SAFIR ABC10: Targeted maintenance therapy versus first-line standard of care in advanced biliary cancer

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Background

The first-line standard of care (1L-SoC) for advanced biliary tract cancers (ABC), a heterogeneous group of malignancies of the bile ducts and gallbladder, is cisplatin and gemcitabine (CISGEM) combined with anti-PD-(L)1. In second line and beyond, molecular targeted therapies (MTT) are the preferred option for the 30-50% of ABC that harbour actionable molecular alterations. To date, no randomised data exist for MTT in the first-line setting.

Trial design

SAFIR-ABC10 is an international, randomised, Phase 3 umbrella trial comparing the efficacy of on-target MTT maintenance after 12-week 1L-SoC versus continued 1L-SoC using a predefined, scalable portfolio of target/MTT combinations with a firm level of evidence of potential efficacy according to the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT I or II):

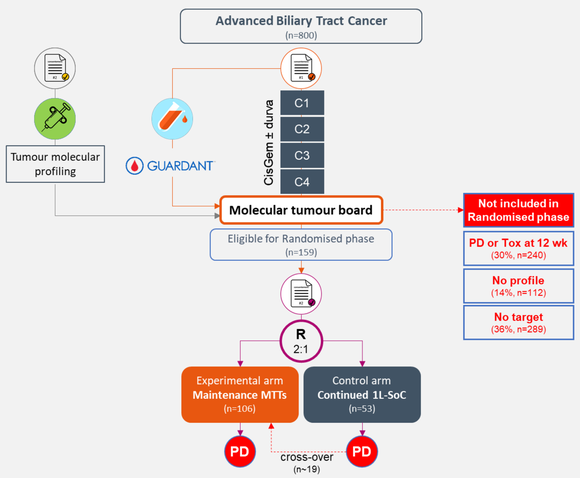
Molecular Alteration	Frequency in ABC	Matched Therapy	ESCAT
IDH1 mutation	10%	Ivosidenib	I-A
FGFR2 fusion/rearrangement	10%	Futibatinib	I-B
FGFR2 mutation	2%	Futibatinib	II-B
HER2 amplification/over-expression	10%	Zanidatamab	I-C
HER2 mutation	5%	Neratinib/Trastuzumab	II-B
BRAF^{V600E} mutation	3%	Encorafenib/Binimetinib	I-B

In an initial screening phase, 800 patients with ABC will initiate treatment with 4 cycles of 1L-SoC. During this time, a tumour molecular profile will be obtained for each participating patient. Genomic profiling is offered within the National Healthcare System (France, UK) or will be performed specifically for the trial (Belgium). A circulating tumour DNA profile will also be obtained for each patient using the Guardant 360® CDx test.

An international molecular tumour board (MTB) will provide a treatment orientation for each participating patient. Patients with disease control (response or stable disease) and no limiting toxicity, and whose tumour harbours at least one targetable molecular alteration, will be invited to participate in the randomised phase of the trial in which 159 eligible patients will be randomised (2:1) to receive either:

- Experimental arm: Maintenance therapy with a matched MTT, as determined by the MTB
- Control arm: Continuation of 1L-SoC

Patients will be treated until progression (RECIST v1.1). For patients in the control arm, cross-over to second-line MTT will be allowed, within the framework of the trial.



Biological sample collection

Plasma samples will be collected for translational research projects at study entry (prior to treatment initiation), prior to randomisation, after 4 cycles of randomised treatment and at disease progression. These samples will be used to:

- Evaluate whether ctDNA levels at baseline and during therapy are associated with the patient characteristics and outcome.
- To describe the genetic landscape of ctDNA at baseline and during therapy, and its association with treatment efficacy.

Where possible, a tumour tissue sample will be obtained at study entry and at disease progression post-randomisation.

Objectives

Primary Objective
To evaluate whether maintenance treatment with MTTs to "actionable" targets after 4 cycles of 1L-SoC is superior to continuation of 1L-SoC in terms of progression-free survival (PFS).

Secondary objectives

- To assess the efficacy of:
  - Precision oncology vs. 1L-SoC in ABC patients with 'actionable' tumour molecular alterations
  - Each MTT (or MTT combination)
- To assess the feasibility of molecular screening in a multinational, academic trial
- To compare the health-related quality of life (HRQoL) of patients treated with MTTs vs. 1L-SoC
- To assess the safety of the MTTs
- To study prognostic value of molecular alterations, regardless of the randomisation

Translational objectives

- To identify biomarkers associated with disease prognosis and response to MTTs
- To explore the association between emergent (on-treatment) molecular co-alterations and acquired resistance to treatment

Main inclusion criteria

Screening phase

- Histologically-proven intrahepatic, perihilar or distal CCA, or gallbladder carcinoma (ampullary carcinoma excluded)
- De novo or recurrent, locally advanced (non-resectable) or metastatic disease
- Availability of a suitable archived sample of primary or metastatic tumour tissue (frozen, or FFPE) or able to undergo a biopsy to obtain a suitable malignant tissue sample
- Aged ≥18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Estimated life expectancy >3 months
- Candidate for 1L-SoC therapy, or has initiated first cycle of 1L-SoC therapy

Randomised trial

- Molecular profile showing the tumour harbours at least one targetable molecular alteration with a MTT in the study portfolio (as determined by the trial MTB)
- Disease controlled (stable or responsive) after 4 cycles of 1L-SoC, compared to a pre-treatment disease evaluation, as assessed by the investigator
- ECOG performance status of 0 or 1
- Presence of at least one evaluable lesion according to RECIST v1.1, or complete response to 12 weeks 1L-SoC
- Adequate bone marrow, liver, renal and cardiac function

+ Additional criteria depending on target MTT identified.

Statistical hypothesis and sample size

We estimate 159 pts will be sufficient to detect a HR of 0.60 for PFS, with 80% power and 2-sided 5% significance level. To obtain the required sample size, we expect to screen and enroll approximately 800 patients:

- Based on the results of the ABC-02 and BINGO trials (Valle, 2010; Malka, 2014), we expect that 560 (70%) of the patients screened will have controlled disease without severe toxicity after 12 weeks of 1L-SoC.
- We hypothesis that 448 (80%) of these patients will have an exploitable genetic profile (20% technical failure rate)
- From the estimated incidence of each of the molecular targets (see table), and taking into account co-occurrences, we expect that only 35% of these 448 patients will have an actionable alteration, representing approximately 159 patients.

Analysis

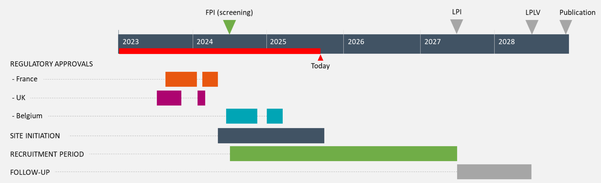
Efficacy

The Primary endpoint is PFS, defined as the time from randomisation to the first documented PD as assessed by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Secondary endpoints include overall survival, objective response rate, time to treatment failure, PFS after next line of treatment (PFS2) and duration of response.

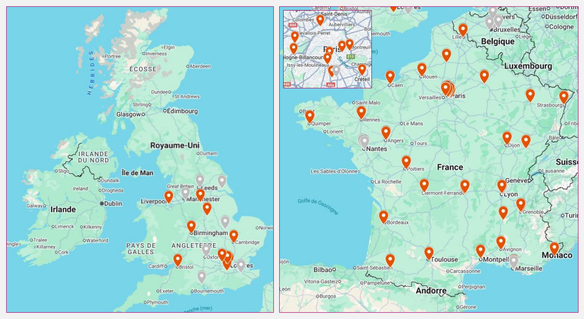
Safety

The number and percentage of patients will be presented for each type of adverse event/adverse reaction by the reported worst severity grade (NCI CTCAE v5.0) and by treatment arm. The number and percentage of patients experiencing any adverse event will also be reported by severity and by treatment arm.

Study timetable



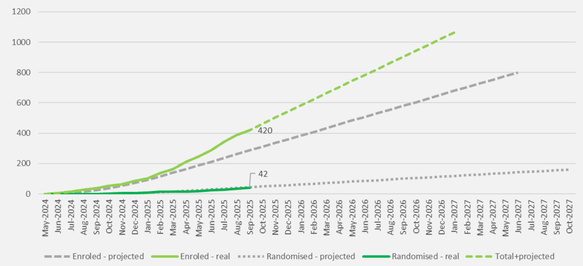
Participating centres



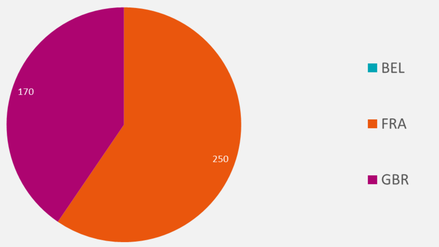
Current status

Recruitment began in June 2024. As of September 30, 2025, 54 centres have been activated in France and UK, and 420 patients have been enrolled. Additional centres in France and UK and 4 centres in Belgium are to be activated by the end of 2025.

Recruitment rate – Screening and Randomised phases



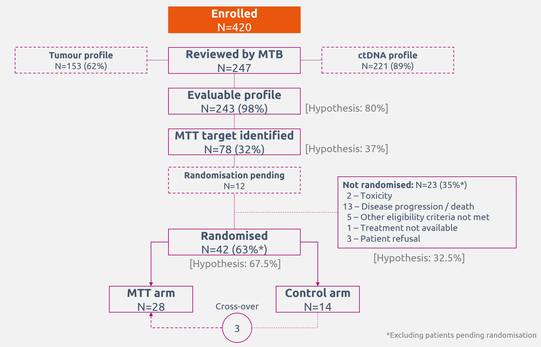
Proportion of inclusions by country



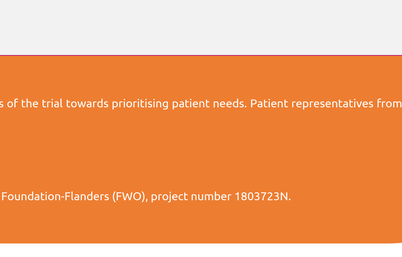
Baseline characteristics	FRA	GBR	TOTAL
Sex			
Male	120 (54%)	65 (45%)	185 (50%)
Female	103 (48%)	81 (55%)	184 (50%)
Not yet reported*	27	25	52
Age			
Mean	65.5	59	62.9
Median	68	61	64
Min - Max	19-92	24-88	19-92
Primary tumour type			
Intrahepatic CCA	147 (74%)	60 (45%)	207 (62%)
Perihilar CCA	25 (13%)	25 (19%)	50 (15%)
Distal CCA	7 (4%)	9 (7%)	16 (5%)
Gall bladder carcinoma	20 (10%)	39 (29%)	59 (18%)
Not yet reported*	51	38	89
Stage at diagnosis			
Local disease	32 (15%)	9 (7%)	41 (12%)
Locally Advanced	47 (23%)	31 (22%)	78 (23%)
Metastatic	128 (62%)	98 (71%)	226 (66%)
Not yet reported*	43	33	76
Induction Regimen			
CISGEM	6 (3%)	1 (1%)	7 (2%)
CISGEM + durvalumab	202 (97%)	142 (99%)	344 (98%)
Not yet reported*	42	28	70

*Note that for many patients currently in Screening, this CRF data has not yet been fully completed

Consort diagram



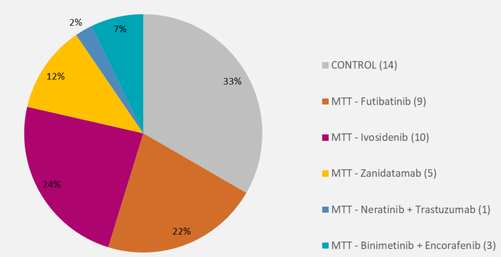
MTB review (N=247)



MTB guidance to select treatment in case of co-occurrence of alterations

Genetic alteration	Order of preference	Response rate (From literature)	Therapeutic intervention
BRAF V600E mut	1	53%	Encorafenib + binimetinib
FGFR2 fusions	2	42%	Futibatinib
HER2 amplification/overexpression	3	41%	Zanidatamab
FGFR2 extracellular domain deletion	4	Unknown, but suspected to be similar to *FGFR2* fusions	Futibatinib
HER2 activating mutations	5	16%	Neratinib + trastuzumab
FGFR2 activating mutations	6	13%	Futibatinib
IDH1 mutations	7	2%	Ivosedinib
• No alteration • ESCAT III or IV alteration • Contraindication to the MTT	8	ESCAT III or IV or No ESCAT	None

Distribution of randomised patients (N= 42)



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Disclosures
Dr Malka declares 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

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