Study overview

Study title: A randomized phase II study comparing atezolizumab after concurrent chemoradiotherapy with chemoradiotherapy alone in limited disease small-cell lung cancer

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Study purpose and objectives

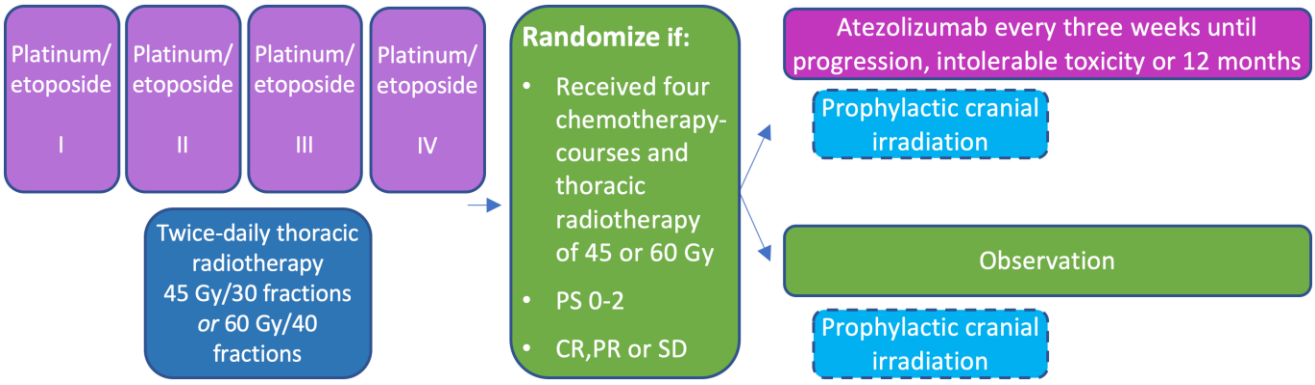
The primary aim of the trial is to investigate whether adjuvant atezolizumab treatment after standard, concurrent chemoradiotherapy improves survival compared with no treatment after standard, concurrent chemoradiotherapy in LD SCLC.
Secondary aims are to investigate whether atezolizumab increases the best response rate, prolongs progression free survival, to what extent atezolizumab causes severe toxicity, and whether the atezolizumab therapy significantly influences patients' health related quality of life (HRQoL).
An important part of the trial is to collect tissue, blood and urine before, during, after study therapy and at progression. This biological material will be utilized in translational research aiming at identifying the patients who are A) cured after chemoradiotherapy, and B) those who benefit the most from atezolizumab.

Background and rationale

Only one third of patients with limited stage (LS) small cell lung cancer (SCLC) are cured by chemoradiotherapy (CRT) and there is urgent need for better treatment. Immune checkpoint inhibitors prolong survival when added to chemotherapy in extensive stage SCLC and as consolidation therapy after CRT in locally advanced irresectable non-small-cell lung cancer. We performed a randomized trial investigating whether atezolizumab after CRT prolongs survival in LS SCLC.

Study design and methodology

Patients ≥18 years with PS 0-2, confirmed SCLC and LS without progressive disease (PD) after 4 cycles of platinum/etoposide and concurrent twice-daily thoracic radiotherapy (TRT) of 45 Gy/30 fractions or 60 Gy/40 fractions were randomized 1:1 to observation or atezolizumab 1200 mg q3weeks for up to 1 year. Randomization was stratified by PS (0-1 vs. 2), response to CRT (stable disease vs. complete/partial response) and TRT-schedule (45 Gy vs. 60 Gy). Those who responded to CRT were offered PCI of 25-30 Gy. Primary endpoint was overall survival (OS), secondary endpoints were response rates, progression-free survival (PFS), toxicity, and health-related quality of life. To detect an increase in 2-year OS from 53% to 66% with a 1-tailed alpha of 0.10, 75 patients were required in each group. Primary OS analyses will be performed after 99 deaths, estimated to occur in 2025.



Main eligibility criteria

1. Age ≥ 18 years
2. Written informed consent
3. Histologically or cytologically confirmed small-cell lung cancer
4. Stage I-III according to TNM v8 ineligible for surgery provided all lesions can be included in a tolerable radiotherapy field ("limited disease")
5. ECOG performance status 0-2
6. Measurable disease according to the RECIST 1.1. if the patient is enrolled before chemoradiotherapy commences. *If patients are included after start of chemoradiotherapy, measurable disease is not required.*
7. Adequate kidney, liver and bone marrow function. *For patients who are enrolled after chemoradiotherapy, the only criterion is creatinine <1.5 ULN*
8. No malignant cells in pericardial or pleural fluid
9. Pulmonary function: FEV1 >1 L or >30 % of predicted value and DLCO >30 % of predicted value. If there are reasons to believe that the lung function is reduced due to tumour obstruction of the lung or central airways, the patient is still eligible as long as a radiotherapist consider the patient eligible for thoracic radiotherapy. *This criterion is not relevant for patients who are included after thoracic radiotherapy has commenced.*
10. No serious concomitant systemic disorders including disease requiring systemic steroids in doses of >10 mg prednisolone (or equivalent dose of other steroid), previous allogeneic or organ transplant, autoimmune disease or immune deficiency, idiopathic pulmonary fibrosis, or pneumonitis.
11. No live vaccine last 30 days, active infection requiring IV antibiotics, no active viral hepatitis or HIV
12. No clinically active cancer other than SCLC with the exception of malignancies with a negligible risk of metastases or death (i.e. 5-years OS rate of >90%).
13. No history of severe allergic anaphylactic reactions to chimeric, human or humanized antibodies, or fusion proteins as well as known hypersensitivity to CHO cell products or any component of atezolizumab

Eligibility criteria for randomization

- Completed four courses of platinum plus etoposide (provided no course was delayed more than 3 weeks) and thoracic radiotherapy of 45 Gy or 60 Gy
- Non-progression at CT evaluation 1-4 weeks after the last chemotherapy-course
- ECOG performance status 0-2
- Negative pregnancy test in women of childbearing potential

Timeline and current status

Between 2018-2022, 216 patients were included at 37 European hospitals. All patients have completed study treatment.

We are working on completing the statistical analysis plan, and plan to perform the first analyses next spring, hopefully in time to submit an abstract for ASCO 2025. We have started collecting biological samples, radiotherapy treatment plans and CT scans.