

Clinical Trials

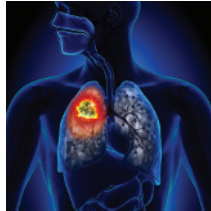
Major finding: Capmatinib plus gefitinib had a 27% to 29% response rate in patients who progressed on prior EGFR TKI therapy.

Approach: A phase Ib/II trial assessed capmatinib plus gefitinib in patients with EGFR-mutant MET-dysregulated NSCLC.

Impact: Combination therapy with capmatinib and gefitinib may be effective after resistance to prior EGFR TKIs.

CAPMATINIB PLUS GEFITINIB IS ACTIVE IN EGFR-MUTANT MET-AMPLIFIED TUMORS

MET dysregulation occurs frequently in patients with non-small-cell lung cancer (NSCLC) and can confer resistance to tyrosine kinase inhibitors (TKI) targeting EGFR. Preclinical studies have suggested that the potent specific MET inhibitor capmatinib may be combined with the EGFR inhibitor gefitinib to suppress acquired EGFR inhibitor resistance. Thus, Wu and colleagues evaluated the safety and efficacy of capmatinib plus gefitinib in a phase Ib/II study of patients with EGFR-mutant NSCLC with MET amplification or overexpression who progressed while receiving EGFR TKI treatment. A total of 61 patients were treated in the phase I part of the study and 100 patients were treated in phase II. The primary end point was the overall response rate. Across phases Ib and II the overall response rate was 27%. The treatment combination achieved greater activity in the 36 patients with MET-amplified tumors (with at least 6 copies of MET), with 47%



experiencing an overall response. Combination therapy had an acceptable safety profile, with treatment-related grade 3–4 adverse events occurring in 46 of 161 (29%) patients. Adverse events led to treatment discontinuation in 27 of 161 (17%) patients. No significant drug–drug interactions were observed between capmatinib and gefitinib. Taken together, these findings indicate that combination therapy with capmatinib and gefitinib is safe and exhibits antitumor activity in patients with EGFR-mutant, MET-dysregulated tumors. Further, this combination may overcome resistance to other EGFR TKIs. ■

Wu YL, Zhang L, Kim DW, Liu X, Lee DH, Yang JC, et al. Phase Ib/II study of capmatinib (INC280) plus gefitinib after failure of endothelial growth factor receptor (EGFR) inhibitor therapy in patients with EGFR-mutated, MET factor-dysregulated non-small-cell lung cancer. *J Clin Oncol* 2018 Aug 29 [Epub ahead of print].

Noncoding RNA

Major finding: NORAD binds to RBMX to facilitate the assembly of a topoisomerase I complex termed NARC1.

Concept: Depletion of NORAD or RBMX induces chromosome segregation defects and genomic instability.

Impact: The role of NORAD in assembling NARC1 suggests a role in suppressing genomic instability and cancer.

THE lncRNA NORAD CONTRIBUTES TO THE MAINTENANCE OF GENOMIC STABILITY

Only a fraction of the long noncoding RNAs (lncRNA) in the genome have been functionally characterized. NORAD is a highly conserved lncRNA expressed at high levels in many cell types. It is upregulated upon DNA damage, and its loss promotes chromosomal instability and aneuploidy. However, the mechanism by which NORAD regulates chromosomal instability has not been determined. To identify proteins that directly interact with NORAD, Munschauer and colleagues performed RNA antisense purification (RAP) combined with quantitative liquid chromatography/mass spectrometry using mass tag quantification (RAP MS). This approach revealed that NORAD binds to a number of nuclear proteins in colon cancer cells including RBMX. Knockdown of RBMX resulted in impaired DNA damage repair and premature sister-chromatid separation, similar to the NORAD depletion. NORAD contains the strongest RBMX-binding site in the transcriptome, and RNA immunoprecipitation confirmed that NORAD and RBMX interact in the nucleus of cells. NORAD was required

for RBMX to assemble a ribonucleoprotein complex, termed NORAD-activated ribonucleoprotein complex I (NARC1), which contains known suppressors of genomic instability including topoisomerase I, ALYREF, and the PRPF19–CDC5L complex. Depleting NORAD or RBMX promoted chromosome segregation defects, reduced replication fork speed, and disrupted cell-cycle progression, effects that could be rescued by wild-type NORAD expression. However, NORAD could not restore genome stability when the RBMX binding domain was deleted, indicating that the interaction with RBMX is required for NORAD function. Altogether, these findings indicate that DNA damage-mediated induction of NORAD can promote the assembly of the NARC1 complex in the nucleus to promote genome stability. ■

Munschauer M, Nguyen CT, Sirokman K, Hartigan CR, Hogstrom L, Engreitz JM, et al. The NORAD lncRNA assembles a topoisomerase complex critical for genome stability. *Nature* 2018;561:132–6.

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CANCER DISCOVERY

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