ANTI-TUMOR EFFECTS OF THE NOVEL KIT INHIBITOR IDRX-42 (FORMERLY M4205) IN GASTROINTESTINAL STROMAL TUMOR (GIST) XENOGRAFT MODELS

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Disclosures

- Related to this presentation
  - Personal honorarium for an advisory function from the healthcare business of Merck KGaA, Darmstadt, Germany
  - Institutional funding for laboratory work presented here

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Patrick Schöffski

Background

- The majority of GISTs are driven by constitutively activated kinases, either KIT or platelet-derived growth factor alpha (PDGFRA) and respond to tyrosine kinase inhibitors (TKI) such as imatinib, sunitinib, regorafenib and ripretinib.
- Most GISTs develop heterogeneous resistance to TKI, typically due to the occurrence of secondary mutations (*KIT* or *PDGFRA*).
- There is a strong need for novel therapies to prevent the emergence of resistant subclones and to treat TKI-resistant GIST.
- This preclinical study aimed to test efficacy of IDRX-42, a novel specific KIT inhibitor with activity against the most relevant *KIT* mutations, in patient-derived GIST xenograft models.[1]
- According to biochemical and cellular *in vitro* assays, *KIT* mutations in exons 11, 13 and 17 are sensitive to IDRX-42.

[1] Blum et al. *Proceedings: AACR Annual Meeting* 2021.

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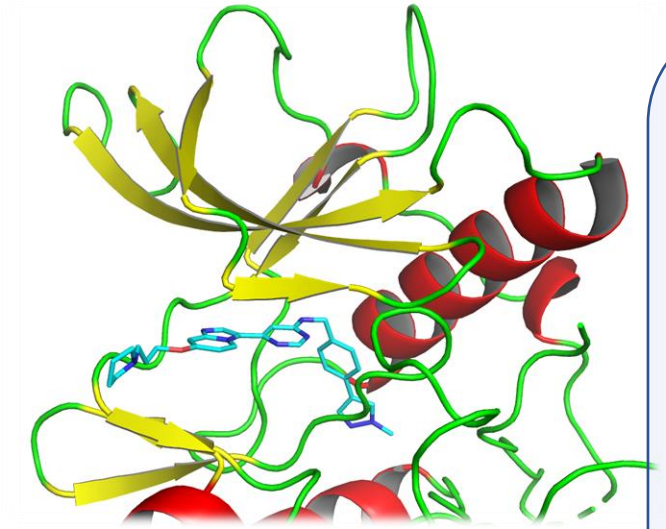
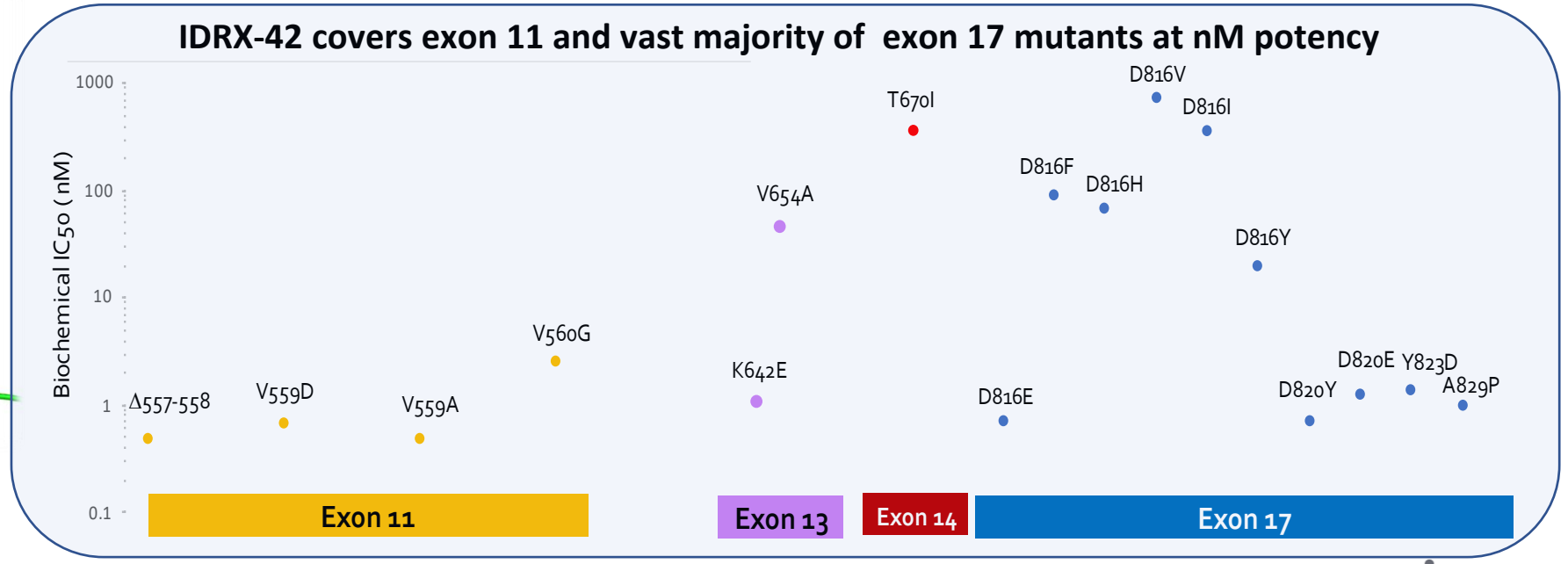
IDRX-42: a Potent, Highly Selective, Pan-Mutant KIT TKI

- IDRX-42 is an ATP-competitive type II inhibitor of the receptor tyrosine kinase KIT
- Broad coverage of disease-relevant *KIT* mutations *in vitro*
- Excellent enzyme- and cell-based kinase selectivity
- Favorable human PK profile with low peak-trough ratio and no brain penetration predicted



X-ray structure of KIT kinase domain in complex with IDRX-42



Blum et al. *Proceedings: AACR Annual Meeting* 2021.

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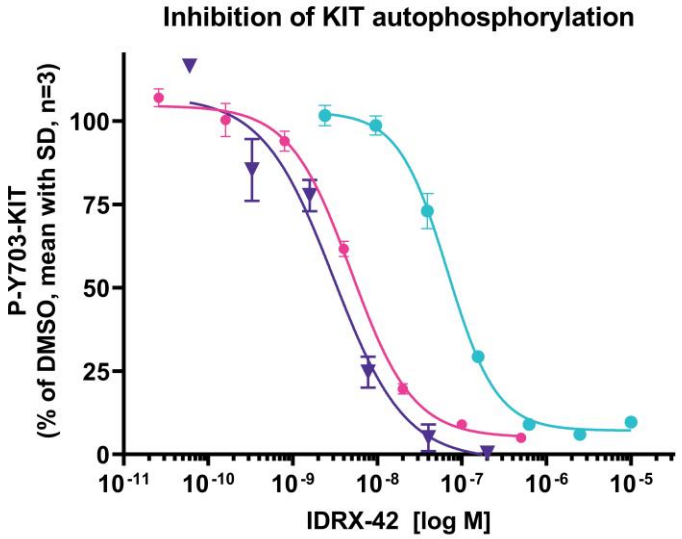
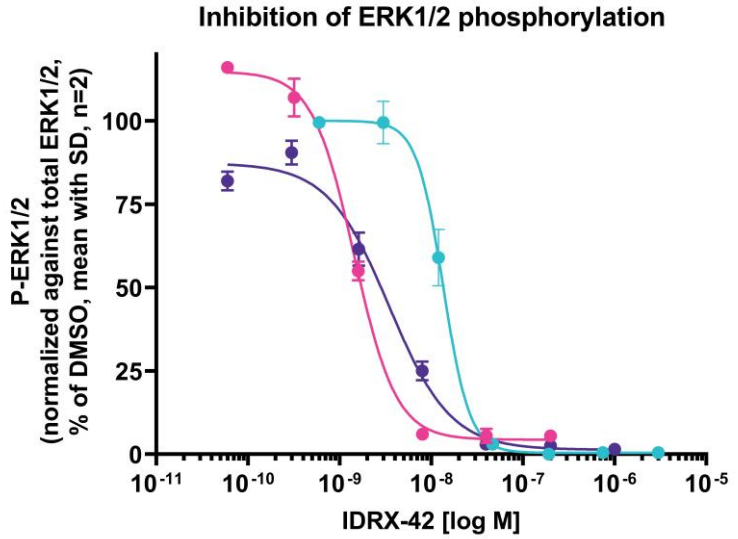
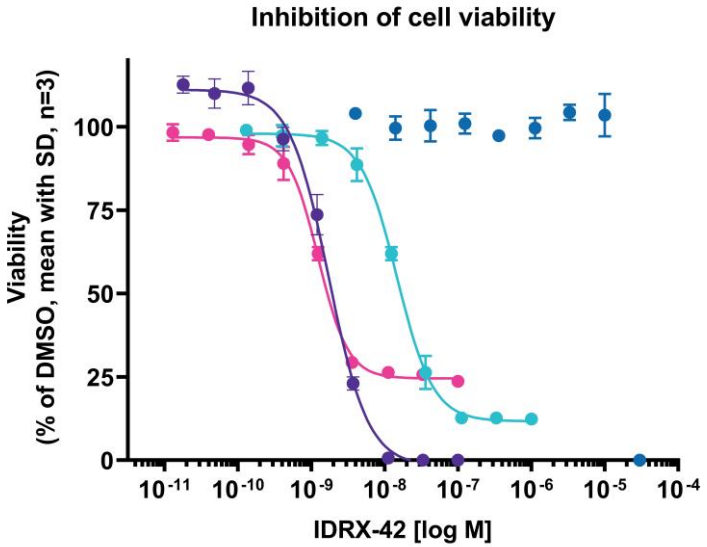
IDRX-42 Cellular Potency Against Mutated KIT (mutations in exons 11, 13, 17)







	Cell line KIT mutation	GIST430 Ex11 V560_L576del	GIST430/654 Ex11+13 V560_L576del; Ex13 V654A	Kasumi-1 Ex17 N822K	GIST48B wildtype
IC_{50} [nM]	p-KIT	5	59	3	-
	p-ERK1/2	2	14	6	-
	Viability	1	15	2	> 10,000

- The potency of IDRX-42 has been assessed *in vitro* by viability studies and evaluation of the phosphorylation of KIT and downstream pathways
- Cellular inhibition of KIT autophosphorylation translates into downstream signaling effects and reduced cell viability

Blum et al. *Proceedings: AACR Annual Meeting* 2021.

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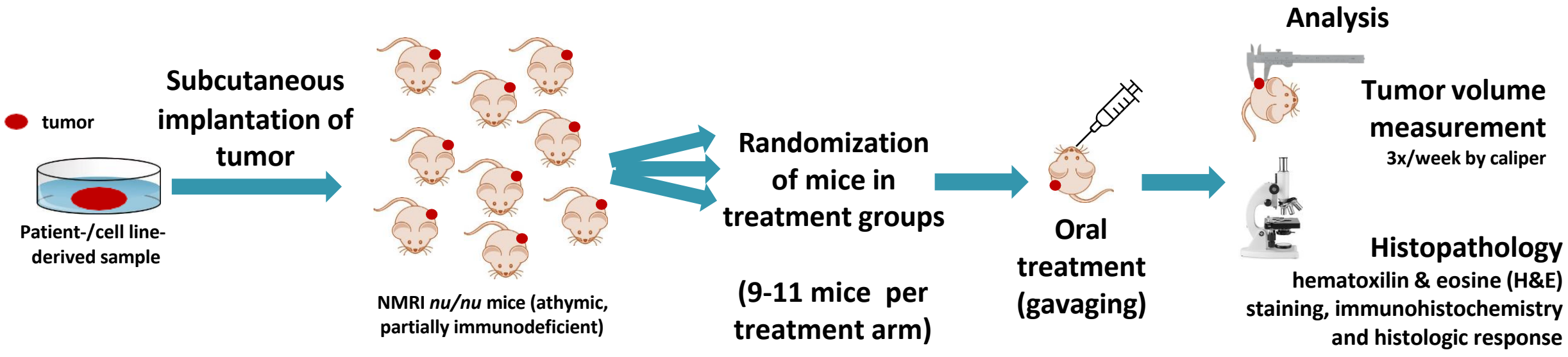
Creation and Experimental Use of Patient-derived GIST Mouse Models



Models used:

- GIST9$^{KIT11+17}$
- GIST25^{KIT13}
- GIST2B^{KIT9}
- GIST882^{KIT13}

Experimental treatment:

- IDRX-42_25 (25mg/kg)
- IDRX-42_10 (10mg/kg)

Evaluated against untreated controls and selected standard of care for 2-4 weeks

- The current *in vivo* study involved three patient-derived and one cell-line-derived models

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Used Xenograft Models and Experimental Treatments

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)	/	/
• IDRX-42_10	10 mg/kg/qd (n=9)	10 mg/kg/qd (n=10)	/	/
• IDRX-42_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)

*0.1% carboxymethyl cellulose supplemented with 0.25% Tween 20 in 50mM Na-citric buffer (pH 3.0)

bid, twice-daily; d, day; n, number of mice; p., passage; qd, daily.

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Tumor Growth Evaluation *In Vivo*

- IDRX-42_25 caused tumor volume shrinkage in models UZLX-GIST25, -GIST882 and -GIST2B with a relative decrease to 45.6%, 57.3% and 35.1%, on the last day of treatment vs. baseline.
- In UZLX-GIST9 (KIT exon 11 + 17 mutation), significant tumor growth delay (160.9% vs. baseline) was observed in IDRX-42_25-treated tumors.
- This antitumor activity of IDRX-42_25 was superior to imatinib in UZLX-GIST9, -GIST882 and -GIST2B and also superior to sunitinib in -GIST25.
- In summary, three models with primary *KIT* mutation showed shrinkage and one model with secondary *KIT* mutation showed growth delay, compared to untreated control.

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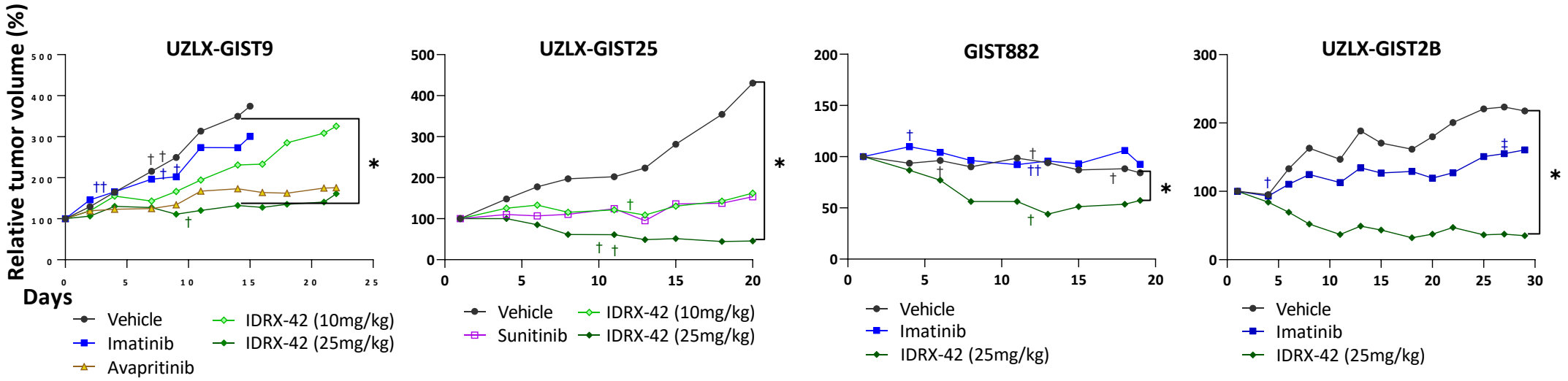

†/‡ found dead/sacrificed

*Significantly reduced ($p<0.05$) in IDRX-42 (25 mg/kg) group compared to control

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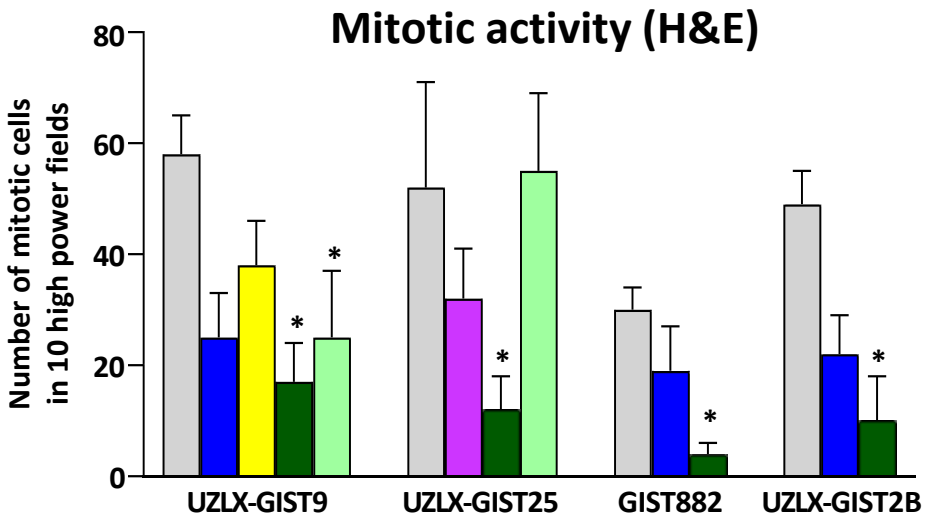
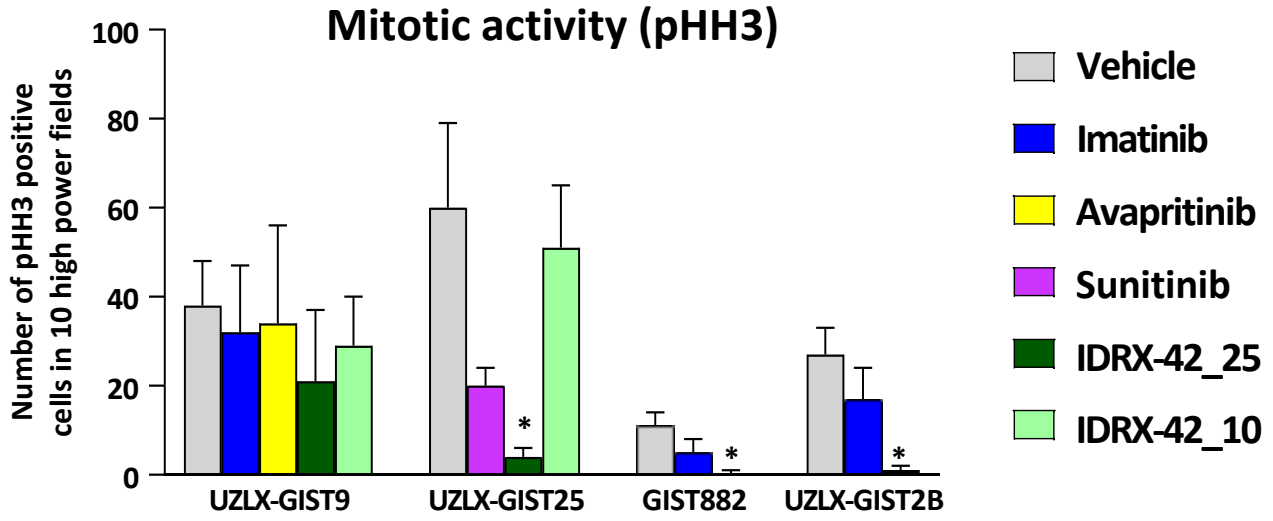
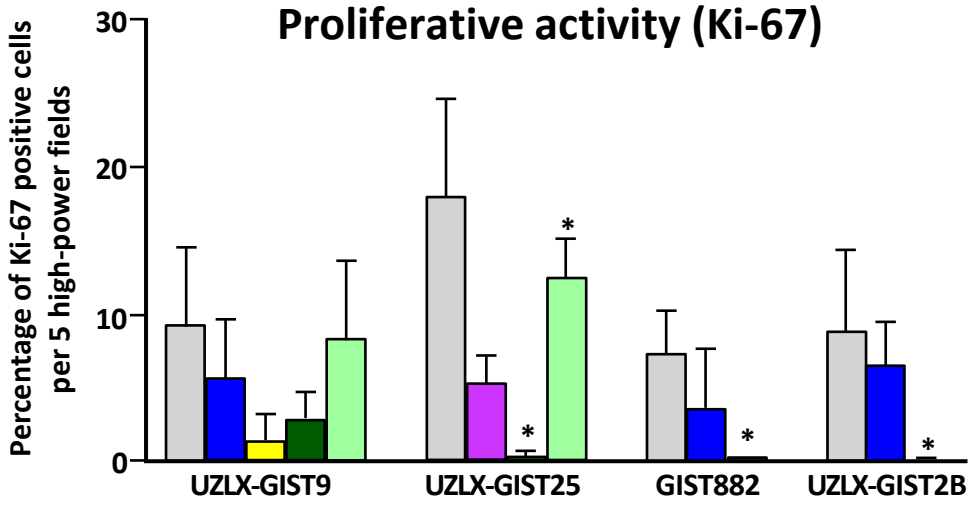
Histological and Immunohistochemical Assessment of Mitosis and Proliferation





- Compared to controls, IDRX-42_25 induced a significant decrease in mitotic cells on H&E-stained slides in all models, confirmed with pHH3 and Ki-67 immunostaining in three models.



pHH3, phospho-histone H3

*Significantly reduced ($p<0.05$) in IDRX-42 groups compared to control

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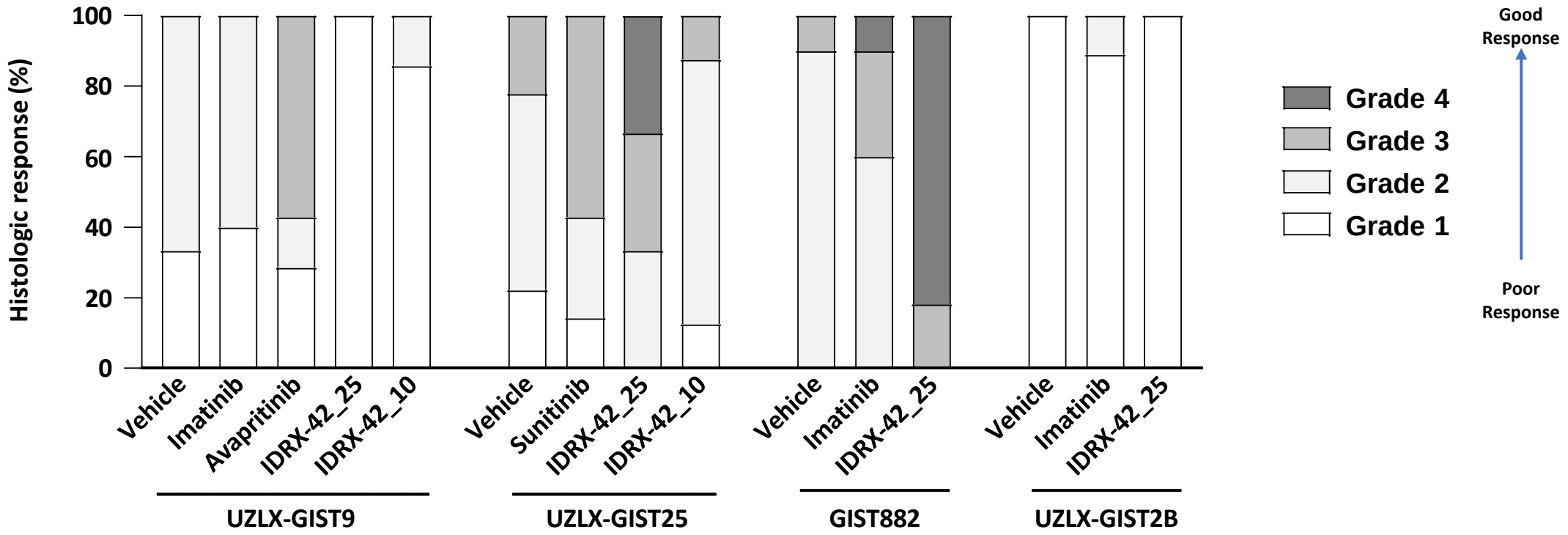
Histologic Response



- In UZLX-GIST25 and GIST882, the models with KIT exon 13 primary mutation, grade 2-4 histologic response[1] with myxoid degeneration was observed in all tumors treated with IDRX-42_25.

[1]Agaram et al. *Clin Cancer Res.* 2007;13:170-81.

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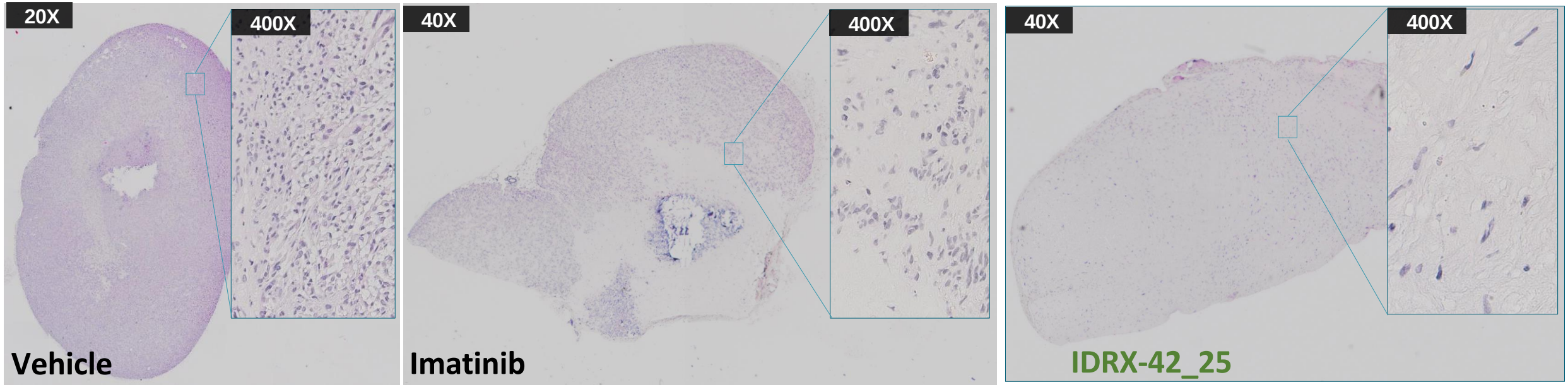
Morphology of GIST882 (*KIT* Exon 13 Primary Mutation) Xenografts on Treatment



- Significantly reduced cellularity and typical myxoid degeneration in imatinib- and IDRX-42 treated tumors on H&E-stained slides

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Conclusions

- IDRX-42 is well tolerated in mice and has broad antitumor activity in biochemical assays *in vitro* and in patient- and cell-line-derived xenograft models.
- Based on preclinical assays activity is seen in oncogenic driver mutations in *KIT* exon 11 as well as in secondary mutations in *KIT* exons 13 and 17.
- In xenograft models the novel TKI induces volumetric tumor responses, decreases mitotic activity and has antiproliferative effects.
- In models with primary *KIT* exon 13 mutation, IDRX-42 leads to strong myxoid degeneration.
- IDRX-42 was recently granted Orphan Drug designation by the U.S. Food and Drug Administration for the treatment of GIST.
- A Phase 1 first-in-human study (NCT05489237) has been initiated in patients with GIST to translate these preclinical findings into a clinical application, with the aim to identify the optimal dose and to assess safety as well as early signs of clinical activity.

Acknowledgements

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- Jonathan Fletcher for providing GIST882 cell line
- The healthcare business of Merck KGaA, Darmstadt, Germany for allowing us to test the compound in the lab
- IDRX for investing in the further development of the compound for difficult to treat GIST