MADRID 2017 ESMO congress

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

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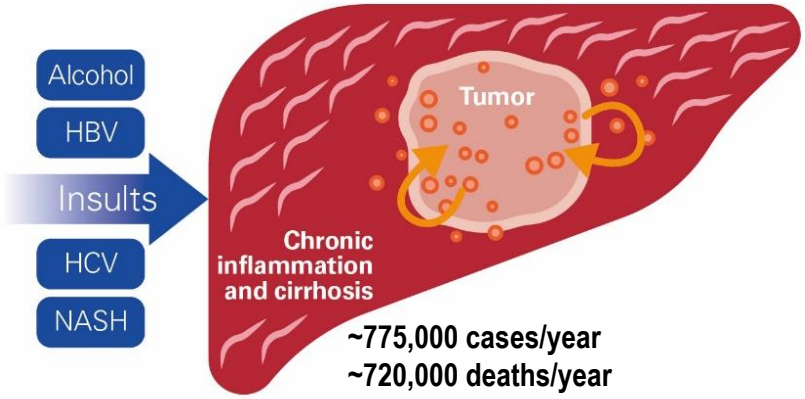
DISCLOSURES

- 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

HCC, hepatocellular carcinoma

HEPATOCELLULAR CARCINOMA (HCC) AND FGF19[1-4]

HCC is a worldwide medical need

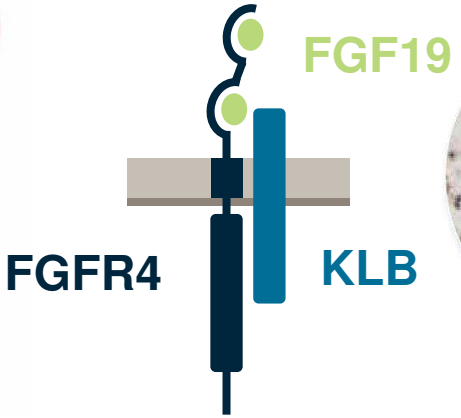


Treatment for advanced disease

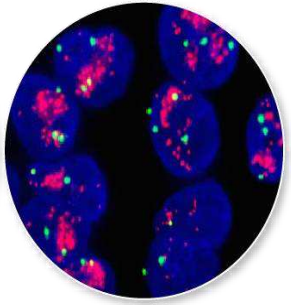
sorafenib 1st line → regorafenib 2nd line

- Multi-kinase inhibitors provide OS < 1 year

FGF19 - a potential HCC driver



FGF19 IHC+
~30% HCC



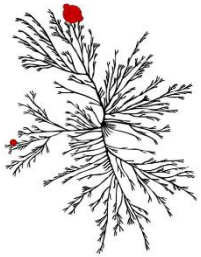
FGF19 FISH+
~7% HCC

- 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

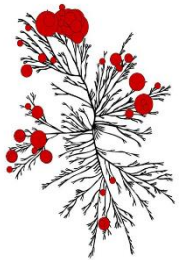
FGFR4, fibroblast growth factor receptor 4; FGF19, fibroblast growth factor 19; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; KLB, klotho-β

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

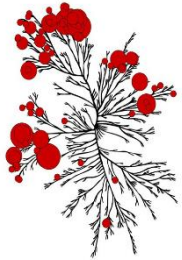
BLU-554



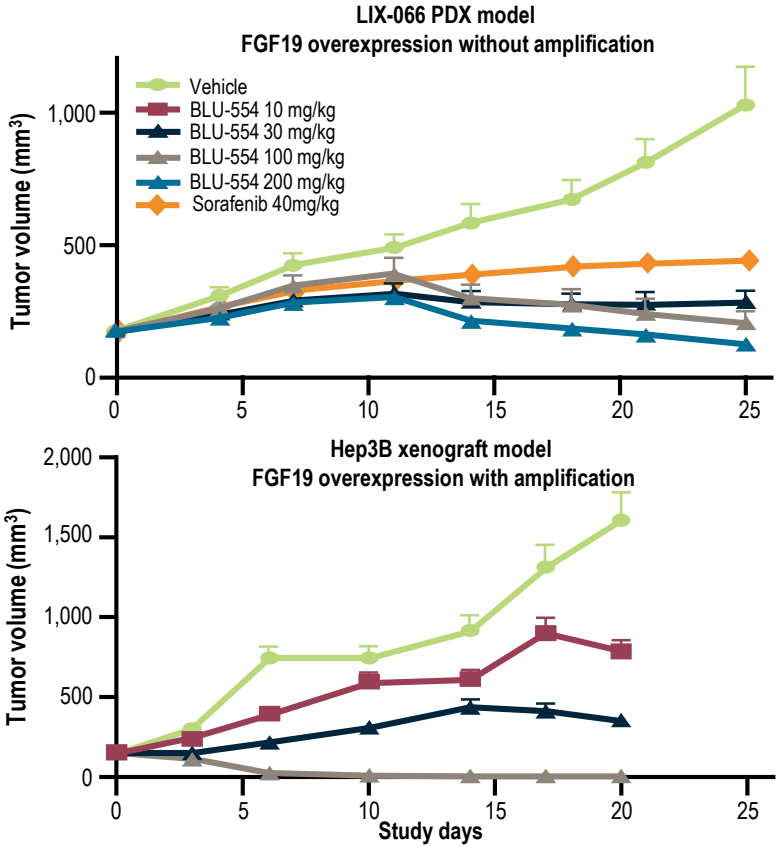
Sorafenib



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

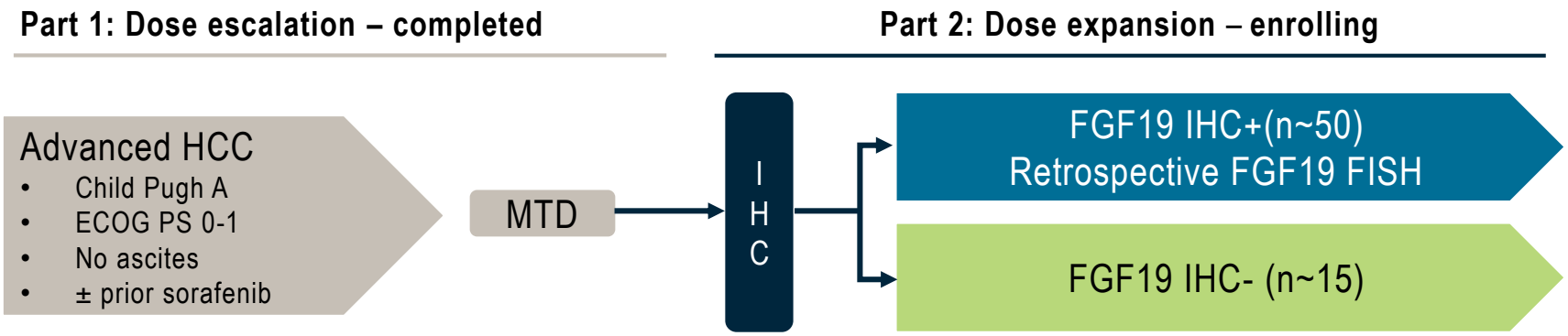


Kinome illustration reproduced courtesy of CSTI (www.cellsignal.com).
Sorafenib QD (once daily) dosing, BLU-554 BID (twice daily) dosing

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

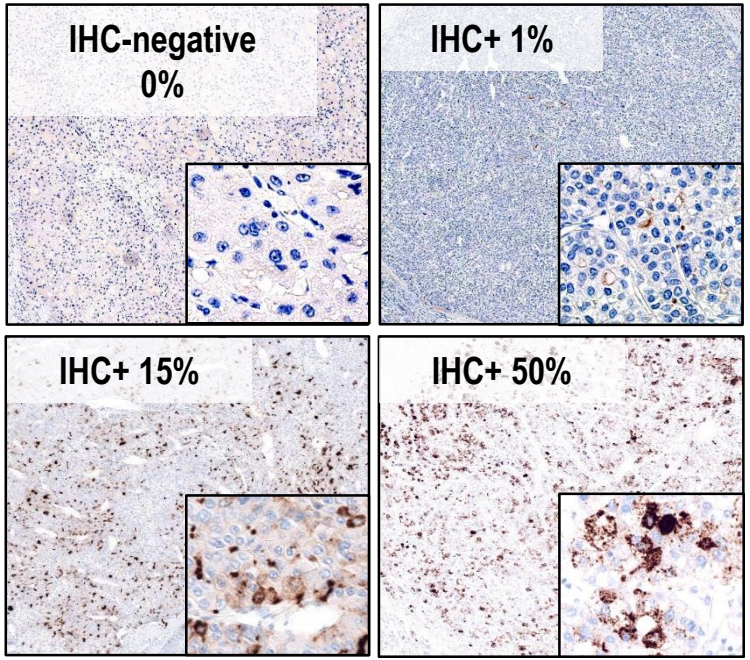


- 3+3 dose escalation (140-900 mg PO QD)
- 600 mg established as MTD

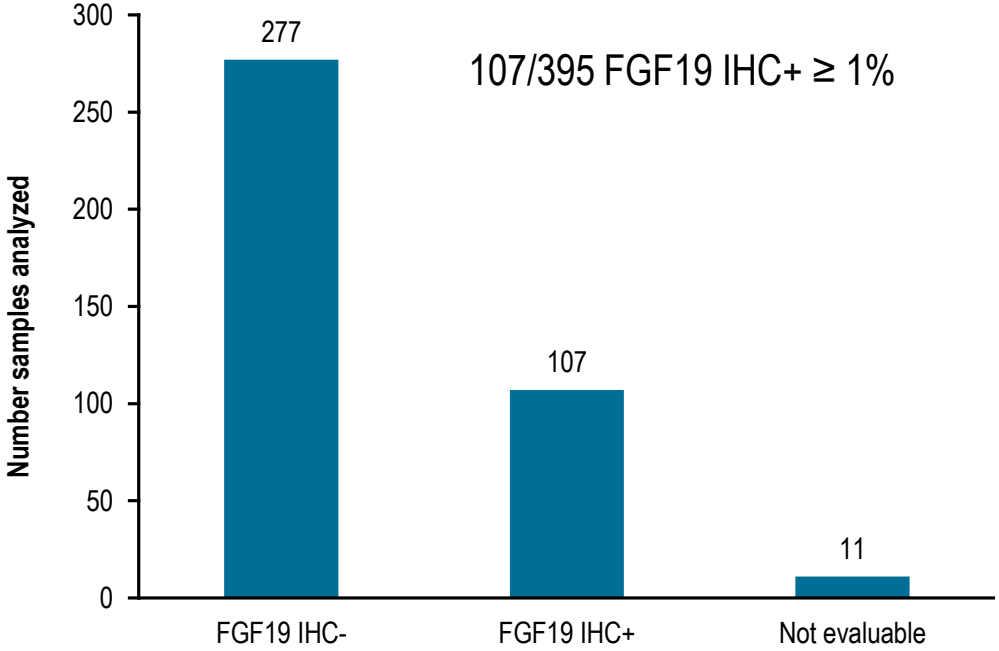
NCT02508467
ECOG PS, Eastern Cooperative Oncology Group performance status; MTD, maximum tolerated dose

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**

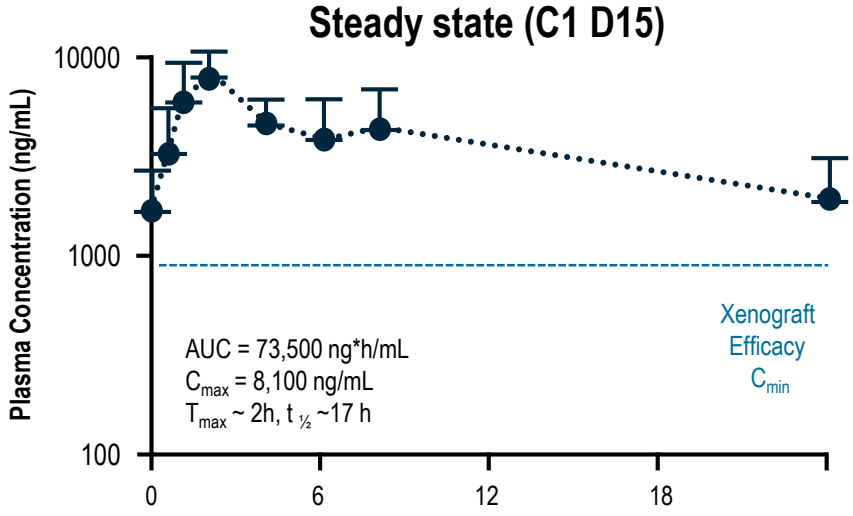
Parameter, n (%)	All patients, N = 77 n=25 escalation; n=52 expansion
Age – years, median (range)	61 (18–85)
Gender – male	60 (78)
Etiology	
Non-viral	10 (13)
HBV	36 (47)
HCV	10 (13)
Other/unknown	21 (27)
Metastatic Disease	61 (79)
FGF19 IHC	
IHC ≥1% (IHC+)	44 (57)
IHC <1% (IHC-)	28 (36)
Unknown	5 (6)

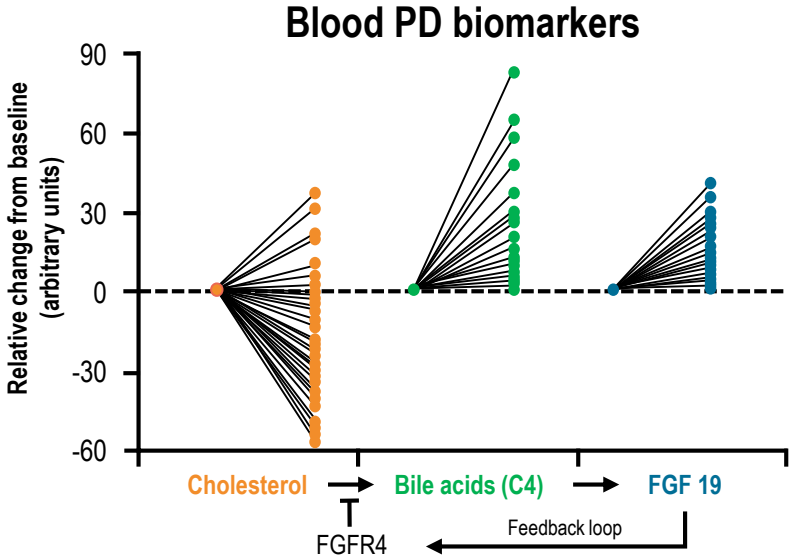
Parameter, n (%)	All patients, N = 77 n=25 escalation; n=52 expansion
FGF19 FISH	
FISH+	5 (6)
FISH-	58 (75)
Unknown	11 (14)
Pending	3 (4)
Prior Therapy	
Surgical resection	58 (75)
Radiotherapy	25 (32)
TACE / embolization	40 (52)
Immunotherapy	18 (23)
nivolumab	15 (19)
Kinase inhibitor	63 (82)
sorafenib	62 (81)
Systemic therapy	70 (91)

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

Data are preliminary as of data cut off: 18 August 2017
AFP, alpha-fetoprotein; MVI, macrovascular invasion; TACE, transarterial chemoembolisation

BLU-554 PHARMACOKINETICS AND PHARMACODYNAMICS



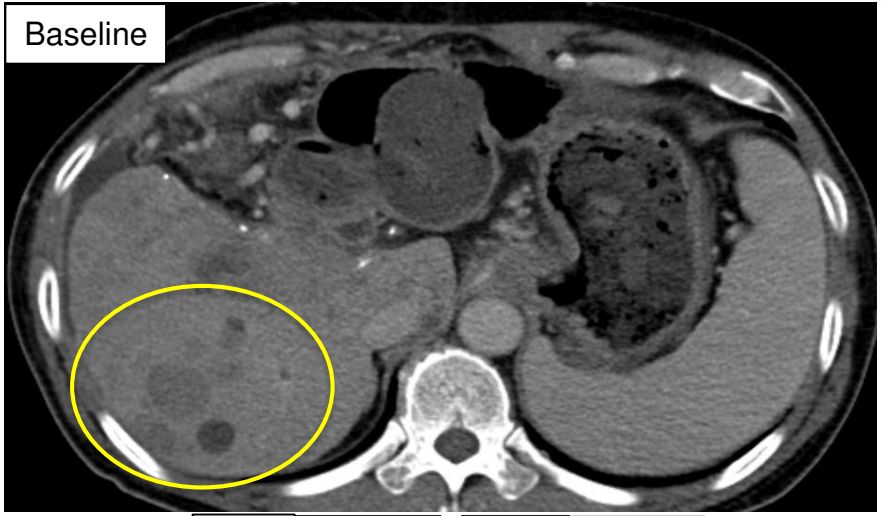


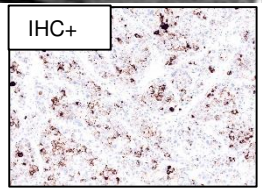
- Steady state exposure provides C_{trough} > C_{min} associated with xenograft efficacy
- Long half life supports QD dosing
- Blood biomarkers demonstrate consistent pathway modulation

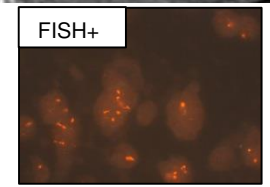
Data are preliminary as of data cut off: 18 August 2017
PK and PD represent 600mg expansion dose
AUC, area under the curve; C1, Cycle1; C_{max}, maximum blood plasma concentration; C_{min}, minimum blood plasma concentration; D15, Day15; PD, pharmacodynamics; PK, pharmacokinetic; QD, one a day; T_{max},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

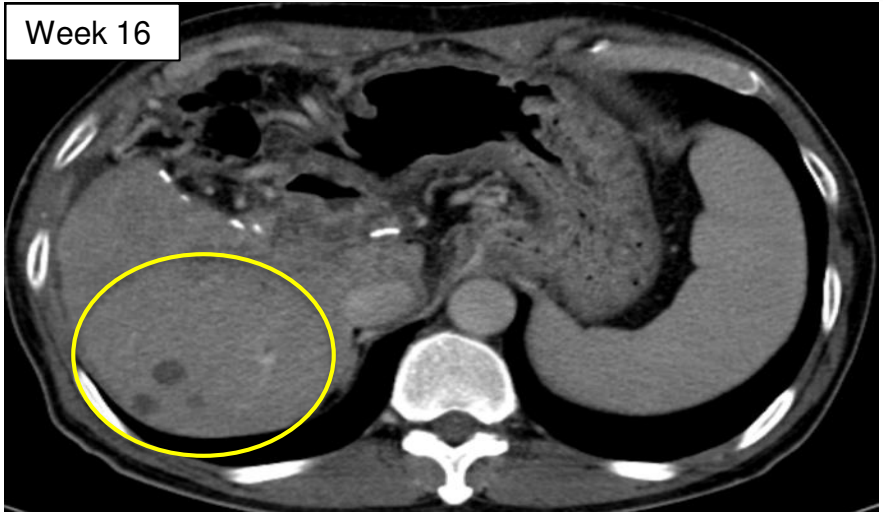
RADIOGRAPHIC RESPONSE IN POST-SORAFENIB HBV-RELATED HCC

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







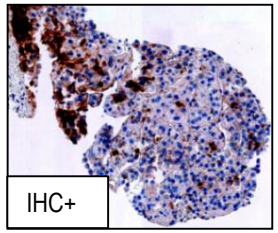


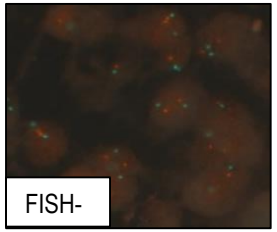
ctDNA	Measure	Baseline	Week 8
P53 Q192*	Allele fraction	31.1%	Undetectable
FGF19 amp	Copy number	8.3	Undetectable

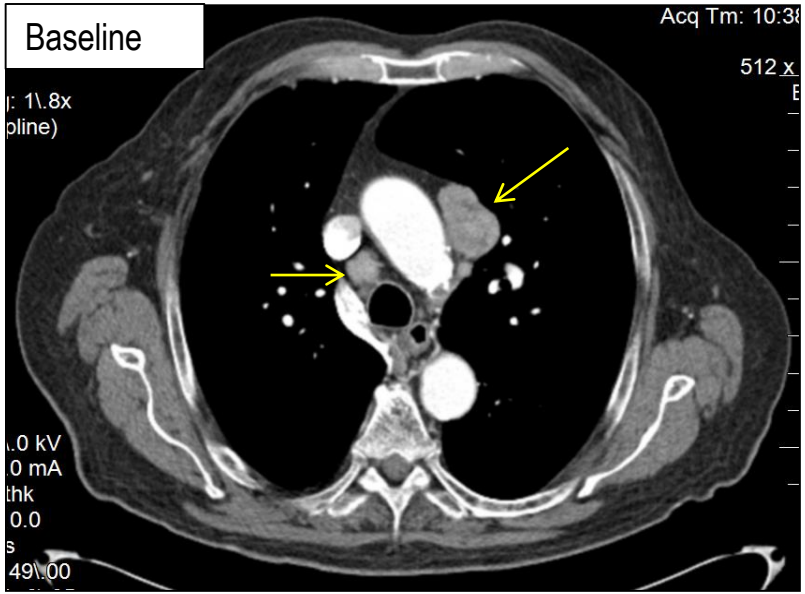
ctDNA, circulating tumor PD, progressive disease; PR, progressive response

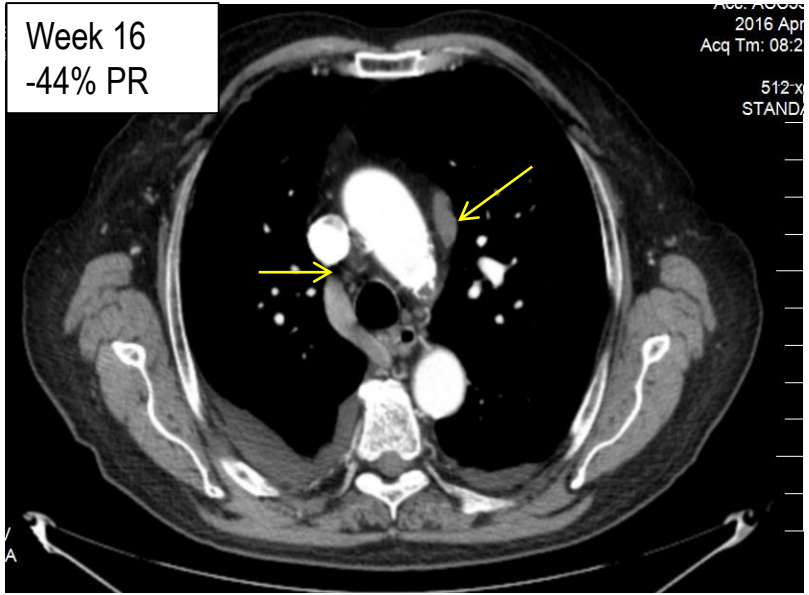
RADIOGRAPHIC RESPONSE IN POST-SORAFENIB NON-VIRAL HCC

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







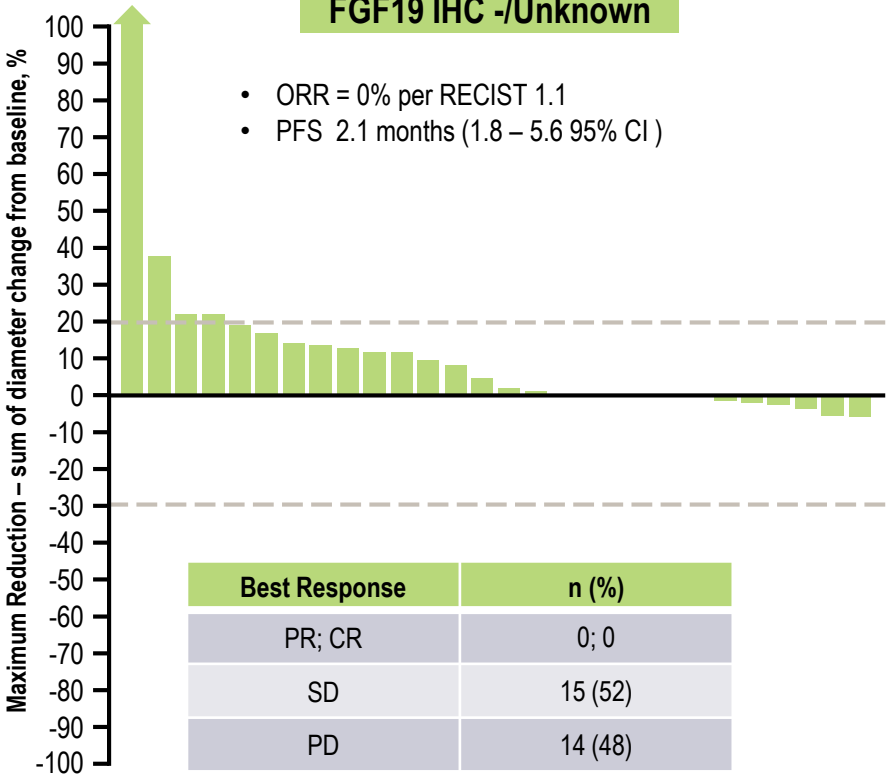


SD, stable disease

IHC-POSITIVITY ENRICHES FOR RADIOGRAPHIC TUMOR REDUCTION AND RESPONSE

FGF19 IHC -/Unknown

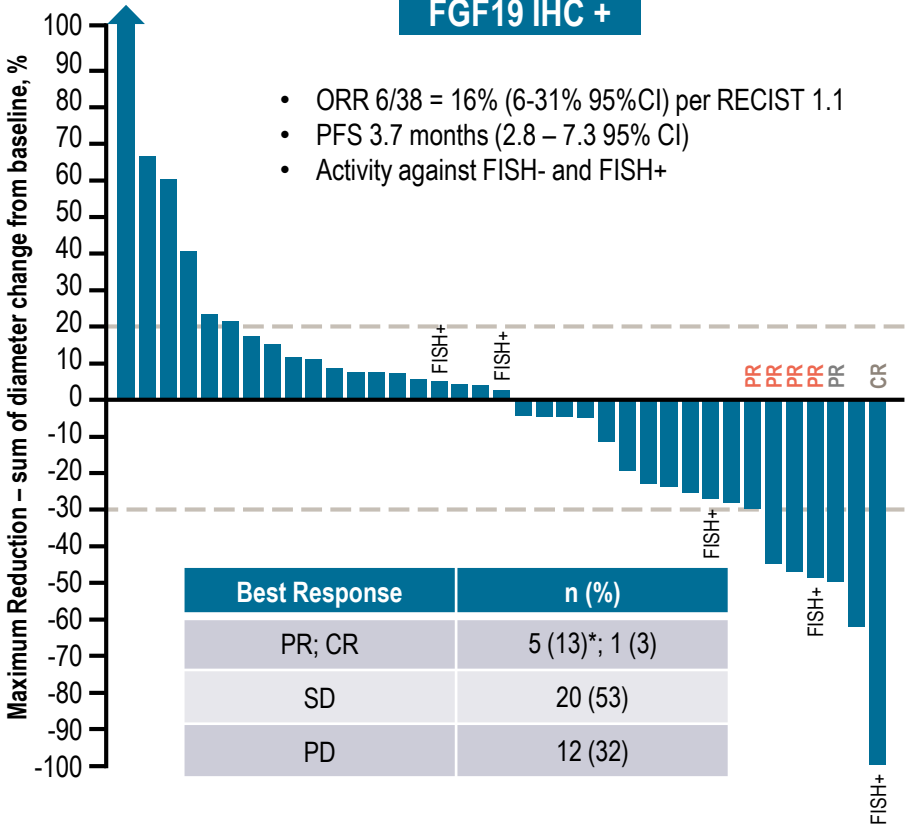
- ORR = 0% per RECIST 1.1
- PFS 2.1 months (1.8 – 5.6 95% CI)



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

FGF19 IHC +

- ORR 6/38 = 16% (6-31% 95%CI) per RECIST 1.1
- PFS 3.7 months (2.8 – 7.3 95% CI)
- Activity against FISH- and FISH+

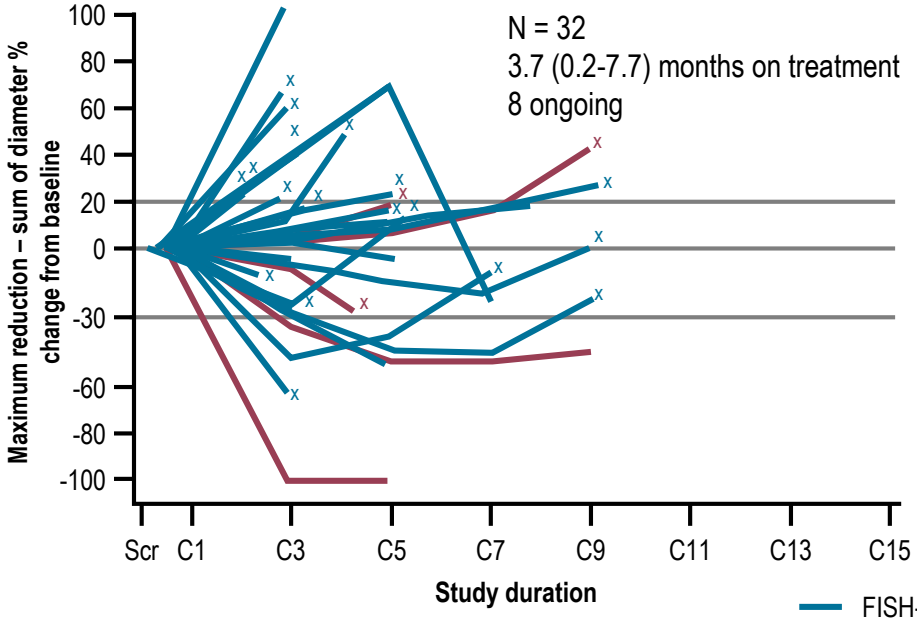


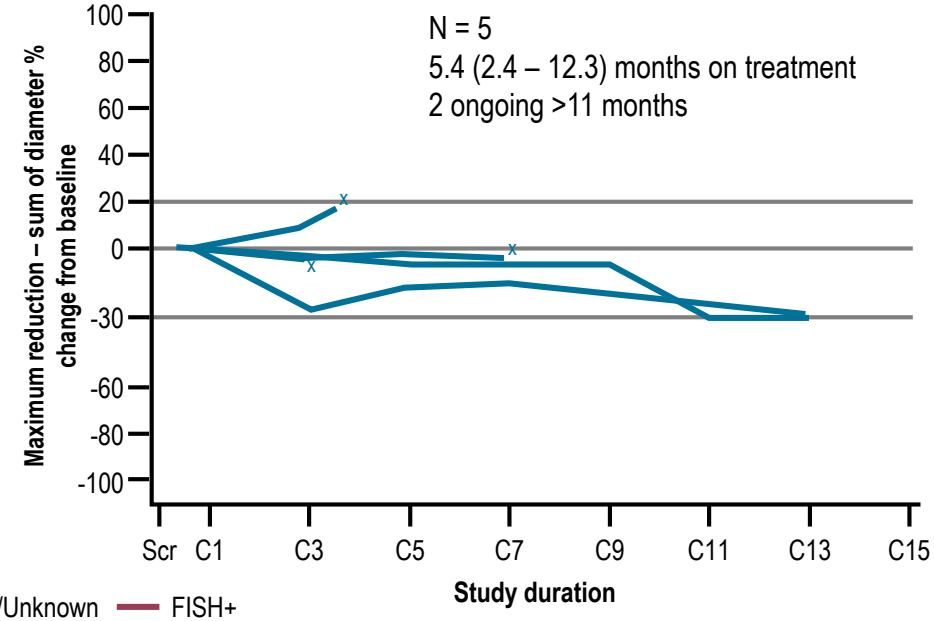
Best Response	n (%)
PR; CR	5 (13)*; 1 (3)
SD	20 (53)
PD	12 (32)

*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





FISH-/Unknown FISH+

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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- 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
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REFERENCES

1. Llovet JM et al (2016) Nature Reviews Disease Primers 2: 1–23
2. Miura S et al (2012) BMC Cancer 12:56
3. Hyeon J et al (2013) Dig Dis Sci 58:1916-1922
4. Schultze et al. (2015)Nature Genetics 47:505–511