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Avacta Group: pre|CISION platform generates efficacy data

To kick off my new writing project, I am introducing readers to ***Avacta Group (123p, £344m)*** a UK life sciences company that operates two separate divisions: a clinical stage biotechnology business primarily focussed on developing cutting-edge cancer drugs; and a vertically integrated diagnostics business that currently has an annual revenue run-rate of approximately £20m to £25m.

I have been invested in Avacta for approaching four years now, having initially built a stake in the business in late 2019 at around 17p. My rationale was simple: Avacta had, in 2018, secured the global exclusive license to a patented technology invented at Tufts University School of Medicine, Massachusetts, US. This technology – now branded *pre|CISION* – can be used to modify many types of existing cancer drugs that are used to treat the large majority of solid tumours, in order to dramatically reduce their side effects. Moreover, a reduction in side effects means that higher doses of the modified drug can be administered, thus also resulting in a simultaneous boost in efficacy.

In August 2021, Avacta commenced its first ever clinical trial when it brought its first drug, AVA6000, into a Phase 1a study. AVA6000 is a pre|CISION-modified version of doxorubicin – a half-century old chemotherapy drug that is still widely used, owing to its exceptional cell-killing abilities. Doxorubicin's use must be strictly limited, however, as it kills not just cancer cells, but *all* cells. This results in severe side effects such as hair loss, vomiting, etc. – but above all, cardiotoxicity (i.e. damage to the heart, which is usually irreversible). Consequently, cancer patients treated with the drug (and indeed with most chemotherapies) are limited to a lifetime cumulative dose (for example, six cycles).

Phase 1a is a 'dose escalation' study, which is designed to find a 'maximum tolerated dose' ('MTD'), i.e. the highest dose that can be administered to a patient without causing life-threatening side effects. The design of the study follows that three patients (a 'cohort') are treated with a relatively low dose of the drug under investigation. If the drug is well tolerated and no MTD is found in those patients, then a second cohort is launched, in which three new patients are treated with a higher dose of the drug. Successive cohorts are launched, each with incrementally higher doses, until an MTD is discovered.

Prior to commencement of Phase 1a, Avacta had estimated that an MTD would be discovered for AVA6000 well within the first four cohorts. Yesterday, 25 months after the trial began, the Company announced that it had completed the *sixth* cohort of patients – who had received doses of AVA6000 2.8x greater than an equivalent dose of doxorubicin typically administered – and still an MTD had not been found. This is a stunning result and blows Avacta's initial expectations for improvements in safety and tolerability of AVA6000 (in comparison to doxorubicin) out the water. But yesterday's announcement contained a whole lot more besides, which I shall endeavour to explain below:

- *Significant reduction in tumour volume confirmed in a patient with soft tissue sarcoma.*
- *Cohort 7 to be the final dose escalation cohort in the Phase 1a study.*
- *Short study to commence in Q4, to explore fortnightly dosing.*
- *Phase 1b to be replaced with a pivotal Phase 2 study in soft tissue sarcoma, commencing in 2024.*

Improving the safety and tolerability of the modified drug in comparison to the standard drug is one thing; but proving that the modified drug *also* demonstrates an improvement in efficacy, is a whole other matter. It is important to note that the patients that have taken part in the AVA6000 Phase 1a trial have all been extremely sick people, often terminally ill with no other treatment options available. Many are taking part for altruistic reasons, to help improve treatments for future cancer patients. It is

thus extraordinary to see a significant reduction in tumour volume for one such patient with soft tissue sarcoma ('STS'); as well as signs of efficacy in patients with other types of tumours.

Avacta has determined that the seventh cohort, commencing imminently, will be the last cohort in Phase 1a, regardless of whether an MTD is found. This cohort will receive doses of AVA6000 equivalent to approximately 3.5 times the standard dose of doxorubicin. Moreover, given just how targeted AVA6000 is (with the latest patients *still* not experiencing major side effects), Avacta is launching a mini-study in the next three months, to examine whether fortnightly dosing further boosts efficacy, in comparison to the current trial in which patients are dosed every three weeks.

Finally, on the back of the astonishing success of Phase 1a, Avacta has fast-tracked its clinical development plans for AVA6000. It is now seeking to convert the next trial – until yesterday, planned as a Phase 1b study – into a *pivotal* Phase 2 trial for treating STS. In a pivotal study, if the investigational drug successfully meets the endpoints of the trial (i.e. the targeted goals of the study), then regulators such as the FDA in the US and the MHRA in the UK can approve the drug for marketing.

So, what does this mean for AVA6000 and Avacta? Firstly, the time it will take to bring AVA6000 to market – to get it into the hands of practising clinical oncologists – has been potentially been cut dramatically. If the fortnightly dosing mini-study can commence before Christmas, then the new pivotal Phase 2 study could be launched in H2 next year. Assuming all goes well, accelerated approval for AVA6000 in treating STS patients could be granted in the US and elsewhere, *within two years from now*.

Furthermore, fewer trials equate to fewer patients dosed, and lower clinical costs overall. My estimate is that all clinical costs from today to accelerated approval for STS in the US, should not exceed £25m. With the granting of marketing approval in the US, other jurisdictions should quickly follow in granting approval, opening up at least an initial $1 billion per annum revenue opportunity for AVA6000.

Avacta is focussed on STS as it is the fastest route to market for AVA6000 (given that doxorubicin is already the standard-of-care (i.e. the first drug of choice for oncologists) for treating STS). However, doxorubicin is also used to treat numerous other solid tumours such as breast and ovarian cancer. These are much larger markets than that of STS. As the ongoing Phase 1a trial for AVA6000 is a tumour-agnostic study (patients with numerous different types of cancer have taken part), it is not unreasonable to assume that pivotal studies for these other indications could also be fast-tracked.

Now consider this: the current doxorubicin market is expected to grow from $1.5bn pa at present, to $2bn within 5 years. Due to AVA6000's substantially enhanced safety profile, patients could endure *3-4 times more cycles* of AVA6000 treatment, than they could with standard doxorubicin. AVA6000 could also be given to a much larger population: many cancer patients simply cannot be treated with doxorubicin, as they are too old or frail to endure the severe side effects. Finally, AVA6000 would be branded and patented, and would thus command a much higher pricing point than the generic (i.e. 'off-patent') doxorubicin. Taking all this into account, it is simple to understand why AVA6000 could become a true blockbuster, generating annual revenue at peak sales of $5bn to $10bn.

However, recall that AVA6000 is only the first cancer drug that Avacta has modified. Its second most advanced drug, AVA3996 – a pre|CISION-modified version of another chemotherapy, bortezomib – is undergoing pre-clinical studies with a view to moving it into a Phase 1 study, next year. These studies have already yielded highly impressive data. Beyond AVA3996, Avacta has alluded to another 15 or so chemotherapies that it believes can be enhanced with the pre|CISION technology. It has also more recently indicated that it will look to modify even more potent cancer drugs than chemotherapies, that are too dangerous to dose patients with, without some form of delivery vehicle. I'm expecting the Company to enter into joint ventures with the owners of these incredibly powerful drugs (e.g. MMAE).

The global chemotherapy market is currently valued at circa $65bn per annum, and growing. The market for antibody-drug conjugates ('ADC') – a novel class of powerful, *targeted* cancer treatment – is *rapidly* growing and is expected to be *double* the size of the chemotherapy market, within a decade.

These are the markets that Avacta's pre|CISION-modified prodrugs will be fighting to take a slice of. The AVA6000 trial has already proved that the technology can revolutionise conventional chemotherapy (both in reducing side effects *and* in boosting efficacy); the key question now is, can its targeting ability surpass that of ADCs? The Phase 1a data would suggest that it already has.

Recall the global exclusive license that Avacta holds over the patented technology developed at Tufts. Those patents – and Avacta's license – expire around 2032-34. Until that time, Avacta can develop – and submit patent applications for – dozens of new pre|CISION-modified drugs, securing protection on them until as far out as the early 2050s.

Some many now be thinking, *This is all well and good, but what drives a proper share price rerating*? My answer would be, *The catalyst for the rerate has just landed*. Yesterday's news has proved that Avacta's pre|CISION platform can not only dramatically improve the safety profile of the world's most potent chemotherapy, but also its *efficacy* – its cancer-killing ability. In my mind, the path to regulatory approval – to getting AVA6000 into the hands of practising clinical oncologists – is now procedural. Avacta can easily self-fund its way down the path, and major revenues are no longer many years away (late 2025, in my view).

The leading companies focussed on targeted oncology that are listed on NASDAQ – at similar points in their clinical trials to Avacta's AVA6000 – have market capitalisations in the several $ billions. I would argue that Avacta has a *much* higher probability of bringing its lead asset to market than those companies; and, owing to the *platform* nature of its technology (i.e. it can be used to modify dozens of cancer drugs targeting many types cancer), has a market opportunity many times as large. As Avacta's CEO stated yesterday, "***I believe that we are on the verge of a paradigm shift in how chemotherapy is delivered to cancer patients***."

Yesterday, Avacta stated it would present the data package from Phase 1a in Q4. I suspect this could be a major share price catalyst, especially if details emerge of further impressive efficacy in the last patients in the study. In the coming months, I also expect we see out-licensing deals with Big Pharma for multiple chemotherapies in the pipeline after AVA6000, including possibly AVA3996; joint ventures with leading ADC developers; and potentially more left-field announcements, such as the splitting up of Avacta (either via a spin out, or a disposal, of one or the other of the divisions).

A near-term cash injection – through whatever means – would be most welcome and could, I believe, also drive a powerful rerating of the share price. I was therefore delighted to hear the CEO state in an interview yesterday, *"We are prioritising non-dilutive sources of capital, either through partnership or licensing… From a funding perspective, we're in no rush to raise capital at the moment. There's a lot of optionality*."

To conclude: I think yesterday's efficacy news was vital for the investment community and for Big Pharma to start taking Avacta very seriously. I am now in no doubt that it will become a multi-billion $ company in the not-too-distant future. As a long-term investment, I can't find another stock on the LSE that offers such vast upside at such an attractive risk/reward ratio.

As a short-term trade for Q4? I think there are enough potential major news catalysts (coupled with exceptionally positive sentiment around the stock) for the share price to enjoy a serious rerating from the current price of **123p**. The key risks to the short-term trade are concerns over funding; and a continued lack of understanding of the blue sky potential of pre|CISION. However, as I've tried to explain, I think these risks can be quickly put to bed by the right news flow in the near term.

Disclosure

The author of this paper, Myles McNulty, is a private investor. He and his family hold ordinary shares in Avacta Group.

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