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CORRESPONDENCE

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.

Genomic studies have revealed that cholangiocarcinomas (CCAs) exhibit a broad spectrum of site-specific molecular characteristics, and it is estimated that genomic alterations can be detected in approximately 40%-45% of cases.[1] In *ESMO Open*, Vogel and colleagues[2] report the final results from FIGHT-202, and the updated findings of this trial further confirm that a proportion of CCA patients harboring fibroblast growth factor receptor 2 (*FGFR2*) fusions or rearrangements may derive considerable and durable benefit from pemigatinib, as also suggested by some recent real-world evidence.[2,3]

We have some concerns, however, that might affect the interpretation of this trial.

First, the design of FIGHT-202 precludes comparative assessment of the possible influence of *FGFR* alterations to the survival results; moreover, the inclusion of patients with extrahepatic cholangiocarcinoma (eCCA) could have introduced some bias, since intrahepatic cholangiocarcinoma (iCCA) and eCCA present important differences in terms of prognosis and therapeutic options. And most importantly, iCCA and eCCA show different molecular profiles, since *KRAS* mutations and *ERBB2* amplifications are more frequent in extrahepatic histotypes, while intrahepatic tumors report *IDH* mutations and *FGFR2* fusions or rearrangements.[4,5]

In addition, a specific point would deserve discussion. Despite the strong biological rationale behind the use of targeted therapies, the 14.8% of patients harboring *FGFR2* fusions or rearrangements experience progressive disease (PD) as best response to pemigatinib in FIGHT-202. This subset, deemed as primary refractory, may exhibit resistance to other anticancer drugs, and the performance status of these pretreated patients may quickly decline during pemigatinib treatment. Moreover, this CCA population has not been characterized fully in terms of risk factors and outcome.

CCA patients with *FGFR2* fusions or rearrangements and primary refractory to pemigatinib represent a neglected population with a poor prognosis and given the substantial percentage of CCAs experiencing PD as best response, it will be interesting to understand how this group may respond to previous treatment options, such as chemo-immunotherapy. Prospective randomized trials investigating this issue are awaited to shed light to this timely topic and to raise some questions regarding sequence therapies.

We invite the authors to share their opinion on these remarks.

Systemic options and prognosis of primary refractory CCA patients, particularly those with *FGFR2* fusions or rearrangements and receiving targeted therapies such as pemigatinib, are among the major challenges that we need to face in this field.

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