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

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OBJECTIVES
- To characterize the HER3-DXd exposure-response (ER) relationships between the anti-HER3 antibody conjugate (anti-HER3-DXd) and predicted (DXd) exposure and efficacy as measured by the Objective Response Rate (ORR) in NSCLC patients.
- To characterize the ER relationships between anti-HER3-DXd and DXd exposures and efficacy as measured by the ORR and safety in NSCLC patients.
- To assess the predictive value of anti-HER3-DXd exposure in relation to efficacy and safety.
- To determine the recommended dose for expansion (RDE) in NSCLC patients.

RESULTS
- The exposure-response (ER) relationships were characterized for both efficacy and safety.
- Among the exploratory variables considered, the only predictive covariate was prior chemotherapy.
- The ER relationships showed that the overall safety profile is predominantly dose-dependent.
- The probability of adverse events was positively associated with higher risk of AEDR (Figure 1).
- The probability of AEDR was positively associated with higher risk of AEDC and ARDI (Figure 2).
- The probability of AEDR was positively associated with higher risk of AEDC (Figure 3).
- The probability of AEDR was positively associated with higher risk of AEDC and ARDI (Figure 4).

CONCLUSIONS
- ER analyses showed that the 5.6-kg QW regimen offers a positive benefit-risk profile with clinically meaningful efficacy and manageable tolerable safety profile.
- There was a positive trend in the ER relationship between anti-HER3-DXd and ORR (Figure 5).
- There was a positive trend in the ER relationship between anti-HER3-DXd and safety (Figure 6).
- There was a positive trend in the ER relationship between anti-HER3-DXd and safety (Figure 7).
- There was a positive trend in the ER relationship between anti-HER3-DXd and safety (Figure 8).
- There was a positive trend in the ER relationship between anti-HER3-DXd and safety (Figure 9).

INTRODUCTION
- Patritumab deruxtecan (U3-1402) is a HER3-directed, antibody-drug conjugate that targets breast cancer, with clinical studies in breast cancer.
- For each safety endpoint, anti-HER3-DXd exposure was not examined.
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METHODS

ER Efficacy
- The objective response rate (ORR) was assessed using anti-HER3-DXd exposure (Figure 1). ORR was determined using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.
- Among the exploratory variables considered, the only predictive covariate was prior chemotherapy.

ER Safety
- The safety analysis population consisted of 250 evaluable patients with 50 yr age.
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Model Development
- Linear regression models were used to describe the ER relationships for both efficacy and safety.
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Table 1: Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
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<tbody>
<tr>
<td>ER analysis</td>
<td>Exploratory analysis of ORR across varying treatment regimens (4.8 mg/kg Q3W, 5.6 mg/kg Q3W, and 6.4 mg/kg Q3W)</td>
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<tr>
<td>Predictive Covariates</td>
<td>Prior chemotherapy, age, race, and ECOG (&gt;=1 vs. 0)</td>
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Model Evaluations
- Logistic regression models were performed using posterior predictive checks (PPC).
- The probability of adverse events (AEDR) and adverse events (AEDC) were evaluated using posterior predictive distributions.
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Model-based Simulation
- Virtual patient populations with 250 patients were created by randomly sampling with replacement from the observed patients.
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Acknowledgements
- This study was supported by the National Cancer Institute of Canada, the Cancer Research Group, and the HER3 Study Group.

Footnotes
- The probability of adverse events was positively associated with higher risk of AEDR (Figure 1).
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