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Integrated Safety Analysis of Anti-Programmed Cell Death-1 (PD-1) Antibody Penpulimab in Advanced Solid tumor or Lymphoma

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Background

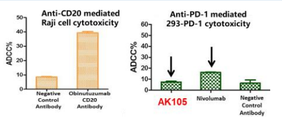
Penpulimab (AK105): Potential for Best-in-class

- Penpulimab is a humanized IgG1 mAb that blocks PD-1 binding to PD-L1, Penpulimab is engineered to eliminate FcγR binding and ADCC/ADCP completely, as compared to majority of marketed IgG4 PD-1 antibodies with ADCC/ADCP activity.
- Penpulimab demonstrates a slower PD-1 antigen binding off-rate than marketed PD-1 antibodies, which results in better cellular activity and higher receptor occupancy.
- Penpulimab also shows numerous contacts with N58 glycosylation on the BC loop of PD-1 which could be an advantage to facilitate interaction of PD-1 antibody.
- These structural differentiations offer more robust biological effect and enhance anti-tumor activity of Penpulimab.

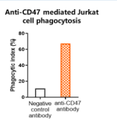
Structurally and Functionally Differentiated

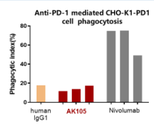
#1. Complete removal of Fc receptor binding (Elimination of ADCC/ADCP): better safety

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

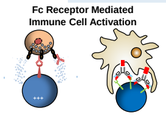


Penpulimab (AK105) exhibits no ADCP, as compared to nivolumab





Implication on Toxicity



Cytokine release

Chemokine release

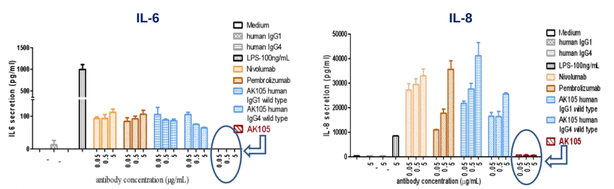
Amplification of Immune Reaction Cascade

Exacerbation of Immune Related Adverse Events

- Literature indicated a large number of IrAE is related to recruitment of immune cells bearing FcgR *(Abbas et al Crit Rew Immunol 2019; Collins et al Ann Oncol 2017；Jodai et al Immun Inflamm Dis 2019; Occhipinti et al Drug Saf Case Rep 2018)*
- Penpulimab: Removal of Fc receptor binding eliminates Fc receptor mediated immune cell recruitment and activation and could potentially reduce subsequent immune related adverse events.

IL-6 and IL-8 Effect on Efficacy and Toxicity

Penpulimab: No IL-6 or IL-8 secretion by human monocyte derived macrophages when cultured with PD-1 expressing cells.

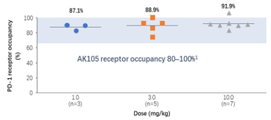


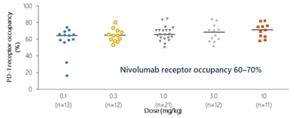
- PD-1 blockade in patients was found to prompt PD-1+ macrophages to produce IL-6 in the tumor microenvironment, and an increase of IL-6 during treatment was correlated with the poor clinical response to PD-1 blockade *(Tsukamoto et al. Cancer Res 2018)*.Moreover, upregulation of IL-6 is considered to play a critical role in irAE, such as cytokine release syndrome, ranged from mild to life-threatening symptoms in some patients with anti-PD-1 treatment *(Rotz et al. Pediatr Blood Cancer. 2017; Tanaka et al. J Dermatol Sci. 2017)*.
- Elevated serum IL-8 is known to associate with enhanced intratumor neutrophils and reduced clinical benefit of PD-1 antibody*(Schalper et al. Nat Med. 2020)*. Increased tumor IL-8 level was negatively associated with tumor IFN-γ and T-cell infiltration-related transcript signatures. An immune-suppressive effect of IL-6 on T-cell-mediated anti-tumor immunity has been widely reported *(Tsukamoto et al. Cancer Sci. 2018)*.

Abbreviations:IL-8= serum interleukin-8 ; irAE =immune-related adverse events.

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

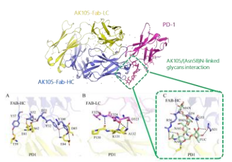
Higher receptor occupancy compared to Nivolumab may potentially result in higher clinical efficacy





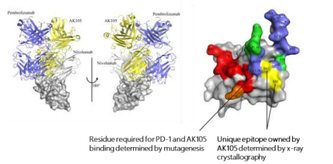
#3. Unique binding epitope as shown by x-ray crystal structure

AK105 shows contacts with (Asn58)N-linked 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.

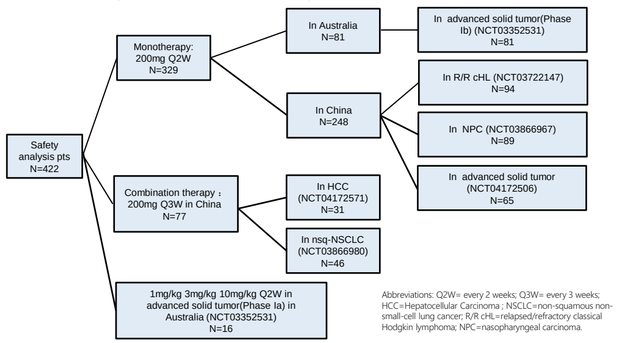
AK105 has different epitope from Pembrolizumab and Nivolumab



(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.

Methods

- This integrated safety analysis includes data from 422 patients (pts) treated with monotherapy or combination therapy of Penpulimab from 6 clinical trials: *NCT03352531* ,*NCT03722147* ,*NCT03866967* ,*NCT04172571* ,*NCT04172506* and *NCT03866980(Part 1)*.
- In this analysis, immune-related adverse events (irAEs) of Penpulimab is based on suspected irAEs confirmed by medical review.



Abbreviations: Q2W= every 2 weeks; Q3W= every 3 weeks; HCC=Hepatocellular Carcinoma ; NSCLC=non-squamous non-small-cell lung cancer; R/R cHL=relapsed/refractory classical Hodgkin lymphoma; NPC=nasopharyngeal carcinoma.

Results

Patient Characteristics

		200mg Q2W(N=329)	200mg Q3W(N=77)	All pts (N=422)
Age (n)		50.6[18,91]	58.8[24,74]	52.6[18,91]
Male n,(%)		203(61.7%)	57(74.0%)	263(62.3%)
Female n,(%)		126(38.3%)	20(26.0%)	159(37.7%)
ECOG	0	8(2.4%)	0	13(3.1%)
	1	143(43.5%)	30(39.0%)	184(43.6%)
	2	185(56.2%)	47(61.0%)	237(56.2%)

Drug exposure

	200mg Q2W(N=329)	200mg Q3W(N=77)	All pts (N=422)
Exposure time(days)	114.0[13,527]	143.5[16,388]	124.8[8,741]
≥3 months n,(%)	149(45.3%)	56(72.7%)	214(50.7%)
≥6 months n,(%)	65(19.8%)	19(24.7%)	90(21.3%)
≥9 months n,(%)	8(2.4%)	0	13(3.1%)
Exposure doses(n)	7.9[1,37]	6.5[1,16]	8.0[1,52]
Relative dose intensity(%)	98.43	95.26	97.91

Main types of tumor (≥10 pts)

types of tumor	n
R/R cHL	94
NPC	89
NSCLC	56
HCC	53
Gastric/GEJ cancer	21
Ovarian cancer	21
Pancreatic cancer	11
Esophageal cancer	11
Biliary duct carcinoma	11

Abbreviations: ECOG=Eastern Cooperative Oncology Group; GEJ=gastroesophageal junction; TRAE=treatment related AE; G:grade.

Safety Summary

	200mg Q2W(N=329)	200mg Q3W(N=77)	All pts (N=422)
TRAE n,(%)	226 (68.7%)	72 (93.5%)	309 (73.2%)
≥G3 TRAE n,(%)	34 (10.3%)	24 (31.2%)	60 (14.2%)
Serious TRAE n,(%)	19 (5.8%)	15 (19.5%)	35 (8.3%)
irAEs n,(%)	74 (22.5%)	16 (20.8%)	97 (23.0%)
≥G3 irAEs n,(%)	6 (1.8%)	3 (3.9%)	10 (2.4%)

irAEs	Penpulimab（N=422）	Sintilimab[a]（N=540）	Camrelizumab[b]（N=986）	Toripalimab[c]（N=598）	Pembrolizumab[d]（N=3830）	Nivolumab[e]（N=2578）
Pneumonia，%（≥G3 %）	0.9%（0.2%）	6.9%（3.5%）	2.7%（1.7%）	1.8%（1.0%）	3.6%（1.3%）	3.4%（0.9%）
Diarrhea/colitis，%（≥G3 %）	0.5%（0.0%）	0.2%（0.2%）	0.9%（0.9%）	0.2%（0.2%）	1.9%（1.2%）	13.1%（1.6%）
Hepatitis，%（≥G3 %）	1.2%（0.9%）	3.5%（3.2%）	9.1%（9.0%）	3.5%（3.2%）	0.6%（0.5%）	6.7%（2%）
Nephritis/renal dysfunction，%（≥G3 %）	0.2%（0.2%）	0.4%（0.2%）	0.4%（0.3%）	0.8%（0.7%）	0.4%（0.3%）	2.8%（0.5%）
Endocrinopathies，%（≥G3 %）	18.0%（0.2%）	17.8%（0.2%）	29.7%（1.0%）	21.0%（0.7%）	13.0%（0.5%）	9.6%（0.1%）
Skin AEs，%（≥G3 %）	4.0%（0.7%）	3.5%（0.9%）	2.8%（0.7%）	3.2%（0.0%）	1.6%（1.4%）	26.4%（1.2%）
Pancreatitis，%（≥G3 %）	0	3.1%（3.1%）	1.3%（1.3%）	2.7%（2.5%）	0.1%-1%	<1%
Thrombopenia，%（≥G3 %）	0	1.5%（1.5%）	1.7%（1.7%）	1.0%（1.0%）	0	0
Myocarditis，%（≥G3 %）	0	0.6%（0.2%）	0.3%（0.1%）	0	existed	<1%

a,b,c,d,e: from their package insert, respectively.

Conclusion

- Penpulimab has well safety characteristics compared with other marketed PD-1 inhibitors.
- Penpulimab demonstrates impressive safety profile with relatively lower incidence rate of ≥ Grade 3 immune-related adverse events.

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