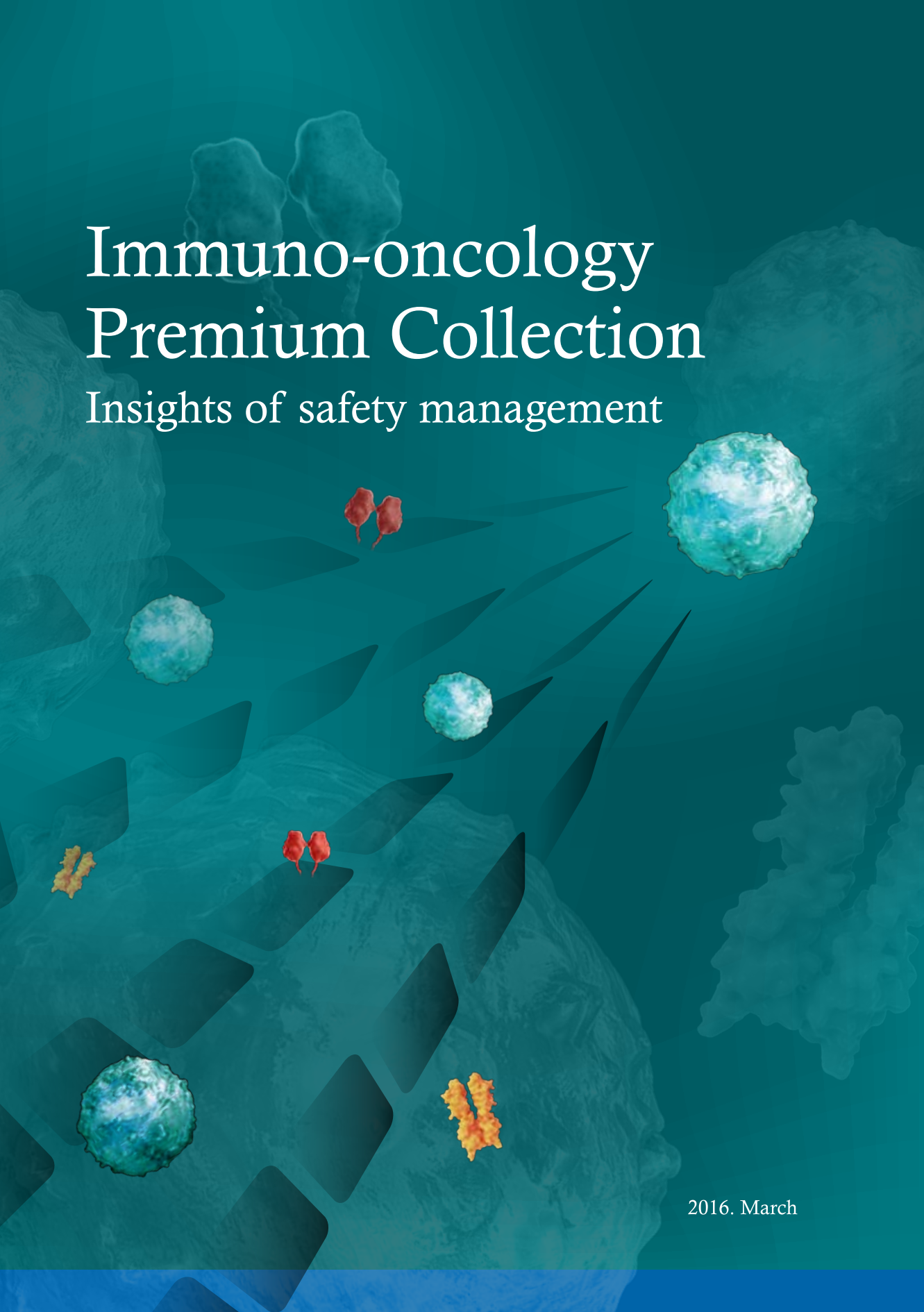
Immuno-oncology Premium Collection

Insights of safety management



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Preface

The diagnosis and treatment of cancer is always a long and difficult road for patients, family members, and physicians. The same can be said for the development of anticancer therapy: The earliest cytotoxic regimens, which used chemotherapy drugs to try and reduce tumor burden, ended up having limited efficacy while devastating patients with unwanted side effects. The success of targeted therapies over the past 10 years has been exhilarating, but the medical community remains dissatisfied by the limited prolongation of survival seen with such treatments. However, since the advent of immuno-oncology (I-O) therapies in 2011, hailed by the prestigious *Science* journal as a breakthrough development, physicians and patients now have a much better chance than ever before of curing cancer or achieving long-term survival.

Looking back, every major breakthrough in anticancer therapy has elicited strong excitement in physicians, and raised the hopes of patients and their families. This Booklet presents the latest advances in I-O therapy, in the spirit of disseminating up-to-date medical knowledge and promoting continuous learning, and hopes to serve as a beneficial companion on the long journey of cancer treatment.

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前言

癌症的診斷與治療，對病患、家屬、與醫師來說，都是一條漫長的路。最早醫學發展毒殺性治療，設想利用化學藥物消滅體內腫瘤，然而不但成效不彰，其副作用亦同時傷害病患本身。過去10年，標靶治療的成功振奮人心，然而，醫學界無法以此爲滿足，因爲標靶治療只能短暫延長病患生命。2011年因爲免疫學在癌症治療的應用，被《科學 (*Science*)》期刊榮稱爲重大發展的一年，持續到今天，「免疫腫瘤學 (immuo-oncology)」 變成最眾所矚目的議題，帶給醫者有治癒癌症、或是長期存活的希望。

回顧過去癌症治療，每一次的重大突破都使醫者興奮、使病患有希望。本期刊秉持發揚醫學新知、推動學術進修的原則，期待與各位先進一同成長，帶來助益，造福更多病患。

臨床腫瘤醫學會 理事長
高尚志

3 Understanding Immuno-Oncology (I-O) Therapy

Immuno-oncology (I-O) therapies represent an important step forward in the evolution of anti-cancer drugs. Before the advent of targeted therapy and immunotherapy, cancer treatment strategies primarily sought to exploit the difference in division rates between cancer cells and normal cells, eventually resulting in the development of chemotherapy drugs directed at DNA synthesis or chromosome separation. However, these drugs can also adversely affect rapidly dividing normal cells of the bone marrow, intestinal tract, and hair follicles. Therefore, therapies that target specific proteins expressed by tumor cells were developed, examples of which include imatinib (targets mutated Bcr-Abl tyrosine kinase), trastuzumab (targets overexpressed HER2 receptors), and gefitinib (targets activating EGFR mutations). Unfortunately, response rates to targeted therapy can be quite low in patients that do not fit the target profile; for example, breast cancers overexpressing HER2 receptors can be effectively treated with trastuzumab, but the drug is ineffective against tumors that do not express HER2. Treatments that target the general tumor environment have also been developed, including angiogenesis inhibitors and hormonal therapies, but again, these strategies can only be effective in a certain context. By contrast, I-O therapies are designed to enhance the ability of innate immune systems to identify and destroy cancer cells (Figure 1), and therefore have the potential to be effective against all types of cancers, irrespective of histology or mutation status.

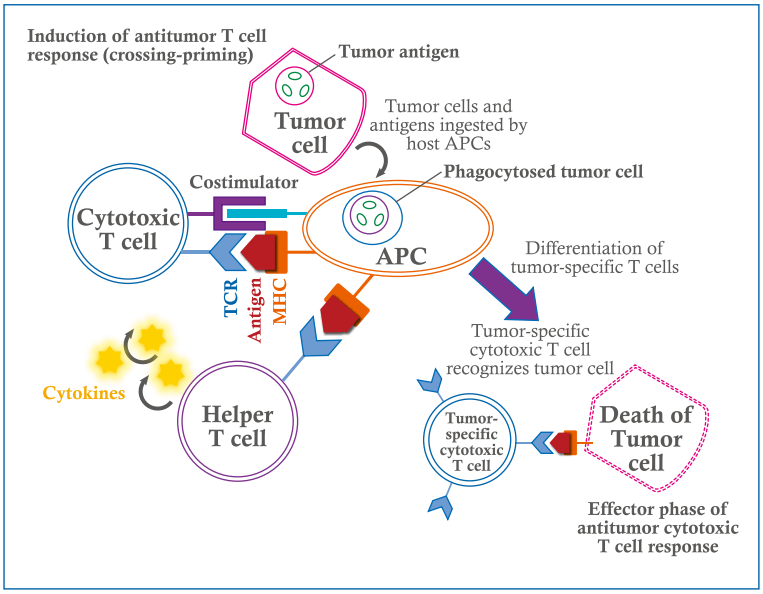


Figure 1. *The immune response to cancer cells.*

The idea of harnessing the immune system to combat cancer cells is not new. As early as 1893, the American surgeon William Coley reported inoculating 10 cases of bone or soft tissue sarcomas with mixtures of dead *Streptococcus pyogenes* and *Serratia marcescens*, which were dubbed "Coley's toxins"[1]. Although responses and remission were observed in several patients, Coley's toxins were never tested in controlled trials, and the subsequent emergence of radiotherapy and chemotherapy eclipsed these findings. Fortunately, research into immuno-oncology continued, and the German physician Paul Erlich subsequently proposed in 1909 that the immune system may play an active role in keeping transformed cells in check[2]. This eventually formed the basis of "immunosurveillance", a concept initially

proposed by the Australian immunologist Frank Burnet in 1957 and further developed by the American physician Lewis Thomas in 1982[2]. Immunosurveillance considers the recognition of tumor-associated antigens (TAA) and the elimination of transformed cells to be among the key roles of the immune system[2]. In 1991, MAGE-A1 became the first human TAA to be identified[2]. Clinical studies into the use of cytokines to enhance anti-tumor immune responses were also being conducted during this period of time, and subsequently led to the 1992 approval by the US Food and Drug Administration (FDA) of interleukin-2 (IL-2) as the first I-O therapy[2]. However, the high toxicities observed with IL-2 and other cytokine treatments have limited their clinical application thus far[1-3].

In recent years, molecular advances have allowed researchers to better elucidate the roles of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptors, programmed cell death protein 1 (PD-1), and the PD-1 ligand, PD-L1, in regulating T cell function and the immune response to tumor cells. CTLA-4, PD-1, and PD-L1 act as key mediators of **immune checkpoints**, which serve to deactivate T cells and prevent the immune response from spiraling out of control[4]. This process protects against autoimmunity, but also offers a loophole that tumor cells can exploit. Inhibition of CTLA-4, PD-1, and PD-L1 has been found to enhance T cell activation and the anti-tumor response[4], and this has led to the development of monoclonal antibodies that have demonstrated remarkable clinical efficacy against advanced melanoma[5-10], non-small cell lung cancer (NSCLC)[11-13], and renal cell carcinoma[14]. The following sections will provide a comprehensive overview of the development, mechanisms, efficacy, and safety of anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies, and a number of case studies will also be discussed, to better illustrate the use of these novel I-O therapies in a clinical setting.

3-1 Anti-CTLA-4 Antibodies - Insights & Mechanisms

T cell activation requires two signals: the first signal is antigen-specific, and involves interaction between T cell receptors (TCR) and the antigen-major histocompatibility complex (MHC) on the surface of antigen-presenting cells (APCs). The second signal involves interaction between co-stimulatory molecules on the surface of T cells and APCs (Figure 2). CD28 has been identified

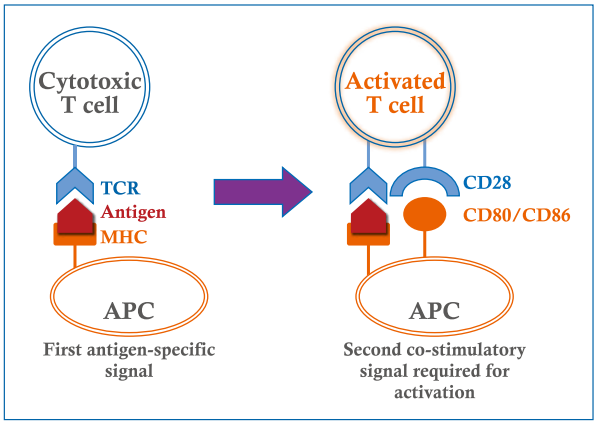


Figure 2. *Two signals are required for the activation of T cells, an antigen-specific signal triggered by binding between the T cell TCR and the APC antigen-MHC complex, and a second co-stimulatory signal between CD28 and the CD80/CD86 (B7-1/B7-2) ligands.*

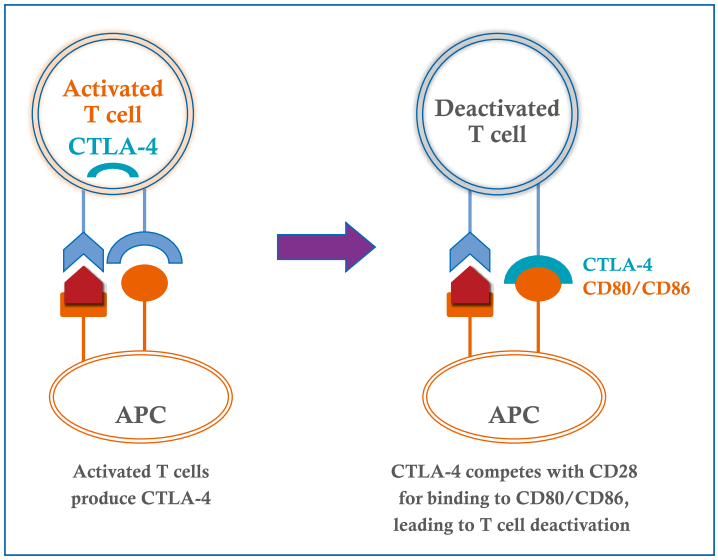


Figure 3. *The CTLA-4 receptor is expressed in activated T cells, and is subsequently transported to the cell surface to compete with CD28 for binding to CD80/CD86 (B7-1/B7-2) ligands; this then triggers a negative signal that deactivates T cells and attenuates the immune response.*

as the co-stimulatory molecule on the surface of T cells, while the APC surface proteins CD80 (B7-1) and CD86 (B7-2) have been shown to be ligands of CD28[1]. For cytotoxic T cells, binding between the TCR and the antigen-MHC complex presented by APCs must be followed by binding between CD28 and CD80/CD86 in order to induce activation; in the absence of the co-stimulatory signal, T cells will become tolerant to the antigen presented (Figure 2)[1]. However, once T cells are activated, CTLA-4 receptors will be expressed and then translocated to the surface of T cells. Compared to CD28, CTLA-4 has significantly greater affinity for CD80/CD86, and can therefore compete with CD28 to disrupt the second activation signal. Once CTLA-4 binds with CD80/CD86, a negative signal is triggered, resulting in suppression of IL-2 production and T cell proliferation (Figure 3)[1]. A recent study further suggests that CTLA-4 may be capable of capturing and removing CD80/CD86 ligands from the surface of APCs, rendering them completely unavailable for recognition and binding by CD28[15].

The immunosuppressive properties of CTLA-4 have already been harnessed for use in the treatment of autoimmune disorders; for example, CTLA-4 agonists such as abatacept are now deployed to dampen the overblown immune response in rheumatoid arthritis. However, immunosuppression by CTLA-4 may also be an important factor in allowing tumor cells to escape recognition by the immune system. Early research in mice by Dr. James P. Allison, a key pioneer of anti-CTLA-4 antibody therapy, revealed that an immune response could be partially engendered against a transplantable murine colon carcinoma, once the tumor cells were engineered to express CD80[1]. Moreover, mice that developed an immune response to CD80-expressing tumor cells were also able to target and eliminate the same type of tumor cells, regardless of CD80 expression[1]. Dr. Allison thus reasoned that complete CTLA-4 blockade might serve to enhance the co-stimulatory T cell activation signal and induce stronger anti-tumor effects. In studies with mice, Dr. Allison confirmed that the deployment of anti-CTLA-4 antibodies led to dramatic reductions in the size of implanted tumors, and

good results were observed with large, advanced tumors as well[1]. These studies paved the way for the development of ipilimumab and other anti-CTLA-4 antibodies, and Dr. Allison was subsequently awarded the 2015 Lasker-DeBakey Clinical Medical Research Award for his contributions.

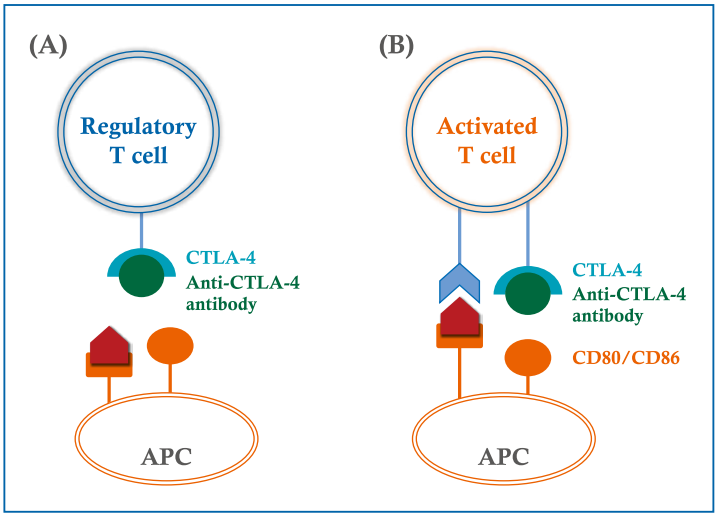


Figure 4. *It has been proposed that anti-CTLA-4 antibodies act to strengthen the immune response through two pathways: (A) Anti-CTLA-4 antibodies block surface CTLA-4 on regulatory T cells, preventing these T cells from accumulating in tumors and dampening the immune response. (B) Anti-CTLA-4 antibodies bind with CTLA-4 on the surface of cytotoxic T cells to block binding with CD80 and allow the cellular immune response to remain active.*

It has been proposed that anti-CTLA-4 antibodies can act through two different pathways[1]: in the first pathway, anti-CTLA-4 antibodies block surface CTLA-4 on regulatory T cells, thus preventing these cells from accumulating in tumors and dampening the immune response (Figure 4A)[1]. In the second pathway, anti-CTLA-4 antibodies bind with CTLA-4 on the surface of cytotoxic T cells to prevent competition with CD80, allowing the cellular immune response to remain active (Figure 4B)[1]. However, the precise mechanism by which CTLA-4 blockade enhances and extends the T cell anti-tumor response has not yet been defined.

3-2 Current Indications for Anti-CTLA-4 Antibodies

The first anti-CTLA-4 antibody for I-O therapy, ipilimumab, was approved by the US FDA in 2011, with the following indications:

- Treatment of unresectable or metastatic melanoma.
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

Ipilimumab has also been approved for the treatment of advanced (unresectable or metastatic) melanoma in adults by the European Medicines Agency (EMA) in 2013, and by the Ministry of Health and Welfare (MOHW) of Taiwan in 2014.

Another anti-CTLA-4 antibody, tremelimumab, received orphan drug designation for the treatment of malignant mesothelioma[16] from the US FDA in 2015.

3-3 Anti-PD-1 and Anti-PD-L1 Antibodies - Insights & Mechanisms

PD-1 was first identified in 1992 as part of a group of genes expressed during the programmed cell death of T cells[1]. PD-1 has been found to be highly upregulated during T cell activation, and it can dampen the immune response via binding to its ligands, PD-L1 and PD-L2 (Figure 5A). Many tumor cells are known to express PD-L1/PD-L2, and it has been posited that PD-1 signaling triggers anergy in T cells. Studies in mice have shown that antibody blockade of PD-1 signaling can enhance the overall anti-tumor response[1].

Anti-PD-1 antibodies act by blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 (Figure 5B). This was shown to enhance immune responses *in vitro* and *in vivo*, and may serve to maintain T cell activation against tumors. Interestingly, the immune-enhancing effect of anti-PD-1 antibodies has been found to be effective in eradicating human immunodeficiency virus (HIV)-infected T cells from the immune system as well, and studies investigating the use of these drugs for the treatment of HIV are currently ongoing[17].

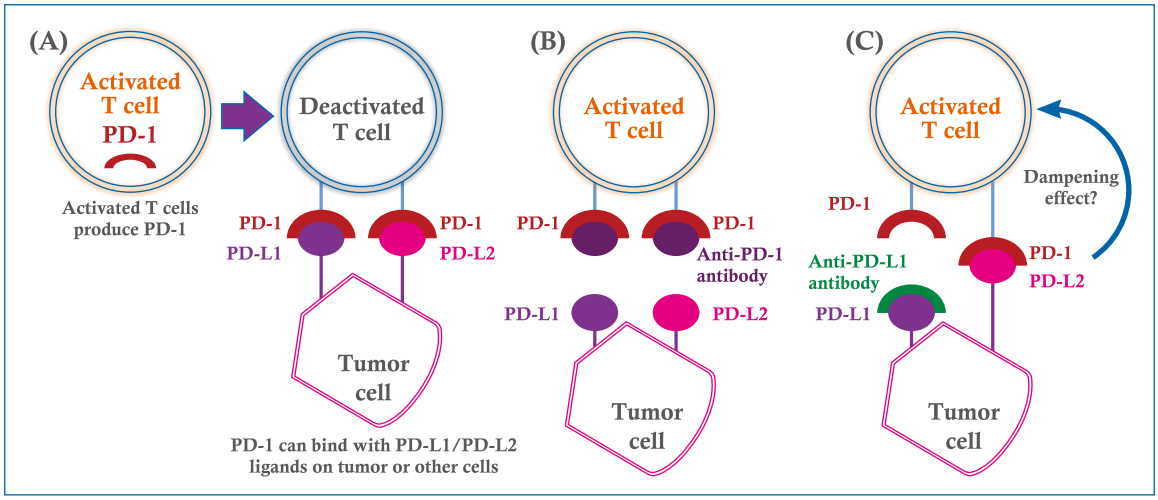


Figure 5. *(A) PD-1 is highly upregulated during T-cell activation, and acts to dampen the immune response via binding to its ligands, PD-L1 and PD-L2. (B) Anti-PD-1 antibodies bind to PD-1 to prevent this dampening effect, and this may serve to maintain the cytotoxic T cell response against tumors. (C) Anti-PD-L1 antibodies exclusively disrupt the interaction between PD-1 and PD-L1; however, although this approach may result in less toxicity, it may also result in a weaker immune response as the interaction between PD-1 and PD-L2 remains valid.*

Anti-PD-L1 antibodies similarly act by blocking the interaction between PD-1 and PD-L1, but these antibodies target the PD-L1 ligand instead (Figure 5C). This approach may be able to reduce some of the toxicity seen with current anti-PD-1 antibody therapy, but may also result in a diminished anti-tumor immune response, as PD-1 may still be able to undercut the anti-tumor effect via binding to PD-L2 (Figure 5C)[18].

3-4 Current Indications for Anti-PD-1 Antibodies

The first anti-PD-1 antibody to gain regulatory approval was nivolumab; in 2014, Japan approved nivolumab for the treatment of unresectable melanoma. In late 2014, the US FDA also approved nivolumab for several indications, including:

- Use as a single agent in patients with *BRAF* V600 wild-type unresectable or metastatic melanoma.
- Use as a single agent in patients with unresectable or metastatic, *BRAF* V600 mutation-positive melanoma and disease progression following ipilimumab and a *BRAF* inhibitor*.
- Use in combination with ipilimumab, of patients with *BRAF* V600 wild-type unresectable or metastatic melanoma*.
- For patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy (those with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab).
- For patients with advanced renal cell carcinoma who have received prior antiangiogenic therapy.

*: *This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.*

In 2015, the EMA approved nivolumab for the treatment of advanced (unresectable or metastatic) melanoma in adults, and for the treatment of locally advanced or metastatic squamous non-small cell lung cancer after prior chemotherapy in adults.

Pembrolizumab, another anti-PD-1 antibody, was granted approval in 2015 by the US FDA for the treatment of metastatic non-small cell lung cancer in patients whose tumors express PD-L1 and who have failed treatment with other chemotherapeutic agents, and by the EMA for the treatment of advanced (unresectable or metastatic) melanoma in adults.

As of January 2016, no anti-PD-L1 antibodies have been approved for any indications as yet, but recent results of Phase II trials against advanced urothelial cancer are promising[19].

4 Clinical Efficacy of Anti-CTLA-4 Antibodies

Phase I/II clinical trials with anti-CTLA-4 antibodies showed good response rates in patients with advanced melanoma, lymphoma, castration-resistant prostate cancer (CRPC), NSCLC, and malignant mesothelioma[16,20]. Building on these promising results, the first Phase III trial was completed in 2010, and compared the anti-CTLA-4 antibody ipilimumab to a peptide vaccine in 676 metastatic melanoma patients[5]. The trial evaluated overall survival instead of response rate, and showed that patients receiving ipilimumab (3 mg/kg body weight every 3 weeks) alone or ipilimumab + gp100 vaccine achieved median overall survival of 10 months, compared to just 6.4 months for patients who received the gp100 vaccine alone (Figure 6)[5].

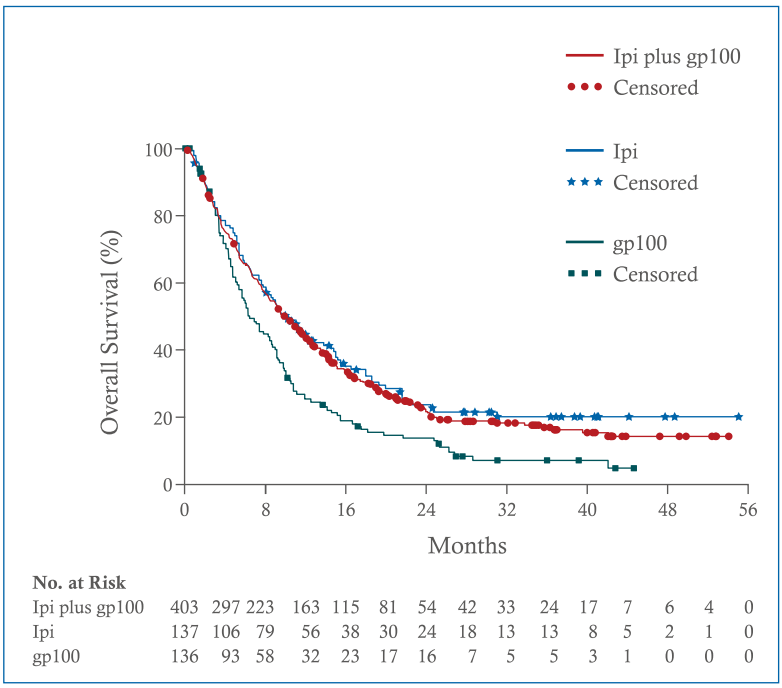


Figure 6. *Compared to advanced melanoma patients who received the gp100 vaccine alone, patients who received the anti-CTLA-4 antibody ipilimumab or ipilimumab + gp100 demonstrated significantly better overall survival during the study period.*

A 36% reduction in the risk of tumor progression was observed for the ipilimumab-only group, as compared to the gp100-only group, and at 24 months, overall survival rates for the ipilimumab-only, ipilimumab + gp100, and gp100-only patient groups were 23.5%, 21.6%, and 13.7%, respectively[5]. Importantly, among those patients who received ipilimumab and were still surviving at 24 months, there were very few relapses[5]. This was further confirmed in a recent pooled analysis of Phase II/III ipilimumab trials in unresectable or metastatic melanoma, which examined data for 1,861 patients from 10 prospective and 2 retrospective trials, and found that at 3 years of follow-up, the survival curve bottomed out at around 20%[7]. For treatment-naïve patients, the survival curve bottomed out at 26% after 3 years of follow-up[7]. This suggests that 20-26% of metastatic melanoma patients can be fully cured by ipilimumab therapy (Figure 7)[7]. Historically, 5-year survival rates for advanced melanoma have hovered around 10%, and therefore a long-term survival rate of 20% represents a significant breakthrough in treatment.

In 2011, ipilimumab was assessed in 502 previously untreated metastatic melanoma patients as an add-on to dacarbazine, the current standard of treatment for metastatic melanoma[6]. Study results showed that overall survival was significantly longer for the ipilimumab + dacarbazine group vs. the dacarbazine + placebo group (11.2 months vs. 9.1 months), with higher survival rates observed in the ipilimumab + dacarbazine group at 1 year (47.3% vs. 36.3%), 2 years (28.5% vs. 17.9%), and 3 years (20.8% vs. 12.2%; Figure 8)[6].

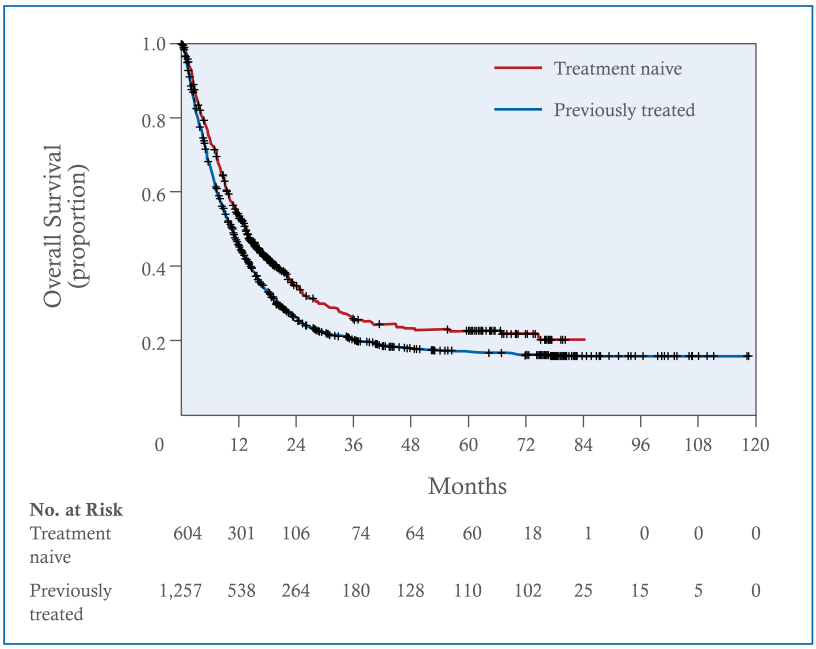


Figure 7. *A pooled analysis of 12 ipilimumab trials in metastatic melanoma showed that 3-year survival rates of 26% for treatment-naïve patients and 20% for previously treated patients could be achieved with ipilimumab therapy.*

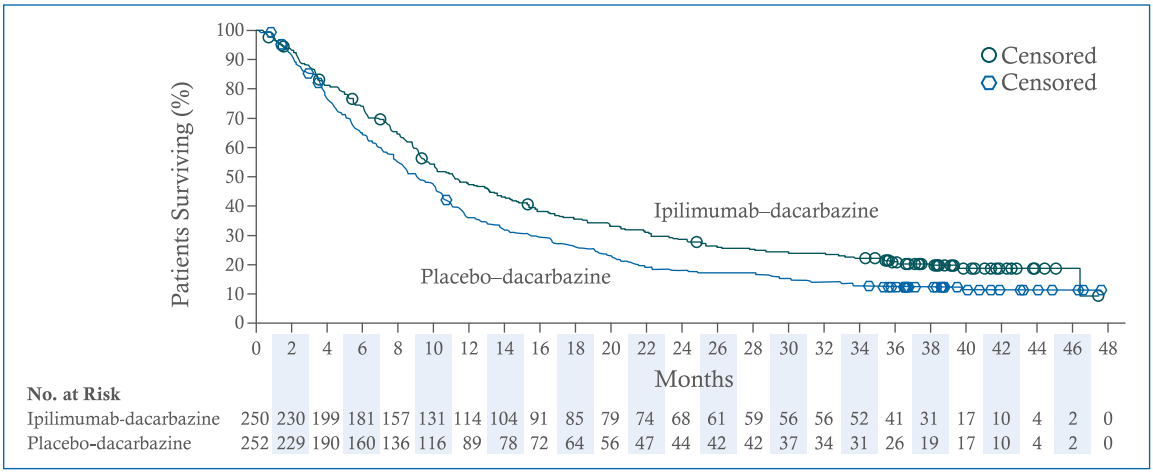


Figure 8. *Kaplan-Meier overall survival curves for previously untreated metastatic melanoma patients receiving ipilimumab + dacarbazine or dacarbazine + placebo; 1-year (47.3% vs. 36.3%), 2-year (28.5% vs. 17.9%), and 3-year (20.8% vs. 12.2%) survival rates were all higher for the ipilimumab + dacarbazine treatment group.*

5 Clinical Efficacy of Anti-PD-1 and Anti-PD-L1 Antibodies

Anti-PD-1 antibodies similarly achieved 20-25% objective response rates in a broad range of cancers during early clinical trials, including melanoma, NSCLC, and renal cell cancer[21]. Several Phase III trials of anti-PD-1 antibodies for these three cancers were therefore initiated, and 2015 inadvertently turned out to be a pivotal year, as results from no less than 7 studies were published, all showing significant benefits in terms of survival[8-14]. The first of these studies examined the anti-PD-1 antibody nivolumab in 418 previously untreated metastatic melanoma patients without *BRAF* mutations[8]. In this study, nivolumab was compared with the current standard treatment for metastatic melanoma, dacarbazine. The 1-year survival rate was 72.9% for the nivolumab group, and 42.1% in the dacarbazine group, with a clear separation in the curves for both overall survival and progression-free survival occurring quite early in the study (Figure 9)[8]. Patients receiving nivolumab had an objective response rate of 40.0% and median progression-free survival of 5.1 months, in contrast to 13.9% objective response rate and 2.2 months of median progression-free survival for patients treated with dacarbazine[8]. Interestingly, overall survival and nivolumab efficacy was not significantly affected by tumor PD-L1 status[8].

In 631 metastatic melanoma patients who progressed after ipilimumab and *BRAF* inhibitors, nivolumab also demonstrated better efficacy than chemotherapy (dacarbazine or paclitaxel combined with carboplatin), achieving a 31.7% response rate (vs. 10.6% for chemotherapy) while exhibiting lower toxicity[9]. Patients were able to benefit from nivolumab regardless of *BRAF* status, PD-L1 status, or previous benefit from ipilimumab[9]. And in another study of 834 advanced melanoma patients, the anti-PD-1 antibody pembrolizumab was also shown to be effective in terms of prolonging progression-free survival and overall survival[10].

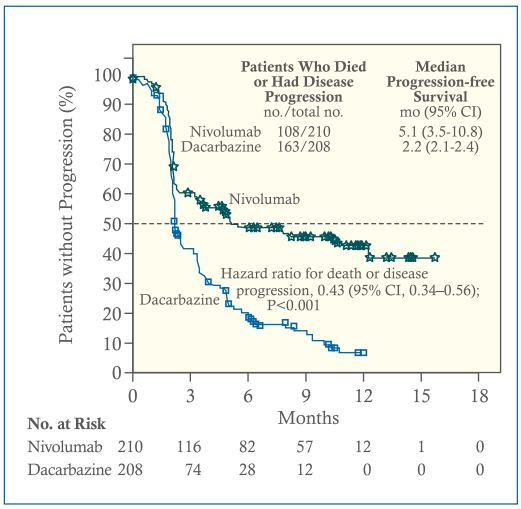


Figure 9. *Kaplan-Meier progression-free survival curves for previously untreated BRAF wild-type metastatic melanoma patients receiving nivolumab or dacarbazine; note the clear separation of the curves after just 3 months of treatment.*

Anti-PD-1 antibodies have also been shown to be effective for NSCLC[11-13]. In a pair of studies examining the efficacy of nivolumab for squamous-cell NSCLC (n = 272)[11] or non-squamous NSCLC (n = 582)[12], nivolumab achieved a median overall survival of 9.2 months in squamous NSCLC patients, versus 6.0 months with docetaxel[11]. Response rates were 20% for the nivolumab group and 9% for the docetaxel group, and overall survival rates at 1 year were 42% with nivolumab and 24% with docetaxel (Figure 10)[11]. Again, the PD-L1 status of tumor cells was stated as being "neither prognostic nor predictive of benefit"[11].

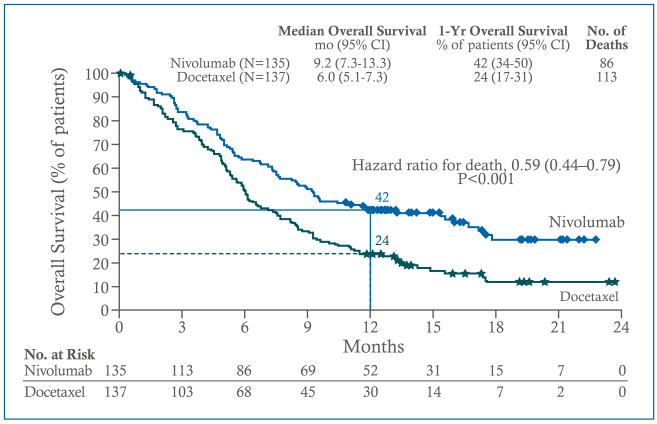


Figure 10. *Kaplan-Meier overall survival curve for advanced squamous NSCLC patients receiving either nivolumab or docetaxel; after 1 year of treatment, the overall survival rate was 42% with nivolumab versus 24% with docetaxel, a significant difference.*

As for non-squamous NSCLC patients, median overall survival was longer for the nivolumab group compared to the docetaxel group (12.2 months vs. 9.2 months), and survival rates at 18 months of treatment was 39% versus 23%, again favoring nivolumab therapy[12]. In this group of patients, a strong predictive association between clinical outcomes of nivolumab treatment and PD-L1 expression was noted[12]. Moreover, subgroup analysis results indicated that nivolumab was more effective in patients with *KRAS* mutations[12]. Pembrolizumab was also compared with docetaxel in a Phase III study of 1,034 previously treated squamous and non-squamous NSCLC patients with positive PD-L1 status, and the results showed that the pembrolizumab group demonstrated better overall survival and progression-free survival compared to the docetaxel group[13].

In advanced renal cell carcinoma patients, nivolumab was shown to have a better objective response rate compared to everolimus (25% vs. 5%), and the nivolumab group also had longer median overall survival (25.0 months vs. 19.6 months)[14]. PD-L1 status did not affect nivolumab efficacy in this group of patients[14].

It appears that PD-1 blockade is effective in patients who failed to respond or acquired resistance to CTLA-4 blockade, as results of a Phase III study in metastatic melanoma patients who progressed after ipilimumab and *BRAF* inhibitors showed[9]. For patients who did not respond to ipilimumab, a 28% objective response rate to nivolumab was observed[9]. This suggests that PD-1 blockade and CTLA-4 blockade may have non-overlapping benefits, and subsequent studies assessing ipilimumab + nivolumab combinations for metastatic melanoma patients progressing on anti-CTLA-4 therapy have yielded good results[22], subsequently resulting in the approval by the US FDA in 2015 of ipilimumab + nivolumab combination therapy for the treatment of patients with *BRAF* V600 wild-type, unresectable or metastatic melanoma.

Although no anti-PD-L1 antibodies have been approved for any indication as of now (January 2016), good responses have been observed in Phase I trials with melanoma, renal cell cancer, and NSCLC[23], and preliminary results of a Phase II trial in metastatic urothelial carcinoma are promising[17]. Interestingly, this Phase II study also found that 84% of patients who initially responded to anti-PD-L1 antibody therapy continued to respond during an 11.7-month follow-up period, regardless of their PD-L1 status[17].

6 Safety Management in I-O Therapy

Under normal circumstances, both CTLA-4 receptors and PD-1 act to dampen the immune response and prevent autoimmunity. Therefore, the inhibition of these factors during I-O therapy can be expected to induce immune-related adverse events (irAEs), which can occur in the skin, gastrointestinal tract, liver, kidneys, lungs, eyes, joints, endocrine system, or nervous system (Figure 11). However, the majority of irAEs can be managed by withholding or discontinuing treatment, together with the administration of corticosteroids to alleviate autoimmunity and inflammation as necessary. Moreover, most irAEs are reversible under proper management. Early recognition of irAEs and management according to specific algorithms can help to mitigate severe toxicity.

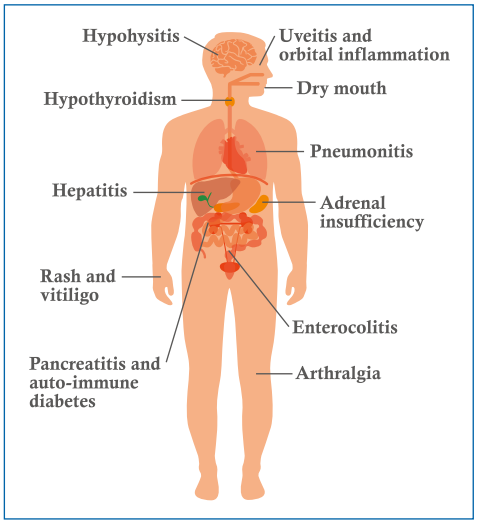


Figure 11. *Overview of possible irAEs that can occur in I-O therapy.*

According to the Common Terminology Criteria for Adverse Events (CTCAE)[24], published by the US National Cancer Institute (NCI), adverse events can be classified by severity as grade 1 — Mild; grade 2 — Moderate; grade 3 — Severe; grade 4 — Life-threatening; and grade 5 — Fatal. In Phase III trials of anti-CTLA-4 antibodies, grade 3 or 4 irAEs were reported in 10-15% of metastatic melanoma patients treated with ipilimumab[5]. The most common irAE was diarrhea, which occurred in 27-31% of patients; however, 86-90% of these cases were graded as being mild to moderate[5]. Other irAEs of concern included fatigue and colitis[5]. A recent study examining rare but severe irAEs associated with CTLA-4 blockade in 752 melanoma patients documented cases of drug rash with eosinophilia and systemic symptoms (DRESS), granulomatous inflammation of the central nervous system, and aseptic meningitis[25]. Importantly, these rare irAEs were primarily documented in patients who responded rapidly to anti-CTLA-4 therapy, suggesting that immune-related reactions can have an early onset, and may be reflective of overtreatment[25].

In Phase III clinical trials of anti-PD-1 antibodies, grade 3 or 4 treatment-related adverse events were reported in 5-19% of patients, with fatigue, pruritus, nausea, diarrhea, skin rash, decreased appetite, and asthenia being the most common events associated with therapy[8-14]. Of the immune checkpoint inhibitors currently used in I-O therapy, anti-PD-1 antibodies are considered to be less toxic and more tolerable than anti-CTLA-4 antibodies[26].

6-1 General Rules of Safety Monitoring and Management

The primary obstacles to effective management of irAEs in I-O therapy include patient delay in reporting symptoms, and difficulty in differentiating irAEs from AEs caused by other

factors, such as tumor complications, bacterial or viral infection, or steroid use[25]. Evidence from clinical trials has shown that adherence to the following approach will be conducive to safety management in I-O therapy, and can help to minimize morbidity and hospitalizations:

- While most irAEs occur during the induction period of immune checkpoint inhibition therapy with anti-CTLA-4 or anti-PD-1 antibodies, there have been reports of irAEs appearing months after the last dose of treatment.
- Rash, diarrhea, increased stool frequency, bloody stool, endocrinopathies, and liver enzyme elevations should be considered to be inflammatory and treatment-related, unless an alternate etiology has been identified.
- Other AEs suspected to be immune-related include eosinophilia, lipase elevation, iritis, hemolytic anemia, amylase elevations, and multi-organ failure.
- **Patient education:** Patients, family members, and caregivers should be instructed in the primary signs and symptoms of dermatitis, enterocolitis, endocrinopathy, neuropathy, and hepatotoxicity, and clinicians should emphasize the importance of reporting any new and/or worsening symptom.
- **Early screening:** Patients should be assessed for signs and symptoms of autoimmunity at baseline and before each subsequent dose.
- **Frequent monitoring:** After the initiation of immune checkpoint inhibition therapy, it is suggested that clinicians follow up with a weekly call over the next 16 weeks. For patients with ongoing irAEs, a minimum biweekly call should be made to monitor the resolution of irAEs. For patients admitted to another hospital for irAEs, clinicians should maintain frequent contact with the admitting physician and consulting specialist, and provide guidance on the detection and management of irAEs.
- **Early intervention:** For low-grade irAEs, the scheduled dose should be delayed until severity declines to grade 1 or baseline, whereupon immune checkpoint inhibition therapy can be resumed. For high-grade irAEs, stopping treatment and administering corticosteroids is recommended, possibly in conjunction with immunosuppressants such as anti-TNFα antibodies or cyclophosphamide. Once irAEs resolve, I-O therapy may be continued or permanently discontinued, according to the patient's condition.
- **Adverse event reporting:** All AEs should be reported to the relevant pharmacovigilance monitoring authorities (in Taiwan, the National Adverse Drug Reaction Reporting Center is the relevant authority).
- For specific irAEs, please refer to the corresponding management algorithms.

6-2 Guidelines for Permanent Discontinuation or Dose Withholding

Immune checkpoint inhibition therapy should be permanently discontinued under the following circumstances:

- Severe gastrointestinal symptoms such as grade 3 or 4 diarrhea or colitis; abdominal pain; significant change in the number of stools; blood in stool; gastrointestinal hemorrhage; or gastrointestinal perforation.

- Nephritis, pneumonitis, and other irAEs ≥ grade 3 in the kidneys or lungs.
- Severe elevations in liver function tests for aspartate aminotransferase (AST; AST > 8 x Upper Limit of Normal), alanine aminotransferase (ALT; ALT > 8 x ULN), or total bilirubin (> 5 x ULN), and other symptoms of hepatotoxicity.
- Grade 4 skin rash, including Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN); or ≥ grade 3 pruritus that interferes with daily activities or requires medical attention.
- Grade 3 or 4 new-onset or worsening motor/sensory neuropathy.
- Pancreatitis; non-infectious myocarditis; all irAEs ≥ grade 3 in other organ systems; or ≥ grade 2 immune-related eye disorders NOT responding to topical immunosuppressive therapy.

Immune checkpoint inhibition therapy should be temporarily withheld under the following circumstances, until an irAE resolves to grade 0/1 or baseline. If resolution does not occur, it may be prudent to discontinue immune checkpoint inhibition therapy.

- Immune checkpoint inhibition therapy should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressants, and prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.
- Grade 2 diarrhea or colitis that is not controlled with medical management, persists for 5-7 days, or recurs.
- Moderate elevations in liver function tests (AST or ALT > 5 to ≤ 8 x ULN; total bilirubin > 3 to ≤ 5 x ULN).
- Grade 3 irAEs in the endocrine glands such as hypophysitis or thyroiditis, and which are not adequately controlled with hormone replacement therapy or immunosuppressants at high doses.
- Grade 2 or 3 skin rash; widespread/intense pruritus.
- Grade 2 unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting more than 4 days.
- All grade 2 irAEs in other organ systems.

6-3 Managing Gastrointestinal Adverse Events

Results from clinical trials indicate a median time to onset of grade 3-5 gastrointestinal (GI) irAEs of 8 weeks (range of 5-13 weeks) from the beginning of immune checkpoint inhibition therapy, with a median time from onset to resolution of 4 weeks. Clinical presentation may include diarrhea, increased frequency of bowel movements, abdominal pain, or blood in stool, perhaps accompanied by fever. Diarrhea or colitis occurring after the initiation of immune checkpoint inhibition therapy must be promptly evaluated to exclude infections or other alternate etiologies. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation with or without ulcerations, as well as lymphocytic and

neutrophilic infiltration. It is important to note that the great majority of treatment-related diarrhea or colitis was classified as grade 1 or 2 in severity, and 90% of cases achieved full resolution. However, if patients are initiated on steroids, it is best to taper slowly, and if opportunistic infections develop in patients receiving high-dose steroids for more than 4 weeks, prophylactic antibody treatment may be considered (Figure 12).

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

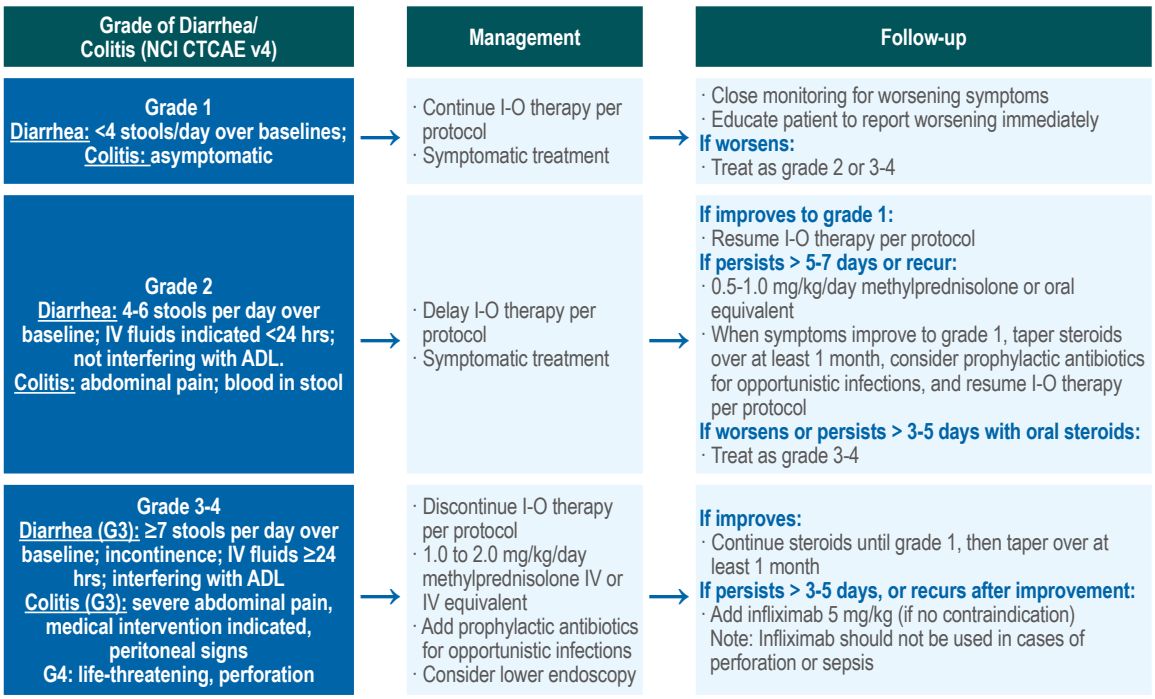


Figure 12. *GI adverse event management algorithm.*

6-4 Managing Renal Adverse Events

Patients on immune checkpoint inhibition therapy should be monitored for signs and symptoms of nephritis, glomerulonephritis, and renal dysfunction, most likely to present as asymptomatic increases in serum creatinine. Therefore, creatinine levels should be monitored for signs of renal toxicity, and the monitoring schedule should be shortened if irAEs develop. If patients are initiated on steroids, it is best to taper slowly over at least 1 month (Figure 13).

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

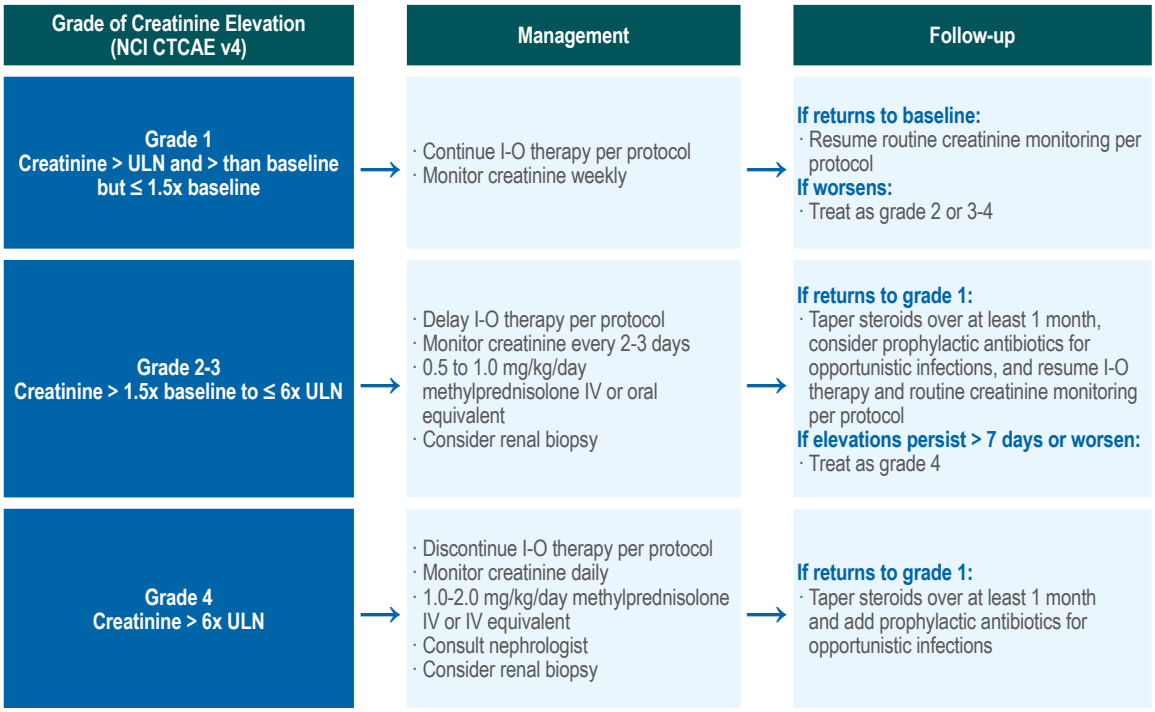


Figure 13. *Renal adverse event management algorithm.*

6-5 Managing Pulmonary Adverse Events

Pulmonary toxicity has been rarely observed in immune checkpoint inhibition therapy, and the majority of cases have been classified as grade 1 or 2. However, cases of grade 3-5 pneumonitis and interstitial lung disease have been reported, and therefore patients should be monitored for radiographic changes (e.g., focal ground glass opacities or patchy infiltrates), dyspnea, hypoxia, and other signs and symptoms of pneumonitis. It is important to note that pulmonary toxicity may present with clinical symptoms, or may simply be an incidental finding from regular scans. Patients with pulmonary irAEs have been successfully treated with prompt initiation of corticosteroids at an appropriate dose, and those with low-grade pulmonary toxicity may resume treatment once steroid tapering has been completed; however, prophylactic antibiotics for opportunistic infections may still be considered for patients expected to receive high-dose steroids for more than 4 weeks (Figure 14).

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 **Radiographic changes only**	· Consider delay of I-O therapy · Monitor for symptoms every 2-3 days · Consider Pulmonary and ID consults	· Re-image at least every 3 weeks **If worsens:** · Treat as grade 2 or 3-4
Grade 2 **Mild to moderate new symptoms**	· Delay I-O therapy per protocol · Pulmonary and ID consults · Monitor symptoms daily, consider hospitalization · 1.0 mg/kg/day methylprednisolone IV or oral equivalent · Consider bronchoscopy, lung biopsy	· Re-image every 1-3 days **In improves:** · When symptoms return to near baseline, taper steroids over as least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics **If not improving after 2 weeks or worsening:** · Treat as grade 3-4
Grade 3-4 **Severe new symptoms; New/worsening hypoxia; Life-threatening**	· Discontinue I-O therapy per protocol · Hospitalize · Pulmonary and ID consults · 2-4 mg/kg/day methylprednisolone IV or IV equivalent · Add prophylactic antibiotics for opportunistic infections · Consider bronchoscopy, lung biopsy	**If improves to baseline:** · Taper steroids over at least 6 weeks **If not improving after 48 hours or worsening:** · Add additional immunosuppression (e.g. infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil)

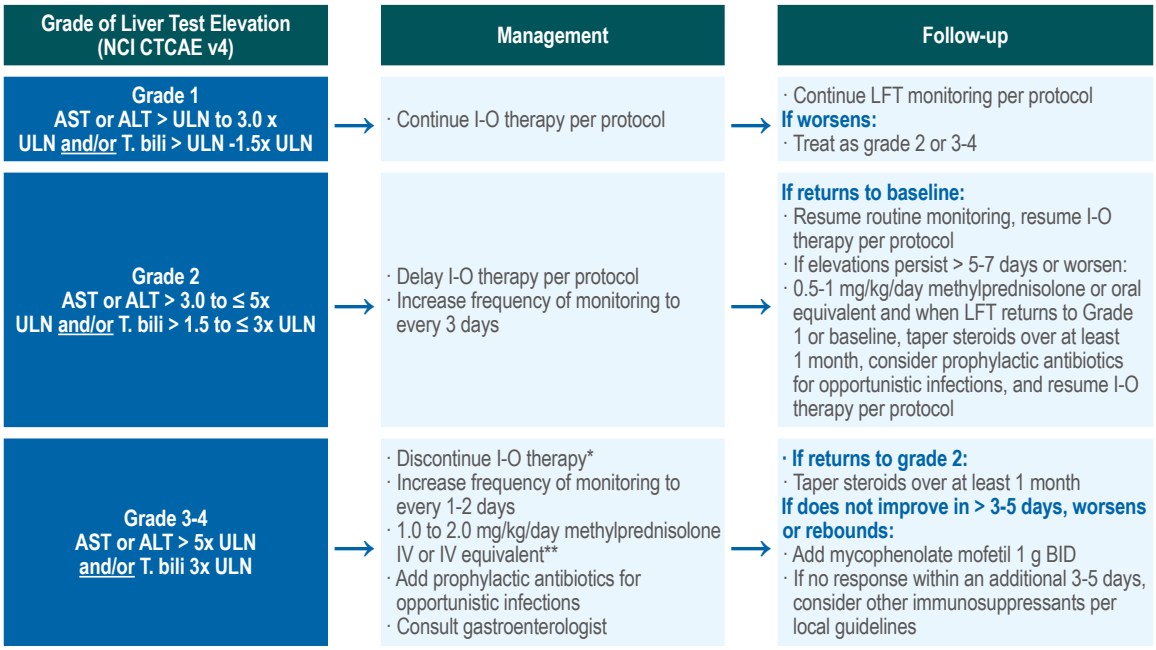
Figure 14. *Pulmonary adverse event management algorithm.*

6-6 Managing Hepatic Adverse Events

Hepatotoxicity is very rare in immune checkpoint inhibition therapy (< 0.1% observed in clinical trials), and isolated abnormal liver function test results are uncommon. However, cases of serious immune-related hepatotoxicity and fatal hepatic failure have been reported in clinical trials, with time to onset of grade 2-5 immune-related hepatotoxicity ranging between 3 to 9 weeks from the start of treatment. With the application of appropriate management guidelines (Figure 15), time to resolution ranged from 0.7 to 2 weeks. It is important to note that multiple adverse events can develop simultaneously, and drug-related causes should be considered even if confounding factors are present; furthermore, a long steroid taper is indicated, even if improvement occurs rapidly.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8x ULN and T. bili ≤ 5x ULN
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV

Figure 15. *Hepatic adverse event management algorithm.*

6-7 Managing Endocrinopathies

Immune checkpoint inhibition therapy can cause inflammation of the endocrine system, manifesting as hypophysitis, hypopituitarism, adrenal insufficiency, or hypothyroidism. Clinical experience with endocrinopathies related to immune checkpoint inhibition therapy remain limited for now, compounded by the fact that patients may present with non-specific symptoms resembling those that arise as a result of brain metastasis or underlying disease complications. The most common clinical presentations are headache and fatigue, and symptoms may also include visual field defects, behavioral changes, electrolyte disturbances, and hypotension. Note that adrenal crisis must be taken into account and excluded as a cause of symptoms. Severe endocrine-related adverse events are infrequent, with adrenal insufficiency and hypothyroidism occurring in less than 1% of patients in clinical trials; hyperthyroidism and hypophysitis are also rare (<0.1%). However, when non-specific symptoms such as fatigue or weakness emerge, it may be conducive to think of endocrinopathies first and immediately take steps to consult with an endocrinologist.

Treatment may be continued once appropriate hormone replacement therapy has been initiated. It is important to note that subjects with endocrinopathy may require replacement-dose steroids, rather than high-dose steroids.

If there are signs of adrenal crisis such as severe dehydration, hypotension, or shock, immediate administration of intravenous corticosteroids with mineralocorticoid activity is recommended, and the patient must be evaluated for the presence of sepsis or infections. If there are signs of adrenal insufficiency but adrenal crisis is ruled out, further investigations should be considered, including laboratory and imaging assessments. Lab tests of endocrine function may be conducted before the initiation of corticosteroid therapy. If pituitary imaging or lab test results are abnormal, a short course of high-dose corticosteroid therapy (e.g. dexamethasone 4 mg every 6 hrs or equivalent) is recommended to treat the inflammation of the affected gland, and the scheduled dose of immune checkpoint inhibition therapy should be withheld. Appropriate hormone replacement therapy should also be initiated, for long-term treatment if necessary (Figure 16).

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual filed testing, endocrinology consultation, and imaging.

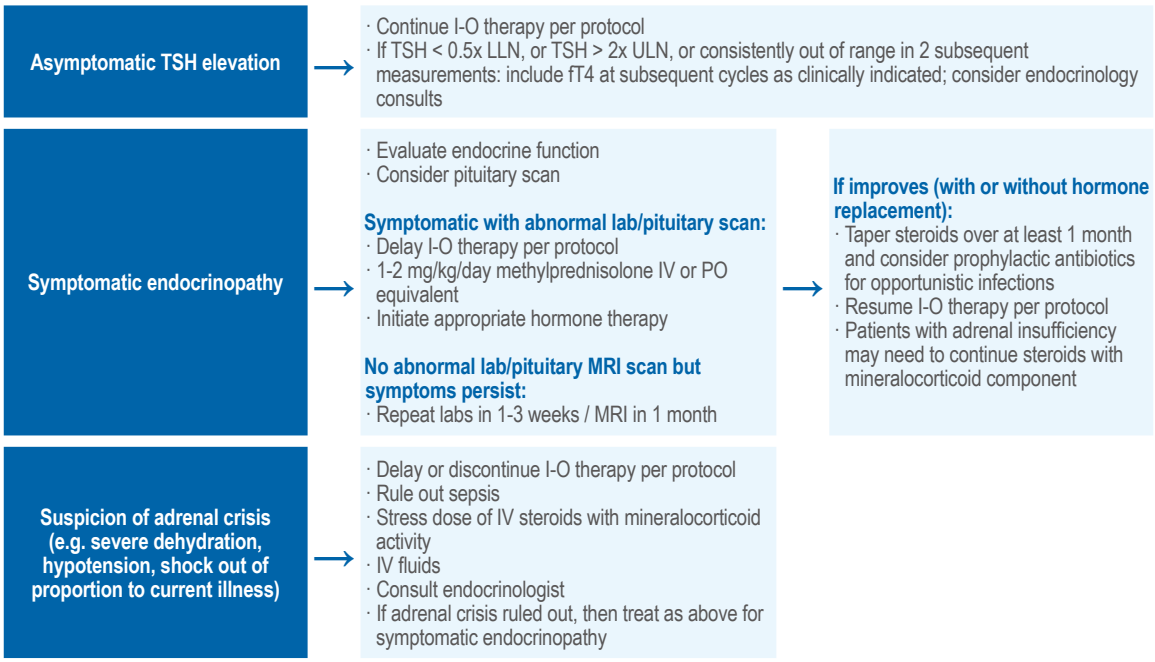


Figure 16. *Endocrinopathy management algorithm.*

6-8 Managing Skin Adverse Events

Immune checkpoint inhibition therapy has been associated with a range of skin adverse reactions. Cases of DRESS and fatal cases of TEN have been reported in clinical trials and post-marketing use, albeit very rarely (< 0.1%). Rash and pruritus are more common. Clinical trial results showed that the median time to onset of grade 2-5 skin irAEs was 3 weeks (ranging between 0.9-16 weeks) from the start of treatment. 87% of cases eventually resolved, with a median time from onset to resolution of 5 weeks (range of 0.6-29 weeks).

DRESS typically presents as a rash with eosinophilia that is associated with one or more of the following features: fever, lymphadenopathy, facial edema, and organ involvement (liver, kidneys, or lungs); note that there may be a long latency (2-8 weeks) between initial drug exposure and reaction onset. Rash and pruritus typically exhibit a focal maculopapular appearance on the trunk, back, or extremities. If patients report skin rash, a visual exam is recommended, and for grade 3-4 rash, high-dose intravenous steroids may be necessary, followed by a long taper upon improvement (Figure 17).

Skin Adverse Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Rash (NCI CTCAE v4)	Management	Follow-up
Grade 1-2 **Covering ≤ 30% BSA***	· Symptomatic therapy (e.g. antihistamines, topical steroids) · Continue I-O therapy per protocol	**If persists > 1-2 weeks or recurs:** · Consider skin biopsy · Delay I-O therapy per procotol · Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol **If worsens:** · Treat as grade 3-4
Grade 3-4 **Covering > 30% BSA;** **Life threatening consequences***	· Delay or discontinue I-O therapy per protocol · Consider skin biopsy · Dermatology consult · 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent	**If improves to grade 1:** · Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections · Resume I-O therapy per protocol

*Refer to NCI CTCAE v4 for term-specific grading criteria.

Figure 17. *Skin adverse event management algorithm.*

6-9 Managing Neurological Adverse Events

Neurological adverse events are extremely rare in immune checkpoint inhibition therapy, but have the potential to become life-threatening. Dizziness, lethargy, and headache may occur, and studies have reported cases of cranial nerve neuropathy and optic nerve ischemia, as well as ataxia and tremor. Serious neurological irAEs such as Guillian-Barré syndrome, meningo-radiculoneuritis, enteric neuropathy, cerebral edema with convulsions, and myasthenia gravis-like symptoms have also been reported. Therefore, unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting for more than 4 days must be investigated, and non-inflammatory causes such as disease progression, infections, metabolic syndrome, and concomitant medication should be excluded. Progressive signs of motor neuropathy must be considered immune-related and managed accordingly. Steroid treatment is generally effective for Grade 3-4 adverse events, and tapering over at least 1 month is recommended.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 **Asymptomatic or mild symptoms; Intervention not indicated**	· Continue I-O therapy per protocol	· Continue to monitor the patient **If worsens:** · Treat as grade 2 or 3-4
Grade 2 **Moderate symptoms; Limiting instrumental ADL**	· Delay I-O therapy per protocol · Treat symptoms per local guidelines · Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	**If improves to baseline:** · Resume I-O therapy per protocol when improved to baseline **If worsens:** · Treat as grade 3-4
Grade 3-4 **Severe symptoms; Limiting self-care ADL; Life-threatening**	· Discontinue I-O therapy per protocol · Obtain neurology consult · Treat symptoms per local guidelines · 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent · Add prophylactic antibiotics for opportunistic infections	**If improves to grade 2:** · Taper steroids over at least 1 month **If worsens or atypical presentation:** · Consider IVIG or other immunosuppressive therapies per local guidelines

Figure 18. *Neurological adverse event management algorithm.*

6 癌症免疫治療之安全管理

CTLA-4受體與PD-1平時負責緩和免疫反應以防止自體免疫， 故透過癌症免疫治療抑制這兩項因子的作用後，可能會在各種器官引起免疫相關的不良反應 (irAE; Figure 11)。所幸絕大部分的irAE經由停藥和適度投予類固醇即可改善，早期發現並遵循公式進行管理也有助於降低衝擊。

根據美國國家癌症中心的標準，AE可分爲輕度 (grade 1)、中度 (grade 2)、重度 (grade 3)、危及生命 (grade 4)、死亡 (grade 5) 等五級，而臨床試驗結果顯示CTLA-4抗體僅會在10-15%的受試者引發grade 3-4的irAE，以腹瀉最爲常見[5]。嚴重但極爲罕見的irAE包含藥疹合併嗜伊紅血症及全身症狀(DRESS)、中樞神經系統肉芽腫性發炎、及無菌性腦膜炎等[25]。PD-1抗體被認爲耐受度優於CTLA-4抗體[26]，約在5-19%受試者引起grade 3-4的irAE，以疲倦、搔癢症、噁心、腹瀉、皮疹、食慾下降、和乏力爲主[8-14]。

6-1 安全監視與管理原則

患者延遲回報症狀以及難以區分irAE和其他因素引起的AE爲安全管理的主要障礙，不過臨床實證顯示遵循以下原則將有助於降低發病率和住院率：

- 儘管irAE多在治療期間發生，但仍有治療結束後數月出現irAE的零星報導。
- 皮疹、腹瀉、排便次數增加、血便、內分泌失調、和肝指數升高均應視爲與發炎和治療相關，除非已確定有其他病因。
- 其他疑似irAE包含嗜伊紅血症、脂酶/澱粉酶血中濃度升高、虹膜炎、溶血性貧血、和多重器官衰竭等。
- **病患衛教：**患者、眷屬、和看護人員均需知道常見irAE的主要症狀，若出現新症狀或惡化情形均應回報。
- **早期篩檢：**在治療及給予每劑藥物之前均應評估患者是否有自體免疫症狀。
- **頻繁監視：**建議醫師於用藥後16週內應每週致電患者，若出現irAE則至少每兩週致電患者追蹤：而若患者前往他院接受irAE治療，醫師亦須與該院主治醫師保持密切聯繫。
- **早期介入：**面對輕中度irAE可先延後或中斷治療至症狀好轉，而Grade 3-4的irAE則建議先停藥並投予類固醇，亦可視情況搭配較強效的免疫抑制劑。
- **適時通報：**所有AE均須通報主管機關 (在台灣爲全國藥物不良反應通報中心)。
- 針對特定irAE的處置建議可參考各項管理公式 (Figure 12-18)。

6-2 停藥或暫緩給藥指引

治療期間若出現以下irAE，建議永久停藥或暫緩給藥。切記患者在進行免疫抑制療法期間不可接受癌症免疫治療，必要時也可提供預防性抗生素治療防止感染。

發生位置	永久停藥	暫緩給藥
消化道	Grade 3-4的腹瀉或腸道炎等irAE	不受藥物控制、持續5-7天、或復發之grade 2腹瀉/腸道炎
腎臟	Grade 3以上的腎炎等irAE	
肺部	Grade 3以上的肺炎等irAE	
肝臟	肝指數 > 8 x ULN或膽紅素 > 5 x ULN 等irAE	肝指數 > 5-8 x ULN或膽紅素 > 3-5 x ULN
內分泌系統	Grade 4的irAE	不受藥物控制之grade 3 irAE
皮膚	Grade 4皮疹或Grade 3-4搔癢症	grade 2-3皮疹或大面積搔癢症
神經系統	Grade 3-4神經病變	持續超過四天之grade 2不明神經病變、肌肉無力、或感覺神經病變
其他	其他器官發生之grade 3-4 irAE和不受局部免疫抑制治療控制之grade 2-4眼部irAE	其他器官發生之grade 2 irAE

ULN: 正常值最高上限

6-3 消化道不良反應之處置

Grade 3-5消化道irAE可能於用藥5-13週後出現 (中位數：8週)，治癒時間中位數爲4週。相關症狀包含腹瀉、排便次數增加、腹痛、血便等，可能會伴隨發燒；而腸道炎可能會有黏膜發炎和淋巴球及中性球浸潤情形。治療後出現之腹瀉和腸道炎均應立即評估是否爲irAE，處置公式請見Figure 12。

6-4 腎臟不良反應之處置

治療期間應注意腎炎、腎小球腎炎、和腎衰竭相關症狀，而這類irAE的早期指標爲無症狀之血中肌酸酐濃度上升，故應定期追蹤患者的肌酸酐濃度。相關irAE的處置公式請見Figure 13。

6-5 肺部不良反應之處置

肺部irAE相當罕見且絕大多數爲grade 1-2，不過有少數grade 3-5之肺炎和間質性肺病的報導，故應注意患者是否出現X光顯影異常 (如毛玻璃樣陰影或斑塊狀浸潤)、喘不過氣、缺氧、或其他肺炎症狀。相關處置公式請見Figure 14。

6-6 肝臟不良反應之處置

肝臟irAE非常罕見 (臨床試驗出現率 < 0.1%)，但仍有少數嚴重肝毒性和致死性肝衰竭的案例。grade 2-5肝臟irAE的出現時機在治療後3-9週，經適當處置後 (Figure 15) 多可於0.7-2週痊癒。值得注意的是，多重AE可能會同時發生，而即使有其他致病因素存在，醫師也不應忽略與藥物治療相關的可能性；此外，肝臟irAE雖可快速痊癒，但若有使用全身性類固醇則仍需花至少一個月逐漸減量方能停藥。

6-7 內分泌系統不良反應之處置

免疫哨點抑制療法可能會引起腦下垂體炎、腦垂體前葉功能減退、腎上腺機能不全、或甲狀腺功能低下等irAE，但目前相關臨床經驗很有限，內分泌irAE、腦部轉移、和癌症併發症往往也很難區分。最常見的症狀爲頭痛和疲倦，患者也可能出現視野缺陷、行爲變化、電解質異常、或低血壓。嚴重內分泌irAE非常少見，但如果患者持續有疲倦或無力等問題，則可尋求內分泌專科醫師會診。診斷時應考慮並確實排除腎上腺危象 (adrenal crisis)，而相關處置公式請見Figure 16。

6-8 皮膚不良反應之處置

免疫哨點抑制療法會引起一系列的皮膚irAE，包含可能致死的DRESS、SJS、和TEN。皮疹和搔癢症是最常見的irAE，約在治療後0.9-16週 (中位數：3週) 出現，治癒時間中位數爲5週。DRESS可能會伴有發燒、淋巴腺病變、臉部水腫、和其他器官問題；而皮疹和搔癢症多在軀幹、背部、和四肢以集中性斑狀丘疹的形式呈現。相關處置公式請見Figure 17。

6-9 神經系統不良反應之處置

神經性irAE極爲罕見但有致死的可能性，目前已有Guillian-Barré症候群、腦脊髓膜神經根神經炎.、腸神經病變、腦水腫併發痙攣、和類似重症肌無力症狀的案例報導。患者可能會有頭暈、無精打采、頭痛、共濟失調、顫抖等症狀，而出現超過4天之不明運動神經病變、肌肉無力、或感覺神經病變即應進行調查。如果運動神經病變持續惡化就應視爲irAE，並按公式建議進行處置 (Figure 18)。

CASE 1: Ipilimumab for Metastatic Melanoma

Dr. John Wen-Cheng Chang

Attending Physician, Division of Oncology, Chang-Gung Memorial Hospital-Linkou, Taoyuan, Taiwan

CASE BACKGROUND

This 57-year-old male patient was diagnosed with ulcerated left heel acral lentiginous melanoma (Breslow thickness of 10 mm, Clark Level V) in November 2012. Sentinel lymph node biopsy (SLNB) results showed melanoma metastasis, and immunohistochemistry (IHC) results revealed many tumor cells positively stained for HMB-45 and S-100. Complete lymph node dissection subsequently uncovered 10 metastatic lymph nodes in the left groin. Positron emission tomography (PET) imaging did not show any distant metastasis, and the patient was subsequently graded as T4bN3M0, Stage IIIc metastatic melanoma.

This case refused high-dose interferon adjuvant therapy due to its high toxicity and limited effect, but unfortunately lung and liver metastases developed in May 2013. The patient therefore received first-line biochemotherapy of dacarbazine and low-dose IL-2. The disease remained stable over the next 6 months, but tumor progression in the liver and lungs was noted in November 2013. The patient was then enrolled in the ipilimumab Expanded Access Program (EAP), and following comprehensive patient education and a thorough examination of organ function, ipilimumab was administered at 3 mg/kg in 100 mL saline for 90 minutes without premedication on December 01, 2013. No immediate infusion reaction was observed. Eight days later, the patient returned to the clinic with a general itchy skin rash (pruritus) over his face, trunk, and upper extremities (Figure 19A), which had persisted for 3 days and caused insomnia. It was estimated that less than 50% of the skin area was involved, and systemic antihistamines as well as topical steroids were prescribed. Symptoms persisted over the next 3 days, and systemic steroids (prednisolone 1 mg/kg) were therefore administered; pruritus subsequently improved within a week (Figure 19B). The dosage of prednisolone was then tapered by half every week, and completely discontinued at Week 4. During this time, the patient continued to receive ipilimumab every 3 weeks, for a

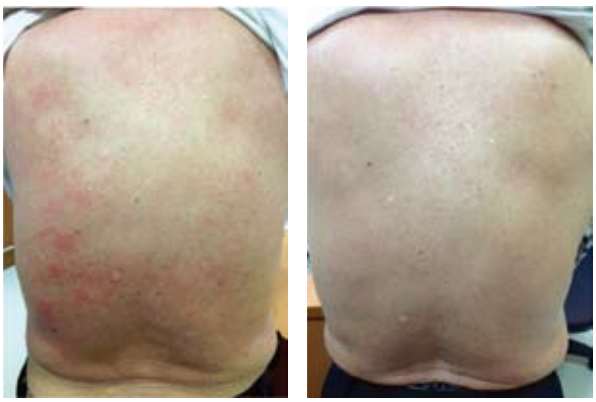


Figure 19. *Development and resolution of skin rash and pruritus in melanoma patient treated with ipilimumab.*
(A) Skin rash and pruritus developed on the upper trunk 8 days after initial dose of ipilimumab.
(B) Skin rash and pruritus improved within a week after administration of systemic steroids.

total of 4 doses. No other adverse events occurred, and pruritus did not recur thereafter.

CASE ANALYSIS

This case exhibited an early occurrence of grade 2 skin rash related to ipilimumab treatment. The most common immune-related adverse events (irAEs) reported with ipilimumab therapy are skin reactions (e.g. rash, pruritus), which can occur in about 42% of Western patients; however, results derived from Taiwanese patients suggest that rates of pruritus can reach 51.7%, while rates of skin rash may be as high as 74.2%. Moreover, Taiwanese patients appear to develop skin reactions at a much earlier stage (~1 week after the initial dose) than Western patients (3-4 weeks after the initial dose; Figure 20)[27]. Fortunately, > 95% of irAEs occurring in the skin are low-grade (grade 1-2), and can be easily managed by topical symptom care or oral steroids. For skin reactions and other irAEs, an algorithm is available to guide management and should be followed. The algorithm recommends that patients with grade 1-2 skin reactions should be treated with symptomatic therapy (e.g. antihistamines or topical steroids) while continuing ipilimumab therapy, and if symptoms persist for > 1-2 weeks or later recur, moderate- to high-dose steroids (e.g. prednisone 0.5-1 mg/kg/day) should be administered while continuing ipilimumab therapy. Once systemic steroids are started, tapering over at least 1 month is recommended. For rare but serious grade 3-4 skin reactions, ipilimumab therapy should be stopped or delayed regardless of whether the reaction is related to treatment or not, and a dermatologist should be consulted. High-dose IV steroids (e.g. methylprednisolone 1-2 mg/kg/day) are recommended for management, and prophylactic antibodies may be added to prevent opportunistic infections. If symptoms resolve or severity is reduced to grade 1, IV steroids should be tapered over at least 1 month prior to stopping, and ipilimumab may be resumed. However, for grade 4 toxicities that are considered to be treatment-related, ipilimumab therapy should be discontinued.

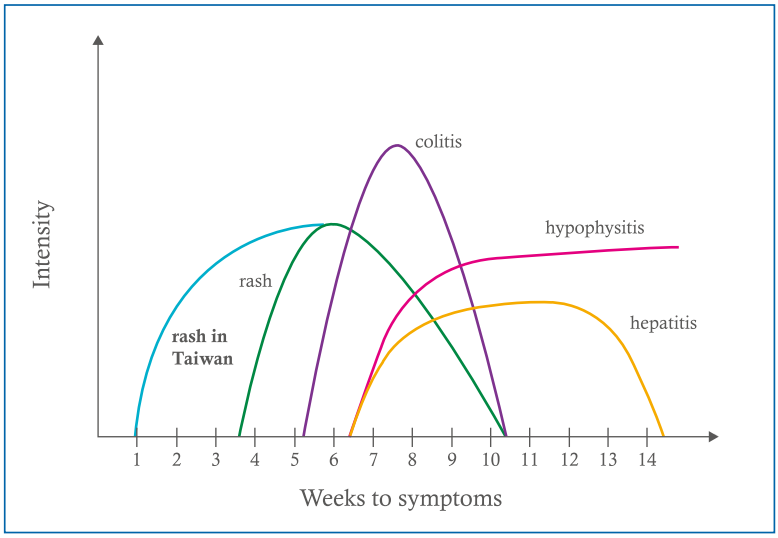


Figure 20. *Time course of adverse events in patients treated with anti-CTLA-4 antibodies[27]. The onset of skin rash in Taiwanese patients (blue curve) has been obsessved to occur at an earlier stage of treatment as compared to Western patients.*

CASE 1: 以益伏 (IPILIMUMAB) 治療惡性黑色素瘤

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林口長庚紀念醫院血液腫瘤科副教授級主治醫師

案例背景

案例是一位57歲男性，於2012年11月被診斷有左腳跟肢端痣樣型黑色素瘤 (acral lentiginous melanoma, ALM)，其Breslow厚度達100 mm並帶有潰瘍，侵犯程度爲Clark Level V。前哨淋巴結切片檢查 (sentinel lymph node biopsy, SLNB) 結果顯示已發生轉移，而免疫組織化學 (immunohistochemistry, IHC) 染色結果也出現多顆HMB-45和S-100陽性的腫瘤細胞。經過完整淋巴結廓清術後，左鼠蹊部發現有十個轉移性淋巴結。正子斷層造影 (positron emission tomography) 的結果則未顯示有遠端轉移現象，故確診爲T4bN3M0、Stage IIIc的轉移性黑色素瘤。

案例拒絕接受高劑量干擾素輔助性治療，因爲考量到治療效果有限卻可能有高毒性。但案例不幸於2013年05月出現肺部和肝臟轉移問題，因此接受第一線dacarbazine和低劑量IL-2生物化療。接下來的六個月病情穩定，但2013年11月又再度觀察到肺臟和肝臟轉移出現進展。我們協助案例登錄參加ipilimumab延續使用計畫 (Expanded Access Program, EAP)，而經過完整的病患衛教和器官功能檢查後，案例於2013年12月01日接受首劑ipilimumab 治療，其劑量爲每公斤體重3 mg溶於100 mL生理食鹽水，在無其他療程前用藥下以靜脈輸注90分鐘投藥。當下未出現輸注後不良反應，但案例於8天後因臉部、軀幹、和上肢出現廣泛搔癢性皮疹 (搔癢症; Figure 19A) 而再度回診 ，並表示搔癢情形已持續三天且造成失眠。評估結果顯示不到50%的皮膚受影響，因此初期決定以全身性抗組織胺和外用類固醇進行治療。不過症狀在接下來的三天仍持續未歇，故選擇進一步投入全身性類固醇治療 (每公斤體重1 mg之prednisolone)；結果搔癢症在一週之內順利獲得緩解 (Figure 19B)。接下來每週逐步將prednisolone劑量減半，並於第四週完全停藥。案例在這段期間繼續接受每三週一次的ipilimumab治療，共接受四劑。期間內未再發生其他不良反應，搔癢症後來也沒有再復發。

案例分析

這個案例出現與ipilimumab治療相關的早發性grade 2皮疹。Ipilimumab治療最常見的免疫相關不良反應 (immune-related adverse events, irAEs) 即爲皮膚副作用 (如：皮疹、搔癢症)，在西方患者的發生率約42%。不過根據統計結果，搔癢症在台灣患者的發生率可達51.7%，皮疹甚至可高達74.2%。此外，台灣患者在初次給藥一週後即可能出現皮膚副作用，似乎比西方患者更早 (西方患者一般在用藥後3-4週才會出現皮膚副作用，如Figure 20所示)[27]。所幸超過95%的皮膚irAE均爲grade 1-2，以外用局部用藥或口服類固醇即可有效控制症狀。目前已經有針對皮膚和其他器官系統之用藥副作用的管理公式，在處置上應遵照其指示決定是否需停藥或投予局部用藥、口服類固醇、或全身性類固醇 (Figure 17)。務須注意的是，若使用全身性類固醇則至少需花一個月的時間逐步減量停藥；而若患者出現與藥物相關之grade 4副作用，依照建議應就此中斷ipilimumab治療。

CASE 2: Ipilimumab for Lung Cancer

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CASE BACKGROUND

A 57-year-old man was a heavy smoker and did not have significant past medical history. He initially presented with cough and dyspnea for 2 months. He was later diagnosed with non-small cell lung cancer, left upper lobe, adenocarcinoma, *EGFR* wild type, no *ALK* fusion, cT3N2M1b (bone metastasis). He then received chemotherapy with pemetrexed / cisplatin for 4 cycles with a partial response, followed by pemetrexed maintenance for 12 cycles.

Upon progressive disease, he received immunotherapy with nivolumab. The first three infusions were uneventful. Immediately after the fourth infusion, he developed dyspnea and cough without fever. Chest computed tomography (CT) revealed ground-glass opacities and reticular opacities in the peripheral and lower lobes, indicative of non-specific interstitial pneumonia. The primary tumor and effusions remained unchanged. He discontinued nivolumab for 8 weeks and received oral glucocorticoids as an outpatient, and the pneumonitis resolved after

CASE ANALYSIS

Pneumonitis is defined as inflammation of the lung parenchyma, and has been described in around 1% of patients receiving anti-PD-1/PD-L1 therapy either alone or in combination. The incidence of pneumonitis may be higher in studies where anti-PD-1/PD-L1 monoclonal antibodies are combined with other agents also known to carry a risk of pneumonitis, such as chemotherapies and targeted therapies. This toxicity led to three treatment-related deaths in an early phase trial of nivolumab[21]. Pneumonitis appears to occur more commonly in patients with lung cancer[11, 28]. Interestingly, pneumonitis was not described in major studies of anti-CTLA-4 monoclonal antibodies, where pulmonary toxicities such as sarcoid-like granulomatous reactions were reported[29].

Patients with suspected pneumonitis may present with dry cough, progressive dyspnea, fever, chest pain, or fine inspiratory crackles[30]. Standard diagnostic algorithms recommend radiologic investigation with a chest computed tomography. Pneumonitis shows ground glass lesions and/or disseminated nodular infiltrates, predominantly in the lower lobes. In cases of grade 2 or higher pneumonitis, consultations from infection specialists / pulmonologists (to rule out infection and malignancy) and spirometry (with measurement of the carbon monoxide diffusing capacity) / bronchoscopy (with bronchoalveolar lavage to search infectious agents) can be considered. Management is guided by clinical symptoms. Mild cases are managed by withholding therapy. Moderate cases may be managed with oral or intravenous corticosteroids. Severe cases require hospitalization for intravenous corticosteroids, and other forms of immunosuppression may be used such as infliximab or mycophenolate mofetil.

CASE 2: IPILIMUMAB治療肺癌

林家齊 醫師
台大醫院腫瘤醫學部主治醫師

案例背景

57歲男性是老菸槍，並無重要的過去病史。他開始的時候喘、咳2個月，接著被診斷爲左上肺葉的非小細胞肺癌 (腺癌)，基因檢測表皮生長子因子受體 (EGFR) 沒有突變、ALK沒有融合，臨床分期T3N2M1b (骨骼轉移)。他接受化學治療 (pemetrexed加上cisplatin) 4個療程，腫瘤有部分反應 (partial response)，接著接受pemetrexed 維持性治療12個療程。

腫瘤惡化後，他改接受免疫治療nivolumab。前3次給藥沒有特別的副作用，第4次給藥後，他開始出現喘、咳，但是沒有發燒。胸腔電腦斷層顯示在肺部邊緣、下葉有毛玻璃狀、網狀不透明的病灶，表示非特異性間質性肺炎，原發腫瘤和本來的惡性肋膜積水沒有改變。他停止使用nivolumab達8周，開始服用類固醇，肺炎逐漸消退。

案例分析

免疫相關肺炎的定義是肺實質發炎，在約1%接受抗PD-1、PD-L1治療 (單獨使用或合併使用) 的病患會出現。免疫相關肺炎的發生率在抗PD-1、PD-L1單株抗體和其他會誘發肺炎的治療 (化學治療、標靶治療) 合併使用可能更高。在nivolumab的早期試驗中，肺炎導致3起死亡案例[21]。免疫相關肺炎似乎比較容易出現在肺癌的患者身上[11,28]。免疫相關的肺癌不會出現另一種免疫治療，抗CTLA-4單株抗體；反而是酷似類肉瘤病 (sarcoidosis) 的肉芽腫反應曾在使用抗CTLA-4單株抗體的患者身上出現過[29]。

免疫相關肺炎的患者會出現乾咳、進行性喘、發燒、胸痛的徵狀，吸氣時聽診有細爆裂音[30]。標準流程建議做胸腔電腦斷層診斷，免疫相關肺炎是毛玻璃狀病灶、瀰漫性結節狀浸潤，主要在下肺葉。在第2級或以上的免疫相關肺炎，可考慮照會感染科、胸腔科醫師 (排除感染、癌症) 以及進行肺功能檢查 (包括一氧化碳擴散能力測定)、支氣管鏡檢查 (包括支氣管肺泡灌洗術以尋找可能的感染病因)。處置方式依症狀決定：輕微的案例只要停止免疫治療即可、中度的案例需在門診投予口服或注射的類固醇、嚴重的案例需住院投予注射的類固醇，甚至加上其他免疫抑制劑 (例如：infliximab、mycophenolate mofetil [MMF])。

CASE 3: Ipilimumab for Metastatic Melanoma

Dr. Shih-Tsung Cheng

Assistant Professor, Department of Dermatology, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan

CASE BACKGROUND

This case was a 65-year-old male patient, who initially visited our hospital in 2011 to discuss treatment for a pigmented skin plaque on his hand. The patient stated that the plaque had already received a diagnosis of melanoma at another institution, and wished to seek consultation for subsequent treatment; however, after the consultation, the patient elected to surgically remove the plaque at another institution. Incidentally, a sentinel lymph node biopsy (SLNB) was not conducted before surgery to check for microscopic metastasis, and when the patient returned to our hospital in October 2014, he already had mild respiratory symptoms. A CT scan subsequently confirmed that several tumors of varying size were present in his lungs. Up to this point, the patient appeared to be relatively unaffected by the metastasis, and considering that his melanoma was *BRAF*-negative, targeted therapy would not have been effective, and therefore the only treatment option available was I-O therapy. Initially, the patient refused to receive I-O therapy due to cost concerns, but after several rounds of consultation over a six-month period, the patient elected to begin ipilimumab therapy on May 21, 2015. Less than 1.5 months after receiving the first dose of ipilimumab, the patient developed dyspnea symptoms, and was diagnosed at our hospital with acute respiratory failure on July 08, 2015 (Figure 21). In addition, liver enzyme (GOT/GPT) levels were observed to rise in the patient after initiation of I-O therapy, with GOT levels rising from 28-29 units pre-treatment to 3,744 units on July 08, 2015, while GPT levels also rose from 23-27 units pre-treatment to 1,214 units (Figure 22). As no metastasis was observed in the liver, it was suspected that an excessive immune response may have induced acute fulminant hepatitis and caused the rise in liver enzymes. Due to severe dysfunction in both the lung and liver organ systems, the patient worsened rapidly and passed away on July 10, 2015 before steroids or other measures could be initiated.

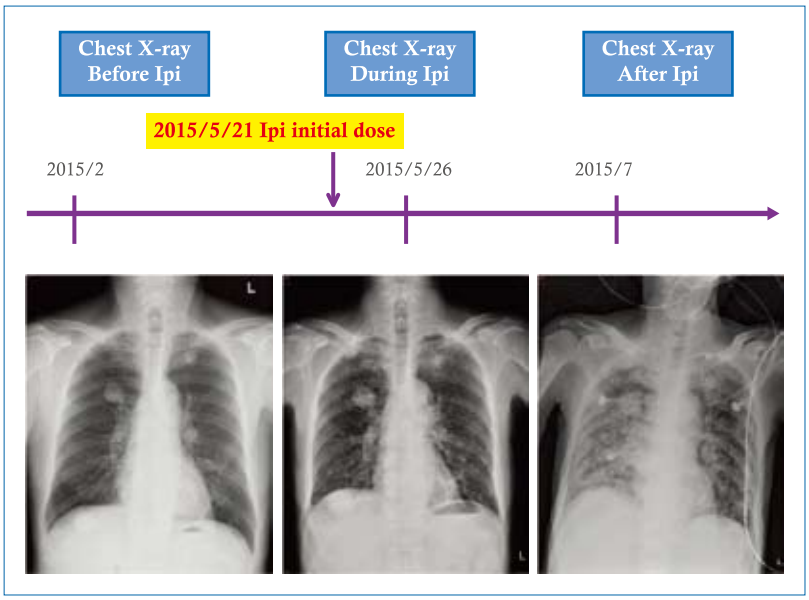

Figure 21. *Chest X-ray before, during and after ipilimumab treatment.*

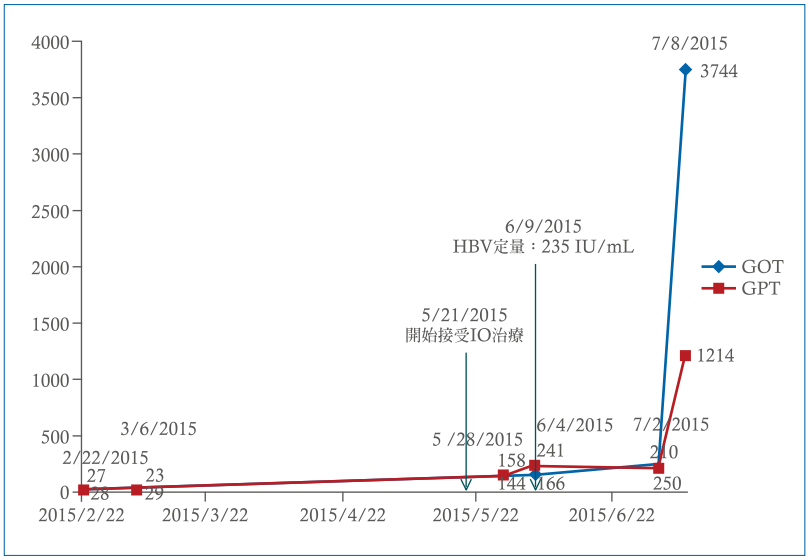

Figure 22. *GOT/GPT levels in metastatic melanoma patient treated with ipilimumab.*

CASE ANALYSIS

Acute respiratory failure and liver enzyme increases are common side effects seen with I-O therapy, as the enhanced immune response resulting from checkpoint inhibition by I-O therapy may lead to autoimmune reactions against the lung, liver, skin, and other organ systems. These immune-related adverse events (irAEs) are very different from the adverse events typically observed with conventional cancer treatments, and oncologists should maintain particular vigilance for such irAEs. However, in practice it may be challenging to differentiate between adverse events caused by autoimmune reactions and side effects stemming from reduced immunity caused by the cancer itself. Moreover, irAEs can appear anywhere from 2 weeks to 6 months after initial dosing. For autoimmune reactions, stopping I-O therapy, followed by the administration of steroids as deemed appropriate, will serve to rapidly alleviate symptoms in most cases. However, it is necessary to exclude the possibility of infection in such cases prior to the use of steroids, lest the resultant dampening of the immune response cause infections to flare up instead. The abovementioned case was a stable hepatitis B carrier and had very low viral titers 20 days after initiating I-O therapy, but it is unclear whether such viral titers can induce an immune response, and it is not known if steroid treatment could cause the underlying infection to flare up. Under such circumstances, one potential solution is to simultaneously giving steroids and anti-viral drugs to combat both autoimmune reactions and viral flare-ups, and it is also recommended that hepatitis B carriers receive anti-viral treatment prior to I-O therapy, in order to reduce viral titers to non-detectable levels. This may allow viral reactions to be excluded when adverse events develop. Currently, clinical experience with ipilimumab and other I-O therapies remains insufficient in Taiwan, and several key issues need to be addressed. Do Taiwanese patients develop similar adverse event profiles as western patients receiving I-O therapy? Are there any special characteristics of irAEs in Taiwanese patients? What special precautions will be needed when administering I-O therapy in hepatitis B carriers? Although rates of serious adverse events are quite low for ipilimumab and other I-O therapies, and fatal cases such as the one described above are very rare, appropriate awareness and vigilance will certainly help to reduce the risks of treatment.

CASE 3: 惡性黑色素瘤

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案例背景

這個案例是一位65歲男性患者，於2011年因爲手上出現黑色斑塊而初次來本院就診。案例表示已經在外院確診斑塊爲惡性黑色素瘤 (melanoma)，希望諮詢後續治療方法，不過案例在諮詢後選擇赴他院接受手術切除斑塊，而術前並未進行前哨淋巴結切片檢查 (sentinel lymph node biopsy, SLNB) 確認腫瘤是否轉移。後來案例於2014年10月再回診本院時就已出現輕微肺部症狀，電腦斷層掃描也顯示肺部有多顆大小不一的腫瘤。案例此時的狀況和生活仍無大礙，而由於該惡性黑色素瘤沒有*BRAF*突變，因此案例不適合標靶治療，僅能接受免疫療法。患者原先因爲藥價因素而不願意進行免疫治療，但在後續就診的半年期間經過多次溝通，患者終於在2015年05月21日選擇展開ipilimumab治療。在施打第一劑後不到1.5個月，案例即出現喘不過氣的症狀，2015年07月08日到院檢查結果爲急性呼吸衰竭 (Figure 21)。此外，案例的肝指數 (GOT/GPT) 在實施免疫療法後即逐漸上升，在2015年07月08日就診當天，GOT由治療前的28-29單位升至3,744單位，GPT則由治療前之23-27單位上升至1,214單位 (Figure 22)。由於肝臟並未發生轉移，因此肝指數的上升可能與過度免疫反應引起猛爆性肝炎相關。基於肺部和肝臟兩大器官系統出現嚴重問題，案例的病情進展相當快速，在不及給予類固醇或進行其他處置的情況下，案例即於2015年07月10日過世。

案例分析

急性呼吸衰竭和肝指數上升是免疫療法的常見副作用，因爲經由免疫療法加強免疫反應後，過度激發的免疫作用可能會反噬患者自身的器官系統，包含肺部、肝臟、皮膚等等。這類免疫相關副作用 (immune-related adverse event, irAE) 與過去抗癌藥物的副作用截然不同，腫瘤科醫師須特別留意。不過有時很難判斷患者的副作用是因爲免疫治療引起自體免疫，抑或是癌症造成的免疫低下現象；況且副作用可能是在用藥後2週至6個月才會出現，不會立即反映。對於自體免疫反應，暫停免疫療法並施予類固醇將有助於快速改善症狀，但使用類固醇之前也必須排除感染的可能性，以免用藥後反而使症狀加劇。例如上述案例爲穩定的B型肝炎帶原者，進行免疫療法後二十天的病毒量相當低，但多少病毒量會引起免疫反應，施予類固醇會不會反而使B型肝炎病毒更活躍而傷害到肝臟，目前無法得知。現在可能的做法是同時給予類固醇和抗病毒藥物控制自體免疫和病毒活化，甚至會建議B型肝炎帶原者在進行免疫療法前應先用抗病毒藥物把病毒量降至測不到的程度，若發生不良反應就比較能排除病毒發作的因素。台灣在使用ipilimumab等免疫療法的經驗尚有不足，目前比較需要觀察的是台灣患者的副作用類型和發生部位是否與西方患者相同、免疫相關副作用在台灣患者有沒有可用於辨識的特徵、以及B型肝炎帶原者使用免疫療法的注意事項等等。雖然ipilimumab等免疫療法引起嚴重副作用的比率不高，像這樣的死亡案例也非常少，但多加留意這些問題將有助於降低風險。

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Summary

Anti-CTLA-4[5-7] and anti-PD-1 antibodies[8-14] have demonstrated good efficacy against metastatic melanoma, NSCLC, and renal cell carcinoma in Phase III clinical trials, thus proving the effectiveness of immune checkpoint blockade and offering hope for advanced cancer patients with poor prognosis and few options for treatment. Immune checkpoint inhibition therapy has also been shown to be generally less toxic and better tolerated than standard chemotherapy; however, as the inhibition of immune checkpoints leads to an enhanced and sustained immune response, there remains the possibility that autoimmunity and irAEs will occur. Interestingly, a recent study examining rare but severe irAEs associated with CTLA-4 blockade found that these events tended to occur in patients who had a rapid and robust response to therapy[25]. There is also evidence suggesting that patients who experience colitis during anti-CTLA-4 antibody treatment have higher objective response rates than patients who never developed any irAEs[31]. The key message here is that irAEs should be viewed as an integral part of the response to immune checkpoint inhibition therapy. Therefore, patients and physicians should maintain vigilance during treatment, and seek to manage irAEs according to established protocols and algorithms as soon as possible. Moreover, when managing irAEs, patients and physicians should not hesitate to withhold checkpoint blockade or initiate immunosuppressive therapy when necessary. Studies have shown that overall survival is neither affected by the development of an irAE *per se*, regardless of type or severity, nor the use of systemic corticosteroids[32, 33]. In light of this, patients and physicians should not be overly worried that the use of immunosuppressants to treat irAEs will compromise the benefits of immune checkpoint inhibition therapy.

It is important to note that the great majority of irAEs can be effectively resolved by providing supportive care, withholding or discontinuing immune checkpoint inhibition therapy, and administering corticosteroids and immunosuppressants as needed. When recognized early and managed appropriately, most irAEs are reversible and should have no lasting effects. A retrospective review of 30 advanced melanoma patients with pre-existing autoimmune disorders who received anti-CTLA-4 antibodies found that only 27% of patients developed exacerbations of their autoimmune conditions, while 33% experienced grade 3-5 irAEs; of these, most were reversible with corticosteroids or infliximab therapy[34]. These findings indicate that with appropriate monitoring and management, patients will be able to make the most of immune checkpoint inhibition therapy, even those with pre-existing autoimmune disorders.

In conclusion, I-O therapy represents the next step forward in anti-cancer treatment, and immune checkpoint inhibition therapy with anti-CTLA-4 antibodies such as ipilimumab, and anti-PD-1 antibodies such as nivolumab and pembrolizumab, have demonstrated good efficacy against metastatic melanoma, NSCLC, and renal cell cancer. The effectiveness of these treatments against other types of cancer continues to be explored in several ongoing clinical trials. Immune checkpoint inhibition therapy was also found to be more tolerable than standard chemotherapy, but patients and physicians should nevertheless remain vigilant for potential irAEs that can arise as the result of a more robust and sustained immune response induced by immune checkpoint blockade. Fortunately, the great majority of irAEs are mild in severity and manageable with supportive therapy, dose withholding or discontinuation, or immunosuppressive therapy such as corticosteroids. With proper monitoring and management mechanisms in place, the potential impact from irAEs can be significantly reduced, allowing the therapeutic benefits of immune checkpoint inhibition therapy to be maximized and made available to a broader patient population. As clinical experience with the use of immune checkpoint blockade continues to grow around the world, many more breakthroughs and exciting advances can be expected in the years to come. This booklet has provided an overview of the development and mechanisms of immune checkpoint inhibition therapy, as well as the latest efficacy and safety data available, and may hopefully serve as a convenient guide for the effective management of patients currently receiving I-O therapy.

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References: **1.** YERVOY® Summary of Product Characteristics. **2.** Hodi FS *et al. N Engl J Med.* 2010;363:711–23. **3.** European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) Assessment Report For YERVOY® (ipilimumab) 19 September 2013. **4.** Margolin KA *et al.* Abstract submitted to the European Cancer Congress (ECCO-ESTRO), 27 Sep-1 Oct 2013, Amsterdam, Netherlands.**5.** Patt D *et al.* Abstract submitted to the European Cancer Congress (ECCO-ESMO-ESTRO), 27 Sep-1 Oct 2013, Amsterdam, Netherlands. **6.** Eggermont AM *et al. Eur J Cancer. 2011;47:2150-7.*

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Reference

1. Littman DR. *Cell* 2015; 162:1186-90.
2. Eggermont AM. *Ann Oncol* 2012; 23 Suppl 8:viii53-7.
3. Garbe C et al. *Oncologist* 2011; 16:5-24.
4. Kobold S et al. *Dtsch Arztebl Int* 2015; 112:809-15.
5. Hodi FS et al. *N Engl J Med* 2010; 363:711-23.
6. Robert C et al. *N Engl J Med* 2011; 364:2517-26.
7. Schadendorf D et al. *J Clin Oncol* 2015; 33:1889-94.
8. Robert C et al. *N Engl J Med* 2015; 372:320-30.
9. Weber JS et al. *Lancet Oncol* 2015; 16:375-84.
10. Robert C et al. *N Engl J Med* 2015; 372:2521-32.
11. Brahmer J et al. *N Engl J Med* 2015; 373:123-35.
12. Borghaei H et al. *N Engl J Med* 2015; 373:1627-39.
13. Herbst RS et al. *Lancet* 2015 Dec 18. doi: 10.1016/S0140-6736(15)01281-7. [Epub ahead of print]
14. Motzer RJ et al. *N Engl J Med* 2015; 373:1803-13.
15. Qureshi OS et al. *Science* 2011; 332:600-3.
16. Calabro L et al. *Lancet Oncol* 2013; 14:1104-11.
17. Porichis F & Kaufmann DE. *Curr HIV/AIDS Rep* 2012; 9:81-90.
18. Philips GK & Atkins M. *Int Immunol* 2015; 27:39-46.
19. Hoffman-Censits J et al. 2016 ASCO Genitourinary Cancers Symposium, January 8, 2016: San Francisco, CA, USA. Abstract 355.
20. Tarhini A et al. *Cancer Biother Radiopharm* 2010; 25:601-13.
21. Topalian SL et al. *N Engl J Med* 2012; 366:2443-54.
22. Larkin J et al. *N Engl J Med* 2015; 373:23-34.
23. Brahmer JR et al. *N Engl J Med* 2012; 366:2455-65.
24. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03; June 14, 2010.
    http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
25. Voskens CJ et al. *PLoS One* 2013; 8:e53745.
26. Redman JM et al. *BMC Med* 2016; 14:20.
27. Kaehler KC et al. *Semin Oncol* 2010; 37:485-98.
28. Gettinger SN et al. *J Clin Oncol* 2015; 33:2004-12.
29. Berthod G et al. *J Clin Oncol* 2012; 30:e156-9.
30. Nishino M et al. *N Engl J Med* 2015; 373:288-90.
31. Beck KE et al. *J Clin Oncol* 2006; 24:2283-9.
32. Ascierto PA et al. *J Transl Med* 2014; 12:116.
33. Horvat TZ et al. *J Clin Oncol* 2015; 33:3193-8.
34. Johnson DB et al. *JAMA Oncol* 2016; 2:234-40.

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