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Preventing Infusion-related Reactions with Intravenous Amivantamab: Updated Results From SKIPPirr, a Phase 2 Study

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Background

- Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity[1–4]
- IV amivantamab is now FDA-approved in combination with lazertinib for the first-line treatment of NSCLC with common *EGFR* mutations, is EMA-approved with chemotherapy for second-line treatment of disease with common *EGFR* mutations after progression on osimertinib, and is FDA- and EMA-approved with chemotherapy for first-line treatment of NSCLC with *EGFR* exon 20 insertion mutations[4,5]
- Like many other IV therapies, IV amivantamab is associated with an increased rate of IRRs[6]
  - Approaches to manage IV amivantamab IRRs in other clinical trials included a split first dose over 2 days and premedication with antihistamines, antipyretics, and glucocorticoids
- In the phase 2 SKIPPirr (ClinicalTrials.gov Identifier: NCT05663866) study, additional prophylactic strategies to reduce the incidence and severity of IRRs with IV amivantamab were evaluated[7]

Here we present secondary endpoints and additional safety data from SKIPPirr

1L, first-line; 2L, second-line; BID, twice daily; EGFR, epidermal growth factor; Ex20ins, exon 20 insertions; IRR, infusion-related reaction; IV, intravenous; NSCLC, non-small cell lung cancer.

1. Moores SL, et al. *Cancer Res*. 2016;76(13):3942–3953. 2. Vijayaraghavan S, et al. *Mol Cancer Ther*. 2020;19(10):2044–2056. 3. Yun J, et al. *Cancer Discov*. 2020;10(8):1194–1209. 4. RYBREVANT® (amivantamab-vmjw) injection for intravenous use [package insert]. Janssen Biotech, Inc.; 2024. 5. European Commission approves RYBREVANT® (amivantamab) in combination with chemotherapy for the treatment of adult patients with advanced EGFR-mutated non-small cell lung cancer after failure of prior therapy. News release. Johnson & Johnson. August 27, 2024. 6. Park K, et al. *Lung Cancer*. 2023;178:166–171. 7. Lopes G, et al. Presented at: World Conference on Lung Cancer (WCLC); September 7–10, 2024; San Diego, CA, USA.

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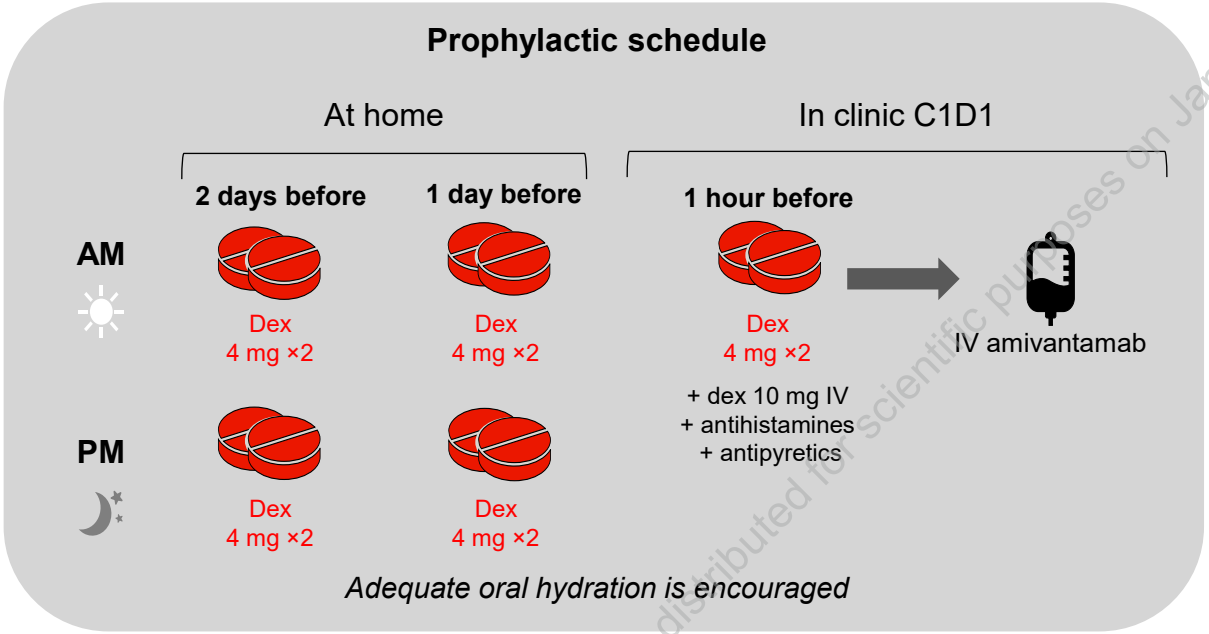
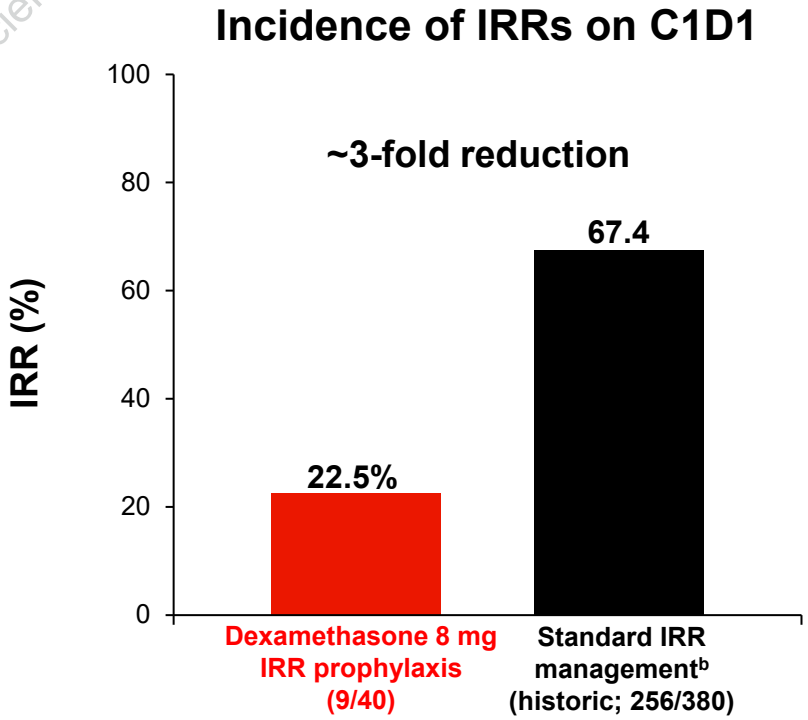
Background: Primary results from SKIPPirr[1]

- Prophylaxis with oral dexamethasone 8 mg BID for 2 days before infusion and another dose 1 hour before infusion (5 total doses) led to a ~3-fold reduction in IRRs from IV amivantamab (**Figure 1**)[1]





Clinical cutoff: C1D2. [a]Includes standard premedications (antihistamines, antipyretics, and glucocorticoids).

BID, twice daily; C, Cycle; D, Day; dex, dexamethasone; IRR, infusion-related reaction; IV, intravenous.

1. Lopes G, et al. Presented at the World Conference on Lung Cancer (WCLC); September 7-10, 2024; San Diego, CA, USA.

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Methods

- SKIPPirr is a phase 2 study that evaluated prophylactic strategies to reduce the incidence and severity of IRRs with IV amivantamab
- The study enrolled patients with *EGFR* Ex19del or L858R-mutated advanced or metastatic NSCLC whose disease progressed on prior osimertinib and platinum-based chemotherapy
- All patients received IV amivantamab 1050 mg (1400 mg if ≥80 kg) once weekly for 4 weeks and then every 2 weeks thereafter, and oral lazertinib 240 mg QD
- All patients also received standard IRR management with antihistamines, antipyretics, and IV dexamethasone 10 mg
- A Simon's 2-stage design with an expansion stage was used to evaluate 4 independent prophylactic strategies

EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; IRR, infusion-related reaction; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; QD, once daily.

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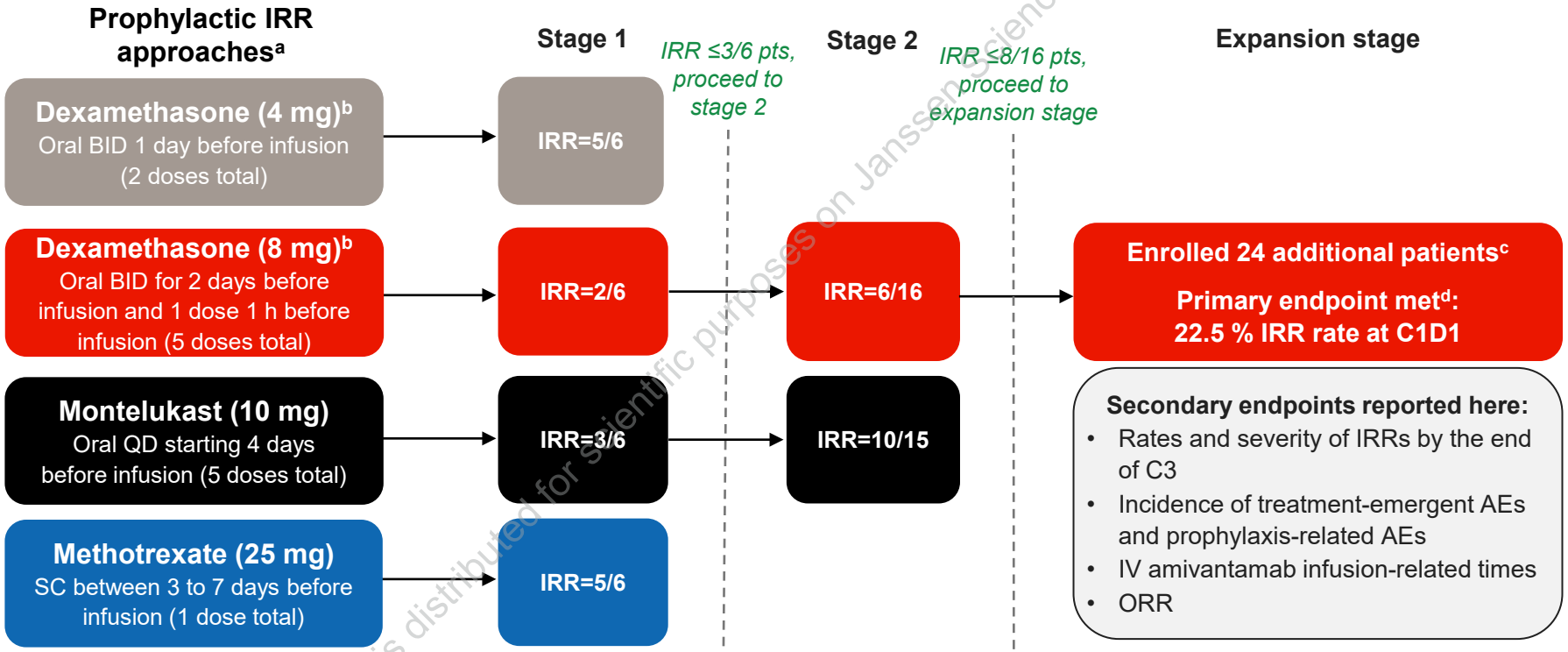
Methods: SKIPPirr study design

- Only the dexamethasone 8 mg cohort passed stages 1 and 2 (2/6 and 6/16 pts with IRRs, respectively), enrolling an additional 24 patients (**Figure 2**)



Clinical cutoff: 24 June 2024. [a]Patients were sequentially enrolled into prophylactic regimens, with the dexamethasone 8 mg cohort enrolling last. Patients in all cohorts also received standard premedication with antihistamines, antipyretics, and glucocorticoids. [b]If both cohorts had positive results, only 1 cohort moved on to stage 2, as determined by the SET. [c]1 patient did not receive amivantamab infusion as scheduled on C1D1 per protocol and was excluded from the primary endpoint analysis. [d]Defined as IRR events with onset within 24 hours of the start of the C1D1 amivantamab infusion and prior to the start of the C1D2 infusion.

AE, adverse event; BID, twice daily; C, Cycle; D, Day; IRR, infusion-related reaction; IV, intravenous; ORR, objective response rate; pt, patient; QD, once daily; SC, subcutaneous; SET, study evaluation team.

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Results: Demographic and baseline characteristics

- Demographic and baseline characteristics were well balanced between the dexamethasone 8 mg cohort and the overall population (**Table 1**)

Characteristics	Dexamethasone 8 mg (n=41)	All Cohorts (N=68)
Median age (range), years	62 (32–82)	63.5 (32–82)
Female, n (%)	26 (63)	44 (65)
Race, n (%)		
Asian	24 (59)	42 (62)
White	10 (24)	18 (26)
Black or African American	1 (2)	1 (1)
Not reported	6 (15)	7 (10)
ECOG PS score of 1, n (%)	32 (78)	51 (75)
Brain metastases, n (%)	15 (37)	30 (44)
EGFR mutation type, n (%)		
Exon 19 deletion	29 (71)	45 (66)
Exon 21 L858R	12 (29)	23 (34)
Median prior lines of therapy (range)	3 (2–9)	3 (2–9)

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.

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Results: IRRs through the end of Cycle 3

- In the dexamethasone 8 mg cohort, 10/41 (24%) patients experienced IRRs
  - 9 patients had IRRs on C1D1 (with 1 also on C1D2); 1 patient had an IRR on C2D1
  - All IRRs up to C3 were grades 1–2, except for one grade 3 IRR on C2D1

C, Cycle; D, Day; IRR, infusion-related reaction.

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Results: Safety

- Aside from the significantly reduced rate of IRRs, the safety profile of IV amivantamab + lazertinib was consistent with previous reports, with no new safety signals identified (**Table 2**)
- Common AEs associated with steroids (eg, fractures, Cushingoid features, and hyperglycemia)[1] were not observed in the dexamethasone 8 mg cohort
- Prophylaxis-related AEs occurred in 3 (7%) patients receiving dexamethasone 8 mg (1 event each of gastroesophageal reflux disease, muscle atrophy, and somnolence) and were all grades 1–2

Most common treatment-emergent AEs (≥15%), n (%)	Dexamethasone 8 mg (n=41)		All cohorts (N=68)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Associated with EGFR inhibition				
Rash	17 (41)	0	30 (44)	4 (6)
Paronychia	16 (39)	0	30 (44)	0
Stomatitis	14 (34)	1 (2)	20 (29)	1 (1)
Pruritis	5 (12)	0	14 (21)	1 (1)
Dermatitis acneiform	7 (17)	0	12 (18)	0
Diarrhea	7 (17)	1 (2)	12 (18)	1 (1)
Associated with MET inhibition				
Hypoalbuminemia	17 (41)	0	24 (35)	1 (1)
Peripheral edema	9 (22)	0	14 (21)	0
Other				
IRR	10 (24)	1 (2)	31 (46)	2 (3)
Nausea	10 (24)	1 (2)	22 (32)	2 (3)
Epistaxis	9 (22)	0	13 (19)	0
Dyspnea	8 (20)	1 (2)	11 (16)	2 (3)
Hypoesthesia	8 (20)	0	14 (21)	0
Headache	8 (20)	0	10 (15)	0
Constipation	8 (20)	0	12 (18)	0
Hypotension	8 (20)	2 (5)	9 (13)	2 (3)
Asthenia	7 (17)	2 (5)	12 (18)	3 (4)
Dry skin	6 (15)	0	10 (15)	1 (1)
Pain in extremity	5 (12)	0	10 (15)	0
Decreased appetite	4 (10)	0	11 (16)	2 (3)
Chills	0	0	10 (15)	0

AE, adverse event.

1. Hodgens A, et al. Corticosteroids. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; May 1, 2023.

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Results: Response by investigator

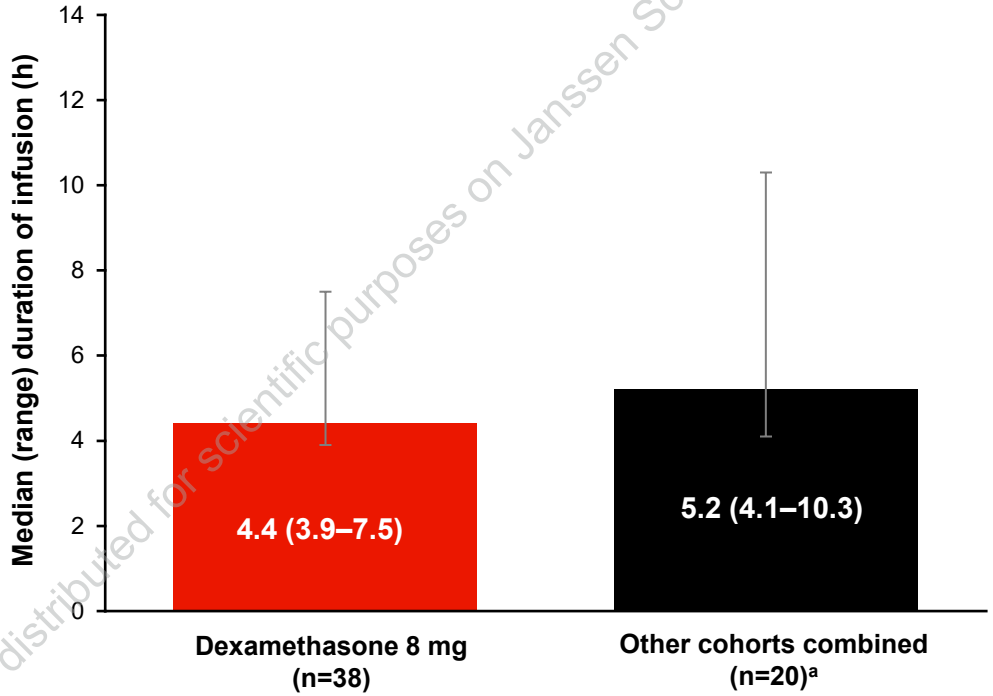
- Investigator-assessed ORR among all responders and confirmed responders in the dexamethasone 8 mg cohort was similar to historic IV amivantamab data from CHRYSALIS-2 Cohort A and PALOMA-3 (**Table 3**)[1–3]

Investigator-assessed response	SKIPPirr: dexamethasone 8 mg IRR prophylaxis (n=40)[a]	CHRYSALIS-2: Cohort A[1,3] (n=162)	PALOMA-3: IV arm[2] (n=212)
ORR, % (95% CI)			
All responders	33 (19–49)	33 (26–41)	33 (26–39)
Confirmed responders	28 (15–44)	28 (22–36)	27 (21–33)
Best response, n (%)[b]			
CR	0	1 (0.6)	1 (0.5)
PR	11 (28)	45 (28)	68 (32)
SD	16 (40)	79 (49)	81 (38)
Non-CR/non-PD	2 (5)	–	–
PD	10 (25)	34 (21)	42 (20)
NE/unknown	1 (3)	3 (2)	20 (9)
CBR, % (95% CI)	73 (56–85)[c]	58 (50–66)[c]	71 (64–77)[d]

[a]1 patient did not receive amivantamab infusion as scheduled on C1D1 per protocol and was excluded from this analysis. [b]Among confirmed responders, except for PALOMA-3, which shows all responders. [c]CBR is defined as the percentage of patients with CR, PR, SD, or non-CR/non-PD (SKIPPirr) or the percentage of patients with CR, PR, or durable SD (≥11 weeks; CHRYSALIS-2 Cohort A). [d]Not protocol-specified. Calculated as the sum of CR, PR, and SD; all responders were included.
C, cycle; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; D, day; IRR, infusion-related reaction; IV, intravenous; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. 1. Shu CA, et al. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 3–7, 2022; Chicago, IL, USA. 2. Leighl NB, et al. *J Clin Oncol*. Published online June 10, 2024. 3. Data on file.

Results: Duration of amivantamab infusion

- At C1D1, the median amivantamab infusion time was numerically shorter for the dexamethasone 8 mg cohort versus the other cohorts combined (4.4 h vs 5.2 h; **Figure 3**)
- By C1D15 and onward, the median duration of amivantamab infusion was approximately 2.3 h for all cohorts, which was consistent with the low IRR incidence after C1D1 and increased infusion rate over time



Note: Duration of infusion includes both actual infusion time and interruption time, if any. Patients who aborted infusions due to AEs and those with an infusion end time recorded incorrectly were excluded. [a]Includes the dexamethasone 4 mg, montelukast, and methotrexate cohorts.
AE, adverse event; C, cycle; D, day.

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Results: Time and motion on C1D1

- On C1D1, patients receiving dexamethasone 8 mg spent a numerically shorter amount of time in the treatment room and infusion chair and required a numerically shorter amount of active HCP time vs the other cohorts combined (**Figure 4**)

Note: Patients who aborted infusions due to AEs and those who inadvertently excluded the line flush time from their infusion calculation were excluded. [a]Includes the dexamethasone 4 mg, montelukast, and methotrexate cohorts.

AE, adverse event; C, Cycle; D, Day; HCP, health care provider.

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Conclusions

- Prophylactic treatment with oral dexamethasone 8 mg BID resulted in reduced IRRs with IV amivantamab on C1D1 compared with historical data
  - Most IRRs occurred on C1D1, and the majority were grade 1–2
- No new safety signals were observed with the addition of dexamethasone 8 mg BID
  - Patients experienced low rates of prophylaxis-related AEs (7%)
- Prophylaxis with dexamethasone 8 mg BID led to a similar treatment response compared with historical IV data[1,2]
- The duration of amivantamab infusion was numerically shorter with the dexamethasone 8 mg cohort compared with other cohorts, and patients also had a numerically shorter treatment room, chair, and active HCP time

AE, adverse event; BID, twice daily; C, cycle; D, day; HCP, health care provider; IRR, infusion-related reaction; IV, intravenous; PO, by mouth.

1. Shu CA, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 3–7, 2022; Chicago, IL, USA. 2. Leighl NB, et al. *J Clin Oncol*. Published online June 10, 2024. doi:10.1200/JCO.24.01001.

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Key takeaway

Prophylaxis with oral dexamethasone 8 mg BID effectively reduces IV amivantamab-related IRRs, with a similar safety profile and no additional safety findings compared with historical IV data

IRR, infusion-related reaction; IV, intravenous.

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Also at ESMO 2024

MARIPOSA-2

Second interim overall survival for amivantamab + chemotherapy vs chemotherapy in *EGFR*-mutated NSCLC

Saturday, Sep 14 9:10-9:20am
(LBA54; Popat)

MARIPOSA

Mechanisms of acquired resistance to first-line amivantamab + lazertinib in *EGFR*-mutant advanced NSCLC

Saturday, Sep 14 9:20-9:30am
(LBA55; Besse)

ORIGAMI-1

Amivantamab + FOLFOX/FOLFIRI in metastatic colorectal cancer

Saturday, Sep 14 3:45-3:50pm
(513MO; Pietrantonio)

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