

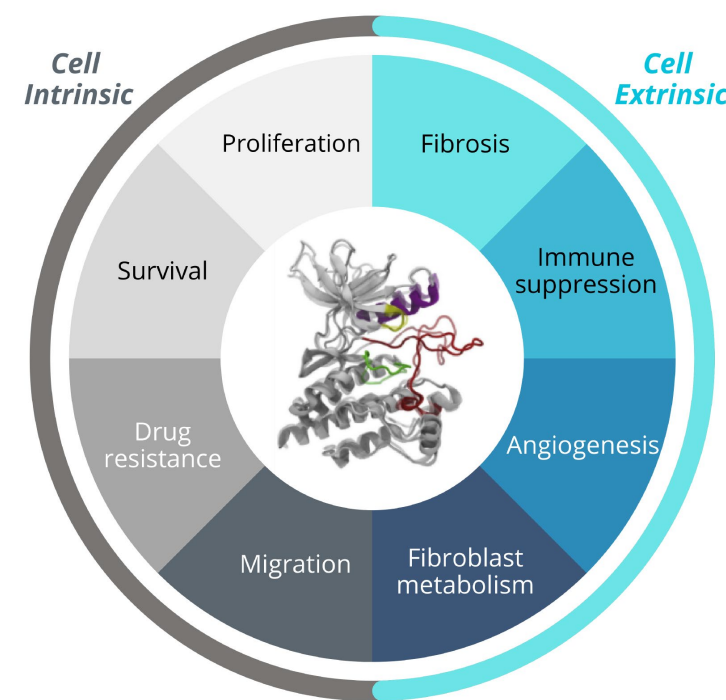
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Background

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 key signaling pathways to mediate communication between cells and their environment and plays a crucial role in normal cellular stress response, acting to buffer healthy cells from dying when exposed to extreme cellular stress¹.



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 microenvironment²⁻⁴. FAK is frequently overexpressed in a variety of cancers, including pancreatic ductal adenocarcinoma (PDAC)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}.

ACCENT Study Overview

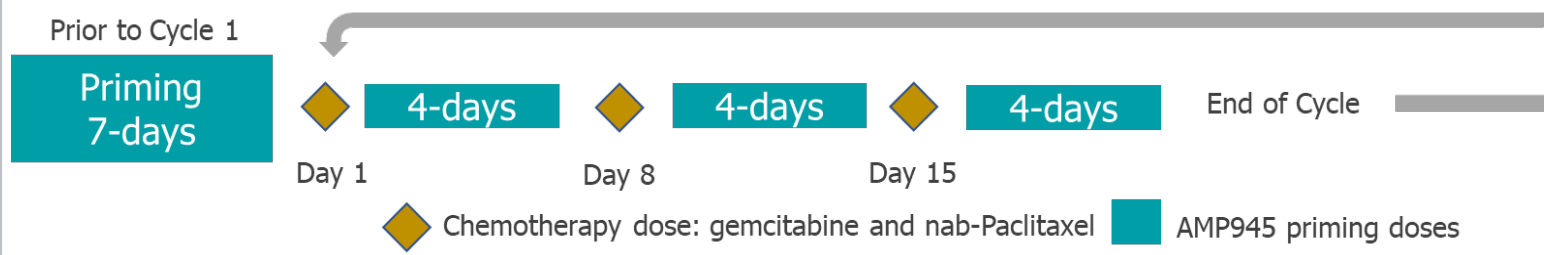
ACCENT trial (NCT05355298) is a Phase 1b/2a, open label study of the pharmacokinetics, safety and efficacy of narmafotinib in combination with gemcitabine and nab-paclitaxel (Abraxane®) standard of care as first-line therapy in patients with advanced pancreatic cancer. The trial is a single-arm open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



Part A (Phase 1b), patients were enrolled in a 3+3 design to determine the narmafotinib recommended Phase 2 dose (RP2D), with dose-escalation (100, 200 and 400 mg), with a primary objective of determining recommended RP2D, and assessing safety and tolerability of oral narmafotinib administered prior to IV administration of gemcitabine and nab-paclitaxel in participants with advanced pancreatic cancer.

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 (central read by indep't reviewers).

Dosing Regimens



All participants receive 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 the first treatment cycle. Each 28-day treatment cycle includes IV nab-paclitaxel (Abraxane®) and gemcitabine on Days 1, 8 and 15, and oral narmafotinib priming on Days 3 to 6, 10 to 13, and 24 to 27, inclusive.

Key Eligibility Criteria

Inclusion	Exclusion
<ul style="list-style-type: none"> Diagnosis of metastatic or not surgically resectable PDAC ECOG status of 0 or 1 Measurable disease per RECIST 1.1 Life expectancy ≥ 3 months Acceptable hematologic and clinical laboratory chemistry values 	<ul style="list-style-type: none"> Received prior systemic treatment for PDAC, except as a radiosensitizer, provided >6 months have elapsed since last dose and no toxicities >grade 1 are still present Known brain metastases, unless treated and well-controlled for > 3 months GI condition that could interfere with swallowing or absorption of medication

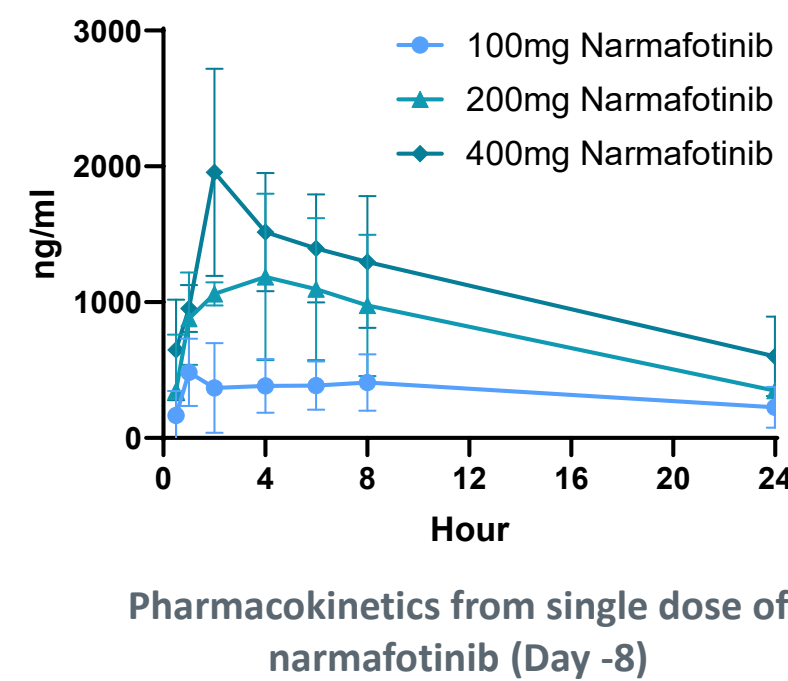
Patient demographics: Part A dose escalation

14 patients were treated with narmafotinib + gemcitabine/nab-paclitaxel (Abraxane®)

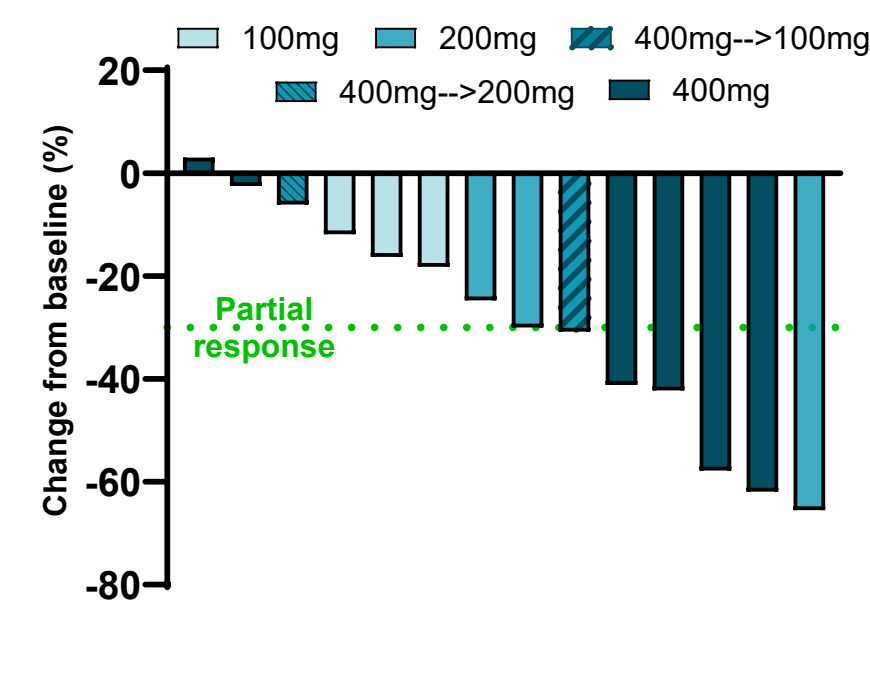
- Males n=7 (50%)
- Females n=7 (50%)
- Average age: 62 years old
- Predominantly Caucasian

Pharmacokinetics

- Narmafotinib plasma PK samples were collected on Days -8, -7, 1, 3, 8, and 10 of Run-In/Cycle 1
- The PK for narmafotinib is dose-proportional across the dose range tested, and the half-life supports once a day dosing
- The chemotherapy regimen used in this study did not impact narmafotinib PK



Best Response by RECIST v 1.1

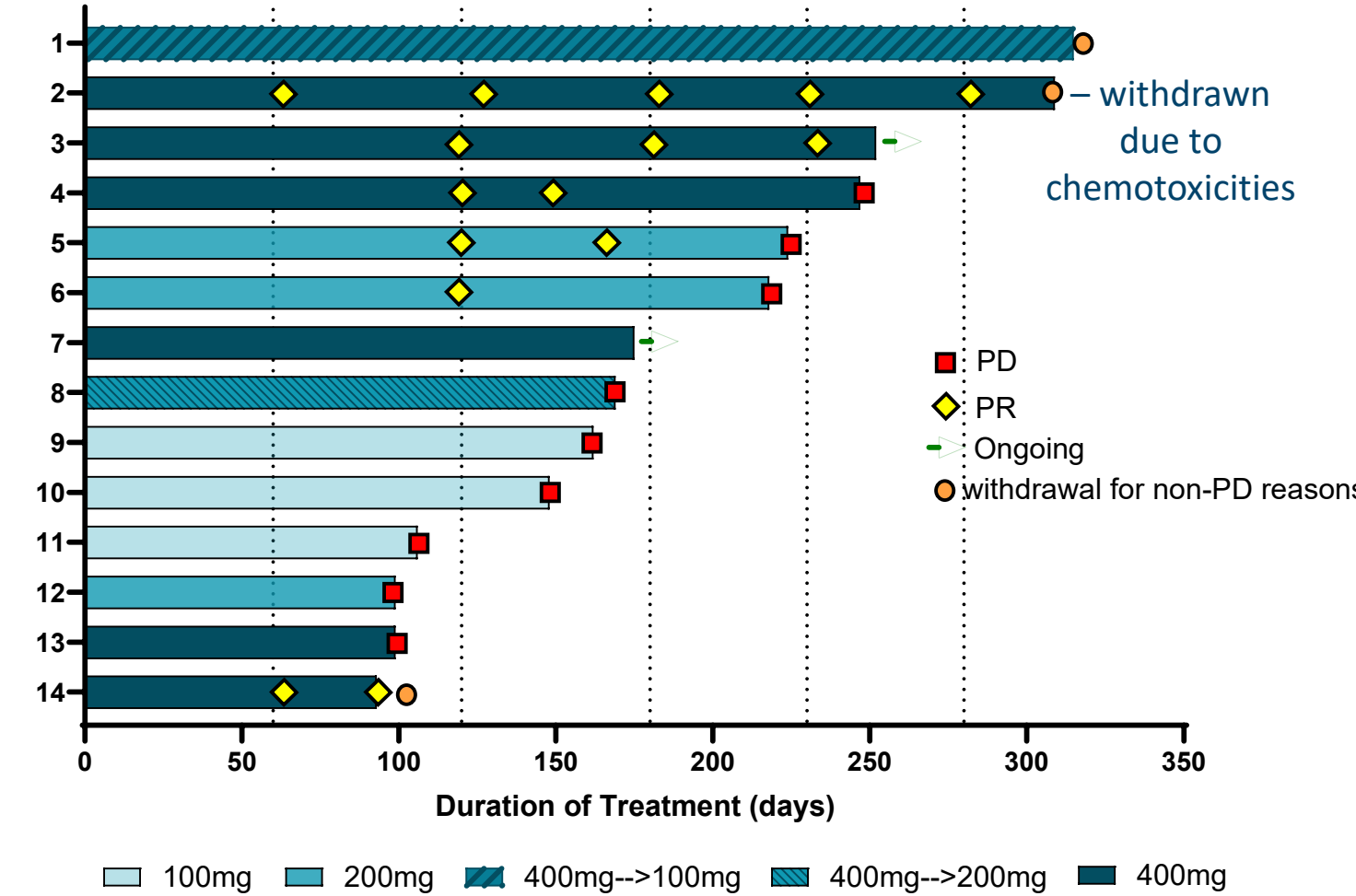


Classification	Best Overall Response
(n)	14
CR	0 (0%)
PR	6 (43%)
SD	8 (57%)
DCR (PR+SD)	14 (100%)
PD	0 (0%)
Not Evaluable	0 (0%)

Investigator assessed

- Narmafotinib combined with gemcitabine/nab-paclitaxel (Abraxane®) demonstrated promising dose related trend in the first 14 patients – with ORR of 43%.
- This compares favorably with the reported response rate of 23% with gemcitabine/Abraxane® in the pivotal Phase III trial⁸.
- Two patients had dose adjustments due to AEs from 400mg to 100mg and 400mg to 200mg

Time on treatment



- All patients who completed their first 28-day cycle of treatment elected to stay on narmafotinib
- 9 of 14 patients on drug > 5 months
- There was a dose dependent trend in duration of treatment with the highest dose of narmafotinib (400 mg QD) associated with the longest duration of treatment, 212 days (mean duration)

Safety

- Narmafotinib-related events - the following occurred in more than one participant: diarrhea, gastroesophageal reflux disease, nausea, vomiting, fatigue, pyrexia, and macro-papular rash
- No treatment related deaths and only two narmafotinib related SAEs: febrile infection, and fatigue
- All other SAEs reported to date have either been unrelated or assessed as related to gemcitabine/Abraxane®
- No dose limiting toxicities (DLTs) were noted in the 100 mg and 200 mg cohorts. A single DLT (Grade 3 Nausea >72 h) was reported at the 400 mg dose
- Two patients had dose adjustments due to AEs from 400mg to 100mg and 400mg to 200mg
- No MTD was defined for narmafotinib

System Organ Class	Preferred Term	Grade 3 or above					
		Related Narmafotinib (N=15)	Related Gemcitabine (N=14)	Related Nab-Paclitaxel (N=14)	Unrelated Any Related	Unrelated Not Related	All Events
n (%) E							
Blood and lymphatic system disorders	Anaemia	0	1 (7) 1	1 (7) 1	1 (7) 1	0	1 (7) 1
Gastrointestinal disorders	Nausea	1 (7) 1	1 (7) 1	1 (7) 1	1 (7) 1	0	1 (7) 1
	Vomiting	1 (7) 1	1 (7) 1	1 (7) 1	1 (7) 1	0	1 (7) 1
General disorders & administration site conditions	Fatigue	1 (7) 1	1 (7) 1	1 (7) 1	1 (7) 1	0	1 (7) 1
	Febrile infection	1 (7) 1	0	0	1 (7) 1	0	1 (7) 1
	Pyrexia	0	2 (13) 3	2 (13) 3	2 (13) 3	2 (13) 2	3 (20) 5
Injury, poisoning & procedural complications	Toxicity to various agents	0	1 (7) 1	1 (7) 1	1 (7) 1	0	1 (7) 1
Metabolism & nutrition disorders	Dehydration	0	1 (7) 1	1 (7) 1	1 (7) 1	0	1 (7) 1

Participants who experienced multiple events within a category are counted only once in the specific category (n), however each instance of the event is counted (E). Percentage (%) of participants (n) are calculated based on the number of participants for the respective dose level (N).

Conclusions

- ✓ Dose escalation assessed 100 mg, 200 mg, 400 mg once daily
- ✓ Excellent once a day, dose proportional pharmacokinetics
- ✓ Safe and well tolerated
- ✓ Narmafotinib combined with gemcitabine/nab-paclitaxel (Abraxane®) demonstrates promising activity, with investigator assessed response rate of 43%
- ✓ Based on this promising Phase 1b data, 400 mg of narmafotinib has been selected for RP2D and the trial will proceed through Simon's Two Stage design and enroll up to 50 patients as part of the Phase 2 expansion cohort



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