Amivantamab plus capmatinib in advanced non-small cell lung cancer (NSCLC) harboring *MET* alterations: Recommended phase 2 combination dose and preliminary dose-escalation results from the phase 1/2 METalmark study

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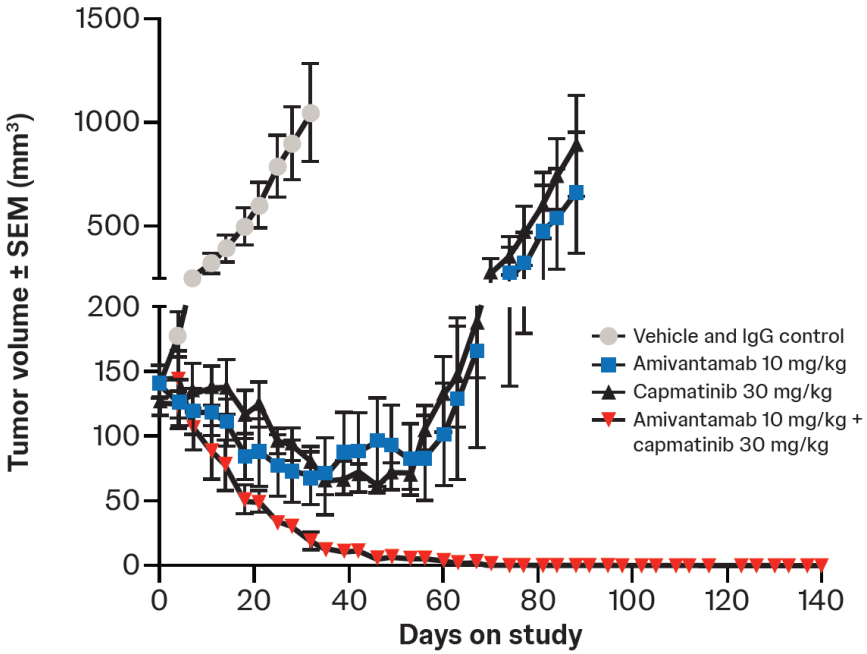
Background

- Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity[1-3]
- Amivantamab monotherapy has demonstrated meaningful clinical activity in patients with *MET*-driven advanced NSCLC, including those harboring *MET* Exon 14 skipping mutations and *MET* amplification[4,5]
- Capmatinib is an intracellular-targeting type 1b MET TKI approved for the treatment of patients with *MET* Exon 14–mutated advanced NSCLC[6-8]
- Simultaneously targeting the extracellular and intracellular regions of MET could achieve more potent inhibition than either agent alone, as shown in a patient-derived xenograft model with wild-type *EGFR* and *MET* Exon 14 skipping mutation (**Figure 1**)
- Here, preliminary results and the identification of the RP2CD are presented for the phase 1/2 METalmark study (ClinicalTrials.gov Identifier: NCT05488314)

Figure 1: Preclinical activity of amivantamab + capmatinib



EGFR, epidermal growth factor receptor; MET, mesenchymal epithelial transition; NSCLC, non-small cell lung cancer; RP2CD, recommended phase 2 combination dose; TKI, tyrosine-kinase inhibitor.

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Methods

- METalmark is a global, open-label, phase 1/2 study evaluating the safety and efficacy of amivantamab + capmatinib in patients with unresectable metastatic NSCLC
- The study includes a combination dose selection phase (enrolled patients regardless of baseline mutation) followed by an expansion phase in patients with NSCLC with treatment-naïve or refractory *MET* Exon 14 skipping mutation (METex14) or *MET* amplification (3 cohorts)
- For phase 1 dose selection, patients must have had disease progression on or intolerance to prior therapy
  - The primary objective was to identify the RP2CD; the dose levels assessed were:
    - Dose Level 0: amivantamab IV 700 mg (1050 mg if body weight ≥80 kg) + capmatinib oral 400 mg BID
    - Dose Level +1: amivantamab IV 1050 mg (1400 mg if body weight ≥80 kg) + capmatinib oral 400 mg BID
  - Primary endpoints were DLT during Cycle 1 and safety
- The study design is shown in **Figure 2**; this presentation focuses on phase 1 dose selection

BID, twice daily; DLT, dose-limiting toxicity; IV, intravenous; MET, mesenchymal epithelial transition; METex14, *MET* Exon 14; NSCLC, non-small cell lung cancer; RP2CD, recommended phase 2 combination dose.

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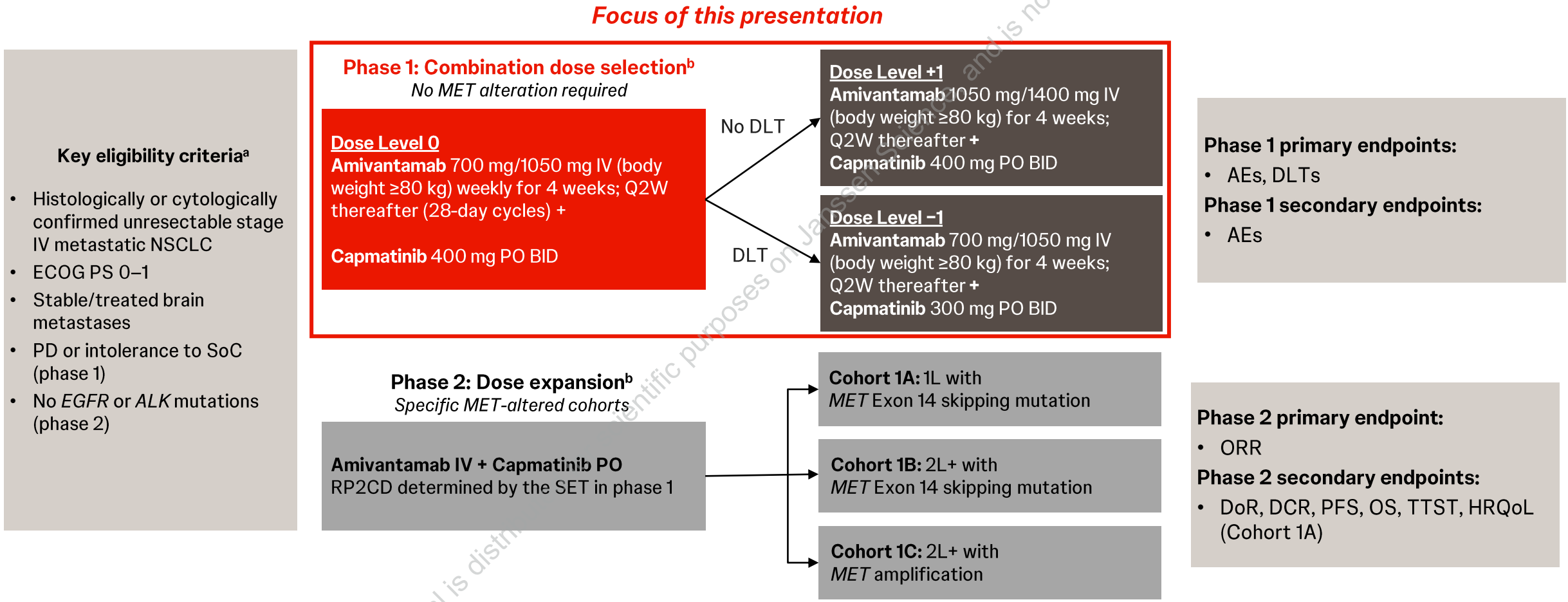
Figure 2: METalmark Study Design



[a]Patients were enrolled in phase 1 regardless of mutation status of *EGFR*, *MET*, or other actionable genomic aberrations.[b]28-day cycles.

1L, first-line; 2L+, second-line and beyond (no more than 3 lines of prior systemic anticancer therapy); AE, adverse event; ALK, anaplastic lymphoma kinase; BID, twice daily; DCR, disease control rate; DLT, dose-limiting toxicity; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; IV, intravenous; MET, mesenchymal epithelial transition; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, oral; Q2W, every 2 weeks; RP2CD, recommended phase 2 combination dose; SET, safety evaluation team; SoC, standard of care; TTST, time to subsequent therapy.

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Results: Demographic and Baseline Characteristics

- As of November 8, 2023, 18 patients were dosed (**Table 1** and **Figure 3**), with a median follow-up of 3.3 months

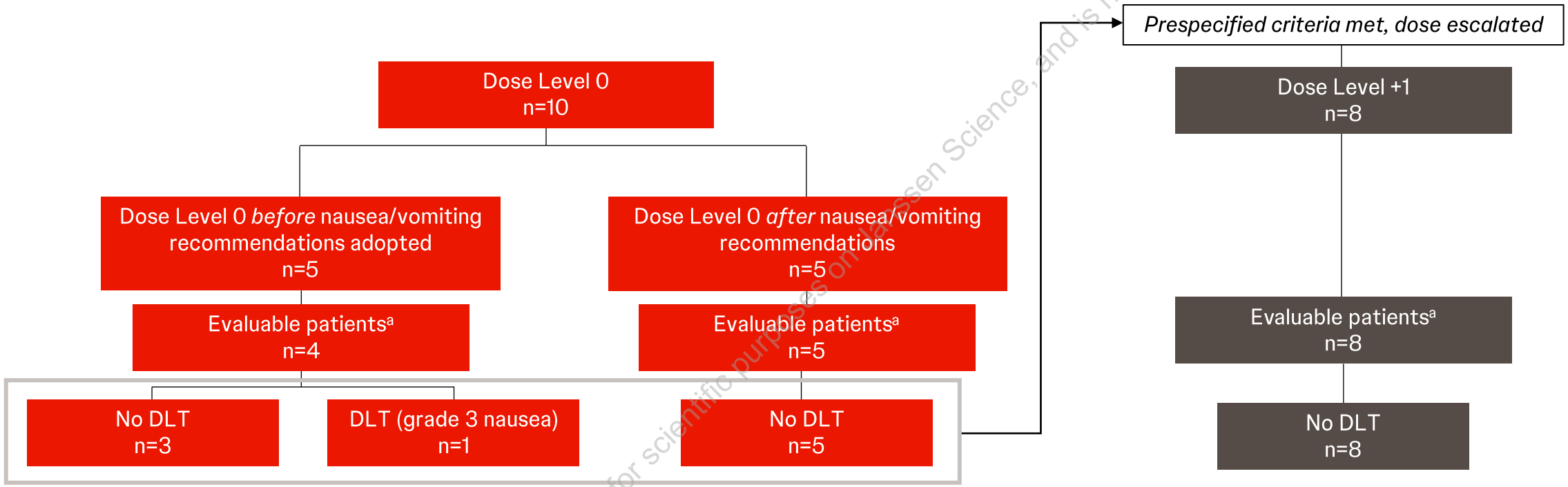
Table 1: Demographic and baseline characteristics

Characteristic	Dose Level 0 (n=10)	Dose Level +1 (n=8)
Median age, (range) years	62 (36–68)	59 (48–65)
Female, n (%)	8 (80)	5 (63)
Body weight <80 kg, n (%)	10 (100)	6 (75)
Race, n (%)		
Asian	7 (70)	4 (50)
White	2 (20)	4 (50)
Not reported	1 (10)	0
ECOG PS, n (%)		
0	2 (20)	1 (13)
1	8 (80)	7 (88)
Median no. of prior systemic therapies (range)	3 (1–5)	3 (1–5)
Baseline brain metastases, n (%)	4 (40)	4 (50)
Mutation type, n[a]		
EGFR Ex19del	4	2
L858R	2	4
MET Ex14	2	2
MET amp	1	2
EGFR Ex20ins	1	0
KRAS G12V[b]	1	0

[a]The number of patients tested for each individual mutation at baseline varied based on availability of appropriate samples; patients could have had more than 1 mutation type. [b]*KRAS* mutations were detected by central laboratory testing.

amp, amplification; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex14, Exon 14; Ex19del, Exon 19 deletion; Ex20ins, Exon 20 insertion; MET, mesenchymal epithelial transition; KRAS, Kirsten rat sarcoma viral gene homolog.

Figure 3: Dose-limiting Toxicities



[a]Evaluable patients were patients with ≥28 days of follow-up in the study; in Cycle 1, these patients either received ≥75% of the planned doses of both amivantamab and capmatinib or received <75% of the planned doses due to toxicity (dose reduction, dose interruption, dose delay, or treatment discontinuation due to an AE in Cycle 1).

AE, adverse event; DLT, dose-limiting toxicity.

Results: Safety Profile

Table 2: Safety profile

TEAEs by preferred term, n (%)	Dose Level 0 (n=10)		Dose Level +1 (n=8)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition (≥20%), n (%)				
Paronychia	4 (40)	0	3 (38)	0
Rash[a]	4 (40)	0	4 (50)	0
Stomatitis	2 (20)	0	0	0
Pruritus	2 (20)	0	0	0
Associated with MET inhibition (≥20%), n (%)				
Hypoalbuminemia	5 (50)	2 (20)	4 (50)	0
Generalized edema	2 (20)	1 (10)	0	0
Peripheral edema	2 (20)	0	3 (38)	0
Other (≥30%), n (%)				
Nausea	5 (50)	1 (10)	3 (38)	0
Infusion-related reaction	5 (50)	0	3 (38)	0
Fatigue	4 (40)	0	2 (25)	0
Anemia	4 (40)	2 (20)	1 (13)	1 (13)
Vomiting	4 (40)	0	1 (13)	0
Decreased appetite	4 (40)	0	0	0
Constipation	3 (30)	0	1 (13)	0

- The most common TEAEs were EGFR- and MET-related, and primarily grade 1 to 2 (**Table 2**)
  - Amivantamab + capmatinib does not appear to be associated with synergistic toxicity[1,2]
- Treatment-related grade ≥3 AEs occurred in 4 (40%) patients at Dose Level 0 (2 of which were serious AEs) and none at Dose Level +1
- No patient experienced pneumonitis/ILD
- Among the 8 treatment discontinuations, 6 were due to progressive disease and none were due to treatment-related AEs
- One death occurred in the Dose Level +1 group (unrelated to treatment)

1. Johnson & Johnson. RYBREVANT® (amivantamab-vmjw). Accessed March 21, 2024. https://www.rybrevant.com. 2. Novartis. TABRECTA® (capmatinib) tablets, for oral use [prescribing information]. Accessed May 10, 2024. https://www.novartis.com/us-en/sites/novartis_us/files/tabrecta.pdf.

[a]Preferred term shown in table; 6 (60%) and 6 (75%) patients in Dose Level 0 and Dose Level +1 groups, respectively, reported grouped term rash (includes acne, dermatitis, dermatitis acneiform, erythema, folliculitis, rash, and rash maculopapular), with none being grade ≥3.

AE, adverse event; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; MET, mesenchymal epithelial transition; TEAE, treatment-emergent adverse event.

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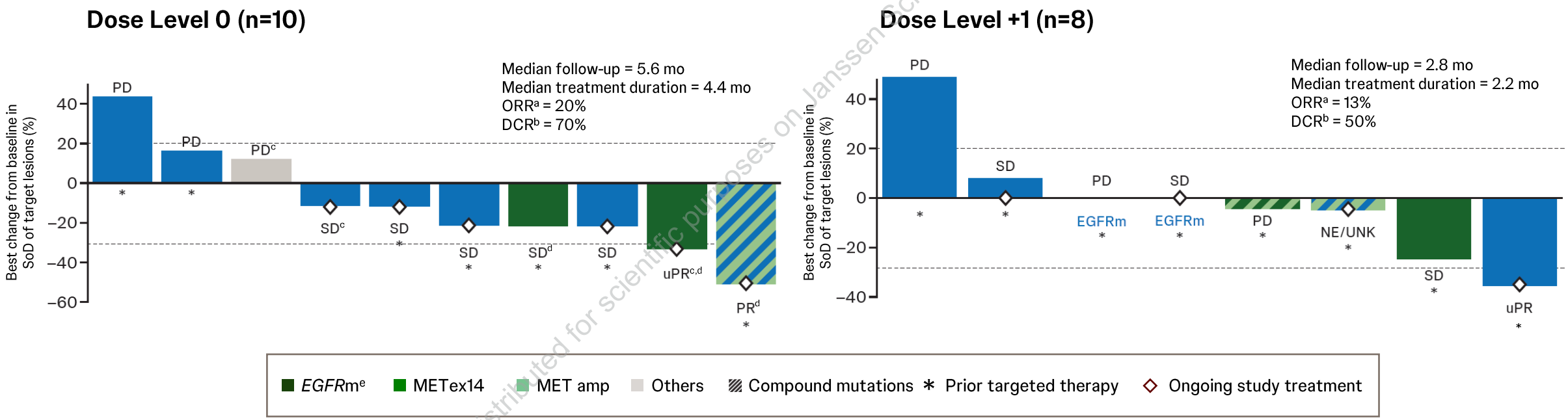
Results: Overall Response Rate

- Antitumor activity was seen in 2 patients with NSCLC with METex14, 1 patient with NSCLC with *MET* amplification, and 3 patients with *EGFR*-mutated NSCLC post-osimertinib (**Figure 4**)

Figure 4: Best percentage change from baseline in SoD of target lesions per investigator



[a]Including confirmed and unconfirmed CR and PR. [b]Defined as achieving confirmed or unconfirmed CR, PR, or SD duration of ≥6 weeks during the study. [c]Received prior checkpoint inhibitor and/or chemotherapy. [d]MET inhibitor-naive. [e]*EGFR*m includes Exon 19 deletion, Exon 20 insertion, or Exon 21 L858R.

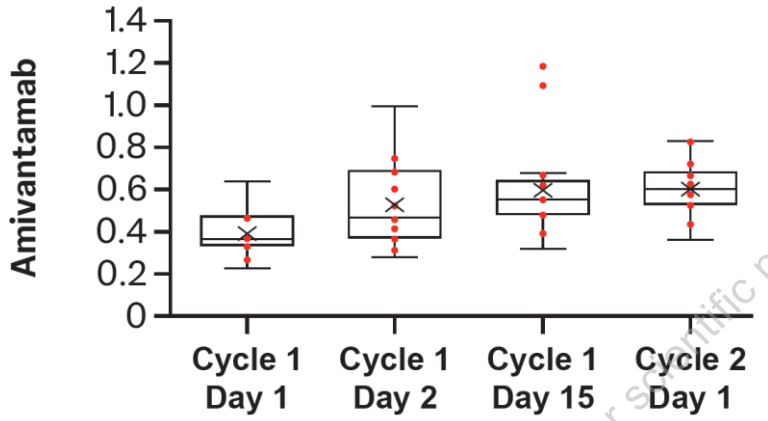
amp, amplification; CR, complete response; DCR, disease control rate; EGFR, epidermal growth factor receptor; *EGFR*m, epidermal growth factor receptor-mutated; MET, mesenchymal epithelial transition; METex14, MET Exon 14 skipping mutation; NE, not estimable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters; UNK, unknown; uPR, unconfirmed partial response.

Results: Pharmacokinetics

- Preliminary pharmacokinetic data suggest similar exposure for amivantamab versus historical amivantamab monotherapy data from CHRYSALIS (**Figure 5**)

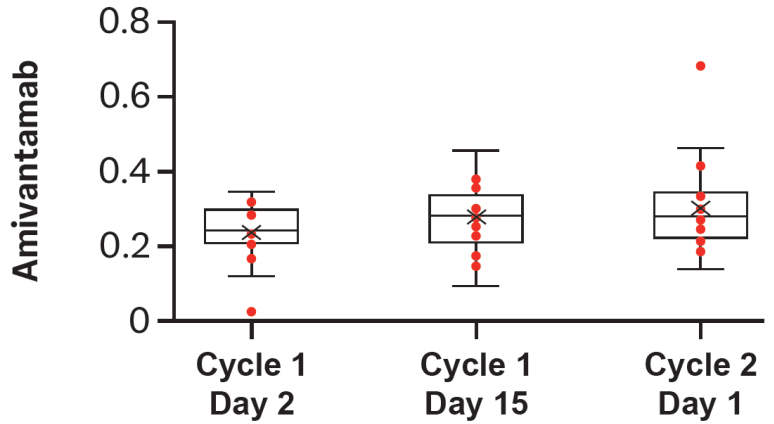
Figure 5: Pharmacokinetics of amivantamab and capmatinib

A. Dose-normalized amivantamab C_{max} (µg/mL/mg)



		Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day 15	Cycle 2 Day 1
METalmark	Mean	0.389			0.612
	SD	0.099			0.121
	N	17			17
CHRYSALIS (historical RP2D)	Mean	0.337			0.719
	SD	0.094			0.263
	N	32			34

B. Dose-normalized amivantamab C_{trough} (µg/mL/mg)



		Cycle 1 Day 2	Cycle 1 Day 15	Cycle 2 Day 1
METalmark	Mean	0.276		0.304
	SD	0.090		0.124
	N	17		17
CHRYSALIS (historical RP2D)	Mean	0.195		0.303
	SD	0.071		0.104
	N	228		209

C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; RP2D, recommended phase 2 dose; SD, standard deviation.

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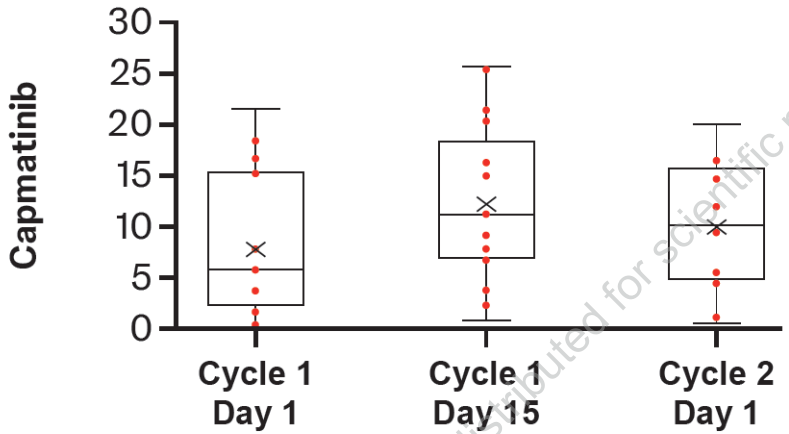
Results: Pharmacokinetics (continued)

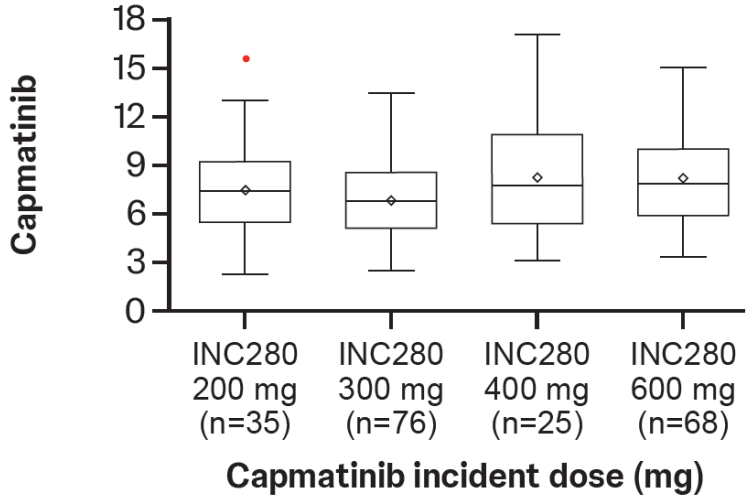
- Pharmacokinetic data for capmatinib (n=17) suggested similar exposure for capmatinib versus historical data[1]
  - Data should be interpreted with caution due to a high degree of variability associated with missed doses of capmatinib

Figure 5 (continued): Pharmacokinetics of amivantamab and capmatinib

C. Dose-normalized capmatinib C_{max} (ng/mL/mg)



D. Dose-normalized capmatinib C_{max} (ng/mL/mg) by dose levels[1]



C_{max}, maximum plasma concentration.

1. US Food and Drug Administration. NDA/BLA multi-disciplinary review and evaluation (NDA 213591). Accessed May 10, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213591Orig1s000MultidisciplineR.pdf.

Conclusions

- The Dose Level +1 combination was selected as the RP2CD (amivantamab 1050 mg [1400 mg if body weight ≥80 kg] + capmatinib 400 mg)
- No new significant safety findings were observed for either dose level, with no DLTs at the RP2CD
  - No events of pneumonitis/ILD, increased amylase/lipase levels, or progressive hypoalbuminemia were reported
- At a median follow-up of 3.3 months in this heterogeneous population with largely *EGFR*-mutated NSCLC without *MET* alterations, 8 patients had a best response of stable disease, 3 patients had confirmed or unconfirmed partial response, 1 patient was not evaluable, and 6 patients had progressive disease
- Preliminary pharmacokinetic data showed similar exposure for the combination compared to individual agents

DLT, dose-limiting toxicity; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; RP2CD, recommended phase 2 combination dose.

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Key Takeaways

- The RP2CD for amivantamab + capmatinib was identified as a combination of each agent at the approved dose
- The initial safety profile of amivantamab + capmatinib (at both dose levels) does not appear to have synergistic toxicities
- Amivantamab + capmatinib showed early antitumor activity in a heterogenous population with advanced NSCLC; expansion cohorts will evaluate amivantamab + capmatinib in *MET*-driven NSCLC

MET, mesenchymal epithelial transition; NSCLC, non-small cell lung cancer; RP2CD, recommended phase 2 combination dose.

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Disclosures

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