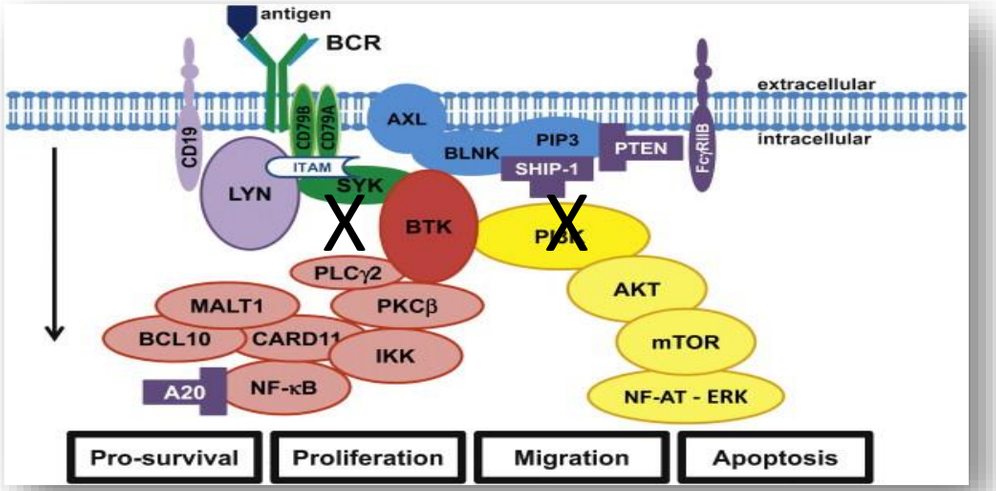
Updated Results of a Multicenter Phase I/IB Study of Umbralisib (TGR-1202) in Combination with Ibrutinib in Patients with Relapsed or Refractory MCL or CLL



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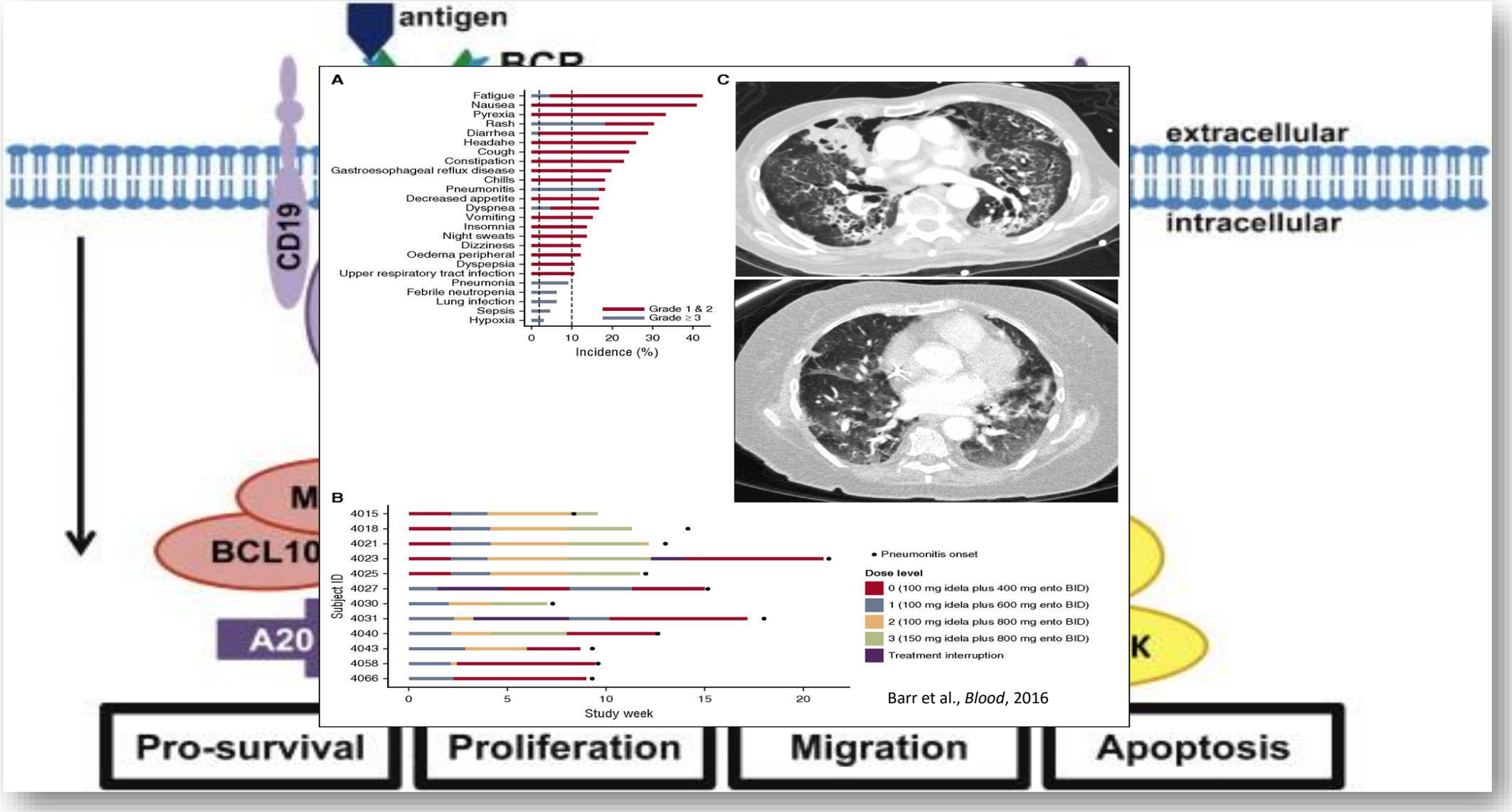
Background

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

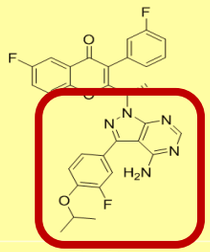
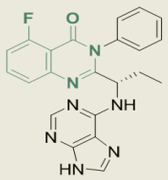
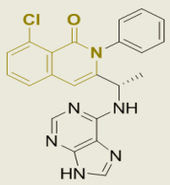


Barr et al., *Blood*, 2016

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

Background

Umbralisib (TGR-1202) is a next generation PI3Kδ inhibitor with a differentiated safety profile from other PI3Kδ inhibitors

TGR-1202	Idelalisib (GS-1101)	Duvelisib (IPI-145)
		
Delta	Delta	Delta/Gamma
QD	BID	BID

Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
TGR-1202	>1000	>50	>48	1
[1]Idelalisib	>300	>200	>40	1
[2]IPI-145	>640	>34	>11	1

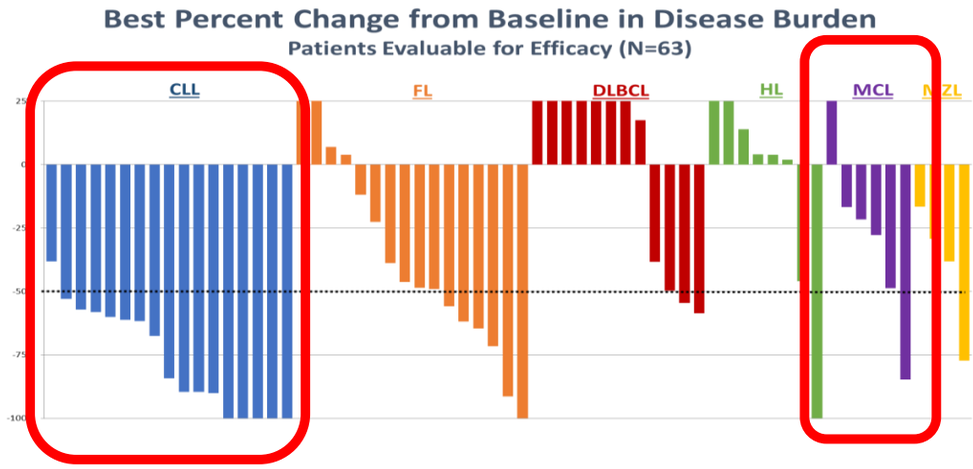
Safety

In 165 patients treated with umbralisib (TGR-1202) alone or with anti-CD20:

- **80 patients on study over 6 cycles, and 43 patients have been on study over 12 cycles**
- **Grade 3/4 AST/ALT increase was 3% (8% all grades)**
- **Diarrhea in 47%, mainly grade 1, with 5 patients (3%) with Grade 3/4**
- **8% of patients off study due to an AE**

Burris et al, ASCO 2016

Efficacy



O'Connor et al, ASH 2015

[1]Flinn et al. 2009, [2]Porter et al. 2012

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

Safety Analysis

Summary of Phase I portion (n=18 patients)

- 3 CLL and 3 MCL patients each treated at TGR-1202 400 mg, 600 mg, 800 mg qd
- There were no DLTs, and an MTD was not identified
- TGR-1202 maximum administered dose/RP2D: 800 mg qd for both CLL and MCL

Hematologic Toxicity (n=32)

CLL (n=18)

- Neutropenia (38%, 17% Gr 3-4)
- Thrombocytopenia (11%, all Gr 1)
- Anemia (15%, all Gr 1/2)

MCL (n=14)

- Neutropenia (36%; 7.1% Gr 3/4)
- Thrombocytopenia (36%; 7.1% Gr 3)
- Anemia (29%, 7.1% Gr 3)

Toxicities of Special Interest

- Diarrhea: 11/32 (34%) pts (28% Gr 1, 6% Gr 2, with no inflammatory colitis)
- Transaminitis: 7/32 (22%) pts, all Gr 1 and self-limited, no treatment interruption
- Pneumonitis: 1/32 (3%) pts, Gr 1
- Bleeding events: Gr 1 epistaxis, hematuria, vitreous hemorrhage in 1 CLL pt each
- Atrial fibrillation: 2/32 (6%) pts (both Gr 3)
- Infection: 8/32 (25%) pts (4 Gr 1/2, 2 Gr 3 aspergillus, 1 C. diff, 1 Gr 4 influenza)

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:

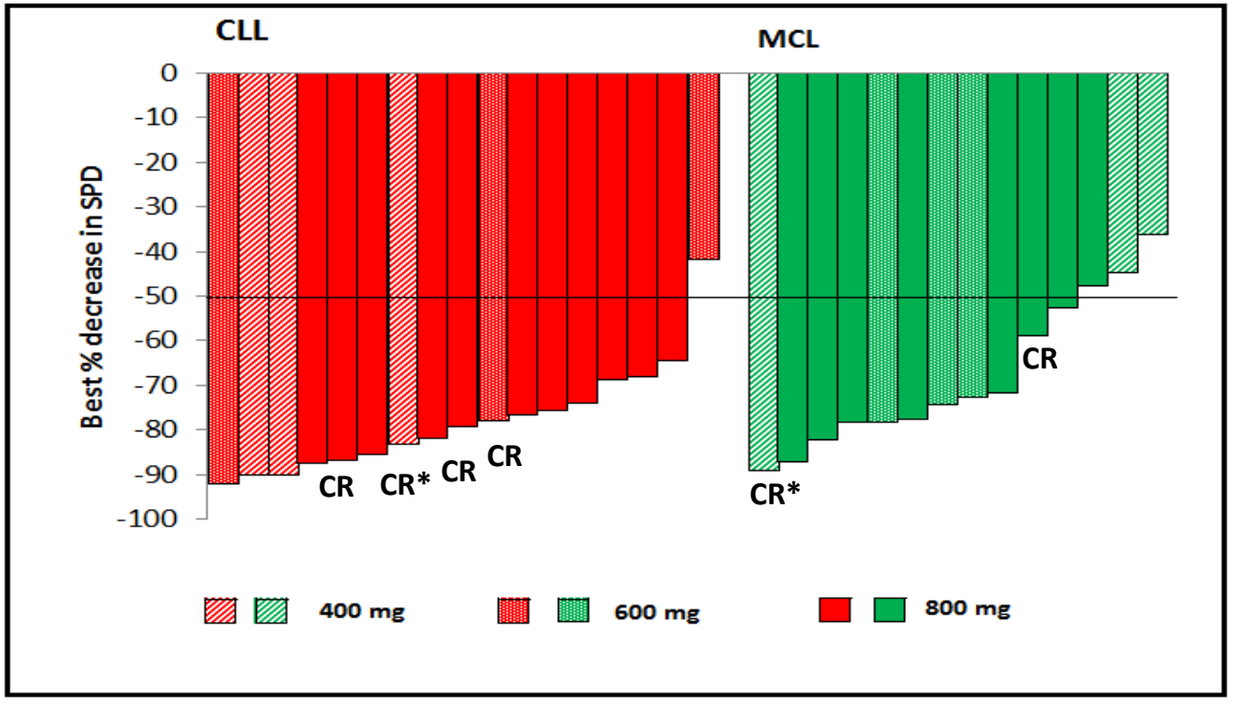
- Hypophosphatemia (n=2, both Gr 3)
- Lipase elevation (n=1, Gr 4)
- Atrial fibrillation (n=1, Gr 3)
- C. difficile infection (n=1, Gr 3)
- Influenza A infection (n=1, Gr 4)

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)

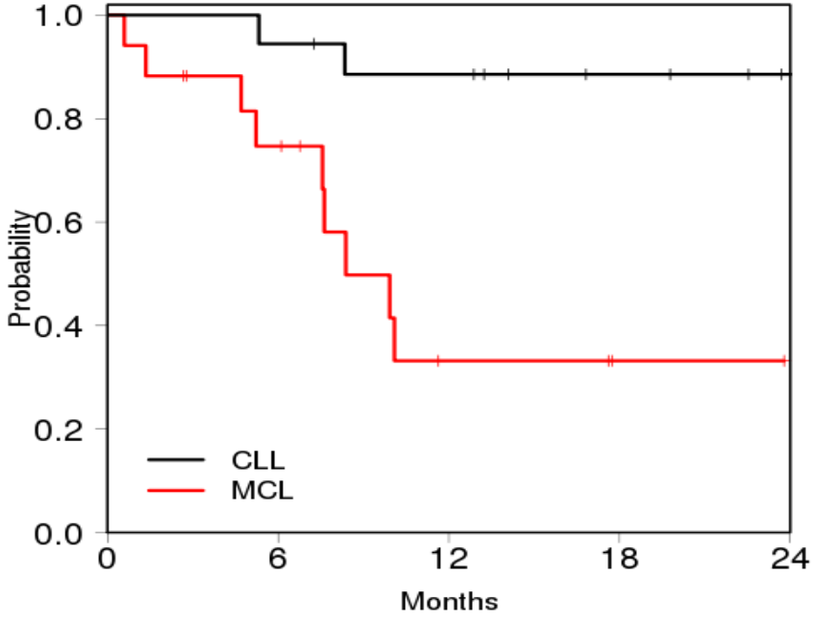
- ORR: 11/14 (79%)
- PR: 10/11 (71%)
- CR: 1/11 (9%), 1 other pt with radiographic CR
- Marked clinical benefit observed in 2 additional pts

*meets formal disease–specific criteria for CR

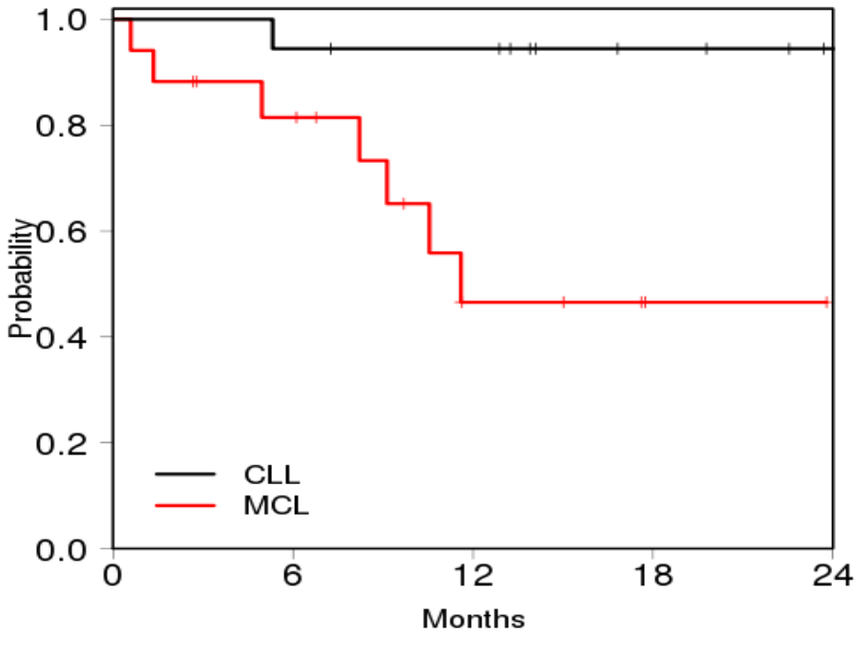
Results

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)

Conclusions

- We report updated clinical data on the first study of PI3K plus BTK inhibitor doublet therapy in B cell malignancies

- Umbralisib (TGR-1202) + ibrutinib is well-tolerated in R/R CLL and MCL, with no DLTs observed and an RP2D of umbralisib of 800 mg daily

- Toxicities of umbralisib (TGR-1202) + ibrutinib are manageable and comparable to the additive toxicity profiles of the 2 drugs individually

- Preliminary efficacy results show a high response rate in both diseases
    - CLL patient achieved CR at 1 yr, several others with radiographic CR
    - MCL patient achieved CR at 6 mo, another with radiographic CR

- Correlative studies in progress

- Patients continue to accrue to the MCL arm (NCT02268851)

Acknowledgments

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