Outcomes by occurrence of immune-mediated adverse events with tremelimumab plus durvalumab in the Phase 3 HIMALAYA study in unresectable hepatocellular carcinoma

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- Senior Member of Governance Board, Asian-Pacific Digestive Week Federation (APDWF)
Background

• In the Phase 3 HIMALAYA study (NCT03298451) in uHCC, the STRIDE (Single Tremelimumab Regular Interval Durvalumab) regimen significantly improved OS versus sorafenib; durvalumab monotherapy was noninferior to sorafenib for OS\(^1\)

• STRIDE has been approved globally for the treatment of adults with uHCC, including in the United States, the European Union, and Japan, and durvalumab monotherapy has been approved for the treatment of adults with uHCC in Japan\(^2\)–\(^4\)

• imAEs are known side effects of immune checkpoint inhibitors and may impact efficacy outcomes\(^5\)–\(^6\); in HIMALAYA, the majority of imAEs were low grade, and there was a low rate of imAEs leading to discontinuation\(^1\)

Here, we report an exploratory analysis, which assessed the association between occurrence of imAEs and OS in HIMALAYA

imAE, immune-mediated adverse event; OS, overall survival; uHCC, unresectable hepatocellular carcinoma.

HIMALAYA study design

HIMALAYA is an open-label, multicenter, global, Phase 3 trial

Study population
- Adults with confirmed unresectable HCC
- Child–Pugh A
- BCLC B (not eligible for locoregional therapy) or C
- No prior systemic therapy
- ECOG PS 0–1
- No main portal vein thrombosis
- EGD was not required

Stratification factors
- Etiology of liver disease: HBV / HCV / nonviral
- Macrovacular invasion: yes / no
- ECOG PS: 0 / 1

STRIDE (n=393):
- tremelimumab 300 mg × 1 dose +
- durvalumab 1500 mg Q4W

Durvalumab (n=389):
- durvalumab monotherapy
- 1500 mg Q4W

Sorafenib (n=389):
- sorafenib 400 mg BID

Primary objective
- OS superiority: STRIDE vs sorafenib

Secondary objectives
- OS noninferiority: durvalumab vs sorafenib
- 36-month OS rate
- PFS, ORR, and DCR (investigator-assessed per RECIST v1.1)
- Safety

T75+D (n=153):
- arm closed to enrollment*
- tremelimumab 75 mg Q4W × 4 doses +
- durvalumab 1500 mg Q4W

OS superiority for STRIDE vs sorafenib
- Noninferiority margin: 1.08

OS noninferiority for durvalumab vs sorafenib
- 36-month OS rate for STRIDE vs sorafenib

Multiple testing procedure

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*The T75+D arm was closed to enrollment 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; EGD, esophagogastroduodenoscopy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; 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.

The safety analysis set comprised participants who received ≥1 dose of study treatment.

imAEs were AEs of special interest associated with drug exposure and consistent with an immune-mediated mechanism of action with no alternate etiology found.

OS was assessed in subgroups of participants with or without an imAE during the study.

*Participants with ≥1 imAE were counted once.

AE, adverse event; imAE, immune-mediated adverse event; OS, overall survival.
Baseline demographics and disease characteristics in imAE subgroups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>STRIDE (n=388)</th>
<th>Durvalumab (n=388)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>imAE (n=139)</td>
<td>No imAE (n=249)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>66.0 (23–82)</td>
<td>64.0 (22–86)</td>
</tr>
<tr>
<td>Asian region,* n (%)</td>
<td>47 (33.8)</td>
<td>109 (43.8)</td>
</tr>
<tr>
<td>ECOG PS, 0 / 1, n (%)</td>
<td>90 (64.7) / 49 (35.3)</td>
<td>151 (60.6) / 97 (39.0)</td>
</tr>
<tr>
<td>BCLC score B / C, n (%)</td>
<td>39 (28.1) / 100 (71.9)</td>
<td>38 (15.3) / 211 (84.7)</td>
</tr>
<tr>
<td>Viral etiology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV†</td>
<td>38 (27.3)</td>
<td>84 (33.7)</td>
</tr>
<tr>
<td>HCV‡</td>
<td>39 (28.1)</td>
<td>69 (27.7)</td>
</tr>
<tr>
<td>Nonviral§</td>
<td>62 (44.6)</td>
<td>96 (38.6)</td>
</tr>
<tr>
<td>MVI and / or EHS, n (%)</td>
<td>79 (56.8)</td>
<td>180 (72.3)</td>
</tr>
<tr>
<td>No MVI or EHS, n (%)</td>
<td>59 (42.4)</td>
<td>68 (27.3)</td>
</tr>
</tbody>
</table>

*Excludes Japan. †Presence of HBsAg and / or anti-HBcAb with detectable HBV DNA. ‡Presence of anti-HCV antibodies. §No active viral hepatitis identified.

BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; imAE, immune-mediated adverse event; MVI, macrovascular invasion; PS, performance status.
imAEs in HIMALAYA

Most imAEs with STRIDE or durvalumab were low grade, and most occurred within the first 3 months of treatment\(^1,2\)

### Preferred term*

- Hypothyroidism
- Hyperthyroidism
- Diarrhea
- Rash
- Hepatitis
- ALT increased
- AST increased
- Adrenal insufficiency
- Colitis
- Lipase increased
- Rash maculopapular
- Arthralgia
- Amylase increased
- Abnormal hepatic function

### Most common imAEs\(^1,\dagger\)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>STRIDE Grade 3 or 4</th>
<th>STRIDE Grade 1 or 2</th>
<th>Durvalumab Grade 3 or 4</th>
<th>Durvalumab Grade 1 or 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>10.1</td>
<td>0.3</td>
<td>2.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>4.7</td>
<td>1.0</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.4</td>
<td>0.6</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Rash</td>
<td>2.3</td>
<td>0.8</td>
<td>2.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>2.0</td>
<td>0.8</td>
<td>1.8</td>
<td>0.3</td>
</tr>
<tr>
<td>ALT increased</td>
<td>1.6</td>
<td>0.3</td>
<td>1.3</td>
<td>0.3</td>
</tr>
<tr>
<td>AST increased</td>
<td>1.5</td>
<td>0.3</td>
<td>1.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1.0</td>
<td>0.3</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Colitis</td>
<td>1.0</td>
<td>0.3</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>0.3</td>
<td>0.3</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>0.3</td>
<td>0.3</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

### Overall frequency of any imAE by time in participants with imAEs\(^2,\dagger\)

Further characterization of the temporal patterns of imAEs in HIMALAYA will be reported in Poster 4073

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\(^*\)Preferred term was as reported by the investigator. \(^1\)ImAEs that occurred in ≥1% of participants in the in the STRIDE or durvalumab treatment arms are included. \(^\dagger\)The percentage of participants with an event is the number of participants who experienced ≥1 imAE event at each time interval divided by the number of participants who experienced ≥1 imAE event at any time; includes first imAE only, regardless of grade.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; imAE, immune-mediated adverse event.

A numerical improvement in OS was observed in participants who had an imAE versus those who did not

A numerical improvement in OS was observed in participants who had an imAE versus those who did not.

<table>
<thead>
<tr>
<th>Number at risk (number of events)</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>imAE</td>
<td>Number of events</td>
</tr>
<tr>
<td>139 (0)</td>
<td>97 (42)</td>
</tr>
<tr>
<td>69 (70)</td>
<td>12 (82)</td>
</tr>
<tr>
<td>No imAE</td>
<td></td>
</tr>
<tr>
<td>249 (0)</td>
<td>137 (110)</td>
</tr>
<tr>
<td>88 (159)</td>
<td>20 (175)</td>
</tr>
</tbody>
</table>

*OS HRs and 95% CIs were calculated using Cox modeling, with imAEs as a time-varying covariate to properly account for immortal time bias and stratified by etiology, ECOG (0 / 1), and macrovascular invasion (yes / no) for participants with versus without imAEs of any grade.

CI, confidence interval; HR, hazard ratio; imAE, immune-mediated adverse event; OS, overall survival.
Landmark 36-month OS rates for STRIDE in imAE subgroups

OS rates at 36 months were higher with STRIDE than with sorafenib (ITT population) irrespective of imAE occurrence.

**STRIDE and sorafenib: ITT population**

- STRIDE (n=393): 30.7%
- Sorafenib (n=389): 20.2%

**STRIDE: imAE subgroups**

- STRIDE imAE (n=139): 36.2%
- STRIDE no imAE (n=249): 27.7%

imAE, immune-mediated adverse event; ITT, intent-to-treat; OS, overall survival.
PRESENTED BY: George Lau, MD, FRCP, FAASLD

OS by imAE occurrence for durvalumab

OS was similar for participants treated with durvalumab with or without imAEs

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>imAE</th>
<th>No imAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month OS (95% CI)</td>
<td>60.9% (50.1–74.1)</td>
<td>58.2% (53.1–63.8)</td>
</tr>
<tr>
<td>12-month OS (95% CI)</td>
<td>39.1% (28.8–53.0)</td>
<td>39.3% (34.3–45.0)</td>
</tr>
<tr>
<td>24-month OS (95% CI)</td>
<td>20.6% (12.2–34.8)</td>
<td>25.7% (20.8–31.9)</td>
</tr>
<tr>
<td>36-month OS (95% CI)</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*OS HRs and 95% CIs were calculated using Cox modeling, with imAEs as a time-varying covariate to properly account for immortal time bias and stratified by etiology, ECOG (0 / 1), and macrovascular invasion (yes / no) for participants with versus without imAEs of any grade.

CI, confidence interval; HR, hazard ratio; imAE, immune-mediated adverse event; OS, overall survival.
Conclusions

- Among participants in HIMALAYA who received STRIDE or durvalumab monotherapy, imAEs were manageable and generally low grade, and the majority occurred within the first 3 months of treatment.
- The occurrence of imAEs did not preclude participants from experiencing an OS benefit with STRIDE, and long-term survival was observed with STRIDE, irrespective of imAE occurrence.

The results of this exploratory analysis further support the benefit of STRIDE in a diverse population reflective of uHCC globally.

imAE, immune-mediated adverse event; OS, overall survival; uHCC, unresectable hepatocellular carcinoma.
Acknowledgments

- We thank the participants who volunteered for this study and their families and loved ones, all the investigators and study site personnel, and the members of the independent data-monitoring committee.
- Medical writing support, under the direction of the authors, was provided by Derrick Bond, PharmD, CMC Connect, a division of IPG Health Medical Communications, funded by AstraZeneca, in accordance with Good Publication Practice (GPP 2022) guidelines.
Thank you to all of the investigators

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Supplementary Information and Plain Language Summary Infographic

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Characterization of the temporal patterns of imAEs in HIMALAYA will be reported in Poster 4073