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NEWS

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A NEW ERA OF FIBROBLAST GROWTH FACTOR RECEPTOR INHIBITION IN CHOLANGIOCARCINOMA

Management of cholangiocarcinomas (CCAs) has significantly changed since the identification of targetable alterations such as isocitrate dehydrogenase-1 (*IDH-1*) mutations, fibroblast growth factor receptor-2 (*FGFR2*) fusions, human epidermal growth factor-2 (HER-2) amplifications, and B-Raf proto-oncogene serine/threonine kinase (*BRAF*) V600E mutations, among others.[1] Latest ESMO guidelines do recommend carrying out molecular profiling for patients diagnosed with CCA as soon as advanced disease is identified, to be able to plan adequately for subsequent lines of therapies at the time of progression to first-line treatment.[2]

Since the identification of FGFR2 as a potential target, many FGFR inhibitors have been developed in CCA and other solid tumors, targeting FGFR2 mutations, amplifications, and fusions. Within the molecules explored (most being small-molecule tyrosine kinase inhibitors), there are differences in their structure, mechanisms of target engagement, and specificities for FGFR1-4 (Table 1). First-generation FGFR inhibitors were characterized by not being FGFR specific, thus producing off target toxicity. Derazantinib[4] is one of the examples.

A second generation of tyrosine kinase inhibitors, with selective FGFR inhibition, was developed with promising results. This second generation was able to inhibit FGFR with a reversible and ATP-competitive binding. Most of them are pan-FGFR inhibitors, even though they tend to be more specific for FGFR2 over FGFR1, 3, and 4. Compounds within this group include erdafitinib,[3] pemigatinib,[5] and infigratinib,[6] among others. Response rates of 23.1% and 35.5% for infigratinib and pemigatinib, respectively, were reported in phase II studies recruiting patients with advanced CCA with FGFR2 fusions who had progressed to prior chemotherapy. Based on these results, these two compounds were approved (accelerated approval pending confirmatory data for full approval) by regulatory agencies [pemigatinib was approved by the Food and Drug Administration (FDA) in 2020 and by the European Medicines Agency (EMA) in 2021, while infigratinib was initially approved by the FDA in 2021, but the approval was withdrawn in 2022] for patients with CCA harboring FGFR2 fusion/rearrangement. Unfortunately, their activity in CCA for FGFR amplifications and mutations has not been too promising.

The activity of the second-generation inhibitors summarized above seems to be superior to second-line chemotherapy options such as FOLFOX [objective response rate (ORR) of 5%].[12] However, whether the activity of these inhibitors could be improved by the development of a third generation of compounds with a covalent and irreversible binding to the ATP site is currently being tested. These are irreversible inhibitors, such as futibatinib and RLY-4008 (lirafugratinib). Futibatinib is in more advanced stages of development. It is an oral, irreversible, highly selective pan-FGFR (FGFR1-4) inhibitor. Futibatinib was tested in a phase II study recruiting 108 patients diagnosed with chemotherapy-refractory CCA with FGFR2 fusion/rearrangements who received futibatinib treatment (20 mg once daily).[7] The reported ORR was 42% (95% confidence interval 32%-52%), which was slightly superior to the ones reported by second-generation FGFR inhibitors. The median progression-free survival (PFS) and overall survival were 9.0 and 21.7 months, respectively. Based on these data, futibatinib was approved (accelerated approval pending confirmatory data for full approval) by regulatory agencies in this indication (the FDA approved it in 2022, whereas the EMA approved it in 2023) with an ongoing confirmatory study currently open to recruitment.

The second third-generation inhibitor under development is RLY-4008, an irreversible FGFR inhibitor, but what seems to differentiate it from futibatinib is that it is highly selective for FGFR2, which may have a beneficial impact on both toxicity profile and activity. RLY-4008 has reported the highest ORR to date, with an 88% response rate for chemotherapy-resistant, FGFR-naïve CCA with FGFR2 fusion/rearrangement (17 patients) at the recommended phase II dose of 70 mg once daily.[8] Longer follow-ups and an increased number of patients are required to confirm these results. Its activity is currently being explored in other FGFR2 alterations (mutations/amplifications) and also in progression to other FGFR inhibitors. In June 2023, Subbiah and colleagues[13] published a research article summarizing the design and preclinical development of RLY-4008. The rationale at the time of development of this new compound was as follows. First, to maximize the response to FGFR inhibitors by targeting FGFR2 selectively, avoiding off-target FGFR-related dose-limiting toxicities such as hyperphosphatemia (FGFR1) and diarrhea (FGFR4). Second, for this binding to be potent and irreversible, to maximize activity. Third, to overcome the mechanism of primary and secondary resistance to other FGFR inhibitors such as the emergence of acquired FGFR2-resistance kinase domain mutations at the gatekeeper residue (FGFR2V564F/L/I) as well as FGFR2N549K/D/H and FGFR2K659N/M mutations that promote ligand-independent kinase activation to explore RLY-4008 as salvage therapy after progression to prior FGFR inhibitor.

Based on the results presented, RLY-4008 is the first highly selective, irreversible, small-molecule FGFR2

Table 1. Summary of FGFR inhibitors that are currently under advanced development, with special focus on CCA.

Generation of FGFR inhibitor	Compound	FGFR specificity		FGFR2 specificity		Type of inhibition		Clinical outcomes				Current development
		Other kinase inhibition	FGFR specific	Pan-FGFR	FGFR2 specific	Reversible inhibitor	Irreversible inhibitor	Population tested	ORR	Reference	Approval status	
1st	Derazantinib	No	*Yes*	**Yes**	No	**Yes**	No	CCA FGFR2 f/r	20.7%	[4]	—	—
2nd	Erdafitinib	No	*Yes*	**Yes**	No	**Yes**	No	Solid tumors, FGFR1-4 alterations	30.0%	[3]	—	—
2nd	Pemigatinib	No	*Yes*	**Yes**	No	**Yes**	No	CCA FGFR2 f/r	35.5%	[5]	*FDA/EMA CCA FGFR2 f/r*	Pending confirmatory data (phase III first-line fFGFR2 CCA) NCT03656536
2nd	Infigratinib	No	*Yes*	**Yes**	No	**Yes**	No	CCA FGFR2 f/r	12.3%	[6]	**Withdrawn**	—
3rd	Futibatinib	No	*Yes*	**Yes**	No	No	*Yes*	CCA FGFR2 f/r	42%	[7]	*FDA/EMA CCA FGFR2 f/r*	Pending confirmatory data (phase II second-line fFGFR2 CCA) NCT05727176
3rd	RLY-4008 (Lirafugratinib)	No	*Yes*	No	*Yes*	No	*Yes*	CCA FGFR2 f/r	88%	[8]	—	Pending confirmation of activity, ongoing phase I/II NCT04526106
3rd	KIN-3248	No	*Yes*	**Yes (FGFR2-3)**	No	No	*Yes*	Solid tumors, FGFR2-3 alterations	TBD	[9]	—	Ongoing phase I NCT05242822
TBD	TT-00420 (Tinengotinib)	**Yes**	No	**Yes (FGFR1-3)**	No	**Yes**	No	Solid tumors, FGFR alterations	16.7%	[10,11]	FDA fast-track designation for CCA	Ongoing phase III in FGFR-refractory fFGFR2 CCA

RLY-4008 seems to provide a unique mechanism of action with potent and irreversible specific FGFR2 inhibitions which seems to translate on high ORR.
In bold are the 'unfavorable factors' and in italics are the 'favorable factors'.
CCA, cholangiocarcinoma; EMA, European Medicines Agency; f, fusion; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; f/r, fusion or rearrangement; ORR, objective response rate; TBD, to be determined.

inhibitor specifically designed to overcome the limitations of pan-FGFR inhibitors via targeting of oncogenic FGFR2 alterations and resistance mutations. This could explain the high ORR reported in their first 17 patients. However, this clinical activity requires confirmation in larger cohorts with longer follow-ups. Besides, other FGFR inhibitors are being developed to overcome resistance. KIN-3248 is a selective, irreversible pan-FGFR inhibitor able to inhibit secondary kinase domain mutations associated with progression to FGFR inhibitors, in addition to the wild-type (WT) form. It is of particular interest for gatekeeper mutations such as V565F and molecular brake mutations such as N550K, both resistant to pemigatinib, infigratinib, and futibatinib. KIN-3248 is currently being tested in phase I dose escalation for solid tumors harboring FGFR2 and/or FGFR3 gene alterations.[9] Tinengotinib (TT-00420), a spectrum-selective multikinase inhibitor that targets cell proliferation, angiogenesis, and immune-oncology pathways by inhibiting aurora kinases A/B, Janus kinases (JAK), and receptor tyrosine kinases [FGFRs, vascular endothelial growth factor receptors (VEGFRs)], is being tested on progression to approved FGFR inhibitor in FGFR2 fusion/rearrangement-positive CCA in an ongoing phase III clinical trial compared with physician's choice of treatment.[10,11] Other selective and pan-FGFR inhibitors are entering the clinic to broaden our understanding of FGFR inhibitor resistance and increase our therapeutic potential.

Pan-KRAS inhibitor disables oncogenic signaling and tumor growth

KRAS mutations are among the most frequent gain-of-function alterations across solid tumors. KRAS activation depends on a GTPase cycle between an active (GTP-bound) and an inactive (GDP-bound) state. During the last few years, the development of targeted agents able to block KRAS G12C mutant tumors has opened new options for patients diagnosed with advanced cancers. Therefore several efforts to identify compounds that enable broad inhibition of KRAS mutants, beyond KRAS G12C, are ongoing. In general, the most prevalent non-G12C KRAS mutants found in cancer are thought to be deficient in GTPase-activating protein (GAP)-assisted GTP hydrolysis and exist in a non-excitable or constitutively active state. Thus, it is not clear whether the inactive-state selective trapping mechanism afforded by covalent G12Ci will work against non-G12C mutants.[14]

In an interesting article published in *Nature* by Kim et al.,[14] the authors described the potential role of a novel compound able to act like a pan-KRAS inhibitor (KRASi) that does not discriminate between KRAS-mutant variants. In this relevant project, the investigators removed the covalent warhead from the G12C-selective inhibitor BI-0474 and applied structure-based design optimizations to obtain a potent noncovalent inhibitory activity. Although the removal of the covalent warhead greatly reduced the potency of G12C inhibition, interestingly it was found that the warhead-free scaffold indiscriminately inhibited proliferation driven by the noted KRAS variants, albeit with a low potency. Extensive optimization of the compound led to the generation of BI-2865, which interestingly inhibited the proliferation of isogenic G12C-, G12D-, or G12V-mutant KRAS expressing BaF3 cells with high affinity. However, the drug prevented effector binding to active KRAS only at high concentrations. Their data also suggest that the drug's inhibitory activity in cells relies predominantly on targeting the inactive or GDP-bound state of KRAS. Furthermore, it was found that those compounds are selective against KRAS, spearing HRAS, and NRAS.

The authors next sought to determine, in an unbiased manner, the presence of other amino acids that allosterically modulate inactive-state selective KRAS inhibition. As expected from previous findings with covalent G12C inhibitors, mutations in residues defining the drug-binding pocket led to resistance and were positively selected by treatment. By comparison, mutations in residues at the interface of RAS-GDP and the catalytic subunit of SOS1 were negatively selected by treatment. The latter suggests that blockade of nucleotide exchange enhances the effect of treatment and is consistent with the inhibitory mechanism of the pan-KRASi. The presented data also indicate that rather than being fixed in an active state, common KRAS mutants undergo nucleotide cycling in cancer cells, which is necessary for the drug to access the GDP-bound conformation. The data also argue that KRAS mutants cycle with slower kinetics than WT KRAS. KRASi treatment inhibited extracellular signal-related kinase (ERK) and ribosomal S6 kinase (RSK) phosphorylation predominantly in KRAS-mutant models.

To further evaluate the effect on downstream signaling, and to identify transcripts and pathways immediately deregulated following KRAS inactivation, the authors carried out RNA sequencing across 22 different models. They ultimately found that KRASi treatment suppressed mitogen-activated protein kinase kinase (MEK)/ERK inhibitor (ERKi) downregulated genes while inducing MEK/ERKi upregulated genes in a panel of 274 cancer cell lines. Again, this effect was more pronounced in cells with mutant as compared with KRAS-amplified or WT cells. The antitumor effects were associated with favorable pharmacokinetic features as well as with a concordant inhibition of ERK phosphorylation and DUSP6 messenger RNA expression in tumor models.

The pan-KRASi developed works by preferentially targeting the inactive state of KRAS to prevent its reactivation by nucleotide exchange. In cells with mutant KRAS, this led to suppressed downstream signaling and cancer cell growth, suggesting that common KRAS mutants found in cancer depend on nucleotide exchange for activation. In cells with WT KRAS, drug treatment led to an increase in the activation of other RAS isoforms, which limit the antiproliferative effect of treatment. Selective inhibition of KRAS, while sparing HRAS and NRAS, is likely to produce a wide therapeutic index in the clinic. The results of clinical data across cancer patients are awaited.

BLOCKADE OF CYTOTOXIC T-LYMPHOCYTE PROTEIN 4 TO REVERT CLINICAL RESISTANCE TO PROGRAMMED CELL DEATH PROTEIN 1 INHIBITORS IN METASTATIC MELANOMA

A recent publication in *Nature Medicine* reports a phase II randomized trial in patients with metastatic melanoma who progressed after programmed cell death protein 1 (PD-1) blockade.[15] The purpose of this trial, which was designed when single-agent PD-1 blockade was considered as standard of care, was to explore the role of the addition to a cytotoxic T-lymphocyte protein 4 (CTLA-4) inhibitor (ipilimumab) to nivolumab to potentially revert intrinsic resistance to anti-PD-1 blockade. Patients progressing after PD-1 blockade, without achieving earlier a partial or a complete response, to avoid acquired resistance, were randomized in a 3 : 1 relation to nivolumab plus ipilimumab versus ipilimumab single agent. A series of translational studies including sequential tumor biopsies were carried out to monitor pharmacodynamic aspects related to treatment, such as the difference in CD8 T-cell infiltrates in responders versus nonresponders.

PFS was significantly prolonged in patients receiving the combination (hazard ratio 0.63; $P = 0.04$). This benefit was observed across all subgroups. The 6-month PFS estimate was 34% for the combination and only 13% for monotherapy. Moreover, the ORR in patients receiving the combination of nivolumab and ipilimumab was confirmed in 28% of them, while only 9% of those receiving single-agent ipilimumab responded ($P = 0.05$). As expected, grade $\geq$3 treatment-related adverse events were more commonly observed in the combination arm (57%) versus the single-agent arm (33%). However, the proportion of those that resulted in the end of therapy was similar for both arms. Changes in CD8 T-cell density were assessed by comparing biopsies taken before therapy and 4 weeks after treatment. No differences in CD8 T-cell density were observed between responders and nonresponders before starting treatment. By contrast, no differences in CD8 T-cell infiltration between baseline and on-treatment biopsies could be confirmed.

This study showed that primary resistance to PD-1 blockade can be efficiently reverted by the combination of CTLA-4 and PD-1 blockade in more than one-third of patients with melanoma nonresponding and progressing to single-agent PD-1 blockade. However, the biological hypothesis suggesting higher T-cell infiltration after CTLA-4 treatment could not be confirmed in this cohort of patients with melanoma. As a conclusion, this study justifies the combination of ipilimumab plus nivolumab in patients progressing after first-line single-agent nivolumab, rather than the use of CTLA-4 inhibitors as single agents. A significantly prolonged PFS and a better response rate have to be counterbalanced by the higher risk of severe treatment-related toxicities. These findings may also have some implications in other solid tumors different from melanoma and may deserve confirmation in second-line trials after progression with PD-1 blockade.

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