Amivantamab in Wild-type Advanced Non-small Cell Lung Cancer (NSCLC) After Disease Progression on Checkpoint Inhibition and Chemotherapy: Results from the Phase 1b CHRYSALIS Study

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Presented by BC Cho at American Association for Cancer Research; April 5–10, 2024; San Diego, CA, USA.

Declaration of Interests: Byoung Chul Cho

- **Stock or stock options:** TheraCanVac Inc, Gencurix Inc, BridgeBio Therapeutics, KANAPH Therapeutic Inc, Cyrus Therapeutics, Interpark Bio Convergence Corp., J INTS BIO
- **Royalties/intellectual property/patent beneficiary:** Champions Oncology, Crown Bioscience, Imagen
- **Research funding:** MOGAM Institute, LG Chem, Oscotec, Interpark Bio Convergence Corp, GIInnovation, GI-Cell, Abion, Abbvie, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Champions Oncology, CJ Bioscience, CJ Blossom Park, Cyrus, Dizal Pharma, Genexine, Janssen, Lilly, MSD, Novartis, Nuvalent, Oncternal, Ono, Regeneron, Dong-A ST, Bridgebio Therapeutics, Yuhan, ImmuneOncia, Illumina, Kanaph Therapeutics, Therapex, J INTS BIO, Hanmi, CHA Bundang Medical Center
- **Advisory board:** KANAPH Therapeutic Inc, Bridgebio Therapeutics, Cyrus Therapeutics, Guardant Health, Oscotec Inc
- **Consultant:** Abion, BeiGene, Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, CJ, CureLogen, Cyrus Therapeutics, Ono, Onegene Biotechnology, Yuhan, Pfizer, Eli Lilly, GI-Cell, Guardant, HK Inno-N, Imnewrun Biosciences Inc., Janssen, Takeda, MSD, Medpacto, Blueprint Medicines, RandBio, Hanmi
- **Founder:** DAAN Biotherapeutics (Founder)
- **Member of the board of directors:** Interpark Bio Convergence Corp., J INTS BIO

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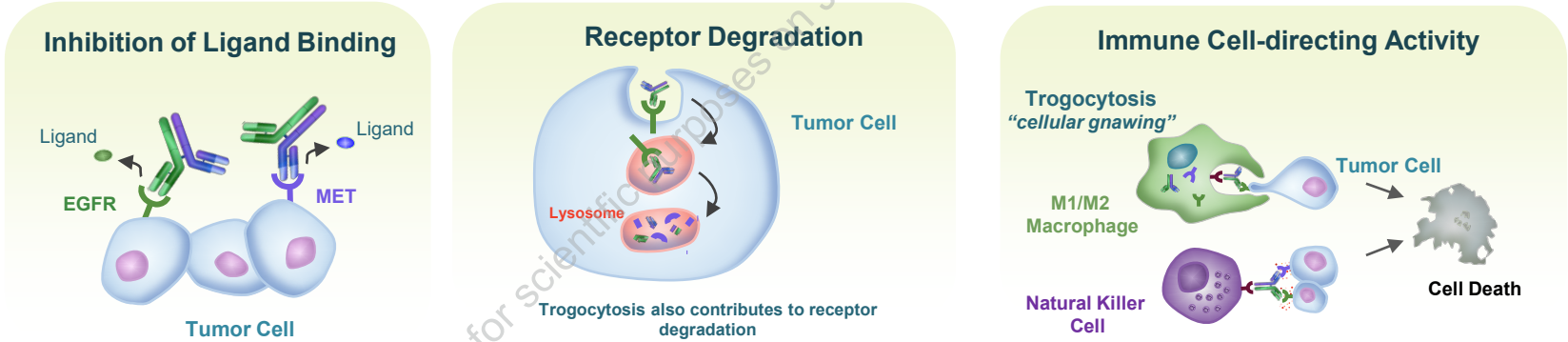
Background

- Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity that has shown antitumor clinical activity across a range of *EGFR*- and *MET*-driven disease[1-4]
- Overexpression of *EGFR* and *MET* have been observed in previously untreated wild-type adenocarcinoma and squamous NSCLC and are associated with cancer progression[5,6]
- Amivantamab has demonstrated anti-tumor activity through multiple mechanisms of action, with ligand binding identified as the primary mechanism in wild-type NSCLC patient-derived xenograph models[7]
  - Additionally, preclinical inhibition of ligand binding by amivantamab led to reduced *EGFR* and *MET* signaling in wild-type NSCLC[1]



We evaluated amivantamab monotherapy activity in patients with wild-type NSCLC after disease progression on platinum-based chemotherapy and anti-PD-1 or PD-L1 therapy

2L, second-line; ADCC, antibody-dependent cellular cytotoxicity; *EGFR,* epidermal growth factor receptor; Ex20ins, exon 20 insertions; HGF, hepatocyte growth factor; *MET*, mesenchymal-epithelial transition factor; *MET*ex14, MET exon 14 skipping mutation; NSCLC, non-small cell lung cancer; WT, wild-type.

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Methods

Dose-escalation phase

RP2D was identified:
Amivantamab 1050 mg IV
(1400 mg if ≥80 kg)

Eligibility Criteria for WT Cohorts

- Patients with advanced NSCLC that did not have *EGFR*, *ALK,* or *MET*ex14 activating mutations (wild-type NSCLC)
- Adenocarcinoma (for **WT-Ad**) or squamous cell carcinoma (for **WT-Sq**) histology
- Confirmed EGFR and/or MET expression by IHC[a]
- Previously treated with anti-PD-1/PD-L1 and chemotherapy

Dose-expansion cohorts

Cohort A: Post–any *EGFR* TKI (T790M+, C797S+)

Cohort B: Post–any *EGFR* TKI (T790M–, C797S–)

Cohort C: Post-osimertinib (C797S+)

Cohort D: *EGFR* Ex20ins[b]

Cohort MET-1: Post–any *EGFR* TKI (*MET* amplified)

Cohort MET-2: *MET*ex14[c]

Cohort WT-Ad[d]: *EGFR* wild-type status adenocarcinoma

Cohort WT-Sq[d]: *EGFR* wild-type status SCC

Focus of this presentation

CHRYSALIS also included 2 additional combination cohorts:
- *Amivantamab + lazertinib*
- *Amivantamab + carboplatin-pemetrexed*

All cohorts in the CHRYSALIS study are now closed

Endpoints[e]
- Objective response rate (primary)
- Duration of response
- Clinical benefit rate[f]
- Progression-free survival
- Overall survival
- Adverse events
- Biomarker analyses (exploratory)

Plasma samples were collected pre-treatment, with ctDNA analyzed by Guardant Health (Redwood City, CA)

[a]Patients had to have 1+ staining (defined as ≥50% positive 1+/2+/3+) using archival tissue submitted during prescreening or fresh tissue during screening. [b]Cohort D was presented at WCLC 2020 (Sabari, JK. *J Thorac Oncol*. 2021;16(3):S108-109. OA04.04). [c]Primary *MET*ex14 mutation was confirmed locally; all patients must have failed or be ineligible for standard of care therapy. Data for patients with *MET*ex14 (including those in cohorts other than Cohort MET-2) was presented at WCLC 2023 (Leighl, N. *J Thorac Oncol.* 2023;18(11S):S93-94. OA21.04). [d]Due to slow enrollment progress, both cohorts were closed to further enrollment once one cohort (WT-Ad) had reached the protocol-defined interim analysis. [e]Response was assessed by the investigator per RECIST v1.1. [f]Percentage of patients with confirmed response or SD of ≥11 weeks duration.

EGFR, epidermal growth factor receptor; ex20ins; exon 20 insertion mutation; IHC, immunohistochemistry; IV, intravenous; MET, mesenchymal-epithelial transition factor; METex14, MET exon 14 skipping mutation; NSCLC, non-small cell lung cancer; RP2D, recommended phase 2 dose; SCC, squamous cell carcinoma; SD, stable disease; TKI, tyrosine kinase inhibitor; WT, wild-type.

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Results: Demographic and Baseline Characteristics

Characteristic, n (%)	WT-Ad cohort (n=41)	WT-Sq cohort (n=14)
Median age, years (range)	62 (35–86)	71 (60–81)
Male / female	26 (63) / 15 (37)	8 (57) / 6 (43)
Race		
White	8 (20)	3 (21)
Asian	15 (37)	6 (43)
Black or African American	1 (2)	0
Not reported	17 (41)	5 (36)
ECOG PS		
0	7 (17)	2 (14)
1	33 (80)	12 (86)
2	1 (2)	0
Median number of prior lines (range)	2 (1–5)	2 (1–3)

- In the **WT-Ad cohort**, 41 patients received amivantamab, with a median follow-up of 6.2 months
  - 30 patients had ≥1 post-baseline disease assessment
- In the **WT-Sq cohort**, 14 patients received amivantamab, with a median follow-up of 6.3 months
  - 12 patients had ≥1 post-baseline disease assessment

Clinical cutoff: 31 Jan 2024

Ad, adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; Sq, squamous cell carcinoma; WT, wild-type.

Results: Safety Profile

AEs (≥15%) by preferred term, n (%)	WT-Ad cohort (n=41)		WT-Sq cohort (n=14)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Rash	13 (32)	0	4 (29)	0
Dermatitis acneiform	13 (32)	0	2 (14)	0
Paronychia	11 (27)	0	3 (21)	0
Associated with MET inhibition				
Hypoalbuminemia	16 (39)	1 (2)	4 (29)	1 (7)
Peripheral edema	6 (15)	0	4 (29)	0
Other				
Infusion-related reactions	26 (63)	4 (10)	8 (57)	1 (7)
Dyspnea	11 (27)	3 (7)	2 (14)	0
Constipation	10 (24)	1 (2)	3 (21)	0
Decreased appetite	9 (22)	0	2 (14)	0
Nausea	9 (22)	1 (2)	1 (7)	0
Asthenia	9 (22)	0	1 (7)	1 (7)
Fatigue	8 (20)	1 (2)	1 (7)	0
Pneumonia	6 (15)	5 (12)	6 (43)	3 (21)
Gamma-glutamyltransferase increased	6 (15)	1 (2)	2 (14)	0
Headache	2 (5)	0	3 (21)	0

- Most common AEs were EGFR- or MET-related, primarily grade 1-2
- Treatment-related grade ≥3 AEs:
  - **WT-Ad** cohort: 17%
  - **WT-Sq** cohort: 21%
- Discontinuations of amivantamab due to treatment-related AEs
  - **WT-Ad** cohort: 4 (10%) patients
  - **WT-Sq** cohort: 2 (14%) patients
- There was 1 event of interstitial lung disease, of grade 2 and occurred in the **WT-Ad** cohort

Ad, adenocarcinoma; AE, adverse event; EGFR, epidermal growth factor receptor; Sq, squamous cell carcinoma; WT, wild-type.

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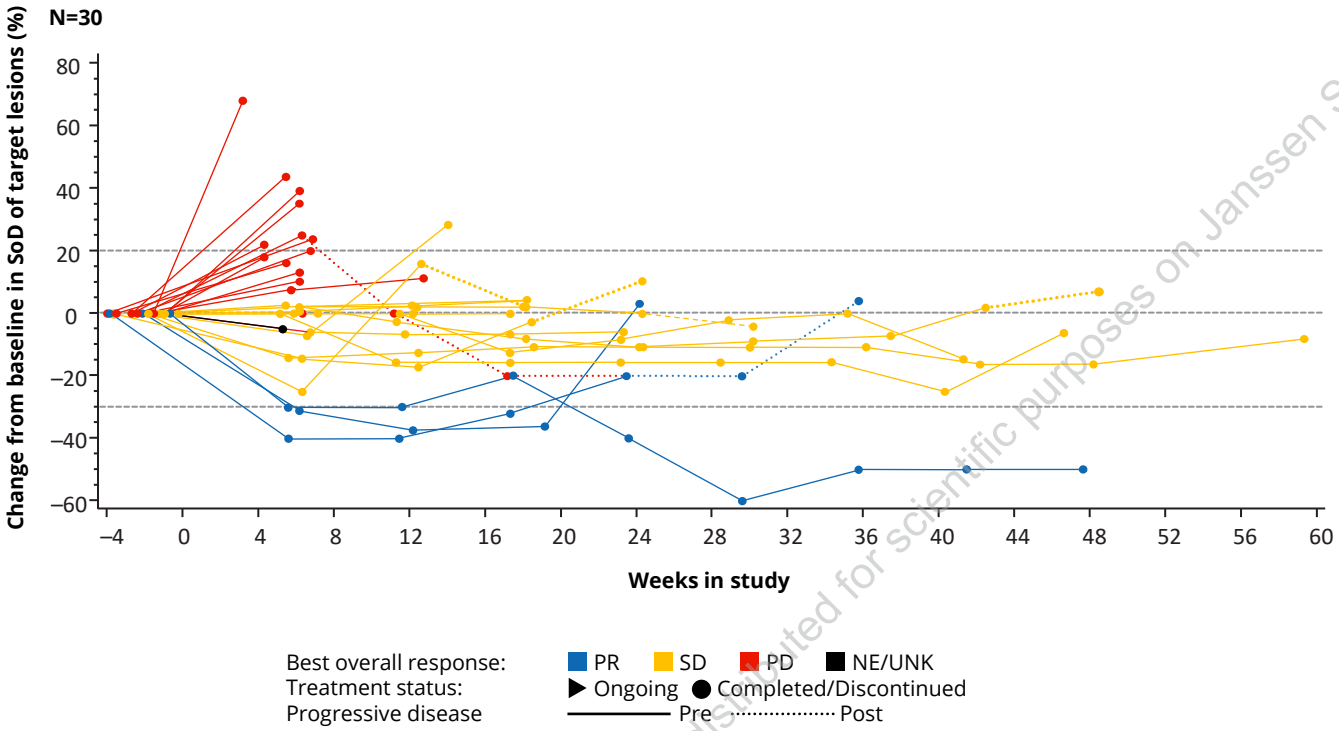
Results: Amivantamab in WT-Ad Cohort

Percent change from baseline in Sum of Diameters of target lesions[a]

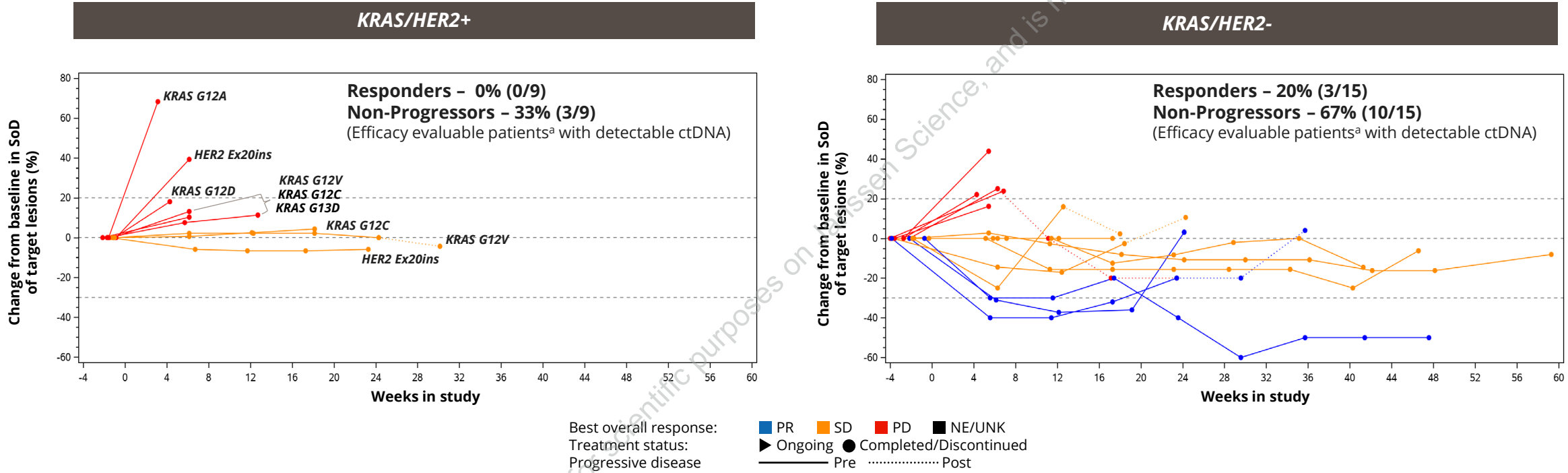


Investigator-assessed response (n=41)	
Median follow-up	6.2 mo (range, 0–18)
ORR	7% (95% CI, 1.5–20)
Median DoR	4.2 mo (95% CI, 4.1–NE)
DoR ≥6 months, n (%)	1 (33)
Best overall response, n (%)	
CR	0
PR	3 (7)
SD	12 (29)
PD	22 (54)
NE/unknown	4 (10)
CBR[b]	29% (95% CI, 16.1–45.5)
Median PFS	1.6 mo (95% CI, 1.4–3.6)
Median OS	9.5 mo (95% CI, 5.7–12.0)

[a]30 patients had ≥1 post-baseline disease assessment, 11 patients discontinued due to adverse events (n=5), disease progression (n=4), or physician decision (n=2). [b]CBR is defined as the percentage of patients achieving confirmed complete or partial response, or durable stable disease (duration of at least 11 weeks).

Ad, adenocarcinoma; DoR, duration of response; CBR, clinical benefit rate; CI, confidence interval; mo, months; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SoD, sum of diameters; UNK, unknown; WT, wild-type.

Results: Amivantamab Activity in Biomarker-defined Subgroups



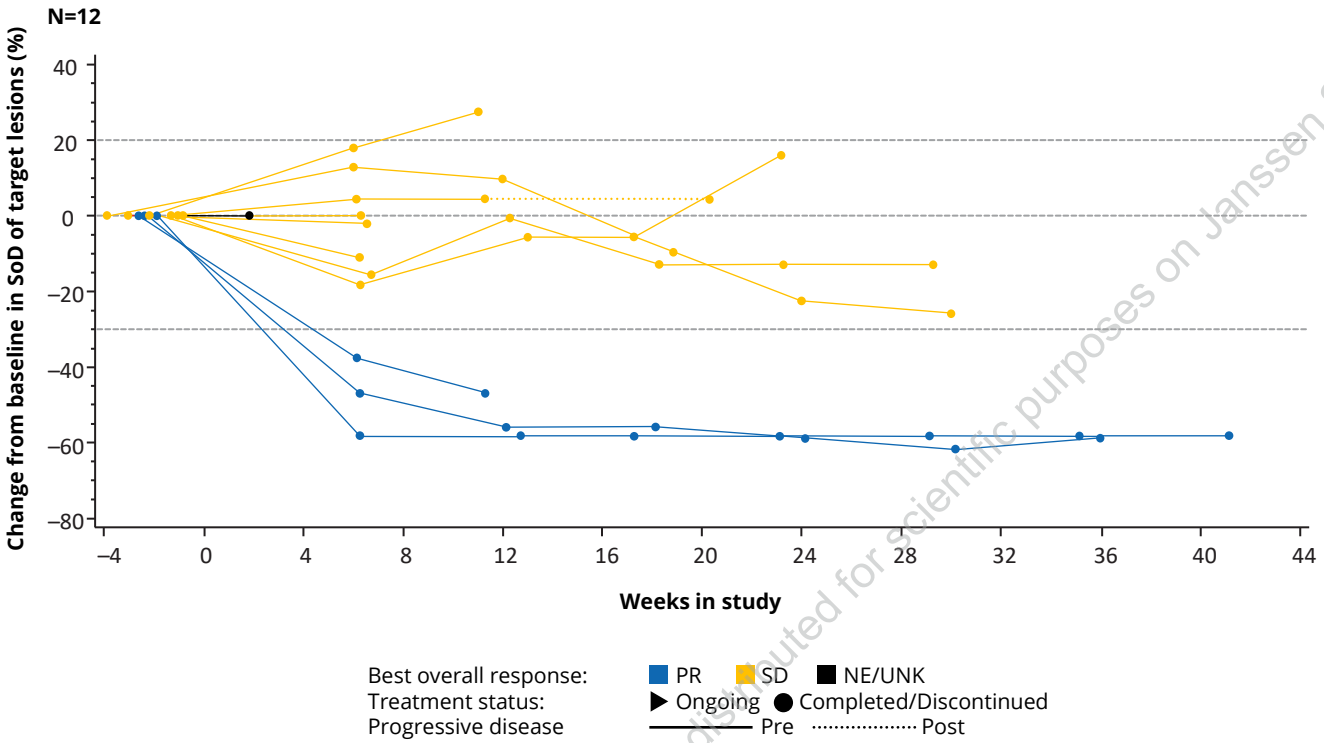
- Among patients with detectable ctDNA (n=24), 9 patients were *KRAS*/*HER2*+
- ORR was **0% (0/9)** for *KRAS*/*HER2*+ and **20% (3/15)** for *KRAS*/*HER2*-
- Median PFS was shorter for *KRAS*/*HER2*+ (**1.4 months** [95% CI, 0.7–NE] vs **4.2 months** [95% CI, 1.2–9.4] for *KRAS*/*HER2*-)

[a]Patients were efficacy evaluable if they received at least one dose of study drug and have undergone at least 1 scheduled post-baseline disease assessments or discontinued treatment for any reason.

CI, confidence interval; ctDNA, circulating tumor DNA; KRAS/HER2+, patients with KRAS/HER2 mutations; KRAS/HER2-, patients without KRAS/HER2 mutations; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SoD, sum of diameters; UNK, unknown.

Results: Amivantamab in WT-Sq Cohort

Percent change from baseline in SoD of target lesions[a]



Investigator-assessed response (n=14)	
Median follow-up	6.2 mo (range, 1–19)
ORR	21% (95% CI, 5–51)
Median DoR	NE
DoR ≥6 months, n (%)	2 (67%)
Best overall response, n (%)	
CR	0
PR	3 (21)
SD	8 (57)
PD	0
NE/unknown	3 (21)
CBR[b]	43% (95% CI, 17.7–71.1)
Median PFS	4.0 mo (95% CI, 2.2–7.3)
Median OS	NE

[a]12 patients had ≥1 post-baseline disease assessment, 2 patients discontinued due to an AE (IRR) or refusal of further study treatment. [b]CBR is defined as the percentage of patients achieving confirmed complete or partial response, or durable stable disease (duration of at least 11 weeks).

DoR, duration of response; CBR, clinical benefit rate; CI, confidence interval; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SoD, sum of diameters; Sq, squamous cell carcinoma; UNK, unknown; WT, wild-type.

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Conclusions

- Amivantamab demonstrated antitumor activity in patients with refractory WT adenocarcinoma or refractory WT squamous cell NSCLC
  - No progressive disease was seen in the WT squamous cell carcinoma cohort
- Amivantamab activity was stronger in patients whose tumors lacked *KRAS/HER2* mutations
  - No response was seen in patients with *KRAS/HER2* mutations

NSCLC, non-small cell lung cancer; WT, wild-type.

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Key Takeaways

- Amivantamab monotherapy demonstrated antitumor activity in patients with wild-type squamous and adenocarcinoma NSCLC after disease progression on platinum-based chemotherapy and anti-PD-1 or PD-L1 therapy
- No new safety signals of amivantamab monotherapy were identified

NSCLC, non-small cell lung cancer; PD-1, Programmed Cell Death Protein 1; PD-L1, Programmed Cell Death Ligand 1.

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Acknowledgements

- Patients who participated in the study and their families and caregivers
- Physicians and nurses who cared for patients and staff members who supported this clinical trial
- Staff members at the study sites and involved in data collection/analyses
- Medical writing assistance was provided by Lumanity Communications Inc., and funded by Janssen Global Services, LLC

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