ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

EDITORIAL

Futibatinib: second EMA approval for FGFR inhibitor in cholangiocarcinoma

The binding of fibroblast growth factor (FGF) ligands to their respective receptors (FGFR) at the cell surface results in activation of downstream intracellular signalling pathways, including Ras-Raf-MAPK, PI3K-AKT-mTOR and JAK-STAT.[1] Dysregulation and hyperactivation of FGFR signalling is involved in cancer development and tumour progression and has been described to be present in around 9%-15% of cholangiocarcinoma (CCA).[2] Targeting FGFR alterations has become one of the cornerstones of precision medicine in advanced CCA[3] and is now a recognised option of treatment by most national and international guidelines.[4]

Multiple FGFR inhibitors have been developed for CCA and other solid tumours harbouring FGFR mutations, amplifications and fusions. Of special interest in CCA have been the FGFR2 inhibitors, specially targeting FGFR2 fusions and rearrangements.[3]

The compounds that are in the most advanced stage of development and which were explored specifically in CCA harbouring FGFR2 fusions are: infigratinib, pemigatinib and futibatinib.

These compounds were all tested in phase II studies after progression to prior chemotherapy. Response rates of 23.1%, 35.5% and 42% were reported for infigratinib,[5] pemigatinib[6] and futibatinib,[7] respectively. Based on these results, these compounds were approved (accelerated approval pending confirmatory data for full approval) by regulatory agencies: pemigatinib—Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved in 2020 and 2021, respectively; infigratinib—FDA approved in 2021, FDA withdrawn in 2022; and futibatinib—FDA approved in 2022, EMA approved in 2023.

While these approvals are fantastic news for our patients and their treating clinicians, they also come with some challenges.

Firstly, approval by regulatory agencies does not always mean reimbursement being in place. With the exception of some countries such as Germany where approval implies almost immediate reimbursement, the reality in most countries is that there is a significant delay in reimbursement from the time of drug approval, thus delaying access to effective treatments. According to the European Federation of Pharmaceutical Industries and Associations report on 'The root cause of unavailability and delay to innovative medicines',[8] 'the average time to reimbursement for innovative treatments across the European Union and European Economic Area countries continues to be as long as 511 days, ranging from 133 days in Germany to over 899 days in Romania'. Thus, 'patients in different countries can wait more than seven times longer than patients in other countries to get access to the same medicine'. 'There are some common patterns: typically, patients in Northern and Western Europe get access to new treatments between 100 and 200 days after market authorisation has been granted, whereas patients mainly in Southern and Eastern Europe wait between 600 and 1000 days. This means that at any point in time, availability of medicines varies dramatically across Europe'. Unfortunately, 'there is little evidence that delays are reducing—in fact, the contrary'. As of September 2023, some of the new therapies for the management of biliary tract tumouts that have been recently approved by regulatory agencies are still not available in many countries and access to these therapies remains a challenge despite proven activity and approval by the EMA and FDA (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.102049). This is not exclusive for FGFR inhibitors, and similar issues exist for other targeted therapies such as IDH1 inhibitors (ivosidenib)[9] or immunotherapy such as durvalumab.[10] In fact, similar issues have also been identified for accessing biomolecular technologies in oncology for molecular profiling and identification of patients who would derive benefit from these innovative treatments.[11] Futibatinib, recently approved, is currently only available in two countries (Figue 1A). This may be understandable, since it is only 62 days since the EMA approval of futibatinib to the time of developing Figue 1. It is, however, of very much concern to explore the situation of other FGFR inhibitors [such as pemigatinib (Figue 1A)], already approved by EMA for 914 days at the time of this figure development. As of September 2023, pemigatinib is reimbursed (excluding access through "named patient" or alternative "special" accesses) in 11 countries across Europe. In three countries (Netherlands, Spain and Sweden) re-negotiations are ongoing. Within the 11 countries with reimbursement in place, the median and mean time to such reimbursement from the time of EMA approval were 396 days and 360.4 days, respectively. In two countries the process took 610 days and in one up to 914 days. In contrast, Germany and Austria had immediate reimbursement following EMA approval. This variability in access to treatment is a significant source of inequity across countries and unethical for patients diagnosed with such

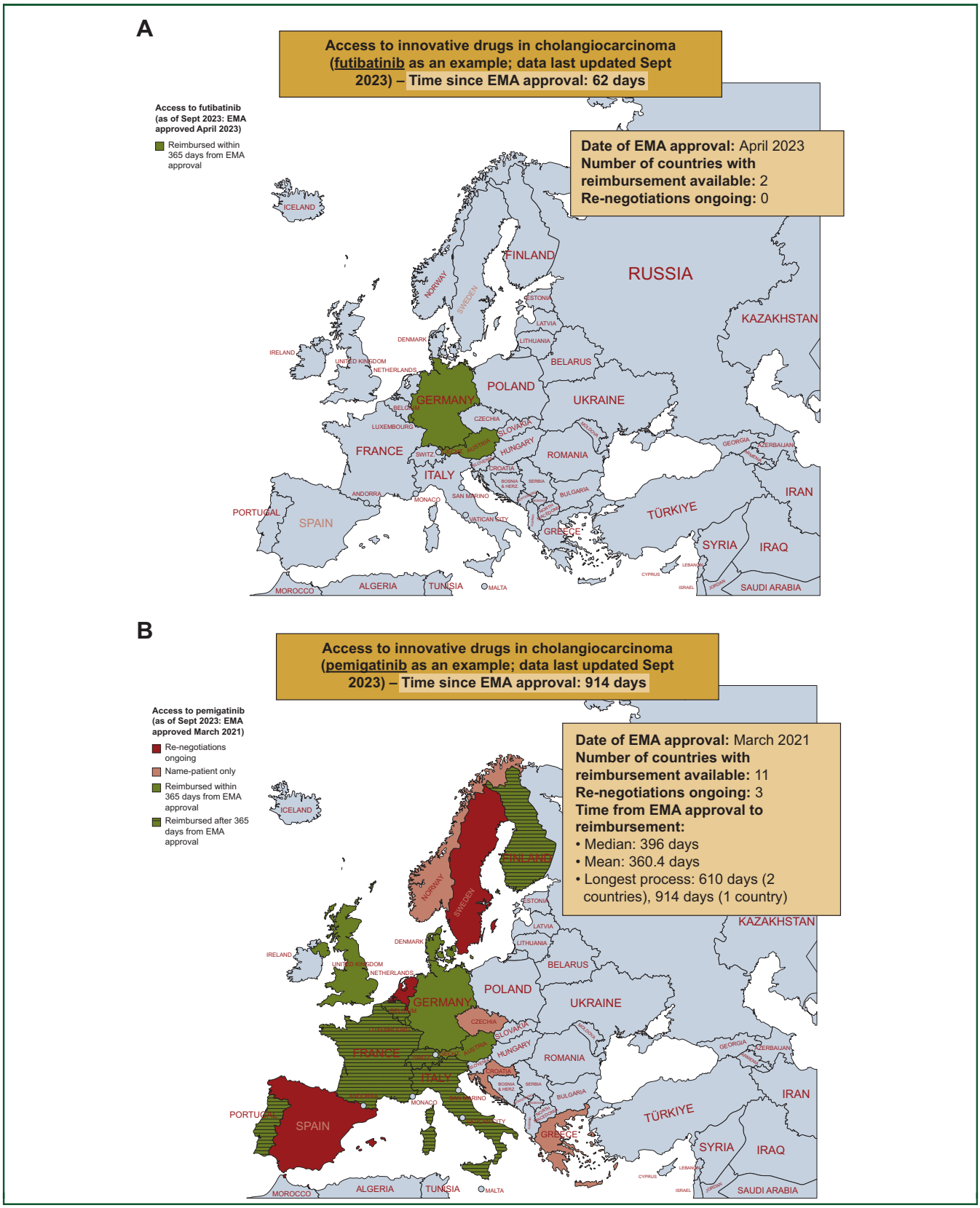

Figure 1. **Current access status to innovative drugs in cholangiocarcinoma; EMA-approved FGFR inhibitors are shown as examples (Plot A: futibatinib; Plot B: pemigatinib); data last updated in September 2023.**

aggressive cancers in desperate need of effective therapies.

Secondly, granted accelerated approval (which has been the case for FGFR inhibitors due to activity being based on non-randomised phase II studies) does require a confirmatory study for final approval. In order to meet these criteria, all compounds started recruitment in three very similar clinical trials, all of them being phase III randomised studies, in the first-line setting, comparing the FGFR inhibitor with cisplatin and gemcitabine chemotherapy. Slow recruitment led to premature closure of the PROOF-301 clinical trial (NCT03773302 with infigratinib) and the drug has been withdrawn from the market. Similarly, futibatinib's phase III (FOENIX-CCA3, NCT04093362) study in the first-line setting experienced severe recruitment challenges and the confirmatory study was modified into the randomised phase II FOENIX-CCA4 clinical trial (NCT05727176), now comparing two different doses of futibatinib after progression to chemotherapy. As of September 2023, FIGHT-302 with pemigatinib is the only one of the three confirmatory first-line phase III studies that is now ongoing with similar slow recruitment as it has been observed for the other studies (NCT03656536). Useful lessons are to be learned from these past experiences. The frequently small number of patients within genetic subgroups of rare tumours will inevitably lead to lengthy patient recruitment into classical phase III trials. The situation is aggravated when the respective drugs are available concomitantly in later-line settings and when several drugs with the same mechanism of action are tested in the same subgroup of the same tumour within early-phase clinical trials. These challenges substantially slow the pace at which new therapeutic drugs are approved and become widely available in clinical practice. Therefore, optimised design of meaningful clinical trials and strategies for approval from the regulatory agencies are urgently required to accelerate 'global' availability of effective treatments. With new FGFR inhibitors such as tinengotinib (TT-00420),[12] RLY-4008[13] and KIN-3248[14] under development, this will be an ongoing—never ending—challenge in the future.

Thirdly, with the increasing number of FGFR inhibitors available, sequencing of these compounds becomes a potential therapeutic strategy. While the response rate of futibatinib is slightly higher than the one reported by pemigatinib, futibatinib has also shown to have activity against some of the resistance mutations that may arise following treatment with pemigatinib. Thus futibatinib or any of the new FGFR inhibitors such as tinengotinib (TT-00420),[12] RLY-4008[15,16] and KIN-3248[14] may be an interesting option not only for FGFR inhibitor naive patients, but also as a salvage therapy after progression to other FGFR inhibitors.[17]

Finally, in order to reliably identify FGFR fusions, state-of-the-art molecular profiling is crucial. RNA-based next-generation sequencing (NGS) testing is strongly recommend and, in many cases, required to identify patients with FGFR2 fusions. In many countries, custom-made NGS panels are in use, which have a very high chance to end up on false-negative findings.[18] Therefore, a close interaction between clinicians and (molecular) pathologists is critically important to not only carry out NGS assays that are capable of detecting fusions, but also to interpret the results, which might be challenging due to the multiple genetic alterations that can be found in FGFR2.

Approval of new compounds, especially for aggressive malignancies with poor prognosis such as CCA where new therapies are urgently needed, is always welcome news. However, challenges arise at the time of making these therapies widely accessible to all patients. Current reimbursement and access to testing are challenging across many countries, deriving on significant imbalances depending on the country of residence.

A. Lamarca[1,2]* & A. Vogel[3,4]

[1]*Department of Medical Oncology — OncoHealth Institute, Fundación Jiménez Díaz University Hospital, Madrid, Spain;*
[2]*Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK;*
[3]*Toronto Centre for Liver Disease,Toronto General Hospital, University Health Network, Toronto;*
[4]*Medical Oncology, Margaret Cancer Centre, Toronto, Canada*
(*E-mail: angela.lamarca@quironsalud.es).

Available online xxx

https://doi.org/10.1016/j.esmoop.2023.102049

ACKNOWLEDGEMENTS

Dr Angela Lamarca received funding from the Spanish Society of Medical Oncology (SEOM) Fellowship Programme (Return Fellowship) and the European Union's Horizon 2020 Research.

FUNDING

None declared.

DISCLOSURE

AL declares travel and educational support from Ipsen, Pfizer, Bayer, AAA, SirtEx, Novartis, Mylan, Delcath Advanz Pharma and Roche; speaker honoraria from Merck, Pfizer, Ipsen, Incyte, AAA/Novartis, QED, Servier, AstraZeneca, EISAI, Roche, Advanz Pharma and MSD; advisory and consultancy honoraria from EISAI, Nutricia, Ipsen, QED, Roche, Servier, Boston Scientific, Albireo Pharma, AstraZeneca, Boehringer Ingelheim, GENFIT, TransThera Biosciences, Taiho and MSD; Principal Investigator-associated Institutional Funding from QED, Merck, Boehringer Ingelheim, Servier, AstraZeneca, GenFit, Albireo Pharma, Taiho, TransThera and Roche; she is also a member of the Knowledge Network and NETConnect Initiatives funded by Ipsen. AV declares honoraria for consultancy/advisory role and speaker role from AstraZeneca, Amgen, BeiGene, Böhringer

Mannheim, BMS, BTG, Daichi-Sankyo, EISAI, Incyte, Ipsen, MSD, PierreFabre, Roche, Servier, Sirtex, Tahio and Terumo.

REFERENCES

1. Hallinan N, Finn S, Cuffe S, Rafee S, O'Byrne K, Gately K. Targeting the fibroblast growth factor receptor family in cancer. *Cancer Treat Rev*. 2016;46:51-62.
2. Kendre G, Murugesan K, Brummer T, Segatto O, Saborowski A, Vogel A. Charting co-mutation patterns associated with actionable drivers in intrahepatic cholangiocarcinoma. *J Hepatol*. 2023;78:614-626.
3. Lamarca A, Barriuso J, McNamara MG, Valle JW. Molecular targeted therapies: ready for 'prime time' in biliary tract cancer. *J Hepatol*. 2020;73(1):170-185.
4. Vogel A, Bridgewater J, Edeline J, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34:127-140.
5. Javle M, Roychowdhury S, Kelley RK, et al. Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. *Lancet Gastroenterol Hepatol*. 2021;6(10):803-815.
6. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020;21(5):671-684.
7. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. *N Engl J Med*. 2023;388(3):228-239.
8. EFPIA The root cause of unavailability and delay to innovative medicines. EuroGCT [Internet]. Available at https://www.eurogct.org/efpia-root-cause-unavailability-and-delay-innovative-medicines. Accessed September 29, 2023.
9. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(6):796-807.
10. Oh DY, Ruth HA, Qin S, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. *NEJM Evidence*. 2022;1(8):EVIDoa2200015.
11. Bayle A, Bonastre J, Chaltiel D, et al. ESMO study on the availability and accessibility of biomolecular technologies in oncology in Europe. *Ann Oncol*. 2023;34(10):934-945.
12. Piha-Paul SA, Goel S, Liao CY, et al. Preliminary safety and efficacy of tinengotinib tablets as monotherapy and combination therapy in advanced solid tumors: a phase Ib/II clinical trial. *J Clin Oncol*. 2023;41.
13. Hollebecque A, Borad M, Goyal L, et al. Efficacy of RLY-4008, a highly selective FGFR2 inhibitor in patients (pts) with an FGFR2-fusion or rearrangement (f/r), FGFR inhibitor (FGFRi)-naïve cholangiocarcinoma (CCA): reFocus trial. *Ann Oncol*. 2022;33(suppl 7):S808-S869.
14. Franovic A, Mohan A, Uryu S, et al. Activity of KIN-3248, a next-generation pan-FGFR inhibitor, against acquired FGFR-gatekeeper and molecular-brake drug resistance mutations. *J Clin Oncol*. 2022;40(suppl 4).
15. Borad MJ, Schram AM, Kim RD, et al. Updated dose escalation results for ReFocus, a first-in-human study of highly selective FGFR2 inhibitor RLY-4008 in cholangiocarcinoma and other solid tumors. *J Clin Oncol*. 2023;41(suppl 16).
16. Subbiah V, Sahai V, Maglic D, et al. RLY-4008, the first highly selective FGFR2 inhibitor with activity across FGFR2 alterations and resistance mutations. *Cancer Discov*. 2023;13:2012-2031.
17. Goyal L, Shi L, Liu LY, et al. TAS-120 overcomes resistance to ATP-competitive FGFR inhibitors in patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma. *Cancer Discov*. 2019;9(8):1064-1079.
18. Bekaii-Saab TS, Bridgewater J, Normanno N. Practical considerations in screening for genetic alterations in cholangiocarcinoma. *Ann Oncol*. 2021;32(9):1111-1126.