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Avacta Group PLC
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Avacta Group plc

("Avacta" or "the Group" or "the Company")

Avacta Reported Updated Phase 1 Clinical Data of AVA6000 at the European Society for Medical Oncology (ESMO) Congress Demonstrating Multiple Ongoing, Durable Responses in Solid Tumors

AVA6000 is safe and well-tolerated in both study arms: every three weeks (Q3W) and every two weeks (Q2W) dosing, with an early lack of serious cardiac safety signal and preliminary evidence of efficacy

Multiple ongoing and durable RECIST responses observed in patients with FAP^{high} and doxorubicin sensitive diseases including in patients with stroma-only expression of FAP

pre|CISION-enabled doxorubicin (AVA6000) results in multiple fundamental changes in the pharmacokinetics of released doxorubicin in plasma and tumor versus conventional doxorubicin

Avacta Group plc (AIM: AVCT), a life sciences company developing innovative, targeted cancer treatments and powerful diagnostics, has presented updated data from the ongoing Phase 1a trial of AVA6000 in patients with FAP-positive solid tumors at the 2024 European Society for Medical Oncology (ESMO) Congress, in Barcelona, Spain.

The results, presented on Saturday September 14, demonstrate that AVA6000 is well-tolerated across the every 2 weeks and every 3 weeks dosing schedules with early evidence of efficacy supported by ongoing and durable RECIST responses in patients with FAP^{high} disease. AVA6000 is the first peptide drug conjugate (PDC) in the Avacta pipeline and consists of doxorubicin conjugated with a peptide moiety that is specifically cleaved by Fibroblast Activation Protein (FAP) in the tumor microenvironment (TME).

Professor Chris Twelves, Lead Investigator and Professor of Medicine, University of Leeds, commented:

"The AVA6000 data presented at ESMO continue to demonstrate encouraging efficacy with several ongoing, durable responses. The observed efficacy aligns with a highly favorable safety profile including a lack of the significant cardiac toxicity that is often seen with doxorubicin treatment.

"The mechanism of action of the pre|CISION™ peptide drug conjugates with the observed warhead release in tumors with lower FAP activity together speak to the potential of this platform to treat a broad range of solid tumor patient populations with clinical needs that are not being met. I am looking forward to working with the Company, colleagues and patients on the continued development of AVA6000."

Christina Coughlin MD, PhD, Chief Executive Officer of Avacta, added:

"With nearly six months of added follow-up, these compelling data strengthen the clinical validation for AVA6000 and the pre|CISION™ drug delivery platform to challenge current drug delivery methods and expand the reach of highly potent therapeutics using peptide drug conjugates.

"We believe our platform has the potential to revolutionize cancer treatment by enabling patients to achieve improved outcomes with fewer side effects by leveraging the tumor specific enzyme FAP to protect normal tissues from toxic drugs. The observation of warhead release in the tumor even in the setting of lower FAP activity is highly encouraging for our pipeline. We are excited to move our Company into the next stage of development, implementing these findings of this drug release mechanism across our innovative pipeline."

Trial Results Summary

As at the latest data cut-off date, ten dose cohorts (n=57) have completed the Phase 1a trial under the Arm 1 dosing schedule of every three weeks ("Q3W") and the Arm 2 dosing schedule of every two weeks ("Q2W"). In total, 57 patients were enrolled and are evaluable for safety (primary outcome measure) and 49 patients formed the efficacy evaluable dataset (secondary outcome measure).

Efficacy data

Cancer indications were categorized based on published data regarding both immunohistochemistry and FAPI-PET studies as FAP^{high} (soft tissue sarcoma and salivary gland cancer) or FAP^{mid} (pancreatic cancer, colorectal cancer, lung cancer and other malignancies). Patients with indications considered FAP^{low} were excluded from the trial. Patients had a median of two prior systemic cancer therapies (range 0-7) with 65% including cytotoxic exposure. Reduction in the sum of longest diameters (SLD) is used to measure response per RECIST 1.1 with partial responses of >30% reduction and minor responses of between >10% and <30% reduction.

- Among patients with FAP^{high} cancers (n=23), three partial responses and four minor responses were observed, including:
    - A durable, confirmed partial response at 12 weeks in a 79-year-old male patient with progressive salivary gland cancer (SGC). After an initial minor response (22% reduction in SLD), the observed durable PR is ongoing despite patient discontinuation due to lifetime maximum dosing (duration of response >18 weeks, with 46.2% reduction in SLD). Tumor histology demonstrates no expression of FAP in tumor cells with only stromal cell expression noted.
    - A minor response (14.6% reduction in SLD at first 8-week scan) in a 65-year-old female patient with SGC who remains on the trial. This patient was dosed in the 250 mg/m2 Q2W cohort of the trial and had progression on a prior line of therapy. This patient continues on study. Similarly, the histology shows FAP-negative tumor cells and FAP expression only in the stromal compartment.
    - A partial response (40.5% reduction in SLD) in a 55-year-old male patient with dedifferentiated liposarcoma who had progressed on two prior lines of therapy in the metastatic setting. After an initial minor response this patient experienced a partial response with SLD change of -40.6%. The patient experienced new lesions at their latest follow-up scan.
- Eight patients remain on study in the Phase 1a cohorts with a diagnosis of FAP^{high} cancers

Among patients with FAP^{mid} cancers (n=26), two minor responses were observed.

Safety and Pharmacokinetics Data

Treatment with AVA6000 continues to be well-tolerated with the addition of the Q2W dosing regimen (Arm 2) with a favorable safety profile and reduction in severe and mild-to-moderate treatment-emergent toxicities as compared with conventional dose doxorubicin. A maximum tolerated dose has not been identified in either arm of the trial.

- Severe (CTCAE grade 3 or 4) neutropenia was observed in 14% of AVA6000 patients vs 49% treated with conventional dose doxorubicin (comparison made to a Ph III trial where doxorubicin monotherapy is the comparator arm in a similar patient population).[1] There were no cases of febrile neutropenia in the AVA6000 trial compared to 16.5% of patients receiving conventional doxorubicin alone in a similar patient population[1]
- The observed cardiac safety profile of AVA6000 compares favorably to conventional dose doxorubicin, with low incidence of left ventricular ejection fraction (LVEF) changes (LVEF dysfunction 12.3% v. 48.4% with conventional doxorubicin[1,2]) and no grade 3 or 4 severe cardiac events reported
- Reductions were observed in toxicities that impact quality of life including nausea, mouth sores, decreased appetite, constipation and vomiting and similar reductions were observed with both the Q3W and Q2W dosing schedules.as compared to conventional doxorubicin dosing[1]
- No new dose limiting toxicities were observed and neither arm has determined an MTD

Treatment with AVA6000 results in multiple fundamental changes in the PK of released doxorubicin (compared to conventional doxorubicin administration[3]) including:

- Extension of the plasma half-life by ~40%
- Reduction of approximately 40-50% in both C_{max} and the peripheral volume of distribution, suggesting AVA6000-released doxorubicin demonstrates a more limited distribution into normal tissues versus conventional doxorubicin[4,5]

Tumor biopsies taken 24 hours after the first dose of AVA6000 reveal additional insights regarding the role of FAP, in that the level of FAP positivity in the tumor appears not to correlate with the level of released doxorubicin in the TME (n=9). This lack of correlation indicates that lower levels of FAP activity are sufficient for warhead release. These

data provide evidence for targeting of the FAP^{mid} tumor types with novel warheads.

pre|CISION™ technology

Many solid tumors have higher levels of FAP compared with healthy tissues. Avacta's pre|CISION™ technology is designed to leverage the tumor-specificity of FAP expression by rendering a therapeutic warhead inert with the bound peptide moiety attached to the warhead, until it encounters FAP and is cleaved, releasing active warhead into the TME. FAP targeted release of the warhead specifically in the TME aims to reduce damage to healthy tissues and systemic side effects, improving the tolerability for patients and allowing optimization of the dosing schedule to improve efficacy.

References

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[3]Villalobos VM, *et al.* Pharmacokinetics of doxorubicin following concomitant intravenous administration of olaratumab (IMC-3G3) to patients with advanced soft tissue sarcoma. *Cancer Med*. 2020;9(3):882-893. doi: 10.1002/cam4.2728

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About Avacta Group plc - www.avacta.com

Avacta Group is a UK-based life sciences company focused on improving healthcare outcomes through targeted cancer treatments and diagnostics.

Avacta Therapeutics: a clinical stage oncology biotech division harnessing proprietary therapeutic platforms to develop novel, highly targeted cancer drugs.

Avacta Diagnostics focuses on supporting healthcare professionals and broadening access to diagnostics.

Avacta has two proprietary platforms, pre|CISION™ and Affimer®.

The pre|CISION™ platform is a highly specific substrate for fibroblast activation protein (FAP) which is upregulated in most solid tumors compared with healthy tissues. The pre|CISION™ platform harnesses this tumor specific protease to activate pre|CISION™ peptide drug conjugates and pre|CISION™ antibody/Affimer® drug conjugates in the tumor microenvironment, reducing systemic exposure and toxicity, allowing dosing to be optimised to deliver the best outcomes for patients.

The lead pre|CISION™ program AVA6000, a peptide drug conjugate form of doxorubicin, is in Phase 1 studies. It has shown an improvement in safety and tolerability in clinical trials to date compared with standard doxorubicin and preliminary signs of clinical activity in multiple patients.

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