Editorial

Durvalumab plus tremelimumab in unresectable hepatocellular carcinoma

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Introduction

The results of the Phase 3 HIMALAYA trial were presented at ASCO-GI 2022 (1). Durvalumab + tremelimumab (Durva/Treme) has also been approved for the treatment of urothelial cancer and non-small cell lung cancer. For hepatocellular carcinoma (HCC), nivolumab + ipilimumab has received accelerated approval from the FDA as second line therapy after sorafenib with Phase 1/2 study results, and a Phase 3 trial is currently underway. Durva/Treme is the first anti-PD-L1 + anti-CTLA-4 combination immunotherapy to be successfully tested in Phase 3.

In this editorial, the results of Phase 3 study is reviewed and the role of Durva/Treme in the future treatment of advanced liver cancer is discussed.

Results of Phase 3 HIMALAYA trial

The HIMALAYA trial was initially launched with 4 arms (1): Arm 1: tremelimumab (300 mg, one dose) + durvalumab (1,500 mg every 4 weeks, STRIDE regimen = T300 + D group in the Phase 1/2 trials); Arm 2: durvalumab (1500 mg every 4 weeks); Arm 3: tremelimumab (75 mg every 4 weeks, 4 doses) + durvalumab (1,500 mg every 4 weeks; T75 + D); or Arm 4: sorafenib (400 mg twice daily). However, the enrollment to T75 + D arm of Arm 3 was stopped during the study owing to the poor results of the Phase 1/2 study (Study 22) (2). As a result, a total of 1171 patients were randomized into STRIDE regimen (n=393), durvalumab (n=389), or sorafenib (n=389).

The results showed that the median OS (95% CI) of the STRIDE group was 16.43 (14.16–19.58) months and that of sorafenib group was 13.77 (12.25–16.13) months. The statistically significant OS advantage of the STRIDE regimen over sorafenib was demonstrated (HR =0.78; 96.02% CI: 0.65–0.93; P=0.0035). Additionally, the non-inferiority of durvalumab to sorafenib was demonstrated (HR =0.86; 95.67% CI: 0.73–1.03; pre-specified non-inferiority margin, 1.08) (*Table 1*).

Neither STRIDE (3.78 months) nor durvalumab (3.65 months) significantly extended progression-free survival (PFS) versus sorafenib (4.07 months). The objective response rate (ORR) [including complete response rate (CR rate) was 20.1% (3.1%)] for the STRIDE regimen and 17.0% (1.5%) for durvalumab. The disease control rate (DCR) for the STRIDE regimen, durvalumab, and sorafenib was 60.1%, 54.8%, and 60.7%, respectively. The duration of response (DOR) for STRIDE, durvalumab, and sorafenib was 22.34, 16.82, and 18.43 months, respectively.

The percentages for any grade of TRAEs in STRIDE, durvalumab, and sorafenib were 75.8%, 52.1%, and 84.8%, respectively. Serious TRAEs and TRAEs leading to death tended to be slightly more common in STRIDE (*Table 2*). Regarding the safety, there was no significant difference between the three groups (*Table 2*). Grade 3/4 immune-mediated TRAEs, immune-mediated AEs requiring treatment with a high-dose of a steroid, and immune-mediated AEs leading to discontinuation of study treatment tended to be slightly higher in STRIDE regimen but were not considered to be intolerable (*Table 2*).

Table 1 Results of Phase 3 HIMALAYA trial: efficacy outcome

Efficacy outcome	HIMALAYA trial		
	STRIDE (D + T300) (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Median follow-up, months	33.2	32.6	32.2
Median OS, months (95% CI)	16.4 (14.2–19.6)	16.6 (14.1–19.1)	13.8 (12.3–16.1)
OS HR (96.02% CI)	0.78 (0.65–0.93)	0.86 (0.73–1.03)	
P value	0.0035	0.0674	
Median PFS, months (95% CI)	3.8 (3.7–5.3)	3.7 (3.2–3.8)	4.1 (3.8–5.5)
PFS HR (95% CI)	0.90 (0.77–1.05)	1.02 (0.88–1.19)	
ORR, %	20.1	17.0	5.1
CR, n (%)	12 (3.1)	6 (1.5)	0
PR, n (%)	67 (17.0)	60 (15.4)	20 (5.1)
SD, n (%)	157 (39.9)	147 (37.8)	216 (55.5)
PD, n (%)	157 (39.9)	176 (45.2)	153 (39.3)
DCR, n (%)	236 (60.1)	213 (54.8)	236 (60.7)
Median DOR, months (IQR)	22.34 (8.54–NR)	16.82 (7.43–NR)	18.43 (6.51–25.99)
Median TTR, months (95% CI)	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Remaining in response, months			
6	82.3	81.8	78.9
12	65.8	57.8	63.2

STRIDE, Single Tremelimumab Regular Interval Durvalumab; D + T300, durvalumab plus high dose tremelimumab; OS, overall survival; HR, hazard ratio; PFS, progression free survival; ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; DOR, duration of response; NR, not reached; TTR, time to response.

Table 2 Results of Phase 3 HIMALAYA trial: safety outcome

Event, n (%)	STRIDE (n=388)	Durvalumab (n=388)	Sorafenib (n=374)
TRAE	294 (75.8)	202 (52.1)	317 (84.8)
Grade 3/4 TRAE	100 (25.8)	50 (12.9)	138 (36.9)
Serious TRAE	68 (17.5)	32 (8.2)	35 (9.4)
TRAE leading to death	9 (2.3)[(a)]	0	3 (0.8)[(b)]
TRAE leading to discontinuation	32 (8.2)	16 (4.1)	41 (11.0)
Grade 3/4 hepatic SMQ TRAE	23 (5.9)	20 (5.2)	17 (4.5)
Grade 3/4 hemorrhage SMQ TRAE	2 (0.5)	0	4 (1.1)
Grade 3/4 immune-mediated TRAE	49 (12.6)	24 (6.2)	9 (2.4)
Immune-mediate AE requiring treatment with high-dose steroids	78 (20.1)	37 (9.5)	7 (1.9)
Immune-mediated AE leading to discontinuation of study treatment	22 (5.7)	10 (2.6)	6 (1.6)

[(a)], nervous system disorder (n=1), acute respiratory distress syndrome (n=1), hepatitis (n=1), myocarditis (n=1), immune-mediated hepatitis (n=2), pneumonitis (n=1), hepatic failure (n=1), myasthenia gravis (n=1); [(b)], hematuria (n=1), cerebral hematoma (n=1), hepatic failure (n=1). STRIDE, Single Tremelimumab Regular Interval Durvalumab; TRAE, treatment-related adverse event; SMQ, Standardized MedDRA Query.

The Grade 3/4 treatment-related AEs (25.8%) in the STRIDE regimen tended to be slightly less compared to the Grade 3/4 treatment-related AEs (>50%) of Arm A [nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg flat dose every 2 weeks] in the CheckMate 040 nivolumab + ipilimumab combination therapy previously reported (3). This result may be attributed to the difference in regimen, in which only one initial priming with anti-CTLA-4 was performed in the HIMALAYA Study. In addition, the hypertension, proteinuria, hand-foot skin reaction, and bleeding events, which are frequently observed in patients treated with anti-PD-1/PD-L1 antibody + anti-VEGF/TKI combination immunotherapy (4-6), were rarely observed.

In terms of post-treatment, 40.7%, 43.2%, and 45.0% of patients received some form of anticancer therapy after STRIDE, durvalumab, and sorafenib, respectively. Especially after sorafenib, 17.2% of patients received immunotherapy. This proportion was much higher than the number of patients treated with immunotherapy after STRIDE (1.8%) and durvalumab (0.8%). As in the CheckMate 459 study (7), this post-treatment with immunotherapy may have contributed to the tail plateau in the sorafenib group.

Role of Durva/Treme for unresectable HCC in real-world clinical practice

The STRIDE regimen demonstrated a distinct superiority to sorafenib, with a Kaplan-Meier curve showing a good 3-year survival rate of 30.7%. The STRIDE regimen was also superior to the single-agent durvalumab in terms of ORR, OS, and CR rate, indicating that single high-dose priming with anti-CTLA-4 antibody has a clear add-on effect to anti-PD-L1 antibody and certainly works as theorized in patients with HCC; additionally, it has been shown to be effective in HCC patients. This regimen was the first combination of anti-PD-L1 and anti-CTLA4 antibodies in HCC, with an acceptable and manageable toxicity. In addition, although anti-CTLA-4 antibody is used, the number of AEs is lower than expected, without a bleeding risk; therefore, endoscopy immediately before the treatment may not be necessary. Furthermore, in ICI + anti-VEGF/TKI combination therapy for advanced HCC, the absence of AEs such as proteinuria, hypertension, ascites, and encephalopathy due to the anti-VEGF effect of all TKIs is a major advantage. In contrast, the HIMALAYA Study excludes HCC patients with VP4, and the lack of data on HCC patients with VP4 is one of existing limitations. In addition, combination immunotherapy with anti-PD-1/PD-L1 antibody and anti-VEGF antibody or TKI showed no significant difference in terms of response in patients with and without WNT/β-catenin mutations (8,9) and NASH-related HCC (10). However, whether the combination of anti-PD-L1 and anti-CTLA-4 antibodies has any effect on these patients is unclear (11). The combination of anti-PD-L1 + anti-CTLA-4 antibodies might be less effective on these patients, and therefore, the PD rate of the STRIDE regimen may be high. Furthermore, the absence of anti-VEGF effect on the improvement of immune microenvironment (12-14) may be a reason for high PD rate as compared with the anti-PD-L1 + anti-VEGF.

Atezolizumab + bevacizumab (Atezo/Bev), which is currently the choice of first-line treatment, has good efficacy against VP4. The OS hazard ratio of Atezo/Bev to sorafenib is favorable (0.66) when compared to the OS hazard ratio of 0.78 in the STRIDE regimen. Moreover, the PFS hazard ratio of the Atezo/Bev regimen against sorafenib was 0.65. The PFS hazard ratio of the STRIDE regimen to sorafenib was 0.90; thus, the PFS of the STRIDE regimen was poor compared to the Atezo/Bev regimen. PD rate is lower in Atezo/Bev group (19%) than that in STRIDE regimen (40%). Furthermore, the ORR was better in the Atezo/Bev group (30% *vs.* 20%), and the CR rate was better in the Atezo/Bev group (8% *vs.* 3%). However, the duration of the response was longer in the STRIDE regimen group (22.34 months) than that in the Atezo/Bev group (18.1 months).

The results of the Phase III IMbrave150 and HIMALAYA trials suggest that Atezo/Bev is generally the first choice of first-line treatment. However, when Atezo/Bev becomes PD, combination therapy with durvalumab and tremelimumab, which have different modes of action, may be indicated as second-line therapy. Atezo/Bev treatment does not impair liver function (15), and most patients can be switched to Durva/Treme (A + B followed by D + T sequential therapy).

Another option is to begin treatment with Durva/Treme and then subsequently switch to Atezo/Bev as soon as PD is achieved, because anti-CTLA-4 antibody priming is performed only once. Substantial triple therapy with anti-CTLA4 + anti-PD-L1 + anti-VEGF will be possible in the practice. The sequence of this triple therapy is also quite attractive (D + T followed by A + B sequential therapy).

The third option is to start with Atezo/Bev, then systematically administer Durva/Treme for a short period of time, and then return to Atezo/Bev (A + B followed by D + T,

then A + B sequential therapy).

In any case, sequential treatment with the ICI-ICI combo and ICI + anti-VEGF is a viable treatment strategy whichever of them are used first, and targeted therapy is expected to become a common treatment strategy only when PD is achieved with both of them.

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Footnote

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