TROPION-Lung02: Datopotamab Deruxtecan (Dato-DXd) Plus Pembrolizumab and Platinum-Based Chemotherapy in Advanced NSCLC

Benjamin Levy,1 Konstantinos Leventakos,2 Yanyan Lou,3 Panayiotis Savvides,4 Oliver Rixe,5 Anthony Tolcher,6 Xiangfeng Wu,7 Yasushi Goto8

1The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; 2Mayo Clinic, Rochester, MN, USA; 3Mayo Clinic, Jacksonville, FL, USA; 4Mayo Clinic, Phoenix, AZ, USA; 5Quantum Santa Fe, Santa Fe, NM, USA; 6NEXT Oncology, San Antonio, TX, USA; 7Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; 8National Cancer Center Hospital, Tokyo, Japan
## Presenter DISCLOSURES

<table>
<thead>
<tr>
<th>Relationship(s)</th>
<th>Ineligible Company</th>
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<tbody>
<tr>
<td>Consulting or Advisory Role</td>
<td>AstraZeneca, Daiichi Sankyo/AstraZeneca, Genentech/Roche, Guardant Health, Lilly, Merck, Novartis, Pfizer, Takeda</td>
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<tr>
<td>Research Funding</td>
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Dato-DXd Structure and 7 Key Attributes

- Datopotamab deruxtecan is an antibody drug conjugate (ADC) composed of a humanized anti-trophoblast cell-surface antigen 2 (TROP2) IgG1 monoclonal antibody\(^1\) attached to a topoisomerase I inhibitor payload, an exatecan derivative\(^2,3\), via a tetrapeptide-based cleavable linker\(^2,3\).

Payload mechanism of action:
- topoisomerase I inhibitor\(^2,a\)

High potency of payload\(^3,a\)

Optimized drug-to-antibody ratio \(\approx 4\)^{2,a,b}

Payload with short systemic half-life\(^3,a,b\)

Stable linker-payload\(^3,a\)

Tumor-selective cleavable linker\(^3,a\)

Bystander antitumor effect\(^3,5,a\)

\(^a\) The clinical relevance of these features is under investigation. \(^b\) Based on animal data.

TROPION-Lung02: Background and Rationale

- TROP2 is a transmembrane glycoprotein that is highly expressed in non-small cell lung cancer (NSCLC) and is associated with a poor prognosis\textsuperscript{1-4}

- Despite immune checkpoint inhibitors, which have transformed survival outcomes in NSCLC without actionable genomic alterations, most patients still experience disease progression within <12 mo. Subsequent therapy options are limited; therefore, a significant unmet need remains\textsuperscript{5}

- Results from the TROPION-PanTumor01 study evaluating the efficacy and safety of Dato-DXd demonstrated an ORR of 24\% at 4 mg/kg and 26\% at 6 mg/kg
  - Median duration of response was 10.5 mo with Dato-DXd 6 mg/kg\textsuperscript{6}; updated results will be presented at this congress (mini oral presentation MA03.02 on September 8, 2021)

- Preclinical studies suggest that combining a DXd ADC and an immune checkpoint inhibitor may enhance antitumor activity and improve clinical outcomes\textsuperscript{7}

ORR, objective response rate.
TROPION-Lung02 (NCT04526691) is a phase 1b, global, multicenter, 2-part, dose-escalation and dose-expansion study of Dato-DXd combined with pembrolizumab ± 4 cycles of platinum-based chemotherapy in previously treated or treatment-naive patients with advanced/metastatic non-small cell lung cancer without actionable genomic alterations

- **Primary objective**: to assess tolerability and safety, including but not limited to dose-limiting toxicities (part 1), as well as treatment-emergent adverse events, serious adverse events, and adverse events of special interest (parts 1 and 2)

- **Secondary objective**: to evaluate efficacy (parts 1 and 2), including objective response rate, duration of response, progression-free survival, and overall survival, and assess pharmacokinetics and the incidence of antidrug antibodies
**TROPION-Lung02: Study Design**

**Sequential dose escalation**

<table>
<thead>
<tr>
<th>Cohort 1:</th>
<th>4 mg/kg + 200 mg</th>
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<tr>
<td>Cohort 2:</td>
<td>6 mg/kg + 200 mg</td>
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<tr>
<td>Cohort 3:</td>
<td>4 mg/kg + 200 mg + carboplatin AUC 5</td>
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<tr>
<td>Cohort 4:</td>
<td>6 mg/kg + 200 mg + carboplatin AUC 5</td>
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<tr>
<td>Cohort 5:</td>
<td>4 mg/kg + 200 mg + cisplatin 75 mg/m²</td>
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<tr>
<td>Cohort 6:</td>
<td>6 mg/kg + 200 mg + cisplatin 75 mg/m²</td>
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**Dose expansion**

Each cohort will start with part 1 (dose escalation), in which DLTs will be assessed in the first cycle. If the DLT incidence is acceptable, part 2 (dose expansion) in the same study cohort will enroll patients for further evaluation of safety and treatment activity.

The study will be conducted sequentially, and dose escalation will occur from lower to higher dose in the same combination regimen and from 2- to 3-drug combination.

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AUC, area under the curve; CT, chemotherapy; DLT, dose-limiting toxicity; IV, intravenous; Q3W, every 3 weeks.

* Drugs within each cohort will be given simultaneously.  
  b From cohort 1 to 2, from cohort 1 to cohorts 3 and 5, and from cohorts 3 and 5 to 4 and 6, respectively.
**TROPION-Lung02: Key Eligibility Criteria**

**Key Inclusion Criteria**

- Age ≥18 years
- Histologically confirmed advanced or metastatic NSCLC at diagnosis
  - Documented negative test results for *EGFR* and *ALK* genomic alterations
  - No known genomic alterations in *ROS1*, *NTRK*, *BRAF*, *RET*, or *MET* or other actionable genomic alterations with approved therapies
- Documented radiological disease progression while on or after receiving the most recent treatment regimen, if any, for advanced or metastatic NSCLC
- Must meet the following prior therapy requirements:
  - Dose escalation (all cohorts): has received ≤2 lines of prior anticancer therapy for advanced or metastatic NSCLC
  - Dose expansion (cohorts 1-2): has not received PD-1/PD-L1–, PD-L2–, or CTLA-4–directed immunotherapy and may or may not have been treated with systemic chemotherapy for advanced or metastatic NSCLC
  - Dose expansion (cohorts 3-6): has not been treated with systemic anticancer therapy for advanced or metastatic NSCLC
- Willing and able to undergo a mandatory pretreatment tumor biopsy

ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; CTLA-4, cytotoxic T-lymphocyte associated protein 4; EGFR, epidermal growth factor receptor; MET, MET proto-oncogene; NTRK, neurotrophic receptor tyrosine kinase; PD-1, programmed cell death 1 protein; PD-L1, programmed cell death 1 ligand 1; PD-L2, programmed cell death 1 ligand 2; RET, ret proto-oncogene; ROS1, ROS proto-oncogene 1.
TROPION-Lung02: Key Eligibility Criteria (cont)

Key Exclusion Criteria

- Experienced grade ≥3 immune-related AEs with prior treatment with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX40, CD137)
- Received a live vaccine within 30 days prior to the first dose of study treatment
- Active, known, or suspected autoimmune disease
- Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications, except for managing AEs
- Prior organ transplant, including allogeneic tissue or solid organ transplant
- Spinal cord compression or clinically active CNS metastasesa
- Current or history of (noninfectious) ILD/pneumonitis that required steroids or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
- Clinically severe pulmonary compromise resulting from intercurrent pulmonary illness

AE, adverse event; CNS, central nervous system; ILD, interstitial lung disease.
a Defined as untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.
# TROPION-Lung02: Study Endpoints

<table>
<thead>
<tr>
<th><strong>Primary endpoints</strong></th>
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<tr>
<td>Dose-limiting toxicities</td>
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<tr>
<td>Treatment-emergent adverse events</td>
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<tr>
<td>Serious adverse events</td>
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<td>Adverse events of special interest(^a)</td>
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<th><strong>Secondary endpoints</strong></th>
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<tr>
<td>Objective response rate(^b)</td>
<td>Duration of response(^b)</td>
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<td>Disease control rate(^b)</td>
<td>Clinical benefit rate(^b)</td>
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<td>Progression-free survival(^b)</td>
<td>Time to response(^b)</td>
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<td>Overall survival</td>
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<td>Best percentage change in sum of diameters of measurable tumors</td>
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<td>Pharmacokinetic concentration and parameters</td>
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<td>Incidence of antidrug antibodies with both Dato-DXd and pembrolizumab</td>
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<th><strong>Exploratory endpoints</strong></th>
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<tr>
<td>Biomarker/tumor gene expression</td>
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<td>TROP2 expression</td>
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<td>Exposure-response relationships</td>
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\(^a\) Including interstitial lung disease, infusion-related reactions including anaphylaxis, stomatitis, hepatic events, and overdose of pembrolizumab. \(^b\) By investigator assessment per Response Evaluation Criteria in Solid Tumors version 1.1.
TROPION-Lung02: Enrollment Summary

- TROPION-Lung02 has 22 study sites in North America, Europe, and Asia; is recruiting patients in the US and Japan; and will soon open sites in Italy, Spain, and Taiwan
  - As of July 27, 2021, 22 patients have been enrolled in cohorts 1-4; the first patient received study drug on October 1, 2020
  - No dose-limiting toxicities (DLTs) have occurred in the dose-escalation parts in cohorts 1 and 2
  - Thus far, 1 DLT has been observed (an incidence of grade 4 thrombocytopenia in cohort 3 [Dato-DXd 4 mg/kg + pembrolizumab 200 mg + carboplatin 5 AUC])
  - The dose-expansion parts in cohorts 1 and 2 and the dose-escalation parts in cohorts 4 and 5 are open for enrollment
  - The dose-expansion part in cohort 5 and both parts in cohort 6 are not yet open for enrollment
We thank the patients, their families, and their caregivers for their participation and study staff for their contributions.

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In July 2020, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for datopotamab deruxtecan (Dato-DXd).

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