Avacta®

Affimer®

Innovative Immunotherapies

September 2019

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Affimer®

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Introductions

Affimer®

Dr Eliot Forster, Non-Executive Chairman

- Over 25 years experience in pharma and Biotech.
- 2015 – 2018 CEO of Immunocore Limited.
- 2018- CEO F-Star.
- Held a number of senior roles in Pfizer where he became Head of Development and Operations for the EU and Asia.
- Joined Avacta in 2018.

Dr Jose Saro, CMO

- Over 20 years' experience in the pre-clinical, translational and early clinical development of oncology assets.
- Joined Avacta from Roche Innovation Center Zurich where he was Senior Translational Medicine Leader.
- Previously in senior roles at Bristol Myers Squibb, Novartis, Eisai and Wyeth.
- Joined Avacta in 2018.

Dr Alastair Smith, CEO

- Over 12 years experience as a public company CEO.
- A leading UK biophysicist - founded Avacta in 2006.
- World class scientific and technical knowledge with a highly commercial mindset.

Dr Amrik Basran, CSO

- Over 10 years' experience of both the biotech and pharma industries.
- Director of Protein Biosciences at Domantis, Head of Topical Delivery (Biopharm) at GSK.
- Joined Avacta in 2013.

David Wilson, Commercial Director (Diagnostics)

- >25 years commercial experience of in-vitro diagnostics.
- Led the sales, marketing and business development functions at Genzyme Diagnostics
- Joined Avacta in 2019.

Tony Gardiner, CFO

- Over 20 years senior financial and operational experience across multiple sectors.
- 4 years as CFO of AIM listed Fusion IP plc, 5 years as Finance Director of Aedas/AHR Architects.
- Joined Avacta in 2016.

Matthew Vincent, VP Business Development (Therapeutics)

- Senior executive with over 25 years' experience in biotech.
- Joined Avacta from Arisaph Pharmaceuticals where he led corporate development and therapeutic innovation strategy.
- Trained as a lawyer and patent attorney.
- Joined Avacta in 2017

Dr Matt Johnson, CTO

- Genetics & Microbiology Molecular Biology.
- 8 years at Abcam becoming global Head of R&D.
- Joined Avacta in 2014.

Introduction

Affimer®

Addressing the lack of a durable response to existing immunotherapies experienced by most patients through combinations of two proprietary therapeutic platforms: Affimer® - best-in-class antibody mimetic platform - and a tumour targeted chemotherapy platform

Near-term value inflection points arising from planned phase I clinical trial of AVA6000 pro-doxorubicin, and other commercial and pre-clinical milestones

Validating partnerships in place with LG Chem, Moderna and Tufts, and new discussions with additional third parties

Based in Cambridge and Wetherby UK and listed on the London Stock Exchange (AVCT)

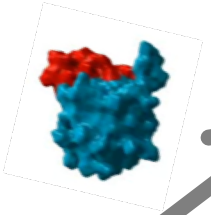
Recent Progress

Affimer®

Major therapeutics co-development partnership based on ground-breaking co-Invention with Tufts University School of Medicine to develop drug combinations activated in the tumour micro-environment. **Avacta has sole commercial rights**

Multi-target (oncology/ inflammatory) development partnership and licensing deal with LG Chem worth up to $310m with $2.5m upfront, $5.5m in near-term milestones, royalties on future products and full research costs

Development candidate selected to remain on track for IND 4Q20. Lead PD-L1 antagonist shown to perform as well as Imfinzi, Tecentriq and Bavencio in animal efficacy models



3Q18

Appointment of Dr Eliot Forster as non-executive Chairman

4Q18

Appointment of Dr Jose Saro as Chief Medical Officer from Roche

1Q19

Moderna exercises its option to take one or more of lead Affimer molecules arising from research collaboration established in 2015 into clinical development; potential for undisclosed clinical development milestones and royalties on future sales

2Q19

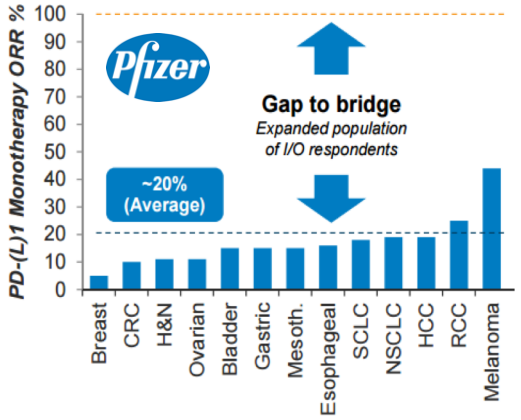
Announcement of **planned phase I study 1Q20 of TMAC linker** in pro-doxorubicin format – first clinical milestone for TMAC programme well in advance of schedule

The Cancer Immunotherapy Challenge

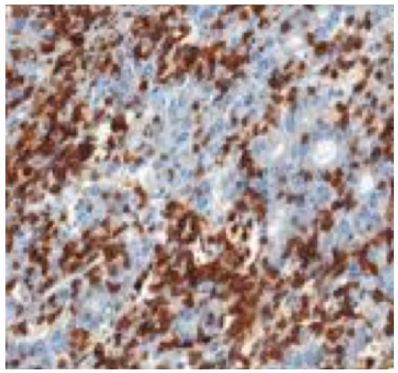
Affimer®

Only ~20% of patients respond to current immune checkpoint monotherapies

PD-1 Monotherapy Response Rates

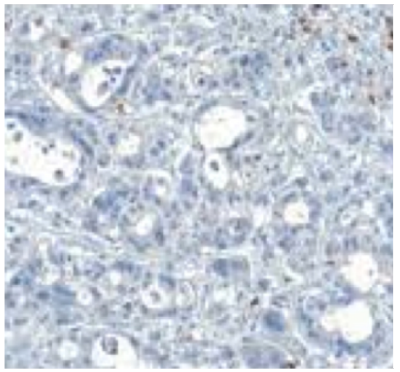


"Inflamed tumours" respond well to checkpoint inhibitors



20-30% patients

"Non-inflamed" tumours do not



70-80% patients

Avacta has two proprietary therapeutic platforms positioning the company well to address this gap in cancer immunotherapy market through **clinically differentiated combinations of pro-inflammatory drugs with Affimer immune checkpoint modulators**

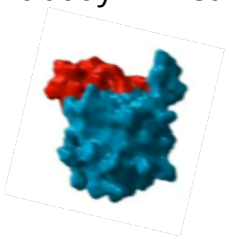
Technology and Strategy Overview

Affimer®

Two proprietary platforms well positioned to generate multiple clinically differentiated products addressing the gap in cancer immunotherapy

Affimer®

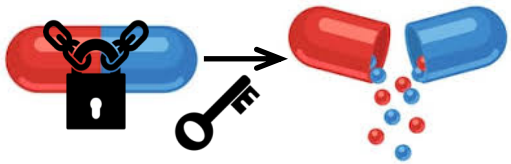
Antibody mimetic



→ **Mono- and bi-specific ICP therapies**

\+

Tumour Targeted Chemo



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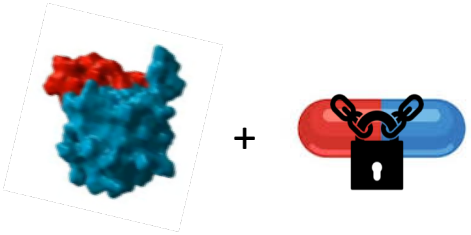
Tufts UNIVERSITY | School of Medicine

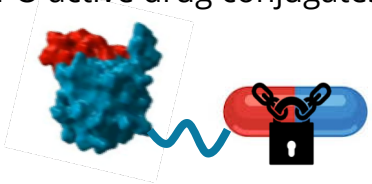
→ **Tumour targeted chemotherapy**

Clinically Differentiated Cancer Therapies

Co-administered combination therapies



I-O active drug conjugates



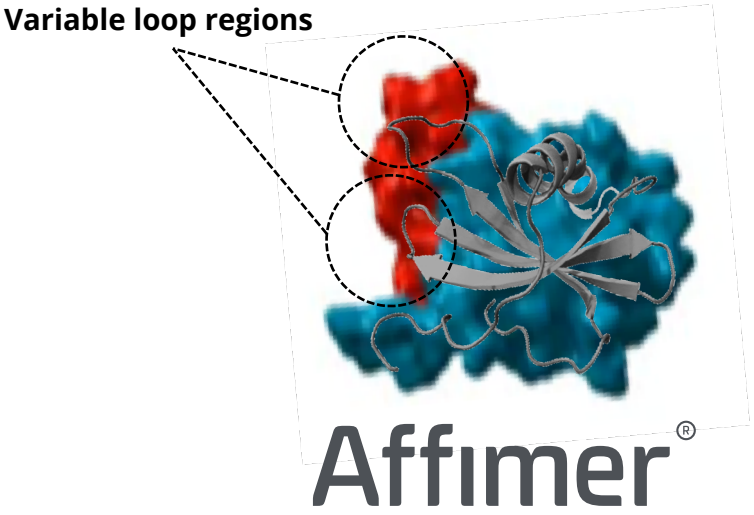
TMAC™

Avacta's Proprietary Affimer® Platform

Affimer®

What is an Affimer?

- Based on a **naturally occurring human protein** (stefin A) and engineered to **display two loops that create an antigen binding surface.**
- **Variable loop regions of 9 amino acids each are randomised** to create very large (10^{10}) libraries for phage selections.



Technical Advantages

- **Smaller, simpler and more robust, soluble and stable** than antibodies.
- **High affinity** Affimer® generated for new targets in a matter of weeks, **much quicker** than antibodies.
- **Flexible formatting** for multi-specifics, agonism, drug conjugates.
- **High expression levels** in a range of cells and tissues.
- **Fully human: lower immunogenicity risk.**

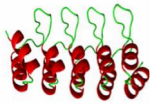
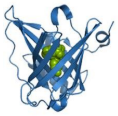
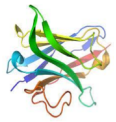
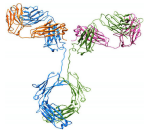
Commercial Advantages

- **Proprietary and unencumbered IP.**
- **Freedom to operate** where there is antibody IPR.
- **Security of supply.**
- **Cheaper to produce (*E.coli*).**

Comparator Technologies

Affimer®

Affimers exhibit all the properties of a best-in-class therapeutic protein platform

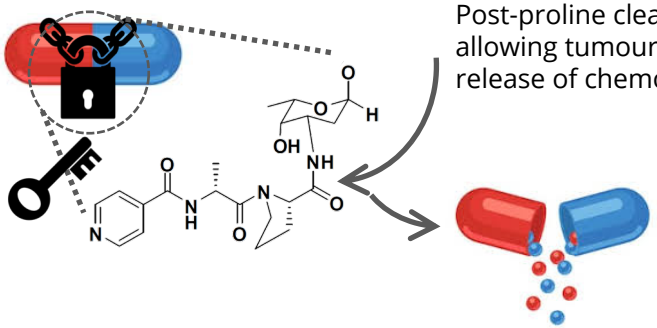
Key Attributes of a Therapeutic Protein Platform	Affimer®	Darpin®	Anticalin®	Nanobody®	Antibody
	Avacta	Molecular Partners	pieris	Ablynx (Sanofi)	
					
Small, monomeric, full length human protein, no disulphide, no PTM	Y	N	Y	N	N
Rapid discovery process yielding highly specific nM binders routinely	Y	N	Y	N	N
Low immunogenicity risk	Y	Y	Y	Y	Y
Flexible formatting for multi-specifics	Y	Y	N	Y	N
High expression of monomers and multimers in a range of cells, human tissues and in *e. coli.*	Y	N	N	N	N
Tunable pharmacokinetics	Y	Y	Y	Y	N
Very high solubility (>250mg/ml PBS) with low viscosity	Y	N	N	N	N
Simple, unencumbered IP, with freedom to operate around antibody IP	Y	Y	Y	N	N

Avacta's Proprietary FAPα Sensitive Substrate

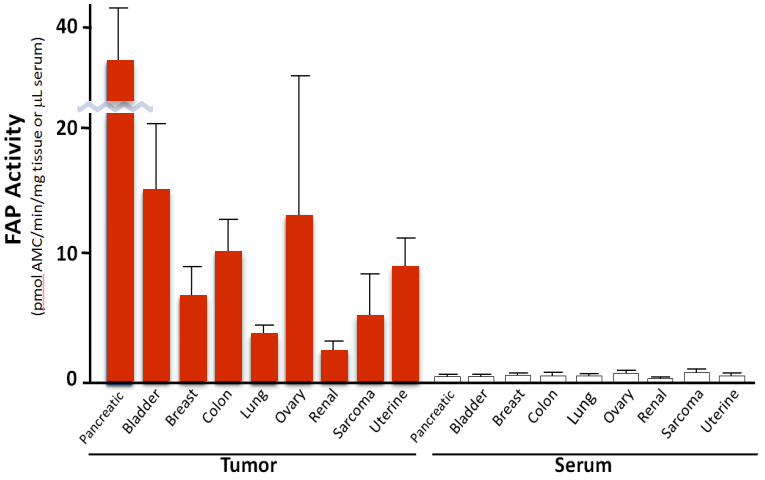
Affimer®

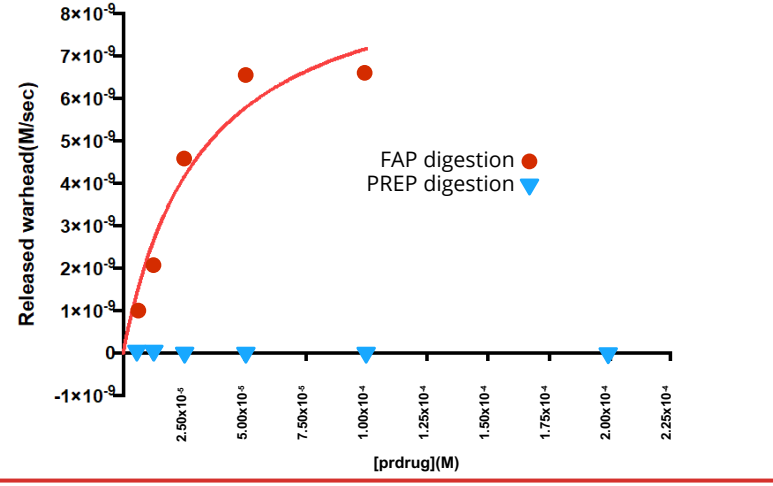
FAPα Sensitive Substrate

- Substrate is **highly specific** to cleavage by an enzyme, **fibroblast activation protein-α (FAPα)** that is **highly upregulated in the tumour microenvironment of most solid tumours**
- Substrate alone **prevents chemotoxins from entering cells rendering them inactive** until activated in the tumour
- Substrate can also be incorporated into a **drug conjugate linker**
- Linker and chemo-toxins exclusively licensed from Tufts University School of Medicine



Average Induction of FAPα Activity in Tumour Relative to Sample Matched Serum





Wholly Owned Pipeline, Fully Funded Partnerships

Affimer®

Avacta's lead cancer immunotherapy programmes

Discovery	Clinical Candidate	IND	Phase 1
AVA004 PD-L1			
AVA6000 FAP SUBSTRATE (PRO-DOXORUBICIN)			
AVA021 PDL1/LAG-3 BISPECIFIC			
AVA004-100 PD-L1/I-DASH			
I-O PIPELINE			

Tufts University School of Medicine

Tufts University School of Medicine

Undisclosed	LG Chem Life Sciences	Multi-target development partnership and licensing deal worth up to $310m with $2.5m upfront, $5.5m in near-term milestones, royalties on future products and full research costs
Undisclosed	moderna	Multi-target research collaboration initiated 2015. Commercial option exercised 1Q19 to take one or more Affimer lead molecules into clinical development.

Tumour Targeted Chemotherapy: AVA6000 Pro-doxorubicin Phase I Study in 2Q2020

Affimer®

Avacta's lead FAP activiated chemotherapy programme AVA6000 (Pro-doxorubicin) addresses a significant unmet need in a $1bn market

Existing Doxorubicin Market

- Doxorubicin has been the standard of care treatment for over 40 years for patients with advanced soft tissue sarcomas (ASTS).
- However, patients are taken off treatment due to irreversible heart failure once the cumulative dose reaches 450 mg/m^2, even if they are experiencing clinical benefit.
- As a result, median progression free survival for ASTS patients is approximately 6 months, with median overall survival of 12-15 months.
- **This severe cardiotoxicity limits the size of the Doxorubicin market, but it is still nearly $1bn.**

Global liposomal doxorubicin market: $910m (2018) and is expected to reach $1.41bn by the end of 2025 (6% CAGR)

Avacta's Pro-doxorubicin Opportunity

- **AVA6000 Pro-doxorubicin is inert until activated in the tumour thus reducing the exposure of the heart to the drug.**
- In mice:
  - Maximum tolerated dose >6x that of Doxorubicin
  - 18 x higher exposure of tumour to activated Doxorubicin compared with heart tissue
- No dose limiting toxicities or severe toxicity reported in dogs up to 2mg/kg

Avacta will file IND/CTA in 1Q2020 to dose first patients with AVA6000 pro-doxorubicin in 2Q2020 with initial read-out expected in 3Q2020.

Positive data could lead to a significant licensing opportunity for AVA6000 and other tumour targeted chemotherapies

AVA6000 Potential Partnering Opportunities

Affimer®

Companies with Existing Doxorubicin Products

Companies with sales forces and relevant doxorubicin commercialization experience and contacts

- **Approved Generic Doxorubicin HCl**
  - Brand Names: Adriamycin, Adriamycin RDF, Rubex, Adriamycin PFS
  - **Most notable companies include BMS, Pharmachemie and Abraxis**
- **Approved Liposomal Doxorubicin Formulations**
  - Brand Names: Doxil, Dox-SL, LipoDox, Evacet, Nudoxa, Myocet
  - **Most notable companies include J&J, Sun Pharma, Teva**

Companies with Ongoing Checkpoint Inhibitor + Doxorubicin Clinical Studies

Large pharma testing combinations of antibodies/ receptor traps with doxorubicin (including liposomal Dox)

- **Involving PD-L1/PD-1 Inhibitors**
  - **AstraZeneca/Medimmune, BMS, Merck, Roche/Genentech, Pfizer**
- **Involving Other Checkpoint Inhibitors**
  - **BMS**: Ipilimumab (anti-CTLA-4)
  - **AstraZeneca/Medimmune**: Tremelimumab (anti-CTLA-4)

Companies with Other Ongoing Doxorubicin Clinical Studies of Note

- **Roche, Biocon and/or Mylan**: Trastuzumab (anti-HER2)
- **Genentech**: Bevacizumab (anti-VEGF-A)
- **Eli Lilly/Merck KGaA**: Cetuximab (anti-EGFR)

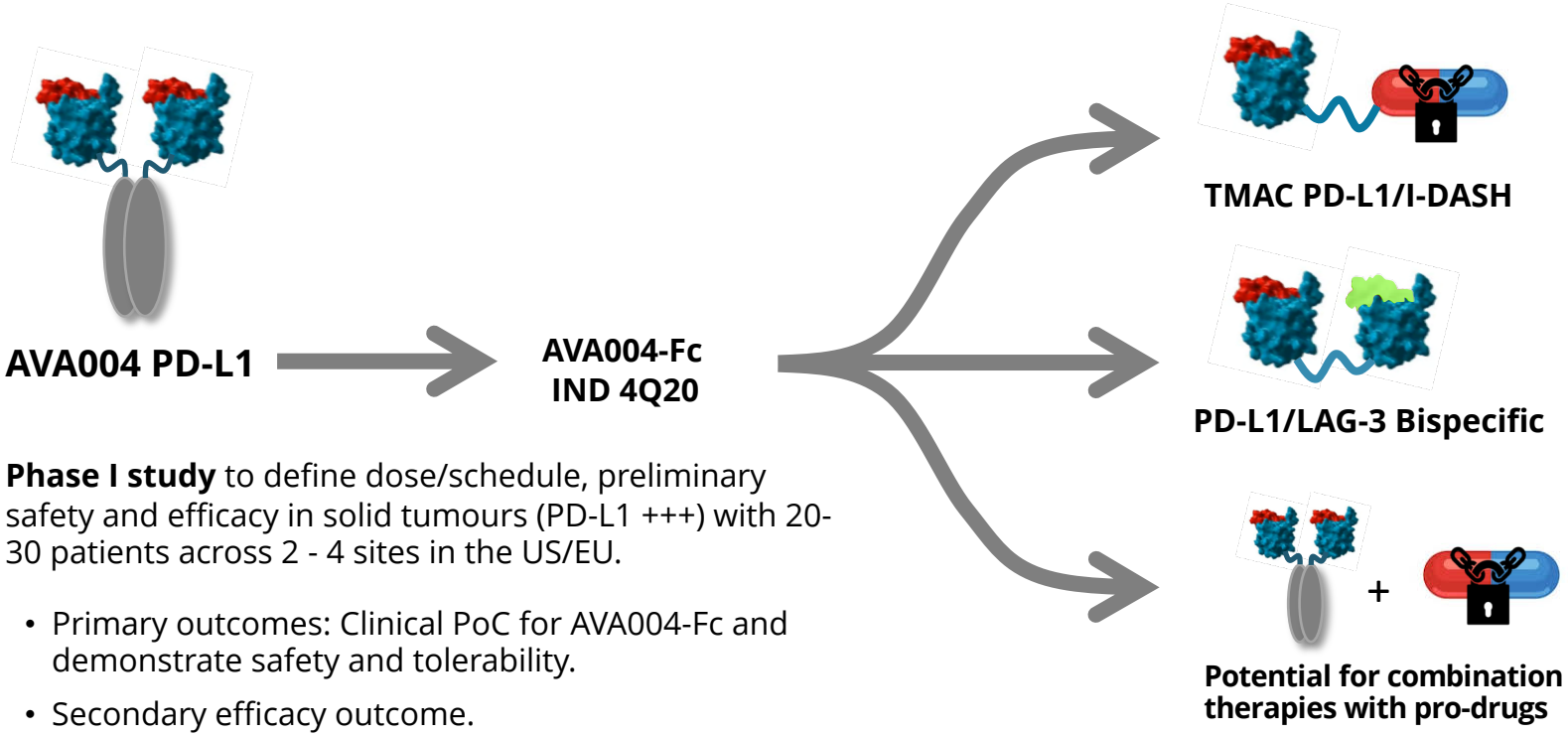
Indicative Deal Structure

- $50M in upfront and near-term milestones
- $300-500M in pivotal and market authorization milestones
- Low to mid-single digit royalties

AVA004-Fc Timeline

Affimer®

De-risking the Affimer platform and generating a proprietary basis for TMAC conjugates, bispecifics and combination therapies



Phase I study to define dose/schedule, preliminary safety and efficacy in solid tumours (PD-L1 +++) with 20-30 patients across 2 - 4 sites in the US/EU.

- Primary outcomes: Clinical PoC for AVA004-Fc and demonstrate safety and tolerability.
- Secondary efficacy outcome.
- Validates the Affimer platform, de-risks it for partners.
- Supports the development of PDL1 anchored TMAC molecules and bispecifics.

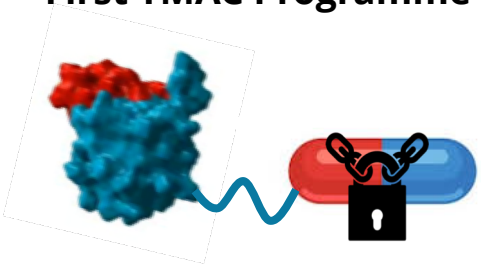
Avacta's Proprietary TME Activated Drug Conjugates (TMAC™)

Affimer®

Targeting and release of pro-inflammatory drugs in the tumour microenvironment synergises the innate and adaptive immune responses

First TMAC Programme

Affimer® **PD-L1 inhibitor**



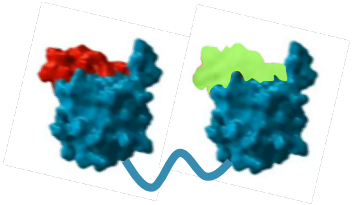
FAPα sensitive linker

I-DASH inhibitor warhead

Tufts University School of Medicine

Future Developments

Immuno-oncology Active Targeting



Induction/maintenance of adaptive immune response overcoming immune evasion.

- PD-L1, other immune-checkpoints, bispecifics and costimulatory receptors
- Additional tumour targeting

Synergistic Toxins

I-O Active warheads **targeting "bystander" cells**, including macrophage, NK cells, etc. and supporting tumor stroma – e.g:

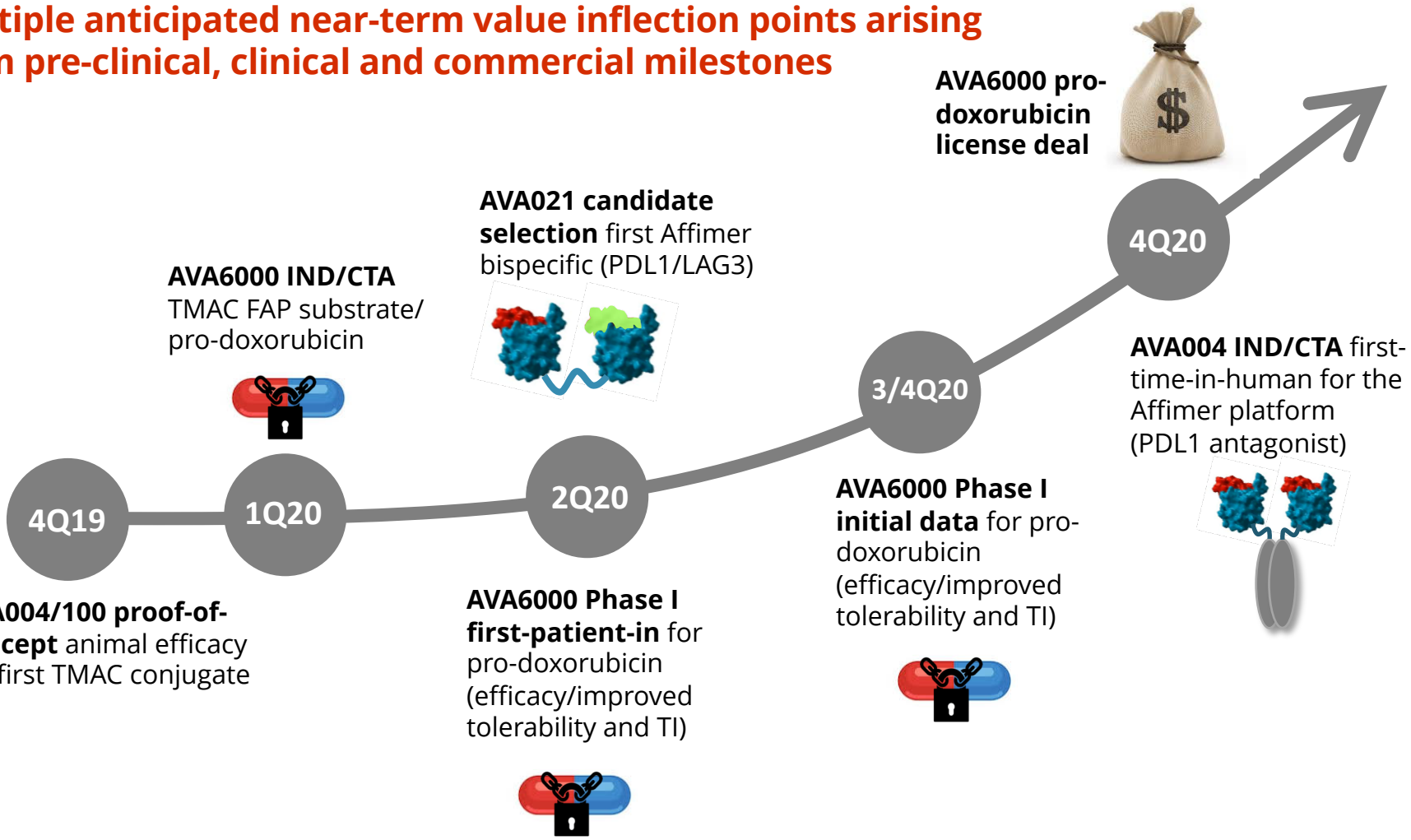
- I-DASH = DPP8/9 inhibitor
- Proteasome; AKT; CDK inhibitors
- STING; TLR7/8 agonists

Patent Application July 2018: *Tumor Microenvironment – Activated Drug-Binder Conjugates, and Uses Related Thereto.* US Patent Application Serial Number 62/680,300

Key Anticipated Milestones 2019-20

Affimer®

Multiple anticipated near-term value inflection points arising from pre-clinical, clinical and commercial milestones



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Geoff Nash / Giles Rolls – Nominated Advisors
Tim Redfern / Alice Lane – Corporate Broking
www.finncap.com
T +44 (0) 207 220 0500

WG Partners (Broker)
Nigel Birks / Nigel Barnes
Andrew Craig/ Claes Spang
T +44 (0) 203 705 9318
www.wgpartners.co.uk

Yellow Jersey PR
Sarah Hollins / Katie Bairsto
Sarah@yellowjerseypr.com
www.yellowjerseypr.com
M +44 (0)7764 947 137

Solebury Trout Investor Relations
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Intellectual Property

Affimer®

Protection of the Affimer background technology, individual Affimers and applications

First Generation Affimer Technology for Therapeutics (WO 2009/136182; PCT/GB2009/050380)

- Acquired from the Medical Research Council and Leeds University UK in 2012.
- Based on human stefin A with multiple mutations to reduce dimerisation and prevent binding to cathepsin.
- Patents granted in EU, US, Asia; Priority date: 2009.
- Current technology for therapeutic programmes.

Next Generation Affimer Technology for Therapeutics (PCT/GB2018/051855)

- Developed in-house and based on human stefin A with improved biophysical properties and minimal mutations from human sequence for therapeutics; broad claims based on protein engineering and not on a specific sequence.
- Priority date: July 2017.
- New technology for future therapeutic programmes.

Affimer Technology for Research and Diagnostics (WO 2014/125290; PCT/GB2014/050435)

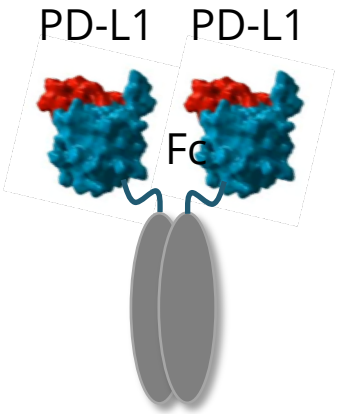
- Affimer technology based on plant cystatin consensus sequence; high stability suitable for challenging applications in research and diagnostics.
- IP exclusively licensed to Avacta by Leeds University; Priority date: 2014.

Recent Application Patents

- PD-L1 Binding Affimers, and Uses Related Thereto. UK Patent Application Serial Number 805963.4
- Tumor Microenvironment – Activated Drug-Binder Conjugates, and Uses Related Thereto. US Patent Application Serial Number 62/680,300
- Multiple patent applications in preparation covering Affimer Xt, LAG-3 antagonists etc.

1. AVA004 PD-L1 Antagonist IND/CTA 4Q20

First-time-in-human for the Affimer platform and creating a proprietary PD-L1 backbone for TMAC conjugates, bispecifics and combination therapies



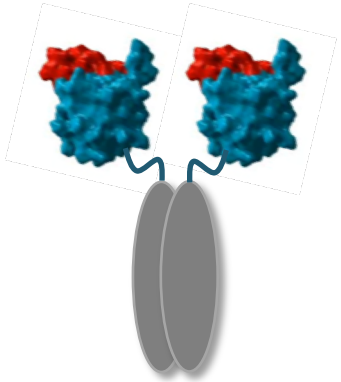
Selected Pre-clinical Data

AVA004-Fc Candidate *in-vitro* Performance

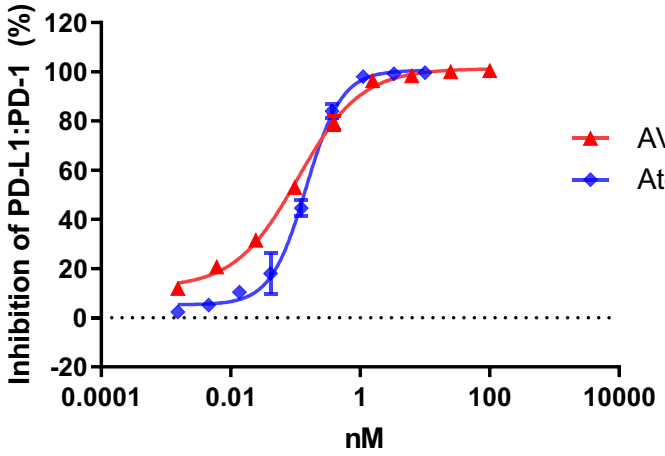
Affimer®

Fc formatted Affimer PD-L1 antagonist shows blockade and cytokine response similar to approved mAbs indicating that the potency is sufficient to overcome the immunosuppressive effect of PD-L1 expression

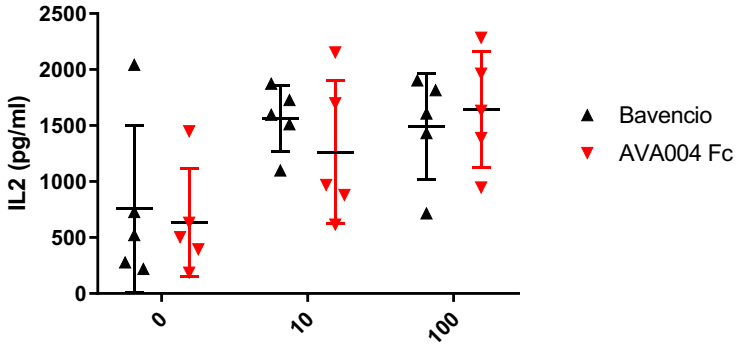
PD-1/PD-L1 Blockade vs Tecentriq (atezolizumab)

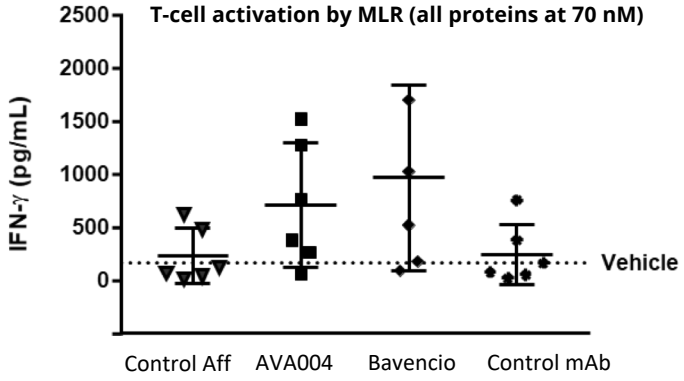


	EC_{50} (nM)
AVA004-Fc4	0.096
Tecentriq	0.147



AVA004-Fc T-cell Activation vs Bavencio (avelumab)





AVA004-Fc PK in Mice

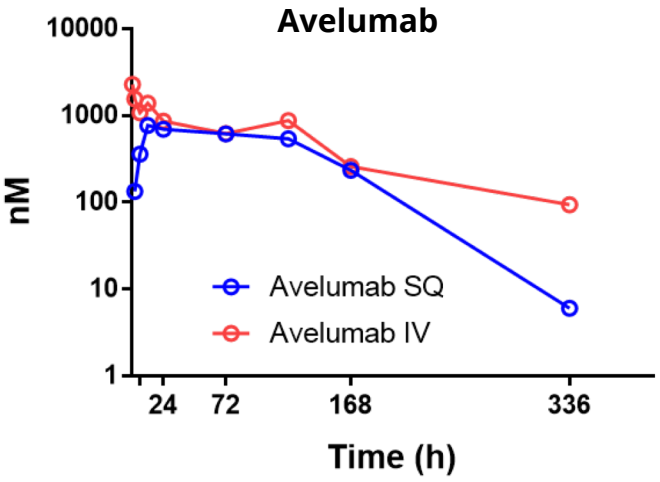
Affimer®

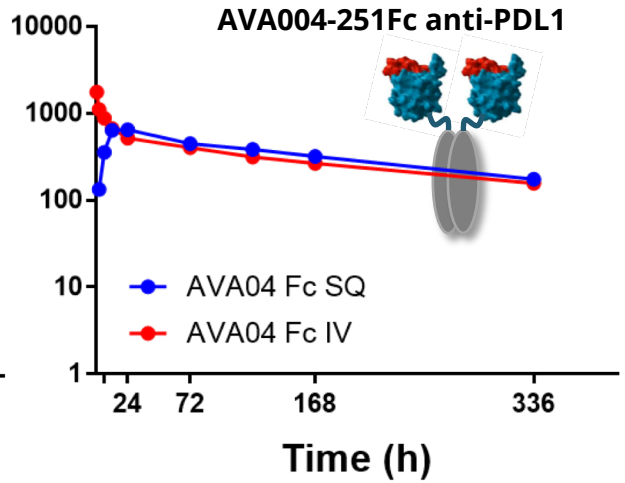
Optimal PK properties when injected both intra-venously and sub-cutaneously compared with Bavencio (avelumab)

C57/Black6 Mice PK

- C57/Black6 mice were injected with AVA004-Fc or Bavencio at 10 mg/kg via IV or sub-cutaneous (SQ) route.

Affimer Fc vs Bavencio IV and SQ





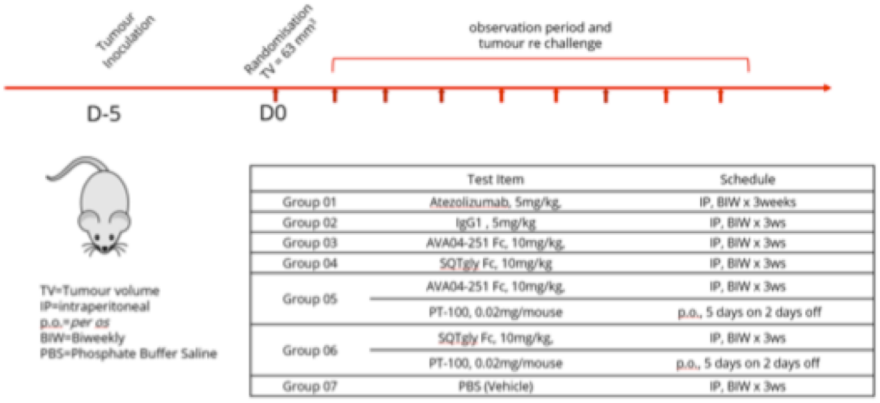
Sample	Est. T1/2 (h)
Avelumab SQ	61
Avelumab IV	83
AVA004 Fc SQ	184
AVA004 Fc IV	172

AVA004-Fc Efficacy vs Tecentriq

Affimer®

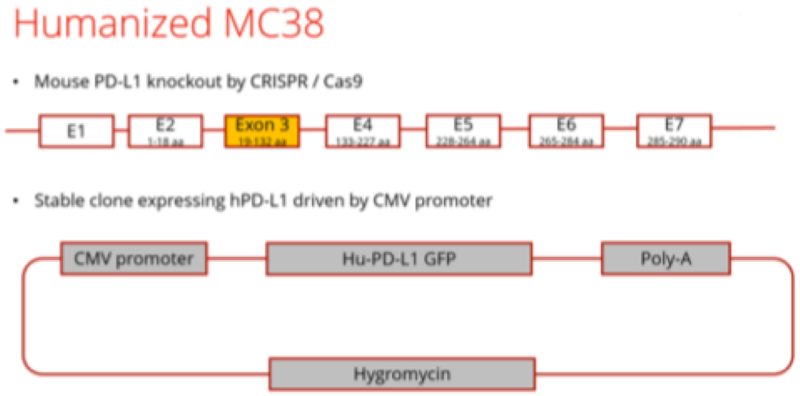
Affimer PD-L1 antagonist in shows comparable performance to Tecentriq in MC38 humanized PD-L1 mouse model

Humanized MC38 Model

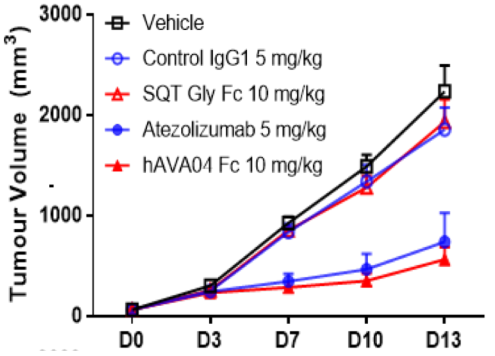


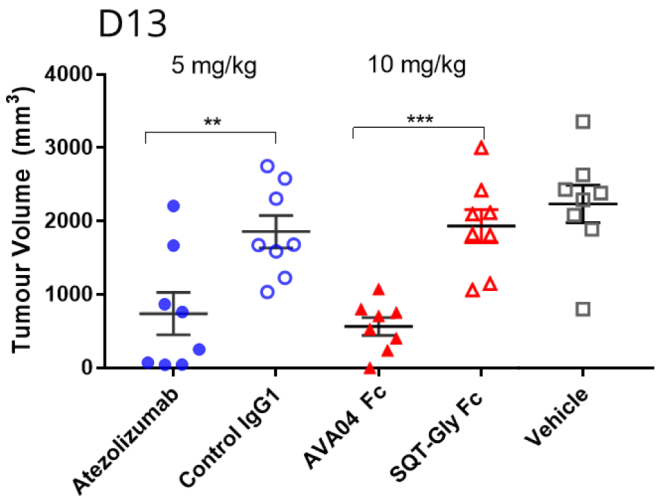
	Test Item	Schedule
Group 01	Atezolizumab, 5mg/kg,	IP, BIW x 3weeks
Group 02	IgG1 , 5mg/kg	IP, BIW x 3ws
Group 03	AVA04-251 Fc, 10mg/kg,	IP, BIW x 3ws
Group 04	SQTgly Fc, 10mg/kg	IP, BIW x 3ws
Group 05	AVA04-251 Fc, 10mg/kg,	IP, BIW x 3ws
	PT-100, 0.02mg/mouse	p.o., 5 days on 2 days off
Group 06	SQTgly Fc, 10mg/kg,	IP, BIW x 3ws
	PT-100, 0.02mg/mouse	p.o., 5 days on 2 days off
Group 07	PBS (Vehicle)	IP, BIW x 3ws

TV=Tumour volume
IP=intraperitoneal
p.o.=*per os*
BIW=Biweekly
PBS=Phosphate Buffer Saline



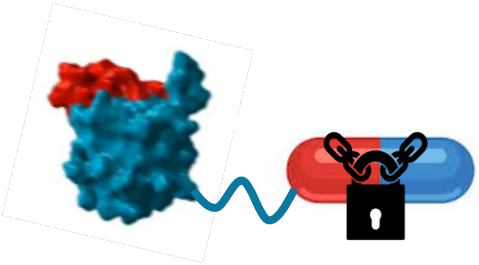
Affimer vs Tecentriq (atezolizumab)





2. Tumour Microenvironment Activated Drug Conjugates (TMACs™)

A **novel drug conjugate platform** that seeks to synergistically combine stimulation of the innate immune response by pro-inflammatory drugs with induction/maintenance of the adaptive immune response using Affimer checkpoint modulators.



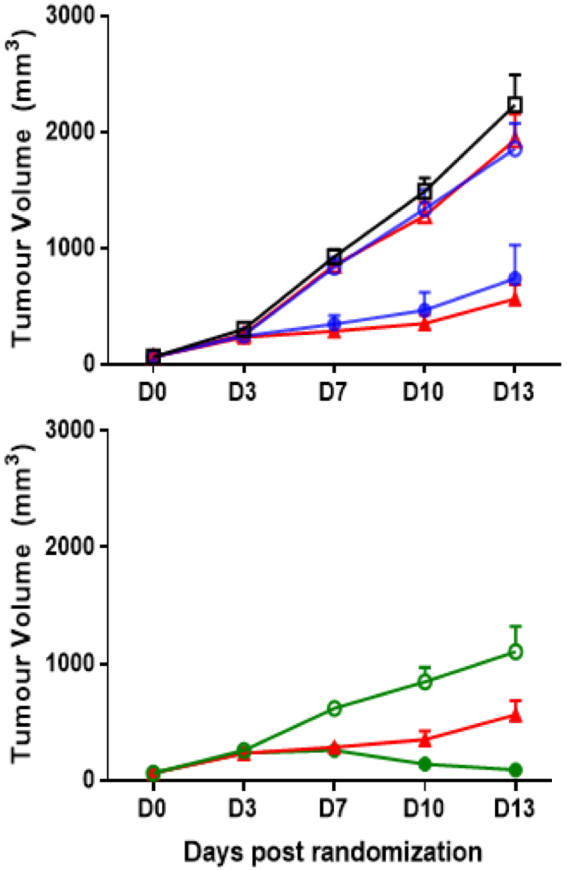
Selected Pre-clinical Data

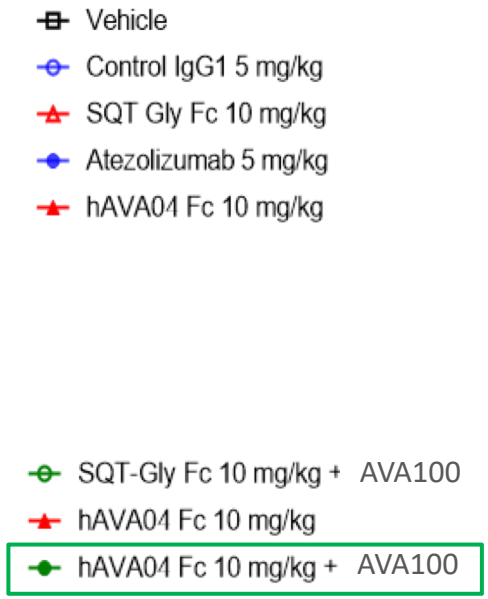
AVA004 Fc anti-PD-L1/AVA100 Combination

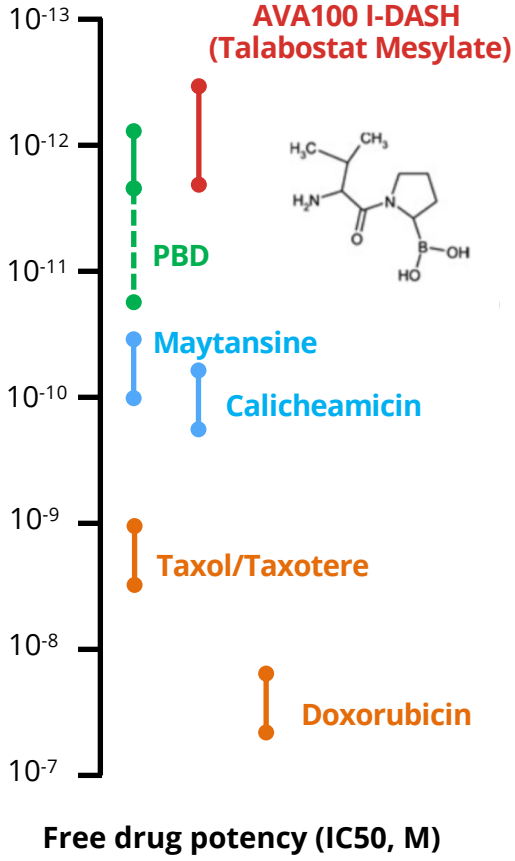
Affimer®

Affimer PD-L1 antagonist in combination with AVA100 I-DASH inhibitor in MC38 humanized PD-L1 model shows improved tumour response

Affimer PD-L1 + AVA100 Combination in MC38 Model





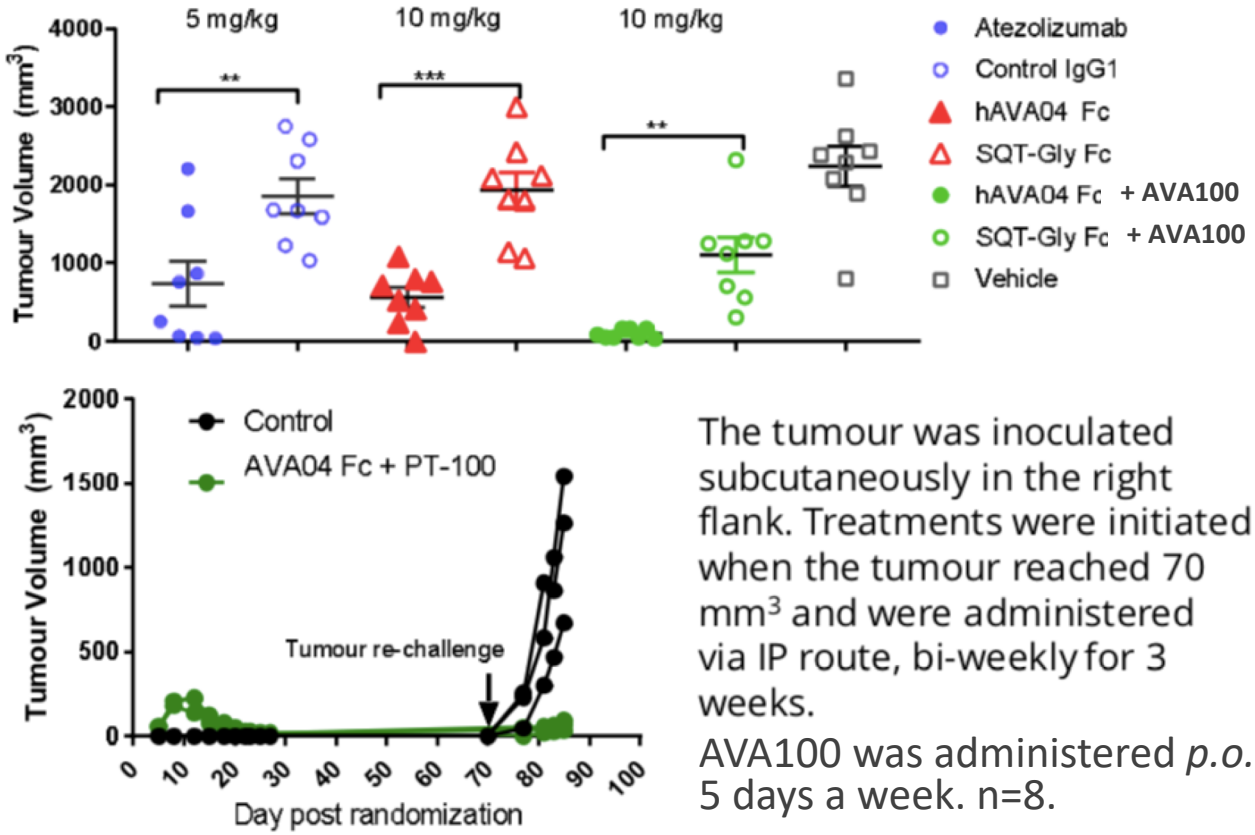


AVA004 Fc anti-PDL1/AVA100 Combination

Affimer®

Affimer PD-L1 antagonist in combination with AVA100 I-DASH inhibitor in MC38 humanized PD-L1 model shows immunity to re-challenge

Affimer PD-L1 + AVA100 Combination in MC38 Model



The tumour was inoculated subcutaneously in the right flank. Treatments were initiated when the tumour reached 70 mm^3 and were administered via IP route, bi-weekly for 3 weeks.

AVA100 was administered *p.o.* 5 days a week. n=8.

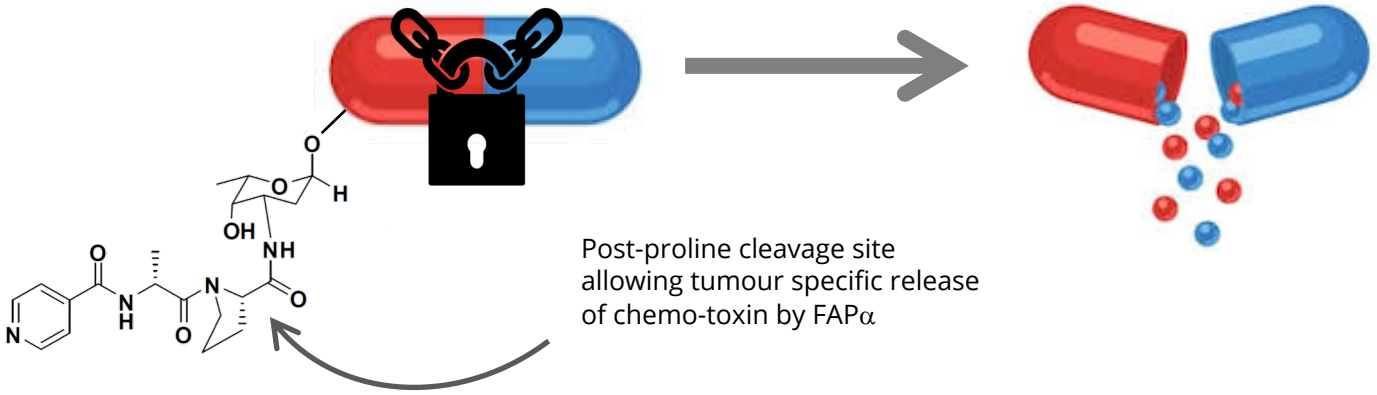
TMAC First Base: FAP Activated Pro-drugs

Affimer®

Tumour specific activation limits systemic exposure, improves safety and therapeutic index for stand-alone chemo and in combination with checkpoint therapies

Circulating pro-drug cannot enter cells and is therefore inert

Tumour targeted activation of drug by FAP

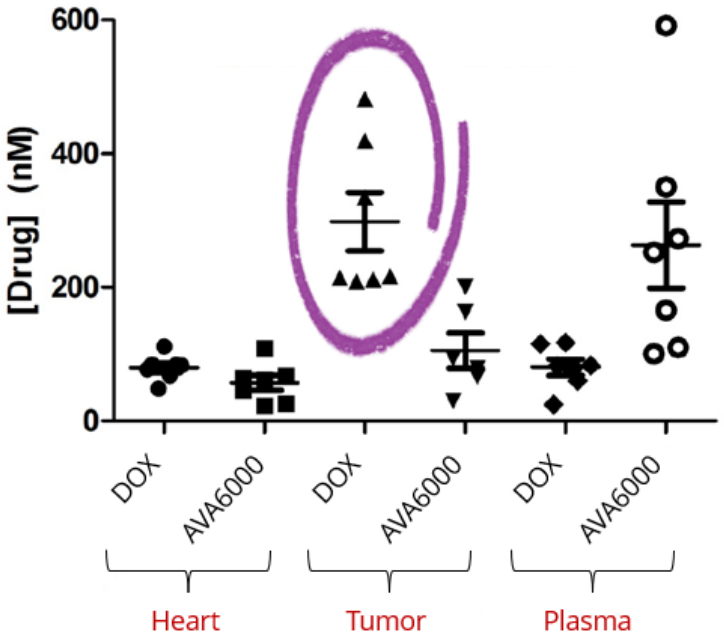


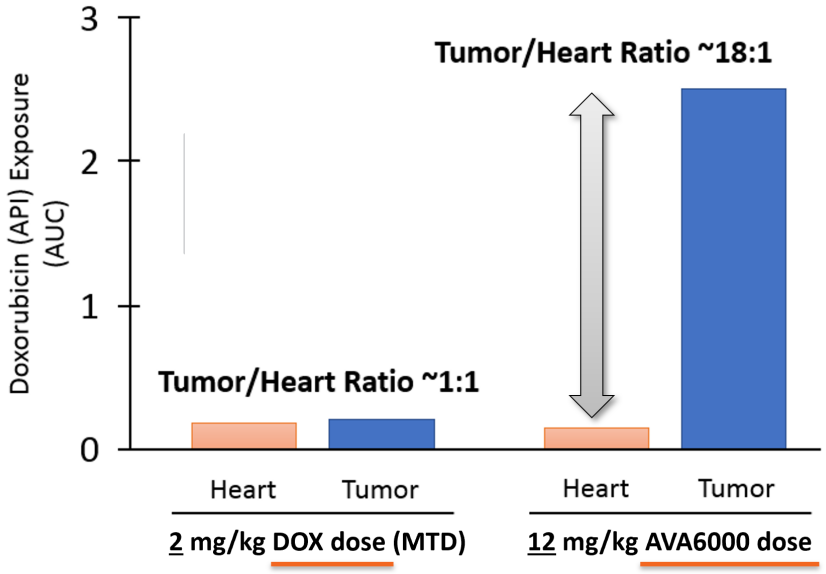
Post-proline cleavage site allowing tumour specific release of chemo-toxin by FAPα

AVA6000 Pro-doxorubicin Selectively Delivers Doxorubicin to the Tumour

Affimer®

Differential intra-tumoural exposure relative to cardiac tissue creates substantial opportunity for improved therapeutic index for chemotherapies

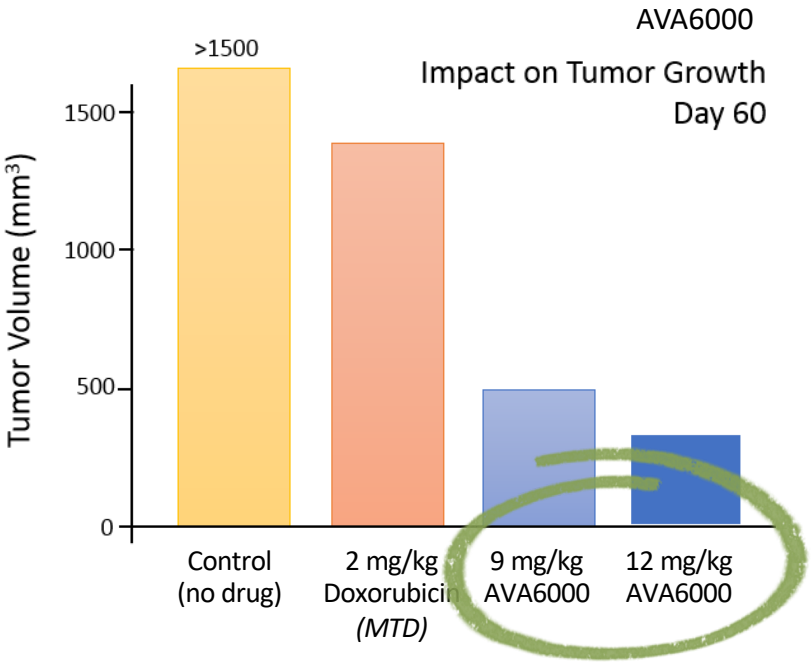




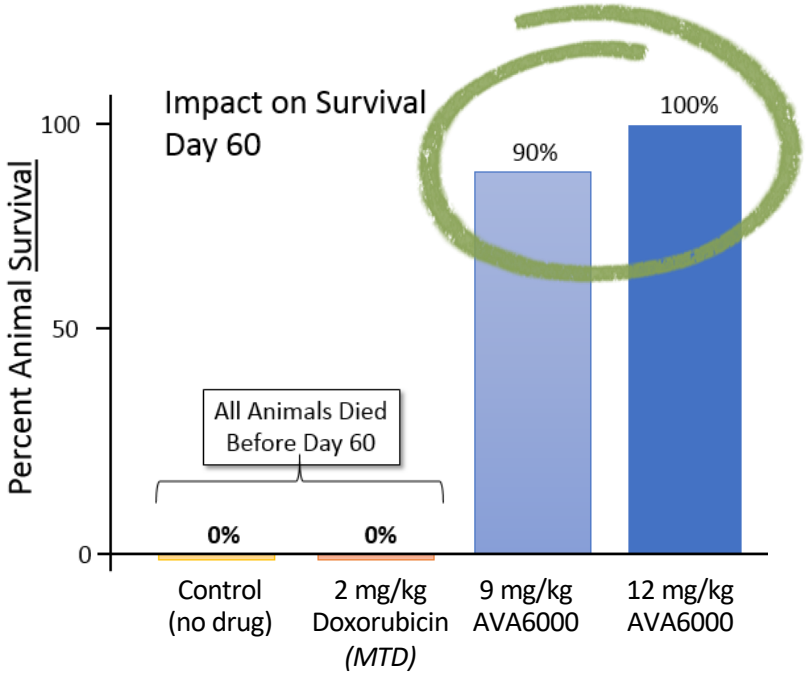
AVA6000 Pro-doxorubicin Efficacy

Affimer®

AVA6000 Pro-doxorubicin permits higher doses than the MTD for doxorubicin resulting in better anti-tumour activity in mouse xenograft model



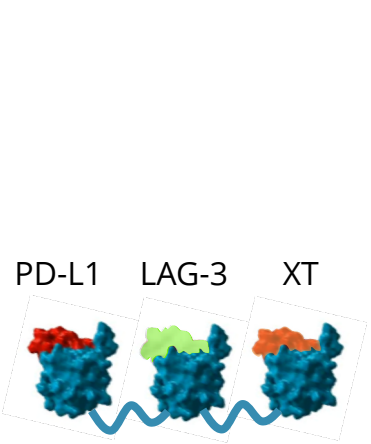
AVA6000 can be dosed at higher concentrations than the MTD for doxorubicin

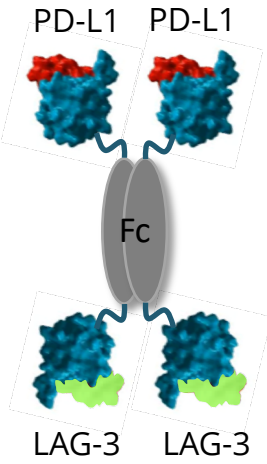


AVA6000 significantly reduced tumour volume and improved survival, relative to doxorubicin

3. AVA021 PDL1 x LAG3 Bispecific

First Affimer bispecific combining AVA004 PD-L1 antagonist with a LAG-3 antagonist to tackle two established treatment resistant pathways in a single entity





- Programme: AVA021 PD-L1/LAG-3 Bispecific
- Progress: *(selected data in Appendix)*
  - Several LAG-3 inhibitor lead molecules generated
  - AVA021 PD-L1/LAG-3 bispecific lead molecule shows a higher level of cytokine release than PD-L1 blockade alone in T-cell activation assay
- Next milestones:
  - LAG-3 lead molecule selection 4Q19
  - Pre-clinical animal models and bispecific candidate selection 2Q20
  - IND/CTA application early 2022

AVA021 PD-L1/LAG-3 Bispecific Programme

Affimer®

Fc and In-line Formats for Evaluation

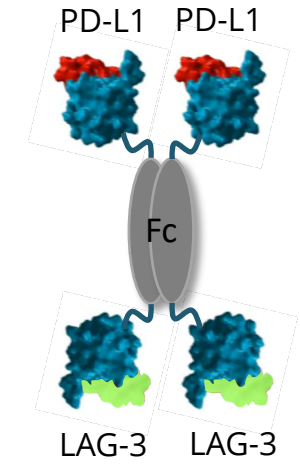
Clinical/Biological Rationale:

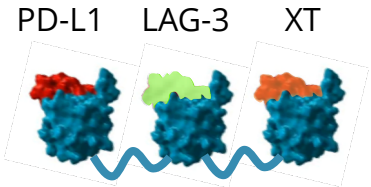
- T cells that are continuously exposed to tumour antigen become progressively inactivated through a process termed “exhaustion”.
- Inhibition of LAG-3 interaction with MHC II both activates T effector cells (by downregulating the LAG-3 inhibiting signal into pre-activated LAG3+ cells) and inhibits induced (i.e. antigen-specific) Treg suppressive activity.

Ongoing Clinical Studies:

- >50 clinical trials involving LAG-3 inhibitors, including BMS, Merck, Novartis & Regeneron as sponsors
  - Across a wide range of tumour types – including TNBC and metastatic breast cancer, NSCLC, melanoma, esophagogastric cancer, metastatic renal carcinoma and Head and Neck Cancer (HNSCC).
  - About half of the ongoing trials are testing combinations with PD-1/PD-L1 inhibitors.
  - Two bispecifics in Phase I of note: LAG-3/PD-L1 (F-Star & Merck) bispecific Ab and LAG-3/PD-1 DART (Macrogenics)

Fc Bispecific Format



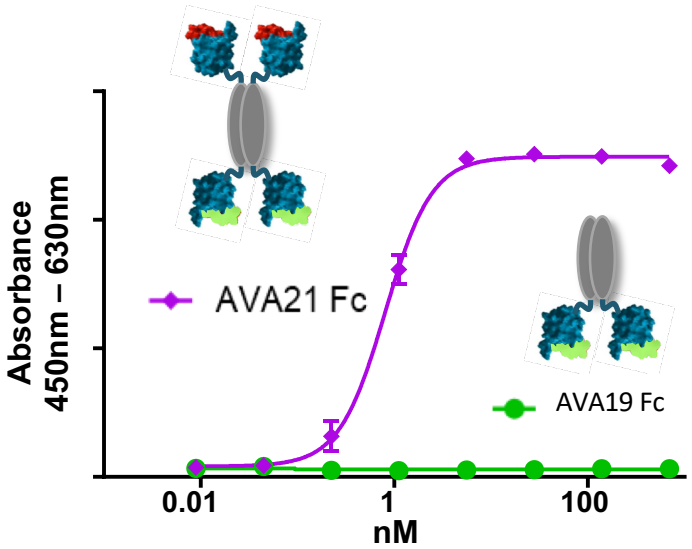


AVA004/019/021 Human PBMC SEB Assay

Affimer®

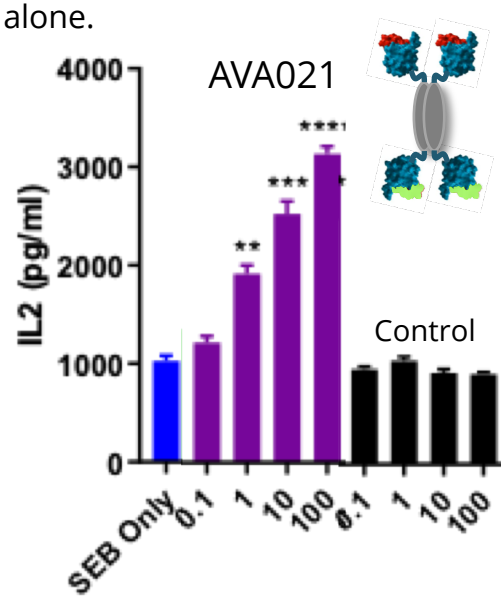
The combination of anti-PD-L1 and anti-LAG-3 Affimers is more potent, and causes a greater level of cytokine release than anti-PD-L1 blockade alone

Bridging ELISA



Cytokine Release

- The functionality of the bispecific was tested with human PBMCs from three donors stimulated with SEB.
- The AVA021 PD-L1/LAG-3 bispecific shows a higher level of cytokine release than PD-L1 blockade alone.



Data for the pooled donors are presented as mean +/- S.E.M. pg/ml (n=3). **p<0.01, ***p<0.001, ****p<0.0001, using two-way ANOVA with Dunnett's post-test comparing test substances to SEB only.

AVA021 PD-L1/LAG-3 Bispecific Timeline

Affimer®

LAG3 candidate selection likely to occur well ahead of schedule - IND submission for AVA021 PD-L1/LAG-3 bispecific early 2022