Focal Adhesion Kinase Inhibitor Narmafotinib Targets the Tumor and Microenvironment to Enhance and Sustain Sensitivity to Chemotherapy

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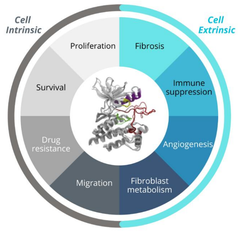
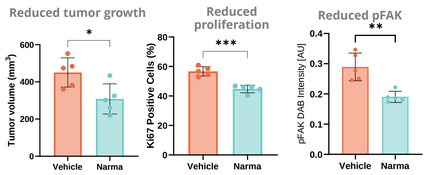
1. Narmafotinib (AMP945) is a selective and orally bioavailable inhibitor of Focal Adhesion Kinase (FAK)

- FAK is a non-receptor tyrosine kinase that acts through numerous signaling pathways to mediate communication between cells and their environment.
- FAK plays a crucial role in normal cellular stress response[1].
- Aberrant FAK signaling has been implicated in the progression of cancer, where it is involved in promoting tumor growth, adhesion, angiogenesis, invasion, and migration, as well as immunomodulation and remodeling of the fibrotic tumor microenvironment[2-4].
- FAK is frequently overexpressed in a variety of cancers, including pancreatic ductal adenocarcinoma[4], a highly fibrotic and aggressive malignancy with a poor 5-year survival rate[5], in which high FAK expression correlates with poor prognosis[6,7].

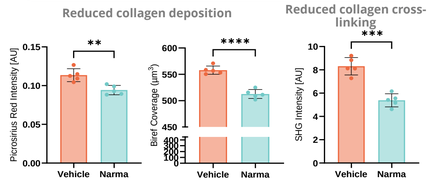


2. Narmafotinib treatment directly affects the tumor and microenvironment

Narmafotinib treatment reduced tumor growth & proliferation

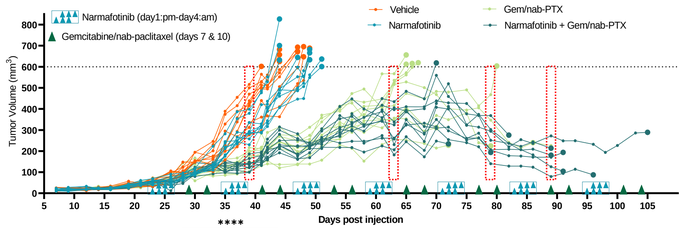


Narmafotinib treatment reduced tumor fibrosis

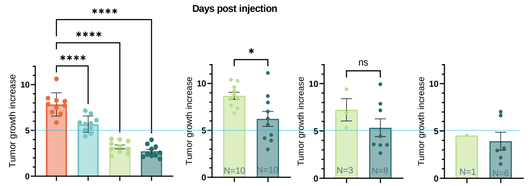


Mean ± SD; p-values determined using Welch's t test

3. Narmafotinib improves responsiveness to gemcitabine and nab-paclitaxel; tumors showed enhanced sensitivity to chemotherapy with sustained reduction in growth



90% of mice treated with a **narmafotinib combined with gemcitabine/ nab-paclitaxel** sustain sensitivity to chemotherapy

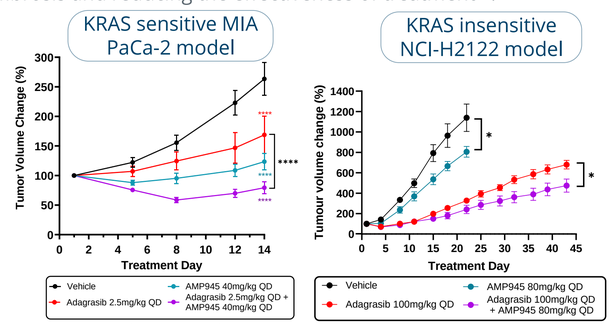


Mean ± SD; p-values determined using one-way ANOVA or Welch's t test.

Preclinical pancreatic cancer model: Patient-derived TKCC10lo cell line subcutaneous xenograft model treated with **vehicle**, **narmafotinib alone**, **gemcitabine/nab-paclitaxel** or **narmafotinib in combination with gemcitabine/nab-paclitaxel.**

5. Narmafotinib increases and sustains tumor responsiveness to KRAS G12C inhibitor adagrasib

KRAS mutations are common oncogenic drivers; KRAS G12C inhibition can hyperactivate FAK signaling, which can lead to fibrosis and reducing the effectiveness of treatment[10].



Mean ± SEM; p-values determined using 2-way ANOVA with Sidak's multiple comparison test (left panel) or unpaired t test (right panel).

Preclinical KRAS G12C mutant cancer model: MIA PaCa-2 (pancreatic) and NCI-H2122 (lung) subcutaneous xenograft model treated with **vehicle**, **narmafotinib alone**, **adagrasib alone** or **narmafotinib in combination with adagrasib.**

4. Clinical dose-dependent benefit of narmafotinib in combination with gemcitabine and nab-paclitaxel (Abraxane®) standard of care as first-line therapy in patients with metastatic pancreatic cancer: ACCENT trial (provisional analysis of Phase 1b)

The **ACCENT trial (NCT05355298)** is a Phase 1b/2a, open label study of the pharmacokinetics, safety and efficacy of narmafotinib in combination with gemcitabine and nab-paclitaxel (Abraxane®) standard of care (SOC), as first-line therapy in patients with advanced pancreatic cancer. The trial is a single-arm open-label study conducted in two stages.

*Dose selected for Phase 2

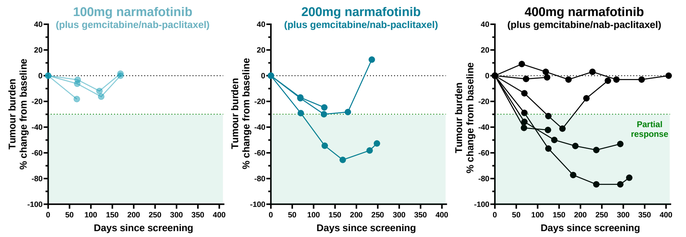
Part A (Phase 1b): patients with advanced pancreatic cancer were enrolled in a 3+3 design, with narmafotinib dose escalation (100, 200 and 400 mg), and the primary objective of determining recommended Phase 2 dose, and assessing safety and tolerability of oral narmafotinib administered prior to IV administration of gemcitabine and nab-paclitaxel.

Part B (Phase 2a) is a Simon's two-stage design, with the primary objectives of assessing safety, tolerability, and efficacy of the combination using RECIST v1.1.

- All participants received oral narmafotinib once daily at the selected dose on Day -8 to Day -2 (7 doses total) of a monotherapy run-in period, prior to first treatment cycle.
- Each 28-day treatment cycle includes IV gemcitabine and nab-paclitaxel on Days 1, 8 and 15, and oral narmafotinib priming on Days 3 to 6, 10 to 13, and 24 to 27, inclusive.

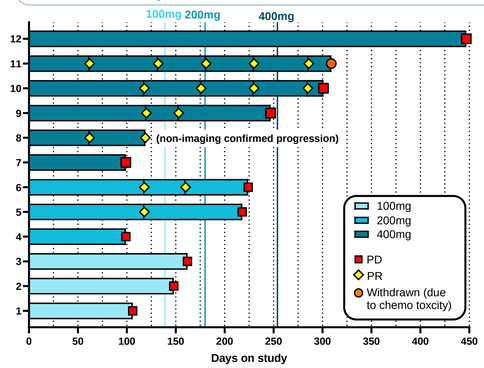
Dose-dependent reduction in tumor burden

- There were five confirmed partial responses (4 at 400 mg narmafotinib; 1 at 200 mg), indicating increased response with increasing dose.



Note: investigator read provisional analysis

Dose-dependent increase in treatment duration



Mean time on study for patients receiving **100mg**, **200mg** or **400mg** narmafotinib is indicated by bold lines on graph.

Note: Two dose-adjusted patients (400mg→100mg & 400mg→200mg) were included in safety and overall response analysis but are not shown on graphs.

- 6 patients on 400 mg narmafotinib had mean treatment duration of 8.3 months, with 4 of 6 patients on study for >6 months.
- Historical median duration of treatment for gemcitabine & nab-paclitaxel is 3.9 - 4.1 months; median time to treatment failure/duration of response is ~5 months[8,9].
- Narmafotinib in combination SOC was generally well-tolerated.

6. Conclusions

- Narmafotinib reduces tumor growth and fibrosis in a patient-derived pancreatic cancer xenograft model
- Narmafotinib enhances sensitivity to gemcitabine/nab-paclitaxel in preclinical models to sustain tumor growth reduction and increase overall survival
- Preclinical analysis indicates that narmafotinib shows efficacy in combination with KRAS G12C inhibitor adagrasib
- In the clinic (Phase 1b), narmafotinib combined with gemcitabine/nab-paclitaxel demonstrated promising activity in a dose-dependent manner in response and duration of treatment
  - Five confirmed partial responses (4 at 400 mg narmafotinib; 1 at 200 mg), indicating increased response with increasing dose
  - 400 mg of narmafotinib and gemcitabine/nab-paclitaxel mean duration of treatment was 8.3 months, out-performing historical SOC ~4 months
  - Narmafotinib in combination SOC was generally well-tolerated

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** p < 0.05*
*** p < 0.01*
**** p < 0.001*
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