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Envafolimab (KN035) in advanced tumors with mismatch-repair deficiency

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Background:

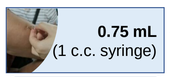
- Envafolimab (KN035), a novel subcutaneously administered PD-L1 single domain antibody, showed acceptable safety and encouraging antitumor activity in preclinical and early clinical studies[1,2].
- Microsatellite instability-high or mismatch repair deficient (MSI-H/dMMR) results in exceptionally high number of mutations/mutant neoantigens and predicts sensitivity to PD-(L)1 blockade regardless of cancers' tissue of origin[3].
- Patients with advanced MSI-H/dMMR cancer who failed standard of care have no satisfactory alternative treatment options and poor prognosis.
- Pembrolizumab and nivolumab have been approved for the treatment of patients with previously treated dMMR/MSI-H advanced cancers. However, no PD-(L)1 inhibitors has been approved in China.

Methods:

- This is a single arm, pivotal, multicenter, phase 2 study performed in China to evaluate efficacy and safety of envafolimab in subjects with previously treated dMMR/MSI-H advanced cancer.

Key Eligibility Criteria

- Age ≥ 18 years
- Locally advanced or metastatic solid tumors
- Centrally confirmed MSI-H for colorectal cancer (CRC) and gastric cancer (GC), and locally confirmed dMMR for other tumors
- ≥ 1 prior line of therapy
- ECOG PS 0~1
- Measurable disease per RECIST 1.1



0.75 mL (1 c.c. syringe)

Tumor assessments were every 8 weeks

Envafolimab 150 mg weekly → Until PD, unacceptable toxicity, or withdrawal → Survival follow-up

- **Primary endpoint:** objective response rate (ORR) per RECIST v1.1 by blinded independent radiology review (BIRC).
- **Secondary endpoints:** duration of response (DoR), disease control rate (DCR), progression free survival (PFS) and overall survival (OS).

- The primary efficacy population (PEP) included subjects with CRC who had failed fluoropyrimidine (F), oxaliplatin (O), and irinotecan (I) plus those with advanced GC who had failed at least one prior systemic treatment.
- The report is based on a pre-planned analysis after the first 50 subjects in the PEP had at least two on-study tumor assessments (PEP_i).

Results:

- From August 22, 2018 to December 5, 2019, 103 subjects with MSI-H/dMMR advanced cancers were enrolled at 25 centers.
- The PEPi included 39 subjects with CRC and 11 with GC, with a median follow-up of 7.5 months. The median number of prior systemic treatment was 3.
- The overall population (n=103) included 65 subjects with CRC (24 had prior therapy with F and O or I), 18 with GC, and 20 with other tumors, with a median follow-up of 6.7 months. The median number of prior systemic treatment was 2.
- The confirmed ORR (BIRC) was 34.0% (35/103, 5 CRs and 30 PRs) in overall population.

Table 1. Efficacy results in subjects who had completed ≥ 2 on-study tumor assessments

	PEPi			CRC failed F and O or I (n=24)	Other tumors (n=20)
	CRC (n=39)	GC (n=11)	Total (n=50)		
Confirmed ORR (BIRC)	28.2%	36.4%	30.0%	54.2%	35.0%
DCR (BIRC)	59.0%	72.7%	62.0%	66.7%	65.0%
6-month DoR (BIRC)	63.0%	100.0%	71.9%	88.9%	100%
Median PFS (BIRC), months	4.9	11.1	6.6	11.1	5.6
Median OS, months	Not reached				
12-month OS rate	61.5%	68.2%	63.7%	90.5%	76.8%

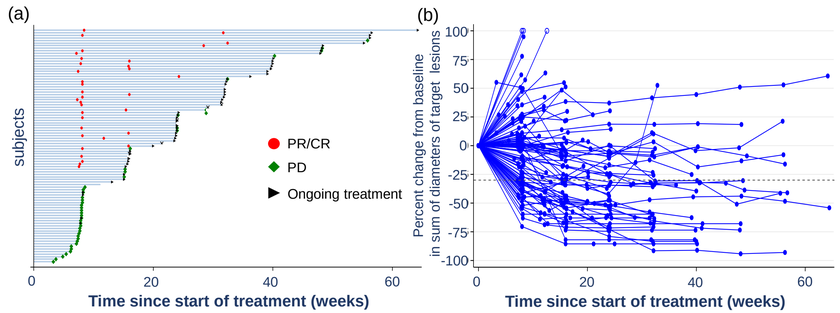


Figure 1. Tumor response over time in overall population
Swimmer plot of disease status over time (a)
Spider plot of change in sum of diameters of target lesions by subjects over time (b)

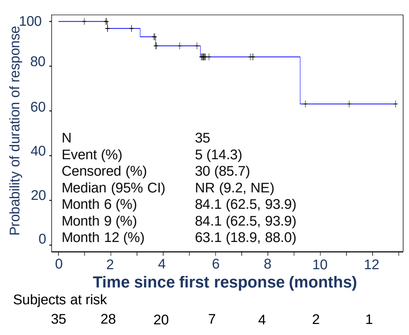


Figure 2. DoR in subjects with a confirmed response per BIRC in overall population

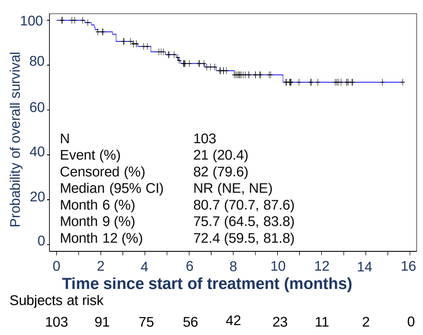


Figure 3. OS in overall population

- Efficacy results (**Table 1**) were similar across tumor types and independent of central (PCR/MSI-H: CRC/GC) or local tests (IHC/dMMR: other tumors).
- The most common drug related treatment emergent adverse events (TEAEs) were shown in **Table 2**.
- Injection site reactions were observed in 6 (5.8%) subjects (all grade 1~2) without drug related serious TEAEs or dose modification reported.
- No infusion reactions, pneumonitis, colitis, or unexpected safety signal was reported.

Table 2. Drug Related TEAEs

Drug related TEAEs	Overall population (n=103)	
Any grade	79 (76.7%)	
Grade 3-4	14 (13.6%)	
Grade 5	0	
Lead to discontinuation	1 (1.0%)	
Incidence≥ 10%	**Any grade**	**Grade 3-4**
White blood cell count decreased	16 (15.5%)	0
Fatigue	15 (14.6%)	0
Rash	15 (14.6%)	1 (1.0%)
Hypothyroidism	13 (12.6%)	0
Neutrophil count decreased	11 (10.7%)	1 (1.0%)

Conclusion:

- Envafolimab demonstrated robust durable antitumor activity in patients with previously treated advanced MSI-H/dMMR cancer, a population with high unmet need for effective treatment options in China.
  - Confirmed ORR per BIRC were 30.0%, 35.0% and 34.0% in PEPi, other tumors and overall population, respectively.
  - Median DoR not reached with 6-month DoR of 71.9%, 100% and 84.1% in PEPi, other tumors, and overall population, respectively.
  - Median OS not reached with 12-month OS rates of 63.7%, 76.8% and 72.4% in PEPi, other tumors, and overall population, respectively.
- Safety profile was similar to other PD-(L)1 antibodies but without infusion reactions. No colitis or pneumonitis case was reported in the study.
- The data support envafolimab as a new promising and convenient treatment option with durable benefit for patients with heavily previously treated advanced MSI-H/dMMR cancer.

References

1. *Xu JM et al. 2019 ASCO annual meeting, Abstract 2608.*
2. *Shimizu T et al. 2019 ASCO annual meeting, Abstract 2609.*
3. *Le DT et al. Science. 2017; 357(6349): 409-413.*

- *For questions or comments on this poster, please contact Dr. Shen at linshenpku@163.com.*