Poster 1

Four-year overall survival update from the Phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma

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Objective

- This updated analysis of the HIMALAYA study evaluated the overall survival (OS) and safety of the STRIDE (Single **T**remelimumab **R**egular **I**nterval **D**urvalumab) regimen or durvalumab monotherapy versus sorafenib with 4 years of follow-up in participants with unresectable hepatocellular carcinoma (uHCC)

Conclusions

- This 4-year updated analysis of the Phase 3 HIMALAYA study presents the longest follow-up to date in Phase 3 studies in uHCC
- Long-term OS benefit with STRIDE versus sorafenib was not driven by any particular subgroup of participants
  - Long-term OS benefit was observed for participants treated with STRIDE, regardless of response,* and OS rates were nearly 45% at 3 years and 36% at 4 years in participants who achieved disease control with STRIDE
- The STRIDE regimen maintained a tolerable and differentiated safety profile from other current uHCC therapies[1–4]
- These results reinforce the sustained, long-term OS benefit of STRIDE versus sorafenib and demonstrate unprecedented 3- and 4-year OS rates, with one in four alive at 4 years

*Response determined by Response Evaluation Criteria in Solid Tumors v1.1.

Plain language summary

Why did we perform this research?

- HCC is the most common type of liver cancer
- STRIDE is a treatment that combines a single dose of tremelimumab with multiple doses of durvalumab (these are types of immunotherapy called immune checkpoint inhibitors [ICIs]). The previous HIMALAYA study showed that participants who took STRIDE lived longer than those who took a medication called sorafenib
- Long-term survival is important for people with uHCC and as a measure of how well ICIs work in clinical studies
- We performed this research to assess long-term survival and safety for STRIDE or durvalumab compared with sorafenib after 4 years of follow-up

How did we perform this research?

Survival and safety data of STRIDE, durvalumab, and sorafenib were collected after 4 years of follow-up and assessed. The characteristics of long-term survivors (participants who lived at least 36 months) were also assessed

What were the findings of this research and what are the implications?

This is the longest follow-up to date in Phase 3 studies in uHCC. After 4 years of follow-up, participants who took STRIDE continued to live longer than those who took sorafenib, with one in four participants alive at 4 years. No new serious side effects occurred for participants treated with STRIDE with longer follow-up. Long-term survivors included people from all different subgroups. These results provide additional support for the use of STRIDE treatment in all people with uHCC

Where can I access more information?

Information about the medicines being used in this study and the people who could participate can be found here: https://clinicaltrials.gov/ct2/show/NCT03298451

Previous results from this study can be found here: https://evidence.nejm.org/doi/full/10.1056/EVIDoa2100070

Poster

Supplementary material

Plain language summary infographic

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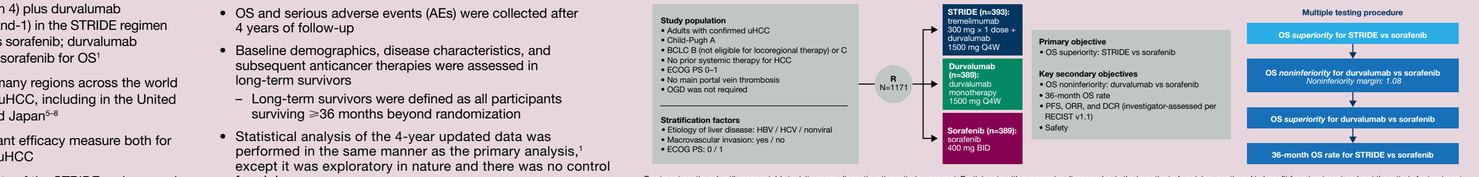
Introduction

- In the Phase 3 HIMALAYA study (NCT03298451) in uHCC, a single priming dose of tremelimumab (anti-cytotoxic T-lymphocyte-associated antigen 4) plus durvalumab (anti-programmed cell death ligand-1) in the STRIDE regimen significantly improved OS versus sorafenib; durvalumab monotherapy was noninferior to sorafenib for OS[1]
- STRIDE has been approved in many regions across the world for the treatment of adults with uHCC, including in the United States, the European Union, and Japan[5–8]
- Long-term survival is an important efficacy measure both for ICI studies and for people with uHCC
- Here, we report the OS and safety of the STRIDE regimen and durvalumab monotherapy versus sorafenib in participants with uHCC from the HIMALAYA study with 4 years of follow-up, the longest follow-up to date in Phase 3 studies in uHCC

Methods

- HIMALAYA was a randomized, open-label, multicenter, global, Phase 3 study (**Figure 1**)
- OS and serious adverse events (AEs) were collected after 4 years of follow-up
- Baseline demographics, disease characteristics, and subsequent anticancer therapies were assessed in long-term survivors
  - Long-term survivors were defined as all participants surviving ⩾36 months beyond randomization
- Statistical analysis of the 4-year updated data was performed in the same manner as the primary analysis,[1] except it was exploratory in nature and there was no control for alpha

Figure 1. Study design

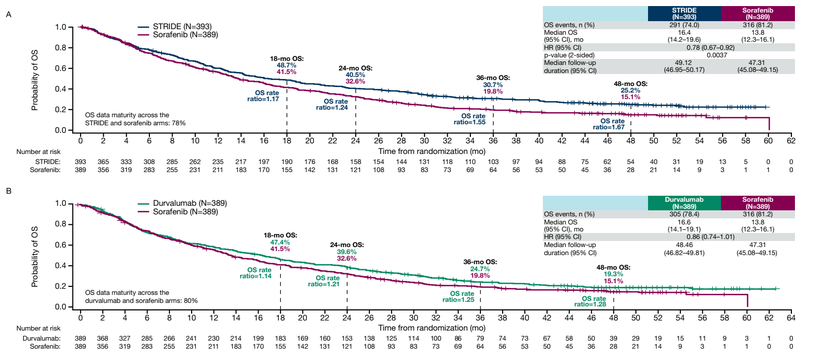


Treatment continued until unacceptable toxicity or any discontinuation criteria were met. Participants with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment.
The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Participants randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.
BCLC, Barcelona Clinic Liver Cancer; BID, twice a day; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; OGD, esophagogastroduodenoscopy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q4W, every 4 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; T75+D, tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W; uHCC, unresectable hepatocellular carcinoma.

Results and interpretation

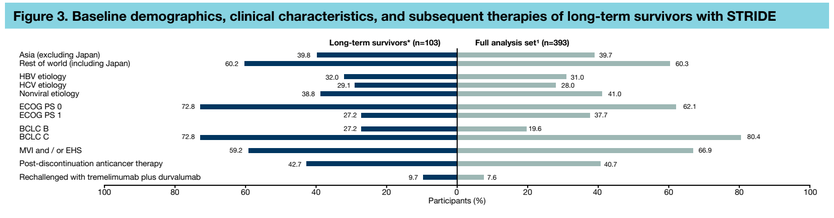
- The data cut-off for this updated analysis was January 23, 2023
- In total, 1171 participants were randomized to STRIDE (n=393), durvalumab (n=389), or sorafenib (n=389)
- Follow-up duration was approximately 4 years across treatment arms, and there was 78% OS data maturity for STRIDE (**Figure 2**)
- The OS hazard ratio versus sorafenib (0.78; 95% confidence interval, 0.67–0.92) and estimated 36-month OS rate (30.7%) for STRIDE were consistent with the primary analysis.[1] STRIDE demonstrated an unprecedented one in four survival rate at 4 years (**Figure 2A**)
- Durvalumab maintained OS noninferiority to sorafenib, consistent with the primary analysis[1] (**Figure 2B**)
- Baseline demographics, clinical characteristics, and subsequent therapies, including percentage of participants rechallenged with tremelimumab, for long-term survivors in the STRIDE arm were generally consistent with the full analysis set. All participants, regardless of subgroup, were represented in the long-term survivors; no subgroup drove long-term survival (**Figure 3**)
- OS was improved with STRIDE versus sorafenib, regardless of viral etiology (**Figure 4**)
- Long-term OS benefit was observed for participants treated with STRIDE, regardless of response (**Table 1**)
- OS rates were nearly 45% at 3 years and 36% at 4 years in participants who achieved disease control with STRIDE (**Figure 5**)
- No new serious treatment-related AEs occurred after the primary analysis[1] for STRIDE (17.5%; **Figure 6**)

Figure 2. Overall survival for (A) STRIDE and (B) durvalumab versus sorafenib in the 4-year updated analysis



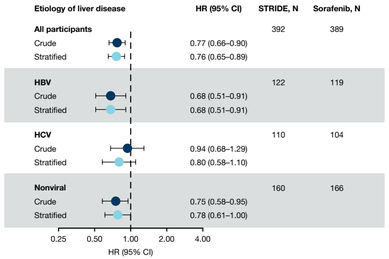
OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, etiology, ECOG PS, and MVI. The OS rate for STRIDE versus sorafenib at 36 months had a nominal 2-sided p-value of 0.0006. The noninferiority margin for durvalumab versus sorafenib was 1.08. Updated analysis data cut-off: January 23, 2023.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mo, month; MVI, macrovascular invasion; OS, overall survival; PS, performance status.

Figure 3. Baseline demographics, clinical characteristics, and subsequent therapies of long-term survivors with STRIDE



HBV: participants who tested positive for HBsAg or anti-HBcAb with detectable HBV DNA; HCV: participants who tested positive for HCV or had history of HCV infection; Nonviral: no active viral hepatitis identified. Viral etiology, MVI, and / or EHS determined at screening. BCLC determined at study entry.
*Long-term survivors were defined as participants surviving ⩾36 months beyond randomization. An exploratory, ad hoc analysis was performed to characterize the participants who experienced long-term survival at the updated data cut-off. Additional characteristics of long-term survivors are available in the supplementary information. Updated analysis data cut-off: January 23, 2023.
BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macrovascular invasion; PS, performance status.

Figure 4. Overall survival analysis for STRIDE versus sorafenib by viral etiology



The HR and 95% CI from the crude analysis are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and using the Efron method to control for ties. The HR and 95% CI from the stratified model are estimated from a stratified Cox proportional hazards model adjusting for EHS (no vs yes / missing) and ALBI grade (1 vs 2 / 3), and using the Efron method to control for ties. Analysis of OS by other subgroups is available in the supplementary information. Updated analysis data cut-off: January 23, 2023.
ALBI, albumin-bilirubin; CI, confidence interval; EHS, extrahepatic spread; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; OS, overall survival.

Table 1. Best objective response of long-term survivors

	ITT[1]		LTS*	
	STRIDE (N=393)	Sorafenib (N=389)	STRIDE (N=103)	Sorafenib (N=64)
BOR, n (%)				
CR	12 (3.1)	0	12 (11.7)	0
PR	67 (17.0)	20 (5.1)	41 (39.8)	10 (15.6)
SD	157 (39.9)	216 (55.5)	39 (37.9)	45 (70.3)
PD	141 (35.9)	118 (30.3)	10 (9.7)	6 (9.4)
NE	16 (4.1)	35 (9.0)	1 (1.0)	3 (4.7)
DCR,† n (%)	**236 (60.1)**	**236 (60.7)**	**92 (89.3)**	**55 (85.9)**

Responses were based on investigator assessment according to RECIST v1.1. Responses were confirmed. Response data for both the ITT and LTS were from the primary analysis (data cut-off: August 27, 2021).
*LTS were defined as participants surviving ⩾36 months beyond randomization. †Disease control was defined as CR, PR, or SD.
BOR, best objective response; CR, complete response; DCR, disease control rate; ITT, intent-to-treat; LTS, long-term survivors; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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Disclosures

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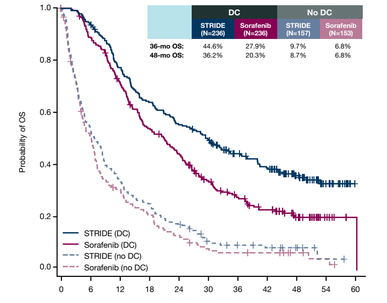
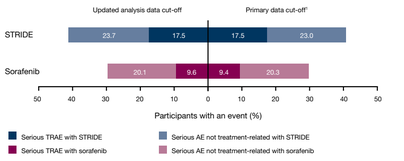
Figure 5. Overall survival by disease control (yes / no) for STRIDE versus sorafenib



Responses were based on investigator assessment according to RECIST v1.1. Disease control was defined as CR, PR, or SD. Updated analysis data cut-off: January 23, 2023.
CR, complete response; DC, disease control; mo, month; OS, overall survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Figure 6. Serious adverse events in the safety analysis set



AEs include AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy. Treatment-related was as described by the investigator. Additional safety data are available in the supplementary information. Updated analysis data cut-off: January 23, 2023.
AE, adverse event; TRAE, treatment-related AE.

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