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Study of DS-1062a with or without pembrolizumab in advanced or metastatic non-small cell lung cancer

Submission date 04/03/2022	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 16/05/2022	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 11/05/2026	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
Lung cancer is the most common cancer and the leading cause of cancer-related mortality worldwide, with an estimated 2.2 million new cases of lung cancer in 2020 (11.4% of all new cases) and 1.8 million deaths (18.0% of all cancer deaths) globally. Advances in the early detection of lung cancer have been slow, and more than half of lung cancers are still diagnosed at an advanced stage. Only 18.6% of all patients with lung cancer are alive 5 years or more after diagnosis. Non-small-cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers. The introduction of immunotherapy to treat metastatic NSCLC (cancer that has spread) has significantly improved patients' prognoses. The aim of this study is to assess the effectiveness and safety of Dato-DXd (investigational drug) when added to pembrolizumab versus pembrolizumab alone as the first-line treatment of advanced or metastatic NSCLC. Dato-DXd has demonstrated encouraging antitumour activity and a manageable safety profile in heavily pretreated subjects with NSCLC in a study in participants with advanced solid tumours.

Who can participate?
Patients aged 18 years or over with NSCLC

What does the study involve?
Participants will be randomly allocated to receive either Dato-Dxd plus pembrolizumab, or pembrolizumab alone. Participation in the treatment phase of the study can last up to 2 years. Once the participant's treatment under the study has ended, they will enter a long-term follow-up period, where their general health will be checked every 3 months.

What are the possible benefits and risks of participating?
There is no guarantee that there will be any benefit to the participant. Information from this study may benefit other people now or in the future. There is a risk of side effects from the study treatment, some of the reported side effects to date have been feeling tired, nausea, hair loss, inflammation of the mouth lining or digestive tract, anaemia, vomiting, loss of appetite,

rash, diarrhoea, dry eye, lung problems, constipation, skin problems, cough, itching, joint pain, back pain, fever, stomach pain and inflammation. Some study procedures may also have side effects.

Where is the study run from?
Syneos Health (Germany)

When is the study starting and how long is it expected to run for?
February 2022 to May 2025

Who is funding the study?
Daiichi-Sankyo (Japan)

Who is the main contact?
Bernardo Gomez, bernardo.gomez@syneoshealth.com

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
2021-002555-10

Integrated Research Application System (IRAS)
1004940

Protocol serial number
DS1062-A-U304

Study information

Scientific Title
A randomized, open-label, Phase III trial of Dato-DXd plus pembrolizumab vs pembrolizumab alone in treatment-naïve subjects with advanced or metastatic PD-L1 high (TPS ≥50%) non-small cell lung cancer without actionable genomic alterations (Tropion-Lung08)

Study objectives
1. To compare the efficacy of Dato-DXd in combination with pembrolizumab versus pembrolizumab alone, as measured by progression-free survival (PFS) by blinded independent central review (BICR)
2. To compare the efficacy of Dato-DXd in combination with pembrolizumab versus pembrolizumab alone, as measured by overall survival (OS)
3. To evaluate the efficacy of Dato-DXd in combination with pembrolizumab versus pembrolizumab alone, as measured by objective response rate (ORR) by BICR
4. To further evaluate the efficacy of Dato-DXd in combination with pembrolizumab versus pembrolizumab alone
5. To evaluate the patient-reported outcomes (PROs) of Dato-DXd in combination with pembrolizumab and of pembrolizumab alone
6. To further evaluate the safety of Dato-DXd in combination with pembrolizumab
7. To assess the immunogenicity of Dato-DXd in combination with pembrolizumab

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 05/07/2022, East Midlands - Leicester South Research Ethics committee (Equinox House, City Link, Nottingham, NG2 4LA, United Kingdom; +44 (0)207 104 8193; leicestersouth.rec@hra.nhs.uk), ref: 22/EM/0118

Primary study design
Interventional

Study design
Randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Advanced or metastatic non-small cell lung cancer (NSCLC)

Interventions
Randomisation will be performed by interactive response technology. Half of the participants will be assigned to Arm 1, and half will be assigned to Arm 2.

Arm 1: 6.0 mg/kg (per kg of body weight) of Dato-DXd, in combination with 200 mg pembrolizumab, every 3 weeks
Arm 2: 200 mg pembrolizumab every 3 weeks by itself

Dato-DXd and pembrolizumab are administered intravenously (IV).

Participation in the treatment phase of the study can last up to 2 years. Once the participant’s treatment under the study has ended, they will enter a long-term follow-up period, where their general health will be checked every 3 months.

Intervention Type

Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Datopotamab deruxtecan, pembrolizumab

Primary outcome(s)
1. Progression-free survival (PFS), defined as the time from randomization to the first documented radiographic disease progression or death due to any cause, whichever occurs first, as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, at the time of the primary analysis of PFS.
2. Overall survival (OS), defined as the time from randomization to death due to any cause, at the time of the interim and primary analyses of OS.

Subjects will undergo radiographic assessment of tumor response based on Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 every 9 weeks (±7 days) for the first 2 years and then every 12 weeks (±7 days) thereafter, from randomization until radiological disease progression as determined by BICR, death, lost to follow-up, or withdrawal of consent, regardless of discontinuing study treatment or starting a new anticancer therapy (tumor assessment is not restricted to the Treatment Period)

Key secondary outcome(s)
1. Efficacy:
1.1. Objective response rate (ORR), defined as the proportion of subjects who achieved a best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR), as assessed by blinded independent central review per RECIST, Version 1.1, at the time of the primary analysis of PFS
1.2. PFS, defined as the time from randomization to the first documented radiographic disease progression or death due to any cause, whichever occurs first, as assessed by the investigator per RECIST, Version 1.1, at the time of the primary analyses of PFS.
1.3. PFS2, defined as the time from date of randomization to the first documented disease progression on next-line therapy or death due to any cause, whichever occurs first, as assessed by local standard clinical practice, at the time of the primary analysis of PFS, interim and primary analyses of OS.
1.4. ORR, defined as the proportion of subjects who achieved a BOR of confirmed CR or confirmed PR, as assessed by the Investigator per RECIST Version 1.1 at the time of the primary analysis of PFS
1.5. Duration of response (DoR), defined as the time from the date of the first documentation of objective response (confirmed CR or confirmed PR) to the date of the first radiographic disease progression or death due to any cause, whichever occurs first, as assessed by BICR and by the Investigator per RECIST Version 1.1, at the time of the primary analysis of PFS
1.6. Time to response (TTR), defined as the time from randomization to the date of the first documentation of objective response (confirmed CR or confirmed PR) in responding subjects, as assessed by BICR and by the Investigator per RECIST Version 1.1 at the time of the primary analysis of PFS
1.7. Disease control rate (DCR), defined as the proportion of subjects who achieved a BOR of confirmed CR, confirmed PR, or stable disease (SD), as assessed by BICR and by the Investigator per RECIST Version 1.1 at the time of the primary analysis of PFS
2. Patient-reported outcomes (PROs): time to deterioration (TTD), defined as the time from

randomization to first onset of a ≥10-point increase in cough, chest pain, or dyspnea, confirmed by a second adjacent ≥10- point increase from randomization in the same symptom, or confirmed by death within 21 days of a ≥10-point increase from randomization, as assessed by the European Organisation for Research and Treatment of Cancer Lung cancer module (EORTC-QLQ-LC13) questionnaire at the time of the primary analysis of PFS, interim and primary analyses of OS
3. Safety: treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), Eastern Cooperative Oncology Group performance status (ECOG PS), vital sign measurements, standard clinical laboratory parameters (hematology, clinical chemistry, and urinalysis), electrocardiogram parameters, echocardiogram (ECHO) /multigated acquisition (MUGA) scan findings, and ophthalmologic findings. AEs will be coded by the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and both AEs and laboratory test results will be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 from after the subject signs the Tissue Screening ICF and up to 90 (+7) days after the last dose of study drug (or 30 [+7] days following cessation of study treatment if the subject initiates new anticancer therapy, whichever is earlier), reported at the time of the primary analysis of PFS and the interim and primary analyses of OS.
4. Immunogenicity: anti-drug antibody (ADA) prevalence: the proportion of subjects who are ADA-positive at any point in time (at baseline or post-baseline) ADA incidence: the proportion of subjects having a treatment-emergent ADA Titer and neutralizing antibodies will be determined when the ADA is positive. For subjects receiving Dato-DXd: C1 – Day 1 (within 8 h before infusion), C2 – Day 1 (within 8 h before infusion), C4, C6, C8, and then every four cycles (i.e., C12, C16 and so on) until EOT for subjects receiving pembrolizumab: C1 – Day 1 (within 8 h before infusion), C2 – Day 1 (within 8 h before infusion), and then every two cycles (i.e., C4, C6) until C8 or pembrolizumab discontinuation, whichever occurs first.

Exploratory:
Symptoms and health-related quality of life assessed using Patient Global Impression of Change and Quality of Life questionnaires at the time of the primary analysis of progression-free survival, interim and primary analyses of overall survival

Completion date
23/07/2028

Eligibility

Key inclusion criteria
1. Sign and date the Tissue Screening and Main ICFs, prior to the start of any study-specific qualification procedures
2. Adults aged ≥18 years or the minimum legal adult age (whichever is greater) at the time of informed consent (following local regulatory requirements if the legal age of adult voluntary consent for study participation is >18 years old)
3. Histologically documented NSCLC that meets all of the following criteria:
3.1. Stage IIIB or IIIC disease and not candidates for surgical resection or definitive chemoradiation, or Stage IV NSCLC disease at the time of randomization (based on the American Joint Committee on Cancer, Eighth Edition)
3.2. Documented negative test results for EGFR, ALK, and ROS1 actionable genomic alterations based on analysis of tumor tissue. If test results for EGFR, ALK, and ROS1 are not available, subjects are required to undergo testing performed locally for these genomic alterations
3.3. No known actionable genomic alterations in NTRK, BRAF, RET, MET, or other actionable

driver kinases with locally approved therapies (testing for genomic alterations besides EGFR, ALK, and ROS1 is not required prior to enrollment)
4. Has provided a formalin-fixed tumor tissue sample (minimum of 10 [preferably 15] × 4-micron sections or block equivalent) for the measurement of TROP2 protein expression and for the assessment of other exploratory biomarkers. This tissue requirement is in addition to the tissue required for PD-L1 testing for tissue screening purposes. If a documented law or regulation prohibits (or does not approve) sample collection, then such sample will not be collected.
5. Tumor has high PD-L1 expression (TPS ≥50%) as determined by PD-L1 IHC 22C3 pharmDx assay by central testing (minimum of six slides)
6. Has an adequate treatment washout period before Cycle 1 Day 1 as defined in protocol Section 5.1
7. Measurable disease based on local imaging assessment using RECIST Version 1.1
8. Has left ventricular ejection fraction (LVEF) ≥50% by either an echocardiogram (ECHO) or multigated acquisition scan (MUGA) within 28 days before randomization
9. ECOG PS of 0 or 1 at screening.
10. Has a life expectancy of at least 3 months
11. Adequate bone marrow function within 7 days before randomization as defined in protocol Section 5.1
12. If the subject is a female of childbearing potential, she must not be pregnant, breastfeeding or intend to become pregnant during the study; she must also have a negative serum pregnancy test at screening and must be willing to use highly effective birth control (as detailed in protocol Section 10.3.4) or avoid heterosexual intercourse upon randomization, during the treatment period, for 7 months following the last dose of Dato-DXd, and for 4 months following the last dose of pembrolizumab, whichever occurs later. A female is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
13. If male, the subject must be surgically sterile or willing to use highly effective birth control or avoid heterosexual intercourse upon enrollment, during the Treatment Period, and for 4 months following the last dose of the study drug
14. Male subjects must not freeze or donate sperm starting at screening and throughout the study period, and at least 4 months after the last dose of the study drug
15. Female subjects must not donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 7 months after the last dose of Dato-DXd, or for at least 4 months after the last dose of pembrolizumab, whichever occurs later
16. Is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
740

Key exclusion criteria
1. Has received prior systemic treatment for advanced or metastatic NSCLC
2. Has received prior treatment with any of the following, including in the adjuvant/neoadjuvant setting:
2.1. Any agent, including an antibody-drug conjugate, containing a chemotherapeutic agent targeting topoisomerase I
2.2. TROP2-targeted therapy
2.3. Any anti-programmed death receptor-1 (PD-1), anti-PD-L1, or anti-PD-ligand 2 (L2) agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX40, CD137)
2.4. Any other immune checkpoint inhibitors. Subjects who received adjuvant or neoadjuvant therapy OTHER than those listed above, are eligible if the adjuvant/neoadjuvant therapy was completed at least 6 months prior to the diagnosis of advanced/metastatic disease
3. Has spinal cord compression or active and untreated central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of progression) for at least 4 weeks by repeat imaging (note: repeat imaging should be performed during study screening), clinically stable, and without the requirement of steroid treatment for at least 7 days before the first dose of study drug. Note: A computed tomography (CT) scan or magnetic resonance imaging (MRI) scan of the brain at baseline (MRI preferred) is required for all subjects. For those subjects in whom CNS metastases are first discovered at the time of screening, the treating Investigator should consider a delay of study treatment to document the stability of CNS metastases with repeat imaging at least 4 weeks later (in which case, a repeat of all screening activity may be required).
4. Has received prior radiotherapy ≤4 weeks of the start of the study intervention or more than 30 Gy to the lung within 6 months of Cycle 1 Day 1. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 2-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
5. History of another primary malignancy (beyond NSCLC) except for:
5.1. Malignancy treated with curative intent and with no known active disease ≥3 years before the first dose of study treatment and of low potential risk for recurrence
5.2. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
5.3. Adequately treated carcinoma in situ without evidence of disease- Participants with a history of prostate cancer (tumor/node/metastasis stage) of Stage ≤T2cN0M0 without biochemical recurrence or progression and who in the opinion of the Investigator are not deemed to require active intervention.
6. Has a history of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening
7. Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses

including, but not limited to, any underlying pulmonary disorder (eg, pulmonary emboli diagnosed within 3 months of Cycle 1 Day 1, severe asthma, severe chronic obstructive pulmonary disease, restrictive lung disease, pleural effusion, etc.), or any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (e.g., rheumatoid arthritis, Sjögren's syndrome, sarcoidosis, etc), or prior complete pneumonectomy.
8. Uncontrolled or significant cardiovascular disease, including:
8.1. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) interval >470 msec regardless of sex (based on the average of the 12-lead electrocardiogram determination at screening)
8.2. Myocardial infarction within 6 months prior to randomization
8.3. Uncontrolled angina pectoris within 6 months prior to randomization
8.4. LVEF <50% by ECHO or MUGA scan within 28 days before randomization
8.5. New York Heart Association Class 2 to 4 congestive heart failure (CHF) at screening. Subjects with a history of Class 2 to 4 CHF prior to screening, must have returned to Class 1 CHF and have LVEF ≥50% (by either an ECHO or MUGA scan within 28 days before randomization) in order to be eligible
8.6. Uncontrolled hypertension (resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) within 28 days before randomization
9. Clinically significant corneal disease. For a full list of principal exclusion criteria please see Clinical Study Protocol Section 5.2.

Date of first enrolment
31/01/2022

Date of final enrolment
30/09/2023

Locations

Countries of recruitment
United Kingdom

England

Scotland

Argentina

Australia

Belgium

Brazil

Canada

Chile

China

France

Germany

Greece

Hong Kong

Hungary

Italy

Japan

Mexico

Netherlands

Poland

Portugal

Romania

Russian Federation

Spain

Switzerland

Taiwan

Thailand

Türkiye

Ukraine

Study participating centre
Heartlands Hospital
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Study participating centre
Nottingham City Hospital
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Study participating centre
Beatson West of Scotland Cancer Centre
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Study participating centre
Weston Park Hospital
Whitham Rd
Broomhall
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S10 2SJ

Sponsor information

Organisation
Syneos Health (Germany)

ROR
https://ror.org/00ahg0572

Funder(s)

Funder type
Industry

Funder Name
Daiichi-Sankyo

Alternative Name(s)
Daiichi Sankyo Company, Limited, Daiichi Sankyo Co., Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Japan

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Anne Jaeger-Huelsmann (anne.jaeger-huelsmann@syneoshealth.com).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No