**Clinical Trials**

**Major finding:** Cabozantinib achieved an overall response rate of 28% in patients with RET-rearranged NSCLC.

**Approach:** The safety and activity of cabozantinib were tested in an open-label, single-arm, phase II trial.

**Impact:** RET rearrangements may be targeted with cabozantinib in patients with NSCLC.

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**CABOZANTINIB IS ACTIVE IN PATIENTS WITH ADVANCED RET-REARRANGED NSCLC**

RET rearrangements occur in 1% to 2% of non-small cell lung cancers (NSCLC) and drive ligand-independent RET signaling, suggesting that these alterations are potential therapeutic targets. The multikinase inhibitor cabozantinib, which has activity against RET, has antitumor activity in mouse models of RET-rearranged lung cancer and achieved a 10% overall response rate in an unselected population of patients with lung cancer. Drilon and colleagues evaluated the safety and activity of cabozantinib in 26 patients with advanced RET-rearranged NSCLC in an open-label, single-arm, phase II trial. The primary objective was to determine the overall response, and secondary outcomes included progression-free survival and overall survival, and safety. The overall response rate was 28%, with 7 of 25 evaluable patients achieving a partial response, including patients with KIF5B–RET, TRIM33–RET, and CLIP1–RET fusions. The median progression-free survival was 5.5 months, and median overall survival was 9.9 months. Treatment-related adverse events occurred in 96.2% of patients, but were primarily grade 1 or grade 2. Dose reductions were required in 73% of patients due to drug-related toxicities. Next-generation sequencing of 102 cases did not find activating alterations in other kinases targeted by cabozantinib, indicating that the therapeutic effects of cabozantinib are likely due to targeting of RET. In addition to suggesting that cabozantinib has antitumor activity and an acceptable tolerability in patients with RET-rearranged NSCLC, these findings indicate that RET rearrangements are targetable oncogenic drivers. The results of this study support further investigation of cabozantinib or RET-specific kinase inhibitors in patients with RET-rearranged lung cancer.


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**Epigenetics**

**Major finding:** RB–E2F1 recruits EZH2 to repetitive sequences, promoting repression via H3K27me3 deposition.

**Concept:** A mutation in Rb1 that prevents its recruitment to repeats induces spontaneous lymphoma in mice.

**Impact:** Derepression of repetitive sequences via RB–EZH2 loss of function may increase cancer susceptibility.

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**REPETITIVE DNA ELEMENTS ARE SILENCED BY RB-MEDIATED EZH2 RECRUITMENT**

Approximately half of the human genome is composed of repetitive genomic elements, which can be silenced by repressive heterochromatic domains. Derepression of repetitive elements has been linked to cancer, but the mechanisms underlying the silencing of repetitive sequences are not well understood. Ishak and colleagues found that the retinoblastoma protein (RB) bound to diverse repetitive genomic sequences, including short interspersed nuclear elements, long interspersed nuclear elements, long terminal repeat-containing endogenous retroviruses, and simple repeat-containing sequences. A cell cycle-independent interaction between RB and the transcription factor E2F1 enhanced the interaction with repetitive elements, and, in Rb1F832A mice that are homozygous for a substitution that disrupts the RB-E2F1 interaction, RB occupancy of repetitive sequences was reduced. RNA sequencing of mouse embryonic fibroblasts (MEF) revealed that RB-E2F1 was required for silencing of repetitive elements, as Rb1F832A MEFs displayed greater expression of a variety of repeats including transposable elements, satellites, and simple repeats. Mechanistically, RB–E2F1 recruited the histone methyltransferase EZH2 to repetitive sequences, promoting H3K27me3 deposition that led to heterochromatin spreading and silencing at repetitive elements. Notably, Rb1F832A mice had an increased susceptibility to cancer, most commonly lymphoma, and the tumors expressed diverse repetitive sequences. Expression of repetitive sequences can stimulate an immune response, and interferon α and β were upregulated in splenocytes, suggesting that the immune response may clear cells with aberrant repeat expression, which may explain why normal splenocytes from Rb1F832A mice did not consistently show expression of repetitive elements. Collectively, these findings provide a mechanism by which RB promotes silencing of repetitive elements through EZH2 recruitment, and show that misexpression of repetitive elements may increase susceptibility to cancer.


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*Research Watch is written by Cancer Discovery editorial staff. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit Cancer Discovery online at [http://cancerdiscovery.aacrjournals.org/content/early/by/section](http://cancerdiscovery.aacrjournals.org/content/early/by/section).*
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