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CORRESPONDENCE

Reply to letter comments on: Molecular targeted maintenance therapy versus standard of care in advanced biliary cancer: an international, randomised, controlled, open-label, phase III umbrella trial (SAFIR-ABC10-Precision Medicine)

Ruan and colleagues cite the example of the ClarIDHy trial[1] to highlight the risk of dilution, in the event of crossover upon disease progression, of any overall survival (OS) benefit of molecular targeted therapies (MTT) over first-line standard of care (1L-SoC; chemoimmunotherapy) in the SAFIR ABC10 trial.[2] In fact, in the ClarIDHy trial, 70% of patients in the placebo arm switched to the experimental treatment [the isocitrate dehydrogenase 1 (IDH1) inhibitor ivosidenib], so that the numerical OS benefit [a secondary endpoint, progression-free survival (PFS) having logically been chosen as the primary endpoint] did not reach statistical significance [median 10.3 versus 7.5 months, hazard ratio (HR) 0.79, 95% confidence interval (CI) 0.56-1.12, $P = 0.09$]. The context, however, is different for SAFIR ABC10. Although a crossover may be ethically justified, it is now unavoidable given the widespread availability of MTT, which all patients in the trial will potentially receive at some point. Therefore, we opted for a crossover within the trial rather than outside it, to ensure maximum standardization. Indeed, OS, as opposed to PFS, is sensitive to the confounding effects of post-study treatment, generally at the investigators' discretion. In addition to the intention-to-treat (ITT) analysis, we will adjust for the impact of crossover on OS using the rank-preserving structural failure time (RPSFT) approach.[3] This approach is based on a common assumption: the treatment effect is the same for all patients, regardless of when treatment is received. Although not intended to provide a formal proof-of-treatment effect, the RPSFT method compares treatment groups as randomized, with results that have the same significance level as those of the ITT analysis. In ClarIDHy, The RPSFT-adjusted median OS was 5.1 months with placebo (HR 0.49, 95% CI 0.34-0.70, $P < 0.001$).[1] Correcting for crossover has been employed for decades in other phase III studies, and the RPSFT model has been recognized by health technology assessment bodies, e.g. the National Institute of Clinical Excellence in the UK.[4]

Second, we agree that the umbrella design aggregates a heterogeneous portfolio of MTTs, with reported objective response rates ranging from 2% with ivosidenib to up to 50% with fibroblast growth factor receptor (FGFR), human epidermal growth factor receptor 2 (HER2) and v-Raf murine sarcoma viral oncogene homolog B/mitogen-activated protein kinase kinase inhibitors. Our statistical analysis plan includes subgroup analyses stratified by alteration and Bayesian hierarchical models to account for heterogeneity.

Lastly, Ruan and colleagues emphasize the value of circulating tumour DNA (ctDNA) analysis for elucidating the primary or secondary mechanisms of resistance to chemo-immunotherapy and MTT. In fact, we have planned ctDNA analysis at study entry, to assist in tumour molecular profiling, and to compare tissue versus 'liquid' molecular profiling (all patients); after four cycles of 1L-SoC (all patients); after three cycles of treatment in randomized patients (MTT, including after crossover, or continuation of 1L-SoC); and at first disease progression in randomized patients (including after crossover) and non-randomized patients (including early dropouts, before the fourth cycle of 1L-SoC). Of note, randomization is based on baseline alterations, and will occur before progression develops, thus limiting the risk of variation of resistance mechanisms, although this is unlikely with 1L-SoC chemoimmunotherapy.[5]

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Available online xxx

https://doi.org/10.1016/j.esmoop.2025.105536

DOI of original articles: https://doi.org/10.1016/j.esmoop.2025.105535

https://doi.org/10.1016/j.esmoop.2025.104540

FUNDING

The SAFIR ABC10 trial is supported by the French National Cancer Institute (INCa) [grant number PHRC-K19-184], Cancer Research UK [grant number CRCPJT\100012], and the Belgian Fondation Contre le Cancer [FAF-Grants 2020-C/2020/1531]. Experimental treatments, assays and

additional financial support are provided by Accord Healthcare, Guardant Health, Jazz Pharmaceuticals, Pierre-Fabre Oncologie, Servier, Taiho Oncology Ltd. TV is a senior clinical investigator at the Research Foundation-Flanders (FWO), project number 1803723N.

DISCLOSURE

DM: Consulting/advisory role: AbbVie, Amgen, AstraZeneca, Bayer, Bionest Partners, Bristol Myers Squibb (BMS), Incyte, Merck Serono, Merck Sharp & Dohme (MSD), Pierre Fabre Oncologie, Roche, Sanofi, Simon-Kutcher & Partners, Servier, Taiho. Invited lectures/medical writing: Amgen, AstraZeneca, Bayer, BMS, Foundation Medicine, Incyte, Leo Pharma, Medscape, Merck Serono, MSD, Pierre Fabre Oncologie, Roche, Sanofi, Servier, Veracyte, Viatris. Travel/accommodation expenses for medical congresses: Amgen, Bayer, BMS, Merck Serono, MSD, Pierre Fabre Oncologie, Roche, Sanofi, Servier, Viatris.

IB: Consulting: Eisai, AstraZeneca, Roche, Ipsen, Servier; travel expense: Ipsen, Servier, Roche; research funding (institutional): Servier.

TV: Consultancy, advisory roles, honoraria from AstraZeneca, Bayer, BMS, Eisai, ElmediX, Ipsen, Novartis, MSD, Roche, Sirtex, Servier. Research funding (institutional) from Ipsen and Novartis. Support for travel/accommodation from Ipsen and Servier.

JE: Consulting: MSD, Eisai, BMS, AstraZeneca, Bayer, Roche, Ipsen, Basilea, Merck Serono, Incyte, Servier, BeiGene, Taiho, Boston Scientific; travel expense: Amgen; research funding (institutional): BMS, BeiGene, Boston Scientific, Exeliom Biosciences.

JB: Speakers fees: Incyte, Servier. Consultancy: Roche, Bayer, AstraZeneca, Incyte, Taiho, Basilea. Research funding: Incyte.

REFERENCES

1. Zhu AX, Macarulla T, Javle MM, et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the phase 3 randomized clinical ClarIDHy trial. *JAMA Oncol*. 2021;7(11):1669-1677.
2. Malka D, Borbath I, Lopes A, et al. Molecular targeted maintenance therapy versus standard of care in advanced biliary cancer: an international, randomised, controlled, open-label, phase III umbrella trial (SAFIR-ABC10-Precision Medicine). *ESMO Open*. 2025;10(5):104540.
3. Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. *Commun Stat Theory Methods*. 1991;20(8):2609-2631.
4. National Institute for Health and Care Excellence (NICE). Sunitinib for the treatment of gastrointestinal stromal tumours. NICE Technology Appraisal Guidance [TA179]; 2009. Available at: https://www.nice.org.uk/guidance/ta179. Accessed May 16, 2025.
5. van de Haar J, Hoes LR, Roepman P, et al. Limited evolution of the actionable metastatic cancer genome under therapeutic pressure. *Nat Med*. 2021;27(9):1553-1563.