

Table S1. System Organ Classes, High Level Terms and corresponding Preferred Terms included in the analysis of neuropsychiatric ADRs.

System Organ Class	High Level Term	Preferred Term
Nervous system disorder	Abnormal reflexes	Areflexia
		Hyporeflexia
		Reflexes abnormal
	Acute polyneuropathies	Guillain-Barre syndrome
	Alzheimer's disease (incl subtypes)	Dementia Alzheimer's type
	Arterial infections and inflammations	Giant cell arteritis
	Central nervous system aneurysms and dissections	Carotid artery aneurysm
		Intracranial aneurysm
	Central nervous system haemorrhages and cerebrovascular accidents	Brain stem haemorrhage
		Cerebellar haemorrhage
		Cerebellar infarction
		Cerebral artery embolism
		Cerebral artery occlusion
		Cerebral haematoma
		Cerebral haemorrhage
		Cerebral infarction
		Cerebral ischaemia
		Cerebral thrombosis
		Cerebrovascular accident
		Haemorrhage intracranial
		Haemorrhagic stroke
		Ischaemic stroke
		Subarachnoid haemorrhage

	Thalamus haemorrhage
Central nervous system vascular disorders NEC	Brain hypoxia
	Cerebral microangiopathy
Cerebrovascular and spinal vascular disorders NEC	Migraine
Coma states	Coma
	Coma hepatic
Coordination and balance disturbances	Ataxia
	Balance disorder
	Coordination abnormal
	Dysstasia
Cortical dysfunction NEC	Nystagmus
	Aphasia
	Apraxia
	Dysgraphia
	Visuospatial deficit
Dementia (excl Alzheimer's type)	Dementia
	Dementia with Lewy bodies
Demyelinating disorders NEC	Demyelination
Disturbances in consciousness NEC	Altered state of consciousness
	Depressed level of consciousness
	Lethargy
	Loss of consciousness
	Somnolence
	Syncope
Disturbances in sleep phase rhythm	Irregular sleep phase
	Irregular sleep wake rhythm disorder
Dyskinesias and movement disorders NEC	Akathisia

	Akinesia
	Dyskinesia
	Hypokinesia
	Motor dysfunction
	Movement disorder
Dyssomnias	Poor quality sleep
Encephalopathies NEC	Encephalopathy
	Hypertensive encephalopathy
	Hypoxic-ischaemic encephalopathy
	Leukoencephalopathy
	Posterior reversible encephalopathy syndrome
Encephalopathies toxic and metabolic	Hepatic encephalopathy
Eye movement disorders	IIIrd nerve paralysis
	VIth nerve paralysis
Facial cranial nerve disorders	Bell's palsy
	Facial nerve disorder
	Facial paralysis
	Facial paresis
Generalised tonic-clonic seizures	Generalised tonic-clonic seizure
Headaches NEC	Headache
Hydrocephalic conditions	Hydrocephalus
Increased intracranial pressure disorders	Brain oedema
	Idiopathic intracranial hypertension
	Intracranial pressure increased
Lumbar spinal cord and nerve root disorders	Sciatica
Memory loss (excl dementia)	Amnesia

	Memory impairment
	Transient global amnesia
	Cognitive disorder
Mental impairment (excl dementia and memory loss)	Disturbance in attention
	Mental impairment
Mononeuropathies	Carpal tunnel syndrome
	Nerve compression
Motor neurone disease	Motor neurone disease
Motor neurone diseases	Amyotrophic lateral sclerosis
Multiple sclerosis acute and progressive	Multiple sclerosis
Muscle tone abnormal	Hypertonia
Muscular autoimmune disorders	Myasthenia gravis
	Myasthenic syndrome
Narcolepsy and hypersomnia	Hypersomnia
	Central nervous system lesion
	Cerebral disorder
Nervous system disorders NEC	Nervous system disorder
	Neurotoxicity
	Paraneoplastic neurological syndrome
Neurologic visual problems NEC	Hemianopia homonymous
	Dizziness
	Drooling
Neurological signs and symptoms NEC	Head discomfort
	Myoclonus
	Nervous system disorder
	Patient elopement

	Presyncope
	Unresponsive to stimuli
Neuromuscular disorders NEC	Muscle spasticity
	Anosmia
Olfactory nerve disorders	Parosmia
Optic nerve disorders NEC	Optic neuritis
	Burning sensation
	Dysaesthesia
	Formication
Paraesthesias and dysaesthesias	Hyperaesthesia
	Hypoaesthesia
	Paraesthesia
	Hemiparesis
	Hemiplegia
	Monoparesis
	Monoplegia
Paralysis and paresis (excl cranial nerve)	Paralysis
	Paraparesis
	Paraplegia
	Paresis
	Peripheral paralysis
	On and off phenomenon
Parkinson's disease and parkinsonism	Parkinsonism
	Parkinson's disease
	Axonal neuropathy
Peripheral neuropathies NEC	Ischaemic neuropathy
	Neuritis

Seizures and seizure disorders NEC	Neuropathy peripheral
	Polyneuropathy
	Convulsions local
	Epilepsy
Sensory abnormalities NEC	Seizure
	Ageusia
	Complex regional pain syndrome
	Decreased vibratory sense
	Dysgeusia
	Hypogeusia
	Neuralgia
	Restless legs syndrome
	Sensory disturbance
	Sensory loss
	Taste disorder
	Vibratory sense increased
Speech and language abnormalities	Electric shock sensation
	Dysarthria
	Incoherent
	Language disorder
	Repetitive speech
Spinal cord and nerve root disorders NEC	Speech disorder
	Myelopathy
	Spinal cord compression
Structural brain disorders NEC	Spinal cord disorder
	Brain injury
Transient cerebrovascular events	Transient ischaemic attack

Psychiatric disorder	Tremor (excl congenital)	Asterixis
		Tremor
	Vagus nerve disorders	Vocal cord paralysis
	Abnormal behaviour NEC	Abnormal behaviour
		Staring
		Agitation
		Anxiety
	Anxiety symptoms	Nervousness
		Stress
		Tension
	Attention deficit and disruptive behaviour disorders	Attention deficit hyperactivity disorder
		Aggression
	Behaviour and socialisation disturbances	Paranoia
		Personality change
		Daydreaming
	Cognitive and attention disorders and disturbances NEC	Distractibility
		Executive dysfunction
	Confusion and disorientation	Confusional state
		Disorientation
	Deliria	Delirium
	Delusional symptoms	Delusion
	Depressive disorders	Depression
	Disturbances in initiating and maintaining sleep	Insomnia
	Eating disorders NEC	Anorexia nervosa
		Eating disorder
	Emotional and mood disturbances NEC	Emotional disorder

	Euphoric mood
	Frustration tolerance decreased
	Irritability
	Claustrophobia
Fear symptoms and phobic disorders (incl social phobia)	Fear
	Fear of death
Fluctuating mood symptoms	Mood swings
Hallucinations (excl sleep-related)	Hallucination
Impulse control disorders	Pyromania
Increased physical activity levels	Restlessness
Mental disorders NEC	Mental disorder
	Mental status changes
	Decreased interest
Mood alterations with depressive symptoms	Depressed mood
	Psychomotor retardation
	Affective disorder
Mood disorders NEC	Apathy
	Laziness
	Listless
Panic attacks and disorders	Panic attack
	Abnormal dreams
Parasomnias	Sleep talking
	Somnambulism
Perception disturbances NEC	Near death experience
Personality disorders NEC	Personality disorder
Psychiatric symptoms NEC	Abulia
	Psychiatric decompensation

Psychotic disorder NEC	Psychotic disorder
Schizophrenia NEC	Schizophrenia
Sexual desire disorders	Loss of libido
Sleep disorders NEC	Sleep disorder
Somatic symptom disorders	Illness anxiety disorder
Stereotypies and automatisms	Bruxism
Suicidal and self-injurious behaviour	Completed suicide
	Suicidal ideation
	Suicide attempt
Thinking disturbances	Bradyphrenia
	Thinking abnormal
	Thought blocking

Table S2. ROR of ICSRs with ADRs by SOC.

System Organ Class	AVA (n = 1,112)		IM (n = 4,931)		REG (n = 231)		RIP (n = 176)		SU (n = 2,062)		Total (n = 8,512)
	n	ROR (95% CI)	n	ROR (95% CI)	n	ROR (95% CI)	n	ROR (95% CI)	n	ROR (95% CI)	
Genrl	559	1.21 (1.06-1.37)	1,847	0.43 (0.40-0.46)	78	0.59 (0.44-0.78)	102	1.62 (1.18-2.23)	1,343	2.79 (2.52-3.09)	3,929
Neopl	71	0.10 (0.08-0.13)	2,042	1.80 (1.65-1.96)	57	0.58 (0.42-0.79)	33	0.41 (0.28-0.60)	848	1.35 (1.22-1.49)	3,051
Gastr	404	1.79 (1.56-2.05)	1,139	0.72 (0.66-0.79)	42	0.63 (0.45-0.90)	46	1.02 (0.72-1.45)	564	1.11 (0.99-1.24)	2,195
Skin	170	1.05 (0.88-1.25)	659	0.77 (0.69-0.87)	80	3.20 (2.39-4.29)	36	1.50 (1.03-2.20)	310	1.03 (0.90-1.18)	1,255
Nerv	375	4.63 (3.99-5.37)	391	0.34 (0.30-0.39)	26	0.84 (0.55-1.29)	30	1.38 (0.92-2.08)	286	1.10 (0.95-1.27)	1,108
Blood	73	0.47 (0.37-0.60)	611	1.05 (0.93-1.20)	12	0.39 (0.22-0.70)	4	NC	335	1.59 (1.38-1.83)	1,035
Metab	193	1.73 (1.45-2.06)	488	0.67 (0.59-0.76)	26	0.96 (0.63-1.46)	14	0.65 (0.37-1.13)	274	1.22 (1.05-1.41)	995
Resp	108	0.99 (0.80-1.23)	522	1.24 (1.08-1.44)	17	0.73 (0.44-1.21)	18	1.05 (0.64-1.73)	168	0.77 (0.65-0.92)	833
Inv	81	0.90 (0.71-1.15)	433	1.33 (1.13-1.56)	10	0.52 (0.27-0.99)	19	1.42 (0.87-2.31)	132	0.74 (0.61-0.91)	675
Inj&P	231	4.84 (4.05-5.80)	204	0.34 (0.28-0.40)	20	1.23 (0.77-1.98)	43	4.42 (3.07-6.37)	113	0.69 (0.56-0.86)	611
Musc	117	1.64 (1.33-2.04)	314	0.75 (0.64-0.88)	18	1.10 (0.67-1.80)	26	2.30 (1.49-3.54)	136	0.89 (0.73-1.08)	611
Infec	76	0.96 (0.74-1.23)	348	0.99 (0.84-1.17)	16	0.98 (0.58-1.64)	23	2.01 (1.28-3.17)	140	0.94 (0.77-1.15)	603
Vasc	48	0.61 (0.45-0.83)	214	0.43 (0.36-0.51)	24	1.70 (1.09-2.63)	17	1.55 (0.93-2.60)	251	2.81 (2.36-3.35)	554
Eye	168	3.55 (2.92-4.33)	305	1.03 (0.86-1.23)	4	NC	2	NC	42	0.26 (0.19-0.36)	521
Card	23	0.31 (0.21-0.48)	283	0.99 (0.83-1.19)	14	1.06 (0.61-1.84)	19	2.02 (1.23-3.31)	151	1.42 (1.17-1.74)	490
Hepat	40	0.58 (0.41-0.80)	311	1.28 (1.06-1.54)	33	2.85 (1.93-4.22)	5	0.47 (0.19-1.16)	101	0.80 (0.64-1.00)	490
Renal	40	0.67 (0.48-0.94)	262	1.15 (0.95-1.41)	12	1.04 (0.57-1.88)	6	0.66 (0.29-1.51)	108	1.06 (0.85-1.32)	428
Psych	182	6.36 (5.15-7.84)	137	0.36 (0.29-0.44)	4	NC	9	1.09 (0.55-2.15)	71	0.66 (0.51-0.85)	403
Surg	53	1.81 (1.33-2.47)	136	0.85 (0.66-1.09)	3	NC	60	21.94 (15.39-31.27)	0	-	252
Endo	7	0.47 (0.22-1.02)	28	0.26 (0.17-0.40)	6	2.20 (0.95-5.10)	1	NC	63	4.81 (3.24-7.13)	105
Immun	31	3.45 (2.23-5.35)	43	0.63 (0.42-0.96)	1	NC	1	NC	16	0.66 (0.38-1.13)	92
Ear	15	1.62 (0.92-2.86)	45	1.02 (0.65-1.61)	1	NC	0	-	16	0.82 (0.47-1.42)	77
Repro	2	0.22 (0.05-0.89)	44	1.69 (0.98-2.89)	1	NC	1	NC	15	0.98 (0.55-1.75)	63

Cong	0	-	23	NC	0	-	0	-	1	NC	24
SocCi	7	2.75 (1.14-6.65)	6	0.24 (0.10-0.61)	2	NC	3	NC	6	1.04 (0.41-2.63)	24
Prod	5	2.57 (0.91-7.22)	12	1.45 (0.55-3.88)	0	-	0	-	1	NC	18
Preg	0	-	5	NC	0	-	0	-	0	-	5

Significant RORs are in bold type. NC, not calculated because there were fewer than five reports or there were reports only for one drug. ADR, adverse drug reactions; AVA, avapritinib; Blood, blood and lymphatic system disorders; Card, cardiac disorders; CI, confidence interval; Cong, congenital, familial and genetic disorders; Ear, ear and labyrinth disorders; Endo, Endocrine disorders; Eye, eye disorders; Gastr, gastrointestinal disorders; Genrl, general disorders and administration site conditions; Hepat, hepatobiliary disorders; ICSR, Individual Case Safety Report; IM, imatinib; Immun, immune system disorders; Infec, infections and infestations; Inj&P, injury, poisoning and procedural complications; Inv, investigations; Metab, metabolism and nutrition disorders; Musc, musculoskeletal and connective tissue disorders; Neopl, neoplasms benign, malignant and unspecified (incl cysts and polyps); Nerv, nervous system disorders; Preg, pregnancy, puerperium and perinatal conditions; Prod, product issues; Psych, psychiatric disorders; REG, regorafenib; Renal, renal and urinary disorders; ROR, reporting odds ratio; Repro, Reproductive system and breast disorders; Resp, respiratory, thoracic and mediastinal disorders; RIP, ripretinib; Skin, skin and subcutaneous tissue disorders; SocCi, social circumstances; SU, sunitinib; Surg, surgical and medical procedures; SOC, System Organ Class; Vasc, vascular disorders.