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Targeting KRAS mutated NSCLC – novel TKIs and beyond

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SUMMARY

KRAS mutated non-small cell lung cancer (NSCLC) is the most common genetically altered subtype of NSCLC, yet targeted therapies remain limited. Multiple studies have investigated combinations of MEK inhibitors with chemotherapy without success. Here we discuss these studies and novel approaches to targeting KRAS mutated NSCLC.

In this issue of *Clinical Cancer Research*, Gadgeel and colleagues evaluated the combination of trametinib, a MEK inhibitor, with docetaxel in patients with *KRAS* mutated(m) non-small cell lung cancer (NSCLC) following first line platinum containing regimens in a phase II single arm study (1). Mutations in the *KRAS* gene, specifically *KRAS*^{G12C}, are common oncogenic driver mutations identified in NSCLC, however, targeted therapies remain limited and modestly beneficial in part due to the challenge of pharmacologically inhibiting KRASm (2). There has been focus on targeting downstream effector pathways such as the MEK-ERK and PI3K/AKT pathways (Figure 1) with either single agents or combinatorial approaches. Trametinib, a MEK1/2 inhibitor, when evaluated as a single agent demonstrated similar efficacy compared to docetaxel in *KRAS*m NSCLC following first line therapy (3). Additional evidence suggested a synergistic effect of combination trametinib with docetaxel with improved response rates in *KRAS*m NSCLC.

Based on these early encouraging results, Gadgeel and colleagues conducted a multi-site cooperative group Phase II clinical trial to determine the efficacy of this combination in *KRAS*m NSCLC, with a specific interest in the activity of this combination in the *KRAS*^{G12C} cohort (1). The combination led to an objective response rate (ORR) of 34%,

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with a median progression free survival (mPFS) of 4.1 months, and a median overall survival (mOS) of 10.9 months. There was no improvement in ORR amongst the *KRAS*^{G12C} subset as had been suggested in pre-clinical and earlier phase studies. These findings are similar to outcomes in SELECT-1, a phase III trial evaluating combination MEK inhibition with selumetinib and docetaxel versus docetaxel in a similar population, which failed to demonstrate superior outcomes with the addition of selumetinib (4). The results presented by the authors add to the existing evidence of limited clinical benefit of the addition of MEK inhibitors to chemotherapy for *KRAS*m NSCLC.

Since the development of the discussed trial, strategies have focused on developing KRAS inhibitors based on the structure of allele specific mutations. Sotorasib and adagrasib are KRAS^{G12C} specific inhibitors that bind to an allosteric pocket and lock it into its inactive GDP-bound state (Figure 1) (5). In single arm phase II trials, both sotorasib and adagrasib demonstrated activity in relapsed *KRAS*^{G12C} NSCLC leading to FDA approval. Sotorasib demonstrated an ORR of 37.1% and mPFS of 6.8 months whereas adagasib demonstrated an ORR of 42.9% and a mPFS of 6.5 months (6,7). Codebreak 200, a phase III trial comparing sotorasib to docetaxel in *KRAS*^{G12C} NSCLC after 1st line treatment, demonstrated a clinically significant albeit modest increase in mPFS (5.6 v 4.5 months). No difference was seen in mOS although the data remain immature (8). While these efforts have established the use of sotorasib and adagrasib in the second line, ongoing clinical trials are investigating novel KRAS^{G12C} inhibitors as well as the combination KRAS^{G12C} inhibitors with inhibitors of RAS signaling pathway effectors in efforts to improve outcomes (9).

An additional area of interest is the development of agents for non-G12C *KRAS*m NSCLC. Non-G12C *KRAS* subtypes have been hypothesized to have a lower GTPase activity and thus challenging to target therapeutically. Recently however, novel approaches targeting non-G12C variants, including G12D and G12V as well as pan-*KRAS* inhibitors, are in development (2). A KRAS^{G12D} specific inhibitor has shown promising pre-clinical activity and is currently being tested in patients with *KRAS*^{G12D} mutated solid cancers (NCT05737706) (10).

Beyond small molecule inhibitors, a significant effort is underway to target *KRAS*m cancers by engaging the anti-tumor immune response (Figure 1). Unlike other subsets of oncogene driven NSCLCs such as those with alterations in *EGFR* and *ALK*, *KRAS*m NSCLC is often associated with high PDL1 expression, high tumor mutational burden, and increased responsiveness to immune checkpoint inhibition (ICI). Several retrospective analyses have demonstrated similar outcomes with ICI monotherapy compared to chemoimmunotherapy in patients with *KRAS*m and PDL1 >50% NSCLC which is distinct from those with *KRAS* wild-type tumors where chemoimmunotherapy is likely superior (11,12). Additionally, preclinical studies have suggested synergy between KRAS^{G12C} inhibitors and ICI and based on these observations, numerous clinical trials are assessing combinatorial approaches (NCT04185883, NCT04613596, NCT04449874).

Cancer vaccines have again emerged as a promising approach to enhance anti-tumor CD8 T cell responses. While older methods using peptide-based and DC-based vaccines have demonstrated *KRAS*m specific immune responses, newer approaches utilizing mRNA

vaccine technology combined with ICI have demonstrated the most promise (9), and a mRNA vaccine expressing the four most common KRAS mutations (G12C, G12V, G12D, and G13D) is currently being tested in patients with *KRAS*m solid tumors (NCT03948763). A recent study utilizing a personalized neoantigen mRNA vaccine, autogene cevumeran, combined with atezolizumab resulted in the expansion and activation of antigen specific CD8 T cells and prolonged recurrence free intervals in patients with resected pancreatic cancer highlighting the potential of this approach across *KRAS* mutated cancers (13). Another emerging strategy is the generation of autologous T cells expressing KRASm specific T cell receptors (TCRs). Preclinical studies have identified numerous mutant KRAS epitopes that can be processed and presented by the MHC machinery and thus be effectively targeted with engineered TCRs against KRASm (14). Indeed, an engineered TCR has been effective in a patient with metastatic *KRAS*^{G12D} pancreatic cancer (15) and multiple early phase clinical trials evaluating KRASm targeted TCRs are ongoing (NCT03190941, NCT03745326, NCT04146298).

In *KRAS*m NSCLC, another factor to consider is the presence or absence of co-mutations, such as *TP53, STK11,* and *KEAP1.* These mutations are commonly identified and influence responsiveness to both KRAS^{G12C} inhibitors and immunotherapies (2). Co-mutations in *TP53* and *STK11* have been associated with biologically distinct subtypes of *KRAS*m NSCLC and impacted outcomes following MEK inhibition in mouse models of *KRAS*m NSCLC (16,17). On this trial, in an exploratory analysis, the authors assessed whether outcomes varied among patients with these co-mutations. There was no difference in outcomes between *STK11*m vs *STK11* wild-type (wt) tumors, however, *TP53*m tumors were associated with worse ORR (0% vs 56%) and mOS (5.6 vs 10.9 months)(1). While the overall number of evaluable patients with co-mutation status in this analysis is small, these findings are consistent with emerging evidence that co-mutational status provides important prognostic and predictive information and should be incorporated into clinical trial design and factor into treatment decisions in both the first- and second-line settings.

In summary, the data presented by Gadgeel and colleagues highlights the difficulty in developing therapies that improve outcomes for *KRAS*m NSCLC. However, with the advent of *KRAS*^{G12C} specific small molecular inhibitors, there is increased excitement in the ability to effectively target *KRAS* specific mutations across tumor types. Together with efforts to develop small molecule inhibitors against effectors of the RAS pathway and strategies to enhance *KRAS*m directed immune responses, we anticipate an increase in the treatment options for *KRAS*m NSCLC in the coming years. Moreover, with continued increase in biomarker testing in clinical practice, treatment decisions can be further optimized based on both driver mutation and co-mutation status. Altogether this is good news for our patients.

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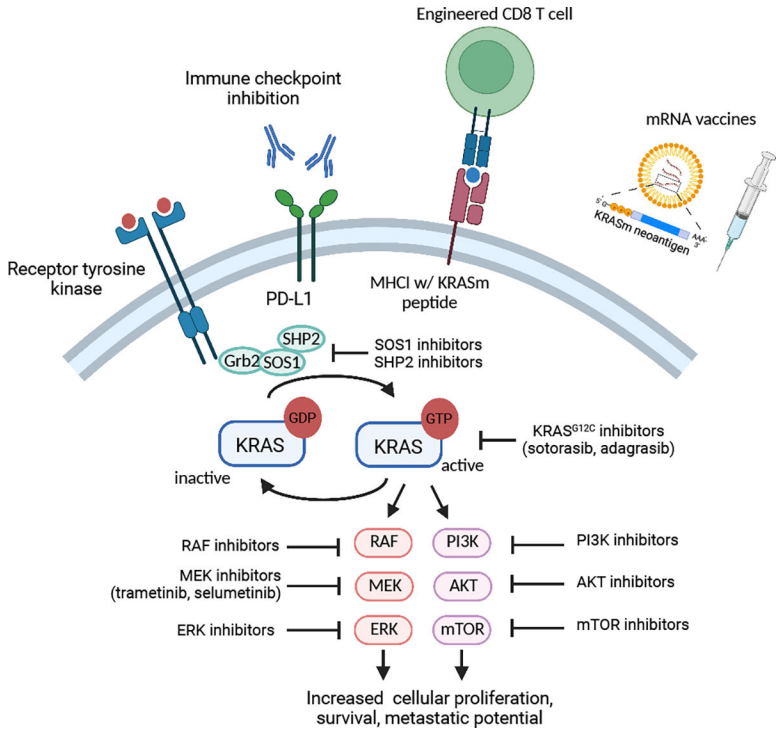

Strategies for targeting *KRAS*m NSCLC. Represented is canonical KRAS signaling. In its inactive state, KRAS is bound to GDP. Following activation of membrane receptors, KRAS bound GDP is exchanged for GTP resulting in KRAS activation. KRAS subsequently activates downstream signaling pathways such as the MAP/ERK and PI3K/AKT pathway leading to cellular proliferation and survival. Mutant KRAS as well as upstream and downstream effectors of the KRAS pathway are targets for small molecule inhibitors. Strategies to activate the anti-tumor immune response includes immune checkpoint inhibitors, engineered T cells expressing KRASm TCRs, and mRNA vaccines expressing KRASm neoantigens.
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