A phase 1b dose escalation study of AV-380 in combination with standard of care chemotherapy in metastatic cancer patients with cachexia and elevated GDF-15 levels

Arvind Chaudhry,[1] Richard Zuniga,[2] J. Eva Selfridge,[3] Bruno Bastos,[4] Vipin Lohiya,[5] Vijay Kasturi,[6*]

[1]Summit Cancer Centers, Spokane Valley, WA, US; [2]New York Blood and Cancer Specialists, New York, NY, US; [3]University Hospitals Cleveland Medical Center, Cleveland, OH, US; [4]Baptist Health Miami Cancer Institute, Miami, FL, US; [5]Piedmont Cancer Institute, Fayetteville, GA; [6]AVEO Oncology, Boston, MA US

Background and Rationale

- Cachexia is a complex metabolic syndrome characterized by involuntary weight loss leading to progressive weakness, atrophy, resistance to therapy, and ultimately death.
- Cachexia affects more than 5 million people in the United States[1], and 400,000 cancer patients
- The prevalence and mortality of cachexia represent a significant unmet therapeutic need given that the current treatment, traditionally focused on nutrition, has very limited efficacy.[2]

Growth Differentiation Factor-15 (GDF-15) and Cachexia

- Chronically elevated levels of circulating growth differentiation factor-15 (GDF-15) are associated with cachexia.[2]
- Tumors have been shown to markedly overexpress GDF-15 in patients with colorectal cancer (CRC), pancreatic cancer, prostate cancer, metastatic breast cancer, and other malignancies. [3-9]
- In nonclinical tumor models, GDF-15 was consistently elevated in tumor bearing mice and was very low or undetectable in the non-tumor bearing controls[10, 11, 12].
- Treatment with humanized GDF-15 neutralizing antibody reversed the cachectic phenotype without affecting tumor growth kinetics or proliferation rate.

Rationale for AV-380

- AV-380 is an antibody that binds with high affinity to GDF-15 resulting in its elimination from circulation.
- AV-380 has been shown to reverse weight loss and increase recovery of muscle in animal cancer models and was well tolerated without serious AEs in a phase 1 study.
- The study is designed to determine whether the addition of AV-380 to standard-of-care (SoC) chemotherapy will confer additional clinically meaningful benefits in metastatic cancer patients with cachexia.

Study Protocol and Procedures

Objectives

- **Primary:** Refine the dose and schedule of AV-380 and establish adverse event (AE), pharmacokinetic (PK), and pharmacodynamic (PD) profiles in metastatic cancer patients with cachexia (as defined by Fearon criteria) and elevated GDF-15 (>1200 pg/mL), receiving SoC chemotherapy in the first line setting for metastatic cancer.
- **Secondary:** Assess validated measures of cachexia in metastatic cancer patients receiving AV-380 and determine its immunogenic potential.
- **Exploratory:** Establish the benefit/risk of combining AV-380 with SoC chemotherapy and assess exploratory biomarkers.

Study Design

- Phase 1, open-label, dose escalation, multicenter study (**NCT05865535**).
- Approximately 4-6 patients per each of 5 cohorts is planned (**Figure 1**).
- Enrollment will follow a standard 3+3 design.
- Dose de-escalation may be initiated after review of the data obtained from Cohort 1.
- If dose de-escalation occurs, the de-escalation cohorts will replace cohorts 4 and 5.
- Eligible patients will initiate their SoC chemotherapy regimen and have received at least 2 cycles of chemotherapy prior to enrolling into this study **(Figure 2)**.
- Patients will remain enrolled until they start 2nd-line systematic anticancer therapy, have unacceptable toxicity related to AV-380, complete 4 course of AV-380, withdraw consent, or sponsor terminates study.

Figure 1: Study schema

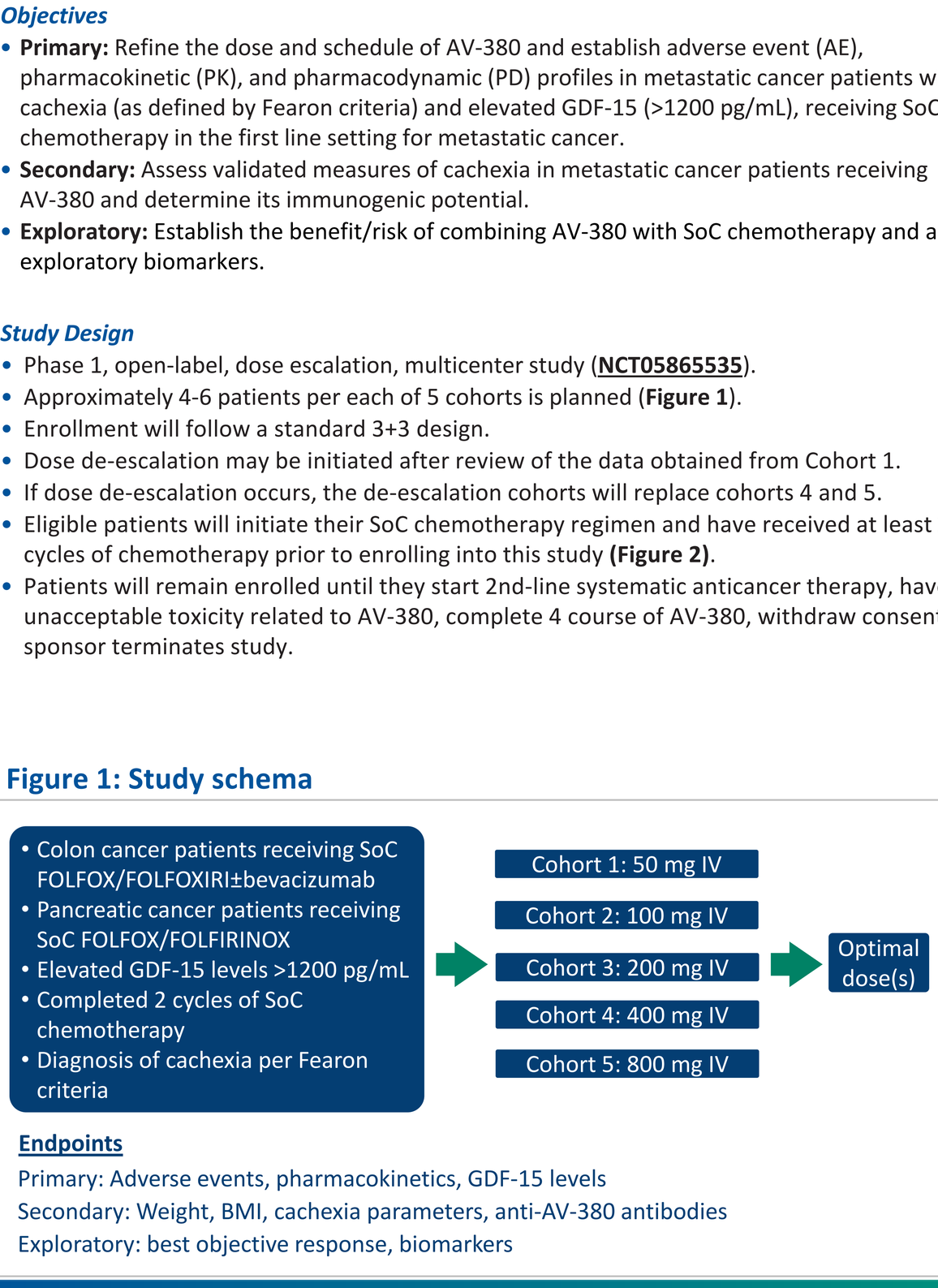
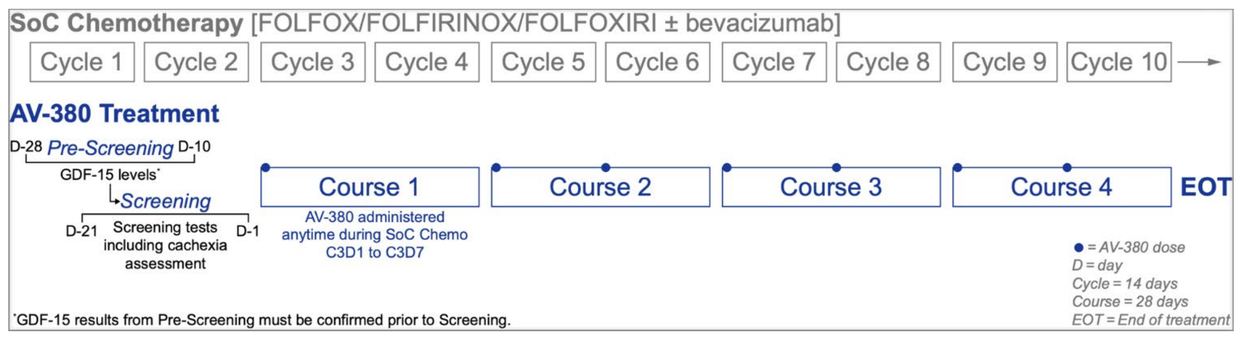


Figure 2: Study design flow



Enrollment Criteria

- Key enrollment criteria are shown in **Table 1**

Table 1. Key Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Age ≥18 years	Significant clinical manifestation of any allergic, dermatological, hepatic, renal, hematological pulmonary, metabolic, cardiovascular, gastrointestinal, neurological, or psychiatric disorders.
Histologically confirmed metastatic CRC or pancreatic cancer, who are actively receiving SoC chemotherapy in the first line setting for metastatic disease; eligible patients must have completed at least 2 cycles of chemotherapy: • CRC patients who are receiving FOLFOX/FOLFOXIRI ± bevacizumab • Pancreatic patients who are receiving FOLFOX/FOLFIRINOX	Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery and stable for 2 weeks before first dose of study treatment.
Patients with cachexia as defined by Fearon criteria: • Weight loss > 5% over past 6 months (in absence of simple starvation) • BMI < 20 kg/m2 and any degree weight loss of > 2% • Sarcopenia and any degree of weight loss > 2%	Significant cardiovascular disease, including myocardial infarction within 3 months prior to start of protocol.
Patients with life expectancy ≥ 3 months	Corrected QT interval calculated by the Fridericia formula (QTcF) > 460ms within the screening period prior to the first dose of study treatment.
Patients with elevated GDF-15 of >1200 pg/mL	Uncontrolled pleural effusion or pericardial effusion
ECOG PS 0-1	Cachexia that is caused by other reasons (severe COPD, heart failure, or AIDS)
	Patients receiving parenteral nutrition at the time of screening.

Summary

- Cachexia has long been recognized as an adverse effect of cancer and is thought to be responsible for 20% to 30% of all cancer deaths.
- Elevated levels of circulating GDF-15 are associated with cachexia and tumors have shown to overexpress GDF-15 in patients with many types of cancer including CRC and pancreatic.
- AV-380 Is an antibody targeting GDF-15 that reversed weight loss and increased recovery of lost muscle in animal cancer models.
- This study is designed to determine whether the addition of AV-380 to SoC chemotherapy will provide additional clinically meaningful benefits in metastatic cancer patients with cachexia.

This phase Ib dose escalation study (NCT05865535) will evaluate the safety, pharmacokinetics, pharmacodynamics, and immunogenicity of AV-380 in metastatic colorectal and pancreatic cancer patients with cachexia who are undergoing standard of care chemotherapy.

References

1.Von Haehling S, Anker SD. J Cachexia Sarcopenia Muscle. 2014;5.
2.Johnen H, et al. Nat Med. 2007;13.
3.Mehta RS, et al. J Natl Cancer Inst. 2014;106.
4.Brown DA, et al. Clin Cancer Res. 2003;9.
5.Welsh JB, et al. Proc Natl Acad Sci USA. 2003; 100.
6.Brown DA, et al. Clin Cancer Res. 2003;9.
7.Rasiah KK, et al. *Cancer Epidemiol Biomarkers Prev*. 2006;14.
8.Wakchoure S, et al. *Prostate*. 2009;69:625-61.
9.Ganapathy V, et al. *Mol Cancer*. 2010; 9.
10. Lerner L, et al. *Oncol Lett*. 2016;12.
11. Lerner L, et al. *J Cachexia Sarcopenia Muscle*. 2016;7.
12. Lerner L, et al. *J Cachexia Sarcopenia Muscle*. 2015; 6.

Presented at the 7th Cancer Cachexia Conference, 28-30 September 2023, Edinburgh, Scotland

*Current affiliation: CG Oncology, Irvine, CA, US.