ASCO® Gastrointestinal Cancers Symposium

KIN-3248, a next-generation pan-FGFR inhibitor, is active against FGFR gatekeeper and molecular brake drug resistance mutations

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Targeting FGFR for the treatment of GI cancers

- Oncogenic FGFR2 alterations observed in ~10-20% CCA and other GI cancers (<1%)[1]
- Pemigatinib and infigratinib approved for treatment of CCA patients with FGFR2 gene fusions / rearrangements
- FGFR2 kinase domain (KD) resistance mutations observed in > 50% CCA patients treated with approved & clinical-stage FGFRi[2]
- **KIN-3248** is a **next-generation, irreversible FGFRi** that **targets FGFR kinase domain mutations that confer clinical resistance**

Biochemical IC50 Values (nM)					
FGFR Status	Kinase Domain Mutation	Janssen Erdafitinib	Incyte Pemigatinib	Taiho Futibatinib	**Kinnate KIN-3248**
FGFR1 WT	-	0.2	0.4	2.1	**3.9**
FGFR2 WT V565F N550H	- Gatekeeper Mol. Brake	0.15 330 4.1	0.4 >500 19.8	1.4 >500 36.4	**5.3** **20.8** **22.8**
FGFR3 WT V555M K650M	- Gatekeeper Activ. Mut.	0.7 137 3.5	1.5 >500 20	5.3 324 8.3	**9.7** **24.3** **4.6**

Inhibition of wild type and mutant FGFR family kinases was determined using a fluorescence-based microfluidic mobility shift assay in multiple independent experiments.

References: [1]Krook et al. 2020 Br. J. Cancer; [2]Goyal et al. 2020 EORTC-NCI-AACR Symposium .
Abbreviations: CCA, cholangiocarcinoma; FGFR, fibroblast growth factor receptor; FGFRi, FGFR inhibitor; GI, gastrointestinal cancers.

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KIN-3248 is active in human CCA cell lines expressing FGFR2 kinase domain resistance mutations

				Fold Difference in EC50 (Mutant : Wild Type)			
Cancer Type	**Cell Line**	**FGFR Status**	**Kinase Domain Alteration**	**Pemigatinib**	**Infigratinib**	**Futibatinib**	**KIN-3248**
CCA	CCLP-1 (FGFR2-PHGDH)	WT	-				
		V565F	Gatekeeper				
		V565I					
		V565L					
		N550H	Molecular Brake / Regulatory Triad				
		N550K					
		E566A					
		K642R					
		C492F	Other				
		K660M	Activating Mutation				
		L618F					
		L618V					
		M538I					
		M538I / M539L					
	ICC13-7* (FGFR2-PHGDH)	WT	-				
		V565F	Gatekeeper				
		N550K	Molecular Brake				
		L618V	Activating Mutation				

*ICC13-7 express endogenous FGFR2-OPTN fusion
KIN-3248 inhibition of cellular proliferation was measured by MTT following 5 or 10 days of treatment in multiple independent experiments.

Fold change in activity versus WT: 0 10 20 30 40 > 50

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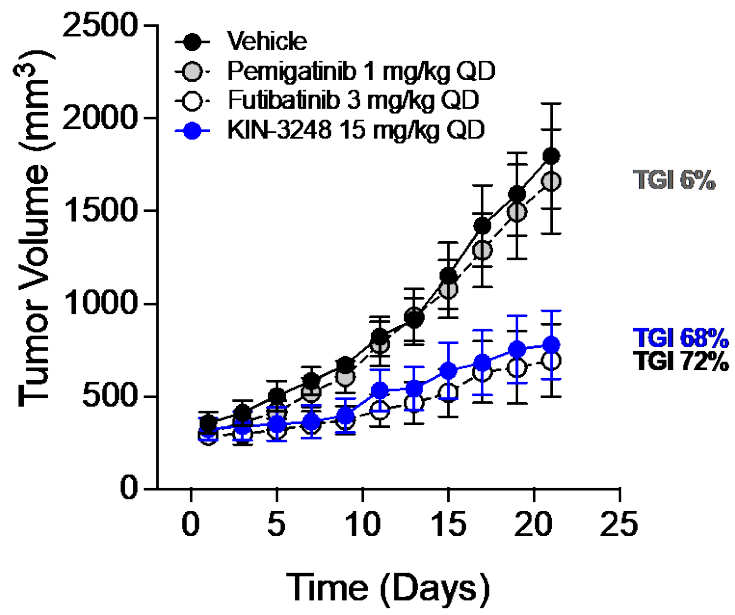
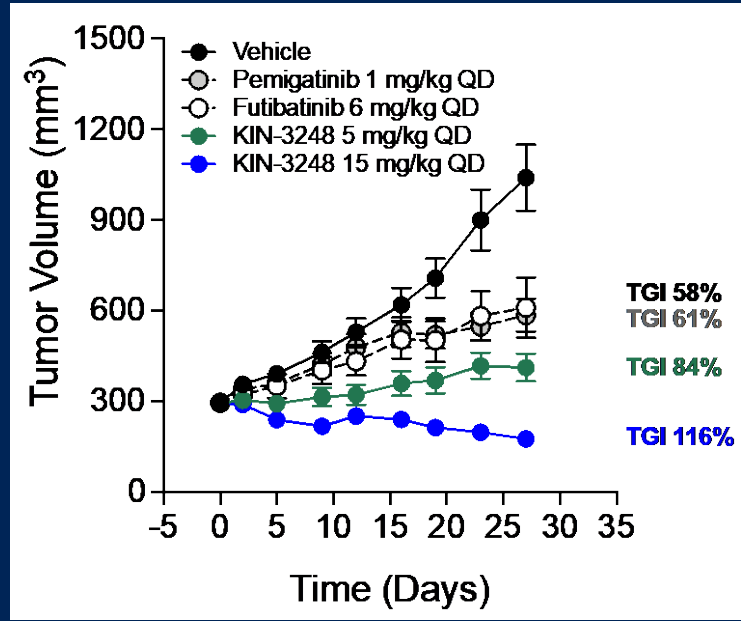
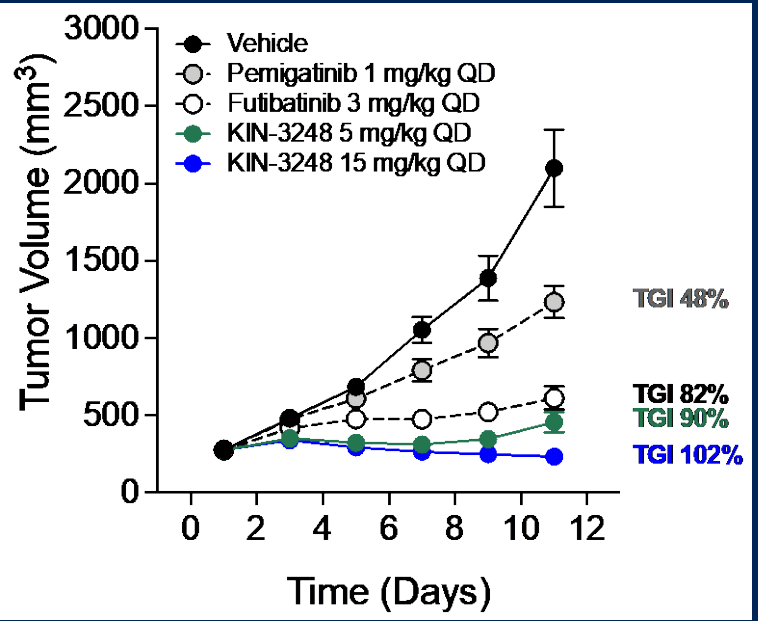
KIN-3248 is efficacious against clinically-relevant FGFR2 resistance mutations *in vivo*

Kinase Domain Mutant CCA	Gatekeeper Mutant Gastric Cancer	Mol. Brake Mutant Endometrial Cancer
FGFR2-CBX5 + M538I / M539L	FGFR2 amp + V565L	FGFR2 N550K







- KIN-3248 demonstrates **comparable or superior activity against clonally distinct and polyclonal FGFR2 resistance mutations** compared to approved and clinical-stage FGFRi in P/CDX models

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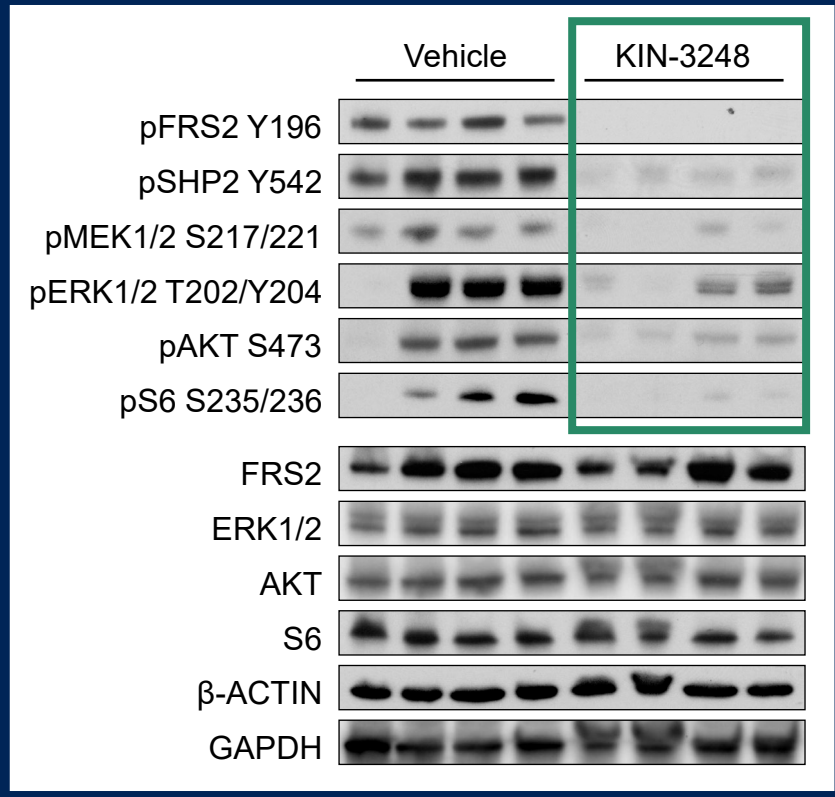
KIN-3248 ablates FGFR signaling in a patient-derived CCA model harboring a KD resistance mutation

- Three-day PK / PD study conducted in **CCA PDX model harboring FGFR2-CBX5 and secondary M538I / M539L** resistance mutations
  - Animals treated with 15 mg/kg QD KIN-3248 and tumors harvested 4 hours post-final dose to evaluate FGFR pathway activation
- **KIN-3248 led to significant FGFR pathway inhibition *in vivo*** as measured by western blot analysis of downstream phospho-proteins



Conclusions

- Potentially **actionable FGFR2 gene fusions and mutations** are observed in **10-20% of CCA patients** and to a lesser extent in other GI cancers (e.g., **gastroesophageal and pancreatic cancers**)
- Emergence of **on-target acquired FGFR resistance mutations limit the duration of response** to approved and clinical-stage FGFR inhibitors
- KIN-3248 has **pronounced *in vitro* and *in vivo* activity against clinically-relevant FGFR2 resistance mutations** including those associated with progressive disease
- A phase 1 / 1b dose escalation and expansion clinical trial evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of KIN-3248 in patients with advanced tumors harboring *FGFR2* and *FGFR3* gene alterations is expected to initiate in 2022