ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

## CORRESPONDENCE

### Response to: Cholangiocarcinoma patients with *FGFR2* fusions/rearrangements but primary refractory to pemigatinib: the real challenge?

Re: Vogel A, Sahai V, Hollebecque A, et al. An open-label study of pemigatinib in cholangiocarcinoma: final results from FIGHT-202. *ESMO Open*. 2024 Jun;9(6):103488. https://doi.org/10.1016/j.esmoop.2024.103488. Epub 2024 Jun 4. PMID: 38838500; PMCID: PMC11190465.

We thank Rizzo et al. for their astute observations and remarks on our publication of the results from the FIGHT-202 study.[1] The results from the final analysis of the FIGHT-202 study showed that over an extended follow-up period, pemigatinib provided benefits for patients with previously treated advanced or metastatic cholangiocarcinoma (CCA) with *FGFR2* rearrangements or fusions, including a 37% overall response rate, a median duration of response of 9.1 months, a median progression-free survival of 7.0 months, and a median overall survival (OS) of 17.5 months.[2] No patients with other or no *FGF/FGFR* alterations responded to pemigatinib.[2]

Rizzo et al. noted that the design of FIGHT-202 precluded assessment of the influence of *FGFR2* alterations. We acknowledge that this is a limitation of a single-arm study, which was discussed in the original FIGHT-202 manuscript. Another limitation of this study that Rizzo et al. denoted is that patients with extrahepatic cholangiocarcinoma (eCCA) as well as intrahepatic cholangiocarcinoma (iCCA) were included, as these malignancies exhibit different clinical and molecular profiles. Of the 107 patients in cohort A, however, in which all patients had *FGFR2* fusions or rearrangements, only 1 had eCCA and thus is unlikely to significantly bias the interpretation of the data and conclusions.[2] Note, only 12 (8%) of all 146 enrolled patients had eCCA, 4 with other *FGF/FGFR* alterations and 7 without *FGF/FGFR* alterations.

An excellent observation of Rizzo et al. was that a subset of patients (14.8%) with *FGFR2* fusions or rearrangements experienced progressive disease (PD) as their best response to pemigatinib. Similar to other FGFR inhibiting agents, the pathophysiology of pemigatinib resistance is not fully understood and therefore remains an area of interest. In addition, the small number of patients in this group precludes any strong conclusions. Primary and secondary resistance to pemigatinib treatment is well documented. Tumors harbor much heterogeneity, however, and capturing the integral alteration landscape of a solid tumor is challenging; hence, some patients may have tumors driven by *FGFR2* rearrangements or fusions and/or other genetic drivers at treatment initiation, which may explain why some patients may not respond to pemigatinib. Our FIGHT-202 article reported that patients with *TP53* and *PBRM1* co-alterations showed significantly shorter OS, and those with *BAP1* alterations experienced a numerically shorter OS. Investigation into the risk factors and other genetic alterations that contribute to primary refractory disease is necessary. Further, we agree with Rizzo et al. that patients who are primarily refractory to pemigatinib may benefit from alternative therapies and/or sequencing of FGFR inhibitor therapies; however, this warrants further investigation, and Rizzo et al. has provided some direction for this future research.

A. Vogel[1,2,3]*, H. Zhen[4], M. L. Veronese[5] & G. K. Abou-Alfa[6,7,8]

[1]*Hannover Medical School, Hannover, Germany;*
[2]*Toronto General Hospital, Toronto;*
[3]*Princess Margaret Cancer Centre, Toronto, Canada;*
[4]*Incyte Corporation, Wilmington, USA;*
[5]*Incyte International Biosciences Sàrl, Morges, Switzerland;*
[6]*Memorial Sloan Kettering Cancer Center, New York;*
[7]*Weill Medical College at Cornell University, New York, USA;*
[8]*Trinity College Dublin School of Medicine, Dublin, Ireland*
(*E-mail: vogela@me.com).

Available online xxx



https://doi.org/10.1016/j.esmoop.2024.103937
DOI of original articles: https://doi.org/10.1016/j.esmoop.2024.103488
https://doi.org/10.1016/j.esmoop.2024.103936

### ACKNOWLEDGEMENTS

Writing assistance was provided by Nestor G. Davila, PhD, an employee of ICON (Blue Bell, PA, USA), and was funded by Incyte (Wilmington, DE, USA).

### FUNDING

This work was supported by Incyte (no grant number).

### DISCLOSURE

AV received personal fees from Amgen, AstraZeneca, Bayer, BeiGene, BMS, Celgene, Delcath, Eisai, Eli Lilly and Company, Hengrui, Incyte Corporation, Ipsen, Medac Pharma, Merck, Pieris, QED Therapeutics, Roche, Sanofi, Servier, and Shire. HZ and MLV are employees and shareholders of Incyte. GKA-A received research funding from Arcus, AstraZeneca, BioNTech, Bristol Myers Squibb, Celgene,

Genentech/Roche, Helsinn, Puma, QED, Servier, Silenseed, Yiviva, and has a consulting or advisory role in Alnylam, AstraZeneca, Autem, BeiGene, Berry Genomics, Boehringer Ingelheim, Celgene, Cend, CytomX, Eisai, Eli Lilly, Exelixis, Flatiron, Genentech/Roche, Helio, Helsinn, Incyte, Ipsen, Merck, Newbridge, Novartis, QED, Rafael, Servier, Silenseed, Sobi, Vector, and Yiviva.

## REFERENCE

1. Rizzo A, Ricci AD, Brandi G. Cholangiocarcinoma patients with FGFR2 fusions/rearrangements but primary refractory to pemigatinib: the real challenge? *ESMO Open*. 2024;9(10):103936.
2. Vogel A, Sahai V, Hollebecque A, et al. An open-label study of pemigatinib in cholangiocarcinoma: final results from FIGHT-202. *ESMO Open*. 2024;9(6):103488.