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Penpulimab, an IgG1 anti-PD-1 antibody with Fc-engineering to eliminate effector functions and with unique epitope and binding properties

Presenter: Dr. Baiyong Li
Akeso Biopharma Co., Ltd.

DECLARATION OF INTERESTS

First name Last name: Baiyong Li

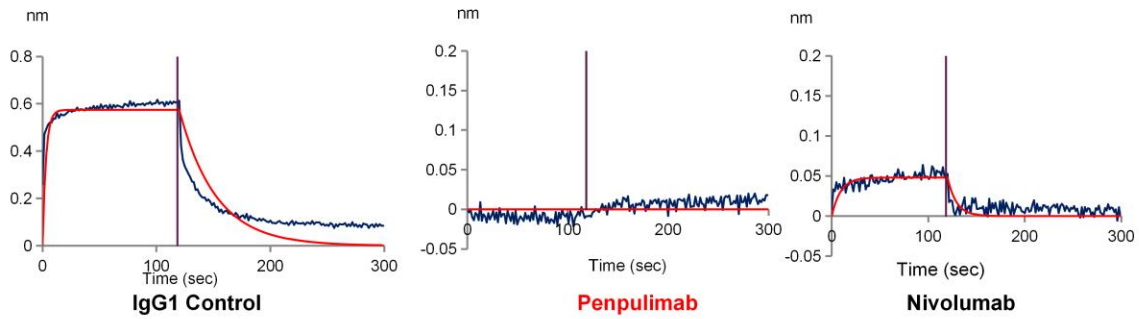
Please state your disclosures here: Baiyong Li has nothing to declare

Penpulimab (AK105): Differentiated PD-1 Antibody

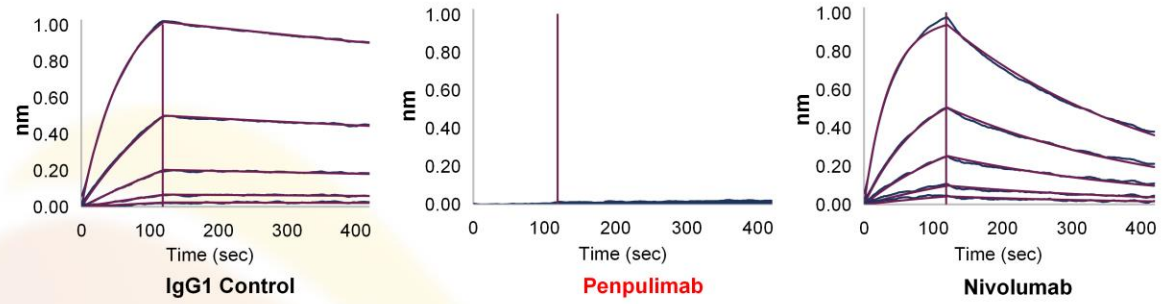
- Penpulimab (AK105) is an IgG1 PD-1 antibody developed by Akesobio
- Penpulimab features point mutations in the antibody Fc region to eliminate all Fc gamma receptor binding and associated effector function, and prevent the induction of pro-inflammatory cytokines
- Penpulimab was approved for marketing in China for cHL in August 2021
- Penpulimab for Nasopharyngeal carcinoma received Breakthrough Designation from the FDA, and the BLA has been submitted to the FDA

Penpulimab Fc-engineering to completely eliminate binding to FcγRs and thus avoid ADCC, ADCP

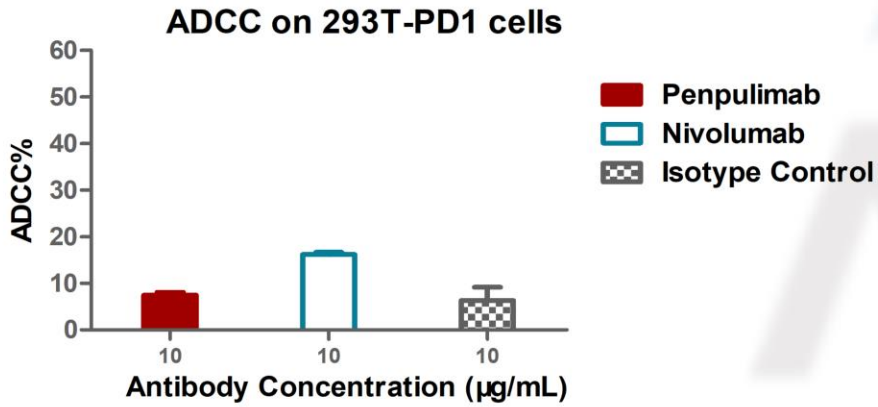
Penpulimab exhibits no binding to FcγRIIIa



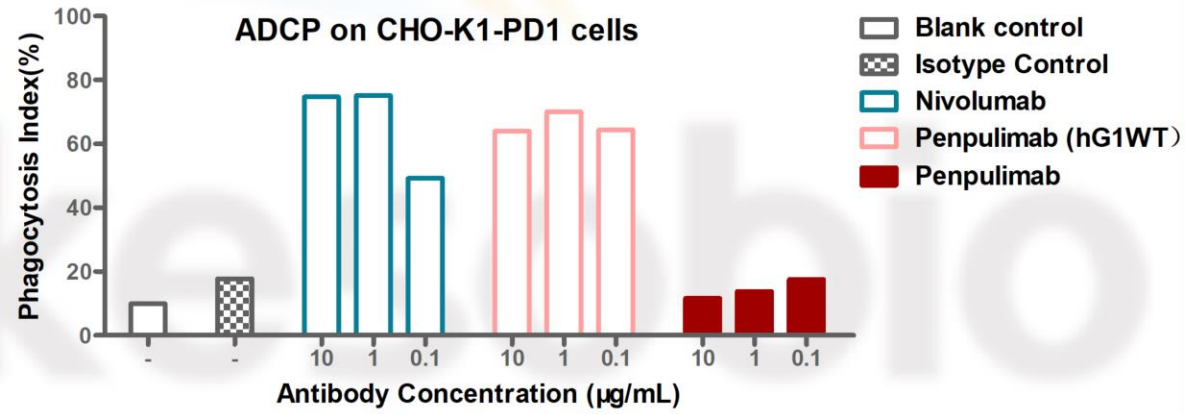
Penpulimab exhibits no binding to FcγRIa



Penpulimab exhibits no ADCC, as compared to nivolumab



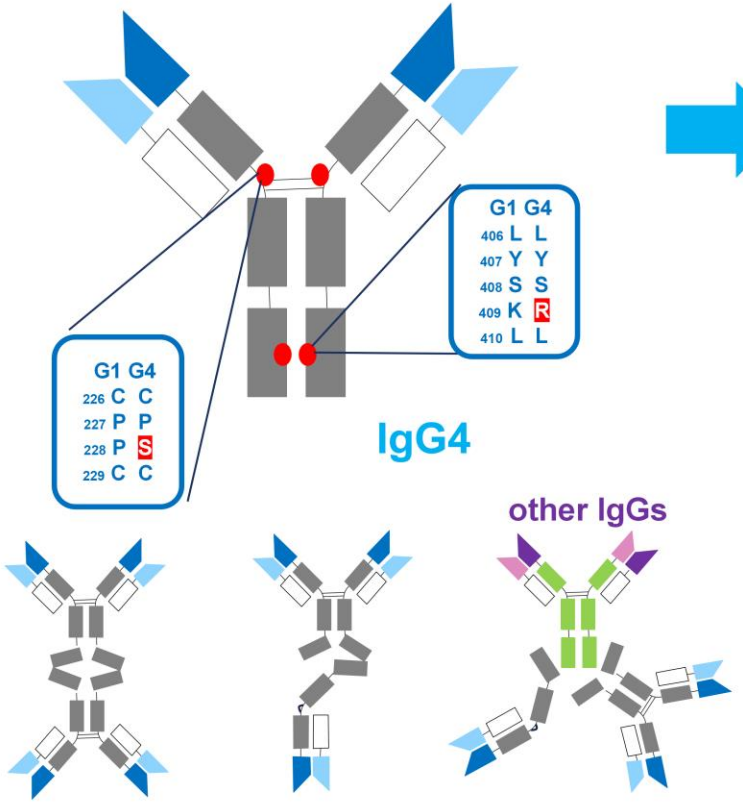
Penpulimab exhibits no ADCP, as compared to nivolumab



Ref: Dahan, Rony et al. Cancer cell. 2015

IgG4 intrinsic instability may compromise safety and efficiency

instability of IgG4 antibody



- **IgG4 is prone to interact with other IgGs via Fc-Fc interaction**
- **IgG4 is prone to leave more residual host cell protein compared to IgG1**

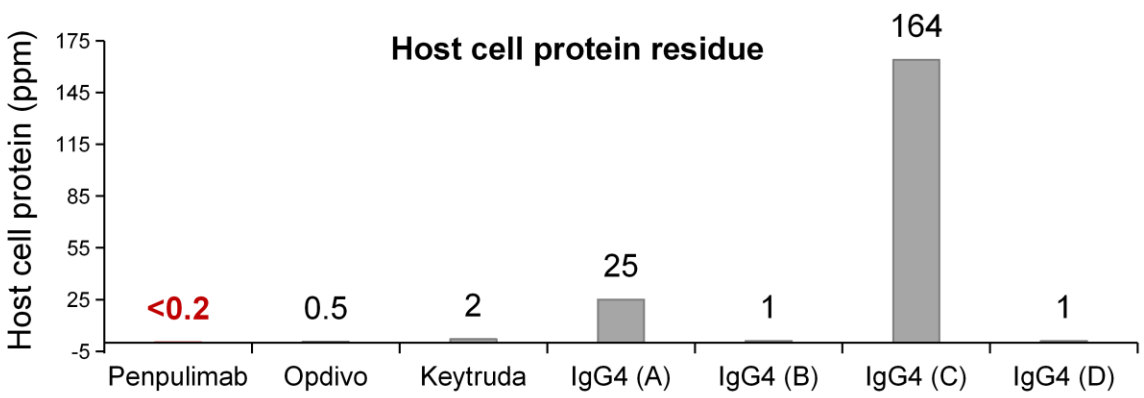
- **compromise of antitumor immunity**
- **risk of allergic reaction**

➢ Impair Fc-mediated antitumor immunity of endogenous tumor-specific antibody might contribute to the disease progress in cancers
(Rispens T. et al., Mol Immunol. 2013; Karagiannis P et al., J Clin Invest. 2013; Wang H. et al., J Immunother Cancer. 2020)

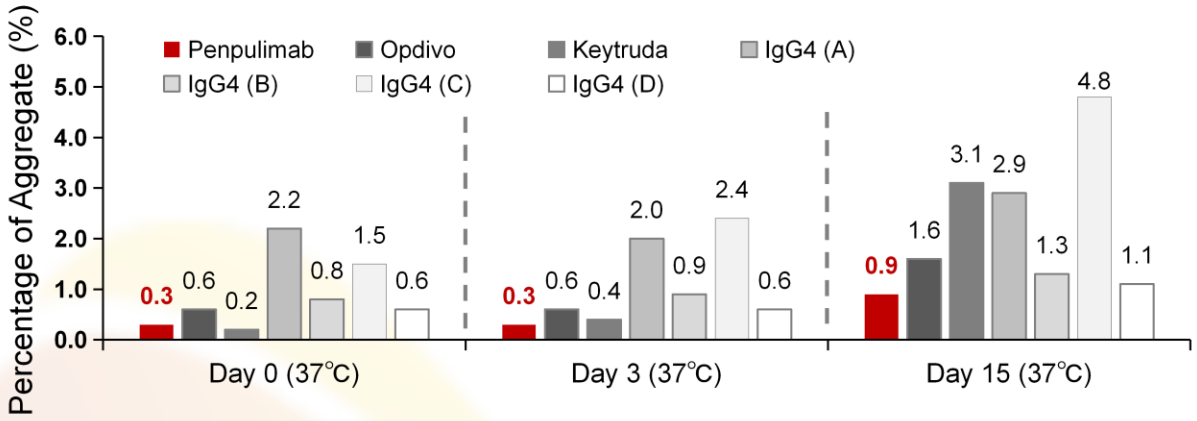
➢ Residual of host-cell protein, such as lipases of the host cells have been identified to trigger immune response in human, and as a potential causative agent for the degradation of formulation excipients
(Tran B et al., J Chromatogr A. 2016; Dixit et al., J. Pharm. Sci. 2016)

➢ **Penpulimab: IgG1 backbone more stable during manufacturing and storage process, thus may contribute to better safety and efficiency in the clinical**

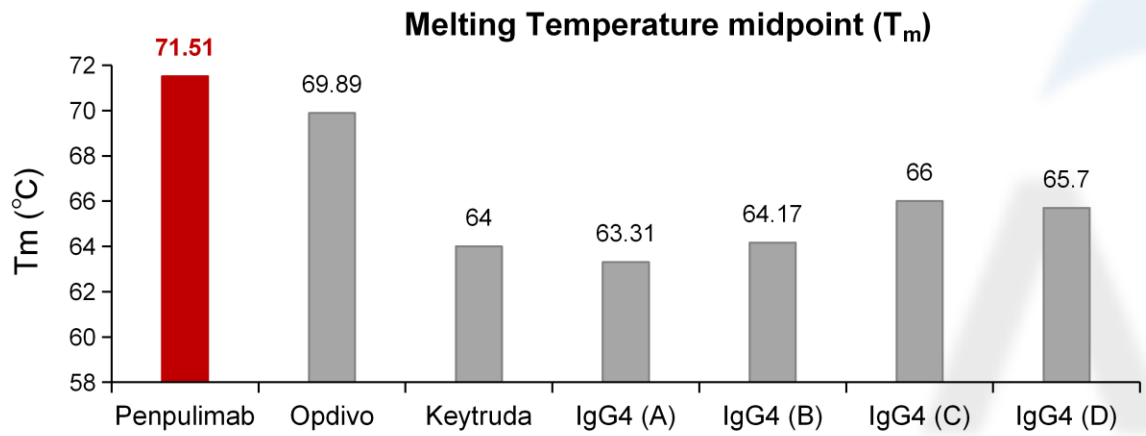
Penpulimab demonstrates better stability and quality features compared to PD-1 antibodies with IgG4 backbone



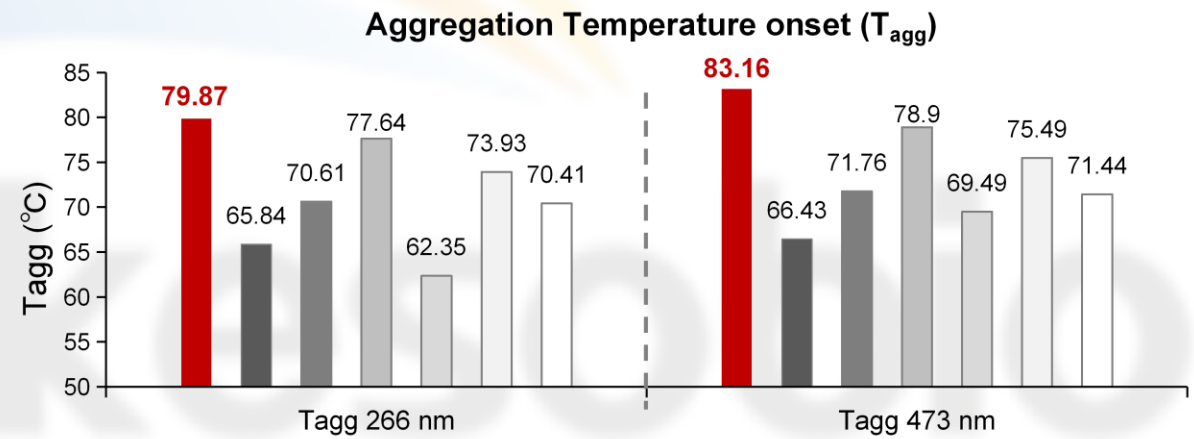
Low level HCP residue of Penpulimab compared with IgG4 backbone anti-PD1 antibody



Less aggregate of Penpulimab found in dilution stability test than IgG4 backbone anti-PD1 antibody



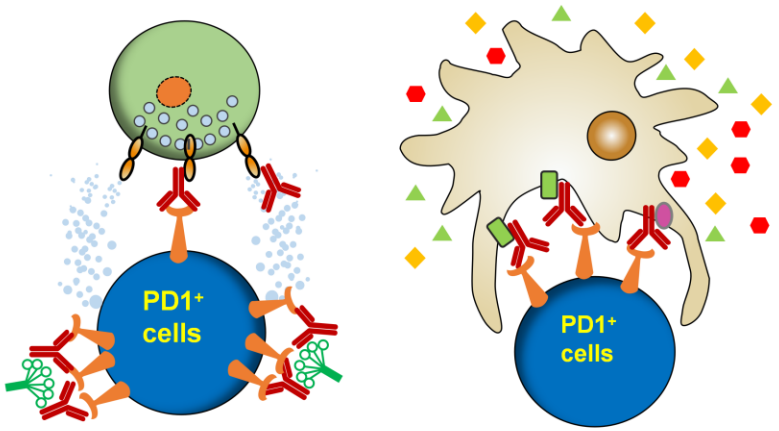
Higher T_m shows a better conformational stability of Penpulimab



Higher T_{agg} shows good colloidal stability of Penpulimab

Penpulimab Structural Differentiation: Implication on Adverse Events

Fc Receptor Mediated Immune Cell Activation



- **Cytokines release**
- **Chemokines release**
- **Amplification of Immune Reaction Cascade**
- **Effector functions**

Exacerbation of Immune Related Adverse Events

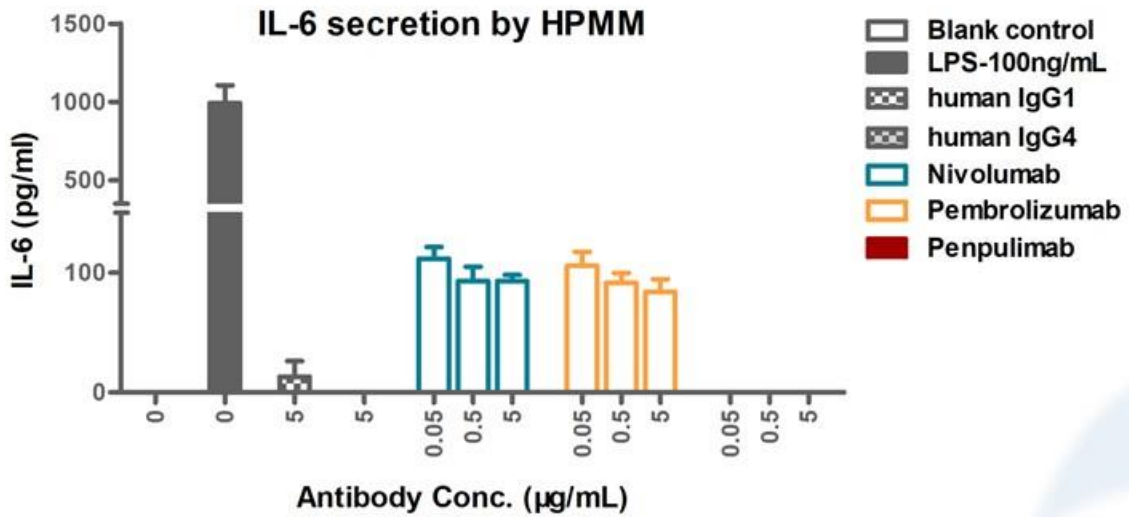
- Literature indicated a large number of irAEs are related to recruitment of immune cells bearing FcγR

(Abbas et al., 2019; Collins et al., 2017; Jodai et al., 2019; Occhipinti et al., 2018)

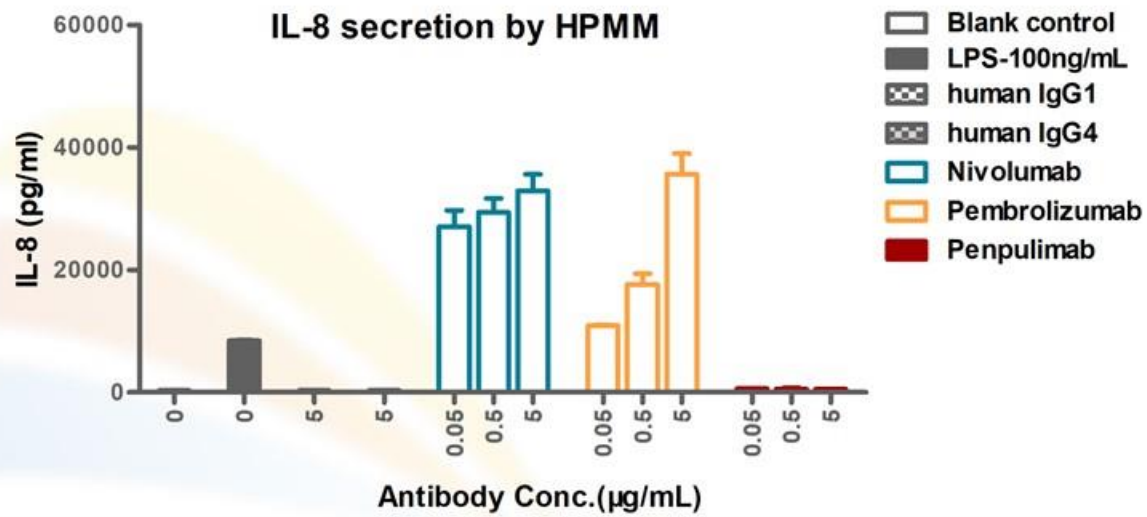
- **Penpulimab: Removal of Fcγ receptor binding eliminates Fcγ receptor mediated immune cell recruitment and pro-inflammatory cytokines production and could potentially reduce subsequent immune related adverse events**

Penpulimab Fc-engineering to avoid Fc-mediated pro-inflammatory cytokines release

Reduced IL-6 release may lower irAE



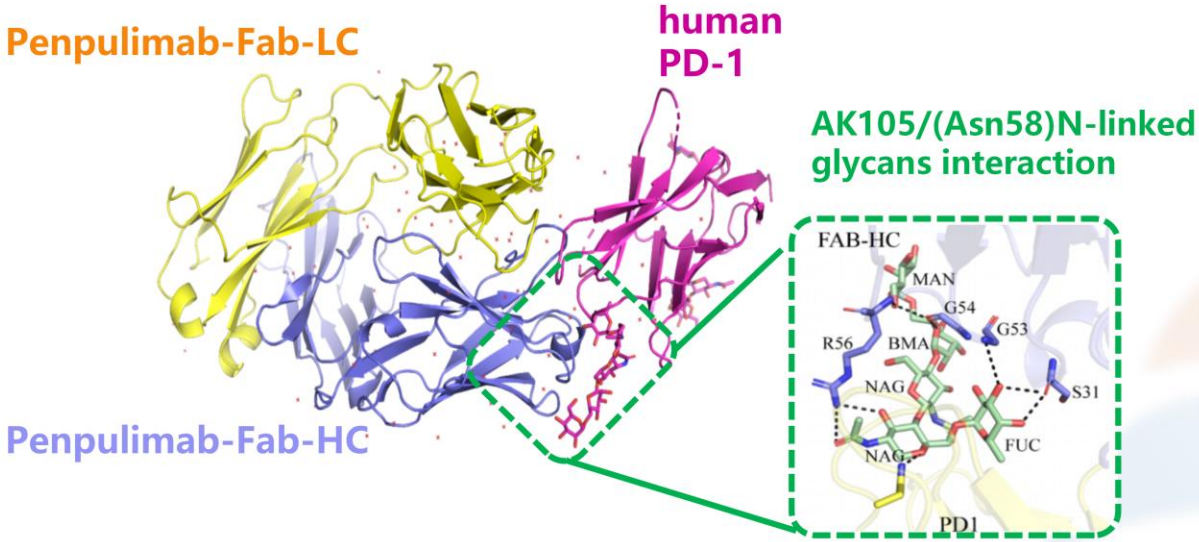
Reduced IL-8 release may enhance efficacy



- **IL-6 plays a critical role in immune-related adverse events (irAE) in patients with anti-PD-1 treatment**
  (Rotz et al. Pediatr Blood Cancer. 2017; Tanaka et al. J Dermatol Sci. 2017)
- **IL-6 and IL-8 are known to generate immune suppressive environment and play inhibitory role against therapeutic effect of PD-1 antibody**
  (Tsukamoto et al. Cancer Sci. 2018; Tsukamoto et al. Cancer Res 2018; Schalper *et al*. Nat Med. 2020)

Penpulimab Glycosylation dependent PD-1 binding

- **Penpulimab shows contacts with ASN_{58} glycosylation on PD-1 BC loop which are not reported in Pembrolizumab and Nivolumab**

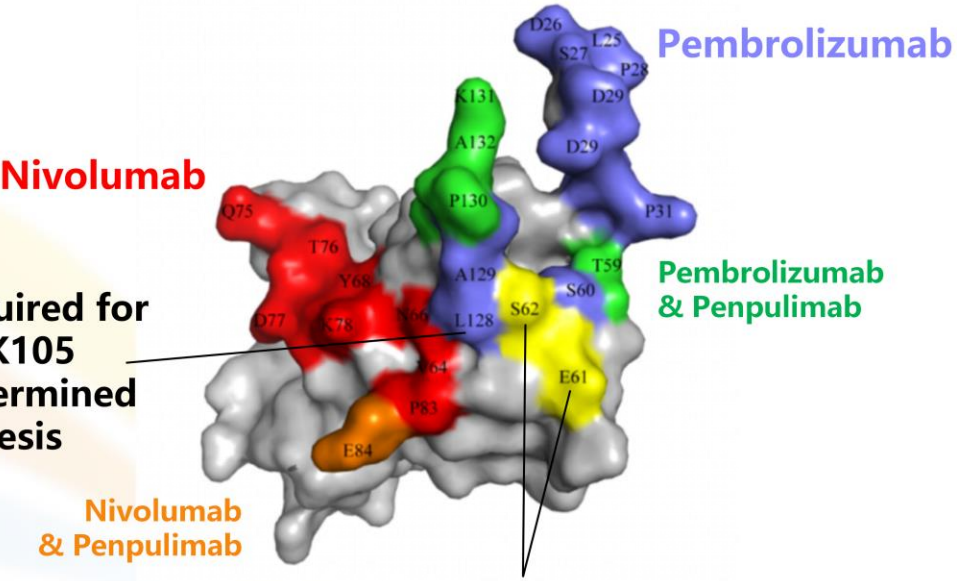


Interactions between Fab-HC and (Asn58)N-linked glycans. Residues involved in the hydrogen bond and salt bridge interaction are shown as sticks and labeled. Hydrogen bonds and salt bridges are shown as dashed black lines.

Antibody-antigen binding kinetics measured by Biacore

	K_D (M)	k_a (1/ms)	k_d (1/s)
Penpulimab	5.88E-10	1.62E+05	**9.51E-05**
Nivolumab	5.40E-10	4.50E+05	2.43E-04
Pembrolizumab	7.17E-10	3.91E+05	2.80E-04

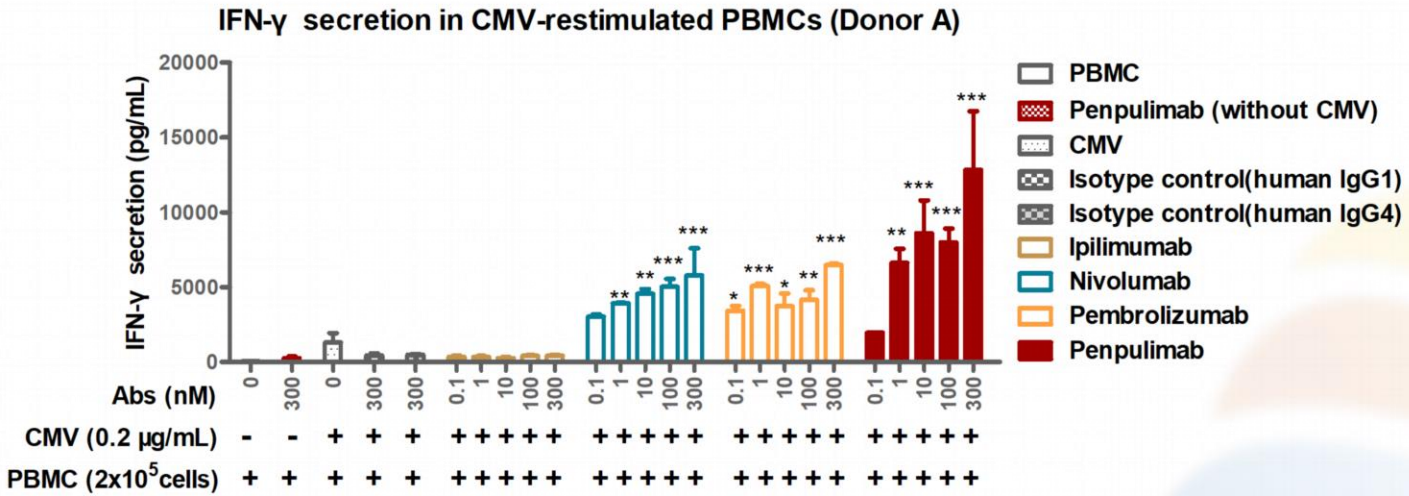
- **Penpulimab has a different epitope from Pembrolizumab and Nivolumab**

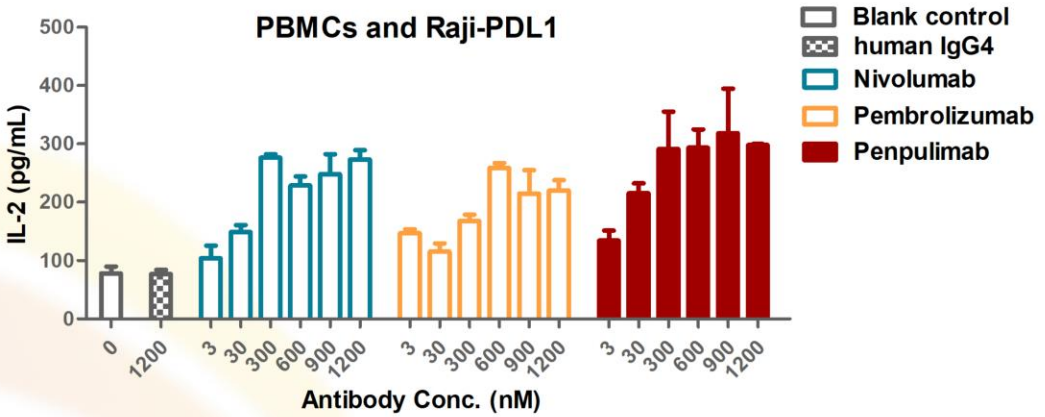


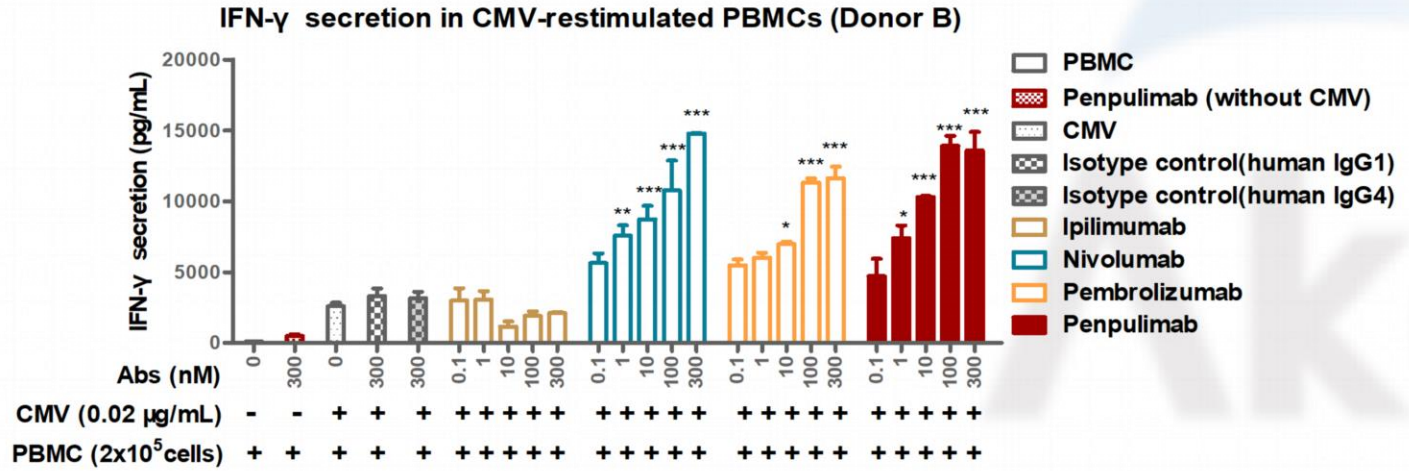
Unique epitope owned by Penpulimab determined by x-ray crystallography

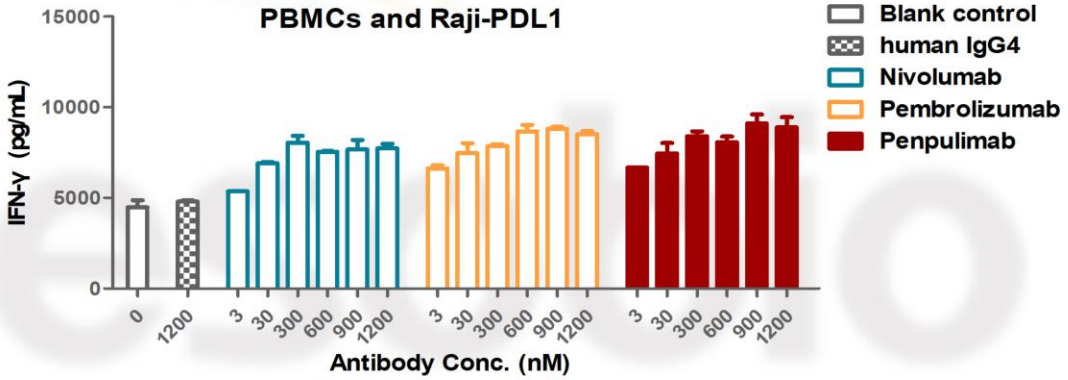
Binding surface of PD-1 with Penpulimab, Pembrolizumab and Nivolumab. The residues in contact with AK105 are colored in yellow, whereas residues in contact with Nivolumab are colored in red, respectively, and the overlapping residues bounded by both AK105 and Nivolumab are colored in orange. The residues in contact with Pembrolizumab are colored in slate, and the overlapping residues bounded by both AK105 and Pembrolizumab are colored in green.

Penpulimab Robust Cellular Activity: Cytokines Production in MLR









Note: Compared with isotype control, *p<0.05, **p<0.01, ***p<0.001.

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Anti-tumor Activity of Penpulimab in Dose Escalation (AUS, N=14) Trial

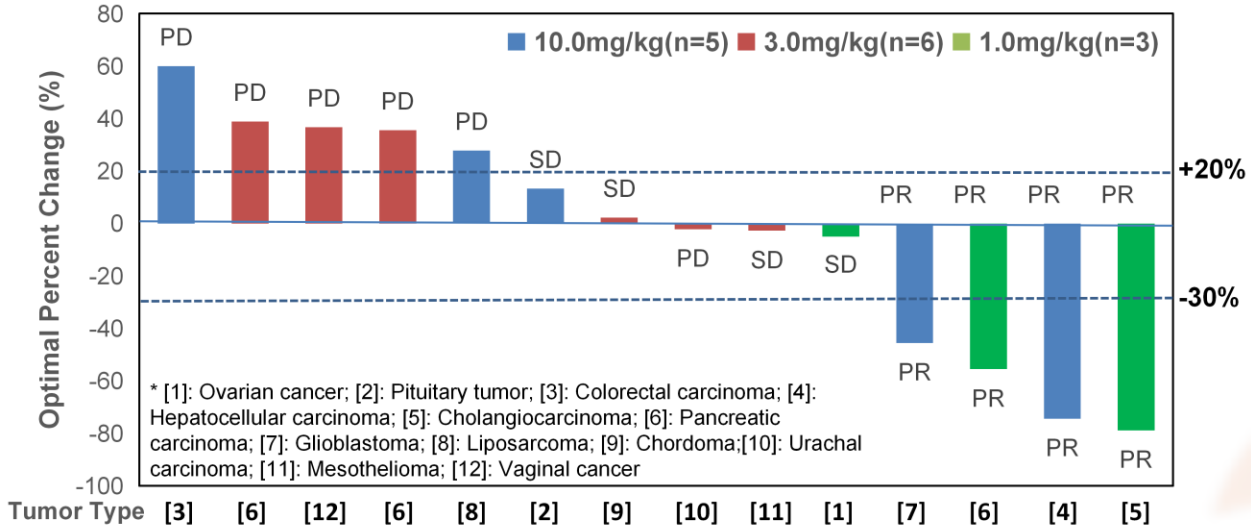


Figure 1 Waterfall plot of optimal percent change from baseline in tumor burden of target lesions – Phase Ia

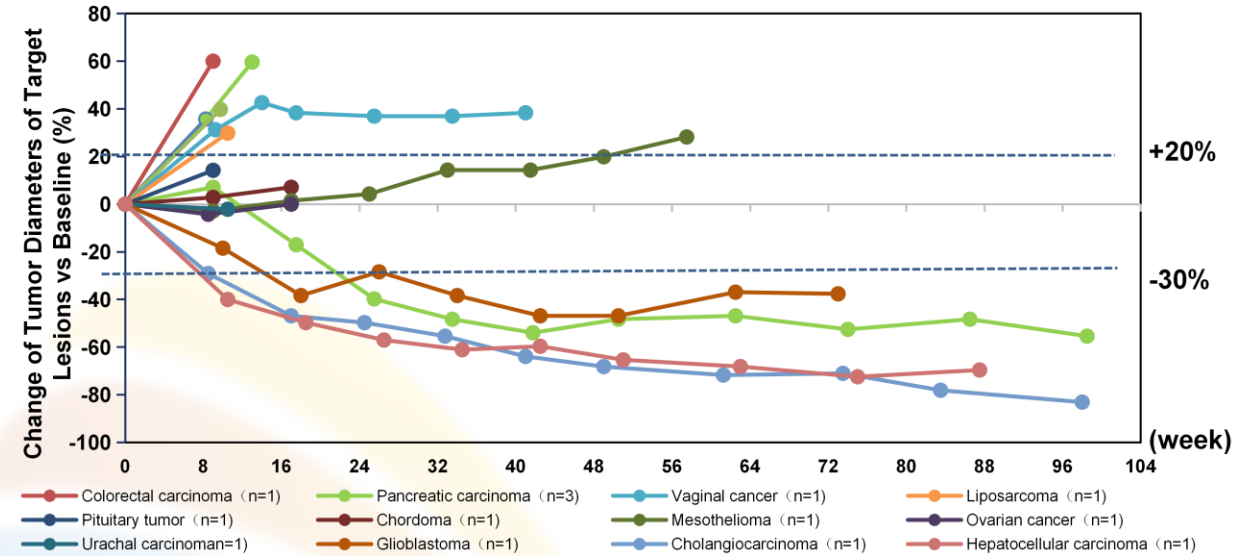


Figure 2 Spider plot of percent change over time from baseline in tumor burden of target lesions – Phase Ia

Overall ORR is 28.6%
DCR is 57.1%

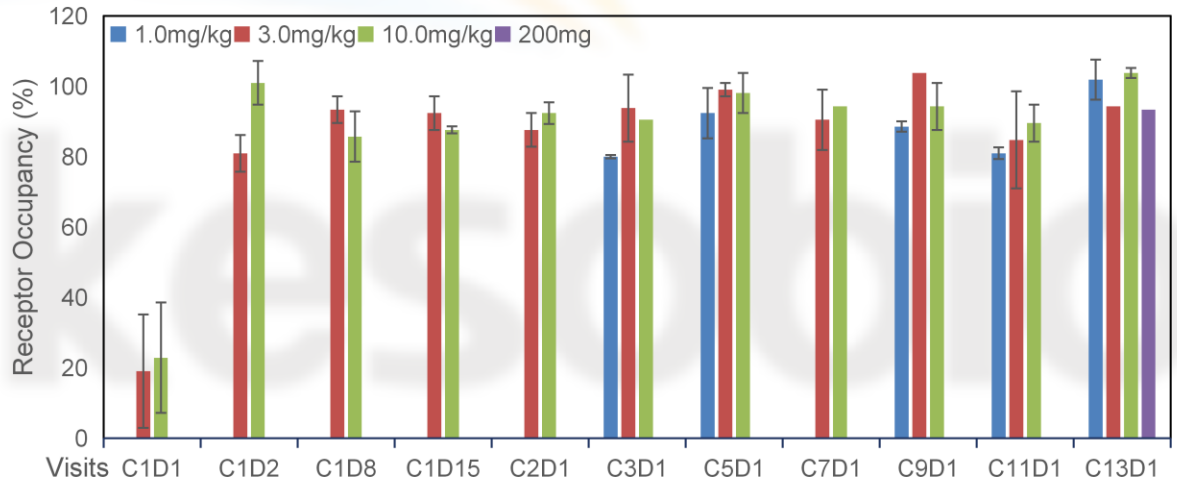


Figure 3 PD-1 receptor occupancy (RO) in different dose groups post-dose

Anti-tumor Activity of Penpulimab in relapsed or refractory classic Hodgkin lymphoma (cHL) Trial

Table 1. Efficacy measurements

	Evaluable patients (N=85)	
ORR	76 (89.4%)	(95% CI, 80.8%–95.0%)
CR	40 (47.1%)	
PR	36 (42.4%)	
SD	6 (7.1%)	
PD	3 (3.5%)	
DCR	82 (96.5%)	(95% CI, 90.0%–99.3%)
DoR, months	NR (1.7–24.5+)	
12-month PFS	72.1%	(95% CI, 60.5%–80.8%)

Values are shown as median (range), or n (%). NR, not reached; PR, partial response; SD, stable disease.

Figure 1. Progression-free survival

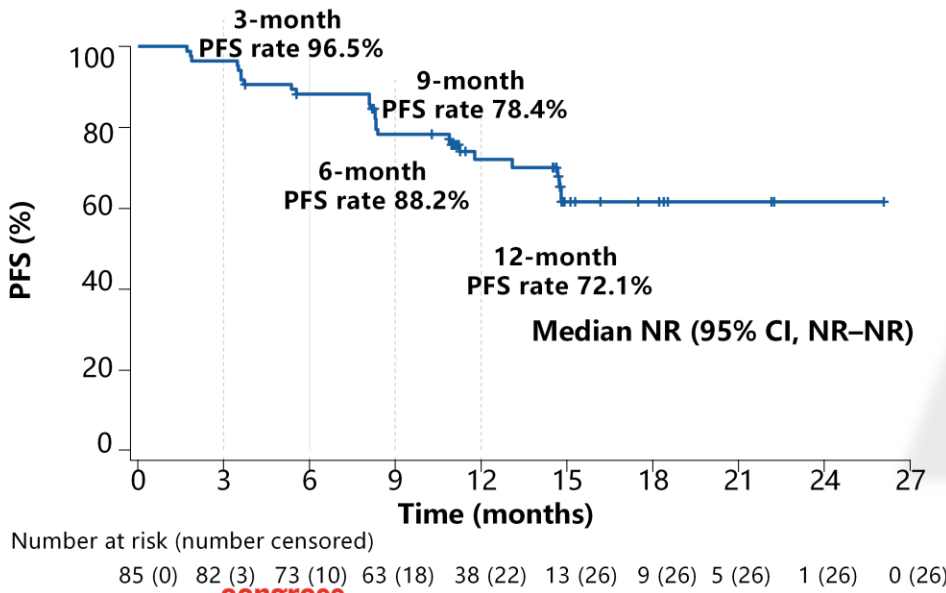
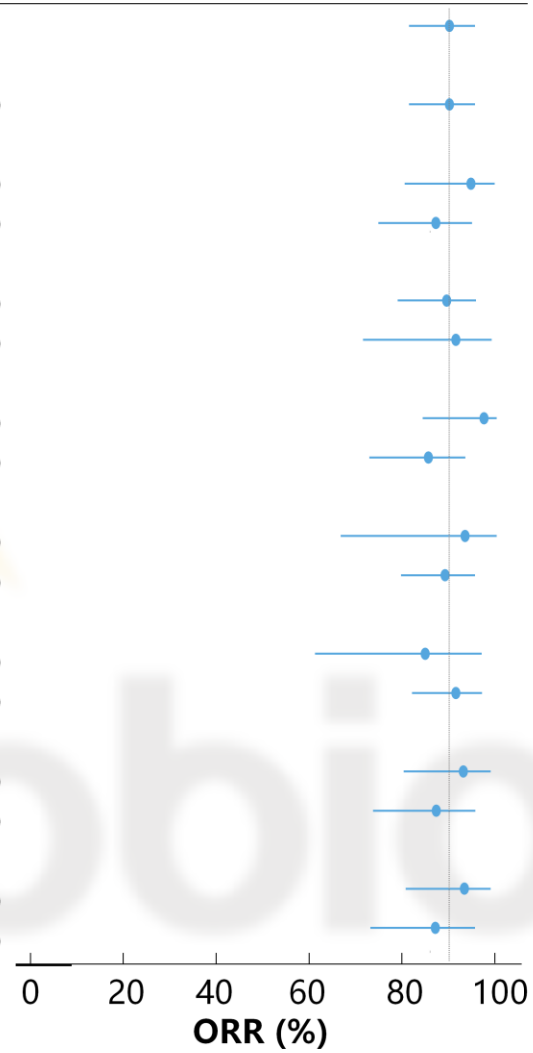


Figure 2. Subgroup analysis

Subgroup	ORR (%)	95% CI
All patients	85 (89.4)	(80.8-95.0)
Age		
≤65	84 (89.3)	(80.6–95.0)
Sex		
Female	33 (93.9)	(79.8–99.3)
Male	52 (86.5)	(74.2–94.4)
ECOG PS		
0	63 (88.9)	(78.4–95.4)
1	22 (90.9)	(70.8–98.9)
B-symptom(s)		
Yes	32 (96.9)	(83.8–99.9)
No	53 (84.9)	(72.4–93.3)
Prior ASCT		
Yes	14 (92.9)	(66.1–99.8)
No	71 (88.7)	(79.0–95.0)
Time form diagnosis to first dose		
<1 year	19 (84.2)	(60.4–96.6)
≥1 year	66 (90.9)	(81.3–96.6)
Prior lines of therapy for cHL		
<3	40 (92.5)	(79.6–98.4)
≥3	45 (86.7)	(73.2–94.9)
Prior radiation therapy		
Yes	41 (92.7)	(80.1–98.5)
No	44 (86.4))	(72.6–94.8)



CTCAE grade 3 or above irAEs in the study population

Preferred terms	R/R cHL*200 mg Q2W (N=94)	Phase Ib* (Australia) (N=81)	Chinese patients including cHL patients* (N=248)	All 200mg Q2W patients (N=329)	200 mg Q3W in combination with other drugs# (N=77)	200 mg and other doses$ (N=422)
Hepatotoxicities (hepatitis)	0	0	3 (1.2%)	3 (0.9%)	0	4 (0.9%)
ALT elevations	0	0	1 (0.4%)	1 (0.3%)	0	2 (0.5%)
AST elevations	0	0	1 (0.4%)	1 (0.3%)	0	2 (0.5%)
Elevated conjugated bilirubin	0	0	1 (0.4%)	1 (0.3%)	0	1 (0.2%)
Transaminase abnormalities	0	0	1 (0.4%)	1 (0.3%)	0	1 (0.2%)
Cutaneous toxicities	1 (1.1%)	0	2 (0.8%)	2 (0.6%)	1 (1.3%)	3 (0.7%)
Psoriasis	1 (1.1%)	0	1 (0.4%)	1 (0.3%)	0	1 (0.2%)
Rashes	0	0	1 (0.4%)	1 (0.3%)	0	1 (0.2%)
Generalized rashes	0	0	0	0	1 (1.3%)	1 (0.2%)
Pulmonary toxicities (pneumonia)	0	0	0	0	1 (1.3%)	1 (0.2%)
Viral pneumonia	0	0	0	0	1 (1.3%)	1 (0.2%)
Pulmonary inflammation	0	0	0	0	1 (1.3%)	1 (0.2%)
Nephrotoxicities (nephritis and renal insufficiency)	1 (1.1%)	0	1 (0.4%)	1 (0.3%)	0	1 (0.2%)
Other nephrotoxicities	1 (1.1%)	0	1 (0.4%)	1 (0.3%)	0	1 (0.2%)
Kidney injury[a]	1 (1.1%)	0	1 (0.4%)	1 (0.3%)	0	1 (0.2%)
Endocrine toxicities	0	0	0	0	1 (1.3%)	1 (0.2%)
Hypophysitis	0	0	0	0	1 (1.3%)	1 (0.2%)

Note: *, R/R cHL patients in the AK105-201 study, Australian patients in the AK105-101 phase 1b study, and Chinese patients from AK105-201, AK105-202, and AK105-204 trials; #, Patients from AK105-203 and AK105-301 (part I); $, Patients from AK105-101 (Phase 1a and 1b), AK105-201, AK105-202, AK105-203, AK105-204 and AK105-301 (part I); a, IgA nephropathy, refractory/ relapsed cHL.

Abbreviations: cHL, classic Hodgkin lymphoma; CTCAE, Common Terminology Criteria for Adverse Events; irAEs, immune related adverse events; Q2W, once every two weeks; Q3W, once every three weeks; R/R cHL, refractory/relapsed cHL.

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Q&A