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Editorial

Recent advances, patient selection & challenges in managing cancer patients undergoing treatment with immune checkpoint inhibitors

Cancer immunotherapy with humanized monoclonal antibodies (mAbs) that target co-inhibitory immune checkpoint molecules (ICMs) is the most meaningful advance in the management of malignant diseases in recent years[1]. This has coincided with the acquisition of eloquent, cutting edge insights into the molecular mechanisms, which regulate cell–cell interactions that are fundamental to maintain a balanced, well-synchronized human immune system. These developments have also revitalized the practice of immunotherapy, especially the realization of novel immunomodulatory therapeutic modalities that have the potential to restore weakened anti-cancer immune responses.

Only in recent times, however, has the notion been dispelled that spontaneous human cancers arise and progress due to their apparent lack of immunogenicity, implying redundancy of the immune system in this setting. This misplaced belief has been overtaken by a compelling awareness not only of the key role played by the immune system in anti-tumour host defence but also of the capability of human malignancies to subdue and subvert innate and adaptive cellular immune mechanisms. In this context, the most significant trigger driving the development of the field of clinical oncoimmunology was the discovery that co-inhibitory and co-stimulatory ICMs were the key regulators of cellular immune reactivity. Co-inhibitory ICMs include programmed cell death protein-1 (PD-1), programmed cell death protein ligand-1 (PDL-1), cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte activation gene-3 (LAG-3), B and T lymphocyte attenuator (BTLA) and herpesvirus entry mediator. Prominent co-stimulatory ICMs include CD27, CD40, CD134 (OX40), glucocorticoid-induced tumor necrosis factor receptor (TNFR) related protein (GITR), inducible T cell co-simulator and CD137[1].

Co-inhibitory checkpoint ICMs are expressed most prominently by T cells, especially regulatory T (Treg) cells and antigen-presenting dendritic cells, as well as by other cell types, including cells of the innate and adaptive immune systems, structural cells in the tumour microenvironment (TME) and, somewhat ominously, by cancer cells *per se*[2]. The primary function of co-inhibitory ICMs is to downregulate T cell activation. This immunoregulatory function of co-inhibitory ICMs is essential in maintaining immune homoeostasis, thereby preventing the loss of peripheral self-tolerance that underpins the pathogenesis of autoimmune disease. Tumour cells, on the other hand, utilize the expression of co-inhibitory ICMs, such as CTLA-4 and PDL-1 in particular, as a strategy to outmanoeuvre anti-tumour host defences. This results in interference with the recruitment of cytotoxic T cells to the TME, as well as the inhibition of their anti-tumour activity, enabling immune evasion[3].

The co-inhibitory ICMs, PD-1 and CTLA-4, were discovered by Tasuku Honjo[4] and James P. Allison[5] in 1992 and 1996, respectively, for which these renowned medical scientists were awarded the 2018 Nobel Prize for Physiology and Medicine. These discoveries provided the impetus for the development and pre-clinical/clinical evaluation of the first-generation ICM-targeted therapeutic mAbs, specifically ipilimumab (blockade of CTLA-4) and pembrolizumab (blockade of PD-1) that heralded new standards in the care of various types of malignancies[1]. This was followed by FDA approval of these and other subsequently engineered, novel co-inhibitory

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ICM-targeted ICMs, including nivolumab, cemiplimab, durvalumab, atezolizumab and avelumab[1]. Cancers responsive to these various co-inhibitory ICM-targeted therapeutic ICMs include lung cancer (small and non-small cell types), malignant melanoma, bladder cancer, Hodgkin's disease, renal cell carcinoma and others[1]. Of note, however, is the issue that although anti-cancer immunotherapy with co-inhibitory ICM-targeted mAbs is associated with durable responses in some patients, many patients fail to respond to these therapeutic modalities, with some malignancies remaining refractory to these treatments. Although of concern, these limitations of co-inhibitory ICM-targeted immunotherapy may be overcome by the discovery of additional types of ICM with different mechanisms of induction of immunosuppression, raising the potential option of combination of immunotherapy with mAbs, which target different types of ICM. These novel co-inhibitory ICMs currently under pre-clinical/clinical evaluation include research, TIM-3, LAG-3, V-domain Ig-containing suppressor of T cell activation and BTLA[1].

In a recently reported study, treatment of patients with previously untreated metastatic or unresectable melanoma with the combination of an anti-LAG-3-targeted mAb (relatlimab) with an anti-PD-1-targeted agent (nivolumab) was associated with a significant prolongation of progression-free survival relative to that observed with nivolumab alone[6]. Notably, the combination of both agents showed no new safety signals[6].

In addition, as a strategy to improve efficacy and outcomes, numerous clinical studies are currently investigating the therapeutic potential of combinations of ICM-targeted therapy with conventional anti-cancer treatment modalities such as chemotherapy and radiotherapy and novel targeted therapies and anti-angiogenic agents (small molecules or mAbs). In this context, several different types of combination treatment are currently approved and in routine use in clinical settings, such as non-small cell lung cancer (NSCLC), renal cell cancer and triple-negative breast cancer (TNBC). Some of these novel combination treatments are currently used in the metastatic malignant melanoma and the neoadjuvant settings, potentially translating into curing some of these patients[7].

Several biomarkers have been identified in recent years, which improve the selection of patients for ICM-based treatments. For example, PDL-1 testing using immunohistochemical assays is currently the most widely utilized, validated and accepted biomarker to select patients for treatment with anti-PD-1 or anti-PDL-1-targeted mAbs. A challenge for the clinical use of these assays is the necessity of using different companion diagnostic assays for specific ICM agents[8].

In this context, it is essential to point out that the response to ICM-targeted mAbs differs depending on the numbers and composition of cells in the TME. Among responders to ICM-targeted ICMs, tumours have a high neoantigen load, high numbers of tumour-infiltrating lymphocytes (TILs), particularly effector cells, and an increased T effector cell: Treg ratio favouring secretion of interferon-γ, as well as low levels of Tregs and myeloid-derived suppressor cells (MDSCs)[9]. In non-responding patients, the TME is associated with high infiltration of immunosuppressive cells, such as Tregs, tumour-associated macrophages and MDSCs, in the setting of low numbers of natural killer (NK) cells and activated lymphocytes[10].

Co-inhibitory ICMs, including CTLA-4 and PD-1, are present on activated T cells and PD-1 on antigen-presenting dendritic cells. These interactions lead to T cell exhaustion, defined as a state of T cell dysfunction, most commonly seen in chronic infections and cancer. T cell exhaustion is characterized by poor effector function, sustained expression of inhibitory receptors and a transcriptional state distinct from functional effector or memory T cells. Exhaustion is associated with suboptimal control of infection and tumours. These abnormalities can be eliminated by targeting these inhibitory checkpoints with mAbs, leading to the re-activation of T cells targeting cancer cells through the secretion of effector cytokines and cytotoxic granules[10].

Three major categories of TME have been characterized across various tumour types: immune-desert (cold tumours largely devoid of lymphocytes), immune-excluded (lymphocytes are present in the peri-tumoural stroma only) and immune-infiltrated/inflamed (hot tumours)[11]. Immune-inflamed tumours have a higher response to ICM-targeted immunotherapy than cold tumours or immune-excluded tumours. Reports suggest that inflamed immune tumours have higher sensitivity because therapeutic ICM-targeted mAbs inhibit immune evasion[12]. Studies have demonstrated that favourable responses to ICI-based treatments are associated with

the presence of TILs and other anti-tumour immune cells in the TME[12].

In breast cancer (BC), the molecular subtype of the tumour has a substantial impact on its interaction with the immune system. In this context, higher numbers of TILs more frequently infiltrate TNBC and HER2-positive BC than hormone receptor-positive tumours[13].

Tumour mutational burden (TMB) is defined as the number of mutations per DNA megabase and was first evaluated as a biomarker for co-inhibitory ICM-based immunotherapy following observations of favourable responses in tumours with high TMBs, including NSCLC, melanoma and bladder cancer. Pre-clinical data indicated that the association between TMB and the efficacy of ICM-based immunotherapy could be explained by the expression of neoantigens that increase tumour immunogenicity and responses to ICM-based treatments[14]. Neoantigens may develop during DNA replication via DNA mismatch repair (MMR). MMR is a physiological mechanism that identifies and repairs erroneous insertion, deletion and misincorporation of bases that appear during DNA recombination and DNA damage[15]. In mammalian cells, five MMR proteins have been identified. These proteins include MutS-homologs 2, 3 and 6, MutL-homolog 1 and post-meiotic segregation 2[16]. Some cases of colorectal cancer are associated with microsatellite instability (MSI), characterized by elevated rates of small indels (insertion/deletions) and point mutations of one to six or more base pairs described as microsatellites[17].

In metastatic colorectal cancer, mismatch repair-deficient/microsatellite instability (dMMR/MSI) represents a small subset of approximately five per cent and is associated with a prognosis[18]. In this patient population, the combination of the co-inhibitory ICM-targeted mAbs, nivolumab and ipilimumab, was investigated in 119 dMMR/MSI-H metastatic colorectal cancer patients in the CheckMate 142 trial. The treatment was associated with a consistent clinical benefit manifested as an objective response rate of 55 per cent[19]. Responses were durable, with a progression-free survival rate of 71 per cent and overall survival of 85 per cent after one year. Another group of metastatic colorectal patients responsive to ICM-based treatment are those who have tumours known as hypermutated tumours. This condition has been described as tumours harbouring polymerase proofreading domain mutations[20]. In addition, MSI can be found in other types of malignancy, including gastric cancer, endometrial cancer and many other types of cancer[21]. Despite these advances, novel biomarkers are urgently needed to improve patient selection, assess prognosis and monitor treatment. In this context, biomarkers should ideally be accessed via minimally invasive procedures, using matrices such as plasma or liquid biopsies[22].

Co-inhibitory ICM-based treatments are generally well tolerated and are significantly less toxic than standard chemotherapy regimens. Nevertheless, co-inhibitory ICM-targeted ICMs have side effects related to their lack of specificity, resulting in over-activation of the immune system. These side effects are called immune-related adverse events (IrAEs) and include fatigue, dermatological, gastrointestinal, hepatic, pulmonary, endocrine, ophthalmic, neurological and unusual toxicities such as type 1 diabetes mellitus and cardiac haematological disorders[23]. Dermatological side effects are frequently present and manifest as skin rashes that are often maculopapular and mild[23]. Severe skin toxicities such as Stevens–Johnson syndrome or toxic epidermal necrolysis are seen in only a minority of patients[23]. Vitiligo also occurs in only a few patients receiving ICM-targeted mAbs; interestingly, this IrAE is commonly associated with clinical benefit and long-term survival[23]. Diarrhoea and enterocolitis are the most commonly encountered gastrointestinal toxicities. Rarely, in severe cases, these complications can be associated with toxic megacolon and perforation[23]. Endocrine IrAE symptoms are non-specific and include fatigue, mental status changes, headaches and dizziness, with hypothyroidism being the most frequent endocrine abnormality. Other endocrinopathies such as hypophysitis or adrenal insufficiency occur more often with ipilimumab. Type 1 diabetes, although uncommon, may present with severe acute symptoms[23]. Other, less frequently occurring IrAEs include ophthalmological conditions such as episcleritis, uveitis or conjunctivitis[23]. Neurologic IrAEs include myasthenia gravis, aseptic meningitis, encephalitis, motor and sensory neuropathies, including Guillain–Barre syndrome, and other rare conditions such as enteric or autonomic neuropathies and transverse myelitis[23]. Musculoskeletal IrAEs include inflammatory arthritis, myositis, polymyalgia rheumatic and osteitis[23].

Although the pathogenesis of co-inhibitory ICM-targeted immunotherapy-mediated IrAEs remains unknown, several immune mechanisms have been implicated. These include the emergence/activation

of auto-reactive T cells and B cells/autoantibodies, resulting in tissue damage due to complement activation and production of pro-inflammatory cytokines/chemokines, possibly related to changes in the intestinal microbiome. In this context, auto-reactive T cells (CD4+ and CD8+) play a role in the development of co-inhibitory ICM-targeted mAb-induced fulminant myocarditis, myositis and diabetes mellitus[24]. Moreover, the presence of T cell infiltrates has been demonstrated in cases of colitis, some dermatological complications, nephritis, sicca syndrome, liver injury and pneumonitis[24], while dysregulation of Th1 and Th17 cell numbers and reactivity has been suggested as a potential mechanism for co-inhibitory ICM-targeted mAb-induced colitis[24].

Das *et al*[25] showed a reduction in the numbers of total circulating B cells in the setting of an increase in a $CD21^{lo}$ PD-1+ B cell sub-population, as well as the presence of plasmablasts that preceded and was correlated with the frequency and timing of adverse events in melanoma patients undergoing combination ICM-targeted treatment.

There is no clear relationship regarding the role of auto-antibodies in the pathogenesis of IrAE-related thyroid dysfunction. In this setting, auto-antibodies (thyroglobulin and/or thyroid peroxidase antibodies) are detected in only 18-70 per cent of patients, whereas in Hashimoto's thyroiditis, these are present in 90-95 per cent of patients[26]. Limited evidence exists that thyroid auto-antibodies at baseline may increase the risk of thyroid dysfunction following the administration of ICM-targeted immunotherapy. With respect to the possible involvement of auto-antibodies in the pathogenesis of co-inhibitory ICM-targeted immunotherapy-induced inflammatory arthritis, it is noteworthy that these patients are usually seronegative[27].

In the case of IrAE-related hypophysitis, the proposed mechanism leading to pituitary cell destruction involves the binding of anti-CTLA-4 mAbs to CTLA-4 expressed on pituitary cells, with resultant complement activation, macrophage/phagocyte infiltration, enhanced antigen presentation and infiltration of B and T cells and destruction of pituitary cells[28].

The gut microbiome has been proposed to play a role in both the anti-tumour therapeutic efficacy of ICM-targeted mAbs and the development of IrAEs in cancer patients undergoing this type of immunotherapy. In the case of melanoma patients undergoing treatment with anti-CTLA-4-targeted mAbs, those patients whose baseline gut microbiomes were enriched for *Faecalibacterium* and other *Firmicutes* had a better response to treatment and more prolonged progression-free survival in the setting of more frequent colitis. In contrast, those enriched with *Bacteroidetes* had less frequent colitis[29].

An additional largely unexplored challenge is represented by the potential threat of the development of severe IrAEs posed to cancer patients by the presence of underlying autoimmune disorders. For this reason, cancer patients with pre-existing autoimmune diseases were not included in the early co-inhibitory ICM-based clinical trials. Although the risk of development of IrAEs or exacerbation of their underlying autoimmune disease is not well understood in these patients, there is evidence that the onset of IrAEs may occur faster in these patients[30]. Accordingly, ongoing close monitoring of these patients early in the treatment course is necessary[30].

Professional organizations such as the American Society of Clinical Oncology[31], the National Comprehensive Cancer Network[31], the European Society for Medical Oncology[32], the Society for Immunotherapy of Cancer[33] and the Multinational Association of Supportive Care in Cancer[34] have established guidelines and recommendations for the management of IrAEs. However, it must be highlighted that these guidelines and recommendations are primarily based on clinical recommendations from experience gained from clinical trials, daily clinical practice and general clinical consensus. Although these management recommendations are widely accepted, the level of evidence is low, and currently, no prospective, randomized trials have been undertaken to evaluate whether one treatment strategy is superior to another[34].

Early recognition of IrAEs and pro-active management by clinicians remain critical to lower the morbidity and mortality associated with co-inhibitory ICM-targeted immunotherapy in cancer patients. IrAEs are usually manageable low-grade, particularly with single-agent co-inhibitory ICM-targeted mAbs. However, it is essential to point out that reporting of IrAEs outside of a clinical trial setting remains suboptimal[15]. A multidisciplinary team of specialists is required to manage patients diagnosed with severe IrAEs.

Anti-CTLA-4- and anti-PD-1- or anti-PDL-1-targeted mAbs have different mechanisms

of action, and this has been clearly documented in the numerous clinical trials examining combination therapies, which have shown that the occurrence of grade 3 and grade 4 IrAEs in cancer patients receiving the combination of ipilimumab and nivolumab was approximately 50 per cent. This was significantly higher than either agent administered individually and resulted in treatment disruption and terminations in approximately one-third of patients[35].

Clinicians, nurses and healthcare professionals who administer anti-cancer immunotherapeutic antibodies should be aware of possible new toxicities and side effects that can be severe and unpredictable. In addition, these antibodies are being increasingly administered in combination with chemotherapy, radiation therapy, targeted therapies or other agents; therefore, the incidence and severity of these toxicities may change in the future. These variations in side effect patterns will require a regular update of the various guidelines and recommendations to attain better IrAEs management. In addition and somewhat paradoxical, there is a growing body of evidence that patients who developed IrAEs are associated with a better outcome[36]. Biomarkers to individualize and categorize patients at risk of severe IrAEs would be clinically helpful.

Finally, co-inhibitory ICM-based treatments undoubtedly represent a significant breakthrough in the treatment of cancer patients. Such advances in treatment, however, come at high financial costs. The estimated cost of one year of co-inhibitory ICM-based treatment is approximately 100,000 USD[37]. Financial toxicity, therefore, remains the main barrier to access to care for our patients requiring co-inhibitory ICM-based treatment.

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References

1. Archilla-Ortega A, Domuro C, Martin-Liberal J, Muñoz PJ. Blockade of novel immune checkpoints and new therapeutic combinations to boost antitumor immunity. *Exp Clin Cancer Res* 2022; *41* : 62.
2. Zhang H, Dutta P, Liu j, Sabri N, Song Y, LI WX, *et al*. Tumor cell intrinsic CTLA4 regulates PD-L1 expression in non-small cell lung cancer. *J Cell Mol Med* 2019; *23* : 535-42.
3. Contardi E, Palmisano GL, Tazzari PL, Martelli AM, Fala F, Fabbi M, *et al*. CTLA-4 is constitutively expressed on tumor cells and can trigger apoptosis upon ligand interaction. *Internat J Cancer* 2005; *117* : 538-50.
4. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J* 1992; *11* : 3887-95.
5. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science* 1996; *271* : 1734-6.
6. Tawbi HA, Schadendorf D, Lipson EJ, Ascierto PA, Matamala L, Castillo Gutiérrez E, *et al*. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med* 2022; *386* : 24-34.
7. Powles T, Plimack ER, Soulières D, Waddell T, Stus V, Gafanov R, *et al*. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): Extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2020; *21* : 1563-73.
8. Doroshow DB, Bhalla S, Beasley MB, Sholl LM, Kerr KM, Gnjatic S, *et al*. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. *Nat Rev Clin Oncol* 2021; *18* : 345-62.
9. Groth C, Hu X, Weber R, Fleming V, Altevogt P, Utikal J, *et al*. Immunosuppression mediated by myeloid-derived suppressor cells (MDSCs) during tumour progression. *Br J Cancer* 2019; *120* : 16-25.
10. Genova C, Dellepiane C, Carrega P, Sommariva S, Ferlazzo G, Pronzato P, *et al*. Therapeutic implications of tumor microenvironment in lung cancer: Focus on immune checkpoint blockade. *Front Immunol* 2021; *12* : 799455.
11. Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, *et al*. Understanding the tumor immune microenvironment (TIME) for effective therapy. *Nat Med* 2018; *24* : 541-50.
12. Cogdill AP, Andrews MC, Wargo JA. Hallmarks of response to immune checkpoint blockade. *Br J Cancer* 2017; *117* : 1-7.
13. Denkert C, von Minckwitz G, Darb-Esfahani S, Lederer B, Heppner BI, Weber KE, *et al*. Tumour-infiltrating lymphocytes

and prognosis in different subtypes of breast cancer: A pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol* 2018; *19* : 40-50.

14. Greillier L, Tomasini P, Barlesi F. The clinical utility of tumor mutational burden in non-small cell lung cancer. *Transl Lung Cancer Res* 2018; *7* : 639-46.
15. Rapoport BL, van Eeden R, Sibaud V, Epstein JB, Klastersky J, Aapro M, *et al*. Supportive care for patients undergoing immunotherapy. *Support Care Cancer* 2017; *25* : 3017-30.
16. Jiricny J. The multifaceted mismatch-repair system. *Nat Rev Mol Cell Biol* 2006; *7* : 335-46.
17. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr., Kinzler KW. Cancer genome landscapes. *Science* 2013; *339* : 1546-58.
18. Colle R, Cohen R, Cochereau D, Duval A, Lascols O, Lopez-Trabada D, *et al*. Immunotherapy and patients treated for cancer with microsatellite instability. *Bull Cancer* 2017; *104* : 42-51.
19. Overman MJ, Lonardi S, Wong KYM, Lenz HJ, Gelsomino F, Aglietta M, *et al*. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol* 2018; *36* : 773-9.
20. Bourdais R, Rousseau B, Pujals A, Boussion H, Joly C, Guillemin A, *et al*. Polymerase proofreading domain mutations: New opportunities for immunotherapy in hypermutated colorectal cancer beyond MMR deficiency. *Crit Rev Oncol Hematol* 2017; *113* : 242-8.
21. Li K, Luo H, Huang L, Luo H, Zhu X. Microsatellite instability: A review of what the oncologist should know. *Cancer Cell Int* 2020; *20* : 16.
22. Honrubia-Peris B, Garde-Noguera J, García-Sánchez J, Piera-Molons N, Llombart-Cussac A, Fernández-Murga ML. Soluble biomarkers with prognostic and predictive value in advanced non-small cell lung cancer treated with immunotherapy. *Cancers* 2021; *13* : 4280.
23. Poto R, Troiani T, Criscuolo G, Marone G, Ciardiello F, Tocchetti CG, *et al*. Holistic approach to immune checkpoint inhibitor-related adverse events. *Front Immunol* 2022; *13* : 804597.
24. Anderson R, Theron AJ, Rapoport BL. Immunopathogenesis of immune checkpoint inhibitor-related adverse events: Roles of the intestinal microbiome and Th17 cells. *Front Immunol* 2019; *10* : 2254.
25. Das R, Bar N, Ferreira M, Newman AM, Zhang L, Bailur JK, *et al*. Early B cell changes predict autoimmunity following combination immune checkpoint blockade. *J Clin Invest* 2018; *128* : 715-20.
26. Mazarico I, Capel I, Giménez-Palop O, Albert L, Berges I, Luchtenberg F, *et al*. Low frequency of positive antithyroid antibodies is observed in patients with thyroid dysfunction related to immune check point inhibitors. *J Endocrinol Invest* 2019; *42* : 1443-50.
27. Cappelli LC, Dorak MT, Bettinotti MP, Bingham CO, Shah AA. Association of HLA-DRB1 shared epitope alleles and immune checkpoint inhibitor-induced inflammatory arthritis. *Rheumatology* 2019; *58* : 476-80.
28. Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. *Sci Transl Med* 2014; *6* : 230ra45.
29. Chaput N, Lepage P, Coutzac C, Soularue E, Le Roux K, Monot C, *et al*. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. *Ann Oncol* 2017; *28* : 1368-79.
30. Danlos FX, Voisin AL, Dyevre V, Michot JM, Routier E, Taillade L, *et al*. Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease. *Eur J Cancer* 2018; *91* : 21-9.
31. Rapoport BL, Anderson R, Cooksley T, Johnson DB. MASCC 2020 recommendations for the management of immune-related adverse events of patients undergoing treatment with immune checkpoint inhibitors. *Support Care Cancer* 2020; *28* : 6107-10.
32. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, *et al*. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *J Clin Oncol* 2018; *36* : 1714-68.
33. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, *et al*. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; *29* (Suppl 4) : iv264-iv266.
34. Puzanov I, Diab A, Abdallah K, Bingham CO 3rd, Brogdon C, Dadu R, *et al*. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* 2017; *5* : 95.
35. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, *et al*. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015; *373* : 23-34.
36. Eggermont AMM, Kicinski M, Blank CU, Mandala M, Long GV, Atkinson V, *et al*. Association between immune-related adverse events and recurrence-free survival among patients with stage III melanoma randomized to receive pembrolizumab or placebo: A secondary analysis of a randomized clinical trial. *JAMA Oncol* 2020; *6* : 519-27.
37. Thom B, Mamoor M, Lavery JA, Baxi SS, Khan N, Rogak LJ, *et al*. The experience of financial toxicity among advanced melanoma patients treated with immunotherapy. *J Psychosoc Oncol* 2021; *39* : 285-93.