 doi:10.20944/preprints202105.0772.v1

Immune-related Endocrine Dysfunctions in Combined Modalities of Treatment: Real-world data

Wing-Lok Chan[1], Horace Choi[1], Patty Pui-Ying Ho[2], Johnny Lau[2], Rosa Pui-ying Tse[2], Joyce Au[2], Vivian Lam[2], Ronald Liu[2], Isaac Ho[2], Charlotte Wong[2], Ben Cheung[2], Eric Lam[2], Daryn Chow[2], Ka-On Lam[1], Kwok-keung Yuen[2], Dora Kwong[1]
[1]Department of Clinical Oncology, the University of Hong Kong, Hong Kong
[2]Department of Clinical Oncology, Queen Mary Hospital, Hong Kong

Corresponding author:

Wing-Lok Chan

Email: winglok@hku.hk

Address:

Department of Clinical Oncology, 1/F Professorial Block, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong

Word count: 2625

 doi:10.20944/preprints202105.0772.v1

Immune-related Endocrine Dysfunctions in Combined Modalities of Treatment: Real-world data

Abstract

Background

The number of immune-related endocrine dysfunctions (irEDs) has concurrently increased with the widespread use of immunotherapy in clinical practice and further expansion of the approved indications for immune checkpoint inhibitor (ICI) combinations using different modalities of anti-cancer treatment.

Method

A retrospective analysis was conducted on consecutive patients ≥18 years of age with advanced solid malignancies who had received at least one dose of anti-programmed cell death protein 1 (anti-PD-1) and/or anti-CTLA4 antibodies between January 2014 and December 2019 at a Hong Kong university hospital. Patients were reviewed for up to two months after the last administration of an ICI. The types, onset times and grades of irEDs, including hypothyroidism, hyperthyroidism, adrenal insufficiency and immune-related diabetes mellitus, were recorded. Factors associated with irEDs were identified using multivariate analysis.

Result

A total of 953 patients (male: 603, 64.0%; median age: 62.0 years) received ICIs during the study period. Of these, 580 patients (60.9%) used *ICI-alone*, 132 (13.9%) used *dual-ICI*, 187 (19.6%) used an ICI combined with chemotherapy (*chemo+ICI*), and 54 (5.70%) used immunotherapy with a targeted agent (*targeted+ICI*).

A significantly higher proportion of patients using *targeted+ICI* had irEDs and hypothyroidism; in contrast, a higher proportion of patients using dual-ICI had adrenal insufficiency. There was no significant difference in the incidence of irED between the younger (<65 years) and older (≥65 years) patients. Using logistic regression, only treatment type was significantly associated with irEDs. Notably, older patients had a higher risk of having immune-related diabetes mellitus.

Conclusions

This large, real-world cohort demonstrates that combining ICI with targeted therapy has a higher risk of overall irED and hypothyroidism. Immunotherapy is safe and well-tolerated regardless of age, but close monitoring of fasting glucose is needed in older populations.

 doi:10.20944/preprints202105.0772.v1

Keywords:

Immune checkpoint inhibitors; immune-related endocrine dysfunction; hypothyroidism; targeted therapy; malignancy

 doi:10.20944/preprints202105.0772.v1

Immune-related Endocrine Dysfunctions in Combined Modalities of Treatment: Real-world data

Introduction

Immune checkpoint inhibitors (ICIs) have become a powerful tool in the management of cancer in recent years. These monoclonal antibodies (mAb) block immune checkpoints, unleashing T-cells to fight cancer.[1] The ICIs approved for the treatment of different cancers include agents that target the programmed cell death protein 1 receptor (PD-1: nivolumab, pembrolizumab, cemiplimab), programmed death-ligand 1 (PD-L1: atezolizumab, avelumab, durvalumab), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4: ipilimumab, tremelimumab).[23]

Anti-PD-1 or anti-PD-L1 monotherapy has been approved for the treatment of more than 10 cancer types, with objective response rates (ORRs) of 15–20% and good safety profiles.[4] Because of the broad-spectrum anti-tumour activity and good tolerability of ICIs, a multitude of clinical trials have investigated combining ICIs with other immunomodulatory agents or conventional systemic anti-cancer therapy, including cytotoxic chemotherapy or targeted molecular therapy. These combination therapies demonstrated improved clinical outcomes across various types of cancers and, in turn, led to their respective approval statuses by the U. S. Food and Drug Administration (FDA). For example, the combination of pembrolizumab with pemetrexed and carboplatin improved the overall survival (OS) and progression-free survival (PFS) in metastatic non-small cell lung carcinoma;[5] axitinib with pembrolizumab improved the OS and PFS in advanced renal cell carcinoma;[6] nab-paclitaxel and atezolizumab improved in OS and PFS in PD-L1 positive advanced triple-negative breast cancer; [7] bevacizumab and atezolizumab hepatocellular carcinoma resulted in better OS and PFS compared with sorafenib,[8] etc.

Immune checkpoints also play a critical role in maintaining immunological self-tolerance and preventing autoimmune disorders. ICIs remove the self-tolerance, triggering autoimmune adverse events leading to toxicities termed immune-related adverse events (irAEs).[9] These irAEs

 doi:10.20944/preprints202105.0772.v1

can affect any organ in the body and include colitis/diarrhoea, dermatitis, hepatitis, renal impairment, endocrinopathies, and less commonly, neuropathy, myocarditis and ocular involvement. Endocrinopathies are among the most common irAEs associated with ICI therapy. Immune-related endocrine dysfunctions (irEDs) include hypophysitis, thyroid dysfunction, insulin-deficient diabetes mellitus and adrenal insufficiency. These irEDs are frequently reported in previous randomised controlled trials and usually manageable if treated early.[10,11,12] Yet, these can be life-threatening if not recognised and treated appropriately; deaths have been reported.

With the increasing widespread use of ICIs in clinical practice and further expansion of the approved indications of ICIs combinations with different modalities of anti-cancer treatments, the number of irED episodes also tends to increase. It is important to know the irED patterns in order to achieve earlier detection and better monitoring.

Previous meta-analyses revealed that higher risks of irEDs were seen in the combination of anti-PD-1 plus anti-CTLA4. However, it is unclear about the real-world situation and the pattern of irEDs when ICIs are combined with other treatment modalities. Our study evaluates the incidence and patterns of different irEDs and compares them across different combination treatment modalities. In addition, since the older populations are under-represented in clinical trials, the safety of ICIs in this population has not been adequately assessed. The second aim is to compare the irED profiles of older cancer patients with those of younger patients.

Methods

a. Study design, setting, samples

We retrospectively analysed data on consecutive patients aged ≥18 years with advanced solid malignancy who had received at least one dose of anti-PD-1 and/or anti-CTLA4 antibodies with

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2021 doi:10.20944/preprints202105.0772.v1

or without combined chemotherapy or targeted agent between January 2014 and December 2019 at Queen Mary Hospital, an university hospital and tertiary oncology centre. Patients with haematologic malignancies were excluded. Inclusion criteria were: 1) a histologically confirmed diagnosis of solid malignancy; 2) locally advanced or metastatic disease; 3) age ≥18 years at ICI initiation; 4) receipt of at least one cycle of ICI. Study drugs in this study included antibodies targeting PD-1 (nivolumab and pembrolizumab), PD-L1 (atezolizmab, durvalumab) and CTLA-4 (ipilimumab).

b. Data collection

All patient data were extracted from the computerised management system (CMS) under the Hospital Authority. The following clinical, biological and laboratory data were captured at baseline: a) age, gender, Eastern Cooperative Oncology Group – Performance Status (ECOG-PS); b) primary tumour site, site of metastasis, cancer type and histological subtype, site of metastasis; c) immunotherapy used: type of ICI, treatment start date, concomitant anti-cancer treatment, previous use of ICI; d) baseline serum endocrine blood tests.

c. Endpoint definition

The primary endpoint is immune-related endocrine dysfunction (irED). irEDs were recorded and reviewed by the principal investigator up to two months after the last administration. The types of irEDs captured included hypothyroidism, hyperthyroidism, adrenal insufficiency and immune-related diabetes mellitus. The date of onset, duration after starting ICIs and grade were collected. The data cut-off was on July 31, 2020, and data were censored at patients' last documented clinic visit.

d. Statistical analysis

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2021 doi:10.20944/preprints202105.0772.v1

Patients were categorised into four groups: use of immunotherapy alone (ICI-alone), dual immune-checkpoint inhibitors (dual-ICI), ICI with chemotherapy (chemo+ICI) and ICI with targeted therapy (targeted+ICI). The population was also categorised into younger and older age groups according to age at treatment initiation: <65 years and ≥65 years old.

Descriptive analyses were used to summarise study sample characteristics and toxicity data. The proportion of toxicities was compared across age categories using the Pearson X2, or Fisher-exact test. Univariable analyses were performed to examine the individual effect of age category, site of metastasis, or concomitant use of other systemic anti-cancer treatment on irED.

Multivariable analyses were also performed to account for the effect of multiple factors on toxicity. Age group, site of metastasis and concomitant use of other systemic anti-cancer therapy were used as independent variables. Logistic regression was used to generate odds ratios for the independent variables. All reported p-values were two-sided, and the significance threshold was set at <0.05. All statistical analyses were performed using SPSS, version 25 (IBM).

Results

Baseline demographics are shown in Table 1.

A total of 953 eligible patients were identified. Six hundred and ten patients (64.0%) were male. The median age of the patients was 62.0 years, and 218 patients were in the older age group. The median age of patients in the older age group was 71.9 years (range: 65–103), whereas that in the younger age group was 54.7 years (range: 20–65). The percentage use of ICI-alone, dual-ICIs, chemo+ICI and targeted+ICI was 60.9%, 13.9%, 19.6% and 5.70%, respectively. All patients who used dual ICIs received nivolumab combined with ipilimumab. The types of immunotherapy used are shown in Table 2.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2021 doi:10.20944/preprints202105.0772.v1

a. Overall immune-related endocrine dysfunction

Total 279 patients (29.3%) experienced any kind of irED. None of the patients had life-threatening conditions or death due to irED. A significantly higher proportion of patients in the targeted+ICI group had irEDs (n=25, 46.3%, p=0.002) compared with ICI-alone, dual-ICIs and chemo+ICI groups. In both older and younger age groups, patients who received targeted+ICI had a significantly higher percentage of irEDs compared with ICI alone. Details on the irEDs in each subgroup are listed in Table 3.

b. Thyroid dysfunction:

Hypothyroidism (n=171, 17.9%) is the most common irED. There was a significantly higher rate of hypothyroidism in the targeted+ICI group, with 35.2% affected versus 16.9% in the immunotherapy-alone group, 22.0% in the dual-ICI group and 13.4% in the chemo+ICI group. In both the younger and older age groups, the percentage of hypothyroidism was significantly higher in patients who received targeted+ICI (older: 45.5%; younger: 32.6%). The median time of onset was 12.55 weeks, and patients on targeted+ICI treatment had an earlier onset of hypothyroidism (median onset: 9.75 weeks). Two patients had grade 3 hypothyroidism complicated with hyponatremia. Both patients were in the younger age group and had targeted+ICI. They needed temporary treatment discontinuation and hospitalisation for management; subsequently, their condition improved, and ICI treatment was resumed.

Fifty-nine patients (6.19%) had hyperthyroidism and needed antithyroid medications. None of them had grade 3 or above hyperthyroidism. There was no significant difference in percentage with or without concomitant anti-cancer agents. The incidence of hyperthyroidism in both age groups was comparable. The median time of onset of hyperthyroidism was 11.4 weeks, with the earliest onset seen in the dual-ICI group.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2021 doi:10.20944/preprints202105.0772.v1

c. Adrenal insufficiency

Adrenal insufficiency was the second most common irED (n=71, 7.45%). There was a significantly higher rate of adrenal insufficiency in the dual-ICI group (14.4%) compared with the ICI-alone group. The median time of onset of adrenal insufficiency was 18.7 weeks. The incidence of adrenal insufficiency was higher in the younger age group than the older age group (8.57% vs 3.67%, p=0.023). In the younger age group, significantly higher proportion of adrenal insufficiency was seen in the dual-ICI group (16.5%) compared with other groups. Three patients had grade 3–4 adrenal insufficiency. Two patients (aged 50 and aged 64) on combined chemo+ICI had sepsis and found adrenal insufficiency. One patient (age 70) on dual-ICI experienced severe malaise, and blood tests reported adrenal insufficiency.

d. Immune-related diabetes mellitus

Twenty-eight patients (2.90%) had hyperglycaemia while on ICI. There was no significant difference in incidence between the four treatment groups. The median onset of hyperglycaemia was 19.6 weeks. The incidence was significantly higher in the older age group (n=14, 6.40%) than the younger age group (n=14, 1.90%). None of the patients had diabetes ketoacidosis or needed hospitalisation due to hyperglycaemia alone.

Logistic regression was performed to assess the relative influence of age category, treatment type and sites of metastasis on the risk of irED (Table 4). With both univariable and multivariable analysis, only treatment modality was significantly associated with overall irEDs. Patients receiving targeted+ICI had a higher risk of irED toxicities (OR: 2.34; 95% CI: 1.32–4.41 for targeted+ICI relative to ICI alone).

Further analysis was performed on each type of irED. Patients who received targeted+ICI had a higher risk of hypothyroidism compared with those who received ICI alone (OR: 2.54; 95% CI:

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 31 May 2021 doi:10.20944/preprints202105.0772.v1

1.36–4.61). For adrenal insufficiency, patients on dual-ICI had a higher risk compared with those with ICI-alone (OR: 3.25; 95% CI: 1.70–5.99). The younger age group also had a higher risk compared with the older age group (OR: 0.39, 95% CI: 0.17–0.80). For immune-related diabetes, the older age group had a higher risk compared with the younger age group (OR: 3.78; 95% CI: 1.73–8.32). Sex and sites of metastasis were not related to the risk of irED.

Discussion

Immune checkpoint inhibitors have undoubtedly been a breakthrough in cancer therapy in recent years and have been widely used in the management of various cancers. In order to further improve treatment outcomes, combinations of immunotherapy with other systemic anti-cancer treatments have been tested in different advanced tumours and have been increasingly and extensively used. While the main goal is to improve overall survival and maintain quality of life, it is essential to consider the implicated toxicity of these combined treatment modalities.

Previous studies focused mainly on irAEs after combination immunotherapies or combination of immunotherapy with chemotherapy. Zhang's meta-analysis, which involved 11 randomised controlled trials (RCTs) and 5,207 patients, demonstrated that combination immunotherapies had a higher risk of immune-related adverse events, with ratios of all-grade diarrhoea of 1.95 (95% CI: 1.54; 2.46; P <0.00001) and all-grade colitis of 4.45 (95% CI: 3.04, 6.51; P <0.00001).[13] Sousa's study, which involved 38 RCTs comprising 7,551 patients, found that patients on combination immunotherapies were significantly more likely to experience hypothyroidism and hyperthyroidism than those on mono-immunotherapy.[14] Another study by Carretero-González et al., which involved 10 RCTs and 4,379 patients, revealed that the combination of immunotherapy with chemotherapy presented more grade 3/4 adverse events (RR: 1.32; 95% CI: 1.12–1.55) and discontinuations (RR: 2.31; 95% CI: 1.28–4.16).[15]

 doi:10.20944/preprints202105.0772.v1

Our study observed a significantly higher incidence of irEDs in patients treated with targeted+ICI compared with ICI-alone. The combination of targeted+ICI was also strongly associated with hypothyroidism using logistic regression. Additionally, the onset of hypothyroidism was found to be significantly earlier in patients who received targeted+ICI. These findings are important, as the combination of immunotherapy with targeted therapy has been increasingly used, and a large number of phase II and III studies are investigating the efficacy of combining the two anti-cancer modalities in both solid cancers and haematologic malignancies. For example, from clinictrials.gov, currently there are already over 50 phase II/III studies investigating the use of ICIs with either chemotherapy or targeted agents.

Some of the targeted agents, such as tyrosine kinase inhibitors, are well known to cause thyroid dysfunction. Suggested mechanisms for targeted-agent-indced hypothyroidism include direct toxic effects on thyrocytes, reduced TPO activity, impaired iodine uptake, attenuation of thyroid blood flow due to vascular epithelial growth factor receptor inhibition, and activation of cytotoxic T cells in combination with pre-existing intrathyroidal lymphocytes causing damage to the thyroid cells. Cytotoxic T cells are also the backbone of ICIs. The addition of ICIs on top of targeted agents probably exacerbates the risk of thyroid dysfunction.

Previous studies investigated the association between age and irAEs; however, the results were conflicting. Betof's study demonstrated an increased incidence of irEDs and hypothyroidism with age in melanoma patients who underwent immunotherapy.[16] Baldini's study showed that the incidence of grade 2 or above irAEs was higher in patients over 70.[17] Alternatively, Sattar's study demonstrated that patients ≥75 years of age did not experience excess toxicity and concurrently had similar benefits from immunotherapy as younger patients.[18] Samani's study even showed that there was a lower incidence of endocrine toxicity in the older patients (age ≥75) compared with the younger patients (age <65).[19]

 doi:10.20944/preprints202105.0772.v1

Our study showed no significant difference in overall irEDs between the younger and older age groups. We suggest no particular difference in endocrine monitoring in younger and older populations who are on immunotherapy. Also, old age is not the only reason for reconsidering the use of ICIs.

There was a higher incidence of immune-related diabetes mellitus in our cohort's older patient group. Immune-related diabetes mellitus is rare but potentially life-threatening. Patients should be monitored for blood glucose level and any signs of diabetic ketoacidosis, which often presents with nausea, vomiting, abdominal pain, hyperventilation, lethargy, and/or coma. Older patients on ICIs should have regular blood glucose checks (e.g. fasting glucose every 3–4 weeks). If a high glucose level is detected, intensive insulin treatment, anti-hyperglycaemic medications and supportive measures, including hydration and correction of electrolytes, should be administered.

Our study has several limitations. First, this is a retrospective study conducted in a single institution and therefore may not be generalisable. Second, we only focused on irEDs; other irAEs were not reported. Third, we did not analyse the risk of each targeted agent when combined with ICI; some targeted agents may have a higher risk of causing endocrine dysfunction than others. Despite these weaknesses, our study has several strengths. We included a large cohort of patients with different tumour types and treatment types. There was a large proportion of patients (40.0%) who used combined modalities of treatment. The combination of ICIs with chemotherapy or targeted agents is now increasingly used to treat different cancers. In addition, more than one-third of our patients were over 65 years old. This allowed us to have a good comparison of irEDs between the older and younger populations. Moreover, data on different irEDs were meticulously collected in this study.

 doi:10.20944/preprints202105.0772.v1

Conclusion and Future Work:

Our study demonstrated a higher risk of irEDs in patients who received targeted+ICIs. The incidence of hypothyroidism was higher and the onset of hypothyroidism was earlier in targeted+ICI treatment patients. Prospective studies are warranted to better capture irEDs in patients using ICIs combined with other treatment modalities. Future prospective studies and clinical trials could lend more solid evidence and suggest mechanisms for the observed higher incidence. Future research on biomarkers may shed light on the mechanisms and predictions on irAEs. Although older patients are usually frailer and have a higher chance of getting treatment-related toxicities in chemotherapy and targeted therapies than younger ones, our study did not show increased endocrine toxicities in the former group. Research should also focus on whether geriatric assessments or geriatric valuables can better predict both outcomes and toxicities.

Funding: none declared

Disclosure Statement:
The authors have declared no conflicts of interest. All authors have nothing to disclose. All authors received no funding or sponsorship. No financial disclosure. There is no conflict of interest to disclose.

Authors contribution:
- Conception and design: Wing-Lok Chan
- Data collection: Wing-Lok Chan, Johnny Lau, Patty Pui-ying Ho, Rosa Tse, Charlotte Wong, Ronald Liu, Isaac Ho, Eric Lam, Vivian Lam, Joyce Au
- Analysis and interpretation of data: Horace Choi, Wing-Lok Chan
- Manuscript writing: Wing-Lok Chan, Ka-on Lam
- Manuscript editing: Wing-Lok Chan, Dora Kwong, Kwok-keung Yuen
- Approval of final article: Wing-Lok Chan

References:

[1] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer*. 2012;12(4): 252–264.
[2] Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. International Immunopharmacology. 2018;62: 29–39.

[3] Rotte A, Jin JY, Lemaire V. Mechanistic overview of immune checkpoints to support the rational design of their combinations in cancer immunotherapy. *Annals of Oncology*. 2018;29(1): 71–83.
[4] Callahan MK, Postow MA, Wolchok JD. Targeting T cell co-receptors for cancer therapy. *Immunity*. 2016;44(5): 1069–1078.
[5] Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *New England Journal of Medicine*. 2018;378(22): 2078–2092.
[6] Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *New England Journal of Medicine*. 2019;380(12): 1116–1127.
[7] Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *New England Journal of Medicine*. 2018;379(22): 2108–2121.
[8] Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *New England Journal of Medicine*. 2020;382(20): 1894–1905.
[9] Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *European Journal of Cancer*. 2016;54: 139–148.
[10] Joshi MN, Whitelaw BC, Palomar MT, Wu Y, Carroll PV. Immune checkpoint inhibitor-related hypophysitis and endocrine dysfunction: Clinical review. *Clinical Endocrinology*. 2016;85(3): 331–339.
[11] Barroso-Sousa R, Ott PA, Hodi FS, Kaiser UB, Tolaney SM, Min L. Endocrine dysfunction induced by immune checkpoint inhibitors: Practical recommendations for diagnosis and clinical management. *Cancer*. 2018;124(6): 1111–1112.
[12] Arima H, Iwama S, Inaba H, Ariyasu H, Makita N, Otsuki M, et al. Management of immune-related adverse events in endocrine organs induced by immune checkpoint inhibitors: Clinical guidelines of the Japan Endocrine Society. *Endocrinology Journal*. 2019;66(7): 581–586.
[13] Zhang B, Wu Q, Zhou YL, Guo X, Ge J, Fu J. Immune-related adverse events from combination immunotherapy in cancer patients: A comprehensive meta-analysis of randomized controlled trials. *International Immunopharmacology*. 2018;63: 292–298.
[14] Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: A systematic review and meta-analysis. *JAMA Oncology*. 2018;4(2): 173–182.

[15] Carretero-González A, Lora D, Ghanem I, Otero I, López F, Castellano D, et al. Comparative safety analysis of immunotherapy combined with chemotherapy versus monotherapy in solid tumors: A meta-analysis of randomized clinical trials. *Oncotarget*. 2019;10(35): 3294–3301.

[16] Betof AS, Nipp RD, Giobbie-Hurder A, Johnpulle RAN, Rubin K, Rubinstein SM, et al. Impact of age on outcomes with immunotherapy for patients with melanoma. *Oncologist*. 2017;22(8): 963–971.

[17] Baldini C, Martin Romano P, Voisin AL, Danlos FX, Champiat S, Laghouati S, et al. Impact of aging on immune-related adverse events generated by anti-programmed death (ligand)PD-(L)1 therapies. *European Journal of Cancer*. 2020;129: 71–79.

[18] Sattar J, Kartolo A, Hopman WM, Lakoff JM, Baetz T. The efficacy and toxicity of immune checkpoint inhibitors in a real-world older patient population. *Journal of Geriatric Oncology*. 2019;10(3): 411–414.
[19] Samani A, Zhang S, Spiers L, Mohamed AA, Merrick S, Tippu Z, et al. Impact of age on the toxicity of immune checkpoint inhibition. *Journal of Immunotherapy of Cancer*. 2020;8(2): e000871.