Favorable Outcomes for Patients with Co-morbidities or Concomitant Medications Treated with U2: A Retrospective Analysis of UNITY-CLL Phase 3 Trial

Javier Pinilla-Ibarz, MD, PhD[1], Wojciech Jurczak, MD, PhD[2], Suman Kambhampati, MD[3], Ewa Lech Maranda, MD, PhD[4], Tomasz Wróbel, MD, PhD[5], Jeff P. Sharman, MD[6], Syed F. Zafar, MD[7], Marc Hoffmann, MD[8], Scott F. Huntington, MD, MPH[9], Ryan Jacobs, MD[10], Chris Rowland, PhD[11], Hari P. Miskin, MSc[11], Peter Sportelli, BS[11], Owen A. O'Connor, MD, PhD[11], Michael S. Weiss[11], and Ian W. Flinn, MD, PhD[12]

[1]Department of Immunology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; [2]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [3]Sarah Cannon Research Institute At Research Medical Ctr, Kansas City, MO; [4]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [5]Department of Hematology, Wroclaw Medical University, Wroclaw, Poland; [6]Willamette Valley Cancer Institute and US Oncology Research, Eugene, OR; [7]Florida Cancer Specialists South / Sarah Cannon Research Institute, Fort Myers, FL; [8]University of Kansas Medical Center, Kansas City, KS; [9]Yale Cancer Center, New Haven, CT; [10]Department of Hematology, Lymphoma Division, Assistant Professor of Medicine, Levine Cancer Institute/Atrium Health, Charlotte, NC; [11]TG Therapeutics, Inc., New York, NY; [12]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN

BACKGROUND AND METHODS

- Comorbidities and concomitant medications present challenges in the management of chronic lymphocytic leukemia (CLL) with a higher number of comorbid conditions associated with shorter survial[1]
- Certain comorbidities present potential risk factors for medical complications on BTKi (e.g., history of cardiovascular or bleeding issues)[2,3]
- Other comorbidities (e.g., hypertension[4], joint pain) threaten the ability of patients to stay on long-term, continuous BTKi, compromising therapeutic benefit
- Depending on the class, concomitant medications may require dose modifications or limit the absorption of currently available BTKi with others increasing the potential risks of developing severe AEs
- These challenges emphasize the need for chemotherapy-free regimens that do not conflict with various concomitant medications patients with CLL may require and do not exacerbate any accompanying comorbidities

AEs: adverse events; BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukemia. [1]Strati P, et al. Br J Haematol 2017;178:394–402. [2]Wiczer T, et al. Blood Adv 2017;1(20):1739-48. [3]Shatzel J, et al. J Thromb Haemost 2017;15:835-47. [4]Dickerson T, et al. Blood 2019;134(22):1919-28.

UNITY-CLL Study Design (UTX-TGR-304)

- Umbralisib, a selective phosphoinositide 3-kinase delta (PI3Kδ) and casein kinase-1epsilon (CK1ε) inhibitor, is pharmacologically distinct from other PI3K inhibitors[1], exhibiting limited interaction with the CYP450 pathway
- Ublituximab is a novel anti-CD20 monoclonal antibody glycoengineered for enhanced antibody-dependent cellular cytotoxicity that targets a unique epitope on CD20[2]
- Umbralisib + ublituximab (U2) prolonged progression-free survival compared to chemoimmunotherapy in the primary analysis of the randomized, multicenter, Phase 3 UNITY-CLL trial[3]

Broad inclusion/exclusion criteria with limited restrictions on:

- CIRS score
- CrCl (>30mL/min)
- Cardiovascular disease
- Arrythmias
- History of hemorrhage
- CYP450 inhibitor/inducers
- Anticoagulants/ vitamin K antagonists
- PPIs

umbralisib[a] + ublituximab[b] (U2)
[a]800 mg PO QD
[b]900 mg IV on D1/2, 8, 15 of Cycle 1, D1 of Cycles 2 – 6, D1 Q3 cycles

obinutuzumab[c] + chlorambucil[d] (O+Chl)
[c]1000 mg IV on D1/2, 8, 15 of Cycle 1, D1 of cycles 2 – 6
[d]0.5 mg/kg PO on D1 and D15 Cycles 1 – 6

The current analysis focuses on a subgroup of U2-treated patients who had a pre-existing **comorbidity or concomitant medication** that could potentially preclude the use of BTKi

Patients were treatment-naïve or previously treated and met iwCLL criteria for requiring therapy

BTKi: Bruton's tyrosine kinase inhibitor; CIRS: cumulative illness rating scale; CR: complete response; CrCl: creatinine clearance; IV: intravenously; PO: orally; PPI: proton pump inhibitor; Q3: every 3; QD: daily. D1/2 signifies split doses ublituximab (150 mg / 750 mg) obinutuzumab (100 mg /900 mg); cycles were 28 days. U2 combination continued until progressive disease, unacceptable toxicity, or withdrawal of consent. [1]Burris H, et al. Lancet Oncol 2018;19:486-96. [2]Sawas A, et al. Br J Hematol 2017;177(2):243-253. [3]Gribben J, et al. Blood 2020;136:37-39.

Characterization of Comorbid Conditions & Concomitant Medications

131 (64%) of U2 treated patients had at least 1 comorbid condition or concomitant medication that could pose potential issues with BTKi therapy

Comorbidities	N	% of U2 Patients[a]
Arrythmia	31	15%
HTN & 2 anti hypertensives	45	22%
Cardiovascular dysfunction (myocardial infarction, coronary artery disease myocardial ischemia, etc.)	50	24%
History of hemorrhage	5	2%
Arthritis/arthralgia	46	22%
Unique patients	**114**	**55%**

Concomitant Medications	N	% of U2 Patients[a]
Anticoagulant[b]	9	4%
CYP3A4 moderate inhibitor	7	3%
CYP3A4 strong inducer	2	1%
CYP3A4 strong inhibitor	1	0.5%
Dual antiplatelet or anticoagulant	2	1%
Polypharmacy	5	2%
PPI	37	18%
Vitamin K antagonist	2	1%
Unique patients	**53**	**26%**

- Pre-existing cardiac[1] or bleeding[2] complications may be underlying risk factors for recurrence on BTKi
- Hypertension has been shown to increase the likelihood of major adverse cardiac events on BTKi[3]
- History of autoimmune disease trended towards increased incidence of arthralgia/myalgia on BTKi[4]
- Currently available BTKi exhibit DDI with CYP3A inhibitors & inducers[5,6] and PPIs[6]
- BCL-2 inhibitors also exhibit DDI with CYP3A pathway
- Anticoagulant/antiplatelet therapy increases the risk of major hemorrhage on BTKi[5,6]

AEs: adverse events; BCL-2: b-cell lymphoma-2; BTKi: Bruton's tyrosine kinase inhibitor; DDI: drug-drug interaction; HTN: hypertension; PI3K: phosphoinositide 3-kinase; PPI: proton pump inhibitor; U2: umbralisib + ublituximab. [a]Percentages calculated out of patients treated with U2 (N=206). [b]Therapies included direct oral anticoagulants and low-molecular weight heparin. [1]Wiczer T, et al. Blood Adv 2017;1(20):1739-48. [2]Shatzel J, et al. J Thromb Haemost 2017;15:835-47. [3]Dickerson T, et al. Blood 2019;134(22):1919-28. [4]Rhodes J, et al. Clin Lymphoma Myeloma Leuk 2020;20(7) 438-44. [5]IMBRUVICA® USPI. [6]CALQUENCE® USPI

RESULTS

Patient Demographics & Baseline Characteristics

Characteristic	Entire U2 Population N=210	No Comorbidity or Conmed N=79	Any Comorbidity or Conmed N=131	At least 1 Comorbidity N=114	At least 1 Conmed N=53
Age, median (range), years	67 (39 – 88)	65 (39 – 83)	69 (43 – 88)	69 (43 – 88)	69 (50 – 88)
≥65 years, n (%)	125 (60)	41 (52)	84 (64)	75 (66)	35 (66)
<65 years, n (%)	85 (40)	38 (48)	47 (36)	39 (34)	18 (34)
ECOG-PS, n (%)					
0	104 (50)	37 (47)	67 (51)	56 (49)	27 (51)
1	99 (47)	42 (53)	57 (44)	52 (46)	23 (43)
2	6 (3)	-	6 (5)	5 (4)	3 (6)
High-Risk Features, n (%)					
Del(17p)	19 (9)	5 (6)	14 (11)	11 (10)	6 (11)
Del(11q)	47 (22)	18 (23)	29 (22)	25 (22)	12 (23)
Unmutated IGHV	113 (54)	40 (51)	73 (56)	62 (54)	31 (58)
Treatment Status, n (%)					
Treatment Naive	119 (57)	45 (57)	74 (56)	66 (58)	27 (51)
Previously Treated	91 (43)	34 (43)	57 (44)	48 (42)	26 (49)

Conmed: concomitant medication; ECOG PS: Eastern Cooperative Oncology Group performance status; IGHV: immunoglobulin heavy-chain variable gene; U2: umbralisib + ublituximab

- Slight trend towards older age among population with any comorbidity or conmed
- Disease characteristics, high-risk features, and treatment status aligned with overall population

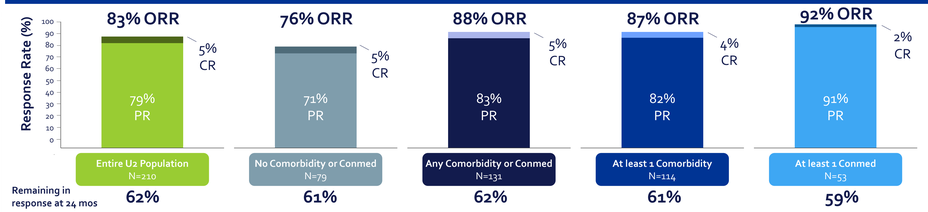
Patient Disposition

Treatment status, n (%)	Entire U2 Population N=210	No Comorbidity or Conmed N=79	Any Comorbidity or Conmed N=131	At least 1 Comorbidity N=114	At least 1 Conmed N=53
Never Treated	**4 (2)**	**4 (5)**	**-**	**-**	**-**
Ongoing	**77 (37)**	**25 (32)**	**52 (40)**	**45 (39)**	**21 (40)**
Discontinued regimen	**129 (61)**	**50 (63)**	**79 (60)**	**69 (61)**	**32 (60)**
Progressive disease	52 (25)	24 (30)	28 (21)	23 (20)	14 (26)
Adverse event	35 (17)	12 (15)	23 (18)	22 (19)	6 (11)
Withdrew consent	23 (11)	6 (8)	17 (13)	13 (11)	8 (15)
Investigator decision	11 (5)	5 (6)	6 (5)	6 (5)	3 (6)
Death	5 (2)	3 (4)	2 (2)	2 (2)	1 (2)
Other	2 (1)	-	2 (2)	2 (2)	-
Lost to follow-up	1 (0.5)	-	1 (1)	1 (1)	-

"-": not applicable; AE: adverse event; Conmed: concomitant medication; U2: umbralisib + ublituximab

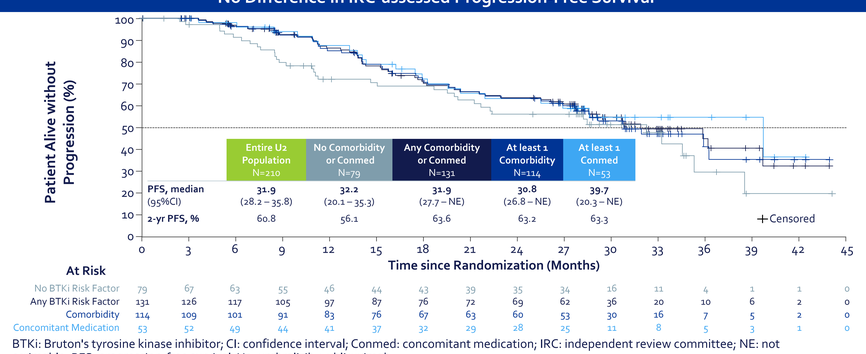
- Comorbidities & conmeds did not increase discontinuation rates
- In particular, discontinuations due to AEs and deaths were not exacerbated by comorbidities or conmeds

IRC-assessed Response Rates



Conmed: concomitant medication; CR: complete response (includes complete response with incomplete marrow recovery); IRC: independent review committee; Mos: months; ORR: overall response rate; PR: partial response; U2: umbralisib + ublituximab.*Note: CR + PR may not sum to ORR due to rounding

No Difference in IRC-assessed Progression-Free Survival



BTKi: Bruton's tyrosine kinase inhibitor; CI: confidence interval; Conmed: concomitant medication; IRC: independent review committee; NE: not estimable; PFS: progression-free survival; U2: umbralisib + ublituximab

Safety Overview

AE type, n (%)	Entire U2 Population N=206	No Comorbidity or Conmed N=75	Any Comorbidity or Conmed N=131	At least 1 Comorbidity N=114	At least 1 Conmed N=53
Median exposure, mos					
Umbralisib	21	21	18	19	21
Ublituximab	21	19	22	21	25
Patients with ≥1 AE[b]	206 (100)	75 (100)	131 (100)	114 (100)	53 (100)
Serious AEs	95 (46)	29 (39)	66 (50)	56 (49)	31 (59)
Grade ≥3	169 (82)	60 (80)	109 (83)	94 (82)	45 (85)
Fatal AEs	8 (4)[a]	4 (5)	4 (3)	4 (4)	1 (2)

Safety was assessed in all patients who received ≥1 dose of treatment. [a]Grade 5 AEs on U2 included: glioblastoma, neutropenic sepsis, sepsis, sudden cardiac death, cardiac arrest, acute myocardial infarction, progressive multifocal leukoencephalopathy, pneumonia. [b]Includes all grade adverse events. AE: adverse event; Conmed: concomitant medication; U2: umbralisib + ublituximab

- Safety profile in this subpopulation was consistent with the overall U2 population
- Pre-existing comorbidities and conmeds did not significantly alter the safety profile of U2

All Causality AEs (≥20%) in Any Cohort

	Entire U2 Population N=206		No Comorbidity or Conmed N=75		Any Comorbidity or Conmed N=131		At least 1 Comorbidity N=114		At least 1 Conmed N=53	
AEs, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	115 (56)	25 (12)	36 (48)	1 (1)	79 (60)	24 (18)	68 (60)	20 (18)	32 (60)	7 (13)
Nausea	105 (51)	3 (1.5)	32 (43)	1 (1)	73 (56)	2 (2)	66 (58)	1 (1)	28 (53)	2 (4)
IRR	95 (46)	4 (2)	33 (44)	2 (3)	62 (47)	2 (2)	54 (47)	2 (2)	24 (45)	-
Fatigue	72 (35)	4 (2)	23 (31)	2 (3)	49 (37)	2 (2)	44 (39)	2 (2)	16 (30)	1 (2)
Neutropenia	69 (34)	64 (31)	28 (37)	26 (35)	41 (31)	38 (29)	36 (32)	33 (29)	19 (36)	19 (36)
Cough	59 (29)	-	15 (20)	-	44 (34)	-	39 (34)	-	19 (36)	-
Headache	53 (26)	1 (0.5)	17 (23)	-	36 (28)	1 (1)	30 (26)	-	18 (34)	1 (2)
Pyrexia	51 (25)	1 (0.5)	21 (28)	-	30 (23)	1 (1)	27 (24)	1 (1)	16 (30)	-
Chills	50 (24)	1 (0.5)	22 (29)	-	28 (21)	1 (1)	24 (21)	1 (1)	12 (23)	1 (2)
URTI	45 (22)	-	16 (21)	-	29 (22)	-	24 (21)	-	14 (26)	-
Dizziness	44 (21)	2 (1)	16 (21)	1 (1)	28 (21)	1 (1)	25 (22)	1 (1)	10 (19)	1 (2)
Constipation	39 (19)	-	10 (13)	-	29 (22)	-	26 (23)	-	11 (21)	-
Insomnia	40 (19)	1 (0.5)	17 (23)	-	23 (18)	1 (1)	21 (18)	1 (1)	10 (19)	1 (2)
Dyspnea	38 (18)	3 (1)	11 (15)	-	27 (21)	3 (2)	24 (21)	3 (3)	12 (23)	3 (6)
Vomiting	36 (17)	1 (0.5)	11 (15)	-	25 (19)	1 (1)	21 (18)	1 (1)	11 (21)	-
Back pain	32 (16)	4 (2)	10 (13)	1 (1)	22 (17)	3 (2)	20 (18)	3 (3)	12 (23)	-

- Incidence and severity of AEs was not impacted by the presence of comorbidities or conmeds
- Incidence of diarrhea was associated with increased age

AE: adverse event; Conmed: concomitant medication; IRR: infusion-related reaction; URTI: upper respiratory tract infection

Events of Clinical Interest – PI3K Specific

AEs, n (%)	Entire U2 Population N=206		No Comorbidity or Conmed N=75		Any Comorbidity or Conmed N=131		At least 1 Comorbidity N=114		At least 1 Conmed N=53	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
ALT elevation	35 (17)	17 (8)	11 (15)	7 (9)	24 (18)	10 (8)	21 (18)	9 (8)	7 (13)	2 (4)
AST elevation	28 (14)	11 (5)	9 (12)	6 (8)	19 (15)	5 (4)	16 (14)	4 (4)	4 (8)	1 (2)
Colitis (non-infectious)[a]	11 (5)	5 (2)	2 (3)	1 (1)	9 (7)	4 (3)	8 (7)	3 (3)	4 (8)	2 (4)
Pneumonitis	6 (3)	1 (0.5)	1 (1)	-	5 (4)	1 (1)	5 (4)	1 (1)	1 (2)	-

Discontinuations, n (%)[b]	Entire U2 Population N=206	No Comorbidity or Conmed N=75	Any Comorbidity or Conmed N=131	At least 1 Comorbidity N=114	At least 1 Conmed N=53
ALT elevation	5 (2)	2 (3)	3 (2)	3 (3)	-
AST elevation	4 (2)	1 (1)	3 (2)	3 (3)	-
Colitis (non-infectious)[a]	3 (1)	-	3 (2)	2 (2)	1 (2)
Pneumonitis	4 (2)	1 (1)	3 (2)	3 (3)	1 (2)

[a]Group includes multiple MedDRA terms. [b]Discontinuations reflect n (%) of patients that discontinued any agent due to respective AEs. AE: adverse event; Conmed: concomitant medication; U2: umbralisib + ublituximab

SUMMARY

- In a population generally characterized as unsuitable for BTKi based on comorbidities and concomitant medications, U2 elicited efficacy outcomes in line with the overall population
- These comorbidities and concomitant medications did not significantly impact the safety profile of U2, including discontinuations due to AEs
- Patients with underlying comorbidities and concomitant medications that may render them unsuitable for BTKi treatment constitute an unmet need; these results suggest that U2 may have utility in this patient population.

ACKNOWLEDGMENTS

- Thank you to the patients, their families and caregivers for their participation
- Thank you to the investigators, research staff, and the entire UNITY-CLL study team

Disclosures

JPI - AbbVie Inc., AstraZeneca, Janssen, MEI Pharma, Novartis, Sellas, Sunesis, Takeda, and TG Therapeutics, Inc. **WJ** - AbbVie Inc., AstraZeneca, Bayer, BeiGene, Celgene, Celltrion Healthcare, Debiopharm, Epizyme, Incyte, Janssen, Lova Oncology, Mei Pharma, Merck, MorphoSys, Novo Nordisk, Roche, Sandoz, Takeda, and TG Therapeutics, Inc. **SK, SFZ, and MH** have nothing to disclose. **ELM** - AbbVie Inc., Amgen, Astellas Pharma, Gilead Sciences, Inc., Janssen, Novartis, Roche, Sanofi, and Takeda. **TW** - BeiGene, Bristol Meyers Squibb, Janssen, Novartis, Roche, and Takeda. **JPS** - AbbVie Inc, AstraZeneca, BeiGene, Bristol Meyers Squibb, Centessa, Lilly, Pharmacyclics LLC, an AbbVie Company, and TG Therapeutics, Inc. **SFH** - AbbVie Inc., AstraZeneca, Bayer, Celgene, DTRM Biopharm, Flatiron Health Inc., Genentech, Novartis, Pharmacyclics LLC, an AbbVie Company, Seagen Inc., Servier, TG Therapeutics, Inc., and Thyme Inc. **RJ** - AbbVie Inc., Adaptive Biotechnologies, ADC Therapeutics, AstraZeneca, Genentech, Janssen, MEI Pharma, Pharmacyclics LLC, an AbbVie Company, Sanofi, SecuraBio, TeneoBio, TG Therapeutics, Inc., and Verastem. **CR, HPM, PS, and MSW** disclose financial relationships with TG Therapeutics, Inc. **OAO** - Dren, Kymera, Mundipharma, Myeloid Therapeutics, Nomocan, and TG Therapeutics, Inc. **IWF** - AbbVie Inc., Acerta Pharma, Agios, AvOute, AstraZeneca, BeiGene, Calithera Biosciences, Celgene, Century Therapeutics, Constellation Pharmaceuticals, Curis, FormaTherapeutics, Forty Seven, Genentech, Gilead Sciences, Inc., Great PointPartners, Hutchison MediPharma, IGM Biosciences, Iksuda Therapeutics, Incyte, Infinity Pharmaceuticals, Janssen, Johnson & Johnson, Juno Therapeutics, Karyopharm Therapeutics, Kite, a Gilead Company, Lova Oncology, Merck, MorphoSys, Novartis, Nurix Therapeutics, Pfizer, Pharmacyclics LLC, an AbbVie Company, Portola Pharmaceuticals, Rhizen Pharmaceuticals, Roche, Sarah Cannon Research Institute, Seagen Inc., Seattle Genetics, Servier Pharmaceuticals, Takeda, Teva, TG Therapeutics, Inc., Trillium Therapeutics, Triphase Research & Development Corp., Unum Therapeutics, Verastem, Vincerx Pharma, and Yingli Pharmaceuticals.

American Society of Hematology 63rd Congress December 11, 2021.