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This Week's Top Global Headlines

The Anatomy of an Approval

For an adult with advanced cholangiocarcinoma who has already received treatment, the next therapeutic option may depend on a molecular result i.e., does the tumour harbour an FGFR2 fusion or other rearrangement?

On 23 September, FDA approved Lyrfigtu (lirafugratinib) for adults with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma with an FGFR2 gene fusion or other rearrangement. It is worth unpacking how the evidence for this approval was built.

There was no large randomized comparative trial. Instead, FDA evaluated the multicenter, open-label, single-arm REFOCUS study in 116 patients with unresectable or metastatic cholangiocarcinoma who had received prior chemotherapy or chemoimmunotherapy and had not previously received an FGFR inhibitor.

The major efficacy outcomes were objective response rate and duration of response, independently assessed using RECIST v1.1. FDA reported an objective response rate of 46%, with a median duration of response of 11.8 months.

This week's Anatomy of an Approval looks at what those results can tell regulators, what they cannot tell us without a comparator, and why precision oncology makes patient identification part of the evidence and access strategy.

Deep Dive

Randomized trials provide a direct comparison between what happens with the treatment and what happens with the comparator. A single-arm study cannot provide that same counterfactual. The evidence therefore has to answer the regulatory question in a different way.

In REFOCUS, the population was tightly defined. Patients had previously treated unresectable or metastatic cholangiocarcinoma, had tumors carrying an FGFR2 fusion or other rearrangement, and were naïve to FGFR-inhibitor therapy. Rather than comparing treatment arms, FDA assessed the magnitude and durability of tumor response. An objective response rate of 46% provides evidence of anti-tumor activity in this selected population, while the median response duration of 11.8 months adds information about whether those responses were sustained rather than transient.

Yet, without a randomized comparator, the study does not directly establish how Lyrfigtu compares with another therapy on survival, symptoms, quality of life or healthcare utilization. The evidence therefore has to be interpreted in its broader clinical context i.e., the disease, prior

therapy, molecularly defined population, magnitude and durability of response, safety profile and available treatment options.

The benefit-risk assessment also extends beyond efficacy. FDA's prescribing information includes warnings and precautions for ocular toxicity, hyperphosphatemia and soft-tissue mineralization, and embryo-fetal toxicity. The regulatory decision therefore reflects the overall evidence supporting treatment of a specifically defined patient population.

Precision Medicine Changes the Pathway to Treatment

For Lyrfigtu, eligibility is defined by the presence of an FGFR2 fusion or other rearrangement. In practical terms, that means identifying the appropriate patient requires molecular characterization of the tumor before treatment selection. Diagnosis and prior treatment need to be followed by appropriate molecular testing, identification of the relevant alteration, treatment selection and subsequent monitoring of response and safety. That has implications well beyond regulatory approval.

A targeted therapy can receive FDA approval, but its clinical reach will still depend on whether eligible patients are tested, whether testing occurs at the right point in the treatment pathway, and whether the resulting information reaches clinicians in time to influence the next treatment decision. For precision-medicine developers, the drug strategy and the testing strategy are therefore increasingly interconnected.

The Regulatory Strategy Behind the Review

There is another layer to this approval. FDA granted the Lyrfigtu application Priority Review, while lirafugratinib had previously received Breakthrough Therapy and Orphan Drug designations. FDA also used its Real-Time Oncology Review program and the Assessment Aid, both intended to support more efficient submission and regulatory assessment.

Those mechanisms do not replace the need for convincing evidence. Their value is in helping sponsors and FDA structure the development and review process more efficiently when a program qualifies.

Taken together, the Lyrfigtu story illustrates how several elements of development can converge: a biomarker-defined population, a focused clinical evidence package, regulatory-designation strategy, submission planning and a clear intended treatment pathway.

ECNE Insight

Precision medicine changes the evidence question. It is no longer enough to ask simply whether a treatment works. Developers also need to define for whom it works, how those patients will be identified, what the available evidence can reasonably establish, and where uncertainty remains.

The Lyrfigtu approval illustrates that clearly. A relatively small, single-arm study supported the decision, but the strength of the evidence lies in how its components fit together: a biologically defined population, prior-treatment context, magnitude and durability of response, independent assessment and a characterized safety profile.

The access question then goes one step further. If treatment depends on finding an FGFR2 alteration, molecular testing becomes part of the pathway through which an approved therapy reaches the appropriate patient. For developers, this argues for connecting therapeutic

development, biomarker strategy, clinical evidence and eventual implementation earlier rather than treating them as separate workstreams.

On Our Radar

- **EU | 28 September–1 October 2026 — EMA PRAC meeting:** EMA's Pharmacovigilance Risk Assessment Committee will meet to review safety signals, risk-management measures, and other pharmacovigilance issues affecting medicines in the EU. This is worth watching for any new safety reviews or changes that could influence ongoing benefit-risk assessments. **More info here.**
- **USA | 1 October 2026 — FDA vaccine advisory committee meeting:** FDA's Vaccines and Related Biological Products Advisory Committee will meet to discuss strain selection for influenza vaccines intended for the 2027 Southern Hemisphere season. The committee's recommendations will inform FDA's subsequent strain-selection decision. **More info here.**
- **Australia | 2 October 2026 — TGA medical-device transparency consultation closes:** TGA is seeking feedback on proposals to publish more information following post-market reviews and investigations of medical devices, including information relating to safety, quality, performance, and use. Greater transparency could have implications for manufacturers well beyond formal recalls or regulatory actions. **More info here.**
- **EU | 5 October 2026 — First EMA–ISCT bilateral meeting:** EMA and the International Society for Cell & Gene Therapy will hold their first bilateral meeting to exchange views on issues affecting cell and gene therapy development and regulation. It is a useful signal of continued regulatory engagement as advanced therapies become more complex. **More info here.**