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Acquired Resistance Mechanism in Cancer Cells Derived from an Amivantamab-Resistant EGFR exon 20 Insertion Mutation-Positive NSCLC Patient.

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INTRODUCTION

EGFR exon 20 insertion-positive NSCLC has limited sensitivity to conventional EGFR TKIs, representing an unmet clinical need (1,2).

Amivantamab, a bispecific antibody targeting EGFR and MET, has demonstrated clinical benefit in these patients (3). However, acquired resistance to amivantamab remains a major clinical challenge, and its mechanisms are not fully understood.

Amivantamab exerts antitumor activity through both EGFR/MET signaling inhibition and Fc-mediated immune effector functions, including antibody-dependent cellular cytotoxicity (ADCC). Changes in EGFR/MET expression and tumor cell phenotype may therefore influence amivantamab sensitivity.

We investigated potential mechanisms of acquired amivantamab resistance using the patient-derived resistant cell line KRM-1.

METHODS

Patient-derived resistant model

KRM-1 was established from a patient with EGFR exon 20 insertion-positive NSCLC who developed acquired resistance following fifth-line amivantamab treatment.

EGFR/MET expression

EGFR and MET expression was evaluated in paired patient tumor samples (pre-treatment and post-resistance) by IHC, and in KRM-1 and reference NSCLC cell lines by western blotting and flow cytometry.

ADCC assay

Amivantamab-mediated ADCC activity was evaluated using human PBMC cells as effector cells.

EGFR/MET transfection

Wild-type EGFR and/or MET was transfected into KRM-1 cells using Lipofectamine, followed by evaluation of amivantamab-mediated ADCC.

In vivo study

KRM-1 cells were implanted subcutaneously into mice, followed by amivantamab treatment to evaluate tumor response.

EMT analysis

Expression of E-cadherin, ZEB1, and Vimentin was evaluated by western blotting.

RESULTS

Patient background

Diagnosis

47♂, LUAD Stage 4, TTF-1 + (2018-July)

EGFR exon 20ins (EGFR mutational analysis v2.0, SRL, detail unknown)

Smoking

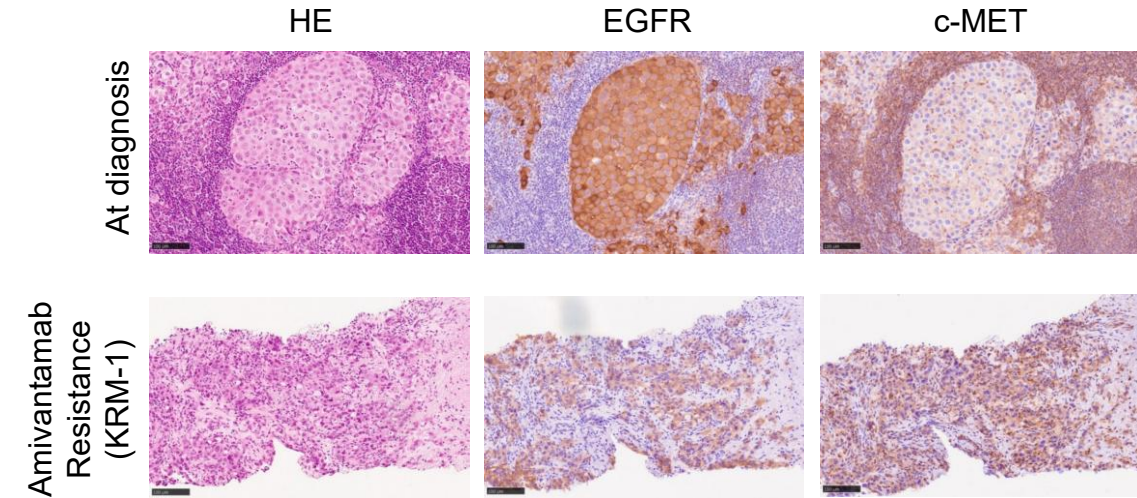
20 × 27 years (Brinkman Index 540)

Treatment

	Best response
① CDDP+PEM (Cisplatin/Pemetrexed×4 ⇒ Pemetrexed ×1)	: PR
② Osimertinib (10 days, discontinuation due to grade 3 AST/ALT elevation)	: NE
③ DTX (Docetaxel×8)	: PR
④ CBDCA+S-1 (Carboplatin/S-1×4)	: PD
⑤ Amivantamab (Phase I)	: PR

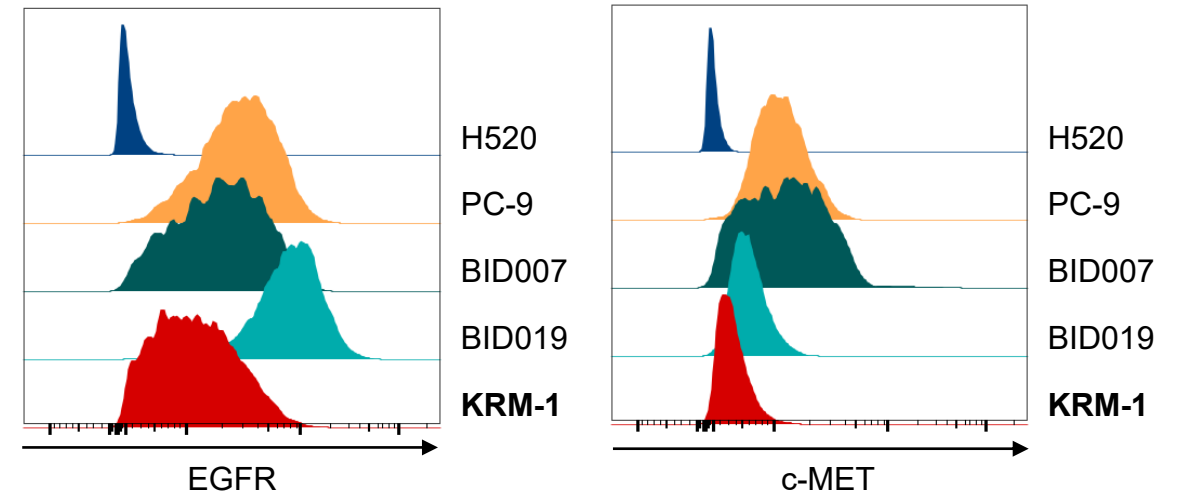
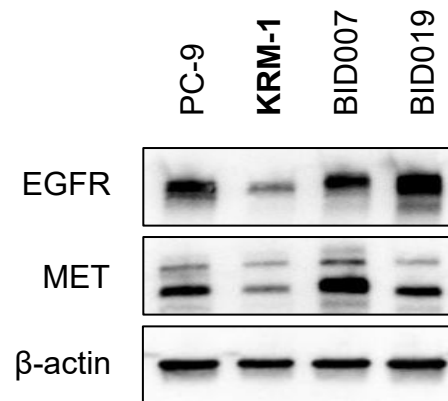
→ **KRM-1** cells were established after developing resistance to amivantamab.

IHC results of clinical samples showed a significant decrease in EGFR expression after the development of amivantamab resistance compared to the time of diagnosis



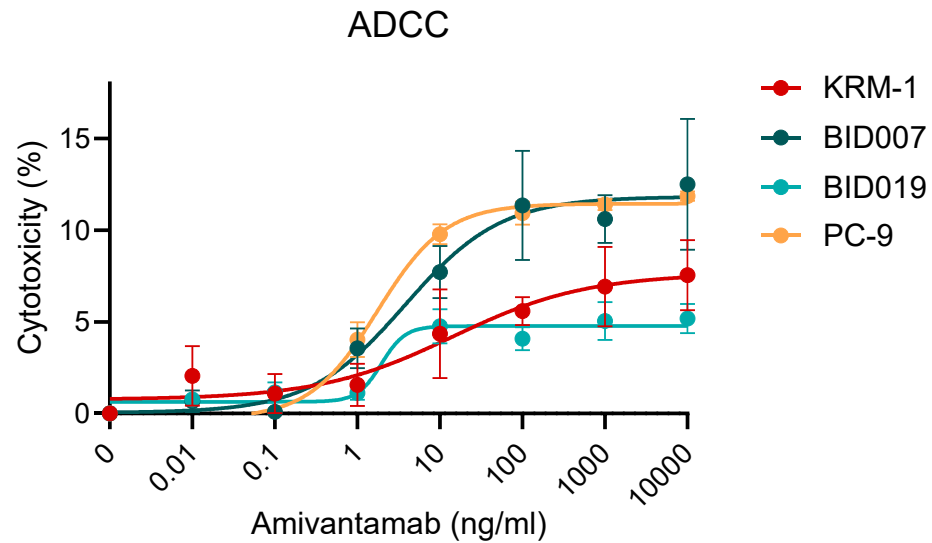
KRM-1 cells showed reduced EGFR and MET expression compared with other EGFR exon 20ins cell lines.

-Cell lines-
PC-9:EGFR exon 19del
KRM-1:EGFR exon 20ins
(Amivantamab resistance)
BID007:EGFR-A763_Y764insFQEA
BID019:EGFR-N771_H772insH

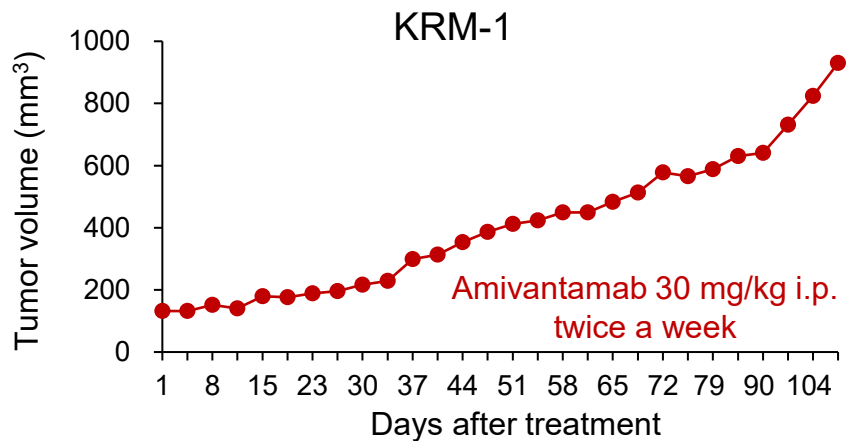


RESULTS

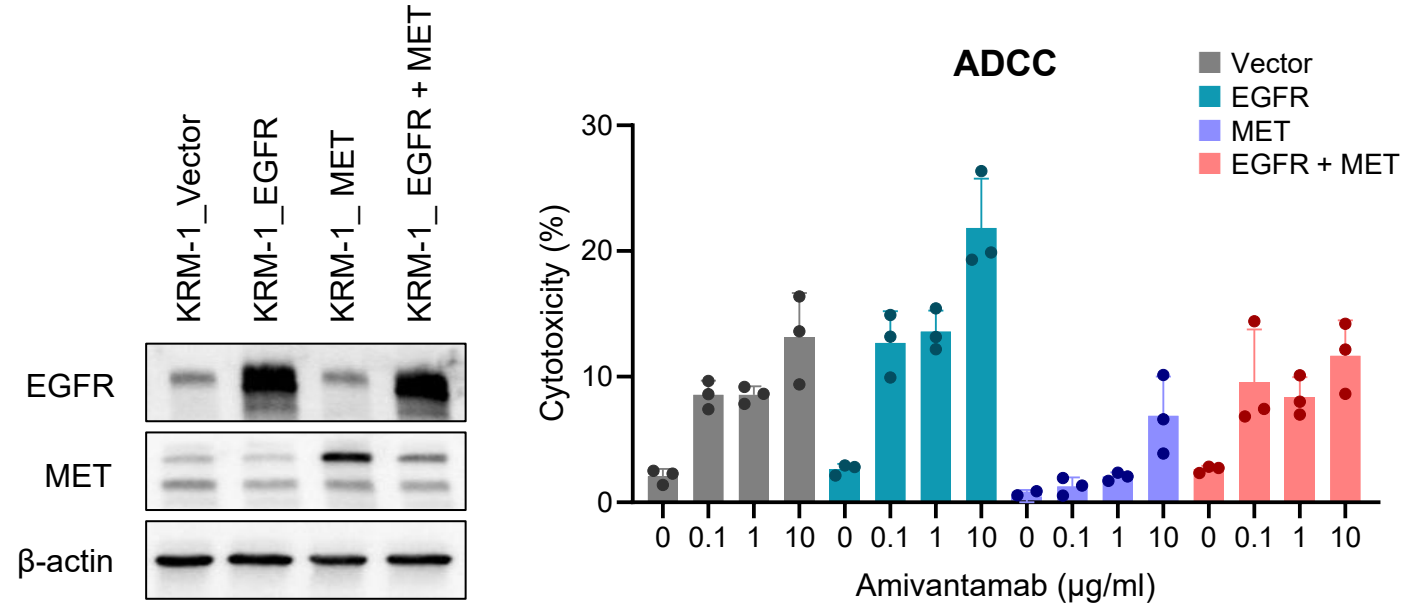
ADCC was assessed 4 h after drug treatment in PBMC-target cell co-cultures.



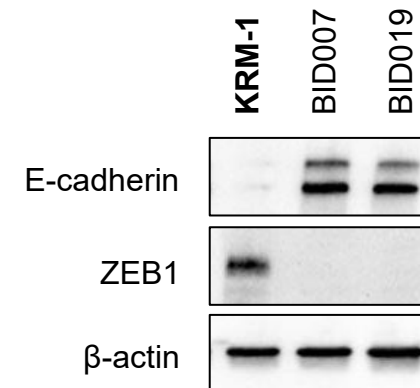
KRM-1 cells showed resistance to amivantamab in a mouse xenograft model.



EGFR/MET transfection revealed a trend toward increased amivantamab-mediated ADCC activity in KRM-1 cells, particularly with EGFR expression.



KRM-1 cells showed reduced E-cadherin and increased ZEB1 expression, indicating an EMT-associated phenotype.



DISCUSSION AND CONCLUSION

DISCUSSION AND CONCLUSION

Our previous study demonstrated that MET enhances amivantamab binding to EGFR and ADCC (4). In the present study, EGFR expression was markedly reduced after acquisition of amivantamab resistance in the patient tumor, and KRM-1 cells showed relatively low EGFR/MET expression and reduced ADCC activity.

Importantly, EGFR transfection tended to increase ADCC activity in KRM-1 cells, supporting a potential role of EGFR downregulation in impaired amivantamab-mediated ADCC. KRM-1 also showed limited response to amivantamab *in vivo* and exhibited an EMT-associated phenotype.

These findings suggest that EGFR downregulation may contribute to acquired amivantamab resistance through impaired ADCC. KRM-1 provides a clinically relevant model for further investigation of resistance mechanisms and therapeutic strategies.

ACTIONABLE TAKE-HOME MESSAGE

EGFR downregulation may impair amivantamab-mediated ADCC and contribute to acquired resistance.

FUTURE DIRECTION FOR RESEARCH

Further studies are needed to determine whether restoring EGFR/MET expression or targeting EMT-associated phenotypes can enhance amivantamab-mediated ADCC and overcome resistance.

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ChatGPT (OpenAI) was used as a supportive tool for English language editing, organization of poster content, and presentation structure. All scientific data, interpretations, and conclusions were reviewed and verified by the authors.