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Menin Inhibitor Ziftomenib Synergizes with Imatinib in Tyrosine Kinase Inhibitor-Resistant Gastrointestinal Stromal Tumor Models

Exposing the epigenetic Achilles heel of KIT-driven tumors

Asako McCloskey, Quinn Reilly, Judy Wu, and Francis Burrows
Kura Oncology, Inc.

2024 ANNUAL MEETING
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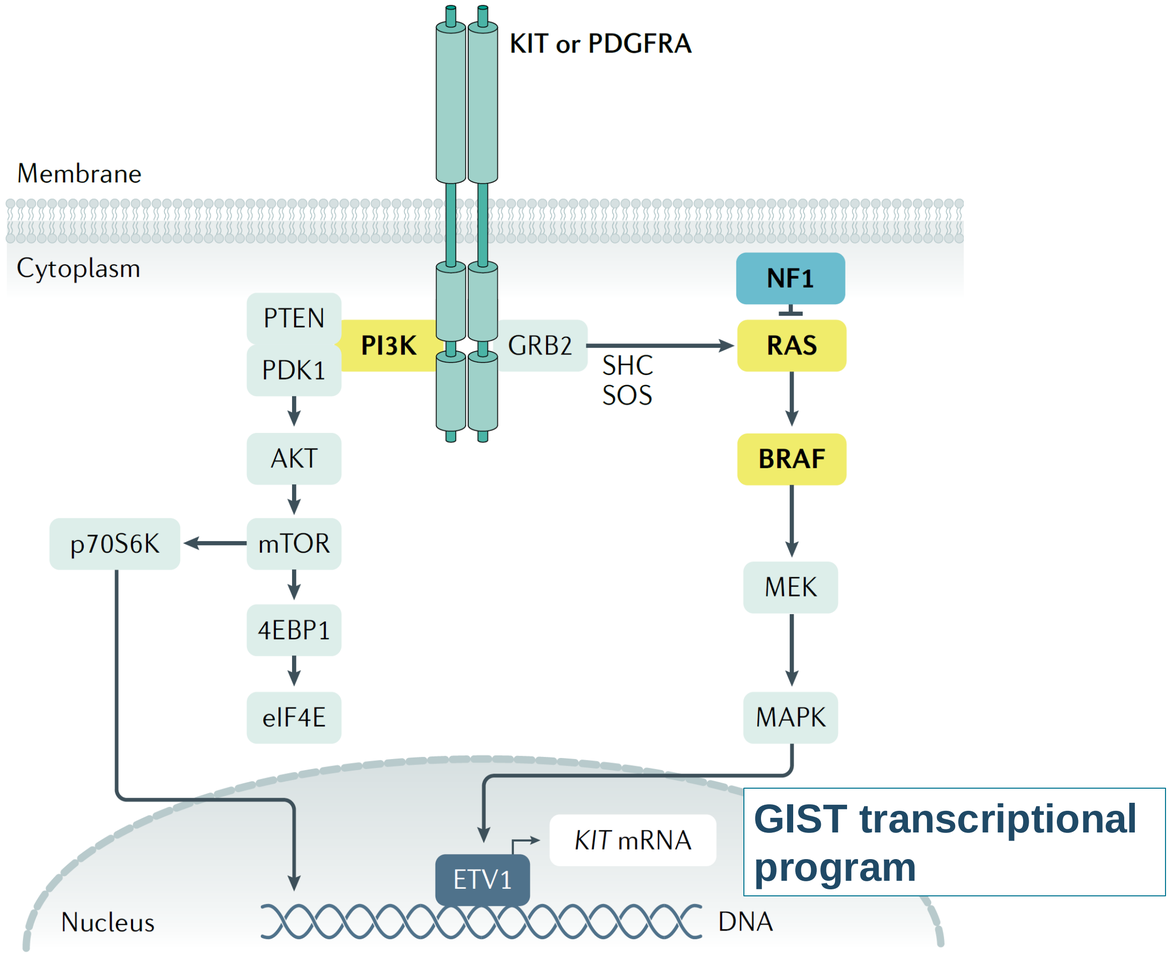
Disclosures

- **Asako McCloskey (Presenter):** Employee and stockholder of Kura Oncology, Inc.; holds patents and/or patent applications with Kura Oncology, Inc.
- **Quinn Reilly:** Former employee and stockholder of Kura Oncology, Inc.
- **Judy Wu:** Employee and stockholder of Kura Oncology, Inc.
- **Francis Burrows:** Employee and stockholder of Kura Oncology, Inc.; holds patents and/or patent applications with Kura Oncology, Inc.

The GIST transcriptional program is involved in oncogenesis via epigenetic mechanisms

Signaling pathways of KIT-mutated GIST[1]



- Oncogenic KIT activates the GIST transcriptional program required for tumorigenesis through transcription factors such as ETV1[2]

1. Blay JY (2021) *Primer* 7-21 (modified); 2. Chi P (2010) *Nature* 467 849-853;
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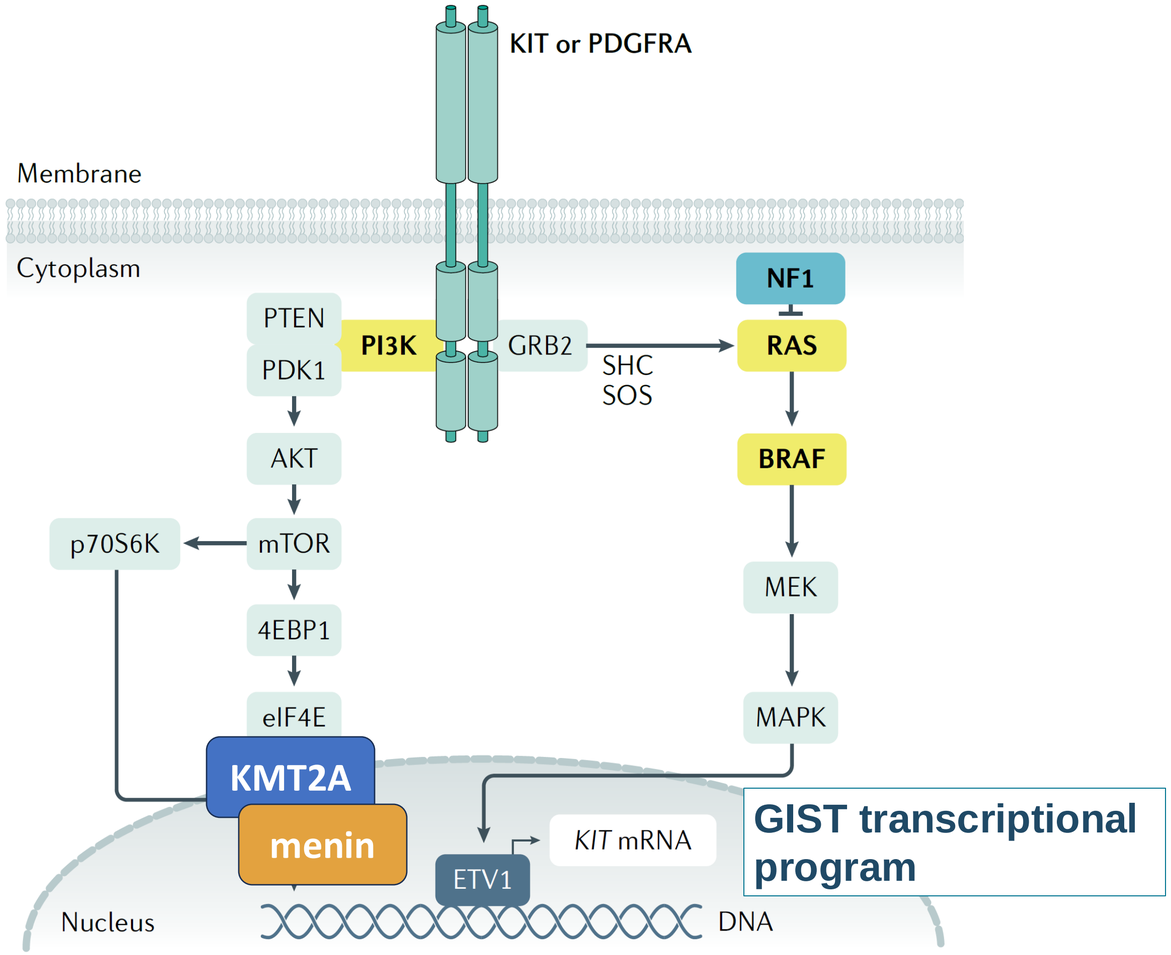

- Oncogenic KIT activates the GIST transcriptional program required for tumorigenesis through transcription factors such as ETV1[2]
- Menin is a scaffold protein known to regulate epigenetic gene expression in several cancers
- Epigenetic transcriptional upregulation mediated by the menin-KMT2A complex underpins oncogenic overexpression of mutant *KIT* in GIST cells, and menin inhibition enhanced imatinib activity in 1L GIST models[3]

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MENIN INHIBITOR ZIFTOMENIB SYNERGIZES WITH IMATINIB IN TYROSINE KINASE INHIBITOR (TKI)-RESISTANT GASTROINTESTINAL STROMAL TUMOR MODELS

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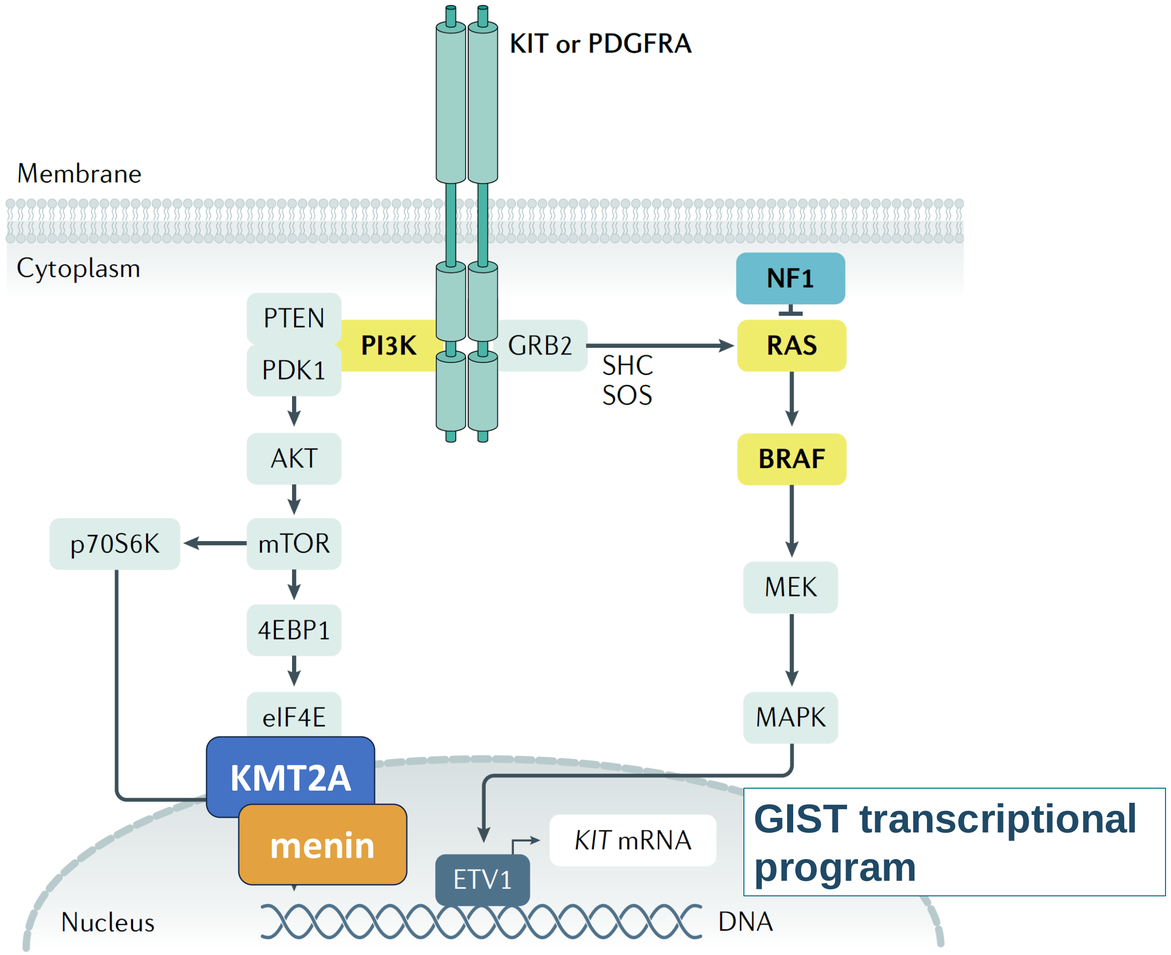

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- Epigenetic transcriptional upregulation mediated by the menin-KMT2A complex underpins oncogenic overexpression of mutant *KIT* in GIST cells, and menin inhibition enhanced imatinib activity in 1L GIST models[3]
- Ziftomenib is an orally available, potent, and selective menin inhibitor currently in clinical testing for acute leukemias, including a registration-enabling, Phase 2 clinical trial in *NPM1*-mutated acute myeloid leukemia
- **The antitumor activity of ziftomenib in combination with TKIs was evaluated using GIST PDX models**

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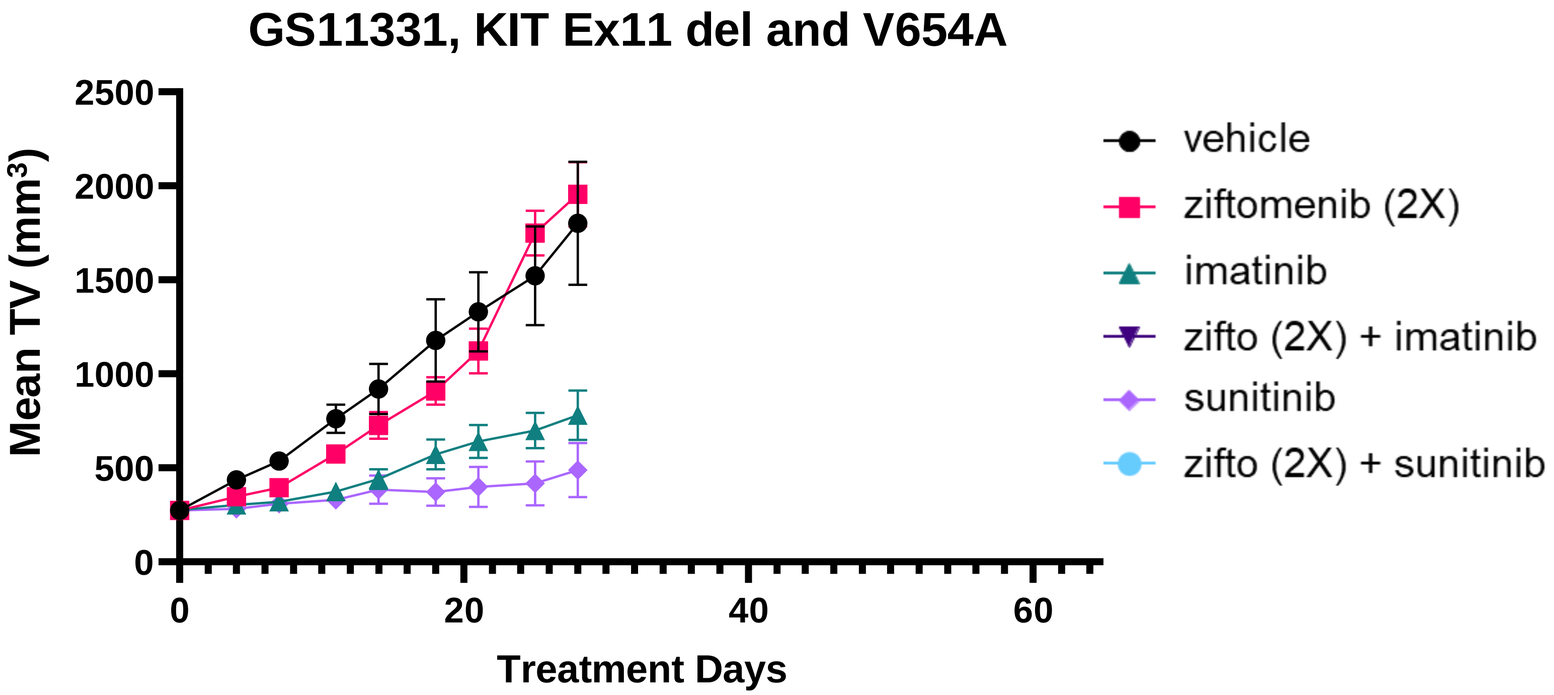
Combination treatments of ziftomenib and TKIs manifested synergistic antitumor activity in a partially imatinib-resistant second-line GIST PDX model



- Both TKI monotherapies slowed tumor growth, but neither induced tumor regression

Data were presented as Mean ± SEM; t-test; *P<0.05,**P<0.01,***P<0.001,****P<0.0001, not significant (ns)

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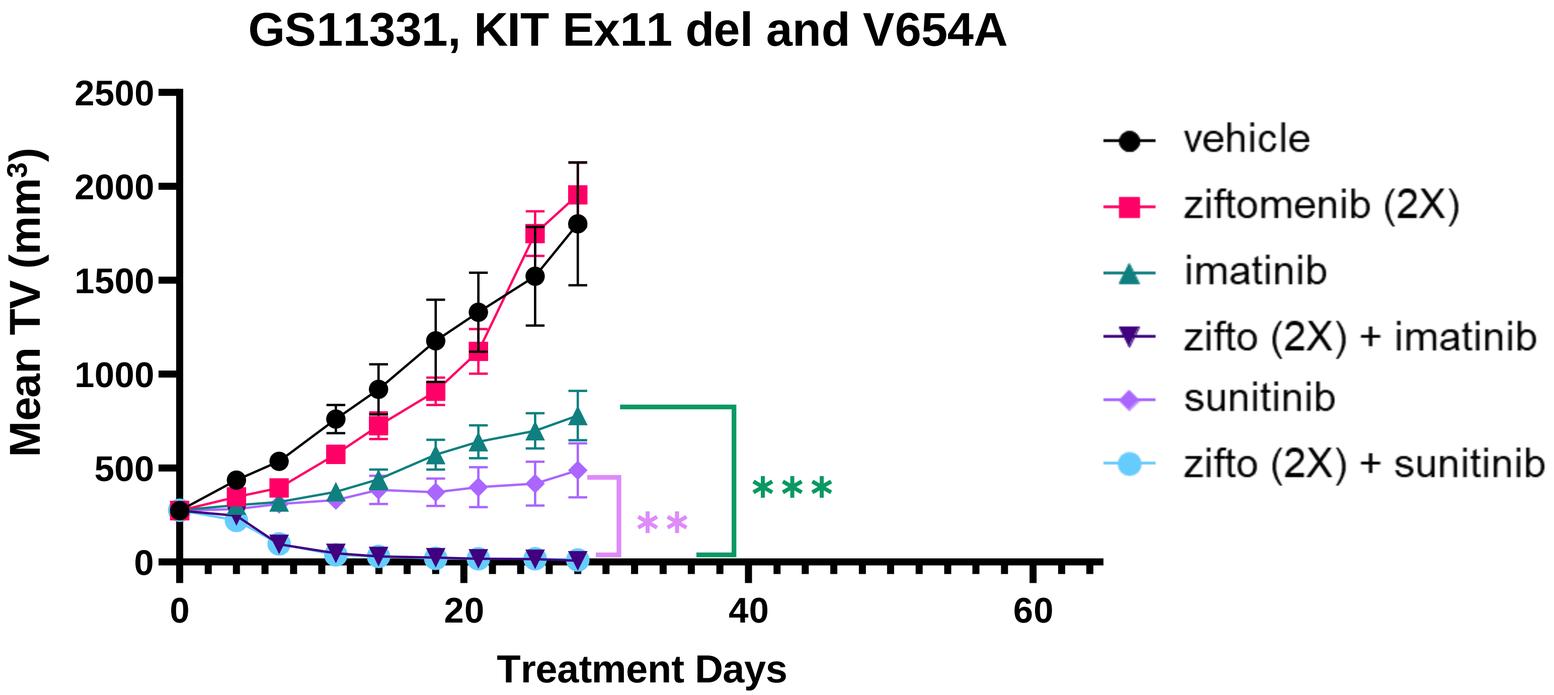

- Both TKI monotherapies slowed tumor growth, but neither induced tumor regression
- Ziftomenib-TKI combinations induced deep regressions in all animals, including some complete responses (CRs)

Data were presented as Mean ± SEM; t-test; *P<0.05,**P<0.01,***P<0.001,****P<0.0001, not significant (ns)

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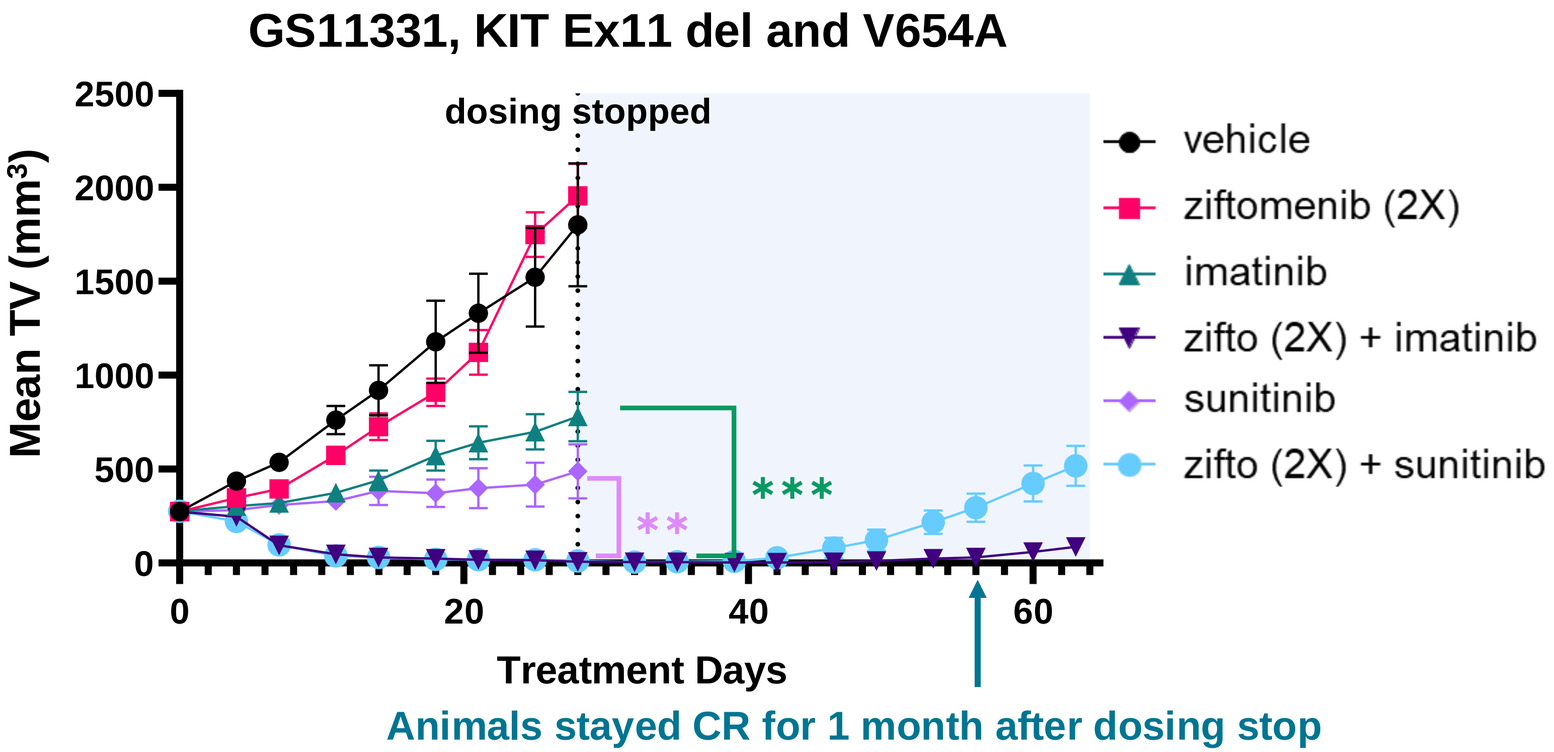

Animals stayed CR for 1 month after dosing stop

- Both TKI monotherapies slowed tumor growth, but neither induced tumor regression
- Ziftomenib-TKI combinations induced deep regressions in all animals, including some complete responses (CRs)
- Full suppression of tumor growth was maintained for up to four weeks after dosing stop

Data were presented as Mean ± SEM; t-test; *P<0.05,**P<0.01,***P<0.001,****P<0.0001, not significant (ns)

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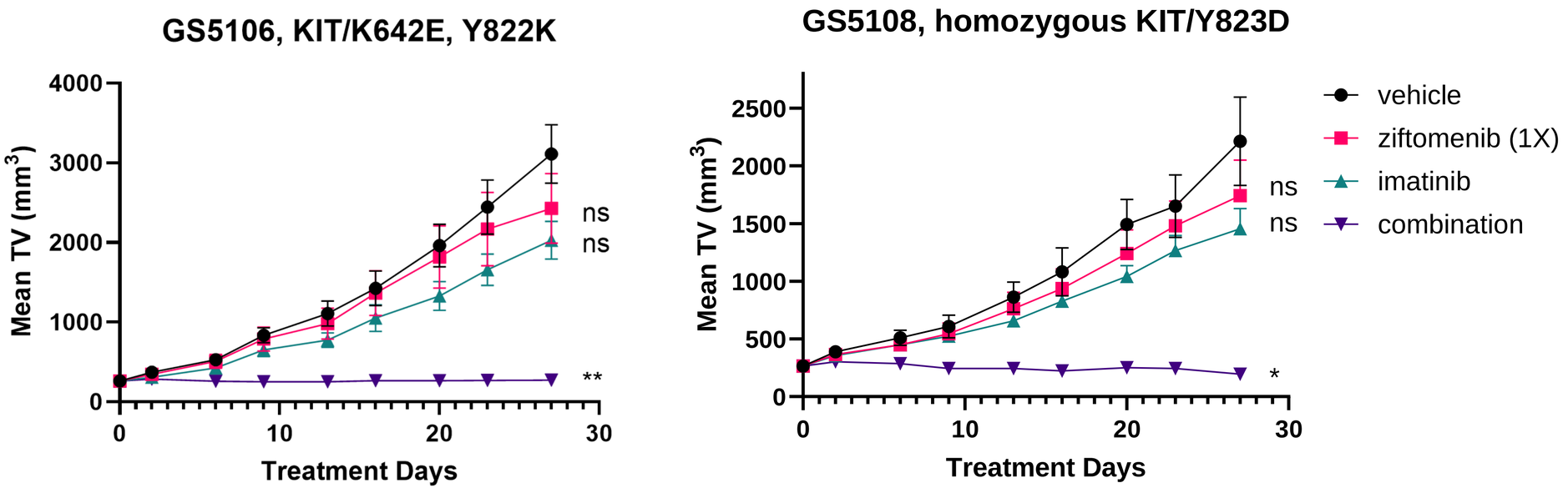
Ziftomenib and imatinib display synthetic lethal activity in fully imatinib-resistant Ex17 GIST PDX models



- Ziftomenib and imatinib were inactive in Ex17 mutant models, but the combination completely suppressed tumor growth
- In these models, the ziftomenib-imatinib combination inhibited KIT activity in a synthetic lethal manner
- The combination effect was agnostic with respect to KIT mutation type

Data were presented as Mean ± SEM; t-test; *P<0.05,**P<0.01,***P<0.001,****P<0.0001, not significant (ns)

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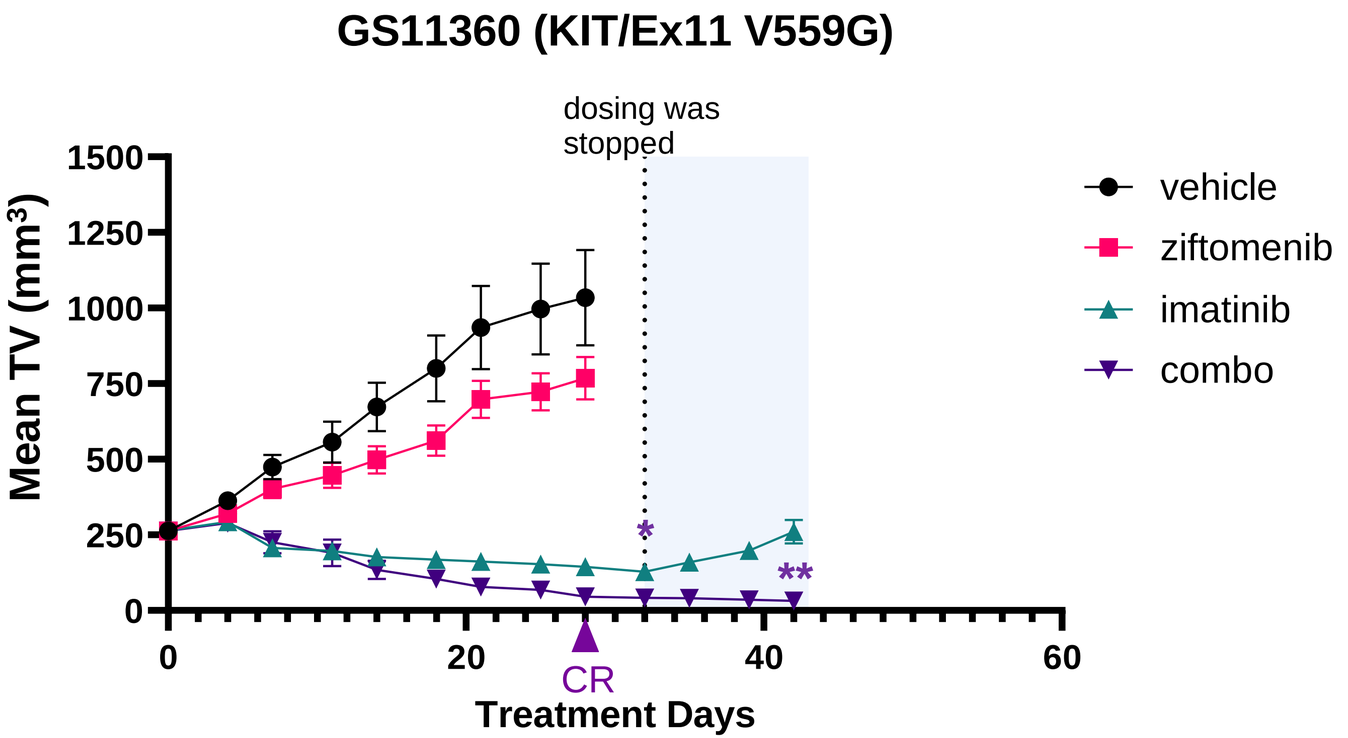
Ziftomenib significantly enhanced the activity of imatinib in an imatinib-sensitive first-line GIST PDX model



- Imatinib monotherapy was tumoristatic, but the ziftomenib-imatinib combination induced deep regressions in all animals, including some CRs
- Cessation of dosing resulted in rapid regrowth in imatinib-treated tumors, but tumors treated with the combination continued to regress

Data were presented as Mean ± SEM; t-test; *P<0.05,**P<0.01,***P<0.001,****P<0.0001, not significant (ns)

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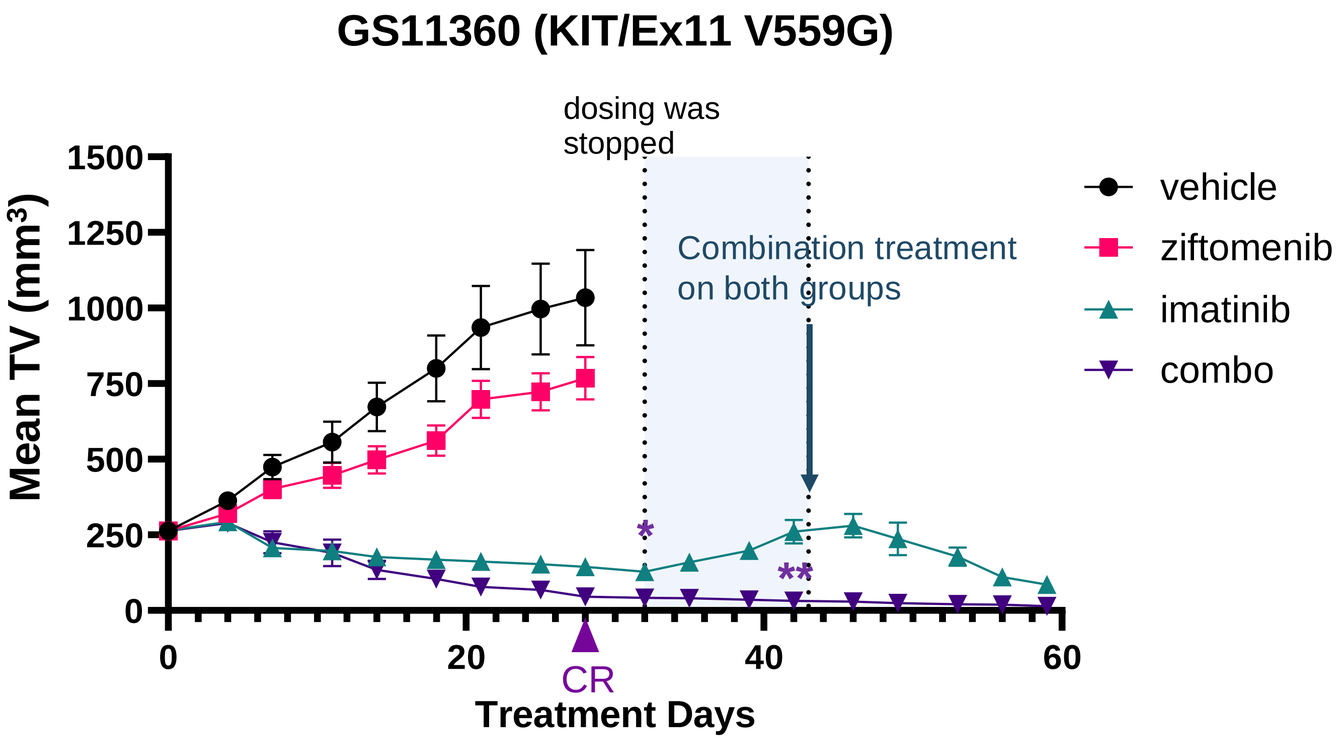

- Imatinib monotherapy was tumoristatic, but the ziftomenib-imatinib combination induced deep regressions in all animals, including some CRs
- Cessation of dosing resulted in rapid regrowth in imatinib-treated tumors, but tumors treated with the combination continued to regress
- Imatinib-treated tumors that relapsed after dosing was stopped then regressed when exposed to the combination

Data were presented as Mean ± SEM; t-test; *P<0.05,**P<0.01,***P<0.001,****P<0.0001, not significant (ns)

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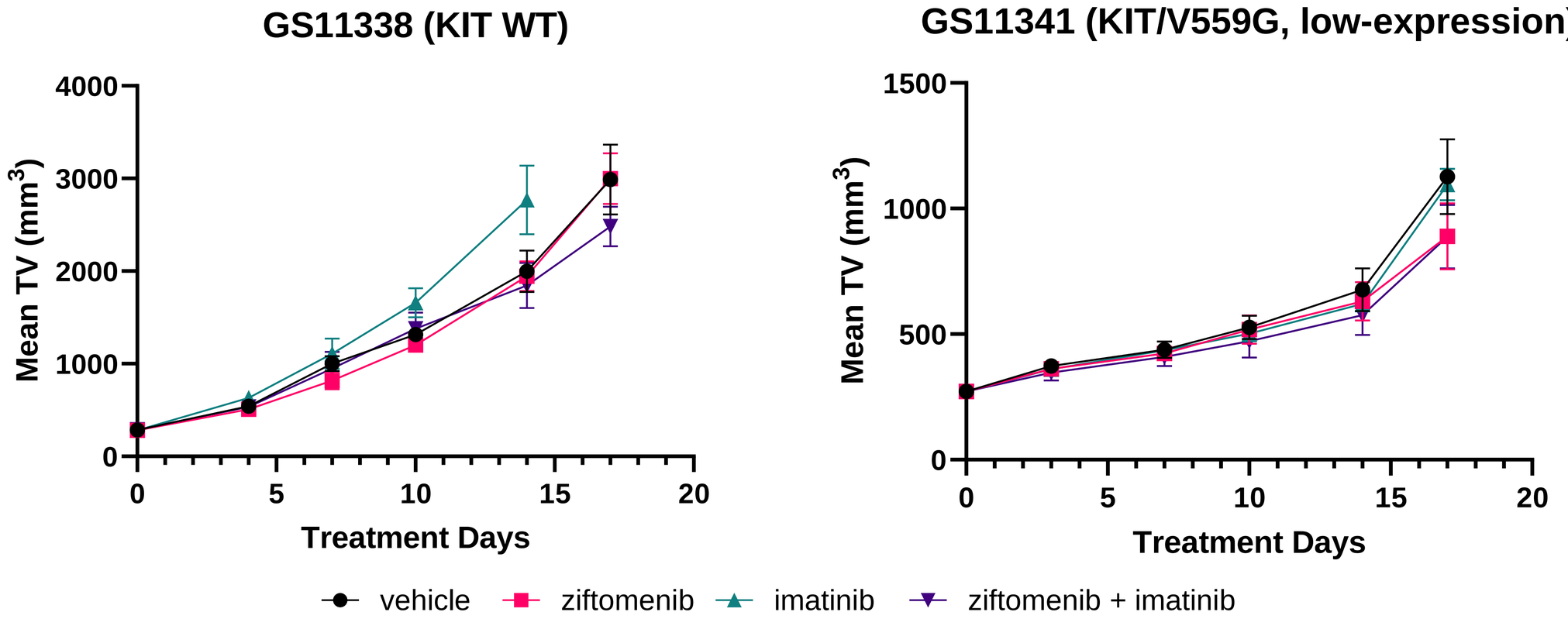
The ziftomenib-imatinib combination is inactive in KIT-independent GIST PDX models



The mechanism of action of the combination is dependent on oncogenic KIT

Data were presented as Mean ± SEM

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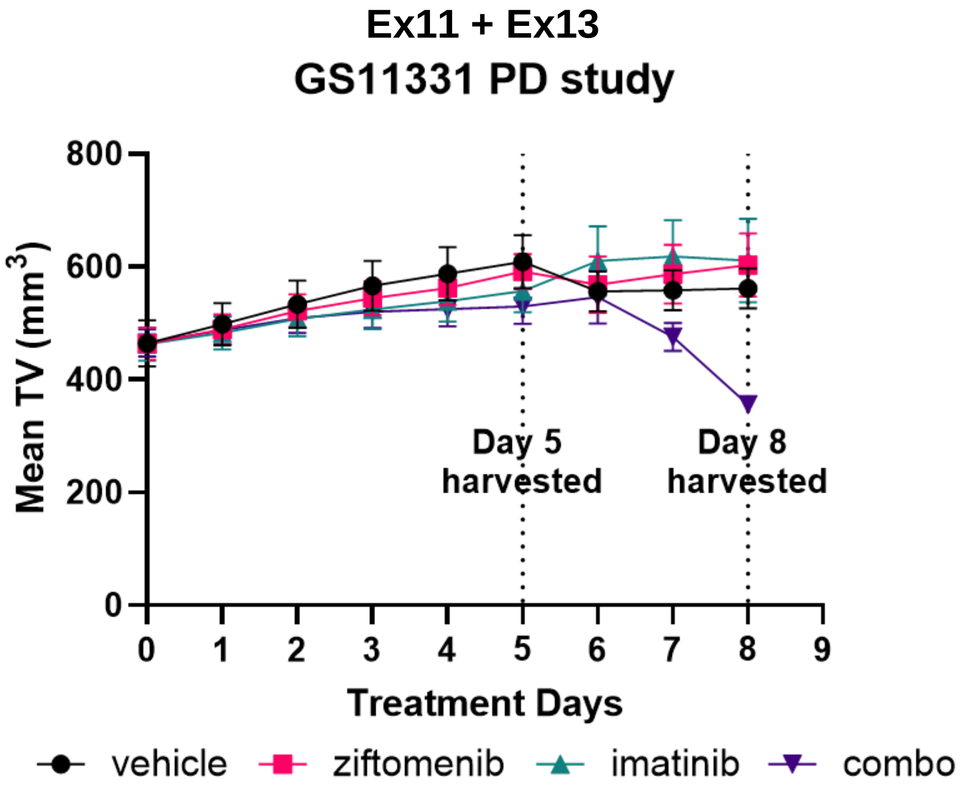
A pharmacodynamic study was conducted to investigate the mechanism of action of the combination



- A western blot test was conducted to investigate KIT protein level changes and downstream oncogenic signaling
- qPCR was conducted to measure KIT gene transcription

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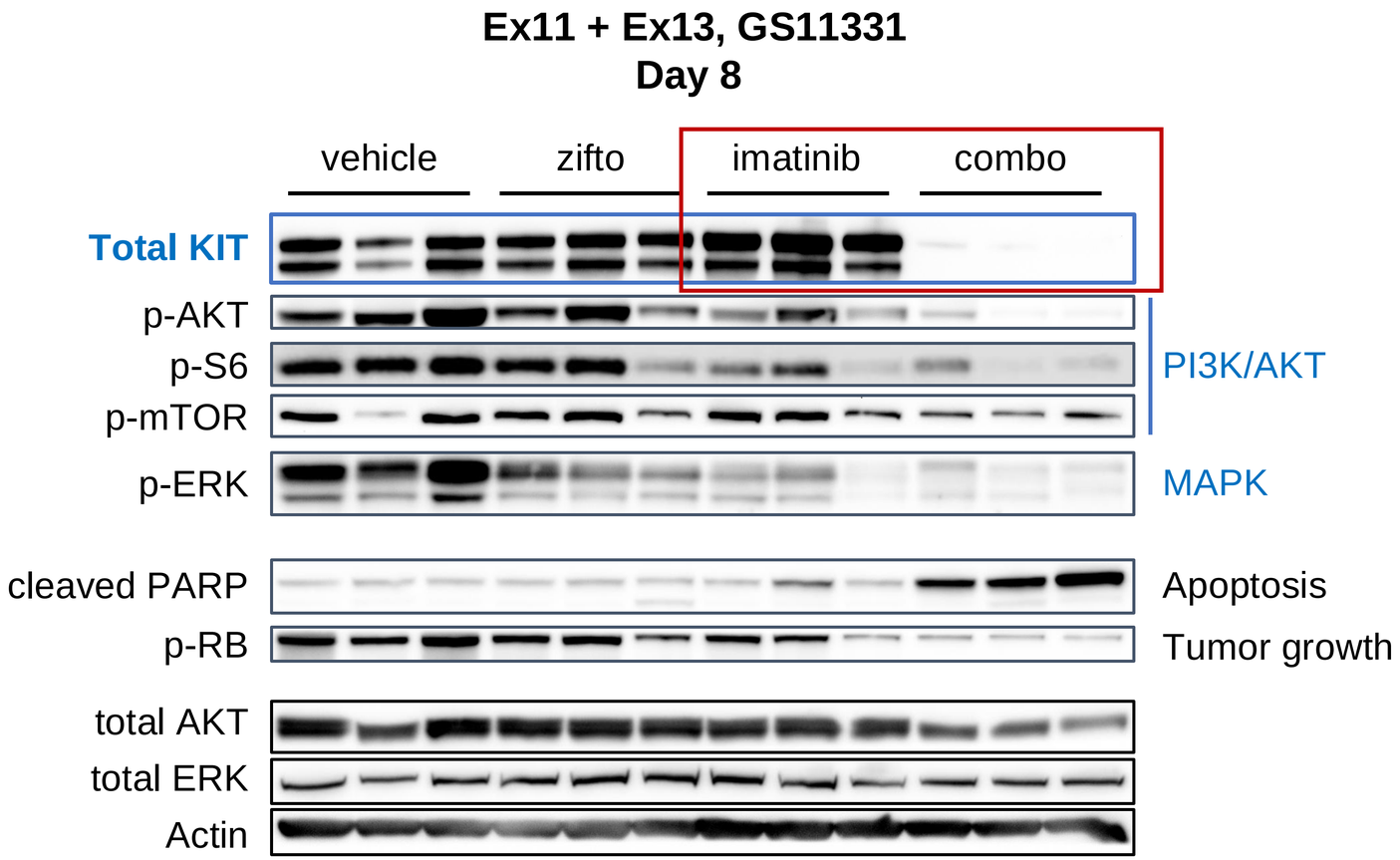
Ziftomenib and imatinib combine to drive complete KIT protein depletion in a partially imatinib-resistant second-line GIST PDX model



- Although imatinib increased total KIT protein levels, the combination with ziftomenib resulted in complete KIT depletion

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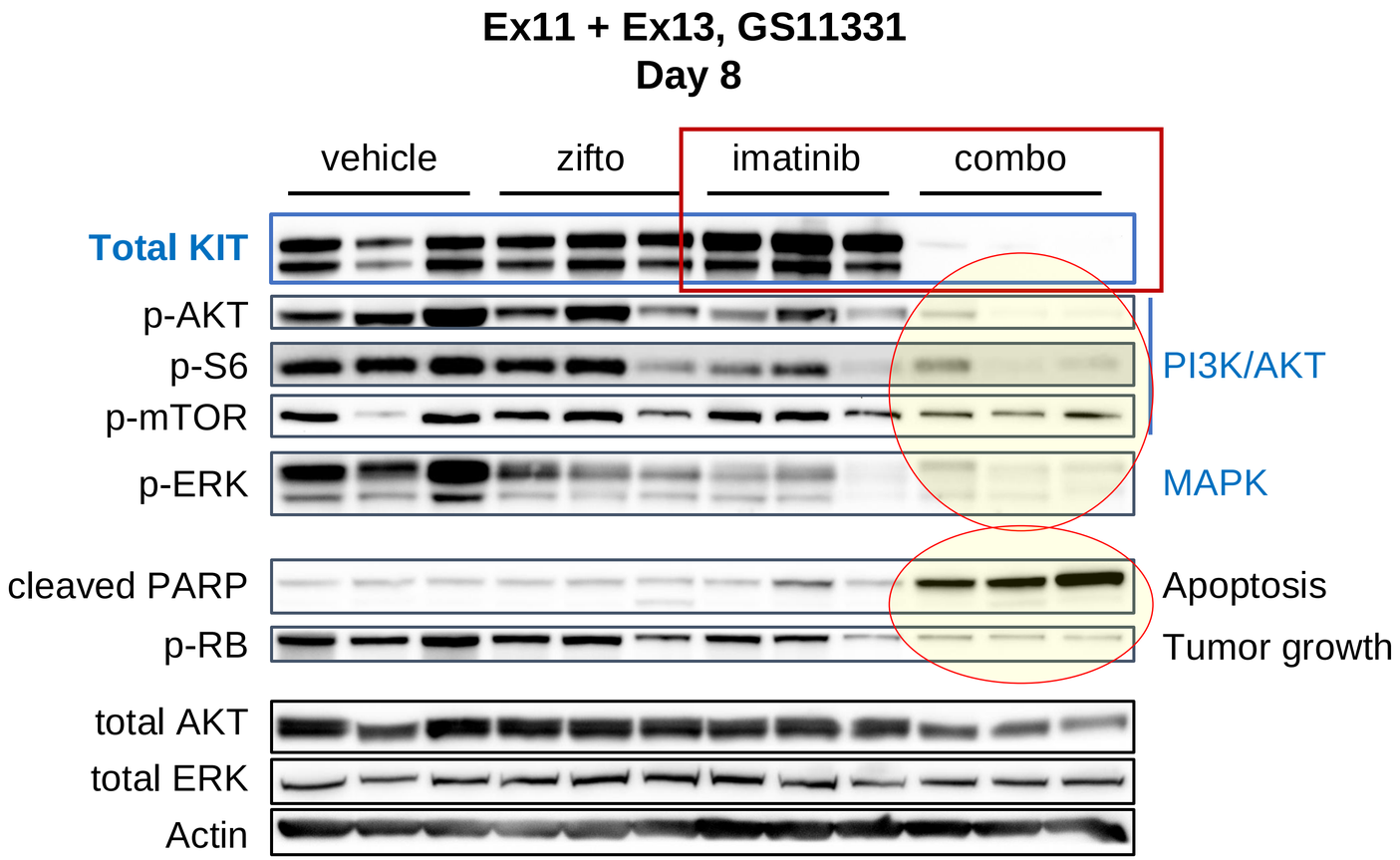

- Although imatinib increased total KIT protein levels, the combination with ziftomenib resulted in complete KIT depletion
- As a result, downstream signaling through the MAPK and PI3K/AKT pathways was sharply reduced
- Robust cell cycle arrest (p-RB) and apoptosis (cleaved PARP) ensued from the simultaneous blockade of proliferation and survival signaling

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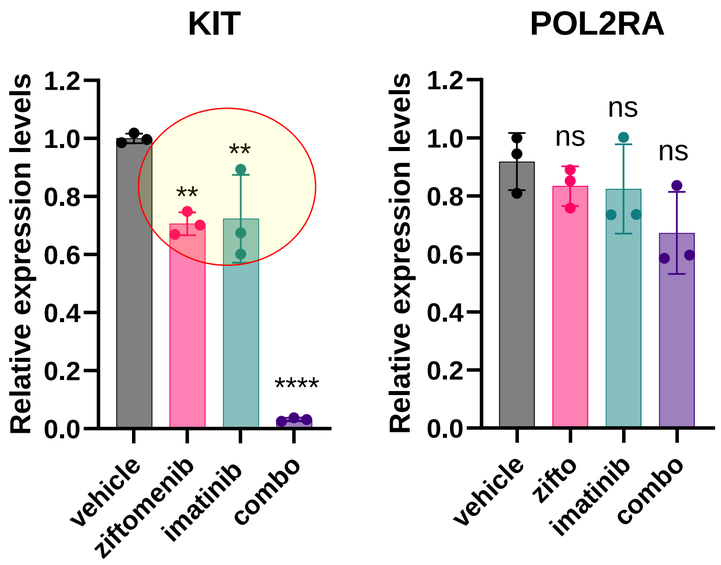
Ziftomenib and imatinib combine to silence KIT gene transcription

RT-qPCR
Ex11 + Ex13, GS11331
Day 5



- Both imatinib and ziftomenib modestly inhibited KIT transcription, as previously reported[1]

1. Hemming M (2022) Cancer Discov.12 1804-1823

Gene levels were quantified by qPCR and normalized by IPO8. Data were presented as Mean ± SD; two-way ANOVA followed by Dunnett test; *P<0.05,**P<0.01,***P<0.001,****P<0.0001, not significant (ns)

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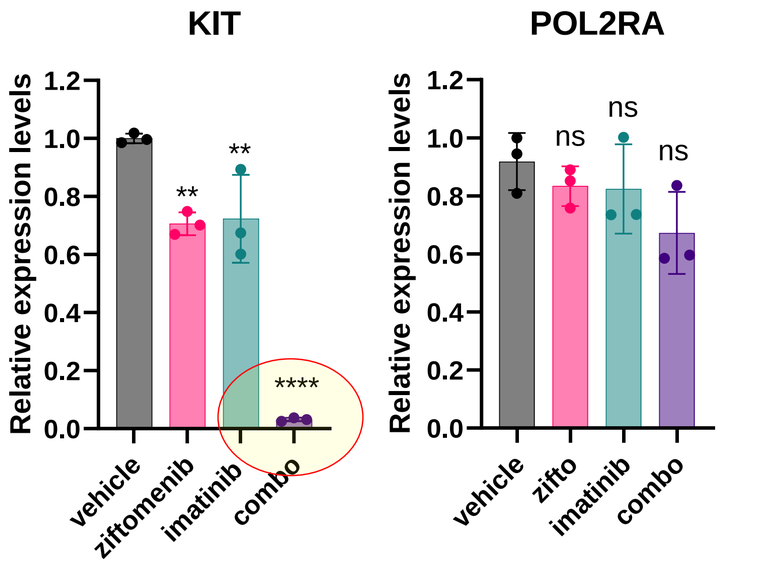

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- Combination treatment almost completely shut down KIT gene transcription, while the control gene (POLR2A) was not affected

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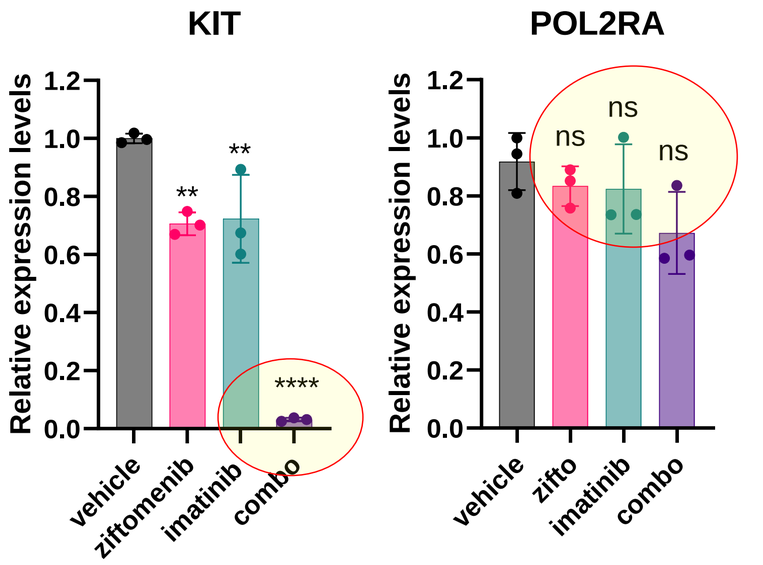

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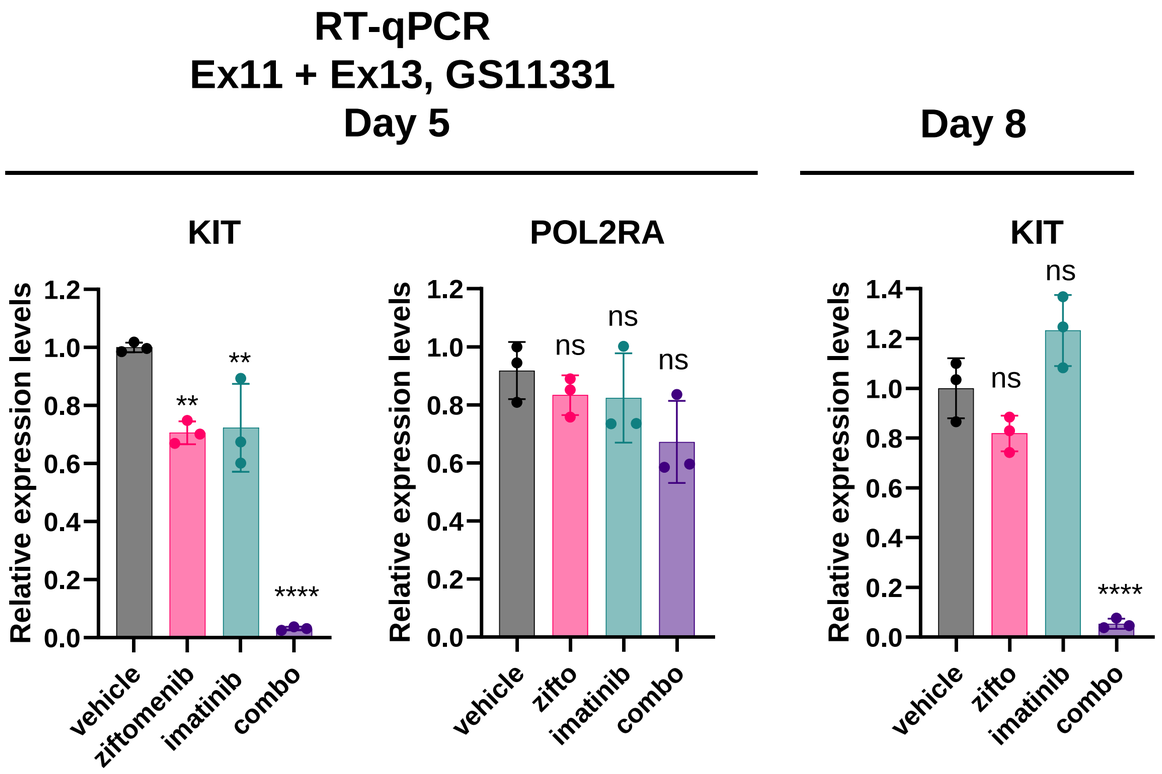

- Both imatinib and ziftomenib modestly inhibited KIT transcription, as previously reported[1]
- Combination treatment almost completely shut down KIT gene transcription, while the control gene (POLR2A) was not affected
- KIT transcription remained silenced on Day 8

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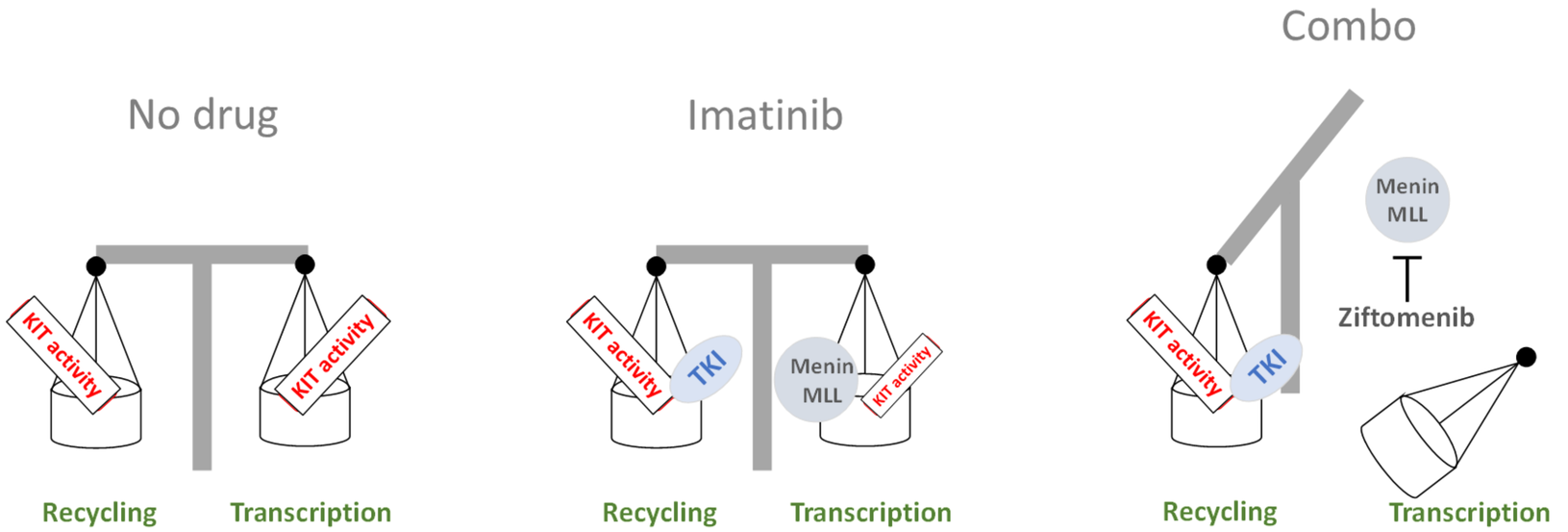
Ziftomenib (menin inhibitor) and imatinib (TKI) combine to silence KIT in a mutation-independent manner



KIT expression is maintained by a balance between degradation and replacement, both driven by KIT activity

Imatinib increases KIT degradation, which can be rescued by epigenetic transcriptional upregulation by menin-MLL

The imatinib-ziftomenib combo enhances KIT recycling while simultaneously reducing KIT transcription

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Summary

- **Ziftomenib-imatinib combination treatment unexpectedly showed robust antitumor activity not only in imatinib-sensitive but also in imatinib-resistant KIT-dependent GIST models representing the full GIST treatment continuum**

- **The combination of ziftomenib + imatinib exerts antitumor activity by a synthetic lethal mechanism through which ziftomenib epigenetically targets a vulnerability of GIST tumors actively induced by ineffective TKI treatments**

- **A proof-of-concept study of ziftomenib + imatinib in patients with advanced GIST after imatinib failure is expected to start in 1H 2025 (NCT06655246)**

Acknowledgements

- **Translational Research team at Kura Oncology, Inc.**