HCC is a severe disease, and even with current treatment options available, median survival for patients with advanced HCC is less than one year: 4–8 months if untreated and 6–11 months with sorafenib treatment. There is therefore a clear unmet need for new treatments which delay progression and improve survival without negatively impacting patients' quality of life. Lenvatinib (LENVIMA®) is the first therapy in over 10 years to demonstrate non-inferiority in overall survival (OS) with superior progression-free survival (PFS), time to progression (TTP), and overall rate of response (ORR) versus sorafenib. Sorafenib is currently the only reimbursed targeted systemic therapy for the first-line treatment of HCC in Norway.

Lenvatinib has demonstrated a clear potential to improve OS after adjustment for baseline imbalances in AFP and HCV etiology as well as post-treatment anti-cancer therapy use. Notable imbalances include a greater proportion of patients with baseline AFP levels ≥200 ng/mL (a proven adverse prognostic factor in HCC (1)), in the lenvatinib (46.4 %) than in the sorafenib (39.3 %) arm, and a greater proportion of patients who received post-treatment anticancer therapy in the sorafenib (51.1 %) than in the lenvatinib (43.1 %) arm.

From the subgroup analysis for OS, the treatment effect may appear consistent across subgroups, but the baseline risk of death is not. This is especially pronounced for baseline AFP levels (sorafenib arm: median OS 16.3 months for AFP <200 ng/ml subgroup and 8.2 months for the AFP ≥200 ng/ml subgroup), and subsequent anticancer therapy, (sorafenib arm: median OS 17.0 months for patients who received anticancer therapy and 7.9 months for patients who did not receive anticancer therapy).

This suggests that baseline AFP levels and receipt of subsequent anticancer therapy are highly predictive of outcomes, and these notable differences may have favored sorafenib. Current EMA guidance on adjustment for baseline characteristics in clinical trials suggests that in the presence of imbalances for strong predictors of outcomes, adjustment for such covariates generally improves the precision and efficiency of the analysis and avoids conditional bias from chance covariate imbalance. The National Institute for Health and Care Excellence (NICE) recommended Lenvima for HCC, and accepted a multivariable adjustment to account for the imbalance in baseline characteristics. (2)

Therefore, the submitted cost-effectiveness base-case assumptions adjusting for imbalance in prognostic baseline characteristics and subsequent therapies provide an analysis less subject to bias than the assumptions which NoMA has adopted. In this scenario, the log-logistic distribution for OS, and gamma distribution for PFS are most appropriate based on statistical best fit and clinical plausibility. Furthermore, while it is not appropriate to conclude the proportional hazards assumption is violated for OS, the proportional odds assumptions which underlie the log-logistic (and log-normal) models were not tested. For this reason and for consistency with PFS, the most appropriate base-case assumption remains independent statistical models for OS. We agree that the inclusion of 7 days drug wastage may be reasonable. This results in an ICER of 833,503 NOK/QALY, and with the [redacted] % discount being offered, a further ICER decrease to [redacted] NOK/QALY.

Lenvatinib has demonstrated a statistically significant and clinically meaningful improvement across all secondary efficacy endpoints in comparison to sorafenib: a 34 % improvement in PFS (median 7.4 vs 3.7 months), a 37 % improvement in TTP (median 8.9 vs 3.7 months), and a 2.6-fold increase in the proportion of patients with an ORR. The increased ORR is relevant in clinical practice because lenvatinib is highly effective in reducing tumor size, and achievement of tumor downstaging facilitates the use of curative treatments (e.g., resection, ablation), which in turn improve patient survival even further. Furthermore, lenvatinib has demonstrated a clinically meaningful delay in deterioration of health-related quality of life outcomes for multiple domains and a consistent and manageable safety profile relative to sorafenib, without the increased risk of developing hand-foot syndrome, a debilitating adverse event.

Lenvatinib offers a valuable treatment option to a patient population with severe disease and poor survival rates. With its distinctive side-effect profile, and statistically and clinically significant response rates in comparison to current standard of care, it can provide a meaningful benefit to patients who currently have no other treatment options aside from sorafenib. Patients should be given the opportunity for the best treatment option as early as possible and in line with their tolerance profile.

References

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