Effects of the Innate Immune System, Body Habitus, and Sex on the Pharmacokinetics (PK) and Antitumor Response of Anetumab Ravtansine in Patients with Solid Tumor

Li Chen[1,2], Andrew Lucas[1], Aaron Mansfield[3], Stephanie Lheureux[4], Claire O'Connor[1], Beth Zamboni[5], Kashish Patel[1], Jeffery Moscow[6], William Zamboni[1]

[1]University of North Carolina at Chapel Hill, Eshelman School of Pharmacy and Lineberger Comprehensive Cancer Center [2]Allucent [3]Mayo Clinic [4]Princess Margaret Cancer Centre [5]Carlow University [6]National Cancer Institute

BACKGROUND

- Anetumab ravtansine is an antibody-drug conjugate (ADC) targeting mesothelin and conjugated to the microtubule inhibitor DM4
- Antibodies and ADCs, like anetumab ravtansine, undergo clearance via Fc gamma receptors (FcγRs CD64, CD32, CD16) on cells of the innate immune system (IIS)[1].
- Most of antibodies and ADCs are dose based on metrics of body habitus, such as total body weight. However, high interpatient PK variability still exists after dosing based on total body weight[1].
- This study evaluated the association between patient covariates, including IIS biomarkers, body habitus and sex, and pharmacokinetics (PK) and pharmacodynamics (PD) variability of anetumab ravtansine.

METHODS

➢ Study 10150 (n = 16 patients)

- Patients with platinum-resistant or platinum refractory ovarian cancer
  - Treated with weekly anetumab ravtansine plus bevacizumab
    - Anetumab ravtansine 2mg/kg IV on Day 1, 8, 15, 22 every 28 days

➢ Study 10107 (n = 14 patients)

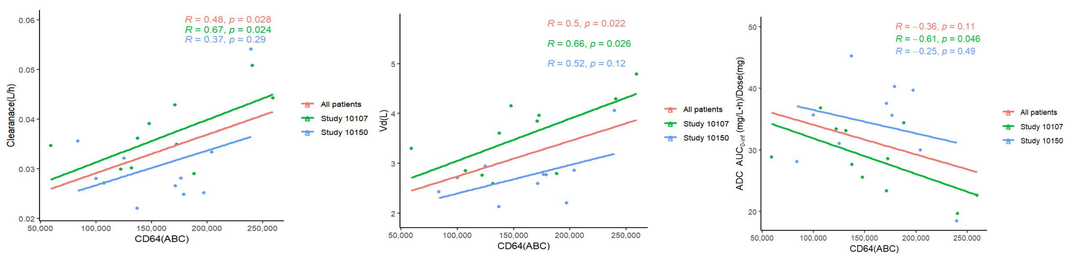
- Patients with mesothelin-positive pleural mesothelioma
  - Treated with anetumab ravtansine every 3 weeks plus pembrolizumab
    - Anetumab ravtansine 6.5 mg/kg IV on Day 1 of every 21 days
    - In obese patients, a maximum weight of 100 kg was used to calculate the dose of anetumab ravtansine

➢ PK Studies and Covariates Evaluated

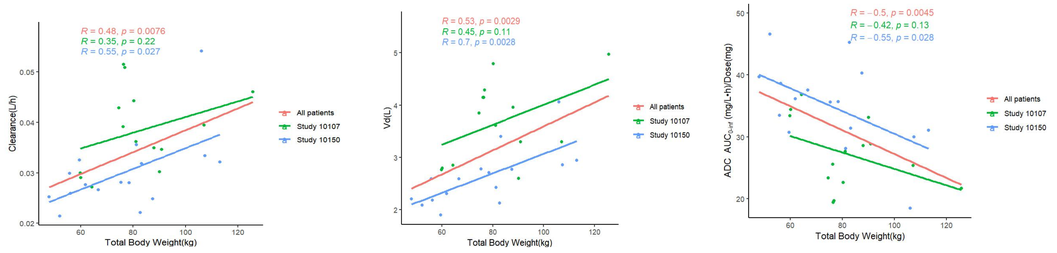
- Serial plasma concentrations of anetumab ravtansine (ADC), total antibody, and released DM4 and S-methyl metabolite of DM4 (DM4-Me) were measured.
- Noncompartmental PK analysis were generated using Phoenix WinNonlin
  - $AUC_{0\text{-}inf}$, $AUC_{0\text{-}168h}$, CL, Vd, C_{max}, T_{max}, k_e, and $T_{1/2}$
  - Dose normalized AUC and C_{max} were calculated:
    - By prescribed dose cohort = mg/kg
    - Per Unit Mg Dose Administered (PUMDA) = mg/kg x TBW kg = mg
- IIS FcγRs biomarkers: CD64, CD32, CD16 and total FcγRs on cycle 1 day 1 and cycle 1 day 8
- Body habitus metrics: Total body weight (TBW), Body surface area (BSA), Body mass index (BMI), and the ratio of total body weight and ideal body weight (TBW/IBW)
- Other covariates: Sex and age

RESULTS

➢ Relationship between IIS Biomarkers (FcγR CD64) and Anetumab Ravtansine PK

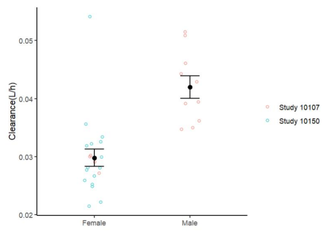


➢ Relationship between Metrics of Body Habitus and Anetumab Ravtansine PK

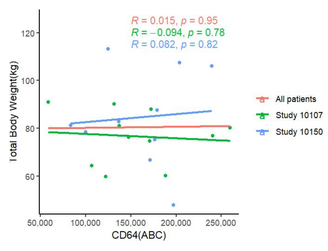


➢ Relationship between IIS Biomarkers, Body Habitus, and Sex and Anetumab Ravtansine PK

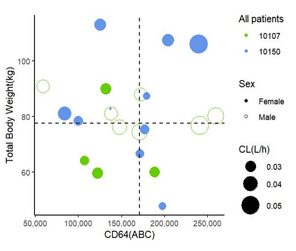
Effect of Sex on CL



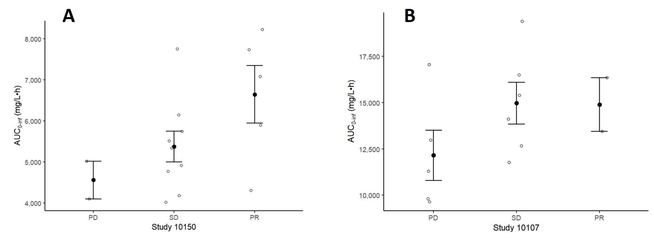
IIS CD64 and Total Body Weight



IIS CD64,Total Body Weight, and Sex Effects on CL



➢ **Anetumab Ravtansine PK and Antitumor Response**



CONCLUSIONS

- Individualizing the dose of anetumab ravtansine and potentially other mAbs and ADCs based on TBW is not optimal.
- The PK disposition of mAbs and ADCs is highly complex and influenced by more factors than just body size.
- Novel factors and biomarkers for the PK and PD of these agents need to be evaluated, such as the IIS biomarkers and sex of the patient.
- Results were consistent across two separate studies.
- The effect of cancer type on the IIS and the PK of antibodies and ADCs needs further evaluation.
- Limitation of our study.
  - The sample size of our studies was relatively small.

REFERENCES

1. Zamboni WC. Et al. *J Clin Pharmacal*. 2023;63 Suppl 2:S85-S102