Arrival Date: 18.08.2023 | Published Date: 30.09.2023 | Vol: 8, Issue: Özel Sayı | pp: 678-684 | Doi Number: http://doi.org/10.5281/zenodo.8402529

THE ASSOCIATION BETWEEN SERUM VITAMIN D LEVEL AND EFFICACY OF NIVOLUMAB TREATMENT IN PATIENTS WITH ADVANCED NSCLC

KÜÇÜK HÜCRE DIŞI AKCİĞER KANSERİ OLGULARINDA SERUM VİTAMİN D DÜZEYİ VE NİVOLUMAB TEDAVİSİNİN ETKİNLİĞİNİN İLİŞKİSİ

Oktay ÜNSAL [1], Ozan YAZICI [1]

[1] Gazi University, Faculty of Medicine, Ankara, Türkiye

ABSTRACT

Objective: Vitamin D is known to be associated with better responses and prognosis positively proportional to serum levels in patients with non–small cell lung cancer (NSCLC). The goal of this report was to examine the association between serum Vitamin D levels and efficacy of Nivolumab treatment in patients with metastatic NSCLC.

Methods: A total of 38 patients with a diagnosis of metastatic NSCLC, received Nivolumab immunotherapy in the second-line therapy were enrolled in the study. Clinical and demographic data and also the levels of 25 hydroxy vitamin D (25(OH)D) that were analyzed before starting Nivolumab treatment were recorded. The association between the vitamin D and progression free survival (PFS) and overall survival (OS) was analyzed. Statistical evaluation was done using SPSS 23.

Results: The median 25(OH)D level of the patients was found as 17.3 (3-37) ng/ml. When the PFS of patients were evaluated according to vitamin D status, PFS of the patients with 25(OH)D ≥20 ng/ml was longer than other groups that was not significant (p= 0.17).

Conclusion: Achievement longer PFS with sufficient vitamin D supports the fact that higher baseline vitamin D levels are associated with better Nivolumab efficacy in metastatic NSCLC patients.

Keywords: 25-hydroxy vitamin D, Nivolumab, Non–small cell lung cancer.

ÖZET

Amaç: D vitamininin serum düzeyleri ile pozitif yönde orantılı olarak küçük hücre dışı akciğer kanseri (KHDAK) olan hastalarda daha iyi yanıt ve prognoz ile ilişkili olduğu bilinmektedir. Bu yazının amacı, metastatik KHDAK'li hastalarda serum D vitamini seviyeleri ile Nivolumab tedavisinin etkinliği arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Metastatik KHDAK tanılı, ikinci basamak tedavide Nivolumab immünoterapisi alan toplam 38 hasta çalışmaya dâhil edildi. Klinik ve demografik veriler ile Nivolumab tedavisine başlamadan önce analiz edilen 25(OH)D düzeyleri kaydedildi. Vitamin D seviyeleri ile progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) arasındaki ilişki analiz edildi. İstatistiksel değerlendirme SPSS 23 kullanılarak yapıldı.

Bulgular: Hastaların ortanca 25(OH)D düzeyi 17.3 (3-37) ng/ml olarak bulundu. Hastaların PFS'leri vitamin D düzeyine göre değerlendirildiğinde, 25(OH)D düzeyi ≥20 ng/ml olan hastaların PFS'si istatistiksel olarak anlamlı olmayan düzeyde diğer gruplara göre daha uzundu (*p*= 0,17).

Sonuç: Yeterli vitamin D seviyeleri ile daha uzun PFS elde edilmesi, daha yüksek bazal vitamin D seviyelerinin metastatik KHDAK hastalarında daha iyi Nivolumab etkinliği ile ilişkili olduğu gerçeğini destekler.

Anahtar Kelimeler: 25-hidroki vitamin D, Küçük hücre dışı akciğer kanseri, Nivolumab

Sorumlu Yazar / Corresponding Author: Oktay ÜNSAL, Dr, Department of Medical Oncology, Gazi University Faculty of Medicine, Ankara, Türkiye. **E-mail:** oktayunsal@uludag.edu.tr

Bu makaleye atıf yapmak için / Cite this article: Ünsal, O., & Yazıcı, O. (2023). The Association Between Serum Vitamin D Level and Efficacy of Nivolumab Treatment in Patients with Advanced NSCLC. *Gevher Nesibe Journal of Medical & Health Sciences*, 8 (Özel Sayı), 678-684. http://doi.org/10.5281/zenodo.8402529

INTRODUCTION

Lung cancer is a well-known cause of cancer-related mortality (Liu et al., 2023). Non-small cell lung cancer (NSCLC) is the most frequent subtype of lung cancer that causes both mortality and morbidity. Advacements in cancer therapeutics have led to markedly improved overall survival (OS) (Reck et al., 2022). Recently, programmed death ligand 1 (PD-L1) or programmed death 1 (PD-1) inhibitors that members of the immune checkpoint inhibitors (ICIs) have beeen discovered as important treatment options (Liu et al., 2023).

After came in use, PD-L1/PD-1 inhibitors have provided significant clinical response and long-term OS (Gettinger, 2018; Reck, 2021; Spigel, 2022). Immune checkpoint inhibitors act on and destroy the tumor cells using the PD-L1/PD-1 pathway and as a result they reactivate effector T cells (Boussiotis, 2016). Nowadays, after approval of ICI-monotherapy as second- or first-line treatment, studies have focused on effective treatment strategies with ICI to improve outcomes (Brahmer, 2015; Herbst, 2016; Rittmeyer, 2017; Socinski, 2018; West, 2019). Nivolumab, a PD-1 antibody, is one of the ICIs that acts by blocking ligand interaction and downstream signaling pathway (Cusato et al., 2019). It has been found be associated with overall response rate of approximately 20% in patients with previously treated NSCLC (Brahmer, 2015; Borghaei, 2015).

Vitamin D, an immunomodulatory, may induce apoptosis of cancer cells which is important for cancer therapy (Ness et al., 2015). The vitamin D receptor (VDR) exists in many tumor tissues (Dimitrov et al., 2017). Excess levels of vitamin D leads to up-regulation of VDR (Kim et al., 2012). As a result, anti-proliferative and pro differentiating effects of vitamin D comes out. Menezes et al. (2008) stated that decreased VDR expression has been seen in many types of metastatic malignancies (Menezes et al., 2008). Furthermore, Singh et al. demonstrated that VDR mRNA is excess in malignant lung, pancreatic and ovarian tissues and associated with poor prognosis (Singh et al., 2020). Also, using vitamin D pills prolonged the OS in lung carcinoma (Samet et al., 2009). Where as Zhou W et al. (2005) demonstrated that Vitamin D is related to improved survival in early-stage NSCLC patients, they (2007) also stated that higher serum vitamin D levels have a better prognosis than patients with reduced vitamin D serum levels (Zhou, 2005; Zhou, 2007).

The goal of this report was to analyze the association between serum Vitamin D levels and efficacy of Nivolumab treatment in patients with advanced NSCLC.

MATERIALS AND METHODS

Patients

The patients with a diagnosis of metastatic NSCLC, followed up by Department of Medical Oncology between January 2022 and June 2023 were evaluated retrospectively. Among these patient population, patients progressed after first-line platinum-based chemotherapy treatment and patients received Nivolumab immunotherapy in the second-line therapy were included in further evaluation. Patients with bone metastases, taking vitamin D or calcium replacement, with history of targeted and immune checkpoint inhibitor therapy, and those with endocrine or metabolic disease associated with secondary osteoporosis, such as multiple myeloma, chronic renal failure, primary hyperparathyroidism, hyperthyroidism, and connective tissue disease have been excluded from the study. Consequently, a total of 38 patients, met the criterias of the study were evaluated in this report.

Data collection

The levels of 25(OH)D that were analyzed before starting Nivolumab treatment were noted. Vitamin D levels were categorized according to Medicine Institute Criteria; patients with 25(OH)D <10 ng/ml was stated as vitamin D deficiency, 25(OH)D between 10–20 ng/ml was stated as vitamin D insufficiency and 25(OH)D ≥ 20 ng/ml was stated as sufficient (Ross et al., 2011). Demographic data such as gender, age and clinical data such as histopathological subtype of cancer, presence of prior systemic therapy, PD-L1 expression level were examinated.

In the study, progression free survival (PFS) and OS also were evaluated. Where as OS was stated as the time between start of nivolumab treatment and last visit or death of the patients, PFS was stated as the time between start of treatment and disease progression, last visit, or patient death whichever comes first.

Nivolumab was infused intravenously at a dose of 3 mg/kg every 2 weeks over a 60-minute period. In case of withdrawal of consent, disease progression, unacceptable toxicity, or death, treatment was stopped.

Statistical evaluation

Statistical evaluation was done using the SPSS software version 23. Presence of normal distribution examined by using both visual and analytical methods. While nonnormally distributed quantitative variables such as age, vitamin D levels were stated with median values (min-max), qualitative variables such as gender, NSCLC pathologic subtype, classification of vitamin D status, presence of PD-L1 expression, history of systemic therapy were expressed as proportions. To test the OS and PFS with Nivolumab usage, Kaplan-Meier method was used. The *p* value <0.05 is stated as a statistically significant.

RESULTS

A total of 38 patients with median age of 67 years (52-82) were examined in the study. The most of the patients were male (86.8%). Some demographic and clinical characteristics of the patients are demonstrated in Table 1. Adenocarcinoma was the most frequent pathologic subtype (63.2%).

The median 25(OH)D of the population was found as 17.3 (3-37) ng/ml. Classification of the patients according to 25(OH)D levels are shown in Table 1. Also, treatment that received as a first line therapy and status of PD-L1 expression of the patients are demonstrated in Table 1..

Table 1. Some demographic and clinical characteristics of the patients

Parameters		**Results**
Age, years		67 (52-82)
Gender, n/%	Male	33 (86.8)
	Female	5 (13.2)
NSCLC pathologic subtype, n (%)	Adenocarcinoma	24 (63.2)
	Squamous cell carcinoma	14 (36.8)
25(OH)D (ng/mL), n (%)	<10	11 (29)
	10–20	13 (34.2)
	≥20	14 (36.8)
PD-L1 expression, n (%)	Negative	12 (31.6)
	1% - 49%	20 (52.6)
	≥50%	6 (15.8)
Presence of prior systemic therapy, n (%)	Cisplatine	20 (52.6)
	Carboplatine	18 (47.3)
	Pemetrexed	14 (36.8)
	Paclitaxel	12 (31.6)
	Gemcitabine	12 (31.6)

NSCLC: Non–small-cell lung cancer
25(OH)D: 25 hydroxy vitamin D

Median PFS of the patient population was found as 4.9 months (95% CI 2.5-7.2) (Figure 1). When we evaluated the PFS of patients according to vitamin D status, PFS of the patients with 25(OH)D ≥20 ng/ml was longer than other groups that was not significant (*p*= 0.17) (Figure 2).

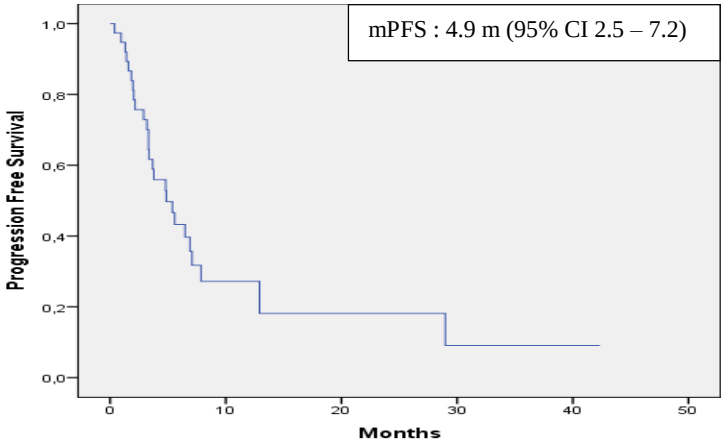

Figure 1. PFS of the study population

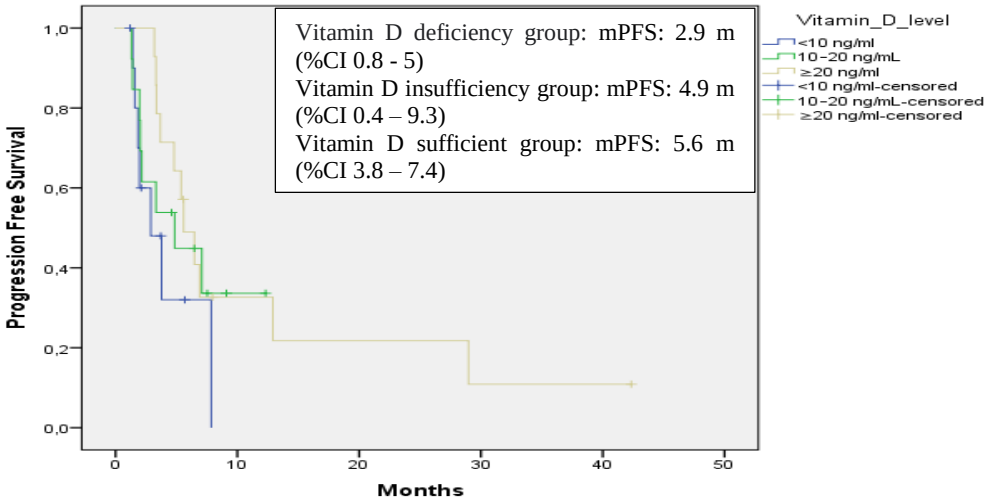

Figure 2. PFS according to 25(OH)D status of the patients

When the PFS and OS of the patients were evaluated based on the PD-L1 expression levels; median PFS was 2.2 months (95% CI 1.3 - 6.85) in the PD-L1 negative group, Also, median PFS was found as 6.5 months (95% CI 1.5 - 11.5) in the group with PD-L1 expression between 1-50 (p=0.09). Although there was a numerical difference between these two groups, it was not statistically significant. The median OS of Nivolumab in the PD_L1 expression negative group was 6.4 months (95% CI 1.8 to 13.5). PD-L1 expression in groups 1-50, median OS data was still immature. In the group with PD-L1 level ≥50% (6 patients), the median value has not yet been reached for both PFS and OS data.

During the follow-up period, 15 patients (39.4%) died. Because of this reason, data of OS is immature. Folllow up of other patients continues. In addition, 12 patients of them are still taking Nivolumab treatment.

DISCUSSION

This study represents the association between the vitamin D status of the patients and Nivolumab efficacy in patients with metastatic NSCLC. We evaluated some demographic, clinical data, and also PFS and OS of the patients. Data of OS immature but when we examinate PFS it was seen that PFS of the patients with sufficient vitamin D levels was longer than other groups which is not statistically significant. Our finding was consistent with literature (Samet, 2009; Zhou, 2005; Zhou, 2007). There are few studies in the literature on this subject. This may also be the first study on this subject in Turkey.

Nivolumab, one of the ICIs, is a monoclonal antibody and it acts by blocking PD-L1 ligand interaction. This action results in positive regulation of T-cell function and also results in antitumor effects (Tykodi, 2018; Alsaab, 2017). A meta-analysis demonstrated significant advantages with ICI usage in terms PFS and OS, compared with conventional chemotherapy in patients with advanced

NSCLC disease (Khan et al., 2018). In our country, according to health communique, Nivolumab usage is supported as a second- line therapy. Due to this economical issue, in our study all patients had a history of systemic therapy.

Vitamin D is a known important immunomodulatory agent (Cusato et al., 2019). Its level is usually low in patients with malignancy. Bochen et al. showed in their study that vitamin D levels were significantly lower in patients with a diagnosis of head and neck cancer patients than controls (Bochen et al., 2018). Many studies examined the association between low 25(OH)D and negative findings in lung cancer. Feng et al. showed a statistically significant association between 25(OH)D and lung cancer risk, and mortality (Feng et al., 2017).

Pathogenesis of vitamin D and immunomodulatory effect is controversial. Vitamin D receptor is known to be upregulated in many malignant cells. Although many studies showed that the adipose tissue overexpressed VDR in colorectal cancers, some studies demonstrated that VDR expression in tumor cells is associated with better prognosis and treatment response (Castellano-Castillo, 2018; Kim, 2012; Hendrickson 2011). You et al (2023) examinated 77 patients with a diagnosis of advanced lung cancer in their prospective cohort study. They showed that baseline 25(OH)D of partial response patients were significantly higher than patients not response (You et al., 2023). Furthermore, OS was significantly longer in patients with higher vitamin D levels. In our study we could not evaluate OS of the patients but PFS was longer in patients with sufficient 25(OH)D. This finding was not statistically significant that might be associated with small size of our population. Based on these finding, it was thought that measurement of vitamin D before starting the treatment and especially in cases with serum vitamin D <10 ng/ml, supplementation might improve the survival rate in cancer patients. Akiba et al (2018) evaluated 155 NSCLC patients and they found that vitamin D supplementation might have positive effects on survival of patients with early-stage NSCLC with lower 25(OH)D (Akiba et al., 2018).

The limitations of the study; it was a retrospective study that may asssociated with bias. Furthermore, OS was immature and could not be evaluted. We analyzed vitamin D levels before the start of the first Nivolumab rather than each Nivolumab. Because Nivolumab usage is supported in the second line of therapy in our country, patient were treated with different chemotherapeutic agents firstly. So, patient population was heterogenous that may be related to weakness of our study. Further studies with longer period and bigger patient population will enlighten the science by giving valuable information.

CONCLUSION

Our report showed that patients with higher vitamin D levels at the beginning first Nivolumab treatment was associated with longer PFS. This finding may suggest assesment of baseline vitamin D and giving supplementation to increase Nivolumab efficacy. This finding should be support with larger studies.

Author Contributions

Plan, design: OÜ, OY; Materials, methods, and data collection: OÜ, OY; Analysis and interpretation: OÜ, OY; Writing and critical assessment: OÜ, OY.

Conflict of interest

There is no conflict of interest to declare in this study.

Funding

This study was not financially supported.

REFERENCES

Akiba, T., Morikawa, T., Odaka, M., Nakada, T., Kamiya, N., Yamashita, M.,… Urashima, M. (2018). Vitamin d supplementation and survival of patients with non-small cell lung cancer: a randomized, double-blind, placebo-controlled trial. *Clin Cancer Res an Off J Am Assoc Cancer Res* 24(17):4089–4097.

Alsaab, H.O., Sau, S., Alzhrani, R., Tatiparti, K., Bhise, K., Kashaw, S.K., Iyer, A.K. (2017). PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: Mechanism, combinations, and clinical outcome. *Front. Pharm.*, *8*, 561.

Bochen, F., Balensiefer, B., Korner, S., Bittenbring, J.T., Neumann, F., Koch, A.,…Linxweiler, M. (2018). Vitamin D deficiency in head and neck cancer patients-prevalence, prognostic value and impact on immune function. *Oncoimmunology*, *7*, e1476817.

Borghaei, H., Paz-Ares, L., Horn, L., Spigel, D.R., Steins, M., Ready, N.E.,...Brahmer, J.R. (2015). Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*; 373: 1627–1639.

Boussiotis V.A. (2016). Molecular and biochemical aspects of the PD-1 checkpoint pathway. N Engl J Med ; 375:1767–1778.

Brahmer, J., Reckamp, K.L., Baas, P., Crinò, L., Eberhardt, W.E.E., Poddubskaya, E.,... Spigel, D.R. (2015). Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. *N. Engl. J. Med.* 373, 123–135.

Castellano-Castillo, D., Morcillo, S., Clemente-Postigo, M., Crujeiras, A.B., Fernandez-García, J.C., Torres, E.,… Macias-Gonzalez, M. (2018). Adipose tissue inflammation and VDR expression and methylation in colorectal cancer. *Clin Epigenetics* 10:60.

Cusato J, Genova C, Tomasello C, Carrega P, Ottonello S, Pietra G,… D'Avolio, A.(2019) Influence of Vitamin D in Advanced Non-Small Cell Lung Cancer Patients Treated with Nivolumab. *Cancers*. 11(1):125.

Dimitrov, V., Bouttier, D., Boukhaled, G., Salehi-Tabar, R., Avramescu, R.G., Memari, B.,...White, J.H. (2017) Hormonal vitamin D up-regulates tissue-specific PD-L1 and PD-L2 surface glycoprotein expression in humans but not mice. J Biol Chem 292(50):20657–20668.

Feng, Q., Zhang, H., Dong, Z., Zhou, Y., Ma, J. (2017). Circulating 25-hydroxyvitamin D and lung cancer risk and survival: A dose-response meta-analysis of prospective cohort studies. *Medicine (Baltimore)* , *96*, e8613.

Gettinger, S., Horn, L., Jackman, D., Spigel, D., Antonia, S., Hellmann, M.,…Brahmer J. (2018). Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer: results from the CA209-003 study. J Clin Oncol. 36:1675–1684.

Hendrickson, W.K., Flavin, R., Kasperzyk, J.L., Fiorentino, M., Fang, F., Lis, R.,… Giovannucci, E. (2011). Vitamin d receptor protein expression in tumor tissue and prostate cancer progression. *J Clin Oncol Off J Am Soc Clin Oncol*. 29(17):2378–2385.

Herbst, R.S., Baas, P., Kim, D-W., Felip, E., Pérez-Gracia, J.L., Han, J-Y.,... Garon, E.B. (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*, 387; 1540–1550

Khan, M., Lin, J., Liao, G., Tian, Y., Liang, Y., Li, R.,…Yuan, Y. (2018) Comparative analysis of immune checkpoint inhibitors and chemotherapy in the treatment of advanced non-small cell lung cancer: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)*, *97*, e11936.

Kim, S.H., Chen, G., King, A.N. Jeon, C.K. Christensen, P.J., Zhao, L.,...Ramnath, N. (2012) Characterization of vitamin D receptor (VDR) in lung adenocarcinoma. Lung Cancer 77(2):265–271

Liu, S.Y.M., Zheng, M.M., Pan, Y., Liu, S.Y., Li, Y., Wu, Y.L. (2023). Emerging evidence and treatment paradigm of non-small cell lung cancer. *J Hematol Oncol* 16, 40.

Menezes, R.J., Cheney, R.T., Husain, A., Tretiakova, M., Loewen, G., Johnson, C.S.,...Reid, M.E. (2008) Vitamin D receptor expression in normal, premalignant, and malignant human lung tissue. Cancer Epidemiol Prev Biomarkers 17(5):1104–1110

Ness, R.A., Miller, D.D., Wei, L. (2015) The role of vitamin D in cancer prevention. Chin J Nat Med 13(7):481–497.

Reck, M., Rodríguez-Abreu, D., Robinson, A.G., Hui, R., Csőszi, T., Fülöp, A.,…Brahmer JR. (2021). Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥ 50. J Clin Oncol. 39:2339–2349.

Reck, M., Remon, J., Hellman, M.D. (2022). First-line immunotherapy for non–small-cell lung cancer. *Journal of Clinical Oncology*, 40.6: 586-597.

Rittmeyer, A., Barlesi, F., Waterkamp, D., Park, K., Ciardiello, F., Pawel, J.v.,…Gandara, D.R. (2017) Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 389, 255–265.

Ross, A.C., Taylor, C.L., Yaktine, A.L., Valle. H.B.D. eds. Dietary Reference Intakes for Calcium and Vitamin D. National Academies Press (US); 2011. Institute of Medicine. Committee to Review Dietary Reference Intakes for Vitamin D, Calcium. The National Academies Collection: Reports funded by National Institutes of Health.

Samet, J.M., Avila-Tang, E., Boffetta, P., Hannan, L.M., Olivo-Marston, S., Thun, M.J., Rudin, C.M. (2009). Lung cancer in never smokers: clinical epidemiology and environmental risk factors. *Clinical Cancer Research*, *15*(18), 5626-5645.

Singh, R.K., Kim, K., Rowswell-Turner, R.B., Hansen, J.N., Khazan, N., Jones, A.,…Moore, R.G. (2020) Targeting Vitamin-D receptor (VDR) by a small molecule antagonist MeTC7 inhibits PD-L1 but controls THMYCN neuroblastoma growth PD-L1 independently. *bioRxiv*, 2020.08. 16.252940.

Socinski, M.A., Jotte, R.M., Cappuzzo, F., Orlandi, F., Stroyakovskiy, D., Nogami, N.,...Reck, M. (2018) Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N. Engl. J. Med.* 378, 2288–2301.

Spigel, D.R., Faivre-Finn, C., Gray, J.E., Vicente, D., Planchard, D., Paz-Ares, L.,…Antonia, S.J. (2022). Five-year survival outcomes from the PACIFIC Trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. J Clin Oncol. 40:1301–1311.

Tykodi, S.S, Schadendorf, D., Cella, D., Reck, M., Harrington, K., Wagner, S., Shaw, J.W. (2018) Patient-reported outcomes with nivolumab in advanced solid cancers. *Cancer Treat. Rev.*, *70*, 75–87.

West, H., McCleod, M., Hussein, M., Morabito, A., Rittmeyer, A., Conter, H.J.,...Cappuzzo, F. (2019) Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 20, 924–937.

You, W., Liu, X., Tang, H., Lu, B., Zhou, Q., Li, Y.,…Tan B. (2023). Vitamin D Status Is Associated With Immune Checkpoint Inhibitor Efficacy and Immune-related Adverse Event Severity in Lung Cancer Patients: A Prospective Cohort Study. *Journal of Immunotherapy*, *46*(6), 236-243.

Zhou, W., Suk, R., Liu, G., Park, S., Neuberg, D.S., Wain, J.C.,… Christiani, D.C. (2005) Vitamin D is associated with improved survival in early-stage non-small cell lung cancer patients. Cancer Epidemiol Biomark Prevent. 14(10):2303–2309.

Zhou, W., Heist, R.S., Liu, G., Asomaning, K., Neuberg, D.S., Hollis, B.W.,… Christiani, D.C. (2007). Circulating 25-hydroxyvitamin D levels predict survival in early-stage non-small-cell lung cancer patients. J Clin Oncol. 25(5):479–485.