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Comparison of flat-dose versus weight-based dose nivolumab treatment in NSCLC patients.

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Abstract

Background/Objectives: Nivolumab is currently widely used in the treatment of lung cancer. Studies have been conducted using flat doses of 240 mg and 3 mg/kg. In fact, studies involving a small number of patients have begun to explore low-dose immunotherapies. The literature on the optimal dose of immunotherapy, the use of weight based, or fixed doses is very recent and has become a one of the subject of ongoing research.

Methods: This multicenter study included 716 patients with NSCLC. Patients receiving standard doses of 3 mg/kg and 240 mg of nivolumab

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were divided into subgroups based on their weight. Patients weighing 80 kg have already received a flat dose. However, patients weighing < 80 kg who received a flat dose were considered to be receiving high-dose therapy. Conversely, patients weighing more than 80 kg who received a flat dose were maintained on a low dose. Therefore, overall survival, progression-free survival, and toxicity were examined according to weight-based usage.

Results: The median progression free survival (PFS) for those receiving a 3 mg/kg dose was 6 months, whereas it was 9.8 months for those receiving a flat dose ($p<0.001$). The median (metastatic overall survival) OS for those receiving a 3 mg/kg dose was 12 months, whereas it was 14 months for those receiving a 240 mg dose ($p=0.03$).

Conclusion: This study was based on real-world data. Therefore, our results may be instructive regarding the nivolumab dose, which is a commonly used treatment for NSCLC patients. Our results suggest that a flat dose may be preferred in all groups and as a subgroup, especially in patients weighing <80 kg.

***Keywords**:* Non-small cell lung cancer, Flat dose, Weight based, Standard dose, Survival, Nivolumab

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INTRODUCTION

Nivolumab was first introduced as a PD-1 inhibitor in 2014 (1). Especially in advanced non-small lung cancer (NSCLC), survival is extremely low, and 5-year survival rates are around 13% (2). Therefore, novel therapies,

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including immunotherapies, are being developed. In a study reported in Germany, the survival rate after nivolumab was stated to be 22% (3). Nivolumab is now a widely used treatment, both because lung cancer is a fatal and aggressive disease and because of the good treatment responses (4).

In the dosage studies of nivolumab, doses of 1, 3, and 10 mg/kg were initially used. Virtually similar efficacy was observed at the 3 and 10 mg/kg doses. Subsequently, Feng et al. suggested that side effects are more common at 10 mg/kg, whereas flat doses of 3 mg/kg and 240 mg may have similar effects (5). Another study conducted in 2017 compared flat doses of 3 mg/kg. However, Zhao et al. included diverse types of cancer, such as renal cell carcinoma, head and neck cancer, melanoma, and NSCLC. It was considered that nivolumab clearance increased with body weight, but toxicity increased at higher weights. The results suggested that the flat dose and the 3 mg/kg dose had similar efficacy (6).

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Subsequently, a flat dose of 3 mg/kg was administered to the patients with NSCLC. Patients weighing 80 kg have already received a flat dose. However, patients weighing < 80 kg who received a flat dose were considered to be receiving high-dose therapy. Conversely, patients weighing more than 80 kg who received a flat dose were maintained on a low dose. Therefore, in our study, we aimed to retrospectively examine the effect of flat and 3 mg/kg doses on the survival of patients with NSCLC.

MATERIAL AND METHODS

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Data Collection

This was a multicenter retrospective study. Eighteen centers from all regions of Türkiye were included in the study. As these centers are located across all areas of the country, they represent a diverse range of patient profiles and provide real-world data. Between February 2020 and September 2024, 716 patients with NSCLC received nivolumab therapy. The use of nivolumab at a dose of 3 mg/kg every two weeks in NSCLC was demonstrated in the CheckMate 057 and 017 studies (4,7). In September 2016, the FDA approved the dosage of nivolumab to 240 mg every two weeks for renal cell carcinoma, metastatic melanoma, and NSCLC (8).The decision to use 3 mg/kg or 240 mg depends on the physician. However, there were almost the same number of patients in both groups. The number of patients using a flat dose was 382, whereas the number of patients using 3 mg/kg was 334.

The inclusion criteria were receiving nivolumab treatment for metastatic NSCLC and an age range of > 18 years. Most of the patients' treatments were second-line metastatic due to coverage by national health insurance During the period when the study was planned and conducted in Türkiye, nivolumab was covered by second-line health insurance for patients with advanced NSCLC. Currently, chemotherapy and immune checkpoint inhibitors (ICI) combinations are also used in our country, starting from July 2025. However, as mentioned, during the period when the study was conducted, ICI could be used alone as a second-line treatment. EGFR, ALK, and ROS mutations were ruled out in all patients. No prior immunotherapy has been administered in our patient cohort. Platinum-

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based chemotherapy was used in the first-line setting. A total of 52.6% of our patients received paclitaxel in combination with platinum, 20.7% received pemetrexed, and 21.2% received gemcitabine. Furthermore, 5.5% received vinorelbine in the first-line setting. Our patients did not have active brain metastases. Corticosteroids were not used concurrently (Figure 1).

Patients who discontinued follow-up or treatment or were under 18 years of age, who had concurrent active malignancies, were excluded from the study. Patient comorbidities and medications, side effects after nivolumab, disease progression times, and survival were analyzed retrospectively using the hospital file system.

Disease Evaluation (Response Assessment)

Patients underwent pre-treatment imaging using computed tomography (CT) or positron emission tomography (PET-CT). Each institution performed imaging at 3-month intervals in accordance with protocols to understand disease progression. Progression was determined according to the Immune Response Evaluation Criteria in Solid Tumors (iRECIST).

The development and management of adverse events in patients were performed according to the Common Terminology Criteria for Adverse Events (CTCAE 5.0).

Outcome Measures

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The primary endpoint of this study was metastatic overall survival (OS). OS was defined as the time between the date of death and the start of treatment and was calculated in months. Patients who were still alive at the time of the analysis were censored at their last follow-up. The secondary endpoint was defined as metastatic progression-free survival (OS). PFS was defined as the interval between the date of progression and the start of the treatment.

Patients without progression at the data cutoff were censored at their most recent follow-up. Follow-up times were estimated using the reverse Kaplan-Meier method.

Ethical Approval

This study received ethical approval, including a waiver of informed consent owing to its retrospective nature, from the Erciyes University Health Sciences Research Ethics Committee (Decision Number: 2025/211). All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Declaration of Helsinki, as revised in 2024.

Data Classification

Our patient received nivolumab treatment for metastatic NSCLC. Patients were evaluated according to whether they received a 3 mg/kg or a flat dose of 240 mg. Survival was assessed according to the patients' weight, body surface area, and body mass index.

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Statistical analysis

Study analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Descriptive data of the patients are presented as numbers and percentages (n, %). PFS was calculated from the date of nivolumab treatment initiation. Progression during nivolumab treatment was accepted according to the iRECIST criteria. PFS and OS were calculated in months. It was calculated by subtracting the date of nivolumab initiation from the date of death. For patients who were still alive during the analysis, the data were censored at their last follow-up.

The estimated PFS and OS curves were obtained using the Kaplan-Meier method and the log-rank test was performed for group comparisons. Statistical significance was set to $p < 0.05$. Univariate and multivariate Cox regression analyses were used to analyze the risk factors affecting PFS and OS.The hazard ratio (relative risk) was obtained by taking the 95% confidence interval, and a p-value of 0.05 was considered statistically significant. Variables found to be statistically significant at $p<0.05$ in the univariate analysis were included in the multivariate analyses. A stepwise backward selection method was used to identify independent risk factors at a precision level of $p<0.10$.

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RESULTS

As shown in Table 1, 716 patients were included in this study. Forty-six percent of the patients were aged 65 years or younger, whereas 53.4%

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were over 65 years of age. The majority of patients were male (87.3%), with a female-to-male ratio of 12.7%. When the distribution of diagnoses was examined, the most common histopathological subtype was squamous cell carcinoma at 46.3%, followed by adenocarcinoma (44.4%). Other diagnoses included invasive carcinoma not otherwise specified (3.2%), adenosquamous carcinoma (3.2%), and different types (9.1%). In terms of smoking history, 39.5% of the patients were active smokers, 44.2% were ex-smokers, and 16.3% had never smoked.

PFS was evaluated in all patients regardless of weight. The PFS for those receiving a 3 mg/kg dose was 6 months (95% CI, 4.7–7.6), whereas it was 9.8 months (95% CI, 7.2–12.3) for those receiving a flat dose ($p<0.001$) (Figure 2). Similarly, when looking at OS, the OS for those receiving a 3 mg/kg dose was 12 months (95% CI, 9–14.9), while it was 14 months (95% CI, 10.8–17.1) for those receiving a 240 mg dose ($p=0.03$) (Figure 3).

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When examining PFS by weight, the PFS of patients weighing ≥80 kg who received 3 mg/kg was 5.9 months, whereas the PFS of patients who received a flat dose of 240 mg was 10.2 months ($p=0.144$). In patients weighing less than 80 kg, PFS was 5.7 months in those receiving 3 mg/kg and 8.4 months in those receiving 240 mg ($p<0.001$) (Figure 4). When considering OS based on weight, the OS of patients weighing ≥80 kg who received 3 mg/kg was 14 months, whereas the OS of patients who received a flat dose of 240 mg was 17 months ($p=0.08$). In patients weighing less than 80 kg, the OS was 11 months for those receiving 3

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mg/kg and 14 months for those receiving 240 mg (p=0.03) (Figure 5). As shown in the table 2, there was no difference in toxicity between the 3 mg/kg dose and the flat dose (p=0.052). Grade 2 or 3 toxicity was observed in 9% and 12.2% of patients receiving 3 mg/kg and a flat dose, respectively. No statistically significant difference was observed in the side effect profile between patients receiving 3 mg/kg and those receiving a flat dose. Thyroiditis was observed in 6% of our patients, fatigue in 5%, thyroiditis in 2.5%, rash or dermatopathy in 2.2%, anemia, thrombocytopenia, or neutropenia in 1%, and myalgia or myopathy in 1.3%.

In the Cox regression analysis PFS, hazard ratios were interpreted relative to the predefined reference categories indicated in Table 3. In the univariate analysis, ECOG performance status, lactate dehydrogenase (LDH), number of metastatic sites, and nivolumab dose were significantly associated with PFS. Specifically, patients with better performance status (ECOG 0–1 vs. ECOG 2, HR=0.63, 95% CI: 0.49–0.81, p<0.001), normal LDH levels (<ULN vs. ≥ULN, HR=0.79, 95% CI: 0.66–0.96, p=0.02), a single metastatic site (1 vs. ≥1, HR=0.73, 95% CI: 0.60–0.90, p=0.003), and those receiving a flat dose of nivolumab (240 mg vs. 3 mg/kg, HR=0.72, 95% CI: 0.57–0.85, p<0.001) had a significantly lower risk of progression compared to their respective reference groups. In the multivariate analysis, ECOG performance status (HR=0.64, 95% CI: 0.49–0.83, p=0.001), LDH (HR=0.77, 95% CI: 0.64–0.94, p=0.01), number of metastatic sites (HR=0.77, 95% CI: 0.62–0.95, p=0.01), and nivolumab dose (HR=0.71, 95% CI: 0.59–0.86, p<0.001) remained independent

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predictors of PFS. Importantly, a hazard ratio below 1 indicates a reduced risk of progression compared to the reference category. Accordingly, the flat-dose nivolumab regimen (240 mg) was associated with a significantly lower risk of disease progression compared to the weight-based 3 mg/kg regimen. These findings are consistent with the Kaplan–Meier analysis, which demonstrated longer PFS in patients receiving the flat dose.

For OS, hazard ratios were similarly interpreted according to the specified reference categories in Table 4. In the univariate analysis, ECOG performance status, LDH, albumin level, metastatic site number, and nivolumab dose were associated with OS. Patients with better performance status (ECOG 0–1 vs. ECOG 2, HR=0.46, 95% CI: 0.35–0.59, p<0.001), normal LDH levels (<ULN vs. ≥ULN, HR=0.72, 95% CI: 0.59–0.88, p=0.002), higher albumin levels (≥4 g/dL vs. <4 g/dL, HR=0.66, 95% CI: 0.54–0.80, p<0.001), and fewer metastatic sites (1 vs. ≥1, HR=0.80, 95% CI: 0.65–0.98, p=0.03) demonstrated a lower risk of death. In the multivariate analysis, ECOG performance status (HR=0.48, 95% CI: 0.36–0.63, p<0.001), LDH (HR=0.74, 95% CI: 0.60–0.91, p=0.005), and albumin level (HR=0.67, 95% CI: 0.53–0.83, p<0.001) remained independent predictors of OS. In addition, nivolumab dose was associated with OS (HR=0.83, 95% CI: 0.66–1.03, p=0.03), indicating a reduced risk of death in patients receiving the flat dose compared to the 3 mg/kg regimen. Although the effect size for nivolumab dose was more modest for OS compared to PFS, the direction of the association remained consistent, favoring the flat-dose regimen. This is in line with

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the Kaplan–Meier curves, which also demonstrated longer OS in the flat-dose group.

DISCUSSION

NSCLC is a common and deadly cancer (9); therefore, current drugs and immunotherapies are being investigated for treatment (10). Though nivolumab is frequently administered, studies on its dosage and efficacy are limited (11). Studies are currently underway to determine which patients benefit most from immunotherapy (12). It has been found that the clearance and distribution volume of nivolumab increase with increasing body weight, but the increase is not proportional. Body weight-based dosing may lead to higher exposure in obese patients with higher body weight (13). Conversely, it is unclear whether a flat dose results in higher exposure in lighter patients (14).

When comparing 3 mg/kg and 240 mg in all our patients without stratification by weight, the OS was 12 and 14 months, respectively, and the flat dose may be significantly superior. Regarding PFS, a statistically significant difference was observed, with 6 months versus 9.8 months. Therefore, when considering the entire patient group, the flat dose may superior to in terms of both the PFS and OS. Zhao et al.(6) compared flat doses and 3 mg/kg doses in patients with renal cell carcinoma, melanoma, and NSCLC. Of the 647 patients with a median body weight of 77 kg, 647 were assigned to the NSCLC group. Zhao et al.(6) the flat and 3 mg/kg doses were found to be similar. In our study, however, there were more patients, and the flat dose may be more specific.

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Nivolumab treatment is calculated based on weight. Therefore, the patients weighing 80 kg had already received a flat dose. Hence, patients weighing 80 kg and above, as well as those weighing 80 kg, were evaluated. When considering patients weighing 80 kg or less(< 80 kg), the PFS ranged from 5.7 to 8.4 months, with a statistically significant difference between the 3 mg/kg and 240 mg doses, respectively. In the same group, OS is 11 months versus 14 months. There was statistically significant difference in the OS. Based on this result, if our patients weighed less than 80 kg, the treatment response may be lower when treatment was administered according to weight. Therefore, a flat dose may be preferred.

Bei et al. (15) compared 240 mg and 3 mg/kg in a study conducted in Japan. The average body weight in Japan is lower, at approximately 60 kg. However, Japanese study evaluated hematological and solid cancers. A flat dose was similarly found to be effective in patients who are underweight.

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When evaluated in reverse, the 3 mg/kg and 240 mg doses were compared in patients with ≥80 kg. PFS was 5.9 months and 10.2 months, respectively, while the OS was 14 months and 17 months, respectively. Although this difference was not statistically significant, the numerical difference was quite considerable. Therefore, physicians may prefer 3 mg/kg or a flat dose in this group. Consequently, there was no need for doses higher than 240 mg. The flat dose is may be cost-effective and easy to use.

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A probable reason for not observing a difference in OS when classified by weight ≥80 kg may be that most of our patients received second-line nivolumab treatment. During the data collection period, nivolumab was covered by health insurance in the second line of our country. Another limitation of our study is that efficacy was assessed without considering PDL-1 status, cachexia status, and the study was retrospective. All these factors may affect clearance. Also, although the distribution of groups and patient numbers in our study are similar, the retrospective nature of our study and the lack of randomization in the distribution are limiting factors. Nevertheless, our hypothesis regarding immunotherapy doses contributes to the literature. Therefore, further studies are required (16).

However, when we looked at PS, the risk of death may significantly reduced in patients with a good PS score, high albumin levels, and those receiving a flat dose of nivolumab. Similarly, nivolumab may provided more prolonged survival in patients with a good PS, less metastatic disease, and those receiving a flat dose of nivolumab.

This study was based on real-life data. A large number of patients from multiple centers were evaluated. Therefore, our results may be instructive regarding the nivolumab dose, which is a commonly used treatment in NSCLC patients. In our results, a flat dose may be preferred in all groups and as a subgroup, especially in patients weighing <80 kg. A flat dose eliminates the need for precise dose calculations, making it easier to use. It may be cost-effective, especially for patients weighing 80

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kg or more. However, these studies were retrospective. Prospective studies are needed to confirm these findings.

In a study conducted by Yoo et al. (17), doses of 3 mg/kg were compared to doses of 20 mg and 100 mg. However, the study included only 47 patients, which was a relatively small sample size. The objective response rate was 13.8% at low doses and 16.7% at a dose of 3 mg/kg. Therefore, even low doses of immunotherapies may be effective. However, Yoo et al. (17) study was incomplete due to its small sample size, retrospective nature, and lack of dose standardization.

In conclusion, the efficacy of immunotherapy at standard and lower doses is emerging in recent studies. However, studies comparing flat doses or 3 mg/kg doses only in NSCLC patients are still limited. A flat dose may be preferred in all groups, particularly in patients weighing <80 kg. No significant differences in toxicity were observed. Similarly, PS, flat-dose administration, albumin level, and number of metastatic sites may be independent prognostic predictors of prolonged OS.

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Disclosures/conflict of interests

None declared.

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Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Consent for Publication

All authors have read and approved the final version of the manuscript.

Authors' Contributions

O.B. and M.C. are the coordinators of this study; they designed the study protocol. M.O., M.I, U.K, D.C, M.E, S.K, İ.O.K, D.B., D.C.G, M.U, M.B, T.S, N.M., E.M.O, C.A., A.N.C., M.E, E.S, P.C.S, B.U, E.K, G.A, E.K, E.T, S.Y, B.M.E, A.K, H.A, M.M.K, S.B, H.Y.C, and L.K, A.E.A.R. made the mandatory requirements for the study. M.C., A.N.C., O.B., U.K., D.V., E.B., D.B., M.U., R.C., T.S., E.M.O., M.E., E.S., P.C.S., B.U., E.K., G.A., E.T., S.Y., B.M.E., A.K., H.A., M.M.K., S.B., and H.Y.C. were responsible for data collection. M.C. and O.B. were responsible for data collection and statistical analysis, designing figures and tables, and interpreting the results. M.C. and O.B. wrote this manuscript. The final manuscript was revised collaboratively by M.I., M.O., M.C., and O.B.

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REFERENCES

1. Beaver JA, Theoret MR, Mushti S, He K, Libeg M, Goldberg K, et al.

ARTICLE IN PRESS

FDA approval of nivolumab for the first-line treatment of patients with BRAFV600 wild-type unresectable or metastatic melanoma. Clin Cancer Res. 2017;23(14):3479–83.

2. Woodard GA, Jones KD, Jablons DM. Lung cancer staging and prognosis. Cancer Treat Res. 2016;170:47–75.

3. Tzschoppe T, Ohlinger J, Vordermark D, Bedir A, Medenwald D. Population based study on the progress in survival of primarily metastatic lung cancer patients in Germany. Sci Rep [Internet]. 2024;14(1):1–10. Available from: https://doi.org/10.1038/s41598-024-66307-3

4. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. N Engl J Med. 2015;373(2):123–35.

5. Feng Y, Wang X, Bajaj G, Agrawal S, Bello A, Lestini B, et al. Nivolumab exposure–response analyses of efficacy and safety in previously treated squamous or nonsquamous non–small cell lung cancer. Clin Cancer Res. 2017;23(18):5394–405.

6. Zhao X, Suryawanshi S, Hruska M, Feng Y, Wang X, Shen J, et al. Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. Ann Oncol. 2017;28(8):2002–8.

7. Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M, et al. Nivolumab versus docetaxel in previously treated patients with

ARTICLE IN PRESS

advanced non-small-cell lung cancer: Two-year outcomes from two randomized, open-label, phase III Trials (CheckMate 017 and CheckMate 057). J Clin Oncol. 2017;35(35):3924–33.

8. U.S. Food and Drug Administration. Modification of the Dosage Regimen for Nivolumab [Internet]. U.S. Food and Drug Administration; 2016. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/modification-dosage-regimen-nivolumab

9. Zhou J, Xu Y, Liu J, Feng L, Yu J, Chen D. Global burden of lung cancer in 2022 and projections to 2050: Incidence and mortality estimates from GLOBOCAN. Cancer Epidemiol [Internet]. 2024;93(July):102693. Available from: https://doi.org/10.1016/j.canep.2024.102693

10. Brahmer JR, Tykodi SS, Chow LQM, Hwu W-J, Topalian SL, Hwu P, et al. Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer. N Engl J Med. 2012;366(26):2455–65.

11. Rajan A, Kim C, Heery CR, Guha U, Gulley JL. Nivolumab, anti-programmed death-1 (PD-1) monoclonal antibody immunotherapy: Role in advanced cancers. Hum Vaccines Immunother [Internet]. 2016;12(9):2219–31. Available from: http://dx.doi.org/10.1080/21645515.2016.1175694

12. Disli SY, Ayas E, Disli AK, Ozdemir F. Prognostic Value of Inflammatory and Nutritional Index in Advanced Stage Non-Small Cell Lung Cancer Patients Treated with Nivolumab in Second-Line

ARTICLE IN PRESS

Therapy. UHOD - Uluslararasi Hematol Derg. 2024;34(2):68–73.

13. Zhao X, Shen J, Ivaturi V, Gopalakrishnan M, Feng Y, Schmidt BJ, et al. Model-based evaluation of the efficacy and safety of nivolumab once every 4 weeks across multiple tumor types. Ann Oncol Off J Eur Soc Med Oncol. 2020 Feb;31(2):302–9.

14. Souza IADA, Dobbert BDM, Jose BGS, Homse-netto JP, Furlan LL. Low-Dose Anti-PD (L) 1 for the Treatment of Solid Malignancies. Immunotherapy [Internet]. 2024;10(L):e2400122. Available from: https://doi.org/10.1200/GO.24.00122

15. Bei D, Osawa M, Uemura S, Ohno T, Gobburu J, Roy A, et al. Benefit-risk assessment of nivolumab 240 mg flat dose relative to 3 mg/kg Q2W regimen in Japanese patients with advanced cancers. Cancer Sci. 2020;111(2):528–35.

16. Kumar A, Kapoor A, Noronha V, Patil VM, Joshi A, Menon N, et al. Efficacy and Safety of Low-Dose Nivolumab in Treatment of Advanced Solid Tumors: A Retrospective Audit from Resource-Constrained Settings. South Asian J Cancer. 2024;70–6.

17. Yoo SH, Keam B, Kim M, Kim SH, Kim YJ, Kim TM, et al. Low-dose nivolumab can be effective in non-small cell lung cancer: Alternative option for financial toxicity. ESMO Open. 2018;3(5):1–8.

Table 1. Characteristics of participants according to Nivolumab dose

Variables			**Total (*n*=716)**	***p*-value**
	3 mg/kg *n*=334(%)	**Flat dose *n*=382 (%)**		
Smoking No	52(15.8)	61(16.7)	113(16.3)	0.70

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Yes	282(84.2)	321(83.3)	603(83.7)	
Age (years) <65 ≥65	 184(55.1) 150(44.9)	 214(56) 168(44)	 334(46.6) 382(53.4)	 0.81
Gender Female Male	 52(15.6) 282(84.4)	 39 (10.2) 343(89.8)	 91(12.7) 625(87.3)	 0.06
ECOG performance status 0-1 2	 287(86) 47(14)	 323(87.4) 59(12.6)	 610(86.8) 106(13.2)	 0.58
Metastatic site 1 >1	 246(73.7) 88(26.3)	 286(74.9) 96(25.1)	 532(74.5) 184(25.5)	 0.71
Brain Metastasis No Yes	 269(80.5) 65(19.5)	 303(87.6) 79 (12.4)	 572(79.9) 144(20.1)	 0.68
Lactate dehydrogenase (LDH)[a] <ULN ≥ULN	 209(61.6) 125(38.4)	 233(61.6) 149(38.4)	 442(79.9) 274(20.1)	 0.90
Body Mass Index < 25 ≥ 25	 182(54.5) 152(45.5)	 188(49.2) 194(50.8)	 370(51.7) 346(48.3)	 0.1

Values are expressed as n (%). ECOG: Eastern Cooperative Oncology Group; a: Upper limit of reference range: 250 U/L; ULN: Upper limit of normal.
Statistically significant *p* values are shown in bold.

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Table 2. Adverse effects according to nivolumab dose

Variables			***p*-value**
	3 mg/kg *n*=334(%)	**Flat dose *n*=382 (%)**	
Grade 0-1	304 (91)	333 (87.1)	0.09
Grade 2-3	30 (8.9)	49 (12.8)	

Values are expressed as n (%). Mg: Milligram. Kg: kilogram.
Statistically significant *p* values are shown in bold.

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Table 3. Univariate and multiple Cox regression analysis of variables for PFS

Variables	Univariate		Multiple	
	HR (95%CI)	***p*-value**	**HR (95%CI)**	***p*-value**
Smoking Yes (ref) No	1.06(0.82-1.38)	0.73		
Age (years) ≥65 (ref) <65	1.01 (0.84-1.21)	0.91		
Weight **<**80 kg (ref) ≥80 kg	0.81 (0.63-1.05)	0.10		
Sex Male (ref) Female	0.82 (0.64-1.01)	0.21		
ECOG performance status 2 (ref) 0-1	0.63 (0.49-0.81)	**<0.001**	0.64 (0.49-0.83)	**0.001**
Lactate dehydrogenase (LDH)[a] <ULN (ref) ≥ULN	0.79 (0.66-0.96)	**0.02**	0.77 (0.64-0.94)	**0.01**
Albumin <4g/d (ref) ≥4g/d	1.07 (0.88-1.28)	0.40		
Metastatic sites ≥1 (ref) 1	0.73 (0.60-0.90)	**0.003**	0.77 (0.62-0.95)	**0.01**
Nivolumab dose 3 mg/kg (ref) 240 mg	0.72(0.57-0.85)	**<0.001**	0.71 (0.59-0.86)	**<0.001**

CI: Confidence interval; HR: Hazard ratio; PFS: Progression-free survival; ECOG PS: Eastern Cooperative Oncology Group performance status; mg: milligram; kg: kilogram. a: Upper limit of reference range: 250 U/L; ULN: Upper limit of normal. Statistically significant p values are shown in bold.

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Table 4. Univariate and multiple Cox regression analysis of variables for OS.

Variables	**Univariate**		**Multiple**	
	HR (95%CI)	***p*-value**	**HR (95%CI)**	***p*-value**
Age (years) ≥65 (ref) <65	0.96 (0.83-1.21)	0.94		
Smoking No (ref) Yes	0.77 (0.57-1.03)	0.08		
Sex Male (ref) Female	0.80 (0.60-1.07)	0.36		
Weight **<**80 kg (ref) ≥80 kg	0.79 (0.62-1.00)	0.06		
ECOG performance status 0-1 (ref) 2	0.46 (0.35-0.59)	**<0.001**	0.48 (0.36-0.63)	**<0.001**
Lactate dehydrogenase (LDH)[a] <ULN (ref) ≥ULN	0.72 (0.59-0.88)	**0.002**	0.74 (0.60-0.91)	**0.005**
Albumin <4g/d (ref) ≥4g/d	0.66 (0.54-0.80)	**<0.001**	0.67(0.53-0.83)	**<0.001**
Metastatic sites 1 (ref) ≥1	0.80 (0.65-0.98)	**0.03**	0.83 (0.66-1.03)	0.10
Nivolumab dose 3 mg/kg (ref) 240 mg	0.81 (0.67-0.99)	**0.04**	0.83(0.66-1.03)	**0.03**

CI: Confidence interval; HR: Hazard ratio; PFS: Progression Free Survival; ECOG PS: Eastern Cooperative Oncology Group performance status; mg: milligram; kg: kilogram. a: Upper limit of reference range: 250 U/L; ULN: Upper limit of normal; Statistically significant p values are shown in bold.

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FIGURE LEGENDS

Figure 1 The study population obtained in the registration database**.**

Figure 2. Kaplan-Meier curves of PFS according to the dose

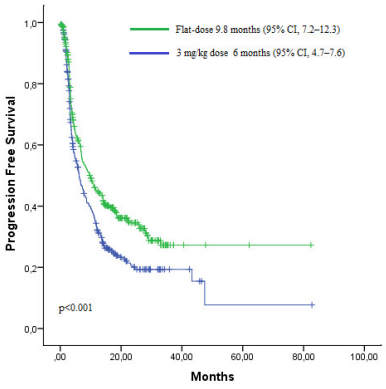
Figure 3. Kaplan-Meier curves of OS according to the dose

Figure 4. Kaplan-Meier curves of PFS according to the weight and dose.

Figure 5. Kaplan-Meier curves of OS according to the weight and dose.

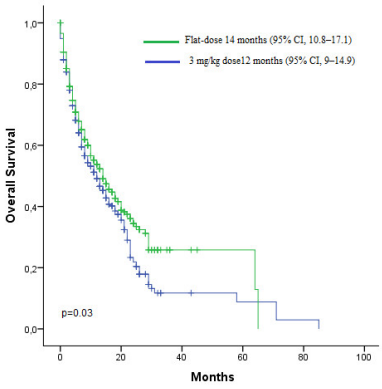
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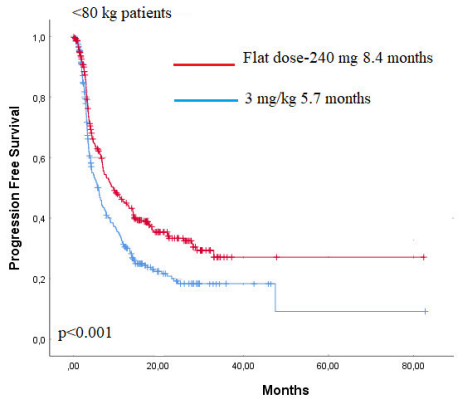
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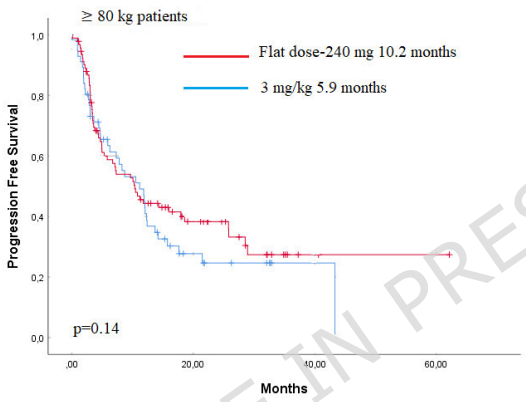
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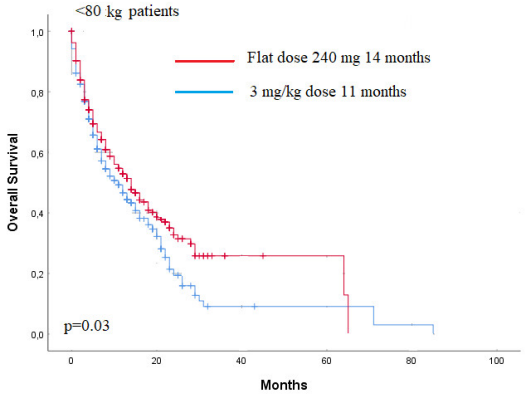
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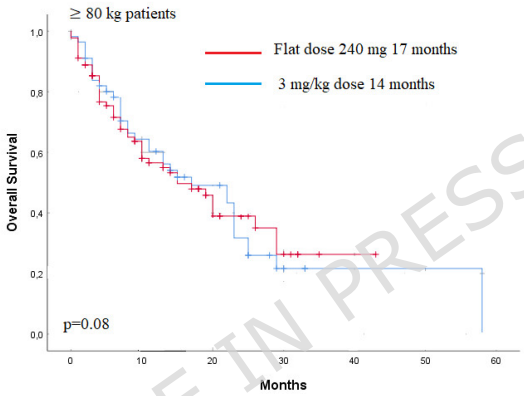




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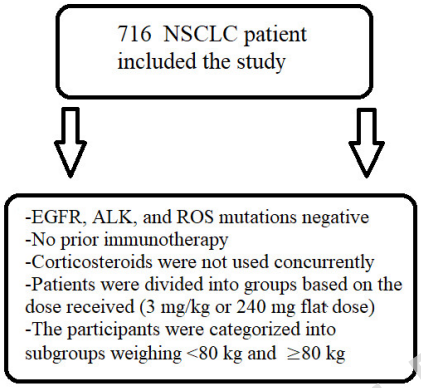
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Table 2. Adverse effects according to nivolumab dose

Variables			***p*-value**
	3 mg/kg *n*=334(%)	**Flat dose *n*=382 (%)**	
Grade 0-1	304 (91)	333 (87.1)	0.09
Grade 2-3	30 (8.9)	49 (12.8)	

Values are expressed as n (%). Mg: Milligram. Kg: kilogram.
Statistically significant *p* values are shown in bold.

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Table 3. *Univariate and multiple Cox regression analysis of variables for PFS*

Variables	**Univariate**		**Multiple**	
	HR (95%CI)	***p*-value**	**HR (95%CI)**	***p*-value**
Smoking				
Yes	1.00	-		
No	1.0 (0.8-1.3)	0.69		
Age (years)				
≥65	1.00	-		
<65	1.0 (0.8-1.2)	0.83		
Weight				
<80 kg	1.00	-		
≥80 kg	0.8 (0.7-1.0)	0.10		
Sex				
Male	1.00	-		
Female	0.8 (0.6-1.0)	0.21		
ECOG performance status	1.00	-	1.00	-
2	0.6 (0.4-0.8)	**<0.001**	0.6 (0.4-0.8)	**0.001**
0-1				
Lactate dehydrogenase (LDH)[a]	1.00	-	1.00	-
<ULN	0.7 (0.6-0.9)	**0.02**	0.7 (0.6-0.9)	**0.01**
≥ULN				
Albumin	1.00	-		
<4g/d	1.0 (0.8-1.2)	0.40		
≥4g/d				
Metastatic sites	1.00	-	1.00	-
≥1	0.7 (0.6-0.9)	**0.003**	0.7 (0.6-0.9)	**0.01**
1				
Nivolumab dose	1.00	-	1.00	-
240 mg	1.4 (1.1-1.6)	**<0.001**	1.4 (1.1-1.6)	**<0.001**
3 mg/kg				

CI: Confidence interval; HR: Hazard ratio; PFS: Progression-free survival; ECOG PS: Eastern Cooperative Oncology Group performance status; mg: milligram; kg: kilogram. a: Upper limit of reference range: 250 U/L; ULN: Upper limit of normal. Statistically significant p values are shown in bold.

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Table 4. *Univariate and multiple Cox regression analysis of variables for OS.*

Variables	**Univariate**		**Multiple**	
	HR (95%CI)	***p*-value**	**HR (95%CI)**	***p*-value**
Age (years)				
≥65	1.00	-		
<65	0.9 (0.8-1.2)	0.94		
Smoking				
No	1.00	-		
Yes	0.7 (0.5-1.0)	0.08		
Sex				
Male	1.00	-		
Female	0.8 (0.6-1.1)	0.36		
Weight				
<80 kg	1.00	-		
≥80 kg	0.8 (0.64-1.0)	0.07		
ECOG performance status	1.00	-	1.00	-
0-1	0.4 (0.35-0.59)	**<0.001**	0.4 (0.3-0.6)	**<0.001**
2				
Lactate dehydrogenase (LDH)[a]	1.00	-	1.00	-
<ULN	1.3 (1.1-1.6)	**0.002**	0.7 (0.6-0.9)	**0.005**
≥ULN				
Albumin	1.00	-	1.00	-
<4g/d	0.6 (0.54-0.8)	**<0.001**	1.4 (1.2-1.8)	**<0.001**
≥4g/d				
Metastatic sites				
1	1.00	**-**	1.00	
≥1	1.2 (1.0-1.5)	**0.03**	0.8 (0.6-1.0)	0.10
Nivolumab dose				
3 mg/kg	1.00	-	1.00	-
240 mg	0.8 (0.6-0.9)	**0.03**	1.2 (1.0-1.5)	**0.03**

CI: Confidence interval; HR: Hazard ratio; PFS: Progression Free Survival; ECOG PS: Eastern Cooperative Oncology Group performance status; mg: milligram; kg: kilogram. a: Upper limit of reference range: 250 U/L; ULN: Upper limit of normal; Statistically significant p values are shown in bold.

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Table 1. Characteristics of participants according to Nivolumab dose

Variables			Total (*n*=716)	*p*-value
	3 mg/kg *n*=334(%)	Flat dose *n*=382 (%)		
Smoking				
No	52(15.8)	61(16.7)	113(16.3)	0.70
Yes	282(84.2)	321(83.3)	603(83.7)	
Age (years)				
<65	184(55.1)	214(56)	334(46.6)	0.81
≥65	150(44.9)	168(44)	382(53.4)	
Gender				
Female	52(15.6)	39 (10.2)	91(12.7)	0.06
Male	282(84.4)	343(89.8)	625(87.3)	
ECOG performance status	287(86)	323(87.4)	610(86.8)	0.58
0-1	47(14)	59(12.6)	106(13.2)	
2				
Metastatic site				
1	246(73.7)	286(74.9)	532(74.5)	0.71
>1	88(26.3)	96(25.1)	184(25.5)	
Brain Metastasis				
No	269(80.5)	303(87.6)	572(79.9)	0.68
Yes	65(19.5)	79 (12.4)	144(20.1)	
Lactate dehydrogenase (LDH)[a]	209(61.6)	233(61.6)	442(79.9)	0.90
<ULN	125(38.4)	149(38.4)	274(20.1)	
≥ULN				
Body Mass Index				
< 25	182(54.5)	188(49.2)	370(51.7)	0.1
≥ 25	152(45.5)	194(50.8)	346(48.3)	

Values are expressed as n (%). ECOG: Eastern Cooperative Oncology Group; a: Upper limit of reference range: 250 U/L; ULN: Upper limit of normal.
Statistically significant *p* values are shown in bold.

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