Poster 714P

Impact of viral aetiology in the Phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma

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Objective

- This exploratory analysis evaluated the efficacy and safety of tremelimumab plus durvalumab in the STRIDE (Single Tremelimumab Regular Interval Durvalumab) regimen and durvalumab monotherapy versus sorafenib in subgroups of participants with unresectable hepatocellular carcinoma (uHCC) categorised by hepatitis B virus (HBV), hepatitis C virus (HCV) or nonviral aetiology in the Phase 3 HIMALAYA study

Conclusions

- HIMALAYA is a large, global study that is generally representative of the worldwide uHCC population and well balanced across treatment arms
- The relative safety profiles of STRIDE and durvalumab were consistent across aetiology subgroups
- For all aetiology subgroups, including the nonviral subgroup, there was a trend in overall survival (OS) benefit for STRIDE versus sorafenib (hazard ratios [HR] <1), and durvalumab showed consistent treatment effects versus sorafenib, when adjusted for imbalances in prognostic factors in the HCV subgroup
- HIMALAYA is currently the only Phase 3 study to show a survival benefit of immunotherapy in participants with nonviral HCC
- These results support the benefits of STRIDE in participants with uHCC, irrespective of underlying viral or nonviral aetiology

Plain language summary

Why did we perform this research?

- Hepatocellular carcinoma (HCC) is the most common type of liver cancer. HCC is frequently caused by infections with HBV or HCV
- The STRIDE regimen is a treatment that combines a single dose of tremelimumab with multiple doses of durvalumab (types of immunotherapy). The previous HIMALAYA study showed that participants who took STRIDE lived longer than those who took a medication called sorafenib
- We performed this research to see whether the cause of HCC, either HBV, HCV or other factors, affected how well the STRIDE regimen or durvalumab alone worked for treating HCC

How did we perform this research?

We examined how long groups of participants with HBV, HCV or no viral hepatitis infection lived after being treated with the STRIDE regimen, durvalumab alone or sorafenib while participating in the HIMALAYA study

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

Participants who took the STRIDE regimen lived longer than those who took sorafenib, whether they had HBV, HCV or no viral hepatitis infection. The cause of HCC did not affect how well durvalumab alone worked. Therefore, these treatments could be used to treat HCC whether caused by a viral hepatitis infection or other factors

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/10.1056/EVIDoa2100070

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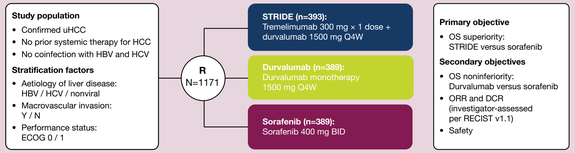
Introduction

- In the Phase 3 HIMALAYA study (NCT03298451), the STRIDE regimen significantly improved OS versus sorafenib, and durvalumab monotherapy was noninferior to sorafenib, in participants with uHCC[1]
- Approximately 75% of HCC cases worldwide can be attributed to HBV or HCV, with HBV being the dominant HCC aetiology in Asia[2]
- Viral aetiology is associated with hepatic impairment in HCC development and may influence immunotherapy activity[3,4]
- A recent meta-analysis suggested that immune checkpoint inhibitors may not benefit people with nonviral HCC, particularly those with non-alcoholic steatohepatitis[4]
- Herein, we report efficacy and safety outcomes in subgroups of participants by viral aetiology from the HIMALAYA study

Methods

- HIMALAYA is a randomised, open-label, multicentre, global, Phase 3 trial (Figure 1)

Figure 1. HIMALAYA study design



BID, twice daily; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; ORR, objective response rate; OS, overall survival; Q4W, every 4 weeks; R, randomised; RECIST, Response Evaluation Criteria In Solid Tumours; uHCC, unresectable hepatocellular carcinoma

- Randomisation was stratified by viral aetiology status, determined at screening:
  - **HBV:** positive for hepatitis B surface antigen and / or anti-hepatitis B core antibodies with detectable HBV DNA
  - **HCV:** positive for anti-HCV antibodies, detectable HCV RNA or history of HCV infection
  - **Nonviral:** no detectable hepatitis virus
  - People coinfected with HBV and HCV were excluded from the study
- A pre-planned exploratory analysis of OS and secondary efficacy endpoints in aetiology subgroups was performed
- OS HRs were calculated using a Cox proportional hazards model
- As subgroups were not sized for formal comparisons, and no multiplicity adjustments were made, a post hoc multivariate analysis was used to identify chance imbalances in key prognostic factors that may bias estimated treatment effects

Results and interpretation

Study population

- Of 1171 randomised participants, 360 had HBV, 321 had HCV and 490 had nonviral aetiology
- Most baseline demographic and disease characteristics were generally well balanced across treatment arms within the HBV and nonviral subgroups (Table 1)
- In the HCV subgroup, extrahepatic spread (EHS) was more frequent in the STRIDE arm than in the durvalumab and sorafenib arms, and albumin-bilirubin (ALBI) score >2 was more frequent for STRIDE and durvalumab than for sorafenib (Table 1)
- Multivariate analysis confirmed imbalances in the HCV subgroup in the two prognostic variables: EHS and ALBI

Safety

- There were 354 participants with HBV, 315 with HCV and 481 with nonviral aetiology who received at least one dose of study treatment and were included in the safety analysis (Table 2)
- The incidences of treatment-related adverse events (TRAEs) or grade 3 or 4 TRAEs were generally lower for STRIDE and durvalumab than for sorafenib across aetiology subgroups

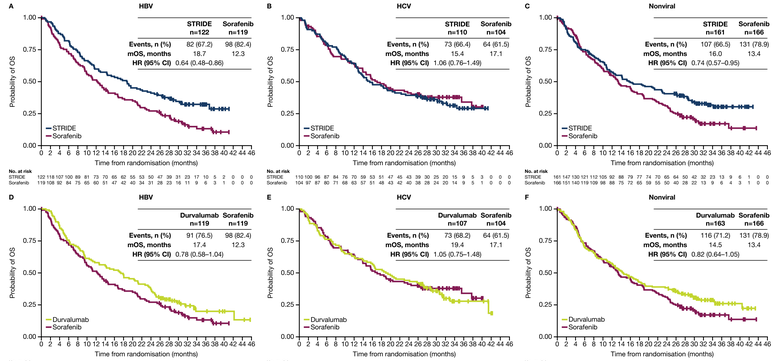
Overall survival

- OS was improved with STRIDE versus sorafenib in the HBV subgroup (HR, 0.64), similar to the full analysis set (HR, 0.78),[1] but not in the HCV subgroup (HR, 1.06; Figure 2)
- In the nonviral subgroup, OS was improved with STRIDE versus sorafenib (HR, 0.74) similar to the full analysis set (HR, 0.78[1]; Figure 2)
- The treatment effect of durvalumab versus sorafenib was also similar to the full analysis set (HR, 0.86)[1] in the HBV (HR, 0.78) and nonviral (HR, 0.82) subgroups but not in the HCV subgroup (HR, 1.05; Figure 2)
- A stratified Cox proportional hazards model accounting for the imbalances in EHS and ALBI of the HCV subgroup was applied to all subgroups and resulted in an adjusted OS HR that favoured STRIDE versus sorafenib in the HCV subgroup (HR, 0.89; Figure 3)
- Application of the model to the full analysis set did not meaningfully impact OS HRs for STRIDE or durvalumab versus sorafenib, affirming that the overall study was well balanced
- Application of the model to the HBV and nonviral subgroups did not meaningfully impact OS HRs for STRIDE or durvalumab versus sorafenib, and OS HRs continued to favour STRIDE, affirming that these factors were balanced and demonstrating a consistency of treatment effect across aetiologies

Secondary efficacy endpoints

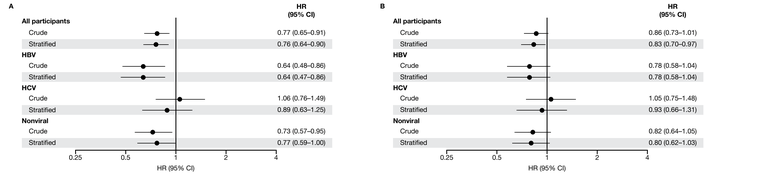
- In all aetiology subgroups, objective response rates (ORRs) were numerically higher in the STRIDE and durvalumab arms than in the sorafenib arm (Table 3)
- The HCV subgroup had the highest ORR across treatment arms
- ORR for participants with viral hepatitis (HBV or HCV) was highest in the STRIDE arm
- Disease control rates for STRIDE and durvalumab were generally similar across aetiology subgroups

Figure 2. Overall survival for STRIDE (A–C) and durvalumab (D–F) versus sorafenib in aetiology subgroups



The HR and 95% CI are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and using the Efron method to control for ties
CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; mOS, median OS; OS, overall survival

Figure 3. Stratified overall survival analysis for STRIDE* (A) and durvalumab (B) versus sorafenib



The HR and 95% CI from the crude analysis are estimated from an unstratified Cox proportional hazards model 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 versus yes / missing) and ALBI grade (1 versus 2 / 3) and using the Efron method to control for ties
*One participant from the nonviral subgroup STRIDE arm was excluded due to missing ALBI score
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. Baseline demographic and disease characteristics in aetiology subgroups

	HBV (n=360)			HCV (n=321)			Nonviral (n=490)		
Parameter	**STRIDE (n=122)**	**Durvalumab (n=119)**	**Sorafenib (n=119)**	**STRIDE (n=110)**	**Durvalumab (n=107)**	**Sorafenib (n=104)**	**STRIDE (n=161)**	**Durvalumab (n=163)**	**Sorafenib (n=166)**
Median age (range), years	59.0 (28–78)	57.0 (24–79)	60.0 (30–81)	65.0 (42–84)	64.0 (41–88)	64.5 (40–84)	70.0 (22–86)	68.0 (20–86)	67.0 (18–88)
Asia region,* n (%)	98 (80.3)	97 (81.5)	100 (84.0)	27 (24.5)	31 (29.0)	21 (20.2)	31 (19.3)	39 (23.9)	35 (21.1)
ECOG PS, n (%)									
0	90 (73.8)	81 (68.1)	80 (67.2)	64 (58.2)	65 (60.7)	65 (62.5)	92 (57.1)	98 (60.1)	94 (56.6)
1	32 (26.2)	38 (31.9)	39 (32.8)	46 (41.8)	42 (39.3)	38 (36.5)	69 (42.9)	65 (39.9)	71 (42.8)
BCLC score, n (%)									
B	23 (18.9)	25 (21.0)	13 (10.9)	19 (17.3)	27 (25.2)	26 (25.0)	35 (21.7)	28 (17.2)	27 (16.3)
C	99 (81.1)	94 (79.0)	106 (89.1)	91 (82.7)	80 (74.8)	78 (75.0)	126 (78.3)	135 (82.8)	139 (83.7)
MVI, n (%)	30 (24.6)	28 (23.5)	28 (23.5)	30 (27.3)	26 (24.3)	26 (25.0)	43 (26.7)	40 (24.5)	46 (27.7)
EHS, n (%)	71 (58.2)	71 (59.7)	70 (58.8)	59 (53.6)	43 (40.2)	42 (40.4)	79 (49.1)	98 (60.1)	91 (54.8)
ALBI score, n (%)									
1	74 (60.7)	73 (61.3)	71 (59.7)	48 (43.6)	43 (40.2)	50 (48.1)	95 (59.0)	82 (50.3)	82 (49.4)
2 or 3	48 (39.3)	46 (38.7)	48 (40.3)	62 (56.4)	64 (59.8)	54 (51.9)	65 (40.4)	81 (49.7)	84 (50.6)

*Excludes Japan
ALBI, albumin-bilirubin; 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

Table 2. Safety in aetiology subgroups

	HBV (n=354)			HCV (n=315)			Nonviral (n=481)		
Participants with event, n (%)	**STRIDE (n=122)**	**Durvalumab (n=117)**	**Sorafenib (n=115)**	**STRIDE (n=108)**	**Durvalumab (n=107)**	**Sorafenib (n=100)**	**STRIDE (n=158)**	**Durvalumab (n=164)**	**Sorafenib (n=159)**
Any AE	116 (95.1)	96 (82.1)	108 (93.9)	105 (97.2)	99 (92.5)	97 (97.0)	157 (99.4)	150 (91.5)	152 (95.6)
Any TRAE	88 (72.1)	57 (48.7)	98 (85.2)	82 (75.9)	64 (59.8)	85 (85.0)	124 (78.5)	81 (49.4)	134 (84.3)
Any grade 3 or 4 AE	53 (43.4)	35 (29.9)	52 (45.2)	54 (50.0)	47 (43.9)	57 (57.0)	89 (56.3)	62 (37.8)	87 (54.7)
Any grade 3 or 4 TRAE	26 (21.3)	14 (12.0)	32 (27.8)	26 (24.1)	19 (17.8)	39 (39.0)	48 (30.4)	17 (10.4)	67 (42.1)
Any serious TRAE	16 (13.1)	9 (7.7)	7 (6.1)	12 (11.1)	11 (10.3)	9 (9.0)	40 (25.3)	12 (7.3)	19 (11.9)
Any TRAE leading to death	0	0	1 (0.9)	2 (1.9)	0	0	7 (4.4)	0	2 (1.3)
Any TRAE leading to discontinuation	4 (3.3)	2 (1.7)	5 (4.3)	8 (7.4)	8 (7.5)	18 (18.0)	20 (12.7)	6 (3.7)	18 (11.3)
Any imAE	38 (31.1)	13 (11.1)	6 (5.2)	39 (36.1)	30 (28.0)	14 (14.0)	62 (39.2)	21 (12.8)	10 (6.3)

AE, adverse event; HBV, hepatitis B virus; HCV, hepatitis C virus; imAE, immune-mediated adverse event; TRAE, treatment-related adverse event

Table 3. Secondary efficacy endpoints in aetiology subgroups

	HBV (n=360)			HCV (n=321)			Nonviral (n=490)		
Parameter	**STRIDE (n=122)**	**Durvalumab (n=119)**	**Sorafenib (n=119)**	**STRIDE (n=110)**	**Durvalumab (n=107)**	**Sorafenib (n=104)**	**STRIDE (n=161)**	**Durvalumab (n=163)**	**Sorafenib (n=166)**
ORR, n (%)	26 (21.3)	17 (14.3)	6 (5.0)	39 (35.5)	24 (22.4)	10 (9.6)	29 (18.0)	31 (19.0)	10 (6.0)
DCR, n (%)	72 (59.0)	59 (49.6)	58 (48.7)	72 (65.5)	62 (57.9)	73 (70.2)	92 (57.1)	92 (56.4)	105 (63.3)
Median TTR (IQR), months	1.91 (1.81–3.78)	1.94 (1.84–3.71)	2.83 (1.91–3.88)	3.55 (1.87–5.42)	1.97 (1.87–3.75)	7.33 (1.87–11.01)	2.07 (1.91–3.78)	3.68 (1.87–5.62)	3.65 (1.81–3.81)
Median DoR (IQR), months	25.69 (1.99–NR)	9.46 (3.84–NR)	17.00 (3.52–28.55)	13.54 (5.55–NR)	12.94 (6.36–27.43)	15.74 (4.76–25.99)	13.21 (5.65–NR)	13.83 (7.43–NR)	6.01 (4.01–18.43)

DCR, disease control rate; DoR, duration of response; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; ORR, objective response rate; TTR, time to response; NR, not reached

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Disclosures

SLC, BS, RKK, J-WP, TY, A-LC, MR, MY, ARH and GKA-A report consulting for advisory fees from AstraZeneca. BS, PS and TY report honoraria from AstraZeneca. EA reports participation on a Data Safety Monitoring Board or Advisory Board for AstraZeneca. DR, MM and AN are employees of and /or shareholders in AstraZeneca. RKK, TK, SA and GKA-A report research funding from AstraZeneca. MK, JF and AF have no AstraZeneca-related conflicts of interest to declare. Full author disclosures are available with the published abstract.

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