

Phase Ib/II Trial of Envafolimab, a Novel Subcutaneous Single-domain Anti-PD-L1 Monoclonal Antibody, Plus Lenvatinib in Patients with Selected Advanced Solid Tumors

FPN: 1049P

Tianshu Liu¹, Yi Feng¹, Xiaojing Xu¹, Xiubao Ren², Jun Jia³, Hongming Pan⁴, Baocheng Wang⁵, Bin Wu⁶, Xiaoming Cao⁷, Jiwei Liu⁸, Yong Yang⁹, Shen Xiao¹⁰, Lan Qin¹⁰, Siying Xu¹⁰, Wensheng Huang¹⁰, Dizhu¹⁰

1. Zhongshan Hospital Affiliated with Fudan University, Shanghai, China; 2. Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; 3. Dongguan People's Hospital, Guangdong, China; 4. Sir Run Run Shaw Hospital Zhejiang University School of Medicine, Zhejiang, China; 5. The 960th Hospital of the PLA Joint Logistic Support Force, Shandong, China; 6. Shengjing Hospital of China Medical University, Liaoning, China; 7. First hospital of Shanxi Medical University, Shanxi, China; 8. The First Affiliated Hospital of Dalian Medical University, Liaoning, China; 9. Yunnan Cancer Hospital, The Third Affiliated Hospital of Kunming Medical University, Yunnan, China; 10. 3DMedicines Co. Ltd. Sichuan, China.

BACKGROUND

- Envafolimab is a novel fusion protein of humanized anti-PD-L1 single domain antibody and human IgG1 Fc fragment formulated for subcutaneous injection.
- The Fc part was mutated to remove the antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) effects to minimize side effects.
- Envafolimab is the world’s first subcutaneously injectable anti-PD-L1 antibody approved by China’s National Medical Products Administration with the injection time of less than 20 seconds.
- Envafolimab has been investigated globally (the United States, Japan, and China) in approximately 1200 subjects enrolled in thirteen clinical studies.

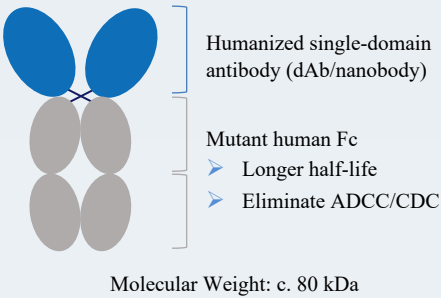


Figure 1. Envafolimab

METHOD

- This was a multicenter, open-label phase Ib/II study of envafolimab (400 mg Q4W) in combination with lenvatinib in patients with advanced solid tumors conducted in China.
- Phase Ib evaluated the safety, tolerability of envafolimab in combination with lenvatinib and determined recommended phase II dose (RP2D) of lenvatinib.
- Phase II was divided into two cohorts. Cohort 1, PD-(L)1 inhibitor therapy resistant advanced non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC). Cohort 2, subjects with advanced RCC who had not received prior systemic therapy for advanced stage were enrolled and randomized 1:1 to receive either envafolimab in combination with lenvatinib or sunitinib monotherapy.
- The primary endpoint of Phase II was objective response rate (ORR) per RECIST v1.1, and the secondary endpoint of Phase II were median duration of response (mDOR) and median progression-free survival (mPFS).
- Study design is shown in Figure 2.

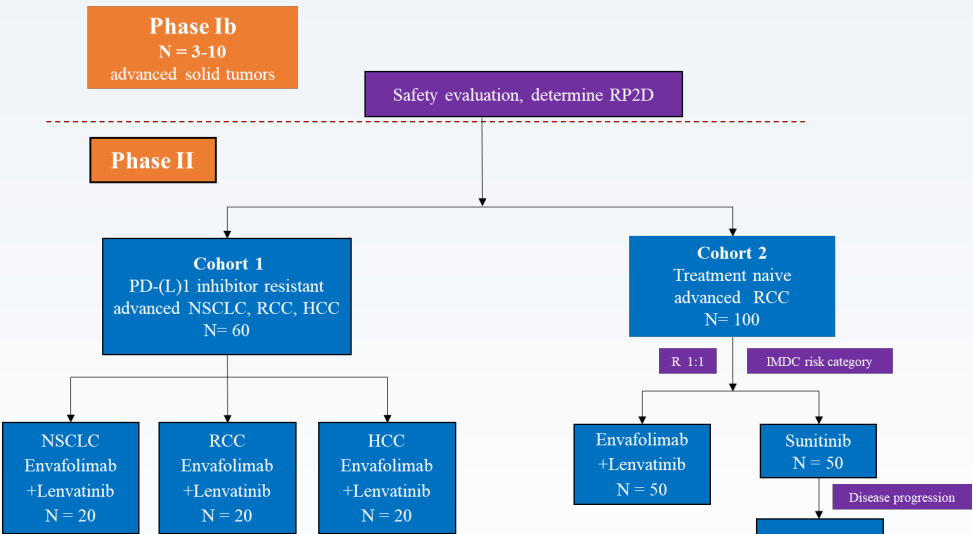


Figure 2. Study Design

RESULTS

- As cutoff date of March 31 2023, 28 patients were enrolled in phase Ib (n = 6) and the phase II expansion (n = 22). There were no subjects enrolled in the PD-(L)1 resistant HCC.
- The RP2D established in Phase Ib was envafolimab 400 mg every 4 weeks plus lenvatinib 20 mg/d.
- The median follow-up was 10.9 months in Phase II.

Efficacy

- Phase II Cohort 1:
 - In PD-(L)1 resistant NSCLC (n=11), the ORR was 27.3 % (95% CI: 6.0% to 61.0%), the median duration of response (mDOR) was 4.2 months (95% CI: 3.7 to NE) and the median progression-free survival (mPFS) was 8.1 months (95% CI: 1.8 to NE).
 - In PD-(L)1 resistant RCC (n=2), the ORR was 50.0 % (95% CI: 1.3% to 98.7%), the mDOR was NE (95% CI: NE to NE) and the mPFS was NE (95% CI, 7.4 to NE).
- Phase II Cohort 2:
 - In the treatment group of envafolimab in combination with lenvatinib (n=5), the ORR was 80.0% (95% CI: 28.4% to 99.5%), the mDOR was NE (95% CI: NE to NE) and the mPFS was NE (95% CI, NE to NE).
 - In the treatment group of sunitinib (n=4), the ORR was 50.0% (95% CI: 6.8% to 93.2%), the mDOR was NE (95% CI: NE to NE) and the mPFS was NE (95% CI, NE to NE).

Table 1. Best Overall Response of Phase II Patients				
	PD-(L)1 inhibitor resistant NSCLC	PD-(L)1 inhibitor resistant RCC	Treatment naive advanced RCC	Treatment naive advanced RCC
	Envafolimab+ Lenvatinib N=11	Envafolimab+ Lenvatinib N=2	Envafolimab+ Lenvatinib N=5	Sunitinib N=4
BOR				
CR	0	0	0	0
PR	3 (27.3%)	1 (50.0%)	4 (80.0%)	2 (50.0%)
SD	6 (54.5%)	1 (50.0%)	0	1 (25.0%)
PD	2 (18.2%)	0	0	0
NE	0	0	1 (20.0%)	1 (25.0%)
ORR	3 (27.3%)	1 (50.0%)	4 (80.0%)	2 (50.0%)
ORR 95%CI	6.0% - 61.0%	1.3% - 98.7%	28.4% - 99.5%	6.8% - 93.2%
mDoR (month, 95%CI)	4.2 (3.7, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
mPFS (month, 95%CI)	8.1 (1.8, NE)	NE (7.4, NE)	NE (NE, NE)	NE (1.1, NE)
BOR: best overall response; CR: complete response; mDOR: median duration of response; mPFS: median progression-free survival; NE: not evaluated; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.				

Safety:

- Patients in the treatment group of envafolimab in combination with lenvatinib:
 - 100% had treatment-related adverse events (TRAEs);
 - 70.8% had Grade 3 or higher TRAEs;
 - 20.8% had serious TRAEs;
 - No grade 5 TRAEs and no TRAEs leading to permanent discontinuation of envafolimab or lenvatinib.
 - The most common TRAEs were proteinuria (75.0%), hypothyroidism (70.8%), hypertension (62.5%), platelet count decreased (41.7%) and palmar-plantar erythrodysesthesia syndrome (33.3%).
- Patients in the treatment group of sunitinib:
 - 75.0% had treatment-related adverse events (TRAEs);
 - 50.0% had Grade 3 or higher TRAEs;
 - 25.0% had serious TRAEs;
 - No grade 5 TRAEs and no TRAEs leading to permanent discontinuation of sunitinib.
 - The most common TRAEs were platelet count decreased (75.0%), hypertension (50.0%), white blood cell count decreased (50.0%), neutrophil count decreased (50.0%), hyponatremia (50.0%), blood thyroid stimulating hormone increased (50.0%), diarrhea (50.0%).

Table 2. Safety Summary		
Adverse Events	Envafolimab+ Lenvatinib N=24	Sunitinib N=4
Any grade, n(%)	24 (100.0%)	4 (100.0%)
Treatment-related	24 (100.0%)	3 (75.0%)
Grade 3-4, n(%)	18 (75.0%)	2 (50.0%)
Treatment-related	17 (70.8%)	0
Grade 5, n(%)	1 (4.2%)	2 (50.0%)
Treatment-related	0	0
Serious AE, n(%)	8 (33.3%)	1 (25.0%)
Treatment-related	5 (20.8%)	1 (25.0%)
Leading to permanent discontinuation of treatment	0	0

CONCLUSIONS

- Envafolimab in combination with lenvatinib demonstrated a robust preliminary ORR and mPFS in PD-(L)1 resistant NSCLC patients with manageable safety profile.
- In consistent with the results from other intravenous anti-PD-1 antibody plus Lenvatinib in RCC patients, subcutaneous injection of envafolimab with lenvatinib provided a more convenient dose regimen in this population.
- Further evaluation of this combination therapy are underway in both populations and endometrial cancer.