AVACTA GROUP LTD

VALIDATION OF THE PRE|CISION™ PLATFORM – AN IMPENDING REVOLUTION IN CANCER TREATMENT?

03.02.2023

Ticker:	**AVCT.L**
Price (p):	**161.1**
Shares in issue (m):	**269.9**
Market cap. (£m):	**434.8**

https://aimchaos.com/category/investment-notes/

Introduction

On 17 January, Avacta Group ('Avacta') announced that it had successfully completed the fourth cohort of patients in its Phase 1a clinical trial for AVA6000, its first-in-clinic prodrug developed from the Company's tumour targeted therapy platform, pre|CISION. In short, the pre|CISION platform is used to modify existing cancer drugs such as chemotherapies, in order to dramatically reduce their side effects, thus greatly reducing the safety and tolerability of the existing drugs. Moreover, an enhanced safety profile enables significantly higher doses of the modified 'prodrug' to be administered to patients, in comparison to the standard drug. Consequently, pre|CISION-modified drugs should also provide superior efficacy compared to the standard.

AVA6000 is a pre|CISION-modified version of the well-known chemotherapy drug, doxorubicin. Doxorubicin is considered one of the most powerful anti-cancer drugs in existence, and has been used in cancer treatment for a half-century. Despite its severe side effects (including alopecia, myelosuppression, vomiting, and most significantly, cardiotoxicity – which limits the amount that a patient can be dosed with doxorubicin), the global doxorubicin market is steadily growing, and is forecast to reach $2bn per annum by 2028.

For the first time since the AVA6000 trial commenced in August 2021, Avacta has provided commentary on the performance of the prodrug. It included two vital pieces of information that in our view not only proves that AVA6000 is working exactly as intended – replicating (or surpassing) the impressive pre-clinical data; but also validates the entire pre|CISION platform. Firstly, Avacta reported that the safety profile of AVA6000 has improved dramatically over standard doxorubicin. In the 19 patients dosed at varying levels, "*significant reduction in the usual toxicities*" was observed. Critically, cardiotoxicity was not observed whatsoever, even in the patients of the fourth cohort, who received a dose equivalent to more than double the normal dose of doxorubicin.

The second piece of information was that, having analysed six biopsies taken from patients in various cohorts, Avacta could confirm that doxorubicin was being released in "*significant levels in the tumour tissue*" in all biopsies taken. This was absolutely vital for shareholders to hear. A dramatic improvement in safety and tolerability of the drug would be pointless, were the drug not 'activating' at the tumour and destroying it.

We consider the RNS to be the single most important update provided by the Company in its 17-year history. In our view, AVA6000 now has a high probability of coming to market and displacing (and enlarging) the existing doxorubicin market. Much more significantly, however, is that the trial to date has now confirmed that the pre|CISION technology works in humans. The Company can now apply it to *dozens* of other existing drugs, to transform their safety and tolerability, and efficacy profiles.

In this note, we focus specifically on Avacta's pre|CISION platform. Firstly, we provide a recap of the background and science of the technology. We then detail the progress of AVA6000, and how it acts as a successful proof of concept for pre|CISION. Next, we discuss the implications of a now-validated platform both for cancer patients, and for the Company. We go on to discuss possible valuations and why we believe the Company to be materially undervalued at a share price of 161p and valuation of £435m. Finally, we ponder the possible next steps for Avacta Therapeutics. It is our intention to incorporate this note into a larger revised investment thesis for the overall Avacta Group, in the coming weeks.

Background

In July 2018, Avacta entered into a co-development partnership with Bach BioSciences ('Bach'), a company commercialising the research of William Bachovchin, Professor of Developmental, Chemical and Molecular Biology at Tufts University School of Medicine, Boston. The collaboration was originally centred upon a ground-breaking co-invention named *TMAC* ('tumour microenvironment activated drug conjugates'). The TMAC platform utilises the platform technologies of both parties – Avacta's Affimers and Bach's FAPα-activated linker technology (now banded as *pre|CISION*) – to generate a new class of drug conjugate that combines immunotherapy and highly targeted chemotherapy in a single molecule.

Whilst this research note is specifically focussed on Bach's pre|CISION technology as a standalone platform, it is nevertheless important to understand the TMAC platform and how the pre|CISION linker constitutes a key component of it.

For a detailed breakdown of the TMAC platform, please see Appendix I at the end of this note.

In June 2019, Avacta announced its intention to fast-track the TMAC programme by first testing Bach's FAPα-activated linker technology as a standalone therapeutic (it was formally branded as *pre|CISION* in November 2019). As we shall explain in this note, the technology can be applied to standard chemotherapies in use today to create 'targeted' chemotherapies: these are designed to become active only at the site of the tumour, thus drastically reducing side effects for the patient, compared to standard chemotherapy drugs.

The rationale for fast-tracking a pre|CISION drug (prior to a TMAC molecule) into the clinic was twofold:

Firstly, to improve the probability of successfully developing the TMAC platform itself. A TMAC molecule consists of three components, each with a dual purpose (see Appendix I). Two of these components (the Affimer and linker) were at the time as yet untested in humans. Therefore not only is the molecule novel and highly complex (thus most certainly requiring three full phases of clinical trials to bring the drug to market, which would take 7-8 years), but moreover no clinical data (i.e. in-human) has been generated for two of the three components. By securing positive clinical data for each of the pre|CISION and Affimer platforms in separate Phase 1 trials, Avacta would be in a much stronger position to bring a first TMAC molecule into the clinic, with the development risk significantly reduced. This remains the Company's strategy.

Secondly, pre|CISION as a standalone platform represents a faster, and significantly lower-risk route, to commercialisation of a multi-billion dollar asset, than does the TMAC platform. The reason for this is that pre|CISION is essentially a *delivery* platform, as we explain in the following pages. It simply enables the modification (and thus improvement in therapeutic index) of already marketed, highly effective chemotherapies. Not only is there a much higher probability of successful clinical development for a pre|CISION 'chemotherapy prodrug' than for a novel TMAC molecule; but the clinical development roadmap itself is significantly shorter (and less expensive). It is probable that only a Phase 1 trial and a Pivotal Phase 2 trial will be required to bring pre|CISION prodrugs to market.

Over the past three years, Avacta has altered its therapeutics pipeline such that it now intends to bring multiple pre|CISION prodrugs into clinic, before the first TMAC molecule.

Essentially, Avacta has gone after the low-hanging fruit – which makes perfect sense from a clinical, commercial and shareholder's perspective.

[To note: whilst the TMAC platform is a co-development between Avacta and Bach, with the patent (pending) jointly owned, the pre|CISION platform remains wholly owned by Bach. However, Avacta exclusively licenses the platform to develop and commercialise chemotherapy prodrugs, and all other applications. Other commercial parties seeking to use pre|CISION must sub-license it from Bach and Avacta.]

pre|CISION: the Science

The pre|CISION technology is, in short, a method of targeting cancer therapies to the tumour microenvironment ('TME').

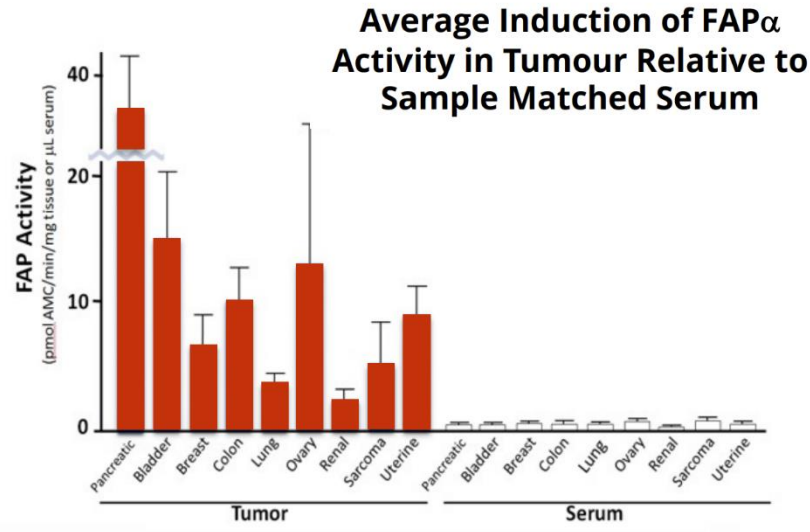
The chemistry itself is a *substrate* – a molecule on which a particular enzyme acts – developed by Professor Bachovchin. The chemical substrate is highly specific to an enzyme called fibroblast activation protein-α ('FAPα'). The FAPα enzyme is highly upregulated (i.e. found in large, concentrated quantities) in the TME of most solid tumours, compared with healthy tissues.

Critically, the pre|CISION substrate is not hydrolysed by any other enzyme in the human body. This extremely high level of specificity to FAPα is the core intellectual property of the platform. Other entities have previously attempted to develop such a substrate, but without success: their attempts have been susceptible to cleavage by other enzymes closely related to FAPα.

So: how is the pre|CISION substrate used to create chemotherapy prodrugs? The concept relies on both the exquisite specificity of the substrate to FAPα; and on extracellular FAPα enzyme activity in the TME.

FAPα is overexpressed on the surface of stromal cells (especially fibroblasts) of most solid tumours. FAPα-positive fibroblasts and extracellular fibrosis can contribute up to 90% of the gross tumour mass.

However, FAPα is present in only very low concentration in healthy tissue. In fact, FAPα expression can be difficult to detect at all in non-diseased organs.

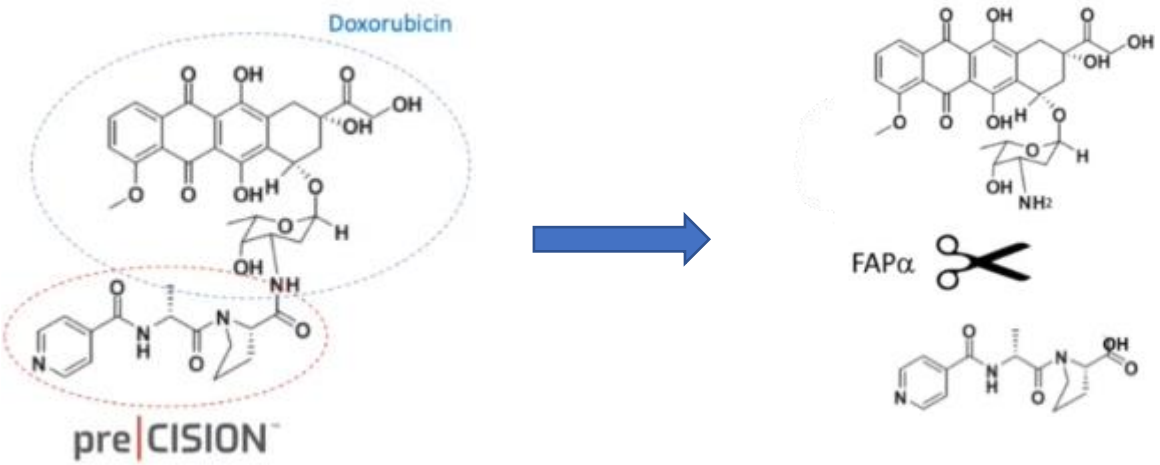


Now to the chemotherapy prodrug itself. Using Avacta's first prodrug under development, AVA6000, as an example:

AVA6000 is a prodrug form of doxorubicin, a well-known and long-used chemotherapy. In its standard form, doxorubicin is cell permeable: like most drugs, it enters cells via passive diffusion, where it then binds to DNA-associated enzymes and intercalates with DNA base pairs, to produce a range of cytotoxic effects.

Due to its cell permeability coupled with its lack of tumour-targeting, doxorubicin's effects are indiscriminate throughout the human body, resulting in severe side effects to patients – most notably, cardiotoxicity and myelosuppression. Damage caused to healthy organs (especially the heart) thus strictly limits the use of doxorubicin in cancer patients to a certain number of treatment cycles – even if the treatment is having a positive effect. These 'dose limiting toxicities' caused by indiscriminate action are in fact common to most chemotherapies, and are a major downside to the drug class.

As the AVA6000 Phase 1a trial is now demonstrating, these dose limiting toxicities can be dramatically reduced by the attachment of the pre|CISION substrate to standard chemotherapies. Take the diagram of an AVA6000 molecule below: the pre|CISION substrate (a dipeptide molecule) is covalently bonded to a doxorubicin molecule.



In this state, the cell permeability of the enlarged molecule is drastically reduced. The doxorubicin cannot enter cells via passive diffusion – and consequently, it is inactive throughout the body whilst it is bonded to the pre|CISION substrate.

This changes when the molecule encounters FAPα enzymes – which, as discussed on the previous page, are only present (in notable concentration) on the surface of stromal cells in the tumour microenvironment. At this point, the pre|CISION substrate is hydrolysed (i.e. 'cleaved away'), leaving an active doxorubicin molecule in the TME. With its cell permeability restored, the doxorubicin can now diffuse into surrounding cells (which happen to be cancer cells in the TME, and not healthy tissues), and get to work in breaking them down.

Moreover, given that prodrug molecules are unable to distribute throughout the body into healthy cells, the *concentration* of doxorubicin molecules becoming 'active' at the site of the TME is greatly enhanced, in comparison to the concentration of doxorubicin molecules reaching the TME in conventional chemotherapy at the equivalent dose size.

Accordingly, not only do pre|CISION prodrugs enjoy a substantial improvement in therapeutic index (i.e. relative safety), but they also should have a much improved efficacy due to a significantly higher proportion of active drug reaching the TME (as opposed to being squandered on healthy cells).

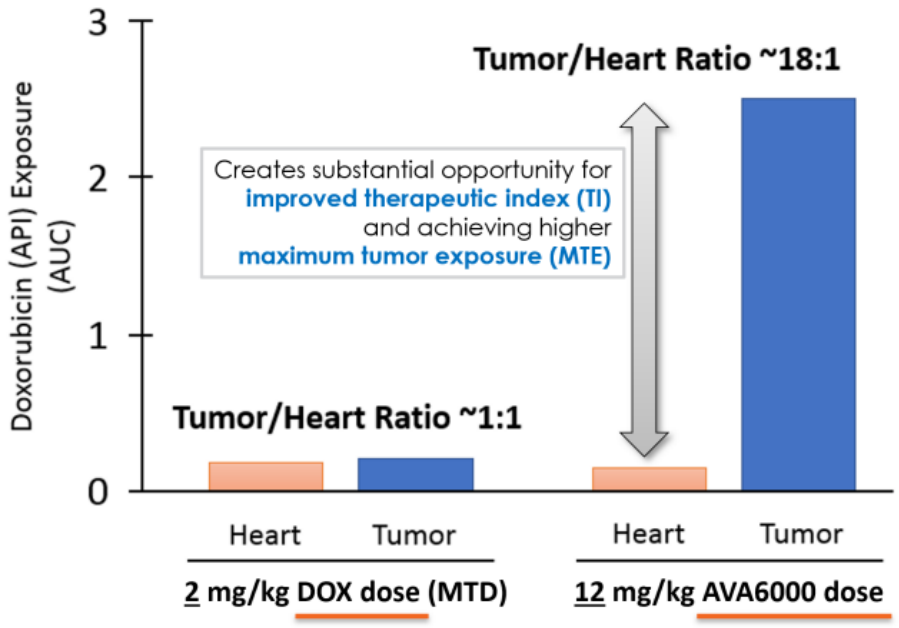
The First pre|CISION Prodrug: AVA6000

Pre-clinical data

Avacta conducted extensive pre-clinical work on its first selected pre|CISION prodrug candidate, AVA6000 – a prodrug form of doxorubicin. Animal models included mouse, rat and dog.

Of particular note, the mouse study was a patient-derived xenograft ('PDX') model. In such a model, the tissue or cells from a patient's tumour are implanted into an immuno-deficient or humanized mouse. For AVA6000, Avacta created a PDX model of osteosarcoma (i.e. human sarcoma tumour tissue was implanted in the mice) in order to evaluate drug efficacy / anti-tumour activity. To note, the human sarcoma tissue used was from a patient who had already been heavily treated with four different chemotherapy agents, including doxorubicin.

Because of the exquisite specificity of the pre|CISION substrate to FAPα, Avacta found that the AVA6000 prodrug was not activating indiscriminately throughout the animals' bodies in healthy tissue. Rather it was predominantly activating at the site of the TME, where FAPα enzymes were present in high concentration. As healthy tissues (especially the heart) were not being damaged, Avacta could increase the dose given to the animals, to a level that was multiple times more concentrated than the maximum tolerated dose ('MTD') of standard doxorubicin.



Tissue levels ($AUC_{15\text{-}45\ mins}$) of doxorubicin in HEK-mFAP-tumor bearing mice following a single intravenous dose of doxorubicin or AVA6000

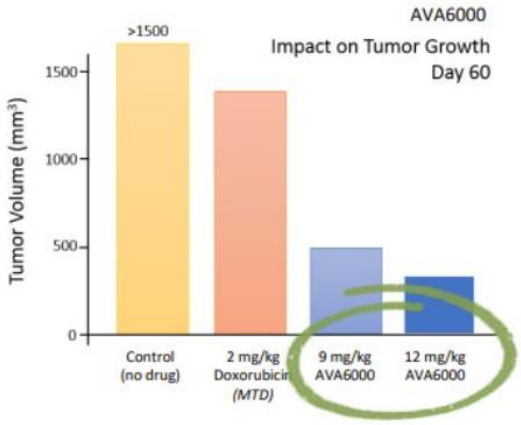
The highest AVA6000 dose administered (at 12 mg/kg) was 6 times more concentrated than the doxorubicin dose administered (at 2 mg/kg). The latter was the MTD equivalent; it could not have been increased further without unacceptably high risk of mortality (through severe cardiotoxicity).

As the AVA6000 molecules were not activating throughout the mice in healthy cells, the *concentration* of doxorubicin molecules reaching, and becoming 'active', at the site of the TME was greatly enhanced – relative to the concentration of doxorubicin molecules reaching the TME in those mice dosed with standard doxorubicin (where much of the doxorubicin had activated in healthy cells before ever reaching the TME).

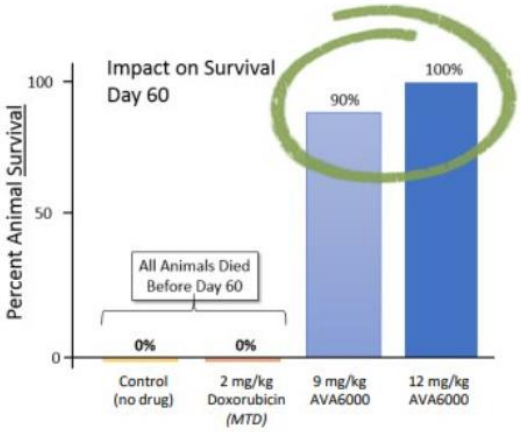
So whilst the AVA6000 dose was 6 times as concentrated as the standard doxorubicin dose, the distribution ratio of doxorubicin in tumour tissue relative to heart tissue was 18:1.

The distribution ratio resulting from the standard doxorubicin dose was, predictably, 1:1 – given that standard doxorubicin is not targeted to tumour tissue and therefore activates indiscriminately throughout all tissue.

The resulting difference in efficacy (i.e. anti-tumour activity) of the two drugs was dramatic.



AVA6000 can be dosed at higher concentrations than the MTD for doxorubicin



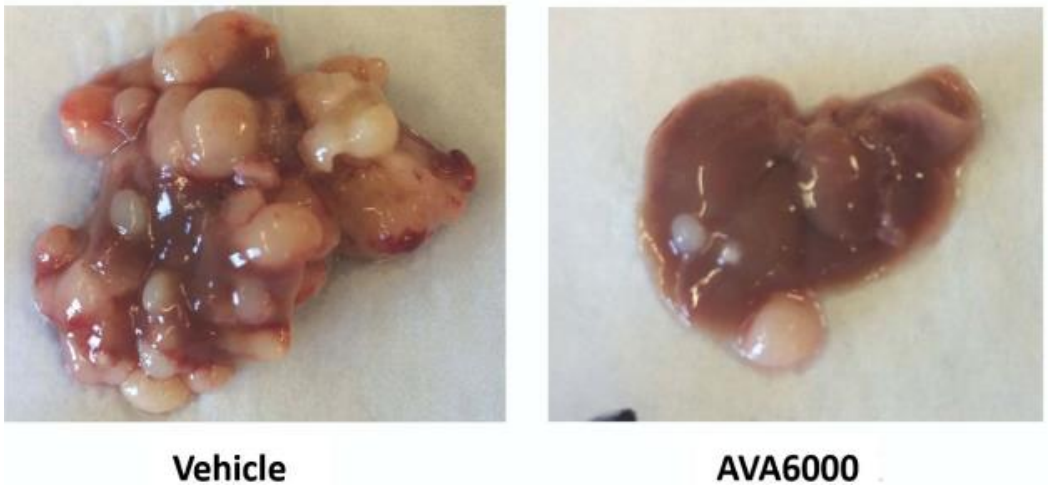
AVA6000 significantly reduced tumour volume and improved survival, relative to doxorubicin

It is not surprising that the standard doxorubicin (even at the MTD) had limited effect on tumour growth: after all, the sarcoma tissue implanted in the mice had derived from a patient who had already been dosed with, and did not respond to, doxorubicin.

However, the impact on tumour growth by AVA6000 is clearly immense, owing to the concentration of doxorubicin that it releases only in the TME being many multiple times higher than standard doxorubicin.

As a result of the gulf in difference in anti-tumour activity, all animals that were dosed with standard doxorubicin (at the MTD, being 2mg/kg) died before Day 60, whilst all animals dosed with the higher concentration of AVA6000 (12 mg/kg) were alive at Day 60.

AVA6000 Reduces Colorectal Cancer (CRC) Liver Metastasis



Vehicle **AVA6000**

Phase 1 trial: commenced on 11 August 2021

In February 2021, Avacta received approval from the Medicines and Healthcare Products Regulatory Agency ('MHRA') for its Clinical Trial Authorisation ('CTA') in the UK for a Phase 1 ('P1') study of its lead pre|CISION prodrug, AVA6000. Phase 1 studies typically focus on the safety and tolerability of the drug under investigation, as their primary objective. A secondary objective may be (but not always) to examine preliminary efficacy of the drug.

The AVA6000 P1 study has been structured in two parts, Phase 1a ('P1a') and Phase 1b ('P1b'). P1b would commence only if and when P1a were successfully completed.

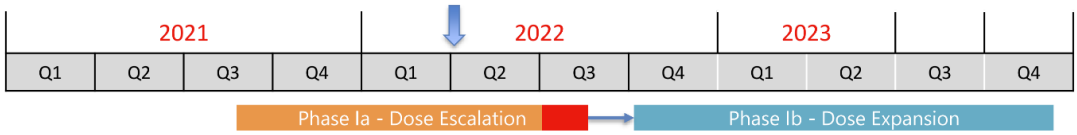
P1a comprises the 'Dose Escalation' phase. Besides safety and tolerability, the key purpose of P1a is to determine the maximum tolerated dose, and/or the Recommended Phase 2 Dose ('RP2D') for P1b. As many as eight different types of locally advanced and/or metastatic solid tumours are being tested in P1a.

P1b comprises the 'Dose Expansion' phase. P1b would use a consistent dose (the RP2D) as determined by P1a on a patient population that includes only 1-3 types of tumour (based on the assessment of P1a data). The study would examine safety and tolerability of the RP2D in these 1-3 specific tumour types, as well as preliminary anti-tumour activity. In P1b, 15-20 patients would be recruited for each tumour type.

Prior trial to commencement, P1a was structured into 3-4 'cohorts' of 3-5 patients each, with cohorts running consecutively.

Patients are dosed once every 3 weeks with AVA6000 via intravenous infusion, until disease progression, unacceptable toxicities, withdrawal from treatment for other reasons, reaching maximum lifetime cumulative exposure to doxorubicin, or death – whichever occurs first.

All patients in each cohort receive the same dose concentration, each time they are dosed. New patients are recruited for each new cohort.



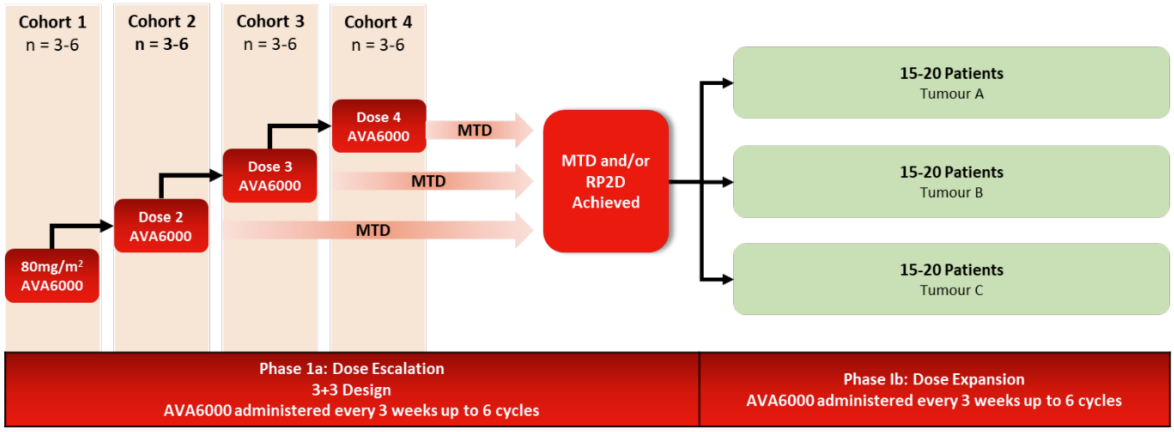
Phase 1a

- **Objective:** Assess safety and tolerability of AVA6000; determine MTD and/or recommended dose for further development.
- **Approximately 4 Cohorts** of 3-5 patients per cohort to achieve maximum tolerated dose (MTD) - 15 to 20 patients.
- **Patient Population:** Locally advanced and/or metastatic pancreatic, colorectal, non-small cell lung, breast, head and neck (SCCHN), soft tissue sarcoma, ovarian and bladder cancer.

Phase 1b

- **Objective:** Confirm safety and tolerability of AVA6000 at the MTD (or recommended dose) determined in Part 1; explore preliminary anti-tumour activity.
- Up to 3 cohorts & 15-20 patients/cohort
- **Patient Population: S**elected on the basis of Part 1 data.

[N.B. this timeline has since slipped by approximately nine months.]



The starting dose for the first cohort ('C1') was set at 80mg/m², which is equivalent to a 54mg/m² dose of standard doxorubicin. To note, the MTD of standard doxorubicin is circa 60mg/m². Lifetime cumulative doses are usually limited to 450mg/m².

On 3 February 2022, Avacta announced that the trial's Safety Data Monitoring Committee ('SDMC') had completed its review of the safety data from C1. Following the review, the SDMC recommended that the clinical trial continue as planned. The second cohort ('C2') was launched, with its patients being dosed with AVA6000 at 120mg/m² (being a 50% increase on the dose used in C1).

On 29 June 2022, Avacta announced that C2 had successfully completed, and that it was commencing the third cohort ('C3') at a dose of 160mg/m² (being a 33% increase on the dose used in C2).

On 1 September 2022, Avacta announced that C3 had successfully completed, and that it was commencing the fourth cohort ('C4') at a dose of 200mg/m² (being a 25% increase on the dose used in C3).

Finally, on 17 January this year – as part of the update that confirmed that AV6000's safety and tolerability profile was significantly better than that of standard doxorubicin, and moreover that the drug was activating at the site of the tumour – Avacta announced that it was "*in a position to proceed beyond the fourth cohort in the dose escalation study to even higher doses than originally anticipated.*"

It confirmed that the SDMC has recommended "*continuation to high dose cohorts*" in order to identify an MTD, and that it anticipates that these additional cohorts should complete in H1 2023. No commentary was made on what the dose increase in the fifth cohort will be, nor on just how many more cohorts beyond C4 will be required.

The January update

In the update, Avacta informed the market that a total of 19 patients had been dosed across C1 to C4. Had there not been any supporting commentary, and given that only three patients are required to successfully complete a particular cohort's dosing regimen before the next cohort can commence, one might have assumed that *19* patients dosed points to there having been multiple instance of dose limiting toxicities ('DLT') across the cohorts.

However, given that no cardiotoxicity was observed even in the patients of C4, we can deduce that seven patients would sadly most likely have withdrawn or been withdrawn from the trial due to entering palliative care, or due to death.

In the update, Avacta was unambiguous that the safety and tolerability profile of AVA6000 had been improved *dramatically* in comparison to standard doxorubicin. Below is a list of direct quotes lifted from the RNS and from the accompanying CEO interview:

- *"Positive safety profile of AVA6000 continues in the fourth cohort."*

- *"AVA6000 continues to show a very favourable safety profile."*

- *"AVA6000 continues to be well tolerated by patients in cohort 4 with a marked reduction in the incidence and severity of the typical toxicities associated with the standard doxorubicin chemotherapy administration. Typical toxicities include:*
  - alopecia (hair loss)
  - myelosuppression (reduction in bone marrow activity)
  - nausea
  - vomiting
  - mucositis (painful inflammation of the gastro-intestinal tract, which runs from the mouth to the anus)
  - cardiotoxicity (damage to the heart)*"*

- *"Even at the highest dosing levels in cohort 4, equivalent to more than double the normal dose of doxorubicin, the typical drug-related cardiotoxicity of doxorubicin was not observed."*

- *"Very significant reduction in the usual toxicities."*

- *"It is extremely encouraging that we've seen a marked reduction in the significant toxicities that are normally associated with doxorubicin treatment."*

- *"The safety profile looks very encouraging indeed."*

- *"We work towards realising our vision of* ***chemotherapy without side effects****."*

The Company also made it crystal clear that the pre|CISION substrate *is* being cleaved by FAPα in the tumour microenvironment. Again, a list of direct quotes lifted from the RNS and from the accompanying CEO interview:

- *"Analysis of tumour biopsies obtained from six patients across several cohorts indicates that doxorubicin is being released within the tumour tissue confirming the tumour targeting potential of the pre|CISION technology."*

- *"Analysis shows that AVA6000 targets the release of doxorubicin to the tumour tissue at therapeutic levels which are much higher than the levels being detected in the bloodstream at the same timepoint."*

- *"Observed release of doxorubicin at significant levels in the tumour tissue."*

- *"The data are unequivocal. I'm delighted to say that doxorubicin is being released in the tumour tissue, and at significant levels – therapeutically relevant levels."*

- *"We're seeing doxorubicin in all of the tumour biopsies that we've taken."*

- *"**It's clear that AVA6000 can deliver a therapeutically meaningful dose of doxorubicin into the tumour tissue**, whilst when we measure in the bloodstream at exactly the same time, the concentration is very much lower."*

It was also stressed by the CEO that continuing with the dose escalation phase of the trial, in order to find an MTD for AVA6000, is vital for several reasons. To quote the CEO again, knowing the MTD is:

- *"Essential for us to understand the range of possible doses for all future efficacy studies."*

- *"Essential for regulatory approvals."*

- *"Hugely valuable for the future development of the drug."*

- *"Important from a commercial perspective."*

Inevitably a MTD will be found. Although FAPα levels in the TME are many multiples higher than FAPα in plasma, FAPα *is* nevertheless present in the bloodstream. As the dose concentration of AVA6000 continues to be increased, eventually there will be instances of undesired cleavage of the pre|CISION substrate away from the dox by FAPα in plasma (and not by FAPα in the TME). Eventually, this will result in DLTs being observed in patients.

We expect to hear of commencement (and the dosing details) of the fifth cohort ('C5') in the near term. We speculate that Avacta is in the process of getting permission from both the MHRA and the SDMC to alter the trial protocol, so that it can continue to increase the dose (and perhaps at a *steeper* rate than a 25% increase in dose, from C4 to C5).

We also expect limited data from C1 to C4 to be released in the next three weeks, ahead of the Science Day for the Therapeutics Division, that Avacta has arranged for analysts and professional investors on 23 February.

We do however stress 'limited data'. Firstly, as P1a is an ongoing trial and there are a number of very sick patients shortly to be dosed (at even higher concentration levels) with AVA6000, it may be that Avacta wishes to limit detailed commentary on side effects (or lack thereof). Furthermore, we believe that the Company may wish to make a big splash at one of the key global oncology conferences, such as AACR (in April) or ASCO (in June). Companies presenting at these conferences are usually required to present fresh, unseen data. If this is indeed the case, then up until those conferences, Avacta will have to limit the data from the P1a trial that it shares with the investment community.

The implications of the January update

The dose escalation stage of the Phase 1 study would have been largely based on the extensive pre-clinical data generated. The Company expected the MTD to have been found – or at the very least, for *some* DLTs to have been observed – by the end of C4.

Accordingly, given that Avacta last month stated:

"E*ven at the highest dosing levels in cohort 4, equivalent to more than double the normal dose of doxorubicin, the typical drug-related cardiotoxicity of doxorubicin was not observed*"

And that:

"*We are now in a position to proceed beyond the fourth cohort in the dose escalation study* ***to even higher doses than originally anticipated, which is an unexpected and very positive development***"

…we believe that the data generated to date in the first four cohorts *exceed* the data from the pre-clinical animal models.

Management has in the past suggested that the tumour-targeting capability of the platform could be even more precise in humans than it is in mice, owing to a much higher FAPα activity in plasma (which would catalyse undesired release of active doxorubicin) in mice compared to in humans (circa 5x higher in mice). In light of the above words of the CEO, we believe that this has indeed come to pass.

It is also significant to note that the P1a trial has focussed on eight different solid tumour types. Accordingly, it is reasonable to assume that the six biopsies came from a range of different tumour types. This is testament to the 'tumour-agnostic' nature of AVA6000, and validates the words of Dr Fiona McLaughlin, Avacta's Chief Science Officer, in an interview last year that the data have been "*remarkably consistent*."

So: what does this mean? In our view, it is simple. Avacta has now proved that its pre|CISION substrate has drastically improved doxorubicin as a cancer treatment. Many readers many now be thinking, "*Hold on. There has been zero data released by Avacta yet, and zero mention of efficacy*."

Our response to that is this:

The statement, "*doxorubicin is being released in the tumour tissue, and at significant levels – therapeutically relevant levels*", should in our view be taken as a proxy for good efficacy. There is 50 years of real-world data, demonstrating what occurs when doxorubicin is released in tumour tissue at therapeutically relevant levels. It is one of the most powerful chemotherapeutic agents in existence, and is highly effective at destroying cancer cells. If active doxorubicin is being dumped in meaningful levels in tumour tissues, how could anti-tumour activity not be occurring?

We strongly believe that the Company will have already generated very promising early efficacy data (although as to whether this is published ahead of Science Day, or held back for a major oncology conference, we are uncertain).

We would encourage readers to look back at the mouse models on pp.5-6. From them, one can perceive that for the patients of C4, who received a dose of AAV6000 equivalent to more than double the normal dose of doxorubicin – the doxorubicin actually being released at their tumours could have been *several more times* than double the amount of doxorubicin that would have reached their tumours, under the standard drug.

Remember – given that prodrug molecules are unable to distribute throughout the body into healthy cells, the *concentration* of doxorubicin molecules becoming 'active' at the site of the TME is greatly enhanced, in comparison to the concentration of doxorubicin molecules reaching the TME in conventional chemotherapy at the equivalent dose size.

Consider the stark difference in reduction in tumour volume, caused by standard doxorubicin and by AVA6000, in the mouse models. Whilst we believe that that sort of data is unlikely to have been generated in the P1a trial so far (as the patients taking part have been extremely sick, and likely terminal in many cases), in our view Avacta has now essentially implied that AVA6000 will be capable of producing those results in humans.

Clinical trials and the securing of marketing approval for drugs are long, arduous and expensive processes. It cannot be stressed enough, however, that Avacta's pre|CISION technology is a *delivery platform*. In layman's terms, the substrate was designed to achieve two simple tasks (simple on face-value – but evidently extremely difficult, in light of the many failures of past attempts):

- To reduce the cell permeability of the drug molecule that it is bonded to (by virtue of the combined molecule being larger in size).

- To cleave away from the drug molecule, when it encounters FAPα (which is predominantly found in the tumour microenvironment).

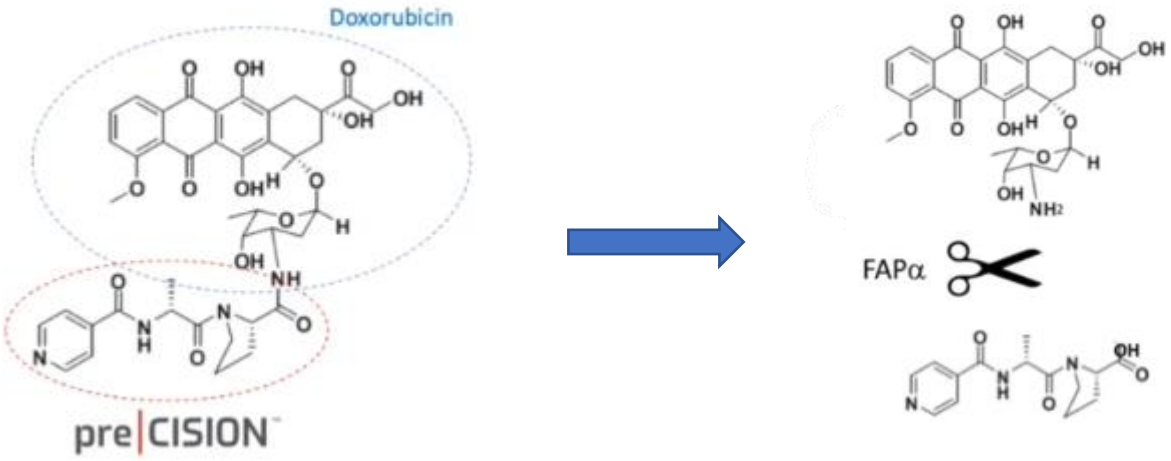
In the announcement of 17 January, Avacta declared that the pre|CISION substrate has achieved these goals with AVA6000. Firstly, the substrate molecule is not being separated from the doxorubicin molecule anywhere in healthy tissues (in notable volume) – as otherwise there would have been reported DLTs in patients and an MTD would have been discovered. Secondly, the substrate molecule is being cleaved by FAPα in the TME – as active doxorubicin is being found in significant volumes in all biopsies.

The role of the substrate has been accomplished. The role of doxorubicin – successfully delivered to, and activated in, tumour tissue – in breaking down cancer cells, should not be considered a daunting clinical hurdle to overcome. In fact, we firmly believe that clinical progression of AVA6000 from this point onwards, all the way through to marketing approval, is now procedural. P1a and P1b will determine the optimum level of dosing; and a Pivotal Phase 2 study will simply generate the necessary volume of in-human data for each tumour type to satisfy the various regulators such as the MHRA and the FDA.

Validation of the pre|CISION Platform

A unique delivery platform, under global patent protection

The pre|CISION platform is, quite literally, the molecule that Professor William Bachovchin developed, refined and perfected. The substrate that is so exquisitely specific to FAPα, that no one else has managed to create.



It is that specific molecule – a dipeptide N-(pyridine-4-carbonyl)-D-Ala-L-Pro – that constitutes the intellectual property of the pre|CISION platform. As far as we are aware, there is no other therapy in clinical development that uses FAPα as a *cleaving* mechanism. There are numerous drugs in the clinic that use FAPα as a biomarker – a target to *bind* to – but that is a very different mechanism of action to Avacta's AVA6000 and other future pre|CISION prodrugs.

Clinical projects targeting fibroblast activation protein (FAP)			
Project	**Company**	**Mechanism**	**Status**
Simlukafusp alfa/ RG7461	Roche	Anti-FAP MAb-IL2 fusion protein	Phase 2
Talabostat/ BXCL701	Bioxcel (ex Midatech)	Small-molecule DPP VIII & IX & FAP inhibitor	Phase 2 academic trial
FAP-2286	Clovis Oncology/ 3B	Anti-FAP radionuclide	Phase 1/2
RG7827/ RO7122290	Roche	Anti-FAP 4-1BB ligand MAb	Phase 1/2
NG-641	Psioxus	Oncolytic virus coding for FAP	Phase 1
AVA6000	Avacta Group	Anti-FAP MAb	Phase 1
RG6189/ RO7300490	Roche	Anti-FAP 4-CD40 ligand MAb	Phase 1
MP0317	Molecular Partners	FAP & CD40 targeting darpin	Phase 1
MP0310/ AMG 506	Molecular Partners (Amgen discontinued)	FAP & 4-1BB targeting darpin	Phase 1

Source: Evaluate Pharma & clinicaltrials.gov.

(N.B. the 'Mechanism' description for AVA6000 is incorrect in the above table – just another example of many, that even some industry analysts don't yet understand Avacta's pre| CISION technology).

As we explained on p.3, the pre|CISION substrate is not cleaved by any other enzyme in the human body. This extremely high level of specificity to FAPα is the core intellectual property of the platform. Other entities have previously attempted to develop such a substrate, but without success: their attempts have been susceptible to cleavage by other enzymes closely related to FAPα. The broad patent family that Avacta has licensed from Bach until patent expiry (from early 2030s to early 2040s), provides globally exclusive usage of the substrate in therapeutic agents (small molecules, biologics, ADCs, etc). During that time, each individual drug that has been modified with the pre|CISION substrate, can then be patented by Avacta, for at least a further 20 years.

Applying the pre|CISION technology to other chemotherapies

Avacta's CSO, Dr McLaughlin, in a recent interview referred to AVA6000 as the 'pathfinder' for the pre|CISION platform.

"*That demonstrates that the technology, the scientific hypothesis, is correct.*"

The pre|CISION substrate has now been proved – in the AVA6000 P1a trial – to remove (or at the least, drastically reduce) a small molecule's cell permeability, thus preventing it from entering healthy cells. And it has been proved to cleave away from that same molecule when it encounters FAPα on and around tumour cells – thus restoring that molecule's cell permeability, so that it can diffuse into said cancer cells.

Consider the diagram on p.13. Of course, it is a tad more complicated than this on the scientific level(!), but the lay investor need only understand that in future pre|CISION prodrugs that Avacta (or others) may develop, the pre|CISION substrate molecule will not change from how it is represented in the diagram. Similarly, the chemotherapy molecule will not be altered from its standard state. It is simply the peptide bond (NH) between the pre|CISION substrate and the chemotherapy molecule – which is susceptible to cleavage *only* by FAPα – that would be created for each new pre|CISION pro-chemotherapy.

Avacta has already disclosed to the market that the substrate has worked successfully in multiple other small molecules that it has been attached to, in in-vivo (animal) trials.

After AVA6000, the most advanced of Avacta's pre|CISION pro-chemotherapies is ***AVA3996***, which has been in formal pre-clinical development since January 2022. AVA3996 is a FAPα-activated proteasome inhibitor that is an analogue of Velcade (which was generating sales of in excess of $1bn per annum for its owner, Japanese pharma giant Takeda Pharmaceuticals, before patents expired last year).

Avacta had already carried out "*efficacy studies in several liquid and solid tumour models, safety studies and a review of manufacturability*" – all of which evidently yielded positive results – before selecting AVA3996 for pre-clinical development in preparation for Clinical Trial Authorisation ('CTA') and/or Investigational New Drug ('IND')-enabling studies. Indeed, management's commentary in January 2022 on the first studies for AVA3996 was:

"*We are excited by the early pre-clinical data for AVA3996.*"

As the Company highlighted, the pre-clinical studies yielded both efficacy and safety data for the prodrug. To be 'excited' about that data would suggest that the pre|CISION substrate must have worked for AVA3996 in animal models, as it did for AVA6000, with regards to both efficacy and safety. Otherwise, if only safety and tolerability had been improved, but activation at the TME (which is a proxy for efficacy) had not occurred – or vice versa – then why be excited? Both aspects are critical for a 'working' pre|CISION platform.

Thus we can be sure that the pre|CISION substrate has worked consistently for different prodrugs in animals. The obvious question is then, "*Why would it not work consistently for different prodrugs in humans?*"

Assuming the further pre-clinical work has been a success over the past 12 months, Avacta intends to file a CTA and/or IND, in order to commence a P1 trial for AVA33996 towards the end of this year.

After AVA3996, Avacta has stated that its next most advanced pre|CISION prodrugs are:

- ***AVA7000***, a prodrug form of paclitaxel, a chemotherapy from the taxane family of medications.

- ***AVA7500***, a prodrug form of oxaliplatin, a powerful alkylating agent.

The fact that Avacta has already codenamed these next prodrugs beyond AVA3996, suggested it has already carried out extensive research and development on them (albeit, limited to in-vitro at this stage).

In fact, beyond AVA6000 (pro-doxorubicin), in presentations and reports over the past several years Avacta has identified and named at least 15 other chemotherapies, that it believes can be successfully modified with pre|CISION. It has also emphasised that this list is by no means exhaustive.

- FAPα-activated proteasome inhibitors (e.g. drug name: bortezomib; brand name: 'Velcade')
- FAPα-activated taxanes (e.g. paclitaxel ('Taxol') and docetaxel ('Taxotere'))
- FAPα-activated oxaliplatin ('Elotaxin')
- FAPα-activated irinotecan ('Camptosar')
- FAPα-activated pemetrexed ('Alimta')
- FAPα-activated gemcitabine ('Gemzar')
- FAPα-activated capecitabine ('Xeloda')
- FAPα-activated PARP inhibitor – olaparib ('Lynparza')
- FAPα-activated PARP inhibitor – rucaparib ('Rubraca')
- FAPα-activated PARP inhibitor – niraparib ('Zejula')
- FAPα-activated PARP inhibitor – talazoparib ('Talzenna')
- FAPα-activated balixafortide (still in clinical development)
- FAPα-activated PBD Dimer (still in clinical development)
- FAPα-activated AKT inhibitor (still in clinical development)
- FAPα-activated PD-1 inhibitor – possible drugs to target have not been disclosed to date

Together, the identified chemotherapies above cover all the major sub-classes of chemotherapy:

- ***Alkylating agents*** – oxaliplatin
- ***Antimetabolites*** – pemetrexed; gemcitabine; capecitabine
- ***Antitumour antibiotics (anthracyclines)*** – doxorubicin
- ***Topoisomerase inhibitors*** – irinotecan
- ***Mitotic inhibitors*** – taxanes (e.g. paclitaxel and docetaxel)

The *breadth* of pre|CISION's applicability across the various sub-classes of chemotherapy is an incredibly valuable attribute: it heightens the probability that it will 'work' on a great many (dare we say, large majority?) of existing chemotherapies.

Applying the pre|CISION technology to other drug classes beyond chemotherapy

We estimate that Avacta has circa £38m in net cash at the time of writing. This is a modest balance sheet, relative to the immense size of the commercial opportunity that the pre|CISION platform has opened up for the Company. We believe that it is in the best interest of shareholders for Avacta to focus – for the time being, at least – on developing the pre|CISION pro-chemotherapies, as they represent the *low hanging fruit*.

Nevertheless, it is vital to highlight that the pre|CISION substrate can be used to create new, or modify existing, therapeutics *beyond* chemotherapy.

As detailed on p.2 and in Appendix 1, Avacta originally partnered up with Bach in order to create a new class of drug conjugate – combining an Affimer or antibody, the pre|CISION substrate as a linker, and a warhead (chemotherapy or other small molecule). This class of next-generation drug conjugate has been named, TMAC.

In last month's RNS, Avacta also stated that:

"The pre|CISION platform has the potential to significantly improve the safety and tolerability of chemotherapies, ***and other drugs***, by targeting their release to the tumour."

Avacta could be referring to modifying other *small molecules* (i.e. chemically-derived therapeutics) and/or *biologics* (i.e. therapeutics derived from living organisms).

Small molecules beyond chemotherapies may include kinase inhibitors; as well as antineoplastic agents that are too toxic to be used as standalone chemotherapies – an example being the extremely powerful monomethyl auristatin E (or 'MMAE').

With regards to ***biologics*** (which tend to be physically larger molecules than chemically-derived therapeutics), again there is no reason why the substrate could not be used to modify:

- ***Monoclonal antibody-based immunotherapies***. [Prime examples are PD-1 inhibitors, such as Keytruda and Opdivo; and PD-L1 inhibitors, such as Bavencio and Tecentriq.]

- ***Cytokine therapies***. [Cytokines are substances made by immune cells, and play an important role in boosting the immune system. The main cytokine treatments for cancer are based on two particular cytokines, namely interleukins and interferons.]

Therapies using interleukins and interferons tend to generate more severe side effects than do therapies that use monoclonal antibodies. As such, we believe that were Avacta indeed to look at modifying biologics, it would start with cytokine therapies (being the area with the greater clinical need for reduced side effects).

At this juncture, it is important to highlight that even if a therapeutic's physical structure is not suited to being modified with the pre|CISION substrate, it nevertheless could – in some instances – be altered so that it *were* suitable for modification.

An example: Avacta's AVA3996 is a pre|CISION-modified version of an *analogue* of the proteasome inhibitor, bortezomib. It is our understanding that an analogue version – a drug whose physical structure is very similar to the original – of bortezomib had to be used by Avacta, as the original did not possess the necessary 'binding site' at which the pre|CISION substrate could be bonded to (see diagram on p.13).

In this light, the list of small molecules and biologics that could be possible targets for pre|CISION modification, appears incredibly extensive.

pre|CISION: the Clinical Proposition

Avacta's pre|CISION technology could now revolutionise chemotherapy

We are firmly of the belief that Avacta's pre|CISION platform is well placed to revolutionise chemotherapy as we know it. We appreciate that that is an extremely punchy statement, so we shall endeavour to explain such a bullish outlook. Before we do so, however, it is worth noting that Avacta itself has titled recent public presentations with the following words:

REVOLUTIONISING THE TREATABILITY OF SOLID TUMOURS

If you think that the author is deranged, then you must think that Avacta's management team is too.

Firstly, let us start with what it would mean for existing patients who undergo chemotherapy, using doxorubicin as an example. Due to cardiotoxicity, patients are currently limited to lifetime cumulative doses of approximately 450mg/m² of standard doxorubicin. That equates to as few as eight doses in total. Even if the drug is proving highly effective in breaking down the patient's cancer cells, the patient can no longer receive the treatment after reaching that lifetime cumulative dose total.

Replace doxorubicin with Avacta's pro-doxorubicin, AVA6000. Following last month's P1a trial update, it would appear that a patient will in future be able to receive many more, or much more powerful, doses of pro-doxorubicin, than they would have been able to of standard doxorubicin. As no (or substantially less) doxorubicin would be accumulating in the patient's heart tissue when they were dosed with AVA6000 (as opposed to standard doxorubicin), the lifetime cumulative dose total would be *multiples* greater than 450mg/m².

More potent dosing would substantially increase the probability of tumour regression, as suggested by Avacta's pre-clinical animal models (see pp.5-6). Various academic research using clinical data have also demonstrated that a higher cumulative dose of doxorubicin is likely to yield superior efficacy.[1]

What has not been made clear yet by Avacta (and we would not expect it anyway until after the full data readout for P1b) is whether the preferred clinical strategy would be to increase the dose by as much as possible, so that it is many times more potent (than standard doxorubicin) and thus has a greater probability of killing all cancer cells *quickly*; or else to set patients on a course that lasts for say 15-20 cycles, with a less potent version but which causes only negligible (or zero?) side effects.

In any event, the drastically reduced cardiotoxicity caused by the prodrug will provide incredible optionality to oncologists, with regards to both the potency and the duration of chemotherapy courses that they could provide for patients. Depending on the stage and type of cancer, as well as the age and health of the patient, an oncologist may decide to go for the 'nuclear' option – in which the patient may be dosed with AVA6000 that is many multiples more concentrated than standard doxorubicin; or for the 'chronic illness treatment' option (many cycles at a comparatively lower concentration) – which may be easier on the patient.

This brings us to the second key point on how the pre|CISION platform can revolutionise chemotherapy. Not only could those patients who were already eligible for chemotherapy, now be dosed many more times and/or with much more powerful doses; but those patients who were previously not suited to receive chemotherapy *at all* (due to poor health or old age) could now also receive pre|CISION pro-chemotherapies.

In effect, the population of patients eligible for chemotherapy could be increased dramatically; and all patients could receive dramatically more (or more potent) doses.

And – as we have attempted to demonstrate in this note – this will not just be the case for doxorubicin, but for *many* chemotherapies that Avacta believes it can modify with the pre|CISION substrate.

[1] e.g. www.ncbi.nlm.nih.gov/pmc/articles/PMC7684756/

The improvement in safety and tolerability of a pre|CISION prodrug over the equivalent standard chemotherapy would not just be a mere +20% to +40% (as is often the target in novel oncology drug trials); and it wouldn't improve treatment outcomes for say only 25% of patients. It would represent an improvement in safety and tolerability of multiples, compared to existing, marketed chemotherapies – and moreover, for 100% of patients. Consequently, from a clinical perspective, it would be difficult to argue why any standard chemotherapy would remain on the market *at all* – if an equivalent pre|CISION prodrug version had become available.

[On a non-clinical, but nevertheless related note, consider also how marketing campaigns of cancer research and patient support charities may have to gradually change their current range of advertising images, as pre|CISION prodrugs with drastically reduced side effects displaced standard chemotherapies.]

It's also worthwhile considering how a working, fully rolled out pre|CISION platform could impact on the whole oncology industry. Numerous types of cancer drugs have been developed in recent years, with billions of dollars invested in them. One of the major reasons for these developments is the dose limiting toxicities of chemotherapy drugs. Chemotherapy is in fact a highly effective form of treatment. Its anti-tumour activity kicks in within hours of dosing. In contrast, it may take 2-3 months before any response from an immunotherapy (such as the leading PD-1 inhibitor, Keytruda).

Furthermore, the overall response rate of patients to immunotherapies on the market is only 15% to 20%. In contrast, only a small percentage of tumours are *entirely* resistant to chemotherapy treatment.

Generally speaking, chemotherapy is also a significantly cheaper form of treatment than new therapies such as conventional immunotherapy (e.g. PD-1 / PD-L1 inhibitors), CAR-T therapy, and antibody-drug conjugates.

How does pre|CISION compare to the ADC, the current leading form of targeted therapy for cancer?

To appreciate the potential of the pre|CISION platform, it is vital to understand the closest form of competition: the antibody-drug conjugate ('ADC'). The ADC is a relatively new class of targeted cancer therapy. The first ADC was approved by the FDA in 2000; by end 2021, there were 14 approved ADCs on the market worldwide.

An ADC is comprised of three components:

i) Targeting moiety

This is the monoclonal antibody (or antibody mimetic) itself, the role of which is to localise the drug conjugate to the tumour, to deliver the drug payload (or 'warhead') specifically to cancer cells. The antibody targets a specific antigen that is overexpressed on the surface of cancer cells. The most commonly targeted antigens are the proteins, HER2, trop2, nectin4 and EGFR.

Once the ADC binds to the antigen on the surface of the cancer cell, it triggers internalization of the antibody, together with the drug payload (or 'warhead').

ii) Linker

The linker physically binds the targeting moiety to the warhead. In conventional ADCs, the linker is designed to be cut by certain enzymes *after* the drug conjugate is internalised by the cancer cell, thus releasing its warhead inside the cell. This is a similar technology to Avacta's pre|CISION substrate, in that the linker renders the warhead inert whilst it moves through the body and bypasses healthy tissue.

iii) Warhead

This is a powerful anti-cancer agent, such as a chemotherapy. It remains inactive when attached to the targeting moiety via the linker; but, once internalised and released inside the cell's cytoplasm, has a cytotoxic activity (i.e. cell-killing).

ADCs are significantly more targeted, and have a higher efficacy, than conventional chemotherapies. However, the class of therapy nevertheless comes with several major challenges:

- ***Unavoidable side effects***
  Severe side effects (grade 3 or higher) are common with ADCs. The most notable are:

  i) ***blood toxicity***, including neutropenia, thrombocytopenia, leukopenia, and anaemia;

  ii) ***hepatotoxicity*** (i.e. chemical-driven liver damage);

  iii) ***gastrointestinal reaction*** (including nausea, vomiting, diarrhoea, abdominal cramps).

  These three types of side effect are all believed to be related to premature release of cytotoxic payloads in the blood circulation.

  iv) ***nephrotoxicity*** (i.e. toxicity in the kidneys). This can be caused by the immune response induced by the antibody component of the ADC.

  v) ***interstitial lung disease ('ILD')***. Whilst it remains unclear, it has been speculated that ILD might be associated with the uptake of the ADC in healthy lung cells, and the subsequent payload release from the ADC. [The lungs enjoy abundant blood flow and long retention – more so than other organs – and as such, are more under threat from undesirable uptake of ADCs.]

- ***Drug resistance***
  ADCs target an antigen expressed on the tumour cell itself, such as HER2 expression on breast tumours. One defence mechanism that tumour cells have is that, when faced with long-term exposure to an ADC, they will reduce the expression of the antigen that the ADC targets. This decrease in cell-surface antigen reduces the amount of antibody binding, and thus the amount of ADCs that are internalised.

- ***Large size causes issues with drug penetration***
  ADCs have a much greater molecular weight than traditional cytotoxic drugs such as chemotherapies. Accordingly, drug penetration into tumour cells is comparatively lower. Only a small part of ADC input into patients actually end up reaching and being internalised by tumour cells.

- ***Complex pharmacokinetic profiles***
  ADCs are highly complex drugs, being combinations of both biologics (the antibody) and cytotoxic payload. After administration of an ADC, three main forms may be present in the systemic circulation: the intact ADC, the naked antibody, and the free cytotoxic payload. This makes it difficult to establish PK and PD models, and to design new ADCs.

Despite these major challenges, the ADC class is growing rapidly, with many billions of dollars being invested into its development and commercialisation by Big Pharma. Various works of market research suggest that the global ADC market will enjoy a compound annual growth rate of as high as 25% over the next five years, to $14.4bn pa. Some analysts believe that just AstraZeneca's blockbuster ADC, named Enhertu, could achieve peak sales in excess of $10bn per annum.

So, how would Avacta's pre|CISION prodrugs compare? We believe that they could enjoy a number of key advantages over ADCs.

To address the major challenges facing ADCs, in order of the above:

- ***Unavoidable side effects***
  The exquisite specificity of the pre|CISION substrate to FAPα should dramatically reduce the probability of the severe side effects numbered i) to iii) above, that ADCs can cause. This is due to the fact that there will be a significantly lower probability of premature release of the payload (chemotherapy) in the bloodstream.

  With regards to the fourth side effect – toxicity in the kidneys – pre|CISION prodrugs do not have an antibody component. An accidental immune response – at least through binding of an antigen – would not be possible.

  The probability of ILD occurring should also be significantly lower, again as a result of the very high specificity of the substrate to FAPα (of which there is barely a trace, on the surface of healthy lung cells).

- ***Drug resistance***
  FAPα is expressed on tumour cells in some cases, but more so on the activated fibroblasts in the tumour microenvironment. As such, mutation by tumour cells in order to reduce FAPα expression on their cell surfaces, as a defence mechanism against long-term exposure to FAP-activated pre|CISION prodrugs, will not be particularly effective. [The FAPα in the TME will remain over-expressed, and thus will cleave the substrate and release the active chemotherapy, *regardless* of FAPα reduction/mutation on the tumour cell surface itself.]

- ***Large size causes issues with drug penetration***
  Chemotherapy molecules are a small fraction of the size of ADCs. They easily enter cells via passive diffusion. Internalisation of a large protein (i.e. a monoclonal antibody) is not an issue that chemotherapies must contend with.

- ***Complex pharmacokinetic profiles***
  Chemotherapies are very well understood drugs, with years – and in some cases, decades – of real-world experience. Yes, modifying a chemotherapy with the pre|CISION substrate does increase the complexity of the PK and PD models, but with only two components (linker and warhead) in comparison to the three of an ADC, they remain much simpler molecules to design, develop, track and understand.

The pre|CISION platform may well face its own major challenges. Indeed, we reiterate that no data has yet been shared with the market by Avacta for its first prodrug, AVA6000. Nevertheless, we have provided the above comparisons between ADCs and Avacta's prodrugs in order to demonstrate how the pre|CISION platform could ultimately change the face of targeted therapy for cancer. And, following Avacta's 17 January market update, we are convinced that the Company is wholly aware that it does indeed have a 'working' pre|CISION platform on its hands.

Technically, a working pre|CISION platform would *not* be considered a new class of therapy for cancer. The mechanism of action for the cytotoxic payloads would remain unchanged. However, the modification made to standard chemotherapies via the attachment of the pre|CISION substrate would have such a profound impact, not only on the safety and tolerability profile of the drug, but also on efficacy (as a much higher proportion of the administered prodrug would be entering into cancer cells, compared to the standard version of the drug), that we believe pre|CISION *would* be looked upon by the industry as a new type of therapy.

In recent years, much has been made of ADCs embodying the 'Magic Bullet for Cancer' concept that German Nobel Laureate, Paul Ehrlich, imagined in the early 1900s. Given that last month Avacta itself stated that it was working towards its vision of "*chemotherapy without side effects*", we believe we are justified in proffering that pre|CISION prodrugs could soon become the de-facto Magic Bullet for Cancer.

pre|CISION: the Commercial Proposition

We believe that Avacta's pre|CISION platform carries colossal commercial value that has not been appreciated by the market, following the Company's Phase 1a trial update last month.

Let us start with AVA6000. Doxorubicin is a now a generic drug – that is to say, it is off-patent. Whether branded or not, the generic status means that the drug will sell for significantly less than the previously on-patent, branded drug once did. [Competitors all selling the same product naturally squeezes margins.]

Despite this, and despite the severe dose limiting toxicities examined in the previous pages, global sales of standard doxorubicin still generate approximately $1.2bn per annum. Market research suggests that this will have increased to almost $2bn pa in the next five years.

Why is the doxorubicin market growing, despite many billions of dollars being pumped into the development of novel cancer treatments in the past couple of decades? Well, because doxorubicin is extremely potent and a highly efficient killer of cancer cells, whose effect on tumours can be rapid (mere days, even hours, for anti-tumour activity to commence).

Two years ago, with the assistance of external consultants, Avacta carried out work on the potential total addressable market ('TAM') for its prodrug form of doxorubicin, AVA6000. The commercial evaluation estimated that the market size (at peak sales) – in just three indications (namely, breast, ovarian, and advanced soft-tissue sarcoma), and just in the EU and US – could be $1.5bn pa.

This work was of course completed *long before* the Phase 1a data had exceeded management's expectations.

Consider this: if AVA6000 simultaneously reduces side effects and increases efficacy over standard doxorubicin (which we proffer it does), why would it not displace the large majority, if not the entirety, of the existing doxorubicin market?

Now consider that a branded drug does, by rule of thumb, command a price tag approximately twice that of the generic version of the drug.

A *branded* doxorubicin, under global patent protection, would be generating annual sales of approximately $4bn, based on the aforementioned market forecasts ($2bn pa by 2028).

Now consider that AVA6000 could double, treble or even quadruple the TAM of standard doxorubicin. How? The population of patients eligible for chemotherapy would be increased dramatically; and all patients could receive dramatically more (or more potent) doses.

Across 8+ tumour targets, and all geographies, it is straightforward to perceive how AVA6000 could become a $10bn+ pa drug.

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That's just doxorubicin, which constitutes less than 2% of global chemotherapy sales. It has been estimated that by 2027, in four years' time, the global chemotherapy market will be worth $74.3bn.

In 2022, the global market for a *generic* bortezomib (Takeda's final patents on the drug expired last year) was estimated to be $1.2bn. With ***AVA3996*** (Avacta's prodrug form of bortezomib), there is no reason to think that it could not bring about a similar multiplying of that market size, to what we suggested may occur for AVA6000. Indeed, we believe that the increase in market size brought about by AVA3996 may be even greater: Avacta has suggested that not only would the prodrug be an improvement over standard bortezomib in treating the blood cancers multiple myeloma and mantle cell lymphoma (which it is currently only used for), but that it may *also* be able to target *solid* tumours, such as pancreatic.

AA7000 is a prodrug form of the generic drug, paclitaxel. Global sales for paclitaxel were estimated to be $4.5bn in 2021. Market research suggests that it could reach $11.2bn by 20230.

Global sales for the generic drug, oxaliplatin – of which Avacta's ***AVA7500*** is a prodrug form – were estimated to be $934m in 2021. Market research suggests that it could reach $1.8bn by 2027.

We have detailed the above in order to demonstrate to readers just how vast the markets for Avacta's pre|CISION prodrugs could be. These first four generic drugs the Company is targeting for modification with pre|CISION, *already* command (multi-) billion dollar markets.

As is the case with doxorubicin – bortezomib, paclitaxel and oxaliplatin all have severe side effects that, for varying reasons, limit the cumulative lifetime dose permitted.

Question: what stands in the way of the pre|CISION platform eventually displacing a large majority of the conventional chemotherapy market (i.e. every existing drug that can be physically modified by the substrate, is)? And were *that* to occur, the $74bn pa global sales estimate for conventional chemotherapy could be multiplied several times.

Two potential barriers that may stand in the way of a rapid monopolisation of the market would be:

1) cost to manufacture

2) existing patents over standard chemotherapies currently in use

To answer the first point, through discussions with management we understand that the increase in cost of manufacture for pre|CISION prodrugs over standard chemotherapies would be only very modest.

With regards to the question of patents, we would point out that of the chemotherapies in Avacta's pipeline that it is planning on modifying, the first eight (including doxorubicin) on the list on p.15 are already off-patent. Two of the four the PARP inhibitors are also set for patent expiry within the next five years.

For those drugs in the pipeline still on-patent, Avacta could either work with analogue versions to develop prodrugs (as it has done with AVA3996 / bortezomib); or it could seek to partner with the owners of the on-patent drugs, most likely via licensing the pre|CISION platform to those owners who could then redevelop, rebrand and relaunch their drugs.

The bull case for pre|CISION is that it could displace the large majority of these existing global markets, relatively quickly – with the key question being:

Why wouldn't it, if clinical outcomes for patients were improved so spectacularly and on a consistent basis?

Not only could it steadily displace existing products from that $74bn pa chemotherapy market (forecast to be reached by 2027), but the nature of the prodrug treatment (more cycles, for many more patients) would multiply the size of that market. pre|CISION pro-chemotherapies could also eat into the market share of *other* targeted therapies – notably ADCs – that are currently being used partially as a result of dose limiting toxicities of standard chemotherapies.

A summary of the commercial proposition

To summarise: in our view, the entity with control over a *working* pre|CISION platform (currently Avacta) *could* hold the power to eventually dominate the global chemotherapy market. How?

- Provided the controller of the platform had deep pockets, they could push a dozen pre|CISION prodrugs into pre-clinical and clinical development, simultaneously.

- For those drugs that were already off-patent (doxorubicin, paclitaxel, docetaxel, oxaliplatin, irinotecan, pemetrexed, gemcitabine, capecitabine), the controller could develop these prodrugs as wholly owned assets.

- For those drugs still on-patent, they could license the pre|CISION substrate to the current patent holders / brand owners of those drugs, and receive royalties on future sales; or else they could actively develop the prodrugs with those existing owners, in joint ventures.

- The route to market for pre|CISION prodrugs would be significantly faster and cheaper than it is for novel drugs such as ADCs, as they would not be required to go through Phase 3 trials (which involve many hundreds more patients than Phase 1 and 2 trials).

- The clinical development risk for pre|CISION prodrugs would similarly be significantly lower than it is for novel drugs: the mechanisms of action of the standard chemotherapies being modified are well understood already, and boast many years of clinical data. Drug efficacy is not being questioned. Rather, it is the (enhanced) delivery aspect of the prodrug that is being tested.

- Moreover, given that AVA6000 (the first prodrug that will have been brought through clinical development successfully) has now already provided the proof of concept for pre|CISION in humans, the clinical development risk of subsequent prodrugs would be reduced even further.

- Because of the licensing agreement with Bach BioSciences, no other entity would be permitted to develop pre|CISION prodrugs. During this time, each newly created prodrug could be brought to market, patented and branded by the controller of pre|CISION.

- Each prodrug would rapidly displace the competition from the market: why would any standard chemotherapy continue to be used, assuming costs were comparable?

- Not only would the controller of pre|CISION have an opportunity to dominate the existing market, but it could *multiply* the size of that existing market. Those patients who were already eligible for chemotherapy, could now enjoy a much higher maximum lifetime cumulative exposure; and those patients who were not (namely, the sick and old), could now be eligible for chemotherapy as well.

Frankly, we believe it highly improbable that Avacta will be the entity to achieve this. It does not yet have the financial resources nor the operational scale to realise that vision. However, it is possible that Avacta *could* remain independent by raising considerable cash through a combination of equity raises (a NASDAQ IPO already beckons) and out-licensing deals of pre|CISION prodrugs in the pipeline, or simply of the pre|CISION substrate itself. In doing so, Avacta could retain 100% of the majority of its assets, and start to push them into pre-clinical development.

More realistically though, it is our view that Big Pharma will be watching Avacta's AVA6000 P1a trial very closely. As we have attempted to explain in this note, the greatest challenge – the creation of the substrate that is specific *only* to FAPα, and not to any closely related enzyme – has already been achieved.

We are of the belief that the pre|CISION platform could revolutionise cancer treatment efficacy *and* patient experience, multiply the total addressable market, and reset the clocks on patents and exclusivity – and all that with a lower clinical risk, lower cost and shorter development timeline than developing novel drugs.

Discussion on Valuation

The dilemma: an impossibly large total addressable market

The investment community is evidently having issues in getting to grips with the scale of the opportunity that has just been opened up to Avacta by confirmation that AVA6000 is exceeding management's expectations, in the P1a clinical trial. The targeting mechanism is working extraordinarily well, critically in *both* respects: side effects are being dramatically reduced (over standard doxorubicin), and active drug is "*being released in the tumour tissue, and at significant levels – therapeutically relevant levels.*"

On the back of this update, our view is that the prospect of AVA6000 coming to market and displacing (and multiplying) the existing doxorubicin market, has risen from *quite possible* to *highly probable*.

We could suggest an exact percentage figure for this increased probability of AVA6000 coming to market, but for now we will not.

Similarly, we are not going to attempt to estimate potential market sizes for each of the pre|CISION prodrugs under development. As we detailed on pp.21-22, market research for the first four *generic* drugs (doxorubicin, bortezomib, paclitaxel, oxaliplatin) that Avacta is targeting for modification with the pre|CISION substrate, suggest a total market size of in excess of $16bn per annum by 2030.

If AVA6000, AVA3996, AVA7000 and AVA7500 are all successfully developed and brought to market, we have demonstrated in this note how that aggregate figure could be multiplied several times over (patenting and branding could double the value of the generic drug; and then increased dosing (both frequency, and concentration) could multiply it again).

Avacta has openly highlighted at least 12 more chemotherapies that it could modify; and last month it alluded to "*other drugs*" (possibly other small molecules, as well as biologics, as we have speculated in this note) that pre|CISION could be used on. Then of course there is Avacta's TMAC concept which incorporates the pre|CISION substrate (see Appendix I), which could turn the current global ADC market on its head.

We have constructed numerous versions of discounted cash flow ('DCF') models in our attempt to account for all these possible target markets that have now been opened up to Avacta, by the successful pathfinder drug that is AVA6000. The platform valuations the models arrive at range from the mid-single billions of dollars, to several tens of billions of dollars. In reality, they are pie-in-the-sky estimates.

As a result, we have chosen not to present the models here. We believe that at the current stage of development for the pre|CISION platform, investors should be considering the Big Picture. Only a handful of very simple questions need be contemplated:

- *"The data are unequivocal. I'm delighted to say that doxorubicin is being released in the tumour tissue, and at significant levels – therapeutically relevant levels."* Can this reliably be taken as a proxy for efficacy?

- How easily can other drugs, besides doxorubicin, be modified with the pre|CISION substrate, and would their modification produce a similar enhanced performance (both safety and tolerability, and efficacy) in humans?

- Will pre|CISION prodrugs be clinically superior to competing therapeutics?

- Is the development pathway and route-to-market for pre|CISION prodrugs, commercially attractive?

We have endeavoured to address each of these topics in this note. If readers' own answers to the above four questions are all positive, then they should very much be considering that $74bn per annum forecast for the global *conventional* chemotherapy market by 2027, as a starting point.

Precedent transactions

Below we highlight a selection of transactions in the targeted cancer therapy space (including immunotherapies and ADCs) over the past three years, so as to provide some insight into the value attributed to these classes of drugs by Big Pharma, even at relatively early stages of clinical development.

Collaborations (pre-clinical):

- ***Genentech and Bicycle Therapeutics collaboration (up to $1.7 billion)***
  In February 2020, Genentech (a member of Roche Group) and Bicycle Therapeutics announced an exclusive strategic collaboration to develop and commercialise Bicycle®-based targeted immunotherapies against multiple targets. The collaboration involves the discovery and pre-clinical development of novel therapies, and does not include any candidate from Bicycle's existing and wholly owned pipeline.

  Bicycle received a $30 million upfront payment. The upfront payment and potential discovery, development, regulatory and commercial-based milestone payments could total up to $1.7bn.

- ***Johnson & Johnson's Janssen and Mersana Therapeutics collaboration (over $1.0 billion)***
  In February 2022, J&J's Janssen unit announced a research collaboration and license agreement with Mersana, to develop novel ADCs (with an initial three targets). The ADCs would be based on Mersana's proprietary ADC platform, 'Dolasynthen', and would use Janssen's proprietary antibodies. Mersana received a $40m cash payment upfront, and could be entitled to potentially more than $1bn in milestone payments, plus a mid-single-digit to low double-digit percentage royalty on net sales. After joint collaboration on pre-clinical work, Janssen will be solely responsible for clinical development and commercialisation.

- ***GSK and Mersana Therapeutics option agreement (up to $1.5 billion)***
  In August 2022, GSK and Mersana announced an option agreement for the co-development and commercialisation of Mersana's XMT-2056, an Immunosynthen ADC that targets a novel epitope of HER2. Mersana received a $100m upfront option purchase fee. If GSK were to exercise its option, Mersana would also be eligible to receive up to a further $1.36bn in the form of an option exercise payment, and development, regulatory and commercial milestone payments. It would also be eligible to receive royalties on any future sales.

  Extensive pre-clinical data had been generated for XMT-2056 at the time of the option agreement.

- ***Merck and Kelun-Biotech collaboration (up to $9.5 billion)***
  In December 2022, Merck and Kelun-Biotech announced an exclusive license and collaboration agreement to develop seven investigational pre-clinical ADCs for the treatment of cancer. Under the agreement, Kelun-Biotech granted Merck exclusive global licenses to research, develop, manufacture and commercialize multiple investigational pre-clinical ADC therapies. Kelun-Biotech retained the right to research, develop, manufacture and commercialize certain licensed and option ADCs for mainland China, Hong Kong and Macau.

  Kelun-Biotech received an upfront cash payment of $175m from Merck. It is also eligible to receive future development, regulatory and sales milestone payments totalling up to $9.3bn; plus tiered royalties on net sales for any commercialized ADC product.

Collaborations (early clinical):

- ***AstraZeneca and Daiichi Sankyo collaboration (up to $6 billion)***
  In July 2020, AstraZeneca and Daiichi Sankyo Company entered into a new global development and commercialisation agreement for DS-1062, Daiichi Sankyo's proprietary trophoblast cell-surface antigen 2 ('TROP2')-directed antibody-drug conjugate. Using Daiichi Sankyo's proprietary DXd ADC technology, DS-1062 is designed to deliver chemotherapy selectively to cancer cells and to reduce systemic exposure.

  AstraZeneca would pay Daiichi Sankyo an upfront fee of $1bn; and pay additional conditional amounts of up to $1bn for the successful achievement of regulatory approvals and up to $4bn for sales-related milestones.

  At the time of the agreement, Daiichi Sankyo had only just commenced enrolling patients for a Phase 1 trial. Neither safety nor efficacy for DS-1062 had been established.

- ***Bristol Myers Squibb and Eisai collaboration (up to $3.1 billion)***
  In June 2021, BMS and Eisai entered into a global strategic collaboration agreement for the co-development and co-commercialisation of Eisai's first antibody-drug conjugate, MORAb-202. The ADC combines Eisai's in-house developed anti-folate receptor alpha (FRα) antibody, and Eisai's anticancer agent eribulin, using an enzyme cleavable linker. At the time, MORAb-202 was being tested in two studies: a Phase 1 study in Japan and a Phase 1/2 study in the US.

  Under the financial terms of the agreement, BMS paid $650m to Eisai ($200m of which was to cover Eisai's R&D expenses). Eisai is also entitled to receive up to $2.45bn in potential future development, regulatory, and commercial milestones.

Phase 1 / 2 acquisitions:

- ***Gilead acquires Forty Seven for $4.9 billion***
  In March 2020, Gilead agreed to acquire Forty Seven for $4.9bn in cash. Forty Seven's investigational lead product candidate, magrolimab, is a monoclonal antibody therapy targeting the CD47 protein overexpressed on the surface of many types of cancer cells (i.e. an immunotherapy). At the time of the acquisition announcement, magrolimab was in the middle of a Phase 1b clinical trial.

- ***Merck acquires VelosBio for $2.8 billion***
  In November 2020, Merck announced that it would be acquiring VelosBio for $2.75bn in cash. At the time, VelosBio's lead investigational candidate – VLS-101, an antibody-drug conjugate targeting ROR1 – was being evaluated in Phase 1 and Phase 2 clinical trials for the treatment of patients with haematological malignancies and solid tumours, respectively. [The P2 trial had commenced only in October 2020.]

- ***Boehringer Ingelheim acquires NBE Therapeutics for €1.2 billion***
  In December 2020, Boehringer Ingelheim announced that it would be acquiring NBE-Therapeutics for €1.18bn. NBE-Therapeutics's lead compound, an antibody-drug conjugate named NBE-002, was in the middle of a Phase 1 clinical trial.

- ***Pfizer acquires Trillium Therapeutics for $2.3 billion***
  In August 2021, Pfizer agreed to acquire Trillium Therapeutics for $2.26bn in cash. Trillium had two lead candidates – both next-generation, investigational immuno-therapeutics for haematological malignancies – in Phase 1b/2 trials. The target launch date for both drugs (assuming successful clinical development) is 2026.

- ***Bristol Myers Squibb acquires Turning Point Therapeutics for $4.1 billion***
  In June 2022, BMS agreed to acquire Turning Point Therapeutics for $4.1bn in cash. Turning Point was a precision oncology company. Its lead asset, repotrectinib, is a next-generation, potential best-in-class tyrosine kinase inhibitor targeting the ROS1 and NTRK oncogenic drivers of non-small cell lung cancer and other advanced solid tumours. At the time of the acquisition announcement, repotrectinib had already been granted three Breakthrough Therapy Designations from the US FDA. It was midway through a P1/2 clinical trial.

Phase 3 acquisitions:

- ***Gilead acquires Immunomedics for $21 billion***
  In September 2020, Gilead agreed to acquire NASDAQ-listed Immunomedics for $21bn in cash. Immunomedics' lead product is a first-in-class antibody-drug conjugate, branded Trodelvy. Following a successful Phase 3 trial, Immunomedics had been granted FDA approval in April 2020 for the treatment of adult patients with metastatic triple-negative breast cancer who have received at least two prior therapies for metastatic disease.

  At the time of the acquisition, Immunomedics had only generated sales of $20m from Trodelvy (it had, after all, only just gone on market). The deal valued Immunomedics at over 5x peak sales of $4bn, which was estimated to be reached in 2029.

- ***GlaxoSmithKline acquires Sierra Oncology for $1.9 billion***
  In April 2022, GSK reached an agreement to acquire NASDAQ-listed Sierra Oncology for $1.9bn in cash. Sierra's lead candidate, momelotinib, is a JAK inhibitor for the treatment of myelofibrosis (an uncommon type of bone marrow cancer). It announced positive results from its Phase 3 trial in January of this year, and is awaiting FDA approval.

[For a comprehensive list of billion dollar dealmaking in the oncology world in 2020 and 2021 – including both licensing deals and acquisitions – please see the footnote below.[2]]

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When considering how Avacta may be valued against its peers, it is vital to keep in mind that pre|CISION is a *platform* technology. Not only that, but it is a *delivery* platform technology, that happens to be highly agnostic with regards to the classes of drug it could be primed to modify and deliver.

This means that it is immensely scalable (potentially *dozens* of existing oncology therapeutics could be enhanced by the pre|CISION substrate), and that its clinical development pathway is both shorter and lower risk than most other novel drugs in targeted oncology (no requirement for Phase 3 trials; and the efficacy of new drugs is not being tested (at least from scratch) in pre|CISION prodrug clinical trials).

We believe that these three fundamental advantages over other targeted oncology platforms place pre|CISION in a truly unique position. Accordingly, we think that the platform is deserving of a premium valuation rating over its peers.

That is before taking safety, tolerability and efficacy into account. In this note we have attempted to portray how pre|CISION prodrugs could well prove to be more effective, from a clinical perspective, than the current leading class of targeted therapy – the ADC.

[2] www.nature.com/articles/d43747-021-00024-y (2020)
www.nature.com/articles/d43747-022-00033-5 (2021)

Rationale for undervaluation?

It is one matter to point out that Avacta (or much more likely, the pre|CISION platform under new ownership) could ultimately be valued in the tens of billions of dollars. However, from an investor's perspective, it is also critical to point out why the wider investment community is not yet appreciating the blue sky upside that has been unlocked by the AVA6000 update in January.

- ***Lack of data published to date***
  In the AVA6000 update in January, Avacta confirmed the mechanism of action of the pre|CISION platform was performing in patients as (in fact, better than) management had hoped, i.e. that the safety and tolerability of AVA6000 had been improved drastically over standard doxorubicin; and that the pre|CISION substrate was being cleaved by FAPα in the TME, thus releasing active doxorubicin in tumour tissue.

  Avacta did *not* however provide any data from the trial. We have proffered in this note that that second aspect should be considered a proxy for *efficacy*. What else would doxorubicin do in the TME, when deposited there in "*therapeutically meaningful*" volumes?

  The wider market, however, evidently is waiting on hard data.

  As noted earlier, we anticipate this hard data will start to emerge in the next three weeks, in anticipation of Science Day, scheduled for 23 February. We then expect considerably more data to be published in the next 2-5 months, at the global oncology conference that we believe Avacta will attend, being either AACR in April or ASCO in June.

- ***Lack of understanding of the technology in the UK investment community***
  Avacta has given numerous and obvious signals to the market that it is sitting on an oncology delivery platform that could revolutionise the industry. Yes, Avacta *is* valued at considerably more than other clinical stage, pre-revenue biotechs listed on the LSE; but comparable peers listed on NASDAQ are valued at several (and in some cases, many) multiples of Avacta.

  Earlier this week, Avacta CEO Alastair Smith wrote in the *Letters to the Editor* section of *The Times* newspaper:

  "*In the past four years, 11 UK biotechs have chosen to make their initial public offering in the US. Why are we so bad at holding on to long-term value generated by our innovative science?*

  There are many factors but in my view it's primarily due to overburdensome regulation, compounded by a paucity of expert analysts to guide risk-averse UK investment managers."

  The last clause hits home. We are aware of only two analysts covering Avacta. The research of Stifel, the Company's Nominated Adviser and Broker, is not accessible to retail investors whatsoever. The research of Trinity Delta, an equity research house specialising in healthcare and life sciences, still attributes a 10% chance of success of AVA6000 – unchanged from what it was prior to the P1a trial commencing, 19 months ago. In those 19 months, Avacta has announced that both aspects of the delivery platform are 'working' even better than management had hoped for.

  It hardly requires reading in-between the lines of Dr Smiths' letter, to perceive that he is frustrated by the lack of understanding – both of UK analysts and investment managers – of the enormity of what Avacta is achieving.

- ***A story that appears too good to be true***
  We are of the belief that the pre|CISION platform could revolutionise cancer treatment efficacy *and* patient experience, multiply the total addressable market, and reset the clocks on patents and exclusivity – and all that with a lower clinical risk, lower cost and shorter development timeline than developing novel drugs.

We do appreciate the seeming absurdity of the next statement, but in our view: the total revenue opportunity, at peak sales, of all drugs that could be modified and improved with the pre|CISION substrate, could ultimately run into the many tens of billions of dollars. Avacta's current market capitalisation is £435m – even though the 'pathfinder' drug, AVA6000, has indeed just proved that the delivery technology works *at least* as well in humans as it did in mice.

In our experience, stocks that appear "*too good to be true*" usually are, and do not live up to expectations. Many market participants evidently consider Avacta to be one such stock, and are of the opinion that the bull case for the pre|CISION platform that we have presented in this note, simply will not come to fruition for one reason or another.

As Avacta begins to deliver hard data from the AVA6000 trial and other pre-clinical studies, and signs its first licensing deals, we expect that this doubt within the UK investment community will begin to evaporate, and Avacta's share price to respond accordingly.

Possible Next Steps for Avacta Therapeutics

Global rollout of the pre|CISION platform: a task far too large for Avacta to achieve singlehandedly?

In the above pages, we hope that we demonstrated that there is, at the very least, a real possibility – and frankly, we believe a real *probability* – of Avacta's pre|CISION technology transforming the treatability of cancer.

As ever, though, nothing in this world comes free. Each pre|CISION prodrug will have to be put through a Phase 1 dose escalation trial. Each will then have to be put through a dose expansion phase, with at least 20 patients required *for each tumour target*. Thereafter, each prodrug will have to complete a Pivotal Phase 2 trial, which may require 50-100 patients, again for each tumour target.

Whilst the cost savings of not having to complete Phase 3 trials for pre|CISION prodrugs (in comparison to most other novel oncology drugs) will be substantial, the cash required to run multiple Phase 1a, Phase 1b and Pivotal Phase 2 trials – in tandem – will still be very considerable.

If the pre|CISION technology – validated by the upcoming AVA6000 P1a data – is as revolutionary as we believe it to be, then there will be an urgent need, from a clinical perspective, to bring a whole suite of pre|CISION prodrugs to market as quickly as possible.

With its current balance sheet and human resources, Avacta doesn't have the capacity to bring AVA6000 to the market, even at half speed – elsewise we would see an intention to commence a much larger Phase 1b (dose expansion) study immediately after Phase 1a, encompassing for example 5-6 tumour targets when used as a monotherapy, and another 3-4 targets when used in combination with other therapies (such as Keytruda).

Vast sums of cash are required to commercialise and roll out multiple pre|CISION prodrugs, simultaneously, so that cancer patients may benefit from the breakthrough technology as soon as possible.

Broadly, there are three ways that this could be achieved.

1) Avacta secures licensing deals, and/or possibly major partnerships

In a typical licensing deal, a licensee will pay the owner (or licensor) of the drug an upfront cash sum, and will be required to make various milestone payments to the owner, as the drug successfully passes clinical milestones and receives marketing approval. Thereafter the owner is usually also entitled to royalties on sales. The licensee is also typically required to fund the lion's share – if not all – of the clinical development costs. In return, the licensee typically is entitled to the large majority of revenues generated by sales of the drug until patent expiry (or otherwise stated in the deal).

For smaller biotech companies such as Avacta, licensing out assets to larger players is a well-trodden path, and brings two key benefits. Firstly, the strategy uses the balance sheet of the licensee to progress the therapeutic through clinical development. Such cash preservation is often very welcome amongst shareholders of pre-revenue, heavily lossmaking biotech companies. Secondly and in the same vein, the upfront cash component of a licensing deal removes the requirement for an equity placing, thus staving off dilution for shareholders.

AVA6000 has now successfully proved the mechanism of the pre|CISION delivery system in humans. Owing to Avacta's already deep in-house pipeline of prodrugs, as well as to the broad applicability of the pre|CISION substrate, Avacta is now ideally placed to secure a very wide range of licensing deals with larger drug developers. Here a just a few theoretical examples of the many licensing opportunities now open to the Company:

- Licensing out AVA3996 or other earlier stage prodrugs in Avacta's in-house pipeline. The examples of pre-clinical collaborations provided on p.25 should be a useful guide for readers, on just how much cash Avacta could raise – both upfront and in milestone payments – in such a licensing deal.

- Licensing out AVA6000 for only a single, or limited number of, targets (e.g. soft-tissue sarcoma); or for marketing rights in only one particular territory (e.g. China).

- Licensing out the pre|CISION substrate to an entity developing a novel ADC or chemotherapy.

- Licensing out the pre|CISION substrate to an owner of an existing therapy (chemotherapy, ADC, other small molecule, biologic), so that the owner can modifying the therapy, and relaunch it into the market as an improved drug.

It may be that Avacta decides to partner with a single major from Big Pharma (such as Novartis or AstraZeneca). The benefits in doing this would be in having the access to very deep pockets, and human resources, required to accelerate the development of the entire pre|CISION portfolio. The downside to such an arrangement would be in the ceding of total control of the platform at such an early stage in its commercialisation – thus potentially missing out on greater value for shareholders in the long-term.

[In addition to the obvious benefits of a cash injection, a licensing deal would be considered very favourably by the investment community, as third part validation of the pre|CISION platform.]

2) <u>Avacta goes it alone with a NASDAQ listing</u>

Avacta has stated publicly that it wishes to keep AVA6000 in-house – and possibly AVA3996 too – for as long as possible. It is highly improbable that Avacta will ever go the whole way and bring its therapeutics to market itself, transforming itself into a vertically integrated pharmaceutical company. However, by funding AVA6000 in-house for as long as possible (right up through to FDA / MHRA approval), the Company would subsequently enjoy a much larger share of the revenue split with its commercial partner, who would be brought on board to take charge of commercialisation / distribution.

[Hypothetically, a licensing deal signed now might deliver a 10% to 12% royalty on net sales to Avacta; whereas if the Company brought AVA6000 through to marketing approval itself, its ultimate revenue share may be around the 30% mark.]

As discussed above, progressing multiple prodrugs (each targeting multiple tumour types) through the clinic simultaneously will burn through vast sums of cash. Hundreds of millions of dollars, in fact. However, the potential upside is of course phenomenal.

The London Stock Exchange – or more accurately, its investment community – has demonstrated that it is not a particularly apt home for pre-revenue biotech companies, regardless of their potential. If Avacta wants to go it alone for as long as possible, it'll need to start raising fresh equity in $100m+ blocks, minimum. That is difficult, with a market capitalisation of only £435m, and also unpalatable to existing shareholders.

The US investment community is much happier to value pre-revenue biotech on long-term potential – and to invest the sort of sums of cash that Avacta Therapeutics will require to accelerate the in-house clinical development of multiple pre|CISION prodrugs.

In our view, Avacta should secure at least one licensing deal to both bring in an immediate and substantial cash sum, and to drive up the Company's market capitalisation, before seeking a listing on NASDAQ (and a simultaneous fundraise with US investors) at a much higher share price.

3) <u>Avacta Therapeutics is acquired by Big Pharma</u>

The final option for getting a suite of pre|CISION prodrugs to the market as soon as possible, would be for a top tier pharmaceutical company to acquire Avacta (or perhaps more likely, just Avacta Therapeutics) outright, and then launch a dozen prodrugs into pre-clinical development simultaneously, whilst advancing AVA6000 into Phase 1b for 5-6 tumour targets.

Is this likely? Management and shareholders alike are now acutely aware of the immense inherent value in the pre|CISION platform, following the AVA6000 update last month; and of the vast disconnect between current market capitalisation and said inherent value.

As such, it would likely require an exceptional premium to the current share price of 161p, for the Board to even consider bringing any proposed offer to shareholders.

That said, it is possible. On pp.26-27, we detailed notable acquisitions in the targeted therapy space over the past three years. Two of them are particular standouts:

- ***The acquisition of Forty Seven by Gilead, in 2020, for $4.9bn cash***

- ***The acquisition of Turning Point Therapeutics by BMS, in 2022, for $4.1bn cash***

Forty Seven's lead drug was only in a Phase 1b trial; whilst Turning Point's was in Phase 1/2. This is the stage Avacta will be at, later this year.

These are very real, very recent and very relevant transactions. They set precedent for Avacta to be acquired for a sum in the range $4.1bn to $4.9bn, *this year*. That would equate to a share price range of £12.30 to £14.71.

Of course, there is much more to relative valuation analysis than just highlighting acquisition values of companies similar to Avacta in size and development timelines. Nevertheless, the deals do assist in highlighting the very large sums that Big Pharma is willing to pay for promising targeted therapeutics in oncology.

It has been suggested by industry analysts (which has been picked up in the financial press) that Big Pharma is primed for an M&A spending spree in 2023, with the majors sitting on a combined war chest of half a trillion dollars. Who might theoretically be interested in acquiring Avacta Therapeutics?

GSK is trying to rebuild its capability in oncology. It's on the hunt for biotechs – especially for those focussed on cancer therapies – that are "*hiding in plain sight*", to quote the company's chief commercial officer.

Swiss giant ***Novartis*** is a next-door neighbour of Avacta, following the relocation of the Therapeutics division to West London last year. It has plenty of cash to deploy; has stated it is on the lookout for acquisitions; and has recently demonstrated an interest in FAPα-targeting therapeutics, having acquired the lead clinical asset of Clovis Oncology for up to $681m, when Clovis filed for bankruptcy last December.

The other Swiss giant, ***Roche***, has an even greater interest in FAPα-targeting therapeutics, as is demonstrated in the table on p.13.

Given that pre|CISION prodrugs will be a director competitor to the ADC class, we presume that the leading ADC players, notably ***AstraZeneca*** and ***Gilead Sciences***, could also be watching Avacta closely.

Concluding Remarks

We are of the belief that the pre|CISION platform could revolutionise cancer treatment efficacy and patient experience, multiply the total addressable market, and reset the clocks on patents and exclusivity – and all that with a lower clinical risk, lower cost and shorter development timeline than developing novel drugs.

Prior to reading this note, we appreciate that readers may have considered the above statement completely ludicrous. We hope that in the preceding pages, we have demonstrated that this could become a reality, now that the proof of concept for the platform has been so successfully proved by AVA6000 in man.

The beauty of the science is in its simplicity. FAPα is found in very high concentrations in most solid tumours (which account for circa 90% of cancer cases in adults), whilst present in very low concentration elsewhere in the human body (plasma, healthy tissue). As such, pre|CISION prodrugs should not only be 'tumour-agnostic', but also should 'mop up' any smaller secondary tumours (even those not yet identified).

As FAPα is present primarily on stromal cells in the tumour microenvironment, and less so on the surface of cancer cells themselves, tumours should find it more difficult to build resistance to pre|CISION prodrugs, than they do to drugs such as ADCs that target antigens *on* the surfaces of cancer cells.

Moreover, without a biologics component, pre|CISION prodrugs will be significantly cheaper to manufacture than those classes of drugs that do have one (namely, immunotherapies and ADCs).

In short, we see pre|CISION prodrugs ultimately becoming the standard-of-care for many different tumour types – both as monotherapies and in combination with other drug classes such as immunotherapies.

No one else has ben able to successfully develop a drug that uses FAPα as a cleaving mechanism. There are not even any other such therapeutics in clinical development, as far as we are aware. Avacta's exclusive, global license of the pre|CISION platform from Bach Biosciences and Tufts University until patent expiry (early 2030s to early 2040s), ensures that only *it* can develop pre|CISION prodrugs in that time period – each of which Avacta can then individually patent for another 20 years, upon successful development.

In this light, it is straightforward to see how the owner or licensee of the pre|CISION platform (at this stage, Avacta) could dominate the chemotherapy market over the next 2-3 decades.

Avacta's dilemma now is, how to capitalise on such a colossal commercial opportunity? How to finance the accelerated pre-clinical and clinical development of a dozen or more prodrugs spanning multiple tumour targets, which will require many, many times the resources (both cash and human) that the Company presently has at its disposal?

There are several paths that the Company could take, as we detailed on pp.30-32. We have no idea which one it will take, but we are very confident that equity holders are likely to reap substantial rewards going forward.

It is unusual that the investment community is given a heads up on how a clinical trial has been faring, before the completion of that trial. These words of CEO Alastair Smith, in the January interview, are vital:

"The data are unequivocal. I'm delighted to say that doxorubicin is being released in the tumour tissue, and at significant levels – therapeutically relevant levels."

If one believes that this should be accepted as a proxy for efficacy – that anti-tumour activity will be inevitable, as a result of delivering active chemotherapy to the tumour in significant concentration – then the thesis set out in this note should be valid.

We strongly believe that it *should* be accepted as a proxy for efficacy, and anticipate confirmation in the data that Avacta will publish shortly.

Appendix I: the TMAC® Platform

The 'TMAC platform' – derived from 'tumour microenvironment activated drug conjugates' – is built on both Avacta's Affimer technology and Bach's pre|CISION technology. In essence, TMAC molecules utilise immunotherapy and chemotherapy in a single, extremely potent anti-cancer treatment that is highly targeted to the tumour.

Unlike the pre|CISION technology – which is exclusively licensed by Avacta from Bach – the TMAC platform is a co-invention of Avacta and Bach, with the patent application jointly owned.

Antibody-drug conjugates ('ADC') are a relatively new form of anti-cancer drug, and have demonstrated huge promise thus far. In order to appreciate the potential of the TMAC platform, it is important to first understand the mechanism of action of this competing, first-generation technology. In very simple terms, ADCs were designed to target anti-cancer agents specifically to the tumour – as Avacta's pre|CISION technology has been designed to do. However, the mechanism of action of an ADC differs somewhat from pre|CISION. A conventional ADC is comprised of three components:

- ***Targeting moiety***
  This is the monoclonal antibody (or antibody mimetic) itself, the role of which is to localise the drug conjugate to the tumour, to deliver the drug payload (or 'warhead') specifically to cancer cells. The antibody targets a specific antigen only found on target cells. Once it binds to the cell, it triggers internalization of the antibody, together with the drug payload (or 'warhead').

- ***Linker***
  The linker physically binds the targeting moiety to the warhead. In conventional ADCs, the linker is designed to be cut by certain enzymes *after* the drug conjugate is internalised by the cancer cell, thus releasing its warhead inside the cell. This is a similar technology to Avacta's pre|CISION substrate, in that the linker renders the warhead inert whilst it moves through the body and bypasses healthy tissue.

- ***Warhead***
  This is a powerful anti-cancer agent, such as a chemotherapy. It remains inactive when attached to the targeting moiety via the linker; but, once internalised and released inside the cell's cytoplasm, has a cytotoxic activity (i.e. cell-killing).

It is important to note that Avacta has explored the use of Affimers in drug conjugates in collaborations, both before and after the invention of the TMAC platform. An Affimer-drug conjugate ('AfDC') employs the same mechanism of action as an ADC, but with the obvious difference of utilising an Affimer instead of a monoclonal antibody as the targeting moiety.

Avacta's TMAC molecule, however, employs a different mechanism of action to the conventional drug conjugate. It is comprised of the same three components, but has several key differences:

- ***Targeting moiety AND immunotherapy – the Affimer***
  The Affimer component of the TMAC molecule provides a dual role. Firstly, its tumour-targeting capabilities come into play: it takes the DC directly to the tumour mass, as it is specific only to a certain type of antigen present on the surface of cancer cells.

  Unlike the antibody component of conventional ADCs, however, the Affimer does not need to be internalised by the cancer cell. This is as a result of the unique pre|CISION substrate (see below), which enables the linker between Affimer and warhead to be cleaved in the tumour *microenvironment* – the ecosystem immediately *around* the tumour (including the surrounding blood vessels, immune cells, fibroblasts, etc.). Conversely, the linkers that are used in existing ADCs can only be cleaved by enzymes *inside* the cancer cell. Thus the targeting moiety of a conventional ADC – the monoclonal antibody – must first be internalised, taking the warhead with it.

The monoclonal antibody component of a conventional ADC therefore cannot offer a second function to the therapeutic, beyond being a targeting moiety.

The Affimer in a TMAC molecule *can* offer an additional function, as it need not be internalised by the cancer cell to release the warhead. In its first two TMAC molecules, Avacta has incorporated an Affimer that also acts as an immunotherapy – namely, an inhibitor of the immune checkpoint, PD-L1.

PD-L1 receptors are checkpoint proteins located on the external surfaces of cancer cells. PD-L1 can bind to an opposing checkpoint protein on a T-cell, named PD-1, and in doing so prevent that T-cell from binding elsewhere with the cancer cell and destroying it. In effect, the PD-L1 / PD-1 pathway can encourage tumour growth.

By binding to PD-L1, the Affimer component of the TMAC molecule prevents the binding of the 'T-cell blocking' pathway between PD-L1 and PD-1 – thus enabling T-cells to more freely bind to and attack cancer cells.

It is important to note that there could be *multiple* Affimers incorporated into a single TMAC molecule that might block different types of immune checkpoints, to enhance the support given to the patient's immune response.

- ***Linker – the pre\|CISION substrate***
  As explained on p.3-4, the pre\|CISION substrate is only cleaved by FAPα, an enzyme that is highly upregulated (i.e. found in large, concentrated quantities) in the tumour microenvironment of most solid tumours. Thus it not only renders the warhead component of the TMAC molecule inert whilst moving through the body, but it also enables both the warhead *and* the Affimer to have a therapeutic effect *outside* of the cancer cell. This greatly expands the mechanisms of action possible.

- ***Warhead – wider range of options available***
  For circa 30% of tumours, the immune system is already present in the tumour mass – even if not active. Such tumours are known as 'hot' tumours. In the other circa 70% of tumours, there is no immune infiltration. No T-cells are present within the tumour mass. These are referred to as 'cold' tumours.

  The warhead that Avacta has selected for its first two TMAC molecules is a potent anti-cancer drug named I-DASH Inhibitor. This warhead attacks various bystander cells in the tumour microenvironment (once it has become active), such as macrophage and NK cells. This causes a massive pro-inflammatory response within the tumour microenvironment. The inflammatory response enables the patient's immune system – which will have been on the periphery of the tumour mass – to enter the tumour itself and also attack the cancer cells. This in turn causes the immunotherapy component of the TMAC molecule (i.e. the Affimers) to kick in, as the tumour has turned from 'cold' to 'hot'. The Affimers enhance and sustain the attack of the immune system.

In summary then:

- The TMAC molecule is comprised of three components, each with a dual role:

  i) ***Affimer(s)*** acts as both the targeting moiety and a supporting immunotherapy;

  ii) ***pre\|CISION substrate*** acts as the linker, which serves to both hold the molecule together, and to ensure highly specific targeting to the tumour microenvironment;

  iii) ***Warhead*** not only directly destroys cancer cells, but also serves to turn 'cold' tumours, 'hot'.

- The Affimer's targeting ability (to specific immune checkpoints on the surface of cancer cells) results in an accumulation of TMAC molecules in the tumour microenvironment.

- On the journey to the tumour, healthy tissues are unharmed, as the warhead component of the TMAC molecule is inactive (FAPα enzymes capable of cleaving the pre|CISION linker and activating the warhead are in very low concentration in healthy tissue).

- Upon reaching the tumour, FAPα enzymes that are present in high concentration only in the tumour microenvironment are activated and *cleave* the linker.

- At this point, the warhead becomes active. A major inflammatory response within the tumour microenvironment occurs, as the potent cytotoxins attack various bystander cells. The 'cold' tumour becomes 'hot'.

- The T-cells of the patient's immune system are now able to identify the tumour as unhealthy; infiltrate it; and attack the cancer cells.

- The Affimer component of the TMAC molecule (be it a monotherapy or a bispecific) enhances and sustains the attack of the immune system. It is not simply a targeting moiety, but an active immunotherapy.

The TMAC molecule destroys tumours by a triple combination of deployment of toxic warheads (e.g. chemotherapies); triggering of the innate immune system (turning cold tumours 'hot' to mobilise white blood cells against the tumour); and synthetic support of the immune system's response (i.e. Affimers working as an immunotherapy).

To our knowledge, the TMAC platform is the *only* drug class in existence that combines immunotherapy with targeted chemotherapy in a single drug molecule.

As with the pre-clinical data for the pre|CISION platform (AVA6000), the initial in-mouse data generated by Avacta's first TMAC molecules have been extraordinary. In a pre-clinical trial of one particular (undisclosed) TMAC molecule, the Company used a colorectal tumour model ('CT26'), which is renowned as a tough, 'cold' tumour model. 60% of the animals experienced full regression of the tumours. Moreover, those animals that experienced full tumour regression then had a T-cell mediated immunity to being re-challenged with the same tumour, 60 days later.

Disclosure

The author of this paper, Myles McNulty, is a private investor. He holds shares in Avacta Group.

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