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Original Article

Clinical Outcome of Patients with Advanced Biliary Tract Cancer in a Dedicated Phase I Unit

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Abstract

Aims: Advanced biliary tract carcinomas (ABC) are malignancies with limited effective therapies for advanced disease. There is little published evidence of outcomes of ABC patients participating in phase I clinical trials.
Materials and methods: Patient characteristics, treatment details and outcomes of ABC patients treated at a dedicated phase I unit were captured and analysed from case and trial records.
Results: In total, 123 ABC patients were included in the study, of which 48 patients participated in 41 different phase I trials; 75 (61%) did not participate due to rapid disease progression or patient choice. Molecular characterisation of tumours using a targeted panel was conducted in 15 (31%), yielding several potentially actionable mutations, including *BRCA*, *PIK3CA*, *FGFR*, *AKT* and PTEN loss. Of the 39 evaluable patients there was one exceptional responder. Eighteen (46%) other patients achieved stable disease as their best response, with a clinical benefit rate at 4 months of 10%. Treatment was generally well tolerated with grade 3 or 4 adverse events only observed in eight patients (17 %), of which six were drug related and led to trial discontinuation in one (3%), with no toxicity-related deaths.
Conclusion: Carefully selected ABC patients have been found to tolerate experimental phase I clinical trials without excess toxicity. The aggressive nature of this disease warrants consideration of early referral to a phase I unit. Future work will require comprehensive molecular profiling in an attempt to understand the biology underlying the exceptional responders and to match patients in real-time to targeted therapies.

Key words: Biliary tract cancer; developmental therapeutics; drug development; phase I clinical trial

Introduction

Biliary cancers are a heterogeneous group of cancers, with varied definitions and classifications. Most commonly, they include tumours of the gallbladder, extrahepatic ducts, perihilar and intrahepatic ducts and ampullary cancer. Large clinical trials involving systemic therapy for biliary cancer have broad inclusion criteria, including almost all tumours of biliary tract origin [1]. The standard of care for advanced biliary tract cancers (ABC) is systemic therapy, usually with combination chemotherapy, including platinum and gemcitabine [1], but patients invariably progress, with a median survival of less than 1 year [2]. There are currently no standard second-line options [3] and patients are often referred for participation in clinical trials involving various novel agents targeting multiple potential pathways, as well as trials using non-systemic local therapy. Early phase clinical trials investigating these agents are therefore an important option for patients with ABC, but there are limited published data on the impact of experimental drug therapies on the safety and outcome of chemo-refractory ABC to guide recommendations and policy.

In the era of precision medicine, molecular characterisation of tumours has helped to create more efficient clinical trial design and is considered essential in late phase

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trials [4]. However, it is now recognised that identification of these patient subgroups must start in early phase trials, allowing for validation of these results in late phase studies. Increasingly, phase I units throughout the world have started to routinely perform molecular characterisation of tumours and use these results to guide trial allocation for patients [5].

We conducted a retrospective analysis of all patients with ABC treated in the specialist phase I unit in our institution. The aim of this study was to describe the rates of toxicities and treatment-related trial discontinuation in these patients, as well as to describe the anti-tumour activity of these agents. We additionally explored the prognostic role of baseline variables for this group of patients and report on the results of molecular characterisation carried out on ABC tumours.

Materials and Methods

All consecutive patients with ABC treated within phase I clinical trials in the Drug Development Unit at the Royal Marsden National Health Service Foundation Trust, Sutton, UK from March 2002 to March 2016 were included. Patients eligible for phase I participation were $\geq$18 years old and had progressing ABC tumours for which approved treatments were no longer available. Patients were discussed at weekly trial allocation meetings to identify suitable trials based on disease characteristics, tumour molecular characterisation results (if available) and trial slot availability. Patients who received at least one dose of an experimental agent and provided written informed consent for participation in phase I trials as approved by the local Research Ethics Committee were included in this study.

Clinical data that were prospectively collected for each clinical trial were collated. These included patient characteristics, tumour characteristics and laboratory results. For each phase I trial: drug name, class of drug, mechanism, date starting trial, best response, grade of toxicities and date of progression were collected.

Toxicity data were collected as originally recorded in the electronic medical records or the case report forms when required. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) for adverse events. Tumour responses were confirmed by a radiologist using Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.

Molecular Characterisation

From 2011 onwards, patients treated at the Drug Development Unit, Royal Marsden Hospital (RMH) were consented to undergo characterisation of key molecular drivers in the patients' archival tumour tissue. Through the years, various panels of targeted next generation sequencing have been used, for example, from 2013 to mid-2015, 48 genes were tested using the TruSeq panel, and from the end of 2015 to currently, 113 genes were tested using the Generead DNA damage panel. Immunohistochemistry (IHC) for ATM was carried out from 2015. Panels and other additional tests were also dependent on the types of trial and the biomarkers being selected for these trials during that period of time. Of particular note, these panels were not specifically designed to identify mutations peculiar to ABC. The results of these tests, if available, were used to match the molecular aberration identified to a rationally selected experimental trial, if available.

Statistical Methods

Descriptive statistics were used to summarise patient and tumour characteristics. The clinical benefit rate was calculated as the sum of complete response, partial response and proportion of patients with stable disease at 4 months. For patients included in more than one trial, data for progression-free survival (PFS) and overall survival from the first trial therapy were used. Overall survival and PFS were determined using Kaplan–Meier analysis and specified as median survival. Data are presented as survival plots.

Analysis of the effect of potential prognostic factors on survival was undertaken using Cox proportional hazard modelling. Categorisation of numeric variables was based on their deviation from standard reference values. The RMH prognostic was calculated from a model previously described [6]. In brief, the RMH prognostic index uses a composite score of albumin, lactate dehydrogenase and number of metastatic sites to predict survival in phase I trials. Factors identified in univariate models were used to construct an adjusted survival model.

Results

Patient and Tumour Characteristics

Between March 2002 and March 2016, 123 patients with ABC were reviewed for the consideration of phase I clinical trials. Eventually, 48 patients (39% of total) participated in a trial. Of the 75 patients who were reviewed in the clinic but did not participate in a phase I trial, 15 (20%) patients were deemed initially eligible for a study trial, but did not receive any investigational agent due to rapid interim disease progression. Five patients had passed screening for a study, but had deterioration of disease condition and performance status between screening and cycle 1 day 1 and did not receive drug. The average time between the first visit and screening was 3 weeks. Among the other ABC patients reviewed in the unit for the consideration of a phase I study, the most common reasons not to be considered were biliary-related disease leading to abnormal liver function and/or bilirubin that would have qualified as exclusion criteria for trials (21%), poor performance status (18%) and patient's choice (8%).

In total, 48 patients participated in 41 different phase I clinical trials. Eight (17%) entered a second phase I study upon progression on the first study. The primary site of the tumour was the bile duct in 36 (75%); patients had a median of two previous lines of systemic chemotherapy (range

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1–6). Fourteen (29%) had a biliary stent *in situ* at the time of entering a clinical trial. Twenty-eight (58%) had been diagnosed with upfront metastatic disease, with most receiving a platinum-based doublet therapy in the first line (90%). Further details of patient and tumour characteristics are described in Table 1.

Molecular Characterisation

Fifteen patients (31%) had results of molecular characterisation available from targeted next generation sequencing panels. The most common mutation detected was in *p53* ($n = 5$; 33%), with other potentially targetable mutations being detected in *PI3KCA* ($n = 2$), *FGFR* ($n = 2$), *ERCC* ($n = 1$) and *AKT* ($n = 1$). PTEN loss was detected by IHC in two patients. Two patients also had known germline BRCA mutations prior to enrolling into a clinical trial (one with *BRCA1* and one with *BRCA2*). Nine patients had ATM IHC carried out, of which one had complete nuclear loss of expression. Due to logistical considerations of tissue access and processing, none of the patients with actionable mutations prospectively received treatment on a trial matched to these mutations.

Phase I Study Outcomes

Thirty-nine patients (81%) participated in novel single agent trials, whereas nine (19%) participated in trials combining novel agents with traditional chemotherapeutic agents. Novel agents targeted several pathways, with the most common being PI3K pathway inhibitors (35%), epigenetic agents (17%), DNA damage repair pathway inhibitors (10%) and 10% participated in trials utilising oncolytic viruses. Figure 1 describes the various classes of phase I trials into which patients were enrolled.

Table 1
Patient characteristics at baseline

Age at diagnosis - years (range)	55 (33–77)
Gender - *n* (%)	
Female	24 (50%)
Male	24 (50%)
Performance status - *n* (%)	
0	14 (29%)
1	34 (71%)
≥2	0 (0%)
Primary tumour - *n* (%)	
Bile duct	36 (75%)
Gallbladder	6 (13%)
Ampulla of Vater	6 (13%)
Previous lines of treatment - *n* (%)	
1	18 (38%)
2	24 (50%)
≥3	6 (12%)
Presence of biliary stent - *n* (%)	
Yes	34 (71%)
No	14 (29%)
Time from diagnosis to metastatic disease - months (range)	4 (0–21)
Time from metastatic disease to phase I study - months (range)	12 (2–47)

Toxicities of Phase I Trials

Experimental therapies were well tolerated, with most toxicities being grade 1 or 2 (83%). The most common toxicities were fatigue (69%), nausea (50%), transaminitis (33%) and anaemia (33%). Only 17% of patients experienced a grade 3 or 4 toxicity, with the most common treatment-related toxicities being neutropenia ($n = 2$) and transaminitis ($n = 2$). Most toxicities occurred within the first month of treatment (75%). Dose reductions due to toxicity were required in 10%, whereas a further 25% of patients with toxicity were able to continue dosing with a dose delay. Two (4%) patients had treatment-related inpatient admissions and one patient (2%) required cessation of therapy due to toxicity. There were no treatment-related deaths. Table 2 summarises the various toxicities experienced by patients.

Efficacy

Of the 39 evaluable patients there was one exceptional responder who had a partial response that was maintained for 1.5 years on a PARP inhibitor study. Molecular characterisation of this patient's archival tumour sample revealed mutations in an in-frame codon deletion of *ERBB2*, a truncated *PTEN* and a mutation in *ERCC3*. Eighteen other patients (46%) achieved stable disease as their best response. The median PFS was 1.9 months (95% confidence interval 1.5–2.4) (Figure 2) and the median overall survival was 5.1 months (95% confidence interval 3.2–6.2) (Figure 3). The clinical benefit rate at 4 months was 10% ($n = 5$).

Prognostic Factors

Cox proportional hazard modelling identified the following factors as significantly ($P < 0.1$) associated with overall survival: performance status, site of primary tumour (bile duct versus gallbladder or ampullary cancer), number of metastatic sites (two or more), peritoneal metastases, albumin, lactate dehydrogenase, RMH score and previous lines of therapy. In an adjusted model, the site of primary tumour (bile duct versus gall bladder/ampulla), RMH score (score of 2 or more versus 0) and number of previous lines of therapy (two versus one) remained significant ($P < 0.05$). Table 3 presents the various prognostic factors, their univariate and adjusted hazard ratios, 95% confidence intervals and significance levels.

Discussion

Clear conclusions regarding the efficacy of treatment for ABC have been hindered by the relative rarity of various individual primary sites (e.g. gallbladder, intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma),

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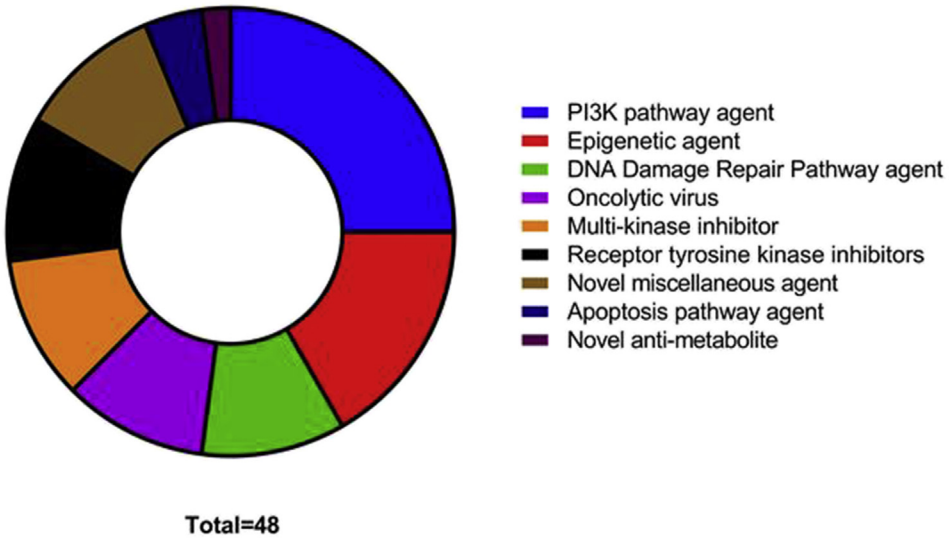

Fig 1. Various classes of phase I trial into which patients were enrolled for the management of advanced biliary tract carcinomas at the Royal Marsden Hospital Drug Development Unit.

Table 2
Adverse events on phase I trials

Toxicity	All grades - *n* (%)	Grades 3–4 - *n* (%)
Cutaneous/oral		
Mucositis	13 (27%)	1 (2%)
Rash	13 (27%)	1 (2%)
Gastrointestinal		
Diarrhoea	13 (27%)	0 (0%)
Nausea/vomiting	24 (50%)	0 (0%)
Transaminitis	16 (33%)	3 (6%)
Haematological		
Anaemia	16 (33%)	0 (0%)
Neutropenia	8 (17%)	5 (10%)
Febrile neutropenia	2 (4%)	2 (4%)
Thrombopenia	11 (23%)	1 (2%)
Respiratory		
Pneumonitis	0 (0%)	0 (0%)
Neurological		
Peripheral neuropathy	1 (2%)	0 (0%)
Miscellaneous		
Arrhythmia	2 (4%)	0 (0%)
Anorexia	6 (13%)	0 (0%)
Fatigue	33 (69%)	0 (0%)
Hyperglycaemia	5 (10%)	0 (0%)
Other	22 (46%)	2 (4%)

making it difficult to conduct large randomised trials for a particular group. Moreover, it has been shown that the molecular profile between these various tumours is different [7,8]. However, for logistical reasons, most trials tend to include all the various types into the study, leading to heterogeneous and inconclusive results. Nevertheless, several novel therapies are currently undergoing trials investigating their role in the management of ABC; results (of definitive benefit from these agents) are eagerly awaited [3].

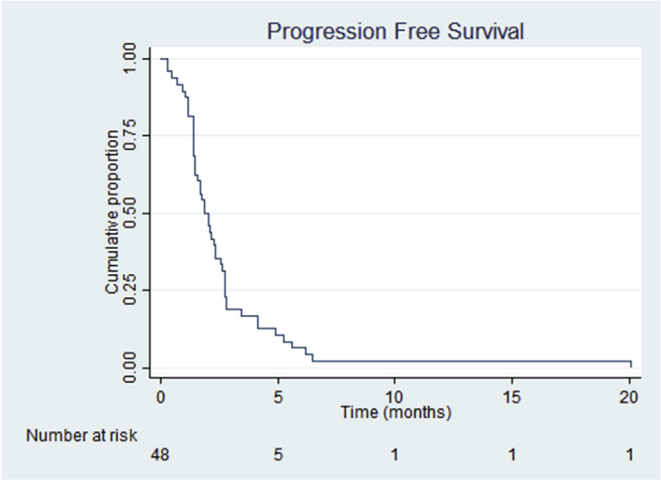

Fig 2. Kaplan–Meier curve of progression-free survival of advanced biliary tract carcinomas patients on phase I trials. Median progression-free survival: 1.9 months (95% confidence interval 1.5–2.4).

Anatomic tumour factors often play a role in the outcome of patients with ABC, as biliary obstruction is a common complication, and deranged liver function is often encountered. Due to the highly experimental nature of phase I studies, strict inclusion criteria with respect to organ function often render this subgroup of patients ineligible for all-comer studies. This is reflected in our study, with more than a fifth of the patients being referred having abnormal liver function and only a third of the patients able to enrol into a study. Of importance is the 20% of patients who were allocated a study, suggesting fitness at the point of first consultation, but had a deterioration in condition over a short period of time (usually less than a month), that led to eventual exclusion from the study. Given the aggressive nature of the disease, an early or fast-track referral to a

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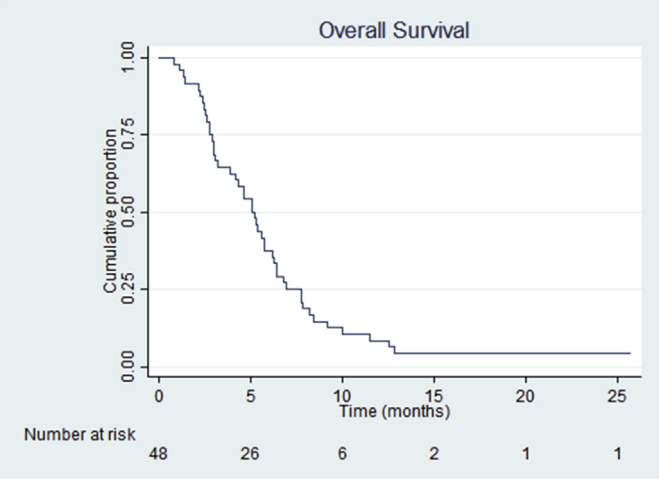

Fig 3. Kaplan–Meier curve of overall survival of advanced biliary tract carcinomas patients on phase I trials. Median overall survival: 5.1 months (95% confidence interval 3.2–6.2).

phase I unit may be considered, to allow patients to enter trials before the natural course of the disease reaches this inflexion point. It is interesting to note that ABC patients who did eventually enter a phase I study tolerated treatment well, with toxicity rates similar to other tumour groups, including the rate of transaminitis and hepatotoxicity, which would be of particular concern in this tumour group [9,10]. Drug-induced liver toxicity is a major concern for drug development and historical experience suggests that ABC patients are possibly at higher risk compared with other tumour groups (even with broadly similar inclusion criteria); for example, the rate of liver toxicity with sorafenib in biliary tract cancer was 6.5% [11] compared with <1% in renal cell cancer [12]. The clinical benefit rate at 4 months of 10% is at the lower end of average for phase I trials [10] and is reflective of disease biology. This is suggested by the multivariate analysis, which also identified higher tumour burden (number of metastatic sites and RMH score) as a poor prognostic factor. Among ABC

Table 3
Factors examined in overall survival models

Variable ($n = 48$)	Unadjusted		Adjusted	
	Hazard ratio (95% confidence interval)	*P* value	Hazard ratio (95% confidence interval)	*P* value
Age	1.00 (0.97–1.03)	0.997		
Gender: female	0.88 (0.49–1.58)	0.678		
ECOG PS	2.88 (1.45–5.70)	0.002	1.05 (0.42–2.63)	0.912
Primary site of disease				
Gall bladder versus bile duct	1.87 (0.77–4.58)	0.165	6.52 (1.78–23.94)	0.005
Ampulla versus bile duct	2.86 (1.17–6.97)	0.021	4.07 (1.22–13.55)	0.022
Biliary stent *in situ*	1.60 (0.83–3.06)	0.158		
Number of metastatic sites				
2	2.46 (1.26–4.84)	0.009	5.29 (2.02–13.85)	0.001
3	2.43 (0.96–6.19)	0.062	0.49 (0.10–2.43)	0.385
4	12.31 (2.50–60.74)	0.002	0.87 (0.06–12.22)	0.916
Hepatic metastasis	1.42 (0.74–2.71)	0.287		
Distant lymph node metastasis	0.95 (0.52–1.72)	0.858		
Peritoneal metastasis	1.96 (0.99–3.85)	0.052	1.16 (0.34–3.95)	0.808
Lung metastasis	1.12 (0.60–2.11)	0.715		
Bone metastasis	1.45 (0.51–4.12)	0.49		
Other metastases	3.03 (1.04–8.88)	0.043	2.97 (0.57–15.46)	0.196
Haemoglobin	0.88 (0.70–1.10)	0.268		
White cell count	1.08 (0.94–1.24)	0.253		
Neutrophil count	1.08 (0.94–1.25)	0.276		
Lymphocyte count	0.89 (0.53–1.49)	0.662		
Platelet count	1.00 (1.00–1.01)	0.137		
Albumin	0.93 (0.88–0.99)	0.013	0.92 (0.83–1.02)	0.124
Alanine transaminase	1.00 (0.99–1.01)	0.819		
Aspartate transaminase	1.00 (0.99–1.01)	0.702		
Gamma-glutamyl transpeptidase	1.00 (1.00–1.00)	0.671		
Alkaline phosphatase	1.00 (1.00–1.00)	0.487		
Lactate dehydrogenase	1.00 (1.00–1.00)	0.006	1.00 (1.00–1.00)	0.087
Bilirubin	1.00 (0.97–1.03)	0.789		
Calcium	0.64 (0.06–7.41)	0.724		
RMH score				
1 versus 0	1.77 (0.86–3.61)	0.119	1.17 (0.41–3.36)	0.774
2 or 3 versus 0	3.85 (1.67–8.86)	0.002	8.28 (1.72–39.90)	0.008
Number of lines of previous systemic therapy				
2 versus 1	0.55 (0.29–1.04)	0.066	0.29 (0.11–0.77)	0.012

ECOG PS, Eastern Cooperative Oncology Group performance status; RMH, Royal Marsden Hospital.

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cancers, bile duct cancer has a poorer prognosis compared with gallbladder and ampullary cancer, consistent with other studies of ABC [13]. In general, ABC patients enrolled onto phase I trials in our unit had survival outcomes similar to other tumour groups such as upper gastrointestinal, lung and mesothelioma [9,14,15]. The outcomes of ABC patients enrolled on phase I trials were also similar to several second-line studies conducted with chemotherapeutic agents, with a median PFS of 3 months and a median overall survival of 6 months [16]. These poor results explain the lack of second-line therapies approved for this tumour group and underpin the efforts required to identify novel mechanisms to target this disease through experimental therapeutics and phase I clinical trials.

Molecular profiling of biliary tract cancer has revealed five major groups of aberrations, each of which could be potentially targetable [17]. These include mutations in the MAPK pathway (such as *KRAS* and *BRAF*), cell cycle-related *p53* mutations and amplification of *CCND1*, FGFR-related fusions, *IDH* mutations and chromatin-modifying genes such as *ARID1A* and *BAP1*. The results of our molecular characterisation of ABC patients revealed a similar spectrum of mutations. Of note, our next generation sequencing panels did not include *IDH* mutations and, hence, these may have been missed in our cohort. The results from the molecular characterisation of the exceptional responder to PARP inhibitor therapy revealed PTEN loss on IHC as well as *ERBB2* and *ERCC3* mutations on next generation sequencing. It must be highlighted that the results of the molecular characterisation of the exceptional responder were not known at the time of enrolment into the study. PTEN loss has been shown to respond to PARP inhibition in preclinical models of other tumour types, such as endometrial cancer [18], as PTEN is involved in maintaining the stability of the DNA and loss of PTEN leads to synthetic lethality when combined with PARP inhibition. Similarly, ERCC is a key protein in the nucleotide excision repair pathway, and tumours with ERCC defects may also respond to PARP inhibition [19]. This highlights the emerging importance of molecular characterisation as a means to improving cancer outcomes and personalised medicine. However, one major concern with ABC is the access to easily available tumour tissue for testing, which is evident from our study as well, as several patients did not have sufficient tumour tissue to perform molecular characterisation. However, with the advent of analysis using newer technologies such as cfDNA and circulating tumour cells, perhaps these problems can be circumvented in the future [20].

Future trial design for ABC must consider moving away from grouping the various heterogeneous primary sites together and focusing on molecularly similar tumours [7]. Our study shows a prognostic difference between bile duct and gallbladder or ampullary cancer, supporting the need to study these tumour groups as individual entities. Several new trial designs are evolving for rare tumour groups, including basket and umbrella trials, Bayesian designs and *n* equals 1 trials [21]. Advances in liquid biopsies and the development of prognostic and predictive biomarkers will allow for easier characterisation of tumours that are notorious for deficiency of tissue samples, even for definitive clinical diagnosis [22].

Conclusion

Novel agents are required in the management of ABC and an early referral to a clinical trials unit is suggested. Although liver dysfunction is a common cause for screen failure prior to entering a study, carefully selected patients do not have a higher incidence of hepato-toxicity once enrolled on to a novel therapeutic trial. Future work will require more comprehensive molecular profiling in an attempt to understand the biology underlying the exceptional response, to identify new treatment options, to match patients in real time to targeted therapies and to design more innovative trials for these rare tumour groups.

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