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ORIGINAL ARTICLE

SAKK 19/17: safety analysis of first-line durvalumab in patients with PD-L1 positive, advanced nonsmall cell lung cancer and a performance status of 2

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Abstract

Introduction The safety of first-line (1L) durvalumab in patients with advanced nonsmall-cell lung cancer (NSCLC) and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 (PS2) is unknown. This is an interim unplanned safety analysis of the study SAKK 19/17 for patients with metastatic NSCLC with programmed death-ligand 1 (PD-L1) expression in ≥ 25% of tumor cells and an ECOG PS2 treated with 1L durvalumab. This safety analysis was triggered by the SAKK data and safety monitoring board due to a high mortality rate observed after the recruitment of the first 21 patients.

Methods This single-arm phase II study recruited patients with metastatic NSCLC with PD-L1 in ≥ 25% and ECOG PS2. Patients received durvalumab 1500 mg every four weeks. The trial aims to recruit 48 patients in total. This report includes safety analyses only. Adverse events (AEs) were assessed using National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) Version 5.0. Efficacy data including the primary endpoint overall survival at 6 months and secondary endpoints (objective response rate, progression-free survival, and quality of life) will be reported at a later time point.

Results The data from 21 patients were available at this interim safety analysis. Among these, 13 deaths (13/21; 62%) were reported, including one treatment-related fatal colonic perforation at 9 months after treatment initiation (1/13; 8%). Twelve deaths were not treatment-related (12/13; 92%), and mostly attributed to tumor progression (10/13; 77%). Of note, seven deaths (7/13; 54%) occurred during the first 5 weeks (range 0.6–4.7 weeks) after treatment initiation. Four (4/7; 57%) were respiratory failures attributed to tumor progression. One of these patients (25%) had pre-existing COPD, and three (75%) had baseline dyspnea grade 2–3 related to the tumor. Grade ≥ 3 treatment-related AEs (TRAEs) included colonic perforation (grade 5), abdominal pain, and colitis (grade 3 each) in one patient, and fatigue (grade 3) in another. Other Grade ≥ 3 AEs unrelated to treatment were all of pulmonary origin: lung infections (19%), dyspnea (24%), cough (5%), and bronchial obstruction (5%).

Conclusions 1L durvalumab in patients with ECOG PS2 and metastatic NSCLC with PD-L1 expression ≥ 25% resulted in an unexpectedly high number of fatal early events due to rapid tumor progression. We recommend to avoid treatment with 1 L durvalumab of patients who are highly symptomatic from the tumor, particularly those with respiratory symptoms. The study is continuing its accrual after an amendment excluding these patients.

Keywords Durvalumab · Metastatic nonsmall cell lung cancer · NSCLC · ECOG performance status 2

Introduction

Programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibition disrupts the PD-1 axis, reverses T cell suppression, and enhances endogenous antitumor immunity, fundamentally changing the therapeutic landscape of NSCLC [1]. PD-L1 is an established predictive marker for

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immunotherapy in NSCLC [2]. Based on the proven superiority of pembrolizumab, a PD-1 inhibitor, and atezolizumab, a PD-L1 inhibitor, to standard chemotherapy in first-line (1L) therapy of patients with advanced NSCLC with PD-L1 expression in ≥ 50% tumor cells, both drugs have approved in this setting [3, 4].

The Eastern Cooperative Oncology Group (ECOG) performance status (PS) of patients included in all conducted registration trials was either 0 or 1. However, an estimated 30–40% of NSCLC patients have an ECOG PS score of 2 (PS2) [5]. PS remains the most powerful independent prognostic factor in advanced NSCLC [6]. Therefore, registration trials have excluded a relevant proportion of NSCLC patients.

In the 2019 European Society for Medical Oncology (ESMO) Guidelines [7], a meta-analysis of randomized trials comparing platinum-based doublets to single-agent regimens in 1L therapy in PD-L1 unselected patients with PS2 and advanced NSCLC revealed platinum-based regimens to be superior, both in terms of response rate (RR) and survival (74% higher probability of being alive at 1 year) [8–10]. Therefore, platinum-based doublets are considered standard of care in eligible patients with PS2, despite increased toxicity including a concerning toxic death rate of 4%.

Durvalumab is a humanized engineered immunoglobulin G1κ that blocks PD-L1 binding to PD-1 [11, 12]. A phase I/II study evaluating durvalumab as monotherapy [13] revealed encouraging antitumor activity in advanced NSCLC patients, with grade 3/4 adverse events (AEs) in 8% of patients and drug-related AEs leading to discontinuation in only 5%. The confirmed objective response rate (ORR) with durvalumab was higher in patients with high PD-L1 expression (cut off 25% of tumor cells stained) as compared to those with low PD-L1 expression, at 27% [95% confidence interval (CI) 18.2–38.2] versus 5% (95% CI 1.8–12.2), respectively. Of note, only patients with PS 0 or 1 were included in this trial.

In prior durvalumab studies, high PD-L1 status was defined using a ≥ 25% positive tumor cell cut off. As durvalumab efficacy was shown to be dependent on high PD-L1 expression [7, 11], we decided to assess in patients with PS2 whose tumors harbor high PD-L1 expression (≥ 25%), the efficacy of 1L 4-weekly durvalumab.

Triggered by a high early death rate the SAKK data and safety monitoring board decided to run an interim safety analysis although the preplanned criteria being ≥ 2 treatment-related deaths observed among the first 20 accrued patients were not met.

Here, we report on this unplanned interim safety analysis of the multicenter, single-arm SAKK phase II 19/17 trial, including a summary of patient characteristics, AEs, serious adverse events (SAEs), and toxicities, based on the data collected on December 18th, 2019.

Materials and methods

Study design and study population

The SAKK phase II 19/17 trial is an ongoing, multicenter, single-arm, and open-label trial. Eligible patients have locally advanced, stage IIIB to IV, cytology or histology proven NSCLC, with PD-L1 expression ≥ 25% of tumor cells by local testing. In case of nonsquamous histology, the most common driver mutations have to be ruled out in other to be recruited in the study (EGFR, ALK, ROS1). Further inclusion criteria are ECOG PS2, evaluable disease [according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and modified RECIST criteria for use in trials with immunotherapeutic—iRECIST], patients unsuitable for platinum-based combination chemotherapy, as judged by the investigator based on the previous expert panel publication [14], and adequate bone marrow and organ function. Patients have to be immunotherapy-naive, with no prior systemic treatment for metastatic NSCLC. Symptomatic treated brain metastases are allowed provided there are no ongoing requirements for corticosteroids as therapy for brain disease and no evidence of progression after completion of brain-directed therapy. Further brain disease inclusion criteria are also containing a maximum of 5 asymptomatic supratentorial brain metastases ≤ 10 mm. Patients with baseline autoimmune disorders or use of immunosuppressive medication (> 10 mg/day of prednisone) are excluded by the study. All patients provided written informed consent prior to enrollment. The trial was approved by the institutional ethical committees of the respective centers. The trial was registered with ClinicalTrials.gov, number NCT03620669.

The trial drug, durvalumab, is administered intravenously every four weeks (q4w) at a flat dose of 1500 mg, from registration until disease progression, loss of clinical benefit, or unacceptable toxicity. Other reasons for treatment discontinuation are intercurrent illnesses or withdrawal of consent.

Endpoints and assessments

The primary endpoint is overall survival (OS) at 6 months. Secondary endpoints are ORR, duration of response, progression-free survival (PFS) according to RECIST 1.1 and iRECIST 1.1, median OS, safety, quality of life and geriatric assessment. No efficacy data were mature for presentation as no specific analysis on it was planned at that time. To this end, all AEs and SAEs including AEs/SAEs for dyspnea are classified and graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE), Version 5.0, and monitored from the start of the study, with their relation to study treatment assessed by the investigator.

Statistical analysis

The baseline patient characteristics were summarized by frequencies and percentages for categorical variables; descriptive statistics including median and range were employed for continuous variables.

Tolerability was based on the safety population, i.e., all patients having received at least one study drug dose. All AEs reported until 28 days after the last administration of the trial treatment were taken into account and summarized by system organ class. The cause of death and reason for treatment discontinuation were presented as categorical variables. All analyses were performed using SAS® 9.4 (SAS Institute Inc., Cary, NC) on a Windows platform (Table 1).

Results

Patient characteristics

Between October 23, 2018, date of trial activation, and December 18, 2019, the date of data lock for this interim analysis, 21 patients were enrolled by eight Swiss sites. All 21 patients received at least one dose of durvalumab and were therefore included in this safety analysis. The patient baseline characteristics are descriptively summarized in Table 1.

At the interim analysis cut off, treatment was given for a median of two cycles over 63 days. The longest treated patient received 11 durvalumab cycles over 306 days. Seven dose delays were reported among four patients, three patients each had two dose delays, and another, a single dose delay. The reasons for these dose delays are listed in ESM Table 1.

Of the 21 patients, 17 (81%) discontinued treatment. The most frequent reason for treatment discontinuation was death, observed in nine patients (53%). All reasons for treatment discontinuation are listed in ESM Table 2.

Safety assessment and toxicities

Death cases At the time of the analysis, 13 out of 21 (62%) patients had died. One patient died due to colonic perforation that occurred nine months following treatment initiation under ongoing study medication while responding which has been confirmed by CT scan. This fatal event was considered treatment-related (1/13; 8%). The 12 other deaths were mainly attributed to tumor progression documented by clinical assessment (10/13; 77%) (Table 2). Of note, seven deaths (7/13; 54%) were observed during the first five weeks (range 0.6–4.7 weeks) following treatment initiation. Baseline dyspnea grade 2–3 was reported in four patients (4/7; 57%). Of these early fatal events, four (4/7; 57%) were caused by respiratory failure in patients with symptomatic lung tumors. Three (3/4; 75%) of these patients had baseline dyspnea grade 2–3, and one (1/4; 25%) had pre-existing COPD.

Adverse events All 21 patients experienced at least one AE, with 17 (17/21; 81%) reporting grade ≥ 3 events. One patient developed grade 4 hypertension (1/21; 5%).

The most commonly reported grade 3 AEs were dyspnea (5/21; 24%), followed by pneumonia (4/21; 19%),

Table 1 Baseline characteristics

Parameter	Total ($N=21$) *n* (%)
Median age (range), years	74 (55–82)
Sex	
Female	10 (48%)
Male	11 (52%)
Smoking history	
Current smokers	11 (52%)
Former smokers	9 (43%)
Never smokers	1 (5%)
Pulmonary disease at baseline	
COPD	8 (38%)
Interstitial lung disease	0 (0%)
Tumor stage	
Stage IIIb	2 (10%)
Stage IIIc	2 (10%)
Stage IV	17 (81%)
Histology	
Adenocarcinoma	14 (67%)
Squamous cell carcinoma	6 (29%)
NSCLC not otherwise specified	1 (5%)
PD-L1 status	21 (100%)[a]
Dyspnea at baseline (according to NCI CTCAE)	
Grade 2	5 (24%)
Grade 3	7 (33%)
Liver metastases	
No	18 (86%)
Yes	3 (14%)
Brain metastases	
No	18 (86%)
Yes	3 (14%)
Previous radiotherapy	
Brain	1 (5%)
Lung	1 (5%)
Mediastinum	1 (5%)
Bone	1 (5%)
Supraclavicular region	1 (5%)

NSCLC, nonsmall-cell lung cancer

[a]By local testing (Ventana SP142 excluded). A confirmatory central PD-L1 testing (no data at this timepoint) by the Ventana SP263 assay will be performed

Table 2 Causes of death

Parameter	Total ($N^a = 13$) *n* (%)
Death cause, term	
. Progressive disease[b]	10 (77%)
Cardiac arrest	1 (8%)
. Multiple underlying comorbidities following pneumonia	1 (8%)
. Intestinal perforation	1 (8%)
Treatment-related death	
. No	12 (92%)
. Yes	1 (8%)

[a]Total number of deaths

[b]All progressive disease cases were documented by clinical assessment only and could not be confirmed by CT scan

noncardiac chest pain (2/21; 10%), and hypertension (2/21; 10%). All grade ≥ 3 AEs are listed in ESM Table 3.

Treatment-related grade ≥ 3 AEs were abdominal pain (1/21; 5%), colitis (1/21; 5%), fatal colonic perforation (1/21; 5%), and fatigue (1/21; 5%) (Table 3).

Discussion

Single-agent pembrolizumab is a standard of care for fit (ECOG PS 0–1) patients with metastatic NSCLC expressing PD-L1 in ≥ 50% of tumor cells. An essential question in everyday clinical practice is whether these data can be extrapolated to patients with PS2. PS2 patients represent a heterogeneous population. Although these patients are capable of self-care and are active over > 50% of waking hours, they are unable to perform any work activities [15]. In the preimmunotherapy era, ECOG PS was considered a relevant independent prognostic factor, as well as a predictor of response and AEs in advanced stage NSCLC [16]. Whether outcomes of PS2 patients are similarly poor in the immunotherapy era is less clear [17]. Theoretically, due to lower toxicity rates of immunotherapy as compared to chemotherapy, immunotherapy would be expected to be more tolerable in a fragile population. On the other hand PS2 is known to be a heterogeneous group and within this, patients with severe interstitial lung disease or COPD and suffering from autoimmune disorders on active treatments may not be candidates for immune checkpoint inhibitors (ICIs) [18]. PS assessment by ECOG is imprecise and does not take into account the reason for the impaired function, namely whether it is due to

Table 3 Grade of treatment-related adverse events

System organ class	Term	Highest grade per patient	Total ($N = 21$)		
			Possible	Probable	Definite
Gastrointestinal disorders	Abdominal pain	3	1 (5%)		
	Belching	1	1 (5%)		
	Colitis	3		1 (5%)	
	Colonic perforation	5		1 (5%)	
	Diarrhea	1	1 (5%)		
		2	1 (5%)		
	Flatulence	1	1 (5%)		
	Nausea	2		1 (5%)	
	Vomiting	2		1 (5%)	
General disorders and administration site conditions	Fatigue	2	3 (14%)		
		3		1 (5%)	
	Fever	1	1 (5%)		
Investigations	Alkaline phosphatase increased	1	1 (5%)		
	Weight loss	1	1 (5%)		
Metabolism and nutrition disorders	Anorexia	2	1 (5%)		
Musculoskeletal and connective tissue disorders	Arthralgia	1			1 (5%)
	Arthritis	1	1 (5%)		
	Myalgia	1		1 (5%)	
Nervous system disorders	Dysgeusia	1	1 (5%)		
Psychiatric disorders	Confusion	1	1 (5%)		
Skin and subcutaneous tissue disorders	Dry skin	1	1 (5%)		
	Rash maculo-papular	1			1 (5%)

age, tumor burden, comorbidities, or polypharmacy. Moreover, PS assessment is subjective and can entail significant interobserver variability [19, 20].

In the first immunotherapy trials including PS2 patients, the anti-PD-1 antibody, nivolumab was proven safe in metastatic, pretreated NSCLC patients [21, 22]. A retrospective real-life data analysis of nivolumab in metastatic NSCLC revealed similar treatment-related adverse events (AEs) among patients with PS0-1 and 2 [23]. In a recent meta-analysis, ECOG PS ≥ 2 retains an important prognostic validity in patients treated with ICIs similar, in terms of effect size, to that reported for chemotherapy in NSCLC [24]. In a retrospective analysis of elderly NSCLC patients (≥ 70 years) treated with PD-1/PD-L1 inhibitors ECOG PS was a more relevant prognostic factor than age [25]. So far, no valid prospective data on efficacy of ICIs in NSCLC patients with poor ECOG PS are available. Retrospective studies showed conflicting results [26]. The study by Facchinetti suggested that the outcome in patients with ECOG PS2 is strongly dependent on the reason conditioning the poor PS itself [27]. Among published trials evaluating ICIs, mostly in the setting of pretreated NSCLC, the safety profile for patients with PS2 did generally not differ from that of the overall study population, although survival tended to be poorer [6, 21, 22, 28–32]. Only one of these studies [28] specifically addressed the activity of ICI monotherapy with pembrolizumab in a PS2 population in a prospective manner, including both treatment-naive and pretreated patients. Overall, of the 60 patients enrolled, nine were treatment-naive and 15 had a high PD-L1 expression (≥ 50%). Grade 3–4 toxicity occurred in 12% of patients. Patients with strong PD-L1 expression benefitted most (median OS of 14.6 months in the PD-L1 ≥ 50% group versus 9.8 months overall).

Several recent studies have investigated the role of ICIs in patients with PS2. One of these was a retrospective, single-center analysis involving 237 patients with advanced NSCLC treated with ICIs in the second-line setting or later [33]. Cox regression analysis was applied to compare the OS of patients with PS ≥ 2 at ICI initiation with that of patients with PS0-1. The median OS was significantly shorter among patients with PS ≥ 2 than PS0-1 (4.5 months vs. 14.3 months, P = 0.002). Moreover, among patients who died, 29% of those with PS ≥ 2 had received ICIs in their last 30 days of life compared to 11% of those with PS ≤ 2 (odds ratio, 0.29; $P = 0.008$). The authors highlight the need for careful discussion about potential tradeoffs of ICIs, particularly in the second-line or later setting.

Another recent, retrospective, multicenter study analyzed the role of PS in 246 patients with previously untreated advanced NSCLC with PD-L1 expression ≥ 50% and treated with front-line pembrolizumab [34]. The median PFS was 2.6 months (95% CI 1.9–5.1) and 11.3 months (95% CI 8.5–14.4) among patients with PS2 and PS0-1, respectively, while OS was 7.8 months (95% CI: 2.5–10.7) in the PS2 cohort and not reached in the PS0-1 group. The authors note that patients with PS2 did not appear to derive greater benefit from pembrolizumab than from platinum-based doublets in historical data.

In addition, according to a recent presentation, a combined immunotherapy of nivolumab with ipilimumab in patients with PS2 with untreated advanced NSCLC showed a similar safety profile for these patients [35].

Furthermore, the occurrence of immune-related adverse events (irAEs) has been described as a possible surrogate of clinical activity for ICIs in several cancers [36]. This aspect has been further highlighted in a large multicenter study [37] that has analyzed 1010 patients with treatment-naive metastatic NSCLC and a PD-L1 expression of ≥ 50% receiving first-line pembrolizumab. After a 6-week landmark selection, 877 patients were included in the efficacy analysis with 173 having PS ECOG 2. In general, the occurrence of irAEs was proven to be a surrogate predictor of clinical efficacy for pembrolizumab. However, the incidence of irAEs was lower in patients with PS2, so was the ORR and the PFS as compared to patients with ECOG 0–1. As highlighted by other studies, having a poor PS ECOG is a major prognostic factor which could tamper the possible benefit of ICIs.

To the best of our knowledge SAKK 17–19 is the largest safety analysis investigating prospectively an ICI, durvalumab administered every 4 weeks at a flat dose of 1500 mg, in patients with PS2 and untreated advanced NSCLC harboring PD-L1 expression ≥ 25%. Of the 21 patients included, there was one fatal treatment-related colonic perforation, along with grade 3 colitis and fatigue. All other treatment-related AEs were in line with the data reported from the previous trials. However, we observed a high number of early fatal events, with seven deaths (54%) occurring after only one dose of durvalumab within the first five weeks. Upon further analysis, four (57%) of these were related to rapid clinical deterioration in heavily symptomatic patients with advanced primary lung tumors. These fatal events could not be fully explained by the presence of pre-existing lung conditions as only one patient (25%) had baseline COPD. Nevertheless, a relevant proportion of the patients stated baseline dyspnea grade 2–3. This raises the question on the patients' selection and the challenge imposed by assessing PS without having robust objective tools [17]. Further efforts are needed to better identify patients for treatment with durvalumab, as using PD-L1 expression ≥ 25% as a solo biomarker could potentially be insufficient. In the aforementioned trials [21, 22, 28–31], no restrictions with respect to disease-related symptoms caused by the primary lung tumor were noted in the eligibility criteria for patients with PS2 and no specified tool or extra cautiousness were required or reported. Considering our preliminary results, additional selection

criteria are needed for patients with PS2 to help better define both a subpopulation which benefits from front-line ICIs and one in which their use may be detrimental.

With respect to future perspectives, NSCLC treatment has moved in the direction of combining immunotherapy with chemotherapy regimens. As PS2 patients are often unable to tolerate standard therapies, particularly combination chemotherapy regimens, and given that there is a lack of prospective trial data, it is currently unclear whether treating PS2 patients with combination chemoimmunotherapy is appropriate.

Several phase II and III clinical trials evaluating different ICIs in patients with NSCLC and PS2 are ongoing. Of these, one (the eNERGY trial; ClinicalTrials.gov identifier: NCT03351361) is a randomized phase III trial comparing nivolumab in combination with ipilimumab versus 1L carboplatin-based chemotherapy in elderly or PS2 patients. Another trial is investigating the efficacy and safety of atezolizumab as compared to chemotherapy in treatment-naive advanced NSCLC patients who are ineligible for platinum-containing therapy. Another single-arm study involving durvalumab in PD-L1 unselected patients with treatment-naive NSCLC (NCT02879617) is currently recruiting patients.

Although awaiting further safety data from these trials, we have issued a study protocol amendment designed to exclude patients with grade ≥ 3 dyspnea according to the modified Medical Research Council (mMRC) dyspnea scale. In addition, we now recommend that PS2 be confirmed by a second physician, taking into account the interobserver variability of ECOG PS assessment. Presently, patient accrual is still ongoing, and further durvalumab safety as well as efficacy in patients with advanced NSCLC and PS2 will become available shortly. In the meantime, we believe it is important to communicate our observations, namely the potentially inferior outcomes, and risk of rapid death, when treating highly symptomatic patients with PD-L1 positive tumors and impaired PS with first-line durvalumab.

In our study, 1L durvalumab in patients with PS2 and advanced NSCLC with PD-L1 $\geq 25\%$ showed an unexpectedly high early number of fatal events due to tumor progression. We cannot recommend treatment with 1 L durvalumab in patients who are highly symptomatic from the tumor, particularly those with respiratory symptoms.

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Author contributions All authors contributed equally to the drafting and finalization of the manuscript.

Compliance with ethical standards

Conflict of interest Dr. Mark received advisory fees from BMS, MSD, AstraZeneca, Roche, and Takeda; and received institutional research grants from AstraZeneca. Dr. Froesch received advisory fees from Roche, Takeda, Pfizer, and Boehringer Ingelheim. Dr. Addeo received compensation from Bristol-Myers Squibb, AstraZeneca, Merck Sharpe & Dohme, Takeda, Pfizer, Roche, and Boehringer Ingelheim for participating in advisory boards. Dr. Früh received advisory fees (paid to institution) from Bristol-Myers Squibb, Merck Sharpe & Dohme, AstraZeneca, Boehringer Ingelheim, Roche, and Takeda; and received institutional research grants from Bristol-Myers Squibb and AstraZeneca. Dr. Rothschild received honoraria (paid to institution) from Roche and AstraZeneca; and received consultancy/advisory fees (paid to institution) from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Eisai, and Eli Lilly. Dr. Pless received compensation from Abbvie, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eisai, Merck Sharpe & Dohme, Novartis, Pfizer, Roche, Takeda, and Merck for participating in advisory boards; received travel grants from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Roche, Takeda, and Vifor; and received speaking fees from Janssen. Dr. Weindler received honoraria (paid to institution) from Merck; and received travel grants (paid to institution) from Roche. The remaining authors declare no conflict of interest.

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