

Becotatug vedotin vs. chemotherapy in pre-heavily treated advanced nasopharyngeal carcinoma: A randomized, controlled, multicenter, open-label study.

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Background: Becotatug vedotin (MRG003) is a novel EGFR-targeted antibody-drug conjugate. Previous Phase I/II studies have demonstrated optimistic efficacy in R/M NPC pts who had failed platinum chemotherapy and PD-(L)1 inhibitor. This study aimed to assess clinical efficacy and safety of MRG003 in pts compared with chemotherapy. **Method:** Eligible pts with R/M NPC had failed ≥ 2 lines of systemic chemotherapy and PD-(L)1 inhibitor, and were randomized to receive MRG003 (2.3 mg/kg, d1, iv, Q3W) or chemotherapy (capecitabine 1000 mg/m², po, twice daily, d1-14, Q3W; or docetaxel 75 mg/m², iv, d1, Q3W). Randomization was stratified according to liver metastasis (yes or no) and ECOG PS (0 or 1). The primary endpoints were ORR and PFS assessed by BICR, and OS. Pts in the chemotherapy arm were allowed to cross over to receive MRG003 after disease progression. **Result:** A total of 173 R/M NPC pts were randomly assigned to MRG003 (n=86) or capecitabine(n=36)/docetaxel (n=51). The median prior treatment lines (range) were 3 (2-10) vs. 3 (2-11), and the ECOG score 0 was 17.4% vs. 17.2% for two arms. 40 pts (46.5%) vs. 41 pts (47.1%) of two arms had liver metastasis. By 30 June 2024, the study reached the significantly improved BICR-assessed ORR with MRG003 compared to chemotherapy (30.2% vs. 11.5%, difference: 18.7%, 95%CI: 7.0%, 30.5%, P=0.0025). Also, PFS was significantly improved in the MRG003 arm (HR=0.63, 95% CI: 0.43, 0.91, P=0.0146). Median PFS (95%CI) by BICR were 5.8m (4.2, 6.2) vs. 2.8m (2.0, 5.5). As of 30 December 2024, the updated mOS (95%CI) were 17.1m (11.4, NE) vs. 12.0m (9.7, 15.4) of two arms (HR=0.73, 95%CI: 0.48, 1.12). By supplementary analysis excluding the impact of crossover treatment, the HR of OS was 0.59 (95%CI: 0.37, 0.93). MRG003 has shown a trend of survival benefits. The OS will be continually followed up. The incidence of adverse events in the two arms was similar. 39 pts (45.3%) vs. 44 pts (50.6%) in two arms experienced grade ≥ 3 TRAEs. White blood cell count decreased was the most common grade ≥ 3 TRAE of two arms (9.3% vs. 35.6%). **Conclusions:** As the first ADC clinical study targeting heavily pretreated R/M NPC, becotatug vedotin demonstrated statistically and clinically meaningful benefits while maintaining a manageable safety profile in this population. This study will lead to a paradigm shift in the treatment of R/M NPC. Sponsor: Lepu Biopharma Co., Ltd. Clinical trial information: NCT05126719. Research Sponsor: None.

| | MRG003 (N=86) | Chemotherapy (N=87) | HR (95% CI) |
|-----------------------------|-------------------|------------------------|-------------------|
| ITT analysis | | | |
| Information fraction (n, %) | | 87, 71.3 | - |
| Median follow-up (m) | 13.5 | 13.6 | - |
| mOS (m, 95% CI) | 17.1 (11.4, NE) | 12.0 (9.7, 15.4) | 0.73 (0.48, 1.12) |
| 12-m rate (%; 95% CI) | 55.9 (44.2, 66.0) | 48.9 (37.7, 59.2) | - |
| Supplementary analysis* | | | |
| mOS (m, 95% CI) | 17.1 (11.4, NA) | 11.1 (8.5, NA) | 0.59 (0.37, 0.93) |

*Using hypothetical strategy to exclude the impact of crossover treatment.