Poster # 75

Abstract # 9087

Phase II results of Ivonescimab (AK112/SMT112) a novel PD-1/VEGF bispecific in combination with chemotherapy for first line treatment of advanced or metastatic non-small cell lung cancer (NSCLC) without actionable genomic alterations (AGA) in EGFR/ALK

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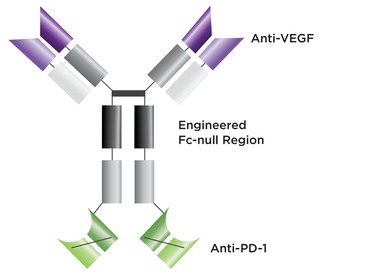
BACKGROUND

Since the initial approval of bevacizumab (bev) with chemo in NSCLC, the subsequent focus of bev use in combination with PD1 therapy for first line metastatic disease has largely focused on non-squamous (non-sq) histology. Ivonescimab is a novel anti-PD-1/VEGF bispecific antibody. The bispecific approach to these targets has the potential to recalibrate the malignant immuno-architecture in favor of a more immune-responsive and anti-tumor microenvironment. In this trial, we aimed to assess the efficacy and safety of ivonescimab combined with chemotherapy for first line advanced or metastatic NSCLC in patients (pts) with squamous (Sq) or non-sq NSCLC.[1]

Ivonescimab (AK112/SMT112):
First-in-Class PD-1/VEGF Bispecific Antibody
Brings two established mechanisms in oncology into ONE tetravalent molecule



Simultaneously engages both PD-1 & VEGF via 4 binding sites
Designed to optimize the balance of anti-tumor activity and safety

Ivonesimab Mechanism Of Action

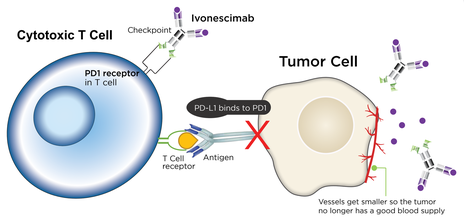
Dual, simultaneous PD-1/VEGF blockade drives anti-tumor activity[2,3]
- PD-1 blockade helps activate T cells[4]
- Antagonizing VEGF inhibits angiogenesis and leads to a more immuno-responsive tumor microenvironment (TME)[5]

Ivonescimab's structure enables higher avidity with >10-fold increase in PD-1 affinity in the presence of VEGF in vitro[6]

Potential to steer ivonescimab to the tumor versus healthy tissue
- High levels of PD-1 and VEGF expression in and around tumor tissue potentially allowing ivonescimab to simultaneously bind to both targets within the TME[1,6,7]

Engineered Fc-null region could lead to reduced adverse events
- Modification of Fc-null region reduces FcgR binding leading to reduction in ADCC, ADCP, and CDC in vitro[2,8] and no meaningful infusional cytokine release (IL-6 and TNFα) in patients[2]

Ivonescimab's $T_{1/2}$ of 6-7 days provides sufficient blockade of both targets. A shorter $T_{1/2}$ could potentially lead to a favorable safety profile[1,7]



METHODS

METHODS

An open-label, multi-center phaseII study evaluating the efficacy and safety of ivonescimab combined with chemotherapy in pts with advanced or metastatic NSCLC. Pts were enrolled into 3 cohorts based on prior therapy and presence of AGA. Data from pts with prior therapy for advanced or metastatic disease were presented in ASCO 2022 and here we report additional pts and longer follow-up data (see Table 4) from pts with NSCLC without AGA receiving first line therapy for advanced/metastatic disease. Pts were treated with 10 or 20 mg/kg ivonescimab once every 3wks combined with carboplatin and pemetrexed (non-sq) or carboplatin and paclitaxel (Sq). The primary endpoint was ORR per RECIST 1.1 by investigator (Figure 1).

Study Design[1]

Cohort 1 1L without EGFR/ALK alterations	Ivonescimab + pemetrexed 500 mg/m² + carboplatin AUC 5 mg/min/ml (non-squamous)	Ivonescimab + paclitaxel 175 mg/m² + carboplatin AUC 5 mg/min/ml (squamous)
Cohort 2 (non-sq) EGFR+ adv Progressed after EGFR-TKI	Ivonescimab + pemetrexed 500 mg/m² + carboplatin AUC 5 mg/min/ml	
Cohort 3 Progressed after platinum-doublet and PD-1	Ivonescimab + docetaxel 75 mg/m²	

Primary Endpoints:
- ORR
- Safety

Baseline Characteristics

As of data cut-off Feb 1, 2023, 135 pts were enrolled with advanced or metastatic NSCLC received ivonescimab plus chemotherapy including 63 with Sq and 72 with non-Sq. Median age was 61 yrs. 78% male, 3% and 97% pts had ECOG PS 0 and 1, respectively, and 20% pts had brain metastasis at baseline.

See Table 1 for Baseline Characteristics.

Table 1. Baseline Characteristics

	Squamous NSCLC (N=63)	Non-Squamous NSCLC (N=72)	Total (N=135)
Age, median (range), years	60 (40 - 76)	62 (38 - 72)	61 (38 - 76)
Male, n (%)	52 (83)	53 (74)	105 (78)
ECOG PS 1, n (%)	61 (97)	70 (97)	131 (97)
Smoking status, n (%): Former or Current Never	 47 (75) 16 (25)	 43 (60) 29 (40)	 90 (67) 45 (33)
PD-L1 TPS, n (%): <1 % 1-49% ≥50%	24 (38) 24 (38) 14 (22)	38 (53) 17 (24) 15 (21)	62 (46) 41 (30) 29 (22)
Stage IV, n (%)	45 (71)	70 (97)	115 (85)
Distant metastatic sites ≥3 Brain metastasis, n (%) Liver metastasis, n (%) Bone, n (%)	8 (13) 5 (8) 10 (16) 13 (21)	32 (44) 22 (31) 14 (19) 34 (47)	40 (30) 27 (20) 24 (18) 47 (35)
Central squamous NSCLC Tumors with necrosis/cavitation Invasion of large vessels History of hemoptysis	38 (60) 12 (19) 9 (14) 13 (21)	n/a n/a n/a n/a	n/a n/a n/a n/a

SAFETY

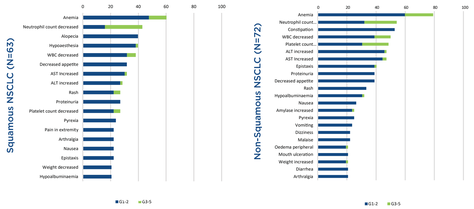
Table 2. Ivonescimab Chemo Combination in 1L Advanced/Metastatic NSCLC
Safety Results

Summary of Safety	Squamous (N=63) n (%)	Non-squamous (N=72) n (%)
Grade ≥3 TEAE	38 (60)	40 (56)
Grade ≥3 TRAE	26 (41)	14 (19)
TESAE	21 (33)	25 (35)
TRSAE	16 (25)	11 (15)
TEAE leading to AK112 discontinuation	7 (11)	2 (3)
TRAE leading to AK112 discontinuation	7 (11)	2 (3)
TEAE leading to death	1 (2)	7 (10)
TRAE leading to death	0 (0)	3 (4)

TEAE: Treatment-emergent adverse event
TESAE: Treatment-emergent serious adverse event
TRAE: Related Treatment-emergent adverse event
TRSAE: Related treatment-emergent serious adverse event

The most common treatment-emergent adverse events (TEAEs) in SCC were anemia, neutrophil count decreased, and alopecia. In non-SCC, they were anemia, neutrophil count decreased, and constipation (details see figures above). Grade ≥3 TEAEs occurred in 60% and 56% of pts in Sq and non-Sq, respectively.

Ivonescimab Chemo Combination in 1L Advanced/Metastatic NSCLC TEAE >=20% (%)



- In Squamous NSCLC: all grade and grade ≥3 creatine increase were 8% and 0%, all grade and grade ≥3 blood pressure increased were 13% and 2%
- In Non-squamous NSCLC: all grade and grade ≥3 creatine increase were 19% and 0%, all grade and grade ≥3 blood pressure increased were 8% and 0%

Table 3. Ivonescimab Chemo Combination in 1L Advanced/Metastatic NSCLC
Adverse events of interest

Immune-related Adverse Events

Adverse Event in >1%	Total (N=135) Any Grade (%)	Total (N=135) Grade ≥3 (%)
Hypothyroidism	8 (5.9)	0 (0)
Immune-mediated lung disease	6 (4.4)	3 (2.2)
Rash	6 (4.4)	1 (0.7)
Pruritus	6 (4.4)	0 (0)
TSH increased	5 (3.7)	0 (0)
Hyperthyroidism	4 (3.0)	0 (0)
AST increased	2 (1.5)	1 (0.7)
ALT increased	2 (1.5)	1 (0.7)

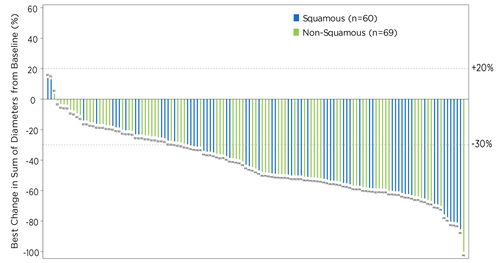
VEGF-related Adverse Events

Adverse Event in >1%	SQ (N=63) Any Grade (%)	SQ (N=63) Grade ≥3 (%)	Non-SQ (N=72) Any Grade (%)	Non-SQ (N=72) Grade ≥3 (%)
Epistaxis	13 (20.6)	0 (0)	25 (34.7)	1 (1.4)
Gingival bleeding	5 (7.9)	0 (0)	6 (8.3)	0 (0)
Hemoptysis	6 (9.5)	1 (1.6)	3 (4.2)	0 (0)
Hematochezia	1 (1.6)	0 (0)	1 (1.4)	0 (0)
Proteinuria	18 (28.6)	0 (0.0)	17 (23.6)	0 (0)
Hypertension	9 (14.3)	3 (4.8)	5 (6.9)	2 (2.8)

RESULTS

Ivonescimab Chemo Combination in 1L Advanced/Metastatic NSCLC
Median follow up 13.3 months

Percent Changes from Baseline in Target Lesions
Sum of Diameters (N=129*)

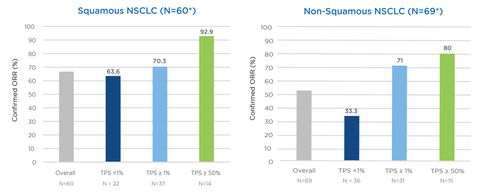


*ORR 59% (N=129)
*includes subjects with at least one post-baseline tumor assessment

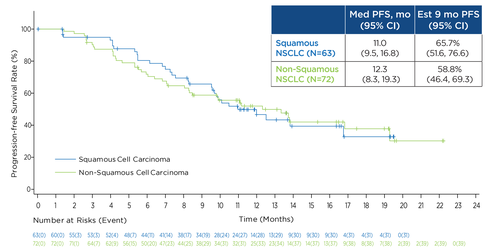
ORR, DCR, and Median DOR

	Squamous N=60*	Non-squamous N=69*
ORR† [95% CI]	67% [53, 78]	52% [40, 64]
DCR† [95% CI]	93% [84, 98]	93% [84, 98]
Median DOR [95% CI], mo	15 [8, NE]	18 [11, NE]

*includes subjects with at least one post-baseline tumor assessment
† ORR & DCR based on confirmed BOR
*NE=Non-estimable

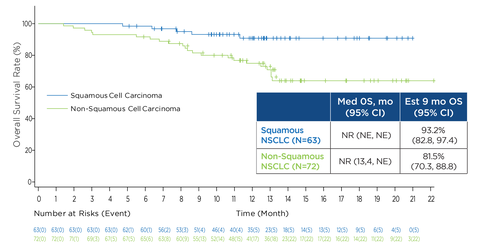


Ivonescimab Chemo Combination 1L Advanced/Metastatic NSCLC
Progression Free Survival (N=135) - Median follow up 13.3 months



	Med PFS, mo (95% CI)	Est 9 mo PFS (95% CI)
Squamous NSCLC (N=63)	11.0 (9.5, 16.8)	65.7% (51.6, 76.6)
Non-Squamous NSCLC (N=72)	12.3 (8.3, 19.3)	58.8% (46.4, 69.3)

Ivonescimab Chemo Combination 1L Advanced/Metastatic NSCLC
Overall Survival (N=135) - Median follow up 13.3 months



	Med OS, mo (95% CI)	Est 9 mo OS (95% CI)
Squamous NSCLC (N=63)	NR (NE, NE)	93.2% (82.8, 97.4)
Non-Squamous NSCLC (N=72)	NR (13.4, NE)	81.5% (70.3, 88.8)

Median follow-up was 13.3 mo. Pts with Sq experienced a 67% ORR with median DOR 15 mo, 93% DCR, the 9-mo PFS and OS rate was 66% and 93%, respectively. Pts with non-Sq experienced a 52% ORR, median DOR 18 mo, 93% DCR, the 9-mo PFS rate and OS rate was 59% and 82%, respectively.

Table 4. Updated Ivonescimab in Combination with Chemo in ≥2L for Cohorts 2 & 3

	Cohort 2 (EGFR-TKI Relapsed NSCLC) N=19	Cohort 3* (PD-1/Platinum Relapsed NSCLC) N=20
Median Follow Up (range)	16.8 (3.8, 22.3)	16.8 (2.2, 20.3)
Confirmed ORR, %	68 (43, 87)	40 (19, 64)
DCR, % (95% CI)	95 (74, 99)	70 (46, 88)
DoR, mo (95% CI)	8.5	12.4
Median PFS, mo (95% CI)	8.5	7.1
Median OS, mo (95% CI)	NR (10.4, NE)	15.6 (8.4, NE)
Est 12 mo OS, % (95% CI)	74 (50, 88)	65 (40, 82)
Median duration of treatment (range), mo	8.5 (1.4, 23.0)	5.9 (1.4, 20.3)
Percent of patients on treatment at 12 months	6 (31.6)	7 (35.0)

In Sq, 4 (21%) and 15 (79%) pts received 1 and 2 prior line of therapy, respectively,
In non-Sq, 14 (70%), 5 (25%), and 1 (5%) pts received, 1, 2, and ≥3 prior line of therapy, respectively.

*n=7 (35%) are squamous and n=13 (65%) are non-squamous pts

CONCLUSION

- Ivonescimab plus chemotherapy has shown promising anti-tumor activity in patients with advanced/metastatic NSCLC without EGFR and ALK genomic alterations.
- Ivonescimab can be administered safely in combination with platinum doublet chemotherapy to patients with Squamous and Non-Squamous histology.
- Ivonescimab is currently being evaluated in Phase III studies in NSCLC (NCT05184712).

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Ivonescimab is an investigational therapy that is not approved by any regulatory authority. It is currently being investigated in Phase III clinical studies. Data generated and analysed by Akeso.