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Efficacy and Safety of Penpulimab (AK105), a New Generation Anti-Programmed Cell Death-1 (PD-1) Antibody, in Upper Gastrointestinal Cancers

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Background

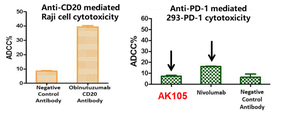
Penpulimab (AK105): Potential for Best-in-class

- Upper gastrointestinal (UGI) cancers are a group of highly aggressive malignancies with poor prognoses. Immunotherapy is emerging as an effective treatment option for some of these cancers.
- Penpulimab, a new generation anti-PD-1 monoclonal antibody, with unique binding epitope, was engineered to eliminate Fc-mediated effector function that compromises anti-tumour immune cell function, and to optimize receptor occupancy by improving duration of drug binding.
- Here, we present the preliminary antitumor and safety data on Penpulimab in patients with advanced UGI malignancies.

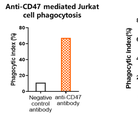
Structurally and Functionally Differentiated

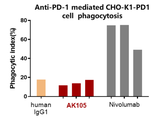
#1. Complete removal of Fc receptor binding (Elimination of ADCC/ADCP): better safety

Penpulimab (AK105) exhibits no ADCC, as compared to nivolumab



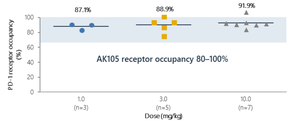
Penpulimab (AK105) exhibits no ADCP, as compared to nivolumab

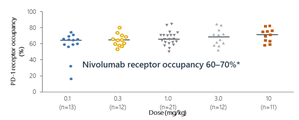




#2. Slower antigen binding off-rate: better receptor occupancy and efficacy

Higher receptor occupancy compared to Nivolumab may potentially result in higher clinical efficacy

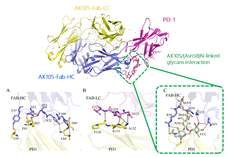




*Agrawal S, *et al.* Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. *J. for immunotherapy of cancer* 4, 72 (2016).

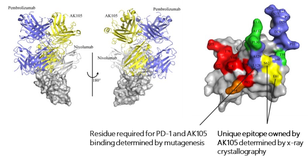
#3. Unique binding epitope as shown by x-ray crystal structure

Penpulimab (AK105) shows contacts with ASN58 glycosylation on PD-1 BC loop which are not reported in Pembrolizumab and Nivolumab



(a) Fab-HC (b) Fab-LC. (c) Interactions between Fab-HC and (Asn58)N-linked glycans. Residues involved in the hydrogen bond and salt bridge interaction are shown as sticks and labeled. Hydrogen bonds and salt bridges are shown as dashed black lines.

Penpulimab (AK105) has different epitope from Pembrolizumab and Nivolumab



(left) Superposition of PD-1-Nivolumab-Fab, PD-1-Pembrolizumab-Fab with the PD-1-AK105 complex structure. Nivolumab-Fab , Pembrolizumab-Fab and AK105 are colored in slate, grey and yellow, respectively. PD-1 is shown as surface representation.
(right) Binding surface of PD-1 with AK105, Pembrolizumab or Nivolumab. The residues in contact with AK105 are colored in yellow, whereas residues in contact with Nivolumab are colored in red, respectively, and the overlapping residues bounded by both AK105 and Nivolumab are colored in orange. The residues in contact with Pembrolizumab are colored in slate, and the overlapping residues bounded by both AK105 and Pembrolizumab are colored in green.

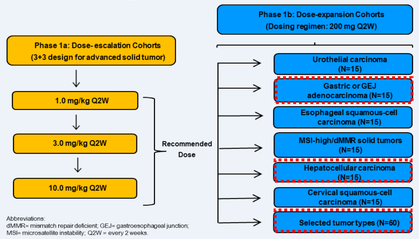
Study Design

- Patients with advanced cancers, relapsed or refractory to standard therapy, or for which no effective standard therapy is available, or the subject refuses standard therapy were enrolled in two Phase 1 trials of Penpulimab (NCT03352531 and NCT04172506).
- Patient received Penpulimab IV at 1-10 mg/kg Q2W or 200mg Q2W until disease progression or unacceptable toxicity.
- Tumour assessments were performed 8-weekly.

Key Inclusion & Exclusion Criteria

- Age ≥ 18 years
- ECOG PS of 0-1
- ≥ 1 measurable lesion according to RECIST 1.1
- No prior exposure to immune checkpoint inhibitors (ICIs)
- No active or prior documented autoimmune disease within the past 2 years

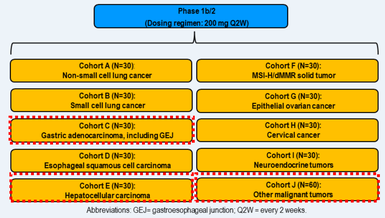
Study Design (NCT03352531) Phase 1a/1b



Abbreviations:
dMMR= mismatch repair deficient; GEJ= gastroesophageal junction; MSI= microsatellite instability; Q2W = every 2 weeks.

Primary endpoints Safety & Tolerability, MTDs
Secondary endpoints Preliminary antitumor activity, PK & Immunogenicity, Pharmacodynamic markers

Study Design (NCT04172506) Phase 1b/2



Abbreviations: GEJ= gastroesophageal junction; Q2W = every 2 weeks.

Primary endpoint ORR
Secondary endpoints DoR, PFS, DCR, OS
Exploratory endpoints PD-L1, TMB

Results

Patient Characteristics

Safety Analysis Set (n=67)

Characteristics	PCA n=11	CCA n=12	Gastric/GEJ * n=21	HCC n=23
Age (Years)				
Median	65.0	66.0	61.0	62.0
Min - Max	49 - 80	48 - 79	30 - 78	33 - 79
Gender (%)				
Male	4 (36.4)	7 (58.3)	18 (85.7)	19 (82.6)
Female	7 (63.6)	5 (41.7)	3 (14.3)	4 (17.4)
ECOG (%)				
0	6 (54.5)	2 (16.7)	8 (38.1)	14 (60.9)
1	5 (45.5)	10 (83.3)	13 (61.9)	9 (39.1)
Prior lines of therapy (%)				
0	1 (9.1)	0	0	0
1	5 (45.5)	7 (58.3)	12 (57.1)	13 (56.5)
2	3 (27.3)	2 (16.7)	6 (28.6)	10 (43.5)
>2	2 (18.2)	3 (25.0)	3 (14.3)	0
Race (%)				
White	8 (72.7)	8 (66.7)	13 (61.9)	11 (47.8)
Asian	1 (9.1)	2 (16.7)	9 (42.9)	12 (52.2)
Other	2 (18.2)	2 (16.7)	1 (4.8)	0

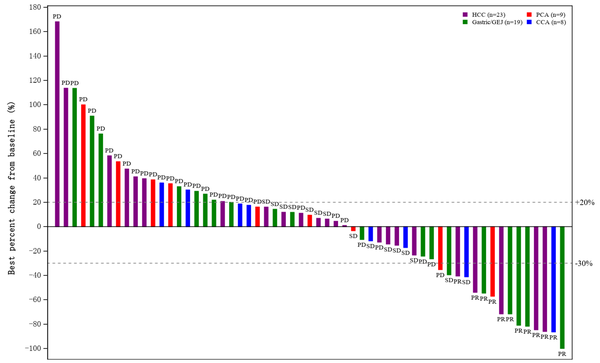
* In the Gastric/GEJ Adenocarcinoma cohort, HER2 status was: HER2+ n=2, HER2– n=13, and unknown n=6.
PCA, Pancreatic Cancer ; CCA, Cholangiocarcinoma; Gastric/GEJ, Gastric or GEJ adenocarcinoma; HCC, Hepatocellular carcinoma

Efficacy Summary

Best Overall Response
Efficacy Analysis Set (n=60)

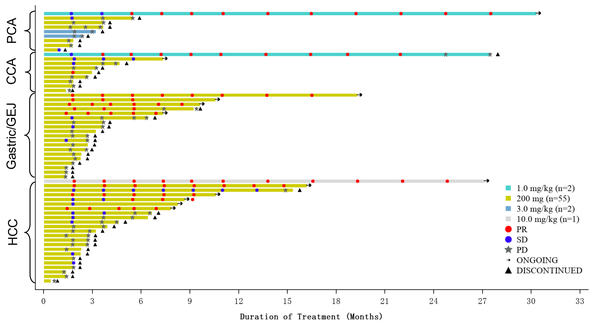
Response n (%)	PCA n=9	CCA n=9	Gastric/GEJ n=19	HCC n=23
CR	0	0	0	0
PR	1 (11.1)	2 (22.2)	5 (26.3)	5 (21.7)
SD	2 (22.2)	2 (22.2)	3 (15.8)	7 (30.4)
PD	6 (66.7)	5 (55.6)	11 (57.9)	11 (47.8)
ORR (95% CI)	11.1 [0.3, 48.2]	22.2 [2.8, 60.0]	26.3 [9.1, 51.2]	21.7 [7.5, 43.7]
DCR (95% CI)	33.3 [7.5, 70.1]	44.4 [13.7, 78.8]	42.1 [20.3, 66.5]	52.2 [30.6, 73.2]
Median for DoR (95% CI)	NR [NE, NE]	21.1 [NE, NE]	NR [NE, NE]	NR [NE, NE]

Best Percentage Change in Tumour Size from Baseline (n=59)*



* One subject with CCA was assessed to have PD at first post-baseline scan but tumour measurements are not available.

Duration of Treatment (n=60)



Conclusion

- **Penpulimab was well tolerated and demonstrated encouraging antitumor activity with durable response in pts with advanced UGI cancers, including PCA and CCA, which are generally resistant to single agent ICI**
- **Penpulimab in combination with anlotinib, a multi-targeted receptor tyrosine kinase inhibitor, is being evaluated in Phase 3 studies for 1L HCC (NCT04344158) and 2L Gastric/GEJ (NCT04385550).**

- As of 1st July 2020, 67 pts with UGI cancers had received Penpulimab with a median of 6 (1–64) doses.
- Of 60 pts evaluable for response, ORRs of 11.1% to 26.3% across cohorts were seen with maximum tumour shrinkage of up to 100% seen in a pt with Gastric/GEJ adenocarcinoma.
- 11/13 (85%) responders had ongoing responses at data cutoff date.
- 4 out of 12 (33.3%) Gastric /GEJ pts with PR were HER2 negative. Neither of the two HER2 positive patients responded to Penpulimab. The HER2 status of 1 responder is unknown.

Safety Summary

Safety Analysis Set (n=67)

Subjects with at least one AE n (%)	PCA n=11	CCA n=12	Gastric/GEJ n=21	HCC n=23
Subjects with at least one AE	11 (100.0)	11 (91.7)	20 (95.2)	22 (95.7)
TRAEs	5 (45.5)	4 (33.3)	10 (47.6)	11 (47.8)
Grade ≥ 3 AE	6 (54.5)	7 (58.3)	10 (47.6)	8 (34.8)
Grade ≥ 3 TRAE	0 (0.0)	1 (8.3)	2 (9.5)	2 (8.7)
irAE	3 (27.3)	3 (25.0)	4 (19.0)	8 (34.8)
Grade ≥ 3 irAE	1 (9.1)	1 (8.3)	1 (4.8)	1 (4.3)
SAE	5 (45.5)	7 (58.3)	9 (42.9)	5 (21.7)
Related SAE	0 (0.0)	1 (8.3)	3 (14.3)	2 (8.7)

AE, adverse events; TRAE, treatment-related adverse events; irAE, immune-related AE; SAE, serious AE.

- 30 treatment-related adverse events (TRAEs) (44.8%).
- No TRAEs leading to drug discontinuation or death in study.
- 5 Grade ≥3 TRAEs (7.5%):
  - ◇ Raised liver enzymes (n=2)
  - ◇ Adrenal insufficiency & Hyponatraemia (n=1 each, in the same patient)
  - ◇ Intestinal obstruction (n=1)
  - ◇ Hypertension (n=1)

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