Poster
P076A

First-in-human study of BLU-554, a potent, highly selective FGFR4 inhibitor designed for hepatocellular carcinoma (HCC) with FGFR4 pathway activation

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Hypothesis and objectives

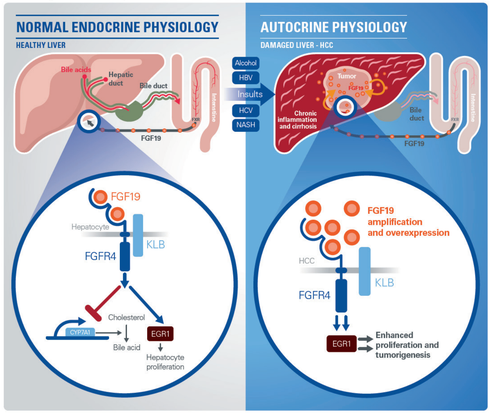
- A Phase I study was initiated in advanced HCC to explore the hypothesis that targeting FGFR4 will have therapeutic benefit in HCC driven by the FGFR4 ligand, FGF19
- The key objectives were to determine the maximum tolerated dose (MTD) and to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary anti-tumor activity of BLU-554, an investigational, potent, highly-selective, oral FGFR4 inhibitor

HCC – a worldwide medical need[1]

- >700,000 new cases/year; 600,000 deaths/year
- Sorafenib, standard of care for advanced disease, provides a response rate of ~2% and median survival <11 months
- Viral and non-viral etiologies are well known, but molecular drivers are largely undefined; consequently, there are no molecular diagnostics to guide patient care

FGF19 identified as a potential HCC driver[1–5]

- ~5% of HCCs have genomic amplification of the FGF19/CCND1 locus (Immunohistochemistry [IHC]+ Fluorescent In Situ Hybridization [FISH]+)
- ~25% of HCCs overexpress FGF19 in the absence of genomic amplification (IHC+ FISH-)
- Transgenic overexpression of FGF19 causes HCC in mice



HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis

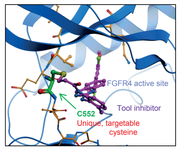
- Normal liver does not express FGF19, but expresses high levels of FGFR4 and klotho-beta (KLB). FGF19 produced by the ileum acts in an endocrine fashion on the liver to initiate signaling (left panel)
- HCC retains high levels of FGFR4/KLB and remains poised to bind FGF19. Aberrant FGF19 expression in HCC promotes autocrine signaling (right panel)

Methods

- Patients were given BLU-554 orally, once daily (QD) on a 4-week cycle following a 3+3 design. Adverse events (AEs), PK and PD were assessed. Baseline tumor FGF19 expression was analyzed via IHC as a marker of pathway activation. FISH was assessed retrospectively. Response was determined by RECIST 1.1 every 8 weeks
- All data are preliminary and based on a cut-off of November 7, 2016

BLU-554

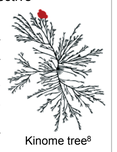
Irreversible FGFR4 inhibition



Highly potent and selective

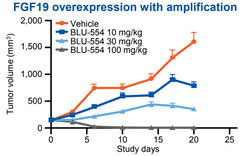
Inhibitor[6,7]	IC_{50} (nM)	
	FGFR4	FGFR1–3
BLU-554	5	624–2203
AZD4547*	160	0.2–2.5
NVP-BGJ398*	60	0.9–1.4

*Pan FGFR inhibitors

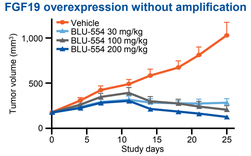


Kinome tree[8]

Hep3B xenograft model
FGF19 overexpression with amplification



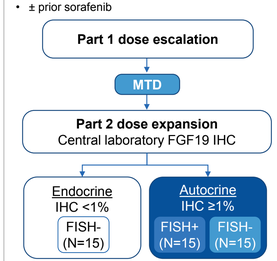
LIX-066 PDX model
FGF19 overexpression without amplification



Phase I study design

Key inclusion criteria

- Unresectable HCC
- Child-Pugh class A with no clinically apparent ascites
- ECOG performance status 0–1
- ± prior sorafenib



Part 1 dose escalation

BLU-554 mg/day	Patients treated	DLT
140	3	0
280	3	0
420	3+3 enrichment	0
600	3+3 enrichment	0
900	7	2

- 3+3 dose escalation with FGF19+ patient enrichment via additional accrual to dose levels declared safe
- MTD defined as 600 mg QD
- Dose expansion now enrolling

Baseline demographics and characteristics

- 25 patients were enrolled over 12 months; 7 (28%) patients remain on study
- 18 (72%) patients discontinued BLU-554:
  - 15 due to disease progression, 2 due to AEs, 1 due to investigator's decision

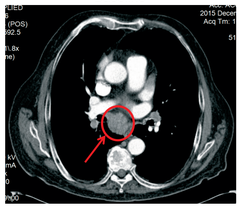
Characteristic, n (%)	Total (N=25)	Characteristic, n (%)	Total (N=25)
Mean age, years (range)	61 (19–81)	**FGF19 FISH**	
Gender		FISH+	1 (4)*
Male	19 (76)	FISH-	13 (52)
Etiology		Unknown	11 (44)
Non-viral	4 (16)	**Prior therapy**	
HBV	8 (32)	Surgical resection	14 (56)
HCV	4 (16)	Radiotherapy	6 (24)
Other/unknown	9 (36)	TACE/embolization	10 (40)
Metastatic disease		Kinase inhibitor	20 (80)
Yes	17 (68)	Sorafenib	19 (76)
FGF19 IHC		Systemic therapy	23 (92)
IHC ≥1% (IHC+)	10 (40)		
IHC <1% (IHC-)	10 (40)		
Unknown	5 (20)		

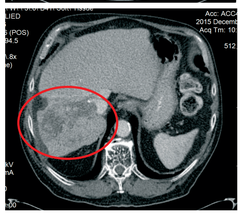
*CN=4, low level copy number gain; TACE, transarterial chemoembolization

Proof-of-concept

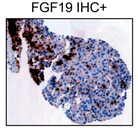
Case study 1 (280 mg)

- 81 year old male; alcohol-related cirrhosis; metastatic HCC; prior radiation therapy; prior sorafenib; remained on study for 8 cycles

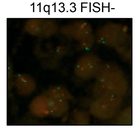




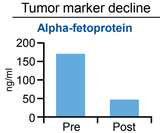
FGF19 IHC+



11q13.3 FISH-

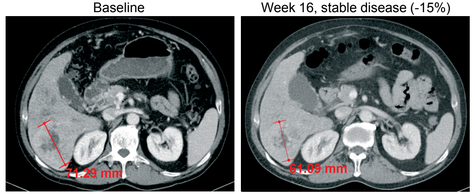


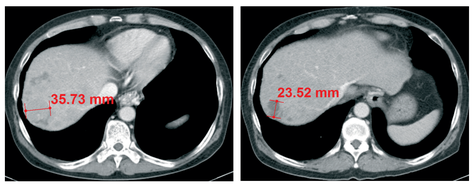
Tumor marker decline
Alpha-fetoprotein

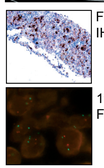


Case study 2 (600 mg)

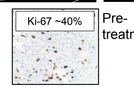
- 64 year old male; HBV-related HCC; Barcelona clinic liver cancer stage C with macrovascular invasion; prior sorafenib; ongoing at cycle 6





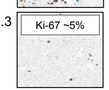


FGF19 IHC+



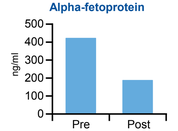
Pre-treatment

11q13.3 FISH-



Post-treatment

Tumor marker decline
Alpha-fetoprotein



Safety

Adverse events

- 2 patients experienced dose-limiting toxicities at 900 mg:
  - Grade 3 abdominal pain; Grade 3 fatigue lasting more than 7 days
- 2 patients discontinued BLU-554 due to treatment-related toxicity:
  - Grade 3 hemorrhage; Grade 4 AST increase
- 17 patients had Grade ≥3 AEs which were treatment-related in 12 patients
- AEs occurring in >15% of patients are summarized in the table below

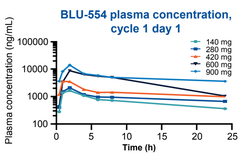
AE category, n (%)	Any grade	Grade ≥3	AE category, n (%)	Any grade	Grade ≥3
Diarrhea	18 (72)	2 (8)	**ALP increased**	5 (20)	0
Nausea	11 (44)	0	**Dyspnea**	5 (20)	1 (4)
Abdominal pain	10 (40)	3 (12)	**Peripheral edema**	5 (20)	1 (4)
Vomiting	10 (40)	0	**Maculo-popular rash**	5 (20)	1 (4)
Fatigue	9 (36)	2 (8)	**Bilirubin increased**	4 (16)	1 (4)
ALT increased	8 (32)	3 (12)	**Hyperhidrosis**	4 (16)	0
AST increased	7 (28)	4 (16)	**Hyponatremia**	4 (16)	2 (8)
Decreased appetite	6 (24)	0	**Lymphocytes decreased**	4 (16)	3 (12)
Anemia	5 (20)	5 (20)			

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase

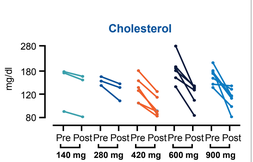
Pharmacokinetics and pharmacodynamics

- PK shows rapid absorption (T_{max} ~1–3 hours) and half-life of ~10 hours
- Exposure increases over the 140–900 mg dose range with significant AUC overlap between 600 and 900 mg dose levels
- Blood PD markers show pathway engagement at all dose levels

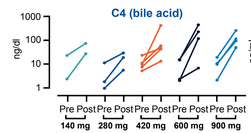
BLU-554 plasma concentration, cycle 1 day 1



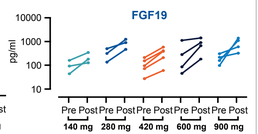
Cholesterol



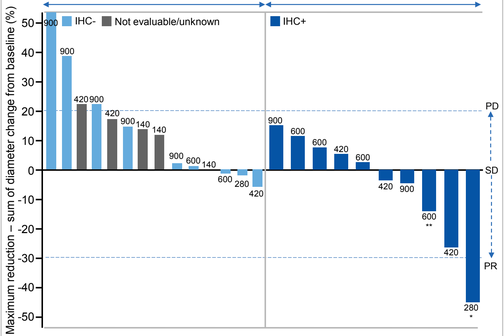
C4 (bile acid)

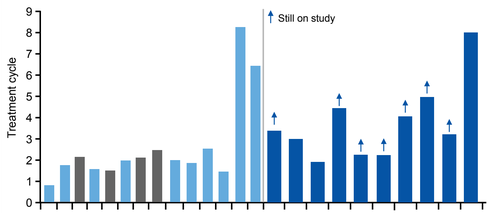


FGF19



Anti-tumor activity and duration on study





*Case study 1; **Case study 2; PD, progressive disease; PR, partial response; SD, stable disease

Conclusions

- Proof-of-concept established for highly selective targeting of FGFR4 with BLU-554 in advanced HCC
  - 5 of 10 FGF19 IHC+ patients with radiographic tumor shrinkage including 1 confirmed partial response
  - 7 of 10 FGF19 IHC+ patients remain on study
- The QD MTD and recommended dose for expansion (600 mg) provides tolerability, pathway modulation, and exposure in the expected therapeutic range based on xenograft models
- FGF19 IHC data suggest potential for autocrine FGF19-FGFR4 pathway activation in approximately 30% of HCC patients
- Part 2 dose expansion underway with central laboratory FGF19 IHC and FISH testing to better define responsive patient population(s) based on pathway status

Acknowledgments

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