Efficacy of a highly potent and selective KIT V654A inhibitor for treatment of imatinib-resistant GIST

Poster Number
LB205

Alexandra Grassian,[1] Joseph Kim,[1] Omar Ahmad,[1] Kevin Barvian,[1] Alison Davis,[1] Tom Dineen,[1] Wei Hu,[1] Ebby Job,[1] Ludivine Moine,[1] Kate Newberry,[1] Maria Roche,[1] Doug Shorten,[1] Yeon Sook Choi,[1] Francis Wolenski,[1] Sebastian Bauer,[2] Cesar Serrano,[3] Jonathan Trent,[4] Suzanne George[5]

[1]Blueprint Medicines Corporation, Cambridge, MA, USA; [2]Westdeutsches Tumorzentrum Essen, Department of Medical Oncology, Essen, Germany; [3]Vall d'Hebron Institute of Oncology, Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain; [4]University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL, USA; [5]Sarcoma Center, Dana Farber Cancer Institute, Department of Medical Oncology, Boston, MA, USA.

Background

- Gastrointestinal stromal tumor (GIST) is the most common type of sarcoma, with an annual incidence of 0.70 per 100,000 people in the United States[1,2]
- Approximately 80% of patients with GIST present with primary mutations in the c-*KIT* oncogene at exon 9 or 11 (**Table 1**), which leads to constitutive, ligand-independent activation of the KIT receptor tyrosine kinase[2,3]
- For patients with metastatic GIST, frontline therapy with imatinib is effective, with a response rate of approximately 51–54% and median progression-free survival (PFS) of 19–23 months, in a molecularly unselected population[4]
- Agents that are approved for advanced GIST, without molecular selection, after progression on imatinib, include sunitinib, regorafenib, and ripretinib; however, response rates are less than 10% with PFS of approximately 5–6 months[5–7]
- On-target resistance mutations in the *KIT* oncogene frequently occur following treatment with tyrosine kinase inhibitors (TKIs), such as those in exon 17, exon 13, and less commonly in exon 14[8–10] (**Figure 1**)
- Several KIT inhibitors potently target the exon 17 resistance mutations (avapritinib and ripretinib); however, there remains an important medical need for potent and specific inhibitors that target the exon 13 resistance mutation
- Here we report the antitumor activity of avapritinib in patients with GIST harboring the *KIT* exon 13 (V654A) secondary resistance mutation, and investigate the activity of newly developed TKIs, BLU5675 and BLU7444, which were designed to target the KIT V654A mutation

Table 1: Molecular classification of GIST[3,10]

Gene/exon	Primary mutation frequency (%)	Secondary mutation frequency (%)
KIT	**70–80**	
Exon 9	10	
Exon 11	60–70	
Exon 13	1	56
Exon 17	1	41
PDGFRα	**5–10**	
Exon 12	1	
Exon 14	<1	
Exon 18	6	3
Wildtype	**10–15**	

Figure 1: Secondary mutations drive resistance to GIST treatment[8,9,11,12]

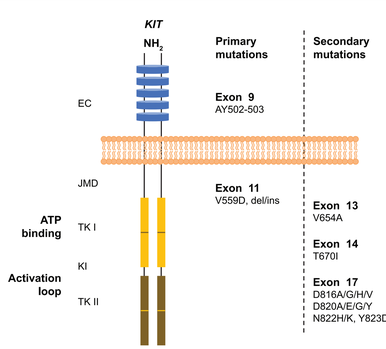
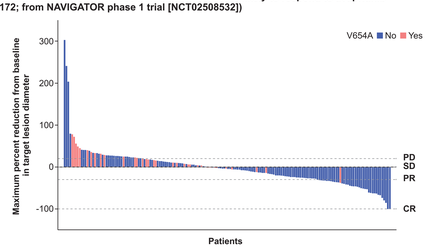


Figure adapted from Hapkova I et al. Gastrointestinal stromal tumour: From the clinic to the molecules. *J Cancer Res Ther.* 2014;2:54–67.

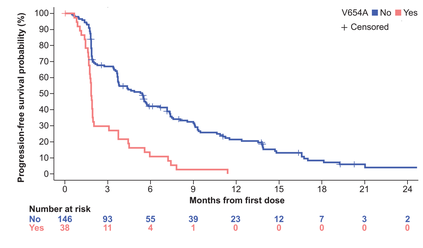
Results

Figure 2: Patients with GIST harboring the *KIT* V654A mutation had poorer outcomes when treated with avapritinib

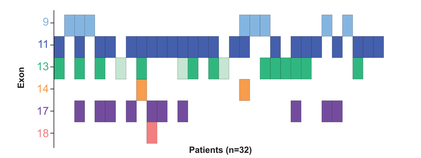
A. Patients with *KIT* exon 13 V654A mutation were less likely to respond to avapritinib (n=172; from NAVIGATOR phase 1 trial [NCT02508532])



B. Progression-free survival (PFS) was shorter in patients with the *KIT* V654A mutation (n=184; from NAVIGATOR phase 1 trial [NCT02508532])



C. End of treatment (EOT) mutation data showed an emergence of the *KIT* V654A mutation in patients who progressed on avapritinib (from VOYAGER phase 3 trial [NCT03465722])



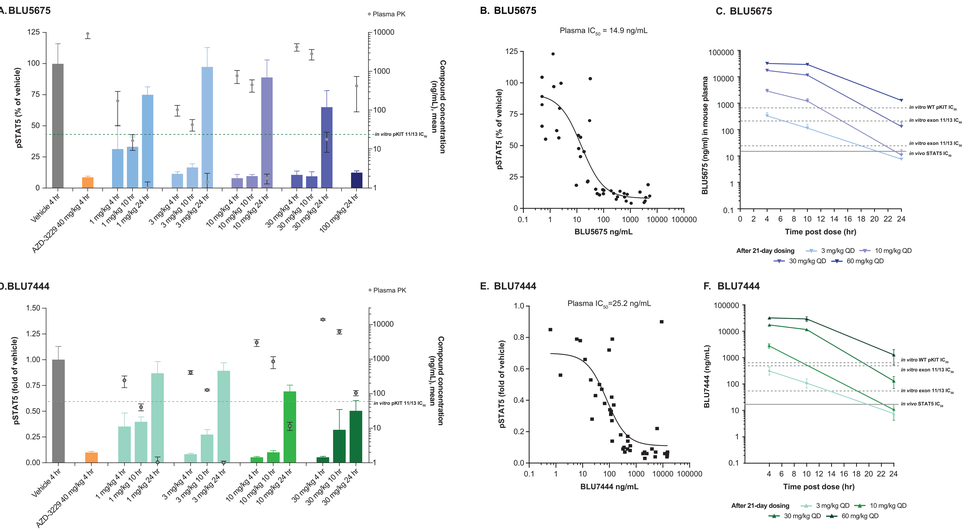
Changes in (A) tumor burden and (B) PFS in avapritinib-treated patients with GIST harboring the *KIT* V654A mutation. *Post hoc* analyses on the efficacy of avapritinib in patients with GIST harboring the *KIT* V654A mutation from the NAVIGATOR phase 1 trial (NCT02508532), measured per mRECIST 1.1. NGS was used to correlate the presence of V654A mutation with tumor regression and PFS. **(C) EOT mutation data.** NGS of ctDNA from patients in the VOYAGER phase 3 trial (NCT03465722) was used to assess the acquisition of the V654A mutation while on treatment. Patients in the VOYAGER study who had an exon 17 mutation and were negative for V654A mutation at the start of treatment, who showed response to avapritinib (PR) or had SD, and then progressed, and for whom an EOT sample was available were examined. Only patients with detectable *KIT* mutations at EOT in exon 9, 11, 13, 14 or 17 are shown. Twelve out of 32 patients had a detectable V654A mutation at EOT (highlighted in darker green).
CR, complete response; ctDNA, circulating tumor DNA; EOT, end of treatment; mRECIST 1.1., modified Response Evaluation Criteria in Solid Tumors, version 1.1; NGS, next-generation sequencing; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 2: BLU5675 and BLU7444 are potent inhibitors of KIT V654A mutations at concentrations which spare wildtype (WT) KIT

	pKIT (11/13) IC_{50} (nM)	pKIT (WT) IC_{50} (nM)	KIT (WT) proliferation IC_{50} (nM)	pPDGFRb (WT) IC_{50} (nM)	S-score (10) @ 3 mM
BLU5675	3.5	62 (18x)	189	1180 (340x)	0.025
BLU7444	6.0	95 (16x)	311	1360 (230x)	0.060
Imatinib	320	276 (0.9x)	164	188 (0.6x)	0.025
Sunitinib	4.8	0.7 (0.1x)	6.2	58 (12x)	0.228
Regorafenib	153	53 (0.3x)	93	193 (1.3x)	0.091
Avapritinib	298	99 (0.3x)	98	30 (0.1x)	0.035
Ripretinib	27	14 (0.5x)	25	24 (0.9x)	0.203

IC_{50}, half-maximal inhibitory concentration; pKIT, phosphorylated KIT; pPDGFRb, phosphorylated PDGFRb; WT, wildtype.

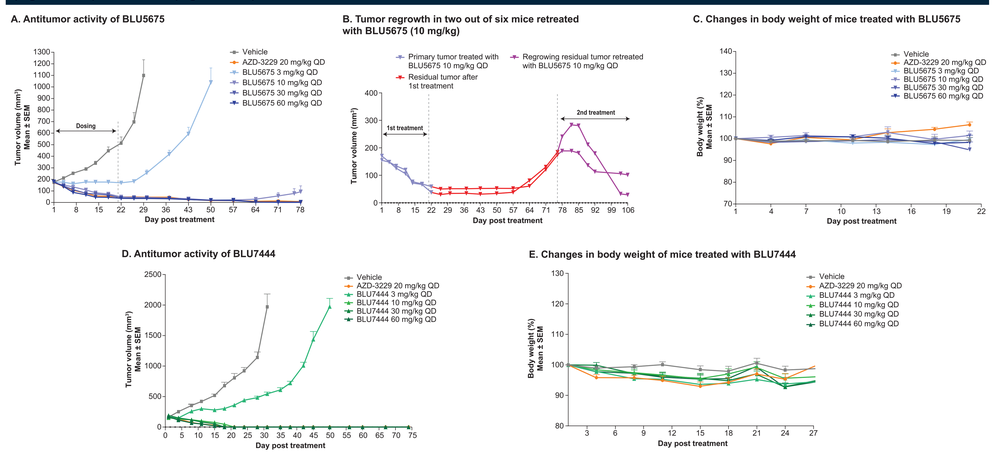
Figure 3: Exposure and inhibition of STAT5 phosphorylation with BLU5675 (Figure 3A–B) and BLU7444 (Figure 3C–D) were dose-dependent



(A) Plasma concentration-time profile, and (B) pSTAT5 PD modulation, and (C) Plasma concentration of BLU5675. (D) Plasma concentration-time profile, (E) pSTAT5 pharmacodynamic modulation, and (F) Plasma concentration of BLU7444. For (A) and (D) AZD-3229, a potent KIT/PDGFRα inhibitor for treatment of GIST, used as a control.[13] PK/PD data were examined using a mast cell leukemia model harboring mutations in *KIT* exon 11 and V654A. NOD/SCID tumor bearing mice were administered a single dose of compound and samples were harvested for PK/PD 4hr after dose.
IC_{50}, 90% inhibitory concentration; NOD/SCID, nonobese diabetic/severe combined immunodeficiency; PK/PD, pharmacokinetics/pharmacodynamics.

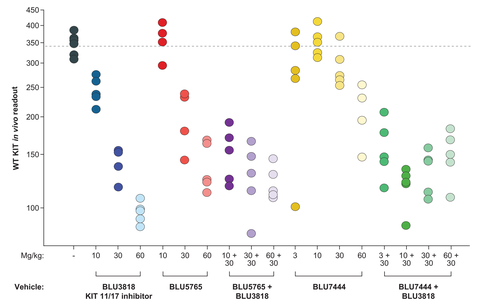
- Tumor regrowth occurred in two mice treated with BLU5675 10 mg/kg QD. Both mice received an additional treatment of BLU5675 10 mg/kg (starting at day 76) which led to tumor regression, indicating these tumors remain dependent on KIT signaling (**Figure 4A and B**)

Figure 4: Sustained antitumor activity in a HMC 1.1 CDX mouse model carrying an exon 11/13 mutation was observed with oral daily administration of BLU5675 (Figure 4A–C) or BLU7444 (Figure 4D–E)



(A) Antitumor activity, (B) Tumor regrowth, and (C) Changes in body weight of BLU5675. (D) Antitumor activity, and (E) Changes in body weight of BLU7444. The *in vivo* antitumor activity of BLU5675 (A, B and C) and BLU7444 (D and E) were evaluated in a HMC 1.1 cell line-derived xenograft (CDX) model carrying an exon 11/13 mutation. Mice were divided into groups of 6 and treated with BLU5675 or BLU7444 at doses of 3–60 mg/kg once daily (QD) for 21 and 27 days respectively. SEM, standard error of the mean.

Figure 5: WT KIT toxicity was not exacerbated due to treatment with BLU5675 or BLU7444



Conclusions

- Several agents are approved for advanced GIST, without molecular selection, after progression on imatinib, including sunitinib, regorafenib, and ripretinib; however, there are no potent and specific inhibitors that target the KIT V654A resistance mutation
- In the NAVIGATOR trial (NCT02508532), patients with GIST harboring the *KIT* V654A mutation experienced poorer responses and shorter PFS with avapritinib treatment when compared to other patients on the trial, highlighting an important medical need in this subset of patients
- BLU5675 and BLU7444 were designed to selectively target the KIT V654A mutation
- BLU5675 and BLU7444 are potent, dose-dependent, and selective inhibitors for the KIT V654A mutation at doses that spare WT KIT
- Preclinically, oral daily administration of BLU5675 or BLU7444 as single agents resulted in prolonged antitumor activity
- These preclinical findings suggest these novel KIT inhibitors have the potential to be used in combination therapy for patients with imatinib-resistant GIST harboring the *KIT* V654A mutation

References

1. Patel N et al. *Cureus.* 2019;11(2):e4120.
2. NCCN National Comprehensive Cancer Network. Gastrointestinal Stromal Tumors (GISTs) (Version 1). 2022. https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf. Published 2022. Accessed February 11, 2022.
3. Lopes LF et al. *J Cell Mol Med.* 2010;14(1-2):42–50.
4. GLEEVEC® (imatinib mesylate). Prescribing Information. August 2020. Novartis Pharmaceuticals Corporation.
5. QINLOCK® (ripretinib). Prescribing Information. May 2020. Deciphera Pharmaceuticals LLC.
6. STIVARGA® (regorafenib). Prescribing Information. February 2022. Bayer.
7. SUTENT® (sunitinib malate). Prescribing Information. August 2021. Pfizer.
8. Lee JH et al. *J Gastrointestin Liver Dis.* 2013;22(4):413–418.
9. Heinrich MC et al. *J Clin Oncol.* 2008;26(33):5352–5359.
10. Hemming ML et al. *Ann Oncol.* 2018;29(10):2037–2045.
11. Nishida T et al. *Gastric Cancer.* 2016;19(1):3–14.
12. Hapkova I et al. *J Can Res Ther.* 2014;2(3):54–67.
13. Banks E et al. *Sci Transl Med.* 2020;12(541).

Acknowledgements

Medical writing support was provided by Kyle Wild, MSc, and editorial support was provided by Travis Taylor, BA, all of Paragon, Knutsford, UK, supported by Blueprint Medicines Corporation, Cambridge, MA, according to Good Publication Practice guidelines.

Disclosures

A Grassian, J Kim, K Barvian, T Dineen, W Hu, E Job, L Moine, K Newberry, M Roche, D Shorten, and F Wolenski are current employees and shareholders of Blueprint Medicines Corporation. O Ahmad, A Davis, and Y S Choi are former employees and current shareholders of Blueprint Medicines Corporation. S Bauer has received research funding from Blueprint Medicines Corporation, Incyte, Novartis; served on scientific advisory boards for Blueprint Medicines Corporation, ADC Therapeutics, Eli Lilly & Co., Novartis, Daiichi-Sankyo, Plexxikon, Deciphera, Exelixis, Janssen-Cilag, and CME-related; and received honoraria from Novartis, Pfizer, Bayer, Eli Lilly & Co., PharmaMar, and GlaxoSmithKline. C Serrano has received research funding from Deciphera and Pfizer, has served on scientific advisory boards for Blueprint Medicines Corporation and Deciphera, received honoraria from Blueprint Medicines Corporation and Bayer, and has been reimbursed travel expenses from Pfizer, Bayer, Eli Lilly & Co., Novartis, and PharmaMar. J Trent acted as consultant to Blueprint Medicines Corporation, Deciphera Pharmaceuticals, Daiichi-Sankyo, Epizyme, Foghorn Therapeutics, C4 Therapeutics, Bayer, and Agios. S George has received consulting fees from Deciphera, Bayer, KayoThera, Ayala Pharmaceuticals, and Blueprint Medicines Corporation; received personal fees from Research to Practice, and MORE Health; received grants from Pfizer, Novartis, Bayer, ARIAD, Blueprint Medicines Corporation, Deciphera, SpringWorks Therapeutics, Merck, Eisai, TRACON Pharmaceuticals, outside the submitted work; owns stock in Abbott Laboratories; and receives royalties from UpToDate. This research was funded by Blueprint Medicines Corporation. Blueprint Medicines Corporation reviewed and provided feedback on the poster. The authors had full editorial control of the poster and provided their final approval of all content.

Poster available for download at:

Presented at AACR Meeting 2022, April 8–13, 2022. Please contact medinfo@blueprintmedicines.com for permission to reprint and/or distribute