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Preclinical and Phase 1/2 Data of the CHK1 Inhibitor BBI-355 in Development for Esophageal and Gastric Cancers (EGC) with *EGFR* or *FGFR2* Amplifications

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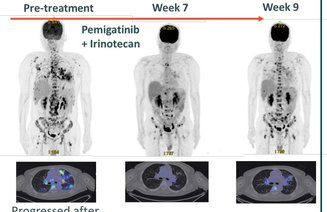
Background

- High-copy number amplifications of oncogenes frequently occur on **extrachromosomal DNA (ecDNA)**, highly transcribed units of cancer-specific, circular, non-chromosomal DNA
- Most targeted therapies have failed to improve survival in cancer patients with oncogene amplification
- Gastrointestinal (GI) cancers are associated with amplification of oncogenes and a paucity of actionable, activating mutations in druggable oncogenes
- GI cancers have a high frequency of ecDNA-based amplification (Bailey et al., Nature 2024) and ecDNA-related genomic rearrangement signatures are associated with significantly worse overall survival (Saito-Adachi et al., Nature Communications 2023)
- In EGC, ~7% and ~3% have high copy ***EGFR*** **and** ***FGFR2*** **amplifications**, respectively, and **targeted therapies demonstrate low response rates (<18%) and short duration of response**
- Tumor cells with oncogene amplifications, particularly on ecDNA, are hyper-transcribed, resulting in increased DNA replication stress (RS) and sensitivity to inactivation of checkpoint kinase 1 (CHK1)
- We developed **BBI-355**, an oral, potent, and selective small molecule inhibitor of CHK1, which is in Phase 1/2 clinical development (NCT05827614) to **overcome oncogene amplification/ ecDNA-driven resistance** to targeted therapy

GI cancer patient with *FGFR2* amplification treated with FGFR inhibitor experienced robust regression followed by rapid tumor progression

Patient with high copy *FGFR2* amplified (Copy number: 108) GI cancer previously treated with chemotherapy + nivolumab was subsequently treated with the pan-FGFR inhibitor, pemigatinib. Week 7 scans demonstrated remarkable tumor response, however, by Week 9 patient scans revealed rapid tumor progression. Tumor molecular profiling at progression indicated sustained *FGFR2* amplification with associated multiple gatekeeper mutations in *FGFR2* as well as *MYC* amplification induced by ecDNA.



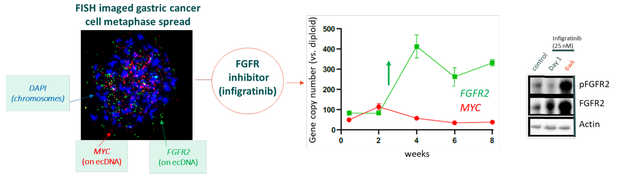
Case in National Cancer Center Hospital East

FGFR inhibitors demonstrate transient anti-tumor activity in EGC, which limits ORR and potential patient benefit

	Futibatinib	Lirafugratinib
Mechanism of action	Pan-FGFR inhibitor	FGFR2 selective inhibitor
Patient population	Gastric or gastroesophageal junction cancer with *FGFR2* amplifications	Gastric cancer with *FGFR2* amplifications
Patients achieving ≥30% tumor reduction	**35.7% (10/28)**	**38.9% (7/18)**
	vs.	vs.
Overall Response Rate	**17.9% (5/28)**	**16.7% (3/18)**
Duration of Response	Median: 3.9 months Range: 2.1-5.6 months	Range: ~2.8 - ~6 months
Source	Adapted from Satoh et al., 25th World Congress on Gastrointestinal Cancer; 2023	Adapted from Scham et al., AACR-NCI-EORTC Int Conf. 2023

Tumor reduction is transient and does not qualify as RECIST response

Genomic plasticity afforded by ecDNA enables rapid resistance to targeted therapy pressure *in vitro* by increased amplification and oncoprotein overexpression



Treatment of *FGFR2* ecDNA amplified gastric cancer cells with the pan-FGFRi infigratinib results in rapid selection/expansion of cells with higher copy *FGFR2*

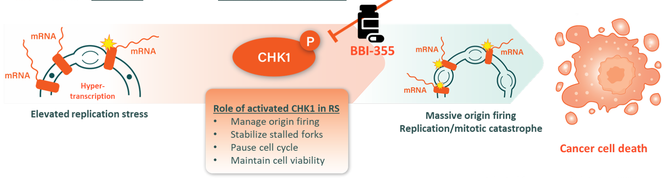
Resultant overexpression of FGFR2 protein out-titrates effects of the inhibitor, leading to drug resistance and reinitiation of tumor cell growth

Hyper-transcription/expression of ecDNA amplified oncogenes increases replication stress (RS), resulting in tumor cell sensitivity to Checkpoint Kinase 1 (CHK1) inhibitor BBI-355

High copy number amplification and rampant transcription on ecDNA results in elevated RS

Consequently, ecDNA amplified cells have significantly increased reliance on CHK1 for survival

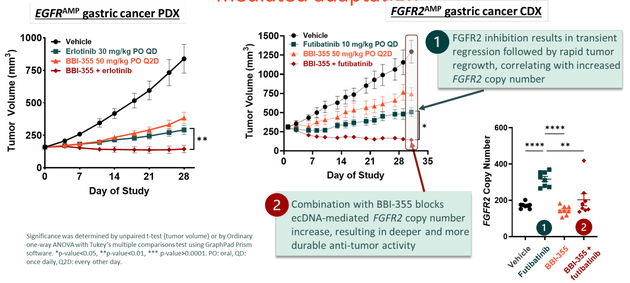
Inhibition of CHK1 further exacerbates RS, resulting in synthetic lethality in ecDNA+ cancer cells



Role of activated CHK1 in RS
- Manage origin firing
- Stabilize stalled forks
- Pause cell cycle
- Maintain cell viability

Adapted from Tang et al. Nature 2024

BBI-355 overcomes rapid resistance to targeted therapy in *EGFR* and *FGFR* amplified gastric cancer xenografts by blocking ecDNA-mediated adaptation

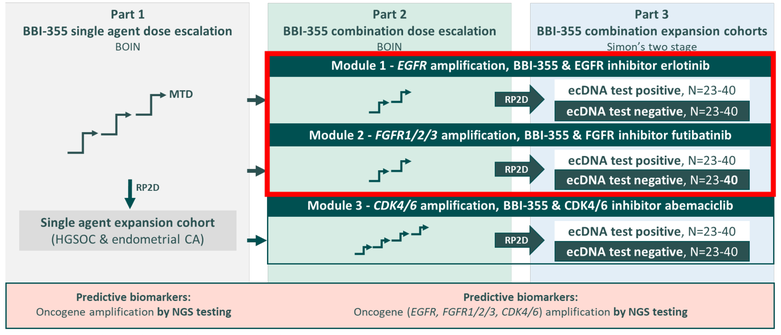


1 FGFR2 inhibition results in transient regression followed by rapid tumor regrowth, correlating with increased *FGFR2* copy number

2 Combination with BBI-355 blocks ecDNA-mediated *FGFR2* copy number increase, resulting in deeper and more durable anti-tumor activity

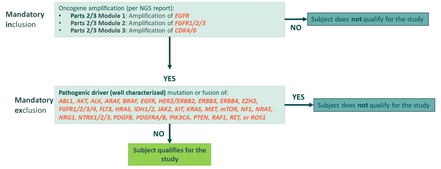
Significance was determined by unpaired t-test (tumor volume) or by Ordinary one-way ANOVA with Tukey's multiple comparisons test using GraphPad Prism software. *p-value≤0.05, **p-value≤0.01, *** p-value≤0.0001. PO: oral, QD: once daily, Q2D: every other day.

BBI-355 is being evaluated in the Phase 1/2 BBI-355-101 (POTENTIATE) clinical trial (NCT05827614) targeting patients with solid tumors harboring oncogene amplification(s)

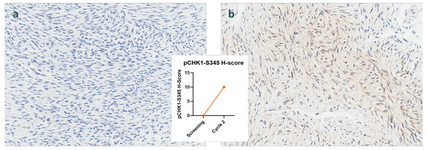


BOIN: Bayesian optimal interval design; HGSOC: High-grade serous ovarian carcinoma; MTD: Maximum Tolerated Dose; RP2D: Recommended Phase 2 Dose

Mandatory molecular in-/exclusion criteria



On-target pharmacodynamic biomarker modulation observed in tumor from patient after treatment with BBI-355



Pre- and post-treatment tumor biopsies were evaluated for pharmacodynamic modulation of CHK1 via immunohistochemistry. Induction of pCHK1-S345 staining (brown nuclei) following treatment with BBI-355 demonstrates CHK1 inhibition in tumor cells. The pCHK1-S345 H-score (inset graph) showed marked increase in the tumor sample after BBI-355 treatment.

Conclusions

- EGFR inhibitor (EGFRi) and FGFR inhibitor (FGFRi) therapies show modest response rates and short durability in EGC patients harboring high copy *EGFR* or *FGFR2* amplification, including those on ecDNA
- ecDNA biology facilitates rapid tumor adaptation and acquired therapy resistance to both EGFRi and FGFRi
- The first ecDNA-directed therapy, BBI-355, demonstrated significant synergistic antitumor activity in combination with EGFRi and FGFRi, in multiple ecDNA+ oncogene amplified EGC models
- Clinical testing in patients with *EGFR* or *FGFR2* oncogene amplifications is ongoing
  - A key objective of this trial is to provide clinical proof-of-concept for BBI-355 plus EGFRi or FGFRi combination to block rapid acquired resistance to targeted therapy mediated by ecDNA biology, thereby potentially improving outcomes in patients underserved by current treatments
  - To date, BBI-355 alone and in combination with erlotinib or futibatinib has been tested at multiple dose levels. AEs are mostly hematologic, which are evidence of expected, on-target pharmacology for a CHK1i
  - PK analysis indicates that BBI-355 is orally available and demonstrates a dose-dependent increase in plasma exposure
  - BBI-355 treatment induced pCHK1(S345) in tumor biopsy samples, demonstrating on-target pharmacodynamic activity in patients
  - The clinical study is currently open in the US, with planned expansion to South Korea and Spain