Efficacy of TAS-120, an irreversible fibroblast growth factor receptor (FGFR) inhibitor, in cholangiocarcinoma patients with FGFR pathway alterations who were previously treated with chemotherapy and other FGFR inhibitors

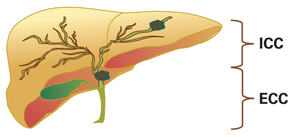
O-001

Funda Meric-Bernstam,[1] Hendrik-Tobias Arkenau,[2] Ben Tran,[3] Rastilav Bahleda,[4] Robin Kate Kelley,[5] Cinta Hierro,[6] Daniel H. Ahn,[7] Andrew X. Zhu,[8] Milind Javle,[1] Robert Winkler,[9] Helen He,[9] Jerry Huang,[9] Lipika Goyal[8]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Sarah Cannon Research Institute, HCA Healthcare, London, UK; [3]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [4]Gustave Roussy Cancer Centre, Villejuif, France; [5]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA; [6]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [7]Mayo Clinic, Scottsdale, AZ, USA; [8]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [9]Taiho Oncology, Inc., Princeton, NJ, USA

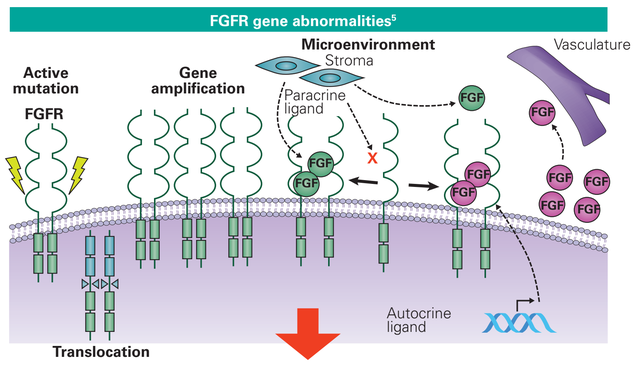
Introduction

Cholangiocarcinoma (CCA) and FGFR pathway



- CCA has poor prognosis and limited treatment options
- In previously treated CCA, median PFS is 3.2 months and objective response rate is 5-11%[1]
- FGFR2 fusions: ~15% of intrahepatic CCAs[2-4]

FGFR gene abnormalities[5]



- **Ligand-independent, unregulated activation of downstream pathway**
- **Activation by micro-environmental stimulus**

TAS-120: Highly selective, irreversible pan-FGFR inhibitor

- TAS-120 inhibits FGFR1-4

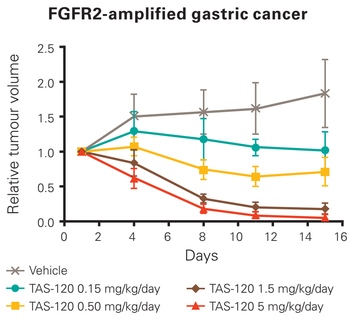
Enzyme IC_{50} (nM)	
FGFR1	3.9
FGFR2	1.3
FGFR3	1.6
FGFR4	8.3

- TAS-120 exhibited similar IC_{50} for FGFR2 wild type and key mutants (eg, gatekeeper mutant V565I)

pFGFR2 inhibition IC_{50} (nM)	
FGFR2 WT	0.9
FGFR2 V565I	1.3
FGFR2 N550H	3.6
FGFR2 E566G	2.3
FGFR2 K660M	5.2

- Strong anti-tumour efficacy of TAS-120 in OCUM-2MD3 nude mice xenograft model bearing gastric tumours with *FGFR2* amplification[6]

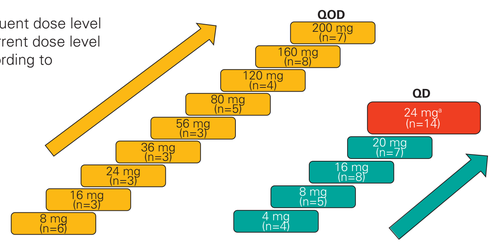
FGFR2-amplified gastric cancer



Methods

TAS-120: Study design and patient enrolment in Phase 1 dose escalation

Escalation to each subsequent dose level occurred only after the current dose level was found to be safe according to a '3+3' design



Objectives: Primary: MTD/RP2D
Secondary: safety, tolerability and preliminary anti-tumour activity

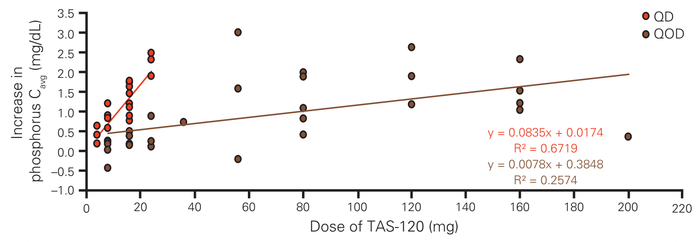
Key inclusion/exclusion criteria

- Age ⩾18 years
- Locally confirmed FGF/FGFR alteration[b]
- Unresectable or metastatic disease
- Failed standard therapies
- Prior FGFR inhibitor was allowed
- Adequate AST, ALT (⩽3 × ULN, if liver metastases ⩽5 × ULN) and total bilirubin (⩽1.5 × ULN)
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Excluded if evidence of ectopic mineralisation / calcification or keratopathy

NCT02052778. The dose-escalation part of the study is completed and 20 mg QD is the MTD/RP2D
[a]24 mg QD is the dose-limiting toxicity level; [b]From dose level 1 in QD and dose level 5 in QOD
ALT, alanine aminotransferase; AST, aspartate aminotransferase; MTD, maximum tolerated dose; QOD, every other day; QD, once daily; RP2D, recommended Phase 2 dose; ULN, upper limit of normal

Results

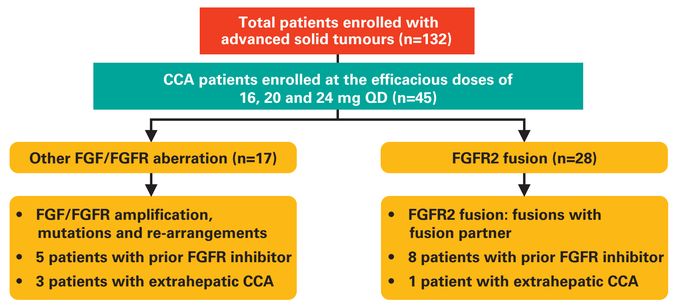
Increase in serum phosphorus with TAS-120 dose



Increase in phosphorus C_{avg} (mg/dL) = $(AUC_{pi,ss} - AUC_{pi,D1})/T_{last}$
$AUC_{pi,ss}$; AUC of phosphorous after repeated doses
$AUC_{pi,D1}$; AUC of phosphorous after a single dose
T_{last}: QD 24 hours, QOD 48 hours

- In both dosing schedules, C_{avg} of phosphorus was increased with increasing dose of TAS-120
- The steeper response of C_{avg} of phosphorus and the stronger correlation of C_{avg} of phosphorus with dose were observed in the QD schedule compared with the QOD schedule

TAS-120: Patients in the CCA subgroup (as of 2 February 2018)



Cut-off date: 2 February 2018

Patient characteristics at baseline

Characteristic	Total (n=45)
Gender, n (%)	
Female	34 (75.6)
Male	11 (24.4)
Median age, years (range)	54 (29-73)
Race, n (%)	
Caucasian / white	35 (77.8)
Black	1 (2.2)
Asian	3 (6.7)
Other	3 (6.7)
Not collected	3 (6.7)
Primary tumour, n (%)	
Intrahepatic	41 (91.1)
Extrahepatic	4 (8.9)
Number of prior regimens, n (%)	
1	13 (28.9)
2	13 (28.9)
⩾3	19 (42.2)
Prior FGFR inhibitor	13 (28.9)

Most frequently reported adverse events >20%

Preferred term	16, 20 and 24 mg QD (n=45), %		
	All grades	Grade 3	Drug-related grade 3
All events	97.8	62.2	51.1
Hyperphosphataemia	80.0	24.4	22.2
Constipation	37.8	2.2	2.2
Increased AST	35.6	4.4	2.2
Increased ALT	31.1	6.7	6.7
Diarrhoea	31.1	2.2	2.2
Dry skin	28.9	0	0
Dry mouth	26.7	0	0
Nausea	24.4	4.4	0
Palmar-plantar erythrodysesthesia syndrome	22.2	4.4	4.4
Stomatitis	22.2	0	0

Grade 3 hyperphosphataemia = 7.0 < p⩽10.0 (mg/dL); no grade 4 events were seen for the above preferred terms

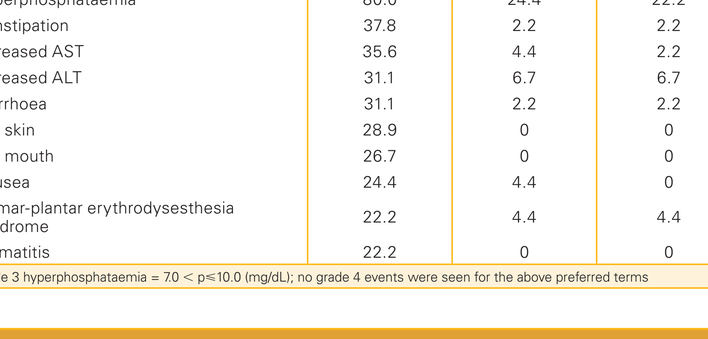
TAS-120: FGF/FGFR status in the CCA subgroup

FGF/FGFR status	Alteration	Patients, n (%) (n=45)[a]
FGFR1	Amplification	2 (4.4)
	Re-arrangement	1 (2.2)
FGFR2	**Fusion**	**28 (62.2)**
	Re-arrangement	5 (11.1)
	Amplification	2 (4.4)
	Mutation	5 (11.1)
FGF	Amplification	4 (8.8)
Unknown		3 (6.6)

FGFR2 fusion partner	Patients, n
BICC1	8
SPERT	2
POC1B	2
WAC	2
CCDC6	1
ATF1	1
CBX5	1
SORBS1	1
TRA2B	1
ZYMY4	1
TNS1	1
NRAP	1
AHCYL1	1
ETV6	1
KIAA1217	1
AFF1	1
PAWR	1
C10ORF118	1

[a]5 patients have >1 FGF/FGFR abnormality so the percentages do not add up to 100

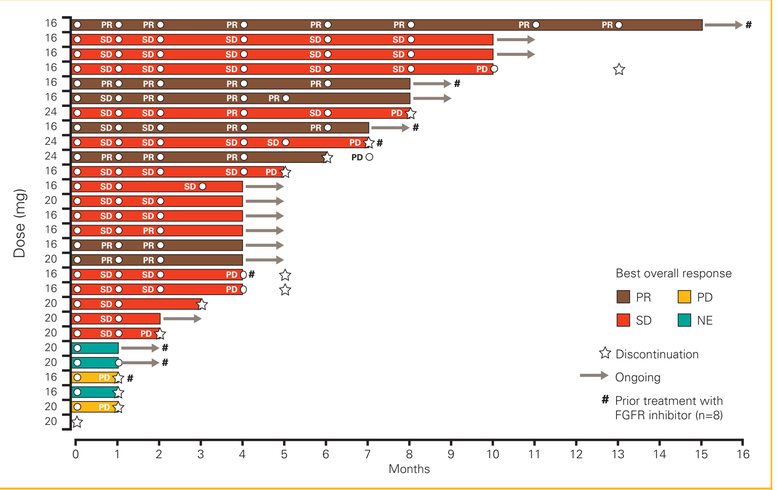
Waterfall plot in CCA patients with FGFR2 gene fusions (n=28)



- 24 patients were evaluable for efficacy
- 20 had tumour shrinkage
- 7 had confirmed partial response (objective response rate = 25%)
- 15 had stable disease
- Disease control rate = 78.6%

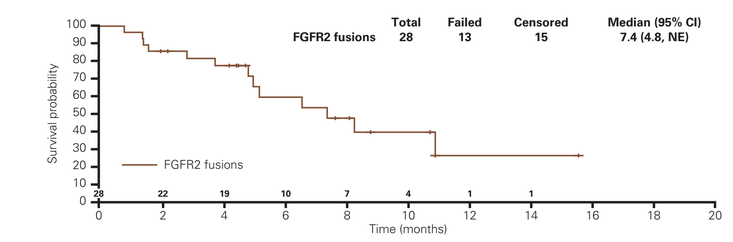
*Prior FGFR inhibitor
Cut-off date: 2 February 2018
NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

Duration of treatment in CCA with FGFR2 gene fusions (n=28)



NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

Kaplan-Meier plot of time on treatment in CCA patients with FGFR2 gene fusions



- Median duration of treatment: 7.4+ months
- 15/28 patients are ongoing

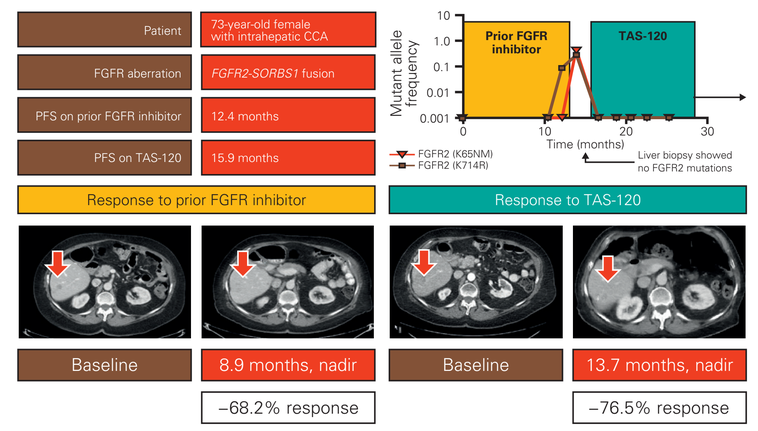
Cut-off date: 2 February 2018
NE, not evaluable

TAS-120: Waterfall plot in non-FGFR2 fusion CCA (n=17)

- 11 patients had tumor shrinkage
- 3 had confirmed partial response
- 10 had stable disease

*FGFR2 re-arrangement; **FGFR2 amplification
3 patients had no post-baseline tumour assessment as of data cut-off (2 February 2018)
NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

TAS-120: Overcoming acquired resistance in a patient with FGFR2 gene fusion



Conclusions

- **TAS-120 demonstrates meaningful clinical benefit in CCA patients with FGFR2 gene fusions**
  - **Including patients who progressed on a prior FGFR inhibitor**
- **The most frequent adverse events were expected and manageable (hyperphosphataemia, cutaneous and gastrointestinal toxicity)**
- **The Phase 1 dose-escalation study has been presented at AACR 2018**
- **The Phase 1 dose-expansion study is currently recruiting in multiple cohorts**
  - **CCA with other FGF/FGFR aberrations**
  - **Gliomas with FGFR gene fusions or activating mutations**
  - **Basket of other advanced solid tumours with FGFR amplifications, fusions and mutations**
- **A global Phase 2 study has been initiated in intrahepatic CCA patients with FGFR2 gene fusions**

References: 1. Brieau B et al. Cancer 2015;121:3290-3297; 2. Wu YM et al. Cancer Discov 2013;3:636-647; 3. Graham RP et al. Hum Pathol 2014;45:1630-1638; 4. Ross JS et al. Oncologist 2014;19:235-242; 5. Turner N et al. Nat Rev Can 2010;10:116-129; 6. Nakatsuru Y et al. AACR-NCI-EORTC International Conference 2013; abstract A272

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