RESEARCH ARTICLE

Neurologic Outcomes in People With Multiple Sclerosis Treated With Immune Checkpoint Inhibitors for Oncologic Indications

Carson M. Quinn, MD,* Prashanth Rajarajan, MD, PhD,* Alexander J. Gill, MD, PhD, Hannah Kopinsky, MD, Andrew B. Wolf, MD, Celeste Soares de Camargo, MD, Jessica Lamb, MS, Tamar E. Bacon, BA, Joseph C. Murray, MD, PhD, John C. Probasco, MD, Kristin M. Galetta, MD, Daniel Kantor, MD, Patricia Coyle, MD, Vikram Bhise, MD, Enrique Alvarez, MD, PhD, Sarah E. Conway, MD, Shamik Bhattacharyya, MD, MS, and Ilya Kister, MD

Correspondence
Dr. Kister
ilya.kister@nyulangone.org

Neurology® 2024;103:e210003. doi:10.1212/WNL.0000000000210003

Abstract

Background and Objectives

Immune checkpoint inhibitors (ICIs) are increasingly used against various cancers but are associated with immune-related adverse events (irAEs). Risk of irAEs may be higher in patients with certain preexisting autoimmune diseases, and these patients may also experience exacerbation of the underlying autoimmune disease following ICI initiation. People with multiple sclerosis (MS) have mostly been excluded from clinical trials of ICIs, so data on the safety of ICIs in MS are limited. This study aims to assess the rate of MS activity, as well as neurologic and nonneurologic irAEs in persons with MS treated with ICIs for cancer.

Methods

Participating sites were invited to this retrospective observational study through the Medical Partnership 4 MS+ listserv. Seven large academic centers participated in the study, each conducting a systematic search of their electronic medical record system for patients with MS and history of ICI treatment. The participating neurologist reviewed each chart individually to ensure the inclusion criteria were met. Demographics and data on MS and cancer history, treatments, and outcomes were abstracted from patient charts using a structured instrument.

Results

We identified 66 people with MS (median age 66 years, 73% female, 68% not on disease-modifying therapy for MS) who were treated with ICIs for lung cancer (35%), melanoma (21%), or another oncologic indication. During post-ICI follow-up (median: 11.7 months, range 0.2–106.3 months), 2 patients (3%) had relapse or MRI activity, 3 (5%) had neurologic irAEs, and 21 (32%) had nonneurologic irAEs. At the last follow-up, 25 (38%) participants had partial or complete remission of their cancer, while 35 (53%) were deceased.

Discussion

In this multi-institutional systematic retrospective study of predominantly older patients with MS, most of whom were not on disease-modifying therapy, MS activity and neurologic irAEs following ICI treatment were rare. These data suggest that preexisting MS should not preclude the use of ICIs for cancer in older patients, but the results may not be generalizable to younger patients with active MS. Prospective studies of ICI safety that enroll younger patients with MS are needed.

MORE ONLINE

CME Course
NPub.org/cmelist

*These authors contributed equally to this work as co-first authors.

From the Department of Neurology (C.M.Q., P.R., S.E.C., S.B.), Brigham and Women's Hospital, Boston, MA; Department of Neurology (A.J.G., J.C.P.), Johns Hopkins University School of Medicine, Baltimore, MD; Department of Neurology (H.K., T.E.B., I.K.), NYU Grossman School of Medicine, New York; Department of Neurology (A.B.W., E.A.), University of Colorado School of Medicine, Aurora; Department of Neurology (C.S.d.C., V.B.), Rutgers–Robert Wood Johnson Medical School, New Brunswick, NJ; Department of Neurology (J.L., P.C.), Stony Brook University Medical Center, NY; Sidney Kimmel Comprehensive Cancer Center (J.C.M.), Johns Hopkins University School of Medicine, Baltimore, MD; Department of Neurology (K.M.G.), Stanford University, CA; Medical Partnership 4 MS+ (MP4MS+) (D.K.), LaBelle, FL

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

DMT = disease-modifying therapy; **EMR** = electronic medical record; **ICI** = immune checkpoint inhibitor; **irAE** = immune-related adverse event; **MG** = myasthenia gravis; **MOGAD** = myelin oligodendrocyte glycoprotein antibody disease; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disease; **PD-1** = programmed cell death protein 1; **pwMS** = people with MS.

Introduction

Immune checkpoint inhibitors (ICIs) are increasingly used for a variety of cancers.[1] ICIs enhance the host antitumor immune response by blocking "immune checkpoints"—T-cell expressed programmed cell death protein 1 (PD-1), PD-1 ligand (PD-L1), and cytotoxic T-lymphocyte antigen 4. A well-recognized side effect of immune upregulation is the development of off-target autoimmunity, termed immune-related adverse events (irAEs). It is estimated that 5% of irAEs involve the nervous system. These neurologic irAEs—henceforth "neuro-irAEs"—manifest as meningitis, encephalitis, myasthenia gravis (MG), myositis, Guillain-Barre Syndrome, or peripheral neuropathies.[2,3]

Patients with systemic autoimmune diseases who develop cancer and receive ICIs have increased rates of irAEs and may experience worsening of their autoimmune disease.[4] Because typical multiple sclerosis (MS) syndromes, such as optic neuritis, transverse myelitis, and tumefactive demyelinating lesions, have been reported as neuro-irAEs of ICI therapy, there is concern that the risk of these events would be increased in patients with preexisting MS who receive ICI.[3,5] For this reason, people with MS (pwMS) were excluded from the major ICI trials. Thus, the safety profile of ICI in MS is not well-characterized.[6]

Early case reports of pwMS receiving ICIs raised concerns about the risk of disease activity. Of the first 10 published cases of pwMS receiving ICIs for cancer treatment, 60% reported "MS relapses" after an average of 13.6 weeks, with symptoms of weakness, ataxia, optic neuritis, and brainstem syndromes.[7] However, only 2 of these 6 patients had poor neurologic outcomes, and in these 2 patients with poor outcomes, it was unclear if neurologic worsening was due to MS or other factors such as CNS radiation or neuro-irAEs. Moreover, it is well recognized that case reports are biased toward worse outcomes, leading to overestimates of the risk of adverse events.[6] More recently, small retrospective case series have documented a modest risk of MS activity with ICI treatment, and in some cases, MS reactivation may have resulted from stopping disease-modifying therapies (DMTs) associated with disease rebound ("antitrafficking therapies").[8–10] Reassuringly, pwMS also do not seem to have increased rates of irAEs, in contrast to what has been reported for other systemic autoimmune diseases.[7,11]

The aim of this study was to systematically assess the rate of MS activity as well as of neurologic and nonneurologic irAEs in all ICI-treated pwMS from 7 large academic centers across the United States.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Investigators from each institution obtained ethical approval from their respective institutional review boards to contribute data to this study. Since only deidentified retrospective clinical data were used, patient consent to participate in this study was not required by the respective institutional review boards. No funding was provided for the study.

Patients

Participating sites were identified through the Medical Partnership 4 MS+ (MP4MS+) network, a platform for advocacy, clinical, and nonindustry-funded research collaborations comprised of more than 1,300 neurologists who treat pwMS. Investigators from the following institutions participated in the study: Mass General Brigham (Boston, MA), University of Colorado School of Medicine (Aurora, CO), Johns Hopkins Medicine (Baltimore, MD), Stanford University Medical Center (Palo Alto, CA), New York University Grossman School of Medicine (New York, NY), Stony Brook Medical Center (Stony Brook, NY), and Robert Wood Johnson Medical—Rutgers (Newark, NJ). Many of the patients from the Boston site were also included in a previously published single-institution series.[10] To reduce bias in patient selection, investigators at each site identified patients through institution-wide searches of the respective electronic medical record (EMR) system using site-specific query tools. Each site bulk queried for patients in a nonhierarchical fashion whose medical records contained ICD-10 diagnosis codes for MS (G35) and documented administration of any of the following FDA-approved ICIs: pembrolizumab, nivolumab, ipilimumab, atezolizumab, cemiplimab, durvalumab, and avelumab. The start date for each site's search depended mainly on when EMRs were introduced in the respective center, while the end date for all was Fall 2023. There was no predetermined study size because we wished to include as many patients as met criteria.

We included all patients with a diagnosis of MS (confirmed by a neuroimmunologist at each site based on the 2017 McDonald criteria[12]) at the time of ICI treatment and who received at least 1 dose of an FDA-approved ICI for the

Table 1 Baseline Characteristics at Initiation of Immune Checkpoint Inhibitor Therapy

	Count (%)/median (range)
Female	48 (72.7)
Age (y)	66.2 (28.7–80.0)
MS disease duration (y)	20.8 (3.2–57.4)
Time since last MS activity[a](y)	9.0 (1.0–36.1)
Progressive MS (primary or secondary)	10 (15.2)
MS DMT within 1 y	
No DMT	41 (62.1)
Glatiramer acetate	8 (12.3)
Interferon beta-1a	5 (7.7)
Dimethyl fumarate	4 (6.1)
Rituximab	3 (4.5)
Fingolimod	3 (4.5)
Natalizumab	2 (3.0)
Time since last received MS DMT (y)	3.62 (0.2–20.4)
Timing of DMT discontinuation relative to cancer/ICI	
Remote to cancer diagnosis or never started	32 (48.5)
At cancer diagnosis	16 (24.2)
Between cancer diagnosis and ICI initiation	2 (3.0)
At ICI initiation	4 (6.1)
Not discontinued	12 (18.2)
Patients with MRI within 6 mo before ICI initiation	
Brain	38 (57.6)
Spine	9 (13.6)
Functional status at ICI initiation	
Ambulatory without support	40 (60.6)
Ambulatory with support (cane, walker)	19 (28.8)
Wheelchair or bed bound	7 (10.6)
Primary malignancy	
Lung	23 (34.8)
Melanoma	14 (21.2)
Squamous cell	5 (7.6)
Renal cell	4 (6.1)
Urothelial	4 (6.1)
Breast	3 (4.5)
Other	13 (19.7)
Cancer staging	
Nodal involvement without distant metastasis	4 (6.1)
Metastatic	61 (92.4)
CNS involvement of cancer (n = 62)[b]	14 (22.6)

Abbreviations: DMT = disease-modifying therapy; ICI = immune checkpoint inhibitor; MS = multiple sclerosis.
[a] Clinical relapse or new MRI lesions.
[b] Total number after removal of patients without sufficient data for given characteristic.

treatment of cancer. Patients with neuromyelitis optica spectrum disease (NMOSD), myelin oligodendrocyte glycoprotein antibody disease (MOGAD), radiographically isolated syndrome, clinically isolated syndrome, and those who developed MS after ICI start were excluded. There was no required minimum duration of post-ICI follow-up.

Data Collection and Analysis

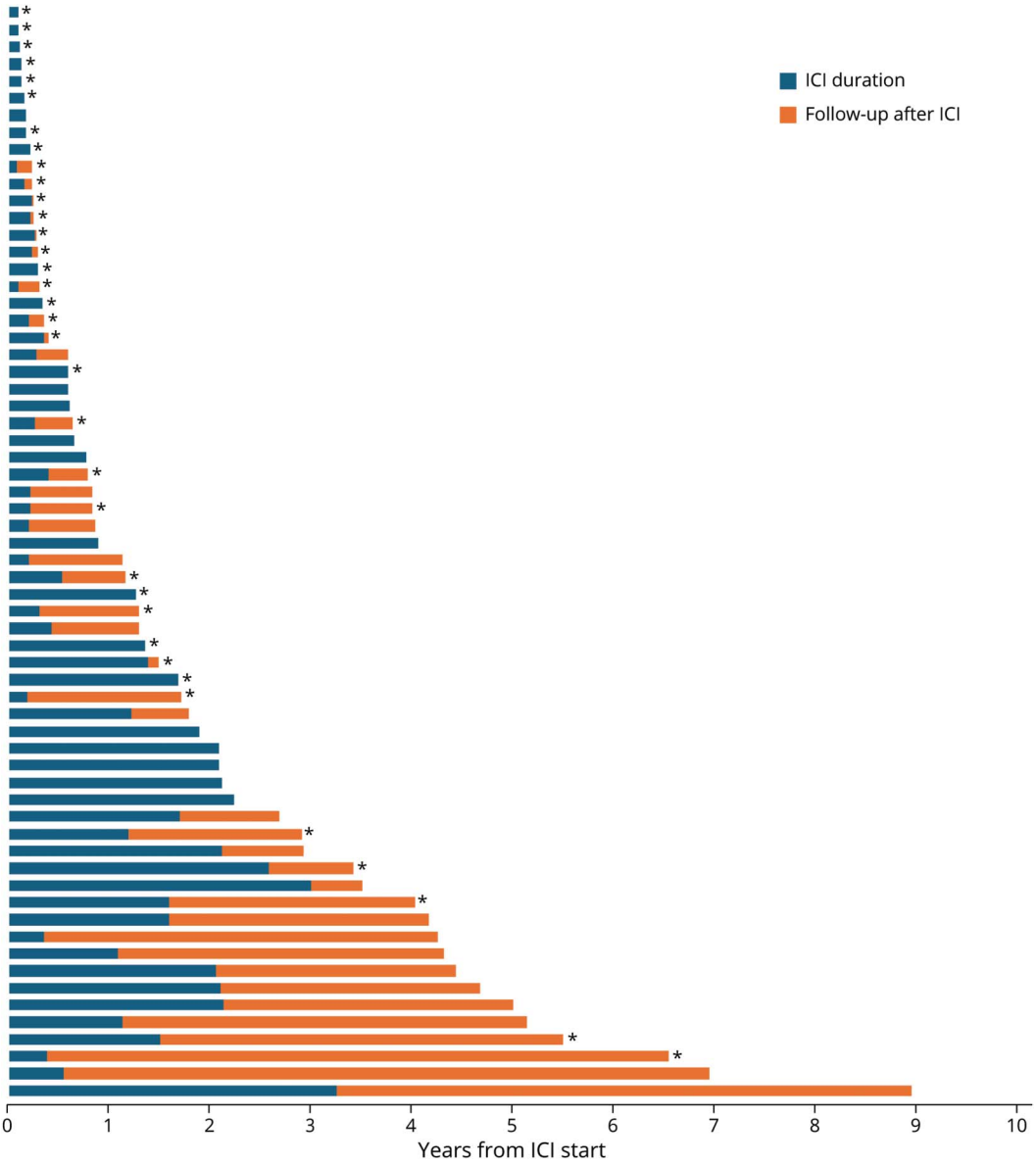
Demographic and relevant clinical, laboratory, and radiologic data were extracted for each patient from the EMR using

Table 2 Cancer Treatment and Oncologic Outcomes

	Count (%)/median (range)
Chemotherapy within 1 y of ICI	51 (77.3)
Cerebral radiation therapy	14 (21.2)
ICI exposure[a]	
Pembrolizumab	42 (63.6)
Nivolumab	23 (34.8)
Ipilimumab	9 (13.6)
Atezolizumab	6 (9.1)
Cemiplimab	2 (3.0)
Durvalumab	2 (3.0)
Avelumab	1 (1.5)
Receipt of 2 or more ICIs	15 (22.7)
Receipt of 3 or more ICIs	3 (4.5)
Duration of ICI therapy (mo)	6.4 (1.0–38.9)
Interval between ICI initiation and last follow-up (mo)	11.7 (0.2–106.3)
Cancer remission, partial or full	25 (37.9)

Abbreviation: ICI = immune checkpoint inhibitor.
[a] Some patients were treated with more than 1 ICI.

Figure 1 ICI Treatment Duration and Follow-Up

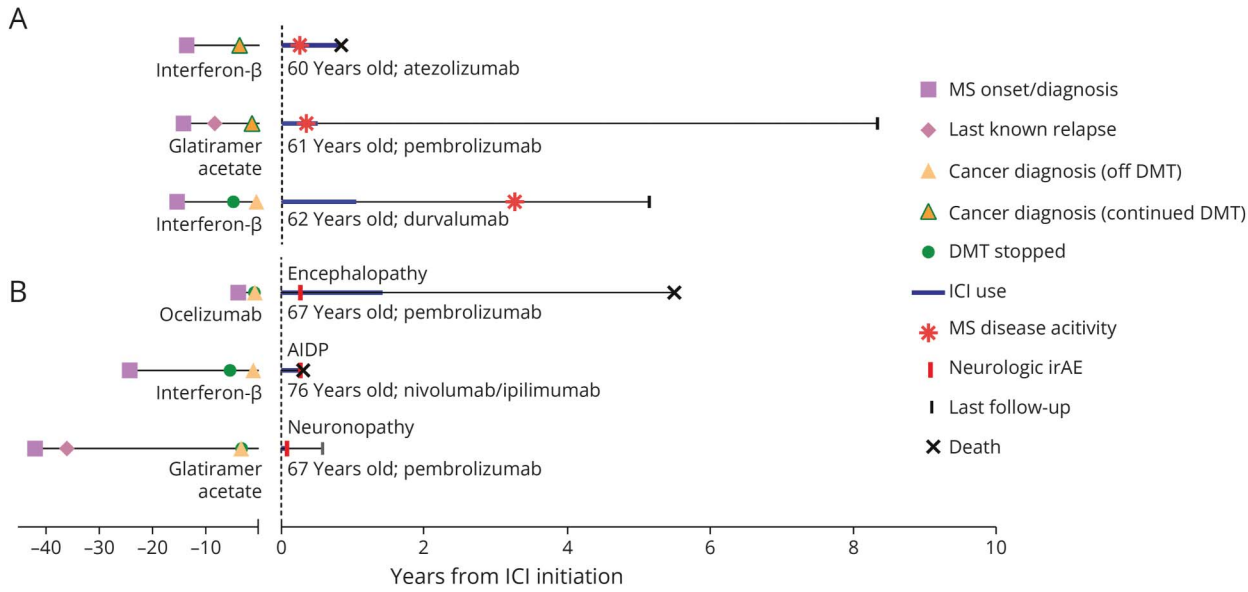


	N	ICI duration in years (median)	Follow-up duration in years (median)
Alive at last follow-up	31	1.09	2.11
Deceased	35	0.24	0.34

A swimmer plot depicting ICI treatment duration (blue) and subsequent follow-up time (orange) in years for each patient. Patients who were deceased at the time of last follow-up are marked with an asterisk (*). In total, of the 31 patients alive at last follow-up, there was a median follow-up of 2.11 years, and of the 35 deceased at last follow-up, there was a median follow-up duration of 0.34 years. ICI = immune checkpoint inhibitor.

a comprehensive, structured instrument (eTable 1) by the investigator at the respective site. All available data in the local EMR were reviewed, with special attention to neurology notes, oncology notes, and emergency or inpatient visits. Radiographic data were collected wherever available; however, patients were not excluded if MRIs had not been completed after ICI initiation. The key outcomes assessed were MS disease activity, neuro-irAEs, nonneurologic irAEs following ICI initiation, and cancer treatment outcomes (including cancer remission, death, and functional status at the last follow-up). "MS disease activity" was defined as clinical relapse or new MRI lesions that could not be better attributed by a study investigator to CNS metastases or an alternative neuro-irAE. MS activity was considered "related to ICI treatment" if it occurred within 1 year of the last ICI dose. In cases where a variable was unable to be abstracted from a patient's clinical chart, the value was excluded from the denominator of that given variable, and those variables whose denominators differed from the total

Figure 2 MS Disease Activity and Neurologic irAEs Clinical Timeline



Timeline in years of patients with (A) MS disease activity and (B) neurologic irAEs within 1 year ICI treatment. Of note, a third patient with MS disease activity post-ICI treatment is depicted, although this activity was more than 1 year after cessation of ICI therapy. ICI = immune checkpoint inhibitor.

sample size were noted in the table. Data were summarized with counts and percentages or medians with ranges for non-normal distributions. Quantitative data were either described continuously or grouped based on logical, clinically meaningful categories, for example, time of DMT discontinuation in categories based on clinical events. A subgroup analysis was performed on younger pwMS, where an age cutoff of 50 years was chosen before analysis of data. We used STROBE cross-sectional reporting guidelines.[13]

Data Availability

Anonymized data can be made available on reasonable request from any qualified investigator.

Results

Initial database searches identified 81 potentially eligible patients, 15 of whom were excluded for not having a diagnosis of MS on a manual chart review. We identified as our cohort 66 patients (73% female) with a preexisting MS diagnosis who received at least 1 dose of ICI. Details of the demographic and disease-related characteristics are summarized in Table 1. Patients' treatment histories are summarized in Table 2, and further details of cancer staging are summarized in eTable 2. The median age at ICI initiation was 66.2 years (range 28.7–80.0 years). Most patients (80.4%) had no MS activity for ≥5 years, and 62.1% were off DMT within 1 year of ICI initiation. Ten patients (15.2%) carried a diagnosis of progressive MS (primary or secondary). For a pre-ICI baseline, 38 (57.6%) and 9 (13.6%) patients had brain and spine MRIs, respectively, within 6 months before ICI initiation. None of these MRIs reported active MS lesions.

Most patients (77%) received a single ICI, while 23% were on combination ICI therapy. It is important that 77% of patients were on cytotoxic chemotherapy at the time of ICI initiation and 21% had received cerebral radiation. The median duration of ICI treatment was 6.4 months (range: 1–39 months), with 17% of patients receiving only a single cycle of ICI. The median post-ICI follow-up was 11.7 months. For the deceased patients (n = 35), the follow-up was, as expected, much shorter (median follow-up: 4 months) compared with those who were alive at the last follow-up (n = 31, median follow-up: 24 months). The follow-up for each patient is shown in Figure 1. It should be noted that a minority of patients (n = 26, 39.4%) did not undergo MRI of any part of neuroaxis during post-ICI follow-up.

Any MS disease activity within 1 year of ICI start was recorded for only 2 patients (3%). One patient was a 61-year-old man without MS activity for 8 years, who was on glatiramer acetate at the time of starting ICI. He experienced a mild clinical relapse consisting of worsening gait with 3 small enhancing MRI lesions in the parietal white matter, which were new compared with an MRI 2 months before starting pembrolizumab. His gait returned to baseline following a short course of corticosteroids. The second patient was a 60-year-old woman, without MS activity for 8 years who was on interferon beta-1a at the time of ICI treatment. She developed 2 small asymptomatic T2 hyperintense lesions on the MRI brain 4 months after starting atezolizumab, which were new compared with brain MRI done 1 year before ICI initiation. One additional patient had radiographic MS disease activity more than 2 years after cessation of durvalumab, which was deemed unrelated to ICI as preceding MRI approximately

Table 3 Outcomes—Adverse Events After ICI Therapy

	Count (%)/median (range)
MS activity post-ICI	2 (3.0)
Neuro irAE	3 (4.5)
Encephalitis	1 (1.5)
AIDP	1 (1.5)
Sensory neuronopathy	1 (1.5)
Nonneuro irAE	21 (31.8)
Colitis	8 (12.1)
Pneumonitis	7 (10.6)
Hepatitis	4 (6.1)
Adrenal insufficiency	2 (3.0)
Nephritis	2 (3.0)
Dermatitis	2 (3.0)
Hypothyroidism	1 (1.5)
Ototoxicity	1 (1.5)
Pancreatitis	1 (1.5)
Tenosynovitis	1 (1.5)
Status at last follow-up (n = 63)[a]	
Ambulatory without support	15 (23.8)
Ambulatory with support (assist, cane, walker)	11 (17.5)
Wheelchair/bed bound	2 (3.2)
Deceased	35 (53.0)

Abbreviations: ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; MS = multiple sclerosis.
[a] Total n after removal of patients without sufficient data for given characteristic.

1 year after starting ICI had been stable. Detailed timelines for the 3 cases with MS activity are shown in Figure 2A, and outcomes after ICI therapy are summarized in Table 3.

As younger patients are at higher risk of MS relapses, we conducted a subanalysis of patients in our series who were 50 years or younger at the time of ICI start. We identified 6 such patients, but these patients too had inactive MS, with a median of 5.3 years (range 2.3–8.3 years) between the last clinical or radiologic MS activity and ICI start. None of the 6 patients were on DMT at the time of ICI start, although 3 had only recently discontinued treatment with interferon beta-1a, rituximab, and ocrelizumab. None of the 6 experienced MS activity or neuro-irAEs during post-ICI follow-up.

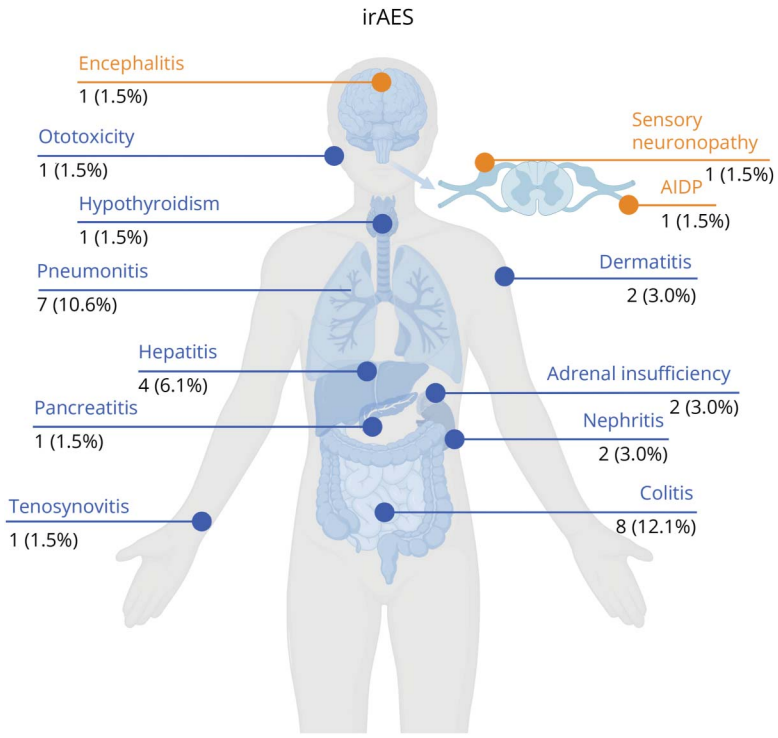
Three patients had neuro-irAEs. The first patient was a 76-year-old man who stopped interferon beta-1a 5 years before starting pembrolizumab. His ICI was switched to ipilimumab and nivolumab due to progression of disease, and 2 weeks later, he developed progressive weakness and areflexia. A lumbar puncture revealed albuminocytologic dissociation consistent with Guillain-Barré syndrome. Ganglioside and paraneoplastic antibody panels were negative. He was treated with 5 days of intravenous immunoglobulin and 3 days of high-dose IV solumedrol but ultimately died of respiratory failure. The second patient was a 67-year-old man whose last dose of ocrelizumab was 8 months before starting ICI. One month following ICI start, he developed encephalopathy and seizure, which his treating physician diagnosed as ICI-related encephalitis. Encephalopathy resolved after discontinuation of pembrolizumab. The third patient was a 67-year-old woman who stopped glatiramer acetate 3 years before ICI initiation. One week after the first dose of pembrolizumab she developed severe burning pain from her feet to her knees. Examination was felt consistent with neuronopathy. MRI of the brain, cervical spine, and thoracic spine did not show new lesion; the nerve conduction study was not performed. She received high-dose IV solumedrol for 3 days followed by an oral steroid taper with marked improvement in her symptoms. The timelines for these 3 patients are shown in Figure 2B. Nonneurologic irAEs were reported for 21 patients (32%); the most common were colitis, pneumonitis, and hepatitis (Figure 3).

As of the last follow-up, 38% of patients had complete or partial cancer remission, 53% were deceased, and the remainder either did not achieve remission or were missing data. Of the 35 patients who were alive at the last follow-up, 17 (48%) were ambulatory without assistance.

Discussion

In our multicenter case series of 66 pwMS who received ICIs for cancer, MS activity was observed in only 3% of patients. This rate is similar to what would be expected in inactive patients with MS of similar age who are not on ICI therapy.[14] We did not observe any patient with "disease rebound" (disease activity out of proportion to what has been observed before ICI). On the contrary, both MS events in our series were mild—one patient had asymptomatic MRI lesions and the other had MRI lesions with transient gait impairment responsive to corticosteroids. In a recently published series from France, the MS activity rate was numerically higher—in 3 of 18 patients (17%)—than in our series; however, their patients were younger (median 48 vs 66 years in our series), and MS activity in 2 of the 3 patients in the French series occurred in the setting of discontinuation of natalizumab, a high-efficacy MS DMT associated with rebound of MS activity.[7,8,15] Thus, post-ICI relapses in the French series could be related to stopping antitrafficking DMT rather than to the initiation of ICI. In our series, only 5 patients stopped antitrafficking agents (fingolimod and natalizumab) in the preceding year, but neither experienced any MS activity. A small, single-center series of 7 patients from UCSF reported

Figure 3 Immune-Related Adverse Events (irAEs) in People With MS



Schematic depicting all neurologic (orange) and non-neurologic (blue) irAEs observed in this cohort of people with MS exposed to ICI therapy. Numbers beneath irAE type depict the number (percentage) of patients with each ICI-associated condition. Created with Biorender.com. AIDP = acute inflammatory demyelinating polyneuropathy; ICI = immune checkpoint inhibitor.

no relapses and 2 cases of asymptomatic radiographic activity.[9] Taken together with our data, the 3 case series that examined MS activity after ICI therapy comprise a total of 91 pwMS of whom 2 (2.2%) had clinical relapses and 5 (5.5%) had asymptomatic MRI activity.[8,9]

It is important that we examined not only MS activity but also rates of neurologic and nonneurologic irAEs in our patients. We found that the rate of neuro-irAEs (5%) was similar to non-MS patients receiving ICI in the clinical trials and consistent with a prior series.[3] The rate of nonneurologic irAE was 31.8% in our patients, which is within the range of what is expected in patients treated with ICIs.[4] Cancer remission was achieved in a minority of our patients (38%), while the majority were deceased at the last follow-up (53%), reflective of the advanced stage of malignancies at the time of ICI initiation. Whether preexisting MS had delayed time to ICI initiation and whether earlier ICI use could have improved outcomes cannot be determined with our data but warrants further investigation.

It is unknown why some autoimmune diseases predispose patients to exacerbation of preexisting disease, whereas MS does not.[4] Perhaps a higher degree of immune dysregulation in systemic autoimmune disorders compared with MS predisposes the former to ICI-related immune complications and to non-ICI–related immune diseases.[16] However, this is unlikely to be the only reason because patients with purely neurologic autoimmune diseases, such as MG, seem to be at high risk for ICI-related MG relapse.[17] At present, despite considerable efforts to identify biomarkers that would predict irAEs after ICI, no biomarker has been validated for clinical use.[18] Better understanding of the immunopathogenesis of irAEs may lead to the development of reliable biomarkers of treatment-emergent autoimmunity that would make ICIs safer.

Our study has several strengths. The model of using the broad network of MP4MS+ allowed us to identify multiple participating academic institutions across the United States, resulting in the largest series of patients with MS exposed to ICI—more than doubling the total number of cases of ICI in pwMS published to date. All investigators conducted comprehensive EMR searches that included all eligible patients from their institution, which reduces the risk of bias, whereby the more severe outcomes are more likely to be recalled and reported. Our median post-ICI follow-up was approximately 1 year, and 51 (78%) of patients had follow-up for 3 months, which is the period when most irAEs would be expected to occur.

Our study shares the well-known limitations of retrospective design, including missing data, loss to follow-up, and lack of controls.[19] Patients receiving ICI typically have advanced cancer and high morbidity despite aggressive therapy. Thus, patients may not be able to follow-up with their treating neurologist and receive a neurologic examination. Absent such data, we are not able to comment on whether ICI has an

effect on disease progression independent of relapse activity. This question will need to be addressed in future studies, ideally with prospective follow-up and regularly scheduled neurologic examinations. It is also important to note that not all patients had brain MRIs after ICI initiation—39% had no MRI data—and it is possible that asymptomatic lesions may have been missed. However, minor asymptomatic MRI changes do not typically have long-term implications for disability.[20] Finally, because a minority of patients were deceased within 3 months of ICI initiation, which is the window for the emergence of most of the treatment-related irAEs, it is not possible to know what their MS course or risk of neuro-irAEs would have been had they survived and been followed longer.

It is important to emphasize that our patients with advanced malignancies were older relative to the typical, "otherwise healthy" MS clinic population[21]: most patients in this series had inactive MS for many years and were off DMTs. Our conclusions about the lack of MS activity post-ICI may not be generalizable to younger pwMS with more active MS or those who stop antitrafficking DMT (anti-integrin monoclonal antibodies, S1P receptor modulators) that are associated with disease rebound on discontinuation. Larger multicenter cohorts including younger MS patients with more active disease are needed to confirm and extend our findings. Moreover, most patients in our cohort were on prior or concomitant cytotoxic chemotherapy, which may reduce the risk of relapse and potentially offset the tendency to ICI-associated relapses. We are not able to comment on whether ICI would be similarly safe—from an MS standpoint—in pwMS who start ICI before receiving cytotoxic chemotherapy. Finally, it should be emphasized that conclusions about the apparent safety of ICI in MS cannot be extrapolated to other neuroinflammatory conditions with different pathogenesis, such as NMOSD or MOGAD. Efforts are currently underway to explore the safety of ICI in these rare neuroinflammatory disorders, with preliminary evidence pointing to a different risk profile with ICI.[22]

Despite the caveats, our data are reassuring in that older patients with inactive MS could receive ICI treatment for cancer without the risk of MS reactivation. Our findings argue that older pwMS should not be excluded from future clinical trials of ICIs. In younger patients, who may be at higher risk for relapses, it may be prudent to continue MS DMT therapy while on ICI if this does not interfere with oncologic treatment. Special care is necessary to weigh the pros and cons of stopping antitrafficking therapy before ICI, which may lead to disease rebound (independent of ICI treatment). Ideally, pwMS who initiate ICI should be under the care of a multidisciplinary team that includes a neurologist experienced with MS.

Study Funding

The authors report no targeted funding.

Disclosure

C.M. Quinn, P. Rajarajan, A.J. Gill, H. Kopinsky, A.B. Wolf, C.S. de Camargo, J. Lamb, T.E. Bacon, J.C. Murray, J.C. Probasco, K.M. Galetta, P. Coyle, V. Bhise, E. Alvarez, S.E. Conway, S. Bhattacharyya, and I. Kister report no disclosures relevant to the manuscript. D. Kantor reports personal fees from Viatris, an institutional research grant from Bristol Myers Squibb outside the submitted work, and serves as a Co-Medical Director of the CorEvitas MS registry, in partnership with the National MS Society and the Founding President of the Medical Partnership 4 MS+ (MP4MS+). Go to Neurology.org/N for full disclosures.

Publication History

Previously published at medRxiv. doi: 10.1101/2024.06.13.24308608. Received by *Neurology* June 7, 2024. Accepted in final form September 4, 2024. Submitted and externally peer reviewed. The handling editors were Assistant Editor Angela Vidal-Jordana, MD, PhD, and Deputy Editor Bradford Worrall, MD, MSc, FAAN.

Appendix Authors

Name	Location	Contribution
Carson M. Quinn, MD	Department of Neurology, Brigham and Women's Hospital, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Prashanth Rajarajan, MD, PhD	Department of Neurology, Brigham and Women's Hospital, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Alexander J. Gill, MD	Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Hannah Kopinsky, MD	Department of Neurology, NYU Grossman School of Medicine, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Andrew B. Wolf, MD, MD	Department of Neurology, University of Colorado School of Medicine, Aurora	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Celeste Soares de Camargo, MD	Department of Neurology, Rutgers–Robert Wood Johnson Medical School, New Brunswick, NJ	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Jessica Lamb, MS	Department of Neurology, Stony Brook University Medical Center, NY	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Tamar E. Bacon, BA	Department of Neurology, NYU Grossman School of Medicine, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Joseph C. Murray, MD, PhD	Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
John C. Probasco, MD	Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Kristin M. Galetta, MD	Department of Neurology, Stanford University, CA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Daniel Kantor, MD	Medical Partnership 4 MS+ (MP4MS+), LaBelle, MD	Major role in the acquisition of data; study concept or design; analysis or interpretation of data
Patricia Coyle, MD	Department of Neurology, Stony Brook University Medical Center, NY	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Vikram Bhise, MD	Department of Neurology, Rutgers–Robert Wood Johnson Medical School, New Brunswick, NJ	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Enrique Alvarez, MD, PhD	Department of Neurology, University of Colorado School of Medicine, Aurora	Drafting/revision of the manuscript for content, including medical writing for content
Sarah E. Conway, MD	Department of Neurology, Brigham and Women's Hospital, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Shamik Bhattacharyya, MD, MS	Department of Neurology, Brigham and Women's Hospital, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Ilya Kister, MD	Department of Neurology, NYU Grossman School of Medicine, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

References

1. Shiravand Y, Khodadadi F, Kashani SMA, et al. Immune checkpoint inhibitors in cancer therapy. *Curr Oncol.* 2022;29(5):3044-3060. doi:10.3390/curroncol29050247
2. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med.* 2018;378(2):158-168. doi:10.1056/NEJMra1703481
3. Dalakas MC Neurological complications of immune checkpoint inhibitors: what happens when you 'take the brakes off' the immune system. *Ther Adv Neurol Disord.* 2018;11:1756286418799864. doi:10.1177/1756286418799864
4. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. *Ann Intern Med.* 2018;168(2):121-130. doi:10.7326/M17-2073
5. Duong SL, Barbiero FJ, Nowak RJ, Baehring JM. Neurotoxicities associated with immune checkpoint inhibitor therapy. *J Neurooncol.* 2021;152(2):265-277. doi:10.1007/s11060-021-03695-w
6. Tang H, Zhou J, Bai C. The efficacy and safety of immune checkpoint inhibitors in patients with cancer and preexisting autoimmune disease. *Front Oncol.* 2021;11:625872. doi:10.3389/fonc.2021.625872
7. Aoun R, Gratch D, Kaminetzky D, Kister I. Immune checkpoint inhibitors in patients with pre-existing neurologic autoimmune disorders. *Curr Neurol Neurosci Rep.* 2023;23(11):735-750. doi:10.1007/s11910-023-01306-x
8. Androdias G, Noroy L, Psimaras D, et al. Impact of immune checkpoint inhibitors on the course of multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm.* 2024;11(2):e200202. doi:10.1212/NXI.0000000000200202
9. Nylander AN, Rowles W, Poole S, Bove R. Clinical outcomes after use of checkpoint inhibitor immunotherapies in people with multiple sclerosis. *Mult Scler J Exp Transl Clin.* 2024;10(2):20552173241252563. doi:10.1177/20552173241252563
10. Conway SE, Pua DKA, Holroyd KB, Galetta K, Bhattacharyya S. Neurologic disease activity in people with multiple sclerosis treated with immune checkpoint inhibitors. *Mult Scler.* 2023;29(3):471-474. doi:10.1177/13524585221117949
11. Danlos FX, Voisin AL, Dyevre V, et al. Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease. *Eur J Cancer.* 2018;91:21-29. doi:10.1016/j.ejca.2017.12.008
12. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17(2):162-173. doi:10.1016/S1474-4422(17)30470-2
13. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg.* 2014;12(12):1495-1499. doi:10.1016/j.ijsu.2014.07.013
14. Corboy JR, Fox RJ, Kister I, et al. Risk of new disease activity in patients with multiple sclerosis who continue or discontinue disease-modifying therapies (DISCOMS): a multicentre, randomised, single-blind, phase 4, non-inferiority trial. *Lancet Neurol.* 2023;22(7):568-577. doi:10.1016/S1474-4422(23)00154-0
15. Roos I, Malpas C, Leray E, et al. Disease reactivation after cessation of disease-modifying therapy in patients with relapsing-remitting multiple sclerosis. *Neurology.* 2022;99(17):e1926-e1944. doi:10.1212/WNL.0000000000201029
16. Cojocaru M, Cojocaru IM, Silosi I. Multiple autoimmune syndrome. *Maedica(-Burcur).* 2010;5(2):132-134.
17. Snavely A, Pérez-Torres EJ, Weber JS, Sandigursky S, Thawani SP. Immune checkpoint inhibition in patients with inactive pre-existing neuromuscular autoimmune diseases. *J Neurol Sci.* 2022;438:120275. doi:10.1016/j.jns.2022.120275
18. Taylor J, Gandhi A, Gray E, Zaenker P. Checkpoint inhibitor immune-related adverse events: a focused review on autoantibodies and B cells as biomarkers, advancements and future possibilities. *Front Immunol.* 2022;13:991433. doi:10.3389/fimmu.2022.991433
19. Talari K, Goyal M. Retrospective studies–utility and caveats. *J R Coll Physicians Edinb.* 2020;50(4):398-402. doi:10.4997/JRCPE.2020.409
20. Río J, Rovira À, Gasperini C, et al. Treatment response scoring systems to assess long-term prognosis in self-injectable DMTs relapsing-remitting multiple sclerosis patients. *J Neurol.* 2022;269(1):452-459. doi:10.1007/s00415-021-10823-z
21. Kister I, Bacon T, Cutter GR. A longitudinal study of symptom botheration in Multiple Sclerosis. *Mult Scler Relat Disord.* 2020;46:102585. doi:10.1016/j.msard.2020.102585
22. Gill A. *Disease Activity in People Living With MS and NMOSD Exposed to Immune Checkpoint Inhibitors: a Multi-Institutional Study*. In Consortium of Multiple Sclerosis Centers Annual Meeting, Nashville, TN. 2024.