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Society for Immunotherapy of Cancer

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A Phase 1 Study of AK104, a Tetrameric Bispecific Antibody that Targets PD-1 and CTLA-4 in Patients with Advanced Solid Tumors

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ClinicalTrials.gov #NCT03261011 Abstract #O30

Disclosures

Ben Markman, MBBS, FRACP

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AK104 is not approved by the Food and Drug Administration.

PD-1 and CTLA-4 Antibody Combo Therapy with Enhanced Efficacy, but Limited by Toxicity

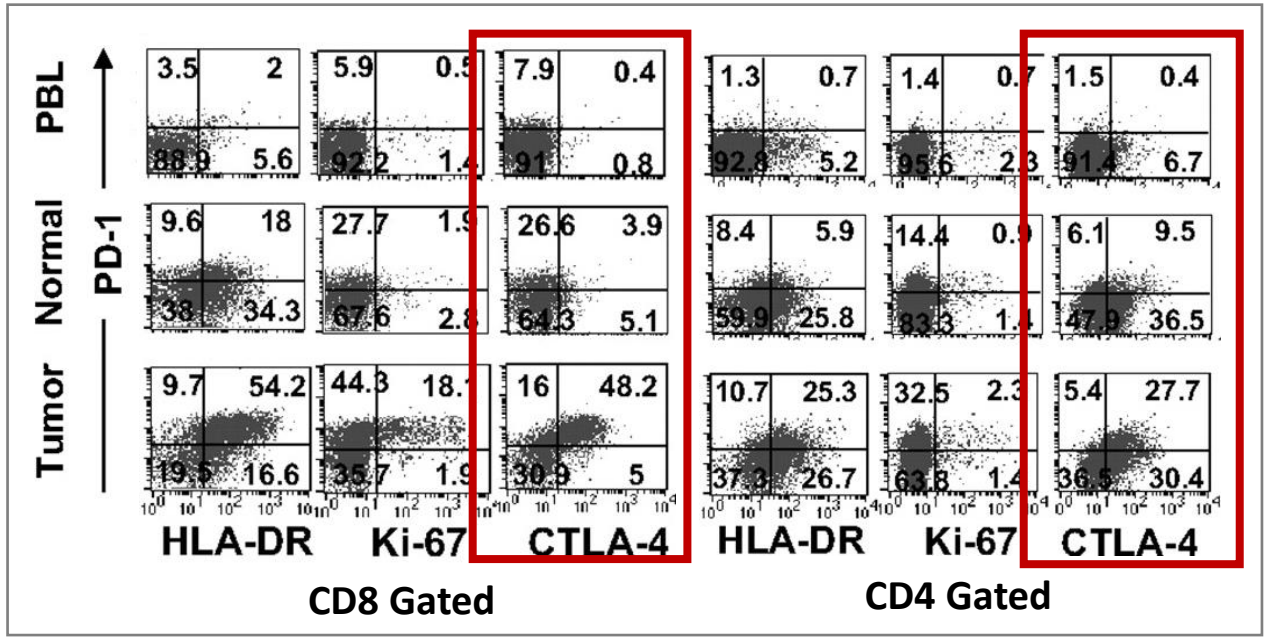
	Overall Response Rate (%)		Treatment-related Grade 3-4 AEs	
	Nivolumab	Nivolumab 1mg/kg + Ipilimumab 3 mg/kg	Nivolumab	Nivolumab 1mg/kg + Ipilimumab 3 mg/kg
Melanoma [1]	44%	58%	16%	55%
RCC[2]	22%	40%	19%	62%
NSCLC[3]	23%	43%*	10%	35%*
SCLC [4]	10%	23%	13%	30%
Gastric/GEJ [5]	14%	26%	17%	45%
UC [6]	24%	39%	22%	31%

- **CTLA-4 is the most heavily evaluated target in combination with PD-1/PD-L1 blockade**
- **Full potential for combination immunotherapy is limited by toxicities**

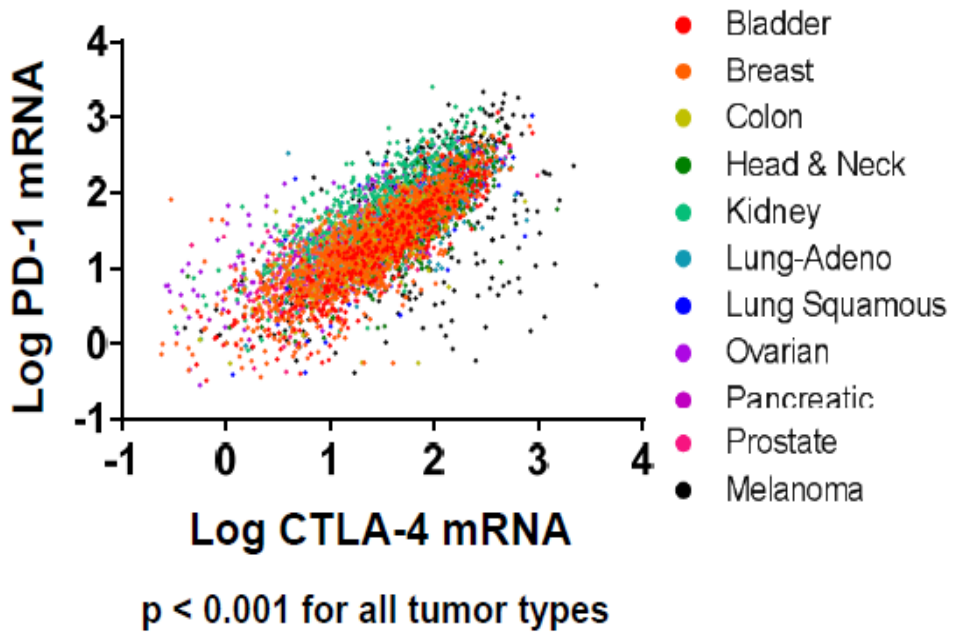
[1] Larkin J, NEJM 2015
[2] Hammers HJ, JCO 2017; Motzer RJ, NEJM 2015
[3] Hellmann MD, Lancet Oncol. 2017
[4] Antonia SJ, Lancet Oncol. 2016
[5] Janjigian YY, ASCO 2016
[6] Sharma P, Lancet Oncol. 2016

*Nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W or Q12W

PD-1 and CTLA-4 Co-Express in Tumor Infiltrating Lymphocytes but NOT in Normal Peripheral Tissues



Phenotypic comparison of CD8 and CD4 T cells infiltrating into tumor, normal tissue, and peripheral blood in the same melanoma patient. Ahmadzadeh et al., Blood 2009



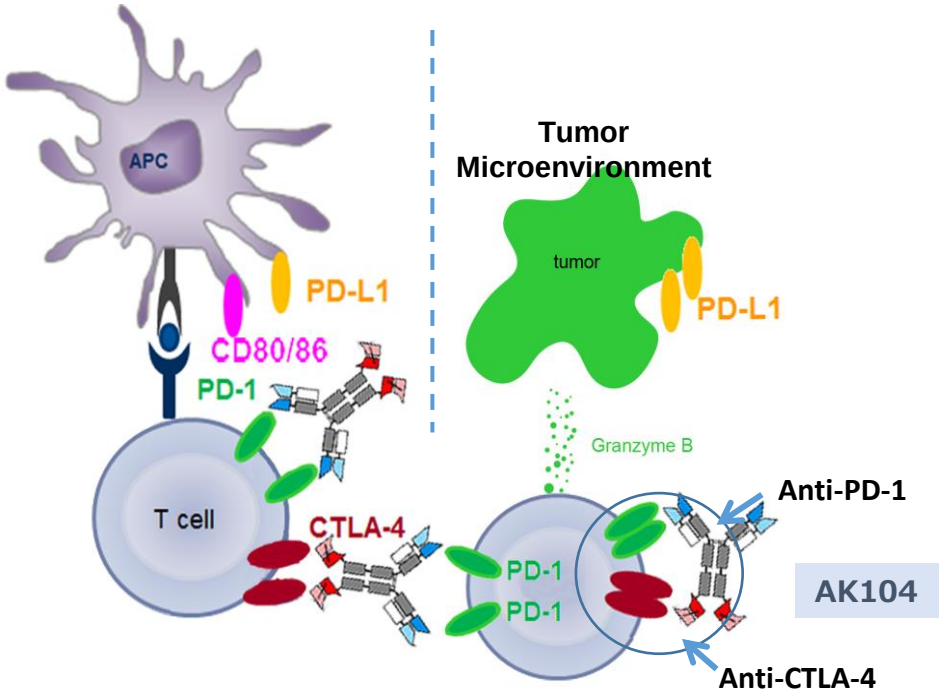
$p < 0.001$ for all tumor types

TCGA Research Network:
http://cancergenome.nih.gov/

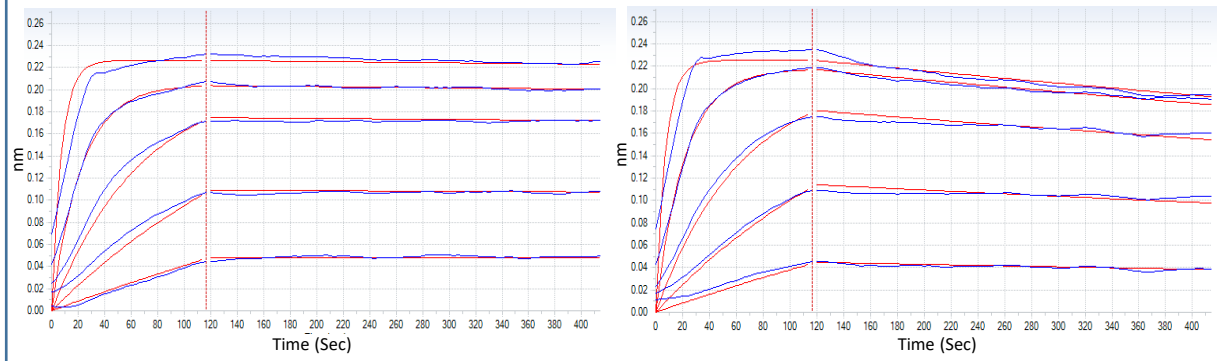
- PD-1 and CTLA-4 co-express in tumor infiltrating lymphocytes (TILs), but not in normal peripheral tissues
- Tetrameric bispecific antibody against PD-1 and CTLA-4 may display higher avidity by design in tumor micro-environment v.s. normal peripheral

AK104 – Bispecific Antibody Against PD-1 and CTLA-4

- AK104 is a humanized IgG1 bispecific antibody targeting both PD-1 and CTLA-4.
- AK104 is designed as a tetrameric form, which is able to bind to PD-1 and CTLA-4 simultaneously.
- AK104 blocks PD-1 binding to PD-L1 and PD-L2, and blocks CTLA-4 binding to B7-1 and B7-2.
- AK104 is designed to achieve the efficacy of PD-1 and CTLA-4 combination blockade with lowered toxicity.



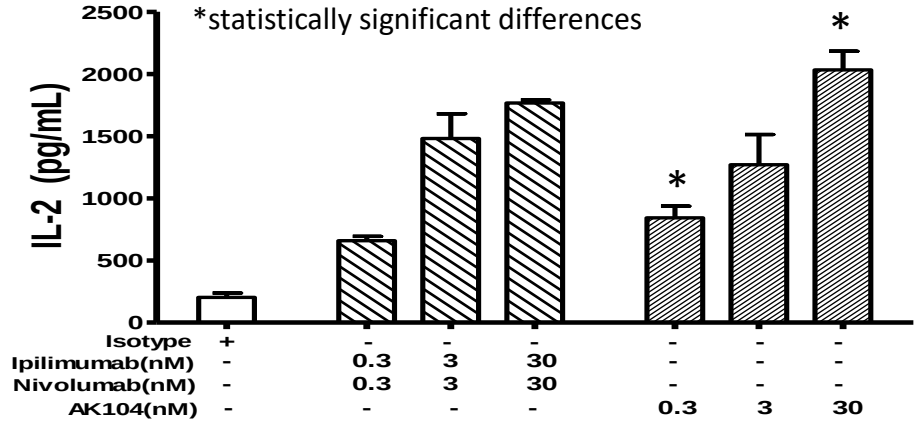
AK104 Comparison with Ipi &Nivo Combination: Higher Binding Affinity and More Robust Cytokine Production



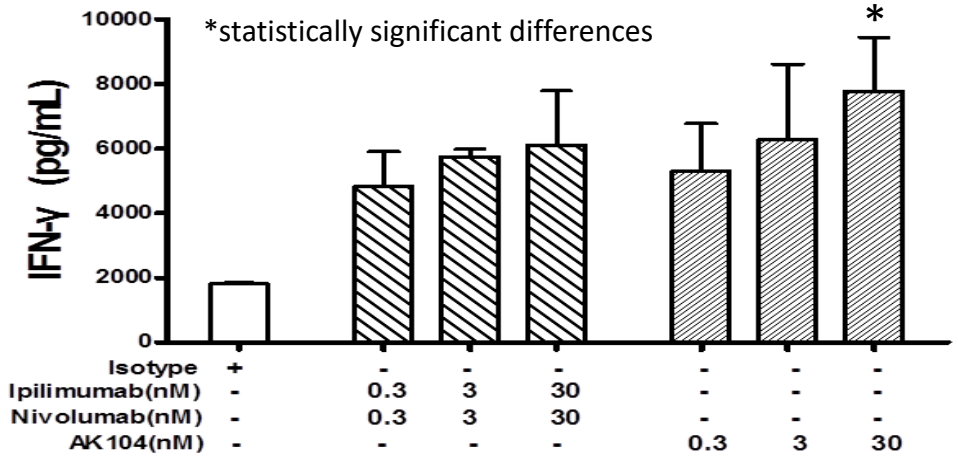
AK104 **Nivo+Ipi**

Sample ID	KD (M)	kon(1/Ms)	kdis(1/s)
AK104	1.96E-11	2.68E+06	5.27E-05
Ipilimumab+Nivolumab	1.91E-10	2.77E+06	5.29E-04

Fortebio measurement to compare antibody binding to immobilized PD-1 and CTLA-4.



IL-2 secretion from mixed culture of PBMC and DC



IFN-γ secretion from mixed culture of PBMC and DC

AK104 First-in-Human Phase 1a Study Design

Main inclusion criteria:

- Histologically or cytological advanced or metastatic solid tumor;
- Refractory/relapsed to standard therapies, or for which no effective standard therapy is available.

Dose-escalation Cohorts (Part 1)

- 10 mg/kg Q2W (n=6)
- 6 mg/kg Q2W (n=7)
- 4 mg/kg Q2W (n=3)
- 2 mg/kg Q2W (n=3)
- 1 mg/kg Q2W (n=6)
- 0.5mg/kg Q2W (n=3)
- 0.2mg/kg Q2W (n=1)

Primary Objectives:

- **Safety and tolerability, DLTs**
- **MTD/MAD, RP2D**

Pharmacodynamic Confirmation Cohorts (Part 2)

- 6mg/kg Q2W
- 450 mg Q2W

- SCLC
- SCCHN
- Gastric or GEJ cancer
- Esophageal cancer;
- RCC
- MSI high/dMMR cancers
- Urothelial carcinoma
- TNBC
- Ovarian cancer
- Cervical cancer
- Endometrial cancer;
- Merkel cell carcinoma
- Skin squamous cell carcinoma
- Mesothelioma
- Nasopharyngeal carcinoma
- Undifferentiated pleomorphic sarcoma
- NSCLC, melanoma, or urothelial carcinoma refractory or relapsed to anti-PD-1 or anti PD L1 therapy.

Secondary Objectives:

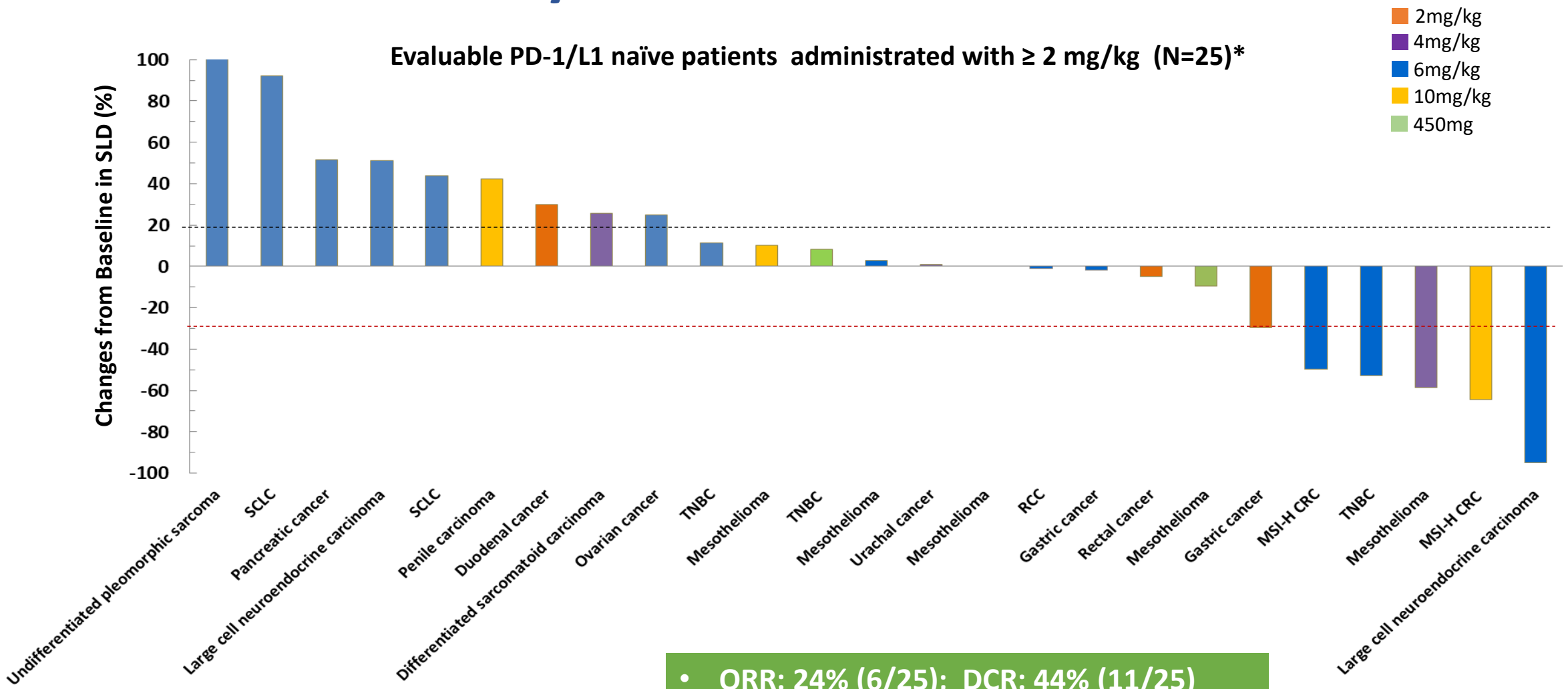
- **Preliminary antitumor activity**
- **PK, immunogenicity and PD markers**

Summary of Baseline Characteristics and Exposure

	Dose Escalation Cohorts (Q2W, N=29)							Pharmacodynamic Confirmation Cohorts (Q2W, N=26)		Total (n=55)
Cohort	**0.2mg/kg (n=1)**	**0.5mg/kg (n=3)**	**1mg/kg (n=6)**	**2mg/kg (n=3)**	**4mg/kg (n=3)**	**6mg/kg (n=7)**	**10mg/kg (n=6)**	**6mg/kg (n=17)**	**450mg (n=9)**	-
Age, median (range), y	42	49 (45-62)	44.5 (31-69)	56 (34-73)	66 (47-68)	71 (60-77)	56.5 (47-80)	65 (38-85)	55.5 (45-78)	61 (31-85)
Male/Female	-/1	-/3	3/3	3/-	2/1	5/2	5/1	9/8	4/5	31/24
Lines of prior therapy, median (range)	3	2 (0-5)	2 (2-3)	3 (2-6)	2 (2-4)	1 (0-3)	1 (1-1)	2 (1-4)	2 (1-4)	2 (0-6)
Number of AK104 doses, median (range)	8	4 (4-6)	3.5 (2-10)	7 (4-31)	7 (2-33)	5 (2-22)	3.5 (2-10)	4 (1-15)	2 (1-4)	4 (1-33)

Data cut-off date: Sep 24, 2019

Antitumor Activity in Advanced Solid Tumor

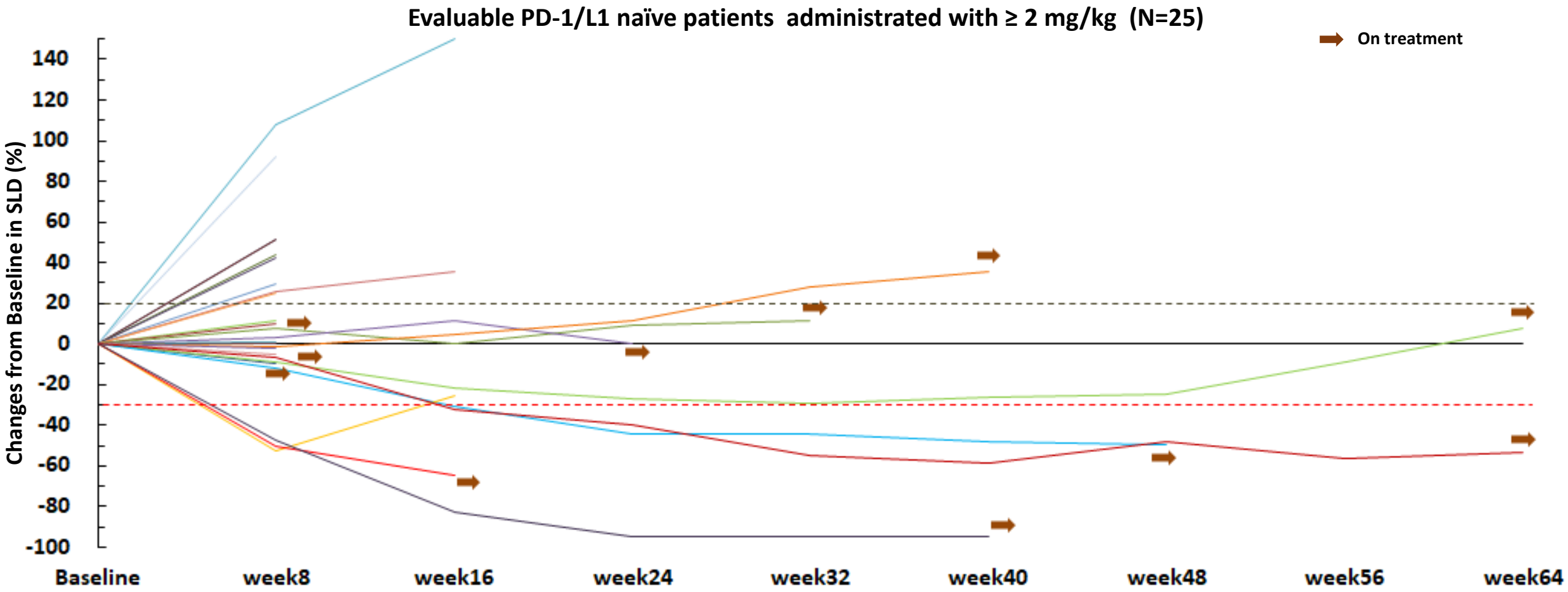


- **ORR: 24% (6/25); DCR: 44% (11/25)**

Data cut-off date: Sep 24, 2019

** Evaluable patient defined as patient with at least one post-baseline tumor assessment.*

Antitumor Activity in Advanced Solid Tumor



Data cut-off date: Sep 24, 2019

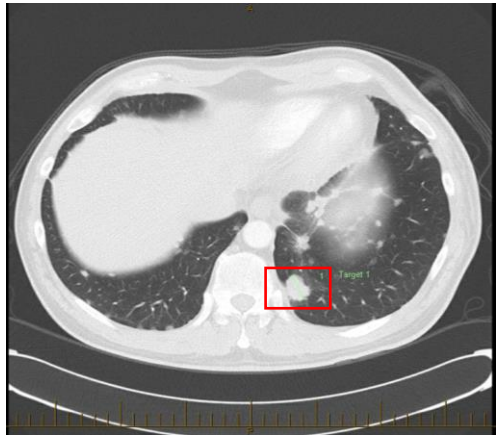
- **Durable objective responses and disease stabilization**

Partial Response to AK104

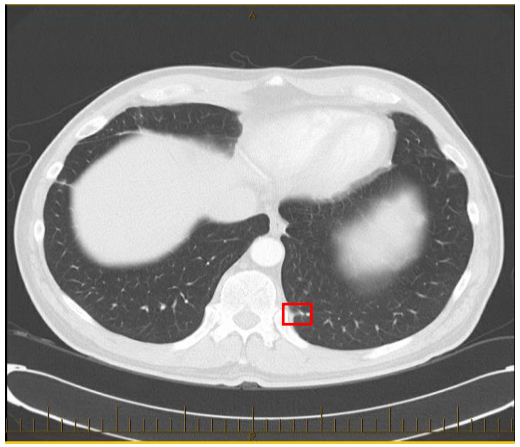
Large Cell Neuroendocrine Carcinoma

Male, 62yrs, Stage IV, treated with AK104 6mg/kg Q2W (23 doses received); No prior anti-cancer therapy

Baseline



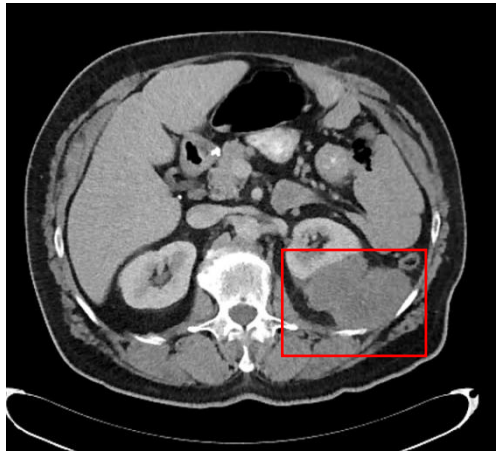
Week 24



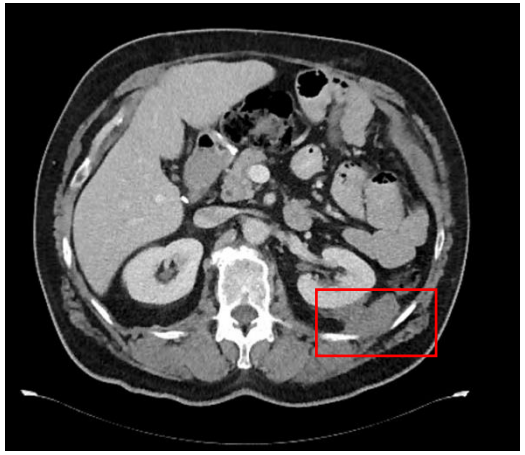
Gastric cancer

Male, 56yrs, Stage IV, treated with AK104 2mg/kg Q2W (31 doses received); Prior anti-cancer therapy: ECF, FOLFOX, XELOX, paclitaxel, irinotecan,regorafenib

Baseline



Week32



Safety Summary

	Total (N=55) n (%)	6.0mg/kg (n=24)	10mg/kg (n=6)	450mg (n=9)
Treatment-related AE (TRAE)	35 (63.6%)	15 (62.5%)	4 (66.7%)	5 (55.6%)
≥ Grade 3 TRAE	6 (10.9%)	1 (4.2%)	2 (33.3%)	1 (11.1%)
Immune-related AEs (irAE)	19 (34.5%)	11 (45.8%)	2 (33.3%)	2 (22.2%)
≥ Grade 3 irAE	2 (3.63%)	0	0	1 (11.1%)
Treatment-related SAE	8 (14.5%)	2 (8.3%)	3 (50%)	1 (11.1%)
TRAE leading to discontinuation	3 (5.5%)	2 (8.3%)	0	1 (11.1%)

- **≥ Grade 3 TRAE included infusion reaction (n=3), fever (n=1), polyneuropathy (n=1) and AST elevation (n=1)**
- **Only 1 DLT reported in one patient (1mg/kg) : AST elevation (Grade 3)**
- **No treatment-related AE leading to death**

Data cut-off date: Sep 24, 2019

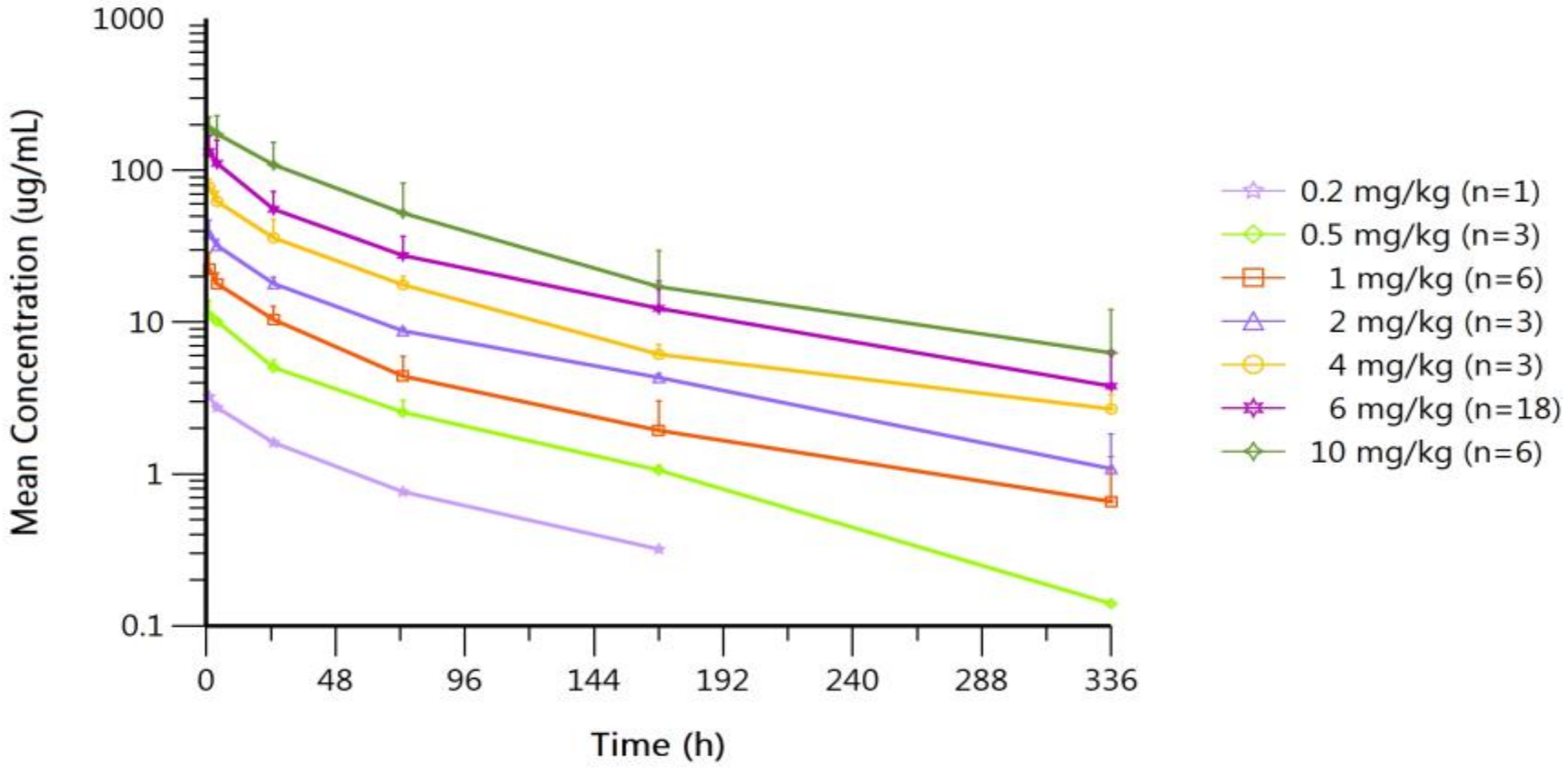
TRAE with Incidence ≥5%

TRAE	All subjects （N=55）				6mg/kg （n=24）			
	Any Grade	Grade 1	Grade 2	≥Grade 3	Any Grade	Grade 1	Grade 2	≥Grade 3
Rash	12 (22%)	9	3		5 (21%)	4	1	
Infusion reaction	10 (18%)	1	6	3	3 (13%)		2	1
Nausea	8 (15%)	7	1		4 (17%)	3	1	
Fatigue	8 (15%)	5	3		4 (17%)	3	1	
Pruritus	5 (9%)	4	1		4 (17%)	3	1	
Fever	5 (9%)	1	1	1	1 (4%)	1		
ALT elevation	3 (5%)	2	1		1 (4%)		1	
AST elevation	3 (5%)	2		1	1 (4%)	1		
Hyperthyroidism	3 (5%)	3			1 (4%)	1		
Diarrhea	3 (5%)	2	1		1 (4%)		1	

- **Only 1 grade 4 event reported: infusion reaction**

Data cut-off date: Sep 24, 2019

Pharmacokinetics



- **AK104 exposure is proportional to dose increase, indicating a linear PK**

Pharmacokinetics

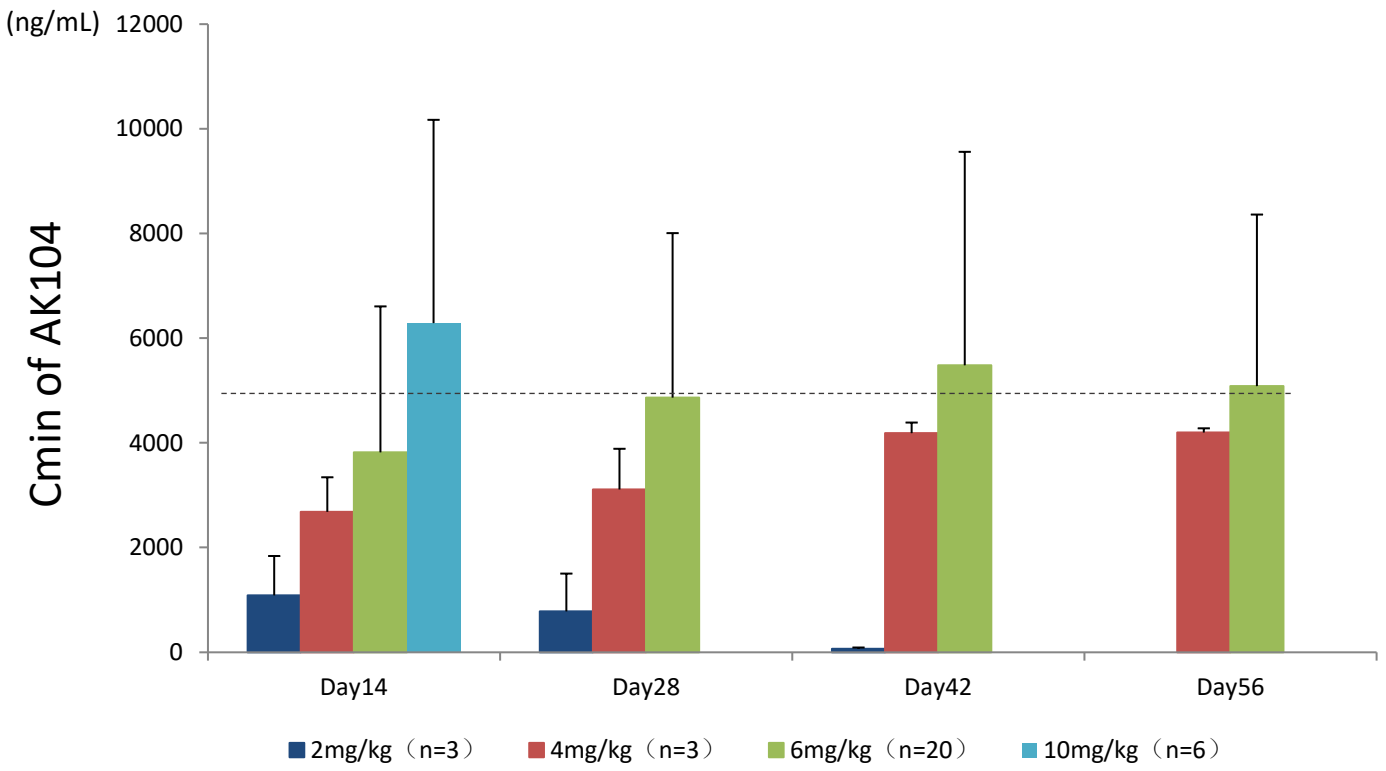


Figure: PK concentration at the end of Q2W dosing interval

In Vitro measurement of Receptor Occupancy

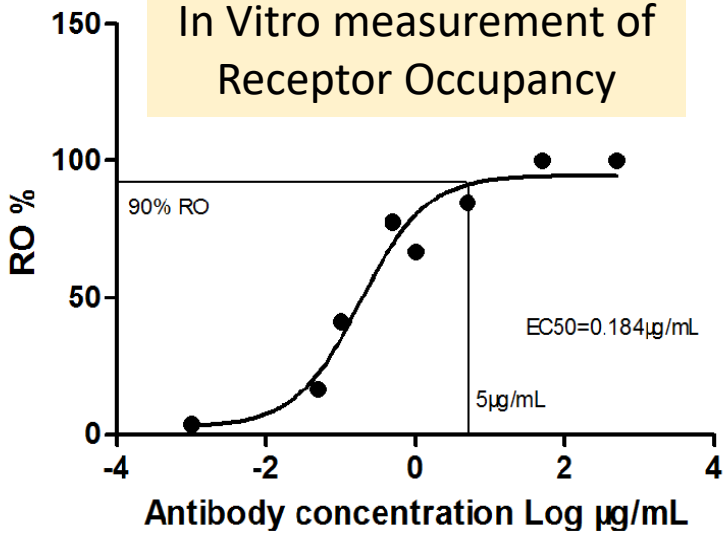
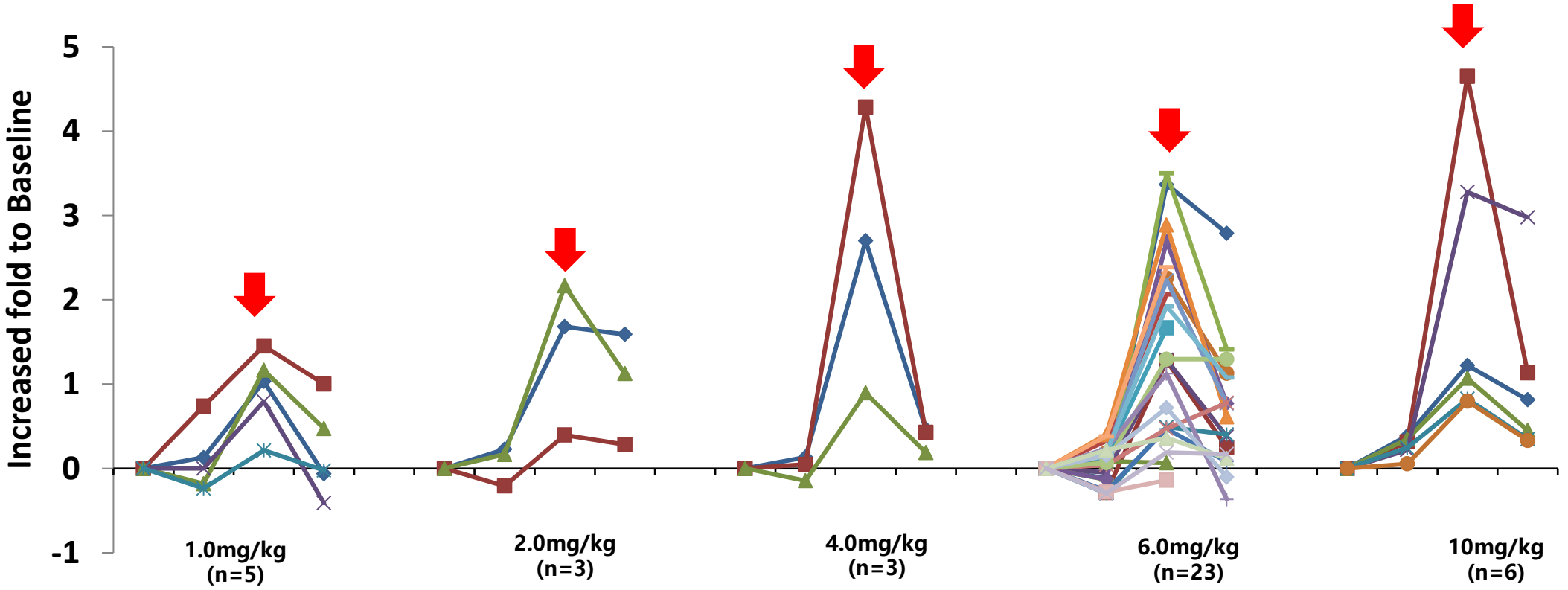


Figure: PD-1/CTLA-4 Receptor occupancy (RO) in whole blood in vitro examined using FACS at different AK104 concentration.

- **Saturating RO in the whole blood estimated to be ~5 μg/mL.**

- **AK104 6mg/kg Q2W maintains a trough concentration of approx 5 μg/mL, suggesting saturation of RO**
- **Dose level of 6mg/kg Q2W selected to be explored in PD confirmation cohort.**
- **Base on PK modelling, a flat dose of 450mg Q2W is also being explored in the PD confirmation cohort**

Pharmacodynamic Biomarker： CD4+Ki67



- Expression of Ki67 on circulating T cells was explored as a PD biomarker of T cell proliferation in the context of CTLA-4 and PD-1 blockade
- Peripheral CD4+ T cells demonstrated increased Ki67 expression at day 8 at all dose levels but greater increases were noted at higher dose

Conclusions

- AK104 is a novel, tetrameric bispecific antibody targeting both PD-1 and CTLA-4.
- AK104 showed encouraging anti-tumor activities across a range of tumor types.
- AK104 had an acceptable safety profile:
  - *Early data suggested that AK104 may have improved tolerance compared the combination of a PD-1 inhibitor and CTLA-4 inhibitor.*
- Enrolment into the PD confirmation cohort is ongoing at both 6mg/kg Q2W and a flat dose of 450mg Q2W.

Acknowledgements

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