VIRTUAL 2020 ESMO congress

Safety and Antitumor Activity of AK104, a Bispecific Antibody Targeting PD-1 and CTLA-4, in Patients with Mesothelioma which is Relapsed or Refractory to Standard Therapies

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DISCLOSURE INFORMATION

- **Advisory Board Member**
  - AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, Roche, Novartis, Takeda.

- **Travel/Conference Support**
  - Roche, AstraZeneca, Bristol Myers Squibb.

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Immune Checkpoint Inhibitors in Mesothelioma

- Mesothelioma is a rare cancer occurring in the pleura (81%), peritoneum (8%), pericardium and tunica vaginalis testis[1]. Median OS ~1 year.
- Standard first line systemic therapy is cisplatin/pemetrexed +/- bevacizumab.
- Pembrolizumab or nivolumab +/- ipilimumab can be used as subsequent therapy[1].

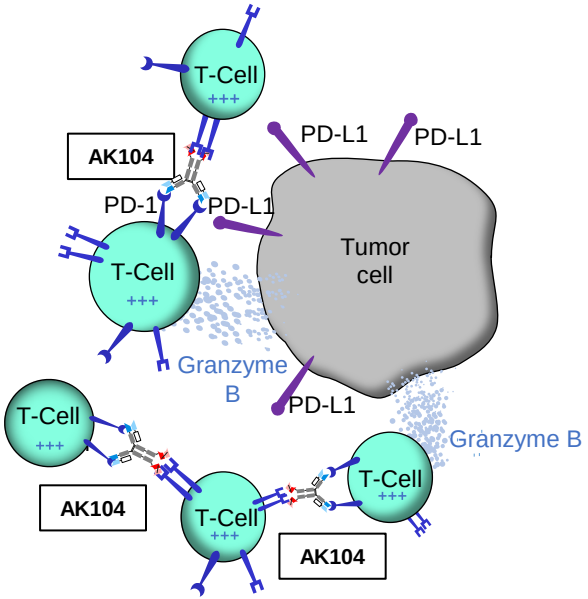
- *CheckMate-743: Phase 3, randomized, open-label study evaluating NIVO + IPI vs SOC chemotherapy in 1L unresectable MPM.*
  - *NIVO + IPI superior to chemo (median OS 18.1 vs 14.1 months, HR 0.74)*
  - *Survival benefit most pronounced in non-epithelioid MPM (median OS 18.1 vs 8.8 months, HR 0.46)*
  - *Similar median PFS rates (6.8 vs 7.2 months, HR 1.0)*
  - *Similar treatment-related (TR) Grade 3-4 AE rates in both arms (30% vs 32%) but higher TR-SAE rate with NIVO + IPI (21% vs 8%)*
  - *Higher TRAE leading to discontinuation with NIVO + IPI (23% vs 16%)*

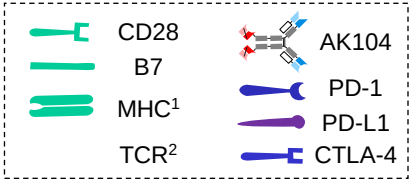
[1] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Malignant Pleural Mesothelioma. Version 1.2020 – November 27, 2019. Available from: https://www.nccn.org/patients/guidelines/cancers.aspx

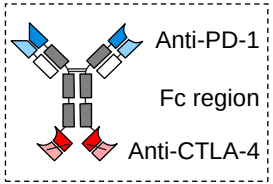
AK104 – mechanism of action

- AK104 is a next-generation, potential first-in-class humanized bi-specific antibody drug candidate targeting PD-1 and CTLA-4 simultaneously
- AK104 is designed as a novel tetrameric form, which can bind tetravalently to only TILs co-expressing PD-1 & CTLA-4 with higher avidity
- Therefore, AK104 is designed to retain the efficacy of dual blockade of PD-1 and CTLA-4 and improve the safety profile of this combination therapy

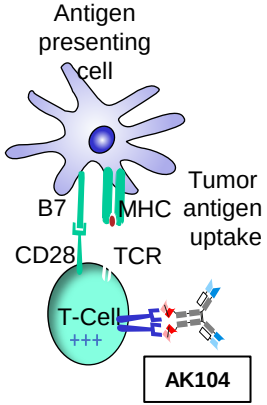
Tumor microenvironment (high functional affinity or avidity)







Peripheral (lower binding avidity)



- PD-1 and CTLA-4 are co-expressed in tumor infiltrating lymphocytes (TILs), but not in normal peripheral tissue lymphocytes
- Anti-PD-1/CTLA-4 bi-specific may display higher avidity for lymphocytes in the tumor microenvironment versus peripheral sites

Phase Ia/Ib Study Design (1)

Eligibility

- ≥ 18 years of age
- Dose-escalation cohorts: Advanced or metastatic solid tumor that is refractory/ relapsed to standard therapies, or for which no effective standard therapy is available
- ≥ 1 measurable lesion according to RECIST Version 1.1
- No prior IO therapy (except for one PD confirmation cohort)
- No active or prior documented autoimmune disease within the past 2 years.
- ECOG performance score of 0 or 1
- Adequate organ function
- Life expectancy ≥ 3 months

Treatment

AK104 60min (± 5 min) IV

Dose-escalation cohorts

Pharmacodynamic (PD) Confirmation Cohorts

Treatment until toxicity or progression or a maximum of 24 months

Follow-up

- Tumor assessments every 8 weeks for the first 12 months; then every 3 months thereafter
- Subjects permitted to continue with AK104 treatment beyond initial disease progression until progression is confirmed

- **Primary endpoint:** Safety & Tolerability, DLTs
- **Secondary endpoints:** Antitumor activity, PK & Immunogenicity of AK104, Pharmacodynamic Markers

 # Study previously presented at SITC 2019. Markman B, et al. A Phase 1 Study of AK104, a Tetrameric Bispecific Antibody that Targets PD-1 and CTLA-4 in Patients with Advanced Solid Tumors. Proceedings of The 34th Annual Meeting & Pre-Conference Programs of the Society for Immunotherapy of Cancer (SITC 2019); 2019 Nov 6-10; Maryland. Abstract #O30

Study Design (2)

Dose-escalation Cohorts (Part 1)

- 15 mg/kg Q3W (2 Mesothelioma subjects)
- 10 mg/kg Q2W (4 Mesothelioma subjects)
- 6 mg/kg Q2W
- 4 mg/kg Q2W (1 Mesothelioma subject)
- 2 mg/kg Q2W
- 1 mg/kg Q2W (2 Mesothelioma subjects)
- 0.5mg/kg Q2W
- 0.2mg/kg Q2W

Pharmacodynamic Confirmation Cohorts (Part 2)

- 6mg/kg Q2W (IO-Naïve) (4 Mesothelioma subjects)
- 6mg/kg Q2W [Prior PD-(L)1] (1 Mesothelioma subject)
- 450 mg Q2W (IO-Naïve) (4 Mesothelioma subjects)

- 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
- Advanced solid tumors refractory or relapsed to anti-PD-1 or anti PD-L1 therapy.

Mesothelioma Patient Characteristics (N=18)

Age, Years	
Median	68.5
Min - Max	45 – 80
Gender, n	
Male	15
Female	3
Prior lines of therapy, n	
1	9
2	6
>2*	3

ECOG at Baseline, n	
0	9
1	9
Histology Subtype, n	
Epithelioid	16
Biphasic	1
Sarcomatoid	1

* inclusive of 1 subject who received prior anti-PD-1 therapy

Data cut-off date: 10Jul, 2020

Mesothelioma Patients Safety Summary

Subjects with at least one	Total (N=18)
Adverse Event (AE)	17 (94.4%)
AE related to the study drug	12 (66.7%)
≥ Grade 3 AE related to the study drug	**3 (16.7%)**
Immune-related AE (irAE)	9 (50.0%)
Grade ≥ 3 irAE	**2 (11.1%)**
Serious Adverse Event (SAE)	9 (50.0%)
SAE related to the study drug	3 (16.7%)
Treatment-related AE leading to study drug discontinuation	**1 (5.6%)**

- ≥ Grade 3 TRAE:
  - Pyrexia (n=1, 10 mg/kg Q2W)
  - Infusion related reaction (n=1, 450 mg Q2W)
  - Type 1 diabetes mellitus (n=1, 4mg/kg Q2W)
- No DLT reported in Study AK104-101
- No treatment-related AE leading to death in Study AK104-101

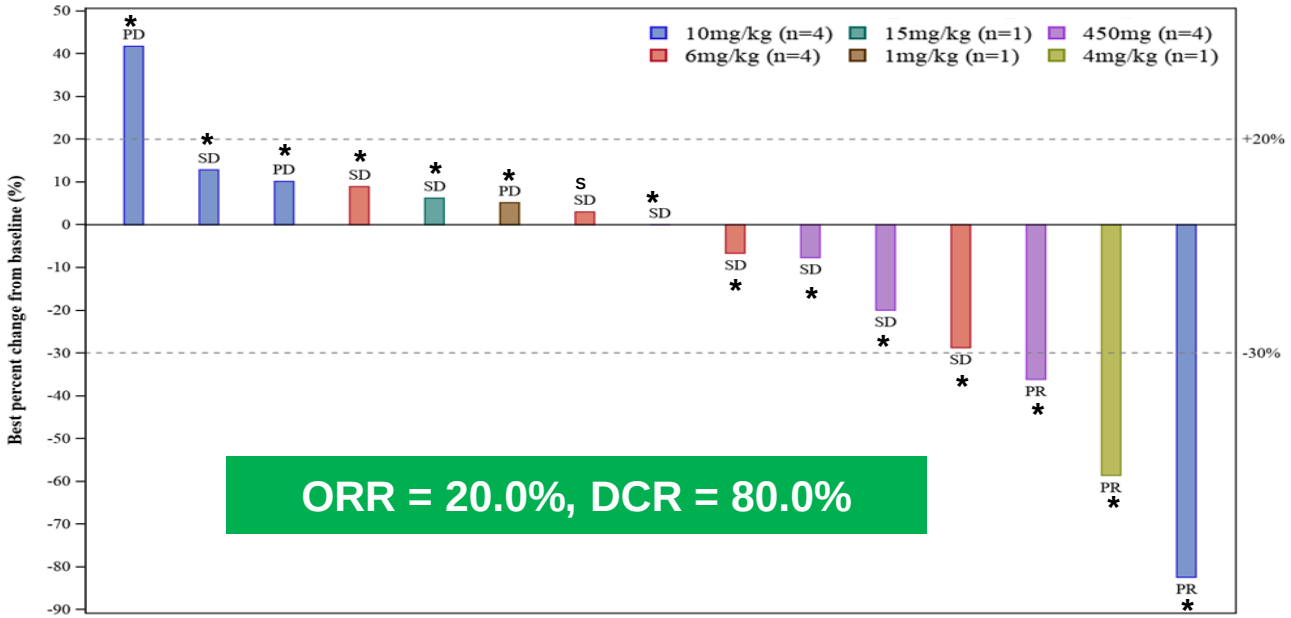
Data cut-off date: 10Jul, 2020

Immune-related AEs in Mesothelioma Patients

Immune-Related Adverse Event	Total (N=18)
Rash	5 (27.8%)
Arthralgia	2 (11.1%)
Arthritis	2 (11.1%)
Infusion related reaction	2 (11.1%)
Pruritus	1 (5.6%)
Autoimmune arthritis	1 (5.6%)
Tendonitis	1 (5.6%)
Peripheral swelling	1 (5.6%)
Alanine aminotransferase increased	1 (5.6%)
Type 1 diabetes mellitus	1 (5.6%)
Cough	1 (5.6%)
Autoimmune Hypophysitis	1 (5.6%)
Bulky Enhancing Pituitary	1 (5.6%)

Data cut-off date: 10Jul, 2020

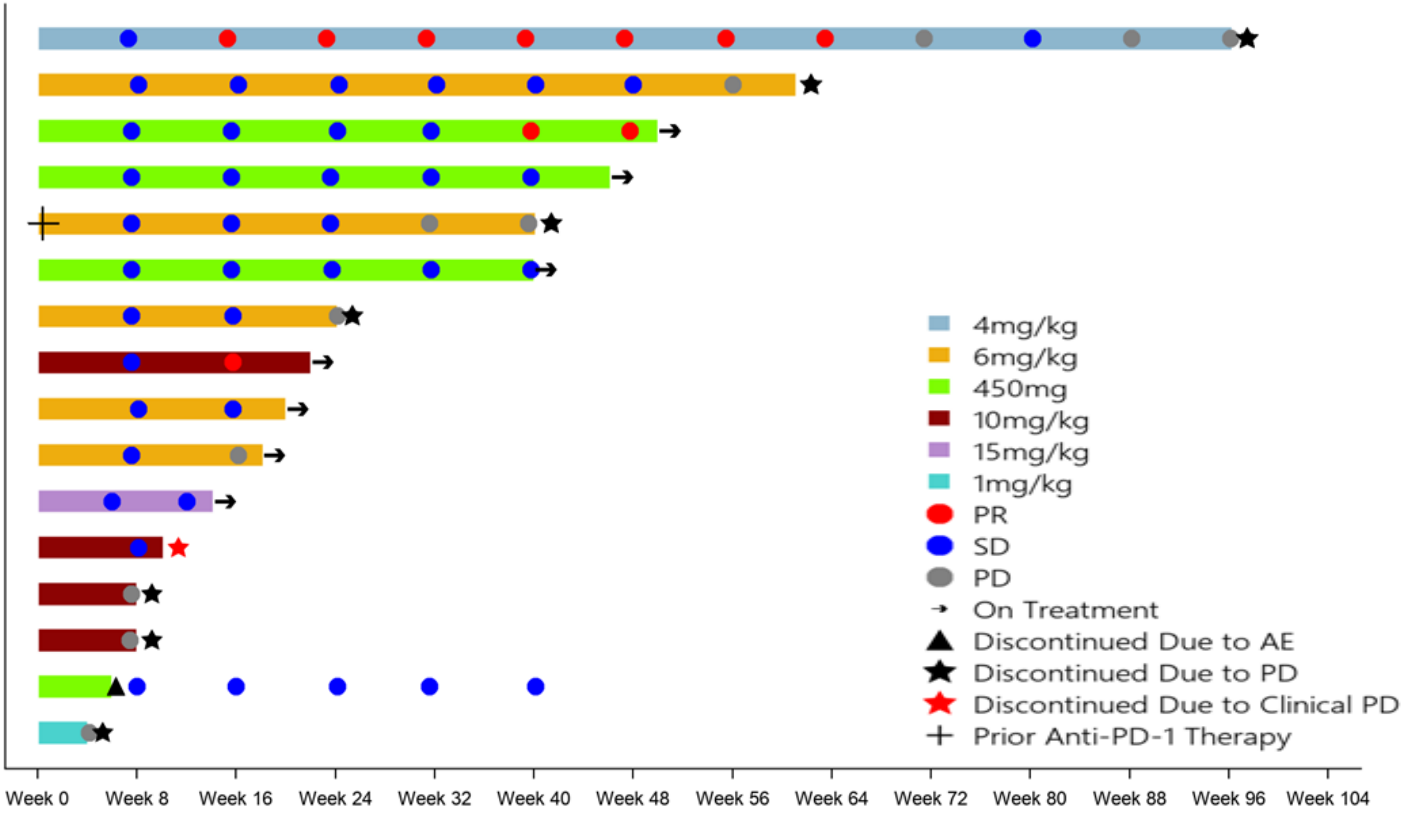
Maximum Percentage Change in Tumour Size in Evaluable IO-Naïve Subjects (N=15)



[*]: Epithelioid; [S]: Sarcomatoid

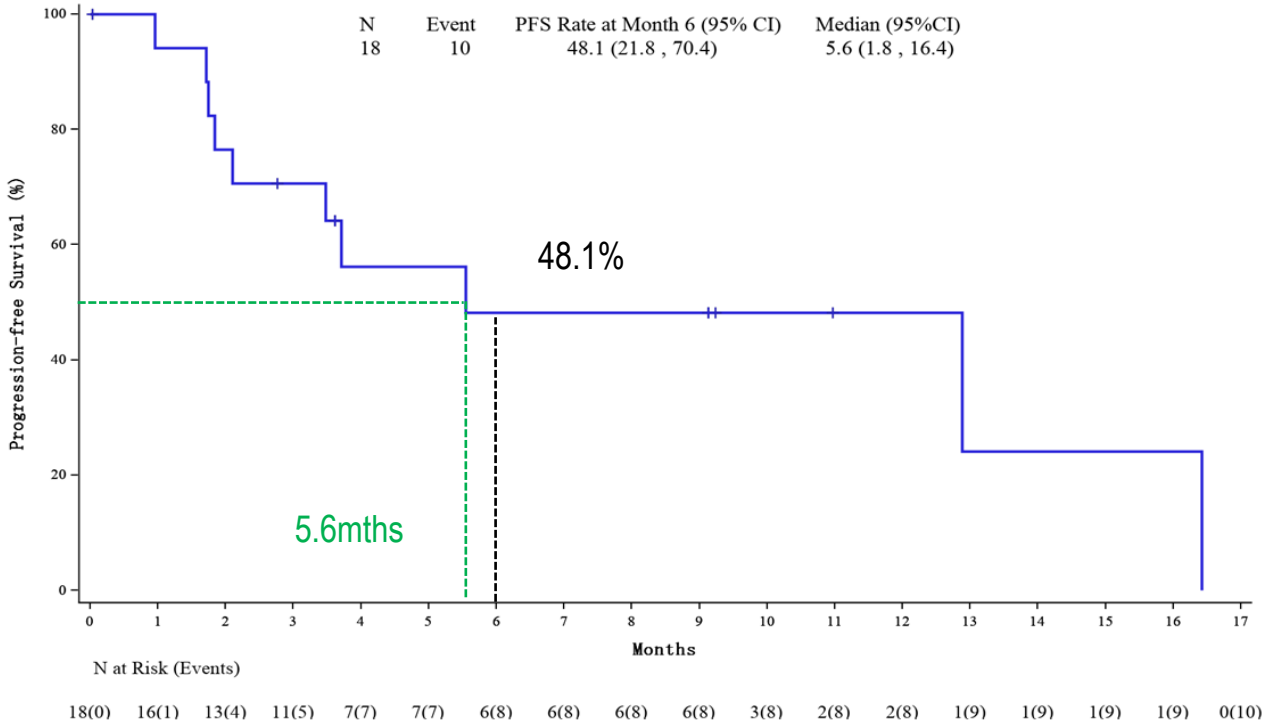
Data cut-off date: 10Jul, 2020

Time on Treatment for Evaluable Subjects (N=16)



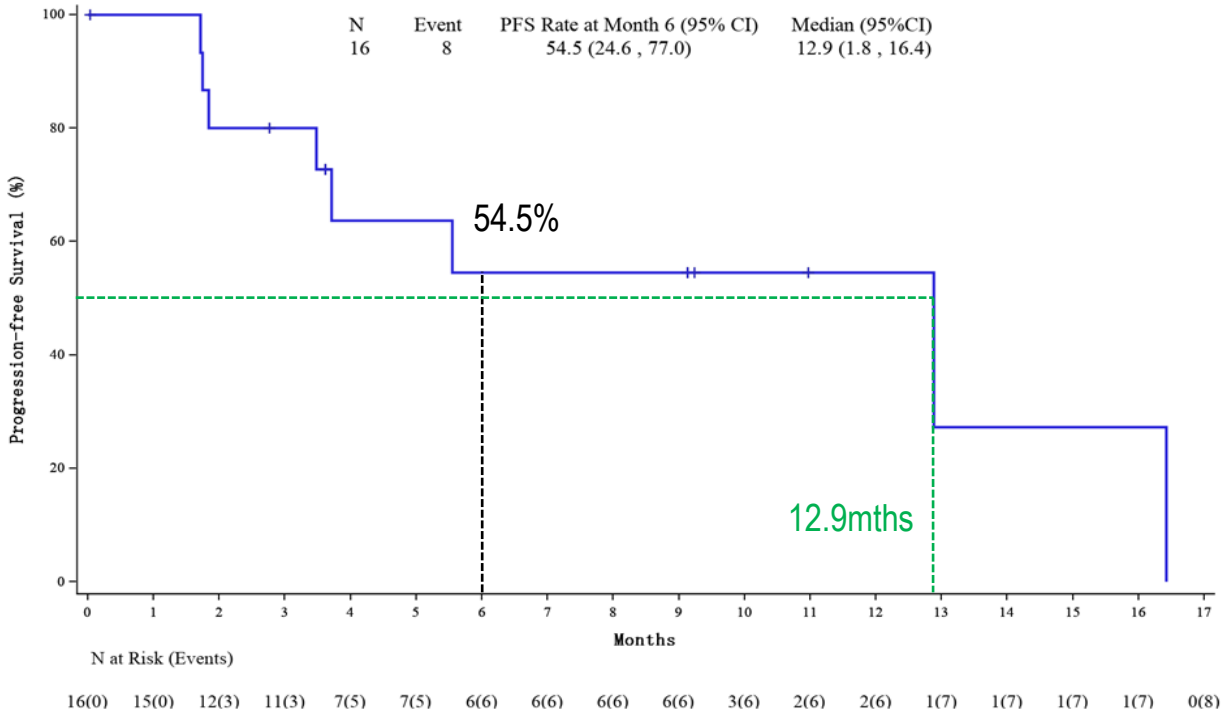
Data cut-off date: 10Jul, 2020

Progression-Free Survival in All Subjects (N=18)



Data cut-off date: 10Jul, 2020

Progression-Free Survival in Subjects Administered ≥ 4mg/kg Q2W AK104 (N=16)



Data cut-off date: 10Jul, 2020

Conclusions

- AK104 up to 10 mg/kg Q2W or 15 mg/kg Q3W in mesothelioma patients is safe and well-tolerated.
- Based on 15 evaluable IO-naïve mesothelioma subjects, ORR was 20.0% and DCR was 80.0%
- In subjects who have received ≥4 mg/kg Q2W AK104, PFS at 6 months was 54.5% and median PFS was 12.9 months.
- AK104 warrants further evaluation for the treatment of mesothelioma, possibly in combination with chemotherapy.

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