Official journal of the Spanish Society of Chemotherapy

Mario Fernández-Ruiz[1,2,3]

Diagnostic and therapeutic approach to pulmonary infiltrates in cancer patients receiving immune checkpoint inhibitors

[1]Unit of Infectious Diseases, Hospital Universitario "12 de Octubre", Instituto de Investigación Hospital "12 de Octubre" (imas12), Madrid, Spain
[2]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain
[3]School of Medicine, Universidad Complutense, Madrid, Spain

Revista Española de Quimioterapia
doi:10.37201/req/s03.15.2022

ABSTRACT

The advent of immune checkpoint inhibitors (ICIs) targeting cytotoxic T lymphocyte antigen 4 (CTLA-4) and the programmed cell death (PD-1)/PD-1 ligand 1 (PD-L1) axis has transformed the treatment paradigm for multiple cancer types. ICIs are able to restore T-cell-mediated antitumor responses and do not entail an increased risk of infection *per se*. However, immunotherapy is associated to a unique form of toxicity due to the off-target effects on healthy tissues of the excessively enhanced immune response in form of immune-related adverse events (irAEs). Although ICI-induced pneumonitis ranks the fifth of all irAEs in terms of frequency of occurrence, it is associated with a relevant attributable mortality. This review summarizes the incidence, risk factors, clinical and radiological presentation, and therapeutic approach of ICI-induced pneumonitis. Particular focus is on the differential diagnosis of new or worsening pulmonary infiltrates in cancer patients receiving ICI therapy. Finally, the impact on the risk of opportunistic infection of ICIs and immunosuppressive therapy used to treat associated irAEs is reviewed. The diagnosis and management of suspected ICI-induced pneumonitis remains clinically challenging.

Keywords: immune checkpoint inhibitors; pneumonitis; immune-related adverse events; pulmonary infiltrates; diagnosis; cancer.

INTRODUCTION: IMMUNE CHECKPOINT INHIBITORS AND IRAES

Cytotoxic T lymphocyte antigen 4 (CTLA-4 or CD152) and programmed cell death 1 (PD-1) are two co-inhibitory receptors expressed on the surface of CD4+ and CD8+ T-cells that negatively regulate T-cell-mediated responses. In detail, CTLA-4 modulates CD28 co-stimulatory signaling by competing for its activating ligands (CD80 and CD86) on antigen-presenting cells, whereas PD-1 recognizes and binds to its endogenous ligands PD-L1 and PD-L2. Tumor cells exploit these inhibitory pathways to induce T-cell exhaustion and tumor evasion [1]. Accordingly, the disruption of CD28/CTLA-4/CD80/86 and PD-1/PD-L1 axes by monoclonal antibodies is able to restore T-cell-mediated antitumor responses and may induce durable anticancer effects [2].

Since the Food and Drug Administration approval of ipilimumab —a fully human anti-CTLA-4 IgG1 monoclonal antibody— for the treatment of metastatic melanoma in 2011, the use of immune checkpoint inhibitors (ICIs) has experienced a dramatic increase over the past years and revolutionized the therapeutics of solid malignancies. Beyond ipilimumab, six approved ICIs are currently available: nivolumab, pembrolizumab and cemiplimab (anti-PD-1 agents), and atezolizumab, avelumab and durvalumab (anti-PD-L1 agents). In addition, other anti-CTLA-4 (tremelimumab) and anti-PD-1 agents (lambrolizumab and pidilizumab) are being evaluated in phase I and II randomized clinical trials (RCTs) [3]. All of them are humanized or fully human monoclonal antibodies. These agents have been proven particularly effective in malignancies with strong immunogenicity, such as non-small-cell lung cancer (NSCLC) or melanoma, becoming the standard treatment option. In addition, ICI therapy has been approved by US and European regulatory agencies for an expanding range of indications, including renal cell carcinoma, head and neck squamous cell cancer, Hodgkin's lymphoma, gastric cancer, urothelial carcinoma, hepatocellular carcinoma and microsatellite instability-high cancers, among others [4].

Immune-related adverse events (irAEs) are a unique form of toxicity that results from the off-target effects on healthy tissues of an excessively activated immune response induced by ICIs. The most common sites of involvement are the skin, gastrointestinal tract, liver, endocrine organs (mainly hy-

Correspondence:
Mario Fernández-Ruiz, MD, PhD.
Unit of Infectious Diseases. Hospital Universitario "12 de Octubre". Centro de Actividades Ambulatorias, 2ª planta, bloque D. Avda. de Córdoba, s/n. Postal code 28041. Madrid, Spain.
E-mail: mario_fdezruiz@yahoo.es

Table 1 Risk factors for the development of ICI-induced pneumonitis.

Treatment-related factors
Combination anti-CTLA-4 and anti-PD-1/PD-L1 therapy
Anti-PD-1/PD-L1 therapy (versus anti-CTLA-4)
Combination of ICI and conventional chemotherapy (versus ICI therapy alone)
Cancer-related factors
Cancer type (higher risk for NSCLC and RCC)
Histological subtype of NSCLC (higher risk for squamous cell carcinoma than adenocarcinoma)
Patient-related factors
Older age
Preexisting pulmonary conditions (i.e. COPD, interstitial lung disease, pneumothorax, asthma)
Preexisting autoimmune markers (i.e. rheumatoid factor, antinuclear antibody, antithyroglobulin or antithyroid peroxidase)
Male gender and smoking history (less consistent association)
Previous thoracic radiotherapy

COPD: chronic obstructive pulmonary disease; CTLA-4: Cytotoxic T lymphocyte antigen 4; ICI: immune checkpoint inhibitor; NSCLC: non-small cell lung cancer; PD-1: programmed cell death-1; PD-L1: programmed cell death 1 ligand 1; RCC: renal cell carcinoma.

pophysitis) and the lungs. The spectrum of organs affected, however, is very broad (e.g. myocarditis, encephalitis, aseptic meningitis, myasthenia gravis, uveitis or inflammatory arthritis). The overall incidence of irAE is higher for anti-CTLA-4 than for anti-PD-1 or anti-PD-L1 agents [5]. Almost two thirds of ipilimumab-treated patients experience at least one irAE of any grade, with 10-30% being considered serious (grade ≥3). In contrast, about 10% of patients receiving anti-PD-1 agents develop grade ≥3 irAEs [6]. Kinetics of appearance also depends on the type of ICI therapy. Fatal irAEs are rare (0.3-1.3%), with colitis and pneumonitis as the most frequent causes in patients receiving anti-CTLA-4 and anti-PD-1/PD-L1 antibodies, respectively.

ICI-INDUCED PNEUMONITIS

Incidence and risk factors. The most common pulmonary adverse event associated to immunotherapy is ICI-induced pneumonitis (also occasionally termed as ICI-induced interstitial lung disease). The development of pneumonitis in the setting of pivotal RCTs, however, was uncommon (<5%), and this irAE ranks the fifth after skin toxicity, hepatitis, thyroiditis and colitis. The incidence depends on the type of malignancy, with NSCLC patients being at the highest risk [7]. The incidence of any-grade pneumonitis in phase III trials ranged from <0.5% to 10%, whereas the corresponding figure for severe events (grade ≥3) varied from 0.5% to 3%. The majority of cases occur within the first 6 months from the initiation of treatment, although late-onset pneumonitis may appear up to 2 years later [8]. The median interval to the onset of pneumonitis in patients receiving anti-PD-1/PD-L1 therapy varies according to the type of cancer, from 7.8 weeks in melanoma to 15-30 weeks in NSCL [9], and is usually longer than in irAEs that affect other organs (skin, digestive tract or endocrine glands). It should be noted that restrictive enrollment criteria in RCTs may have underestimated the true incidence of this complication in clinical practice. Indeed, observational studies have usually reported higher incidence rates (3.5% to 19% of ICI-exposed patients) [8,10]. Despite its relative rarity, pneumonitis constitutes the most common pulmonary complication during the course of ICI therapy, as well as the leading cause of immune-related death.

Various risk factors for the development of ICI-induced pneumonitis have been identified (Table 1). The presence of preexisting pulmonary conditions —such as chronic obstructive pulmonary disease (COPD), interstitial lung disease, pneumothorax or asthma— acts as a strong predictor of this complication [10-12]. The histological subtype of NSCLC also plays a role, with a higher incidence in patients with squamous cell carcinoma compared with the adenocarcinoma subtype [8]. The association with older age, male gender, and former or current smoking is less consistent [13]. The previous receipt of radiotherapy revealed as a risk factor for pembrolizumab-induced pneumonitis in the KEYNOTE-001 trial [14]. More importantly, different regimens of ICI therapy are associated to distinct incidence rates of pneumonitis in NSCLC patients. A two- to three-fold risk increase has been observed for combination therapy (ICI plus platinum-based chemotherapy) compared with ICI monotherapy [15]. In addition, the combination of different ICIs targeting both CTLA-4 and PD-1 is associated with a higher incidence of pulmonary toxicity [16], as is the use of PD-1/PD-L1 inhibitors compared to CTLA-4 blockade

Table 2 **Differential diagnosis of ICI-induced pneumonitis.**

Conditions	Diagnostic clues and approaches
Infections	
Bacterial pneumonia	Fever, purulent sputum, pleuritic pain, high white blood cell count, increased acute phase reactants
Viral pneumonia	Nasopharyngeal swab for respiratory virus PCR testing
Pneumocystis jirovecii pneumonia	Cumulative corticosteroid exposure, prior use of purine analogs or T-cell-depleting agents, lymphopenia (low CD+ T-cell counts), positive serum β-D-glucan test (typically high levels)
Invasive pulmonary aspergillosis	High cumulative exposure to corticosteroids, severe COPD, positive culture for *Aspergillus* spp. in respiratory tract sample, positive galactomannan in BAL fluid
Pulmonary tuberculosis	History of untreated or partially treated tuberculosis, positive acid-fast bacilli smear or *M. tuberculosis* PCR assay in sputum or respiratory tract specimens, *M. tuberculosis* PCR in gastric aspirate samples (in patients unable to expectorate)
Non-infectious conditions	
Tumor progression	Hemoptysis, weight loss, increasing serum tumor markers, new or increasing nodular shadows and interlobular septal thickening, lung biopsy and histological examination
Pseudoprogression	Stable serum tumor markers, decreasing circulating tumor DNA levels, lung biopsy and histological examination
Radiation pneumonitis	Usually occurs in, or in close proximity to, the irradiated field (while ICI-induced pneumonitis most commonly develops at the edge of the radiation field or in a non-irradiated region)
Drug-induced pneumonitis	Increased eosinophil count in the BAL fluid
Other (congestive heart failure, dermatomyositis, polymyositis, allergic bronchopulmonary aspergillosis)	

BAL: bronchoalveolar lavage; COPD: chronic obstructive pulmonary disease; ICI: immune checkpoint inhibitor; PCR: polymerase chain reaction.

[13]. Finally, a meta-analysis shown that patients receiving PD-1 inhibitors have a higher incidence of any grade pneumonitis than those treated with PD-L1 inhibitors (3.6% versus 1.3%; *P*-value = 0.001) [17]. Although there are no clinically validated biomarkers to predict the occurrence of irAEs, one study showed that NSCLC patients with preexisting autoantibodies (rheumatoid factor, antinuclear antibody, antithyroglobulin or antithyroid peroxidase) were more prone to develop nivolumab or pembrolizumab-induced pneumonitis [18]. Interleukin-17 levels, eosinophil count or the clonal expansion of CD8+ T-cells are other biomarkers explored [19].

The mortality rates observed in real-life studies are often higher than that reported from RCTs, with figures as high as 27% is some series [12,20]. An analysis of the World Health Organization global individual case safety reports database, with data from more than 130 countries, revealed an attributable mortality of 17.5% among 1,694 cases of ICI-induced pneumonitis reported through November 2018. Patients with NSCLC were overrepresented in the group of fatal cases (versus melanoma), as were pembrolizumab treated patients (versus nivolumab) [21]. The timing of onset of ICI-induced pneumonitis also seems to influence outcome, with early events tending to be more severe and be associated with higher fatality rates than late-onset episodes [8,21].

Since the developement of irAEs suggests an enhanced T-cell-mediated immune activation in both healthy and tumor tissues, various studies have reported that patients developing this complication may have a better response to ICI therapy. This association, however, remains controversial and is determined by the type, timing and severity of irAE. A recent meta-analysis involving 12,600 participants from 51 studies showed that the occurrence of irAEs —particularly those with cutaneous and endocrine involvement— exerted a beneficial effect on overall survival and response rates in patients with advanced NSCLC. Although the development of ICI-induced pneumonitis had no significant effect on overall survival (hazard ratio: 1.14; 95% confidence interval [22]: 0.70 – 1.86), it was associated with a better response rate. Nevertheless, treatment discontinuation due to severe pneumonitis led to a poorer outcome [23].

Clinical presentation and radiological features. The majority of cancer patients developing ICI-induced pneumonitis are men (63.6%) with a median age of 65 years at the time of diagnosis [21]. The most common symptoms at presentation are dyspnea (41-80%) and cough (23-53%), and less than one third of the patients may be asymptomatic at diagnosis in the setting of routine surveillance imaging [9]. Hypoxemia and acute respiratory distress syndrome appear in about one third of patients, whereas the presence of fever is relatively uncommon. The underlying cancer is usually controlled at the onset

of pneumonitis, with 23% to 61% of patients having achieved an objective response [9]. Interestingly, other types of irAE may be concurrently present in up to one quarter of cases, mainly with gastrointestinal and endocrine involvement [21].

Chest computed tomography (CT) scan is performed in the majority of patients with clinical suspicion of ICI-induced pneumonitis. The radiological features are variable, since the elementary lesions observed may comprise ground glass opacities (GGO) (66.7% of cases examined in a recent narrative review), consolidations (56.6%), reticular opacities (26.1%), bronchiectasis (10.5%), micronodules (4%), a "crazy-paving" pattern (1.1%), and bronchiolitis (5%). On the other hand, the presence of isolated pleural effusion or hilar or mediastinal lymphadenopathies —other than those related to the underlying cancer— is uncommon [9]. The number of lobes involved varies between one and five, with a median of three [24]. There have been described several patterns of radiological presentation in the CT scan: cryptogenic organizing pneumonia (COP), non-specific interstitial pneumonia (NSIP), hypersensitivity pneumonitis, acute interstitial pneumonia (AIP), sarcoid-type reactions and acute respiratory distress syndrome. The most common radiological pattern is COP —manifested as discrete patchy or confluent shadows with or without air bronchography— followed by hypersensitivity pneumonitis and NSIP [6]. In addition, up to one fifth of cases do not fit into one of these well-defined radiological patterns, and atypical features such as GGO confined to the area around the tumor (peritumoral infiltration), nodules or unclassifiable interstitial changes are described [24]. The prognostic implications of different radiological patterns remain unclear, and some authors have reported that NSCLC patients with peritumoral infiltration had better response to corticosteroids and lower rate of disease progression [20].

Differential diagnosis. The diagnosis of ICI-induced pneumonitis is largely one of exclusion, since no clinical, laboratory or radiological features may be considered pathognomonic. The analysis of the bronchoalveolar lavage (BAL) fluid usually reveals an increased number of lymphocytes and a small number of eosinophils and neutrophils, and some studies have reported a large number of macrophages with high PD-L1 expression in the alveolar space [25]. The median proportion of lymphocytes in the BAL fluid is about 20% to 35% [20,26,27], with an inversion in the CD4+/CD8+ ratio due to the increase of CD8+ T-cell counts [26]. In contrast to sarcoidosis and other connective lung diseases with COP patterns, the neutrophil count in the BAL fluid is not increased in ICI-induced pneumonitis and there is no evidence of foamy macrophages found in hypersensitivity pneumonia. On the other hand, cases of pneumonitis with a NSIP pattern such as idiopathic pulmonary fibrosis are often associated with a paucity of lymphocyte in BAL [26]. None of these findings in the BAL fluid, however, are specific enough to make a diagnosis.

The differential diagnosis of ICI-induced pneumonitis is broad and comprises bacterial or viral pneumonia, active pulmonary tuberculosis, invasive fungal disease (IFD) and *Pneumocystis jirovecii* pneumonia (PCP). Non-infectious alternative diagnoses include tumor progression and pseudoprogression, radiation pneumonitis and other forms of drug-induced pulmonary toxicity (Table 2). In comparison with bacterial pneumonia, ICI-induced pneumonitis is less likely to be associated with fever (which, if present, is usually of low grade) and more prone to have respiratory failure. Pseudoprogression constitutes an atypical response of solid tumors under ICI therapy defined by an increase in the size of the primary tumor or the appearance of a new lesion followed by tumor regression. It is believed that pseudoprogression is due to an ICI-induced lymphocytic infiltration of the tumor or to the edema and necrosis of tumor tissue following therapy rather than real tumor growth [28]. Radiation pneumonitis and ICI-induced pneumonitis may exhibit overlapping symptoms and common radiological features that hamper the differential diagnosis.

Nasopharyngeal swab for respiratory virus testing and sputum and blood cultures must be systematically collected, as well as *Legionella* and pneumococcal urinary antigen. If the patient's respiratory status is acceptable, bronchoscopic examination should be performed to obtain a lower respiratory tract sample (bronchial aspirate, protected specimen brush or BAL fluid). In addition to bacterial culture, acid-fast bacilli smear and respiratory virus PCR testing, the BAL fluid is useful to made the diagnosis of PCP through the detection of ascii or trophic forms of *P. jirovecii* by direct conventional staining (i.e. Giemsa, toluidine blue O or Gömöri methenamine silver) or immunofluorescence (a more sensitive method). The diagnosis of PCP can be ruled out in the presence of a negative *P. jirovecii* real-time quantitative PCR in the BAL fluid, but not in an upper respiratory specimen (such as induced sputum, oral washing or nasopharyngeal aspirate). In case of discordance between both techniques (immunofluorescence-negative, PCR-positive samples), the detection of high fungal load by quantitative PCR would be suggestive of PCP, although diagnostic thresholds have not been established. In patients in whom the collection of a BAL sample is not feasible, a negative serum β-D-glucan result can virtually exclude PCP given the high sensitivity of this biomarker, in particular if the pre-test probability is relatively low [29].

Regarding the diagnosis of IFD —namely invasive pulmonary aspergillosis (IPA)— it should be born in mind the low sensitivity (below 50%) of the galactomannan antigen assay in serum samples in non-neutropenic patients [30]. In addition, the radiological features of IPA in patients with solid cancer patients are often non-specific, and the classical halo sign or air-crescent sign are absent in most of the cases [31]. On the other hand, ICI-induced pneumonitis may present with well-defined nodules or the "reversed halo" sign, resembling IPA or pulmonary mucormycosis [13]. Therefore, the clinical suspicion of IPA in a cancer patient on ICI therapy is most often raised by the isolation of *Aspergillus* spp. in a respiratory sample in the presence of underlying predisposing conditions such as severe COPD with multiple exacerbations or high cumulative corticosteroid doses. The diagnostic performance of the galactomannan assay in the BAL fluid (optical density

Table 3 Management of ICI-induced pneumonitis (modified from Zhou et al [25] and Haanen et al [32]).

Grade of pneumonitis	Clinical manifestations	Immunosuppressive treatment	Management of ICI therapy
Grade 1	No symptoms, radiological changes (GGO, non-specific interstitial pneumonia) limited to a single lobe or <25% lung parenchyma	Not required Monitor symptoms every 2-3 days Repeat chest imaging in 3-4 weeks	Consider holding ICIs
Grade 2	New or worsening symptoms affecting daily life, radiological changes involve multiple lobes and reaches 25-50% of lung parenchyma	Oral prednisone (1 mg/Kg daily or equivalent), with tapering over 4-6 weeks after recovery Monitor symptoms daily Repeat chest imaging every 1-2 weeks If no improvement after 48 hours of oral prednisone, manage as per grade 3	Hold ICIs Reintroduction should be delayed until a daily steroid dose ≤10 mg of oral prednisone
Grade 3 Grade 4	Serious new complications requiring oxygen inhalation and hospitalization, radiological changes involve all lobes or >50% of lung parenchyma, limited personal self-care ability Life-threatening dyspnea, ARDS requiring urgent intervention such as intubation	Intravenous methylprednisolone (2-4 mg/Kg daily or equivalent), with slow tapering over ≥6 weeks If not improving or worsening after 48 hours add: - infliximab IV 5 mg/kg or - MMF IV 1 g BID or - IVIGs for 5 days or - cyclophosphamide	Permanently discontinue ICIs

ARDS: acute respiratory distress syndrome; BID: two times a day; GGO: ground glass opacities; ICI: immune checkpoint inhibitor; IVIGs: intravenous immunoglobulins; MMF: mycophenolate mofetil.

index ≥1.0) in non-hematological patients with immunosuppressive conditions is good in terms of sensitivity and negative predictive value [30].

Therapeutic management. The suspicion of ICI-induced pneumonitis should prompt the initiation of immunosuppressive therapy. Therefore, it is important to rule out the presence of concomitant infection (in particular in the case of grade ≥2 pneumonitis) or, alternatively, to administer a broad-spectrum antibiotic in parallel to immunosuppression. The type and amount of immunosuppressive therapy —oral prednisone, intravenous methylprednisolone or, for steroid-refractory cases, infliximab, tocilizumab, mycophenolate mofetil or cyclophosphamide— depends on the severity of the pneumonitis (Table 3) [25,32]. Since corticosteroid tapering should be performed slowly, PCP prophylaxis should be added in patients who are expected to receive 20 mg of prednisone daily (or equivalent doses) for >4 weeks. In addition, and due to the potential requirement of additional immunosuppressive therapy, conventional screening for latent tuberculosis and chronic hepatitis B virus infection is advisable before initiating ICIs, followed by appropriate prophylaxis or therapy if needed [22].

IMPACT OF ICI THERAPY ON THE RISK OF INFECTION

As discussed above, ICIs enhance T-cell-mediated immunity and this therapy is not associated *per se* with direct immunosuppressive effects. Indeed, pivotal RCTs did not show an increased risk of infection in patients receiving anti-CTLA-4 or anti-PD-1/PD-L1 agents [22]. Nevertheless, the management of irAEs often requires the administration of corticosteroids and other immunosuppressive therapies, which in turn may increase the risk of opportunistic infections such as PCP, IFD, cytomegalovirus disease or reactivation of latent tuberculosis infection [22,33,34]. A recent single-center retrospective study compared the occurrence of infectious complications in patients with advanced NSCLC that received ICIs associated to conventional chemotherapy and those treated with chemotherapy alone. There were no significant differences in the cumulative incidence of infection (15% versus 22%, respectively), with pneumonia as the most common event in both groups. In fact, urinary tract infection was more common among patients receiving only chemotherapy. The diagnosis of COPD and neutropenia and the previous use of corticosteroids (but not ICs) were identified as independent risk factors for infection. Interestingly there were no cases of opportunistic infection within the subgroup of patients with irAE [35]. These findings are in line with those previously reported from a large cohort (n = 740) of melanoma patients treated with ipilimumab, pembrolizumab or nivolumab, 7.3% of which experienced serious infection after a mean interval of 135 days from the initiation of ICIs. Again, the prior or concomitant use of corticosteroids and infliximab for the treatment of irAEs were the only predictive factors identified [36]. It has been recently suggested that PD-1/PD-L1 blockade may lead to

active tuberculosis, and PD-1 knockout mice exhibit impaired immune responses against *Mycobacterium tuberculosis* [37]. A systematic review including 27 studies identified 35 cases of active occurring in patients treated with anti-PD-1/PD-L1 agents (mainly nivolumab). The pooled estimate incidence was 2,000 cases per 100,000 persons, which is 35 times higher than that in the general population [38]. Nevertheless, it is difficult to control for the confounding effect resulting from the use of immunosuppressive therapy for irAE. The relative contribution of anti-PD-1/PD-L1 therapy on the incidence of active tuberculosis remains controversial, and no risk increase has been demonstrated in population-based studies [39]. On the other hand, an alternative explanation proposes that PD-1 blockade may actually unmask latent or subclinical tuberculosis by boosting *M. tuberculosis*-specific T-cell immunity, similar to the immune reconstitution inflammatory syndrome observed in people with human immunodeficiency virus infection that initiate antiretroviral therapy [40].

FUNDING

This study has been funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union — *European Social Fund Plus (ESF+).* M.F.R. holds a research contract "Miguel Servet" (CP18/00073) from the ISCIII, Spanish Ministry of Science and Innovation.

CONFLICT OF INTEREST

The author has received personal fees for educational activities from Merck Sharp & Dohme, Astellas Pharma, Gilead Sciences and Pfizer.

REFERENCES

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64. doi: 10.1038/nrc3239
2. Korman AJ, Garrett-Thomson SC, Lonberg N. The foundations of immune checkpoint blockade and the ipilimumab approval decennial. Nat Rev Drug Discov 2021;doi: 10.1038/s41573-021-00345-8
3. Xiao Q, Nobre A, Pineiro P, Berciano-Guerrero MA, Alba E, et al. Genetic and epigenetic biomarkers of immune checkpoint blockade response. J Clin Med 2020;9:doi: 10.3390/jcm9010286
4. Shiravand Y, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, et al. Immune checkpoint inhibitors in cancer therapy. Curr Oncol 2022;29:3044-60. doi: 10.3390/curroncol29050247
5. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Oncol 2017;28:2377-85. doi: 10.1093/annonc/mdx286
6. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol 2019;16:563-80. doi: 10.1038/s41571-019-0218-0
7. De Velasco G, Je Y, Bosse D, Awad MM, Ott PA, et al. Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients. Cancer Immunol Res 2017;5:312-8. doi: 10.1158/2326-6066.CIR-16-0237
8. Suresh K, Voong KR, Shankar B, Forde PM, Ettinger DS, et al. Pneumonitis in non-small cell lung cancer patients receiving immune checkpoint immunotherapy: incidence and risk factors. J Thorac Oncol 2018;13:1930-9. doi: 10.1016/j.jtho.2018.08.2035
9. Cadranel J, Canellas A, Matton L, Darrason M, Parrot A, et al. Pulmonary complications of immune checkpoint inhibitors in patients with nonsmall cell lung cancer. Eur Respir Rev 2019;28:190058. doi: 10.1183/16000617.0058-2019
10. Cho JY, Kim J, Lee JS, Kim YJ, Kim SH, et al. Characteristics, incidence, and risk factors of immune checkpoint inhibitor-related pneumonitis in patients with non-small cell lung cancer. Lung Cancer 2018;125:150-6. doi: 10.1016/j.lungcan.2018.09.015
11. Shibaki R, Murakami S, Matsumoto Y, Yoshida T, Goto Y, et al. Association of immune-related pneumonitis with the presence of preexisting interstitial lung disease in patients with non-small lung cancer receiving anti-programmed cell death 1 antibody. Cancer Immunol Immunother 2020;69:15-22. doi: 10.1007/s00262-019-02431-8
12. Atchley WT, Alvarez C, Saxena-Beem S, Schwartz TA, Ishizawar RC, et al. Immune checkpoint inhibitor-related pneumonitis in lung cancer. Chest 2021;160:731-42. doi: 10.1016/j.chest.2021.02.032
13. Zhang Q, Tang L, Zhou Y, He W, Li W. Immune checkpoint inhibitor-associated pneumonitis in non-small cell lung cancer: current understanding in characteristics, diagnosis, and management. Front Immunol 2021;12:663986. doi: 10.3389/fimmu.2021.663986
14. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol 2017;18:895-903. doi: 10.1016/S1470-2045(17)30380-7
15. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018;379:2040-51. doi: 10.1056/NEJMoa1810865
16. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. J Clin Oncol 2017;35:709-17. doi: 10.1200/JCO.2016.68.2005
17. Khunger M, Rakshit S, Pasupuleti V, Hernandez AV, Mazzone P, et al. Incidence of pneumonitis with use of programmed death 1 and programmed death-ligand 1 inhibitors in non-small cell lung cancer: A systematic review and meta-analysis of trials. Chest 2017;152:271-81. doi: 10.1016/j.chest.2017.04.177
18. Toi Y, Sugawara S, Sugisaka J, Ono H, Kawashima Y, et al. Profiling preexisting antibodies in patients treated with anti-PD-1 therapy for advanced non-small cell lung cancer. JAMA Oncol 2019;5:376-83. doi: 10.1001/jamaoncol.2018.5860
19. Tarhini AA, Zahoor H, Lin Y, Malhotra U, Sander C, et al. Baseline circulating IL-17 predicts toxicity while TGF-beta1 and IL-10 are

prognostic of relapse in ipilimumab neoadjuvant therapy of melanoma. J Immunother Cancer 2015;3:39. doi: 10.1186/s40425-015-0081-1

20. Baba T, Sakai F, Kato T, Kusumoto M, Kenmotsu H, et al. Radiologic features of pneumonitis associated with nivolumab in non-small-cell lung cancer and malignant melanoma. Future Oncol 2019;15:1911-20. doi: 10.2217/fon-2019-0102
21. Moey MYY, Gougis P, Goldschmidt V, Johnson DB, Lebrun-Vignes B, et al. Increased reporting of fatal pneumonitis associated with immune checkpoint inhibitors: a WHO pharmacovigilance database analysis. Eur Respir J. 2020;55:2000038. doi: 10.1183/13993003.00038-2020
22. Redelman-Sidi G, Michielin O, Cervera C, Ribi C, Aguado JM, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators and proteasome inhibitors). Clin Microbiol Infect 2018;24 Suppl 2:S95-S107. doi: 10.1016/j.cmi.2018.01.030
23. Li Y, Zhang Y, Jia X, Jiang P, Mao Z, et al. Effect of immune-related adverse events and pneumonitis on prognosis in advanced non-small cell lung cancer: A comprehensive systematic review and meta-analysis. Clin Lung Cancer 2021;22:e889-e900. doi: 10.1016/j.cllc.2021.05.004
24. Miller AR, Manser R. The knowns & unknowns of pulmonary toxicity following immune checkpoint inhibitor therapies: a narrative review. Transl Lung Cancer Res 2021;10:2752-65. doi: 10.21037/tlcr-20-806
25. Zhu S, Fu Y, Zhu B, Zhang B, Wang J. Pneumonitis induced by immune checkpoint inhibitors: From clinical data to translational investigation. Front Oncol 2020;10:1785. doi: 10.3389/fonc.2020.01785
26. Strippoli S, Fucci L, Negri A, Putignano D, Cisternino ML, et al. Cellular analysis of bronchoalveolar lavage fluid to narrow differential diagnosis of checkpoint inhibitor-related pneumonitis in metastatic melanoma. J Transl Med 2020;18:doi: 10.1186/s12967-020-02650-z
27. Suzuki K, Yanagihara T, Matsumoto K, Kusaba H, Yamauchi T, et al. Immune-checkpoint profiles for T cells in bronchoalveolar lavage fluid of patients with immune-checkpoint inhibitor-related interstitial lung disease. Int Immunol 2020;32:547-57. doi: 10.1093/intimm/dxaa022
28. Zhou L, Zhang M, Li R, Xue J, Lu Y. Pseudoprogression and hyperprogression in lung cancer: a comprehensive review of literature. J Cancer Res Clin Oncol 2020;146:3269-79. doi: 10.1007/s00432-020-03360-1
29. Alanio A, Hauser PM, Lagrou K, Melchers WJ, Helweg-Larsen J, et al. ECIL guidelines for the diagnosis of *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother 2016;71:2386-96. doi: 10.1093/jac/dkw156
30. Fortun J, Martin-Davila P, Gomez Garcia de la Pedrosa E, Silva JT, Garcia-Rodriguez J, et al. Galactomannan in bronchoalveolar lavage fluid for diagnosis of invasive aspergillosis in non-hematological patients. J Infect 2016;72:738-44. doi: 10.1016/j.jinf.2016.02.019
31. Dandachi D, Wilson Dib R, Fernandez-Cruz A, Jiang Y, Chaftari AM, et al. Invasive pulmonary aspergillosis in patients with solid tumours: risk factors and predictors of clinical outcomes. Ann Med 2018;50:713-20. doi: 10.1080/07853890.2018.1518581
32. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv119-iv42. doi: 10.1093/annonc/mdx225
33. Uslu U, Agaimy A, Hundorfean G, Harrer T, Schuler G, et al. Autoimmune colitis and subsequent CMV-induced hepatitis after treatment with ipilimumab. J Immunother 2015;38:212-5. doi: 10.1097/CJI.0000000000000081
34. Malek AE, Taremi M, Spallone A, Alvarez-Cardona JJ, Kontoyiannis DP. Necrotizing soft tissue invasive aspergillosis in a cancer patient treated with immunosupressants due to checkpoint inhibitor-induced hepatitis. J Infect 2020;80:232-54. doi: 10.1016/j.jinf.2019.10.022
35. Malek AE, Khalil M, Hachem R, Chaftari AM, Fares J, et al. Impact of checkpoint inhibitor immunotherapy, primarily pembrolizumab, on infection risk in patients with advanced lung cancer: A comparative retrospective cohort study. Clin Infect Dis 2021;73:e2697-e704. doi: 10.1093/cid/ciaa802
36. Del Castillo M, Romero FA, Arguello E, Kyi C, Postow MA, et al. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. Clin Infect Dis 2016;63:1490-3. doi: 10.1093/cid/ciw539
37. Tousif S, Singh Y, Prasad DV, Sharma P, Van Kaer L, et al. T cells from Programmed Death-1 deficient mice respond poorly to *Mycobacterium tuberculosis* infection. PLoS One 2011;6:e19864. doi: 10.1371/journal.pone.0019864
38. Liu K, Wang D, Yao C, Qiao M, Li Q, et al. Increased tuberculosis incidence due to immunotherapy based on PD-1 and PD-L1 blockade: A systematic review and meta-analysis. Front Immunol 2022;13:727220. doi: 10.3389/fimmu.2022.727220
39. Kim HW, Kim JS, Lee SH. Incidence of tuberculosis in advanced lung cancer patients treated with immune checkpoint inhibitors - A nationwide population-based cohort study. Lung Cancer 2021;158:107-14. doi: 10.1016/j.lungcan.2021.05.034
40. Picchi H, Mateus C, Chouaid C, Besse B, Marabelle A, et al. Infectious complications associated with the use of immune checkpoint inhibitors in oncology: reactivation of tuberculosis after anti PD-1 treatment. Clin Microbiol Infect 2018;24:216-8. doi: 10.1016/j.cmi.2017.12.003