ATEZOLIZUMAB + BEVACIZUMAB VERSUS OTHER SYSTEMIC THERAPIES FOR THE FIRST LINE TREATMENT OF UNRESSECTABLE HEPATOCELLULAR CARCINOMA: A SYSTEMATIC LITERATURE REVIEW AND INDIRECT TREATMENT COMPARISON

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1 – Background

Globally over 905 000 new cases of liver cancer were diagnosed in 2020 making it the sixth most common cancer worldwide and 90% of these cases consist of hepatocellular carcinoma (HCC)[1,2].

Atezolizumab is an anti-PD-L1 antibody. By attaching to the PD-L1 transmembrane protein, present on many cancer cells, it increases the immune system's ability to specifically attack cancer cells and slow down disease progression. Atezolizumab in combination with bevacizumab (A+B) is indicated for the treatment of adult patients with advanced or unresectable HCC (uHCC) who have not received prior systemic therapy[3].

Sorafenib (SOR) and lenvatinib (LEN) are the two drugs approved by the European Medicines Agency for the first line systemic treatment of patients with uHCC. The combination of A+B presents a new therapeutic option for these patients.

In its pivotal phase III trial (IMbrave150 study), A+B demonstrated greater efficacy than SOR and comparable safety[4]. However, there are no head-to-head trials comparing A+B with LEN. A recent publication has indirectly compared first-line treatment options for uHCC[5].

The aim of this study was to determine the comparative clinical efficacy of A+B versus SOR and LEN for the first line systemic treatment of uHCC by means of an indirect treatment comparison (ITC).

2 – Methods

A systematic literature review (SLR) was performed using MEDLINE, EMBASE and Cochrane databases from inception to October 28th 2020 to identify all relevant studies that could contribute to a network of evidence between the interventions of interest.

Conference abstracts were reviewed for the last three available years. The websites of health technology assessment agencies were also reviewed to identify submissions regarding the interventions of interest, without time restriction.

All prospective randomised controlled trials (phase II-IV), with no restriction on blinding, reporting results for the first line treatment of adult patients with uHCC were included. Outcomes of interest included overall survival (OS), progression free survival (PFS) and objective response rate (ORR).

The Bucher method was used to estimate, by outcome, the relative effect of treatment with A+B versus LEN using SOR as a common comparator[6]. The published results of hazard ratios (HR) and respective 95% confidence intervals (CI) were used for the OS, PFS, while for the ORR outcomes the odds ratios (OR) were calculated, per study, based on the published number of patients with events and total number of patients in each treatment arm.

3 – Results

The SLR identified 9 717 potential references of interest and a total of 94 references were included in the final qualitative analysis.

A global network of evidence composed of 24 different studies was formed. However, only two studies actively contributed to estimate the treatment effects between the three interventions of interest: IMbrave150 (NCT03434379) and REFLECT (NCT01761266)[7] (Figure 1). The results of the remaining studies do not influence the comparison between the interventions of interest and therefore were excluded from the analysis.

The IMbrave150 and REFLECT study populations are very comparable. Patients included in both studies had confirmed diagnosis of uHCC and did not receive previous treatement with any systemic therapy. Baseline demographic and clinical characteristics were also balanced between the two studies. Nevertheless, patients with more than 50% liver involvement by HCC, clear invasion into the bile duct and main portal vein invasion were excluded in REFLECT and included in IMbrave150.

Relative treatment effects between A+B and SOR can be obtained directly from the IMbrave150 study, where A+B has shown a superiority on all efficacy outcomes (Figure 2 and Figure 3).

For the comparison of A+B versus LEN, the ITC results estimate that:

- A+B significantly reduces the risk of death by 37% (OS HR=0.63; 95%CI: 0.44 – 0.89) (Figure 2);
- There is a comparability between interventions regarding the PFS, with a suggestion of a moderate improved benefit with A+B, and ORR (Figure 2 and Figure 3).

Figure 1. Specific network of evidence for the comparison of A+B vs. SOR and LEN

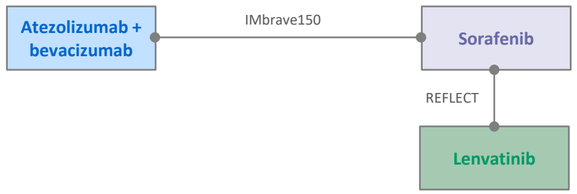


Figure 2. OS and PFS results for A+B vs. SOR (IMbrave150) and vs. LEN (ITC) comparisons

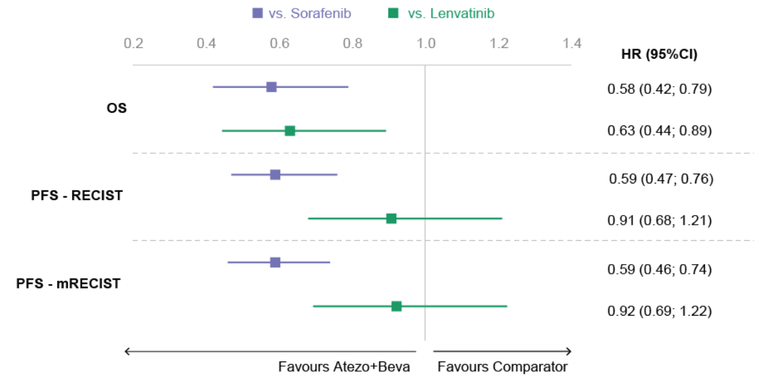
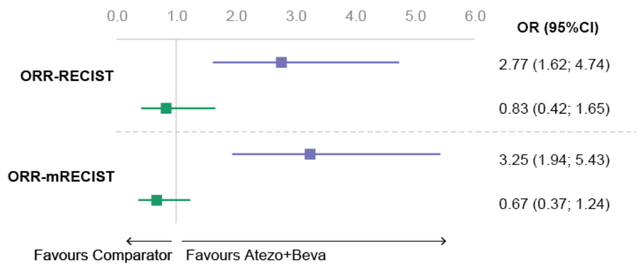


Figure 3. ORR results for A+B vs. SOR (IMbrave150) and vs. LEN (ITC) comparisons



PFS and ORR were evaluated using the RECIST criteria and the modified version for HCC (mRECIST).
95%CI: 95% confidence interval; HR: hazard ratio; OR: odds ratio; ORR: objective response rate; OS: overall survival; PFS: progression free survival; RECIST: Response Evaluation Criteria In Solid Tumors

4 – Conclusion

IMbrave150 is the first study in more than a decade where an alternative therapeutic option (A+B) demonstrated superior OS compared to SOR. This result was also observed when comparing A+B versus LEN by means of this ITC.

The combination of A+B has also proven to have superior efficacy versus SOR in all the remaining evaluated outcomes as well as a similar PFS and ORR to LEN for the first line systemic treatment of patients with uHCC. Our findings were similar to other published results reinforcing A+B benefit over the available treatment alternatives.

References: 1. International Agency for Research in Cancer. GLOBOCAN: Cancer Today. 2020 2. European Association For The Study Of The Liver, EASL clinical practice guidelines: management of hepatocellular carcinoma. Journal of hepatology, 2018. 69(1): p. 182-236 3. Roche, Summary of Product Characteristics: Tecentriq® (atezolizumab). 2021 4. Finn, R.S., et al., Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. New England Journal of Medicine, 2020. 382(20): p. 1894-1905 5. Vogel, A., et al., Comparative Efficacy of Atezolizumab plus Bevacizumab and Other Treatment Options for Patients with Unresectable Hepatocellular Carcinoma: A Network Meta-Analysis. Liver Cancer, 2021.10(3): p240-248. 6. Bucher, H.C., et al., The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology, 1997. 50(6): p. 683-691. 7. Kudo, M. and R.S. Finn, Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet (London, England), 2018. 391(10126): p. 1163-1173

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