ANTICANCER RESEARCH *40*: 1219-1227 (2020)
doi:10.21873/anticanres.14063

Review

Immune-related Adverse Effects and Outcome of Patients With Cancer Treated With Immune Checkpoint Inhibitors

ONDREJ FIALA[1,2], ONDREJ SOREJS[1,2], JAN SUSTR[1], RADEK KUCERA[3], ONDREJ TOPOLCAN[3] and JINDRICH FINEK[1]

[1]*Department of Oncology and Radiotherapeutics, Medical School and University Hospital in Pilsen, Charles University, Pilsen, Czech Republic;*
[2]*Biomedical Center, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic;*
[3]*Department of Immunochemistry Diagnostics, Medical School and University Hospital in Pilsen, Charles University, Pilsen, Czech Republic*

Abstract. *Immunotherapy based on immune checkpoint inhibitors (ICIs) represents a novel anticancer treatment strategy. Monoclonal antibodies targeting cytotoxic T-lymphocyte antigen-4 (CTLA4), programmed cell death-1 receptor (PD1) and programmed cell death-1 ligand (PD-L1) have shown efficacy and safety in the treatment of various malignancies. Some of them have recently found their place in a routine clinical practice, while others are at different phases of clinical trials. Treatment with ICIs may be accompanied by undesirable impairment of immunotolerance to non-tumoural tissues, leading to a specific side-effect also called immune-related adverse events (irAE). There is an increasing body of evidence that the development of irAEs is associated with a beneficial effect of immunotherapy, thus it has become a hot topic in the field of clinical oncology. This review is focused on data from recently published studies evaluating the association between irAEs and outcome of patients with cancer treated with ICIs.*

Immunotherapy based on the blocking of immune checkpoints represents an innovative anticancer treatment strategy that has been currently changing the world of clinical oncology. There are several agents that have shown efficacy and safety in the treatment of various malignancies. Some of them have recently found their place in a routine clinical practice, while others are at different phases of clinical trials. Among the malignancies where ICIs have been well established and have already been widely used in the routine clinical practice include malignant melanoma (MM), lung cancer and renal cell carcinoma (RCC). Furthermore, ICIs show efficacy and have been approved for the treatment of urothelial carcinoma, breast, head and neck squamous cell cancer, gastric cancer, hepatocellular cancer, colorectal cancer with microsatellite instability, Hodgkin lymphoma and Merkel cell carcinoma (1-12).

The most frequently used immune checkpoint inhibitors (ICIs) are monoclonal antibodies against cytotoxic T-lymphocyte antigen-4 (CTLA4), programmed cell death-1 receptor (PD1) and programmed cell death-1 ligand (PD-L1). The most commonly studied CTLA4 inhibitor is ipilimumab; among PD1 inhibitors, nivolumab, pembrolizumab and avelumab; among PD-L1 inhibitors, atezolizumab and durvalumab.

In contrast to chemotherapy or targeted therapies, immunotherapy has several specific characteristics in terms of the clinical response and side-effects. Overcoming tumour immunotolerance induced by ICIs may be accompanied by undesirable impairment of immunotolerance to non-tumoural tissues. The consequence of this is the emergence of specific side-effects also called immune-related adverse events (irAE). The nature of irAEs is similar to an autoimmune disease. These are to a large extent typical for immunotherapy. In general, irAEs can be divided into organ-specific and organ non-specific; according to the timing of onset they can be divided into early and late. IrAEs can result in damage of any organ, including the skin, intestines, liver, kidneys, lungs, eyes, endocrine glands, heart, muscle, and central or peripheral nervous system (13-15). The most commonly seen are dermatological and gastrointestinal irAEs.

Correspondence to: Ondrej Fiala, MD, Ph.D., Department of Oncology and Radiotherapy, Medical School and University Hospital Pilsen, Charles University Prague, alej Svobody 80, CZ-304 60 Pilsen, Czech Republic. Tel: +42 0728655488, e-mail: fiala.o@centrum.cz

Key Words: Immunotherapy, checkpoint inhibitor, adverse effects, outcome, efficacy, review.

There is an increasing body of evidence that the development of irAEs is associated with a beneficial effect of immunotherapy (16). This association has been described so far in malignancies for which there is the greatest experience with immunotherapy, including MM, non-small cell lung cancer (NSCLC) and RCC.

IrAEs and Outcome in MM

The association between irAEs and the efficacy of ICIs was first reported in patients with advanced-stage MM. The published data on treatment with CTLA4 (ipilimumab) and PD1 (nivolumab, pembrolizumab) inhibitors are not entirely consistent.

The first retrospective analysis of patients with metastatic MM (n=56) treated with ipilimumab which was conducted by Attia *et al*. showed that 36% of patients with grade 3-4 irAEs reached an objective response to the therapy (ORR), whereas among patients without or with a low-grade irAEs, only 5% had a treatment response (p=0.008) (17). These results were subsequently confirmed by a combined analysis of the data obtained from two prospective clinical trials (n=139), which showed that irAEs of any grade in patients with metastatic MM treated with ipilimumab were significantly associated with ORR (p=0.0004) and a significantly longer duration of response was observed in patients with grade 3-4 irAEs as compared to those with low-grade irAEs (34 *vs*. 11 months) (18). Nevertheless, the study showed that the duration of treatment response was not adversely affected by the use of high doses of corticosteroids to treat irAEs (p=0.23) (18). On the other hand, two retrospective analyses of larger patient cohorts treated with ipilimumab (n=833 and n=298, respectively) did not show any significant association between irAEs and outcome (19, 20). However, the retrospective design of these studies potentially conferring a bias in the form of underestimation and grade underscoring of irAEs should be emphasized (19, 20).

Several studies have shown the impact of specific types of irAEs. A significant association between development of vitiligo and survival was observed in a meta-analysis of published studies in patients with advanced MM treated with various immunotherapy strategies, which was conducted by Teulings *et al*. (21). Their results showed that vitiligo was associated with longer progression-free survival (PFS) and overall survival (OS) [hazard ratio (HR)=0.51, p=0.005 and HR=0.25, p=0.003, respectively] (21). Similar results have been reported in patients with metastatic MM treated with high-dose interferon or high-dose interleukin-2 (22, 23). Endocrine irAEs, most frequently in the form of hypopituitarism or hypothyroidism, represent another specific type of irAE whose incidence is described in association with a beneficial effect of immunotherapy with ICIs. Fujisawa *et al*. observed a significant association of endocrine irAEs with OS in patients with unresectable or metastatic MM (n=60) treated with ipilimumab (HR=0.22, p=0.015) (24). A pooled analysis of safety data of nivolumab obtained from four prospective clinical trials in patients with advanced MM (n=576) showed a significantly higher ORR in patients with irAEs of any grade (48.6 *vs*. 17.8%, p<0.0001) (25). Similarly, in a small retrospective study including patients with advanced MM treated with nivolumab (n=15), Okada *et al*. reported a higher disease control rate (DCR) (75% *vs*. 14%, p<0.05) and longer OS (p<0.05) in patients with any irAE compared to those without (26). A retrospective study focusing on the role of irAEs in patients with resected and unresectable MM (n=148) treated with nivolumab was conducted by Freeman-Keller *et al*. (27). They found a significantly longer OS in patients who experienced an irAE *versus* those who did not (p<0.001), while the OS benefit was noted in patients who reported three or more irAE events (p<0.001) (27). Moreover, a 12-week landmark survival analysis closely focusing on the role of specific type of irAEs found that only skin rash and vitiligo were significantly associated with OS (p=0.0004 and p=0.028), while no statistically significant differences in OS were seen in patients with any grade of hypothyroidism (p=0.117), hyperthyroidism (p=0.489), diarrhoea (p=0.132), or pneumonitis (p=0.493) (27). Another retrospective study by Maeda *et al*. also recorded a significant association of endocrine irAEs with DCR (84.6% *vs*. 37.5%, p=0.004) in patients treated with nivolumab for metastatic MM (n=69); there was also a trend for longer PFS in the 20-week landmark analysis, however, it was not statistically significant (p=0.07) (28). The data published on the linkage between irAEs and outcome in patients treated with pembrolizumab are still limited, however, several studies suggest similar results to those obtained from studies with nivolumab. The retrospective study conducted by Indini *et al*. including patients with metastatic MM (n=173) treated with pembrolizumab or nivolumab found a higher DCR (p=0.029) and longer PFS and OS in patients with any irAE in the multivariate Cox regression analysis (HR=0.47, p=0.016; HR=0.39, p=0.007) (29). Analysis of prospectively collected data from patients with advanced MM treated with pembrolizumab (n=147) found a higher DCR in patients who developed any irAE (75.0 *vs*. 17.9%, p=0.02) and the best results were achieved in patients with higher grade irAEs, in whom a significantly longer PFS and OS were found compared to patients without irAEs (HR=0.54, p<0.001; HR=0.51, p<0.001) (30). There was no significant association between the use of corticosteroids and PFS nor OS (p=0.8 and p=0.6, respectively) (30). The results of selected studies on patients with MM are summarised in Table I.

Table I. *Summary of selected studies in patients with malignant melanoma.*

Authors (Ref)	Year	Immune checkpoint inhibitor	Study design	Patients, n	Results
Attia *et al*. (17)	2005	Ipilimumab	Retrospective	56	• Higher ORR in patients with grade 3-4 irAEs *vs*. those without or with a low-grade irAEs (36% *vs*. 5%, p=0.008).
Downey *et al*. (18)	2007	Ipilimumab	Retrospective	139	• Higher ORR in patients with irAEs *vs*. those without (grade 3/4: 28% *vs*. grade 1/2: 22% *vs*. no irAEs: 2%, p=0.0004).
Ascierto *et al*. (19)	2014	Ipilimumab	Retrospective	855	• No difference in DCR between patients with irAEs of any grade and those without (35% *vs*. 34%). • No difference in OS between patients with irAEs of any grade and those without after adjusting for the number of doses completed (10.1 *vs*. 9.7 months).
Horvat *et al*. (20)	2015	Ipilimumab	Retrospective	298	• No association of irAEs with TTF and OS.
Teulings *et al*. (21)	2016	Various immunotherapy strategies	Meta-analysis	5,737	• Vitiligo was associated with longer PFS (HR=0.51, p=0.005) and OS (HR=0.25, p=0.003).
Freeman-Keller *et al*. (27)	2016	Nivolumab	Retrospective	148	• Longer OS for patients with any irAEs *vs*. those without irAEs (p<0.001) • Skin rash and vitiligo were associated with OS (p=0.0004 and p=0.028) in a 12-week landmark survival analysis. • No association of OS with other irAEs (endocrinopathies, colitis, pneumonitis) in a 12-week landmark survival analysis.
Weber *et al*. (25)	2017	Nivolumab	Retrospective	576	• Higher ORR in patients with any irAEs compared to those without (48.6 *vs*. 17.8%, p<0.0001).
Fujisawa *et al*. (22)	2018	Ipilimumab	Retrospective	60	• Endocrine irAEs are associated with longer OS (HR=0.22, p=0.015).
Okada *et al*. (26)	2018	Nivolumab	Retrospective	15	• Higher DCR in patients with any irAE (p<0.05). • Longer OS in patients with any irAE (p<0.05).
Maeda *et al*. (28)	2018	Nivolumab	Retrospective	69	• Higher DCR in patients with endocrine irAEs (84.6% *vs*. 37.5%, p=0.004). • Trend for longer PFS in patients with endocrine irAEs (p=0.07) in the 20-week landmark analysis.
Indini *et al*. (29)	2018	Pembrolizumab or nivolumab	Retrospective	173	• Higher DCR in patients with any irAE (p<0.029). • Longer PFS and OS in patients with any irAE in the multivariate Cox regression analysis (HR=0.47, p=0.016; and HR=0.39, p=0.007, respectively). • Vitiligo was significantly associated with OS (p=0.003).
Bisschop *et al*. (30)	2019	Pembrolizumab	Retrospective	147	• Higher DCR in patients with any irAE (75.0 *vs*. 17.9%, p=0.02). • Longer PFS and OS in patients with high-grade irAEs in multivariate Cox regression analysis (HR=0.54, p<0.001; HR=0.51, p<0.001). • No significant association between the use of corticosteroids and PFS or OS (p=0.8 and p=0.6, respectively).

irAE: Immune-related adverse effect; ORR: objective response rate; DCR: disease control rate; PFS: progression-free survival; TTF: time to treatment failure; OS: overall survival; HR: hazard ratio.

IrAEs and Outcome in NSCLC

In patients with advanced and metastatic NSCLC, the association of irAEs with the effect of immunotherapy has been documented particularly in treatment with anti-PD1 and anti-PD-L1 inhibitors, which are commonly used in advanced NSCLC.

The association of the effect of nivolumab with irAE in patients with metastatic NSCLC (n=40) was first reported by Hasan Ali *et al*., who observed the association of treatment response with skin toxicity (31). Skin irAEs were associated with ORR (42% in patients with skin irAEs *vs*. 7% in those without) (31). Sato *et al*. observed that irAEs were associated with longer PFS (HR=0.10, p<0.001) in patients with advanced NSCLC treated with nivolumab (n=38), however, subsequent 60-day landmark analysis did not show any significant difference (HR=0.28, p=0.13) (32). Longer OS in patients with metastatic NSCLC (n=91) who developed any

irAEs during the course of nivolumab treatment as compared to those with no irAEs (HR=2.75, $p<0.001$) was reported by Owen *et al*. (33). They did not observe significant differences in a 3-month landmark analysis, which was similar to the study by Sato *et al*. (32). Another retrospective analysis of patients with advanced NSCLC treated with nivolumab (n=134) showed higher ORR (52.3% *vs*. 27.9%, $p=0.02$) in patients with any irAE; moreover, in a Cox multivariable analysis, irAEs remained a significant factor for longer PFS (HR=0.542, $p=0.04$) as well as for OS (HR=0.285, $p=0.003$) (34). Regarding the specific type of irAE, skin irAEs were significantly associated with longer PFS (HR=0.476, $p=0.03$) and OS (HR=0.209, $p=0.003$), and endocrine irAEs were significantly associated with longer PFS (HR=0.237, $p=0.02$) (34).

The prognostic role of irAEs developing early after initiation of nivolumab treatment was demonstrated in the analysis of prospective data of patients with advanced NSCLC (n=43) conducted by Teraoka *et al*. (35). They found a significant correlation of longer PFS with any irAE ($p=0.01$) and irAE in the form of skin rash ($p=0.01$) in a 2-week landmark analysis (35). By shifting the boundary of the landmark analysis to 6 weeks, the differences in PFS were no longer significant but there was a significant trend for both parameters ($p=0.06$ and $p=0.08$); the shift beyond statistical significance might have been affected by a small group of patients (35). Subsequently, two larger retrospective studies were published. The study conducted by Ricciuti *et al*., including patients with advanced NSCLC treated with nivolumab (n=195), showed significantly higher ORR (43.5% *vs*. 10.0%, $p<0.0001$) and DCR (70.5% *vs*. 18.1%, $p<0.0001$), as well as longer PFS and OS (HR=0.41, $p<0.0001$ and HR=0.33, $p<0.0001$) in patients with irAEs compared with patients without any (36). The results of the Cox multivariate model showed the following factors to be significant for PFS: any irAE (HR=0.48, $p<0.0001$), pulmonary (HR=0.56, $p=0.038$), gastrointestinal (HR=0.055, $p=0.021$), endocrine (HR=0.59, $p=0.011$) and skin irAEs (HR=0.57, $p=0.031$); significant factors for OS were: any irAE (HR=0.38, $p<0.0001$), pulmonary (HR=0.46, $p=0.022$), gastrointestinal (HR=0.50, $p=0.045$), endocrine (HR=0.45, $p=0.001$) and skin irAEs (HR=0.80, $p=0.043$) (36). A 6-weeks landmark analysis showed a significant association of irAEs with OS (HR=0.55, $p=0.021$) and a 12-weeks landmark analysis showed an even deeper and statistically significant association with PFS (HR=0.48, $p<0.0001$) and OS (HR=0.40, $p<0.0001$) (36). The results of the study also showed longer PFS and OS in patients with two or more types of irAEs *versus* those with only one *versus* those without any irAE (PFS: 8.5 *vs*. 4.6 *vs*. 2.0 months, $p<0.0001$; OS: 26.8 *vs*. 11.9 *vs*. 4.0 months, $p<0.0001$) (36).

The association of the incidence of irAEs with the effect of anti-PD1 (nivolumab, pembrolizumab) and anti-PD-L1 (atezolizumab) inhibitors in patients with advanced NSCLC (n=270) was recently confirmed by a retrospective study by conducted by Grangeon *et al*. (37). The results of this study showed a significant association between the incidence of irAEs and higher ORR (22.9% *vs*. 5.7%, $p<0.0001$), DCR (72.4% *vs*. 36.7% $p<0.001$) as well as longer PFS (HR=0.42, $p<0.001$) and OS (HR=0.29, $p<0.001$) (37). The study confirmed a significant association of irAE in a form of hypothyroidism with longer PFS (HR=0.56, $p=0.005$) and OS (HR=0.46, $p=0.01$) and did not show significant differences according to the grade of irAEs (37). The association of immune-related thyroid dysfunction with effect of ICIs has been observed also in two other studies by Osorio *et al*. (38) and Toi *et al*. (39). Moreover, both studies reported that the development of thyroid dysfunction was significantly higher in patients with pre-existing antithyroid antibodies than in those without (80% *vs*. 8%, $p<0.0001$; and 40% *vs*. 2%, $p<0.001$, respectively) (38, 39).

The largest study focused on the association of irAEs with ICI treatment efficacy to date was recently conducted by Cortellini *et al*. (40). Their retrospective study included 559 patients with advanced NSCLC treated with nivolumab or pembrolizumab (40). The results of a multivariate analysis showed a higher ORR was related to experiencing any irAE ($p<0.0001$), and endocrine ($p=0.0043$) and skin ($p=0.0005$) irAEs; significantly longer PFS was associated with irAEs of any grade ($p<0.0001$), endocrine ($p=0.0084$) and skin ($p=0.0001$); and significantly longer OS was associated with irAEs of any grade ($p<0.0001$), endocrine ($p=0.0044$), gastrointestinal ($p=0.0437$), and skin ($p=0.0006$) irAEs. The 6-weeks landmark analysis revealed irAEs of any grade as an independent predictive factor for higher ORR, and longer PFS and OS (40). The results of selected studies on patients with NSCLC are summarised in Table II.

IrAEs and Outcome in RCC

As compared to MM and NSCLC, the data on the relationship between irAEs and outcome of patients with advanced RCC treated with ICIs are limited to several recently published retrospective studies. The study conducted by Ishihara *et al*. (n=47) showed significantly higher ORR (60.9% *vs*. 12.5%, $p=0.0006$), and longer PFS ($p<0.0001$) and OS ($p=0.0072$) in patients with irAEs as compared to those without (41). The Cox multivariate model confirmed the occurrence of irAEs as an independent factor for better PFS (HR=0.25, $p=0.0009$); OS analysis was not performed (41). A landmark analysis after two cycles of treatment (i.e. after 1 month of the treatment) showed significant association only for PFS ($p=0.0279$); for OS the difference was not statistically significant ($p=0.193$). Regarding the grade of irAEs, PFS was significantly longer both in patients with grade 1-2 irAEs ($p=0.0024$) and those with grade 3 or

Table II. *Summary of selected studies in patients with non-small cell lung cancer.*

Authors (Ref)	Year	Immune checkpoint inhibitor	Study design	Patients, n	Results
Hasan Ali *et al*. (31)	2016	Nivolumab	Retrospective	40	• Skin irAEs were associated with ORR (42% in patients with skin irAEs *vs*. 7% in those without).
Teraoka *et al*. (35)	2017	Nivolumab	Prospective	43	• Longer PFS in patients with any irAEs (p=0.01) in a 2-weeks landmark analysis. • Longer PFS in patients with skin rash (p=0.01) in a 2-weeks landmark analysis.
Osorio *et al*. (38)	2017	Pembrolizumab	Retrospective	51	• Thyroid dysfunction was significantly higher in patients with pre-existing antithyroid antibodies vs. those without (80% *vs*. 8%, p<0.0001). • Longer OS in patients who developed thyroid dysfunction (HR=0.29, p=0.04).
Haratani *et al*. (34)	2018	Nivolumab	Retrospective	134	• Higher ORR in patients with any irAEs (52.3% *vs*. 27.9%, p=0.02). • IrAEs remained a significant factor for longer PFS (HR=0.542, p=0.04) and also for OS (HR=0.285, p=0.003) in a Cox multivariate analysis. • Skin irAEs were associated with longer PFS (HR=0.476, p=0.03) and OS (HR=0.209, p=0.003). • Endocrine irAEs were associated with longer PFS (HR=0.237, p=0.02).
Ricciuti *et al*. (36)	2018	Nivolumab	Retrospective	195	• Higher ORR (43.5% *vs*. 10.0%, p<0.0001) and DCR (70.5% *vs*. 18.1%, p<0.0001) in patients with irAEs *vs*. those without irAEs. • Longer PFS and OS in patients with irAEs *vs*. those without irAEs (HR=0.41, p<0.0001 and HR=0.33, p<0.0001). • Significant factors for PFS: Any irAE (HR=0.48, p<0.0001), pulmonary irAEs (HR=0.56, p=0.038), gastrointestinal irAEs (HR=0.05.5, p=0.021), endocrine irAEs (HR=0.59, p=0.011) and skin irAEs (HR=0.57, p=0.031); • Significant factors for OS: Any irAE (HR=0.38, p<0.0001), pulmonary irAEs (HR=0.46, p=0.022), gastrointestinal irAEs (HR=0.50, p=0.045), endocrine irAEs (HR=0.45, p=0.001) and skin irAEs (HR=0.80, p=0.043) in a Cox multivariate model. • Longer PFS and OS in patients with ≥2 types of irAEs *vs*. patients with 1 irAE *vs*. patients without any irAE (PFS: 8.5 *vs*. 4.6 *vs*. 2.0 months, p<0.0001; OS: 26.8 *vs*. 11.9 *vs*. 4.0 months, p<0.0001).
Owen *et al*. (33)	2018	Nivolumab	Retrospective	91	• Longer PFS (HR=2.75, p<0.001) in patients with irAEs *vs*. those without irAEs. • No significant PFS difference in 3-months landmark analysis.
Sato *et al*. (32)	2018	Nivolumab	Retrospective	38	• Longer OS (HR=0.10, p<0.001) in patients with irAEs *vs*. those without irAEs. • No significant OS difference in 60-days landmark analysis (HR=0.28, p=0.13).
Toi *et al*. (39)	2018	Nivolumab	Retrospective	70	• Thyroid dysfunction was higher in patients with pre-existing antithyroid antibodies *vs*. those without (40% *vs*. 2%, p<0.001). • Pre-existing antithyroid antibodies were independent predictors of ORR (OR=0.22, p=0.033).
Grangeon *et al*. (37)	2019	Nivolumab, pembrolizumab, atezolizumab	Retrospective	270	•Higher ORR (22.9% *vs*. 5.7%, p<0.0001) and DCR (72.4% *vs*. 36.7% p<0.001) in patients with irAEs *vs*. those without irAEs. • Longer PFS (HR=0.42, p<0.001) and OS (HR=0.29, p<0.001) in patients with irAEs *vs*. those without irAEs.
Cortellini *et al*. (40)	2019	Nivolumab, pembrolizumab	Retrospective	559	• Higher ORR in patients with any irAEs (p<0.0001), endocrine (p=0.0043) and skin irAEs (p=0.0005). • Longer PFS was associated with irAEs of any grade (p<0.0001), endocrine irAEs (p=0.0084) and skin irAEs (p=0.0001). • Longer OS was associated with irAEs of any grade (p<0.0001), endocrine irAEs (p=0.0044), gastrointestinal irAEs (p=0.0437), skin irAEs (p=0.0006).

irAE: Immune-related adverse effect; ORR: objective response rate; DCR: disease control rate; PFS: progression-free survival; TTF: time to treatment failure; OS: overall survival; HR: hazard ratio; OR: odds ratio.

more irAEs (p=0.0023) as compared to patients without irAEs; for OS, there was significant correlation only in patients with grade 1-2 irAEs (p=0.0124). With regard to the specific type of irAEs, a significant association with PFS and OS was demonstrated only for skin irAEs (p=0.011) (41). The results of a recently published retrospective study (n=389) conducted by Verzoni *et al*. confirmed a significant association of irAEs with OS (p=0.01); furthermore, irAEs remained an independent factor for OS in a multivariable Cox model (HR=0.57, p=0.02) (42). A 6-week OS landmark analysis showed significant association with irAEs (p=0.006). The results of a 1-year OS analysis found no statistically significant difference between those with grade 1-2 and those with grade 3-4 irAEs (60.9% *vs*. 79.6%, p=0.19), nor between those with early (occurring within 6 weeks from the treatment initiation) and those with late (occurring over 6 weeks from the treatment initiation) irAEs (78.7% *vs*. 85.2%, p=0.34) (42); neither ORR nor PFS were evaluated in the study. A development of vitiligo was recently reported in a case of metastatic RCC which achieved a durable complete response after treatment with nivolumab, suggesting this type of irAE to be a factor associated with the efficacy of ICIs in RCC, similarly to that in MM and NSCLC (43).

IrAEs and Outcome in Other Malignancies

Gastrointestinal cancer. The relationship between irAEs and the efficacy of anti-PD1 therapy in patients (n=61) with various types of advanced gastrointestinal cancer including hepatocellular carcinoma, colorectal cancer with microsatellite instability and gastric cancer was assessed in a retrospective study (44). The study found significantly longer PFS and OS in patients experiencing irAEs as compared to those who not (p=0.0001 and p=0.0036) (44). A sub-analysis found no statistically significant differences in PFS nor OS according to the grade, timing of onset or use of corticosteroid therapy (44).

A retrospective study focusing on patients with advanced gastric cancer treated with nivolumab (n=65) conducted by Masuda *et al*. found significantly longer PFS and OS in patients with irAEs compared to those without (p<0.001 and p<0.001, respectively) (45). Furthermore, the results of multivariable Cox model demonstrated that absence of irAEs represented an independent factor associated with a poor prognosis (HR=9.54, p<0.001) (45).

Head and neck cancer. In patients with metastatic head and neck cancer receiving anti-PD1 therapy (n=114), a retrospective study conducted by Foster *et al*. found higher ORR (p=0.02) and also longer PFS and OS in patients with irAEs compared to those without (p=0.0004 and p=0.007, respectively) (46). The results of multivariate analyses shown that the development of irAEs was independent factor for improved ORR (p=0.03), PFS (p=0.009), and OS (p=0.003) (46).

Urothelial cancer. In patients with metastatic urothelial cancer, Morales-Barrera *et al*. reported higher DCR (79% *vs*. 36.3%, p=0.002) and longer OS (21.91 *vs*. 6.47 months, p=0.004) for those with irAEs as compared to those without in a single-institution retrospective study (n=52) (47). A pooled analysis of seven randomised clinical trials including cisplatin-refractory or cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer treated with pembrolizumab or atezolizumab (n=1,747) was conducted recently by Maher *et al*. (48). The study focused on the role of irAEs and adverse events of special interest, which were defined separately from irAEs as autoimmune events not requiring corticosteroid therapy (48). They found longer OS in patients with adverse events of special interest (HR=0.45) and those with irAEs (HR=0.53) as compared to those without (48). The duration of response was not affected significantly by the use of corticosteroids in management of irAEs (48).

Conclusion

There is increasing evidence suggesting that irAEs are associated with treatment response and survival of patients with cancer treated with ICIs. This could be used for the estimation of the prognosis of patients treated with ICIs, suggesting development of irAEs as a feasible on-treatment predictive biomarker. Moreover, this can be helpful information for distinguishing between real progression and pseudoprogression. Most of the published studies are recent, thus it is a hot topic in the field of clinical oncology. However, the vast majority of studies published to date are limited by the relatively low number of patients and retrospective design introducing possible bias. There remain many open questions. The detailed pathophysiological mechanisms underlying various irAEs, as well as the association of specific types of irAEs with the efficacy of ICIs in various cancer types, should be elucidated in the future, optimally under the conditions of prospective clinical trials.

Conflicts of Interest

OF received honoraria from Roche, GSK and Pfizer for consultations and lectures unrelated to this project. JF has received honoraria from Astra Zeneca, Roche and Novartis for consultations and lectures unrelated to this project. OS, JS, RK and OT declare that they have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence this work.

Authors' Contributions

OF wrote the article with support from OS, JS, RK, OT and JF.

Acknowledgements

This study was supported by the National Sustainability Program I (NPU I) Nr. LO1503 provided by the Ministry of Education Youth and Sports of the Czech Republic and by the Charles University Research Fund (Progres Q39) and by the European Regional Development Fund Project "Application of Modern Technologies in Medicine and Industry" (No. CZ.02.1.01/0.0/0.0/17_048/0007280) and by the grant of Ministry of Health of the Czech Republic - 17-30748A.

References

1 Pennock GK and Chow LQ: The evolving role of immune checkpoint inhibitors in cancer treatment. Oncologist *20(7)*: 812-822, 2015. PMID: 26069281. DOI: 10.1634/theoncologist.2014-0422

2 La-Beck NM, Jean GW, Huynh C, Alzghari SK and Lowe DB: Immune checkpoint inhibitors: New insights and current place in cancer therapy. Pharmacotherapy *35(10)*: 963-976, 2015. PMID: 26497482. DOI: 10.1002/phar.1643

3 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 and Ribas A: Pembrolizumab *versus* ipilimumab in advanced melanoma. N Engl J Med *372(26)*: 2521-2532, 2015. PMID: 25891173. DOI: 10.1056/NEJMoa1503093

4 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 and Ascierto PA: Nivolumab in previously untreated melanoma without *BRAF* mutation. N Engl J Med *372(4)*: 320-330, 2015. PMID: 25399552. DOI: 10.1056/NEJMoa1412082

5 Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R and Brahmer JR: Pembrolizumab *versus* chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med *375(19)*: 1823-1833, 2016. PMID: 27718847.

6 Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gurney H, Donskov F, Bono P, Wagstaff J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM and Sharma P: Nivolumab *versus* everolimus in advanced renal-cell carcinoma. N Engl J Med *373(19)*: 1803-1813, 2015. PMID: 26406148. DOI: 10.1056/NEJMoa1510665

7 Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, Vogelzang NJ, Climent MA, Petrylak DP, Choueiri TK, Necchi A, Gerritsen W, Gurney H, Quinn DI, Culine S, Sternberg CN, Mai Y, Poehlein CH, Perini RF and Bajorin DF: Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med *376(11)*: 1015-1026, 2017. PMID: 28212060. DOI: 10.1056/NEJMoa1613683

8 Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Iglesias Docampo LC, Haddad R, Rordorf T, Kiyota N, Tahara M, Monga M, Lynch M, Geese WJ, Kopit J, Shaw JW and Gillison ML: Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med *375(19)*: 1856-1867, 2016. PMID: 27718784.

9 El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB and Melero I: Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet *389*(10088): 2492-2502, 2017. PMID: 28434648. DOI: 10.1016/S0140-6736(17)31046-2

10 Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, Desai J, Hill A, Axelson M, Moss RA, Goldberg MV, Cao ZA, Ledeine JM, Maglinte GA, Kopetz S, André T: Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): An open-label, multicentre, phase 2 study. Lancet Oncol *18(9)*: 1182-1191, 2017. PMID: 28734759. DOI: 10.1016/S1470-2045(17)30422-9

11 Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA and Diaz LA Jr.: Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science *357(6349)*: 409-413, 2017. PMID: 28596308. DOI: 10.1126/science.aan6733

12 Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, Sun W, Jalal SI, Shah MA, Metges JP, Garrido M, Golan T, Mandala M, Wainberg ZA, Catenacci DV, Ohtsu A, Shitara K, Geva R, Bleeker J, Ko AH, Ku G, Philip P, Enzinger PC, Bang YJ, Levitan D, Wang J, Rosales M, Dalal RP and Yoon HH: Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: Phase 2 clinical KEYNOTE-059 trial. JAMA Oncol *4(5)*: e180013, 2018. PMID: 29543932. DOI: 10.1001/jamaoncol.2018.0013

13 Abdel-Wahab N, Alshawa A and Suarez-Almazor ME: Adverse events in cancer immunotherapy. Adv Exp Med Biol *995:* 155-174, 2017. PMID: 28321817. DOI: 10.1007/978-3-319-53156-4_8

14 Nagai H and Muto M: Optimal management of immune-related adverse events resulting from treatment with immune checkpoint inhibitors: A review and update. Int J Clin Oncol *223(3)*: 410-420, 2018. PMID: 29516216. DOI: 10.1007/s10147-018-1259-6

15 Daniels GA, Guerrera AD, Katz D and Viets-Upchurch J: Challenge of immune-mediated adverse reactions in the emergency department. Emerg Med J *36(6)*: 369-377, 2019. PMID: 31113799. DOI: 10.1136/emermed-2018-208206

16 Saleh K, Khalife-Saleh N and Kourie HR: Do immune-related adverse events correlate with response to immune checkpoint inhibitors? Immunotherapy *11(4)*: 257-259, 2019. PMID: 30678551. DOI: 10.2217/imt-2018-0201

17 Attia P, Phan GQ, Maker AV, Robinson MR, Quezado MM, Yang JC, Sherry RM, Topalian SL, Kammula US, Royal RE, Restifo NP, Haworth LR, Levy C, Mavroukakis SA, Nichol G, Yellin MJ and Rosenberg SA: Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. J Clin Oncol *23(25)*: 6043-6053, 2005. PMID: 16087944. DOI: 10.1200/JCO.2005.06.205

18 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 and Rosenberg SA: Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. Clin Cancer Res *13*(22 pt 1): 6681-6688, 2007. PMID: 17982122. DOI: 10.1158/1078-0432.CCR-07-0187

19 Ascierto PA, Simeone E, Sileni VC, Pigozzo J, Maio M, Altomonte M, Del Vecchio M, Di Guardo L, Marchetti P, Ridolfi R, Cognetti F, Testori A, Bernengo MG, Guida M, Marconcini R, Mandalà M, Cimminiello C, Rinaldi G, Aglietta M and Queirolo P: Clinical experience with ipilimumab 3 mg/kg: Real-world efficacy and safety data from an Expanded Access Programme cohort. J Transl Med *12:* 116, 2014. PMID: 24885479. DOI: 10.1186/1479-5876-12-116

20 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 and 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 *33(28)*: 3193-3198, 2015. PMID: 26282644. DOI: 10.1200/JCO.2015.60.8448

21 Teulings HE, Limpens J, Jansen SN, Zwinderman AH, Reitsma JB, Spuls PI and Luiten RM: Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: A systematic review and meta-analysis. J Clin Oncol *33(7)*: 773-781, 2015. PMID: 25605840. DOI: 10.1200/JCO.2014.57.4756

22 Gogas H, Ioannovich J, Dafni U, Stavropoulou-Giokas C, Frangia K, Tsoutsos D, Panagiotou P, Polyzos A, Papadopoulos O, Stratigos A, Markopoulos C, Bafaloukos D, Pectasides D, Fountzilas G and Kirkwood JM: Prognostic significance of autoimmunity during treatment of melanoma with interferon. N Engl J Med *354(7)*: 709-718, 2006. PMID: 16481638. DOI: 10.1007/s00281-011-0247-y

23 Boasberg PD, Hoon DS, Piro LD, Martin MA, Fujimoto A, Kristedja TS, Bhachu S, Ye X, Deck RR and O'Day SJ: Enhanced survival associated with vitiligo expression during maintenance biotherapy for metastatic melanoma. J Invest Dermatol *126(12)*: 2658-2663, 2006. PMID: 16946711. DOI: 10.1038/sj.jid.5700545

24 Fujisawa Y, Yoshino K, Otsuka A, Funakoshi T, Uchi H, Fujimura T, Matsushita S, Hata H, Okuhira H, Tanaka R, Nagai K, Ishida Y, Nakamura Y, Furudate S, Yamamura K, Imafuku K and Yamamoto Y: Retrospective study of advanced melanoma patients treated with ipilimumab after nivolumab: analysis of 60 Japanese patients. J Dermatol Sci *89(1)*: 60-66, 2018. PMID: 29079332. DOI: 10.1016/j.jdermsci.2017.10.009

25 Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, Sznol M, Long GV, Li H, Waxman IM, Jiang J and Robert C: Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol *35(7)*: 785-792, 2017. PMID: 28068177. DOI: 10.1200/JCO.2015.66.1389

26 Okada N, Kawazoe H, Takechi K, Matsudate Y, Utsunomiya R, Zamami Y, Goda M, Imanishi M, Chuma M, Hidaka N, Sayama K, Kubo Y, Tanaka A and Ishizawa K: Association between immune-related adverse events and clinical efficacy in patients with melanoma treated with nivolumab: A multicenter retrospective study. Clin Ther *41(1)*: 59-67, 2019. PMID: 30528047. DOI: 10.1016/j.clinthera.2018

27 Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G and Weber JS: Nivolumab in resected and unresectable metastatic melanoma: Characteristics of immune-related adverse events and association with outcomes. Clin Cancer Res *22(4)*: 886-894, 2016. PMID: 26446948. DOI: 10.1158/1078-0432.CCR-15-1136

28 Maeda T, Yoshino K, Nagai K, Oaku S, Kato M, Hiura A and Hata H: Development of endocrine immune-related adverse events and improved survival in advanced melanoma patients treated with nivolumab monotherapy. Eur J Cancer *115:* 13-16, 2019. PMID: 31082687. DOI: 10.1016/j.ejca.2019.04.005

29 Indini A, Di Guardo L, Cimminiello C, Prisciandaro M, Randon G, De Braud F and Del Vecchio M: Immune-related adverse events correlate with improved survival in patients undergoing anti-PD1 immunotherapy for metastatic melanoma. J Cancer Res Clin Oncol *145(2)*: 511-521, 2019. PMID: 30539281. DOI: 10.1007/s00432-018-2819-x

30 Bisschop C, Wind TT, Blank CU, Koornstra RHT, Kapiteijn E, Van den Eertwegh AJM, De Groot JWB, Jalving M and Hospers GAP: Association between pembrolizumab-related adverse events and treatment outcome in advanced melanoma: Results from the Dutch Expanded Access Program. J Immunother *42(6)*: 208-214, 2019. PMID: 31145233. DOI: 10.1097/CJI.0000000000000271

31 Hasan Ali O, Diem S, Markert E, Jochum W, Kerl K, French LE, Speiser DE, Früh M and Flatz L: Characterization of nivolumab-associated skin reactions in patients with metastatic non-small cell lung cancer. Oncoimmunology *5(11)*: e1231292, 2016. PMID: 27999741. DOI: 10.1080/2162402X.2016.1231292

32 Sato K, Akamatsu H, Murakami E, Sasaki S, Kanai K, Hayata A, Tokudome N, Akamatsu K, Koh Y, Ueda H, Nakanishi M and Yamamoto N: Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab. Lung Cancer *115:* 71-74, 2018. PMID: 29290265. DOI: 10.1016/j.lungcan.2017.11.019

33 Owen DH, Wei L, Bertino EM, Edd T, Villalona-Calero MA, He K, Shields PG, Carbone DP and Otterson GA: Incidence, risk factors, and effect on survival of immune-related adverse events in patients with non-small-cell lung cancer. Clin Lung Cancer *19(6)*: e893-e900, 2018. PMID: 30197259. DOI: 10.1016/j.cllc.2018.08.008

34 Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, Kaneda H, Hasegawa Y, Tanaka K, Takeda M and Nakagawa K: Association of immune-related adverse events with nivolumab efficacy in non-small cell lung cancer. JAMA Oncol *4(3)*: 374-378, 2018. PMID: 28975219. DOI: 10.1001/jamaoncol.2017.2925

35 Teraoka S, Fujimoto D, Morimoto T, Kawachi H, Ito M, Sato Y, Nagata K, Nakagawa A, Otsuka K, Uehara K, Imai Y, Ishida K, Fukuoka J and Tomii K: Early immune-related adverse events and association with outcome in advanced non-small cell lung cancer patients treated with nivolumab: A prospective cohort study. J Thorac Oncol *12(12)*: 1798-1805, 2017. PMID: 28939128. DOI: 10.1016/j.jtho.2017.08.022

36 Ricciuti B, Genova C, De Giglio A, Bassanelli M, Dal Bello MG, Metro G, Brambilla M, Baglivo S, Grossi F and Chiari R: Impact of immune-related adverse events on survival in patients

with advanced non-small cell lung cancer treated with nivolumab: Long-term outcomes from a multi-institutional analysis. J Cancer Res Clin Oncol *145(2)*: 479-485, 2019. PMID: 30506406. DOI: 10.1007/s00432-018-2805-3

37 Grangeon M, Tomasini P, Chaleat S, Jeanson A, Souquet-Bressand M, Khobta N, Bermudez J, Trigui Y, Greillier L, Blanchon M, Boucekine M, Mascaux C and Barlesi F: Association between immune-related adverse events and efficacy of immune checkpoint inhibitors in non-small-cell lung cancer. Clin Lung Cancer *20(3)*: 201-207, 2019. PMID: 30442524. DOI: 10.1016/j.cllc.2018.10.002

38 Osorio JC, Ni A, Chaft J, Pollina R, Kasler MK, Stephens D, Rodriguez C, Cambridge L, Rizvi H, Wolchok JD, Merghoub T, Rudin CM, Fish S and Hellmann MD: Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Ann Oncol *28(3)*: 583-589, 2017. PMID: 27998967. DOI: 10.1093/annonc/mdw640

39 Toi Y, Sugawara S, Kawashima Y, Aiba T, Kawana S, Saito R, Tsurumi K, Suzuki K, Shimizu H, Sugisaka J, Ono H, Domeki Y, Terayama K, Nakamura A, Yamanda S, Kimura Y and Honda Y: Association of immune-related adverse events with clinical benefit in patients with advanced non-small-cell lung cancer treated with nivolumab. Oncologist *23(11)*: 1358-1365, 2018. PMID: 29934411. DOI: 10.1634/theoncologist.2017-0384

40 Cortellini A, Chiari R, Ricciuti B, Metro G, Perrone F, Tiseo M, Bersanelli M, Bordi P, Santini D, Giusti R, Grassadonia A, Di Marino P, Tinari N, De Tursi M, Zoratto F, Veltri E, Malorgio F, Garufi C, Russano M, Anesi C, Zeppola T, Filetti M, Marchetti P, Berardi R, Rinaldi S, Tudini M, Silva RR, Pireddu A, Atzori F, Iacono D, Migliorino MR, Porzio G, Cannita K, Ficorella C and Buti S: Correlations between the immune-related adverse events spectrum and efficacy of anti-PD1 Immunotherapy in NSCLC patients. Clin Lung Cancer *20(4)*: 237-247, 2019. PMID: 30885550. DOI: 10.1016/j.cllc.2019.02.006

41 Ishihara H, Takagi T, Kondo T, Homma C, Tachibana H, Fukuda H, Yoshida K, Iizuka J, Kobayashi H, Okumi M, Ishida H and Tanabe K: Association between immune-related adverse events and prognosis in patients with metastatic renal cell carcinoma treated with nivolumab. Urol Oncol *37(6)*: 355.e21-355.e29, 2019. PMID: 30935847. DOI: 10.1016/j.urolonc.2019.03.003

42 Verzoni E, Cartenì G, Cortesi E, Giannarelli D, De Giglio A, Sabbatini R, Buti S, Rossetti S, Cognetti F, Rastelli F, Sobrero A, Turci D, Sternberg CN, Porta C, Cappuzzo F, Tortora G, Tassinari D, Panni S, Pazzola A, Surico G, Raimondi A, De Giorgi U and Procopio G: Real-world efficacy and safety of nivolumab in previously-treated metastatic renal cell carcinoma, and association between immune-related adverse events and survival: The Italian Expanded Access Program. J Immunother Cancer *7(1)*: 99, 2019. PMID: 30944023. DOI: 10.1186/s40425-019-0579-z

43 Billon E, Walz J, Brunelle S, Thomassin J, Salem N, Guerin M, Vicier C, Dermeche S, Albiges L, Tantot F, Nenan S, Pignot G and Gravis G: Vitiligo adverse event observed in a patient with durable complete response after nivolumab for metastatic renal cell carcinoma. Front Oncol *9:* 1033, 2019. PMID: 31649889. DOI: 10.3389/fonc.2019.01033

44 Das S, Ciombor KK, Haraldsdottir S, Pumpalova Y, Sahin IH and Shyr Y: Immune checkpoint inhibitors (ICIs) in gastrointestinal (GI) cancer: Immune-related adverse events (IRAEs) and efficacy. J Clin Oncol *37(15)*: S4116, 2019. DOI: 10.1200/JCO.2019.37.15_suppl.4116

45 Masuda K, Shoji H, Nagashima K Yamamoto S, Ishikawa M, Imazeki H, Aoki M, Miyamoto T, Hirano H, Honma Y, Iwasa S7 Okita N, Takashima A, Kato K and Boku N: Correlation between immune-related adverse events and prognosis in patients with gastric cancer treated with nivolumab. BMC Cancer *19(1)*: 974, 2019. PMID: 31638948. DOI: 10.1186/s12885-019-6150-y

46 Foster CC, Kochanny S, Khattri A, Acharya R, Dekker A, Tan IHC, Klema E, Brisson RJ, Saloura V, Pearson AT, Vokes EE, Leidner RS, Mehanna HM and Seiwert TY: Association of immune-related adverse events (irAEs) with improved response, progression-free survival, and overall survival for patients with metastatic head and neck cancer receiving anti-PD-1 therapy. J Clin Oncol *36(15)*: 6014, 2018. DOI: 10.1200/JCO.2018.36.15_suppl.6014

47 Morales-Barrera R, Suarez Rodriguez C, Gonzalez M, Ros J, Semidey ME, Hernandez ES, Mateo J, Sáez CF, Lozano F, Mast R, Roche S, Quintana A, Gutiérrez Fernández S, Serrano C, Valverde C, de Torres I, Maldonado X, Morote J and Carles J: Impact of immune-related adverse events on survival in patients with metastastic urothelial carcinoma treated with immune-checkpoint inhibitors. J Clin Oncol *37(15)*: S4531, 2019. DOI: 10.1200/JCO.2019.37.15_suppl.4531

48 Maher VE, Fernandes LL, Weinstock C, Tang S, Agarwal S, Brave M, Ning YM, Singh H, Suzman D, Xu J, Goldberg KB, Sridhara R, Ibrahim A, Theoret M, Beaver JA and Pazdur R: Analysis of the association between adverse events and outcome in patients receiving a programmed death protein 1 or programmed death ligand 1 antibody. J Clin Oncol *37(30)*: 2730-2737, 2019. PMID: 31116675. DOI: 10.1200/JCO.19.00318

Received January 12, 2020
Revised January 21, 2020
Accepted January 24, 2020