

eTable 1. Oncological treatments other than ICI among Hu-Ab n-irAEs and Hu-Ab PNS with neurological onset after cancer diagnosis from the study center.

	Hu-Ab n-irAEs (n=11)	Hu-Ab PNS with neurological onset after cancer diagnosis (n=10)	p
Chemotherapy, n (%)	10 (91)	8 (80)	0.59
Before ICI*	2 (18)	-	
Concomitant with ICI*	9 (82)	-	
Etoposide	10 (91)	7 (70)	0.31
Carboplatin	6 (55)	6 (60)	1
Cisplatin	4 (36)	4 (40)	1
Other	0 (0)	1 (0) **	0.48
Radiotherapy, n (%)	1 (9)	4 (40)	0.15
Thoracic	0 (0)	3 (30)	0.09
Cranial	1 (9)	1 (10)	1
Surgery, n (%)	1 (9)		
Primary tumor	0 (0)	5 (50)	0.01
Brain metastasis	1 (9)	0 (0)	1

In 82/92 Hu-Ab PNS patients (89%) the PNS antedated the diagnosis of cancer, therefore oncological treatments before neurological symptoms could be compared only with Hu-Ab PNS with onset of neurological symptoms after cancer (10/92, 11%); in this subgroup, cancer types included small cell lung cancer (n=5: extensive stage, n=3, limited stage, n=2), lung adenocarcinoma (n=1), lung carcinoid (n=1), neuroendocrine prostate cancer (n=1), ganglioneuroblastoma (n=1), and cervical squamous cell carcinoma (n=1).

*1 patient received chemotherapy before ICI and concomitant with ICI.

**irinotecan, temozolomide, cyclophosphamide.

eTable 2. Literature review series: demographic characteristics, clinical and paraclinical findings, treatment, and outcome.

Ref.	Sex, age (y)	Cancer (stage)	ICI (n° of cycles prior to nirAE onset)	Clinical syndrome	MRI findings	NCS	CSF (white cells per mm ³ / protein (g/l) / OCB)	Treatment	Treatment response	Final outcome (FU months)
Papadopoulos et al. 2017 ¹⁷	M / 46	Myxoid chondrosarcoma (IV)	Cemiplimab (4)	Anxiety, depression, memory deficits (onset); altered consciousness, dysarthria, weakness (peak)	FLAIR bilateral MTL hyperintensity	-	17 / 0.38 / NA	CCS, IVIG, RTX	Partial improvement	Death due to severe pneumonia (11 months)
Raskin et al. 2017 ¹⁸	58 / M	NSCLC (IV)	Nivolumab (17)	Right arm myoclonus, mild dysarthria and apraxia, recurrent dysphasia	FLAIR hyperintensity involving left insula and subcortical white matter, (onset), completely disappeared after 5 weeks; FLAIR hypersignal involving left insula and thalamus (relapse)	-	63 / 0.74 / +	CCS	Complete improvement	Two relapses, but complete neurological improvement (>15 weeks)
Hottinger et al. 2018 ¹⁹	71 / F	SCLC (IV)	Nivolumab + ipilimumab (1)	Altered mental status, memory deficits, dysexecutive disorder, alexia, agraphia	FLAIR bilateral MTL hyperintensity with CE	-	16 / 1.145 / NA	CCS, NTZ	Partial improvement	Moderate disability (>2 months)
Matsuo et al. 2018 ²⁰	60 / M	Lung pleomorphic carcinoma (IV)	Nivolumab (3)	Daytime drowsiness, memory deficits (onset), four limbs weakness, loss of consciousness and respiratory arrest (peak)	FLAIR hyperintensity involving bilateral MTL, thalamus, cerebral aqueduct, and spinal cord	-	16 / 1.62 / +	CCS, PEX	No improvement	Death due to cancer progression (6 months)
Gill et al. 2019 ²¹	68 / F	Merkel cell carcinoma of the breast (lymph node)	Nivolumab (1)	SNN (+ altered mental status, nystagmus, pharyngeal weakness, and orofacial dyskinesias due to NMDAR encephalitis)	FLAIR hyperintensity involving bilateral MTL	Sensory axonal	3 / 0.33 / +	CCS, IVIG, RTX	No improvement	Death due to NMDAR encephalitis

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Kang et al. 2020 ²²	66 / F	SCLC (IV)	Sintilimab (2 doses)	New-onset seizures, enteric neuropathy	Normal	-	12 / N / NA	CCS	Complete improvement	Complete neurological improvement (1 month)	
Sechi et al. 2020 ²⁴	62 / F	SCLC (NA)	Atezolizumab (NA)	Limbic encephalitis, cerebellar ataxia, hearing loss, optic neuritis	T2 hyperintensity involving MTL	-	25 / 0.80 / +	CCS, CYC	Mild improvement	Mild improvement (1)	
Sechi et al. 2020 ²⁴	56 / M	Melanoma (NA)	Nivolumab + Ipilimumab (NA)	Cerebellar ataxia and peripheral neuropathy	NA	-	11 / 0.50 / NA	CCS	Moderate improvement of ataxia	Moderate improvement of ataxia (NA)	
Chompoopong et al. 2021 ²⁵	NA / M	Merkel cell carcinoma (NA)	Pembrolizumab (3)	SNN, enteric neuropathy	-	Sensory axonal	16 / 1.13 / NA	CCS	NA	Death due to neurological syndrome (NA)	
Morimoto et al. 2021 ²⁶	70 / M	SCLC (IV)	Atezolizumab (1)	SNN	Normal	Sensory axonal	1 / 1.46 / NA	IVIG	No improvement	NA	
Nakashima et al. 2022 ²⁷	66 / M	SCLC (IV)	Atezolizumab (3)	Altered mental status (disorientation → coma), dysphagia, gait disturbances due to muscle weakness	FLAIR hyperintensity involving bilateral MTL	-	5 / 0.94 / NA	CCS, IVIG	Partial neurological improvement	Severe neurological disability (6 months)	
Arai et al. 2022 ²⁸	69 / M	SCLC (IV)	Atezolizumab (3)	Opsoclonus-myoclonus	Normal	-	17 / 0.71 / NA	CCS	No improvement	Severe neurological disability, ventilator-dependent (NA)	

Abbreviations: CE (contrast enhancement), CCS (corticosteroids), CSF (cerebrospinal fluid), F (female), FLAIR (fluid-attenuated inversion recovery), FU (follow-up), IVIG (intravenous immunoglobulins), M (male), MTL (medial temporal lobe), MRI (magnetic resonance imaging), mRS (modified Rankin Scale), N^o (number), NA (not available), NCS (nerve conduction studies), NSCLC (non-small cell lung cancer), NTZ (natalizumab), OCB (oligoclonal bands), RTX (rituximab), SCLC (small cell lung cancer), SNN (sensory neuronopathy), TCZ (tocilizumab).

eTable 3. Comparison of patients with Hu-Ab n-irAEs identified in the study center to those identified in the literature.

	Study center (n=11)	Literature review (n=12)	p
Median age, years (range)	66 (44-76)	66 (46-71)	0.62
Sex, male, n (%)	8 (73)	8 (67)	1.0
SCLC, n (%)	10 (91)	6 (50)	0.068
CNS involvement, n (%)	5 (45)	5 (42)	1.0
PNS involvement, n (%)	2 (18)	3 (25)	1.0
CNS+PNS involvement, n (%)	4 (36)	3 (25)	0.67
Areas involved, n (%)			
Limbic	6 (54)	5 (42)	0.68
Cerebellar	3 (27)	2 (17)	1.0
Brainstem	3 (27)	3 (25)	1.0
Diencephalic	0	1 (8)	1.0
Basal ganglia	1 (9)	0	0.48
Root/peripheral nerves	2 (18)	2 (17)	1.0
DRG	5 (45)	3 (25)	0.4
NMJ	0	0	1.0
Muscle	0	0	1.0
Myoenteric plexus	1 (9)	2 (17)	1.0
Single area involvement, n (%)	3 (27)	4 (36)	1.0
PNS Care-score, n (%)			
Non-PNS (≤ 3)	0	0	
Possible (4-5)	0	0	
Probable (6-7)	0	1 (8)	
Definite (≥ 8)	11 (100)	71 (92)	1.0

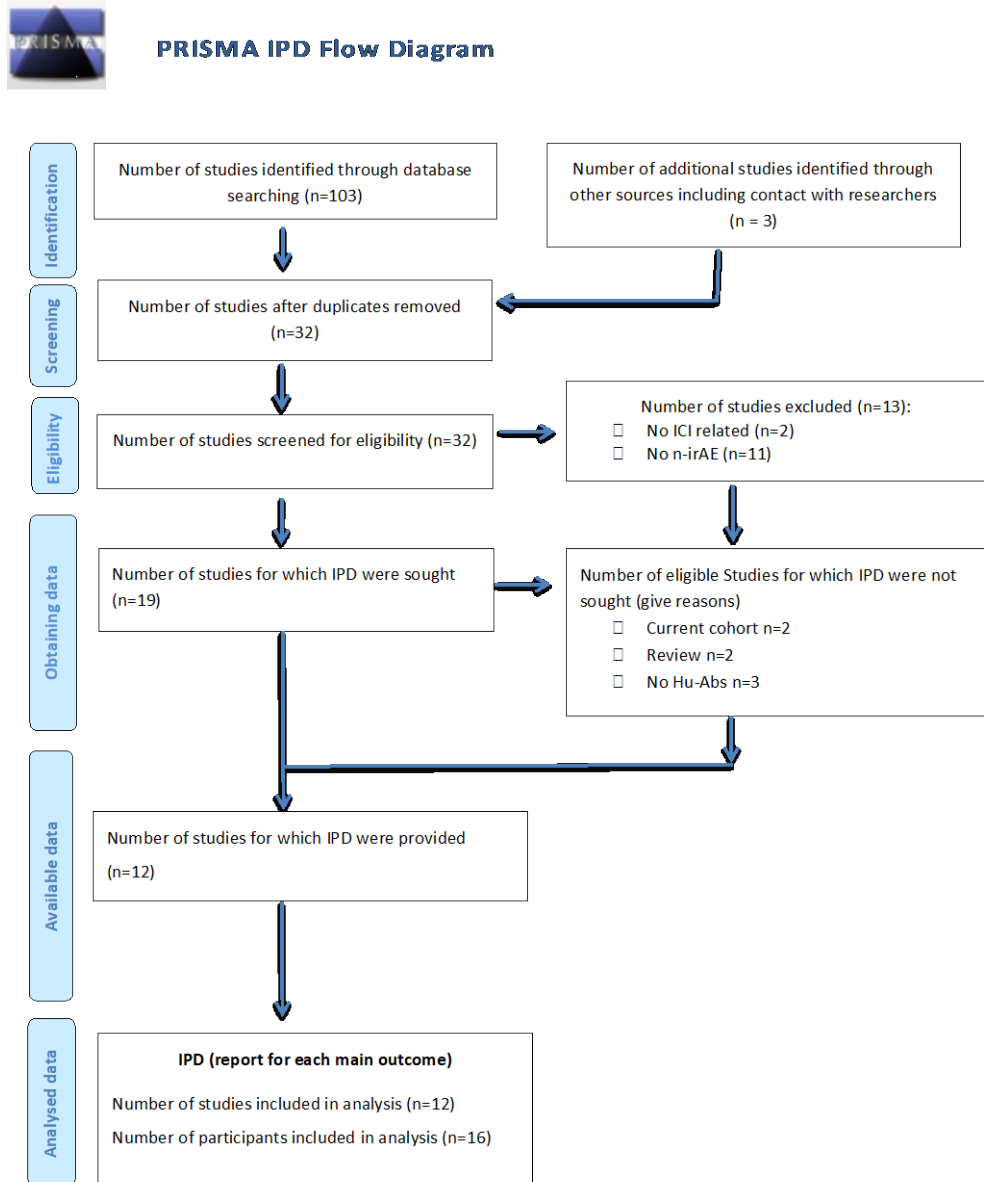
Abbreviations. CNS (central nervous system), CSF (cerebrospinal fluid);,DRG (dorsal root ganglia), ICI (immune checkpoint inhibitor), mRS (modified Rankin Score); PNS (peripheral nervous system), SCLC (small cell lung cancer).

eTable 4. Patients with Hu-Ab PNS that worsened after ICI administration

Case	Age (y) / Sex	Cancer (stage)	ICI (n° of cycles prior to neurological worsening)	Clinical picture	Worsening/relapse of symptoms after ICI	Treatment	Treatment response	Final outcome (FU months)
Present series	56 / F	Undifferentiated adenocarcinoma of unknown primary	Pembrolizumab (4)	SNN	Worsening of gait ataxia, impossibility to stand autonomously, paraesthesia spreading to the face, and urinary incontinence	IVMP, IVIG, CYC	No improvement	Severe neurological disability (6)
Gill et al. 2019 ²¹	58 / M	Merkel cell carcinoma (IV)	Pembrolizumab (1)	SNN	Rapid worsening of severe ataxia and loss of proprioception with pseudo athetosis	None	-	Severe neurological disability (2)
Raibagkar et al. 2020 ²³	62 / F	SCLC (IV)	Nivolumab (NA)	SNN	Proximal spreading of sensory loss and numbness in four limbs, tremor, loss of dexterity, pseudo athetoid movements of hands, dysmetria on finger-nose testing	IVIG, CCS	No improvement	Severe neurological disability (2)
Chompoopong et al. 2021 ²⁵	NA / M	SCLC (NA)	Atezolizumab (1)	Polyradiculoneuropathy	Progressive numbness and weakness (bedridden)	CCS, PEX	No improvement	Death for neurological toxicity (1)
Sechi et al. 2020 ²⁴ , Chompoopong et al. 2021 ²⁵	51 / M	SCLC (NA)	Nivolumab (3)	SNN, cerebellar ataxia	Relapse of progressive asymmetric numbness, sensory ataxia, cerebellar ataxia (wheelchair dependent)	CCS, IVIG, PEX, CYC	No improvement	Severe neurological disability (16)

Abbreviations: CCS (corticosteroids), CYC (cyclophosphamide), F (female), FU (follow-up), IVIG (intravenous immunoglobulins), M (male), N° (number), NA (not available), PEX (plasma exchange), SCLC (small cell lung cancer), SNN (sensory neuropathy)

eFigure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for Individual Patient Data systematic reviews flow diagram.



The PRISMA IPD flow diagram

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