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Evaluation of Innate Immune System, Body Habitus, and Sex on the Pharmacokinetics and Pharmacodynamics of Anetumab Ravtansine in Patients With Cancer

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ABSTRACT

Anetumab ravtansine, like other ADC drugs, has high inter-patient variability in its pharmacokinetic (PK) and pharmacodynamic (PD) outcomes, which raises concerns about whether current dosing regimens are optimal for patients. The objective of this study was to evaluate covariates, especially body habitus and the innate immune system (IIS), which may affect anetumab ravtansine PK and PD as part of two clinical trials in patients with ovarian cancer and mesothelioma. Biomarkers of Fcγ receptors(FcγR) CD64 on IIS cells, total body weight (TBW), body surface area (BSA), and other covariates, such as sex and age, were analyzed for an association with anetumab ravtansine PK. Higher FcγR CD64, TBW, and BSA were associated with higher clearance (CL) of anetumab ravtansine ($p < 0.05$). However, there was no relationship between TBW or BSA and FcγR CD64. Female patients had a lower anetumab ravtansine CL (0.030 ± 0.007 L/h) compared to male patients (0.042 ± 0.006 L/h) ($p < 0.05$). In both studies, patients with stable disease (SD) and partial response (PR) had higher anetumab ravtansine $AUC_{0\text{-inf}}$ compared to patients with progressive disease (PD). Individualizing the dose of anetumab ravtansine and potentially other ADCs based only on TBW is not optimal, whereas precision dosing of an ADC based on the inclusion of novel metrics of IIS biomarkers, body habitus, and sex may be more appropriate to reduce variability in PK exposure, reduce toxicity, and improve response.

1 | Introduction

Anetumab ravtansine is an immunoglobulin G1 (IgG1) antibody-drug conjugate (ADC) consisting of a human anti-mesothelin monoclonal antibody (mAb) conjugated to the microtubule inhibitor, ravtansine (DM4) [1, 2]. ADC drugs, like anetumab ravtansine, preferentially deliver potent cytotoxic payloads, like DM4, to the specific cells expressing the targets that can be

Summary

- What is the current knowledge on the topic?
  - The significance and clinical impact of covariates, such as measures of body habitus or size on pharmacokinetic variability and optimal dosing of mAbs and ADCs is currently unclear. Many mAbs and ADCs are dosed based on weight(mg/kg) or administered as a flat mg dose in clinical practice, and both dosing methods appear to be suboptimal. The additional covariates associated with PK variability of mAbs and ADCs need to be evaluated and used in novel dosing calculations.
- What question did this study address?
  - We evaluated the association between possible covariates, including IIS biomarkers, body habitus, and sex, and the pharmacokinetics of anetumab ravtansine.
- What does this study add to our knowledge?
  - Patients with higher TBW or BSA, and higher CD64 FcγRs biomarkers, and patients who are male showed higher CL and Vd of anetumab ravtansine. In addition, patients with stable disease (SD) and partial response (PR) had higher anetumab ravtansine $AUC_{0\text{-inf}}$ compared to patients with progressive disease (PD).
- How might this change clinical pharmacology or translational science?
  - From our study, individualizing the dose of anetumab ravtansine and potentially other ADCs based only on TBW may not be optimal, and individualizing patients' doses, including other patient covariates such as IIS biomarkers and sex, may be more appropriate.

recognized by the antibodies, which may enhance the killing of cancer cells and minimize the toxicity to other normal tissues [3, 4]. Anetumab ravtansine, similar to other mAbs and ADCs, has high inter- and intra-patient pharmacokinetic (PK) variability [5], which highlights the importance of understanding the potential patient covariates altering the PK and pharmacodynamics (PD) of the agent and evaluating novel ways to optimize the dose of ADCs, such as anetumab ravtansine.

Compared to small molecule drugs, mAbs, and ADCs are too large to undergo renal clearance and/or hepatic metabolism, so they are mainly recognized, taken up, and cleared via the innate immune system (IIS) [6]. The IIS serves as a natural mechanism of antibodies and immune complexes' clearance via their Fcγ receptors (FcγRs) on IIS cells [7–9]. There are various forms of FcγRs (CD64, CD32, CD16) with different affinities that interact with extracellular monomeric or aggregated IgGs, mAbs, and ADCs [8]. Variations in FcγR expression can lead to significant variability in the ability of IIS cells to clear immune complexes from the blood and their ability to take up mAbs and ADCs [10–13], which will further influence PK and PD of mAbs and ADCs [14, 15]. Previous studies of pertuzumab demonstrated that the difference in the clearance of pertuzumab was associated with differences in the expression of CD64 on circulating monocytes in the blood of patients with breast cancer [16, 17]. In addition to this pathway cleared via IIS, several other clearance pathways, including via target-mediated clearance, which is saturable, may result in nonlinear PKs [18, 19].

Body habitus refers to the physical and constitutional characteristics of a person being underweight, normal weight, or overweight [20, 21]. It represents the general physical and constitutional characteristics of a person, including body shape, size, and composition. The effect of body habitus on PK and PD variability of mAbs and ADCs is critically important because different dosing strategies have been employed for these agents, such as dosing based on total body weight (TBW; mg/kg) and flat mg dose [15, 22]. In PK studies of several mAbs and ADCs, TBW, and/or other metrics of body habitus showed an association with clearance and/or volume of distribution [23–28]. In addition, PK and PD variability still exist despite weight-based dosing for some mAbs and ADCs. These results support the need for studies comparing the association between metrics of body habitus and other novel factors (e.g., IIS biomarkers and sex) and on the PK and PD of ADCs [14].

The objective of our study was to evaluate the association between patient covariates, including IIS biomarkers, body habitus, and sex, on the PK and PD variability of anetumab ravtansine as part of two clinical trials. This current study is also the first study to evaluate the association between IIS FcγRs and anetumab ravtansine PK and PD. This study is consistent with recent publications and FDA guidelines highlighting the need for precision doing of biologics, such as antibodies and ADCs [15, 29, 30].

2 | Materials and Methods

2.1 | Study Designs

NCI studies 10150 and 10107 were conducted as part of the NCI Experimental Therapeutics Clinical Trials Network (ETCTN) and approved by the NCI Central IRB [31, 32]. In study 10150, patients with platinum-resistant or platinum-refractory high-grade ovarian cancer were treated with anetumab ravtansine 2.2 mg/kg IV × 1 weekly and bevacizumab 10 mg/kg IV × 1 every 2 weeks in phase 1–2 clinical trials. In study 10107, patients with pleural mesothelioma were treated with anetumab ravtansine 6.5 mg/kg IV × 1 and pembrolizumab 200 mg IV every 3 weeks.

2.2 | Pharmacokinetic Endpoints

In both studies during the first dose of anetumab ravtansine IV over 1 h on cycle 1, serial blood samples were obtained prior to the infusion, and at 1 h (end of the infusion), 3 h (study 10150 only), 7 h, and 168 h after the start of the infusion. The concentrations of anetumab ravtansine ADC, total antibody, maytansinoid-derivative toxophore (DM4; BAY 1006640), and active S-methyl metabolite of DM4 (DM4-Me; BAY 1006641) in plasma were measured by a specific liquid chromatographic tandem mass spectrometric assay (LC–MS/MS) as previously described [33].

Noncompartmental PK analysis was performed using Phoenix WinNonlin Version 8.3.5.340 to calculate PK parameters. PK parameters for anetumab ravtansine (ADC), total antibody, DM4, and DM4-Me included area under the concentration-time curve

from time 0 to infinity ($AUC_{0\text{-}inf}$), area under the concentration-time curve from time 0 to 168 h ($AUC_{0\text{-}168h}$), clearance (CL), volume of distribution (Vd), elimination rate constant (k), elimination half-life ($t_{1/2}$), maximum concentration (C_{max}) and time to reach maximum concentration (T_{max}). AUC and Cmax values normalized by prescribed dose (mg/kg) and per mg dose administered (PUMDA; mg) were also calculated.

2.3 | Antitumor Response

In both studies, antitumor response was defined as the overall best response and included progressive disease (PD), stable disease, and partial response (PR). For 10107, modified pleural response evaluation criteria in solid tumors were used given the spatial complexities of pleural mesothelioma [34, 35]. The overall best response is the best response recorded from the start of the treatment until disease progression/recurrence.

2.4 | IIS FcγR Biomarkers Endpoints

In each clinical study, studies of FcγRs on IIS cells in blood were performed on days 1 and 8 of cycles 1 using our validated methods [8, 9, 36]. Blood samples (20 mL) were obtained using K2 EDTA (purple-top) tube and processed to peripheral blood mononuclear cells (PBMCs) using density-gradient centrifugation and stored under cryo-preservation. PBMCs were processed to determine the number of FcγRs on circulating monocytes and DCs via flow cytometry (FCM). The antibodies bound per cell (ABC) were determined using phycoerythrin (PE) probes of CD64 (FcγRI), CD32 (FcγRII), and CD16 (FcγRIII) FcγRs with appropriate fluorescence quantification bead standards (Quantbrite beads) [8, 9, 36]. Antibodies and ADC standards were obtained from BD Biosciences, San Jose, CA, and flow cytometric analyses were performed using the Thermo Attune with FCSExpress software. Samples for each FcγR were prepared and evaluated in triplicate with a minimum of 100 k PBMCs being evaluated in each sample.

2.5 | Anti-Drug Antibody (ADA)

To measure ADA, 2 mL blood samples were collected from patients who received anetumab ravtansine at pre-treatment on day 1 of cycles 1, 3, 6, 9 and pre-dose every 3 months after cycle 9 in the first year and every 6-months in the second year of treatment [5].

2.6 | Statistical Analysis

The relationship between body habitus metrics, IIS FcγRs, sex, age, and race and PK parameters was evaluated combined and separately for patients with mesothelioma and ovarian cancer. Patients with missing data were excluded from the statistical analysis. Body habitus parameters included total body weight (TBW), body surface area (BSA), body mass index (BMI), and the ratio of total body weight/ideal body weight (TBW/IBW). IIS FcγR biomarkers included CD64, CD32, CD16, and total FcγRs. Pearson correlations were employed to assess the relationship between patient covariates and PK parameters. In addition, simple linear regression and stepwise linear regression analyses were performed to further evaluate the relationship between body habitus, FcγR biomarkers, and anetumab ravtansine PK. A p-value of < 0.05 was used to define statistical significance. When assessing the anti-tumor response, ANOVA was used to test if there was a difference in $AUC_{0\text{-}inf}$ results for the different responses. All the analysis were performed in R version 4.3.1.

TABLE 1 | Patient demographic characteristics in study 10150 and study 10107.

	Study 10150 Ovarian cancer ($N=16$)	Study 10107 Mesothelioma ($N=14$)
Age		
N	16	14
Mean (SD)	62.9 (9.5)	71.5 (11.5)
Median	63.0	71.5
Range	(39.0, 78.0)	(42.0, 81.0)
Sex, *n* (%)		
Female	16 (100%)	4 (28.6%)
Male	0	10 (71.4%)
Race, *n* (%)		
White	15 (93.8%)	13 (92.9%)
Asian	1 (6.3%)	1 (7.1%)
Total body weight (TBW, kg)		
N	16	14
Mean (SD)	75.9 (20.4)	82.2 (17.9)
Median	76.9	78.5
Range	(47.9, 113.1)	(59.8, 125.7)
Body surface area (BSA) (m^2)		
N	16	14
Mean (SD)	1.8 (0.3)	2.0 (0.26)
Median	1.9	2.0
Range	(1.4, 2.3)	(1.6, 2.6)

3 | Results

3.1 | Demographics

A summary of the number of patients with PK and IIS biomarker results is included in Table 1. In patients with ovarian cancer, the mean ± Std.Dev age was 62.9 ± 9.5 years, and the mean ± Std.Dev TBW was 82.2 ± 17.9 kg. In patients with mesothelioma, the mean ± Std.Dev age was 71.5 ± 11.5 years, and the mean ± Std.Dev TBW was 75.9 ± 20.4 kg. In this study, four patients (29%) were female patients (Table 1).

3.2 | PK Disposition

Plasma concentration versus time profiles of anetumab ravtansine, total antibody, DM4, and DM4-Me are included in Figure S1. In both studies, anetumab ravtansine ADC reached the peak level at the end of infusion (approximately 1 h) and was detectable out to 168 h. Total antibody showed a comparable maximum concentration to anetumab ravtansine ADC, but total antibody had a longer half-life and higher AUC than anetumab ravtansine. After normalization to molarity concentration, the mean ± Std. Dev ratio of DM4 to anetumab ravtansine $AUC_{0\text{-}168h}$ was 0.009 ± 0.003 in patients with ovarian cancer and 0.012 ± 0.007 in patients with mesothelioma. A summary of the PK parameters of anetumab ravtansine for both studies is included in Tables 2 and S1, S2.

3.3 | Relationship Between IIS FcγR Biomarkers and Anetumab Ravtansine PK

Results evaluating the relationship between IIS FcγR biomarkers and anetumab ravtansine PK are presented for each study alone and combined for both studies (Figure 1). For the combination of both studies, higher CD64 FcγR biomarkers on cycle 1 day 1 were associated with higher CL of anetumab ravtansine ($r = 0.48$, $p = 0.028$, Figure 1A). In addition, higher CD64 FcγR biomarkers were associated with higher Vd of anetumab ravtansine ($r = 0.50$, $p = 0.022$, Figure 1B). In patients with mesothelioma, higher CD64 FcγR biomarkers on cycle 1 day 1 were associated with higher CL of anetumab ravtansine ($r = 0.67$, $p = 0.024$) and also higher Vd of anetumab ravtansine ($r = 0.66$, $p = 0.026$). In patients with ovarian cancer, there were similar relationships between CD64 FcγR biomarkers on cycle 1 day 1 and anetumab ravtansine CL and Vd, but they were not statistically significant. In both studies, the IIS FcγR biomarkers on cycle 1 days 1 and 8 were similar, with a mean ± SD ratio of CD64 FcγR day 8 to day 1 of 0.99 ± 0.10 (Table S3).

In patients with mesothelioma, there was an inversion relationship between CD64 FcγR biomarkers and anetumab ravtansine $AUC_{0\text{-}inf}$ ($r = -0.66$, $p = 0.028$, Figure 2A). In addition, in patients with ovarian cancer, there was a similar relationship between CD64 FcγR biomarkers and anetumab ravtansine $AUC_{0\text{-}inf}$, but it was not statistically significant. After dose normalizing exposure by dose in mg/kg, there was an inverse relationship between CD64 FcγR biomarkers on cycle 1 day 1 and anetumab ravtansine $AUC_{0\text{-}inf}$/(mg/kg) that was not significant ($p = 0.12$, Figure 2B). Similar inverse relationships occurred for individual studies.

In our study, there is no significant difference in CD64 in patients with mesothelioma and ovarian cancer.

As it is currently unclear if the normalization of exposure of biologics across doses should be based on prescribed dose in mg/kg or mg dose administered, we also evaluated the relationship between CD64 and $AUC_{0\text{-}inf}$/mg. For all patients after normalizing exposure by mg dose administered, there was an inverse relationship between CD64 FcγR biomarkers and anetumab ravtansine $AUC_{0\text{-}inf}$/mg but not statistically significant. Similar inverse relationships occurred for each individual study.

TABLE 2 | PK parameters of anetumab ravtansine in study 10150 and study 10107.

Parameter	Units	Mean	SD	SE	CV%	Median	Min	Max
Study 10150 patients with ovarian cancer								
CL	L/h	0.03	0.008	0.002	25.34	0.03	0.02	0.05
Vd	L	2.62	0.54	0.13	20.76	2.59	1.90	4.06
C_{max}	mg/L	58.61	10.75	2.69	18.35	56.46	41.14	77.26
C_{max}/mg/kg	mg/L/(mg/kg)	26.64	4.89	1.22	18.35	25.67	18.70	35.12
C_{max}/mg	mg/L/mg	0.37	0.07	0.02	20.50	0.36	0.19	0.49
$AUC_{0\text{-}inf}$	mg/L•h	5671.81	1379.87	344.97	24.33	5427.18	4023.32	8226.02
$AUC_{0\text{-}inf}$/mg/kg	mg/L•h/(mg/kg)	2578.10	627.21	156.80	24.33	2466.90	1828.78	3739.10
$AUC_{0\text{-}inf}$/mg	mg/L•h/mg	34.90	6.85	1.71	19.64	35.61	18.47	46.60
Study 10107 patients with mesothelioma								
CL	L/h	0.038	0.007	0.002	20.79	0.038	0.027	0.051
Vd	L	3.67	0.77	0.20	20.84	3.72	2.60	4.98
C_{max}	mg/L	133.45	25.23	6.74	18.91	132.67	106.02	190.14
C_{max}/mg/kg	mg/L/(mg/kg)	21.02	4.17	1.12	19.85	20.92	16.31	29.25
C_{max}/mg	mg/L/mg	0.26	0.05	0.01	17.73	0.26	0.20	0.33
$AUC_{0\text{-}inf}$	mg/L•h	13,921.92	2830.90	756.59	20.33	13,771.53	9640.32	19,383.39
$AUC_{0\text{-}inf}$/mg/kg	mg/L•h/(mg/kg)	2194.53	475.86	127.18	21.68	2154.67	1483.13	2982.06
$AUC_{0\text{-}inf}$/mg	mg/L•h/mg	27.17	5.63	1.51	20.74	26.60	19.41	36.82

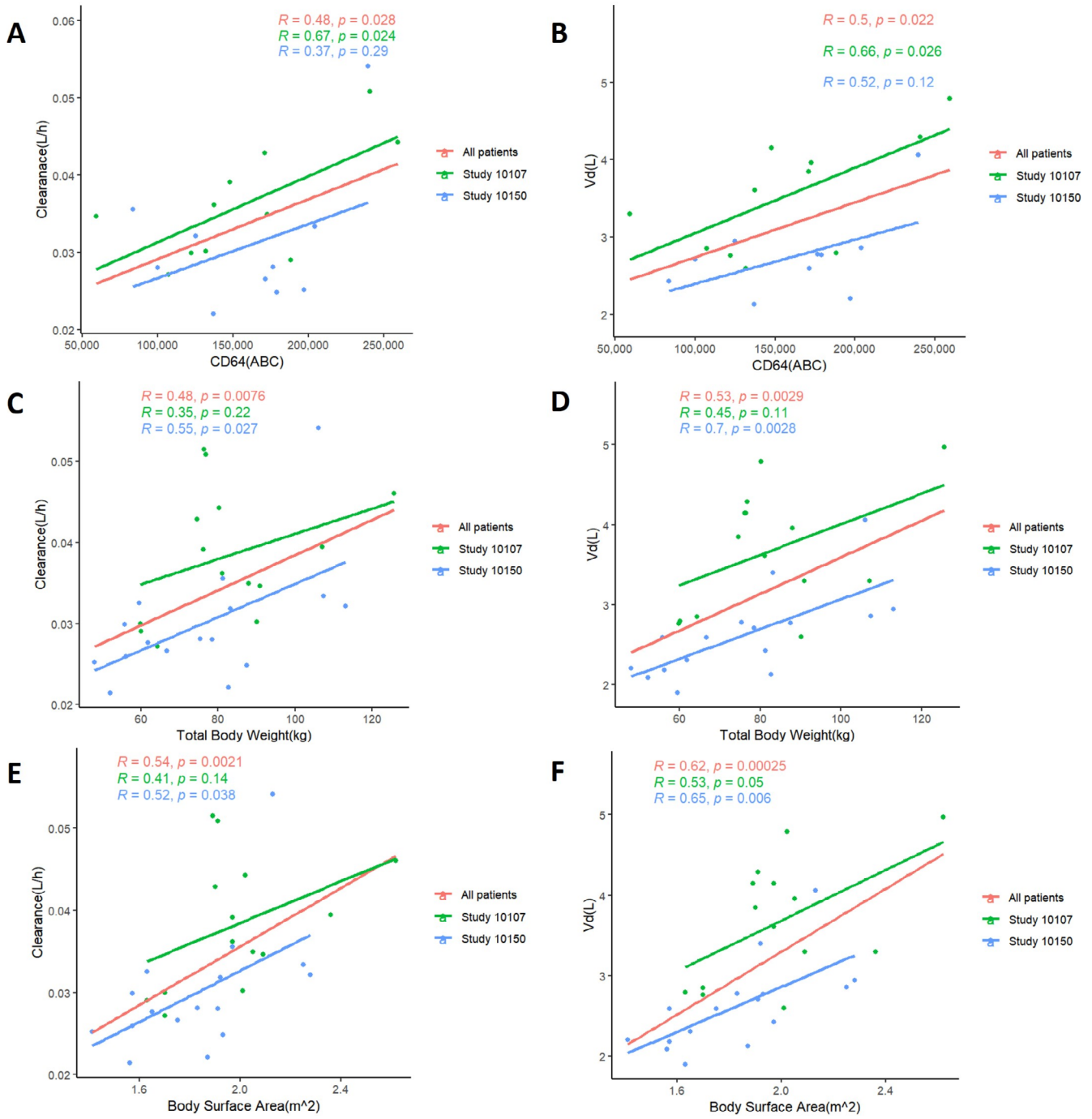

FIGURE 1 | Relationships between biomarkers of the IIS and metrics of body habitus and anetumab ravtansine plasma CL and Vd in all patients and in study 10107 in patients with mesothelioma, and in study 10150 in patients with ovarian cancer. Panels A and B include the relationships between CD64 and CL and Vd, respectively. Panels C and D include the relationships between TBW and CL and Vd, respectively. Panels E and F include the relationships between TBW and CL and Vd, respectively. The red line represents the linear regression for all patients. The green line and symbols represent linear regression and patients in study 10,107, respectively. The blue line and symbols represent linear regression and patients in study 10150, respectively. Higher FcγR CD64, TBW, and BSA are associated with higher CL and Vd of anetumab ravtansine ($p < 0.05$).

3.4 | Relationship Between Body Habitus and Anetumab Ravtansine PK

Results evaluating the relationship between body habitus metrics and anetumab ravtansine PK are presented for each study alone and combined for both studies. For the combination of both studies, higher TBW ($r = 0.48$, $p = 0.0076$, Figure 1C) and BSA ($r = 0.54$, $p = 0.0021$, Figure 1E) were associated with higher CL of anetumab ravtansine. In addition, higher TBW ($r = 0.53$, $p = 0.0029$, Figure 1D) and BSA ($r = 0.42$, $p = 0.00025$, Figure 1F) were associated with higher Vd of anetumab ravtansine. A similar association between BSA and TBW and anetumab PK parameters (CL and Vd) occurred in each study alone.

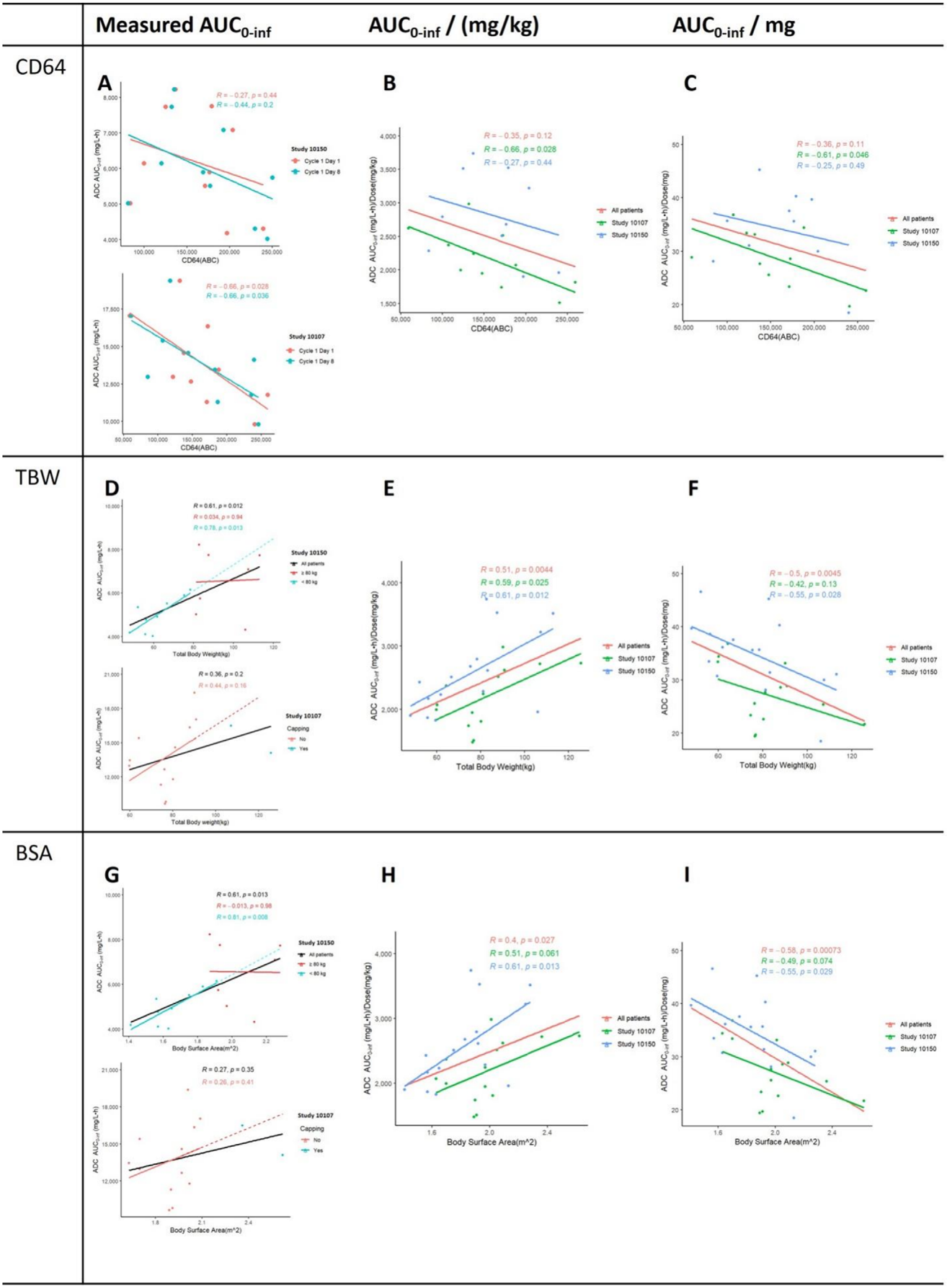

FIGURE 2 | Legend on next page.

FIGURE 2 | The relationship between biomarkers of the IIS and metrics of body habitus and anetumab ravtansine PK exposure in plasma in all patients and in study 10107 in patients with mesothelioma, and in study 10150 in patients with ovarian cancer. Panels A, B, and C include the relationships between CD64 and measured AUC (top = study 10150; bottom = study 10107), AUC dose normalized by mg/kg, and AUC dose normalized by mg, respectively. Panels D, E, and F include the relationships between TBW and measured AUC (top = study 10150; bottom = study 10107), AUC dose normalized by mg/kg, and AUC dose normalized by mg, respectively. Panels G, H, and I include the relationships between BSA and measured AUC (top = study 10150; bottom = study 10107), AUC dose normalized by mg/kg, and AUC dose normalized by mg, respectively. In panels A, D, and G, the top figure is for study 10150, and the bottom figure is for study 10107. In panel A, the results for individual patients (symbols) and the regression line for cycle 1 day 1 and day 8 are presented in red and blue, respectively. In panels D and G top, the individual patient results (symbols) and regression lines for all patients, patients with high TBW (≥ 80 kg), and patients with low TBW (< 80 kg) are presented in black, red, and blue, respectively. In panels D and G bottom, the individual patient results (symbols) and regression lines for all patients and patients with and without capping of the dose are presented in black, blue, and red. In panels B, C, E, F, H, and I, the red line represents the linear regression for all patients. The green line and symbols represent linear regression and patients in study 10107, respectively. The blue line and symbols represent linear regression and patients in study 10150, respectively. There is high PK variability in Anetumab ravtansine AUC when the dose is based on TBW (mg/kg dosing) and in general, patients with higher TBW have higher measured AUC. However, exposure based on administered unit dose (mg) is inversely related to TBW, which suggests larger patients achieve less exposure per administered ADC.

In patients with ovarian cancer, higher TBW ($r = 0.61$, $p = 0.012$, Figure 2D) and higher BSA ($r = 0.61$, $p = 0.013$, Figure 2G) were significantly associated with higher anetumab ravtansine $AUC_{0\text{-inf}}$. In patients with mesothelioma, higher TBW and higher BSA were associated with higher anetumab ravtansine $AUC_{0\text{-inf}}$ ($p = 0.2$ and $p = 0.35$, respectively). After dose normalizing exposure by dose in mg/kg, higher TBW ($r = 0.51$, $p = 0.0044$, Figure 2E) and higher BSA ($r = 0.4$, $p = 0.027$, Figure 2H) were still associated with higher anetumab ravtansine $AUC_{0\text{-inf}}$/mg/kg. In patients with ovarian cancer, higher TBW ($r = 0.61$, $p = 0.012$) and higher BSA ($r = 0.61$, $p = 0.013$) were associated with $AUC_{0\text{-inf}}$/mg/kg. In addition, in patients with mesothelioma, there were similar associations between TBW and BSA and anetumab ravtansine $AUC_{0\text{-inf}}$/mg/kg. After dose normalizing exposure by mg dose administered, there was an inverse relationship between TBW ($r = -0.50$, $p = 0.0045$, Figure 2F) and BSA ($r = -0.58$, $p = 0.00073$, Figure 2I) and anetumab ravtansine $AUC_{0\text{-inf}}$/mg. In patients with ovarian cancer, higher TBW ($r = -0.55$, $p = 0.028$) and higher BSA ($r = -0.55$, $p = 0.029$) were associated with lower $AUC_{0\text{-inf}}$/mg. In patients with mesothelioma, there were similar inverse relationships between TBW and BSA and anetumab ravtansine $AUC_{0\text{-inf}}$/mg.

As per protocol for study in patients with mesothelioma, there were two male patients with total body weight (TBW) ≥ 100 kg who had their dose capped at 650 mg instead of administering a dose based on actual TBW. For one patient who weighed 107.1 kg and had a dose capped at 650 mg, the measured C_{max} and $AUC_{0\text{-inf}}$ of anetumab ravtansine were 149.6 mg/L h and 16,491.7 mg/L h, respectively. For the second patient who weighed 125.7 kg and had a dose capped at 650 mg, the measured C_{max} and $AUC_{0\text{-inf}}$ of anetumab ravtansine ADC were 131.1 mg/L and 14,102.5 mg/L h, respectively. After dose normalizing exposure by mg dose administered, the mean ± SD C_{max}/mg and $AUC_{0\text{-inf}}$/mg of the two patients with capped doses were 0.22 ± 0.02 mg/L/mg and 23.5 ± 2.6 mg/L h/mg, which is lower than C_{max}/mg (0.27 ± 0.05 mg/L/mg) and $AUC_{0\text{-inf}}$/mg (27.8 ± 5.8 mg/L h/mg) of patients who were not capped.

3.5 | Sex, Age, and Antidrug Antibodies (ADA) and Anetumab Ravtansine PK

Female patients had a lower CL of anetumab ravtansine (0.030 ± 0.007 L/h) compared to male patients (0.042 ± 0.006 L/h) in the combined studies ($p = 0.00008$, Figure S3D). Overall, female patients had lower TBW compared to male patients. However, in male and female patients with the same TBW, the CL was lower in female patients. There was no significant difference in cycle 1 day 1 CD64 between female and male patients. There was no significant association between age and CL of anetumab ravtansine (Figure S3B). The number of patients with measured ADA in studies 10107 and 10150 was 1 of 12 and 1 of 11, respectively, and both detectable ADA occurred on cycle 3 day 1. The low incidence of ADA suggests it is not a major factor affecting PK variability.

3.6 | Relationships Between Covariates (Body Habitus, CD64 and Sex) and Anetumab Ravtansine PK

As reported above, higher CD64 FcγR and higher body habitus metrics (TBW and BSA) were associated with higher anetumab ravtansine CL and Vd. However, there is no association between CD64 and TBW or BSA in combined studies ($p = 0.95$ and $p = 0.92$, respectively) or each individual study (Figure 3A,C). When evaluating CD64 FcγRs and body size covariates at the same time, patients with high BSA or TBW and high CD64 had higher CL compared to other patients (Figure 3B,D). In patients with similar median body size, male patients had higher CL compared to female patients. Similar results are also shown with Vd (Figure S4). The statistical results for simple linear and stepwise linear regressions of patient covariates and anetumab ravtansine PK were similar to those presented above, with body size, CD64, and sex associated with variability in PK (Table S4).

3.7 | Anetumab Ravtansine PK and Antitumor Response

The associations between anetumab ravtansine exposure and best response in the two studies are presented in Figure 4. In patients with ovarian cancer, patients with partial response (PR) had a higher mean anetumab ravtansine $AUC_{0\text{-inf}}$ than patients with stable disease (SD) and progressive disease (PD), but it was not statistically significant ($p = 0.12$, Figure 4A). In patients

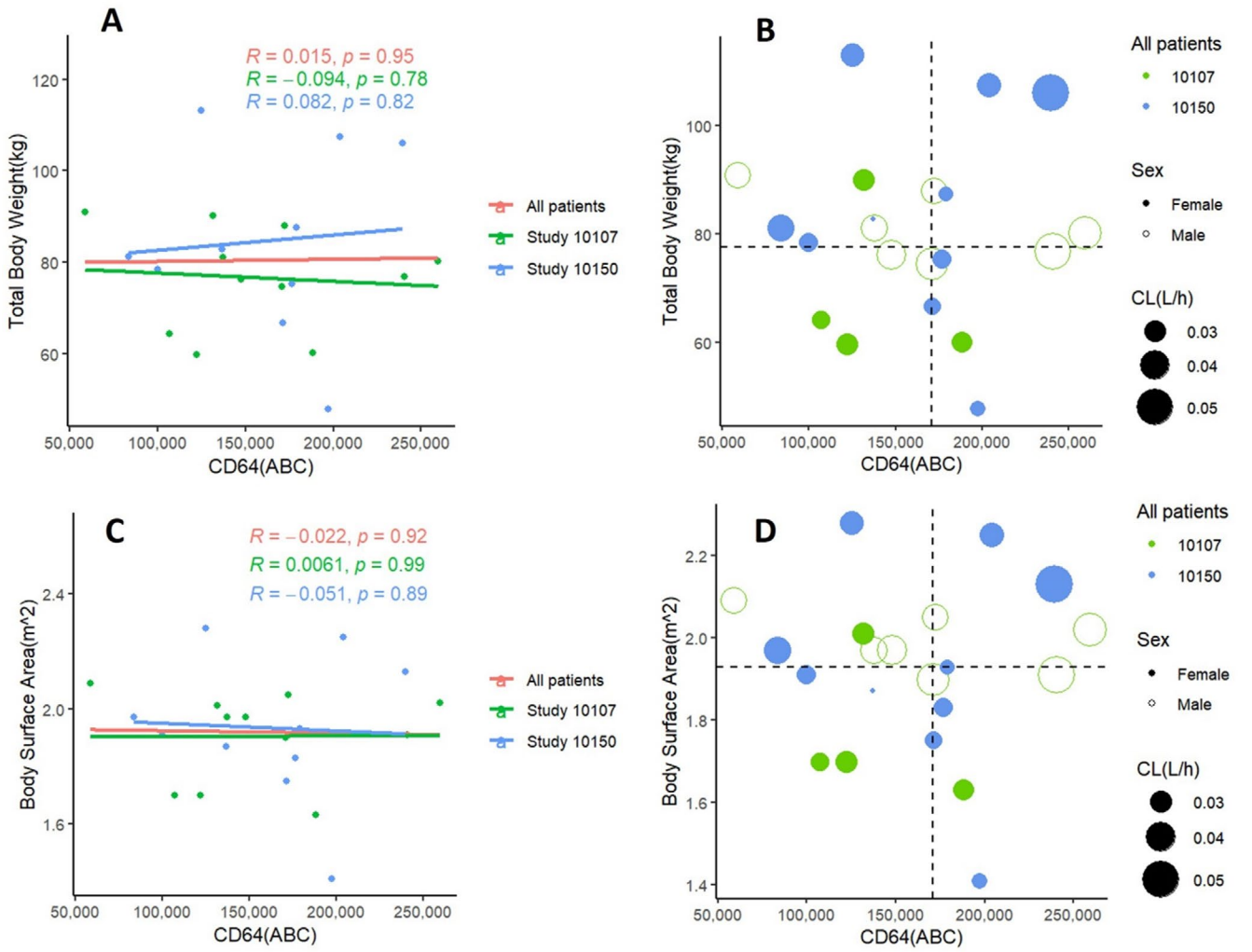

FIGURE 3 | Relationships between TBW or BSA, FcγR CD64, and anetumab ravtansine CL in all patients and in study 10107 in patients with mesothelioma, and in study 10150 in patients with ovarian cancer. In panels (A) and (C) evaluating the relationship between CD64 and TBW or BSA, the red line represents the linear regression for all patients, the green line and symbols represent linear regression and patients in study 10107, and the blue line and symbols represent the linear regression and patients in study 10150. In these patient groups, there is no relationship between CD64 and TBW or BSA. In panels (B) and (D), the green and blue symbols represent patients in studies 10107 and 10150, respectively. The size of the symbol represents the rank order of anetumab ravtansine CL with larger symbols representing higher CL and smaller symbols representing lower CL. Solid symbol represents female and open symbol represents male. Patients with higher CD64 and higher TBW or higher BSA had higher anetumab ravtansine CL. Around the median TBW or BSA, male patients had higher CL compared to Female patients.

with mesothelioma, patients with PR and SD had a higher mean anetumab ravtansine $AUC_{0\text{-inf}}$ than patients with PD, but it was not statistically significant ($p = 0.27$, Figure 4B).

4 | Discussion

Our study is the first to report the association between FcRs on IIS, metrics of body habitus, and sex on the PK and PD variability of an ADC. The PK, efficacy, and toxicity variability of mAbs and ADCs, including anetumab ravtansine, are high and clinically relevant. This is the case even though the dose of anetumab ravtansine and other ADCs is individualized based on TBW (dosed as mg/kg). As mAbs and ADCs are primarily cleared by FcRs on IIS cells in blood and tissues, there is a need to evaluate the association between metrics of body habitus, the IIS, and other factors on the PK and PD of mAbs and ADCs.

There was high interpatient variability in the exposure of anetumab ravtansine when individualizing the dose based on TBW (dosing by mg/kg) in patients with mesothelioma and ovarian cancer. The range of anetumab ravtansine $AUC_{0\text{-inf}}$ in patients with mesothelioma was 9640–19,383 mg/L•h, and the range of anetumab ravtansine $AUC_{0\text{-inf}}$ in patients with ovarian cancer was 4023–8226 mg/L•h. In addition, the range of released DM4 $AUC_{0\text{-168h}}$ in patients with mesothelioma and ovarian cancer was 0.285–1.717 mg/L•h and 0.006–0.015 mg/L•h, respectively.

As it is currently unclear if it is more appropriate to dose normalize PK exposures of biologics using the prescribed dose in mg/kg or per unit mg dose administered (PUMDA) (dose in mg/kg × TBW kg = mg), we evaluated both methods in our study. The evaluation of dose normalization by PUMDA is especially important for mAbs and ADCs, as they are cleared via binding to receptors on IIS cells and the tumor, which can be saturated, and

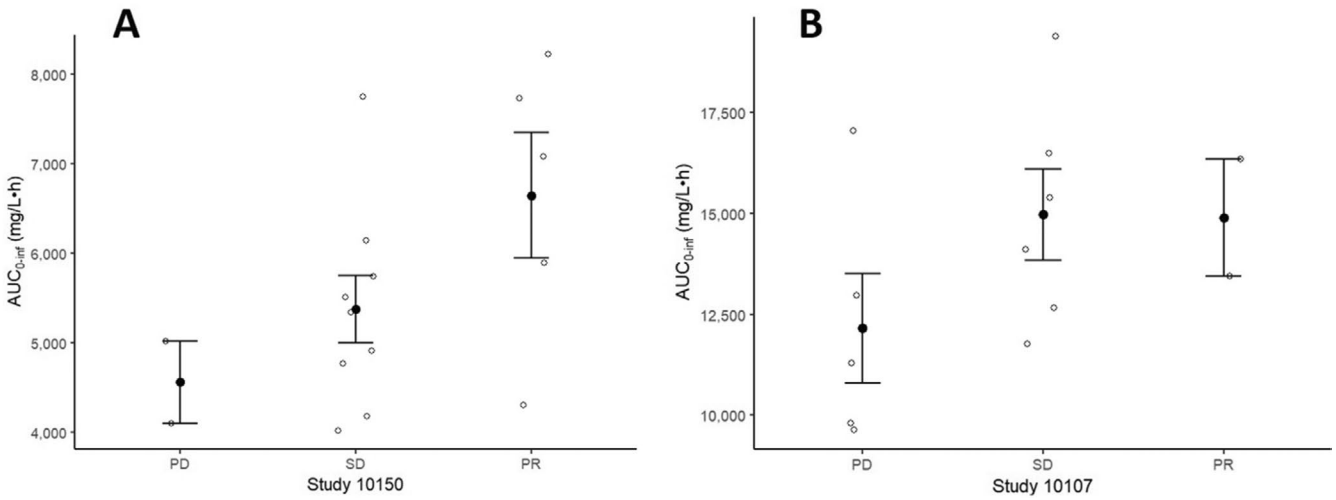

FIGURE 4 | Relationship between anetumab ravtansine $AUC_{0\text{-inf}}$ and best antitumor response for patients with ovarian cancer (study 10150) and patients with mesothelioma (study 10107). Individual patient results are presented as the open circles. Mean and SD results are presented as the black solid circle and whiskers, respectively. Panel A shows in study 10150, patients with partial response (PR) had higher mean anetumab ravtansine $AUC_{0\text{-inf}}$ than patients with stable disease (SD) and progressive disease (PD) ($p = 0.12$). Panel B shows in study 10107, patients with PR and SD had higher mean anetumab ravtansine $AUC_{0\text{-inf}}$ than patients with PD ($p = 0.27$).

is consistent with non-linear clearance of these agents at high doses [15]. Whereas normalizing the exposure by dose administered in mg/kg does not take into account the actual number of mg of drug administered to a patient. Our results show that higher TBW was associated with higher anetumab ravtansine CL and Vd, and that higher TBW was inversely associated with anetumab ravtansine AUC/mg (PUMDA). These results follow standard relationships, equations, and modeling of PK principles for all drugs, whereas normalizing exposures by the prescribed dose in mg/kg did not. Thus, normalizing PK exposures of biologics by PUMDA appears to be more pharmacologically meaningful than normalizing by mg/kg.

Importantly, even after normalizing anetumab ravtansine $AUC_{0\text{-inf}}$ by mg (PUMDA) or mg/kg, there was still high interpatient variability in the exposure of anetumab ravtansine (AUC = 18.5–46.6 mg/L•h/mg). This indicates possible higher interpatient variability in exposures of mAbs and ADCs with the use of flat mg dosing. In addition, previous studies for other mAbs and ADCs showed similar high interpatient variability, especially in obese patients, with dosing based on TBW (mg/kg) or flat mg dose [28, 37]. This may indicate weight-based dosing and flat dosing are both insufficient methods for dosing mAbs and ADC in patients and especially patients who are obese [15].

In the combined study, there was a significant positive linear association between the level of CD64 FcγRs biomarkers and CL and Vd of anetumab ravtansine. This is consistent with our hypothesis that mAbs and ADCs are cleared via the FcγRs on IIS cells. These results are consistent with a previous study by our group that showed pertuzumab had a lower serum trough concentration in patients with advanced gastric cancer than in patients with metastatic breast cancer [36]. This lower trough level was also associated with higher expression of CD64 FcγRs in patients with gastric cancer as compared to breast cancer [16, 17, 38]. Thus, biomarkers of FcγRs, such as CD64, can be used to evaluate patient-specific differences in PK and PD of mAbs, ADCs, and liposomal drugs [39–42]. Based on these results, it may be possible to individualize the dose of mAbs and ADCs based on biomarkers of the IIS.

This study also showed that metrics of body habitus, TBW, and BSA had significant positive associations with CL and Vd of anetumab ravtansine. In patients with ovarian cancer, there is a positive association between patients' TBW and anetumab ravtansine $AUC_{0\text{-inf}}$ ($p = 0.012$), which is mainly driven by the positive association in patients < 80 kg. In patients with mesothelioma, there was also a positive association between TBW and anetumab ravtansine $AUC_{0\text{-inf}}$. Similar results also occurred between body habitus metrics and Cmax in both studies. These results occurred even though the dose of anetumab ravtansine was based on total body weight (mg/kg), which by design should have normalized the exposure of the ADC across patients with different TBW. This may indicate that even though there is a positive relationship between TBW and measured AUC, the gain in AUC per TBW is not linear or proportional. TBW and BSA are both related to body size. However, the numerical difference between patients and the rank order of patients from smallest to biggest based on TBW and BSA is not the same. This is highlighted by the differences in the relationships between TBW and BSA and the same PK parameter. The optimal metric of body habitus (e.g., TBW or BMI) to use for dosing of mAbs and ADCs is still unclear and suggests that a new metric of body habitus is needed.

As per the protocol for patients with mesothelioma, the dose of anetumab ravtansine was capped at 650 mg in patients with TBW ≥ 100 kg. Among FDA-approved ADCs, there are two ADCs, brentuximab vedotin and enfortumab vedotin, that use a weight-based capping of the dose in patients ≥ 100 kg [22]. In our study, only two male patients had their anetumab ravtansine doses capped at 650 mg. Both of their AUC and C_{max} exposures were still higher than the mean level of other non-capped male patients. As expected, for the patient with a TBW of 107.1 kg,

which is closer to the capping (TBW of 100 kg), the anetumab exposures were closer to those in the non-capped patients (TBW < 100 kg). The male patient with a TBW of 125.7 kg and a capped dose of 650 mg had lower anetumab exposure than other male patients weighing > 90 kg. Further studies are needed to evaluate the appropriateness of capping doses of ADCs and to identify the TBW cutoff for capping doses.

In general, CD64 FcγRs and body habitus metrics (TBW and BSA) were associated with anetumab ravtansine PK disposition. However, there was no association between CD64 FcγRs and body habitus metrics (TBW and BSA). These results support that CD64 FcγRs and body habitus metrics independently affect the disposition of anetumab ravtansine. As a result, patients with high CD64 FcγRs and high body size would be most likely to have low exposures of anetumab ravtansine, and this is what our studies confirmed (Figure 3). In addition to CD64 FcγRs, TBW, and BSA, sex was also associated with differences in anetumab ravtansine PK. Male patients had a significantly higher clearance of anetumab ravtansine as compared to female patients. Previous studies of some other ADC drugs also reported a difference in the PK based on gender [6, 43]. The causes and clinical significance of differences in the PK disposition of ADCs between female and male patients need to be further evaluated. Thus, the optimal individualized dosing strategy may include the combination of IIS biomarkers and metrics of body habitus and may be different for male and female patients. In addition, other potential biomarkers, such as genetic factors, have been reported to be associated with the PK and PD variability of antibodies and ADCs [44–46].

The need for precision dosing of mAbs, ADCs, and any drug starts with data showing there is a relationship between PK exposures and PD response (efficacy or toxicity). In patients with ovarian cancer, there was a relationship between anetumab ravtansine $AUC_{0\text{-inf}}$ and best response, with higher anetumab ravtansine $AUC_{0\text{-inf}}$ in patients with partial response (PR) compared to stable disease (SD) or progressive disease (PD) In patients with mesothelioma, patients with PR and SD also had a higher anetumab ravtansine $AUC_{0\text{-inf}}$ compared to patients with PD (Figure 4B). Three patients with mesothelioma, who had a dose reduction from 6.5 mg/kg to 5.5 mg/kg, and three patients with ovarian cancer, who had a dose reduction from 2.2 mg/kg to 1.8 mg/kg, were included in the anti-tumor relationship analysis. All of them achieved SD or PR. The number of patients with matched PK and antitumor response is low. However, the potential relationship between anetumab ravtansine exposure and best response heightens the need to optimize the precision dosing methods and metrics of anetumab ravtansine and potentially other biologics. Future studies need to evaluate these same biomarkers and factors in larger phase 2 and 3 studies that include PFS and overall survival. In addition, performing biomarker and PK studies over serial cycles to more adequately evaluate the relationship between PK exposure and response may be necessary in the future.

Our study is the first study to report the association between CD64 FcγRs biomarkers and the PK of an mAb and ADC in individual patients with different types of cancer. In addition, our study is the first to report the relationship between CD64 FcγRs biomarkers, metrics of body habitus, sex, and anetumab ravtansine PK in patients. The results of this study also suggest that individualizing the dose of mAbs and ADCs based on TBW is not optimal. This data suggest that current metrics of body size may be insufficient and new measures of body habitus need to be evaluated and validated for precision dosing [15]. Moreover, our results suggest that the PK disposition of mAbs and ADCs is highly complex and influenced by more factors than just body size and thus, novel factors and biomarkers need to be evaluated, such as IIS biomarkers. As the degree of association between the IIS biomarkers and metrics of body habitus and PK of anetumab ravtansine was different in patients with mesothelioma and ovarian cancer, this suggests that new methods for individualizing the dose of biologics may be cancer specific. A limitation of our study is the overall low number of patients with PK and biomarkers studies. This limitation highlights the need to perform pharmacologic studies in all patients enrolled in clinical trials. In summary, the results of our study and proposed plans are consistent with recent publications and workshops highlighting the need for precision dosing of biologics and the need to evaluate novel precision dosing methods and metrics for biologics, especially in overweight and obese patients [15, 29].

Author Contributions

L.C., B.A.Z., and W.C.Z. wrote the manuscript. A.M, S.L., T.M., J.M., and W.C.Z. designed the study. A.M, S.L., L.C., A.T.L., and W.C.Z. performed the research. A.T.L., C.O., and K.P. contributed new reagents and analytical tools. L.C., B.A.Z., A.T.L., C.O., K.P., and W.C.Z. performed data analyses.

Disclosure

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Conflicts of Interest

Andrew T. Lucas contributed to this manuscript while employed at the University of North Carolina, Chapel Hill. This manuscript reflects the views of the author and should not be construed to represent his new employer, PumasAI's, views or policies.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.