non covalently binding BTK?, cellular therapies?
- Needed – Sequencing data upon progression / intolerance to U2 based therapy (real world data, planned sequencing studies)
- Needed – Research in mechanisms of resistant to Pi3K based combinations / biomarkers of response
- Needed – Which patients benefit from doublets and triplets as compared to umbralisib or umbralisib/ublituximab – We want to optimally treat patients and NOT over or under treat them.
- Direct comparisons to other PI3K, probably not needed.