Editorial Commentary

The sooner, the better: early clearance of plasma circulating tumor DNA in patients with advanced *KRAS G12C* mutant non-small cell lung cancer

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Comment on: Paweletz CP, Heavey GA, Kuang Y, *et al.* Early Changes in Circulating Cell-Free KRAS G12C Predict Response to Adagrasib in KRAS Mutant Non-Small Cell Lung Cancer Patients. Clin Cancer Res 2023;29:3074-80.

Keywords: Kirsten rat sarcoma viral oncogene homologue glycine-to-cysteine (KRAS G12C); non-small cell lung cancer (NSCLC); circulating tumor DNA (ctDNA)

Submitted Dec 18, 2023. Accepted for publication Jan 23, 2024. Published online Feb 20, 2024.
doi: 10.21037/tlcr-23-838
View this article at: https://dx.doi.org/10.21037/tlcr-23-838

Kirsten rat sarcoma viral oncogene homologue glycine-to-cysteine (KRAS G12C)-mutated non-small cell lung cancer (NSCLC)

Activating mutations in *KRAS* are the most prevalent oncogenic driver in advanced NSCLC in Western population, occurring in approximately 25–30% of lung adenocarcinomas (1,2). Notably, more than 80% of oncogenic *KRAS* mutations arise at codon 12, where the glycine residue is substituted by different amino acids (3). The *KRAS* glycine-to-cysteine mutation (G12C) represents more than 40% of *KRAS* mutations in NSCLC, comprising approximately 13% of all patients with lung adenocarcinoma (3).

In the last decade, substantial advances have been made in the treatment of NSCLC, including the development of targeted therapies for patients with tumors harboring specific actionable genomic alterations such as *EGFR*, *ALK*, *ROS1*, among others (4). *KRAS* mutation had been considered undruggable until recently, when preclinical advances led to the development of small molecules designed for the direct inhibition of mutant *KRAS G12C* tumors (5-7). Among these agents, sotorasib (AMG-510) and adagrasib (MRTX-849) have demonstrated clinical benefit in pretreated patients with *KRAS G12C*-mutated NSCLC (2,8). Both are approved by the Food and Drugs Administration (FDA) and the European Medicines Agency (EMA), and have become available as a second or later line of therapy in this setting.

KRAS-mutated NSCLC constitutes a large and notably diverse group of tumors. As opposed to other actionable genomic alterations, *KRAS G12C*-mutated NSCLC is associated with smoking history, higher PD-L1 expression, and responsiveness to (chemo-)immunotherapy (9). The survival outcomes of patients with *KRAS*-mutated versus *KRAS* wild-type NSCLC treated with first-line (chemo)-immunotherapy are similar (10,11), and also among patients with G12C and non-G12C *KRAS* subtypes (12). Therefore, current guidelines recommend immune checkpoint inhibitors alone or combination chemoimmunotherapy as the preferred frontline treatment for patients with *KRAS G12C*-mutated metastatic NSCLC, according to the tumor programmed cell death-ligand 1 (PD-L1) status (4).

Beyond PD-L1 expression, additional biomarkers such as co-mutation status are emerging to better stratify patients for optimal treatment selection. In patients with *KRAS*-mutated NSCLC, co-mutations in tumor suppressor

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genes *STK11/LKB1* or *KEAP* are associated with worse outcomes with immunotherapy (13), and may benefit from a different approach. On the other hand, patients with *KRAS G12C*-mutated NSCLC with high PDL1 expression and co-mutation in *TP53* have favorable long-term survival outcomes with immunotherapy (14). Additionally, co-occurring genomic alterations in *KEAP1*, *SMARCA4*, and *CDKN2A* were prognostic of poor clinical outcomes with KRAS G12C inhibitors monotherapy in pretreated advanced NSCLC patients in a retrospective study conducted by Negrao and colleagues (15).

The management of patients with *KRAS G12C*-mutant NSCLC is becoming increasingly complex and new strategies including the use of *KRAS G12C* inhibitors in combination with chemotherapy (NCT05920356) or immunotherapy (NCT04613596) are being explored, with hope for improved outcomes but caution due to the potential increase in toxicity. In this scenario, it may be relevant to identify as soon as possible whether patients are benefiting from the selected therapy.

Plasma circulating tumor DNA (ctDNA) assessment for non-invasive monitoring in NSCLC

Peripheral blood analysis to detect circulating-free DNA (cfDNA) and ctDNA has shown clinical utility in advanced NSCLC molecular diagnosis, assessing for the presence of actionable genomic alterations at diagnosis in order to guide treatment decisions (16). Plasma ctDNA testing is also an alternative or complementary tool to tumor profiling in patients with acquired resistance to targeted therapy (17).

Monitoring treatment response to therapy is an emerging application of ctDNA testing. In advanced NSCLC, ctDNA changes can be detected before radiographic response in some settings, making it a potential tool to monitor and guide patient therapy (18,19). Total or partial plasma ctDNA clearance has been associated with improved outcomes in patients receiving first line immunotherapy (20,21). In the advanced EGFR-mutant setting, early clearance of plasma mutant clones has also been associated with longer progression-free survival (PFS) and overall survival (OS) in patients treated with targeted agents (22,23). Taking into account the increasing complexity of the *KRAS*-mutant NSCLC landscape, including combinations' strategies, new treatment options or different management based on the co-mutation status, early assessment of response using ctDNA monitoring may be of special interest.

Early ctDNA response in KRAS G12C-driven NSCLC treated with adagrasib

In a recent article published at *Clinical Cancer Research* (24), Paweletz and colleagues described the role of early ctDNA changes in advanced KRAS G12C-mutant NSCLC patients enrolled in the KRYSTAL-1 phase 1/2 single arm trial. This study evaluated adagrasib in patients with advanced solid tumors harboring *KRAS G12C* mutations (25). Cohort A explored adagrasib 600 mg twice daily in 60 patients with advanced NSCLC previously treated with at least one platinum-containing chemotherapy regimen and checkpoint inhibitor therapy and confirmed *KRAS G12C* mutation in tumor tissue. The utility of detection of KRAS G12C mutations in plasma and pharmacodynamic markers of KRAS inhibition in ctDNA was an exploratory objective of the trial, herein reported. Plasma for ctDNA analysis was collected at three time points: before starting adagrasib on cycle 1 (C1D1), three weeks after, on cycle 2 (C2D1), and on cycle 4 (C4D1). For baseline samples, quantitative plasma assessment of *KRAS G12C* was performed by plasma-based next-generation sequencing (NGS); droplet digital PCR (ddPCR) was performed for C2D1 and C4D1 specimens, and also at baseline if DNA was available after plasma NGS (***Figure 1***).

Of the 60 patients enrolled, 7 were excluded due to missing baseline draws. Thirteen patients did not have baseline detectable *KRAS G12C* ctDNA in plasma (sensitivity 75.5%, 40/53), 1 patient missed C2D1 draw, and 4 patients missed C4D1 draw. Therefore, 39 and 36 patients were evaluable for plasma response assessment at C2D1 and C4D1, respectively.

At C2D1, 85% patients (33/39) had a complete *KRAS G12C* plasma clearance and 81% (29/36) at cycle 4. Most important, early ctDNA clearance was associated with improved overall response rate (60.6% *vs.* 33.3%), and median OS (14.1 *vs.* 8.7 months; P=0.04; hazard ratio =0.3) at cycle 2. The results were similar at C4D1 (median OS 14.7 *vs.* 5.4 months; P>0.001; HR =0.1). Although baseline KRAS G12C ctDNA levels were not predictive for clinical response to adagrasib by RECIST 1.1. criteria in this study, ctDNA clearance at C2D1 was associated with the magnitude of radiographic response (median tumor diameter reduction 46% in those with complete ctDNA response, versus 19.5% in the 6 patients with incomplete ctDNA clearance).

This study also arises some questions. In this particular trial, the clinical impact of the clearance was similar at

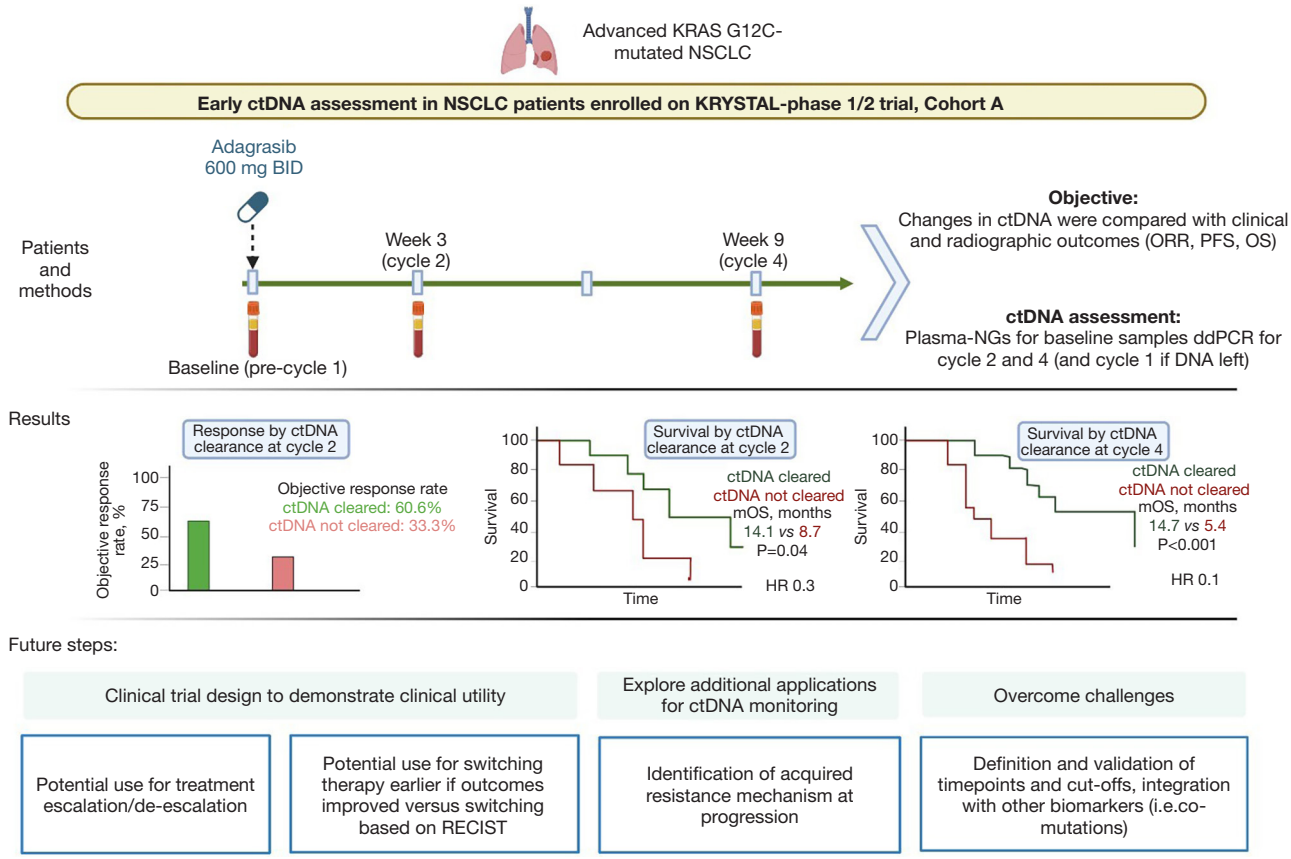

Figure 1 Early ctDNA assessment in patients with KRAS G12C-mutated NSCLC enrolled on KRYSTAL-1 phase 1/2 trial, Cohort A. NSCLC, non-small cell lung cancer; ctDNA, circulating tumor DNA; ORR, overall response rate; PFS, progression-free survival; mOS, median overall survival; NGS, next-generation sequencing; HR, hazard ratio.

C2 and C4, which poses the doubt on one hand, whether longitudinal ctDNA monitoring (i.e., every 3 weeks) adds value compared to isolated assessment at one specific timepoint to predict the clinical outcomes. On the other hand, ctDNA assessment can provide additional value beyond anticipating radiographic response, especially at progression when the identification of the mechanism of resistance—particularly in patients treated with targeted therapy—could be relevant to guide subsequent treatments. Additionally, complete ctDNA clearance seems to be the more reliable biomarker, but the value of plasma response, defined as ≥50% decrease in maximum allelic fraction (AF) in ctDNA, or near complete response (defined as >95% clearance of plasma ctDNA) could also be of interest (24). Finally, the prognostic and predictive value of the baseline ctDNA level and ctDNA clearance should be defined in prospective clinical trials designed to answer these questions.

Conclusions

Early ctDNA clearance in pretreated patients with advanced *KRAS G12C*-mutated NSCLC treated with adagrasib is associated with improved outcomes in the KRYSTAL-1 study, and therefore could become a relevant predictive biomarker of response to targeted therapy. However, further studies are needed to explore whether making treatment decisions based on ctDNA response can impact favorably patients' outcomes. Additionally, determining whether early ctDNA changes can guide treatment intensification or de-intensification will become important next steps to validate the clinical utility of this observation, especially in the metastatic *KRAS*-mutant NSCLC setting.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-838/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-838/coif). Dr. M.G.P. reports personal and institutional grants from "Sociedad Española de Oncología Médica" (SEOM Beca Retorno) and "Asociación Española Contra el Cáncer" (AECC Ayuda Clínico Junior en Territorio Nacional) and Payment for travel expenses and accommodation for European Society of Medical Oncology (ESMO) organized conferences/preceptorships. Dr. P.G. reports consultancy/honoraria from: Abbvie, Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi and Takeda, and direct funding from Medscape and Touch Medical; and institutional research funding from Amgen, AstraZeneca, Blueprint, BMS, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Janssen, IO Biotech, Lilly, MSD, Novartis, Pharmamar, Pfizer, Roche, Sanofi, Takeda, and Theradex Oncology. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: García-Pardo M, Garrido P. The sooner, the better: early clearance of plasma circulating tumor DNA in patients with advanced *KRAS G12C* mutant non-small cell lung cancer. Transl Lung Cancer Res 2024;13(2):215-219. doi: 10.21037/tlcr-23-838