Supplemental Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Variables from the literature review data set entered for imputation of missing data

VARIABLE	PROPORTION OF CASES IMPUTED*	INCLUDED IN REGRESSION MODELS	NOTES
Demographics			
Sex	1.80%	Yes	
Age	0.90%	Yes	Recoded as categorical variable after imputaton
Clinical features			
Abnormal behaviour and/or cognitive dysfunction	5.62%	Yes	
Speech dysfunction	11.25%	Yes	
Seizures	8.21%	Yes	
Movement disorder	10.01%	Yes	
Autonomic dysfunction/central hypoventilation	10.69%	Yes	
Decreased level of consciousness	11.02%	Yes	
Worst mRS in the acute phase	24.63%	Yes	Binarised after imputation (mRS 5 versus mRS <5)
Intensive care unit admission	33.86%	Yes	
Tumour	0.56%	Yes	
Investigations			
Abnormal MRI brain	28.68%	Yes	
CSF pleocytosis (binary)	36.22%	Yes	
CSF WBC count (continuous)	61.53%	No	Included only for NEOS validation
EEG: focal or diffuse slow or disorganised activity	45.44%	Yes	
EEG: extreme delta brush	45.33%	Yes	
EEG: epileptiform activity**	45.33%	Yes	
First-line treatment			
Corticosteroids only	6.41%	Yes	
IVIG only	6.41%	Yes	
Therapeutic apheresis only	6.41%	Yes	
Corticosteroids and IVIG	6.41%	Yes	
Corticosteroids and Therapeutic apheresis	6.41%	Yes	
IVIG and Therapeutic apheresis	6.41%	Yes	
Corticosteroids, IVIG and Therapeutic apheresis	6.41%	Yes	
Days from symptom onset to immunotherapy	66.93%	No	Already included in binarised form
No immunotherapy within 30 days of disease onset^	47.69%	Yes	
Second-line treatment			
Rituximab	5.40%	Yes	
Cyclophosphamide	5.29%	Yes	
Bortezomib	1.69%	No	Excluded due to low occurrence (9/889 cases, 1.01%)
Tocilizumab	1.69%	No	Excluded due to low occurrence (4/889 cases, 0.45%)
Maintenance treatment			
Corticosteroids for at least 6 months from first event	1.46%	Yes	
IVIG for at least 6 months from first event	1.57%	Yes	
Mycophenolate mofetil	1.80%	Yes	
Azathioprine	1.57%	Yes	
Methotrexate	1.46%	No	Excluded due to low occurrence (5/889 cases, 0.56%)

Mean	**16.07%**		

eTable 1. Variables from the literature review dataset entered for imputation of missing data.
Legend: CSF: cerebrospinal fluid; EEG: electroencephalography; IVIG: intravenous immunoglobulin; MRI: magnetic resonance imaging; mRS: modified Rankin Scale.
*Number of cases with missing data per variable, divided by the total 889 cases included in one or both regression models.
**Defined as the presence of interictal epileptiform discharges, electrical seizures and/or electrical status epilepticus
^Data on time to first immunotherapy was available in 505/1551 patients. 287/505 patients did not receive immunotherapy within 30 days from symptom onset; these also included 128 patients who did not receive any immunotherapy at first event.

eTable 2. Demographic characteristics, clinical data, investigations, disease course, and outcome in the total literature cohort of patients with NMDAR antibody encephalitis

	Total literature cohort (*N*=1550)	**Pre-Titulaer et al. 2013[1] (*N*=387)**	**Post-Titulaer et al. 2013[1] (*N*=1163)**	***P***
ARTICLE DATA				
Total number of articles and year of publication	652	228	424	-
Year of publication 2007-2010	60/652 (9.2%)	60/228 (26.3%)	0/424 (0%)	<0.001
Year of publication 2011-2014	254/652 (39.0%)	157/228 (68.9%)	97/424 (22.9%)	<0.001
Year of publication 2015-2018	338/652 (51.8%)	11/228 (4.8%)	327/424 (77.1%)	<0.001
Full text/Abstract				
Full text	635/652 (97.4%)	215/228 (94.3%)	420/424 (99.1%)	<0.001
Abstract only	17/652 (2.6%)	13/228 (5.7%)	4/424 (0.9%)	<0.001
Language (full text)				
English	608/635 (95.7%)	202/215 (94.0%)	406/420 (96.7%)	0.14
Spanish	19/635 (3.0%)	8/215 (3.7%)	11/420 (2.6%)	0.47
French	7/635 (1.1%)	4/215 (1.9%)	3/420 (0.7%)	0.23
Portuguese	1/635 (0.2%)	1/215 (0.5%)	0/420 (0%)	0.34
Number of patients per article	Median 1, mean 2.4, range 1-48 (d.a.: 652/652)	Median 1, mean 1.7, range 1-15 (d.a.: 228/228)	Median 1, mean 2.7, range 1-48 (d.a.: 424/424)	0.22
Articles reporting 1 patient with NMDARE	479/652 (73.5%)	174/228 (76.3%)	305/424 (71.9%)	0.26
Articles reporting 2 patients with NMDARE	64/652 (9.8%)	25/228 (11.0%)	39/424 (9.2%)	0.49
Articles reporting 3-10 patients with NMDARE	84/652 (12.9%)	27/228 (11.8%)	57/424 (13.4%)	0.62
Articles reporting 11-20 patients with NMDARE	17/652 (2.6%)	2/228 (0.9%)	15/424 (3.6%)	0.04
Articles reporting >20 patients with NMDARE	8/652 (1.2%)	0/228 (0%)	8/424 (1.9%)	0.06
DEMOGRAPHICS				
Total number of patients	1550	387	1163	-
Proportion of females	1105/1508 (73.3%)	310/387 (80.1%)	795/1121 (70.9%)	<0.001
Proportion of children (≤18 years)	707/1526 (46.3%)	161/387 (41.6%)	546/1139 (47.9%)	0.03
Age at onset of NMDARE (years)	Median 20, mean 23.0, range 0-85 (d.a.: 1517/1550)	Median 21, mean 22.5, range 2-84 (d.a.: 386/387)	Median 19, mean 23.1, range 0-85 (d.a.: 1131/1163)	0.27
CLINICAL DATA AT FIRST EVENT OF NMDARE				
Days from symptom onset to hospitalization	Median 10, mean 30.3, range 0-2190 (d.a.: 452/1550)	Median 7, mean 20.0, range 1-274 (d.a.: 142/387)	Median 10, mean 35.1, range 0-2190 (d.a.: 310/1163)	0.51
≤7 days	213/452 (47.1%)	72/142 (50.7%)	141/310 (45.5%)	0.31
≤10 days	252/452 (55.8%)	85/142 (59.9%)	167/310 (53.9%)	0.26
≤21 days	347/452 (76.8%)	113/142 (79.6%)	234/310 (75.5%)	0.40
Clinical symptoms in the acute phase: main symptoms				
Abnormal (psychiatric) behaviour or cognitive dysfunction	1177/1409 (83.5%)	328/366 (89.6%)	849/1043 (81.4%)	<0.001
Speech dysfunction (pressured speech, verbal reduction, mutism)	521/1341 (38.9%)	183/356 (51.4%)	338/985 (34.3%)	<0.001
Seizures	944/1382 (68.3%)	255/365 (69.9%)	689/1017 (67.7%)	0.47
Movement disorder, dyskinesias, or rigidity/abnormal postures	855/1357 (63.0%)	267/359 (74.4%)	588/998 (58.9%)	<0.001
Decreased level of consciousness	744/1343 (55.4%)	257/358 (71.8%)	487/985 (49.4%)	<0.001

Autonomic dysfunction or central hypoventilation	583/1351 (43.2%)	222/366 (60.7%)	361/985 (36.6%)	<0.001
Clinical symptoms in the acute phase: other symptoms				
Prodromal flu-like symptoms	233/1361 (17.1%)	108/352 (30.7%)	125/1009 (12.4%)	<0.001
Sleep-wake cycle disturbances	223/1359 (16.4%)	91/351 (25.9%)	132/1008 (13.1%)	<0.001
Memory disturbances	234/1376 (17.0%)	70/355 (19.7%)	164/1021 (16.1%)	0.12
Worst mRS in the acute phase				
mRS 2	8/1113 (0.7%)	0/320 (0.0%)	8/793 (1.0%)	0.11
mRS 3	144/1113 (12.9%)	27/320 (8.4%)	117/793 (14.8%)	0.004
mRS 4	309/1113 (27.8%)	89/320 (27.8%)	220/793 (27.7%)	1.00
mRS 5	652/1113 (58.6%)	204/320 (63.7%)	448/793 (56.5%)	0.03
Admission to the intensive care unit	488/964 (50.6%)	165/300 (55.0%)	323/664 (48.6%)	0.07
Mechanical ventilation	302/834 (36.2%)	104/268 (38.8%)	198/566 (35.0%)	0.32
Length of hospitalisation ≥60 days	225/336 (67.0%)	100/126 (79.4%)	125/210 (59.5%)	<0.001
Associated tumour*	389/1524 (25.6%)	132/377 (35.0%)	257/1147 (22.4%)	<0.001
Ovarian teratoma	312/1524 (20.5%)	114/377 (30.2%)	198/1147 (17.3%)	<0.001
Other ovarian tumour	12/1524 (0.8%)	7/377 (1.9%)	5/1147 (0.4%)	0.01
Other tumour (extra-ovarian tumour)	66/1524 (4.3%)	11/377 (2.9%)	54/1147 (4.7%)	0.14
Preceding/concomitant/subsequent associated demyelinating CNS disease	54/1517 (3.6%)	7/373 (1.9%)	47/1144 (4.1%)	0.05
INVESTIGATIONS AT FIRST EVENT OF NMDARE				
Abnormal brain MRI	434/1069 (40.6%)	159/328 (48.5%)	275/741 (37.1%)	<0.001
Abnormal EEG**	725/855 (84.8%)	244/280 (87.1%)	481/575 (83.7%)	0.19
Focal or diffuse slow or disorganised activity	594/822 (72.3%)	209/280 (74.6%)	385/542 (71.0%)	0.29
Epileptic activity (epileptic discharges)	244/829 (29.4%)	95/281 (33.8%)	149/548 (27.2%)	0.05
Seizures recorded	132/829 (15.9%)	65/281 (23.1%)	67/548 (12.2%)	<0.001
Status epilepticus recorded	43/827 (5.2%)	24/280 (8.6%)	19/547 (3.5%)	0.003
Extreme delta brush	56/827 (6.8%)	1/280 (0.4%)	55/547 (10.1%)	<0.001
Periodic lateralized epileptic discharges (PLEDs)	13/827 (1.6%)	7/280 (2.5%)	6/547 (1.1%)	0.14
Abnormal CSF***	692/924 (74.9%)	246/296 (83.1%)	446/628 (71.0%)	<0.001
Pleocytosis >4 cells/uL	618/911 (67.8%)	225/296 (76.0%)	393/615 (63.9%)	<0.001
Hyperproteinorrachia >50 mg/dL	189/873 (21.6%)	55/293 (18.8%)	134/580 (23.1%)	0.16
Positive oligoclonal bands	223/356 (62.6%)	99/143 (69.2%)	124/213 (58.2%)	0.04
NMDAR-antibodies				
Positive in serum	702/796 (88.2%)	206/226 (91.2%)	496/570 (87.0%)	0.11
Positive in CSF	973/986 (98.7%)	252/255 (98.8%)	721/731 (98.6%)	1.00

eTable 2. Demographics, clinical data, investigations, disease course and outcome in the total literature cohort of patients with NMDAR-antibody encephalitis and according to pre and post-Titulaer *et al*., 2013[1] epoch.

CNS: central nervous system; CSF: cerebrospinal fluid; d.a.: data available; EEG: electroencephalography; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; NMDARE: NMDAR-antibody encephalitis. The Fisher exact test was used for nominal data and the Mann-Whitney U test for continuous or ordinal data.

*One patient had both ovarian teratoma and extra-ovarian tumour.

Among 66 patients with extra-ovarian tumours, 49.2% (32/65) were females, and 18.2 (12/66) were in paediatric age.

Most frequent extra-ovarian tumour locations were: lung (11/66), mediastinum (5/66), brain, uterus, lymphoma (4/66 each). Less common tumour locations were: adrenal glands, breast, fallopian tubes, pancreas, testicle (3/66 each); thymus, kidney, liver, prostate (2/66 each); abdomen, stomach, bladder, gluteal muscle, heart, inguinal region, parotid glands, perineum, retroperitoneum, tonsils, acute myeloid leukemia, neuroendocrine tumours (1/66 each); tumour location was not available in 3/66.

**Abnormal EEG was considered the presence of focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush.[2]

***Abnormal CSF was considered CSF with pleocytosis or oligoclonal bands.[2]

eTable 3. First-line immunotherapy at first event of NMDAR antibody encephalitis

DATA ON FIRST-LINE IMMUNOTHERAPY AT FIRST EVENT OF NMDARE IN THE TOTAL LITERATURE COHORT (*N*=1550)	
FIRST-LINE IMMUNOTHERAPY	**1395/1528 (91.3%)**
Corticosteroids	**1205/1485 (81.1%)**
*Type of corticosteroids (regardless of the route of administration)**	
Methylprednisolone	666/776 (85.8%)
Prednisone	294/776 (37.9%)
Other (dexamethasone, ACTH, hydrocortisone, bethamethasone)	29/776 (3.7%)
*Route of administration (regardless of the type of corticosteroid)**	
Intravenous	814/911 (89.4%)
Oral	315/911 (34.6%)
Intramuscular or intrathecal	7/911 (0.8%)
Intravenous immunoglobulin	**980/1476 (66.4%)**
*Number of courses**	
1 course	845/970 (87.1%)
≥2 courses	125/970 (12.9%)
Therapeutic apheresis	**500/1482 (33.7%)**
*Type of apheresis**	
Plasmapheresis	478/500 (95.6%)
Immune adsorption	29/500 (5.8%)
*Number of courses and total number of exchanges**	
1 course	468/496 (94.4%)
≥2 courses	28/496 (5.6%)
Total number of exchanges	Median 5, mean 6.6, range 1-23 (d.a.: 196/500)
Total number of first-line immunotherapies	
0	132/1478 (8.9%)
1	307/1478 (20.8%)
2	738/1478 (49.9%)
3	301/1478 (20.4%)

eTable 3. First-line immunotherapy at first event of NMDAR-antibody encephalitis.
Legend: ACTH: adrenocorticotropic hormone; d.a.: available data; n.a.: not available.
*Denominators refer to the total number of patients who received the treatment, with available data (i.e. total number of patients who received corticosteroids, with available data on corticosteroid type).

eTable 4. Demographic characteristics, data in the acute phase of the first event, treatment, disease course, and outcome in the subgroups of patients who received bortezomib, tocilizumab, or intravenous/intrathecal methotrexate

DATA ON LITERATURE PATIENTS WITH NMDARE WHO RECEIVED BORTEZOMIB, TOCILIZUMAB OR INTRAVENOUS/INTRATHECAL METHOTREXATE AT FIRST DISEASE EVENT OR AFTER RELAPSE	Patients treated with intravenous or intrathecal Methotrexate^ (n=14)	Patients treated with intravenous or subcutaneous Bortezomib^^ (n=20)	Patients treated with intravenous Tocilizumab^^^ (n=11)
ARTICLE DATA AND DEMOGRAPHICS			
Total articles (year of publication)	9 (2013-2018)	9 (2016-2018)	3 (2017-2018)
Proportion of females	10/13 (76.9%)	16/19 (84.2%)	8/11 (72.7%)
Proportion of children (≤18 years)	9/14 (64.3%)	1/20 (5%)	2/11 (18.2%)
Age at onset (years)	Median 16, mean 17.5, range 7-31 (d.a.: 13/14)	Median 27, mean 33, range 17-61 (d.a.: 20/20)	Median 26, mean 31.6, range 17-58 (d.a.: 11/11)
CLINICAL DATA AT FIRST EVENT OF NMDARE			
Main clinical symptoms in the acute phase			
Abnormal (psychiatric) behaviour or cognitive dysfunction	12/13 (92.3%)	16/18 (88.9%)	11/11 (100%)
Speech dysfunction (pressured speech, verbal reduction, mutism)	3/13 (23.1%)	6/15 (40%)	8/11 (72.7%)
Seizures	11/13 (84.6%)	17/19 (89.5%)	11/11 (100%)
Movement disorder, dyskinesias, or rigidity/abnormal postures	9/13 (69.2%)	13/17 (76.5%)	10/11 (90.9%)
Decreased level of consciousness	9/13 (69.2%)	10/15 (66.7%)	10/11 (90.9%)
Autonomic dysfunction or central hypoventilation	8/13 (61.5%)	11/17 (64.7%)	10/11 (90.9%)
mRS in the acute phase	Median 5, mean 4.5, range 3-5 (d.a.: 14/14)	Median 5, mean 4.9, range 4-5 (d.a.: 20/20)	Median 5, mean 4.8, range 4-5 (d.a.: 11/11)
mRS 2	0/14 (0%)	0/20 (0%)	0/11 (0%)
mRS 3	2/14 (14.3%)	0/20 (0%)	0/11 (0%)
mRS 4	3/14 (21.4%)	2/20 (10%)	2/11 (18.2%)
mRS 5	9/14 (64.3%)	18/20 (90%)	9/11 (81.8%)
Admission to the intensive care unit	7/12 (58.3%)	14/19 (73.7%)	3/6 (50%)
Mechanical ventilation	7/12 (58.3%)	13/17 (76.5%)	3/4 (75%)
Length of hospitalization (days)	Median 328.5, mean 384.2, range 120-760 (d.a.: 4/14)	Median 339, mean 342.7, range 243-450 (d.a.: 4/20)	313 (d.a.: 1/11)
Associated tumour	4/14 (28.6%)	7/20 (35%)	6/11 (54.5%)
Association with demyelinating CNS disease (preceding/concomitant/subsequent)	0/14 (0%)	0/20 (0%)	0/11 (0%)
INVESTIGATIONS			
Abnormal brain MRI	4/10 (40%)	7/12 (58.3%)	8/11 (72.7%)
Abnormal EEG*	9/11 (81.8%)	9/9 (100%)	11/11 (100%)
Abnormal CSF**	7/11 (63.6%)	9/11 (81.8%)	9/11 (81.8%)
NMDAR-antibodies in serum	6/7 (85.7%)	15/15 (100%)	6/6 (100%)
NMDAR-antibodies in CSF	13/13 (100%)	17/17 (100%)	6/6 (100%)
IMMUNOTHERAPY AT FIRST EVENT			
Any immunotherapy	14/14 (100%)	19/20 (95%)	11/11 (100%)
First-line immunotherapy	14/14 (100%)	19/20 (95%)	11/11 (100%)
Corticosteroids	14/14 (100%)	16/20 (80%)	10/11 (90.9%)
Intravenous immunoglobulin	10/14 (71.4%)	17/20 (85%)	11/11 (100%)
Therapeutic apheresis	6/14 (42.8%)	13/20 (65%)	4/11 (36.4%)

Second-line immunotherapy	12/14 (85.7%)	16/20 (80%)	11/11 (100%)
Rituximab	9/14 (64.3%)	16/20 (80%)	11/11 (100%)
Cyclophosphamide	5/14 (35.7%)	7/20 (35%)	5/11 (45.4%)
Intravenous or intrathecal Methotrexate	10/14 (71.4%)	1/20 (5%)	1/11 (9.1%)
Bortezomib	1/14 (7.1%)	16/20 (80%)	7/11 (63.6%)
Tocilizumab	1/14 (7.1%)	7/20 (35%)	11/11 (100%)
Other	1/14 (7.1%)	1/20 (5%)	3/11 (27.3%)
Long-term immune modulation ≥6 months	2/14 (14.3%)	10/20 (50%)	6/11 (54.5%)
Mycophenolate mofetil	1/14 (7.1%)	0/20 (0%)	0/11 (0%)
Azathioprine	0/14 (0%)	0/20 (0%)	0/11 (0%)
Intravenous immunoglobulin	0/14 (0%)	5/20 (25%)	5/11 (45.4%)
Methotrexate	0/14 (0%)	4/20 (20%)	0/11 (0%)
Corticosteroids	0/14 (0%)	0/20 (0%)	0/11 (0%)
Rituximab re-dosing	1/14 (7.1%)	6/20 (30%)	6/11 (54.5%)
Other	0/14 (0%)	0/20 (0%)	0/11 (0%)
Time from onset to first immunotherapy (days)	Median 10, mean 15.2, range 5-35 (d.a.: 9/14)	Median 13, mean 20.5, range 7-70 (d.a.: 8/20)	Median 10, mean 20, range 7-70 (d.a.: 6/11)
First immunotherapy ≤30 days from onset	8/10 (80%)	8/10 (80%)	5/6 (83.3%)
Number of different immunotherapies received before Bortezomib / Tocilizumab / intravenous or intrathecal Methotrexate	Median 3.5, mean 3.6, range 2-6 (d.a.: 14/14)	Median 4, mean 4.2, range 2-6 (d.a.: 20/20)	Median 3, mean 3.4, range 2-4 (d.a.: 11/11)
RELAPSES AND OUTCOME AT FOLLOW-UP			
Length of follow-up (months)	Median 12, mean 12.9, range 4-25 (d.a.: 10/14)	Median 13, mean 35.1, range 4-268 (d.a.: 17/20)	Median 5.5, mean 9, range 4-20 (d.a.: 10/11)
Proportion of patients who relapsed	3/14 (21.4%)	4/15 (20.7%)	0/6 (0%)
mRS at last follow-up	Median 1, mean 2.2, range 0-6 (d.a.: 13/14)	Median 3, mean 3.1, range 0-5 (d.a.: 20/20)	Median 5, mean 4.6, range 2-5 (d.a.: 11/11)
mRS 0-1	7/13 (53.8%)	4/20 (20%)	0/11 (0%)
mRS 2-3	3/13 (23.1%)	8/20 (40%)	1/11 (9.1%)
mRS 4-5	0/13 (0%)	8/20 (40%)	10/11 (90.9%)
mRS 6	3/13 (23.1%)	0/20 (0%)	0/11 (0%)

eTable 4. Demographics, data in the acute phase of the first event, treatment, disease course and outcome in the subgroups of literature patients who received bortezomib, tocilizumab or intravenous/intrathecal methotrexate for NMDAR-antibody encephalitis, at onset or after relapse (total 37 patients; 11/37 children; 7/37 received both bortezomib and tocilizumab).
CNS: central nervous system; CSF: cerebrospinal fluid; d.a.: data available; EEG: electroencephalography; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; NMDARE: NMDAR-antibody encephalitis.
*Abnormal EEG was considered the presence of focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush.[2]
**Abnormal CSF was considered CSF with pleocytosis or oligoclonal bands.[2]

^*Intravenous or intrathecal methotrexate*. The use of intravenous or intrathecal methotrexate as a second-line treatment was reported in 14 patients (median age 16 years, range 7-31), described in 9 articles published between 2013 and 2018. Disease severity in this subgroup was slightly higher than in the total cohort: 69.2% (9/13) had decreased level of consciousness, 61.5% (8/13) had dysautonomias, 64.3% (9/14) had mRS 5, and 58.3% (7/12) required ICU admission. In 71.4% (10/14), intravenous/intrathecal methotrexate was administered at first disease event, and in the remaining 28.6% (4/14) only after relapse. A median of 3.5 other immunotherapies were administered before intravenous/intrathecal methotrexate. Two of the patients in this subgroup experience adverse reactions, although not directly attributable to intravenous/intrathecal methotrexate: 1 had lymphopenia secondary to overall immunotherapy, and another 1 died due to septic shock after receiving cyclophosphamide. While most patients had good outcome (mRS 0-1 in 7/13, 53.8%), 23.1% died (3/13).

^^*Bortezomib*. The use of subcutaneous or intravenous bortezomib was reported in 20 patients, mostly adults (median age 27 years, range 17-61), described in 9 articles published between 2016 and 2018. Disease severity in this subgroup was higher than in the total cohort: 66.7% (10/15) of patients had

decreased level of consciousness, 64.7% (11/17) had dysautonomias, 90% (18/20) had mRS 5, and 73.7% (14/19) were admitted to the ICU. In 80% (16/20), bortezomib was administered at first disease event, and in the remaining 20% (4/20) only after relapse. A median of 4 other immunotherapies were administered before bortezomib. 7 patients in this subgroup experienced adverse reactions: 1 had lymphopenia secondary to overall immunotherapy, and the remaining 6 had side effects to bortezomib (infections in 2/6, neurotropenia in 5/6, anemia in 4/6). While none of the patients in this subgroup died, rate of good neurological outcome was low (mRS 0-1: 4/20, 20%).

^^^*Tocilizumab*. The use of intravenous tocilizumab was reported 11 patients, mostly adults (median age 26 years, range 17-58), described in 3 articles published between 2017 and 2018. Similar to the bortezomib group, disease severity in this subgroup was higher than in the total cohort: 90.9% (10/11) had decreased level of consciousness, 90.9% (10/11) had dysautonomias, 81.8% (9/11) had mRS 5, and 50% (3/6) were admitted to the ICU. In all cases tocilizumab was administered at first disease event, and none of the patients with available data relapsed (0/6, 0%). A median of 3 other immunotherapies were administered before tocilizumab. 6 patients in this subgroup experienced adverse reactions, although not directly attributable to tocilizumab: 1 had lymphopenia secondary to overall immunotherapy, and the remaining 5 had side effects to bortezomib (infections, neutropenia, anemia). While none of the patients in this subgroup died, 90.9% had poor neurological outcome (mRS 4-5: 10/11).

eTable 5. Severe immunotherapy-related adverse events

A. Type of treatment-related severe adverse events (CTCAE grades 3-5)	**Number of patients**
Infection	22
Hypotension	9
Neutropenia	7
Anaphylaxis or allergic reactions	6
Anaemia	4
Thrombosis or thromboembolism	3
Intestinal perforation	2
Hyperpyrexia	2
Disseminated intravascular coagulation	1
Hypothermia, hypersalivation, and cardiac arrhythmias	1
Elevated serum creatine kinase	1
Hemoptysis secondary to hypofibrinogenemia	1
Shock	1
Flushing, diaphoresis, coarse breath sounds	1
Diarrhea	1
B. Immunotherapy to which severe adverse events (CTCAE grades 3-5) were attributed to*	**Number of patients (%)**
Therapeutic apheresis	12/47 (25.6%)
Rituximab	10/47 (21.3%)
Intravenous immunoglobulin	4/47 (8.5%)
Cyclophosphamide	2/47 (4.3%)
Corticosteroids	2/47 (4.3%)
Bortezomib	2/47 (4.3%)
Treatment combinations	6/47 (12.8%)
Not available	9/47 (19.1%)

eTable 5. Adverse events to immunotherapy were categorised according to the National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) v5.0, with a focus on severe events: grade 3 (severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living), grade 4 (life-threatening consequences; urgent intervention indicated) and grade 5 (death related to adverse event).
Severe immunotherapy-related adverse events (CTCAE v5.0 grades 3-5) occurred in 47 patients. Multiple adverse reactions could occur in an individual patient. Of the 47 patients with severe adverse events to immunotherapy, 63.8% (30/47) were treated with second-line immunotherapy.
Among 486 patients who received second-line treatments, 415/486 patients received rituximab only (244/415), cyclophosphamide only (79/415), or rituximab and cyclophosphamide only (92/415) (excluding patients who received additional second-line treatments beside rituximab and/or cyclophosphamide). Among these subgroups, rates of adverse events to immunotherapy (any immunotherapy) were 4.3% (10/231), 2.7% (2/74), and 11.2% (10/89), respectively (P=0.03, 3x2 Chi square).
Most patients suffering severe adverse events had severe disease: 91.4% (32/35) had mRS 5 at nadir (versus 58.6% [601/1025] in those without severe adverse events [X2=15.1, P=0.001]) and 73.5% (25/34) required ICU admission (versus 51.4% [453/882] in those without [X2=6.45, P=0.01]).
*According to the original article.

eTable 6. Logistic regression model (single iteration) predicting poor functional outcome at 12 months—Statsmodel Logit() report (A) and derived odds ratios (B)

A

Logit Regression Results

Dep. Variable:	y	No. Observations:	582
Model:	Logit	Df Residuals:	548
Method:	MLE	Df Model:	33
Date:	Sat, 20 Mar 2021	Pseudo R-squ.:	0.1671
Time:	15:48:37	Log-Likelihood:	-304.36
converged:	True	LL-Null:	-365.41
Covariance Type:	nonrobust	LLR p-value:	3.742e-12

	coef	std err	z	P>|z|	[0.025	0.975]
const	-1.2231	0.643	-1.901	0.057	-2.484	0.038
Female	0.2931	0.242	1.210	0.226	-0.182	0.768
Infant	1.3138	0.810	1.622	0.105	-0.274	2.901
Child	-0.2267	0.296	-0.765	0.445	-0.808	0.354
Adolescent	-0.8683	0.289	-3.005	0.003	-1.435	-0.302
Older adult	1.0687	0.502	2.129	0.033	0.085	2.053
SpeechDys	-0.3038	0.221	-1.375	0.169	-0.737	0.129
Seizures	0.1566	0.244	0.642	0.521	-0.321	0.634
MvmtDis	0.3118	0.244	1.280	0.201	-0.166	0.789
Obtunded	0.2344	0.235	0.999	0.318	-0.225	0.694
BrainstemDys	0.4842	0.233	2.082	0.037	0.028	0.940
BehCogImp	-0.3757	0.297	-1.267	0.205	-0.957	0.206
ITU	0.5582	0.285	1.961	0.050	0.000	1.116
AbnMRIBrain	0.2757	0.210	1.316	0.188	-0.135	0.686
EEGSlowWithoutDB	-0.0818	0.248	-0.329	0.742	-0.569	0.405
EEGSlowWithDB	0.9443	0.378	2.496	0.013	0.203	1.686
EEGEpileptiform	0.1727	0.236	0.731	0.465	-0.290	0.636
CSFPleo	-0.0253	0.234	-0.108	0.914	-0.483	0.433
Tumour	-0.5964	0.254	-2.347	0.019	-1.095	-0.098
NoTreatmentWithin30Days	0.8089	0.228	3.552	0.000	0.363	1.255
IT1stLineComboCS	-0.4906	0.529	-0.927	0.354	-1.528	0.547
IT1stLineComboIVIG	-0.7771	0.585	-1.329	0.184	-1.923	0.369
IT1stLineComboTPE	-1.6607	0.949	-1.751	0.080	-3.520	0.199
IT1stLineComboCS_IVIG	-1.0094	0.460	-2.193	0.028	-1.911	-0.107
IT1stLineComboCS_TPE	-1.1854	0.545	-2.176	0.030	-2.253	-0.117
IT1stLineComboCS_IVIG_TPE	-0.9741	0.498	-1.955	0.051	-1.951	0.002
IT1stLineComboIVIG_TPE	-0.1970	0.664	-0.297	0.767	-1.498	1.104
IT2ndLineRTX	0.1366	0.256	0.533	0.594	-0.366	0.639
IT2ndLineCYC	0.3722	0.285	1.304	0.192	-0.187	0.932
ITMaintenanceMMF	-0.0443	0.676	-0.066	0.948	-1.368	1.280
ITMaintenanceAZA	0.1775	0.686	0.259	0.796	-1.166	1.521
IT6mSteroid	-1.5908	1.139	-1.396	0.163	-3.824	0.642
IT6mIVIG	2.1934	0.910	2.411	0.016	0.410	3.977
WorstMRSAcute 5	0.1799	0.279	0.645	0.519	-0.366	0.726

B

Feature	Odds ratio (95% CI)	p
Female	1.34 (0.83-2.16)	0.226
Infant (<2 years)	3.72 (0.76-18.19)	0.105
Child (2-11 years)	0.80 (0.45-1.43)	0.445
Adolescent (12-19 years)	0.42 (0.24-0.74)	0.003 *
Older adult (>=65 years)	2.91 (1.09-7.79)	0.033 *
Speech dysfunction	0.74 (0.48-1.14)	0.169
Seizures	1.17 (0.73-1.89)	0.521
Movement disorder	1.37 (0.85-2.20)	0.201
Decreased level of consciousness	1.26 (0.80-2.00)	0.318
Autonomic dysfunction/central hypoventilation	1.62 (1.03-2.56)	0.037 *
Abnormal behaviour and/or cognitive dysfunction	0.69 (0.38-1.23)	0.205

Intensive care unit admission	1.75 (1.00-3.05)	0.050 *
Abnormal MRI brain	1.32 (0.87-1.99)	0.188
EEG: background slowing without extreme delta brush	0.92 (0.57-1.50)	0.742
EEG: background slowing with extreme delta brush	2.57 (1.22-5.40)	0.013 *
EEG: epileptiform activity	1.19 (0.75-1.89)	0.465
CSF pleocytosis	0.97 (0.62-1.54)	0.914
Tumour	0.55 (0.33-0.91)	0.019 *
No immunotherapy within 30 days of disease onset	2.25 (1.44-3.51)	0.000 *
Corticosteroids only	0.61 (0.22-1.73)	0.354
IVIG only	0.46 (0.15-1.45)	0.184
TPE only	0.19 (0.03-1.22)	0.080
Corticosteroids and IVIG	0.36 (0.15-0.90)	0.028 *
Corticosteroids and TPE	0.31 (0.11-0.89)	0.030 *
Corticosteroids, IVIG and TPE	0.38 (0.14-1.00)	0.051
IVIG and TPE	0.82 (0.22-3.01)	0.767
Rituximab	1.15 (0.69-1.89)	0.594
Cyclophosphamide	1.45 (0.83-2.54)	0.192
Mycophenolate mofetil	0.96 (0.25-3.60)	0.948
Azathioprine	1.19 (0.31-4.58)	0.796
Corticosteroids for at least 6 months from first event	0.20 (0.02-1.90)	0.163
IVIG for at least 6 months from first event	8.97 (1.51-53.33)	0.016 *
Severe disability (mRS 5) in the acute phase	1.20 (0.69-2.07)	0.519

eTable 6. Logistic regression model (single iteration) predicting poor functional outcome at 12 months - Statsmodel *Logit()* report (A) and derived odds ratios (B).

eTable 7. Logistic regression model (single iteration) predicting relapsing disease course at ≥24 months—Statsmodel Logit() report (A) and derived odds ratios (B)

A

Logit Regression Results

Dep. Variable:	y	No. Observations:	410
Model:	Logit	Df Residuals:	376
Method:	MLE	Df Model:	33
Date:	Sat, 20 Mar 2021	Pseudo R-squ.:	0.1285
Time:	15:53:28	Log-Likelihood:	-245.41
converged:	True	LL-Null:	-281.60
Covariance Type:	nonrobust	LLR p-value:	9.017e-05

	coef	std err	z	P>|z|	[0.025	0.975]
const	0.1110	0.629	0.176	0.860	-1.123	1.345
Female	0.2195	0.278	0.789	0.430	-0.326	0.765
Infant	-0.0722	1.080	-0.067	0.947	-2.188	2.044
Child	0.2174	0.333	0.652	0.514	-0.436	0.871
Adolescent	0.6006	0.283	2.125	0.034	0.047	1.155
Older adult	-0.3426	0.923	-0.371	0.710	-2.151	1.466
SpeechDys	0.0793	0.261	0.304	0.761	-0.433	0.591
Seizures	0.0524	0.266	0.197	0.844	-0.468	0.573
MvmtDis	-0.3264	0.253	-1.288	0.198	-0.823	0.170
Obtunded	-0.1126	0.247	-0.456	0.649	-0.597	0.372
BrainstemDys	-0.2327	0.265	-0.880	0.379	-0.751	0.286
BehCogImp	-0.0633	0.332	-0.191	0.849	-0.714	0.588
ITU	-0.0054	0.329	-0.017	0.987	-0.649	0.639
AbnMRIBrain	-0.2703	0.236	-1.144	0.252	-0.733	0.193
EEGSlowWithoutDB	-0.3660	0.250	-1.465	0.143	-0.855	0.123
EEGSlowWithDB	0.3601	0.500	0.720	0.472	-0.620	1.340
EEGEpileptiform	-0.1548	0.266	-0.582	0.560	-0.676	0.366
CSFPleo	0.1859	0.243	0.765	0.444	-0.290	0.662
Tumour	-0.8392	0.324	-2.587	0.010	-1.475	-0.203
NoTreatmentWithin30Days	0.4318	0.273	1.582	0.114	-0.103	0.967
IT1stLineComboCS	0.1965	0.393	0.500	0.617	-0.574	0.967
IT1stLineComboIVIG	-0.1313	0.936	-0.140	0.888	-1.966	1.703
IT1stLineComboTPE	0.6685	1.483	0.451	0.652	-2.239	3.576
IT1stLineComboCS_IVIG	0.3195	0.341	0.936	0.349	-0.349	0.988
IT1stLineComboCS_TPE	0.1246	0.500	0.249	0.803	-0.855	1.105
IT1stLineComboCS_IVIG_TPE	-0.5978	0.454	-1.316	0.188	-1.488	0.293
IT1stLineComboIVIG_TPE	0.2951	0.749	0.394	0.694	-1.173	1.764
IT2ndLineRTX	-1.3081	0.412	-3.175	0.001	-2.116	-0.501
IT2ndLineCYC	-0.3335	0.434	-0.768	0.442	-1.184	0.517
ITMaintenanceMMF	-0.5899	0.925	-0.638	0.523	-2.402	1.222
ITMaintenanceAZA	-1.1538	0.800	-1.443	0.149	-2.721	0.413
IT6mSteroid	0.1159	0.827	0.140	0.889	-1.505	1.737
IT6mIVIG	-1.8327	1.163	-1.576	0.115	-4.112	0.447
WorstMRSAcute 5	-0.2393	0.320	-0.747	0.455	-0.867	0.389

B

Feature	Odds ratio (95% CI)	p
Female	1.25 (0.72-2.15)	0.430
Infant (<2 years)	0.93 (0.11-7.72)	0.947
Child (2-11 years)	1.24 (0.65-2.39)	0.514
Adolescent (12-19 years)	1.82 (1.05-3.17)	0.034 *
Older adult (>=65 years)	0.71 (0.12-4.33)	0.710
Speech dysfunction	1.08 (0.65-1.81)	0.761
Seizures	1.05 (0.63-1.77)	0.844
Movement disorder	0.72 (0.44-1.19)	0.198
Decreased level of consciousness	0.89 (0.55-1.45)	0.649
Autonomic dysfunction/central hypoventilation	0.79 (0.47-1.33)	0.379
Abnormal behaviour and/or cognitive dysfunction	0.94 (0.49-1.80)	0.849
Intensive care unit admission	0.99 (0.52-1.89)	0.987

Abnormal MRI brain	0.76 (0.48-1.21)	0.252
EEG: background slowing without extreme delta brush	0.69 (0.43-1.13)	0.143
EEG: background slowing with extreme delta brush	1.43 (0.54-3.82)	0.472
EEG: epileptiform activity	0.86 (0.51-1.44)	0.560
CSF pleocytosis	1.20 (0.75-1.94)	0.444
Tumour	0.43 (0.23-0.82)	0.010 *
No immunotherapy within 30 days of disease onset	1.54 (0.90-2.63)	0.114
Corticosteroids only	1.22 (0.56-2.63)	0.617
IVIG only	0.88 (0.14-5.49)	0.888
TPE only	1.95 (0.11-35.71)	0.652
Corticosteroids and IVIG	1.38 (0.71-2.69)	0.349
Corticosteroids and TPE	1.13 (0.43-3.02)	0.803
Corticosteroids, IVIG and TPE	0.55 (0.23-1.34)	0.188
IVIG and TPE	1.34 (0.31-5.83)	0.694
Rituximab	0.27 (0.12-0.61)	0.001 *
Cyclophosphamide	0.72 (0.31-1.68)	0.442
Mycophenolate mofetil	0.55 (0.09-3.40)	0.523
Azathioprine	0.32 (0.07-1.51)	0.149
Corticosteroids for at least 6 months from first event	1.12 (0.22-5.68)	0.889
IVIG for at least 6 months from first event	0.16 (0.02-1.56)	0.115
Severe disability (mRS 5) in the acute phase	0.79 (0.42-1.47)	0.455

eTable 7. Logistic regression model (single iteration) predicting relapsing disease course at ≥24 months - Statsmodel *Logit()* report (A) and derived odds ratios (B).

eTable 8. Prior published studies comparing effectiveness of immunotherapy combinations

Reference	Study type Number of patients (age) Additional data on Methods	Main findings (Statistical significance)	Interpretation according to the article's authors
A. Literature data from articles comparing efficacy of first-line immunotherapies or first-line immunotherapy combinations (corticosteroids, IVIG, therapeutic apheresis)			
DeSena 2015[3]	Observational, retrospective. 14 patients (children and adults). The mRS of 10 of 14 NMDARE patients that received CS and TPE were retrospectively evaluated; all the 14 patients were also subjectively assessed with the point of largest sustained improvement.	In the patients who received both CS and TPE (10/14 patients), 7/10 after TPE had improved mRS versus 3/10 patients after CS. The average mRS improvement after CS in this group was -0.1 as compared with 0.4 after TPE. Based on subjective chart review analysis of all 14 patients, the largest sustained improvement occurred immediately following the third–fifth exchange in 9/14 patients, whereas only 2/14 patients appeared to have had significant benefit immediately following CS. (Statistics not available)	This is compelling preliminary data that suggests that CS may not be as effective compared to CS followed by TPE.
Suppiej 2016[4]	Systematic literature review. 242 patients (children). Systematic literature review on TPE in paediatric NMDARE (2007–2015).	TPE was given with CS and IVIG in 69.5%, with CS only in 18%, with IVIG only in 7%, or was the only first-line treatment in 5.5%. Higher rates of full/substantial recovery at follow-up were observed with immunotherapy given within 30 days from onset (69.4%) compared to later (59.2%), and when TPE was associated with CS (66.7%) rather than not (46.7%). (Statistics not available)	Trend towards a better outcome when TPE was used early, and when given with CS.
Zhang 2017[5]	Systematic literature review. 432 patients (children and adults). Aim: to provide an overview of the clinical characteristics, treatments, and outcomes of NMDARE.	There were no significant differences among CS, IVIG or TPE used alone (p= 0.9172) or among combinations of every two of them (p=0.3059). With regard to the use of CS and IVIG, there were no significant differences between the outcomes of early combined treatment and sequential treatment (p=0.7277), or between using CS first and IVIG first (p=0.5422).	No significant differences were found among different first-line immunotherapies.
Sakpichaisakul 2018[6]	Observational, retrospective + prospective. 19 patients (children). Aim: to investigate outcomes from different treatments for NMDARE. Three treatments group: CS alone, IVIG alone, and IVIG and CS were reviewed.	IVIG was administered to 13 (68%) and 6 (32%) only received CS. Those receiving IVIG treatment with or without CS had greater improvement in mRS at 6 (p=0.04) and 12 months (p=0.03).	Such findings suggest the benefits of IVIG over CS despite the higher immediate cost.
Zhang 2019[7]	Prospective. 40 patients (children and adults).	Compared with the non-TPE group, the TPE group exhibited greater clinical improvement after 1 month and 2 months following treatment (P < 0.05). After 3 months, 6 months, and 12	TPE might rapidly improve the clinical manifestations in patients with severe refractory NMDARE.

	Patients with severe NMDARE with no improvement after CS and/or IVIG for at least 10 days were enrolled. All received immunotherapy and were divided into a TPE group (19 patients, total 118 procedures) and a non-TPE group (21 patients).	months, there were no significant differences in the outcomes between the TPE group and non-TPE group.	
Zhang 2021[8]	Prospective. 57 patients with severe refractory autoimmune encephalitis, including NMDARE (n = 51).	Of all 57 patients, 33 patients received TPE. Compared with the non-TPE group, the TPE group exhibited greater clinical improvement: 21 (37%) versus 8 (14%) after 1 month (P = 0.03) and 31 (54%) versus 16 (28%) after 2 months (P = 0.01), respectively. Complications and adverse events associated with TPE occurred in 91 procedures (47%) without serious adverse events associated with the use of TPE.	TPE might be an effective rescue therapy associated with rapid functional improvement in patients with severe steroid/IVIG refractory antibody-associated autoimmune encephalitis.
B. Literature data from articles comparing the efficacy of adjunctive second-line immunotherapy (rituximab and/or cyclophosphamide) with first-line only			
Titulaer 2013[1]	Observational, retrospective. 577 patients (children and adults). Multi-institutional observational study (2007-2012).	Of 221 patients who failed first-line therapy, 125 (57%) received second-line immunotherapy resulting in better outcome than those who did not (OR 2·69, CI 1·24-5·80, p=0·012).	Second-line immunotherapy is usually effective when first-line therapies fail.
Nosadini 2019[9]	Observational, retrospective. 62 patients (children). Retrospective study of an Italian cohort of patients with paediatric (≤18y) onset NMDARE.	At the survival analysis, the risk of relapsing was significantly lower in patients who received three or more different immunotherapies at first disease event (hazard ratio 0.208, 95% confidence interval 0.046-0.941; p=0.042). In this subgroup, 58.8% of patients received TPE (20/34), and 88.2% received second-line immunotherapy (30/34).	Aggressive immunotherapy at onset appears to decrease risk of relapse.
Lee 2020[10]	Prospective. 78 patients (children and adults). Consecutive patients treated for NMDARE between Jan 2014 and Oct 2019 in a national referral hospital. T-SIRT= tumor removal, CS, IVIG, RTX, TCZ	In a linear mixed model analysis, using the SIRT regimen was more effective than SIR or SI regimens in lowering CASE scores (P < 0.001 and P = 0.001, respectively). Completion of the (T)-SIRT regimen within 1 month of onset resulted in better 1-year improvements in CASE score (P < 0.001) and mRS scores (P = 0.001), compared to those of using other regimens within 1 month or delaying teratoma removal for more than 1 month.	Early application of combined immunotherapy consisting of T-SIRT had better efficacy than delayed or partial application of this combination.

eTable 8. Prior published studies comparing effectiveness of immunotherapy combinations. A. Literature data from articles comparing efficacy of first-line immunotherapies or first-line immunotherapy combinations (corticosteroids, IVIG, therapeutic apheresis) in NMDAR-antibody encephalitis. B. Literature data from articles comparing the efficacy of adjunctive second-line immunotherapy (rituximab and/or cyclophosphamide) with first-line only in NMDAR-antibody encephalitis.
Legend: CS: corticosteroids; IVIG: intravenous immunoglobulin; mRS: modified Rankin Scale; NMDARE: anti-N-methyl-D-aspartate receptor encephalitis; RTX: rituximab; TCZ: tocilizumab; TPE: therapeutic plasma exchange.

eTable 9. Age-stratified associations of rituximab with relapsing disease course

Age group	Total	Proportion with relapsing disease course		Odds ratio (95% CI)	*P*
		Treated with rituximab	Not treated with rituximab		
Infant (≤2 years)	4	0/0	2/4 (50.0%)	1.00 (0.01-80.05)	1.00
Child (2-11 years)	94	4/19 (21.1%)	37/73 (50.7%)	0.26 (0.08-0.86)	0.03
Adolescent (12-19 years)	117	2/13 (15.4%)	49/91 (53.8%)	0.16 (0.03-0.74)	0.02
Adult (20-64 years)	179	2/18 (11.1%)	64/147 (43.5%)	0.16 (0.04-0.73)	0.02
Older adult (≥65 years)	8	0/1 (0.0%)	2/7 (28.6%)	1.25 (0.03-54.23)	0.91

eTable 9. Age-stratified relationship of rituximab with relapsing disease course. Cases with known long-term relapse outcome (clinical relapse at any time, or absence of relapse after ≥24 months follow-up) were selected from the unimputed dataset and univariate comparisons performed for each age category separately. Odds ratios and *P* values calculated with statsmodels v0.12.2. Rituximab was associated with significantly reduced risk for relapsing disease across all three main age categories (child, adolescent and adult).

eTable 10. Comparison of patients receiving earlier vs later second-line immunotherapy

	Second-line IT initiation <60 days after disease onset	**Second-line IT initiation ≥60 days after disease onset**	***P***
Number of patients with data available	88	71	-
Worst mRS in the acute phase	Median 5, mean 4.6, range 3-5 (d.a.: 87/88)	Median 5, mean 4.6, range 3-5 (d.a.: 63/71)	0.80
Admission to the intensive care unit	54/88 (61.4%)	35/61 (57.4%)	0.63
Length of follow-up (months)	Median 8.7, mean 10.5, range 1.4-48 (d.a.: 74/88)	Median 16, mean 22.4, range 3-93 (d.a.: 59/71)	<0.001
mRS at last follow-up*	Median 2, mean 2.0, range 0-6 (d.a.: 80/88)	Median 2, mean 2.3, range 0-6 (d.a.: 67/71)	0.30
Poor functional outcome at 12 months**	10/46 (21.7%)	22/33 (66.7%)	<0.001

eTable 10. Comparison of patients receiving earlier (<60 days from onset) vs. later (≥60 days after onset) second-line immunotherapy. The Chi-square test was used for nominal data and the Mann-Whitney U test for continuous or ordinal data. Those receiving earlier second-line immunotherapy had significantly reduced odds for poor functional outcome at 12 months compared to those receiving later second-line immunotherapy (OR 0.14, 95% CI 0.05-0.38).
d.a., data available.
*Including all patients with available data (at any follow-up duration).
**Including only cases with available data for ascertainment of good vs. poor functional outcome at 12 months, as defined in the main methods.

eTable 11. Main factors associated with outcome and disease course in the large cohort by Titulaer et al[1] and our systematic review

	Association with good functional outcome		Association with fewer relapses	
Variable	**Titulaer *et al.* 2013[a]**	**Our analysis[b]**	**Titulaer *et al.* 2013[c]**	**Our analysis[b]**
Early treatment	+	+	na	ns
Use of first-line immunotherapy	na	+	+[d]	ns
Use of second-line immunotherapy	+	ns	+[d]	+
Use of maintenance IVIG	na	-	na	+
Presence of tumour	na	ns	+	ns
ICU admission	-	-	na	ns
Infant or older adult age	na	-	na	ns
Adolescent age	na	+	na	-
EEG extreme delta brush pattern	na	-	na	ns

eTable 11. Main factors associated with outcome and relapsing disease course in the large cohort by Titulaer *et al.*[1] and our systematic review. Only variables with statistical significance in one or both analyses are displayed.

+	Positive association
-	Negative association
na	Not assessed
ns	Not significant at $p<0.05$

a, Multivariable analysis
b, Bootstrapped multivariable analysis
c, Univariate analysis
d, Patients without tumour only

eTable 12. Logistic regression models for poor functional outcome at 12 months with interaction terms

Model	Variables included	Coef	SE	z	Odds ratio (95% CI)	*P*
1 (Base)	Female	0.0359	0.213	0.169	1.04 (0.68-1.57)	0.87
	Infant (<2 years)	1.5515	0.739	2.100	4.72 (1.11-20.08)	0.04
	Child (2-11 years)	-0.3446	0.243	-1.420	0.71 (0.44-1.14)	0.16
	Adolescent (12-19 years)	-1.0439	0.257	-4.061	0.35 (0.21-0.58)	<0.001
	Older adult (>=65 years)	1.0991	0.457	2.408	3.00 (1.23-7.34)	0.02
	ICU admission	0.5914	0.257	2.301	1.81 (1.09-2.99)	0.02
	Severe disease (mRS 5) in the acute phase	0.2925	0.255	1.148	1.34 (0.81-2.21)	0.25
	First-line IT without second-line	-1.2624	0.423	-2.987	0.28 (0.12-0.65)	0.003
	First-line and second-line IT	-0.8762	0.439	-1.998	0.42 (0.18-0.98)	0.05
2	Female	0.0471	0.214	0.220	1.05 (0.69-1.59)	0.83
	Infant (<2 years)	1.5440	0.737	2.095	4.68 (1.10-19.85)	0.04
	Child (2-11 years)	-0.3886	0.245	-1.589	0.68 (0.42-1.09)	0.11
	Adolescent (12-19 years)	-1.0932	0.262	-4.167	0.34 (0.20-0.56)	<0.001
	Older adult (>=65 years)	1.0372	0.457	2.270	2.82 (1.15-6.91)	0.02
	ICU admission	0.9332	0.926	1.007	2.54 (0.41-15.63)	0.31
	Severe disease (mRS 5) in the acute phase	0.3262	0.257	1.269	1.39 (0.84-2.29)	0.21
	First-line IT without second-line	-1.0147	0.498	-2.039	0.36 (0.14-0.96)	0.04
	First-line and second-line IT	-1.1597	0.556	-2.087	0.31 (0.11-0.93)	0.04
	ICU admission * First-line IT without second-line	-0.6623	0.951	-0.696	0.52 (0.08-3.33)	0.49
	ICU admission * First-line and second-line IT	0.1766	0.981	0.180	1.19 (0.17-8.16)	0.86
3	Female	0.0391	0.214	0.183	1.04 (0.68-1.58)	0.86
	Infant (<2 years)	1.5731	0.738	2.133	4.82 (1.14-20.47)	0.03
	Child (2-11 years)	-0.3542	0.243	-1.457	0.70 (0.44-1.13)	0.15
	Adolescent (12-19 years)	-1.0645	0.260	-4.097	0.34 (0.21-0.57)	<0.001
	Older adult (>=65 years)	1.0880	0.458	2.377	2.97 (1.21-7.28)	0.02
	ICU admission	0.6074	0.259	2.348	1.84 (1.11-3.05)	0.02
	Severe disease (mRS 5) in the acute phase	0.4908	0.853	0.575	1.63 (0.31-8.69)	0.57

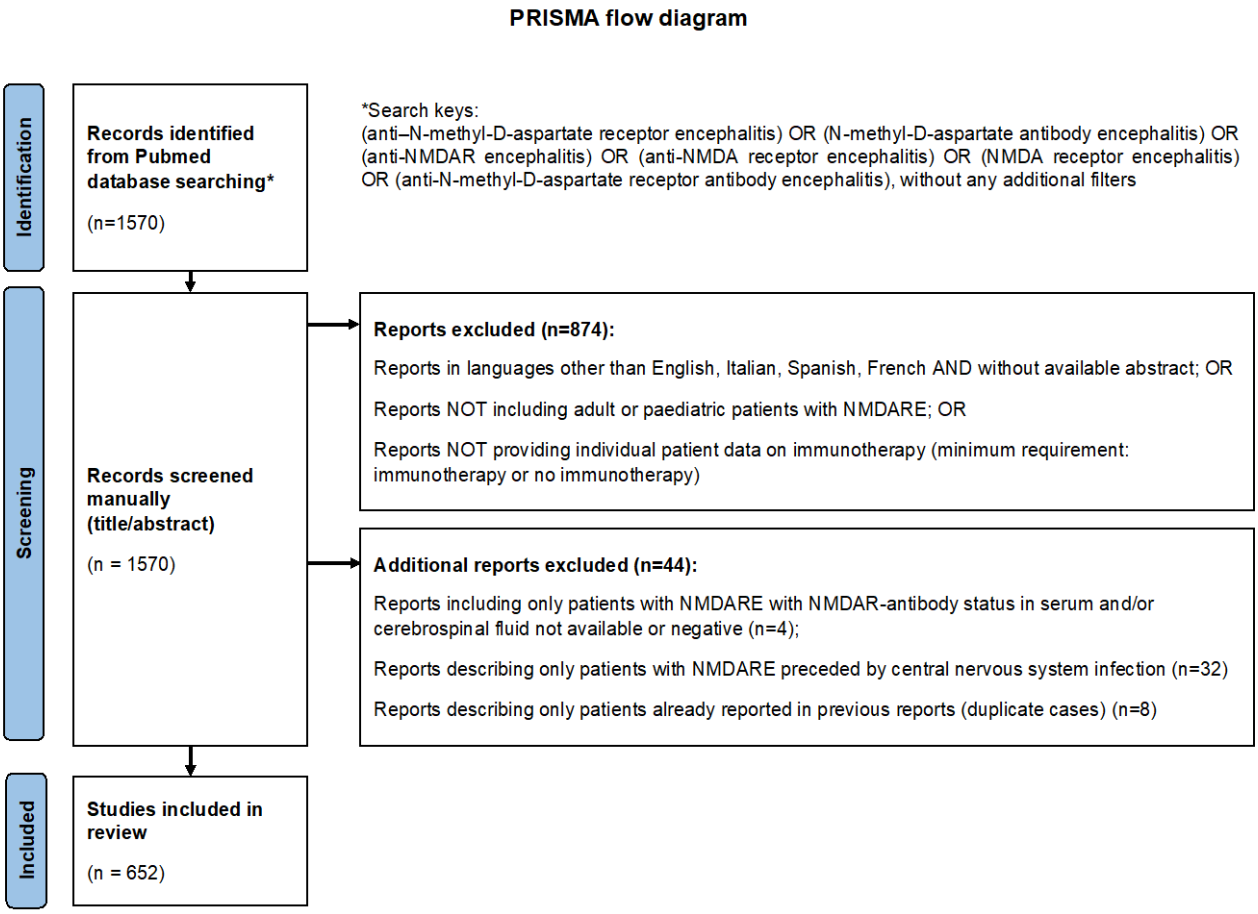
	First-line IT without second-line	-1.1309	0.530	-2.133	0.32 (0.11-0.91)	0.03
	First-line and second-line IT	-0.9268	0.575	-1.612	0.40 (0.13-1.22)	0.11
	mRS 5 in the acute phase * First-line IT without second-line	-0.3158	0.884	-0.357	0.73 (0.13-4.12)	0.72
	mRS 5 in the acute phase * First-line and second-line IT	-0.0373	0.912	-0.041	0.96 (0.16-5.76)	0.97
4	Female	-0.7896	0.891	-0.886	0.45 (0.08-2.60)	0.38
	Infant (<2 years)	1.5855	0.737	2.150	4.88 (1.15-20.72)	0.03
	Child (2-11 years)	-0.3209	0.244	-1.318	0.73 (0.45-1.17)	0.19
	Adolescent (12-19 years)	-1.0631	0.259	-4.109	0.35 (0.21-0.57)	<0.001
	Older adult (>=65 years)	1.1500	0.461	2.496	3.16 (1.28-7.79)	0.01
	ICU admission	0.6166	0.258	2.388	1.85 (1.12-3.07)	0.02
	Severe disease (mRS 5) in the acute phase	0.2733	0.256	1.068	1.31 (0.80-2.17)	0.29
	First-line IT without second-line	-1.7374	0.780	-2.228	0.18 (0.04-0.81)	0.03
	First-line and second-line IT	-1.7784	0.819	-2.171	0.17 (0.03-0.84)	0.03
	Female * First-line IT without second-line	0.6772	0.931	0.728	1.97 (0.32-12.20)	0.47
	Female * First-line and second-line IT	1.2614	0.966	1.306	3.53 (0.53-23.44)	0.19
5**	Female	0.0322	0.215	0.150	1.03 (0.68-1.57)	0.88
	Infant (<2 years)	7.4272	6227	0.003	3.7x10^7 (0.00-inf)	1.00
	Child (2-11 years)	-0.3549	0.243	-1.461	0.70 (0.44-1.13)	0.14
	Adolescent (12-19 years)	-1.0460	0.257	-4.068	0.35 (0.21-0.58)	<0.001
	Older adult (>=65 years)	1.0995	0.457	2.406	3.00 (1.23-7.35)	0.02
	ICU admission	0.5969	0.258	2.315	1.82 (1.10-3.01)	0.02
	Severe disease (mRS 5) in the acute phase	0.2615	0.256	1.021	1.30 (0.79-2.15)	0.31
	First-line IT without second-line	-1.2470	0.427	-2.919	0.29 (0.12-0.66)	0.004
	First-line and second-line IT	-0.8063	0.443	-1.821	0.45 (0.19-1.06)	0.07
	Infant * First-line IT without second-line	-4.8001	6227	-0.002	0.00 (0.00-inf)	1.00
	Infant * First-line and second-line IT	-4.6203	8403	-0.004	0.00 (0.00-inf)	1.00
6	Female	0.0319	0.214	0.149	1.03 (0.68-1.57)	0.89
	Infant (<2 years)	1.5610	0.739	2.111	4.76 (1.12-20.29)	0.04
	Child (2-11 years)	-0.1808	1.110	-0.163	0.83 (0.09-7.35)	0.87
	Adolescent (12-19 years)	-1.0471	0.258	-4.061	0.35 (0.21-0.58)	<0.001

	Older adult (>=65 years)	1.0985	0.458	2.401	3.00 (1.22-7.35)	0.02
	ICU admission	0.5965	0.258	2.310	1.82 (1.09-3.01)	0.02
	Severe disease (mRS 5) in the acute phase	0.2980	0.256	1.166	1.35 (0.82-2.22)	0.24
	First-line IT without second-line	-1.2602	0.462	-2.726	0.28 (0.11-0.70)	0.006
	First-line and second-line IT	-0.8158	0.479	-1.702	0.44 (0.17-1.13)	0.09
	Child * First-line IT without second-line	-0.0736	1.145	-0.064	0.93 (0.10-8.76)	0.95
	Child * First-line and second-line IT	-0.3168	1.165	-0.272	0.73 (0.07-7.15)	0.79
7	Female	0.0444	0.214	0.208	1.05 (0.69-1.59)	0.84
	Infant (<2 years)	1.5601	0.739	2.111	4.76 (1.12-20.25)	0.04
	Child (2-11 years)	-0.3482	0.243	-1.433	0.71 (0.44-1.14)	0.15
	Adolescent (12-19 years)	-0.8433	0.828	-1.019	0.43 (0.08-2.18)	0.31
	Older adult (>=65 years)	1.1011	0.457	2.409	3.01 (1.23-7.37)	0.02
	ICU admission	0.5843	0.257	2.275	1.79 (1.08-2.97)	0.02
	Severe disease (mRS 5) in the acute phase	0.3009	0.255	1.181	1.35 (0.82-2.23)	0.24
	First-line IT without second-line	-1.2090	0.517	-2.339	0.30 (0.11-0.82)	0.02
	First-line and second-line IT	-0.7630	0.534	-1.429	0.47 (0.16-1.33)	0.15
	Adolescent * First-line IT without second-line	-0.0909	0.885	-0.103	0.91 (0.16-5.17)	0.92
	Adolescent * First-line and second-line IT	-0.4222	0.923	-0.457	0.66 (0.11-4.00)	0.65
8**	Female	-0.0045	0.215	-0.021	1.00 (0.65-1.52)	0.98
	Infant (<2 years)	1.5735	0.739	2.129	4.82 (1.13-20.53)	0.03
	Child (2-11 years)	-0.3535	0.244	-1.451	0.70 (0.44-1.13)	0.15
	Adolescent (12-19 years)	-1.0524	0.258	-4.084	0.35 (0.21-0.58)	<0.001
	Older adult (>=65 years)	9.9740	17300	0.001	4.7x10^8 (0.00-inf)	1.00
	ICU admission	0.6587	0.260	2.533	1.93 (1.16-3.22)	0.01
	Severe disease (mRS 5) in the acute phase	0.2494	0.257	0.970	1.28 (0.78-2.12)	0.33
	First-line IT without second-line	-1.2386	0.435	-2.846	0.29 (0.12-0.68)	0.004
	First-line and second-line IT	-0.7567	0.450	-1.682	0.47 (0.19-1.13)	0.09
	Older adult * First-line IT without second-line	-8.1675	17300	-0.001	0.00 (0.00-inf)	1.00
	Older adult * First-line and second-line IT	-0.1446	17300	-0.001	0.00 (0.00-inf)	1.00

eTable 12. Logistic regression models for poor functional outcome at 12 months with interaction terms.

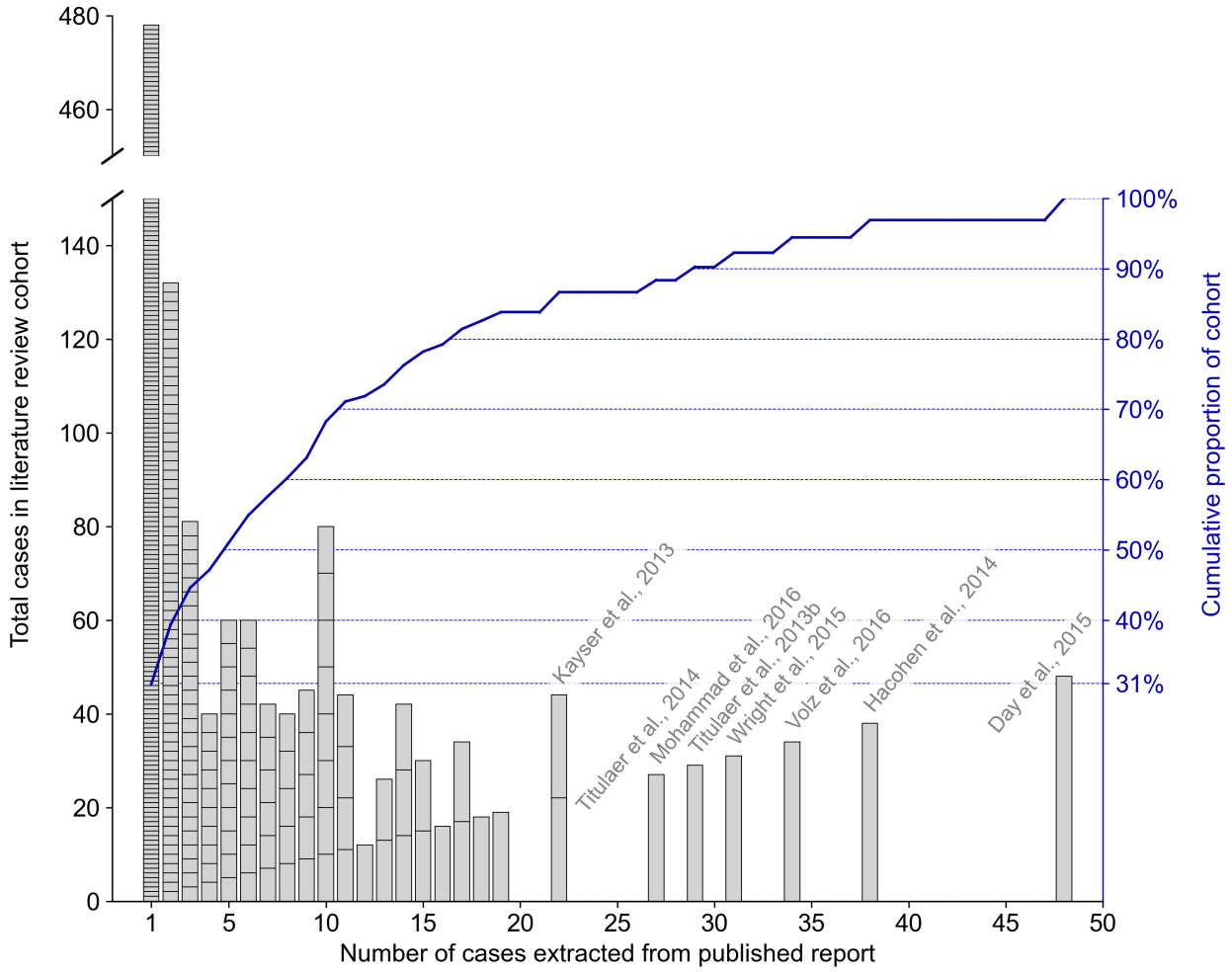
x1 * x2 indicates the interaction term between x1 and x2.
**Model failed to converge. Coef: beta coefficient; ICU: intensive care unit; IT: immunotherapy; mRS: modified Rankin Scale; SE: standard error.
In each model the dependent variable was poor functional outcome at 12 months (defined as in the main multivariable modelling), first-line immunotherapy was defined as corticosteroids, therapeutic apheresis or IVIG (alone or in any combination), and second-line immunotherapy was defined as rituximab, cyclophosphamide, bortezomib or tocilizumab (alone or in any combination). Patients receiving second-line immunotherapy without first-line immunotherapy (n=2) were excluded, leaving 580 patients in the dataset, entered in full to each model (i.e. without bootstrapping).
Model 1 is the base model (without interaction terms). This can be regarded as a feature-reduced version of the multivariable model presented in the main manuscript. As in the main model, infant age, older adult age and ICU admission were significantly associated with increased odds of poor outcome, while adolescent age was significantly associated with good outcome (i.e. decreased OR for poor outcome). Immunotherapy (first-line immunotherapy alone or first-line and second-line immunotherapy together) was also associated with good outcome.
In models 2-8, additional interaction terms (indicated by x1 * x2 in the table) were added to the base model, to evaluate specific interaction effects between severity and demographic factors and immunotherapy. In none of these models were the interaction terms significant at $p<0.05$. We conclude that there were no significant interactions between immunotherapy and severity or demographic factors on the dependent variable (functional outcome at 12 months) in this dataset, while acknowledging that our power to detect such interactions may be limited by the sample size.

eFigure 1. PRISMA flow diagram



Legend: PRISMA flow diagram.

eFigure 2. Number of patients extracted per published report



Legend: 1550 cases were extracted from 652 primary reports. For cases described over multiple papers, the paper contributing the most cases overall to the cohort was considered the primary report. Each bounded grey area represents one primary report, with size proportional to the number of cases extracted.
Reports providing ≥20 cases are cited:
Kayser et al., 2013[11]
Titulaer et al., 2014[12]
Mohammad et al., 2016[13]
Titulaer et al., 2013b[14]
Wright et al., 2015[15]
Volz et al., 2016[16]
Hacohen et al., 2014[17]
Day et al., 2015[18]

eMethods 1. Additional data on temporal epochs

Changes in immunotherapy use and disease outcome with time were primarily analysed over two epochs: before and after Titulaer *et al.*[1] Where year of disease onset was reported, cases with onset in 2013 or later were assigned to the later epoch and others to the early epoch; otherwise, cases extracted from papers published after 2013 (or in 2013 if citing Titulaer et al.[1]) were assigned to the later epoch and others to the early epoch. Additional post hoc analyses over six epochs (with cutoffs at two-year intervals) were performed for relapse rate and functional outcome, tested for significance with the Cuzick-Wilcoxon nonparametric test for trend.

eMethods 2. Statistical appendix

Alternative imputation methods
As data were not missing completely at random (Little's MCAR test: X2=359.005, DF=228, P<0.001),[19] multivariable imputation approaches were explored. Three imputation methods were evaluated[20] on an earlier version of the model targeting functional outcome at 12 months: (i) hot deck imputation, (ii) k-Nearest Neighbours (KNN) imputation implemented in Python 3.6 with MissingPy,[21] and (iii) multiple regression imputation implemented with SPSS.[22, 23]

In KNN imputation each sample's missing values are imputed as the average of the *n* nearest neighbors found in the training set. This can lead to imputed values which would not be possible in the observed data (e.g., mRS = 2.6). SPSS uses a fully conditional specification, or imputation through chain of equations, which employs the filled-in variable from one step as a predictor in all subsequent steps of imputation. Linear regression is applied to the continuous variables, and logistic regression is used for the categorical variables. It is known that, for high proportions of data missing not at random, this method introduces relevant biases.

Hot deck imputation was favoured for this study due to its more conservative approach and superior prediction accuracy:
Accuracy for KNN imputation = 80.5%
Accuracy for hot deck imputation = 81.1%
Accuracy for multiple regression imputation = 80.0%

Hot deck procedure and stability
Hot deck methods impute missing values within a database, by using available values (donors) from the same database. In this study, hot deck method was deployed, with no limit on the number of single donor selections. Case distance was weighted by univariate association of each variable with the target (functional outcome at 12 months). Missing values were filled sequentially, starting with the variable with minimum frequency of missingness (reference imputation). To test the stability of the donors selection, imputations were repeated by introducing single-variable weight changes equal to ±1%, ±5% and ±10% of the original univariate weight. In all tests (weight change x variable) the complete imputed database differed from the reference imputation in less than 2% of imputed values. Reference imputation was employed in all the analyses.

Bootstrapped multivariable regression
Regression models were implemented with the Statsmodels *Logit()* function in Python 3.6. Model parameters were not carried forward between iterations. Odds ratios, confidence intervals and P-values were derived from the distributions of the regression coefficients over the 10,000 folds.

Class-balanced pseudorandomisation procedure
In order to stabilise the Statsmodel *Logit()* function against algebraic errors caused by 100% imbalance in the target variable with respect to infrequently occurring predictor variables, an additional balancing procedure was applied within the bootstrapped regression. The procedure was applied homogeneously across all variables to avoid bias. Prior to the train-test shuffle, one case meeting the criteria [Predictor=1, Target=1] and one case meeting the criteria [Predictor =1, Target=0] were randomly selected from the dataset for each of the 33 predictors (without replacement). These 66 cases were held out of the train-test shuffle, then appended to the training set within each fold of the bootstrap. The train-test ratio was adjusted to compensate for the procedure, such that the final number of cases in the training and testing sets was equal.

eResults. Descriptive data on outcome and relapses in relation to immunotherapy

Data on relapses in patients treated with rituximab and with maintenance immunotherapy

Among 363 patients who received rituximab at first event, relapses occurred in 2.5% (8/319; data on relapses available in 319/363). In these relapsing patients with available data, rituximab was administered within 60 days from onset in 4/6 (data available in 6/8), and time between onset and relapse was median 3.5 months (mean 23.3, range 2.3-84; data on time between onset and relapse was available in 4/8); in the 4 relapsing patients with available time to relapse, rituximab had been administered within 60 days from onset in 2/3 (data available in 3/4).

Among the 146 patients who received maintenance immunotherapy for 6 months or longer at first event, relapses occurred in 6.3% (8/128; data on relapses available in 128/146). In these relapsing patients with available data, relapses occurred at median 35.5 months from onset (mean 33.1, range 1.5-72; data available in 6/8).

Data on outcome and relapses in relation to timing of second-line immunotherapy

Among 486 patients who received second-line immunotherapy at first disease event, in 55.3% (88/159) this was administered <60 days from disease onset (data on timing of administration available in 159/486).
In this subgroup who received second-line immunotherapy <60 days from disease onset, worst mRS in the acute phase was: mRS 3 in 11.5% (10/87), mRS 4 in 19.5% (17/87), mRS 5 in 69% (60/87) (data on mRS in the acute phase available in 87/88). 61.4% (54/88) required admission to the intensive care unit.
Relapses occurred in 4.8% (4/84; data on relapses available in 84/88).
At last follow-up (median 8.7 months, mean 10.5, range 1.4-48; data available in 74/88), median mRS was 2 (mean 2, range 0-6; data available in 80/88); 21.3% (17/80) patients had mRS 0, 21.3% (17/80) patients had mRS 1, 25% (20/80) had mRS 2, 16.3% (13/80) had mRS 3, 5% (4/80) had mRS 4, 7.5% (6/80) had mRS 5, 3.8% (3/80) died.

Among 486 patients who received second-line immunotherapy at first disease event, in 44.7% (71/159) this was administered ≥60 days from disease onset (data on timing of administration available in 159/486).
In this subgroup who received second-line immunotherapy ≥60 days from disease onset, worst mRS in the acute phase was: mRS 3 in 6.3% (4/63), mRS 4 in 23.8% (15/63), mRS 5 in 69.8% (44/63) (data on mRS in the acute phase available in 63/71). 57.4% (35/61; data available in 61/63) required admission to the intensive care unit.
Relapses occurred in 5.7% (4/70; data on relapses available in 70/71).
At last follow-up (median 16 months, mean 22.4, range 3-93; data available in 59/81), median mRS was 2 (mean 2.3, range 0-6; data available in 67/71); 16.4% (11/67) patients had mRS 0, 23.9% (16/67) patients had mRS 1, 11.9% (8/67) had mRS 2, 31.3% (21/67) had mRS 3, 6% (4/67) had mRS 4, 1.5% (1/67) had mRS 5, 9% (6/67) died.

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