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ORIGINAL ARTICLE

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

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Background: In the phase III HIMALAYA study (NCT03298451) in unresectable hepatocellular carcinoma (uHCC), STRIDE (Single Tremelimumab Regular Interval Durvalumab) significantly improved overall survival (OS) versus sorafenib; durvalumab monotherapy was noninferior to sorafenib for OS. Results reported herein are from a 4-year updated OS analysis of HIMALAYA.

Patients and methods: Participants with uHCC and no previous systemic treatment were randomized to STRIDE ($n = 393$), durvalumab ($n = 389$), or sorafenib ($n = 389$). The updated data cut-off was 23 January 2023. OS and serious adverse events (AEs) were assessed. Additionally, baseline characteristics and subsequent therapies were analyzed in long-term survivors ($\geq$36 months beyond randomization).

Results: For STRIDE, durvalumab, and sorafenib, median [95% confidence interval (CI)] follow-up was 49.12 months (46.95-50.17 months), 48.46 months (46.82-49.81 months), and 47.31 months (45.08-49.15 months), respectively. OS hazard ratio (95% CI) for STRIDE versus sorafenib was 0.78 (0.67-0.92). The 36-month OS rate for STRIDE was 30.7% versus 19.8% for sorafenib. The 48-month OS rate remained higher for STRIDE at 25.2%, versus 15.1% for sorafenib. The long-term OS benefit of STRIDE was observed across clinically relevant subgroups and was further improved in participants who achieved disease control. Long-term survivors with STRIDE ($n = 103$) included participants across clinically relevant subgroups, and 57.3% (59/103) had no reported subsequent anticancer therapy. No new serious treatment-related AEs occurred with STRIDE from the primary analysis (17.5%; 68/388). Durvalumab maintained OS noninferiority to sorafenib and no late-onset safety signals were identified.

Conclusions: These data represent the longest follow-up to date in phase III studies in uHCC. The unprecedented 3- and 4-year OS rates reinforce the sustained long-term OS benefit of STRIDE versus sorafenib. STRIDE maintained a tolerable yet differentiated safety profile from other current uHCC therapies. Results continue to support the long-term benefits of STRIDE in a diverse population, reflective of uHCC globally.

Key words: durvalumab, tremelimumab, immune checkpoint inhibitor, overall survival, unresectable hepatocellular carcinoma

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INTRODUCTION

Liver cancer is the third most common cause of cancer-related death worldwide.[1] Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer.[2] Until 2020, first-line treatment for unresectable HCC (uHCC) was limited to the tyrosine kinase inhibitors sorafenib and lenvatinib.[3,4] Immune checkpoint inhibitor (ICI)-based combination regimens, including STRIDE (Single Tremelimumab Regular Interval Durvalumab), atezolizumab plus bevacizumab, and camrelizumab plus rivoceranib, significantly improved OS versus sorafenib, in randomized phase III clinical studies in uHCC.[5-7] The STRIDE regimen has gained approval globally as first-line treatment for uHCC.[8-12] Durvalumab monotherapy has also been approved for the treatment of adults with uHCC in Japan and the European Union.[12,13]

The phase III HIMALAYA study (NCT03298451) evaluated the STRIDE regimen, a dual ICI combination, and durvalumab monotherapy versus sorafenib in participants with uHCC who had not been previously treated with systemic therapy.[6] The STRIDE regimen consists of treatment with a single priming dose of tremelimumab, an anti-cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4) antibody, plus durvalumab, an anti-programmed cell death ligand-1 (anti-PD-L1) antibody, at cycle 1 followed by durvalumab monotherapy every 4 weeks thereafter.[6] The HIMALAYA study enrolled a diverse population of participants,[6] reflective of the global uHCC population, and was balanced across etiologies of liver disease. In the primary analysis of HIMALAYA, with a median duration of follow-up of ∼33 months (data cut-off: 27 August 2021), the STRIDE regimen demonstrated a significant improvement in OS versus sorafenib, with an OS hazard ratio (HR) of 0.78 [96.02% confidence interval (CI) 0.65-0.93; $P = 0.0035$].[6] Durvalumab monotherapy was noninferior to sorafenib for OS (HR 0.86, 95.67% CI 0.73-1.03, noninferiority margin 1.08).[6] Although not formally tested, there was a nominally statistically significant improvement in the 36-month OS rate with STRIDE (30.7%) versus sorafenib (20.2%; $P = 0.0029$).[6] The STRIDE regimen demonstrated a tolerable and differentiated safety profile from other currently available uHCC therapies.[5,6,14] The incidence, frequency, and severity of adverse events (AEs) with STRIDE and durvalumab were consistent with the known safety profiles of each agent, and the frequency of treatment-related AEs was lower with STRIDE and durvalumab monotherapy than with sorafenib.[6] Furthermore, the majority of immune-mediated AEs with STRIDE or durvalumab were observed within the first 3 months after treatment initiation.[15]

This 4-year follow-up analysis of the HIMALAYA study reports OS and safety of the STRIDE regimen and durvalumab monotherapy versus sorafenib, including characterization of long-term survivors. This is the longest follow-up to date in a pivotal phase III study in uHCC.

PATIENTS AND METHODS

Study design and participants

The HIMALAYA study was a randomized, open-label, multicenter, global, phase III study.[6] The study methodology has been described in detail in the primary report.[6]

The HIMALAYA study was conducted in accordance with the Declaration of Helsinki and was consistent with the International Council for Harmonisation and Good Clinical Practice guidelines, applicable regulatory requirements, and the AstraZeneca Bioethics Policy. Written informed consent was obtained from participants or their legal representatives before participation.

Participants were randomly assigned to receive 300 mg of tremelimumab (one dose) plus 1500 mg of durvalumab every 4 weeks (STRIDE), 1500 mg of durvalumab monotherapy every 4 weeks, or 400 mg of sorafenib twice daily. Participants in all treatment arms who had disease progression but who, in the investigator's opinion, continued to receive benefit from their assigned treatment and who met the criteria for treatment in the setting of progressive disease, could continue to receive their assigned treatment. Participants in the STRIDE arm who had disease progression during the phase of the STRIDE regimen when durvalumab was given as monotherapy, but who, in the investigator's opinion, were benefiting from treatment and who met the retreatment criteria, were eligible for one-time retreatment with tremelimumab (300 mg) plus continuous durvalumab.[6]

Outcomes

The primary objective of the HIMALAYA study was to assess OS with STRIDE versus sorafenib for superiority. The key secondary objectives of the HIMALAYA study were to assess OS with durvalumab versus sorafenib for noninferiority, then superiority, followed by the 36-month OS rate for STRIDE versus sorafenib, as part of a multiple testing procedure (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.02.005). Other secondary objectives included OS rates at 18 and 24 months, progression-free survival, objective response rate, and disease control rate, per investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, as well as safety. Efficacy and safety results from the primary analysis (considered final for formal comparisons) were reported previously.[6]

Four-year updated analysis

OS follow-up data from participants enrolled in HIMALAYA were collected until the 23 January 2023 data cut-off. An exploratory analysis of OS with 4 years of OS follow-up from the start of the study was carried out, including assessment of OS HRs for STRIDE and durvalumab versus sorafenib, OS medians, OS rates at 18, 24, 36, and 48 months, and OS by prespecified subgroups.

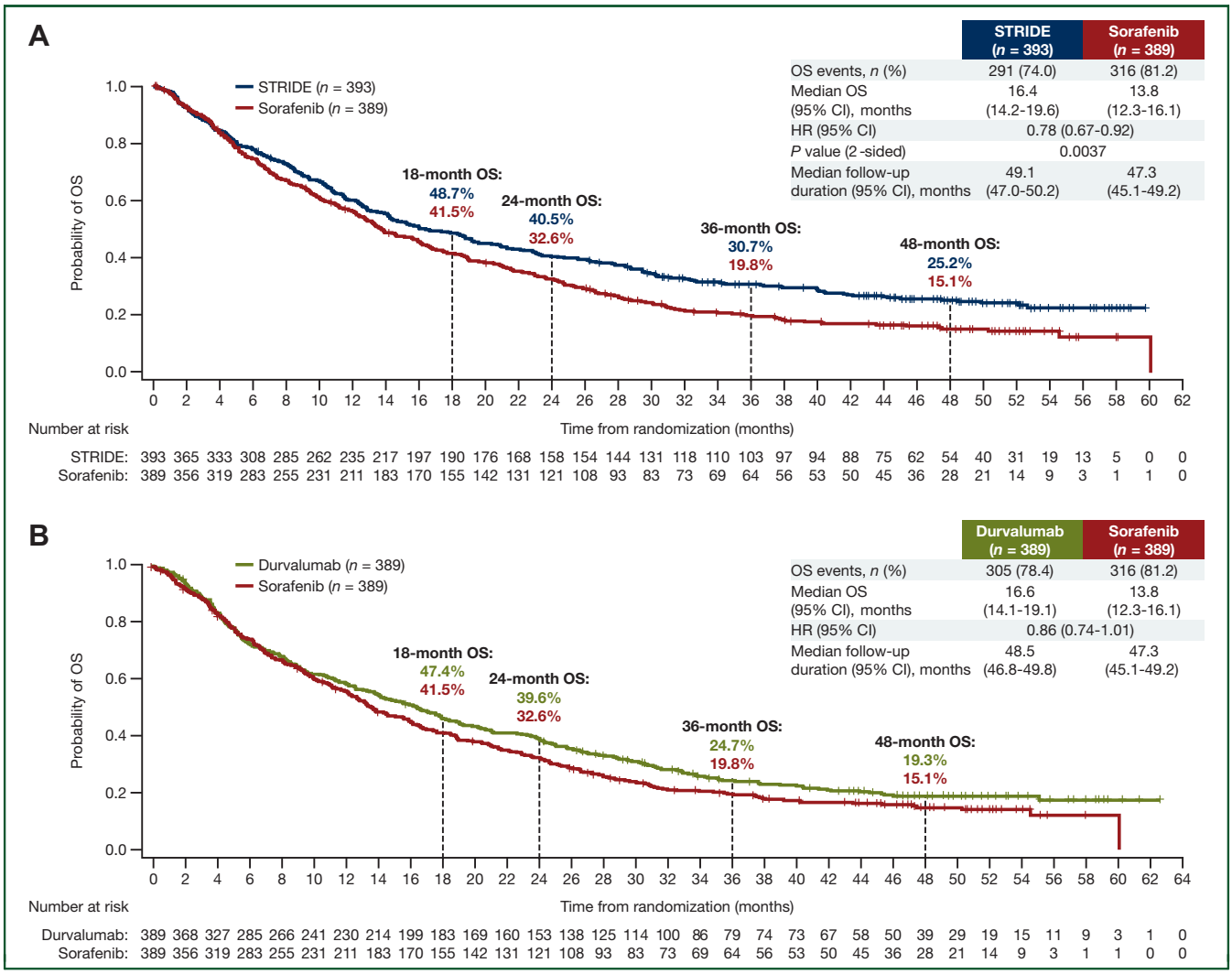

Figure 1. (A) OS for STRIDE vs sorafenib and (B) OS for durvalumab vs sorafenib in the 4-year updated analysis. OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, etiology of liver disease (hepatitis B or C virus or other/nonviral), ECOG performance status (0 or 1), and macrovascular invasion (yes or no). The OS rate for STRIDE versus sorafenib at 36 months had an exploratory two-sided *P* value of 0.0006. Noninferiority margin for durvalumab versus sorafenib was 1.08. Updated analysis data cut-off: 23 January 2023.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

In addition, OS from the 23 January 2023 data cut-off was assessed by disease control (yes or no), which included participants with a best objective response of complete response (CR), partial response (PR), or stable disease (SD).

Long-term survivors were defined as all participants surviving ≥36 months since randomization. Exploratory analyses of baseline demographics, disease characteristics, and subsequent anticancer therapies were carried out in the long-term survivors' subgroup. The proportion of long-term survivors in each best objective response category [CR, PR, SD, or progressive disease (PD)] was assessed. Objective responses were classified based on investigator assessment according to RECIST v1.1. Objective response and disease control data were collected at the primary analysis data cut-off (27 August 2021).

Serious AEs were also collected and assessed with 4 years of follow-up from the start of the study (23 January 2023 data cut-off).

Statistical analysis

In this exploratory analysis, OS was assessed in the intent-to-treat population, which included all randomized participants. OS was analyzed using a stratified log-rank test, and OS HRs and CIs were calculated using a Cox proportional hazards model adjusting for treatment, etiology of liver disease, Eastern Cooperative Oncology Group (ECOG) performance status, and macrovascular invasion. OS rates were estimated using the Kaplan—Meier technique.

Serious AEs were assessed in the safety analysis set, which included all participants who received at least one dose of study treatment, and summarized descriptively.

RESULTS

Study population

In the HIMALAYA study, 1171 participants were randomized to receive the STRIDE regimen (n = 393), durvalumab

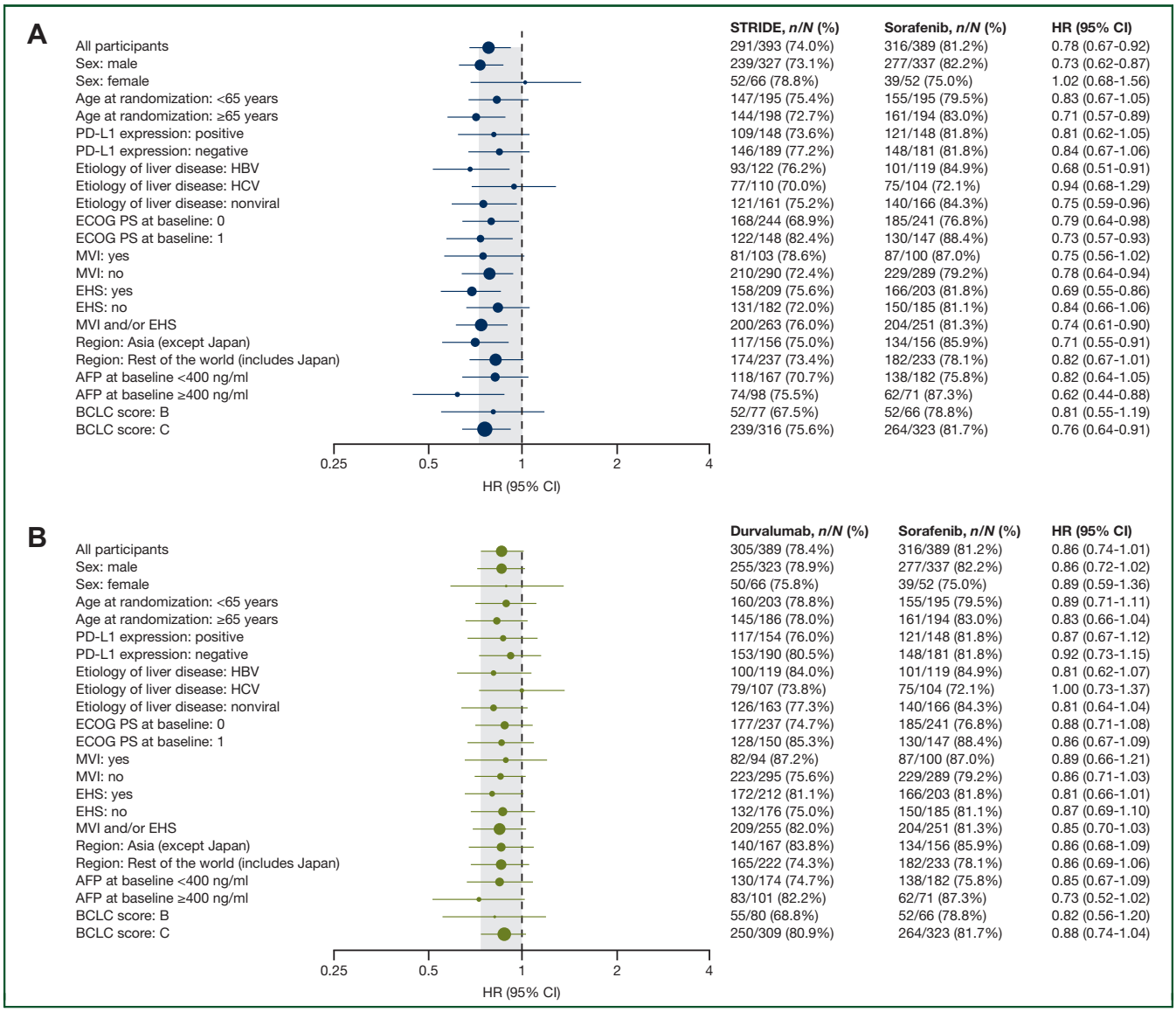

Figure 2. (A) OS for STRIDE vs sorafenib and (B) OS for durvalumab vs sorafenib, by subgroup. For all participants, OS HRs and 95% CIs were calculated using a Cox proportional hazards model, adjusting for treatment, etiology of liver disease (hepatitis B or C virus or other/nonviral), ECOG performance status (0 or 1), and macrovascular invasion (yes or no). For the subgroup analysis, OS HRs and 95% CIs are estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and using the Efron method to control for ties. Updated analysis data cut-off: 23 January 2023.

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; MVI, macrovascular invasion; OS, overall survival; PD-L1, programmed cell death ligand-1; PS, performance status; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

monotherapy ($n = 389$), or sorafenib ($n = 389$).[6] Baseline demographics and disease characteristics were generally balanced between treatment arms.[6]

At the 4-year updated analysis data cut-off, the OS data maturity (the proportion of OS events out of the number of participants at risk for the OS analysis) was 74.0% for STRIDE, 78.4% for durvalumab, and 81.2% for sorafenib. The median (95% CI) follow-up duration was 49.12 months (46.95-50.17 months) for STRIDE, 48.46 months (46.82-49.81 months) for durvalumab, and 47.31 months (45.08-49.15 months) for sorafenib. In the STRIDE arm, 24.4% (96/393) of participants remained in follow-up and 7.2% (28/389) continued receiving treatment (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.02.005). In the durvalumab arm, 20.3% (79/389) of participants remained in follow-up and 6.2% (24/386) continued receiving treatment. In the sorafenib arm, 14.4% (56/389) of participants remained in follow-up and 2.6% (10/374) continued receiving treatment.

Among participants who received at least one dose of the study drug, the percentage of participants who were treated beyond progression was 47.4% (184/388) for STRIDE, 47.9% (186/388) for durvalumab, and 51.3% (192/374) for sorafenib (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.02.005). The percentage of participants re-treated with tremelimumab plus

Table 1. Baseline demographics and disease characteristics of long-term survivors

Characteristic	STRIDE (n = 103)	Durvalumab (n = 79)	Sorafenib (n = 64)
Sex (male), n (%)	90 (87.4)	64 (81.0)	54 (84.4)
Age, median (range), years	66.0 (32-86)	63.0 (35-86)	64.0 (32-84)
Region, n (%)			
Asia (excluding Japan)	41 (39.8)	30 (38.0)	23 (35.9)
Rest of the world (including Japan)	62 (60.2)	49 (62.0)	41 (64.1)
Etiology of liver disease,[a,b] n (%)			
HBV	33 (32.0)	25 (31.6)	16 (25.0)
HCV	30 (29.1)	23 (29.1)	26 (40.6)
Nonviral	40 (38.8)	31 (39.2)	22 (34.4)
ECOG PS, n (%)			
0	75 (72.8)	58 (73.4)	51 (79.7)
1	28 (27.2)	19 (24.1)	13 (20.3)
2	0	2 (2.5)	0
BCLC,[c] n (%)			
B	28 (27.2)	23 (29.1)	14 (21.9)
C	75 (72.8)	56 (70.9)	50 (78.1)
Child–Pugh class/score, n (%)			
A/5	87 (84.5)	61 (77.2)	54 (84.4)
A/6	15 (14.6)	17 (21.5)	9 (14.1)
B/7	1 (1.0)	1 (1.3)	1 (1.6)
MVI,[b] n (%)	19 (18.4)	10 (12.7)	11 (17.2)
EHS,[b] n (%)	52 (50.5)	38 (48.1)	27 (42.2)
MVI and/or EHS,[b] n (%)	61 (59.2)	44 (55.7)	37 (57.8)
AFP,[b] n (%)			
<400 ng/ml	69 (67.0)	60 (75.9)	53 (82.8)
≥400 ng/ml	33 (32.0)	18 (22.8)	10 (15.6)

AFP, alpha-fetoprotein; 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; STRIDE, Single Tremelimumab Regular Interval Durvalumab.
[a]HBV: participants who tested positive for HBsAg and/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.
[b]Determined at screening.
[c]Determined at study entry. Updated analysis data cut-off: 23 January 2023.

durvalumab in the STRIDE arm was 8.0% (31/388; Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.02.005). After study treatment discontinuation, 42.2% (166/393), 44.0% (171/389), and 45.8% (178/389) of participants in the STRIDE, durvalumab, and sorafenib arms, respectively, reported at least one subsequent anticancer therapy (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.02.005).

Efficacy

There were 291 (74.0%) deaths in the STRIDE arm and 316 (81.2%) deaths in the sorafenib arm. The OS HR (95% CI) for STRIDE versus sorafenib was 0.78 (0.67-0.92; Figure 1A), similar to the OS HR reported at the time of the primary analysis.[6] The survival rates at 18 and 24 months were 48.7% and 40.5%, respectively, in the STRIDE arm, and 41.5% and 32.6%, respectively, in the sorafenib arm. The survival rate at 36 months was 30.7% for STRIDE and 19.8% for sorafenib (P = 0.0006). The survival rate at 48 months was 25.2% for STRIDE and 15.1% for sorafenib.

There were 305 (78.4%) deaths in the durvalumab arm. The OS HR (95% CI) for durvalumab versus sorafenib was 0.86 (0.74-1.01; Figure 1B). The survival rates at 18, 24, 36, and 48 months were 47.4%, 39.6%, 24.7%, and 19.3%, respectively, in the durvalumab arm.

OS in the prespecified subgroups favored STRIDE over sorafenib (Figure 2A), including etiology of liver disease (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2024.02.005). Additional analyses accounting for imbalances within subgroups of two key prognostic factors, extrahepatic spread and albumin–bilirubin,[16] confirmed improvement in OS with STRIDE versus sorafenib across all viral and nonviral etiologies (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2024.02.005). Durvalumab maintained noninferiority versus sorafenib across subgroups (Figure 2B).

Characterization of long-term survivors

There were 103 long-term survivors in the STRIDE arm, 79 long-term survivors in the durvalumab arm, and 64 long-term survivors in the sorafenib arm. Baseline demographics and disease characteristics of long-term survivors are presented in Table 1 and Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2024.02.005. Among participants who received at least one dose of study drug, the percentage of long-term survivors who continued treatment beyond progression was 38.8% (40/103) of participants in the STRIDE arm, 49.4% (39/79) of participants in the durvalumab arm, and 59.4% (38/63) of participants in the sorafenib arm (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.02.005). The majority of long-term survivors in the STRIDE arm reported no subsequent anticancer therapy (57.3%, 59/103; Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.02.005). Conversely, the majority of long-term survivors in the sorafenib arm reported subsequent anticancer therapy (56.3%, 36/64; Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.02.005), and this proportion was higher than in the full analysis set (45.8%, 178/389; Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.02.005). Furthermore, the percentage of long-term surviors who were retreated with tremelimumab plus durvalumab in the STRIDE arm was 9.7% (10/103; Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.02.005), which was similar in proportion to the full analysis set.

Participants in the STRIDE arm of the full analysis set who achieved disease control (CR, PR, or SD) demonstrated higher 3- and 4-year OS rates (44.6% and 36.2%, respectively) compared with those in the sorafenib arm (27.9% and 20.3%, respectively; Figure 3). Among the long-term survivors treated with STRIDE, 51.5% had an objective response by RECIST v1.1 (11.7% had a confirmed CR and 39.8% had a confirmed PR), 37.9% had a best objective response of SD, and 9.7% had a best objective response of PD (Table 2).

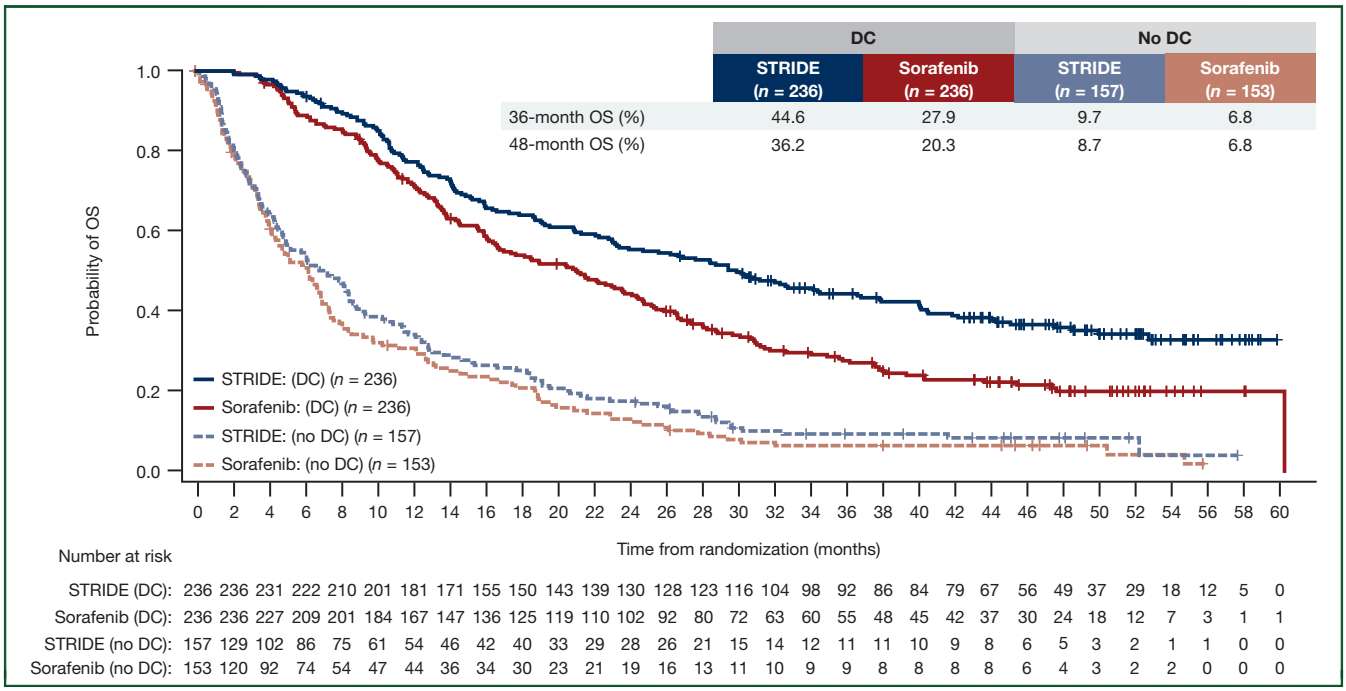

Figure 3. OS by disease control (yes/no) for STRIDE versus sorafenib. Responses were based on investigator assessment according to RECIST v1.1. Disease control was defined as complete response, partial response, or stable disease at the primary analysis data cut-off. Updated OS analysis data cut-off: 23 January 2023.
DC, disease control; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

Safety

The safety analysis set included 1150 participants who received at least one dose of study treatment in the STRIDE ($n = 388$), durvalumab ($n = 388$), and sorafenib ($n = 374$) arms. The median (range) total duration of durvalumab treatment was similar in the STRIDE and durvalumab arms, 5.5 months (0.3-58.8 months) and 5.5 months (0.2-61.3 months), respectively. The median (range) total duration of sorafenib treatment was 4.1 months (0.1-53.7 months).

Serious AEs, regardless of attribution, occurred in 41.2% (160/388), 31.7% (123/388), and 29.7% (111/374) of participants receiving STRIDE, durvalumab, and sorafenib, respectively (Table 3). Serious treatment-related AEs occurred in 17.5% (68/388) of participants treated with STRIDE, 8.5% (33/388) of participants treated with durvalumab, and 9.6% (36/374) of participants treated with sorafenib (Table 3). No new serious treatment-related AEs occurred after the primary analysis for STRIDE.

Table 2. Best objective response of long-term survivors

Best objective response, *n* (%)	STRIDE ($n = 103$)	Durvalumab ($n = 79$)	Sorafenib ($n = 64$)
Objective response rate	53 (51.5)	42 (53.2)	10 (15.6)
Complete response	12 (11.7)	5 (6.3)	0
Partial response	41 (39.8)	37 (46.8)	10 (15.6)
Stable disease	39 (37.9)	25 (31.6)	45 (70.3)
Progressive disease	10 (9.7)	12 (15.2)	6 (9.4)
Not evaluable	1 (1.0)	0	3 (4.7)

Responses were based on investigator assessment according to RECIST v1.1. Updated analysis data cut-off: 23 January 2023.
RECIST, Response Evaluation Criteria in Solid Tumors; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

DISCUSSION

This 4-year updated analysis of the phase III HIMALAYA study presents the longest follow-up to date from a pivotal phase III study in uHCC.[17,18] After an additional 17 months of follow-up from the primary analysis, the STRIDE regimen demonstrated a sustained OS benefit, versus sorafenib. One in four (25.2%) participants was alive at 4 years following treatment with STRIDE versus 15.1% with sorafenib, representing an unprecedented survival rate in this disease setting. OS was improved with STRIDE versus sorafenib across clinically relevant subgroups, including geographical region, ECOG performance status, Barcelona Clinic Liver Cancer staging, etiology of liver disease, baseline alpha-fetoprotein level, and presence of macrovascular invasion and/or extrahepatic spread. At the 4-year updated analysis, durvalumab maintained a noninferior OS HR versus sorafenib.

Long-term survival with combination anti-PD-L1/programmed cell death-1 (PD-1) and anti-CTLA-4 regimens has previously been observed in studies of nivolumab plus ipilimumab in advanced melanoma, metastatic non-small-cell lung cancer, and advanced sarcomatoid renal cell carcinoma.[19-21] Long-term survival with combination anti-PD-L1/PD-1 and anti-CTLA-4 therapy may potentially be driven through anti-CTLA-4-induced expansion of CD4+ Ki67+ and CD8+ Ki67+ T cells priming an immune response that is sustained by anti-PD-L1/PD-1 therapy.[22]

Although disease control rates were similar (60.1% for STRIDE and 60.7% for sorafenib), the OS rates were further improved at 3 and 4 years for participants who achieved disease control with STRIDE, compared with those who achieved disease control with sorafenib. Survival rates in

Table 3. Serious AEs in the safety analysis set

Participants with an event, *n* (%)	STRIDE (*n* = 388)	Durvalumab (*n* = 388)	Sorafenib (*n* = 374)
Any serious treatment-related AEs (including death)	68 (17.5)	33 (8.5)	36 (9.6)
Any serious AEs (including death)	160 (41.2)	123 (31.7)	111 (29.7)
Infections and infestations	46 (11.9)	25 (6.4)	24 (6.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	8 (2.1)	5 (1.3)	4 (1.1)
Blood and lymphatic system disorders	6 (1.5)	2 (0.5)	3 (0.8)
Immune system disorders	1 (0.3)	2 (0.5)	0
Endocrine disorders	4 (1.0)	5 (1.3)	0
Metabolism and nutrition disorders	18 (4.6)	13 (3.4)	7 (1.9)
Psychiatric disorders	1 (0.3)	3 (0.8)	0
Nervous system disorders	14 (3.6)	9 (2.3)	7 (1.9)
Eye disorders	3 (0.8)	0	0
Ear and labyrinth disorders	0	1 (0.3)	1 (0.3)
Cardiac disorders	10 (2.6)	7 (1.8)	8 (2.1)
Vascular disorders	6 (1.5)	4 (1.0)	2 (0.5)
Respiratory, thoracic, and mediastinal disorders	9 (2.3)	12 (3.1)	10 (2.7)
Gastrointestinal disorders	48 (12.4)	25 (6.4)	36 (9.6)
Hepatobiliary disorders	14 (3.6)	17 (4.4)	15 (4.0)
Skin and subcutaneous tissue disorders	7 (1.8)	2 (0.5)	10 (2.7)
Musculoskeletal and connective-tissue disorders	6 (1.5)	4 (1.0)	2 (0.5)
Renal and urinary disorders	7 (1.8)	4 (1.0)	7 (1.9)
General disorders and administration site conditions	10 (2.6)	19 (4.9)	9 (2.4)
Investigations	9 (2.3)	6 (1.5)	0
Injury, poisoning, and procedural complications	6 (1.5)	6 (1.5)	4 (1.1)

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. Updated analysis data cut-off: 23 January 2023.
AE, adverse event; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

participants who achieved disease control were 60% higher (44.6% versus 27.9%) at 36 months and 78% higher (36.2% versus 20.3%) at 48 months for STRIDE versus sorafenib. Thus, consistent with other ICI studies, achieving disease control with STRIDE may be a meaningful measure of clinical benefit.[23] Long-term survivors with STRIDE included participants across all clinically relevant subgroups, including those with a response, as well as those with SD or even PD. This observation is not unique to patients treated with STRIDE in uHCC, as a subset of melanoma patients treated with tremelimumab monotherapy who did not meet the criteria for an objective response remained disease free for over 12 years without having received subsequent systemic therapy.[24] Furthermore, similar findings were observed in studies of ipilimumab (anti-CTLA-4) as monotherapy or combination therapy in metastatic melanoma, which reported that 39% or more of long-term survivors alive at least 4 years did not achieve an objective response.[25-27] This may suggest that response is not a critical indicator of long-term survival for anti-CTLA-4 regimens. In addition, a larger proportion of patients in the sorafenib arm received subsequent anticancer systemic therapy compared with those treated with STRIDE, and literature suggests that this may confer a survival benefit,[28] which raises the possibility that without subsequent anticancer therapy the survival differences between the two arms could be even more pronounced.

The proportions of long-term survivors in the STRIDE arm who continued treatment beyond disease progression, were retreated with tremelimumab plus durvalumab, or who received subsequent anticancer therapy, were similar to the corresponding proportions in the full analysis set. Combined with data pertaining to clinically relevant subgroups represented in the long-term survivors, these results suggest that the long-term survival benefit of STRIDE was not driven by any particular subgroup of participants. Future studies to understand clinically relevant predictors of the long-term survival benefit of STRIDE would be useful.

The survival curve for durvalumab-containing regimens appeared to plateau at ∼3 years after treatment initiation, which was most prominent with STRIDE. This trend is consistent with that observed in other trials evaluating single-agent or combination anti-PD-L1/PD-1 and anti-CTLA-4 regimens, where the emergence of the OS curve plateau begins near year 3 and extends with further follow-up.[19-21,29-31] The sustained long-term survival benefits in participants treated with combination anti-PD-L1/PD-1 and anti-CTLA-4 inhibitor regimens are often further improved in participants who achieve disease control, supporting the concept that combination ICI regimens are associated with long-term clinical activity.[32]

In this updated analysis with extended follow-up, the STRIDE regimen maintained a manageable safety profile, which is differentiated from other currently available uHCC therapies.[5,14,33] No new serious treatment-related AEs occurred after the primary analysis for STRIDE.[6] In this updated analysis, a larger percentage of participants in the STRIDE arm remained on study treatment when compared with sorafenib, further supporting tolerability of the STRIDE regimen. The durvalumab safety profile was tolerable and manageable per treatment guidelines. No new safety signals beyond the established safety profiles of each regimen were identified.[6] Thus, long-term survival after treatment with STRIDE or durvalumab did not appear to be associated with any substantial safety issues.

Limitations of the HIMALAYA study have been described previously[6] and include the open-label study design and the exclusion of participants with thrombosis in the main trunk of the portal vein. In addition, no formal statistical comparisons were carried out in this updated exploratory analysis. However, the consistency of the OS data with that previously reported[6] strengthens the inferences of this updated analysis.

In conclusion, STRIDE is a novel treatment option that prolongs survival while maintaining a tolerable and manageable safety profile that is differentiated from other current available therapies, supporting the positive benefit risk profile of this regimen. These data present the longest

OS follow-up to date from a pivotal phase III study in uHCC, and demonstrate the unprecedented long-term survival benefits of STRIDE, with over one in four participants remaining alive at 4 years.

APPENDIX 1

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DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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