Editorial

KRAS G12C mutation: from undruggable target to potentially agnostic biomarker

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I want to commend Dr. Santarpia *et al.* for their effort to write a comprehensive review on Kristen rat sarcoma (*KRAS*) mutant lung cancers (1). In this editorial accompanying their article "Targeted therapies for *KRAS*-mutant non-small cell lung cancer: from preclinical studies to clinical development-a narrative review", I comment on the next steps in *KRAS* inhibitors clinical trial development after a concise review of this topic.

KRAS activating somatic mutations represent the most common genetic alteration in non-small cell lung cancers (NSCLC) (2,3). They are reported in 25% to 30% of non-small cell lung adenocarcinomas and in approximately 4% of squamous cell lung carcinomas. *KRAS* mutations commonly occur in hotspots at codon 12 (the most common, *KRAS* G12C) and codon 13 (3). They were identified and remained hard to treat for more than four decades. They recently joined the ranks of targetable molecular drivers in NSCLC with the Food and Drug Administration (FDA) approval of two *KRAS* G12C selective covalent inhibitors, sotorasib and adagrasib (4,5).

The original efforts to target *KRAS* by inhibiting its downstream signaling pathways have been unsuccessful (6). This has changed when Ostrem *et al.* (7) identified a binding pocket in *KRAS* G12C and selectively targeted its mutant cysteine residue with an inhibitor that prevented guanosine exchange factor (GEF) from binding and displacing guanosine diphosphate (GDP) from *KRAS*, and subsequently inactivated the mutation. This led to the development of several *KRAS* G12C selective covalent inhibitors.

With respect to the limitations of cross-trial comparison, the two newly approved *KRAS* G12C inhibitors showed similar efficacy and drug discontinuation rate due to treatment-related adverse events in patients with NSCLC harboring this mutation who were previously treated with a platinum-based regimen and a programmed cell death 1 (*PD-1*) or programmed cell death ligand 1 (*PD-L1*) immune checkpoint inhibitor (ICI) (*Table 1*). In addition, adagrasib showed excellent central nervous system (CNS) penetration and activity on untreated brain metastases in these patients with a response rate of 33% (5) and unbound brain to unbound plasma concentration ratio ($K_{p,uu}$) comparable to osimertinib (8) and therefore warrant testing in treatment naïve patients with *KRAS* mutant NSCLC with brain metastases. Of note, outcomes outside CNS were not as striking as the one seen with current *EGFR* and *ALK* inhibitors and therefore warrant optimizing future *KRAS* G12C inhibitors target effect in addition to ongoing

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Table 1 Results of the trials that led to the approval of two *KRAS* inhibitors

Variables	Sotorasib	Adagrasib
Phase 2	CodeBreaK100	KRYSTAL-1
Number of patients	126	116
Objective response rate	37.1%	42.9%
Duration of response (median), months	11.1 (95% CI: 6.9–NE)	8.5 (95% CI: 6.2–13.8)
Progression free survival (median), months	6.8 (95% CI: 5.1–8.2)	6.5 (95% CI: 4.7–8.4)
Overall survival (median), months	12.5 (95% CI: 10–NE)	12.6 (95% CI: 9.2–19.2)
Intracranial objective response rate	Being studied in CodeBreaK101 subprotocol G and Lung-Map S1900E	33.3% (95% CI: 18.0–51.8%)
Treatment-related adverse events, all and severe	69% and 20.6%	97.4% and 44.8%
Drug discontinuation rate	7.1%	6.9%

KRAS, Kristen rat sarcoma; CI, confidence interval; NE, not evaluable.

exploration of dose optimization.

Patients with brain metastases are often excluded from clinical trials due to concerns related to their poor performance status, their increased risk of toxicity to new treatments, and their short life expectancy. There is an urgent need for appropriate selection rather than empiric exclusion of these patients from participation in clinical trials. This may be their only hope to improve their condition in a disease where the incidence of developing intracranial metastases can be as high as 42% (9) and where targeted therapies have historically often showed meaningful efficacy and manageable adverse events in patients with brain metastases from NSCLC (10,11).

We look forward to the results of the prospective trials, CodeBreaK101 and Lung-Map sub-study S1900E, that are evaluating sotorasib intracranial activity in this population. In addition, S1900E is evaluating sotorasib outcomes with different *KRAS* co-mutations (*TP53*, *STK-11*, others). This will have a clinical impact on current agent selection and options in the presence of intracranial disease and selective co-mutations in patients with *KRAS G12C* NSCLC.

In CodeBreaK200, a phase 3 study presented at the European Society for Medical Oncology (ESMO) meeting 2022, sotorasib showed an improvement in median progression-free survival (PFS), primary endpoint, (5.6 *vs.* 4.5 months, HR 0.66, P=0.002) and 12-month PFS (24.8% *vs.* 10.1%) when compared to docetaxel in patients with NSCLC that progressed on platinum and ICIs given concurrently or sequentially. This study permitted cross-over and did not show a difference in overall survival (OS), secondary endpoint, between both arms. In addition, the study did not explore the sequence of use of sotorasib and docetaxel. It would be interesting to use the current best standard of care, docetaxel with ramucirumab, as a control arm in drug evaluations for oncogene-driven NSCLC, specifically *KRAS* mutant, in future trials as a small retrospective study has shown a trend toward prolonged time to treatment discontinuation in these patients compared to patients with *KRAS* wild-type NSCLC (3.9 *vs.* 2.3 months, P=0.05, N=45) (12).

It is important to explore the sequence of these agents and their activity in the front line metastatic and the adjuvant treatment settings in future trials and learn whether better outcomes can be achieved similar to the experience reported with other targeted therapies such as *EGFR* (13,14) and *ALK* (15) inhibitors.

Awad *et al.* (16) described a diverse mechanism of acquired resistance to adagrasib and classified in three main categories: development of mutations or amplification in *KRAS*, alterations in the *RTK-RAS-MAPK-PI3K* signaling pathways and gene fusion (*ALK*, *RET*, *BRAF*, *FGFR3*), and histologic transformation from adenocarcinoma to squamous cell carcinoma. This is an important knowledge that will shape the challenging future of clinical trials development to tackle highly variable mechanisms of resistance to *KRAS* G12C inhibitors not only by developing newer inhibitors but also by exploring cross toxicity and efficacy of combination with currently approved treatments for the specific alteration causing the resistance.

Currently, the first line treatment for *KRAS* mutant

Table 2 Results of the exploratory analysis of hard-to-treat mutations in 612 patients with non-small cell lung cancer treated with chemotherapy with *vs.* without *PD-L1/CTLA-4* checkpoint inhibitors on POSEIDON trial

Mutation-evaluable tumor/blood	N [%]	Median OS (months)	2-year OS rate	Median PFS (months)	12-month PFS rate	ORR	Median DOR (months)
STK11	87 [14]	15 *vs.* 10.7 (HR 0.56; 95% CI: 0.30–1.03)	32.3% *vs.* 4.5%	6.4 *vs.* 4.6 (HR 0.47; 95% CI: 0.23–0.93)	34.6% *vs.* 0%	45.2% (27.3–64.0%) *vs.* 27.3% (10.7–50.2%)	13.6 (5.1%–NE) *vs.* 3.3 (2.8%–NE)
KEAP1	37 [6]	13.7 *vs.* 8.7 (HR 0.43; 95% CI: 0.16–1.25)	35.0% *vs.* 0%	5.0 *vs.* 5.1 (HR 0.94; 95% CI: 0.33–3.35)	30.6% *vs.* 0%	45.5% (24.4–67.8%) *vs.* 33.3% (3.3%–NE)	16.4 (3.4%–NE) *vs.* 4.6 (3.3%–NE)
KRAS	182 [30]	25.7 *vs.* 10.4 (HR 0.56; 95% CI: 0.36–0.88)	51.7% *vs.* 25.6%	8.5 *vs.* 4.7 (HR 0.57; 95% CI: 0.35–0.92)	40.0% *vs.* 20.0%	55.0% (41.6–67.9%) *vs.* 21.2% (11.1–34.7%)	NR (7.9%–NE) *vs.* 5.4 (3.3%–NE)

PD-L1, programmed cell death ligand 1; *CTLA-4*, cytotoxic T-lymphocyte-associated antigen 4; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; DOR, duration of response; *STK11*, serine/threonine kinase 11; *KEAP1*, Kelch-like ECH-associated protein 1; *KRAS*, Kristen rat sarcoma; HR, hazard ratio; CI, confidence interval; NE, not evaluable; NR, not reached.

NSCLC is guided by histology, performance status, and *PD-L1* expression as the use of *KRAS* targeted therapy in front line setting remains investigational. While ICI registration trials did not stratify patients according to the presence or absence of *KRAS* mutation, a recent FDA-pooled analysis (17) of 12 registrational NSCLC clinical trials (n=8,888) presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting showed that patients with reported *KRAS* mutation (n=555) benefited from the combination of chemotherapy and immunotherapy similarly to those with reported *KRAS* wild-type (n=875). In addition, higher response rates (46% *vs.* 37%) and median survival (22.4 *vs.* 16.2 months) were seen across all *PD-L1* expression with the combination of chemotherapy and immunotherapy than with immunotherapy alone. No conclusions were drawn regarding *KRAS* G12C as this was a small subgroup within *KRAS* (n=157).

KRAS mutant NSCLC is a heterogeneous group that is generally responsive to *PD-1* or *PD-L1* ICI unless associated with co-mutation *STK11* or *KEAP1* (18). These co-mutations render the tumor immunogenically "cold" by lacking T-cell infiltration and are associated with poor prognosis. Expanding T-cell infiltration at the tumor site by adding anti-*CTLA-4* to anti-*PD-1* or anti-*PD-L1* in this setting makes it a good rationale to improve outcomes. Peters *et al.* (19) presented an exploratory analysis and outcomes of this heterogenous group by *STK11*, *KEAP1*, and *KRAS* mutations from POSEIDON, a phase 3, global, randomized, open-label, multicenter study comparing the combination of durvalumab (anti-*PD-L1*) with tremelimumab (anti-*CTLA-4*) and platinum-based chemotherapy every 3 weeks followed by maintenance durvalumab to platinum-based chemotherapy alone as a first line treatment in patients with naïve, metastatic *EGFR/ALK* wild-type NSCLC. Six hundred and twelve (96%) of 637 patients with non-squamous lung cancer had a tissue and/or blood evaluable mutation. The combination of anti *PD-L1/CTLA-4* ICI with chemotherapy led to more frequent, deeper, and more durable response than chemotherapy alone with a trend for OS and PFS benefit. The small sample size limited interpretation for *KRAS* co-mutations and therefore investigators analyzed each mutation separately (*Table 2*). This exploratory analysis showed the combination of anti *PD-L1/CTLA-4* ICI with platinum-based chemotherapy as a potential first line treatment in patients with *STK11*, *KEAP1*, or *KRAS* mutant NSCLC. This combination was recently FDA-approved for the treatment of adult patients with metastatic *EGFR/ALK* wild-type NSCLC.

With the universal adoption of tumor sequencing in metastatic NSCLC, future trials in this setting should also stratify patients by *KRAS* subtype and co-mutations status to identify predictors of response to therapy and use the combination of chemotherapy and immunotherapy as a control arm. With the expansion of these inhibitors to other solid malignancies and the reported promising outcomes (20,21), *KRAS G12C* mutation has the potential to become the next agnostic cancer biomarker in the era of precision oncology.

It is important to note that less than 20% of participants accrued on CodeBreak100 and KRYSTAL-1 were non-white (4,5). More efforts are warranted to understand

this disparity and make diversity in clinical trials accrual a priority in lung cancer research to promote health equity and understand the incidence of molecular targets, the safety and efficacy of precision oncology treatments in under-represented populations with NSCLC.

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