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A DOUBLE-BLIND, RANDOMIZED PHASE 3 STUDY TO COMPARE EFFICACY AND SAFETY OF CT-P10 TO INNOVATOR RITUXIMAB IN COMBINATION WITH CVP IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA

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Background CT-P10 is the first biosimilar of innovator rituximab (RTX), approved for all indications by the European Medicines Agency. CT-P10 has demonstrated pharmacokinetics (PK) and efficacy equivalence in patients with rheumatoid arthritis (Yoo, ACR 2016) and PK equivalence in patients with advanced follicular lymphoma (AFL) (Coiffier, ASH 2016).

Aims This study aimed to demonstrate non-inferiority (NI) of efficacy and PK equivalence between CT-P10 and RTX in patients with newly diagnosed advanced follicular lymphoma (AFL) (NCT02162771).

Methods A total of 140 patients were randomized in a 1:1 ratio to receive CT-P10 or RTX (375 mg/m^2 intravenous) plus CVP (cyclophosphamide, vincristine, and prednisone) therapy every 3 weeks over 8 cycles. Overall response rate (ORR) based on best overall response over 24 weeks was assessed by the independent review committee, according to the 1999 International Working Group criteria.

Results Therapeutic NI of CT-P10 to RTX has been demonstrated in terms of ORR over 8 cycles (Ta ble 1). The ORR difference between two treatment groups was 4.3% in per-protocol (PP) population and 5.7% in intent-to-treat (ITT) population. Considering the statistical Non-Inferiority test using confidence interval (CI) approach with the exact binomial CI for the difference of ORR between two treatment groups, the lower bound of 95% CI lies on the positive side of -7% NI margin (-4.25% in PP population and -3.41% in ITT population). The pre-defined non-inferiority criterion has been met with the descriptive point estimate difference approach and the formal statistical NI test with a 5% significance level.

Median number of B-cells decreased to the lower limit of quantification (LLoQ) after the 1st infusion and remained at the LLoQ over 8 cycles in both groups.

Overall safety profile of CT-P10 was consistent with that of RTX (Table 2). No progressive multifocal leukoencephalopathy or Hepatitis B virus reactivation were reported in either groups. The proportion of patients with positive anti-drug antibody were similar between both groups (4.3% and 2.9%) over 24 weeks in the induction period.

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Table 1. Summary of Efficacy [Number (%) of patients]

PP population	CT-P10 (N=66)	RTX (N=68)	Difference* [lower bound of 95% CI]
ORR (CR+CRu+PR)	64 (97.0)	63 (92.6)	4.3% [-4.25%]
Complete response (CR)	20 (30.3)	15 (22.1)	
Unconfirmed CR (CRu)	6 (9.1)	8 (11.8)	
Partial response (PR)	38 (57.6)	40 (58.8)	

* Difference was calculated using percentages not the round off values.

Table 2. Summary of Treatment-emergent adverse event (TEAE) related to the study drug [Number (%) of patients]

Safety population	CT-P10 (N=70)	RTX (N=70)	P-value (Fisher's exact test)
TEAE	37 (52.9)	34 (48.6)	0.7354
Serious TEAE	6 (8.6)	4 (5.7)	0.7447
Infusion-related reaction	15 (21.4)	17 (24.3)	0.8407
Infection	6 (8.6)	9 (12.9)	0.5861

Conclusions This study demonstrates therapeutic non-inferiority of CT-P10 to RTX combined with CVP therapy in previously untreated AFL. CT-P10 was well-tolerated and the safety profile including immunogenicity of CT-P10 was comparable to that of RTX over 8 cycles in induction period.