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Overall survival and role of programmed death ligand 1 expression in patients with metastatic non-small-cell lung cancer and immunotherapy: an observational study from central Switzerland

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Summary

BACKGROUND: In clinical trials, therapy with immune checkpoint inhibitors has improved the survival of patients with metastatic non-small-cell lung cancer (NSCLC). These trials were important for drug approval and for defining new treatment standards but the effect of checkpoint inhibitors in patients treated outside of clinical trials is not well known. The goal of this study was to assess the effect of immunotherapy on the overall survival of patients with metastatic NSCLC in the region of central Switzerland.

MATERIALS AND METHODS: The study included 274 patients with histologically confirmed metastatic (stage IV) NSCLC in central Switzerland in the years 2015 to 2018. Patients with NSCLC and actionable driver mutations were excluded. Patients with checkpoint inhibitor treatment (immuno-oncology [IO] group, n = 122) were compared with patients without checkpoint inhibitor treatment (no-IO group, n = 152). Baseline demographics, disease characteristics and therapies applied were collected retrospectively. The primary endpoint was median overall survival calculated either from diagnosis or from the start of checkpoint inhibitor therapy to death or data cut-off (21 July 2021). We used the Kaplan-Meier method and an adjusted Cox proportional-hazards regression model. The expression of programmed-death ligand 1 (PD-L1) on tumour cells was used for exploratory analysis.

RESULTS: Patients had a median age of 68.4 years, most were male (61.7%) and more than half were current or former smokers (65%). A test for PD-L1 expression was available for 55.8% of the tumours. Patients in the IO group were younger than patients in the no-IO group. Among the 122 patients in the IO group, the median overall survival was 15 months (95% confidence interval [CI] 12–20). In the no-IO group, the median overall survival was 4 months (95% CI 3–7) with chemotherapy and 2 months (95% CI 1–2) with best supportive care. Patients with high (≥50%) PD-L1 expression and checkpoint inhibitor therapy had a slightly longer overall survival than patients with low PD-L1 and checkpoint inhibitor therapy.

CONCLUSION: These results suggest that treatment with checkpoint inhibitors improves overall survival in patients with metastatic NSCLC and that PD-L1 expression could have a predictive value in patients treated outside of clinical trials. Further studies are needed to study the magnitude of the benefit of checkpoint inhibitors according to molecular NSCLC subtype.

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Introduction

Lung cancer represents a major global health burden. The main cause of lung cancer is smoking [1, 2]. Although many countries have made notable efforts to control tobacco use, lung cancer remains the leading cause of cancer-related deaths in the Western world [3, 4]. In Switzerland, smoking rates remain high and lung cancer is frequent [5]. According to the statistics of the Swiss Federal Office of Public Health, approximately 2700 men and 1800 women are diagnosed with lung cancer each year [6]. Switzerland does not yet have a national lung-cancer screening programme [7]. Approximately 50% of patients with lung cancer present with metastatic disease at the time of diagnosis [8]. These patients have a poor prognosis [6]. In previous studies, the median overall survival ranged from 3 to 6 months with best supportive care and from 9 to 12 months with platinum-based chemotherapy [9–12].

Lung cancer includes two histopathological types: small-cell lung cancer (SCLC) and non-small-cell lung cancer

(NSCLC). NSCLC accounts for 80–90% of all lung cancers and includes the subtypes adenocarcinoma, squamous-cell carcinoma and large-cell carcinoma [13, 14]. In pulmonary adenocarcinoma, the discovery of oncogenic driver mutations and the development of targeted therapy have improved the prognosis of a substantial proportion of patients [15–18]. Today, the routine diagnostic workup for metastatic NSCLC in Switzerland depends on the histology. For both adenocarcinoma and squamous-cell carcinoma, the workup includes testing for the programmed-death ligand 1 (PD-L1), and in cases of newly diagnosed adenocarcinoma, it also includes sequencing the epidermal growth factor receptor (EGFR), the anaplastic lymphoma kinase (ALK), the V-RAF murine sarcoma viral oncogene homologue B1 (BRAF), the Kirsten rat sarcoma homologue (KRAS), the receptor tyrosine kinase MET proto-oncogene (MET), neurotrophic tropomyosin receptor kinases (NTRKs), the RET proto-oncogene (RET), and the ROS proto-oncogene 1 (ROS1) [14]. Approved targeted therapies can be offered to approximately 20–25% of patients with metastatic pulmonary adenocarcinoma [19–22].

For treating patients with metastatic NSCLC without actionable driver mutations, monoclonal antibodies targeting the programmed cell death protein 1 (PD-1) or PD-L1 pathway have been the most important clinical advance in the last decade [21]. Checkpoint inhibitors such as nivolumab, pembrolizumab and atezolizumab were initially tested in patients with a metastatic NSCLC progressing after first-line chemotherapy. Randomised clinical trials demonstrated superior activity for checkpoint inhibitors compared with docetaxel in the second line, with an improvement of overall survival of approximately 9 to 12 months (measured from the time of randomisation) [10, 11, 23–25]. Based on these results, Swissmedic approved nivolumab in 2015 and pembrolizumab and atezolizumab in subsequent years. Tumour PD-L1 expression has been correlated with the magnitude of clinical benefit from checkpoint inhibitor therapy in registration trials [25].

Further randomised clinical trials have studied checkpoint inhibitors in the first line of therapy at different levels of PD-L1 expression. For NSCLC with PD-L1 expression of 50% or more, pembrolizumab was compared with chemotherapy in the trial KN024 (on squamous and non-squamous NSCLC), and pembrolizumab (overall survival 95% CI 18.3 months to not reached) exhibited significantly better overall survival results than chemotherapy (overall survival 14.2 months, 95% CI 9.8–19.0) [26]. For NSCLC with PD-L1 expression below 50%, the trials KN189 (on non-squamous NSCLC) and KN407 (on squamous NSCLC) compared pembrolizumab plus chemotherapy with chemotherapy alone. The combination therapy was significantly better (overall survival 15.9 and 22.0 months) than chemotherapy alone (overall survival 10.7 and 11.3 months) [27, 28]. It should be noted that patients with tumours harbouring EGFR or ALK alterations were excluded from these trials, because checkpoint inhibitors have limited activity against such tumours [29]. In the IMPOWER-150 study (on non-squamous NSCLC), atezolizumab plus bevacizumab and chemotherapy (overall survival 21.3 months) produced significantly better results than chemotherapy (overall survival 16.3 months) [30, 31]. There is a lack of head-to-head trials testing different checkpoint inhibitors, so therapeutic decisions are based on regional approval and reimbursement status [21].

The availability of checkpoint inhibitors and targeted therapies have significantly changed the treatment of NSCLC in the last decade [32]. Elderly patients over 70 years old, who account for most patients with NSCLC in many countries including Switzerland, are underrepresented in clinical trials. Moreover, patients with NSCLC and a poor Eastern Cooperative Oncology Group performance status (ECOG-PS ≥2), active brain metastases, autoimmune disease, organ dysfunction, or a life expectancy below 3 months are generally excluded from checkpoint inhibitor registration studies [33]. Patients with such conditions are very common in the clinic and are now treated with checkpoint inhibitors [25, 34, 35], but few studies have addressed the impact of these therapies on patients treated outside of registration trials [36].

In a previous study in central Switzerland on metastatic NSCLC with actionable driver mutations, we showed that targeted therapy led to prolonged overall survival [37]. In the present paper, we report the results of a new retrospective observational study from the same region between 2015 and 2018 in collaboration with the Cancer Registry of Central Switzerland [38].

Our primary aim was to assess overall survival from the time of diagnosis of stage IV NSCLC among patients treated with checkpoint inhibitors in any line of treatment and among patients who did not receive checkpoint inhibitors in the same period of time. Other aims were to describe the survival of patients receiving checkpoint inhibitors in the first line and in further lines and to correlate tumour PD-L1 expression level with survival.

Patients, materials and methods

Study design

This retrospective cross-sectional study includes clinical data from five non-university hospitals located in four selected cantons (Lucerne, Uri, Nidwalden and Obwalden) across central Switzerland. To account for the population density of the canton of Lucerne and improve data diversity (publicly and privately managed hospitals), we included the privately managed St Anna Clinic (Lucerne) and the public Cantonal Hospital of Lucerne as well as the Cantonal Hospital of Uri, the Cantonal Hospital of Obwalden and the Cantonal Hospital of Nidwalden. The hospitals form a network and provide health care for approximately 700,000 residents [39, 40].

Patients who received a new diagnosis of stage IV NSCLC between 1 January 2015 and 31 December 2018 were identified from the Cancer Registry of Central Switzerland. Data regarding the diagnosis, vital status and patient characteristics were provided by the cancer registry. For each patient who met the eligibility criteria, electronic and paper-based medical records were used to complement and validate the data set.

The observation period was chosen on the one hand because of the approval and administration of immunotherapy in Switzerland in 2015 and on the other hand because the epidemiological data of the cancer registry were vali-

dated only until the end of 2018 at the time of data collection.

Further inclusion criteria were an age over 18 years, histologically confirmed NSCLC and Union for International Cancer Control (UICC) stage IV (TNM 7th or 8th edition) at diagnosis. We excluded patients with SCLC and SCLC-NSCLC mixed histology, neuroendocrine tumours, pulmonary metastases of other tumour entities, with missing clinical data on histology, stage or therapy, or with stage I–III NSCLC. We also excluded patients receiving first-line targeted therapy for NSCLC with actionable driver mutations, as these tumours are a unique entity regarding biology and treatment [41].

The oncologists' choices of treatment for the patients were in particular based on ECOG-PS, age, sex, histology, smoking history, the patient's wish and the availability of checkpoint inhibitors (according to their approval in Switzerland and reimbursement). Because there were selection criteria for therapy, these factors (date of incidence, age, sex, histology, smoking status, and PD-L1 expression) were included as covariates for the sensitivity analysis.

Our reporting conforms with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [42].

Data collection

To achieve the study goal, the Cancer Registry of Central Switzerland provided us with a patient list containing all C34 diagnoses (malignant neoplasms of the bronchus or lung) according to ICD-10 from 1 January 2015 until 31 December 2018. Data relevant to the study were extracted from the electronic and paper-based medical records for each patient who met the eligibility criteria [43].

The eligibility and data collection criteria were determined by an interdisciplinary team (OG, DD, VA) prior to data collection. The data collection included the date of diagnosis (date of pathological examination), the histological type (adenocarcinoma, squamous-cell carcinoma, not-otherwise specified histology), the TNM stage as defined by the UICC, the TNM classification (7th edition for the years 2015–2016 and 8th edition for the incidence years 2017–2018), the date of death, age (at year of diagnosis), sex, smoking history, the PD-L1 expression status on tumour cells (in %), molecular tests performed (EGFR, ALK, ROS1, BRAF, KRAS) and the type of therapy received (palliative surgery and radiotherapy, type of systemic therapy) with specification of the drug names. Additionally, hospital medical record databases were systematically searched for the type of therapy, the duration of therapy in days, the number of therapy lines and the reasons for discontinuation of therapy in cases with immunotherapy.

Following an intention-to-treat approach, even a single administration of checkpoint inhibitors was considered sufficient to include the patient in the checkpoint inhibitor group. The patient survival status was provided by the health registry office of each canton in central Switzerland. Patients who moved outside the cantons of central Switzerland or discontinued the therapy were censored at the date of their last contact or 21 July 2021, whichever occurred first.

Data were collected and curated by the first author, supported by DD and the team of the Cancer Registry of Central Switzerland. In cases of inconsistent or missing data, each case was reassessed and adjusted based on the electronic and paper-based medical records and the database located at the Cancer Registry of Central Switzerland in Lucerne, and unclear cases were discussed with a medical expert (OG). In cases where the data remained unclear or missing, the corresponding patient was excluded from the study (n = 9). Only patients without any missing information on histology, stage, treatment and outcome were included in the outcome analysis. Unfortunately, ECOG-PS and smoking status were not available for a large proportion of the population, because these are not routinely collected in Swiss hospitals and the cancer registry. Each patient for whom the data were complete was assigned a consecutive number in order to anonymise the data. The key for the data set was kept independently of the data records.

Histological diagnosis and molecular testing

The Institute of Pathology at the Cantonal Hospital of Lucerne examined all except one specimen and preformed the histological and molecular analyses. Light microscopy and immunohistochemistry (thyroid transcription factor-1, TTF-1) were used to confirm the diagnosis of NSCLC [37]. Routine testing for PD-L1 was implemented in 2015. For the PD-L1 analysis of tumour cells, the antibody SP263 from Roche-Ventana was used, and immunohistochemistry was performed on a benchmark automated stainer (Roche-Ventana, USA). Tumours with at least 1% expression of PD-L1 were considered PD-L1 positive. The PD-L1 stained slides were all assessed by the same pathologist (JD).

Statistical analysis

Three groups of patients were compared: one group of patients received immunotherapy with an checkpoint inhibitor (nivolumab, pembrolizumab, atezolizumab) in any line of treatment via regular approval, an early-access programme or a clinical trial. For comparison, two groups of patients were considered who received only chemotherapy or best supportive care without an checkpoint inhibitor. Patient and treatment characteristics were analysed descriptively.

Median overall survival was determined by treatment group and, where appropriate, by subgroups together with corresponding 95% confidence intervals (CIs). Overall survival was described using Kaplan–Meier survival curves and is presented with risk tables of the number of subjects at risk and event counts. Treatment outcomes are reported separately for patients treated in first-line or second-/further-line settings. Overall survival was calculated from the date of a stage IV NSCLC diagnosis to the date of death, with living subjects censored on the date of their last follow up (21 July 2021).

To avoid a survivorship bias for checkpoint inhibitors used in the second and further lines, overall survival was also calculated from the start of a line of therapy with an checkpoint inhibitor to death or the last follow-up. A Cox proportional-hazards regression model, adjusted for the year

of incidence and age, was used to estimate hazard ratios (HRs) and 95% CIs. Sensitivity analyses were performed utilising further covariates including sex, smoking status and histology. Missing data were categorised and reported as such (smoking status unknown in 16.4%; PD-L1 status not tested in 44.2%).

Because of the exploratory nature of this study, there was no formal sample-size determination. To avoid selection bias, all patients who met the criteria of a predefined selection strategy were included in the study as described above. The sample size resulting from this process was considered sufficient to support the exploratory objectives of this study. All statistical analyses were performed with STATA version 17.0 (StataCorp LLC, College Station, Texas, USA) [44].

Ethical considerations

This study was performed in line with the principles of the Declaration of Helsinki and was reviewed and approved by the Ethikkomission Nordwest- und Zentralschweiz (EKNZ, BASEC identification number 2019-01865). General consent forms were available from the electronic medical records (EMRS) of patients treated at the Cantonal Hospital of Lucerne from August 2016 onward. Patients who withheld informed consent were excluded from the study.

Results

Patient selection

The Cancer Registry of Central Switzerland provided electronic records for 978 patients with a diagnosis of a malignant disease of the chest (ICD-10 code C34) between 2015 and 2018. After the exclusion of 520 patients with UICC stage I–III NSCLC, 127 patients with histology other than NSCLC or missing histology, a total of 331 patients with a diagnosis of stage IV NSCLC (adenocarcinoma, squamous-cell carcinoma, NSCLC-NOS (NSCLC-not otherwise specified), but excluding those with a mixed histology) from January 2015 to December 2018 remained for further investigation. Another 12 patients were excluded because of withholding of informed consent, 9 patients because of missing data and/or inconclusive histology and 36 patients because of targeted therapies. Ultimately, 274 patients were included in the statistical analysis. (fig. 1)

According to the systemic therapy received, patients were divided into three groups. The immune-oncology (IO) group (n = 122) included patients who received treatment with an checkpoint inhibitor regardless of the line of therapy, and a comparator group (n = 152, no-IO), which was divided into two subgroups, treated either with conventional chemotherapy only (n = 70) or best supportive care (n = 82). The median follow-up for the patients was 6.5 months.

Clinical characteristics

Patient characteristics are shown in table 1. Across the study population (n = 274), the median age at diagnosis was 68.4 years (range 39–89). Most of the patients were male (61.7%) and 65.0% were current or former smokers. The most frequent tumour histology was adenocarcinoma (73.0%), followed by squamous-cell carcinoma (20.4%) and NSCLC-NOS (6.6%). Bone metastases were present in 45.5% of the patients and brain metastases in 33.6%. PD-L1 expression was documented for 55.8% of the tumours, and 44.2% of the tumours had not yet been tested for PD-L1 expression.

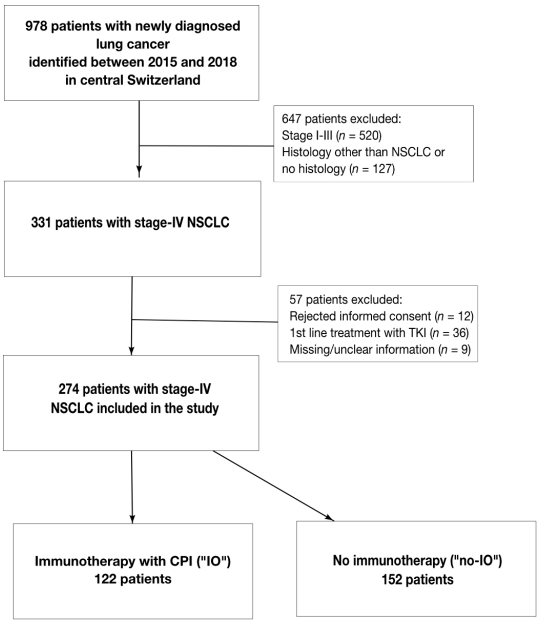
Less than half of the study population (44.5%, n = 122) received checkpoint inhibitors, and these patients were assigned to the IO group. With a median age of 65.5 years (range 43–85), these patients were younger than the patients who did not receive checkpoint inhibitors (median 70.7 years, range 39–89).

The majority of patients in the IO group had adenocarcinoma (72.1%). Central nervous system (CNS) metastases were present in 40.2% and adrenal metastases in 24.3%. Both were more frequent in this group than in the no-IO group (28.3% and 19.1%, respectively). Hepatic metastases were less frequent in the IO group than in the no-IO group (17.8% vs 23.5%).

In the majority of patients (79.5%, n = 97) in the IO group, tumours were tested for PD-L1, whereas testing for PD-L1 was not performed in 20.5% (n = 25). Among the tested tumours, 42.3% (n = 41) had high PD-L1 (≥50%), while 57.7% (n = 56) had low or no PD-L1 (<50%).

In the first-line IO subgroup, all patients (n = 31) had tumours tested for PD-L1 expression, and 87.1% (n = 27) scored PD-L1 ≥50%. In the second-line IO subgroup (n = 91), the majority (57.1%, n = 52) of patients had tumours with low or no PD-L1 expression (<50%). High tumour PD-L1 expression (≥50%) was seen in 14 patients (15.4%), whereas 25 patients (27.5%) had no tumour testing and therefore had an unknown PD-L1 expression status.

Figure 1: Flowchart of patient inclusion and exclusion criteria. Patient selection and division of patients with metastatic non-small-cell lung cancer (NSCLC) into two groups according to the type of therapy. CPI: checkpoint inhibitor; IO: immuno-oncology; no-IO: no immuno-oncology; NSCLC: non-small-cell lung cancer; TKI: tyrosine kinase inhibitor



Therapy

Across all patients, 58.8% (n = 161) received chemotherapy as a first line of therapy. Carboplatin and pemetrexed (n = 98) was the most frequently administered regimen (approved for non-squamous NSCLC), followed by carboplatin and paclitaxel (n = 22) and by carboplatin and gemcitabine (n = 21). Of all patients, 11.3% (n = 31) had checkpoint inhibitors as a first line of therapy (3 patients out of this group received a combination of chemotherapy and checkpoint inhibitors), while 29.9% of patients received only best supportive care.

Among the 122 patients treated with checkpoint inhibitors, 31 patients (25.4%) received them in the first line and 91 patients (74.6%) had checkpoint inhibitors in further lines. The most commonly administered checkpoint inhibitor in the first line was pembrolizumab (93.6%, n = 29). In further lines, 58.2% (n = 53) of patients received nivolumab, 28.6% (n = 26) pembrolizumab, and 13.2% (n = 12) were treated with atezolizumab.

Survival

The median overall survival for all patients receiving checkpoint inhibitor therapy (IO group) was 15 months (95% CI 12–20). Patients treated with chemotherapy had a median overall survival of 4 months (95% CI 3–7), and patients with best supportive care had a median overall survival of 2 months (95% CI 1–2) (fig. 2a).For the analysis from the time of diagnosis, the adjusted risk (for the date of incidence and age) of death for patients treated with chemotherapy was approximately 2.7 times higher (adjusted HR [aHR] 2.67, 95% CI 1.92–3.71; p <0.001), and it was approximately 7 times higher (aHR 6.96, 95% CI 4.95–9.79; p <0.001) for patients treated with best supportive care compared with those treated with anti-PD-1/PD-L1 in any line.

The median overall survival calculated from the time of diagnosis of metastatic NSCLC (fig. 2b) was 15 months (95% CI 4–37) in patients receiving checkpoint inhibitor therapy in the first line and also 15 months (95% CI 12–20) in patients receiving checkpoint inhibitor therapy in further lines. The median overall survival from the start of checkpoint inhibitor therapy (fig. 2c) was 15 months (95% CI 4–37) in the first line and 7 months (95% CI 5–10) in further lines. The calculated and adjusted risk for death in patients with IO in further lines was 1.6 times higher than in patients receiving checkpoint inhibitor therapy in the first line (aHR 1.60, 95% CI 0.91–2.80; p = 0.102). The unadjusted HR was also 1.67 (95% CI 1.01–2.74; p = 0.044).

The median overall survival for PD-L1 ≥50% from the time of diagnosis of metastatic NSCLC was 15 months (95% CI 8–29) and for PD-L1 <50% it was 13 months (95% CI 11–20) (fig. 2d). The calculated and adjusted risk of death for PD-L1 expression <50% was 1.2 times higher than for PD-L1 ≥50% (aHR 1.21, 95% CI 0.75–1.96 p = 0.442) (see supplementary table S1in the appendix).

Table 1:
Baseline and disease characteristics of included patients with metastatic (stage IV) non-small-cell lung cancer (NSCLC) between 2015 and 2018.

Characteristics		All (n = 274)	IO (n = 122)	No-IO (n = 152)	
				CTX, n = 70	BSC, n = 82
Median age, years (range)		68.4 (39–89)	65.5 (43–85)	66.1 (39–88)	74.6 (43–89)
Sex, n (%)	Male	169 (61.7)	82 (67.2)	45 (64.3)	42 (51.2)
	Female	105 (38.3)	40 (33)	25 (35.7)	40 (48.8)
Geographic region, n (%)	Lucerne	198 (72.3)	82 (67.2)	59 (84.3)	57 (69.5)
	Uri	26 (9.5)	10 (8.2)	7 (10.0)	9 (11.0)
	Nidwalden	28 (10.2)	18 (14.8)	2 (2.9)	8 (9.8)
	Obwalden	22 (8.0)	12 (9.8)	2 (2.9)	8 (9.8)
Smoking status, n (%)	Never smoker	51 (18.6)	25 (20.5)	9 (12.9)	17 (20.7)
	Former or current smoker	178 (65.0)	85 (69.7)	44 (62.9)	49 (59.8)
	Unknown	45 (16.4)	12 (9.8)	17 (24.3)	16 (19.5)
Histology, n (%)	Adenocarcinoma	200 (73.0)	88 (72.1)	53 (75.7)	59 (72.0)
	Squamous-cell carcinoma	56 (20.4)	27 (22.1)	13 (18.6)	16 (19.5)
	Other (e.g., NSCLC-NOS)	18 (6.6)	7 (5.8)	4 (5.7)	7 (8.5)
Metastases at diagnosis, n (%)	Central nervous system	92 (33.6)	49 (40.2)	21 (30.0)	22 (26.8)
	Bone	92 (45.5)	39 (38.6)	27 (52.9)	26 (52.0)
	Pleura	42 (18.9)	22 (20.6)	11 (19.6)	9 (15.3)
	Pulmonary	56 (25.2)	28 (26.2)	15 (26.8)	13 (22.0)
	Hepatic	46 (20.7)	19 (17.8)	15 (26.8)	12 (20.3)
	Adrenal	48 (21.6)	26 (24.3)	7 (12.5)	15 (25.4)
	Other	59 (26.6)	25 (23.4)	15 (26.8)	19 (32.2)
PD-L1 status, n (%)	Negative	51 (18.6)	25 (20.5)	17 (24.3)	9 (11.0)
	Positive	102 (37.2)	72 (59.0)	17 (24.3)	13 (15.9)
	1–49%	45 (16.4)	31 (25.4)	10 (14.3)	4 (4.9)
	≥50%	57 (20.8)	41 (33.6)	7 (10.0)	9 (11.0)
	Not tested	121 (44.2)	25 (20.5)	36 (51.4)	60 (73.2)

Baseline and disease characteristics of included patients with NSCLC stage IV between 2015 and 2018 according to their distribution to the IO group, where patients received immunotherapy with an checkpoint inhibitor and to the no-IO group, where patients received chemotherapy or best supportive care (BSC). The table shows data regarding median age, sex, geographic region, smoking status, histology, metastases at diagnosis as well as PD-L1 status (programmed death ligand 1). All values are n (%) unless otherwise marked.

BSC: best supportive care; CTX: chemotherapy; IO: immuno-oncology; No-IO: no immuno-oncology; NOS: not otherwise specified; NSCLC: non-small-cell lung cancer;PD-L1: programmed death ligand 1

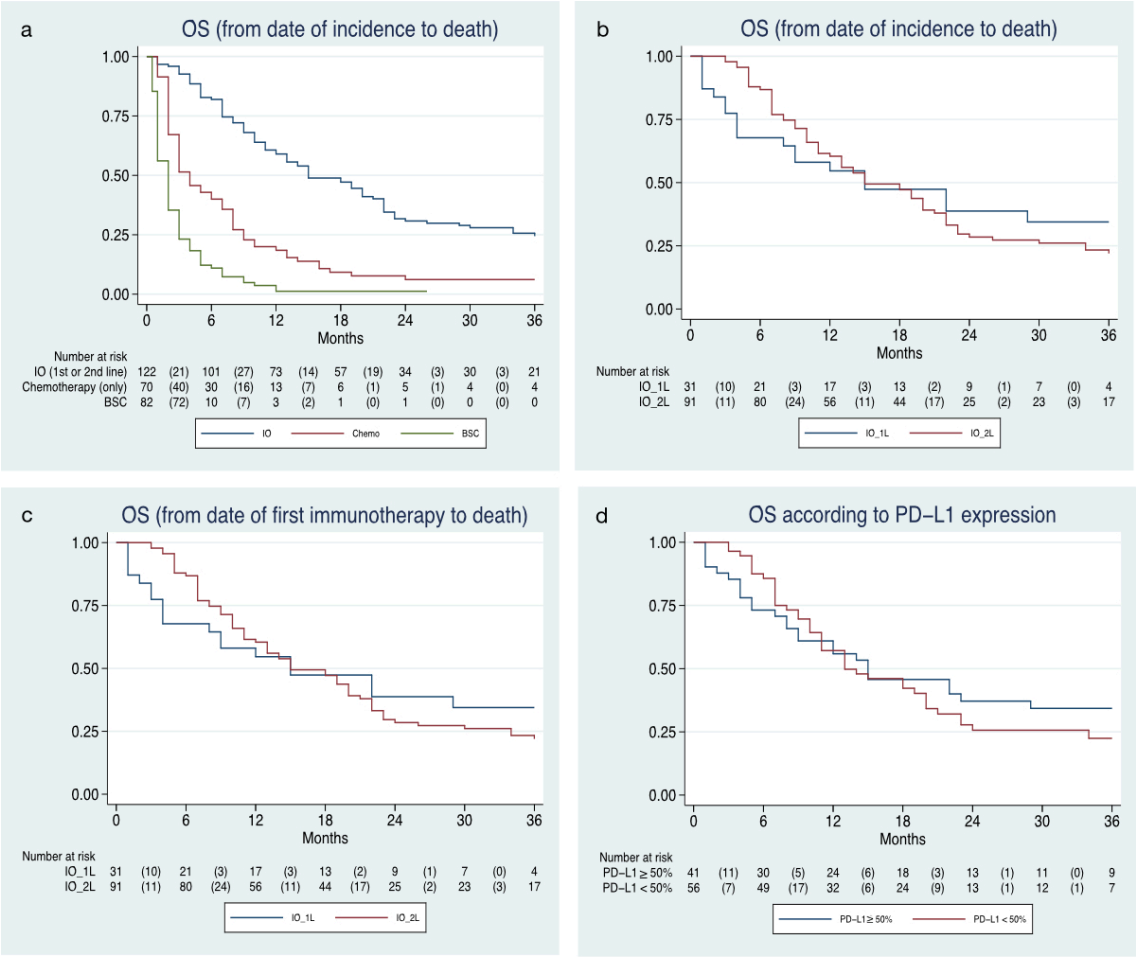
Discussion

The primary aim of this retrospective study was to assess overall survival and treatment patterns in an unselected population of patients with stage IV NSCLC receiving immunotherapy or standard care (chemotherapy or best supportive care) in central Switzerland since the first approval of checkpoint inhibitors in Switzerland in 2015.

Until 2015, patients with metastatic NSCLC had access only to chemotherapy and targeted therapy [45]. All patients included in this study had histologically proven stage IV NSCLC. In this group of patients, 58.7% (n = 161) had received chemotherapy, 11.3% (n = 31) had received immunotherapy, and approximately one third of all patients (29.9%, n = 82) had been treated with no systematic therapy as a first-line treatment. Most of the patients treated with chemotherapy had received, according to clinical guidelines, platinum-based chemotherapy as the first line, as this had been the standard of care for several years [14]. Furthermore, most of the newly implemented checkpoint inhibitors, namely nivolumab, required disease progression after platinum-based therapy.

Between 2015 and 2018, three checkpoint inhibitors were approved for the treatment of metastatic NSCLC by Swissmedic. First, nivolumab was available in an early-access programme and atezolizumab in the OAK trial for patients with previous chemotherapy. Then, nivolumab and atezolizumab were approved by Swissmedic, and pembrolizumab was approved for PD-L1-positive NSCLC. Later, pembrolizumab was approved as a first-line monotherapy for PD-L1-high tumours and in combination with chemotherapy for PD-L1-low tumours. The results of our study reflect this timeline, in that nivolumab was the most frequently used checkpoint inhibitor, whereas pembrolizumab and atezolizumab were used less in the study period [27]. The results of this study, conducted after the availability of checkpoint inhibitor monotherapy for metastatic NSCLC in Switzerland, indicate that most ther-

Figure 2: Overall survival of included patients with NSCLC stage IV from 2015 to 2018. (a) Overall survival of patients treated with checkpoint inhibitor (IO, blue), chemotherapy (red), and BSC (green). Kaplan–Meier curve shows a median OS of 15 months (95% CI 12–20 months) for IO, a median OS of 4 months (95% CI 3–7 months) for chemotherapy, and a median OS of 2 months (95% CI 1–2 months) for BSC. (b) Overall survival (from diagnosis of metastatic NSCLC) with checkpoint inhibitor in the first line (IO_1L, blue) or in the second line (IO_2L, red). Kaplan–Meier curves show a median OS of 15 months (95% CI 4–37 months) for IO in the first line and a median OS of 15 months (95% CI 12–20 months) for IO in the second line. (c) Overall survival (from the start of checkpoint inhibitor therapy) with checkpoint inhibitor in the first line (IO_1L, blue) or in the second line (IO_2L, red). Kaplan–Meier curves show a median OS of 15 months for IO in the first line (95% CI 4–37 months) and median OS of 7 months (95% 5–10 months) for IO in the second line. (d) Overall survival with checkpoint inhibitor therapy according to PD-L1 expression (50% threshold). Kaplan–Meier curve shows a median OS of 15 months (95% CI 8–29 months) for PD-L1 ≥50% and a median OS of 13 months (95% CI 11–20 months) for PD-L1 <50%. BSC: best supportive care; CPI: checkpoint inhibitor; NSCLC: non-small-cell lung cancer; IO: immuno-oncology; IO_1L: immuno-oncology first line; IO_2L: immuno-oncology first line second line; OS: overall survival; PD-L1: programmed death ligand 1



apies administered were in accordance with the national guidelines (according to the ESMO; European Society for Medical Oncology guidelines) for the observed study period (January 2015 to December 2018).

Our study results suggest that patients have a longer overall survival when treated with checkpoint inhibitors compared with patients who are not treated with checkpoint inhibitors and that patients with high PD-L1 expression receiving checkpoint inhibitor treatment have a slightly longer overall survival than patients with low PD-L1 receiving checkpoint inhibitor treatment, as PD-L1 expression has been described as a predictive marker in treating NSCLC [46, 47]. Although expected and described previously, this finding is relevant because cancer registry data in this field are limited.

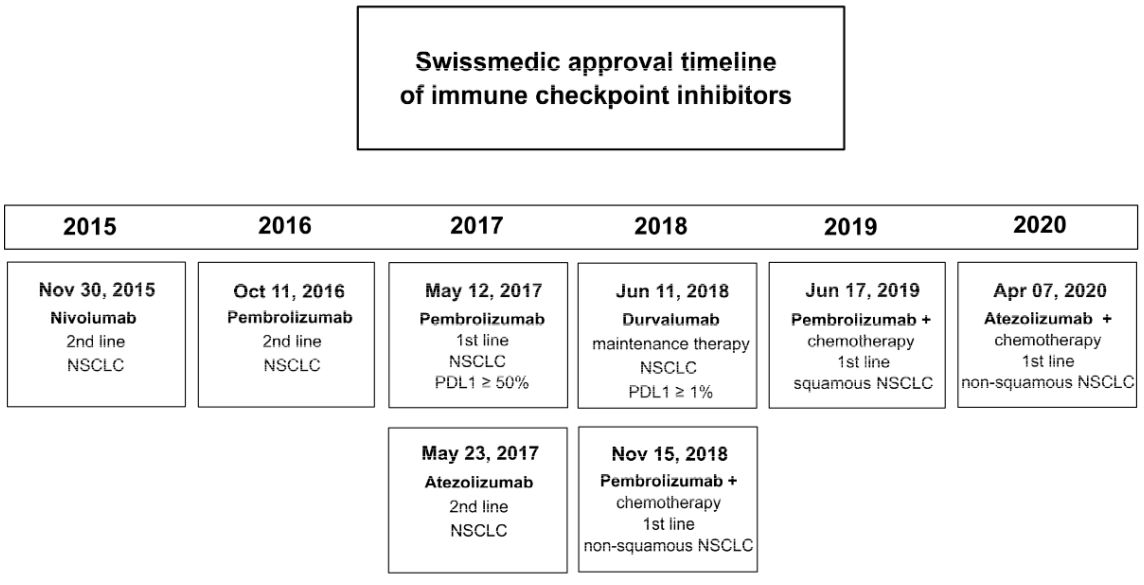
The baseline characteristics of the patients enrolled in our study − related to median age, sex, non-squamous histology and the presence of brain metastases − were comparable to those included in other cancer-registry populations. Our findings of median overall survival with first- and second-line treatments with checkpoint inhibitors were generally consistent with reports of other national and international studies [48–51].

Compared with randomised clinical trials, the median overall survival with checkpoint inhibitors in the first line and in further lines observed in this study (15 months and 7 months, respectively) were shorter than the reported median overall survival in clinical trials, where an overall survival of 15.9–30 months for the first line [27, 32, 52–57] and of 9.2–13.8 months for the second line [10, 11, 23, 58] have been described.

The difference in overall survival may be explained by the differences in the characteristics of the patients included in this study versus clinical trials, as we analysed an unselected study population. In comparison with the eligibility criteria of randomised clinical trials, our study population (median age 68.4 years), especially the group of patients receiving checkpoint inhibitors (median age 65.5 years) was older than the patients included in clinical trials. Since age-related immune dysregulation may affect the effectiveness of immunotherapy, this could be a reason for the different results regarding overall survival [59]. Furthermore, patients with active brain metastases, clinically relevant comorbidities and previous malignancies are generally excluded from clinical trials [10]. The presence of liver, bone or brain metastases is related to poor prognosis in NSCLC; they correlate with a shorter overall survival compared with metastases in other organs [18]. These could be possible explanations for the differences in overall survival between our data and the results of clinical trials, as many of our patients had tumour metastases at different sites (33.6% brain, 45.5% bone, 20.7% liver).

In comparison with randomised clinical trials, it was noticeable that our study population was treated for a shorter period of time with checkpoint inhibitors. The observed median duration of checkpoint inhibitor therapy in our study was 127 days (4.2 months) in the first line and 81.5 days (2.7 months) in the second line, whereas patients in registration trials received up to 7 months of checkpoint inhibitor therapy [11, 25, 52]. Given that nivolumab (240 mg every 2 weeks) was the most frequent agent used in second-line therapy and pembrolizumab (200mg every 3 weeks) in first-line therapy in this study, patients received overall approximately five or six doses before the discontinuation of therapy. The most frequent reason for the discontinuation of checkpoint inhibitor treatment in this study was tumour progression and a lack of a response to treatment in 53.3% (n = 65). The second most frequent reason was because of severe treatment- and immune-related adverse events (n = 13, 10.7%), and in 9.8% (n = 12) treatment was stopped because of deterioration of the patient's general condition that was not clearly attributed to checkpoint inhibitor treatment. Only 10 patients (= 8.2%) among the group receiving checkpoint inhibitor treatment were treated for the entire recommended therapy duration of 2 years [60]. In the group of patients with checkpoint

Figure 3: Timeline of approval of checkpoint inhibitors for NSCLC in Switzerland by Swissmedic. Timeline from 2015 to 2020 (left to right) with drug names, date and criteria of approval of the different checkpoint inhibitors in Switzerland according to approval of Swissmedic. CPIs: checkpoint inhibitors; NSCLC: non-small-cell lung cancer; PD-L1: programmed death ligand 1. Source: compendium.ch



inhibitor treatment and tumour progression (n = 65), only 30 (46.2%) patients were treated with subsequent systemic therapy and none of the patients with immune-related adverse events were re-exposed to checkpoint inhibitors. The high frequency of immune-related adverse events and the fact that no subsequent therapy was administered after such events suggest that these patients had poor ECOG-PS and relevant comorbidities, and that oncologists were cautious regarding the newly introduced checkpoint inhibitors and their toxicity profiles.

With regard to the limitation that no data on ECOG-PS was collected, indirect evidence shows that our study population, especially in the chemotherapy group, was in poor general health. Despite the availability of PD-L1 testing and the use of second-line checkpoint inhibitors (nivolumab) from 2015 on, approximately half of the included patients (51.4%, n = 36) treated with chemotherapy had neither PD-L1 testing nor checkpoint inhibitor therapy after a failure of chemotherapy, which could be interpreted as a selection bias in patients unwilling or unfit to undergo therapy, as the choice of treatment is not only determined by histology but also by ECOG-PS, which is an important and independent factor for response [61–63]. These findings could explain the fact that that overall survival of patients with chemotherapy was shorter compared with the results of other national and international clinical trials. [23, 28, 64, 65]

Despite the introduction of targeted therapies and immunotherapy and their impact on overall survival, a significant proportion (29.9%) of the patients in our study received best supportive care and not tumour-directed systemic therapy. This proportion is in line with other studies [49, 66] and with the results of our previous study on targeted therapies from the same region covering the years 2010–2014 [37]. The rate of best supportive care is consistent with the high proportion of patients with ECOG-PS ≥2 and with the age distribution of our population, which reflects the high proportion of patients with metastatic NSCLC who are elderly and frail and are therefore not considered by clinicians for active treatment of NSCLC [67, 68].

In the present study, patients with tumours with known actionable driver mutations were excluded from the analysis. However, during data selection and analysis, we observed an additional KRAS codon 12 mutation in about 20.4% (n = 56) of the included patients with adenocarcinoma. According to the literature, approximately 20–25% of all non-squamous NSCLC and 6% of all squamous NSCLC harbour an additional KRAS mutation [69, 70]. KRAS is the most common oncogenic mutation detected in patients suffering from NSCLC, but the role of KRAS as a prognostic or predictive factor remains unclear. Of the KRAS-mutated patients in this study, 53.5% (n = 30) received immunotherapy, 21.4 % (n = 12) were treated with chemotherapy and 25% (n = 14) received no systematic therapy. A meta-analysis of 43 selected studies (including clinical trials and observational studies) suggested that KRAS is a negative prognostic factor for survival and response to therapy in metastatic NSCLC [71]. The role of KRAS in the overall survival of patients with NSCLC who are treated with immunotherapy remains unclear [72]. A meta-analysis by Landre et al. suggested that treatment with anti-PD-L1 seemed to achieve a longer overall survival than chemotherapy for patients with KRAS-mutant NSCLC [73]. Since the role of KRAS in the therapeutic landscape as a prognostic and prospective factor needs to be defined and is debated in the literature [74–77], we are currently unable to draw any conclusions about this finding for the moment; further prospective studies are needed. The KRAS G12c mutation is of particular interest because there is a specific inhibitor (Sotorasib, Lumykras®) with approval in Switzerland since January 2022 and with proven clinical activity [78, 79], so further explorations regarding its role in diagnostic and therapeutic strategies and regarding its potential field of application in pretreated NSCLC are necessary [80].

One of the strengths of this study is that it represents an unselected population of patients in central Switzerland with biopsy-confirmed metastatic NSCLC and with a complete data set on the applied therapies. But there are several limitations of this study. As this was a retrospective observational study, the effect of selection and allocation bias needs to be addressed. According to the national guidelines in central Switzerland, clinicians selected the appropriate systemic therapy based on age, histology, PD-L1 status, ECOG-PS, relevant comorbidities, and patients' preferences [60]. This approach may have led to a selection of patients with better health conditions (ECOG-PS 0−1, fewer comorbidities) and therefore also to a selection of patients with better prognoses (namely patients with IO therapy). As a consequence, the measured effect on overall survival cannot be assigned to treatment with checkpoint inhibitors alone. The additional sensitivity analyses showed that, although we included covariates as mentioned above (sex, histology, smoking status), the hazard ratios (HRs) did not differ much from the unadjusted hazard ratios, so we consider the HRs and results robust.

Since ECOG-PS and smoking status are not routinely collected by clinicians, these variables are missing in the clinical databases as well as in the database of the cancer registry. On account of this, important adjustments to verify the effects of immunotherapy could not be made. Furthermore, data on patients' comorbidities and medications prescribed outside of the oncology-clinic setting were not recorded, so additional analyses could not be performed. A further limitation is the small number of patients with first-line checkpoint inhibitor therapy, as this therapy was only available from 2017 and only for tumours with a high expression of PD-L1. As a consequence, follow-up was significantly shorter than in patients with second-line checkpoint inhibitor therapy. In addition, we admit that this study was conducted at selected cantons and clinical centres of central Switzerland and that the results may not represent the entire patient population in Switzerland.

Conclusion

Considering the limitations of this retrospective and population-based study, the results suggest an improvement in overall survival in unselected patients with metastatic NSCLC from the introduction of checkpoint inhibitors, regardless of the line of therapy. The reported outcomes regarding overall survival were shorter compared with published results from randomised clinical trials but were in line with other registry data. This is one of the first cancer-

registry-based studies about the use of checkpoint inhibitors in unselected patients with metastatic NSCLC in central Switzerland. To confirm the effect of checkpoint inhibitor therapy on overall survival and to identify further prognostic and predictive factors beyond PD-L1 expression, larger studies at a national level are needed.

Data availability

Anonymised raw data and the associated statistical analyses are stored securely at the Institute of Pathology of the Cantonal Hospital of Lucerne and can be provided upon reasonable request by interested researchers. Data will be available immediately after publication.

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Potential conflict of interest

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. OG reports participation in advisory boards (Amgen, Bayer, Eli Lilly, Novartis, Roche), data safety monitoring boards (Bayer, Boehringer), and clinical trials (Eli Lilly, Novartis, Roche), all honoraria being paid to his institution. VA received support from the University of Basel for proofreading by an external academic proofreading service of the University of Basel. All other authors certify that they have no affiliations with or involvement in any organisation or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Appendix

Table S1:
Adjusted and not adjusted hazard ratios (HR) from the results of figure 2.

	Therapy	Not adjusted	Adjusted for years of incidence and age at diagnosis	Additionally adjusted for further covariates (sex, smoking, histology)
		Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
HR for overall survival (from date of incidence to death) − figure 2a (n = 274).	Chemotherapy only (no-IO) vs IO	2.66 (1.92−3.67), p <0.001	2.67 (1.92−3.71), p <0.001	2.75 (1.97−3.85), p <0.001
	Best supportive care (BSC) vs IO	7.18 (5.15−10.01), p <0.001	6.96 (4.95−9.79), p <0.001	7.54 (5.31−10.72), p <0.001
HR for overall survival (from date of incidence to death) − figure 2b (n = 122).	IO second line vs IO first line	1.04 (0.63−1.71), p = 0.871	1.03 (0.59−1.80), p = 0.912	1.04 (0.59−1.84), p = 0.889
HR for overall survival (from date of first immunotherapy to death) − figure 2c (= 122)	IO second line vs IO first line	1.67 (1.01−2.74), p = 0.044	1.60 (0.91−2.80), p = 0.102	1.66 (0.93−2.95), p = 0.086
HR for overall survival (OS according to PD L1–expression) − figure 2d (n = 97).	PD-L1 ≥ 50% vs PD-L1 <50%	1.21 (0.74−1.96), p = 0.444	1.21 (0.75−1.96), p = 0.442	1.27 (0.77−2.11), p = 0.354

Figure S1: Figure S1 a-d: Overall survival of included patients with NSCLC stage IV from 2015 to 2018 (figure 2 with displayed 95% CI) . BSC: best supportive care; CPI: checkpoint inhibitor; NSCLC: non-small-cell lung cancer; IO: immuno-oncology; IO_1L: immuno-oncology first line; IO_2L: immuno-oncology first line second line; OS: overall survival; PD-L1: programmed death ligand 1