Clinical Activity and Safety of Penpulimab (Anti-PD-1) with Anlotinib as First-line Therapy for Advanced Hepatocellular Carcinoma (HCC)

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Background

- Advanced HCC is a deadly disease with few systemic therapeutic options. The immunomodulatory effects of VEGF inhibitor (increased DC maturation, enhanced T-cell infiltration, reduced MDSCs and T_{regs} in tumors) create a more favorable tumor microenvironment that potentiates the efficacy of anti-PD-1(L1) inhibitor.
- The combination of anti-PD-1(L1) and anti-VEGF(R) agents has gained attentions world-wide as an important breakthrough in the first-line treatment of advanced HCC. A sBLA has been submitted for an anti-PD-L1 + anti-VEGF combination as first-line treatment for advanced HCC.
- Penpulimab is a novel humanized anti–PD-1 IgG1 antibody with slower PD-1 antigen binding off-rate and complete removal of Fc receptor mediated effect, resulting in potentially enhanced anti-tumor activity.
- Anlotinib is a multi-targeted tyrosine kinase inhibitor selective for VEGFR1/2/3, FGFR 1-4, PDGFRα/β, and c-kit.
- According to previous trials, both Penpulimab and Anlotinib monotherpay showed its potential to treat advanced HCC separately (*Fig.1*).

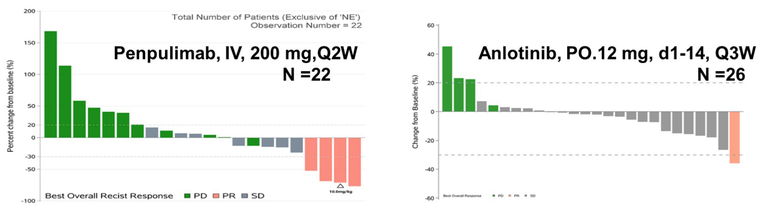

Fig.1 Waterfall plots from previous trials of Penpulimab and Anlotinib treating advanced HCC

Design

Clinicaltrial: NCT04172571

- Pathologically confirmed unresectable HCC
- No prior systemic therapy
- Predicted life expectancy >3 months
- ECOG PS 0-1
- BCLC Stage C or B disease
- Child-Pugh class A and B (≤7)
- Adequate hematologic and organ function

Penpulimab
IV, 200 mg, Q3W
+
Anlotinib
PO, 8 mg,day1-14, Q3W

Primary endpoint

- Objective Response rate (ORR)

Secondary endpoints

- Durartion of Response (DoR)
- Disease Control Rate (DCR)
- Time to Progression (TTP)
- Overall Survival
- Safety and tolerability

Tumour assessments were performed every 6 weeks according to RECIST v1.1 by the investigator.

Results

- As of Nov 13, 2020, 31 pts were enrolled with a median of 8.0 (1–28) doses of penpulimab in combination with anlotinib. Baseline characteristics are shown in *Tab.1*.
- As shown in *Tab.2*, of 29 evaluable pts, confirmed ORR per RECIST v1.1was 31.0% (9/29) and DCR was 82.8% (24/29).
- As shown in *Tab.2* and *Fig.2*, after a median follow-up of 7.0 months, median TTP was 8.8 months and 6m-TTP rate was 65.7 % (95% CI: 44.2%, 80.6%). Median PFS was 8.8 months and 6m-PFS rate was 63.2 % (95% CI: 42.2%, 78.4%). Median OS was not reached and 6m-OS rate was 93.2% (95% CI: 75.5%, 98.3%).

Tab.1 Baseline characteristics of enrolled pts

		Pts (n=31)
Age, median (range)		56 (23 - 74)
Gender n(%)	**Male**	25(80.6)
	Female	6(19.4)
ECOG PS n(%)	**0**	20(64.5)
	1	11(35.5)
Child-Pugh	**A**	31 (100)
BCLC n(%)	**B**	7(22.6)
	C	24(77.4)
Infection n(%)	**HBV**	19(61.3)
	HCV	2(6.5)
	Uninfected	10(32.3)
AFP n(%)	**>400**	9(29.0)
	≤400	22(71.0)
Extrahepatic spread n(%)	**Yes**	19(61.3)
	No	12(38.7)

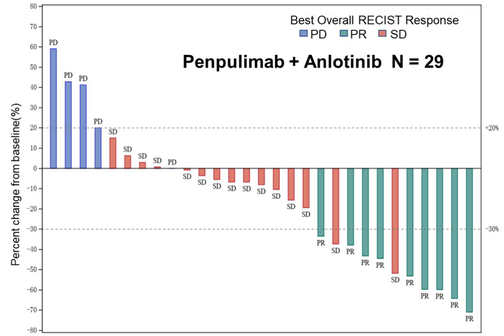

Fig.2a Waterfall plots of pts received penpulimab + anlotinib as first-line therapy in advanced HCC

Tab.2 Summary of clinical activities

RECIST Response (per Investigator) [a]	
Confirmed ORR, % (n/N)	31.0 (9/29)
DCR, % (n/N)	82.8 (24/29)
Time to Progression (ITT population)	
Median, month (95% CI)	8.8 (4.0, 12.9)
6m-TTP, % (95% CI)	65.7 (44.2, 80.6)
Progression Free Survival (ITT population)	
Median, month (95% CI)	8.8 (4.0, 12.3)
6m-PFS, % (95% CI)	63.2 (42.2, 78.4)
Overall Survival (ITT population)	
Median, month (95% CI)	NE (9.8, NE)
6m-OS, % (95% CI)	93.2 (75.5, 98.3)

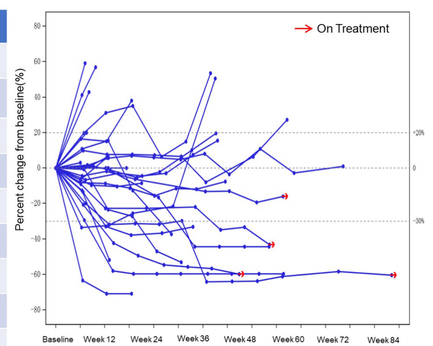

Fig.2b Spider plots of pts received penpulimab + anlotinib as first-line therapy in advanced HCC

[a] Response evaluable =patients with ≥12 weeks' follow-up + measurable disease at baseline + ≥1 follow-up scan.

Safety-Profile

- Median duration of therapy (range) was 7.1 months (0.7 –19.9) with penpulimab+anlotinib. TRAE leading to discontinuation included rash (6.5%) and pneumonia (3.2%). ≥ Grade 3 irAE included rash (6.5%) . No TRAE led to death.

Tab.3 Overview of Treatment Related Adverse Events (TRAE)[a] by Preferred Term

	Pts（n=31）, n(%)
Any TRAE	28 (90.3)
Most common TRAEs(≥10% of patients)	
AST increased	12 (38.7)
ALT increased	11 (35.5)
Asthenia	7 (22.6)
Bilirubin conjugated increased	7 (22.6)
Platelet count decreased	7 (22.6)
Rash	5 (16.1)
Dysphonia	4 (12.9)
Hypertension	4 (12.9)
Hypothyroidism	4 (12.9)
≥Grade 3 TRAEs	6 (19.4)
Rash	2 (6.5)
Hypertension	2 (6.5)
Chest pain	1 (3.2)
Edema	1 (3.2)
Treatment Related SAE	2 (6.5)
TRAE leading to drug discontinuation	3 (9.7)

[a] Treatment related indicates either study drug (penpulimab or anlotinib) related

Conclusion

- The combination of penpulimab (200 mg iv q3w) and anlotinib (8 mg qd day1-14) had a manageable safety profile and encouraging anti-tumor activities as first-line therapy in patients with advanced HCC (Confirmed ORR: 31.0%; DCR: 82.8%; 6m-TTP: 65.7%; 6m-PFS:63.2%; 6m-OS: 93.2%).
- No unexpected AEs were identified beyond the established safety profile for each agent. The combination of penpulimab+ anlotinib was well tolerated with lower rate (9.7%) for TRAE leading to drug discontinuation.
- Current safety profile and clinical activities supports further investigation on higher dose of anlotinib in combination with penpulimab in patients with advanced HCC, resulting in potentially enhanced anti-tumor activity.
- Evaluation of penpulimab (200 mg iv q3w) in combination with higher dose of anlotinib (10 mg qd day1-14, q3w) in a phase 3 study for first-line HCC versus sorafenib (NCT04344158) is currently underway.

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