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Clinical Pharmacology of the Antibody-Drug Conjugate Enfortumab Vedotin in Advanced Urothelial Carcinoma and Other Malignant Solid Tumors

Mei Tang[1]*; Amit Garg[2]*; Peter Bonate[1]; Jonathan Rosenberg[3]; Takeshi Kadokura[4]; Akihiro Yamada[4]; Risa Fukushi[4]; Akira Koibuchi[4]; William D Hanley[2]; Srinivasu Poondru[1]

[1]Astellas Pharma, Inc., Northbrook, IL, USA; [2]Seagen Inc., South San Francisco, CA, USA; [3]Memorial Sloan Kettering Cancer Center, New York City, NY, USA; [4]Astellas Pharma, Inc, Tokyo, Japan

*co-first author

Background

- Enfortumab vedotin (EV) is an antibody-drug conjugate (ADC) comprised of a fully human monoclonal antibody directed against Nectin-4 and monomethyl auristatin E (MMAE), a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker[1]
- In the phase 3, randomized, controlled EV-301 trial, EV significantly reduced risk of death by 30% versus chemotherapy in patients with locally advanced or metastatic urothelial carcinoma (la/mUC) who previously received a PD-1/L1 inhibitor and platinum-based chemotherapy[2]
  - Progression-free survival was also significantly longer and confirmed overall response rates were higher with EV compared with chemotherapy
  - Safety and tolerability were comparable between EV and chemotherapy groups

Aim/Objective

- Data from five clinical studies (N=748) were used to describe the clinical pharmacology of EV

Methods

- Pharmacokinetics (PK) of EV (ADC), free (unconjugated) MMAE, and total antibody (TAb) were studied in patients with la/mUC (n=699) and malignant solid tumors (n=49) receiving EV in phase 1, 2, and 3 studies (Table 1)

Table 1. Baseline Patient Characteristics From Five Clinical Studies in the PK Population

Covariate	N=748
Sex (%): Female/Male	27/73
Age (years): Median (range)	68 (24, 90)
Race (%): White/Asian/Black/Others or missing	69/21/1/8
Cancer type (%): Urothelial/Others	93/7
Renal impairment (%): Normal/Mild/Moderate/Severe/Unknown or missing	17/36/42/3/-[a]
Hepatic impairment (%): Normal/Mild/Moderate/Unknown or missing	89/9/-[b]/2
ECOG performance status (%): 0/1/2	37/62/1
Liver metastases (%): Yes/No	32/68
ATA (%): Negative/Positive/Unknown or missing	87/3/10
Body weight (kg), median (range)	74.8 (36.9, 158)
Albumin (g/L), median (range)	39 (22, 51)
Alanine aminotransferase (IU/L), median (range)	15 (5, 139)
Aspartate aminotransferase (IU/L), median (range)	18 (5, 191)
Total bilirubin (mg/dL), median (range)	0.40 (0.099, 1.96)
Serum creatinine (mg/dL), median (range)	1.12 (0.39, 4.45)
Creatinine clearance (mL/min), median (range)	63.3 (11.8, 213)

[a]n=6.
[b]n=3.
Abbreviations: -, indicates non-zero percentage; ATA, antitherapeutic antibodies; ECOG, Eastern Cooperative Oncology Group; PK, pharmacokinetic.

- EV, MMAE, and TAb PK parameters were calculated with noncompartmental analysis
- Population PK (PopPK) analysis was used to characterize/assess impact of covariates on EV and MMAE PK
  - The final models of EV and MMAE were used to simulate EV 1.25 mg/kg administered on Days 1, 8, and 15 of a 28-day cycle for three cycles based on baseline characteristics of the combined population in the modeling datasets
- Antitherapeutic antibodies (ATA) were assessed in all studies

Results

- EV 0.5 to 1.25 mg/kg administered intravenously on Days 1, 8, and 15 of a 28-day cycle showed linear, dose-proportional PK
- Mean EV and MMAE clearance was 0.110 and 2.11 L/h, respectively (Table 2 and Table 3); elimination half-life was 3.6 and 2.6 days
- Steady state was reached by Cycle 1; accumulation was minimal for EV and MMAE between cycles
- The magnitude of differences in exposure observed for some covariates was not considered clinically meaningful

Table 2. Parameter Estimates of Base and Final PopPK Models for EV

Parameter [Unit]	*Base Model* Parameter Estimate With (%RSE[a]) or [Shrinkage]	*Final Model* Parameter Estimate With (%RSE[a]) or [Shrinkage]	*Final Model* Bootstrap Estimate Median (95% CI)
CL_A [L/h]	0.101 (1.0)	0.110 (1.3)	0.109 (0.107, 0.112)
V1 [L]	3.47 (0.9)	3.63 (1.1)	3.63 (3.55, 3.70)
Q2 [L/h]	0.00437 (7.2)	0.00446 (7.0)	0.00448 (0.00395, 0.00516)
V2 [L]	5.50 (16)	5.79 (12)	5.89 (4.43, 7.97)
Q3 [L/h]	0.0381 (2.6)	0.0397 (2.6)	0.0397 (0.0380, 0.0421)
V3 [L]	2.78 (2.6)	3.42 (2.9)	3.42 (3.24, 3.60)
Covariate effects (%RSE)			
Weight ~ CL_A, Q2, Q3	0.686 (7.2)	0.572 (9.0)	0.576 (0.469, 0.692)
Weight ~ V1, V2, V3	0.702 (6.5)	0.607 (8.0)	0.608 (0.511, 0.702)
Age ~ CL_A	–	-0.325 (17)	-0.323 (-0.441, -0.223)
Albumin ~ CL_A	–	-0.507 (16)	-0.508 (-0.685, -0.348)
Manuf. process (A) ~ CL_A	–	-0.110 (14)	-0.110 (-0.140, -0.0797)
Sex (female) ~ CL_A	–	-0.138 (14)	-0.138 (-0.175, -0.0986)
SOD ~ CL_A	–	0.0555 (22)	0.0548 (0.0303, 0.0783)
Hemoglobin ~ V1	–	-0.380 (17)	-0.382 (-0.508, -0.253)
Sex (female) ~ V1	–	-0.148 (14)	-0.147 (-0.185, -0.106)
Anal. lab (Intertek) ~ V3	–	-0.355 (7.8)	-0.353 (-0.404, -0.298)
Sex (female) ~ V3	–	-0.139 (28)	-0.139 (-0.207, -0.0745)
Inter-individual variability [shrinkage]			
ω_{CLA} [CV%]	22.8 [6.0]	20.3 [6.5]	20.1 (19.0, 21.3)
ω_{V1} [CV%]	22.5 [11]	21.3 [12]	21.2 (19.6, 22.8)
ω_{V3} [CV%]	43.5 [17]	37.4 [19]	37.1 (33.5, 40.7)
Residual variability (%RSE)			
Proportional error [CV%]	20.5 (2.3)	20.4 (2.3)	20.4 (19.5, 21.3)
Additive error [µg/mL]	0.0449 (9.1)	0.0459 (9.1)	0.0458 (0.0383, 0.0535)

[a]Relative standard error (%RSE= 100*standard error/mean) is listed for PopPK parameters, covariate effects, and residual variability. η-shrinkage is listed for inter-individual variability parameters.
Abbreviations: CI, confidence interval; CL_A, clearance of EV; CV%, coefficient of variance; EV, enfortumab vedotin; PopPK, population pharmacokinetics; Q2, inter-compartment clearance of EV to the first peripheral compartment; Q3, inter-compartment clearance of EV to the second peripheral compartment; SOD, baseline sum of diameters for tumor in different organs; V1, volume of distribution of EV to central compartment; V2, volume of distribution of EV to the first peripheral compartment; V3, volume of distribution of EV to the second peripheral compartment.

Table 3. Parameter Estimates of Base and Final PopPK Models for Free MMAE

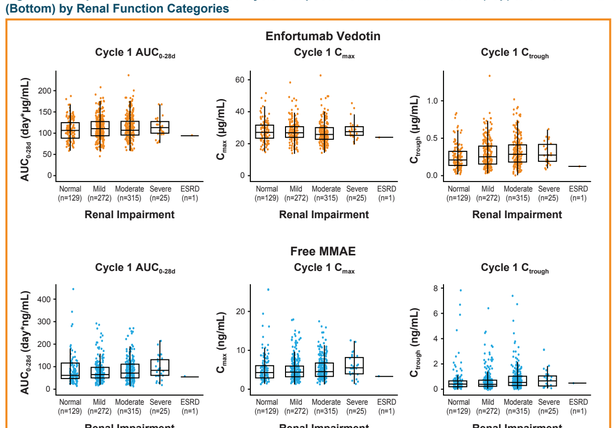
Parameter [Unit]	*Base Model* Parameter Estimate With (%RSE[a]) or [Shrinkage]	*Final Model* Parameter Estimate With (%RSE[a]) or [Shrinkage]	*Final Model* Bootstrap Estimate Median (95% CI)
CL_M [L/h]	2.39 (2.7)	2.11 (3.2)	2.11 (1.98, 2.26)
V_M [L]	108 (2.5)	125 (3.4)	125 (117, 134)
Q_M [L/h]	13.8 (7.5)	14.5 (0.9)	14.5 (12.8, 16.4)
V_{MP} [L]	102 (5.3)	58.5 (4.3)	58.3 (48.9, 68.4)
DAR0 [Unitless]	3.8 Fixed	3.8 Fixed	3.8 Fixed
BETA [1/h]	0.00117 (6.7)	0.00115 (6.7)	0.00115 (0.000988, 0.00130)
Covariate effects (%RSE)			
WT ~ CL_M, Q_M	0.75 Fixed	0.75 Fixed	0.75 Fixed
WT ~ V_M, V_{MP}	1 Fixed	1 Fixed	1 Fixed
Albumin ~ CL_M	–	1.42 (13)	1.42 (1.02, 1.79)
ECOG (0) ~ CL_M	–	0.218 (20)	0.215 (0.135, 0.312)
Hemoglobin ~ CL_M	–	1.14 (14)	1.13 (0.818, 1.42)
Manuf. process (A) ~ CL_M	–	0.231 (20)	0.229 (0.142, 0.324)
Bilirubin ~ CL_M	–	-0.233 (17)	-0.232 (-0.311, -0.148)
Albumin ~ V_M	–	1.26 (17)	1.25 (0.812, 1.68)
Manuf. process (A) ~ V_M	–	-0.255 (14)	-0.257 (-0.319, -0.191)
SOD ~ V_M	–	-0.161 (22)	-0.159 (-0.228, -0.0902)
Albumin ~ V_{MP}	–	1.38 (24)	1.39 (0.682, 2.14)
ECOG (0) ~ V_{MP}	–	0.321 (26)	0.318 (0.139, 0.530)
Hemoglobin ~ V_{MP}	–	1.61 (19)	1.62 (1.00, 2.19)
Manuf. process (A) ~ V_{MP}	–	1.04 (10)	1.06 (0.759, 1.41)
Sex (female) ~ V_{MP}	–	0.563 (15)	0.564 (0.368, 0.781)
Inter-individual variability [shrinkage]			
ω_{CLM} [CV%]	53.6 [4.1]	43.4 [5.0]	43.2 (40.5, 45.9)
ω_{VM} [CV%]	62.0 [10]	55.0 [10]	54.8 (50.9, 59.5)
ω_{VMP} [CV%]	86.0 [25]	62.8 [31]	62.2 (55.2, 68.4)
Residual variability (%RSE)			
Proportional error [CV%]	32.0 (1.8)	32.2 (1.8)	32.2 (31.1, 33.3)

[a]Relative standard error (%RSE =100*standard error/mean) is listed for PopPK parameters, covariate effects, and residual variability. η-shrinkage is listed for inter-individual variability parameters.
Abbreviations: BETA, conversion rate of free MMAE from conjugated antibody-drug conjugate; CI, confidence interval; CL_M, clearance of MMAE; CV%, coefficient of variance; DAR0, drug-antibody ratio at the time of dosing; ECOG, Eastern Cooperative Oncology Group; EV, enfortumab vedotin; MMAE, monomethyl auristatin E; PopPK, population pharmacokinetics; Q_M, inter-compartment clearance of MMAE; SOD, baseline sum of diameters for tumor in different organs; V_M, MMAE volume of distribution to central compartment; V_{MP}, MMAE volume of distribution to peripheral compartment; WT, body weight.

Special Populations

- EV PK differences in special populations were not considered clinically meaningful
- For renal impairment, no significant differences in exposure of EV and MMAE were observed in mild (creatinine clearance [CrCl] ≥60 to <90 mL/min) (n=272), moderate (CrCl ≥30 to <60 mL/min) (n=315), or severe (CrCl ≥15 to <30 mL/min) (n=25) impairment versus normal renal function (Figure 1)

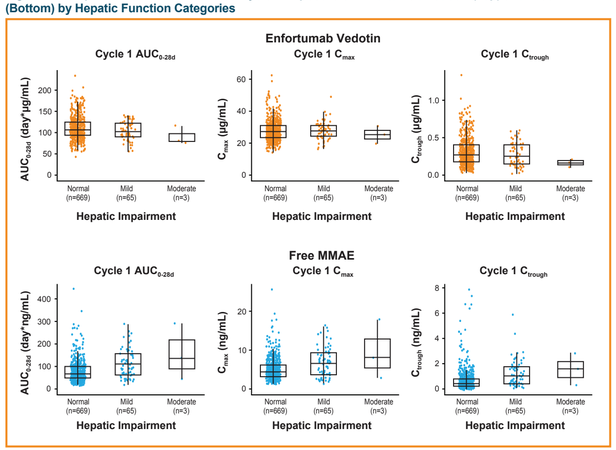
Figure 1. Comparison of Model-Predicted Cycle 1 Exposure of Enfortumab Vedotin (Top) and Free MMAE (Bottom) by Renal Function Categories



Note: Cycle 2 Day 1 predose concentration was used as Cycle 1 C_{trough}. Orange and blue circles were individual model-predicted Cycle 1 exposures of ADC and free MMAE, respectively, following 1.25 mg/kg enfortumab dose with dose capped at 125 mg for body weights ≥100 kg. Six subjects with missing or unknown renal impairment category were excluded from the plots.
Abbreviations: ADC, antibody-drug conjugate; AUC_{0-28d}, area under the concentration-time curve from 0 to 28 days; C_{max}, maximum concentration; C_{trough}, trough concentration; ESRD; end-stage renal disease; MMAE, monomethyl auristatin E.

- For hepatic impairment, bilirubin was a significant covariate for MMAE only; patients with mild impairment (n=65) had a 37% increase in area under the concentration-time curve from time 0 to 28 days post infusion and a 31% increase in maximum concentration of MMAE versus patients with normal hepatic function (Figure 2)

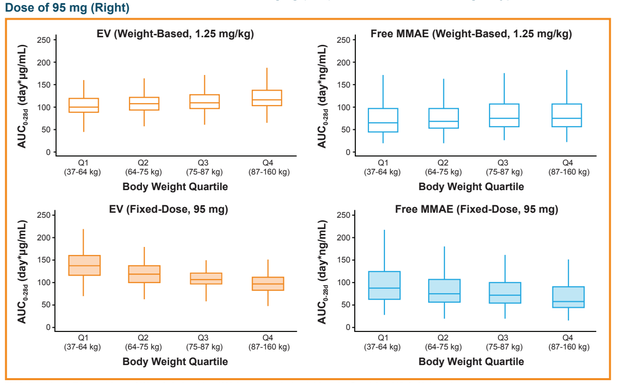
Figure 2. Comparison of Model-Predicted Cycle 1 Exposure of Enfortumab Vedotin (Top) and Free MMAE (Bottom) by Hepatic Function Categories



Note: Cycle 2 Day 1 predose concentration was used as Cycle 1 C_{trough}. Orange and blue circles were individual model-predicted Cycle 1 exposures of enfortumab vedotin and free MMAE, respectively, following 1.25 mg/kg enfortumab dose (capped at 125 mg for body weights ≥100 kg). Eleven patients with missing or unknown hepatic impairment category were excluded from the plots.
Abbreviations: AUC_{0-28d}, area under the concentration-time curve from time 0 to 28 days post infusion; C_{trough}, trough concentration; MMAE, monomethyl auristatin E.

- No clinically significant differences in EV and MMAE PK were observed based on age, sex, or race/ethnicity
- Weight-based dosing showed similar exposure for all patients across body weight quartiles (Figure 3)

Figure 3. Model-Predicted Exposure for Enfortumab Vedotin and Free MMAE Across Different Weight Quartiles Based on Enfortumab Vedotin 1.25 mg/kg (Left) and When Administering a Hypothetical Fixed Dose of 95 mg (Right)



Weight-based dose (utilizing a weight cap of 125 mg for body weights ≥100 kg) was assumed to be administered on Days 1, 8, and 15 of a 28-day cycle.
Abbreviations: AUC_{0-28d}, area under the concentration-time curve from time 0 to 28 days post infusion; EV, enfortumab vedotin; MMAE, monomethyl auristatin E; Q1, minimum to 25th percentile of body weight; Q2, 25th to 50th percentile of body weight; Q3, 50th to 75th percentile of body weight; Q4, 75th percentile to maximum of body weight.

- EV did not prolong mean QTc interval to a clinically relevant extent based upon electrocardiogram and PK data from the EV-102 study[3] (n=17; advanced UC)
- Based on the population-based PK model for EV used to predict MMAE exposure, concomitant use with dual P-glycoprotein (P-gp) and strong CYP3A4 inhibitors may increase MMAE exposure and may increase the risk of adverse events (Table 4)
- EV did not appear to affect the exposure of CYP3A4 substrates

Table 4. Predicted (Simulated) Effects of Ketoconazole or Rifampin on Enfortumab Vedotin and Effects of Enfortumab Vedotin on Midazolam Pharmacokinetic Parameters

	AUC_{last}	C_{max}
Drug	**Geometric mean (90% CI)**	
Ketoconazole: combined P-gp and strong CYP3A inhibitor	1.38 (1.35, 1.41)	1.15 (1.14, 1.16)
Rifampin: combined P-gp and strong 3A inducer	0.47 (0.46, 0.49)	0.72 (0.71, 0.73)
Midazolam: CYP3A4 substrate	1.14 (1.13, 1.16)	1.00 (1.00, 1.00)

Abbreviations: AUC_{last}, area under the concentration-time curve up to the last measurable concentration; CI, confidence interval; C_{max}, maximum concentration; CYP, cytochrome; P-gp, P-glycoprotein.

- Following EV 1.25 mg/kg, 16/590 (2.7%) patients tested positive for ATA against EV at ≥1 postbaseline time point
  - Transiently positive: n=13
  - Persistently positive: n=3

Conclusions

- **Integration of EV and free MMAE PK findings support the approved EV weight-based dose of 1.25 mg/kg on Days 1, 8, and 15 of a 28-day cycle**
  - **This EV dose has demonstrated clinically meaningful efficacy and manageable safety in patients with previously treated la/mUC and is in approved labeling[2,4]**
- **No dose adjustments were required for special populations, including those with patients with mild, moderate, and severe renal impairment, those with mild hepatic impairment, or by age, sex, or race**
- **Patients should be closely monitored for signs of adverse events when EV is used during concomitant treatment with dual P-gp and strong CYP3A4 inhibitors**
- **A low rate of immunogenicity was observed in patients receiving EV**

References

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