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### Novel treatments for progressive multifocal leukoencephalopathy

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<b>Abstract:</b>	Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disorder of the central nervous system caused by JC virus that occurs in those with impaired immune systems. Existing treatment options are ineffective or unproven. This article reviews recent research into novel therapies: 1) immune checkpoint blocking antibodies (nivolumab and pembrolizumab); 2) allogenic BK virus-specific T cell treatment and 3) filgrastim. Results for these therapies in small clinical trials are promising, but further research is required to assess efficacy fully.
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<b>Response to Reviewers:</b>	Response to comments: All changes have been highlighted in the document in yellow.  1. The use of IL-7 in patients with idiopathic lymphopenia should be discussed in more detail. This may require a short separate section.  I have included a short separate section on the use of IL-7 in idiopathic lymphopenia. This can be found on page 2.  2. In the text discussion of the Cortese (2019) paper of use of pembrolizumab an adjustment needs to be made to aid clarity. It needs to be clear that the "three remaining" patients are the non-responders from the original 8 and not part of the 5 responders.  Thank you for alerting me to this. I have amended this paragraph for clarity.  3. The terms highly active antiretroviral therapy (HART) and combined antiretroviral therapy (CART) for HIV are both use. Please standardise for one or other throughout the whole text.

	Thank you. I have now used the term highly active antiretroviral therapy (HAART) throughout the manuscript.
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## **TITLE**

Novel treatments for Progressive Multifocal Leukoencephalopathy

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## **DISCLOSURES**

No conflicts of interest to declare.

## **CONTRIBUTORSHIP**

KMB and PMF prepared and approved the manuscript. All authors fulfil ICJME criteria for authorship.

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## Abstract

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disorder of the central nervous system caused by JC virus that occurs in those with impaired immune systems. Existing treatment options are ineffective or unproven. This article reviews recent research into novel therapies: 1) immune checkpoint blocking antibodies (nivolumab and pembrolizumab); 2) allogenic BK virus-specific T cell treatment and 3) filgrastim. Results for these therapies in small clinical trials are promising, but further research is required to assess efficacy fully.

## Case Study

A 67-year-old man presented with left-sided weakness and reduced left hand dexterity four months after autologous stem-cell transplant for multiple myeloma. He had no other past medical history. Computerised tomography scan of the head showed multiple areas of low attenuation and magnetic resonance imaging demonstrated numerous hyper-intense T2 lesions within the subcortical white matter of both cerebral hemispheres. Over 6 months his clinical symptoms continued to progress such that he developed emotional lability, motion sickness, cognitive dysfunction and was unable to walk 2 metres unaided. An extensive set of investigations were performed to determine the cause. John Cunningham virus (JC virus) was found to be positive along with compatible clinical and radiological findings which met the diagnostic criteria for Progressive multifocal leukoencephalopathy (PML) (Berger et al 2013). In this case there was no scope to improve immune functioning and he was commenced on mirtazapine as a potential anti-viral therapy. Despite this intervention he continued to deteriorate and died shortly afterwards (Bennett et al., 2020).

## Introduction

PML is a rare demyelinating disorder of the central nervous system caused by JC virus, a neurotropic polyomavirus. JC virus is present in around 50% of the population, causing an asymptomatic latent infection in the renal tract and/or bone marrow (Sabath & Major, 2002). Failure of immune control allows penetration of the virus into the central nervous system, resulting in widespread oligodendrocyte lysis (Major et al., 2018), often with devastating consequences. The clinical presentation varies depending on the location and extent of demyelination, but symptoms often include muscle weakness, sensory deficit, hemianopia, cognitive dysfunction and coordination difficulties (Pavlovic et al., 2015).

PML usually only affects those who are immunosuppressed (Clifford, 2015) with three associations accounting for 90% of cases: 1) human immunodeficiency virus (HIV); 2) immunosuppressing haematological malignancies, and 3) multiple sclerosis patients treated with natalizumab (Pavlovic et al., 2015). Less commonly, PML is associated with organ transplantation, solid malignancies, sarcoidosis, autoimmune disorders and other immunosuppressant medications (e.g. prednisolone, dimethyl fumarate and rituximab) (Maas et al., 2016; Pavlovic et al., 2015).

The diagnostic criteria for PML are either characteristic findings on brain biopsy or a combination of the appropriate clinical symptoms, radiological features and JC virus in the cerebrospinal fluid (CSF) (Berger et al., 2013). Prognosis in PML is poor unless

immunosuppression can be reversed (Pavlovic et al., 2015). In a Swiss HIV cohort, patients infected with PML had a 1-year mortality rate of 30%, even with highly active antiretroviral therapy (HAART), though this is much improved compared to the rate of 83% in the pre-HAART era (Khanna et al., 2009). In those with multiple sclerosis treated with natalizumab 77% are alive at three years and in those with active immunosuppressing haematological malignancies just 10% are alive beyond two months (Pavlovic et al., 2015).

The restoration of central nervous system (CNS) immunocompetence in PML patients carries the risk of immune reconstitution inflammatory syndrome (PML-IRIS) (McCarthy & Nath, 2010). This is defined as the paradoxical sudden worsening of PML signs and symptoms in the setting of immune reconstitution, often with contrast enhancement in the PML lesion on MRI. The pathophysiological process in IRIS is thought to be high levels of inflammation causing damage to previously intact brain tissue; this can be fatal if significant vasogenic oedema occurs. Treatment of PML-IRIS is with high dose corticosteroids to reduce CNS inflammation.

## Existing treatments

Current treatment options for PML focus on restoring immune function through reversing exogenous immunosuppression. For example, patients with HIV are started on HAART and patients on natalizumab have their treatment stopped, often using plasma exchange to more rapidly eliminate the drug from the circulation. However, in some circumstances, immunosuppression cannot be reversed, such as in patients with heart-lung transplants or patients with conditions causing intrinsic immunosuppression e.g. sarcoidosis or primary immunodeficiency. In these situations, the only remaining therapeutic possibility is to attack the virus. Pavlovic et al conducted a review of these potential options, dividing them into anti-viral agents, immune response modulators, and immunisation strategies (Pavlovic et al., 2015). As shown in Table 1, small-scale clinical trials have taken place for the following drugs: cytarabine, topotecan, cidofovir, mefloquine, interferon-alpha 2b and zidovudine; all have demonstrated negative or inconclusive results. Research for other drug options are limited to case studies and retrospective studies with no strong consensus. The identification of successful treatments is challenged by inadequate animal models, small patient numbers and rapid disease progression.

Treatment with interleukin-7 (IL-7) aims to boost depleted T-cell response. It is a cytokine which stimulates proliferation of cells in the lymphoid lineage and supports their maturation, survival and homeostasis (Pavlovic et al., 2015). Individual case studies have reported promising results on the use of IL-7 in treating those with PML and idiopathic lymphocytopenia (Alstadhaug et al., 2014; Harel et al., 2016; Miskin et al., 2016).

**Table 1: Current medications used to treat PML (Pavlovic et al., 2015)**

	Drug name	Presumed mechanism	Efficacy in clinical trials
Anti-viral agents	Mefloquine	Inhibits viral replication	Negative/inconclusive
	Mirtazepine	Blocks serotonin receptors	None
	Cidofovir	Inhibits infection	Negative
	Ganciclovir	Inhibits viral polymerases	None
	Topotecan	Inhibits replication	Inconclusive/poorly tolerated
	Cytarabine	Decrease replication	Negative
	Interferon A	Increases cell-mediated immunity	Negative

<b>Immune response modulators</b>	IL-2	Increases T cell function	None
	IL-7	Increases lymphoid proliferation	None
	Maraviroc	Decreases inflammation	None
	Corticosteroids	Decreases inflammation	None
<b>Immunisation strategies</b>	Intravenous immunoglobulin (IVIg)	Uncertain	None
	Anti-JCV Ab	Neutralises virus	None
	Anti-JC virus vaccine	Neutralises virus	None

## Novel PML treatments

Recent research has begun to test novel immune boosting agents in the treatment of PML. These comprise three main groups of therapies, all of which show promise: 1) immune checkpoint blocking antibodies (nivolumab and pembrolizumab); 2) allogenic BK virus-specific T-cell treatment and 3) filgrastim.

### Immune checkpoint blocking antibodies: nivolumab and pembrolizumab

The immune system has a complex set of checks and balances to avoid damaging overstimulation, known as immune checkpoints. One aspect of this process involves programmed cell death-1 (PD-1) a negative immune regulator expressed on activated T cells. Nivolumab and pembrolizumab are anti-cancer drugs that block this inhibitory pathway, reinvigorating T-cell activity, and thereby boosting the immune response against cancer (Wykes & Lewin, 2018). Both drugs have similar pharmacological features, differing on the precise PD-1 epitope recognised, and are licensed in the UK for the treatment of melanoma, Hodgkin's lymphoma, and non-small cell lung cancer (Koralnik, 2019).

An indication of the potential benefit of immune checkpoint inhibitors against JC virus came from the finding that PD-1 expression is elevated on the CD4+ and CD8+ T lymphocytes of patients with PML and is especially elevated on JC virus-specific CD8+ T cells (Tan et al., 2012). Initial clinical studies have been promising, with Cortese et al. presenting a case series of eight patients treated with pembrolizumab for PML (Cortese et al., 2019). These patients had a mixture of underlying conditions including HIV, haematological malignancies (chronic lymphocytic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma), and idiopathic lymphopenia. All eight patients showed down-regulation of lymphocytes in the peripheral blood and CSF prior to pembrolizumab treatment. After pembrolizumab treatment five patients showed clinical improvement or stabilisation, with concomitant reduction in CSF JC viral load and increased in-vitro CD4+ and CD8+ anti JC virus activity. In three of the eight patients there was no clinical improvement and no change in viral load. In retrospect one of the five patients showing clinical improvement was noted to have had some clinical, radiologic and virologic stabilisation of PML before treatment. Two of the five patients showing clinical improvement had HIV and were concurrently started on antiretroviral therapy which will have contributed to immune system restoration (Koralnik, 2019). None of the patients had complete resolution of PML brain lesions.

Promising results with pembrolizumab or nivolumab have also been demonstrated in individual case studies, with outcomes ranging from partial to full recovery (Audemard-Verger et al., 2019; Hoang et al., 2019; Uzunov et al., 2019; Walter et al., 2019). Perhaps unsurprisingly, patients treated early seemed to do better than those treated with late-stage disease. A case series of nivolumab usage in three patients with kidney transplants and PML

showed poor outcomes, with all three dying shortly after diagnosis (Medrano et al., 2019). Interestingly, these three patients and the three patients with no clinical improvement described by Cortese et al (2019) all had significant lymphopenia, suggesting the use of immune checkpoint blocking antibodies may be limited in this subset of patients. These studies are summarised in Table 2. Additionally, there are no reports of the successful use of immune checkpoint inhibitors in organ transplant patients (Focosi et al., 2019).

Table 2: Outcomes of patients with PML treated with immune checkpoint inhibitors.

Treatment	Age/sex	Underlying condition(s)	Time between onset of symptoms and treatment initiation	CSF viral load at treatment onset (copies per ml)	PML-IRIS	Outcome	Reference
Pembrolizumab	67/M	Chronic lymphocytic leukaemia	15 months	232	No	(=) Symptoms stabilised prior to treatment	(Cortese et al., 2019) 1
Pembrolizumab	78/M	Chronic lymphocytic leukaemia	7 months	6044	No	(+) Confusion, language and ataxia improved slightly.	(Cortese et al., 2019) 2
Pembrolizumab	48/F	HIV/AIDS	6 months	63	No	(+) Improvement in language and cognition, independent in activities of daily living.	(Cortese et al., 2019) 3
Pembrolizumab	69/F	Non-Hodgkin lymphoma	12 months	26,494	No	(-) Clinical deterioration.	(Cortese et al., 2019) 4
Pembrolizumab	31/M	Idiopathic lymphopenia	2 months	5,248	No	(+) Improvement in confusion and increased independence with activities of daily living.	(Cortese et al., 2019) 5
Pembrolizumab	62/F	Idiopathic lymphopenia, common variable immunodeficiency	3 months	28,350	No	(-). Clinical deterioration and became wheelchair bound.	(Cortese et al., 2019) 6
Pembrolizumab	70/M	Hodgkin's lymphoma	2	261	No	(+) Modest improvements in gait and speech.	(Cortese et al., 2019) 7
Pembrolizumab	58/M	HIV/AIDS	12	286	No	(+) Subjective clinical improvement.	(Cortese et al., 2019) 8
Pembrolizumab	42/M	Idiopathic primary immunodeficiency	5 months	38	No	(-) Clinical deterioration.	(Kupper et al., 2019)
Pembrolizumab	38/M	Combined immunodeficiency and Behçet's disease	4 weeks	2,561,955	No	(-) Died 4 weeks after treatment initiation.	(Pawlitzki et al., 2019)
Pembrolizumab	Unknown /M	Variable immunodeficiency and diffuse B cell lymphoma.	10 weeks	119,000	Yes	(+) Speech recovery but ongoing psychomotor slowing, aphasia and disorientation	(Rauer et al., 2019)
Nivolumab	53/M	Silicosis	12 weeks	Not detected	No	(++) Stabilised aphasia and regression of motor deficit.	(Audemard-Verger et al., 2019)
Nivolumab	65/F	Hodgkin's Lymphoma	0 days	Not detected	Yes	(++) Clinical function improved.	(Hoang et al., 2019)
Nivolumab	81	Kidney transplant	<6 weeks	3,162	No	(-) Death 6 weeks after diagnosis.	(Medrano et al., 2019) 1
Nivolumab	77	Kidney transplant	<6 weeks	794	No	(-) Death 6 weeks after diagnosis.	(Medrano et al., 2019) 2
Nivolumab	67	Kidney transplant	<6 weeks	794	No	(-) Death 4 weeks after diagnosis.	(Medrano et al., 2019) 3
Nivolumab	47/F	Acute myeloid leukaemia after allo-stem cell transplantation	4 weeks	47,377	No	(++). Complete recovery from motor deficit. Visual symptoms stabilised.	(Uzunov et al., 2019)
Nivolumab	60/F	Idiopathic primary immunodeficiency	8 weeks	200,000	Yes	(++) Improved focal deficits and alertness.	(Walter et al., 2019)

Key: (-) unfavorable outcome; (+) mild improvement; (++) marked improvement and (=) no change. IRIS = immune reconstitution inflammatory syndrome. F = female and M = male.



The development of immune reconstitution inflammatory syndrome (IRIS) in PML patients treated with immune checkpoint inhibitors was variable. In the cases showing clinical improvement, some did show IRIS (Hoang et al., 2019; Rauer et al., 2019) but this was not universal (Audemard-Verger et al., 2019; Cortese et al., 2019; Walter et al., 2019). Thus, IRIS does not appear to be a prerequisite for clinical improvement, though differentiating between PML-IRIS and PML alone can be challenging. It should be noted that none of the patients with poor outcomes developed IRIS, indicating that IRIS may be an indicator of a positive outcome. Other side-effects of immune checkpoint inhibitors in PML cohorts include rashes (Cortese et al., 2019), diarrhoea (Rauer et al., 2019) and myositis (Uzunov et al., 2019). In cancer cohorts immune checkpoint inhibitors are associated with serious side effects involving all organ systems (Heinzerling & Goldinger, 2017) including myasthenia gravis and cardiotoxicity (Hottinger, 2016; Suzuki et al., 2017). One case report details PML developing after treatment with nivolumab in a patient with refractory stage IV Hodgkin lymphoma (Martinot et al., 2018); though it cannot be determined whether PML was caused by nivolumab or the underlying immunocompromised state.

There does not appear to be a discernible difference between nivolumab and pembrolizumab and there are no reports on other immune checkpoint inhibitors such as ipilimumab, atezolizumab, avelumab or durvalumab. All these treatments are expensive and use in PML patients is currently unlicensed.

#### **Allogeneic BK virus-specific T cells**

BK is a polyoma virus closely related to JC virus, causing renal tract infections in immunocompromised patients after stem-cell or solid organ transplant. A novel treatment for BK virus infections involves screening donated blood for BK-specific T-cells, clonally expanding these cells, and transfusing these into BK-infected immunocompromised patients, with promising results (Tzannou et al., 2017). It was therefore postulated that T-cells developed against BK virus may also be effective against JC virus, due to the similarities between these related pathogens. This theory was tested in three patients with different underlying conditions: acute myeloid leukaemia treated with cord-blood transplant, myeloproliferative neoplasm treated with ruxolitinib, and HIV treated with HAART (Muftuoglu et al., 2018). Each patient received HLA-matched BK virus-specific T-cells. In two patients (myeloproliferative neoplasm treated with ruxolitinib and HIV treated with high active retroviral therapy) there was significant clinical improvement. JC virus in the CSF disappeared and lesions on MRI decreased. Both patients developed IRIS. However, these results are confounded by the respective discontinuation of ruxolitinib and the commencement of anti-retroviral therapy. The third patient stabilised but did not improve, with concomitant reduction – but not clearance – of CSF JC virus. She died 8 months after starting treatment. The authors postulate that the lack of clinical improvement in this patient may have been due to late initiation of anti-PML treatment. No side effects from allogeneic T-cell therapy were reported in any patient. The heterogeneity in underlying conditions in this small case series and the use of multiple treatments makes assessing efficacy challenging. The potential use of patient-specific products and/or third-party products may expand the feasibility of this therapy (Fatic et al., 2020).

## Filgrastim

Filgrastim (also known as granulocyte colony-stimulating factor) is often used to boost the immune system after chemotherapy. It promotes production of granulocytes, lymphocytes, antigen presenting cells and improves adhesion of T-cells to the blood vessel wall. These features promote immune system function, potentially enabling an anti-PML effect.

Stefoski et al published a retrospective cohort study of 17 patients treated with filgrastim for natalizumab induced PML (Stefoski et al., 2019). Natalizumab was stopped in all patients after PML diagnosis. All patients were treated with daily filgrastim until lymphocyte counts doubled. In addition, 8 patients underwent plasma exchange, 14 received mefloquine, 15 received mirtazapine, and 9 were treated with maraviroc. 15 patients developed IRIS which was treated with intravenous methylprednisolone followed by tapering doses of corticosteroids. Filgrastim was well-tolerated, with the only side effect reported being bone pain not necessitating cessation of treatment. Outcomes were very good, with all 17 patients surviving 2-years after PML onset; survival after natalizumab induced PML has been reported in other cohorts as 76% (Dong-Si et al., 2015). Functional outcomes were mixed, with 7 patients improving to baseline at PML diagnosis, 3 improving but not to baseline, and 7 having poor outcomes (requiring full care). Patients who developed immune activation after filgrastim and/or IRIS had better clinical outcomes; the authors note that careful timing of steroid treatment for PML-IRIS is important. Plasma exchange had no effect on outcome. The retrospective nature of the study and the use of multiple drugs means that cause and effect are difficult to establish. The benefit of this study was that the population was a homogenous MS population allowing more specific conclusions about PML in this population to be drawn.

## Conclusion

PML is a devastating disease, especially when immunosuppression cannot be reversed. Previous treatments have not been shown to be efficacious in clinical trials. The growing number of patients with iatrogenic immunosuppression is likely to result in a rising PML incidence, highlighting the importance of developing effective anti-PML therapies. Novel treatments for PML focus on boosting the anti-JC virus immune response via immune checkpoint inhibitors (pembrolizumab and nivolumab), BK-specific T-cell therapy, and filgrastim, all of which have shown benefit in cohort studies. Limitations of these studies include small sample sizes, heterogeneous patient cohorts, and multiple confounding factors. As usage of these expensive therapies increase it may be possible to identify patient factors that predict good response and to develop combinatory treatment modalities. Future studies should test these treatment methods in more specified patient groups, with standardized outcome measures. A multi-centre randomised controlled trial would be the best way of showing efficacy, though the rarity of PML may make this approach challenging. Despite the initial promise of these novel treatments it is important to set realistic patient expectations given that many patients remain extremely disabled even after successful PML treatment.

### KEY POINTS

- PML is a devastating disease with poor prognosis, particularly where immunosuppression cannot be reversed.
- Existing treatments are ineffective or unproven.

- Novel treatments for PML boost the anti-JC virus immune response via immune checkpoint inhibitors (pembrolizumab and nivolumab), BK-specific T-cell therapy, and filgrastim.
- These treatments have shown benefit in cohort studies, but conclusions are limited by small sample sizes, heterogeneous patient cohorts, and multiple confounding factors.
- Multi-centre randomised controlled trials will help establish why treatment appears to be effective in some patients, but less so in others.

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**Table 1: Current medications used to treat PML (Pavlovic et al., 2015)**

	<b>Drug name</b>	<b>Presumed mechanism</b>	<b>Efficacy in clinical trials</b>
<b>Anti-viral agents</b>	Mefloquine	Inhibits viral replication	Negative/inconclusive
	Mirtazepine	Blocks serotonin receptors	None
	Cidofovir	Inhibits infection	Negative
	Ganciclovir	Inhibits viral polymerases	None
	Topotecan	Inhibits replication	Inconclusive/poorly tolerated
	Cytarabine	Decrease replication	Negative
<b>Immune response modulators</b>	Interferon A	Increases cell-mediated immunity	Negative
	IL-2	Increases T cell function	None
	IL-7	Increases lymphoid proliferation	None
	Maraviroc	Decreases inflammation	None
	Corticosteroids	Decreases inflammation	None
<b>Immunisation strategies</b>	Intravenous immunoglobulin (IVIg)	Uncertain	None
	Anti-JCV Ab	Neutralises virus	None
	Anti-JC virus vaccine	Neutralises virus	None

Table 2: Outcomes of patients with PML treated with immune checkpoint inhibitors.

Treatment	Age/sex	Underlying condition(s)	Time between onset of symptoms and treatment initiation	CSF viral load at treatment onset (copies per ml)	PML-IRIS	Outcome	Reference
Pembrolizumab	67/M	Chronic lymphocytic leukaemia	15 months	232	No	(=) Symptoms stabilised prior to treatment	(Cortese et al., 2019) 1
Pembrolizumab	78/M	Chronic lymphocytic leukaemia	7 months	6044	No	(+) Confusion, language and ataxia improved slightly.	(Cortese et al., 2019) 2
Pembrolizumab	48/F	HIV/AIDS	6 months	63	No	(+) Improvement in language and cognition, independent in activities of daily living.	(Cortese et al., 2019) 3
Pembrolizumab	69/F	Non-Hodgkin lymphoma	12 months	26,494	No	(-) Clinical deterioration.	(Cortese et al., 2019) 4
Pembrolizumab	31/M	Idiopathic lymphopenia	2 months	5,248	No	(+) Improvement in confusion and increased independence with activities of daily living.	(Cortese et al., 2019) 5
Pembrolizumab	62/F	Idiopathic lymphopenia, common variable immunodeficiency	3 months	28,350	No	(-). Clinical deterioration and became wheelchair bound.	(Cortese et al., 2019) 6
Pembrolizumab	70/M	Hodgkin's lymphoma	2	261	No	(+) Modest improvements in gait and speech.	(Cortese et al., 2019) 7
Pembrolizumab	58/M	HIV/AIDS	12	286	No	(+) Subjective clinical improvement.	(Cortese et al., 2019) 8
Pembrolizumab	42/M	Idiopathic primary immunodeficiency	5 months	38	No	(-) Clinical deterioration.	(Kupper et al., 2019)
Pembrolizumab	38/M	Combined immunodeficiency and Behçet's disease	4 weeks	2,561,955	No	(-) Died 4 weeks after treatment initiation.	(Pawlitcki et al., 2019)
Pembrolizumab	Unknown /M	Variable immunodeficiency and diffuse B cell lymphoma.	10 weeks	119,000	Yes	(+) Speech recovery but ongoing psychomotor slowing, aphasia and disorientation	(Rauer et al., 2019)
Nivolumab	53/M	Silicosis	12 weeks	Not detected	No	(++) Stabilised aphasia and regression of motor deficit.	(Audemard-Verger et al., 2019)
Nivolumab	65/F	Hodgkin's Lymphoma	0 days	Not detected	Yes	(++) Clinical function improved.	(Hoang et al., 2019)
Nivolumab	81	Kidney transplant	<6 weeks	3,162	No	(-) Death 6 weeks after diagnosis.	(Medrano et al., 2019) 1
Nivolumab	77	Kidney transplant	<6 weeks	794	No	(-) Death 6 weeks after diagnosis.	(Medrano et al., 2019) 2
Nivolumab	67	Kidney transplant	<6 weeks	794	No	(-) Death 4 weeks after diagnosis.	(Medrano et al., 2019) 3
Nivolumab	47/F	Acute myeloid leukaemia after allo-stem cell transplantation	4 weeks	47,377	No	(++). Complete recovery from motor deficit. Visual symptoms stabilised.	(Uzunov et al., 2019)
Nivolumab	60/F	Idiopathic primary immunodeficiency	8 weeks	200,000	Yes	(++) Improved focal deficits and alertness.	(Walter et al., 2019)

Key: (-) unfavorable outcome; (+) mild improvement; (++) marked improvement and (=) no change. IRIS = immune reconstitution inflammatory syndrome. F = female and M = male.