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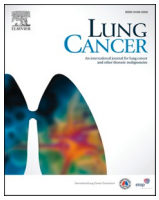

Long-term effectiveness and treatment sequences in patients with extensive stage small cell lung cancer receiving atezolizumab plus chemotherapy: Results of the IFCT-1905 CLINATEZO real-world study

Lionel Falchero [a], Florian Guisier [b], Marie Darrason [c], Arnaud Boyer [d], Charles Dayen [e], Sophie Cousin [f], Patrick Merle [g], Régine Lamy [h], Anne Madroszyk [i], Josiane Otto [j], Pascale Tomasini [k], Sandra Assoun [l], Anthony Canellas [m], Radj Gervais [n], José Hureaux [o], Jacques Le Treut [p], Olivier Leleu [q], Charles Naltet [r], Marie Tiercin [s], Sylvie Van Hulst [t], Pascale Missy [u], Franck Morin [u], Virginie Westeel [v], Nicolas Girard [w,*]

[a] *Service de Pneumologie et Cancérologie Thoracique, Hôpitaux Nord-Ouest, Villefranche Sur Saône, France*
[b] *Univ Rouen Normandie, LITIS Lab QuantIF team EA4108, Rouen, France, CHU Rouen, Inserm CIC-CRB 1404, Department of Pneumology, Thoracic oncology and respiratory intensive care, Rouen, France*
[c] *HCL, Centre Hospitalier Lyon Sud, URCC Secteur essais cliniques, Pierre-Bérard, France*
[d] *Hôpital Saint Joseph, Service de Pneumologie, Marseille, Franc'*
[e] *Clinique de l'Europe, Service de Pneumologie, Amiens, France*
[f] *Institut'Bergonié, Département d'Oncologie Médicale, Bordeaux, France*
[g] *CHU, Hôpital Gabriel Montpied, Hôpital de jour, Service d'oncologie Thoracique, Clermont Ferrand, France*
[h] *CHBS, Hôpital Du Scorff, Oncologie médicale, Lorient, France*
[i] *Institut Paoli Calmettes, Département d'Oncologie Médicale, Marseille, France Centre Antoine Lacassagne, Oncologie, Nice, France*
[j] *Centre Antoine Lacassagne, Nice, France*
[k] *APHM, Service d'Oncologie Multidisciplinaire &Franceations Thérapeutiques, Hôpital Nord, Marseille, France*
[l] *APHP, Service de Pneumologie, Hôpital Bichat, Paris, France*
[m] *APHP, Service de Pneumologie, Hôpital Tenon, Paris, France*
[n] *Service de Pneumol'gie, Centre François Baclesse, Caen, France*
[o] *Service de Pneumologie, CHU Angers, Angers, France*
[p] *Service de Pneumologie, Hôpital Européen, Marseille, France*
[q] *Service de Pneumologie, Centre Hospitalier, Abbeville, France*
[r] *Service de Pneumologie Oncologie, Groupe Hospitalier ParisFrance Joseph, Paris, France*
[s] *Fédération de Pneumologie, Centre Hospitalier, Saint Malo, France*
[t] *Service de Cancérologie, Centre Hospitalier Universitaire, Nîmes, France*
[u] *IFCT, Unité de Recherche Clinique, Paris, France*
[v] *CHU Besançon, Hôpita Minjoz, Service de Pneumologie, Besançon, France*
[w] *Institut du Thorax Curie Montsouris, Institut Curie, Paris, France, Paris Saclay University, University Versailles Saint Quentin, Versailles, France*

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ABSTRACT

Background: Small cell lung cancer (SCLC) has a tendency towards recurrence and limited survival. Standard-of-care in 1st-line is platinum-etoposide chemotherapy plus atezolizumab or durvalumab, based on landmark clinical trials.
Methods: IFCT-1905 CLINATEZO is a nationwide, non-interventional, retrospective study of patients with extensive-SCLC receiving atezolizumab plus chemotherapy as part of French Early Access Program. Objectives were to analyse effectiveness, safety and subsequent treatments.
Results: The population analyzed included 518 patients who received atezolizumab in 65 participating centers. There were 66.2% male, mean age was 65.7 years; 89.1% had a performance status (PS) 0/1 and 26.6% brain metastases. Almost all (95.9%) were smokers. Fifty-five (10.6%) received at least 1 previous treatment. Median number of atezolizumab injections was 7.0 (range [1.0–48.0]) for a median duration of 4.9 months (95% CI 4.5–5.1). Atezolizumab was continued beyond progression in 122 patients (23.6%) for a median duration of 1.9

* Corresponding author.
E-mail address: nicolas.girard2@curie.fr (N. Girard).

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months (95% CI: [1.4–2.3]). Best objective response was complete and partial in 19 (3.9%) and 378 (77.1%) patients. Stable disease was observed in 50 patients (10.2%). Median follow-up was 30.8 months (95% CI: [29.9–31.5]). Median overall survival (OS), 12-, 24-month OS rates were 11.3 months (95% CI: [10.1–12.4]), 46.7% (95% CI [42.3–50.9]) and 21.2% (95% CI [17.7–24.8]). Median real-world progression-free survival, 6-, 12-month rates were 5.2 months (95% CI [5.0–5.4]), 37.5% (95% CI [33.3–41.7]) and 15.2% (95% CI [12.2–18.6]). For patients with PS 0/1, median OS was 12.2 months (95% CI [11.0–13.5]). For patients with previous treatment, median OS was 14.9 months (95% CI [10.1–21.5]). Three-hundred-and-twenty-six patients (66.4%) received subsequent treatment and 27 (5.2%) were still under atezolizumab at date of last news.
Conclusions: IFCT-1905 CLINATEZO shows reproductibility, in real-life, of IMpower-133 survival outcomes, possibly attributed to selection of patients fit for this regimen, adoption of pragmatic approaches, including concurrent radiotherapy and treatment beyond progression.

1. Introduction

Small cell lung cancer (SCLC) is a highly aggressive type of lung cancer with a rapid tumor growth, and tendency toward early recurrence after first-line treatment [1]. SCLC accounts for 10–15% of all newly diagnosed lung cancer cases, and most patients are diagnosed with metastatic, so-called extensive-stage (ES) disease [2,3]. While the historical 5-year survival rate for ES-SCLC has been estimated to be <5% with first-line platinum-etoposide chemotherapy [1,2,4], landmark clinical trials recently reported a survival benefit with the addition of anti-PD-L1 immune checkpoint inhibitors (ICIs), including atezolizumab or durvalumab [5–7]. Especially, the IMpower-133 double-blind, placebo-controlled, phase 3 trial demonstrated the benefit atezolizumab vs. placebo in combination with carboplatin and etoposide for 4 cycles, followed by a maintenance phase with atezolizumab vs. placebo alone, as first-line therapy in 403 patients with ES-SCLC [5,7]. After a median follow-up of 22.9 months, median overall survival (OS) was 12.3 months in the atezolizumab group and 10.3 months in the placebo group (hazard ratio (HR) 0.76; 95% confidence interval (CI) 0.60–0.95; $p = 0.0154$); median progression-free survival (PFS) was 5.2 months and 4.3 months, respectively (HR 0.77; 95% CI 0.63–0.95; $p = 0.02$). The safety profile of this regimen was consistent with the previously reported safety profile of the individual agents, with no new findings observed. Based on these data, ICIs plus platinum and etoposide regimens are now standard-of-care is ES-SCLC [3,8].

Besides randomized clinical trials in which ES-SCLC patient population may be highly selected, real-world data represent a major piece of knowledge in the clinical decision-making for treatment in SCLC, aiming at providing clinicians with data from special population not enrolled or analyzed in randomized trials, such as patients with poor general condition or brain metastases that were expected to be treated in the routine practice setting, capturing the actual treatment sequences after immunotherapy, and ultimately assessing the reproducibility of results in patients, especially in the long-term setting. Here we report the results of IFCT-1905 CLINATEZO, a nationwide, non interventional, retrospective chart review of consecutive patients with ES-SCLC who received atezolizumab plus chemotherapy as part of the French Early Access Program (EAP), that provide with a unique opportunity to address those objectives.

2. Materials and Methods

2.1. Study design

IFCT-1905 CLINATEZO is a nationwide, non-interventional, retrospective chart review study of patients with ES-SCLC who received atezolizumab plus chemotherapy as part of the French EAP that ran from May 2019 to March 2020 (1402 patients concerned). Inclusions were exhaustive per participating centers (65 out of the 307). Based on on-site visits, data collection period ran from March to December 2022 (main data collection plus survival update), by trained French Cooperative Thoracic Intergroup (IFCT) clinical research associates. Atezolizumab (1200 mg flat dosing) was available upon physician request for treatment-naïve patients with ES-SCLC, in combination with carboplatin and etoposide chemotherapy, every 3 weeks. A total of 1402 patients received atezolizumab through this program; requests had to be done through a web platform, and median time from request to first treatment dose in patients who were actually treated was 6.3 days. As part of the secondary data use, the present protocol has been made in accordance with the compliance commitment to reference method MR-004 submitted to the CNIL (French National Commission for the protection of private data and rights). This research was registered in the Health Data Hub (HDH) public directory (https://www.health-data-hub.fr/projets) and in clinicaltrials.gov database under the ID NCT04920981. The search for the patient's non-opposition had to be conducted, verbally and in writing (providing the information leaflet), by the physician who followed up the patient during the course of a consultation. This had to be written in the patient medical record. Information pertaining to deceased patients may be subject to data processing, except if the concerned patient voiced his refusal while still alive.

2.2. Eligibility criteria

French EAP required patients to fulfill the main inclusion criteria of the landmark IMpower- 133 trial [5,7]: 1/ pathological or cytological diagnosis of SCLC, 2/ extensive stage, i.e. stage IIIB or IV, 3/ age of 18 years or older, 4/ life expectancy of at least 3 months, 5/ Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, 6/ adequate hematologic, hepatic, and renal function. Exclusion criteria included: 1/treatment with steroids $\geq$ 10 mg equivalent prednisone in the last 14 days before the initiation of atezolizumab, 2/human immunodeficiency virus infection or known autoimmune disease, with the exception of residual hypothyroidism due to an autoimmune condition, type 1 diabetes mellitus, or psoriasis not requiring systemic treatment, 3/ symptomatic or active central nervous system (CNS) metastasis, 4/ previous treatment with any immune checkpoint inhibitor, 5/absence of eligibility for an ongoing, recruiting clinical trial. Eligibility was centrally reviewed within the program.

For IFCT-1905 CLINATEZO, selection criteria included: 1/ administration of at least one dose of treatment with atezolizumab and chemotherapy as part of the EAP, 2/ information about the study and acceptance of patients for their data to be collected, 3/ selection period from May 6th 2019 until January 31st 2020 for initiation of treatment with atezolizumab plus chemotherapy in order to have sufficient follow-up time.

2.3. Study endpoints

Key objectives were to assess effectiveness and safety of atezolizumab; analyze subsequent treatment sequences; we also aimed at defining a subset of patients with characteristics similar to that of the IMpower-133 trial, so-called IMpower-133-like population; outcomes were to be described in special population including patients with brain metastases and PS $\geq$ 2. Pre-specified endpoints were the following: 1/ Overall Survival (OS), defined as the time from the first dose of treatment with atezolizumab and chemotherapy to death from any cause; 2/

real-world progression-free survival (rw-PFS), defined as the time from first dose of treatment with atezolizumab and chemotherapy to first occurrence of disease progression or death from any cause during the study – in this real-life data study, disease progression was assessed by the treating physician, and PFS will be indicative given possible heterogeneity in the time interval between patients visits at the hospital and tumor radiological assessments, even if imaging assessment using brain, thorax, abdomen computed tomography (CT) scan had – as part of the EAP- to be performed every 6 weeks, and reports sent centrally before continuation of atezolizumab was allowed; these reports were reviewed for this study; 3/ best objective response, recorded from the start of treatment with atezolizumab and chemotherapy until disease progression or start of further anti-cancer treatment; 4/ duration of treatment, defined as the time from first dose of treatment to discontinuation (interruption of more than 2 months) – this included duration of treatment with atezolizumab beyond progression; 5/ pattern of disease progression; 6/ time to subsequent treatment initiation, and information about the type and the duration (time between first dose of treatment and its discontinuation) of systemic therapies administered immediately after atezolizumab and chemotherapy - local treatment during or immediately after treatment with atezolizumab and chemotherapy was also recorded; 7/ safety profile adverse events (AEs) were collected from medical record of the patient after onsite review by research study assistants from IFCT. With this methodology, maximal grade 3-4-5 treatment-related adverse events (TRAEs) were systematically recorded, and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

2.4. Collection of data

Clinical data from 518 patients enrolled in the EAP were collected from medical records at 65 investigator sites, by research study assistants working at the IFCT, using a dedicated case report form. The expected precision according to the sample size of this data-driven analysis is based on the results of IMpower-133 [5,7], to obtain an acceptable precision for 6-month OS; with the above information, the inclusion of at least 500 patients was allowing a precision of<5% in the 6 months OS. Data collection period ranges from March to December 2022. Besides study endpoints, a total of 206 variables were actually collected, including the above-mentioned eligibility criteria, patients' characteristics - performance status, auto-immune and paraneoplastic disorders, smoking history -, sites of metastases at baseline and disease progression, and reason for discontinuation of treatments.

2.5. Statistical analyses

Database lock was done on July 25th 2022. The cut-off date (i.e. date beyond which events were no longer taken into account in the survival analysis) was set at June 1st, 2022.

Quantitative variables were described by the number of values entered, the number of missing data, the mean, the standard deviation, the median, the 1st and the 3rd quartile. Qualitative variables were described by the number of values entered, the number of missing values, the frequency and the percentage per category. If relevant, the 95% confidence interval was calculated. The alpha-risk was fixed at 5%, two-sided. OS and rw-PFS were estimated using the Kaplan-Meier method. The log-rank test was used for survival comparisons. A univariate proportional hazards regression model was used to test the association of each factor with rw-PFS and OS (the proportional hazards assumption was tested), then a multivariate model with a stepwise selection including all factors was applied to identify the independent prognostic roles of patient characteristics. Statistical analyses were computed with SAS 9.4 software.

3. Results

3.1. Patient population and characteristics

ITT population included a total of 518 patients, of which 491 had discontinued atezolizumab at cut-off date and for whom 326 (66.4%) did receive subsequent treatment. As shown in Table 1, a majority of patients were male (66.2%) and more than a half were above 65 years of age (53.5%); mean age was 65.7 years (range: 36.7–88.0). A total of 55 (10.6%) patients had received previous therapy for limited-stage SCLC (n = 46) or ES-SCLC (n = 9). Almost all (95.9%) patients had a tobacco-smoking history, with current and former smokers in 22.2% and 73.7% respectively. The median number of pack-years was 40.0 (range: 5.0–150). Most patients (89.1%) had a performance status (PS) 0–1, and 26.6% had baseline brain metastases.

3.2. Atezolizumab treatment

All but 2 patients receive carboplatin and etoposide regimen in combination with atezolizumab; the 2 other patients received cisplatin and paclitaxel respectively. Median number of chemotherapy cycles was 4.0 (range:1.0–9.0). Median number of atezolizumab injections was 7.0 (range:1.0–48.0), for a median time of 4.9 (95% CI 4.5–5.1) months. Concurrent radiotherapy was administered on brain metastases in 28 (5.4%) patients, on other sites in 101 (19.5%) patients – lung in 25 (4.8%) patients, mediastinum in 23 (4.4%) patients, bone metastases in 28 (5.4%) patients; 9 (1.7%) patients had surgery of bone, brain, or digestive tract metastases. In addition, 67 (12.9%) patients had prophylactic brain irradiation.

Atezolizumab was continued beyond disease progression in 122 (23.6%), for a median duration of 1.9 (95% CI 1.4–2.3) months; 42 (8%)

Table 1
Baseline characteristics.

	n	(%)
Total	518	(100%)
Gender		
Man	343	(66%)
Woman	175	(34%)
Age at atezolizumab initiation		
≤ 65 years	241	(47%)
> 65 years	277	(53%)
Smoking		
Yes	497	(96%)
Current Smoker	115	(22%)
Former smoker	381	(74%)
Unknown	1	(4%)
No (Never smoker)	21	(4%)
Paraneoplasic disease		
Yes	26	(5%)
No	492	(95%)
Performance status at atezolizumab initiation		
0–1	390	(89%)
2	37	(8%)
3–4	11	(3%)
Unknown	80	
Metastatis sites		
Lung	466	(90%)
Mediastinum	400	(77%)
Pleura	119	(23%)
Liver	216	(42%)
Bone	213	(41%)
Brain	138	(27%)
Adrenal	132	(26%)
Previous treatment		
Yes	55	(11%)
Surgery +/- chemotherapy + radiotherapy	12	(22%)
Chemo-radiotherapy	30	(55%)
Radiotherapy	4	(7%)
Chemotherapy	9	(16%)
No	463	(89%)

of these patients had radiotherapy on progressive lesions. At data cut-off, 491 (95.0%) patients had discontinued atezolizumab, because of disease progression in 385 (78.4%), toxicity in 34 (6.9%) patients, death in 29 (5.9%) patients, and patient refusal, intercurrent event, second cancer, loss of follow-up and other reason - - in 43 (8.3%).

Atezolizumab-related adverse events are presented in Table 2; grade $\geq$ 3 events were reported in 101 (19.5%) patients. Grade $\geq$ 3 events were not higher in patients who received radiotherapy during treatment with atezolizumab.

3.3. Response and progression

Best objective response was reported as complete response in 19 (3.9%) patients, partial response in 378 (77.1%) patients, and stable disease in 50 (10.2%) patients; progressive disease was observed in 43 (8.8%) patients. Disease control was observed in 447 (91.2%) patients.

Ultimately, at data cut-off, 430 (83.0%) patients had shown disease progression. Sites included the brain in 149 (34.6%) patients, the mediastinum in 147 (34.2%) patients, the liver in 97 (22.6%) patients, the bone in 64 (14.9%) patients.

3.4. Outcomes

After a median follow-up of 30.8 (95% CI 29.9–31.5) months, median, 12- and 24-month OS rate in the ITT population were 11.3 (95% CI 10.1–12.4) months, 46.7% (95% CI 42.3–50.9), and 21.2% (95% CI 17.7–24.8), respectively (Fig. 1**A**). Median, 6- and 12-month rw-PFS rate was 5.2 (95% CI 5.0–5.4) months, 37.5% (95% CI 33.3–41.7) and 15.2% (95% CI 12.2–18.6), respectively (Fig. 1**B**). In the IMpower-133-like patient population with PS 0–1, median OS and rw-PFS were 11.9 (95% CI 10.7–13.5) and 5.3 (95% CI 5.1–5.7) months, respectively (**Supplemental** Table 1). At multivariate analysis, OS was not different in patients with or without baseline brain metastases (median of 9.9 (95% CI 8.0–12.5) and 11.6 (95% CI 10.4–13.0) months, respectively (p = NS). Age was a prognostic factor with median OS in patients $\leq$ 65 years and greater than 65 years corresponding to 13.2 (95% CI 11.4–14.4) and 9.8 (95% CI 8.8–11.3) months respectively (HR = 1.26 (95% CI 1.02–1.55, p = 0.03) (Table 3). The performance status was also a prognostic factor with median OS in patients with PS 0–1 and PS $\geq$ 2 corresponding to 12.2 (95% CI 11.0–13.5) and 6.3 (95% CI 4.5–9.2) months respectively (HR = 1.88 (95% CI 1.4–2.6) p < 0.001). For PFS, the performance status and brain metastasis were prognostics factors with a HR = 1.80 (95% CI 1.3–2.5) p = 0.0002 and HR = 1.30 (95% CI 1.0–1.6) p = 0.02 respectively (Table 4).

3.5. Subsequent therapies

A total of 326 patients, among the 491 who discontinued the treatment, received subsequent therapy after atezolizumab (66.4%), consisting of chemotherapy in 235 (72.1%) patients, chemo-radiotherapy in 69 (21.2%) patients, and radiotherapy alone in 22 (6.7%) patients- in the setting of oligoprogressive disease. Chemotherapy regimens included carboplatin and etoposide for 98 (32.2%) patients - combined with atezolizumab in 4 (1.3%) patients, carboplatin and paclitaxel in 32 (10.5%) patients, topotecan in 72 (23.7%) patients, or other single-agent cytotoxic agents in 81 (27%). Two patients received EGFR inhibitors combined with chemotherapy. Objective response rate was 41.6%, and stable disease rate was 25.8%. Response rate was significantly higher in patients who received platinum and etoposide vs. other second-line therapies (62.6% vs. 30.7%, p < 0.001). Median duration of first subsequent therapy was 2.1 (95% CI 1.8–2.3) months.

4. Discussion

IFCT-1905 CLINATEZO is, to our knowledge, one of the largest cohort of patients with ES-SCLC who received atezolizumab plus

Table 2
Atezolizumab-related adverse events.

ALL (N = 518)	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Any adverse event	**101 (19.5)**	**70 (13.5)**	**28 (5.4)**	**3 (0.6)**
Investigations	**48 (9.3%)**	**21 (4.1%)**	**25 (4.8%)**	**2 (0.4%)**
Platelet count decreased	34 (6.6%)	18 (3.5%)	14 (2.7%)	2 (0.4%)
Neutrophil count decreased	27 (5.2%)	12 (2.3%)	15 (2.9%)	0 (0%)
Aspartate aminotransferase increased	3 (0.6%)	3 (0.6%)	0 (0%)	0 (0%)
White blood cell count decreased	2 (0.4%)	0 (0%)	1 (0.2%)	1 (0.2%)
Alanine aminotransferase increased	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Gamma-glutamyltransferase increased	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Blood and lymphatic system disorders	**36 (6.9%)**	**33 (6.4%)**	**3 (0.6%)**	**0 (0%)**
Anaemia	30 (5.8%)	28 (5.4%)	2 (0.4%)	0 (0%)
Febrile neutropenia	6 (1.2%)	5 (1%)	1 (0.2%)	0 (0%)
Gastrointestinal disorders	**10 (1.9%)**	**9 (1.7%)**	**1 (0.2%)**	**0 (0%)**
Diarrhoea	4 (0.8%)	4 (0.8%)	0 (0%)	0 (0%)
Colitis	2 (0.4%)	1 (0.2%)	1 (0.2%)	0 (0%)
Cheilitis	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Constipation	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Nausea	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Proctitis	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Stomatitis	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Skin and subcutaneous tissue disorders	**7 (1.4%)**	**5 (1%)**	**2 (0.4%)**	**0 (0%)**
Alopecia	3 (0.6%)	2 (0.4%)	1 (0.2%)	0 (0%)
Dermatitis exfoliative generalised	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Dermatomyositis	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Pemphigoid	1 (0.2%)	0 (0%)	1 (0.2%)	0 (0%)
Psoriasis	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	**5 (1%)**	**5 (1%)**	**0 (0%)**	**0 (0%)**
Dyspnoea	2 (0.4%)	2 (0.4%)	0 (0%)	0 (0%)
Aspiration	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Respiratory distress	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Respiratory failure	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Infections and infestations	**4 (0.8%)**	**3 (0.6%)**	**0 (0%)**	**1 (0.2%)**
Encephalitis	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Hepatic infection	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Rash pustular	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Septic shock	1 (0.2%)	0 (0%)	0 (0%)	1 (0.2%)
Cardiac disorders	**3 (0.6%)**	**3 (0.6%)**	**0 (0%)**	**0 (0%)**
Cardiac failure	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Myocarditis	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Pericarditis	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Endocrine disorders	**3 (0.6%)**	**3 (0.6%)**	**0 (0%)**	**0 (0%)**
Hyperthyroidism	2 (0.4%)	2 (0.4%)	0 (0%)	0 (0%)
Adrenal insufficiency	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
General disorders	**3 (0.6%)**	**3 (0.6%)**	**0 (0%)**	**0 (0%)**
Fatigue	3 (0.6%)	3 (0.6%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders	**3 (0.6%)**	**3 (0.6%)**	**0 (0%)**	**0 (0%)**
Arthralgia	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Muscular weakness	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Myositis	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Nervous system disorders	**3 (0.6%)**	**2 (0.4%)**	**0 (0%)**	**1 (0.2%)**
Hepatic encephalopathy	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)
Immune-mediated encephalitis	1 (0.2%)	0 (0%)	0 (0%)	1 (0.2%)
Peripheral sensory neuropathy	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)

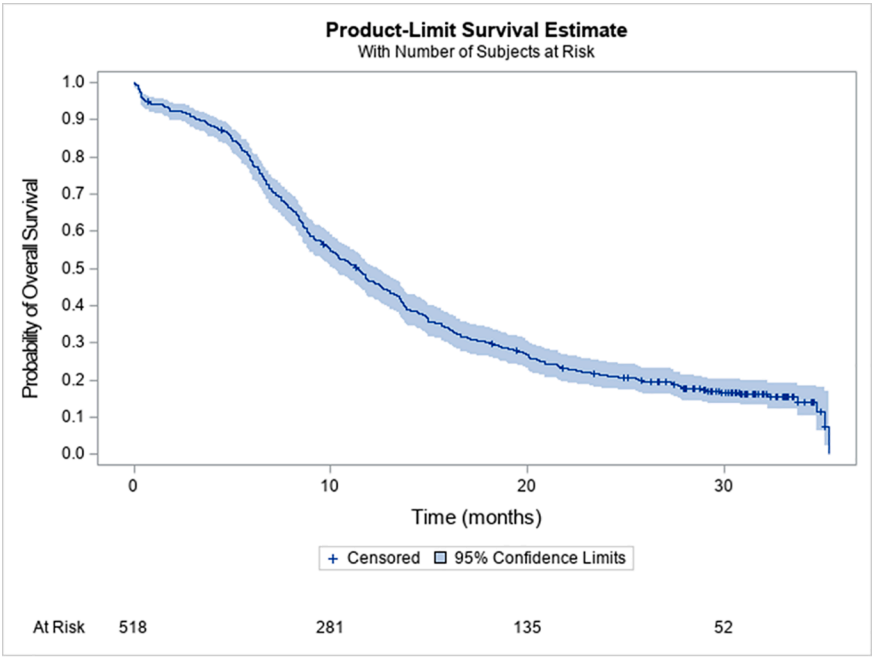
(*continued on next page*)

Table 2 (*continued*)

Renal and urinary disorders	**1 (0.2%)**	**1 (0.2%)**	**0 (0%)**	**0 (0%)**
Renal failure	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)

chemotherapy in first-line treatment. Taken together, our results indicate 1/ the reproducibility in a real-life setting, of the key survival outcomes of the landmark IMpower-133 trial, that may be related to a selection of patients fit for this regimen, 2/ the adoption of pragmatic approaches for the management of patients receiving atezolizumab, that includes concurrent radiotherapy and treatment beyond progression, and 3/ the high access to second-line therapies, mostly based on chemotherapy.

IFCT 1905-CLINATEZO demonstrates the reproducibility of the landmark effectiveness outcomes of atezolizumab combined with chemotherapy in first-line treatment of ES-SCLC, as demonstrated in the landmark IMpower-133 randomized trial, with median rw-PFS and OS of 5.2 and 11.3 months, vs. 5.3 and 12.3 months, respectively [5,7], and 12-month OS of 51.7% and 46.7%, respectively (**Supplemental** Table 1**)** [7]. In the IFCT-1905 CLINATEZO versus IMpower-133 trial, there were more patients with poor PS (11% versus none) and more cerebral metastases (27% versus 8%). In other, more limited real-world cohorts, similar outcomes were reported. The Italian MAURIS study enrolled 155 patients, with similar baseline characteristics to IFCT-1905 CLINATEZO, and median rw-PFS and OS of 5.5 (95 %CI 5.3–5.8) months and 10.7 (95% CI 9.9–13.7) months [9]. IMfirst is a phase IIIb prospective, open-label trial of 155 patients who received atezolizumab combined with



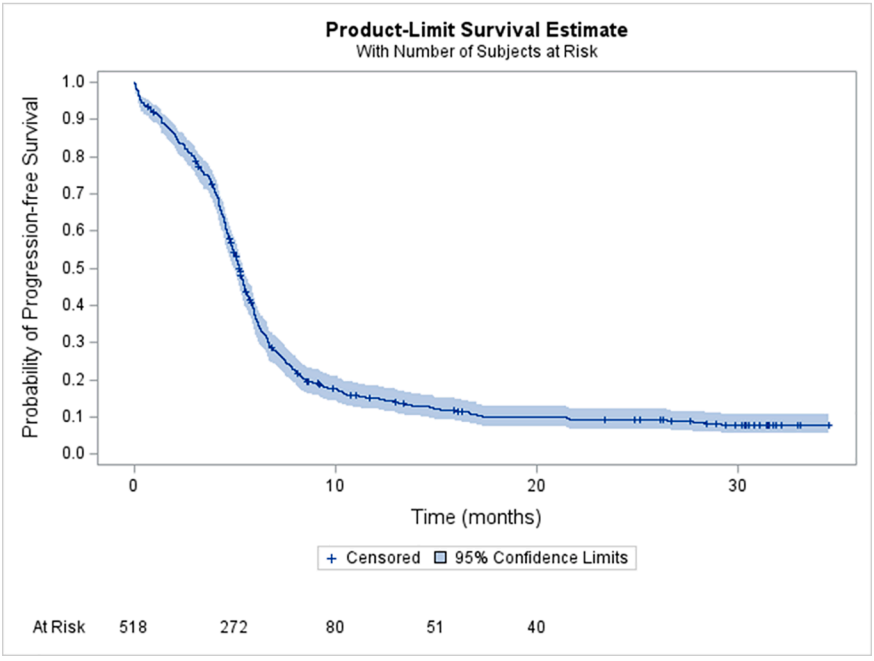


Fig. 1. Overall (A) and Progression-Free (B) Survival.

Table 3
Multivariate analysis for overall survival.

	Univariate model					Multivariate model		
Factors		N	HR	95% CI	p	HR	95% CI	p
Age	≤ 65	241	1.00	–	–	1	–	–
	> 65	277	1.34	[1.11—1.63]	0.002	1.26	[1.02 – 1.55]	0.03
PS	0–1	390	1.00	–	–	1	–	–
	≥ 2	48	1.95	[1.42—2.68]	< 0.0001	1.88	[1.37 –2.59]	< 0.0001
Brain metastasis	No	380	1.00	–	–			
	Yes	138	1.07	[0.86—1.33]	0.53			
Previous treatment	No	463	1.00	–	–			
	Yes	55	0.73	[0.53 – 1]	0.05			

Table 4
Multivariate analysis for progression-free survival.

		Univariate model				Multivariate model (stepwise selection)		
Factors		**N**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**p**
Age	≤ 65 yrs	241	1.00	–	–			
	> 65 yrs	277	1.05	[0.87—1.26]	0.60			
PS	0–1	390	1.00	–	–	1	–	–
	≥ 2	48	1.72	[1.26—2.34]	0.0006	1.80	[1.32 –2.47]	0.0002
Brain metastasis	No	380	1.00	–	–	1	–	–
	Yes	138	1.21	[0.99—1.49]	0.07	1.30	[1.04 –1.63]	0.02
Previous treatment	No	463	1.00	–	–			
	Yes	55	0.97	[0.72 – 1.30]	0.83			

platinum and etoposide combination, with possible enrolment of patients with PS 2, and/or untreated, stable brain metastases, and/or autoimmune disorders; PFS and OS were 6.2 (95 %CI 5.8–6.4) and 10.0 (95 %CI 8.6–11,9) months [10]. Other cohorts [11], as well as some with durvalumab immunotherapy [12], based on the CASPIAN regimen [6], reported similar results.

Meanwhile, the significant heterogeneity of patient baseline characteristics in those studies may question the value of such comparisons; indeed, several real-world studies in ES-SCLC reported similar OS – ranging from 7.0 to 14.0 months - without the addition of immunotherapy to platinum and etoposide chemotherapy [13–15]. Meanwhile, results from a French cohort of patients who did not receive immunotherapy recently reported median rw-PFS of 6.2 and 6.1 months, and OS of 13.2 months and 11.8 months for cisplatin/etoposide and carboplatin/etoposide doublet regimens, respectively [16].

Interestingly, in IFCT-1905 CLINATEZO, the majority of patients had a PS 0–1 and nearly half were < 65 years-old; in real-world cohorts, a higher proportion of patients were elderly, or had co-morbidities and poorer general condition [13–15]. It has been estimated that only one third of patients is actually eligible to immunotherapy [17]. Still, an unmet need remains the identification of patients actually benefiting, in terms of long-term outcomes, of this regimen; in that matter, molecular signatures have shown some promise, with a correlation between the so-called SCLC-I subtype and survival [5].

IFCT-1905 CLINATEZO provides unique insight into the practical management of immunotherapy with atezolizumab in first-line treatment of ES-SCLC. Our study shows that this IMpower-133 regimen has been used for 55 (11%) patients in the setting of platinum and etoposide rechallenge in ES-SCLC platinum-sensitive cases or after recurrence after definitive chemo-radiotherapy for limited-stage disease; OS, not rw-PFS, was numerically higher - median of 14.9 months (95% CI 10.1–21.5) – in this setting. While it is standard to rechallenge patients with chemotherapy [18], the benefit of immunotherapy in such situation was not formally assessed; only 4% of such patients were not enrolled in the IMpower-133 trial [5]. Second, many patients did receive radiotherapy concurrently with atezolizumab (19.5%), including brain radiotherapy in 5% of patients. Interestingly, baseline brain metastases did not significantly impact outcomes in our cohort, which may be related to a selection of asymptomatic, stable cases, as well as to the delivery of radiotherapy, that was previously reported to be safe [19]. Third, while radiotherapy may have been administered upfront, IFCT-1905 CLINATEZO shows that a high proportion −24%- of patients were treated with atezolizumab beyond progression, for a median duration of 1.9 (95% CI [1.4–2.3]) months, possibly in the setting of focal treatment of oligo-progressive disease, found in 42 (8%) patients who continued atezolizumab post-progression, and 22 (4%) patients who discontinued atezolizumab, a strategy adopted in clinical practice in non-small cell lung cancer (NSCLC), treated with immunotherapy or targeted agents [20,21].

In IFCT-1905 CLINATEZO, sites of disease progression after atezolizumab included the brain and/or the mediastinum in more than one third of patients. This raises the question of the administration of prophylactic brain irradiation (PCI) in the 4% of patients achieving complete response, as reported previously [22], and/or consolidation radiotherapy on mediastinal oligoresidual disease, such as in the randomized, phase III CREST trial [23], that both demonstrated some benefit. Thoracic radiotherapy, as well as prophylactic brain radiotherapy, is considered optional in the most recent current guidelines for the treatment of ES-SCLC, for patients not receiving immune checkpoint inhibitors [8]; indeed, thoracic radiotherapy was not part of landmark clinical trials with immunotherapy, as sequencing with maintenance remains complex; PCI was authorized in the CASPIAN trial, with no reported data so far.

Ultimately, IFCT-1905 CLINATEZO shows that a majority of patients – 326 cases (63%) - were eligible for second-line therapy after atezolizumab; a total of 98 (32%) patients did receive platinum and etoposide regimen as second-line, suggesting these were platinum-sensitive cases. Interestingly, atezolizumab was discontinued in all these patients, which may be questioned as the mechanism of resistance is historically understood as being related to a reduction of the cytotoxic effect chemotherapy, not a true acquired resistance to immunotherapy; continuation of immunotherapy in the setting of initiation of second-line chemotherapy was shown to produce significant response rates, PFS and OS in NSCLC [24]. Our study indicates, beyond platinum-sensitive cases, the major unmet need of active options after the failure of atezolizumab plus chemotherapy, as median duration of first subsequent therapy was 2.1 (95% CI [1.8–2.3]) months.

In conclusion, IFCT-1905 CLINATEZO shows the reproductibility in a

real-life setting, of the key survival outcomes of IMpower-133, that may be related to a selection of patients fit for this regimen, the adoption of pragmatic approaches for the management of patients receiving atezolizumab, that includes concurrent radiotherapy and treatment beyond progression, and the high access to second-line therapies, mostly based on chemotherapy, with limited outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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