

Relationship between KIT inhibition by bezucblastinib and effects on disease burden in mouse models of systemic mastocytosis



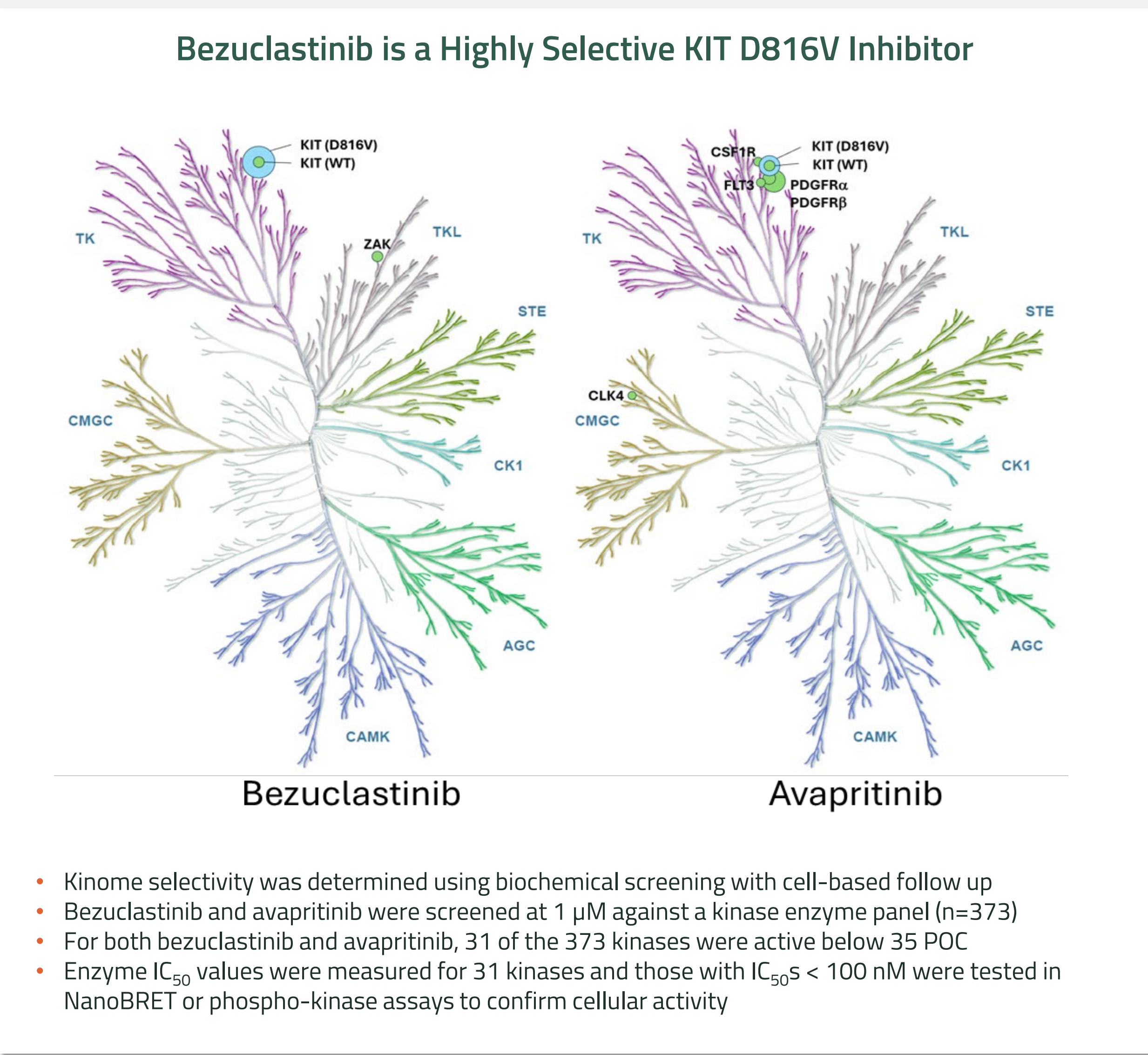
Poster #5531

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BACKGROUND

- Nonadvanced Systemic Mastocytosis (NonAdvSM) is largely driven by the KIT D816V mutation, causing constant KIT activation, tissue infiltration by mast cells, and excessive mediator release leading to inflammation¹
- The approval of the first KIT-targeted therapy, avapritinib (AVA), demonstrated proof-of-concept clinical efficacy in these patients, but effects on mast cell burden in blood and bone marrow are limited
- The KIT inhibition threshold required for optimal mutant clone clearance remains undefined and the impact of higher target engagement on molecular remission is unclear
- Bezuclastinib (BEZU) is a potent, selective oral KIT D816V inhibitor with a unique selectivity profile enabling high target engagement in NonAdvSM, as supported by results from Summit (NCT05186753)
- This work utilized nonclinical models to delineate in vivo target engagement and to correlate these findings to clinical target engagement observed in this indication

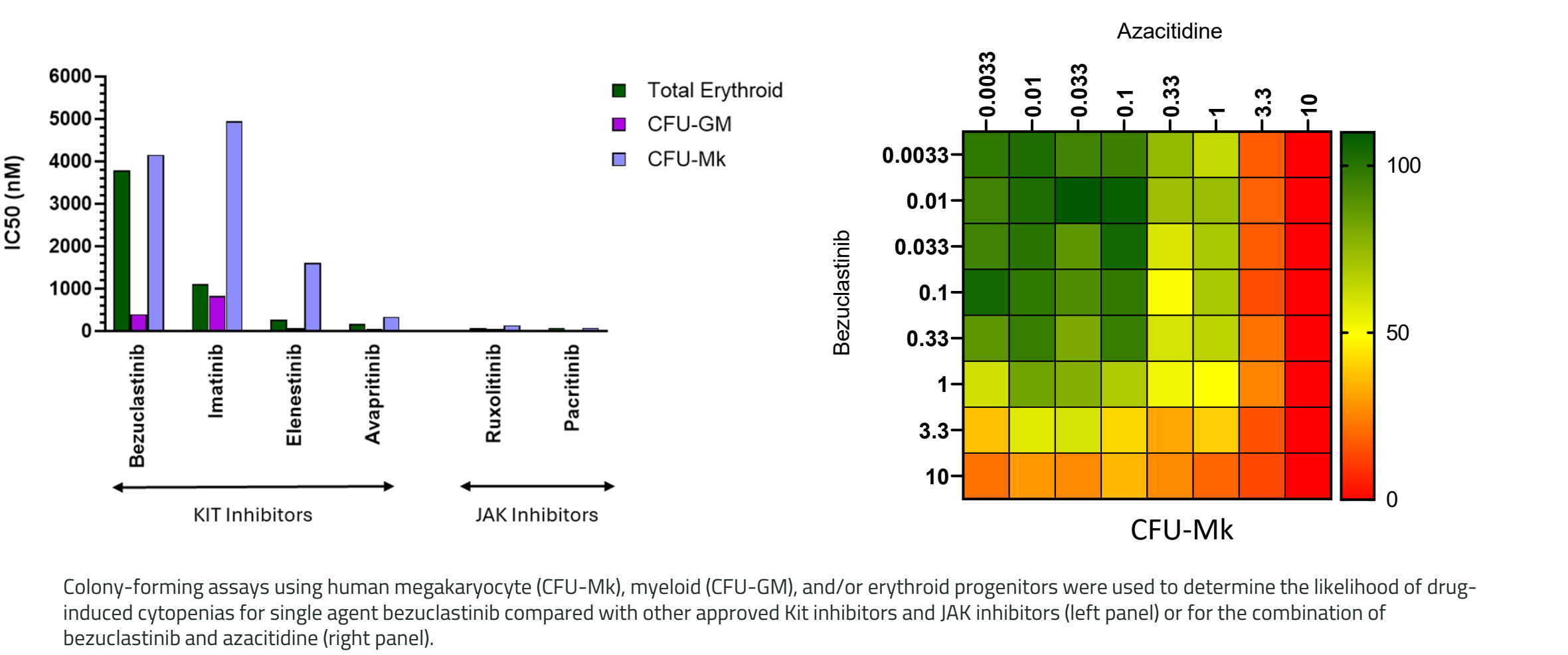


Bezuclastinib's Selectivity Profile is Unique Amongst Inhibitors Approved or in Development for Systemic Mastocytosis							
Compound	KIT V560G/D816V ¹ (HMC 1-2)	Cell IC ₅₀ (nM)					KDR ² (HEK-KDR)
		PDGFRα ² (H1703)	PDGFRβ ² (NH-3T3)	CSF1R ² (HEK-CSF1R)	FLT3 ² (HEK-FLT3)	KIT ¹ (M-07e)	
Bezuclastinib	14	>10,000	>10,000	>10,000	>1000	121	>1000
Avapritinib	13	53	10	249	305	114	>1000
Elenestinib	6	21	6	161	345	355	>1000
Midostaurin	316	301	88	542	17	191	>1000
Imatinib	>1000	75	247	1027	>1000	>1000	>1000
Within 10x potency of KIT-D816V Within 5x potency of KIT-D816V Potency < KIT-D816V							

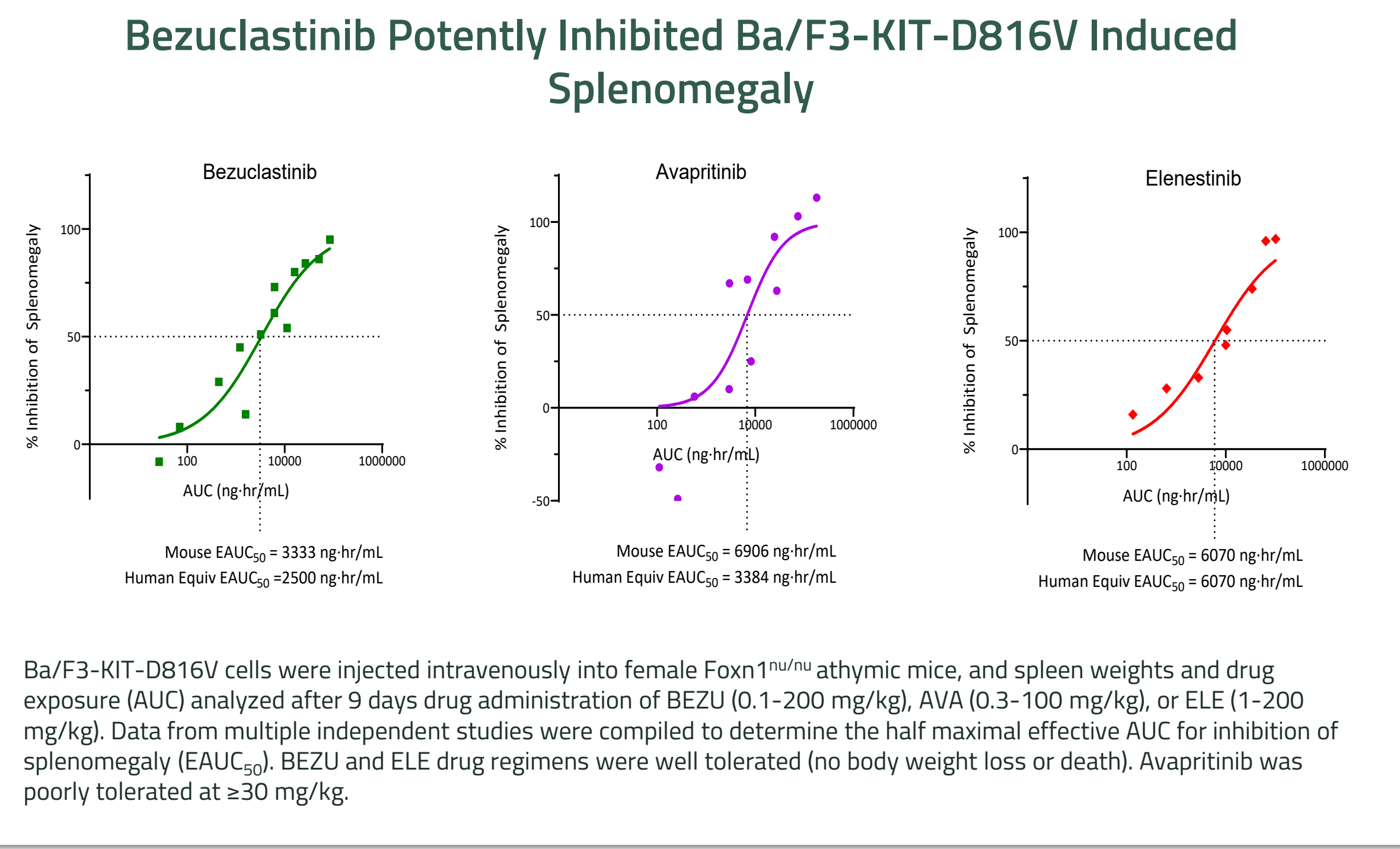
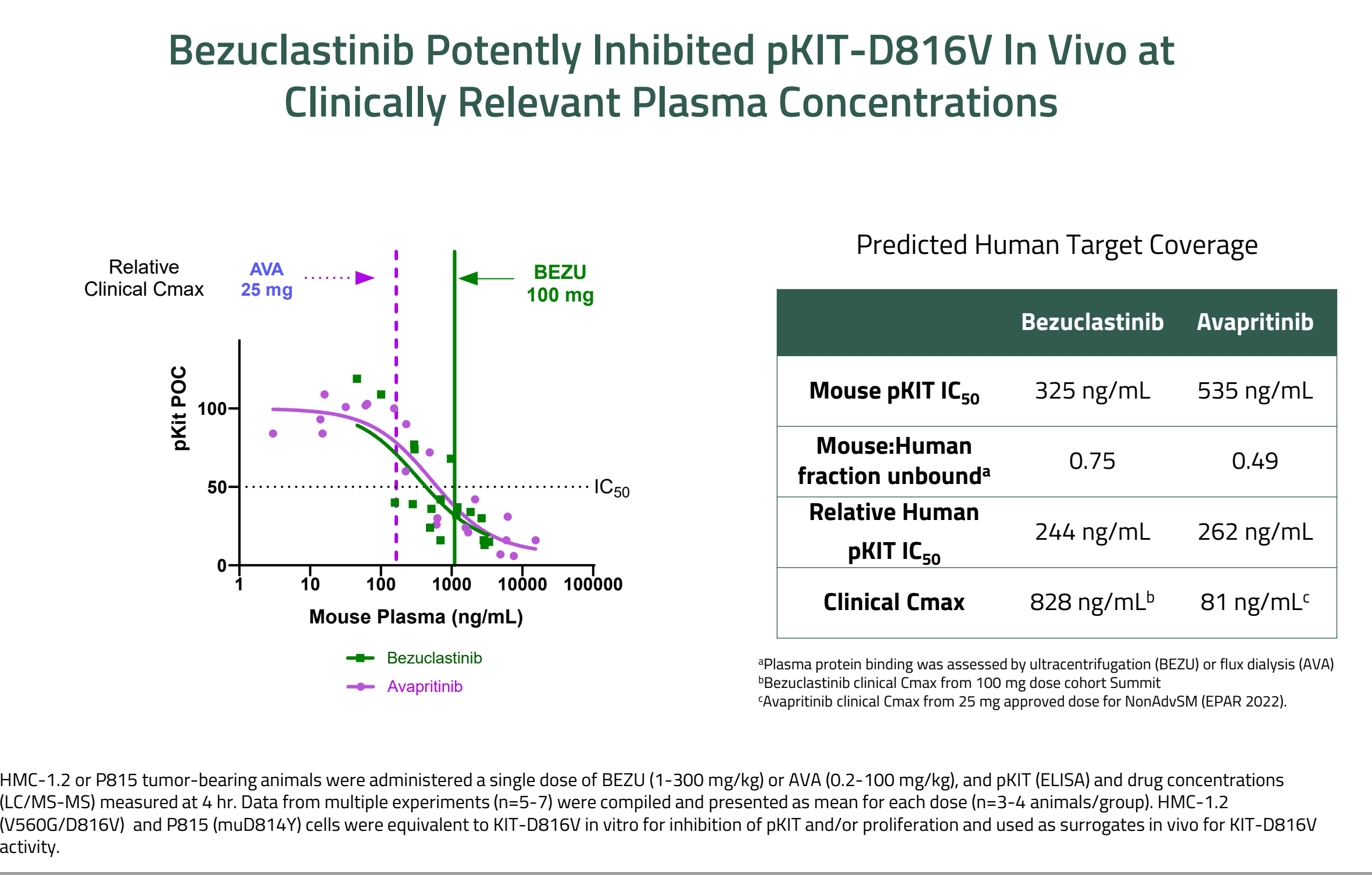
Guarnieri A., et al, Poster presented at: American Association for Cancer Research Annual Meeting; April 10, 2022

RESULTS

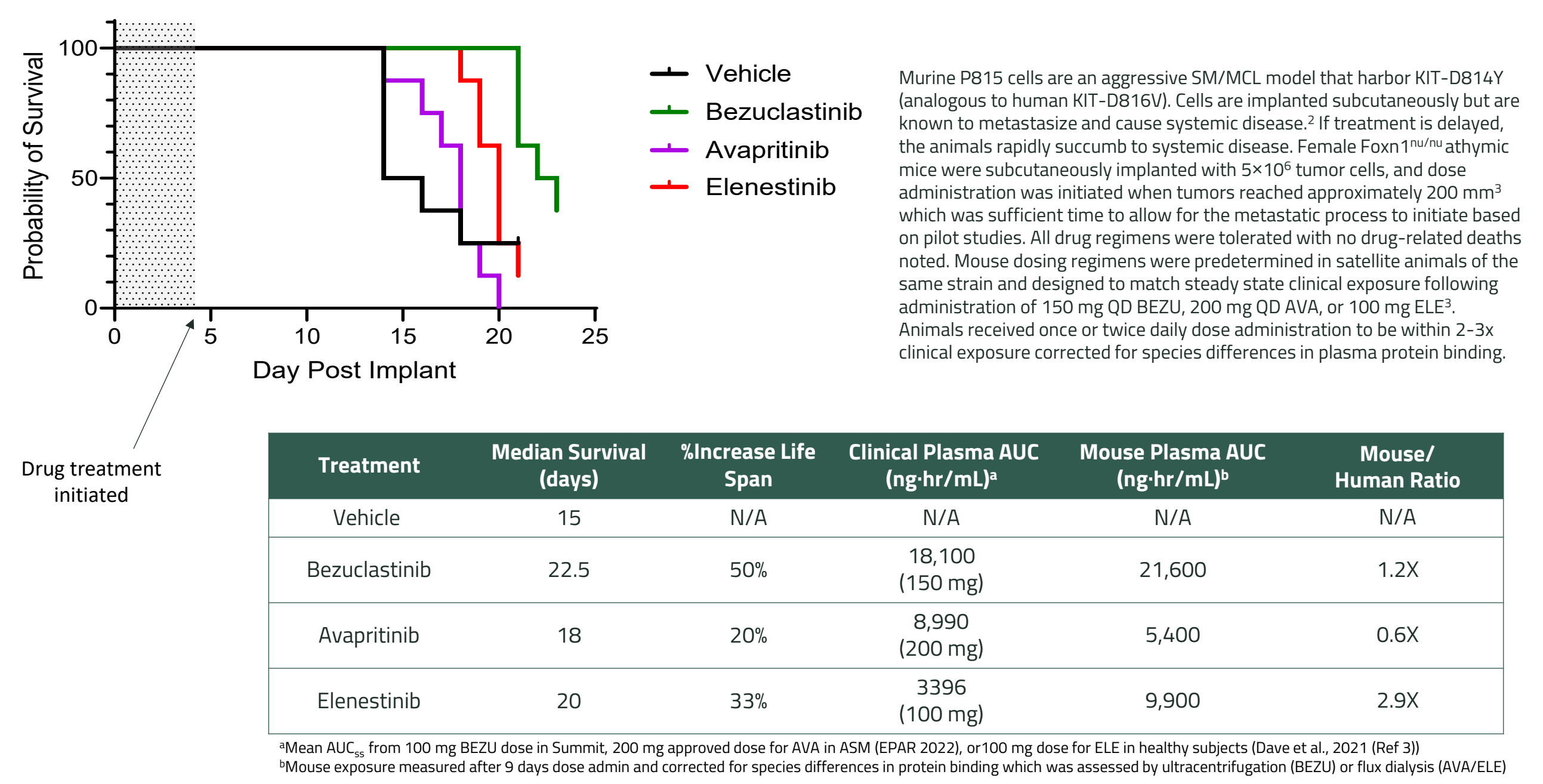
Bezuclastinib is Predicted to Have Less Myelotoxicity Compared to Other Kinase Inhibitors and is Non-Interactive in Combination with Azacitidine



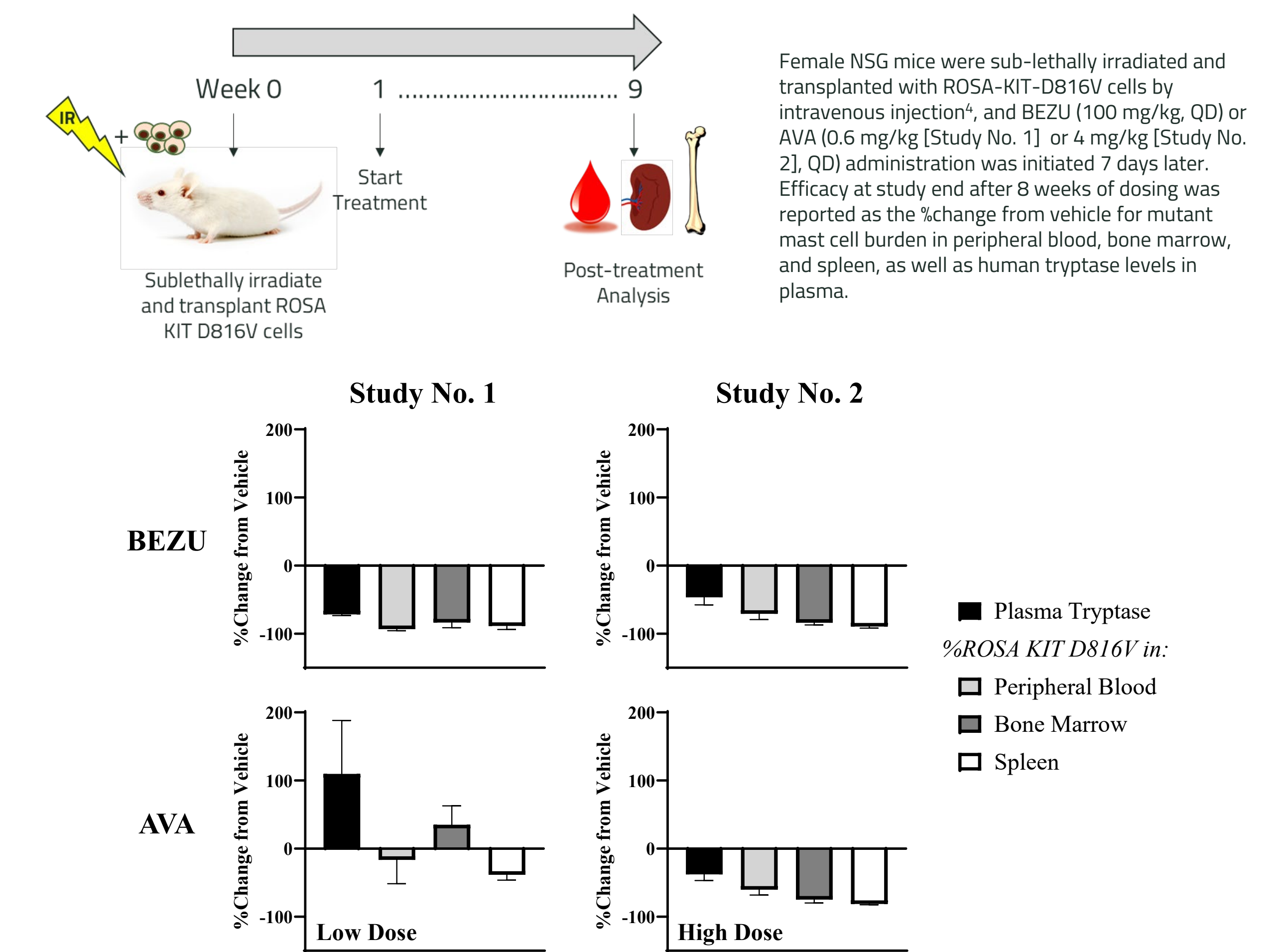
- Colony forming assays can be used to predict thrombocytopenia (CFU-Mk), neutropenia (CFU-GM), and anemia (total erythroid)
- Bezuclastinib had a limited effect on megakaryocytes, granulocytes/macrophages, and erythroid cells predicting a lower risk for hematotoxicity compared with other KIT inhibitors and other known myelosuppressive agents
- Dose-response matrix data demonstrated the percent inhibition of CFU-Mk relative to various doses of BEZU-AZA combo
- The drug combination data from CFU-Mk assays suggested that the combination of bezuclastinib with azacitidine is **non-interactive** with a Bliss synergy score of -6.32



Bezuclastinib Increased Life Span in a Murine Aggressive SM/MCL Survival Model



Bezuclastinib Lead to Significant Decreases in Mutant Mast Cell Burden and Reduced Human Plasma Tryptase in the ROSA Model of Systemic Mastocytosis



	Clinical Dose Level	Clinical Plasma AUC (ng-hr/mL)	Mouse Plasma AUC ^c (ng-hr/mL)	Mouse/Human Ratio
Study No. 1 (low dose AVA)				
Bezuclastinib	100 mg	17100 ^a	11775 ^c	0.7X
Avapritinib – 25 mg	25 mg	1548 ^b	1318 ^c	0.9X
Study No. 2 (high dose AVA)				
Bezuclastinib	100 mg	17100 ^a	16575 ^c	0.9X
Avapritinib – 200 mg	200 mg	8990 ^b	7105 ^c	0.8X

^aMean exposure at 100 mg in Summit
^bMean for avapritinib exposure administered at 25 mg or 200 mg (EPAR, 2022)
^cBezuclastinib and avapritinib were administered QD, PO, for study duration plasma measured at study end and displayed here as corrected for species differences in plasma protein binding.

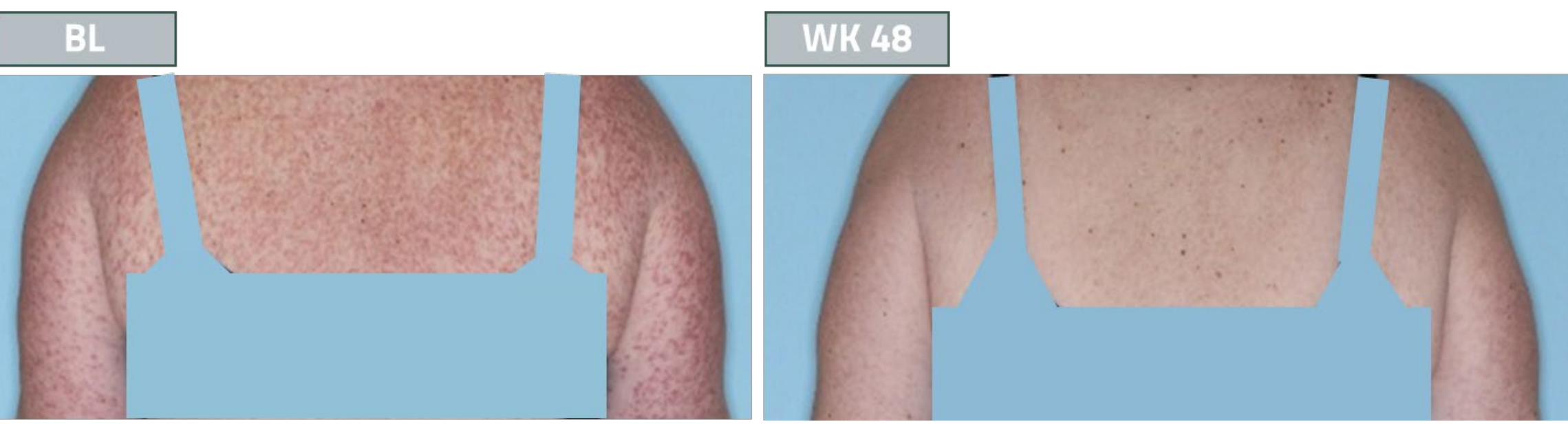
- Efficacy in the ROSA model was evaluated using mouse dose levels selected to match human exposures reported in NonAdvSM or AdvSM clinical studies, specifically 100 mg in the Summit Trial for BEZU and 25 mg or 200 mg AVA to represent approved doses in NonAdvSM and AdvSM, respectively (EPAR, 2022)
- Both drugs were well tolerated and were within 0.7-0.9x reported clinical exposures at study end
- BEZU treatment compared to vehicle resulted in statistically significant inhibition of mutant mast cell burden in peripheral blood, bone marrow, and spleen, and reduced human plasma tryptase (-72%). The positive control, AVA, was relatively ineffective in this model when matched to the approved nonAdvSM dose of 25 mg
- A second study was performed with the AVA dose increased to match higher exposures reported at the approved dose in AdvSM (200 mg). At this higher exposure, statistical significance was observed confirming higher target coverage is necessary to control disease in this model

In the Summit clinical trial, 100mg bezuclastinib QD reduced mast cell burden, improved symptoms, and demonstrated a favorable safety profile

- A patient case of a 44 yo woman randomized to bezuclastinib 100mg QD is shown below

	BL	Wk 12	Wk 24	Wk 48	% Decrease BL → Wk48
Tryptase (ng/mL)	39.4	3.5	2.7	3.4	91%
KIT D816V VAF (%)	0.19	0.03	Not Detected	0.03	84%
BM MC Burden (%)	10		1		90% ¹
CD25 Expression (%)	100		0		100% ¹
MS2D2 TSS (0 – 110)	67.9	29.4	27.8	22	68%
Most Severe Domain: Neurocognitive (0-10)	7.8	3.4	2.7	2.8	65%

¹ BM not collected at week 48 for this patient, so % reduction is based on week 24



- During the study, patient experienced G1 (mild) treatment related adverse events
- Patient remains on treatment more than 1 year with continued benefit
- At Week 24, the patient demonstrated normalization of objective measures of disease and improvement in symptoms

CONCLUSIONS

- Bezuclastinib is a potent and selective inhibitor of KIT-D816V, with no activity demonstrated against closely related kinases
- Bezuclastinib has less predicted heme tox compared with other approved KIT inhibitors and is non-interactive in combination with azacitidine
- Bezuclastinib potently inhibits pKIT-D816V and KIT-D816V driven splenomegaly in vivo when dosed to clinically relevant exposures. This activity drives an increased life span in a KIT-D814Y driven murine survival model
- Bezuclastinib dosed to match clinical exposures in NonAdvSM reduces mutant mast cell burden in all tissue compartments by 70-90% in the ROSA Model of Systemic Mastocytosis. Similar depth of response is observed in clinical case studies at similar exposures
- Overall, these analyses suggest that while partial inhibition of KIT achieved clinically may yield a measurable clinical effect, substantially higher target coverage is likely required to observe significant impact on clonal mast cell expansion

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