HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

HSR in Oncology:

Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with Anti-PD-1/ PD-L1Therapy in Real-World Practice

A Pilot Project in Cooperation with
Tirol Kliniken GmbH & KAGes

Final report

AIHTA Project Report No.: 126 | ISSN: 1993-0488 | ISSN-online: 1993-0496

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Vienna, August 2021

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This report should be referenced as follows:

Geiger-Gritsch et al. Health Services Research in Oncology: Patients with Non-small Cell Lung Cancer Treated with Anti-PD-1/PD-L1 Therapy in Real-World Practice – A Pilot Project in Cooperation with Tirol Kliniken GmbH & KAGes. AIHTA Project Report No. 126; 2020. Vienna: HTA Austria–Austrian Institute for Health Technology Assessment.

Conflict of interest

The first author Geiger-Gritsch and the co-authors Absenger, Endel, Hermann, Kocher, Wurm, Zechmeister involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).
The co-authors Pall and Flicker received honoraria from BMS and Roche for speaking at symposia and were Advisory Board Members for Roche and BMS. In addition, Pall received honoraria from MSD for speaking at symposia and was Advisory Board Member for MSD, Olschewski was Advisory Board Member for MSD and BMS.

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the AIHTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the AIHTA.

IMPRINT

Publisher:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Garnisongasse 7/Top20 | 1090 Vienna – Austria
https://www.aihta.at/

Responsible for content:
Priv.-Doz. Dr. phil. Claudia Wild, managing director

AIHTA Project Reports do not appear on a regular basis and serve to publicize the research results of the Austrian Institute for Health Technology Assessment.

AIHTA Project Reports are only available to the public via the Internet at http://eprints.aihta.at/view/types/hta_report.html.

AIHTA Project Report No.: 126

ISSN 1993-0488

ISSN online 1993-0496

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List of Abbreviations

AE.....Adverse Event
ALK.....Anaplastic Lymphoma Kinase
BRAF .....B-Raf proto-oncogene
CCI.....Charlson Comorbidity Index
CI.....Confidence Interval
CR .....Complete Response
CRF.....Case Report Form
CT.....Computer Tomography
CTAE .....Common Terminology Criteria for Adverse Events
DCR .....Disease Control Rate
DRG .....Diagnosis-Related Groups
ECOG.....Eastern Cooperative Oncology Group
EGFR .....Epidermal Growth Factor Receptor
EHR .....Electronic Health Records
EMA .....European Medicines Agency
EML4 .....Echinoderm Microtubule-associated Protein-Like 4
EPAR .....European Public Assessment Report
ESMO.....European Society for Medical Oncology
FDA.....US Food and Drug Administration
HR.....Hazard Ratio
HTA .....Health Technology Assessment
IC.....Tumour-infiltrating Immune Cells
ICI .....Immune Checkpoint Inhibitors
IHC .....Immunohistochemistry
ITT .....Intention-To-Treat
LBI .....Ludwig Boltzmann Institute
mAbs..... monoclonal Antibodies
NSCLC..... Non-Small Cell Lung Cancer
NTRK..... Neurotrophic Tyrosine Receptor Kinase
ORR..... Objective Response Rate
OS ..... Overall Survival
PD..... Progressive Disease
PD-1 ..... Programmed Cell Death-1 pathway
PD-L1..... Programmed Death Ligand 1
PFS ..... Progression-Free Survival
PR..... Partial Response
PS..... Performance Status
RCT ..... Randomised Controlled Trial
ROS1 ..... c-ROS oncogene 1
RWD ..... Real-World Data
RWE ..... Real-World Evidence
SCC ..... Squamous Cell Carcinoma
SD..... Stable Disease
SD..... Standard Deviation
SCLC..... Small Cell Lung Cancer
TC..... Tumour Cells
TNM..... Tumour, Node, Metastasis (TNM staging system)
TPS ..... Tumour Proportion Score
TRK..... Tropomyosin Receptor Kinase
UICC ..... Union for International Cancer Control
WHO ..... World Health Organisation

Keywords

non-small cell lung cancer; immune checkpoint inhibitors; pembrolizumab; nivolumab; atezolizumab; anti-PD-1; anti-PD-L1; lung cancer

Executive Summary

Introduction

Health Problem

In 2018, lung cancer occurred in approximately 2.1 million patients (11.6% of all new cancer cases) worldwide and caused an estimated 1.7 million deaths (18.4% of all cancer-related deaths). In Europe, 470,039 new lung cancer cases were diagnosed in 2018 and 387,913 patients died of this disease. In Austria, a total of 2,868 new cases of lung cancer in men and 2,009 new cases in women were reported in 2016 and lung cancer was the second most common cancer in both sexes (12% of all new cancer cases). Moreover, 2,415 men and 1,534 women died of this disease, making lung cancer the leading cause of cancer-related death in men and the second most common cause of cancer-related death in women (20% of all cancer-related deaths) in 2016 in Austria.

lung cancer:
11.6% of all new cancer cases worldwide

Lung cancer has been sub-classified into two major categories (non-small cell lung cancer [NSCLC] and small cell lung carcinoma [SCLC]) as the result of differences in histological characteristics, approaches to treatment, and clinical outcomes. Non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancers. NSCLC can be divided mainly into non-squamous (adenocarcinoma) (70%) and squamous (30%) histologic subtypes.

lung cancer is sub-classified in NSCLC and SCLC

Rapid advances in understanding the molecular pathogenesis of NSCLC have demonstrated that NSCLC is a heterogeneous group of diseases. Although the initial treatment of localised disease is the same, the molecular characterisation of tumour tissue in patients with NSCLC serves as a guide to treatment both in those who present with metastatic disease and in those who relapse after primary therapy. Currently defined NSCLC subsets for which specific targeted therapies have been standard therapy include those with mutations in the epidermal growth factor receptor (EGFR), as well as B-Raf proto-oncogene (BRAF), those with anaplastic lymphoma kinase (ALK) fusion oncogene, and c-ROS oncogene 1 (ROS1) fusions. Other driver mutations have also been identified and specific treatments are being developed. For those without driver mutations, in whom programmed death ligand 1 (PD-L1) expression is observed, immunotherapy is available as a treatment option.

molecular pathogenesis

EGFR
BRAF
ALK
ROS1

PD-L1

The TNM stage at presentation in patients with NSCLC is the factor that has the greatest impact on prognosis. Survival decreases progressively with more advanced disease. Metastatic disease is present in 50% of new NSCLC diagnoses and the prognosis for these patients with metastatic or stage IV NSCLC is poor, with five-year survival rates reported at about 6%. Novel treatment options like immunotherapy may contribute to improve five-year survival rates for metastatic or stage IV NSCLC.

prognosis determined by cancer stage

Description of Technology

Depending on the tumour stage, histology, molecular characteristics, the patients' overall health and preferences, surgery, radiation therapy and/or chemotherapy may be used alone or in combination to treat NSCLC. The treatment decisions should ideally be discussed within a multidisciplinary tumour board. Patients with stage I, II, or III non-small cell lung cancer (NSCLC) are generally treated with curative intent using surgery, chemotherapy, radiation therapy (RT), or a combined-modality approach. In appropriately selected patients, chemotherapy, molecularly targeted therapy, and/or immunotherapy may be used to treat advanced or metastatic NSCLC.

surgery, radiation therapy and/or chemotherapy as treatment options

programmed cell death pathway

In recent years, immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) axis have shown significant anti-tumour activity in NSCLC. PD-1 is an immune checkpoint that has emerged as an important therapeutic target. PD-1 is expressed on the surface of activated T cells, B cells, and natural killer cells. The interaction of PD-1 with one of its two known ligands, PD-L1 and PD-L2, leads to the disruption of intracellular signalling and downregulation of effector T-cell function. PD-L1 expression can also be upregulated on tumour cells and other cells in the local tumour environment. PD-L1 expression has been reported across a range of malignancies, including NSCLC.

3 monoclonal antibodies approved

Nivolumab and pembrolizumab (PD-1 inhibitors) and atezolizumab (PD-L1 inhibitor) are monoclonal antibodies (mAbs) and are approved for metastatic NSCLC treatment.

nivolumab as second-line monotherapy

Nivolumab (BMS-936558/MDX-1106/ONO-4538) is a fully human immunoglobulin G4 (IgG4) PD-1 inhibitor and was approved by the European Medicines Agency (EMA) in June 2015. Nivolumab as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

pembrolizumab as first- or second-line monotherapy

Pembrolizumab is a humanised, IgG4 monoclonal antibody directed against PD-1 and received marketing authorisation by the EMA in July 2015, and is approved for the treatment of locally advanced or metastatic NSCLC.

- Pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK-positive tumour mutations.
- Pembrolizumab, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK-positive mutations.
- Pembrolizumab, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.
- Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK-positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.

atezolizumab as second-line monotherapy

Atezolizumab (MPDL-3280A) is a high-affinity human monoclonal IgG1 antibody directed against PD-L1 and was approved by the EMA in September 2017. Atezolizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR-mutant or ALK-positive NSCLC should also have received targeted therapies before receiving atezolizumab.

pivotal clinical trials

The approval of these three immune checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab for NSCLC monotherapy was based on pivotal randomised controlled trials (Keynote-024, Keynote-010, CheckMate017, CheckMate057, OAK -GO28915).

Real-World Evidence

routine clinical practice differs from RCTs

Experience in routine clinical practice may differ from that seen in a controlled clinical trial. Although randomised clinical trials (RCTs) are considered to be the standard for generating clinical evidence, they lack generalisability to real-world evidence due to selected patient populations (strict and complex enrolment criteria). Therefore, the use of real-world evidence (RWE) to evaluate the effectiveness and safety of medical interventions is gaining interest.

retrospective pilot study with routine data

As there is limited evidence regarding the real-world effectiveness of immunotherapy in Austria, we conducted a retrospective pilot study in six Austrian hospitals to present data on patient characteristics, effectiveness and safety from real-world practice in an NSCLC population treated with anti-PD1/PD-L1 monotherapy.

Methods

Aim of the study

The pilot project had four key objectives:

4 key objectives

1. To describe the demographic and clinical characteristics of patients treated with anti-PD1/PD-L1 therapy in real-world practice;
2. To analyse effectiveness end points [overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and disease control rate (DCR)] and safety end points [grade 3 and 4 adverse events (AEs)] in identified and eligible patients;
3. To compare these real-world patient characteristics and outcomes with clinical end points as measured in pivotal RCTs;
4. To conduct a matched-pair analysis in order to compare overall survival and progression-free survival in patients with anti-PD1/PD-L1 therapy to patients from the Tyrolean Lung Cancer Project (Tyrol Study).

protocol approved by Ethics Committee Innsbruck and Graz

The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. The protocol was approved by the Ethics Committee of the Medical University Innsbruck (reference number 1048/2019) and the Ethics Committee of the Medical University Graz (reference number 31-490 ex 18/19).

Study Population

6 Austrian hospitals

This was a multicentre, retrospective, observational study carried out at six hospitals in Austria (two hospitals in Tyrol, four hospitals in Styria). All adult NSCLC patients receiving anti-PD-1/PD-L1 monotherapy containing nivolumab, pembrolizumab or atezolizumab between January 2017 and June 2018 at the participating hospitals were included. Patients receiving anti-PD-1/PD-L1 therapy as part of a clinical trial were excluded. Data acquisition was performed based on a prespecified case report form (CRF). All study variables were collected from the available hospital electronic health records. Patient's Medical Files of eligible NSCLC patients were retrospectively analysed.

data from hospital electronic health records

follow-up period: at least 12 months

Patient records were reviewed from initiation of immunotherapy (first dosing) until the end of data collection, providing the opportunity for at least 12 months of follow-up. The follow-up period was closed on 30 June 2019 (Ty-

rol) and on 31 October 2019 (Styria), respectively. Chart review was conducted by medical students and subsequently checked by the responsible oncologists to ensure data quality and validity.

Data Management

only pseudonymised data

Only pseudonymised data were used for this retrospective study. As part of the data collection, personal data were only processed within the participating hospitals.

project partner dexhelpp responsible for data management and statistical analysis

The project partner "Verein dexhelpp" (http://www.dexhelpp.at/) was responsible for data management and statistical analysis. Data were transferred to dexhelpp independently of one another and processed in a secure working environment. The dexhelpp infrastructure storage was secured and encrypted several times. The upload of the data and the transfer within the file storage was automatically logged.

Statistical Analysis

eligible patients stratified into 3 subgroups

The sample size was determined by the available patients meeting the inclusion criteria. Data collected for all eligible patients were stratified into three subgroups according to the study population of pivotal randomised controlled trials:

- Cohort 1: Patients with first-line pembrolizumab monotherapy
- Cohort 2: Patients with second-line anti-PD-1/PD-L1 monotherapy (nivolumab, pembrolizumab or atezolizumab)
- Cohort 3: Patients with third- (or more) line anti-PD-1/PD-L1 monotherapy (nivolumab, pembrolizumab or atezolizumab)

database locked 10 January 2020

All statistical analyses were performed stratified to these three cohorts. The database was locked on 10 January 2020.

descriptive analyses

best response evaluation

progression-free survival and overall survival estimation

matched-pair analyses

Descriptive analyses were conducted for patient and tumour characteristics stratified by subgroups. Comorbidities and adverse events (grade 3 or 4) were summarised in terms of patient counts and percentages. No statistical tests were applied. Patients evaluable for response (i.e., with documented best response) were included to calculate both the objective response rate (ORR), defined as the proportion of patients with complete or partial response to immunotherapy, and the disease control rate (DCR), defined as the proportion of patients with complete or partial response or stable disease during immunotherapy. The Kaplan Meier method was used to estimate survival curves for the three cohorts and to assess progression-free survival (PFS) and overall survival (OS). In addition, a matched-pair analysis was conducted in order to compare overall survival and progression-free survival in patients with anti-PD-1/PD-L1 therapy to patients from the Tyrolean Lung Cancer Project (Tyrol Study) as historical control group. Finally, the effectiveness results, patient characteristics and tumour information of this real-life NSCLC population were compared to results from pivotal randomised controlled trials.

R version 3.6.1

All statistical analyses were performed using R, version 3.6.1 (R Foundation for Statistical Computing; https://www.r-project.org/).

Results

Study Population

In total, 103 patients were analysed, 42 patients with first-line pembrolizumab monotherapy, 47 patients with second-line anti-PD-1/PD-L1 monotherapy and 14 patients with third- (or more) line anti-PD-1/PD-L1 monotherapy.

103 patients

The majority of patients were male (58.3%) and aged ≥60 years (81.6%). The median age in the overall study population was 68.0 years (range 43-85), 67.5 (range 49-85) in cohort 1, 69.0 (range 55-82) in cohort 2, whilst cohort 3 was slightly younger with median age 64.0 years (range 43-77). Fourty-three (41.7%) patients were treated in Styrian hospitals and 60 (58.3%) in Tyrolean hospitals.

median age in overall study population 68.0 years

Most patients had a history of smoking, 64.1% were active smokers and 25.2% were former smokers. Ninety-three patients (90.3%) had an ECOG performance status score of 0 or 1 at the beginning of the anti-PD-1/PD-L1 therapy, only six patients (5.8%) had ECOG ≥2. Most patients had adenocarcinoma (72.8%) followed by squamous carcinoma (21.4%). Most patients had stage IV disease (76.7%) at the beginning of immunotherapy, and 21 patients had advanced NSCLC (14 patients with stage IIIB and seven patients with stage IIIA).

smoking history in most patients

PD-L1 TPS results were not available for all patients. Eighty-one patients (78.6%) were identified as PD-L1 positive, 61 (75.3%) thereof had PD-L1 ≥50%.

78.6% PD-L1 positive

Treatment Outcomes

The ORR was 36.5% (n=27) for the overall cohort, and 43.3%, 31.4% and 33.3% for the three cohorts, respectively. Moreover, 20.3% of the evaluable patients had stable disease (SD) and 43.2% had progressive disease (PD). Twenty-nine patients were not evaluable for response due to death before response evaluation or missing data.

ORR was 43.3%, 31.4% and 33.3% for the 3 cohorts

The median OS and PFS were 16.99 months (95% CI 11.73-21.45) and 6.06 months (95% CI 3.12-17.02), respectively, for all patients in **cohort 1**.

median OS 16.9 and median PFS 6.1 months

The median OS and PFS were 18.73 months (95% CI 9.46-23.36) and 3.71 months (95% CI 2.30-9.86), respectively, for all patients in **cohort 2**. For stratification by compound (nivolumab, pembrolizumab, atezolizumab), the median OS were 20.47 months (95% CI 8.80-26.15), 22.87 months (95% CI 10.94-27.70) and 1.91 months (95% CI 0.36-NA), respectively, in cohort 2. The median PFS were 4.06 months (95% CI 2.37-13.63), 3.06 months (95% CI 2.30-26.18) and 1.38 months (95% CI 0.36-NA), respectively, in cohort 2 for stratification by compound. In addition, OS and PFS in patients of cohort 2 were estimated stratified by PD-L1 TPS % (PD-L1 TBS available in 38 out of 47 patients): The median OS were 12.75 months (95% CI 7.39-NA), 6.87 months (95% CI 2.76-NA), and 21.57 months (95% CI 9.46-26.68) for patients with PD-L1 ≥50%, respectively, for stratification by PD-L1 (%). The median PFS were 2.00 months (95% CI 1.48-NA), 1.97 months (95% CI 1.61-NA) and 8.31 months (95% CI 2.53-26.68) in patients with PD-L1 ≥50%, respectively, for stratification by PD-L1 (%).

median OS 18.7 and median PFS 3.7 months

The median OS and PFS were 12.96 months (95% CI 2.46-27.20) and 3.06 months (95% CI 2.33-14.82), respectively, for all patients of **cohort 3.**

median OS 12.9 and median PFS 3.1 months

Treatment-related adverse events (AEs) occurred in 24 patients. Grade 3 or 4 adverse events were reported in 11 patients. These adverse events were skin rash, thyroiditis, pneumonitis, diarrhoea (immune-related colitis), toxic pneu-

AEs in 24 patients in total, 11 AEs grade 3 or 4

monitis or immune-mediated hepatitis und drug-induced exanthema, leading to discontinuation or interruption of treatment in eight cases.

Exploratory Comparison with Clinical Trial Populations

cohort 1 slightly older and 7.1% with ECOG ≥2

Compared to Keynote-024, the first-line pembrolizumab cohort in our setting was slightly older and included three patients (7.1%) with ECOG performance status ≥2. Moreover, six patients (14.3%) with advanced NSCLC (stage IIIA and IIIB) were administered pembrolizumab as first-line therapy.

cohort 2 slightly older and 2 patients with ECOG ≥2

Compared to clinical trials, the second-line anti-PD-1/PD-L1 monotherapy cohort in our setting was slightly older, and included two patients with ECOG performance status ≥2. Compared to clinical trials with nivolumab or atezolizumab, fewer patients in our cohort 2 had PD-L1 TPS<1%. In contrast to pivotal studies testing one compound, the patients in our cohort 2 received either nivolumab (n=26, 55.3%), pembrolizumab (n=15, 31.9%) or atezolizumab (n=6, 12.8%) as second-line monotherapy and were analysed together.

no pivotal clinical trials for third-line or more

No specific trials for patients with third- or more line therapy for NSCLC are available for a comparison with cohort 3. In the Keynote-010 trial, 27% of patients had ≥2 lines of therapy for advanced disease. In the CheckMate017 trial, patients who had received more than one prior systemic therapy for metastatic disease were excluded. In the CheckMate057 trial, 12% had two prior systemic regimes. Finally, in the OAK trial, 25% of patients had two previous therapies in the locally advanced or metastatic setting.

Matched-Pair Analysis (Historical Cohort)

historical controls with either platine or taxane therapy

The matched-pair analysis was conducted for cohort 1 (first-line pembrolizumab) and for cohort 2 (second-line nivolumab, pembrolizumab, atezolizumab). Cohort 1 was matched to patients with first-line platine therapy, cohort 2 was matched to patients with second-line taxane therapy.

median OS 15.2 versus 9.8 months

For cohort 1, the matched-pair analysis showed a median OS of 15.21 months (95% CI 7.56-20.44) for pembrolizumab monotherapy compared to 9.81 months (95% CI 7.79-11.60) for the historic cohort with first-line platine therapy (p= 0.43). The PFS was 5.22 months (95% CI 2.53-17.61) for cohort 1 and 4.87 months (95% CI 3.94-6.01) for the first-line platine group (p=0.14).

median OS 20.3 versus 5.4 months

For cohort 2, the matched-pair analysis showed a median OS of 20.34 months (95% CI 6.87-26.18) for anti-PD-1/PD-L1 monotherapy compared to 5.40 months (95% CI 3.15-11.66) for the historic cohort with first-line taxane therapy (p=0.18). The PFS was 2.60 months (95% CI 1.91-20.34) for cohort 2 and 3.05 months (95% CI 1.97-5.78) for the first-line taxane group (p=0.36).

Discussion

immune checkpoint inhibitors changed lung cancer treatment

The development of immune checkpoint inhibitors has changed cancer treatment in the last years, and immunotherapy nowadays plays an important role in the treatment of patients with non-small lung cancers. The place in therapy is based on results from pivotal clinical trials which lead to the approval of these compounds for the treatment of NSCLC by the FDA and the EMA. Although the results of relevant registrational trials are promising, they do not always reflect anti-PD-1/PD-L1 therapy of patients with NSCLC in real-world practice.

retrospective pilot study in 6 Austrian hospitals

Our retrospective pilot study in six Austrian hospitals provides important data on both effectiveness and safety for real-life NSCLC patients treated with anti-PD-1/PD-L1 therapy in six Austrian hospitals. Patients in our cohort were comparable to the populations included in clinical trials regarding stage, ECOG performance status and PD-L1 TPS. Our cohort was slightly older but still in adherence to ESMO guidelines which recommend to consider immunotherapy in elderly patients, too.

comparable PFS and OS, higher ORR in second-line

Especially for second-line anti-PD-1/PD-L1 monotherapy we could show comparable median progression-free survival, but a higher response rate and longer median overall survival. In contrast, the results from pivotal clinical trials for first-line pembrolizumab monotherapy could not be confirmed in our real-world setting. Nevertheless, our results are in line with other published real-world studies. As our analyses showed wide confidence intervals, trials with larger study populations and an appropriate follow-up duration should enable a more precise estimation of overall survival. Moreover, this issue should be addressed in further trials using real-world data as pembrolizumab in first-line therapy is increasingly used in Austrian hospitals. Regarding safety, particularly for adverse events grade ≥3, our overall cohort showed a favourable safety profile.

further studies needed for first-line

longer median OS for immuno-therapy compared to historic controls

In addition, our matched-pair analysis for patients with anti-PD-1/PD-L1 therapy compared to historic controls from the Tyrolean Lung Cancer Project (Tyrol Study) showed a longer median overall survival for immunotherapy in the first-line comparison to platine therapy, as well as in the second-line comparison to taxane therapy. No difference was found for progression-free survival between immunotherapy and historic controls.

Contrasting Results with Similar Studies

retrospective studies from other countries

To the best of our knowledge, this is the first retrospective study analysing real-world data for immunotherapy in Austria, but we found several recently published analyses of real-world data from other countries. Our findings are in line with other reported NSCLC real-life studies, but one important difference from other published real-world retrospective analyses is the presence of a low number of patients having an ECOG performance status of ≥2 in our cohort. The administration of immunotherapy in our clinical settings seems to follow the recommendation to restrict anti-PD-1/PD-L1 therapy to patients with ECOG 0-1.

International Debate on Real-World Data

real-world data (RWD) for real-world evidence (RWE)

Randomised clinical trials are the standard method to demonstrate causal effects between treatment and outcome, but do not always reflect the real clinical setting. Therefore, real-world evidence of the effectiveness of newly approved and funded therapies is being increasingly requested by funding bodies, decision-makers, as well as clinicians themselves. Contemporary and robust real-world evidence is crucial for helping clinicians tailor new treatments to real-world patients. Both the EMA and the FDA have already addressed this topic and there is currently an intensive debate about when and how to use real-world data and whether real-world evidence can be incorporated in decision-making. Further research is still needed to either develop methodological standards for real-world data collection and analysis, and to more and more incorporate real-world evidence into clinical decision-making.

Limitations

retrospective study, small sample size, short follow-up, lack of detailed information, only 6 Austrian hospitals

The results of our study have to be interpreted with caution due to several limitations. First, it was a retrospective observational study and clinically relevant data were extracted from electronic health records in hospitals which are primarily designed for oncologists to treat patients and manage clinical care. Secondly, the small size of our three cohorts is a weakness of our study. Thirdly, although we defined at least 12 months of follow-up for included patients, the recruitment period from January 2017 to June 2018 seemed to be too long to ensure an adequate duration of follow-up to estimate certain overall survival for all patients. Fourthly, the comparison of our cohort with study populations in pivotal clinical trials was only possible for some criteria, e.g., age, ECOG, PD-L1 TPS, but could not be done for further aspects like brain metastases. Fifthly, we only included six hospitals in two Austrian states which might limit the generalisability of our results to all Austrian hospitals. Finally, we neither performed univariate or multivariate data analysis to identify covariates nor stratified survival analysis due to the small sample sizes in subgroups.

Conclusion

important data on effectiveness and safety

larger (prospective) real-world studies expected

In conclusion, our real-world pilot study presents clinically relevant results regarding the use of immunotherapy in routine practice and underlines the value of retrospective studies using real-world data to contribute to the generation of real-world evidence. Larger (prospective) real-life studies are needed to better understand real-world outcomes of patients treated with immunotherapy approved based on the results of conventional clinical trials with narrow eligibility criteria leading to potential deficits in external validity. A comprehensive, contemporary and more structured/standardised tumour documentation in Austrian hospitals could support the participation in such real-world studies.

Zusammenfassung

Einleitung

Gesundheitsproblem

Lungenkrebs: 11,6 % aller neuen Krebsfälle weltweit

Im Jahr 2018 trat Lungenkrebs bei etwa 2,1 Millionen Patienten (11,6 % aller neuen Krebsfälle) weltweit auf und verursachte geschätzte 1,7 Millionen Todesfälle (18,4 % aller krebsbedingten Todesfälle). In Europa wurden 2018 470.039 neue Lungenkrebsfälle diagnostiziert und 387.913 Patienten starben an dieser Krankheit. In Österreich wurden 2016 insgesamt 2.868 neue Fälle von Lungenkrebs bei Männern und 2.009 neue Fälle bei Frauen gemeldet, und Lungenkrebs war die zweithäufigste Krebsart bei beiden Geschlechtern (12 % aller neuen Krebsfälle). Insgesamt starben 2.415 Männer und 1.534 Frauen an dieser Krankheit. Damit war Lungenkrebs die häufigste Ursache für krebsbedingte Todesfälle bei Männern und die zweithäufigste Ursache für krebsbedingte Todesfälle bei Frauen (20 % aller krebsbedingten Todesfälle) im Jahr 2016 in Österreich.

Unterteilung in NSCLC und SCLC

Lungenkrebs wird in zwei Hauptkategorien, das nicht-kleinzelliges Bronchialkarzinom (NSCLC) und das kleinzellige Bronchialkarzinom (SCLC), aufgrund von Unterschieden in der Histologie, im Verlauf und in der Behandlung eingeteilt. Das nicht-kleinzellige Bronchialkarzinom macht mehr als 85 % aller Lungenkrebserkrankungen aus und wird weiter in Adenokarzinom, Plattenepithelkarzinom sowie weiteren weniger verbreitete histologische Subtypen unterteilt.

molekulare Veränderungen

EGFR
BRAF
ALK
ROS1

PD-L1 Expression

Durch das zunehmende Verständnis der molekularen Grundlagen von Krebsentstehung ist deutlich geworden, dass das nicht-kleinzellige Bronchialkarzinom aus zahlreichen weiteren Untergruppen bestehen. Diese Untergruppen sind durch molekulare Veränderungen charakterisiert (Mutationen, Translokationen, Amplifikationen u. a.). Da diese für das maligne Wachstum der Tumorzellen verantwortlich sind, nennt man sie auch Treibermutationen („driver mutations“). Immer mehr dieser Treibermutationen werden entdeckt und ermöglichen eine zielgerichtete Therapie, die effizienter und besser verträglich als eine konventionelle Chemotherapie zu sein scheint. Zu den bereits bekannten molekularen Veränderungen zählen u. a. EGFR-Mutationen, BRAF-Mutationen, ALK-Translokationen oder ROS1-Translokationen. Bei Patienten ohne genetische Veränderungen, für die zielgerichtete Therapien zugelassen sind, ist die Bestimmung der PD-L1-Expression für eine mögliche Immuntherapie mit Checkpoint-Inhibitoren vorgesehen.

Prognose hängt vom Stadium ab

Nur wenige Patienten werden zu einem frühen Zeitpunkt der Erkrankung (Stadium I oder II) diagnostiziert. In über 60 % der Fälle findet sich ein lokal fortgeschrittenes oder metastasiertes Karzinom (Stadium III oder IV), bei dem eine Resektion nicht mehr möglich ist. Das Überleben nimmt mit fortgeschrittener Krankheit progressiv ab. Eine Metastasierung ist in ca. 50 % der neu diagnostizierten NSCLC bereits vorhanden und die Prognose für diese Patienten daher schlecht (die 5-Jahres-Überlebensrate liegt bei etwa 6 %). Neuartige Behandlungsoptionen wie die Immuntherapie können dazu beitragen, die 5-Jahres-Überlebensrate bei metastasiertem bzw. Stadium IV NSCLC zu verbessern.

Beschreibung der Technologie

Operation, Strahlentherapie, Radiotherapie

zielgerichtete Therapie

Immuntherapie

Abhängig vom Tumorstadium, der Histologie, den molekularen Eigenschaften, dem allgemeinen Gesundheitszustand und den Präferenzen der Patienten, gehören Operation, Strahlentherapie und/oder Chemotherapie allein oder in Kombination zu den Behandlungsoptionen des nicht-kleinzelligen Bronchialkarzinoms. Die Behandlungsentscheidungen wird idealerweise in einem multidisziplinären Tumorboard diskutiert. Patienten mit nicht-kleinzelligem Bronchialkarzinom im Stadium I, II oder III werden im Allgemeinen mit kurativer Absicht behandelt. Weiters können zielgerichtete Therapie und/oder Immuntherapie vor allem zur Behandlung von fortgeschrittenem oder metastasiertem NSCLC eingesetzt werden.

Immun-Checkpoint Inhibitoren

In den letzten Jahren wurden die sogenannten Immun-Checkpoint-Inhibitoren entwickelt. Dabei handelt es sich um monoklonale Antikörper, die sich u. a. gegen PD-1 und PD-L1 (als Immuncheckpoint wirkenden Proteine) richten. PD-1 („Programmed Death 1“) ist ein Immun-Checkpoint, der sich als wichtiges therapeutisches Ziel herausgestellt hat. PD-1 wird auf der Oberfläche von aktivierten T- Zellen, B-Zellen und natürlichen Killerzellen exprimiert. Die Interaktion von PD-1 mit einem seiner beiden bekannten Liganden, PD-L1 und PD-L2, führt zu der Störung der intrazellulären Signalübertragung und Herunterregulierung der Effektor-T-Zellfunktion. Die PD-L1-Expression kann auch auf Tumorzellen und anderen Zellen in der lokalen Tumorumgebung hochreguliert sein. Eine solche PD-L1-Expression wurde bei einer Reihe von Krebserkrankungen identifiziert, darunter auch beim nicht-kleinzelligen Bronchialkarzinom.

Nivolumab, Pembrolizumab, Atezolizumab

Zur Therapie von NSCLC sind bereits PD-1- und PD-L1-Hemmer zugelassen. Nivolumab und Pembrolizumab (PD-1-Inhibitoren) und Atezolizumab (PD-L1-Inhibitor) sind monoklonale Antikörper, welche u. a. bei der Behandlung des metastasierten NSCLC eingesetzt werden.

Zweitlinientherapie mit Nivolumab

Nivolumab (BMS-936558/MDX-1106/ONO-4538) ist ein humaner Immunoglobulin-G4-(IgG4) monoklonaler Antikörper (HuMAb), der an den „Programmed Death“-1-(PD-1)-Rezeptor bindet und die Interaktion des Rezeptors mit den Liganden PD-L1 und PD-L2 blockiert. Nivolumab wurde im Juni 2015 von der Europäischen Arzneimittel-Agentur (EMA) zugelassen und ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierten nichtkleinzelligen Lungenkarzinoms nach vorheriger Chemotherapie bei Erwachsenen indiziert.

Erst- und Zweitlinientherapie mit Pembrolizumab

Pembrolizumab ist ein humanisierter monoklonaler Antikörper, der an den „Programmed cell death-1“-(PD-1)-Rezeptor bindet und die Interaktion mit seinen Liganden PD-L1 und PD-L2 blockiert. Die Zulassung durch die EMA wurde im Juli 2015 erteilt. Pembrolizumab ist u. a. für die Behandlung von lokal fortgeschrittenem oder metastasiertem NSCLC zugelassen:

- als Monotherapie zur Erstlinienbehandlung des metastasierenden nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1-exprimierenden Tumoren (Tumor Proportion Score [TPS] ≥ 50 %) ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen;
- in Kombination mit Pemetrexed und Platin-Chemotherapie zur Erstlinienbehandlung des metastasierenden nicht-plattenepithelialen NSCLC ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen;

- in Kombination mit Carboplatin und entweder Paclitaxel oder nab-Paclitaxel zur Erstlinienbehandlung des metastasierenden plattenepithelialen NSCLC bei Erwachsenen;
- als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden NSCLC mit PD-L1-exprimierenden Tumoren (TPS≥ 1 %) nach vorheriger Chemotherapie bei Erwachsenen (Patienten mit EGFR- oder ALK-positiven Tumormutationen sollten vor der Therapie mit Pembrolizumab ebenfalls eine auf diese Mutationen zielgerichtete Therapie erhalten haben).

Zweitlinientherapie mit Atezolizumab

Atezolizumab (MPDL-3280A) ist ein im Fc-Teil modifizierter, humanisierter monoklonaler Immunglobulin G1(IgG1)-Antikörper, der direkt an PD-L1 bindet und zu einer dualen Blockade der PD-1- und B7.1-Rezeptoren führt. Atezolizumab wurde von der EMA im September 2017 zugelassen. Atezolizumab wird u. a. als Monotherapie bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten NSCLC nach vorheriger Chemotherapie angewendet.

Zulassung basiert auf RCTs

Die Zulassung dieser drei Immun-Checkpoint-Inhibitoren Nivolumab, Pembrolizumab und Atezolizumab für die NSCLC Monotherapie basiert auf randomisierten kontrollierten Studien (Keynote-024, Keynote-010, CheckMate-017, CheckMate057, OAK -GO28915).

Real World Evidenz

Verwendung von Routinedaten

Real World Evidenz (RWE) erweitert die Daten randomisierter klinischer Studien, die auf selektierten, homogenen Patientenkollektiven und einer befristeten Studiendauer beruhen, um Langzeiterfahrungen der klinischen Praxis. Die randomisierte kontrollierte klinische Studie gilt als Goldstandard um kausale Beziehungen zwischen Behandlung und Outcome zu untersuchen, jedoch sind die Ergebnisse dieser Studien nicht immer auf den klinischen Alltag in der Patientenversorgung übertragbar. Aus diesem Grund werden zunehmend Daten aus der Routineversorgung herangezogen, um die Wirksamkeit und Sicherheit neuer Therapien unter Alltagsbedingungen zu evaluieren.

bisher keine Real World Daten zur Immuntherapie in Österreich

Da bisher keine Evaluierung der Immuntherapie im Versorgungsalltag in Österreich vorlag, wurde eine retrospektive Pilotstudie in sechs österreichischen Krankenhäusern zur Wirksamkeit und Sicherheit der Anti-PD-1/PD-L1-Monotherapie bei Patienten mit NSCLC unter Verwendung von Routinedaten durchgeführt.

Methoden

Ziel der Studie

Das Pilotprojekt hatte vier Hauptziele:

4 Ziele

1. Beschreibung der Charakteristika von mit Immuntherapie behandelten NSCLC Patienten im Versorgungsalltag der Krankenhäuser;
2. Analyse des Gesamtüberlebens (OS), des progressionsfreien Überlebens (PFS), der objektiven Ansprechrate (ORR) und der Krankheitskontrollrate (DCR) sowie von Sicherheitsendpunkte (unerwünschte Ereignisse Grad 3 und 4);
3. Vergleich der Patientencharakteristika und der Ergebnisse aus dem Versorgungsalltag mit den Ergebnissen der Zulassungsstudien;

4. Durchführung einer Matched-Pair Analyse, um das Gesamtüberleben und das progressionsfreie Überleben von Patienten mit Immuntherapie mit jenen Patienten mit Chemotherapie aus dem Tiroler Lungenkrebsprojekt („Tyrol Study“) zu vergleichen.

Genehmigungen der Ethikkommissionen Innsbruck und Graz

Die Studie wurde gemäß der Deklaration von Helsinki und den Richtlinien für gute klinische Praxis durchgeführt. Das Protokoll wurde von der Ethikkommission der Medizinischen Universität Innsbruck (Referenznummer 1048/2019) und der Ethikkommission der Medizinischen Universität Graz (Referenznummer 31-490 ex 18/19) genehmigt.

Studienpopulation

retrospektive Beobachtungsstudie

Patienten mit Start der Immuntherapie im Zeitraum Jänner 2017 bis Juni 2018

Es handelt sich um eine multizentrische, retrospektive Beobachtungsstudie, die in sechs Krankenhäusern in Österreich durchgeführt wurde (zwei Krankenhäuser in Tirol, vier Krankenhäuser in der Steiermark). Alle erwachsenen Patienten mit NSCLC, die zwischen Jänner 2017 und Juni 2018 in den teilnehmenden Krankenhäusern eine Anti-PD-1/PD-L1-Monotherapie mit Nivolumab, Pembrolizumab oder Atezolizumab erhielten, wurden eingeschlossen. Patienten, die im Rahmen einer klinischen Studie eine Anti-PD-1/PD-L1-Therapie erhielten, wurden ausgeschlossen. Die Datenerfassung wurde auf der Grundlage eines vorgegebenen Datensammlungsformulars (CRF) durchgeführt. Alle benötigten Daten wurden aus den verfügbaren elektronischen Krankenakten des jeweiligen Krankenhauses extrahiert und gesammelt.

zumindest 12 Monate Nachbeobachtungszeit

Die notwendigen Daten wurden vom Beginn der Immuntherapie bis zum Ende der Datenerfassung erhoben, um eine Nachbeobachtungszeit von mindestens 12 Monaten zu gewährleisten. Die Nachbeobachtungszeit endete am 30. Juni 2019 (Tirol) bzw. am 31. Oktober 2019 (Steiermark). Die Extraktion der Daten wurde von je einem Medizinstudenten in Tirol und der Steiermark durchgeführt und anschließend von den zuständigen Onkologen überprüft, um die Datenqualität und -validität sicherzustellen.

Datenmanagement

Verwendung pseudonymisierter Daten

Für die Auswertungen der vorliegenden retrospektiven Studie wurden ausschließlich pseudonymisierten Daten verwendet. Im Rahmen der Datenerhebung wurden personenbezogene Daten nur in den teilnehmenden Krankenhäusern verarbeitet.

Datenmanagement durch dexhelpp

Der Projektpartner „Verein dexhelpp“ (http://www.dexhelpp.at/) war für das Datenmanagement und die statistische Analyse verantwortlich. Die Daten der verschiedenen Krankenhäuser wurden unabhängig voneinander an dexhelpp übertragen und in einer sicheren Arbeitsumgebung verarbeitet. Der Transfer der Daten wurde auf mehrfache Art gesichert, wobei eine Kombination an Maßnahmen zur Verschlüsselung, Authentifizierung und persönlichen Zuordnung der Datensätze und Zugriffsrechte eingesetzt wurde.

Statistische Analyse

Unterteilung in 3 Kohorten

Für die Analyse wurden die eingeschlossenen Patienten entsprechend den Studienpopulationen der randomisierten kontrollierten Studien in drei Untergruppen unterteilt:

- Kohorte 1: Patienten mit Pembrolizumab Monotherapie als Erstlinientherapie
- Kohorte 2: Patienten mit Immuntherapie (Nivolumab, Pembrolizumab oder Atezolizumab Monotherapie) als Zweitlinientherapie

- Kohorte 3: Patienten mit Immuntherapie (Nivolumab, Pembrolizumab oder Atezolizumab Monotherapie) als Drittlinientherapie (oder weitere Linie)

Alle statistischen Analysen wurden getrennt für diese drei Kohorten durchgeführt.

deskriptive Analysen

Deskriptive Analysen wurden für Patienten- und Tumorcharakteristika sowie Begleiterkrankungen und Nebenwirkungen (Grad 3 oder 4) durchgeführt. Es wurden keine statistischen Tests angewendet. Bezüglich dem besten Ansprechen auf die Immuntherapie wurde die objektive Ansprechrate (ORR), definiert als der Anteil der Patienten mit vollständiger oder teilweiser Remission, und die Krankheitskontrollrate (DCR), definiert als der Anteil der Patienten mit vollständiger oder teilweiser Remission oder stabiler Erkrankung unter Immuntherapie, berechnet. Die Kaplan-Meier-Methode wurde verwendet, um die Überlebenskurven für die drei Kohorten zu schätzen und das progressionsfreie Überleben (PFS) und das Gesamtüberleben (OS) zu analysieren. Zusätzlich wurde eine Matched-Pair-Analyse durchgeführt, um das Gesamtüberleben und das progressionsfreie Überleben bei Patienten mit Anti-PD-1/PD-L1-Therapie mit jenem von Patienten aus dem Tiroler Lungenkrebsprojekt („Tyrol Study“) als historische Kontrollgruppe zu vergleichen. Die Patientencharakteristika und Wirksamkeitsergebnisse der Kohorte aus dem Versorgungsalltag wurden abschließend noch mit jenen aus den randomisierten Studien deskriptiv verglichen.

ORR
DCR

Gesamtüberleben
progressionsfreies Überleben

Matched-Pair Analyse

Alle statistischen Analysen wurden mit R, Version 3.6.1 (R Foundation for Statistical Computing; https://www.r-project.org/) durchgeführt .

Ergebnisse

Studienpopulation

103 Patienten

Insgesamt wurden 103 Patienten analysiert, 42 Patienten mit Pembrolizumab-Monotherapie als Erstlinientherapie, 47 Patienten mit Anti-PD-1/PD-L1-Monotherapie in der zweiten Linie und 14 Patienten mit Anti-PD-1/PD-L1 Monotherapie in der dritten (oder weiteren) Linie.

Durchschnittsalter
68,0 Jahre

Die Mehrheit der Patienten war männlich (58,3 %) und ≥ 60 Jahre alt (81,6 %). Das Durchschnittsalter in der gesamten Studienpopulation betrug 68,0 Jahre (43-85 Jahre), 67,5 Jahre (49-85 Jahre) in Kohorte 1, 69,0 Jahre (55-82 Jahre) in Kohorte 2, während Kohorte 3 mit einem Durchschnittsalter von 64,0 Jahren (43-77 Jahre) etwas jünger war. 43 (41,7 %) Patienten wurden in steirischen Krankenhäusern und 60 (58,3 %) in Tiroler Krankenhäusern behandelt.

64,1 % aktive Raucher

90,3 % mit
ECOG 0 oder 1

Die meisten Patienten hatten eine Raucheranamnese, 64,1 % waren aktive Raucher und 25,2 % waren ehemalige Raucher. 93 Patienten (90,3 %) hatten zu Beginn der Anti-PD-1/PD-L1-Therapie einen ECOG Performance Status von 0 oder 1, nur sechs Patienten (5,8 %) hatten ECOG ≥ 2, für vier Patienten lag keine Information zum ECOG vor. Die meisten Patienten hatten ein Adenokarzinom (72,8 %), gefolgt von einem Plattenepithelkarzinom (21,4 %). Die meisten Patienten hatten zu Beginn der Immuntherapie eine NSCLC Erkrankung im Stadium IV (76,7 %), und 21 Patienten hatten eine fortgeschrittene NSCLC Erkrankung (14 Patienten im Stadium IIIB und sieben Patienten im Stadium IIIA).

78,6 % waren
PD-L1 positiv

Die PD-L1 TPS (in %) Ergebnisse waren nicht für alle Patienten verfügbar. 81 Patienten (78,6 %) wurden als PD-L1 positiv identifiziert, 61 (75,3 %) davon hatten PD-L1 ≥ 50 %.

Behandlungsergebnisse

ORR 43,3 %, 31,4 % bzw. 33,3 %

Die ORR betrug 36,5 % (n=27) für die Gesamtkohorte und 43,3 %, 31,4 % bzw. 33,3 % getrennt für die drei Kohorten. Darüber hinaus hatten 20,3 % der auswertbaren Patienten eine stabile Erkrankung (SD) und 43,2 % eine progressive Erkrankung (PD). 29 Patienten konnten nicht für die Auswertung zum Ansprechen („best response") herangezogen werden, da entweder die entsprechenden Daten fehlten oder sie vorher verstorben sind.

medianes OS 16,9 und medianes PFS 6,1 Monate

Das mediane Gesamtüberleben und das mediane progressionsfreie Überleben betrugen 16,99 Monate (95 % CI 11,73-21,45) bzw. 6,06 Monate (95 % CI 3,12 bis 17,02) für alle Patienten in **Kohorte 1**.

medianes OS 18,7 und medianes PFS 3,7 Monate

Das mediane Gesamtüberleben und das mediane progressionsfreie Überleben betrugen 18,73 Monate (95 % CI 9,46-23,36) bzw. 3,71 Monate (95 % CI 2,30-9,86) für alle Patienten in **Kohorte 2**.

medianes OS 12,9 und medianes PFS 3,1 Monate

Das mediane Gesamtüberleben und das mediane progressionsfreie Überleben betrugen 12,96 Monate (95 % CI 2,46-27,20) bzw. 3,06 Monate (95 % CI 2,33-14,82) für alle Patienten der **Kohorte 3.**

11 Nebenwirkungen Grad 3 oder 4

Behandlungsbedingte unerwünschte Ereignisse traten bei 24 Patienten auf. Nebenwirkungen Grad 3 oder 4 wurden bei 11 Patienten berichtet. Diese unerwünschten Ereignisse waren Hautausschlag, Thyreoiditis, Pneumonitis, Durchfall (immunbedingte Kolitis), toxische Pneumonitis oder immunvermittelte Hepatitis und medikamenteninduziertes Exanthem, was in acht Fällen zum Absetzen oder Unterbrechen der Behandlung führte.

Explorativer Vergleich mit den Patienten der klinischen Studien

Kohorte 1: 7,1 % ECOG ≥2 und 14,3 % Stadium IIIA/B

Im Vergleich zur Keynote-024 Studie (Erstlinientherapie mit Pembrolizumab Monotherapie) war Kohorte 1 etwas älter und drei Patienten (7,1 %) mit ECOG Performance Status ≥ 2 waren eingeschlossen. Weiters wurde Pembrolizumab bei sechs Patienten (14,3 %) mit fortgeschrittenem NSCLC (Stadium IIIA und IIIB) als Erstlinientherapie verabreicht.

Kohorte 2: etwas älter und 2 Patienten mit ECOG ≥2

Im Vergleich zu klinischen Studien mit einer Immuntherapie in der zweiten Linie, war die Kohorte 2 etwas älter und zwei Patienten mit ECOG Performance Status ≥ 2 waren eingeschlossen. Im Vergleich zu klinischen Studien mit Nivolumab oder Atezolizumab hatten weniger Patienten in unserer Kohorte 2 ein PD-L1-TPS < 1 %. Im Gegensatz zu den randomisierten kontrollierten Studien, die jeweils nur eine Substanz untersuchten, erhielten die Patienten der Kohorte 2 entweder Nivolumab (n=26; 55,3 %), Pembrolizumab (n=15; 31,9 %) oder Atezolizumab (n=6; 12,8 %) als Zweitlinientherapie und wurden zusammen ausgewertet.

keine RCTs mit Immuntherapie als Drittlinie

Es sind keine gesonderten randomisierten kontrollierten Studien zur Drittlinientherapie (oder weiterer Linie) mit Immuntherapie bei Patienten zur Behandlung des NSCLC verfügbar, diese Patienten wurden aber zum Teil in den Studien eingeschlossen. In der Keynote-010 Studie, hatten 27 % der Patienten eine Therapielinie ≥ 2 für die Behandlung der fortgeschrittenen NSCLC Erkrankung. In der CheckMate017-Studie wurden Patienten ausgeschlossen, die zuvor mehr als eine systemische Therapie für das metastasierte NSCLC erhalten hatten. In der CheckMate057-Studie hatten 12 % zwei vorherige systemische Therapieregime. Während in der OAK-Studie 25 % der Patienten zwei frühere Therapielinien für die lokal fortgeschrittene oder metastasierte NSCLC Erkrankung erhalten haben.

Matched-Pair-Analyse (historische Kohorte)

historische Kontrollen mit Platin- oder Taxantherapie

Die Matched-Pair-Analyse wurde für Kohorte 1 (Erstlinientherapie mit Pembrolizumab) und für Kohorte 2 (Zweitlinientherapie mit Nivolumab, Pembrolizumab oder Atezolizumab) durchgeführt. Kohorte 1 wurde mit Patienten mit einer platinhaltigen Erstlinientherapie und Kohorte 2 mit Patienten mit einer taxanhaltigen Zweitlinientherapie verglichen.

medianes OS 15,2 versus 9,8 Monate

Für **Kohorte 1**, betrug das mediane Gesamtüberleben in der Pembrolizumab-Gruppe 15,21 Monaten (95 % CI 7,56 bis 20,44) versus 9,81 Monaten (95 % CI 7,79 bis 11,60) für die historische Kohorte mit einer Platintherapie. Das mediane progressionsfreie Überleben betrug 5,22 Monate (95 % CI 2,53 bis 17,61) für Kohorte 1 und 4,87 Monate (95 % CI 3,94-6,01) für die Gruppe mit einer Platintherapie (p=0,14).

medianes OS 20,3 versus 5,4 Monate

Für **Kohorte 2** zeigte die Matched-Pair-Analyse ein medianes Gesamtüberleben von 20,34 Monaten (95 % CI 6,87-26,18) für die Anti-PD-1/PD-L1-Monotherapie im Vergleich zu 5,40 Monaten (95 % CI 3,15-11,66) für die historische Kohorte mit einer Taxantherapie (p=0,18). Das mediane progressionsfreie Überleben betrug 2,60 Monate (95 % CI 1,91 bis 20,34) für die Kohorte 2 und 3,05 Monate (95 % CI 1,97-5,78) für die Gruppe mit Taxantherapie (p=0,36).

Diskussion

Änderung der Krebsbehandlung durch Immun-Checkpoint Inhibitoren

Die Entwicklung von Immun-Checkpoint-Inhibitoren hat die Krebsbehandlung in den letzten Jahren verändert, und die Immuntherapie spielt heutzutage eine wichtige Rolle bei der Behandlung von Patienten mit nicht-kleinzelligem Bronchialkarzinom. Der Platz in der Therapie basiert auf Ergebnissen aus randomisierten klinischen Studien, die zur Zulassung dieser Substanzen für die Behandlung von NSCLC durch die FDA und die EMA führten. Obwohl die Ergebnisse der Zulassungsstudien vielversprechende Ergebnisse zeigten, sind dies nicht immer in den Versorgungsalltag der klinischen Praxis übertragbar.

Wirksamkeit und Sicherheit im Versorgungsalltag

Unsere retrospektive Pilotstudie in sechs österreichischen Krankenhäusern liefert deshalb wichtige Informationen zur Wirksamkeit und Sicherheit der Anti-PD-1/PD-L1-Therapie in der Versorgung von NSCLC Patienten.

weitere Studien zur Erstlinientherapie mit Pembrolizumab

Vor allem für die Zweitlinientherapie mit einer Immuntherapie konnte eine höhere objektive Ansprechrate und ein etwas längeres medianes Gesamtüberleben in unserer Kohorte 2 im Vergleich zu den klinischen Studien sowie ein vergleichbares medianes progressionsfreies Überleben gezeigt werden. Im Gegensatz dazu konnten die Ergebnisse aus zulassungsrelevanten klinischen Studien für die Erstlinientherapie mit Pembrolizumab Monotherapie nicht mit unserer Kohorte 1 bestätigt werden. Das mediane Gesamtüberleben von 16,9 Monaten in unserer Kohorte 1 lag deutlich unter den 26,3 Monaten aus der randomisierten kontrollierten Studie. Die Analyse der Kohorte 1 zeigt jedoch ein sehr breites Konfidenzintervall, sodass eine verlässliche Aussage zum medianen Gesamtüberleben derzeit nicht möglich ist. Studien mit größeren Patientenzahlen und einer entsprechend längeren Nachbeobachtungszeit könnten eine genauere Schätzung des medianen Gesamtüberlebens ermöglichen. Da die Erstlinientherapie mit Pembrolizumab Monotherapie zunehmend in Versorgungsalltag verwendet wird, sollten weiteren Studien die Wirksamkeit und Sicherheit unter Alltagsbedingungen bei Patienten mit NSCLC untersuchen.

längeres medianes OS unter Immuntherapie im Vergleich zu historischer Kohorte

Die Matched-Pair Analyse für Patienten mit Anti-PD-/PD-L1-Therapie im Vergleich zu historischen Kontrollen aus dem Tiroler Lungkrebsprojekt („Tyrol Study") zeigte ein längeres medianes Gesamtüberleben für die Immuntherapie sowohl in der Erstlinien- als auch in der Zweitlinientherapie und weist damit auf eine Verbesserung der Prognose von Patienten mit fortgeschrittenem bzw. metastasierten NSCLC durch die Immuntherapie hin.

Vergleich mit Ergebnissen von ähnlichen Studien

internationale Real World Studien verfügbar

in vorliegender Kohorte weniger Patienten mit ECOG ≥2

Das vorliegende Pilotprojekt ist die erste retrospektive Studie zur Analyse von Real World Daten zur Immuntherapie bei der Behandlung von NSCLC Patienten in Österreich. Mittels Literatursuche konnten aber weitere kürzlich veröffentlichte Analysen von Real World Daten aus anderen Ländern identifiziert werden. Unsere Studie zeigt vergleichbare, zum Teil auch bessere Ergebnisse als diese internationalen Publikationen. Ein wichtiger Unterschied zu anderen veröffentlichten retrospektiven Real World Studien ist jedoch das Vorhandensein einer geringeren Anzahl an Patienten mit einem ECOG Performance Status ≥ 2 in unserer Kohorte, was auf ein verstärktes Einhalten der Empfehlung, die Anti-PD-1/PD-L1-Therapie auf Patienten mit ECOG 0-1 zu beschränken, hinweist.

Internationale Diskussion zu Real World Evidenz

zunehmende Forderung nach Real World Evidenz

Randomisierte klinische Studien sind die Standardmethode, um kausale Effekte zwischen Behandlung und dem Outcome nachzuweisen, aber nicht immer spiegeln diese Studien mit ihren strengen Ein- und Ausschlusskriterien die reale klinische Situation wider. Daher wird zunehmend Real World Evidenz zur Wirksamkeit von neu zugelassenen Therapien von Entscheidungsträgern aber auch Klinikern gefordert. Sowohl die europäische Zulassungsbehörde (EMA) als auch die amerikanische FDA haben bereits dieses Thema aufgegriffen und es gibt derzeit eine intensive Debatte darüber, wann und wie solche Real World Daten in deren Entscheidungsfindungsprozesse miteinbezogen werden können. In diesem Bereich ist noch einiges an Forschung erforderlich, um einerseits methodische Standards zur Erfassung und Analyse von Real World Daten zu entwickeln, aber auch um Real World Evidenz zunehmend in die klinische Entscheidungsfindung zu integrieren.

Limitationen

retrospektive Studie,

kleine Patientenzahlen in den 3 Kohorten,

kurzes Follow-up,

fehlenden Informationen,

nur 6 Krankenhäuser in Österreich

Die Ergebnisse unserer Studie müssen aufgrund mehrerer Limitationen mit Vorsicht interpretiert werden. Erstens handelte es sich um eine retrospektive Beobachtungsstudie bei der klinisch relevante Daten aus elektronischen Patientenakten in Krankenhäusern extrahiert wurden, die jedoch in erster Linie für Onkologen zur Behandlung von Patienten und zur Verwaltung der klinischen Versorgung bestimmt sind. Zweitens ist die geringe Patientenzahl in den drei Kohorten eine Schwäche der Studie, die allerdings als Pilotstudie konzipiert wurde. Weiters wurden mindestens 12 Monate Nachbeobachtungszeit definiert, allerdings schien der Einschlusszeitraum von Januar 2017 bis Juni 2018 zu lang zu sein, um das mediane Gesamtüberleben für alle Patienten zuverlässig zu schätzen. Der Vergleich unserer Kohorten mit Studienpopulationen aus zulassungsrelevanten klinischen Studien war nur für wenige Parameter möglich (u. a. Alter, ECOG, PD-L1 TPS %), nicht aber für weitere relevante Aspekte, wie z. B.: ZNS-Metastasen. In der Studie waren nur sechs Krankenhäuser aus zwei Bundesländern vertreten, sodass eine Übertragbarkeit der Ergebnisse auf alle österreichischen Krankenhäuser nur eingeschränkt möglich ist.

Schlussfolgerung

Zusammenfassend zeigt die vorliegende retrospektive Pilotstudie klinisch relevante Ergebnisse bezüglich der Verwendung der Immuntherapie in der täglichen Versorgungspraxis im Krankenhaus und unterstreicht die Notwendigkeit von Real World Evidenz zur Darstellung der Wirksamkeit und Sicherheit neuer Therapien. Größere (prospektive) Real World Studien sind erforderlich, um zum besseren Verständnis der Wirksamkeit der Immuntherapie im Versorgungsalltag beizutragen und um ergänzend zu den Ergebnissen aus den randomisierten kontrollierten Studien, die Versorgung der Patienten, die von einer Immuntherapie am meisten profitieren, zu gewährleisten.

wichtige Ergebnisse für die klinische Praxis

größere (prospektive) Real World Studien notwendig

1 Introduction

1.1 Non-Small Cell Lung Cancer

In 2018, **lung cancer** occurred in approximately 2.1 million patients (11.6% of all new cancer cases) worldwide and caused an estimated 1.7 million deaths (18.4% of all cancer-related deaths) [1]. In Europe, 470,039 new lung cancer cases were diagnosed in 2018 and 387,913 patients died of this disease [1]. In Austria, a total of 2,868 new cases of lung cancer in men and 2,009 new cases in women were reported in 2016 and lung cancer was the second most common cancer in both sexes (12% of all new cancer cases). Moreover, 2,415 men and 1,534 women died of this disease, making lung cancer the leading cause of cancer-related death in men and the second most common cause of cancer-related death in women (20% of all cancer-related deaths) in 2016 in Austria [2].

lung cancer: 11.6% of all new cancer cases worldwide

The term lung cancer, or bronchogenic carcinoma, refers to malignancies that originate in the airways or pulmonary parenchyma. Lung cancer has been sub-classified into two major categories (non-small cell lung cancer [NSCLC] and small cell lung carcinoma [SCLC]) as the result of differences in histological characteristics, approaches to treatment, and clinical outcomes. In general, SCLC tends to have a faster growth rate, more central and mediastinal localisation, earlier metastasis to extra-thoracic sites, and shorter overall survival time. Approximately 95% of all lung cancers are classified as either SCLC or NSCLC. This distinction is essential for staging, treatment, and prognosis. Other cell types comprise approximately 5 percent of malignancies arising in the lung [3].

lung cancer is sub-classified in NSCLC and SCLC

Lung cancer is staged from I through IV based on tumour size, and presence or absence of lymph node involvement and distant metastases (TNM classification 8th Edition). Stage I lung cancer is a small tumour that has not spread to any lymph nodes, and is divided into two substages based on the size of the tumour (IA ≤3 cm, IB >3 but ≤4 cm); stage II lung cancer is divided into two substages, stage IIA (tumour larger than 4 cm but ≤5 cm not spread to the nearby lymph nodes, and stage IIB (≤5 cm that has spread to the lymph nodes or>5 cm that has not spread to the lymph nodes); stage III lung cancers are classified as either stage IIIA, IIIB, or IIIC, the stage is based on the size of the tumour and which lymph nodes the cancer has spread to. Stage III cancers have not spread to other distant parts of the body; stage IV NSCLC is divided into two substages; stage IVA (cancer has spread within the chest and/or has spread to one area outside of the chest) and stage IVB (spread outside of the chest to more than one place in one organ or to more than one organ) [4].

stages I to IV according to TNM classification

Overall, the risk of lung cancer increases with age, tobacco use, radiation exposure, air pollution, and occupational exposure to asbestos, arsenic, chromium beryllium, nickel, second-hand smoking and other agents. The risk of developing lung cancer is typically tenfold higher in smokers compared to lifetime non-smokers. Smoking cessation decreases precancerous lesions and reduces the risk of developing lung cancer [3, 5].

smoking as major risk factor

The diagnosis of lung cancer is primarily based upon evaluation of individuals with symptoms. Screening for lung cancer was not previously recommended because chest radiography and sputum cytology had not been shown

screening for lung cancer

to reduce mortality from lung cancer. In the meantime, prospective, single-arm, observational studies have shown that a large percentage of lung cancers detected by computed tomography (CT) screening are early stage tumours, which have a favourable prognosis. These findings led to the randomised National Lung Screening Trial that compared CT screening with chest radiograph. This trial demonstrated a 20% decrease in lung cancer-specific mortality in heavy smokers who were screened annually for three years [3]. In addition, the recently published NELSON trial (the Dutch-Belgian Randomised Lung Cancer Screening Trial) investigated whether volume-based, low-dose computed tomographic (CT) screening can reduce lung cancer mortality among male former and current smokers and showed that at ten years of follow-up, the incidence of lung cancer was 5.58 cases per 1.000 person-years in the screening group and 4.91 cases per 1.000 person-years in the control group. The lung cancer mortality was 2.50 deaths per 1.000 person-years and 3.30 deaths per 1.000 person-years, respectively. The cumulative rate ratio for death from lung cancer at ten years was 0.76 (95% confidence interval [CI], 0.61 to 0.94; p = 0.01) in the screening group as compared with the control group [6]. The Multicentric Italian Lung Detection (MILD) prospective randomised trial evaluated the benefit of prolonged low-dose computed tomography (LDCT) screening beyond five years, and its impact on overall and lung cancer-specific mortality at ten years. The LDCT arm showed a 39% reduced risk of lung cancer mortality at ten years [hazard ratio (HR) 0.61; 95% confidence interval (CI) 0.39-0.95], compared with the control arm, and a 20% reduction of overall mortality (HR 0.80; 95% CI 0.62-1.03). LDCT benefit improved beyond the fifth year of screening, with a 58% reduced risk of lung cancer mortality (HR 0.42; 95% CI 0.22-0.79), and a 32% reduction of overall mortality (HR 0.68; 95% CI 0.49-0.94) [7].

chest x-ray, CT, biopsy and molecular tests for diagnosis

Whilst some lung cancers may be found through screening, most are identified when they become symptomatic. Following a clinical history and physical exam, a chest x-ray may be done to identify any abnormal areas in the lungs. A computed tomography (CT) scan may show the size, shape and location of any lung tumours or enlarged lymph nodes and guide a needle biopsy if a suspected area is identified. Lung cancer is diagnosed by examining cells derived through biopsy and cytology for the presence of cancer cells. Immunohistochemistry (IHC) and molecular tests may be conducted to identify specific changes in the genome (mutations, chromosomal rearrangements) of cancer cells to target lung cancer treatment [5, 8].

cough, haemoptysis, chest pain, and dyspnoea as symptoms

Most patients with lung cancer have advanced disease at clinical presentation. This may reflect the aggressive biology of the disease and the frequent absence of symptoms until locally advanced or metastatic disease is present. Symptoms may result from local effects of the tumour, from regional or distant spread, or from distant effects not related to metastases (paraneoplastic syndromes). The most common symptoms are cough, haemoptysis, chest pain, and dyspnoea [3].

85% are non-small cell lung cancer

Non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancers. NSCLC arises from the epithelial cells of the lung of the central bronchi to terminal alveoli. The histological type of NSCLC correlates with the site of origin, reflecting the variation in respiratory tract epithelium of the bronchi to alveoli. Squamous cell carcinoma usually starts near a central bronchus. Adenocarcinoma and bronchioloalveolar carcinoma usually originate in peripheral lung tissue [9]. NSCLC can be divided mainly into non-squamous (adenocarcinoma) (70%) and squamous (30%) histologic subtypes.

molecular pathogenesis

Rapid advances in understanding the molecular pathogenesis of NSCLC have demonstrated that NSCLC is a heterogeneous group of diseases. Although the initial treatment of localised disease is the same, the molecular characterisation of tumour tissue in patients with NSCLC serves as a guide to treatment both in those who present with metastatic disease and in those who relapse after primary therapy. Currently defined NSCLC subsets for which specific targeted therapies have been standard therapy include those with mutations in the epidermal growth factor receptor (EGFR), as well as B-Raf proto-oncogene (BRAF), those with anaplastic lymphoma kinase (ALK) fusion oncogene, and c-ROS oncogene 1 (ROS1) fusions. Other driver mutations have also been identified and specific treatments are being developed. For those without driver mutations, in whom programmed death ligand 1 (PD-L1) expression is observed, immunotherapy is available as a treatment option [8, 9]. Approximately 7-35% of NSCLC patients have driver gene alterations in EGFR, ALK or ROS1, whilst 1-3% have BRAF mutations [5, 10].

EGFR
BRAF
ALK
ROS1

PD-L1

prognosis determined by cancer stage

The TNM stage at presentation in patients with NSCLC is the factor that has the greatest impact on prognosis. Survival decreases progressively with more advanced disease. Metastatic disease is present in 50% of new NSCLC diagnoses and the prognosis for these patients with metastatic or stage IV NSCLC is poor, with five-year survival rates reported at about 6% [11]. Novel treatment options like immunotherapy may contribute to improve five-year survival rates for metastatic or stage IV NSCLC.

brain metastasis as reason for poor prognosis

A major reason for the poor prognosis is that lung cancer is the most common solid tumour to metastasise to the brain and the incidence of brain metastases is increasing. Approximately 16-20% of NSCLC patients present with brain metastases and 50-60% develop brain metastases at some point during their disease, which often reduces life expectancy further [12].

1.2 Current Treatment

surgery, radiation therapy and/or chemotherapy as treatment options

Depending on the tumour stage, histology, molecular characteristics, the patients' overall health and preferences, surgery, radiation therapy and/or chemotherapy may be used alone or in combination to treat NSCLC. The treatment decisions should ideally be discussed within a multidisciplinary tumour board. Patients with stage I, II, or III non-small cell lung cancer (NSCLC) are generally treated with curative intent using surgery, chemotherapy, radiation therapy (RT), or a combined-modality approach. In appropriately selected patients, chemotherapy, molecularly targeted therapy, and/or immunotherapy may be used to treat advanced or metastatic NSCLC. Treatment per NSCLC stages involves the following options [5, 13]:

treatment depends on stage

- Stage I and II NSCLC patients typically undergo surgery to remove the cancer. Stage II patients and a subset of patients with stage IB tumours may benefit from postoperative adjuvant chemotherapy.
- Patients with stage I or II cancers, who are not surgical candidates due to co-morbidities or limited lung function, may undergo local radiation therapy.
- Stage III NSCLC patients are highly heterogeneous and may undergo a combination of treatment modalities including chemotherapy and radiation and/or surgery, depending on the extent and localisation of disease.

- Patients with stage IV disease are treated with systemic therapy or a symptom-based palliative approach.

EGFR, ALK, ROS1 as molecular targets

An improved understanding of the molecular pathways that drive malignancy in NSCLC, as well as other neoplasms, led to the development of agents that target specific molecular pathways (see Figure 1.2-1) [14]. The identification of oncogenic activation of particular tyrosine kinases in some advanced NSCLC tumours, most notably mutations in the epidermal growth factor receptor (EGFR) or rearrangements of the anaplastic lymphoma kinase (ALK) gene or c-ROS oncogene 1 (ROS1) gene, has led to a paradigm shift and the development of specific molecular treatments for patients.

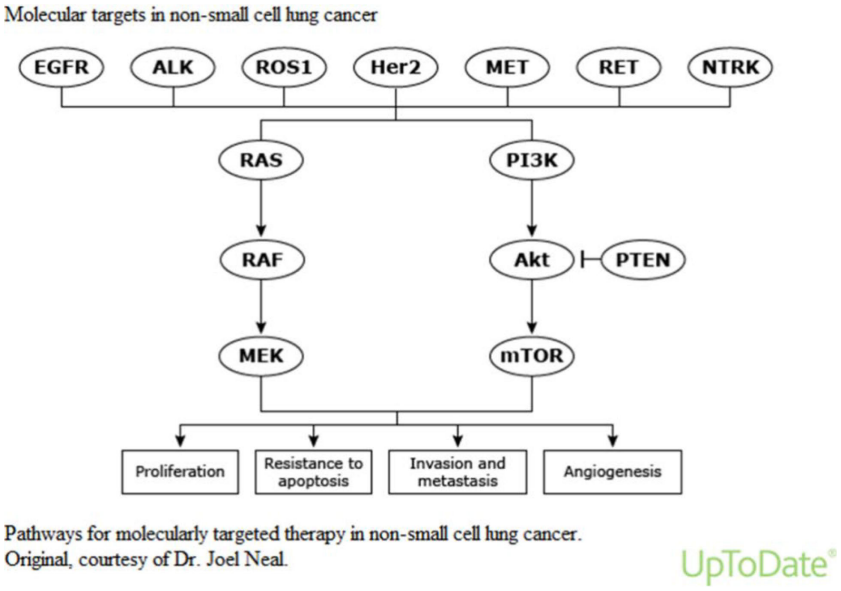

Figure 1.2-1: Molecular targets in NSCLC [66]

approved targeted therapies for several NSCLC genotypes

NSCLC genotypes with approved targeted therapies are:

- **EGFR mutation**: In EGFR-positive NSCLC, EGFR tyrosine kinase inhibitors (e.g., erlotinib, gefitinib, afatinib, osimertinib) can be used as targeted therapy.
- **ALK rearrangements**: In ALK-positive NSCLC, ALK tyrosine kinase inhibitors (e.g., crizotinib, ceritinib, alectinib, brigatinib) can be used as targeted therapy.
- **ROS1 rearrangements**: In ROS1-positive NSCLC, tropomyosin receptor kinase (TRK)/ROS1 inhibitors (entrectinib, crizotinib), due to a high degree of homology between the ALK and ROS tyrosine kinase domains, can be used as targeted therapy.
- **BRAF mutation**: For patients with NSCLC with BRAF V600E mutations, the combination of dabrafenib plus trametinib is approved by the FDA and EMA.
- **NTRK fusion** (fusions involving one of three tropomyosin receptor kinases [TRK]): in NTRK-positive NSCLC, entrectinib and larotrectinib are available as targeted therapy.

non-driver-mutated NSCLC:

PD-1/PD-L1

Although targeted therapies have redefined treatment options for patients with molecularly-defined NSCLC, these therapies are ineffective in those whose tumours lack such genetic alterations, who comprise the majority of NSCLC patients. For the management of patients with non-driver-mutated NSCLC, immunotherapy (so-called immune checkpoint inhibitors targeting either programmed cell death protein 1 [PD-1] or programmed cell death ligand 1 [PD-L1]) has become integrated into the clinical approach for management of NSCLC [15]. As platinum-based chemotherapy was the standard first-line therapy for patients with non-small cell lung cancer (NSCLC) who do not carry any targetable "driver" mutations, the incorporation of programmed death-1 (PD-1) pathway inhibitors in the treatment of metastatic non-small cell lung cancer (NSCLC) has recently modified the therapeutic landscape of NSCLC.

ESMO Guidelines for early-stage and advanced NSCLC

The ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of **early-stage and locally advanced non-small cell lung cancer** [16] recommends in its latest version the following treatment options (for complete representation see [16]):

- Surgery should be offered to all patients with stage I and II NSCLC as the preferred treatment to all who are willing to accept procedure-related risks.
- Adjuvant chemotherapy should be offered to patients with resected stage II and III NSCLC and can be considered in patients with resected stage IB disease and a primary tumour >4 cm; a two-drug combination with cisplatin is preferable. The most frequently studied regimen is cisplatin-vinorelbine.
- The non-surgical treatment of choice for stage I NSCLC is stereotactic ablative radiotherapy; for medically inoperable patients with tumours with a size >5 cm and/or moderately central location, radical RT using more conventional or accelerated schedules is recommended.
- Resectable locally advanced NSCLC (stage III): for curative-intent management, patients should be able to undergo platinum-based chemotherapy (preferably cisplatin).
- Unresectable locally advanced NSCLC (stage III): Concurrent chemoradiotherapy is the treatment of choice in patients evaluated as unresectable in stage IIIA and IIIB.
- Personalised medicine: There is currently no role for targeted agents in stage III NSCLC outside clinical trials. Immunotherapy is being studied in early NSCLC as (neo-)adjuvant therapy and as consolidation after chemoradiotherapy; data should be awaited before any clinical use.

update of ESMO Guidelines

This guideline is currently being updated and e.g. durvalumab, an anti-PD-L1 monoclonal antibody in patients with stage III, locally advanced, unresectable NSCLC and progression after chemoradiation therapy, is included.

ESMO Guidelines for metastatic NSCLC

The ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of **metastatic non-small cell lung cancer** [17] recommends the following selected treatment options (for complete representation see [17]):

- Systemic therapy should be offered to all stage IV patients with performance status 0-2.
- First-line treatment of EGFR- and ALK-negative NSCLC, PD-L1 ≥50%: Pembrolizumab is considered a standard first-line option for patients with advanced NSCLC and PD-L1 expression ≥50% who do not have contraindications to use of immunotherapy.

- First-line treatment of NSCLC without actionable oncogenic driver regardless of PD-L1 status: Combinations of platinum-based chemotherapy and anti-PD-(L1) inhibitors have reproducibly demonstrated superiority to standard platinum-based chemotherapy. In the absence of contraindications and conditioned by the registration and accessibility of anti-PD-(L)1 combinations with platinum-based chemotherapy, this strategy will be preferred to platinum-based chemotherapy in patients with PS 0-1 and PD-L1 <50%.
- First-line treatment of squamous cell cancer: Platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced SCC patients without major comorbidities and performance status 0-2.
- First-line treatment of non-squamous cell cancer: Combination of pembrolizumab and carboplatin with paclitaxel is a standard choice in patients with metastatic squamous NSCLC.
- Second-line treatment of NSCLC without actionable oncogenic driver: In patients with progression after first-line immunotherapy with pembrolizumab, platinum-based chemotherapy is recommended as a second-line treatment option; PD-L1 and PD-1 inhibitors (nivolumab, pembrolizumab and atezolizumab) are the treatment of choice for most patients with advanced, previously treated, PD-L1-naive NSCLC, irrespective of PD-L1 expression: Nivolumab is recommended in both squamous and non-squamous NSCLC; pembrolizumab is recommended in patients with previously treated NSCLC with PD-L1 expression >1% and atezolizumab is recommended in patients with advanced NSCLC previously treated with one or two prior lines of chemotherapy.

recommendations for targeted therapies

The ESMO Guidelines for metastatic NSCLC additionally provide recommendations for the treatment of EGFR-mutated NSCLC, ALK-rearranged NSCLC, ROS1-rearranged NSCLC, BRAF-mutated NSCLC and for the treatment of patients with NSCLC with other actionable oncogenic drivers [17].

1.3 Immune Checkpoint Inhibitors

programmed cell death pathway

In recent years, immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) axis have shown significant anti-tumour activity in NSCLC (see Figure 1.3-1). PD-1 is an immune checkpoint that has emerged as an important therapeutic target. PD-1 is expressed on the surface of activated T cells, B cells, and natural killer cells. The interaction of PD-1 with one of its two known ligands, PD-L1 and PD-L2, leads to the disruption of intracellular signalling and downregulation of effector T-cell function. PD-L1 expression can also be upregulated on tumour cells and other cells in the local tumour environment. PD-L1 expression has been reported across a range of malignancies, including NSCLC [18].

3 monoclonal antibodies approved

Nivolumab and pembrolizumab (PD-1 inhibitors) and atezolizumab (PD-L1 inhibitor) are monoclonal antibodies (mAbs) and are approved for metastatic NSCLC treatment.

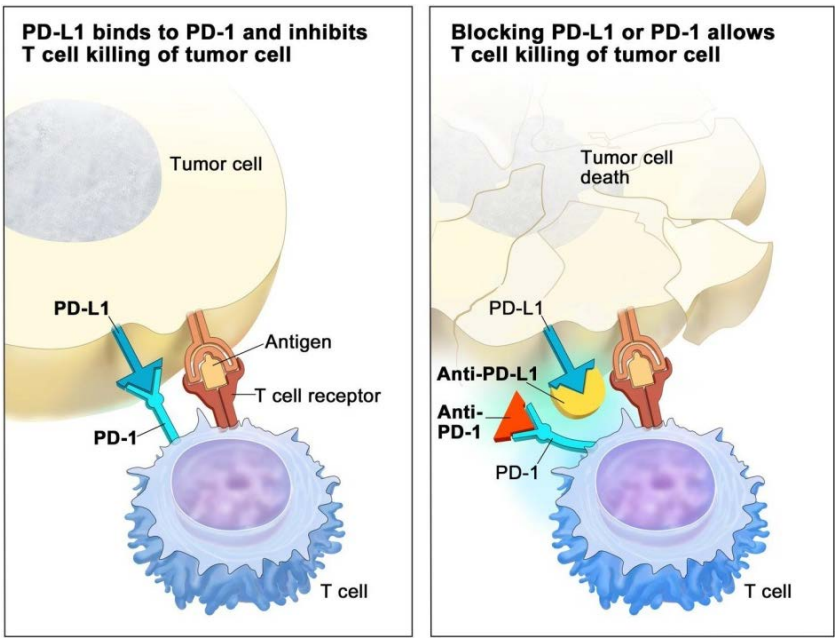

Figure 1.3-1: The programmed cell death pathway [67]

nivolumab as second-line monotherapy

Nivolumab (BMS-936558/MDX-1106/ONO-4538) is a fully human immunoglobulin G4 (IgG4) PD-1 inhibitor and was approved by the European Medicines Agency (EMA) in June 2015. Nivolumab as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults [19].

pembrolizumab as first- or second-line monotherapy

Pembrolizumab is a humanised, IgG4 monoclonal antibody directed against PD-1 and received marketing authorisation by the EMA in July 2015, and is approved for the treatment of locally advanced or metastatic NSCLC [20]:

- Pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK-positive tumour mutations.
- Pembrolizumab, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK-positive mutations.
- Pembrolizumab, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.
- Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK-positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.

atezolizumab as second-line monotherapy

Atezolizumab (MPDL-3280A) is a high-affinity human monoclonal IgG1 antibody directed against PD-L1 and was approved by the EMA in September 2017. Atezolizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemother-

apy. Patients with EGFR-mutant or ALK-positive NSCLC should also have received targeted therapies before receiving atezolizumab [21]. Since July 2019, atezolizumab is additionally recommended by the CHMP (EMA) for:

- the first-line treatment of adult patients with metastatic non-squamous NSCLC in combination with bevacizumab, paclitaxel and carboplatin. In patients with EGFR-mutant or ALK-positive NSCLC, tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after the failure of appropriate targeted therapies,
- the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR-mutant or ALK-positive NSCLC in combination with nab paclitaxel and carboplatin [22].

1.4 Description of Pivotal Clinical Trials

The approval of these three immune checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab for NSCLC monotherapy was based on the following pivotal randomised controlled trials.

Nivolumab

CheckMate017 phase III trial:

nivolumab vs. docetaxel for second-line therapy in squamous NSCLC

median OS 9.2 vs. 6.0 months

median PFS 3.5 vs. 2.8 months

The safety and efficacy of nivolumab 3 mg/kg as monotherapy for the treatment of **advanced or metastatic squamous NSCLC** were evaluated in a phase 3, randomised, open-label study (CA209017, CheckMate017). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen and an ECOG performance status score of 0 or 1. Patients were enrolled regardless of their tumour PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or active brain metastases were excluded. A total of 272 patients were randomised to receive either nivolumab 3 mg/kg (n=135) administered intravenously over 60 minutes every two weeks or docetaxel (n=137) 75 mg/m^2 every three weeks. The primary efficacy outcome measure was overall survival [19]. The median overall survival was 9.2 months (95% confidence interval [CI], 7.3 to 13.3) with nivolumab versus 6.0 months (95% CI, 5.1 to 7.3) with docetaxel. At one year, the overall survival rate was 42% (95% CI, 34 to 50) with nivolumab versus 24% (95% CI, 17 to 31) with docetaxel. The response rate was 20% with nivolumab versus 9% with docetaxel (p=0.008). The median progression-free survival was 3.5 months with nivolumab versus 2.8 months with docetaxel (hazard ratio for death or disease progression, 0.62; 95% CI, 0.47 to 0.81; p<0.001). Treatment-related adverse events of grade 3 or 4 were reported in 7% of the patients in the nivolumab group as compared with 55% of those in the docetaxel group [23].

CheckMate057 phase III trial:

nivolumab vs. docetaxel for second-line therapy in non-squamous NSCLC

The safety and efficacy of nivolumab 3 mg/kg as a single agent for the treatment of **advanced or metastatic non-squamous NSCLC** were evaluated in a phase 3, randomised, open-label study (CA209057, CheckMate057). The study included patients (18 years or older) who have experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen which may have included maintenance therapy and who had an ECOG performance status score of 0 or 1. An additional line of TKI therapy was allowed for patients with known EGFR mutation or ALK translocation. Patients were enrolled regardless of their tumour PD-L1 status. Patients with active autoimmune disease, symptomatic interstitial lung disease, or active

brain metastases were excluded. A total of 582 patients were randomised to receive either nivolumab 3 mg/kg administered intravenously over 60 minutes every two weeks (n=292) or docetaxel 75 mg/m^2 every three weeks (n=290).

The primary efficacy outcome measure was overall survival [19]. Median overall survival was 12.2 months (95% CI, 9.7 to 15.0) for nivolumab (n=292) and 9.4 months (95% CI, 8.1 to 10.7) for docetaxel (n=290) (hazard ratio, 0.73; 96% CI, 0.59 to 0.89; p=0.002). One-year overall survival rates were 51% (95% CI, 45 to 56) for nivolumab and 39% (95% CI, 33 to 45) for docetaxel. Updated efficacy results with additional follow-up are available for overall survival only: 18-month overall survival rates were 39% (95% CI, 34 to 45) for nivolumab and 23% (95% CI, 19 to 28) for docetaxel. Response rates were 19% for nivolumab and 12% for docetaxel (P=0.02). Progression-free survival did not favour nivolumab (2.3 months for nivolumab versus 4.2 months for docetaxel); one-year progression-free survival was higher for nivolumab (19%) than docetaxel (8%). Grade 3-5 treatment-related adverse events were reported in 10% of patients treated with nivolumab and 54% treated with docetaxel [24].

median OS
12.2 vs. 9.4 months

median PFS
2.3 vs. 4.2 months

Pembrolizumab

The safety and efficacy of **first-line pembrolizumab monotherapy** were investigated in KEYNOTE-024, a multicentre, controlled study for the treatment of **previously untreated metastatic NSCLC**. Patients had PD-L1 expression with a ≥50% tumour proportion score (TPS) based on the PD-L1 IHC 22C3 pharmDxTM Kit. Patients were randomised (1:1) to receive pembrolizumab at a dose of 200 mg every 3weeks (n=154) or investigator's choice platinum-containing chemotherapy (n=151; including pemetrexed+carboplatin, pemetrexed+cisplatin, gemcitabine+cisplatin, gemcitabine+carboplatin, or paclitaxel+carboplatin. Non-squamous patients could receive pemetrexed maintenance). The study excluded patients with EGFR or ALK genomic tumour aberrations; autoimmune disease that required systemic therapy within two years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks. The primary efficacy outcome measure was progression-free survival [20]. Median progression-free survival was 10.3 months (95% CI, 6.7 to not reached) in the pembrolizumab group versus 6.0 months (95% CI, 4.2 to 6.2) in the chemotherapy group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.37 to 0.68; p<0.001). The estimated rate of overall survival at six months was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (hazard ratio for death, 0.60; 95% CI, 0.41 to 0.89; p=0.005). The response rate was higher in the pembrolizumab group than in the chemotherapy group (44.8% vs. 27.8%), the median duration of response was longer (not reached [range, 1.9 to 14.5 months] vs. 6.3 months [range, 2.1 to 12.6]), and treatment-related adverse events of any grade were less frequent (occurring in 73.4% vs. 90.0% of patients), as were grade 3, 4, or 5 treatment-related adverse events (26.6% vs. 53.3%) [25].

Keynote-024:
first-line pembrolizumab
vs. platine therapy

median PFS
10.3 vs. 6.0 months

An updated analysis of Keynote-024 in patients with advanced NSCLC with a PD-L1 Tumour Proportion Score (TPS) of 50% or greater with a median follow-up of 25.2 months resulted in a median OS of 30.0 months (95% CI, 18.3 months to not reached) with pembrolizumab and 14.2 months (95% CI, 9.8 to 19.0 months) with platinum-based chemotherapy (hazard ratio, 0.63; 95% CI, 0.47 to 0.86) [26]. The latest update from these Keynote-024 results presented in September 2019 at the International Association for the Study of

median OS
30.0 vs. 14.2 months
in PD-L1 TPS ≥ 50%

latest update of trial results: median OS 26.3 vs. 14.2 months

Lung Cancer (IASLC) – World Conference on Lung Cancer (WCLC) showed a median overall survival length among patients in the pembrolizumab arm of 26.3 months vs. 14.2 months in the chemotherapy arm [27].

Keynote-042: PD-L1 TPS ≥1% first-line pembrolizumab vs. platine therapy

In addition, the safety and efficacy **of first-line pembrolizumab monotherapy** in **patients with a PD-L1 TPS of 1%** or greater were investigated in KEYNOTE-042, a randomised, open-label, phase 3 study in patients with **previously untreated locally advanced or metastatic NSCLC** without a sensitising EGFR mutation or ALK translocation. Enrolled patients were randomly assigned 1:1 in blocks of four per stratum to receive pembrolizumab 200 mg every three weeks for up to 35 cycles or the investigator's choice of platinum-based chemotherapy for four to six cycles. Primary endpoints were overall survival in patients with a TPS of 50% or greater, 20% or greater, and 1% or greater. 1274 patients with a PD-L1 TPS of 1% or greater were allocated to pembrolizumab (n=637) or chemotherapy (n=637). Overall survival was significantly longer in the pembrolizumab group than in the chemotherapy group in all three TPS populations (≥50% hazard ratio 0.69, 95% CI 0.56-0.85, p=0.0003; ≥20% 0.77, 0.64-0.92, p=0.0020, and ≥1% 0.81, 0.71-0.93, p=0.0018). The median overall survival values by TPS population were 20.0 months (95% CI 15.4-24.9) for pembrolizumab versus 12.2 months (10.4-14.2) for chemotherapy, 17.7 months (15.3-22.1) versus 13.0 months (11.6-15.3), and 16.7 months (13.9-19.7) versus 12.1 months (11.3-13.3), respectively. Treatment-related adverse events of grade 3 or worse occurred in 113 (18%) of 636 treated patients in the pembrolizumab group and in 252 (41%) of 615 in the chemotherapy group and led to death in 13 (2%) and 14 (2%) patients, respectively [28].

OS by TPS: ≥50%: 20.0 vs. 12.2 months, ≥20%: 17.7 vs. 13.0 months ≥1%: 16.7 vs. 12.1 months

Keynote-010: second-line pembrolizumab vs. taxane therapy

The safety and efficacy of **second-line pembrolizumab monotherapy** were investigated in KEYNOTE-010, a multicentre, open label, controlled study for the treatment of **advanced NSCLC in patients previously treated with platinum-containing chemotherapy.** Patients had PD-L1 expression with a ≥1% TPS based on thePD-L1 IHC 22C3 pharmDxTM Kit. Patients were randomised (1:1:1) to receive pembrolizumab at a dose of 2 (n=344) or 10 mg/kg (n=346) every three weeks or docetaxel at a dose of 75 mg/m^2 every three weeks (n=343) until disease progression or unacceptable toxicity. The trial excluded patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks. The primary efficacy outcome measures were overall survival and progression-free survival [20]. In the total population, median overall survival was 10.4 months with pembrolizumab 2 mg/kg, 12.7 months with pembrolizumab 10 mg/kg, and 8.5 months with docetaxel. Overall survival was significantly longer for pembrolizumab 2 mg/kg versus docetaxel (hazard ratio [HR] 0.71, 95% CI 0.58-0.88; p=0.0008) and for pembrolizumab 10 mg/kg versus docetaxel (0.61, 0.49-0.75; p<0.0001). Median progression-free survival was 3.9 months with pembrolizumab 2 mg/kg, 4.0 months with pembrolizumab 10 mg/kg, and 4.0 months with docetaxel, with no significant difference for pembrolizumab 2 mg/kg versus docetaxel (HR 0.88, 0.74-1.05; p=0.07) or for pembrolizumab 10 mg/kg versus docetaxel (HR 0.79, 95% CI 0.66-0.94; p=0.004). Among patients with at least 50% of tumour cells expressing PD-L1, overall survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (median 14.9 months vs. 8.2 months; HR 0.54, 95% CI 0.38-0.77; p=0.0002) and with pembrolizumab 10 mg/kg than with docetaxel (17.3 months vs. 8.2 months; 0.50, 0.36-0.70; p<0.0001). Likewise, for this patient population, progression-free survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (me-

median OS 10.4 vs. 8.5 months

median PFS 3.9 vs. 4.0 months

dian 5.0 months vs. 4.1 months; HR 0.59, 95% CI 0.44-0.78; p=0.0001) and with pembrolizumab 10 mg/kg than with docetaxel (5.2 months vs. 4.1 months; 0.59, 0.45-0.78; p<0.0001). Grade 3-5 treatment-related adverse events were less common with pembrolizumab than with docetaxel (43 [13%] of 339 patients given 2 mg/kg, 55 [16%] of 343 given 10 mg/kg, and 109 [35%] of 309 given docetaxel) [29].

Atezolizumab

OAK (GO28915): second-line atezolizumab vs. platine therapy

The safety and efficacy of atezolizumab compared with docetaxel were investigated in a phase III, open-label, multicentre, international, randomised study (OAK, GO28915) in patients with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen. Patients were randomised (1:1) to receive either atezolizumab or docetaxel. Atezolizumab was administered as a fixed dose of 1,200 mg by intravenous infusion every three weeks and docetaxel was administered 75 mg/m^2 by intravenous infusion on day 1 of each three-week cycle until disease progression. The primary efficacy endpoint was overall survival [21]. 425 patients were randomly assigned to receive atezolizumab and 425 patients were assigned to receive docetaxel. Overall survival was significantly longer with atezolizumab in the intention-to-treat (ITT) and PD-L1-expression populations. In the ITT population, overall survival was improved with atezolizumab compared with docetaxel (median overall survival was 13.8 months [95% CI 11.8-15.7] vs. 9.6 months [8.6-11.2]; hazard ratio [HR] 0.73 [95% CI 0.62-0.87], p=0.0003).

median OS 13.8 vs. 9.6 months

Overall survival in the TC1/2/3 or IC1/2/3 population[1] was improved with atezolizumab (n=241) compared with docetaxel (n=222; median overall survival was 15.7 months [95% CI 12.6-18.0] with atezolizumab vs. 10.3 months [8.8-12.0] with docetaxel; HR 0.74 [95% CI 0.58-0.93]; p=0.0102). Patients in the PD-L1 low or undetectable subgroup (TC0 and IC0) also had improved survival with atezolizumab (median overall survival 12.6 months vs. 8.9 months; HR 0.75 [95% CI 0.59-0.96]). Overall survival improvement was similar in patients with squamous (HR 0.73 [95% CI 0.54-0.98]; n=112 in the atezolizumab group and n=110 in the docetaxel group) or nonsquamous (0.73 [0.60-0.89]; n=313 and n=315) histology. Fewer patients had treatment-related grade 3 or 4 adverse events with atezolizumab (90 [15%] of 609 patients) versus docetaxel (247 [43%] of 578 patients) [30].

Table 1.4-1 presents major results and relevant characteristics of the aforementioned pivotal randomised clinical trials.

[1] Patients were stratified by PD-L1 expression (IC0 vs. IC1 vs. IC2 vs. IC3 level). TC1/2/3 or IC1/2/3 was defined as PD-L1 expression on 1% or more of tumour cells or tumour-infiltrating immune cells; TC2/3 or IC2/3 was defined as PD-L1 expression on 5% of these cells; TC3 was defined as PD-L1 expression on 50% or more of tumour cells and IC3 was defined as 10% or more of tumour-infiltrating immune cells; and TC0 as PD-L1 expression on less than 1% of tumour cells and IC0 on less than 1% of tumour-infiltrating immune cells.

Table 1.4-1: Results of pivotal RCTs

	Keynote-024[1] (n=154)	Keynote-010[2] (n=344, 2mg/kg)	CheckMate017[3] (n=135)	CheckMate057[3] (n=292)	OAK-GO28915[4] (n=425)
Median age, years (range)	64.5 (33-90)	63 (56-69)	63 (39-85)	61 (37-84)	63 (33-82)
Male sex (%)	59.7%	62%	82%	52%	61%
ECOG 0-1 ≥2	 100% 0%	 100% <1%	 100% 0%	 100% 0%	 100% 0%
UICC stage IIA/B IIIA/B IV	 0% 0% 100%	 0% 0% 100%	 0% 21% (IIIB) 78%	 0% 7% (IIIB) 93%	NR
Histology squamous non-squamous other	 18.8% 81.2% 0%	 22% 70% 0%	 100% 0% 0%	 0% 100% 0%	 26% 74% 0%
EGFR mutation status, % positive	0%	8%	NR	15%	10%
ALK transl. status, % positive	0%	1%	NR	4%	<1%
BRAF mutation	NR	NR	NR	NR	NR
ROS1 rearrangement	NR	NR	NR	NR	NR
PD-L1 TPS, (%)	30.2% had PD-L1 TPS of ≥50%	≥50%: 40% 1-49%: 60%	NR	NR	NR
Median overall survival, months, 95%CI	median overall survival not reached[5]	10.4 (9.5, 11.9)	9.23 (7.33, 13.27)	12.19 (9.66, 14.98)	13.8 (11.8, 15.7)
Median progression-free survival, months 95%CI	10.3 (6.7, not reached)	3.9 (3.1, 4.1)	3.48 (2.14, 4.86)	2.33 (2.17, 3.32)	2.8 (2.6-3.0)
ORR %, 95%CI	44.8% (36.8 to 53.0)	20% (16, 25)	20% (13.6, 27.7)	19.2% (14.8, 24.2)	14%

[1] first-line pembrolizumab monotherapy; [2] second-line pembrolizumab monotherapy; [3] second-line nivolumab monotherapy; [4] second-line atezolizumab monotherapy; [5] Updated analysis of Keynote-024 (Reck et al. 2019): median OS 30.0 months (95% CI 18.3, NA) and latest results presented at WCLC 2019: median OS 26.3 months.

ECOG=Eastern Co-operative of Oncology Group, UICC=Union for International Cancer Control, EGFR=Epidermal-Growth-Factor-Receptor, ALK=anaplastic lymphoma kinase, PD-L1=programmed death-ligand 1, ORR=objective response rate

Other clinical trials that investigate immunotherapy in combination with chemotherapy (e.g. Keynote-189, Keynote-407, IMpower150, IMpower130) are not mentioned here in detail as our report aims at anti-PD-1/PD-L1 monotherapy.

1.5 Real-World Evidence

routine clinical practice differs from RCTs

Experience in routine clinical practice may differ from that seen in a controlled clinical trial. Although randomised clinical trials (RCTs) are considered to be the standard for generating clinical evidence, they lack generalisability to real-world evidence due to selected patient populations (strict and complex enrolment criteria). Therefore, the use of real-world evidence (RWE) to evaluate the effectiveness and safety of medical interventions is gaining interest [31-36].

real-world data from electronic health records, claims data, registries

real-world evidence derived from real-world data

Real-world data (RWD) are defined by the US Food and Drug Administration (FDA) as "*data related to patient health status and/or the delivery of healthcare routinely collected from a variety of sources like electronic health records (EHRs), claims and billing activities, product and disease registries, patient-generated data including in home-use settings or data gathered from other sources that can inform on health status, such as mobile devices*". Moreover, the FDA defines real-world evidence (RWE) as "*the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWE can be generated by different study designs or analyses, including but not limited to, randomised trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective)*" [37].

retrospective pilot study with routine data

As the experiences of patients and physicians in routine clinical practice are often different from those in a controlled clinical trial setting, and as there is limited evidence regarding the real-world effectiveness of immunotherapy in Austria, we conducted a retrospective pilot study in six Austrian hospitals to present data on patient characteristics, effectiveness and safety from real-world practice in an NSCLC population treated with anti-PD1/PD-L1 monotherapy.

2 Methods

2.1 Aim of the Pilot Study

real-world data for anti-PD-1/PD-L1 therapy from 6 Austrian hospitals

The aim of this retrospective study was to assess the effectiveness and safety of nivolumab, pembrolizumab and atezolizumab monotherapy (anti-PD-1/PD-L1therapy) in patients with non-small cell lung cancer in real-world practice in six Austrian hospitals (two hospitals in Tyrol, four hospitals in Styria).

4 key objectives

This pilot project had four key objectives:

1. To describe the demographic and clinical characteristics of patients treated with anti-PD-1/PD-L1 therapy in real-world practice;
2. To analyse effectiveness end points [overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and disease control rate (DCR)] and safety end points [grade 3 and 4 adverse events (AEs)] in identified and eligible patients;
3. To compare these real-world patient characteristics and outcomes with clinical end points as measured in pivotal RCTs;
4. To conduct a matched-pair analysis in order to compare overall survival and progression-free survival in patients with anti-PD-1/PD-L1 therapy to patients from the Tyrolean Lung Cancer Project (Tyrol Study) [38].

2.2 Ethics Approval

protocol approved by Ethics Committee Innsbruck and Graz

The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. The protocol was approved by the Ethics Committee of the Medical University Innsbruck (reference number 1048/2019) and the Ethics Committee of the Medical University Graz (reference number 31-490 ex 18/19). Because this study was intended to reflect usual clinical practice and real-world data and because a retrospective study design was used, no informed consent by the included patients was necessary and no compensation was provided to the participating physicians.

2.3 Study Population

retrospective study in adult NSCLC patients

This was a multicentre, retrospective, observational study carried out at six hospitals in Austria. All adult NSCLC patients receiving anti-PD-1/PD-L1 monotherapy containing nivolumab, pembrolizumab or atezolizumab between January 2017 and June 2018[2] at the participating hospitals were included. Patients receiving anti-PD-1/PD-L1 therapy as part of a clinical trial were excluded. Eligible patients were either identified through the electronic chemotherapy order history at the pharmacy department of the University Hospital Innsbruck (Tyrol) or through a specific database held by the Medical Innovation Board (MIB, Styria) in which the administration of new anticancer drugs is registered.

prespecified case report form

Data acquisition was performed based on a prespecified case report form (CRF). All study variables were collected from the available hospital electronic health records. Patient's Medical Files of eligible NSCLC patients were retrospectively analysed. Information included the patient age, gender, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, selected comorbidities, cancer history (tumour histology, clinical TNM staging, UICC disease stage, date of initial diagnosis, date of disease progression), prior chemotherapy lines, prior NSCLC treatment, anti-PD-1/PD-L1 therapy (compound, dose, line and duration of treatment, best response to treatment), presence of targetable mutations (EGFR, ALK, ROS-1, BRAF), PD-L1 protein expression, adverse events (AEs), survival status at last follow-up and death date.

PD-L1 TPS, ECOG status and comorbidities reported

PD-L1 protein expression is determined by using the Tumour Proportion Score (TPS), which is the percentage of viable tumour cells showing partial or complete membrane staining. The ECOG performance status at the time of the beginning with anti-PD-1/PD-L1 therapy was documented (if not stated explicitly in the chart, the reviewing oncologist made an estimate based on the medical history). Several medical conditions included in the definition of the Charlson Comorbidity Index (CCI) score were selected to report comorbidities in eligible patients.

extraction of adverse events

Adverse events related to anti-PD-1/PD-L1 treatment, reported based on review of the medical records, were extracted. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) [39].

follow-up period: at least 12 months

Patient records were reviewed from initiation of immunotherapy (first dosing) until the end of data collection, providing the opportunity for at least 12 months of follow-up. The follow-up period was closed on 30 June 2019 (Tyrol) and on 31 October 2019 (Styria), respectively. Chart review was conducted by medical students and subsequently checked by the responsible oncologists to ensure data quality and validity.

[2] Two patients were administered immunotherapy outside this period (one started in December 2016, one started in January 2019).

2.4 Outcomes

Effectiveness measures included:

- Progression-free survival (PFS) (time from the start of immunotherapy until progression of disease or death),
- Overall survival (OS) (time from the start of immunotherapy until death or censoring),
- Objective response rate (ORR), defined as the proportion of patients with documented complete response or partial response,
- Disease control rate (DCR), defined as the proportion of patients with documented complete or partial response, or stable disease.

PFS, OS, ORR and DCR as effectiveness outcomes

Patients without an event who remained in follow-up were censored on 30 June 2019 (Tyrol) or on 31 October 2019 (Styria).

Grade 3 or 4 treatment-related adverse events (AEs) reported in the electronic health records were collected for the safety analysis.

2.5 Data Management

Data Sources

Several data sources were used to collect comprehensive data based on the prespecified case report form:

- Medication data from the Pharmacy Department of the University Hospital Innsbruck including posology, method of administration, duration of treatment, compound, dose modification,
- Hospital electronic health records including patient characteristics, tumour characteristics and outcomes information (Tyrolean and Styrian hospitals),
- Austrian DRG data (from Tyrolean hospitals) [40]: In the DRG model, data of inpatient hospital stays are collected. These include the medical procedures carried out, the disease, age, the hospital departments involved, and the date of hospital admission and discharge. Diseases are recorded based on the globally recognised index of diseases produced by the World Health Organisation (WHO), the International Classification of Diseases (Version ICD-10).

medication data, hospital electronic health records, DRG data

Data Protection

Only pseudonymised data were used for this retrospective study. As part of the data collection, personal data were only processed within the participating hospitals. The data described above were retrospectively collected from the existing systems within the hospitals and were subsequently extracted and provided in the Microsoft Open XML Document (xlsx) format. This format was used to export the data after pseudonymisation and did not contain any directly identifying characteristics of the affected patient, such as name or social security number. The export of the data from the hospital systems was completed with the pseudonymisation. A uniform internal ID was used as the personal identifier of the pseudonymous data records.

only pseudonymised data, but uniform internal ID as personal identifier

pseudonymisation with hash function

To reduce the risk of re-identification of individual patients, e.g., to make it difficult to link to the data source, the patient IDs were pseudonymised using a hash function. The pseudonymisation with HMAC-SHA256 takes place with the help of an open source macro in Microsoft Excel[3]. This procedure prevents the patients ID from being restored to the original ID. It is thereby impossible to re-identify the pseudonymised data with the natural person.

risk reduction for bidirectional exchange of information

The chosen form of pseudonymisation directly at the hospital or as a direct consequence of the export from the hospital system reduces the risk of subsequent identification of individual patients and enables the secure, bidirectional exchange of information. The measures enable communication of corrections, content clarifications and change/deletion requests in both directions without using internal pseudonyms of the data source (such as an internal patient ID) or personal characteristics such as name and social security number. Furthermore, the linkage of exports with external, personal information is prevented, since the secret, project-specific key, i.e. "salt", is necessary to reproduce the pseudonymisation.

project partner dexhelpp responsible for data management and statistical analysis

The project partner "Verein dexhelpp" (http://www.dexhelpp.at/)[4] was responsible for data management and statistical analysis. Data were transferred to dexhelpp independently of one another and processed in a secure working environment. The transfer was secured in several ways, whereby a combination of measures for encryption, authentication and personal assignment of the data records and access rights was used. In order to gain access to the dexhelpp infrastructure and to start the transfer, a VPN tunnel (Cisco SSL AnyConnect) was set up, whereby the authentication of the users required a second, time-dependent factor in addition to an individual username and password. As soon as the connection was established, the data records could be loaded into a personal area. In addition to encryption through the VPN tunnel, transport security (via TLS) was also enforced. As soon as the data was saved in the personal area, it could be passed on to individual employees of the project.

file storage

The dexhelpp infrastructure storage was secured and encrypted several times. The upload of the data and the transfer within the file storage was automatically logged.

granular rights management, automatic, and encrypted backups of the database

The processing takes place exclusively within the secure environment. Every service of the dexhelpp infrastructure, e.g., the working environment of the researchers, central data storage, historicised programme archives and databases can only be used by means of personal logins for an existing VPN tunnel. The database has granular rights management, its own process area and secure storage space. Automatic, hourly, incremental, and encrypted backups of the database to a second data centre reduce the risk of data loss. Automatic routines for the storage and deletion of back-ups, personalised log data for database access and active monitoring systems enable state-of-the-art data protection and the comprehensible preparation of any security incident.

For all statistical analyses, data were pseudonymised.

[3] The implementation of the algorithm comes from Microsoft's .Net Framework 3.5, which is under a proprietary license.

[4] Verein DEXHELPP, Neustiftgasse 57-59, 1070 Vienna, Austria www.dexhelpp.at.

Data Processing

focus on reproducibility and traceability

As soon as the transfer was complete, the data records were prepared, linked using the common pseudonym and loaded into a project-specific database. In addition to data security, the focus of these processes was on reproducibility and traceability. For this purpose, the preparation, linking and loading processes were automated, and the programs developed for this purpose were stored in archived, individual developers' archives.

upload of data in database

The first processing step involved loading the data into the database and creating an overview to identify faults in the data. Based on this overview, the data could be checked and corrected, and the final dataset could be chosen. Using this dataset, the analysis was conducted.

data processing in R version 3.6.1

The whole process was performed in R version 3.6.1 (R Foundation for Statistical Computing; https://www.r-project.org/), which is a well-known open-source software programme for statistical analysis. All steps are saved as scripts, which guarantees the reproducibility of the results.

2.6 Statistical Analysis

eligible patients stratified into 3 subgroups

The sample size was determined by the available patients meeting the inclusion criteria. Data collected for all eligible patients were stratified into three subgroups according to the study population of pivotal randomised controlled trials:

- Cohort 1: Patients with first-line pembrolizumab monotherapy
- Cohort 2: Patients with second-line anti-PD1/PD-L1 monotherapy (nivolumab, pembrolizumab or atezolizumab)
- Cohort 3: Patients with third- (or more) line anti-PD1/PD-L1 monotherapy (nivolumab, pembrolizumab or atezolizumab)

database locked 10 January 2020

All statistical analyses were performed stratified to these three cohorts. The database was locked on 10 January 2020.

descriptive analyses of patient and tumour characteristics

Descriptive analyses were conducted for patient and tumour characteristics stratified by subgroups mentioned above. Absolute numbers and percentages were computed for all demographic and cancer characteristics to describe the study population. The median and range, as well as the mean and standard deviation (SD) were calculated for age.

comorbidities and adverse events

Comorbidities and adverse events (grade 3 or 4) were summarised in terms of patient counts and percentages. No statistical tests were applied.

best response evaluation: complete response

partial response

stable disease

progressive disease

Best response was assessed as radiologic response in combination with clinical assessment of whether the patient experienced benefit from immunotherapy at any time during the entire follow-up period (response to therapy was assessed using response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) [41] and classified as follows: complete response (CR; the disappearance of all target lesions), partial response (PR; 30.0% or more reduction in the sum of the diameters of the target lesions), progressive disease (PD; 20.0% or more increase in the sum of the diameters of the target lesions), and stable disease (SD; not in category to qualify as PR or PD). Patients evaluable for response (i.e., with documented best response) were included to calculate both the objective response rate (ORR), defined as the

proportion of patients with complete or partial response to immunotherapy, and the disease control rate (DCR), defined as the proportion of patients with complete or partial response or stable disease during immunotherapy. Patients not evaluable for response (i.e., patients who died before response evaluation or patients with missing response data) were excluded from ORR and DCR calculation.

survival curves with Kaplan Meier method

The Kaplan Meier method was used to estimate survival curves for the three cohorts and to assess progression-free survival (PFS) and overall survival (OS), which were expressed as the median survival times (months), with the 95% confidence interval (95% CI). If applicable, the log-rank test was used to compare the curves. Survival data were censored when patients had not experienced an event at the predefined cut-off date of 30 June 2019 (Tyrol) or of 31 October 2019 (Styria) or when the date of death was unknown (patient lost to follow-up). The median follow-up is the median observation time to the event of interest and median follow-up times with 95% CI were computed as the difference between the beginning of the immunotherapy and the end of the follow-up (i.e., death or the end of the observation period (Tyrol: 30 June 2019; Styria: 31 October 2019).

matched-pair analysis with patients from the Tyrolean Lung Cancer Project

We conducted a matched-pair analysis in order to compare overall survival and progression-free survival in patients with anti-PD-1/PD-L1 therapy to patients from the Tyrolean Lung Cancer Project (Tyrol Study) [38] as historical control group. The matched-pair analysis was conducted for cohort 1 (first-line pembrolizumab) in a 1:3 arrangement and for cohort 2 (second-line nivolumab, pembrolizumab, atezolizumab) in a 1:2 arrangement using the SPSS fuzzy extension command. Cases and controls were individually matched for age (+/– 5 years), sex, ECOG performance status and histology. Cohort 1 was matched to patients with first-line platine therapy, cohort 2 was matched to patients with second-line taxane therapy. The Kaplan Meier method was used to estimate survival curves and to assess progression-free survival (PFS) and overall survival (OS), which were expressed as the median survival times (months), with the 95% confidence interval (95% CI). The log-rank test was used to compare the curves for cases (patients with anti-PD-1/PD-L1 therapy) and controls (historical control group).

p values if applicable

All p values were based on two-sided hypothesis tests, and it was considered statistically significant when $p<0.05$. All statistical analyses were performed using R, version 3.6.1 (R Foundation for Statistical Computing; https://www.r-project.org/) and R packages tidyverse version 1.3.0, survminer version 0.4.6 and survMisc version 0.5.5.

comparison of RWE with pivotal studies

descriptive only

The effectiveness results (PFS, OS, ORR, DCR) and patient characteristics (age, sex, ECOG performance status) as well as tumour information (UICC stage, histology, EGFR mutation status, ALK translation status, PD-L1 TPS) of this real-life NSCLC population were compared to results from pivotal randomised controlled trials (see Table 1.4-1) and to the product information in full scientific assessments reports (EPARs, European Public Assessment Reports) published by the European Medicines Agency (EMA) when granting a central marketing authorisation at the European Union level [19-21]. The comparison is descriptive in nature, and no statistical testing was applied.

3 Results

3.1 Characteristics of the Study Population

111 patients with NSCLC identified

103 finally analysed

Data of 111 patients with NSCLC and anti-PD-1/PD-L1 therapy were collected from six Austrian hospitals located in two federal states, namely Tyrol (two hospitals: University Hospital Innbruck and Hospital Natters) and Styria (four hospitals: Hospital Graz II, Hospital Hochsteiermark, Hospital Feldbach-Fürstenfeld, University Hospital Graz). Eight patients were excluded because of incomplete data or not matching our three predefined cohorts. Figure 3.1-1 presents the composition of the study population. Finally, 103 patients were analysed and subdivided into the following three cohorts:

analyses of 3 cohorts

- Cohort 1: Patients with first-line pembrolizumab monotherapy (n=42)
- Cohort 2: Patients with second-line anti-PD-1/PD-L1 monotherapy (nivolumab, pembrolizumab or atezolizumab) (n=47)
- Cohort 3: Patients with third- (or more) line anti-PD-1/PD-L1 monotherapy (nivolumab, pembrolizumab or atezolizumab) (n=14)

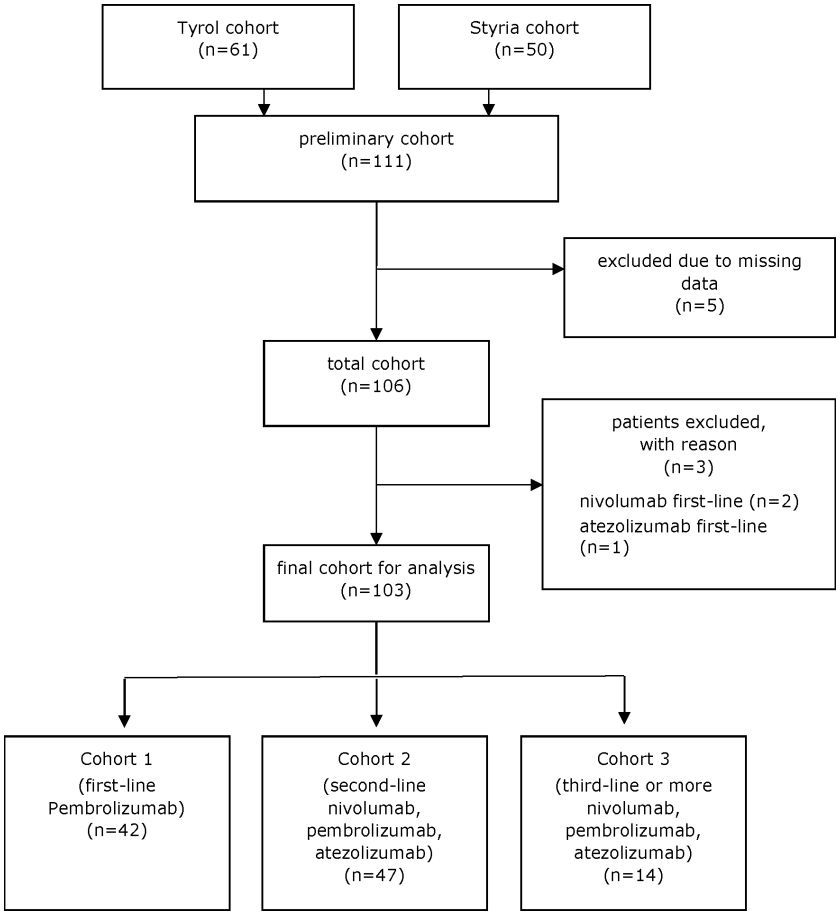

Figure 3.1-1: Flow chart of the study population

42 patients in cohort 1, 47 in cohort 2 and 14 in cohort 3

In total, 103 patients were analysed, 42 patients with first-line pembrolizumab monotherapy, 47 patients with second-line anti-PD-1/PD-L1 monotherapy and 14 patients with third- (or more) line anti-PD-1/PD-L1 monotherapy. Characteristics of all patients are presented in Table 3.1-1. The patients were treated with nivolumab at a dose of 3.0 mg/kg body weight every two weeks, pembrolizumab at 200 mg fixed dose or at a dose of 2.0 mg/kg body weight every three weeks, and atezolizumab at 1,200 mg fixed dose every three weeks.

Table 3.1-1: Study population characteristics (n=103)

	Cohort 1 (n=42)		Cohort 2 (n=47)		Cohort 3 (n=14)		Total
	n	%	n	%	n	%	n
Age (y), years							
40-49	1	2.38	0	0.00	1	7.14	**2**
50-59	7	16.67	8	17.02	2	14.29	**17**
60-69	14	33.33	15	31.91	6	42.86	**35**
70-79	15	35.71	18	38.30	5	35.71	**38**
80-89	5	11.90	6	12.77	0	0.00	**11**
median age, yrs (range)	67.5 (49-85)		69.0 (55-82)		64.0 (43-77)		**68.0 (43-85)**
mean age, yrs (SD)	67.1±9.9		68.0±8.0		63.1±9.9		**67.1±9.1**
Gender							
female	16	38.1	22	46.81	5	35.71	**43**
male	26	61.9	25	53.19	9	64.29	**60**
State							
Styria	26	61.9	14	29.79	3	21.43	**43**
Tyrol	16	38.1	33	70.21	11	78.57	**60**
Smoking Status							
current	24	57.14	32	68.09	10	71.43	**66**
former	16	38.10	8	17.02	2	14.29	**26**
never	2	4.76	6	12.77	1	7.14	**9**
not reported	0	0.00	1	2.13	1	7.14	**2**
ECOG Performance Status (at the beginning of immunotherapy)							
0-1	38	90.48	44	93.62	11	78.57	**93**
2	2	4.76	1	2.13	1	7.14	**4**
3	1	2.38	1	2.13	0	0.00	**2**
not reported	1	2.38	1	2.13	2	14.29	**4**
Histology							
squamous	8	19.05	11	23.40	3	21.43	**22**
non-squamous	33	78.57	33	70.21	9	64.29	**75**
other	1	2.38	3	6.38	1	7.14	**5**
not reported	0	0.00	0	0.00	1	7.14	**1**
Stage (UICC) at the beginning of immunotherapy							
IB	0	0.00	1	2.13	0	0.00	**1**
IIB	0	0.00	1	2.13	0	0.00	**1**
IIIA	3	7.14	2	4.26	2	14.29	**7**
IIIB	3	7.14	7	14.89	4	28.57	**14**
IV	36	85.71	36	76.60	7	50.00	**79**
Not reported	0	0.00	0	0.00	1	7.14	**1**

	Cohort 1 (n=42)		Cohort 2 (n=47)		Cohort 3 (n=14)		Total
	n	%	n	%	n	%	n
Grading							
Well differentiated grade 1	0	0	0	0	1	7.14	**1**
Moderately differentiated grade 2	9	21.43	13	27.66	2	14.29	**24**
Poorly differentiated grade 3	19	45.24	29	61.70	9	64.29	**57**
Undifferentiated grade 4	2	4.76	1	2.13	0	0	**3**
Not reported	12	28.57	4	8.51	2	14.29	**18**
Relapse							
No	6	14.29	10	21.28	2	14.29	**18**
Yes	23	54.76	9	19.15	1	7.14	**33**
Not reported	13	30.95	28	59.57	11	78.57	**52**
Metastases (cM)							
M0	5	11.90	10	21.28	6	42.86	**21**
M1	36	85.71	36	76.60	6	42.86	**78**
MX	0	0.00	1	2.13	1	7.14	**2**
Not reported	1	2.38	0	0.00	1	7.14	**2**
Tumour molecular aberrations							
EGFR mutation -	36	85.71	44	93.62	13	92.86	**93**
EGFR mutation +	0	0	0	0	0	0	**0**
Not determined	6	14.29	3	6.38	1	7.14	**10**
ALK rearrangement -	36	85.71	44	93.62	11	78.57	**91**
ALK rearrangement +	0	0	0	0	0	0	**0**
Not determined	6	14.29	3	6.38	3	21.43	**12**
ROS1 rearrangement -	33	78.57	37	78.72	9	64.29	**79**
ROS1 rearrangement +	0	0.00	0	0.00	1	7.14	**1**
Not determined	9	21.43	10	21.28	4	28.57	**23**
BRAF mutation -	18	42.86	18	38.30	5	35.71	**41**
BRAF mutation +	2	4.76	2	4.26	0	0.00	**4**
Not determined	22	52.38	27	57.45	9	64.29	**58**
TPS (% PD-L1 positive cells)							
<1	0	0.00	9	19.15	2	14.29	**11**
1 to <50	1	2.38	13	27.66	6	42.86	**20**
≥50	41	97.62	16	34.04	4	28.57	**61**
Not reported	0	0.00	9	19.15	2	14.29	**11**
Prior surgery							
No	24	57.14	11	23.40	3	21.43	**38**
Yes	5	11.90	11	23.40	2	14.29	**18**
Not reported	13	30.95	25	53.19	9	64.29	**47**
Prior radio-chemotherapy							
No	28	66.67	17	36.17	1	7.14	**46**
Yes	3	7.14	6	12.77	3	21.43	**12**
Not reported	11	26.19	24	51.06	10	71.43	**45**

	Cohort 1 (n=42)		Cohort 2 (n=47)		Cohort 3 (n=14)		Total
	n	%	n	%	n	%	n
Number of prior systemic therapy regimes							
0	42	100	1	2.13	0	0.00	**43**
1	0	0	46	97.87	0	0.00	**46**
2	0	0	0	0.00	9	64.29	**9**
3	0	0	0	0.00	3	21.43	**3**
4	0	0	0	0.00	1	7.14	**1**
Not reported	0	0	0	0.00	1	7.14	**1**
Drug name							
nivolumab	0	0	26	55.32	10	71.43	**36**
pembrolizumab	42	100	15	31.91	3	21.43	**60**
atezolizumab	0	0	6	12.77	1	7.14	**7**
Monotherapy							
No	0	0	1	2.13	0	0	**1**
Yes	42	100	46	97.87	14	100	**102**
Number of applications of immunotherapy							
1-10	16	38.10	27	57.45	9	64.29	**52**
11-20	6	14.29	6	12.77	2	14.29	**14**
21-30	10	23.81	10	21.28	1	7.14	**21**
31-40	6	14.29	2	4.26	1	7.14	**9**
>40	4	9.52	2	4.26	1	7.14	**7**
Additional therapy regimes after immunotherapy							
No	31	73.81	31	65.96	6	42.86	**68**
Yes	9	21.43	14	29.79	8	57.14	**31**
Not reported	2	4.76	2	4.26	0	0.00	**4**

ECOG=Eastern Co-operative of Oncology Group, UICC=Union for International Cancer Control, EGFR=Epidermal-Growth-Factor-Receptor, ALK=anaplastic lymphoma kinase, PD-L1=programmed death-ligand 1, yrs=years

median age in overall study population 68.0 years

The majority of patients were male (58.3%) and aged ≥60 years (81.6%). The median age in the overall study population was 68.0 years (range 43-85), 67.5 (range 49-85) in cohort 1, 69.0 (range 55-82) in cohort 2, whilst cohort 3 was slightly younger with median age 64.0 years (range 43-77). 43 (41.7%) patients were treated in Styrian hospitals and 60 (58.3%) in Tyrolean hospitals.

smoking history in most patients

Most patients had a history of smoking, 64.1% were active smokers and 25.2% were former smokers. Ninety-three patients (90.3%) had an ECOG performance status score of 0 or 1 at the beginning of the anti-PD1/PD-L1 therapy, only six patients (5.8%) had ECOG ≥2. Most patients had adenocarcinoma (72.8%) followed by squamous carcinoma (21.4%). Most patients had stage IV disease (76.7%) at the beginning of immunotherapy, and 21 patients had advanced NSCLC (14 patients with stage IIIB and seven patients with stage IIIA).

78.6% PD-L1 positive

There were 93 patients whose EGFR gene mutation status was evaluated, but none of the patients showed EGFR mutations. Of 91 patients with a test for ALK rearrangement, no one was positive. Moreover, only one out of 80 was ROS1-positive, and BRAF mutation was present in four out of 45 tested patients. PD-L1 TPS results were not available for all patients. Eighty-one patients (78.6%) were identified as PD-L1 positive, 61 (75.3%) thereof had PD-L1 ≥50%.

13.6% third-line or more

The lines of administered anti-PD-1/PD-L1 therapies were diverse, as 42 (40.8%), 47 (45.6%), and 14 (13.6%) of the patients received anti-PD-1 treatment as first-line, second-line, or subsequent to second-line therapy, respectively. Thirty-six patients (34.9%) were administered nivolumab, 60 patients (58.3%) received pembrolizumab and only seven patients (6.8%) received atezolizumab.

50.8% received 1-10 cycles

Half of the patients (50.8%) received 1-10, 13.3% received 11 to 20, 20.4% received 21 to 30, and 15.3% more than 30 applications of immunotherapy.

additional therapy regimes in 21.4%, 29.8% and 57.1%

Additional therapy regimes after discontinuation of anti-PD-1/PD-L1 therapy was administered to 21.4% in cohort 1, 29.8% in cohort 2 and 57.1% in cohort 3.

3.2 Treatment Outcomes

ORR was 43.3%, 31.4% and 33.3% for the 3 cohorts

The treatment outcomes objective response rate (ORR) and disease control rate (DCR) for all patients and for the three cohorts separately are shown in Table 3.2-1 and Table 3.2-2. The ORR was 36.5% (n=27) for the overall cohort, and 43.3%, 31.4% and 33.3% for the three cohorts, respectively. Moreover, 20.3% of the evaluable patients had stable disease (SD) and 43.2% had progressive disease (PD). Twenty-nine patients were not evaluable for response due to death before response evaluation or missing data.

*Table 3.2-1: Objective Response Rate (ORR)**

	Cohort 1 (n=42)		Cohort 2 (n=47)		Cohort 3 (n=14)		Total	
	n	%	n	%	n	%	n	%
ORR (CR/PR)**	13	43.33	11	31.43	3	33.33	**27**	**36.49**
SD**	6	20.00	6	17.14	3	33.33	**15**	**20.27**
PD**	11	36.67	18	51.43	3	33.33	**32**	**43.24**
patients evaluable for response	30	100.00	35	100.00	9	100.00	**74**	**100.0**
patients NOT evaluable for response***	12		12		5		**29**	

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease

** proportion of patients with complete or partial response to immunotherapy (documented best response to therapy)*

*** calculated for patients evaluable for response*

**** cohort 1: five patients died before response evaluation, seven patients with missing data;*
cohort 2: two patients died before response evaluation, ten patients with missing data;
cohort 3: two patients died before response evaluation, three patients with missing data

DCR was 63.3%, 48.6% and 66.7% for the 3 cohorts

The DCR was 56.8% (n=42) for the overall cohort, and 63.3%, 48.6% and 66.7% for the three cohorts, respectively.

*Table 3.2-2: Disease Control Rate (DCR)**

	Cohort 1*** (n=42)		Cohort 2*** (n=47)		Cohort 3*** (n=14)		Total	
	n	%	n	%	n	%	n	%
DCR** (CR/PR/SD)	19	63.33	17	48.57	6	66.67	**42**	**56.76**
PD**	11	36.67	18	51.43	3	33.33	**32**	**43.24**
patients evaluable for response	30	100.00	35	100.00	9	100.00	**74**	**100.0**
patients NOT evaluable for response***	12		12		5		**29**	

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease

** proportion of patients with complete or partial response or stable disease to immunotherapy (documented best response to therapy)*

*** calculated for patients evaluable for response*

**** cohort 1: five patients died before response evaluation, seven patients with missing data; cohort 2: two patients died before response evaluation, ten patients with missing data; cohort 3: two patients died before response evaluation, three patients with missing data*

median follow-up 16.4 months

In addition, we calculated **overall survival and progression-free survival for the three cohorts** separately. Kaplan Meier plots are shown in Figure 3.2-1 to Figure 3.2-10. The median duration of follow-up for overall survival (OS) was 16.36 months (range 0.13 to 29.63).

Cohort 1: First-line pembrolizumab monotherapy

median OS 16.9 months and median PFS 6.1 months

The median OS and PFS were 16.99 months (95% CI 11.73-21.45) and 6.06 months (95% CI 3.12-17.02), respectively, for all patients in cohort 1 (see Figure 3.2-1 and Figure 3.2-2). Cohort 1 was divided in patients with first-line pembrolizumab and stage III & IV (FL pemb all, n=42) and patients with first-line pembrolizumab and stage IV only (FL pemb stage IV, n=36). The median OS and PFS for patients with stage IV only were 15.79 months (95% CI 5.22-21.55) and 4.88 months (95% CI 2.56-17.61), respectively.

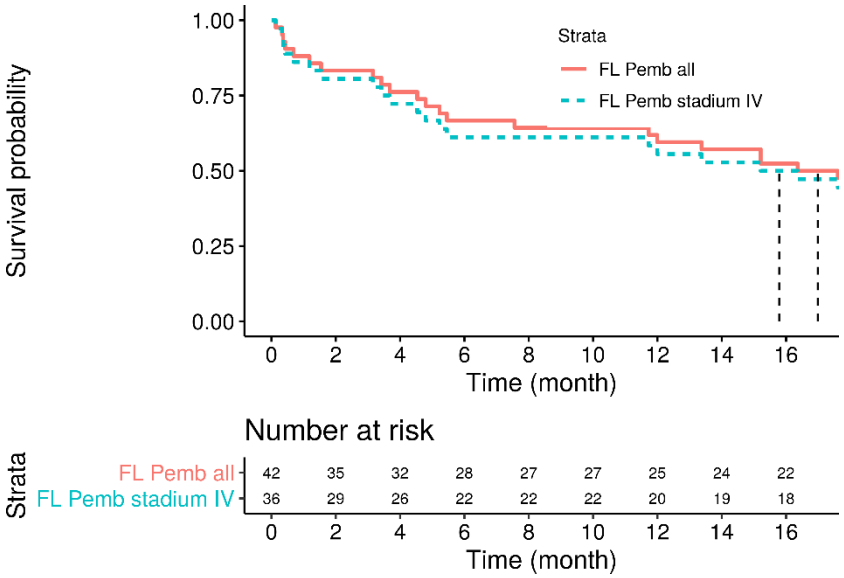

Figure 3.2-1: Kaplan Meier curve for overall survival in cohort 1

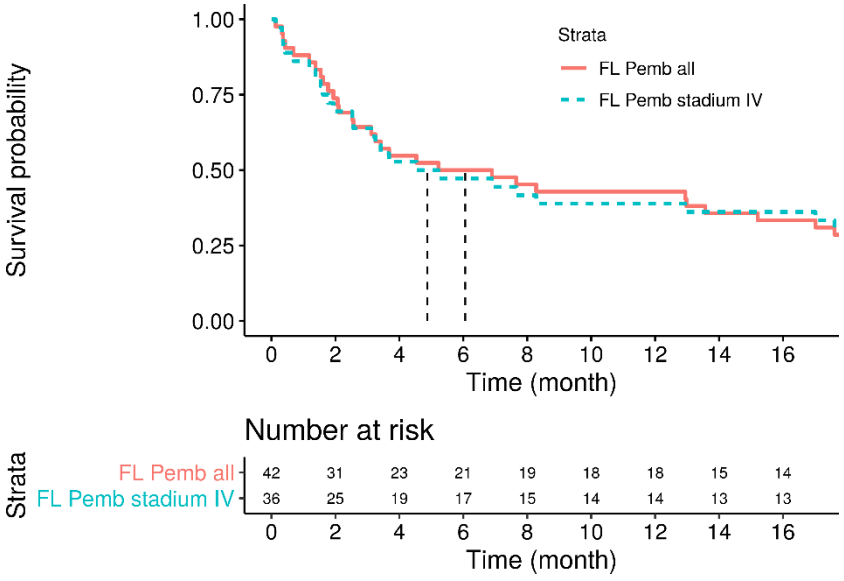

Figure 3.2-2: Kaplan Meier curve for progression-free survival in cohort 1

Cohort 2: Second-line anti-PD-1/PD-L1 monotherapy

median OS 18.7 months and median PFS 3.7 months

The median OS and PFS were 18.73 months (95% CI 9.46-23.36) and 3.71 months (95% CI 2.30-9.86), respectively, for all patients (see Figure 3.2-3 and Figure 3.2-4).

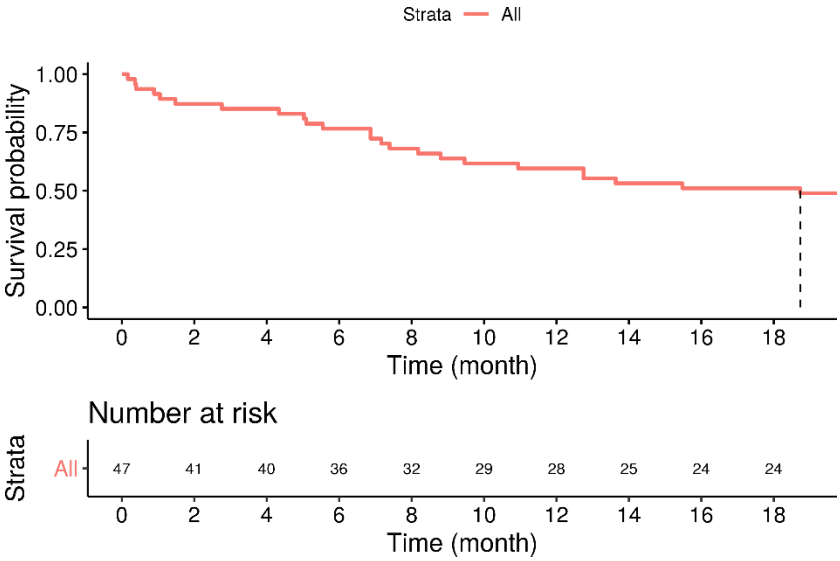

Figure 3.2-3: Kaplan Meier curve for overall survival in cohort 2

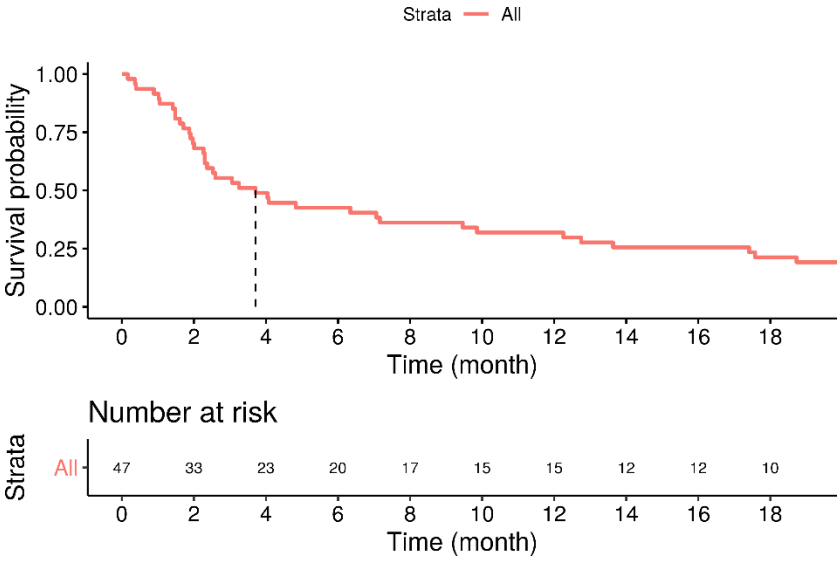

Figure 3.2-4: Kaplan Meier curve for progression-free survival in cohort 2

stratification by compound in cohort 2

We further investigated OS and PFS in patients of cohort 2 stratified by compound (nivolumab, pembrolizumab, atezolizumab) (see Figure 3.2-5 and Figure 3.2-6). The median OS were 20.47 months (95% CI 8.80-26.15), 22.87 months (95% CI 10.94-27.70) and 1.91 months (95% CI 0.36-NA), respectively, for stratification by compound. The median PFS were 4.06 months (95% CI 2.37-13.63), 3.06 months (95% CI 2.30-26.18) and 1.38 months (95% CI 0.36-NA), respectively, for stratification by compound.

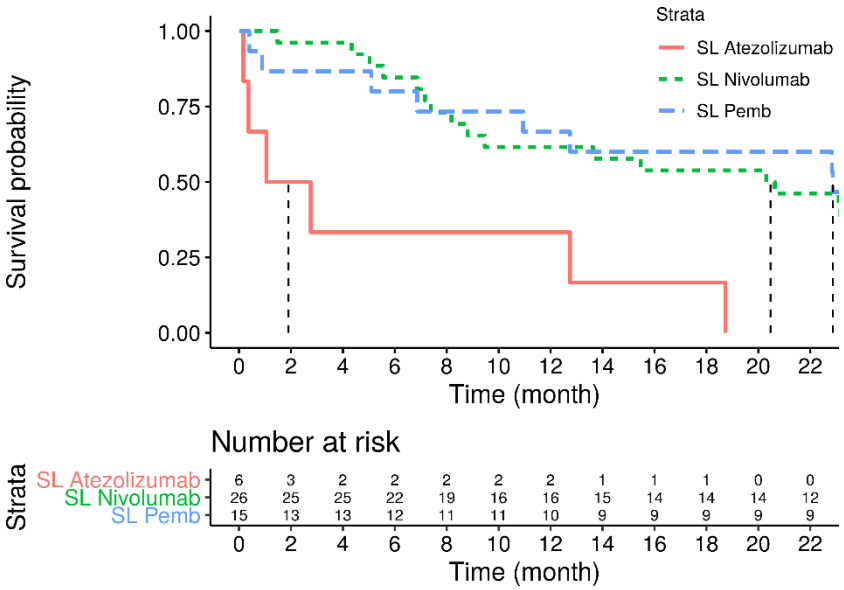

Figure 3.2-5: Kaplan Meier curve for overall survival in cohort 2 by compound

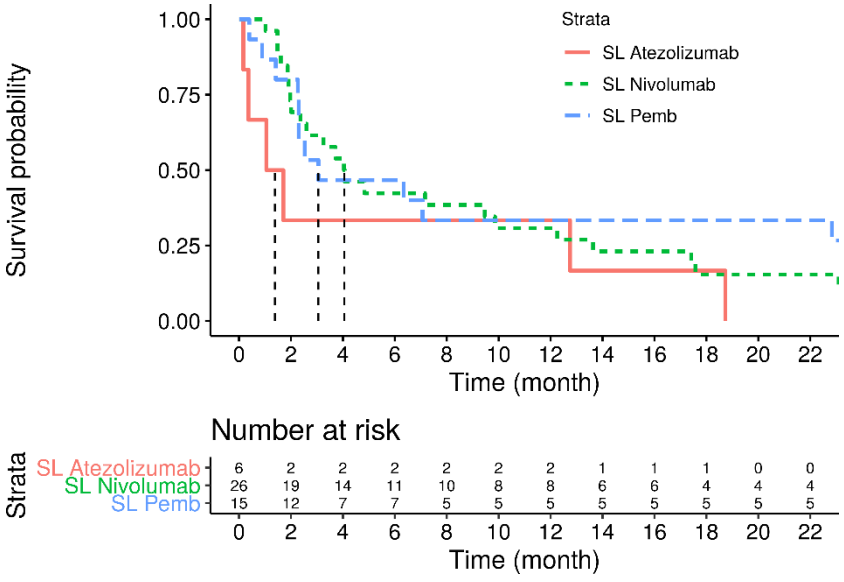

Figure 3.2-6: Kaplan Meier curve for progression-free survival in cohort 2 by compound

stratification by PD-L1 TPS % in cohort 2

In addition, we estimated OS and PFS in patients of cohort 2 stratified by PD-L1 TPS % although PD-L1 TPS was not available for all patients (only in 38 out of 47 patients). The median OS were 12.75 months (95% CI 7.39-NA), 6.87 months (95% CI 2.76-NA), and 21.57 months (95% CI 9.46-26.68) for patients with PD-L1 ≥50%, respectively, for stratification by PD-L1 (%) (see Figure 3.2-7). The median PFS were 2.00 months (95% CI 1.48-NA), 1.97 months (95% CI 1.61-NA) and 8.31 months (95% CI 2.53-26.68) in patients with PD-L1 ≥50%, respectively, for stratification by PD-L1 (%) (see Figure 3.2-8).

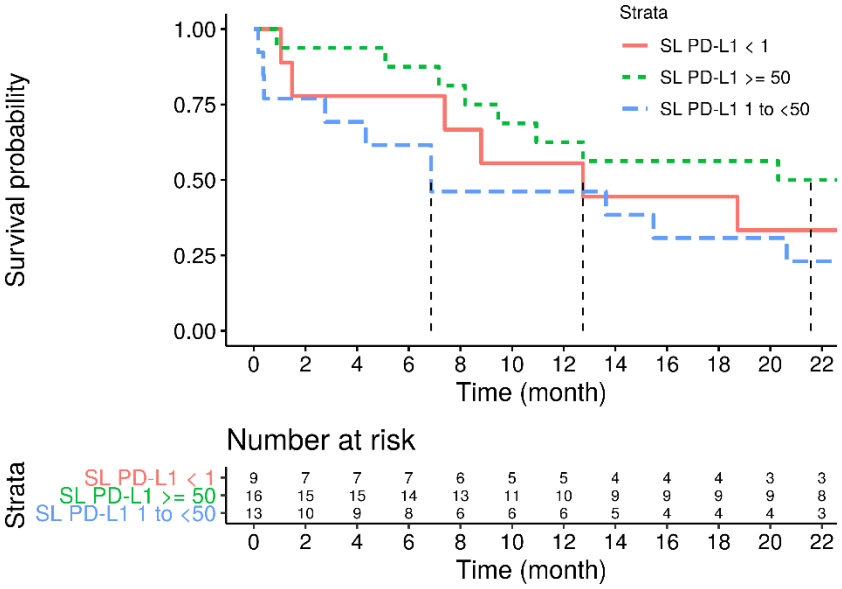

Figure 3.2-7: Kaplan Meier curve for overall survival in cohort 2 by PD-L1 TPS

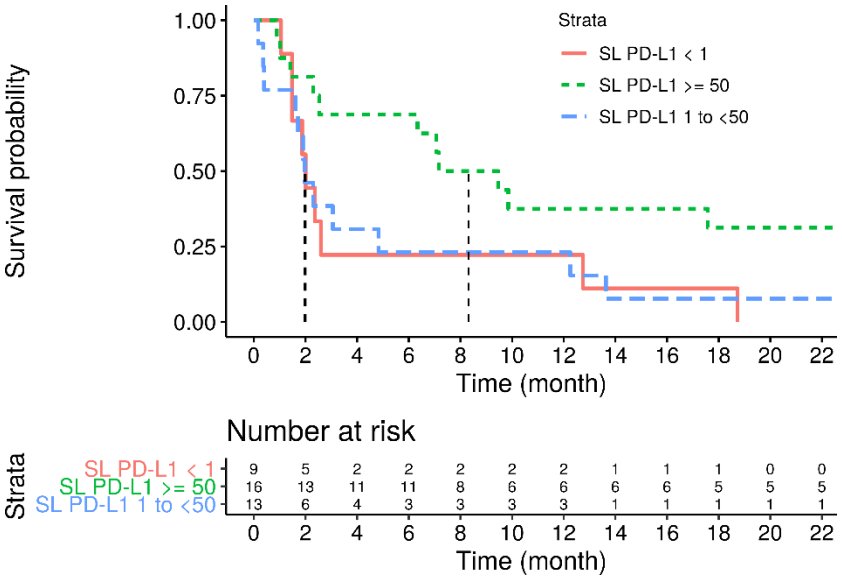

Figure 3.2-8: Kaplan Meier curve for progression-free survival in cohort 2 by PD-L1 TPS

Cohort 3: Third-line (or more) anti-PD-1/PD-L1 monotherapy

The median OS and PFS were 12.96 months (95% CI 2.46-27.20) and 3.06 months (95% CI 2.33-14.82), respectively, for all patients of cohort 3 (see Figure 3.2-9 and Figure 3.2-10).

median OS 12.9 months and median PFS 3.1 months

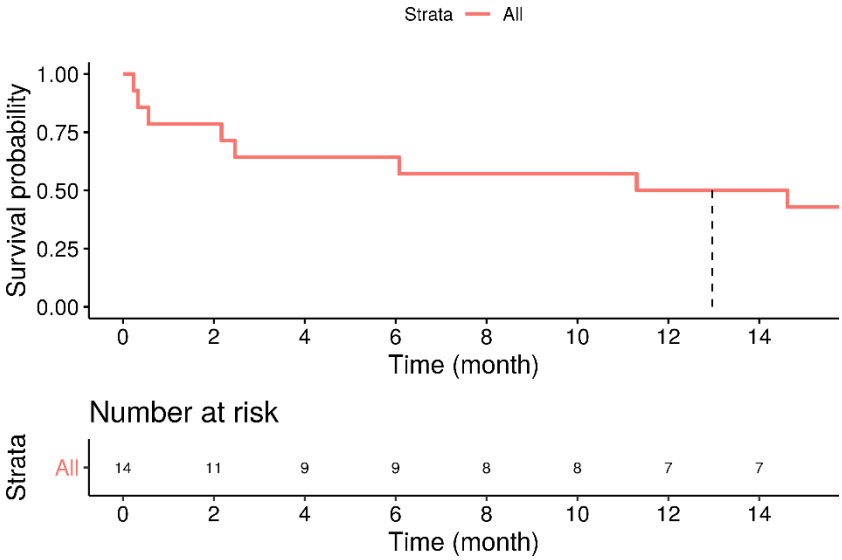

Figure 3.2-9: Kaplan Meier curve for overall survival for cohort 3

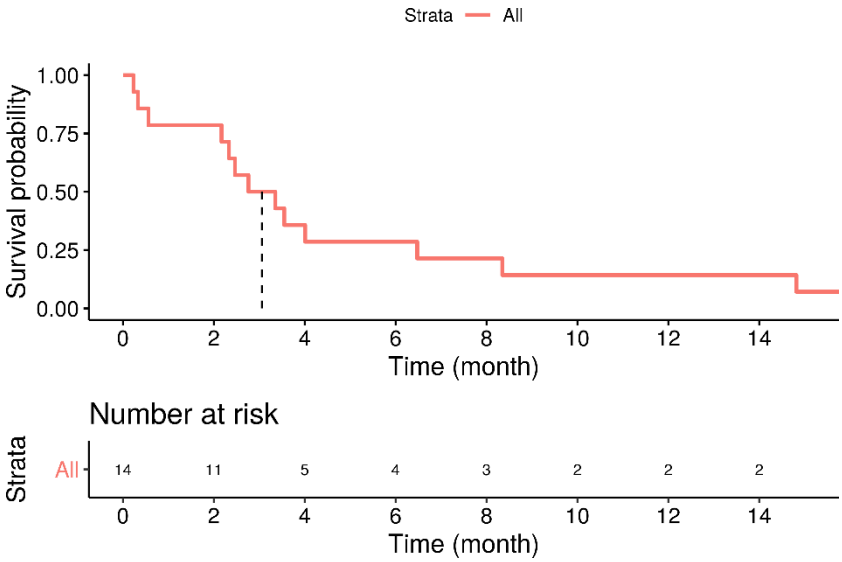

Figure 3.2-10: Kaplan Meier curve for progression-free survival in cohort 3

3.3 Comorbidities and Adverse Events

comorbidities from electronic health records

Table 3.3-1 presents comorbidities which were available from electronic health records (Tyrol) or from discharge diagnosis encoded as ICD-10 codes (Styria).

Table 3.3-1: Overview of reported comorbidities

	Cohort 1 (n=42)		Cohort 2 (n=47)		Cohort 3 (n=14)		Total
	n	%	n	%	n	%	n
myocardial infarction	4	9.52	2	4.26	1	7.14	**7**
heart failure	2	4.76	2	4.26	1	7.14	**5**
peripheral artery disease	4	9.52	7	14.89	1	7.14	**12**
cerebrovascular disease	9	21.43	3	6.38	1	7.14	**13**
dementia	1	2.38	1	2.13	0	0.00	**2**
chronic pulmonary disease	14	33.33	19	40.43	8	57.14	**41**
collagenosis	0	0.00	1	2.13	0	0.00	**1**
peptic ulcer disease	0	0.00	3	6.38	4	28.57	**7**
mild liver disease	1	2.38	1	2.13	1	7.14	**3**
diabetes mellitus	7	16.67	10	21.28	3	21.43	**20**
moderate or severe renal impairment	3	7.14	0	0.00	0	0.00	**3**

AEs in 24 patients in total, 11 AEs grade 3 or 4

Treatment-related adverse events (AEs) occurred in 24 patients and are listed in Table 3.3-2. Adverse events documented in electronic health records were analysed for the three cohorts. Grade 3 or 4 adverse events were reported in 11 patients. These adverse events were skin rash, thyroiditis, pneumonitis, diarrhoea (immune-related colitis), toxic pneumonitis or immune-mediated hepatitis und drug-induced exanthema, leading to discontinuation or interruption of treatment in eight cases (see Table 3.3-3).

Table 3.3-2: Overview of treatment-related adverse events

	Cohort 1 (n=42)		Cohort 2 (n=47)		Cohort 3 (n=14)		Total
adverse event (AE)	n	%	n	%	n	%	n
grade 1	4	9.52	3	6.38	0	0.00	**7**
grade 2	0	0.00	4	8.51	2	14.29	**6**
grade 3	7	16.67	1	2.13	1	7.14	**9**
grade 4	0	0.00	2	4.26	0	0.00	**2**
no AE reported	31	73.81	37	78.72	11	78.57	**79**

Table 3.3-3: Consequence of treatment-related adverse events grade 3 or grade 4

	Grade 3		Grade 4		
	n	%	n	%	total
discontinuation of treatment	3	33.33	2	100	**5**
treatment interruption	3	33.33	0	0	**3**
no consequence	1	11.11	0	0	**1**
dose reduction	1	11.11	0	0	**1**
unknown	1	11.11	0	0	**1**
total	**9***	**100.00**	**2****	**100**	**11**

** skin rash, thyroiditis, pneumonitis, diarrhoea (immune-related colitis), toxic pneumonitis*

*** immune-mediated hepatitis und drug-induced exanthema*

3.4 Exploratory Comparison with Clinical Trial Populations

real-world practice versus clinical trials

To determine how patients treated with anti-PD-1/PD-L1 therapy in real-world practice differ from those enrolled in relevant registrational trials (see Table 1.4-1), we compared available information from nivolumab, pembrolizumab and atezolizumab clinical trial cohorts with patients from our Austrian cohort. This was done in a descriptive manner; no formal statistical procedures were applied.

First-line pembrolizumab: Keynote-024 [25, 26]

cohort 1 slightly older and 7.1% with ECOG ≥2

Compared to Keynote-024, the first-line pembrolizumab cohort in our setting was slightly older and included three patients (7.1%) with ECOG performance status ≥2. Moreover, six patients (14.3%) with advanced NSCLC (stage IIIA and IIIB) were administered pembrolizumab as first-line therapy (see Table 3.4-1).

Table 3.4-1: Comparison of cohort 1 with Keynote-024

	Keynote-024	Cohort 1
Inclusion criteria	❁ patients 18 years of age or older ❁ stage IV NSCLC with no sensitizing EGFR mutations or ALK translocations ❁ no previous systemic therapy for metastatic disease, ❁ Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 ❁ PD-L1 tumour proportion score of 50% or greater	❁ age 18 years and older ❁ 6 pts (14.3%) with stage III ❁ No prior systemic therapy ❁ 3 pts with ECOG ≥2 ❁ 1 pts with PD-L1 TPS<50%
Exclusion criteria	❁ receiving systemic glucocorticoids or other immunosuppressive treatment ❁ had untreated brain metastases, active autoimmune disease for which they had received systemic treatment during the previous two years, ❁ active interstitial lung disease, or a history of pneumonitis for which they had received glucocorticoids	none
Population characteristics		
Median age (range), years	64.5 (33-90)	67.5 (49-85)
Male sex %	59.7	61.9
Outcomes		
Grade ≥3 AEs %	26.6%	16.7%
ORR	44.8%	43.3%
Median OS months	26.3 (95% CI: not reported)*	16.99 (95% CI, 11.73; 21.45)
Median PFS months	10.3 (95% CI, 6.7 to not reached)	6.06 (95% CI, 3.12; 17.02)

AE=adverse event, OS=overall survival, PFS=progression-free survival, ORR=objective response rate

** Latest updated analysis of Keynote-024 (presented at WCLC 2019), only abstract available.*

Second-line nivolumab, pembrolizumab and atezolizumab: Keynote-010 [29], CheckMate017 [23], CheckMate057 [24] and OAK (GO28915) [30]

patients received either nivolumab, pembrolizumab or atezolizumab

In contrast to pivotal studies testing one compound, the patients in our cohort 2 received either nivolumab (n=26, 55.3%), pembrolizumab (n=15, 31.9%) or atezolizumab (n=6, 12.8%) as second-line monotherapy and were analysed together.

In Table 3.4-2 some characteristics and outcomes of cohort 2 are compared to the corresponding relevant clinical trials.

cohort 2 slightly older and 2 patients with ECOG ≥2

Compared to clinical trials, the second-line anti-PD-1/PD-L1 monotherapy cohort in our setting was slightly older, and included two patients with ECOG performance status ≥2.

Compared to clinical trials with nivolumab or atezolizumab, fewer patients in our cohort 2 had PD-L1 TPS<1%.

Table 3.4-2: Second-line nivolumab, pembrolizumab and atezolizumab compared to pivotal RCTs

	Keynote-010[29]	CheckMate017[23]	CheckMate057[24]	OAK[30]	Cohort 2
Inclusion criteria	patients aged at least 18 years	18 years of age or older	18 years of age or older	18 years or older	patients aged ≥18 years
	progression after two or more cycles of platinum-doublet chemotherapy, as well as an appropriate tyrosine kinase in advanced NSCLC	recurrence after one prior platinum-containing regimen stage IIIB or IV	stage IIIB/IV or recurrent non-squamous NSCLC following radiation therapy or surgical resection, disease recurrence or progression during or after one prior platinum-based regimen	squamous or non-squamous non-small cell lung cancer received 1-2 previous cytotoxic chemotherapy regimens for stage IIIB or IV non-small cell lung cancer. Patients with EGFR mutations or an ALK fusion oncogene were additionally required to have received previous tyrosine kinase inhibitor therapy	pts with one systemic therapy regime prior to immunotherapy
	ECOG performance status of 0 or 1	ECOG performance status of 0 or 1	ECOG performance status of 0 or 1	ECOG performance status of 0 or 1	2 pts with ECOG ≥2
	PD-L1 expression on at least 1% of tumour cells (i.e., a TPS ≥1%)	PD-L1 was no criterion	PD-L1 was no criterion	Patients were stratified by PD-L1 expression	9 pts with PD-L1 TPS<1%
Exclusion criteria	previous treatment with PD-1 checkpoint inhibitors or docetaxel, known active brain metastases or carcinomatous meningitis, active autoimmune disease requiring systemic steroids, interstitial lung disease or history of pneumonitis requiring systemic steroids	autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior therapy with T-cell costimulation or checkpoint-targeted agents, or prior docetaxel therapy. Patients who had received more than one prior systemic therapy for metastatic disease	autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior treatment with immune-stimulatory anti-tumour agents including checkpoint-targeted agents, or docetaxel	a history of autoimmune disease and those who had received previous treatments with docetaxel, CD137 agonists, anti-CTLA4, or therapies targeting the PD-L1 and PD-1 pathway	none
Population characteristics					
Median age (range), years	63.0 (56.0-69.0)	62 (39-85)	61 (37-84)	63.0 (33.0-82.0)	69.0 (55-82)
Male sex %	62%	82%	52%	61%	53.2%
PD-L1 TPS %	≥50%: 40% 1-49%: 60%	83% with TPS<1%	47% with TPS<1%	42% with TPS<1%	≥50%: 34.0% 1-49%: 27.7% 19.1% <1% TPS 19.1% not reported
Stage (UICC)	Advanced NSCLC	stage IIIB (21%) or IV (78%) squamous-cell NSCLC	7% stage IIIB 93% stage IV	stage IIIB or IV NSCLC	Advanced and metastatic disease: 76.6% stage IV
Outcomes					
Grade ≥3 AEs %	13%	7%	10%	15%	6.4%
ORR	20%	20%	19%	14%	31.4%
Median OS months	10.4 (95% CI, 9.5, 11.9)*	9.2 (95% CI, 7.3, 13.3)	12.2 (95% CI, 9.7 to 15.0)	13.8 (95% CI 11.8-15.7)	18.73 (95% CI 9.46; 23.36)
Median PFS months	3.9 (95% CI, 3.1, 4.1)	3.5 (95% CI, 2.1, 4.9)	2.3 (95% CI, 2.2 to 3.3)	2.8 (95% CI 2.6-3.0)	3.71 (95% CI 2.30; 9.86)

* *Median follow-up was 13.1 months (IQR 8.6-17.7).*

Third-line (or more) nivolumab, pembrolizumab and atezolizumab:

no pivotal clinical trials for third-line or more

No specific trials for patients with third- or more line therapy for NSCLC were conducted. The abovementioned pivotal trials included or excluded such patients. In the Keynote-010 trial, 27% of patients had ≥2 lines of therapy for advanced disease. In the CheckMate017 trial, patients who had received more than one prior systemic therapy for metastatic disease were excluded. In the CheckMate057 trial, 12% had two prior systemic regimes. Finally, in the OAK trial, 25% of patients had two previous therapies in the locally advanced or metastatic setting.

3.5 Matched-Pair Analysis (Historical Cohort)

historical controls with either platine or taxane therapy

The matched-pair analysis was conducted for cohort 1 (first-line pembrolizumab) and for cohort 2 (second-line nivolumab, pembrolizumab, atezolizumab). Cohort 1 was matched to patients with first-line platine therapy, cohort 2 was matched to patients with second-line taxane therapy.

matching 1:3 for cohort 1; matching 1:2 for cohort 2

For 31 patients of cohort 1, there were 92 matching historic control patients with platine therapy. For 21 patients of cohort 2, there were 38 matching historic control patients with taxane therapy.

Cohort 1 matched to historic cohort with platine therapy

median OS 15.2 vs. 9.8 months (p=0.43)
median PFS 5.2 vs. 4.9 months (p=0.14)

The matched-pair analysis showed a median OS of 15.21 months (95% CI 7.56-20.44) for cohort 1 with pembrolizumab monotherapy compared to 9.81 months (95% CI 7.79-11.60) for the historic cohort with first-line platine therapy (p=0.43). The PFS was 5.22 months (95% CI 2.53-17.61) for cohort 1 and 4.87 months (95% CI 3.94-6.01) for the first-line platine group (p=0.14).

The Kaplan Meier plots for OS and PFS are displayed in Figure 3.5-1 and Figure 3.5-2.

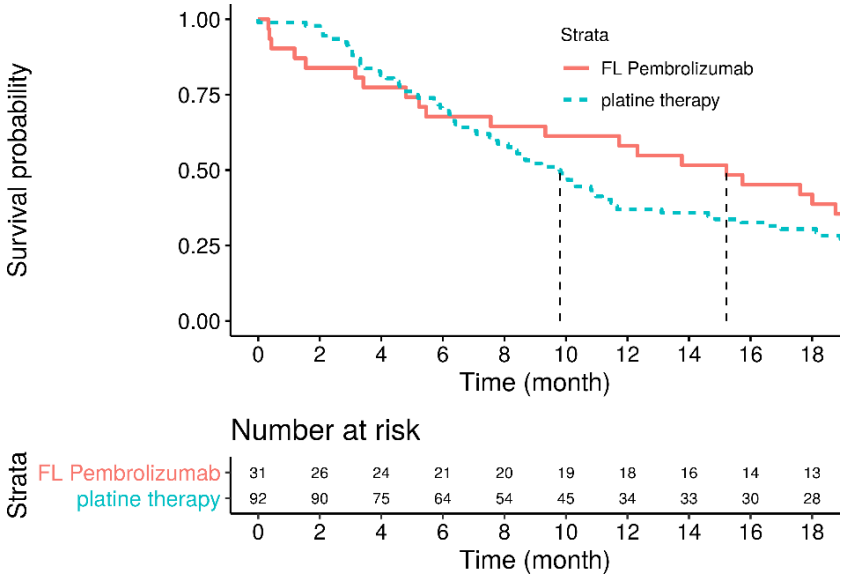

Figure 3.5-1: Overall survival for cohort 1 compared to historical cohort with platine therapy

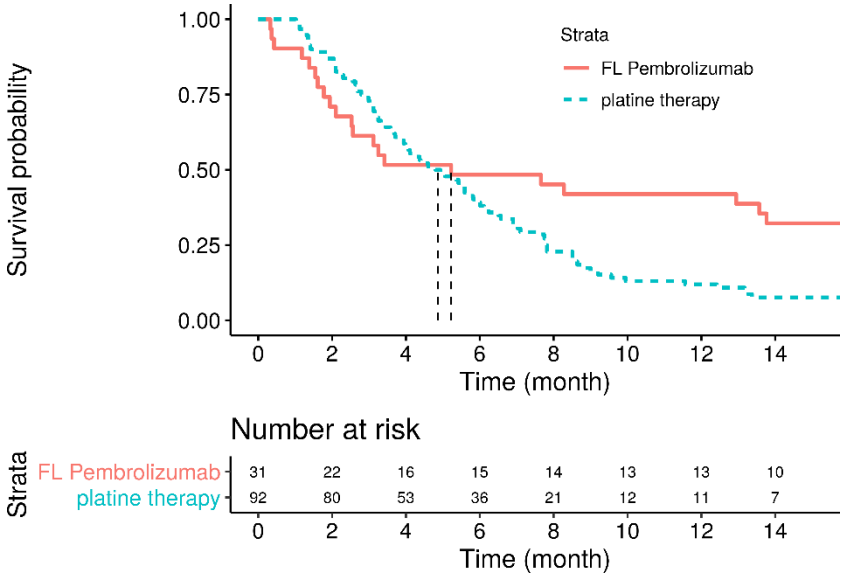

Figure 3.5-2: Progression-free survival for cohort 1 compared to historical cohort with platine therapy

Cohort 2 matched to historic cohort with taxane therapy

median OS 20.3 vs. 5.4 months (p=0.18) median PFS 2.6 vs. 3.1 months (p=0.36)

The matched-pair analysis showed a median OS of 20.34 months (95% CI 6.87-26.18) for cohort 2 with anti-PD-1/PD-L1 monotherapy compared to 5.40 months (95% CI 3.15-11.66) for the historic cohort with first-line taxane therapy (p=0.18). The PFS was 2.60 months (95% CI 1.91-20.34) for cohort 2 and 3.05 months (95% CI 1.97-5.78) for the first-line taxane group (p=0.36).

The Kaplan Meier plot for OS and PFS are displayed in Figure 3.5-3 and Figure 3.5-4.

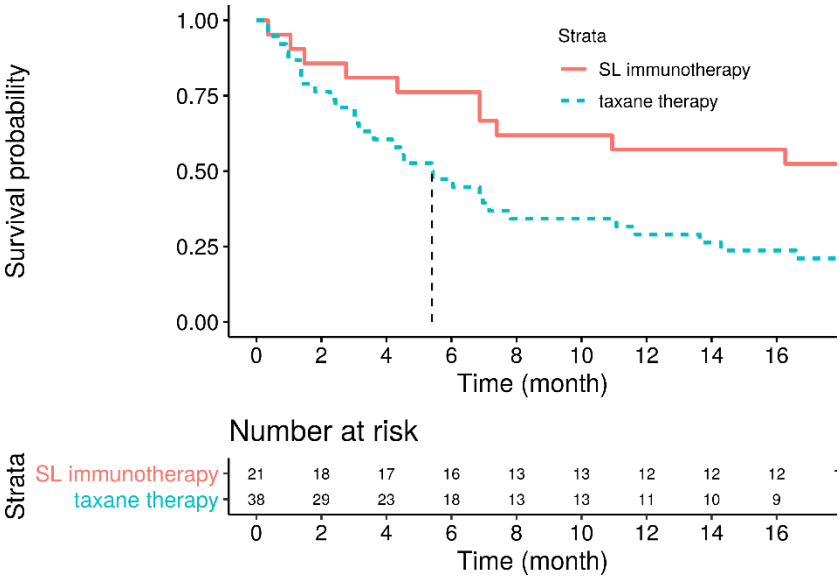

Figure 3.5-3: Overall survival for cohort 2 compared to historical cohort with taxane therapy

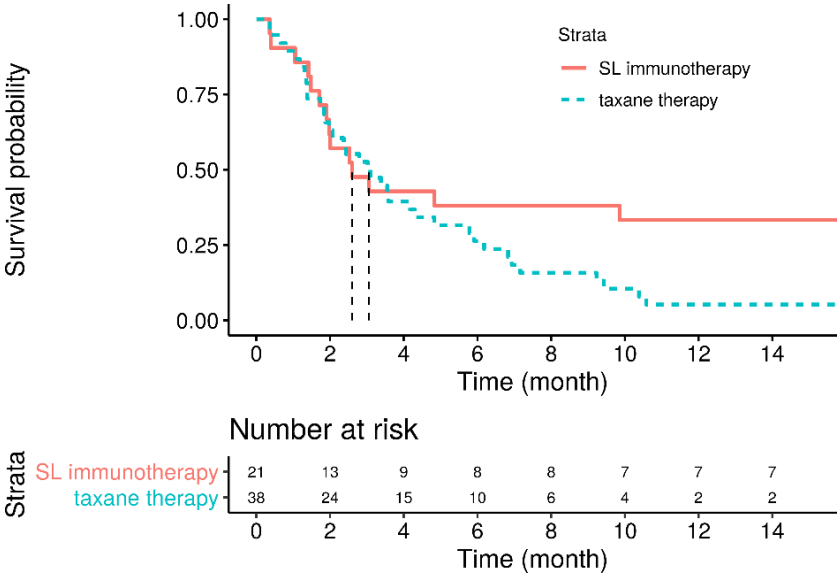

Figure 3.5-4: Progression-free survival for cohort 2 compared to historical cohort with taxane therapy

4 Discussion

4.1 Summary of the Retrospective Pilot Study

immune checkpoint inhibitors changed lung cancer treatment

The development of immune checkpoint inhibitors has changed cancer treatment in the last years, and immunotherapy nowadays plays an important role in the treatment of patients with non-small lung cancers. According to the current ESMO Guidelines, the PD-1 inhibitors nivolumab and pembrolizumab and the PD-L1 inhibitor atezolizumab are the second-line treatment of choice for most patients with advanced, previously treated, PD-L1-naive NSCLC, irrespective of PD-L1 expression. In addition, pembrolizumab is considered a standard first-line option for patients with advanced NSCLC and PD-L1 expression ≥50% [10]. The place in therapy is based on results from pivotal clinical trials which lead to the approval of these compounds for the treatment of NSCLC by the FDA and the EMA. Although the results of relevant registrational trials are promising, they do not always reflect anti-PD-1/PD-L1 therapy of patients with NSCLC in real-world practice. Therefore, we conducted this retrospective pilot study in six Austrian hospitals to analyse the effectiveness and safety of immunotherapy in routine clinical practice. In accordance to pivotal clinical trials, we subdivided our 103 finally included patients into three cohorts: first-line pembrolizumab monotherapy (cohort 1), second-line nivolumab, pembrolizumab or atezolizumab monotherapy (cohort 2) and third- (or more) line nivolumab, pembrolizumab or atezolizumab monotherapy (cohort 3).

cohort 1: ORR 43.3%; median OS 16.9 and median PFS 6.1 months

Our results for cohort 1 (first-line pembrolizumab) showed a comparable response rate (ORR) and fewer adverse events grade ≥3, but a shorter median overall survival and progression-free survival than observed in clinical trials (43.3%, 16.9 months, 6.1 months vs. 44.8%, 26.3 months, 10.3 months) [25-27]. The results of our cohort showed a wide confidence interval (OS 95% CI 11.7-21.5, PFS 95% CI 3.1-17.0) indicating high uncertainty in our estimates, which should be confirmed by additional data. This issue should be addressed in further trials in real-world practice as particularly the long overall survival from clinical trials was neither observed in other retrospective analyses from real-world data (see section 4.2). Our population was comparable to the clinical trial population for first-line pembrolizumab (Keynote-024) in respect to stage, ECOG performance status and PD-L1 TPS, but was slightly older. We did not compare further inclusion or exclusion criteria from clinical trials (e.g., proportion of patients with brain metastasis), as this information was not available for our cohort.

cohort 2: ORR 31.4% median OS 18.7 and median PFS 3.7 months

Although our cohort 2 represents a composition of patients with either second-line nivolumab, pembrolizumab or atezolizumab, the results of the total cohort showed a longer median OS, a higher ORR (31.4%), a comparable median PFS and fewer adverse events grade ≥3 than observed in clinical trials with second-line anti-PD-1/PD-L1 monotherapy [23, 24, 29, 30]. Again, our results of cohort 2 showed a wide confidence interval (OS 95% CI 9.5-23.4, PFS 95% CI 2.3-9.9) indicating uncertainty in our estimates which should be confirmed by additional data from studies with larger population sizes. Cohort 2 was slightly older than the clinical trial populations but included fewer patients with PD-L1 TPS<1% than corresponding clinical trials. In ad-

dition, we estimated OS in patients of cohort 2 stratified by PD-L1 TPS %. In line with clinical trials results, patients with PD-L1 TPS ≥50% showed the longest median overall survival of 21.6 months (95% CI 9.5-26.7).

cohort 3: ORR 33.3% median OS 12.9 and median PFS 3.1 months

small sample size (n=14)

The ORR, PFS, and OS (33.3%, 3.06 months, and 12.96 months, respectively) in our study for cohort 3 (third-line or more nivolumab, pembrolizumab or atezolizumab monotherapy) were comparable to those results of the aforementioned clinical trials for second-line therapy. The sample size of cohort 3 was very small (n=13), and these results have to be confirmed by studies with larger study populations. To our knowledge, there are no specific clinical trials in patients with third- or more line therapy for NSCLC, but these patients were included in the Keynote-010 trial (27% of patients had ≥2 lines of therapy for advanced disease), in the CheckMate057 trial (12% had two prior systemic regimes) and in the OAK trial (25% of patients had two previous therapies in the locally advanced or metastatic setting). Only the CheckMate017 trial excluded patients who had received more than one prior systemic therapy for metastatic disease. Our results for cohort 3 correspond to a previously published retrospective analysis of real-world data in Taiwan. **Lin et al.** retrospectively reviewed 74 patients with stage IIIB/IV NSCLC who received monotherapy with nivolumab or pembrolizumab in Taiwan. The median follow-up time was 12.4 months. Adenocarcinoma was the most common histology and nearly half of the population had an ECOG status of ≥2. 68.9% received immunotherapy as a third-line or subsequent treatment. The median PFS and OS were 1.8 and 7.9 months, respectively. The objective response rate was 32% in the evaluable population [42].

matched-pair analysis to historical controls from Tyrol registry

In addition, we performed a matched-pair analysis for cohort 1 and cohort 2. Both cohorts were matched to historic controls (treated with first-line platine or second-line taxane therapy) from the TYROL registry [38]. The results for cohort 1 showed a longer median OS compared to patients with platine therapy, although not significant (15.21 vs. 9.81 months, p=0.43) and a comparable PFS (5.22 vs. 4.87 months). The same was observed for cohort 2 matched to taxane therapy (median OS: 20.34 vs. 5.40, p=0.18; median PFS: 2.60 vs. 3.05, p=0.36). Although the differences between immunotherapy and controls were not significant, the results are similar to a previous published case-control study. **Faehling et al.** present the data of a case-control study in 557 consecutive patients with inoperable stage III or stage IV NSCLC diagnosed in a German lung cancer centre. Patients who received at least one line of systemic treatment and treatment with a PD-1 antibody (nivolumab or pembrolizumab) or a PD-L1 antibody (atezolizumab or durvalumab) were compared to historic controls treated before the availability of immunotherapy. 24.3% received first-line and 55.6% received second-line immunotherapy. The median follow-up was 37.2 months. For 63% of patients with immunotherapy, there was a matching historic control patient. The analysis showed significantly longer OS in patients with immunotherapy compared to historic controls (21.2 vs. 10.9 months, HR 0.53, CI 0.37-0.72) [43]. Nevertheless, our results have to be interpreted with caution as a matching historic control patient was not available for all patients (cohort 1: 31/42; cohort 2: 21/47), historic controls were treated earlier and some of the benefit may be due to general advances in the care of cancer patients.

4.2 Contrasting Results with Similar Studies

retrospective studies from other countries

To the best of our knowledge, this is the first retrospective study analysing real-world data for immunotherapy in Austria, but we found several recently published analyses of real-world data from other countries. Our findings are in line with other reported NSCLC real-life studies, but one important difference from other published real-world retrospective analyses is the presence of a low number of patients having an ECOG performance status of ≥2 in our cohort. The administration of immunotherapy in our clinical settings seems to follow the recommendation to restrict anti-PD-1/PD-L1 therapy to patients with ECOG 0-1. The results of similar studies are described below and are summarised in Table 4.2-1.

nivolumab or pembrolizumab in 155 Korean patients

Ahn et al. conducted a retrospective analysis in 155 Korean patients with advanced NSCLC who were administered nivolumab or pembrolizumab in real-world practice [44]. They included 67.7% with adenocarcinoma, 21.9% with an ECOG performance status score of ≥2 whilst 63.9% were identified as PD-L1 positive. 10.3%, 39.4%, and 50.3% of the patients received anti-PD-1 treatment as first-line, second-line, or subsequent to second-line therapy, respectively. The median follow-up duration was 17.0 months and the ORR for all patients was 23.9%. The median OS and PFS were 10.25 months (95% CI 5.39-15.11) and 3.06 months (95% CI 1.89-4.21), respectively, for all patients.

nivolumab in 188 patients from Galician centres

Areses Manrique et al. analysed the characteristics, the treatment outcomes and safety of 188 patients with advanced stage NSCLC treated with nivolumab in second-line in nine different Galician centres [45]. They included 60% of patients with adenocarcinoma; 97% did not show any molecular abnormality. All patients previously received at least one platinum-based therapy, whereas 38% patients received two or more prior systemic therapy lines. Among 163 patients included in analysis, the ORR was 25.5%. The median PFS was 4.83 months (95% CI, 3.69-5.97) and OS was 12.85 months (95% CI, 9.07-16.62).

nivolumab or pembrolizumab in 118 patients from Denmark

Bjørnhart et al. present descriptive data on patient characteristics, effect and toxicity in an unselected real-life NSCLC population (n=118) undergoing treatment with nivolumab or pembrolizumab in Denmark. The majority of patients had stage IV disease, and 18% of all patients had brain metastasis. 31% of patients received ≥2 previous systemic therapies. The median follow-up was 15.7 (range 7.0-40.1) months, and the overall response rate (ORR) was 33%. A median OS of 16.1 months [95% CI 10.7-21.5] and a median PFS of 6.4 months [95% CI 4.9-7.8] was found [46].

nivolumab in 260 patients from Israel

Dudnik et al. reviewed the Israeli experience with nivolumab given to 260 patients either within an expanded access programme or as a standard of care treatment for advanced NSCLC. 46% of patients were reported to have an ECOG performance status of ≥2 at the time of treatment initiation, and patients with non-squamous cell histology predominated. The majority of tumours included in the analysis did not show any molecular abnormality. 26% of patients received ≥2 prior systemic therapies. The median follow-up duration for OS was 18.5 months (range, 12.0-26.9). The median OS was 5.9 months (95%CI, 4.7-7.4), the ORR was 35%, and median PFS was 2.8 months (95%CI,1.8-7.7) [47].

nivolumab in 15 centres in Japan (n=613)

Fujimoto et al. conducted an observational, retrospective cohort study of 613 patients with advanced NSCLC who were previously treated and received nivolumab monotherapy in 15 centres in Japan. 77% of patients had an ECOG

performance status of 0 or 1 and 67% had adenocarcinoma. EGFR mutations and ALK rearrangements were detected in 19% and 3% of patients, respectively. The ORR was 20% and the DCR was 44%. The estimated one-year PFS was 18%, and the estimated one-year OS was 54%. 11% of patients had AEs of grades ≥3 [48].

nivolumab in 472 Canadian patients

Juergens et al. evaluated the real-world benefit of nivolumab in 472 Canadian patients with advanced or metastatic NSCLC who had progressed during or after at least one line of systemic therapy, including one line of platinum-containing chemotherapy. 9% had an ECOG performance status of 2; 13% had central nervous system metastases; 73% had non-squamous NSCLC. EGFR mutations were identified in 5% of the cohort; a confirmed ALK translocation was present in fewer than 1%. Most patients had received one or two prior lines of therapy; 26% of patients had received three or more lines of therapy. The median OS was 12.0 months (95% CI: 11.0 months to 13.9 months) [49].

nivolumab or pembrolizumab in 1,344 US patients

Khozin et al. analysed real-world outcomes of 1,344 patients with metastatic non-small cell lung cancer treated with nivolumab or pembrolizumab in the first year following U.S. regulatory approval. 64% were diagnosed at stage IV, and 65% had tumours with non-squamous histology. The median OS was 8.0 months (95% CI 7.4-9.0 months), and one-year survival probability was 39% (95% CI 37%-42%), suggesting that OS in their real-world patients may be shorter than in conventional clinical trial patient cohorts, potentially due to narrow trial eligibility criteria [50].

nivolumab in 142 patients from Japan

Kobayashi et al. evaluated the real-world efficacy and safety of nivolumab in 142 patients with advanced non-small cell lung cancer in Japan. 40.1% received second-line and 59.9% received third-line or more immunotherapy. The objective response rate was 17.0%, the median progression-free survival (PFS) was 58 days (95% CI, 50-67 days), and the proportion of patients with adverse events of grade ≥3was 13.3%. Overall survival was not analysed due to short follow-up [51].

pembrolizumab in 190 Canadian patients

Ksienski et al. performed a multicentre retrospective analysis of 190 patients with advanced NSCLC treated with pembrolizumab to investigate its efficacy in routine clinical practice. 34% had ECOG PS≥2 at baseline, 9% had liver metastases, and 14% brain metastases. 74.2% received pembrolizumab in the first-line setting whilst 25.8% had progressed onto platinum-based doublet chemotherapy. 92.6% of tumours had PD-L1 TPS≥50% whilst EGFR mutations were reported in 3.7% and ALK rearrangements in none. The median PFS for the entire cohort was 3.7 months (95% CI, 2.8-4.3); the median OS was 13.4 months (95% CI, 9.7-25.1). The proportion of patients with adverse events of grade ≥3 was 8.4% [52].

551 patients from 24 centres in 10 countries: nivolumab, pembrolizumab or atezolizumab

Mazieres et al. conducted a retrospective study for patients receiving immune checkpoint inhibitors monotherapy for advanced NSCLC with at least one oncogenic driver alteration. They studied 551 patients treated in 24 centres from ten countries with the following molecular alterations involved KRAS (n=271), EGFR (n=125), BRAF (n=43), MET (n=36), HER2 (n=29), ALK (n=23), RET (n=16), ROS1 (n=7), and multiple drivers (n=1). The majority of tumours were adenocarcinoma. The objective response rate by driver alteration was: KRAS=26%, BRAF=24%, ROS1=17%, MET=16%, EGFR=12%, HER2=7%, RET=6% and ALK=0%. In the entire cohort, median PFS was 2.8 months, OS 13.3months and the best response rate19% [53].

nivolumab in 221 patients from Spain

Merino Almazán et al. conducted a retrospective, multicentre, observational study involving 221 patients who experienced progression after first-line therapy for non-small cell lung cancer and were treated with nivolumab in Spain. The median PFS was 5.3 months (95% CI 3.2-7.3), and OS was 9.7 months (95% CI 7.6-11.8) [54].

nivolumab, pembrolizumab or atezolizumab in 39 patients from Beijing

Song et al. analysed 39 patients with advanced non-small cell lung cancer and immunotherapy in a real-world setting in Beijing. 26 patients received immunotherapy as first-line treatment, seven patients as second-line and six patients received as third-line and above. Pembrolizumab was applied in 31 patients, nivolumab in four patients and atezolizumab in four patients. The ORR was 28.2%, and DCR was 69.2%. The median PFS was 25.5 months (95% CI 6.8-44.1 months), OS was not available [55].

213 patients with first-line pembrolizumab in Japan

Tamiya et al. conducted a multicentre retrospective study across 11 medical centres in Japan and analysed clinical data from 213 patients receiving first-line pembrolizumab for NSCLC. 67.6% had stage IV disease, and 60.6% were adenocarcinoma. The overall response rate, median PFS, and median OS was 51.2%, 8.3 months, and 17.8 months, respectively. Adverse events of grades ≥3 were observed in 18.3% [56].

124 patients with nivolumab or atezolizumab in 1 US centre

Weis et al. retrospectively compared immunotherapy response rates and toxicity in 124 patients with stage IV or recurrent non-small cell lung cancer following progression during or after platinum-based chemotherapy. The objective response rate was 14.8% in the nivolumab group (n=81) vs. 13.9% in the atezolizumab group (n=43) (p=0.897). Median overall survival was 8.4 months with nivolumab (95% CI 6.3 to 11.2) vs. 6.5 months with atezolizumab (95% CI, 4.7 to not reached). Median progression-free survival was 2.2 months (95% CI, 1.7 to 2.8) and 2.0 months (95% CI, 1.8 to 2.7) in the nivolumab and atezolizumab groups, respectively. Treatment-related adverse events occurred in 70.4% of patients in the nivolumab group and 65.1% in the atezolizumab group [57].

safety: 10.7% AEs grade 3 or 4

Moreover, immunotherapy in our total cohort was well tolerated, the proportion of patients who experienced grade 3 or 4 AEs was low (11/103, 10.7%) and consistent with that previously reported in clinical trials. **Wang et al**. evaluate the incidences of treatment-related adverse events of PD-1 and PD-L1 inhibitors and the differences between various drugs and cancer types reported in published clinical trials. The systematic review and meta-analysis included 125 clinical trials involving 20,128 patients; 12,277 (66.0%) of 18,610 patients from 106 studies developed at least one adverse event of any grade (severity), and 2,627 (14.0%) of 18,715 patients from 110 studies developed at least one adverse event of grade 3 or higher severity [58]. In addition, **Ksienski et al.** evaluated the correlation between immune-related adverse events (irAE) and treatment interruption due to irAE on clinical efficacy of PD-1 antibodies nivolumab and pembrolizumab in advanced NSCLC. In a cohort of 271 patients, irAEs were observed in 116 patients (42.8%). Nivolumab recipients developing colitis had lower OS compared to those who did not at the six-week landmark (p=0.010) and 12-week landmark (p=0.072). For the entire cohort, 56 patients (20.7%) needed treatment interruption because of an irAE. Treatment interruption correlated with lower OS at the six-week landmark (p=0.005) and 12-week landmark (p=0.008). Six-week landmark multivariable analysis identified a Charlson Comorbidity Index score of 3 or higher, an Eastern Cooperative Oncology Group Performance Status of 2 or higher, the presence of liver metastases, and an irAE greater than grade 2 versus no irAE to be associated with decreased OS (each p<0.05) [59].

Table 4.2-1: Overview of similar retrospective studies

Author	Compound	Line of therapy	Number of patients	Median Follow-up (months)	ORR (%)	Median OS 95% CI (months)	Median PFS 95% CI (months)	Grade ≥3 AEs (%)
Ahn et al. [44]	nivolumab or pembrolizumab	10.3% first-line 39.4% second-line 50.3% subsequent line	155	17.0	23.9	10.3 (5.4-15.1)	3.1 (1.9-4.2)	pneumonia 6.5% pneumonitis 3.2%
Areses Manrique et al. [45]	nivolumab	Second-line (but 38% with ≥2 prior systemic therapies	188 (163 analysed)	Not reported	25.5	12.9 (9.1-16.6)	4.8 (3.7-6.0)	4.8%
Bjørnhart et al. [46]	nivolumab or pembrolizumab	31% with ≥2 prior systemic therapies	118	15.7	33	16.1 (10.7-21.5)	6.4 (4.9-7.8)	33% termination of therapy due to immune-related AE grades 3 and 4
Dudnik et al. [47]	nivolumab	26% with ≥2 prior systemic therapies	260	18.5	35	5.9 (4.7-7.4)	2.8 (1.8-7.7)	fatigue 6%
Fujimoto et al. [48]	nivolumab	42% with ≥3 prior treatment	613	Not reported	20	one-year OS was 54%	one-year PFS was 18%	11%
Juergens et al. [49]	nivolumab	26% with ≥3 prior treatment	472	9.3	Not reported	12.0 (11.0-13.9)	Not reported	Not reported
Khozin et al. [50]	nivolumab or pembrolizumab	49.8% second-line 33.3% third or more line	1,344	5.3	Not reported	8.0 (7.4-9.1)	Not reported	Not reported
Kobayashi et al. [51]	nivolumab	40.1% second-line 59.9% third-line or more	142	Not reported	17	Not reported	58 days (50-67)	13.3%
Ksienski et al. [52]	pembrolizumab	74.2% first-line 25.8% second-line	190	6.1	Not reported	13.4 (9.7-25.1)	3.7 (2.8-4.3)	8.4%
Maziers et al. [53]	94% nivolumab or pembrolizumab 6% atezolizumab or durvalumab	5% first-line 41% second-line 53% third- or later line	551	16.1	Not reported	13.3(10.0-14.9)	2.8 (2.5-3.1)	Not reported
Merino Almazán et al. [54]	nivolumab	Second-line	221	Not reported	16.7	9.7 (7.6-11.8)	5.3 (3.2-7.3)	71% (any grade)
Song et al. [55]	79.6% pembrolizumab 10.2% nivolumab 10.2% atezolizumab	66.7% first-line	39	11	28.2	Not reported	25.5 (6.8-44.1)	none
Tamiya et al. [56]	pembrolizumab	First-line	213	11	51.2	17.8 (17.8-NA)	8.3 (6.0-10.7)	18.3%
Weis et al. [57]	nivolumab or atezolizumab	Second-line	124	7.5 for nivolumab 4.9 for atezolizumab	14.8% for nivolumab 13.9% atezolizumab	nivolumab: 8.4 (6.3 to 11.2) atezolizumab: 6.5 (4.7 to not reached)	nivolumab: 2.2 (1.7 to 2.8) atezolizumab: 2.0 (1.8 to 2.7)	70.4% in nivolumab group 65.1% in atezolizumab group (any grade)

ORR=objective response rate, OS=overall survival, PFS=progression-free survival, AEs=adverse events, NA=not available

4.3 International Debate on Real-World Data

randomised clinical trials as standard method for causal effects

Randomised clinical trials are the standard method to demonstrate causal effects between treatment and outcome, but do not always reflect the real clinical setting. Our aim was to evaluate outcomes of anti-PD-1/PD-L1 monotherapy in NSCLC patients in routine clinical practice by using data from hospital electronic health records. Similar studies were done by other author groups in several countries (see section 4.2) and real-world evidence of the effectiveness of newly approved and funded therapies is being increasingly requested by funding bodies, decision-makers, as well as clinicians themselves. Contemporary and robust real-world evidence is crucial for helping clinicians tailor new treatments to real-world patients. Both the EMA and the FDA have already addressed this topic [37, 60] and there is currently an intensive debate about when and how to use real-world data and whether real-world evidence can be incorporated in decision-making.

real-world data (RWD) for real-world evidence (RWE)

real-world data are partly feasible to replicate clinical trial evidence

Bartlett et al. investigated whether using real-world data are feasible to replicate clinical trial evidence. In a cross-sectional analysis they identified the number of clinical trials published in high-impact journals in 2017 that could be feasibly replicated using observational data from insurance claims and/or electronic health records (EHRs). They found that only 15% of these US-based clinical trials could be feasibly replicated, and although the potential to use real-world data for RWE is substantial, the current ability to replicate the design elements from clinical trials may be limited. They suggest that further development of observational methods and data systems may help realise the potential of RWE and may, in turn, translate into more generalisable medical research [61].

framework for Canadian provinces to generate and use real-world evidence

The Canadian Real-world Evidence for Value of Cancer Drugs (CanREValue) collaboration, consisting of researchers, recommendation-makers, decision-makers, payers, patients and caregivers, are developing and testing a framework for Canadian provinces to generate and use real-world evidence (RWE) for cancer drug funding in a consistent and integrated manner. They want their framework to enable the reassessment of cancer drugs, the refinement of funding recommendations and the use of novel funding mechanisms by decision-makers/payers across Canada [32].

slow uptake of real-world evidence in clinical and therapeutic guidelines

Oyinlola et al. found in their systematic review that there is a slow uptake of real-world evidence in clinical and therapeutic guidelines, but there seems to be an increasing trend in the use of healthcare system data to inform clinical practice, especially as the real-world validity of clinical trials is being questioned. In order to accommodate the increasing demand that organisations need to work together to enable or improve data access, they suggest undertaking translational and relevant research and establishing sources of reliable evidence [36].

In general, there are increasing research activities using real-world data (RWD) to generate evidence, but several questions that have to be addressed still remain [33-35], e.g.:

address, e.g., methodological questions

- How to ensure the high quality of real-world data?
- What are the appropriate statistical/scientific methods to analyse these data and to reduce bias?
- How can real-world evidence be used for answering questions about clinical effectiveness and safety and for decision-making?

good procedural practices for RWE studies

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) created a task force to make recommendations regarding good procedural practices that would enhance decision-makers' confidence in evidence derived from RWD studies. They have already defined good procedural practices as policies about the planning, execution and dissemination of RWD studies [31].

real-world data are useful but appropriate methods are needed

Regarding immunotherapy for NSCLC, an exploratory analysis by **Stewart et al.** examined the ability to operationalise the collection of real-world data to explore the potential use of real-world end points extracted from data from diverse health care data organisations and to assess how these relate to similar end points in clinical trials for immunotherapy-treated advanced non-small cell lung cancer [62]. They found that although real-world data are useful to address clinically relevant questions, it is necessary to determine appropriate analytic methodologies to provide better confidence in associated findings. Moreover, **Griffith et al.** evaluated the reliability, clinical relevance and large-scale feasibility of electronic health record (EHR) data to characterise cancer progression outcomes in advanced non-small cell lung cancer. They presented an approach to yield an EHR-generated progression variable which can be incorporated into large, contemporary, real-world analyses. Data from electronic health records are not collected intentionally for research purposes and are limited by missing data, measurement error, or unmeasured confounders. Therefore, more work is needed to investigate how real-world measures relate to treatment effects observed in clinical trials [63].

methodological issues

Although methodological issues about real-world data remain, real-world evidence is necessary to investigate questions which are not addressed in clinical trials, but arise in clinical practice. **Rashdan et al**. critically discussed the way from clinical trials to real-world practice [64]. They concluded that little data regarding the safety and efficacy of anti-PD-1/anti-PD-L1 agents exists, especially in patients with poor ECOG PS, the elderly, patients with untreated asymptomatic brain metastases, patients with autoimmune diseases and patients on chronic steroids, and that broader, more inclusive eligibility criteria with large phase III clinical trials, along with retrospective studies examining drug efficacy and tolerability in real-world patient populations, are needed to fill the data gap between real-world practice and clinical trials.

tail of the survival curve of PD-1/PD-L1 checkpoint inhibitor

Zimmermann et al. discussed how to interpret the tail of the survival curve in the era of PD-1/PD-L1 Checkpoint inhibitor, as a plateau in the overall survival curve indicates that a subset of patients exhibits long-term survival. They underline that, on the one hand, it is still necessary to define subsets of patients where these agents yield sufficient efficacy, and, on the other hand, there is need for an appropriate predictive biomarker to avoid the indiscriminate administration of PD-1/PD-L1 checkpoint inhibitors [65].

Our pilot study analysing real-world data for immunotherapy in patients with NSCLC contributes to these discussions. Further research is needed to either develop methodological standards for real-world data collection and analysis, and to more and more incorporate real-world evidence into clinical decision-making.

4.4 Limitations

retrospective observational study using data from hospitals' electronic health records

The results of our study have to be interpreted with caution due to several limitations. ***First***, it was a retrospective observational study and clinically relevant data were extracted from electronic health records in hospitals which are primarily designed for oncologists to treat patients and manage clinical care. These electronic health records included structured and mainly unstructured information and vary between hospitals. There was neither a specific oncology information system including structured and comprehensive patient and tumour information nor a central data management for quality assurance available within the hospitals. These real-world data lacked complete information, e.g., on grading, relapse and tumour molecular aberration, as well as prior cancer treatment and comorbidities – information that is not always routinely and structured documented at the point of care. Furthermore, the reporting of adverse events is in the oncologist's responsibility and therefore documented in different systems. In addition, we used other data sources like medication data from the Pharmacy Department of the hospital or data from the Austrian DRG system to gather more information, but the handling of this secondary date was complex and did not add beneficial information to reach our study aim. Nevertheless, to ensure complete and valid data for our study, we predefined a specific case report form (CRF) including all relevant variables that are necessary for our analyses. Two medical students carefully extracted data from electronic health records according to our CRF and the responsible oncologist checked the corresponding documentation before transfer to our central data management unit.

small sample size in 3 cohorts

Secondly, the small size of our three cohorts is a weakness of our study. We primarily chose the year 2017 as the start for immunotherapy to ensure at least a 12-month follow-up for included patients, which was also the start of the introduction of immunotherapy in the involved hospitals. As a consequence, only a limited use of immunotherapy could be observed in 2017. However, our study was planned as a pilot study to gather experience in the handling of secondary data from routine clinical practice. Follow-up studies should involve a larger patient population.

longer follow-up needed

Thirdly, although we defined at least 12 months of follow-up for included patients and the median follow-up was 16.4 months, the recruitment period from January 2017 to June 2018 seemed to be too long to ensure an adequate duration of follow-up to estimate certain overall survival for all patients. Almost half of patients were still alive 15 months after start of immunotherapy, especially in cohort 1 and 2. In addition, against our inclusion criteria, one patient had started immunotherapy in the year 2019, resulting in less than 12 months' follow-up. Anyway, future studies should guarantee appropriate follow-up duration.

more detailed data

Fourthly, the comparison of our cohort with study populations in pivotal clinical trials was only possible for some criteria, e.g., age, ECOG, PD-L1 TPS, but could not be done for further aspects like brain metastases. These data were not available in our retrospective study. Future studies should provide more detailed patient and tumour characteristics to enable further analysis.

only 6 Austrian hospitals of 2 federal states

Fifthly, we only included six hospitals in two Austrian states which might limit the generalisability of our results to all Austrian hospitals. As the handling of electronic health records in hospitals for our project was very complex and time-consuming, and as there is a lack of structured and standardised oncologic documentation, not all hospitals were willing to participate in our study. The willingness to participate would be better if more hospitals were to use an effective and structured cancer documentation system.

no analysis of covariates

Finally, we neither performed univariate or multivariate data analysis to identify covariates nor stratified survival analysis due to the small sample sizes in subgroups. Moreover, for ORR calculation we had between 25% and 35% of patients per cohort who were not evaluable for response. As ORR refers only to patients evaluable for response, this could possibly overestimate the response rate. Further studies should address these issues.

Despite these limitations, we have demonstrated the feasibility of using hospital electronic health records for effectiveness and safety analysis of anti-PD-1/PD-L1 therapy in NSCLC patients in the Austrian hospital setting.

5 Conclusion

Our study provides important data on both effectiveness and safety for real-life NSCLC patients treated with anti-PD-1/PD-L1 therapy in six Austrian hospitals. Patients in our cohort were comparable to the populations included in clinical trials regarding stage, ECOG performance status and PD-L1 TPS. Our cohort was slightly older but still in adherence to ESMO guidelines which recommend considering immunotherapy in elderly patients, too.

important data on effectiveness and safety

Especially for second-line anti-PD-1/PD-L1 monotherapy we could show comparable median progression-free survival, but a higher response rate and longer median overall survival. In contrast, the results from pivotal clinical trials for first-line pembrolizumab monotherapy could not be confirmed in our real-world setting. Nevertheless, our results are in line with other published real-world studies. As our analyses showed wide confidence intervals, trials with larger study populations and an appropriate follow-up duration should enable a more precise estimation of overall survival. Moreover, this issue should be addressed in further trials using real-world data as pembrolizumab in first-line therapy is increasingly used in Austrian hospitals. Regarding safety, particularly for adverse events grade ≥3, our overall cohort showed a favourable safety profile.

comparable PFS and OS, higher ORR in second-line

further studies needed for first-line

In addition, our matched-pair analysis for patients with anti-PD1/PD-L1 therapy compared to historic controls from the Tyrolean Lung Cancer Project (Tyrol Study) showed a longer median overall survival for immunotherapy in the first-line comparison to platine therapy, as well as in the second-line comparison to taxane therapy. No difference was found for progression-free survival between immunotherapy and historic controls.

longer median OS for immuno-therapy compared to historic controls

In conclusion, our real-world pilot study presents clinically relevant results regarding the use of immunotherapy in routine practice and underlines the value of retrospective studies using real-world data to contribute to the generation of real-world evidence. Larger (prospective) real-life studies are needed to better understand real-world outcomes of patients treated with immunotherapy approved based on the results of conventional clinical trials with narrow eligibility criteria leading to potential deficits in external validity. A comprehensive, contemporary and more structured/standardised tumour documentation in Austrian hospitals could support the participation in such real-world studies. In addition, further research should focus on the identification of an appropriate biomarker to identify those patients who show the best benefit from immunotherapy.

clinically relevant real-world evidence

larger (prospective) real-world studies expected

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