AVACTA GROUP LTD

THE PRE|CISION™ PLATFORM

21.04.2022

Ticker:	**AVCT.L**
Price (p):	**136.0**
Shares in issue (m):	**255.3**
Market cap. (£m):	**347.2**

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

Introduction

Avacta Group ('Avacta') is a biotechnology company listed on the London Stock Exchange's growth market, AIM. At the core of its business is a proprietary technology, the Affimer® platform. Affimers are small, single domain binding proteins derived either from Stefin A in humans, or from Cystatin A in plants. They possess a number of qualities that make them ideal for use both in a therapeutics setting and in diagnostics applications. The Affimer platform is an 'antibody mimetic': it was specifically designed to overcome the numerous and varying limitations of *antibodies*, which are the market standard, core 'building blocks' in both therapeutics and diagnostics. The global market for antibody-based diagnostic and therapeutic applications was worth $146 billion in 2021, and is estimated to reach $249bn by 2026. Thus there is evidently a colossal commercial opportunity for Avacta, if it is able to gradually displace monoclonal and polyclonal antibodies from diagnostic and therapeutic applications, and introduce its superior – and critically, *proprietary* – Affimer platform into these applications instead.

However, it is Avacta's second platform technology – pre|CISION™, that the Company has exclusively licensed from Tufts University School of Medicine in the US – that is the focus of this research note.

At the heart of the pre|CISION platform is a novel linker technology that can be used to develop chemotherapy prodrugs or drug conjugates. In short, the pre|CISION linker ensures that the drug will only be activated at the site of the tumour itself. This compares to standard-of-care chemotherapies that activate indiscriminately, thus killing tumour tissue and healthy tissue alike.

The primary reason for most patients stopping chemotherapy treatment is because of severe side effects such as cardiotoxicity (i.e. damage to the heart) caused by the chemotherapy itself. If Avacta can prove that the pre|CISION technology works in humans in a similar manner to how it has performed in animal models (which yielded extraordinary results), the platform could go on to develop multiple chemotherapy 'prodrugs'. As these drugs would cause drastically reduced side effects compared to conventional chemotherapy drugs, patients could endure multiple more treatment cycles – and at higher doses – thus *significantly* increasing their chances of survival.

In August last year, Avacta commenced its first clinical trial – a Phase 1a study for 'AVA6000', a pre|CISION prodrug form of the well-known chemotherapy, doxorubicin. This first stage of the Phase 1 trial is due to complete in the middle of 2022. Although Avacta has been very guarded with the data generated over the first eight months of the trial, there are multiple positive indicators that suggest the trial is progressing exceedingly well.

We believe that in the coming weeks, interest from the investment community in Avacta could build rapidly, due to a number of potential major news catalysts and to the rapidly approaching top line data for the AVA6000 P1a trial. The purpose of this note is to explain, in layman's terms, the science behind pre|CISION; to detail how the AVA6000 trial is progressing; and to express why we think the pre|CISION platform could potentially revolutionise chemotherapy as we know it, and impact the wider oncology industry.

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 success of 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').

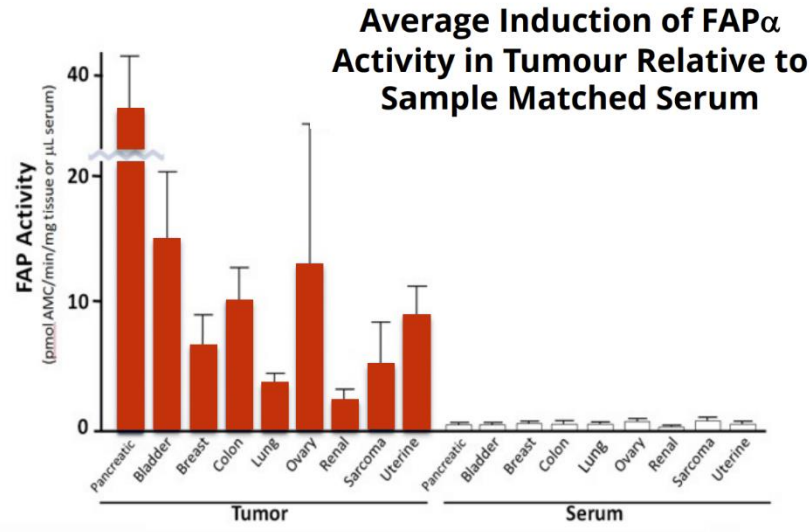
The chemistry itself is a *substrate* – a molecule on which a particular enzyme acts – developed by Professor Bachovchin. The chemical substrate is highly specific to an enzyme called fibroblast activation protein-α ('FAPα'). The FAPα enzyme is highly upregulated (i.e. found in large, concentrated quantities)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

Critically, the pre|CISION substrate is not 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.

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.

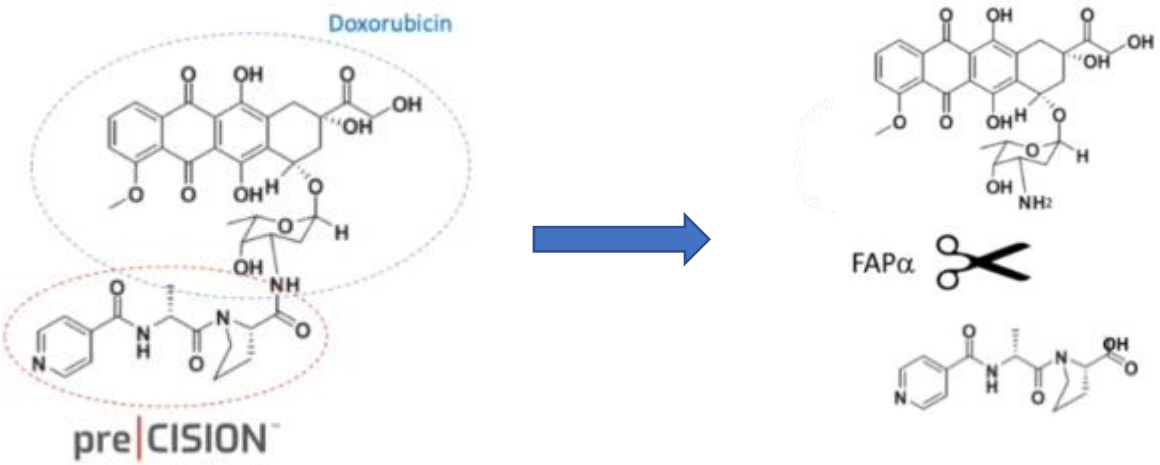


Now to the chemotherapy prodrug itself. Using Avacta's first prodrug under development, AVA6000, as an example:

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.

Avacta believes that these dose limiting toxicities *could* be drastically reduced – or even removed entirely – by the attachment of its 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 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.

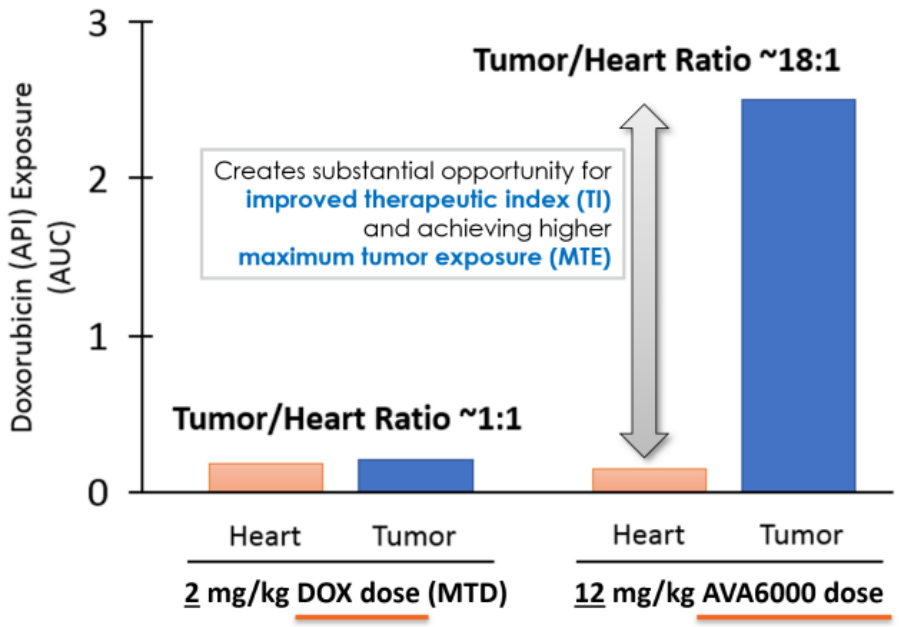
The First pre|CISION Prodrug: AVA6000

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

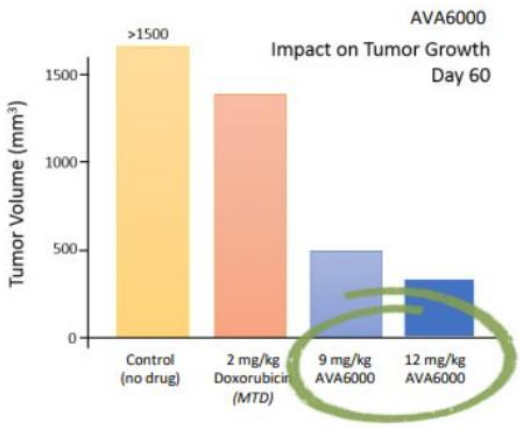
The highest AVA6000 dose administered (at 12 mg/kg) was 6 times more concentrated than the doxorubicin dose administered (at 2 mg/kg). The latter was the MTD equivalent; it could not have been increased further without unacceptably high risk of mortality (through severe cardiotoxicity).

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 before ever reaching the TME).

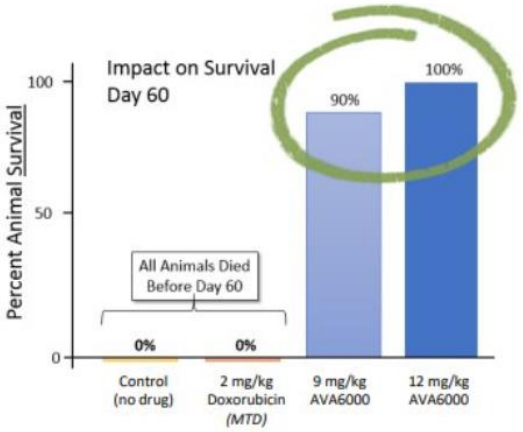
So whilst the AVA6000 dose was 6 times as concentrated as the standard doxorubicin dose, the distribution ratio of doxorubicin in tumour tissue relative to heart tissue was 18:1.

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.

Phase 1 trial: commenced on 11 August 2021

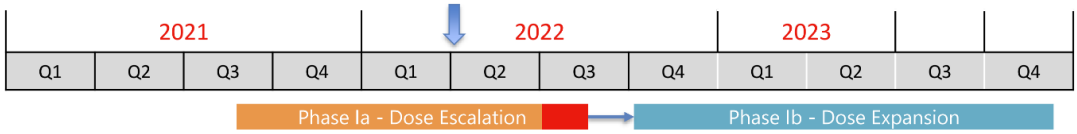
In February 2021, Avacta received approval from the Medicines and Healthcare Products Regulatory Agency ('MHRA') for its Clinical Trial Authorisation ('CTA') in the UK for a Phase 1 ('P1') study of its lead pre|CISION prodrug, AVA6000. Phase 1 studies typically focus on the safety and tolerability of 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.



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.

P1a is structured into 3-4 'cohorts' of 3-5 patients each, with cohorts running consecutively.

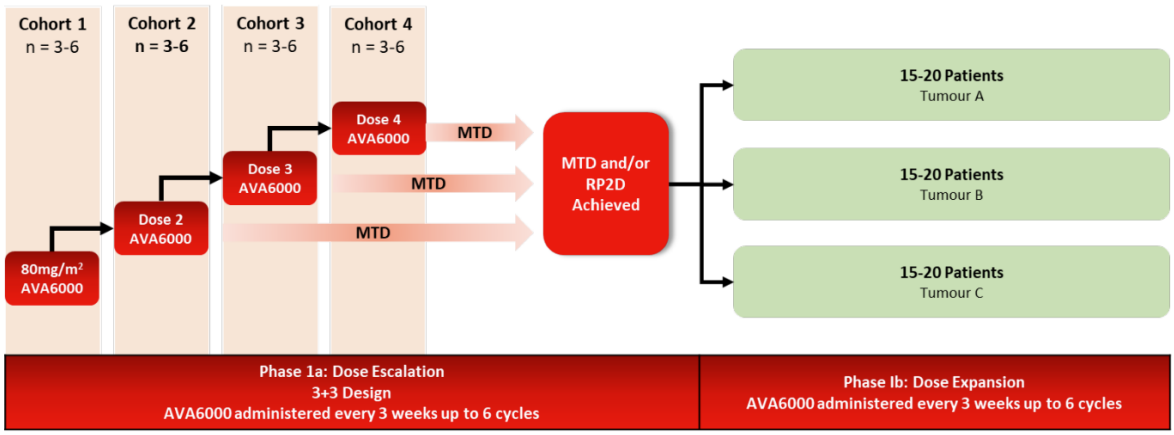
Patients are dosed once every 3 weeks with AVA6000 via intravenous infusion, until disease progression, unacceptable toxicities, withdrawal from treatment for other reasons, reaching maximum lifetime cumulative exposure to doxorubicin, or death – whichever occurs first.

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

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.

The first patient in C1 was dosed on 11 August 2021. By February this year, a total of four patients had been recruited to C1 and dosed multiple times.

On 3 February, 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.



Is it working?

The multi-billion dollar question.

The AVA6000 trial has now been running for over eight months. Throughout that time, Avacta has guarded the clinical data very closely. The only definitive clinical progress reported in the period has been the first dose escalation in February (i.e. the launch of C2).

However, in its 2021 Preliminary Results published on 6 April, Avacta confirmed that the full data readout for P1a was still expected "in the middle of 2022".

For the investor, logic and inference are thus required until that data readout.

Firstly, let us consider the question itself: *is AVA6000 working*? Very basically, the answer is conditional on *two* sets of biological reactions regarding the pre|CISION substrate component of the AVA6000 molecule.

1) The pre|CISION substrate ***must not*** be hydrolysed either by freely circulating FAPα in the human body, or by other enzymes closely related to FAPα. This will ensure enhanced ***safety and tolerability*** relative to standard doxorubicin, as healthy tissues will no longer be harmed by active doxorubicin.

2) The pre|CISION substrate ***must*** be hydrolysed by FAPα in the tumour microenvironment. This will result in ***anti-tumour activity***.

If *both* of these are occurring, AVA6000 has a high probability of 'working' in human patients. [There are in fact several more important questions that Avacta's CEO explained recently to investors – but for the lay investor, these two are the most critical.][1]

It is straightforward to perceive that 1) is currently occurring, owing to the fact that the trial's SDMC recommended a 50% increase in dose concentration for C2, following a review of the safety data from C1. At least three patients in the first cohort were dosed as many as six times (and possibly more) with an AVA6000 drug that was only circa 10% less potent than the MTD of standard doxorubicin.

Bear in mind that at the increased dose of 120mg/m², the AVA6000 being used in C2 is equivalent to a standard doxorubicin dose of 81mg/m² - which is some 35% more potent than the MTD of standard doxorubicin used in treatment today. Six doses of this concentration of AVA6000 would equate to 481 mg/m² in total – which exceeds the recommended limit for lifetime cumulative doses of 450mg/m² for standard doxorubicin.

It is also worth noting that a 50% increase in dose for C2 patients relative to C1 patients, is a large initial leap in dose concentration. In a research paper published last year, the American Society of Clinical Oncology ('ASCO') recommended that a 50% dose increase should only be made if the highest grade of toxicity experienced by patients in the previous cohort was grade 1.[2] ASCO's recommendations were based on toxicity grades defined in the Common Terminology Criteria for Adverse Events ('CTCAE'), which is an internationally accepted standard for defining and categorizing adverse events.

The CTCAE's definition for 'Grade 1' adverse events:[3]

"*Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.*"

Whether or not Avacta is following the ASCO recommendations is another matter. However, logic suggests that such a substantial increase in dose concentration for C2, indicates that the patients in C1 had no serious issues whatsoever in tolerating the side effects (if any) of the AVA6000 dosing course.

[1] avacta.wistia.com/medias/kv40kul5b2 (from 02:53)
[2] www.ascopubs.org/doi/full/10.1200/EDBK_319783
[3] ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

With regards to C2: the first patient in the cohort will now have been dosed four times at 120mg/m². The trial has not been stopped – which would have been the case, had the patient experienced dose limiting toxicities.

Furthermore, simply by stating in the Preliminary Results that the P1a full data readout is on track for "the middle of 2022", Avacta is implying that further cohorts will be launched – and thus that further dose escalations will occur. In fact, in the investor presentation, management stated that there will be "probably four cohorts" in total, in P1a. That would entail two further dose escalations from the current dose concentration being used in C2. If management was confident in stating that only two weeks ago, clearly the safety and tolerability data for the patients in C2 remain very impressive.

Accordingly, it seems a near-certainty that the pre|CISION substrate is ***not*** being hydrolysed either by freely circulating FAPα in the human body, or by other enzymes closely related to FAPα. One half of the biological challenge has already been achieved: Avacta has a technology that can circulate chemotherapies in the human body that causes drastically reduced adverse side effects, relative to conventional chemotherapies.

The more difficult question to answer is the second biological challenge. Yes, the pre|CISION substrate in AVA6000 is not activating in healthy tissues, thus ensuring the doxorubicin remains inert whilst circulating throughout the body; but is the substrate actually being cleaved at the site of the tumour microenvironment, thus permitting doxorubicin molecules to diffuse into cancer cells, and anti-tumour activity to occur?

This is where we as investors must apply logic, until the 'top line' data readout this summer. Only via the analysis of tumour biopsies will the Company definitively know whether the cleavage of the substrate and activation of doxorubicin in the TME is actually occurring.

Avacta has stated that it is confident of obtaining biopsies from patients (although it is not mandatory for patients in P1a). However, even if and when those biopsies are obtained, it is improbable that the Company will provide commentary before the full data readout.

In the meantime, then, we must make use of other methods of data collection that have been utilised in the study from the outset.

Whilst the primary objectives of P1a are to evaluate safety and tolerability, and to find the MTD and/or RP2D, the *secondary* objectives are to characterise the pharmacokinetics ('PK') of:

- the AVA6000 molecule itself;
- the pre|CISION leaving group (i.e. the cleaved substrate);
- the active metabolites of AVA6000 (i.e. the products of the enzyme reaction) – namely doxorubicin and doxorubicinol.

The key PK data being recorded are: the movement of each of the above molecule groups, and for how long they are staying in certain places – in plasma, urine and tumour tissue.

[A second secondary objective focuses on anti-tumour activity – which, as explained above, relies on the analysis of tumour biopsies.]

In greenlighting a dose escalation of 50% for C2, the trial's Safety Data Monitoring Committee must have not only examined the data pertaining to the safety and tolerability of AVA6000 (patient wellbeing), but also the PK data in blood and urine. Amongst many other data points, the SDMC would have noted the metabolites and the leaving group in urine. That would infer that the AVA6000 molecule is being cleaved *somewhere* in the patient's body.

We can confidently assume this, because if only whole AVA6000 molecules were present in the urine, then that would imply that the drug was simply passing straight through the patient, without activating whatsoever. In such an event, the trial would have been paused.

To recall: the considerable uplift in dose escalation for C2 (+50%) implied that the C1 patients experienced, at worst, only mild side effects.

So, we can infer that somewhere within the patient, AV6000 is being cleaved – which would entail that somewhere, doxorubicin is becoming 'active' (i.e. diffusing into cells and destroying them).

Were doxorubicin becoming active in healthy tissues, we know that the side effects would have been substantially more severe than 'Grade 1', as defined by the CTCAE (i.e. only asymptomatic or mild symptoms). Common side effects of *standard* doxorubicin include hair loss; nausea and vomiting; sores in the mouth and on lips; darkening of the soles, palms, or nails; diarrhoea; etc.

The most logical explanation, therefore, is that AVA6000 is activating in unhealthy tissues – namely, in the tumour microenvironment.

Needless to say, this deductive reasoning could be incorrect. Something entirely different could be occurring with the AVA6000 molecules within the body. That is the reason the tumour biopsies are so crucial. They represent *physical evidence*, as opposed to *inference*.

However, numerous activities on the part of Avacta and other entities involved in the AVA6000 trial, suggest that they themselves are making this inference regarding AVA6000 activating at the site of the TME:

- ***Indications by management and additional hospital openings that there will be further cohorts***
  In the 2021 Preliminary Results published in early April, and in the accompanying video presentation delivered by management, it was made clear by the Company – on multiple occasions – that:

  "*The dose escalation phase is anticipated to complete in the middle of 2022 with minimal delay and should be followed by initiation of the dose expansion phase in 2022 which would be expected to complete by the end of 2023*."

  CEO Alastair Smith also stated:

  "*We expect to go through three, or probably four, cohorts. That's certainly the timeline that we've described – to go through four cohorts*."

  Consider that this statement was made over two months after the first dosing of the first patient in C2. At this point in time, that first patient would have just received their fourth dose of AVA6000 (assuming said patient had not dropped out of the trial). It is highly probable that the second and third patients would also have received multiple doses. As such, for the CEO to state confidently, only last week, that they would probably be going through *four* cohorts, speaks volumes as to the quality of the data.

  On the day of the Preliminary Results (6 April), a fourth site in the UK – The Beatson West of Scotland Cancer Centre, in Glasgow – joined the existing three hospitals in England in screening for new patients for the AVA6000 P1a trial.

  Again, assuming that all patients in C2 had already been recruited and dosed multiple times, it stands to reason that the Safety Data Monitoring Committee and Avacta are extremely confident in launching both C3 and C4.

  Remember – whilst the primary objectives of P1a are to evaluate safety and tolerability, the SDMC would have analysed the PKPD data from C1 and C2, and *inferred* that cleavage of the pre|CISION substrate was likely occurring at the TME. Had no cleavage at all been occurring, then would additional hospitals that could only be recruiting for C3 and beyond, be opening now?

- ***US FDA Approval for Investigational New Drug Application for AVA6000***

  On 29 November 2021, the US Food and Drug Administration ('FDA') approved Avacta's Investigational New Drug ('IND') application for AVA6000. This enabled Avacta to expand its Phase 1 trial into clinical trial sites in the US.

  The FDA has a 30-day review and turnaround time for such applications. Accordingly, we can assume that Avacta submitted the IND application around 22-26 October. The first patient in C1 at the Royal Marsden, London was dosed on 11 August, and so would have received their 4th dose on 13th October.

  The IND application was obliged to contain "*any previous experience with the drug in humans (often foreign use)*." [4]

  As with the first bullet point above, the FDA would not only have examined safety and tolerability, but the early PKPD data – from which it would have inferred activation of doxorubicin somewhere in the patient.

  Separately, but following on from the first bullet point, Avacta confirmed in its Preliminary Results presentation that two US clinical trial sites are currently being initiated and should contribute to the dose escalation phase. This is further evidence that C3 and C4 are highly likely to be going ahead.

- ***Second pre\|CISION prodrug, AVA3996, selected for pre-clinical development***

  On 18 January 2022 – two weeks before the first escalation in the AVA6000 trial and the launch of C2 – Avacta announced that it had selected the next pre\|CISION drug candidate for pre-clinical development.

  The candidate, AVA3996, is a proteasome inhibitor and an analogue of Velcade. Avacta intends to submit a CTA filing in the UK and/or an IND filing in the US in the first half of 2023. Assuming the filing(s) are approved, a Phase 1 trial would begin in the second half of 2023.

  By 18 January, at least three patients in C1 would have received multiple doses of AVA6000. Would Avacta have made this significant commitment to the pre-clinical development of the next pre\|CISION prodrug, unless the AVA6000 data had demonstrated improved safety and tolerability, *and* evidence of cleavage of the substrate (and thus an inference of enhanced efficacy)?

- ***New non-executive directors and members of the scientific advisory board joining Avacta***

  Since the first patient in the first cohort was dosed on 11 August 2021, Avacta has recruited two new Non-Executive Directors to its Board. Both are highly experienced oncologists.

  The Company has also made three new appointments to its Scientific Advisory Board, all three of whom are regarded as world-leading oncologists.

  Readers know the questions to be asking…

- ***Avacta presents 3-year old pre-clinical data for AV6000 at a leading oncology conference in the US***

  Only last week, Avacta presented a poster at the American Association of Cancer Research (AACR) 2022 Annual Meeting in New Orleans, Louisiana.

  The poster described the pre-clinical rationale for AVA6000. It was based on in-vitro data and in-vivo data generated in mouse, rat and dog models, three years ago.[5]

[4] www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
[5] www.avacta.com/wp-content/uploads/2022/04/AACR2022_1815.pdf

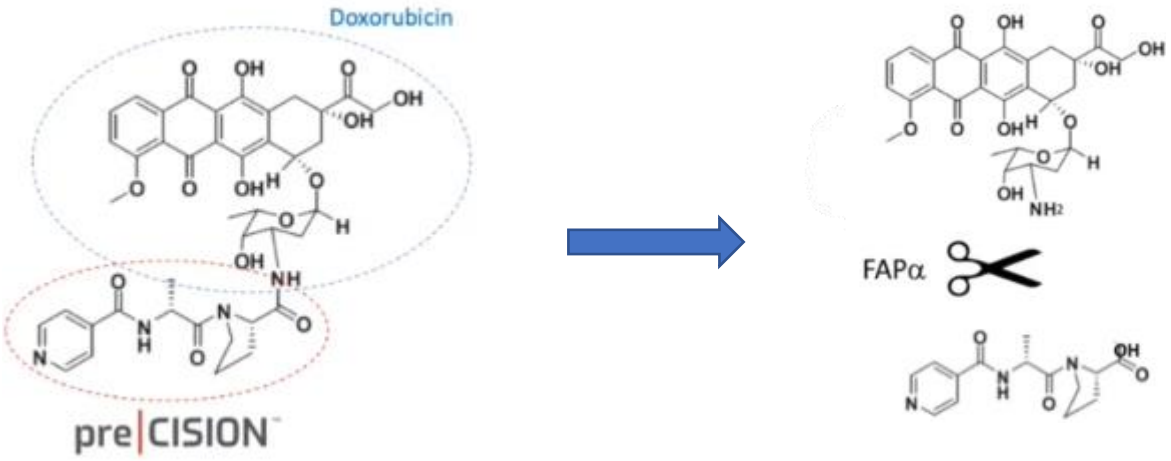
Why would Avacta present three-year-old pre-clinical data at such a prestigious oncology event, unless the *clinical* data that had been accumulating for eight months in the AVA6000 trial, was at least to some extent similar to it?

That includes *early efficacy*, and not just safety and tolerability.

pre|CISION: the Clinical Proposition

Success in AVA6000 P1 unlocks the pre|CISION platform

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 IP of the pre|CISION platform.

In the first attempt to commercialise the pre|CISION substrate, Avacta has created a prodrug form of doxorubicin (AVA6000).

Doxorubicin is an extremely potent chemotherapy that has been in use for over 40 years. Its mechanism of action is very well understood. It also happens to be a generic drug (i.e. off-patent). Accordingly, it was an ideal chemotherapy drug for Avacta to first apply the pre|CISION chemistry to.

It is vital to bear in mind that the *efficacy* of doxorubicin itself is not being (primarily) tested in the AVA6000 trial. If the pre|CISION substrate is cleaved – as is hoped for – by FAPα enzymes *only* in the tumour microenvironment, the subsequent anti-tumour activity should not come as a surprise (although of course, the *level* of that activity will be dependent on the amount of free doxorubicin that successfully diffuses into cancer cells, once cleaved – which remains the key unknown matter in the ongoing trial).

If the results of the AV6000 P1a trial – due to be published in the next several months – are positive, then Avacta will be in a position to apply the pre|CISION chemistry to a wide range of other chemotherapies that are extensively used across the globe.

In essence, pre|CISION is a *delivery platform*. Despite representing a potentially multi-billion dollar asset merely as a standalone product, AVA6000 does in fact play a much more valuable role for Avacta: it acts as the critical proof of concept for pre|CISION *in humans*.

Consider the diagram above. 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.

The most difficult task – the heavy lifting, so to speak – has already been achieved: the creation of the exquisitely specific FAPα substrate. If the substrate 'works' when covalently bonded to doxorubicin (by not activating anywhere throughout the body, apart from the TME), then it has a high probability of working for other chemotherapy molecules that it is covalently bonded to.

Early evidence of this theory has already been generated: in January this year, Avacta announced that it had selected a second pre|CISION prodrug for pre-clinical development "with a view to a first-in-human Phase 1 clinical trial beginning in the second half of 2023." The prodrug, named AVA3996, is a FAPα-activated proteasome inhibitor that is an analogue of Velcade (which generates sales of in excess of $1.2bn per annum, and is marketed by Japanese pharma giant Takeda Pharmaceuticals).

Avacta stated that it was "excited by the early pre-clinical data for AVA3996", and that "following a review of efficacy studies in several liquid and solid tumour models, safety studies and a review of manufacturability, AVA3996 has been selected as a candidate for pre-clinical development."

Evidently, Avacta has already generated data for AVA3996 in mice and/or rats that is not dissimilar to the AVA6000 animal data presented on pp.5-6.

Avacta has already identified as many as fifteen existing, widely used drugs (besides doxorubicin) that it believes could be transformed into pre|CISION prodrugs.

- 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

Revolutionising chemotherapy?

Were AVA6000 to 'work' in man in a similar way to how it worked in mouse models, there is reason to suggest that the pre|CISION platform could go on 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.

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 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.

Were AVA6000 to work in humans as Avacta hopes it will, then that patient would conceivably be able to receive *many* more doses of pro-doxorubicin. As no (or substantially less) doxorubicin would be accumulating in the patient's heart tissue when they are 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 the pre-clinical animal models (see pp.5-6).

What has not been made clear yet by Avacta (and we would not expect it anyway until after the full data readout for P1a, in the coming months) 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 would 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 could 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 – if the pre|CISION substrate works for doxorubicin, there is a high probability it will also work for many other chemotherapy drugs.

[On a non-clinical, but nevertheless related note, consider also how marketing campaigns of cancer research and patient support charities would 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 2-4 months before any response from an immunotherapy (such as the leading PD-1 inhibitor, Keytruda). 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.

pre|CISION: the Commercial Proposition

If pre|CISION does indeed work in man, it evidently carries colossal commercial value.

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 billion per annum. Market research suggests that this will have increased to $1.4bn pa in the next two years.[6]

With external consultants, Avacta has carried out work on the potential total addressable market ('TAM') for its prodrug form of doxorubicin, AVA6000. Its 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 – is $1.5bn pa.

Bear in mind that the AVA6000 P1a trial will include as many as eight different types of cancer (which provides Avacta with a broad data set across multiple targets) – and it's simple to perceive how the *global* market for AVA6000, at peak sales, could ultimately be several multiples of that $1.4bn forecast by 2024, for standard doxorubicin.

However, that's just doxorubicin, which constitutes less than 2% of global chemotherapy sales. It has been estimated that by 2027, in five years' time, the global chemotherapy market will be worth $74.3bn.[7]

If pre|CISION works in man, what would stand in the way of the platform eventually displacing a large majority – or even the entirety – of the chemotherapy market? And if *that* were to occur, the $74bn pa global sales estimate could be multiplied several times.

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.

Two potential barriers that may stand in the way of a rapid monopolisation of the market would be 1) cost to manufacture; and 2) existing patents over standard chemotherapies currently in use. To answer the first point, we believe that the increase in cost of manufacture for pre|CISION prodrugs over standard chemotherapies would be negligible.

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.14 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; 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.

[6] www.prnewswire.com/news-releases/doxorubicin-market-size-is-expected-to-reach-138-billion-by-2024-grand-view-research-inc-602613665.htm

[7] www.globenewswire.com/news-release/2021/02/08/2171622/0/en/Cancer-Chemotherapy-Market-Value-Anticipated-To-Reach-US-74-3-Billion-By-2027-Acumen-Research-and-Consulting.html

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, 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 would have been brought through clinical development successfully) would have 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. In doing so, it 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. If the P1a trial provides positive data on early efficacy / anti-tumour activity, then Avacta has an extraordinarily valuable platform technology on its hands.

A platform that could revolutionise treatment efficacy *and* patient experience, multiply the target 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.

Low hanging fruit indeed.

Valuation?

Ascribing a fair value to a company that has the technology to potentially revolutionise the $60bn+ chemotherapy market in the relatively near term, is extremely challenging. Avacta's pre|CISION platform is, to our knowledge, unique. There are various forms of targeted therapy used in oncology already, but none that works in the same manner as the pre|CISION platform. If the extremely high specificity of the substrate to FAPα that was demonstrated in animals, is also replicated in man (and we believe it is being replicated in the P1a trial), Avacta will be sitting on a *class* of drug that has a significantly higher degree of tumour targeting than any existing class of drug in oncology that could be considered direct competition.

Whilst we have previously presented discounted cash flow models for both AVA6000 as a standalone product, and for pre|CISION as a platform technology, we believe those models are less relevant now.[8]

The issue revolves around getting to grips with the total addressable market ('TAM') of a working, fully rolled out pre|CISION platform. Each prodrug could conceivably double, treble or perhaps even quadruple the TAM of the equivalent standard chemotherapy that is already on the market. How many drugs are suited to being transformed by the pre|CISION substrate? In various presentations over the past few years, Avacta has suggested at least 15 generic drugs ranging from several different sub-classes of chemotherapy and targeted therapy (see p.14). It has also emphasised that this list is by no means exhaustive.

Let us take chemotherapy, for instance. There are several sub-classes of chemotherapy:

- Alkylating agents
- Antimetabolites
- Antitumour antibiotics (anthracyclines)
- Topoisomerase inhibitors
- Mitotic inhibitors

Avacta's target list on p.14 contains at least one drug that belongs to *each* of those sub-classes of chemotherapy:

- Alkylating agents – FAPα-activated oxaliplatin
- Antimetabolites – FAPα-activated pemetrexed; FAPα-activated gemcitabine; FAPα-activated capecitabine
- Antitumour antibiotics (anthracyclines) – FAPα-activated doxorubicin
- Topoisomerase inhibitors – FAPα-activated irinotecan
- Mitotic inhibitors – FAPα-activated taxanes (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.

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 would 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* treatments that are currently being used partially as a result of dose limiting toxicities of standard chemotherapies.

We will not create a new DCF model now, given that that ultimate TAM for a fully rolled out pre|CISION platform, at peak sales (when all prodrugs remain on-patent) is impossible to calculate with any degree of accuracy.

[8] aimchaos.files.wordpress.com/2020/06/avacta-group-update-ii-part-iii-1.pdf (pp.15-17)

Rather, we will simply highlight a selection of recent transactions in the targeted cancer therapy space (including immunotherapies and antibody-drug conjugates ('ADC')), 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:

- ***Genentech and Bicycle Therapeutics collaboration (up to $1.7 billion)*** [9]
  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 $1.7 billion.

- ***AstraZeneca and Daiichi Sankyo collaboration (up to $6 billion)*** [10]
  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)*** [11]
  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.

[9] investors.bicycletherapeutics.com/news-releases/news-release-details/bicycle-therapeutics-announces-exclusive-strategic-collaboration
[10] www.astrazeneca.com/media-centre/press-releases/2020/astrazeneca-and-daiichi-sankyo-enter-collaboration-to-develop-and-commercialise-new-antibody-drug-conjugate.html
[11] news.bms.com/news/details/2021/Eisai-and-Bristol-Myers-Squibb-Enter-Into-Global-Strategic-Collaboration-for-Eisais-MORAb-202-Antibody-Drug-Conjugate/default.aspx

Phase 1 / 2 acquisitions:

- ***Gilead acquires Forty Seven for $4.9 billion*** [12]
  In March 2020, Gilead agreed to acquire Forty Seven for $4.9 billion 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*** [13]
  In November 2020, Merck announced that it would be acquiring VelosBio for $2.75 billion 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*** [14]
  In December 2020, Boehringer Ingelheim announced that it would be acquiring NBE-Therapeutics for €1.18 billion. 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*** [15]
  In August 2021, Pfizer agreed to acquire Trillium Therapeutics for $2.26 billion 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.

Phase 3 acquisitions:

- ***Gilead acquires Immunomedics for $21 billion*** [16]
  In September 2020, Gilead agreed to acquire NASDAQ-listed Immunomedics for $21 billion 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 $4 billion, which was estimated to be reached in 2029.

- ***GlaxoSmithKline acquires Sierra Oncology for $1.9 billion*** [17]
  In April 2022, GSK reached an agreement to acquire NASDAQ-listed Sierra Oncology for $1.9 billion 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.

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[12] www.gilead.com/news-and-press/press-room/press-releases/2020/3/gilead-to-acquire-forty-seven-for-49-billion
[13] www.merck.com/news/merck-to-acquire-velosbio/
[14] www.nbe-therapeutics.com/newsroom/news-press-releases/2020/2020-12-10
[15] www.pfizer.com/news/press-release/press-release-detail/pfizer-acquire-trillium-therapeutics-inc?msclkid=ca5a80d2c0cf11ec9acc32b31434c53e
[16] www.gilead.com/news-and-press/press-room/press-releases/2020/9/gilead-sciences-to-acquire-immunomedics
[17] www.gsk.com/en-gb/media/press-releases/gsk-reaches-agreement-to-acquire-late-stage-biopharmaceutical-company-sierra-oncology-for-19bn/

[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.[18]]

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 many *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 in the event of pre|CISION proving effective in man, the platform could earn a premium valuation rating over its peers.

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

Concluding Remarks

The first-in-man clinical study of a pre|CISION prodrug – the AVA6000 P1a trial – is due to complete in 2-3 months. Shortly afterwards, Avacta will publish the top line data. If the trial has been successful, it will relay the improvement in safety and tolerability of AVA6000 over standard doxorubicin, as well as the maximum tolerated dose and/or the recommended phase 2 dose that will be used for P1b. It will likely also relay early efficacy data, notably anti-tumour activity.

We believe that the progress of the P1a trial over the past eight months has demonstrated that the safety and tolerability of AVA6000 compared standard doxorubicin has (almost certainly) been improved dramatically. It would seem that the pre|CISION substrate is not being cleaved in healthy tissue.

For numerous reasons expressed on pp.10-12, we also *infer* that the pre|CISION substrate *is* being cleaved within the tumour microenvironment. We believe that tumour biopsies will prove this inference.

If we are correct in this inference, it is our view that the pre|CISION platform – whether under the control of Avacta or (more likely) another larger pharma entity – could go on to revolutionise the global chemotherapy industry.

If the maximum lifetime cumulative exposure of pre|CISION prodrugs is multiple times greater than the equivalent standard chemotherapies, the probability of tumour regression for patients is substantially increased. Drug efficacy would increase, whilst side effects would decrease. It would be an extraordinary double victory for pre|CISION prodrugs over the current standard-of-care chemotherapies.

Provided that costs remain competitive, the question investors should now be asking is: *Why wouldn't pre|CISION pro-chemotherapies rapidly displace their existing counterparts?*

We have highlighted that the pre|CISION substrate is broadly applicable across most chemotherapy sub-classes. The platform therefore has an *existing* target market of circa $60bn – which it could multiply as a result of increasing both the maximum lifetime cumulative exposure of the prodrugs over standard drugs, and the patient population eligible for chemotherapy. Moreover, there is the prospect of the pre|CISION substrate being used to modify other oncology drug classes, including targeted therapies and drug conjugates.

This is all theoretically possible, *if* the AVA6000 molecule is behaving as expected in the patients of the P1a trial. We must stress that despite all of the evidence we have presented for the case of activation of doxorubicin in the TME, investors must bear in mind that AVA6000 is in an *early stage trial*. ***Drug development is a high risk business. Things can go horribly wrong overnight.***

Besides clinical risk, investors must consider risk from competition – namely, new classes of targeted oncology therapies, including other targeted chemotherapy technologies under development (based on FAPα or other enzymes).

Our investment thesis for Avacta is founded on the belief that despite the numerous risks and threats that the Company must overcome in its pursuit of developing and commercialising the pre|CISION platform, Avacta's current market capitalisation of £347m represents only a tiny fraction of the platform's risked net present value.

Our *trade* thesis is based on the prospect of Avacta publishing top line data from the AVA6000 P1a trial in the next several months that could (assuming positive results) shock the oncology world. If the data is as hoped for, the immense scalability of the pre|CISION platform is unlocked.

With regards to Avacta's current position: the Company has adequate cash in the bank to see it through into 2023 (consensus forecasts estimate cash at end 2022 of £6.5m).

Working on the assumption that the P1a trial is highly successful, Avacta will require considerable cash to continue with the clinical development of AVA6000, as well as to commence pre-clinical development of numerous other pre|CISION prodrugs in its pipeline.

Avacta could either raise fresh equity on the capital markets; or it could secure a large upfront cash payment via a licensing deal.

In our opinion, the first option could involve the splitting of Avacta into two completely separate entities: Avacta Therapeutics and Avacta Diagnostics. We imagine that the former would list on NASDAQ, raising a large sum of cash in the process from US investors who are more appreciative of biotechnology; whilst the latter would become a pure-play Diagnostics business and retain the AIM listing. In such a scenario, existing investors may receive a proportionate number of shares in the 'spin-out' Therapeutics business.

The second option could involve AVA3996, Avacta's second pre|CISION prodrug. In investor presentations, the Company has repeatedly emphasised that the market leading proteasome inhibitor, bortezomib (branded Velcade and marketed in the US by Takeda), witnesses its final patent expiry this year. An obvious solution for Takeda to not only extend its existing proteasome inhibitor sales, but to potentially dramatically expand those sales, would be to license Avacta's AVA3996 candidate. Assuming the AVA6000 Pa trial is a success, then the clinical development risk for AVA3996 would be significantly reduced.

A 'working' AVA3996 would take market share from the other two existing proteasome inhibitors (Kyprolis and Ninlaro) on the market (as why would any patients use those?); would generate greater sales than Velcade (as many more doses could now be administered, and to many more patients); and would enjoy patent protection for another two decades (thus benefitting from premium pricing).

In any event, a large injection of cash would enable Avacta to retain 100% ownership of the majority (if not all) of its pre|CISION prodrug candidates. AVA6000, as the Company's lead candidate, is highly unlikely to be licensed out, as we believe that NASDAQ investors would require the Company to retain 100% ownership – at the very least until the end of P1b.

In addition to enabling the Company to launch an accelerated clinical development programme for multiple pre|CISION prodrugs, a large cash injection would also better protect Avacta against the threat of hostile takeovers.

But for now, we await that potentially Company-making data readout from the AVA6000 P1a trial.

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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