

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

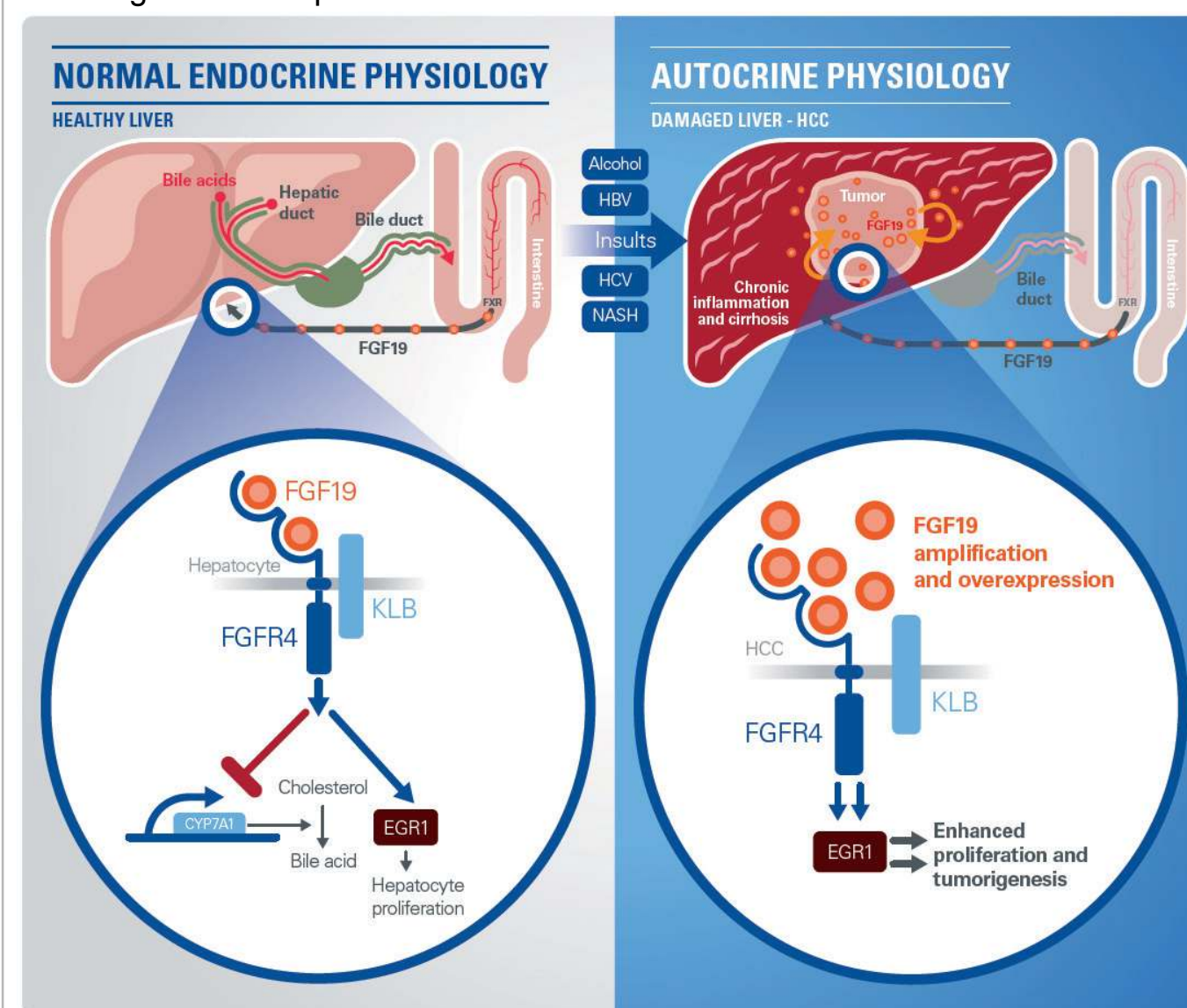
- A Phase I study was initiated in advanced HCC to explore the hypothesis that targeting FGFR4 will have therapeutic benefit in HCC driven by the FGFR4 ligand, FGF19
- The key objectives were to determine the maximum tolerated dose (MTD) and to evaluate the safety, pharmacokinetics (PK), pharmacodynamics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

HCC – a worldwide medical need¹

- >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 driver¹⁻⁵

- ~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

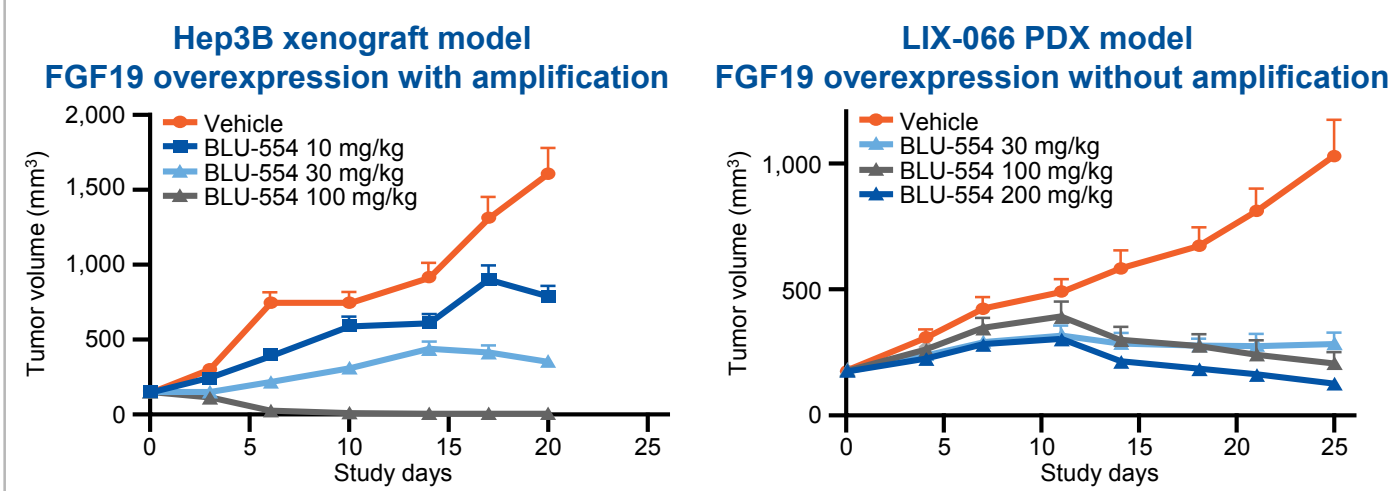
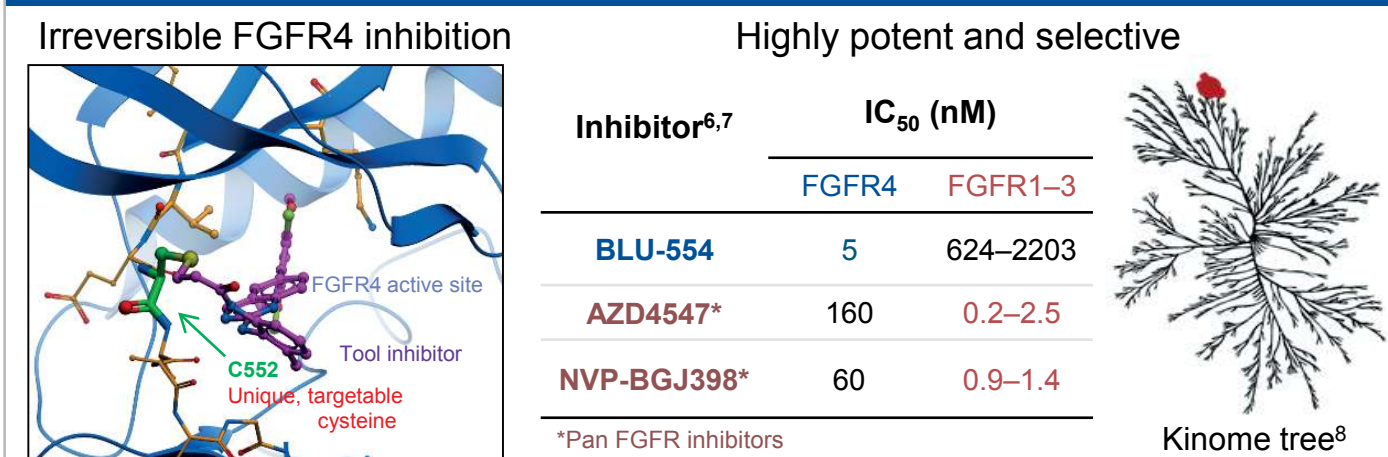


- HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis
- Normal liver does not express FGF19, but expresses high levels of FGFR4 and Klotho-beta (KLB). FGF19 produced by the ileum acts in an endocrine fashion on the liver to initiate signaling (left panel)
- HCC retains high levels of FGFR4/KLB and remains poised to bind FGF19. Aberrant FGF19 expression in HCC promotes autocrine signaling (right panel)

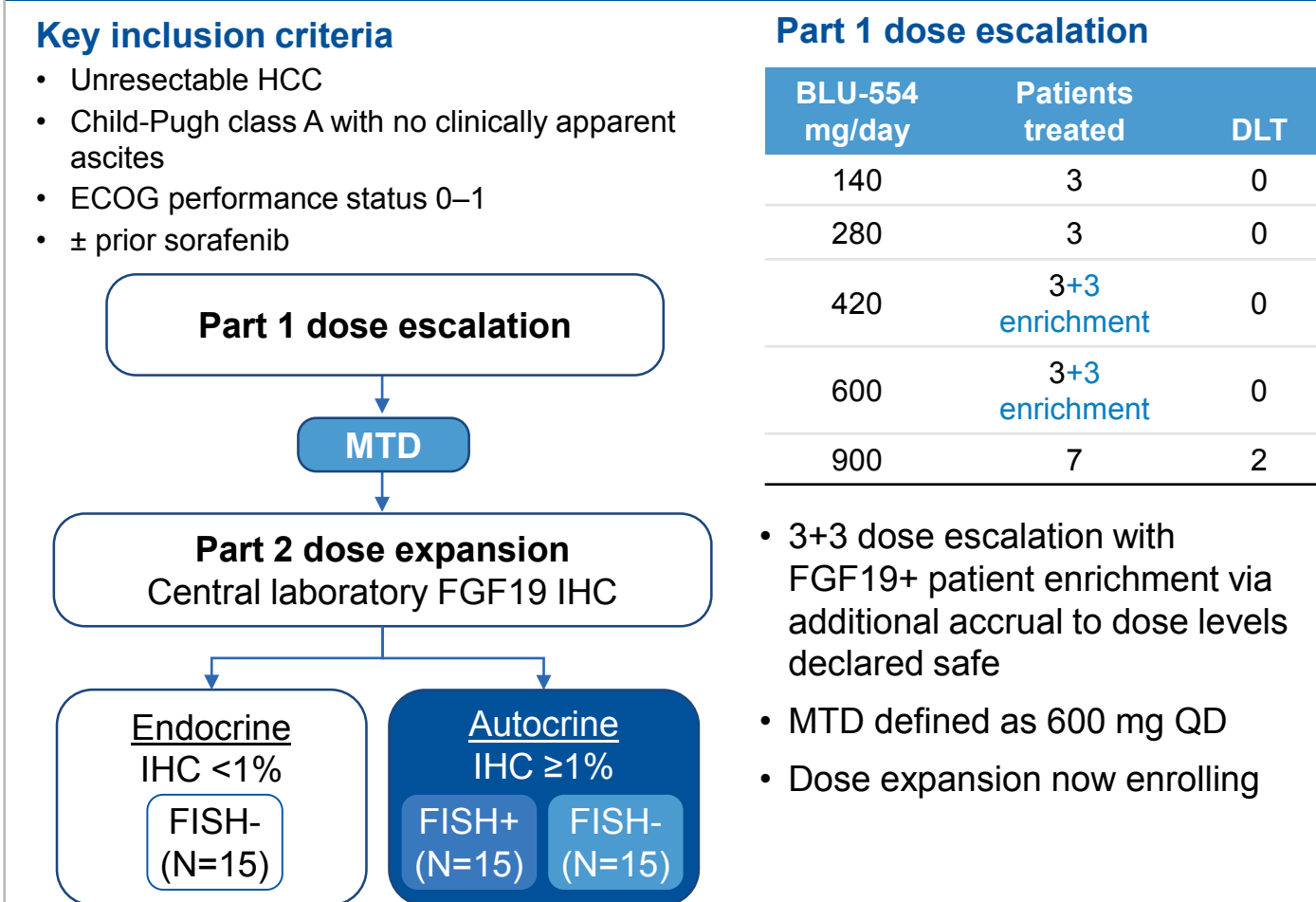
Methods

- 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



Phase I study design



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

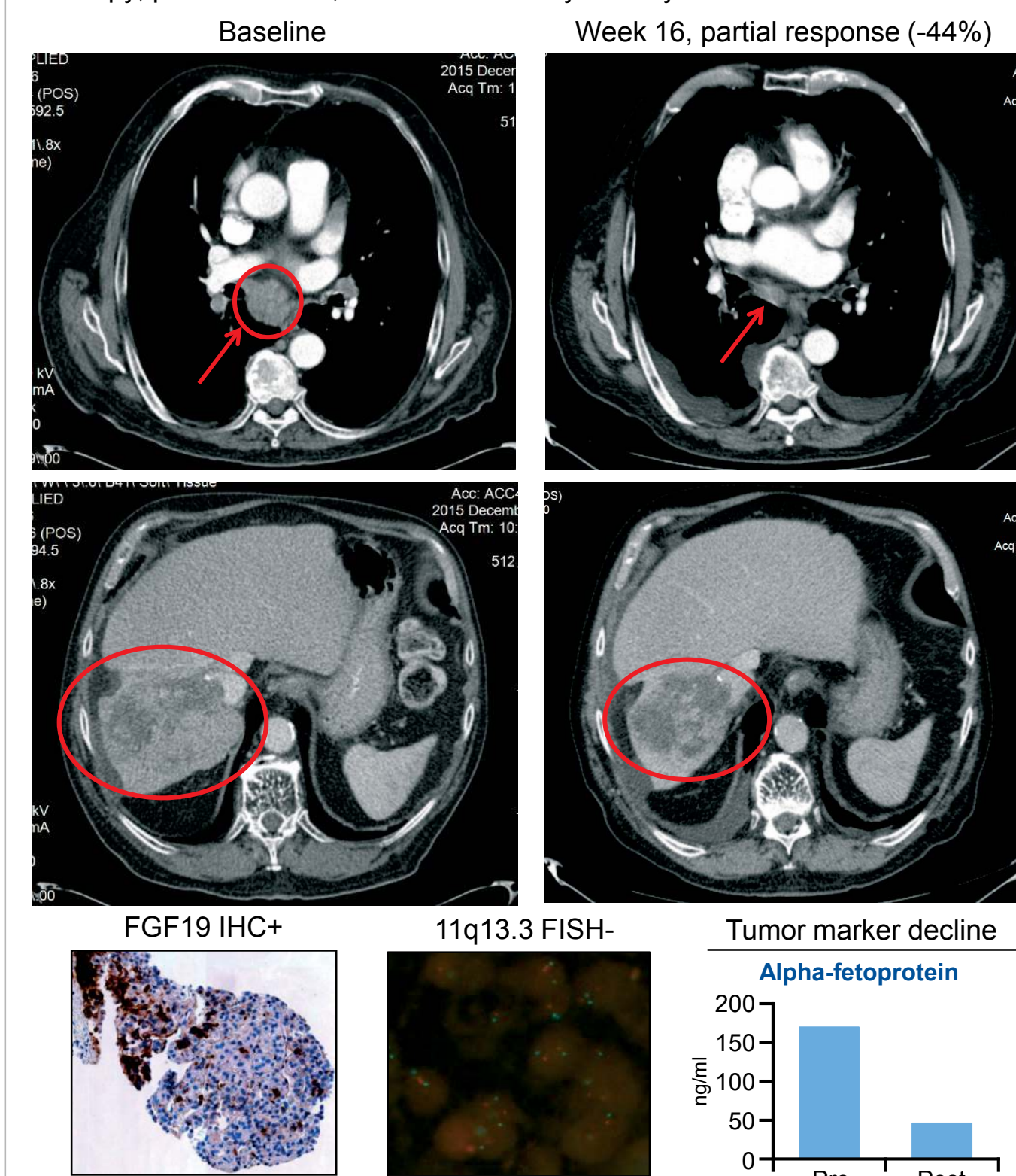
| Characteristic, n (%) | Total (N=25) | Characteristic, n (%) | Total (N=25) |
|--------------------------------|--------------|-----------------------|--------------|
| Mean age, years (range) | 61 (19-81) | FGF19 FISH | |
| Gender | | FISH+ | 1 (4)* |
| Male | 19 (76) | FISH- | 13 (52) |
| Etiology | | 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

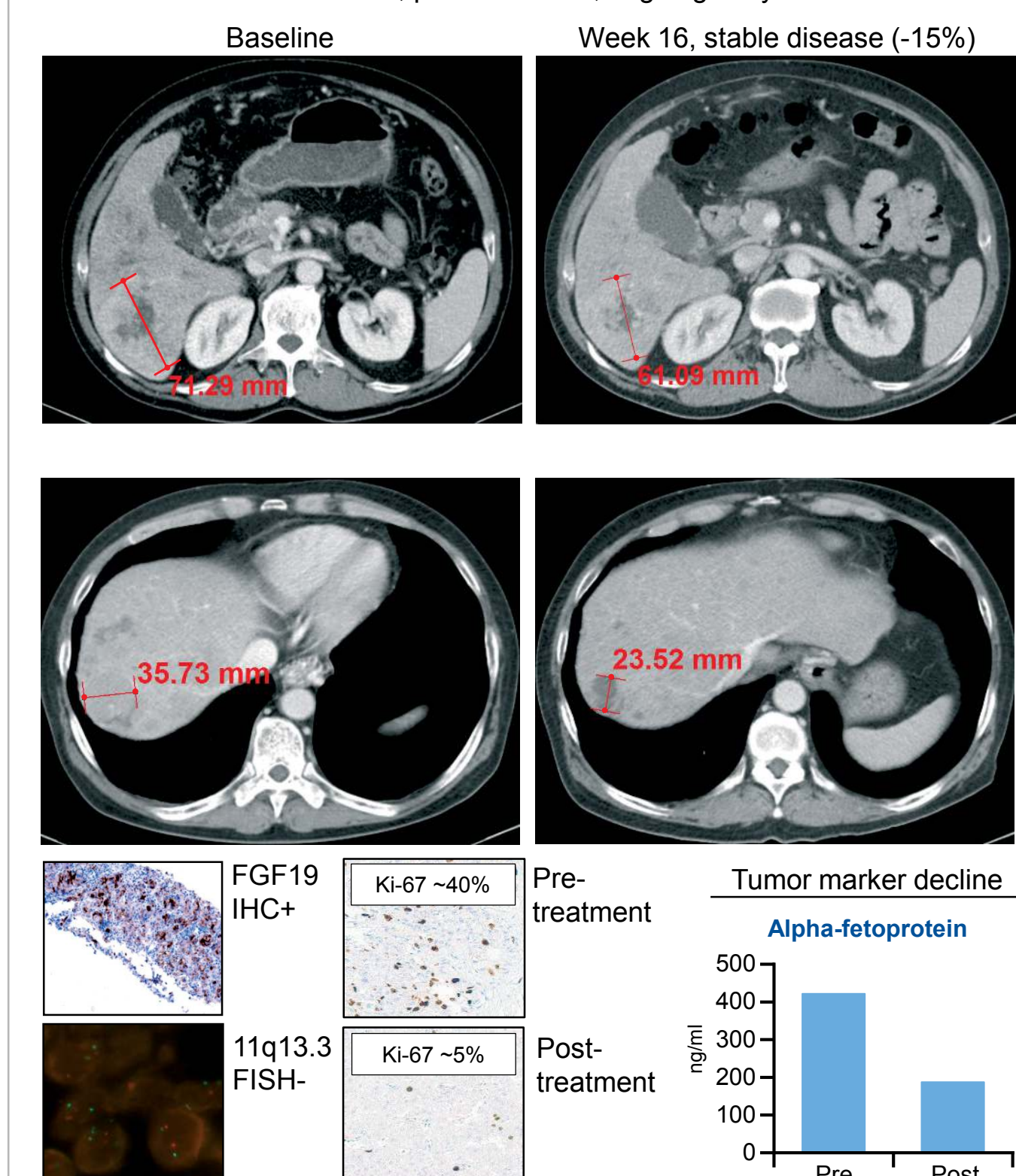
Case study 1 (280 mg)

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

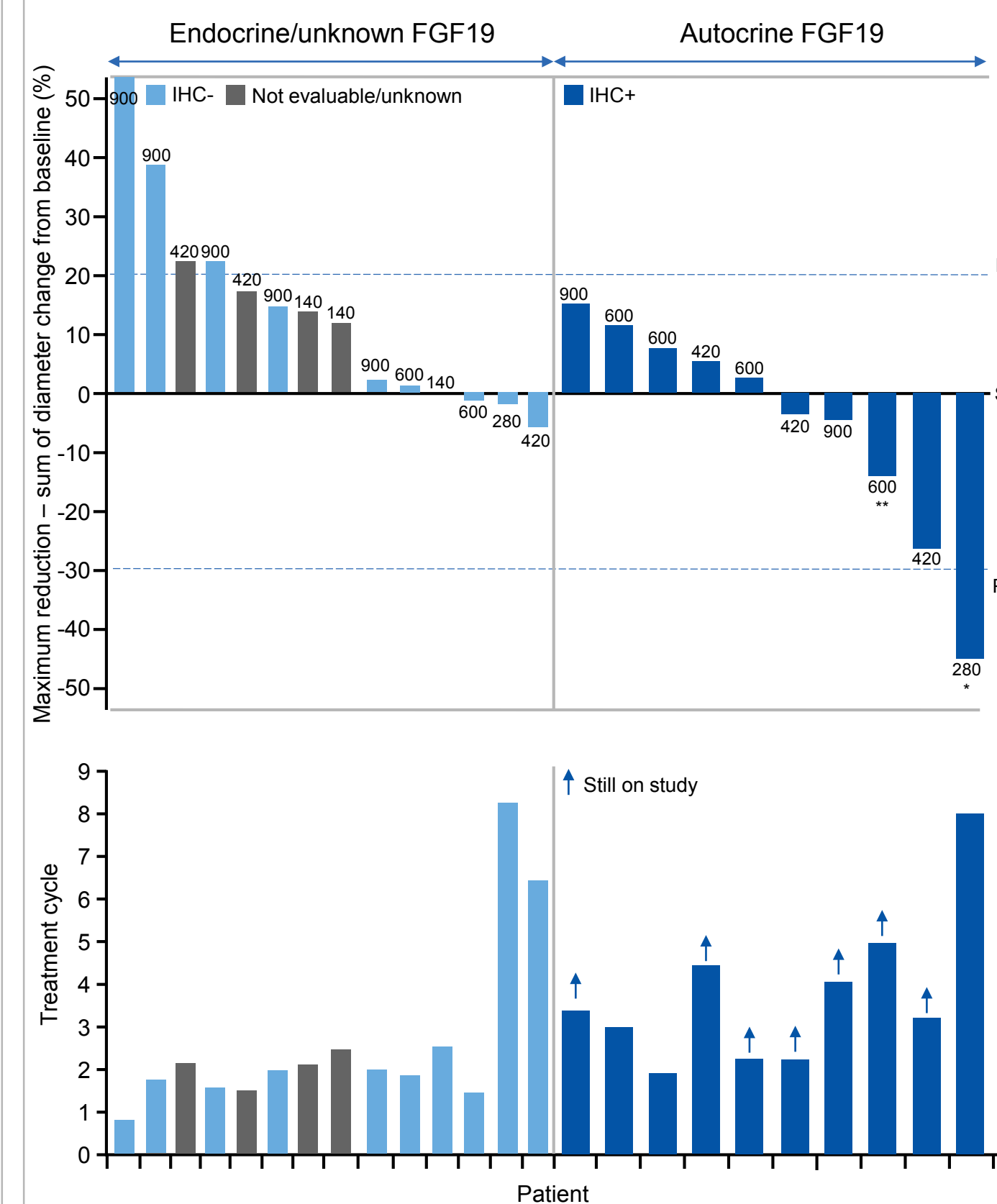


Case study 2 (600 mg)

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



Anti-tumor activity and duration on study



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

Safety

Adverse events

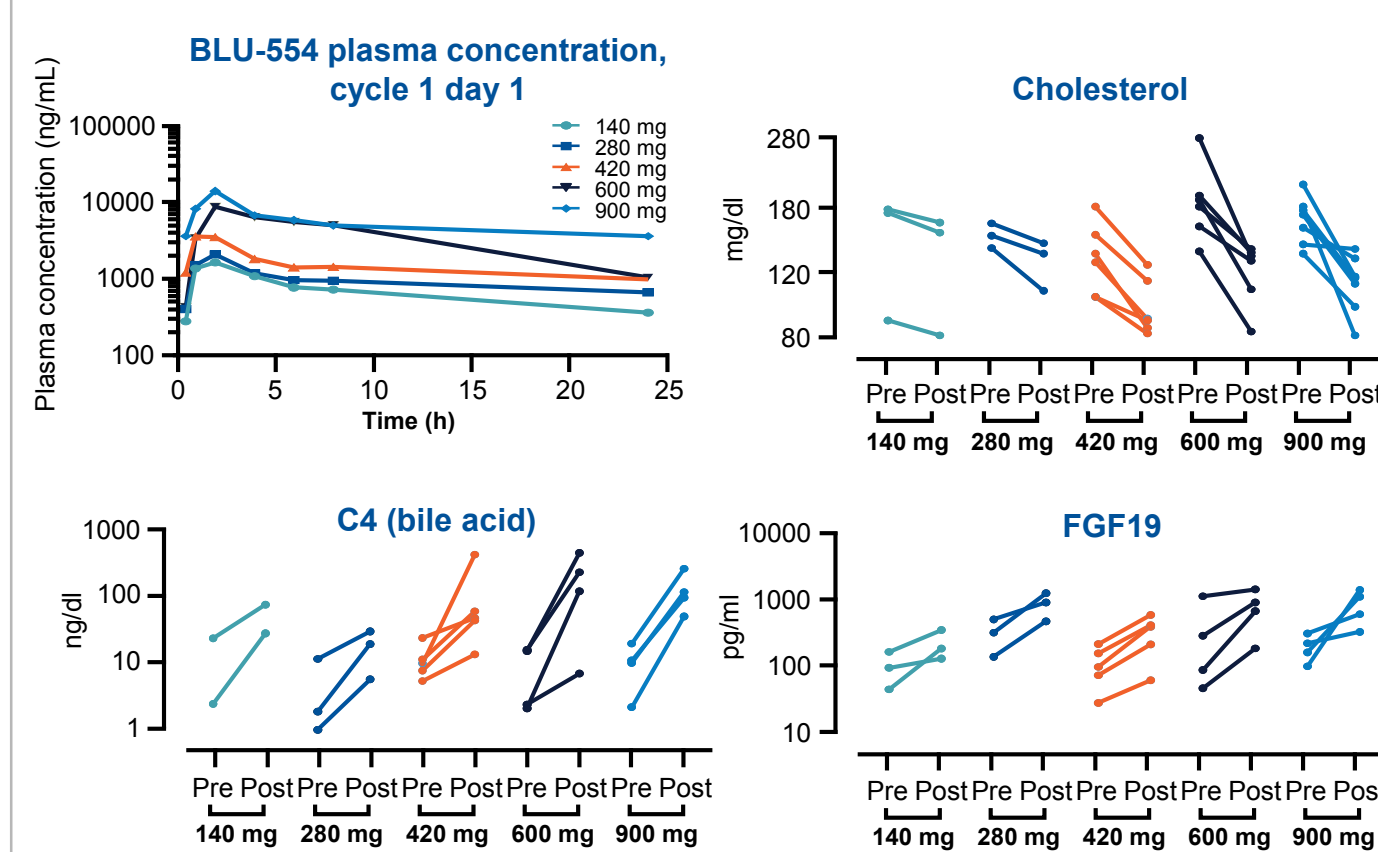
- 2 patients experienced dose-limiting toxicities at 900 mg:
 - Grade 3 abdominal pain; Grade 3 fatigue lasting more than 7 days
- 2 patients discontinued BLU-554 due to treatment-related toxicity:
 - Grade 3 hemorrhage; Grade 4 AST increase
- 17 patients had Grade ≥3 AEs which were treatment-related 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



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

This study was sponsored by Blueprint Medicines. We would like to thank the participating patients and their families for volunteering to take part in the study and all co-investigators and clinical and nursing staff for conduct of the study. We also thank Leah Evans, MNeuroSci, from iMed Comms, an Ashfield company, who provided medical writing support funded by Blueprint Medicines.

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