BLU-554 in FGFR4-driven Hepatocellular Carcinoma

Clinical Development Program Update

MONDAY, SEPTEMBER 11, 2017

Conference call participants

Jeff Albers

Chief Executive Officer, Blueprint Medicines

Andy Boral, M.D.

Chief Medical Officer, Blueprint Medicines

Richard Kim, M.D.

Associate Professor, Moffitt Cancer Center

Forward-looking statements

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. The words “may,” “will,” “could,” “would,” “should,” “expect,” “plan,” “anticipate,” “intend,” “believe,” “estimate,” “predict,” “project,” “potential,” “continue,” “target” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

In this presentation, forward-looking statements include, without limitation, statements about plans and timelines for the clinical development of BLU-554 and the ability of Blueprint Medicines Corporation (the “Company”) to implement those clinical development plans; the potential benefits of BLU-554 in treating patients with hepatocellular carcinoma; the potential for fibroblast growth factor receptor 4 as a therapeutic target; plans and timelines for regulatory submissions, filings or discussions; expectations regarding potential milestones; and the Company’s strategy, business plans and focus. The Company has based these forward-looking statements on management’s current expectations, assumptions, estimates and projections. While the Company believes these expectations, assumptions, estimates and projections are reasonable, such forward-looking statements are only predictions and involve known and unknown risks, uncertainties and other important factors, many of which are beyond the Company’s control and may cause actual results, performance or achievements to differ materially from those expressed or implied by any forward-looking statements. These risks and uncertainties include, without limitation, risks and uncertainties related to the delay of any current or future clinical trials or the development of the Company’s drug candidates, including BLU-285, BLU-554 and BLU-667; the Company's advancement of multiple early-stage efforts; the Company’s ability to successfully demonstrate the efficacy and safety of its drug candidates; the preclinical and clinical results for the Company’s drug candidates, which may not support further development of such drug candidates; actions or decisions of regulatory agencies or authorities, which may affect the initiation, timing and progress of current or future clinical trials; the Company’s ability to obtain, maintain and enforce patent and other intellectual property protection for any drug candidates it is developing; the Company’s ability to develop and commercialize companion diagnostics for its current and future drug candidates, including a companion diagnostic for BLU-554 with Ventana Medical Systems, Inc. and a companion diagnostic for BLU-285 with QIAGEN Manchester Limited; and the success of the Company’s cancer immunotherapy collaboration with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc.

These and other risks and uncertainties are described in greater detail under “Risk Factors” in the Company’s Quarterly Report on Form 10-Q for the quarter ended June 30, 2017, as filed with the Securities and Exchange Commission (“SEC”) on August 2, 2017, and any other filings the Company may make with the SEC in the future. The Company cannot guarantee future results, outcomes, levels of activity, performance, developments, or achievements, and there can be no assurance that the Company’s expectations, intentions, anticipations, beliefs, or projections will result or be achieved or accomplished. The forward-looking statements in this presentation are made only as of the date hereof, and except as required by law, the Company undertakes no obligation to update any forward-looking statements contained in this presentation as a result of new information, future events or otherwise.

This presentation also contains estimates, projections and other statistical data made by independent parties and by the Company relating to market size and growth and other data about the Company’s industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of the Company’s future performance and the future performance of the markets in which the Company operates are necessarily subject to a high degree of uncertainty and risk.

Jeff Albers

Chief Executive Officer
Blueprint Medicines

Continued cadence of clinical data expected through year end

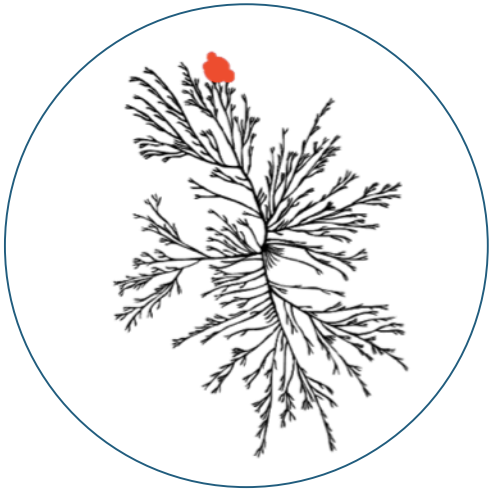
DRUG CANDIDATE	DISCOVERY	PRECLINICAL	CLINICAL	COMMERCIAL RIGHTS
BLU-285 Inhibitor of KIT, including exon 17 mutations, and PDGFRα, including the D842V mutation	REGISTRATION TRIAL – PDGFRα-DRIVEN GIST PHASE 1 – KIT-DRIVEN GIST PHASE 1 – SYSTEMIC MASTOCYTOSIS			
BLU-554 Inhibitor of FGFR4	PHASE 1 – HEPATOCELLULAR CARCINOMA			
BLU-667 Inhibitor of RET fusions, mutations and resistant mutants	PHASE 1 – NSCLC, THYROID & OTHER CANCERS*			
PRKACA Fusions	FLC			
ALK2 Mutations	FOP**			
Cancer immunotherapy Immunokinases	UP TO 5 PROGRAMS, TARGET AND DEVELOPMENT STAGE UNDISCLOSED***			Roche

FLC, fibrolamellar carcinoma; FOP, fibrodysplasia ossificans progressiva. All Phase 1 clinical trials are in advanced disease. * Phase 1 trial includes a basket cohort that consists of other advanced solid tumors with RET alterations. ** On July 26, 2017, Blueprint Medicines received written notice from Alexion of its election to terminate the FOP collaboration for convenience. The termination will become effective on October 24, 2017, and Blueprint Medicines plans to evaluate opportunities to advance this discovery program. *** Blueprint Medicines has U.S. commercial rights for up to two programs. Roche has worldwide commercialization rights for up to three programs and ex-U.S. commercialization rights for up to two programs.

BLU-554: a potent and exquisitely selective FGFR4 inhibitor

Nexavar (sorafenib)

BLU-554



- Discovered and developed by Blueprint Medicines
- First potential biomarker-driven therapy for HCC
  - ~30% of patients have FGFR4-driven HCC
  - ~18,900 first-line and ~8,000 second-line patients*
- Updated Phase 1 data at ESMO 2017
  - Show encouraging clinical activity in selected patients
  - Validate FGFR4 as therapeutic target in HCC
  - Support IHC-based patient selection strategy
- Blueprint Medicines holds global commercial rights

ESMO, European Society for Medical Oncology; FGFR4, fibroblast growth factor receptor 4; IHC, immunohistochemistry.
Kinome illustration reproduced courtesy of CSTI (cellsignal.com). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.
*Represents estimated incidence of HCC patients with aberrantly activated FGFR4 signaling in major markets (US, EU5 and Japan).

MADRID 2017 ESMO congress

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

Richard Kim[1], Debashis Sarker[2], Teresa Macarulla[3], Thomas Yau[4], Su Pin Choo[5], Tim Meyer[6], Antoine Hollebecque[7], Jonathan Whisenant[8], Max Sung[9], Jung-Hwan Yoon[10], Ho Yeong Lim[11], Andrew Zhu[12], Joong-Won Park[13], Sandrine Faivre[14], Vincenzo Mazzaferro[15], Hongliang Shi[16], Terri Alvarez-Diaz[16], Oleg Schmidt-Kittler[16], Corinne Clifford[16], Beni Wolf[16], Yoon-Koo Kang[17]

[1]Gastrointestinal Oncology, Moffitt Cancer Center, Tampa, United States, [2]Early Phase Trials Unit, Guy's Hospital, London, United Kingdom,[3]Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain, [4]Department of Medicine, Queen Mary Hospital, Hong Kong, Hong Kong, [5]Medical Oncology, National Cancer Centre, Singapore, Singapore, [6]Oncology, UCL Cancer Institute, London, United Kingdom, [7]Oncology, Institut Gustave Roussy, Villejuif, France, [8]Internal Medicine, Huntsman Cancer Institute, Salt Lake City, United States, [9]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, United States, [10]Oncology, Seoul National University Hospital, Seoul, Republic of Korea, [11]Department of Medicine, Divisions of Hematology-Oncology, Samsung Medical Center, Seoul, Republic of Korea, [12]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, United States, [13]Center for Liver Cancer, National Cancer Center, Goyang, Republic of Korea, [14]Oncology, Beaujon University Hospital, Clichy, France, [15]Department of Surgery, Liver Transplantation and Gastroenterology, Fondazione Istituto Nazionale Tumori (National Cancer Institute) IRCCS, Milan, Italy, [16]Clinical Development, Blueprint Medicines Corporation, Cambridge, United States, [17]Oncology, Asan Medical Center, Seoul, Republic of Korea

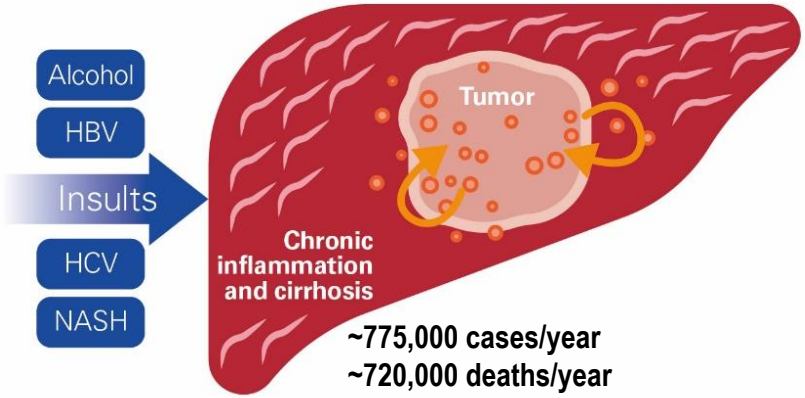
DISCLOSURES

- 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

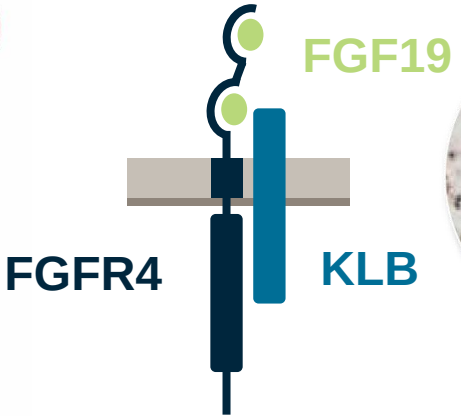


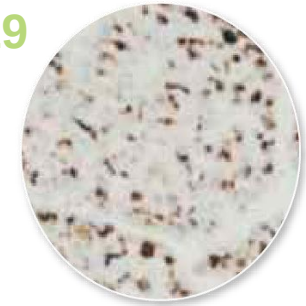
Treatment for advanced disease

sorafenib 1st line → regorafenib 2nd line

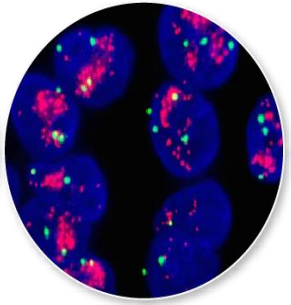
- Multi-kinase inhibitors provide OS < 1 year

FGF19 - a potential HCC driver





FGF19 IHC+
~30% HCC

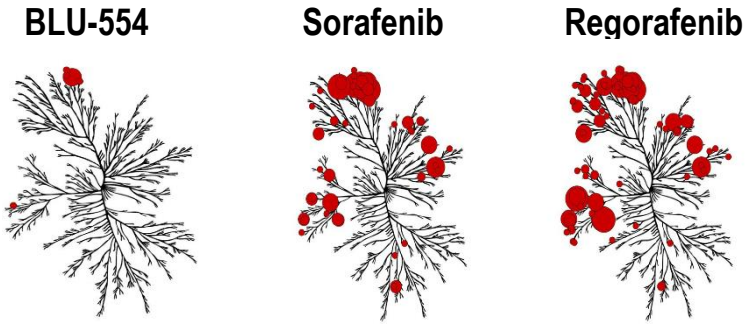


FGF19 FISH+
~7% HCC

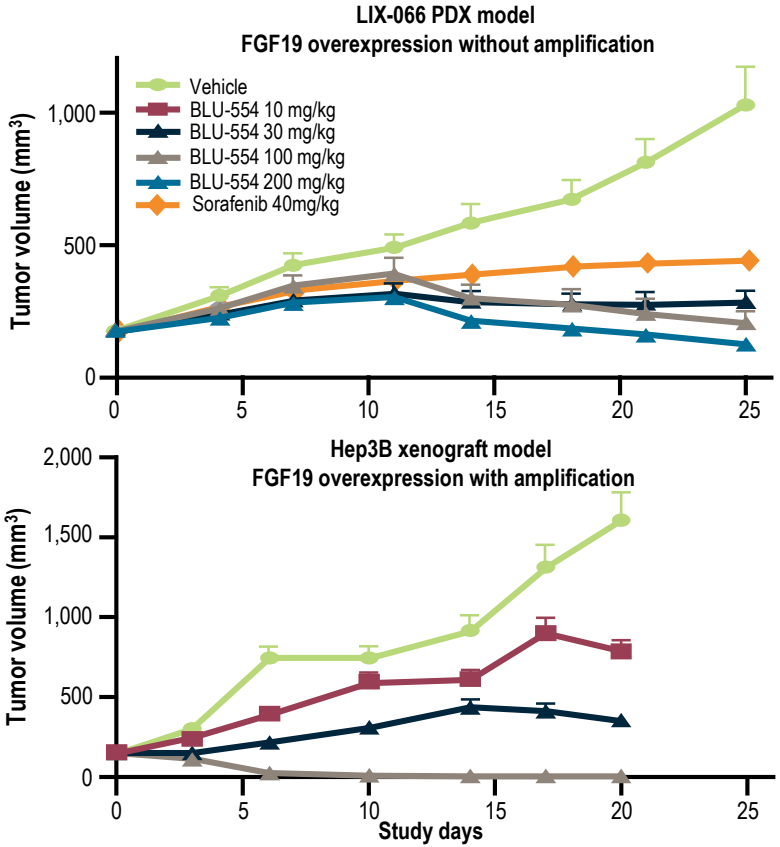
- FGF19 is a mitogen that signals via FGFR4 and KLB
- Normal liver and HCC express FGFR4 and KLB
- Aberrant FGF19 expression may drive HCC and confer poor prognosis

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



	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

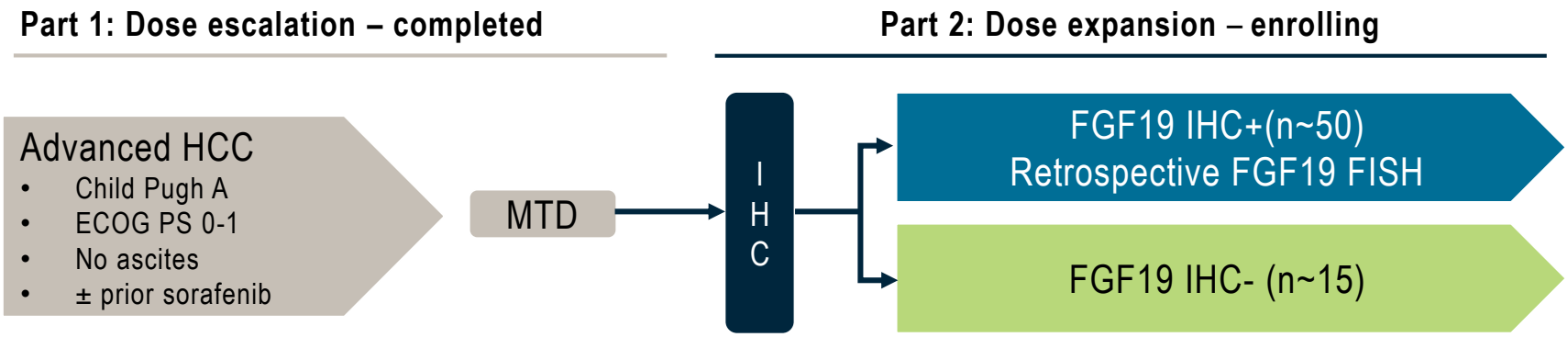


Kinome illustration reproduced courtesy of CSTI (www.cellsignal.com).
Sorafenib QD (once daily) dosing, BLU-554 BID (twice daily) dosing

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

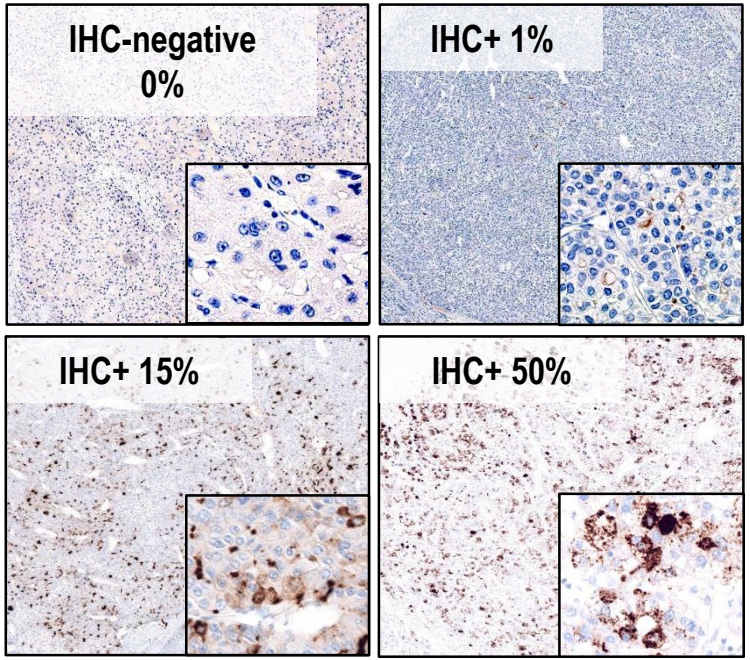


- 3+3 dose escalation (140-900 mg PO QD)
- 600 mg established as MTD

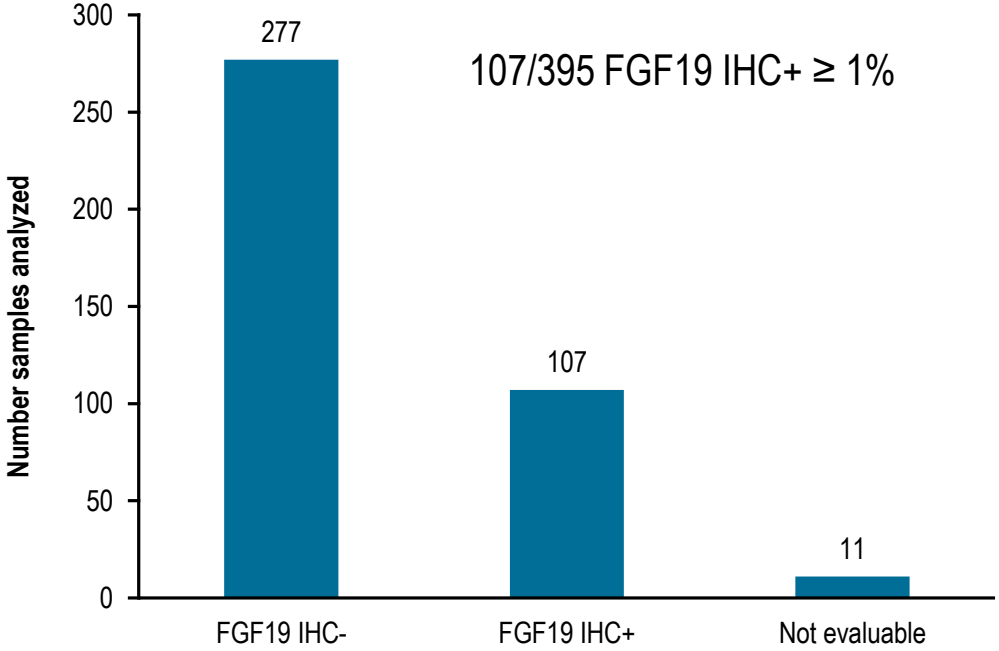
NCT02508467
ECOG PS, Eastern Cooperative Oncology Group performance status; MTD, maximum tolerated dose

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**

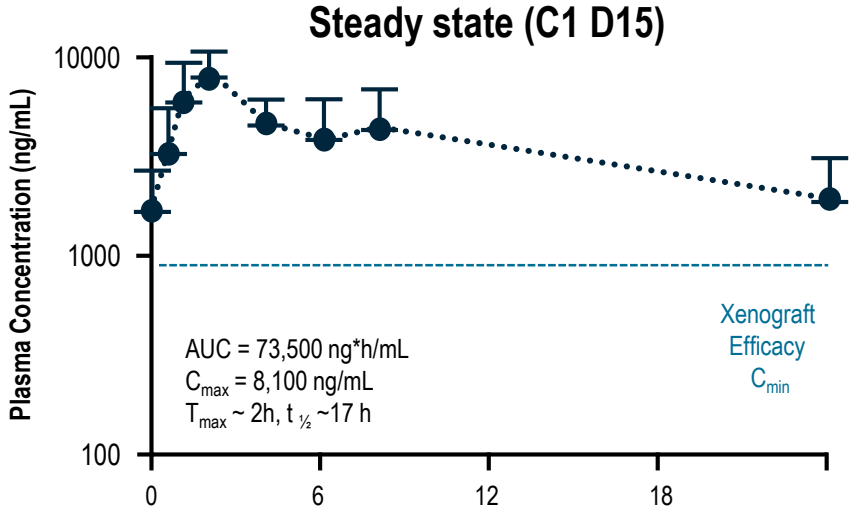
Parameter, n (%)	All patients, N = 77 n=25 escalation; n=52 expansion
Age – years, median (range)	61 (18–85)
Gender – male	60 (78)
Etiology	
Non-viral	10 (13)
HBV	36 (47)
HCV	10 (13)
Other/unknown	21 (27)
Metastatic Disease	61 (79)
FGF19 IHC	
IHC ≥1% (IHC+)	44 (57)
IHC <1% (IHC-)	28 (36)
Unknown	5 (6)

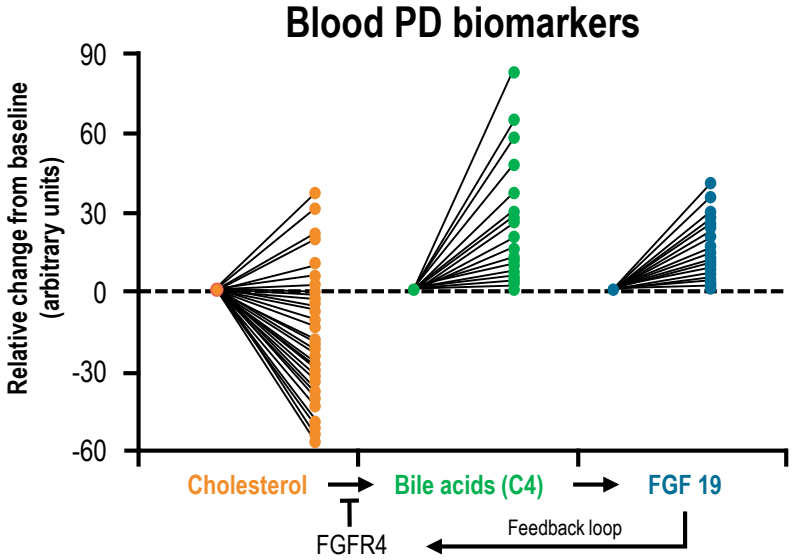
Parameter, n (%)	All patients, N = 77 n=25 escalation; n=52 expansion
FGF19 FISH	
FISH+	5 (6)
FISH-	58 (75)
Unknown	11 (14)
Pending	3 (4)
Prior Therapy	
Surgical resection	58 (75)
Radiotherapy	25 (32)
TACE / embolization	40 (52)
Immunotherapy	18 (23)
nivolumab	15 (19)
Kinase inhibitor	63 (82)
sorafenib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



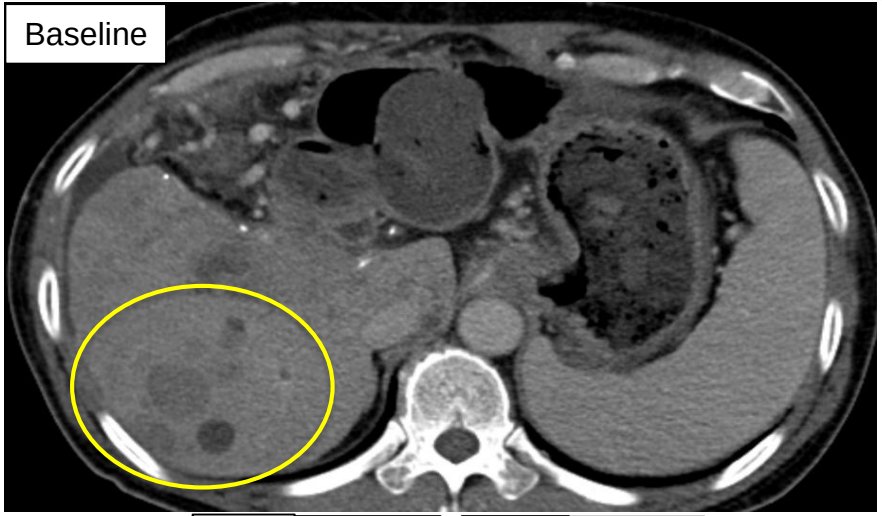


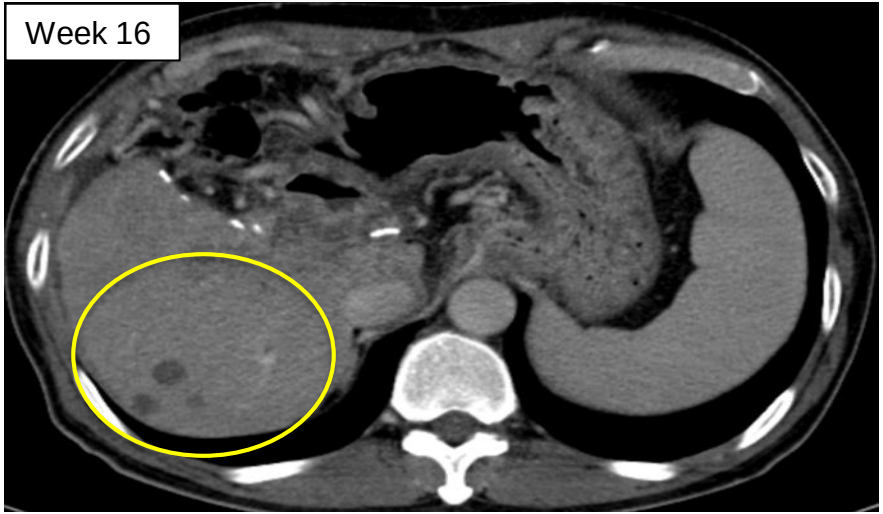
- Steady state exposure provides C_{trough} > C_{min} associated with xenograft efficacy
- Long half life supports QD dosing
- Blood biomarkers demonstrate consistent pathway modulation

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



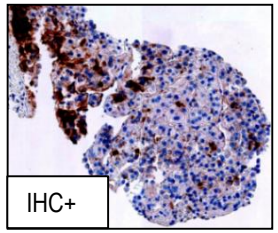


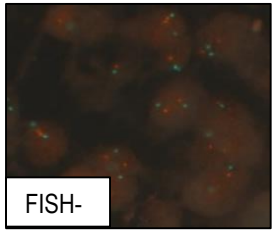
ctDNA	Measure	Baseline	Week 8
P53 Q192*	Allele fraction	31.1%	Undetectable
FGF19 amp	Copy number	8.3	Undetectable

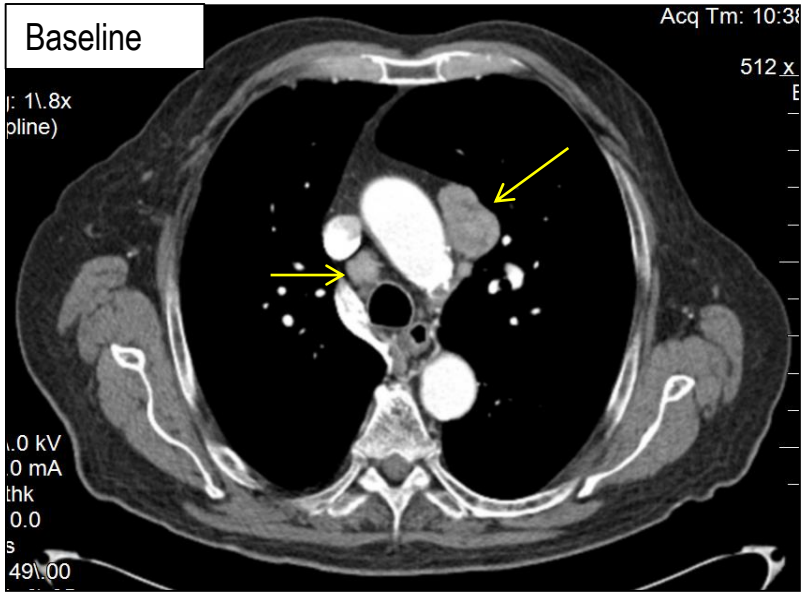
ctDNA, circulating tumor PD, progressive disease; PR, progressive response

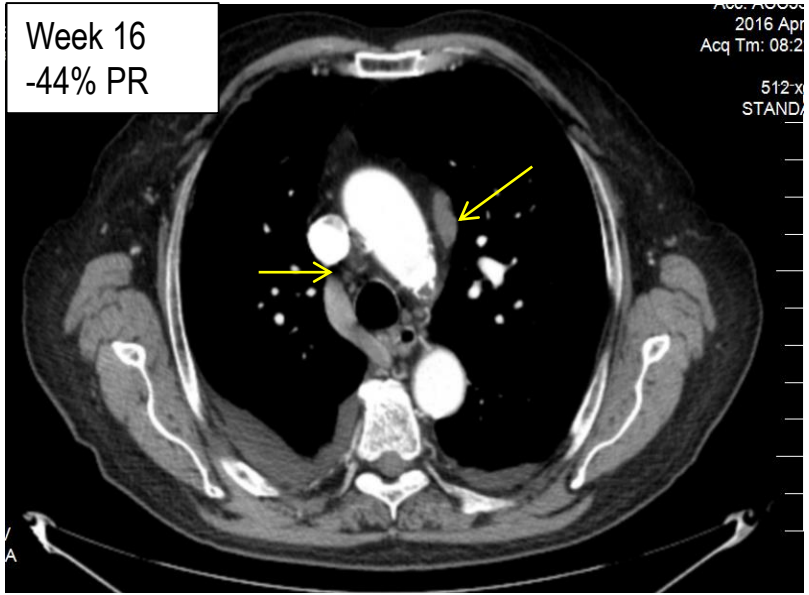
RADIOGRAPHIC RESPONSE IN POST-SORAFENIB NON-VIRAL HCC

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







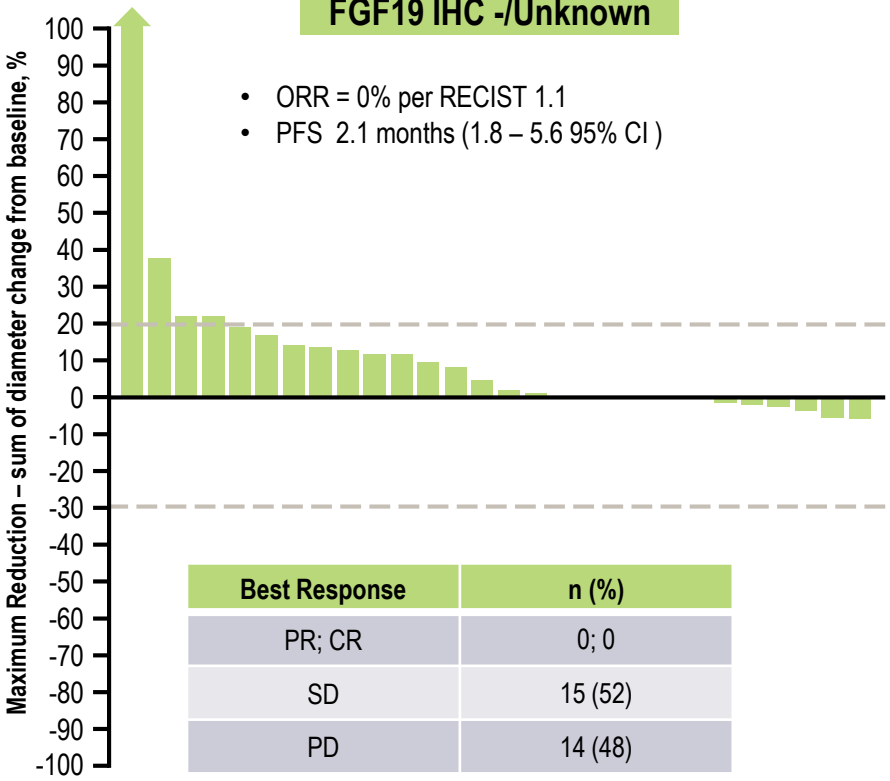


SD, stable disease

IHC-POSITIVITY ENRICHES FOR RADIOGRAPHIC TUMOR REDUCTION AND RESPONSE

FGF19 IHC -/Unknown

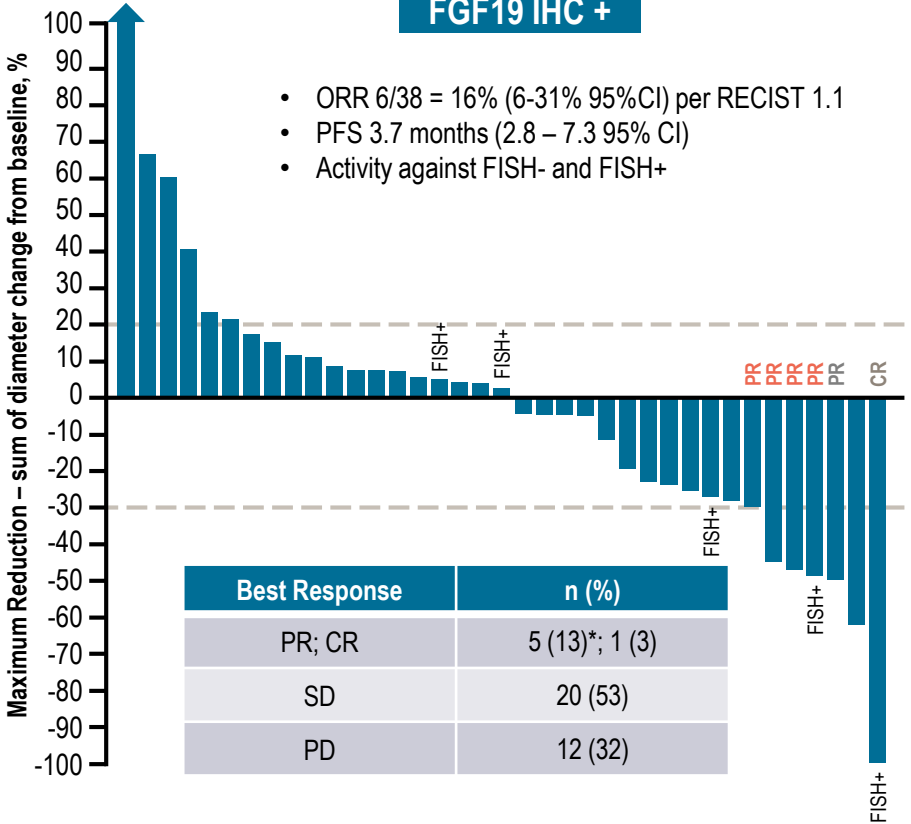
- ORR = 0% per RECIST 1.1
- PFS 2.1 months (1.8 – 5.6 95% CI)



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+

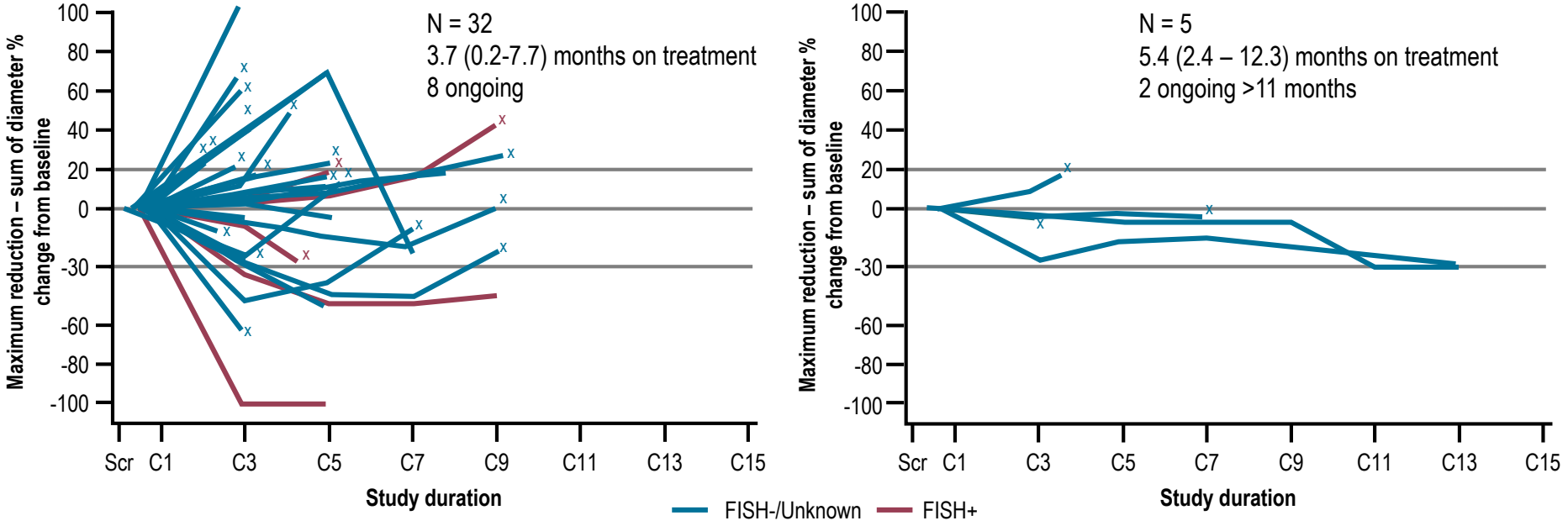


Best Response	n (%)
PR; CR	5 (13)*; 1 (3)
SD	20 (53)
PD	12 (32)

*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



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

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

REFERENCES

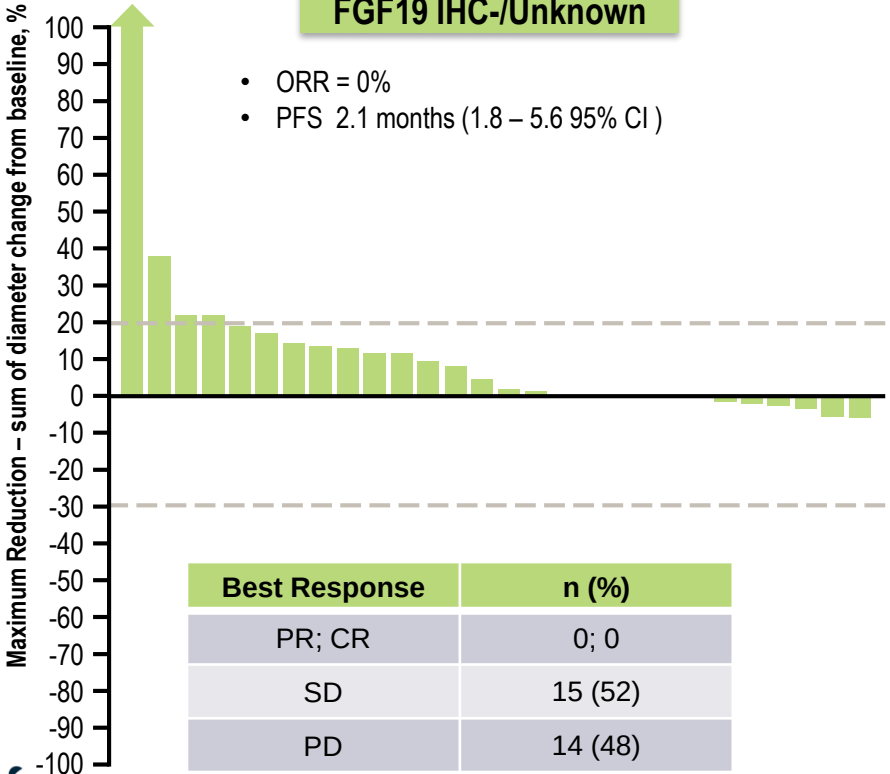
1. Llovet JM et al (2016) Nature Reviews Disease Primers 2: 1–23
2. Miura S et al (2012) BMC Cancer 12:56
3. Hyeon J et al (2013) Dig Dis Sci 58:1916-1922
4. Schultze et al. (2015)Nature Genetics 47:505–511

Andy Boral, M.D.
Chief Medical Officer
Blueprint Medicines

Encouraging BLU-554 clinical activity in IHC+ population

FGF19 IHC-/Unknown

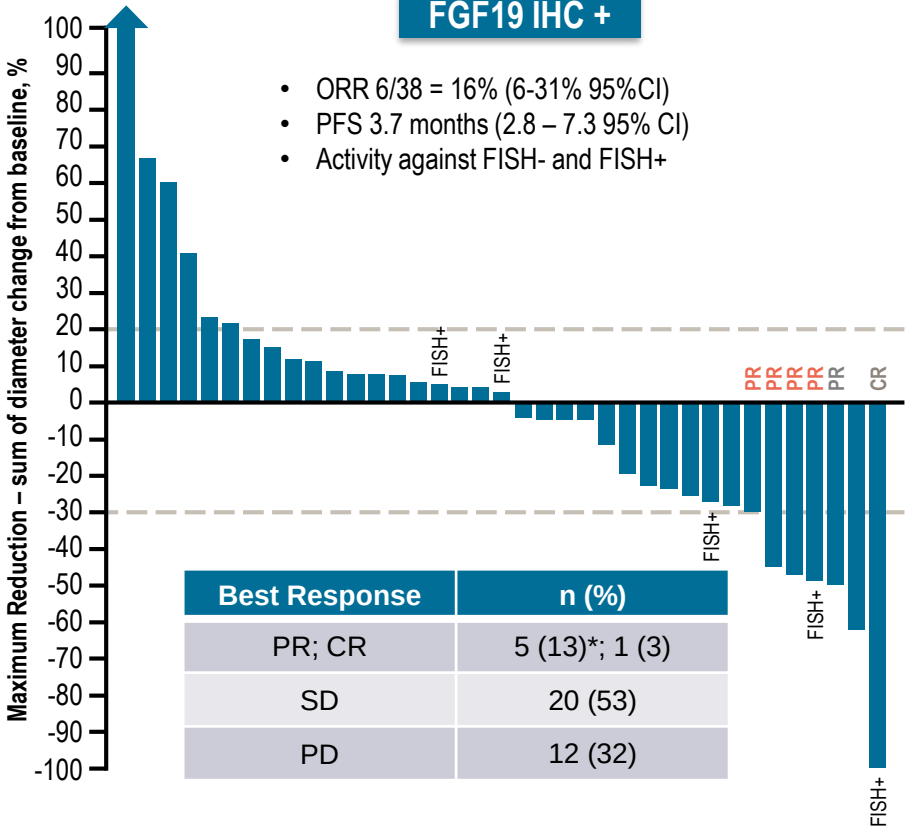
- ORR = 0%
- PFS 2.1 months (1.8 – 5.6 95% CI)



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

FGF19 IHC +

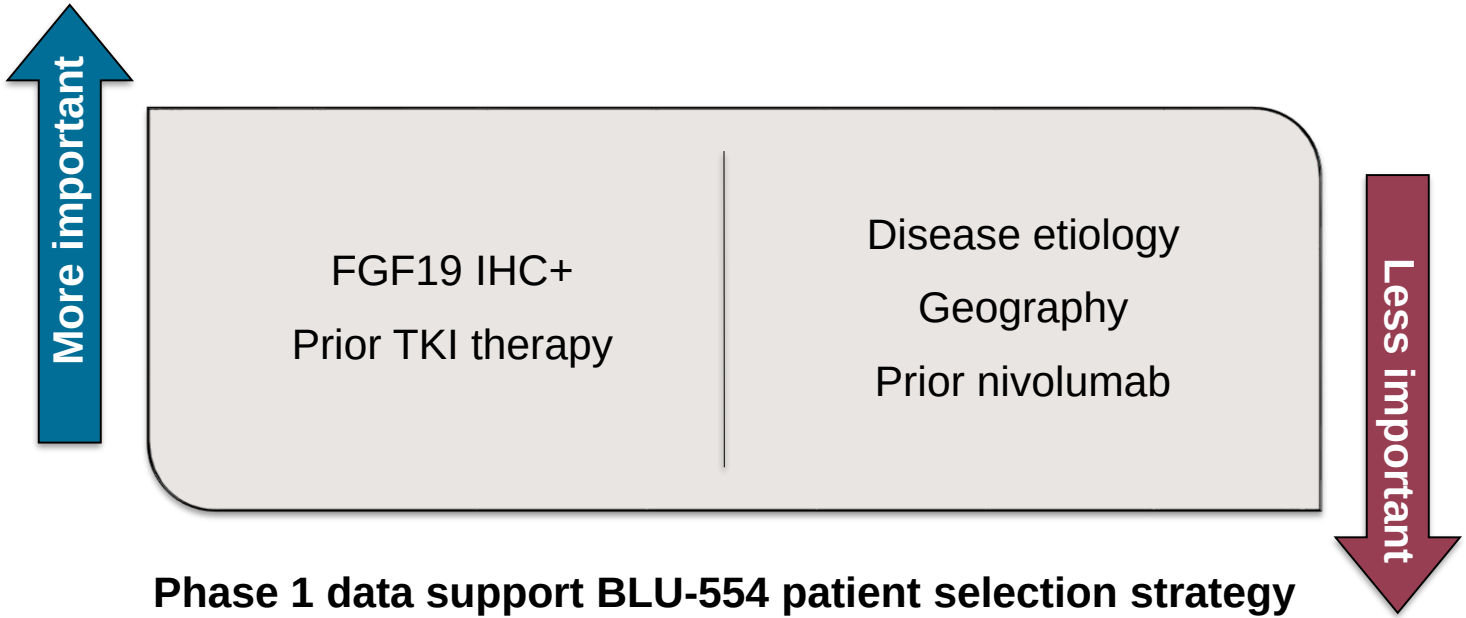
- ORR 6/38 = 16% (6-31% 95%CI)
- PFS 3.7 months (2.8 – 7.3 95% CI)
- Activity against FISH- and FISH+



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.

Preliminary analyses of patient characteristics

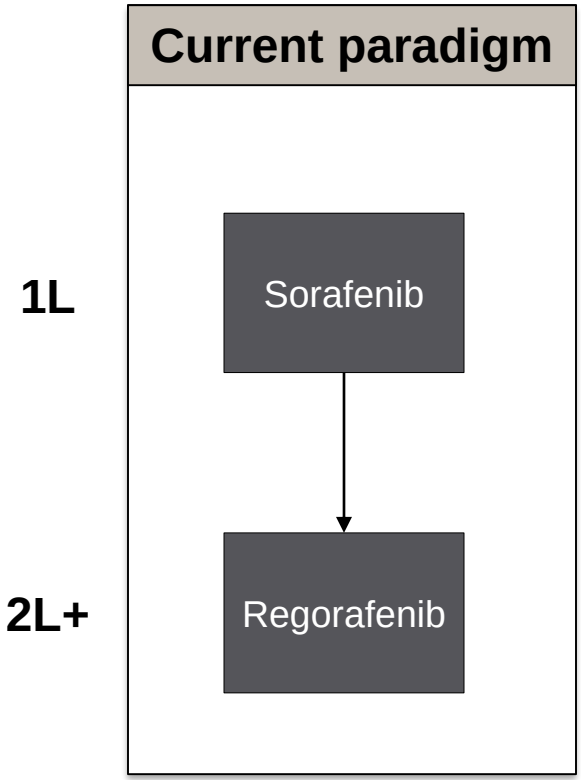


Phase 1 data support BLU-554 patient selection strategy

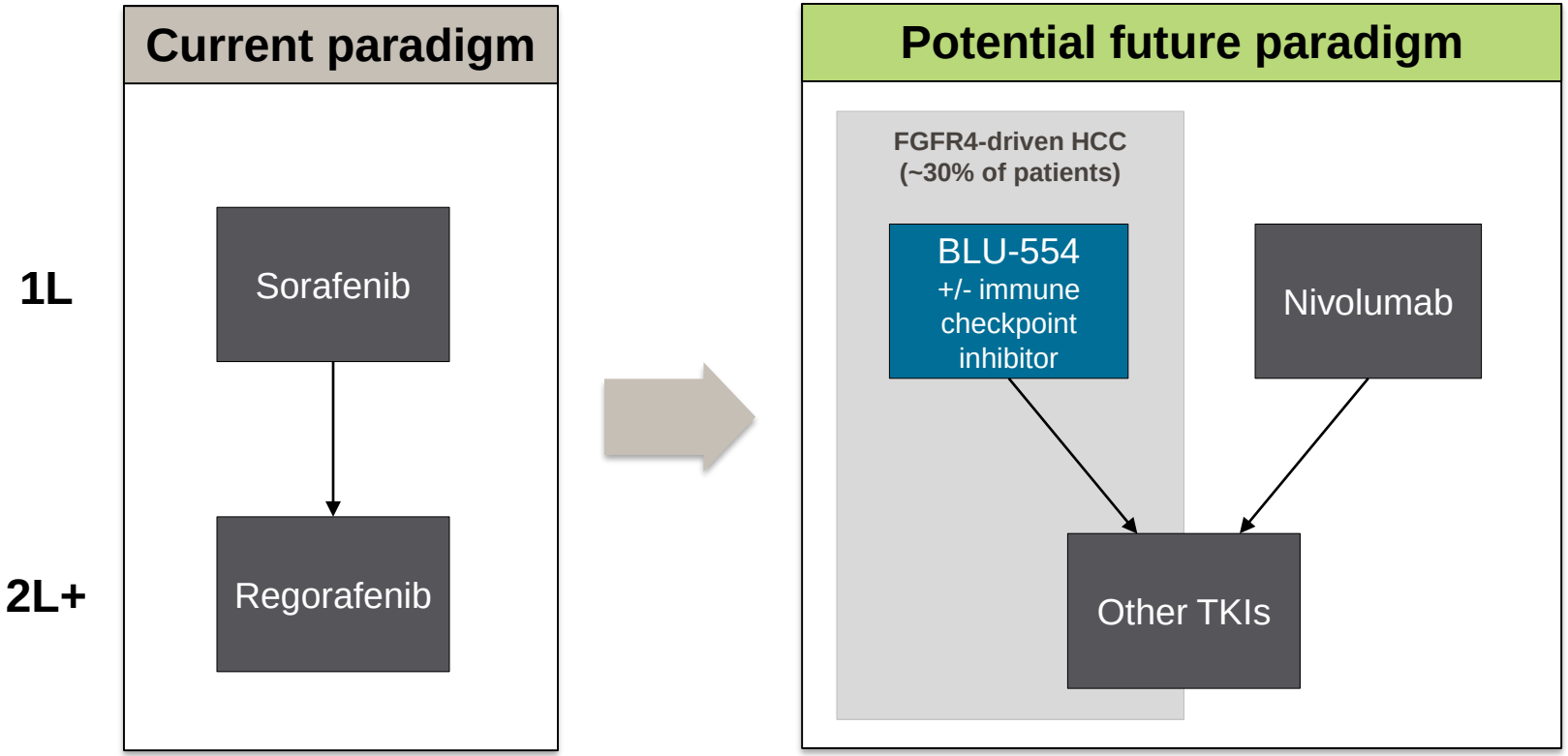
- BLU-554 was active in patients with ≥1% IHC+, with or without FISH+
- Trial screening showed ≥1% IHC+ in 27% of patients (n=379), consistent with estimated frequency of patients with FGFR4-driven HCC

FISH, fluorescent in situ hybridization; TKI, tyrosine kinase inhibitor.

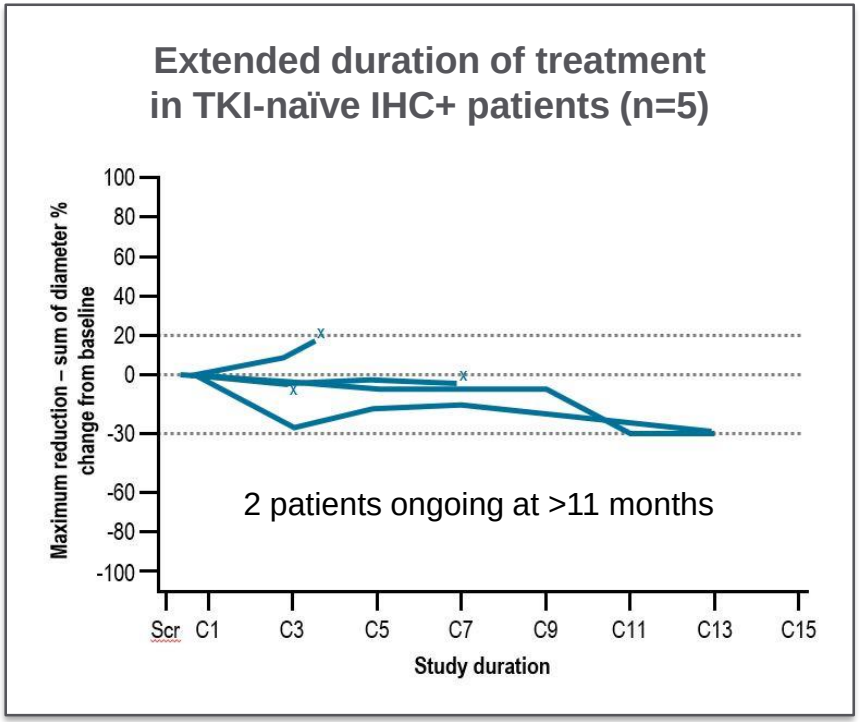
Opportunities for BLU-554 in the evolving HCC landscape



Opportunities for BLU-554 in the evolving HCC landscape



Priorities for further development of BLU-554 in HCC



TKI-naïve FGF19 IHC+ patients

Hypothesis

- Less disease burden
- Less genetic heterogeneity
- Supported by Phase 1 data

Next steps

- Add cohort to Phase 1 trial

Combination with immunotherapy

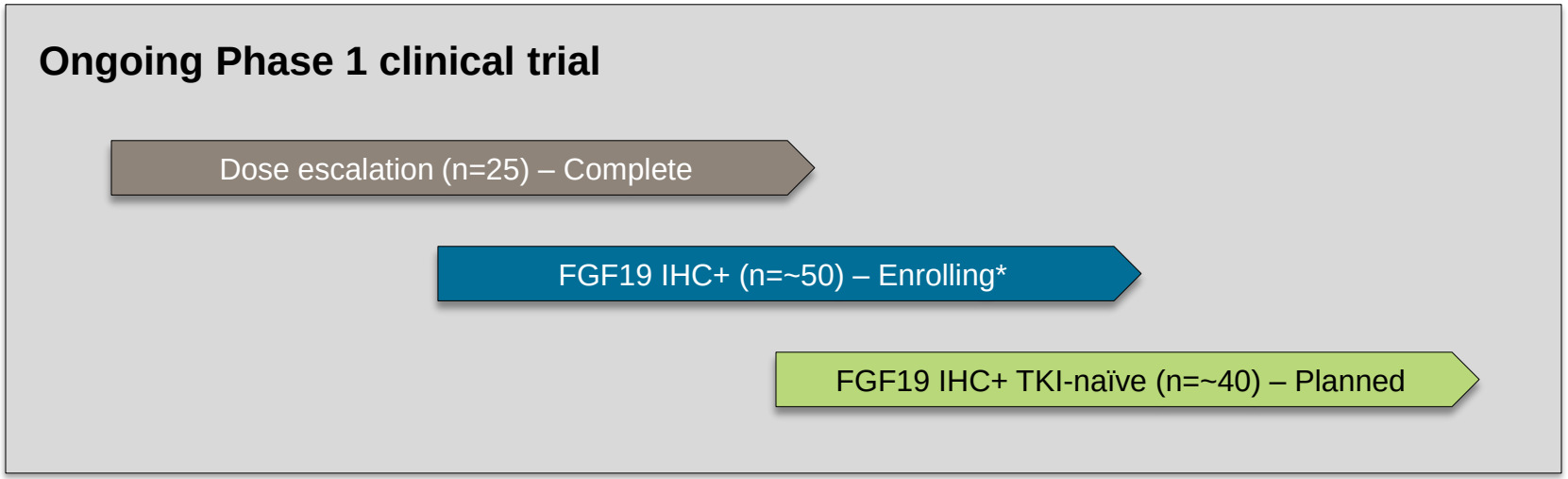
Hypothesis

- TKI-induced apoptosis may enhance antigen presentation
- High target selectivity may enable combo safety profile

Next steps

- Preclinical studies ongoing
- Explore clinical trial options

Overview of ongoing and planned BLU-554 development activities



- Explore options for clinical trial in combination with an immune checkpoint inhibitor

*Includes sorafenib-naïve patients who have declined sorafenib or do not have access to sorafenib.

Question & Answer

Thank you