Case Report 3353

Efficacy and Safety of AK104, an Anti-PD-1/CTLA-4 Bispecific Antibody, in a Patient with Large Cell Neuroendocrine Carcinoma of the Lung

Sophia Frentzas[1,2], Kon Yew Kwek[3], Adam Konpa[3], Xiaoping Jin[3]

[1] Monash Health, Clayton, VIC, Australia, [2] Monash University, Clayton, VIC, Australia, [3] Akeso Biopharma, Inc, Zhongshan, China

DISCLOSURES

Commercial Interest	Relationship(s)
Akeso Biopharma	Study Sponsor. Employer of Kon Yew Kwek, Adam Konpa, and Xiaoping Jin.

Immune Checkpoint Inhibitors in LCNEC

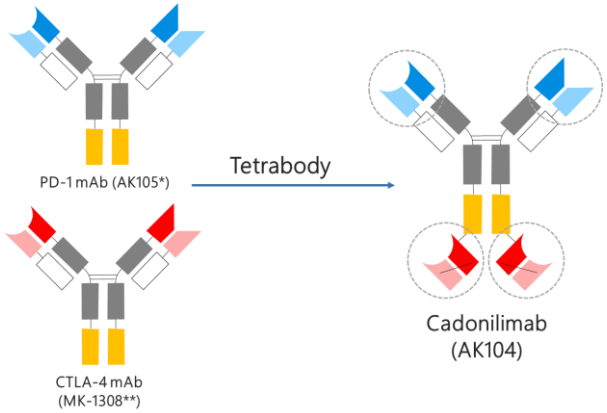
- Large cell neuroendocrine carcinoma (LCNEC) is a rare and aggressive tumor that accounts for about 3% of lung cancers.
- Currently, there are limited systemic therapy options for advanced or metastatic LCNEC; and immunotherapy is not standard therapy for LCNEC.
- A recent retrospective study reported that only 37 out of 661 eligible patients with LCNEC had received immune checkpoint inhibitors [1].
- To date, the largest prospective study of LCNEC treated with immune checkpoint inhibitors after failure of first-line chemotherapy demonstrated an overall response rate (ORR) of 33%, with a complete response (CR) rate of 11 % and median progression-free survival (PFS) of 4.2 months [2].

[1] Komiya T, Powell R. Role of immunotherapy in stage IV large cell neuroendocrine carcinoma of the lung. Journal of Clinical Oncology 2020; no. 15_suppl:9060
[2] Sherman S, Rotem O, Shochat T, Zer A, Moore A, Dudnik E. Efficacy of immune check-point inhibitors (ICPi) in large cell neuroendocrine tumors of lung (LCNEC). Lung Cancer. 2020; 143:40-46

AK104 (CADONILIMAB)

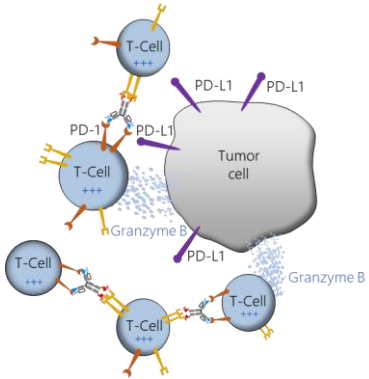
- AK104 is a next-generation, potential first-in-class humanized bi-specific antibody drug candidate targeting PD-1 and CTLA-4 simultaneously
- AK104 is designed as a novel tetrameric form, which can bind tetravalently to TILs co-expressing PD-1 & CTLA-4 with higher avidity
- Therefore, AK104 is designed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

First-in-class bi-specific antibody

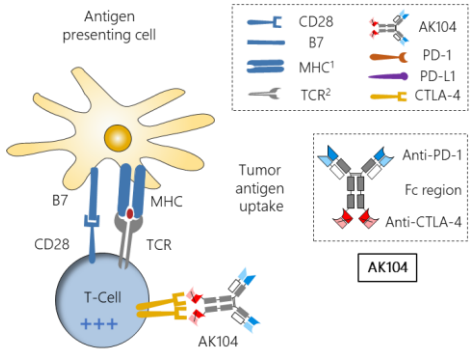


*: Penpulimab **: CTLA-4 mAb out-licensed to MSD

Tumour Microenvironment

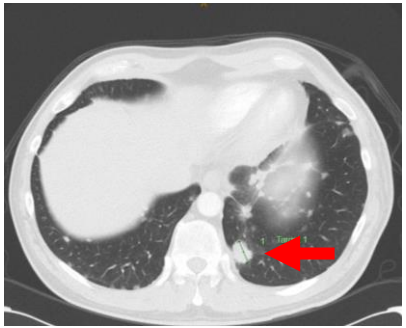


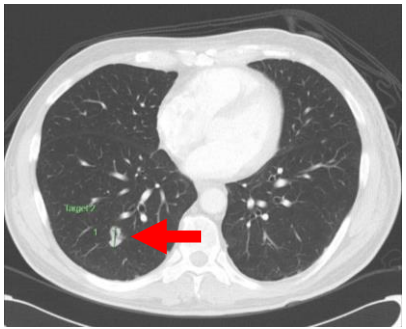
Peripheral Sites



- 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

Case presentation





- 64-year-old, non-smoker, male.
- Presented with large axillary lymphadenopathy and chest wall disease in September 2018.
- Underwent a left-sided mastectomy and left axillary node dissection. Histopathology from the axillary lymph node confirmed a metastatic, high grade LCNEC (Ki67 proliferation index = 50%). No malignancy was found in the mastectomy specimen.
- Further imaging demonstrated bilateral lung lesions.
- Assessed to have Stage IV LCNEC.
- Performance Status: ECOG 0.
- Enrolled in a dose escalation cohort of Study AK104-101 (NCT03261011) – a first-in-human, Phase 1a/1b, open-label, single-arm dose-escalation and dose-expansion study.
- No systemic treatment for the LCNEC prior to receiving AK104.

Study design

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)
- ECOG PS of 0 or 1

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

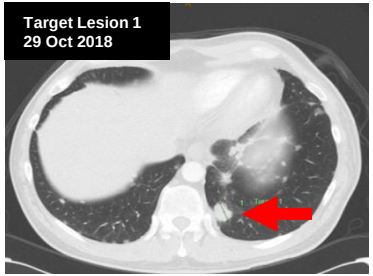
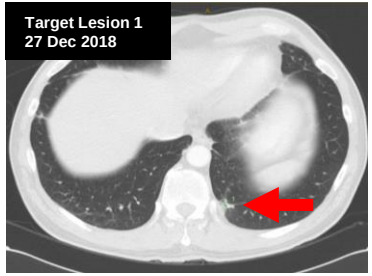
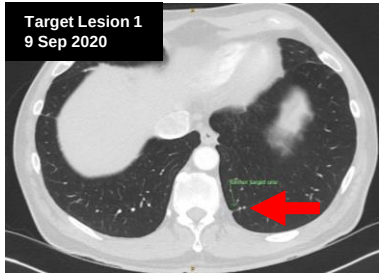
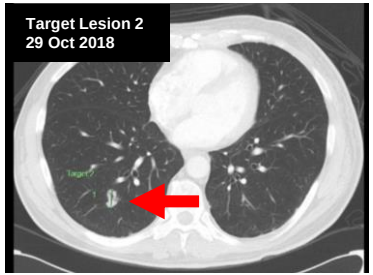
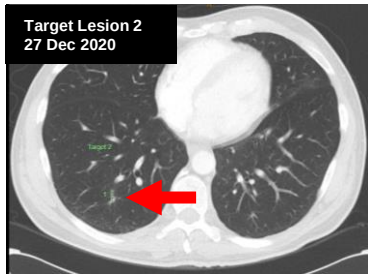
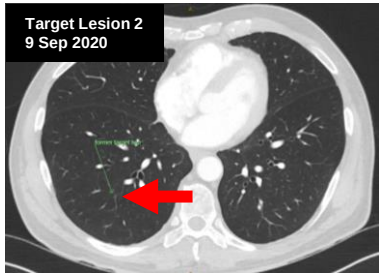
- Tumor assessments every 6 or 8 weeks for the first 12 months; then every 3 months thereafter
- Subjects permitted to continue with AK104 treatment beyond initial disease progression until progression is confirmed

Phase 1a: Dose-escalation Cohorts (3+3+3 design for advanced solid tumors)

- 15 mg/kg Q3W
- 10 mg/kg Q2W
- 6 mg/kg Q2W
- Subject with LCNEC
- 4 mg/kg Q2W
- 2 mg/kg Q2W
- 1 mg/kg Q2W
- 0.5mg/kg Q2W
- 0.2mg/kg Q2W

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

Results

Baseline	Initial PR (Week 8)	Confirmed CR (Week 96)
		
		

- The patient received 6mg/kg Q2W AK104 by IV infusion on a 28-day cycle.
- At the first tumor assessment on Week 8, a partial response (PR) with a 47.5% reduction in the tumor sum of diameters (SoD) was noted.
- By Week 24, the SoD had decreased from 40 mm at baseline to 2 mm, representing a maximum tumor shrinkage of 95%. SoD remained unchanged until Week 88 when a complete response (CR) was achieved.
- At the latest tumor assessment on 9 Sep 2020 (Week 96), the CR was confirmed with a duration of response of 20.4+ months. The patient completed treatment on 19 Nov 2020.
- The patient had no treatment emergent adverse events (AEs) above Grade 1. Treatment-related Grade 1 AEs were dry mouth and rash.

Conclusions

- AK104 administered as a first-line systemic therapy for metastatic LCNEC was well-tolerated and efficacious, producing a CR and DoR of 20.4+ months.
- Further evaluation of AK104 for the treatment of LCNEC is warranted.

Acknowledgements

- The patient and his family.
- Prof Jayesh Desai, Study Chair of AK104-101.
- Dr Wenjing Wang for her assistance with this presentation.