Case Report

# MYC amplification-conferred primary resistance to capmatinib in a *MET*-amplified NSCLC patient: a case report

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**Background:** Capmatinib, a potent and selective mesenchymalepithelial transition factor (MET) inhibitor, is an effective treatment option for non-small cell lung cancer (NSCLC) patients with *MET* exon 14 skipping mutations or gene amplification. However, the mechanisms that confer resistance to capmatinib remain elusive. Here, we present a case of primary resistance to capmatinib in a *MET*-amplified NSCLC patient which was conferred by concurrent *MYC* amplification.

**Case Description:** Capmatinib was administered as first-line treatment in an 82-year-old *MET*-amplified [gene copy number (GCN) 13.5] and MET overexpressed (immunohistochemical staining 3+/3, >50%) NSCLC patient. However, the tumor rapidly progressed and showed primary resistance to capmatinib. Next-generation target sequencing using rebiopsy tumor samples revealed *MYC* amplification. We also performed functional drug susceptibility testing using patient-derived cells (PDCs), which showed overexpression of *MYC* mRNA and resistance to capmatinib. Meanwhile, ICX-101, an investigational MYC inhibitor, successfully inhibited the growth of PDCs at a relatively low IC50 value. Also, a synergistic effect was shown when capmatinib treatment was followed by ICX-101.

**Conclusions:** Concurrent *MYC* amplification could potentially confer primary resistance to capmatinib in highly *MET* amplified NSCLC patients. Further clinical studies are warranted to corroborate these findings, and treatment with MYC inhibitors could be suggested as an alternative therapeutic strategy for this subset of patients.

**Keywords:** Capmatinib; mesenchymal-epithelial transition factor (MET); MYC; lung cancer; case report

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## Introduction

The treatment of advanced non-small cell lung cancer (NSCLC) has been revolutionized by selectively targeted agents that match driver oncogenic alteration. Genetic alterations that lead to dysregulation of the mesenchymal-epithelial transition factor (MET) have been identified as primary oncogenic drivers in NSCLC, therefore MET regulation presents a promising therapeutic target for advanced NSCLC (1-3). Recently, capmatinib, a potent and selective MET inhibitor, has been reported to elicit good responses in NSCLC with *MET* exon 14 skipping mutation (*MET*ex14), or *MET* amplification defined by a gene copy number (GCN) of 10 or higher (1,3). The responses were generally higher when capmatinib was administered as the first-line therapy, with an overall response rate of 68% for *MET*ex14 and 40% for *MET* GCN ≥10 (1). Based on these data, capmatinib was granted accelerated approval by the Food and Drug Administration (FDA) for NSCLC with *MET*ex14 (4). Despite these promising results, there exists a lack of knowledge, especially in terms of the molecular

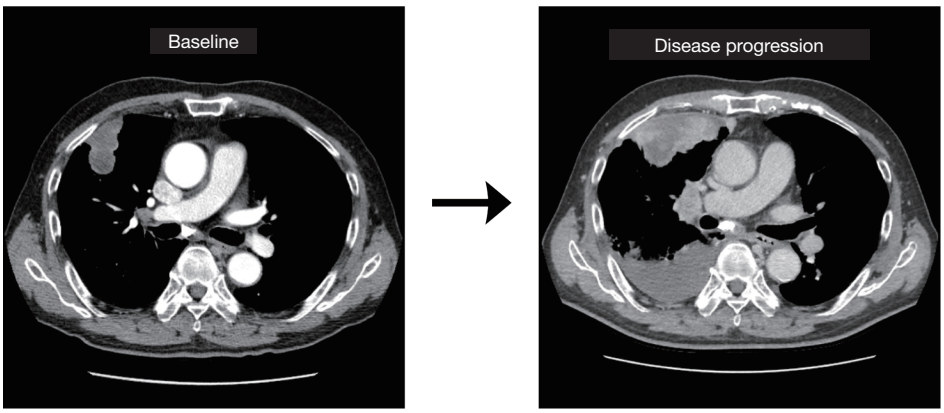


**Figure 1** Representative CT images at baseline and disease progression in response to capmatinib.

mechanisms that cause primary resistance to MET inhibitors. Here, we report a case of metastatic NSCLC with *MET* amplification (GCN ≥10) who showed primary resistance to the first-line use of capmatinib, and refractory to subsequent chemotherapies. Targeted sequencing of the re-biopsied tumor tissue revealed *MYC* amplification, and patient-derived tumor cells were successfully inhibited with a MYC inhibitor in vitro. These results suggest that MYC amplification could be a potential mechanism for resistance to MET inhibition in NSCLC. We present the following case in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-176/rc).

## Case presentation

An 82-year-old male patient was referred to our institute with a right upper lobe (RUL) lung nodule. He had a smoking history of 60 pack-years, and presented with underlying hypertension, diabetes, and rheumatoid arthritis. Initial staging evaluation with chest computed tomography (CT) revealed an RUL mass which was confirmed as adenocarcinoma with percutaneous biopsy. Molecular analyses showed no epidermal growth factor receptor (EGFR) mutation, negative immunostaining results for ALK, but intense staining for MET (intensity 3+/3, and proportion of positive cells >50%). The clinical stage was T1bN0M0, and the patient was considered a candidate for surgical resection. Nevertheless, he was reluctant to undergo surgery due to the potentially high risks associated with old age and underlying medical conditions. Alternatively, radiation therapy was recommended, but he declined and decided to undergo surveillance. However, three months later, CT scans revealed enlargement of the RUL tumor and a new lesion in the liver.

As the initial tumor tissue was intensely stained for MET, he was screened for a phase 2 trial of capmatinib (GEOMETRY mono-1, NCT02414139) as first-line treatment. Real-time polymerase chain reaction (RT-PCR) analysis for *MET*ex14 was negative, but *MET* GCN as determined by fluorescence *in situ* hybridization (FISH) was 13.5 indicating gene amplification. In addition, immunohistochemistry revealed MET overexpression (3+/3, >50%). Thus, he was enrolled in the trial and received capmatinib (400 mg, twice daily) as the first-line therapy. However, his disease progressed during capmatinib treatment. At the first response evaluation, which was performed after the initial 6 weeks of treatment, CT scans showed systemic progression of the disease including new metastatic lesions (*Figure 1*). We performed fluorescent *in situ* hybridization (FISH) for *MET*, and an amplicon-based next-generation sequencing (NGS, Illumina), with a panel consisting of 91 genes using the re-biopsied tumor samples from the liver. The NGS analysis revealed gene amplification of *MYC* (estimated copy number 5) and *CEBPA* without other nucleotide variants or fusion mutations, as well as *MET* amplification on FISH.

Subsequently, he received paclitaxel and carboplatin as second-line therapy and irinotecan and cisplatin as third-line therapy, without tumor response to either regimen. Multiple brain metastases developed during third-line therapy, and the patient underwent stereotactic radiosurgery but eventually succumbed to death due to disease progression 6 months after the initial diagnosis of metastatic NSCLC.

Following capmatinib treatment, patient-derived cells

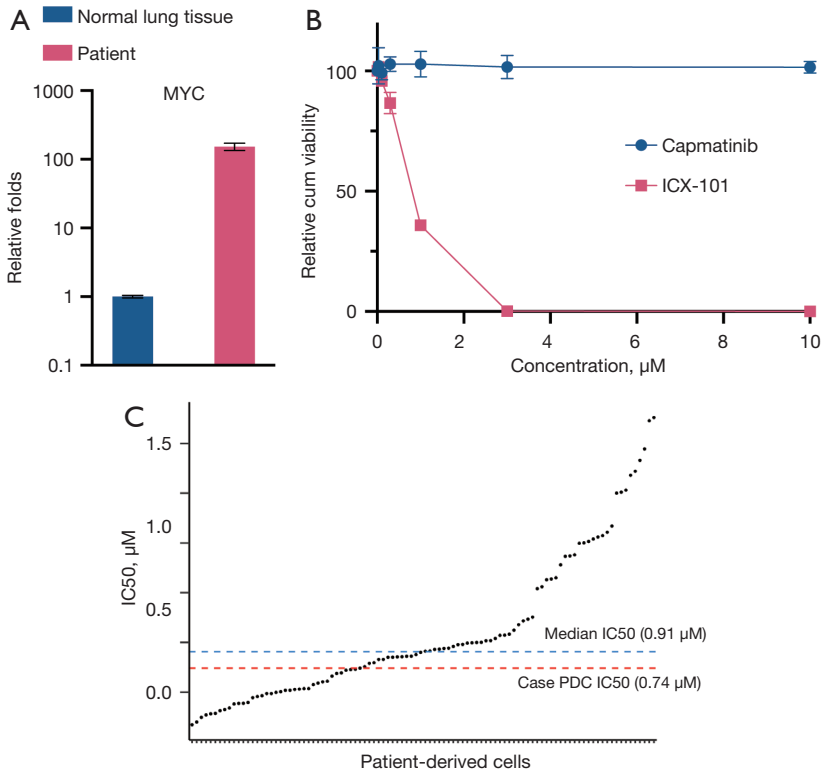


**Figure 2** Molecular analyses with patient-derived cells (PDCs). (A) Real-time quantitative polymerase chain reaction (RT-qPCR) results of *MYC* gene expression of the tumor from the case patient compared with normal lung tissue. (B) Drug sensitivity test of capmatinib and ICX-101 with PDCs from the case patient. (C) IC50 values of ICX-101 among PDCs of all non-small cell lung cancer(n=100).

(PDCs) were cultured *in vitro* to determine the resistance mechanisms and identify novel treatment strategies. We performed drug susceptibility tests for cytotoxic agents (gemcitabine, cisplatin, paclitaxel, and SN-38), targeted agents (crizotinib, dacomitinib, afatinib, and capmatinib), and investigational agents (OTX-015, BET bromodomain inhibitor; ICX-101, MYC inhibitor). In concordance with *MYC* amplification shown by NGS, PDCs showed marked overexpression of *MYC* mRNA (*Figure 2A*). In the drug susceptibility assay, the viability of PDCs was not suppressed with capmatinib with doses ranging from 0 - 10 μM, which reflected *in vivo* drug resistance. Notably, the response to ICX-101 (Incurix, Goyang, Korea), an investigational MYC inhibitor (Figures S1,S2), was surprisingly high with an IC50 value of 0.74 μM (*Figure 2B*). So far, we tested the sensitivity of ICX-101 using multiple NSCLC PDC samples developed in our institute (n=100) and the median IC50 value was 0.91 μM (interquartile range, 0.54–1.54 μM) for all NSCLC PDCs. These data suggest that the case reported here is sensitive to ICX-101, a MYC inhibitor (*Figure 2C*). In order to see if there is a synergistic effect between ICX-101 and capmatinib, we treated the PDCs of the case patient with both drugs either in combination or as sequential treatments. Co-treatment of ICX-101 and capmatinib was not synergistic, and ICX-101 followed by capmatinib showed only an additive antitumor effect (Figures S3,S4A). However, a synergistic effect was shown when capmatinib was treated with subsequent ICX-101 (Figure S4B). These clinical and *in vitro* data imply that the primary resistance to capmatinib in this patient even with *MET* amplification may be conferred by the concurrent *MYC* amplification, and a MYC inhibitor could be utilized to inhibit resistance to capmatinib.

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

**Table 1** Summary of genetic alterations that cause resistance to MET inhibitors

| Gene alteration | Method of detection | Reference |
|---|---|---|
| On-target mechanisms | | |
| *MET* mutation | | |
| H1094Y | NGS (Post-treatment, Tissue/Plasma) | (5) |
| L1195V | NGS (Post-treatment, Tissue/Plasma) | (5) |
| G1163R | NGS (Post-treatment, Tissue/Plasma) | (5) |
| D1228X (H/N/Y) | NGS (Post-treatment, Tissue/Plasma) | (5-7) |
| Y1230X (C/H/S) | NGS (Post-treatment, Tissue/Plasma) | (5,7) |
| *MET* amplification | NGS (Post-treatment, Tissue) | (5) |
| *HGF* amplification | NGS (Post-treatment, Tissue) | (6) |
| Off-target mechanisms | | |
| *KRAS* mutation | | |
| G12X(D/S) | NGS (Post-treatment, Tissue/Plasma) | (5,6) |
| G13V | NGS (Post-treatment, Plasma) | (6) |
| G60D | NGS (Post-treatment, Tissue/Plasma) | (5) |
| V14I | NGS (Post-treatment, Plasma) | (7) |
| *KRAS* amplification | NGS (Post-treatment, Tissue) | (5,6) |
| *EGFR* amplification | NGS (Post-treatment, Tissue) | (5,6) |
| *BRAF* mutation (V600E) | NGS (Post-treatment, Plasma) | (7) |
| *BRAF* amplification | NGS (Post-treatment, Tissue/Plasma) | (5,7) |
| *ERBB3* amplification | NGS (Post-treatment, Tissue/Plasma) | (5,7) |
| *PI3KCA* mutation | NGS (Pre-treatment) | (8) |
| PTEN Loss of expression | IHC (Pre-treatment) | (8) |

NGS, next generation sequencing; IHC, immunohistochemistry.

## Discussion

MET inhibitors have recently been demonstrated as promising novel therapeutic agents for NSCLC with MET aberrations (1,2). Although the clinical benefit of MET inhibitors in these tumors has been shown, questions remain regarding the molecular mechanisms that drive primary or acquired resistance. Studies that investigated the resistance mechanisms against various MET inhibitors in NSCLC with *METex14* have shown that alterations in mitogen-activated protein kinase (MAPK) pathway genes (*EGFR*, *KRAS*, *HER3*, and *BRAF*), *de novo* mutations of *MET*, and phosphoinositide-3 kinase (PI3K) signaling alterations were highly implicated (5-8) (*Table 1*). For *MET*-amplified lung cancer, a preclinical study demonstrated the importance of EGFR and PI3K signaling in conferring resistance to capmatinib in an NSCLC cell line (9). Notably, another preclinical study suggested the role of MYC as a downstream effector to dictate the therapeutic response of MET inhibitors, and also a driver that leads to both primary and acquired resistance in *MET*-amplified cancer cells (10). In this study, a lung cancer cell line with *MET* amplification showed high sensitivity to an investigational MET inhibitor. After generating acquired resistance to this drug, these cells still showed a similar level of *MET* amplification but an enhanced expression of MYC. They also demonstrated that overexpression of MYC in the parental cell line resulted in diminished drug sensitivity to the MET inhibitor. Together these results suggest that MYC confers both primary and acquired resistance to MET inhibitors, suggesting its role as

an essential mediator of therapy resistance (10).

MYC deregulation is a well-known oncogenic alteration that is pervasive in many solid tumors and has also been reported to cause resistance to many anti-cancer agents (11). In accordance with this notion, *MYC* amplification was suggested as a potential cause of primary resistance to crizotinib in a case of advanced NSCLC with ALK-rearrangement (12). However, the prevalence of MYC alteration in MET-driven lung cancer is largely unknown, and the clinical importance of MYC in conferring resistance to MET inhibitors has yet to be validated. Nevertheless, a report showed that concurrent *MYC* amplification is more common in tumors with *MET* amplification than in *MET*ex14, implying that MYC activation might be more important in *MET* amplified NSCLC (13).

The MYC family has three paralogs: C-MYC (encoded by *MYC*), N-MYC (encoded by *MYCN*), and L-MYC (encoded by *MYCL*). MYC is enhanced and deregulated in many types of malignancies, which is one of the most frequently deregulated driver genes in human cancer. However, despite its critical role, MYC has been traditionally regarded as an undruggable target because it lacks a preferred pocket to allow high-affinity binding by small molecule drugs (14).

ICX-101 (United States Patent US9951021B2) is an investigational MYC inhibitor developed by Incurix (Goyang, Korea). It is a potent and selective small molecule inhibitor that directly inhibits the binding of MYC/MAX dimers to the DNA binding sequence E-box (Supplementary Data). ICX-101 not only showed very high selectivity for the function of MYC in protein-based assays and cellular-level transcriptome analysis but was also shown to be particularly effective in KRAS mutant NSCLC and small cell lung cancer (SCLC) PDCs compared to other drugs evaluated in the aforementioned PDC screening. Indeed, daily oral administration of ICX-101 in KRAS-mutant NSCLC animal models was found to effectively inhibit cell growth, leading to tumor regression.

As in this case, concurrent *MYC* amplification could potentially confer primary resistance to capmatinib in NSCLC with *MET* GCN ≥10 and MET overexpression. Further clinical studies are needed to corroborate these findings, and treatment with MYC inhibitors could be considered as an alternative therapeutic strategy for this subset of patients.

## Acknowledgments

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## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-176/rc

*Peer Review File:* Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-176/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-176/coif). KCJ has equity in Incurix Co., Ltd. and serves as the president of Incurix Co., Ltd. JYH has received honoraria from AstraZeneca, BMS, F. Hoffmann-La Roche Ltd., MSD, and Takeda; has acted as a consultant or advisor for AstraZeneca, BMS, Eli Lilly, MSD, Novartis, Pfizer, Takeda, Medpacto, Abion, and ONO Pharmaceutical; and has received research funding from F. Hoffmann-La Roche Ltd., ONO Pharmaceutical, Pfizer, and Takeda. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.



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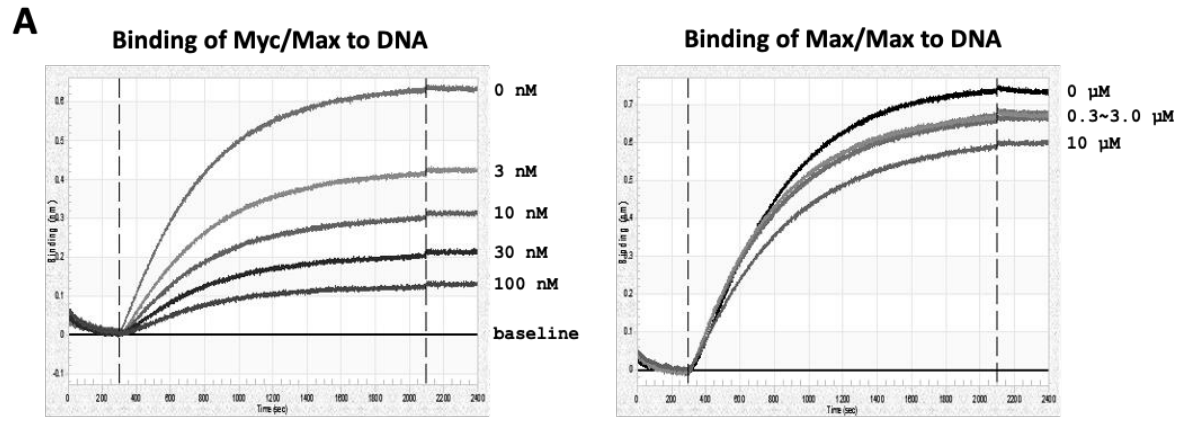


| Target | Myc/Max | Max/Max | Jun/Fos |
|---|---|---|---|
| $IC_{50}$ | 30 nM | 3 μM | 3 μM |

**Figure S1** Selective inhibition of Myc/Max-DNA complex. The inhibitory effect and selectivity of ICX-101 at the protein level were confirmed by SPR analysis (A) and electrophoretic mobility shift assay (EMSA)(B). ICX-101 selectively inhibited the binding of Myc/Max dimer to DNA and had little effect on Max/Max dimer or AP-1 having a similar structure.

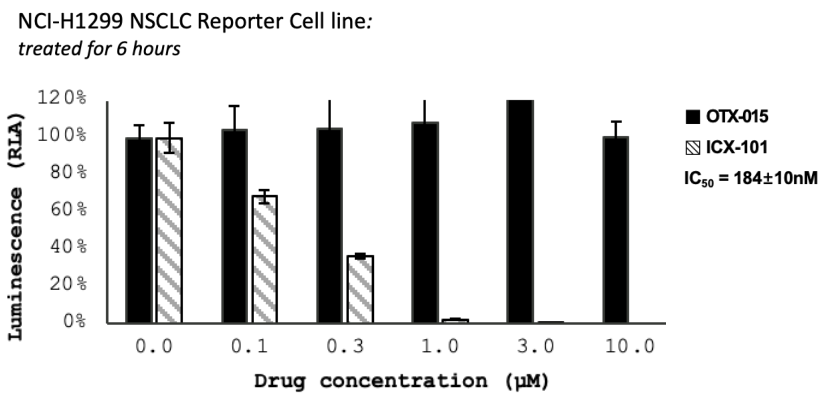


**Figure S2** Myc signaling inhibitory effect. ICX-101 strongly inhibited Myc signal in NCI-H1299 reporter cells and had little effect on CMV negative control signal. When the compounds were treated with sequential concentrations for 6 hours, ICX-101 completely blocked the signal of Myc, whereas OTX-015, an indirect inhibitor of Myc through BRD4, had no effect. This is due to the direct inhibitory effect of ICX-101 and shows that it is superior to the indirect inhibitors.


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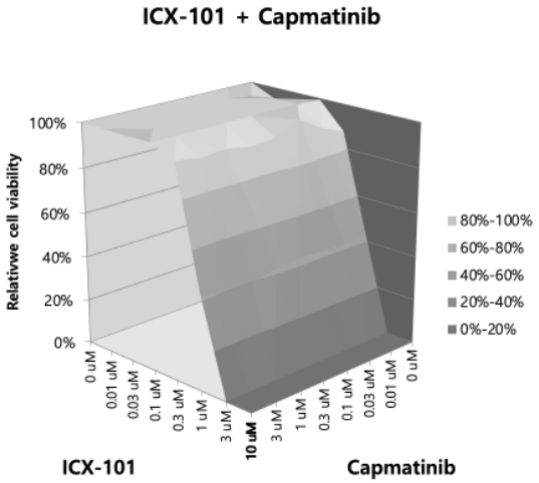


**Figure S3** Combination treatment of ICX-101 and capmatinib in patient-derived cells. Patient-derived cancer cells were plated in 96-well plates at passage 3 and treated with each concentration of ICX-101 and capmatinib simultaneously after 24 hours of incubation. Cell viability after 72 hours was measured by ATP measurement method. Capmatinib did not show any antitumor effect up to 10 uM, and co-treatment with ICX-101 did not show a synergistic effect. Co-treatment with capmatinib did not affect the effect of ICX-101.

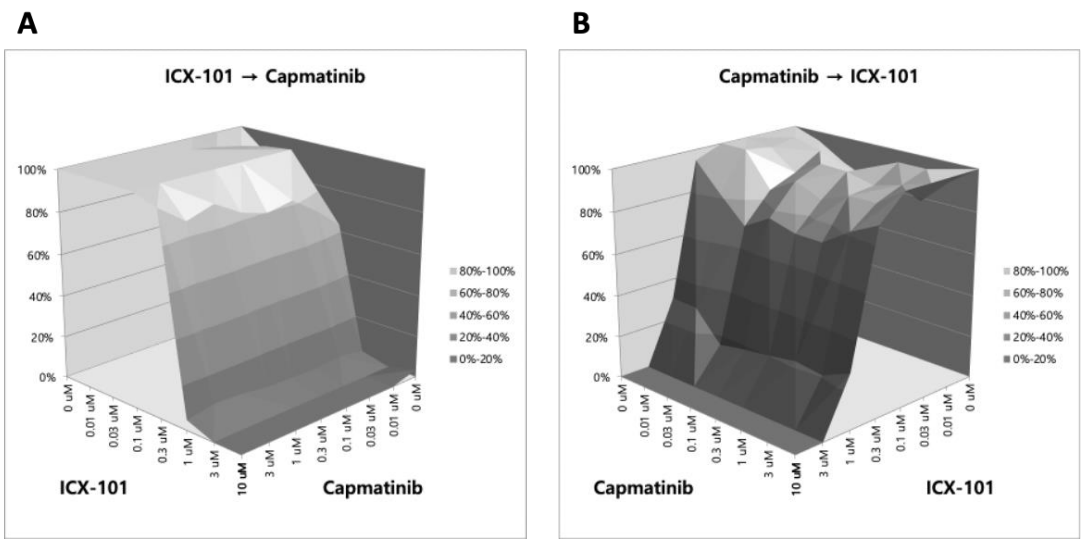


**Figure S4** Sequential treatment of ICX-101 and capmatinib in patient-derived cells. Patient-derived cancer cells were seeded in 96-well plates at passage 3, and after 24 hours of incubation, each concentration of ICX-101 or capmatinib was treated. After 48 hours, the other drug was treated in a dose-matrix manner. After further incubation for 72 hours, cell viability was measured by ATP assay. (A)When ICX-101 was treated first, an additive effect, not a synergistic effect, was shown. (B) When capmatinib was treated first, a synergistic effect was shown.


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