Anti-tumor effects of the novel KIT inhibitor IDRX-42 (formerly M4205) in patient- and cell line-derived xenograft models of gastrointestinal stromal tumor (GIST)

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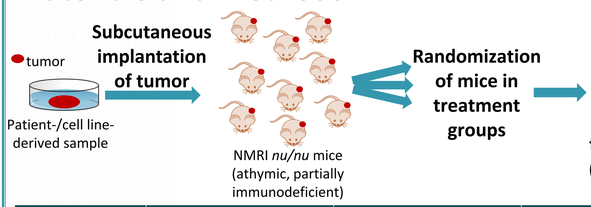
Background

- The majority of GISTs are driven by constitutively activated kinases, either KIT or platelet-derived growth factor alpha (PDGFRA), and respond to treatment with tyrosine kinase inhibitors (TKI) such as imatinib, sunitinib, regorafenib and ripretinib.
- During the treatment most GISTs develop heterogeneous resistance to TKI, nearly universally *via* evolution of secondary mutations in the primary kinase oncogene (*KIT* or *PDGFRA*).
- There is a strong need for novel therapies to prevent emergence of resistant subclones or to treat TKI-resistant GIST.

AIM: to test the efficacy of M4205/IDRX-42[1], a novel specific KIT inhibitor with activity against the most relevant KIT mutations, in xenograft models of GIST.

Materials and methods



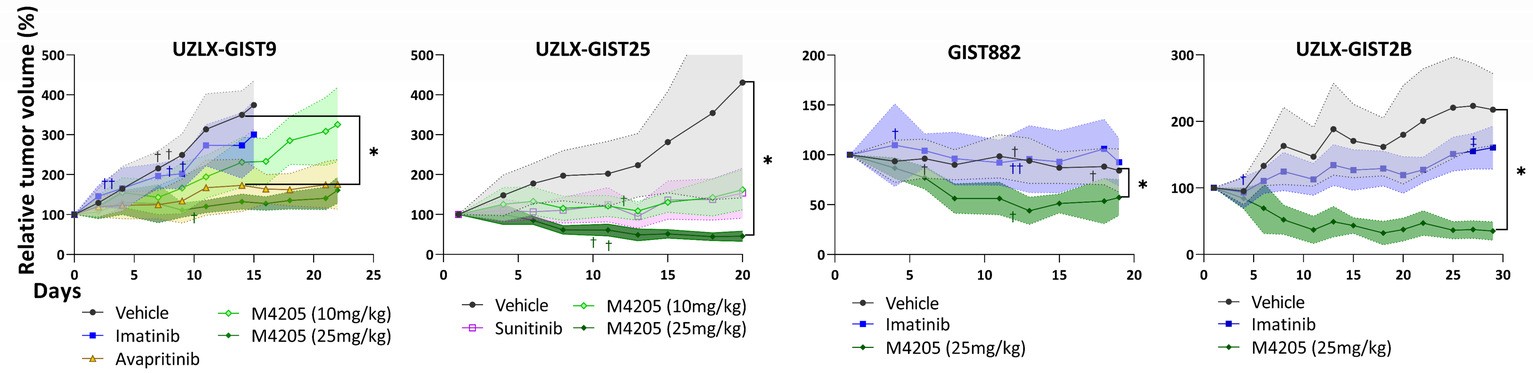
Model	UZLX-GIST9 xp. 16	UZLX-GIST25 xp. 11	GIST882 p.1	UZLX-GIST2B xp.10
- Origin	Patient-derived	Patient-derived	Cell line-derived	Patient-derived
- Primary *KIT* mutation	Exon 11: p.P577del	Exon 13: p.K642E	Exon 13: p.K642E	Exon 9: p.A502_Y503dup
- Secondary *KIT* mutation	Exon 11: p.W557LfsX5, Exon 17: p.D820G	/	/	/
- *In vivo* TKI sensitivity	Imatinib and sunitinib resistant	Imatinib dose-dependent sensitivity; sunitinib sensitive	Imatinib dose-dependent sensitivity; sunitinib sensitive	Imatinib dose-dependent sensitivity, sunitinib sensitive
- Control (vehicle*)	10ml/kg qd (n= 9)	10ml/kg qd (n=10)	10ml/kg qd (n=10)	10ml/kg qd (n=10)
- Imatinib	100 mg/kg/qd (n=9)	/	100 mg/kg/qd (n=10)	100 mg/kg 5d bid 2d qd (n=10)
- Avapritinib	5 mg/kg/qd (n=9)	/	/	/
- Sunitinib	/	20 mg/kg 5d ON 2d OFF (n=10)	/	/
- M4205_10	10 mg/kg/qd (n=9)	10 mg/kg/qd (n=10)	/	/
- M4205_25	25 mg/kg/qd (n=9)	25 mg/kg/qd (n=11)	25 mg/kg/qd (n=10)	25 mg/kg/qd (n=10)

p.: passage; *0.1% carboxymethyl cellulose supplemented with 0.25% Tween 20 in 50mM Na-citric buffer (pH 3.0); qd: daily; d: day; bid: bi-daily; n: number of mice

Results

Tumor growth evaluation *in vivo*

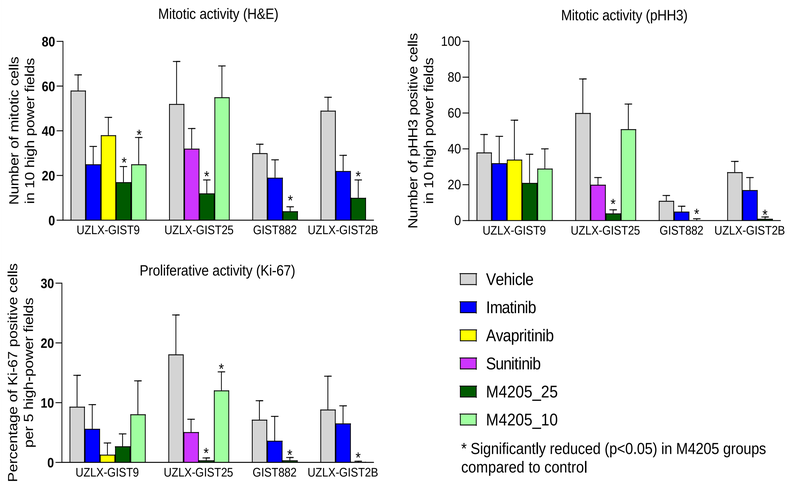
M4205_25 caused tumor volume shrinkage in models UZLX-GIST25, GIST882 and UZLX-GIST2B with a relative decrease to 45.6%, 57.3% and 35.1%, respectively on the last day of treatment as compared to baseline. In UZLX-GIST9 tumor growth to 160.9% was observed in M4205_25-treated tumors as compared to baseline. In all models we saw significant tumor volume decrease (UZLX-GIST25, GIST882 and UZLX-GIST2B) or tumor growth delay (UZLX-GIST9) in M4205_25-treated tumors compared to control, and this antitumor activity was superior to imatinib in UZLX-GIST9, GIST882 and UZLX-GIST2B, and also superior to sunitinib in UZLX-GIST25.



†/‡ found dead/sacrificed * Significantly reduced ($p<0.05$) in M4205 groups compared to control shadows: standard deviation

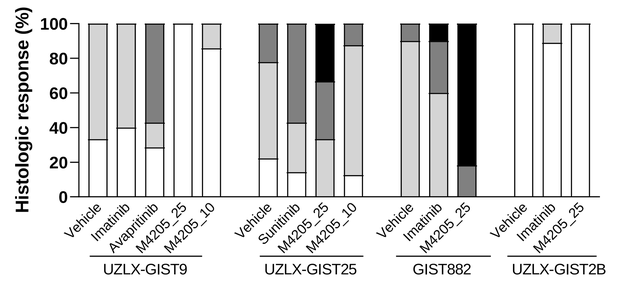
Histological assessment of mitosis and proliferation

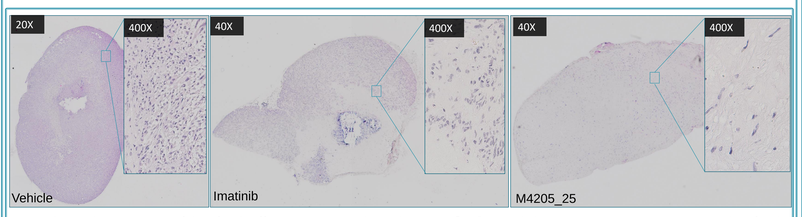
Compared to controls, M4205_25 induced a significant decrease in mitotic cells on H&E stained slides in all models, confirmed with phospho-histone H3 (pHH3) and Ki-67 immunostaining in three models.



Histologic response

In UZLX-GIST25 and GIST882 grade 2-4 histologic response[2] with myxoid degeneration, characteristic response to TKI in GIST, was observed in all tumors treated with M4205_25.





Overview pictures: one histologically representative picture of H&E staining per treatment group. Histologic response with myxoid degeneration is most present in M4205_25 group.

Conclusions

M4205/IDRX-42 has strong antitumor activity in patient- and cell line-derived GIST xenograft models. The novel tyrosine kinase inhibitor induces volumetric tumor responses, decreases mitotic activity, has antiproliferative effects and in models with *KIT* exon 13 mutation leads to myxoid degeneration. All treatments were well tolerated.

M4205/IDRX-42 was recently granted Orphan Drug designation by the U.S. Food and Drug Administration (FDA) for the treatment of GIST[3], and a Phase 1 first-in-human study of M4205/IDRX-42 has been initiated (NCT05489237) in participants with GIST to translate these intriguing preclinical findings into the potential to prevent or overcome resistance to currently available kinase inhibitor drugs.

[1] Blum et al. *Proceedings: AACR Annual Meeting* 2021. [2] Agaram et al. *Clin Cancer Res* 2007; 13:170-81. [3] IDRx, Inc. *Press Release* 2022.

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Met steun van Kom op tegen Kanker