BLU-554, A Novel, Potent and Selective Inhibitor of FGFR4 for the Treatment of Liver Cancer

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blueprint MEDICINES

EASL
European Association for the Study of the Liver

50th THE INTERNATIONAL LIVER CONGRESS™ 2015
APRIL 22-26, VIENNA, AUSTRIA

Disclosures

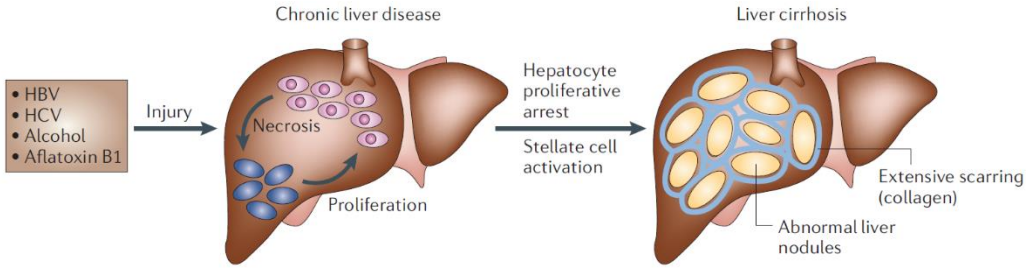
- Employee and shareholder of Blueprint Medicines

Blueprint Medicines makes kinase drugs to treat patients with genomically defined diseases.

Liver Cancer Represents Significant Unmet Need

Hepatocellular Carcinoma (HCC)

- Liver cancer is the 2nd leading cause of cancer death worldwide, and HCC is the most common form of this disease
- 16,000 first line and 5,000 second line patients/year expected to be eligible for systemic treatment in USA
- Incidence of HCC has tripled while the 5-year survival rate has remained <12% in USA
- Limited treatment options; no genomically-targeted therapies available
- Potential expansion opportunity for HCC drug candidates in intrahepatic cholangiocarcinoma



Farazi *et al.,* Nat Rev Cancer 2006; Khan *et al.,* HBP 2008; Bragazzi *et al*., *Transl Gastrointest Cancer* 2012, UptoDate, American Cancer Society.

Hepatocellular carcinoma is the most common form of liver cancer.
Insights from genomic data are enabling new treatment approaches for this disease.

New Era in Understanding Liver Cancer and Identifying Potential Therapeutic Targets

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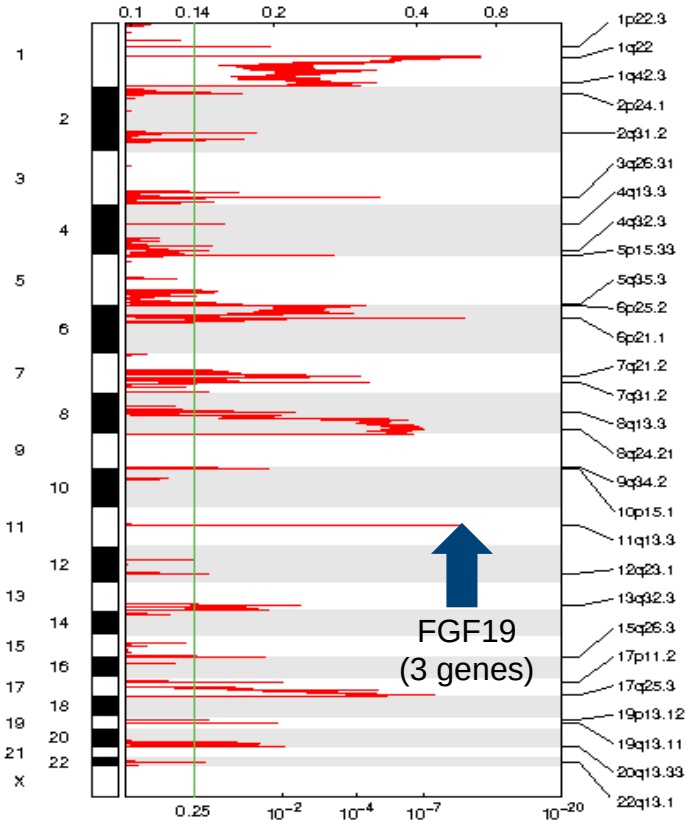
Genomic profiling of liver cancer has lagged behind that of other tumor types

- Diagnosis commonly done without tissue analysis for disease confirmation

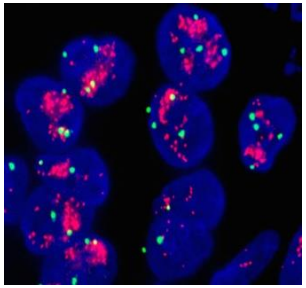


Characterization of FGF19-CCND1 amplification

- Scott Lowe and colleagues *(Cancer Cell, 2011)*
- Blueprint Medicines *(Cancer Discovery, 2015)*

Results confirmed in recent reports describing comprehensive genomic profiling of HCC

- Amplification frequency is similar in Asian and European patients
- Schulze, *Nat Genet*, 2015; Totoki, *Nat Genet*, 2014



High-level *FGF19* amplification detected by FISH

(Courtesy of Dr Josep Llovet, Mount Sinai School of Medicine)

Blueprint Medicines is driving personalized medicine approaches for liver cancer.

Activated FGFR4 Signaling Pathway is a Key Driver of Liver Cancer

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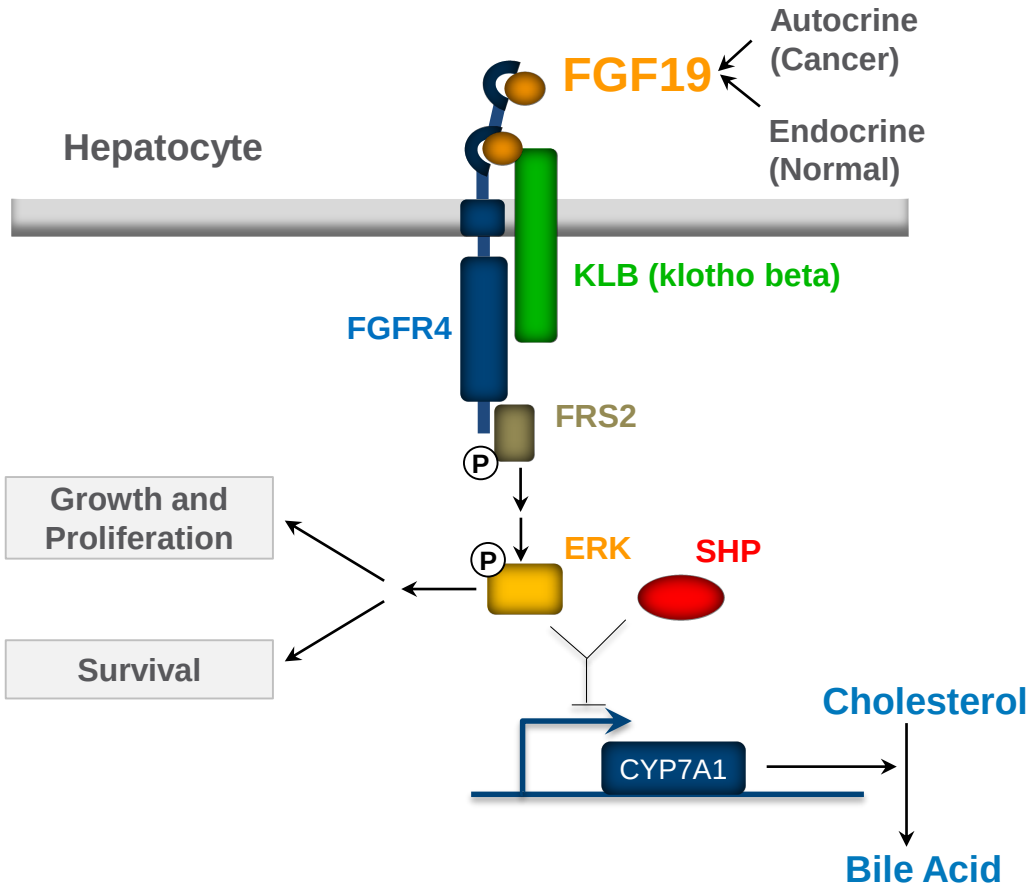

- In normal liver, circulating FGF19 drives liver cell proliferation and regulates bile acid production
- Overexpression of FGF19 is common in liver cancer (up to 25%)
- A subset of HCC (6-12%) have focal amplification of the FGF19 gene
- Aberrant expression of FGF19 in the liver drives HCC tumorigenesis and FGFR4 regulates proliferation and survival of malignant liver cells

FGFR4 and FGF19 are validated drivers in up to 25% of HCC.
Potential for FGFR4 inhibitor to change the HCC treatment paradigm.

BLU-554 is an Exquisitely Selective, Potent Inhibitor of FGFR4

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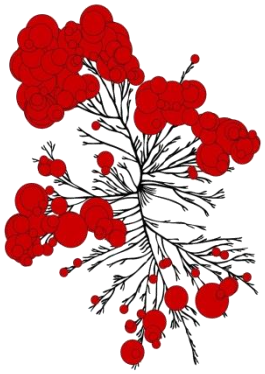
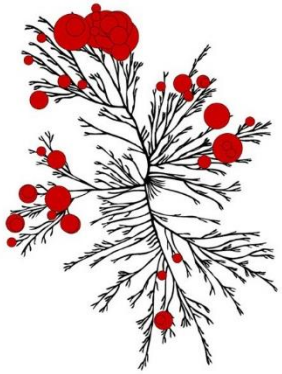
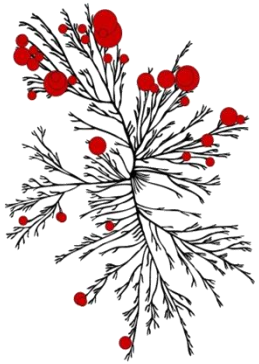
Selectivity



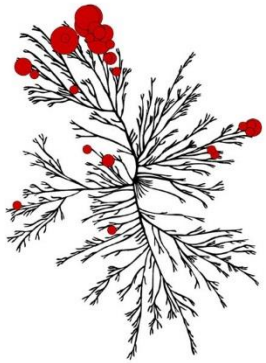
Ponatinib (FGFR, multi-kinase inhibitor)



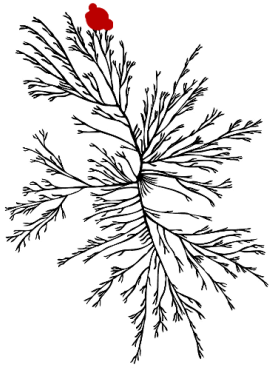
Sorafenib (Liver cancer)



Vemurafenib (Targeted therapy, melanoma)



Pan-FGFR inhibitor



BLU-554 (FGFR4-selective)

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)

- Similarity between FGFR family members has made selectivity a challenge
- Pan-FGFR drugs do not sufficiently inhibit FGFR4
- BLU-554 exploits a unique interaction with FGFR4 to confer potency and selectivity

Kinome Selectivity		
	BLU-554	**Pan-FGFR inhibitor**
FGFR4 IC_{50} (nM)	5	26
FGFR1 IC_{50} (nM)	624	<1
FGFR2 IC_{50} (nM)	1202	<1
FGFR3 IC_{50} (nM)	2203	<1

Significant Anti-Tumor Efficacy of BLU-554 in Liver Cancer Models that are Dependent on FGFR4 Signaling

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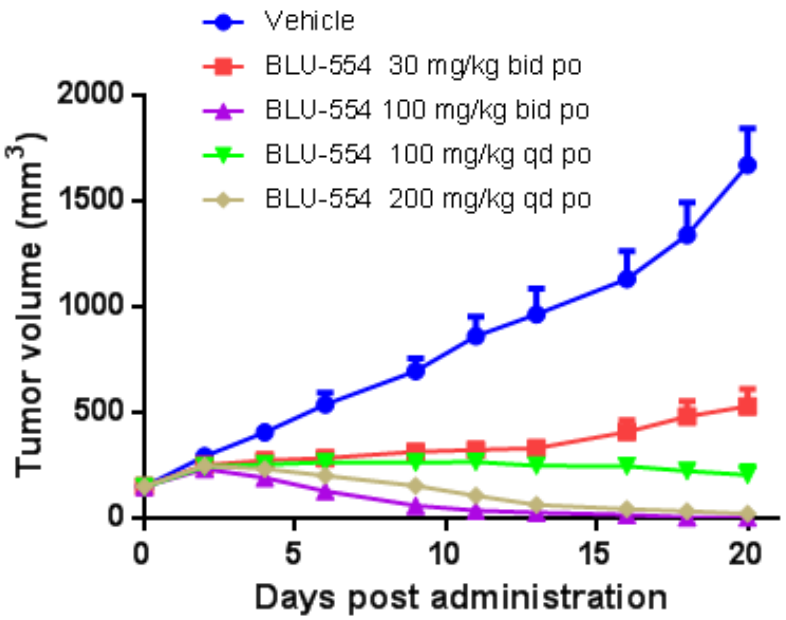
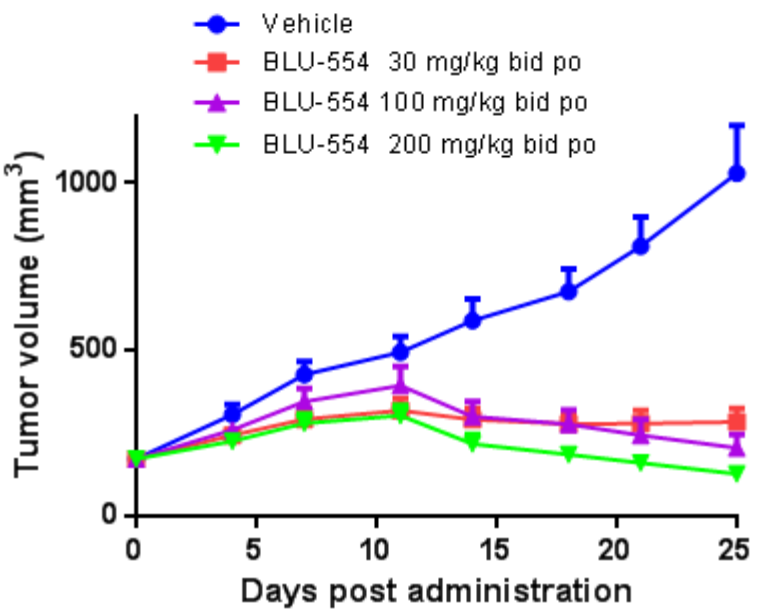
Hep3B - *FGF19* amplification



LIX-066 - FGF19 overexpression (no amplification)



- BLU-554 induced Hep3B tumor shrinkage (100% regression, >20% CRs)
- BLU-554 efficacy surpassed that of sorafenib in patient-derived xenografts
- BLU-554 was well tolerated in these tumor models
- Potential flexibility in scheduling (e.g. once- or twice-daily dosing)

Initiating Clinical Trial for Genomically Selected HCC and Cholangiocarcinoma Patients

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- Phase 1 clinical trial planned to start in mid-2015
- Molecular selection of liver cancer patients
  - Diagnostically-defined patient population based on FGF19 and FGFR4 pathway activation
- Tumor tissue biopsy and circulating biomarker analyses planned to detect early signs of biological activity

Mid-2015 → **2016**

HCC Dose Escalation

- Assess FGF19 expression and amplification status

HCC Expansion

- HCC with FGFR4 pathway activation

Key Endpoints	
Primary	• Safety • Tolerability • MTD
Secondary	• Response rate (RECIST) • Biomarkers

Follow-on Studies to Include

- Cholangiocarcinoma, front line HCC

Key Takeaways

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- Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) patients have poor prognosis, limited treatment options and no genomically-targeted therapies are currently available
- Aberrant activation of the FGFR4 signaling pathway has been associated with development of liver cancer and FGFR4 has been validated in preclinical studies
- BLU-554 is a novel, exquisitely selective, small molecule inhibitor of FGFR4. Administration of BLU-554 induces tumor regression in liver cancer models
- Phase 1 clinical trials will commence in mid-2015 to develop BLU-554 in a molecularly-defined subset of HCC and cholangiocarcinoma patients