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EDITORIAL

Cracking KRAS^{G12C} across all solid tumors: the new kid on the block for tissue-agnostic precision medicine

The landscape of oncologic treatments has transformed substantially over the past several decades, with the proliferation of molecularly targeted therapeutic approaches. Some molecular alterations are inextricably tied to the underlying biology of a tumor in a histology-specific manner, such as epidermal growth factor receptor (*EGFR*) mutations in non-small-cell lung cancer (NSCLC) or estrogen and progesterone receptor expression in breast cancer. Others may be predominantly present in a specific histology, but nevertheless occur throughout the spectrum of tumor histologies, which has promoted the assessment of candidate therapeutic targets and agents in a tissue-agnostic manner. The immune checkpoint inhibitor pembrolizumab was the first drug to receive approval by the United States Food and Drug Administration for a tissue-agnostic indication in 2017 for the treatment of microsatellite instability-high or mismatch repair-deficient tumors followed by an approval for another tissue-agnostic indication: high tumor mutation burden ($\geq$10 mutations per megabase).[1,2] The precision medicine list of tissue-agnostic targetable alterations which have achieved regulatory approval also includes neurotrophic tyrosine receptor kinase fusion, BRAF^{V600E}, and rearranged during transfection fusions.[3-5] Still other tissue-agnostic targets are emerging such as the fibroblast growth factor receptor alterations and neuregulin-1 fusions. It is anticipated that this list will continue to grow with the widespread adoption of next-generation sequencing (NGS) and novel agents in the developmental pipeline.

Pathogenic mutations involving the Kirsten rat sarcoma virus (*KRAS*) gene are present across the spectrum of human cancers, and represent a promising target given their role in oncogenesis and high prevalence across various histologies.[6] Oncogenic KRAS mutations reduce GTPase activity, which prolongs the duration of KRAS in the active GTP-bound state.[7] Mutations in *KRAS* most commonly involve codon 12 with KRAS^{G12C} being the third most common variant.[6,8] Therapeutic targeting of *KRAS* had long been hampered by difficulties in identifying structural and chemical vulnerabilities for adequate drug binding, until the discovery of compounds which were able to covalently bind the switch-II pocket in KRAS^{G12C}-mutant preclinical models.[9] This important discovery led to the development of orally bioavailable irreversible inhibitors of KRAS^{G12C} which have moved into the clinic. The agents which have advanced the furthest in clinical development, sotorasib and adagrasib, have been predominantly evaluated in patients with NSCLC and colorectal cancer (CRC) where the estimated prevalence of KRAS^{G12C} mutations is among the highest (9%-13% and 3%, respectively).[8,10]

In KRAS^{G12C}-mutated NSCLC, sotorasib and adagrasib administered as a single agent were associated with response rates of 37% and 43%, respectively; moreover, sotorasib has demonstrated superiority over docetaxel with respect to median progression-free survival (PFS) (5.6 versus 4.5 months, $P < 0.01$) in previously treated cases.[11-13] In CRC, the single-agent activity of sotorasib and adagrasib was not as robust due to adaptive feedback mediated by EGFR.[14-16] Concurrent blockade of EGFR and KRAS^{G12C} in CRC has been a more successful strategy, resulting in response rates mirroring single-agent activity in NSCLC and highlights the need for histology-specific and histology-agnostic resistance mechanisms to be systematically addressed similar to the BRAF^{V600E} story.[5,15,17] Importantly, both KRAS^{G12C} agents are well tolerated with a manageable toxicity profile and both have achieved regulatory approval for NSCLC.

Beyond NSCLC and CRC, a small but significant percentage of pancreatic cancers, biliary tract cancers, intestinal cancers, and gynecologic malignancies among others harbor mutations in KRAS^{G12C} (Figure 1). In the phase I/II CodeBreaK 100 study evaluating sotorasib in advanced solid tumors with a KRAS^{G12C} mutation, 28 patients with advanced solid tumors other than NSCLC and CRC were enrolled among which four responses were noted (one pancreatic cancer, one endometrial cancer, one appendiceal cancer, and one melanoma).[18] In pooled results from the CodeBreaK 100 study evaluating sotorasib in patients with advanced pancreatic cancer, 8 of 38 patients (21%) achieved a confirmed response with a median PFS of 4.0 months.[19] This was the largest study demonstrating activity of KRAS^{G12C} inhibition in a tissue histology other than NSCLC and CRC, and supported the principle that KRAS^{G12C} can be evaluated as a tissue-agnostic target. On the basis of demonstrated activity of KRAS^{G12C} inhibition in multiple tumor types, pan-cancer evaluation of adagrasib was conducted and recently published in the *Journal of Clinical Oncology*.[20]

In a single-arm phase II cohort of the KRYSTAL-1 study, Bekaii-Saab et al. evaluated adagrasib administered as a single agent in patients with advanced solid tumors other than NSCLC and CRC harboring a KRAS^{G12C} mutation as

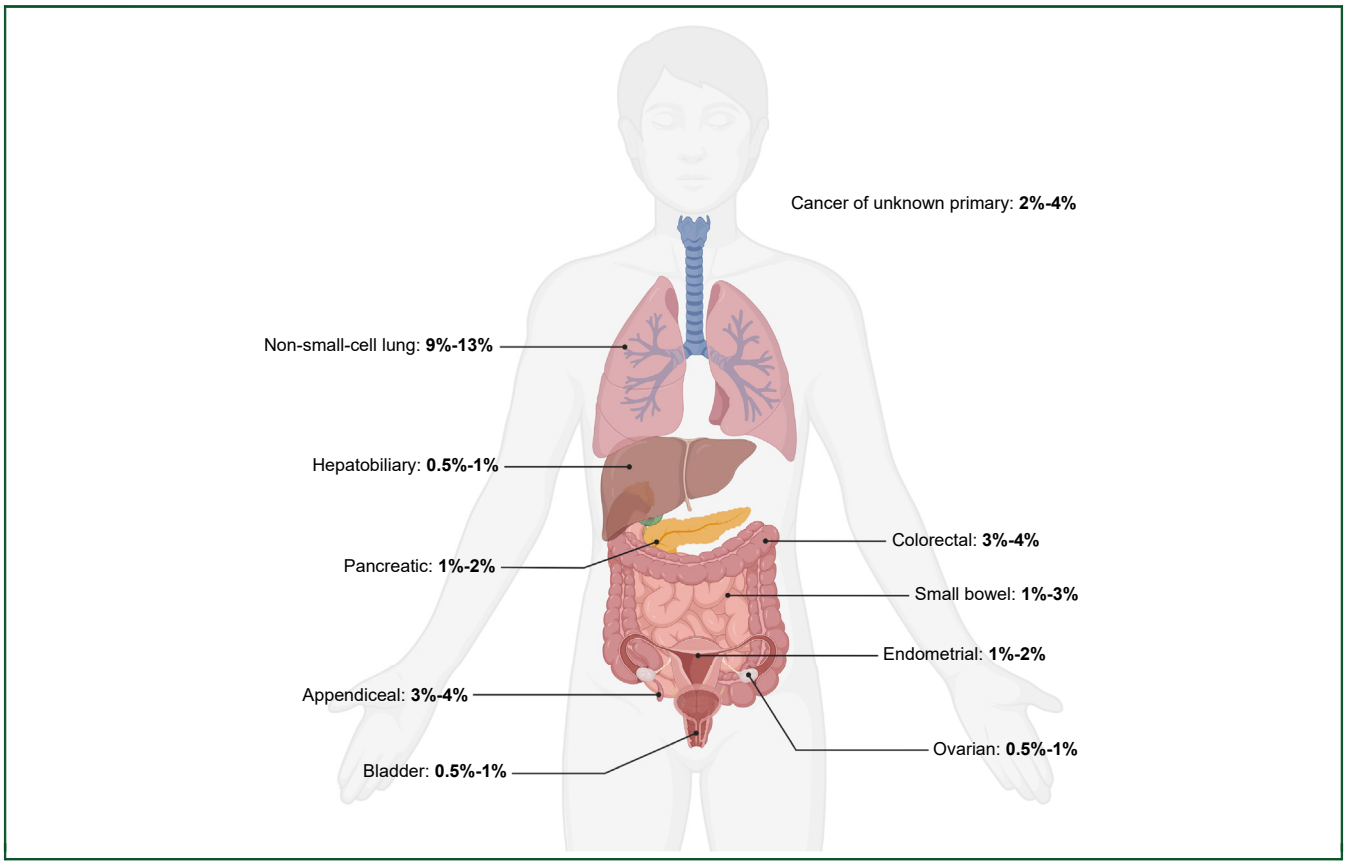

Figure 1. Incidence of KRAS^{G12C} across tumor histologies. The figure displays the estimated incidence of KRAS^{G12C} across various tumor histologies based on genomic sequencing data from large datasets.

identified on NGS of the tissue or blood. In total, 64 patients with mostly treatment-refractory disease were enrolled, of which the most common malignancies included pancreatic cancer ($n = 21$), biliary tract cancer ($n = 12$), and appendiceal cancer ($n = 10$); however, patients with gynecologic malignancies such as ovarian cancer ($n = 5$) and endometrial cancer ($n = 3$) were also included. Among 57 patients with measurable disease, the overall response rate was 35.1%, median PFS was 7.4 months, and median overall survival was 14 months. High response rates were seen across typically treatment-resistant malignancies such as pancreatic cancer (33%), biliary tract cancer (42%), and gynecologic cancers (57%). The lone exception was appendiceal tumors in which no responses were observed. While the data are early, the results are promising given the limited availability of effective treatment options particularly for patients with pancreatic and hepatobiliary cancers where PFS with standard therapies in the second line is dismal.[21,22] In KRYSTAL-1, there were patients who were able to achieve disease control lasting >6 months which compares favorably to systemic chemotherapy. Importantly, the study confirms that KRAS^{G12C} is indeed a therapeutic vulnerability across multiple histologies and can be considered a tissue-agnostic target—a major milestone for precision medicine.

Unlike other approved tissue-agnostic therapies which produce deep and durable responses, however, acquired resistance to single-agent KRAS^{G12C} inhibition is nearly universal and often occurs with several months. Therefore, evidence of pan-cancer activity should not obfuscate relevant issues with respect to treatment resistance and the development of rational combinations. The differential response to single-agent KRAS^{G12C} inhibition between NSCLC and CRC is demonstrative; even though sotorasib and adagrasib have single-agent activity in CRC, combination with anti-EGFR antibodies clearly enhances antitumor activity. Likewise, adagrasib did not elicit a response in appendiceal tumors for reasons which warrant further exploration. This raises the possibility that histology or tumor-dependent resistance mechanisms are at play and need to be addressed in order to identify the most sensible combination strategies for each patient. Evaluation of matched tissue and blood samples from patients with NSCLC or CRC who developed resistance to adagrasib and sotorasib reveals diverse alterations including acquired secondary KRAS mutations, mutations in other receptor tyrosine kinase (RTK)—RAS—MAPK pathway members, and in some cases histologic transformation.[23,24] In one such study, gene fusions emerged after treatment with adagrasib exclusively in patients with CRC highlighting another potential tissue-specific pattern.[24] Translational efforts characterizing the patterns of resistance in a diverse array of tumor histologies will likewise be enlightening and are highly anticipated.

Despite the influence of tumor histology on response and acquired resistance, there is promise in tissue-agnostic

development of drug combinations targeting KRAS^{G12C}. Evidence that sotorasib increases T-cell priming and antigen recognition and displays synergy with immune checkpoint inhibitors has prompted evaluation of immunotherapy combination strategies in the clinic, with promising results thus far.[25,26] Additionally, there may be other targets integral for RTK signaling across various histologies, such as SHP2, which are potential candidates for co-inhibition with KRAS^{G12C}.[27] Indeed preliminary evidence demonstrates encouraging activity of SHP2 and KRAS^{G12C} inhibition in preclinical tumor models from various tissue origins.[28] Of course, close monitoring for combined toxicity of these new combinations in the clinic will be essential.

The story of KRAS^{G12C} from the initial identification of the switch-II pocket to the regulatory approval of clinically active oral inhibitors is nothing short of remarkable. The encouraging pan-cancer efficacy results published by Bekaii-Saab et al. and the Krystal-1 investigators almost certainly confirm that KRAS^{G12C} is a clinically relevant, tissue-agnostic target which represents a triumph for personalized cancer care. With this success, the focus now shifts to both tissue-specific and tissue-agnostic strategies which can enhance the activity of KRAS^{G12C} inhibitors.

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REFERENCES

1. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA approval summary: pembrolizumab for the treatment of microsatellite instability-high solid tumors. *Clin Cancer Res*. 2019;25(13):3753-3758.
2. Marcus L, Fashoyin-Aje LA, Donoghue M, et al. FDA approval summary: pembrolizumab for the treatment of tumor mutational burden—high solid tumors. *Clin Cancer Res*. 2021;27(17):4685-4689.
3. Gouda MA, Nelson BE, Buschhorn L, Wahida A, Subbiah V. Tumor-agnostic precision medicine from the AACR GENIE database: clinical implications. *Clin Cancer Res*. 2023. https://doi.org/10.1158/1078-0432.CCR-23-0090.
4. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol*. 2022;23(10):1261-1273.
5. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. *Nat Med*. 2023;29(5):1103-1112.
6. Prior IA, Hood FE, Hartley JL. The frequency of Ras mutations in cancer. *Cancer Res*. 2020;80(14):2969-2974.
7. Kim D, Xue JY, Lito P. Targeting KRAS(G12C): from inhibitory mechanism to modulation of antitumor effects in patients. *Cell*. 2020;183(4):850-859.
8. Salem ME, El-Refai SM, Sha W, et al. Landscape of *KRAS*^{G12C}, associated genomic alterations, and interrelation with immuno-oncology biomarkers in *KRAS*-mutated cancers. *JCO Precis Oncol*. 2022;6:e2100245.
9. Janes MR, Zhang J, Li L-S, et al. Targeting KRAS mutant cancers with a covalent G12C-specific inhibitor. *Cell*. 2018;172(3):578-589.e17.
10. Nassar AH, Adib E, Kwiatkowski DJ. Distribution of *KRAS*^{G12C} somatic mutations across race, sex, and cancer type. *N Engl J Med*. 2021;384(2):185-187.
11. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with *KRAS* p.G12C mutation. *N Engl J Med*. 2021;384(25):2371-2381.
12. Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non-small-cell lung cancer harboring a *KRAS*^{G12C} mutation. *N Engl J Med*. 2022;387(2):120-131.
13. de Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRAS^{G12C} mutation: a randomised, open-label, phase 3 trial. *Lancet*. 2023;401(10378):733-746.
14. Fakih MG, Kopetz S, Kuboki Y, et al. Sotorasib for previously treated colorectal cancers with KRAS^{G12C} mutation (CodeBreaK100): a prespecified analysis of a single-arm, phase 2 trial. *Lancet Oncol*. 2022;23(1):115-124.
15. Yaeger R, Weiss J, Pelster MS, et al. Adagrasib with or without cetuximab in colorectal cancer with mutated *KRAS* G12C. *N Engl J Med*. 2023;388(1):44-54.
16. Amodio V, Yaeger R, Arcella P, et al. EGFR blockade reverts resistance to KRAS^{G12C} inhibition in colorectal cancer. *Cancer Discov*. 2020;10(8):1129-1139.
17. Gouda MA, Subbiah V. Precision oncology for BRAF-mutant cancers with BRAF and MEK inhibitors: from melanoma to tissue-agnostic therapy. *ESMO Open*. 2023;8(2):100788.
18. Hong DS, Fakih MG, Strickler JH, et al. KRAS^{G12C} inhibition with sotorasib in advanced solid tumors. *N Engl J Med*. 2020;383(13):1207-1217.
19. Strickler JH, Satake H, George TJ, et al. Sotorasib in *KRAS* p.G12C—mutated advanced pancreatic cancer. *N Engl J Med*. 2023;388(1):33-43.
20. Bekaii-Saab TS, Yaeger R, Spira AI, et al. Adagrasib in advanced solid tumors harboring a KRAS^{G12C} mutation. *J Clin Oncol*. 2023. https://doi.org/10.1200/JCO.23.00434.
21. Lamarca A, Palmer DH, Wasan HS, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol*. 2021;22(5):690-701.
22. Wang-Gillam A, Li C-P, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet*. 2016;387(10018):545-557.
23. Zhao Y, Murciano-Goroff YR, Xue JY, et al. Diverse alterations associated with resistance to KRAS(G12C) inhibition. *Nature*. 2021;599(7886):679-683.
24. Awad MM, Liu S, Rybkin II, et al. Acquired resistance to KRAS^{G12C} inhibition in cancer. *N Engl J Med*. 2021;384(25):2382-2393.
25. Canon J, Rex K, Saiki AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature*. 2019;575(7781):217-223.
26. Frontline promise for adagrasib—pembrolizumab combination. *Cancer Discov*. 2023;13(2):OF2.

27. Ruess DA, Heynen GJ, Ciecielski KJ, et al. Mutant KRAS-driven cancers depend on PTPN11/SHP2 phosphatase. *Nat Med*. 2018;24(7):954-960.

28. Ryan MB, Fece de la Cruz F, Phat S, et al. Vertical pathway inhibition overcomes adaptive feedback resistance to KRASG12C inhibition. *Clin Cancer Res*. 2020;26(7):1633-1643.