# UMBRALISIB (TGR-1202) IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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2nd Postgraduate CLL conference

Bologna, Italy

# Anthony Mato - 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
  - Verastem

# Umbralisib: Background

- Umbralisib (TGR-1202) is a next generation PI3Kδ inhibitor with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development, including:
  - A differentiated safety profile, notably with respect to hepatic toxicity and colitis[1]
  - A prolonged half-life that enables once-daily dosing;
  - High selectivity to the δ isoform of PI3K; and
  - Also targets casein kinase-1 epsilon (CK-1ε), a protein which may inhibit Treg function[2]

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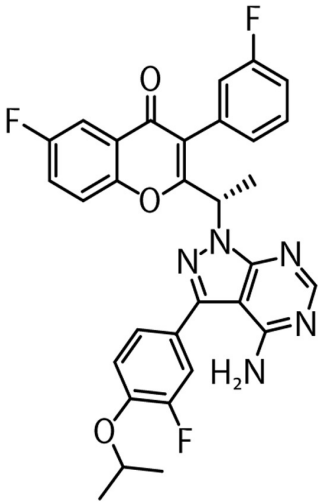
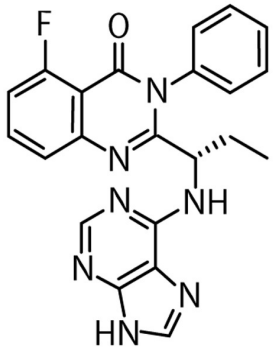
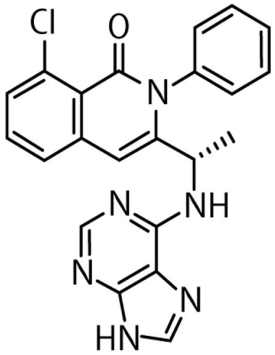
| |  |  |  |
| **Isoform** | | **$K_d$ (nM)** | |
| PI3Kα | >10 000 | 600 | 40 |
| PI3Kβ | >10 000 | 19 | 0·89 |
| PI3Kγ | 1400 | 9·1 | 0·21 |
| PI3Kδ | 6·2 | 1·2 | 0·047 |
| CK1ε | 180 | >30 000 | >30 000 |

[1]Davids et al. EHA 2018, [2]Deng C, et al. *Blood.* 2017;129:88-99

# Umbralisib Development in CLL: Key Studies

- TGR-1202-101: First-in-Human Phase 1 Study of Single Agent Umbralisib
- UTX-TGR-103: Phase 1 Dose-Escalation study of "U2" in CLL & NHL
- TGR-1202-201: Phase 2 Umbralisib in TKI (BTK or PI3K) intolerant CLL
- TG-UPCC-108: Phase 1 Umbralisib + Pembrolizumab or TG1501 in R/R CLL & RT
- UTX-TGR-304: UNITY-CLL – Pivotal Phase 3 Study of U2 in CLL
- U2-VEN-207: Phase 2 Study of U2 + Venetoclax in CLL
- UTX-TGR-208: Phase 2 Study of U2 in Subjects Currently on Ibrutinib or Venetoclax

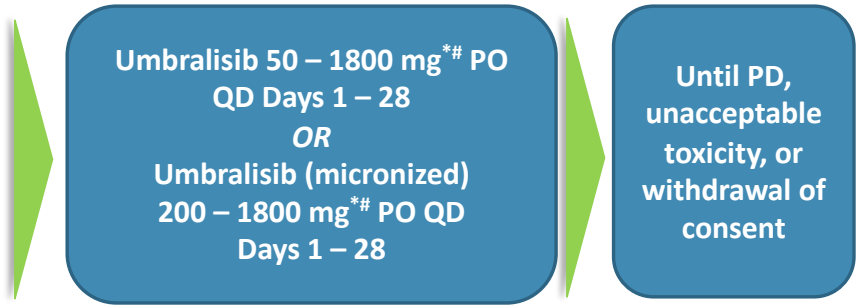
# UMBRALISIB, A NOVEL PI3Kδ AND CASEIN KINASE-1E INHIBITOR, IN RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA AND LYMPHOMA: AN OPEN-LABEL, PHASE 1, DOSE-ESCALATION, FIRST-IN-HUMAN STUDY

Howard A Burris III, Ian W Flinn, Manish R Patel, Timothy S Fenske, Changchun Deng, Danielle M Brander, Martin Gutierrez, James H Essell, John G Kuhn, Hari P Miskin, Peter Sportelli, Michael S Weiss, Swaroop Vakkalanka, Michael R Savona, Owen A O'Connor

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20

# Umbralisib in Relapsed/Refractory Lymphoid Malignancies

- Open-label, phase 1, dose-escalation study at seven clinics in the USA
  - Relapsed and/or refractory NHL, CLL, HL, or T-cell
  - ≥ 1 prior treatment regimen




**Primary endpoint:**
Safety, MTD, PK

**Secondary endpoints:**
ORR, DOR

*Intra-patient dose escalation permitted for patients in earlier cohorts following establishment of safety at higher doses

- Response assessments were performed every two cycles until cycle 12, and then at least every six cycles
- *Pneumocystis jiroveci* pneumonia prophylaxis was permitted but not mandated during the study

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

# Umbralisib in Relapsed/Refractory Lymphoid Malignancies: Patient Demographics and Baseline Characteristics

| Characteristic | All patients (safety population; N=90) | MITT population (patients assessable for activity, n=73) |
|---|---|---|
| Age, years (range) | 64 (51–72) | 65 (51–71) |
| Sex, M:F, n (%) | 57 (63) / 33 (37) | 45 (62) / 28 (38) |
| ECOG PS (range) | 1 (0 – 1) | 1 (0 – 1) |
| Histology, n (%) | | |
| CLL | 24 (27) | 20 (27) |
| B-cell NHL | | |
| FL | 22 (24) | 17 (23) |
| DLBCL | 16 (18) | 13 (18) |
| MCL | 6 (7) | 6 (8) |
| MZL | 5 (6) | 5 (7) |
| Waldenström macroglobulinemia | 3 (2) | 2 (3) |
| Hodgkin lymphoma | 11 (12) | 9 (12) |
| T-cell lymphoma | 2 (1) | 1 (1) |
| HCL | 1 (1) | - |
| Prior therapies, n (range) | 3 (2 – 5) | 3 (2 – 5) |
| Patients receiving ≥3 prior therapies, n (%) | 52 (58) | 41 (56) |
| Refractory to prior therapy, n (%) | 44 (49) | 36 (49) |

- Of the 24 patients with CLL, ten (42%) had high-risk cytogenetics,
  - two with a *17p* deletion, seven with an *11q* deletion, and one with both
- 44 patients (49%) had received umbralisib for more than six cycles (168 days), and 23 patients (26%) had received treatment for more than 12 cycles (336 days)
- Median duration of treatment and follow-up was 4.7 cycles (IQR 2.0–14.0) or 133 days (IQR 55–335), with a mean of 9.6 cycles (SD 11.2) administered

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

# Umbralisib in Relapsed/Refractory Lymphoid Malignancies: Adverse Events ≥15% (all causality) in the Safety Population (N=90)

| AE, n (%) | All Grades | Grade 1-2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Diarrhea | 39 (43) | 36 (40) | 3 (3) | - |
| Nausea | 38 (42) | 37 (41) | 1 (1) | - |
| Fatigue | 28 (31) | 25 (28) | 3 (3) | - |
| Vomiting | 25 (28) | 25 (28) | - | - |
| Cough | 19 (21) | 19 (21) | - | - |
| Headache | 19 (21) | 17 (19) | 2 (2) | - |
| Rash | 17 (18) | 13 (14) | 4 (4) | - |
| Constipation | 14 (16) | 13 (14) | 1 (1) | - |
| Decreased appetite | 14 (16) | 14 (16) | - | - |
| Hypokalemia | 14 (16) | 10 (11) | 4 (4) | - |
| Anemia | 13 (15) | 5 (6) | 8 (9) | - |
| Neutropenia | 13 (15) | 1 (1) | 9 (10) | 3 (3) |

- Most diarrhea events were grade 1 (n=30; 77%) and resolved without intervention
- ALT/AST increase uncommon, occurring in 7 (8%) of patients (3% Grade ≥3)
- AEs of note occurring <10% of patients include pneumonia (8%, Grade 3/4 - 3%), febrile neutropenia (3%, Grade 4 - 1%), and colitis (2%)

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

# Umbralisib in Relapsed/Refractory Lymphoid Malignancies: Clinical Efficacy

- Responses according to disease type:

| Disease | Objective response, n (%) | CR, n (%) | PR, n (%) | PR-L, n (%) | Duration of Response, mo (n) |
|---|---|---|---|---|---|
| CLL, n=20 | 17 (85) | - | 10 (50)* | 7 (35) | 13.4 (16) |
| CLL, del 17p/del 11q,n=8 | 6 (75) | - | 4 (50%)* | 2 (25%) | - |
| FL, n=17 | 9 (53) | 2 (12) | 7 (41) | - | 9.3 (9) |
| DLBCL, n=13 | 4 (31) | - | 4 (31) | - | 6.4 (4) |

HL: 1 CR, 4 SD, 4 PD; MZL: 1 PR, 4 SD; Waldenström macroglobulinemia: 2 SD; MCL: 1 PR, 4 SD, 1 PD.*iwCLL 2008

- Umbralisib was clinically active in most treated patients
  - 56 of 90 (62%) study patients had reductions in disease burden by CT scan
  - ORR 37% (PR 33%) amongst all evaluable patients (N=73)
- Responses increased over time amongst patients with CLL and iNHL

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

# A PHASE 2 STUDY TO ASSESS THE SAFETY AND EFFICACY OF UMBRALISIB (TGR-1202) IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WHO ARE INTOLERANT TO PRIOR BTK OR PI3Kδ INHIBITOR THERAPY


**Anthony R. Mato, MD[1], Stephen J. Schuster, MD[2], Nicole Lamanna, MD[3], John M. Pagel, MD, PhD[4], Ian W. Flinn, MD, PhD[5], Jacqueline Barrientos, MD[6], James A. Reeves, MD[7], Bruce D. Cheson, MD[8], Paul M. Barr, MD[9], Suman Kambhampati, MD[10], Frederick Lansigan, MD[11], Jeffrey J. Pu, MD, PhD[12], Alan Skarbnik, MD[13], Gustavo Fonseca, MD[14], Colleen Dorsey, RN, BSN[1], Nicole M. LaRatta, MPH[2], Hanna Weissbrot, BS[3], Jakub Svoboda, MD[2], Eline T. Luning Prak, MD, PhD[15], Patricia Tsao, MD, PhD[15], Andrea Sitlinger, MD[16], Dana Paskalis[17], Peter Sportelli, BS[17], Hari P. Miskin, MS[17], Michael S. Weiss[17], Danielle M. Brander, MD[16]**

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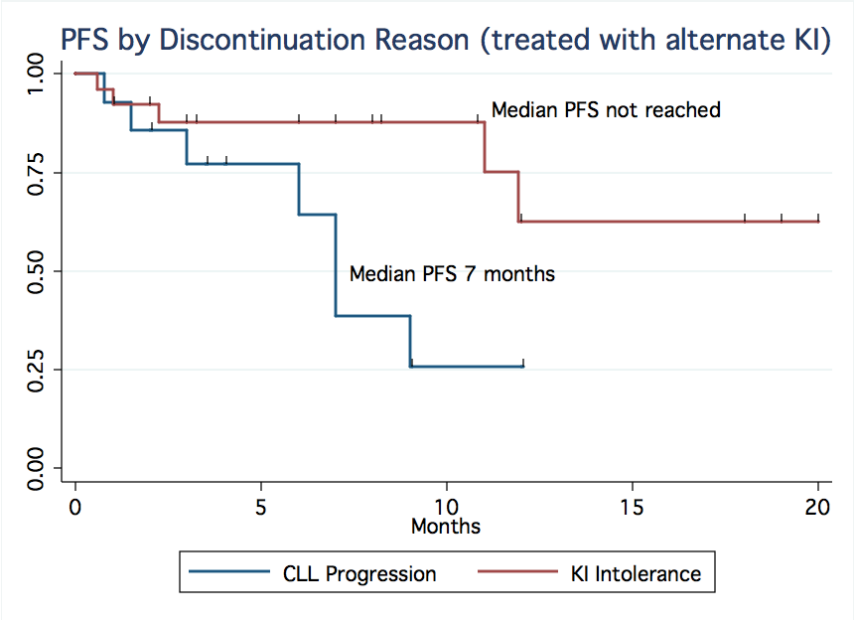
# Rationale

- Kinase inhibitor (KI) therapies are generally well tolerated, although intolerance is the most common reason for discontinuation in practice (~20% discontinuation rate due to AE)[1]

- AEs leading to BTK and PI3Kδ discontinuation are non-overlapping
- Retrospective data show that KI-intolerant patients can be successfully treated with an alternate KI

| Discontinuation due to intolerance | |
|---|---|
| US series TN ibrutinib | 63% of discontinuations |
| US series R/R ibrutinib | 50% of discontinuations |
| UK series R/R ibrutinib[2] | 43% of discontinuations |
| US series R/R idelalisib | 52% of discontinuations |




***Patients who discontinue a KI due to intolerance represent an unmet medical need***

[1]Mato et al., Blood 2016, Annals Oncology 2017; [2]Follows, et al., Haematologica 2016

## Study Design

- **Study design:** Phase II, multicenter, single-arm trial of umbralisib monotherapy in CLL patients who are intolerant to prior KI therapy and warranting therapy per investigator discretion (NCT02742090)
  - Primary objective: PFS of umbralisib in CLL pts intolerant to prior BTK/PI3Kδ inhibitors
  - Secondary objectives: Time to Treatment Failure with umbralisib as compared to prior KI therapy; safety profile of umbralisib as compared to prior KI therapy
- **Enrollment:** Up to 50 patients, study was fully accrued in June 2018
- **Definition of KI Intolerance:** unacceptable toxicity where, in the opinion of the investigator, treatment should be discontinued in spite of optimal supportive care as a result of one of the following:
  - 2 or more Grade ≥ 2 non-hematological toxicities; OR
  - 1 or more Grade ≥ 3 non-hematological toxicity; OR
  - 1 or more Grade 3 neutropenia with infection or fever; OR
  - Grade 4 heme toxicity which persists to the point that the investigator chose to stop therapy due to toxicity NOT progression

Mato et al., ICML 2019

# Demographics

| | |
|---|---|
| Evaluable for Safety, n | 51 |
| Evaluable for PFS†, n | 50 |
| Measurable Disease at Study Entry, n | 36 |
| Median Age, years (range) | 70 (48 – 96) |
| Male/Female | 28 / 23 |
| ECOG, 0/1/2 | 23 / 24 / 4 |
| 17p del and/or TP53 mutated, n (%) | 12 (24%) |
| 11q del, n (%) | 9 (18%) |
| IGHV Unmutated, % | 65% |
| Bulky Disease, n (%) | 21 (41%) |
| Prior Therapies, median (range) | 2 (1 – 7) |
| Prior BTK inhibitor, n | 44 (86%) |
| Prior PI3K inhibitor, n | 7 (14%) |
| Median Time on Prior KI, mos (range) | 9 (0.7 – 38 mos) |
| Median Time from D/C of Prior KI to Enrollment, mos (range) | 3 (1 – 12) |
| Required Tx within 6 mos of Prior KI, n (%) | 39 (76%) |

| Gene | CLL related variants |
|---|---|
| ATM | 11 (24%) |
| BTK | 1 (2%) |
| NOTCH 1 | 4 (9%) |
| PLCG2 | 2 (4%) |
| SF3B1 | 7 (15%) |
| TP53 | 9 (20%) |

Data available for 46/51 pts

†1 patient with confirmed Richter's Transformation at enrollment (not eligible); excluded from PFS analysis

Median follow-up 14 months as of data cutoff

Mato et al., ICML 2019

# Safety: Umbralisib was well tolerated

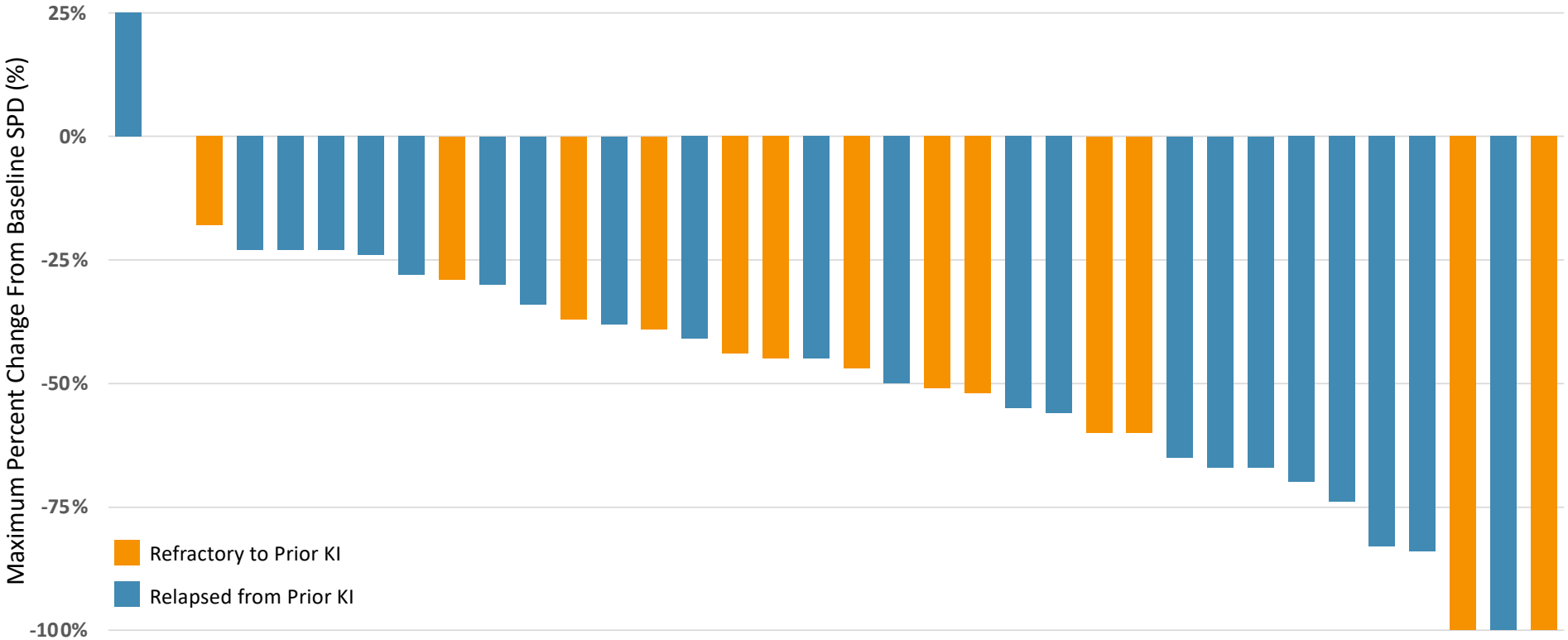
- 4 patients had recurrence of an AE that led to prior KI intolerance
  - 3 were of lesser severity and did not lead to dose modification or d/c of umbralisib
  - 1 patient discontinued for recurrent rash (prior ibrutinib)
- 1 case of colitis reported after 6 weeks on treatment – 17p del CLL patient
  - Recovered after 2 week hold
  - Did not recur on re-challenge at 600 mg
  - Patient achieved a CR and on study for 25 months
- No fatal AE's occurred
- 8 pts (16%) had dose reductions allowing them to continue umbralisib therapy
- 6 pts (12%) discontinued treatment due to an umbralisib AE (pneumonitis (2), pancreatitis, pneumonia, dermatitis, rash)

**All Causality Adverse Events in >10% of Patients (N=51)**

| | All Grades | | Grade 3/4 | |
|---|---|---|---|---|
| | N | % | N | % |
| **Diarrhea** | 32 | 63% | 4 | 8% |
| **Nausea** | 27 | 53% | | |
| **Thrombocytopenia** | 13 | 25% | 6 | 12% |
| **Fatigue** | 13 | 25% | | |
| **Insomnia** | 13 | 25% | | |
| **Neutropenia** | 12 | 24% | 9 | 18% |
| **Headache** | 12 | 24% | | |
| **Dizziness** | 10 | 20% | | |
| **Peripheral Edema** | 9 | 18% | | |
| **Cough** | 8 | 16% | | |
| **Rash** | 8 | 16% | | |
| **Leukocytosis** | 7 | 14% | 7 | 14% |
| **Pneumonia** | 7 | 14% | 6 | 12% |
| **Anemia** | 7 | 14% | 2 | 4% |
| **Pyrexia** | 7 | 14% | 1 | 2% |
| **Arthralgia** | 7 | 14% | | |
| **Contusion** | 7 | 14% | | |
| **Decreased appetite** | 7 | 14% | | |
| **Myalgia** | 7 | 14% | | |
| **Upper respiratory tract infection** | 7 | 14% | | |
| **Vomiting** | 7 | 14% | | |
| **AST/ALT Increase** | 6 | 12% | 3 | 6% |

Mato et al., ICML 2019

# Efficacy – Best % Change in Nodal Lesions




Note: Patients were not required to have relapsed or refractory disease following prior KI discontinuation
Plot only includes patients with measurable disease at study entry

**Refractory to prior KI: Progression from 14 days to 6 mos post KI; Relapsed from prior KI: Progression after 6 mos post KI**

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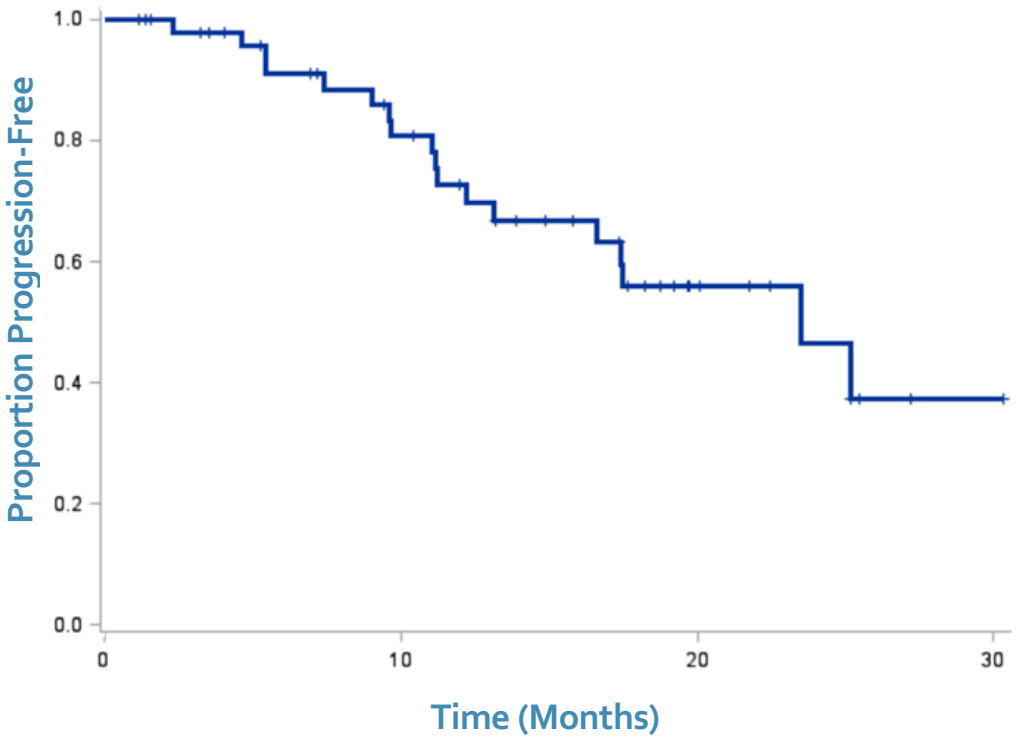
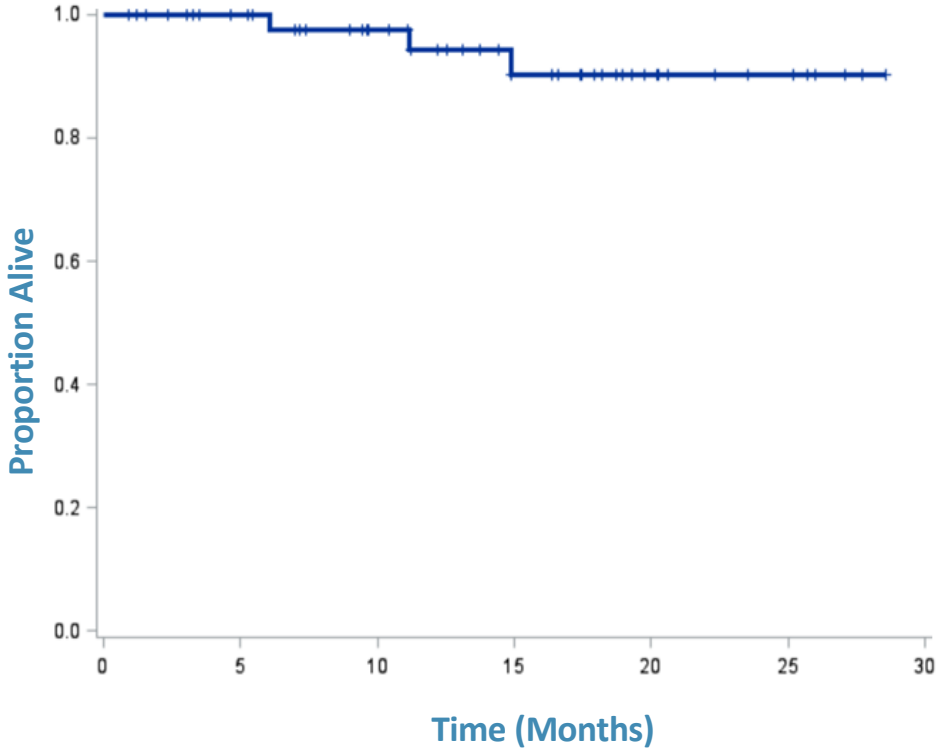
# Efficacy – Progression-Free Survival and Overall Survival




- Estimated median PFS: 23.5 months (95% CI 13.1 – NE)
- Median OS not reached

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## Conclusions- TKI Intolerance

- Umbralisib demonstrates a *favorable safety profile* in pts intolerant to prior BTK or PI3Kδ therapy
- *Well tolerated:*
  - Only 1 pt (2%) discontinued due to a recurrent AE also experienced with prior KI therapy
  - Only 6 pts 12% discontinued due to an umbralisib AE
- *Significant clinical activity:*
  - **Primary endpoint was met** with a **median PFS of 23.5 mos**
  - **High-risk population:** 76% required treatment within 6 months of prior KI discontinuation, 67% had a high-risk molecular / genetic marker and 6% had an ibrutinib resistance mutation
  - 94% of patients with measurable disease at baseline had a reduction in lymphadenopathy

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# 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

Anthony R. Mato, MD[1], Jakub Svoboda, MD[2], Eline T. Luning Prak, MD, PhD[3], Stephen J. Schuster, MD[2], Patricia Y. Tsao, MD, PhD[3], Colleen Dorsey, BSN, RN[1], Lisa M Sarmasti, BSN RN[1],Pamela S. Becker, MD, PhD[4], Danielle M. Brander, MD[5], Mark Geyer MD[1], Jae Park MD[1], Isaac Deonarine BS[1], Cara M. King, MPH[2], Beth Morrigan[4], Jill Elwell[4], Kaitlin Kennard, RN, BSN[2], Lindsey Roeker[1], MD, Andrew D. Zelenetz MD[1], Michelle Purdom, PhD, RN[6], Dana Paskalis[6], Peter Sportelli[6], Hari P Miskin, MSc[6], Michael S. Weiss[6] and Mazyar Shadman, MD, MPH[4]

*[1]CLL Program, Leukemia Service, Division of Hematologic Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY; [2]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [3]University of Pennsylvania, Department of Pathology and Laboratory Medicine, Philadelphia PA; [4]Fred Hutchinson Cancer Research Center, Seattle, WA; [5]Duke University Medical Center, Durham, NC; [6]TG Therapeutics, Inc., New York, NY*

## Background and Rationale

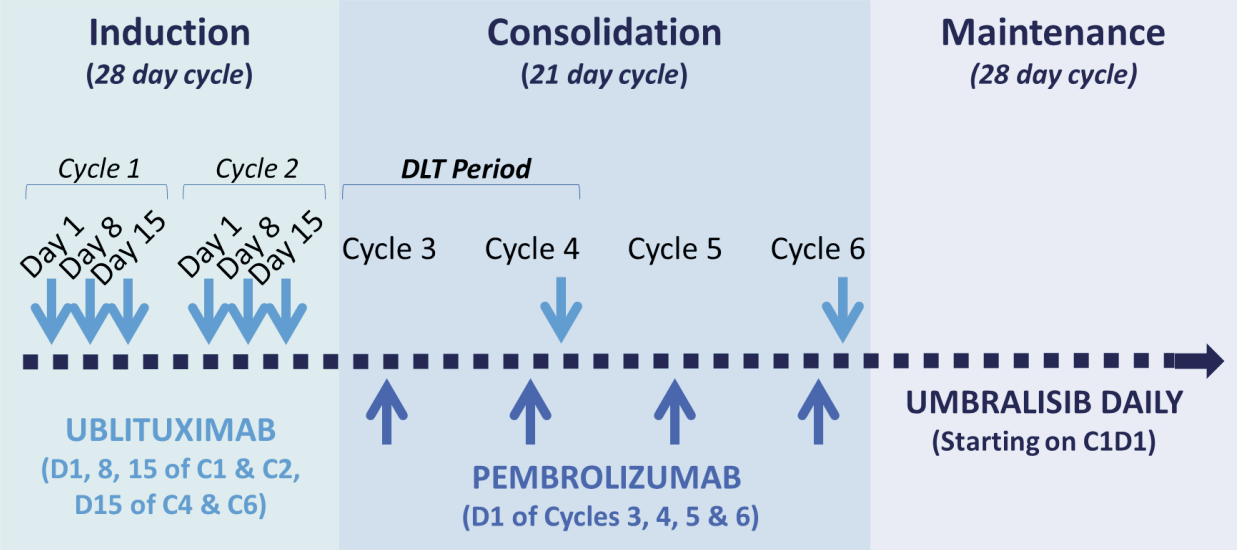
- ***PI3Kδ inhibition is hypothesized to increase innate / adaptive cell-mediated immune responses***
- ***PI3Kδ inhibition + PD-1 blockade:***
  - A key interaction exists between **PI3K signaling** and **immune checkpoint surveillance** by which **inhibition of PI3Kδ decreases PD-L1 tumor expression**, 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

Mato et al., ICML 2019

# Study Design

- Phase I/II dose-escalation (3+3 design), multicenter study to assess the safety & efficacy of Umbralisib + Ublituximab (U2) with pembro in patients with R/R CLL and RT (NCT02535286)
  - **Cohort 1: Pembo 100 mg**
  - **Cohort 2: Pembro 200 mg**

- **Key Eligibility for CLL:** Progressed on at least one prior tx; mid-study amendment required CLL pts to be BTK refractory (PD within 6 months of prior BTK)

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# 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%) |

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# 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)

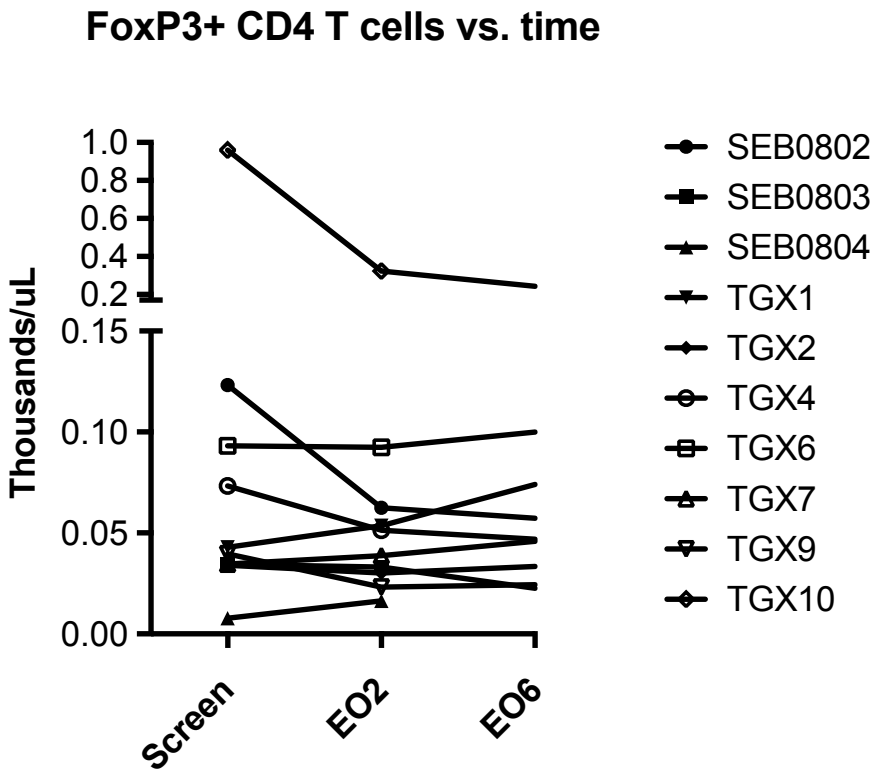
**Adverse Events for (All Causality) >20% (N=20)**

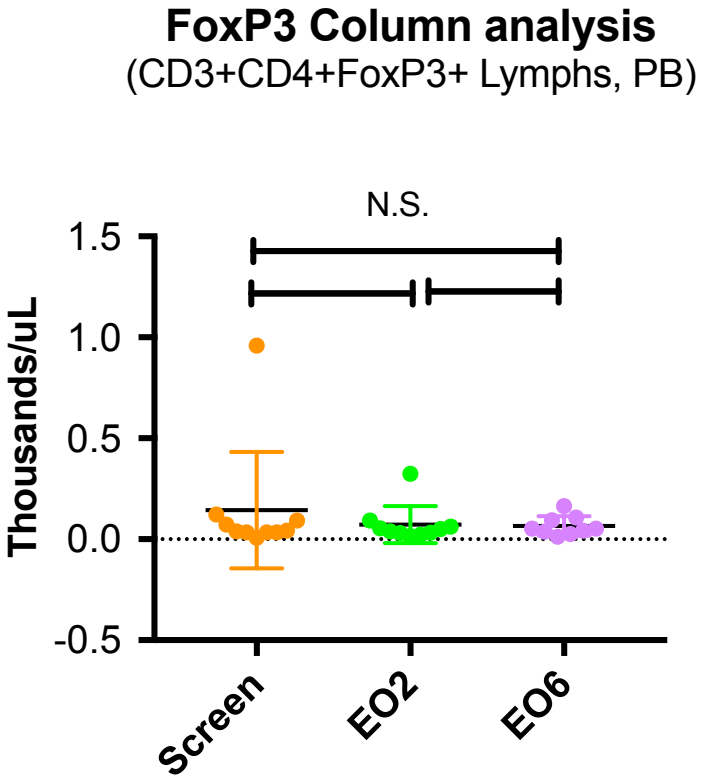
| | All Grades | | Grade 3/4 | |
|---|---|---|---|---|
| | N | % | N | % |
| **Neutropenia** | 13 | 65% | 8 | 40% |
| **Fatigue** | 11 | 55% | 1 | 5% |
| **Cough** | 10 | 50% | | |
| **Diarrhea** | 10 | 50% | | |
| **Pyrexia** | 10 | 50% | | |
| **Infusion related reaction** | 9 | 45% | | |
| **Nausea** | 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% | | |

Mato et al., ICML 2019

# Correlatives: T-reg population

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



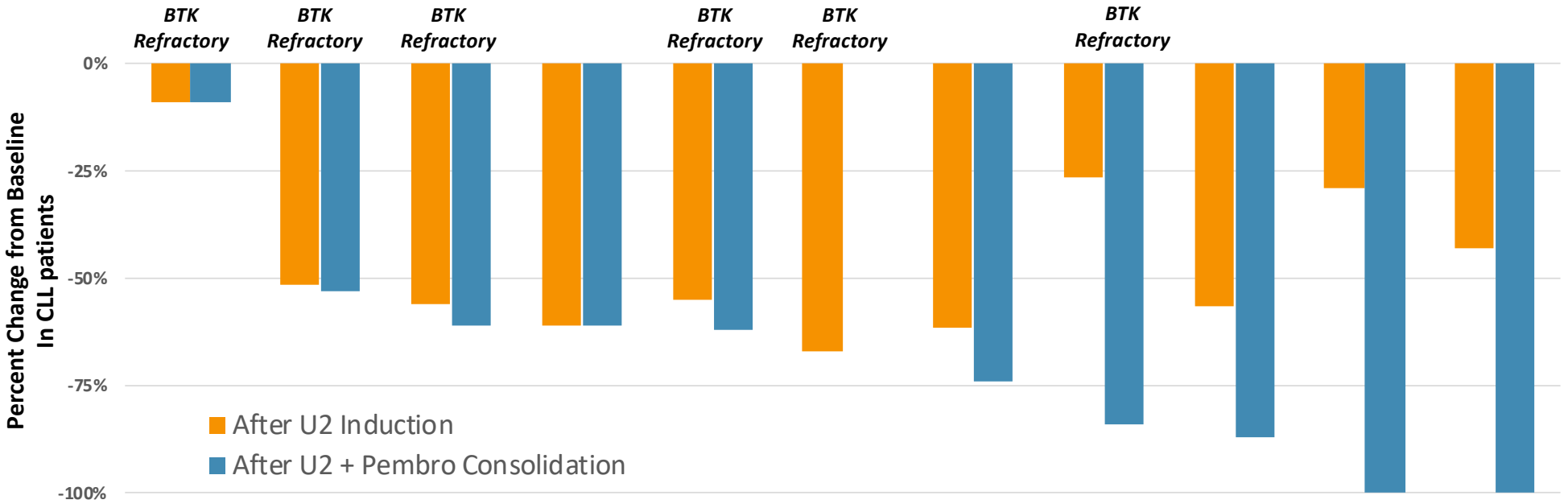




Mato et al., ICML 2019

# Efficacy: ORR in CLL

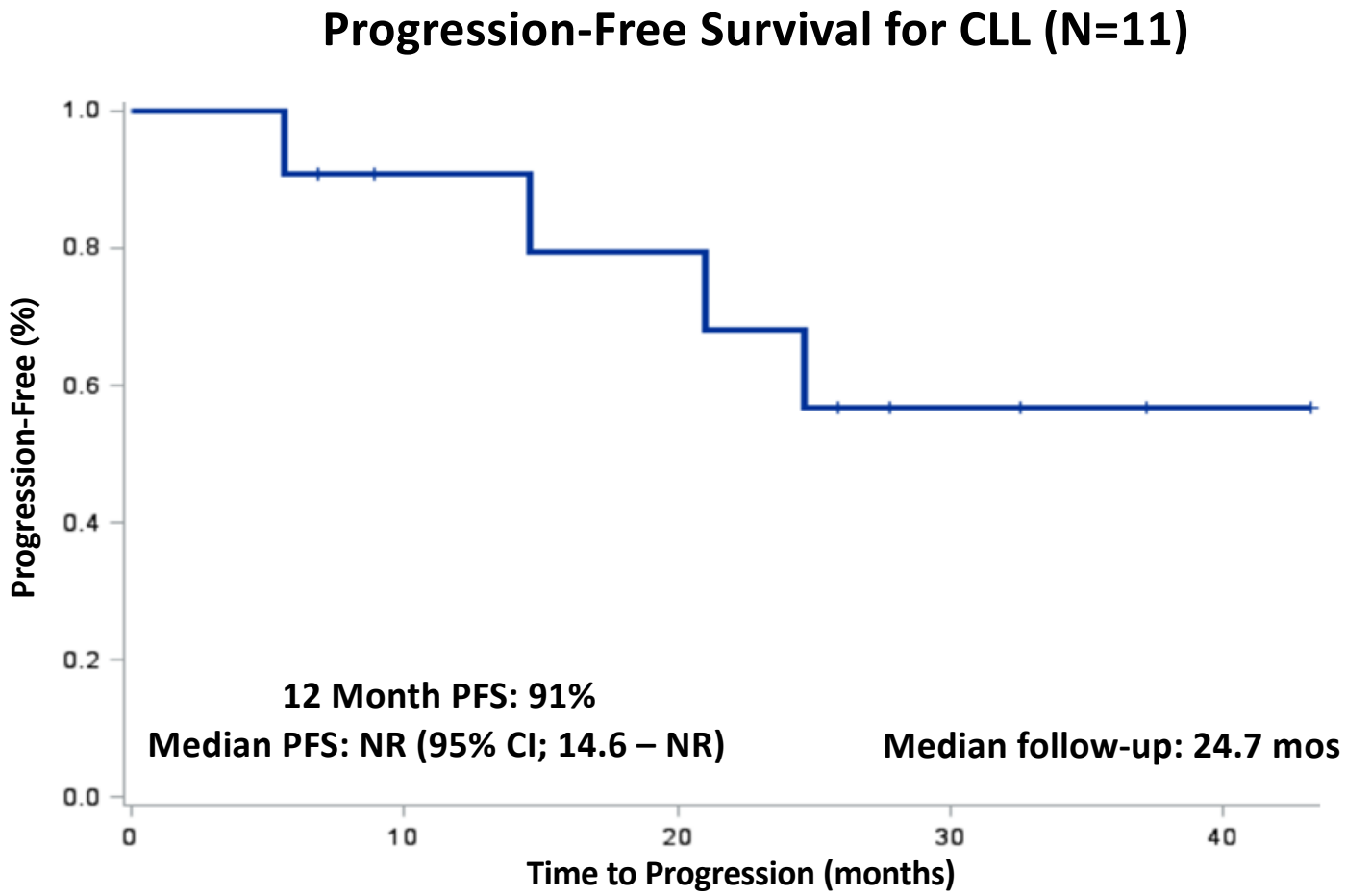
| Group | N | CR N (%) | PR N (%) | SD N (%) | ORR N (%) |
|---|---|---|---|---|---|
| **CLL** | 11 | 1 (9%) | 9 (82%) | 1 (9%) | 10 (91%) |

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




Mato et al., ICML 2019

# Efficacy: PFS for the CLL Subjects




Mato et al., ICML 2019

## Conclusions: U2 + Pembro in CLL and RT

- 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
- Protocol has now been amended to replace pembro with novel anti-PD-L1 (TG-1501)

Mato et al., ICML 2019

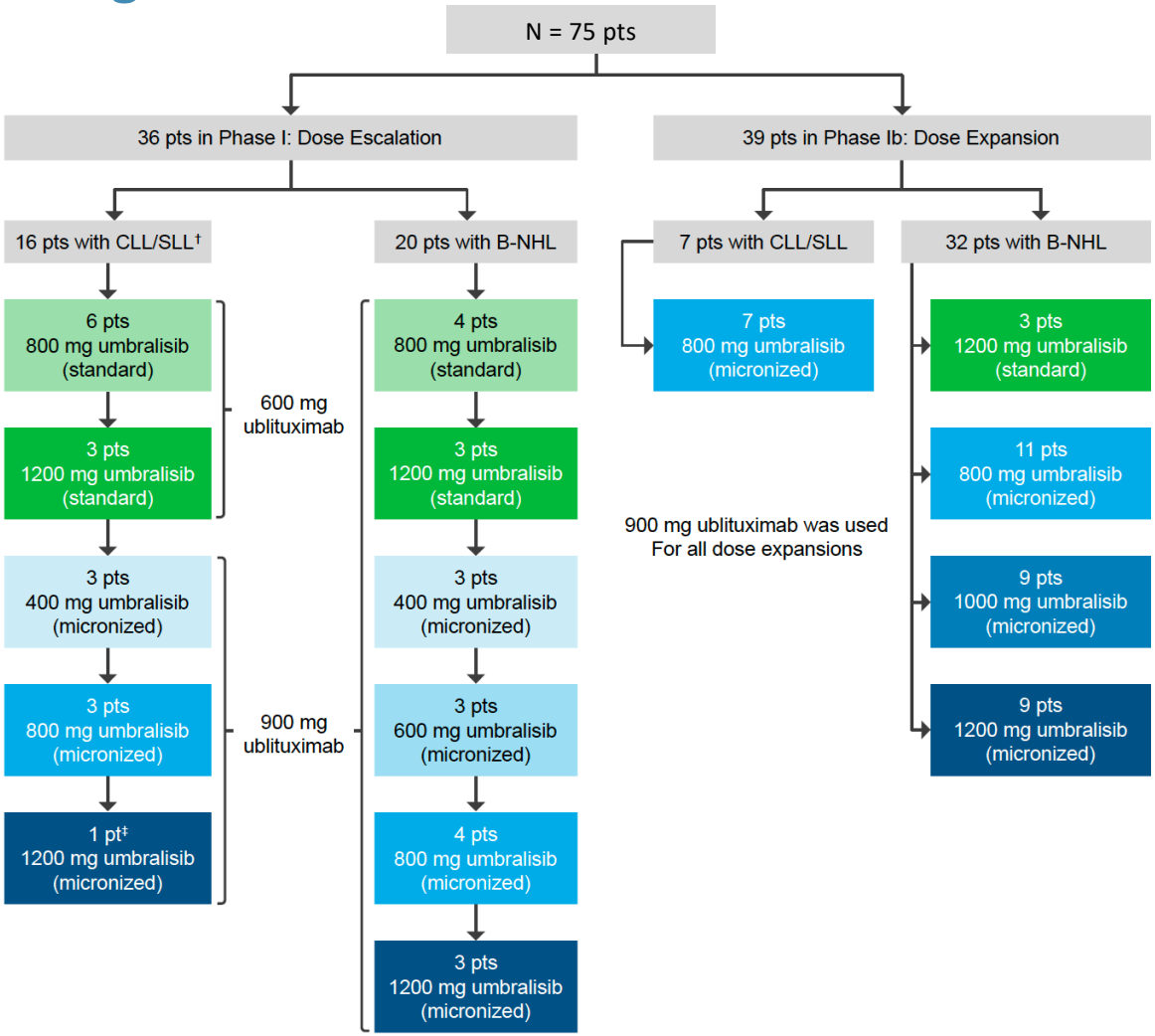
# UBLITUXIMAB AND UMBRALISIB IN RELAPSED/ REFRACTORY B-CELL NON-HODGKIN LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA

**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], Peter Sportelli[6], Hari P. Miskin, MS[6], Michael S. Weiss[6] and Susan O'Brien, MD[7]**

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

Lunning, et al. *Blood*. 2019 doi: 10.1182/blood.2019002118

# Study Design




- 75 pts for Safety
- 69 pts for Efficacy
- Ublituximab
  - 900mg NHL
  - 600 or 900mg CLL

Lunning, et al. *Blood*. 2019 doi: 10.1182/blood.2019002118

# Ublituximab + Umbralisib – Subject Demographics

| | | |
|---|---|---|
| **Evaluable for Safety (n)** | | 75 |
| **Evaluable for Efficacy** | | 69 |
| **Median Age, years (range)** | | 64 (26-86) |
| **Male/Female** | | 49/26 |
| **Histology** | DLBCL | 26 |
| | CLL/SLL* | 22 |
| | FL | 19 |
| | MZL | 5 |
| | MCL | 2 |
| | Richter's | 1 |
| **ECOG 0/1/2** | | 21/50/4 |
| **Prior Therapy Regimens, median (range)** | | 3 (0-10) |
| **Refractory to Prior Therapy, n (%)** | | 43 (57) |
| **Refractory to prior anti-CD20 regimen, n (%)** | | 39 (54) |

*9 /22 (41%) of patients with CLL/SLL had 17p (del) and 6 had prior BTK inhibitor therapy

- Heavily pre-treated subject population with high-risk features, including 57% refractory to last treatment with multiple previous lines of rituximab (RTX) based therapy

Lunning, et al. *Blood*. 2019 doi: 10.1182/blood.2019002118

# Ublituximab + Umbralisib : Safety

## All Causality AE's Occurring in ≥ 10% of Subjects (n = 75)

| Adverse Event | All Patients | | | | CLL/SLL | | | |
|---|---|---|---|---|---|---|---|---|
| | All Grades | | Grade 3/4 | | All Grades | | Grade 3/4 | |
| | N | % | N | % | N | % | N | % |
| Diarrhea | 45 | 60% | 6 | 8% | 14 | 64% | 0 | 0 |
| Nausea | 42 | 56% | 3 | 4% | 18 | 82% | 1 | 5% |
| Fatigue | 36 | 48% | 2 | 3% | 11 | 50% | 0 | 0 |
| Neutropenia | 24 | 32% | 21 | 28% | 12 | 55% | 11 | 50% |
| Vomiting | 23 | 31% | 1 | 1% | 7 | 32% | 0 | 0 |
| Infusion-related reaction | 23 | 31% | 1 | 1% | 13 | 59% | 1 | 5% |
| Cough | 18 | 24% | 0 | 0 | 7 | 32% | 0 | 0 |
| Sinusitis | 17 | 23% | 0 | 0 | 10 | 45% | 0 | 0 |
| Back pain | 17 | 23% | 1 | 1% | 6 | 27% | 1 | 5% |
| Decreased appetite | 17 | 23% | 1 | 1% | 5 | 23% | 0 | 0 |
| Dizziness | 17 | 23% | 0 | 0 | 6 | 27% | 0 | 0 |
| Pyrexia | 16 | 21% | 2 | 3% | 5 | 23% | 1 | 5% |
| Edema Peripheral | 15 | 20% | 1 | 1% | 5 | 23% | 0 | 0 |
| Insomnia | 15 | 20% | 0 | 0 | 8 | 36% | 0 | 0 |
| Dyspnea | 15 | 20% | 2 | 3% | 5 | 23% | 0 | 0 |
| Headache | 13 | 17% | 0 | 0 | 6 | 27% | 0 | 0 |
| Abdominal pain | 12 | 16% | 5 | 7% | 5 | 23% | 2 | 9% |
| Anemia | 12 | 16% | 3 | 4% | 2 | 9% | 1 | 5% |
| Upper respiratory tract infection | 12 | 16% | 0 | 0 | 5 | 23% | 0 | 0 |

- 11 subjects (15%) had their umbralisib dose reduced
- 31 (49%) had a temporary hold of umbralisib
- Diarrhea had a median onset of 21 days, and resolved in a median of 7 days
- 3 subjects had Grade 3/4 elevations in AST/ALT

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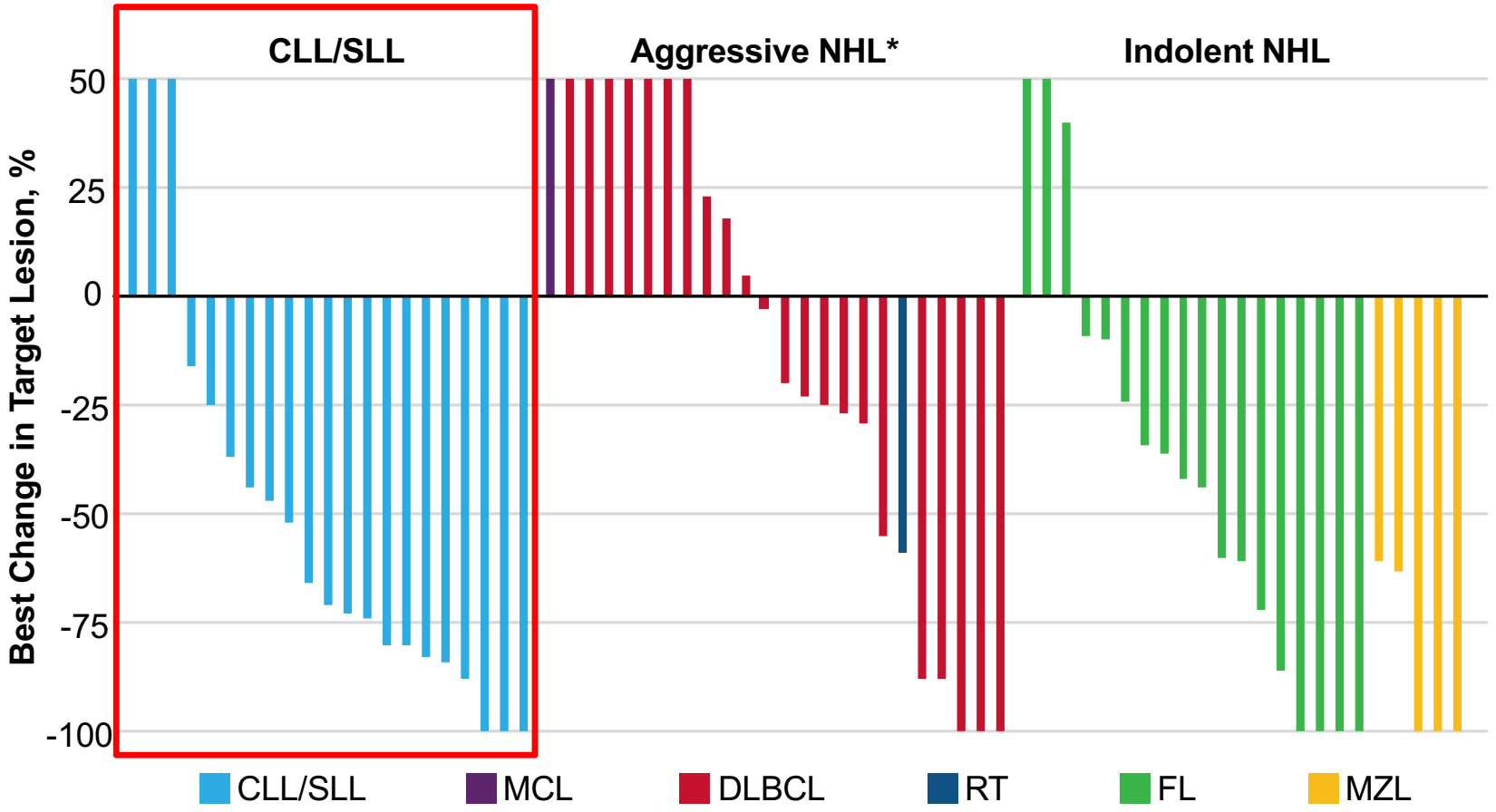
# Ublituximab + Umbralisib: Efficacy




Lunning, et al. *Blood*. 2019 doi: 10.1182/blood.2019002118

# Response by Histology in Patients Receiving Therapeutic Doses of Umbralisib

- Therapeutic Doses include
  - ≥1200mg qd non-micronized
  - ≥600mg qd micronized

| Histology | Response, n/N (%) | | | | |
|---|---|---|---|---|---|
| | ORR | CR | PR | SD | PD |
| **All patients** | **29/57 (51)** | **12/57 (21)** | **17/57 (30)** | **11/57 (19)** | **17/57 (30)** |
| **CLL/SLL** | **10/15 (67)** | **2/15 (13)** | **8/15 (53)** | **2/15 (13)** | **3/15 (20)** |
| **Aggressive B-NHL** | **6/22 (27)** | **3/22 (14)** | **3/22 (14)** | **5/22 (23)** | **11/22 (50)** |
| DLBCL | 5/19 (26) | 3/19 (16) | 2/19 (11) | 5/19 (26) | 9/19 (47) |
| MCL | 0/2 (0) | – | – | – | 2/2 (100) |
| RT | 1/1 (100) | – | 1/1 (100) | – | – |
| **Indolent B-NHL** | **13/20 (65)** | **7/20 (35)** | **6/20 (30)** | **4/20 (20)** | **3/20 (15)** |
| FL | 8/15 (53) | 4/15 (27) | 4/15 (27) | 4/15 (27) | 3/15 (20) |
| MZL | 5/5 (100) | 3/5 (60) | 2/5 (40) | – | – |

**67% ORR in R/R CLL with 41% pts 17 p del**

Lunning, et al. *Blood*. 2019 doi: 10.1182/blood.2019002118

# LONG TERM INTEGRATED SAFETY ANALYSIS OF UMBRALISIB (TGR-1202), A PI3Kδ/CK1E INHIBITOR WITH A DIFFERENTIATED SAFETY PROFILE, IN PATIENTS WITH RELAPSED/REFRACTORY LYMPHOID MALIGNANCIES


**Matthew S. Davids, MD, MMSc[1], Ian W. Flinn, MD, PhD[2,3], Anthony R. Mato, MD[4], Owen A. O'Connor, M.D., Ph.D.[5], Danielle M. Brander, MD[6], Matthew A. Lunning, DO[7], Julie M. Vose, MD, MBA[7], Loretta Nastoupil, MD[8], Nathan Fowler, MD[8], Christopher Flowers, MD, MS[9], Jennifer R. Brown, MD, PhD[1], Marshall T. Schreeder, MD[10], Nilanjan Ghosh, MD, PhD[11], Frederick Lansigan, MD[12], Bruce D. Cheson, MD[13], Paul M. Barr, MD[14], John M. Pagel, MD, PhD[15], Alexey Danilov, MD, PhD[16], Javier Pinilla Ibarz, MD, PhD[17], Changchun Deng, MD, PhD[5], John M. Burke, MD[18,19], Tanya Siddiqi, MD[20], Manish R Patel, MD[2,21], Charles M. Farber, MD, PhD[22], Parameswaran Venugopal, MD[23], John G. Gribben, MD DSc FMedSci[24], Pier Luigi Zinzani, MD, PhD[25], Hari P Miskin, MSc[26], Peter Sportelli, BS[26], Michael S. Weiss[26], and Susan M. O'Brien, MD[28]**

*[1]Dana-Farber Cancer Institute, Boston, MA; [2]Sarah Cannon Research Institute, Nashville, TN; [3]Tennessee Oncology PLLC, Nashville, TN; [4]University of Pennsylvania, Philadelphia, PA; [5]Center for Lymphoid Malignancies, Columbia University Medical Center, New York, NY; [6]Duke University Medical Center, Durham, NC; [7]University of Nebraska Medical Center, Omaha, NE; [8]The University of Texas MD Anderson Cancer Center, Houston, TX; [9]Winship Cancer Institute Bone Marrow & Stem Cell Transplantation, Atlanta, GA; [10]Clearview Cancer Institute, Huntsville, AL; [11]Levine Cancer Institute, Charlotte, NC; [12]Dartmouth-Hitchcock Medical Center, Lebanon, NH; [13]Georgetown University Medical Center, Washington, DC; [14]Wilmot Cancer Institute, University of Rochester, Rochester, NY; [15]Swedish Cancer Institute, Seattle, WA; [16]Oregon Health & Science University, Portland, OR; [17]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; [18]Rocky Mountain Cancer Centers, Aurora, CO; [19]US Oncology Research, The Woodlands, TX; [20]City of Hope National Medical Center, Duarte, CA; [21]Florida Cancer Specialists, Sarasota, FL; [22]Summit Medical Group, Morristown, NJ; [23]Rush University Medical Center, Chicago, IL; [24]Barts Hospital Cancer Institute, Queen Mary University of London, London, United Kingdom; [25]Institute of Hematology "L. e A. Seràgnoli", University of Bologna, Bologna, Italy; [26]TG Therapeutics, Inc., New York, NY; [27]University of California Irvine, Chao Family Comprehensive Cancer Center, Orange, CA*

# Integrated Safety Analysis of Umbralisib in R/R Lymphoid Malignancies

- Safety data were pooled from 4 completed or ongoing Phase 1 or 2 studies containing umbralisib. All studies shared similar key eligibility criteria
  - 347 hematologic malignancy patients treated with umbralisib either as monotherapy or in combination with other agents

| **TGR-1202-101: Single Agent Umbralisib** |
| --- |
| Phase 1, first-in-human, dose-escalation study evaluating umbralisib monotherapy in patients with relapsed or refractory hematologic malignancies. Umbralisib administered daily until progression or off study (50 mg – 1800 mg). (*Burris et al., Lancet Oncology 2018*) |
| **UTX-TGR-103: Umbralisib + Ublituximab +/- Ibrutinib or +/- Bendamustine** |
| Phase 1, dose-escalation study evaluating the combination of umbralisib + ublituximab (U2), U2 + ibrutinib, and U2 + bendamustine, in patients with hematologic malignancies. Umbralisib administered daily; UTX administered D1, 8 and 15 of Cycles 1 & 2, and D1 of Cycles 2-6; Ibrutinib 420 mg CLL/560 mg NHL; Benda 90 mg/m$^2$. (*Nastoupil et al., ICML 2017; Lunning et al., ICML 2017*) |
| **TGR-1202-201: TKI Intolerant CLL** |
| Phase 2, multi-center, single arm study evaluating umbralisib monotherapy (800 mg QD) in CLL patients who are intolerant to prior PI3Kδ or BTK therapy. Umbralisib administered daily until progression or off study. (*Mato et al., EHA 2018*) |
| **TGR-IB-105: Umbralisib + Ibrutinib in CLL & MCL** |
| Phase 1, dose-escalation study evaluating umbralisib + ibrutinib in patients with relapsed or refractory CLL or MCL. Umbralisib (400, 600, or 800 mg) + Ibrutinib (420 mg CLL/560 mg MCL) administered daily. (*Davids et al., ICML 2017*) |

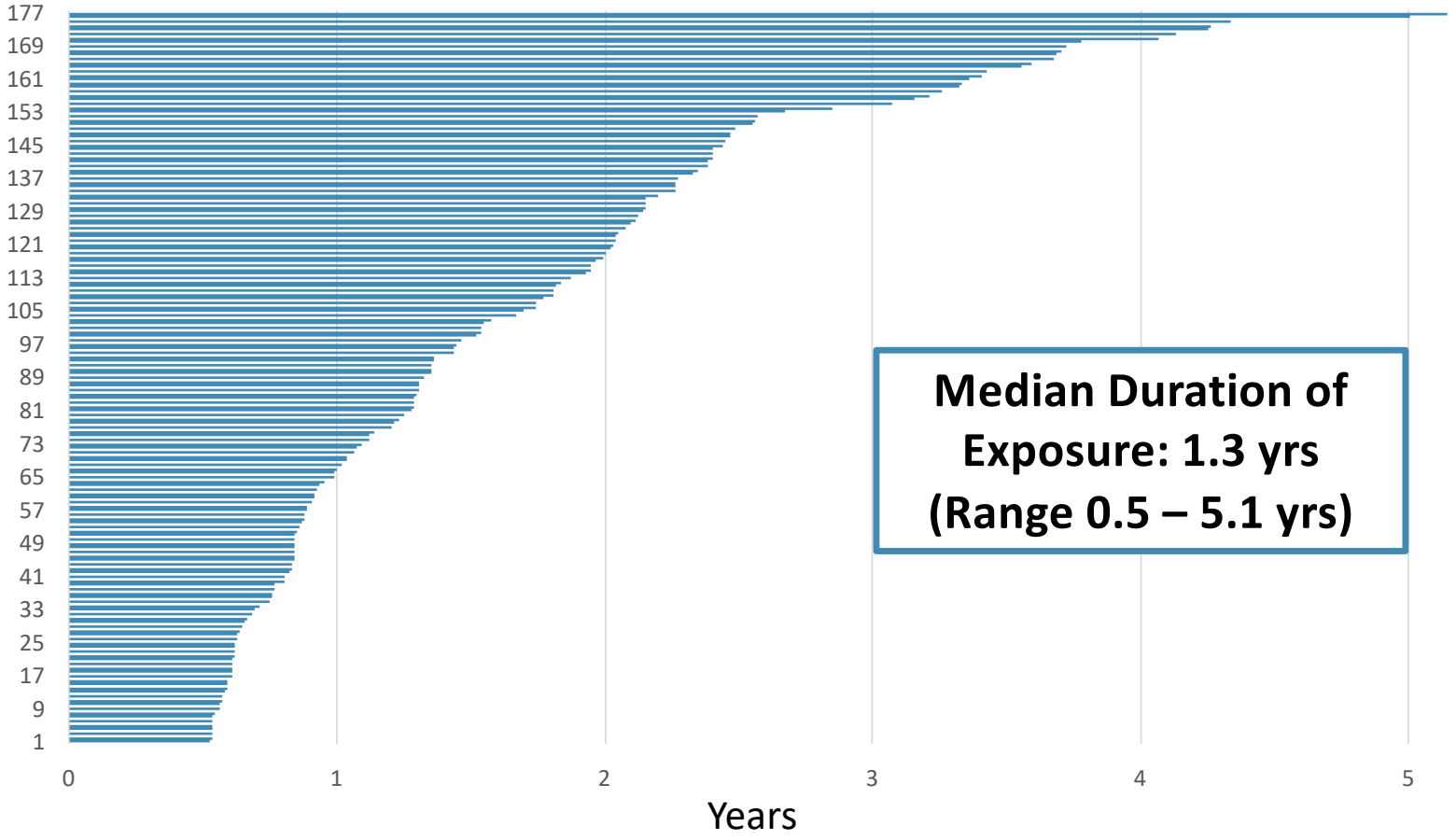
Davids MS, et al. EHA Library, 2018 214906; (abstr PF444). Presented at: EHA Annual Meeting 2018 (poster).

# Long Term Safety Analysis - Patients on Umbralisib for 6+ months: Safety

| | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| Diarrhea | 18 | 10% | 10 | 6% | 14 | 8% | - | - |
| Nausea | 17 | 10% | 7 | 4% | 3 | 2% | - | - |
| Cough | 16 | 9% | 9 | 5% | - | - | - | - |
| Neutropenia | 6 | 3% | 3 | 2% | 8 | 5% | 7 | 4% |
| Fatigue | 6 | 3% | 13 | 7% | 2 | 1% | - | - |
| Sinusitis | 4 | 2% | 15 | 8% | - | - | - | - |
| Vomiting | 12 | 7% | 4 | 2% | 2 | 1% | - | - |
| Anemia | 8 | 5% | 5 | 3% | 4 | 2% | - | - |
| Insomnia | 13 | 7% | 3 | 2% | - | - | - | - |
| URT infection | 4 | 2% | 12 | 7% | - | - | - | - |
| Hypokalemia | 10 | 6% | 3 | 2% | 2 | 1% | - | - |
| Thrombocytopenia | 8 | 5% | 3 | 2% | 3 | 2% | 1 | 1% |
| Abdominal pain | 7 | 4% | 4 | 2% | 3 | 2% | - | - |
| Arthralgia | 9 | 5% | 4 | 2% | - | - | - | - |
| Dizziness | 8 | 5% | 4 | 2% | 1 | 1% | - | - |
| Hypophosphatemia | 2 | 1% | 5 | 3% | 5 | 3% | 1 | 1% |
| Pyrexia | 10 | 6% | 2 | 1% | 1 | 1% | - | - |
| Headache | 8 | 5% | 2 | 1% | 2 | 1% | - | - |
| Pneumonia | - | - | 3 | 2% | 9 | 5% | - | - |
| Creatinine increase | 7 | 4% | 4 | 2% | - | - | - | - |
| Dyspnea | 7 | 4% | 2 | 1% | 1 | 1% | 1 | 1% |
| Constipation | 7 | 4% | 2 | 1% | 1 | 1% | - | - |

Davids MS, et al. EHA Library, 2018 214906; (abstr PF444). Presented at: EHA Annual Meeting 2018 (poster).

# Long Term Safety Analysis - Patients on Umbralisib for 6+ months: Duration on Therapy




R/R, relapsed/refractory.

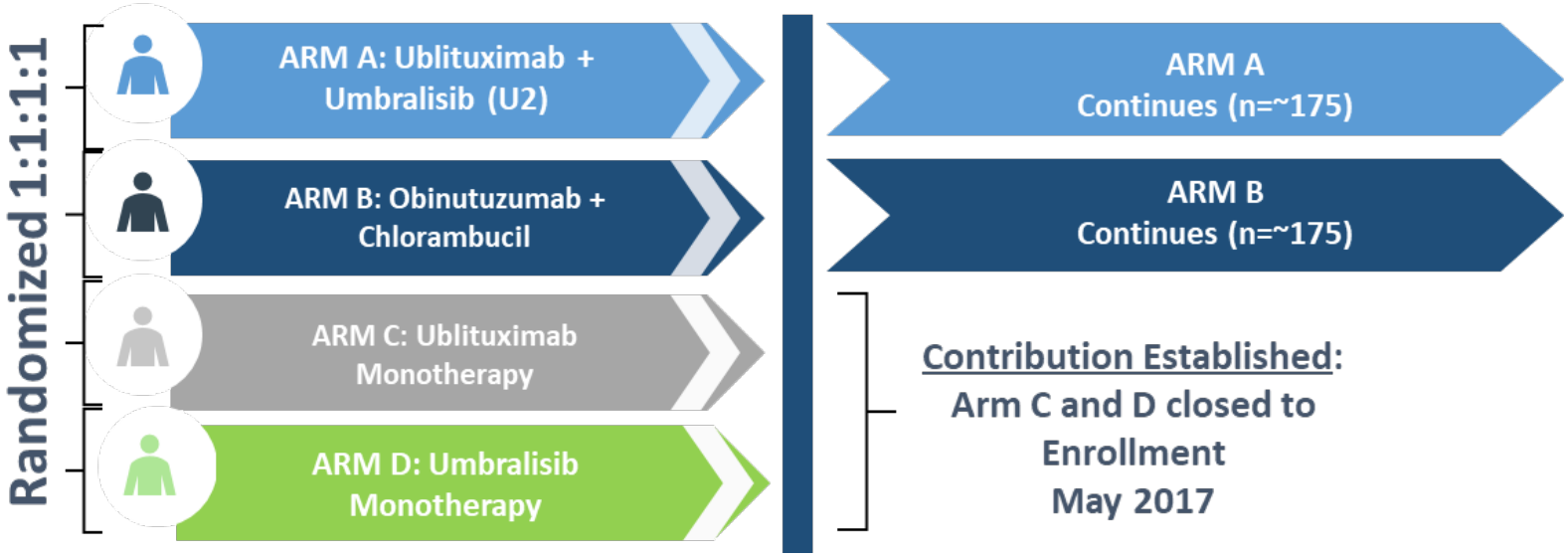
Davids MS, et al. EHA Library, 2018 214906; (abstr PF444). Presented at: EHA Annual Meeting 2018 (poster).

# Long Term Safety Analysis - Patients on Umbralisib for 6+ months: Conclusions

- Umbralisib is associated with low rates of immune-mediated toxicity and exhibits a favorable long-term tolerability profile at a median follow-up of 1.3 years, with up to 5 years of exposure in this integrated cohort of patients. In particular:
  - Only 2% of patients discontinued as a result diarrhea/colitis after being on umbralisib for more than 6 months; and
  - Discontinuations due to other AEs of interest for prior generation PI3K inhibitors were also rare
- The mechanism for decreased immune-mediated toxicity is still being elucidated through ongoing pre-clinical and correlative studies examining umbralisib's selectivity for PI3Kδ over PI3Kγ, complimentary CK1ε inhibition, and enhancement of regulatory T-cell function.
- Registration directed trials in CLL and NHL for umbralisib have completed enrollment with data pending

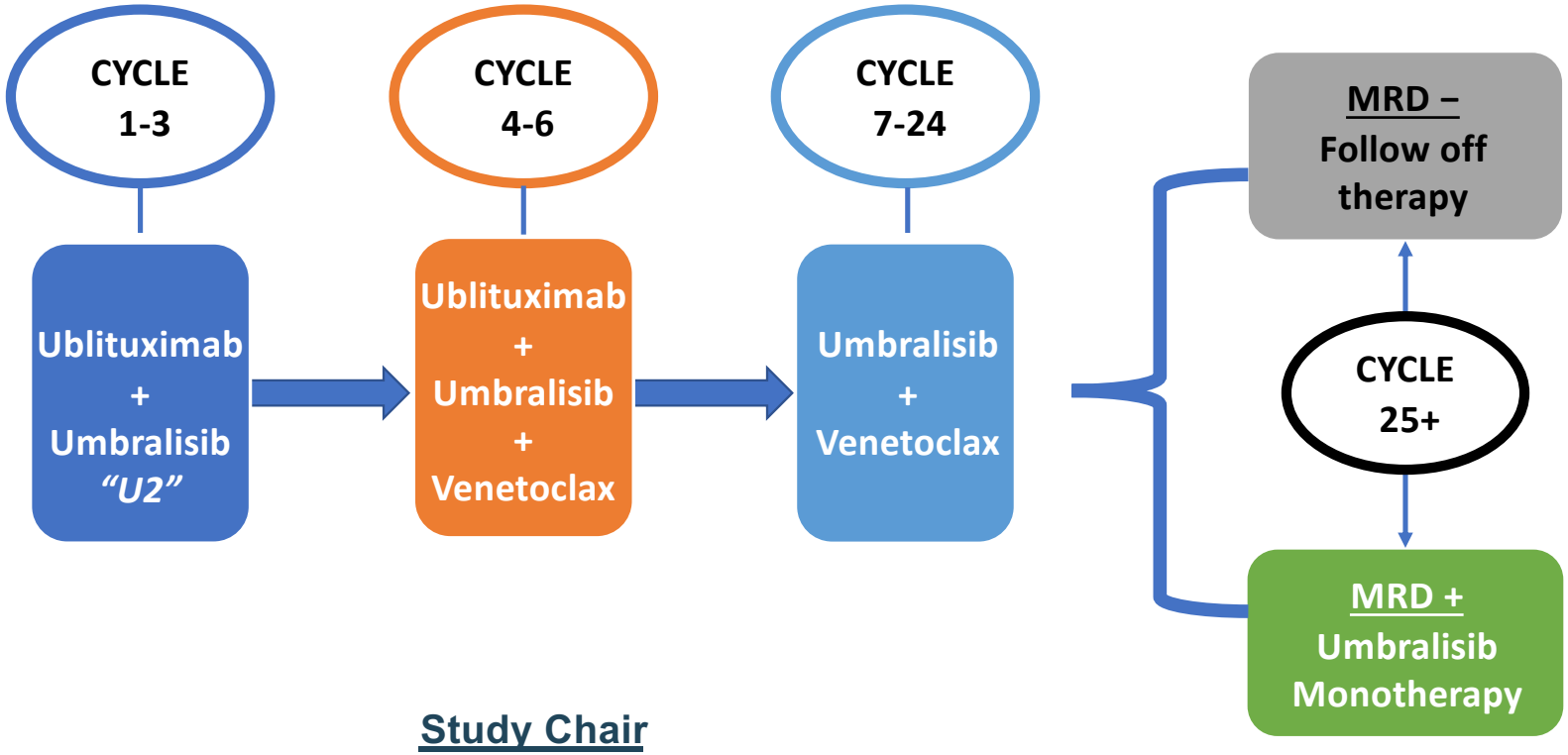
Davids MS, et al. EHA Library, 2018 214906; (abstr PF444). Presented at: EHA Annual Meeting 2018 (poster).

# UNITY-CLL: Ph 3 Trial of Umbralisib + Ublituximab (U2) Treatment Naïve and R/R CLL



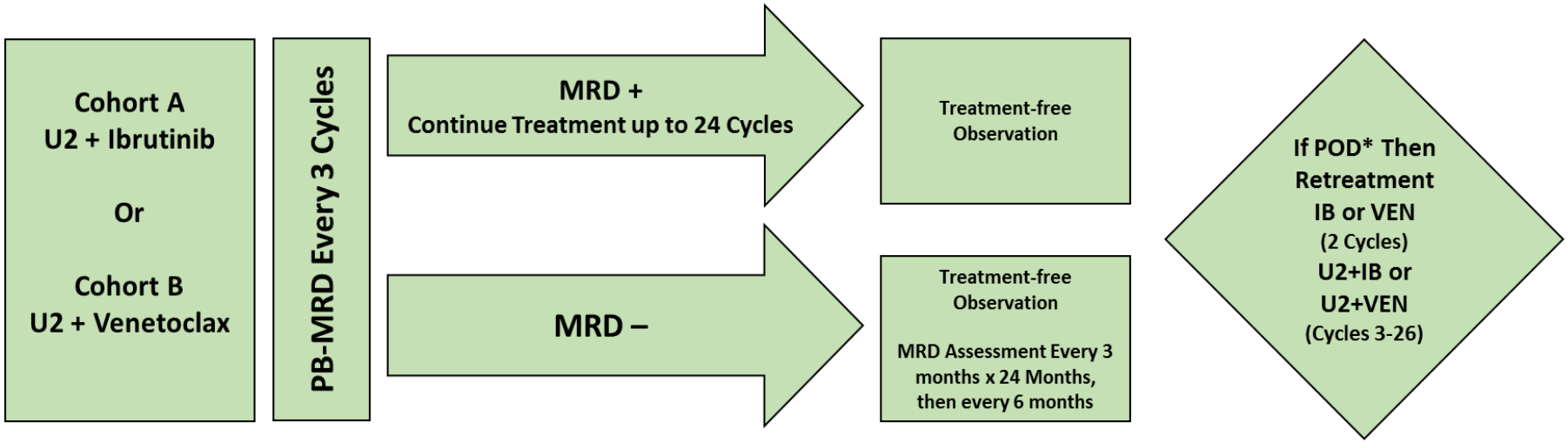

- Design, Endpoints, and Statistics agreed to via Special Protocol Assessment (SPA)
- Arm B, C, & D eligible for crossover to Arm A upon progression
- Primary Endpoint: Progression-Free Survival
- Enrollment completed October 2017

# ULTRA-V Phase 2: U2+Venetoclax in Treatment Naïve & R/R CLL




**Study Chair**
Richard R. Furman, MD
Weill Cornell College of Medicine, New York, NY

# Phase 2, open-label, two treatment cohort trial to evaluate addition of ublituximab and umbralisib on rate of U-MRD in subjects with CLL who fail to achieve U-MRD after a minimum 6-month treatment with ibrutinib or venetoclax




*Progression Of Disease – Defined per the iwCLL Criteria (Hallek 2018)
U2 – ublituximab and umbralisib; IB – ibrutinb; VEN – venetoclax; MRD – miminal residual disease

# Conclusions

- Umbralisib is a novel PI3Kδ/CK-1ε inhibitor with suggested differentiated tolerability profile from currently available TKI's (no direct comparison data)
- Long term integrated analyses demonstrate low rates of immune mediated toxicities
- Umbralisib and the U2 combination studies in front line, r/r settings (vs. CLL 11) also utilized as backbone agents for combination regimens (with ibrutinib, venetoclax, PD-1/L1, etc.)