Poster CO70

Matching Adjusted Indirect Comparison (MAIC) of Single Tremelimumab Regular Interval Durvalumab (STRIDE) Versus Atezolizumab with Bevacizumab (A+B) for the Treatment of Unresectable Hepatocellular Carcinoma (uHCC)

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Plain language summary

Why did we perform this research?

- Current international guidelines recommend the use of A+B as the first-line treatment for patients with unresectable or metastatic HCC who have not received prior treatment.[1,2]
- It is therefore important to compare the efficacy and safety of STRIDE to A+B but no head-to-head trials have been conducted (respectively assessed in HIMALAYA and IMbrave150)
- A standard indirect treatment comparison was not deemed appropriate due to differences between trials in terms of population characteristics and follow-up duration

How did we perform this research?

- An anchored Matched Adjusted Indirect Comparison of STRIDE vs A+B, was conducted through the common comparator arm (sorafenib) used in both trials
- A comparison of STRIDE vs A+B was conducted in terms of OS (assuming constant and time-varying relative treatment effects), ORR, grade 3/4 TEAEs and TEAEs leading to discontinuation

What were the findings of this research?

- STRIDE had similar OS and ORR to A+B over the common 2-year follow-up, with a similar pairwise HR between 9-month and 26.9-month timeframes in which medians were established in each trial.
- No long-term OS comparison could be generated given the limited duration of follow-up and maturity in IMbrave150, while the long-term data of STRIDE support the assumption of a long-term sustained benefit, with HR improving over time
- STRIDE was associated with fewer grade 3/4 TEAEs and TEAEs leading to discontinuations

What are the implications of this research?

These findings show that STRIDE offers a similar OS and ORR as A+B up to 26.9 months, suggesting that mOS alone does not reflect the overall clinical benefits of STRIDE. Due to the limited duration of follow-up and maturity of IMbrave150, comparison of A+B to the long-term OS benefit observed in STRIDE was not possible. STRIDE is the only treatment option with long-term data showing a sustained OS benefit while maintaining a favourable safety profile.

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Abbreviations

A+B: Atezolizumab-bevacizumab, BCLC: Barcelona clinic liver cancer, CI: Confidence interval, ECOG: Eastern cooperative oncology group, EGD: Esophagogastroduodenoscopy, EHS: Extrahepatic spread, EMA: European medicines agency, ESS: Effective sample size, FDA: Food and drug administration, HBV: Hepatitis B, HCV: Hepatitis C, HCC: Hepatocellular carcinoma, HR: Hazard ratio, IPD: Individual patient data, ITC: Indirect treatment comparison, MAIC: Matching-adjusted indirect comparison, MVI: Macrovascular invasion, OR: Odds ratio, ORR: Objective response rate, OS: Overall survival, STRIDE: Single tremelimumab regular interval durvalumab, TEAE: Treatment-emergent adverse event, TEM: Treatment effect modifier, uHCC: Unresectable hepatocellular carcinoma

Disclosures

Qin L, Gaughan A., Makowsky M, Kurland J, Negro A are employees and stockholders of AstraZeneca. Le Nouveau P and Gauthier A are employees of Amaris Consulting, which received funding from AstraZeneca to conduct this work. Palmer S received personal consulting fees from AstraZeneca for advice on the conduct and interpretation of this work. Chan S has acted as an advisor to AstraZeneca

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Introduction

Hepatocellular carcinoma (HCC) ranks as the fifth most frequently diagnosed cancer and the third highest contributor to cancer-related deaths globally.[3]

Due to its high resistance to chemotherapy, advanced HCC has limited treatment options and poor survival outcomes. The Food and Drug Administration (FDA) and European Medical Agency (EMA) have approved several systemic therapies, with atezolizumab-bevacizumab combination (A+B) and Single tremelimumab regular interval durvalumab (STRIDE) the main treatments for patients with untreated unresectable or metastatic HCC.[4-7] STRIDE was only a single priming dose of tremelimumab and did not require an esophagogastroduodenoscopy (EGD) which was required for A+B combination. However, the relative efficacy and safety of A+B and STRIDE have not been assessed.

In the absence of a head-to-head trial, an indirect treatment comparison (ITC) can be considered as a valuable tool to assess the relative effectiveness and safety of different treatments.[8,9]

Aim

This study aimed to conduct an ITC analysis to evaluate and compare the effectiveness and safety of STRIDE and A+B as first-line treatments for patients with unresectable HCC.

Methods

The validity of the ITC is predicated upon the fulfillment of key assumptions, namely, the establishment of connectivity, transitivity, and exchangeability between the trials under examination.

Connectivity was obtained through the sorafenib arm in both HIMALAYA[10] and IMbrave150[11], therefore an anchored ITC was considered.

Transitivity and exchangeability assumptions require a balance between trials regarding eligibility criteria and distribution of potential treatment effect modifiers (TEMs, i.e. factors that may impact the relative treatment effect).

Potential TEMs were identified based on a review of the published literature, subgroups analyses reported in HIMALAYA[10] and IMbrave150[11] and validated by a clinical expert in HCC treatment. Identified TEMs are illustrated in Figure 1. Notably, differences in the proportion of patients recruited from mainland China correlates with differences in the etiology of liver disease: while HIMALAYA had similar proportions of patients with hepatitis B, hepatitis C, and non-viral etiology, almost half of patients enrolled in IMBRAVE150 had hepatitis B.

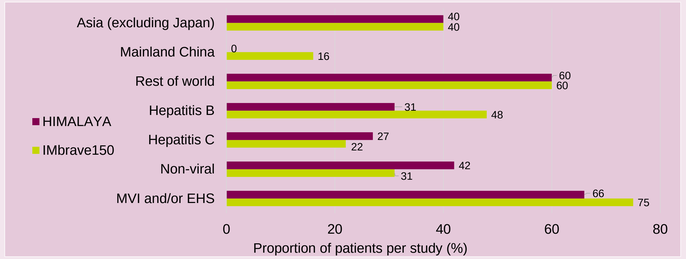


Figure 1. ITT patient characteristics by study for key TEMs

Abbreviations: A+B: Atezolizumab-bevacizumab, CI: Confidence interval, EHS: extrahepatic spread, HBV: Hepatitis B, HCV: Hepatitis C, HR: Hazard ratio, MVI: microvascular invasion, OS: Overall survival, STRIDE: Single tremelimumab regular interval durvalumab, TEM: treatment effect modifier

A twice longer median follow-up was also observed for STRIDE with a demonstrated long-term impact with a median follow-up of 33.2 vs 15.6 months for A+B, with no results available for IMbrave150 after 26.9 months (maximum length of follow-up for sorafenib).

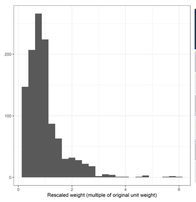
To address the heterogeneity observed in TEMs, a population-adjusted ITC between IMbrave150 and HIMALAYA was required. The NICE DSU TSD 18 was used to identify approach to use.[9]

- **Matching-adjusted indirect comparison (MAIC) performed through the sorafenib arms**

1. HIMALAYA trial was restricted to patients who matched the eligibility criteria of the IMbrave150 trial.
2. Individual patient data was used from HIMALAYA to match the baseline characteristics of IMbrave150 identified as TEMs. The individual weights were estimated through logistic regression ($\hat{w}_i$), adjusted for all TEMs except the albumin-bilirubin (ALBI) score due to a lack of reported data for IMbrave150.
   - All TEMs, imbalanced or not between trials, need to be in the reweighting model.[9]
   - The quality of the reweighting process was assessed through the effective sample size (ESS) and the distribution of weights. ESS being approximated by $\frac{(\sum_{i=1}^{N_{HIMALAYA}} \hat{w}_i)^2}{\sum_{i=1}^{N_{HIMALAYA}} \hat{w}_i^2}$.
   - The baseline characteristics of the reweighted HIMALAYA trial were compared to those of the IMbrave150 trial to confirm homogeneity between the two populations.
3. Outcomes estimation:
   - OS as primary endpoint, assessed through:
     - Reweighted Cox model following validation of proportional hazards assumption
     - Reweighted piecewise Cox model between 0-9 months (as done on original HIMALAYA data to further investigate observed delays in Kaplan-Meier curves separation[10]) and between 9-26.9 months (maximum length of follow-up for sorafenib in IMbrave150)
   - Objective response rate (ORR), grade 3/4 treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation were assessed through reweighted rates.

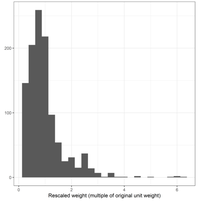
Results and interpretation

1. After restricting the population treated with STRIDE or sorafenib in the HIMALAYA trial, 766 patients out of 782 were considered for efficacy analyses and 747 out of 762 for safety analyses.
2. Following weighting:
   - An ESS of 514 patients was obtained for efficacy analyses, which represents 66% of the initial sample size from HIMALAYA. For safety, an ESS of 498 was obtained, corresponding to 65% of the original sample size.
   - The weights did not highlight any extreme individuals (see Figure 2 and Figure 3).



Rescaled weights – efficacy	
Min	0.1437
Q1	0.5702
Median	0.8309
Mean	1.0000
Q3	1.2076
Max	6.2042

Figure 2. Distributions of rescaled weights for efficacy



Rescaled weights – safety	
Min	0.1406
Q1	0.5597
Median	0.8349
Mean	1.0000
Q3	1.1768
Max	6.2922

Figure 3. Distributions of rescaled weights for safety

- The distribution of TEMs was balanced between the HIMALAYA and IMbrave150 populations after reweighting (see Figure 4), with higher proportions of patients having MVI, EHS, and hepatitis B, and a lower proportion of patients having hepatitis C compared to the original HIMALAYA population.

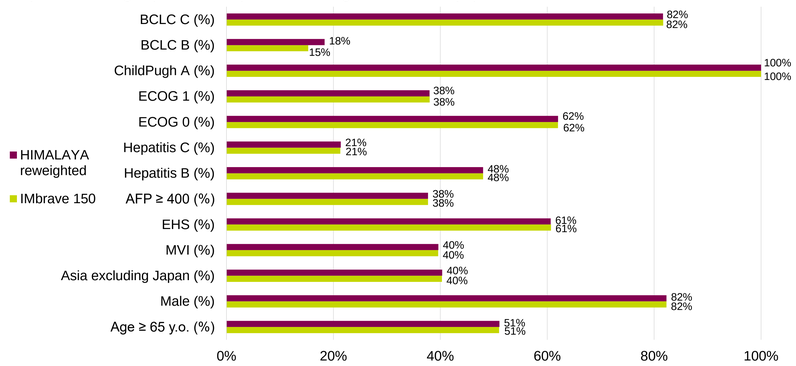


Figure 4. Distributions of key TEMs between reweighted HIMALAYA and IMbrave150

Abbreviations: AFP: alpha-foetoprotein, BCLC: Barcelona Clinic Liver Cancer, ECOG: Eastern Cooperative Oncology Group, EHS: extrahepatic spread, MVI: microvascular invasion

3. For OS:
   - The HR [95%CI] for STRIDE vs sorafenib in the original HIMALAYA trial and after reweighting were respectively 0.77 [0.66, 0.92] and 0.72 [0.60, 0.87].
   - Over the common follow-up available across the two trials (~2 years), no significant difference was found between STRIDE and A+B with a HR [95%CI] of 1.09 [0.80,1.48] overlapping a finding of no difference between treatments (HR=1; Table 2).
   - The piecewise analysis highlighted slight numeric differences in HR between the two periods, with a slight improvement in HIMALAYA and a slight decrease in IMbrave150 as reported in Table 2. The indirect comparison based on the piecewise HRs showed a trend in favor of a sustained effect of STRIDE vs A+B in the long-term.
   - No comparison was possible beyond 26.9 months due to the limited follow-up duration in IMbrave150.

Study	Comparison	All period HR [95% CI]	Piecewise - Before 9 months HR [95% CI]	Piecewise - 9 to 26.9 months HR [95% CI]
HIMALAY reweighted	STRIDE vs. sorafenib	0.72 [0.60, 0.87]	0.74 [0.55, 1.00]	0.69 [0.52, 0.92]
IMbrave150	A+B vs. sorafenib	0.66 [0.52, 0.85]	0.62 [0.44, 0.87]	0.72 [0.51, 1.03]
MAIC	**STRIDE vs. A+B**	**1.09 [0.80,1.48]**	**1.19 [0.76, 1.87]**	**0.96 [0.61, 1.51]**

Table 2. OS results from Cox model and piecewise analyses for the MAIC between STRIDE and A+B

Abbreviations: A+B: Atezolizumab-bevacizumab, CI: Confidence interval, HR: Hazard ratio, MAIC: Matching-adjusted indirect comparison, OS: Overall survival

No significant differences were observed for ORR, with an odds ratio (OR) [95% CI] of 1.18 [0.44, 3.21] for STRIDE vs A+B.

For safety, results of STRIDE were found to be numerically better than those of atezolizumab-bevacizumab:

- OR [95% CI] for grade 3/4 TEAEs was 0.73 [0.44, 1.19], indicating a potential trend towards a lower incidence for STRIDE.
- OR [95% CI] for AEs leading to treatment discontinuation was 0.49 [0.23, 1.04], suggesting a clearer trend towards a lower incidence for STRIDE.
- Notably, fewer treatment related bleeding events were observed in patients treated with STRIDE, with gastrointestinal bleeding observed in no patient treated with STRIDE in HIMALAYA vs 0.8% in the in the sorafenib arm) compared to 0.9% in patients in A+B arm from IMbrave150 and 1.3% for sorafenib).

Conclusion

This study indirectly compared the effectiveness and safety of STRIDE and A+B in treating patients with unresectable HCC as a first-line treatment. Despite long-term survivorship being largely excluded from these analyses, the comparison suggest similar efficacy outcomes are expected from these regimens until 2 years. Additional follow-up from IMbrave150 would be necessary to compare longer term effects. In addition, STRIDE showed a trend towards more favorable safety results compared to A+B, especially in terms of TEAEs leading to discontinuation and bleeding events.

It should be noted that the anchored MAIC analysis conducted had some limitations, including the possibility of unknown or additional TEMs not accounted for in this indirect comparison and factors that could not be adjusted, such as main portal vein thrombosis and patients from mainland China inclusion. Also, the difference in follow-up between the two trials meant that the longer-term data from HIMALAYA were not considered as part of the analysis.

Overall, STRIDE shows an unprecedented and consistent treatment effect while maintaining a favourable safety profile for patients with uHCC.