Targeting KRAS – a developmental therapeutic highlight

KRAS, part of the Ras superfamily, is an oncogene that is mutated in a significant portion of cancer cases. The protein functions as a GTPase, acting as a molecular switch that regulates cell proliferation, growth, and survival. Mutations in KRAS are associated with poor prognosis. Targeting the KRAS protein has been a substantial hurdle for many years. The clinical landscape of KRAS-targeted therapies has recently seen promising developments (1). Swissmedic's approval of sotorasib, a drug specifically targeting the $KRAS^{G12C}$ mutation, marks a significant milestone, as this has become a new 2nd-line treatment option in $KRAS^{G12C}$ mutated metastatic non-small cell lung cancer (NSCLC). Here, we summarize a phase 1 study, presented at the ESMO annual meeting 2023, of a promising new panRAS inhibitor.

Phase 1 study of RMC-6236 in patients with KRAS Mutant Pancreatic Ductal Adenocarcinoma (PDAC) and Non-Small Cell Lung Cancer (NSCLC)

The novel molecule RMC-6236 is an orally administered non-covalent RAS^{MULTI}(ON) inhibitor. It is uniquely selective for the active GTP-bound RAS proteins for both the mutant and the wild-type variants. Preclinical studies of RMC-6236 have shown tumor regressions, especially in PDAC and NSCLC with $KRAS^{G12X}$ mutations.

Pretreated patients with advanced PDAC and NSCLC harboring $KRAS^{G12X}$ mutations were included in the trial. Patients with $KRAS^{G12C}$ mutated tumors were not included, as there was already an existing approved treatment with sotorasib. Further eligibility criteria included ECOG performance status of 0-1 and no active brain metastases. The primary endpoints of this dose-escalation study were safety, tolerability, and anti-tumor activity.

A total of 46 NSCLC patients with a median age of 65 years and 2 (1-6) median prior therapies were included. Regarding the PDAC, 65 patients with a median age of 64 and with a median of 3 (1-7) prior therapy lines were included. The most prevalent mutations were G12D, G12V and G12R. The dose was escalated from 10 mg up to 500 mg and 220 mg was found to be the dose-limiting toxicity dose. A dose of 200 mg was selected for optimization.

The most common treatment-related adverse events (TRAEs) included rash (81 %), nausea (46 %), diarrhoea (39 %), vomiting (33 %), stomatitis (22 %) and fatigue (15 %). The severity of these events varied, but they were predominantly grade 1 or 2, and there were no fatal TRAEs.

In the group of NSCLC patients, the treatment with RMC-6236 showed a disease control rate (DCR) of 85 %. The DCR comprises of complete response, partial response, and stable disease. For PDAC patients, the DCR was 87 %. These responses were observed across several dose levels and $KRAS^{G12X}$ genotypes. Many patients are still continuing the treatment (2).

Conclusion

The molecule RMC-6236 is a promising new substance that demonstrates encouraging anti-tumor activity. Also, RMC-6236 seems to have a manageable adverse effect profile, which is only a little less favorable compared to sotorasib, apart from the rash (3). This is remarkable for an inhibitor of all active RAS proteins, where one would expect a worse adverse effect profile than a selective $KRAS^{G12X}$ inhibitor. Besides RMC-6236, there is currently a broad range of RAS inhibitors with different mechanisms of action being developed. This sparks a blend of optimism as after decades of research, KRAS has finally become a druggable target.

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