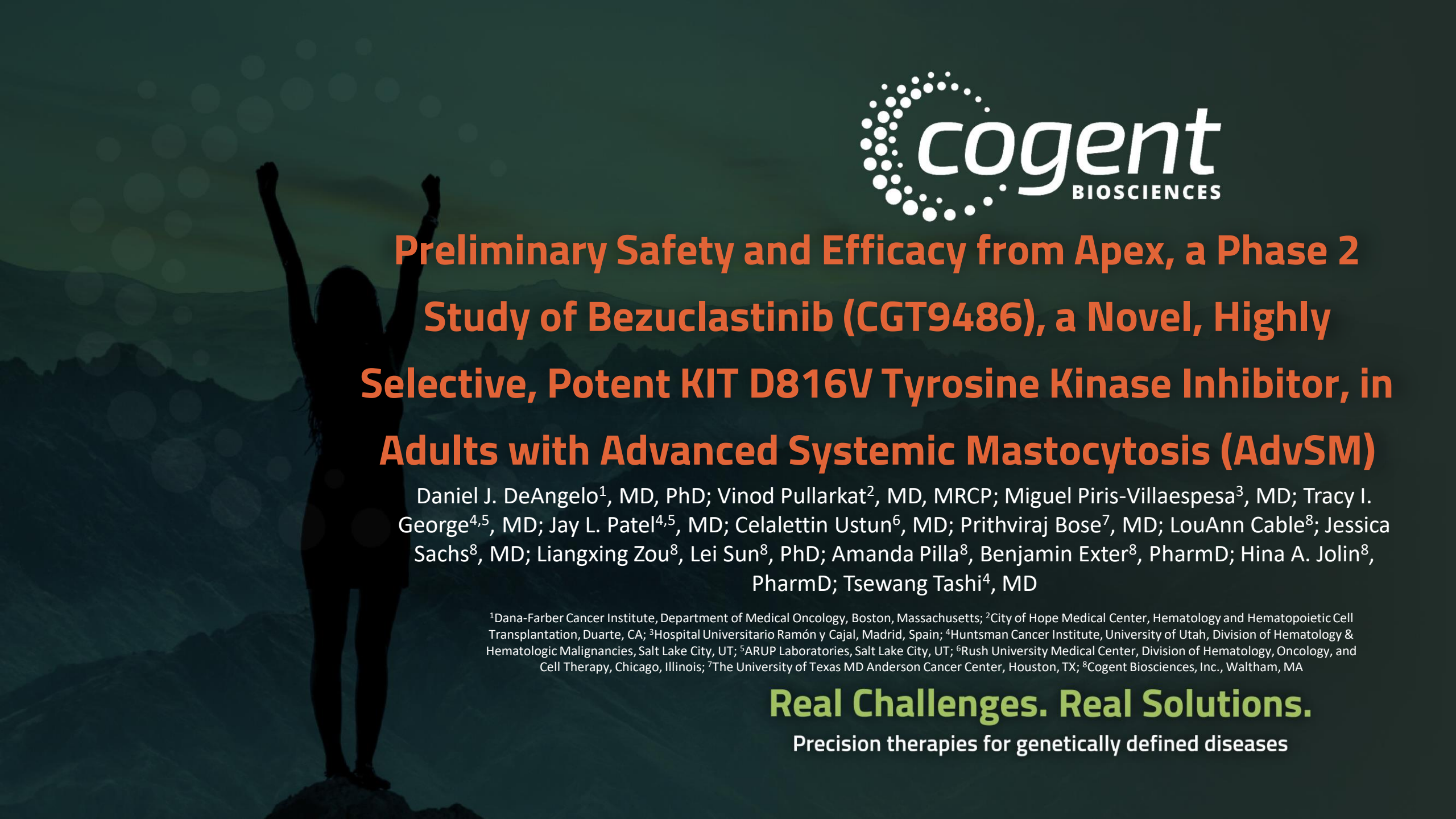

Preliminary Safety and Efficacy from Apex, a Phase 2 Study of Bezuclastinib (CGT9486), a Novel, Highly Selective, Potent KIT D816V Tyrosine Kinase Inhibitor, in Adults with Advanced Systemic Mastocytosis (AdvSM)

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Real Challenges. Real Solutions.

Precision therapies for genetically defined diseases

Unmet Need Remains for Advanced Systemic Mastocytosis Patients

Disease Overview: Aggressive and life-threatening form of systemic mastocytosis (SM) that is primarily driven by KIT D816V mutation and leads to uncontrolled proliferation of mast cells (MC)[1,2]

- Subtypes: aggressive SM (ASM); SM with associated hematologic neoplasm (SM-AHN); mast cell leukemia (MCL)[1]
- Based on subtype, the median overall survival ranges from <6 months to 3-4 years[3,4]

Unmet Need Remains: Approved therapies with associated dose-limiting toxicities

- Reported toxicities for marketed therapies: nausea, vomiting, diarrhea, edema, intracranial bleeding, cognitive effects[5-7]

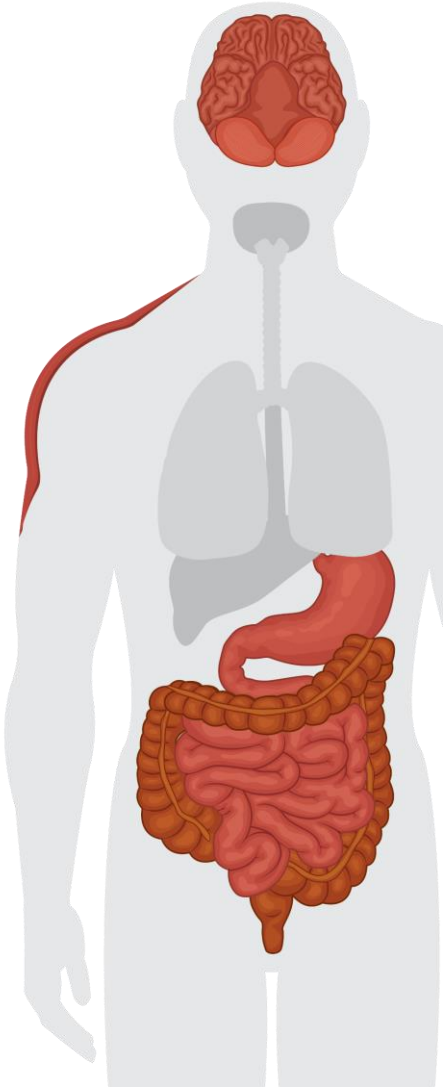
Neurological
Headache, brain fog, cognitive dysfunction, anxiety, depression

Systemic
Anaphylaxis

Cutaneous (skin)
Flushing of the face/neck/chest, hives, skin rashes, itching with or without rash

Gastrointestinal
Diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux disease (GERD)

Other
Cardiovascular
Ear/Nose/Throat/Respiratory
Skeletal
Gynecological
Urinary



References: 1Pardanani A. Am J Hematol. 2021;96(4):508-525. 2DeAngelo DJ et al. Nat Med. 2021;27(12):2183-2191. 3Ustun C et al. Haematologica. 2016;101(10):1133-1143. 4Lim K-H et al. Blood. 2009;113(23):5727-5736. 5AYVAKIT (avapritinib) [package insert]. Blueprint Medicines Corporation; 2021. 6Magliacane D et al., Transl Med UniSa. 2014;8:65-74. 7RYDAPT (midostaurin) [package insert]. Novartis Pharmaceuticals; 2021.

Bezuclastinib: Highly Selective and Potent KIT D816V Inhibitor

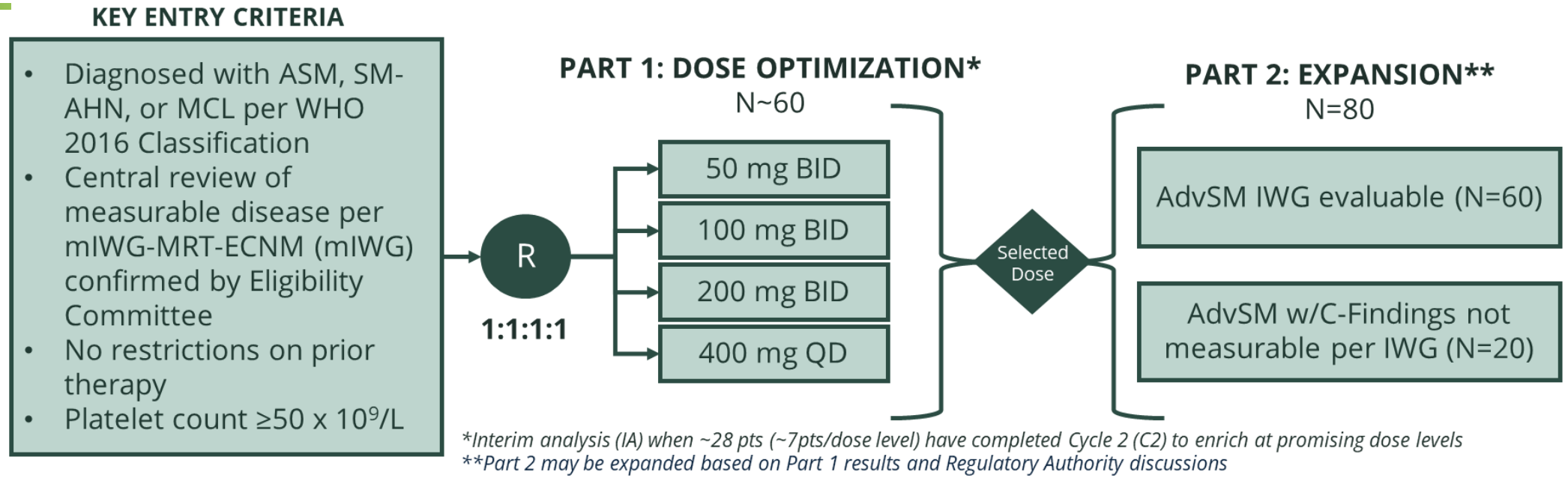
- Oral, selective, and type I tyrosine kinase inhibitor (TKI) with potent activity against KIT D816V, an activation loop mutation
- Preclinically, highly active with specificity for mutations in KIT exons 9, 11, 17, and 18
- Spares closely related kinases, has minimal brain penetration, and favorable PK properties[1]
  - Inhibition of closely related kinases have been linked to off-target toxicities, such as bleeding, edema, and pleural effusions[2, 3]

Kinase Inhibition Profile of Clinical Stage and Approved KIT D816V Agents; Cell IC_{50} (nM)

Compound	KIT V560G/D816V (HMC 1.2)	WT KIT	PDGFRα	PDGFRβ	CSF1R	FLT3	KDR
Bezuclastinib	14	121	> 10,000	> 10,000	> 10,000	> 1000	> 1000
Avapritinib	13	114	53	10	249	305	> 1000
BLU-263	6	355	21	6	161	345	> 1000

References: 1Guarnieri A. et al. Abstract P257 Molecular Cancer Therapeutics, 2021. 20(12_Supplement), P257-P257. 2Giles FJ et al, Leukemia. 2009;23(10):1698-1707. 3Liu S, Kurzrock R. Seminars in Oncology. 2015;42(6):863-875

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



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

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 Patient Reported Outcomes (PROs)
- Efficacy: DOR, TTR, PFS, OS, pure pathologic response
- PK/PD: plasma concentration of bezuclastinib, serum tryptase, KIT D816V burden

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Patient Demographics and Characteristics

- 16 patients enrolled; median age: 69 years; Range: 33-87

	Total (N=16)	50mg BID (N=4)	100mg BID (N=3)	200mg BID (N=4)	400mg QD (N=5)
Male, n (%)	**13 (81)**	3 (75)	3 (100)	3 (75)	4 (80)
ECOG PS 0-1, n (%)	**14 (88)**	4 (100)	3 (100)	4 (100)	3 (60)
AdvSM Subtype per Central Eligibility Review, n (%)					
ASM	**3 (19)**	1 (25)	0 (0)	0 (0)	2 (40)
SM-AHN	**12 (75)**	3 (75)	2 (67)	4 (100)	3 (60)
MCL	**1 (6)**	0 (0)	1 (33)	0 (0)	0 (0)
Prior therapy for AdvSM, n (%)[∫]					
Treatment Naïve*	**11 (69)**	3 (75)	2 (67)	3 (75)	3 (60)
Avapritinib	**3 (19)**	0 (0)	1 (33)	1 (25)	1 (20)
Midostaurin	**3 (19)**	0 (0)	1 (33)	1 (25)	1 (20)
***KIT* D816V in Whole Blood, Positive, n (%)**	**14 (88)**	4 (100)	3 (100)	3 (75)	4 (80)
Median KIT D816V VAF, % (range)[‡]	**10.6 (0.02-47.18)**	14.3 (0.02 – 37.4)	7.98 (7.04 – 32.28)	27.85 (8.7 – 47.18)	7.18 (0.93 – 13.48)
Median Bone Marrow MC Burden, % (range)	**30 (7-80)**	45 (20-70)	70 (30-80)	20 (7-30)	30 (10-80)
Median Serum Tryptase, ng/mL (range)	**178 (50-1578)**	334 (169-605)	253 (144-1578)	97 (67.9-121)	232 (50-370)

**Patients who have received no prior SM directed therapies*

[∫] Additional therapies included PEG interferon-α, cladribine, hydroxyurea, azacytidine, decitabine, brentuximab vedotin, and other

[‡] Includes patients with positive KIT D816V

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Safety and Tolerability of Bezuclastinib

Treatment Related Adverse Events in > 10% Patients and all Related SAEs

	Total (n=16)		TKI‡ Therapy Naïve (n=13)	Prior TKI‡ Exposure (n=3)	50 mg BID (n=4)	100 mg BID (n=3)	200 mg BID (n=4)	400 mg QD (n=5)
Preferred Term	**All grade**	**Grade ≥3**	**All grade**	**All grade**	**All grade**	**All grade**	**All grade**	**All grade**
Hair color changes	**4 (25)**	**0**	2	2	0	2	1	1
Taste disorder^	**4 (25)**	**0**	3	1	1	0	1	2
Neutropenia∫	**4 (25)**	**2 (13)**	4	0	1	1	1	1
Edema peripheral	**3 (19)**	**0**	1	2	0	0	1	2
Thrombocytopenia	**3 (19)**	**1 (6)**	3	0	0	1	0	2
Nausea	**2 (13)**	**0**	1	1	0	1	0	1
Fatigue	**2 (13)**	**0**	1	1	1	0	1	0
Vomiting	**2 (13)**	**0**	1	1	0	1	0	1
Anemia	**2 (13)**	**1(6)**	0	2	0	1	1	0
Hypersensitivity (mediator flare)#	**1 (6)**	**1(6)**	1	0	0	0	0	1

‡SM-directed therapy with midostaurin and avapritinib
^ includes pooled preferred terms of terms of Taste disorder and Dysgeusia
∫Includes pooled preferred terms of Neutropenia, Neutrophil count decreased, and WBC decreased
#Serious adverse event

- The majority of TEAEs were of low grade with one related SAE and no related Grade 4 events
- No related cognitive effects or bleeding events reported
- The majority of hematological TEAEs were of low grade, reversible and did not require dose modification
- No discontinuations with 3 patients dose reduced due to TEAEs; one re-escalated to randomized dose

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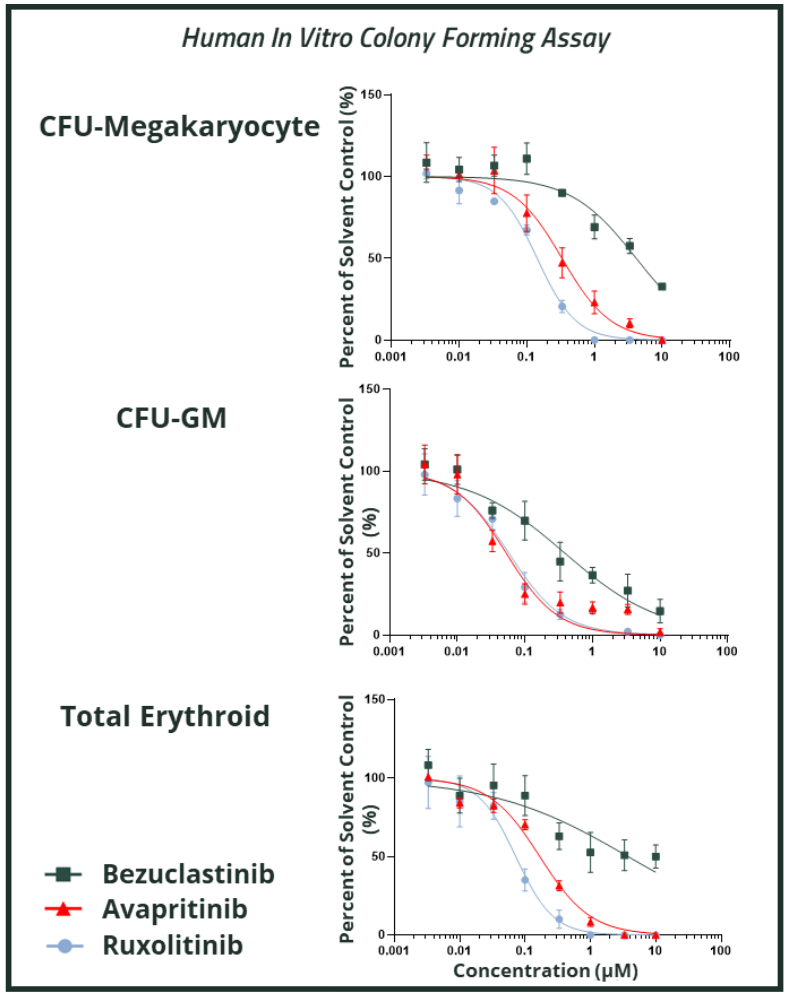
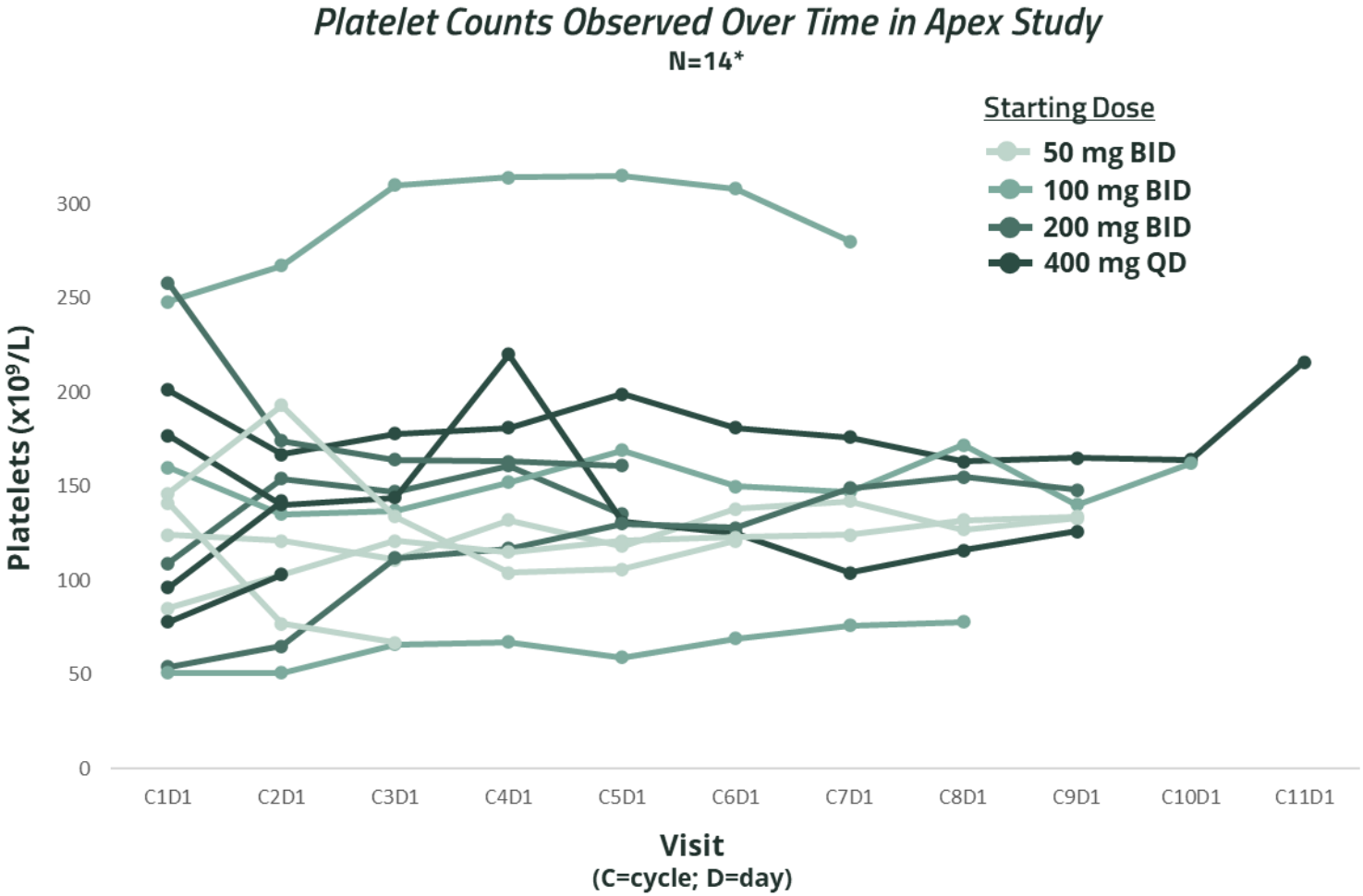
Limited Effect of Bezuclastinib on Platelet Counts in Apex Study, Supported by Preclinical Data





All patients in Apex were required to have platelet count ≥50 x 10^9/L for 2 weeks prior to the first dose of study drug
**Two patients excluded: (1) due to presence of essential thrombocythemia at baseline; (1) no post-baseline assessment*

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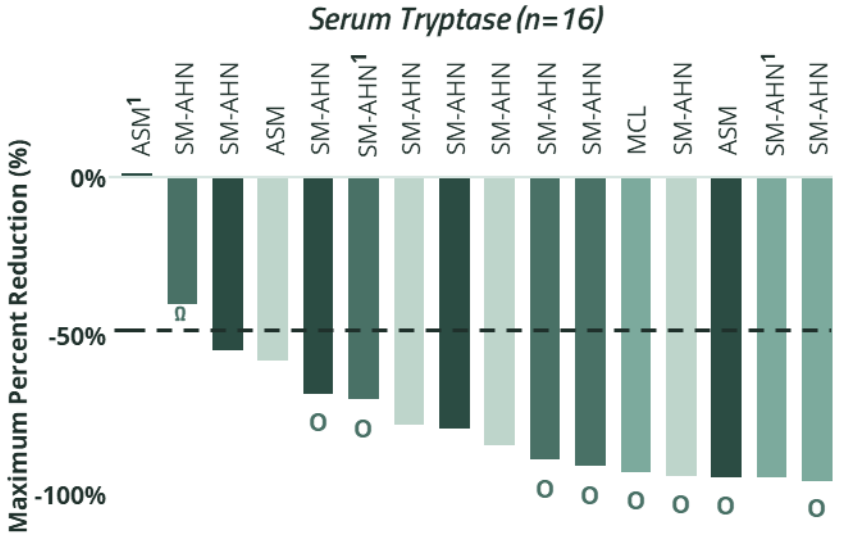
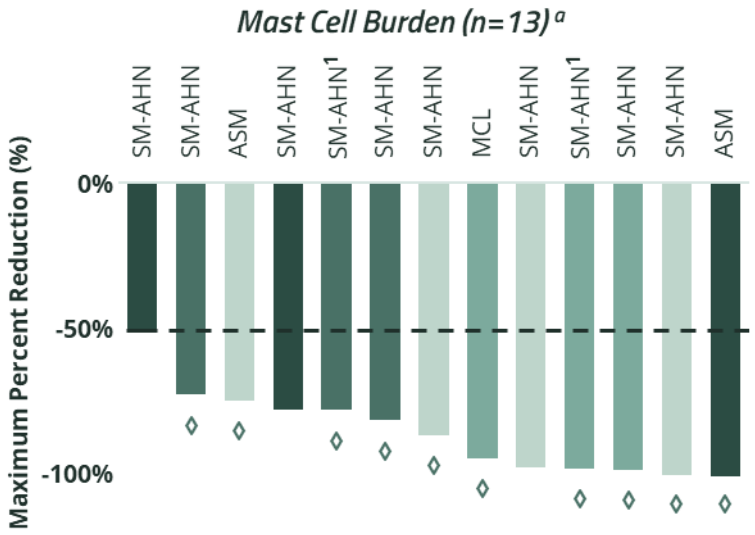
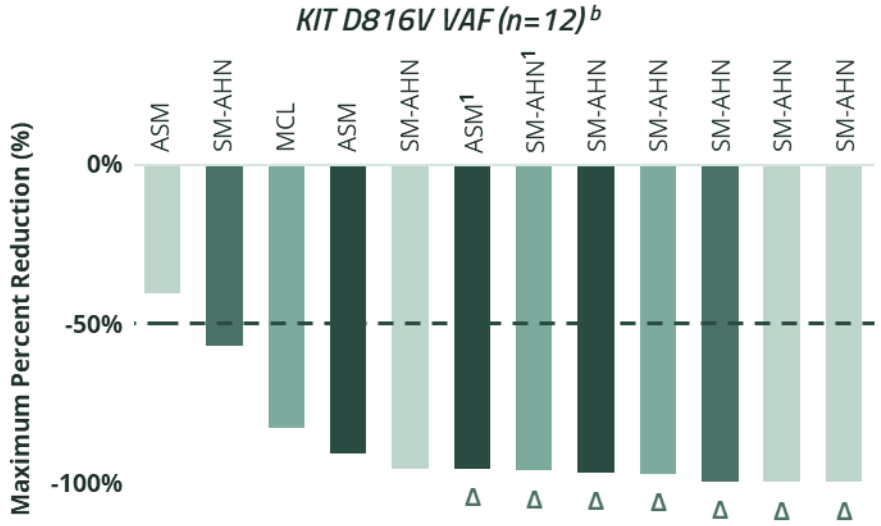
Bezuclastinib Demonstrates Reductions in Markers of Mast Cell Burden

- Serum Tryptase
  - 88% of patients achieved a ≥ 50% reduction
  - 85% median reduction
  - 50% achieved levels <20 ng/mL
- Bone Marrow MC Burden
  - 100% of patients with at least 2 cycles of treatment achieved a ≥ 50% reduction
  - 77% achieved complete clearance of mast cell aggregates by central review
- *KIT* D816V VAF
  - 92% of patients with at least 2 cycles of treatment achieved a ≥ 50% reduction





[a] *Three patients excluded: no post-baseline assessment available*



[b] *Four patients excluded: (2) KIT D816V negative at baseline; (2) no post-baseline assessment available*

Starting Dose
- 50 mg BID
- 100 mg BID
- 200 mg BID
- 400 mg QD

Milestone Achieved
- O < 20 ng/mL serum tryptase
- ◊ Complete clearance of mast cell aggregates
- Δ < 1% *KIT* D816V VAF

[1] *Prior avapritinib and midostaurin*

Ω *Discontinued after 2 doses of study treatment due to investigator decision (femur fracture)*

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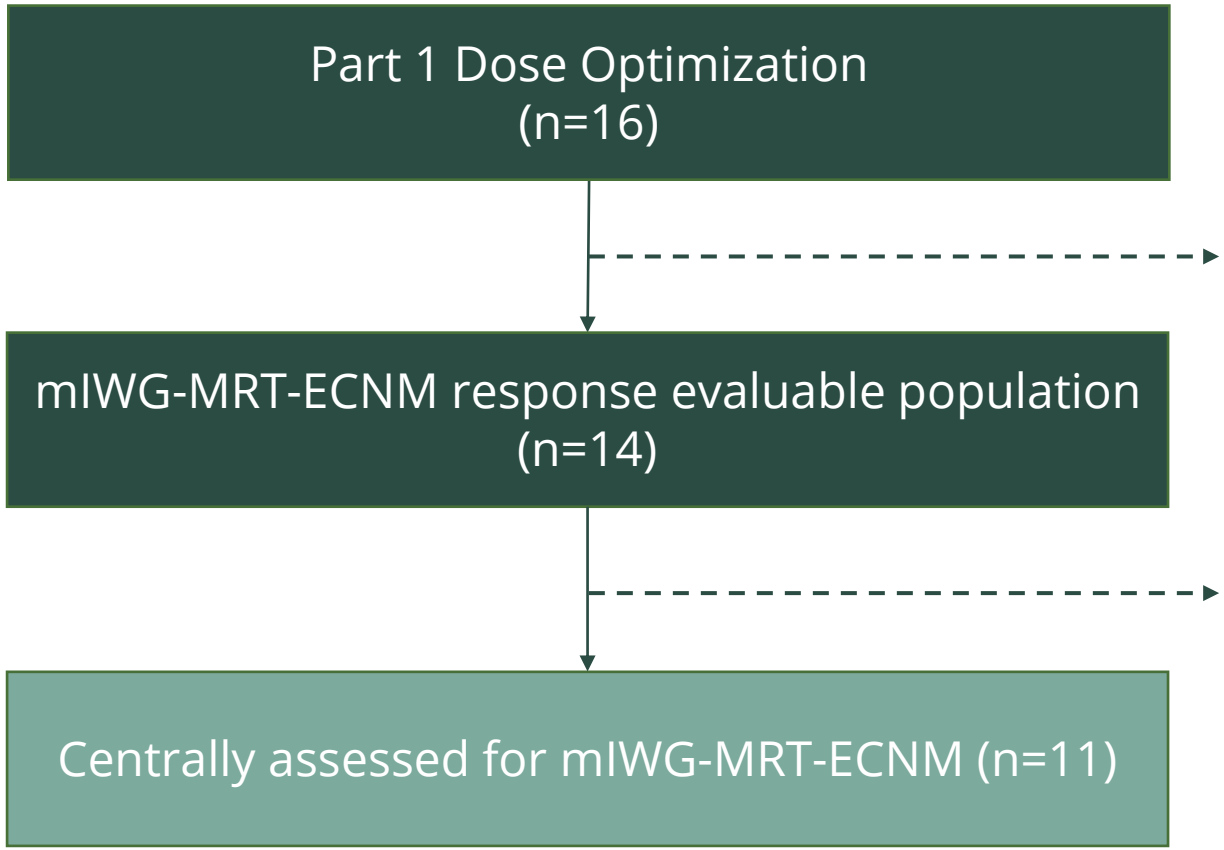
Patients included in mIWG-MRT-ECNM Response Evaluable Population



- **Patients inevaluable (n=2)**
  - n=1 no measurable C-finding at baseline
  - n=1 received confounding concomitant medication
- **Patients excluded (n=3)**
  - n=2 off study prior to first response timepoint
  - n=1 ongoing; has not reached first response timepoint

Response Assessment per mIWG-MRT-ECNM and PPR Criteria

Response Assessment	mIWG-MRT-ECNM Response Criteria*	Pure Pathological Response Criteria
Complete Remission (CR)	✓ Absence of neoplastic MC aggregates in bone marrow ✓ Serum tryptase ≤ 20 ng/mL ✓ Remission of peripheral blood counts ✓ Complete resolution of all mIWG C-findings	✓ Absence of neoplastic MC aggregates in bone marrow ✓ Serum tryptase < 20 ng/mL ✓ Remission of peripheral blood counts
Partial Remission (PR)	✓ Reduction of neoplastic MC in bone marrow by ≥ 50% ✓ Reduction of serum tryptase by ≥ 50% ✓ Resolution of ≥ 1 mIWG C-finding	✓ Reduction of neoplastic MC in bone marrow by ≥ 50% ✓ Reduction of serum tryptase by ≥ 50%
Clinical Improvement (CI)	✓ Resolution of ≥1 mIWG C-finding in the absence of CR, CRh, PR, or PD	Not a part of PPR Criteria

*confirmed response duration must be ≥ 12 weeks

Early Responses Observed by mIWG-MRT-ECNM and PPR Criteria

Best Response, n (%) * β (confirmed and unconfirmed)	Total (n=11)	mIWG-MRT-ECNM per CRRC Assessment (TKI‡ Therapy Naïve) (n=9)	mIWG-MRT-ECNM per CRRC Assessment (Prior TKI‡ Exposure) (n=2)
Overall response rate			
CR + CRh + PR + CI†	**8 (73)**	8 (89)	0 (0)
CR + CRh + PR	**6 (55)**	6 (67)	0 (0)
Complete Response (CR + CRh)	**2 (18)**	2 (22)	0 (0)
Partial Response (PR)	**4 (36)**	4 (44)	0 (0)
Clinical Improvement (CI)	**2 (18)**	2 (22)	0 (0)
Stable Disease (SD)	**3 (27)**	1 (11)	2 (100)

**3 patients pending confirmation of response are included: (2) PR; (1) CR in patients diagnosed with SM-AHN*
β mIWG-evaluable patients who have at least one post-baseline assessment are included
‡ SM-directed therapy with midostaurin and avapritinib
† Primary endpoint of Apex study

Best Response, n (%) α	Total (n=12)	PPR per Investigator Assessment (TKI‡ Therapy Naïve) (n=10)	PPR per Investigator Assessment (Prior TKI‡ Therapy) (n=2)
Overall response rate (CR + PR)	**9 (75)**	7 (70)	2 (100)
Complete Response (CR)	**3 (25)**	3 (30)	0 (0)
Partial Response (PR)	**6 (50)**	4 (40)	2 (100)
Stable Disease (SD)	**3 (25)**	3 (30)	0 (0)

α PPR-evaluable patients who have at least one post-baseline assessment are included.
‡ SM-directed therapy with midostaurin and avapritinib

- Median duration on treatment = 27 weeks (range: 0.3-40)
- First confirmed CRh by mIWG documented as early as 8 weeks and first confirmed CR as early as 20 weeks

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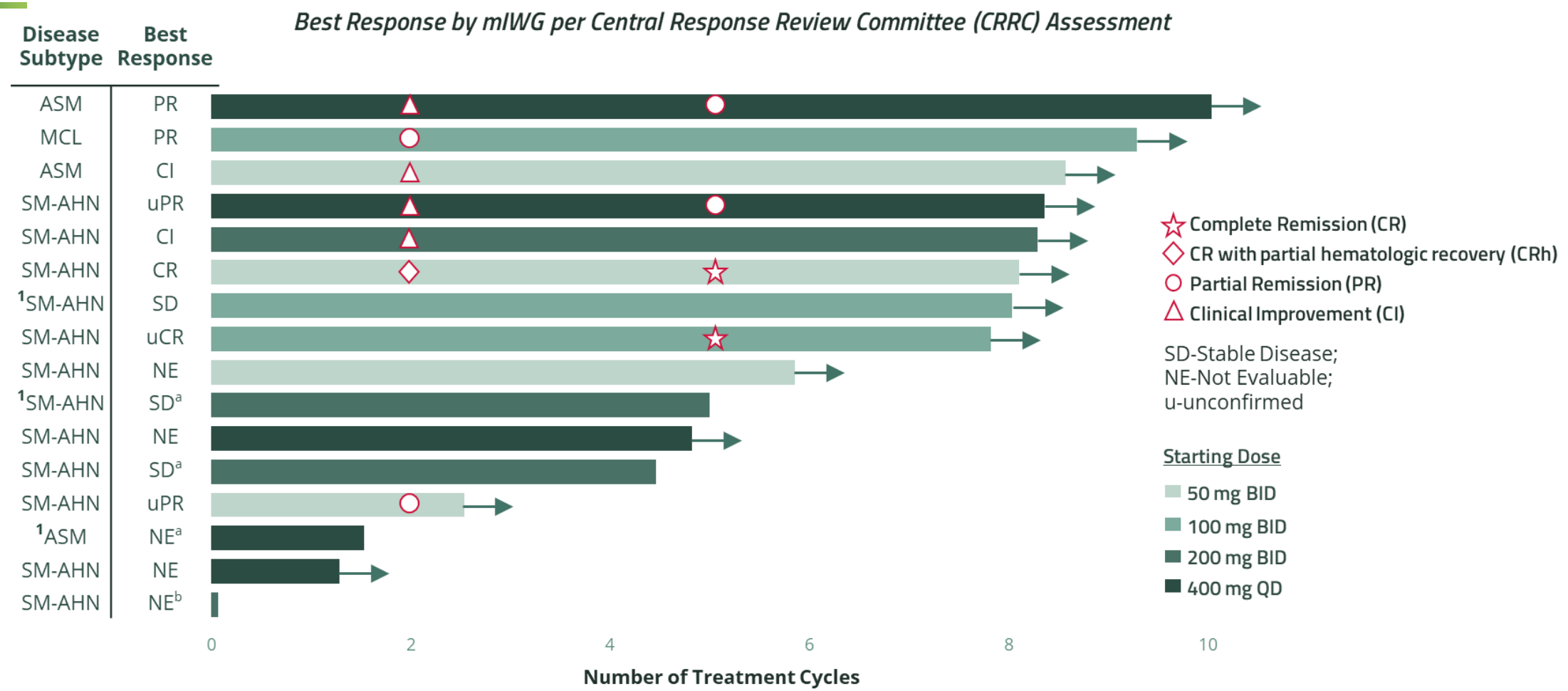
Early Responses Observed by mIWG-MRT-ECNM Criteria



[1] *Prior avapritinib and midostaurin.*

[a] *Discontinued due to disease progression*

[b] *Discontinued after 2 doses of study treatment due to investigator decision (femur fracture)*

Includes confirmed and unconfirmed responses

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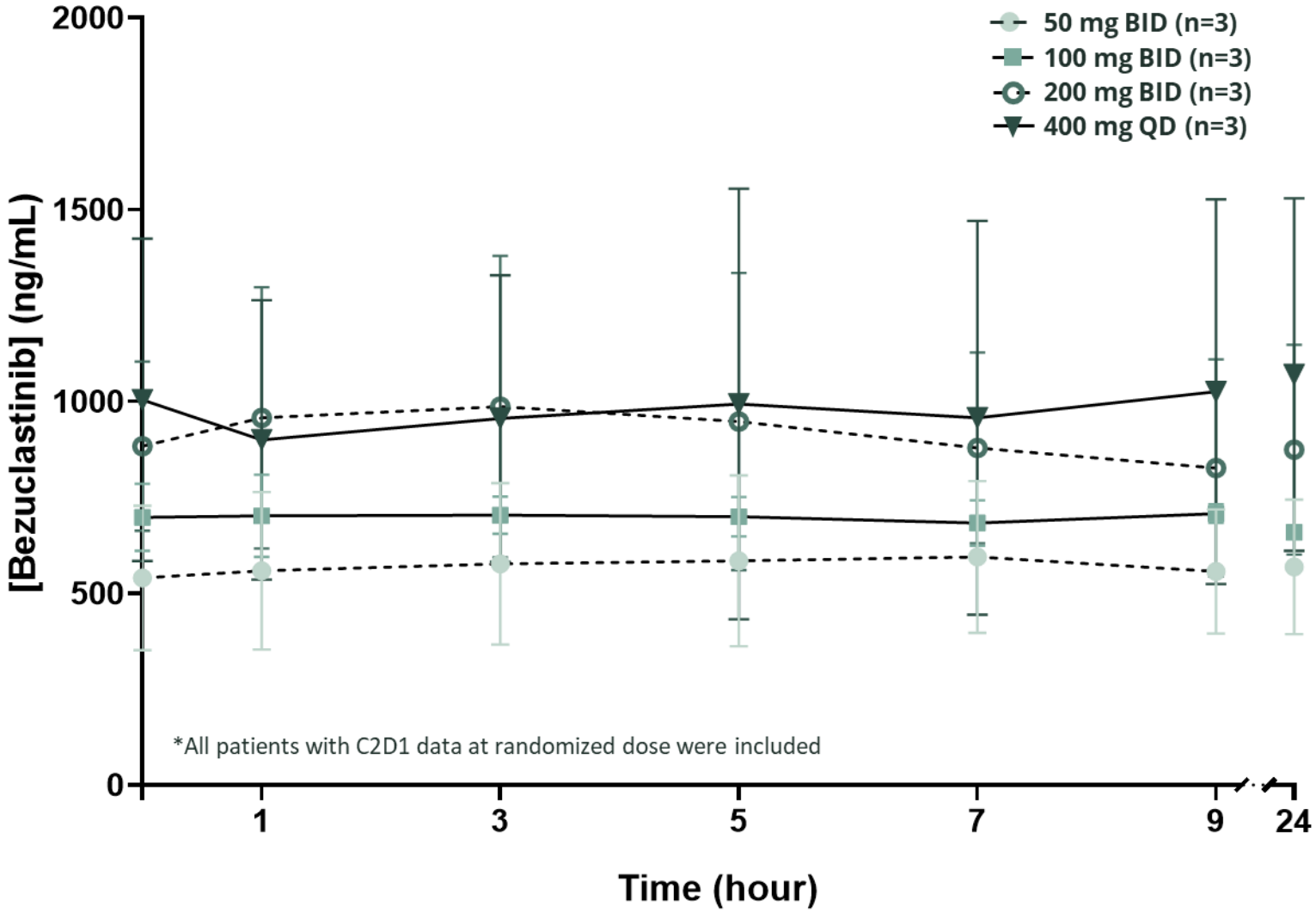
Dose Dependent Increase in Steady State (Cycle 2 Day 1) Bezuclastinib Exposure Regardless of BID or QD Dosing



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Bezuclastinib Clinical Data Summary

- **The highly potent and selective TKI bezuclastinib was generally well-tolerated across all dose levels and continues to demonstrate a differentiated safety profile**
  - No related cognitive effects or bleeding events reported
  - Limited effect of bezuclastinib on platelet counts in patients, supported by preclinical data
- **Treatment with bezuclastinib resulted in encouraging early signs of clinical activity demonstrated across all dose levels**
  - mIWG-MRT-ECNM: 89% overall response rate (CR + CRh + PR + CI) in TKI therapy-naïve patients and 73% in all patients at median follow up of 27 weeks
    - First confirmed CRh by mIWG as early as 8 weeks and first confirmed CR as early as 20 weeks
  - 88%, 92%, and 100% of patients with available data achieved a 50% reduction in serum tryptase, *KIT* D816V VAF, and bone marrow MC burden, respectively
- **Enrollment to Part 1 is ongoing**

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- Members of the Steering Committee: Jason R. Gotlib, Daniel J. DeAngelo, Deepti H. Radia, Cristina Papayannidis, Khalid Shoumariyeh
- Members of the Central Review Response Committee: Jason R. Gotlib, Daniel J. DeAngelo, Deepti H. Radia, Tracy George, Michael Deininger, Andreas Reiter, Gabrielle Hobbs, and Jay Patel

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