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Lung Cancer 196 (2024) 107950

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Research Paper

Real-world overall survival after alternative dosing for pembrolizumab in the treatment of non-small cell lung cancer: A nationwide retrospective cohort study with a non-inferiority primary objective

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ARTICLE INFO

Keywords:
Pembrolizumab
Non-small cell lung carcinoma
Non-inferiority

ABSTRACT

Background: High and increasing expenses on pembrolizumab ask for more cost-effective and sustainable treatment strategies to improve affordability of healthcare. Therefore, a part of the Dutch hospitals implemented an alternative, partially lower, weight-based dosing protocol for pembrolizumab. This provided the unique opportunity to compare the overall survival (OS) of the alternative pembrolizumab dosing protocol to standard dosing using a nationwide registry in non-small cell lung cancer (NSCLC) patients.

Methods: This is a retrospective cohort study with a non-inferiority primary objective. Forty hospitals in the Dutch Medication Audit and Dutch Lung Cancer Audit treated 1966 patients with NSCLC with first line pembrolizumab (mono- or combination therapy) between Jan 1st 2021, and Mar 31st, 2023. Alternative weight-based pembrolizumab dosing (100/150/200 mg Q3W or 200/300/400 mg Q6W) was administered to 604 patients, and 1362 patients received standard pembrolizumab dosing (200 mg Q3W or 400 mg Q6W). A Cox proportional hazard model with selected covariates was used to compare the OS between alternative and standard dosing protocols. The non-inferiority margin was set at a hazard ratio (HR) of 1.2 for OS. Non-inferiority is established by showing that the upper limit of the 95 % confidence interval (CI) of the HR of OS is smaller or equal to 1.2.

Results: Distribution of age (66.7 years +/-9.4), sex (45 % female) and treatment combinations were similar for both groups, comorbidity score was higher in the standard group. Median daily dose in the alternative dosing group was 22 % lower compared to the standard dosing group, 7.14 mg/day (interquartile range

Abbreviations: NSCLC, non-small cell lung carcinoma; ICIs, Immune checkpoint inhibitors; PD-1, programmed cell death-1; OS, overall survival; Q3W, 3 weekly; Q6W, 6 weekly; NVMO, Dutch Society of Medical Oncology; DMA, Dutch Medication Audit; DLCA-L, Dutch Lung Cancer Audit – Lung Oncology; DICA, Dutch Institute for Clinical Auditing; DBC, diagnosis treatment combinations; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; TTNT-D, time to next treatment or death; RCTs, randomised controlled trials; PFS, progression-free survival.

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https://doi.org/10.1016/j.lungcan.2024.107950
Received 18 June 2024; Received in revised form 23 August 2024; Accepted 29 August 2024
Available online 30 August 2024

(IQR):5.48–8.04 mg/day) vs. 9.15 mg/day (IQR:8.33–9.52 mg/day), respectively. Alternative dosing was non-inferior to standard dosing regarding overall survival (adjusted HR 0.83, 95 %CI:0.69–1.003).
Conclusion: This large, retrospective real-world analysis supports the hypothesis that the alternative, partially lower pembrolizumab dosing protocol in NSCLC maintains treatment effectiveness while reducing treatment costs.

1. Introduction

Lung cancer has the second highest incidence of all cancer types worldwide with an estimated incidence of 2.2 million in 2020. Of all lung cancers, around 85% are non-small cell lung carcinoma (NSCLC) [1,2]. Immune checkpoint inhibitors (ICIs) are widely used as NSCLC therapy. Pembrolizumab is an ICI that targets programmed cell death-1 (PD-1) on the surface of immune cells, thereby potentiating T-cell immune response, including antitumor response, resulting in an increased overall survival (OS) and fewer adverse reactions in NSCLC compared to chemotherapy [3–5].

Nevertheless, optimal dose finding studies of pembrolizumab are lacking. For pembrolizumab, the phase I KEYNOTE-001 study had conducted a dose escalation study ranging from 0.005 mg/kg to 10mg/kg [6], the phase II/III KEYNOTE-010 study in NSCLC patients had initially been conducted using a dose of 2 mg/kg 3 weekly (Q3W) [7], but this was changed to a fixed dose of 200 mg Q3W or 400 mg 6 weekly (Q6W) in the following phase II and III studies (e.g., KEYNOTE-024 and KEYNOTE-042) [8,9], This was changed because there was no pharmacokinetic advantage for either regimen, and implementing fixed dosing would eliminate drug wastage and improve compliance [10]. Fixed dosing is currently used as the standard registered dose in Europe and United States [5,11]. A recent study argued that an alternative, partially lower, weight-based dosing protocol of pembrolizumab including vial sharing is not anticipated to compromise effectiveness or safety [12]. This alternative dosing protocol provides the opportunity for cost containment and therefore the Dutch Society of Medical Oncology (NVMO) issued recommendations to initiate alternative dosing of pembrolizumab [13]. Subsequently, a selection of Dutch hospitals has implemented this dosing protocol.

Pembrolizumab therapy is associated with substantial costs as global sales reached 25 billion USD (about 23 billion EUR) in 2023 [14], and this is projected to increase further. Consequently, this presents a challenge to healthcare affordability. Thus, the identification of a more cost-effective dosing regimen of pembrolizumab can contribute to the control of healthcare expenses.

Large studies that investigate the OS of patients with NSCLC receiving a pembrolizumab alternative dosing protocol compared to a standard dosing protocol are lacking. Therefore, we used real-world data from a Dutch Medicines Registry of NSCLC patients treated with pembrolizumab and compared OS under an alternative dosing protocol with OS stemming from the standard dosing protocol.

2. Methods

2.1. Study design and data sources

This analysis was designed as a retrospective cohort study with a non-inferiority design reusing data from a data linkage of the Dutch Medication Audit (DMA) registry and the Dutch Lung Cancer Audit – Lung Oncology (DLCA-L) registry from the Dutch Institute for Clinical Auditing (DICA). This data linkage was performed at the patient level and includes 71% of all Dutch hospitals. The DMA and DLCA-L registries provide insights into the use and real-world outcomes of systemic therapies to participating Dutch hospitals, offering a nearly complete representation of Dutch oncological lung cancer treatment. The DMA registry includes financial and administrative healthcare data of high-cost drugs and medical claims data described in diagnosis treatment combinations (DBC), these data are validated by standardised logistic tests. The DLCA-L registry is linked to the national claims database, Vektis, which is used in this study to collect the official date of death for Dutch citizens. A detailed description of the dataset construction and linkage of DMA and DLCA-L are described elsewhere [15–17]. In compliance with Dutch regulations, no patient informed consent or formal ethical approval were necessary for secondary use of the data collected in the DICA quality registries.

2.2. Study population

All patients with a new diagnosis of NSCLC with at least one prescription of pembrolizumab between January 1st 2021, and March 31st, 2023 were identified from the DMA registry (details on the identification from the medical claims data are described in Table S1). Only patients who received pembrolizumab as first line-NSCLC therapy with standard care treatment combinations following the Dutch Guideline Database were included: i.e., pembrolizumab monotherapy, cis- / carboplatin + pemetrexed + pembrolizumab, or combination therapy with carboplatin + paclitaxel + pembrolizumab [18]. Following this guideline, only stage IIIB and IV NSCLC patients receive these first line therapies [18]. In order to reliably establish the start date of first line therapy, all patients referred from other hospitals were excluded.

2.3. Alternative or standard dosing

From 2021 onwards, 21 Dutch hospitals implemented a pembrolizumab alternative dosing protocol as described in Table 1, which was endorsed by the NVMO [13]. Patients from hospitals that had implemented alternative pembrolizumab dosing were included in the alternative dose group. Patients from these hospitals who initiated pembrolizumab treatment prior to the implementation date of alternative dosing protocol were excluded. Patients from hospitals that did not implement pembrolizumab alternative dosing prior to March 31st, 2023 were included in the standard dose group. The alternative dosing protocol has been increasingly implemented in hospitals from 2021. Consequently, the follow-up duration in the alternative dosing group is shorter, as some hospitals implemented alternative dosing in 2022 and therefore inclusion started in 2022, whereas patient inclusion in the standard dosing group started in 2021.

Hospitals confirmed whether they had implemented the alternative dosing protocol and, if so, when that implementation had taken place. In case no response from a hospital could be collected, or in case the dosing protocol diverged from the protocol outline in Table 1, patients from these hospitals were excluded.

Table 1
Alternative dosing and standard dosing protocols of pembrolizumab for 3 weekly (Q3W) and 6 weekly (Q6W) dosing.

	Alternative dosing		Standard dosing
	Weight	Dose (mg)	Dose (mg)
Q3W	< 65 kg	100	200
	65–90 kg	150	
	≥ 90 kg	200	
Q6W	< 65 kg	200	400
	65–90 kg	300	
	≥ 90 kg	400	

2.4. Endpoints

Overall survival was measured from time of initiation of pembrolizumab treatment to death due to any cause. Patients were censored on the date of last activity in the medical claims data or on the cut-off date (31st of March 2023). If the last activity date was more than six months before the end of the observation period, and no date of death was observed, patients were lost to follow-up on the date of their last activity in medical claims data and censored at that date. The six-month period was determined based on an internal validation.

2.5. Disease characteristics

The comorbidity score was assessed at baseline (initiation of the first pembrolizumab treatment) and was determined using the medical claims database comorbidity score, as defined in Table S2. This comorbidity score is based on the Charlson Comorbidity Index, with several changes that were implemented by the DMA registry to make it more suited for medical claims database analyses.

2.6. Non-inferiority margin

The choice of the non-inferiority margin was based on a power analysis based on the number of included patients, ensuring that the margin is as tight as possible. Furthermore, the margin is the largest difference that can be judged as being clinically acceptable and is smaller than differences observed in superiority trials [19,20]. This analysis contained 1966 individual patients with at least one pembrolizumab prescription, of whom 604 in the alternative dosing group. The one-sided α was set at 0.025, the power at 80%, and the probability of death after two years was estimated at 0.6 for both groups. Therefore, non-inferiority would be established if the upper limit of the 95% confidence interval (CI) for the hazard ratio (HR) of OS of alternative dose versus standard dose was smaller or equal to 1.2.

2.7. Statistical analysis

The distribution of demographic characteristics of patients was described using descriptive statistics. Age is presented as both mean and standard deviation, as well as the median with the minimum and maximum values. Categorical variables are presented as numbers and percentages. The median daily dose per patient was calculated from the dosing regimens, based on dispensed doses of medical claims data, to assess the reduction in dosing for the alternative dosing protocol. Categorical baseline variables were compared with a chi square test, age with an independent samples *t*-test, and follow-up and daily dose with the Mann-Whitney *U* test. A Kaplan Meier analysis was used to assess unadjusted OS for both groups. A Cox proportional hazard model was used to evaluate the association between pembrolizumab dosing groups and OS while controlling for the following covariates: age, sex, treatment-combinations, and comorbidity score. A p-value < 0.05 was considered to be statistically significant. Alternative dosing was considered non-inferior if the confidence interval did not overlap with the pre-established non-inferiority margin. The proportional hazards assumption was tested using the Schoenfeld residuals test.

3. Results

3.1. Study population

Forty-five hospitals delivered data and provided pembrolizumab treatment in NSCLC patients. Two hospitals were excluded since the dosing protocol could not be established, two hospitals were excluded because they implemented a different pembrolizumab dosing protocol than stipulated in Table 1, and one hospital was excluded because the dose registration In the administrative data did not allow accurate dose calculation. In total, 1966 patients were included, 604 patients were included from the 21 hospitals that adopted pembrolizumab alternative dosing protocols and 1362 patients were included from the 19 hospitals using standard dosing protocols, as shown in the flow diagram in Fig. 1.

Baseline characteristics of patients who were included are displayed in Table 2. Overall, distribution of baseline characteristics was similar between treatment groups in terms of age, sex, and treatment combination, although patients who received the alternative dose of pembrolizumab had a significantly lower comorbidity score. Academic hospitals were overrepresented in the alternative dosing group. The median follow-up was lower in the alternative dosing group compared to the standard dosing group, 4.9 and 7.3 months respectively. Second-line treatment (chemotherapy, immunotherapy, targeted therapy, or a combination therapy) was administered to 14.6% of the alternative dosing group and 16.7% of the standard dosing group ($p = 0.27$). The number of events (deaths) after 24 months was 144 in the alternative group and 537 in the standard dosing group. Censoring due to loss to follow-up was the same in both alternative and standard dosing groups (both 5%).

3.2. Pembrolizumab dose

The median daily dose was calculated in order to determine the distribution in dosing schemes, shown in Fig. S1. The median daily dose in the alternative dosing group was 22.0% lower compared to the standard dosing group ($p < 0.001$), 7.14 mg/day (interquartile range (IQR): 5.48–8.04 mg/day), versus 9.15 mg/day (IQR: 8.33–9.52 mg/day). Two of these alternative dosing hospitals did not implement vial sharing. Since only 100 mg vials are available, vial sharing is needed for 150 mg. Consequently, pembrolizumab dose could not be calculated as medical claims data were used, leading to the exclusion of these data from the dose per treatment group calculations only.

3.3. Overall survival

Overall survival did not differ between dosing groups, with a median survival of 18.1 months (95% CI: 15.4–23.0 months) in the alternative dosing group vs. 15.2 months (95% CI: 14.2–17.2 months) in the standard dosing group. The adjusted HR for alternative dosing was 0.83 (95% CI: 0.69–1.003), establishing non-inferiority as the 95% CI fell entirely within the pre-defined non-inferiority margin of 1.2. The unadjusted HR for alternative dosing was similar to the adjusted HR: 0.83 (95% CI: 0.69–1.002). Fig. 2 displays the OS for both treatment groups and Table 3 describes the results of the multivariable Cox regression model. In addition to OS, median time to next treatment or death (TTNT-D) was calculated as a surrogate endpoint which reflects duration of therapeutic benefit and tolerability of the treatment (shown in Fig. S2) [22].

The Schoenfeld residuals test pointed towards a possible violation of proportional hazards caused by the covariate treatment combinations. Additional Kaplan-Meier survival analyses for different treatment combinations showed no severe crossing of the survival curves (Fig. S3), leading to the conclusion that the proportional hazard assumption was not violated.

4. Discussion

This real-world data analysis from a large Dutch registry is the first study which reports the impact on OS after implementing alternative pembrolizumab dosing in the treatment of NSCLC patients in a large population (n=1966). The implementation of the alternative dosing protocol resulted in a reduction in median daily dose per patient of 22%. Importantly, OS after pembrolizumab alternative dosing in the treatment of NSCLC patients was non-inferior to that after a standard dosing protocol. Therefore, these retrospective data suggest that the alternative pembrolizumab dosing protocol in NSCLC has no impact on treatment

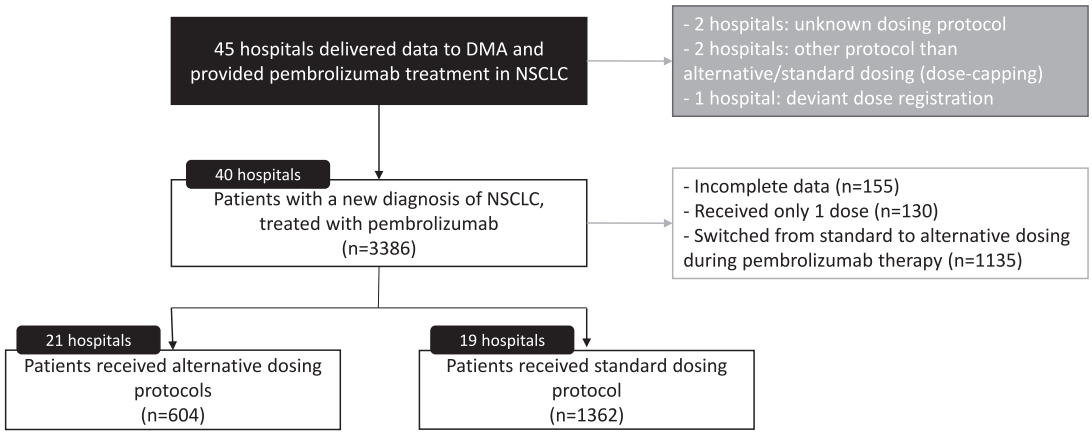

Fig. 1. Study flow diagram of patients included in the alternative dosing or standard dosing group. DMA=Dutch Medication Audit, NSCLC=non-small cell lung carcinoma.

Table 2
Patient characteristics of patients with pembrolizumab alternative and standard dose. Data are numbers (%) unless indicated otherwise.

	Alternative dose (n=604)	Standard dose (n=1362)	p-value
Mean (SD) age (years)	66.3 (9.41)	66.9 (9.43)	0.161
Median [Min, Max] age (years)	67.0 [32.0, 86.0]	68.0 [22.0, 92.0]	
Female	275 (45.5%)	616 (45.2%)	0.940
Treatment combination			
Carboplatin + paclitaxel + pembrolizumab	95 (15.7%)	208 (15.3%)	0.864
Cis-/carboplatin + pemetrexed + pembrolizumab	346 (57.3%)	798 (58.6%)	
Pembrolizumab monotherapy	163 (27.0%)	356 (26.1%)	
Comorbidity score			
<5	217 (35.9%)	390 (28.6%)	0.002
≥5	387 (64.1%)	970 (71.2%)	
Missing	0 (0%)	2 (0.1%)	
Hospital type			
General	225 (37.3%)	1284 (94.3%)	<0.001
Academic	379 (62.7%)	78 (5.7%)	
Median [IQR] follow-up (months)	4.9 [2.6-9.6]	7.3 [3.8-13.3]	<0.001
Median (95% CI) follow-up (months)	4.9 (4.5-5.6)	7.3 (6.9-7.9)	

SD=standard deviation; IQR=interquartile range; CI=confidence interval.

effectiveness while reducing treatment costs. Although no analysis was conducted to compare safety and tolerability of pembrolizumab alternative dosing protocols, it is not probable that a lower dose would lead to a different risk of toxicity, as toxicity is not dose dependent between 1 mg/kg Q2W and 10mg/kg Q2W [6].

Our study supports the hypothesis from Malmberg *et al.* that current doses of pembrolizumab are probably higher than needed for maximum effectiveness and the alternative dosing regimen would maintain effectiveness [12], which was based on previous modeling and simulation studies that reported that pembrolizumab's maximum efficacy plateaus for doses 2 mg/kg to 10 mg/kg [10,22–25]. On top of these modeling findings, exposure–response observations in early phase pembrolizumab studies showed that the efficacy and toxic effects of pembrolizumab is similar between 2 mg/kg up to 10 mg/kg Q3W [6,7]. A complete target saturation was observed at doses of 1 mg/kg Q3W [6,24]. Furthermore, in four retrospective observational studies also no difference was shown in OS between reduced dosing (2 mg/kg Q3W / 4 mg/kg Q6W/100mg Q3W) and standard dosing (200 mg Q3W / 400 mg Q6W) [27–29]. However, these studies had a smaller reduced dosing group: n=64, n=36, n=138, n=95 of which three studies in an Asian population with lower average weight than our Dutch population.

The median OS of pembrolizumab monotherapy in our study for alternative and standard dosing was 23.0 months (95% CI: 19.0 – not reached) and 22.1 months (17.9 – not reached), as also displayed in Fig. S3. This is numerically lower than the median OS observed in a comparable population (pembrolizumab monotherapy in advanced NSCLC patients) in the KEYNOTE-024 study (median OS = 26.3 months (95% CI: 18.3–40.4)) [4]. Although there is still overlap in the confidence intervals, this numerical difference can most likely be attributed to differences in patient and disease characteristics (*e.g.* higher median age in our study: 67.0 years vs 64.5 years in KEYNOTE-024) between the randomised trial and this real-world population [4].

This analysis utilised medical claims real-world data (DMA), linked to DLCA-L. There are several strengths and limitations that are associated with this RWD design compared to randomised controlled trials (RCTs). First, the external validity of this analysis is high, since no patient selection was performed, which is a typical strength of real-world data analyses. Furthermore, the burden on the healthcare system associated with this analysis was minimal, since existing medical claims data were used rather than new data being collected specifically for this analysis.

There are also a few limitations to be considered when interpreting the results of this analysis. Firstly, distribution of several patient characteristics was different between the two treatment groups, as reported in Table 2, and therefore a multivariate analysis was used to control for these differences. Although the reported HR was adjusted for several other covariates, the analysis could not be adjusted for covariates that may influence OS, such as performance status, presence of brain metastases, and weight. This is a limitation of our study, as the alternative dosing group is overrepresented in the academic hospitals, which could result in an unequal distribution of unknown covariates. However, we expect the impact on the main results to be limited, since we could control for important confounders (age, sex, comorbidity score, treatment combinations) and, besides that, the Dutch health care system has no healthcare disparities resulting in equal access and re-imbursement for all patients. Furthermore, the lower median follow-up time in the alternative dosing group can be attributed to a delayed inclusion of patients. Because this discrepancy in follow-up times is unrelated to the OS, it is unlikely that it has influenced the results of this analysis. Although difference in follow-up durations could impact the results if non-proportional hazards are present, we did not observe any deviation from the Cox proportional hazards assumption, which largely mitigates concerns about confounding from time-dependent effects. Lastly, our dataset does not include progression-free survival (PFS) data, which is an important primary endpoint. The PFS is time-consuming to register and cannot be automatically extracted. However, we determined the TTNT-D (Fig. S2), which may serve as a proxy for PFS and showed no

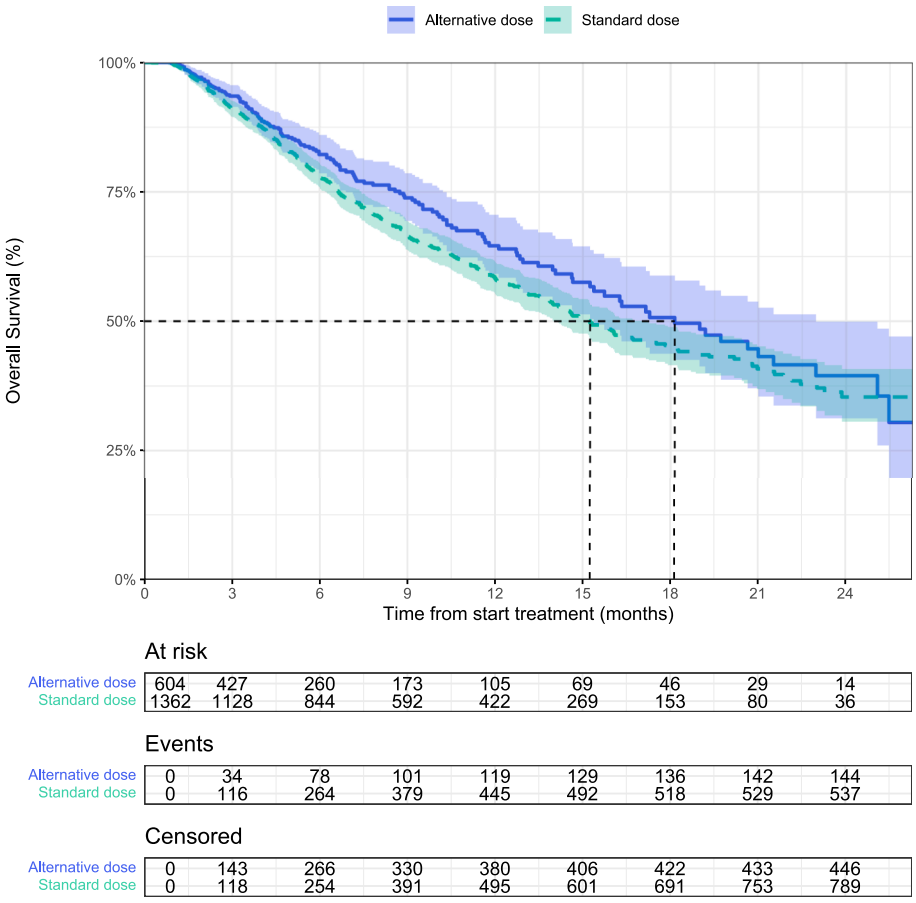

Fig. 2. Kaplan-Meier of the overall survival for alternative and standard dosing protocol.

Table 3
Multivariable Cox Regression model results.

	Adjusted HR	95 %CI	P-value
Dosing protocol: Alternative dose vs. standard dose	0.83	0.69–1.003	0.053
Age (per 10 years)	1.02	0.93–1.12	0.686
Sex male	1.34	1.15–1.57	<0.001
Treatment combination: Cis- / carboplatin + pemetrexed + pembrolizumab vs. Carboplatin + paclitaxel + pembrolizumab	1.04	0.84–1.29	0.699
Treatment combination: Pembrolizumab monotherapy vs. Carboplatin + paclitaxel + pembrolizumab	0.80	0.62–1.02	0.072
Comorbidity score: ≥5	0.96	0.79–1.17	0.710

Dependent variable: overall survival. HR=hazard ratio, CI=confidence interval.

differences between the groups.

The true impact of alternative dosing pembrolizumab on costs is highly dependent on the actual implementation of alternative dosing, including vial sharing. In Europe and the United States, pembrolizumab is currently available in 100 mg vials only [5,11], after the production of 50 mg vial was halted. Consequently, multiple pharmacies in The Netherlands have started sharing vials between patients, where three 100 mg vials are shared between two patients receiving 150 mg pembrolizumab. No data in this analysis were collected to accurately investigate the impact of alternative dosing on costs, as this also depends on confidential price discounts. However, it is expected that this reduction of 22% in median dose results in about a potential ±22% reduction in costs, which is in line with the institutional cost savings of 22.8% of alternative dosing Q6W vs standard dosing Q6W, calculated by Malmberg et al. [12]. This corresponds to several tens of millions of euros in the Netherlands [31], and billions of euros when extrapolated to other countries and indications [14].

Data from registries, such as DMA, offer an opportunity to assess real-world effectiveness after implementation of new treatment protocols among hospitals. While RCTs are the cornerstone of evidence-based medicine, the importance of real-world evidence is getting recognition and promotion as it can be complementary to RCTs [32–33]. Optimal dosing regimens of anti-cancer drugs are often not known at time of authorisation [35], and down titration steps to manage tolerability issues are usually recommended in the Summary of Product Characteristics. The responsibility for investigating these crucial aspects is frequently shifted to clinicians, therefore fit-for-purpose RWD to generate real-world evidence can be an efficient approach to define optimal dosing rules. It will be important for future research to add relevant data on covariates, exposure, and outcomes to the registry to increase the robustness of the generated real-world evidence.

Furthermore, the present analysis supports the uptake of alternative pembrolizumab dosing in the treatment of NSCLC. Since pembrolizumab has multiple indications, it is worth investigating the impact of alternative dosing of pembrolizumab in other indications as well, especially as it is assumable the outcome of alternative dosing would be the same in other tumor types, since a flat dose–response relationship was also observed in advanced melanoma. Moreover, this is supported by the mechanism of action of pembrolizumab, targeting immune cells and not the tumor cells itself [10].

5. Conclusions

Our results suggest that alternative, partially lower pembrolizumab dosing in NSCLC patients is a more cost-effective dosing strategy than the standard dosing protocol since it maintains treatment effectiveness while reducing treatment costs. Secondary use of real-world data analytics has the potential to identify cost-effective treatment strategies by comparing different dosing protocols as used in clinical practice.

CRediT authorship contribution statement

Geeske F Grit: Writing – original draft, Methodology, Investigation. **Esmée van Geffen:** Writing – review & editing, Methodology, Formal analysis. **Ruben Malmberg:** Writing – review & editing. **Roelof van Leeuwen:** . **Stefan Böhringer:** Writing – review & editing, Methodology. **Hans JM Smit:** Writing – review & editing. **Pepijn Brocken:** Writing – review & editing. **Job FH Eijsink:** Writing – review & editing. **Esther Dronkers:** Writing – review & editing, Methodology. **Pim Gal:** Writing – original draft, Methodology. **Eva Jaarsma:** Writing – review & editing, Formal analysis. **Regine JHM van Drie-Pierik:** Writing – review & editing. **Anne MP Eldering-Heldens:** Writing – review & editing. **AN Machteld Wymenga:** . **Peter GM Mol:** Writing – review & editing. **Juliëtte Zwaveling:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Doranne Hilarius:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [**Ruben Malmberg** has received payment for lectures from BMS. **Roelof van Leeuwen** has received grants from BMS and Pfizer, consulting fees from BMS, MDS, Pfizer, Pierre Fabre, AstraZeneca, and Roche, and payment for presentations and attending meetings from AstraZeneca. **Hans Smit** is a member on the advisory board of BMS and MSD and is a member representative of the Dutch scientific committee for pulmonary disease (no payments involved). **Juliëtte Zwaveling** has received a grant from AstraZeneca. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper].

Acknowledgements

G. Grit's and P. Mol's work on this study is funded by the European Union's Horizon Europe Research and Innovation Actions under grant no. 101095479 (More-EUROPA). Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union nor the granting authority. Neither the European Union nor the granting authority can be held responsible for them. We would like to thank the participating hospitals for making the data available for this analysis and their valuable input.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2024.107950.

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