

Review

Navigating Neurologic Adverse Events in Immune Checkpoint Inhibitor Therapy: Challenges and Strategies

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Abstract

The advancement of immunotherapy has changed cancer treatment. Immune checkpoint inhibitors (ICIs) are one of the groundbreaking immunotherapies that have offered patients with advanced cancer new optimism by utilizing the immune system's innate ability to fight cancer with amazing success. Nevertheless, this exceptional approach has drawbacks, including the range of immune-related adverse events (irAEs) that can arise due to ICI therapy. IrAEs that impact various parts and systems of the body can be particularly problematic, and can be difficult to identify and manage. Neurological side effects of ICIs are of particular interest, as they may vary from minor sensory issues to possibly fatal neuroinflammatory reactions. The purpose of this review is to elucidate the peculiarities of neurological immune-related adverse events (n-irAEs) associated with ICIs and to provide a complete overview of the various facets of ICI therapy by exploring the mechanisms, clinical manifestations, and management strategies of n-irAEs. Furthermore, it is crucial to emphasize the importance of caution, early recognition, and collaboration between oncologists and neurologists to optimize patient outcomes while overcoming the challenges posed by these enigmatic neurologic complications.

Keywords: Cancer, neurologic adverse events, immune checkpoint inhibitors, immunotherapy

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Immunology and oncology became interlinked in the late 19th century, following surgeon William Coley's discovery that the insertion of dead bacteria into sarcomas could lead to tumour shrinkage.^[1] Since then, various clinical trials have investigated a range of immunotherapy drugs for multiple cancer types. Immunotherapy boosts the immune system's ability to identify tumor-specific antigens by suppressing immune checkpoints, inhibiting immune-suppressing agents, and enhancing immune-mediated killing. To date, several immunotherapy medications have been developed, including tumor vaccines, cellular immunotherapy, immunomodulatory medications that target T-cells, and ICIs.

ICIs are monoclonal antibodies that specifically target im-

mune checkpoints, including programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which act as critical regulators of the immune system. By targeting these checkpoints, ICIs enable T cells to remain activated, allowing them to attack malignant cells.^[2] Eighteen ICIs have been approved for treating different types of cancer by regulatory bodies such as the United States Food and Drug Administration (FDA), the National Medical Products Administration (NMPA) of China, and the European Medicines Agency (EMA). Please refer to Table 1 for details on the approval status, indications, and dates for widely used ICIs.

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Table 1. Indications and approval status of commonly used ICI agents in clinical practice

Molecular Target	Drug	Approved by	Indication(s)	First Approval	
CTLA-4	Ipilimumab	FDA, EMA, HC, NMPA	Advanced MM, advanced CRC, NSCLC, HL	2011	
PD-1	Nivolumab	FDA, EMA, HC, MHLW, NMPA	HNSCC, NSCLC, GC, ESCC, CRC, HCC, RCC, HL, MM, skin cancer	2014	
	Pembrolizumab	FDA, EMA, HC, NMPA	HNSCC, NSCLC, GC, ESCC, CRC, HCC, RCC, HL, MM, skin cancer, TNBC	2014	
	Cemiplimab	FDA, EMA, HC	Skin cancer, NSCLC	2018	
	Toripalimab	NMPA, EMA	Skin cancer, HNSCC, BRCA	2018	
	Sintilimab	NMPA, EMA, FDA	NSCLC, HCC, HL	2018	
	Camrelizumab	NMPA, FDA	NSCLC, HCC, HL, ESCC, HNSCC	2019	
	Tislelizumab	NMPA	NSCLC, HL, BRCA	2019	
	Penpulimab	NMPA	HCC, GC, NSCLC, NPC, HL	2021	
	Zimberelimab	NMPA	HL	2021	
	Dostarlimab	FDA, EMA, HC	UCEC	2021	
	Serplulimab	NMPA	GC, CRC, NSCLC	2022	
	Pucotenlimab	NMPA	CRC, MM	2022	
	PD-L1	Atezolizumab	FDA, EMA, HC, NMPA	Skin cancer, NSCLC, SCLC, BRCA, HCC, TNBC	2016
		Avelumab	FDA, EMA, HC,	Skin cancer, RCC, BRCA	2017
Durvalumab		FDA, EMA, HC, NMPA	NSCLC, SCLC, BRCA	2017	
Envafoimab		NMPA	CRC	2021	
Sugemalimab		NMPA	NSCLC	2021	

EMA: European Medicines Agency; FDA: United States Food and Drug Administration; HC: Health Canada; MHLW: Ministry of Health, Labour and Welfare of Japan; NMPA: National Medical Products Administration of China; BCC: basal cell carcinoma; BRCA: bladder urothelial carcinoma; CC: cervical cancer; cHL: classical Hodgkin's lymphoma; CRC: colorectal cancer; CSCC: cutaneous squamous cell carcinoma; dMMR: mismatch repair deficiency; EC: endometrial carcinoma; ESCC: esophageal squamous cell carcinoma; GC: gastric cancer; HCC: hepatocellular carcinoma; HL: Hodgkin's lymphoma; HNSCC: head and neck squamous cell carcinoma; MCC: Merkel cell carcinoma; MM: malignant melanoma; MSI-H: high microsatellite instability; MPM: malignant pleural mesothelioma; NSCLC: non-small cell lung cancer; NPC: nasopharyngeal carcinoma; PMBCL: primary mediastinal large B cell lymphoma; PMF: primary myelofibrosis; RCC: renal cell carcinoma; SCLC: small cell lung cancer; TMB-H: high tumor mutation burden; TNBC: triple-negative breast cancer; UC: urothelial carcinoma; UCEC: uterine corpus endometrial carcinoma.

In addition to being used alone or in combination with one another, ICIs are increasingly being used with chemotherapy, targeted therapy, and radiation.^[3, 4] While ICIs have their intended effect on anti-cancer immunity, they also have the potential to impair self-tolerance and trigger irAEs that appear in 90% of patients treated with anti-CTLA-4 and 70% of patients treated with anti-PD-1/PD-L1 agents.^[5, 6] Different medications, doses, exposure times, and malignancy types have varying incidences of irAEs.^[7] Potential risk factors associated with increased incidence of irAEs include thymic tumors, elevated body mass index, certain HLA genotypes, and deviations from normal cytokine levels, such as interleukin (IL) -6 and IL-17.^[8-14]

The National Cancer Institute utilizes the Common Terminology Criteria for Adverse Events (CTCAE) scale to assess the severity of irAEs.^[15] The CTCAE categorizes irAEs using a scale of grades 1 through 4, with grade 1 resulting in minimal symptoms, grade 2 in moderate symptoms, grade 3 in severe but non-fatal symptoms, and grade 4 indicating

life-threatening symptoms. Up to 30% of patients who received CTLA-4 inhibitors, 10% of those who received PD-1 inhibitors, and over 50% of those treated with combination (CTLA-4 and PD-1/PD-L1) therapy typically suffer from severe (grade 3 or 4) irAEs.^[16] This severity grading can be used to guide management. Patients with grade 1 symptoms are monitored for worsening irAEs but continue ICI therapy, while patients with grade 2 irAEs are temporarily withheld from ICI therapy and treated with corticosteroids. If a patient experiences toxicities of grade ≥ 3 , any grade toxicities unresponsive to steroid treatment, toxicities necessitating hospitalization, or certain low-grade toxicities requiring consultation for diagnosis or management, such as neurologic and rheumatologic toxicities, they should be referred to a specialist.^[17]

irAEs are organ-specific, with skin-related irAEs being the most prevalent (especially mild itching or rash), followed by gastrointestinal toxicity, often presenting as diarrhea and colitis.^[18, 19] Endocrine irAEs are the third most frequent,

which include thyroid dysfunction (hypothyroidism and hyperthyroidism), pituitary inflammation, and adrenal insufficiency.^[20] Additionally, musculoskeletal toxicity, such as mild joint or muscle pain, and ocular toxicity, like mild dry eye syndrome and uveitis, are also commonly reported.^[5] Although uncommon, nearly half of all deaths were the result of neurological and cardiac toxic effects.^[21] The incidence of n-irAEs is reported to be 1%–12%,^[22–24] with the peripheral nervous system (PNS) affected twice as frequently as the central nervous system (CNS).^[25–28] Serious n-irAEs affect around 1% to 2% of treated individuals, with approximately two-thirds of those cases impacting the peripheral nervous system (PNS).^[24, 26]

As the use of ICIs and the incidence of n-irAEs increase, the interaction between oncology and neurology in the context of ICI-associated neurologic adverse events represents a rapidly evolving area of clinical practice and research. This review will examine the most common neurological side effects linked to ICIs, emphasizing the significance of promptly recognizing and managing such probable complications. Additionally, it delves into the complexities of initiating ICIs in patients with autoimmune neurological disorders and rechallenging ICIs after n-irAEs emerge.

Neurological Adverse Reactions to ICIs

ICIs have shown remarkable efficacy in various cancer types. However, as with any medical intervention, they are not without their side effects, some of which can affect the nervous system. A systematic review of 59 trials comprising 9,208 patients revealed that neurologic adverse events occurred in 3.8% of patients treated with CTLA-4 antibodies, 6.1% of patients receiving anti-PD-1 antibodies, and 12.0% of patients treated with both CTLA-4 and PD-1 antibodies.^[27] Based on a pharmacovigilance study analyzing data from 18,518,994 patients, lung cancer (33%; n=188/574) and melanoma (36%; n=206/574) were the most commonly associated malignancies with n-irAEs.^[22]

N-irAEs have a wide range of clinical manifestations, from grade 1–2 adverse events such as headache, dysgeusia, paresthesia, and dizziness to grade 3–4 symptoms that can lead to patient death. Patients diagnosed with n-irAEs should be referred to a specialist, regardless of severity.^[17] Grade 3–4 neurological adverse events can impact both the CNS, such as posterior reversible encephalopathy syndrome, multiple sclerosis (MS), encephalitis, aseptic meningitis, and the PNS, such as acute demyelinating polyneuropathy, myasthenia gravis (MG), and necrotizing myositis.^[29, 30] Neurological adverse events may resemble paraneoplastic neurological disorders (PNDs).^[31] One study found that among 147 patients who experienced immunotherapy-related neurologic side effects, 20% of patients developed

paraneoplastic-like n-irAEs, including sensory neuropathy, limbic encephalitis, and cerebellar ataxia.^[32] The only clinical difference between patients with paraneoplastic-like n-irAEs and those with traditional PND was that the former group had advanced malignancy, whereas the latter usually occurred prior to the diagnosis of minimally advanced cancer.^[33, 34] ICI therapy may worsen or trigger PNDs. While some aspects of diagnosis and care may overlap, it is crucial to differentiate between a process driven by an underlying cancer and a n-irAE, as it can have significant implications for cancer treatment.

Grade 1–2 n-irAEs occur in 6–12% of patients and rarely lead to the discontinuation of therapy.^[35] In contrast, grade 3 and 4 adverse effects arise in approximately 1% of cases and as they may be fatal,^[21, 24] permanent cessation of ICIs and extensive immunosuppression is required.^[36, 37] Encephalitis and severe MG represent the most serious and potentially fatal types of neurotoxicity.^[21] Paraneoplastic-like n-irAEs, whether associated with antibodies such as anti-Hu, anti-Ri, anti-Yo, and anti-Ma2 or not, were linked to decreased odds of neurological recovery in conjunction with advancing age.^[38–40]

Recent studies indicate that multisystem irAEs can occur in patients, therefore, it is essential to recognize that different irAEs may overlap. Concurrent non-neurologic irAEs may increase the likelihood that a n-irAE is the cause of neurologic symptoms. When there are established patterns of overlapping disease, a neurologic irAE invites for further investigation of additional irAEs. For instance, a diagnosis of myopathy or MG prompts evaluation for myocarditis, while a diagnosis of meningitis prompts consideration of encephalitis. N-irAEs present challenges in identifying and diagnosing due to variable timing and non-specific symptoms like dyspnea, fatigue, difficulty walking, and generalized weakness. Also, while many irAEs appear soon after treatment, n-irAEs can occur at any point during treatment or within 12 months of the last ICI infusion.^[41–43] A high degree of suspicion and familiarity with n-irAEs is required to differentiate non-specific symptoms from other treatment side effects or the effects of the underlying cancer.

To minimize the divergence in evaluation and categorization of n-irAEs, a multidisciplinary group of neurologists, oncologists, and irAE subspecialists recently published consensus definitions. This classification identifies neurological immune-related adverse events, which comprise 4 CNS (irMeningitis, irEncephalitis, irDemyelinating disease, irVasculitis) and 3 PNS (irNeuropathy, irNeuromuscular junction disorders and irMyopathy) core syndromes (Fig. 1).^[41]

This consensus disease classification aims to aid oncologists in conducting an initial evaluation by identifying whether a CNS or PNS etiology is suspected. Neurologists will then utilize this information to improve diagnosis and treatment.

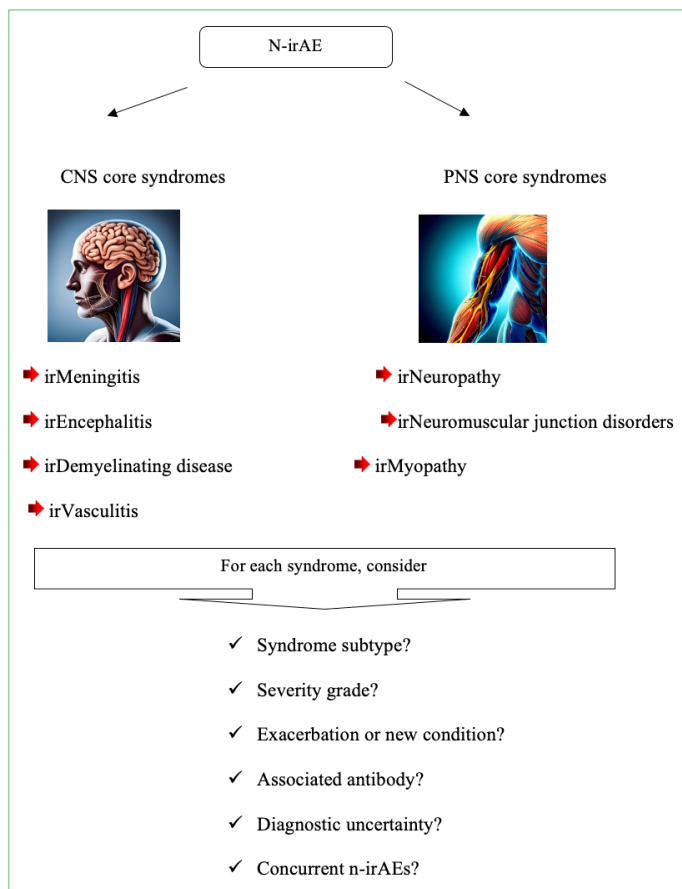


Figure 1. Classification of Neurologic Immune-related Adverse Events. CNS: central nervous system; N-irAEs: neurologic immune-related adverse events; PNS: peripheral nervous system.

This review will focus on neurologic immune side effects in accordance with the aforementioned classification.

N-irAEs Affecting CNS

Aseptic meningitis, encephalitis, demyelinating diseases (such as optic neuritis, transvers myelitis, MS, acute demyelinating encephalomyelitis) and vasculitis are four core syndromes of n-irAEs affecting CNS. In the presence of symptoms indicating CNS involvement, initial evaluation should exclude the development of CNS malignancy, seizure activity, infection, and metabolic imbalance as potential causes. It is also important to consider autoimmune encephalopathies and PNDs.^[44]

Cerebrospinal fluid (CSF) analysis, including cytology, testing for herpes simplex virus, varicella zoster virus and cryptococcal disease is necessary. Before performing a lumbar puncture, it is recommended to conduct head imaging (computerized tomography [CT] or magnetic resonance imaging [MRI]) to exclude the presence of mass lesions that could lead to herniation, and also because lumbar puncture may result in pachymeningeal enhancement. To

detect leptomenigeal and/or pachymeningeal enhancement, as well as for signs of CNS metastases, encephalitis, vasculitis, and demyelination, a brain±spinal MRI with dedicated short tau inversion recovery and pre-contrast and post-contrast T1 sequences with contrast is recommended.^[41] Serologic studies can detect antibodies associated with demyelinating or autoimmune encephalitis. Positive test results for extractable nuclear antigen and antinuclear antibodies may suggest an inclination towards autoimmunity, though their specific pathogenic significance remains uncertain. Brain biopsies are rarely performed due to their invasive nature, but they may be necessary in very rare cases to eliminate other potential causes. Disease specific tests will be discussed in the relevant sections.

ICI-Related Aseptic Meningitis/Encephalitis

Aseptic meningitis and encephalitis have a rare occurrence of only 0.1-0.2% in patients who are taking ICI. The symptoms of both conditions vary widely,^[45] and since they can occur together, in the presence of one condition, it is essential to evaluate the other as well. A pharmacovigilance study analyzed data from 18,518,994 patients and revealed that younger patients had a higher susceptibility to developing meningitis and encephalomyelitis compared to MG and Guillain-Barré syndrome after undergoing ICI therapy.^[22] Aseptic meningitis was found to be more prevalent among patients with melanoma, whereas encephalitis was linked with lung cancer. In the identical study, the frequency of meningitis associated with anti-CTLA-4 and anti-CTLA-4 plus anti-PD-(L)1 combination therapies is higher than that with anti-PD-(L)1 monotherapies.

Meningitis typically manifests as headache, fever, photophobia, nausea, vomiting, and neck stiffness. Conversely, encephalitis can cause confusion, altered mental status, abnormal behavior, seizures, and gait instability, which are indicative of parenchymal involvement.^[46-51] As with any case of meningitis and encephalitis, the likelihood of infections must be properly investigated during diagnosis and treatment, and leptomenigeal metastases must be excluded. Also, hypophysitis should be excluded in patients with headache.

Aseptic meningitis and encephalitis may cause abnormal leptomenigeal enhancement on neuroimaging. In the case of encephalitis, T2/fluid-attenuated inversion recovery hyperintensities on MRI can be present, suggesting parenchymal involvement; nonetheless, normal results do not exclude the diagnosis. Neuroimaging findings are inconclusive, with 51% of MRI scans revealing no abnormalities.^[31] On CSF examination, high lymphocyte counts (>8 cells/mm³) and/or high protein levels (>0.45 g/L) without detection of bacteria, viruses or tumor cells are expected in more than 90% of patients.^[31, 52] Numerous cases of encephalitis

are associated with paraneoplastic antibodies; however, the diagnosis cannot be ruled out solely based on the absence of these antibodies. EEG may be useful in evaluating subclinical seizures. The treatment is high-dose steroids which have shown a good response in aseptic meningitis patients, with occasional use of intravenous immune globulin (IVIG), plasma exchange or rituximab for cases of steroid-unresponsive encephalitis.^[17, 46, 53-55] Patients suspected of having aseptic meningitis or encephalitis should receive antibiotics and antivirals until the possibility of CNS infection is eliminated. In contrast to encephalitis, meningitis typically has a more favorable outcome. Regardless of the severity of the symptoms, ICI therapy should be stopped and only be restarted after a shared decision-making process with the patient, who knows the risks and advantages of the therapy.

ICI-Related Demyelinating Diseases

MS, transverse myelitis, acute disseminated encephalomyelitis, optic neuritis, and neuromyelitis optica are all immune-related demyelinating diseases (DDs). These disorders have been reported to occur at a frequency of 0.47% among complications related to ICI treatment.^[22] Depending on the disease type, individuals may experience one or more of the following symptoms: loss of balance, numbness, diplopia, limb weakness, sensory abnormalities, ataxia, autonomic symptoms (bladder and bowel control, etc.), and altered mental status.

Several studies provide evidence of an immune-mediated component for MS, the most common DD of the CNS, along with the identification of genetic and environmental risk factors.^[58] There is also a T-cell mediated etiology that resembles ICI therapy mechanistically.^[56, 57] Given the immune-mediated origin, it is no surprise that ICI therapy may exacerbate the pre-existing DD or cause de novo cases of demyelination in CNS.^[58-61] Nonetheless, the flare risk level in DDs remains in question.

Transverse myelitis induced by ICIs is a rare, focal inflammatory disorder of medulla spinalis often presenting with rapid onset weakness, sensory deficits, and bowel/bladder dysfunction. The disease can manifest as either short-segmented^[62] or longitudinally extensive myelitis.^[63-66] Spinal cord metastases and radiation-induced myelopathy are two differential diagnoses to consider in cases of myelitis.

ICI-related optic neuritis can occur alone or in combination with other areas of demyelination in the CNS.^[61] It often affects both eyes, is painless (unlike the typical optic neuritis in adults), and is accompanied by disc swelling.^[67, 68]

MRI with contrast of the brain, orbit, cervical, and thoracic spinal cord to the level of the conus medullaris is commonly used in diagnosing ICI-related demyelinating disorders

to detect evidence of parenchymal involvement. CSF investigations exclude alternative diagnoses and search for oligoclonal antibody production limited to the CSF. Serologic testing includes antibodies to aquaporin 4 and myelin oligodendrocyte glycoprotein, which are considered pathogenic in CNS DD. In addition to neuroophthalmic examination, optic coherence tomography, which can show signs of optic neuropathy during ophthalmic assessment, may be helpful, but often anomalies occur many weeks after clinical changes. To provide supporting evidence of demyelination of nerve fibers in the visual, auditory, or somatosensory systems, testing for evoked potentials is recommended. It is also advised to conduct John Cunningham virus PCR testing of CSF to rule out progressive multifocal leukoencephalopathy.

The ICI treatment continues for grade 1 symptoms, and patients are monitored for symptom progression. Prednisone at a dosage of 1 mg/kg is administered, and ICI treatment is ceased for grade 2 symptoms. Grade 3 and 4 symptoms necessitate the daily intake of 1 g of methylprednisolone and complete discontinuation of ICI. In instances where steroids are ineffective, IVIG, plasmapheresis, rituximab and infliximab have been used.^[61, 69]

DDs are rare side effects of ICI treatment and the majority of iatrogenic incidents described are monophasic, with most individuals experiencing total or partial symptom improvement with therapy.^[70, 71] Tumefactive lesions and longitudinally extensive myelitis may have a poor response to corticosteroid therapy.^[59, 72] Notably, patients with a history of MS may experience a more rapid progression.^[73]

ICI-Related CNS Vasculitis

In a pharmacovigilance study, researchers identified 100 cases of vasculitis (including both CNS and PNS vasculitis) among 3619 patients experiencing neurological side effects with ICIs (70). In patients with ICI-related vasculitis, predominant cancer type was non-small cell lung cancer and associated ICI was anti-PD-1 antibodies. In their systematic review, Daxini et al. reported twenty cases of ICI-associated vasculitis, with an average onset time of three months from ICI initiation.^[74] Melanoma stood out as the most commonly observed cancer type. The most common presentation was large-sized vessel vasculitis, including giant cell arteritis (GCA) which has been observed in association with both PD-(L)1 and CTLA-4 blockade. On the other hand, primary angiitis of the central nervous system (PACNS) was only reported during anti-PD-1 therapy. This finding holds great importance, particularly in light of recent publications emphasizing the crucial role of PD-1 in the pathophysiology of large and medium artery vasculitis.^[75, 76] Patients with GCA related to ICI experience temporary

loss of vision, diplopia, headaches, scalp tenderness, and/or jaw pain, which are similar to those in idiopathic GCA.^[68] PACNS may present with symptoms such as headache, stroke with focal neurological symptoms, seizures, encephalitis, myelitis, or meningitis.^[77-79]

MRI brain scans are frequently used to evaluate infarcts and other parenchymal changes in ICI-related vasculitis. Post-contrast vessel wall studies should also be considered if available, as they suggest concentrated vessel wall enhancement, further implying a vasculitic process.^[80] In addition, an MR angiogram or CT angiogram of the head and neck is necessary to assess intracranial and carotid vascular abnormalities, such as stenosis and beaded arteries. If MR angiogram or CT angiogram does not provide sufficient clarity, conventional (digital subtraction) angiography can identify vascular abnormalities. CSF studies, including testing for varicella zoster virus and syphilis (if serum tests are positive), seek to identify signs of CNS inflammation as well as alternative causes of vasculitis. Serum markers, such as C-reactive protein, erythrocyte sedimentation rate (ESR), anti-neutrophil cytoplasmic antibody, anti-nuclear antibody, and others associated with systemic vasculitis support the diagnosis. For systemic manifestations of vasculitis, formal evaluation by a rheumatologist and/or dermatologist may be beneficial. In the case of PACNS, CSF analysis may present as normal^[77] or suggest pleocytosis and increased protein.^[78] Brain biopsy is the gold standard for diagnosis.^[81] To minimize the risk of visual loss in patients with suspected GCA, a low threshold for temporal artery biopsy in conjunction with a rheumatologist and immediate administration of corticosteroids may be necessary. No deaths have been attributed to ICI-induced vasculitis, and symptoms in all cases resolved after discontinuing ICIs and/or corticosteroid therapy. Along with steroids, rituximab or cyclophosphamide induction has also been utilized.

N-irAEs Affecting PNS

Immune-related adverse events can impact the PNS in the form of neuropathy (involving both cranial and peripheral nerves), neuromuscular junction (NMJ) disorders, and myopathy. N-irAEs that affect the PNS are three times more prevalent than those that affect the CNS and have a shorter latency, as reported by previous studies.^[82] PNS disease diagnosis requires a combination of serologic tests, imaging, and electrodiagnostic testing (EDX) performed by neurologists experienced with n-irAE for optimal utility. Large fiber neuropathy can be diagnosed and characterized through nerve conduction tests, whereas needle electromyography (EMG) can identify and report the existence of neuropathic or myopathic illnesses. Repetitive nerve stimulation, used in combination with nerve conduction investigations, can screen for NMJ dysfunction. Individuals presenting with

motor dominant symptoms that are considered peripheral should be screened for NMJ dysfunction (with EDX) and myositis (with EDX and serum creatine kinase [CK]) due to the common overlap of PNS immune-related syndromes such as MG and myositis. Patients with immune-related NMJ issues or myositis must undergo screening for myocarditis as well, via serological troponin testing, electrocardiography, and echocardiography due to the high severity and overlap of these conditions. The workup for serology and radiography is specific to the illness and is elaborated on in the following sections.

ICI-Related Neuropathy

The occurrence rate of peripheral neuropathies varies significantly. Overall, ICIs account for neuropathy in 2.7% of irAEs and up to approximately 37% of n-irAEs reported.^[70] Data indicates that patients receiving dual therapy of CTLA-4 and PD-1 inhibitors experience a higher incidence of ICI-associated neuropathy (1.6%) compared to patients being treated solely with PD-1 inhibitors (0.3%).^[83] Immune-related neuropathy typically arises rapidly during ICI therapy (within four cycles) and has been more frequently observed in patients with melanoma.^[31, 84] While the risk of neurologic adverse events associated with dual ICI therapy is comparable to or higher in older patients, younger and male patients exhibit increased susceptibility to neuropathy. Nonetheless, the incidence of any degree of peripheral neuropathy with ICIs is lower than with traditional chemotherapy.^[26]

Documented cases of neuropathy include neuralgic amyotrophy, cranial neuropathies, painful small-fiber neuropathy, length-dependent polyneuropathy, isolated polyradiculopathy, and sensorimotor presentations more typical of classic inflammatory polyradiculoneuropathy, such as acute inflammatory demyelinating polyradiculopathy (AIDP) and chronic inflammatory demyelinating polyradiculopathy.^[83, 85, 86] In contrast to neuropathies induced by chemotherapy, neuropathies related to immune checkpoint inhibitors mainly impact the myelin sheath and seldom involve the axon and neuron body.^[86-88] They are more likely to present acutely or subacutely, with weakness at presentation and in a non-length-dependent pattern.^[24, 89] AIDP is notable for its high frequency in ICI-related neuropathies and potential impact on patient safety, including severe impairment or even death.^[31, 90] Patients who receive anti-CTLA-4 or anti-CTLA-4 plus anti-PD-1 are at a higher risk of developing AIDP compared to those treated solely with anti-PD-(L)1.^[22] Clinical signs can manifest during the first three cycles of ICI treatment. Early symptoms may include lower back or thigh pain, followed by sensory loss, ascending weakness, and areflexia. Cranial nerve involvement can occur independently or alongside meningitis.^[83] It is more frequently

reported with dual ICI therapy compared to other n-irAEs.^[91] Cranial neuropathy can involve facial, vestibulocochlear, optic, or abducens nerves, often bilaterally.^[31, 83, 91] Autonomic nerve dysfunction can cause irregularities in blood pressure, temperature regulation, digestion, bladder function, and sexual function.

Serum testing, which includes B12, serum protein electrophoresis, hemoglobin A1c, B6, TSH, HIV, ESR, C-reactive protein, syphilis antibodies, and folic acid can assess for alternative causes of neuropathy as well as signs of autoimmunity and inflammation. Ganglioside and onconeural autoantibodies are typically negative.^[50, 65] In most cases, CSF analysis is utilized to exhibit elevated protein levels, with or without white blood cell elevation^[31, 90] and to exclude infection or malignancy. EDX usually reveals changes of an acquired demyelinating polyradiculoneuropathy, with or without secondary axonal loss.^[83, 86] A small number of patients have subclinical evidence of concurrent myopathy.^[31, 83] Spinal MRI is frequently performed to rule out metastatic disease, structural radiculopathy, and spinal stenosis. Inflammatory radiculopathies may show spinal nerve root enlargement or enhancement. There have been reports of cases involving Miller-Fisher and anti-Gq1B syndrome as well.^[31, 65]

Multiple cranial nerves can be damaged, with the most commonly affected ones being the facial, vestibulocochlear, and optic nerves.^[29] Additionally, there have been cases of oculomotor, abducens, trigeminal, vestibulocochlear, and glossopharyngeal nerve involvement.^[46, 62, 83, 92, 93] Abnormal gadolinium enhancement on MRI is frequently associated with cranial neuropathies. Once corticosteroids are administered and ICIs are stopped, most patients achieve complete clinical recovery.^[31, 83, 85]

When managing peripheral neuropathy patient with grade 1 symptoms, temporarily discontinuing medication and monitoring the patient for symptom remission can often be beneficial. As most ICI-induced demyelinating episodes are typically monophasic,^[71] it may be appropriate to continue ICI for asymptomatic individuals with neuroimaging evidence of demyelinating lesions, while ceasing medication immediately if their condition deteriorates. Oral prednisone (0.5-1 mg/kg) is recommended for treating moderate symptoms (grade 2), followed by a gradual taper over 3-5 weeks. However, if the patient has AIDP, IV methylprednisolone should be started promptly.^[17, 55] In contrast to idiopathic AIDP, both the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline and National Comprehensive Cancer Network (NCCN) guidelines suggest that methylprednisolone at a dose of 1-2 mg/kg is a viable option to consider in ICI-related cases,^[47, 55, 94] especially when CSF pleocytosis is higher than anticipated for AIDP.^[95]

Additionally, it is advisable to initiate IVIG or plasmapheresis in all AIDP patients due to the potential for respiratory compromise and rapid deterioration, regardless of the severity of their symptoms.^[55] Permanent discontinuation of immune ICI treatment is recommended in the context of AIDP of any severity or any other neuropathies except AIDP with grade 3-4 symptoms.

ICI-Related Neuromuscular Junction Disorders and Myositis

Myositis and MG are noteworthy irAEs that are commonly observed in the same patients and demand special attention. They have overlapping symptoms (ocular, bulbar, axial, and respiratory weakness)^[96] and frequently occur together with myocarditis. A retrospective study of skin cancer patients found that 32% of myositis cases were associated with myocarditis.^[97] A comprehensive review revealed that MG was associated with myositis and myocarditis at rates of 16% and 9%, respectively.^[22] Given the high mortality rate for individuals with MG (20%) or myocarditis (17%), suspicion of one or more of these irAEs should prompt assessment for all.^[22, 98]

Myositis occurs in a small minority of patients treated with either anti-PD (L)1 ICIs (1%) or anti-CTLA-4 ICIs (<1%).^[22, 99, 100] About 40% of patients diagnosed with ICI-triggered myositis also have MG, which can result in ocular, bulbar, or respiratory symptoms.^[101] It typically manifests 5-6 weeks after ICI administration.^[90, 97] However, patients who receive combination therapy have reported an early onset.^[102-104] It may manifest as a de novo myositis or as the reactivation of a previous case of dermatomyositis or paraneoplastic polymyositis. Symptoms associated with ICI-related myositis comprise weakness primarily in proximal limbs and neck as well as dysphagia, dyspnea and muscle pain.^[24, 105, 106] While there have been reports of myositis that is limited to the ocular muscles, ptosis, and diplopia, these symptoms are not common in other types of myositis. It is possible that myositis related to ICIs has a predisposition for these muscles, or these symptoms could be caused by superimposed NMJ disorder.^[105] Most cases progress rapidly, in contrast to the relatively slow onset of primary autoimmune polymyositis.^[107]

Along with CK used in the diagnosis of myositis to measure muscle breakdown, aspartate aminotransferase and alanine aminotransferase are frequently elevated. Gamma-glutamyl transferase testing assesses liver injury specifically and is considered normal if aspartate aminotransferase /alanine aminotransferase levels are increased due to muscle disease. Some individuals may not display symptoms but exhibit elevated CK levels, while other patients with symptoms may have normal CK levels, particularly in those with

isolated or predominantly oculobulbar symptoms.^[97, 103, 106] Increased aldolase levels in regenerating myocytes, which are primarily involved in myositis, have been proposed as a cause for the discrepancy in aldolase/CK levels.^[108] Therefore, aldolase levels should be assessed even if CK levels appear normal. Myositis-associated antibodies are usually negative.^[40, 104] EDX is used to search for muscle membrane irritability, which can occur in inflammatory or necrotizing myositis, as well as myopathic motor unit potentials. To examine the possibility of an overlapping neuromuscular junction (NMJ) disorder, EDX is often combined with repetitive nerve stimulation of proximal nerve-muscle combinations. Concomitant myocarditis can be screened through troponin-I, EKG, echocardiography and cardiac MRI.^[109] Troponin-I is more specific for detecting cardiac damage than troponin-T, which can be elevated in myositis.^[104, 105, 110] Biopsy of ideally 4/5 MRC strength muscle allows assessment of muscle inflammation, but is not always necessary. The presence of T-cell infiltrate (some reports indicating predominating CD4+ endomysial lymphocytic infiltrates and others indicating predominating CD8+ cells) in the biopsy suggests myositis, but other histological findings have also been reported.^[96, 104, 105] Acetylcholine receptor (AChR) antibodies may serve as a screening tool for a superimposed NMJ disease, particularly in patients presenting ocular or bulbar symptoms. When muscle weakness and increased CK are present in grade 1 myositis, it should be treated as grade 2. If there are no contraindications, oral corticosteroids such as prednisone at a dose of 0.5-1 mg/kg/day is often prescribed as first-line treatment. A suggested approach involves continuing steroid therapy for a period of 4 to 8 weeks, followed by a gradual taper over several months depending on the initial severity of symptoms.^[111] However, there is limited information on appropriate duration and tapering protocols. If a patient experiences grade 3 myositis, it is recommended to avoid the use of ICIs until the myositis decreases to grade ≤ 1 . Furthermore, if any indication of cardiac involvement arises, the ICIs should be permanently stopped. Plasmapheresis or IVIG may be considered as treatment options for patients with grade 3 myositis and significant muscle weakness that severely restricts mobility, cardiac or respiratory involvement, or dysphagia. Additionally, a bolus of 1-2 mg/kg of methylprednisolone IV or higher may be administered.^[24] If symptoms of myositis and CK levels do not improve or worsen after 4-6 weeks, it may be worthwhile to consider other immunosuppressant medications, such as methotrexate, azathioprine, or mycophenolate mofetil. Although treatment improves the condition of approximately 70% of patients, there is a mortality rate of 17%^[31] which increases 13-fold in the presence of concurrent MG and myocarditis.^[90, 112, 113] MG is a serious neurological toxicity with a high risk of mor-

tality.^[22, 114] Following ICI therapy, patients may experience either a new onset of MG or an exacerbation of pre-existing MG. Immune-related MG has an estimated incidence ranging from 0.47% to 1.16%^[23] among all irAEs and constitutes 13.5% of n-irAEs in the largest reported series.^[31] De novo MG has been reported in patients undergoing treatment with anti-CTLA-4 agents, PD-1 inhibitors, and combined (anti-CTLA-4 plus anti-PD-1 or PD-L1) therapy.^[97, 115, 116] Exacerbation of preexisting MG and subclinical AChR antibody positive MG has been noted in patients who received PD-1 inhibitors.^[115, 117, 118] Compared to patients who receive anti-CTLA-4 ICIs, those who receive anti-PD-(L)1 ICIs are at a greater risk of developing MG.^[22] Concomitant myositis (occurring in 51 to 65% of cases)^[31, 112] and myocarditis (occurring in up to 30% of cases)^[112, 119, 120] are more common than in idiopathic MG, which may increase disease severity and mortality.^[70, 96, 121-123] Symptom onset following administration of ICI is shorter than that of other n-irAEs. In one study, median latency was 6.6 weeks,^[90] while a series observed a range of 6-106 days.^[70, 96, 107] The risk of MG appears to be higher in elderly individuals.^[96, 107] Other immune-mediated neurological disorders affecting PNS and CNS may coincide with MG.^[90, 118, 124] The MG myositis overlap syndrome is present in the majority of patients, with around 80% exhibiting associated non-neurological irAEs, predominantly myocarditis up to 30%.^[21, 90] Although the underlying causes of myositis/MG and myocarditis in ICI-treated patients are unknown, molecular mimicry and the critical involvement of PD-1 pathways in regulating autoimmune responses in these tissues may be responsible.^[125, 126] Patients exhibit varying degrees of muscle weakness, which typically affects the proximal muscles (such as the shoulder and neck) more extensively than the distal muscles. MG impacts the bulbar and ocular muscles, causing ptosis, anomalies in extraocular movement resulting in double vision, facial paralysis, and difficulties with swallowing. Respiratory compromise is also possible when the diaphragmatic muscles are involved. Fatigable or fluctuating muscle weakness, typically seen in idiopathic MG, may be absent in ICI-related MG due to overlapping myositis. Diagnosis of ICI-related MG can pose a challenge. Fatigue or widespread weakness is a common symptom of cancer patients. The focus on the cancer could potentially delay the detection of an underlying neuromuscular disease. Evaluation of these patients includes diagnostic antibody testing for MG and testing for concurrent myopathy and myocarditis. In cases of idiopathic MG, AChR binding or muscle-specific kinase (MuSK) antibody positivity in the relevant clinical context is diagnostic, rendering EDX unnecessary.

Nevertheless, patients undergoing ICI therapy may carry AChR antibodies even without any indication of neuromuscular transmission disorder. Lower rates of positivity

for AChR antibodies (approximately 60%) in these patients further complicates the diagnosis.^[24, 112] Therefore, abnormal neuromuscular transmission on EDX, either through abnormal repetitive nerve stimulation or single fiber EMG, is necessary for a definitive diagnosis of immune-mediated MG. As there is no evidence that MuSK antibodies develop as a new disease after ICI therapy, the test is used to detect pre-existing disease. Concurrent myositis can further complicate the diagnosis of MG, especially if ocular and bulbar weakness are present. Imaging of the chest is conducted to eliminate the possibility of thymoma. There was no evidence indicating a correlation between thymoma and the onset of ICI-related MG.^[96, 112] The recommended treatment approach comprises promptly beginning oral prednisone therapy in grade 2 patients and administering high-dose intravenous methylprednisolone in severe cases. An oral prednisone taper over several weeks is required. Pyridostigmine titration from 30 mg three times a day to a maximum of 120 mg four times a day can be beneficial in treating MG. Additionally, in all patients diagnosed with MG, irrespective of the severity, discontinuation of ICI therapy^[17, 55] and initiating IVIG or plasmapheresis due to the possible risk of rapid deterioration and respiratory failure is recommended. The reinitiation of ICI in grade 2 patients is only possible upon the resolution of symptoms and completion of steroid tapering. Patients with grade 3 or 4 MG should stop ICI therapy permanently. Immune-associated MG, in contrast to idiopathic MG, may be monophasic and may not require additional corticosteroid-sparing medications.^[47] However, refractory cases have been reported which require administration of either mycophenolate mophetil^[127, 128] or rituximab.^[129, 130] Despite most patients improving with treatment, immune-related MG, as opposed to classical MG, carries a 20% risk of fatality,^[22] with a higher rate of respiratory paralysis and death, especially in patients with concurrent myositis, and myocarditis.^[31, 90, 112, 122]

Lambert-Eaton myasthenic syndrome (LEMS) related to ICIs is rare, and it remains unclear whether it is a paraneoplastic disorder or an irAE.^[121] Common clinical symptoms include ptosis, generalized weakness that improves after warming up, photophobia, and autonomic signs.^[131-133] If there is clinical suspicion of LEMS or EDX reveals a distinct pattern of facilitation and decrement, testing for P/Q voltage gated calcium channel antibodies is used to test for paraneoplastic LEMS. In the majority of cases, steroid treatment proved ineffective, thus necessitating escalation to IVIG, plasmapheresis, rituximab,^[132] or infliximab.^[134]

Evaluation and Monitoring of Pre-Existing Autoimmune Neurological Disorder

As the incidence and prevalence of autoimmune diseases

(ADs) and cancer continue to rise globally, there is growing overlap between the two conditions. Current research indicates that 11.3% to 24.6% of cancer patients have pre-existing ADs.^[135, 136] Moreover, patients with ADs potentially have a heightened risk of cancer development when compared to the general population due to chronic immune activation and suppression.^[137] It is unclear whether these tumors are generated by the underlying AD or by the long-term use of immunosuppressive medications, which may impair immune surveillance and allow malignant clones to proliferate uncontrollably. Although the exact mechanisms are uncertain, irAEs induced by ICIs bear a close resemblance to ADs. Retrospective data indicates that patients with pre-existing ADs have a higher (up to 75%) likelihood of acquiring immunotoxicity with ICIs.^[117] The risk may increase due to worsening baseline AD or the emergence of new irAEs, typically mild, and treatable with corticosteroids, enabling continued use of ICI treatment.^[138-140] However, a systematic review of patients undergoing ICI therapy with pre-existing autoimmunity showed that while these patients do not appear to experience an increased prevalence of de novo irAEs, autoimmune flares are common following ICI therapy.^[117] On the flip side, patients with preexisting immunosuppression may not derive as much benefit from ICI therapy as a robust immune response against cancer cells cannot be mounted. Menzies et al. conducted a study which revealed that individuals with ADs using high-dose steroids or disease-modifying drugs have a 15% response rate to anti-PD1 antibody therapy, compared to 44% in those not taking immunosuppressants.^[139] Due to concerns about the effectiveness and safety of ICIs in patients with ADs, clinical trials that authorized ICI therapy excluded this challenging population, resulting in a lack of knowledge and experience. Nevertheless, subsequent safety data support the use of ICIs in patients with controlled and inactive AD.^[141, 142]

Regarding patients with neurological ADs, our comprehension of the impacts of ICI treatment is significantly restricted. In patients receiving anti-PD-1 antibodies therapy, there are reports of pre-existing MG and subclinical AChR positive MG exacerbations.^[115, 117, 118] According to international consensus guidelines for MG, prior to starting treatment, patients and their oncologists should discuss the elevated risk of significant irAEs in the underlying MG.^[52] Although well-controlled MG is not regarded as an absolute contraindication to ICI therapy, monotherapy may be preferred due to the higher risk of severe irAEs with combination therapy. Also, respiratory and bulbar function require close clinical monitoring during and after ICI therapy, in particular. Given the high rate of fatality, MG treatment should continue or even be resumed for individuals whose MG was in remission before ICI treatment, despite the less satisfactory

therapeutic response to ICIs in patients using immunosuppressants. A similar approach can be applied to all immune-mediated neuromuscular diseases.

Reports indicate that some MS patients experience relapses following ICI treatment, along with a shift from radiologically isolated syndrome (RIS) to clinically definite MS.^[143, 144] In a recent study,^[145] among the 24 MS patients under ICI therapy, only three individuals diagnosed with RIS exhibited new inflammatory activity, while two developed new asymptomatic demyelinating lesions. Furthermore, one patient experienced a clinical relapse. Based on their observation, Hasan et al. propose that patients with RIS may be at a higher risk for new demyelinating activity after undergoing ICI treatment. The transition from RIS to MS highlights the potential of ICIs to uncover preclinical or subclinical autoimmune conditions. In a systematic review of patients with cancer and various ADs, approximately 33% of MS patients experienced exacerbated symptoms.^[117] After undergoing corticosteroid therapy, they either exhibited improvement or remained stable. In a study by Garcia et al., the FDA database and several patient cases from scientific literature and their own center were analyzed, with a total of 14 patients (8 of whom had pre-existing MS). The researchers concluded that MS relapses or flares following ICI were infrequent, but side effects such as rapid neurologic progression were noted.^[73] Chavaz et al. conducted a study with 11 MS patients who received ICI treatment, revealing a 9% disease exacerbation rate.^[146] In contrast, Conway et al. did not detect any exacerbation.^[147] The overall findings from the studies suggest that MS should not be considered an absolute contraindication to ICI treatment, especially in the case of inactive MS and elderly patients who are likely to have minimal MS-related inflammation. Additionally, this is particularly relevant for individuals with refractory malignancies and limited therapeutic options. Prior to initiating ICI therapy, disease activity should undergo evaluation, and disease-modifying therapy should be considered on an individual basis. Following the start of ICI, close clinical and radiological monitoring is advised.

Therefore, administering immunotherapy to these patients necessitates thorough evaluation. Prior to initiating this treatment, a treatment strategy determined by the effectiveness and potential adverse reactions must be conscientiously contemplated. According to a consensus guideline established by a working group consisting of neurologists, oncologists, and irAE experts, patients who exhibit mild symptoms or stable, well-established neurological conditions rarely necessitate a neurologist's evaluation when initiating ICI therapy.^[41] However, those with immune-mediated neurological disorders (e.g., MG, myositis, MS and inflammatory neuropathies) or systemic autoimmune conditions that affect the nervous system may benefit from ex-

amination before or shortly after starting ICI treatment. The baseline assessment of clinical and/or radiologic disease activity, discussion of risks and benefits, modifying baseline immunomodulation prior to the start of an ICI, and assistance in interpreting changes in neurologic status after the start of an ICI treatment are possible considerations for this patient group.

Rechallenging ICIs after n-irAEs

Resuming ICI therapy after toxicity resolution poses a complex decision that requires careful evaluation of multiple factors. These factors encompass prior tumor response, treatment length, type and severity of toxicity, duration of toxicity resolution, the availability of alternative treatments, and the status of patient performance. Currently, there is limited prospective research regarding the safety of administering ICI following immune-related adverse events (irAEs). It is anticipated that 30-60% of patients may undergo a recurrence of irAE, with most cases being less severe than the initial episode and effectively managed with steroids without necessitating ICI discontinuation.^[148-151] Cancer progression, rather than immunotoxicity, is the primary cause of mortality in this population.^[24] Randomized trials have demonstrated that patients experiencing irAEs may have favorable clinical outcomes following the discontinuation of ICI.^[152-154] This suggests that if a patient responds favorably to the first ICI treatment, it is probable that the response will endure, and it may not be necessary to continue medication, which could lead to toxicity recurrence. In contrast, resuming ICI therapy after toxicity resolution is reasonable for patients who have not yet responded or whose response is regarded inadequate. Additionally, resuming ICI may pose a lower risk for certain individuals who experience a quick remission of mild to severe irAEs after treatment with corticosteroids.

According to a retrospective study that identified the most extensive range of ICI rechallenge cases (452 patients), initial irAEs that are regarded as the most life-threatening, comprising myocarditis and neurological irAEs, did not seem to have a correlation with higher recurrence rates compared to other initial irAEs.^[150] On the other hand, due to the considerable morbidity and mortality linked to n-irAEs, particularly severe n-irAEs categorized as grade 3-4 or any severity of encephalitis, AIDP or MG, the threshold for rechallenge of ICIs is much higher than for other types of immunotoxicity.^[17, 55] To reduce the likelihood of relapse when reintroducing ICI, some authors suggest using steroids or other immunosuppressive treatments simultaneously or changing to a different type of ICI,^[92] since negative effects associated with one ICI group may not necessarily recur with another. Currently, the effectiveness of these strategies is unclear. At present, there is no clear understanding of the efficacy of

these strategies. Regarding the limited data about the risks and potential benefits of rechallenge with ICI therapy, a review board of multidisciplinary experts could prove effective in making the decision of resuming ICI in conversation with the patient together with appropriate monitoring and standard treatment protocols.

Conclusion

Since William Coley's pioneering work, remarkable progress has been made in utilising the power of the immune system to fight malignancies through the development of ICIs. However, challenges have arisen from this progress. While ICIs offer the promise of boosting anti-cancer immunity, they also carry the risk of irAEs. Given the high mortality rates associated with n-irAEs, it is critical to understand and manage the neurological side effects associated with ICIs, as early detection and appropriate treatment are critical to patient safety and well-being. Furthermore, navigating the use of ICIs in patients with pre-existing autoimmune neurological disorders and the consideration of rechallenge with ICIs following the occurrence of n-irAEs adds a layer of complexity to the field. Within this article, we have investigated the intricate nature of n-irAEs, which is a field that rapidly progresses due to the intersection of oncology and neurology. Continued study and cooperation across neurology, oncology and immunology is crucial to maximizing the effectiveness of ICIs whilst minimizing patient risk.

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