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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Appendix
Safety and efficacy of ivosidenib in patients with IDH1-mutant advanced cholangiocarcinoma: first-in-human phase 1 study

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Principal investigators

The following investigators participated in this study (as principal or sub-investigator):
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France: Antoine Hollebecque.

Participating centres, principal investigators and number of CC patients treated

Centre	Principal investigator	No. of CC patients treated
Memorial Sloan Kettering Cancer Center, New York, NY	Ingo Mellinghoff	17
Sarah Cannon Research Institute, Nashville, TN	Howard A. Burris, III	11
University of Texas MD Anderson Cancer Center, Houston, TX	Filip Janku	10
Dana Farber Cancer Institute, Boston, MA	Patrick Wen	8
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University of Texas Southwestern Medical Center, TX	Elizabeth A. Maher	6
University of Colorado Hospital, Aurora, CO	Lia Gore	3
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START Center for Cancer Care, San Antonio, TX	Muralidhar Beeram	2
Sylvester Comprehensive Cancer Center, Miami, FL	Jonathan C. Trent	1

Supplementary methods

Ethical and regulatory considerations

This study (NCT02073994) was conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice and the ethical principles that have their origin in the Declaration of Helsinki. The trial was designed and monitored by the study sponsor, Agios Pharmaceuticals, Inc., Cambridge, MA, together with the study investigators. The protocol, amendments, and informed consent form were approved by each study site's Institutional Review Board/Independent Ethics Committee prior to the start of the study. Safety was regularly evaluated by the Clinical Study Team, which comprised the Sponsor (Medical Officer), Study Medical Monitor, and Investigators. All authors on the study had access to and involvement in the interpretation of the data, as well as input into and control of the content of the manuscript (overseen by Drs Abou-Alfa, Zhu, and Lowery).

The paper was drafted by the first and last authors in collaboration with the study sponsor, and was revised in collaboration with all authors. Assistance in manuscript preparation was provided by Yvonna Fisher-Jeffes, PhD, of Agios Pharmaceuticals, Inc. (Cambridge, MA) and Helen Varley, PhD, of Excel Medical Affairs (Horsham, UK). Confidentiality agreements exist between the sponsor and the study sites.

Screening procedures

Tissue from a pre-treatment biopsy was required for all patients for confirmatory testing and biomarker analysis during screening. Additional screening procedures included medical, surgical, and medication history; radiographic evaluation to determine the extent of disease (computed tomography [CT] or magnetic resonance imaging [MRI]); complete physical examination; vital signs; Eastern Cooperative Oncology Group Performance Status (ECOG PS); 12-lead electrocardiogram (ECG) and left ventricular ejection fraction (LVEF); a buccal swab for germline mutation analysis; clinical laboratory assessments (haematology, chemistry, coagulation, urinalysis, and serum pregnancy test); and blood samples for 2-hydroxyglutarate (2-HG) measurement. Urine samples for 2-HG measurement and blood samples for determination of plasma cholesterol and 4β-OH-cholesterol levels were conducted for patients enrolled in the dose-escalation portion only.

Dose-limiting toxicities

Safety assessments conducted during the treatment period included physical examinations, vital signs, ECOG PS, LVEF, and clinical laboratory assessments (haematology, chemistry, coagulation, and urinalysis). Toxicities were graded and documented according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. A dose-limiting toxicity (DLT) was defined as any CTCAE event of grade 3 or above, reported to be related or possibly related to ivosidenib. Other emergent toxicities that were not explicitly defined by the DLT criteria were also evaluated for possible DLT designation. If none of the three patients in a cohort experienced a DLT, the next three patients were treated at the next higher dose level. However, if one of the first three patients experienced a DLT, three more patients were treated at the same dose level. The dose escalation continued until at least two out of three to six patients experienced DLTs. The dose level just below this dose level was then identified as the maximum tolerated dose (MTD) (ie, the highest dose that caused DLTs in fewer than two of six patients). If the MTD cohort included only three patients, an additional three patients were enrolled to confirm that fewer than two of six patients experience a DLT at that dose.

Increases in the dose of ivosidenib for each dose cohort were guided by an accelerated titration design, where the daily dose could be doubled from one cohort to the next until NCI CTCAE v4.03 grade ≥2 ivosidenib-related toxicity was observed in any patient within the cohort. Subsequent increases in dose were guided by the observed toxicity, and pharmacokinetic (PK) and pharmacodynamic (PD) data, until the MTD was determined. If no DLTs were identified during the dose-escalation portion, dose escalation continued for at least two dose levels above the projected maximum clinically effective exposure, as determined by an ongoing assessment of PK/PD and any observed clinical activity.

Preclinical evidence has suggested that ivosidenib may increase risk for development of QT prolongation. Patients were therefore monitored for QT prolongation using 12-lead ECGs. During the dose-escalation phase, ECGs were conducted three days prior to dosing (day −3; first three patients of each cohort) as well as on days 1, 8, and 15. During the dose-expansion phase, ECGs were conducted in triplicate on day 1 of cycles 1 and 2 at the following time points: pre dose (within 30 min), and at 2, 3, 4, 6, and 8 h post dose (± 15 min). When the timing of a PK/PD blood sample coincided with the timing of an ECG measurement, the ECG was completed before blood sample collection (within 10 min). Single 12-lead ECGs were also conducted on day 1 of every cycle, beginning with cycle 3.

Clinical efficacy

Clinical efficacy was assessed approximately every 56 (± 3) days by the investigators using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[1] Responses of target lesions assessed were complete response (CR), partial response (PR), stable disease (SD), and progressive disease. The objective response rate was defined as the rate of overall best response of CR + PR. Other measures of clinical activity included duration of response, and time to first response. Progression-free survival was defined as the interval in months from the date of the first dose to the date of disease progression, defined as documented progressive disease or death, whichever occurred first. Overall survival (defined as the time from first ivosidenib dose to death by any cause) was added as a secondary endpoint as part of a subsequent amendment to the protocol.

All patients underwent radiographic evaluations (CT/MRI) to obtain tumour measurements at screening and approximately every 56 days thereafter (± 3 days) while on treatment, independent of dose delays and/or dose interruptions, and/or at any time when progression of disease was suspected. An assessment was also conducted at the end-of-treatment visit for patients who discontinued the study owing to reasons other than disease progression. Positron-emission tomography scans were also conducted at screening and, if positive, were conducted post screening at the same timepoints as CT/MRI scans.

Tumour biopsy and plasma sampling were performed at screening, at the time of the first assessment of response (cycle 3 day 1), approximately 4 months later (cycle 7 day 1) if the patient had SD or PR at that assessment, and at any time disease progression was suspected and/or at the end of treatment.

Patients continued treatment with ivosidenib until they experienced disease progression, development of other unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, loss to follow-up, or the sponsor ending the study, whichever occurred first. Patients who experienced disease progression (determined by RECIST), who were, in the opinion of the investigator, benefiting from treatment (eg, progressing slower) could be allowed to continue on the study drug. All patients underwent an end-of-treatment assessment (within ~5 days of last dose); in addition, a follow-up assessment was scheduled 28 days after the last dose.

Patients were contacted every 3 months until 12 months after the last patient discontinued study treatment (or until the patient withdrew consent, was lost to follow-up, or died) for the assessment of survival status and to document the receipt and type of subsequent anticancer therapy.

Pharmacokinetic and pharmacodynamic sampling

In the dose-escalation phase, the first three patients enrolled in each cohort received a single dose of ivosidenib on day −3. To evaluate ivosidenib concentrations and 2-HG levels over time, serial blood samples were then obtained from patients over 3 days: at 30 min; at 1, 2, 3, 4, 6, 8, and 10 h (± 10 min); and at 24, 48, and 72 h (± 1 h) post dose. For those patients who did not undergo the day −3 PK/PD assessments, clinical observations were conducted for the first 4 h following the first dose of ivosidenib on day 1 of cycle 1. All patients underwent additional PK/PD assessments (over a 10-h period) on days 15 and 29 (day 1 of cycle 2). Additional pre-dose urine and/or blood sampling was conducted on days 8 and 22 of cycle 1, day 15 of cycle 2, days 1 and 15 of cycle 3, and day 1 of all subsequent cycles.

In the dose-expansion phase, blood samples for PK/PD assessments were drawn on day 1 of cycles 1 and 2 at the following time points: pre dose (within 30 min), and 2, 3, 4, 6, and 8 h (± 10 min) post dose. Additional blood samples for PK/PD assessments were drawn pre dose (within 30 min) on days 8 and 15 of cycle 1, day 1 of cycle 3 and at the end-of-treatment visit.

Plasma ivosidenib was measured using two validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The lower limit of quantification (LLOQ) was 1·00 ng/mL (low-range assay) or 50·0 ng/mL (high-range assay). The two methods were cross-validated and found to deliver comparable results within acceptable limits.

Plasma 2-HG concentrations were measured using a qualified LC-MS/MS method with an LLOQ of 30·0 ng/mL. 2-HG concentrations in bone marrow were quantified using a qualified LC-MS/MS method with an LLOQ of 100 ng/mL.[2,3]

Analysis of baseline co-occurring mutations

Exploratory assessments included confirmation of baseline mIDH1 status and identification of co-occurring mutations. Archival formalin-fixed paraffin-embedded samples were collected for analysis by next-generation sequencing (NGS) using the FoundationOne® CDX panel (Foundation Medicine, Inc., Cambridge, MA),[4] which includes 361 genes. Fresh-frozen tumour samples were also collected at baseline and at specified on-treatment timepoints, and analysed by NGS using the ACE Extended Cancer Panel (Personalis, Menlo Park, CA), which includes 1642 genes. Because the majority of samples did not have a matched germline sample for comparison, the reported variants may be the result of: 1) normal germline variation between the patient and the hg19 reference genome; 2) somatic passenger mutations that are not known to be oncogenic; 3) somatic mutations that are known or likely to be oncogenic; or 4) a germline cancer susceptibility variant. Foundation Medicine Inc. provided a “known/likely oncogenic” call to identify classes 3 and 4 based on the current literature and

likely somatic status of the variant, but it was also observed that these reported calls changed over time as the oncology literature grew. Personalis does not provide a "known/likely" annotation. Therefore, for both the Foundation Medicine Inc. and Personalis datasets, each variant was curated at Agios using a number of public resources: COSMIC (http://cancer.sanger.ac.uk/cosmic), varsome (https://varsome.com/), gnomad (http://gnomad.broadinstitute.org/), CIVIC (https://civic.genome.wustl.edu/home), oncoKB (http://oncokb.org/#/), cBioPortal (http://www.cbioportal.org/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), and PubMed https://www.ncbi.nlm.nih.gov/pubmed). To provide an overview of co-occurring mutations at baseline for this cohort, detected known/likely oncogenic variants were compiled from pre-treatment samples from both platforms, considering only genes that are included in both panels. A given gene was shown as mutated if a known/likely variant was detected in at least one platform.

Longitudinal DNA mutation analysis was also performed on optional post-treatment fresh-frozen biopsies (ACE Extended Cancer Panel).

Ki-67 immunohistochemistry

Immunohistochemistry (IHC) to assess the proliferation marker Ki-67 was performed in accordance with Mosaic Laboratories' Standard Operating Procedures and validated protocol. The Ki-67 IHC assay (mouse clone MIB-1, Catalog# M7240, Agilent, Carpinteria, CA) was designed and validated to be a laboratory-developed test. After heat-induced epitope retrieval, tissue sections were incubated with the Ki-67 antibody followed by manual detection with EnVision Mouse HRP (Agilent). Staining was visualised with DAB chromogen. Stained slides were scanned using an Aperio AT Turbo system (Aperio, Vista, CA) to produce whole slide images.

Tissues stained for Ki-67 (mouse clone MIB-1) were evaluated by image analysis with a Nuclear v9 algorithm from Aperio to avoid potential bias. The selected region of interest included the area of tumour tissue with intervening stroma. Areas excluded from analysis include normal tissue, larger stromal areas, necrotic tissue, pigment, and staining artefact. The percentage of positive cells within the region of interest was reported.

Supplementary results

The full population of this clinical trial includes patients with a variety of mIDH1 advanced solid tumours, including cholangiocarcinoma (n=73), chondrosarcoma (n=21), glioma (n=66), as well as other mIDH1 solid tumours (n=8). Only results from the cholangiocarcinoma patient cohort are reported here; results from other patient cohorts will be reported separately. In addition, a comprehensive analysis of the PK/PD of ivosidenib in the full mIDH1 solid tumour patient cohort (N=168) has been published.[5]

Treatment duration and exposure

The median treatment duration for the cholangiocarcinoma population (N=73) was 3·7 months (range 0·6–23·5), with 12 (16.4%) patients remaining on treatment as of May 12, 2017. Overall, 27 (37·0%) of 73 patients had been exposed to ivosidenib for ≥6 months, 13 (17·8%) of whom had been treated for ≥12 months; 46 patients had been exposed to ivosidenib for <6 months.

Dose modifications

Dose reductions during the study were uncommon, and most reductions were from 500 mg once daily (QD) to 400 mg QD. In the cholangiocarcinoma population, five of 73 (6·8%) patients had a dose reduction. Of the 73 patients, three (4·1%) had a dose reduction owing to an adverse event.

In the cholangiocarcinoma population, 19 of 73 (26%) patients had at least one dose held during the study, primarily owing to AEs; 14 of these were patients who received the 500 mg QD dose. The median number of days that doses were held was 8 (range 1·0–79·0).

PD evaluation in tumor samples

Based on the limited data from this patient cohort, administration of multiple doses of ivosidenib at 500 mg QD resulted in almost 100% inhibition of 2-HG concentration in tumor biopsy samples. Exploratory PK/PD correlations of 2-HG concentration in tumor biopsy samples versus 2-HG concentration in plasma suggested that plasma 2-HG concentration decreased with decreasing 2-HG concentration in tumors.

Supplementary tables

Table 1: **Treatment-emergent adverse events occurring in >10%* (all grades) of patients with cholangiocarcinoma**

	500 mg QD (n=62)		Overall (N=73)	
	All grades	Grade ≥3	All grades	Grade ≥3
At least one AE	62 (100%)	24 (38·7%)	73 (100%)	32 (43·8%)
Fatigue	29 (46·8%)	1 (1·6%)	31 (42·5%)	2 (2·7%)
Nausea	22 (35·5%)	1 (1·6%)	25 (34·2%)	1 (1·4%)
Diarrhoea	19 (30·6%)	0	23 (31·5%)	0
Abdominal pain	18 (29·0%)	2 (3·2%)	20 (27·4%)	2 (2·7%)
Decreased appetite	19 (30·6%)	0	20 (27·4%)	1 (1·4%)
Vomiting	15 (24·2%)	0	17 (23·3%)	0
Ascites	10 (16·1%)	3 (4·8%)	13 (17·8%)	4 (5·5%)
Peripheral oedema	11 (17·7%)	0	13 (17·8%)	0
Pyrexia	11 (17·7%)	0	12 (16·4%)	0
Cough	10 (16·1%)	0	11 (15·1%)	1 (1·4%)
Abdominal distension	8 (12·9%)	2 (3·2%)	10 (13·7%)	2 (2·7%)
Back pain	10 (16·1%)	0	10 (13·7%)	0
Musculoskeletal pain	9 (14·5%)	0	10 (13·7%)	0
Anaemia	7 (11·3%)	2 (3·2%)	9 (12·3%)	3 (4·1%)
Abdominal pain upper	6 (9·7%)	0	8 (11·0%)	0
Electrocardiogram QT prolongation	8 (12·9%)	1 (1·6%)	8 (11·0%)	1 (1·4%)
Hypokalaemia	7 (11·3%)	1 (1·6%)	8 (11·0%)	1 (1·4%)

Data are n (%). AE=adverse event. QD=once daily. *Based on the overall population of 73 patients.

Table 2: **Most frequent (≥10% of patients overall) treatment-emergent adverse events (any grade) by daily dose**

Event	100 mg BID (n=2)	300 mg QD (n=3)	400 mg QD (n=1)	500 mg QD (n=62)	800 mg QD (n=2)	1200 mg QD (n=3)	All patients with cholangio-carcinoma (N=73)
Fatigue	0	1 (33·3%)	0	29 (46·8%)	0	1 (33·3%)	31 (42·5%)
Nausea	0	1 (33·3%)	1(100%)	22 (35·5%)	0	1 (33·3%)	25 (34·2%)
Diarrhoea	0	1 (33·3%)	0	19 (30·6%)	1 (50%)	2 66·7%)	23 (31·5%)
Abdominal pain	1 (50%)	0	0	18 (29·0%)	0	1 (33·3%)	20 (27·4%)
Decreased appetite	0	0	0	19 (30·6%)	0	1 (33·3%)	20 (27·4%)
Vomiting	1 (50%)	1 (33·3%)	0	15 (24·2%)	0	0	17 (23·3%)
Ascites	1 (50%)	1 (33·3%)	0	10 (16·1%)	0	1 (33·3%)	13 (17·8%)
Peripheral oedema	0	1 (33·3%)	0	11 (17·7%)	0	1 (33·3%)	13 (17·8%)
Pyrexia	0	1 (33·3%)	0	11 (17·7%)	0	0	12 (16·4%)
Cough	0	0	0	10 (16·1%)	0	1 (33·3%)	11 (15·1%)
Abdominal distension	0	0	0	8 (12·9%)	1 (50%)	1 (33·3%)	10 (13·7%)
Back pain	0	0	0	10 (16·1%)	0	0	10 (13·7%)
Musculoskeletal pain	0	0	0	9 (14·5%)	0	1 (33·3%)	10 (13·7%)
Anaemia	1 (50%)	0	0	7 (11·3%)	0	1 (33·3%)	9 (12·3%)
Abdominal pain upper	1 (50%)	1 (33·3%)	0	6 (9·7%)	0	0	8 (11·0%)
Electrocardiogram QT prolongation	0	0	0	8 (12·9%)	0	0	8 (11·0%)
Hypokalaemia	0	0	0	7 (11·3%)	0	1 (33·3%)	8 (11·0%)

Data are n (%). BID=twice daily. QD=once daily.

Table 3: **On-treatment deaths due to AEs (both 500 mg)**

Patient	System organ class/Preferred term [verbatim]	Relationship*	Primary cause of death due to underlying malignancy*
1	Infections and infestations/*Clostridium difficile* infection	Not related	Yes
2	Injury, poisoning and procedural complications/Procedural haemorrhage	Not related	Yes

*According to investigator.

Table 4: **Most common adverse events (≥5% of any grade) considered to be related to ivosidenib by the investigator**

Event	Overall population, N=73	
	Any grade	**Grade ≥3**
Any treatment-related adverse event	46 (63·0%)	4 (5·5%)
Fatigue	17 (23·3%)	2 (2·7%)
Nausea	14 (19·2%)	0
Vomiting	10 (13·7%)	0
Diarrhoea	9 (12·3%)	0
Decreased appetite	6 (8·2%)	0
Electrocardiogram QT prolongation	4 (5·5%)	0
Dysgeusia	4 (5·5%)	0
Peripheral oedema	4 (5·5%)	0

Data are n (%).

Table 5: **Summary of responses in patients achieving a partial response**

Patient	Prior treatment	Duration on last therapy (months)	Ivosidenib dose	Time to response (months)	Treatment duration (months)	Duration of response (months)	Sum of baseline target lesions (mm)	% maximum change in target lesions at PR	PFS on ivosidenib (months)
1	Gem/Cis, Gem/Ox, Cis/ docetaxel	1·1	300 mg QD	3·9	9·4	5.6	99	–45·5%	9·4
2	Gem/Cis, FOLFIRI, paclitaxel, experimental agent	2·1	500 mg QD	7·4	14·7	7.3	161	–50·9%	14·7
3	Gem/Cis, Gem/Carbo	2·7	500 mg QD	3·7	16·6	12.9	72	–81·9%	16·6+
4	Gem/Cis	1·4	500 mg QD	5·6	15·3	9.2	117	–38·5%	14·8+

Carbo=carboplatin. Cis=cisplatin. Gem=gemcitabine. FOLFIRI=folinic acid, fluorouracil and irinotecan. Ox=oxaliplatin. PFS=progression-free survival. PR=partial response. QD=once daily.

Table 6: **Investigator-reported responses and overall survival for all cholangiocarcinoma patients**

Response	Ivosidenib daily dose level						Overall (N=73)
	100 mg BID (n=2)	300 mg QD (n=3)	400mg QD (n=1)	500 mg (n=62)	800 mg QD (n=2)	1200 mg QD (n=3)	
Objective response rate*	0	1 (16·7%)	0	3 (4·8%)	0	0	4 (5·5%) [1·5–13·4]
CR	0	0	0	0	0	0	0
PR	0	1 (16·7%)	0	3 (4·8%)	0	0	4 (5·5%)
SD	1 (16·7%)	1 (16·7%)	1 (16·7%)	36 (58·1%)	1 (16·7%)	1 (16·7%)	41 (56·2%)
PD	0	1 (16·7%)	0	21 (33·9%)	1 (16·7%)	1 (16·7%)	24 (32·9%)
Not evaluable/not assessed	1 (16·7%)	0	0	2 (3·2%)	0	1 (16·7%)	4 (5·5%)
Overall survival, months†	-	-	-	27·3 [9·8–27·3]	-	-	13·8 [11·1–29·3]

Data are n (%) unless otherwise indicated. Overall survival data are not available for dose groups other than 500 mg QG owing to small sample sizes. CR=complete response. NE=not estimable. PR=partial response. SD=stable disease. PD=progressive disease. *Data are n (%) [95% CI]. †Data are median [95% CI].

Table 7: **Kaplan-Meier progression-free survival and overall survival rates (%) at 3, 6, 9, and 12 months by dose level and overall**

	Ivosidenib daily dose level			
	<500 mg (n=6)	**500 mg (n=62)**	**>500 mg (n=5)**	**Overall (N=73)**
Progression-free survival rate				
3 months	80·0%	62·8%	50·0%	63·1%
6 months	80·0%	36·7%	50·0%	40·1%
9 months	80·0%	26·1%	50·0%	31·1%
12 months	26·7%	21·8%	25·0%	21·8%
Overall survival rate				
3 months	100%	95·1%	100%	95·8%
6 months	75·0%	79·2%	75·0%	78·6%
9 months	75·0%	70·6%	75·0%	71·6%
12 months	75·0%	54·7%	50·0%	56·5%

Table 8: **Patients without central mIDH1 detection at baseline**

Subject	Best response	PFS (months)	Baseline plasma 2-HG (ng/mL)	Baseline tumour 2-HG (µg/mL)	Local pathology report
1	PD	1·8	65·7	2·57	R132 (Qiagen PCR, extremely low levels and subclonal to KRAS mutant)
2	SD	7·3	139	<30	R132C (FMI)
3	PD	1·9	160	NA	R132C (MGH), low VAF noted
4	SD	12·1	197	<30	R132C (BWH)
5	PR	16·6	536	NA	R132C (FMI)
6	SD	9·2	714	NA	R132L (FMI)
7	SD	5·1	2390	2150	R132G (NGS), VAF 54%
8	SD	1·9	NA	7·78	R132L (MGH)

BWH=Brigham and Women's Hospital. FMI=Foundation Medicine, Inc. MGH=Massachusetts General Hospital. NA=not available. NGS=next-generation sequencing. PCR=polymerase chain reaction. PD=progressive disease. PR=partial response. SD=stable disease. VAF=variant allele frequency.

Supplementary figures

Figure 1: **Study design**
The dose-escalation phase used a standard 3 + 3 design (three to six patients per dose level) and was to continue until ≥2 patients experienced dose-limiting toxicities. Dosing started with 100 mg twice daily (BID), following which, dosing proceeded once daily (QD), based on a favourable pharmacokinetic profile and long half-life, at 300 mg, 400 mg, 500 mg, 800 mg, and 1200 mg QD. This report focuses solely on the mIDH1-cholangiocarcinoma patient cohort treated with ivosidenib in this study (other cohorts will be reported elsewhere). BID=twice daily. ECOG PS=Eastern Cooperative Oncology Group Performance Status. mIDH1=mutant isocitrate dehydrogenase-1. QD=once daily. RECIST=Response Evaluation Criteria in Solid Tumors. *Determined locally by participating sites with retrospective confirmation.

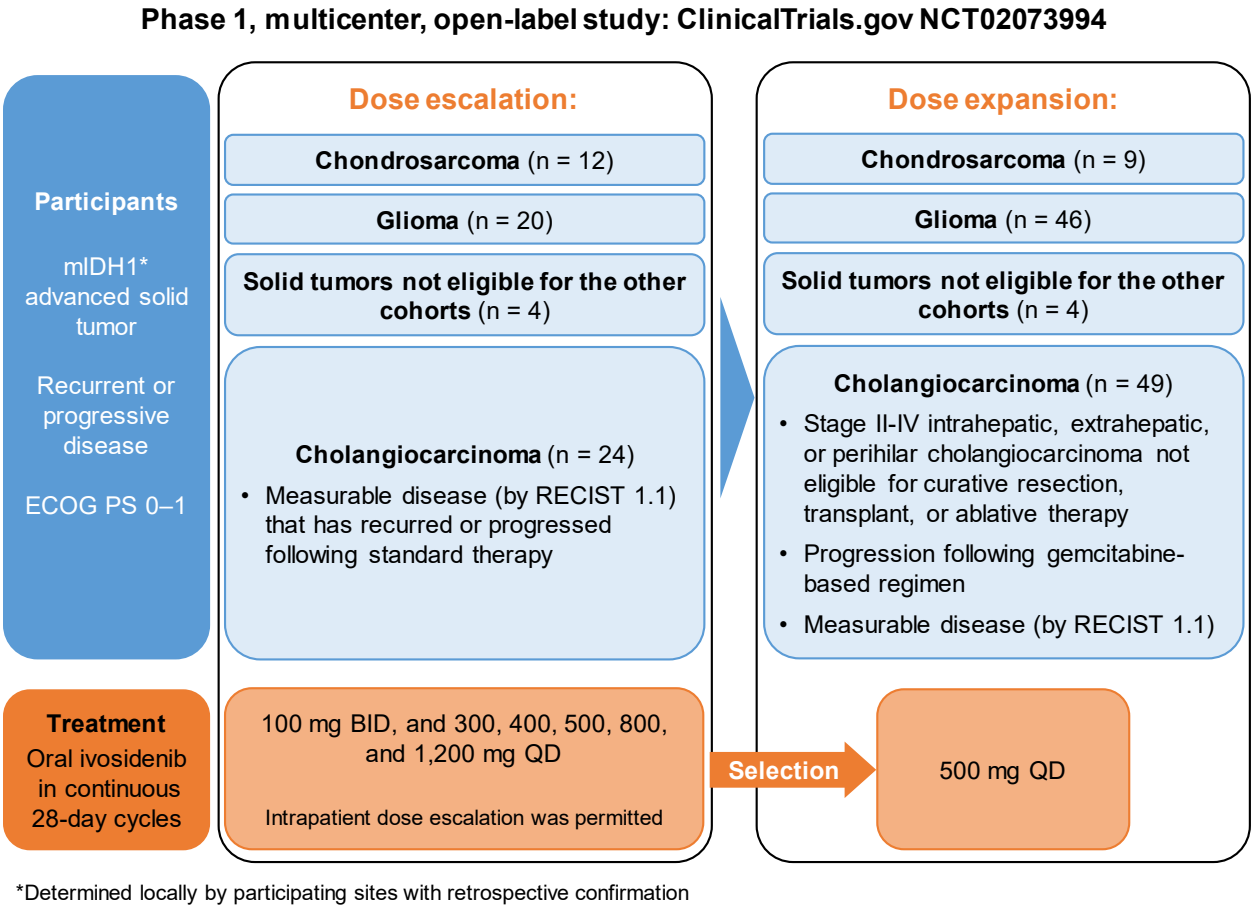
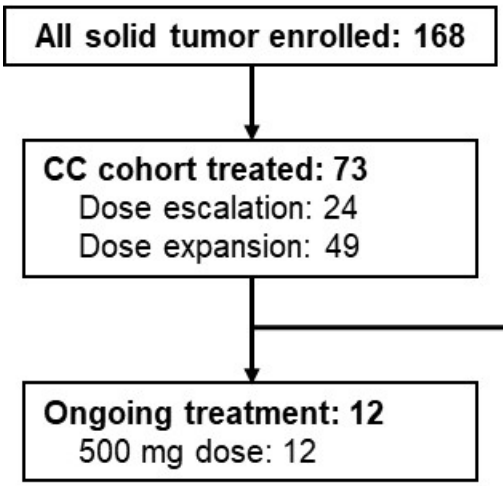


Figure 2: **Patient disposition (as of data cutoff date May 12, 2017)**
CC=cholangiocarcinoma.



	Overall N = 73
Discontinued treatment	**61**
Disease progression	50
Clinical progression	7
Withdrawal of consent	2
Adverse event	1
Death	1
Entered survival follow-up	**27**
Death	21

Figure 3: **2-HG inhibition and correlation with clinical outcome**
Horizontal dashed lines denote median, horizontal solid lines denote mean, boxes denote 25th to 75th percentiles; whiskers were plotted using the Tukey method. For NA, n=3; PD, n=18; PR, n=4; SD, n=37.
2-HG=2-hydroxyglutarate. NA=not assessed. PD=progressive disease. PR=partial response. SD=stable disease.

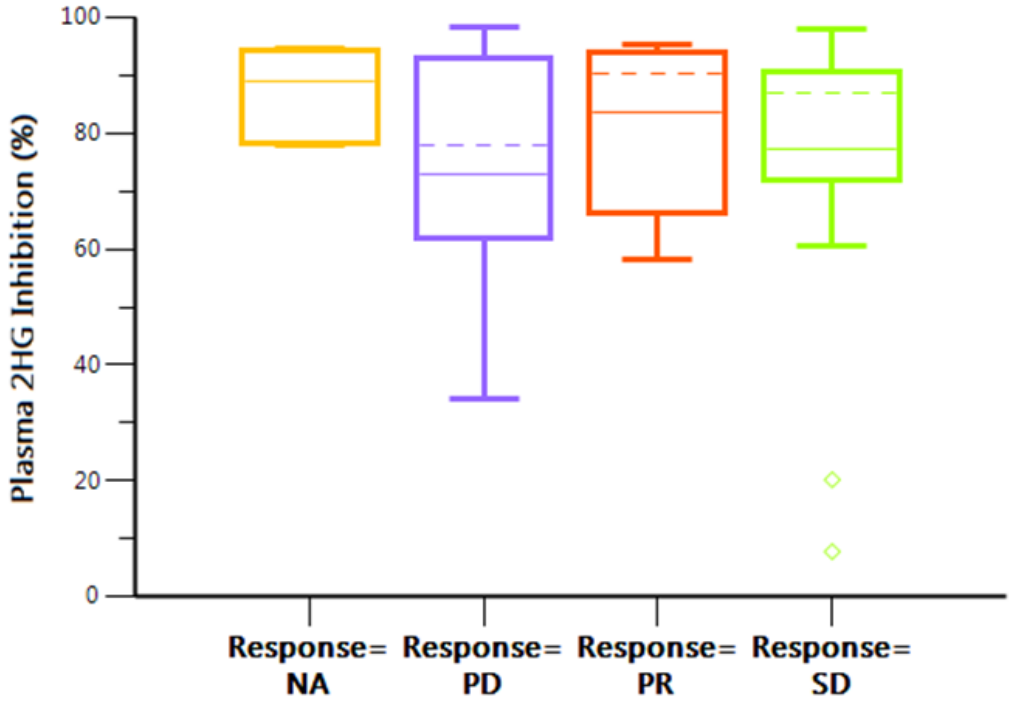
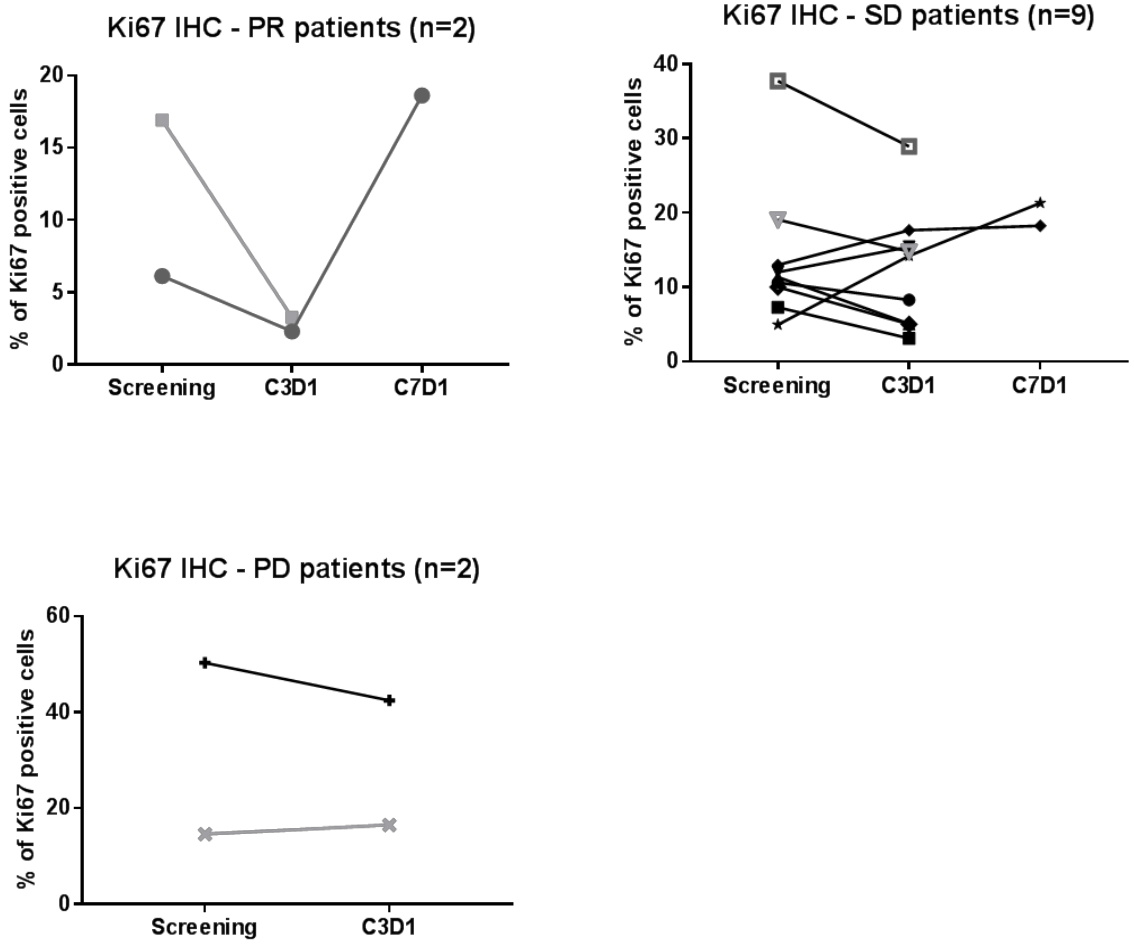


Figure 4: **Ivosidenib was associated with a reduction in the tumour proliferation marker Ki-67**
On cycle 3 day 1, of the patients analysed for Ki-67 (n=13), a reduction in Ki-67-positive cells was observed in two patients achieving a partial response (top left; 100%, p=0·243) and in six of nine patients with stable disease (top right; 66·6%, p=0·50). One of two patients with progressive disease showed modest reduction of Ki67 staining (bottom left; 50%, p=0·99). P-values were calculated by comparing Ki-67 levels at Screening and C3D1 in each plot. BOR=best overall response. C3D1=cycle 3 day 1. C7D1=cycle 7 day 1. IHC=immunohistochemistry. PD=progressive disease. PR=partial response. SD=stable disease. *Best overall response cutoff date: May 12, 2017.



Patient	BOR*	% Ki-67-positive cells		% of change C3D1 *vs* screening
		Screening	C3D1	
1	PR	16·9%	3·3%	–80·7%
2	PR	6·1%	2·3%	–62·7%
3	SD	7·3%	3·1%	–57·2%
4	SD	11·3%	5·1%	–55·2%
5	SD	14·8%	7·4%	–49·9%

6	SD	37·7%	28·9%	–23·3%
7	SD	19·1%	14·8%	–22·6%
8	SD	10·6%	8·3%	–22·0%
9	SD	12·0%	15·4%	28·4%
10	SD	13·0%	17·7%	36·1%
11	SD	5·0%	14·2%	186·7%
12	PD	50·2%	42·4%	–15·6%
13	PD	14·6%	16·5%	12·9%
Mean				–9·6%
Median				–22·6%

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