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Immunotherapy for Metastatic Non-Small Cell Lung Cancer: Real-World Data from an Academic Central and Eastern European Center

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. Immunotherapy with immune checkpoint inhibitors (ICIs) recently became the standard treatment for patients with advanced non-small cell lung cancer (NSCLC). Here, we present the first results of a real-world observational study on the effectiveness of ICI monotherapy in patients with advanced NSCLC treated at a single academic center in a Central and Eastern European (CEE) country.

Materials and Methods. Overall, 66 consecutive patients with advanced NSCLC treated with ICIs in everyday clinical practice, either with first-line pembrolizumab (26 patients) or second-line atezolizumab, nivolumab, or pembrolizumab (40 patients), from August 2015 to November 2018, were included. All data were retrieved from a hospital lung cancer registry, in which the data is collected prospectively.

Results. Included patients had a median age of 64 years, most were male (55%), 6% were in performance status ≥2, and 18%

had controlled central nervous system metastases at baseline. In first-line, the median progression-free survival (mPFS) was 9.3 months, while the median overall survival (mOS) was not reached. The 1-year overall survival (OS) was 62%. In second-line, the mPFS and mOS were 3.5 months and 9.9 months, respectively, with a 1-year OS of 35%. In the overall population, adverse events of any grade were recorded in 79% of patients and of severe grade (3–4) in 12% of patients.

Conclusion. The first real-world outcomes of NSCLC immunotherapy from a CEE country suggest comparable effectiveness to those observed in clinical trials and other real-world series, mainly coming from North America and Western European countries. Further data to inform on the real-world effectiveness of immunotherapy worldwide are needed. **The Oncologist** 2021;26:e2143–e2150

Implications for Practice: Immunotherapy is a standard treatment of advanced non-small cell lung cancer (NSCLC). The real-world data on immunotherapy are still limited. This article presents the first data on the effectiveness of mono-immunotherapy with immune checkpoint inhibitors for patients with advanced NSCLC treated at a single academic center in a Central and Eastern European country. The survival rates and toxicity are comparable to those achieved in randomized clinical trials and other real-world series, coming mainly from North American and Western European countries. There is a pressing need to gather further data on the effectiveness of immunotherapy in everyday practice worldwide.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Over 2 million new cases are diagnosed each year and result in more than 1.7 million deaths [1]. The most common form is non-small cell lung cancer (NSCLC). Nearly half of

patients are diagnosed at an advanced stage of disease, which leads to poor 5-year overall survival (OS). The observed 5-year OS in Europe is 13% and has not changed much in the last few decades [2]. Until this decade, chemotherapy was the standard

of care and, in fact, the only systemic treatment option for advanced NSCLC. The median overall survival (mOS) of patients on chemotherapy was up to 13.4 months [3].

The development of targeted therapies redefined the treatment paradigm for patients with oncogene-driven NSCLC. All pivotal clinical trials, performed in advanced epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive NSCLC, demonstrated improved response rates and progression-free survival in patients treated with targeted therapy compared with standard chemotherapy [3]. Moreover, with the sequential use of ALK-targeted agents, median overall survival of more than 7 years has been observed in patients treated in routine clinical practice [4]. Consequently, predictive biomarker testing and targeted therapies have been introduced into standard care for patients with advanced NSCLC [5,6]. Currently, international guidelines recommend testing for EGFR mutations, ALK and ROS1 rearrangements, and BRAF mutations for all patients with advanced non-squamous NSCLC [6]. In our country, reflex testing for particular predictive biomarkers has been adopted in accordance with European guidelines as soon as they were published. However, access to targeted therapies for NSCLC followed a slower pace, similarly to other Central and Eastern European (CEE) countries [7,8]. This is supported by recently published data reporting a lag time of 14 months between approval of new anticancer drugs by the European Medicines Agency and a positive national reimbursement decision in Slovenia [9]. Despite significant improvements, the benefits of targeted therapies are still restricted to a small proportion of patients with advanced NSCLC who harbor targetable driver mutations.

The unmet need for effective therapies in patients with NSCLC without a targetable oncogene was hoped to be met by immuno-oncology. The immune checkpoint inhibitors (ICIs) atezolizumab, nivolumab, and pembrolizumab were first studied in second-line treatment of advanced NSCLC. Substantial improvements in mOS rates of up to 13.8 months were observed compared with up to 9.6 months achieved with docetaxel [10–13]. Even more impressive results were achieved in the first-line setting. In the pivotal trial of pembrolizumab monotherapy in a patient population with programmed death–ligand 1 (PD-L1) ≥50%, a mOS of 30 months was observed [14,15]. To further improve treatment results, the combination of two previous first-line standards, chemotherapy and immunotherapy, was studied in unselected patient populations and further added efficacy compared with chemotherapy alone while retaining a reasonable safety profile [16]. These significant improvements are indeed coupled with new immune-related adverse events (AEs). But even though treatment-related AEs are recorded in the majority of patients, more than 60%, only approximately 15% experience severe AEs (grade 3 or 4), treatment discontinuation, or, very rarely, fatal toxicity [17].

Although immunotherapy represents a new treatment standard for advanced NSCLC, many questions still need to be answered to ensure its optimal use in everyday clinical practice [18]. It is vital to evaluate how the impressive efficacy data and favorable safety profile reported in randomized clinical trials (RCTs) translate into everyday clinical practice effectiveness. A substantial gap in outcomes between patients included in clinical trials and those treated in the real-world scenario was observed, particularly in cancer populations of older patients with comorbidities [19]. Clinical trials tend to include younger patients in good performance status (PS) with minimal comorbidity, thus making real-world data for populations of advanced NSCLC, who tend to be older and with multiple comorbidities, most interesting [20,21]. There are many published studies on the real-world effectiveness of immunotherapy with ICIs in advanced NSCLC (Tables 1 and 2). Most of them provide reassuring data for second-line mono-immunotherapy, including also patients with poor prognostic characteristics (Table 2). However, data in the first-line setting are limited and not as reassuring, especially when compared with the pivotal trial (Table 1). Of note, real-world data published so far mainly involve patients from North America and Western Europe, similar to those included in pivotal trials. To our knowledge, no real-world data on immunotherapy outcomes in NSCLC for CEE countries, which are still facing a gap in cancer control, have been published so far [22].

Here, we report the first results of a real-world observational study evaluating treatment outcomes for patients with advanced NSCLC treated with ICI monotherapy, either in first- or second-line setting at a single academic center in a Central and Eastern European country.

PATIENTS, MATERIALS, AND METHODS

Patients

The study included consecutive patients with pathologically confirmed advanced NSCLC treated with ICI monotherapy between August 2015 and November 2018 in routine clinical practice at a single academic center in Slovenia. Patients received pembrolizumab in the first-line setting if they had a PD-L1 expression ≥50%, or atezolizumab, nivolumab, or pembrolizumab in the second-line setting. PD-L1 testing was mandatory before first-line but not second-line therapy and was performed on formalin-fixed, paraffin-embedded histology samples or cytospins by using PD-L1 monoclonal antibodies (22C3 clone by DAKO, Glostrup, Denmark or SP263 clone by Ventana/Roche, Oro Valley, AZ).

Nivolumab was available within a compassionate use program already in August 2015, whereas atezolizumab and pembrolizumab were available only after granted the marketing authorization by the European Medicines Agency and national reimbursement. Pembrolizumab, both for first- and second-line, was reimbursed in August 2017, and second-line atezolizumab was reimbursed in May 2018. Included patients may have had controlled central nervous system (CNS) disease, with or without previous CNS irradiation. All patients were free of corticosteroid treatment. All included patients were routinely tested for EGFR mutations and ALK rearrangement and, after 2016, also for ROS1 rearrangements. None of the included patients had a known driver oncogene, and none had known autoimmune disease. All patients are treated and routinely followed at a single institution, where clinicians are encouraged to record and grade all AEs by Common Terminology Criteria for Adverse Events, version 4 and to evaluate the objective response rate (ORR) according to RECIST 1.1 [23,24].

Table 1. First-line immunotherapy outcomes in the pivotal RCTs, real-world studies, and present study

First author, year	Study design (country)	Drug	Patients, n	Age median (range)	Gender: males, n (%)	PS ≥ 2, n (%)	CNS metastases, n (%)	Median PFS, mo	Median OS, mo	1-year OS, %
Reck, 2016 & 2019 [11,12]	RCT, multicentric	Pem	154	64.5 (33–90)	92 (59.7)	1 (0.6)	18 (11.7)	10.3	30.0	70.3
Ksienski, 2019 [34]	Observational, multicentric (Canada)	Pem	141	70.0 (41–91)[a]	97 (51.1)[a]	65 (34.2)[a]	26 (13.7)[a]	3.7[a]	24.3	ND
Velcheti, 2019 [39]	Observational, multicentric (U.S.)	Pem	188	72.0 (46–84)	90 (47.9)	0	23 (12.2)	6.8	19.1	60.4
Amrane, 2019 [24]	Observational, multicentric (France)	Pem	108	67.0 (37–87)	70 (64.8)	25 (23.1)	19 (17.6)	10.1	15.2	ND
Tamiya, 2019 [32]	Observational, multicentric (Japan)	Pem	213	71 (39–91)	176 (82.6)	41 (19.2)	ND	8.3	17.8	ND
Tambo, 2020 [40]	Observational, multicentric (Japan)	Pem	95	72.0 (51–89)	71 (74.7)	21 (22.1)	ND	6.1	NR	58.3
Current study	Observational, single center (Slovenia)	Pem	26	65.5 (39–78)	16 (62.0)	3 (11.0)	4 (15.0)	9.3	NR	62.0

[a]Reported for 190 patients, of which 49 were treated in second-line setting.
Abbreviations: CNS, central nervous system; ND, no data; NR, not reached; OS, overall survival; Pem, pembrolizumab; PFS, progression-free survival; PS, performance status; RCT, randomized clinical trial.

Data Collection

Data were retrieved from the hospital-based lung cancer registry, which prospectively collects comprehensive demographics, pathological and molecular characteristics, and treatment and survival data of all patients with lung cancer diagnosed and treated at the center. The hospital registry includes approximately 600 new patients with lung cancer per year, representing nearly half of all newly diagnosed patients with lung cancer in Slovenia. Patients consent to collecting data in the frame of the lung cancer registry at the time of diagnosis or start of treatment. All data were collected anonymously. For this study, progression and survival status were updated, and the data were retrieved in December 2019.

Outcome Measures and Statistical Analysis

Patient and treatment characteristics were analyzed using descriptive statistics. Treatment outcomes are presented separately for patients treated in the first-line or second-line setting. The Kaplan Meier method was used to estimate progression-free survival (PFS) and OS. PFS was calculated from the date of the first immunotherapy dose until tumor progression or death from any cause, whichever occurred first. OS was calculated from the date of the first immunotherapy dose until death from any reason. Median follow-up time was calculated using the reverse Kaplan-Meier estimator. Statistical analyses were generated using R Studio, R version 3.5.3, with package survminer (R Foundation, Vienna) [25,26].

RESULTS

Patients and Treatments

Overall, 66 patients were treated with ICIs consecutively during the study period from August 2015 to November 2018. Among these, 26 patients were treated with ICIs in the first-line and 40 in the second-line setting.

The included 66 patients had a median age of 64 years (range, 39–78 years), 55% (36/66) of patients were male, 82% (54/66) were current or former smokers. The majority, 83% (55/66), of patients had adenocarcinoma. Most, 94 % (62/66), of patients were in a good PS of 0–1. CNS metastases were present in 18% (12/66) of patients at baseline. Baseline demographics and clinical characteristics by line of therapy are displayed in Table 3.

In the first-line setting, all 26 patients were treated with pembrolizumab monotherapy (200 mg every 3 weeks) and had the required PD-L1 expression ≥50%. In the second-line setting, 10% (4/40) of patients received atezolizumab (1,200 mg every 3 weeks), 58% (23/40) of patients received nivolumab (3 mg/kg every 2 weeks), and 33% (13/40) of patients received pembrolizumab (2 mg/kg every 3 weeks). In this setting, only 25% (10/40) of patients had a PD-L1 expression ≥50%, while most, 48% (19/40), of patients had PD-L1 expression <1%; PD-L1 expression was not known in 10% (4/40) of patients.

Table 2. Second-line immunotherapy outcomes in the pivotal RCTs, real-world studies, and present study

First author, year	Study design (country)	Patients, n	Drug	Age, median (range), yr	Gender: male, n (%)	PS ≥ 2, n (%)	CNS metastases, n (%)	Median PFS, mo	Median OS, mo	1-year OS, %
Brahmer, 2015 [8]	RCT, multicentric	135[a]	Nivo	62.0 (39–85)	111 (82.0)	2 (1.5)	9 (6.6)	3.5	9.2	42.0
Borghaei, 2015 [7]	RCT, multicentric	292[b]	Nivo	61.0 (37–84)	151 (51.7)	0	34 (11.6)	2.3	12.2	51.0
Herbst, 2015 [9]	RCT, multicentric	344[c]	Pem	63.0 (56–69)	212 (61.6)	3 (0.9)	56 (16.3)	3.9	10.4	43.2
Rittmeyer, 2016 [10]	RCT, multicentric	425	Atezo	63.0 (33–82)	261 (61.4)	0	85 (10.0)[d]	2.8	13.8	55.0
Brustugun, 2016 [41]	Observational, single center (Norway)	58	Nivo	64.6 (32–88)	28 (48.3)	14 (24.1)	0	4.0[d]	11.7	50.0
Schouten, 2017 [42]	Observational, multicentric (Netherlands)	248	Nivo	63.0 (29–84)	136 (54.8)	40 (16.1)	56 (22.6)	2.6	10.0	ND
Dudnik, 2018 [26]	Observational, multicentric (Israel)	260	Nivo	67.0 (41–99)	176 (67.7)	139 (53.5)	55 (21.1)	2.8	5.9	ND
Manrique, 2018 [43]	Observational, multicentric (Spain)	188	Nivo	58.0 (45–81)	144 (76.6)	19 (10.1)	42 (22.3)	4.8	12.8	55.0
Lin, 2018 [27]	Observational, single center (Taiwan)	74	Nivo, Pem	62.1 (34–87)	43 (58.1)	36 (48.6)	33 (44.6)	1.8	7.9	46.0
Kobayashi, 2018 [44]	Observational, multicentric (Japan)	142	Nivo	67.0(34–85)	106 (74.6)	23 (16.2)	27 (19.0)	1.9	ND	ND
Geier, 2018 [45]	Observational, multicentric (France)	259	Nivo	62.0 (29–85)	187 (72.2)	15 (5.8)	53 (20.5)	2.3	11.0	47.9
Juergens, 2018 [46]	Observational, multicentric (Canada)	472	Nivo	66.0 (36–92)	203 (43.0)	42 (8.9)	62 (13.1)	3.5[e]	12.0	50.0
Fujimoto, 2018 [47]	Observational, multicentric (Japan)	613	Nivo	66.9 (ND)	433 (71)	141 (23)	ND	ND	ND	54
Montana, 2018 [28]	Observational, multicentric (France)	98	Nivo	65.5 (42–85)	70 (71.4)	39 (39.7)	ND	1.8	6.3	ND
Almazan, 2019 [48]	Observational, multicentric (Spain)	221	Nivo	64.5 (NR)	185 (83.7)	30 (13.8)	22 (10.0)	5.3	9.7	ND
Khozin, 2019 [49]	Observational, multicentric (U.S.)	1,344[f]	Nivo, Pem	69.0 (61–75)	747 (55.6)	ND	ND	ND	8.0	39.0
Khozin, 2019 [50]	Observational, multicentric (U.S.)	5,257[g]	Atezo, Nivo, Pem	69.0 (62–76)	2,819 (53.6)	ND	ND	3.2	9.3	ND
Ahn, 2019 [29]	Observational, single centre (Korea)	155	Nivo, Pem	64.0 (35–58)	113 (72.9)	34 (21.9)	61 (39.4)	3.0	10.2	ND
Crino, 2019 [51]	Observational, multicentric (Italy)	371[a]	Nivo	68.0 (31–91)	298 (80.3)	22 (5.9)	37 (9.9)	4.2	7.9	39.0
El Karak, 2019 [38]	Observational, (Lebanon)	110	Nivo, Pem	66.0 (ND)	75 (68.2)	ND	17 (15.5)	4.0	8.1	ND
Grossi, 2019 [33]	Observational, multicentric (Italy)	1,588[b]	Nivo	66.0 (27–89)	1,029 (64.8)	108 (6.8)	409 (25.7)	3.0	11.3	48.0
Morita, 2020 [52]	Observational, multicentric (Japan)	901[h]	Nivo	67.0 (30–90)	651 (72.3)	157 (17.4)	201 (22.3)	2.1	14.6	54.3
Figueiredo, 2020 [31]	Observational, multicentric (Portugal)	219	Nivo	64.0 (37–83)	154 (70.3)	29 (13.2)	ND	4.9	13.2	56.5
Weis, 2020 [53]	Observational, single centre (U.S.)	43	Atezo	67.2 (ND)	23 (53.5)	9 (20.9)	ND	2.0	6.5	ND
		81	Nivo	64.3 (ND)	39 (48.2)	21 (28.4)	ND	2.2	8.4	ND
Martin, 2020 [37]	Observational, multicentric (Argentina)	109	Nivo	65.0 (56–72)	63 (57.8)	17 (15.6)	ND	6.1	12.1	ND
Barlesi, 2020 [30]	Observational, multicentric (France)	1,420[i]	Nivo	66.0 (35–91)	986 (69.4)	241 (17.1)	282 (19.9)	2.8	11.2	48.6
Current study	Observational, single center (Slovenia)	40	Atezo, Nivo, Pem	63.0 (42–77)	20 (50.0)	1 (3.0)	8 (20.0)	3.5	9.9	35.0

[a] Only squamous cell lung cancer.
[b] Only nonsquamous cell lung cancer.
[c] cohort treated with pembrolizumab 2 mg/kg.
[d] Reported for atezolizumab and docetaxel cohort combined.
[e] Time to treatment failure.
[f] 227 (16.9%) patients in first line.
[g] 1,329 (25.3%) patients in first line.
[h] 38 (4.2%) patients in first line.
[i] Four (0.3%) patients in first line.
Abbreviations: Atezo, atezolizumab; CNS, central nervous system; ND, no data; NR, not reached; Nivo, nivolumab; OS, overall survival; Pem, pembrolizumab; PFS, progression-free survival; PS, performance status; RCT, randomized clinical trial.

Table 3. Baseline characteristics of patients included in the study

	All patients (n = 66)	First-line (n = 26)	Second-line (n = 40)
Median age (range), yr	64.0 (39–78)	65.5 (39–78)	63.0 (42–77)
Gender			
Female	30 (45)	10 (38)	20 (50)
Male	36 (55)	16 (62)	20 (50)
Smoking status			
Former or current smoker	54 (82)	20 (77)	34 (85)
Nonsmokers	12 (18)	6 (23)	6 (15)
ECOG performance status			
0–1	62 (94)	23 (89)	39 (97)
2 or more	4 (6)	3 (11)	1 (3)
Histology			
Adenocarcinoma	55 (83)	21 (81)	34 (85)
Squamous cell carcinoma	8 (12)	2 (8)	6 (15)
NOS or other	3 (5)	3 (12)	0 (0)
PD-L1 expression			
0%	19 (29)	0 (0)	19 (48)
1%–49%	7 (11)	0 (0)	7 (18)
50% or more	36 (55)	26 (100)	10 (25)
Unknown	4 (6)	0 (0)	4 (10)
CNS metastasis	12 (18)	4 (15)	8 (20)

Data presented as n (%), unless otherwise noted.
Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; PD-L1, programmed death–ligand 1.

Treatment Outcomes

In the first-line setting, an ORR was achieved in 46% (12/26) of patients (four complete responses [CR] and eight partial responses [PR]), with a further 27% (7/26) of patients achieving stable disease (SD). Median (m)PFS in the first-line cohort was 9.3 months (95% confidence interval [CI], 3.5–NR; Fig. 1), and median OS has not yet been reached (95% CI, 7.1–NR; Fig. 1). The 1-year OS rate was 62% (95% CI, 45%–83%). The median follow-up (FU) time was 19.9 months.

In the second-line setting, an ORR was achieved in 25% (10/40) of patients (one CR and nine PR), with a further 23% (9/40) of patients achieving SD. Median PFS was 3.5 months (95% CI, 1.9–6.6; Fig. 2), and median OS was 9.9 months (95% CI, 4.9–16.1; Fig. 2). The 1-year OS rate was 35% (95% CI, 23%–53%). The median FU time was 34.2 months.

Safety

Because of the small sample size and because no difference was expected in the AE profile among first- and second-line ICI treatment, safety outcomes are presented for the whole group of patients [17]. Treatment-related AEs were recorded in 79% (52/66) of all patients (Table 4). The most common AEs were fatigue, skin disorders, hypo/hyperthyroidism, and hepatotoxicity, each occurring in more than 15% of patients.
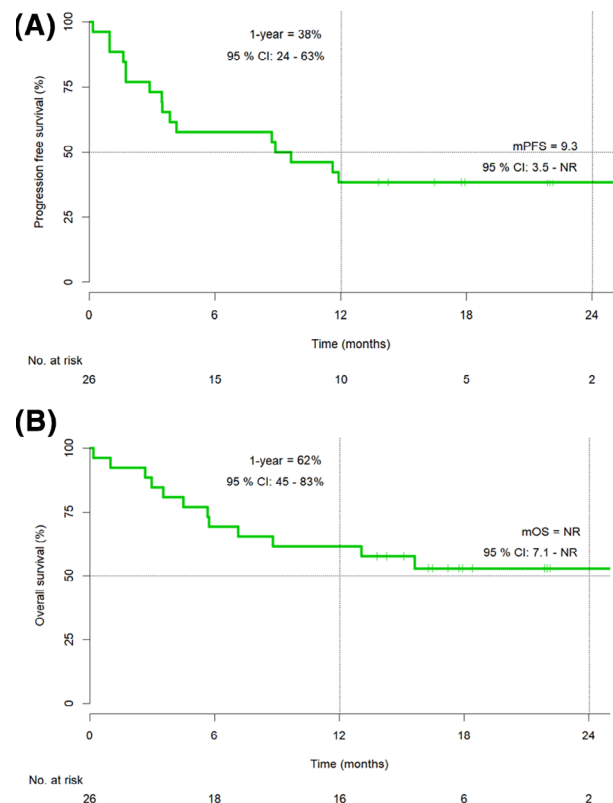

Figure 1. Progression-free survival **(A)** and overall survival **(B)** in the first-line cohort (n = 26).
Abbreviations: CI, confidence interval; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached.
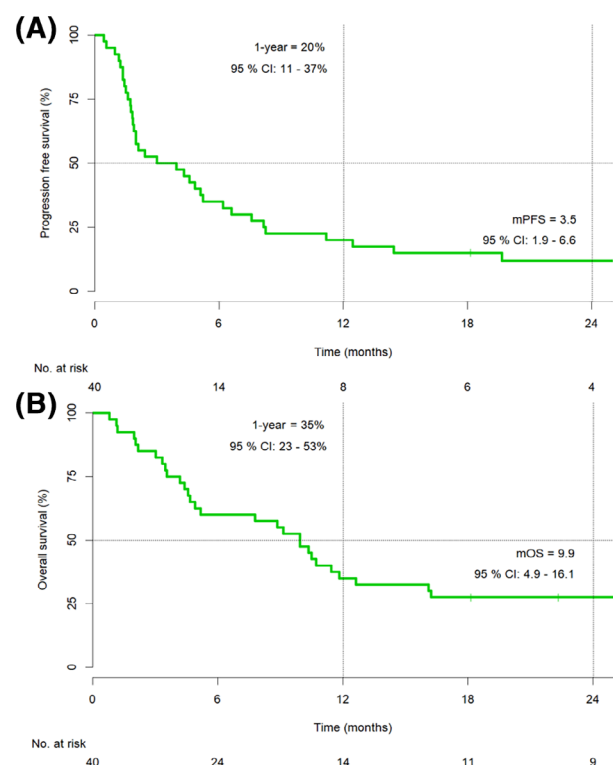

Figure 2. Progression-free survival **(A)** and overall survival **(B)** in the second-line cohort (n = 40).
Abbreviations: CI, confidence interval; mOS, median overall survival; mPFS, median progression-free survival.

Table 4. Adverse events in the whole cohort of patients (*n* = 66)

Adverse event, *n* (%)	Any grade	G 1–2	G 3–4
Any	52 (79)	44 (67)	8 (12)
Fatigue	25 (38)	25 (38)	0 (0)
Skin disorders	19 (29)	18 (27)	1 (2)
Hypo-/hyperthyroidism	11 (17)	11 (17)	0 (0)
Hepatotoxicity	12 (18)	10 (15)	2 (3)
Diarrhea	3 (5)	3 (5)	0 (0)
Colitis	3 (5)	1 (2)	2 (3)
Diabetes mellitus	2 (3)	0 (0)	2 (3)
Other[a]	13 (20)	9 (14)	4 (7)
Led to corticosteroid treatment	11 (17)		
Led to discontinuation	9 (14)		
Led to death	0 (0)		

[a]Other adverse event G1–2: Myalgia, arthralgia, stomatitis, anaemia, agranulocytosis. Other adverse event G 3–4: infection, mesenteritis, Cushing syndrome, agranulocytosis.
Abbreviation: G, grade.

However, AEs were severe, grades 3 or 4, only in 12% (8/66) of patients. Treatment with systemic corticosteroid was required in 17% (11/66) of patients, and permanent treatment discontinuation due to AE occurred in 14% (9/66) of patients. Of the nine patients who discontinued immunotherapy because of toxicity, the two patients with PR had durable remissions. After immunotherapy discontinuation, the first patient was in remission for an additional 5 months, and the second patient was still in remission for more than 26 months at data cut-off. No treatment-related death was recorded.

DISCUSSION

The present study provides the first results of an observational study evaluating the effectiveness and safety of mono-immunotherapy with ICIs in a real-world collective of patients with advanced NSCLC treated at an academic center in Central and Eastern Europe. The reported treatment outcomes for the second-line setting (mPFS of 3.5 months, mOS of 9.9 months, and 1-year OS of 35%) are similar to those published in RCTs and multiple real-world studies (Table 2). However, the results for the first-line setting (mPFS of 9.3 months, mOS not yet reached, and 1-year OS of 62%) are not so reassuring. However, the so far published real-world data on first-line immunotherapy are limited, and the median follow-up of patients in real-world series is still short (Table 1), making any comparison difficult.

The real-world evidence on upfront immunotherapy in advanced NSCLC is limited because of the short time since regulatory approval of pembrolizumab in first-line treatment. Moreover, only one study from Europe has been published, making any additional European real-world data most needed [27]. The herein reported 1-year OS of 62% is broadly similar to those in other published real-world studies. The pivotal RCT KEYNOTE-024, comparing first-line pembrolizumab with chemotherapy in advanced NSCLC with PD-L1 ≥ 50%, reported a remarkable

mOS of 30.0 months and 1-year OS of 70% that have yet not been reproduced in routine clinical practice (Table 1). However, the present and other real-world outcomes compare better to those reported in the subgroup of patients with a PD-L1 ≥ 50% participating in the KEYNOTE-042, with a mOS of 20.0 months [28]. Of note, the KEYNOTE-042 trial was conducted in a larger number of centers and regions, including centers from CEE and Latin America, thus representing a broader and more global population of patients. The comparable outcomes in real-world series were achieved even though most of them also included patients with poor PS ≥2, often representing well above 20% of patients, whereas these were excluded from participation in KEYNOTE-024. As already mentioned, median FU is still very short in most real-world series and is much shorter than in KEYNOTE-024 [15]. Therefore, further evaluation of more extensive real-world series with longer follow-up is awaited.

The real-world evidence on immunotherapy use in second-line is more extensive, with reports including more than thousands of patients and providing a better insight into ICI monotherapy outcomes in routine clinical practice (Table 2). The herein reported 9.9-month mOS is in line with those in RCTs, with mOS ranging from 9.2 to 13.8 months, and within the broad ranges of individual real-world studies, reporting mOS from 5.9 to 14.6 months (Table 2). As expected, shorter mOS was reported in cohorts with a high share of patients with poorer prognostic factors, such as PS ≥2, exceeding 50% of patients in some series, and brain metastases, sometimes exceeding 40% of patients [29–32]. Both PS ≥2 and symptomatic brain metastases were proven as independent predictors of poor survival in a large prospective observational trial evaluating effectiveness of second-line monotherapy with nivolumab in France [33]. In our series only 6% of patients had PS of ≥2, but nearly a fifth (18%) had CNS metastases at baseline.

The herein observed safety of immunotherapy treatment, with most (79%) of patients experiencing an AE but being severe only in 12% of patients, is consistent with data from pivotal mono-immunotherapy RCT trials in NSCLC and a recent meta-analysis of immunotherapy AEs in RCTs in solid tumors [10–15,17]. Interestingly, the discontinuation rate in our cohort of patients (14%) is higher than the up to 8% reported in the abovementioned references, possibly suggesting inadequate AE management with decreasing expertise from clinical trials. In fact, before initiating nivolumab compassionate use program, there were no clinical trials with ICIs for advanced NSCLC running at our institution. No new safety concerns and no treatment-related deaths were noticed in our observational study. Our findings fall within the significant variability reported in the frequency of AE in real-world studies, with the highest being very similar to those observed herein and the lowest reporting any AE in only approximately a third of patients [33–37]. Thus, although the available real-world evidence is reassuring in confirming a favorable tolerability profile for ICI monotherapy in everyday clinical practice, a word of caution still needs to be in place when acknowledging the possible underreporting of adverse events outside the clinical trial setting.

The abundance of real-world evidence on ICI outcomes in NSCLC is limited to North America, Western Europe, and the Asian-Pacific region, mainly Japan. These data are unlikely generalizable to other parts of the world, where

access and availability to cancer care vary significantly. CEE is still a region with a lack of financial and human resources and with substantially higher cancer mortality to incidence ratio than Western Europe [22]. Ensuring access to immunotherapy, with its indications expanding to almost all cancer types, represents a challenge to all health care systems and mandates the evaluation of immunotherapy real-world outcomes. Real-world data are most needed for regions with lack of resources and limited participation in clinical trials, such as CEE countries. In those countries, it might happen that novel drugs are first being used in routine clinical practice without previous expertise and skills gained within clinical trials, thus hampering their safe transfer to everyday clinical practice [38,39]. Although some CEE countries improved their participation in clinical trials during the last decade, this was not the case for smaller countries such as Slovenia [40]. According to our knowledge, there are no published data on real-world immunotherapy outcomes in patients with NSCLC treated in our region. Only two real-world data sets are from regions less often represented in RCT, namely Argentina and Lebanon, with favorable results [41,42]. Hopefully, our report will trigger the publication of more real-world data from regions with a lower development index.

Nevertheless, a few limitations apply to our study. First, our cohort of patients is small, with 66 patients included altogether and only 26 patients in the first-line setting. Second, despite the mFU for second-line therapy reaching almost 3 years, the mFU for first-line therapy is only approximately 1.5 years. Consequently, no subgroup analysis was possible in this report because of the small number of patients and relatively short follow-up. Third, our report is limited to only one academic center in the country. Indeed, the real-world data collected at the national level would provide better insight and more reassuring data.

Conclusion

The first results of our observational trial on the effectiveness of mono-immunotherapy with ICIs in the first- and second-line treatment of advanced NSCLC at a single center in a Central and Eastern European country are in line with pivotal clinical trials and other real-world reports. Our results indicate effective and safe use of mono-immunotherapy with ICIs in routine clinical practice; however, for any firm conclusions, more data derived from larger collectives of patients with longer follow-up times are needed. Further real-world studies, especially of immunotherapy in the first-line setting, either as monotherapy or combined with chemotherapy, are most needed to inform their effectiveness in routine clinical practice. This urge is greater in health care systems and countries traditionally underrepresented in pivotal trials, such as the Central and Eastern European countries.

Author Contributions

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Disclosures

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