Clinical activity Of BLU-554, a potent, highly-selective FGFR4 inhibitor in advanced HCC with FGFR4 pathway activation

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Disclosures

- BLU-554 is an investigational agent currently in development by Blueprint Medicines Corporation (Blueprint Medicines)
- Dr Yoon-Koo Kang is an investigator for Blueprint Medicines' ongoing Phase 1 studies in advanced HCC
- Dr Yoon-Koo Kang has the following disclosures:
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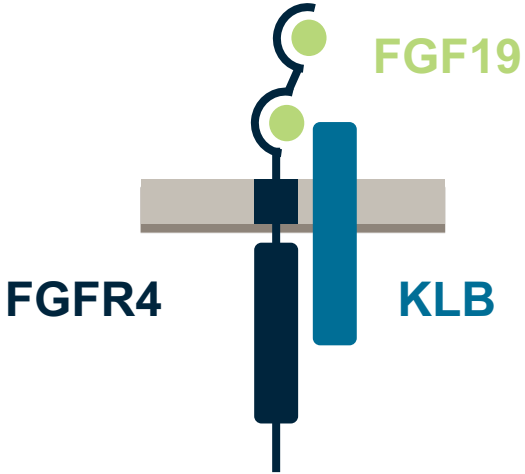
  - Expert testimony: none
  - Patents: none

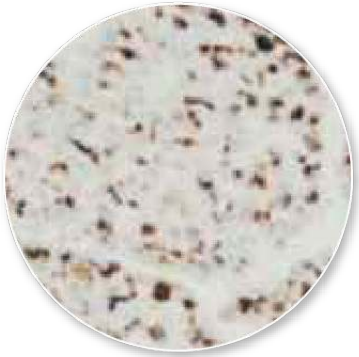
HCC, hepatocellular carcinoma

FGF19 identified as a potential HCC driver[1-4]

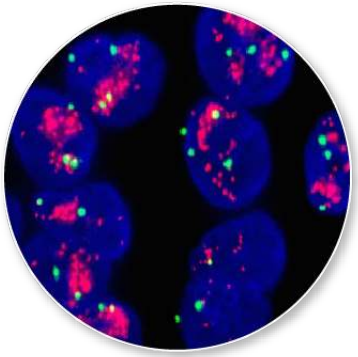
Pathway components



Pathway diagnostics



FGF19 IHC+
~30% HCC

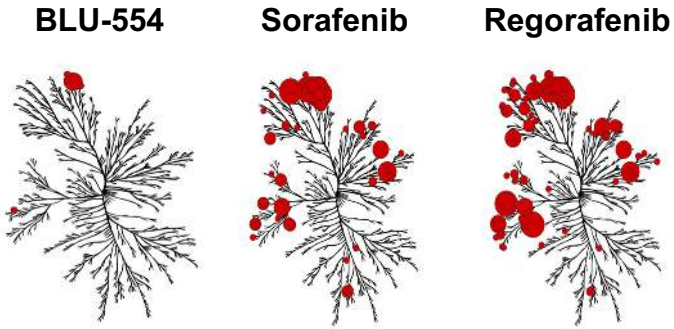


FGF19 FISH+
~7% HCC

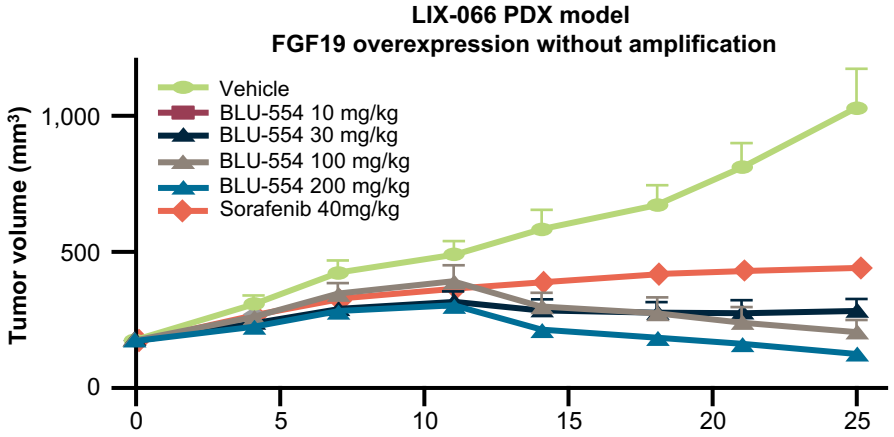
- FGF19 is a mitogen that signals via FGFR4 and KLB
  - Normal liver and HCC express FGFR4 and KLB
- Aberrant FGF19 expression may drive HCC and confer poor prognosis

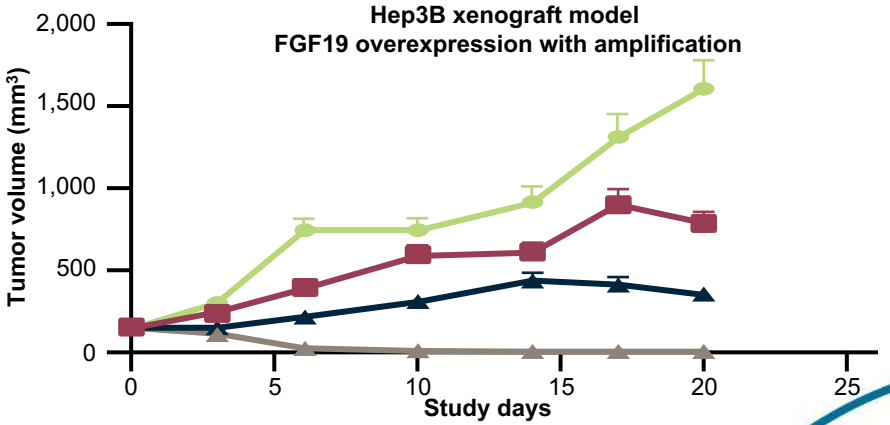
FGFR4, fibroblast growth factor receptor 4; FGF19, fibroblast growth factor 19; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; KLB, klotho-β.

BLU-554: a potent and highly selective FGFR4 inhibitor for HCC



	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

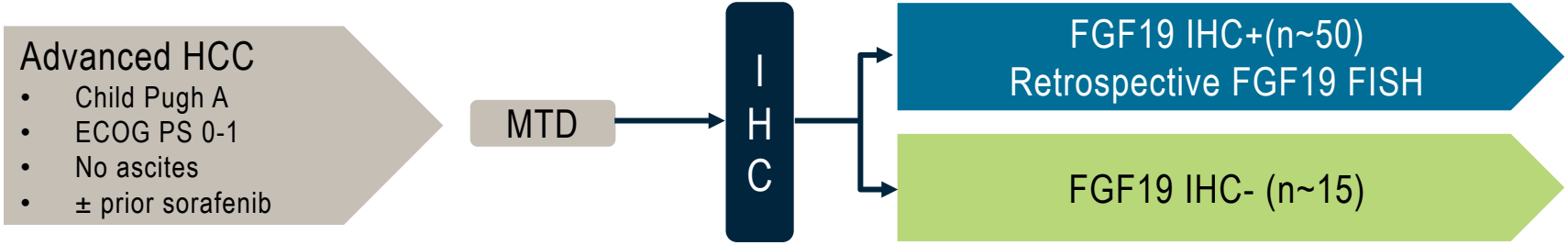
BLU-554: first-in-human study

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



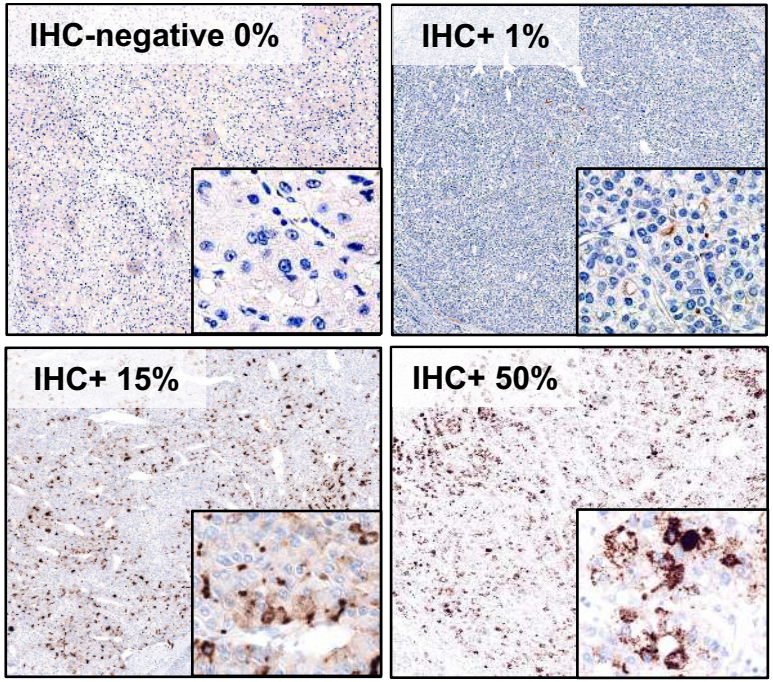
- 3+3 dose escalation (140-900 mg PO QD)
- 600 mg established as MTD

NCT02508467

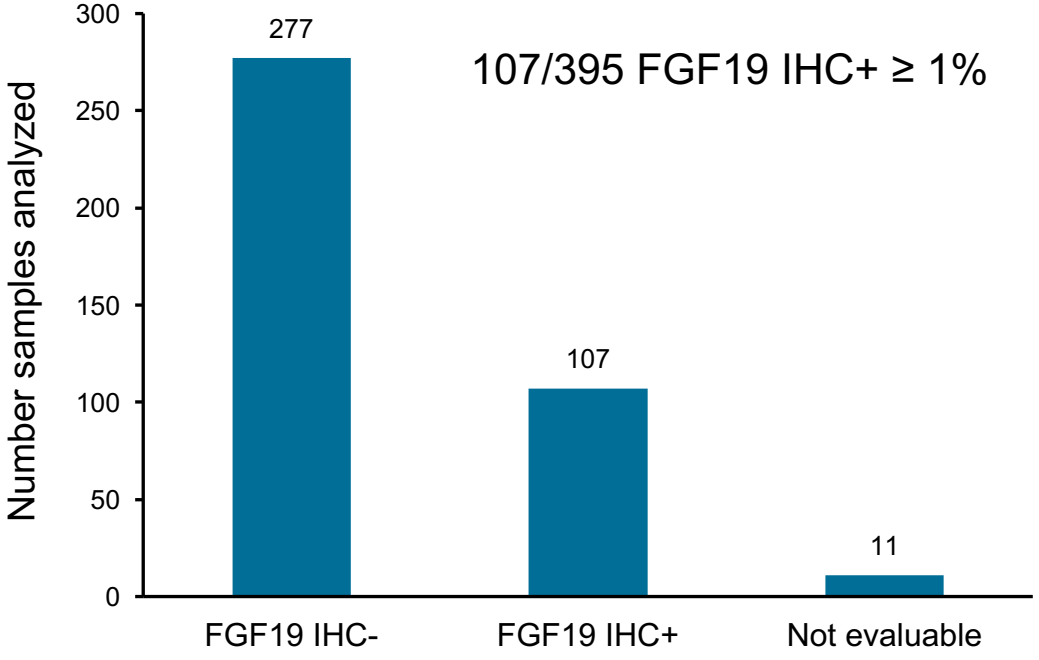
ECOG PS, Eastern Cooperative Oncology Group performance status; MTD, maximum tolerated dose

FGF19 immunohistochemistry (IHC) identifies aberrant pathway activation

Central Laboratory IHC



Aberrant pathway activation in 27%



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

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)

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-
MacroVascular Invasion*	18 (41)	5 (15)
AFP ≥400 (ng/mL)**	27 (61)	8 (24)

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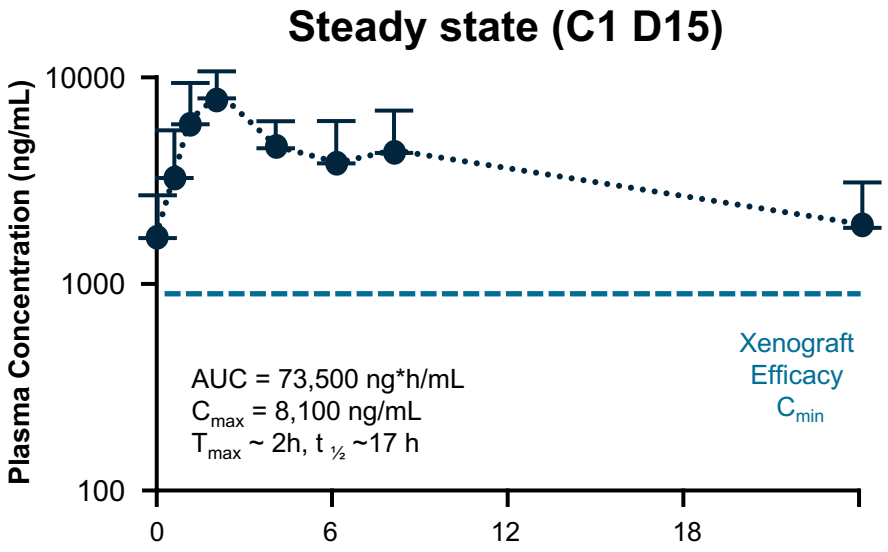
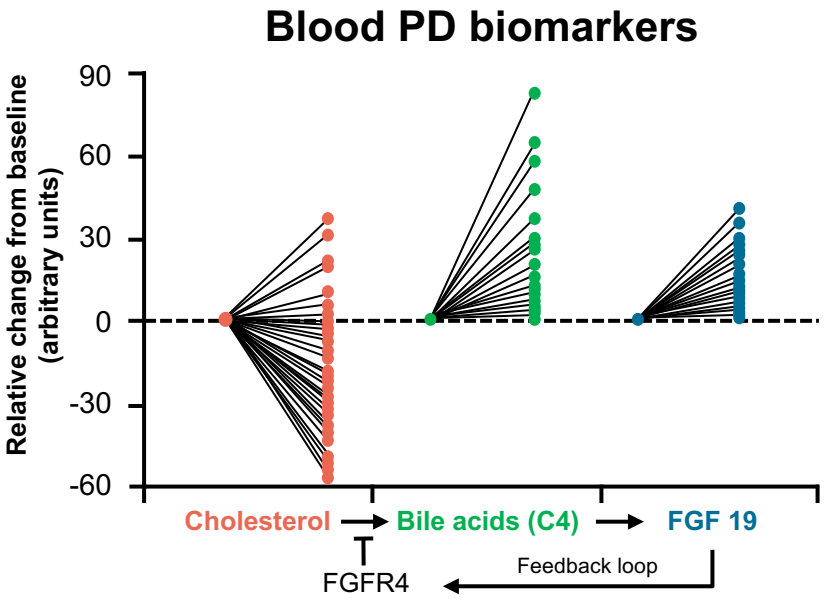
AFP, alpha-fetoprotein; MVI, macrovascular invasion; TACE, transarterial chemoembolisation

BLU-554 pharmacokinetics and pharmacodynamics



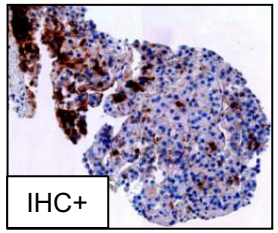


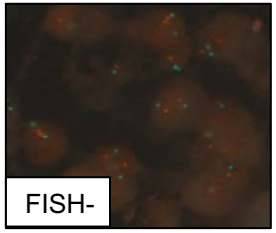
- Steady state exposure provides C_{trough} > C_{min} associated with xenograft efficacy
- Long half life supports QD dosing
- Blood biomarkers demonstrate consistent pathway modulation

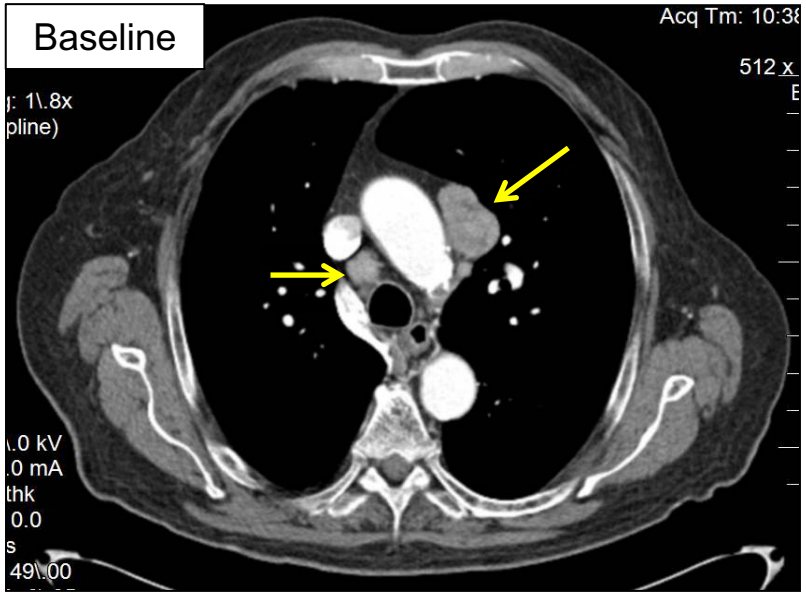
Data are preliminary as of data cut off: 18 August 2017
PK and PD represent 600mg expansion dose
AUC, area under the curve; C1, Cycle1; C_{max}, maximum blood plasma concentration; C_{min}, minimum blood plasma concentration; D15, Day15; PD, pharmacodynamics; PK, pharmacokinetic; QD, one a day; T_{max}, time to maximum blood plasma concentration

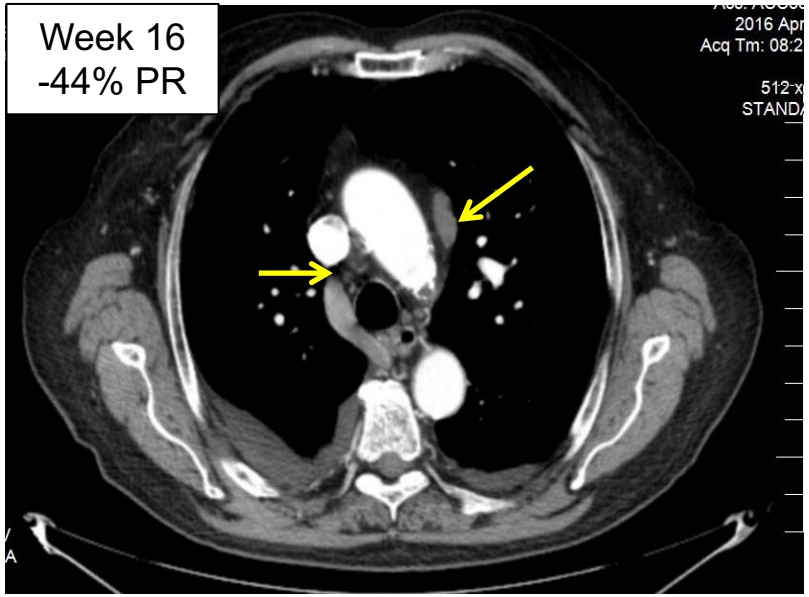
Radiographic response in post-sorafenib non-viral HCC 7

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





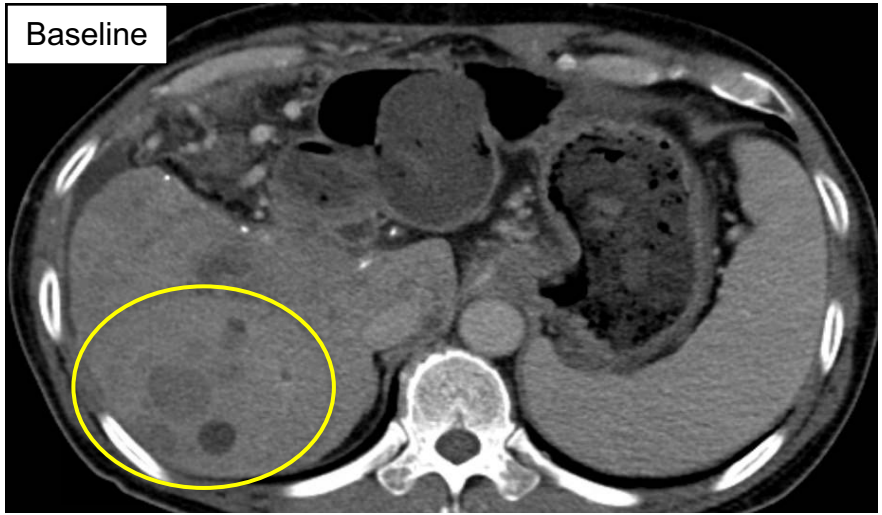


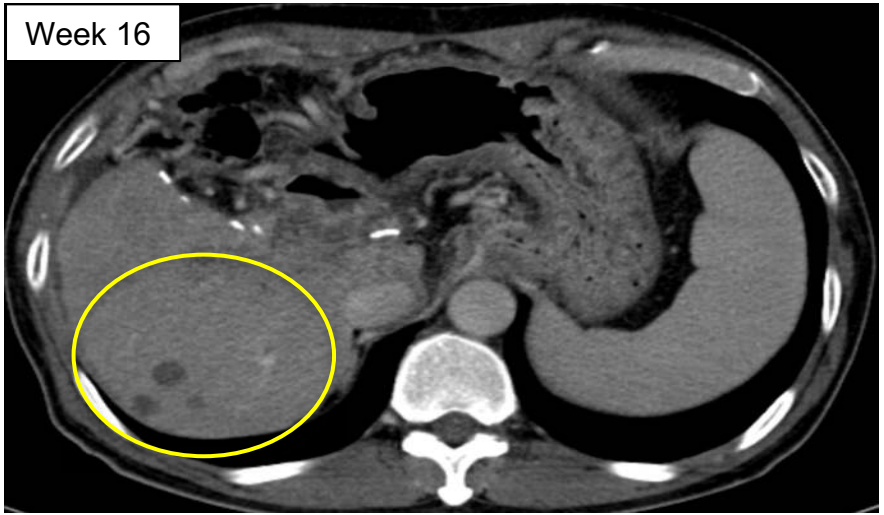


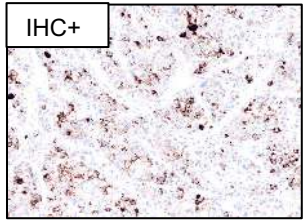
SD, stable disease

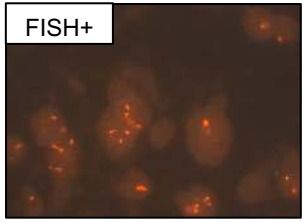
Radiographic response in post-sorafenib HBV-related HCC

Week 0	8	16	24	32
Baseline	-34% **PR**	-49% **PR**	-49% **PR**	PD





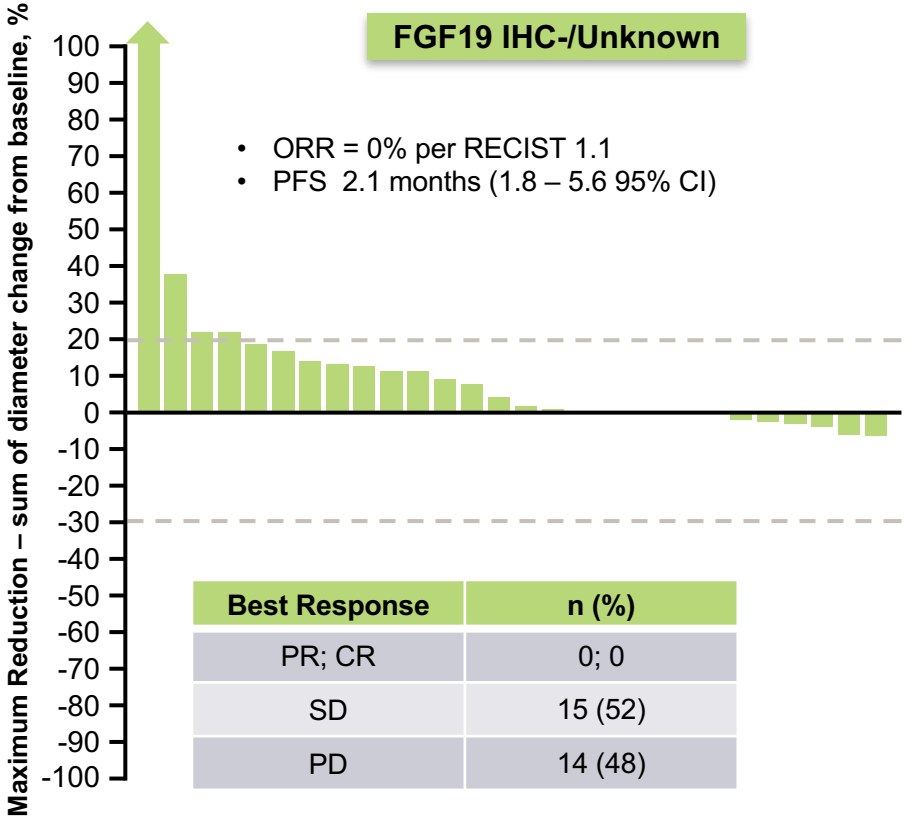




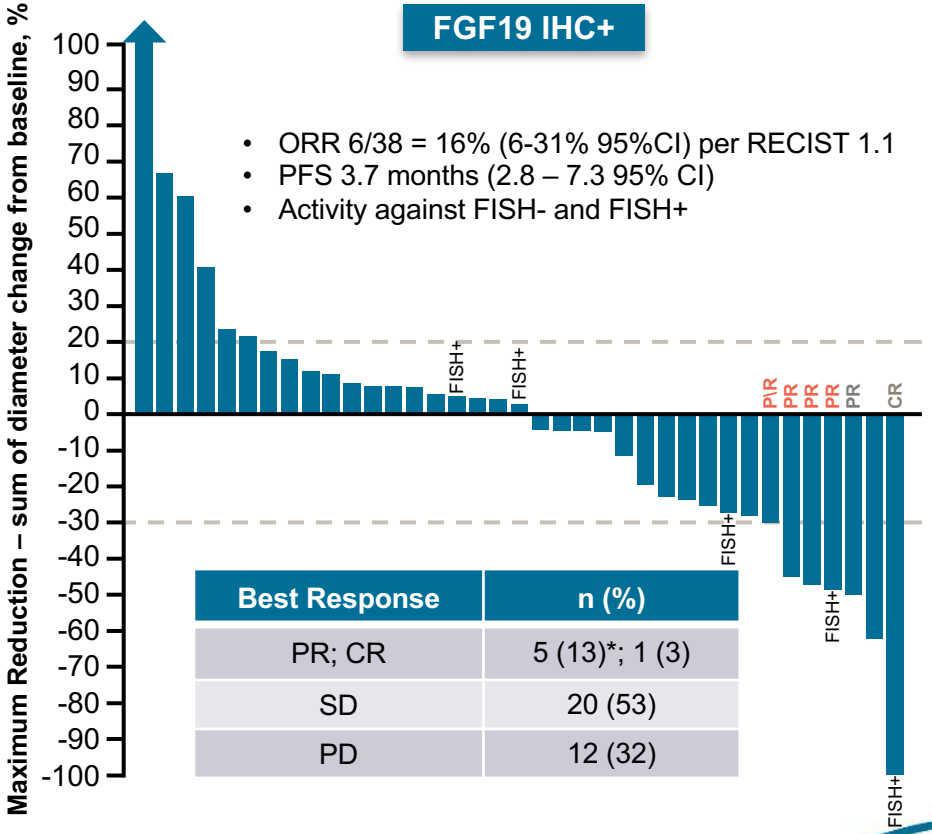
ctDNA	Measure	Baseline	Week 8
P53 Q192*	Allele fraction	31.1%	Undetectable
FGF19 amp	Copy number	8.3	Undetectable

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

IHC-positivity enriches for radiographic tumor reduction and response



Best Response	n (%)
PR; CR	0; 0
SD	15 (52)
PD	14 (48)

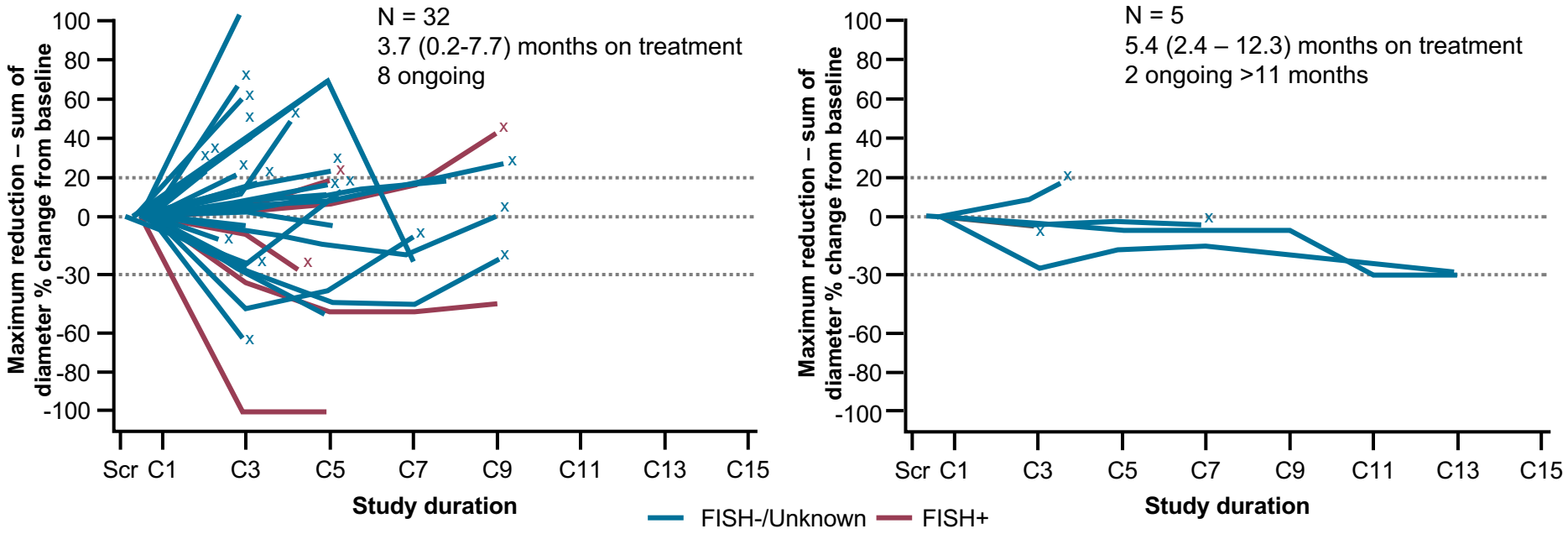


Best Response	n (%)
PR; CR	5 (13)*; 1 (3)
SD	20 (53)
PD	12 (32)

*4 confirmed **PR**; **1 PR/1 CR**, unconfirmed
Data are preliminary as of data cut off: 18 August 2017
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

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

Adverse events*

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

Safety population, N=77	Severity					
Preferred term, n (%)	**Any AE**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
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

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- Seoul National University Hospital, Seoul, Republic of Korea
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Thank you