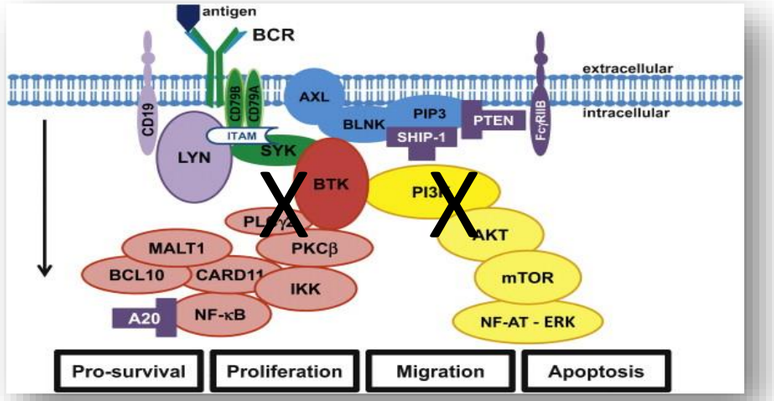
TGR-1202 in Combination with Ibrutinib in Patients with Relapsed or Refractory CLL or MCL: Preliminary Results of a Multicenter Phase I/Ib Study



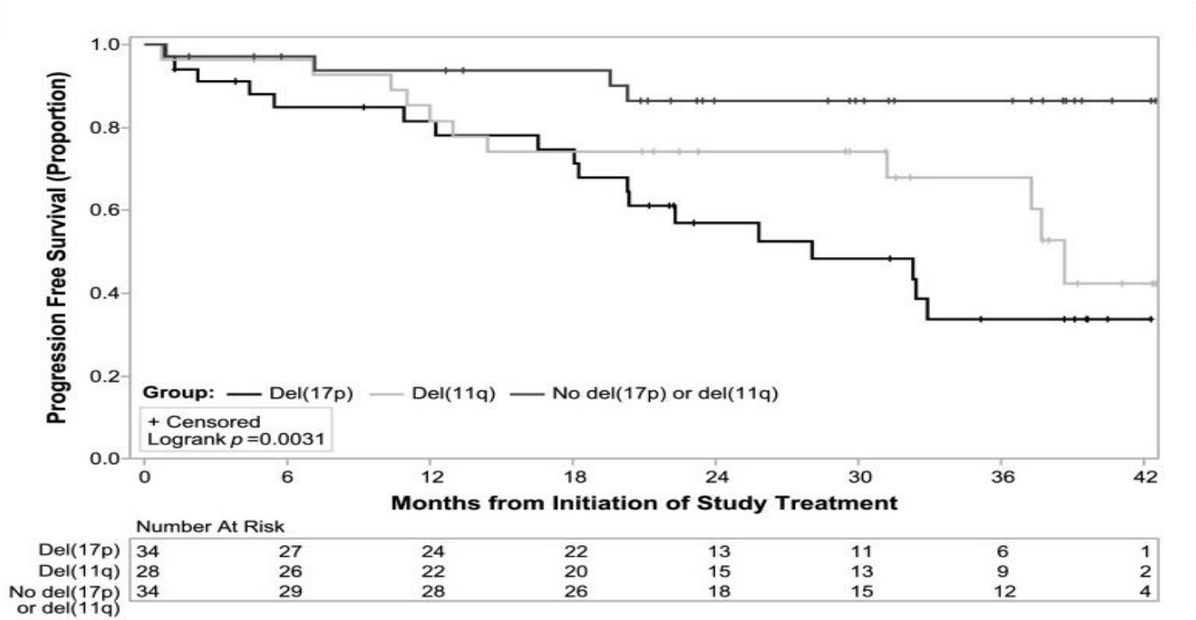
Matthew S. Davids, MD, MMSc[1], Haesook T. Kim, PhD[1], Alyssa Nicotra[1], Alexandra Savell[1], Karen Francoeur, RN[1], Jeffery M. Hellman, PA-C[1], Hari Miskin[2], Peter Sportelli[2], Asad Bashey, MD, PhD[3], Laura Stampleman, MD[4], Jens Rueter, MD[5], Adam Boruchov, MD[6], Jon E. Arnason, MD[7], Caron A. Jacobson, MD, MMSc[1], David C. Fisher, MD[1], and Jennifer R. Brown, MD, PhD[1]

[1] Dana-Farber Cancer Institute, Department of Medical Oncology, Boston, MA, USA, [2] TG Therapeutics, New York, NY, USA, [3] Bone Marrow Transplantation Group of Georgia, Atlanta, GA, USA, [4] Pacific Cancer Care, CA, USA, [5] Eastern Maine Medical Center, Bangor, ME, USA, [6] St. Francis Medical Center, Hartford, CT, USA, [7] Beth Israel Deaconess Medical Center, Department of Medical Oncology, Boston, MA, USA for the *Leukemia & Lymphoma Society Blood Cancer Research Partnership (LLS/BCRP)*

2016 ASH Annual Meeting – San Diego, California – December 5, 2016

The durability of response with ibrutinib monotherapy is limited in high risk R/R CLL and in R/R MCL

Del (17p) CLL
(median PFS 28 mo.)



Number At Risk

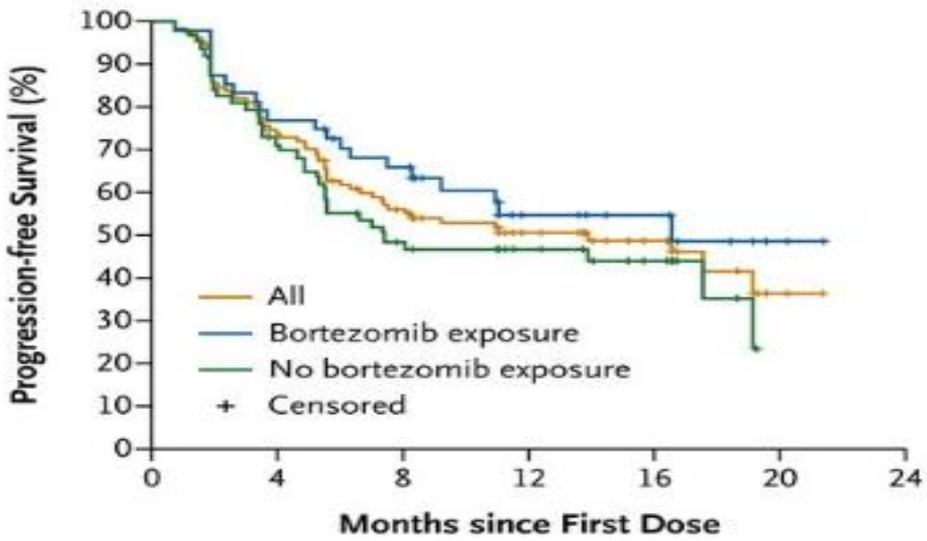
Del(17p)	34	27	24	22	13	11	6	1
Del(11q)	28	26	22	20	15	13	9	2
No del(17p) or del(11q)	34	29	28	26	18	15	12	4

	Del(17p) R/R (n = 34)	Del(11q) R/R (n = 28)	No del(17p/11q) R/R (n = 34)
30-month OS, % (95% CI)	48 (29-65)	74 (53-87)	87 (68-95)
Median OS, mo (95% CI)	28 (18.2-NE)	38.7 (31.2-NE)	NR (NE-NE)

NE, not evaluable; PFS, progression-free survival; R/R, relapsed/refractory.

Byrd et al., *Blood*, 2015

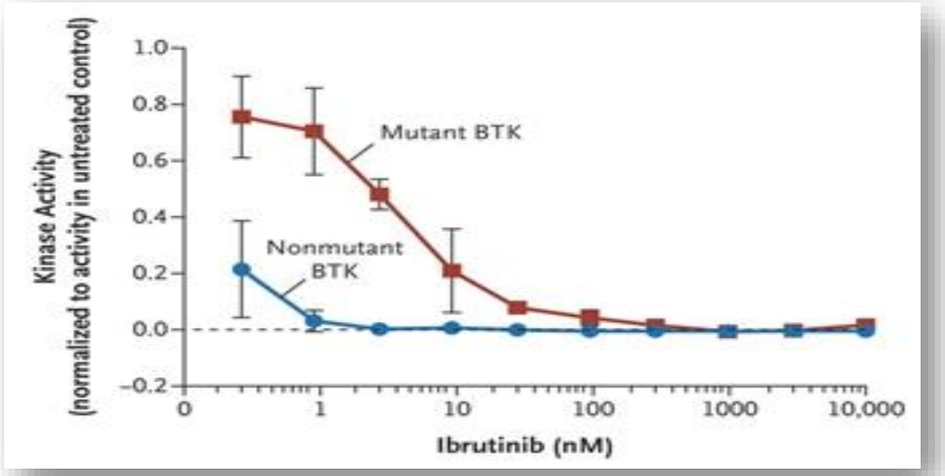
MCL
(median PFS 13.9 mo.)

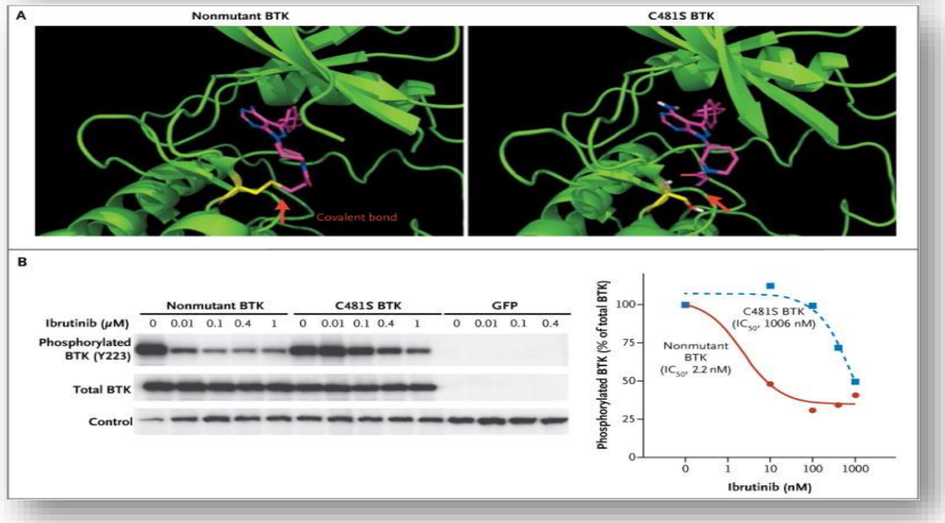


No. at Risk							
No bortezomib exposure	63	44	28	19	12	0	0
Bortezomib exposure	48	37	29	14	10	2	0
All	111	81	57	33	22	2	0

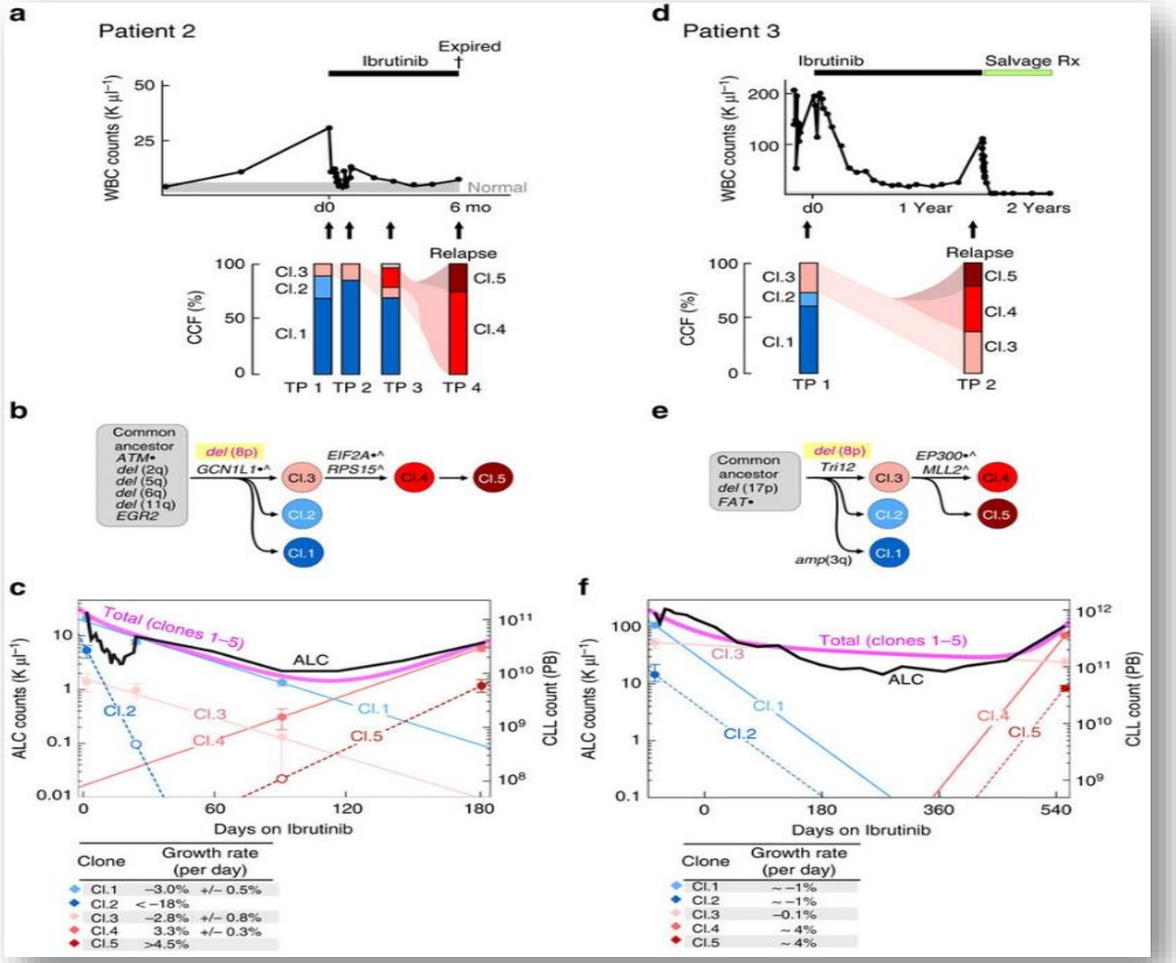
Wang et al., *N Engl J Med*, 2013

Resistance mutations have already been observed in patients on ibrutinib monotherapy



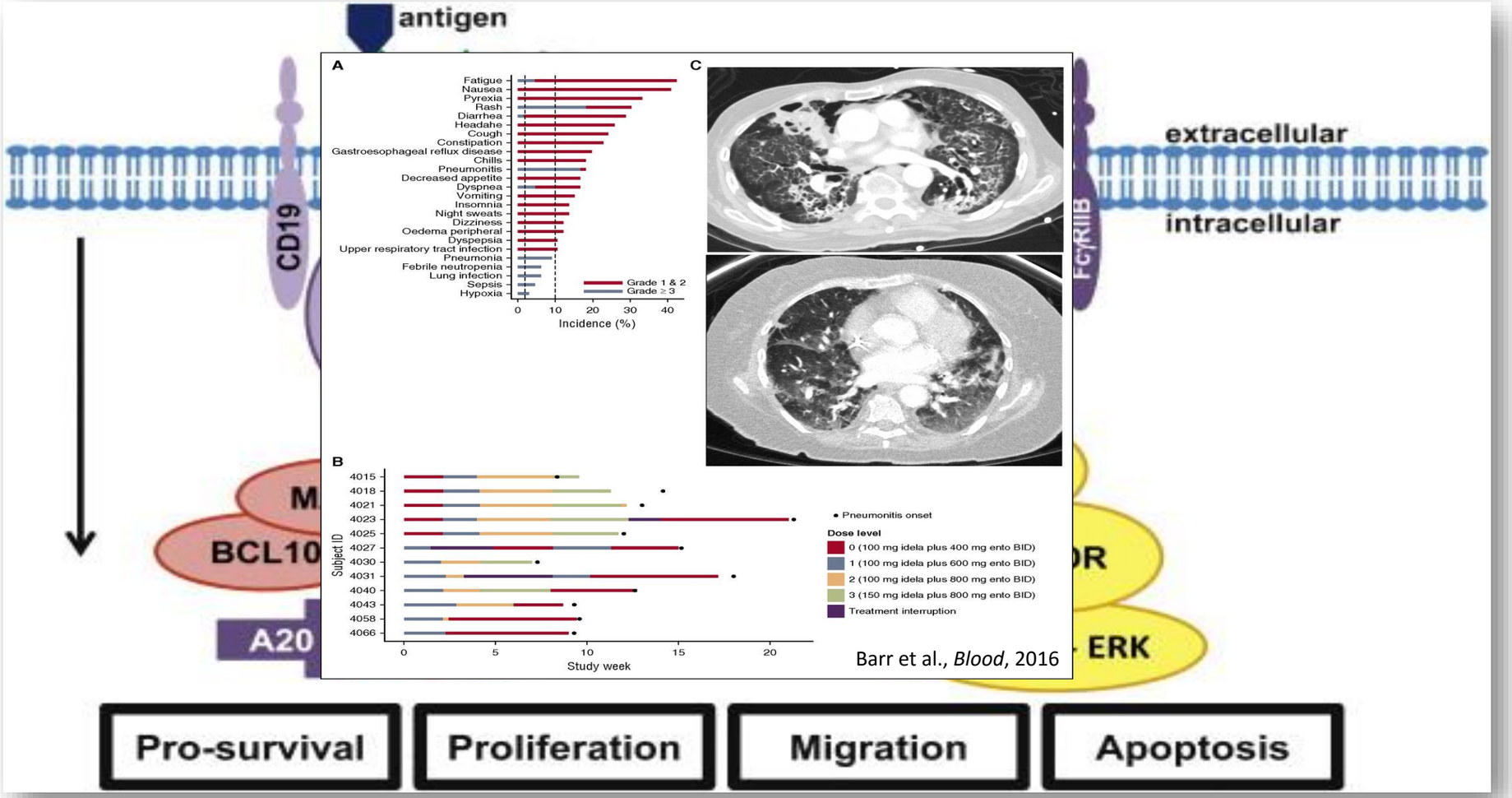


Woyach et al., *N Engl J Med*, 2014
Furman et al., *N Engl J Med*, 2014



Burger et al., *Nat Commun*, 2016

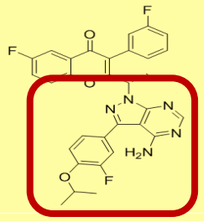
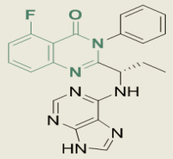
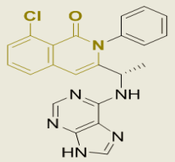
Inhibiting multiple BCR pathway kinases may deepen and prolong response and overcome resistance mutations



Barr et al., *Blood*, 2016

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

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

In 165 patients treated with TGR-1202 alone or in combination with anti-CD20:

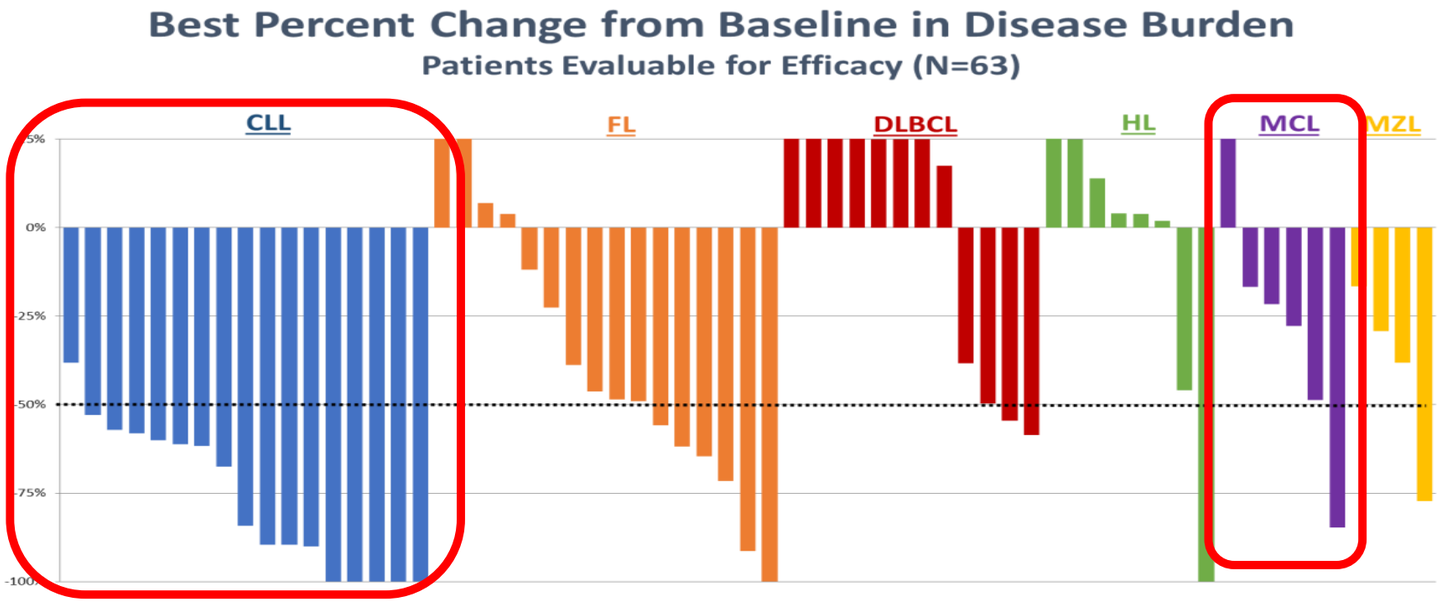
- **80 patients on study over 6 cycles, and 43 patients have been on study over 12 cycles**
- **Grade 3/4 AST/ALT increase was 3% (8% all grades)**
- **5% had Grade 3 pneumonia**
- **Diarrhea in 47%, mainly grade 1, with 5 patients (3%) with Grade 3/4**
- **8% of patients have come off study due to an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

Burris et al, ASCO 2016

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

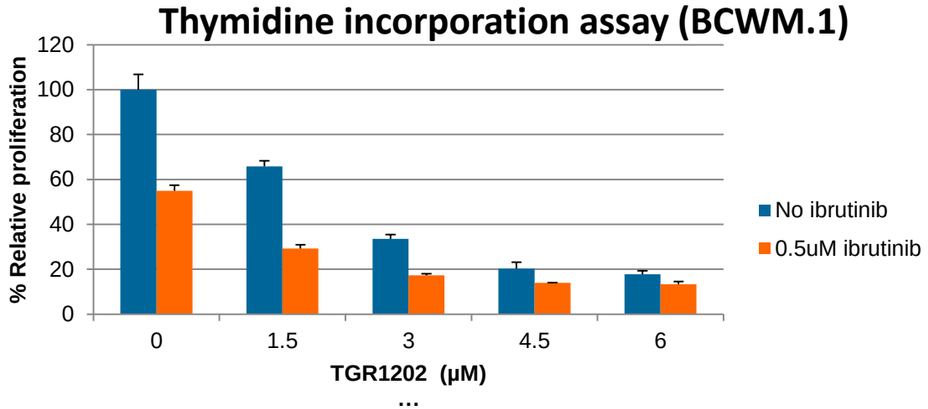
TGR-1202 is active in R/R CLL and MCL, and preclinical data suggest that the combination with ibrutinib is promising

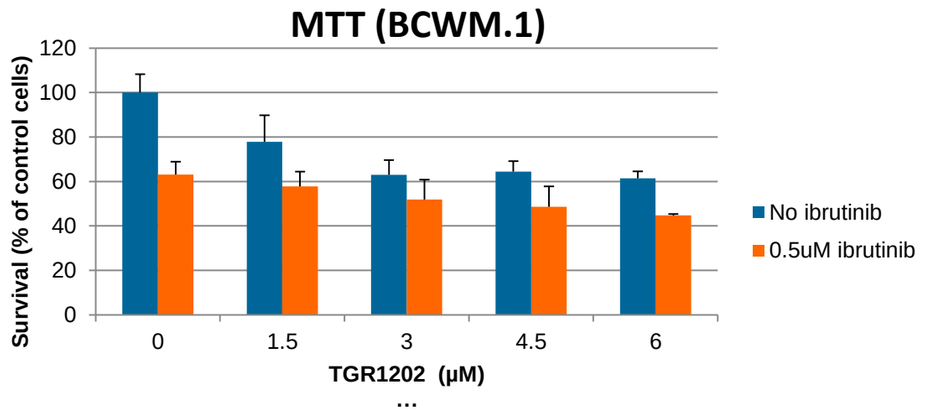
TGR-1202 Monotherapy in Patients



O'Connor et al, ASH 2015

TGR-1202 + Ibrutinib *in vitro*





Unpublished data, Ghobrial Lab

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

Endpoints

Primary:

- MTD, safety, and DLTs of TGR-1202 when used in combination with ibrutinib

Secondary:

- Clinical response: ORR, CR, PR, PR-L, PFS, and remission duration
- Association of CLL prognostic factors (e.g. FISH, *IGHV*, etc.) with response

Exploratory:

- Association of novel prognostic factors such as BH3 profiling and somatic mutations (e.g. *TP53*, *NOTCH1, SF3B1, BTK, PLCγ-2* etc.*)* with response

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

Key Eligibility Criteria

Inclusion

- ≥1 prior standard therapy, an indication for therapy, and ≥1 measurable disease site
- ANC ≥ 0.5 K/uL, platelets ≥ 30 K/uL (except pts w/ >50% CLL in marrow)
- Total bilirubin ≤1.5X ULN, unless due to Gilbert's or hemolysis, ALT/AST ≤ 2.0X ULN or ≤ 4X ULN if known liver involvement
- Creatinine ≤ 2.5 mg/dL OR calculated creatinine clearance ≥ 50 mL/min
- In Ph I portion, patients with prior BTK or PI3Ki therapy were eligible

Exclusion

- AutoSCT within 3 mo. or alloHCT within 12 mo. of study entry
- Post-allo patients must not have active GVHD and be off immune suppression
- Active hepatitis, HIV infection, or central nervous system involvement
- Patients who require warfarin for anticoagulation

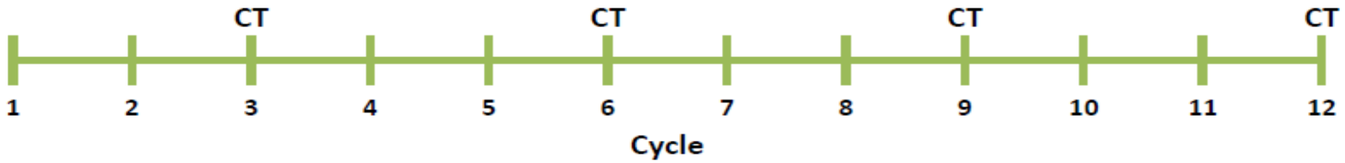
A 3+3 design was utilized with escalation of TGR-1202

- Parallel arms for CLL and MCL which 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
- Standard toxicity assessments by CTCAE v4.03, efficacy by 2008 IW-CLL or 2014 Lugano criteria (MCL)
- Phase Ib expansion cohorts of 12 pts each in CLL and MCL

Dose escalation scheme

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			

Response evaluations



Patient Characteristics (n=31)

	All (n=31)	MCL (n=13)	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	4/31 (13%)	4/13 (31%)	0
Prior ibrutinib	4/31 (13%)	2/13 (15%)	2/18 (11%)
Prior PI3K inhibitor	4/31 (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)			4/17 (24%)
Del(11q)			7/17 (41%)
Unmutated *IGHV*			6/17 (35%)
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

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
- The maximum administered dose of TGR-1202 of 800 mg daily was determined to be the RP2D for both CLL and MCL

Hematologic Toxicity (n=31)

CLL (n=18)

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

MCL (n=13)

- Neutropenia (38%; 7.7% Gr 3/4)
- Thrombocytopenia (38%; 7.7% Gr 3)
- Anemia (31%, 7.7% Gr 3)

Safety Analysis (cont., n=31)

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:
- 3 patients (atrial fibrillation, palpitations, vitreous hemorrhage)

MCL (n=13)

All grade non-heme toxicities in ≥ 20%*:
- Fatigue: 54% (31% Gr 1, 23% Gr 2)
- Diarrhea: 46% (all Gr 1)
- Nausea: 38% (31% Gr 1, 7% Gr 2)
- Dizziness: 31% (all Gr 1)
- Anorexia: 31% (all Gr 1)
- Bruising: 23% (all Gr 1)
- Headache: 23% (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:
- 1 patient (dizziness)

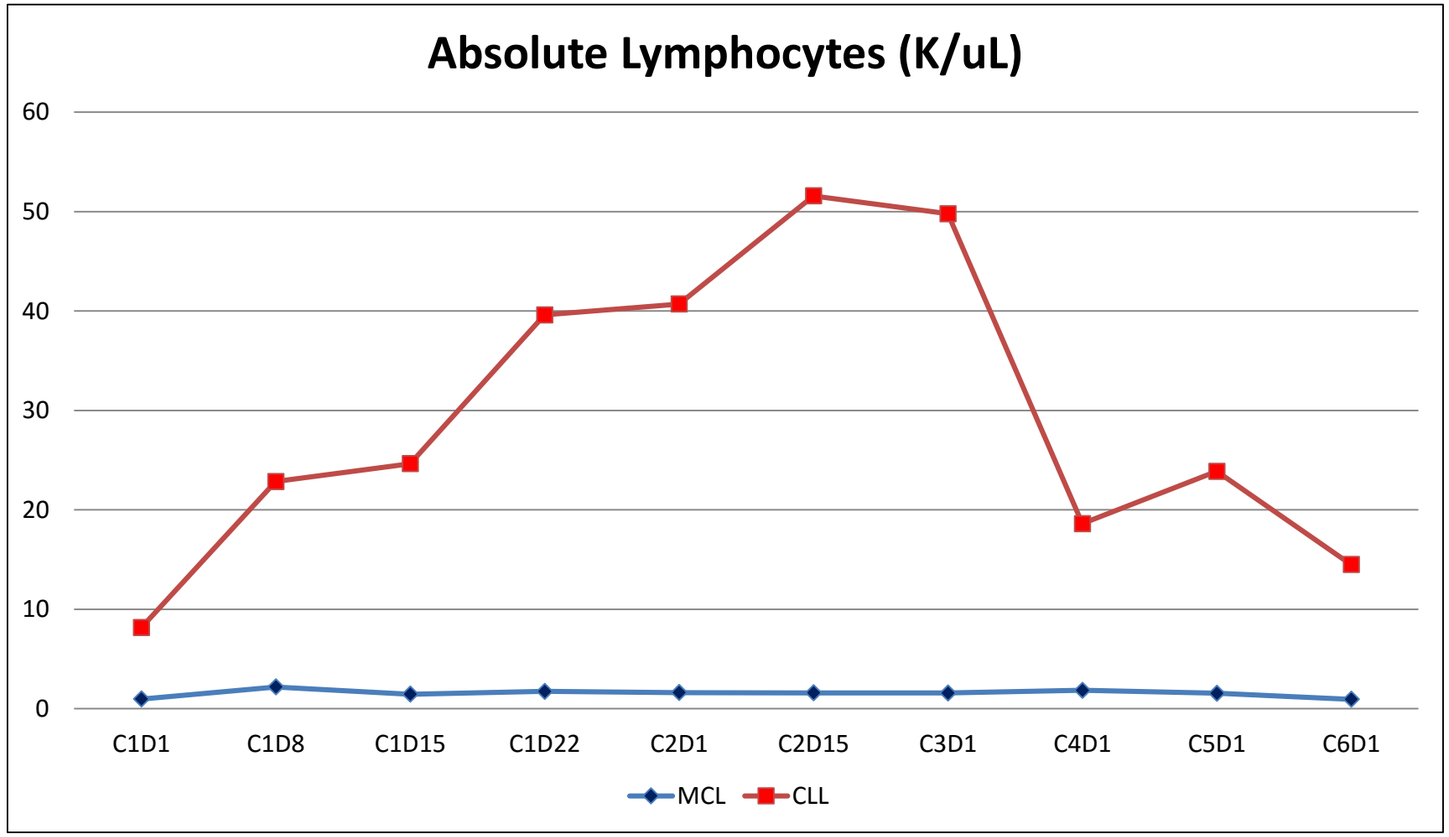
* Excludes asymptomatic , low-grade laboratory abnormalities

Safety Analysis (cont., n=31)

Toxicities of Special Interest

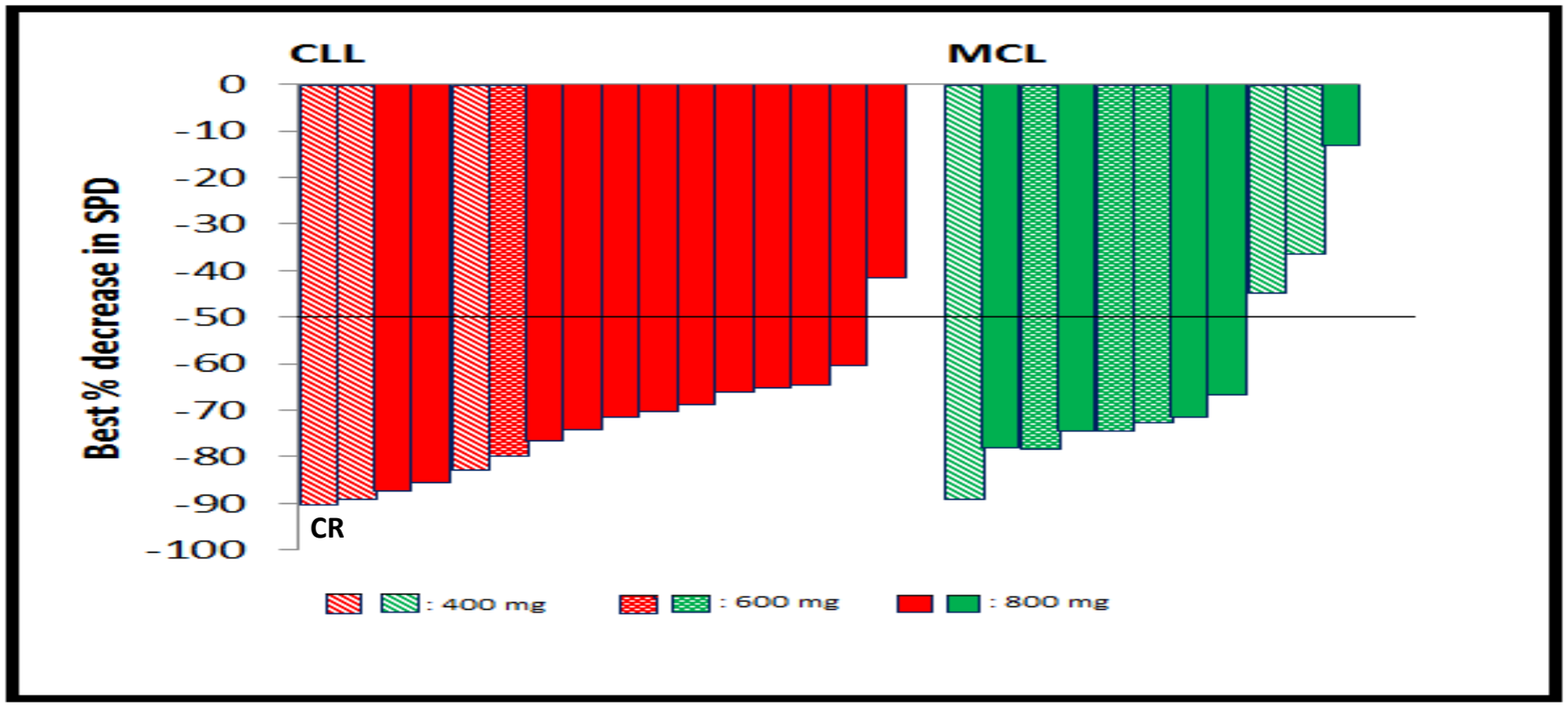
- Diarrhea: 11/31 (35%) pts (29% Gr 1, 6% Gr 2, with no inflammatory colitis)
- Transaminitis: 7/31 (23%) pts, all Gr 1 and self-limited without the need for treatment interruption
- Pneumonitis: 1/31 (3%) pts, Gr 1
- Bleeding events: Gr 1 epistaxis, hematuria, vitreous hemorrhage in 1 CLL pt each
- Atrial fibrillation: 2/31 (6%) pts (both Gr 3)
- Infection: 7/31 (23%) pts (4 Gr 1/2, 2 Gr 3 (CNS aspergillus, C. diff, 1 Gr 4 influenza)

Preliminary Efficacy Analysis (n=28)



- **Lymphocyte redistribution was observed in CLL but not MCL**
- **Resolution of the lymphocytosis was somewhat more rapid than is typically observed with ibrutinib monotherapy**

Preliminary Efficacy Analysis (n=28)



CLL (n=17)

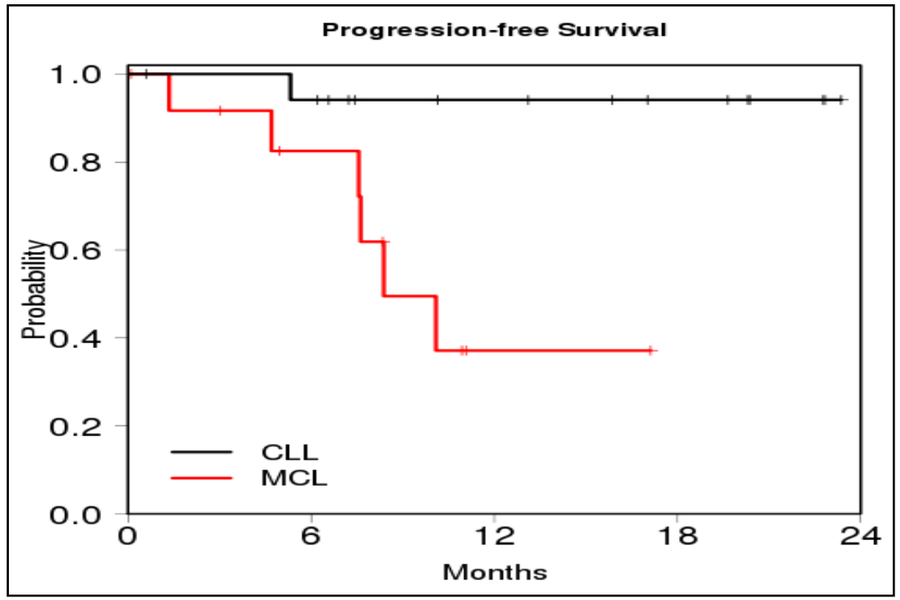
- ORR: 15/17 (88%)
  - -PR or PR-L: 14/17 (82%)
  - -CR: 1/17 (6%)
- 5 PR patients with >80% SPD decrease, nearing radiographic CR
- 3 pts with prior PI3Ki and 1 pt with prior ibrutinib responded

MCL (n=11)

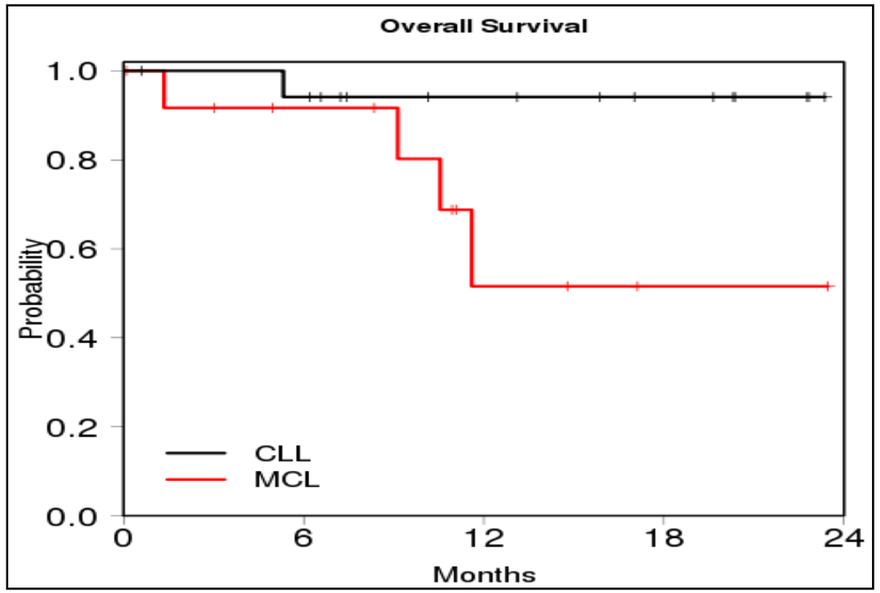
- ORR: 8/11 (73%), all PRs
- Clinical benefit observed in 2 additional patients

Preliminary Efficacy Analysis (n=28)

PFS



OS



- **Median follow-up time among survivors: 11 mo. (range 0.1-23.5)**
- **1-year PFS and OS for CLL is 94% (n=17)**
- **1-year PFS and OS for MCL is 37% and 52%, respectively (n=11)**
- **6 MCL patients have died (5 due to PD, 1 due to toxicity from subsequent therapy)**
- **1 CLL patient had sudden death deemed unlikely due to study drugs**

Conclusions

- We report to our knowledge the first clinical data on a PI3K plus BTK inhibitor doublet in B cell malignancies
- TGR-1202 + ibrutinib is well-tolerated in R/R CLL and MCL, with no DLTs observed and an RP2D of 800 mg daily
- The toxicities of TGR-1202 + ibrutinib are manageable and comparable to the additive toxicity profiles of the two agents given individually
- The preliminary efficacy results show a high response rate in both diseases
  - CLL patient achieved CR at 1 yr, several others approaching CR
- Correlative studies in progress
- The CLL arm has now completed accrual, MCL patients continue to accrue to this ongoing study (NCT02268851)

Acknowledgments

DFCI CLL Center:
Jennifer Brown
Krystle Benedict / Leslie Cowen
Elizabeth Coughlin / Jamie Ye
Stacy Hansen
Monique Girard
Rebecca Liguori
Megan Hiserodt / Mackenzie Wiggin
John Daley / Suzan Lazo-Kallanian
Nina Cingel
Michael Wake
Stacey Fernandes / Kevin Hoang

Patients and their families

Collaborators:
Tony Letai
Jing Deng
Irene Ghobrial
Rob Soiffer

Funding:
TG Therapeutics
BCRP / LLS TAP
(Lee Greenberger, Jun Xu, Keting Chu)
ASCO CDA
NIH LRP

Workshops:
ASH CRTI
AACR/ASCO Vail Workshop

Dana-Farber Cancer Institute

Boston, USA