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## **► To cite this version:**

Jean-Louis Pujol, Laurent Greillier, Clarisse Audigier-Valette, Denis Moro-Sibilot, Lionel Uwer, et al.. A Randomized Non-Comparative Phase II Study of Anti-Programmed Cell Death-Ligand 1 Atezolizumab or Chemotherapy as Second-Line Therapy in Patients With Small Cell Lung Cancer: Results From the IFCT-1603 Trial. *Journal of Thoracic Oncology*, 2019, 14 (5), pp.903-913. <10.1016/j.jtho.2019.01.008>. <hal-02570679>

**HAL Id: hal-02570679**

**<https://hal.science/hal-02570679v1>**

Submitted on 22 Oct 2021

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# **A Randomized Non-Comparative Phase 2 Study of Anti-Programmed Cell Death-Ligand 1 Atezolizumab or Chemotherapy as Second-Line Therapy in Patients with Small Cell Lung Cancer: Results from the IFCT-1603 Trial**

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## Disclosure

*Funding: This work was supported by the Intergroupe Francophone de Cancérologie Thoracique (IFCT: French Cooperative Thoracic Intergroup) and received an unrestricted grant from Roche SA France. Roche also supplied atezolizumab but played no role in trial design, data collection, data interpretation, discussion, or manuscript writing.*

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## ABSTRACT

**Introduction:** This randomized phase 2 trial aimed at evaluating the engineered programmed cell death-ligand 1 (PD-L1) antibody atezolizumab in small cell lung cancer progressing after first-line platinum–etoposide chemotherapy.

**Methods:** Patients were randomized 2:1 to atezolizumab (1200mg intravenously every 3 weeks) until progression or unacceptable toxicity, or conventional chemotherapy (up to six cycles of topotecan or re-induction of initial chemotherapy). Patients were not selected based on PD-L1 tissue expression. The primary endpoint was objective response rate at 6 weeks. A two-stage design with 2:1 randomization and O'Brien-Fleming stopping rules was employed. The null hypothesis was rejected if  $> 12/45$  patients were responders.

**Results:** Overall, 73 patients were randomized (atezolizumab  $n = 49$ ; chemotherapy  $n = 24$ ). At 6 weeks, 1 of 43 eligible atezolizumab patients achieved an objective response (2.3%, 95% CI 0.0; 6.8), while 8 others had stable disease (20.9% disease control rate; CI 8.8 ; 33.1). Among eligible chemotherapy patients ( $n=20$ ), 10% achieved an objective response (65% disease control rate). Median pProgression-free survival was 1.4 months (CI 1.2; 1.5) with atezolizumab and 4.3 months (CI: 1.5; 5.9) with chemotherapy. Overall survival did not significantly differ between groups: median OS: 9.5 months versus 8.7 months for the atezolizumab and the chemotherapy group, respectively; (adjusted  $HR_{atezolizumab} = 0.84$  CI: 0.45 ;1.58) ;  $p=0.60$ . Two atezolizumab patients (4.2%) experienced grade 3 fatigue, and two others grade 1 dysthyroidism. Among 53 evaluable specimens, only 1 (2%) had positive immunohistochemical PD-L1 staining (SP142 clone).

**Conclusions:** Atezolizumab monotherapy in relapsed small cell lung cancer failed to demonstrate significant efficacy. No unexpected safety concerns were observed.

**Keywords:** programmed cell death-ligand 1; atezolizumab; chemotherapy; small cell lung cancer

## Introduction

Small cell lung cancer (SCLC) accounts for 14% of lung cancers, with only modest progress made in recent decades.<sup>1</sup> Chemotherapy remains the backbone of SCLC therapy.<sup>2</sup> Despite the high SCLC chemosensitivity, survival is low (2 to 5 years) due to secondary chemoresistant relapses. Re-induction of platinum–etoposide or single-agent topotecan (or more recently, amrubicin, approved in Japan) are recommended for relapsed or refractory SCLC. In this second line setting, the survival of patients treated with either regimen is about 33 weeks.<sup>3</sup>

Novel therapeutic approaches are under development to overcome secondary SCLC chemoresistance. Poly-(ADP-ribose) polymerase inhibitors,<sup>4</sup> aurora A kinase inhibitors,<sup>5</sup> enhancer of zeste homolog 2 inhibitors,<sup>6</sup> antibody-drug conjugates targeting DLL3,<sup>7</sup> and immune check-point inhibitors (ICPIs)<sup>8</sup> are under evaluation in relapsed SCLC. Meanwhile, SCLC genome-sequencing is providing key insights into genomic alterations like ubiquitous loss of P53 and RB1 gene functions, common amplification of the cMYC proto-oncogene, and common inactivating mutations of the NOTCH gene family.<sup>9</sup> Most studies have highlighted a high tumor mutational burden (TMB) in SCLC.

Though the expression of programmed cell death-ligand 1 (PD-L1) by SCLC tumor cells is low,<sup>10</sup> a strong rationale exists for introducing ICPIs that target the programmed cell death protein 1 (PD-1)/PD-L1 link on account of SCLC's high TMB. Several Phase 2 studies are currently investigating the efficacy and safety of pembrolizumab,<sup>11</sup> nivolumab, or nivolumab plus ipilimumab<sup>12</sup> in patients with SCLC relapse after platinum–etoposide chemotherapy. Several activity clues have emerged from these early development studies.

Atezolizumab (MPDL3280A), an engineered PD-L1 antibody, has been approved in non-SCLC at a 1200mg dose based on most recent clinical data.<sup>13</sup> IFCT 1603 was an open-label randomized non-comparative Phase 2 study that sought to evaluate atezolizumab's activity

as systemic therapy in SCLC progressing after first-line platinum/etoposide-based chemotherapy.

## **Patients and Methods**

### ***Patients***

Patients with histologically confirmed SCLC who experienced a relapse by failure of a first line chemotherapy consisting of platinum compound and etoposide were prospectively accrued. The main eligibility criteria were proven progressive disease other than brain metastasis or carcinomatous meningitis, performance status 0–2, measurable disease according to RECIST 1.1, and no active brain metastases. However, patients with brain metastases upon diagnosis were eligible if they achieved brain response during first-line therapy (including brain radiotherapy), maintaining their brain tumor response for 2 months prior to randomization. Other eligibility criteria were age  $\geq 18$  years; weight loss  $< 10\%$  over previous 3 months; baseline neutrophils  $\geq 2500/\text{mm}^3$ ; platelets  $\geq 100\,000/\text{mm}^3$ ; bilirubin, alkaline phosphatase and transaminase levels  $< 1.5$  times normal upper limits; sodium  $> 125\text{mmol/L}$ ; normal calcium; creatinine clearance  $\geq 40\text{mL/min}$ ; normal electrocardiogram, and signed informed consent. Patients were ineligible if they had received corticosteroids at a daily dose  $> 10\text{mg}$  (prednisolone or equivalent) for more than 10 days during the previous month, or had had prior autoimmune disease, unstable coronary angina or uncontrolled heart disease, prior human immunodeficiency virus infection, or chronic hepatitis B or C. The study was approved by an institutional review board (Sud – Méditerranée IV (Montpellier University, France) and was registered on [clinicaltrials.gov](https://clinicaltrials.gov) under trial number NCT03059667.

For all patients, the evaluation before randomization included a physical examination; standard chest X-ray; computed tomography (CT) of the upper abdomen; brain magnetic

resonance imaging or CT; skeleton CT or positron emission tomography; quality-of-life assessment using the lung cancer symptom scale (LCSS); hematology (cell blood counts including hemoglobin and platelet counts); renal function (creatinine clearance); liver function (aspartate transaminase, alanine aminotransferase, bilirubin, gamma-glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, prothrombin time, and albumin); and assessment of calcium, phosphorus, and sodium levels.

### ***Randomization and Masking***

For minimization purposes, patients were stratified by performance status (0–1 *versus* 2), limited *versus* extensive disease according to Veterans Administration Lung Study Group classification<sup>14</sup> at randomization, gender, and presumed disease sensitivity (refractory *versus* sensitive disease, the latter defined as relapse more than 90 days after ending first-line therapy). They were randomized (2:1) to either a) atezolizumab every 3 weeks until progression or unacceptable toxicity or b) conventional chemotherapy up to six cycles, delivered every three weeks.

### ***Procedure***

Anti-PD-L1 atezolizumab was administered at a fixed dose of 1200mg intravenously (IV). No dose reduction was allowed. Patients who experienced toxicity considered to be study drug-related and required a dose to be withheld, were temporarily suspended from study treatment. If atezolizumab was withheld because of adverse events for 42 days beyond the date when the next dose was due to be administered, then atezolizumab was discontinued, with the patient followed-up for safety and efficacy.

Conventional chemotherapy consisted of either re-induction of carboplatin–etoposide doublet or second-line oral or IV topotecan, the choice being at the investigator’s discretion. The

following protocol recommendations were made: 1) Carboplatin–etoposide was recommended for patients if they were deemed fit and had been relapse-free for at least 90 days after first-line therapy; 2) Topotecan was recommended for patients who did not meet criterion 1 and was to be administered according to an approved regimen of 2.3mg/m<sup>2</sup> orally or 1.5mg/m<sup>2</sup> IV on Days 1 to 5.

Third-line treatment was chosen based on each center's policy. Atezolizumab was not permitted for patients randomly assigned to chemotherapy who experienced secondary progression.

We assessed tumors on imaging at baseline, every 6 weeks for 24 weeks post-randomization, and every 9 weeks thereafter. Tumor response was assessed according to RECIST 1.1 on chest and upper abdomen CT and any other abnormal tests that have shown target lesions at screening and in case of suspicious signs. Tumor assessments continued until progression, irrespective of treatment discontinuation, and were centrally reviewed by reviewers blinded to randomization. Immune-modified RECIST criteria were not employed, and LCSS was recorded at each evaluation.

PD-L1 expression was centrally assessed in archival or fresh tumor samples according to previously published scoring criteria<sup>15</sup> using the VENTANA SP142 PD-L1 immunohistochemistry assay (Ventana Medical Systems, Inc., Tucson, AZ, USA). As described, tumor cell PD-L1 expression was scored as a percentage of total tumor cells, and tumor-infiltrating immune cells expressing PD-L1 was scored as a percentage of tumor area. Briefly, TC0 was defined as PD-L1 expression by less than 1% of tumor cells, TC1 as PD-L1 expression by 1% to less than 5%, TC2 as PD-L1 expression by 5% to less than 50%, and TC3 as PD-L1 expression by 50% or more. Likewise, IC0 was defined as PD-L1 expression in less than 1% of tumor-infiltrating immune cells, IC1 as PD-L1 expression in 1% to less than 5%, IC2 as PD-L1 expression in 5% to less than 10%, and IC3 as PD-L1 expression in



10% or more. A composite score was arrived at by summing the IC and TC scores. PD-L1 expression was not used as a stratification criterion.

## ***Outcomes***

The primary endpoint was the objective response rate (ORR) as assessed by the investigator at Week 6 (with mandatory confirmation at week 12) in eligible patients randomly assigned to the atezolizumab group. Secondary endpoints included overall survival (OS, time from randomization to death) and progression-free survival (PFS, time from randomization to either RECIST 1.1 disease progression or death from any cause, whichever occurred first) in the intention-to-treat population of the experimental group. Further secondary endpoints were adverse events (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0); quality of life; response rate in the experimental group as assessed by panel; response rate according to tissue PD-L1 expression; response rate in control arm.. Particular attention was paid to specific immunological adverse events. The safety and compliance population comprised all randomized patients who received at least one dose, with the actual treatment received being taken into account if this differed from the treatment to which the patient had been randomized.

## ***Statistical Analysis***

Only the experimental group was assessed for efficacy, with conventional chemotherapy group used as a comparator with literature data. This was an attempt to validate the study population while preventing any selection bias. The maximum sample size was calculated based on  $\alpha$ ,  $\beta$ , and the expected effect size using a test for single binomial proportion for a two-stage design with 2:1 randomization and O'Brien-Fleming stopping rules, allowing for early stopping after stage I. The software East 6.0 was used. A response rate of  $P_0 = 0.15$  or less was considered unacceptable. However, we considered the response rate good if  $P_a = 0.33$ . The computation was based on the following assumptions:  $P_0 = 0.15$ ;  $P_a = 0.33$ ; statistical power of 0.90; and a one-sided significance level of 0.05. The null hypothesis was

rejected if at least 12/45 patients were responders. Consequently, the planned accrual was 45 patients in two stages.

The between-group distribution of qualitative variables was compared using the  $\chi^2$  test or Fisher's exact test. For each patient, dose intensity was calculated taking into account the actual cycle number. Probability of survival was estimated by Kaplan-Meier method, with survival differences analyzed using log-rank tests. Hazard ratios and 95% CIs were estimated using a Cox model adjusted for stratification factors. The variables to be tested in the model were selected based on univariate analysis results ( $P < 0.20$ ). A  $P$  level  $< 0.05$  was considered statistically significant. SAS software (Version 9.3) was used.

## Results

### *Patients*

From March to December 2017, 73 patients were accrued by 24 French institutions (Fig. 1). Forty nine patients were randomly allocated to the atezolizumab group and 24, to the chemotherapy group. Six atezolizumab patients were ineligible due to brain metastases (n=3) or corticosteroid use >10mg over the previous month (n=3). Demographic characteristics were well-balanced between both groups (Table 1): 83.7% of atezolizumab patients had a performance status of 0–1, 79.6% extensive disease, and 67.3% sensitive relapse (progression 90 days after last first-line chemotherapy dose). The data cutoff took place on June 30, 2018.

### *Efficacy and Compliance*

In the atezolizumab group, 1 of the 43 eligible patients achieved an objective response at Week 6, resulting in 2.3% objective response rate (95%CI: 0.0; 6.8) while 8 other patients had stable disease, resulting in disease control rate of 20.9% (95%CI: 8.8; 33; Table 2). Of the 20 eligible patients randomly allocated to chemotherapy, two achieved a tumor response at Week 6 (10%, 95%CI: 0.0; 23.1).

One atezolizumab patient did not receive any treatment owing to rapid overall clinical status deterioration. Among the 48 patients who received at least one atezolizumab dose, the median (range) number of cycles administered was 2 (1; 24). At cutoff, 45 of 49 patients had been withdrawn from the atezolizumab group, of whom 39 had developed disease progression (86.7%) and six died (13.3%). Three patients were pursuing the study treatment in the atezolizumab group and none in the chemotherapy group.

## Survival

Median follow-up was 13.7 months (95%CI: 12.7; not reported). Median PFS in the intention-to-treat population significantly differed between both groups (1.4 months [1.2; 1.5] *versus* 4.3 months [1.5; 5.9] in atezolizumab and chemotherapy groups, respectively; adjusted hazard ratio (HR)<sub>atezolizumab arm</sub> = 2.26 [1.30; 3.93];  $p=0.004$ ; Fig. 2a). The 6-month PFS rate for atezolizumab was 6.3% (0.0%; 13.1%). Random allocation had no effect upon OS since date of randomization: median OS: 9.5 months; [3.2 ; 14.4] *versus* 8.7 months; [4.1 ; 12.7] for the atezolizumab and the chemotherapy group, respectively; adjusted HR<sub>atezolizumab arm</sub> = 0.84 [CI: 0.45 ; 1.58] ;  $p=0.60$  (Fig. 2b). The 1-year OS rate for atezolizumab group was 42.5% (26.9%; 58.2%). Exploratory subgroup analyses of unstratified HRs were conducted according to gender, performance status (0–1 *versus* 2), disease sensitivity (refractory *versus* sensitive), and disease stage (limited *versus* extensive). We did not identify features of a favorable effect with atezolizumab (Fig. 2c).

After treatment discontinuation, 30 (65.2%) of the 46 patients in the atezolizumab group for whom post study follow-up is available, were known to have received third-line treatment, primarily chemotherapy (25 of the 30 patients [83.3%]), with almost equal prescription of topotecan and carboplatin–etoposide doublet. In comparison, 16 of the 24 patients (66.7%) in the chemotherapy group received third-line treatment (Appendix). No patient received ICPIs or targeted therapy (Supplemental Table 1).

## Safety

In the 48 atezolizumab-allocated patients who received at least one infusion, immune-mediated adverse events included hepatitis (two patients [4.2%], one Grade 1 and one Grade 2), colitis (two patients [4.2%], both Grade 1), arthralgia (three patients [6.3%], two Grade 1 and one Grade 2) and dysthyroidism (two patients [4.2%], one grade 1 hyperthyroidism, one hypothyroidisms, grade 1 and grade 2). Overall, musculoskeletal and

connective tissue disorders of Grades 1–2 occurred in six patients (12.5%), while gastrointestinal disorders of Grades 1–2 occurred in nine (18.8%). We observed no pneumonitis. Table 3 lists specific toxicities and toxicities that occurred in >10% of atezolizumab-treated patients. No adverse events led to atezolizumab discontinuation, with no atezolizumab-related deaths.

### ***Quality of Life***

We analyzed the proportion of patients who reported a decrease by at least one point in each symptom recorded by the LCSS. Most scores had improved at evaluation. Random allocation had no effect on the magnitude of improvement, with no statistical differences in the patient percentages with decreased scores between atezolizumab and chemotherapy (Fig. 3).

### ***Markers***

Archived tumor tissue specimens were available from 59/73 patients (80.8%). Of these, five contained <10% tumor cells and were not suitable for immunohistochemistry. Only one (1.8%) of the remaining 54 specimens available was proven positive for PD-L1 and was scored TC2, whereas the other 53 tissue samples were scored TC0. This low PD-L1 expression precluded any subgroup analyses by tumor cell score. Tumor-infiltrating immune cell scores were available for 54 specimens. Of these, 16 were positive, of which 10 were scored IC1, 5 were scored IC2 (one of these was the specimen above scored TC2), and 1 was scored IC3. Regardless of the allocated group, Kaplan Meier estimates of PFS and OS in whole patient population with available tumor specimen showed no statistical difference according to SP142 PD-L1 tumor-infiltrating immune cell score (Supplemental Fig. 1). OS estimates showed no statistical interaction between PD-L1 composite score positivity and

treatment group ( $p=0.68$ ). In the atezolizumab group, 25% of patients exhibiting IC0 score achieved disease control at Week 6, whereas all patients with a positive score experienced progressive disease (Supplemental Table 2).

## Discussion

In this trial evaluating an engineered anti-PD-L1 antibody as second-line therapy for SCLC after failure of a first-line treatment by platinum and etoposide, 1200mg atezolizumab monotherapy given once every 3 weeks resulted in a 2.3% response rate and a 1.4-month median PFS, thus precluding initiation of the Phase 3 study part. We would like to briefly discuss three major aspects pertaining to our study: 1) literature update on PD-L1 blockade in second-line SCLC; 2) search for markers as efficacy predictors of anti-PD-L1 or anti-PD-1 antibodies in SCLC; 3) future direction of SCLC immunotherapy, including combined therapy with anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) plus anti-PD-L1 blockade and chemotherapy plus immunotherapy.

Nivolumab and pembrolizumab, two anti-PD-1 antibodies, have been tested in second-line SCLC therapy.<sup>11,12</sup> The CheckMate 032 trial was conducted in patients with disease progression following platinum-containing regimens or subsequent second line treatment.<sup>12</sup> Patients were not selected based on PD-L1 expression. They were allocated to four groups, one group receiving nivolumab at 3mg/kg once every 15 days, and the three other groups receiving different combinations of nivolumab and ipilimumab once every 3 weeks for four cycles followed by nivolumab at 3mg/kg once every 15 days. We discuss the combination groups below. Some 10% of 98 patients who received 3mg/kg nivolumab monotherapy achieved a response after a median 6.5-month follow-up. Median OS was 4.4 months (95%CI;3.0; 9.3) and median PFS 1.4 months (95%CI: 1.4; 1.9). Toxicity was mild-moderate under nivolumab monotherapy. The KEYNOTE 028 trial, which evaluated pembrolizumab efficacy in different tumor types, accrued 24 patients with PD-L1-positive SCLC ( $\geq 1\%$  stained tumor cells) with disease progression after first-line treatment or beyond<sup>11</sup> Those 24 patients were selected from 163 patients screened for PD-L1 expression, with a rather low incidence of positive cases. The response rate was as high as 33%, but median PFS was 1.9 months and median OS 9.7 months.



Maintenance therapy is another approach for overcoming chemoresistant relapse. In a published Phase 2 single-group study, pembrolizumab was given as maintenance therapy after frontline platinum-based chemotherapy in metastatic SCLC patients.<sup>16</sup> Patients were not selected for PD-L1 tumor expression. Overall, 45 patients with response or stable disease after four to six cycles of platinum and etoposide chemotherapy received IV pembrolizumab at 200mg once every 3 weeks. Median PFS was 1.4 months, median OS 9.6 months, and 1-year OS rate 37%. Thus, after first-line chemotherapy, anti-PD-1 and anti-PD-L1 antibodies as second-line treatment or maintenance therapy have yielded low disease control rates. Median PFS has been proven remarkably similar across studies, being 1.4 months in the KEYNOTE 032 study, maintenance pembrolizumab study, and this atezolizumab study, and 1.9 months in the KEYNOTE 028 study. Although between-trial comparisons prove hazardous, these results are no better than those yielded by topotecan in second-line therapy. In a phase 3 study comparing oral with IV topotecan as second-line therapy, oral topotecan yielded an 18.3% response rate, median PFS of 2.8 months, and median OS of 7.7 months.<sup>3</sup> In our randomized Phase 2 study, patients allocated to chemotherapy achieved a median PFS of 4.3 months and median OS of 8.7 months. These results compared well with literature and thus validate the study population. Consequently, one can consider that PD-L1 blockade in second-line therapy for recurrent SCLC does not display a sufficient efficacy signal. These disappointing overall efficacy results notwithstanding, all the aforementioned studies, including ours, have shown that a small proportion of patients receiving PD-1/PD-L1 blockade achieved sustained disease control. For instance, in our study, 12% of patients received at least eight cycles of atezolizumab, with 1-year survival of 42.5%. The challenge is to identify these patients likely to benefit from PD-L1 blockade. In our study, exploratory subgroup analyses of unstratified HRs according to gender, disease sensitivity, performance status, and disease stage did not identify predictors of favorable atezolizumab effects. Other studies likewise failed to identify clinical features for pinpointing a subpopulation that may benefit from PD-1 blockade.

Two important biomarkers predictive of clinical benefit have been identified in non-SCLC patients receiving anti-PD-1 antibodies. These are the tissue expression of PD-L1 and TMB. The PD-L1 expression incidence has been shown to vary in non-SCLC, owing to differing clinical and genotypic features of each population tested. Additionally, the immunohistochemistry method used and positivity threshold led to not entirely concordant findings.<sup>17</sup> Nevertheless, a rough evaluation of PD-L1 expression in non-SCLC yielded rates of between 30 and 40%. In SCLC, the expression has been tested in smaller populations, but the incidence of PD-L1 expression is probably much lower. In our study, we were able to analyze PD-L1 expression in tumors of 54 patients, with only one tumor PD-L1-positive (2%). In the maintenance pembrolizumab study, 3/30 specimens were positive using the 22C3 antibody.<sup>16</sup> In the CheckMate 032 study, of 148 assessable tumor samples, 7 (5%) had 5% or greater PD-L1 expression.<sup>12</sup> A study evaluating SCLC PD-L1 expression only found 1 positive specimen in 39 with a 22C3 test used at the  $\geq 1\%$  tumor cell level.<sup>10</sup> Low expression levels preclude robust subgroup analyses of the relationship between PD-L1 tissue expression and patient outcome. The CheckMate 032 and maintenance pembrolizumab studies reported no survival difference between patient groups based on PD-L1 expression, although it may be said that the small number of patients in the positive PD-L1 subgroups made it difficult to draw any conclusions.<sup>11,12</sup>

Interestingly, a composite score incorporating infiltrating immune cells and tumor cells was used in the maintenance pembrolizumab study.<sup>16</sup> That exploratory analysis suggested that patients with high scores had better prognosis, but no statistical analysis could be conducted due to the small sample size. Because PD-L1 expression by SCLC tumor cells is infrequent whereas expression by infiltrating immune cells is more frequent, there is a case for evaluating the composite score as a predictive biomarker of sensitivity to anti-PD-L1 or PD-1 therapy. However, in our study, the infiltrating immune cell score did not show any relationship with treatment group.

TMB might be a more essential marker, particularly in SCLC, since most studies have reported a high number of complex genomic alterations.<sup>9</sup> Among them, loss of P53 and RB1 gene functions, amplification of cMYC proto-oncogene, frequent inactivating mutation of NOTCH gene family, and evidence of chromothripsis. On exome analysis, the median number of non-synonymous mutations was shown to range from 8 to 10 mutations per megabase pair. In the CheckMate 032 study, an exploratory analysis of the relationship between TMB and ICPI response revealed patients with high TMB to exhibit longer PFS and OS than those with low TMB.<sup>12</sup>

As PD-L1 blockade in SCLC appears insufficient to achieve tumor control in second-line therapy, other strategies could be explored. The first might be to combine CTLA-4 and PD-1 ICPIs. In the CheckMate 032 study, the median survival of patients allocated to the ipilimumab plus nivolumab combination was numerically higher than that observed with nivolumab alone,<sup>12</sup> being 7.7 months for nivolumab at 1mg/kg plus ipilimumab at 3mg/kg and 6.0 months for nivolumab at 3mg/kg plus ipilimumab at 1mg/kg. As for many other cancers, nivolumab plus ipilimumab can lead to lasting responses not seen with second-line chemotherapy for small cell cancer. Ipilimumab plus nivolumab activity also depended on the TMB and was independent of tumor cell PD-L1 expression. The combination caused a higher rate of specific immune-mediated adverse events, including two toxic deaths (one due to myasthenia gravis and the other to pneumonitis). The Stimuli trial (NCT02046733) is evaluating this combination as maintenance for patients successfully treated with concomitant chemoradiotherapy for limited SCLC. Tremelimumab plus durvalumab is another combined anti-CTLA-4 and anti-PD-L1 immunotherapy, which was tested in cohort A of the Baltic Phase 2 study.<sup>18</sup> In this study, 21 patients with platinum-refractory or resistant SCLC and good performance status were accrued. The response rate was 9.5% (95%CI: 1.2; 30.4) and median PFS was 1.9 months (95%CI;1.8; 4.3). Some 47% of patients experienced treatment-related adverse events, of which three were severe and one was fatal. The case for combined ICPIs in SCLC has yet to be borne out in Phase 3 trials.

Combined chemotherapy and immunotherapy is another avenue being explored to improve SCLC patient outcome. In a Phase 1/3 study evaluating atezolizumab plus carboplatin–etoposide in the first line, 403 patients with extensive SCLC, good performance status, measurable disease and no prior systemic therapy were randomly assigned 1:1 to receive carboplatin–etoposide for four cycles with or without atezolizumab.<sup>19</sup> The immunotherapy was maintained until disease progression or unacceptable toxicity. Both PFS and OS improved in the investigational group, with a median OS of 12.3 *versus* 10.3 months for atezolizumab plus carboplatin–etoposide and carboplatin–etoposide alone, respectively (HR: 0.70;  $p=0.0069$ ). The 1-year OS was 51.7% *versus* 38.2%, respectively. In a subgroup analysis of OS, In this study, TMB tested using a blood-based assay, did not modify the favorable effect of atezolizumab. This result may be considered a step forward after three decades of unchanged standard therapy for extensive SCLC. Similarly, durvalumab ± tremelimumab in combination with platinum-based chemotherapy in untreated extensive SCLC is being tested in a phase 3 study (clinicaltrials.gov identifier: NCT03043872).

Whether chemo-naïve patients is a more favorable setting for IPCI efficacy than refractory SCLC, is unknown, but, the synergistic effect of IPCI plus chemotherapy as already suggest in other malignancies might have contributed to the final results of IMpower 133. One could speculate that the unfavorable PFS observed was due to rapid disease progression in patients in whom atezolizumab was inactive. Whether or not chemotherapy plus atezolizumab could overcome this phenomenon remains to be established. Interestingly, several patients in our study had sustained disease control. PD-L1 expression on tumor cells or tumor-infiltrating immune cells did not differ in this subgroup. Next-generation sequencing on tissue- and cell-free DNA extractions is ongoing using base-position error rate analysis. An attempt at identifying gene alterations predictive of atezolizumab-induced disease control is in progress and will be submitted separately.

The main limitation of our study might belong to the choice of ORR as the primary endpoint. It has been reported that there is a frequent lack of consistency between ORR and OS in

ICI trials. Nevertheless, in the setting of early evaluation of atezolizumab in recurrent SCLC we have considered ORR at 6 weeks as a reasonable endpoint for a phase 2, taking into account the lack of knowledge of ICI activity in this setting at time when we designed this study. ORR was chosen in an attempt to detect a signal, as early as possible in the course of the study in order to avoid continuation of an inactive treatment in patients who experienced early progression.

In conclusion, the IFCT-1603 trial failed to demonstrate a significant efficacy signal for single-agent atezolizumab as treatment for relapsed SCLC, with no unexpected safety signal observed. Some patients receiving atezolizumab exhibited sustained disease control. PD-L1 expression did not differ in this subgroup. A genotype analysis of available tumor specimens from these patients is in progress.

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## Figure Captions

**Figure 1.** CONSORT diagram of the phase 2 clinical trial to evaluate atezolizumab as second-line therapy in patients with small cell lung cancer.

**Figure 2.** Survival analysis of the phase 2 clinical trial to evaluate atezolizumab as second-line therapy in patients with small cell lung cancer. Median survival was estimated by Kaplan-Meier analysis stratified for intention to treat and unstratified for subgroups. (A) Kaplan-Meier estimates of progression-free survival from date of random allocation. (B) Kaplan-Meier estimates of overall survival from date of random allocation. (C) Exploratory subgroup analyses of unstratified HRs of overall survival. PFS, progression-free survival; CI, confidence interval; HR, hazard ratio; OS, overall survival; PS, performance status.

**Figure 3.** Percentage of patients with lower Lung Cancer Symptom Scale score at Week 6 for small cell lung cancer patients in second-line therapy randomly assigned to atezolizumab or chemotherapy.

**Supplemental Figure 1.** Kaplan-Meier estimate of (a) progression-free survival and (b) overall survival for the entire patient population with available tumor specimens according to SP142 PD-L1 tumor-infiltrating immune cell score. Overall survival estimates showed no statistical relationship between PD-L1 tumor-infiltrating immune cell score positivity and treatment group ( $p=0.68$ ). PFS, progression-free survival; CI, confidence interval.



Fig. 1

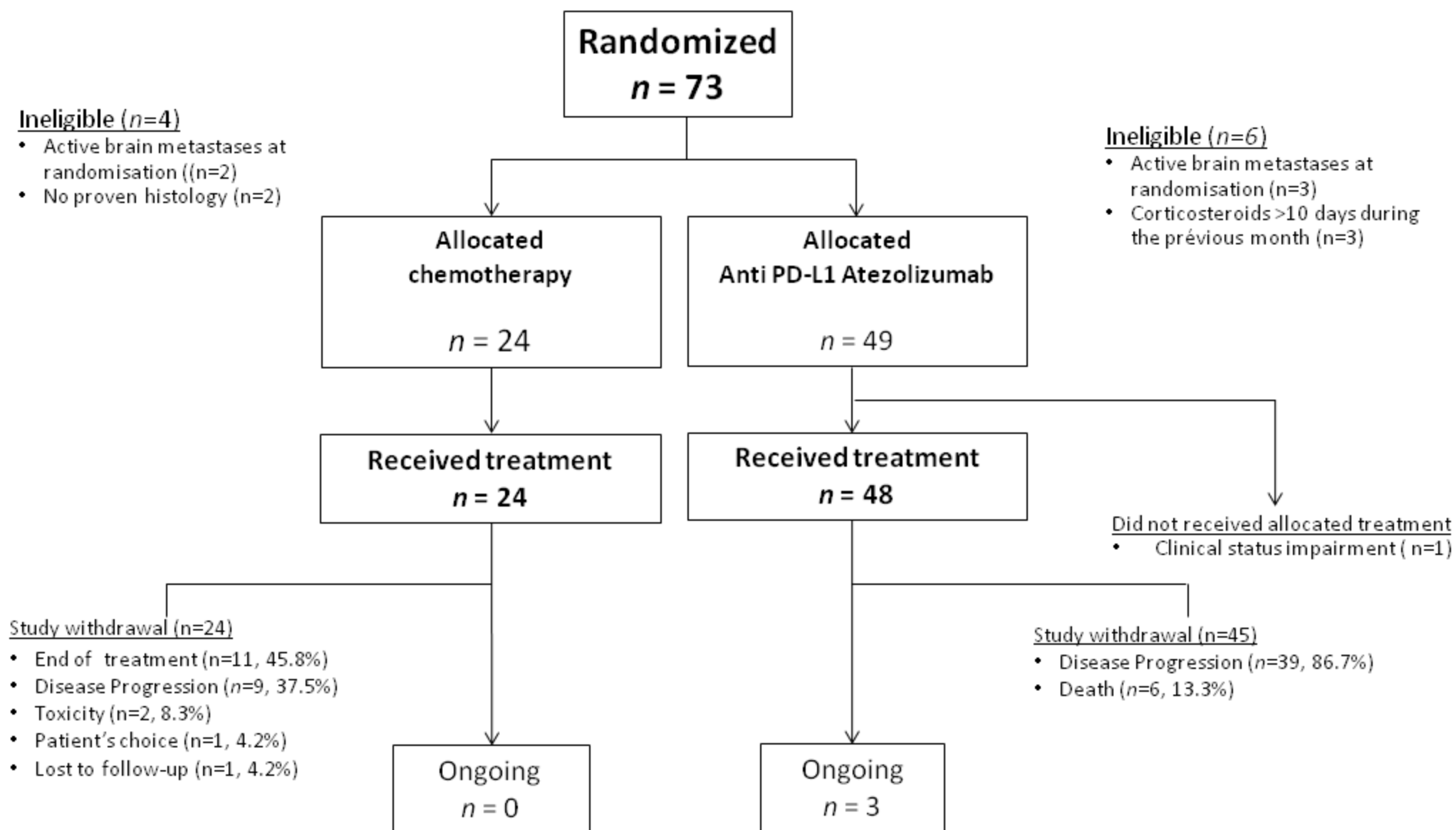


Fig. 2a

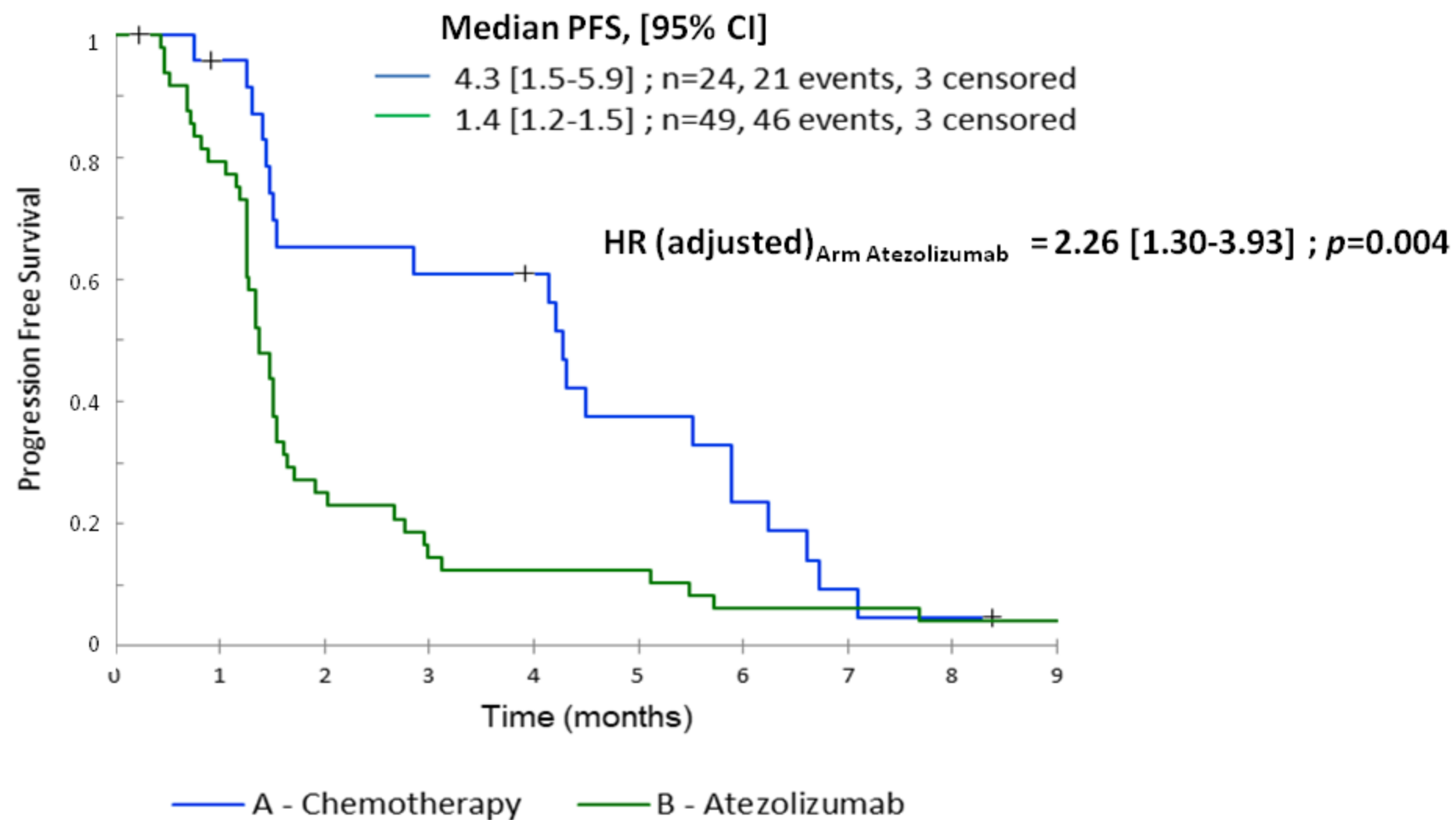


Fig. 2b

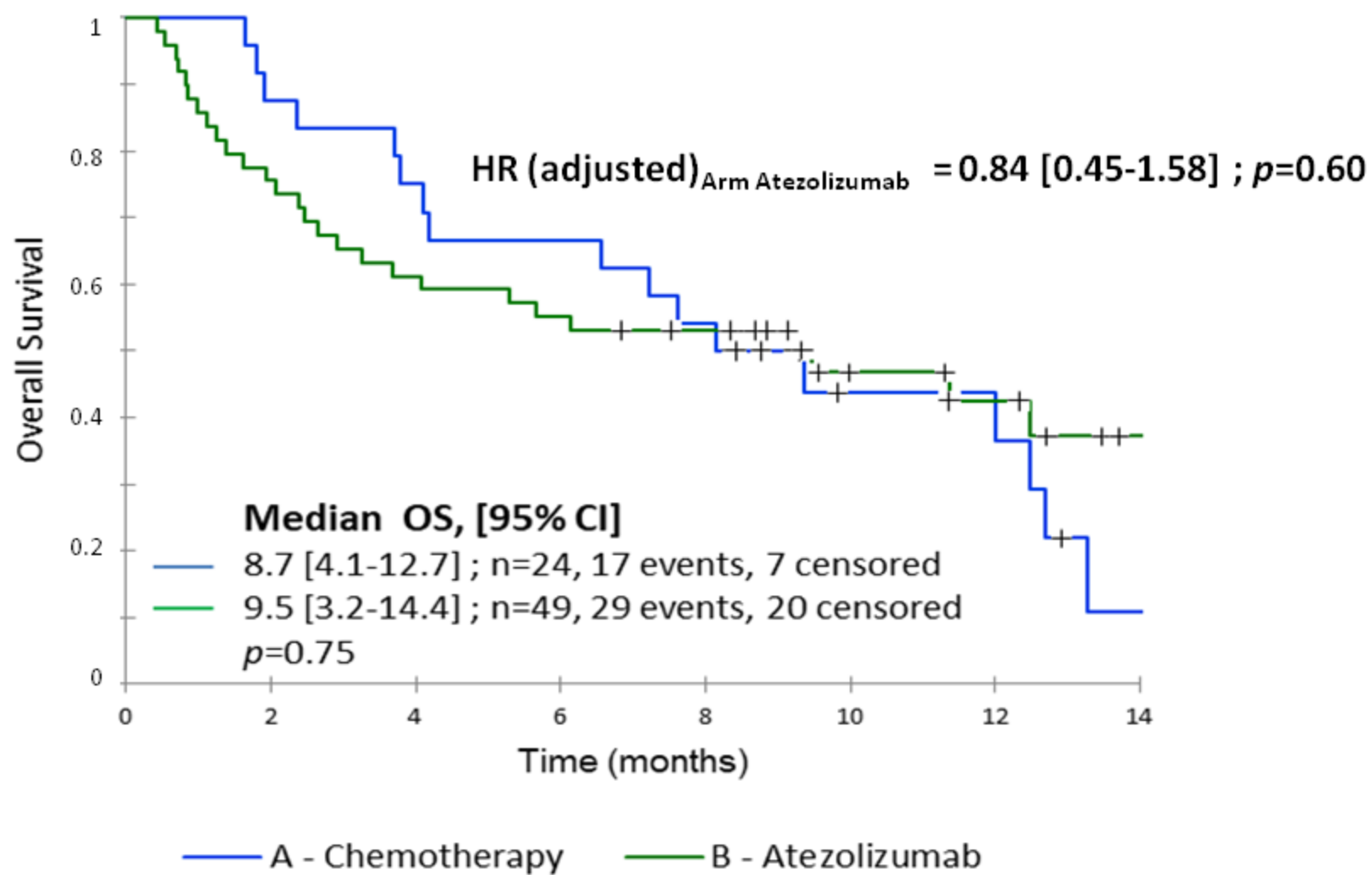


Fig. 2c

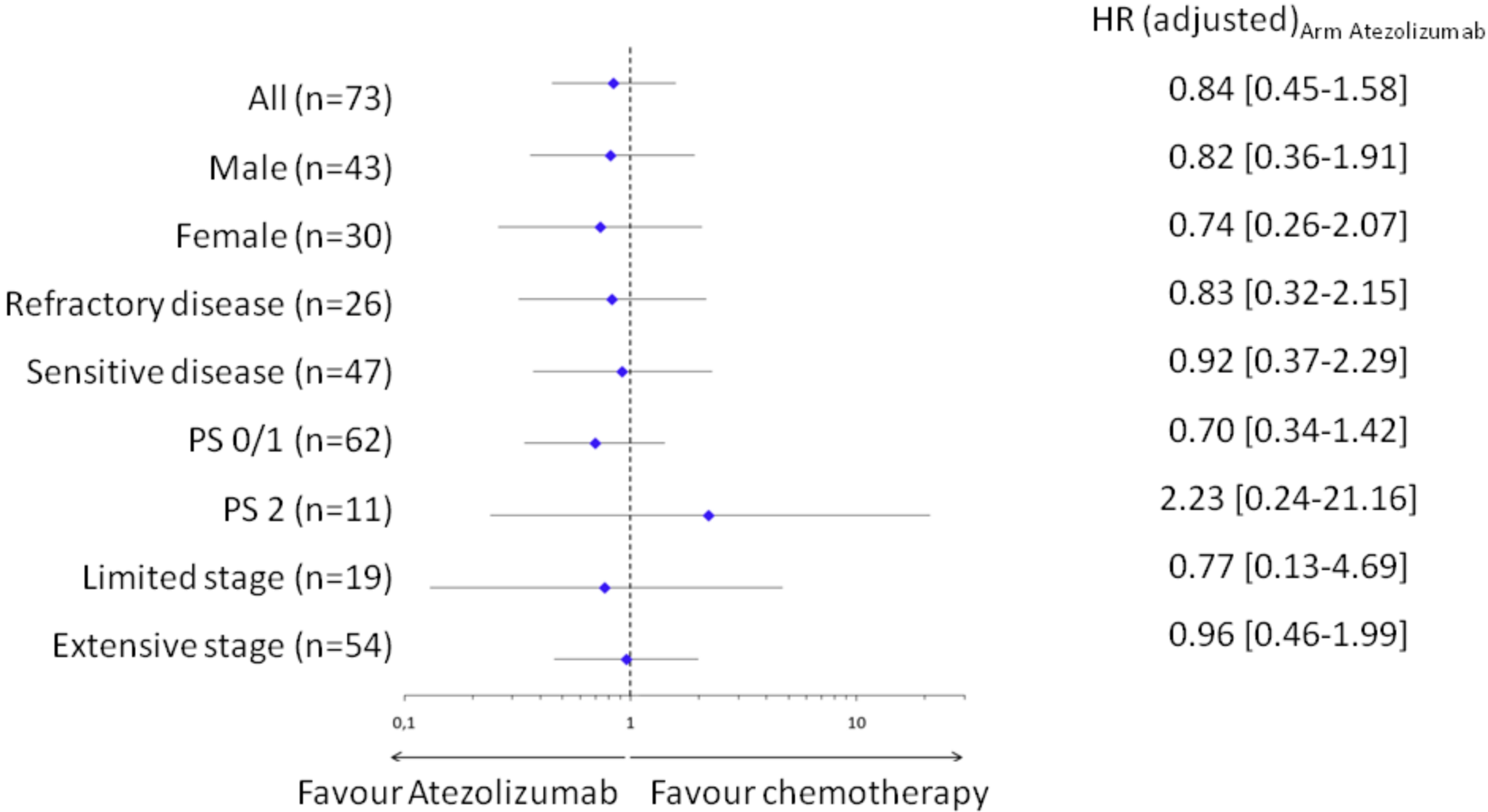
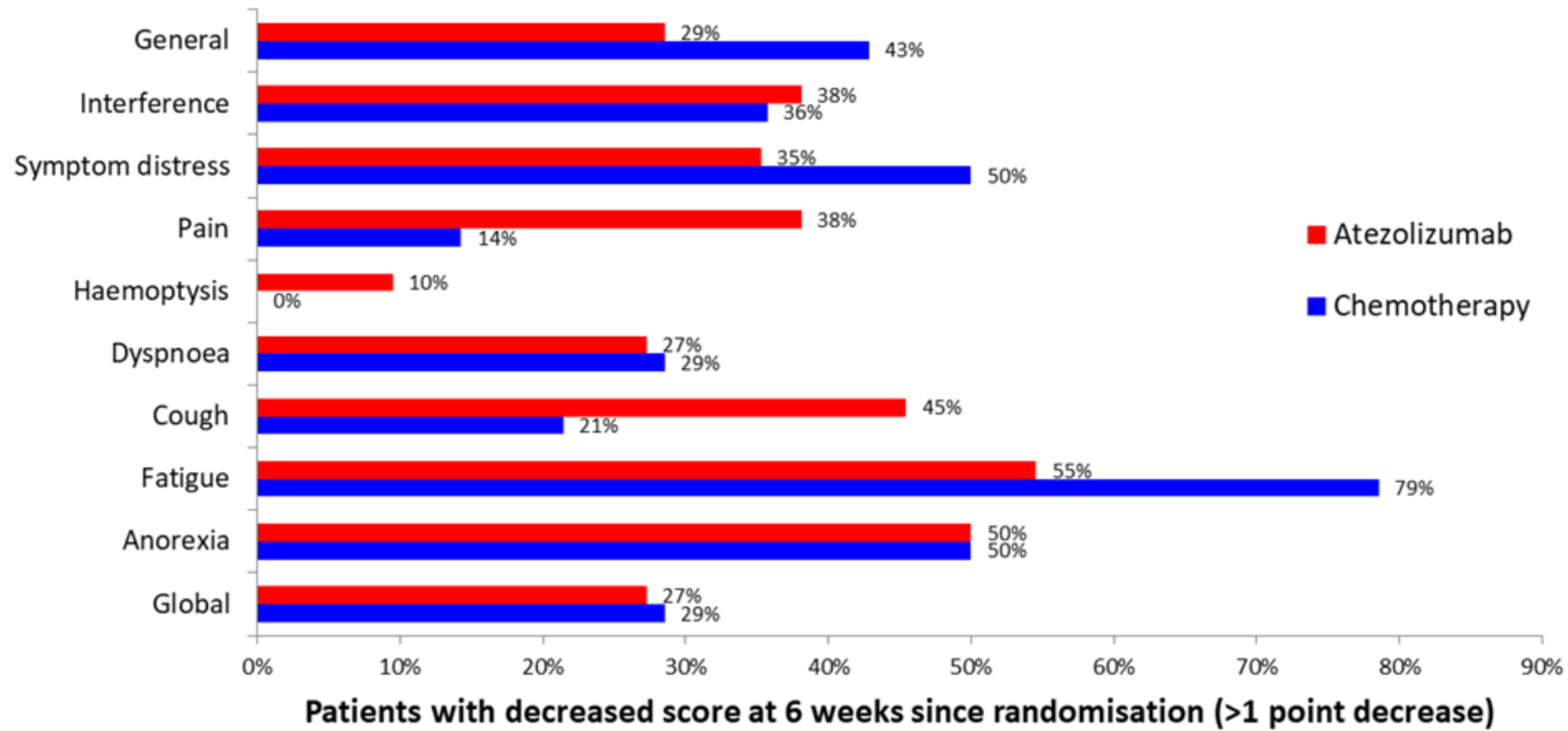


Fig. 3



## Tables

**Table 1.** Comparison of Demographic and Disease Characteristics at Time of Randomization for Small Cell Lung Cancer Patients in Second-Line Therapy Randomly Assigned to Atezolizumab or Chemotherapy

Descriptive Statistics			A - Chemotherapy (N=24)	B - Atezolizumab (N=49)	Total (N=73)	p-value
Gender	Female	N '(%)	11 (45.8)	19 (38.8)	30 (41.1)	0.56
Age (years)		Median	63.5	65.9	64.7	0.15
		Range	[51.8-81.0]	[51.1-85.5]	[51.1-85.5]	
Performance status	0-1	N '(%)	21 (87.5)	41 (83.7)	62 (84.9)	1.00
	2	N '(%)	3 (12.5)	8 (16.3)	11 (15.1)	
Stage at time of random allocation	Extensive	N '(%)	15 (62.5)	39 (79.6)	54 (74.0)	0.12
Relapse status*	Refractory disease	N '(%)	10 (41.7)	16 (32.7)	26 (35.6)	0.45
	Sensitive disease	N '(%)	14 (58.3)	33 (67.3)	47 (64.4)	
Smoker (current or former)	Yes	N '(%)	23 (95.8)	47 (95.9)	70 (95.9)	1

\* Sensitive disease defined as progression 90 days after last dose of first-line chemotherapy; otherwise, refractory.

**Table 2.** RECIST Response Evaluation at Week 6 for Eligible Patients with Small Cell Lung Cancer in Second-Line Therapy Randomly Assigned to Atezolizumab or Chemotherapy

Descriptive Statistics			Chemotherapy (N=20)	Atezolizumab (N=43)	Total (N=64)
Objective response at 6 weeks	Objective response	N (%)	2 (10)	1 (2.3)	3 (4.8)
	Objective response	95% CI	[0.0; 23.1]	[0.0; 6.8]	[0.0; 9.9]
Disease control rate at 6 weeks	DCR	N (%)	13 (65)	9 (20.9)	22 (34.9)
	DCR	95% CI	[44.1; 85.9]	[8.8; 33.1]	[23.1; 46.7]
	Progression	N (%)	6 (30)	30 (69.8)	36 (57.1)
	Progression	95% CI	[9.9; 50.1]	[56.0; 83.5]	[44.9; 69.4]
	Not Done/Not Evaluable	N (%)	1 (5.0)	4 (9.3)	5 (7.9)
	Not Done/Not Evaluable	95% CI	[0.0; 14.6]	[0.6; 18.0]	[1.3; 14.6]

**Table 3.** Summary of Adverse Events in the Safety Population of Eligible Patients with Small Cell Lung Cancer in Second-Line Therapy Randomly Assigned to Atezolizumab or Chemotherapy

Descriptive Statistics			A - Chemotherapy (N=24)	B - Atezolizumab (N=48)
Fatigue	All grades	N (%)	13 (54.2)	8 (16.7)
	Grade 3	N (%)	2 (8.3)	2 (4.2)
Nausea	All grades	N (%)	11 (45.8)	5 (10.4)
	Grades 3-4	N (%)	1 (4.2)	0
Colitis	All grades	N (%)	0	2 (4.2)
	Grades 3-4	N (%)	0	0
Diarrhea	All grades	N (%)	3 (12.5)	2 (4.2)
	Grades 3-4	N (%)	0	0
Decreased appetite	All grades	N (%)	6 (25)	4 (8.3)
	Grades 3-4	N (%)	0	0
Pruritus	All grades	N (%)	2 (8.3)	3 (6.3)
	Grades 3-4	N (%)	0	0
Arthralgia	All grades	N (%)	1 (4.2)	3 (6.3)
	Grades 3-4	N (%)	0	0
Dysthyroidism	All grades	N (%)	0	2 (4.2)
	Grades 3-4	N (%)	0	0
Chronic kidney disease	All grades	N (%)	0	1 (2.1)
	Grades 3-4	N (%)	0	0
Anemia	All grades	N (%)	18 (75)	5 (10.4)
	Grades 3-4	N (%)	7 (29.2)	0
Thrombocytopenia	All grades	N (%)	12 (50)	3 (6.3)
	Grades 3-4	N (%)	8 (33.3)	0