

PHASE 1 SAFETY AND CLINICAL ACTIVITY OF BLU-554 IN ADVANCED HEPATOCELLULAR CARCINOMA

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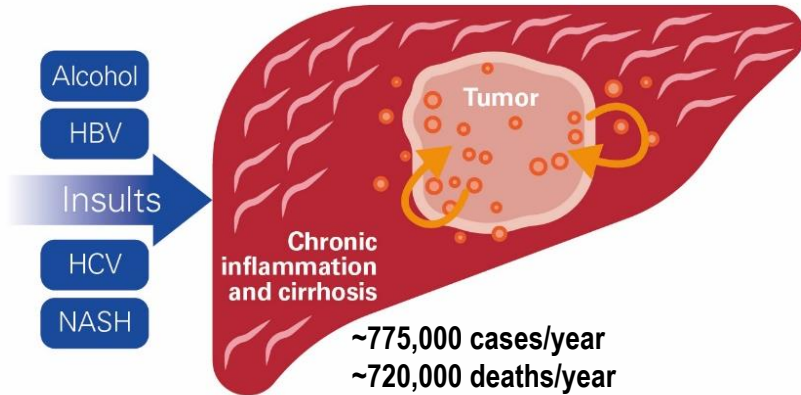
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DISCLOSURES

- BLU-554 is an investigational agent currently in development by Blueprint Medicines Corporation (Blueprint Medicines)
- Dr Richard Kim is an investigator for Blueprint Medicines' ongoing Phase 1 studies in advanced HCC
- Dr Richard Kim has the following disclosures:
 - Research: Blueprint Medicines, Bayer, BMS and Eisai
 - Consultant: Lilly, BMS, Eisai, Bayer
 - Speaker: Lilly

HEPATOCELLULAR CARCINOMA (HCC) AND FGF19¹⁻⁴

HCC is a worldwide medical need



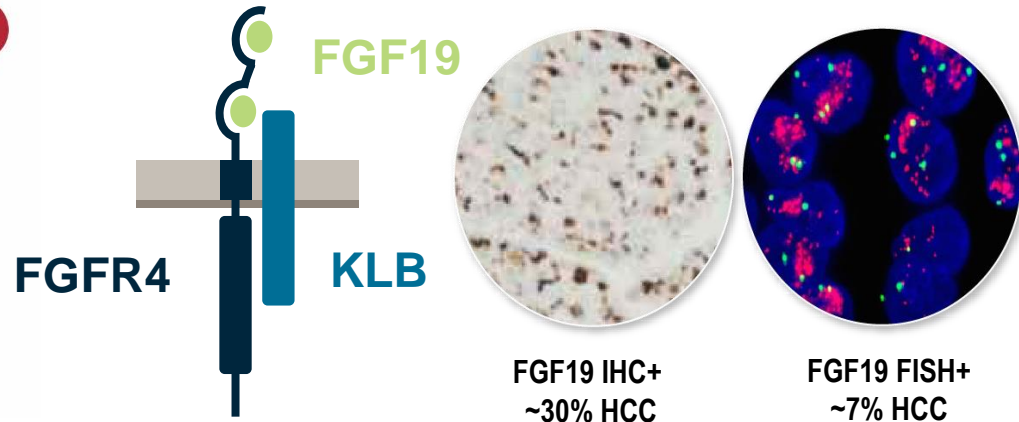
Treatment for advanced disease

sorafenib
1st line

regorafenib
2nd line

- Multi-kinase inhibitors provide OS < 1 year

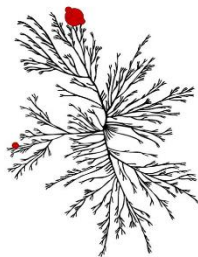
FGF19 - a potential HCC driver



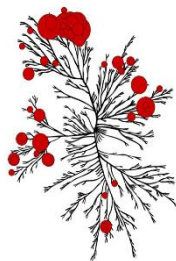
- FGF19 is a mitogen that signals via FGFR4 and KLB
- Normal liver and HCC express FGFR4 and KLB
- Aberrant FGF19 expression may drive HCC and confer poor prognosis

BLU-554: A POTENT AND HIGHLY SELECTIVE FGFR4 INHIBITOR FOR HCC

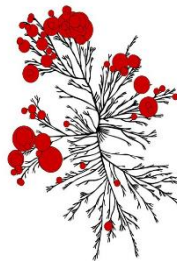
BLU-554



Sorafenib

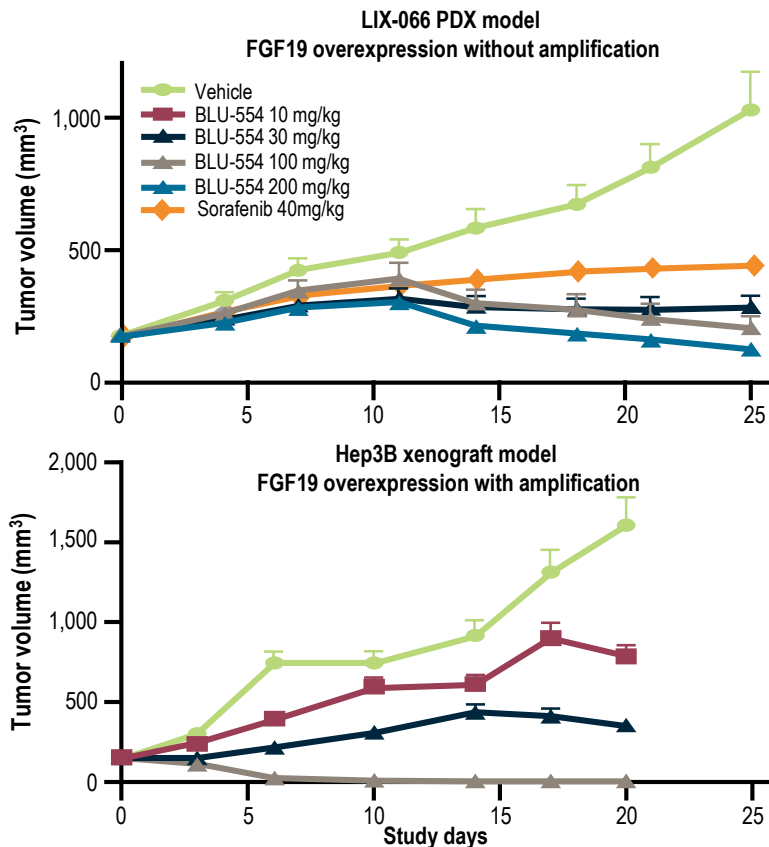


Regorafenib



	Inhibitory Mechanism	TEL-FGFR4 IC ₅₀ nM Cellular
BLU-554	Type 1 Irreversible	3.5
sorafenib	Type 2 Reversible	4,142
regorafenib	Type 2 Reversible	3,021

Kinome illustration reproduced courtesy of CSTI (www.cellsignal.com).
Sorafenib QD (once daily) dosing, BLU-554 BID (twice daily) dosing



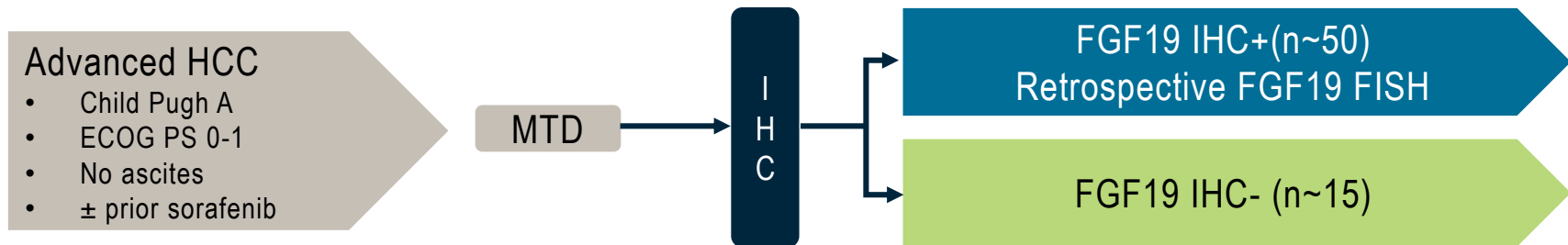
BLU-554: FIRST-IN-HUMAN STUDY

Key objectives

- Define MTD, safety profile, pharmacokinetics and pharmacodynamics
- Assess preliminary anti-tumor activity in relation to FGF19 IHC and FISH status

Part 1: Dose escalation – completed

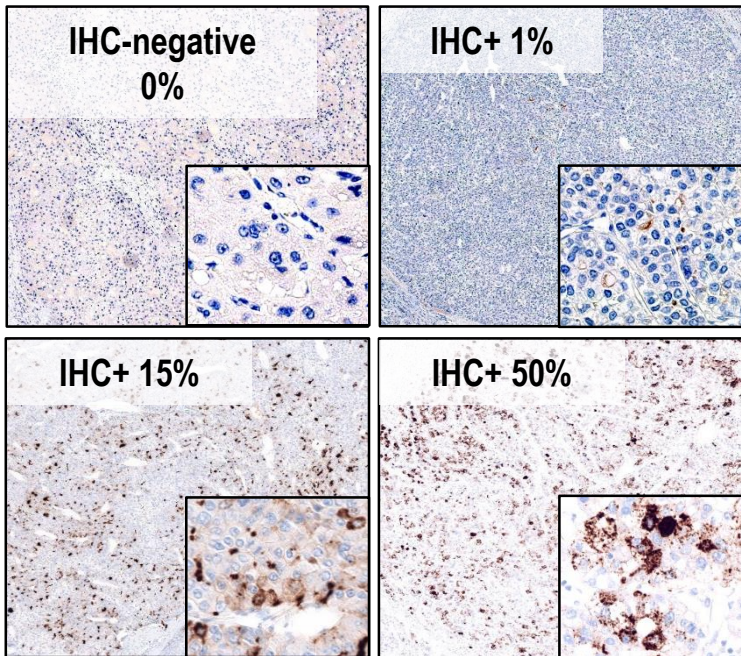
Part 2: Dose expansion – enrolling



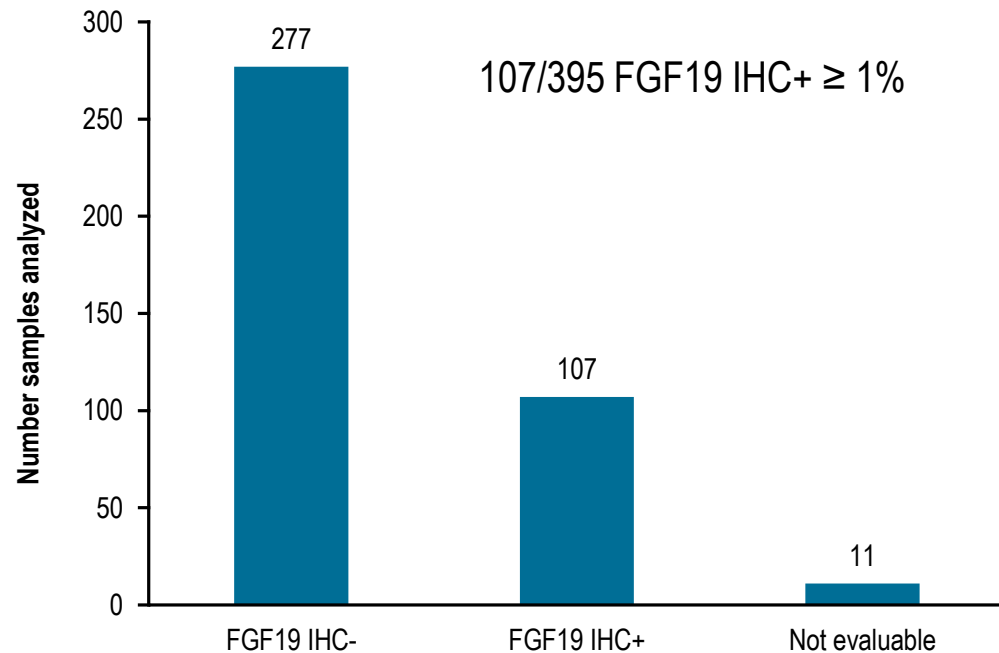
- 3+3 dose escalation (140-900 mg PO QD)
- 600 mg established as MTD

FGF19 IMMUNOHISTOCHEMISTRY (IHC) IDENTIFIES ABERRANT PATHWAY ACTIVATION

Central Laboratory IHC



Aberrant pathway activation in 27%



PATIENT DEMOGRAPHY AND BASELINE CHARACTERISTICS

- Predominantly 2nd line/post-sorafenib patient population
- IHC+: more MVI* and higher AFP**

Parameter, n (%)	All patients, N = 77 n=25 escalation; n=52 expansion
Age – years, median (range)	61 (18–85)
Gender – male	60 (78)
Etiology	
Non-viral	10 (13)
HBV	36 (47)
HCV	10 (13)
Other/unknown	21 (27)
Metastatic Disease	61 (79)
FGF19 IHC	
IHC ≥1% (IHC+)	44 (57)
IHC <1% (IHC-)	28 (36)
Unknown	5 (6)

Data are preliminary as of data cut off: 18 August 2017

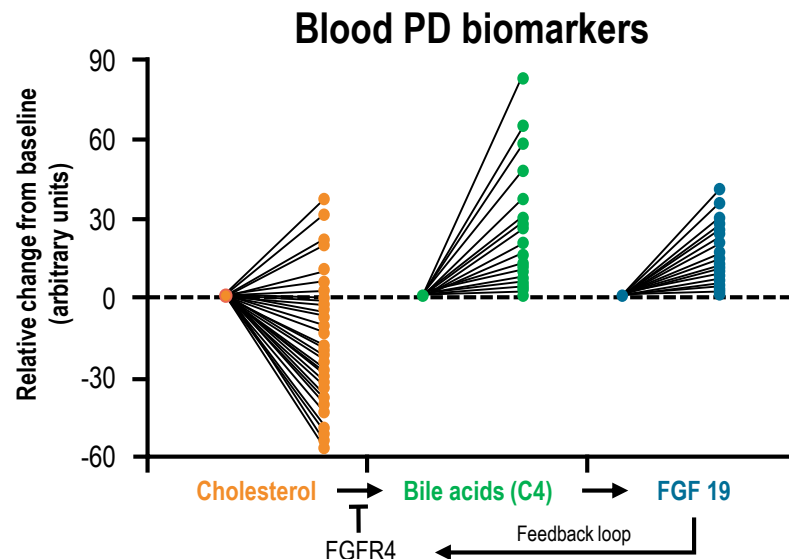
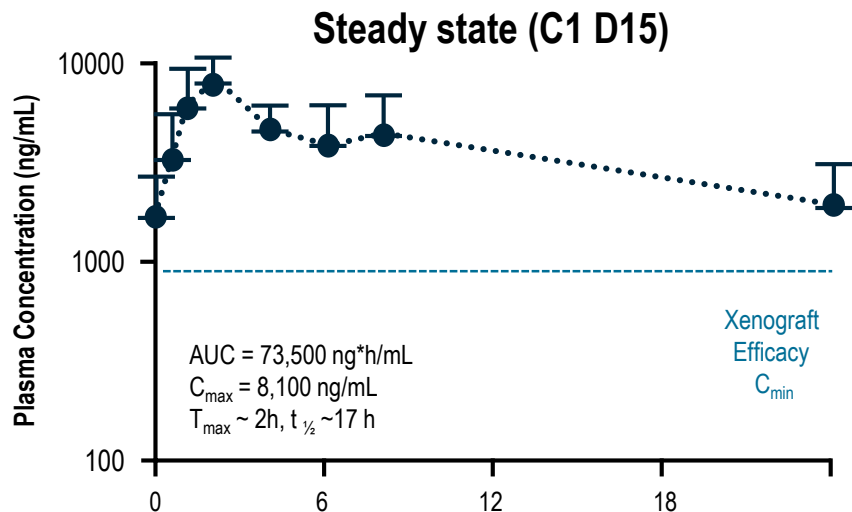
AFP, alpha-fetoprotein; MVI, macrovascular invasion; TACE, transarterial chemoembolisation

Parameter, n (%)	All patients, N = 77 n=25 escalation; n=52 expansion
FGF19 FISH	
FISH+	5 (6)
FISH-	58 (75)
Unknown	11 (14)
Pending	3 (4)

Prior Therapy	
Surgical resection	58 (75)
Radiotherapy	25 (32)
TACE / embolization	40 (52)
Immunotherapy	18 (23)
nivolumab	15 (19)
Kinase inhibitor	63 (82)
sorafenib	62 (81)
Systemic therapy	70 (91)

	FGF19 IHC+	FGF19 IHC-
<u>MacroVascular Invasion*</u>	18 (41)	5 (15)
AFP ≥400 (ng/mL)**	27 (61)	8 (24)

BLU-554 PHARMACOKINETICS AND PHARMACODYNAMICS



- Steady state exposure provides $C_{trough} > C_{min}$ associated with xenograft efficacy
- Long half life supports QD dosing
- Blood biomarkers demonstrate consistent pathway modulation

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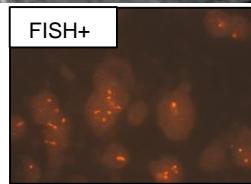
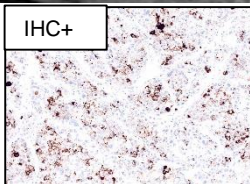
PK and PD represent 600mg expansion dose

AUC, area under the curve; C1, Cycle1; C_{max} , maximum blood plasma concentration; C_{min} , minimum blood plasma concentration; D15, Day15; PD, pharmacodynamics; PK, pharmacokinetic; QD, one a day; T_{max} , time to maximum blood plasma concentration

RADIOGRAPHIC RESPONSE IN POST-SORAFENIB HBV-RELATED HCC

Week 0 8 16 24 32

Baseline -34% PR -49% PR -49% PR PD

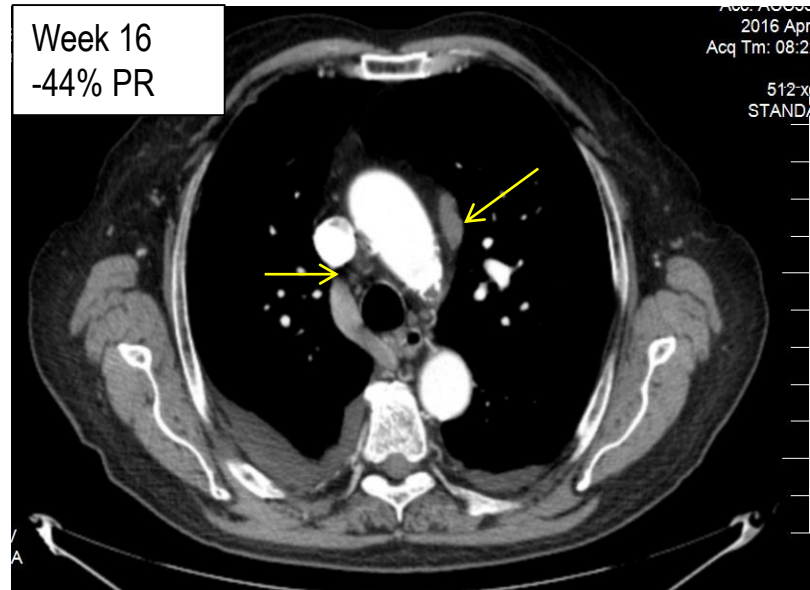
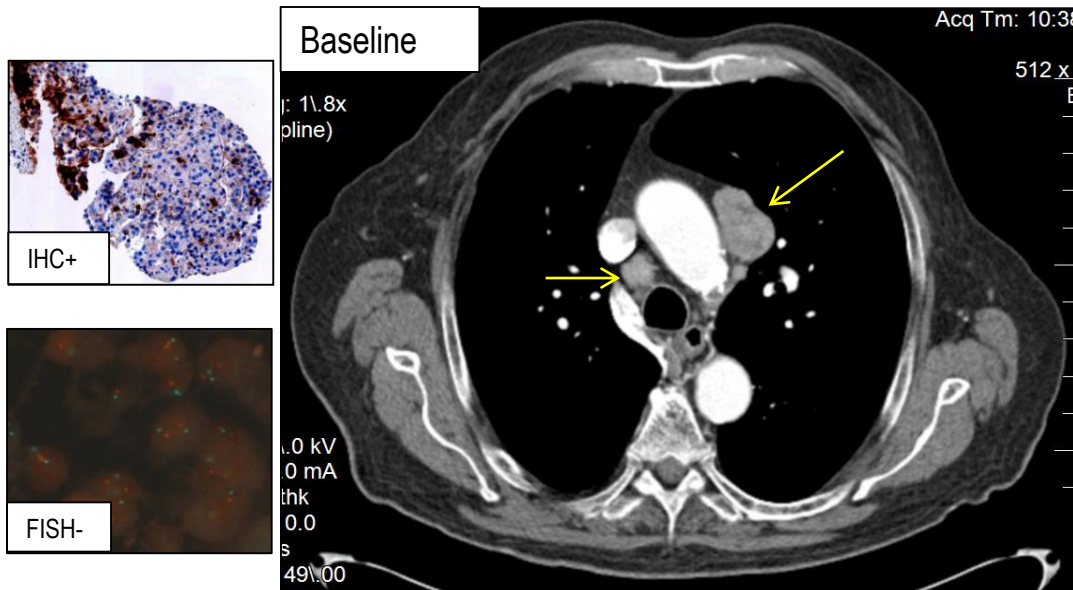


ctDNA	Measure	Baseline	Week 8
P53 Q192*	Allele fraction	31.1%	Undetectable
FGF19 amp	Copy number	8.3	Undetectable

ctDNA, circulating tumor PD, progressive disease; PR, progressive response

RADIOGRAPHIC RESPONSE IN POST-SORAFENIB NON-VIRAL HCC

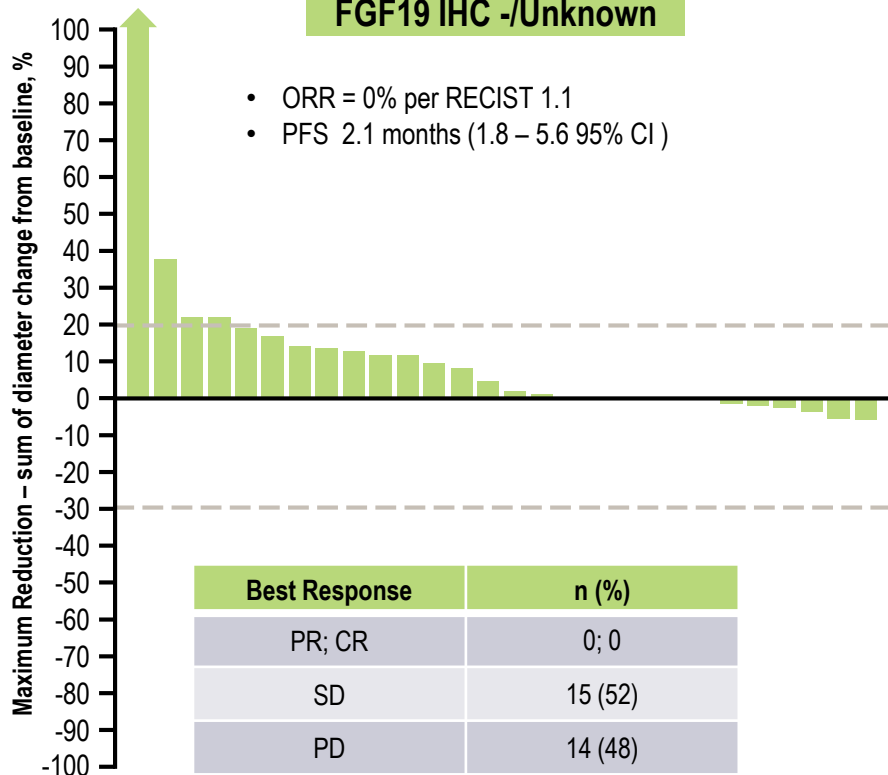
Week 0	8	16	24	32
Baseline	-26% SD	-44% PR	-45% PR	PD



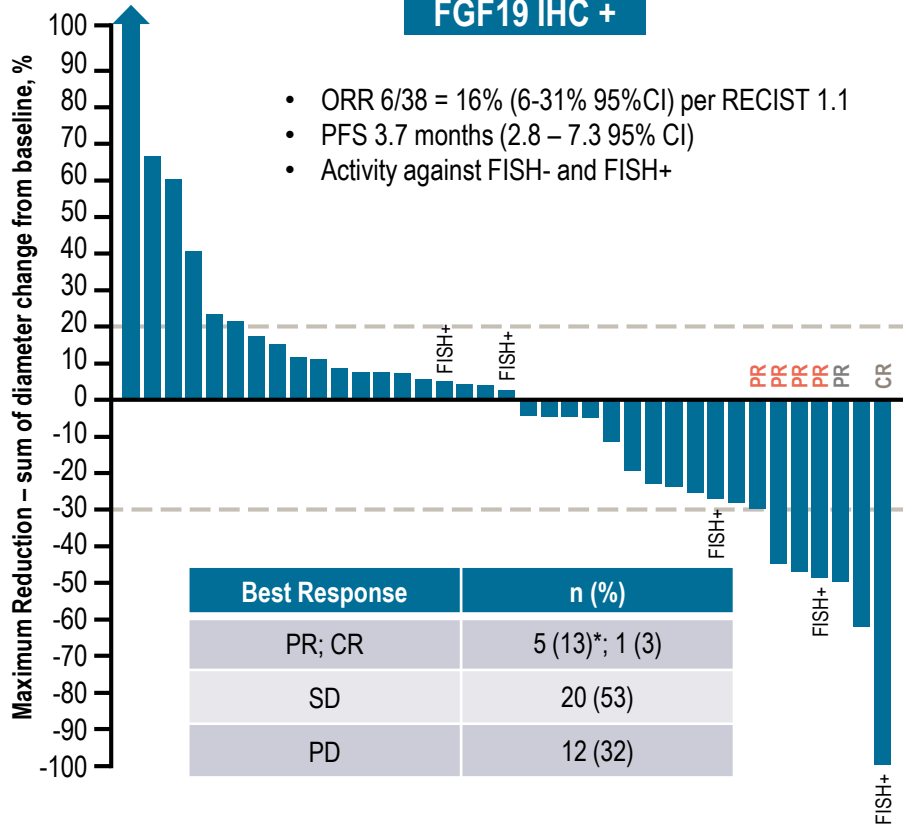
SD, stable disease

IHC-POSITIVITY ENRICHES FOR RADIOGRAPHIC TUMOR REDUCTION AND RESPONSE

FGF19 IHC -/Unknown



FGF19 IHC +



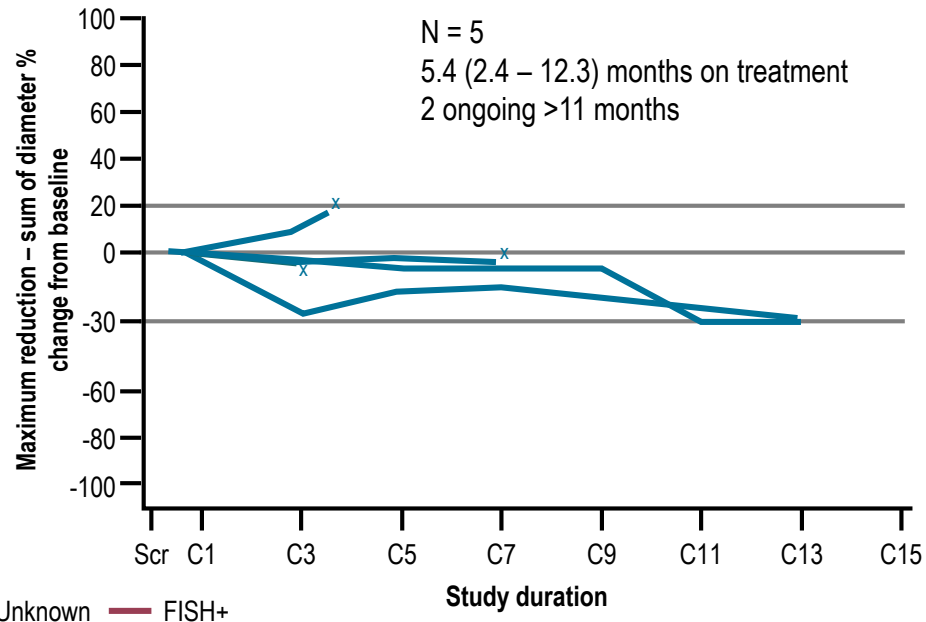
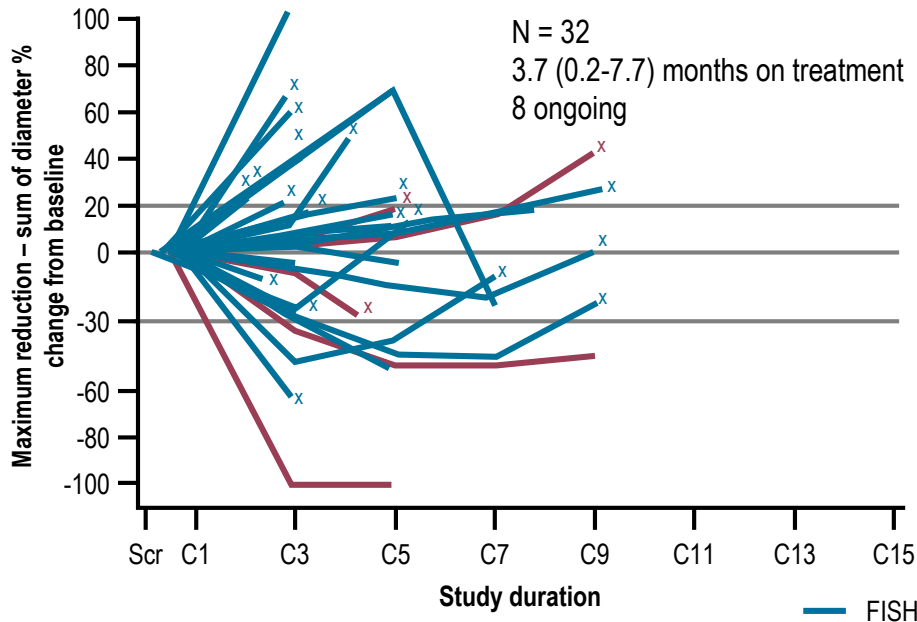
*4 confirmed PR; 1 PR/1 CR, unconfirmed

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CR, complete response; ORR, overall response rate; PFS, progression-free survival;

FGF19 IHC+ TUMOR GROWTH KINETICS PER PRIOR KINASE INHIBITOR TREATMENT

Encouraging duration of treatment, particularly in kinase inhibitor naïve patients



Previous kinase inhibitor treatment

No prior kinase inhibitor treatment

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ADVERSE EVENTS*

Most AEs are Grade 1 or 2: manageable on-target toxicity

Safety population, N=77	Severity					
	Any AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Preferred term, n (%)						
Patients with at least 1 Related AE	75 (97)					
Diarrhea	55 (71)	36 (47)	13 (17)	6 (8)	0	0
Nausea	32 (42)	21 (27)	9 (12)	2 (3)	0	0
Vomiting	28 (36)	19 (25)	5 (6)	4 (5)	0	0
AST	26 (34)	7 (9)	5 (6)	12 (16)	2 (3)	0
ALT	25 (32)	7 (9)	7 (9)	10 (13)	1 (1)	0
Fatigue	22 (29)	9 (12)	11 (14)	2 (3)	0	0
Decreased appetite	14 (18)	6 (8)	8 (10)	0	0	0
Blood bilirubin increased	13 (17)	4 (5)	7 (9)	2 (3)	0	0
Abdominal pain	12 (16)	5 (6)	6 (8)	1 (1)	0	0
Anemia	11 (14)	4 (5)	2 (3)	5 (6)	0	0
Blood alkaline phosphatase increased	10 (13)	2 (3)	5 (6)	3 (4)	0	0
Pruritus	8 (10)	6 (8)	2 (3)	0	0	0

- 2 DLT at 900 mg (1 Gr 3 fatigue lasting > 7 days; 1 Gr 3 abdominal pain)
- BLU-554 discontinuations: PD n=42, AE n=11, investigator's decision n=2, withdrew consent n=3

*Treatment-related adverse events reported in ≥10% patients; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity

CONCLUSIONS

- BLU-554 provides acceptable tolerability, pathway engagement and anti-tumor activity in heavily pre-treated FGF19 IHC+ patients
 - Aberrant pathway activation (FGF19 IHC+) demonstrated in ~30% of HCC patients
 - BLU-554 demonstrates clinical activity regardless of HCC etiology and prognostic factors
- These data validate FGFR4 as a therapeutic target and FGF19 IHC as selection marker for pathway activation in advanced HCC
- Planning is underway for further clinical development of BLU-554 in kinase inhibitor naïve, FGF19 IHC+ HCC alone and in combination with immunotherapy

ACKNOWLEDGEMENTS

We thank the participating patients, their families, all study co-investigators, and research co-ordinators at the following institutions:

- Moffitt Cancer Center, Tampa, United States
- Guy's Hospital, London, United Kingdom,
- Vall d'Hebron University Hospital, Barcelona, Spain
- Queen Mary Hospital, HongKong, Hong Kong
- National Cancer Center, Singapore, Singapore
- UCL Cancer Institute, London, United Kingdom
- Institut Gustave Roussy, Villejuif, France
- Huntsman Cancer Institute, Salt Lake City, United States
- Asan Medical Center, Seoul, Republic of Korea
- Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, United States
- Seoul National University Hospital, Seoul, Republic of Korea
- Samsung Medical Center, Seoul, Republic of Korea
- Massachusetts General Hospital Cancer Center, Boston, United States
- Center for Liver Cancer, National Cancer Center, Goyang, Republic of Korea
- Beaujon University Hospital, Clichy, France
- Fondazione Istituto Nazionale Tumori (National Cancer Institute) IRCCS, Milan, Italy

We also thank Samantha Clark, BSc, of iMed Comms, an Ashfield company, who provided editorial writing support funded by Blueprint Medicines

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