TAYLOR COLLISON

Dr DENNIS HULME
dhulme@taylorcollison.com.au
+612 9377 1500
www.taylorcollison.com.au

Amplia Therapeutics (ATX)

31 October 2023

Speculative Buy

Promising clinical data in pancreatic cancer

Our View

Amplia has completed the dose escalation stage of the ACCENT Phase I/II trial of its focal adhesion kinase (FAK) inhibitor narmafotinib (AMP945) in combination with gemcitabine/Abraxane chemotherapy in pancreatic cancer.

The dose used in the 3rd dose cohort has been selected as the recommended Phase II dose (RP2D), having been shown to be safe and well tolerated and to provide circulating drug levels sufficient to significantly block FAK activity.

- The Phase IIa dose expansion stage of the trial at the RP2D will open next month, putting it on track for the first meaningful efficacy readout mid-2024.
- The important role that FAK inhibition can play in cancer therapy was demonstrated in recent Phase II trial by competitor Verastem in a subtype of ovarian cancer. Adding a FAK inhibitor to RAF/MEK inhibitor therapy increased the response rate to 45% vs 10% for the RAF/MEK inhibitor alone.

Amplia had $5.7m cash on 30 September. Cash burn in the September qtr was $2.2m, and this is expected to increase as the ACCENT trial progresses to the dose expansion stage and clinical trial sites are opened in Korea.

Amplia's market cap of $16m is modest given the prospect for a meaningful efficacy readout in the next 12 months and the recent evidence supporting the efficacy of FAK inhibitor combos.

Key Points

Encouraging signs of efficacy in ACCENT Phase Ib

While the dose escalation stage was not powered for an efficacy readout, it still produced encouraging signs of efficacy, including a **disease control rate (DCR)** of **93%** which compares to DCR of **50%-62%** in prior Phase III trials of gemcitabine/Abraxane chemotherapy in similar patient populations.

Interpretation of the **36%** objective response rate (ORR) reported for ACCENT is less straightforward, particularly as around half the 14 subjects were dosed well below the RP2D of narmafotinib. While the ACCENT ORR is meaningfully higher than the **23-29%** ORR in a pivotal Phase III trial published in 2013, it is same as the **36%** ORR reported in another Phase III trial published earlier this year.

Putting the above cross-trial comparisons to one side, the **37%** unconfirmed response rate in the Phase Ib stage of the ACCENT trial suggests that the narmafotinib combo is well placed to clear the **23% confirmed response rate** futility threshold required to progress to the second portion of the Phase IIa trial.

We expect recruitment of the first 26 patients in the Phase IIa stage of the ACCENT trial to take between 4 and 7 months, which would allow the response rate to be evaluated mid-2024. If at least 6/26 patients achieve objective tumour responses, an additional 24 patient will be recruited, bringing the total to 50.

Preclinical data support other cancer settings and fibrosis

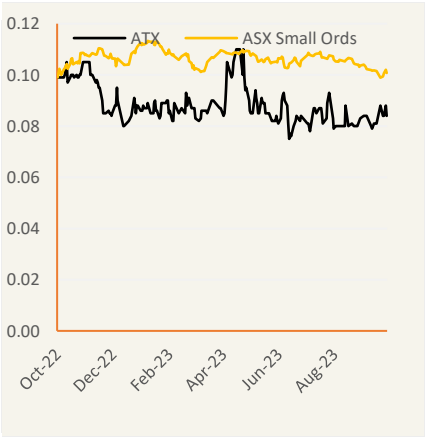
Amplia is also exploring opportunities for narmafotinib in other settings. It has recently reported positive preclinical data supporting the efficacy of narmafotinib in ovarian cancer and in combination with FOLFIRINOX chemotherapy in pancreatic cancer. It has previously reported preclinical data supporting the efficacy of narmafotinib in non-cancer fibrotic diseases of the lung and liver. It recently initiated a collaboration with CSIRO to investigate topical delivery of its FAK inhibitors to wounds and burns. Amplia is assessing the potential for its second FAK inhibitor, AMP886, to be used in a range of cancers. AMP886 also hits two other signalling pathways, VEGFR3 and FLT3, in addition to FAK.

Our conflicts of interests are disclosed on the last page of this report.

Summary (AUD)

Market Capitalisation	**$16M**
Share price	**$0.085**
52 week low	$0.070
52 week high	$0.115
Cash as at 30 September 2023	$5.7m

Share price graph (AUD)



Historical Financials (AUDm)

	FY22A	FY23A
Revenue	2.0	1.3
R&D	(3.8)	(4.7)
SG&A	(2.7)	(1.4)
EBITDA	(3.6)	(6.1)
Reported NPAT	(3.6)	(6.2)
NPAT Adj.	(3.6)	(6.2)
EPS Adj. (c)	(2.5)	(3.2)
PE ratio (x)	n/a	n/a
DPS (c)	0.0	0.0
EV/Sales	n/a	n/a
EV/EBITDA (x)	n/a	n/a
ROE	n/a	n/a

Overview

Amplia holds an exclusive global licence to the drug candidates narmafotinib (AMP945) and AMP886, which both inhibit the Focal Adhesion Kinase (FAK) signalling molecule. FAK is a promising target in cancer combination therapy and is also a potential standalone treatment target in fibrotic disease.

Amplia's lead drug, narmafotinib, is a potent and highly selective FAK inhibitor. Its high degree of selectivity, with minimal inhibition of non-target kinases, is believed to be a key contributor to the clean side effect profile seen in the earlier Phase I trial.

The company is about to commence the Phase IIa component of the ACCENT Phase Ib/IIa trial of narmafotinib in recently-diagnosed (first line) pancreatic cancer, having successfully identified the recommended Phase II dose (RP2D). The trial incorporates combination therapy of narmafotinib and gemcitabine/Abraxane in a novel pulsed dosing regimen, which was developed following a research collaboration with Professor Paul Timpson and his group at the Garvan Institute for Medical Research. Professor Timpson is a leading researcher in FAK biology.

Amplia is also exploring opportunities for narmafotinib in other settings. It has recently reported positive preclinical data supporting the efficacy of narmafotinib in ovarian cancer and in combination with FOLFIRINOX chemotherapy in pancreatic cancer. It has previously reported preclinical data supporting the efficacy of narmafotinib in non-cancer fibrotic diseases of the lung and liver. It recently initiated a collaboration with CSIRO to investigate topical delivery of its FAK inhibitors to reduce scarring following burns and other types of wounds.

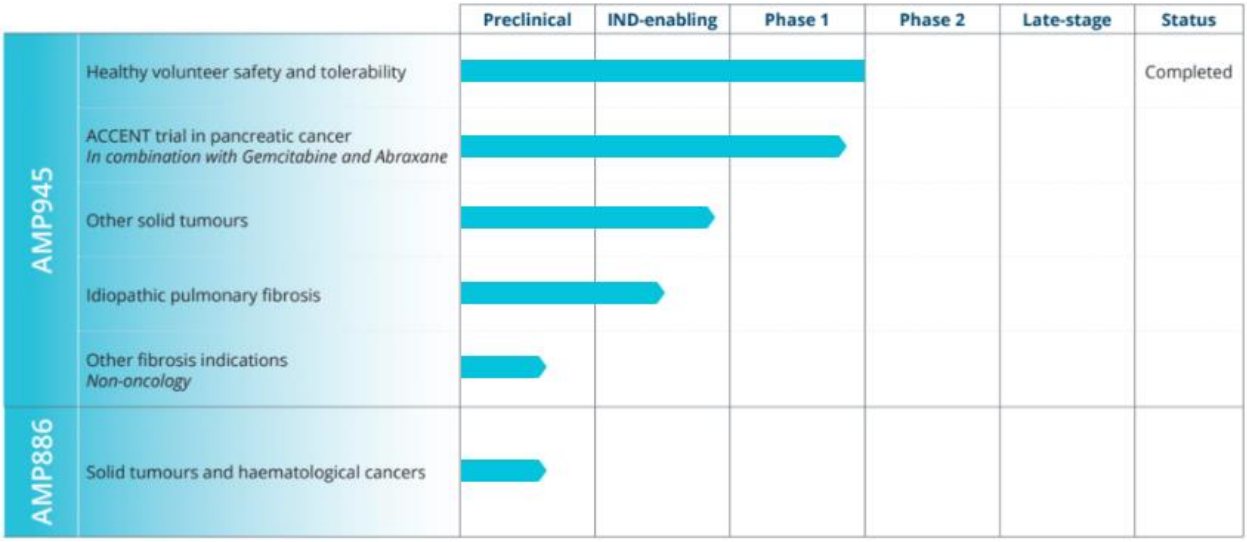
Amplia plans to submit an IND application with the US FDA before the end of the year to enable narmafotinib to be studied in clinical trials in the US. The first US trial of narmafotinib could potentially be a largely grant-funded study in combination with FOLFIRINOX in pancreatic cancer patients.

Amplia also has a second FAK inhibitor, AMP886, in preclinical development. Unlike narmafotinib, which is highly selective for FAK alone, AMP886 also hits two other signalling pathways, VEGFR3 and FLT3, in addition to FAK. Amplia is assessing the potential for AMP886 to be used in a range of cancers.

The US FDA has granted two orphan drug designations for narmafotinib, for the treatment of pancreatic cancer and for the treatment of idiopathic pulmonary fibrosis, in recognition of the unmet need in these two conditions. The designation brings seven years of market exclusivity in the US for use in these indications, a waiver of FDA fees, clinical trial protocol assistance and other incentives.

Both narmafotinib and AMP886 are protected out to 2034 by issued patents in the major markets comprising the US, Europe, Canada, Japan, China, and Australia. Amplia has lodged a patent application covering the preferred salt form of narmafotinib, which would provide patent protection to 2039, if granted. A separate patent application covering the use of FAK inhibitors, and particularly narmafotinib, in combination with FOLFIRINOX and related treatment regimens, would extent patent protection in that setting well beyond 2040, if granted.

Exhibit 1: Amplia's drug development pipeline



Source: Amplia website.

ACCENT pancreatic cancer study about to initiate Phase IIa expansion cohort

The company's ACCENT Phase I/IIa trial is investigating combination therapy of narmafotinib and gemcitabine/Abraxane in newly diagnosed metastatic pancreatic cancer patients, utilising a novel pulsed dosing regimen that was developed following a research collaboration with the Timpson group at the Garvan.

The ACCENT trial commenced with a dose escalation stage, which planned to investigate up to 4 dose levels of narmafotinib.

The Safety Review Committee identified the dose used in cohort 3, which is tested the 2nd highest of the 4 planned doses, as the RP2D.

The RP2D was found to be safe and well tolerated across the 14 subjects in the 3 cohorts. Although one dose limiting toxicity (DLT) event was observed in cohort 3, no treatment-related adverse events greater than Grade 3 were considered to be related to narmafotinib. All patients who completed their first 28-day cycle of treatment elected to stay on narmafotinib, with 7 patients having received narmafotinib for 5 months or more.

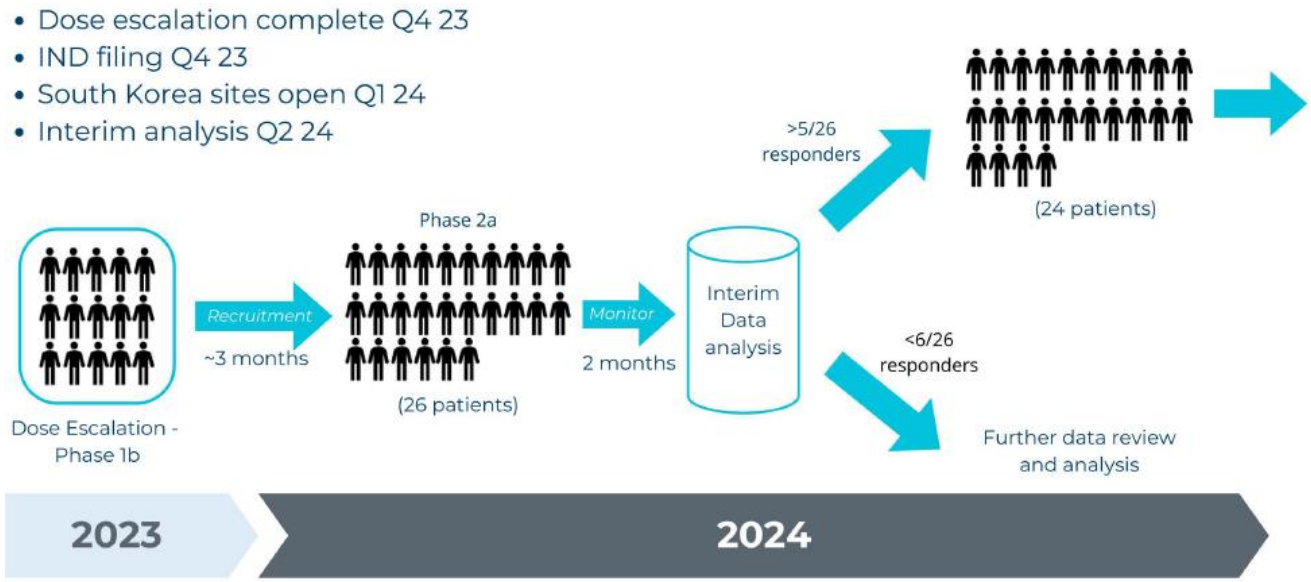
Importantly, the committee concluded that the RP2D provides sufficient circulating drug levels to significantly block the activity of the FAK enzyme in tumour tissue. This assessment included consideration of drug levels measured in patient blood samples and of pharmacodynamic models derived from tumour FAK inhibition data from animal studies.

Recruitment of the first 26 patients in the Phase IIa trial is expected to commence in November at the existing 7 sites in Australia. Five new sites in South Korea are expected to open by the end of the year. If at least 6/26 patients achieve objective tumour responses, an additional 24 patients will be recruited. This would bring the total Phase IIa expansion cohort to 50 patients, in order to increase confidence in the initial estimate of efficacy. Exhibit 2 shows the ACCENT trial design.

We expect recruitment of the first stage of the Phase II expansion cohort to take between 4 and 7 months; this timing would allow the response rate to be evaluated mid-2024.

Chemotherapy with gemcitabine combined with Abraxane (nab-paclitaxel) is a standard first line treatment for metastatic or locally advanced (unresectable) pancreatic cancer. It is administered in a four week cycle, comprising weekly intravenous infusions for 3 weeks, followed by a one-week treatment holiday. In the Phase II trial, narmafotinib will be administered orally once daily for several days prior to each infusion of gemcitabine/Abraxane chemotherapy.

Exhibit 2: Design of the ongoing ACCENT Phase I/IIa trial of narmafotinib in pancreatic cancer



Source: Amplia. Note: IND=Investigational new drug.

Encouraging signs of efficacy in ACCENT Phase Ib

While the Phase Ib dose escalation stage of the ACCENT trial was not powered for an efficacy readout, it still produced encouraging signs of efficacy, which are summarised in the first column in Exibit 3. Key results include:

- 5/14 (36%) of subjects demonstrated a confirmed or unconfirmed partial response (PR)
- As there were no complete responses (CR), the unconfirmed objective response rate (ORR) was also 36%
- The disease control rate (DCR; comprising CR, PR or stable disease for at least 8 weeks) was 93%

In order to put them in context, Exhibit 3 compares the ACCENT preliminary results to response rates reported from two Phase III trials of gemcitabine/Abraxane chemotherapy in similar first line pancreatic cancer patient populations. It is important to note that there are some differences between the way the trials report the results, including whether the objective responses needed to be confirmed at a follow-up scan (confirmed response rate), or whether both confirmed and unconfirmed responses were counted (unconfirmed response rate).

The DCR of 93% in the ACCENT trial compares favourably to DCR of 50%-62% in the two prior Phase III trials of gemcitabine/Abraxane chemotherapy. The DCR is particularly noteworthy given that only half the subjects in the Phase Ib stage received the higher RP2D of narmafotinib.

Interpretation of the 36% objective response rate (ORR) reported for ACCENT trial is less straightforward. While it is meaningfully higher than the 23-29% ORR in the pivotal Phase III trial published a decade ago (von Hoff et al 2013), it is same as the 36% ORR reported in another Phase III trial published earlier this year (Wainberg et al 2023).

The primary efficacy assessments in the upcoming Phase IIa cohorts of the ACCENT trial will be based on the **confirmed** ORR as assessed by the site investigator. The initial futility assessment on the first 26 patients in the Phase IIa trial requires that at least 6/26 subjects achieve a confirmed objective response. If the futility threshold is cleared and the trial is expanded to a total of 50 subjects, the outcome will be considered positive if at least 16/50 (32%) subjects achieve a confirmed objective response.

A substantially higher response rate in the Phase II trial would identify the narmafotinib/gemcitabine/Abraxane combination as a promising new treatment regimen with the potential to significantly improve outcomes of pancreatic cancer patients.

Exhibit 3: ACCENT efficacy data compared to published Phase III trials of gemcitabine/Abraxane chemotherapy in 1L pancreatic cancer

	Narmafotinib + gemcitabine/ Abraxane	Gemcitabine + Abraxane		
	ACCENT (to Oct 2023)	von Hoff et al 2013		Wainberg et al 2023
	Investigator assessed	Blinded Independent Central Review	Investigator assessed	Investigator assessed
Classification	*Unconfirmed + confirmed*	*Confirmed only*	*Confirmed only*	*Unconfirmed + confirmed*
Complete Response (CR)	0 (0%)	<1%		<1%
Partial response (PR)	5 (36%)	23%		36%
Overall Response rate (ORR, CR + PR)	36%	23%	29%	36%
Stable Disease (SD) at least 8 weeks	8 (57%)			26%
Stable Disease (SD) at least 16 weeks		27%		
Disease Control Rate (DCR) (=CR+PR+SD)	13 (93%)	50%		62%
Progressive Disease (PD)	0 (0%)	20%		15%
Not Evaluable	1 (7%)	30%		23%

Source: Amplia, Taylor Collison research; von Hoff et al 2013, Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine, N Engl J Med 2013;369:1691-703. https://doi.org/10.1056/NEJMoa1304369; Wainberg et al 2023, NALIRIFOX versus nab-paclitaxel and gemcitabine…(NAPOLI 3), Lancet 2023; 402: 1272–81, https://doi.org/10.1016/S0140-6736(23)01366-1

Priming doses of Narmafotinib before gemcitabine/Abraxane chemo substantially improves survival in aggressive pancreatic cancer model

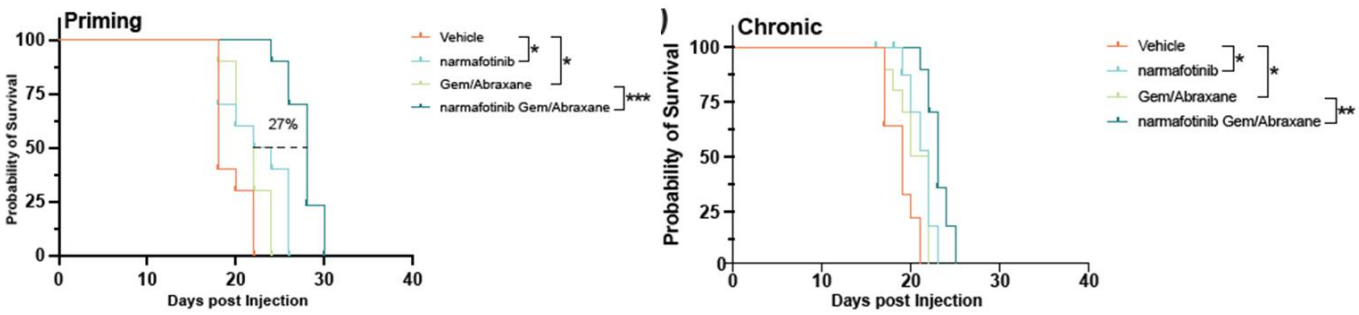
Preclinical studies in collaboration with the Timpson group at the Garvan showed that pulsed priming treatment with narmafotinib prior to administering chemotherapy improved survival in mouse models of pancreatic cancer to a much greater extent than chronic dosing did.

Exhibit 4 shows that adding pulsed priming dosing of narmafotinib prior to gemcitabine/Abraxane chemotherapy improved survival by 27% vs gemcitabine/Abraxane alone, in the aggressive KPC mouse model of pancreatic cancer mouse (median survival 28 vs 22 days, p<0.001). In contrast, chronic dosing of narmafotinib improved survival by less than 10% when combined with gemcitabine/Abraxane chemotherapy.

Exhibit 5 shows that, in a separate study, pulsed dosing of narmafotinib prior to gemcitabine/Abraxane chemotherapy also substantially improved survival in long-term studies using patient-derived tumour mouse models.

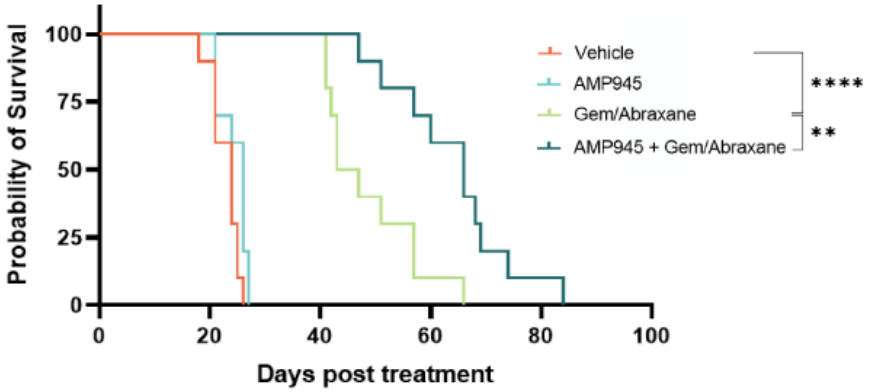
These results strongly support ATX's Phase II clinical trial of pulsed dosing with narmafotinib combined with standard gemcitabine/Abraxane combination therapy in newly diagnosed (first line) pancreatic cancer patients.

Exhibit 4: Pulsed priming with narmafotinib improved survival by 27% vs chemotherapy alone in KPC mouse model of pancreatic cancer, whereas chronic narmafotinib was much less effective



*Source: Amplia. Note: In the Priming model mice dosed with narmafotinib on days 1-4 and with gemcitabine/Abraxane on day5; *p<.05; ; **p<0.01; ***p<0.001.*

Exhibit 5: Intermittent narmafotinib improved survival vs chemotherapy alone in patient-derived tumour mouse model of pancreatic cancer



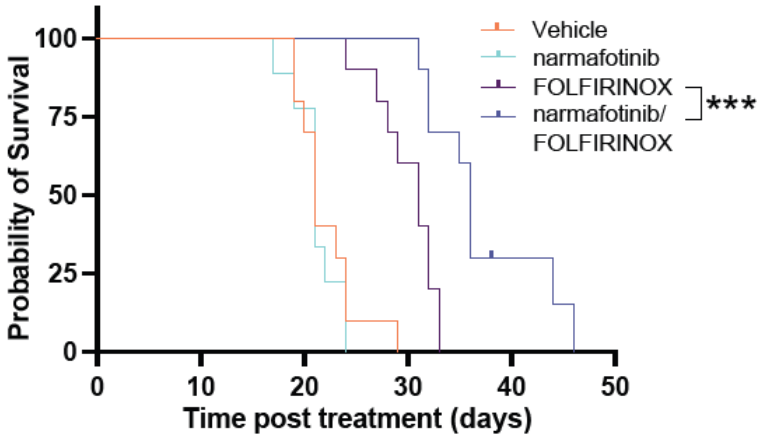
*Source: Amplia. Note: mice dosed with narmafotinib (AMP945) on days 1-4 and with gemcitabine/Abraxane on days 7 and 10 of each 12-day treatment cycle; **p<.01; ***p<0.001.*

Pulsed priming of Narmafotinib prIor to FOLFIRINOX also improves survival in pancreatic cancer model

Exhibit 6 shows that pulsed priming dosing of narmafotinib prior to administering the FOLFIRINOX chemotherapy cocktail significantly improved survival compared to chemotherapy alone. This trial was conducted in the same patient-derived tumour model of pancreatic cancer as the study shown in Exhibit 5. Mice were dosed with narmafotinib on days 1-4 and then dosed with the components of the FOLFIRINOX cocktail on days 8-9 of each 12-day treatment cycle.

FOLFIRINOX is the most common initial treatment for pancreatic cancer in many countries, including the US. Amplia is in discussions regarding the potential for a largely grant-funded trial of narmafotinib in combination with FOLFIRINOX in pancreatic cancer patients.

Exhibit 6: Intermittent narmafotinib improved survival vs FOLFIRINOX alone in patient-derived pancreatic cancer model



Source: Amplia. Note: mice dosed with narmafotinib on days 1-4 and with FOLFIRINOX over days 8-9 of each 12-day cycle.

Narmafotinib inhibits tumour growth in chemotherapy-resistant ovarian cancer model

Narmafotinib shows promise as a potential maintenance therapy following initial chemotherapy in patients with high grade serous ovarian cancer (HGSOC), which represents over 90% of ovarian cancer patients.

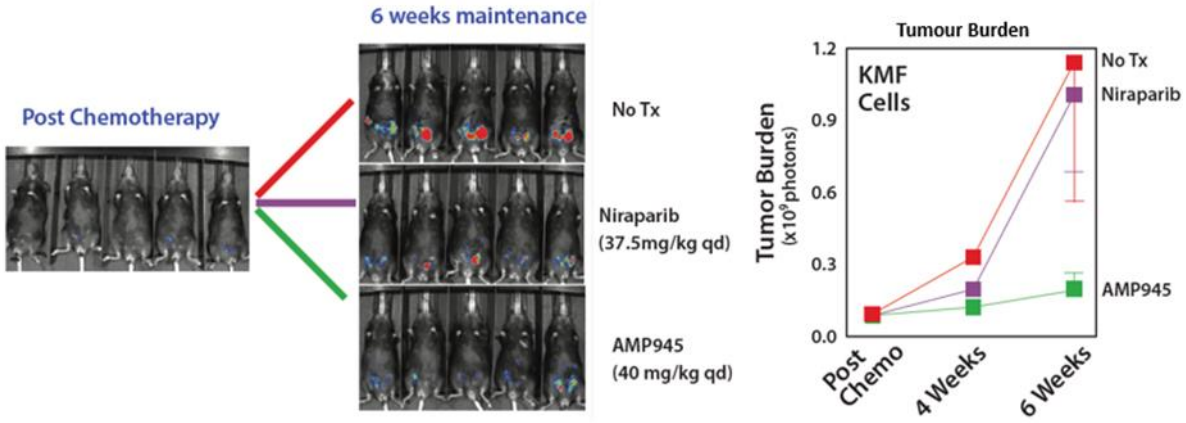
Women with HGSOC commonly achieve clinical remission following surgery and platinum-based chemotherapy, but unfortunately 80% will recur within three years. PARP inhibitors such as niraparib are increasingly being used as part of maintenance therapy regimens to prevent or delay recurrence of HGSOC.

FAK is overexpressed in 72% of HGSOC patients, suggesting that FAK is a promising target for therapy. Research led by Prof Dwayne Stupack at the University of California, San Diego, and presented at the AACR conference in Boston in early October, demonstrated that potential.

Exhibit 7 shows that Narmafotinib significantly reduced tumour growth in a mouse model of ovarian cancer that is resistant to both platinum based chemotherapy and to the PARP inhibitor niraparib.

Data from these studies support clinical study of narmafotinib as a maintenance therapy in HGSOC. Its good tolerability means that narmafotinib could potentially be combined with PARP inhibitor therapy in the maintenance setting. ATX is in discussions with leading international cancer specialists about potential clinical studies.

Exhibit 7: Narmafotinib (AMP945) inhibited tumour growth in a model of recurrent HGSOC



Source: Amplia, Taylor Collison research. Note: AMP945 = narmafotinib.

Narmafotinib is effective in prevention and treatment in an industry-standard model of lung fibrosis

In vitro studies at the Garvan demonstrated that narmafotinib strongly inhibits fibroblast remodelling, new collagen deposition and collagen crosslinking, in a dose dependent fashion. The anti-fibrosis activity of narmafotinib makes it a promising potential treatment for fibrotic diseases in a range of organs including the lungs, liver and kidneys.

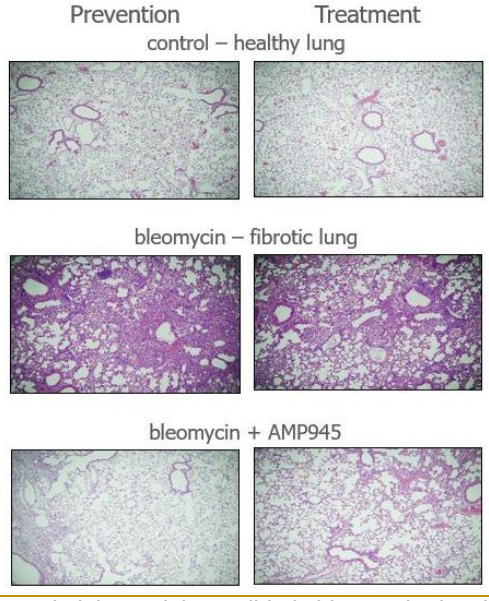
As Exhibit 8 shows, narmafotinib was able to both prevent and treat fibrosis in an industry-standard animal model of the fibrotic lung disease idiopathic pulmonary fibrosis (IPF).

IPF is a chronic progressive and ultimately fatal lung disease. It is characterised by increased fibrosis and loss of lung elasticity that leads to progressive respiratory failure. Anti-inflammatory drugs such as corticosteroids provide symptomatic relief but do not halt progression of fibrosis. The antifibrotic drugs pirfenidone and nintedanib both slow the progression of IPF, but do not reverse the fibrosis that has developed. Data from the bleomycin study indicate that narmafotinib may both prevent and treat fibrosis in the lung, and therefore could potentially provide a better treatment for this fatal disease.

The FDA has awarded Orphan Drug Designation for narmafotinib for its use in the treatment in IPF. The designation brings seven years of market exclusivity in the US, as well as other benefits.

Amplia has developed plans to test narmafotinib in a Phase II trial IPF. However, ATX is currently prioritising development of narmafotinib in cancer rather than non-cancer indications such as IPF.

Exhibit 8: narmafotinib can prevent and treat lung fibrosis in an industry-standard bleomycin mouse model



Source: Amplia. Note: In this model, mice administered the antibiotic bleomycin develop lung fibrosis that is similar to IPF.

Defactinib data illustrates the potential of FAK inhibitor combos as cancer treatments

FAK inhibitors have attracted increased interest, sparked by promising data from a study of a combination therapy involving Verastem's FAK inhibitor defactinib (NASDAQ: VSTM; market cap US$200m).

Data from a study, presented at the American Society for Clinical Oncology (ASCO) this year, showed that defactinib combined with the RAF/MEK inhibitor avutometinib (VS-6766) achieved a **45% overall response rate** (13/29) in patients with heavily pre-treated low grade serous ovarian cancer (LGSOC) (Exhibit 9). LGSOC is a rare subtype (<5%) of ovarian cancer that is typically driven by the RAS signalling pathway. Approximately 70% of LGSOC cases have RAS pathway-associated mutations, including about 30% with KRAS mutations. Responses were observed both in patients with and without KRAS mutations.

Historical data indicates a response rate of 15-26% with the MEK inhibitors such as Mekinist (trametinib) in this cancer type, so a 45% response rate to the defactinib combo therapy is very encouraging.

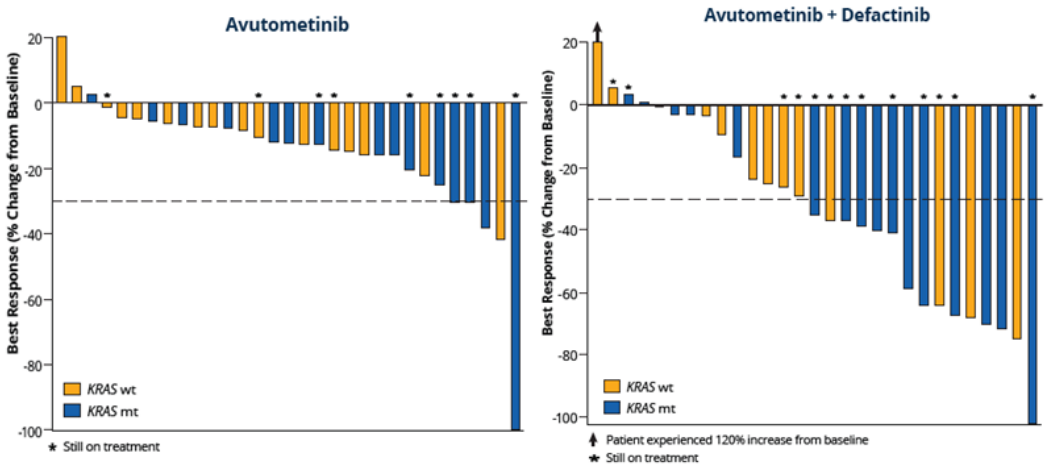
A key positive for ATX is that the response rate was only **10%** (3/31) in patients who were treated with avutometinib on its own . This shows that the **FAK inhibitor defactinib makes an important contribution** to the 45% response rate seen in patients treated with the combination therapy.

The FDA has granted Breakthrough Therapy designation for the combination of avutometinib with defactinib for the treatment of all patients with recurrent LGSOC after one or more prior lines of therapy.

Verastem has completed enrolment in a 72-patient Phase II expansion cohort of LGSOC patients and plans to file for accelerated approval based on the Phase II study data.

Separately, Verastem has initiated a Phase I/II trial of defactinib + avutometinib combined with gemcitabine/Abraxane chemotherapy in pancreatic cancer patients (RAMP 205; NCT05669482). The trial is expected to be completed in May 2025.

Exhibit 9: Efficacy of FAK plus RAF/MEK inhibition in low grade serous ovarian cancer



Source: Bannerjee et al, ASCO 2023; Verastem.

We note that it is likely that ATX would be able to produce a similar mechanism of action by combining narmafotinib with approved RAF and MEK inhibitor drugs, such as Pfizer's Braftovi (encorafenib) and Mektovi (binimetinib), if it chose to do so. While ATX has had some discussions with companies that have developed RAF and MEK inhibitor drugs about combination trials, it is currently focusing on its FAK/chemo combo therapy.

Competitive Landscape: FAK inhibitors

To the best of our knowledge, four companies have investigated FAK inhibitors in clinical studies in a cancer setting to date. None of these companies has trialled their FAK inhibitors in non-cancer fibrotic diseases, presumably because the side effect profile of their drugs was not as clean as that of narmafotinib.

Some studies of FAK inhibitors as single agents in cancer have reported modest efficacy, including one study of defactinib (Verastem) which reported objective tumour responses (tumours shrank by at least 30%) in 4 out of 30 (13%) mesothelioma patients. In a Phase I study of Boehringer-Ingleheim's BI-853520 in Japan, among 21 patients with solid tumours, one patient with gastric cancer had a confirmed partial response (5%). A number of other studies have reported no objective responses, or have been terminated with no results reported. The FAK inhibitors tested in clinical studies have been described as well tolerated, with the more common side effects noted including nausea, vomiting, itching, fevers and muscle pain.

With single agent (monotherapy) studies showing only modest efficacy, the interest is now focused on developing FAK inhibitors in combination therapy regimens. As mentioned above, defactinib produced high response rates when combined with the RAF/MEK inhibitor avutometinib in a Phase II study in a subset of ovarian cancer patients. Pre-clinical studies have also shown impressive efficacy when FAK inhibitors were combined with PD1 checkpoint inhibitors.

As the table below shows, at least seven studies of defactinib in combination with either avutometinib, chemotherapy or with the checkpoint inhibitor pembrolizumab (Keytruda) are ongoing in a range of cancers including pancreatic, lung and ovarian cancers. A separate study of defactinib in combination with the checkpoint inhibitor avelumab (Bavencio) in ovarian cancer was terminated at the completion of the dose escalation phase.

GSK conducted a Phase II study of GSK-2256098 in combination with the MEK inhibitor trametinib in 16 pancreatic cancer patients, without selecting for KRAS mutations. There was one patient with stable disease for 4 months among 11 evaluable subjects. Dose reductions due to drug/drug interactions may have led to the dose of GSK2256098 being sub optimal.

InxMed in-licensed BI-853520 from Boehringer-Ingelheim and is trialling it as IN10018 in Phase I and Phase II studies in combination with chemotherapy and or targeted therapies. Most of these studies are only enrolling subjects in China, including a pivotal randomised Ph II study combined with pegylated doxorubicin in platinum-resistant recurrent ovarian cancer. A Phase Ib study of IN10018 in combination with the MEK inhibitor cobimetinib in melanoma enrolled subjects in the US and Australia.

Exhibit 10: Selected FAK inhibitors in development

Agent	*Company*	Status*	Notes
IN10018 (BI-853520)	Boehringer-Ingelheim/ InxMed	Ph I (NCT01335269) & (NCT01905111); Ph Ib (NCT04109456)	Two trials completed (Aug 14 & Dec 15). InxMed in-licenced BI-853520 and is now developing it as IN10018 in combination therapy studies. Ph Ib reported ORR of 38.5% (5/13) in NRAS mutant melanoma in combination with the MEK inhibitor cobimetinib (US and Australia). IN10018 has been granted FDA Fast-Track designation for platinum-resistant ovarian cancer and is investigating anti PD-1/L1 checkpoint inhibitor combos.
IN10018	InxMed	Ph II (NCT06014528)	Pivotal randomised Ph II study of IN10018 plus pegylated doxorubicin in platinum-resistant recurrent ovarian cancer (n=168). Trial commenced Sep22 at a single site in China.
IN10018	InxMed	Ph II (NCT05827796)	Single arm Ph Ib/II study of IN10018 plus gemcitabine/Abraxane chemotherapy, +/- KN046 (PD-L1 / CTLA-4 bispecific antibody) in 1L **pancreatic cancer** (n=70). Trial commenced Dec22 at a single site in China.
CT-707	Centaurus Pharma	Ph I (NCT02695550)	Unknown status. Last update Mar 17. Single site China
GSK-2256098	GSK	Ph II (NCT02428270)	Combo with trametinib (MEK inhibitor) in pancreatic cancer (n=16). One of 11 evaluable patients had stable disease at 4 months. Concluded the combo was not active in unselected pancreatic cancer patients. Dose may have been sub-optimal.
Defactinib (VS-6063)	Verastem	3 x Ph II (monotherapy)	2 terminated, 1 completed Apr 17 results not reported. NCT02004028, NCT01870609 – mesothelioma -terminated; NCT01951690 – NSCLC - completed.
Defactinib	Verastem	Ph I (NCT03875820)	Combo with RAF/MEK inhibitor avutometinib (VS-6766) in ovarian, NSCLC and colorectal cancer. ORR 46% (11/24) in low-grade serous ovarian cancer; ORR 10% (1/10) in NSCLC with KRAS mutations (ORR in NSCLC possibly 20% including a subsequent partial response).
Defactinib	Verastem	Ph II (NCT04625270)	RAMP 201 – pivotal Ph II combo with RAF/MEK inhibitor avutometinib (VS-6766) in recurrent low-grade serous ovarian cancer, vs avutometinib alone. Part A confirmed ORR 46% (13/29). Enrolment in the primary efficacy cohort for the combo therapy is compete (n=72). Confirmatory Ph III trial planned to commence H223.
Defactinib	Verastem	Ph II (NCT04620330)	RAMP 202 – pivotal Ph II combo with RAF/MEK inhibitor avutometinib in recurrent BRAF mutant NSCLC. Initial Phase n=30 (BRAF V600E and non V600E mutant). Expansion cohort TBD based on initial phase results.
Defactinib	Verastem	Ph I/II (NCT05669482)	RAMP 205 - combo with avutometinib + gemcitabine/Abraxane in **1L pancreatic cancer** (Target n=40). Dose escalation then expansion cohort (n=29). Target completion May25
Defactinib	Verastem	Ph I/II (NCT03287271)	Combo with Standard of Care chemo in high grade ovarian cancer (Target n=90). Target completion Oct 24. Investigator sponsored trial
Defactinib	Verastem	Ph II (NCT05787561)	Combo with avutometinib in mesonephric gynaecologic cancer. (Target n=20). Target completion Mar25. Investigator sponsored trial
Defactinib	Verastem	Ph II (NCT03727880)	Combo with Pembrolizumab in pancreatic cancer (Target n=36). Target completion Dec 23. Investigator sponsored trial
Defactinib	Verastem, Merck KGaA/Pfizer	Ph I/Ib (NCT02943317)	Combo with Avelumab in advanced ovarian cancer. Terminated Dec 18 at completion of dose escalation

*Source: Taylor Collison research. Notes: * Ph I= Phase I; Ph II= Phase II*

Competitive Landscape: Pancreatic cancer

Amplia's initial Phase II study of narmafotinib will be in first line pancreatic cancer patients in combination with gemcitabine and Abraxane. Pancreatic cancer is a highly aggressive disease; the median survival for advanced pancreatic cancer is only 6-8 months, and the 5 year survival rate is approximately 7-8%. There are approximately 3,200 new cases of pancreatic cancer each year in Australia, and 450,000 cases worldwide. The market research group GlobalData estimated that the market for pancreatic cancer therapies was worth US$2bn in 2021, forecast to grow to US$4.1bn by 2029.[1]

Only 15-20% of pancreatic cancers are diagnosed at an early stage that is suitable for surgical removal; the majority have either locally advanced or metastatic cancer. The standard treatment for locally advanced pancreatic cancer that cannot be removed surgically is chemotherapy alone or chemotherapy combined with radiation therapy. For patients with metastatic pancreatic cancer, chemotherapy might be recommended. Depending on the specific kind of pancreatic cancer and its genetic makeup, some patients may be candidates for checkpoint inhibitor immunotherapy or treatment with a polyadenosine diphosphate-ribose polymerase (PARP) inhibitor.

The two main chemotherapy cocktails used in first line pancreatic cancer are the 2-drug combination of gemcitabine and Abraxane and the 3-drug combination known as FOLFIRINOX (5-fluorouracil, irinotecan and oxaliplatin). The choice between the two is dependent on how well the patient is (ie performance status) and what degree of side effects they are willing to tolerate. Other chemotherapy drugs commonly used in pancreatic cancer include platinum agents (cisplatin, oxaliplatin) or taxanes (paclitaxel, docetaxel).

A number of targeted therapies are being investigated in pancreatic cancer, in addition to FAK inhibitors. These include drugs targeting the hedgehog, Wnt-β-catenin and VEGF pathways. The drug PEGPH20 (PEGylated recombinant hyaluronidase) failed to meet the primary endpoint in a Phase III study in pancreatic cancer in November 2019. Similarly, adding the VEGF inhibitor Avastin to gemcitabine chemotherapy did not improve survival in advanced pancreatic cancer patients in a Phase III study published in 2018.

The AVENGER 500 Phase III trial of the intravenously administered mitochondrial enzyme inhibitor CPI-613 (devimistat, Rafael Pharmaceuticals) in combination with a modified FOLFIRINOX regimen in first line pancreatic cancer reached its 500-patient enrolment target ahead of schedule in August 2020. In October 2021 Rafael Pharmaceuticals reported that the trial did not meet its primary endpoint of overall survival (NCT03504423).

Lisata Therapeutics (formerly Cend Therapeutics) is investigating intravenous LSTA1 (formerly CEND-1) plus gemcitabine/Abraxane in first line metastatic pancreatic cancer. CEND-1 modifies the tumour microenvironment via interaction with neuropilin-1 and activates a novel pathway that causes cancer drugs to more selectively penetrate solid tumours. A Phase I trial of the combination in this patient population reported a response rate of 59% (16/29), including one complete response. An investigator initiated randomised Phase IIb trial of CEND-1 plus gemcitabine/Abraxane in 155 first line metastatic cancer patients is expected to complete enrolment in H124. An interim futility analysis in September 2023 cleared the trial to continue as planned (NCT05042128).

The NAPOLI 3 Phase 3 trial (NCT04083235) found the combination of irinotecan liposome injection (Onivyde), 5-fluorouracil (5-FU), oxaliplatin, and leucovorin (NALIRIFOX) was superior in progression-free survival and overall survival compared with gemcitabine plus Abraxane in patients with metastatic pancreatic ductal adenocarcinoma. The NALIRIFOX regimen is similar to FOLFIRNOX, but with the irinotecan replaced with Onivyde. The outcome of this head to head comparison may further increase use of FOLFIRINOX style regimens in preference to gemcitabine/Abraxane in younger and healthier patients who are better able to tolerate the more aggressive FOLFIRINOX regimen.

The NAPOLI 3 result underlines the importance of the improved survival seen when pulsed narmafotinib was added to FOLFIRINOX in preclinical pancreatic cancer models, as shown in Exhibit 6.

Despite the potential for other new pancreatic cancer treatments to emerge in the future, the poor prognosis for pancreatic cancer patients means that we expect that there would be considerable demand for narmafotinib if efficacy studies show that it improves survival rates in this devastating disease.

[1] GlobalData, Pancreatic Cancer –Opportunity Analysis and Forecasts to 2029

Fibrosis of great interest to potential partners

Over the past few years big pharma has been quite active in deals for early stage assets in the fibrosis space. This suggests that Amplia may be able to look at potential licensing or co-development options as alternatives to taking narmafotinib into Phase II testing for fibrotic disease indications itself.

Exhibit 11: Deals for early stage fibrosis assets

Acquirer	Target company	Indication	Deal type	Date	Stage	Upfront (US$m)	Potential (US$m)
Abbvie	Morphic Therapeutics	IPF/ fibrotic disease	Option exercise	Aug-20	Preclinical	20	n/a
AstraZeneca	Redx	IPF/ fibrotic disease	Licence	Aug-20	Preclinical	17	380
Novartis	Pliant Therapeutics	liver- NASH	Licence	Oct-19	Phase I	80	n/a
Boehringer Ingelheim	Bridge Biotherapeutics	lung- IPF	Licence	Jul-19	Phase I	50	1,200
Boehringer Ingelheim	Yuhan Corp	liver- NASH	Licence	Jul-19	Preclinical	40	830
AbbVie	Morphic Therapeutic	Fibrosis indications	Option to licence	Oct-18	Preclinical	100	n/a
United Therapeutics	Samumed	lung- IPF	US licence	Sep-18	Phase I	10	340
AstraZeneca	Ionis Pharmaceuticals	liver- NASH	Licence	Apr-18	Preclinical	30	300
Undisclosed	Oraxion Therapeutics	kidney- FSGS	Option to licence	Feb-18	Preclinical	n/a	125
Novartis	Conatus	liver- NASH	Licence	Dec-16	Phase II	50	650
Roche	Adheron Therapeutics	lung- IPF	Acquisition	Sep-15	Phase I	105	475
Boehringer Ingelheim	Pharmaxis	liver- NASH, eye	Asset purchase	Mar-15	Phase I	A$40	A$750+

Source: Taylor Collison. Note: IPF= idiopathic pulmonary fibrosis; NASH= non-alcoholic steatohepatitis, FSGS= focal segmental glomerular sclerosis

Risks

Amplia is subject to clinical trial, regulatory and commercialisation risks common to all biotech companies. The key sensitivity is clinical progress of narmafotinib, and the safety and efficacy of the drug. Off-target effects can result in severe adverse events that can stop drug development. Inadequate efficacy can result in failure to recruit patients into studies, failure to partner and fund the program, failure to gain regulatory approval, or failure to be adopted for use by prescribing doctors once approved.

Amplia had $5.7m cash at 30 September and may need additional funds to reach the interim efficacy analysis in the Phase IIa trial of narmafotinib in pancreatic cancer and to support ongoing operations. There is no guarantee that Amplia will be able to raise the required funds on acceptable terms.

Disclaimer

IMPORTANT INFORMATION

This report is a private communication to clients and those considering becoming a client and is not intended for public circulation or publication, or for the use of any third party without the approval of Taylor Collison Limited ABN 53 008 172 450 ("Taylor Collison"). It is distributed on the basis that no part of it will be reproduced, altered in any way, transmitted to, copied to or distributed to any other person without the prior express permission of Taylor Collison. Taylor Collison holds Australian Financial Services Licensee (No. 247083) and is a Trading Participant of more than one Relevant Exchange, including the Australian Securities Exchange (ASX), National Stock Exchange of Australia (NSX) and Cboe Australia Pty Ltd (Cboe). TC Corporate Pty Ltd ABN 31 075 963 352 ("TC Corporate") is a wholly owned subsidiary and Authorised Representative of Taylor Collison Limited.

The following **Warning**, **Disclaimer** and **Disclosure** relate to all material presented in this report and should be read before relying on any of its content to make an investment decision.

Warning

This report presents information, being general advice (i.e., a rating, opinions and/or forecasts) and factual information, in relation to a particular financial product(s). The general advice, whether it be explicit or implied, is based solely on the Analyst's assessment of the merits and attributes of the product(s) concerned. Don't interpret it as indicating that taking a course of action in line with the general advice is appropriate for you personally. It is not personal (i.e., personalised) advice. The question of the product's suitability or appropriateness for your or anyone's particular investment objectives, financial circumstances or needs (i.e., your relevant circumstances) has not been considered. Personal advice addresses whether taking a course of action in relation to a financial product(s) is appropriate for you personally, based on what the adviser knows about the product(s) and your relevant circumstances. Therefore, before acting or otherwise relying on its general advice or other information, consider the appropriateness of doing so, in the light of your objectives and circumstances, or seek personal advice from your adviser at Taylor Collison. If you act without first consulting your adviser, you do so at your own risk.

If the general advice promotes acquisition of a product for which there is a current Product Disclosure Statement (PDS) or a Prospectus, you should obtain and consider a copy before making a decision about whether to invest or to remain invested. You should be able to obtain a copy from or through us.

Although analysis of the level, nature and sustainability of past performance is a necessary element of the basis for the insights, statements and forecasts presented by the Analyst, be aware that the past performance itself is not a reliable indicator of future performance of a product or its issuer. Taylor Collison does not guarantee the capital you invest through us against loss, or the performance of (including the payment of income from) your investments, even when they are guided or managed by us.

Disclaimer

This report includes, and was prepared using, information from sources Taylor Collison considers reliable, but we do not guarantee its accuracy and completeness. All opinions, conclusions, forecasts and ratings are reasonably held at the time this report was published but are subject to change without notice. If they do change after publication, Taylor Collison assumes no obligation to update and republish this report. It may include forecasts or statements about the future, including guidance on future earnings, financial position and performance. The words "expect", "should", "could", "may", "predict", "plan" and other similar expressions are intended to identify such "forward-looking statements". The forward-looking statements, opinions and estimates presented in this report are based on assumptions and contingencies which are subject to change without notice, as are statements about market and industry trends, which are based on interpretations of current market conditions.

Except for any liability which by law cannot be excluded, Taylor Collison, its directors, officers, employees, representatives (e.g. our advisers) and agents accept no liability (whether in negligence or otherwise) for any error, inaccuracy in, or omission from the information presented in this report or any loss or damage suffered by the recipient or any other person directly or indirectly as a result of any action taken or not taken on the basis of any of the information presented in this report.

Disclosure – This report was funded by the ASX Equity Research Scheme

This report was prepared solely by Taylor Collison Limited. ASX did not prepare any part of the report and has not contributed in any way to its content. The role of ASX in relation to the preparation of the research reports is limited to funding their preparation, by Taylor Collison Limited, in accordance with the ASX Equity Research Scheme. ASX does not provide financial product advice. The views expressed in this research report may not necessarily reflect the views of ASX. To the maximum extent permitted by law, no representation, warranty or undertaking, express or implied, is made and no responsibility or liability is accepted by ASX as to the adequacy, accuracy, completeness, or reasonableness of the research reports.

Disclaimer continued

Disclosure – Analyst's remuneration and other interests

Analyst remuneration is not linked to the rating, opinions or forecasts presented in any research, or to securing a mandate to provide corporate advisory or fund-raising services or to the successful completion of such a mandate (any other *'conflicted scenario'*). Brokerage paid by institutional clients for dealings (which may be in response to our research) facilitated by our institutional sales team is shared between Taylor Collison (for overheads) and to remunerate the institutional and research teams. The arrangement serves to reimburse Taylor Collison for payment of base salaries, and beyond a threshold, a pool is made available to be allocated quarterly as a discretionary bonus to members of the teams, based on merit, payable annually.

The Analyst does not hold any direct or indirect interest in any shares in ATX.ASX. The Analyst and/or their associate(s) may at any time, during its life, have a holding or interest in any products addressed in this report, or a derivative product, and these (if any) may change during the life of this report.

Disclosure – The remuneration and interests of Taylor Collison and others

Taylor Collison directly or indirectly holds 2.5m listed options in ATX.ASX. Taylor Collison and/or an associate(s) may at any time, during its life, have a position(s) in any products or options addressed in this report and these holdings (if any) may change during the life of this report.

Collectively, other staff (including our directors, officers, our advisers, and their associates) directly or indirectly hold or have an interest in 6m shares and 0.8m listed options in ATX.ASX. This holding or interest may change during the life of this report.

Where this report is distributed to clients of advisers who aren't members of either the research or institutional team, and the client transacts in response to the research, the brokerage paid by clients for dealings facilitated by the adviser is shared between Taylor Collison and the adviser.

Disclosure – Corporate Actions and Fees

Taylor Collison was lead manager for rights issues and placements for ATX.ASX that raised $4.0m in July 2020 and $3.8m in May 2021.

Disclosure - General

Taylor Collison, its directors, officers, employees, representatives and/or agents may during the preparation and the life of this report, for legitimate reasons, have a role or be engaging in activities in relation to the product(s) referred to in this report which do or appear to conflict with the Analyst's views and rating. During the life of this report, we may transact or facilitate transactions in the product(s) concerned for clients or provide oral or written advice to clients which is not consistent with the rating or opinions presented. Taylor Collison may solicit business from any issuer mentioned and may sell or buy the product(s) concerned *'as principal'*. Taylor Collison receives fees (e.g., application fees), brokerage or commissions, and may receive other benefits, for acting in these various ways, which may be shared with those involved, including our advisers (other than members of our research or institutional teams), associated companies or introducers of business.

Analyst Certification: The Analyst certifies that the views expressed accurately reflect their personal, professional opinion about the product(s) addressed in this report.

Date Prepared: October 2023
Analyst: Dr Dennis Hulme
Release Authorised by: David Cutten

TAYLOR COLLISON LIMITED
Sharebrokers and Investment Advisors
Established 1928

ADELAIDE
Level 16, 211 Victoria Square
Adelaide SA 5000
GPO Box 2046
Adelaide SA 5001
Telephone 08 8217 3900
Facsimile 08 8321 3506
broker@taylorcollison.com.au

SYDNEY
Level 10, 167 Macquarie Street
Sydney NSW 2000
GPO Box 4261
Sydney NSW 2001
Telephone 02 9377 1500
Facsimilie 02 9232 1677
sydney1@taylorcollison.com.au

Participant of the Australian Securities Exchange (ASX) Group.

ABN 53008172450
AFSL 247083