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TROPION-Lung08: Datopotamab Deruxtecan (Dato-DXd) Plus Pembrolizumab in Treatment-Naive Advanced/Metastatic (adv/met) Non-Small Cell Lung Cancer (NSCLC) With PD-L1 ≥50% and Without Actionable Genomic Alterations

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Background

• While first-line treatment with immunotherapy (with or without chemotherapy) has improved outcomes in patients with programmed death ligand 1 (PD-L1) expressing adv/met NSCLC, almost all patients inevitably experience disease progression.9,10

• Pembrolizumab as monotherapy has shown superior efficacy compared with chemotherapy in treatment-naive patients with advanced NSCLC and PD-L1 expression ≥50%. However, with initial pembrolizumab monotherapy, only approximately one-third of patients are expected to be alive after 5 years.11,12

• Dato-DXd is an antibody drug conjugate (ADC) composed of a humanized anti-tropoblast cell-surface antigen 2 (TROP2) immunoglobulin G1 (IgG1) monoclonal antibody covalently linked to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker.6

In the ongoing, phase 1 TROPION-ParTumor01 trial (NCT03401385; DS1062-A-J101), Dato-DXd 6 mg/kg monotherapy demonstrated an objective response rate (ORR) of 28% and a manageable safety profile in pretreated patients with adv/met NSCLC at a data cutoff of April 6, 2021.11

In addition, preclinical studies showed that DxD ADCs combined with an anti–programmed cell death 1 (PD-1) antibody were more effective than monotherapy with either agent alone.13

The tolerability of Dato-DXd 6 mg/kg in combination with pembrolizumab was confirmed in the phase 1b TROPION-Lung02 trial (NCT04526891; DS1062-A-U102).10

TROPION-Lung08 (NCT05215340; DS1062-A-U304) is a global, randomized, open-label, phase 3 trial of Dato-DXd plus pembrolizumab alone in treatment-naive patients with adv/met NSCLC without actionable genomic alterations and with PD-L1 ≥50%.5

Structure and 7 Key Attributes of Dato-DXd

Dato-DXd is an ADC composed of 3 components6

• A humanized anti-TROP2 IgG1 mAb, covalently linked to:

  • A topoisomerase I inhibitor payload, an exatecan derivative, via a stable tetrapeptide-based cleavable linker

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• A topoisomerase I inhibitor payload (DXd), a novel topoisomerase I inhibitor that is a derivative of exatecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody; TROP2, trophoblast cell-surface antigen 2.

The clinical relevance of these features is under investigation.10

Methods

Study Design and Population

Table: Patient population (N=740)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III, IV, or NSCLC</td>
<td>705 (95.3)</td>
</tr>
<tr>
<td>No actionable genomic alterations documented</td>
<td>690 (93.4)</td>
</tr>
<tr>
<td>No previous systemic therapy for adv/met NSCLC</td>
<td>704 (95.3)</td>
</tr>
<tr>
<td>ECOG PS 0 or 1</td>
<td>645 (86.9)</td>
</tr>
<tr>
<td>Central PD-L1 TPS ≥50%</td>
<td>632 (85.2)</td>
</tr>
</tbody>
</table>

Stratified by:

• Histology (non-squamous vs squamous)
• Geography (East Asia vs rest of ecdt)
• Smoking status (former/current vs never)
• ECOG PS (0 vs 1)

Dato-DXd 6 mg/kg IV Q2W

Pembrolizumab 250 mg IV Q2W

Treatment until:

• Assurance of progressive disease by RECIST, disease recurrence, or other disease progression criteria

• Completion of 2 cycles of pembrolizumab to maximum dose for Dato-DXd

Endpoints

Primary endpoints

• Progression-free survival by BICR

• Overall survival

Key secondary endpoint

• Objective response rate by BICR

Other secondary endpoints

• Progression-free survival by investigator

• Objective response rate by investigator

• Duration of response by BICR and investigator

• Time to response by BICR and investigator

• Disease control rate by BICR and investigator

• Time to second progression (PFS2)

• Patient-reported outcomes

• Safety

• Immunogenicity

Explosatory endpoints

• Biomarkers, pharmacokinetics, and pharmacodynamics expressions will be evaluated for potential association with efficacy and safety

• Progression-free survival by investigator

• Objective response rate by investigator

• Duration of response by BICR and investigator

• Time to response by BICR and investigator

• Disease control rate by BICR and investigator

• Time to second progression (PFS2)

• Patient-reported outcomes

• Safety

• Immunogenicity

Acknowledgments

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References