Peak Study: A Phase 3, Randomized, Open-Label, Multicenter Clinical Study of Bezuclastinib (CGT9486) and Sunitinib Combination Versus Sunitinib in Patients with Gastrointestinal Stromal Tumors (GIST)

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Rationale for Treatment of GIST with Bezuclastinib in Combination with Sunitinib

- The worldwide standard for first-line therapy of advanced KIT-mutant GIST is treatment with imatinib, which targets primary KIT mutations in exons 9 and 11.
- Secondary resistance mutations in the KIT ATP-binding domain (exons 13, 14), activation loop (exons 17, 18), or both can develop and result in loss of imatinib-sensitivity[1-4]
- While no single tyrosine kinase inhibitor (TKI) inhibits all mutations, the combination of bezuclastinib (targeting exons 9, 11, **17**, and **18**) and sunitinib (targeting exons 9, 11, **13**, and **14**) targets the full spectrum of primary and **secondary resistance mutations**.[5]

Bezuclastinib + Sunitinib Combination Targets the Full Spectrum of Primary and Secondary Mutations

	Primary		Secondary				Broad Coverage of Spectrum of Mutations
	9	11	13	14	17	18	
Imatinib	√	√	-	-	-	-	-
Ripretinib	~	√	~	√	√	√	~
Sunitinib	√	√	√	√	-	-	-
Bezuclastinib	√	√	~	-	√	√	-
Bezuclastinib + Sunitinib	√	√	√	√	√	√	√

√ = strong inhibition
~ = moderate inhibition
- = no inhibition

1. Gramza AW, et al. Clin Cancer Res, 2009;15(24):7510-7518. 2. Arshad J et al. JCO Precis Oncol, 2020;4:66-73. 3. Casali PG, et al. JCO, 2017;35(15):1713-1720. 4. Serrano C and George S. CCR, 2020;26(19):5078-5085. 5. Wagner et al. [abstract 1251848] 2022. In: CTOS 2022: 1251848.

Bezuclastinib Has No Significant Activity Against Closely-Related Kinases, Leading to a Highly Selective Profile That Allows For Combination Treatment

Activity Against Closely Related Kinases

Compound	Cell IC_{50}(nM)*				
	PDGFRα	PDGFRß	CSF1R	FLT3	VEGFR2
Bezuclastinib	**>10,000**	**>10,000**	**>10,000**	**>1000**	**>1000**
Imatinib	75	247	1027	>1000	>1000
Sunitinib	23	14	313	1	4
Regorafenib	138	1180	473	237	101
Avapritinib	53	10	249	305	>1000
Ripretinib	20	34	312	534	110

* Off-target assays were performed using phospho ELISAs (R&D Systems). The following cell lines were used for analysis: H1703 (PDGFRa), NIH3T3 (PDGFRb), HEK293 engineered lines (CSF1R, FLT3, and VEGFR2).

- In preclinical studies, bezuclastinib demonstrated no significant activity against closely-related kinases which have been linked to toxicities including edema, hypertension, and pleural effusion.[1-3]
- The selectivity profile of bezuclastinib allows for combination with sunitinib, resulting in broad activity against a spectrum of KIT mutations, and ultimately may provide more durable response in patients with imatinib-resistant GIST.

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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. Robinson ES et al. Semin Nephrol 2010; 30(6): 591-601.

Bezuclastinib in Combination with Sunitinib Has Demonstrated Encouraging Phase 1/2 Results

- In a Phase 1/2 trial, combination of bezuclastinib + sunitinib was well tolerated and demonstrated clinical activity in pts with relapsed/refractory GIST[1]
  - Median PFS for the combination was 12.1 months
    - In a subset of 6 patients with known exon 17/18 secondary mutations and without exon 13/14 mutations, median PFS was 16.5 months
  - Clinical benefit rate (complete response + partial response + stable disease lasting at least 16 weeks) was 80% (95% CI, 52%-96%)

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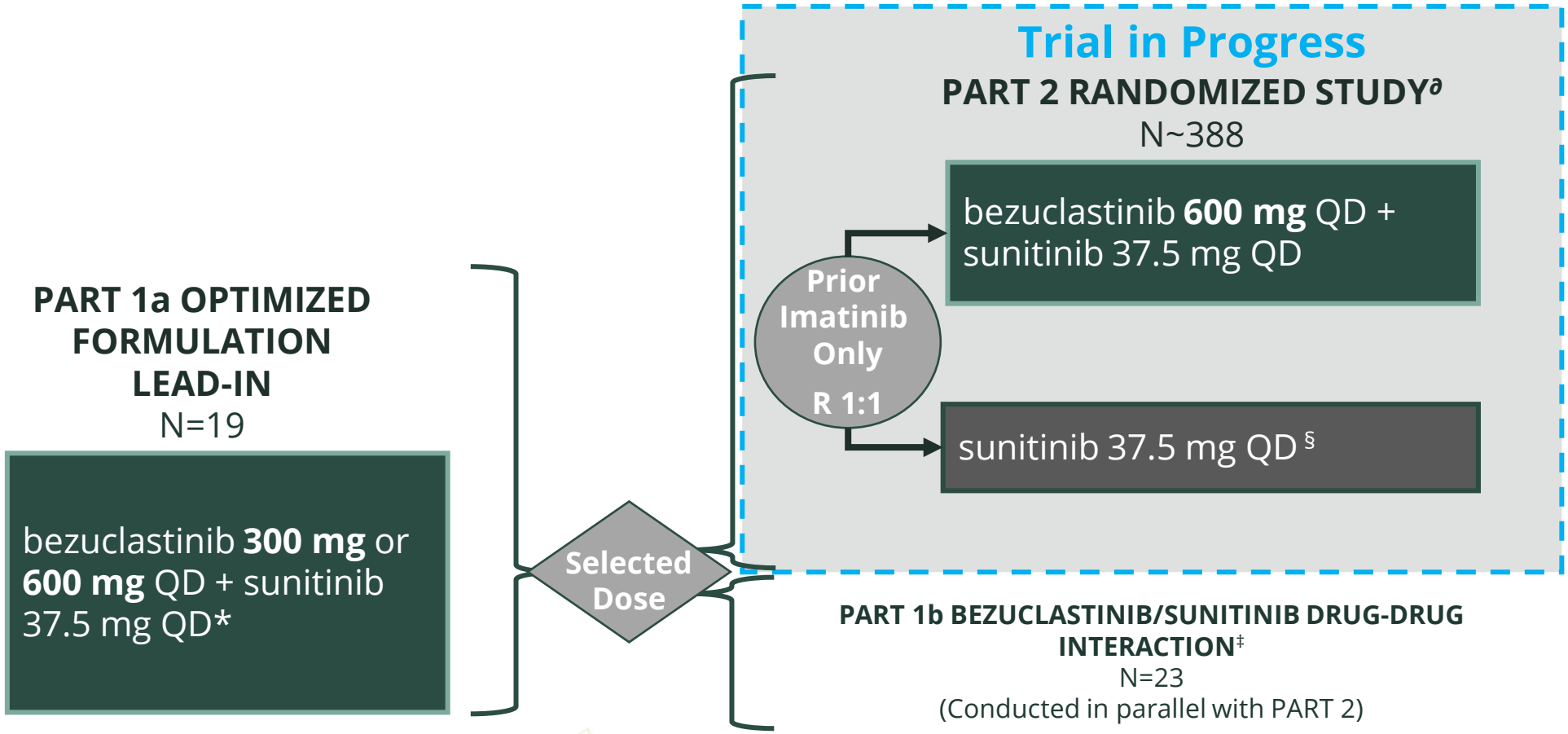
1. Wagner AJ, et al. JAMA Oncol. 2021;7(9): 1343-1350.

Peak: Global, Randomized, Phase 3 Study of Bezuclastinib + Sunitinib in Patients with GIST (NCT05208047)



*Sunitinib treatment begins on Day 2

∂Mutational ctDNA are being collected in Part 2 at baseline and disease progression

§Sunitinib monotherapy patients who progress may be eligible for cross-over

‡Patients receive either bezuclastinib or sunitinib as single agent for 2 weeks, followed by bezuclastinib and sunitinib

Peak Part 2: Phase 3 Study of Bezuclastinib + Sunitinib in Patients with GIST

Peak Study Objectives and Endpoints for Part 2

Primary Objective	Determine the efficacy of bezuclastinib + sunitinib vs sunitinib alone as second-line treatment in adult patients with GIST who were intolerant to imatinib or whose tumors had imatinib resistance
Primary Endpoint	PFS based on blinded independent central review (BICR) per mRECIST v1.1
Secondary Endpoints	• Overall survival • Objective response rate based on BICR per mRECIST v1.1 • Safety and tolerability • Other efficacy parameters based on BICR: Disease control rate, time to response, and duration of response • PFS assessed by Investigator • Quality of Life
Exploratory Endpoints	• ctDNA for mutational analysis • Pharmacodynamics

Key Entry Criteria for Part 2

Histologically confirmed Gastrointestinal Stromal Tumors (GIST) w/at least 1 measurable lesion per mRECIST v1.1
Locally advanced, unresectable or metastatic disease
Documented disease progression on or intolerance to imatinib
ECOG Performance Status 0-2
Prior imatinib only

Updated Data from Peak: Part 1b

- **Primary Objective**:
  - To characterize potential drug-drug interaction between bezuclastinib and sunitinib
- **Design**:
  - Subjects (n = 23) were randomized 1:1 to receive monotherapy (either sunitinib or bezuclastinib) for 2 weeks followed by combination
- **Results**:
  - Combination with sunitinib did not have an impact on PK of bezuclastinib
  - Combination with bezuclastinib resulted in 26% and 35% reduction in median and geometric mean steady state AUC (AUC_{ss}), respectively, of combined sunitinib + its active metabolite
    - Sunitinib AUC_{ss} with the combination is consistent with published meta-analysis of sunitinib monotherapy[1]
  - The sunitinib exposure levels in Part 1 of Peak as well as the early signs of clinical activity, tolerability, and safety observed with the combination are consistent with the completed Phase 1/2 study (PLX121-01)[2]
- **Impact:**
  - Response to bezuclastinib + sunitinib combination treatment and treatment duration are encouraging

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1. Houk et al. Cancer Chemother Pharmacol. 2010;66(2):357-71; 2. Wagner AJ, et al. JAMA Oncol. 2021;7(9): 1343-1350.

Safety in Patients from Peak Part 1a and 1b (n=42)

- Majority of TEAEs were of low CTCAE grade and reversible.
- Low rate (38%) of Grade 3+ events
- Only three patients experienced serious adverse events possibly associated with study medications:
  - Gr 2 neutrophil count decrease and pyrexia and Gr 3 platelet count decrease.
  - Gr 2 bacterial peritonitis and Gr 3 febrile neutropenia.
  - Gr 3 anemia, asthenia, and edema peripheral.
- Limited (24%) dose reductions of any study medications due to TEAEs.
- Infrequent (n=2) discontinuations due to TEAEs.
  - Gr 2 Rash; Gr 1 abdominal pain and Gr 3 diarrhea.
- The safety and tolerability profile appears generally consistent with published sunitinib monotherapy experience.

TEAEs≥15% of Patients All Causality

	Part 1a n=19 (%)		Part 1b *n=23 (%)*		Total *n=42 (%)*	
Preferred Term	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**
Diarrhea	11 (58)	2 (11)	11 (48)	-	**22 (52)**	**2 (5)**
Fatigue	10 (53)	-	8 (35)	-	**18 (43)**	**-**
Nausea	8 (42)	-	6 (26)	-	**14 (33)**	**-**
Hair color changes	8 (42)	-	5 (22)		**13 (31)**	**-**
Hypertension	7 (37)	4 (21)	6 (26)	2 (9)	**13 (31)**	**6 (14)**
Taste disorder*	3 (16)	-	9 (39)	-	**12 (29)**	**-**
GERD	3 (16)	-	5 (22)	-	**8 (19)**	**-**
ALT/AST increased^	3 (16)	1 (5)	5 (22)	1 (4)	**8 (19)**	**2 (5)**
Neutropenia*	4 (21)	-	3 (13)	2 (9)	**7 (17)**	**2 (5)**
Rash*	3 (16)	-	4 (17)	-	**7 (17)**	**-**

** Includes pooled PTs*
^ All subjects with AST elevations experienced ALT elevations. One subject experienced only ALT elevation.
GERD, gastroesophageal reflux disease

As of 25-AUG-2023 Data-cut
Safety Analysis Set: All treated pts

Peak Clinical Activity Update

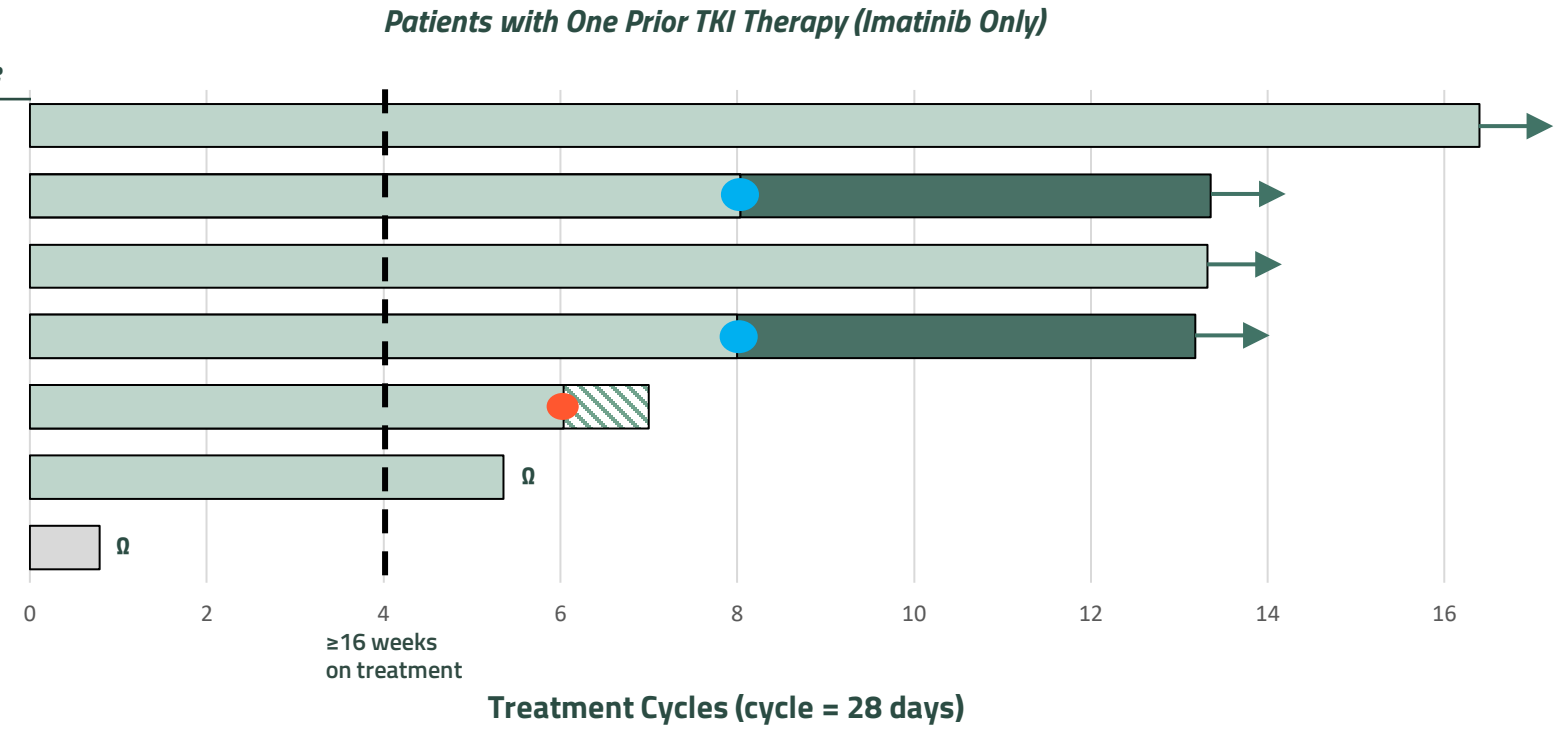
Peak Part 1 Evaluable Patients^ (n=40)

- Objective Response Rate (ORR) is 20% (6 confirmed PRs, 2 unconfirmed PR)
- Data remain immature to estimate median PFS for part 1 patients

Prior Imatinib Only Evaluable Patients^ (n=6)

- Objective Response Rate is 33% (2 confirmed PRs)
- Durable disease control and responses have been observed across a range of bezuclastinib and sunitinib exposures

Steady-State (C2D1) $AUC_{(0\text{-}24h)}$ (ng*h/mL)		*Best Overall Response*
Bezuclastinib	*Sunitinib*	
29400	773	SD
23200	497	PR
78900	486	SD
12800	230	PR
26800	467	SD
12000	807	SD
NE	NE	-



As of 25-Aug-2023 Data-cut

NE, not evaluable

^Received at least 1 cycle of study treatment and had a baseline and at least 1 post-baseline disease assessment

Summary

Efficacy

- Objective response rate (ORR) in Part 1 (n=40) is 20%.
  - Durable disease control and responses have been observed across a range of bezuclastinib and sunitinib exposure.
  - Majority of 2nd-line patients remain on treatment past 12 months with a confirmed 33% ORR.

Safety

- Encouraging safety and tolerability in Part 1, consistent with previously reported clinical data (Ph 1/2 PLX121-01 trial).
  - Majority of TEAEs were low grade and reversible with a low rate of Grade 3+ events.
  - Combination was well-tolerated with limited dose reductions and discontinuations due to adverse events.
  - The safety and tolerability profile appears generally consistent with published sunitinib monotherapy experience.

Conclusions

- The sunitinib exposure levels in Part 1 of Peak as well as the early signs of clinical activity, tolerability, and safety observed with the combination are consistent with the completed Phase 1/2 study (PLX121-01).
- Part 2 of the Peak study is actively recruiting and enrolling patients globally at the selected dose of 600 mg PO bezuclastinib QD and 37.5 mg PO sunitinib QD.

Part 2 of the Peak Study Is Actively Recruiting and Enrolling Patients At More Than 100 Sites Worldwide

Trial in Progress

PART 2 RANDOMIZED STUDY[∂]

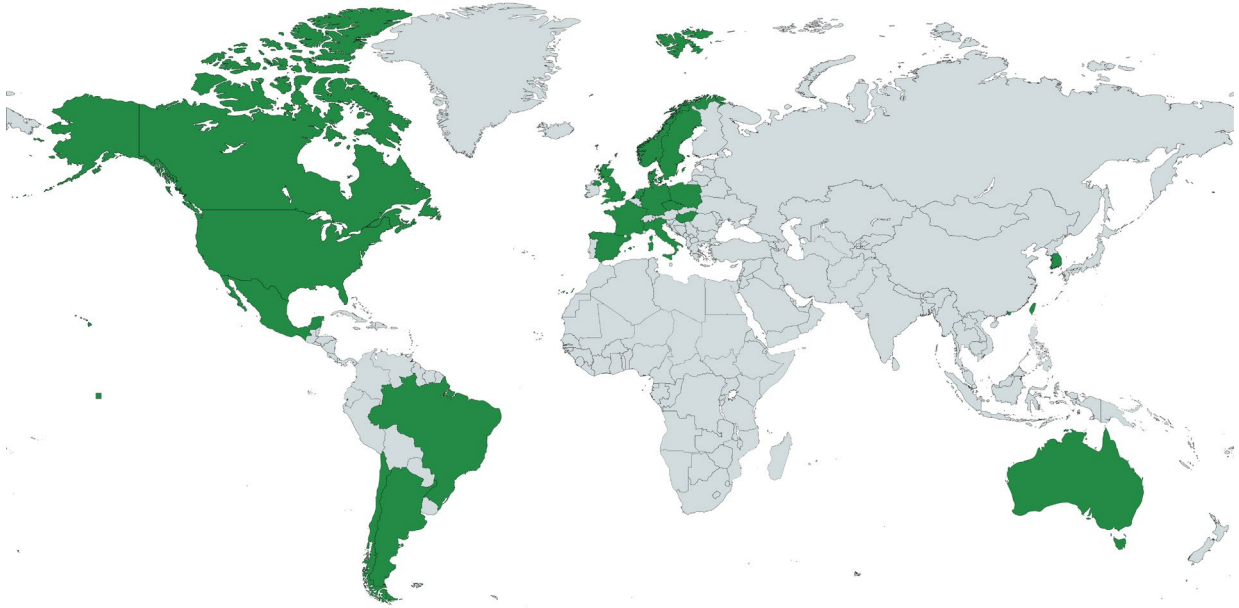
N~388

Prior Imatinib Only

R 1:1

- bezuclastinib **600 mg** QD + sunitinib 37.5 mg QD
- sunitinib 37.5 mg QD [§]

Selected Countries for Peak Study



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- Documented disease progression on or intolerance to imatinib
- ECOG Performance Status 0-2
- Prior imatinib only

An electronic version of this presentation may be obtained by scanning this QR code.

[∂]Mutational ctDNA are being collected in Part 2 at baseline and disease progression
[§]Sunitinib monotherapy patients who progress may be eligible for cross-over