Phase 3 Study of Umbralisib Combined With Ublituximab vs Obinutuzumab Plus Chlorambucil in Patients With Chronic Lymphocytic Leukemia: Results From UNITY-CLL

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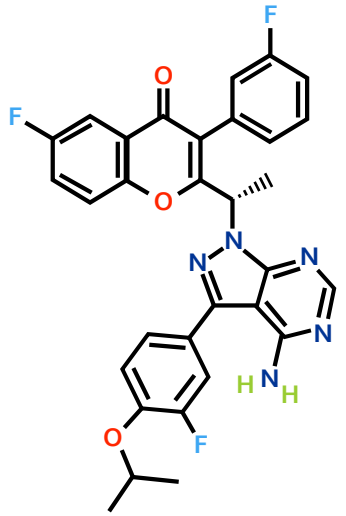
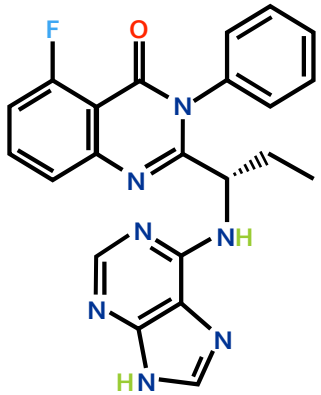
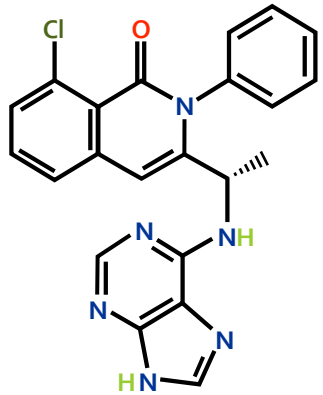
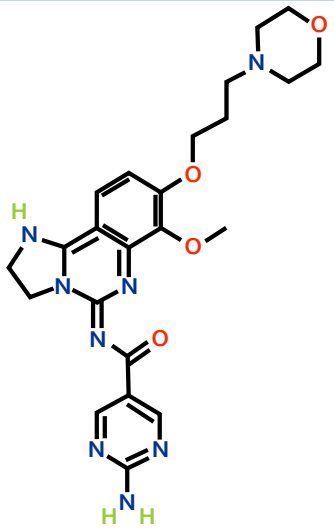
Background

- While Bruton's tyrosine kinase (BTK) and B-cell lymphoma 2 (Bcl-2) inhibitors have dramatically changed the therapeutic landscape of CLL, **not all patients are ideal candidates for these agents** and mechanisms of resistance have already been identified
- Phosphatidylinositol-3-kinase-delta (PI3Kδ) inhibitors offer a distinct mechanism of action from BTK and Bcl-2 inhibitors, and have demonstrated promising activity in relapsed/refractory CLL[1,2]
- However, studies of **previous generations of PI3Kδ inhibitors** in treatment naïve CLL have produced substantial toxicity leading to **discontinuation rates of over 50% due to adverse events**[3] and required early study termination[4]
- **Umbralisib** is a novel, dual inhibitor of PI3Kδ and casein kinase-1ε (CK-1ε) that exhibits **improved selectivity** for the delta isoform of PI3K[5] with **low rates of immune-mediated toxicities** and discontinuations due to AEs[6]
- **Ublituximab** is a novel anti-CD20 monoclonal antibody glycoengineered for **enhanced antibody-dependent cellular cytotoxicity (ADCC)** that targets a unique epitope on CD20[7]
- The combination of **umbralisib and ublituximab (U2)** has been well-tolerated and demonstrated **promising activity** in heavily pre-treated CLL patients[8]

[1]ZYDELIG package insert. [2]COPIKTRA package insert. [3]Ghia P, et al. Clinical Lymphoma, Myeloma and Leukemia 2020;20:S105-107(abstract CLL-091); [4]Lampson B, et al. Blood Adv 2019;3(7):1167–1174. [5]Burris H, et al. Lancet Oncol 2018;19:486-96. [6]Davids M, et al. Blood 2017;130(Supplement 1):4037. [7]Sawas A, et al. Br J Hematol 2017;177(2):243-253. [8]Lunning M, et al. Blood 2019;134(21):1811–1820. AEs: adverse events

Umbralisib Is a Dual Inhibitor of PI3Kδ and CK1ε

	Umbralisib[1]	Idelalisib[1]	Duvelisib[1]	Copanlisib[2]
				

Isoform	K_d (nM)			
PI3kα	>10000	600	40	0.04
PI3Kβ	>10000	19	0.89	1.5
PI3Kγ	1400	9.1	0.21	0.31
PI3Kδ	6.2	1.2	0.047	0.068
CK1ε	180	>30,000	>30,000	>6,000

- Umbralisib is an oral, once daily, dual inhibitor of PI3Kδ and CK1ε
- Umbralisib has >1000-fold greater selectivity for PI3Kδ compared to α and β isoforms[3]
- Umbralisib is also **>200-fold** more selective for PI3Kδ relative to **PI3Kγ**

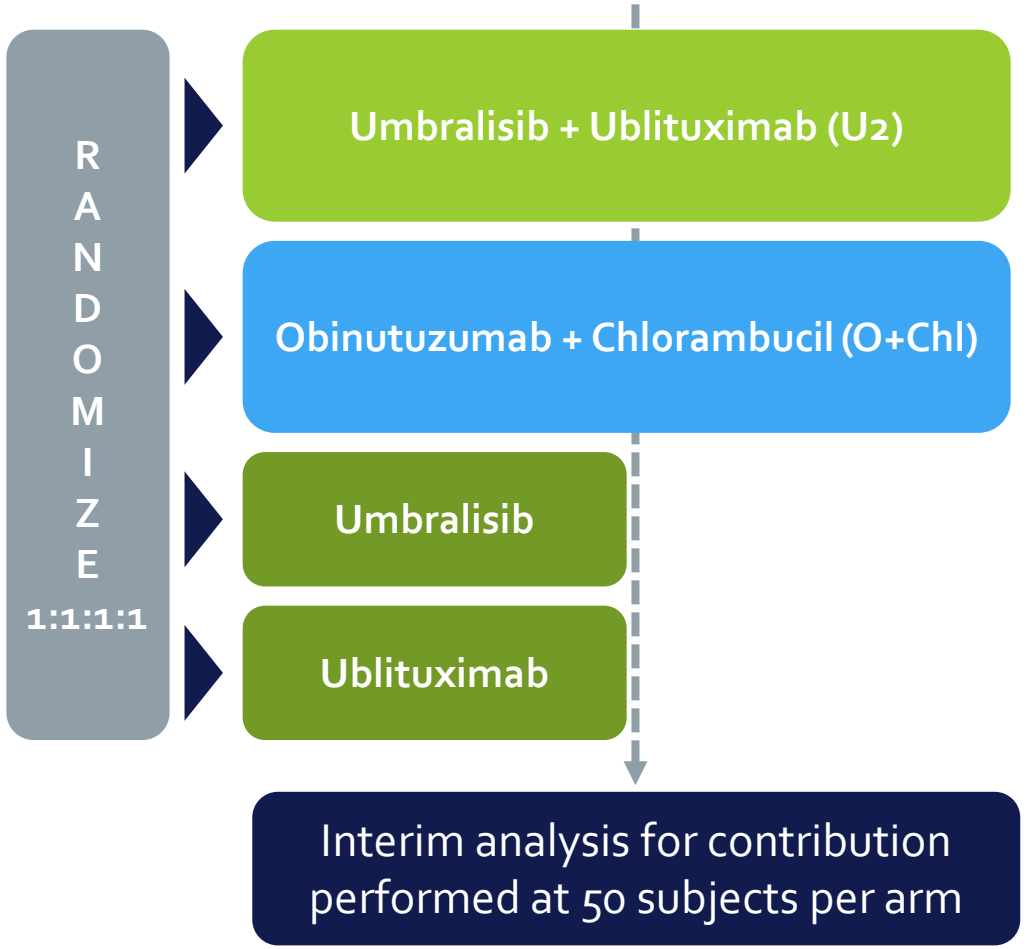
PI3k: phosphoinositide 3-kinase; CK1ε: casein kinase 1ε.

1. Burris HA, et al. *Lancet Oncol*. 2018;19(4):486-496. 2. Data on File [TGR 001]. TG Therapeutics, Inc, New York City, NY.

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

Patients (N=603)
- Treatment-naïve or relapsed/refractory CLL
- Requiring treatment per iwCLL criteria
- Adequate organ function
- ECOG PS ≤2

Stratification
- del(17p): present vs absent
- Treatment status: treatment-naive vs previously treated



Primary endpoint
- IRC-assessed PFS U2 vs O+Chl

Key secondary endpoint
- Contribution by ORR

- On May 2017, the DSMB determined that contribution was met supporting the closure of these arms

CR: complete response; DOR: duration of response; DSMB: data safety monitoring board; ECOG PS: Eastern Cooperative Oncology Group performance status; IRC: independent review committee; IV: intravenously; ORR: overall response rate; PFS: progression-free survival, PO: orally; Q3: every 3; QD: daily; uMRD: undetectable minimal residual disease; 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.

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

Presentation will focus on primary analysis:U2 vs O+Chl (n=421)

Patients (N=421)
- Treatment-naïve or relapsed/refractory CLL
- Requiring treatment per iwCLL criteria
- Adequate organ function
- ECOG PS ≤2

Stratification
- del(17p): present vs absent
- Treatment status: treatment-naive vs previously treated

RANDOMIZE 1:1

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

Primary endpoint
- IRC-assessed PFS U2 vs O+Chl

Secondary endpoints
- IRC-assessed:
  - ORR, CR, DOR
- uMRD (central)
- Safety

- Interim analyses for PFS were performed at:
  - 50% IRC-assessed PFS events to assess futility only
  - 75% IRC-assessed PFS events to evaluate superiority of U2 vs O+Chl

CR: complete response; DOR: duration of response; DSMB: data safety monitoring board; ECOG PS: Eastern Cooperative Oncology Group performance status; IRC: independent review committee; IV: intravenously; ORR: overall response rate; PFS: progression-free survival, PO: orally; Q3: every 3; QD: daily; uMRD: undetectable minimal residual disease; 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.

Patient Demographics & Baseline Characteristics

Characteristic	U2 N=210	O+Chl N=211
Age, median (range), years	67 (39 – 88)	68 (36 – 91)
≥65 years, n (%)	125 (60)	134 (64)
<65 years, n (%)	85 (40)	77 (36)
ECOG-PS[a], n (%)		
0 – 1	203 (97)	199 (94)
2	6 (3)	9 (4)
3	0	1 (0.5)
Rai Stage, n (%)		
III	32 (15)	27 (13)
IV	51 (24)	46 (22)
High-Risk Features, n (%)		
Del(17p)	19 (9)	23 (11)
Del(11q)[b]	47 (22)	38 (18)
Unmutated IGHV[c]	113 (54)	115 (55)
Treatment Status, n (%)		
Treatment Naive	119 (57)	121 (57)
Previously Treated	91 (43)	90 (43)

IGHV: immunoglobulin heavy-chain variable gene; O+Chl: obinutuzumab + chlorambucil; U2: umbralisib + ublituximab; [a]1 patient on U2 and 2 patients on O+Chl had missing ECOG-PS; [b]6 patients on U2 and 3 patients on O+Chl had missing del11q; [c]5 patients on U2 and 3 patients on O+Chl had missing IGHV mutation status

Prior Therapies
Previously Treated Population

	U2 N=91	O+Chl N=90
Prior Therapies, median (range)	2 (1 – 9)	1 (1 – 8)
Number of Prior Therapies, n (%)		
1	44 (48)	50 (56)
2	25 (27)	22 (24)
3	10 (11)	7 (8)
≥4	12 (13)	10 (11)
Prior Therapy Type, n (%)		
Anti-CD20 Antibody	83 (91)	73 (81)
Chemoimmunotherapy	81 (89)	77 (86)
BTK Inhibitor	14 (15)	12 (13)
Venetoclax	1 (1)	0
PI3K Inhibitor[a]	1 (1)	0

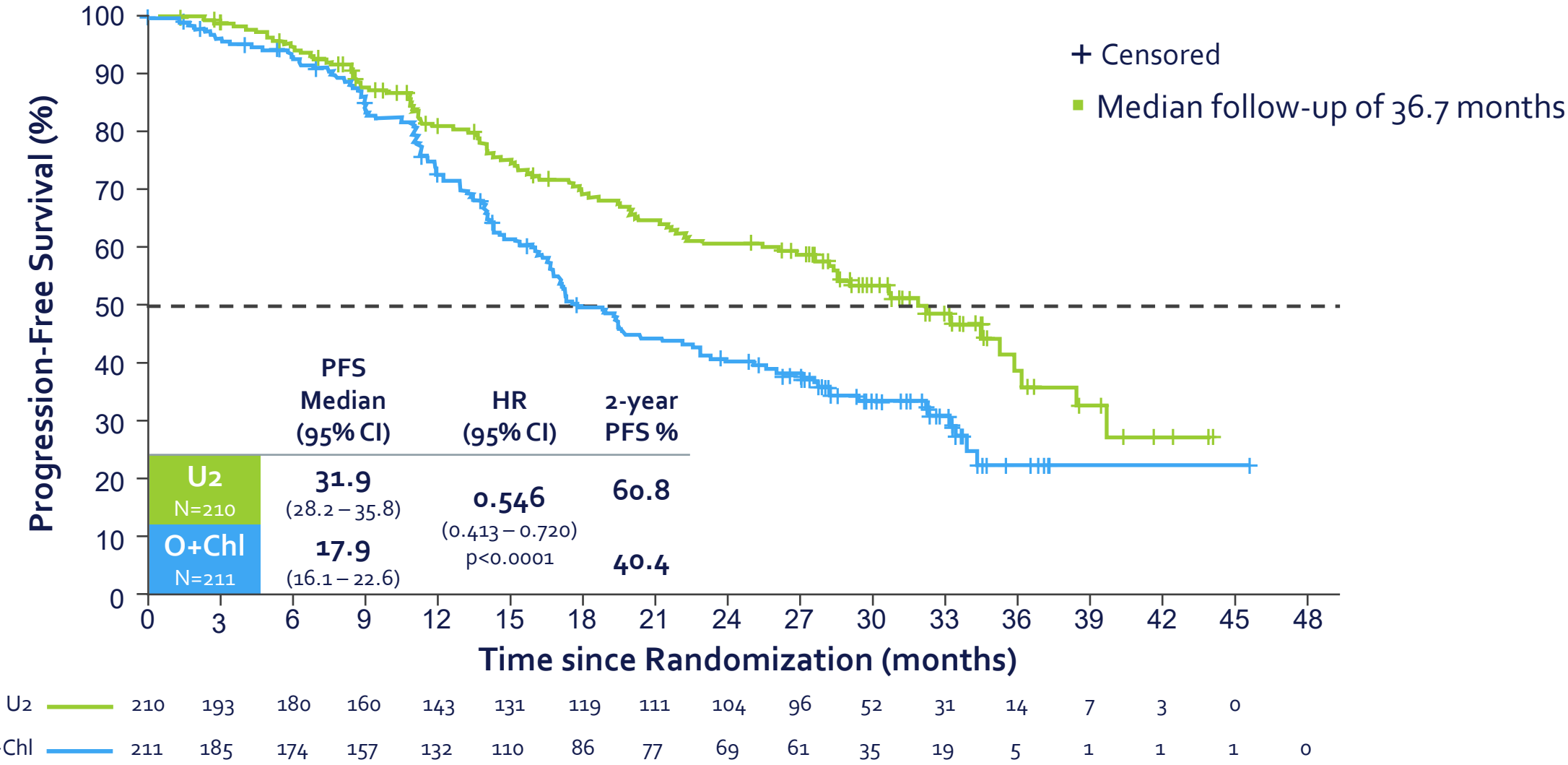
BTK: Bruton's tyrosine kinase; O+Chl: obinutuzumab + chlorambucil; PI3K: phosphatidylinositol-3-kinase-delta; U2: umbralisib + ublituximab. Trial excluded prior PI3K exposure; however, 1 patient with prior PI3K did enroll and was treated with U2.

Patient Disposition & Exposure

	U2 N=210	O+Chl N=211
Treated with at least one day study drug, n (%)	206 (98)	200 (95)
Randomized but not treated, n (%)	4 (2)	11 (5)
Treatment exposure, median (range), months[a]		
Ublituximab	21.1 (0.03 – 46.3)	-
Umbralisib	20.5 (0.03 – 47.2)	-
Obinutuzumab	-	4.7 (0.03 – 7.4)
Chlorambucil	-	5.1 (0.03 – 7.4)
Treatment status, n (%)		
Ongoing	77 (37)	0 (0)
Discontinued regimen	129 (61)	200 (100)
Completed scheduled therapy	-	155 (78)
Progressive disease during treatment	52 (25)	13 (7)
Adverse event	35 (17)	16 (8)
Withdrawal of consent	23 (11)	4 (2)
Investigator decision	11 (5)	7 (4)
Death	5 (2)	3 (2)
Other	2 (1)	2 (1)
Lost to follow-up	1 (0.5)	0 (0)

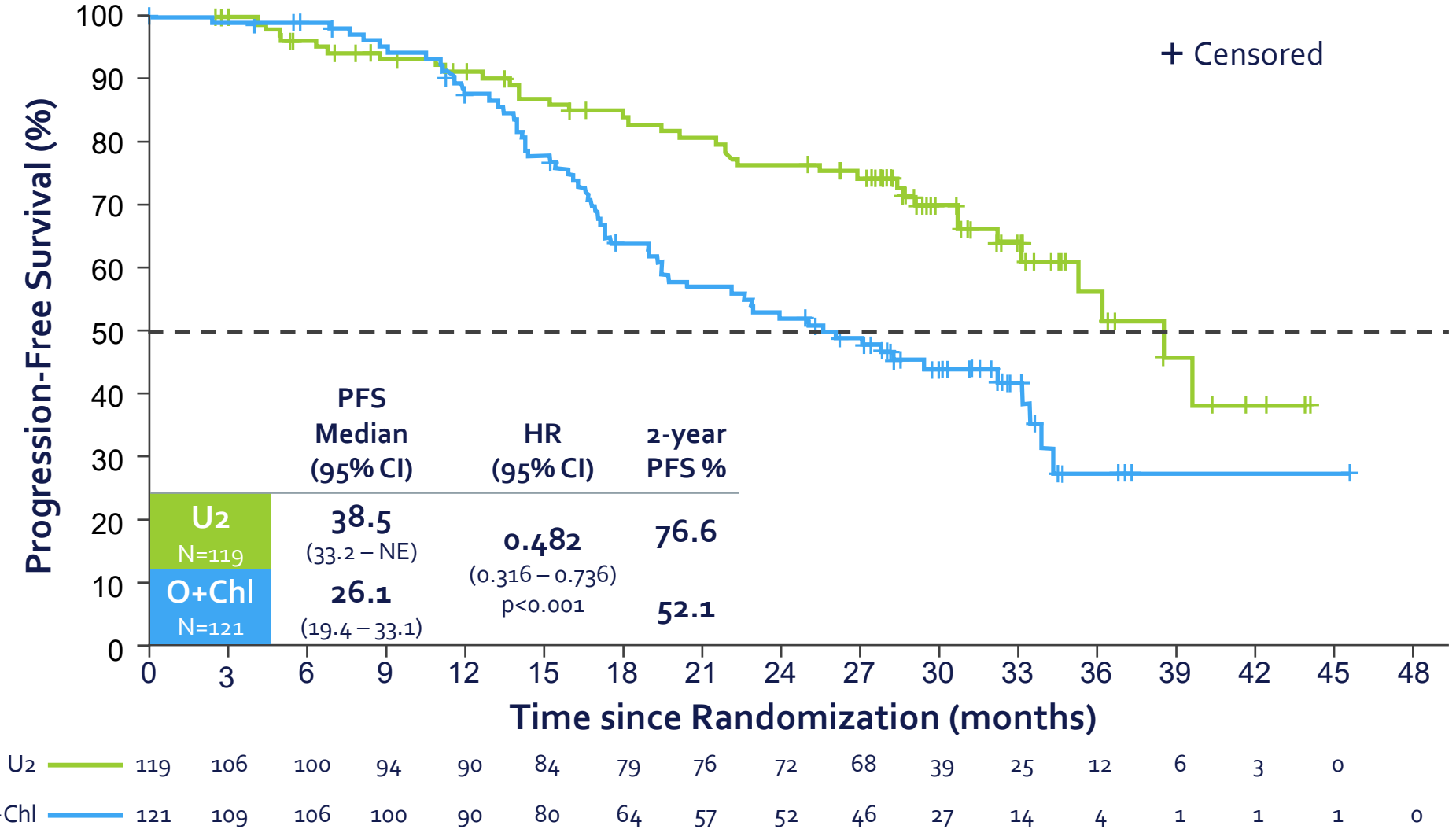
"-": not applicable; O+Chl: obinutuzumab + chlorambucil; U2: umbralisib + ublituximab. [a]Continuous umbralisib and ublituximab treatment resulted in longer reporting periods for those arms.

IRC-Assessed Progression-Free Survival ITT Population



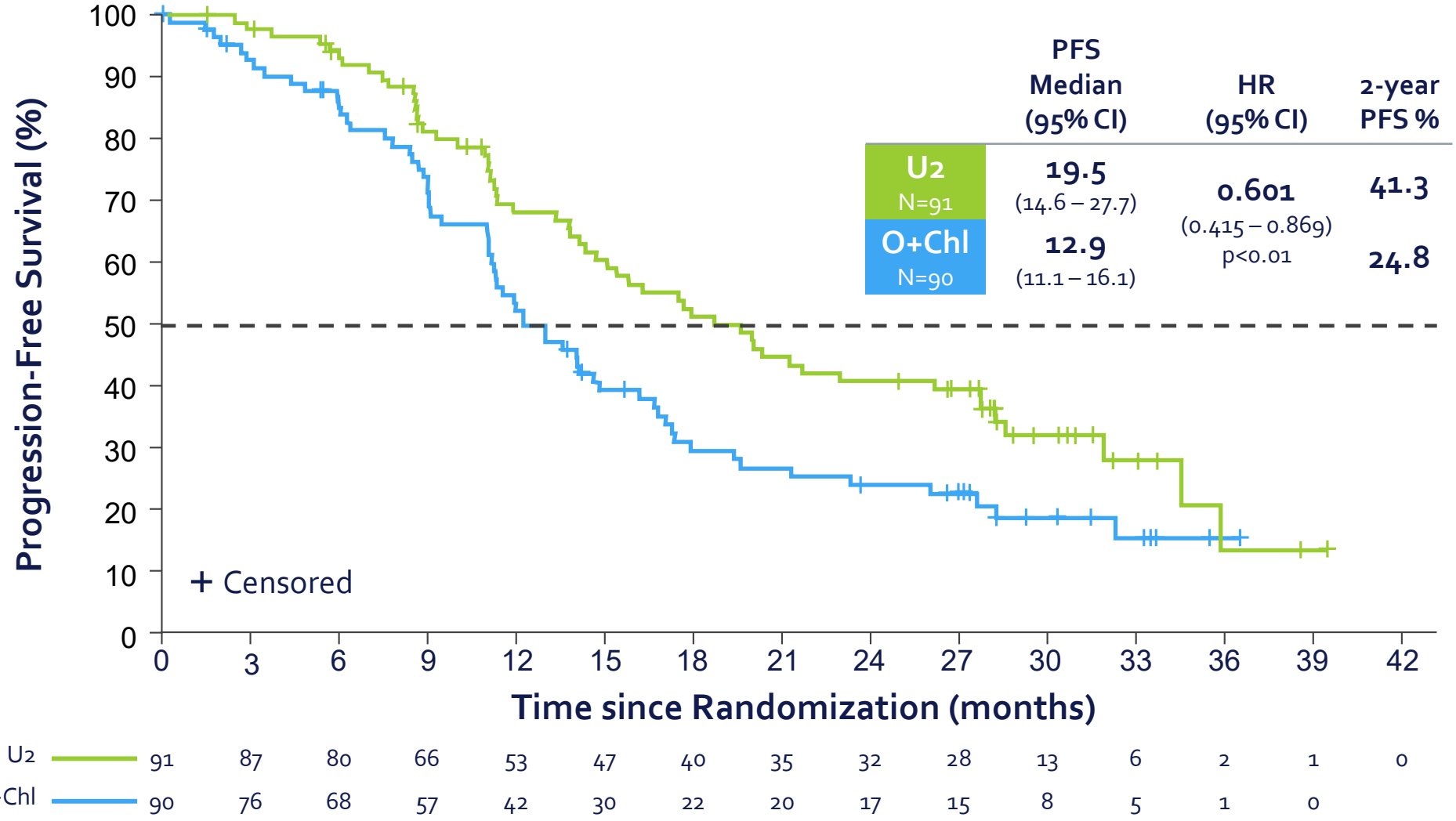
CI: confidence interval; HR: hazard ratio; IRC: independent review committee; ITT: intent to treat; O+Chl: obinutuzumab + chlorambucil; PFS: progression-free survival; U2: umbralisib + ublituximab

IRC-Assessed Progression-Free Survival Treatment-Naïve Population



CI: confidence interval; HR: hazard ratio; IRC: independent review committee; O+Chl: obinutuzumab + chlorambucil; PFS: progression-free survival; U2: umbralisib + ublituximab

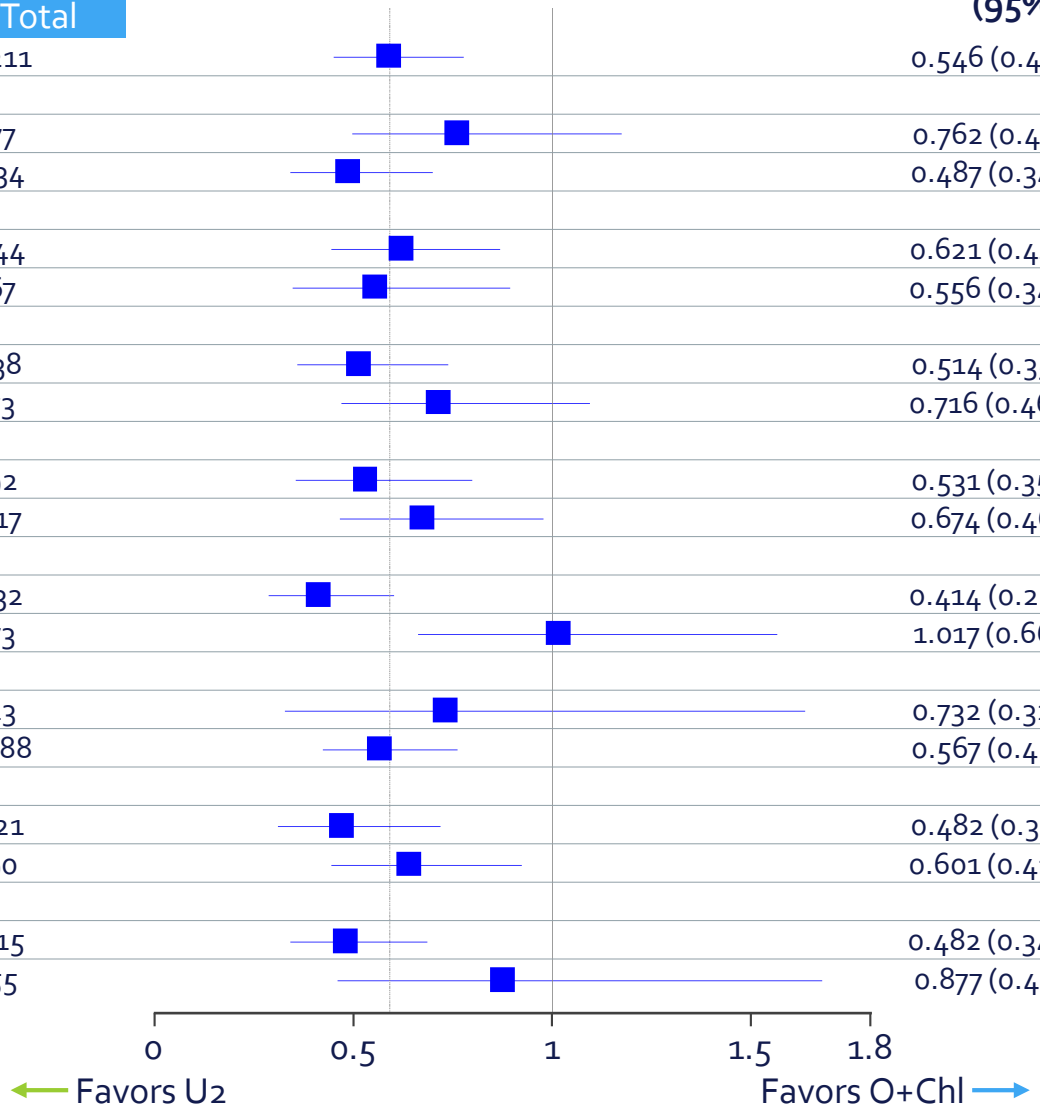
IRC-Assessed Progression-Free Survival Previously Treated Population



CI: confidence interval; HR: hazard ratio; IRC: independent review committee; O+Chl: obinutuzumab + chlorambucil; PFS: progression-free survival; U2: umbralisib + ublituximab

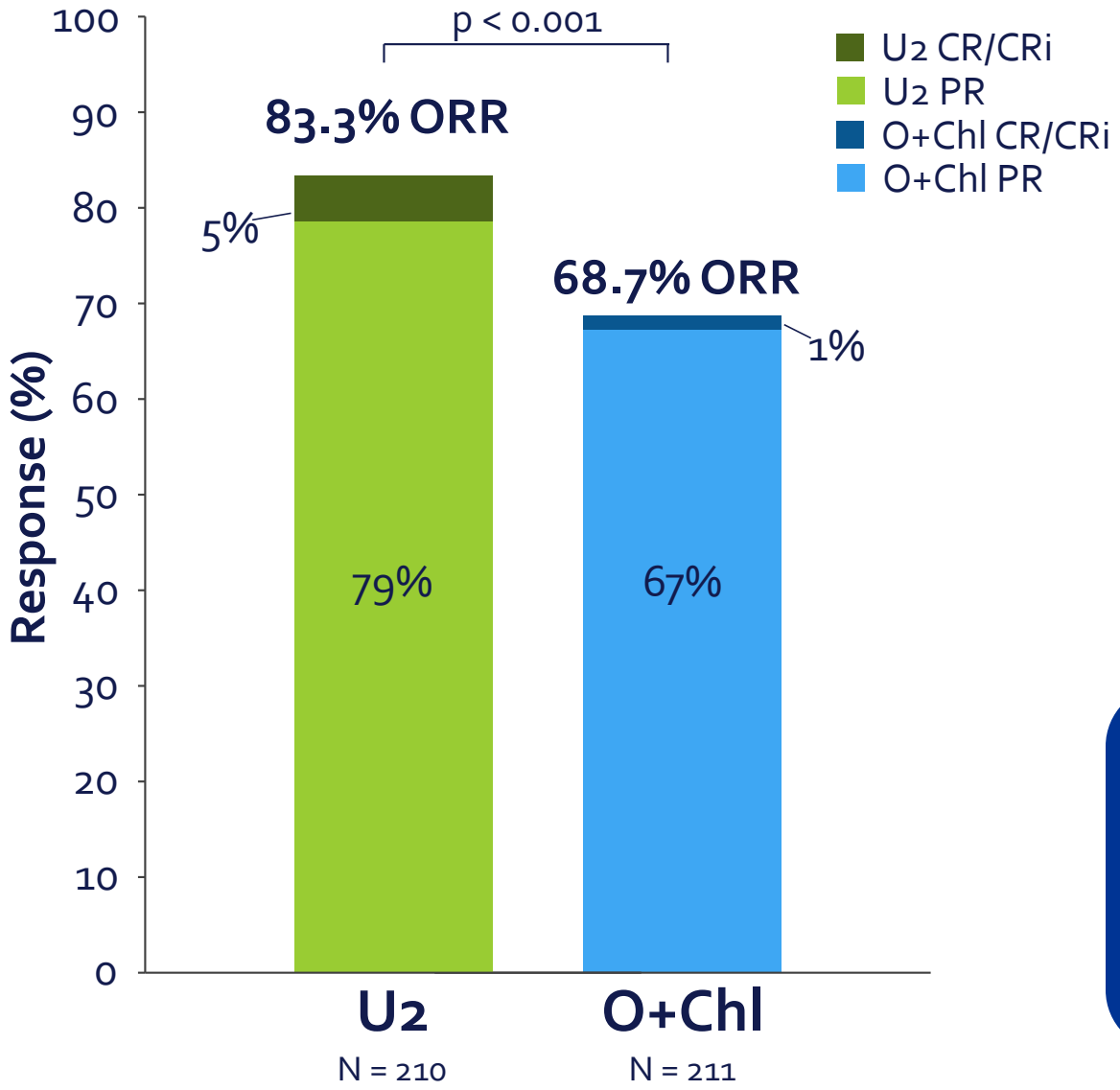
IRC-Assessed PFS Across Subgroups

	U2 Events/Total	O+Chl Events/Total	Hazard Ratio (95% CI)
All Subjects	91/210	124/211	0.546 (0.413, 0.720)
Age			
<65	41/85	44/77	0.762 (0.496, 1.173)
≥65	50/125	80/134	0.487 (0.341, 0.697)
Sex			
Male	60/135	83/144	0.621 (0.445, 0.867)
Female	31/75	41/67	0.556 (0.347, 0.892)
Region			
Us	50/130	77/138	0.514 (0.358, 0.736)
Non-US	41/80	47/73	0.716 (0.469, 1.092)
ECOG-PS			
0	43/104	54/92	0.531 (0.354, 0.796)
≥1	48/105	70/117	0.674 (0.466, 0.975)
Rai Stage			
0 – II	46/127	83/132	0.414 (0.287, 0.599)
III – IV	45/83	39/73	1.017 (0.662, 1.563)
Deletion 17p			
Deleted	13/19	14/23	0.732 (0.328, 1.635)
Not deleted	78/191	110/188	0.567 (0.423, 0.760)
Treatment status			
Treatment-naïve	36/119	61/121	0.482 (0.316, 0.736)
Previously treated	55/91	63/90	0.601 (0.415, 0.869)
IGHV status			
Unmutated	56/113	80/115	0.482 (0.340, 0.684)
Mutated	17/50	20/55	0.877 (0.459, 1.677)



CI: confidence interval; IRC: independent review committee; O+Chl: obinutuzumab + chlorambucil; PFS: progression-free survival; U2: umbralisib + ublituximab. Hazard ratios are unstratified with the exception of the analysis of all subjects and treatment-naïve and previously treated subgroups

IRC-Assessed Response Rates



ORR (%)	U2	O+Chl
Treatment Naïve	84%	78%
Previously treated	82%	57%
Prior BTK inhibitor	57%	25%

- U2 produced higher IRC – assessed response rates across subgroups
- U2 responses were durable with **62%** maintaining response at **2 years**
- **93%** disease control rate achieved by U2

CR: complete response; CRi: complete response with incomplete marrow recovery; Disease control rate = (CR+CRi+nPR+PR+PR-L+SD); IRC: independent review committee; ITT: intent to treat; nPR: nodular partial response; O+Chl: obinutuzumab + chlorambucil; ORR: overall response rate; PR: partial response; PR-L: partial response with lymphocytosis; SD: stable disease; U2: umbralisib + ublituximab

Safety Overview

Note: AE Reporting Period Longer with U2 vs O+Chl

AE type, n (%)	U2 N=206	O+Chl N=200
Median exposure	**21 months**	**5 months**
Patients with ≥1 AE (all grades)	206 (100)	194 (97.0)
Serious AEs	95 (46.1)	47 (23.5)
Grade ≥3	169 (82.0)	132 (66.0)
Grade 5	8 (3.9)[a]	5 (2.5)[b]

- **U2 safety signals consistent across treatment status**
- **Continuous U2 treatment resulted in over 4-fold longer exposure and reporting period compared to O+Chl**

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]Grade 5 AEs on O+Chl included: pulmonary oedema, myocardial infarction, haemorrhage intracranial, and 2 unknown. AE: adverse event; O+Chl: obinutuzumab + chlorambucil; U2: umbralisib + ublituximab

All Causality AEs (≥20%) in Any Treatment Arm

AEs, n (%)	U2 N=206					O+Chl N=200				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	115 (56)	53 (26)	37 (18)	25 (12)	-	43 (22)	25 (13)	13 (7)	5 (3)	0
Nausea	105 (51)	68 (33)	34 (17)	3 (2)	-	75 (38)	49 (25)	24 (12)	2 (1)	0
IRR	95 (46)	13 (6)	78 (38)	3 (2)	1 (0.5)	50 (25)	6 (3)	37 (19)	7 (4)	0
Fatigue	72 (35)	35 (17)	33 (16)	4 (2)	-	60 (30)	37 (19)	17 (9)	6 (3)	0
Neutropenia	69 (34)	1 (0.5)	4 (2)	27 (13)	37 (18)	79 (40)	6 (3)	3 (2)	41 (21)	29 (15)
Cough	59 (29)	36 (18)	23 (11)	-	-	36 (18)	25 (13)	11 (6)	0	0
Headache	53 (26)	41 (20)	11 (5)	1 (0.5)	-	36 (18)	26 (13)	9 (5)	1 (0.5)	0
Pyrexia	51 (25)	34 (17)	16 (8)	1 (0.5)	-	39 (20)	24 (12)	13 (7)	2 (1)	0
Chills	50 (24)	26 (13)	23 (11)	1 (0.5)	-	33 (17)	24 (12)	9 (5)	0	0
URTI	45 (22)	10 (5)	35 (17)	-	-	24 (12)	6 (3)	16 (8)	2 (1)	0
Dizziness	44 (21)	33 (16)	9 (4)	2 (1)	-	18 (9)	16 (8)	2 (1)	0	0
Thrombocytopenia	19 (9)	6 (3)	6 (3)	3 (2)	4 (2)	45 (23)	6 (3)	13 (7)	21 (11)	5 (3)

Safety was assessed in all patients who received 1 dose of treatment. Continuous U2 treatment resulted in a longer reporting period for AEs in that arm with median exposures of 21 (0.03 – 47) months for U2 and 5 (0.03 – 7) months for O+Chl. AE: adverse event; O+Chl: obinutuzumab + chlorambucil; U2: umbralisib + ublituximab. PCP and PJP prophylaxis was mandated for all patients treated with umbralisib.

All Causality Grade 3-4 AEs in U2 Population

AEs, n (%)	**Pooled Safety** N=206	*Treatment Naïve* N=116	*Previously Treated* N=90
Diarrhea	25 (12.1)	16 (13.8)	9 (10.0)
Nausea	3 (1.5)	1 (0.9)	2 (2.2)
Infusion related reaction	4 (1.9)	1 (0.9)	3 (3.3)
Fatigue	4 (1.9)	4 (3.4)	0
Neutropenia	64 (31.1)	28 (24.1)	36 (40.0)
Cough	0	0	0
Headache	1 (0.5)	0	1 (1.1)
Pyrexia	1 (0.5)	1 (0.9)	0
Chills	1 (0.5)	1 (0.9)	0
Upper respiratory tract infection	0	0	0
Dizziness	2 (1.0)	2 (1.7)	0

Safety was assessed in all patients who received 1 dose of treatment. AE: adverse event; U2: umbralisib + ublituximab.

Events of Clinical Interest – PI3K specific

AEs, n (%)	U2 N=206		O+Chl N=200	
	Any	Grade ≥3	Any	Grade ≥3
ALT elevation	35 (17.0)	17 (8.3)	9 (4.5)	2 (1.0)
AST elevation	28 (13.6)	11 (5.3)	9 (4.5)	4 (2.0)
Colitis (non-infectious)[a]	10 (4.9)	4 (1.9)	0	0
Colitis (infectious)[a]	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Pneumonitis	6 (2.9)	1 (0.5)	1 (0.5)	0
Rash[a]	26 (12.6)	5 (2.4)	10 (5.0)	1 (0.5)
Opportunistic Infections[a]	29 (14.1)	12 (5.8)	11 (5.5)	3 (1.5)

[a]Group includes multiple MedDRA terms. AE: adverse event; O+Chl: obinutuzumab + chlorambucil; U2: umbralisib + ublituximab.

Conclusions

- UNITY-CLL is the first randomized trial of a PI3Kδ inhibitor (umbralisib) in treatment-naïve CLL, establishing a new mechanism of action in this treatment setting
- U2 is a novel, non-chemotherapy regimen that is highly active in the treatment of CLL with demonstrated efficacy including prolonged progression-free survival compared to chemoimmunotherapy (O+Chl) and a well-tolerated safety profile
- Benefit of U2 was consistent irrespective of prior treatment status
- U2 regimen is being explored as a backbone for triplet combinations including combinations with venetoclax and BTK inhibitors

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