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# Safety and efficacy of PD-1 inhibitors in non–small cell lung cancer patients positive for antinuclear antibodies

Yasuto Yoneshima[a], Kentaro Tanaka[a], Yoshimasa Shiraishi[a], Kojiro Hata[b], Hiroyuki Watanabe[b], Taishi Harada[c], Kohei Otsubo[a], Eiji Iwama[a], Hiroyuki Inoue[a,d], Satohiro Masuda[b], Yoichi Nakanishi[a,d], Isamu Okamoto[a,*]

[a] Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan
[b] Department of Pharmacy, Kyushu University Hospital, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan
[c] Department of Respiratory Medicine, Japan Community Healthcare Organization Kyushu Hospital, 1-8-1 Kishinoura, Yahatanishi-ku, Kitakyushu, Fukuoka, 806-8501, Japan
[d] Center for Clinical and Translational Research, Kyushu University Hospital, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan

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*Keywords:*
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NSCLC, non-small cell lung cancer
irAE, immune-related adverse event

ABSTRACT

*Objectives:* To examine the possible effects of antinuclear antibodies (ANA) on the safety and efficacy of programmed cell death–1 (PD-1) inhibitors in patients with advanced non–small cell lung cancer (NSCLC).
*Patients and methods:* Clinical data including ANA status were reviewed retrospectively for patients with advanced NSCLC who received monotherapy with a PD-1 inhibitor.
*Results:* Of the 83 patients analyzed, 18 (21.7%) were positive for ANA. The incidence of immune-related adverse events (irAEs) did not differ significantly between patients with ANA (6/18, 33.3%) and those negative for ANA (21/65, 32.3%), although it tended to increase as the ANA titer increased. Progression-free survival (2.9 versus 3.8 months, $p = 0.03$) and overall survival (11.6 versus 15.8 months, $p = 0.03$) were significantly shorter in patients positive for ANA than in those without ANA.
*Conclusion:* PD-1 inhibitors can be administered safely in advanced NSCLC patients positive for ANA without obvious exacerbation of autoimmune disease, although patients with a high titer of such antibodies may warrant close monitoring. However, the presence of ANA might be associated with a poor outcome of such treatment.

## 1. Introduction

Immune checkpoint inhibitors (ICIs) that target the PD-1 (programmed cell death–1)–PD-L1 (programmed cell death–ligand 1) axis have shown unprecedented clinical activity for the treatment of patients with advanced non–small cell lung cancer (NSCLC) and have become a standard therapy for such patients [1–5]. Whereas these agents are generally well tolerated, immune-related adverse events (irAEs) develop in 30%–70% of treated patients [4,6–8]. Most such irAEs can be managed by immunosuppression and supportive care, but it is important that they be recognized and treated early [9,10]. It is not clear which patients are likely to develop severe irAEs, however.

Antinuclear antibodies (ANA) comprise a spectrum of autoantibodies that react with various nuclear and cytoplasmic components of normal human cells. Although ANA are an important serological marker for certain autoimmune diseases, they have also been detected in serum of various cancer patients as frequently as in individuals with rheumatoid arthritis or systemic lupus erythematosus [11–15]. This finding has suggested that ANA might be associated with carcinogenesis and represent a state of pre-autoimmunity or immunologic abnormality. Whether such an abnormality might affect the safety or efficacy of ICIs has remained unknown. We have now investigated whether ANA positivity might affect the toxicity and effectiveness of ICIs in patients with advanced NSCLC.

*Abbreviations:* ICI, immune checkpoint inhibitor; PD-1, programmed cell death–1; PD-L1, programmed cell death–ligand 1; NSCLC, non–small cell lung cancer; irAE, immune-related adverse event; ANA, antinuclear antibodies; HR, hazard ratio; CI, confidence interval; TPS, tumor proportion score; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group

* Corresponding author.
*E-mail address:* okamotoi@kokyu.med.kyushu-u.ac.jp (I. Okamoto).

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## 2. Patients and methods

### 2.1. Patients

We performed a retrospective study of the medical records of all patients with advanced (stage III or IV according to the 8th edition of the TNM classification) or recurrent NSCLC who underwent nivolumab or pembrolizumab monotherapy at Kyushu University Hospital between January 2016 and June 2018. Patients who underwent a serum ANA test were eligible for the study. The presence of ANA in serum was determined by a commercial vendor with an indirect immunofluorescence assay based on human epithelial cell line 2 and fluorescein isothiocyanate–conjugated antibodies to human immunoglobulin G. An ANA titer of 1:40 served as the cutoff between a positive and negative test result. The best response during PD-1 inhibitor treatment was defined with reference to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). This study was approved by the Ethics Committee of Kyushu University and Kyushu Hospital.

### 2.2. Statistical analysis

The relation between the presence of serum ANA and other patient characteristics was examined with Fisher's exact test. Survival outcome was estimated with the Kaplan-Meier method and was compared between patient groups with the log-rank test. The association between patient characteristics and survival outcome was evaluated with a multivariate Cox proportional hazards model, with the results being expressed as a hazard ratio (HR) and its 95% confidence interval (CI). All $p$ values are two-sided, and those of $< 0.05$ were considered statistically significant. All statistical analysis was performed with JMP software version 13 (SAS Institute, Cary, NC, USA).

## 3. Results

### 3.1. Patient characteristics

A total of 83 NSCLC patients treated with single-agent nivolumab or pembrolizumab was included in the study. The baseline characteristics of the study patients are shown in Table 1. The median age was 67 years (range, 36–86 years), 67 (80.7%) patients were male, 58 (69.9%) had adenocarcinoma, and 51 (61.4%) had stage IV disease. PD-L1 expression was analyzed for about half of the study cohort. Eighteen (21.7%) patients were positive for ANA (more than 1:40 serum dilution). At initiation of PD-1 inhibitor treatment, no patient had active symptoms of autoimmune disease.

**Table 1**
Characteristics of the study patients (n = 83, 100%).

| Characteristic | No. of patients (%) |
|---|---|
| [Median age (range), years | 67 (36–86)] |
| Sex | |
| Male | 67 (80.7) |
| Female | 16 (19.3) |
| Smoking history | |
| Current or former | 67 (80.7) |
| Never | 16 (19.3) |
| ECOG performance status | |
| 0 or 1 | 77 (92.8) |
| 2 or 3 | 6 (7.2) |
| Stage | |
| III | 12 (14.5) |
| IV | 51 (61.4) |
| Recurrent | 20 (24.1) |
| Histology | |
| Squamous | 18 (21.7) |
| Adenocarcinoma | 58 (69.9) |
| Other | 7 (8.4) |
| Oncogenic driver | |
| *EGFR* and *ALK* wild type or not investigated | 76 (91.6) |
| *EGFR* mutation | 6 (7.2) |
| *ALK* rearrangement | 1 (1.2) |
| PD-1 inhibitor administered | |
| Nivolmab | 57 (68.7) |
| Pembrolizumab | 26 (31.3) |
| PD-L1 status | |
| TPS ≥50% | 23 (27.7) |
| TPS 1–49% | 16 (19.3) |
| TPS < 1% | 8 (9.6) |
| Unknown | 36 (43.4) |
| Number of prior chemotherapy regimens | |
| 0 | 16 (19.3) |
| 1 | 39 (47.0) |
| ≥2 | 28 (33.7) |
| ANA | |
| Positive | 18 (21.7) |
| Negative | 65 (78.3) |

Abbreviations not defined in text: *EGFR*, epidermal growth factor receptor gene; *ALK*, anaplastic lymphoma kinase gene.

### 3.2. Relation of ANA positivity to other clinical features

Association analysis for ANA positivity and baseline clinical features is summarized in Table 2. None of the clinical characteristics examined showed a significant association with ANA positivity. There was thus no significant difference in the frequency of a tumor proportion score (TPS) for PD-L1 of ≥50% between patients positive and those negative for ANA.

### 3.3. Relation of ANA positivity to irAE development

Association analysis for the presence of ANA and the development of irAEs is summarized in Table 3. Six (33.3%) of the 18 patients positive for ANA and 21 (32.3%) of the 65 patients negative for ANA developed irAEs. The grade and management of irAEs are also summarized in Table 3. Two (11.1%) patients positive for ANA developed irAEs of grades 3–5, one of whom died as a result of interstitial lung disease even though he was treated with systemic corticosteroids. There was no significant difference in the development of irAEs of any grade or of grades 3–5 or in the development of interstitial lung disease between patients positive or negative for ANA ($p =$ 1.00, 0.64, and 1.00, respectively).

Subdivision of the study cohort according to ANA titer cutoffs of 1:40, 1:80, 1:160, or 1:320 serum dilution revealed that the frequency of irAEs increased as the ANA titer increased, although there was no significant difference in irAE prevalence between patients with high or low titers at each cutoff level (Fig. 1).

Of the 18 patients initially positive for ANA, 10 were analyzed for ANA during PD-1 inhibitor therapy. Among these 10 individuals, the ANA titer increased in three patients, all of whom developed irAEs (interstitial lung disease in two and hypothyroidism in one). Of the 65 patients initially negative for ANA, 20 were analyzed for ANA during PD-1 inhibitor therapy. Only one of these 20 individuals became positive for ANA, and this one patient did not develop an irAE.

### 3.4. Association between ANA positivity and PD-1 inhibitor efficacy

The objective response rate (ORR) and disease control rate were 27.8% and 55.6%, respectively, in patients positive for ANA and 29.2% and 64.6% in those negative for ANA. Median progression-free survival (PFS) was 2.9 and 3.8 months in patients positive or negative for ANA, respectively (Fig. 2A). Median overall survival (OS) was 11.6 and 15.8 months in patients with or without ANA, respectively (Fig. 2B). Both PFS and OS were significantly shorter in patients positive than in those negative for ANA ($p =$ 0.03 in each instance). With adjustment for ANA, sex, Eastern Cooperative Oncology Group (ECOG) performance status, and clinical stage in a regression model, ANA positivity remained a significant adverse prognostic indicator for both PFS (HR of

**Table 2**
Association analysis for ANA and other clinical features.

| Characteristic | ANA positive (n = 18, 100%) | ANA negative (n = 65, 100%) | p |
|---|---|---|---|
| Age (years) | | | |
| < 70 | 10 (55.6) | 43 (66.2) | 0.42 |
| ≥70 | 8 (44.4) | 22 (33.8) | |
| Sex | | | |
| Male | 13 (72.2) | 54 (83.1) | 0.32 |
| Female | 5 (27.8) | 11 (16.9) | |
| Smoking history | | | |
| Current or former | 16 (88.9) | 51 (78.5) | 0.50 |
| Never | 2 (11.1) | 14 (21.5) | |
| ECOG performance status | | | |
| 0 or 1 | 16 (88.9) | 61 (93.8) | 0.61 |
| 2 or 3 | 2 (11.1) | 4 (6.2) | |
| Stage | | | |
| III | 2 (11.1) | 10 (15.4) | 0.22[a] |
| IV | 14 (77.8) | 37 (56.9) | |
| Recurrent | 2 (11.1) | 18 (27.7) | |
| Histology | | | |
| Squamous | 2 (11.1) | 16 (24.6) | 0.34[b] |
| Adenocarcinoma | 13 (72.2) | 45 (69.2) | |
| Other | 3 (16.7) | 4 (6.2) | |
| PD-1 inhibitor administered | | | |
| Nivolmab | 10 (55.6) | 47 (72.3) | 0.25 |
| Pembrolizumab | 8 (44.4) | 18 (27.7) | |
| PD-L1 status | | | |
| TPS ≥50% | 7 (38.9) | 16 (24.6) | 0.25[c] |
| TPS 1–49% | 3 (16.7) | 13 (20.0) | |
| TPS < 1% | 1 (5.6) | 7 (10.8) | |
| Unknown | 7 (38.9) | 29 (44.6) | |
| Number of prior chemotherapy regimens | | | |
| 0 | 5 (27.8) | 11 (16.9) | 0.32[d] |
| 1 | 5 (27.8) | 34 (52.3) | |
| ≥2 | 8 (44.4) | 20 (30.8) | |

All *p* values were calculated with Fisher's exact test.
[a] Stage III or IV versus recurrent.
[b] Squamous versus all others.
[c] TPS ≥50% versus all others.
[d] No previous chemotherapy versus all others.

**Table 3**
Association analysis for ANA and irAEs as well as treatment required for irAEs and PD-1 inhibitor dosing.

| | ANA positive (n = 18, 100%) | ANA negative (n = 65, 100%) | *p* |
|---|---|---|---|
| irAEs | | | |
| Any grade | 6 (33.3) | 21 (32.3) | 1.00 |
| Grades 3–5 | 2 (11.1)[a] | 4 (6.2) | 0.64 |
| Interstitial lung disease | 2 (11.1) | 8 (12.3) | 1.00 |
| Treatment required for irAEs | | | |
| No treatment | 16 (88.9) | 50 (76.9) | |
| Supportive care | 1 (5.6) | 12 (18.5) | |
| Systemic corticosteroids | 1 (5.6) | 3 (4.6) | |
| PD-1 inhibitor dosing | | | |
| Continued | 16 (88.9) | 53 (81.5) | |
| Discontinued | 2 (11.1) | 12 (18.5) | |

All *p* values were calculated with Fisher's exact test.
[a] One patient died from interstitial lung disease.

2.06, with a 95% CI of 1.10–3.70; $p = 0.02$) and OS (HR of 2.31, with a 95% CI of 1.09–4.64; $p = 0.03$) (Table 4).

### 3.5. Association between ANA positivity and efficacy of prior platinum-based chemotherapy

Of the 83 study patients, 67 had received cytotoxic chemotherapy before PD-1 inhibitor treatment, with 12 patients positive for ANA and 51 patients negative for ANA having received platinum-based chemotherapy. Association analysis for ANA and the response to previous platinum-based chemotherapy is summarized in Supplementary Table S1. The ORR and median PFS were 33.3% and 6.9 months in patients positive for ANA and 23.5% and 5.4 months in those negative for ANA, with the differences in ORR and PFS between the two groups not being significant ($p = 0.48$ and 0.49, respectively).

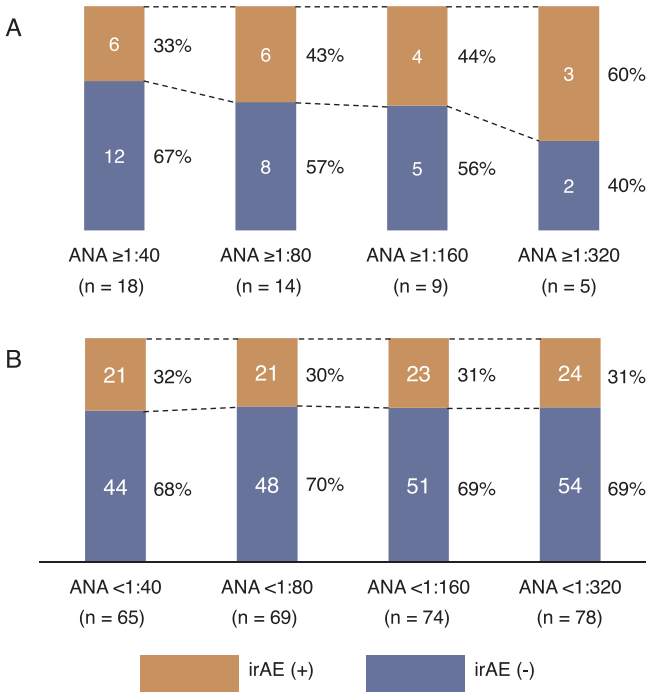


**Fig. 1.** Frequency of irAEs in study patients subdivided according to ANA titer cutoffs of 1:40, 1:80, 1:160, or 1:320 serum dilution. (A) The rate of irAEs in patients with ANA titers of ≥1:40, ≥1:80, ≥1:160, or ≥1:320. (B) The rate of irAEs in patients with ANA titers of < 1:40, < 1:80, < 1:160, or < 1:320.

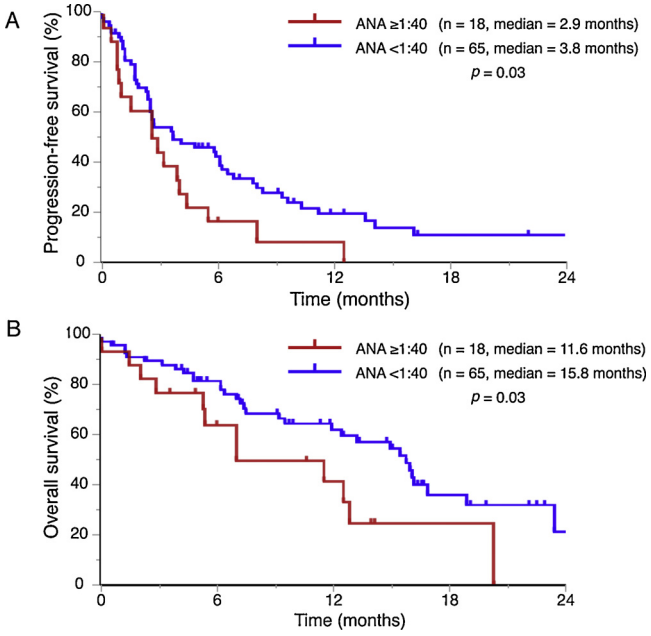


**Fig. 2.** Kaplan-Meier survival curves for the study patients treated with PD-1 inhibitors. (A) PFS according to an ANA titer of < 1:40 or ≥1:40. (B) OS according to an ANA titer of < 1:40 or ≥1:40. The *p* values were calculated with the log-rank test.

**Table 4**
Multivariate analysis of clinical factors for PFS and OS.

| | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| Factor | HR | 95% CI | *p* | HR | 95% CI | *p* |
| ANA | | | | | | |
| Positive | 2.06 | 1.10–3.70 | 0.02 | 2.31 | 1.09–4.64 | 0.03 |
| Negative | | | | | | |
| Sex | | | | | | |
| Female | 1.41 | 0.76–2.50 | 0.26 | 0.46 | 0.17–1.07 | 0.07 |
| Male | | | | | | |
| ECOG PS | | | | | | |
| 2 or 3 | 2.39 | 0.82–5.61 | 0.10 | 0.53 | 0.20–1.83 | 0.28 |
| 0 or 1 | | | | | | |
| Stage | | | | | | |
| III or IV | 1.80 | 0.98–3.19 | 0.05 | 1.13 | 0.57–2.37 | 0.74 |
| Recurrent | | | | | | |

PS, performance status. All *p* values were calculated with a proportional hazards regression model.

## 4. Discussion

PD-1–PD-L1 axis inhibitors have shown marked efficacy in the treatment of advanced NSCLC [1–5]. Such treatment is associated with a new class of toxicities that appear to be of autoimmune or autoinflammatory origin, however [6]. These irAEs have posed substantial challenges to patient care in terms of how they can be optimally managed. Furthermore, it is currently not possible to reliably predict which patients will develop more severe toxicities associated with such treatment.

ANA are a diverse group of autoantibodies that recognize nuclear macromolecules and their associated complexes. They are a key biomarker in the evaluation of autoimmune diseases, with ANA testing being commonly performed in the clinical setting [16]. However, several studies have shown that ANA are also present in the serum of cancer patients [11–15]. Although various factors have been implicated in the high incidence of ANA in cancer patients, their presence may reflect an autoimmune response to nuclear antigens that is the result of cell transformation [17]. ANA may be related to the prognosis of cancer patients. ANA-positive NSCLC patients thus showed a better survival than did ANA-negative patients after surgical therapy [18]. Moreover, PFS was found to be longer in ANA-positive NSCLC patients than in those negative for ANA after chemotherapy [11]. However, limited data are available with regard to the safety and efficacy of PD-1 inhibitors in ANA-positive patients with NSCLC.

Patients with preexisting autoimmune disease have been excluded from clinical trials of ICIs because of a potential increased susceptibility to irAE development. A recent study found that the incidence of irAEs in NSCLC patients with autoimmune diseases treated with PD-1–PD-L1 inhibitors was similar to reported rates in clinical trials in which patients with such diseases were excluded [19]. Although this study suggests that the administration of PD-1–PD-L1 inhibitors is generally safe in NSCLC patients with autoimmune disease, larger trials are required to determine the risks of such ICI treatment in patients with obvious autoimmunity. In the present study, we investigated how ANA positivity might affect the toxicity of PD-1 inhibitors in NSCLC patients, and we found no difference in the incidence of irAE development between patients with or without ANA. However, the frequency of irAEs increased in patients as the ANA titer increased. Patients with higher ANA titers have been shown to be more susceptible to the development of autoimmune disease. The results of our study suggest that the immune system of patients with high ANA titers might be more reactive and therefore more likely to give rise to irAEs on exposure to ICIs, and that such patients should be monitored closely during PD-1 inhibitor treatment. Among 10 patients initially positive for ANA who were analyzed for ANA during PD-1 inhibitor treatment, the ANA titer increased in three patients, all of whom developed irAEs. These results suggest that an increase in ANA titer may be associated with the onset of irAEs.

Our study also revealed that patients positive for ANA had a significantly shorter PFS and OS for PD-1 inhibitor treatment compared with those negative for ANA. It is possible that occult inflammatory disease is present in patients positive for ANA and may influence their survival during ICI treatment, inflammation having been shown to be a critical determinant of tumor progression [20]. However, despite the shorter survival of ANA-positive patients, there was no difference in ORR for PD-1 inhibitors between ANA-positive and ANA-negative groups in our study. In addition, there was no difference in the efficacy of prior platinum-based chemotherapy between ANA-positive and ANA-negative patients. These results suggest that resistance to ICIs tends to develop earlier in patients with ANA. Given that the presence of ANA is closely associated with immunologic disorders, it is possible that the immune system abnormality in these patients limits the therapeutic benefit of PD-1 inhibitors by giving rise to early resistance. Although the underlying biology of ICI resistance is unclear, recent studies have implicated insufficient antitumor T cell generation, inadequate antitumor T cell effector function, and impaired development of T cell memory [21]. Such mechanisms might be more likely to be operative in patients positive for ANA.

Limitations of the present study include the fact that the expression of PD-L1 was not fully addressed because such analysis is not required for nivolumab administration and was not performed for about half of the study cohort. The number of patients was also relatively small, and all patients were treated at a single institution. In addition, the retrospective nature of the study limits the conclusions that can be drawn. Further studies are thus needed to confirm our findings.

In summary, we examined the association of ANA positivity with the safety and efficacy of PD-1 inhibitor treatment in patients with advanced NSCLC. ANA levels may provide a measure of immune reactivity in assessment of the toxicity and efficacy of ICI treatment.

## Conflict of interest

The authors declare no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.01.014.

## References

[1] J. Brahmer, K.L. Reckamp, P. Baas, L. Crino, W.E. Eberhardt, E. Poddubskaya, S. Antonia, A. Pluzanski, E.E. Vokes, E. Holgado, D. Waterhouse, N. Ready, J. Gainor, O. Aren Frontera, L. Havel, M. Steins, M.C. Garassino, J.G. Aerts, M. Domine, L. Paz-Ares, M. Reck, C. Baudelet, C.T. Harbison, B. Lestini, D.R. Spigel, Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer, N. Engl. J. Med. 373 (2015) 123–135.

[2] H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhaufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crino, G.R. Blumenschein Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, J.R. Brahmer, Nivolumab versus docetaxel in advanced non-squamous non-small-cell lung cancer, N. Engl. J. Med. 373 (2015) 1627–1639.

[3] R.S. Herbst, P. Baas, D.W. Kim, E. Felip, J.L. Perez-Gracia, J.Y. Han, J. Molina, J.H. Kim, C.D. Arvis, M.J. Ahn, M. Majem, M.J. Fidler, G. de Castro Jr., M. Garrido, G.M. Lubiniecki, Y. Shentu, E. Im, M. Dolled-Filhart, E.B. Garon, Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial, Lancet 387 (2016) 1540–1550.

[4] M. Reck, D. Rodriguez-Abreu, A.G. Robinson, R. Hui, T. Csoszi, A. Fulop,

M. Gottfried, N. Peled, A. Tafreshi, S. Cuffe, M. O'Brien, S. Rao, K. Hotta, M.A. Leiby, G.M. Lubiniecki, Y. Shentu, R. Rangwala, J.R. Brahmer, KEYNOTE-024 Investigators, Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer, N. Engl. J. Med. 375 (2016) 1823–1833.

[5] A. Rittmeyer, F. Barlesi, D. Waterkamp, K. Park, F. Ciardiello, J. von Pawel, S.M. Gadgeel, T. Hida, D.M. Kowalski, M.C. Dols, D.L. Cortinovis, J. Leach, J. Polikoff, C. Barrios, F. Kabbinavar, O.A. Frontera, F. De Marinis, H. Turna, J.S. Lee, M. Ballinger, M. Kowanetz, P. He, D.S. Chen, A. Sandler, D.R. Gandara, O.A.K.S. Group, 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 (2017) 255–265.

[6] M.A. Postow, R. Sidlow, M.D. Hellmann, Immune-related adverse events associated with immune checkpoint blockade, N. Engl. J. Med. 378 (2018) 158–168.

[7] S.L. Topalian, F.S. Hodi, J.R. Brahmer, S.N. Gettinger, D.C. Smith, D.F. McDermott, J.D. Powderly, R.D. Carvajal, J.A. Sosman, M.B. Atkins, P.D. Leming, D.R. Spigel, S.J. Antonia, L. Horn, C.G. Drake, D.M. Pardoll, L. Chen, W.H. Sharfman, R.A. Anders, J.M. Taube, T.L. McMiller, H. Xu, A.J. Korman, M. Jure-Kunkel, S. Agrawal, D. McDonald, G.D. Kollia, A. Gupta, J.M. Wigginton, M. Sznol, Safety, activity, and immune correlates of anti-PD-1 antibody in cancer, N. Engl. J. Med. 366 (2012) 2443–2454.

[8] J.R. Brahmer, S.S. Tykodi, L.Q. Chow, W.J. Hwu, S.L. Topalian, P. Hwu, C.G. Drake, L.H. Camacho, J. Kauh, K. Odunsi, H.C. Pitot, O. Hamid, S. Bhatia, R. Martins, K. Eaton, S. Chen, T.M. Salay, S. Alaparthy, J.F. Grosso, A.J. Korman, S.M. Parker, S. Agrawal, S.M. Goldberg, D.M. Pardoll, A. Gupta, J.M. Wigginton, Safety and activity of anti-PD-L1 antibody in patients with advanced cancer, N. Engl. J. Med. 366 (2012) 2455–2465.

[9] J. Villadolid, A. Amin, Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities, Transl. Lung Cancer Res. 4 (2015) 560–575.

[10] T.W. Chen, A.R. Razak, P.L. Bedard, L.L. Siu, A.R. Hansen, A systematic review of immune-related adverse event reporting in clinical trials of immune checkpoint inhibitors, Ann. Oncol. 26 (2015) 1824–1829.

[11] F. Fernandez-Madrid, P.J. VandeVord, X. Yang, R.L. Karvonen, P.M. Simpson, M.J. Kraut, J.L. Granda, J.E. Tomkiel, Antinuclear antibodies as potential markers of lung cancer, Clin. Cancer Res. 5 (1999) 1393–1400.

[12] F. Fernandez Madrid, R.L. Karvonen, J. Ensley, M. Kraut, J.L. Granda, H. Alansari, N. Tang, J.E. Tomkiel, Spectra of antinuclear antibodies in patients with squamous cell carcinoma of the lung and of the head and neck, Cancer Detect. Prev. 29 (2005) 59–65.

[13] F.F. Madrid, M.C. Maroun, O.A. Olivero, M. Long, A. Stark, L.I. Grossman, W. Binder, J. Dong, M. Burke, S.D. Nathanson, R. Zarbo, D. Chitale, R. Zeballos-Chavez, C. Peebles, Autoantibodies in breast cancer sera are not epiphenomena and may participate in carcinogenesis, BMC Cancer 15 (2015) 407.

[14] R. Nisihara, M.C.C. Machoski, A. Neppel, C.A. Maestri, I. Messias-Reason, T.L. Skare, Anti-nuclear antibodies in patients with breast cancer, Clin. Exp. Immunol. 193 (2018) 178–182.

[15] H. Imai, R.L. Ochs, K. Kiyosawa, S. Furuta, R.M. Nakamura, E.M. Tan, Nucleolar antigens and autoantibodies in hepatocellular carcinoma and other malignancies, Am. J. Pathol. 140 (1992) 859–870.

[16] D.S. Pisetsky, Antinuclear antibody testing—misunderstood or misbegotten? Nat. Rev. Rheumatol. 13 (2017) 495–502.

[17] M. Abu-Shakra, D. Buskila, M. Ehrenfeld, K. Conrad, Y. Shoenfeld, Cancer and autoimmunity: autoimmune and rheumatic features in patients with malignancies, Ann. Rheum. Dis. 60 (2001) 433–441.

[18] F. Blaes, M. Klotz, H. Huwer, U. Straub, G. Kalweit, K. Schimrigk, H.J. Schafers, Antineural and antinuclear autoantibodies are of prognostic relevance in non-small cell lung cancer, Ann. Thorac. Surg. 69 (2000) 254–258.

[19] G.C. Leonardi, J.F. Gainor, M. Altan, S. Kravets, S.E. Dahlberg, L. Gedmintas, R. Azimi, H. Rizvi, J.W. Riess, M.D. Hellmann, M.M. Awad, Safety of programmed death-1 pathway inhibitors among patients with non-small-cell lung cancer and preexisting autoimmune disorders, J. Clin. Oncol. 36 (2018) 1905–1912.

[20] L.M. Coussens, W. Zena, Inflammation and cancer, Nature 420 (2002) 860–867.

[21] R.W. Jenkins, D.A. Barbie, K.T. Flaherty, Mechanisms of resistance to immune checkpoint inhibitors, Br. J. Cancer 118 (2018) 9–16.