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Maximum length for the paper title, introduction, methods, results and conclusion combined is 450 words.

Improved Efficacy with Response and MRD-guided Ibrutinib–Obinutuzumab (IO) Intensification after Ibrutinib-Venetoclax (IV) in First Line CLL: Primary analysis of the HOVON 158/NEXT STEP Phase 2 Trial

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Introduction

Obinutuzumab-venetoclax (OV) and ibrutinib-venetoclax (IV) are effective time-limited first-line treatments for chronic lymphocytic leukemia (CLL). However, patients not achieving undetectable minimal residual disease ($<10^{-4}$, uMRD) or complete remission (CR/CRi) are prone to early relapse.

Methods

The HOVON 158/NEXT STEP trial is a non–randomized, phase 2, first-line study for CLL patients. Patients are treated with 3 cycles of I followed by 12 cycles of IV according to GLOW study (named cycles 1-15 IV). IWCLL response assessment and MRD evaluation in bone marrow (BM) are performed after cycle 15. Due to centralized review, IV continues through cycle 16. Patients achieving CR(i) with uMRD in BM enter observation. Others proceed to intensification with 6 cycles of IO. Primary endpoint was CR(i) with uMRD in BM 9 months after cycle 16 IV in the intensification group.

Results

Between December 2020 and August 2021, 84 eligible patients were included. Of the 84 patients 73 (87%) completed IV (72 response assessment). Fifteen patients (21%) had CR with uMRD and were assigned to the observation group. During cycles 1-15 IV, AE's were reported per patient as maximum grade 2 (21%), grade 3 (51%), grade 4 (23%) and grade 5 (1%). Progression free survival (PFS) at 24 months was 94%, with 3 PD, of whom 1 during the intensification phase. Overall survival (OS) at 24 months was 98% with two treatment related deaths.

Fifty-seven patients (79%) were assigned to IO intensification due to either MRD positivity (n=13), less than CR(i) (n=17) or both (n=27) (2 patients did not have residual disease in hindsight and were analyzed in the observation group). In the intensification group 33 of 55 patients (60%, 90% CI: 48-71) reached CR(i) and uMRD in BM 9 months after cycle 16, meeting the primary endpoint. At 24 months after start of intensification PFS was 92% (95% CI: 80-97) and OS 94% (95% CI: 82-98).

Of the 55 patients assigned to IO, no infusion related reactions (IRR) on O occurred. During IO, AE's were reported as maximum grade 2 (46%), grade 3 (22%), grade 4 (4%) and grade 5 (2%). Four patients discontinued I and 1 O due to AE's.

Of the 17 patients in the observation group 2 patients (12%) had a grade 2 AE and 1 (6%) grade 3, and none had died, showed PD or received additional treatment during follow up, resulting in PFS and OS at

24 months of 100%.

Conclusion

MRD and response guided IO intensification leads to CR(i) with uMRD in 60% of patients without CR(i) and uMRD after IV in first-line CLL, with limited toxicity and no IRR. This response and MRD-guided intensification approach warrants randomized comparison to current standard of care.