Umbralisib, A Novel PI3Kδ and Casein Kinase-1ε Inhibitor, in Chronic Lymphocytic Leukemia and Lymphoma

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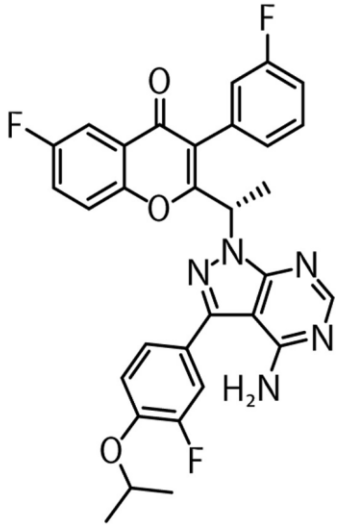
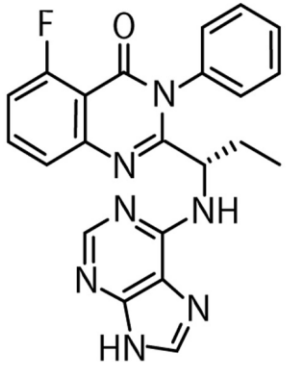
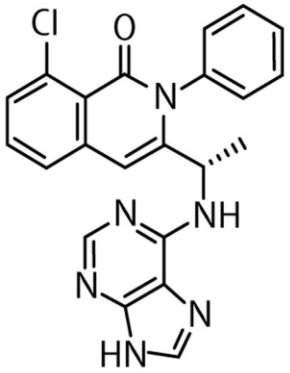
NEW DRUGS IN HEMATOLOGY
BOLOGNA 2018

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

Differentiation of Umbralisib from Other PI3Kδ Inhibitors

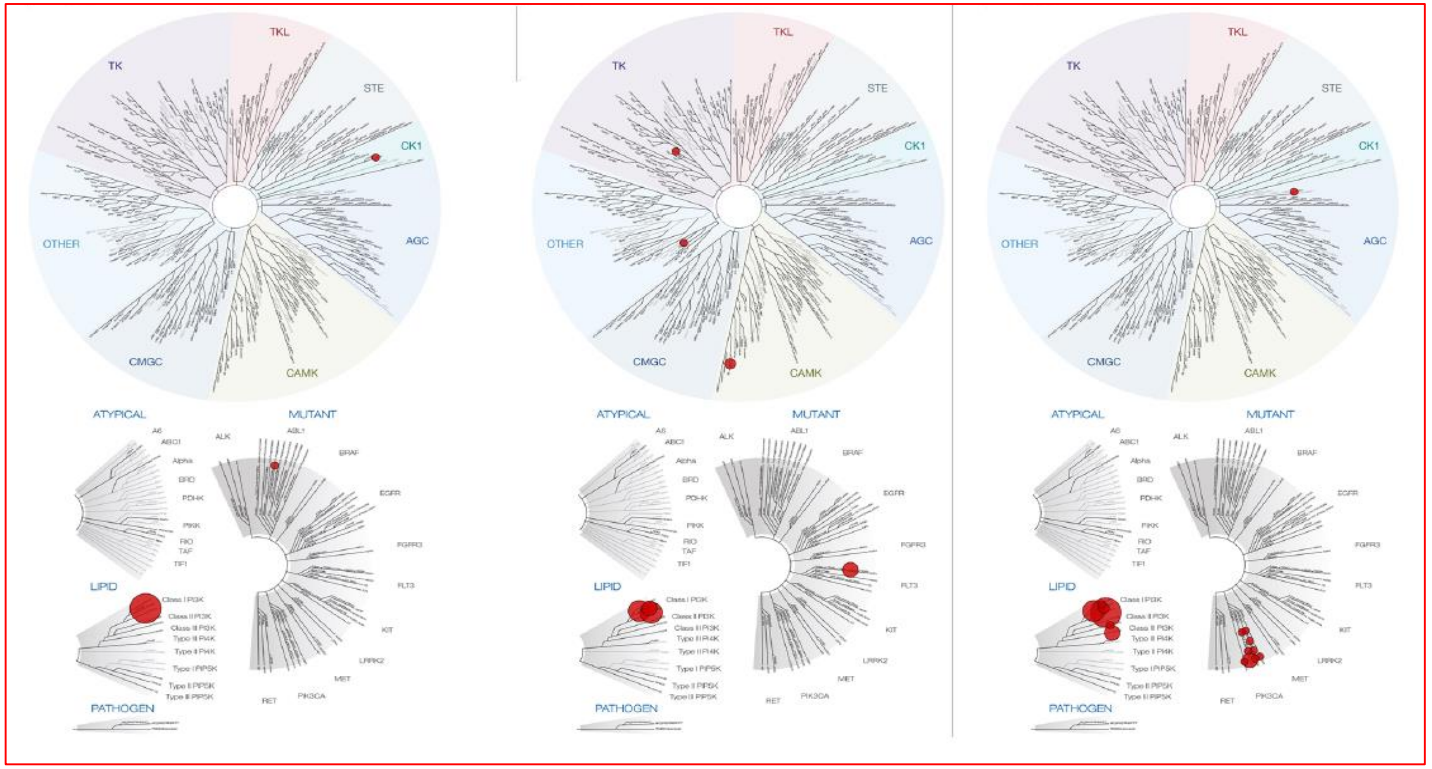
	Umbralisib	Idelalisib	Duvelisib
			
Isoform	**K_d (nM)**		
PI3Kα	>10 000	600	40
PI3Kβ	>10 000	19	0·89
PI3Kγ	1400	9·1	0·21
PI3Kδ	6·2	1·2	0·047
CK1ε	180	>30 000	>30 000

- Umbralisib is a novel next-generation inhibitor of PI3K isoform p110δ, which is structurally distinct from other PI3Kδ inhibitors and shows improved isoform selectivity
- Limited inhibition of CYP450 (DDI)
- Achieves concentration of plasma exposure amenable to once-daily dosing

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

Differentiation of Umbralisib from Other PI3Kδ Inhibitors

UMBRALISIB	IDELALISIB	DUVELISIB



- Kinome profiling confirmed the **specificity** of umbralisib for only PI3Kδ and CK1ε (casein kinase-1ε)
- **Minimal off-target inhibition**, compared with less selective inhibition of idelalisib and duvelisib

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

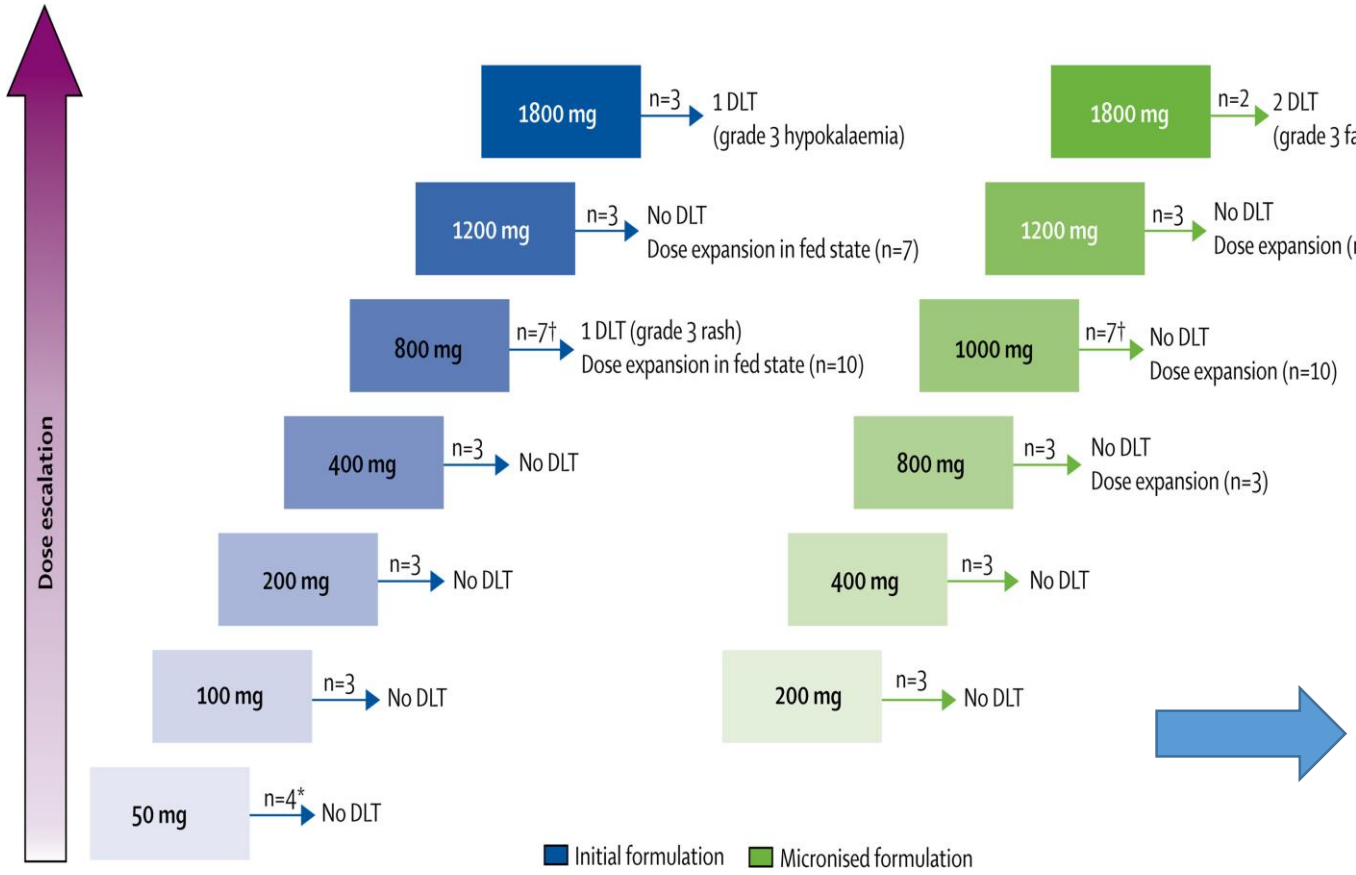
Umbralisib, a novel PI3Kδ and casein kinase-1ε inhibitor, in relapsed or refractory chronic lymphocytic leukaemia and lymphoma: an open-label, phase 1, dose-escalation, first-in-human study

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

THE LANCET
Oncology
Volume 19, Issue 4, April 2018, Pages 486-496

Umbralisib in Relapsed/Refractory Lymphoid Malignancies: Dose Escalation Schema

- Umbralisib administered orally once daily in 28-day cycles



- Dose-limiting toxicity (n=4):
  - Gr. 3 Maculopapular rash (n=1); 800 mg initial formulation
  - Gr. 3 Hypokalemia (n=1); 1800 mg initial formulation
  - Gr. 3 Fatigue (n=2); both at 1800 mg micronized formulation
- MTD 1200 mg umbralisib
- RP2D 800 mg umbralisib

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

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)

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

Tolerability

	N=90
Umbralisib for ≥ 6 cycles, n (%)	44 (49)
Umbralisib for ≥ 12 cycles, n (%)	23 (26)
Umbralisib for ≥ 24 cycles, n (%)	9 (10)
Median duration of treatment, cycles (IQR)	4.7 (2.0 – 14.0)
Remained on study treatment at the end of the trial, n (%)	13 (14)
Reason for treatment discontinuation, n (%)	
Progressive disease	50 (56)
Adverse events	9 (10)
AEs at least possibly related to umbralisib	6 (7)
Received micronized umbralisib at doses of ≥800 mg, n (%)*	56 (62)

- *Pneumocystis jiroveci* pneumonia prophylaxis was used in 18 (20%) of 90 patients
- No treatment-related deaths
  - 1 death on study: *Legionella* pneumonia on umbralisib 800 mg (initial formulation) – assessed as not related

IQR, interquartile range. *Intra-patient dose escalation allowed patients in earlier cohorts to dose-escalate.
Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

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)

- **Few grade 3-4 events. Most common was neutropenia (FN 4%).**
- **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%), and **colitis (2%)**

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

Treatment Discontinuation

- Discontinuation of umbralisib due to treatment related adverse events was uncommon, occurring in 6 (7%) of patients

Reason for Discontinuation	n (%)	Grade
Colitis*	2 (2)	Grade 3 – Both
Elevated liver function tests	2 (2)	Grade 1 – 1; Grade 4 – 1
Diarrhea	1 (1)	Grade 2
Fatigue	1 (1)	Grade 3

*Both occurred at doses higher than the micronized RP2D of 800 mg/day

- Dose delays due to adverse events (n=39/90)
  - Median interruption time: 2 days (IQR 1–7)
- Dose reductions to the next lower dose (n=15/90)
  - Fatigue (n=5), neutropenia (n=4), abnormal LFTs (n=3), and rash, worsened dysgeusia, diarrhea, neutropenic fever, anemia, arthralgia, nausea and vomiting (n=1 each†)

†Same patient had more than one reason for dose reduction.

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

Well tolerated

Approximately 10% discontinuations due to AEs

Possibly fewer immune mediated toxicities than previously observed with other agents in the class.

Clinical Efficacy

- Responses according to disease type:

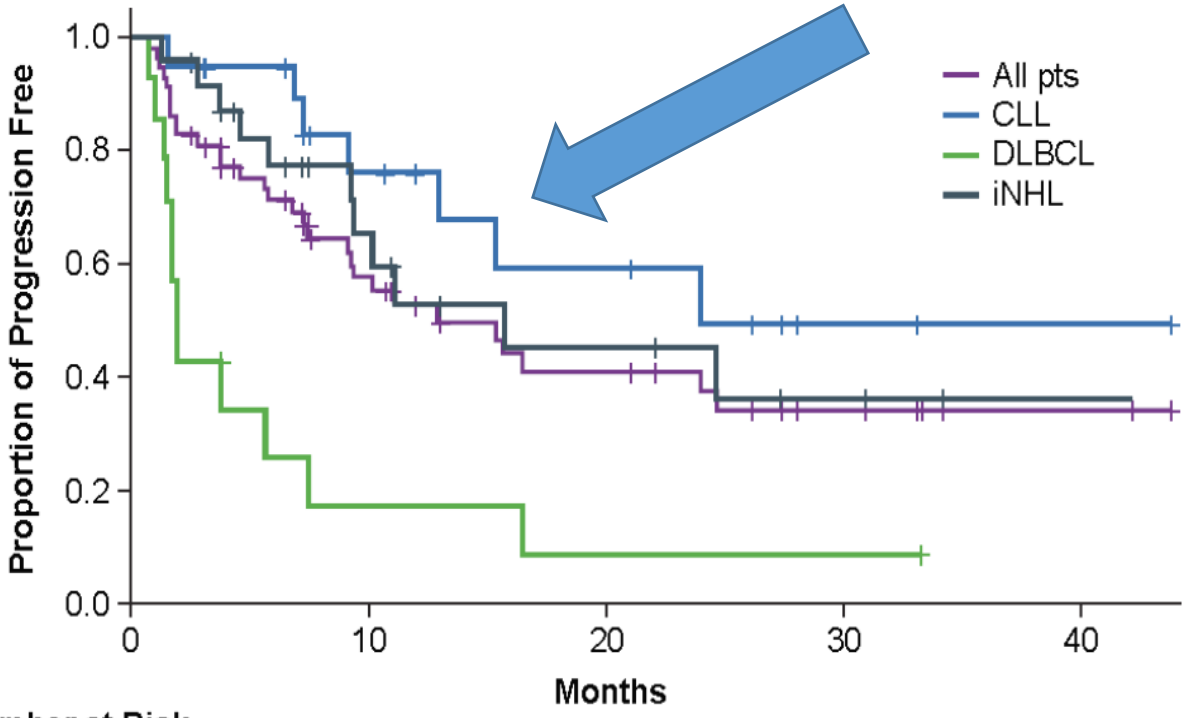
Disease	Objective response, n (%)	CR, n (%)	PR, n (%)	PR-L, n (%)	Duration of Response, mo (n)
CLL, n=20	17 (85)	-	10 (50)*	7 (35)	13.4 (16)
CLL, del 17p/del 11q,n=8	6 (75)	-	4 (50%)*	2 (25%)	-
FL, n=17	9 (53)	2 (12)	7 (41)	-	9.3 (9)
DLBCL, n=13	4 (31)	-	4 (31)	-	6.4 (4)

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].

Umbralisib in Relapsed/Refractory Lymphoid Malignancies: Progression-free Survival (post-hoc analysis)



Number at Risk

All pts	57	38	24	17	14	10	6	2	1
CLL	20	17	11	8	7	5	2	1	1
DLBCL	13	4	2	2	1	1	1	0	0
iNHL	24	17	11	7	6	4	3	1	1

- Median PFS :
  - CLL: 24 mo (95% CI 7.4 – NR)
- Tumor reductions in most patients with lymphoma and CLL tended to **improve over time**

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

Umbralisib in Relapsed/Refractory Lymphoid Malignancies

1. **Well tolerated**, with an improved safety profile compared to first-generation PI3K inhibitors
2. **Clinical activity** with umbralisib monotherapy in **relapsed/refractory CLL** and lymphoid malignancies
3. Favorable drug-drug interaction profile
4. Go forward dose = 800 mg/day
5. **BUT in this series follow up relatively short…More safety data required with more patients and more follow up**

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

An Integrated Safety Analysis of the Next Generation PI3Kδ Inhibitor Umbralisib (TGR-1202) in Patients with Relapsed/Refractory Lymphoid Malignancies

347 patients!

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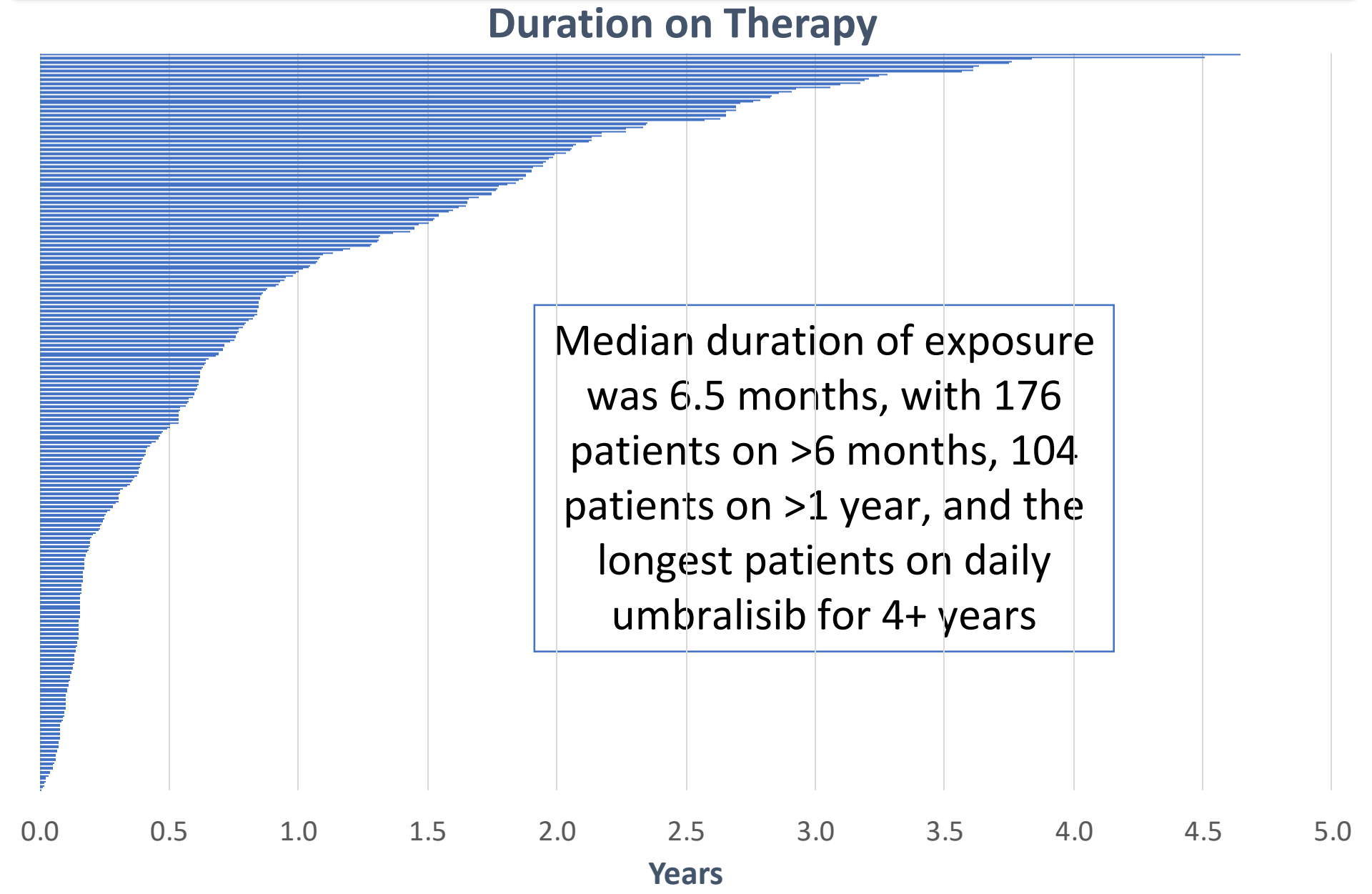
Results

Demographics

Safety data were pooled from **5 completed or ongoing Phase 1 or 2 studies** containing umbralisib. Adverse events were graded by CTCAE v4.03 criteria.

Evaluable for Safety, n	347
Umbralisib Monotherapy	146 (42%)
Umbralisib + Ublituximab	98 (28%)
Umbralisib + Ibrutinib	32 (9%)
Umbralisib + Ublituximab + Ibrutinib	38 (11%)
Umbralisib + Ublituximab + Bendamustine	33 (10%)
CLL/SLL	117 (34%)
DLBCL	116 (33%)
Indolent NHL	73 (21%)
Other lymphoma	41 (12%)
Age, median (range)	66 (22 – 96)
Prior Therapies, median (range)	3 (0-14)
Patients with ≥ 3 Prior Therapies, n (%)	175 (50%)

Results


Duration on Therapy
Median duration of exposure was 6.5 months, with 176 patients on >6 months, 104 patients on >1 year, and the longest patients on daily umbralisib for 4+ years
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Years

Results

Safety

Grade 3/4, All Causality, Adverse Events Occurring in >2% of Patients

	Study 101 Umbra Alone N=90	Study 201 Umbra Alone N=33	Study 105 Umbra + Ibrutinib N=32	Study 103 Umbra + Ubli (U2) N=75	Study 103 U2 + Ibrutinib N=38	Study 103 U2 + Benda N=33	Study 205 U2 or Umbra N=46	TOTAL N=347
Neutropenia	11%	18%	13%	28%	18%	24%	2%	**16%**
Anemia	8%	3%	9%	4%	3%	6%	4%	**5%**
Thrombocytopenia	6%	6%	9%	5%	8%	6%	0%	**5%**
Diarrhea	2%	9%	3%	8%	3%	9%	0%	**4%**
Pneumonia	4%	0%	0%	8%	11%	0%	2%	**4%**
Dyspnea	4%	0%	0%	3%	3%	3%	4%	**3%**
Hypokalemia	4%	3%	3%	3%	0%	9%	0%	**3%**
Febrile Neutropenia	3%	9%	0%	4%	3%	0%	2%	**3%**

Conclusions

- Differentiated safety profile compared to other PI3Kδ inhibitors.
- No significant differences in AEs across different lymphoid malignancies or monotherapy vs. combination
- Few discontinuations due to AEs and high rates of response:
  - 85% ORR for single agent umbralisib in relapsed/refractory CLL

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

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[1]Memorial Sloan-Kettering Cancer Center, New York, NY; [2]University of Pennsylvania Cancer Center, Philadelphia, PA; [3]New York-Presbyterian Columbia University Medical Ctr, New York, NY; [4]Northwell Health/CLL Research and Treatment Program, New Hyde Park, NY; [5]Florida Cancer Specialists/Sarah Cannon Research Institute, Fort Myers, FL; [6]Tennessee Oncology/Sarah Cannon Research Institute, Nashville, TN; [7]Sarah Cannon Research Institute at Research Medical Ctr, Kansas City, KS; [8]Swedish Cancer Institute, Seattle, WA; [9]Georgetown University Hospital Lombardi Comprehensive Cancer Ctr, Washington, DC; [10]Wilmot Cancer Institute, University of Rochester, Rochester, NY; [11]Dartmouth-Hitchcock Medical Ctr, Lebanon, NH; [12]John Theurer Cancer Center, Hackensack, NJ; [13]Florida Cancer Specialists/Sarah Cannon Research Institute, St. Petersburg, FL; [14]Upstate Cancer Ctr., Syracuse, NY; [15]Duke University Medical Center, Durham, NC; [16]TG Therapeutics, Inc., New York, NY

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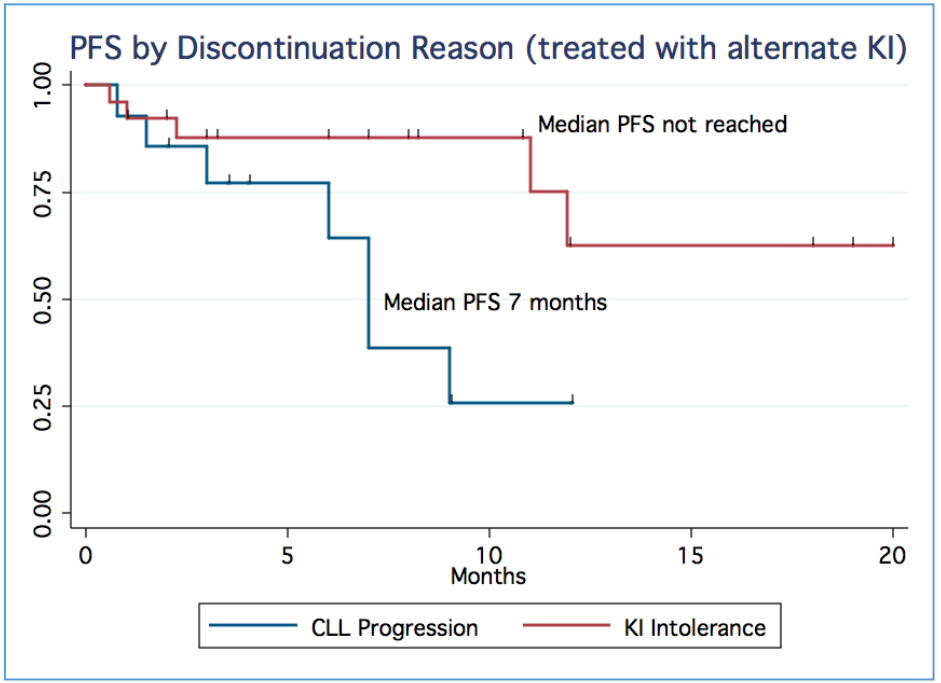
June 14 – 17, 2018 ● Stockholm, Sweden

Background / Rationale

- Kinase inhibitor (KI) therapies are generally well tolerated and effective, although intolerance is the most common reason for discontinuation in practice (~50% of discontinuations)[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)

- **Enrollment**: Up to 50 patients who have discontinued prior therapy with a BTK or PI3Kδ inhibitor due to intolerance
  - Study is fully accrued as of June 7, 2018

- **Correlative studies:** Peripheral blood samples were collected at screening for central analysis of high-risk cytogenetics / mutations and BTK/PLCgamma2 mutations

Study Objectives and Key Eligibility

- **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 the prior KI therapy
- **Key Eligibility**
  - CLL pts whose prior therapy with a BTK inhibitor (ibrutinib, acalabrutinib) or a PI3Kδ inhibitor (idelalisib, duvelisib) was d/c due to intolerance within 12 mos of C1/D1
  - Meets study KI Intolerance definition
  - Off prior KI for at least 14 days following discontinuation w/o disease progression

Definition of KI Intolerance

Intolerance is defined as 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

Toxicity must have resolved to ≤ Grade 1 prior to umbralisib dosing

Demographics

Evaluable for Safety, n	47
Evaluable for PFS†, n	46
Evaluable for Response*	22
Median Age, years (range)	71 (52 – 96)
Male/Female	27 / 20
ECOG, 0/1/2	21 / 22 / 4
17p del, n (%)	7 (15%)
11q del, n (%)	8 (17%)
IGHV Unmutated, n (%)	25 (53%)
Bulky Disease, n (%)	20 (43%)
Prior Therapy, median (range)	2 (1 – 7)
Prior BTK inhibitor, n	40 (85%)
Prior PI3K inhibitor, n	7 (15%)
Median Time on Prior KI, mos (range)	9 (1 – 38)
Median Time from D/C of Prior KI to Enrollment, mos (range)	3 (1 – 12)
Required Tx within 6 mos of Prior KI, n (%)	36 (77%)

Gene	CLL related variants
ATM	9 (22%)
BTK	1 (2%)
NOTCH 1	4 (10%)
PLCG2	2 (5%)
SF3B1	6 (15%)
TP53	9 (22%)

Data available for 41/47 pts

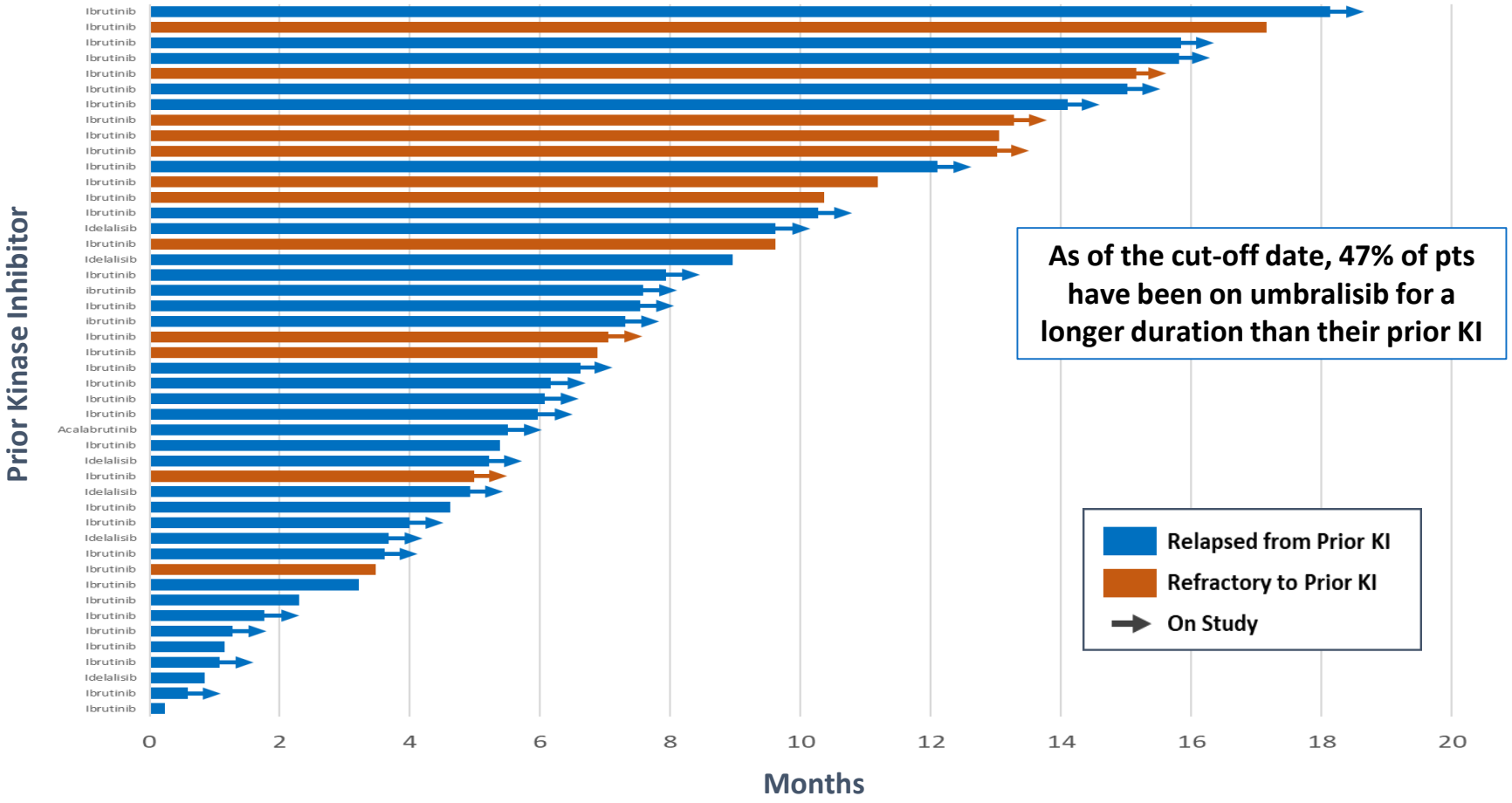
†1 patient with confirmed Richter's Transformation at enrollment (not eligible); excluded from PFS analysis

*Patients with progressive disease at study entry

AEs Leading to Prior KI Intolerance

Intolerant AE on Prior TKI	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)	Total # of events (n)
Rash	5	7		12
Arthralgia	3	5	1	9
Atrial Fibrillation	4	2	1	7
Bleeding	1	3		4
Fatigue	2	2		4
Anorexia/Weight Loss	3			3
Colitis	1	2		3
Congestive Heart Failure	1	1	1	3
Pneumonitis	2	1		3
Mental Status Change	1			1
Myalgia	1			1
Pericardial Effusion			1	1
Respiratory failure			1	1
Thalamic Lesions		1		1
Transaminitis	1			1
TOTAL	37	26	5	**68 events**

Efficacy & Tolerability: Duration of Exposure

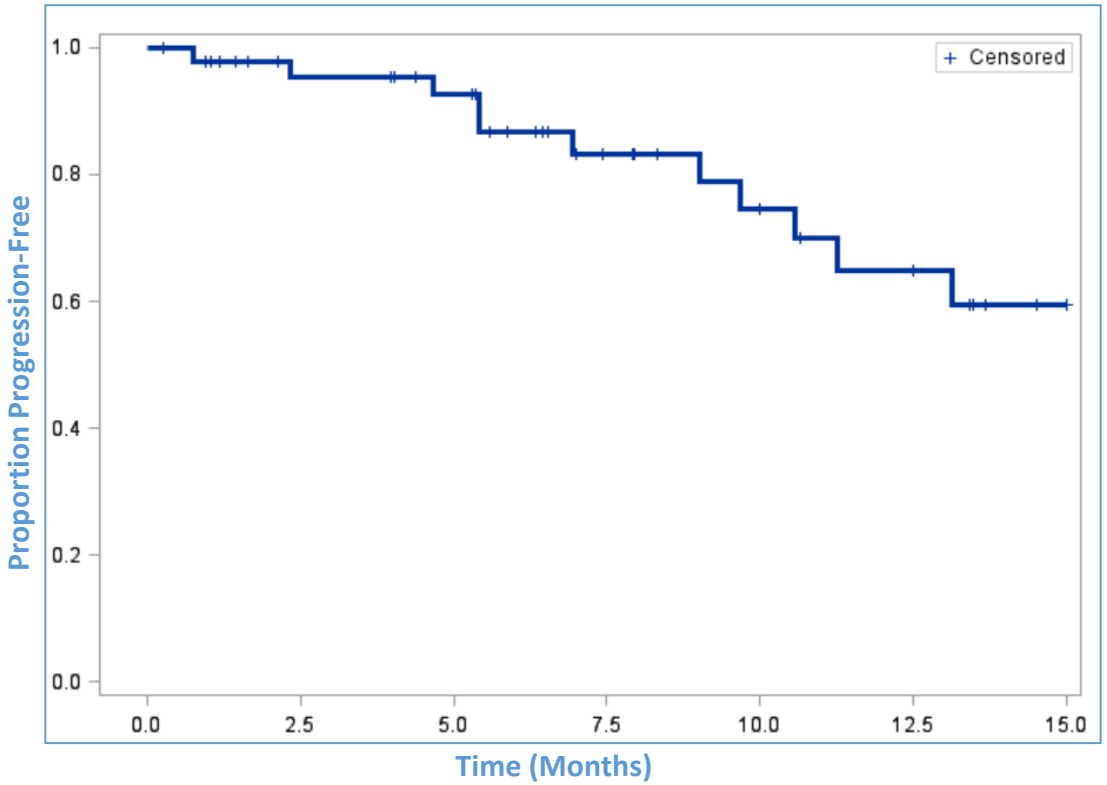


Safety: Umbralisib well tolerated in BTK/PI3K intolerant patients

- **3 patients had recurrence of an AE that led to prior KI intolerance**
  - 2 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 now 16+ months on study
- **3 pts had dose reductions** (headache, neutropenia, colitis)
- 6 (13%) pts discontinued treatment due to an umbralisib AE (pneumonia (2), pancreatitis, pneumonitis, dermatitis, rash)

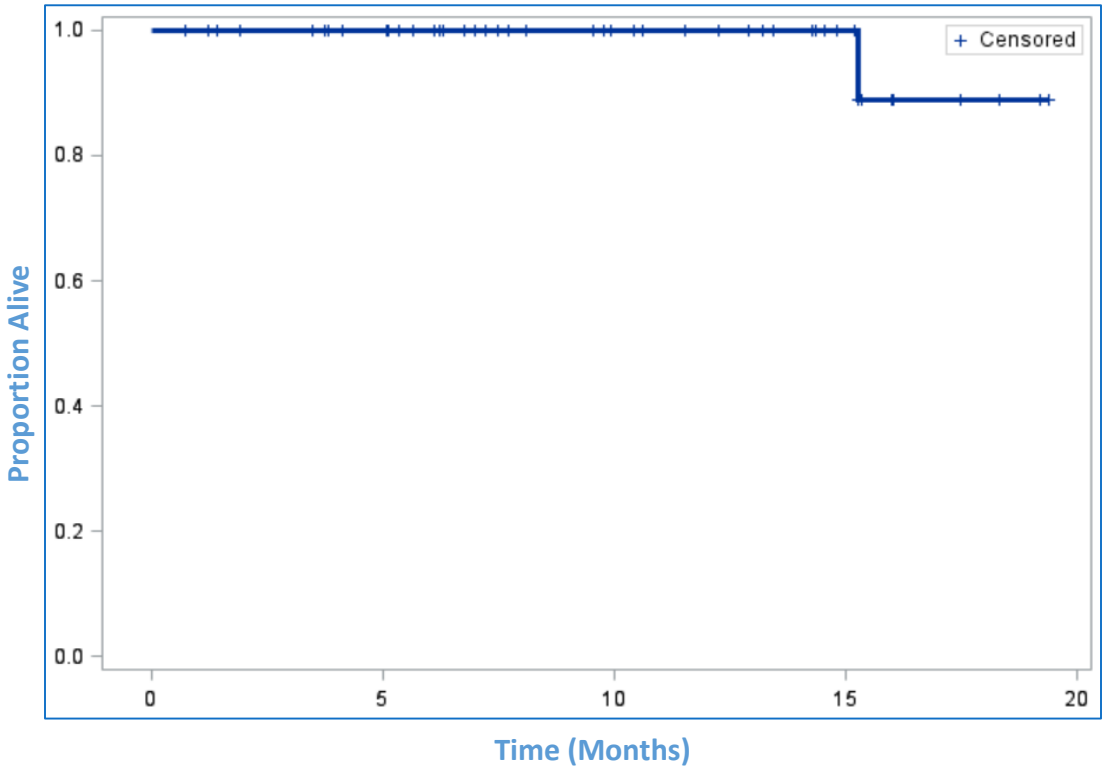
	All Grades		Grade 3/4	
	N	%	N	%
Nausea	20	43%	-	-
Diarrhea	19	40%	3	6%
Thrombocytopenia	12	26%	4	9%
Insomnia	11	23%	-	-
Fatigue	10	21%	-	-
Dizziness	9	19%	-	-
Neutropenia	9	19%	7	15%
Headache	8	17%	-	-
Anemia	6	13%	1	2%
Contusion	6	13%		
Cough	6	13%	-	-
Edema peripheral	6	13%	-	-
Pyrexia	6	13%	1	2%
Arthralgia	5	11%	-	-
Myalgia	5	11%	-	-
Pain in extremity	5	11%	-	-
Paresthesia	5	11%	-	-
Productive Cough	5	11%	-	-
Rash	5	11%	-	-

Progression-Free Survival



- Median PFS has not yet reached with a median follow-up of 9.5 months

Overall Survival



- Median OS not yet reached with a median follow-up of 9.5 months

Conclusions

- **Favorable safety profile**: Umbralisib demonstrates a favorable safety profile in pts intolerant to prior BTK or PI3Kδ therapy
- **Well tolerated**:
  - Only 13% discontinued due to an AE
  - Only 1 discontinued due to a recurrent AE also experienced with prior KI therapy suggesting non-overlapping toxicity profile
- **Significant clinical activity**:
  - **High-risk population:** 77% required treatment within 6 months of prior KI discontinuation, 68% had a high-risk molecular / genetic marker and 6% had an ibrutinib resistance mutation
  - Median PFS and OS have not been reached