Abstract # 8022

Effect of Adding Ublituximab to Ibrutinib on PFS, ORR, and MRD Negativity in Previously Treated High-Risk Chronic Lymphocytic Leukemia: Final Results of the GENUINE Phase III Study

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BACKGROUND

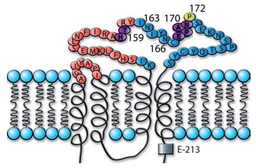
Study Rationale

- Chronic lymphocytic leukemia (CLL) is a heterogeneous disease with genetic abnormalities including 17 deletion (del17p), 11q deletion (del11q), and *TP53* gene mutations (*TP53*mut) identified as markers of high-risk disease conferring poor prognosis
- Ibrutinib (IB) is a Bruton's tyrosine kinase (BTK) inhibitor approved for the treatment of CLL
- Patients with high risk cytogenetic features have inferior outcomes on ibrutinib monotherapy, representing an unmet medical need
- The addition of rituximab to ibrutinib has failed to demonstrate improvement in long term outcomes, however it remains unclear whether the addition of an optimized anti-CD20 antibody could improve outcomes over ibrutinib monotherapy[1,2]
- Early data from the GENUINE study demonstrated improvements in ORR and uMRD. At previous cutoff, PFS was still immature. While PFS favored UTX+IB, it was not statistically significant[3]

Ublituximab

- Ublituximab (TG-1101, UTX) is a novel, glycoengineered, Type I, anti-CD20 monoclonal antibody with several defining features:
  - Targets a unique epitope on the CD20 antigen (Figure 1)
  - Type I maintains complement-dependent cytotoxicity (CDC)
  - Glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab including in 17p deleted CLL cells[4]
- As a single agent, ublituximab is active in rituximab-refractory CLL and Non-Hodgkin's lymphoma (NHL) patients[5]
- Phase 2 study in relapsed/refractory CLL patients demonstrated that combination of ublituximab with ibrutinib is highly active (95% ORR in high-risk CLL) and well-tolerated[6]
- Ublituximab is currently in Phase 3 development in combination with umbralisib for patients with CLL, and in Phase 2b study for patients with NHL.

Figure 1. CD20 Antigen Binding Epitope of Ublituximab



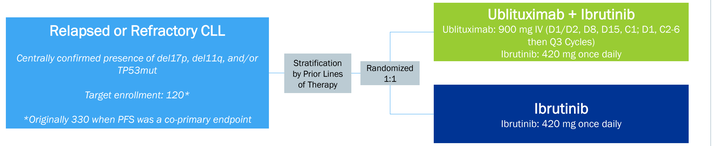
Red: Key ofatumumab epitope amino acids
Purple: Core amino acids of ublituximab epitope
Figure adapted from Ruuls et al, 2008

STUDY DESIGN

Study Schema

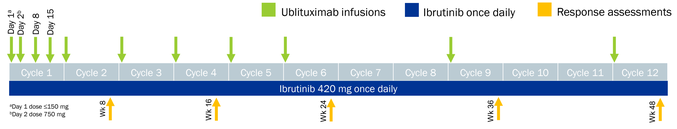
Study UTX-IB-301 (NCT02301156) is an open-label, multicenter, randomized, Phase III study in relapsed or refractory high-risk CLL (del17p, del11q, or *TP53*mut) (Figure 2).

Figure 2. Randomization Schema



Efficacy was assessed at week 8, 16, and 24, and every 12 weeks thereafter (Figure 3). After cycle 6, all patients continued ublituximab every 3 cycles until disease progression, unacceptable toxicity, or withdrawn consent.

Figure 3. Treatment Schedule



Study Objectives

Primary Endpoint

- Overall response rate (ORR) by independent review committee (IRC)

Secondary Endpoints

- Progression free survival (PFS) by independent review committee
- Minimal residual disease (MRD) assessed centrally
- Complete response (CR) rate

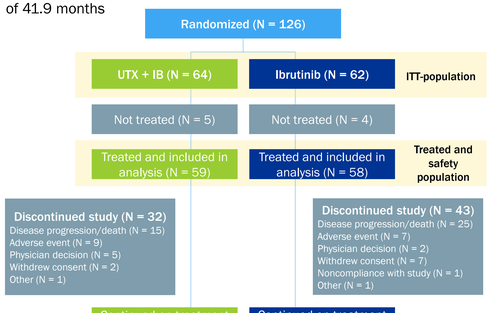
Key Eligibility Criteria

- Age ≥18 years
- CLL requiring treatment per iwCLL criteria[7]
- High-risk cytogenetics (defined as del[17p], del[11q], and/or TP53 mutation)
- ECOG performance status ≤ 2
- No history of transformation of CLL
- No prior BTK inhibitor therapy

RESULTS

Patient Disposition

Data cut-off date was September 1, 2019 with a median follow–up time of 41.9 months



Patient Demographics

Characteristic	Ublituximab + Ibrutinib	Ibrutinib Monotherapy
Evaluable for safety & efficacy, N	59	58
Median age, years (range)	66 (42 – 86)	66 (51 – 85)
Male/Female, n/N	40/19	45/13
ECOG 0-1/2, n/N	56/3	56/2
Prior therapy regimens, median (range)	1 (1 – 5)	1 (1 – 5)
Rai Stage III/IV, n (%)	29 (49)	25 (43)
Bulky disease (≥5 cm), N (%)	28 (47)	16 (28)
17p deletion, N (%)	26 (44)	29 (50)
TP53 mutation, N (%)	17 (29)	27 (47)
11q deletion, N (%)	29 (49)	24 (41)
TP53 mutation and/or 17p deletion, N (%)	27 (46)	36 (62)
IGHV unmutated, N (%)*	49 (83)	48 (83)

*2 patients in the ibrutinib arm had no dominant clone; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy chain

RESULTS

Safety

All Causality Adverse Events (AEs) Occurring in ≥ 20% of Patients

Adverse Event	Ublituximab + Ibrutinib		Ibrutinib Monotherapy	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Diarrhea	56	10	47	5
Infusion related reaction	53	3	0	0
Cough	42	0	31	0
Fatigue	39	3	38	5
Neutropenia	36	19	21	12
Nausea	34	0	33	3
Arthralgia	31	2	21	3
Contusion	31	0	36	2
Insomnia	31	0	17	2
Thrombocytopenia	31	2	21	5
Upper respiratory tract infection	31	2	28	2
Anemia	29	8	21	9
Headache	29	2	29	3
Pyrexia	27	0	14	0
Dizziness	25	0	26	3
Sinusitis	25	2	17	0
Constipation	24	2	19	2
Pneumonia	24	8	14	9
Dyspepsia	20	0	9	0
Dyspnea	20	2	21	7
Vomiting	20	2	7	0

- AEs of special interest in ublituximab + ibrutinib vs ibrutinib alone (all grades): Atrial fibrillation (14% vs 7%) and myalgia (14% vs 24%)

Efficacy

- UTX + ibrutinib produced statistically significant improvements in ORR (P = 0.019) and CR/CRi (P = 0.024) compared with ibrutinib monotherapy (Figure 4)
- Undetectable MRD (uMRD) in PB/BM was achieved at a significantly higher rate with UTX-IB than ibrutinib (P < 0.001) (Figure 5)

Figure 4. Best ORR

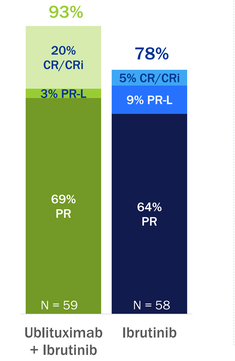
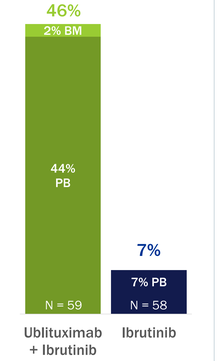
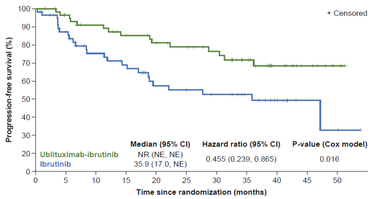


Figure 5. Undetectable MRD

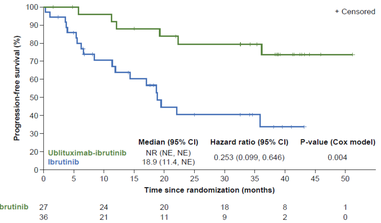


Progression-Free Survival (IRC-Assessed)

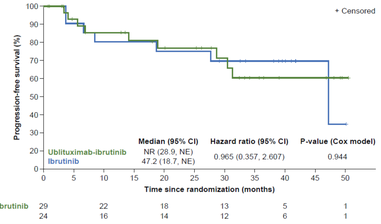
All Patients



Patients With 17p Deletion and/or *TP53* Mutation



Patients With 11q Deletion



Conclusions

- The addition of ublituximab to ibrutinib significantly improved ORR, CR rate, and increased rates of uMRD compared with ibrutinib monotherapy in patients with relapsed/refractory CLL with high-risk cytogenetics
- At a median follow-up of 41.9 months, PFS was significantly improved in patients treated with ublituximab plus ibrutinib compared with ibrutinib monotherapy
- Improvement in PFS was driven by patients with del17p/TP53mut
- Deletion of 11q is no longer categorized as a high-risk feature with ibrutinib monotherapy, and PFS was not significant in this population
- The addition of ublituximab to ibrutinib did not significantly alter the known safety profile of ibrutinib; slightly higher rates of neutropenia and atrial fibrillation were observed with ublituximab plus ibrutinib

Abbreviations: BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; IIT, intention to treat; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PB, peripheral blood; PR, partial response; PR-L, PR with lymphocytosis; Wk, week
References: 1. Burger J, et al. *Blood*. 2019;133(10):1011-1019; 2. Woyach J, et al. *N Engl J Med* 2018;379:2517-28; 3. Sharman J, et al. Ublituximab and ibrutinib for previously treated genetically high-risk chronic lymphocytic leukemia: Results of the GENUINE Phase 3 study. Presented at ASCO. June 3, 2017; 4. Le Garff-Tavernier M, et al. *Leukemia*. 2014;28:230-233; 5. Sawas A, et al. *Br J Haematol*. 2017;177(2):243-253; 6. Sharman J, et al. Br J Haematol. 2017;176:412-420; 7. Hallek M, et al. *Blood*. 2008;111(12):5446-5456.