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Intracranial Activity of Ivonescimab Alone or In Combination with Platinum Doublet Chemotherapy in Patients with Advanced Non-Small Cell Lung Cancer and Brain Metastases

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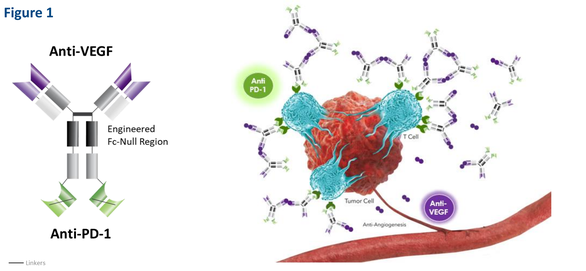
BACKGROUND

- Ivonescimab is an investigational novel bispecific antibody against PD-1 and VEGF[1] (Fig 1, Panel A)
- Ivonescimab demonstrates cooperative binding, as shown in in vitro studies[2]:
  - >18x increase in PD-1 binding in presence of VEGF
  - >4x increase in VEGF binding in presence of PD-1
- The intracranial activity of ivonescimab remains unknown.
- Ivonescimab has been administered to over 1600 patients and is currently being studied in four phase 3 clinical trials in advanced non-small cell lung cancer (NSCLC)[3]
- The current analysis reviews the intracranial activity in patients with advanced NSCLC and untreated brain metastases at baseline who received ivonescimab +/- platinum-based chemotherapy (PC) in phase II trials[4,5]

Figure 1



METHODS

- Patients with adv NSCLC of any histology, no actionable genomic alterations in EGFR/ALK, performance status 0-1 were eligible for phase II clinical trials AK112-201 of ivonescimab with platinum-doublet chemotherapy or AK112-202 of ivonescimab monotherapy.
  - Trial designs are as shown in Figure 2
- Patients with asymptomatic brain metastases (BMs) were eligible and underwent repeat brain MRI scans with cuts 5 mm or less every 6 weeks
- BMs were evaluated for intracranial (IC) response serially by Response Assessment in Neuro-Oncology (RANO) criteria by 2 independent neuroradiologists (in the US and China), with adjudication by a third neuroradiologist (US-based) as needed in the event of discordance in the first two readings.

Figure 2: Trial Designs

AK112-201 Trial: Chemotherapy/Ivonescimab Combination

Advanced NSCLC, Any histology, Any PD-L1 expression, Performance status 0-1, Age 18-75 → Platinum-based chemotherapy* (PC) x 4 cycles + ivo 20 mg/kg every 3 weeks → if no PD → Maintenance ivo 20 mg/kg + pemetrexed (non-squamous only) every 3 weeks for up to 2 years

Baseline chest CT, brain MRI | Repeat chest CT imaging q6 weeks; repeat brain MRI q6 weeks in patients with brain metastases

*Carboplatin with either pemetrexed (for non-squamous) or paclitaxel (for squamous) NSCLC

AK112-202 Trial: Ivonescimab Monotherapy

Advanced NSCLC, Any histology, Any PD-L1 expression, Performance status 0-1, Age 18-75 → Ivo 20 mg/kg every 3 weeks → if no PD → Maintenance ivo 20 mg/kg every 3 weeks For up to 2 years

Baseline chest CT, brain MRI | Repeat chest CT imaging q6 weeks; repeat brain MRI q6 weeks in patients with brain metastases

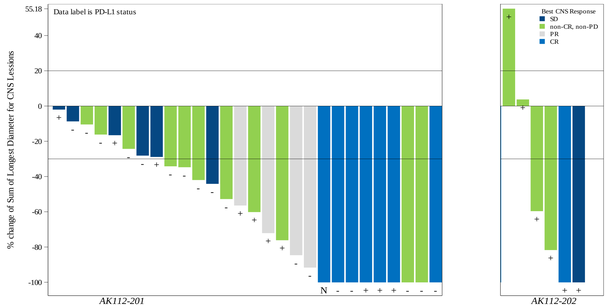
RESULTS

- A total of 35 patients met eligibility criteria for this analysis, including 28 who received ivonescimab + PC (AK112-201), 7 who received ivonescimab monotherapy (AK112-202)
  - Patient demographics shown in Table 1; notably skewed toward adenocarcinoma and negative PD-L1 expression vs. broader population
- IC response rate was 39% with chemo (25% complete responses) by RANO criteria
- IC response rate was 14% for ivonescimab monotherapy (14% complete response)
- Combined IC response rate 34% across both cohorts
  - No correlation with tumor PD-L1 expression
- Median IC progression-free survival was 19.3 months across both cohorts
- Strong concordance observed between intracranial and extracranial/overall RECIST response
- No cases of intracranial bleeding were observed in these patients with pre-existing brain metastases

Table 1: Patient Characteristics

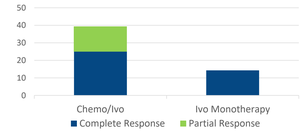
Patient Characteristic	AK112-201: Ivonescimab +Chemo	AK112-202: Ivonescimab Mono	Total
Age, median (range)	58.5 (42, 68)	61.0 (59, 68)	60.0 (42, 68)
Patient Sex, N (%)			
Male	20 (71.4)	7 (100.0)	27 (77.1)
Female	8 (28.6)	0	8 (22.9)
NSCLC Histology, N (%)			
Squamous	4 (14.3)	1 (14.3)	5 (14.3)
Adenocarcinoma	21 (75.0)	5 (71.4)	26 (74.3)
Other	3 (10.7)	1 (14.3)	4 (11.4)
Smoking history			
Yes	16 (57.1)	5 (71.4)	21 (60.0)
No	12 (42.9)	2 (28.6)	14 (40.0)
PD-L1 expression			
Yes	10 (35.7)	1 (14.3)	18 (51.4)
No	17 (60.7)	6 (85.7)	16 (45.7)
Unknown	1 (3.6)	0	1 (2.9)
Performance Status, N (%)			
0	3 (10.7)	0	3 (8.6)
1	25 (89.3)	7 (100.0)	32 (91.4)

Figure 3: Waterfall Plots for CNS activity
AK112-201 (ivonescimab + chemo) and AK112-202 (ivonescimab monotherapy)



RESULTS (*continued*)

Fig 4: Intracranial Response Rates (RANO Criteria)



Safety of ivonescimab in patients with untreated brain metastases

- There were no cases of intracranial hemorrhage identified among these patients with brain metastases identified at baseline
- Grade ≥3 TRAE rate 31.4% (11/35 patients)
- Grade ≥3 TRSAE rate 20% (7/35 patients)

Fig 5A: Intracranial Partial Response to Chemotherapy/Ivonescimab

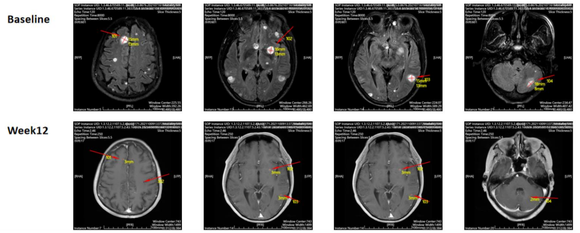


Fig 5B: Intracranial Complete Response to Ivonescimab Monotherapy

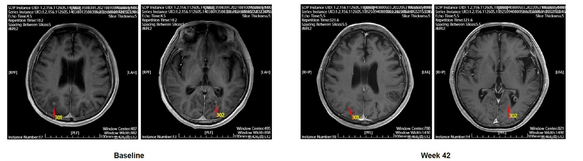


Fig 6: Intracranial Progression-Free Survival

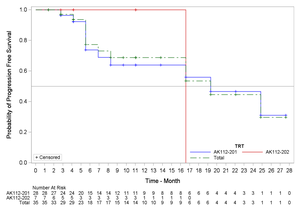
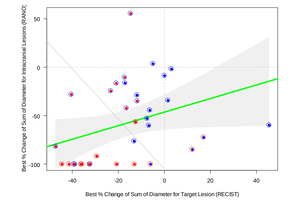


Fig 7: Intracranial vs. Overall (RECIST) Response



Closed dots: RECIST; open circle: RANO; Red: CR/PR; Blue: SD/Non-CR/Non-PR

Fitted line: RANO = 0.6974*RECIST – 46.2545 R-Squared = 0.1138
Residual MSE = 1516.3 Adjusted R-squared = 0.08609

A moderate correlation (Spearman's rho=0.43) is observed between best percentage change for intracranial lesion and best percentage change of target lesions.

DISCUSSION / CONCLUSIONS

- Ivonescimab alone or combined with chemotherapy led to IC responses among more than a third of patients with BMs at baseline, including an IC CR in 1 of 7 patients (14%) who received ivonescimab monotherapy
- All patients who did not achieve an IC response by RANO criteria demonstrated "stable disease" or "non-response/non-progression" as best response
- Overall IC disease control was encouraging for patients with untreated BMs, with median IC progression-free survival of 19.3 months across the combined cohorts of ivonescimab +/- PC
- IC efficacy of ivonescimab +/- PC was not correlated with tumor PD-L1 expression but was well correlated with overall disease response by RECIST criteria
- Administration of ivonescimab to patients with untreated BMs was not associated with any cases of intracranial bleeding complications

Ivonescimab is an investigational therapy that is not approved by any regulatory authority.

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REFERENCES

1) Zhong T, et al. AACR-NCI-EORTC International Conference 2023 Poster #B123, Abstract #35333, Boston, MA USA
2) Zhong T, et al. Journal for Immunotherapy of Cancer 2023; 11: SITC 2023 Poster #1194, San Diego, CA USA
3) Data on file. Summit Therapeutics.
4) Zhao Y, et al. EClinicalMedicine. 2023 Aug 3; 62; 102106
5) Wang L, et al. J Thorac Oncol. 2023 Oct 23: S1556-0864(23)02312-2.
6) Wen PY, et al. J Clin Oncol. 2010 Apr 19: 1863-72.