Ramucirumab in advanced hepatocellular carcinoma in REACH-2: the true value of α-fetoprotein

We appreciate Ghassan Abou-Alfa's[1] comments on our report on the REACH-2 phase 3 study,[2] which showed that ramucirumab improved survival in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (≥400 ng/mL). Although Abou-Alfa acknowledged the importance of this study in the evolving landscape of systemic treatment in advanced hepatocellular carcinoma, their Comment included several statements that were factually incorrect. We, as REACH-2 Steering Committee members, feel obligated to address these comments.

First, the US National Cancer Institute defines a biomarker as "A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition".[3] With this definition in mind, as the only globally applied clinical test in hepatocellular carcinoma, α-fetoprotein is a true biomarker that has been implicated in hepatocarcinogenesis and has been increasingly used in the diagnosis, staging, prognostication, and assessment of treatment response, and has also been exploited as a potential therapeutic target in hepatocellular carcinoma. Second, by contrast with the claim that the prognostic value of α-fetoprotein "has been shown only in a few retrospective studies", its association with poor prognosis at high concentrations has been consistently shown in several phase 3 clinical studies, including SHARP (NCT00105443), REFLECT (NCT01761266), RESORCE,[4] CELESTIAL (NCT01908426), REACH (NCT01140347), and a large Japanese nationwide prospective registry of 173 378 patients.[5] In fact, high baseline α-fetoprotein concentration has been increasingly used as a stratification factor in phase 3 clinical trial design in advanced hepatocellular carcinoma.[4] Third, many efforts to use a biomarker selection strategy have failed in clinical trial design in advanced hepatocellular carcinoma, including in the recent phase 3 trial with tivantinib in second-line treatment of high MET expression hepatocellular carcinoma.[6] Therefore, REACH-2 represents the first positive phase 3 trial in a biomarker-selected population with hepatocellular carcinoma.

In conclusion, α-fetoprotein is a biomarker with proven prognostic and predictive value in hepatocellular carcinoma. REACH-2 is, to our knowledge, the first positive phase 3 study in a biomarker-selected population with hepatocellular carcinoma showing the improved survival of ramucirumab in advanced hepatocellular carcinoma with high baseline α-fetoprotein concentrations.

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