

**Market data**

EPIC/TKR	AVCT
Price (p)	35.0
12m High (p)	83.3
12m Low (p)	27.0
Shares (m)	69.0
Mkt Cap (£m)	24.1
EV (£m)	8.3
Free Float*	60%
Market	AIM

\*As defined by AIM Rule 26

**Description**

Avacta is a pre-clinical stage biotechnology company developing biotherapeutics based on its proprietary Affimer protein technology. It benefits from near-term revenues from research and diagnostic reagents.

**Company information**

CEO	Alastair Smith
CFO	Tony Gardiner
Chairman	Eliot Forster
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	<a href="http://www.avacta.com">www.avacta.com</a>

**Key shareholders**

Directors	6.1%
IP Group	24.8%
Lombard Odier	10.8%
Aviva	9.6%
Ruffer LLP	7.1%
JO Hambro	6.7%

**Diary**

Oct-18	Finals
Jan-19	AGM
1H'19	PD-L1/LAG-3 drug candidate selection

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**Avacta****Ground-breaking new drug conjugate platform**

Avacta (AVCT) is a pre-clinical biotechnology company and the proprietary owner of Affimer technology. Affimers represent a radical alternative to the established antibody technology, which continues to dominate the drug industry, despite its limitations. The significant technical and commercial benefits of Affimers are being recognised increasingly through corporate and academic interest, on-going evaluations, and deal flow. A co-development partnership has been signed with Bach Biosciences (Tufts) for development of a new type of Affimer-drug conjugate (AfDC), that is already attracting attention from large pharma companies.

- **Strategy:** AVCT is aiming to commercialise its Affimer technology through licensing for research and diagnostics, and by identifying and developing its own proprietary therapeutic pipeline for partnering. AVCT has sufficient cash resources to identify an Affimer lead to be ready for first-in-man trials in 2020.
- **Major co-development partnership:** AVCT and Bach Biosciences (Boston, MA) have agreed a co-development partnership to advance a new class of Affimer-drug conjugate, that combines technologies from both parties. The first example of such therapeutic will combine Affimer PD-L1 blockade and I-DASH inhibitors.
- **New class of therapeutics:** Unlike traditional antibody-drug conjugates (ADCs), the mechanism of this ground-breaking new approach is to be effective at the tumour micro-environment. It has a dual and synergistic effect, with checkpoint blockade and enhancement of the immune response at the tumour site.
- **Risks:** Affimers represent a new disruptive technology and the potential customer base might take time to recognise their advantages. While all new drug development carries a high risk, Avacta has hit a number of important milestones over the last two years which have reduced the risk profile greatly.
- **Investment summary:** AVCT has made considerable progress towards its goal of having its own proprietary Affimer-based drugs and growing a separate profitable reagents business. The company has identified potential therapeutic leads and completed both *in-vitro* and *in-vivo* pharmacokinetic pre-clinical, efficacy tests. The rising number of collaborating deals being signed is a clear sign of the value of the technology the market does not seem to recognise yet.

**Financial summary and valuation**

Year-end July (£m)	2015	2016	2017	2018E	2019E	2020E
Sales	1.81	2.17	2.74	3.00	3.50	5.40
R&D spend	-0.03	-1.50	-2.60	-3.25	-4.50	-5.50
EBITDA	-2.28	-4.79	-6.66	-7.95	-9.30	-9.20
Underlying EBIT	-2.85	-5.39	-7.60	-9.02	-10.37	-10.27
Reported EBIT	-5.51	-5.66	-7.98	-9.44	-10.84	-10.78
Underlying PBT	-2.83	-5.29	-7.51	-8.98	-10.37	-10.32
Statutory PBT	-5.48	-5.57	-7.89	-9.40	-10.84	-10.84
Underlying EPS (p)	-4.38	-6.46	-8.75	-11.55	-12.92	-12.48
Statutory EPS (p)	-9.72	-6.86	-9.31	-12.17	-13.59	-13.23
Net (debt)/cash	7.33	19.52	13.17	4.50	-5.98	-16.01
Capital increases	0.02	21.05	0.01	0.06	0.00	0.00
EV/sales (x)	19.3	16.2	12.8	11.7	10.0	6.5

Source: Hardman &amp; Co Life Sciences Research

## A new class of therapeutic

*A co-development partnership has been signed with Boston-based biotech group Bach Biosciences, to develop a new type of therapeutic...*

*... that combines the Affimer platform with a cytotoxic drug to generate a synergistic effect*

*The first product to come from the agreement will combine the PD-L1 Affimer with the I-DASH immune system stimulator*

Avacta recently announced a co-development and risk-sharing partnership with Bach Biosciences, a company that commercialises research from the Chemical and Molecular Biology Group at Tufts University School of Medicine, Boston. This partnership will develop a new type of therapeutic Affimer-drug conjugate (AfDC) that combines the selective PD-L1 Affimer checkpoint inhibitor (CPI) discovered by AVCT with an inhibitor of the I-DASH (pan-dipeptidyl peptidase IV activity and/or structural homologs) family of enzymes. What it is new here is not the AfDC molecule itself, but the specific mechanism of action of the combination (see below), representing a new class of therapeutic. This partnership was originated by Avacta's new US Business development office in Boston. The advantages conferred by the Affimer technology platform compared with antibodies were the key attraction for the Tufts laboratory to collaborate with AVCT, together with the potential for a broad patent position. Avacta already has a collaboration with Glythera for the development of conventional drug conjugates using Affimers, which has provided a solid foundation from which to conclude this new co-development partnership.

### *Novel Affimer drug conjugate*

In this co-development partnership, each party will bring their proprietary technologies to the collaboration, with the aim of producing new drugs with improved clinical outcomes. The molecule, which could be considered as a targeted pro-drug as it is inactive until it encounters specific enzymes within the tumour environment, consists of three parts:

- ▶ **An Affimer inhibitor** that targets immune checkpoint on the tumour cell. This has the dual role of targeting the cytotoxin to the tumour to improve safety, and also inhibiting the immune checkpoint to allow the immune system to attack the tumour more efficiently.
- ▶ **A linker selectively cleavable** by an enzyme over-expressed in the tumour microenvironment. The linker has been developed at the Tufts laboratory.
- ▶ **A small molecule cytotoxin**, which kills cells in the tumour micro-environment causing an inflammatory response that recruits the immune system to attack the tumour. This attack is enhanced by the fact that the Affimer has a synergistic immune system effect.

The PD-L1/I-DASH AfDC represents the first example of this new class of compound. Inhibiting PD-L1 alone is known to lead to a modest overall response rate in patients. The addition of the cytotoxic I-DASH compound causes a powerful recruitment of the immune system to the tumour that can then work synergistically with the PD-L1 blockade of the Affimer. The I-DASH inhibitor kills macrophages in the tumour causing:

- ▶ Potent priming of tumour antigen-specific CD8+ T-cell responses.
- ▶ Enhanced trafficking of key effector immunocytes to the tumour.
- ▶ Increased levels of dendritic cells, responsible for presenting antigens to the T-cells.
- ▶ Activated natural killer (NK) cells, a type of lymphocyte and a component innate immune response that plays an important role in the host-rejection of tumours and viral infected cells.
- ▶ Accelerated expansion of tumour-specific T-cells.

As for the traditional type of antibody-drug conjugates (ADCs), the key and crucial point is the nature of the linker. Many ADCs have failed to enter the clinic or failed in the clinic due to the instability of the linker in the body and/or an unreliable drug-to-antibody ratio (DAR).

### *New mode of action*

***Unlike traditional ADCs, this new therapeutic does not need to be internalised to exhibit its anti-tumour activity***

Unlike the traditional ADCs currently available commercially or in development, which must become internalised within individual tumour cells in order for the cytotoxin to be released and to have an effect. The aim of the new AfDC is not to be internalised but to work at the tumour micro-environment, where the linker is cleaved by specific enzymes overexpressed at the tumour site, thereby releasing the toxic I-DASH warhead. Therefore, the AfDC will have a novel dual and synergistic mode of action in a single molecule.

***The synergistic effect aims to enhance the effect of the PD-L1 inhibitor at the tumour micro-environment***

Despite having a different mechanism of action compared with ADCs, the new AfDC will have the same effect in reducing systemic exposure to the toxic drug, with the Affimer component directing the combination right where it is needed at the tumour site, to exhibit its cytotoxic effect. That will potentially generate a greater therapeutic window for the I-DASH inhibitor, with fewer side effects and lower systemic toxicity.

### *Bach's I-DASH inhibitor*

Bach Biosciences commercialises the research of William Bachovchin, at the School of Medicine in Boston. The I-DASH small molecule inhibitor is an inducer of the innate immune response. It has extensive clinical data having been into Phase III trials. The inhibitor selectively targets tumour-associated macrophages causing major inflammatory events that stimulate the patient's immune system to specifically recognise and attack the tumour. *In-vivo* studies showed that the I-DASH inhibitor possessed potent anti-tumour activity in colorectal and rhabdomyosarcoma mouse models, which was even greater when combined with a cancer immunotherapy. Clinical trials showed the I-DASH inhibitor to be highly potent with a dose limiting toxicity common to many of these types of cytotoxin. The targeting of the I-DASH inhibitor using PD-L1, and the selective cleavage of the toxin only within the tumour will improve the safety profile of the drug when incorporated into the AfDC.

***A broad patent encompassing the platform has been filed already...***

### *Patent position*

Broad patent protection has been filed jointly with Tufts to protect the whole concept that, together, could be considered as a platform technology. The patent application covers a broad range of checkpoint receptors that are upregulated in tumours, linkers that are cleaved by a range of enzymes that are also upregulated in the tumour micro-environment and a range of cytotoxins that causes a major inflammatory event stimulating the patient's immune system. This would be a highly valuable patent if granted, covering the broad concept of a dual mode of action, immune active drug conjugate, however it is implemented.

***... and Avacta having the exclusive right to commercialise***

### *Next steps and conclusion*

Avacta has discussed the concept already with its pharma industry contacts to evaluate the appetite for the new approach and for future licensing. From the clear interest shown in these discussions for this novel drug conjugate platform, AVCT has confidence that a licensing deal can be secured for specific targets at the pre-clinical stage, when it has animal data, which should be in 2019. Avacta has the exclusive rights to commercialise these novel drug conjugates. Together with the PD-L1/LAG-3 bi-specific Affimer project, which Avacta should take into the clinic in 2020, this AfDC programme represents AVCT's second major drug development programme.

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