A phase II clinical trial evaluating the safety and efficacy of durvalumab as first line therapy in advanced and metastatic non-small cell lung cancer patients with Eastern Cooperative Oncology Group performance status of 2

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Summary

Background Approximately 30–40% of patients with advanced and metastatic non-small cell lung cancer (NSCLC) present with an impaired performance status (PS). There are limited prospective data on the safety and efficacy of durvalumab in these patients.

Methods In this single-arm phase II clinical trial (NCT02879617), patients with previously untreated Stage IIIB/IV NSCLC and ECOG PS of 2 received durvalumab 1500 mg every 28 days until progression or unacceptable toxicity. The primary endpoints were overall survival (OS) and safety determined by grade ≥3 treatment-related adverse events (TRAEs).

Findings Between April 2017 and March 2021, 50 patients were enrolled, of whom 47 received durvalumab. With a median follow-up of 28 months, median OS was 6 months (95% CI 4–10). TRAEs grade 3 occurred in nine of 47 patients (19%, 95% CI 9%–33%). OS in patients with a PD-L1 TPS of 0, 1–49%, and ≥50% was six months (95% CI 3–15), 11 months (95% CI 4–16), and 11 months (95% CI 0–not reached (NR)), respectively. Health related quality of life (HQRL) assessed at baseline and during therapy demonstrated no statistically significant change over the course of treatment.

Interpretation This study demonstrates that single agent durvalumab is safe and well tolerated in the 1st line treatment of patients with advanced NSCLC and ECOG PS of 2, with an encouraging OS benefit in patients with PD-L1 positive tumors. This trial is amongst the largest prospective studies evaluating durvalumab in the 1st line treatment of advanced stage NSCLC and a PS of 2.

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Keywords: Durvalumab; Non-small cell lung cancer; Safety; Overall survival; Performance status 2

Introduction

Performance status represents a measure of a patient's functional daily living abilities, usually based on a constellation of symptoms related to lung cancer and pre-existing comorbidities. According to the Eastern Cooperative Group (ECOG) classification, a performance status of 2 (PS 2) is "ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours".[1,2] Several prospective and retrospective studies have demonstrated that an ECOG PS of 2 is an independent prognostic factor in patients with advanced lung cancer and the most potent negative predictor of response to treatment, survival outcomes, and adverse event.[1,2]

Approximately 30–40% of patients with advanced NSCLC present with an impaired ECOG PS of 2 or

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Research in context

Evidence before this study

We conducted a PubMed search for prospective clinical trials evaluating immunotherapy monotherapy or dual checkpoint inhibition in patients with no prior treatment for advanced and metastatic NSCLC and an ECOG performance status (PS) of 2. This search yielded a limited number of studies. The PePS2 clinical trial treated twenty-four patients with pembrolizumab in the 1st line setting, in whom the median OS was 7.9 months, with 15% of patients experiencing grade ≥3 treatment-related adverse events (TRAEs). More recently, the IPSOS clinical trial evaluated 1st line atezolizumab in 302 platinum ineligible NSCLC patients of whom 81% had an ECOG PS of 2 or 3. Atezolizumab in this patient population was associated with a median OS of 10.2 months and a rate of grade ≥3 TRAEs of 16%. The Checkmate 817 clinical trial evaluated nivolumab and ipilimumab in the 1st line treatment of 139 patients with NSCLC and a PS of 2 and demonstrated a median OS of 9 months and the rate of grade ≥3 TRAEs of 27.3%.

Added value of this study

In this single-arm phase II clinical trial of durvalumab in the 1st line treatment of 47 patients with Stage IIIB/IV NSCLC and an ECOG PS of 2, median OS was 6 months in the overall patient population and 11 months in patients with PD-L1 positive NSCLC tumors. Durvalumab was safe and well tolerated with a rate of TRAEs grade ≥3 occurring in 19% patients. Health related quality of life (HQRL) assessed at baseline and during therapy demonstrated no statistically significant change over the course of treatment.

Implications of all the available evidence

This trial is amongst the largest prospective studies evaluating durvalumab monotherapy in the 1st line treatment of advanced stage NSCLC and a PS of 2. Durvalumab is the only agent approved by the FDA and the EMA in the consolidation setting following definitive chemoradiotherapy for patients with unresectable stage III NSCLC, based on profound overall survival benefits over placebo in the PACIFIC clinical trial. The results of the current study provide reassurance that the use of durvalumab in patients with impaired performance is well-tolerated and associated with stable health related quality of life.

more.[2] Historically in patients with advanced NSCLC and borderline PS, platinum-based doublet chemotherapy has been associated with improved survival and reduction in disease-related symptoms compared with single agent therapy with either pemetrexed, paclitaxel, gemcitabine, or erlotinib.[3–6] Despite the establishment of immunotherapy as state of the art in the 1st line treatment of patients with advanced and metastatic NSCLC without actionable oncogenic drivers, patients with a poor PS have been excluded from the randomized clinical trials that have led to the FDA approvals of the anti-PD-1/PD-L1 checkpoint inhibitors nivolumab, pembrolizumab, atezolizumab, and cemiplimab in the first-line setting.[7–14] Durvalumab remains the only FDA and EMA approved agent for consolidation therapy after definitive concurrent chemoradiotherapy in patients with unresectable stage III NSCLC.[15] Similar to the registrational clinical trials of immunotherapy in the advanced and metastatic setting, the randomized clinical trial which demonstrated the survival benefit of durvalumab over placebo as consolidation therapy in Stage III NSCLC patients after definitive chemoradiotherapy excluded patients with borderline performance status.[15]

To understand the efficacy and safety of immunotherapy in NSCLC patients with borderline performance status, we conducted a single-arm, multi-institutional, phase II clinical trial of durvalumab as first-line treatment of patients with advanced and metastatic NSCLC with performance status ECOG PS of 2.

Methods

Study design

This was a multicenter, single-arm, phase 2 clinical trial of durvalumab in newly diagnosed patients with advanced and metastatic NSCLC and an ECOG PS of 2 (NCT02879617). Patients were recruited from the University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center Network in Western Pennsylvania and the Harold C. Simmons Comprehensive Cancer Center at the University of Texas Southwestern Medical Center in Dallas, TX.

Participants had histologically confirmed Stage IIIB or IV NSCLC (American Joint Committee on Cancer, 7th edition; AJCC 7), were 18 years of age or older, had an ECOG PS of 2, and had a life expectancy of 12 weeks or more. Patients must not have received prior systemic therapy for advanced or metastatic NSCLC. Patients may have received previous adjuvant or neoadjuvant chemotherapy or chemotherapy as part of a curative intent chemoradiotherapy approach for NSCLC if completed one year prior to study entry. Patients treated with prior PD-1 or PD-L1-directed therapy were excluded.

The criteria for ECOG PS were explicitly outlined in the study protocol and must have been assessed within 28 days of treatment initiation. Patients with known genomic alterations of *EGFR, ALK,* or *ROS1* were excluded from this study. PD-L1 tumor proportion score (TPS) testing was performed per the institutional

standard of care, utilizing an FDA-approved assay. Patients were eligible regardless of PD-L1 TPS on the tumor specimens. Patients using systemic immunosuppressive medication within 28 days of study treatment were excluded, except corticosteroids not exceeding prednisone 10 mg per day or equivalent within 1 week of study therapy. Other key eligibility criteria included measurable disease according to RECIST version 1.1; adequate hematological, hepatic, and renal function; and the ability to provide written informed consent. Patients with untreated, symptomatic brain or leptomeningeal metastatic disease were excluded.

Ethics

The trial was approved by the University of Pittsburgh Institutional Review Board (STUDY19050393: 16-054) and the University of Texas Southwestern Institutional Review Board (eIRB STU2020-0099). Informed consent was obtained from all enrolled patients.

Procedures

Durvalumab (AstraZeneca/MedImmune) was administered as an intravenous infusion of 1500 mg (fixed dose) over 60 min every 28 days, defining a cycle of treatment, for up to 12 months (maximum 12 doses), until disease progression, death, unacceptable toxicity, or withdrawal of consent. Dose interruptions were permitted for durvalumab in the event of clinically significant toxicities as defined per protocol. Screening assessments included a medical history, clinical examination, laboratory analyses, and tumor assessment by computer tomography (CT) or magnetic resonance imaging (MRI) scan, with measurable lesions being a requirement for the trial. Clinical evaluation and patient-reported quality of life assessment were performed every four weeks during treatment at outpatient clinic visits. CT assessments were scheduled every eight weeks, and the response was assessed by RECIST version 1.1. After discontinuation of treatment, patients were followed up every four weeks for six months and every 12 weeks thereafter, for 12 months after discontinuation of study therapy or until death. All adverse events were recorded in accordance with the Common Terminology Criteria for Adverse Events v4.03. HRQL was assessed at baseline, at the end of each cycle, and at the end of therapy using the FACT-L questionnaire.[16] Total scores were summarized for each patient. The primary analysis outlined baseline QOL and average changes over the course of treatment.

Outcomes

The coprimary end points were OS and safety. Overall survival was defined as the time from the start of treatment to death from any cause, and safety was determined by grade ≥3 treatment-related AEs. Safety was chosen to determine the feasibility of delivering durvalumab to poor performance patients to recapitulate more real-world clinical practice experience. The secondary endpoints were PFS, defined as the time from the start of treatment to time of progression or death, ORR, overall survival rate at 12 months (OS12), as well as OS, PFS, and ORR by PD-L1 expression status and HRQL using the FACT-L questionnaire. Archival tumor-tissue samples were submitted for PD-L1 testing; however, enrollment was not restricted based on PD-L1 expression.

Statistics

The OS and PFS in the entire population and within PD-L1 strata and two-sided 95% confidence intervals for the median OS and PFS were estimated by standard methods (the Kaplan–Meier method for survival and the Greenwood variance formula applied to log-transformed survival). In prior phase II and III clinical trials enrolling newly diagnosed patients with advanced NSCLC and ECOG PS 2, single agent therapy with either pemetrexed, paclitaxel, gemcitabine, or erlotinib was associated with a median OS ranging from three to 6.7 months, compared with a median OS of 5.9–9.7 months with platinum doublet chemotherapy.[3–6] In the current study, a median OS of nine months with durvalumab would represent a clinically meaningful OS benefit as this would be comparable to the survival associated with platinum doublet in this patient population. Assuming 18 months of accrual with six months of follow-up, 50 patients were required to have 85% power for a 90% confidence interval for median survival to exclude five months (and 78% power for a 95% confidence interval). The ORR and OS12 were estimated with a 95% Wilson Score confidence interval.

Safety was summarized for all patients who received at least one dose of the study drug. All adverse events determined to be possibly, probably, or definitely related to treatment were tabulated according to grade and type in order of frequency. Prior studies have suggested a grade ≥3 TRAEs rate of about 40% with platinum doublet chemotherapy in patients with advanced NSCLC and PS of 2.[3] A rate of grade ≥3 treatment-related adverse events of 30% or less would suggest that durvalumab is tolerable compared with platinum doublet in this population. For HQRL, total scores were summarized for each patient at baseline QOL and over the course of treatment.

Role of funding source

AstraZeneca provided drug substance and funding for this clinical trial but had no input on the study design or the interpretation of the results.

Results

Between April 2017 and March 2021, 50 patients were enrolled at the UPMC Hillman Cancer Center Network and the University of Texas Southwestern Medical

Center in Dallas, TX. Forty-two of the fifty patients were accrued and treated across 13 community-based clinics within the UPMC Hillman Cancer Center Network across Western Pennsylvania, including clinics embedded in underserved and rural communities.

Of the 50 patients enrolled, three patients were unable to start study therapy; one due to symptomatic deterioration, one was unable to wean steroids in the setting of uncontrolled brain metastases and one patient died in the setting of their underlying malignancy (Fig. 1). Forty-seven patients received study therapy and were included in the analysis of the survival and safety endpoints. The median number of treatment cycles was four. Thirty-eight patients had at least one disease evaluation and were included in the analysis of overall response rate.

Table 1 summarizes the baseline characteristics of study participants. Patients were a median age of 79 years (range 53–94), were predominantly former (36 of 47 patients, 77%) or current smokers (10 of 47 patients, 21%). Twenty-five of 47 (53%) patients had adenocarcinoma histology, and 12 of 47 (26%) patients had squamous cell histology. PD-L1 expression was assessed in 35 of 47 (74%) patients; 15 of 35 (43%) had a PD-L1 TPS of 0, 14 of 35 (38%) had a PD-L1 TPS of 1–49%, and six of 35 (19%) had PD-L1 TPS ≥50%. The median duration of follow-up was 28 months.

Treatment-related adverse events of grade ≥3 occurred in nine of 47 (19%, 95% CI 9%–33%) patients (Table 2), most commonly pneumonitis (2/47, 4%), colitis (1/47, 2%), fatigue (1/47, 2%), decreased lymphocyte count (1/47, 2%), increased lipase (1/47, 2%), hyponatremia (1/47, 2%), optic nerve disorder (1/47, 2%) and cardiac arrest (1/47, 2%). Any grade TRAEs occurred in 24 of 47 (51%, 95% CI 36%–66%) patients. Most common TRAEs of any grade were fatigue (9/47, 19%), increased ALT (6/47, 13%), decreased lymphocyte count (4/47, 9%), increased AST (3/47, 6%), increased GGT (3/47, 6%), and increased lipase (3/47, 6%).

The median OS in all treated patients was six months (95% CI 4–10) (Fig. 2) with a 12-month overall survival rate of 31%. Overall survival in patients with a PD-L1 TPS of 0, 1–49%, and ≥50% was six months (95% CI 3–15), 11 months (95% CI 4–16), and 11 months (95% CI 0–NR), respectively. The PFS was three months (95% CI 1–4). The PFS in patients with a PD-L1 TPS of 0%, 1–49%, and ≥50% was three months (95% CI 1–5), four months (95% CI 1–14) and one month (0-NR), respectively (Supplementary Figure S1). Antitumor activity was assessed by overall response rate in 38 patients who had at least one disease evaluation after initiation of study therapy. Overall response rate was 26% (95% CI 13–43%) with ten of 38 patients experiencing partial responses. The stable disease rate was 47% (18 of 38 patients, 95% CI 36%–59%) and disease control rate was 73% (28 of 38 patients, 95% CI 57%–87%). Based on PD-L1 expression, the ORR was 31% (four of 13) in patients with PD-L1 TPS of 0%, 30% (three of ten) in patients with PD-L1 TPS 1–49%, and 25% (one of four) in patients with PD-L1 TPS ≥50%. We performed a sensitivity analysis for ORR, assuming all patients unable to undergo at least one disease evaluation after

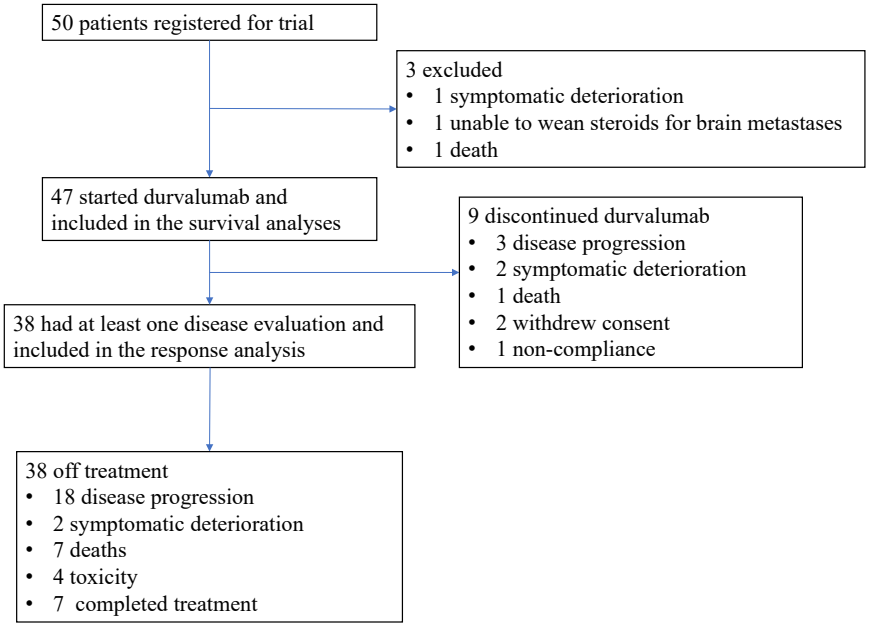

Fig. 1: CONSORT flow chart.

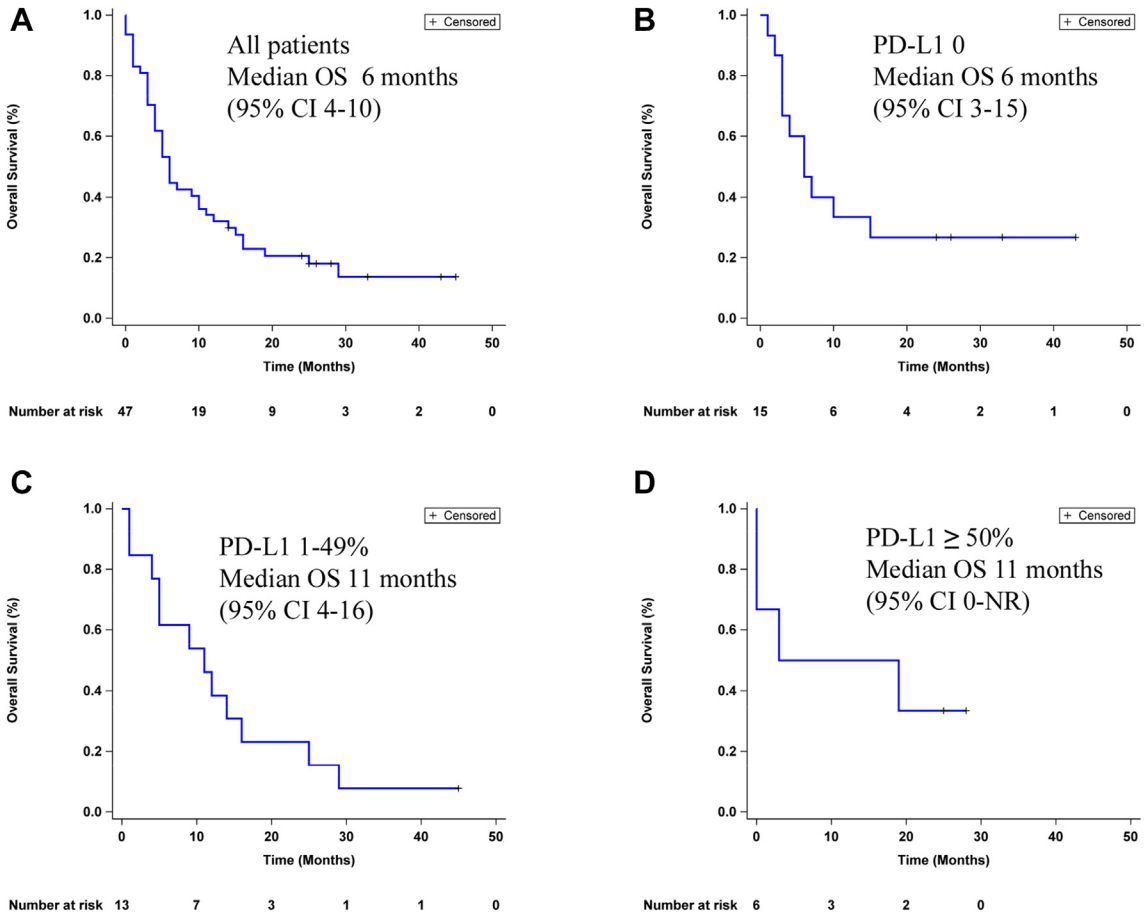

Fig. 2: Median OS in the (A) overall population, in patients with a (B) PD-L1 tumor proportion score of 0, (C) a PD-L1 tumor proportion score of 1–49% and (D) a PD L1 tumor proportion score of ≥50%.

initiation of study treatment experienced progressive disease. The ORR based on this sensitivity analysis was 21% (ten of 47 patients, 95% CI 10%–36%).

In patients remaining in the study and alive and well enough to complete health-related QOL questionnaires, the mean FACT-L scores remained stable over the course of treatment cycles (Fig. 3). The mean values for the subscales of the FACT-L questionnaire, assessing physical, social, emotional and functional well-being as well as the lung cancer specific subscale were stable across all treatment cycles.

Discussion

In this single arm phase II clinical trial of durvalumab as 1st line therapy for patients with advanced and metastatic NSCLC and a PS of 2, we demonstrated a median overall survival of six months in all patients and 11 months in patients with PD-L1 positive tumors. This trial was originally designed around the time of the initial FDA approvals of immunotherapy monotherapy in previously treated PD-L1 unselected NSCLC patients in 2015 and in newly diagnosed PD-L1 positive NSCLC patients in 2016.[17,18] At the time, there were limited data of the safety and efficacy of immunotherapy in patients with NSCLC and a PS of 2. Platinum-doublet based chemotherapy in NSCLC patients with a PS of 2 has been associated with a survival benefit of about 9 months and a rate of grade ≥3 TRAEs of about 40% in several phase II and III clinical trials.[3–6] In the current study, durvalumab was safe and well tolerated, with grade ≥3 TRAEs occurring in 19% of patients, which compares favorably with platinum-based doublet chemotherapy in the same patient population.

To our knowledge this study is amongst the largest prospective trials evaluating durvalumab monotherapy in the 1st line treatment of patients with advanced and metastatic NSCLC and a PS of 2. A limited number of prior studies have prospectively evaluated immunotherapy monotherapy in the 1st line treatment of PS 2

	N = 47
Age	n (%)
Median (years)	79
Range	53–94
Sex	
Male	27 (57%)
Female	20 (43%)
Race	
White	46 (98%)
African American	1 (2%)
Disease stage[a]	
IIIB	6 (13%)
IV	41 (87%)
Smoking status	
Current	10/47 (21%)
Former	36/47 (77%)
Never	1/47 (2%)
Histology	
Adenocarcinoma	25/47 (53%)
Squamous	12/47 (26%)
NSCLC, other[b]	10/47 (21%)
PD-L1 status	
Unknown	12 (26%)
Known	35 (74%)
PD-L1 0	15/35 (43%)
PD-L1 1–49%	14/35 (38%)
PD-L1 ≥ 50%	6/35 (19%)

[a]AJCC 7th Edition. [b]Histologies include adenosquamous, pleomorphic and NSCLC, not otherwise specified.

Table 1: **Patient characteristics.**

N = 47		
Adverse Event	Any Grade, n (%)	≥Grade 3, n (%)
Fatigue	9 (19)	1 (2)
Alanine aminotransferase increased	6 (13)	0 (0)
Lymphocyte count decreased	4 (9)	1 (2)
Aspartate aminotransferase increased	3 (6)	0 (0)
GGT increased	3 (6)	0 (0)
Lipase increased	3 (6)	1 (2)
Myalgia	2 (4)	0 (0)
Pneumonitis	2 (4)	2 (4)
Bullous dermatitis	2 (4)	0 (0)
Cardiac arrest	1 (2)	1 (2)
Hyperthyroidism	1 (2)	0 (0)
Hypothyroidism	1 (2)	0 (0)
Optic nerve disorder	1 (2)	1 (2)
Colitis	1 (2)	1 (2)
Diarrhea	1 (2)	0 (0)
Nausea	1 (2)	0 (0)
Serum amylase increased	1 (2)	0 (0)
Hyponatremia	1 (2)	1 (2)
Decreased appetite	1 (2)	0 (0)
Maculo-papular rash	1 (2)	0 (0)

Table 2: **Most common treatment-related adverse events (maximum grade, all cycles).**

patients with advanced and metastatic NSCLC. Two clinical trials have evaluated pembrolizumab in the 1st line setting in PS 2 patients with newly diagnosed advanced and metastatic NSCLC, the PePS2 clinical trial and the OLCSG 1801 clinical, which enrolled both PS 2 and PS 3 patients.[19,20] In the larger of these 2 trials, PePS2, twenty-four patients were treated with pembrolizumab in the 1st line setting, in whom the median OS was 7.9 months, with 15% of patients experiencing grade ≥3 TRAEs.[20]

The SAK19/17 clinical trial specifically assessed the efficacy and safety of 1st line durvalumab in twenty-one NSCLC patients with a PS of 2 and demonstrated a rate of grade ≥3 TRAEs of 19%.[21] More recently, the randomized phase III clinical trial, IPSOS, evaluated 1st line atezolizumab versus single agent chemotherapy in platinum ineligible NSCLC patients.[22] Three hundred and two patients in this clinical trial were treated with atezolizumab, of whom 75% had an ECOG PS of 2 and 6% had an ECOG PS of 3. Atezolizumab in this patient population was associated with a median OS of 10.2 months and a rate of grade ≥3 TRAEs of 16%. In this randomized clinical trial, single agent atezolizumab was associated with as overall survival benefit over single agent chemotherapy, regardless of PD-L1 expression level. The Checkmate 817 clinical trial evaluated dual checkpoint inhibitor therapy with nivolumab and ipilimumab in 139 treatment naive patients with NSCLC and a PS of 2 and demonstrated a median OS of nine months and the rate of grade ≥3 TRAEs of 27.3%.[23] The safety we demonstrate in the current study is similar to the safety demonstrated in prior studies of immunotherapy monotherapy in the PS 2 population. Not surprisingly, immunotherapy monotherapy is likely associated with better tolerance than dual checkpoint inhibitor therapy in the PS 2 population, as measured by grade ≥3 TRAEs.

It is important to highlight the difficulty in conducting trials in the NSCLC population with borderline PS. The Energy-GFPC 06-2015 study was a randomized phase III clinical trial of nivolumab and ipilimumab versus carboplatin-based chemotherapy in the 1st line treatment of NSCLC patients with either an ECOG PS of 2 or an age of 70 years or more.[24] The trial independent data and safety monitoring committee halted this study early in the setting of excessive deaths, most notably in patients with a PS of 2 in whom the median OS was 2.9 months. In the SAKK 19/17 clinical trial evaluating durvalumab monotherapy, accrual was suspended early in the setting of an unplanned interim safety analysis triggered by a high mortality rate observed in the first 21 patients recruited.[21] Of the 13 deaths in the first 21 patients accrued to this study, there was one treatment related death in the setting of colonic perforation and 12 deaths attributed to clinical progression of disease; seven of these deaths were observed in the first five weeks of treatment.[21] In the current trial, nine patients

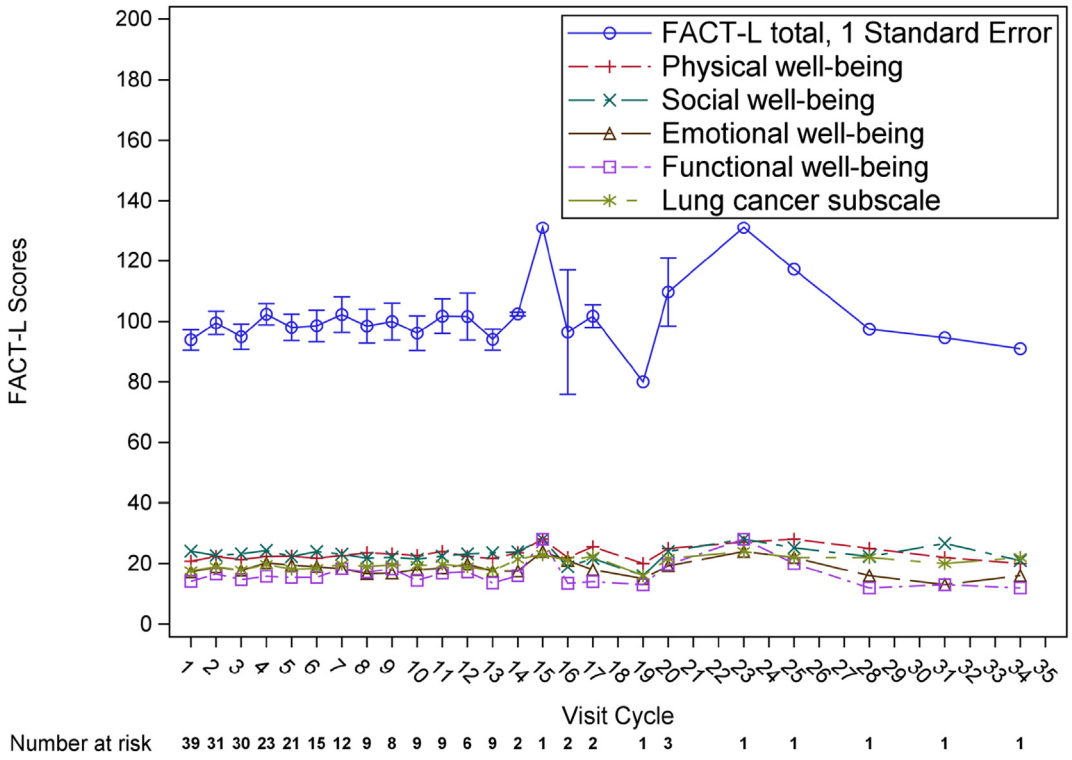

Fig. 3: Average change in health-related quality of life using the FACT-L total score over time.

discontinued study therapy prior to the 1st disease evaluation at eight weeks, three in the setting of disease progression, two in the setting of symptomatic deterioration and one death (Fig. 1). The number of patients that came off treatment in these studies highlights the tenuous nature of these patients and underscores the importance of careful patient selection for immunotherapy in the 1st line setting. It also accentuates the inherent subjectivity in the assessment of performance status by a treating physician.

Preservation of quality of life is an important component of the overall treatment approach of patients with NSCLC and borderline performance status. In our study, there was no change in health-related quality of life across treatment cycles in patients remaining on trial and well enough to fill out quality of life surveys. The mean scores for the components of the FACT-L questionnaire related to physical, social, emotional and functional well-being as well as the lung cancer specific subscale were also stable over time. This suggests that treating borderline performance status patients with immunotherapy in the 1st line setting is likely not detrimental and may be associated with preservation of quality of life.

A weakness of this study is that we did not enumerate medical comorbidities in our PS 2 population, unlike the IPSOS clinical trial where it was known that 97% of patients treated with atezolizumab had one or more ongoing medical conditions.[24] Performance status is based on a constellation of symptoms related not only to lung cancer, but also pre-existing comorbidities. Knowledge of the pre-existing comorbidities in our patient population might lend insight into which borderline performance status patients are more likely to derive benefit from immunotherapy monotherapy in the 1st line setting. An additional limitation of this study is that while patients with known genomic alterations of EGFR, ALK, or ROS1 were excluded, we did not collect data on other genomic alterations which might influence response to immunotherapy. It is known that presence of STK11 mutations is associated with PD-L1 resistance in KRAS-mutant lung adenocarcinoma.[25] Knowledge of STK11 mutations and other genomic alterations in our trial population might further define patients more or less likely to derive benefit in the PS 2 setting.

Durvalumab, as monotherapy, is not approved in the 1st line treatment of advanced and metastatic NSCLC based on the MYSTIC clinical trial which demonstrated no significant improvement in OS compared with chemotherapy in patients with a PD-L1 TPS ≥25%.[26] More recently, durvalumab was approved in combination with tremelimumab and chemotherapy in the 1st line treatment. Durvalumab has been most impactful as the only agent approved by the FDA and the EMA in the consolidation setting following definitive chemoradiotherapy for patients with unresectable stage III

NSCLC, based on profound overall survival benefits over placebo in the PACIFIC clinical trial.[27] In the real-world Stage III NSCLC population, patients often have impaired performance status relative to the initiation of concurrent chemoradiotherapy due to treatment-related toxicity, fatigue, and impaired nutritional status secondary to esophagitis and dysphagia. The results of the current study give some reassurance that the use of durvalumab in patients with impaired performance after chemoradiotherapy is likely to be well-tolerated and associated with stable health related quality of life.

An important strength of this clinical trial is that most of the patients were accrued and treated at community-based clinics, including clinics embedded in rural and underserved communities. The results of this trial have real-world applicability, given a significant proportion of NSCLC patients with borderline performance status will stay in community-based oncology clinics for treatment rather than travel to large academic hubs. These results also indicate that clinical trials involving a medically complex patient population are feasible in the community setting.

Overall, these data suggest that single-agent immunotherapy is well tolerated in patients with advanced and metastatic NSCLC and poor PS; however, careful selection of patients based on the extent of disease burden and existing comorbidities must be considered. There is growing enthusiasm for including borderline performance status patients in clinical trials arising from recent FDA recommendations encouraging principal investigators to enroll patients that recapitulate the real world. This trial demonstrates that such trials are both feasible and informative.

Contributors

K.S: Contributed to data curations and writing of the original draft, also was involved with reviewing, and editing the document. V.R: Contributed the investigation on the trial with revied and editing. H.W.: Performed the formal analysis with reviewing and editing. D.M.: Contributed the investigations, reviewing and editing. C.M: Contributed the investigations, reviewing and editing. J.KW.: Contributed the investigations, reviewing and editing. R.A.V: Contributed the investigations, reviewing and editing. S.M.P.: Contributed the investigations, reviewing and editing. H.L.: Contributed the investigations, reviewing and editing. M.A.S.: Enforced Conceptualization and Methodology. D.E. G: Contributed the investigations, reviewing and editing. J.E.D. Contributed the investigations, reviewing and editing. L.C.V.: Contributed conceptualization, funding acquisition, project administration and supervision, methodology. Also, investigations and the reviewing and editing needed. K.S and L.C.V. have verified the underlying data. All authors have read and approved the final version of the manuscript.

Data sharing statement

Individual participant data that underlie the results reported in this article after deidentification, in addition to the Study Protocol, will be available immediately following publication. Investigators whose proposed use of the data has been approved by an independent review committee may access the data to achieve aims in the approved proposal. Proposals should be directed to villaruzl@upmc.edu. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years after publication.

Declaration of interests

L.C.V. declares research funding from Janssen, BMS, Merck, Regeneron, GSK, AstraZeneca, BioAtla, Black Diamond Therapeutics, Jazz, Genentech, and Beigene and consulting with compensation with Takeda, Janssen, Intervenn Biosciences, Sanofi, Daiichi Sankyo, Jazz, BMS, and Gilead. D.M. declares consulting with fees from AstraZeneca, Beigene, Cardinal Health, Daiichi Sankyo, Janssen, and Karyopharm. M.A.S. declares research funding from Genentech, Spectrum, Novartis, AstraZeneca, Daiichi-Sankyo, Beigene, Cullinan, Mirati, and Pfizer, speaker bureau fees from Genentech, AstraZeneca, Lilly, Janssen, G1 Therapeutics, BMS, Guardant, Regeneron and participation in steering committee/advisory board membership with Lilly, Beigene, Genentech, Mirati, and Spectrum. J.E.D. declares steering committee/advisory board membership with Janssen, Beigene, Astra Zeneca, Catalyst, Takeda, Oncohost. D.E.G. declares research funding from Astra-Zeneca, BerGenBio, Karyopharm, Novocure, consulting fees from Astra-Zeneca, Catalyst Pharmaceuticals, Daiichi-Sankyo, Elevation Oncology, Janssen Scientific Affairs, LLC, Jazz Pharmaceuticals, Regeneron Pharmaceuticals, Sanofi, U.S. patent applications 16/487,335, 17/045,482, 63/386,387, 63/382,972, 63/382,257, stock options with Gilead, Medtronic, Walgreens, and Co-founder and Chief Scientific Officer, OncoSeer Diagnostics, LLC.

The other authors declare that they have no competing financial interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102317.

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