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ORIGINAL ARTICLE

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)

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Background: Advanced biliary tract cancers (ABCs) are a heterogeneous group of rare malignancies of the bile ducts and gall-bladder with a poor prognosis and limited treatment options. Cisplatin—gemcitabine (CISGEM) chemotherapy plus immunotherapy (durvalumab or pembrolizumab) is the current first-line standard of care (1L-SoC). ABCs frequently harbour actionable molecular alterations that suggest a high potential for benefit from molecular targeted therapies (MTTs). However, the assessment of potential first-line MTT treatments is hindered by the scarcity of ABCs harbouring a specific alteration and the time required to carry out tumour molecular profiling.

Materials and methods: We detail here the design of SAFIR-ABC10, an international, randomised, phase III umbrella trial comparing the efficacy of sequential matched targeted therapy after four cycles (12 weeks) of 1L-SoC versus continued 1L-SoC in patients with ABC and an actionable molecular alteration [European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT) tier I or II]. The primary study endpoint is progression-free survival. Besides initial tumour and circulating DNA next-generation sequencing analysis, sequential blood and tumour sampling will be carried out to identify biomarkers of prognosis, response and acquired resistance.

Perspectives: SAFIR-ABC10 is, to our knowledge, the first randomised, umbrella trial assessing the concept of precision medicine in ABC, the ideal setting for addressing this question with a high rate of targetable alterations.

Key words: biliary tract cancer, precision medicine, targeted therapy, maintenance therapy

INTRODUCTION

Biliary tract cancers (BTCs) are a heterogeneous group of malignancies of the bile ducts and gall-bladder that includes intrahepatic, perihilar and distal cholangiocarcinomas (CCAs) and gall-bladder carcinomas.[1,2] Although uncommon in the West, BTCs are common worldwide and are the fifth most common cancer in the developing world. The incidence of BTC, especially CCA, has risen steadily over the past 30 years. Surgery is currently the only curative treatment, but only 20% of cases are resectable at diagnosis, and the 5-year overall survival (OS) after curative-intent surgery remains poor.

The ABC-02 trial[3] defined cisplatin and gemcitabine (CISGEM) as the standard of care for first-line (1L-SoC) treatment of advanced BTC (ABC) based on an improved OS compared with gemcitabine alone (median 11.7 versus 8.1 months, $P = 0.001$). Subsequent studies attempted to improve on CISGEM, either by adding a third drug to the doublet or by testing a novel regimen.[4-6] However, no additional benefit was observed with the exception of combinations of gemcitabine or CISGEM with S-1, an oral fluoropyrimidine derivative, in Asian populations.[7,8] Phase III trials combining CISGEM with immunotherapy have shown statistically significant, albeit modest, improvements in OS compared with CISGEM alone, without any new safety signals. In TOPAZ-1 (NCT03875235), the median OS for patients who received CISGEM + durvalumab was 12.9 (11.6-14.1) months compared with 11.3 (10.1-12.5) months for

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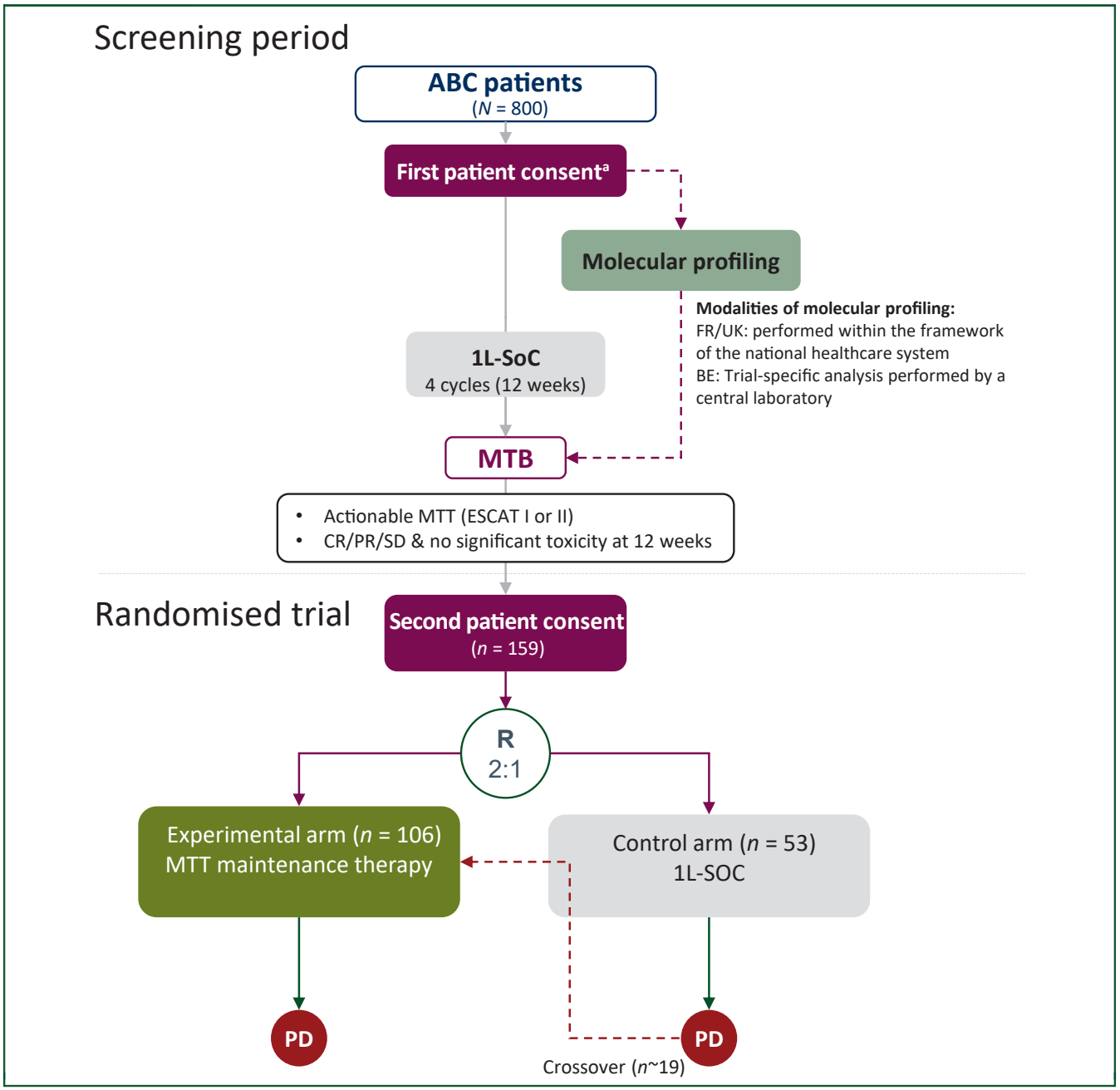

Figure 1. Trial flow chart.
1L-SoC, first-line standard of care; ABC, advanced biliary cancer; BE, Belgium; CR, complete response; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FR, France; MTT, molecular targeted therapy; PD, progression of disease; PR, partial response; R, randomisation; SD, stable disease; UK, United Kingdom.
[a]For France and UK, informed consent will include consent to access to the molecular profiling tests. In Belgium, patients will be asked to consent to tumour genomic profiling carried out as part of the clinical trial.

CISGEM + placebo [hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.64-0.91, $P = 0.021$].[9] In KEYNOTE-966 (NCT04003636), the median OS was 12.7 (11.5-13.6) months in the CISGEM + pembrolizumab group versus 10.9 (9.9-11.6) months in the CISGEM + placebo group (HR 0.83, 95% CI 0.72-0.95, $P = 0.0034$).[10] Based on these results, CISGEM plus immunotherapy has become the new 1L-SoC for the treatment of ABC.

Genomic analysis showed that up to 50% of patients with BTC have tumours harbouring targetable molecular alterations, suggesting that targeted therapies may provide potential benefit.[11,12] Consistent with these observations, results of the CLARIDHy phase III trial testing the isocitrate dehydrogenase 1 inhibitor ivosidenib versus placebo as second- or third-line therapy were positive for the study primary endpoint, progression-free survival (PFS),[13] with ivosidenib now being approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA). Fibroblast growth factor receptor (FGFR) inhibitors have shown promising results in the second-line setting and beyond,[14,15] and two FGFR inhibitors (pemigatinib and futibatinib) have been approved by the FDA and EMA. Several phase II studies have shown the efficacy of different inhibition approaches in human epidermal growth

factor receptor 2-amplified/overexpressed BTCs[16-19] and *BRAF*^{V600E}-mutated BTCs.[20]

The high proportion of BTCs harbouring targetable molecular alterations suggests that BTC could be an ideal platform for demonstrating the clinical benefits of the precision oncology paradigm.[21] A significant challenge to investigators assessing potential first-line treatments in ABC however is enrolment. BTCs are uncommon cancers, and a usable molecular profiling is seldom available because of lack of access to genomic platforms and technical issues, most commonly linked to a scarcity of biopsy material. As such, recruiting sufficient numbers to test a specific alteration with a matched molecular targeted therapy (MTT) in a phase III trial is a slow and costly process requiring cooperation on a global level. As an example, the phase III PROOF trial (NCT03773302), assessing the FGFR inhibitor infigratinib versus 1L-SoC in BTC harbouring *FGFR2* alteration, and the similarly designed FOENIX 3 study (NCT04093362) assessing futibatinib[22] were closed prematurely due to poor accrual (48/300 patients included in the PROOF[23]) despite intensive screening across four continents.[24]

A central issue for these first-line trials was the time required to confirm the presence of the targeted alteration after biopsy, often more than 2 and as long as 6 weeks. Patients are unwilling and often clinically unable to wait this long and so default to SoC. Trial designs need to account for this delay when evaluating targeted treatments.

Genomic profiles present clinicians with complex datasets and challenges for interpretation that they may not be familiar with. To assess the potential actionability of molecular findings, the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT)[25,26] sets out definitions of level of evidence regarding the potential efficacy of a target/MTT combination. The utility of the ESCAT ranking method to guide the clinicians in the relevant use of the multigene sequencing reports was recently validated in metastatic breast cancer in the SAFIR02 BREAST trial.[27] Results in this trial showed that MTTs matched to genomics improve PFS when genomic alterations are classified as level I/II according to ESCAT (adjusted HR 0.41, 90% CI 0.27-0.61, $P < 0.001$).

The SAFIR02 programme also demonstrated the feasibility of generalised genomic screening, carried out during a standard first-line treatment as a tool to orient patients to a range of subsequent treatment options. In the trial setting, this 'umbrella' design makes a more efficient use of screening a given population in which individual targets are rare.[28,29] Provided with enough treatment options, the majority of identified actionable targets can be treated with a matched therapy. This was also recently confirmed in the context of retrospective analyses in BTC.[30] However, to date, the very concept of precision oncology has not been prospectively validated in BTC.

THE SAFIR-ABC10 CLINICAL TRIAL

Trial design

SAFIR-ABC10 is an international, randomised, phase III umbrella trial comparing the efficacy of sequential on-target MTT after four cycles of 1L-SoC (12 weeks) versus continued 1L-SoC in the treatment of patients with ABC (Figure 1). Target/MTT combinations with a defined level of evidence of potential efficacy have been selected using the ESCAT (ESCAT I-II; Table 1).

The sequential setting was chosen to test a range of potential matched MTTs because: (i) this circumvents the issue of the turnaround time needed to identify tumours

Table 1. Target alterations in biliary tract cancer selected in SAFIR-ABC10: frequency, actionability and matched targeted therapy

Gene	Alteration	Frequency (BTC type specificity)	MTT	ESCAT	Supporting evidence
IDH1	Mutations	16%-29% iCCA[11,31]	Ivosidenib	I-A	BTC: ClarIDHy trial[13] (phase III, versus placebo, 2L+): PFS benefit, OS benefit after correcting for crossover
FGFR2	Fusions/ rearrangements	5%-15% iCCA[11,32]	Futibatinib	I-B	BTC: FOENIX-CCA trial (phase II, 2L+): ORR = 42%[15] Similar results with other FGFR2 inhibitors[14,15,33,34]
	Mutations	2% iCCA[11,32]	Futibatinib	II-B	Solid tumours including BTCs: phase I data[35]
HER2	Amplification	5%-10% eCCA/GBC > iCCA[11,16,17,36]	Zanidatamab	I-B	BTC: HERIZON-BTC-01 (phase IIb 2L+) ORR = 41%[17] Similar results with other HER2 inhibitors[16,18,37]
	Mutations	3%-5% eCCA/GBC > iCCA[11,36]	Neratinib + trastuzumab	II-B	BTC: SUMMIT (phase II basket study): ORR = 16% with single-agent neratinib[36] Improved results with other HER2 inhibitors combined with trastuzumab[16,18,38]
BRAF	V600E mutation	5%[11,20]	Encorafenib + binimetinib	I-B	BTC: *BRAF/MEK* inhibitor combinations ROAR (phase II, dabrafenib + trametinib, 2L+): ORR = 53%[39] NCI-MATCH subprotocol H (phase I, dabrafenib + trametinib, 2L+): responses to treatment[40] Melanoma: encorafenib + binimetinib Demonstrated PFS and OS benefit in *BRAF* V600-mutated melanoma[41,42]

2L+, second line of treatment and beyond; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; ESCAT, European Society of Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets; *FGFR2*, fibroblast growth factor receptor 2; GBC, gall-bladder cancer; iCCA, intrahepatic cholangiocarcinoma; *HER2*, human epidermal growth factor receptor 2; *IDH1*, isocitrate dehydrogenase 1; MTT, matched targeted therapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

harbouring a target alteration; (ii) it introduces MTT as a sequential treatment, clinically feasible because of non-overlapping toxicities; (iii) it permits the re-challenge of previously effective chemoimmunotherapy; and (iv) in some of the previous trials of MTTs (e.g. with ivosidenib[13]), early progressors were seen; beginning treatment in a stable situation might provide improved benefit.

The trial is conducted in conformance with the International Conference on Harmonisation Good Clinical Practice Guideline, the principles of the Declaration of Helsinki and applicable local laws and regulations. The protocol was approved by the relevant institutional review boards/independent ethics committees of participating study sites. All patients will provide written informed consent before participation in the study.

The trial is composed of three phases: an initial genomic screening phase, a randomised comparative trial and a follow-up phase.

Screening phase

The aim of the screening phase is to identify a medically suitable population, to obtain a molecular profile of the patient's tumour, to collect baseline data concerning patient demographics and disease characteristics and to obtain pre-treatment blood and tumour samples for further translational research.

Patients with locally advanced (unresectable) or metastatic intrahepatic, perihilar or distal CCA, or gall-bladder carcinoma, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 who are candidates for 1L-SoC treatment (investigator's choice of CISGEM or CISGEM + durvalumab where this is available) are to be enrolled before initiating therapy (see Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2025.104540, for a full list of inclusion/exclusion criteria).

DNA and RNA next-generation sequencing (NGS) analysis (targeted panel or whole genome sequencing) will be carried out on a pre-treatment sample of primary or metastatic tumour tissue. The trial will take advantage of sequencing programmes offered within the National Healthcare System in France and UK. In other countries without such programmes, genomic analysis will be carried out specifically for the trial by a central laboratory in each country. Comprehensive NGS analysis of circulating tumour DNA (ctDNA) will also be carried out using the Guardant360® CDx test (Guardant Health, Palo Alto, CA).

Results of these analyses (tissue and ctDNA) will be transmitted to the trial's Molecular Tumour Board (MTB) before initiation of 1L-SoC cycle 4. The MTB comprises oncologists and molecular biologists from each of the participating countries and a pathologist, selected according to their expertise in their respective fields and their practical experience with conducting clinical trials. The treating physician is also encouraged to participate on an *ad hoc* basis in the discussion of their patients.

The MTB will determine whether the patient's tumour harbours a targetable molecular alteration for one or more of the trial MTTs and recommend a treatment orientation for each patient based on guidance established at trial initiation and updated regularly throughout the trial. Where co-occurrence occurs between two alterations, the MTB will consider other factors, including demonstrated efficacy and safety profiles of the proposed MTTs in their recommendation.

Non-eligible patients will be oriented towards other treatment options, including other trials within the SAFIR-ABC10 programme as these become available. Of note, patients whose tumour harbours an *NTRK* fusion or a microsatellite instability/mismatch repair deficiency will be treated outside the randomised trial but followed for outcome.

Randomised trial

Patients with disease control (response or stable disease) after four cycles (12 weeks) of 1L-SoC and whose tumour harbours a target molecular alteration will be invited to enter the randomised trial. To be eligible, patients must have an ECOG performance status of 0-1 and demonstrate adequate bone marrow, liver, renal and cardiac function with no major toxicity related to their 1L-SoC treatment. Depending on the treatment orientation, additional exclusion criteria may apply (see Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2025.104540, for a full list of inclusion/exclusion criteria).

Eligible patients will be randomised (2 : 1) to receive either a matched MTT, as determined by the MTB (experimental arm), or continuation of 1L-SoC (control arm). During treatment, patients will be asked to attend regular clinical visits to carry out safety and efficacy assessments. Response to treatment will be assessed according to RECIST v1.1 by radiographic exams carried out every 9 ($\pm$1) weeks. Treatment will continue until disease progression. Patients in the control arm will be allowed to cross over to matched MTT (as initially determined by the MTB) in the second line.

Follow-up phase—a cohort of advanced biliary tract cancer patients

All screened patients, including those who do not enter the randomised trial, will continue to be followed up for at least 12 months from the date of initial consent. During this time, information will be collected regarding the date of first-line progression, subsequent antineoplastic treatment, second progression and survival status. Longitudinal blood and tissue samples will also be collected from all patients during treatment and at disease progression. Thus, SAFIR-ABC10 will assemble a prospective, international cohort of ABC patients with a complete dataset of clinical and molecular profiles, treatment outcomes, blood and tissue samples and imaging data. This cohort will provide a wealth of information for future ancillary research projects in this indication.

Statistical analysis plan

The primary objective of SAFIR-ABC10 is to evaluate whether the introduction of maintenance treatment with matched MTTs is superior to continuation of 1L-SoC. The primary endpoint of the study, PFS, will be analysed in the intent-to-treat population using Cox regression and Kaplan—Meier estimates. Sensitivity analyses will include per-protocol population analysis and additional covariates in the Cox model, along with subgroup analysis.

It is estimated that 159 patients will be sufficient to detect an HR of 0.60 (an increase in the median PFS from 6 to 10 months) with 80% power, a two-sided 5% significance level and assuming a 5% dropout rate. To obtain the required sample size, we expect to screen and enrol ∼800 patients. The overall trial duration is estimated to be 60 months.

The futility of the MTT arm compared with the control arm will be assessed periodically during the trial by an independent data monitoring committee (IDMC) using conditional power. This metric indicates the probability of achieving a statistically significant result by study end, based on interim data and assuming future data align with the target PFS HR. If conditional power falls to $\leq$20%, considering safety and all accumulated data, the IDMC may consider discontinuing the study due to futility.

For secondary endpoints, OS will be analysed similarly to PFS, accounting for crossover in the control arm. PFS after the second line of treatment (PFS2) and duration of response will be assessed using standard survival techniques. The overall response rate will be compared between groups. Molecular screening feasibility will be reported. Health-related quality of life [assessed every three cycles using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), EORTC QLQ-BIL20 and Euro Quality of Life 5-Dimension 5-Level (EUROQOL EQ-5D-5L) questionnaires] will be compared between groups over time using mixed modelling. Adverse events will be summarised using descriptive statistics.

Exploratory endpoints include predictive factors of response and mechanisms of primary and acquired resistance (of note, comprehensive ctDNA profiling will also be carried out at the time of disease progression).

PERSPECTIVES

SAFIR-ABC10 is, to our knowledge, the first randomised, umbrella trial assessing the concept of precision medicine in ABC. ABC represents the ideal setting for addressing this question with a high rate of targetable alterations, the likelihood of efficacy of MTTs for many of these alterations and no universally established SoC after progression on first-line regimens. The trial has three main aims:

Firstly, SAFIR-ABC10 aims at providing evidence to support the strategy for early molecular screening. Currently, there is a high level of heterogeneity between countries and between individual treatment centres regarding access to molecular profiling, with no central funding for such profiling in most European countries. The first aim of the SAFIR-ABC10 trial would be to provide evidence of the benefit of tissue- and/or blood-based comprehensive molecular profiling as an incentive to generalise this approach.

Secondly, SAFIR-ABC10 aims to demonstrate the usefulness of this approach to disrupt the current paradigm of disease management. The first-line sequential strategy driven by molecular profiling introduces innovation early in the treatment cycle and offers the best chances to avert relapse. Due to the rarity of the disease, our trial will probably be the first to provide randomised data on the value of diverse MTT; moreover, it will provide such data in a range of alterations that are unlikely to be addressed by industry-funded trials. There are two categories of drugs studied within the trial: (i) Drugs currently approved [ivosidenib, futibatinib and (in the United States to date) zanidatamab] for patients with BTC previously treated with chemotherapy. For these drugs, the SAFIR-ABC10 trial will provide evidence of efficacy at an earlier stage than currently approved. The results of SAFIR-ABC10 may provide the basis for discussions around the extension of approval, in the context of the rarity of the disease, which makes it difficult to provide randomised evidence for each drug in the first-line setting. (ii) Drug combination regimens currently approved in other indications but with no industry plan to develop specifically in BTC (neratinib + trastuzumab, encorafenib + binimetinib). For these drugs, SAFIR-ABC10 might provide first evidence of activity in BTC. Depending on the number of patients treated with each drug, results may provide justification to explore the extension of the indication.

Thirdly, SAFIR-ABC10 aims to standardise practices regarding the evaluation of molecular profiles across European countries. The trial integrates a multinational MTB to ensure that treatment recommendations are made within the framework of collegial discussion by experts in the pathology referencing the most recent data, and thus offers the best chance of observing clinical benefit. The MTB will also produce working standard for the community and, by being open to the treating physicians, will disseminate knowledge on the interpretation of molecular profiles and proper use of matched molecules.

The SAFIR-ABC10 umbrella design offers significant advantages in the investigation of personalised therapy in ABC. It closely resembles a real-life scenario where patients are considered for multiple treatments but with the advantage that these treatments are available within the trial without the need to search for individual open clinical trials.

Furthermore, validated tissue- and blood-based NGS analyses produce robust results and propose opportunity for an 'all-in-one' assay as a substitute for multiple tests. A single upfront multigene profiling test to determine suitability for several different actionable alterations is clearly an efficient use of patient material and molecular laboratory resources, as well as providing timely information for the rationalisation of subsequent treatment plans. Indeed, SAFIR-ABC10 will provide molecular diagnosis available

from the onset of advanced disease, whereas common practice recommends profiling at treatment escape, which sometimes arrives too late for the more aggressive disease.

The trial is also a more attractive approach for patients; a clear implication is that they have a far greater chance of being eligible to receive potentially beneficial innovative treatments than they would in a single target/agent trial.

Umbrella studies are uncommon because of the requirement to provide multiple targeted agents; there are few commercial organisations with a sufficiently large portfolio to allow such studies. As such, academic sponsorship represents the optimum infrastructure, as drugs will be selected for suitability rather than in-house availability. It also provides a level of adaptability where new treatments can be added to the portfolio as additional partners are identified and/or levels of evidence of interactions between other treatments and actionable alterations evolve—with the implication that more and more patients initiating the screening phase of this trial will be likely to enter the randomised phase to benefit from new treatment options over time. Furthermore, the core SAFIR-ABC10 protocol is designed as part of a larger programme with other first- and second-line trials branching off according to patients' profile and response to treatment.

SAFIR-ABC10 provides a variety of opportunities for scientific development. The collection of clinical outcomes and extensive molecular data beyond actionable alterations will permit multiple discovery projects. An example will be the correlation between molecular genotype and phenotype in the context of clinical trial quality data. Identification of treatment-driven molecular alterations associated with acquired resistance will also address one of the major problems related to cancer treatment escape and disease progression.

This trial will explore if a traditional tissue biopsy, which is an additional source of discomfort for patients, or a less invasive liquid biopsy is more suitable for this testing. The turnaround time for obtaining test results will be available to be compared between tissue and liquid biopsy profiling, as well as the detection rate for the biomarkers of interest in the trial. The trial will also examine in detail the feasibility of using central analysis platforms to deliver a molecular profile in terms of logistics and interpretability of results, enabling future improvements in the speed and reliability of the process. Patients with rare cancers could thus have a better chance of receiving the best personalised treatment for their disease.

The decision to design an international trial raises the capacity of recruitment for rare disease patients, maximising the chances of obtaining rapid and conclusive results for a patient population whose therapeutic options are scarce and life expectancy is limited to date.

Finally, SAFIR-ABC10 will represent one of the first randomised uses of a validated ranking system to select 'useful' targets. It will also enhance the value for existing national screening programmes by offering larger-scale access to treatment and coordinating the matching process. If this paradigm is successful, it has the potential to be adopted as standard practice.

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DISCLOSURE

DM: consulting/advisory role: AbbVie, Amgen, AstraZeneca, Bayer, Bionest Partners, BMS, Incyte, Merck Serono, 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: AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Elmedix, Ipsen, Novartis, MSD, Roche, Sirtex, Servier; research funding (institutional): Ipsen and Novartis; support for travel/accommodation: 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. All other authors have declared no conflicts of interest.

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