PMX618

# Exposure-Response Analyses of Efficacy and Safety of Patritumab Deruxtecan in Cancer Patients

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## OBJECTIVES

1. To characterize the HER3-DXd exposure-response (ER) relationships between the anti-HER3 antibody conjugated payload (anti-HER3-ac-DXd) and payload (DXd) exposures and efficacy as measured by the Objective response rate (ORR) in NSCLC patients
2. To characterize the ER relationships between anti-HER3-ac-DXd and DXd exposures and safety in patients with NSCLC or BC:
   a) Grade 3+ platelet count decrease based on lab values (TCP)
   b) Grade 3+ neutrophil count decrease based on lab values (NEU)
   c) any grade adjudicated drug-related interstitial lung disease (ILD)
   d) Adverse events leading to discontinuation (AEDC)
   e) Adverse events leading to dose reduction (AEDR)
   f) Adverse events leading to dose interruption (AEDI)

## CONCLUSIONS

- ER analyses showed that the 5.6 mg/kg Q3W regimen offers a positive benefit-risk profile with clinically meaningful efficacy and overall manageable and tolerable safety profile.
  - There was a positive trend in the ER relationship between anti-HER3-ac-DXd Cavgc Cycle 1 to 3 and confirmed ORR by BICR.
  - Although the probability of platelet and neutrophil count decrease, ILD, AEDC, AEDR, and ARDI increased with increasing dose, the overall safety profile is manageable and tolerable as evidenced by the low rate of ILD and AEDC.
- The analyses results support the selection of 5.6 mg/kg Q3W as the recommended dose for further clinical development of HER3-DXd monotherapy.

## INTRODUCTION

- Patritumab deruxtecan (U3-1402, HER3-DXd) is a HER3-targeting antibody-drug conjugate with a topoisomerase I inhibitor payload (DXd). The drug-to-antibody ratio is approximately 8
- HER3-DXd is currently being investigated as an anticancer agent in several phase 1-3 clinical studies in breast cancer (BC) and non-small cell lung cancer (NSCLC) patients. HER3-DXd has demonstrated significant antitumor activity in HER3-expressing EGFR-mutated, TKI-resistant, patient-derived xenograft models and has been well-tolerated in early clinical readouts
- It is currently being developed as an anticancer agent for treating multiple tumor types including NSCLC and BC

## METHODS

### Data

- **The efficacy analysis population consisted of 136 response evaluable NSCLC patients (Dose range: 3.2-6.4 mg/kg Q3W) from 1 phase I study**
- Study U31402-A-U102 is a multicenter, open-label, Phase 1 study of HER3-DXd in subjects with metastatic or unresectable NSCLC
  - The dose regimens were 3.2, 4.8, 5.6 and 6.4 mg/kg Q3W; up-titration of 3.2, 4.8 and 6.4 mg/kg on day 1 of first 3 cycles, followed by 6.4 mg/kg Q3W
  - The primary objectives for dose escalation part was to assess the safety and tolerability of U3-1402 in metastatic or unresectable NSCLC subjects, and to determine the recommended dose for expansion (RDE) of U3-1402 in metastatic or unresectable EGFRm NSCLC subjects who (a) are T790M mutation-negative after disease progression during treatment
  - The primary objective for dose expansion part was to investigate the antitumor activity of U3-1402
- **The safety analysis population consisted of 400 cancer patients (Dose range: 1.6- 8 mg/kg Q3W) with evaluable exposure from multiple BC and NSCLC studies (U31402-A-U102 and U31402-A-J101)**
- Study U31402-A-J101 is a Phase 1/2, multicenter, open-label, multiple dose, first-in-human study of HER3-DXd in subjects with HER3-positive metastatic BC
  - The dose regimens were 1.6, 3.2, 4.8, 6.4, and 8 mg/kg Q3W; 4.2 mg/kg Q2W in 14-day cycles for 3 cycles, followed by 6.4 mg/kg Q3W; up-titration of 3.2, 4.8 and 6.4 mg/kg on day 1 of first 3 cycles, followed by 6.4 mg/kg Q3W
  - The primary objectives for dose escalation part was to assess safety and tolerability of U3-1402, to determine the maximum tolerated dose (MTD) of U3-1402 and to determine the recommended dose(s) for expansion (RDEs) of U3-1402
  - The primary objectives for dose expansion part was to assess safety and evaluate efficacy of U3-1402 at the RDEs in subjects with human epidermal growth factor receptor 2 (HER2)-negative and hormone receptor (HR)-positive breast cancer

**Table 1. Methods**

| Study | Title | Dose Regimens | Primary Objectives | Analysis |
|---|---|---|---|---|
| U31402-A-U102 | multicenter, open-label, Phase 1 study of HER3-DXd in subjects with metastatic or unresectable NSCLC | 3.2, 4.8, 5.6 and 6.4 mg/kg Q3W; up-titration of 3.2, 4.8 and 6.4 mg/kg on day 1 of first 3 cycles, followed by 6.4 mg/kg Q3W | • Dose escalation part: to assess the safety and tolerability of U3-1402 in metastatic or unresectable NSCLC subjects, and to determine the recommended dose for expansion (RDE) of U3-1402 in metastatic or unresectable EGFRm NSCLC subjects who (a) are T790M mutation-negative after disease progression during treatment<br>• Dose expansion part: to investigate the antitumor activity of U3-1402 | ER efficacy and safety |
| U31402-A-J101 | Phase 1/2, multicenter, open-label, multiple dose, first-in-human study of HER3-DXd in subjects with HER3-positive metastatic BC | The dose regimens were 1.6, 3.2, 4.8, 6.4, and 8 mg/kg Q3W; 4.2 mg/kg Q2W in 14-day cycles for 3 cycles, followed by 6.4 mg/kg Q3W; up-titration of 3.2, 4.8 and 6.4 mg/kg on day 1 of first 3 cycles, followed by 6.4 mg/kg Q3W. | • Dose escalation part: to assess safety and tolerability of U3-1402, to determine the maximum tolerated dose (MTD) of U3-1402 and to determine the recommended dose(s) for expansion (RDEs) of U3-1402<br>• Dose expansion part: to assess safety and evaluate efficacy of U3-1402 at the RDEs in subjects with human epidermal growth factor receptor 2 (HER2)-negative and hormone receptor (HR)-positive breast cancer | ER safety |

### Model Development

- Logistic regression models were used to describe the ER relationships for both the efficacy and safety endpoints
- Average concentration since first dose to the response or censored to the last dose/dosing interval (Cavgc) of anti-HER3-ac-DXd was used for the exposure-efficacy analysis
- For each safety endpoint, anti-HER3-ac-DXd or DXd Cavgc (till AE or censoring at 21 days after the last treatment date), and maximum concentration in the first dosing interval (Cmax1) were tested. The exposure metric that best described the ER relationship was selected using the LOO Information Criterion (LOOIC)
- For each analysis, base model development evaluated log-linear and sigmoidal Emax structural models. The full model included all the pre-specified covariates and their main effects on the log odds. Covariate interaction effects with exposure was not examined
- The final model was obtained by including only the covariate effects that were considered statistically significant by backwards elimination from the full model.
- Investigated baseline covariates:
  - **Efficacy:** age, weight, tumor size, sex, ECOG, race, bone metastasis, liver metastasis, brain metastasis, membrane H score, and the use of prior chemotherapy
  - **Safety:** age, weight, sex, platelet count decrease, neutrophil count decrease, hemoglobin (for neutrophil count decrease and platelet count decrease), ECOG, race, liver metastasis, membrane H score, use of prior IO therapy and tumor type

**Summary of event rate in safety analysis.**

| AE | n | Event | |
|---|---|---|---|
| | | True | False |
| **J101** | | | |
| Gr.3+ platelet count decrease | 181 | 59 (32.6) | 122 (67.4) |
| Gr.3+ neutrophil count decrease | 181 | 21 (11.6) | 160 (88.4) |
| Dose discontinuation | 181 | 11 (6.1) | 170 (93.9) |
| Dose interruption | 181 | 91 (50.3) | 90 (49.7) |
| Dose reduction | 181 | 30 (16.6) | 151 (83.4) |
| Interstitial lung disease | 181 | 8 (4.4) | 173 (95.6) |
| **U102** | | | |
| Gr.3+ platelet count decrease | 219 | 40 (18.3) | 179 (81.7) |
| Gr.3+ neutrophil count decrease | 219 | 39 (17.8) | 180 (82.2) |
| Dose discontinuation | 219 | 17 (7.8) | 202 (92.2) |
| Dose interruption | 219 | 66 (30.1) | 153 (69.9) |
| Dose reduction | 219 | 46 (21.0) | 173 (79.0) |
| Interstitial lung disease | 219 | 12 (5.5) | 207 (94.5) |

Summary is count (percent).
n: number of records summarized.

### Model Evaluations

- Logistic model evaluations were performed using posterior predictive checks (PPC)
- The proportion of responders (for ER efficacy) or subjects with AEs (for ER safety) were simulated across the posterior samples of model parameters. The simulated posterior predictive distributions were summarized by exposure quartile and key dose groups and compared to observed proportions

### Model-based Simulation

- Virtual patient populations with 200 patients were created by randomly sampling with replacement from the NSCLC patients
- Exposures of anti-HER3-ac-DXd and DXd were simulated at the 4.8, 5.6, 6.4 mg/kg Q3W and the up-titration dosing regimens
- The responses were simulated and summarized across joint posterior distribution of ER model parameters

## RESULTS

### ER Efficacy

- The objective response rate increased with increasing anti-HER3-ac-DXd exposure (**Figure 1**)
- There was a positive trend in the ER relationship between anti-HER3-ac-DXd Cavgc and confirmed ORR by BICR (**Figure 1**)
- Among the exploratory variables considered, the only predictive covariate was prior chemotherapy (patients with prior chemotherapy resulted in a 28.4% decrease in odds of being a responder compared to patients without prior chemotherapy) (**Figure 2**)
- Simulations of ORR across varying treatment regimens (4.8 mg/kg Q3W, 5.6 mg/kg Q3W, and 6.4 mg/kg Q3W) demonstrated a positive dose-response relationship, while up-titration regimen showed lower ORR efficacy (**Figure 2**)

**Figure 1: Predicted Probability of Overall Response as a Function of Anti-HER3-ac-DXd Cavgc[a,b]**

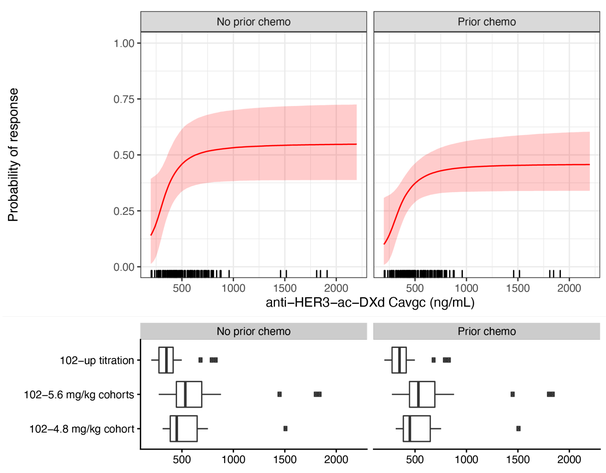
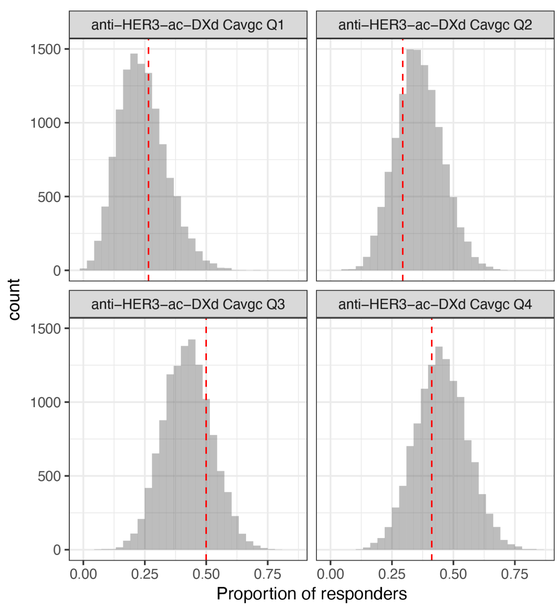



**Figure 2: Posterior Predictive Distribution for Proportion of Partial or Complete Responders in Each Quartile of Anti-HER3-ac-DXd Cavgc. The Vertical Dashed Red Lines Represent Observed Proportions**




The model adequately captured the ER relationship of ORR, as demonstrated by the simulated distribution of responders encompassing the observed median in each quartile of anti-HER3-ac-DXd Cavgc.

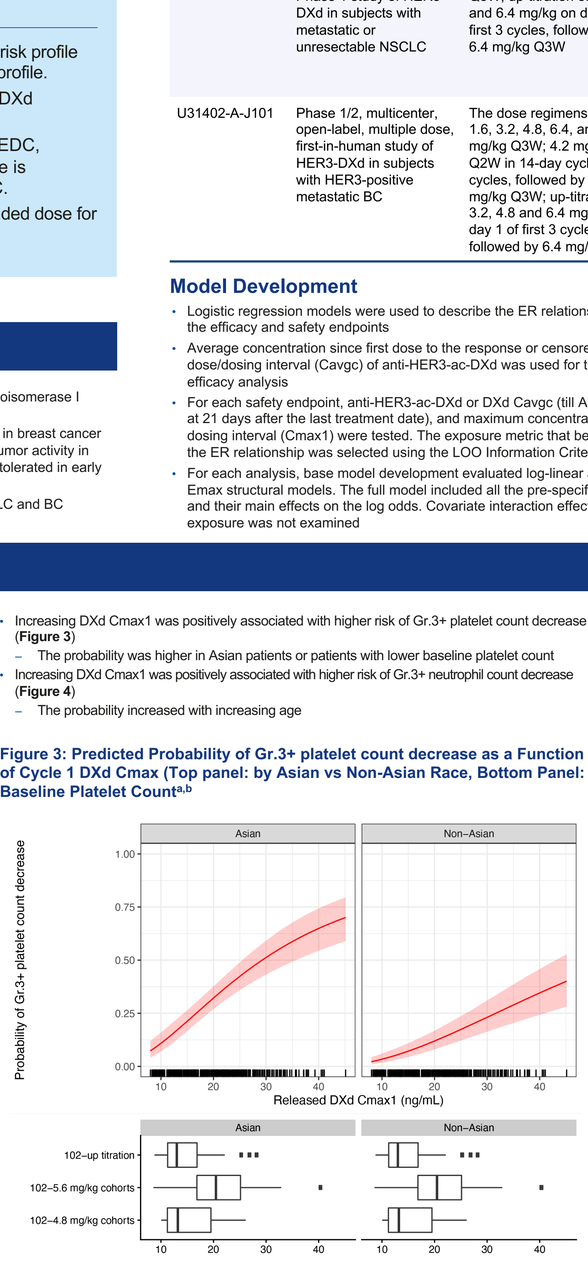
### ER Safety

**Table 2. Predictive Exposure metrics and covariates for safety endpoints**

| AE Endpoint | Predictive Exposure | Predictive Covariates |
|---|---|---|
| Gr.3+ platelet count decrease | DXd Cmax1 (log-linear) | race (Asian vs. non-Asian) and baseline platelet count |
| Gr.3+ neutrophil count decrease | DXd Cmax1 (log-linear) | age |
| Drug-related ILD | Anti-HER3-ac-DXd Cavg (sigmoidal Emax) | none |
| AEDC | DXd Cavg (log-linear) | none |
| AEDR | DXd Cavg (log-linear) | tumor type (BC vs. NSCLC) |
| AEDI | DXd Cavg (log-linear) | age, race and ECOG (>=1 vs. 0) |

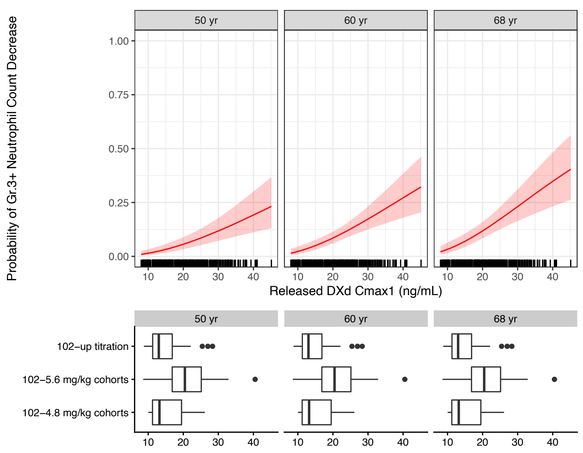
- Increasing DXd Cmax1 was positively associated with higher risk of Gr.3+ platelet count decrease (**Figure 3**)
  - The probability was higher in Asian patients or patients with lower baseline platelet count
- Increasing DXd Cmax1 was positively associated with higher risk of Gr.3+ neutrophil count decrease (**Figure 4**)
  - The probability increased with increasing age

**Figure 3: Predicted Probability of Gr.3+ platelet count decrease as a Function of Cycle 1 DXd Cmax (Top panel: by Asian vs Non-Asian Race, Bottom Panel: Baseline Platelet Count[a,b]**




The presented baseline platelet count values represent the 25th, median and 75th percentiles in the analysis dataset.
The probability of Gr.3+ TCP increased with increasing DXd Cmax in Cycle1.
The probability was higher in Asian patients or patients with higher baseline platelet counts.

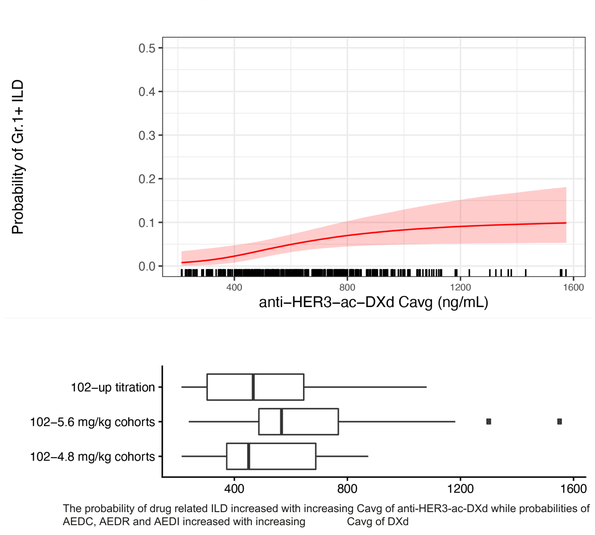
**Figure 4: Predicted Probability of Gr.3+ neutrophil count decrease as a Function of Cycle 1 DXd Cmax[b]**




The presented age values represent the 25th, median and 75th percentiles in the analysis dataset.
The probability of Gr.3+ NEU increased with increasing DXd Cmax in Cycle 1.
The probability also increased with increasing age.

- Increasing anti-HER3-ac-DXd Cavg was positively associated with higher risk of drug-related adjudicated ILD (**Figure 5**)
  - Among the exploratory variables considered, no covariates were identified as predictive

**Figure 5: Predicted Probability of Drug-Related ILD as a Function of anti-HER3-ac-DXd Average Concentration[a,b]**




The probability of drug related ILD increased with increasing Cavg of anti-HER3-ac-DXd while probabilities of AEDC, AEDR and AEDI increased with increasing Cavg of DXd

**Figure 6: Predicted Probability of Adverse Events Leading to Discontinuation as a Function of DXd Average Concentration[a,b]**

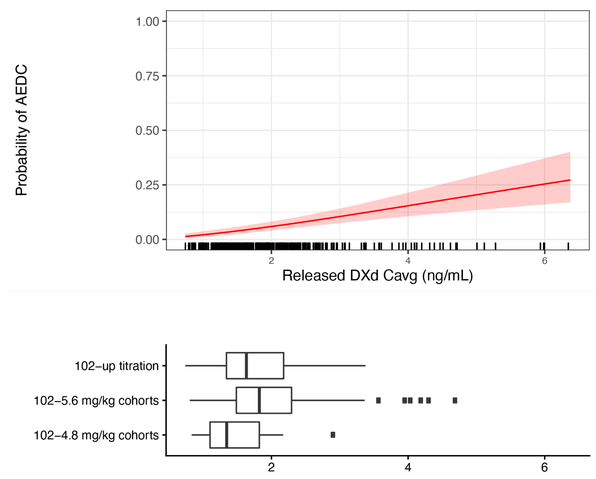
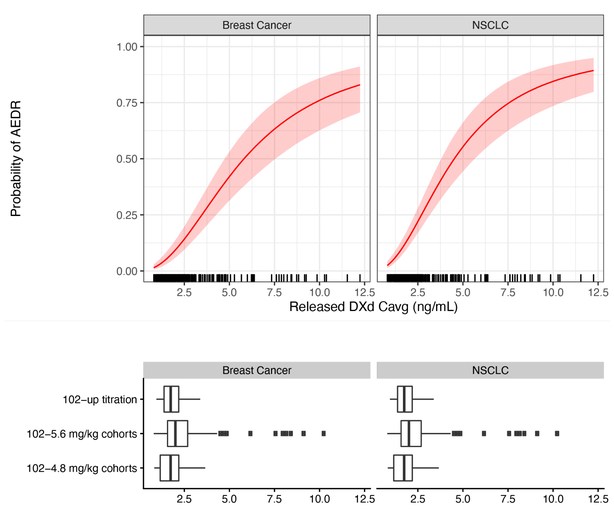



**Figure 7: Predicted Probability of Adverse Events Leading to Dose Reduction as a Function of DXd Average Concentration by Tumor Type[a,b]**




- Increasing DXd Cavg was positively associated with higher risk of AEDC (**Figure 8**)
  - Among the exploratory variables considered, no covariates were identified as predictive
- Increasing DXd Cavg was positively associated with higher risk of AEDR (**Figure 8**)
  - The probability was higher in NSCLC patients compared to BC patients
- Increasing DXd Cavg was positively associated with higher risk of AEDI (**Figure 8**)
  - The probability was higher in older patients, Asian patients or patients with ECOG 0

**Figure 8: Predicted Probability of Adverse Events Leading to Dose Interruption as a Function of DXd Average Concentration by ECOG (top panel), Race( middle panel) and Age (bottom panel)[a,b]**

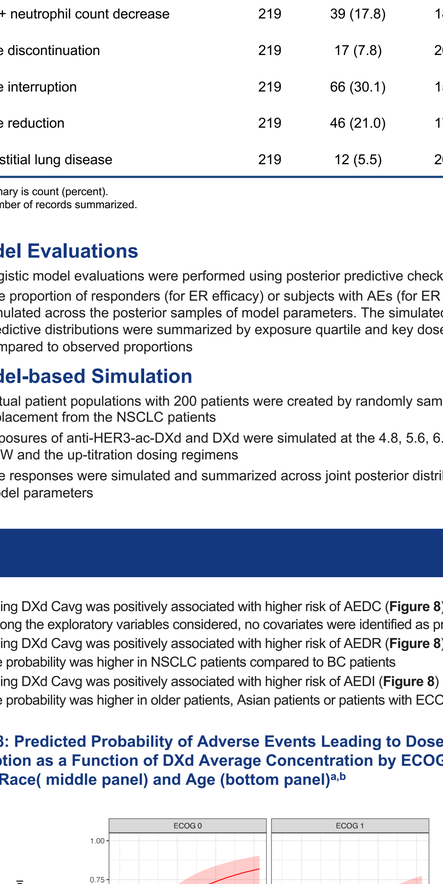
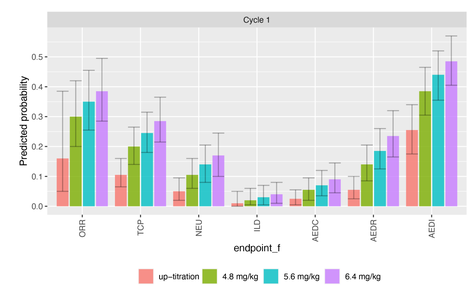



**Figure 9: Predicted ORR and Incidence of Safety Endpoints for HER3-DXd doses 6 mg/kg Q3W and Up-titration Regimens Using ER Analyses**




5.6 mg/kg Q3W dose regimen is predicted to provide a clinically meaningfully higher ORR compared to the other dosing regimen with durable responses and manageable safety events.

## Acknowledgements

We thank the patients, their families, and their caregivers for their participation. We also thank Pavan Vaddady for his valuable scientific contributions to this analysis.

## Footnotes

[a] Red line is posterior median. Colored ribbon is 90% CrI. Vertical bars indicate observed individual exposure values in the overall analysis dataset. Horizontal box plot shows the distribution of the exposure values in the 3 dose regimens observed in U31402-A-U102.

[b] The sample size was 14, 84 and 29 for 4.8 mg/kg, 5.6 mg/kg and up titration cohort, respectively.

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