EVOLUTION CAPITAL

ASX: ATX
Healthcare
Initiation Report

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Cracking Cancer's Code: Amplia's Bid to Transform Pancreatic Cancer Therapy

Evolution Capital initiates coverage on Amplia Therapeutics (ASX: ATX), a clinical-stage biotechnology company on the cusp of a major value inflection point, with topline data from its pivotal Phase 2 ACCENT trial expected by the end of July 2025. Amplia is at the forefront of developing narmafotinib, a highly potent and selective FAK inhibitor poised to transform the standard of care for metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) and other challenging solid tumours. Narmafotinib's unique mechanism enhances the efficacy of standard chemotherapy by dismantling the tumour's protective barriers, offering a significant survival advantage without introducing additional toxicity. Critically, Amplia recently announced two complete responses, where all cancerous lesions disappeared. This is almost unheard of, and ATX did it with just 55 patients at hand.

Tackling a Titan: The 3% Survival Rate in Pancreatic Cancer

Pancreatic cancer presents one of the most formidable challenges in modern oncology. The prognosis is particularly dire for mPDAC where the 5-year overall survival rate is a stark 3%. Over 50% of PDAC is diagnosed metastatic. The result: patients are left with limited and often ineffective treatment options. This is compounded by the fact that most mPDAC patients don't even make it to a year: median overall survival is 8.5 months on current standard of care treatment. Against this backdrop of profound unmet need, narmafotinib offers a novel approach by targeting Focal Adhesion Kinase (FAK) – a master regulator of tumour progression and chemoresistance. By inhibiting FAK, narmafotinib breaks down the dense fibrotic stroma and reverses the immunosuppressive microenvironment that shields tumours, making them vulnerable to chemotherapy.

Unprecedented Clinical Signals of Efficacy

The ongoing Phase 2 ACCENT trial has delivered exceptional early data that sets narmafotinib apart. In combination with standard-of-care chemotherapy, the trial has yielded multiple, extremely rare Complete Responses (CRs), an outcome almost unheard of in metastatic disease. These results massively outperform historical benchmarks from the pivotal MPACT study, suggesting that topline data will demonstrate a paradigm-shifting improvement in patient outcomes.

Just the Beginning: A Valuation Primed for Expansion

Our Price Target is modestly based on an expected market entry solely in first-line mPDAC in the US and Europe. We see significant potential for valuation uplift as Amplia advances its clinical program. Future growth will be driven by label expansion (with positive data in other solid tumours with a similar fibrotic profile such as ovarian and breast); new treatment settings (such as second-line therapy and adjuvant settings for post-surgical patients); and broader market access (with expansion into other jurisdictions, particularly Asia). Should strong topline ACCENT data eventuate, the NPV risking factor will be revised, increasing the valuation.

Narmafotinib is potentially a best-in-class drug that is not just another incremental advance, but a potential game-changer in oncology. Evolution initiates on ATX with a SOTP-derived fair valuation of $0.47, and a Speculative Buy Recommendation.

Key Near-Term Catalysts	
Topline ACCENT Data	End July
Initiation of FOLFIRINOX Phase II Trial	H2 2025
Mature Survival Data (PFS/OS) from ACCENT	Q1 2026

Recommendation	**Spec Buy**
Share Price	**$0.35**
Fair Valuation	**$0.47**

Company Profile	
Market Cap	$136.0M
SOI (undiluted)	388.7M
Free Float	85.7%
ADV (1-month)	$185k
52-Week Range	$0.049 - $0.425

Price Performance

Company Overview

Amplia Therapeutics (ASX: ATX) is a clinical-stage biotechnology company developing targeted therapies for aggressive, treatment-resistant cancers. Its lead asset, narmafotinib (AMP945), is a next-generation FAK inhibitor designed to enhance the efficacy of chemotherapy by dismantling the tumour's fibrotic and immunosuppressive defences. Currently in a pivotal Phase 2 trial (ACCENT) for first-line metastatic pancreatic cancer, narmafotinib has shown early signs of deep and durable responses, including rare complete remissions. With regulatory designations secured and multiple expansion opportunities in play, Amplia is positioned near a major value inflection point.

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Investment Thesis

Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) stands as one of the most formidable challenges in modern oncology, characterized by a dire prognosis and a treatment landscape that has seen only marginal improvements over decades. The global market for pancreatic cancer therapies is substantial and expanding, yet it remains dominated by cytotoxic chemotherapy regimens that offer limited survival benefits, creating a profound and urgent unmet medical need. At the heart of PDAC's recalcitrance are two interconnected biological barriers: a dense, fibrotic stroma that physically shields the tumour from therapeutic agents, and a deeply immunosuppressive tumour microenvironment (TME) that prevents immune-mediated destruction.

Focal Adhesion Kinase (FAK), a non-receptor tyrosine kinase, has been scientifically validated as a master regulator of both of these barriers. The history of FAK inhibitor (FAKi) development is a telling narrative of initial promise, followed by clinical failures when these agents were tested as monotherapies. This journey, however, yielded a crucial understanding: FAK's primary role in cancer is not that of a classical oncogenic driver, but rather a critical facilitator of tumour progression, metastasis, and resistance to treatment. This realization has correctly pivoted the entire development strategy for the class towards intelligent combination therapies designed to dismantle the tumour's defences and sensitize it to other treatments. A landmark moment for this strategy occurred in May 2025 with the FDA's accelerated approval of Verastem Oncology's defactinib, a FAKi, in combination with a MEK inhibitor for low-grade serous ovarian cancer. This approval provides a powerful regulatory and commercial precedent, validating the FAKi combination approach and illuminating a viable path to market.

Against this backdrop, Amplia Therapeutics (ASX: ATX) is developing narmafotinib (AMP945), a next-generation FAKi distinguished by its high potency and selectivity. In the ongoing Phase 2 ACCENT trial for first-line mPDAC, narmafotinib, when added to the standard-of-care chemotherapy of gemcitabine and nab-paclitaxel, is demonstrating a potentially transformative efficacy profile. The observation of multiple, extremely rare complete responses (CRs) and a pathological complete response (pCR) – where no viable tumour cells remain upon surgical examination – places narmafotinib in a class of its own. These early clinical signals starkly differentiate it from the historical efficacy benchmarks of standard chemotherapy and the known profiles of competitor FAK inhibitors.

The investment thesis for Amplia is therefore centred on a high-risk, high-reward opportunity to redefine the standard of care in first-line mPDAC. Narmafotinib's unique selectivity and unprecedented early clinical data suggest it may possess a "best-in-class" profile. The company is approaching several key value-inflection points, most notably the topline data readout from the 55-patient ACCENT trial cohort. Positive results from this trial, particularly on survival metrics, could significantly de-risk the asset, attract a strategic partner, and unlock substantial shareholder value. The primary risks remain those inherent to all small-cap biotechnology ventures: the challenge of replicating Phase 2 results in a larger Phase 3 trial, navigating an evolving competitive landscape, and securing future financing to support late-stage development.

The Therapeutic Quagmire of PDAC

Epidemiology & Prognosis

Pancreatic cancer represents a dire public health challenge, with PDAC accounting for over 96% of all cases. The disease is projected to become the second leading cause of cancer-related mortality by 2026, a testament to its aggressive biology and the limited efficacy of current treatments. Diagnosis often occurs at a late stage, with a substantial proportion of patients presenting with inoperable locally advanced or metastatic disease. Consequently, the 5-year overall survival rate has remained stubbornly low, hovering around 13%, a figure that has seen little meaningful improvement over the past four decades. 5-year overall survival in a metastatic disease setting is 3%. This statistic underscores the profound unmet medical need for novel therapeutic strategies that can offer more than just incremental gains in survival.

The Current Standard of Care

For patients with mPDAC who have a good performance status (Eastern Cooperative Oncology Group [ECOG] score of 0 or 1), the National Comprehensive Cancer Network (NCCN) recommends several first-line chemotherapy regimens. The selection among these is guided by patient-specific factors, toxicity profiles, and, increasingly, germline testing, as a subset of patients with mutations like BRCA1/2 may derive greater benefit from platinum-based regimens.

The primary standard of care (SoC) regimens that serve as the benchmark for new therapies are:

- **Gemcitabine plus nab-paclitaxel (Abraxane):** This combination is a cornerstone of first-line treatment and is the specific chemotherapy backbone being used in Amplia's ACCENT trial. Data from the pivotal MPACT trial established its efficacy, demonstrating a median Overall Survival (OS) of 8.5 months and a median Progression-Free Survival (PFS) of 5.5 months. Later analyses and real-world data place the median OS closer to 9.2 months. The Objective Response Rate (ORR) is approximately 23-29%, with complete responses being exceptionally rare – a landmark study reported just one CR in 431 patients (0.2%). This regimen serves as the most direct historical comparator for narmafotinib.

- **FOLFIRINOX:** This is a more aggressive four-drug regimen (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin). It has demonstrated a superior median OS of approximately 11.1 months. However, its use is generally restricted to younger, fitter patients due to its significantly higher rate of adverse events, particularly haematological toxicity.

- **NALIRIFOX:** Approved by the FDA in early 2024, this regimen represents the first new first-line treatment for mPDAC in over a decade. It is a combination of liposomal irinotecan (Onivyde), 5-fluorouracil/leucovorin, and oxaliplatin. In the NAPOLI-3 clinical trial, NALIRIFOX demonstrated a median OS of 11.1 months, which was a statistically significant but modest improvement over the 9.2-month median OS observed with gemcitabine/nab-paclitaxel (often also referred to as gemcitabine/Abraxane).

The approval of NALIRIFOX is particularly instructive. It demonstrates that a survival benefit of less than two months is sufficient for FDA approval and subsequent adoption into clinical guidelines. This sets a tangible, albeit low, bar for new therapeutic combinations. For a new agent like narmafotinib, achieving a statistically significant improvement over the gemcitabine/nab-paclitaxel backbone is a clear regulatory path. However, the truly disruptive and commercially transformative potential lies not in incremental gains, but in delivering a paradigm-shifting improvement in survival outcomes, as hinted at by the unprecedented early data from the ACCENT trial.

Figure 1: Efficacy Benchmarks of Standard-of-Care Chemotherapy Regimens in First-Line Metastatic Pancreatic Cancer.

Regimen	Pivotal Trial	Objective Response Rate (ORR)	Median Progression-Free Survival (PFS)	Median Overall Survival (OS)
Gemcitabine + nab/paclitaxel	MPACT	23%	5.5 months	8.5 – 9.2 months
FOLFIRINOX	PRODIGE 4 / ACCORD 11	31.6%	6.4 months	11.1 months
NALIRIFOX	NAPOLI-3	41.8%	7.4 months	11.1 months

This table summarizes the key efficacy outcomes from the pivotal clinical trials that established the current standards of care for first-line metastatic pancreatic cancer. It compares the Objective Response Rate (ORR), Median Progression-Free Survival (PFS), and Median Overall Survival (OS) for Gemcitabine + nab/paclitaxel (MPACT trial), FOLFIRINOX (PRODIGE 4 / ACCORD 11 trial), and the more recent NALIRIFOX (NAPOLI-3 trial). These results represent the clinical benchmarks that new therapeutic combinations, such as narmafotinib plus chemotherapy, will be measured against to demonstrate a meaningful improvement in patient outcomes.

Market Landscape and Size

Pancreatic cancer represents one of the most significant unmet needs in oncology. Globally, it is the sixth leading cause of cancer-related death, with an estimated 511,000 new cases and 467,000 deaths in 2022. The disease is characterized by a poor prognosis, with a global five-year survival rate of approximately 13%. This is primarily due to the disease's aggressive biology and the fact that most patients present with advanced, non-resectable disease at the time of diagnosis. For a novel therapeutic like narmafotinib, it is critical to define the specific, addressable patient population and understand the potential for market expansion over time.

Primary Addressable Market: First-line mPDAC

Narmafotinib's initial target indication is for the first-line treatment of metastatic pancreatic cancer in combination with standard-of-care chemotherapy. To quantify this market, we begin with the total incident population and apply a series of clinically justified filters.

1. **Total Pancreatic Cancer Incidence:** The total number of new pancreatic cancer cases forms the broadest population base. In 2024, an estimated 66,440 new cases are projected for the United States. In Europe, the figure was approximately 146,477 in 2022.

2. **Pancreatic Ductal Adenocarcinoma (PDAC) Population:** The vast majority of pancreatic cancers arise from the exocrine tissue. Pancreatic ductal adenocarcinoma (PDAC) is the most common histological subtype, accounting for over 85-90% of all pancreatic cancer diagnoses. Applying a 90% filter, the incident PDAC population is approximately 59,796 in the US and 131,829 in Europe.

3. **Metastatic Disease at Diagnosis:** A key challenge in pancreatic cancer is its late-stage presentation. Due to its largely asymptomatic progression, a significant proportion of patients are diagnosed only after the cancer has spread to distant organs (metastatic disease). Industry models commonly assume that approximately 50% of PDAC patients present with metastatic disease. This reduces the target population to 29,898 patients in the US and 65,915 in Europe. It is also critical to mention that only 10-20% of mPDAC is resectable at diagnosis, further adding to the challenge of pancreatic cancer.

4. **Utilization of First-Line Chemotherapy:** Not all patients with metastatic disease are eligible for or choose to receive systemic chemotherapy, due to factors such as poor performance status, significant comorbidities, or patient preference. Based on a large-scale analysis of the National Cancer Database, approximately 56% of patients with metastatic PDAC receive systemic chemotherapy.

Applying this final filter defines the immediate, addressable patient pool for narmafotinib upon a successful launch in its initial indication. This results in an eligible

first-line metastatic PDAC population of approximately 16,867 patients in the US and 37,176 in Europe, based on current incidence figures. These numbers form the foundation of our revenue forecasts, which are then projected forward with modest annual growth rates.

Market Expansion Potential: Broadening the Indication
The initial addressable market, while substantial, represents only a fraction of the total therapeutic potential for an effective FAK inhibitor. A significant opportunity for growth lies in the future label expansion of narmafotinib to include all first-line PDAC patients receiving chemotherapy, not just those with metastatic disease.

If narmafotinib demonstrates a strong safety and efficacy profile, it could logically be approved for use in combination with chemotherapy for all patients with PDAC, including those with localized or locally advanced, non-metastatic disease. In this scenario, the "metastatic" filter (Filter 3) is removed from our market sizing. The eligible patient pool would then be defined as: (Total Pancreatic Cancer Patients) x (% PDAC) x (% Receiving First-Line Chemotherapy).

This calculation would effectively double the addressable market in the United States to over 33,700 patients annually. This potential for label expansion represents a significant source of upside to our current valuation, which conservatively models only the metastatic setting. Further potential, not factored into our model, could come from use in other treatment lines (e.g., second line) or in the neo-adjuvant setting for pre-surgical patients, reinforcing the long-term strategic value of the asset.

FAK as a Master Regulator of PDAC

FAK Biology

Focal Adhesion Kinase, encoded by the *PTK2* gene, is a cytoplasmic non-receptor tyrosine kinase that serves as a critical intracellular signalling node. Think of a kinase as a light switch inside a cell – its main job is to turn other proteins “on” so they can perform specific tasks. It does this through phosphorylation – flipping the switch – where the kinase takes a small energy packet (a phosphate group) and attaches it to another protein, activating it. This “on/off” switch is incredibly important because it controls almost everything a cell does: when to grow and divide; when to move; and when to survive or die. Often, cancer occurs when a kinase gets stuck in the “on” position.

FAK is uniquely positioned to integrate signals from two major sources: integrins, which mediate cell adhesion to the extracellular matrix (ECM), and receptor tyrosine kinases (RTKs), which bind growth factors. This central role allows FAK to influence a wide array of cellular processes fundamental to cancer progression.

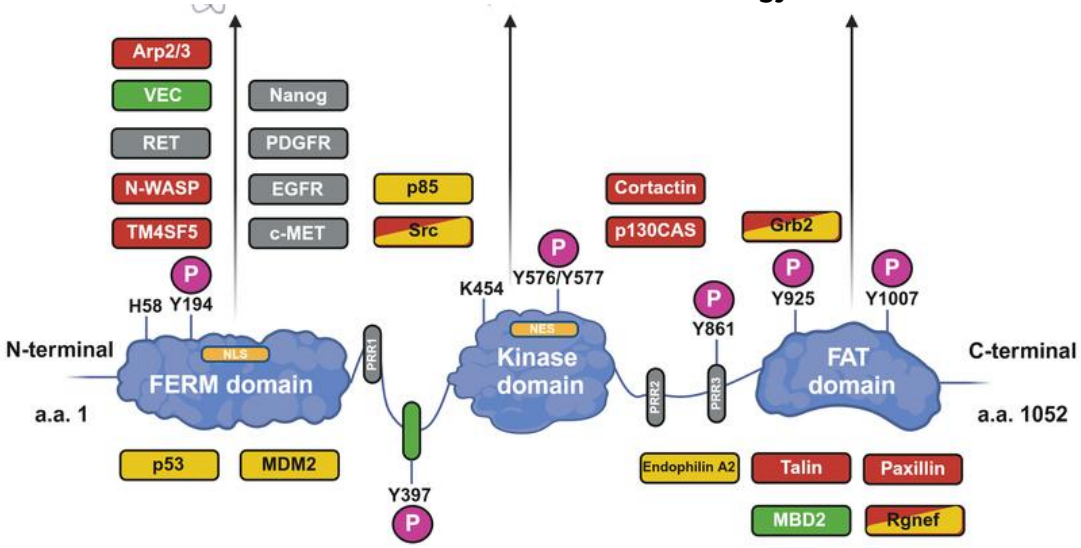
A crucial aspect of FAK biology is its dual functionality, which operates through both kinase-dependent and kinase-independent mechanisms:

1. **Kinase-Dependent Signalling:** Upon activation by integrin clustering or growth factor stimulation, FAK undergoes autophosphorylation (i.e. turns itself “on”) at the tyrosine 397 residue (Y397 in Figure 2 below). This event creates a high-affinity binding site for Src family kinases (in the red/yellow box above Y397). The resulting FAK/Src complex then phosphorylates a host of downstream substrates, triggering oncogenic signalling cascades such as the PI3K/AKT and MAPK/ERK pathways. These pathways are well-established drivers of cell proliferation, survival, and migration. Later in this report, we discuss inhibitors of these pathways in development for solid tumour treatment.

2. **Kinase-Independent Scaffolding:** Beyond its enzymatic activity, FAK possesses a large N-terminal FERM domain (the leftmost domain in Figure 2 below) that functions as a molecular scaffold. This domain facilitates protein-protein

interactions, bringing together over 50 different signalling molecules into functional complexes. This scaffolding role allows FAK to regulate cellular processes and interconnect multiple oncogenic pathways even without its kinase activity. In short, this is how FAK builds the protective "fortress" around the tumour: it organises the cellular machinery needed to remodel the tumour's surroundings.

Figure 2: Structure of the FAK Protein. Source: Frontiers in Oncology.



The image shows the structure of FAK with three main domains. The phosphorylation sites (P) are shown. The main protein interactors of FAK are depicted in the zones corresponding to the binding site; interaction partners are related to cell motility (red), cell survival (yellow) or to both functions (orange and yellow). Additionally, proteins related to FAK activation (grey) and the tumour microenvironment (green) are shown.

FAK's Role in Driving Malignancy

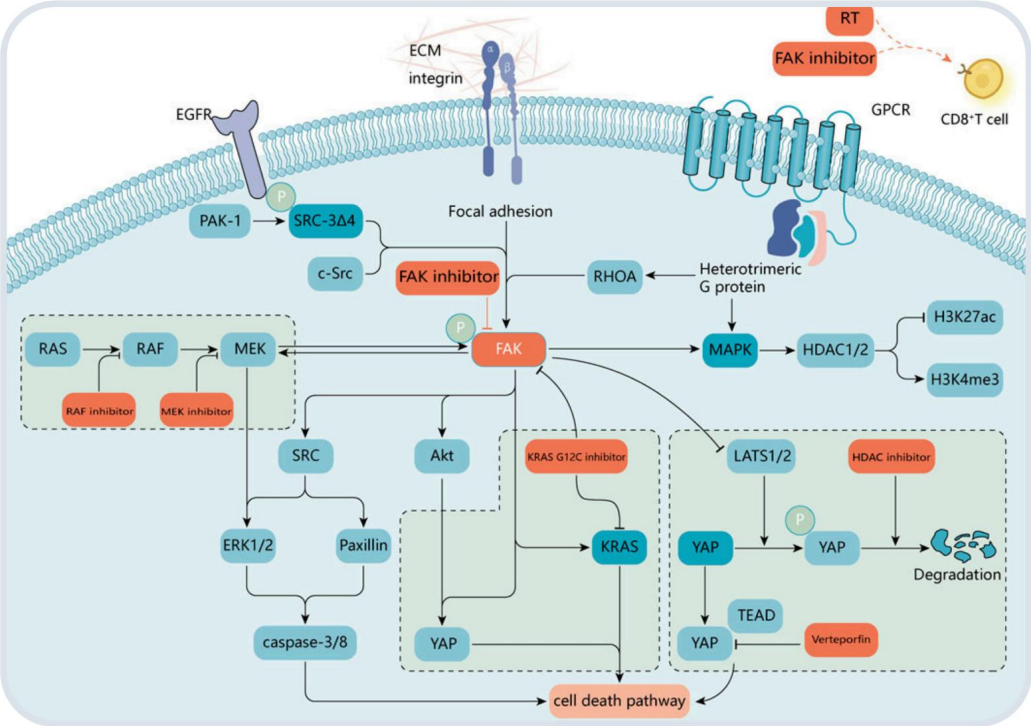
In healthy tissues, FAK activity is tightly regulated. In cancer, however, it is frequently overexpressed and hyperactivated, a status that is strongly correlated with tumour aggressiveness and poor patient prognosis across numerous solid tumours, including PDAC. FAK promotes a malignant phenotype through several key mechanisms:

- **Accelerating Cell Cycle Progression:** FAK signalling, particularly through the ERK1/2 pathway (see bottom left quadrant in Figure 3 below), upregulates the expression of Cyclin D1, a key regulator that pushes cells through the G1/S phase checkpoint of the cell cycle. Accelerated cell cycle progression gives results in uncontrolled and rapid multiplication of cancer cells, which is the fundamental driver of tumour growth.

- **Inhibiting Apoptosis and Promoting Survival:** FAK confers powerful pro-survival signals. It can interact with and promote the degradation of the critical tumour suppressor p53 (pictured as a yellow cell survival interaction partner under the FERM domain in Figure 2 above), thereby preventing p53-mediated apoptosis. It also activates the PI3K/Akt pathway, which inhibits the caspase cascade and protects cells from anoikis – a form of cell death that occurs when cells detach from the ECM.

- **Promoting Invasion and Metastasis:** FAK is a master regulator of cell motility. It localizes to focal adhesions at the leading edge of migrating cells, where it controls their dynamic assembly and disassembly. Through its interaction with adaptor proteins like paxillin (see SRC signalling pathway in Figure 3 below), FAK orchestrates the cytoskeletal rearrangements necessary for cell movement. FAK also promotes epithelial-mesenchymal transition (EMT), a process where epithelial cells acquire migratory and invasive properties, which is a critical step in metastasis.

Figure 3: FAK's Central Position in Key Oncogenic Signaling Pathways. Source: Company presentation.



This signalling map provides a clear visual representation of the mechanisms described in the preceding text, illustrating how FAK acts as a master regulator of malignancy. The diagram shows FAK positioned as a critical hub that translates external cues into internal pro-cancer signals.

FAK as the Architect of the PDAC "Fortress"

Perhaps the most compelling rationale for targeting FAK in PDAC lies in its central role in constructing the tumour's unique and formidable defences. The hallmark of PDAC is a dense, fibrotic stromal reaction known as desmoplasia, which creates a physical and immunological barrier that renders the tumour highly resistant to therapy. FAK is a primary architect of this pathological tumour microenvironment (TME).

- **Driving Fibrosis and Stromal Remodelling:** Hyperactivated FAK drives the excessive deposition of ECM components like collagen. This leads to a dramatic increase in tissue stiffness. This stiff, fibrotic environment not only acts as a physical barrier that impedes drug delivery but also generates mechanical signals that further activate FAK, creating a vicious, self-amplifying feedback loop that enhances cancer cell proliferation and chemoresistance. A FAK inhibitor that can break this cycle would markedly reduce tumour fibrosis.

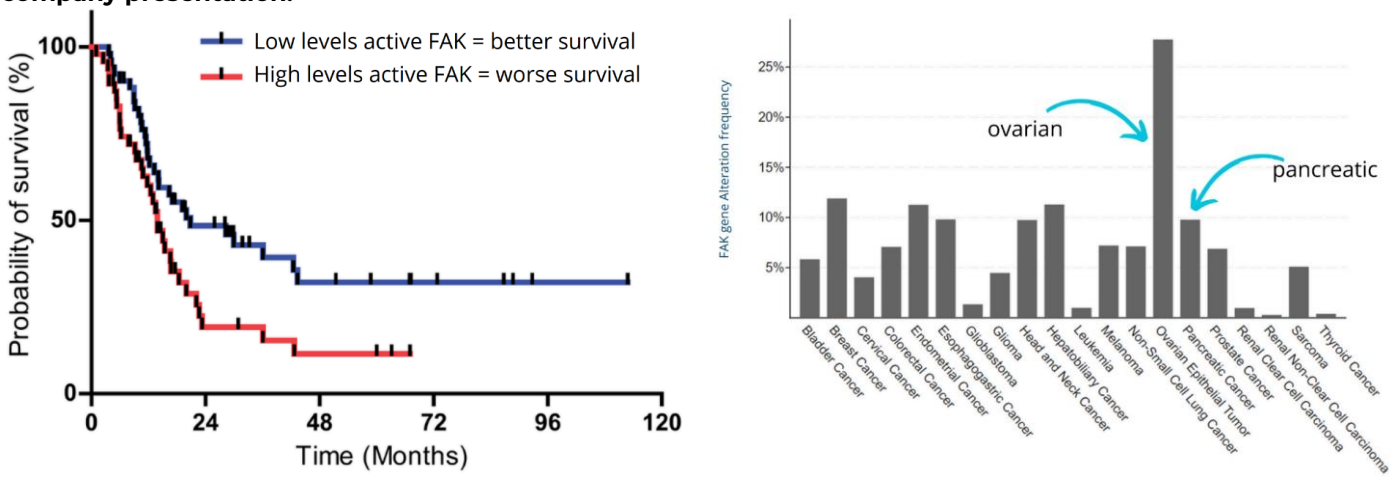
- **Orchestrating Immunosuppression:** Beyond the physical barrier, FAK signalling actively creates an "immunologically cold" TME that is hostile to anti-tumour immunity. FAK hyperactivation in tumour cells leads to the secretion of a specific profile of chemokines. These signalling molecules act as homing beacons, recruiting immunosuppressive cell populations – such as regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs) – into the tumour. At the same time, the dense fibrotic matrix physically excludes and inhibits the function of cytotoxic CD8+ T-cells, the primary effectors of anti-tumour immunity. Critically, pharmacological inhibition of FAK has been shown to reverse this immunosuppressive landscape, decreasing the infiltration of Tregs and MDSCs while allowing cytotoxic T-cells to penetrate the tumour and execute their function.

This multi-faceted role makes FAK a uniquely attractive target in PDAC. Unlike therapies that target only the cancer cell, FAK inhibition offers a three-pronged attack: it can

directly inhibit cancer cell survival and migration, it dismantles the protective fibrotic shield that causes chemoresistance, and it reprograms the TME from an immunosuppressive to an immune-permissive state, potentially unlocking the power of immunotherapy.

The dual kinase and scaffolding functions of FAK, however, present a significant challenge. The fact that FAK can promote pro-tumorigenic signalling independent of its kinase activity helps explain why some early kinase-only inhibitors have shown limited clinical success. This has spurred the development of next-generation strategies like Proteolysis Targeting Chimeras (PROTACs), which aim to degrade the entire FAK protein and thus abrogate both of its functions. Nevertheless, the unprecedented clinical responses being observed with narmafotinib suggest that a highly potent and selective kinase inhibitor may be capable of achieving a level of pathway inhibition so profound that it effectively overcomes the resistance mediated by the residual scaffolding function.

Figure 4: Focal Adhesion Kinase (FAK) is a Clinically Validated Target in Pancreatic and Ovarian Cancer. Source: company presentation.



Graph 1 (Left) depicts the correlation between FAK activity and patient survival. It is a Kaplan-Meier survival curve that demonstrates that that patients with high levels of active FAK in their tumours (red line) have significantly worse survival outcomes compared to patients with low levels of active FAK (blue line). After 48 months, only ~10% of patients in the high-FAK group are alive, compared to ~30% in the low-FAK group, establishing FAK activity as a negative prognostic biomarker.

Graph 2 (Right) shows FAK gene alteration frequency across cancer types. It highlights that FAK is frequently altered in key cancers of interest, including Ovarian Cancer (~18% alteration frequency) and Pancreatic Cancer (~10% alteration frequency). A high gene alteration frequency in a specific cancer suggests that the FAK gene is likely playing an important role in driving that cancer's growth. It provides a strong biological rationale and a layer of clinical validation for targeting FAK in not only pancreatic cancer, but also ovarian, breast and hepatobiliary cancer (which includes cancers arising in the liver, bile ducts, and gallbladder).

FAK Inhibition: A Pan-Cancer Strategy Beyond PDAC

While the dense fibrotic stroma of pancreatic cancer provides a particularly compelling case for FAK inhibition, the mechanisms that make FAK a critical target are not unique to PDAC. As evidenced by genomic data in Figure 4 above showing frequent FAK gene alterations in numerous malignancies – most notably ovarian, breast, and head and neck cancers – FAK represents a common node of vulnerability. This positions narmafotinib not merely as a treatment for a single disease, but as the lead asset in a broader therapeutic platform with significant potential for label expansion after the first regulatory approval.

Ovarian

High-grade serous ovarian cancer (HGSOC), the most common and lethal subtype, is characterized by a similar fibrotic and immunologically "cold" microenvironment to that seen in PDAC. Crucially, FAK hyperactivation has been identified as a key mechanism through which ovarian cancer cells develop resistance to standard-of-care therapies, including platinum-based chemotherapies and PARP inhibitors.

When ovarian cancer cells are treated with these DNA-damaging agents, they often respond by upregulating FAK signalling. The pro-survival pathways triggered by activated FAK help the cancer cells repair the chemo/PARPi-induced DNA damage and evade cell death. This adaptive resistance is a primary reason why many patients who initially respond to treatment eventually relapse. By co-administering a potent FAKi like narmafotinib, the strategy is to block this critical survival signal, preventing the cancer cells from repairing the damage and thereby re-sensitizing them to the effects of chemotherapy or PARPi. This approach supports the clinical development of narmafotinib in ovarian cancer as a means to overcome resistance and improve the durability of response to standard regimens.

The FAK-KRAS Axis: A Critical Vulnerability

KRAS: The Central Oncogene of PDAC

It is impossible to discuss the molecular biology of pancreatic cancer without focusing on the KRAS oncogene. Activating mutations in KRAS are found in over 90% of all PDAC cases, making it the single most dominant driver of the disease. These mutations, most commonly at codons G12, G13, or Q61, impair the protein's intrinsic GTPase activity, effectively locking it in a constitutively "ON" state. This leads to unrelenting downstream signalling through canonical effector pathways, most notably the MAPK (RAS-RAF-MEK-ERK) pathway and the PI3K/AKT pathway (see Figure 5 below), which together drive the core hallmarks of cancer: uncontrolled proliferation, growth, and survival.

For decades, the smooth surface of the KRAS protein and its exceptionally strong binding affinity for GTP made it notoriously "undruggable". A major breakthrough came with the development of highly specific drugs that could permanently attach to a unique structural "pocket" that only exists on the KRAS G12C mutant protein. This includes drugs like sotorasib and adagrasib. However, the G12C mutation is rare in PDAC, accounting for only 1-2% of cases. The major scientific and commercial frontier is now the development of inhibitors against the far more prevalent G12D and G12V mutations, as well as pan-RAS inhibitors that target multiple mutant forms.

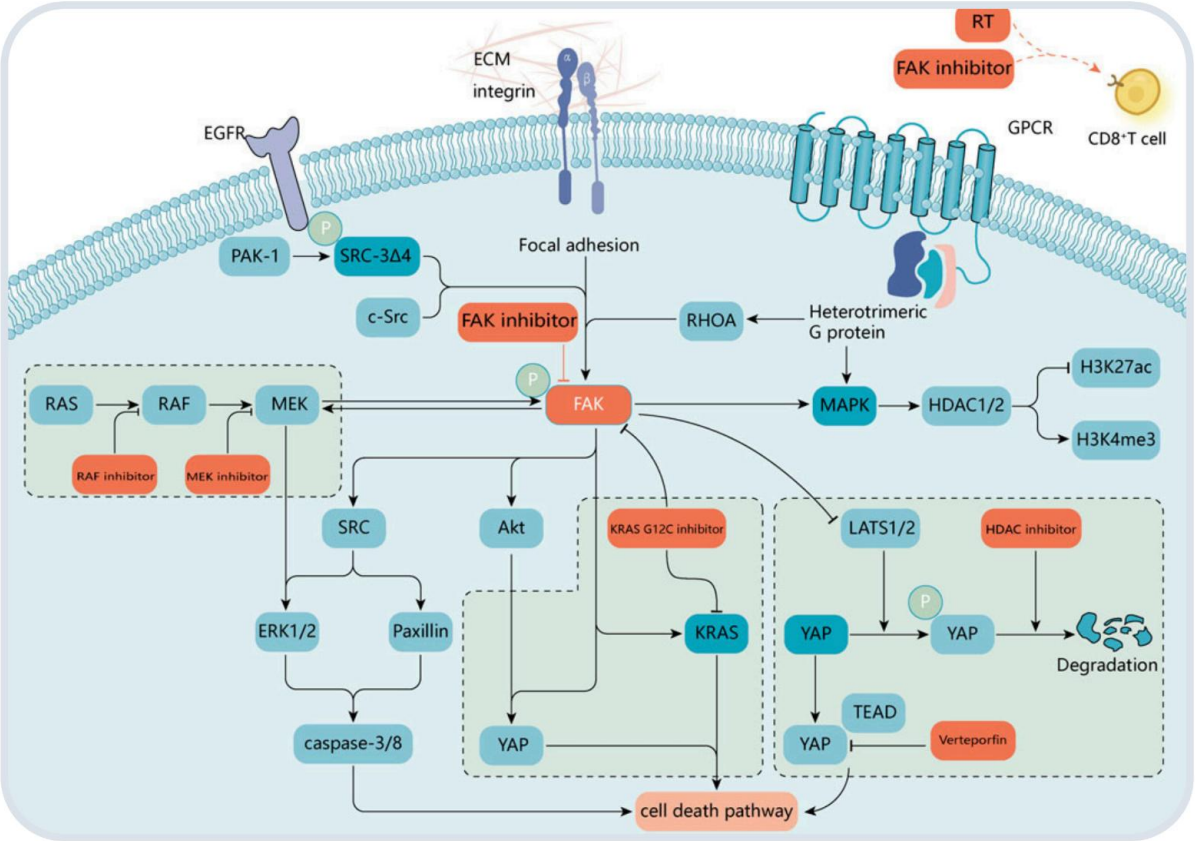
FAK's Position in the KRAS Network

The signalling networks of FAK and KRAS are deeply intertwined, creating a complex and bidirectional relationship that positions FAK as a critical node of vulnerability in KRAS-driven cancers. There is evidence that oncogenic KRAS signalling can directly lead to the activation of FAK.

Specifically, a 2011 study published in Nature – "RAS oncogenes, weaving a tumorigenic web" – demonstrated that KRAS, when mutated and constitutively active, drives the activation of downstream effector pathways, most notably the Ral-GTPase pathway. This cascade results in the autophosphorylation of FAK at a key site (tyrosine 397), which in turn creates a docking platform for Src family kinases (SFKs). The subsequent phosphorylation by Src leads to the full catalytic activation of FAK, which then promotes the cell survival, proliferation, and invasion signals that are hallmarks of KRAS-mutant cancers. This direct mechanistic link, where KRAS hyperactivation leads to sustained FAK signalling, establishes FAK as a highly rational and critical target for therapeutic intervention in pancreatic cancer and others that are notoriously dependent on KRAS mutations.

Perhaps more importantly, FAK signalling represents a major adaptive resistance mechanism to therapies that target the KRAS/MAPK pathway. When the MAPK pathway is blocked downstream of KRAS (e.g. with RAF or MEK inhibitors), cancer cells compensate by hyperactivating FAK signalling. This activated FAK then sustains tumour cell survival and proliferation through parallel pathways, such as PI3K/AKT and YAP, effectively creating an escape route that bypasses the primary therapeutic blockade.

Figure 5: The FAK-KRAS Signalling Axis in Cancer. Source: Company presentation.



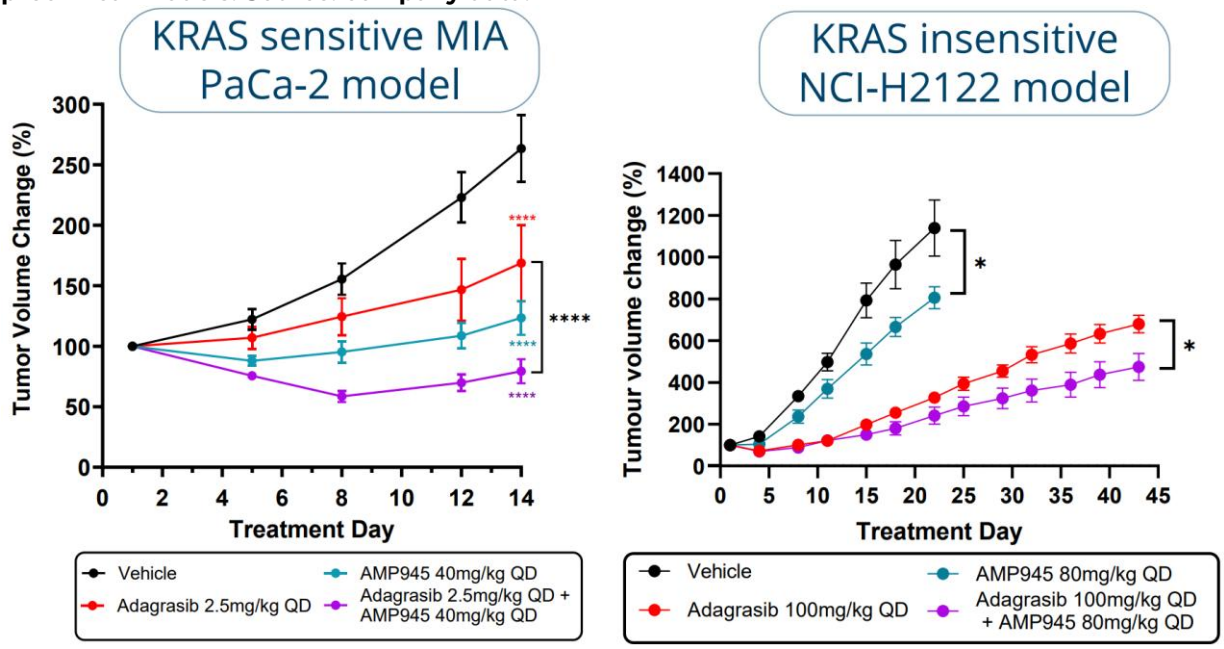
This image provides a schematic map of the key signalling pathways that drive cancer cell growth, survival, and proliferation. **KRAS as the Upstream Driver:** on the left, the RAS node (which includes KRAS) is shown as the starting point for the canonical MAPK pathway (RAS-RAF-MEK-ERK**). FAK as the Central Hub:** FAK is positioned centrally in the diagram, highlighting its role as a critical signalling node. It receives signals from outside the cell (via integrins) and transmits them inwards. Crucially, the diagram shows that FAK's signalling network overlaps and intersects with the pathways driven by KRAS.

The Combination Rationale

The dynamic interplay between the KRAS and FAK pathways creates an exceptionally strong rational for combination therapy. The strategy is to simultaneously block the main oncogenic highway (KRAS/MAPK) and the primary escape route (FAK). This approach is supported by direct preclinical evidence from Amplia, which demonstrated that combining narmafotinib with the KRAS G12C inhibitor adagrasib resulted in enhanced and more durable tumour growth reduction in cancer models. This preclinical work was presented by Amplia at the American Association for Cancer Research (AACR) Special Conference on Pancreatic Cancer in January 2025.

In a mouse model using KRAS G12C-mutant pancreatic cancer cells (see Figure 6 below), Amplia demonstrated that while adagrasib monotherapy initially suppressed tumour growth, the tumours eventually developed resistance and began to regrow. Narmafotinib monotherapy showed only modest activity. However, the combination of narmafotinib and adagrasib resulted in a profound and durable anti-tumour effect. Specifically, the combination therapy led to significant tumour regression that was sustained for the duration of the study, a markedly superior outcome compared to the transient response seen with adagrasib alone.

Figure 6: Graphs depicting the performance of adagrasib + narmafotinib in preclinical KRAS G12C mutant cancer preclinical models. Source: company data.



Graph 1 (Left) – KRAS-sensitive MIA PaCA-2 Model: this study uses a a pancreatic cancer cell model (MIA PaCa-2) that is known to be sensitive to KRAS inhibitors. The goal is to see if adding narmafotinib can enhance the effect of adagrasib. The vehicle is the control group. The tumour grows unchecked, increasing in volume by approximately 250% over the 14-day treatment period. Adagrasib alone (red line) slows down tumour growth compared to the control, with the tumour volume increasing by about 175%. Narmafotinib alone (blue line) shows modest activity restricting tumour growth to ~125% increase. However, the combination is the key result. Combined, narmafotinib and adagrasib (pink line) lead to significant tumour regression. The tumour volume shrinks to approximately 60% of its original size by day 8 and remains suppressed. The asterisks (****) indicate that this outcome is highly statistically significant compared to either drug alone. In short, this graph shows that in a KRAS-sensitive cancer model, adding narmafotinib to adagrasib turns a growth-slowing effect into a powerful tumour-shrinking effect.

Graph 2 (Right) - KRAS-insensitive NCI-H2122 Model: this study uses a lung cancer cell model (NCI-H2122) known to be resistant or insensitive to KRAS inhibitors. The goal here is to see if adding narmafotinib can restore or create sensitivity to adagrasib. Again, tumour grows rapidly in the vehicle (black line). As expected in a resistant model, adagrasib has a very limited effect on its own (red line). While it slows growth compared to the vehicle, the tumour still grows substantially, reaching over 700% of its original volume by day 45. The combination of narmafotinib and adagrasib (pink line) dramatically suppresses tumour growth far more effectively than either drug alone. The tumour volume only increases to about 500% over 45 days, a significant improvement over the 700%+ growth with adagrasib alone. The asterisk (*) indicates this synergistic effect is statistically significant.

The implications of this relationship are profound. FAK inhibition is not merely a complementary strategy to KRAS inhibition; it is likely a necessary component for achieving deep and durable responses. As the field of KRAS-targeted therapies continues to advance, FAK inhibitors are positioned to become a backbone combination partner for this entire new class of drugs. This potential role dramatically expands the long-term commercial opportunity for a successful FAKi like narmafotinib, moving it beyond just combinations with chemotherapy and into the realm of next-generation targeted therapy combinations.

FAKi Development History

You would think the early FAK inhibitors were a walk-out homerun. However, the development of FAK inhibitors has been a long and challenged journey, with at least eight distinct molecules having entered clinical trials. The trajectory of this class provides critical context for evaluating new entrants like namafotinib.

Reasons for Past Failures

A primary reason for past failures is the consistent and significant lack of efficacy when FAK inhibitors are used as a monotherapy. Defactinib, for example, failed to show benefit in a pivotal trial for malignant pleural mesothelioma and demonstrated only modest activity by itself in heavily pretreated KRAS-mutant non-small cell lung cancer (NSCLC). This evidence reinforces the understanding that FAK is not a classic oncogenic driver but rather a facilitator of cancer progression and resistance, making it an unsuitable target for single-agent therapy. This pivot away from monotherapy is further highlighted by the development strategy for other inhibitors like Ifebemtinib (IN10018), which received FDA Fast Track designation for its use in combination with chemotherapy in platinum-resistant ovarian cancer.

The development of GSK2256098, which entered trials for various solid tumours including pancreatic cancer, also illustrates this point: its most promising clinical activity was found in a very specific niche application for NF2-mutated meningiomas rather than as a broad single agent. GSK's Phase II MOBILITY-002 trial (NCT02428270) evaluated its FAK inhibitor, GSK2256098, in combination with the MEK inhibitor trametinib for second-line mPDAC. 16 patients were enrolled, and 5 were not evaluable for response. The trial was an unambiguous failure and was terminated for futility. The combination showed no anti-tumour activity; no patients achieved the primary endpoint of clinical benefit, and the median PFS and OS were just 1.6 months and 3.6 months, respectively – inferior to standard chemotherapy. This outcome demonstrates that simply targeting FAK is not a guaranteed path to success. The discrepancy between GSK's failure and Verastem's promising data suggests that the specific characteristics of the drugs and the combination strategy are paramount.

Furthermore, strong preclinical data has not always translated into clinical success. VS-4718 showed compelling efficacy in PDAC mouse models, where it was able to reduce fibrosis, decrease immunosuppressive cells, and significantly extend survival. Despite this strong preclinical rationale, its clinical trials were ultimately terminated. This translational failure can be attributed to several factors, including potential toxicity from off-target effects. Some earlier FAK inhibitors were developed from less selective chemical scaffolds, leading to the inhibition of other kinases and contributing to toxicity profiles that limit the therapeutic window for effective combination with other treatments. We go into greater detail about the importance of potency and selectivity in the next section – "Narmafotinib: A Differentiated Profile in a High-Need Indication."

A fundamental conceptual hurdle for the entire class is the "scaffolding problem". Conventional kinase inhibitors like Ifebemtinib, which are ATP-competitive, only block FAK's enzymatic function. This leaves the protein's kinase-independent scaffolding role intact, which can still mediate pro-tumorigenic signalling and contribute to resistance. This inherent limitation has prompted research into next-generation FAK degraders (PROTACs) designed to eliminate the entire protein.

Finally, even with effective FAK inhibition, tumours can develop adaptive resistance, a challenge that would theoretically affect all inhibitors in this class. Key identified resistance mechanisms include the compensatory upregulation of the FAK homolog PYK2, which can assume some of FAK's functions, and the hyperactivation of the JAK/STAT3 signaling pathway, which can promote FAK-independent tumour growth after prolonged treatment.

The Defactinib/Avutometinib Combination: Validation & Competition

The narrative for FAK inhibitors changed dramatically in May 2025, when the FDA granted accelerated approval to Verastem's combination of defactinib and avutometinib (a RAF/MEK clamp) for the treatment of recurrent KRAS-mutant low-grade serous ovarian cancer (LGSOC). This was a watershed moment for the field for several reasons. It was the first-ever regulatory approval for a FAK inhibitor; it was based on the RAMP 201 trial, which demonstrated a compelling ORR of 44%; it provided definitive clinical validation for the core scientific rationale of FAKi combinations. Blocking the MAPK pathway with a MEK inhibitor leads to feedback activation of FAK, and therefore, dual blockade is synergistic and highly effective.

This approval is a double-edged sword for competitors like Amplia. On one hand, it powerfully de-risks the FAKi mechanism for investors and provides a clear regulatory blueprint for approval based on combination data. On the other hand, it establishes Verastem as the market leader with an approved drug. Verastem is now aggressively pursuing PDAC with its own combination strategy in the RAMP 205 trial, which is testing a triplet of defactinib, avutometinib and chemotherapy in first-line mPDAC. This trial represents a direct and formidable competitor to Amplia's ACCENT trial, making the differentiation of narmafotinib's clinical profile a matter of paramount strategic importance. We will return to a deeper analysis of competition.

Narmafotinib: A Differentiated Profile in a High-Need Indication

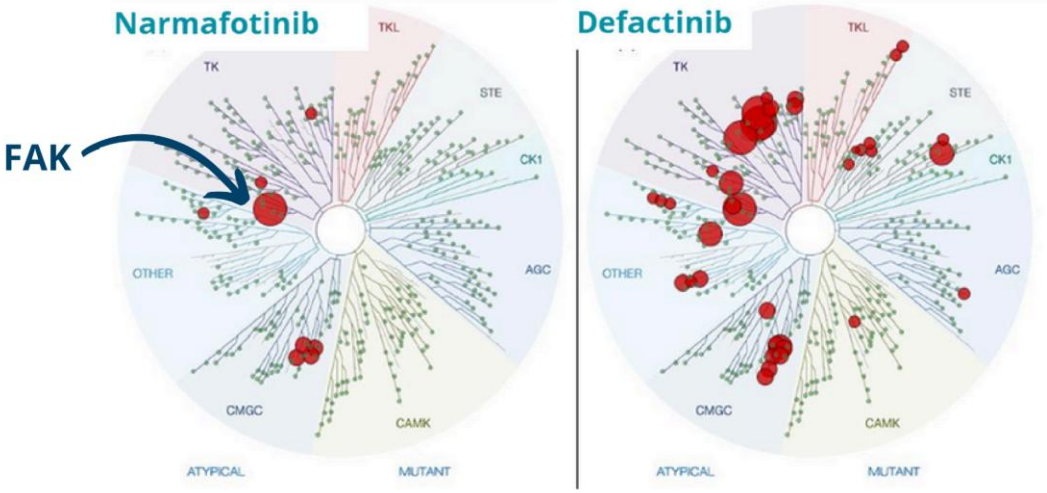
"Best-in-Class": The Selectivity & Potency Advantage

A key differentiating feature of narmafotinib is its high potency combined with a high degree of selectivity for FAK over other kinases. This is a critical distinction from the leading competitor, defactinib, which is a dual inhibitor of both FAK and its homolog PYK2.

Selectivity

While inhibiting PYK2 could be argued as a benefit to pre-emptively block a known resistance pathway, it may also introduce additional off-target effects and toxicities. By potently inhibiting other members of the Tyrosine Kinase (TK) family, it risks disrupting essential cellular signalling pathways. Furthermore, its inhibition of kinases in other critical families, such as the STE and CMGC groups which govern fundamental processes like cell growth and division, can lead to significant, dose-limiting toxicities.

Figure 7: KINOMEscan Selectivity Profile of Narmafotinib vs. Defactinib. Source: company presentation.



The image displays two KINOMEscan profiles, which are a standard industry tool used to map the binding interactions of a drug against a large portion of the human "kinome" – the entire set of protein kinases, grouped by family (e.g. Tyrosine Kinase (TK), Sterile Kinase (STE), and CMGC which is a set of four - CDKs (cyclin-dependent kinases), MAPKs (mitogen-activated protein kinases), GSKs (glycogen synthase kinases), and CLKs (CDC-like kinases).). Each red dot on the map indicates a kinase that the drug binds to. The size of the red dot is proportional to the strength of the binding; a larger dot means stronger inhibition.

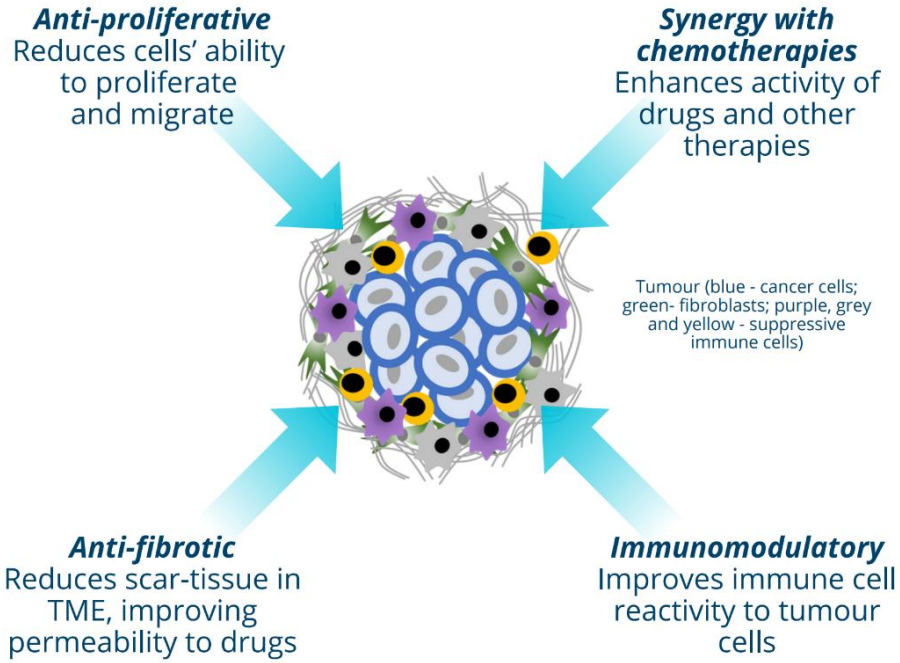
Narmafotinib (Left) has a remarkably clean profile. here is one large, prominent red dot on its intended target, FAK, indicating potent and successful binding. Crucially, there are very few other red dots, and those that are present are small, signifying weak, likely clinically insignificant off-target interactions. This high degree of selectivity is a hallmark of a well-designed, modern drug candidate. On the other hand, Defactinib's (Right) profile shows it as a less selective compound. While it does inhibit FAK, it also potently inhibits numerous other kinases across different families, as shown by the many large red dots scattered around the kinome tree. The superior selectivity of Narmafotinib is a key differentiating feature and a cornerstone of its potential "best-in-class" profile.

The image shows that defacinib and, to a lesser extent, narmafotinib both inhibit certain CMCG kinases. The CMGC family includes the Cyclin-Dependent Kinases (CDKs), which are the master regulators of the cell cycle and are essential for the division of all cells – both cancerous and healthy. While intentionally targeting CDKs is a valid anti-cancer strategy (as seen with CDK4/6 inhibitors), unintentional, off-target inhibition by a drug meant for FAK may create problems. Standard of care chemotherapy regimens which work by killing rapidly dividing cells. This leads to the well-known side effects of myelosuppression (causing neutropenia, anemia, and risk of infection) and severe gastrointestinal toxicity (diarrhea and mucositis), as healthy cells in the bone marrow and gut lining are also affected. In its pivotal MPACT trial, the gem/Abraxane regimen saw significant rates of severe (grade 3+) neutropenia (~38%) and anemia (~13%). FOLFIRINOX, a more aggressive regimen exhibited even higher rates of severe neutropenia (~46%) as well as diarrhea (~13%) in its pivotal studies.

If a FAK inhibitor like defactinib, with its off-target CMGC activity, is added to this regimen, it would essentially be layering a chemotherapy-like toxicity profile on top of an already toxic chemotherapy backbone. This overlapping toxicity would likely be intolerable for patients, forcing dose reductions or treatment discontinuation, ultimately compromising the efficacy of the entire treatment. The goal of adding a FAK inhibitor is to gain its unique anti-fibrotic and immunomodulatory benefits without exacerbating the toxicity of the standard-of-care chemotherapy, an advantage that a highly selective agent like narmafotinib is designed to provide.

In summary, the highly selective nature of narmafotinib is believed to be a primary contributor to the clean safety and tolerability profile observed in its clinical trials to date. This favourable safety profile is a significant advantage, particularly when combining the drug with already toxic chemotherapy regimens, as it may allow for more optimal dosing and longer treatment duration.

Figure 8: The Multi-Pronged Mechanism of Action of FAK Inhibition by narmafotinib in Cancer.



This diagram illustrates the four key ways in which a Focal Adhesion Kinase (FAK) inhibitor like narmafotinib is believed to attack a solid tumour. By targeting both the cancer cells directly (intrinsic effects) and the complex tumour microenvironment (extrinsic effects), FAK inhibition offers a comprehensive approach to overcoming the defences of difficult-to-treat cancers like pancreatic cancer.

High Potency Profile

Narmafotinib has both high biochemical and cellular potency. Biochemical potency refers to how effective a drug is at interacting with its specific molecular target in a controlled, non-biological, "test tube" environment. Essentially, it's a measure of the drug's intrinsic power to do its job. In this regard, narmafotinib exhibits a half-maximal inhibitory concentration (IC_{50}) of just 2.2 nanomolar (nM): you only need 2.2 nanomoles of drug per litre of solution to inhibit 50% of the FAK's enzymatic activity. This is an extremely small concentration. A nanomole is one billionth of a mole. For simplicity's sake, one mole is a chemist's version of a "dozen" – 12 eggs makes a dozen and 2.2nM is an invisible bit of eggshell. This indicates that a very low concentration, and therefore a low dose is required to effectively block the enzyme's activity. With less drug circulating in the body, the likelihood of the drug interacting with unintended targets decreases, meaning few unwanted side effects. Critically, high biochemical potency also widens the therapeutic window, which is the safe and effective range between the dose that provides a benefit and the dose that causes unacceptable toxicity. A highly potent drug can often achieve its therapeutic effect at a concentration well below the level where toxicity becomes a concern, creating a wider, safer margin for dosing.

This is further supported by its extremely strong binding affinity (K_D) of 29 picomolar (pM). Think of binding affinity like the strength of a magnet. A week magnet will attach to a piece of metal, but it's easily knocked off. But a strong magnet will snap onto the metal and hold on tightly. A lower K_D value means the drug binds more tightly and for a longer duration, making it more effective at continuously blocking the target's function. In drug development, a K_D in the low nanomolar range is considered good. A K_D in the picomolar range (i.e. one-trillionth of a molar) is considered exceptional and elite.

As for cellular potency, the primary measure is also half-maximal inhibitory concentration (IC_{50}), but it's determined in a different context. Where biochemical IC_{50} measures the drug's effect on a purified enzyme in a test tube, cellular IC_{50} measures the drug's effect on the target inside a living cell. This is a more complex and arguably more relevant test because the drug must overcome several biological hurdles: it must

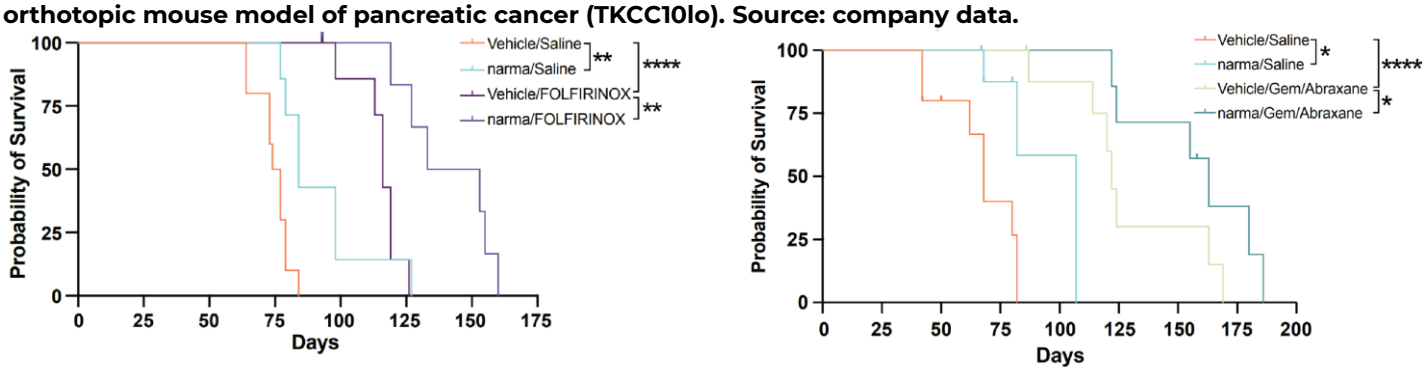
get inside the cell; it must remain stable and not be broken down by cellular machinery; and it must find and bind to its target amidst thousands of other proteins. Narmafotinib exhibited a 4.9nM IC_{50} in a live ovarian cancer cellular assay, which is an excellent result, proving the drug is not only potent in a test tube, but also highly effective at getting into a cancer cell and shutting down its target in a real biological environment. For context, a good cellular IC_{50} in kinase drug development would be 10-50nM. An elite figure is in the single-digit nM range (1-9nM) or sub-nanomolar. In comparison, in ovarian cancer cells, defactinib inhibited FAK phosphorylation with an IC_{50} of approximately 20nM per a 2013 study in the journal of Gynaecologic Oncology.

It therefore comes as no surprise that narmafotinib showed positive signals in early pre-clinical work. Narmafotinib is verging on "best-in-class": High potency & selectivity → lower effective dose → wider therapeutic window → fewer off-target toxicities → better suitability for combination therapy with highly toxic chemotherapy regimens.

Robust Preclinical Foundation

Narmafotinib's clinical development is underpinned by a strong preclinical data package demonstrating its potential in pancreatic cancer. In various mouse models of PDAC, narmafotinib has been shown to have potent anti-fibrotic effects. When combined with either of the two SoC chemo regimens – gemcitabine/nab-paclitaxel or FOLFIRINOX – it significantly enhanced tumour growth inhibition and improved overall survival compared to chemo alone. As outlined in the previous section, preclinical studies also showed that narmafotinib can enhance and sustain the tumour's responsiveness to the KRAS G12C inhibitor adagrasib. This provides a strong rationale for narmafotinib's use in overcoming resistance to next-generation targeted therapies, positioning it as a future combination partner beyond just chemo.

Figure 9: Preclinical survival benefit of narmafotinib in combination with standard-of-care chemotherapies in an orthotopic mouse model of pancreatic cancer (TKCC10lo). Source: company data.



These graphs track the survival of four different groups of mice over time, all of whom have had pancreatic tumours implanted. The Y-axis represents the percentage of mice still alive, and the X-axis represents the number of days post-treatment. Each downward step on a line indicates that one or more mice in that group have died. In Graph 1 (Left), the vehicle (orange line) is the baseline control group receiving no active drug. As expected, they have the worst outcome. All mice in this group die between day 70 and day 85, with a median survival of approximately 75 days. The vehicle/FOLFIRINOX group (purple line) is representative of the standard of care. It provides a substantial survival benefit over the control group, with a median survival of approximately 125 days. Impressively, the narmafotinib/FOLFIRINOX group (blue line) saw a clear and statistically significant survival advantage with the median survival extended to approximately 150 days.

Graph 2 (right) replicates this survival advantage: The addition of narmafotinib to gemcitabine/Abraxane (dark teal line) significantly extended the median survival of the mice to approximately 175 days, a notable improvement over the ~125-day median survival for mice treated with gemcitabine/Abraxane alone (light green line).

ACCENT Trial: Cornerstone of the Investment Case

The ongoing ACCENT trial is the centre pillar of the investment thesis for Amplia. It is a phase 1b/2a, open-label, single-arm study evaluating narmafotinib in combination with standard-of-care gemcitabine and nab-paclitaxel. Crucially, the trail enrolled first-line, treatment-naïve patients with metastatic PDAC, the largest and most commercially relevant patient population. The initial stage of the trial, completed in November 2023,

successfully identified a recommended phase 2 dose (RP2D) of 400mg once daily. This dose was found to be safe and well-tolerated, with pharmacokinetics consistent with achieving target engagement.

The trial then pivoted to a phase 2a efficacy expansion, which has completed recruitment of 55 patients. It features a Simon's two-stage design: the first stage enrolled 26 patients. Upon 6 confirmed responses (defined as ≥ 30% reduction in 'sum of diameters' tumour size reduction), the trial was considered to have met its pre-specified futility hurdle and expanded to enrol and additional 24 patients, for a total cohort size of 50. The 5 added patients, to get to 55 total patients, were enrolled due to certain patients being unevaluable. The primary end points are Objective Response Rate (ORR) and Duration on Trial (DOT), with key secondary endpoints of Progression-Free Survival (PFS) and Overall Survival (OS).

The preliminary data emerging from the trial has been exceptional and suggests a level of activity that far exceeds historical benchmarks. As presented at the 2024 ASCO annual meeting, a clear dose-response relationship has been observed, with a higher number of partial responses (PRs) and better tumour reduction seen at the 400mg RP2D compared to lower doses. Furthermore, the mean duration of treatment for patients on the 400 mg dose was 8.3 months, a striking improvement over the historical median treatment duration of approximately 4-5 months for this chemotherapy regimen alone (MPACT pivotal study of gem/Abraxane).

One of the more significant and potentially transformative finding from the ACCENT trial is the observation of multiple complete responses. Across the 55-patient pool, Amplia has reported two confirmed CRs, where all detectable tumours disappeared for at least two months. The first CR was 'pathological', where no signs of cancer were detectible in tissue examined by a pathologist following surgical removal. The second CR involved complete disappearance as observed via CT. The significance of this CR/pCR data cannot be overstated. In the context of mPDAC, such deep responses are incredibly rare. As previously noted, the benchmark MPACT study of gemcitabine/nab-paclitaxel reported only a single CR out of 431 patients. To observe multiple such events in a small trial of just 55 patients is a massive statistical and clinical outlier. A pCR, in particular, is an outcome almost unheard of in the metastatic setting and is typically associated with significant improvements in long-term survival in earlier-stage disease. This signal suggests that the narmafotinib combination is capable of inducing a depth of response that is fundamentally different from, and superior to, historical standards. If this signal is confirmed with mature survival data, it could represent a true paradigm shift in the treatment of mPDAC.

Figure 10: Interim Efficacy Data from ACCENT Trial vs. Historical MPACT Benchmark. Sources: Company Data; MPACT Publication in New England Journal of Medicine (2013).

Efficacy Metric	ACCENT (so far)	MPACT	Commentary
Response			
ORR	17/55 (~31%)	99/431 (~23%)	Response measures outperform MPACT even before topline data. Given that ACCENT enrolment only finished in January, there is still the strong possibility of further PRs and even CRs as patients stay on drug for longer, which would increase the ORR. ACCENT's greater duration on trial to date suggests more PRs is a strong probability.
Confirmed PRs	15/55 (~27%)	98/431 (~23%)	
Confirmed CRs	2/55 (~4%)	1/431 (<1%)	
Stable Disease	TBD	118/431 (~27%)	
Rate of Disease Control	TBD	206/431 (~48%)	
Progressive Disease	TBD	86/431 (~20%)	
Median DoT	208 days	117 days	
Progression-Free Survival			
Median PFS	TBD	5.5 months	PFS topline data expected at the end of July 2025 is a key upcoming milestone.
Rate of PFS: 6 months	TBD	44%	
Rate of PFS: 12 months	TBD	16%	
Overall Survival			
Median OS	TBD	8.5 months	Overall survival is a critical endpoint. Substantial clinical utility would be demonstrated by even a 25% increase in mOS and 12/18-month OS rates.
Rate of OS: 6 months	TBD	67%	
Rate of OS: 12 months	TBD	35%	
Rate of OS: 18 months	TBD	16%	

The Next Phase

With the ACCENT trial providing compelling proof-of-concept for narmafotinib's activity with gemcitabine/abraxane, Amplia is strategically pivoting to its next major clinical study: a Phase 2 trial combining narmafotinib with FOLFIRINOX. This is a critical and logical step, as FOLFIRINOX is the preferred first-line chemotherapy regimen for a large proportion of newly diagnosed, medically fit patients in the key US market. Generating positive data with both major standard-of-care backbones is essential for establishing narmafotinib as a truly universal combination partner in mPDAC.

A key evolution in the design of this upcoming trial is the planned dosing schedule for narmafotinib. In the ACCENT trial, narmafotinib was administered using an intermittent "pulsed priming" schedule (a 4-day course of the drug prior to each chemotherapy cycle). In the new FOLFIRINOX trial, patients will receive narmafotinib as a continuous, once-daily oral dose.

The scientific rationale for this shift to daily dosing is strong and suggests the potential for even greater efficacy. The dense, fibrotic stroma that protects pancreatic tumours is not a static structure; it is a dynamic environment that is constantly being built and remodelled by cancer-associated fibroblasts. The intermittent dosing in the ACCENT trial was designed to "prime" the tumour by temporarily disrupting this fibrosis before chemotherapy administration. While this has proven remarkably effective, the hypothesis is that a continuous, daily dose of narmafotinib will exert constant pressure on the tumour microenvironment. This sustained FAK inhibition is expected to more effectively and durably break down the fibrotic barrier, prevent its regeneration between chemotherapy cycles, and more profoundly block the FAK-mediated survival signals that drive chemoresistance. By maintaining a constant state of FAK inhibition, this optimized daily dosing regimen has the potential to unlock an even greater synergistic effect with chemotherapy, possibly leading to deeper and more durable responses than those already observed in the ACCENT trial.

Regulatory Prospects

Regulatory Pathway and Advantages

The FDA has granted narmafotinib several key designations for its development in pancreatic cancer. Narmafotinib has received Orphan Drug Designation (ODD) for the treatment of pancreatic cancer, as well as for idiopathic pulmonary fibrosis. This designation is granted to drugs intended for rare diseases and provides substantial development incentives, including a waiver of FDA fees, tax credits for clinical trials, and, most importantly, seven years of market exclusivity in the US upon approval: other manufacturers cannot enter the market, regardless of the patent status.

In September 2024, the FDA granted Fast Track Designation for the treatment of advanced pancreatic cancer. This was a critical milestone: fast track is intended to facilitate the development and expedite the review of drugs that treat serious conditions and fill an unmet medical need. It allows more frequent meetings and communication with the FDA to discuss the drug's development plan and ensure the collection of appropriate data needed to support approval. It also makes the drug eligible for Accelerated Approval and Priority Review.

The FDA's Accelerated Approval pathway is a vital mechanism for bringing promising drugs for serious diseases to patients sooner. It allows for drug approval based on a surrogate endpoint – such as tumour shrinkage (indicated by ORR) – that is considered reasonably likely to predict a clinical benefit, like improved survival. The company must then conduct post-approval confirmatory trials to verify the anticipated clinical benefit.

The unprecedented ORR in interim readouts so far could form the basis of a compelling argument for accelerated approval. The FDA has shown a willingness to use this pathway for targeted therapies in biomarker-defined subsets of pancreatic cancer. Because narmafotinib is being studied in an all-comer population, we expect that any accelerated approval would come upon submission of a dossier with placebo-controlled data. Regardless, securing accelerated approval would dramatically alter the company's trajectory, reducing the time, cost, and risk associated with a traditional, large-scale Phase 3 program.

Lastly, Amplia has a cleared Investigational New Drug (IND) application. This allows the company to conduct clinical trials in the United States. Amplia is leveraging this to launch the aforementioned FOLFIRINOX trial. This parallel trial is a strategically astute move that could broaden narmafotinib's potential market access by generating data with both major standard-of-care backbones.

Intellectual Property

A robust intellectual property (IP) portfolio is the cornerstone of any successful biotechnology company. For Amplia Therapeutics, its IP is not just a legal shield but a critical asset that underpins its valuation and long-term commercial potential.

Deconstructing the Narmafotinib IP Portfolio

Amplia's IP strategy for narmafotinib is not reliant on a single patent but is a carefully constructed, multi-pronged fortress designed to provide overlapping layers of protection, extending market exclusivity well into the 2040s. This approach is critical for maximizing the drug's commercial runway and return on investment. The core of this fortress is the composition of matter patent. This fundamental patent (WO2014140039A1), which covers the narmafotinib molecule itself, provides the broadest and most robust form of protection. This patent has been granted in key pharmaceutical markets, including the United States, Europe, China, and Japan, with an expiry date of March 2034 (the end of FY34).

However, Amplia has proactively sought to extend this protection timeline through additional patent filings:

- **New Salt Form Patent:** Amplia has filed a patent application for a specific crystalline salt form of narmafotinib. This patent, if granted, is expected to provide protection until 2039. Salt form patents are a common and effective strategy in the pharmaceutical industry to extend a drug's life cycle. They can offer advantages in terms of stability, manufacturability, or bioavailability, making them distinct and patentable inventions.

- **Method of Use Patent:** Recognizing the potential of narmafotinib in combination therapies, Amplia has filed a patent application covering the use of the drug in conjunction with the FOLFIRINOX chemotherapy regimen for pancreatic cancer. This "method of use" patent could extend market exclusivity for this specific application beyond 2040. As combination therapies are becoming the standard of care in many cancers, this patent could be particularly valuable.

This multilayered approach creates a formidable barrier to entry for potential generic competitors. It ensures that even if one patent were to be challenged or expire, other layers of protection would remain in place, securing Amplia's market position for a longer duration.

Moreover, in the US, a patent's term can be extended for a period of up to five years to compensate for delays in obtaining regulatory approval from the FDA: Patent Term Extension (PTE). The extension is generally calculated as half the time the drug was in clinical trials plus the full time it was under regulatory review by the FDA. There are specific and strict eligibility requirements, but if narmafotinib is approved for use in the US, Amplia will likely be able to apply for a PTE.

In the European Union, a similar mechanism called a Supplementary Protection Certificate (SPC) is available. An SPC can also provide up to five years of additional protection beyond the patent's expiry date. The duration of the SPC is calculated based on the time between the patent filing date and the date of the first marketing authorization in the European Economic Area (EEA), minus five years. A further six-month extension is possible if the drug has undergone pediatric studies.

Figure 11: Consolidated View of Narmafotinib's IP Protection. Source: Company Data, Evolution Capital.

IP / Exclusivity Type	Patent Family / Application ID / Designation	Key Jurisdictions	Status	Estimated Expiry Date
Composition of Matter	Based on WO2014140039A1 (family of US9120761B2)	US, Europe, Japan, Australia, Canada, China	Granted	2034
Salt Form	International Patent Application (e.g., US20230190746A1)	Global (pending national phase entry)	Pending	2039
Method of Use	Patent Application (undisclosed ID)	Key markets (assumed)	Pending	>2040

The Provenance and Licensing of Narmafotinib

Narmafotinib's journey from a promising laboratory compound to a clinical-stage asset is a testament to successful collaboration in the Australian life sciences ecosystem. The drug was discovered and initially developed by the Cancer Therapeutics Cooperative Research Centre (CTx), a leading Australian research consortium. Following its discovery, the exclusive rights to the molecule were licensed to Cancer Research UK (CRUK), a major British charity, and managed by its commercialization arm, Cancer Research Technology (CRT). From CRT, Amplia acquired the exclusive worldwide rights to develop and commercialise the drug.

The Impact of Patent Dynamics in Valuation

The extension of narmafotinib's patent protection beyond the initial 2034 expiry has significant positive implications for its valuation. Each additional year of market exclusivity translates into another year of peak sales revenue before the onset of generic competition. This extended period of high-margin revenue directly increases the drug's net present value (NPV). The multi-layered patent strategy, therefore, not only protects the asset but substantially enhances its financial value. Conversely, the expiration of patents marks a significant turning point in a drug's life cycle, often referred to as the "patent cliff." Once a drug's patents lapse, generic manufacturers can enter the market with lower-priced versions, leading to a rapid and substantial erosion of the original drug's sales and market share. It is not uncommon for a branded drug to lose up to 80% of its revenue within the first year of generic competition.

ODD: A Regulatory Safety Net

Narmafotinib has orphan drug designation for the treatment of pancreatic cancer. Its primary commercial benefit is that it provides seven years of market exclusivity in the United States, starting from the date of drug approval. This exclusivity is entirely independent of the drug's patent status. As will become evident, this regulatory designation provides a critical backstop in our rNPV modelling.

Competitive Landscape: FAK Inhibitors

Verastem: The Primary Commercial Threat

Verastem Oncology stands as Amplia's most direct and formidable competitor. As afformentioned, the company is developing a combination of avutometinib, a novel RAF/MEK "clamp," and defactinib, a FAK inhibitor. This dual-mechanism approach is designed to block the primary KRAS-driven signalling pathway (RAS/MAPK) while simultaneously inhibiting the FAK-mediated resistance that can arise from such a blockade.

In its Phase 1/2 RAMP 205 trial in first-line mPDAC, the combination plus Gem/Abraxane has produced impressive results, posting an 83% ORR (10 responses in 12 patients) at the recommended Phase 2 dose, with all responses being PRs. This high response rate, coupled with Verastem's significant lead, presents a major challenge to Amplia's commercial opportunity, should narmafotinib be approved.

The most significant advantage for Verastem is its first-mover status. On May 8, 2025, the FDA granted accelerated approval to the avutometinib/defactinib combination (marketed as AVMAPKI/FAKZYNJA) for treating recurrent low-grade serous ovarian cancer (LGSOC) with a KRAS mutation. This approval is a substantial de-risking event. It validates the combination's safety and activity, and it transforms Verastem from a clinical-stage developer into a commercial entity with revenue, established manufacturing and supply chains, and existing relationships within the oncology community.

Should Verastem secure approval for its combination in mPDAC ahead of Amplia, the commercial implications may be dire. Verastem would likely establish its regimen as the standard FAK-based therapy. To displace an entrenched first mover, a follow-on drug typically needs to demonstrate a substantial, not marginal, improvement. In such a scenario, Amplia's path to market would narrow considerably. Its entire commercial strategy would hinge on proving that narmafotinib's unique CR signal translates into a markedly superior survival outcome, a cleaner safety profile, or both. Without a clear and compelling advantage, overcoming Verastem's head start would be an arduous task, likely impossible without the backing of a major pharmaceutical partner.

Inxmed: A Well-Funded International Competitor

InxMed is a private Chinese company. It present a significant, if less immediate threat. The company is well-funded, having raised US$84 million over four funding rounds, and is developing its own selective FAK inhibitor, ifebemtinib (IN10018). While specific clinical data for ifebemtinib in mPDAC is not yet available, the company is actively conducting proof-of-concept studies.

The credibility of this competitive threat is bolstered by very strong results in other KRAS-mutant cancers, which are highly relevant to the KRAS-driven landscape of PDAC. In first-line KRAS G12C-mutant non-small cell lung cancer (NSCLC), ifebemtinib combined with a KRAS inhibitor (garsorasib) yielded a 90.3% ORR, median duration of response (mDOR) of 19.4 months, and an impressive median PFS of 22.3 months. This data includes 33 patients, 31 of whom were evaluable. The ORR data point was reported at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting (data cutoff 10 May 2024). The mDOR and PFS data is accurate to 31 March 2025.

In a study of refractory KRAS G12C-mutant colorectal cancer (CRC), the combination performed very well. As of 21 April 2025, 36 previously treated CRC patients were randomized 1:1 to receive the combination of ifebemtinib + garsorasib or garsorasib alone. The combination nearly doubled the ORR compared to garsorasib alone (44.4% vs 16.7%); mPFS was 7.7 months for the combination compared to just 4 months for the monotherapy; and lastly, disease control rate (DCR) was 100% for the combo and 77.8% for the mono.

This robust validation of ifebemtinib's synergistic mechanism, combined with InxMed's strong financial backing, positions it as a serious long-term competitor that could emerge as a major player in the PDAC space. InxMed has initiated a randomized Phase III pivotal trial in first-line KRAS G12C-mutant NSCLC. Additionally, the company is actively exploring combinations of ifebemtinib with other KRAS-targeted agents, including KRAS G12D inhibitors and multi-RAS inhibitors.

Ascentage Pharma: A Multikinase Competitor

Ascentage Pharma is a global biotechnology company with a broad pipeline of novel small molecules. While much of its late-stage work has focused on haematological cancers, the company possesses a portfolio of assets for solid tumours that are highly relevant to Amplia.

Most notably, Ascentage is developing APG-2449, a multi-kinase inhibitor that potently targets FAK, ALK, and ROS1. Dual ALK/ROS1 inhibition delivers direct cytotoxicity in oncogene-addicted tumours, while FAK blockade tackles tumour-micro-environment-driven resistance (e.g. stroma, stem-cell signalling, immune evasion). The drug's profile is very selective and potent: in biochemical assays APG-2449 inhibits ALK, ROS1 and FAK with single-digit-nanomolar Kd/IC_{50} values; cellular assays confirm sub-10 nM potency in ALK/ROS1-positive lines and robust suppression of p-FAK/AKT/ERK signalling in ovarian-cancer cells.

The development of a direct FAK inhibitor makes Ascentage a direct, if earlier-stage, competitor. While PDAC clinical work is lacking, the company released data on a Phase I/II in NSCLC (n=144) at ASCO 2024:

Figure 12:Key efficacy data from the Phase I/II APG-2449 NSCLC study (ASCO 2024 poster, Ascentage Pharma press-release, 2 June 2024).

Population	ORR	Notable finding
ALK- or ROS1-positive, TKI-naïve	78.6 % (ALK) / 68.2 % (ROS1)	Deep systemic responses
ALK-positive, post-2G TKI resistant	45.5 % PR	Activity despite resistance
Patients with brain metastases (RP2D)	75 % intracranial ORR	Demonstrates BBB penetration

As for safety, grade ≥ 3 treatment-related AEs only occurred in 13.9 % of subjects; most events were mild laboratory or GI abnormalities (creatinine, ALT/AST, nausea, diarrhoea, rash).

The company is pursuing a registrational path in China. China's CDE has cleared two phase III trials including APG-2449 vs platinum-doublet chemotherapy in ALK-TKI resistant NSCLC; and APG-2449 vs crizotinib in front-line ALK-positive NSCLC. These studies target the largest unmet niches where ALK/ROS1 resistance and CNS relapse dominate. On top of this, Ascentage is moving APG-2449 into a Phase Ib/II chemo-combo study in platinum-resistant ovarian cancer (APG-2449 + pegylated liposomal doxorubicin).

For Amplia, the positive is that Ascentage's focus for APG-2449 is lung and ovarian, leaving Amplia a clear runway. However, there is the risk that Ascentage moves into PDAC later on the back of their drug's multi-kinase profile. APG-2449's success in NSCLC nonetheless validates FAK inhibition clinically and provides external proof that deep, durable responses can be achieved when FAK is adequately targeted, reinforcing Amplia's mechanism thesis.

Figure 13: Summary Table of Key FAKi Competitors and Status. Various sources.

Company	FAK Inhibitor	Indications	Status/Recent Milestones
Verastem	Defactinib	Ovarian, urothelial, PDAC	FDA approvals (2025; Ovarian); active in PDAC
InxMed	Ifebemtinib	Ovarian, NSCLC, PDAC, CRC	Breakthrough/Fast Track; strong data
Amplia	Narmafotinib	PDAC	Phase 2; best-in-class selectivity
GSK	GSK2256098	Solid tumors	Failed in PDAC, limited progress
Ascentage	APG-2449	ALK/ROS1-driven tumors	Early trials, multi-kinase profile
Others/Novel	VS-4718, PROTACs	Preclinical/early clinical	Ongoing development

Key Non-FAKi Competitors

Arcus Biosciences' Quemliclustat: The Phase 3 Frontrunner

Quemliclustat is an orally available, small-molecule inhibitor of CD73. The CD73 enzyme is highly expressed in many tumours, including 40-60% of pancreatic cancers, where it plays a key role in producing adenosine within the tumour microenvironment. Adenosine is a potent immunosuppressive molecule that shields cancer cells from immune attack. By blocking CD73, quemliclustat aims to reduce adenosine levels, thereby restoring the immune system's ability to recognize and eliminate cancer cells.

Arcus has reported highly encouraging data from its Phase 1b/1b ARC-8 study, which evaluated quemliclustat in combination with gem/Abraxane, with or without the anti-PD-1 antibody zimberelimab. In a post-hoc analysis comparing 122 patients treated with quemliclustat-based regimens to a matched synthetic control arm of patients receiving chemotherapy alone, the combination demonstrated a robust survival benefit. The key result was a median Overall Survival (mOS) of 15.7 months for the quemliclustat arms, representing a 5.9-month improvement over the 9.8-month mOS of the control arm. This survival figure is currently best-in-class among emerging therapies and significantly exceeds the 11.1-month benchmark of NALIRIFOX. The ORR was more modest, in the range of 38-41%.

Leveraging this strong signal, Arcus, in partnership with Gilead, initiated the global, randomized, double-blind Phase 3 PRISM-1 trial in late 2024. This pivotal study is designed to enrol 610 treatment-naïve mPDAC patients, comparing quemliclustat plus

Gem/Abraxane against Gem/Abraxane plus placebo. Enrolment is expected to be completed by the end of 2025, with final trial completion estimated for November 2030.

Strategic Threat to Amplia: High.
Arcus represents the most immediate and significant competitive threat to Amplia. It is already in a large-scale Phase 3 trial, is well-funded with a major pharmaceutical partner, and has already demonstrated a survival signal that, if replicated in PRISM-1, would likely establish quemliclustat as a new standard of care. A positive outcome for PRISM-1 could potentially close the market window for other agents combined with a Gem/Abraxane backbone.

BioLineRx's Motixafortide

Motixafortide is an inhibitor of the CXCR4 chemokine receptor. The CXCR4/CXCL12 signalling axis is a key pathway that cancer cells exploit to create an immunosuppressive TME, effectively excluding anti-tumour T-cells from infiltrating the tumour. By blocking CXCR4, motixafortide is intended to break down this barrier, allowing an influx of cytotoxic T-cells and rendering the tumour vulnerable to immune attack, particularly when combined with an immune checkpoint inhibitor.

Motixafortide is being evaluated in the investigator-initiated Chemo4METPANC trial as part of a triple combination with the PD-1 inhibitor cemiplimab and standard Gem/Abraxane chemotherapy. A small, single-arm pilot phase of the study (n=11) produced an ORR of 64% and a DCR of 91%. These response rates are substantially higher than the historical ORR of 23% and DCR of 48% for Gem/Abraxane alone. Preliminary median Progression-Free Survival (PFS) from this pilot cohort was reported as 9.6 months, a notable improvement over the historical 5.5-month benchmark for Gem/Abraxane. The trial has now been expanded into a randomized, multi-centre Phase 2 study designed to enrol 108 patients, comparing the motixafortide-cemiplimab-Gem/Abraxane triplet against Gem/Abraxane alone. The primary endpoint is PFS. Full enrolment is planned for 2027, with a prespecified interim analysis to be conducted when 40% of PFS events are observed.

Strategic Threat to Amplia: Medium.
The ORR from the pilot study is eye-catching and suggests a potent anti-tumor effect. However, these results are from a very small, non-randomized cohort and must be interpreted with caution until validated in the larger randomized portion of the trial. Furthermore, the complexity and potential cost of a three-drug regimen (two novel agents plus chemotherapy) could present a significant commercial and reimbursement hurdle compared to a two-drug combination like narmafotinib plus chemotherapy.

Cantargia's Nadunolimab

Nadunolimab is a fully humanized antibody that targets the Interleukin-1 Receptor Accessory Protein (IL1RAP). IL-1 signaling via IL1RAP is a key driver of the fibro-inflammatory TME in pancreatic cancer, promoting immune suppression and resistance to chemotherapy. Nadunolimab has a dual mechanism: it blocks this pro-tumor IL-1 signaling and also induces antibody-dependent cellular cytotoxicity (ADCC), directly flagging cancer cells for destruction by immune cells like NK cells.

Cantargia has reported compelling results from its Phase 1/2a CANFOUR trial (NCT03267316), which evaluated nadunolimab in combination with Gem/Abraxane in 73 first-line mPDAC patients. The combination demonstrated a mOS of 13.2 months in the all-comer population. More impressively, in a pre-specified subgroup of patients whose tumors had high expression of IL1RAP (a potential predictive biomarker), the mOS reached 14.2 months, compared to 10.6 months in the IL1RAP-low subgroup. This survival benefit in a biomarker-selected population rivals the data from Arcus and surpasses the NALIRIFOX benchmark.

A key potential advantage for nadunolimab is its remarkable safety profile, particularly concerning a common and debilitating side effect of chemotherapy. The incidence of Grade 3 or higher chemotherapy-induced peripheral neuropathy (CIPN) in the CANFOUR trial was only 1%, a stark contrast to the 17% rate historically reported for Gem/Abraxane alone. This suggests a potential neuroprotective effect of nadunolimab, which could be a major differentiator in clinical practice, improving patient quality of life and potentially allowing for longer treatment duration. The main added toxicity was an increased incidence of neutropenia, which was manageable with prophylactic G-CSF support.

Strategic Threat to Amplia: High.
Cantargia presents a formidable competitive profile. It has demonstrated a strong survival signal that exceeds the current SoC, a clear biomarker strategy that could lead to a more targeted and effective use of its drug, and a highly differentiated safety profile that addresses a major unmet need in managing treatment toxicity. This powerful combination of efficacy, a precision medicine approach, and superior tolerability makes nadunolimab a very strong challenger in the mPDAC landscape. The phase 2 data is mature, and the company has stated it is preparing for a randomized, potentially pivotal trial in first-line pancreatic cancer.

Immuneering's Atebimetinib:

Immuneering (NASDAQ: IMRX) presents a scientifically sophisticated competitive threat. The company is focused on developing drugs that target the MAPK pathway, which is we note from Figure 3), is directly downstream of FAK, on the same "oncogenic highway that Amplia aims to modulate. The company's lead asset, atebimetinib is not a standard kinase inhibitor. It is designed to provide "deep cyclic inhibition" of the MAPK pathway through a dual-MEK inhibitor mechanism. The therapeutic hypothesis is that by potently shutting down the pathway for a short, defined period, it can kill tumour cells that are highly dependent on MAPK signalling while allowing healthy cells to recover between cycles. This aims to achieve a wider therapeutic window and better tolerability than traditional MEK inhibitors.

The company is targeting a broad range of RAS-mutant cancers, including pancreatic, melanoma, and NSCLC. Early data from its Phase 1/2a trial in combination with modified gem/Abraxane presented at the 2024 ASCO meeting showed promising signals of activity. In heavily pre-treated patients, atebimetinib demonstrated confirmed partial responses in patients with mPDAC and melanoma harbouring KRAS and NRAS mutations, respectively. At the more recent data cutoff of 26 May 2025, the company presented very strong results with limited grade 3 AEs:

Figure 14: Comparison of Efficacy in Immuneering's Phase II vs the Benchmark MPACT Study. Various sources.

Efficacy Metric	Atebimetinib Combination	Historical Benchmark (MPACT)
6-month mOS	94% (n=34)	67%
6-month PFS	72% (n=34)	44%
ORR	39% (n=36)	23%
DCR	81% (n=36)	48%

This early proof-of-concept in pancreatic cancer patients validates the MAPK pathway as a key vulnerability and positions Immuneering as a significant competitor in the race to effectively drug RAS-driven cancers.

BMS' Niraparib: The Maintenance Paradigm

Niraparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. Its development in pancreatic cancer has focused on a different treatment setting: *maintenance therapy*. This approach is for patients whose disease has not progressed after an initial 4-6 months of first-line platinum-based chemotherapy (like FOLFIRINOX). The goal is to use

a less toxic oral agent to delay progression after the initial, more intensive treatment phase.

A randomized Phase 1b/2 trial evaluated niraparib in combination with two different immune checkpoint inhibitors as maintenance therapy. The arm combining niraparib with ipilimumab (an anti-CTLA-4 antibody) was particularly successful, meeting its primary endpoint with a 6-month PFS rate of 59.6% and demonstrating an impressive mOS of 17.3 months.

Strategic Threat to Amplia: Indirect.
Today, Niraparib does not compete directly with narmafotinib in the first-line induction setting. However, the success of the maintenance paradigm is strategically relevant. It carves out a distinct segment of the overall patient journey. A highly effective maintenance therapy could become the standard for a subset of patients who respond to initial chemotherapy, potentially reducing the market size for subsequent lines of treatment.

Competitive Landscape

The competitive field is clearly bifurcating into two primary strategies: broad combination approaches that aim to improve upon SoC in all-comer populations, and precision or biomarker-driven approaches that target specific patient subsets. Amplia, Arcus, and BioLineRx currently fall into the "broad" category, testing their agents in largely unselected patient populations. In contrast, Cantargia has identified a potential predictive biomarker (IL1RAP-high) that correlates with superior survival, while Merus and Amgen are exclusively focused on genetically defined niches. The exceptional CRs observed with narmafotinib, however, are statistically unlikely to be a random occurrence in an all-comer population. This raises the distinct possibility that these two responding patients share an underlying biological characteristic that makes them exquisitely sensitive to FAK inhibition. A key future imperative for Amplia will be to conduct retrospective translational analysis on samples from the ACCENT trial to search for such a predictive biomarker. The discovery of a reliable biomarker would be transformative, elevating narmafotinib from a broad combination agent to a more valuable precision medicine, aligning it with the successful strategy of competitors like Cantargia and potentially justifying a smaller, faster, and less expensive path to registration.

Comparative Analysis: Narmafotinib in the 1L mPDAC Arena

To contextualize Amplia's position, it is essential to directly compare the emerging clinical data for narmafotinib and its key non-FAKi competitors against the newly established standard of care. It is critical to acknowledge the limitations of cross-trial comparisons, especially when dealing with trials of different phases, sizes, and patient populations. The comparative data raises a critical strategic question: what constitutes a more valuable clinical profile in mPDAC? The answer involves a nuanced debate between quantitative and qualitative endpoints.

A high median Overall Survival, such as the 15.7 months reported for Arcus's quemliclustat in the ARC-8 analysis, is a powerful, statistically robust endpoint. Regulators, payers, and clinicians are accustomed to evaluating drugs based on their ability to shift the median of the Kaplan-Meier survival curve. A drug that can reliably extend the life of the "average" patient by several months has a clear and easily communicable value proposition and a straightforward path through regulatory and reimbursement hurdles. This is the quantitative argument, and it is the standard by which most oncology drugs are judged.

Amplia's CR signal represents a qualitative advantage. While the final mOS for narmafotinib is not yet known, the achievement of complete tumour eradication in two of 55 patients is a profound outcome that historical data suggests is almost impossible with chemotherapy alone. This signal speaks to a depth of response that a mOS number alone cannot capture. It suggests that for a small subset of patients, narmafotinib may

not just extend life but offer a chance at a long-term, durable remission – a potential cure (not something to be said lightly). This is an incredibly compelling narrative for patients and clinicians who are accustomed to managing an inexorably progressive disease.

The investment implications of this dichotomy are significant. If the full ACCENT dataset, expected in Q3 2025, reveals a modest mOS benefit (e.g., in the 11.5 to 12.5-month range) but the CR rate is maintained or even increased, and these responses are shown to be durable, narmafotinib could still carve out a significant market niche. It could be positioned as a therapy for patients who may have a biological predisposition to a deep response, a hypothesis that would be greatly strengthened if a predictive biomarker can be identified. In this scenario, narmafotinib's value would not be in raising the survival floor for all patients, but in offering a select few a chance to escape the disease entirely. This "long-tail" value proposition, while harder to quantify than a simple mOS improvement, could be equally, if not more, valuable in the long run.

Valuation

Expected Development Strategy

Our outlook on Amplia is anchored in the expectation that the company will pursue a well-defined development strategy designed to maximize shareholder value by prudently managing clinical and financial risk. We anticipate Amplia will focus on building a comprehensive portfolio of Phase II clinical data to establish narmafotinib's value proposition, with the ultimate goal of securing a licensing agreement with a major pharmaceutical partner. This partner would then assume the financial and operational responsibility for the pivotal, and costly, Phase III trials required for regulatory approval.

The central strategic question for Amplia's board and shareholders is when to crystallize the value of narmafotinib. While successfully taking a drug through a global Phase III program and to market independently can yield the highest theoretical returns, this path carries immense financial and clinical risk. The alternative, and our expected strategy, is to secure a licensing partner after generating a robust and compelling Phase II data package.

We believe this post-Phase II licensing strategy is the most value-accretive path for shareholders. The capital required to fund a global, multi-hundred-patient pivotal Phase III trial in pancreatic cancer would likely exceed A$100 million, necessitating substantial and highly dilutive equity raises that would significantly reduce existing shareholders' stake in the potential upside. Furthermore, the clinical risk at this stage remains formidable. As outlined in the "Probability of Success" section of this report, the historical success rate for a solid tumour oncology drug transitioning from Phase III to approval is only approximately 40-45%. By licensing narmafotinib after Phase II, Amplia can transfer this significant financial and clinical risk to a major pharmaceutical partner who has the balance sheet and infrastructure to absorb it.

This strategy allows Amplia to secure significant non-dilutive funding via upfront and near-term milestone payments, providing a tangible return for shareholders while de-risking the asset. Crucially, by retaining a tiered royalty stream on future global sales, the company and its shareholders maintain significant exposure to the long-term commercial success of narmafotinib. Therefore, we view the assembly of a comprehensive Phase II data dossier – encompassing both gemcitabine/abraxane and FOLFIRINOX combinations – not as a prelude to independent development, but as the primary value-creation exercise designed to maximize leverage in future partnership negotiations.

Licensing Deals: Setting a Precedent

Guiding our expectations as the numerous historical precedents. This strategy allows a smaller firm to leverage the extensive capital, regulatory expertise, and commercial infrastructure of a large pharmaceutical partner to navigate the costly and complex path of Phase III trials and global commercialization. In exchange, the licensor secures non-dilutive funding through upfront and milestone payments, while retaining significant long-term upside via royalties on future sales.

The following table and case studies provide benchmarks for small molecule oncology assets licensed at or after phase II, with a focus on kinase inhibitors, combination therapies, and drugs for difficult-to-treat solid tumours. These comparators establish a reasonable spectrum of potential financial outcomes for Amplia.

Figure 15: Precedent Licensing Deals for Small Molecule Oncology Assets. Various sources.

Licensor / Licensee	Asset / MOA	Year / Stage at Signing	Indication(s)	Upfront Payment	Total Potential Value	Royalties	Notes
Kura Oncology / Kyowa Kirin	Ziftomenib / Menin Inhibitor	2024 / Phase II	Monotherapy R/R Acute Myeolid Leukaemia (AML)	US$300M	US$1.61Bn	50/50 US profit share; mid-teen % ex. US	Deal signed post-completion of registration-directed trial enrolment; BTD designation.
Takeda / HUTCHMED	Fruquintinib / VEGFR1/2/3 inhibitor	2023 / Pre-NDA in US/EU/Jap but approved in China	Refractory metastatic colorectal cancer (mCRC)	US$400M	US$1.13Bn	Tiered (unspecific)	Licensor acquiring ex. China rights.
Relay / Elevar Therapeutics	Lirafugratinib / FGRFR2 inhibitor	2024 / Phase II	FGFR2-driven cholangiocarcinoma (CCA) and other FGFR2-altered solid tumours	US$75M	$500M	Low-teens %	Global rights for an NDA-ready therapy with BTD; partner assumes all future dev.
Mirati / Zai Lab	Adagrasib / KRAS G12C inhibitor	2021 / Phase II	NSCLC, CRC, Pancreatic cancer, other solid tumours with KRAS mutations.	US$65M	US$338M	High-teens to low-20s %	Greater China rights only; partner to accelerate global trial enrolment in region.
AstraZeneca / Merck	MK-1775 / WEE1 kinase inhibitor	2013 / Phase IIa	Ovarian Cancer	US$50M	Undisclosed	Undisclosed	Global rights; combination with standard-of-care chemotherapy.
Blueprint Medicines / Roche	Pralsetinib / RET inhibitor	2020 / NDA submitted (accelerated approval on back of positive Phase Ia/II in ARROW trial	RET fusion +ve NSCLC, thyroid cancers	US$675M cash + US$100M equity	US$1.7Bn	High-teens to mid-20s %	Near-commercial asset due to accelerated approval pathway
Black Diamond / Servier	BDTX-4933 / Pan-RAS/RAF inhibitor	2025 / Phase I	RAS/RAF mutant solid tumors (e.g. pancreatic, CRC, NSCLC)	US&70M	US$780M	Tiered	High Price for a best-in-class Phase I asset.

The value of a licensing deal is intrinsically tied to the maturity of the clinical data. While preclinical deals can attract massive "biobuck" figures, the upfront payments are typically smaller. The true value inflection point occurs upon entering Phase II. Since 2022, the median upfront payment for a Phase II oncology asset licensed to a large pharma partner has been reported at $100 million.

The High-Water Mark for a De-Risked Asset

Moving beyond the headline numbers, a deeper analysis of the strategic rationale and context behind key deals provides a more nuanced framework for evaluating narmafotinib. The late-2024 licensing agreement between Kura Oncology and Kyowa Kirin for the oral menin inhibitor ziftomenib represents the "gold standard" for a Phase 2 out-licensing deal and illustrates the immense value that can be unlocked with a thoroughly de-risked asset. The context behind the US$330M upfront up to nearly US$1.2Bn deal is paramount. At the time of the deal, Kura had already completed enrollment in its Phase 2 registration-directed trial in relapsed/refractory (R/R) NPM1-mutant AML, and the asset had been granted BTD by the FDA. An NDA submission was

anticipated in 2025, and indeed, the submission in the first quarter of 2025 triggered a $45 million milestone payment to Kura.

This transaction was effectively for a pre-commercial asset, a "Phase 3 in disguise." Kyowa Kirin was not primarily acquiring the option to fund a risky and expensive pivotal trial; it was securing partnership on a near-term launch and a broad lifecycle management plan that included multiple new Phase 3 studies in the frontline AML setting. The massive upfront payment and favourable profit-sharing terms reflect the high degree of certainty around the asset's path to market and its strategic value as a "pipeline in a product."

The deal between Blueprint and Roche for pralsetinib represents a similar dynamic: the relatively high upfront payment was partially due to an NDA already having been submitted. For Amplia, these precedents set a high bar but also illuminates the most lucrative path forward. If the Phase 2 data for narmafotinib is so compelling that it could support an accelerated approval pathway – a distinct possibility in a high-unmet-need indication like pancreatic cancer – its negotiating position would be fundamentally transformed, moving it closer to the Kura benchmark.

The Classic Combination Play

The 2013 agreement between AstraZeneca and Merck for the WEE1 kinase inhibitor MK-1775 provides a highly relevant, albeit dated, precedent for namafotinib. AstraZeneca licensed the oral inhibitor, then in Phase 2a studies, for a $50 million upfront fee plus undisclosed future development, regulatory, and sales milestones, as well as tiered royalties. This deal is analogous to the narmafotinib opportunity in several key ways. Like narmafotinib, MK-1775 is a small molecule kinase inhibitor. Crucially, its core therapeutic hypothesis was based on its use in combination with standard-of-care DNA-damaging chemotherapy agents to enhance their anti-tumour effects. The value proposition is not to replace the existing standard of care but to augment it, thereby improving outcomes within a large, established treatment paradigm.

For a major oncology player like AstraZeneca, the strategic fit was clear. The acquisition provided a tool to potentially improve efficacy for a large population of patients already receiving established therapies. While the $50 million upfront payment may seem modest by today's standards, it was a substantial figure in 2013 for a Phase 2a asset. This deal provides a solid baseline for a "standard" Phase 2 combination-play licensing deal where the partner assumes the full financial and operational burden of late-stage development.

The Targeted Therapy & Regional Deal

In 2021, Mirati Therapeutics executed a deal with Zai Lab for its KRAS G12C inhibitor, adagrasib. The deal granted Zai Lab exclusive rights to develop and commercialize adagrasib in greater China only, for US$65m upfront, up to US$273 in milestone, and significant high-teen to low-20s percent tiered royalties. At the time, adagrasib was advancing through registration-enabling studies for non-small cell lung cancer (NSCLC) and was also being investigated in other KRASG12C-mutated tumors, including colorectal and pancreatic cancer. This transaction is a compelling case study for two primary reasons: its focus on a specific genetic biomarker and its regional structure. The deal highlights a viable strategic pathway for emerging biotech companies: partnering an asset in a specific region like Asia or Europe can secure significant non-dilutive capital and accelerate global trial enrollment, while allowing the company to retain full rights and capture greater value in major markets like the US.

Notably, the deal’s rationale extended beyond the lead indication: colorectal and pancreatic cancer were also in the pipeline. The partnership was predicated on the broad potential of the asset, including its use in future combination therapies, which are now coming to fruition with approvals for adagrasib plus cetuximab in CRC. This precedent directly validates the strategic direction outlined for narmafotinib. It demonstrates that demonstrating synergy with next-generation targeted agents—such as KRAS inhibitors—can significantly enhance an asset's appeal and value to

partners who either own a competing or complementary asset or wish to establish a foothold in that evolving treatment landscape.

Modelling a Potential Narmafotinib Licensing Agreement

Synthesizing the analysis of the macro-environment, precedent transactions, and narmafotinib's specific value drivers allows for the construction of a scenario-based framework for a potential licensing agreement. The ultimate terms of a deal will be contingent on the clinical data Amplia generates over the next 12-24 months.

The precedent transactions delineate a clear spectrum of potential deal structures, ranging from modest, risk-mitigated partnerships to transformative, high-value collaborations.

- Lower bound scenario: should the ACCENT final data show a positive but not statistically significant signal – for example, good safety and tolerability with a modest non-significant trend in PFS or OS – a potential deal would likely resemble the structures with low upfront payment, in the US$20M range. The vast majority of the deal's value would be tied to back-end development and sales milestones. In this scenario, the partner would assume all future development risk and costs for pivotal trials.

- Mid-range scenario: If Amplia delivers strong Phase 2 data showing a clear, clinically meaningful, and statistically significant improvement on a key endpoint like PFS, it could command terms more aligned with the Relay/Elevar or Black Diamond/Servier precedents. This outcome, further bolstered by positive data from the FOLFIRINOX combination cohort, would imply a more substantial upfront payment in the US$70-100M range. The total potential value could reach $500 million to $800 million, with tiered royalties on net sales escalating from the low to mid-teens.

- Upper bound (blue sky) scenario: an exceptional outcome where the Phase 2 data is so compelling that it could potentially support a registration filing under an accelerated approval pathway, a deal could begin to approach the territory of the Kura/Kyowa Kirin precedent. This scenario would be predicated on demonstrating an exceptionally high response rate and a strong, durable survival trend. If this is coupled with early proof-of-concept data showing synergy with a KRAS inhibitor, narmafotinib would be positioned as a premier strategic asset. Such a deal could feature a significant upfront payment of US$150M or more, substantial near-term milestones tied to regulatory filings, and a total deal value exceeding $1 billion. This scenario could also open the possibility of a more strategic collaboration structure, such as a co-development and profit-sharing arrangement in key markets like the US.

Probability of Success

The valuation of any clinical-stage biopharmaceutical asset is fundamentally an exercise in risk assessment. The journey from initial human trials to regulatory approval and commercial launch is characterized by a high rate of attrition, with the vast majority of investigational therapies failing to reach the market. Therefore, constructing a credible risk-adjusted Net Present Value (rNPV) model requires a deep, evidence-based understanding of the historical probabilities of success (PoS) that govern this process. PoS is useful in reflecting the "real-world": clinical trials enrol patients using strict inclusion and exclusion criteria, those who are younger, fitter, and with fewer comorbidities. Uptake in the real world will include a more diverse range of patients, a feature that implies results seen in clinical trials may not fully translate to everyday clinical practice, because real-world patients are more varied and often less able to tolerate or benefit from new treatments to the same extent as trial participants.

The path to drug approval is a multi-stage gauntlet, with each phase presenting a significant hurdle. The overall Likelihood of Approval (LOA) from the start of clinical trials

(Phase 1) to final approval for an average drug is starkly low. A comprehensive 2021 study published in *Nature Biotechnology* (BIO) analysing over 10,000 clinical development programs found the overall LOA from Phase 1 to be a mere 7.9%.

However, this figure is a broad average across all therapeutic areas. For oncology, the picture is even more sobering. The same study revealed that oncology drugs have the lowest success rate of any major therapeutic area, with an LOA from Phase 1 of just 5.3%. Oncology consistently had one of the lowest success rates compared to the other 14 disease categories for every developmental clinical transition. There were relative differentials of approximately 20% between Oncology and non-oncology groupings at the Phase II and III stages. This is due to the complex biology of cancer, the high bar for demonstrating efficacy, and the challenging nature of clinical trials in this patient population.

Figure 16: Phase Success Rates for Oncology vs Non-Oncology Drugs. Source: Nature Biotechnology (BIO) 2021 study.

Phase Success	Phase I to II	Phase II to III	Phase III to NDA/BLA	NDA/BLA to Approval
Oncology	48.8%	24.6%	47.7%	92.0%
Non-oncology	53.9%	31.2%	61.3%	90.2%

Phase Success	Phase I to Approval	Phase II to Approval	Phase III to Approval	NDA/BLA to Approval
Oncology	5.3%	10.8%	43.9%	92.0%
Non-oncology	9.3%	17.2%	55.3%	90.2%

The 2021 BIO study also broke down the PoS for oncology drugs by Haematologic vs Solid cancers. Drugs for solid tumours had more than twice as many transitions in the data set (2,982 vs 1,094), but a much smaller LOA from Phase I vs haematological cancers (4.6% vs 7.5%).

Figure 17: Phase Success Rates for Hematologic vs. Solid Tumour Oncology Drugs. Source: 2021 Nature Biotechnology (BIO) study.

Phase Success	Phase I to II	Phase II to III	Phase III to NDA/BLA	NDA/BLA to Approval
Haematologic	50.1%	27.8%	60.0%	90.0%
Solid	48.9%	23.4%	42.9%	92.9%

Phase Success	Phase I to Approval	Phase II to Approval	Phase III to Approval	NDA/BLA to Approval
Haematologic	7.5%	15.0%	54.0%	90.0%
Solid	4.6%	9.3%	39.8%	92.9%

The Orphan Drug Advantage?

The assignment of an Orphan Drug Designation (ODD) by the FDA provides a notable, albeit qualified, advantage to the probability of success for investigational therapies, particularly within the challenging landscape of oncology. Analysis of clinical development success rates consistently shows that drugs with an orphan designation have a higher probability of reaching the market compared to the industry-wide average. However, this advantage is moderated within the oncology therapeutic area due to the inherent biological complexity of cancer.

A pivotal analysis from a 2019 DIA Global Forum issue examined clinical trial PoS in oncology using 108,248 clinical trial data points for 24,448 unique drug development programs across 40 types of cancer from 2000 to 2018, where a drug development program is defined as a set of clinical trials corresponding to a unique drug-indication pair. This study found that the overall probability of success from Phase 1 to approval for an orphan-designated oncology drug was 1.9%. While this figure appears low, it is

important to contextualize it within the broader oncology space, which historically has one of the lowest success rates of any therapeutic area.

The study further breaks down the phase-by-phase transition probabilities, revealing a more nuanced picture. Orphan oncology drugs demonstrate higher success rates in the earlier clinical phases compared to the overall oncology pipeline. For instance, the transition from Phase 1 to Phase 2 for orphan oncology drugs was 76.9% versus 65.0% for all oncology drugs, and the progression from Phase 2 to Phase 3 was 44.6% compared to 38.0%. However, a significant bottleneck appears in the final stage, with a lower proportion of orphan oncology drugs moving from Phase 3 to approval. This suggests that while the orphan designation may facilitate earlier-stage development, the ultimate hurdle of demonstrating sufficient efficacy and safety for regulatory approval remains substantial.

The table below provides a comparative view of the probability of success for orphan drugs, with a specific focus on oncology, based on a synthesis of available data. It is important to note that these figures are derived from different analyses and time periods and should be interpreted as indicative rather than directly comparable in all cases.

Figure 18: Probability of Success for Orphan Drugs in Oncology. Source: DIA Global Forum (2019)

	All oncology	Non-orphan oncology	Orphan Oncology
Phase I to II	65.0%	64.1%	76.9%
Phase II to III	38.0%	37.4%	44.6%
Phase III to approval	24.1%	24.8%	10.1%
Phase I to approval	3.3%	3.3%	1.9%

It's important to note two things: the first is that only 13 of 40 diseases within oncology in this study's orphan drug development sample have one approval or more. Therefore, small sample sizes affect the reliability of the data. If, for example, a further 5 diseases were to have seen an approval, the overall PoS from phase I to approval would likely be significantly greater than 1.9%. Secondly, because of how this study treats missing clinical trial outcomes, path-by-path PoS estimates are not multiplicative (i.e., $POS_{1\text{-}2}$ X $PoS_{2\text{-}3}$ X $PoS_{3\text{-}A} \neq PoS_{1\text{-}A}$, in contrast to phase-by-phase estimates, which do multiply. Therefore, in this case, we cannot attain a $PoS_{2\text{-}A}$ figure.

Deconstructing the Journey

Due to significant differences between the data presented in the 2021 BIO study and the 2019 DIA Global Forum study, calculating a definitive Probability of Success (PoS) is challenging. The DIA study indicates that while orphan-designated oncology drugs have a higher PoS in early clinical phases (Phase I to II and II to III) , they face a significant bottleneck and a much lower success rate in the pivotal Phase III to approval stage. This results in a very low overall Phase I to approval PoS of 1.9%. Conversely, the BIO study data for solid tumors shows lower success rates in the early phases but a substantially higher success rate in the transition from Phase III to NDA. This discrepancy leads to a higher overall Phase I to approval PoS of 4.6% for solid tumors in the BIO study.

Given this variance, the chosen PoS factors in the following table have been adjusted to reflect both BIO study data for solid tumors and the DIA Global Forum data for orphan oncology. This blended approach acknowledges the conflicting data, and the resulting probabilities must be assessed with caution.

Figure 19: Probability of Success (PoS) Assumptions and Justifications. Various Sources.

Phase	PoS	Justification

Phase I to II	62.9%	Midpoint between the solid tumour rate of 48.9% and the orphan oncology rate of 76.9%. his balances the broader historical data with the known early-phase advantage of an ODD.
Phase II to III	34.0%	Midpoint between the solid tumour rate of 23.4% and the orphan oncology rate of 44.6%. This reflects a blended probability of success for advancing from Phase II.
Phase III to NDA	25.0%	Midpoint between the solid tumour rate of 398% and the orphan oncology rate of 10.1%. This harmonises the conflicting late-stage data from the two sources.
Phase II to Approval	**10.0%**	We calculate the baseline $PoS_{2\text{-}A}$ as 0.34 x 0.25 = 8.5%. However, this historical baseline is significantly de-risked for Narmafotinib. The strong interim data from Amplia's ongoing Phase II ACCENT trial suggests a higher-than-average probability of success in moving from Phase II to Phase III, positively impacting the overall Phase II to Approval outlook. Moreover, narmafotinib's potency and selectivity profile places it as a "best-in-class" molecule suitable for combination therapy with a large depth of targeted therapies.

Our 10% $PoS_{2\text{-}A}$ NPV model input is subject to change upon receipt of topline and final ACCENT trial data. While this figure is unlikely to change substantially ahead of any data coming from the recently announced Phase II trial with FOLFIRINOX, the overall LOA should adjust up toward the 25% mark if this trial is successful.

Narmafotinib Pricing

When forecasting pricing for Amplia Therapeutics' narmafotinib, it is essential to reference precedents set by comparable targeted oncology drugs. Understanding these precedents helps inform realistic pricing assumptions, critical for accurately modelling the potential valuation of narmafotinib.

High Annual Cost of Targeted Oncology Drugs

The annual cost of oral small-molecule targeted therapies in oncology has risen dramatically over the past decade, routinely reaching six-figure sums per patient annually. These high prices reflect several factors, including the rarity of targeted patient populations, clinical benefit over existing treatments, and the premium placed on novel mechanisms of action addressing previously underserved cancers. It's important to clarify that "annual pricing" here refers to the drug's approximate cost to US payors, hospitals or patients, most often based on wholesale acquisition cost or list price for one year of therapy. Actual net prices may be lower after discounts.

Examples Across Pancreatic Cancer

In pancreatic cancer, targeted add-on therapies provide useful pricing benchmarks. Erlotinib (Tarceva®), an EGFR inhibitor approved in combination with chemotherapy, cost around US$4,000 to US$5,000 per month at launch in 2005. The cost rose over time, up to US$6,800 per month by the mid-2010s and ranging between US$7,000 to US$15,000 today (even as a generic) depending on the pharmacy. A more contemporary example is olaparib (Lynparza®), a PARP inhibitor approved for maintenance therapy in BRCA-mutated pancreatic cancer. Olaparib carries a US list price between US$102,000 and US$160,000 annually, demonstrating the willingness of payers to support pricing in the low-to-mid six figures for effective targeted treatments in pancreatic cancer, despite relatively modest overall survival benefits.

Examples Across Other Comparable Cancers

Comparable therapies across other cancers further reinforce these high pricing benchmarks. In ovarian cancer, PARP inhibitors such as niraparib (Zejula®) and olaparib typically cost around US$140,000 to US$180,000 annually. Similarly, targeted therapies in non-small cell lung cancer (NSCLC) exhibit even higher annual costs. Osimertinib (Tagrisso®), a leading EGFR inhibitor, is priced above US$150,000 annually, with recent analyses citing figures potentially exceeding US$200,000. KRAS-targeted therapies such as sotorasib (Lumakras®) similarly approach annual prices of around US$250,000.

Pricing of colorectal cancer treatments like regorafenib (Stivarga®) are also consistent with this dynamic.

Implications for Narmafotinib Pricing

Given these precedents, a US pricing assumption of approximately US$120,000 per patient annually for narmafotinib appears well-justified and aligned with market norms. This assumption places narmafotinib within the established range for small-molecule targeted oncology therapies, reflecting both the specialized nature of its indication (metastatic pancreatic cancer) and its positioning as an add-on therapy intended to improve clinical outcomes in a disease characterized by high unmet medical need and limited effective treatment options.

Final Assumptions

Our sum-of-the-parts (SOTP) valuation for Amplia is derived from a risk-adjusted net present value (rNPV) for narmafotinib in two core markets – the US and Europe – both for the specific indication, first-line metastatic PDAC. The following section outlines the key assumptions that underpin our financial forecasts and valuation.

Licensing

We model that Amplia will secure a strategic licensing partner for the global rights to narmafotinib. The deal is assumed to be executed at the end of FY27, following the successful completion of the Phase II trial of narmafotinib in combination with FOLFIRINOX. We expect the agreement to include a total of US$350M in upfront and milestone payments, as well as a tiered royalty structure:

- Upfront payment: US$50M
- US$100M upon FDA approval
- US$50M upon achieving first sales
- US$75M upon reaching cumulative US$1Bn and US$2Bn each.
- Royalties: 12.5% on the first US$500M per annum; 15% on all sales exceeding US$500M per annum.

We expect the licensee will assume all financial and operational responsibility for registration-enabling development, including the pivotal Phase III trial. e expect this trial will evaluate narmafotinib in first-line metastatic pancreatic ductal adenocarcinoma (mPDAC) patients across both standard-of-care chemotherapy regimens (gemcitabine/abraxane and FOLFIRINOX).

Regulatory Approval

We forecast a New Drug Application (NDA) submission to the FDA in early-mid FY29, with regulatory approval for the specific indication – first-line mPDAC in combination with standard of care chemotherapy – to come in late FY29. In Europe, CE Mark approval is expected to follow, occurring in FY30 for the same indication.

Pricing

As per the above section on narmafotinib pricing precedents and justification, we assume a gross price of US$120,000 per patient per year in the US. This is positioned at the lower bound of pricing for novel combination agents in oncology to provide a conservative estimate. For the European market, we assume a lower average annual price of US$90,000 per patient, representing a 25% discount to the US price. Forecasting a single price for Europe is inherently more complex than for the US due to the fragmented nature of the market. Unlike the US, pricing and reimbursement are determined on a country-by-country basis through negotiations with national health authorities (e.g., G-BA in Germany, NICE in the UK). These single-payer systems conduct rigorous Health Technology Assessments (HTAs) to evaluate a drug's cost-effectiveness relative to the standard of care, exerting significant downward pressure on prices. Therefore, our US$90,000 assumption does not represent a list price in any single country, but rather a blended net price expected across the major European territories after accounting for these mandatory discounts and rebates.

Sales & Market Penetration

Our revenue forecast is built on a bottom-up patient model for the addressable first-line mPDAC market in our two core jurisdictions: the US and Europe.

- US Eligible Patient Population: The model starts with 66,440 new pancreatic cancer cases in the US in FY25, growing at 1.1% annually. The addressable market is filtered as follows: 90% are PDAC, of which 50% are metastatic (mPDAC), of which 56% receive first-line chemotherapy. This results in a target patient pool of 17,684 in the first year of sales (FY30).

- Europe Eligible Patient Population: The model starts with 148,742 new pancreatic cancer cases in FY25, growing at 1.2% per annum. Using the same filters the addressable market in the first year of sales in FY31 is calculated from a total base of 159,778 patients to be 40,264.

For both the US and Europe, we assume market penetration begins at 5% in the first year of launch (FY30 for US, FY31 for Europe). Market share increases in 5% increments each subsequent year until reaching a 40% and 35% in FY37 in the US and Europe respectively. Provided the drug demonstrates a meaningful clinical benefit and navigates key uptake factors, this assumption is broadly in-line with precedents.

Our market penetration assumptions for narmafotinib, projecting a peak market share of 40% over an 8-year period in first-line metastatic pancreatic cancer, are strongly supported by historical precedents of chemotherapy add-on therapies in similarly challenging oncology settings. For example, nab-paclitaxel, when combined with gemcitabine in pancreatic cancer, achieved rapid adoption, capturing around 44% of the first-line market within just 2–3 years of its approval. Similarly, durvalumab combined with chemotherapy for advanced cholangiocarcinoma is projected by NICE (the UK's National Institute for Health and Care Excellence) to achieve approximately 70% penetration within two years post-launch, driven by high unmet clinical need and clear survival benefits. Immunotherapy combinations such as nivolumab or pembrolizumab added to chemotherapy in gastric cancer also demonstrated fast uptake, reaching about 40–50% market penetration within one to two years due to robust efficacy and strong guideline endorsements.

Conversely, more modest uptake was observed with bevacizumab in ovarian cancer, peaking at approximately 30% over nearly a decade, reflecting a combination of limited survival benefit, high cost, and payer restrictions. Though, it is worth noting that bevacizumab was approved in Europe in 2011 and was only used "off-label" in the US before FDA approval in 2018. In 2018, market penetration rose sharply. Trastuzumab's experience in HER2-positive gastric cancer further illustrates the potential for swift penetration when clear patient selection criteria are present, ultimately capturing nearly the entire eligible patient population within a few years.

Moreover, We assume an average treatment duration of one year per patient and a terminal growth rate of 3% applied to both programs after the explicit 12-year forecast period.

Costs

We expect the phase II FOLFIRINOX trial to cost an approximate total of A$15 million, split over two years: A$10m in FY26 and A$5m in FY27. A remaining A$3m of ACCENT-related costs are forecasted for FY26. As outlined, we expect Amplia's management to pursue further R&D, such as in combination with KRAS inhibitors, and have factored in continued R&D at A$7m per annum from FY28 to FY31. We expect the company to incur A$2.75m per annum in other operating costs in perpetuity.

Discount Rate

We discount expected future cash flows with a 12.5% weighted average cost of capital (WACC), calculated with the following components: Beta of 0.77 (calculated using 5 years of monthly returns against the ASX200); risk-free rate of 4.25% (the approximate

yield on Australian 10-year government bond); cost-of-equity of 15%; and a capital structure including 100% equity funding (0% target gearing).

Other Key Assumptions

To ensure conservatism in valuing Amplia, our SOTP model is strictly limited in scope. The valuation is based solely on the commercial potential of narmafotinib in first-line metastatic PDAC. We do not assign any value to potential future use in non-metastatic or adjuvant settings, as no clinical development has been initiated for these indications. The model includes only the United States and major European markets. Potential revenues from other regions (e.g., Japan, Rest of World) are excluded and represent a source of potential upside not captured in our valuation. Further, we given that we expect FDA approval in FY30, we forecast ODD-enabled market exclusivity for the duration of the rNPV12 forecasting period.

Sum-of-the-Parts (SOTP) Valuation

We value Amplia therapeutics using a sum-of-the-parts (SOTP) approach. However, due to the absence of clinical data outside of first-line mPDAC, our model includes only two entries: (i) 1L PDAC (both metastatic and early-stage) in the US market via a licensee, and (ii) 1L PDAC (both metastatic and early-stage) in the european market via a licensee. We note that, while narmafotinib may have clinical utility in other solid tumours and Amplia may seek to trial the drug in these indicaitons, the asset can only be valued on what is foreseeable and not reliant on excessive speculation.

Figure 20: Summary Table of Sum-of-the-Parts Valuation. Source: Evolution Capital's Forecasts.

Asset	Market	Indication	Commercialisation path	NPV12 (A$'000s)	Unrisked $/sh	PoS	rNPV12 (A$'000s)	Risked $/sh
Narmafotinib	US	1L PDAC	Licensee	942,340	$2.168	10%	94,234	$0.217
Narmafotinib	Europe	1L PDAC	Licensee	1,292,153	$2.973	10%	129,215	$0.297

In the SOTP model, R&D costs are allocated to the first and largest market – the US. This explains the favourable skew in terms of unrisked dollar of NPV per share toward the European program despite comparable revenue forecasts.

Figure 21: Summary of Financial Forecasts and Risk-Adjusted Net Present Value (rNPV) for Narmafotinib in First-Line Metastatic PDAC in the US and Europe. Sources: Evolution Capital's Forecasts.

EU 1L mPDAC	New pancreatic cancer patients	67,171	67,910	68,657	69,412	70,175	70,947	71,728	72,517	73,315	74,121	74,936	75,761
	New mPDAC patients given chemo 1L	16,927	17,113	17,301	17,492	17,684	17,879	18,075	18,274	18,475	18,678	18,884	19,092
	Patients treated by narmafotinib					884	1,788	2,711	3,655	4,619	5,604	6,609	7,637
	Total Royalty Stream (US$'000s)					13,263	26,818	40,670	54,823	70,639	88,364	106,469	124,960
	Milestone Payments (US$'000s)		50,000		100,000	50,000				75,000	75,000		
	Total R&D costs (US$'000s)	8,580	6,600	4,620	4,620	4,620	4,620						
	Net cash flow (US$'000s)	(8,580)	43,400	(4,620)	95,380	58,643	22,198	36,050	50,203	145,639	163,364	106,469	124,960
	PV of net cash flow	(7,625)	34,278	(3,243)	59,500	32,512	10,937	15,785	19,537	50,369	50,212	29,083	30,336
EU 1L mPDAC	New pancreatic cancer patients	150,527	152,333	154,161	156,011	157,883	159,778	161,695	163,636	165,599	167,586	169,597	171,633
	New mPDAC patients given chemo 1L	37,933	38,388	38,849	39,315	39,787	40,264	40,747	41,236	41,731	42,232	42,739	43,251
	Patients treated by narmafotinib						2,013	4,075	6,185	8,346	10,558	12,822	15,138
	Total Royalty Stream (US$'000s)						22,649	45,841	71,003	100,174	130,032	160,591	191,863
	Milestone Payments (US$'000s)												
	Total R&D costs (US$'000s)												
	Net cash flow (US$'000s)						22,649	45,841	71,003	100,174	130,032	160,591	191,863
	PV of net cash flow						11,159	20,073	27,631	34,645	39,967	43,867	46,577

Final Valuation

Moving from a SOTP to final price target requires adjustments for corporate items. The equity value is calculated as: (Gross SOTP Value) + (Net Cash) – (PV of Unallocated Corporate Costs) + (Other Adjustments). In this regard, we expect Amplia to conduct a A$15-20 million capital raise (the top end chosen for this modelling) in FY26 to fund the FOLFIRINOX trial and further clinical development.

We calculate our final Target Price of $0.47, representing a 34% TSR on the last close price of $0.35. Despite a sharp recent appreciation in share price due in part to the positive interim data points coming out of the ACCENT trial, we assert the market still undervalues Amplia and affirm a Speculative Buy recommendation.

Corporate Adjustments	(A$'000s)
Gross SOTP	223.45
(+) Net Cash	10.86
(-) PV of Corporate Items	7.36
Fair Valuation	241.68
Target Price	**$0.47**

We expect the company to conduct a A$20 million equity capital raise at a price of $0.26 in FY26 to fund the FOLFIRINOX Phase II trial, issuing approximately 76.9 million shares. The Target Price is therefore calculated on a pro-forma capital structure.

Financial Forecasts

Income Statement					
A$'000s	FY25a	FY26e	FY27e	FY28e	FY29e
Revenue	-	-	50.00	-	100.00
Other Income	4.06	5.66	4.35	3.05	3.05
Total Revenue	**4.06**	**5.66**	**54.35**	**3.05**	**103.05**
Operating expenses	-10.49	-15.75	-13.01	-10.30	-10.03
EBITDA	**-6.43**	**-10.10**	**41.34**	**-7.25**	**93.01**
D&A	-0.09	-0.00	-0.00	-0.00	-0.00
EBIT	**-6.52**	**-10.10**	**41.34**	**-7.25**	**93.01**
Net Interest	-0.06	0.21	0.48	1.37	1.17
NPBT	**-6.57**	**-9.89**	**41.82**	**-5.88**	**94.18**
Tax expense	-	-	-	-	-
Discontinued operations	-	-	-	-	-
NPAT	-6.57	-9.89	41.82	-5.88	94.18

Balance Sheet					
$'000s	FY25a	FY26e	FY27e	FY28e	FY29e
Cash	10.86	25.22	70.80	65.09	160.34
Receivables	-	-	-	-	-
Inventory	-	-	-	-	-
R&D Incentive Receivable	3.77	5.66	4.35	3.05	3.05
Other	0.29	0.51	0.39	0.27	0.27
Current assets	**14.93**	**31.38**	**75.54**	**68.41**	**163.66**
Intangibles	7.94	7.94	7.94	7.94	7.94
PPE	0.00	0.00	0.00	0.00	0.00
Other	0.07	0.07	0.07	0.07	0.07
Non-current assets	**8.01**	**8.01**	**8.01**	**8.00**	**8.00**
Total Assets	**22.94**	**39.39**	**83.54**	**76.42**	**171.66**
Payables & Accrued Liabilities	1.80	2.72	2.25	1.78	1.73
Borrowings	-	-	-	-	-
Lease Liabilities	0.01	-	-	-	-
Other	0.07	0.36	0.06	-	-
Current liabilities	**1.89**	**3.08**	**2.31**	**1.78**	**1.73**
Borrowings	-	-	-	-	-
Other liability	0.02	0.03	0.03	0.04	0.04
Non current liabilities	**0.02**	**0.03**	**0.03**	**0.04**	**0.04**
Total Liabilities	**1.91**	**3.10**	**2.34**	**1.81**	**1.77**
Net Assets	**21.02**	**36.29**	**81.21**	**74.60**	**169.89**
Contributed Equity	167.39	188.57	194.08	194.89	194.89
Retained earnings	-145.54	-155.43	-113.60	-119.49	-25.31
Reserves/Other	-0.83	3.14	0.73	-0.80	0.28
Total Equity	**21.02**	**36.28**	**81.21**	**74.61**	**169.87**

Statement of Cashflows					
$ in actual figures	FY25e	FY26e	FY27e	FY28e	FY29e
Net profit for period	-6.57	-9.89	41.82	-5.88	94.18
Depreciation & Amortisation	0.09	0.00	0.00	0.00	0.00
Changes in working capital	-0.82	3.28	-2.19	-1.95	-0.05
Other	-	-	-	-	-
Operating cash flow	**-7.30**	**-6.60**	**39.63**	**-7.83**	**94.13**
	-	-	-	-	0.00
Payments for PPE	-0.00	-	-	-	-
Other payments	-	-	-	-	-
Proceeds from asset sale	-	-	-	-	-
Investing cash flow	**-0.00**	**-**	**-**	**-**	**-**
	-	-	-	-	0.00
Equity raised	17.28	20.00	-	-	-
Transaction costs	-1.33	-1.20	-	-	-
Proceeds from exercise of options	-	2.38	5.51	0.81	-
Net borrowings	-1.47	-	-	-	-
Finance costs	-0.08	-0.05	-0.05	-0.05	-0.05
Other	-0.08	0.21	0.48	1.37	1.17
Financing cash flow	**14.40**	**21.34**	**5.95**	**2.13**	**1.12**
	-	-	-	-	0.00
Free cash flow	**-7.31**	**-6.60**	**39.63**	**-7.83**	**94.13**
Net cash flow	**7.10**	**14.74**	**45.58**	**-5.71**	**95.25**
Effects of exchange rate	-	-	-	-	-
Cash year end	**10.48**	**25.22**	**70.80**	**65.09**	**160.34**

Investment Fundamentals					
	FY25a	FY26e	FY27e	FY28e	FY29e
Liquidity					
Current Ratio	7.9	10.2	32.8	38.5	94.5
Quick Ratio	2.2	2.0	2.1	1.9	1.9
Solvency					
Debt to Equity	0.0	0.0	0.0	0.0	0.0
Debt to Assets	0.0	0.0	0.0	0.0	0.0
LT Debt to Assets	0.0	0.0	0.0	0.0	0.0
Profitability					
Net Margin	n/a	n/a	77%	n/a	91%
ROA	-29%	-25%	50%	-8%	55%
ROE	-31%	-27%	51%	-8%	55%
Valuation					
P/E	n/a	n/a	5.8	n/a	2.6
EV/EBITDA	n/a	n/a	4.1	n/a	0.9
P/B	8.7	6.2	2.9	3.2	1.4

Appendix

Key Risks

Clinical Development & Regulatory Risk

- **Replication of Clinical Results:** Amplia's investment case is heavily reliant on the exceptional early efficacy signals from the Phase 2 ACCENT trial, including multiple, rare Complete Responses (CRs). The primary risk is that these unprecedented results may not be replicated in a larger, randomized, and more stringently controlled pivotal Phase 3 trial. Historically, many promising Phase 2 oncology assets have failed to demonstrate a statistically significant benefit in Phase 3.
- **High-Risk Indication:** Metastatic pancreatic ductal adenocarcinoma (mPDAC) is a notoriously difficult-to-treat cancer with a high rate of clinical trial failure. The complex biology, aggressive nature of the disease, and high bar for demonstrating a meaningful survival benefit present significant hurdles for any new therapeutic.
- **Historical Precedent of FAKi Failure:** While narmafotinib shows a differentiated profile, the broader class of FAK inhibitors has a history of clinical setbacks. The unambiguous failure of GSK's FAK inhibitor in a Phase 2 mPDAC trial serves as a stark reminder that targeting this pathway is not a guaranteed path to success.
- **Mechanism-Specific Limitations:** Like other ATP-competitive kinase inhibitors, narmafotinib only blocks FAK's enzymatic function. This leaves the protein's kinase-independent scaffolding role intact, which can mediate pro-tumorigenic signalling and contribute to adaptive resistance over time.

Competitive Landscape & Market Risk

- **Direct Competition & First-Mover Advantage:** Verastem Oncology represents Amplia's most direct and formidable competitor. Verastem's FAK inhibitor, defactinib, is already FDA-approved for another indication and is being aggressively developed in combination for PDAC. Verastem's significant lead, established manufacturing, and existing relationships with oncologists give it a powerful first-mover advantage that will be difficult to overcome if its combination is approved first.
- **Broader Competitive Field:** The mPDAC treatment landscape is highly competitive and rapidly evolving. Several other companies (e.g., Arcus Biosciences, Cantargia) are developing novel agents with different mechanisms of action that have shown strong survival data in mid-to-late-stage trials. The success of these competitors could establish a new standard of care, raising the efficacy bar and potentially narrowing the market opportunity for narmafotinib.
- **Evolving Standard of Care:** The recent FDA approval of NALIRIFOX, which demonstrated an 11.1-month median Overall Survival, has already raised the benchmark for new first-line therapies. Narmafotinib will need to demonstrate a clinically meaningful and statistically significant improvement over this new standard to achieve widespread clinical adoption and commercial success.

Partnership & Commercialisation Risk

- **Dependency on a Strategic Partner:** Amplia's corporate strategy is predicated on securing a partnership with a major pharmaceutical company to fund the substantial costs of Phase 3 development and global commercialization. The company's ability to negotiate a favourable deal is contingent on the strength of its clinical data. Failure to secure a partner would place the full, significant financial burden on Amplia, a task that would be extremely challenging, if not impossible, to manage independently.

Funding & Financial Risk

- **Future Capital Requirements:** As a clinical-stage biotechnology company with no commercial revenue, Amplia will require substantial additional capital to fund its ongoing operations, including the planned Phase 2 trial of narmafotinib with FOLFIRINOX and any subsequent pivotal studies.
- **Shareholder Dilution:** Future financing will likely involve the issuance of new equity, which will be dilutive to existing shareholders. The terms of future capital raises will depend on clinical trial progress and prevailing market conditions.

Asset Concentration Risk

- **Single Asset Focus:** Amplia's valuation and near-term prospects are almost entirely dependent on the clinical and commercial success of a single lead asset, narmafotinib. Any clinical setbacks, safety issues, regulatory delays, or manufacturing problems related to narmafotinib would have a material and disproportionately adverse impact on the company's valuation.

Intellectual Property Risk

- **Patent Protection:** The long-term commercial success of narmafotinib depends on Amplia's ability to obtain, maintain, and defend its patent portfolio. While the company has a multi-layered IP strategy, patents can be challenged by competitors, and there is no guarantee that pending applications will be granted or that existing patents will provide sufficient protection to prevent the entry of competing products.

SWOT Analysis

Strengths	Weaknesses
• **Differentiated "Best-in-Class" Asset:** Narmafotinib is a highly potent and selective FAK inhibitor. This high selectivity is believed to contribute to a clean safety profile, which is a significant advantage when combining it with toxic chemotherapy. • **Unprecedented Clinical Efficacy Signals:** The ACCENT trial has shown multiple complete responses (CRs) and a pathological complete response (pCR) in first-line metastatic pancreatic cancer. This is a massive statistical and clinical outlier compared to the standard of care, which has a CR rate of ~0.2% (evidenced in benchmark MPACT study). • **Strong Regulatory Position:** Narmafotinib has received both Orphan Drug Designation (ODD) and Fast Track Designation from the U.S. FDA for pancreatic cancer. This provides development incentives, potential for market exclusivity, and enables an expedited review process. • **Robust Intellectual Property:** Amplia has a multi-layered IP strategy, with composition of matter patents providing protection to 2034 and other pending applications that could extend exclusivity towards 2040 or beyond. • **Positive Safety and Tolerability Profile:** The combination of narmafotinib with chemotherapy has been reported as safe and well tolerated, with adverse events similar to chemotherapy alone. This favourable safety profile is a key competitive advantage • **Strong Preclinical Rationale & Execution:** Narmafotinib has demonstrated preclinical synergy with both standard-of-care chemotherapies (Gem/Abraxane and FOLFIRINOX) and targeted therapies like KRAS inhibitors. The company has also demonstrated strong operational execution by accelerating the ACCENT trial timeline.	• **Future Funding Requirements:** As a clinical-stage, small-capitalization biotechnology company, Amplia will require substantial additional capital to fund late-stage clinical trials. Future financing rounds, while necessary, will be dilutive to current shareholders. • **Single Asset Focus:** The company's valuation and investment thesis are heavily reliant on the clinical success of a single lead asset, narmafotinib, primarily through the outcome of the ACCENT trial. • **Clinical Development Stage:** While promising, the exceptional efficacy signals are from a relatively small, single-arm Phase 2 trial. There is a primary risk that these results may not be replicated in a larger, more stringently controlled Phase 3 study, or in the Phase 2 upcoming with FOLFIRINOX. • **Scaffolding Function Limitation:** Like other kinase inhibitors, narmafotinib only blocks FAK's enzymatic function, leaving its kinase-independent scaffolding role intact, which can contribute to resistance. However, the strong clinical data suggests narmafotinib's potency may overcome this limitation.
Opportunities	**Threats**
• **High Unmet Medical Need:** Metastatic pancreatic cancer has a bleak prognosis, a 5-year survival rate of around 3%, and a treatment landscape that has seen only marginal improvements, representing a profound unmet need. • **Large and Growing Market:** The global pancreatic cancer treatment market is substantial, projected to reach between US$5.8 billion and $10.25 billion by 2030-2034. A therapy with a superior profile could rapidly capture significant market share. • **Pathway for Accelerated Approval:** The Fast Track Designation makes narmafotinib eligible for Accelerated Approval. The unprecedented CR rate could form a compelling basis for this pathway, which would dramatically shorten the timeline to market and reduce costs. • **Combination with KRAS Inhibitors:** The deep biological link between FAK and KRAS signalling positions FAK inhibitors as a likely necessary combination partner for the emerging class of KRAS inhibitors. This could dramatically expand the long-term commercial opportunity for narmafotinib beyond chemotherapy. • **Expanding Clinical Strategy:** Amplia is initiating a second trial in the U.S. combining narmafotinib with FOLFIRINOX. This strategically astute move could broaden narmafotinib's potential market by generating data with both major standard-of-care backbones.	• **Direct Competition from Verastem:** Verastem Oncology is Amplia's most direct and formidable competitor. Its FAKi, defactinib, is already FDA-approved for another indication and is being aggressively developed for pancreatic cancer in a competing trial, representing a direct and formidable threat. • **Broader Competitive Landscape:** The pancreatic cancer treatment field is evolving. Other companies are showing promising data with novel mechanisms, such as Actuate Therapeutics' elraglusib and Immuneering's atebimetinib. Narmafotinib must ultimately compete on survival outcomes against the best emerging therapies, regardless of their mechanism. • **First-Mover Disadvantage:** Verastem is ahead in development for PDAC and has a significant first-mover advantage. If defactinib is approved first, it could establish a strong foothold with clinicians, making market penetration more challenging for narmafotinib. • **Evolving Standard of Care:** The recent FDA approval of NALIRIFOX has raised the efficacy bar for new entrants. While it sets a tangible bar for approval, any new therapy will need to demonstrate a clinically meaningful improvement over an 11.1-month median OS to gain widespread adoption. • **Partnership Dependency:** Given the competitive and financial landscape, securing a partnership with a major pharmaceutical company is a critical strategic imperative. Without the backing of a major partner, competing with Verastem would be an arduous, likely impossible, task. • **Historical Precedent of Failure:** The unambiguous failure of GSK's FAK inhibitor in a Phase 2 mPDAC trial demonstrates that targeting FAK is not a guaranteed path to success and serves as a vital reminder of the high bar for success in this disease.

Board & Management

Chris Burns

CEO & MD

Chris is an experienced drug discovery leader having worked in various roles in pharma, biotech and academia for 25 years.

He has a Ph.D. from the University of Melbourne and undertook postodoctoral studies in the USA before moving to Pfizer UK, as a senior scientist. After 5 years he returned to Australia as a Research Fellow at the University of Sydney and then moved to the biotechnology company Ambri as Head of Chemistry.

Chris joined the Melbourne-based biotech Cytopia as Head of Medicinal Chemistry and later as Research Director. He led teams in the discovery of two anti-cancer agents that entered clinical trial, including the drug momelotinib (Ojjaara) now approved for the treatment of myelofibrosis. Chris then held a Laboratory Head position at the Walter and Eliza Hall Institute of Medical Research (WEHI) before taking on executive and leadership roles with a number of privately-held biotechnology companies in Australia.

Dr Burns is the inventor on over 30 patents and a co-author on over 60 scientific publications. He was co-recipient of the 2024 Prime Minister's Prize for Innovation and is a Fellow of the Australian Academy of Health and Medical Sciences, the Royal Society of Chemistry (UK) and the Royal Australian Chemical Institute.

Dr Burns was originally appointed as a Non-Executive Director on 4 May 2018 and was subsequently appointed as Chief Executive Officer and Managing Director on 5 December 2022.

Tim Luscombe

CFO

Tim is a highly experienced Chartered Accountant who holds a Bachelor of Commerce from the University of Melbourne and a Certificate in Governance Practice from the Governance Institute of Australia. Tim brings professional skills gained locally and abroad in both public practice accounting and the corporate sector. Tim acts as CFO and Company Secretary for a number of ASX listed healthcare companies, private University spin out companies and Venture Capital investee companies. Tim provides strategic advice to management and boards on financial reporting, cash forecasting, direct and indirect taxes, governance and management matters.

Tim was appointed as Chief Financial Officer of Amplia Therapeutics Limited on 25 September 2023.

Rhiannon Jones

COO

Rhiannon has a background in research operations and project management and more than 10 years of experience in the medical research and biotechnology sector. Rhiannon has previous appointments as Director, Operations and Governance (Cancer Therapeutics CRC), Project Manager (WEHI, Business Development Office), Scientific Coordinator (WEHI, Inflammation Division) and a postdoctoral researcher in organic chemistry (Monash University, Chemistry Department). Her experience includes project management, communications, policy development and oversight, ethics committee submissions, risk management and staff professional development systems.

Rhiannon has a PhD in chemistry and a BSc(Hons) from the University of Adelaide and a Certificate in Governance Practice from the Governance Institute of Australia and is a graduate of the AICD.

Jason Lickliter

CMO

Dr Jason Lickliter trained as a medical oncologist in Australia and at the University of Minnesota and is currently the Chief Medical Officer at Nucleus Network, a multi-centre phase 1 clinical trials organization. He began working with Amplia on the AMP945 phase 1 trial in healthy volunteers and has since become an adviser for the ACCENT trial. Dr Lickliter has extensive experience in designing and implementing early-phase patient and healthy-volunteer clinical trials, including the integration of biomarker studies and advanced imaging into clinical research.

Andrew J. Cooke

Company Secretary

Andrew holds a law degree from Sydney University and has extensive experience in law, corporate finance, governance and compliance. He has over 30 years of boardroom experience and has developed a practical blend of legal and commercial acumen. He has served as a consultant to listed, public and private companies in the biotech, resources, property, mining services and technology sectors focussing on stock exchange, capital raisings, regulatory compliance and a wide range of corporate transactions.

Andrew was appointed as Company Secretary of Amplia Therapeutics Limited on 11 October 2013.

Warwick Tong

Non-Exec Chair

Warwick is a NZ trained physician with more than 25 years' experience in the Pharmaceutical and Biotechnology industry.

After his early career in General Medical Practice Warwick has held a wide variety of roles in the pharmaceutical and biotech industry in NZ (Glaxo) Singapore (GlaxoWellcome) London (GSK), Boston (Surface Logix) and Melbourne (CTx - Cancer Therapeutics CRC). His roles have included; Medical Director,

Regional Business Development Director (Asia Pacific), Commercial Strategy Director (International) and SVP Development (USA).

He was CEO and Director of CTx from 2011 until April 2018. He is a member of the SAB of the Maurice Wilkins Centre in Auckland NZ, the Advisory Board of Cortex Health, Melbourne, the Industry Advisory Board, School of Biomedical Sciences, University of Melbourne and a member of the CSIRO Manufacturing, Business Advisory Committee.

Warwick was educated at the University of Auckland and Victoria University, Wellington, New Zealand and is a Graduate of the Australian Institute of Company Directors.

Dr Tong was appointed as a Non-Executive Director on the 4th of May 2018 and Chairman on 25 May 2018. Dr Tong is also a member of the Audit and Risk Committee and a member of the Remuneration Committee.

Jane Bell AM

Independent NED

Jane is a banking and finance lawyer and non-executive director with more than 30 years' experience in leading law firms, financial services and corporate treasury operations gained living in Melbourne, London, Toronto, San Francisco and Brisbane. Jane has been a non-executive director since 2002, serving on 14 boards including 10 hospital, life sciences, medical research and funds management boards. Jane currently serves as Deputy Chair of Monash Health, Director of Mesoblast Limited (ASX:MSB)(Nasdaq:MESO), Director of Jessie McPherson Private Hospital, and is a Member of the Administrative Appeals Tribunal.

Jane is a former Chair of Melbourne Health (Royal Melbourne Hospital), Chair of Biomedical Research Vic, Deputy Chair of Westernport Water Corporation, Director of U Ethical Funds Management, WorkSafe Victoria, Hudson Institute of Medical Research-Monash Institute of Medical Research-Prince Henry's Institute of Medical Research, Queensland Institute of Medical Research Trust, Australian Red Cross (Qld), Victorian Women's Housing Association.

Jane holds a Master of Laws from Kings College, London, Bachelor of Laws from the University of Melbourne, Bachelor of Economics from Monash University and is a Fellow of the Australian Institute of Company Directors.

Ms Bell was appointed as an Independent Non-Executive Director on 12 April 2021 and is Chair of the Audit and Risk Committee and a member of the Remuneration Committee.

Robert Peach

Independent NED

Dr Peach has over 25 years of drug discovery and development experience in the Pharmaceutical and Biotechnology industry. In 2009 he co-founded Receptos, becoming Chief Scientific Officer and raising $59M in venture capital and $800M in an IPO and three subsequent follow-on offerings. In August 2015 Receptos was acquired by Celgene for $7.8B. Robert held senior executive and scientific positions in other companies including Apoptos, Biogen Idec, IDEC and Bristol-Myers Squibb, supporting in-licensing, acquisition and venture investments. His extensive drug discovery and development experience in autoimmune and inflammatory diseases, and cancer has resulted in multiple drugs entering clinical trials and 3 registered drugs. He is currently on the Scientific Advisory Board of Eclipse Bioinnovations in San Diego and is a consultant for several other biotechnology companies.

Robert is the co-author of 70 scientific publications and book chapters, and 17 patents. He was educated at the University of Canterbury and the University of Otago, New Zealand.

Dr Peach was appointed as an Independent Non-Executive Director on the 2nd of September 2015 and is Chair of the Remuneration Committee and a member of the Audit and Risk Committee.

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