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

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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, ligandindependent 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 population⁴
- 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 148-10 (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} Primary mutation frequency (%) Secondary mutation frequency (%) 70-80 Exon 9 60–70 Exon 11 Exon 13 Exon 17 PDGFRα 5–10 Exon 12 Exon 14 Exon 18 10–15

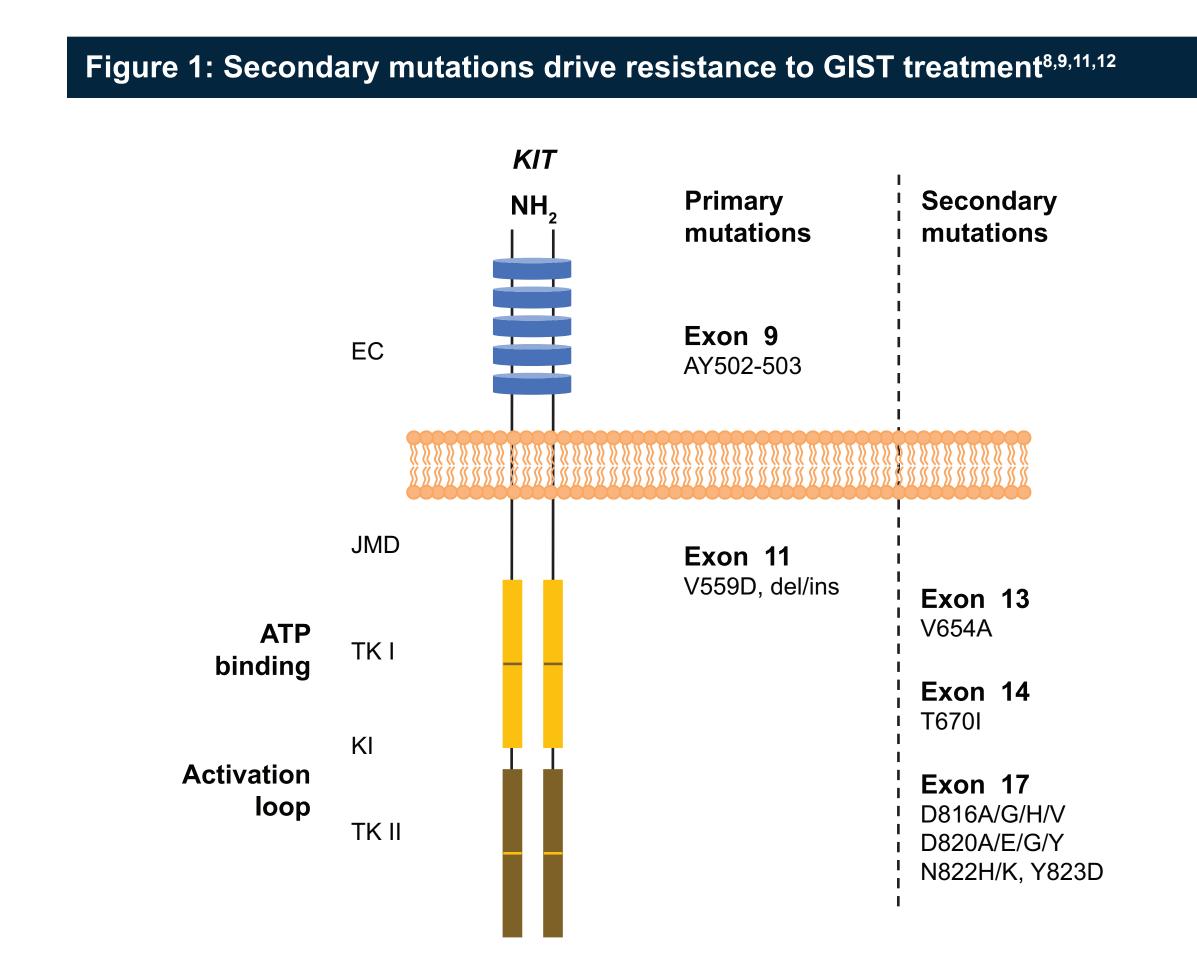
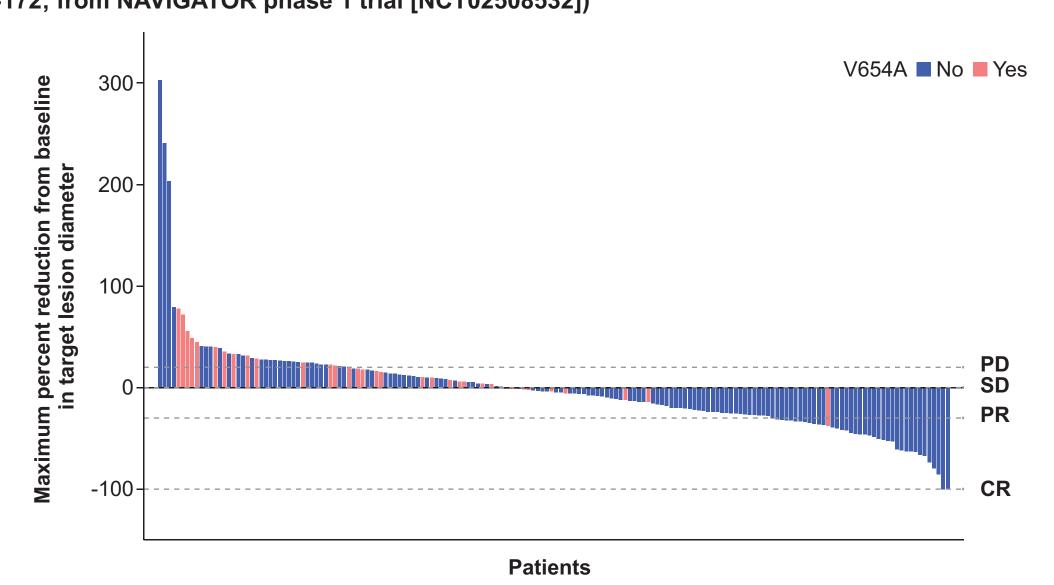


Figure adapted from Hapkova I et al. Gastrointestinal stromal tumour: From the clinic to the molecules. J Cancer Res Ther

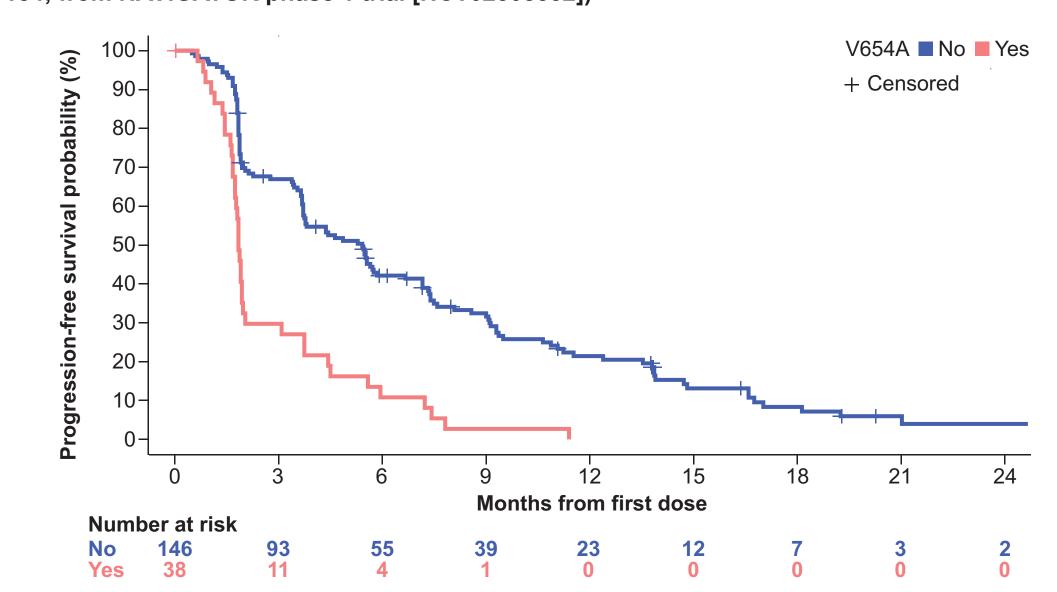
Results

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

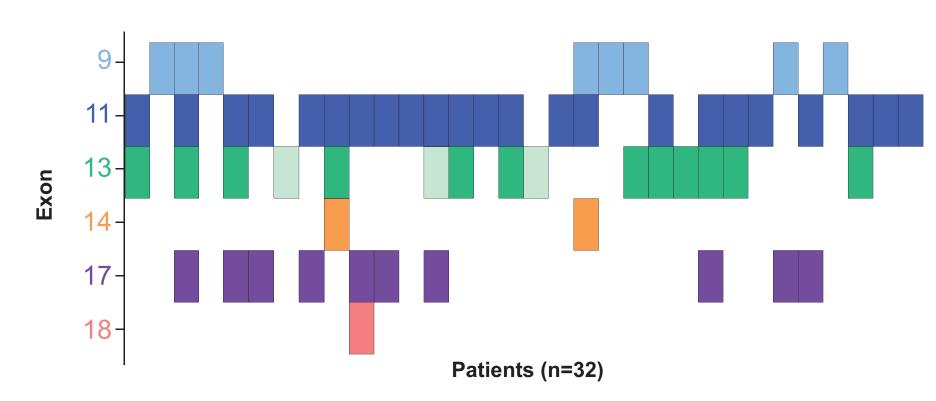
A. Patients with KIT exon 13 V654A mutation were less likely to respond to avapritinib (n=172; from NAVIGATOR phase 1 trial [NCT02508532])



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 avapritnib (from VOYAGER phase 3 trial [NCT03465722])

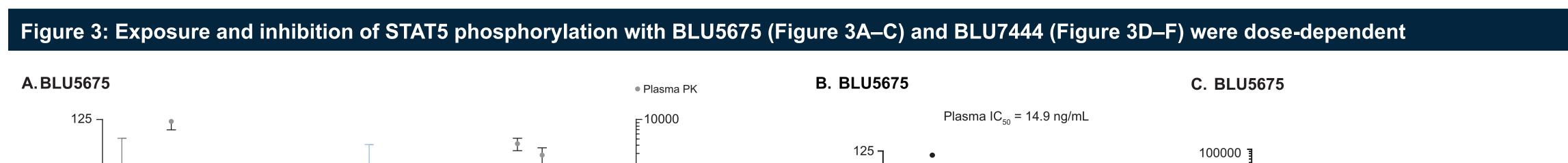


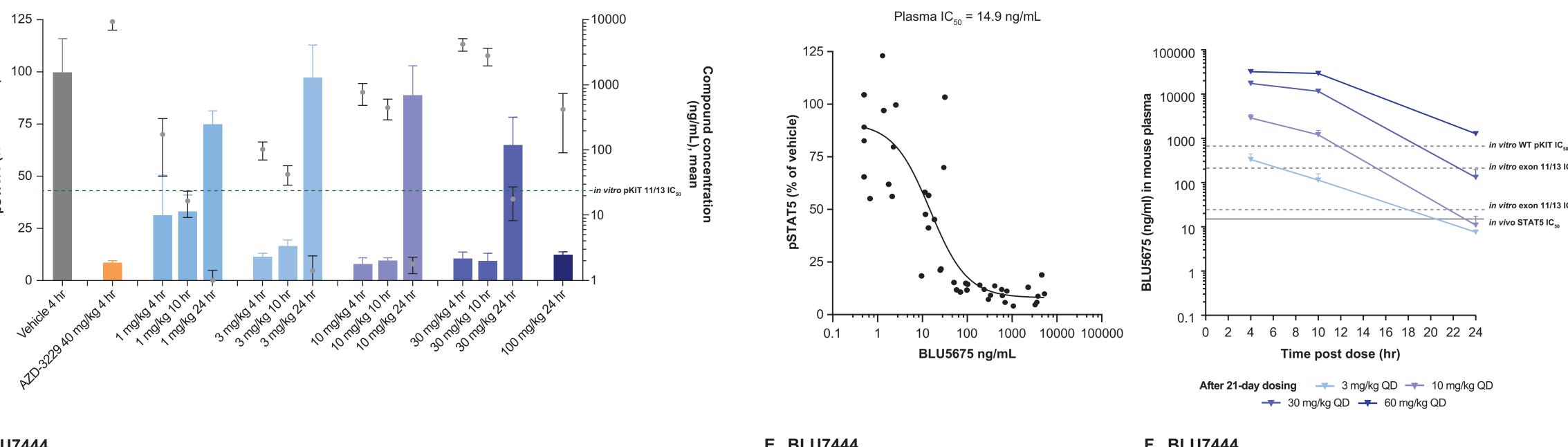
Changes in (A) tumor burden and (B) PFS in avapritinib-treated patients with GIST harboring the KIT V654A mutation.

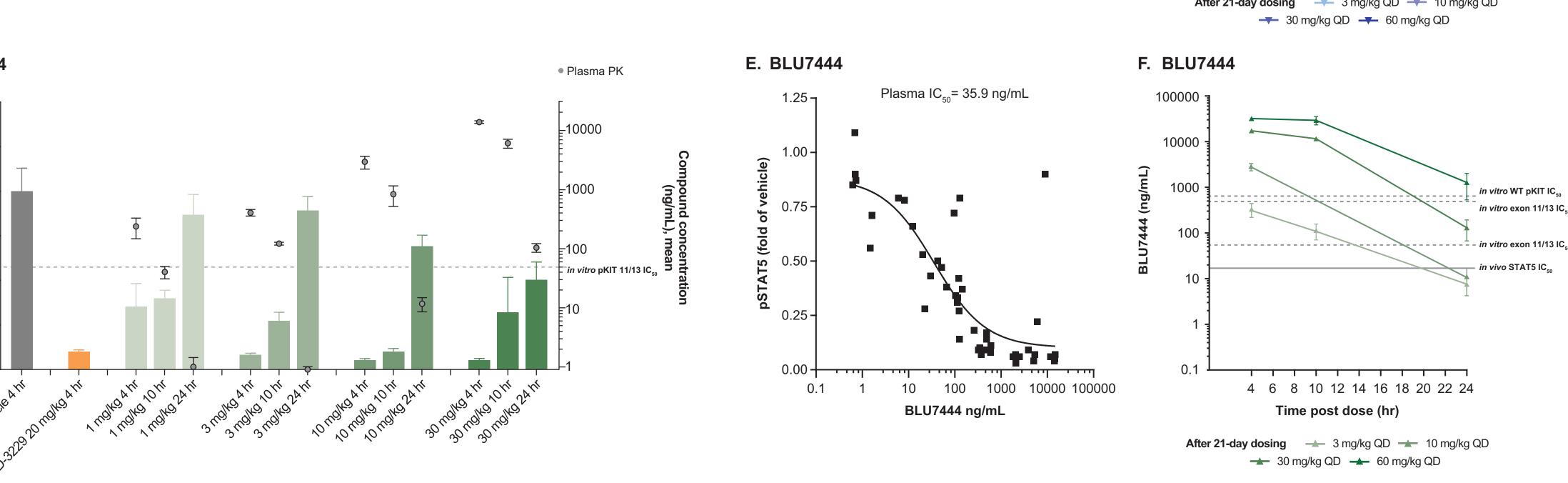
Post hoc analyses on the efficacy of avapritinib in patients with GIST harboring the KIT V654A mutation from the NAVIGATOR phase 1 trial (NCT02508532), measured per mRECIST 1.1. NGS was used to correlate the presence of V654A mutation with tumor regression and PFS. (C) EOT mutation data. NGS of ctDNA 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

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
lmatinib	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



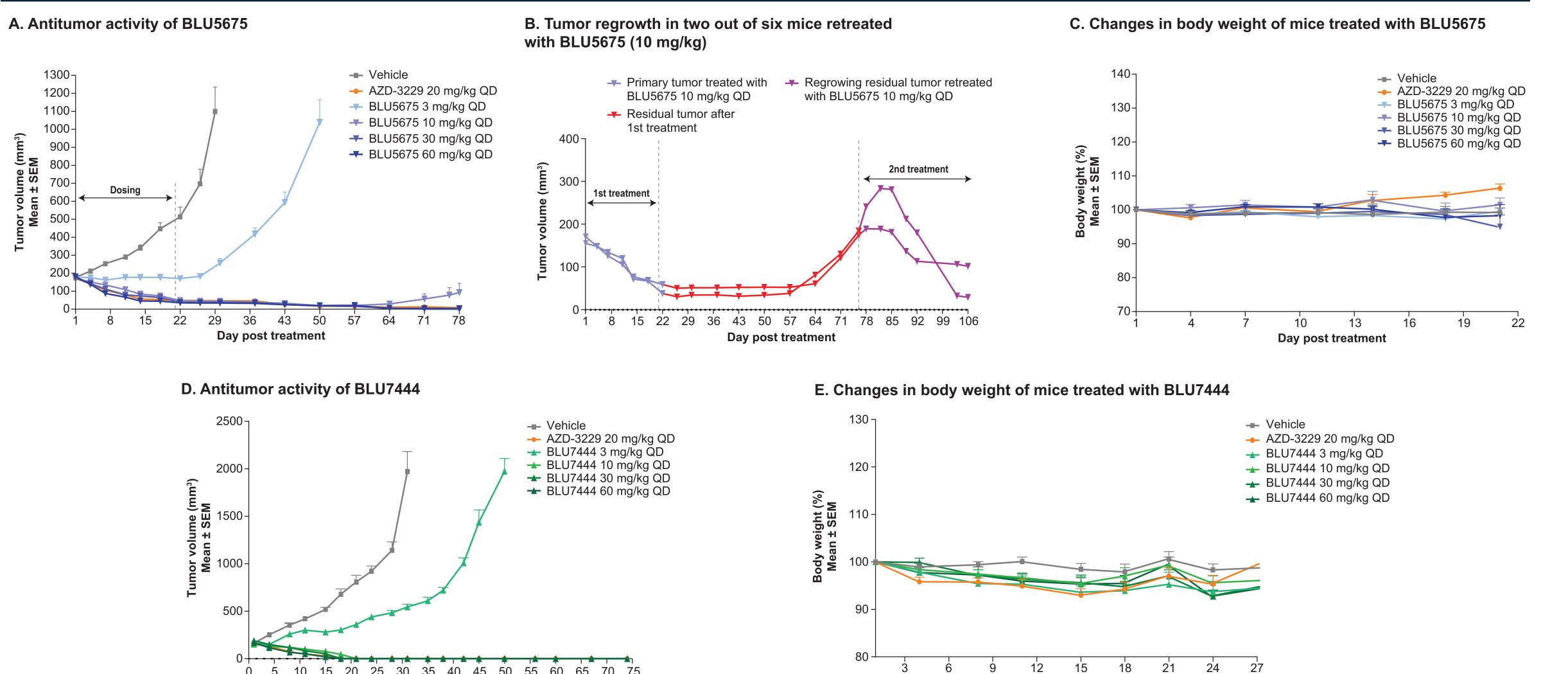




(A) Plasma concentration-time profile, and (B) pSTAT5 PD modulation, and (C) Plasma concentration of BLU7444. For (A) and (D) Plasma concentration-time profile, and (E) pSTAT5 pharmacodynamic modulation, and (F) Plasma concentration of BLU7444. For (A) and (D) AZD-3229, a potent KIT/PDGFRα inhibitor for treatment of GIST, used as a control. 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 IC₀₀, 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)

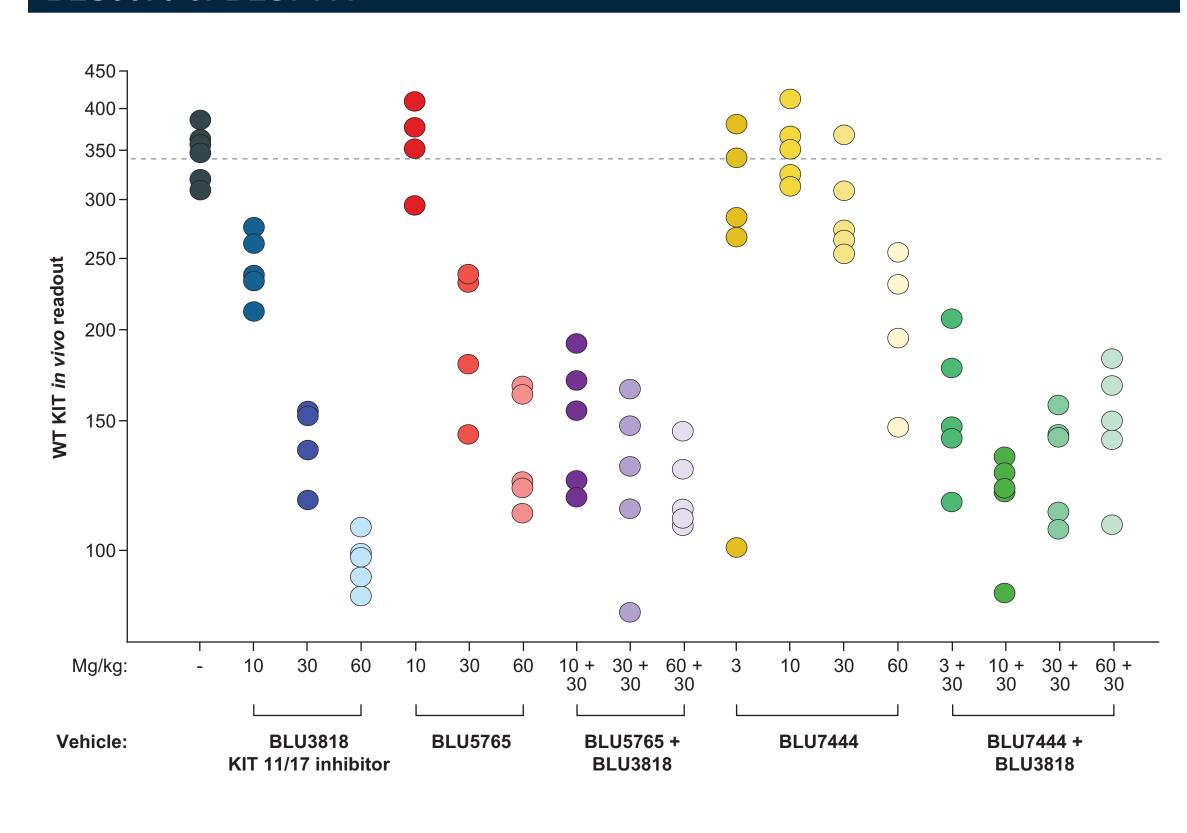
Figure 4: Sustained antitumor activity in a HMC 1.1 CDX mouse model carrying an exon 11/13 mutation was observed with oral daily administration of BLU5675 (Figure 4A–C) or BLU7444 (Figure 4D–E)



Day post treatment

(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. Gastointestinal 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.

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13. Banks E et al. Sci Transl Med. 2020;12(541).

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Day post treatment