cogent BIOSCIENCES

Research & Development Investor Event

April 8, 2022

Forward Looking Statement

This presentation and the accompanying oral commentary contain forward-looking statements that involve risks, uncertainties and assumptions. If the risks or uncertainties ever materialize or the assumptions prove incorrect, our results may differ materially from those expressed or implied by such forward looking statements. All statements other than statements of historical fact could be deemed forward-looking, including, but not limited to, any statements of the plans, strategies, and objectives of management for future operations, including our clinical development and commercialization plans; any projections of financial information; any statement about historical results that may suggest trends for our business; any statement of expectation or belief regarding future events; potential markets or market size, technology developments, our clinical product pipeline, clinical data or the implications thereof, enforceability of our intellectual property rights, competitive strengths or our position within the industry; any statements regarding the anticipated benefits of our collaborations or other strategic transactions; and any statements of assumptions underlying any of the items mentioned.

These statements are based on estimates and information available to us at the time of this presentation and are not guarantees of future performance. Actual results could differ materially from our current expectations as a result of many risks and uncertainties, including but not limited to, risks associated with: the potential impacts of raising additional capital, including dilution to our existing stockholders, restrictions our operations or requirements that we relinquish rights to our technologies or product candidates; business interruptions resulting from the coronavirus disease outbreak or similar public health crises, which could cause a disruption of the development of our product candidates and adversely impact our business; the success, cost, and timing of our product development activities and clinical trials; the timing of our planned regulatory submissions to the FDA for our product candidate bezuclastinib and feedback from the FDA as to our plans; our ability to obtain and maintain regulatory approval for our bezuclastinib product candidate and any other product candidates we may develop, and any related restrictions, limitations, and/or warnings in the label of an approved product candidate; the potential for our identified research priorities to advance our bezuclastinib product candidate; the ability to license additional intellectual property relating to our product candidates from third-parties and to comply with our existing license agreements and collaboration agreements; the ability and willingness of our third-party research institution collaborators to continue research and development activities relating to our product candidates; our ability to commercialize our products in light of the intellectual property rights of others; our ability to obtain funding for our operations, including funding necessary to complete further development and commercialization of our product candidates; the scalability and commercial viability of our manufacturing methods and processes; the commercialization of our product candidates, if approved; our plans to research, develop, and commercialize our product candidates; our ability to attract collaborators with development, regulatory, and commercialization expertise; our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates; among others. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to our business in general, see our periodic filings filed from time to time with the Securities and Exchange Commission. Unless as required by law, we assume no obligation and do not intend to update these forward-looking statements or to conform these statements to actual results or to changes in our expectations.

All of Cogent Biosciences, Inc. (“Cogent”) product candidates are investigational product candidates and their safety and efficacy have not yet been established. Cogent has not obtained marketing approval for any product, and there is no certainty that any marketing approvals will be obtained or as to the timelines on which they will be obtained.

Any data pertaining to Cogent product candidates is interim data and may include investigator-reported interim data for which Cogent has not yet independently reviewed the source data. The interim data may not be representative of the final results that may be obtained in the corresponding trials and results from earlier trials may not be representative of results obtained in later trial or pivotal trials.

Investor Event Agenda

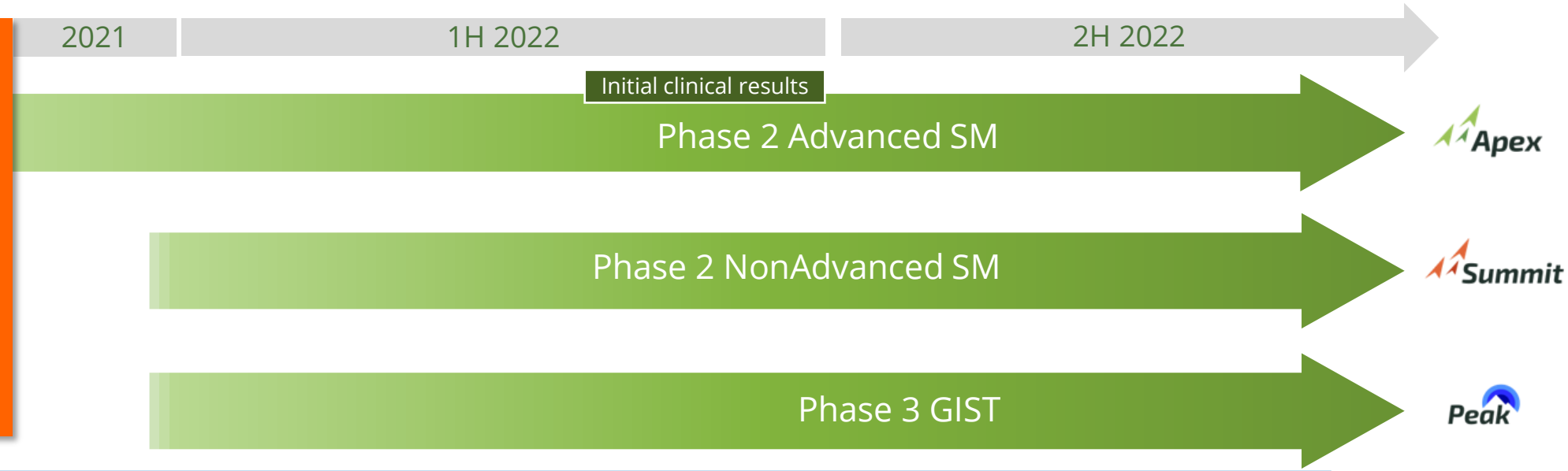
Introduction and Corporate Overview	Andrew Robbins Chief Executive Officer
Differentiated Profile of Bezuclastinib	Jessica Sachs, MD Chief Medical Officer
Building a Novel Pipeline	John Robinson, PhD Chief Scientific Officer
Q&A	

Cogent Biosciences: Emerging Leader in Precision Medicines for Genetically Defined Diseases

Bezuclastinib, a potential best-in-class **selective KIT mutant inhibitor**, has demonstrated a promising pre-clinical profile and positive clinical activity and safety results from a Phase 1/2 clinical trial in patients with gastrointestinal stromal tumors (GIST)

Broad clinical development plan underway

Designed to move bezuclastinib rapidly to high unmet need patient populations



Cogent Research Team is focused on creating a pipeline of novel, small-molecule targeted therapies for patients fighting genetically-driven diseases

Cash balance as of December 31, 2021: $219.7 million

Cogent Research Team Has Made Tremendous Progress in First Year

Created an outstanding team of 35 scientists, targeting ~50 scientists by year-end

- Leveraged external relationships to scale existing team effort >100 FTE

Designed and built-out permanent laboratory facility including in-house vivarium

- 45,000 sq. ft. facility to support future research efforts

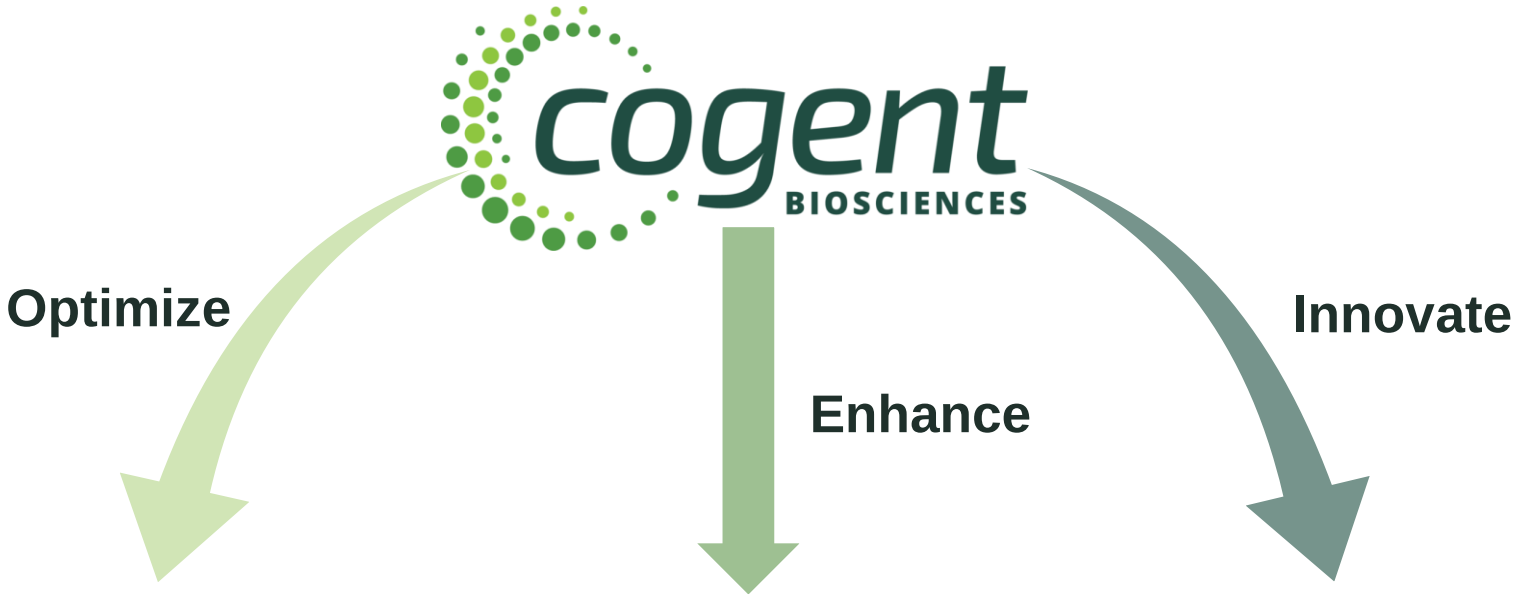
Conducted series of novel pre-clinical experiments to better characterize KIT mutant inhibitor landscape, including bezuclastinib

- Presented results at EORTC 2021 and presenting results at AACR 2022

Established broad portfolio of projects to support long term development and commercial goals

- Progressed first internal program (FGFR2) to Lead Optimization with IND anticipated in 2H23

Cogent Research Goal: Create Novel Small Molecule Kinase Inhibitors for Genetically Driven Diseases with Clear Unmet Medical Need



Create Best-in-Class Molecules
- Designed for well defined patient populations living with suboptimal therapeutic options

Extend efficacy / deepen response
- Designed for patient populations who have developed resistance to existing therapies

Create First-in-Class Molecules
- Designed for patient populations with undefined MOA and/or for biologic targets with an "un-druggable" approach

Cogent Pipeline: Building Portfolio of Best-in-Class Small Molecules

Program	Indication	Early Stage Development	Late Stage Development	Regulatory Submission	Approval
Clinical Programs					
Bezuclastinib (KIT inhibitor)	Advanced Systemic Mastocytosis	Apex			
	Nonadvanced Systemic Mastocytosis	Summit			
	Gastrointestinal Stromal Tumors	Peak			
Research Programs					

Indication	Hit ID	Lead Generation	Lead Optimization	GLP	IND Submission
FGFR2					
ErbB2 mut					
Target 3					
Target 4					
Target 5					
Target 6					

Bezuclastinib is a Differentiated KIT Inhibitor that Exhibits Unique Selectivity to KIT A-loop Mutations, Minimal Brain Penetration, and Favorable Pharmacokinetic Properties in Preclinical Models

Jessica Sachs, MD
Chief Medical Officer

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Abstract Number: 147
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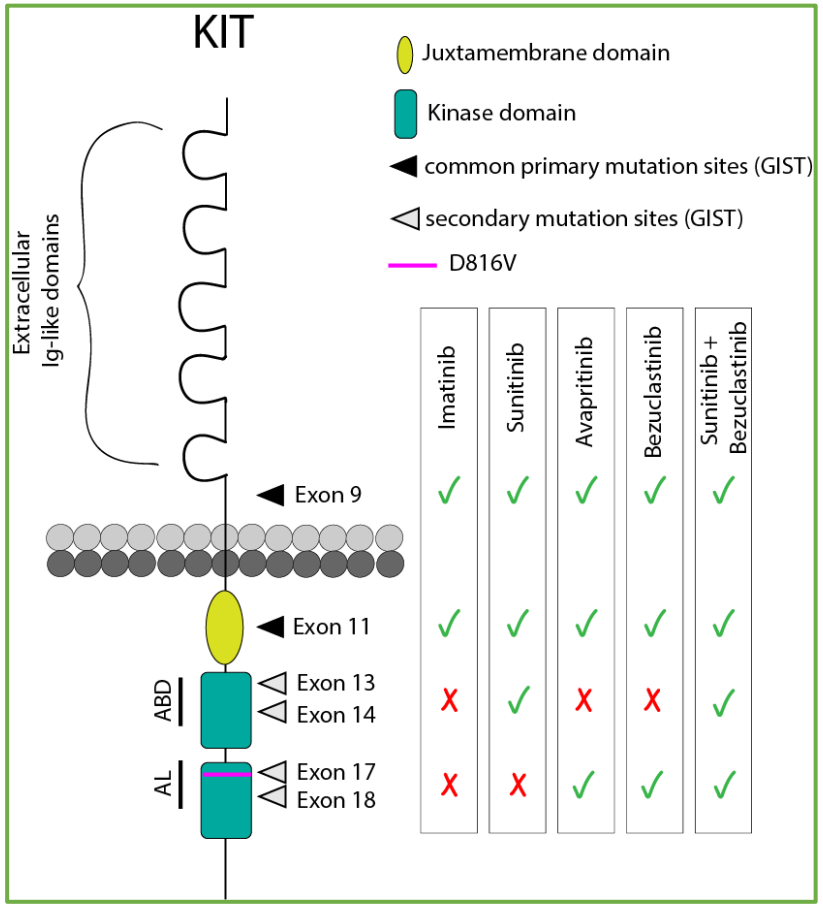
KIT Activation Loop Mutants are Key Targets for Systemic Mastocytosis and Refractory GIST



ABD= ATP-Binding Domain; AL= Activation Loop

- Kit mutations serve as driver mutations in up to 80% of gastrointestinal stromal tumors (GIST) and in over 90% of systemic mastocytosis (SM)[1,2]
- In GIST, patients often relapse after front-line imatinib treatment due to secondary mutations in ATP-binding domain (ABD) or Activation Loop (AL)[3]
  - Second-line sunitinib is active against ABD mutations, but not AL mutations
- Inhibitors targeting AL mutations, notably D816V (a common AL mutation in SM), have shown activity in the treatment of advanced SM, but off-target toxicities of available compounds may limit optimal clinical dosing[4, 5]
- Bezuclastinib is a novel type I TKI that was developed as a highly potent and selective inhibitor of KIT D816V

1. Klug LR et al., Nature Reviews Clinical Oncology, 2022:1-14; 2. Shomali W, Gotlib J. Hematology. 2018;2018(1):127-136; 3. Napolitano A, Vincenzi B, British Journal of Cancer. 2019;120(6):577-578; 4. RyDAPT [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals; 2021; 5. AYVAKIT [package insert]. Cambridge, MA: BluePrint Medicines; 2021

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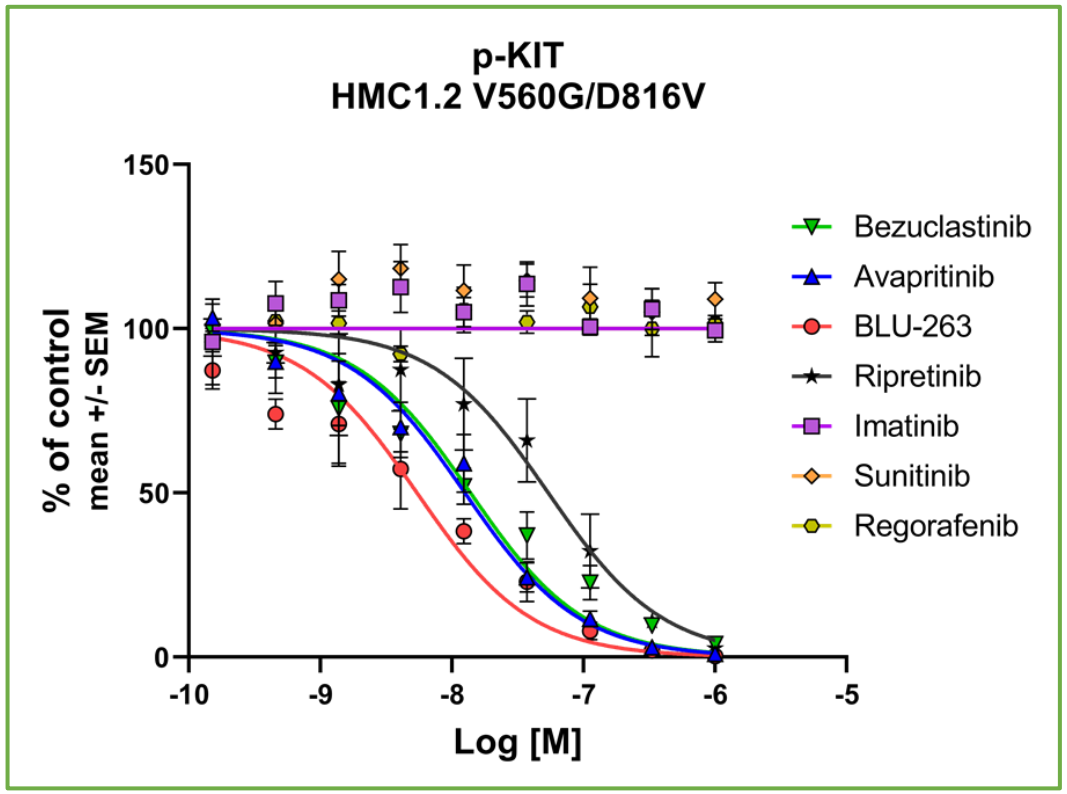
Bezuclastinib is a Potent Inhibitor of KIT D816V, an Activation Loop Mutation



HMC1.2 human mast cells (V560G/D816V) were treated with inhibitors for 1 hour followed by analysis for phosphorylated c-KIT ELISA (R&D Systems)

Compound	Cell IC50 (nM)
	KIT V560G/D816V (HMC 1.2)
Bezuclastinib	**14**
Avapritinib	13
BLU-263	6
Ripretinib	54
Imatinib	>1000
Sunitinib	>1000
Regorafenib	>1000

IC_{50} values from ELISA in (A) in nM are represented for bezuclastinib and other KIT inhibitors

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Bezuclastinib Demonstrates Superior Selectivity Against Closely Related Kinases

- Bezuclastinib demonstrates no activity on closely related kinases, unlike other KIT inhibitors
- Inhibition of these closely related kinases have been linked to off-target toxicities, such as edema and pleural effusions[1,2]

Compound	Cell IC_{50} (nM)				
	PDGFRα	PDGFRß	CSF1R	FLT3	KDR
Bezuclastinib	**>10,000**	**>10,000**	**>10,000**	**>1000**	**>1000**
Avapritinib	53	10	249	305	>1000
BLU-263	21	6	161	345	>1000
Ripretinib	20	34	312	534	110
Imatinib	75	247	1027	>1000	>1000
Sunitinib	23	14	313	1	4
Regorafenib	138	1180	473	237	101

Key: Fold change from on-target KIT activity

Color key displays where the fold change of these values vs. on-target KIT activity falls. On-target KIT activity was based on potency presented in prior slide.

1. Giles FJ et al, Leukemia. 2009;23(10):1698-1707; 2. Liu S, Kurzrock R. Seminars in Oncology. 2015;42(6):863-875 3. Smith BD et al., Cancer Cell. 2019;35(5):738-751;
4. Wilhelm S et al,Molecular Cancer Therapeutics. 2007;6(11_Supplement): B260-B260;

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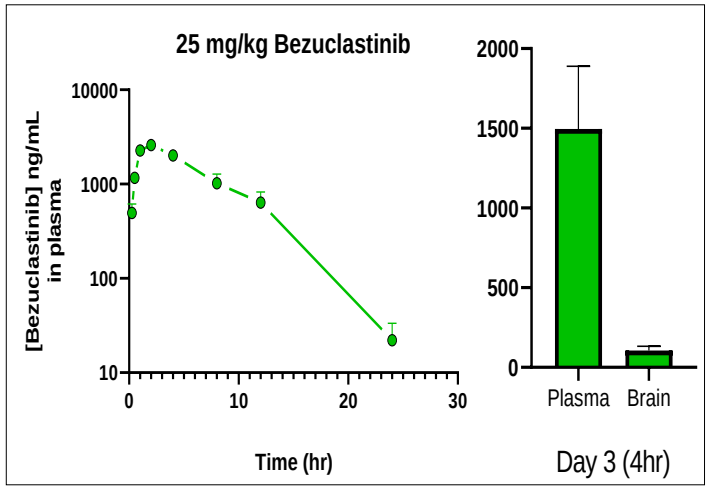
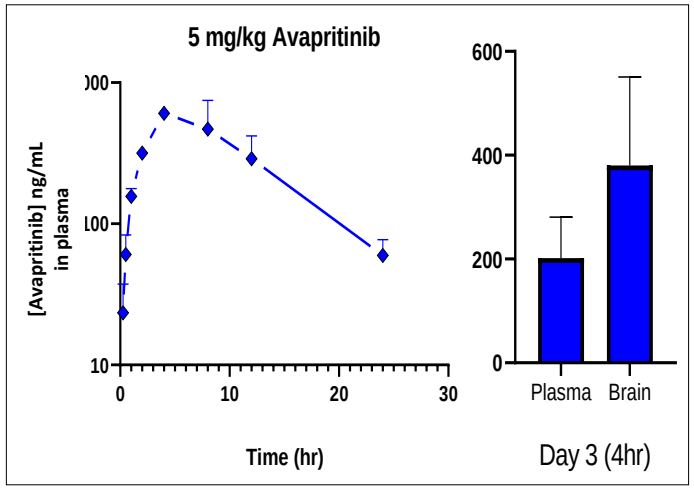
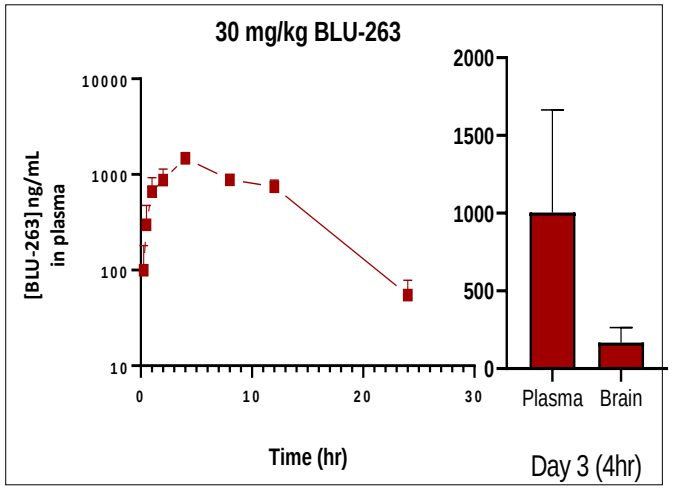
Bezuclastinib Demonstrates Minimal Brain Penetration



$t_{1/2}$ (h)	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	Brain:Plasma ratio
2.8	2592 ± 364	21509 ± 2558	0.07



$t_{1/2}$ (h)	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	Brain:Plasma ratio
5.7	672 ± 102	6980 ± 1156	2.0



$t_{1/2}$ (h)	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	Brain:Plasma ratio
3.3	1470 ± 222	16200 ± 414	0.18

- Bezuclastinib shows minimal brain penetration with brain to plasma ratio of 0.07 compared to 2.0 for avapritinib
- The absence of brain penetration is a preferred feature for a KIT A-Loop inhibitor given the CNS-related adverse events that have been observed in this targeted class[1,2]
- In a separate neurobehavioral (CNS) safety pharmacology study, rats were treated with oral doses of 0, 5, 25, or 100 mg/kg of bezuclastinib. No effect on behavioral endpoints were observed in this study, or in repeat dose toxicology studies (Data on File)

To assess brain distribution, male Sprague Dawley rats were administered 25 mg/kg bezuclastinib SDD, 5 mg/kg avapritinib, or 30 mg/kg BLU-263 by oral gavage. Dose levels were selected to correlate with clinical exposures reported in human clinical studies. Plasma samples were collected after a single dose and assessed for drug concentration by LC-MS/MS. Animals were dose administered for 2 additional days and plasma/brain harvested 4 hr post final dose. This repeat-dose administration – rather than single dose- allowed for a proper survey of steady state brain levels.

1. RyDAPT [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals; 2021; 2. AYVAKIT [package insert]. Cambridge, MA: BluePrint Medicines; 2021

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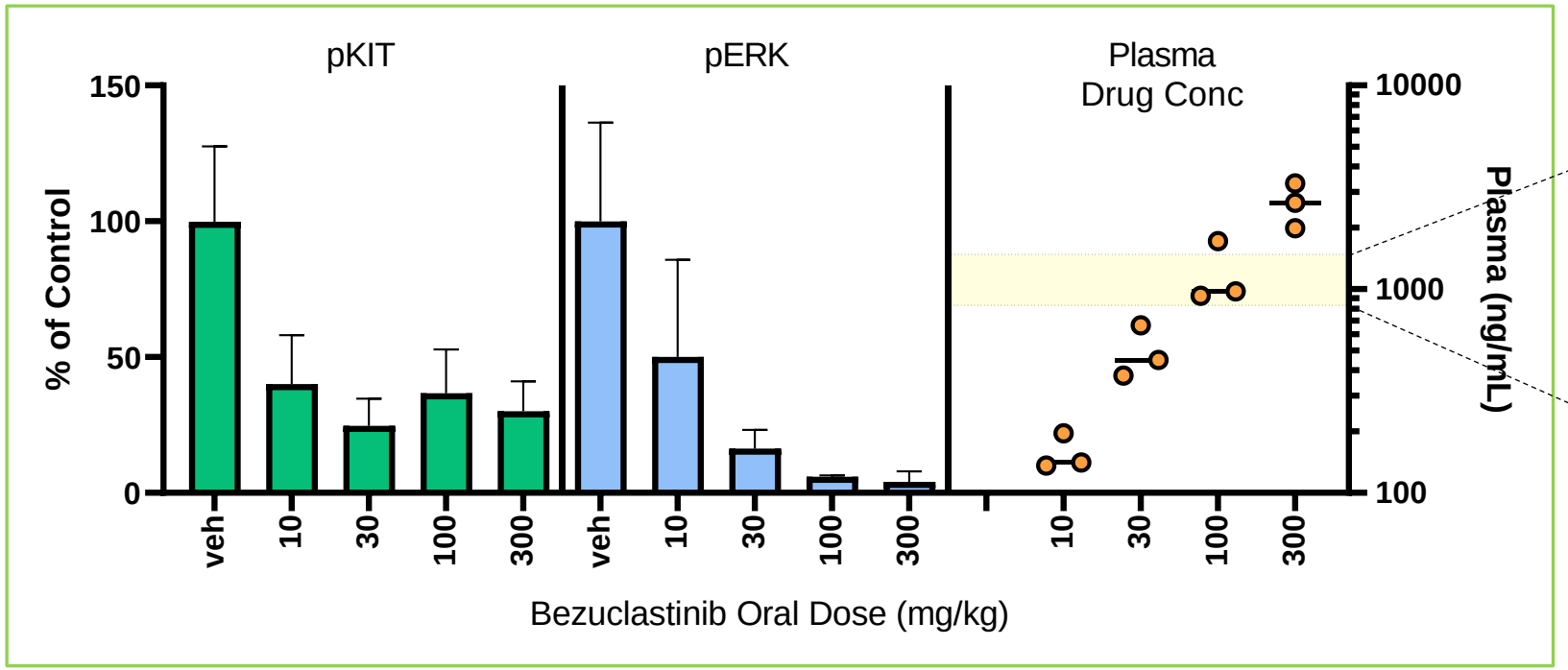
Bezuclastinib Inhibits KIT D816V and Downstream Signaling in vivo at Concentrations Below Previously Observed Clinical Exposures



Bezuclastinib Clinical Cmax Range:
C1D15
250-1000 mg
monotherapy

- HMC1.2 tumor-bearing nu/nu NCr female mice were treated with a single oral dose of bezuclastinib formulated as a spray-dry dispersion (Inotiv, Boulder, CO). Tumor and plasma were collected 4 hr post dose administration then assessed for drug concentration in plasma by LC/MS-MS, pKIT in tumor by ELISA (R&D Systems), and pERK normalized to GAPDH by immunoblot analysis. Phospho-protein data are expressed as a percent of vehicle control and represent n=3-6 individual samples.

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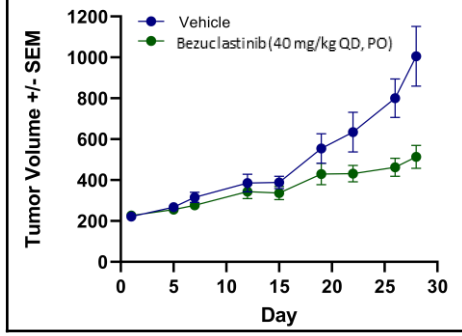
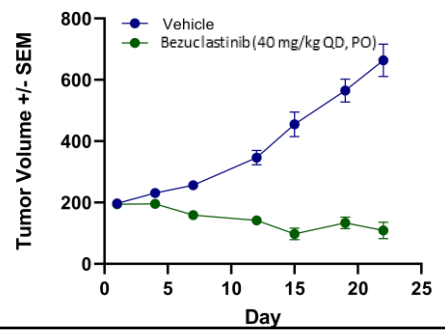
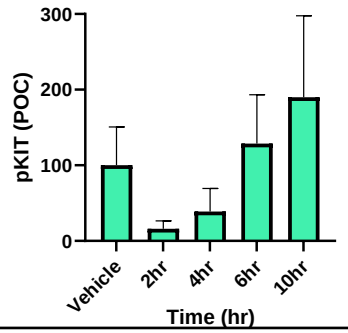
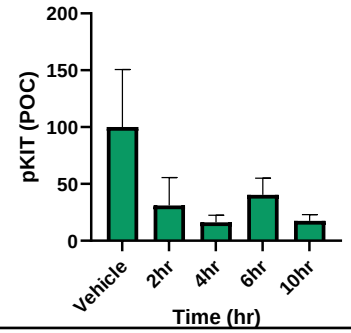
Clinically Achievable Exposures Represented in Nonclinical Models Demonstrate Significant Biological Activity

Model	Tumor growth inhibition GIST011 [KIT-Δ557-8/Y823D]		pKIT PK/PD HMC1.2 (KIT-D560G/D816V)	
Dose	4 mg/kg	40 mg/kg	10 mg/kg	30 mg/kg
AUC	**1310 ng·hr/mL**	**11293 ng·hr/mL**	**2168 ng·hr/mL**	**8342 ng·hr/mL**









GIST011 tumor-bearing NOD SCID female mice were randomized at a starting tumor volume of ~200mm^3 and treated with a single daily oral dose of Bezuclastinib (Crown Bio, San Diego, CA). Tumor volumes were determined three times weekly using the formula V=L*(W)^2/2.

HMC1.2 tumor-bearing nu/nu NCr female mice were treated with a single oral dose of Bezuclastinib formulated as a spray-dry dispersion (Inotiv, Boulder, CO). Tumor and plasma were collected at predetermined time points and assessed as described above (Figure 4).

Clinical AUC (ng·hr/mL) = **18,500 ng·hr/mL**[1]
(C1D15: 250 mg QD monotherapy)

1. Gebreyohannes YK et al., Clinical and Experimental Medicine. 2019;19(2):201-210

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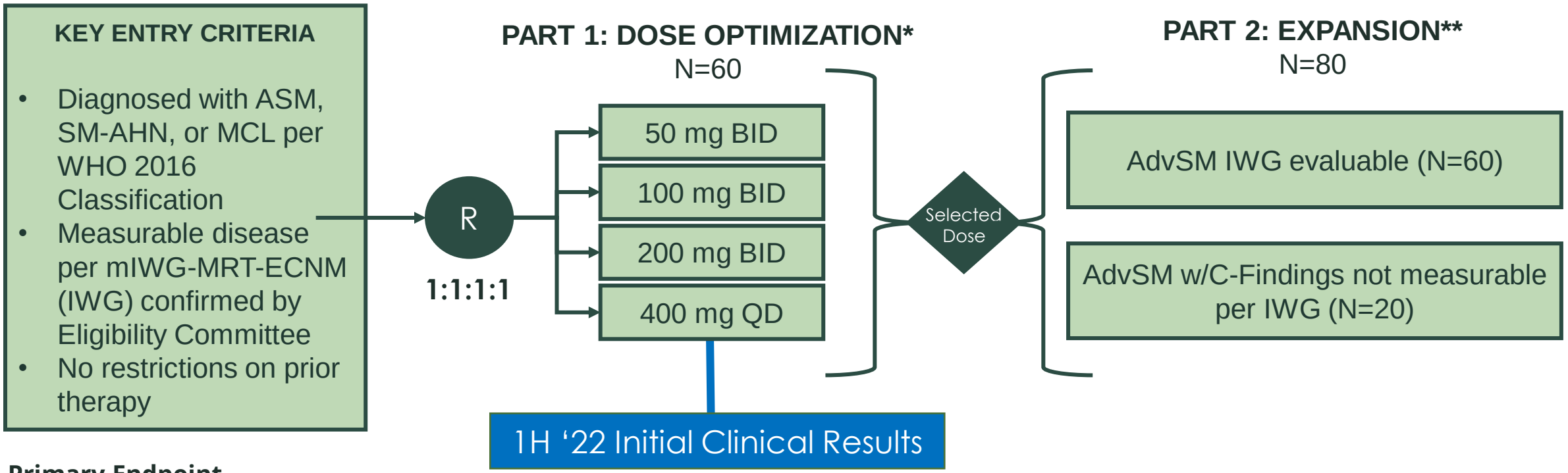
APEX: A Phase 2 Open-Label, Multicenter Clinical Study of Bezuclastinib in Patients with Advanced Systemic Mastocytosis



Primary Endpoint

- **Dose Optimization:** Incidence of AEs/SAEs, laboratory changes, PK, biomarkers, ORR
- **Expansion:** ORR (confirmed CR, CRh, PR and CI) per mIWG-MRT-ECNM and assessed by Central Response Review Committee

Other Endpoints

- Safety/Tolerability: Incidence of AEs leading to dose modification, changes in PROs
- Efficacy: DOR, TTR, PFS, OS, pure pathologic response
- PK/PD: plasma concentration of bezuclastinib, serum tryptase, KIT D816V burden

**Interim analysis (IA) when ~28 pts (~7pts/dose level) have completed C2 to enrich at promising dose levels*
***Part 2 may be expanded based on Part 1 results and Regulatory Authority discussions*

Pre-clinical characterization of a novel series of FGFR2 selective inhibitors with potency against clinically relevant mutations

John Robinson, PhD
Chief Scientific Officer

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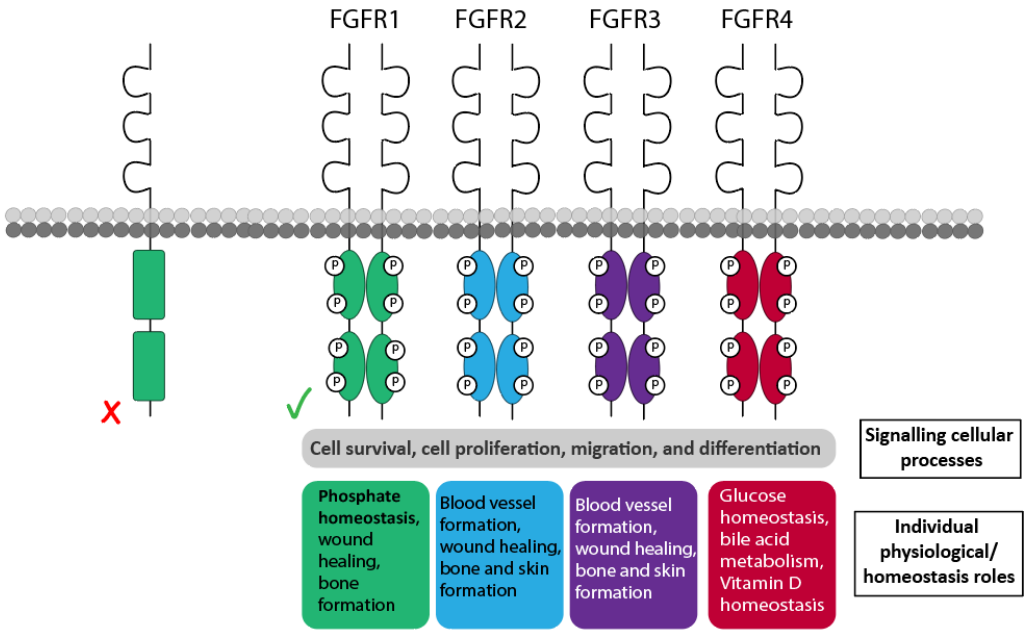
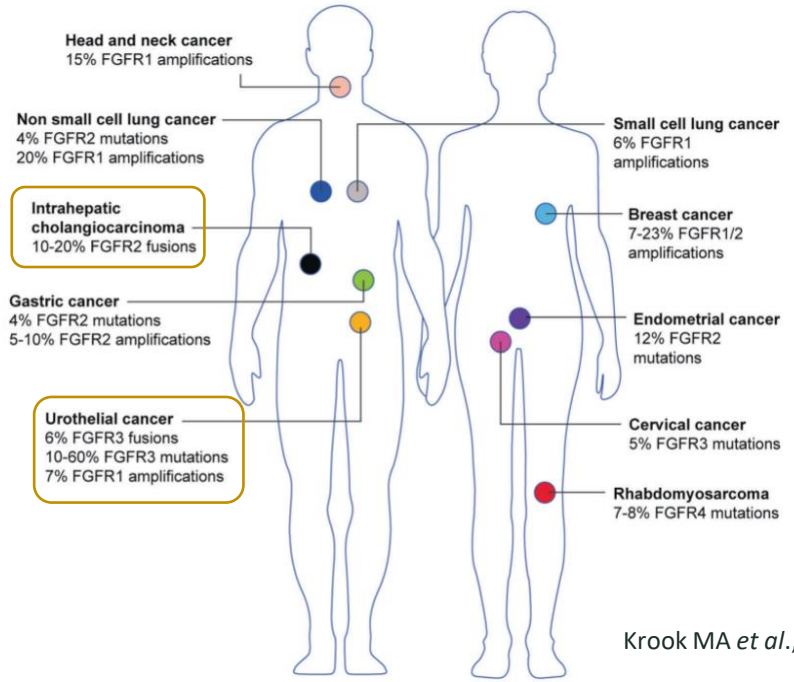
FGFRs are Well Established Oncogenic Drivers in Multiple Indications

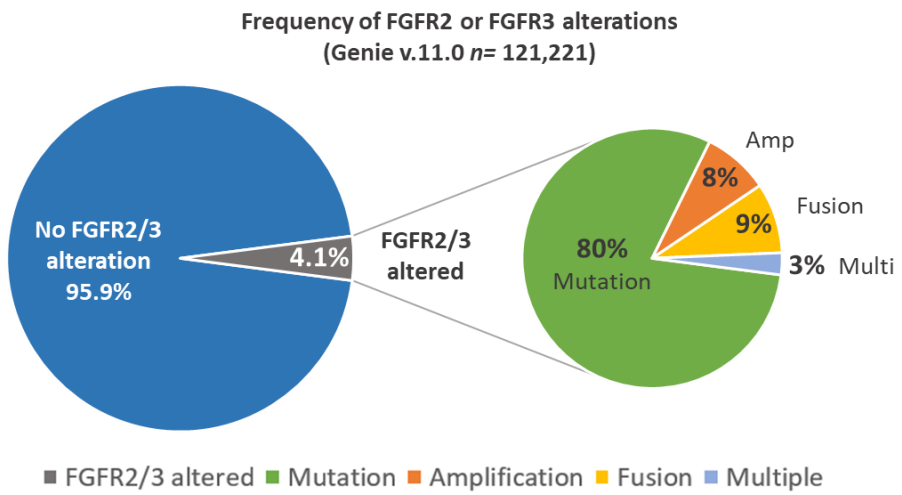


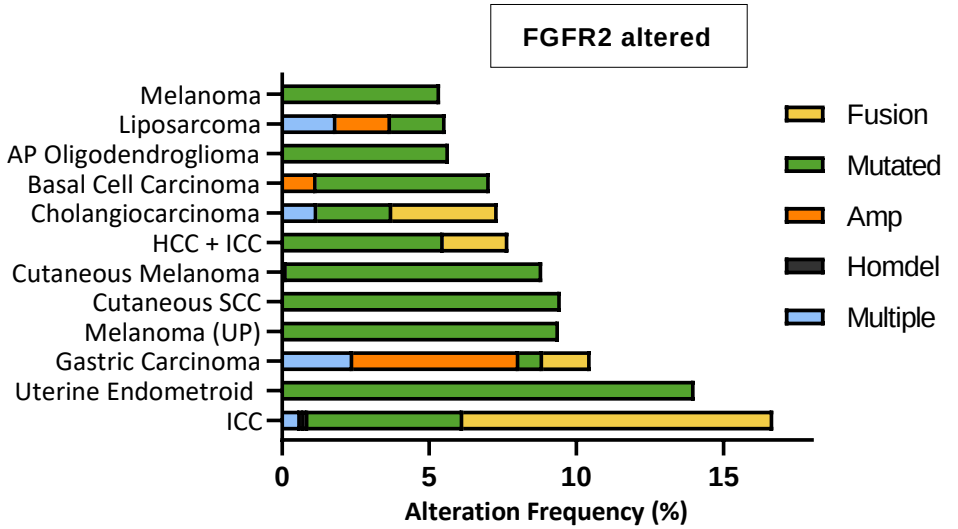


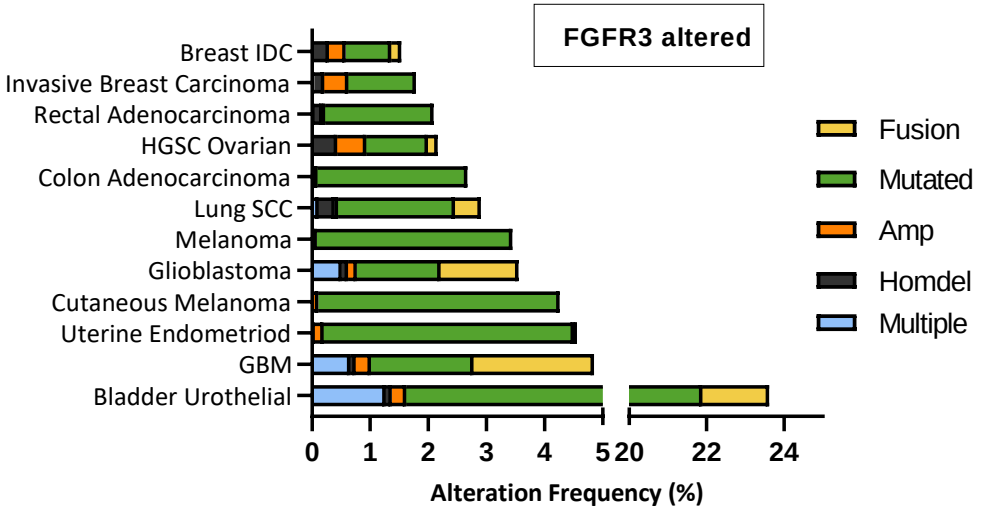
Krook MA *et al.*, *Brit J Can 2021;124(5):880-892*

- FGFRs are transmembrane receptors consisting of FGFR1-4, they are inactive as monomers, and interaction with ligand leads to receptor dimerization, phosphorylation, and downstream signaling
- Inappropriate activation of FGFRs are well-established oncogenic drivers in multiple indications. Aberrations found commonly include activating mutations, amplifications, and fusion events
- Inhibition of FGFR3 mutations in urothelial cancer and FGFR2 fusions in cholangiocarcinoma has led to improved clinical outcomes in molecularly defined patient populations

FGFR2 and FGFR3 are Collectively Altered in up to 4.1% of Cancers



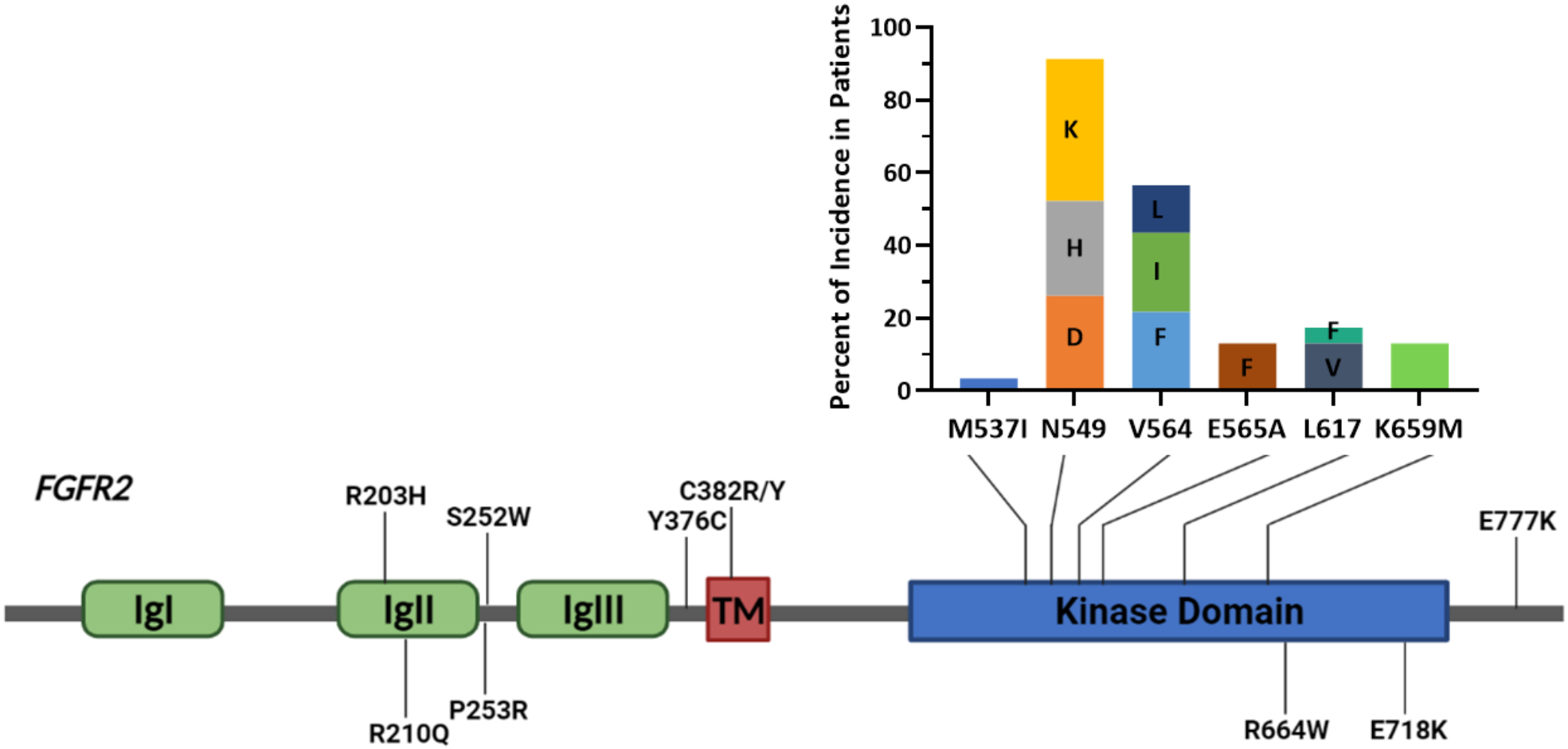




- Unlike FGFR1 and FGFR4 alterations (majority amplified), the majority of FGFR2/3 alterations are activating mutations
- FGFR2 and FGFR3 alterations span indications with intrahepatic cholangiocarcinoma as having the highest frequency of FGFR2 alterations and urothelial carcinoma with the highest number of FGFR3 alterations

Figures generated from information in AACR Project GENIE Consortium. *Cancer Discov* 2017 08; 7(8):818-831

Incidence of Acquired Resistance FGFR2 Kinase Mutations to FGFR Inhibition in Cholangiocarcinoma



Adapted from: Goyal *et al.*, *Cancer Discov* 2017;7(3):252–263

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First Generation Pan-FGFR Inhibitors Have Dose Limiting Toxicities and Poorly Serve the Landscape of FGFR2/FGFR3-Altered Cancers

Clinical Compound	Clinical Features					Approved Clinical Coverage						
	IC50 enzyme (nM) (FGFR1,2,3,4)	Dose Schedule	ORR	Hyperphos	Diarrhea	Adv/met ICC	Adv/met UC	FGFR2 fusions	FGFR3 fusions	FGFR2 Activating mutations	FGFR3 mutations (KD)	FGFR2/3 resistance mutations
Pemigatinib[3,5]	0.4, 0.5, 1, 30	2wk on/ 1wk off	36% (ICC)	92%	47%							
Infigratinib[6,7]	0.9, 1.4, 1, 60	3wk on/ 1 wk off	23% (ICC)	82%	24%							
Erdafitinib[8]	1, 2.5, 3, 6	Daily (schedule based on phosphate levels)	32% (UC)	76%	47%							

UC= Urothelial Carcinoma, ICC= Intrahepatic Cholangiocarcinoma, KD= Kinase Domain **1**. *Abou-Alfa G.K. et al, Lancet Oncol, 2020*; **2**. Pemazyre label; **3**. *Javle, M. et al, Ann. Oncol. 2018*; **4**. Truseltiq label; **5**. Balversa label

- FGFR1 mediated hyperphosphatemia is most common dose limiting toxicity associated with pan-FGFR inhibitors
- Diarrhea is observed in up to 47% of patients taking pan-FGFR inhibitors
- Necessary dose reduction or holiday may limit efficacy of these inhibitors
- The approved pan-FGFR inhibitors fail to capture the full landscape of FGFR2 and FGFR3 altered tumor types
- A selective FGFR inhibitor sparing FGFR1 should result in improved efficacy

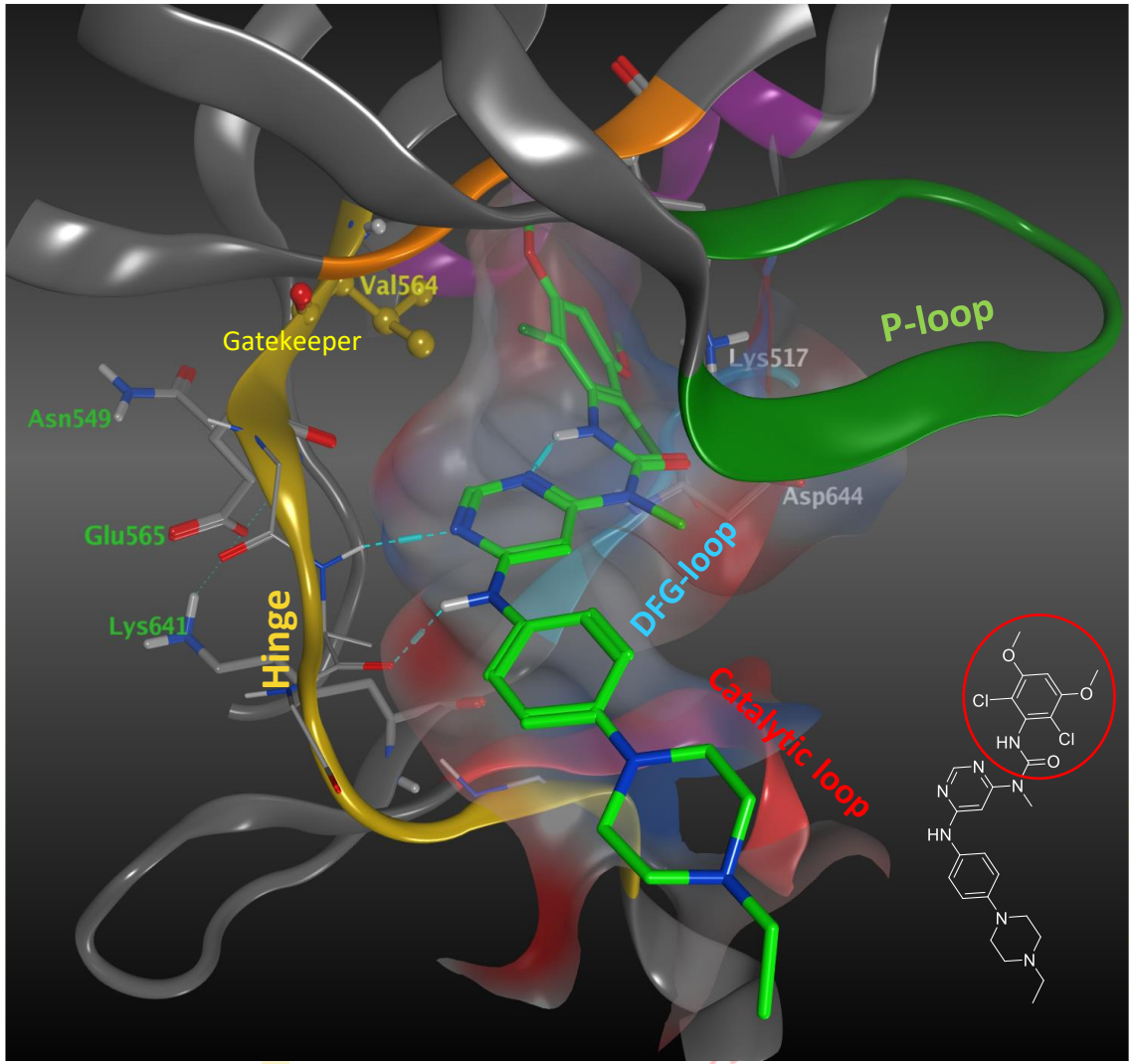
3. Abou-Alfa GK et al., *Lancet Oncol.* 2020;21(5):671-684. 5. PEMAZYRE (pemigatinib; prescribing information). Wilmington, DE: Inctye Corporation; 2021; 6. Javle M et al., *J Clin Oncol.* 2018;36(3):276-282. *2018*; 7. TRUSELTIQ (infigratinib; prescribing information). Brisbane, CA: QED Therapeutics: 2021; 8. BALVERSA® (erdafitinib, prescribing information). Horsham, PA: Janssen Products; 2020

FGFR2 Selective Target Product Profile

Assay	Cogent Compound
FGFR2 Cell IC_{50}	<10 nM
FGFR1 Cell IC_{50}	>200 nM
Solubility	>50 μg/mL
Permeability	Med-High, >3 Pe ratio
Clearance	Med-Low
Cyp Inhibition IC_{50}	>10 μM
PK/PD	90% PD <100 mg/kg
TGI	Equivalent to Competitors
Tolerability	Improved Hyperphosphatemia TI vs competition

- Selectivity >30x for FGFR2 vs. FGFR1 should reduce hyperphosphatemia to a level that does not require holiday or dose reduction
- Solubility and permeability targets will enable formulation and oral bioavailability
- Medium to low clearance will allow for QD or BID dosing
- Cyp inhibition >10 μM enables co-administration of other drugs
- PK/PD/Efficacy correlation leads to human dose prediction
- Hyperphosphatemia will be a key tolerability readout in vitro and in vivo

First Generation Pan-FGFR Inhibitor Infigratinib Bound to FGFR2



- Tetra-substituted phenyl of infigratinib extends into the hydrophobic pocket close to the gatekeeper amino acid **Val564**
- Bulkier gatekeeper mutants, **V564I** and **V564F** cause a steric clash with the substituted phenyl group reducing the binding affinity of infigratinib and other 1st gen compounds
- Molecular brake mutations (**Asn549, Glu565, & Lys641**) activate FGFRs by destabilizing the inactive protein conformation
- While not seen with **N549H** and infigratinib**,** molecular brake mutations can lead to reduced binding affinity of 1st generation compounds

	Enzyme Data			
	FGFR2-WT	FGFR2-N549H	FGFR2-V564I	FGFR2-V564F
Infigratinib	0.5	0.9	63	879

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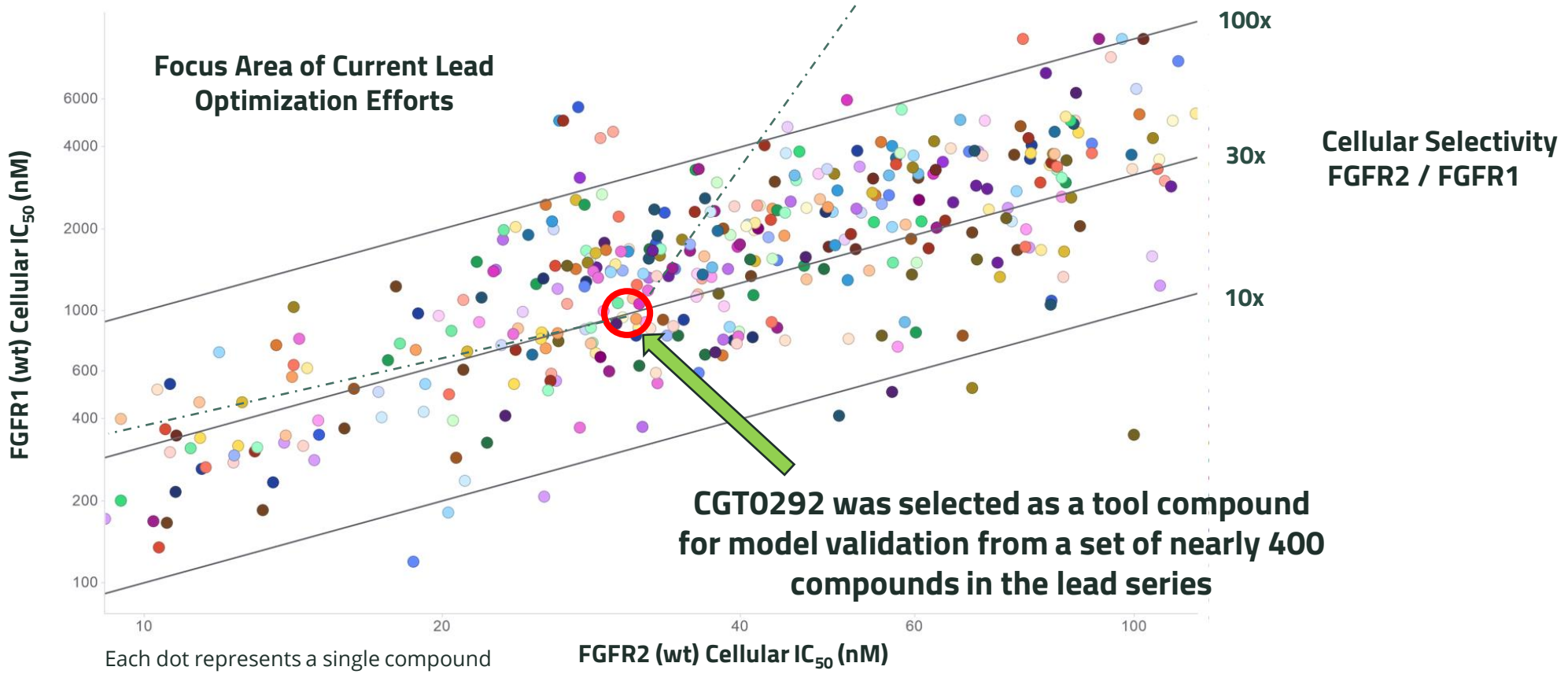
Majority of Lead Series Compounds are >30x Selective for FGFR2 vs. FGFR1



- The Cogent Research Team explored multiple novel templates and SAR to enable selection of a robust lead series

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In vitro Profiling of CGT0292

Assay	CGT0292
tPSA / clogP / MW	~80 / ~2.0 / <400
Solubility (pH 1.2/6.5/7.4)	3250/454/335
Permeability A B Efflux Ratio	16 (10^{-6} cm/sec) 9
Microsomal CL (% ER) M / R / H	10 / 13 / 5
Hepatocyte CL (%ER) M / R / H	61 / 14 / 21
Protein Binding	70.6 % Mouse 72.9 % Rat 64.6% Human
Reversibility Assay Enzyme IC_{50} with Preincubation	0 min = 2.1 nM 30 min = 2.1 nM 60 min = 2.2 nM

CGT0292:

- >30X selective for FGFR2 over FGFR1
- Exhibits BCS Class 1 compound properties
- Low cL potential across species
- Solubility across pH range
- High free fraction / low plasma protein binding across all species tested
- Highly permeable with low potential for CNS exposure
- **Provides a robust scaffold for further compound optimization**

CGT0292 is a reversible inhibitor:

- Avoids potential for time dependent inhibition of FGFR1
- Potential for decreased %CV (GSH metabolism / stability)
- Proteome selectivity advantage

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CGT0292 Demonstrates Superior FGFR1 Selectivity and Mutant Target Coverage Compared to Late Stage / Approved Pan-FGFR Inhibitors

Compound	Cell IC_{50} (nM)		Enzyme IC_{50} (nM)						
	FGFR1-WT	FGFR2-WT	FGFR1-WT	FGFR2-WT	FGFR2 N549H	FGFR2 V564I	FGFR2 V564F	FGFR3-WT	FGFR4-WT
CGT0292	**949**	**30**	**27**	**2.1**	**0.93**	**5.6**	**3.0**	**5.8**	**213**
Infigratinib	10.8	4.2	0.37	0.45	0.93	63	879	4.6	65
Pemigatinib	10.1	1.6	0.49	0.18	1.7	5.2	244	1.1	13
Erdafitinib	5.3	1.4	0.24	0.11	0.32	0.16	173	0.14	1.0
Futibatinib	4.2	2.1	0.55	0.20	0.59	0.70	54	0.32	1.0

- CGT0292 displays ~30x selectivity between FGFR1 and FGFR2 in cellular assays
- Is potent against all tested FGFR2 mutations, enzyme IC_{50} < 10 nM
- Exhibits >100x selectivity for FGFR2 over FGFR4 in the enzyme assay

Cellular assays, KG-1 cells (FGFR1) and KATO-III cells (FGFR2) were treated with compounds for 1 hour, then phosphorylated protein was read using pFGFR1 and pFGFR2 HTRF assays (CisBio); Enzyme assays, purified kinase intracellular domains were assayed using CisBio TK-kinease HTRF assay technology

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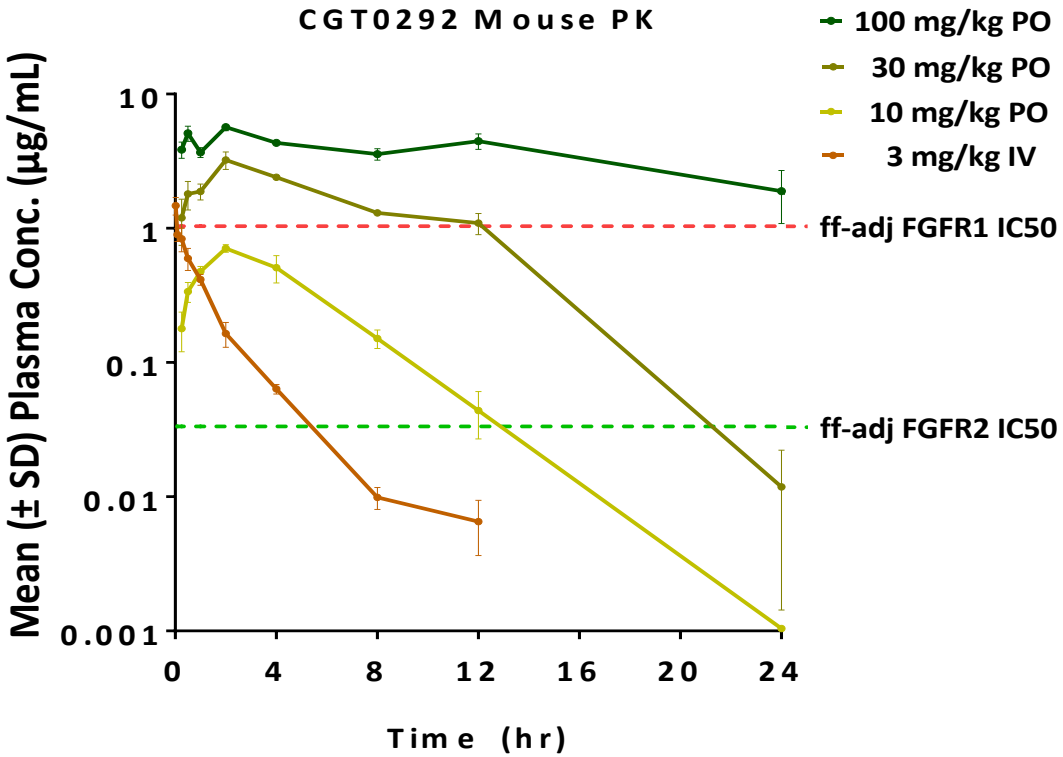
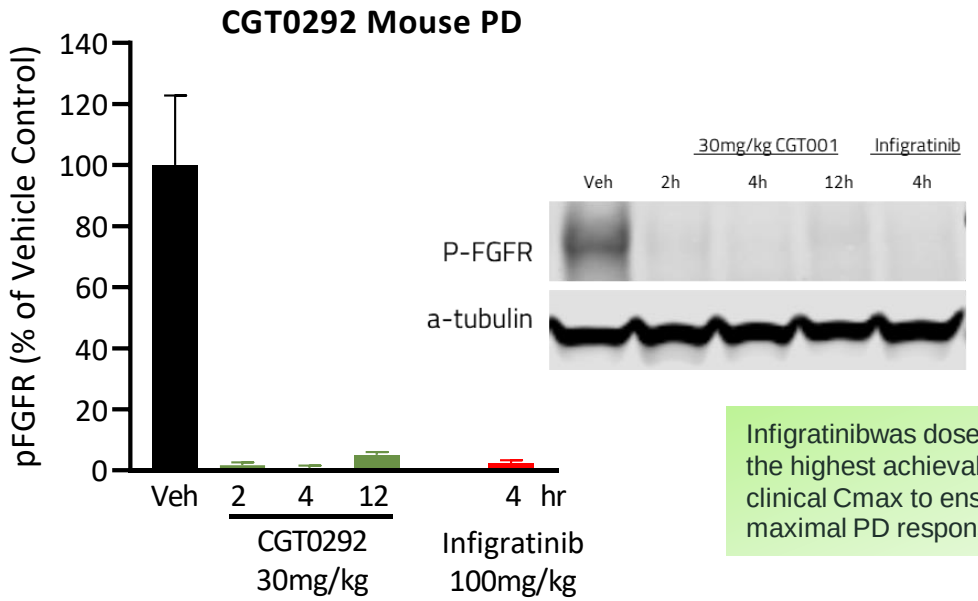
CGT0292 Shows Promising In Vivo Performance and Complete Suppressions of pFGFR





Infigratinibwas dosed above the highest achievable clinical Cmax to ensure a maximal PD response.

Snu-16 xenograft tumors were harvested at the indicated timepoints after a single oral dose and analyzed via Western blot normalized to α-tubulin.

- CGT0292 shows increased exposure with increased dose in mice, as well as complete inhibition of pFGFR2 in the SNU-16 PK/PD model

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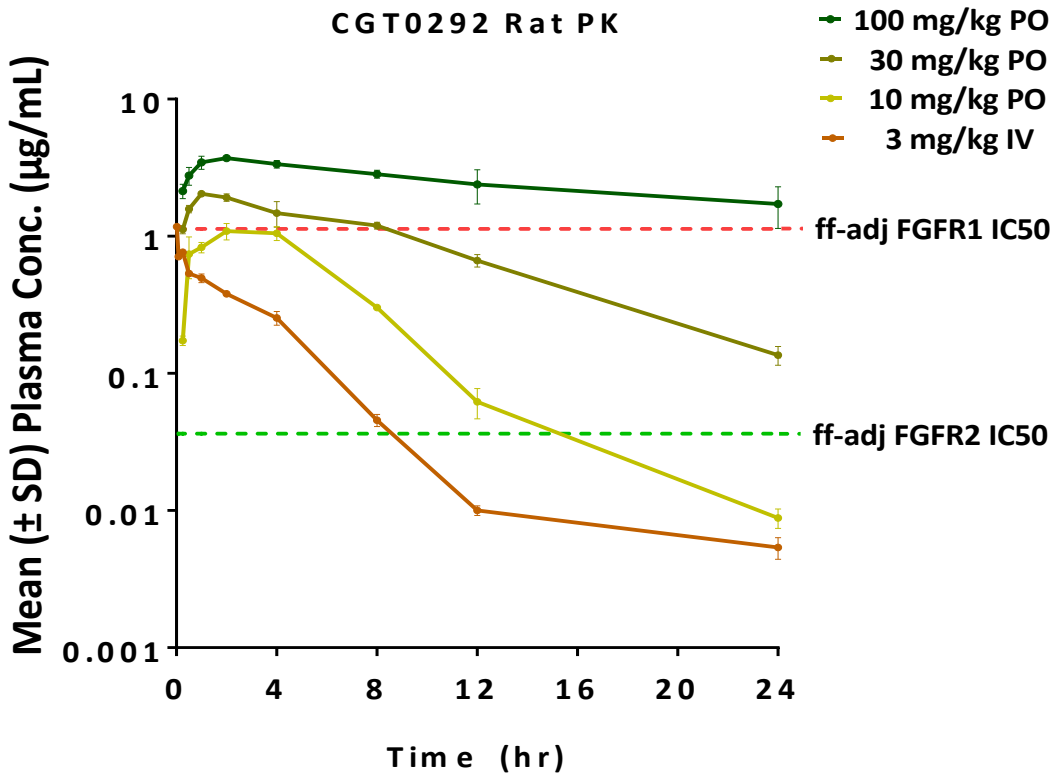
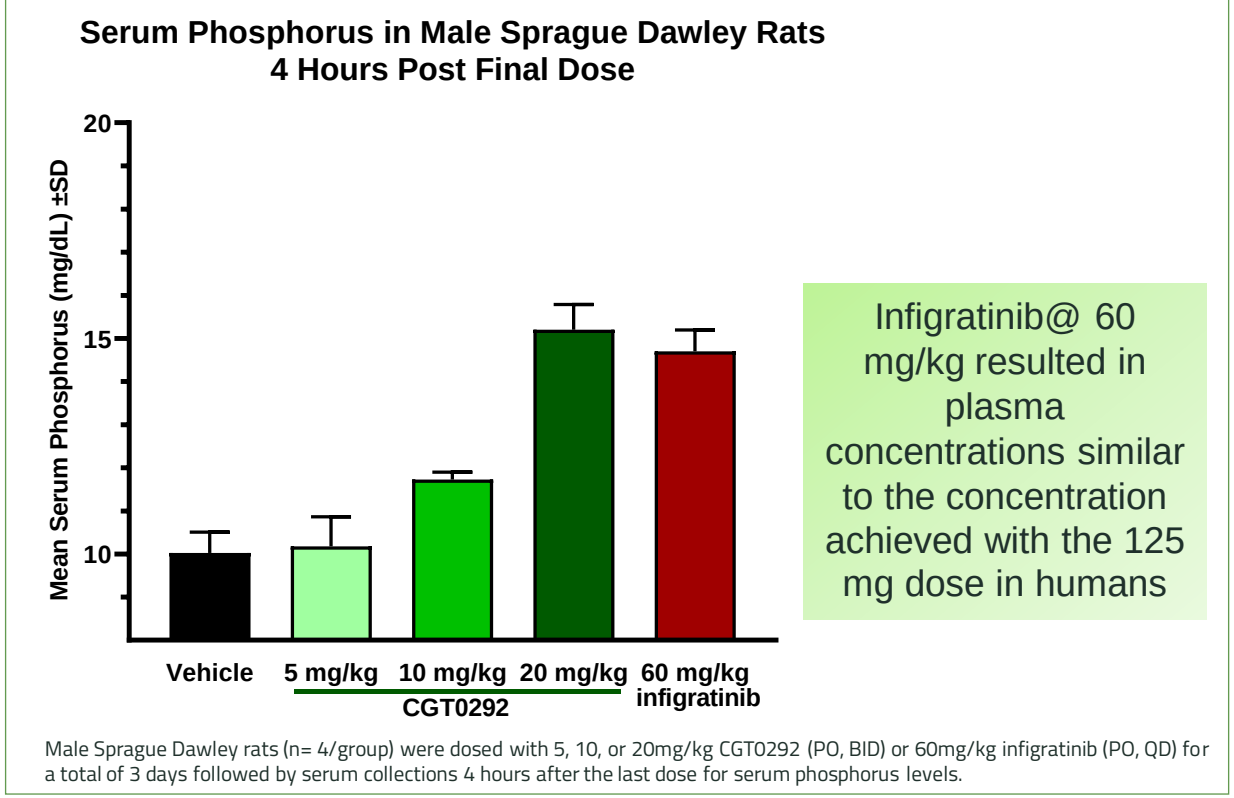
CGT0292 Does Not Show Serum Phosphorus Increase at a 5 mg/kg Dose in the SD Rat Model of Hyperphosphatemia





Infigratinib@ 60 mg/kg resulted in plasma concentrations similar to the concentration achieved with the 125 mg dose in humans

Male Sprague Dawley rats (n= 4/group) were dosed with 5, 10, or 20mg/kg CGT0292 (PO, BID) or 60mg/kg infigratinib (PO, QD) for a total of 3 days followed by serum collections 4 hours after the last dose for serum phosphorus levels.

- Exposures above free cellular IC_{50} of FGFR1 leads to increase in serum phosphorus preclinically

Conclusions and Future Direction

- FGFR1-mediated hyperphosphatemia is the most common dose-limiting toxicity with pan-FGFR inhibitors
- Approved inhibitors fail to capture the full landscape of FGFR2 and FGFR3 altered tumor types

CGT0292:

- Provides >30X selectivity window for FGFR2 vs. FGFR1 in wt pFGFR cell assay
- Potency against a panel of FGFR2 gatekeeper and molecular brake mutations
- Drug-like physiochemical properties with desirable solubility, permeability and plasma protein binding In vitro
- Displays low / moderate IV clearance and high oral bioavailability in mice and rats
- Increased exposure with increased dose

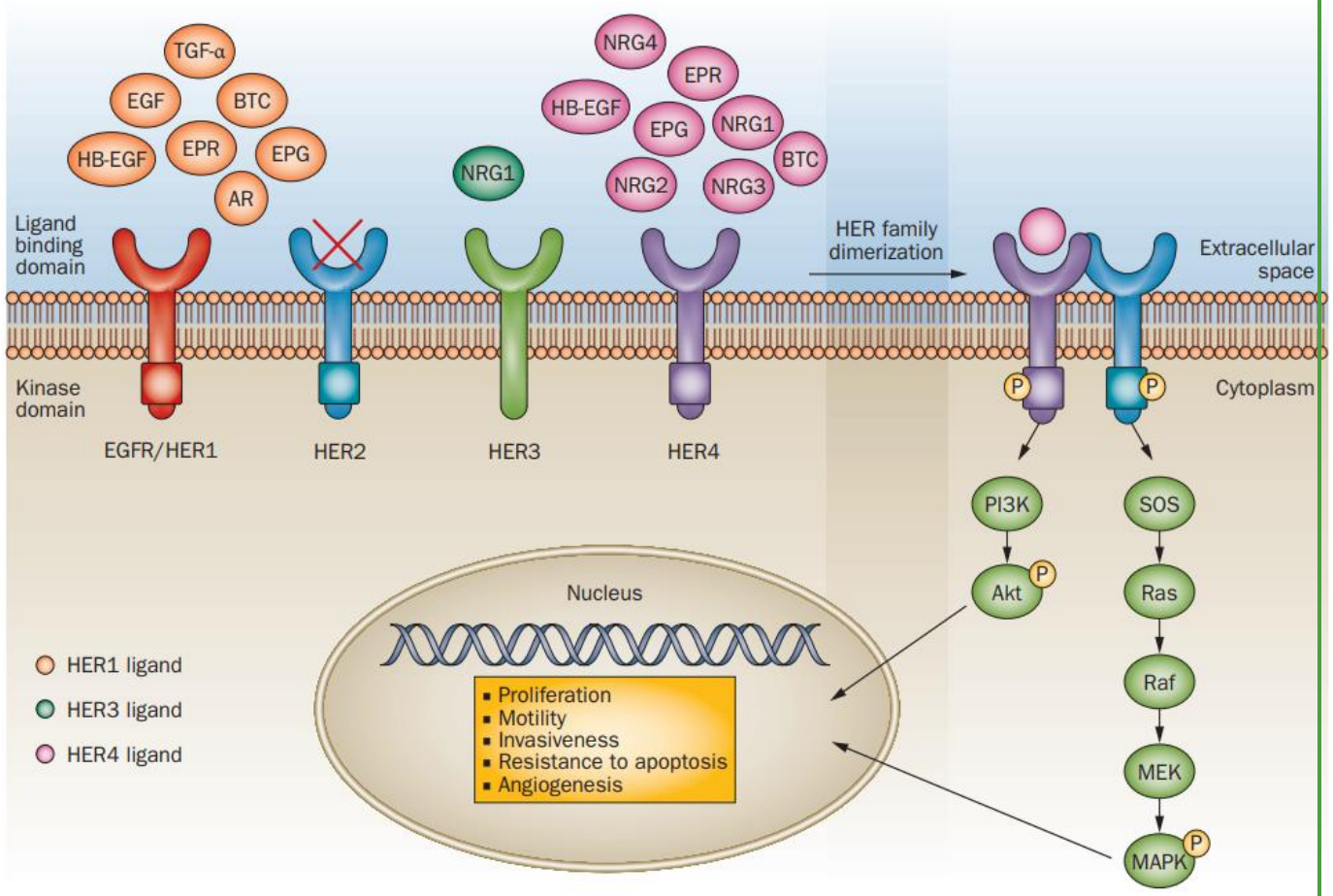
- PK/PD and hyperphosphatemia models have been established to interrogate and enlarge the therapeutic window vs. FGFR1 during further optimization of model compound CGT0292 and related compounds in the series

Introduction to ErbB2 Mutant Selective Program

John Robinson, PhD
Chief Scientific Officer

ErbB2 Receptor Signaling

- ErbB2 is a receptor tyrosine kinase that belongs to a family of four receptors EGFR, ErbB2, ErbB3, ErbB4
- This family is also known as HER1, 2, 3, 4
- ErbB2 has no known direct activating ligand
- Receptor activation induces rapid dimerization, with a marked preference for ErbB2 as a partner
- Following receptor dimerization, phosphorylation of the ErbB kinase domain activates PI3K/Akt and the Ras/Raf pathways which regulate cell growth, survival and differentiation



Arteaga. 2012. Nat Rev Clin Oncol.

Significant Unmet Need Remains for Patients with Non-exon 20 ErbB2 Mutations

Most common cancer types with alteration	Non-exon 20 %	All ErbB2 mut %	CDC Cancer Type	CDC prevalence 2014-2018	Estimated cases with non-exon 20 mutation/year	Estimated cases with any ErbB2 mutation/year
Urothelial Carcinoma	11.4	11.9	Bladder	374,297	8,500	8,900
Endometrial Carcinoma	6.8	7.4	Uterine	281,251	3,800	4,100
Stomach Adenocarcinoma	5.0	6.2	Gastric	121,289	1,200	1,500
Breast – L755S	0.9		Breast	1.3M	2,200	

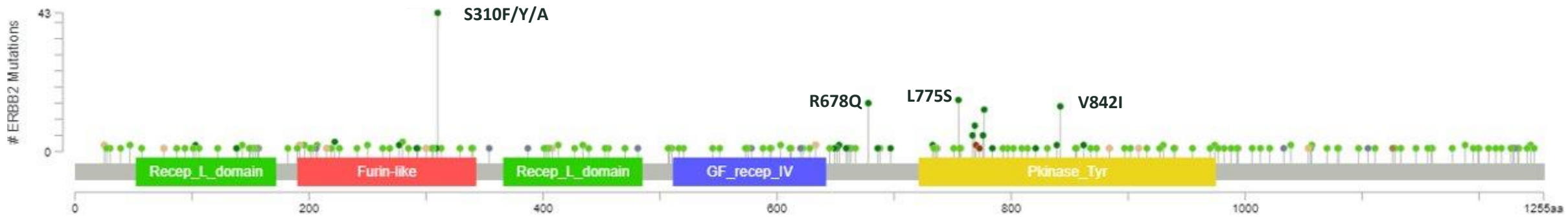
- ErbB2 amplifications and mutations occur in a **mutually exclusive** fashion (80-90% of cases) and thus, represent independent drivers of human cancer pathogenesis
- Activating mutations in the ErbB2 gene have been identified in multiple cancers and demonstrate a tumorigenic role similar to that of ErbB2 amplification
- Emerging mutations result in both acquired and cross resistance

The results shown here are in whole or part based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga."

Frequencies of ErbB2 Mutations Outside of Exon 20

- The most common mutations are **S310F**, **R678Q**, **L755S**, **V842I, D769Y**
- Bladder cancer has the highest frequency of **S310F/Y**
- **L755S** found in endometrial, breast, bladder, gastric, hepatobiliary cancers
- **V842I** highest mutation rates occur in endometrial cancers
- **R678Q** highest in esophagogastric, colorectal, endometrial, and stomach
- **D769Y** mutations occur in breast, colorectal and esophagogastric cancers

Mutation	Percent of ErbB2 (TCGA)	Percent of ErbB2 (Genie)
p.S310F	12.30	7.78
p.V842I	5.50	3.80
p.R678Q	4.53	4.98
p.L755S	4.21	3.80
p.D769Y	1.62	2.08
p.S310Y	1.62	2.47



Most ErbB2 Inhibitors Lack Selectivity Over EGFR

	EGFR – WT Cell IC_{50} (nM)	ERBB2 – WT Cell IC_{50} (nM)	S310F Cell IC_{50} (nM)	S310Y Cell IC_{50} (nM)	L755S Cell IC_{50} (nM)	V842I Cell IC_{50} (nM)	R678Q Cell IC50 (nM)
Afatinib	1	10	17	2	32	7	9
BDTX-189	4	5	6	5	10	6	6
Neratinib	3	5	10	2	9	3	.8
Mobocertinib	18	9	13	2	20	16	25
Lapatinib	58	27	38	20	118	42	18
Osimertinib	528	724	956	277	320	~ 353	216
Tucatinib	> 1000	13	16	9	121	28	5
BI-1622	>1000	5	4	5	<1	6	4

- Stably expressing HEK engineered cells were treated with indicated inhibitors for 1 hour
- Readout is pErbB2 ELISA or pEGFR in-cell western

Though Second Generation ErbB2 Inhibitors Have Improved EGFR Selectivity, They Struggle to Address Key Driver Mutations

	Molecular Weight (g/mol)	Clinical Cmax	hPPB	Mutant	In-house cell IC50 (nM)[1]	ffadj IC50 (nM)	ffadj IC90 (nM)
Tucatinib	480.5	581 ng/mL[1] (**1209 nM**)	97.1% (2.9% free)[2]	S310F S310Y L755S V842I	15 9 121 27	517 310 4172 931	4655 2793 37551 8379
Mobocertinib	585.7	~70 ng/mL[3] (**120 nM**)	99.3% (0.7% free)[4]	S310F S310Y L755S V842I	6 2 20 14	857 286 2857 2000	7714 2571 25714 18000

- ffadj IC_{50} and IC_{90} were calculated from mechanistic cell data and human plasma protein binding
- At clinical Cmax tucatinib does not cover the ffadj IC_{90} in ERBB-WT or any of the tested mutants
- Tucatinib covers S310S/Y and V842I ffadj IC_{50} at Cmax but not L755S

Opportunity: Develop an ErbB2 mutant selective drug which covers key mutations while sparing wtEGFR

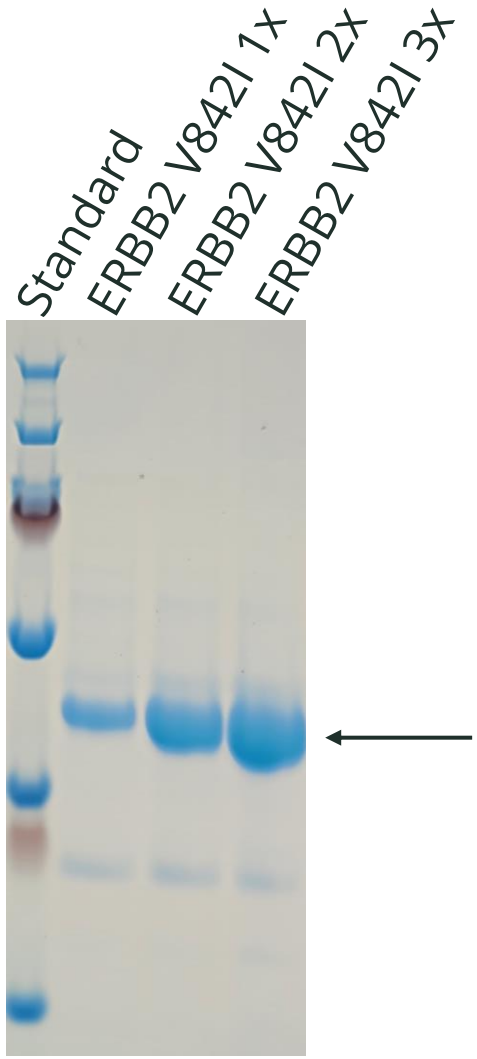
1. https://www.annalsofoncology.org/article/S0923-7534(20)39835-5/fulltext,;
2.https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213411s000lbl.pdf; 3. https://cancerdiscovery.aacrjournals.org/content/11/7/1688.long;
4. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215310s000lbl.pdf

ErbB2 Mutant Selective Target Product Profile

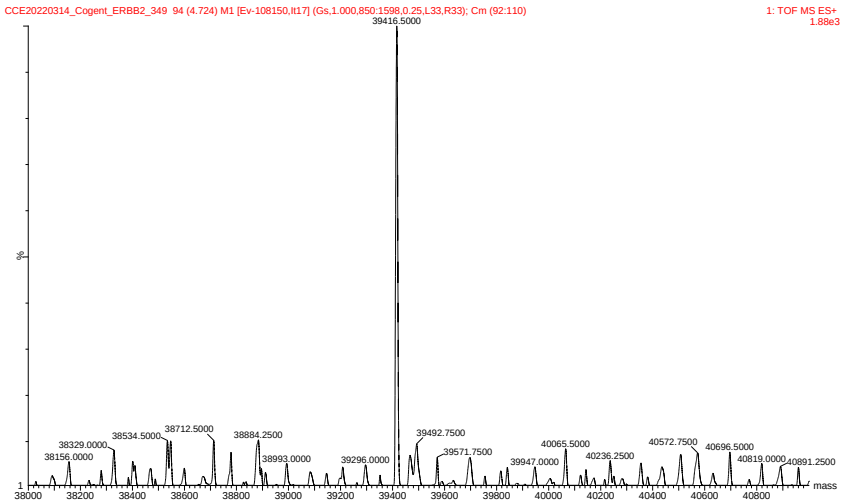
Assay	Cogent Compound
Mutant Cell IC_{50}	<10 nM
EGFR WT Cell IC_{50}	>200 nM
Solubility	>50 mg/mL
Permeability	Med-High
Clearance	Med-Low
Cyp Inhibition IC_{50}	>10 mM
PK/PD	90% PD at ≤30mpk
TGI	Regressions at ≤50mpk
Tolerability	Improved TI vs competition

- <10 nM in Cell for the 4 major mutants (L755S, V842I, S310Y/F)
- Selectivity >20X selectivity for EGFR WT over mutants should reduce EGFR on target AEs and allow us to fully cover the mutants
- Solubility and permeability targets will enable formulation and oral bioavailability.
- Medium to low clearance will allow for QD or BID dosing
- Cyp inhibition >10 µM enables co-administration of other drugs
- PK/PD/Efficacy correlation leads to human dose prediction
- CNS penetration is an upside

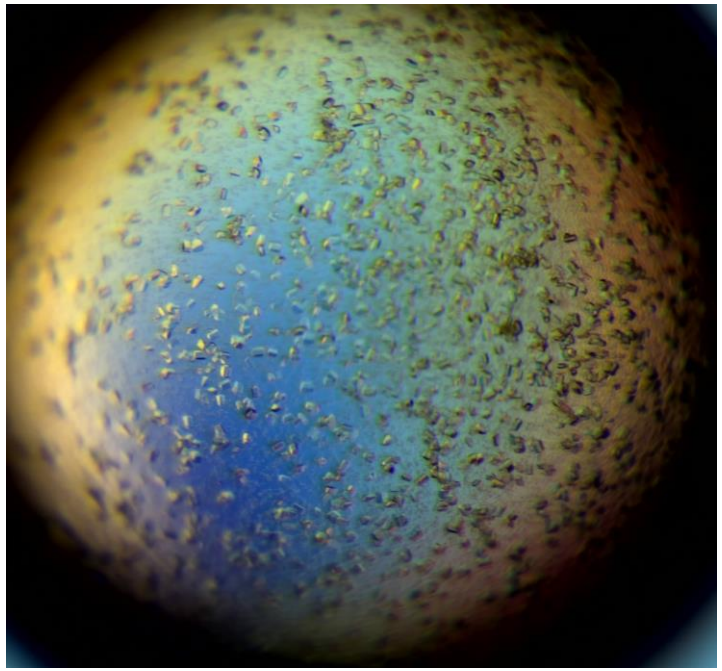
Enabling Structure Based Drug Design for ErbB2 Mutant Driven Disease



ERBB2 V842I



Mass Spec assessment of ErbB2 V842I covalently modified with a selective covalent inhibitor



Crystals of ErbB2 V842I covalently modified with an ErbB2 inhibitor

- First example of ErbB2 mutant protein purification and crystallization

Cogent Research Program in Lead Generation for Novel ErbB2 Mutant Program

Assay Enzyme IC_{50}	Cogent TPP	CGT011199 (series 1)	CGT011237 (series 2)
EGFR WT (nM)	>600	654	230
ErbB2 WT (nM)	<20	12	37
ErbB2 D769H (nM)	<20	17	22
ErbB2 D769Y (nM)	<20	21	21
ErbB2 V777L (nM)	<20	19	32
Phospho-cell assays			
EGFR WT (nM)	>1000	>1000	>1000
ErbB2 L755S (nM)	<25	160	100
ErbB2 V842I (nM)	<25	135	26

- Several novel series with promising enzyme selectivity for ErbB2 over EGFR WT identified
- Compounds have low double digit nM potency against WT and mutant ErbB2
- Mechanistic cell assays show potency on L755S and V842I mutants with selectivity over EGFR WT for our two-novel series

Cogent Biosciences: Emerging Leader in Precision Medicines for Genetically Defined Diseases

Bezuclastinib, a potential best-in-class **selective KIT mutant inhibitor**, has demonstrated a promising pre-clinical profile and positive clinical activity and safety results from a Phase 1/2 clinical trial in patients with gastrointestinal stromal tumors (GIST)

Robust product pipeline highlighted by potential best-in-class KIT inhibitor for Systemic Mastocytosis and GIST patients

Program	Indication	Early Stage Development	Late Stage Development	Regulatory Submission	Approval
Clinical Programs					
Bezuclastinib (KIT inhibitor)	Advanced Systemic Mastocytosis	Apex			
	Nonadvanced Systemic Mastocytosis	Summit			
	Gastrointestinal Stromal Tumors	Peak			

Research Programs

Indication	Hit ID	Lead Generation	Lead Optimization	GLP	IND Submission
FGFR2					
ErbB2 mut					
Target 3					
Target 4					
Target 5					
Target 6					

Cash balance as of December 31, 2021: $219.7 million

Q&A

Scan the QR code to obtain a PDF copy of the Bezuclastnib poster to be presented at AACR

Scan the QR code to obtain a PDF copy of the FGFR2 poster to be presented at AACR