

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, 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 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 14^{8–10} (**Figure 1**)
- Several KIT inhibitors potentially 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

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}

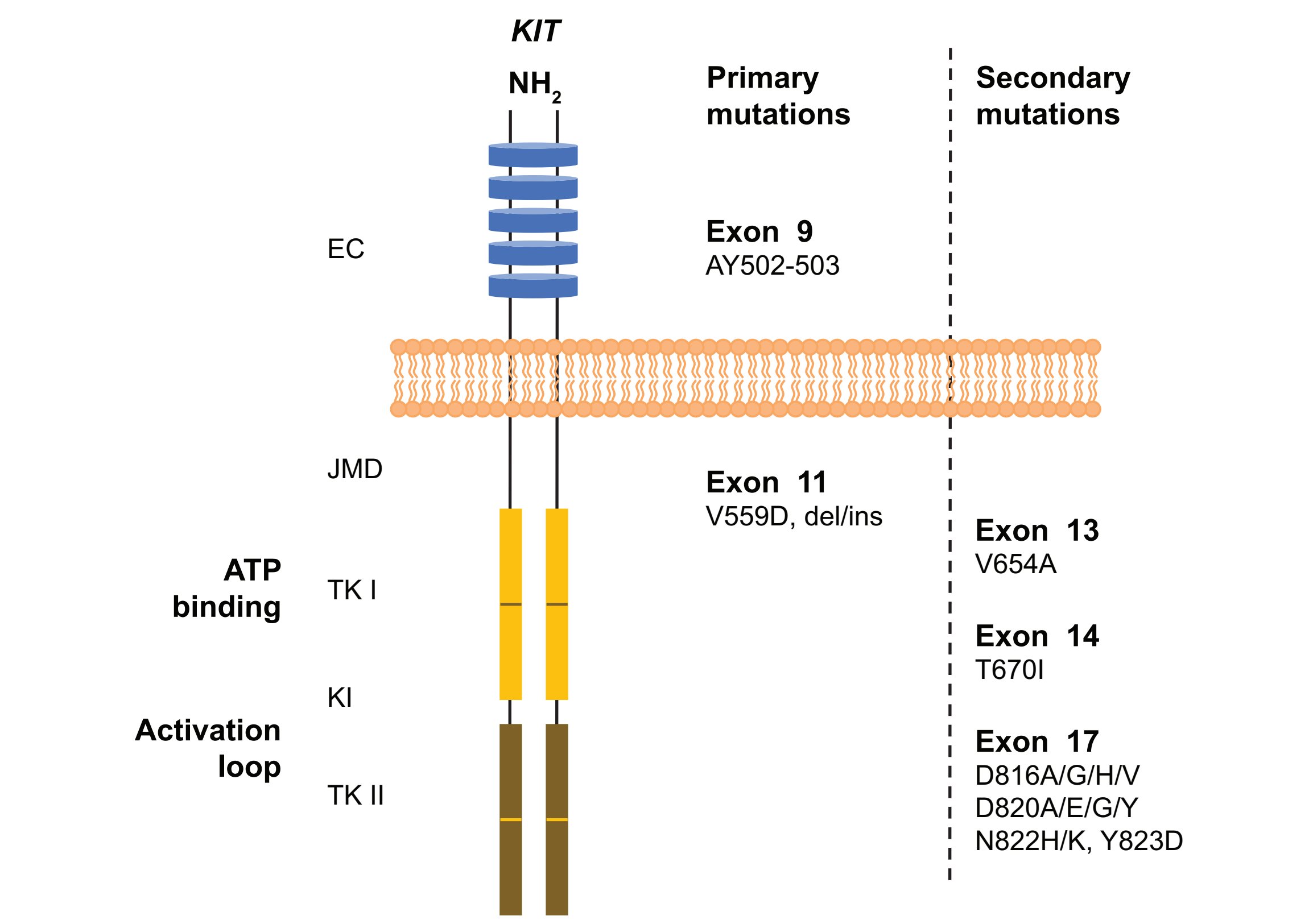


Figure adapted from Hapková I et al. Gastrointestinal stromal tumour: From the clinic to the molecules. *J Cancer Res Ther.* 2014;2:54–67.

Results

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

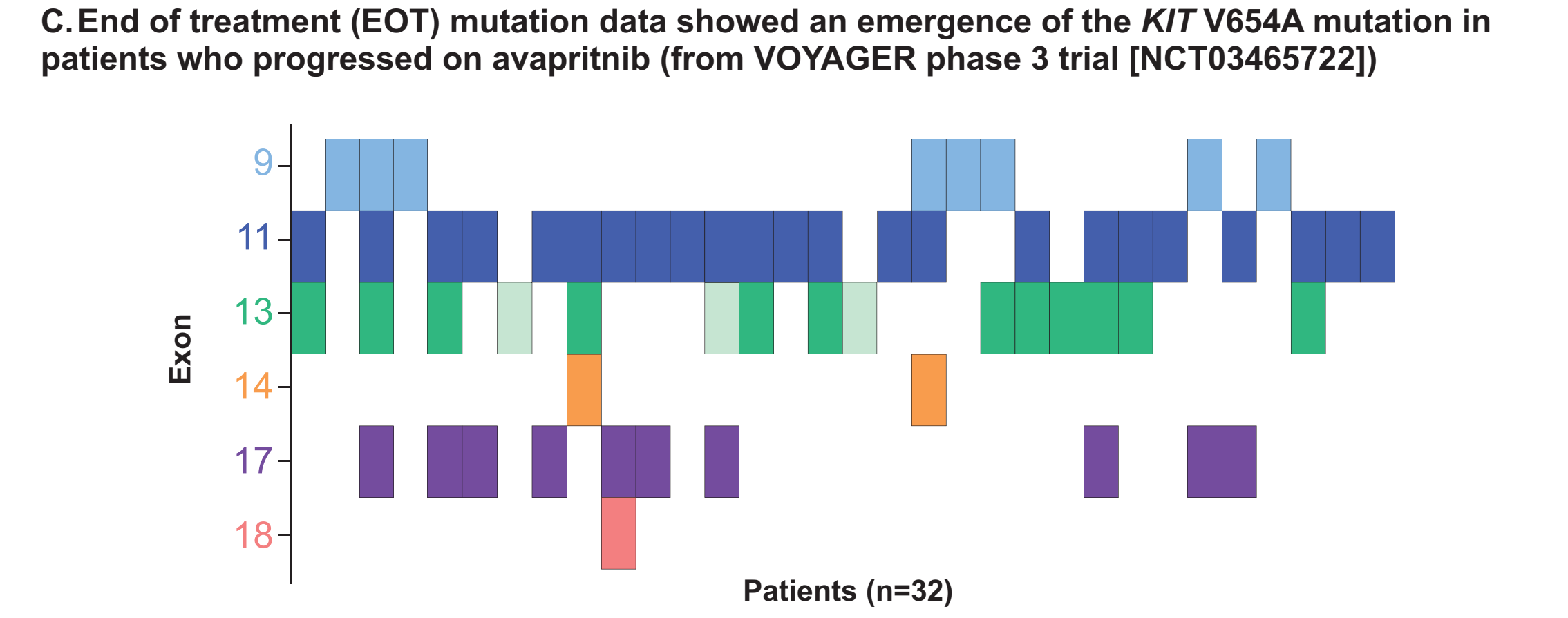
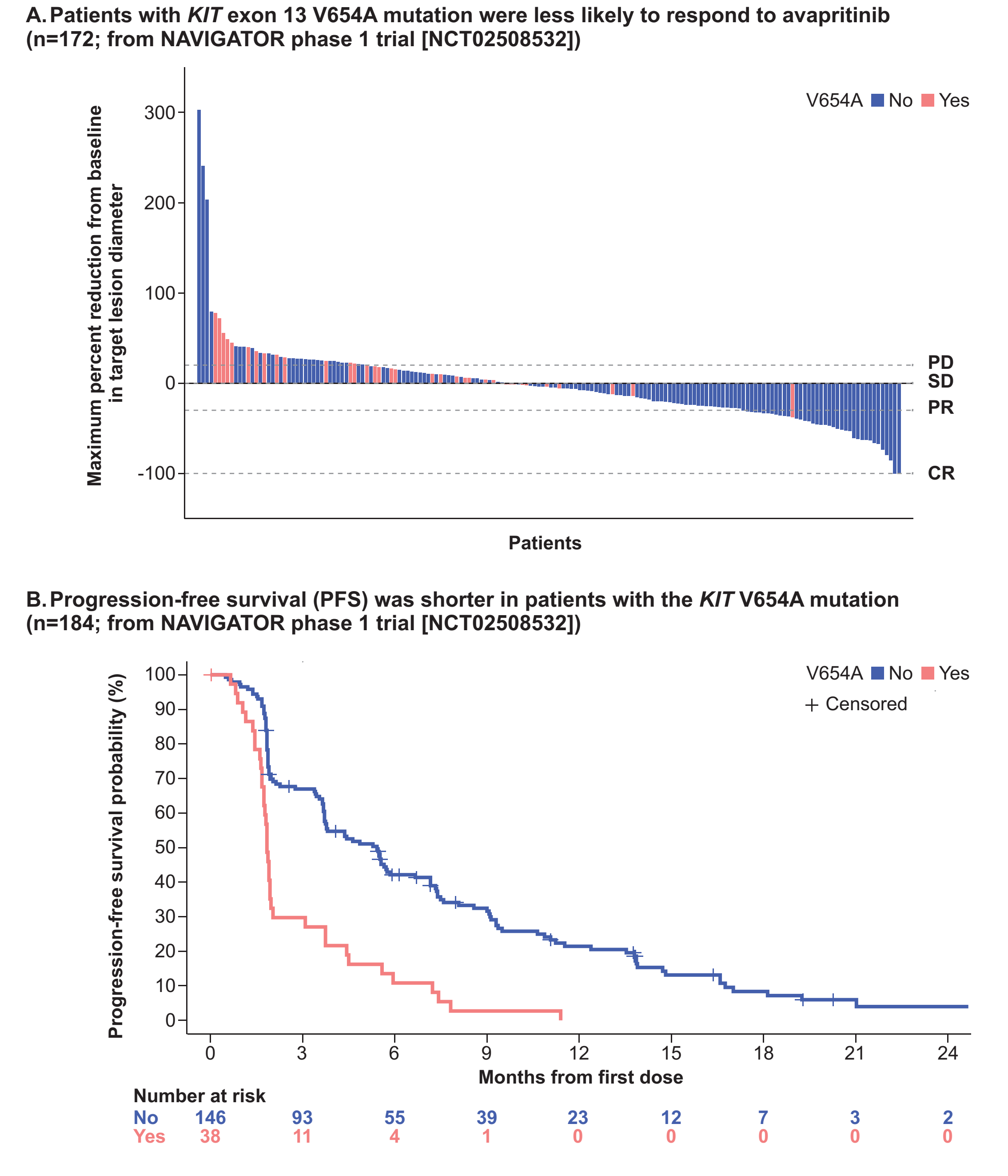
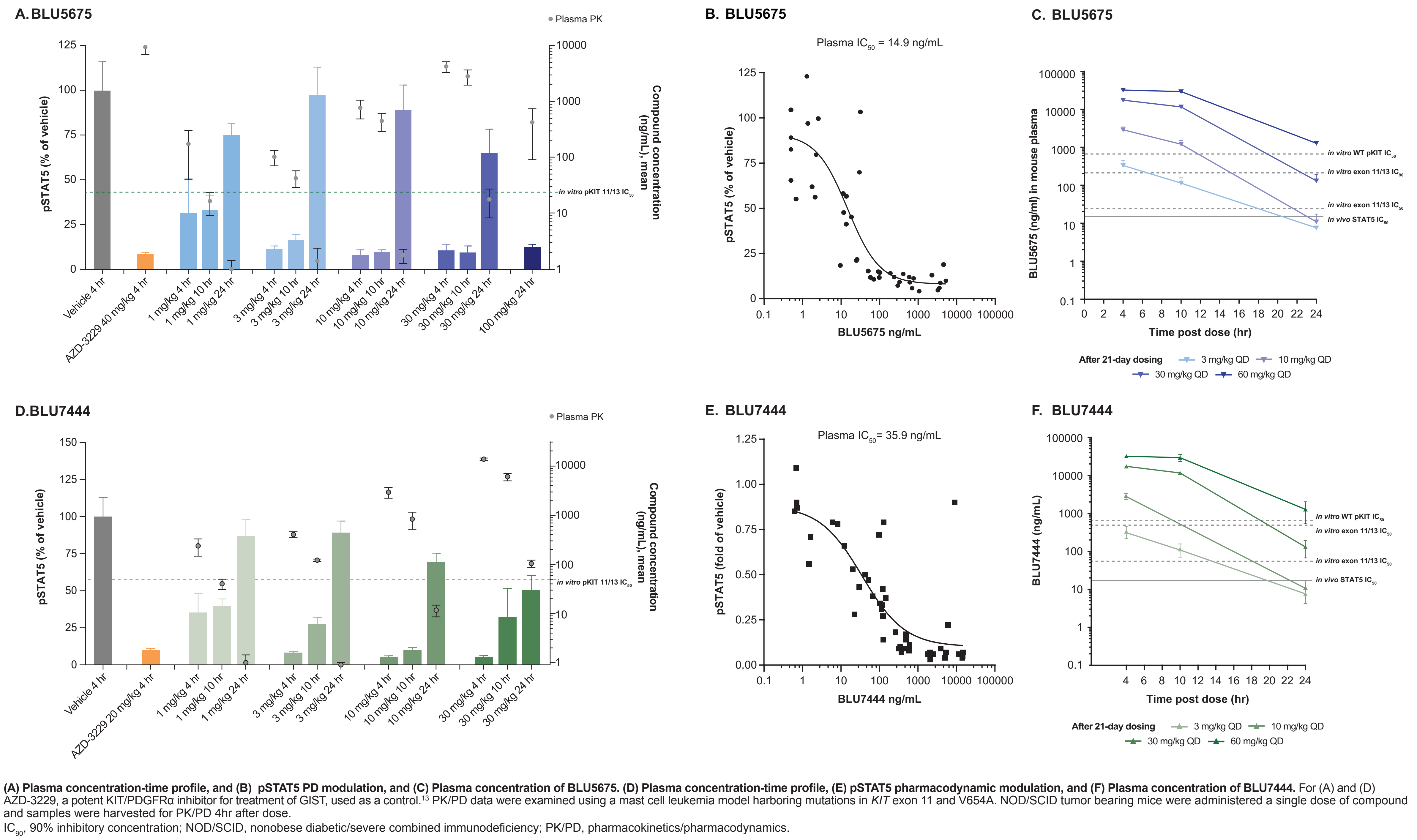


Figure 3: Exposure and inhibition of STAT5 phosphorylation with BLU5675 (Figure 3A–C) and BLU7444 (Figure 3D–F) were dose-dependent



- 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 administration of BLU5675 (Figure 4A–C) or BLU7444 (Figure 4D–E)

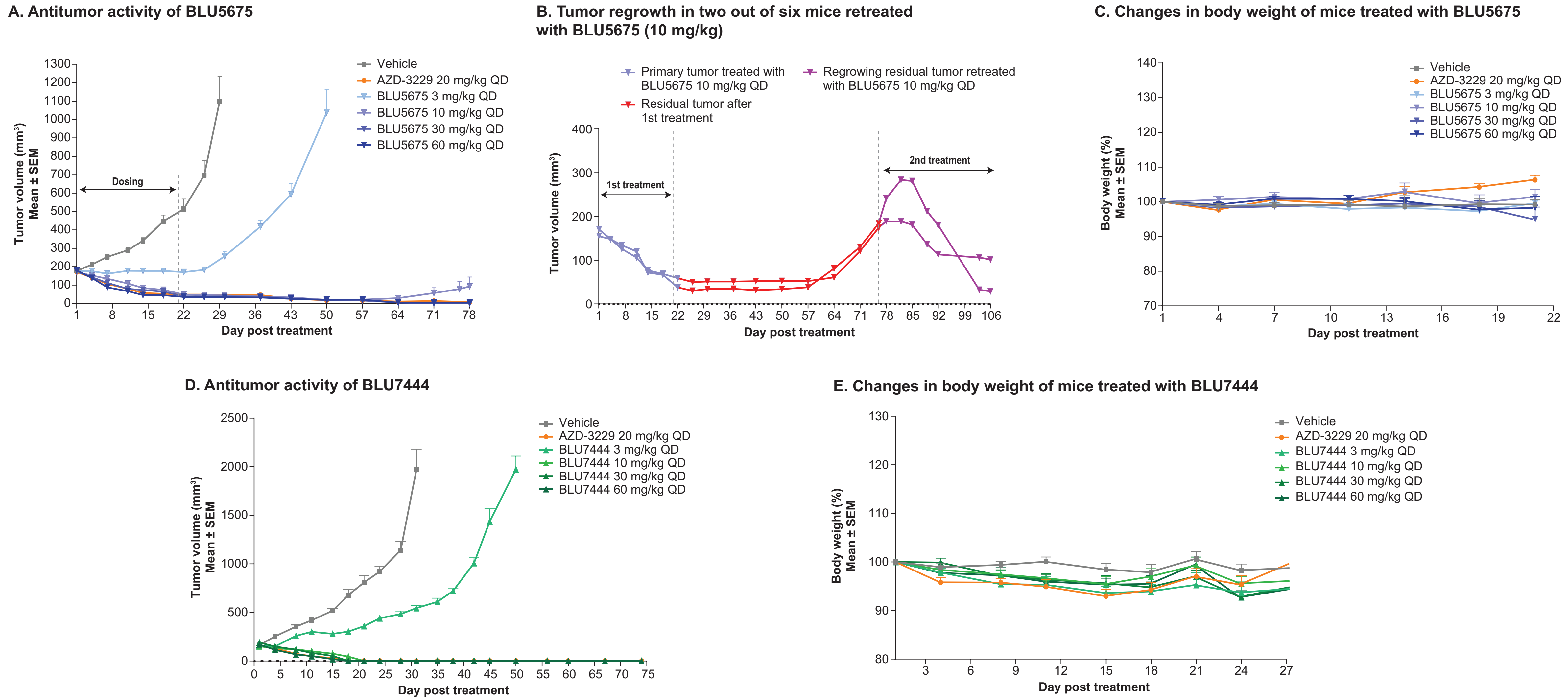
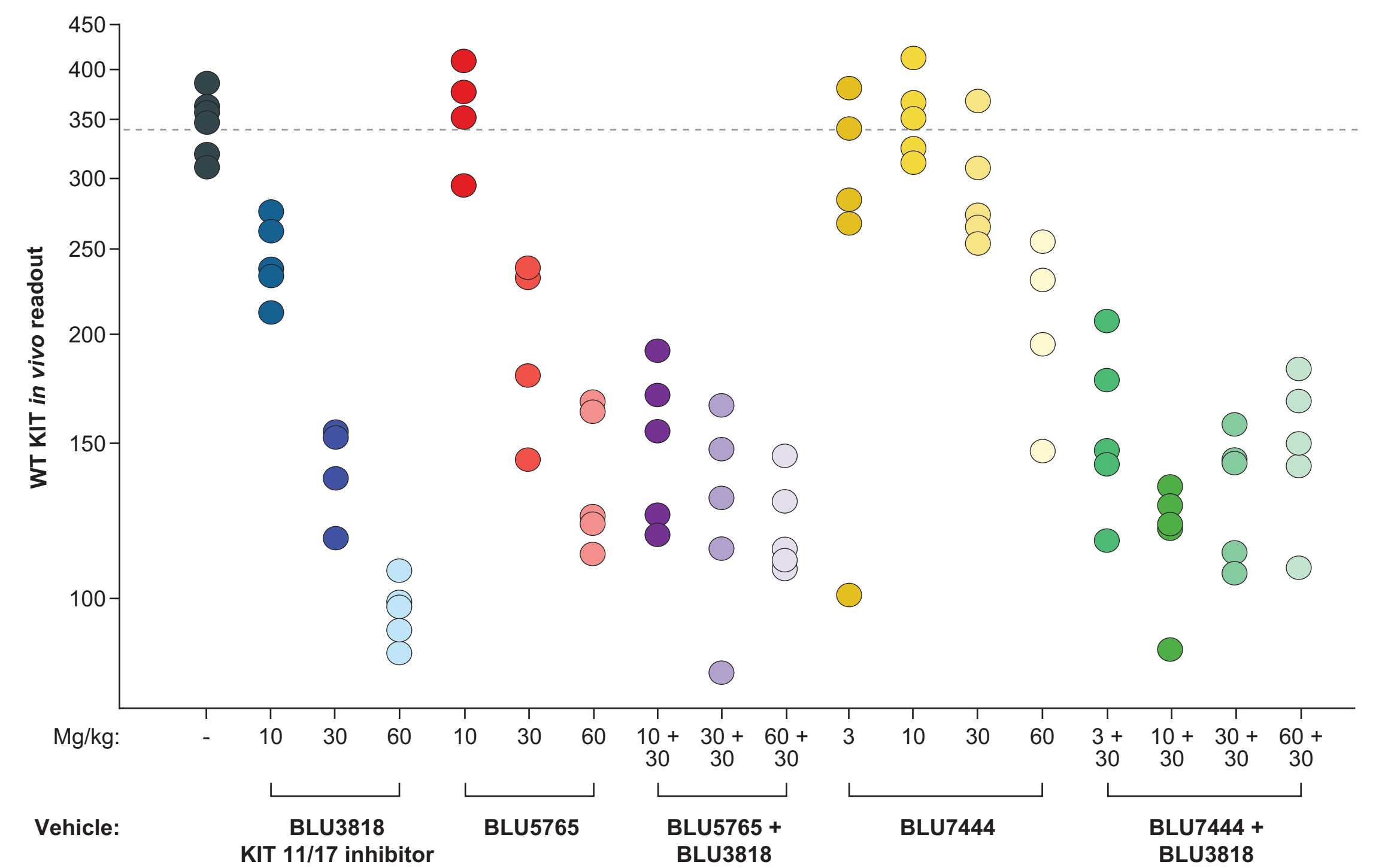


Figure 5: WT KIT toxicity was not exacerbated due to treatment with BLU5675 or BLU7444



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

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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 Almad, 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, Plexikon, 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 Agos. S George has received consulting fees from Deciphera, Bayer, KaryoThera, Avila 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, SpringVox 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.

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