Rationale for the use of pulsed rather than continual dosing of the novel Focal Adhesion Kinase inhibitor AMP945 in pancreatic cancer

Anthony Bishop[1], Mark Devlin[1], Rhiannon Jones[1], John Lambert[1], Kendelle Murphy[2], David Herrmann[2], Paul Timpson[2]
1. Amplia Therapeutics Limited. 17/350 Queen St, Melbourne, Victoria, AUSTRALIA. 2. Garvan Institute of Medical Research and The Kinghorn Cancer Centre, Cancer Division. 384 Victoria St, Darlinghurst, New South Wales, AUSTRALIA
Communication: Anthony@ampliatx.com

Garvan Institute

Amplia THERAPEUTICS

1 Overview

Amplia Introduction

Amplia Therapeutics Limited (ASX: ATX, Amplia) is a clinical-stage drug development company focused on the development of potent, orally available inhibitors of Focal Adhesion Kinase (FAK) for the treatment of cancer and fibrotic diseases.

Amplia's pipeline drugs were originally developed by the Cancer Therapeutics Cooperative Research Centre, an Australian industry/academic collaboration. Amplia was established to advance these promising drugs into clinical development and commercialisation.

FAK in Pancreatic Cancer

FAK is a nonreceptor protein tyrosine kinase that is primarily regulated by integrin signalling. FAK controls fundamental cellular processes such as cell adhesion, migration, proliferation, and survival, and promotes important malignant features in cancer progression including tumour angiogenesis, chemotherapeutic resistance, and fibrosis in the stroma. FAK expression is frequently upregulated in different types of cancer and contributes to cancer progression by regulating the tumour microenvironment. Several FAK inhibitors are currently in early clinical development.

AMP945 Overview

AMP945 is a highly selective and potent inhibitor of FAK and is in clinical development for both pancreatic cancer and Idiopathic Pulmonary Fibrosis. FDA Orphan Drug Designations for both these indications have been granted.

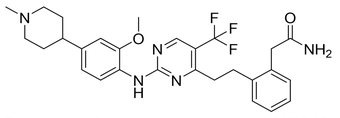

Figure 1: Molecular structure of AMP945

AMP945 has been found to be orally bioavailable in rats and dogs. AMP945 has been shown to inhibit FAK both *in vitro* and *in vivo* and is highly selective for FAK. A comprehensive preclinical and nonclinical development program was undertaken to support clinical development and established good safety margins. As shown by CYP induction, inhibition and phenotyping experiments, AMP945 has a low potential for drug-drug interactions.

A Phase 1 study (ACTRN12620000894998) was undertaken in healthy volunteers. AMP945 oral capsules showed excellent safety, tolerability, and PK properties.[1] No SAEs or study withdrawals were noted. The Phase 1 clinical trial supported the continued development of AMP945.

Amplia is developing AMP945 for the treatment of pancreatic cancer in combination with standard of care gemcitabine and nab-paclitaxel. **The Phase 1b/2a clinical trial is formally known as AMP945-PC-201 and is designated ACCENT**.

2 Preclinical Evidence in Cancer Disease Models

2a. Anti-FAK Activity

FAK has been associated with the activity of myofibroblasts and collagen deposition and remodelling in pancreatic cancer. In preclinical studies, AMP945 displays potent anti-fibrotic activity *in vitro* and *in vivo*.

Using immunohistochemistry it was shown that AMP945 treatment led to significantly decreased levels of p-FAK in the tumour compared to vehicle treated mice (Figure 2). Tumour cells derived from the mouse pancreatic tumour line KPC were implanted subcutaneously into the flanks of Balb/c nude mice. Once tumours became palpable, mice were randomised to receive oral vehicle or AMP945 10 mg/kg BID for 3 days.

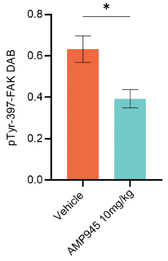

Figure 2: AMP945 leads to reduction in p-FAK in tumour

2b. AMP945 Increased Survival

Mice were implanted with patient derived pancreatic cancer cells (TKCC) and held until the tumour was palpable. The mice were dosed with AMP945 on Day 1-4 and treated with gemcitabine and nab-paclitaxel on Day 7 and Day 10. This cycle was repeated every 12-days until the experimental endpoint was reached. Median survival times for mice receiving AMP945, gemcitabine and nab-paclitaxel were longer than those receiving only gemcitabine and nab-paclitaxel.

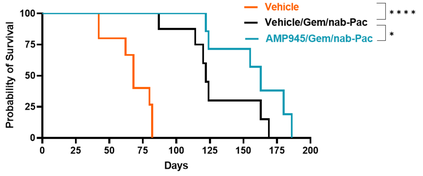

Figure 3: PDX model shows AMP945 boosts efficacy of gemcitabine and nab-paclitaxel

References:
(1) Pharmacodynamics of AMP945, a potent and selective Focal Adhesion Kinase inhibitor, in normal healthy volunteers. Lambert et. al. 2022 AACR Presentation.
(2) Intravital imaging technology guides FAK-mediated priming in pancreatic cancer precision medicine according to Merlin status. Murphy *et al., Sci. Adv.* 2021; 7
(3) Focal adhesion kinase priming in pancreatic cancer, altering biomechanics to improve chemotherapy. Murphy et. al., Biochem Soc Trans (2022) 50 (4): 1129–1141.
(4)Increased Survival in Pancreatic Cancer with nab-paclitaxel plus Gemcitabine. Von Hoff et. al., N Engl J Med 2013; 369:1691-1703

* $p \leq 0.05$ ** $p \leq 0.01$ ***$p \leq 0.001$ ****$p \leq 0.0001$

2c. Pulsed Dosing Increases Survival

Mice were implanted with ectopic KPC pancreatic cancers and were treated with gemcitabine and nab-paclitaxel and either twice daily doses (chronic) of AMP945 (Figure 4) or pulsed doses of AMP945 (Figure 5). After an ethical endpoint their tumours were harvested. Median survival times for mice receiving pulsed doses of AMP945 were longer than those receiving daily doses.[2, 3]

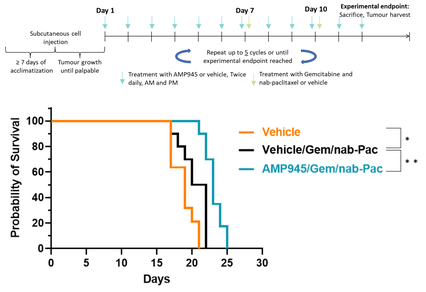

Figure 4: Dosing schedule and Kaplan-Meier survival for KPC tumour-bearing mice treated with vehicle, chronic AMP945, gemcitabine and nab-paclitaxel

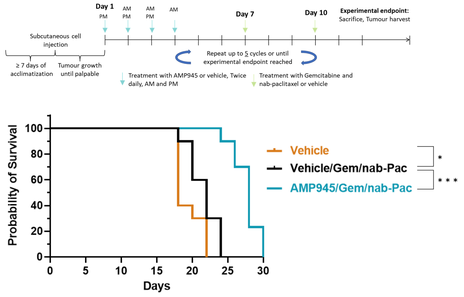

Figure 5: Dosing schedule and Kaplan-Meier survival for KPC Tumour-bearing mice treated with vehicle, pulsed AMP945, gemcitabine and nab-paclitaxel

3 Phase 2 Rationale

Phase 1 Target Engagement

In the Phase 1 study[1], target engagement was an exploratory analysis measured by the inhibition of Y397-FAK (p-FAK) in skin punch biopsies. Figure 6 shows the change in p-FAK from baseline according to dose for volunteers after daily dosing for 1 week. p-FAK levels were reduced by AMP945 in a roughly dose proportional manner.

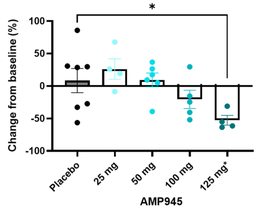

Figure 6: Dose dependent decrease in pFAK levels in skin biopsies

ACCENT Clinical Trial Design

Amplia's Phase 1b/2a clinical trial AMP945-PC-201 (ACCENT, NCT05355298) will assess a pulse dosing regimen of AMP945 in combination with gemcitabine and nab-paclitaxel as first-line therapy in patients with unresectable or metastatic pancreatic cancer. In ACCENT, patients will initially be treated with a one-week priming dose of AMP945 (once a day capsule). Gemcitabine and nab-paclitaxel will be given according to a standard treatment regimen and the patients will be pulse dosed for four days AMP945 prior to weekly chemotherapy administration (Figure 7). Phase 1a of the study is a 3+3 design to find an "optimal biological dose" guided by the FDA's Project Optimus. Part 2a is a Simon Two-Stage design to assess efficacy by ORR compared to historical response rates.[4]

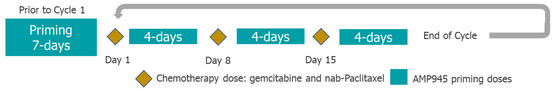

Figure 7: Amplia's investigational chemotherapy treatment cycle

Anticipated benefits of the pulsed dosing schedule:

- Potentiates response to standard of care chemotherapy
- Limits risk of acquired resistance
- Reduces potential for drug-drug interactions
- Patients can self-administer AMP945

ACCENT Status

First patient began treatment in August 2022. Up to 8 sites will be initiated in Australia. The trial will be extended into sites in South Korea for Part B. For more information visit:

www.ampliatx.com/site/clinical-trial