TROPION-Lung04: Datopotamab Deruxtecan (Dato-DXd) Plus Durvalumab and Platinum-Based Chemotherapy in Advanced NSCLC

Hossein Borghaei,1 Martin Gutierrez,2 Saiama Waqar,3 Satoru Kitazono,4 Xiangfeng Wu,5 Kyriakos P. Papadopoulos6

1Fox Chase Cancer Center, Philadelphia, PA, USA; 2John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ, USA; 3Washington University School of Medicine, St Louis, MO, USA; 4Cancer Institute Hospital of JFCR, Tokyo, Japan; 5Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; 6The START Center for Cancer Care, San Antonio, TX, USA
**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>Bristol Myers Squibb, Lilly, Celgene, Genentech, Pfizer, Boehringer Ingelheim, EMD Serono, Trovagene, Novartis, Merck, AstraZeneca, Genmab, Regeneron, Cantargia AB, BioNTech AG, AbbVie, PharmaMar, Takeda</td>
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<td>Travel, Accommodations, Expenses</td>
<td>Bristol Myers Squibb, Lilly, Clovis Oncology, Celgene, Genentech, Novartis, Merck</td>
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<td>Honoraria</td>
<td>Bristol Myers Squibb, Celgene, Axiom Biotechnologies</td>
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<td>Millennium, Merck, Bristol Myers Squibb, Lilly, Celgene</td>
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<td>Other Relationship</td>
<td>Takeda</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\(^3,5,a\)

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

TROPION-Lung04: 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\(^1-^4\).

- Despite immune checkpoint inhibitors, which transform 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 still remains\(^5\).

- 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\(^6\); 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\(^7\).

ORR, objective response rate.
TROPION-Lung04 (NCT04612751) is a phase 1b, global, multicenter, 2-part, dose-escalation and dose-expansion study of Dato-DXd combined with durvalumab ± 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-Lung04: Study Design

**Sequential dose escalation**

<table>
<thead>
<tr>
<th>Cohort 1:</th>
<th>4 mg/kg</th>
<th>+ 1120 mg</th>
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<tbody>
<tr>
<td>Cohort 2:</td>
<td>6 mg/kg</td>
<td>+ 1120 mg</td>
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<tr>
<td>Cohort 3:</td>
<td>4 mg/kg</td>
<td>+ 1120 mg + carboplatin AUC 5</td>
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<tr>
<td>Cohort 4:</td>
<td>6 mg/kg</td>
<td>+ 1120 mg + carboplatin AUC 5</td>
</tr>
<tr>
<td>Cohort 5:</td>
<td>4 mg/kg</td>
<td>+ 1120 mg + cisplatin 75 mg/m²</td>
</tr>
<tr>
<td>Cohort 6:</td>
<td>6 mg/kg</td>
<td>+ 1120 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-Lung04: Key Eligibility Criteria

Key Inclusion Criteria

- Age ≥20 years in Japan, ≥18 years in the United States, and according to local requirements for consent in other countries
- 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 disease
  - Dose expansion (cohorts 1-2): has not received an ICI\(^a\) and may or may not have been treated with systemic chemotherapy for advanced or metastatic NSCLC
  - Dose expansion (cohorts 3-6): ICI naive and has not been treated with systemic anticancer therapy for advanced or metastatic NSCLC
- Willing and able to undergo a mandatory pretreatment tumor biopsy

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TROPION-Lung04: Key Eligibility Criteria (cont)

Key Exclusion Criteria

- Experienced grade ≥3 immune-related AEs with prior immunotherapy
- Received a live vaccine within 30 days prior to the first dose of study treatment
- Active, known, or suspected autoimmune disease
- Required systemic treatment with either corticosteroids (>10 mg daily of prednisone equivalent) or other immunosuppressive medications within 14 days of cycle 1 day 1
- Prior allogeneic organ transplant
- Uncontrolled or significant cardiac disease
- Spinal cord compression or clinically active CNS metastases\(^a\)
- 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 lung illness
- Toxicities from previous anticancer therapy\(^b\)

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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. \(^b\) Defined as toxicities (other than alopecia) not yet improved to grade ≤1 (per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0) or baseline.
## TROPION-Lung04: Study Endpoints

<table>
<thead>
<tr>
<th>Primary endpoints</th>
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<tbody>
<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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<tr>
<td>Adverse events of special interest&lt;sup&gt;a&lt;/sup&gt;</td>
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<th>Secondary endpoints</th>
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<tr>
<td>Objective response rate&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Disease control rate&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Progression-free survival&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<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 durvalumab</td>
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<th>Exploratory endpoints</th>
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<tr>
<td>Biomarker/tumor gene expression</td>
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<tr>
<td>TROP2 expression</td>
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<td>Exposure-response relationships</td>
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<sup>a</sup> Including interstitial lung disease, infusion-related reactions including anaphylaxis, stomatitis, hepatic events, and durvalumab adverse event of special interest including those with a potential inflammatory or immune-mediated mechanism.<br><sup>b</sup> By investigator assessment per Response Evaluation Criteria in Solid Tumors version 1.1.
TROPION-Lung04: Enrollment Summary

- TROPION-Lung04 has 19 study sites in North America, Europe, and Asia; is recruiting patients in the US and Japan; and will soon open sites in France and South Korea
  - As of July 27, 2021, 7 patients have been enrolled in the dose-escalation part in cohorts 1 and 2; the first patient received study drug on March 2, 2021
  - Cohort 1 crossed the dose-limiting toxicity (DLT) assessment to allow cohort 2 to enroll
  - Thus far, no DLTs have occurred in the dose-escalation parts in cohorts 1 and 2
  - The dose-escalation part in cohort 2 is open for enrollment
  - The dose-expansion part in cohort 2 and both parts in cohorts 3-6 are not yet open for enrollment

Countries/territories with participating study sites
France, Japan, South Korea, United States
We thank the patients, their families, and their caregivers for their participation and study staff for their contributions.

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For additional details on ClinicalTrials.gov, scan QR code via a barcode reader application.