Nivolumab plus ipilimumab versus carboplatin-based doublet as first-line treatment for patients with advanced non-small-cell lung cancer aged ≥70 years or with an ECOG performance status of 2 (GFPC 08–2015 ENERGY): a randomised, open-label, phase 3 study

*Hervé Léna, Laurent Greillier, Claire Cropet, Olivier Bylicki, Isabelle Monnet, Clarisse Audigier-Valette, Lionel Falchero, Alain Vergnenègre, Pierre Demontrond, Margaux Geier, Florian Guisier, Stéphane Hominal, Chrystèle Locher, Romain Corre, Christos Chouaid, Charles Ricordel, for the GFPC 08–2015 ENERGY investigators**

Summary

Background Combined treatment with anti-PD-1 and anti-CTLA-4 antibodies has shown superiority over chemotherapy in patients with advanced non-small-cell lung cancer (NSCLC), but data for older patients (aged ≥70 years) with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 or those with an ECOG performance status of 2 are scarce. We aimed to test the superiority of the PD-1 antibody nivolumab and the CTLA-4 antibody ipilimumab over platinum-based doublet chemotherapy as first-line treatment in patients with NSCLC aged 70 years or older or with an ECOG performance status of 2.

Methods This open-label, multicentre, randomised, controlled, phase 3 trial was done at 30 hospitals and cancer centres in France. Eligible patients had stage IV histologically proven NSCLC, with no known oncogenic alterations, and were either aged 70 years or older with ECOG performance status of 0–2 or younger than 70 years with an ECOG performance status of 2. Patients were randomly assigned (1:1) centrally, using a computer-generated algorithm stratified by age (<70 *vs* ≥70 years), ECOG performance status (0–1 *vs* 2), and histology (squamous *vs* non-squamous) to receive nivolumab plus ipilimumab or platinum-based doublet chemotherapy (carboplatin [area under the curve ≤700 mg] plus pemetrexed [500 mg/m² intravenous infusion every 3 weeks] or carboplatin [on day 1; area under the curve ≤700 mg] plus paclitaxel [90 mg/m² as intravenous infusion on days 1, 5, and 15, every 4 weeks]). The primary endpoint was overall survival; secondary endpoints included progression-free survival and safety. All efficacy analyses were performed in the intention-to-treat population, which included all randomly assigned patients. Safety was analysed in the safety analysis set, which included all randomly assigned patients who received at least one dose of study treatment and who had at least one safety follow-up. The trial is registered with ClinicalTrials.gov, NCT03351361.

Findings The trial was stopped early for futility on the basis of a pre-planned interim analysis after 33% of the expected events had occurred. Between Feb 12, 2018, and Dec 15, 2020, 217 patients were randomly assigned, of whom 216 patients were included in the final analysis, with 109 patients in the nivolumab plus ipilimumab group and 107 in the chemotherapy group; median age was 74 years (IQR 70–78). Median overall survival was 14·7 months (95% CI 8·0–19·7) in the nivolumab plus ipilimumab group and 9·9 months (7·7–12·3) in chemotherapy group (hazard ratio [HR] 0·85 [95% CI 0·62–1·16]). Among patients aged 70 years or older with an ECOG performance status of 0–1 (median age 76 years [IQR 73–79]), median overall survival was longer in the nivolumab plus ipilimumab group than the chemotherapy group: 22·6 months (95% CI 18·1–36·0) versus 11·8 months (8·9–20·5; HR 0·64 [95% CI 0·46–0·96]). Among patients with an ECOG performance status of 2 (median age 69 years [IQR 63–75]), median overall survival was 2·9 months (95% CI 1·4–4·8) in the nivolumab plus ipilimumab group versus 6·1 months (3·5–10·4) in the chemotherapy group (HR 1·32 [95% CI 0·82–2·11]). No new safety signals were reported. The most frequent grade 3 or worse adverse events were neutropenia (28 [27%] of 103 patients) in the chemotherapy group and endocrine disorders (five [5%] of 105 patients), cardiac disorders (ten [10%] patients), and gastrointestinal disorders (11 [11%] patients) in the nivolumab plus ipilimumab group.

Interpretation The study showed no benefit of nivolumab plus ipilimumab combination in the overall study population. As a result of early stopping, the trial was underpowered for primary and secondary endpoints; however, the finding of better survival with nivolumab plus ipilimumab compared with platinum doublet in the subgroup of older patients with NSCLC with an ECOG performance status of 0–1 warrants further study.

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*Investigators listed at the end of the Article

Service de Pneumologie, Centre Hospitalier Universitaire de Rennes, Université Rennes 1, INSERM, UMR_S 1242, Centre Eugène Marquis, Rennes, France (H Léna MD, C Ricordel MD); **Multidisciplinary Oncology and Therapeutic Innovations, Aix-Marseille University, APHM, INSERM, CNRS, CRCM, Hôpital Nord, Marseille, France** (Prof L Greillier MD); **Unité de Biostatistique-Direction de la Recherche et de l'Innovation, Centre Léon Bérard, Lyon, France** (C Cropet PhD); **Hôpital d'Instruction des Armées Desgenettes, Lyon, France** (Prof O Bylicki MD); **Service de Pneumologie, Centre Hospitalier Intercommunal Créteil, Créteil, France** (I Monnet MD, Prof C Chouaid MD); **Service de Pneumologie, Orientation Oncologique, Hôpital Sainte-Musse, Toulon, France** (C Audigier-Valette MD); **Service de Pneumologie et Cancérologie Thoracique, Hôpitaux Nord-Ouest, Villefranche sur Saône, France** (L Falchero MD); **Unité d'Oncologie Thoracique, Centre Hospitalier Universitaire Dupuytren, Limoges, France** (Prof A Vergnenègre MD); **Centre de Lutte Contre le Cancer François Baclesse, Caen, France** (P Demontrond MD); **Institut de**

Cancérologie et Imagerie, Hopital Cavale Blanche Centre Hospitalier Universitaire Brest, Brest, France (M Geier MD); **Service de Pneumologie, Centre Hospitalier Universitaire Rouen, Rouen, France** (Prof F Guisier MD); **Service de Pneumologie, Centre Hospitalier Annecy Genevois, Epagny Metz-Tessy, France** (S Hominal MD); **Service de Pneumologie, Grand Hôpital de l'Est Francilien (Meaux), Meaux, France** (C Locher MD); **Centre Hospitalier de Cornouaille, Service de Pneumologie, Quimper, France** (R Corre MD)

Correspondence to:
Dr Hervé Lena, Service de Pneumologie, Centre Hospitalier Universitaire de Rennes, Université Rennes 1, INSERM, UMR_S 1242, Centre Eugène Marquis, Rennes 35000, France
herve.lena@chu-rennes.fr

Introduction

Lung cancer is the leading cause of cancer-related deaths in high-income countries and 85% of lung cancer cases are non-small-cell lung cancer (NSCLC), which is diagnosed at the metastatic stage in the majority of patients.[1] Compared with chemotherapy, first-line immunotherapy-based regimens for the treatment of advanced NSCLC have demonstrated efficacy with regard to overall survival.[2] Consequently, with the exception of metastatic NSCLC harbouring targetable oncogenes, PD-1 or PD-L1 therapy is administered as first-line treatment in almost all patients.[3]

Nivolumab is a fully human PD-1 antibody that restores the antitumour function of T cells; ipilimumab is a fully human CTLA-4 antibody that induces de-novo antitumour T-cell response and increases memory T cells.[4–6] The combination of these two checkpoint inhibitors with complementary mechanisms of action has demonstrated an increase of long-term survival in patients with NSCLC. In the CheckMate 227 study, first-line treatment with nivolumab plus ipilimumab in patients with advanced NSCLC significantly improved progression-free survival in those with a high tumour mutational burden and significantly increased overall survival in patients with tumour PD-L1 expression compared with platinum doublet chemotherapy.[7–9] The safety of the combination of nivolumab plus ipilimumab in the CheckMate 227 study and in previous studies was considered to be manageable; most immune-mediated adverse events occurred within 6 months of treatment and were resolved with systemic corticosteroids.[9–11]

Most phase 3 trials include patients aged younger than 70 years with a preserved Eastern Cooperative Oncology Group (ECOG) performance status (ie, 0–1).[12–14] Extrapolating the results to patients with impaired ECOG performance status or to patients older than 70 years is difficult, since these two populations are substantially under-represented in clinical trials due to poor outcomes

Research in context

Evidence before this study

The standard of care for first-line treatment of advanced non-small-cell lung cancer (NSCLC) without targetable mutations has shifted since 2018 from chemotherapy to immunotherapy-based regimens. Nivolumab (PD-1 antibody) and ipilimumab (CTLA-4 antibody) are fully human antibodies that restore the antitumour function of T cells (nivolumab) and induce de-novo antitumour T-cell responses and increase memory T cells (ipilimumab). In the CheckMate 227 study, the combination of these two checkpoint inhibitors with complementary mechanisms of action demonstrated an increase in long-term survival compared with platinum doublet chemotherapy in patients with advanced NSCLC. Patients older than 70 years or patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 are under-represented in phase 3 comparative immune-oncological studies. The combination of nivolumab and ipilimumab could be a valid option for older patients with NSCLC or those with an ECOG performance status of 2. In the absence of comparative clinical studies, there is no evidence-based recommendation for these patient subgroups. Before this study, we searched PubMed from database inception to Oct 1, 2023, without language restrictions, for randomised studies using various combinations of the keywords "advanced non-small cell lung cancer", "first-line treatment", "platinum-based regimen", "nivolumab", and "ipilimumab". Our search on Oct 1, 2023, did not identify any randomised studies comparing the combination of nivolumab and ipilimumab with chemotherapy specifically in older patients or those with an ECOG performance status of 2.

Added value of this study

This study is the first randomised phase 3 trial to compare nivolumab plus ipilimumab versus carboplatin-based doublet chemotherapy as first-line treatment for advanced NSCLC in patients with an ECOG performance status of 2 or in those aged older than 70 years. In this study, the primary efficacy endpoint (overall survival) was not met. Results from the analysis of the subgroup of older patients (median 76 years [IQR 73–79]) with an ECOG performance status of 0–1 might suggest an improvement in overall survival, but the study was not powered for this outcome. Progression-free survival was numerically longer among patients given nivolumab plus ipilimumab than those given a carboplatin-based doublet, but the difference was not statistically significant. Despite the inclusion of an older population and people with a poor ECOG performance status, the safety profile of nivolumab plus ipilimumab combination was similar to that reported in the CheckMate 227 study. In patients with an ECOG performance status of 2, overall survival was numerically shorter in the nivolumab plus ipilimumab group (2·9 months *vs* 6·1 months for chemotherapy).

Implications of all the available evidence

This study shows that dedicated trials in older patients and those with an ECOG performance status of 2 are feasible. No significant benefit in overall survival was observed among patients with NSLC who received the nivolumab plus ipilimumab combination. A clinical signal of efficacy of this combination was observed in older patients with advanced NSCLC with an ECOG perfomance status of 0–1 and should be investigated in future studies. Nivolumab plus ipilimumab immunotherapy in the population with an ECOG performance status of 2 does not seem to be an option for future trials.

and high toxicity.[15–18] As a consequence, no specific evidence-based guidelines are available for older patients with NSCLC who are older than 70 years or those with an ECOG performance status of 2. The combination of nivolumab and ipilimumab could be a valid option for older patients with NSCLC or those with a poor ECOG performance status.

The aim of the GFPC 08–2015 ENERGY trial was to assess whether the combination of nivolumab plus ipilimumab was superior to platinum-based doublet chemotherapy as first-line treatment in patients with NSCLC who were older than 70 years or had an ECOG performance status of 2.

Methods

Study design and participants

GFPC 08–2015 ENERGY was an open-label, multicentre, randomised, controlled, phase 3 trial performed at 30 hospitals and cancer centres in France.

Eligible patients had cytologically or histologically proven NSCLC; had stage IV or non-treatable by radiotherapy disease, or surgery stage III (7th classification) disease; had received no previous systemic chemotherapy for lung cancer, with the exception of relapse after adjuvant treatment for localised disease with 6 months or longer between the end of previous chemotherapy and relapse; were aged younger than 70 years with an ECOG performance status of 2 or aged 70 years or older with an ECOG performance status of 0, 1 or 2; were considered fit enough to receive a carboplatin-based doublet according to European Society for Medical Oncology guidelines;[19] had at least one measurable target lesion (Response Evaluation Criteria in Solid Tumours [RECIST] version 1·1[20]) in a non-irradiated region that was analysable by CT; had life expectancy of at least 12 weeks; had received previous radiation therapy (ie, authorised by study investigators if it involved less than 25% of the total bone marrow volume and finished 14 days before day 1 of planned treatment); had a white blood cell count of at least 2×10^9 cells per L, a neutrophil count of at least $1{\cdot}5\times10^9$ cells per L, a platelet count of at least 100×10^9 cells per L; haemoglobin higher than 10 g/dL, serum creatinine of 1·5 times the upper limit of normal (ULN) or less or creatinine clearance of 45 mL/min or greater (Cockcroft-Gault formula), transaminase concentrations of 3 times the ULN or less, and total bilirubin of 1·5 times the ULN or less; and had adequate formaldehyde-fixed paraffin-embedded tumour tissues available for PD-L1 testing, but PD-L1 analysis results were not mandatory before inclusion.

Patients with the following were excluded from study participation: other severe concurrent disorders that occurred in the 6 months before enrolment; serious or uncontrolled systemic disease; other previous or concomitant cancer; known activating mutation of *EGFR* (exon 19 deletion, mutation Leu858Arg or Leu861Ter in exon 21, mutation Gly719Ala/Ser in exon 18) or *EML4-ALK* or *ROS-1* translocation; active brain metastases or leptomeningeal metastases (unless metastases had been treated and there was no evidence of progression); active, known, or suspected autoimmune disease; and systemic treatment with steroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study drug administration. Full inclusion and exclusion criteria are available in the study protocol (appendix p 8). Ethnicity data were not collected as per French law.

See Online for appendix

The study was conducted in accordance with the CONSORT 2010 statement[21] and the Declaration of Helsinki, and was approved by a local independent ethics committee (approved on Sept 28, 2017, by the Committee for the Protection of Persons "Sud-Ouest et Outre-Mer IV Limoges"; CPP17062a-PP). Written informed consent was obtained from each patient. The trial is registered with ClinicalTrials.gov, NCT03351361.

Randomisation and masking

Patients were randomly assigned (1:1) to receive nivolumab plus ipilimumab or chemotherapy. Randomisation was done centrally using a computer-generated algorithm, stratified by age (<70 *vs* ≥ 70 years), ECOG performance status (0–1 *vs* 2), and tumour histology (squamous *vs* non-squamous). Patients, treating physicians, study investigators, and data analysts were aware of treatment allocation.

Procedures

Patients randomly assigned to the nivolumab plus ipilimumab (immunotherapy) group received 240 mg nivolumab as an intravenous infusion over 30 min every 2 weeks and 1 mg per kg bodyweight ipilimumab as an intravenous infusion over 30 min every 6 weeks until progression, unacceptable toxicity, withdrawal of consent, or study end, whichever occurred first. Nivolumab and ipilimumab could be continued after disease progression according to RECIST (version 1.1), if the investigator deemed that there was a clinical benefit.

For patients randomly assigned to the standard of care carboplatin-based doublet (chemotherapy) control group, the investigator declared before randomisation which chemotherapy treatment had been chosen at the choice of the investigator. Patients received either: carboplatin (area under the curve [AUC] 5, not exceeding 700 mg) and 500 mg/m² pemetrexed as an intravenous infusion for 4–6 h every 3 weeks (restricted to patients with non-squamous histology), with the option of maintenance with 500 mg/m² pemetrexed; or carboplatin (AUC 6, not exceeding 700 mg) on day 1 and 90 mg/m² paclitaxel on days 1, 5, and 15 as an intravenous infusion for 4–6 h every 4 weeks, with the option of maintenance with pemetrexed for a maximum of four cycles of carboplatin-based doublet permitted for both regimens.

Patients in the nivolumab plus ipilimumab group who did not discontinue due to progression or toxicity were

treated for up to 2 years. In case of subsequent progression, a rechallenge with an additional 1 year of treatment with nivolumab plus ipilimumab was proposed. For patients treated with carboplatin-based doublet chemotherapy, after progression, a second-line therapy was proposed according to standard of care.

At the screening visit (within 28 days before treatment), demographics, medical history, concomitant medications, vital signs, physical measurements (height, weight, and ECOG performance status), and oxygen saturation were recorded, an electrocardiogram was performed, and testing for hepatitis B and C, HIV, and cytomegalovirus was done.

Complete blood count, serum chemistry tests, and liver function tests were performed at the screening visit and within 72 h before dosing. Endocrine tests (thyroid-stimulating hormone, free thryoxine, and free triiodothyronine) were performed every 6 weeks (every three cycles) for patients in the nivolumab plus ipilimumab group because thyroid adverse events are specific to nivolumab and ipilimumab. Oxygen saturation by pulse oximetry at rest was performed within 72 h of dosing and at any time a patient had new or worsening respiratory signs or symptoms consistent with possible lung-related adverse events.

Tumour response was assessed within 28 days before treatment initiation and repeated every 6 weeks (chest abdomen CT scan, PET scan, or bone scan if suspicion of bone disease, and brain or MRI if clinically indicated) and best response to treatment was assessed according to RECIST (version 1.1) criteria.[20] The efficacy evaluation committee reviewed all available tumour assessment scans to determine response (RECIST version 1.1). Collection of survival information (by phone contact or office visit) was performed every 3 months until death, loss to follow-up, or withdrawal of consent.

Adverse events and serious adverse events were assessed using common toxicity scales of the National Cancer Institute (NCI)–Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) before every infusion of treatment. Adverse events and serious adverse events were recorded up to 100 days after last dosing. Adverse events were adjudicated by a central independent committee.

Outcomes

The primary endpoint was overall survival, defined as the time from the date of randomisation until death due to any cause. Any patient whose death was not known at the time of analysis was censored on the basis of the last recorded date on which the patient was known to be alive.

Secondary endpoints were survival rate at 1 year, objective response rate (ORR), progression-free survival, safety, and PD-L1 expression by immunochemistry as a predictive factor of overall survival and progression-free survival. ORR was defined as the rate of patients with an observed tumour response (complete response or partial response) as best response observed during the study treatment period and evaluated according to RECIST (version 1.1). Patients whose tumours were not evaluated after the beginning of study treatment and who did not die of neoplastic causes were considered non-evaluable. Progression-free survival was defined as the time from randomisation until the date of the first progression according to RECIST (version 1.1) or death (by any cause in the absence of progression). Patients who had not progressed or had died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST assessment. The first progression assessment was based on investigator-recorded assessments or on central review of the radiological scans. The assessment of safety rested on the frequency and severity of adverse events based on the Common Toxicity Criteria grade (NCI–CTCAE version 4.0).

Additional secondary endpoints were quality of life, assessed using EQ-5D and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ)-ELD14 questionnaires, and a Geriatric minimum dataset, restricted to patients aged 70 years or older to explore the predictive impact on overall survival and progression-free survival in patients older than 70 years. Geriatric outcomes will be published elsewhere.

Statistical analysis

The study was powered to detect a treatment effect hazard ratio (HR) of 0·65, translating to an improvement in 1-year overall survival rate from 40% (chemotherapy group) to 55% (immunotherapy group). We calculated that 199 events observed at the time of the final analysis would have 85% power to show a statistically significant difference at a two-sided α level of 0·05 (log-rank test). Considering a recruitment duration of 24 months and an 18-month follow-up for the last included patient (estimated total duration of the study 42 months), 242 patients were required for randomisation (121 in each group).

Overall survival and progression-free survival were estimated using the Kaplan-Meier method and were compared between groups at a two-sided significance level of 0·05 (using a log-rank test stratified on randomisation strata). These results were supported by a Cox regression stratified on randomisation strata to estimate the HR comparing the two treatment groups, provided the proportional hazards assumption was fulfilled. Overall survival and progression-free survival were analysed according to stratification factors: age (<70 years *vs* ≥70 years), ECOG performance status (0–1 *vs* 2), and histology (squamous *vs* non-squamous). ORR rates are presented with the associated 95% CIs. The assessment of safety was based mainly on the description of adverse events based on system organ class and preferred term classifications and description adverse events of special interest (selected based on the mechanism of action of

ipilimumab and nivolumab). In an exploratory post-hoc analysis, we evaluated the efficacy of the combination of nivolumab plus ipilimumab in patients aged 75 years and older.

All efficacy analyses were performed in the intention-to-treat population, which included all randomly assigned patients. Safety was analysed in the safety analysis set, which included all randomly assigned patients who received at least one dose of study treatment and who had at least one safety follow-up, regardless of whether they withdrew from the study prematurely.

During the trial, a planned interim analysis for futility was performed, permitting early cessation of the trial if insufficient evidence of efficacy was shown. This analysis was done after 33% of the expected overall survival events had occurred. No adjustment for type I error was required for this futility analysis. Stopping boundaries were defined according to Lan-DeMets spending function to control type II error (HR for futility 1·059 based on the proportion of events observed at the time of the interim analysis). Sample size calculation and interim analysis planning were performed using East software (version 6.3.1; Cytel, Cambridge, MA, USA).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 12, 2018, and Dec 15, 2020, 217 patients were enrolled in the study. The pre-planned interim analysis for futility was performed on Dec 15, 2019, after 174 patients had been randomly assigned and 66 events (deaths) had occurred (74 of 88 patients in the immunotherapy group and 38 of 86 in the control group). The analysis showed a risk of futility for the experimental treatment (inefficacy boundaries met) especially for patients with an ECOG performance status of 2 (HR 1·8 [95% CI 0·99–3·3]). Considering the poor efficacy in patients with an ECOG performance status of 2, on Dec 15, 2019, the data monitoring committee recommended that recruitment was stopped, at which time 217 patients had been randomly assigned; figure 1). The final analysis was performed on Dec 15, 2021, 18 months after the last patient was randomly assigned in the intention-to-treat population, which included 216 patients (n=109 in the nivolumab plus ipilimumab group and n=107 in the chemotherapy group); one patient who was randomly assigned in the chemotherapy group was excluded from the final analysis because the patient was under legal protection (guardianship).

156 (71%) of 216 patients were men and 60 (29%) were women, the median age was 74 years (IQR 70–78), and 170 (79%) patients were older than 70 years (table 1). 56 (26%) of 216 patients had an ECOG performance status of 0, 81 (38%) patients had an ECOG performance status of 1, and 79 (37%) patients had an ECOG performance status of 2; 34 (43%) of the 79 patients with an ECOG status of 2 were aged 70 years or older. Most patients were smokers or former smokers (194 [90%] of 216 patients). The majority had a non-squamous histology (148 [69%] of 216 patients). 199 (92%) of 216 patients had stage IV disease; metastases were most frequently located in the lungs (92 [43%] patients) or bone (88 [41%]). Data on PD-L1 expression were available for 202 (94%) of 216 patients; 114 (56%) patients were classified as PD-L1 negative and 77 (38%) had intermediate PD-L1 expression (1–49%). 11 (5%) of 202 patients had PD-L1 expression higher than 50%.

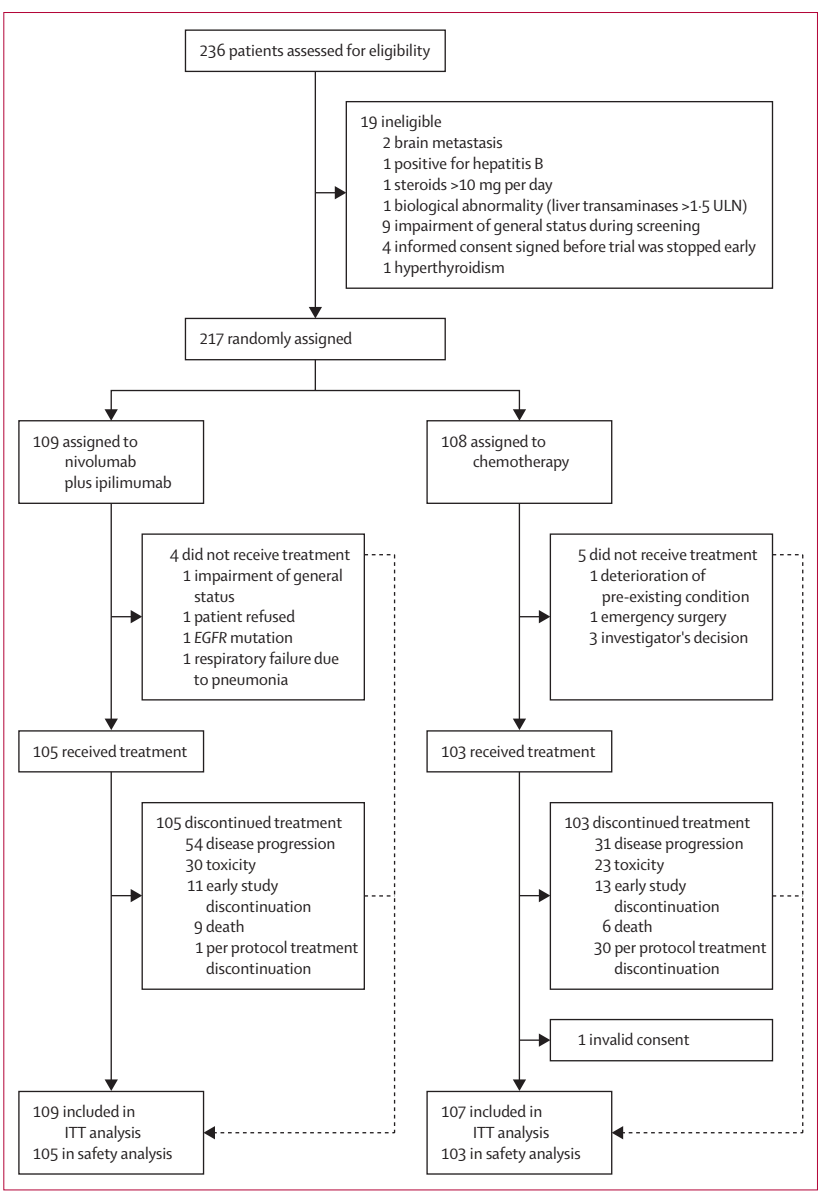

Figure 1: **Trial profile**
ULN=upper limit of normal. ITT=intention-to-treat.

	Nivolumab plus ipilimumab (n=109)	Chemotherapy (n=107)
Age, years		
Median (range)	74 (52–89)	74 (51–88)
≥70	85 (78%)	85 (79%)
Gender		
Men	74 (68%)	80 (75%)
Women	35 (38%)	27 (25%)
ECOG performance status		
0–1	70 (64%)	67 (63%)
2	39 (36%)	40 (37%)
Median age according to performance status, years (range)		
0–1	76 (70–89)	76 (70–88)
2	69 (52–85)	68 (51–83)
Smoking status		
Never smoker	13 (12%)	9 (8%)
Current or former smoker	96 (88%)	98 (92%)
Histology		
Non-squamous	74 (68%)	74 (69%)
Squamous	35 (32%)	33 (31%)
Metastases*		
Lung	54 (50%)	38 (36%)
Bone	41 (38%)	47 (44%)
Adrenal	27 (25%)	29 (27%)
Lymph nodes	28 (26%)	27 (25%)
Liver	16 (15%)	18 (17%)
Central nervous system	9 (8%)	8 (8%)
Other	23 (21%)	28 (26%)
Time between diagnosis and randomisation, months (mean [SD])	2·1 (4·1)	3·6 (1·5)
Tumour stage		
I–II	0	0
III	5 (5%)	12 (11%)
IV	104 (95%)	95 (89%)
Tumour PD-L1 expression,† %		
<1	61 (59%)	53 (54%)
1–49	40 (39%)	37 (38%)
≥50	3 (3%)	8 (8%)
Not available	5 (5%)	9 (8%)

Data are n (%), unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. *Patients could be included in more than one category. †Data for PD-L1 were available for 202 patients (101 patients in the nivolumab plus ipilimumab group and 98 patients in the chemotherapy group).

Table 1: **Baseline patient characteristics (intention-to-treat population)**

Regarding previous treatments, 18 (8%) of 216 patients had undergone lung resection, four (2%) of 216 patients had previous surgery for metastases, nine (4%) had thoracic radiotherapy, 19 (9%) had radiotherapy for metastases, and four (2%) had received adjuvant chemotherapy.

All treated patients (n=208) had stopped study treatment at the time of analysis (figure 1). Among the 208 treated patients, median duration of exposure to immunotherapy (n=105) was 2·8 months (IQR 1·3–6·5) for nivolumab and 2·9 months (IQR 1·0–7·0) for ipilimumab. 38 patients in the chemotherapy group received carboplatin and pemetrexed and 65 patients received carboplatin and paclitaxel. For chemotherapy, the median duration of exposure to carboplatin was 2·8 months (IQR 1·6–3·0) in the carboplatin plus pemetrexed group (n=38) and 3·7 months (IQR 1·8–3·8) in the carboplatin plus paclitaxel group (n=65); the median duration of exposure to pemetrexed was 2·9 months (IQR 1·6–4·8) and the median duration of exposure to paclitaxel was 3·1 months (IQR 1·4–3·7).

At the time of analysis, 11 (10%) of 109 patients in the nivolumab plus ipilimumab group had discontinued the study prematurely (n=1 withdrew consent; n=2 investigator's decision; n=8 other reason) and 13 (12%) of 107 patients in the chemotherapy group had discontinued the study prematurely (n=1 started another treatment; n=3 investigator's decision; n=9 other reason). All violations to eligibility criteria and protocol deviation during the study were discussed during the blind review meeting, which took place every 6 months with all investigators or their representatives. There were no major protocol deviations, with the exception of one patient in the chemotherapy group for whom consent was invalid because they were under legal protection, and thus they were excluded from all analysis populations.

In assessment for the primary efficacy outcome, median follow-up for overall survival was 27·1 months (IQR 24·0–33·3) in the nivolumab plus ipilimumab group and 28·0 months (23·5–38·0) in the chemotherapy group. 165 deaths were observed (78 in the nivolumab plus ipilimumab group *vs* 87 in the chemotherapy group) at the time of the final analysis. The median overall survival was 14·7 months (95% CI 8·0–19·7) in the nivolumab plus ipilimumab group and 9·9 months (7·7–12·3; HR 0·85 [95% CI 0·62–1·16]; p=0·298) in the chemotherapy group (figure 2).

The 1-year overall survival rate was 55·0% (95% CI 45·2–63·8; 60 of 109 patients) in the nivolumab plus ipilimumab group versus 42·0% (32·5–51·2; 45 of 107 patients) in the chemotherapy group, and the 2-year overall survival rate was 36·6% (27·5–45·7; 40 of 106 patients) versus 21·7% (14·3–30·0; 23 of 107 patients). Subgroup analysis according to the stratification factor of ECOG performance status of 0–1 (median age 76 years [IQR 73–79]) showed a significant benefit of nivolumab plus ipilimumab compared with chemotherapy in this older cohort: median overall survival was 22·6 months (95% CI 18·1–36·0) in the nivolumab plus ipilimumab group versus 11·8 months (8·9–20·5) in the chemotherapy group (HR 0·64 [95% CI 0·46–0·96]; figure 3). In patients with an ECOG performance status of 2 (median age 69 years [IQR 63–75]), median overall survival was 2·9 months (95% CI 1·4–4·8) in the nivolumab plus ipilimumab group versus 6·1 months (3·5–10·4) in the chemotherapy group (HR 1·32 [0·82–2·11]; figure 3).

No difference in overall survival was observed between groups when stratified by tumour histology (appendix p 4): median overall survival for patients with squamous histology was 12·4 months (95% CI 3·6–19·7) in the nivolumab plus ipilimumab group versus 11·1 months (6·0–21·3) in the chemotherapy group (HR 0·91 [95% CI 0·53–1·55]), and for patients with non-squamous histology, median overall survival was 16·2 months (5·2–24·6) in the nivolumab plus ipilimumab group versus 9·0 months (6·2–12·3) in the chemotherapy group (0·74 [0·51–1·08]).

No differences were identified in median overall survival between groups when stratified by age: in patients aged younger than 70 years, median overall survival was 4·1 months (95% CI 2·9–12·4) in the nivolumab plus ipilimumab group versus 6·1 months (3·5–14·2) in the chemotherapy group (HR 0·97 [95% CI 0·52–1·81]), and among patients aged 70 years or older, median overall survival was 18·5 months (12·0–24·6) in the nivolumab plus ipilimumab group versus 10·6 months (7·8–15·0) in the chemotherapy group (0·75 [0·53–1·07]). In a post-hoc exploratory analysis using an age cutoff of 75 years, the median overall survival of patients aged 75 years or older was 13·1 months (95% CI 4·9–19·7) in the nivolumab plus ipilimumab group versus 9·7 months (6·0–13·5) in the chemotherapy group (HR 0·89 [95% CI 0·54–1·26]), and in patients younger than 75 years, median overall survival was 18·2 months (4·8–36·0) in the nivolumab plus ipilimumab group versus 10·7 months (6·2–20·5) in the chemotherapy group (0·76 [0·48–1·19]; appendix p 5).

No differences in overall survival were observed in the nivolumab plus ipilimumab group versus the chemotherapy group when patients were stratified by levels of PD-L1 expression (appendix p 4).

Median progression-free survival was numerically longer in the nivolumab plus ipilimumab group than the chemotherapy group, but the difference was not significant (5·5 months [95% CI 2·8–8·7] *vs* 4·6 months [3·5–5·6]; HR 0·75 [95% CI 0·56–1·01]; p=0·061; figure 2B). Progression-free survival at 1 year was 31·9% (95% CI 23·3–40·9) in the nivolumab plus ipilimumab group and 10·9% (5·8–17·8) in the chemotherapy group.

The ORR was 38·1% (95% CI 28·5–48·6; 37 of 97 particiapnts) in the nivolumab plus ipilimumab group and 40·0% (30·3–50·3; 40 of 100 participants) in the chemotherapy group (table 2). No difference in progression-free survival was observed between groups when patients were stratified by PD-L1 expression (appendix p 4).

The safety profile of the nivolumab plus ipilimumab group was acceptable when compared with the chemotherapy group: 78 (74%) of 105 patients in the nivolumab plus ipilimumab group versus 92 (89%) of 103 patients in the chemotherapy group had at least one treatment-related adverse event, 33 (31%) patients versus 51 (50%) patients had at least one grade 3 or worse treatment-related adverse event, 57 (54%) patients versus 35 (34%) patients had at least one treatment-related adverse event that led to permanent discontinuation of any component of the regimen, and 41 (39%) patients versus 26 (25%) patients had at least one serious treatment-related adverse event (appendix p 1).

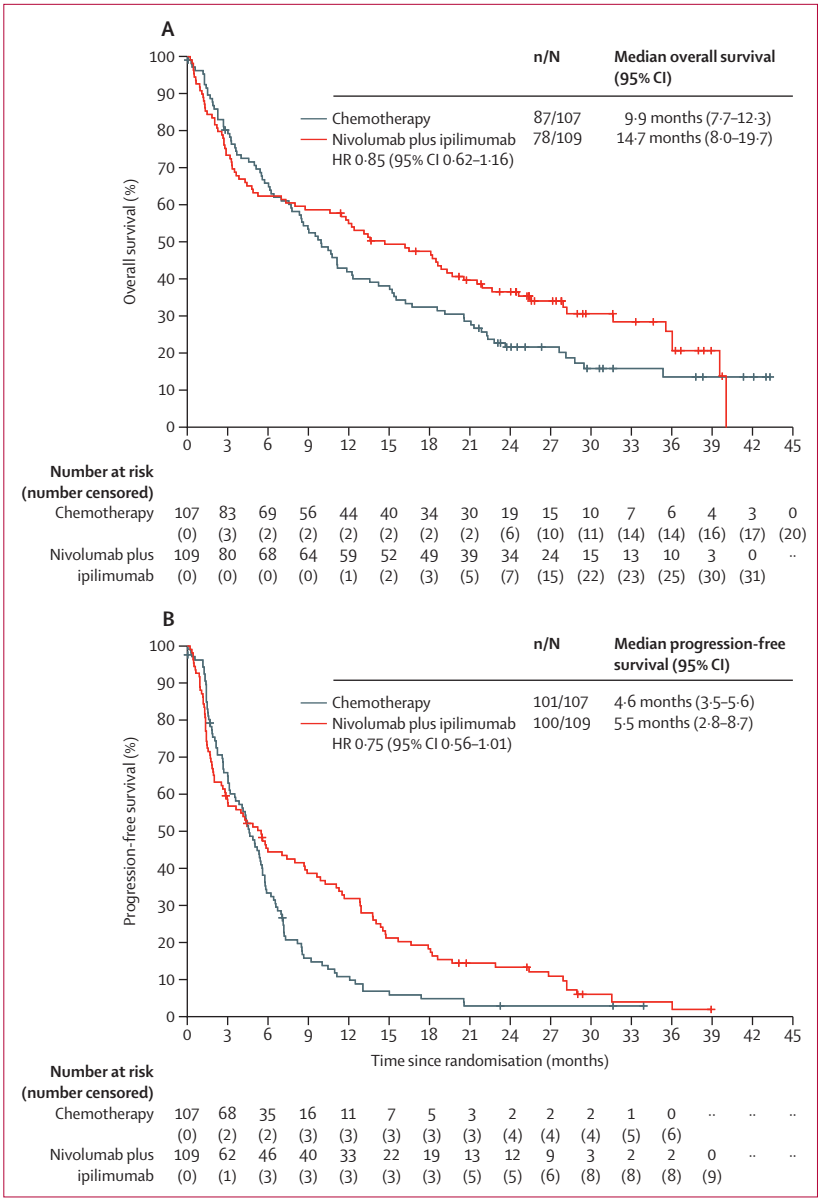

Figure 2: **Overall survival (A) and progression-free survival (B) in the intention-to-treat population**
Crosses indicate censoring. HR=hazard ratio. n=events. N=total number of participants.

The most frequent grade 3 or worse adverse events were neutropenia (28 [27%] of 103 patients) in the chemotherapy group and endocrine disorders (five [5%] of 105 patients), cardiac disorders (ten [10%] patients), and gastrointestinal disorders (11 [11%] patients) in the nivolumab plus ipilimumab group (table 3). At least one immune allergic adverse event was reported in 33 (31%) of 105 patients in the nivolumab plus ipilimumab group and none in the

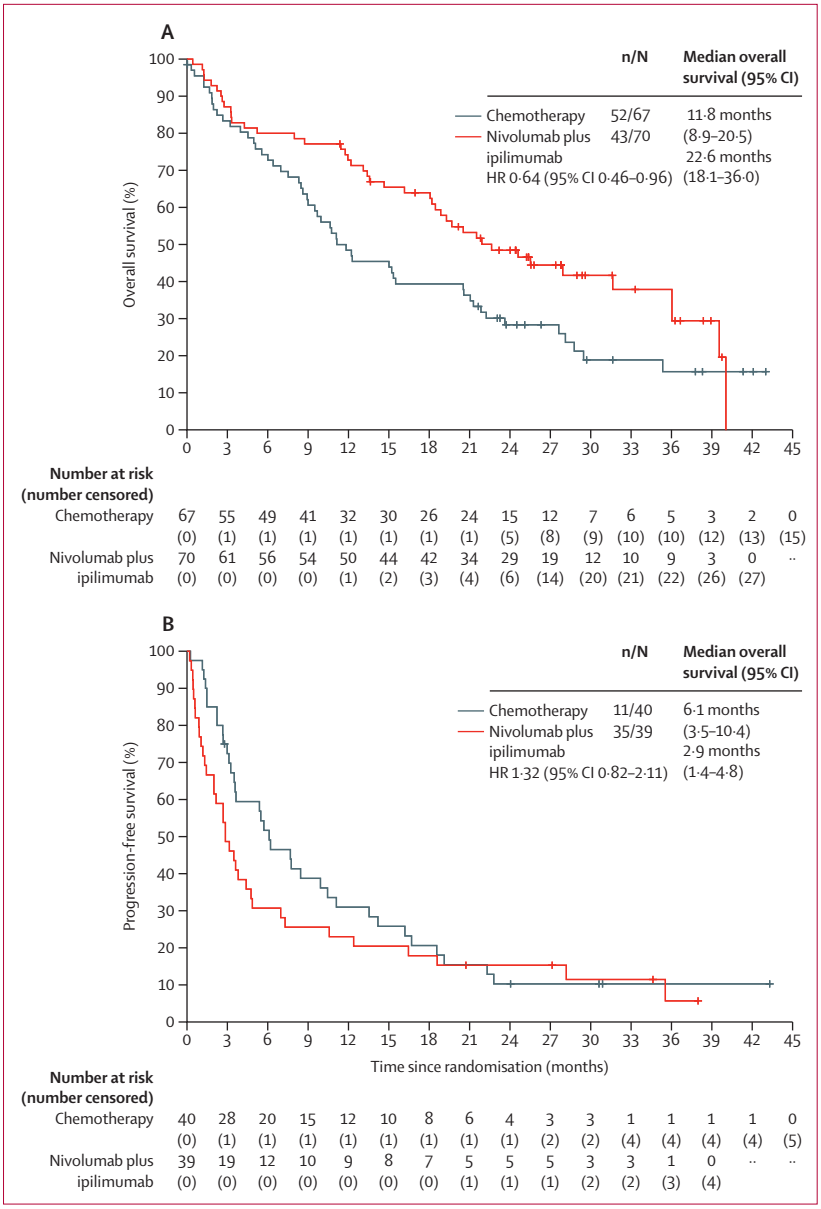

Figure 3: **Overall survival in patients with an ECOG performance status of 0–1 (A) and 2 (B)**
Crosses indicate censoring. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. n=events. N=total number of participants.

	Nivolumab plus ipilimumab (n=109)	Chemotherapy (n=107)
Best treatment response		
Complete	6 (6%)	1 (1%)
Partial	31 (32%)	39 (39%)
Stable	30 (31%)	36 (36%)
Progression	22 (23%)	16 (16%)
Death within 8 weeks after randomisation without tumour measurement	8 (7%)	8 (8%)
Not evaluable*	12 (11%)	7 (6%)
Objective response rate, n/N (%; 95% CI)	37/97 (38·1%; 28·5–48·6)	40/100 (40·0%; 30·3–50·3)

Data are n (%), unless otherwise specified. Best response was defined according to RECIST criteria (version 1.1). RECIST=Response Evaluation Criteria in Solid Tumours. *The 19 patients with missing best response had no tumour evaluation (two patients did not receive treatment and died of their disease; eight patients discontinued treatments due to toxicity within 2 months of randomisation; seven patients died of causes other than their disease during the first month of treatment; one patient withdrew from the study 1 month after randomisation due to infectious pneumonitis; one patient withdrew consent immediately after randomisation).

Table 2: **Best treatment response in the intention-to-treat population**

chemotherapy group; the most frequent immune-related adverse events were colitis (nine [9%] of 105 patients), autoimmune lung disease (eight [8%] patients), and hypothyroidism (seven [7%] patients; table 4). Among the 38 patients in the chemotherapy group who received carboplatin plus pemetrexed, ten (26%) patients required a carboplatin dose reduction and nine (23·6%) patients required a pemetrexed dose reduction due to a toxicity. Among the 65 patients in the chemotherapy group who received carboplatin plus paclitaxel, 22 (34%) patients required a carboplatin dose reduction and 26 (40%) required a paclitaxel dose reduction due to a toxicity.

There were ten deaths related to study treatment in the nivolumab plus ipilimumab group and four deaths in the chemotherapy group (appendix p 2).

At baseline, no significant differences were identified between the two study groups with regard to quality of life based on the QLQ-ELD14 and EQ-5D questionnaires. Considering that a 10-point difference in health-related quality of life scores is considered the minimal clinically important difference, the evolution of QLQ-ELD14 scores between baseline and week 18 showed that Maintaining Purpose, Mobility, Family support, and Joint stiffness scale scores seemed to be stable during the study in the two groups, whereas Worries about other and Future worries scales scores seemed to improve during the study in both groups. Burden of illness seemed to improve at week 6 and week 12 in the nivolumab plus ipilimumab group (appendix p 6). No differences in EQ-5D scores were identified over time in the chemotherapy or nivolumab plus ipilimumab groups. Considering that a 7-point difference is considered clinically significant for a visual analogue scale, patients' perception of their general health over the course of the study seemed to improve from baseline in the nivolumab plus ipilimumab and remained stable over time in the chemotherapy group (appendix p 7).

Discussion

To our knowledge, this is the first study to assess the efficacy of nivolumab plus ipilimumab in patients with an ECOG performance status of 2 and older patients with advanced NSCLC. Older patients (aged ≥70 years) are under-represented in phase 3 trials of immunotherapy, while patients with an ECOG performance status of 2 are

	Nivolumab plus ipilimumab (n=105)		Chemotherapy (n=103)	
	All grades	Grade ≥3	All grades	Grade ≥3
Blood and lymphatic system disorders	25 (24%)	1 (1%)	69 (67%)	41 (40%)
Anaemia	14 (13%)	0	49 (48%)	9 (9%)
Neutropenia	2 (2%)	0	42 (41%)	28 (27%)
Thrombocytopenia	5 (5%)	0	20 (19%)	5 (5%)
Cardiac disorders	14 (13%)	10 (10%)	9 (9%)	6 (6%)
Endocrine disorders	15 (14%)	5 (5%)	0	0
Gastrointestinal disorders	56 (53%)	11 (11%)	51 (50%)	4 (4%)
Constipation	21 (20%)	2 (2%)	11 (11%)	0
Diarrhoea	27 (26%)	3 (3%)	25 (24%)	2 (2%)
Nausea	13 (12%)	0	28 (27%)	2 (2%)
Vomiting	8 (8%)	0	15 (15%)	0
General disorders and administration site conditions	73 (70%)	17 (16%)	70 (68%)	16 (16%)
Asthenia	59 (56%)	9 (9%)	56 (54%)	9 (9%)
Chest pain	11 (11%)	3 (3%)	5 (5%)	1 (1%)
Hepatobiliary disorders	11 (11%)	7 (7%)	3 (3%)	2 (2%)
Infections and infestations	46 (44%)	19 (18%)	32 (31%)	14 (14%)
Pneumonia	14 (13%)	7 (7%)	8 (8%)	5 (5%)
Metabolism and nutrition disorders	34 (32%)	11 (11%)	29 (28%)	7 (7%)
Decreased appetite	14 (13%)	2 (2%)	18 (18%)	2 (2%)
Musculoskeletal and connective tissue disorders	36 (34%)	4 (4%)	17 (17%)	0
Arthralgia	15 (14%)	1 (1%)	3 (3%)	0
Back pain	15 (14%)	3 (3%)	3 (3%)	0
Nervous system disorders	32 (31%)	8 (8%)	28 (27%)	4 (4%)
Neuropathy peripheral	10 (10%)	0	18 (18%)	1 (1%)
Psychiatric disorders	16 (15%)	4 (4%)	9 (9%)	3 (3%)
Renal and urinary disorders	16 (15%)	8 (8%)	5 (5%)	1 (1%)
Acute kidney injury	11 (11%)	6 (6%)	2 (2%)	0
Respiratory, thoracic, and mediastinal disorders	44 (42%)	20 (19%)	36 (35%)	12 (12%)
Dyspnoea	14 (13%)	1 (1%)	16 (16%)	3 (3%)
Skin and subcutaneous tissue disorders	43 (41%)	4 (4%)	21 (20%)	1 (1%)
Alopecia	1 (1%)	0	11 (11%)	0
Pruritus	23 (22%)	0	2 (2%)	0
Vascular disorders	18 (17%)	4 (4%)	14 (14%)	6 (6%)

Data are n (%). Only adverse events with a frequency of ≥10% in either treatment group are reported.

Table 3: **Adverse events (safety population)**

	Nivolumab plus ipilimumab (n=105)	Chemotherapy (n=103)
At least one immune allergic adverse event	33 (31%)	0
Colitis	9 (9%)	0
Autoimmune lung disease	8 (8%)	0
Hypothyroidism	7 (7%)	0
Adrenal insufficiency	4 (4%)	0
Autoimmune hepatitis	4 (4%)	0
Diabetes mellitus	3 (3%)	0
Myocarditis	2 (2%)	0
Tubulointerstitial nephritis	2 (2%)	0
Glomerulonephritis rapidly progressive	1 (1%)	0
Immune-mediated encephalitis	1 (1%)	0
Lymphocytic hypophysitis	2 (2%)	0
Cholangitis	1 (1%)	0
Drug reaction with eosinophilia and systemic symptoms	1 (1%)	0
Lichenoid keratosis	1 (1%)	0

Data are n (%).

Table 4: **Patients with immune allergic adverse events (safety population)**

excluded.[16] The primary endpoint of the study was not achieved, but this study shows that dedicated phase 3 trials in these under-represented patient populations are feasible despite their frailty. Additionally, a clinical signal of efficacy was observed in fit (ie, ECOG performance status of 0–1) older patients (aged ≥70 years), with a doubling of overall survival for nivolumab and ipilimumab over platinum doublet (22·6 months [95% CI 18·1–36·0] *vs* 11·8 months [8·9–20·5]). However, the effect of nivolumab plus ipilimumab seems to be detrimental compared with platinum doublet chemotherapy in patients with an ECOG performance status of 2.

In the CheckMate 227 study, which assessed first-line nivolumab plus ipilimumab in advanced NSCLC, the median age of patients was 64 years; fewer than 10% of patients were aged 75 years or older and all patients had an ECOG performance status of 0–1.[8] Median overall survival in the population with PD-L1 expression of 1% or higher was significantly longer in the immunotherapy group (17·1 months [95% CI 15·0–20·1]) than the chemotherapy group (14·9 months [12·7–16·7]; HR 0·79 [95% CI 0·65–0·96]). Overall survival at 2 years was 40·0% in the immunotherapy group and 32·8% in the chemotherapy group. Median progression-free survival was 5·1 months (IQR 4·1–6·3) in the immunotherapy group and 5·6 months (4·6–5·8) in the chemotherapy group.[9] Comparable overall survival benefit was also reported in patients with a PD-L1 expression of less than 1%. In our study, worse survival outcomes were reported in the chemotherapy group than in the chemotherapy group of the CheckMate 227 study, which might be explained by the poor performance status and older age of our study

population. Despite an older population with poorer performance status, the results in the nivolumab plus ipilimumab group were comparable with those of the same group of the CheckMate 227 study. Median overall survival was 14·7 months in our study versus 17·1 months in the CheckMate 227 study, 2-year survival was 36·6% versus 40·0%, and median progression-free survival was 5·5 months versus 5·1 months. In our study, patients with PD-L1 expression higher than 50% (11 [5%] of 202 patients) were under-represented. This is explained by the availability at the time of the inclusion period of first-line immunotherapy for this group of patients.

Subgroup analyses suggest a benefit for immunotherapy in older patients with an ECOG performance status of 0–1, with a median overall survival of 22·6 months versus 11·8 months for patients receiving chemotherapy; this population tended to be older than the study population with an ECOG performance status of 2. For patients with an ECOG performance status of 2, median overall survival was 2·9 months (95 CI 1·4–4·8) in the nivolumab plus ipilimumab group versus 6·1 months (3·5–10·4) in the chemotherapy group, but this difference was not statistically significant. This finding suggests that these two populations (ie, older patients with an ECOG performance status of 0–1 and patients with poor performance status [ECOG performance status of 2]) must be considered separately to be able to offer the best therapeutic options. Dedicated clinical trials should include patients with NSCLC who have an ECOG performance status of 2.

Fit older patients with NSCLC seem to derive a benefit from immunotherapy with PD-L1 compounds in monotherapy or combined with anti-CTLA-4 antibody. In the study by Borghaei and colleagues, pooled data from four studies (CheckMate 227 part 1, CheckMate 817 cohort A, CheckMate 568 part 1, and CheckMate 012) of first-line nivolumab plus ipilimumab in advanced NSCLC[22] showed that 186 (14%) of 1255 patients were older than 75 years. In these patients, efficacy outcomes were comparable to the entire pooled population, with median overall survival of 20·1 months (95% CI 14·7–26·9). The overall population had an ECOG performance status of 0–1. Median overall survival was similar to that reported here for the subgroup of patients with an ECOG performance status of 0–1 (22·6 months). In this older population with an ECOG performance status of 0–1, the benefit of the combination of immunotherapy and chemotherapy remains unclear. In the CheckMate 9LA study,[23] evaluating the association of PD-L1 and CTLA-4 blockade plus chemotherapy versus chemotherapy, the overall survival primary endpoint was met (HR 0·72 [95% CI 0·61–0·86]) in the entire population. However, patients aged 75 years or older (10% of patients) did not seem to benefit from the addition of nivolumab and ipilimumab to chemotherapy.

For patients with an ECOG performance status of 2, most retrospective analyses have shown a negative impact of immunotherapy,[24–26] even if, according to a prospective study, survival results seem to be better.[27] In CheckMate 817,[27] a phase 3B study evaluating flat-dose nivolumab plus weight-based ipilimumab in patients with metastatic NSCLC, median overall survival of patients with an ECOG performance status of 2 was 9·0 months (95% CI 5·5–12·9), with a 3-year overall survival rate of 18·7%. Median progression-free survival was 3·6 months, which is similar to the median progression-free survival of 2·9 months observed in patients with an ECOG performance status of 2 in our study.This probably reflects the different populations selected in the two trials, with more comorbidities and poorer tolerance to immunotherapy expected in our patient population.

In contrast, the findings of IPSOS differed.[28] This phase 3 study included frail patients considered ineligible for platinum doublet chemotherapy and compared atezolizumab monotherapy *vs* gemcitabine or vinorelbine. Most patients who were randomly assigned had an ECOG performance status of 2 and were older than 70 years. Patients were not selected on the basis of PD-L1 expression, but, similarly, few patients in our study had high PD-L1 expression. Median overall survival was longer in the atezolizumab group (10·3 months [95% CI 9·4–11·9]) than the gemcitabine or vinorelbine group (9·2 months [5·9–11·2]; HR 0·78 [95% CI 0·63–0·97]; p=0·028). It should be noted, however, that the two trials are difficult to compare, since all patients in the IPSOS survival study had a contraindication to platinum, whereas this was an inclusion criterion in our study.

The assessment of performance status by ECOG does not take into account the reasons for impaired function, such as age, tumour burden, comorbidities, or polypharmacy. Moreover, evaluation of performance status differs among assessing physicians, and between physicians and patients. Evidence to guide treatment decisions about using immune checkpoint inhibitors in patients with an ECOG performance status of 2 is scarce. The most important question of whether an ECOG performance status of 2 is also a predictive marker of response to immune checkpoint inhibitors remains unanswered.[29]

Regarding toxicity, the numbers of patients with grade 3 or worse treatment-related adverse events in the nivolumab plus ipilimumab and chemotherapy groups overall (48% *vs* 38%) were comparable to those reported in the CheckMate 227 study (32·8% *vs* 36·0%).[9] No new safety signals were reported. Immune-related adverse events were reported as expected and were manageable. Nevertheless, treatment-related death rates in the nivolumab plus ipilimumab group (ten [10%] of 105 patients) and the chemotherapy group (four [4%] of 103 patients) are higher than in the pivotal CheckMate 227 trial,[9] reflecting the frailty of the population included. For the quality of life analysis, no differences were identified between the two groups at inclusion and during the study for most of the parameters analysed.

Our study had some limitations. The inclusion of patients was stopped after an interim analysis, which showed a risk for futility, more specifically for patients with an ECOG performance status of 2. Initially, we planned to include 242 patients to have the 199 required overall survival events; however, at final analysis, 165 events had been observed among 216 patients. As a consequence, the study was underpowered for both primary and secondary endpoints.

In conclusion, our study shows that dedicated trials in older patients or those with an ECOG performance status of 2 are feasible despite their frailty. The nivolumab plus ipilimumab combination did not demonstrate a statistically significant benefit in overall survival in the entire study population. Although this trial was not powered for this outcome, there was an indication of benefit on overall survival of nivolumab plus ipilimumab combination over platinum doublet in older patients with NSCLC who had an ECOG performance status of 0–1, with a doubling of survival, a result that needs to be confirmed in future studies. Conversely, for patients with an ECOG performance status of 2, the combination of nivolumab plus ipilimumab immunotherapy had no benefit in terms of survival; however, disease progression might have been too fast for immunotherapy to have had an effect.

The GFPC 08–2015 ENERGY investigators

I Monnet (Le Centre Hospitalier Intercommunal de Créteil, France), O Bylicki (Hôpital d'Instruction des Armées Sainte-Anne Toulon, France), C Audigier-Valette (Centre Hospitalier Toulon, France), L Falchero (Centre Hospitalier Villefranche, France), R Gervais (Cancer Centre Caen, France), A Vergnenègre (Le Centre Hospitalier et Universitaire Limoges, France), A Madroszyk (Cancer Centre Marseille, France), F Guisier (Le Centre Hospitalier et Universitaire Rouen, France), C Marcq (Le Centre Hospitalier La Roche-sur-Yon, France), S Hominal (Le Centre Hospitalier Annecy, France), S Martinez (Le Centre Hospitalier Aix-en-Provence, France), M Wislez (Le Centre Hospitalier et Universitaire Cochin, France), G De Chabot (Le Centre Hospitalier et Universitaire Angers, France), P Thomas (Le Centre Hospitalier Gap, France), P Fournel (Institut De Cancérologie Et D'hématologie Universitaire De Saint-Étienne, France), M Pérol (Cancer Centre Lyon, France), C Locher (Le Centre Hospitalier Meaux, France), R Lamy (Le Centre Hospitalier Lorient, France), R Schott (Cancer Centre Strasbourg, France), S Abdiche (Le Centre Hospitalier Libourne, France), J Crequit (Le Centre Hospitalier Beauvais, France), H Le Floch (Hôpital d'Instruction des Armées Clamart, France), G François (Le Centre Hospitalier et Universitaire Amiens, France), J Le Treut (Hôpital Européen Marseille, France), C Dujon (Le Centre Hospitalier Le Chesnay, France), J B Auliac (Le Centre Hospitalier Mantes, France), G Le Garff (Le Centre Hospitalier Saint Brieuc, France).

Contributors

HL, RC, CCh, CCr, and CR wrote the protocol. HL, IM, OB, CAV, CCh, CCr, and CR participated in the implementation of the study. HL, CCh, and CR collected study data. AV, LG, and CCh acquired study funding. HL, IM, OB, CAV, LF, AV, PD, LG, and MG managed the data. HL, LG, RC, CCh, CCr, and CR wrote the manuscript. HL, CCh, and CCr did the statistical analysis. HL, RC, CCh, and CR had access to and verified all data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors validated the final version of the manuscript.

Declaration of interests

HL reports support for attending meetings or travel from Roche, Sanofi, Amgen, Takeda, and Pfizer; and participation on a data safety monitoring board or advisory board for Roche, MSD, Sanofi, Takeda, Daiichi, Amgen, and Pfizer. LG reports grants or contracts to their institution from Bristol-Myers Squibb, MSD, Takeda, Pfizer, Roche, Amgen, Sanofi, Janssen, Lilly, and Novartis; payment or honoraria for lectures or presentations from Bristol-Myers Squibb, MSD, Takeda, Pfizer, Roche, Amgen, Sanofi, Janssen, Lilly and Novartis; support for attending meetings or travel from Pfizer, MSD, AstraZeneca, Takeda, and Amgen; and participation on a data safety monitoring board or advisory board for InhaTarget Therapeutics. OB reports consulting fees from Roche, Takeda, and AstraZeneca; and honoraria for lectures and presentations from MSD, Bristol-Myers Squibb, and Janssen. IM reports honoraria for educational events from Regeneron; and support for attending meetings or travel from Pfizer and MSD. AV reports consulting fees from Pierre Fabre, Amgen, and MSD; support for attending meetings or travel from Pierre Fabre and Amgen; and participation on a data safety monitoring board or advisory board for MSD, AstraZeneca, Sanofi, Amgen, and Pierre Fabre. PD reports support for attending meetings or travel from Takeda and Accord Healthcare; and participation on a data safety monitoring board or advisory board for Bristol-Myers Squibb. FG reports consulting fees from Roche, Takeda, and AstraZeneca; honoraria for lectures or presentations from MSD, Bristol-Myers Squibb, and Janssen; and congress travel expenses from AstraZeneca and MSD. RC reports meeting presentations and participation on boards for Bristol-Myers Squibb. CCh reports consulting fees from AstraZeneca, Boehringer Ingelheim, GSK, Roche, Sanofi Aventis, Bristol-Myers Squibb, MSD, Lilly, Novartis, Pfizer, Takeda, Bayer, and Amgen; and support for attending meetings or travel from AstraZeneca, Boehringer Ingelheim, GSK, Roche, Sanofi Aventis, Bristol-Myers Squibb, MSD, Lilly, Novartis, Pfizer, Takeda, Bayer, and Amgen. CR reports consulting fees from Roche, Takeda, MSD, Bristol-Myers Squibb, Janssen, and Sanofi; honoraria for lectures or presentations from Sanofi, Takeda, and AstraZeneca; and support for attending meetings or travel from MSD and Sanofi. CCr, CAV, LF, MG, SH, and CL declare no competing interests.

Data sharing

The study protocol is available in the appendix (p 8). Individual participant data are not available, but might be made available on request for the purpose of meta-analyses.

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