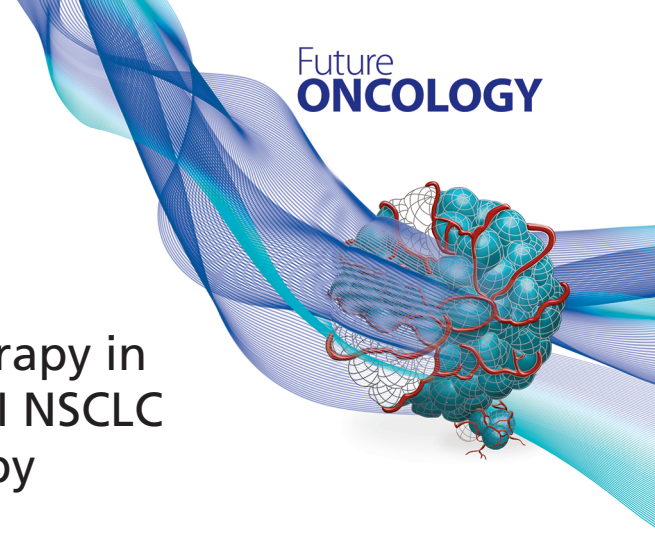
Clinical Trial Protocol

Future ONCOLOGY



DUART: durvalumab after radiotherapy in patients with unresectable, stage III NSCLC who are ineligible for chemotherapy

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Consolidation durvalumab is standard of care in patients with unresectable, stage III non-small-cell lung cancer (NSCLC) without disease progression following chemoradiotherapy (the 'PACIFIC regimen'). However, many patients with poor performance status, older age or comorbidities may be ineligible for chemotherapy due to expected high toxicity. These patients typically receive radiotherapy alone, with poor survival outcomes. Based on the PACIFIC trial data, and the strong biological rationale for combining radiotherapy with anti-programmed cell death ligand-1 therapy, durvalumab following radiotherapy could provide additional survival benefit versus radiotherapy alone. Here, we describe the DUART trial, a Phase II, open-label, single-arm study assessing the safety and tolerability of durvalumab following radiotherapy in patients with unresectable, stage III NSCLC who are ineligible for chemotherapy (ClinicalTrials.gov Identifier: NCT04249362).

Lay abstract: The current standard treatment for patients with stage III non-small-cell lung cancer whose cancer cannot be removed by surgery is chemotherapy plus radiotherapy; if their disease gets no worse after this, patients also receive durvalumab – altogether this is known as the 'PACIFIC regimen'. However, some patients who are older or who have existing health conditions cannot tolerate chemotherapy, so instead of the PACIFIC regimen they receive radiotherapy only. The DUART study described here is an ongoing, Phase II clinical trial looking at the safety and tolerability of durvalumab after radiotherapy in patients with stage III non-small-cell lung cancer who are unsuitable for chemotherapy and whose cancer cannot be removed by surgery.

Clinical Trial Registration: NCT04249362.

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Keywords: anti-PD-L1 • durvalumab • immunotherapy • radiotherapy • unresectable, stage III NSCLC

Lung cancer is the leading cause of cancer-related death globally, accounting for approximately 1.8 million deaths in 2020 [1]. Non-small-cell lung cancer (NSCLC) represents 80–85% of all lung cancer cases and approximately one-third of patients present with stage III disease at diagnosis [2–4], many of whom are deemed inoperable by multidisciplinary assessment [3,4]. The historical standard of care for patients with unresectable, stage III NSCLC and adequate performance status has long been concurrent chemoradiotherapy (cCRT; platinum-based doublet chemotherapy administered concurrently with radiotherapy) [5]. However, survival rates for patients who receive cCRT have been poor, with median progression-free survival (PFS) of approximately 8 months and only 15–32% of patients alive at 5 years [2,6,7].

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Durvalumab is a selective, high-affinity, human immunoglobulin G1 monoclonal antibody that blocks programmed cell death ligand-1 (PD-L1) binding to programmed cell death-1 (PD-1) and CD80, allowing T cells to recognize and kill tumor cells [8]. In the Phase III PACIFIC trial, durvalumab significantly improved PFS and overall survival (OS), with manageable safety, in patients with unresectable, stage III NSCLC whose disease had not progressed after ≥2 cycles of platinum-based cCRT [9,10]. Compared with placebo, durvalumab significantly improved PFS (stratified hazard ratio [HR] 0.52; 95% CI: 0.42–0.65; $p < 0.0001$; median PFS 16.8 vs 5.6 months, respectively) and OS (stratified HR: 0.68; 95% CI: 0.53–0.87; $p = 0.00251$; median OS not reached vs 28.7 months, respectively) [9–11]. A subsequent 4-year analysis has demonstrated sustained PFS and OS benefit of durvalumab over the long term in this patient population [12]. Consequently, the 'PACIFIC regimen' (consolidation durvalumab following platinum-based CRT) is now standard of care in this disease setting, with approvals in the USA, Japan, China, across the EU and in many other countries [11,13,14].

Despite these advancements, a significant proportion of patients with unresectable, stage III NSCLC, in other words, those with advanced age, poor performance status or comorbidities, are ineligible for chemotherapy, due to expected high toxicity [15]. Although there is currently no consensus on the best treatment for patients with unresectable, stage III NSCLC who are ineligible for chemotherapy, such patients typically receive definitive radiotherapy alone. This type of treatment is associated with unsatisfactory survival rates, with 3-year survival ranging from 5 to 10% [4]. Therefore, there is a need for novel, systemic treatment regimens with better efficacy outcomes for patients with unresectable, stage III NSCLC who are ineligible for chemotherapy (and therefore ineligible for the PACIFIC regimen).

Background & rationale

There is a strong biological rationale for combining radiotherapy with anti-PD-L1 consolidation therapy. As well as exerting direct cytotoxic effects on tumor cells, radiotherapy also reprograms the tumor microenvironment to exert a potent antitumor immune response [16]. Radiotherapy is known to induce immunogenic cell death, which promotes the release of danger signals and chemokines that recruit inflammatory cells into the tumor microenvironment, including antigen-presenting cells that activate cytotoxic T-cell function [16,17]. This enhances the ability of the immune system to recognize and respond to tumors [17]. Additionally, radiotherapy has been shown to upregulate tumoral PD-L1 expression, potentially increasing sensitivity to anti-PD-L1 therapies, such as durvalumab [18,19].

Taken together with the PACIFIC trial data, this suggests that durvalumab following radiotherapy could provide additional survival benefit versus radiotherapy alone in patients with unresectable, stage III NSCLC who are ineligible for chemotherapy. The DUART study (ClinicalTrials.gov Identifier: NCT04249362) was designed to assess the safety and tolerability of durvalumab following radiotherapy in this subgroup of patients.

Study design

DUART is a Phase II, open-label, single-arm, multicenter, international study to evaluate the safety and tolerability of durvalumab following radiotherapy in patients with unresectable, stage III NSCLC who are deemed ineligible for chemotherapy by investigator assessment. Approximately 150 patients across Europe and North America will be enrolled into the study. As a safety study, the sample size was not based on formal calculations but rather chosen to provide an appropriate level of precision in the reported summarized safety and efficacy data. Patients will receive 1500 mg durvalumab via intravenous infusion every 4 weeks for up to 12 months or until confirmed disease progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), unacceptable toxicity or withdrawal of consent. Patients will be stratified according to the dose of radiotherapy received prior to study entry (Cohort A: standard radiotherapy [60 Gy ± 10% or hypofractionated bioequivalent dose (BED)]; Cohort B: palliative radiotherapy [40 to <54 Gy or hypofractionated BED]). The study design is summarized in Figure 1.

Key eligibility criteria

Patients must be aged ≥18 years at the time of screening, have histologically or cytologically documented, locally-advanced, unresectable, stage III NSCLC (per International Association for the Study of Lung Cancer Staging Manual version 8), be ineligible for chemotherapy per investigator assessment and have no evidence of disease progression (per RECIST v1.1) following radiotherapy, which must have been completed within 42 days prior to the first dose of durvalumab. Additionally, patients must have a WHO/Eastern Cooperative Oncology Group performance status ≤2 and no prior exposure to immune-mediated therapy. Patients with disease progression

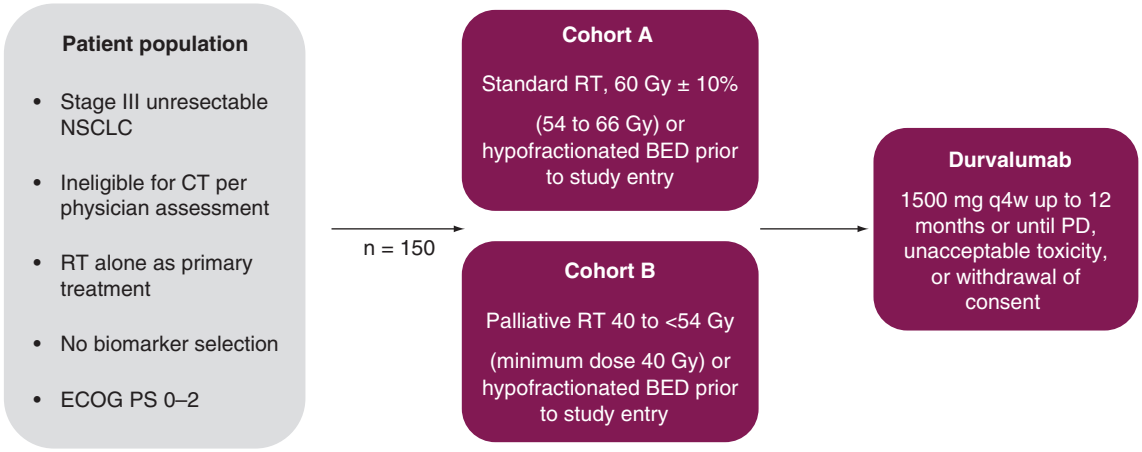

Figure 1. DUART study design.
BED: Bioequivalent dose; CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; Gy: Gray (unit of ionizing radiation); NSCLC: Non-small-cell lung cancer; PD: Progressive disease; PS: Performance status; q4w: Every 4 weeks; RT: Radiotherapy.

following radiotherapy, mixed small-cell and non-small-cell histology, a history of allogeneic organ transplantation, active or prior documented autoimmune or inflammatory disorders, uncontrolled intercurrent illness, history of another primary malignancy or unresolved toxicities from prior anticancer therapies are excluded. Full inclusion and exclusion criteria are provided in Table 1.

Study end points & assessments

The primary end point is safety and tolerability of durvalumab, assessed in terms of grade 3 and 4 possibly-related adverse events (PRAE; defined as any treatment-emergent AE possibly related to durvalumab or where the relatedness is missing) reported within 6 months from the first dose of durvalumab. Secondary safety end points include treatment-emergent AEs, serious AEs, AEs of special interest and immune-mediated AEs. Safety and tolerability will be assessed in terms of AEs (graded per Common Terminology Criteria for Adverse Events version 5.0), deaths, physical examinations, laboratory data, vital signs, electrocardiograms and exposure. These will be collected for all patients throughout the study and for up to 90 days after the last dose of durvalumab.

Secondary response-based end points (investigator-assessed according to RECIST v1.1) are median PFS, PFS at 6 and 12 months, objective response rate and duration of response. Further secondary end points include median OS and OS at 12 months, and lung cancer mortality. A full list of study end points is provided in Table 2. Tumor assessments will be performed by computed tomography or magnetic resonance imaging, per RECIST v1.1 and carried out every 8 $\pm$ 1 weeks for the first 48 weeks (relative to the date of first dose of durvalumab), then every 12 $\pm$ 1 weeks thereafter until RECIST v1.1-defined disease progression, plus an additional, regularly-scheduled follow-up scan. Additional scans will be completed per standard practice after disease progression.

Exploratory end points include health-related quality of life, assessed using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30, version 3) and the lung cancer symptom-specific questionnaire QLQ-LC13.

Ethical considerations

This study is being conducted in accordance with the protocol and principles set out in the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and International Conference of Harmonisation Good Clinical Practice Guidelines. The protocol was approved by an Independent Ethics Committee (IEC)/International Review Board (IRB) prior to study commencement. All protocol amendments will subsequently be approved by an IRB/IEC before implementation. All patients will provide written informed consent before study enrollment. The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

Table 1. Inclusion and exclusion criteria.

Key inclusion criteria
• Written informed consent • Aged ≥18 years at the time of screening • Histologically or cytologically documented NSCLC with locally advanced, unresectable stage III disease (per IASLC Staging Manual Version 8) • No disease progression following radiotherapy (per investigator-assessment according to RECIST v1.1) – Patients with measurable disease and/or non-measurable and/or no evidence of disease assessed at baseline by computed tomography/magnetic resonance imaging will be eligible – Prior irradiated lesions may be considered measurable and selected as target lesions, providing they fulfil the other criteria for measurability • Deemed ineligible for chemotherapy per investigator assessment • Radiotherapy completed within 42 days prior to first dose of durvalumab • Prior total dose of radiotherapy of 40–66 Gy (standard or hypofractionated BED) • WHO/ECOG PS ≤2 • No prior exposure to immune-mediated therapy, including but not limited to, anti-CTLA-4, anti-PD-L1, anti-PD-1 and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines • Adequate organ and marrow function • Life expectancy of at least 12 weeks • Bodyweight >30 kg at study entry and at first dose of study drug
Key exclusion criteria
• Disease progression following radiotherapy • Mixed small-cell and non-small-cell histology • History of allogenic organ transplantation • Active or prior documented autoimmune or inflammatory disorders • Uncontrolled intercurrent illness • History of another primary malignancy, with the exception of: – Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of durvalumab and low potential risk for recurrence – Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease – Treated carcinoma *in situ* without evidence of disease • History of leptomeningeal carcinomatosis • History of active immunodeficiency • Active infection, including tuberculosis, hepatitis B, hepatitis C or HIV • Unresolved toxicity NCI CTCAE grade ≥2 from previous anticancer therapy – Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the study physician • Known allergy or hyposensitivity to study drug • Receipt of live attenuated vaccine within 30 days prior to first dose of durvalumab • Major surgical procedure (as defined by the investigator) within 28 days prior to first dose of durvalumab • Current or prior use of immunosuppressive medication within 14 days prior to first dose of durvalumab • Participation in another clinical trial with an investigational product administered in the last 4 weeks • Concurrent enrollment in another clinical study, unless observational or during the follow-up period of an interventional study • Prior randomization or treatment in a previous durvalumab clinical study, regardless of treatment arm assigned • Patients who refuse chemotherapy by their own decision

BED: Bioequivalent dose; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; ECOG: Eastern Cooperative Oncology Group; Gy: Gray (unit of ionizing radiation); HIV: Human immunodeficiency virus; IASLC: International Association for the Study of Lung Cancer; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC: Non-small-cell lung cancer; PD-1: Programmed cell death 1; PD-L1: Programmed cell death ligand-1; PD-L2: Programmed cell death ligand-2; PS: Performance status; RECIST: Response Evaluation Criteria in Solid Tumors; SCLC: Small-cell lung cancer; WHO: World Health Organization.

Table 2. Study end points.

Primary end point	Assessment
• Safety and tolerability of durvalumab	• Grade 3 and 4 PRAEs within 6 months from first dose of durvalumab
Secondary end points	**Assessment**
• Median PFS	• Investigator-assessed per RECIST v1.1
• PFS at 6 and 12 months	• Investigator-assessed per RECIST v1.1
• Median OS	
• OS at 6 and 12 months	
• Objective response rate	• Investigator-assessed per RECIST v1.1
• Duration of response	• Investigator-assessed per RECIST v1.1
• Lung cancer mortality	
• Safety and tolerability	• AEs, SAEs, AESIs, imAEs, physical examinations, ECG, laboratory data
Exploratory end points	**Assessment**
• Patient-reported symptoms and HRQoL	• Changes from baseline in EORTC QLQ-C30 and EORTC QLQ-LC13 scores

AE: Adverse event; AESI: Adverse event of special interest; ECG: Electrocardiograms; EORTC: European Organisation for Research and Treatment of Cancer; HRQoL: Health-related quality of life; imAE: Immune-mediated adverse event; OS: Overall survival; PFS: Progression-free survival; PRAE: Possibly-related adverse event; QLQ-C30: 30-item core quality of life questionnaire; QLQ-LC13: 13-item lung cancer quality of life questionnaire; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: Serious adverse event.

Conclusion

Despite recent improvements in survival outcomes with the PACIFIC regimen in patients with unresectable, stage III NSCLC and adequate performance status, a significant proportion of this patient population remains ineligible for chemotherapy and consequently receives radiation alone, with poor survival outcomes. Therefore, there is a clear unmet need for novel treatment regimens with greater efficacy in patients for whom curative-intent CRT is not an option. There is a strong rationale for administering anti-PD-L1 consolidation therapy following radiotherapy, given that radiotherapy is known to induce immunogenic cell death, enhance antigen presentation and upregulate expression of PD-L1 in tumor cells [17–19]. The DUART trial will assess the safety and tolerability of the anti-PD-L1 monoclonal antibody durvalumab, following radiotherapy in patients with unresectable, stage III NSCLC who are ineligible for chemotherapy. Study enrollment began in November 2020, with primary completion anticipated in November 2022. The trial is currently recruiting.

Executive summary

Background

- Current standard of care for patients with unresectable, stage III non-small-cell lung cancer (NSCLC) without disease progression following chemoradiotherapy is consolidation therapy with the programmed cell death ligand-1 (PD-L1) inhibitor durvalumab.
- However, a large proportion of patients with unresectable, stage III NSCLC are ineligible for chemotherapy, either due to advanced age, comorbidities or poor performance status and typically receive radiotherapy alone, with poor survival outcomes.
- There is therefore a clear unmet need for novel, systemic treatment regimens with better efficacy outcomes for this subgroup of patients.
- There is a strong biological rationale for combining radiotherapy with anti-PD-L1 consolidation therapy, given that radiotherapy is known to induce immunogenic cell death, enhance antigen presentation and upregulate expression of PD-L1 in tumor cells.

The DUART trial

- The DUART trial (ClinicalTrials.gov Identifier: **NCT04249362**), a Phase II, open-label, single-arm, multicenter, international study, will assess the safety and tolerability of durvalumab following radiotherapy in patients with unresectable, stage III NSCLC who are ineligible for chemotherapy.
- DUART is currently enrolling approximately 150 patients across Europe and North America.
- Eligible patients must have histologically/cytologically confirmed, locally-advanced, unresectable, stage III NSCLC, be ineligible for chemotherapy and have no evidence of disease progression following radiotherapy.
- Patients will receive 1500 mg durvalumab via intravenous infusion every 4 weeks for up to 12 months or until confirmed disease progression, unacceptable toxicity or withdrawal of consent.
- The primary end point is safety and tolerability of durvalumab, assessed in terms of grade 3 and 4 possibly-related adverse events (AEs).
- Secondary safety end points include treatment-emergent AEs, serious AEs, AEs of special interest and immune-mediated AEs.
- Secondary response-based efficacy end points include median progression-free survival, progression-free survival at 6 and 12 months, objective response rate and duration of response.
- Tumor assessments will be carried out every 8 $\pm$ 1 weeks for the first 48 weeks, then every 12 $\pm$ 1 weeks thereafter until disease progression, plus an additional, regularly scheduled follow-up scan.

Conclusion

- Study enrollment began in November 2020, with primary completion anticipated in November 2022.
- The trial is currently recruiting.

Author contributions

All authors listed contributed equally to the study's design, the development of the manuscript and reviewed and approved the final version.

Financial & competing interests disclosure

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