Study overview

Study title: Randomized phase III trial investigating the survival benefit of adding thoracic radiotherapy to durvalumab (MEDI4736) immunotherapy plus chemotherapy in extensive stage small-cell lung cancer

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Study purpose and objectives

The primary aim is to Investigate whether adding TRT to durvalumab plus chemotherapy improves survival.The key objectives of this study are to **i**nvestigate whether adding TRT improves overall response rates, response rates in non-irradiated lesions and PFS, investigate whether TRT improves local control, compare the frequency and severity of adverse events between the treatment arms and compare health related quality of life between treatment arms

Background and rationale

Chemotherapy plus an PD-L1 inhibitor is now standard of care for first-line treatment of small-cell lung cancer, extended stage (ES SCLC). However, the survival benefit is limited, especially for the first 6 months, and a more effective treatment is needed. It has been demonstrated that thoracic radiotherapy (TRT) improves survival in ES SCLC, and the effect in terms of performance status (PFS) is immediate.

Several studies suggest a synergistic effect of combining radiotherapy (RT) and immune checkpoint inhibitor (ICI). Concurrent administration appears to be the most effective approach, and we will administer the TRT between the second and third chemoimmunotherapy courses to increase the chance of achieving a synergistic effect of the TRT and the immunotherapy. Alternatively, concurrent TRT might

improve tumor control, and previous studies indicate a survival benefit of consolidation TRT after chemotherapy in ES SCLC. Combining high-dose TRT, platinum doublet chemotherapy and ICI appears to be well tolerated. Thus, combining medium dose TRT with durvalumab and carboplatin/etoposide should be feasible and well tolerated. However, since there is no data on this combination, investigating whether ading TRT increases the frequency or severity of side effects is an essential part of this trial.

An important part of the trial is to collect biological material (tumor-, blood- and stool samples) for comprehensive translational research aiming at identifying predictive biomarkers. Currently, no biomarkers for clinical decision making in this setting are in routine use.

Study design and methodology

The study is open label randomized phase III trial with approximately 302 participants. Patients included in the trial will receive four courses of durvalumab 1500 mg IV day 1, carboplatin (AUC=5, Calvert's formula) IV day 1 and etoposide 100 mg/m2 BSA IV day 1 followed by either etoposide in a dose of 200 mg/m2 BSA PO days 2-4 or in a dose of 100 mg/m2 BSA IV days 2-3.

Chemoimmunotherapy courses are administered every three weeks. After completing four courses, durvalumab 1500 mg IV is given every four weeks until intolerable toxicity, patient's wish, interruption due to toxicity for more than 12 weeks, or disease progression and need for other systemic treatment.

Patients randomized to the experimental arm will receive TRT of 30 Gy in 10 fractions, one fraction per day, 5 fractions per week, between the second and third chemo-immunotherapy course.

Patients who achieve a response when evaluated after completion of chemo-immunotherapy may be offered PCI of 25 Gy in 10 fractions or 30 Gy in 15 fractions, one fraction per day, 5 fractions per week according to local treatment policy.

Main inclusion criteria

- Capable of giving signed informed consent
- Age > 18 years at time of study entry
- ECOG performance status of 0 or 1
- Confirmed SCLC
- Stage IV disease according to TNM v8 or stage III ineligible for being treated as limited stage SCLC
- Adequate normal organ and marrow function for receiving chemo- and immunotherapy
- Life expectancy of at least 3 months

- At least 1 lesion in the thorax, not previously irradiated, that qualifies as a RECIST 1.1 target lesion (TL) at baseline and is possible to irradiate to 30 Gy in 10 fractions

Main exclusion criteria

- Previous chemo- or radiotherapy for SCLC
- Prior checkpoint inhibitor therapy
- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drugs
- Active or prior documented autoimmune or inflammatory disorders
- Untreated, uncontrolled central nervous system (CNS) metastases
  Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab

Timeline and Current Status

The study is currently recruiting. We expect to complete enrolment in Q4 2025. Primary analyses will be performed one year after last patient entry. All patients will be followed up to 5 years.