ASKG315 – An IL-15 Prodrug with Antibody-Like PK, Enhanced Safety and Expanded Therapeutic Window

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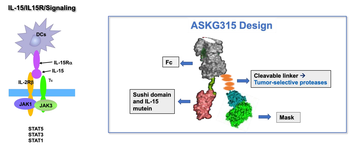
Abstract #1101

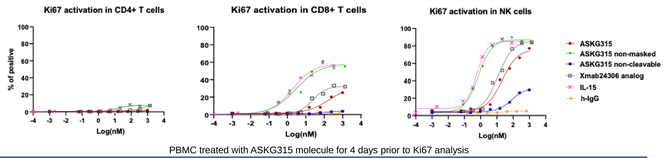
Background

- Cytokines are natural immune stimulators with clinical validation. They have great potential in cancer immunotherapy. Yet their broad application as therapeutics has been hampered due to short PK, severe systemic toxicity, and narrow therapeutic window.
- IL-15 stimulates the proliferation of immune cells such as NK cells, CD8+ T cells and δγT cells.
- IL-15 molecules typically have very short half-lives in vivo due to "cytokine sink", leading to limited exposure and poor efficacy yet dose-dependent systemic toxicities.
  - Cytokines often show target-medicated drug disposition (TMDD) when dosed systemically.
  - TMDD even expands during repeated dosing or continued dosing. The serum concentration of IL-15 decreased almost linearly for a total of over 10-fold during a 10-day continuous infusion[1].
  - It is a challenge to develop a dosing strategy for cytokine molecules including antibody-cytokine fusion molecules[2].
- Delivering cytokines to the disease sites is often challenging even when the cytokines are fused to a disease specific targeting antibodies because the cytokine molecule dominantly control the destinations of the fusion molecules.
- AskGene has established a proprietary cytokine prodrug platform (Smartkine®) to achieve its overarching objective of modulating immune reactions at a disease site in a selective and controlled manner.
- ASKG315 is the first IL-15 prodrug moving into clinical development.

ASKG315 Is Designed to Avoid Cytokine Sink and Induce Tumor-Selective Immune Stimulation



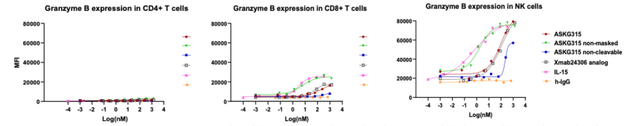
ASKG315 Induced Strong Proliferations of NK and CD8+ T Cells



PBMC treated with ASKG315 molecule for 4 days prior to Ki67 analysis

- The activated ASKG315 induced strong proliferation of the NK cells and CD8+ T cells, but not $CD4^+$ T cells.
- The activated ASKG315 was 10-15 times more potent than the reference molecule in inducing ki67 expression.

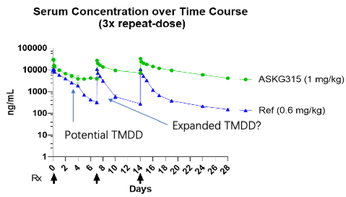
ASKG315 Induced Robust Granzyme B Expression in NK Cells



PBMC treated with ASKG315 molecule for 4 days prior to GB analysis.

- The activated ASKG315 induced strong GB activation: NK > $CD8^+$ T cells >> $CD4^+$ T cells
- The activated ASKG315 was up to 18 times more potent than the reference molecule in activating the NK cells.

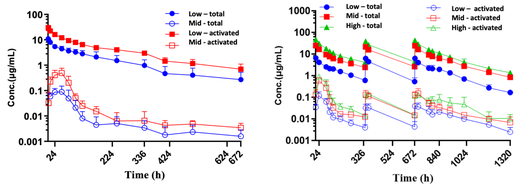
ASKG315 Has Longer $T_{1/2}$, Higher Exposure than the Reference Molecule



ASKG315 has significantly higher exposure.

- ASKG315 at 1 mg/kg has an AUC of 10x as that of the ref at 0.6 mg/kg.
- Smoother PK and higher exposure would improve safety, tumor penetration and efficacy.

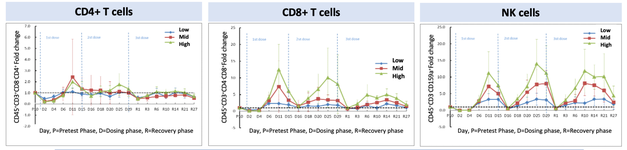
ASKG315 GLP PK/TK Study in Cynomolgus Monkeys



Low % activation of ASKG315 based on Cmax and AUC

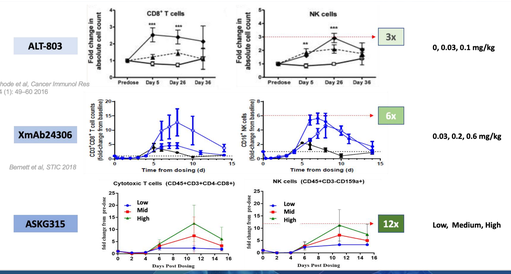
- $T_{1/2}$ 10 days, longest $T_{1/2}$ of any IL-15 or IL-2 molecules in development
- Linear PK for both the prodrug and the active version of the molecule
- Minimal immunogenicity risk

ASKG315 Induced Robust NK and Teff Cell Expansions in Cyno Monkeys

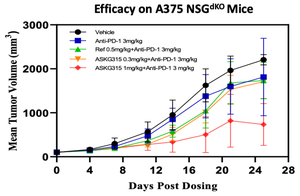


- Induced robust and sustained expansions of NK and Teff cells while with good tolerability
- Minimum expansion of CD4+ T cells

ASKG315 Showed Stronger and More Sustained NK Cell Expansion than the Competitors



ASKG315 Dose-dependently Enhanced αPD-1-mediated Anti-tumor Effect



Group	Tumor growth Suppression on Day 18
Vehicle	-
Anti-PD-1	16.3% (**0 death**)
Anti-PD-1 + Reference 0.5 mg/kg	38.0% (**3 death**)
Anti-PD-1 + ASKG315 0.3 mg/kg	40.5% (**0 death**)
Anti-PD-1 + ASKG315 1 mg/kg	73.6% (**1 death**)

N=10/group

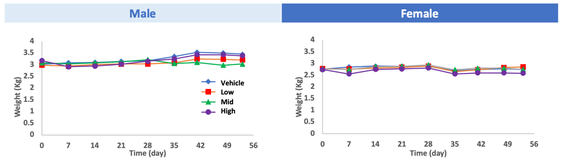
- **ASKG315 at 1 mg/kg vs Reference at 0.5 mg/kg:**
  - ASKG315 showed stronger anti-tumor efficacy, suggesting stronger immune stimulation inside the tumor.
  - ASKG315 was safer and had lower immune stimulation in periphery.
- **Results suggest that ASKG315 has better tumor-selective immune stimulation and expanded therapeutic window relative to the reference molecule.**

Monkey GLP Toxicology Study – Study Design

Study Design	
Animal	A total of 40 cynomolgus monkeys (20M, 20F, age 3-5 years)
Dose	0, low, med, or high every 2 weeks for 3 doses

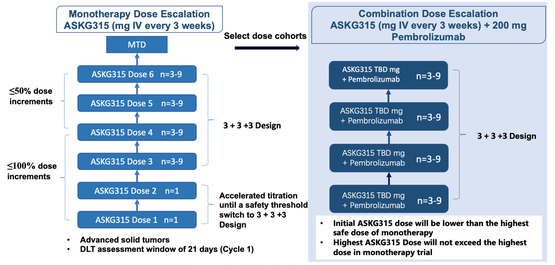
Group Numbers	Group Designation	Study Design			
		Male	Female	Dosing	Necropsy
1	Control	5	5	Day 1, 15, 29	• Six days after the last dose: 3/sex • End of recovery (28 days after the last dose): 2/sex
2	Low Dose	5	5		
3	Mid Dose	5	5		
4	High Dose	5	5		

Changes in Body Weight in Monkey GLP Toxicology Study



- No mortality or moribundity
- No cytokine release (IFN-γ, TNF-α, IL-6, or IL-8)
- Hematological changes were dose dependent and occurred mostly after the first dose and became smaller or back to baseline after the second or third dose.
- Necropsy findings are consistent with systemic inflammation of IL-15 pharmacology.
- Observations were mostly resolved or partially resolved at the end of the recovery period.
- The High Dose is identified as the highest non severe toxicity dose (HNSTD).

ASKG315 Phase I Study Design



- Advanced solid tumors
- DLT assessment window of 21 days (Cycle 1)
- Initial ASKG315 dose will be lower than the highest safe dose of monotherapy
- Highest ASKG315 Dose will not exceed the highest dose in monotherapy trial

Conclusions

	ASKG315	Reference
In vitro potency (PBMC)	Over 10X (activated)	1X
Avoid "cytokine sink"	Y	N
Tumor-selective immune stimulation	Y	N
PK – T1/2 in Cyno Monkey	10 Days	1-2 Days
Exposure (AUC) at highest dosage in Cyno	20X of ref	1X
NK cell expansion at the highest tolerable dose (cyno monkey)	~12X of vehicle	less
Duration of NK cell expansion at the highest tolerable dose (cyno monkey)	~3 weeks	shorter
Therapeutic window	ASKG315 has significantly expanded therapeutic window vs Reference	

- **ASKG315 will be the first IL-15 prodrug entering clinical development.**
- **FIH in Nov 2022**
- **It has multiple significant advantages compared to the reference.**

References
1.Colon et al., Clin Cancer Res. 2019 Aug 15; 25(16): 4945–4954)
2.Grimm et al., PAGE 25 (2016) Abstr 5861 [www.page-meeting.org/?abstract=5861]).