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Phase 1a/1b study of the safety, pharmacokinetics, and antitumor activity of ziftomenib in combination with imatinib in patients with advanced gastrointestinal stromal tumors after imatinib failure

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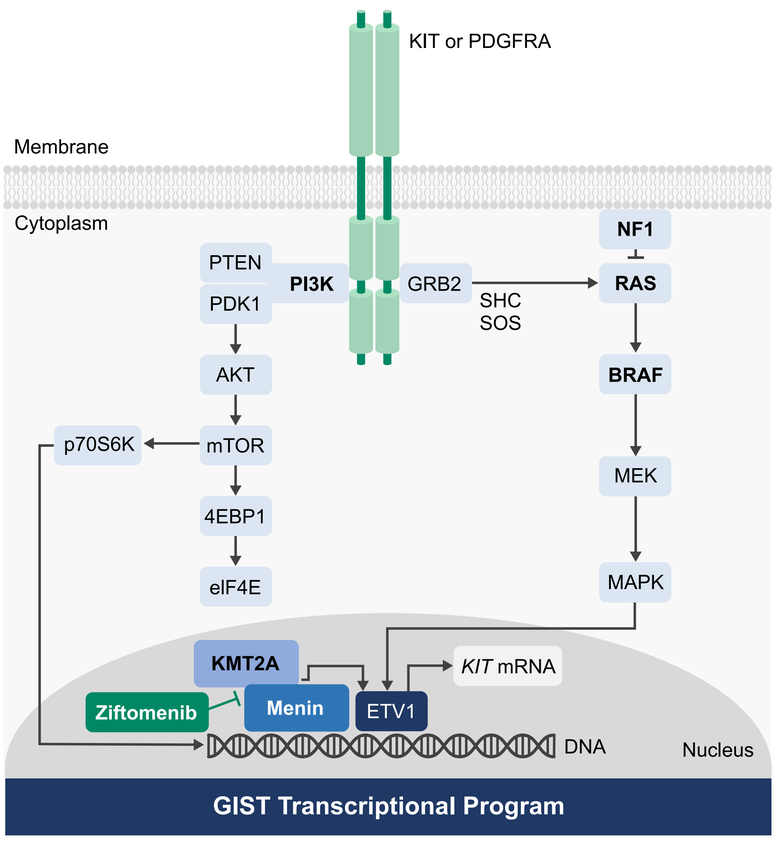
Background

- Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasm of the digestive tract and are often driven by gain-of-function oncogenic mutations in the receptor tyrosine kinase KIT[1]
- Patients with GIST typically receive anti-KIT tyrosine kinase inhibitors (TKIs) such as imatinib; however, few achieve a complete response, and many progress due to secondary *KIT* alterations[1-4]
  - TKIs given in later lines have shown only moderate clinical outcomes[1,5]
- Preclinically, the menin-KMT2A complex has been shown to sit on the *KIT* gene promotor and epigenetically upregulate *KIT* expression in GIST cells[6] (**Figure 1**)
- Ziftomenib is a potent and highly selective oral menin inhibitor that disrupts formation of the menin-KMT2A complex
- **Ziftomenib in combination with imatinib has demonstrated antitumor activity in imatinib-sensitive and -resistant KIT-dependent GIST models[7]:**
  - Ziftomenib plus imatinib reduced *KIT* expression levels
  - The combination drove complete KIT protein depletion in a partially imatinib-resistant second-line patient-derived xenograft (PDX) model
  - Ziftomenib significantly enhanced imatinib activity in an imatinib-sensitive first-line PDX model, while the combination was inactive in a KIT-independent model
- **Ziftomenib plus imatinib combination is being investigated clinically in patients with imatinib-resistant advanced GIST**

Figure 1. Signaling Pathways of *KIT*-Mutated GIST[1,6,8]



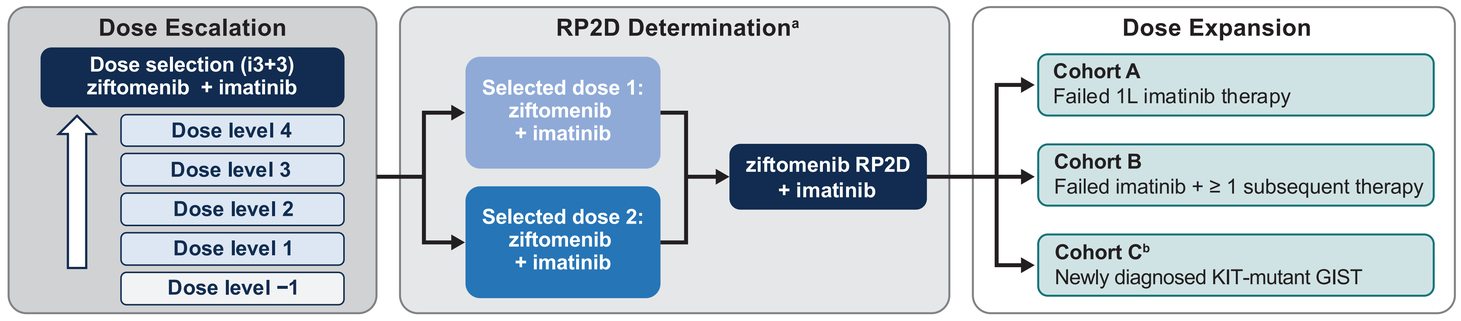
GIST, gastrointestinal stromal tumors.

Methods

Study Design and Patients

- KOMET-015 (NCT06655246) is an open-label, Phase 1a/1b study to determine the safety, tolerability, recommended phase 2 dose (RP2D), and preliminary antitumor activity of ziftomenib plus imatinib 400 mg (or stable dose of imatinib as monotherapy) for patients with advanced/metastatic GIST
- The KOMET-015 study includes 3 parts: dose escalation, RP2D determination, and dose expansion (**Figure 2**)

Figure 2. KOMET-015 Study Design



[a]Up to 2 doses will be selected for RP2D determination based on dose escalation data; [b]Cohort C inclusion pending Safety Monitoring Committee review.
1L, first line; GIST, gastrointestinal stromal tumors; RP2D, recommended phase 2 dose.

- Key eligibility criteria are shown in **Table 1**

Table 1. Key Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• ≥ 18 years of age • Biopsy-proven advanced/metastatic *KIT*-mutated GIST • ≥ 1 measurable lesion per mRECIST • ECOG performance status ≤ 2 • Adequate organ function (liver, kidney, bone marrow) • Prior imatinib therapy: – **Dose escalation/RP2D determination**: Must be failing or have failed imatinib in any prior treatment line[a] – **Dose expansion**: • **Cohort A**: Must have failed imatinib as most recent therapy before enrollment, or must have progression on imatinib as current therapy[a] • **Cohort B**: Previously failed imatinib and received additional therapy since failure • **Cohort C**: Newly diagnosed GIST with no prior treatment[b]	• Diagnosis of non-*KIT* mutation-driven GIST, or known T670X *KIT* mutation-driven GIST • Mean QTc interval by Fridericia's formula > 470 ms • LVEF < 50% at screening • Known active central nervous system metastases • Any concomitant medications other than those allowed at study entry

[a]Those receiving imatinib who did not achieve an objective response after ≥ 1 year may be eligible per Medical Monitor; [b]Cohort C inclusion pending Safety Monitoring Committee review.
ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumors; LVEF, left ventricular ejection fraction; mRECIST, modified Response Evaluation Criteria in Solid Tumors; QTc, QT-corrected; RP2D, recommended phase 2 dose.

- Primary and secondary outcome measures are shown in **Table 2**

Table 2. Outcome Measures

Objectives	Endpoints
Primary	
Dose escalation	
• Determine safety and tolerability of ziftomenib in combination with imatinib	• Rate of DLTs per dose level • AEs per NCI-CTCAE v5.0
RP2D determination	
• Determine RP2D of the combination	• Based on the totality of evidence (eg, PK, safety, pharmacodynamics, preliminary antitumor activity)
• Determine safety and tolerability of the combination	• AEs per NCI-CTCAE v5.0
Dose expansion	
• Evaluate preliminary antitumor activity of the combination	• CBR[a] per mRECIST criteria
• Determine safety and tolerability of the combination	• AEs per NCI-CTCAE v5.0
Secondary (all study parts)	
• Evaluate survival and disease control outcomes of ziftomenib in combination with imatinib	• CBR,[a] ORR,[b] progression-free survival, duration of response, and overall survival
• Characterize the PK of ziftomenib in combination with imatinib	• Multiple dose PK of ziftomenib: C_{max}, T_{max}, $AUC_{(0\text{-last})}$, $AUC_{(tau)}$
• Characterize the PK of imatinib in combination with ziftomenib	• Multiple dose PK of imatinib: C_{max}, T_{max}, $AUC_{(0\text{-last})}$, $AUC_{(tau)}$

[a]Defined as patients achieving a complete response, partial response, or stable disease (for ≥ 16 weeks); [b]Defined as patients achieving a complete response or partial response.
AE, adverse event; $AUC_{(0\text{-last})}$, area under the concentration-time curve from 0 to the time of the last quantifiable concentration; $AUC_{(tau)}$, area under the concentration-time curve over a dosing interval; CBR, clinical benefit rate; C_{max}, maximum plasma concentration; DLT, dose-limiting toxicity; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NCI CTCAE v5.0, National Cancer Institute Clinical Trial Criteria for Adverse Events, version 5.0; ORR, overall response rate; PK, pharmacokinetics; RP2D, recommended phase 2 dose; T_{max}, time to maximum plasma concentration.

Enrollment and Conclusions

- KOMET-015 is exploring the safety, tolerability, and preliminary antitumor activity of ziftomenib plus imatinib in patients with advanced/metastatic GIST
- This trial is open and actively recruiting, with sites in the United States
- For more information, see clinicaltrials.gov/study/NCT06655246

References and Acknowledgements

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Author Contributions

Each author contributed to study conception/design or data collection/analysis/interpretation; and development of this poster or critical review of the content. Each author gave approval for the final poster.

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