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

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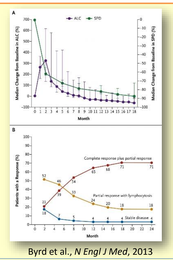
Leukemia & Lymphoma Society | Blood Cancer Research Partnership (LLS/BCRP)

Background

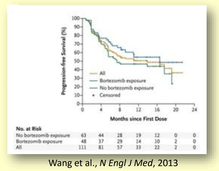
1. Ibrutinib is highly active in R/R CLL and MCL

CLL



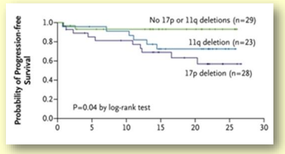
Byrd et al., *N Engl J Med*, 2013

MCL

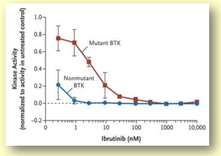


Wang et al., *N Engl J Med*, 2013

2. High risk subgroups have less durable response, resistance mutations have been observed

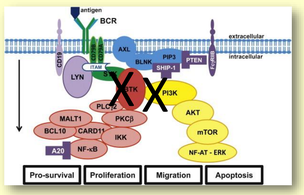


Byrd et al., *N Engl J Med*, 2013



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

3. Hitting multiple BCR pathway targets may help overcome resistance

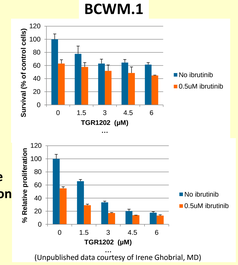


Niemann et al., *Seminars in Cancer Biology*, 2013

MTT

Thymidine incorporation assay

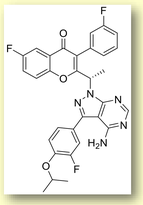
BCWM.1



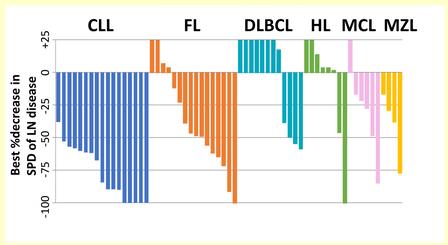
(Unpublished data courtesy of Irene Ghobrial, MD)

4. TGR-1202 is a potent and well-tolerated next-generation PI3K-delta inhibitor

TGR-1202



Single agent efficacy in hematologic malignancies
Best Percent Change from Baseline in Disease Burden
Patients Evaluable for Efficacy (n=63)



Aims/Methods

Endpoints

Primary
- Maximum tolerated dose (MTD) of TGR-1202 when used in combination with ibrutinib in patients with relapsed or refractory CLL or MCL
- Safety and dose limiting toxicities (DLTs) of TGR-1202 in combination with ibrutinib in patients with relapsed or refractory CLL or MCL

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 in *SF3B1, NOTCH1, MYD88* and *BCR/NFKB* with response

Key Eligibility Criteria

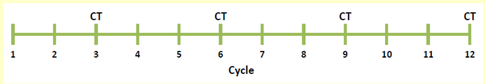
Inclusion
- At least 1 prior standard therapy, an indication for therapy, and at least 1 measurable site of disease
- ANC ≥ 0.5 K/uL, platelets ≥ 30 K/uL (except pts w/ >50% CLL in marrow)
- Total bilirubin ≤1.5X ULN, unless due to Gilbert's or hemolysis, then ≤3.0X ULN, ALT/AST ≤ 2.0X ULN or ≤ 4X ULN 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 IS
- Active hepatitis, HIV infection, or central nervous system involvement
- Patients who require warfarin for anticoagulation

Study Design

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			

- Parallel arms for CLL and MCL which escalated independently
- TGR-1202: oral, once daily in the morning
- Ibrutinib: oral, 420 mg daily in the evening for CLL, 560 mg daily for MCL
- Both agents continued until time of progression or unacceptable toxicity
- Standard toxicity assessments by CTCAE v4.03
- Response evaluations: after cycles 2, 5, 8, 12, and q6 mo. thereafter



Statistical Design

- Phase I with a standard 3 + 3 design with up to 4 dose levels of TGR-1202
- 91% probability of dose escalation if the true rate of DLT is 10% and 17% probability of escalation if the true DLT rate is 50%
- Phase Ib expansion cohorts of 12 pts each in CLL and MCL
- Estimation of toxicity rates in 12 pt cohorts: 90%CI will be within +/- 25%
- Efficacy analyses: CLL: 2008 IW-CLL criteria, MCL: 2014 Lugano criteria

Results

Patient Characteristics (n=27)

- Histology: CLL n=17, MCL n=10
- Median age at enrollment: 66 years (range 48-83)
- Median # prior therapies:
  - -CLL: 2 (range 1-6 with 2 prior ibrutinib, 2 prior PI3Ki)
  - -MCL: 3 (range 2-5 with 2 prior ibrutinib)
- CLL prognostic markers
  - -FISH: 9 pts with del(11q), 3 pts with del(17p), 1 pt without del(17p) but with *TP53* mut
  - -*IGHV*: 7/16 (44%) unmutated, 2 pts with *NOTCH1* mut

Safety Analysis (n=27)

- There were no DLTs, and the TGR-1202 recommended phase 2 dose (RP2D) for both CLL and MCL is 800 mg daily

CLL (n=17)

Hematologic toxicity :
- Neutropenia (35%, all Gr 3-4)
- Thrombocytopenia (24%, all Gr 1)
- Anemia (35%, all Gr 1/2)

All grade non-heme toxicities in ≥ 25% of pts:
- Diarrhea (41%, 35% Gr 1, 6% Gr 2)
- Nausea (35%, all Gr 1)

SAEs (in 1 patient each):
- Amylase/Lipase elevation (Gr 3, required study drug discontinuation)
- Atrial fibrillation (Gr 3)
- CNS infection (Gr 3)
- Adrenal insufficiency (Gr 3)

MCL (n=10)

Hematologic toxicity :
- Neutropenia (30%; 10% Gr 4)
- Thrombocytopenia (40%; 10% Gr 3)
- Anemia (30%, 10% Gr 3)

All grade non-heme toxicities in ≥ 25% of pts:
- Diarrhea (60%, 50% Gr 1, 10% Gr 2)
- Fatigue (50%, all Gr 1/2)
- Nausea (30%, all Gr 1/2)
- Transaminitis, dizziness, hypocalcemia (30% each, all Gr 1)

SAEs (none led to discontinuation):
- Hypophosphatemia (n=2, both Gr 3)
- Amylase/Lipase elevation (n=1, Gr 3)
- Atrial fibrillation (n=1, Gr 3)
- C. difficile infection (n=1, Gr 3)
- Influenza A infection (n=1, Gr 4)

Efficacy Analysis (n=21)

CLL (n=11)*

Pt	TGR-1202 Dose	Best Response	FISH	*IGHV* status
01	400 mg	PR	13q + tri 12	Mut
02	400 mg	CR (BM MRD+)	14q32 + 13q	Unmut
03	400 mg	PR	13q	Mut
04#	600 mg	SD	17p + 11q + 13q	Mut
05	600 mg	PR	N/A	Mut
06#	600 mg	PR	14q32 + tri 12	Mut
07	800 mg	SD	13q	Mut
08	800 mg	PR	11q + 13q	Unmut
09	800 mg	PR	13q	Mut
10	800 mg	PR	13q	Mut
11	800 mg	PR	17p + 13q	Unmut

- ORR: 9/11 (82%)
  - -PR: 5/11 (45%)
  - -PR-L: 3/11 (27%)
  - -CR: 1/11 (9%)

(confirmed with neg. BM)

*6 CLL patients included in the safety analysis have not yet reached their first response evaluation
Already on ibrutinib at time of study enrollment (4 months (Pt 04) and 3 weeks (Pt 06))

MCL (n=10)

Pt	TGR-1202 Dose	Best Response	Comment
01	400 mg	SD	45% SPD reduction
02	400 mg	PR	89% SPD reduction
03	400 mg	SD	Spleen 31 -> 23 cm WBC 342 -> 25
04	600 mg	PR	72% SPD reduction
05	600 mg	PR	74% SPD reduction
06	600 mg	PR	78% SPD reduction
07	800 mg	PD	Rapid PD in 1st month
08	800 mg	PR	54% SPD reduction
09	800 mg	SD	13% SPD reduction
10	800 mg	PR	75% SPD reduction

- ORR: 6/10 (60%), all PRs
- Clinical benefit observed in 2 additional patients

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 in the phase I portion of this study
- The RP2D of TGR-1202 in combination with ibrutinib for both CLL and MCL was 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 suggest a high response rate in both diseases, with a CLL patient achieving CR at 1 yr and several others approaching CR radiographically
- Accrual continues to this ongoing study

Acknowledgements/Disclosures

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- The authors thank the patients and their families for participating

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