IN THE SPOTLIGHT

Beyond First-Generation KRAS Inhibitors: BBO-8520 Tests the Dual Mechanism Hypothesis

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Summary: This issue highlights the development of a first-in-class small-molecule covalent KRAS^{G12C} inhibitor, BBO-8520, which targets both the active (ON) and inactive (OFF) states of KRAS. This dual-state targeting offers a significant opportunity to overcome the resistance mechanisms that have limited the efficacy of first-generation KRAS inhibitors and addresses critical challenges in KRAS-targeted therapy.

See related article by Maciag et al., p. 578

The journey of KRAS inhibitor development has been one of the most compelling narratives in precision oncology, marked by both groundbreaking successes and persistent challenges. *KRAS*, a frequently mutated oncogene found across multiple cancer types, has long been considered a "holy grail" in cancer therapy. Initial clinical breakthroughs came with the development of sotorasib and adagrasib, which specifically target the KRAS^{G12C} mutation through covalent binding to the GDP-bound (inactive/OFF) state of KRAS^{G12C} (1, 2). This approach emerged from the serendipitous discovery that an inducible pocket in KRAS^{G12C}, the dominant allele in lung cancer, could be exploited by covalent chemical fragments (3). These first-generation inhibitors demonstrated clinical efficacy, validating KRAS as a druggable target. However, their impact has been tempered by modest response rates and limited durability compared with other transformative precision oncology therapies, such as osimertinib for *EGFR*-mutated cancers or alectinib for *ALK*-mutated cancers.

The limitations of first-generation KRAS inhibitors have been attributed by some to their mechanism of action. These inhibitors bind exclusively to KRAS in its GDP-bound (OFF) state, leaving the active GTP-bound (ON) form unaffected. Early developers justified this approach based on the observation that KRAS^{G12C} exhibits nucleotide cycling, allowing transient opportunities to target the GDP-bound state (4). However, subsequent research has revealed that cancer cells adapt to KRAS (OFF) inhibitors by increasing the proportion of KRAS in its active state, contributing to drug resistance. This idea and supporting evidence have driven the field to explore whether targeting the KRAS (ON) state alone, or targeting both (ON) and (OFF) states, could yield improved clinical outcomes. The "dual mechanism hypothesis" posits that inhibitors capable of targeting both conformational and functional states of KRAS will achieve superior efficacy (Fig. 1).

BBO-8520 represents a major advance in addressing these challenges. Through meticulous structural optimization, Maciag and colleagues have developed a compound that binds to the same pocket as first-generation inhibitors but with the capacity to engage both GDP-bound and GTP-bound KRAS^{G12C} (5). This dual-state targeting is particularly noteworthy because previous attempts to target the GTP-bound state have often relied on complex strategies, such as tri-complex inhibitors requiring cyclophilin A as a cofactor (6). Although preclinical and early clinical results for tri-complex inhibitors have been promising, their reliance on cofactors raises questions about their broad clinical applicability. It is possible that the interaction could provide significant clinical benefits but also conceivable that this feature could pose limitations in selected patients. In contrast, BBO-8520 circumvents these complexities by directly targeting KRAS^{G12C} while achieving dual-state inhibition.

Several aspects of the design of BBO-8520 make it particularly remarkable. First, it retains the ability to form a covalent bond with cysteine 12 while accommodating GTP in the nucleotide-binding pocket—a significant feat in drug design. Structural studies reveal how subtle modifications to the binding pocket interactions enable this dual-state targeting. Second, BBO-8520 demonstrates remarkably rapid target engagement, achieving significant pathway inhibition within 30 minutes—substantially faster than first-generation inhibitors. This rapid action likely reflects its ability to directly engage KRAS in its active state rather than waiting for nucleotide cycling. Third, and perhaps most importantly, BBO-8520 shows promising activity against RAS-driven laboratory cancer models that are resistant to first-generation inhibitors. These findings suggest that dual-state targeting could overcome some of the most pressing resistance mechanisms associated with first-generation therapies.

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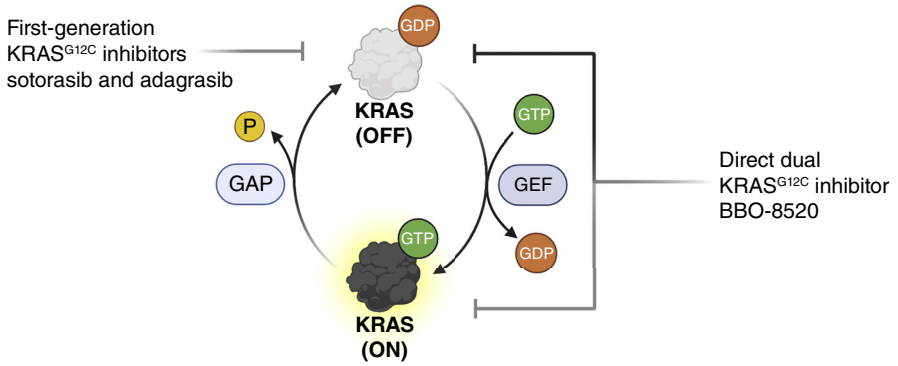

Figure 1. First-generation KRAS inhibitors directly target KRAS^{G12C} (OFF), whereas BBO-8520 directly targets both inactive (OFF) and active (ON) states of KRAS^{G12C}. Targeting of KRAS^{G12C} (ON) is less potent (light gray line) than that of KRAS^{G12C} (OFF), but this may not matter.

Despite these promising advancements, the emergence of BBO-8520 raises critical questions for the field. Although the compound demonstrates that targeting GTP-bound KRAS is feasible through careful optimization, kinetic analysis of BBO-8520 binding showed that KRAS^{G12C} (OFF) is more readily inhibited by BBO-8520 by orders of magnitude. It is unclear if this property can be improved, or if doing that will matter. The analysis suggests that BBO-8520 binding kinetics to KRAS^{G12C}(ON) are already in the ballpark of sotorasib with KRAS^{G12C}(OFF), which may be enough. It also remains unclear if dual-state inhibition will address the root causes of real-world KRAS inhibitor resistance. Recent studies have highlighted the role of nongenetic mechanisms, such as transcriptional reprogramming and cellular plasticity, in KRAS inhibitor resistance (7). Perhaps related, the unfolded protein response has been implicated in resistance to KRAS (OFF) inhibitors (8). Finally, clinical resistance mechanisms to KRAS^{G12C} inhibitors have included the emergence of other activating forms of KRAS or activation of RTK pathways, raising motivation for pan-KRAS–targeted approaches (9). How these mechanisms might affect responses to dual-state inhibitors remains an important area for investigation.

Another challenge lies in identifying the appropriate patient population for KRAS^{G12C} inhibitors. Although *KRAS^{G12C}* mutation status has been the primary biomarker for patient selection, recent analyses of more than 400 *KRAS^{G12C}*-positive patients treated with first-generation inhibitors have suggested that co-mutations in genes such as *KEAP1*, *SMARCA4*, and *CDKN2A* are major independent determinants of dramatically shortened progression-free survival (10). This suggests that intrinsic resistance mechanisms may exist in these patients, though their causality and underlying mechanistic biology remain unelucidated. Dual-state inhibitors like BBO-8520 may hold the potential to overcome such resistance, but additional confirmatory research is needed.

The ongoing phase I trial of BBO-8520 will be pivotal in determining whether its mechanistic advantages translate to superior clinical efficacy. Combination strategies are also likely to play a key role in improving outcomes. For example, *KRAS*-mutated cancers are thought to be responsive to immunotherapy. However, combining KRAS inhibitors with immunotherapies has resulted in liver toxicity (11). It remains unclear whether this is a nonspecific effect of certain KRAS inhibitors or a broader class effect. As these questions are addressed, the results of trials for BBO-8520 and other KRAS (ON) inhibitors are eagerly anticipated and could reshape the landscape of KRAS-targeted therapy.

In summary, BBO-8520 represents a promising advance in KRAS-targeted drug development, with the potential to overcome resistance mechanisms and expand the therapeutic options for patients with RAS-driven cancers. Although significant challenges remain, its innovative approach to dual-state targeting marks a critical step forward in the ongoing effort to tackle one of oncology's most formidable targets.

Authors' Disclosures

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REFERENCES

1. Jänne PA, Riely GJ, Gadgeel SM, Heist RS, Ou SHI, Pacheco JM, et al. Adagrasib in non-small-cell lung cancer harboring a KRAS^{G12C} mutation. N Engl J Med 2022;387:120–31.
2. Hong DS, Fakih MG, Strickler JH, Desai J, Durm GA, Shapiro GI, et al. KRAS^{G12C} inhibition with sotorasib in advanced solid tumors. N Engl J Med 2020;383:1207–17.
3. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. Nature 2013;503:548–51.

4. Hunter JC, Manandhar A, Carrasco MA, Gurbani D, Gondi S, Westover KD. Biochemical and structural analysis of common cancer-associated KRAS mutations. Mol Cancer Res 2015;13:1325–35.
5. Maciag AE, Stice JP, Wang B, Sharma AK, Chan AH, Lin K, et al. Discovery of BBO-8520, a first-in-class direct and covalent dual inhibitor of GTP-bound (ON) and GDP-bound (OFF) KRASG12C. Cancer Discov 2025;15:578–94.
6. Jiang JJ, Jiang LY, Maldonato BJ, Wang YY, Holderfield M, Aronchik I, et al. Translational and therapeutic evaluation of RAS-GTP inhibition by RMC-6236 in RAS-driven cancers. Cancer Discov 2024;14:994–1017.
7. Marasco M, Misale S. The far side of resistance to RAS inhibitors. Cancer Discov 2024;14:2018–20.
8. Lv X, Lu X, Cao J, Luo Q, Ding Y, Peng F, et al. Modulation of the proteostasis network promotes tumor resistance to oncogenic KRAS inhibitors. Science 2023;381:eabn4180.
9. Awad MM, Liu S, Rybkin II, Arbour KC, Dilly J, Zhu VW, et al. Acquired resistance to KRAS^{G12C} inhibition in cancer. N Engl J Med 2021;384:2382–93.
10. Negrao MV, Araujo HA, Lamberti G, Cooper AJ, Akhave NS, Zhou T, et al. Comutations and KRASG12C inhibitor efficacy in advanced NSCLC. Cancer Discov 2023;13:1556–71.
11. Chour A, Denis J, Mascaux C, Zysman M, Bigay-Game L, Swalduz A, et al. Severe sotorasib-related hepatotoxicity and non-liver adverse events associated with sequential anti-programmed cell death (Ligand)1 and sotorasib therapy in KRAS^{G12C}-mutant lung cancer. J Thorac Oncol 2023;18:1408–15.