Impact of Antibiotics and Corticosteroids on The Efficacy of Immune Checkpoint Inhibitors in Patients With Advanced Melanoma

İmmün Kontrol Noktası İnhibitörleri ile Tedavi Edilen Malign Melanom Hastalarında Antibiyotik ve Kortikosteroid Kullanımının Tedaviye Etkileri

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ABSTRACT

Objective: The treatment of malignant melanoma has changed a lot in recent years. The use of immune checkpoint inhibitors has prolonged survival in patients with advanced melanoma. Our study evaluates the impact of antibiotics, corticosteroids, and adjuvant treatment on the efficacy of immune checkpoint inhibitors in patients with advanced melanoma.

Material and Methods: We conducted a retrospective analysis of metastatic melanoma patients treated with ipilimumab and nivolumab. Concomitant antibiotics, corticosteroids for any reason, and prior adjuvant treatment for melanoma were recorded. Progression free survival and overall survival were compared in each group.

Results: We enrolled 29 patients with advanced melanoma treated with immune checkpoint inhibitors. Eighteen (62.1%) patients had concomitant antibiotic therapy, and 16 (55.2%) patients had used corticosteroids for any reason. Seventeen patients (58.6%) had adjuvant therapy with interferon alpha.

Although not significant, PFS and OS were shorter in patients treated with concomitant antibiotics: PFS 15.9 months vs. 9 months, p=0.561; OS 38 months vs. 18 months, p=0.404.

PFS and OS were shorter in patients who had used corticosteroids during immune checkpoint inhibitor treatment: PFS 27.2 months vs. 5.4 months (p=0.007) and OS 50 months vs. 14 months (p=0.009).

PFS was 23.2 months in the adjuvant interferon group vs. 6.2 months with no prior interferon, p=0.019. Overall survival was also longer in patients with prior adjuvant interferon treatment: 39.8 months vs. 12.9 months (p=0.004).

Conclusion: Concomitant use of antibiotics and corticosteroids in patients with advanced melanoma may affect the efficacy of immune checkpoint inhibitors.

Keywords: Malignant melanoma, Immune checkpoint inhibitors, Antibiotics, Corticosteroids, Ipilimumab, Nivolumab

ÖZ

Amaç: Son yıllarda malign melanom tedavisi tamamen değişmiş, özellikle immün kontrol noktası inhibitörlerinin kullanıma girmesiyle yaşam süresi belirgin olarak uzamıştır. Ancak bu ilaçlar hastaların sadece bir kısmında etkili olabilmektedir. Bu tedavilerden fayda gören hastaların belirlenebilmesi için biyobelirteçler ve tedaviye etki eden faktörler araştırılmaktadır. Çalışmamızda immün kontrol noktası inhibitörü kullanan ileri evre malign melanom hastalarında antibiyotik ve kortikosteroid kullanımının ve hastaların melanom için daha önce adjuvant olarak aldıkları tedavilerin tedavi sonuçları üzerine etkilerini araştırdık.

Gereç ve Yöntemler: Çalışmamızda immün kontrol noktası inhibitörleri ile tedavi edilen ileri evre malign melanom hastaları retrospektif olarak tarandı. Yirmidokuz hastanın verilerine ulaşıldı. Hastane kayıtlarından antibiyotik ve kortikosteroid kullanımı ve hastaların daha önce aldıkları adjuvant tedavi verilerine ulaşılarak sağkalım analizleri yapıldı.

Bulgular: Yirmidokuz hastanın 18 i (%62) antibiyotik kullanımıştı, 16 sında (%55) herhangi bir sebeple sistemik kortikosteroid kullanımı vardı. 17 (%58,6) hastada adjuvant interferon kullanılmıştı.

İstatistiki anlamlılığa ulaşmamasına rağmen tedavi sırasında antibiyotik kullananlarda progresyonsuz sağ kalım (PFS) ve genel sağ kalım (OS) daha kısaydı. (PFS 9 ay ile 15,9 ay, p= 0,561, OS 18 ay ile 38 ay, p=0,404).

Progresyonsuz sağ kalım ve OS immün kontrol noktası inhibitörleri ile beraber kortikosteroid kullananlarda daha kısaydı (PFS 27,2 ay ile 5,4 ay, p=0,007, OS 50 ay ile 14 ay, p=0,009).

Adjuvant dönemde interferon kullanmış olan hastaların metastatik evrede immün kontrol noktası inhibitörleri ile hem pfs hem os sürelerinin daha uzun olduğu görüldü (PFS 23,2 ay ile 6.2 ay, p=0,019, OS 39,8 ay ile 12,9 ay, p=0,004).

Sonuç: İleri evre metastatik malign melanom hastalarında immün kontrol noktası inhibitörleri ile beraber antibiyotik ve kortikosteroid kullanımı tedavi sonuçlarını olumsuz etkileyebilmektedir.

Anahtar Sözcükler: İmmün kontrol noktası inhibitörleri, Antibiyotik, Kortikosteroid, İpilimumab, Nivolumab

INTRODUCTION

Melanoma is the most aggressive type of skin cancer. The landscape of melanoma treatment has changed with the intervention of immune checkpoint inhibitors. Ipilimumab, an antibody against the cytotoxic T lymphocyte associated protein (CTLA-4), was the first agent of this group that demonstrated survival benefit in patients with advanced melanoma (1). The programmed death protein 1 (PD-1) blocking antibodies pembrolizumab and nivolumab have shown better efficacy than ipilimumab, with a better toxicity profile (2-4).

Although these checkpoint inhibitors had better survival results, only a proportion of patients can utilise this treatment. Clinicians have focused on biomarkers of response to immunotherapy like programmed death ligand 1 (PD-L1) status and mutation burden. Preclinical and clinical data suggest that the gut microbiome can influence the immune system and response to immune checkpoint inhibitors, and a rich gut microbiota can be a marker of response (5,6). Sivan et al. have demonstrated that the tumour grows more aggressively in the group of rats with unfavourable microbiota (lacking Bifidobacterium), and direct administration of Bifidobacterium improves tumour specific immunity and response to anti PDL-1 therapy (7).

Antibiotics can result in a disturbance in the composition of gut microbiota. Antibiotic-induced microbiota alterations can remain after long periods of time, even years (8). By disturbing the composition and reducing the taxonomic richness, they may also affect the response to checkpoint inhibitors (9). Derosa et al. reported that recent use of antibiotics prior to immune checkpoint inhibitors negatively influences the response in patients with renal cell and non-small cell lung cancer (10).

Corticosteroids are also drugs that may impact the efficacy of checkpoint inhibitors, as they have immunosuppressive effects.

In this study, we analysed the impact of concomitant antibiotics and corticosteroids on the efficacy of immune checkpoint inhibitors in patients with metastatic melanoma.

MATERIALS and METHODS

This retrospective cohort included 29 patients with advanced stage malign melanoma treated with ipilimumab or nivolumab in the second or third lines of therapy. Patients and treatment details were collected from medical records. Progression free survival (PFS) was described as the time from the first date of immune checkpoint inhibitor until confirmed progression or death. Overall survival (OS) was described as the time from the first date of immune checkpoint inhibitor until death or last known follow up visit. Data about the antibiotic usage was collected from the medical and electronic records. Concomitant antibiotic usage was described as the antibiotics used between the first and the last days of treatment. Use of corticosteroids during treatment was also recorded. Adjuvant treatment was collected from the medical reports. The study was approved by the local ethics committee of Akdeniz University with approval number and date of 895/ 02.10.2019.

Analyses were performed with the SPSS 23.0 program. Descriptive statistics are presented with frequency, percentage, mean, standard deviation and median, minimum, maximum. The normality hypothesis was evaluated with the Shapiro-Wilk test, together with the skewness kurtosis values and the q-q plot graphs. For the differences between the numerical values of two independent groups, the Independent Sample t Test was used when the normal distribution assumption was provided, and the Mann-Whitney U test was used when the difference was not provided. In the analysis of the differences between the numerical values of two dependent groups, the Equilibrium Test was used when the normal distribution assumption was provided, and the Wilcoxon Equivalent Test was used when not. The two dependent differences were assessed with the McNemar Test. The log-rank test was used to analyse the difference

between the survival times of the groups. The results are presented with survival graphs. A p value of less than 0.05 was considered statistically significant.

RESULTS

Of the 29 patients with metastatic melanoma treated with immune checkpoint inhibitors, there were 20 men (69%) and 9 women (31%). The median age of the group was 59 (36-81) years. 16 patients were treated with ipilimumab, and 13 patients were treated with nivolumab. The BRAF mutation was positive in 7 (24.1%) of patients. Patients had treatment with checkpoint inhibitors as second or third line treatment. Table I shows the main characteristics of patients with advanced melanoma treated with checkpoint inhibitors.

The PFS was 9.9 months and OS was 16.4 months in the whole group of patients treated with immune checkpoint inhibitors.

Eighteen (62.1%) patients had concomitant antibiotic therapy. Reasons for antibiotic use were pneumonia, urinary tract infections, upper respiratory tract infections, and gastroenteritis. Route of administration of the antibiotics was intravenous for 8 patients, and enteral for 10 patients. The antibiotics used for treatment were ertapenem, piperacillin tazobactam, amoxicillin clavulanate, cephalosporins, clarithromycin and fluoroquinolones. Progression free survival was shorter in the concomitant antibiotic group with 15.9 months vs. 9 months, but this difference was not statistically significant (p=0.561) (Figure 1A). Overall survival was also shorter in patients treated with concomitant antibiotics with 38 months vs. 18 months (p=0.404) (Figure 1B).

Sixteen (55.2%)of patients had used corticosteroids in the treatment period. None of the patients received high dose

Table I: Main characteristics of patients with advanced melanoma treated with check-point inhibitors.

	n (%)
Age	59 (36-61)
Sex	
Men	20 (69)
Women	9 (31)
BRAF	
Positive	7 (24.1)
Negative	22 (75.9)
Checkpoint inhibitor	
Ipilimumab	16 (55.2)
Nivolumab	13 (44.8)
Antibiotics	
Treatment with concomitant antibiotics	18 (62.1)
No antibiotics	11 (37.9)
Corticosteroids	
Treatment with corticosteroids (any reason)	16 (55.2)
No corticosteroids	13 (44.8)
Adjuvant therapy	
Treatment with adjuvant interferon	17 (58.6)
No interferon	12 (41.4)

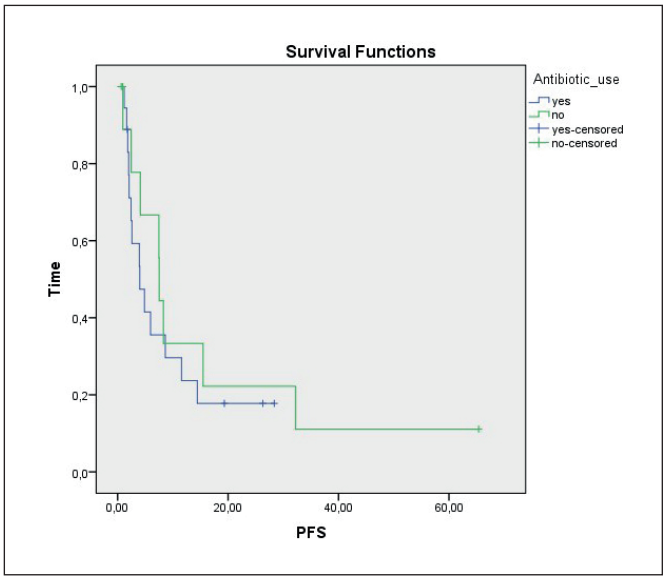

Figure 1A: Progression free survival in patients with concomitant antibiotics and immune checkpoint inhibitors.

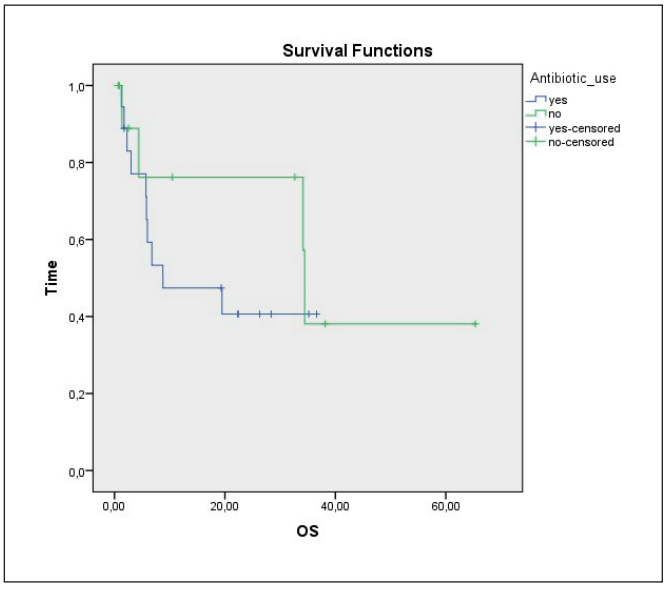

Figure 1B: Overall survival in patients with concomitant antibiotics and immune checkpoint inhibitors.

corticosteroids for immune related adverse events. The most common reasons for corticosteroid use were the palliation of dyspnea and brain metastasis. Patients who used corticosteroids during the treatment period had shorter PFS than the patients who did not use any corticosteroids: 27.2 months vs. 5.4 months (p=0.007) (Figure 2A). Overall survival was also shorter in this group of patients: 50 months vs. 14 months (p=0.009) (Figure 2B).

Progression free survival was longer in patients who used interferon in the adjuvant setting. PFS was 23.2 months in the adjuvant interferon group vs. 6.2 months with no prior interferon (p=0.019) (Figure 3A). Overall survival was also longer in patients with prior adjuvant interferon treatment: 39.8 months vs. 12.9 months (p=0.004) (Figure 3B).

DISCUSSION

In this study, we found that antibiotics could influence the response to immunotherapy in patients with metastatic melanoma. Patients who were exposed to the antibiotics during the treatment period had longer PFS and OS, but this difference did not reach statistical significance, maybe due to small sample size.

Antibiotics are thought to influence treatment by disrupting the fecal microbiota. Preclinical and clinical data suggest

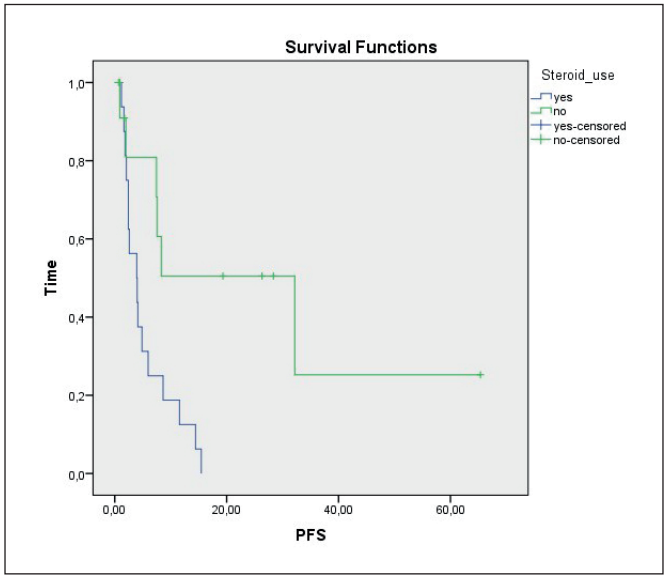

Figure 2A: Progression free survival in patients with concomitant corticosteroids and immune checkpoint inhibitors.

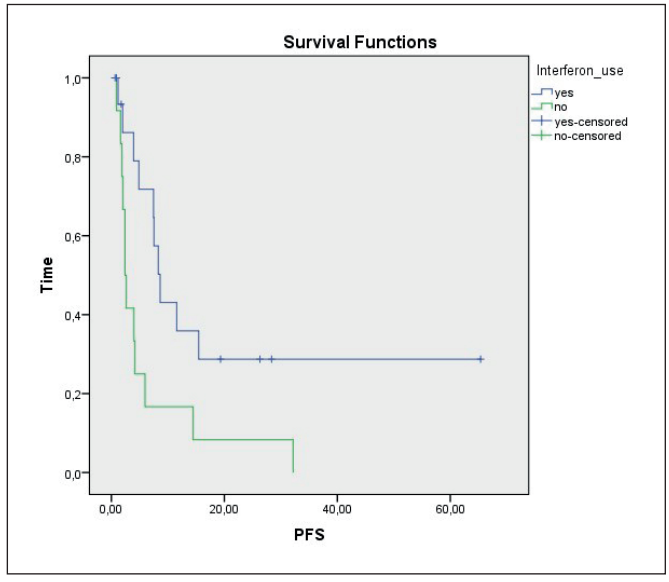

Figure 3A: Progression free survival in patients who had adjuvant interferon before treatment with immune checkpoint inhibitors.

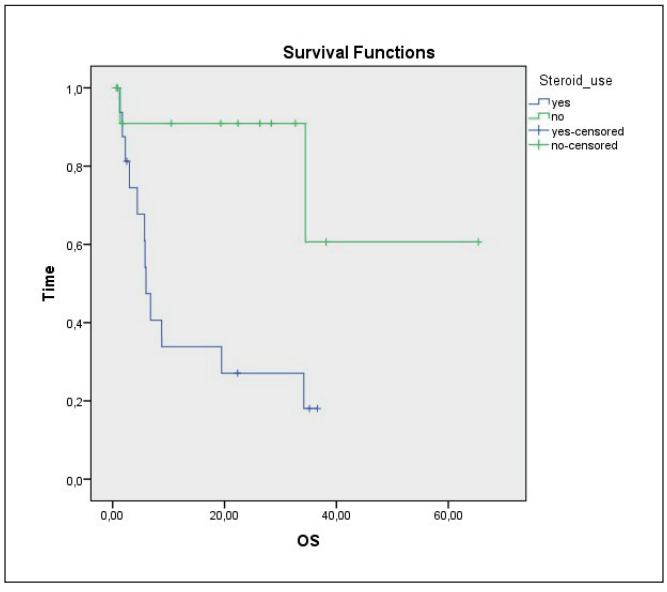

Figure 2B: Overall survival in patients with concomitant corticosteroids and immune checkpoint inhibitors.

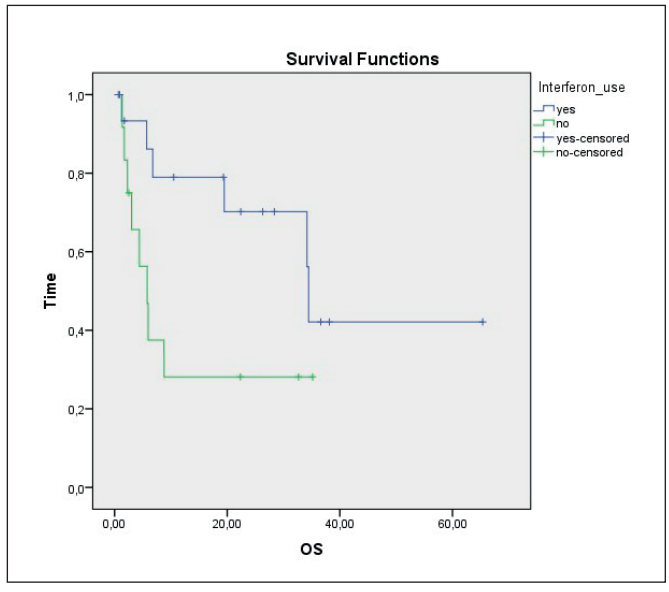

Figure 3B: Overall survival in patients who had adjuvant interferon before treatment with immune checkpoint inhibitors.

that the gut microbiome can influence the immune system and response to immune checkpoint inhibitors and a rich gut microbiota could be a marker of response (5,6).

Routhy B et al. showed that antibiotic treatment significantly reduced the antitumor effects and survival of immune checkpoint inhibitors in mice. They also studied the impact of antibiotics in patients with non-small cell lung cancer, renal cell, and urothelial carcinoma who received PD/PDL-1 monoclonal antibodies. Progression free survival and OS were significantly shorter in the antibiotic-treated groups. They also showed that faecal microbiota transplantation from responder patients to antibiotic-treated mice ameliorated the antitumor effects of PD-1 blockage (11).

In another study, Derosa et al. reported a negative association of antibiotics on the clinical outcomes of immune checkpoint inhibitors in patients with renal cell and non-small cell lung cancer (10).

However, in a retrospective analysis from France, the authors observed no impact of antibiotics on response rate and progression free survival in patients with non-small cell lung cancer treated with nivolumab (12).

Although these observations show us that antibiotics may affect the response to immune checkpoint inhibitors, we need to learn more about what kind, treatment duration, and administration route (iv/oral) of antibiotics could change the treatment results. However, the current observations strongly suggest that antibiotics should not be used in patients treated with immune checkpoint inhibitors unless necessary.

In our study, we also found that corticosteroid use during therapy was associated with poorer outcomes. None of the 16 patients who had received corticosteroids in the treatment period had received high dose corticosteroids for immune-related adverse events. The most common reasons for corticosteroid use were the palliation of dyspnea and brain metastasis.

Corticosteroids, which are now considered the first line therapy in immune related adverse events of immunotherapies, were expected to result in diminished anticancer activity of immune agents due to their immunosuppressive affects. There are reports that the administration of high dose corticosteroids for the treatment of immune mediated adverse events does not affect the efficacy of immune checkpoint inhibitors (13,14). However, Arbour et al. has presented results in parallel to our study at ASCO 2018. They have reported that baseline steroid use for common indications (e.g., dyspnea, fatigue, brain metastasis) was associated with poorer outcomes in non-small cell lung cancer patients treated with PDL-1 blockade (15).

An interesting finding in this analysis was that patients who were treated with interferon in the adjuvant setting had better results with immune checkpoint inhibitors. We could not find much data about adjuvant interferon use and response to these agents in the literature. In 2007, Downey et al. reported that prior interferon therapy was associated with a lower response rate in metastatic melanoma patients treated with ipilimumab (16). Our results conflict with this observation. IFN alpha is known to upregulate the expression of MHC antigens, antigen processing, and co-stimulatory molecules, leading to more effective antigen presentation. IFN alpha also induces the expression of PDL-1 (17). Gerner et al. have reported that CD8+T cells that have matured in the presence of IFN alpha re-express significantly higher levels of PD-1 upon antigen re-stimulation. They also showed that IFN alpha in combination with anti PDL-1 monoclonal antibodies controlled tumour growth very effectively (18). More studies are warranted to explain this observation.

CONCLUSION

Antibiotics and corticosteroids are widely used agents in cancer care. As checkpoint inhibitors show promising efficacy in many different tumour types, doctors have to keep in mind that antibiotics and steroids may influence the efficacy of these drugs.

Author roles: **SSG:** Designing the study and writing the article, **AMT:** Designing the study, writing the article, **GK:** Collecting data, working with statistics, **FYM:** Collecting data, reviewing the article, **MSA:** Collecting data, reviewing the article, **HŞC:** Reviewing the article, mentor.

Ethics Committee Approval: This research complies with all the relevant national regulations, institutional policies and is in accordance the tenets of the Helsinki Declaration, and has been approved by the Akdeniz Medical Faculty Ethical Committee, Akdeniz University (approval number: 895/ 02.10.2019.).

Informed Consent: All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbé C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363(8):711-23.
2. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A. KEYNOTE-006 investigators. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372(26):2521-32.
3. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E, Savage KJ, Hernberg MM, Lebbé C, Charles J, Mihalcioiu C, Chiarion-Sileni V, Mauch C, Cognetti F, Arance A, Schmidt H, Schadendorf D, Gogas H, Lundgren-Eriksson L, Horak C, Sharkey B,Waxman IM, Atkinson V, Ascierto PA. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372(4):320-30.
4. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD. Combined Nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015; 373(1):23-34.
5. Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillère R, Hannani D, Enot DP, Pfirschke C, Engblom C, Pittet MJ, Schlitzer A, Ginhoux F, Apetoh L, Chachaty E, Woerther PL, Eberl G, Bérard M, Ecobichon C, Clermont D, Bizet C, Gaboriau-Routhiau V, Cerf-Bensussan N, Opolon P, Yessaad N, Vivier E, Ryffel B, lson CO, Doré J, Kroemer G, Lepage P, Boneca IG, Ghiringhelli F, Zitvogel L. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science 2013; 342(6161):971-6.
6. Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre ML, Luke JJ, Gajewski TF. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science 2018; 359(6371):104-8.
7. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, Benyamin FW, Lei YM, Jabri B, Alegre ML, Chang EB, Gajewski TF. Commensal bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 2015; 350(6264):1084-9.
8. Francino MP. Antibiotics and the human gut microbiome: Dysbioses and accumulation of resistances. Front Microbiol 2016; 6:1543.
9. Derosa L, Routy B, Enot D, Baciarello G, Massard C, Loriot Y, Fizazi K, Escudier BJ, Zitvogel L, Albiges L. Impact of antibiotics on outcome in patients with metastatic renal cell carcinoma treated with immune checkpoint inhibitors. Journal of Clinical Oncology 2017; (suppl 6):462.
10. Derosa L, Hellmann MD, Spaziano M, Halpenny D, Fidelle M, Rizvi H, Long N, Plodkowski AJ, Arbour KC, Chaft JE, Rouche JA, Zitvogel L, Zalcman G, Albiges L, Escudier B, Routy B. Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. Ann Oncol 2018; 29(6):1437-44.
11. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, Fidelle M, Flament C, Poirier-Colame V, Opolon P, Klein C, Iribarren K, Mondragón L, Jacquelot N, Qu B, Ferrere G, Clémenson C, Mezquita L, Masip JR, Naltet C, Brosseau S, Kaderbhai C, Richard C, Rizvi H, Levenez F, Galleron N, Quinquis B, Pons N, Ryffel B, Minard-Colin V, Gonin P, Soria JC, Deutsch E, Loriot Y, Ghiringhelli F, Zalcman G, Goldwasser F, Escudier B, Hellmann MD, Eggermont A, Raoult D, Albiges L, Kroemer G, Zitvogel L. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 2018; 359(6371):91-7.
12. Kaderbhai C, Richard C, Fumet JD, Aarnink A, Foucher P, Coudert B, Favier L, Lagrange A, Limagne E, Boidot R, Ghiringhelli F. Antibiotic use does not appear to influence response to nivolumab. Anticancer Res 2017; 37(6):3195-200.
13. Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, Carvajal RD, Dickson MA, D'Angelo SP, Woo KM, Panageas KS, Wolchok JD, Chapman PB. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial sloan kettering cancer center. J Clin Oncol 2015; 33(28):3193-8.

14. Garant A, Guilbault C, Ekmekjian T, Greenwald Z, Murgoi P, Vuong T. Concomitant use of corticosteroids and immune checkpoint inhibitors in patients with hematologic or solid neoplasms: A systematic review. Crit Rev Oncol Hematol 2017; 120:86-92.
15. Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, Bernal GM, Chaft JE, Ferrara R, Lai WCV, Hendriks L, Sabari JK, Caramella C, Plodkowski AJ, Halpenny D, Planchard D, Riely GJ, Besse B, Hellmann MD. Deleterious effect of baseline steroids on efficacy of PD-(L) 1 blockade in patients with NSCLC. J Clin Oncol 2018; (Suppl 15): 9003.
16. Downey SG, Klapper JA, Smith FO, Yang JC, Sherry RM, Royal RE, Kammula US, Hughes MS, Allen TE, Levy CL, Yellin M, Nichol G, White DE, Steinberg SM, Rosenberg SA. Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. Clin Cancer Res 2007; 13:6681-8.
17. Rafique I, Kirkwood JM, Tarhini AA. Immune checkpoint blockade and interferon-α in melanoma. Semin Oncol 2015; 42(3):436-47.
18. Gerner MY, Heltemes-Harris LM, Fife BT, Mescher MF. Cutting edge: IL-12 and type I IFN differentially program CD8 T cells for programmed death 1 re-expression levels and tumor control. J Immunol 2013;191(3):1011-5.