Supplementary Material

The effectiveness of antiepileptic drug duotherapies in glioma patients: a multicenter observational cohort study

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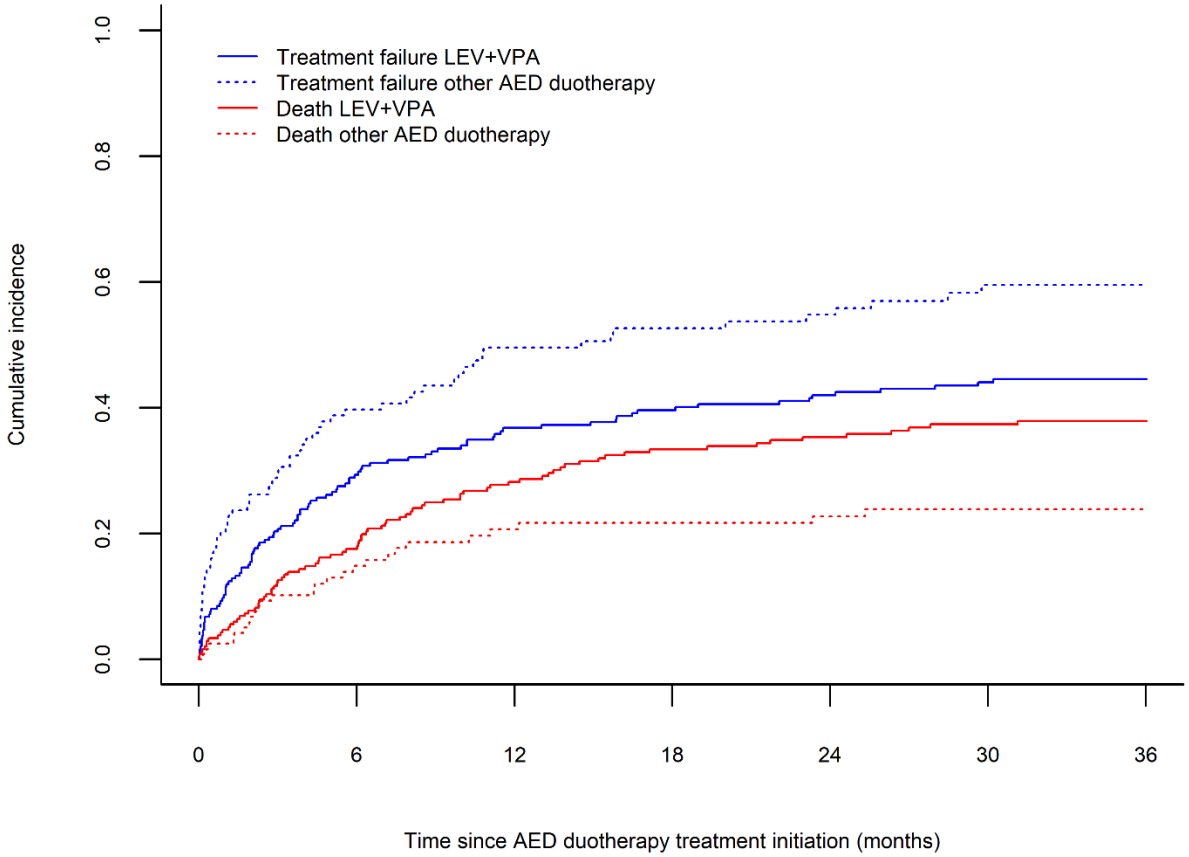
Content

eTable 1. List with defined daily dosages, as defined by the World Health Organisation, of antiepileptic drugs prescribed in this study

Antiepileptic drug	Defined Daily dosage	Unit
Carbamazepine	1	g
Clobazam	20	mg
Clonazepam	8	mg
Gabapentin	1.8	g
Lacosamide	0.3	g
Lamotrigine	0.3	g
Levetiracetam	1.5	g
Oxcarbamazepine	1	g
Phenytoin	0.3	g
Topiramate	0.3	g
Valproic acid	1.5	g

G=gram, mg=milligram

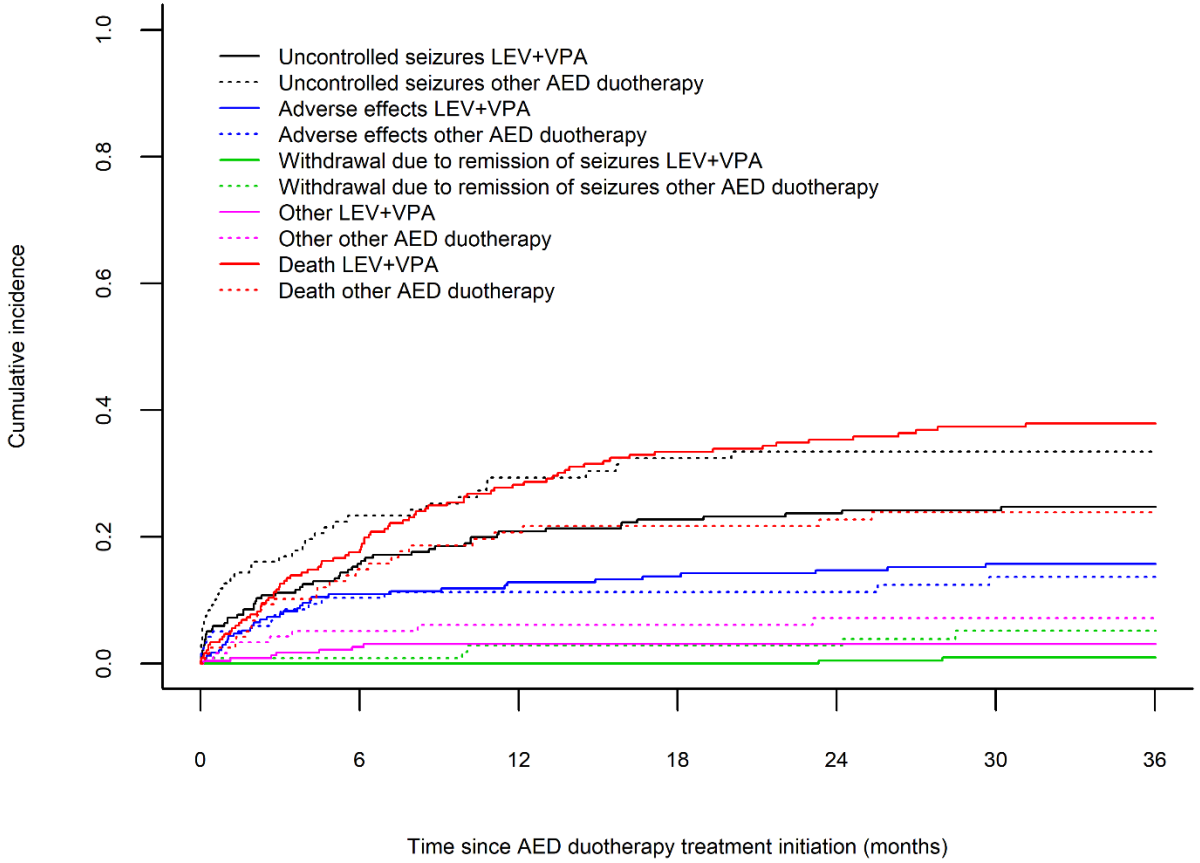
eTable 2. Number at risk, number censored, cumulative incidences for the competing events death and treatment failure for any reason, from antiepileptic drug duotherapy initiation: levetiracetam combined with valproic acid versus other antiepileptic drug duotherapy combinations



Time in months	0	3	6	12	24	36	
No. at risk							
LEV+VPA, no.	236	150	115	74	47	0	
Other duotherapy, no.	119	68	48	29	21	0	
No. censored							
LEV+VPA, no.	0	9	14	16	17	54	
Other duotherapy, no.	0	4	8	11	12	28	
Event treatment failure for any reason							p=0.007
CIF (95%CI), LEV+VPA	0	21 (16-26)	29 (24-35)	37 (30-43)	42 (35-48)	45 (38-51)	
CIF (95%CI), other duotherapy	0	30 (22-38)	40 (31-49)	50 (40-59)	55 (45-64)	60 (49-68)	
Event death							p=0.024
CIF (95%CI), LEV+VPA	0	13 (9-17)	18 (13-23)	28 (22-34)	35 (29-42)	38 (31-44)	
CIF (95%CI), other duotherapy	0	10 (6-17)	15 (9-22)	21 (14-29)	23 (15-31)	24 (16-32)	

AED=Antiepileptic drug; CI=Confidence interval; CIF=Cumulative incidence function; LEV+VPA=Levetiracetam combined with valproic acid; No.=Number of patients

eTable 3. Number at risk, number censored, cumulative incidences for the competing events death and for specific reasons of treatment failure, from antiepileptic drug duotherapy initiation: levetiracetam combined with valproic acid versus other antiepileptic drug duotherapy combinations



Time in months	0	3	6	12	24	36	
No. at risk							
LEV+VPA, no.	236	150	115	74	47	0	
Other duotherapy, no.	119	68	48	29	21	0	
No. censored							
LEV+VPA, no.	0	9	14	16	17	54	
Other duotherapy, no.	0	4	8	11	12	28	
Treatment failure							
Event uncontrolled seizures							p=0.069
CIF (95%CI), LEV+VPA	0	11 (8-16)	16 (11-21)	21 (16-26)	24 (18-29)	25 (19-31)	
CIF (95%CI), other duotherapy	0	17 (11-24)	23 (16-31)	29 (21-38)	33 (25-42)	33 (25-42)	
Event adverse effects							p=0.657
CIF (95%CI), LEV+VPA	0	8 (5-12)	11 (7-15)	13 (9-18)	15 (10-20)	16 (11-21)	
CIF (95%CI), other duotherapy	0	8 (4-13)	10 (6-17)	11 (6-18)	11 (6-18)	14 (8-21)	
Event withdrawal due to remission of seizures[1]							p=0.020
CIF (95%CI), LEV+VPA	0	0 (-)	0 (-)	0 (-)	0 (0-3)	1 (0-3)	
CIF (95%CI), other duotherapy	0	1 (0-4)	1 (0-4)	3 (1-7)	3 (1-7)	5 (2-11)	
Event other reasons[2]							p=0.091
CIF (95%CI), LEV+VPA	0	2 (1-4)	3 (1-5)	3 (1-6)	3 (1-6)	3 (1-6)	
CIF (95%CI), other duotherapy	0	4 (2-9)	5 (2-10)	6 (3-12)	7 (3-13)	7 (3-13)	
Event death							p=0.024
CIF (95%CI), LEV+VPA	0	13 (9-17)	18 (13-23)	28 (22-34)	35 (29-42)	38 (31-44)	
CIF (95%CI), other duotherapy	0	10 (6-17)	15 (9-22)	21 (14-29)	23 (15-31)	24 (16-32)	

[1]Withdrawal due to remission of seizures was defined as discontinuation of the antiepileptic drug with consent of the medical doctor, regardless of the term being treated with the antiepileptic drug; [2]Other encompassed treatment failure due to unknown reasons (n=10), due to phenytoin not orally available in the hospital (n=1), due to possible interaction with temozolomide (n=1), due to possible interaction of clobazam with anesthesia (n=1); AED=Antiepileptic drug; LEV+VPA=Levetiracetam combined with valproic acid; No.=Number of patients

eTable 4. Unadjusted and adjusted cause specific hazard ratios of treatment failure due to uncontrolled seizures

		Treatment failure due to uncontrolled seizures			
Parameter[1]		uHR (95% CI)	p-value	aHR (95% CI)	p-value
AED treatment	LEV+VPA (ref.)				
	Other duotherapy	1.50 (0.99-2.28	0.055	1.73 (1.10-2.73)	0.018*
Age		1.01 (0.99-1.02)	0.400	1.00 (0.98-1.02)	0.956
Tumor grade	2 (ref.)				
	3	0.72 (0.35-1.48)	0.373	0.89 (0.42-1.91)	0.767
	4	1.58 (0.99-2.51)	0.054	1.96 (1.02-3.77)	0.044*
Surgical resection	No (including biopsy, ref.)				
	Yes	1.02 (0.68-1.54)	0.915	1.09 (0.69-1.72)	0.711
Tumor involvement in the temporal lobe	No (ref.)				
	Yes	1.02 (0.67-1.54)	0.932	1.01 (0.65-1.56)	0.971
Karnofsky Performance Status	≥70 (ref.)				
	<70	1.18 (0.50-2.75)	0.706	1.05 (0.43-2.54)	0.918
Seizure type	Focal (ref.)				
	Focal to bilateral tonic clonic[2]	1.22 (0.77-1.93)	0.397	1.26 (0.79-2.03)	0.336

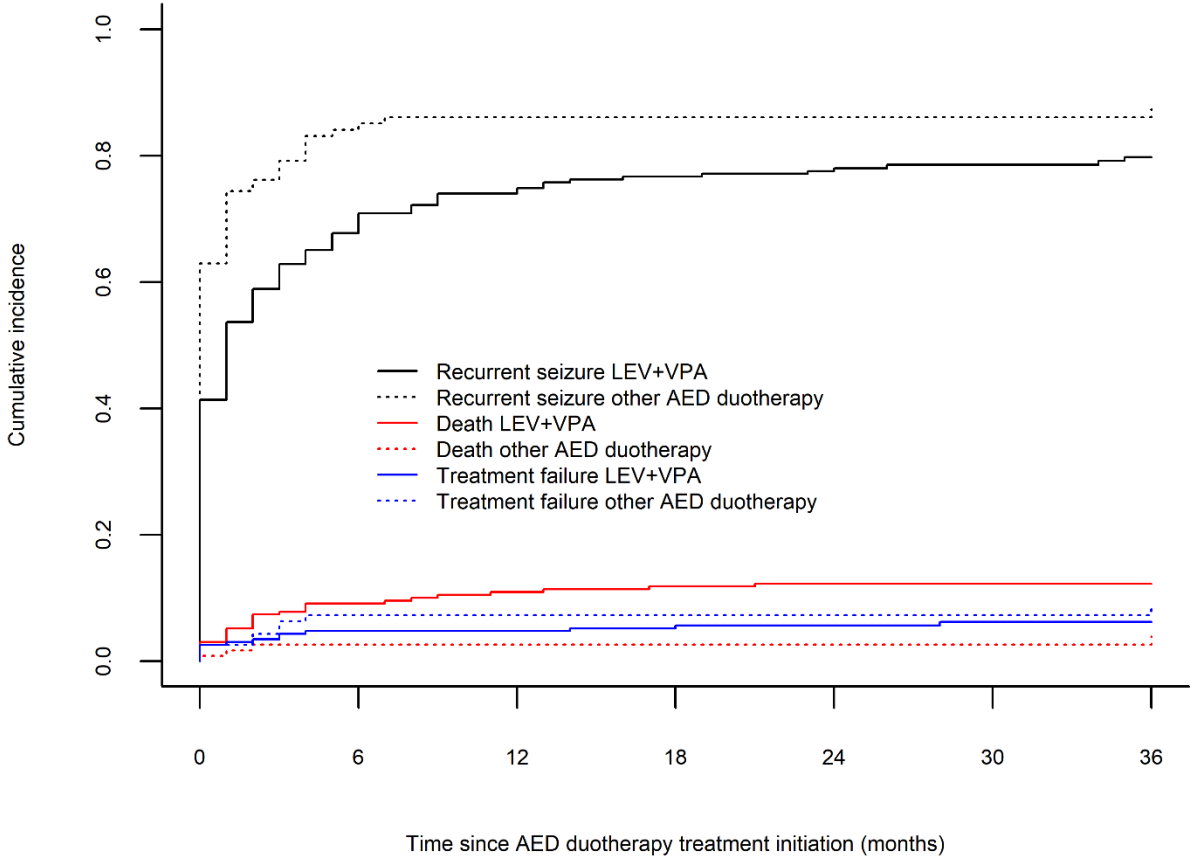
[1]Isocitrate dehydrogenase (IDH)-mutation, radiotherapy, and systemic therapy did not hold the proportionality assumption of the Cox regression model and were therefore stratified; [2]Patients had either solely focal to bilateral tonic-clonic seizures or both focal and focal to bilateral tonic-clonic seizures; *P-value <0.05; AED=Antiepileptic drug; aHR=Adjusted hazard ratio; CI=Confidence interval; LEV+VPA=Levetiracetam combined with valproic acid; uHR=Unadjusted hazard ratio

eTable 5. Unadjusted and adjusted cause specific hazard ratios of treatment failure due to adverse effects

		Treatment failure due to adverse effects			
Parameter		uHR (95% CI)	p-value	aHR (95% CI)	p-value
AED treatment	LEV+VPA (ref.)				
	Other duotherapy	0.96 (0.52-1.75	0.886	0.88 (0.47-1.67)	0.703
Age		1.00 (0.98-1.02)	0.949	1.00 (0.98-1.02)	0.972
Sex	Male (ref.)				
	Female	1.34 (0.76-2.38)	0.316	1.32 (0.73-2.36)	0.357
Surgical resection	No (including biopsy, ref.)				
	Yes	0.84 (0.48-1.47)	0.544	0.80 (0.44-1.49)	0.486
Radiotherapy	No (ref.)				
	Yes	0.99 (0.56-1.74)	0.962	1.35 (0.60-3.03)	0.469
Systemic therapy	No (ref.)				
	Yes	0.81 (0.43-1.51)	0.506	0.78 (0.33-1.83)	0.562
Tumor involvement in the frontal lobe	No (ref.)				
	Yes	1.40 (0.73-2.67)	0.316	1.35 (0.69-2.67)	0.382
Karnofsky Performance Status	≥70 (ref.)				
	<70	1.16 (0.35-3.83)	0.805	1.11 (0.32-3.86)	0.874
History of a psychiatric disease[1]	No (ref.)				
	Yes	2.06 (0.88-4.85)	0.097	1.86 (0.77-4.47)	0.165
Seizure type	Focal (ref.)				
	Focal to bilateral tonic clonic[2]	1.05 (0.57-1.92)	0.887	1.12 (0.60-2.09)	0.717

[1]History of a psychiatric disease included depression, anxiety, or psychotic disorders; [2]Patients had either solely focal to bilateral tonic-clonic seizures or both focal and focal to bilateral tonic-clonic seizures; *P-value <0.05; AED=Antiepileptic drug; aHR=Adjusted hazard ratio; CI=Confidence interval; LEV+VPA=Levetiracetam combined with valproic acid; uHR=Unadjusted hazard ratio

eTable 6. Number at risk, number censored, number missing, cumulative incidences for the competing events death, treatment failure, and recurrent seizure, from antiepileptic drug duotherapy initiation: levetiracetam combined with valproic acid versus other antiepileptic drug duotherapy combinations



Time in months	0	3	6	12	24	36	
No. at risk							
LEV+VPA, no.	236	67	40	23	9	0	
Other duotherapy, no.	119	17	5	2	1	0	
No. censored							
LEV+VPA, no.	0	2	3	3	3	8	
Other duotherapy, no.	0	3	3	3	4	4	
No. missing values							
LEV+VPA, no.	4	4	4	4	4	4	
Other duotherapy, no.	3	3	3	3	3	3	
Event recurrent seizure							p<0.001
CIF (95%CI), LEV+VPA	0	59 (53-65)	68 (62-74)	74 (68-79)	78 (72-83)	80 (74-85)	
CIF (95%CI), other duotherapy	0	77 (68-83)	85 (77-91)	87 (79-92)	87 (79-92)	-	
Event death							p=0.017
CIF (95%CI), LEV+VPA	0	7 (4-11)	9 (6-13)	11 (7-15)	12 (8-17)	12 (8-17)	
CIF (95%CI), other duotherapy	0	3 (1-7)	3 (1-7)	4 (1-9)	4 (1-9)	-	
Event treatment failure[1]							p=0.341
CIF (95%CI), LEV+VPA	0	4 (2-7)	5 (3-8)	5 (3-8)	6 (3-9)	6 (4-10)	
CIF (95%CI), other duotherapy	0	4 (2-10)	7 (3-13)	7 (3-13)	7 (3-13)	-	

[1]Patients who experienced treatment failure (due to adverse effects, withdrawal due to remission of seizures, or other reasons) before experiencing their recurrent seizure, can no longer experience a recurrent seizure on their first-line monotherapy levetiracetam or valproic acid, and therefore treatment failure was handled as competing risk; AED=Antiepileptic drug; CI=Confidence interval; CIF=Cumulative incidence function; LEV=Levetiracetam; No.=Number of patients; VPA=Valproic acid

eTable 7. Adverse effects which led to treatment failure in detail

Adverse Effects According to the CTCAE 5.0	Levetiracetam + Valproic acid							Other antiepileptic drug duotherapy						
	Grade, no.				Improved, no.			Grade, no.				Improved, no.		
	I & II	III & IV	Unknown	Total	Yes	No	Unknown	I & II	III & IV	Unknown	Total	Yes	No	Unknown
Gastrointestinal disorders														
Dyspepsia	-	-	-	-	-	-	-	1	-	-	1	1	-	-
Nausea	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Pancreatitis	-	1	-	1	1	-	-	-	-	-	-	-	-	-
Total	1	1	-	2	2	-	-	1	-	-	1	1	-	-
General and administration site conditions														
Clinical deterioration	-	1	-	1	-	1	-	-	-	-	-	-	-	-
Fatigue	3	-	-	3	3	-	-	1	-	-	1	1	-	-
Gait disturbance	1	-	-	1	1	-	-	1	-	-	1	-	-	1
Total	4	1	-	5	4	1	-	2	-	-	2	1	-	1
Hepatobiliary disorders														
Hepatic failure	-	2	-	2	1	-	1	-	-	-	-	-	-	-
Total	-	2	-	2	1	-	1	-	-	-	-	-	-	-
Injury, poisoning and procedural complications														
Fall	1	-	-	1	-	1	-	-	-	-	-	-	-	-
Total	1	-	-	1	-	1	-	-	-	-	-	-	-	-
Investigations														
Ammonia increased	1	-	-	1	-	-	1	-	-	-	-	-	-	-
Platelet count decreased	2	2	-	4	3	-	1	-	1	1	2	-	2	-
Weight gain	1	-	1	2	1	-	1	1	-	-	1	-	-	1
Total	4	2	1	7	4	-	3	1	1	1	3	-	2	1
Metabolism and nutrition disorders														
Hyponatremia	-	-	-	-	-	-	-	-	-	1	1	1	-	-
Total	-	-	-	-	-	-	-	-	-	1	1	1	-	-
Nervous system disorders														
Bradyphrenia	-	-	-	-	-	-	-	1	-	-	1	-	-	1

Concentration impairment	-	-	-	-	-	-	-	-	1	-	1	1	-	-
Dizziness	1	-	-	1	-	1	-	-	-	-	-	-	-	-
Dysarthria	-	-	-	-	-	-	-	1	-	-	1	-	1	-
Encephalopathy	1	1	-	2	2	-	-	-	1	-	1	1	-	-
Headache	2	-	-	2	1	1	-	1	-	-	1	1	-	-
Lethargy	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Memory impairment	-	-	-	-	-	-	-	-	1	-	1	1	-	-
Presyncope	-	-	-	-	-	-	-	1	-	-	1	1	-	-
Somnolence	2	-	-	2	2	-	-	3	-	-	3	1	-	2
Tremor	8	-	-	8	5	1	2	1	-	-	1	1	-	-
Total	15	1	-	16	11	3	2	8	3	-	11	7	1	3
Psychiatric disorders														
Agitation	2	-	-	2	1	-	1	-	-	-	-	-	-	-
Anxiety	-	-	-	-	-	-	-	1	1	-	2	-	2	-
Depression	1	2	-	3	3	-	-	-	-	-	-	-	-	-
Hallucinations	-	1	-	1	1	-	-	-	-	-	-	-	-	-
Irritability	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Suicidal ideation	-	1	-	1	1	-	-	-	-	-	-	-	-	-
Total	4	4	-	8	7	-	1	1	1	-	2	-	2	-
Skin and subcutaneous tissue disorders														
Alopecia	1	-	-	1	-	-	1	-	-	-	-	-	-	-
Pruritis	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Rash	1	-	1	2	1	-	1	2	-	1	3	3	-	-
Total	3	-	1	4	2	-	2	2	-	1	3	3	-	-
Unknown														
Unknown	1	-	1	2	2	-	-	-	-	1	1	1	-	-
Total	1	-	1	2	2	-	-	-	-	1	1	1	-	-
Total all adverse effects	33	11	3	47	33	5	9	15	5	4	24	14	5	5

CTCAE=Common Terminology Criteria for Adverse Events; No.=Number of patients