Exploratory Network Meta-analyses of Selective Internal Radiation Therapy versus Sorafenib, Lenvatinib, and Atezolizumab-bevacizumab as First-line Treatment in Subgroups of Patients with Hepatocellular Carcinoma

Pollock RF[1], Brennan VK[2], Colaone F[2], Shergill S[2], Agirrezabal I[2]

[1] Covalence Research Ltd, London, United Kingdom; [2] Sirtex Medical United Kingdom Ltd, London, United Kingdom

Introduction and Objectives

Introduction

The IMbrave150 randomized controlled trial (RCT) of atezolizumab-bevacizumab (atezo-bev) versus sorafenib in the treatment of hepatocellular carcinoma (HCC) was the first to demonstrate superiority over sorafenib since the SHARP trial results were published in 2008.[1,2] Specifically, IMbrave150 reported significantly longer survival in patients treated with atezo-bev relative to those treated with sorafenib, with estimated 12-month survival rates of 67.2% (95% confidence interval [CI]: 61.3 to 73.1%) with atezo-bev versus 54.6% (95% CI: 45.2 to 64.0%) with sorafenib.[2]

The subsequent regulatory and reimbursement decisions on atezo-bev have changed the first-line treatment landscape for patients with advanced HCC. In addition to systemic therapies and interventions with curative intent, locoregional therapies such as selective internal radiation therapy (SIRT) and transarterial chemoembolization (TACE) still have an important role to play in the HCC armamentarium.

Objectives

The objective of the present study was to establish the relative efficacy of SIRT with SIR-Spheres Y-90 resin microspheres, lenvatinib, and atezo-bev versus sorafenib in the first-line treatment of HCC based on a series of exploratory network meta-analyses (NMAs) conducted in subgroups of patients potentially eligible for SIRT.

Methods

Systematic Literature Review

A PROSPERO-registered systematic literature review was conducted to identify RCTs of first-line treatments for HCC. Search terms were constructed using a combination of free-text and medical subject heading (MeSH) index terms. Studies were retrieved from PubMed, Embase, and the Cochrane Library. The search results were imported into Sourcerer (Covalence Research Ltd, London, UK), which was subsequently used to remove duplicate studies retrieved from multiple databases and manage the screening and study selection process.

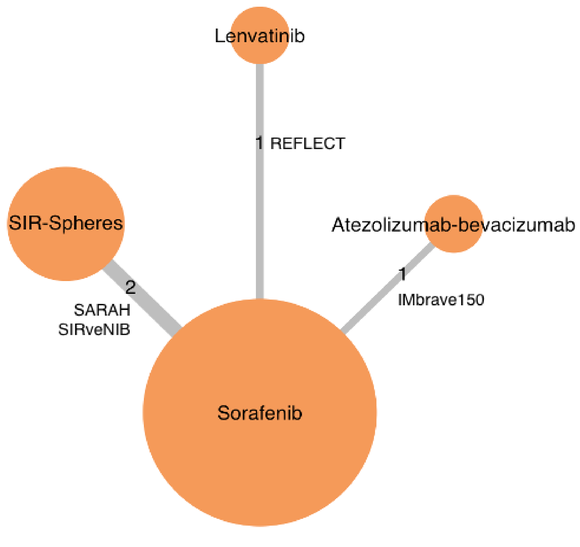
Data on overall survival (OS) were extracted from the included studies, focusing on three patient subgroups: one with no extrahepatic spread (EHS) or macrovascular invasion (MVI) at baseline, one in BCLC stage B at diagnosis, and one in Child-Pugh liver function class A.

Network Meta-analysis

Contrast-based, fixed effect NMAs were then conducted using the `gemtc` R package based on normal identity link models with half-normal priors. The final analyses were run based on 50,000 burn-in iterations and 100,000 simulations with no thinning.

Convergence was checked using Gelman-Rubin-Brooks plots and results presented as mortality hazard ratios (HRs) relative to sorafenib. Probability ranks, and surface under the cumulative ranking curve (SUCRA) plots were also generated.

Figure 1: Network meta-analysis structure



Results

Four RCTs were identified; two RCTs comparing SIR-Spheres Y-90 resin microspheres with sorafenib (SARAH and SIRveNIB), and one RCT each comparing lenvatinib and atezo-bev with sorafenib (REFLECT and IMbrave150, respectively; Figure 1).[2,3,4,5]

All four trials included patients with unresectable HCC. SARAH and SIRveNIB included patients with Child-Pugh A-B7 liver function and free from extrahepatic spread (excepting small lymph node and lung metastases in SARAH), while REFLECT and IMbrave150 included only patients in Child-Pugh class A.

None of the analyses reported significant OS differences between the four treatments, with the small subgroup sizes contributing to a high degree of uncertainty (Table 1 and Figure 2). Lenvatinib was not included in the Child-Pugh A analysis as the most comparable subgroup from REFLECT (patients without EHS in Child-Pugh class A) also excluded all patients with MVI.

Atezo-bev had the highest probability of being the most efficacious treatment in patients without EHS or MVI (71.8% probability), and in patients with Child-Pugh class A liver function (72.6% probability), but the least efficacious treatment in patients diagnosed in BCLC stage B (51.1% probability).

Across the three subgroup analyses, SIRT with SIR-Spheres Y-90 resin microspheres consistently had the highest likelihood of being the second most efficacious treatment option, while sorafenib was consistently ranked as the third most efficacious treatment.

Table 1: Network meta-analysis results from the three sub-group analyses

	No EHS or MVI			BCLC B			Child-Pugh A		
Treatment	**OS HR (95% CrI)**	**SUCRA**	**Most likely rank (likelihood)**	**OS HR (95% CrI)**	**SUCRA**	**Most likely rank (likelihood)**	**OS HR (95% CrI)**	**SUCRA**	**Most likely rank (likelihood)**
Sorafenib	Reference	37.7%	3 (49.3%)	Reference	40.4%	3 (44.8%)	Reference	22.3%	3 (60.2%)
SIR-Spheres Y-90 resin microspheres	0.94 (0.74–1.19)	55.8%	2 (46.3%)	0.95 (0.72–1.26)	54.7%	2 (32.1%)	0.94 (0.78–1.14)	50.1%	2 (55.3%)
Atezolizumab-bevacizumab	0.69 (0.29–1.64)	78.6%	1 (71.8%)	1.08 (0.35–3.30)	41.6%	4 (51.1%)	0.77 (0.43–1.37)	77.5%	1 (72.6%)
Lenvatinib	1.05 (0.79–1.40)	27.8%	4 (49.7%)	0.91 (0.65–1.28)	63.3%	1 (36.4%)	Not analyzed		

BCLC, Barcelona Clinic Liver Cancer; **CrI,** credible interval; **EHS,** extrahepatic metastases; **HR,** hazard ratio; **MVI,** macrovascular invasion; **OS,** overall survival; **SUCRA,** surface under the cumulative ranking curve.

Discussion and Conclusions

The present analysis showed that there is a high degree of uncertainty around the optimal first-line treatment in subgroups of patients with HCC who would potentially be eligible for SIRT.

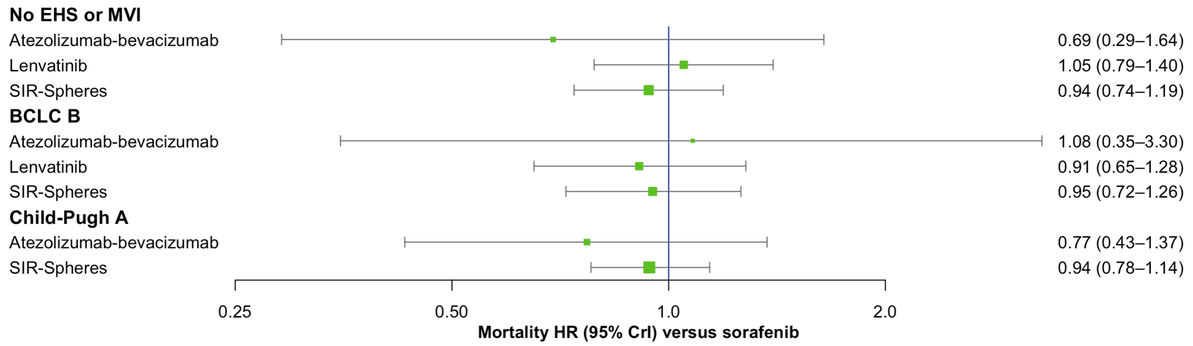
Over the whole population enrolled in IMbrave150, the hazard ratio for death with atezo-bev versus sorafenib was 0.58 (95% CI: 0.42 to 0.79; p<0.001). While the HRs in each of the subgroup analyses in the present study still favored atezo-bev versus sorafenib, the HRs were all less favorable and non-significant.

Recent research shows that the efficacy of SIRT may be significantly improved in patients in whom a higher tumor radiation–absorbed dose can be administered or in patients with low tumor burden and albumin-bilirubin (ALBI) grade.[6,7] For instance, in a *post hoc* subgroup analysis of data from SARAH, patients receiving <100 Gy experienced median OS of 6.1 months (95% CI: 4.9–6.8 months) versus 14.1 months (95% CI: 9.6–18.6 months) in patients receiving ≥100 Gy (HR 0.38; p<0.001).[6] In patients with low tumor burden (≤25%) and ALBI grade 1, median OS was 21.9 months (95% CI: 15.2–32.5, n=37) with SIRT and 17.0 months (95% CI: 11.6–20.8, n=48) with sorafenib (HR 0.73; 95% CI: 0.44–1.21; p=0.22).

The findings of the present study, combined with these dramatic differences in outcomes in *post hoc* subgroup analyses, both highlight the growing importance of careful treatment selection based on a broadening array of patient characteristics.

The non-significance and uncertainty around the present findings was driven primarily by the small size of the subgroups. Further research would be required to confirm the findings, but treatment probability rankings from the NMAs tentatively suggest that atezo-bev may not be the optimal treatment choice in specific subgroups of patients with HCC eligible for locoregional therapy with SIRT.

Figure 2: Network meta-analysis results from the three sub-group analyses showing mortality hazard ratios relative to sorafenib



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Conflicts of interest

RFP reports employment, shareholdings, and a directorship at Covalence Research Ltd, London, UK, which received consultancy fees from Sirtex Medical United Kingdom Ltd to run the analyses, and prepare the abstract and poster. **VKB, FC,** and **IA** report full-time employment at Sirtex Medical United Kingdom Ltd, London, UK. **SS** reports full-time employment and directorship at Sirtex Medical United Kingdom Ltd.

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