

Supplementary Table 1: Cases of immune checkpoint inhibitor related encephalitis and encephalopathy^{4,9-15}

Case	Age (yrs)/ Sex	Cancer type	ICI therapy	Signs and symptoms	Time from start of ICI to symptoms	MRI Brain Findings	Basic CSF studies	Other relevant studies	Immunosuppressive therapy	Symptoms resolved? Time from steroids to symptom resolution	Tumor status
1 ⁹	60's / M	Metastatic small cell lung cancer	Nivolumab 1 mg/kg, Ipilimumab 3 mg/kg concomitantly (1 dose)	difficulty ambulating, dizziness, disorientation, memory loss, paresthesias, lethargy, poor recall, intention tremor, hyper-reflexia, ataxia	4 days	T2 hyper-intensities in right mesial temporal lobe	WBC 18/μL (89% lymphocytes, 11% monocytes), protein 98 mg/dL, normal glucose	Positive serum anti-glial nuclear antibody Matched oligoclonal bands in CSF and serum, normal IgG index	Oral prednisone 60 mg/d discharged with slow taper	Yes, 4 weeks	PR
2 ¹⁰	78 / M	Squamous cell lung cancer	Nivolumab 3 mg/kg q2 weeks	apathy, aphasia, absent verbal response, positive Babinski, bilateral upper extremity myoclonus	28 weeks	No acute findings	WBC 16 lymphocytes/μL, protein 103 mg/dL, low glucose	Negative paraneoplastic and autoimmune antibody testing Negative blood and CSF cultures	1.33 mg/kg methylprednisolone with 9 week taper	Yes, 24 hours	PR
3 ¹⁵	66 / M	Metastatic NSCLC	Pembrolizumab 200 mg q3 weeks x 2 cycles	somnolence, confusion, ataxia, expressive dysphasia, cognitive impairment	3.5 weeks	No acute findings	Normal cell count, normal protein, normal glucose	Negative vasculitis screen, acetylcholine receptor antibodies, paraneoplastic and anti-VGKC antibodies	Methylprednisolone IV 1gm/d x 3 d, then 60 mg prednisolone daily weaned by 10 mg weekly	Yes, 3 days	PR
4 ¹³	64 / M	Castration resistant prostate cancer	Ipilimumab 10 mg/kg q3 weeks x 4 cycles, then Ipilimumab q3 months x 3 doses	adynamia, memory disturbance, disorientation, somnolence, agitation, hallucinations, positive Babinski, myoclonic and focal seizures	11 months	No acute findings	Normal cell count, protein 76 mg/L, normal glucose	Negative CSF and serum anti-NMDA, VGKC and onconeural antibodies Negative vasculitis antibodies Elevated anti-TPO and anti-TG	Methylprednisolone IV 1 gm/d x 3 d, then prednisone 100 mg oral, tapered to 60 mg/d, followed by 4 week taper	Yes, 2 weeks	CR
5 ⁴	61 / M	Advanced melanoma	Nivolumab 1 mg/kg IV + Ipilimumab 3 mg/kg (4 doses) then Nivolumab 3 mg/kg (one dose)	progressive altered mental status, unresponsiveness, seizures	18 weeks	Abnormally high FLAIR signal	WBC 14/μL (32% neutrophils, 25% lymphocytes), protein 85 mg/dL, glucose 212 mg/dL	Negative CSF infectious studies	Methylprednisolone 125 mg IV BID x 5 d, then prednisone 75 mg/d and IVIG 1g/kg	Yes, 7 days	Progressive disease
6 ⁴	83 / F	Advanced melanoma	Nivolumab 3 mg/kg q2 weeks x 4 cycles	sudden change in mental status, seizure, lower extremity weakness, hyporeflexia, comatose state	7 weeks	No acute findings	WBC normal, protein 103 mg/dL, glucose normal	Negative CSF bacterial and fungal staining	Continued on home maintenance oral steroids of prednisone 30 mg daily	No, Died 9 days after presentation	Not assessed

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7 ⁴	57 / M	Advanced melanoma	Nivolumab 3 mg/kg IV q2 weeks x 6 cycles, then Ipilimumab 3 mg/kg IV q3 weeks x 4 cycles, then Nivolumab 3 mg/kg q2 weeks x 8 cycles	headache, confusion, inattention, inability to follow complex commands	10 months	No acute findings	WBC 52/μL (lymphocyte predominance)	Negative CSF infectious studies	Methylprednisolone IV followed by prednisone taper over 48 days	Yes, 6 days	Near CR
8 ⁴	58 / F	Advanced melanoma	Ipilimumab x 4 cycles, then 5 months later Nivolumab 3 mg/kg q2 weeks	progressive confusion, aphasia, disorientation	3 weeks	No acute findings	WBC 18/μL (92% lymphocytes)	Negative paraneoplastic and autoimmune antibody testing Negative CSF infectious studies	Methylprednisolone 100 mg IV (1-2 mg/kg) x 6 days (no improvement), dexamethasone 200 mg/d plus 5 d of IVIG 400 mg/kg/d, followed by steroid taper	Yes, 21 days	Progressive disease
9 ⁴	53 / F	Advanced melanoma	Nivolumab 1 mg/kg plus Ipilimumab 3 mg/kg q3 weeks x 2 cycles	slurred speech, aphasia, agitation, inability to ambulate, dizziness	7 weeks	No acute findings	Lymphocytosis (86% lymphocytes), protein 312 mg/dL, glucose 43 mg/dL	Extensive negative infectious work up Negative CSF cultures and serologies	Dexamethasone IV 10 mg q6 hours	Yes, 5 days	Progressive disease
10 ⁹	50's / F	Advanced melanoma	Nivolumab 1 mg/kg, IPI 3 mg/kg concomitantly (1 dose)	syncope, memory loss, unresponsiveness, gait disturbance, dysautonomia, disorientation, bradykinesia, hyper-reflexia	2 weeks	No acute findings	WBC 8/μL (100% lymphocytes), normal protein, normal glucose	Positive CSF IgG NMDAR antibodies Negative CSF HSV PCR and cytology Matched oligoclonal bands in CSF and serum, normal IgG index	Methylprednisolone IV 1gm/d x 5 d then IVIG 0.4 mg/kg/d x 5 d (no improvement); rituximab 1 gm x 2 doses	Yes, 4 weeks of gradual improvement after starting rituximab	PR
11 ¹¹	41 / M	Advanced melanoma	Ipilimumab 10 mg/kg q3 weeks x 3 cycles	expressive aphasia, decreased motor dexterity, gait ataxia	8.5 weeks	T2 FLAIR hyper-intensity & restricted diffusion of posterior splenium	WBC 125/μL (lymphocyte predominance), minimally elevated protein	Negative anti-DNA, ANA, RF CSF absent oligoclonal bands Negative CSF cytology	Prednisone 30 mg/d x 3 d (no response), increased to 1 mg/kg; methylprednisolone 2mg/kg IV x 5 d after peripheral neuropathy and neurogenic bladder developed; prednisone 1 mg/kg taper	Yes, 8 weeks	Near PR

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12 ¹²	71 / M	Advanced melanoma	Ipilimumab 3 mg/kg q3 weeks x 2 cycles	fatigue, headache, confusion, myoclonic jerks, slow mentation, aphasia, intention tremor, postural tremor, lower extremity dysmetria, ataxia	11 weeks	No acute findings	Normal cell count, protein 137 mg/dL	Negative anti-NMDA Low cortisol, TSH, FT4, testosterone, LH Negative CSF cultures, viral and bacterial PCRs negative	(Hydrocortisone 50 mg/d at home for prior diagnosis of hypophysitis), switched to methylprednisolone IV 1 gm/d x 3 d, followed by 4 week methylprednisolone taper	Yes , 24 hours	Not reported
13 ¹⁴	64 / M	Advanced melanoma	Pembrolizumab x 12 months, skipped 1 month, then resumed x 1 month	slowly progressive memory decline, obsessive over certain tasks	Gradual decline since treatment initiation	Bilateral T2 signal change of limbic structures; hippocampal atrophy	Lymphocytosis, elevated protein	Negative paraneoplastic panel, CSF viral PCRs, bacterial cultures Normal vitamin B12, folate, HIV, syphilis screen	Methylprednisolone IV followed by oral prednisolone taper	No, but steroids helped prevent further decline	Not reported
Our case	20 / M	Primary refractory Hodgkin's lymphoma	Nivolumab 3 mg/kg q2 weeks x 3 cycles	bilateral headache, diplopia, nausea, vomiting, ataxia, dysmetria	6 weeks	T2 hyper-intensities in cerebellum, cerebellar edema	WBC 31/μL (94% lymphocytes, 6% monocytes), protein 161 mg/dL, glucose 73 mg/dL.	Negative CSF cultures and gram stain, HSV PCR, Cryptococcal antigen	Dexamethasone IV 8 mg q6 hours x 6 d followed by 4 week taper	Yes, 6 days	PR

Abbreviations

CR: Complete remission
CSF: cerebrospinal fluid
d: day(s)
dL: deciliters
EEG: electroencephalogram
F: female
FLAIR: fluid-attenuated inversion recovery
FT4: free thyroxine
HIV: human immunodeficiency virus
HSV: herpes simplex virus
ICI: immune checkpoint inhibitor
IV: intravenous
LH: luteinizing hormone
M: male
mg: milligrams
MRI: magnetic resonance imaging
NMDA: N-methyl-D-aspartate
NMDAR: N-methyl-D-aspartate receptor
NSCLC: non-small cell lung cancer
PCR: polymerase chain reaction
PR: Partial response
q: every
TG: thyroglobulin
TPO: thyroid peroxidase

TSH: thyroid stimulating hormone
VGKC: voltage gated potassium channel
WBC: white blood cell
yrs: years
 μL : microliters