Unconjugated MMAE Pharmacokinetics in Combination with Tucatinib in Patients with HER2 Expressing LA/M Breast or Gastric Cancer



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Objective

To characterize the impact of tucatinib, a strong CYP3A4 and a relatively weak P-gp inhibitor, on the PK of the unconjugated MMAE payload of disitamab vedotin in patients with HER2 expressing LA/M breast or gastric cancers.

Conclusion

Unconjugated MMAE exposure increased <1.3-fold in the presence of tucatinib, translating to an overall weak DDI impact.

Background

- **Disitamab vedotin (DV)** is a HER2-targeting ADC with a monomethyl auristatin E (MMAE) payload via a maleimidocaproyl-valine-citrulline (MC-VC) linker. DV is currently being explored for use in 2L+ HER2-expressing mBC in combination with tucatinib.
- **MMAE** is primarily metabolized in vitro by cytochrome P450 3A4 (CYP3A4) and is a substrate of P-glycoprotein (P-gp).
  - Previous DDI studies and PBPK models with vedotin ADCs have shown a 1.3-1.5-fold increase of unconjugated MMAE (uMMAE) in the presence of ketoconazole[1-4], a strong CYP3A4 and strong P-gp inhibitor.
  - Given the strong dual inhibition, determining relative contributions of ketoconazole-mediated CYP3A4 versus P-gp inhibition on uMMAE PK is challenging. Additionally, it is unclear how increases in uMMAE exposure due to CYP3A4/P-gp inhibition may impact overall safety[1].
- **Tucatinib (TUC)** is a strong CYP3A4 inhibitor and a relatively weak P-gp inhibitor[5]. TUC offers a unique opportunity to isolate CYP3A4-mediated effects as TUC P-gp inhibition was previously shown to mainly impact orally administered digoxin gut absorption (C_{max}) and lesser the systemic elimination (AUC_{inf})[5]. DV is administered intravenously (IV), thus any increases in MMAE exposure with concomitant DV and TUC administration are expected to be mainly from CYP3A4 inhibition.
- **Objective: In the clinical study C5731004/SGNDV-004, DV PK was characterized with and without tucatinib to assess the impact of tucatinib-mediated CYP3A4 and P-gp inhibition on unconjugated MMAE PK.**

Methods

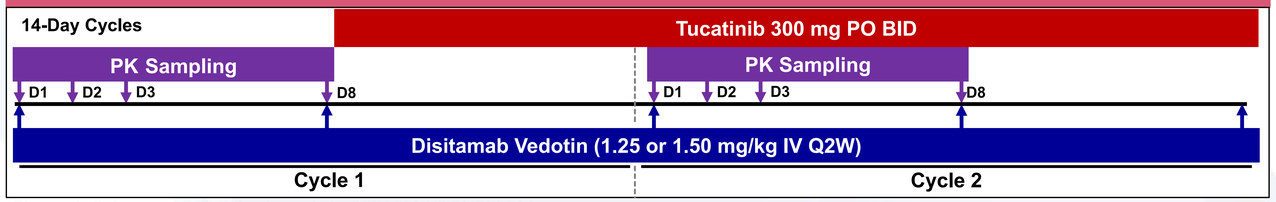


Figure 1. Schema of DDI PK sub-study in C5731004/SGNDV-004

- **Design**: This DDI sub-study is part of the dose escalation in the clinical study C5731004/SGNDV-004 (NCT06157892), a phase 1b/2, open-label, multicenter trial designed to identify the maximum tolerated dose (MTD) and/or optimal dose of DV when administered in combination with TUC.
- **Population**: HER2-positive (IHC 3+ or IHC 2+/ISH+) and HER2-low (IHC 1+ or IHC 2+/ISH-) expressing locally advanced or metastatic (LA/M) breast cancer (BC) or LA/M gastric cancer (GC) and gastroesophageal junction adenocarcinoma (GEJC).
- **Dosage Regimen**: DV (1.25 mg/kg or 1.50 mg/kg IV Q2W) starting Cycle 1 Day 1 + TUC (300 mg PO BID) starting Cycle 1 Day 8 of a 14-day cycle.
- **PK Sampling**: uMMAE PK blood samples were collected on Days 1, 2, 3, and 8 in Cycle 1 (DV alone) and Cycle 2 (DV+TUC).
- **PK Bioanalysis**: A fully validated high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) was used to quantify uMMAE.
- **PK Analysis**: The DDI assessment was made using uMMAE $AUC_{0\text{-}168h}$ and C_{max} in Cycle 2 (test) relative to Cycle 1 (reference).
- **Software**: PKNCA (R v4.3.1, PKNCA v0.10.2)

References
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5. Topletz-Erickson et al. Evaluation of safety and clinically relevant DDIs with TUC in HVs. Clinical Pharmacokinetics August 2022. DOI: 10.1007/s40262-022-01144-z
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Abbreviations
ADC: Antibody Drug Conjugate; **$AUC_{0\text{-}168h}$**: Area Under the Curve from 0 to 168 Hours; **BC**: Breast Cancer; **C_{max}**: Maximal Concentration; **CYP3A4**: Cytochrome P450; **C#**: Cycle #; **DDI**: Drug-Drug Interaction; **DV**: Disitamab Vedotin; **D#**: Day #; **GC**: Gastric Cancer; **GEJC**: Gastroesophageal Junction Adenocarcinoma; **GM**: Geometric Mean; **HER2**: Human Epidermal Growth Factor Receptor 2; **HPLC-MS/MS**: High-Performance Liquid Chromatography-Tandem Mass Spectrometry; **HV**: Healthy Volunteer; **IHC**: Immunohistochemistry; **ISH**: In Situ Hybridization; **IV**: Intravenously; **LA/M**: Locally Advanced/Metastatic; **MTD**: Maximum Tolerated Dose; **MC-VC**: maleimidocaproyl-valine-citrulline; **P-gp**: P-glycoprotein; **PBPK**: Physiologically-Based Pharmacokinetics; **PK**: Pharmacokinetic; **PO BID**: By Mouth Twice Daily; **Q2W**: Every Other Week; **TUC**: Tucatinib; **uMMAE**: Unconjugated Monomethyl Auristatin E; **90% CI**: 90% Confidence Interval.

Results

DV AND UNCONJUGATED MMAE REACHED STEADY STATE IN CYCLE 1 AND THEREFORE HIGHER OBSERVED CYCLE 2 UNCONJUGATED MMAE PK IS ATTRIBUTED TO CONCOMITANT TUC ADMINISTRATION

- PK data were available for n=7 patients at 1.25 mg/kg and n=5 patients at 1.50 mg/kg.
- DV and uMMAE reached steady-state in Cycle 1. Thus, any uMMAE PK differences were attributed to concomitant TUC administration.
  - DV PK is overlapping for Cycles 1 and 2 (Figure 2B).
  - uMMAE pre-dose Cycle 2 concentrations were negligible (median, min-max = 0.17, 0.05 – 0.86 ng/mL).
- TUC Cycle 2 C_{max} (median, min-max = 532, 66.2 – 810 ng/mL) was consistent with previously reported values[6].

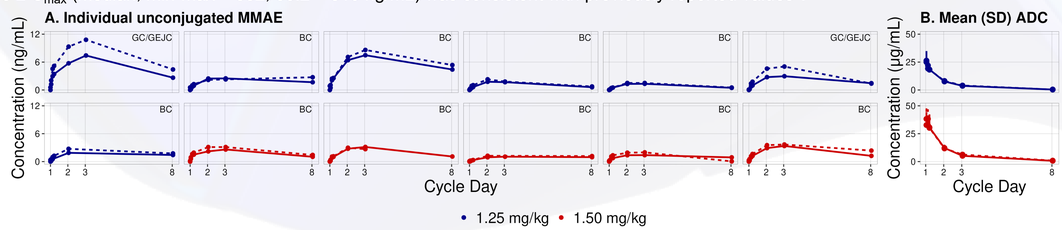


Figure 2. A.) Individual uMMAE and B.) mean (SD) DV ADC PK profiles with TUC (dashed) and without TUC (solid) at 1.25 mg/kg (blue) and 1.5 mg/kg (red). Panels for individual uMMAE PK (A.) show Individual tumor types as BC or GC/GEJC.

UNCONJUGATED MMAE PK WAS 1.1 TO 1.3-FOLD HIGHER IN THE PRESENCE OF TUC

- **AUC**: The geometric mean of $AUC_{0\text{-}168h}$ was higher in the presence of tucatinib compared to DV alone (19.0 vs 14.9 ng*day/mL for 1.25 mg/kg and 11.3 vs 13.0 ng*day/mL for 1.50 mg/kg).
- **C_{max}**: The geometric mean of C_{max} was higher in the presence of tucatinib compared to DV alone (3.83 vs 2.92 ng/mL for 1.25 mg/kg and 2.42 vs 2.49 ng/mL for 1.50 mg/kg).
- **C2:C1 Ratio**: The geometric mean ratio (GM, 90% CI) for C2:C1 $AUC_{0\text{-}168h}$ (1.17, 1.05-1.31) and C_{max} (1.25, 1.15-1.35) showed a statistically significant difference in the presence of TUC compared to DV alone.

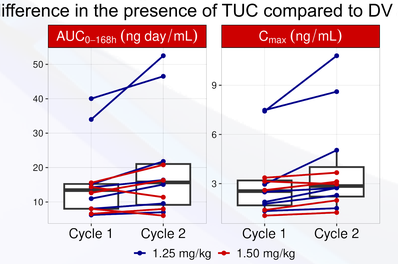


Figure 3. Individual C1 vs. C2 uMMAE PK parameters at 1.25 mg/kg (blue) and 1.5 mg/kg (red)

Table 1. Summary of uMMAE PK parameters in the absence (C1) and presence (C2) of TUC

Cohort	N	$AUC_{0\text{-}168h}$ (day*ng/mL)		C_{max} (ng/mL)	
		DV Alone (C1)	DV+TUC (C2)	DV Alone (C1)	DV+TUC (C2)
1.25 mg/kg	7	14.9 (79%)	19.0 (87%)	2.92 (78%)	3.83 (83%)
1.50 mg/kg	5	13.0 (61%)	11.3 (54%)	2.49 (70%)	2.42 (46%)
C2:C1 (90% CI)	12	**1.17 (1.05 – 1.31)**		**1.25 (1.15 – 1.35)**	

Geomean (%CV) = Geometric mean (Geometric % coefficient of variation); GMR (90% CI) = Geometric mean ratio (90% confidence interval).

Conclusions

- Unconjugated MMAE exposure increased <1.3-fold in the presence of tucatinib, translating to an overall weak DDI impact.
- The exposure-safety relationship is being further evaluated in C5731004/SGNDV-004 to understand the clinical impact of the observed increased unconjugated MMAE exposure due to tucatinib-mediated CYP3A4/P-gp inhibition.

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