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Direct KRAS inhibition: progress, challenges and a glimpse into the future

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1.Introduction

In the modern era of biomarker-driven precision oncology, it is no surprise that the Kirsten rat sarcoma (KRAS) oncogene is topping the current list of our "most-wanted" targets. Developing an effective and well-tolerated targeted agent against KRAS is expected to have a significant impact on the lives of the largest, thus far, subgroup of cancer patients eligible for targeted treatment, and to herald a radical breakthrough in clinical oncology. This highly prevalent oncogenic driver, which is found in 86% of all RAS-mutated cancers and approximately represents one quarter of all malignancies, has remained elusive to our laborious efforts to tame it [1]. Despite initial promising results, either in the preclinical or early clinical trial stage, none of the experimental agents designed for direct or indirect targeting of KRAS mutant solid tumors has yet managed to cross the finish line of drug development and receive the sought-after FDA-approval.

2.The past and present of KRAS targeting: from the bench to the clinic

Smooth as a "tennis ball" [2], with no tractable and large enough allosteric pockets to enable binding of small molecules, the KRAS mutant protein had been, until recently, dismissed as an "undruggable" target, while several attempts to indirectly block its function, by inhibiting its downstream effectors, were similarly unsuccessful [3-5]. Thankfully, in 2013, Shokat and colleagues [6] identified a new allosteric binding site, Switch-II pocket (S-IIP), near the effector region of the KRAS(G12C) molecule, and used this pocket to develop mutation-specific irreversible inhibitors, thus renewing our hopes that direct KRAS targeting may not be an impossible mission after all [3]. This first "adult" step against KRAS was soon followed by the official declaration of a new war on RAS by the U.S. National Cancer Institute

[7], and a series of successful attempts to develop novel KRAS(G12C) inhibitors with improved potency and selectivity. Two lead compounds, AMG 510 (Amgen Inc., ClinicalTrials.gov identifier: NCT03600883), and MRTX849 (Mirati Therapeutics Inc., ClinicalTrials.gov Identifier: NCT03785249), are now well into the clinical trial arena, and preliminary phase 1/2 trial results attesting to their safety and anticancer activity in locally advanced or metastatic KRAS(G12C) mutant non-small cell lung cancer (NSCLC) and colorectal carcinoma (CRC) have been already announced, with lung cancer patients showing a much clearer benefit [8,9]. More specifically, three of six evaluable patients (50%) with NSCLC and one of four (25%) evaluable patients with CRC enrolled in the MRTX849 trial achieved a partial response (PR), while in the AMG 510 trial, 11 of 23 (48%) NSCLC patients and 1 of 29 (3,4%) CRC patients had PR [8,9]. PR rates in NSCLC reached 60% and 54% for MRT849 and AMG 510, respectively, among patients receiving the highest (target) drug dose. Given the sample size limitations of both studies at the latest cut-off date, especially the MRTX849 trial, caution is advised in interpretation or comparison of these early data, since response rates may be significantly altered with ongoing patient recruitment and inclusion of additional follow-up data. Currently, additional investigational KRAS(G12C) inhibitors are entering the clinical development phase: the first-in-human study of the safety, pharmacokinetics, pharmacodynamics and preliminary antitumor activity of JNJ-74699157 (Wellspring Biosciences and Johnson & Johnson, ClinicalTrials.gov identifier: NCT04006301) and the phase 1/2 trial of LY3499446 (Eli Lilly and Company, ClinicalTrials.gov identifier: NCT04165031), investigating its safety and efficacy as monotherapy and in combination with CDK or EGFR inhibition or cytotoxic chemotherapy, are currently recruiting patients (Table 1).

The discrepancy in treatment response between NSCLC and CRC may serve as a reminder of the multi-level biological heterogeneity of KRAS-mutant tumors [5], even among those sharing the same KRAS mutation subtype. Previous experimental data [10,11] have shown

that KRAS mutant tumors may not necessarily depend on KRAS for their survival and proliferation, and may be driven by other genetic alterations [2,12], thus further suggesting that targetable oncogenic drivers may be just the tip of the therapeutic iceberg. Molecular heterogeneity of KRAS(G12C)-mutant tumors due to divergent co-occurring mutations, KRAS-mutant allele amplification or loss of wild-type allele, may affect responses to mutation-specific inhibition, as previously hypothesized [13-15]. Specific co-mutation profiles, such as KRAS-STK11 and KRAS-KEAP1, have been associated with a worse prognosis in patients with KRAS-mutant NSCLC [5,16], while higher response rates of KRAS-TP53 co-mutant lung adenocarcinomas to PD-1 inhibition monotherapy –mainly as compared to those harboring a KRAS-STK11 co-mutation profile- have been consistently demonstrated [17,18]. Interestingly, STK11 co-mutation has been found to predict poor response to immune checkpoint inhibition (ICI), even in PD-L1 positive KRAS-mutant NSCLC [18]. Nevertheless, the potential predictive value of the above co-profiling data as biomarkers of response or resistance to mutation-specific inhibition among the entire spectrum of KRAS(G12C)-mutant tumors remains essentially unexplored.

Hallin et al [13], recently undertook a series of in vitro and in vivo investigations of MRTX849 antitumor activity and molecular predictors of response in KRAS(G12C) cell lines and patient-derived xenograft models. Although failing to demonstrate a clear association between individual or combined genetic alterations with treatment response, the study results revealed key molecular mechanisms and pathways implicated in partial or complete resistance to KRAS inhibitors, including the activation of receptor tyrosine kinases (RTKs), bypass of KRAS dependence or alteration of cell cycle regulators (such as CDKN2A or CDK4). Most importantly, enhancement of antitumor activity was observed following combination of KRAS(G12C) inhibitors with agents targeting RTKs (SHP2 inhibitors such as RMC-4550 or RTK inhibitors such as the pan-HER family inhibitor afatinib), mTOR (such as the mTOR inhibitors vistusertib and everolimus) or cell cycle regulators (such as the CDK4/6 inhibitor

palbociclib). Pending confirmation in future clinical trials, these findings may have significant therapeutic implications, suggesting the potential of combinatorial regimens guided by the specific co-mutation profile of tumors (e.g. combination of KRAS(G12C) inhibition with RTK or mTOR inhibition in the presence of STK11 co-mutations, or with CDK4/6 inhibitors in the presence of CDKN2A co-mutations [13].

3.Current challenges and future perspectives

As we are awaiting more mature trial data, it is far too early to predict the fate of KRAS(G12C) inhibitors, and whether they will ultimately make their way to routine clinical practice or not. Undoubtedly, there is more hope now than in decades, and this is no small victory in our war against RAS. With the myth of the "undruggable" KRAS now debunked, the first barrier to direct targeting of this lethal oncogene has been overcome. Still, there are more challenges further down the road, which may prove equally if not more resistant to attack.

First and foremost, the KRAS(G12C) mutation targeted by currently available inhibitors represents a relatively small minority (approximately 11%) of the entire KRAS mutation spectrum, and is clinically relevant mainly for NSCLC, where its highest prevalence (13%) is found, while it is less frequent in colorectal cancer (3-5%), and extremely rare or almost non-existent in other solid tumors. Targeting of additional KRAS mutation subtypes, such as KRAS(G12D) or KRAS (G12V) mutations which predominate in KRAS-mutant pancreatic ductal adenocarcinoma [19], remains an unmet clinical need of high priority, as pointed out by others [20]. Killing all KRAS mutants with one drug, targeting a wide range of KRAS mutant alleles, might be the ideal strategy to address this gap. The novel pan-KRAS inhibitor BI 1701963 (Boehringer Ingelheim Inc.), designed to block SOS1, a guanine nucleotide exchange factor (GEF) involved in activation of RAS, is currently evaluated in a phase I trial [ClinicalTrials.gov identifier: NCT04111458], both as monotherapy and in combination with

the MEK inhibitor trametinib, for treatment of patients with advanced-stage solid tumors harboring all major KRAS mutations subtypes, including not only G12C but also G12D, G12V,G13D and G12S mutations [21].

Effectiveness of KRAS inhibition will also need to be evaluated within the context of combinatorial regimens including immunotherapy, particularly in solid tumors such as KRAS-mutant NSCLC which has been shown to display increased intrinsic sensitivity –as compared to wild-type KRAS NSCLC- to ICI [5]. Provided that the favorable toxicity profile of currently available covalent KRAS inhibitors, shown in early phase trials, is confirmed in larger scale clinical studies, these agents may be ideal candidates for combination with ICI; the latter may boost therapeutic efficacy to KRAS inhibition and augment overall response rates, as already shown in mouse studies [8]. In a study of immunocompetent mice with KRAS(G12C)-injected tumors, combination of the KRAS(G12C) inhibitor AMG 510 with ICI significantly enhanced treatment efficacy, as compared to monotherapy with either agent, leading to complete and durable responses in 90% of mice treated [8]. A phase 1 trial, evaluating the safety and efficacy of AMG 510, as monotherapy and in combination with various other agents including –but not limited- to ICI, i.e. MEK, PD-1, SHP2, or Pan-ErbB tyrosine kinase inhibitors, respectively, is currently recruiting patients with KRAS(G12C) mutant solid tumors of advanced stage [ClinicalTrials.gov identifier: NCT04185883]. The comparative efficacy of AMG 510 versus cytotoxic chemotherapy (docetaxel) in patients with KRAS(G12C)-mutant NSCLC will also be investigated in a phase 3 trial [ClinicalTrials.gov identifier: NCT04303780], signaling the transition of KRAS(G12C) inhibitors into the late clinical development phase (Table 1).

As the KRAS field will continue to expand, an increasing number of experimental compounds for direct or indirect KRAS targeting will be introduced in the developmental pipeline. Inevitably, emergence of acquired resistance to any first-line approach targeting KRAS may represent the last, but not least of all potential barriers, and timely planning of strategies to

delay or circumvent this event is indispensable to achieve clinically significant and durable responses. A recent preclinical study by Ryan et al [22], investigating the mechanisms of adaptive resistance to treatment with the KRAS(G12C) inhibitors ARS-1620 and AMG 510, both *in vitro* and *in vivo*, revealed that feedback reactivation of RAS signaling was mainly driven by compensatory activation of wild-type RAS (which is not affected by G12C inhibition). Furthermore, this process was found to be mediated by several RTKs (EGFR, HER2, FGFR and c-MET) which varied significantly among different KRAS(G12C) cell line models, while RAS signaling suppression was restored most efficiently with combined G12C and SHP2 inhibition. Co-targeting of KRAS(G12C) and SHP2 may represent a promising strategy to postpone or overcome adaptive resistance to mutation-specific inhibition and has already entered the clinical trial phase.

4. Conclusions

Direct mutation-specific KRAS targeting through covalent inhibition may represent the most promising of all available therapeutic approaches, but is currently applicable only in a small subset of KRAS mutant tumors, i.e. those harboring KRAS(G12C) mutation. Other approaches, such as pan-KRAS compounds or combinations of covalent KRAS inhibition with ICI therapy or targeted agents such as MEK, SHP2, CDK, EGFR or multi-RTK inhibitors are under rigorous clinical trial evaluation, and, if successful, will further expand our therapeutic options in this challenging clinical setting. With time, accumulation of additional clinical data and increasing understanding of the molecular mechanisms underlying discrepant treatment responses, as well as intrinsic and adaptive resistance to KRAS inhibition among the heterogeneous KRAS-mutant population, the treatment landscape will continue to evolve. Personalization of targeted treatments against KRAS, stratified in accordance to clinicopathological and molecular predictors which remain to be more clearly delineated, remains the “Holy Grail” of precision oncology. And although our battle against RAS is still in

its infancy, we have every reason to hope that the best is yet to come.

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Declaration of interest

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TABLE 1: Ongoing clinical trials evaluating the efficacy of covalent KRAS(G12C) inhibitors as monotherapy or in combination with other agents in advanced solid tumors

Trial Identifier (NCT number)	Study Title	Drug(s)	Phase	Status
KRAS(G12C) inhibition as monotherapy				
NCT04006301	*First-in-Human Study of JNJ-74699157 in Participants With Tumors Harboring the KRAS G12C Mutation*	JNJ-74699157 (KRASG12C inhibitor)	1	Recruiting
NCT03785249	*Phase 1/2 Study of MRTX849 in Patients With Cancer Having a KRAS G12C Mutation*	MRTX849 (KRASG12C inhibitor)	1/2	Recruiting
NCT03600883	*A Phase 1/2 Study Evaluating the Safety, Tolerability, PK, and Efficacy of AMG 510 in Subjects With Solid Tumors With a Specific KRAS Mutation (CodeBreak 100)*	AMG 510 (KRASG12C inhibitor)	1/2	Recruiting
KRAS(G12C) inhibition combined with other agents				
NCT04185883	AMG 510 Activity in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation (CodeBreak 101)	AMG 510 +MEK inhibitor ***OR*** AMG 510 +PD-1 inhibitor ***OR*** AMG 510 +SHP2 inhibitor ***OR*** AMG 510 +Pan-ErbB tyrosine kinase inhibitor	1	Recruiting
NCT04165031	A Study of LY3499446 in Participants With Advanced Solid Tumors With KRAS G12C Mutation	LY3499446 (KRASG12C inhibitor) as monotherapy ***OR*** LY3499446+Abemaciclib (KRASG12C+CDK inhibitor) ***OR*** LY3499446+Cetuximab (KRASG12C+EGFR inhibitor) ***OR*** LY3499446+Erlotinib (KRASG12C+EGFR inhibitor) ***OR*** LY3499446+Docetaxel	1/2	Recruiting
NCT04330664	*Phase 1/2 Study of MRTX849 Plus TNO155 in Patients With Cancer Having a KRAS G12C Mutation*	MRTX849+TNO155 (KRASG12C+SHP2 inhibitor)	1/2	Not yet recruiting
NCT04303780	Study to Compare AMG 510 "Proposed INN Sotorasib" With Docetaxel in Non Small Cell Lung Cancer (NSCLC) (CodeBreak 200).	AMG 510 ***VERSUS*** Docetaxel	3	Not yet recruiting