

## **Psychiatric Adverse Reactions to Anaplastic Lymphoma Kinase Inhibitors in Non-Small-Cell Lung Cancer: analysis of spontaneous reports submitted to the FDA Adverse Event Reporting System**

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## SUPPLEMENTARY MATERIAL

### CAUSALITY ASSESSMENT SCORE

Our score is an adaptation of the WHO criteria for causality assessment of spontaneous reports of adverse events, namely, to assess the drug-related component.

We consider time to onset, major and minor alternative causes (separately concomitant drugs and comorbidities), dechallenge, rechallenge, and the role of the drug in adverse event occurrence, as expressed by the reporter (i.e., if the drug was reported as suspect or concomitant). The numerical score obtained was converted to a categorical judgment of probability.

### SCORE

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**Suspect (S)**

0 if the drug is reported as concomitant by the reporter

1 if the drug is suspected as a main cause for the event by the reporter

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**Dechallenge (D)**

0 no information

1 if the event improves/regresses when the drug is withdrawn

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**Rechallenge (R)**

0 no information

1 if the same/similar adverse event reappears when reintroducing the drug

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<b>Concomitant medications (I)</b>	<p>0 no concomitant drugs recorded</p> <p>-2 if concomitant with a drug known to cause the event</p> <p>-1 if concomitant with a drug possibly contributing to the event</p>	<p>-2: (hydroxychloroquine, betamethasone, dexamethasone, fluocortolone, methylprednisolone, paramethasone, prednisolone, prednisone, triamcinolone, hydrocortisone, cortisone, prednylidene, rimexolone, deflazacort, cloprednol, meprednisone, cortivazol, aldosterone, fludrocortisone, desoxycortone)</p> <p>-1: (none)</p>
<b>Comorbidities (P)</b>	<p>0 no comorbidities recorded</p> <p>-2 if comorbidity sufficient to cause the event, reported either as reaction or indication</p> <p>-1 comorbidity contributing to the event, reported either as reaction or indication</p>	<p>-2: (metastases to central nervous system, metastases to meninges, brain neoplasm malignant, brain stem stroke, brain oedema, cerebrovascular accident, brain neoplasm, lumbar spinal stenosis, metastases to spine, spinal cord compression, haemorrhage intracranial, meningioma malignant, basilar artery thrombosis, cerebral artery thrombosis, subarachnoid haemorrhage, leukoencephalopathy, brain abscess, intracranial aneurysm, cerebral haemorrhage, herpes simplex encephalitis)</p> <p>-1: (none)</p>
<b>Time to onset (latency)</b>	<p>0 if time to onset plausible</p> <p>-1 if time to onset not plausible (i.e., the event occurred before the drug was started)</p>	<p>Please note that, apart from excluding negative time to onset, we did not consider any strict interval to identify a plausible latency.</p>

STAGING	COMBINATIONS FOUND
<b>Highly Probable</b>	2/3: S <sub>1</sub> D <sub>1</sub> R <sub>1</sub> ; S <sub>1</sub> D <sub>1</sub> ; S <sub>1</sub> R <sub>1</sub> ; D <sub>1</sub> R <sub>1</sub>
<b>Probable</b>	1: S <sub>1</sub> ; D <sub>1</sub> ; R <sub>1</sub> ; S <sub>1</sub> D <sub>1</sub> R <sub>1</sub> I <sub>-2</sub> ; S <sub>1</sub> D <sub>1</sub> R <sub>1</sub> P <sub>-2</sub>
<b>Possible</b>	0/-1: S <sub>1</sub> D <sub>1</sub> I <sub>-2</sub> ; S <sub>1</sub> I <sub>-2</sub> ; S <sub>1</sub> P <sub>-2</sub> ; S <sub>1</sub> R <sub>1</sub> I <sub>-2</sub> ; S <sub>1</sub> D <sub>1</sub> P <sub>-2</sub>
<b>Unlikely</b>	-2/-3/-4/-5: S <sub>1</sub> I <sub>-2</sub> P <sub>-2</sub> ; S <sub>1</sub> D <sub>1</sub> I <sub>-2</sub> P <sub>-2</sub>

**ALK TKI RELATED PSYCHIATRIC ADVERSE EVENTS: case listing**

ALECTINIB

Case	Psychiatric Event	age	sex	weight	country	time to onset	Stopped*	other drug-related risk factors	other disease-related risk factors	Outcome#	causality score
1	Depression		F		US		N				probable
2	Depression	57	M		US		Y			HO	probable
3	Depression	57	M		US		Y			HO	probable
4	Emotional disorder	43	F	58	US	1	N				probable
5	Depression	49	F	60	GB		N	dexamethasone	metastases to central nervous system	HO	unlikely
6	Depression		M		US		N			HO	probable
7	Feeling abnormal Thinking abnormal		F		US		N				probable
8	Emotional disorder Emotional distress		F		US		N				probable
9	Bradyphrenia	47	F		GR		N			OT	probable
10	Depression		F		US		N				probable
11	Irritability		F		US		N				probable
12	Anxiety	60	F		US		N			HO	probable
13	Suicide attempt Completed suicide	68	M		FR	379	N			DE	probable

14	Psychotic disorder	32	M	110	DE	8	N			HO	probable
15	Acute psychosis Hypomania	36	F	61	IE	25	Y (D)	dexamethasone		HO	possible
16	Mania	48	F		IT	70	N			HO	probable
17	Abnormal behaviour Affective disorder Hypomania	52	F	62	MY		Y			HO	highly probable
18	Mania	46	F		IT		N			HO	probable

BRIGATINIB

Case	Psychiatric Event	age	sex	weight	country	time to onset	Stopped*	other drug-related risk factors	other disease-related risk factors	Outcome#	causality score
1	Psychotic disorder		M	175	US		N			HO	possible
2	Depressed mood Depression Discomfort Emotional distress	62	F		US		N		brain neoplasm malignant	OT	probable
3	Depressed mood Depression Discomfort Emotional distress				US		N		metastases to central nervous system	OT	possible
4	Emotional distress		F	58	US		N		metastases to central nervous system	OT	possible
5	Mania	54	F		CA		N	dexamethasone		HO	possible

6	Depressed mood Depression Emotional distress		F	54	US		N			OT	probable
7	Fear Feeling abnormal		F		US		N				probable
8	Anxiety		M		US		N			OT	probable
9	Anxiety		F		US		N			HO	probable
10	Agitation Hypersomnia	77	F		US		N	dexamethasone			possible

CERITINIB

Case	Psychiatric Event	age	sex	weight	country	time to onset	Stopped*	other drug-related risk factors	other disease-related risk factors	Outcome#	causality score
1	Depression	60	F		US	1076	N				probable
2	Depression	74	F		US		N				probable
3	Emotional disorder Feeding disorder Feeling abnormal	20	F	48	IL		N			HO	probable
4	Depression		F		US		N			OT	probable
5	Anxiety	41	F		US		N			HO	probable
6	Mood altered		F	67	US		N			OT	probable
7	Depression		F		IN		N			OT	probable
8	Psychotic disorder		M		SE		N			OT	probable
9	Anxiety		M		BE		Y			DE	probable
10	Major depression	54	F		BE		N			DE	probable
11	Depressed mood Feeling abnormal	60	M		IL		Y (D)			OT	highly probable
12	Disturbance in attention	87	M		TH		N			DE	probable

## CRIZOTINIB

Case	Psychiatric Event	age	sex	weight	country	time to onset	stopped*	other drug-related risk factor	other disease-related risk factor	Outcome#	causality score
1	Confusional State Feeling Abnormal Speech Disorder	76	F		US	15					probable
2	Hallucination	51	F		US						probable
3	Completed Suicide	53	F	52	JP	17	Y	dexamethasone		DE	possible
4	Suicide Attempt	61	F	43	JP	170	Y			LT	probable
5	Depression Euphoric Mood	60	F		US	7					probable
6	Confusional State Depression Fatigue Insomnia Lethargy	58	F		US					OT	probable
7	Mania	38	M	80	DE	288		dexamethasone		HO	possible
8	Feeling Jittery Irritability Nervousness	69	F		US						probable
9	Insomnia Psychotic Disorder	84	F		US					OT	probable
10	Abnormal Behaviour Cognitive Disorder	70	M	61	FR	60	Y			HO	probable
11	Anxiety Fatigue	67	M		US						probable
12	Hallucination, Visual	56	M		US						probable



13	Completed Suicide	48	F		CN				DE	probable
14	Depression	45	F		US					probable
15	Anxiety	47	M		US		Y			probable
16	Depression	54	F	62	SA				OT	probable
17	Agitation Delirium Persecutory Delusion Irregular Sleep Wake Rhythm Disorder	55	F		FR	241			HO	probable
18	Anxiety Suicidal ideation	56	F	70	US	422			OT	probable
19	Major Depression	62	M	61	JP	264			HO	probable
20	Psychiatric Decompensation Vomiting Psychogenic	48	M		CH		Y (D)		OT	highly probable
21	Cognitive Disorder Eating Disorder Fatigue Memory Impairment Psychotic Disorder Stress	59	F	46	US					probable

22	Incoherent Insomnia Intentional Overdose Memory Impairment Poverty of Speech Psychomotor Hyperactivity Somnolence	37	F		RU		Y (D)			HO	highly probable
23	Hallucination Restlessness	63	F		US	19					probable
24	Abnormal Behaviour Aggression Atered State of Consciousness Insomnia	66	M		TR			dexamethasone		DE	possible
25	Abnormal Behaviour Language Disorder Personality Change	64	F		US					OT	probable
26	Depression	76	M	72	US						probable
27	Completed Suicide	50	F		JP		Y (D)			DE	highly probable
28	Aggression Intentional Self- Injury Mental Disorder Nervousness	69	M		SK					HO	probable
29	Anxiety	75	F		US						probable

## LORLATINIB

Case	Psychiatric Event	age	sex	weight	country	time to onset	Stopped*	other drug-related risk factors	other disease-related risk factors	Outcome#	causality score
1	Hallucination, auditory Hallucination, visual Persecutory delusion	64	F		FR	13	N	prednisone		OT	possible
2	Aggression Depression Hallucination, auditory	63	F	66	US	1	Y (D)			OT	highly probable
3	Aggression Anxiety Hallucination	69	M	82	FR		Y (D)	prednisolone		HO	possible
4	Anger Anxiety Insomnia Mood altered Nightmare	39	F	59	SG		N			OT	probable
5	Depression Psychotic disorder	38	F	58	ES		Y (D)	dexamethasone		DS	unlikely
6	Psychotic disorder	38	F	165	ES		Y (D)			HO	highly probable
7	Mood altered	57	M	68	MY		Y (D)			OT	highly probable
8	Delusion Feeling abnormal Hallucination, auditory Hallucination, visual	72	F		JP		Y (D)			HO	highly probable

9	Depressed mood Feeling abnormal	72	F		US		N			HO	probable
10	Thinking abnormal		F		US		N			HO	probable
11	Hallucination Psychotic disorder	45	M	85	FR		Y			DS	probable
12	Aggression Delirium	70	F		JP	4	N			OT	probable
13	Delirium Hallucination Suicidal ideation	69	M		JP		Y (D;R)			DE	highly probable
14	Anger Irritability		F		US		N				probable
15	Psychotic symptom	39	M	62	JP	16	Y (D)			HO	highly probable
16	Hallucination	62	M	64	JP	5	Y (D)			OT	highly probable
17	Abnormal dreams Nightmare		M		US		N				probable
18	Affective disorder	44	M	80	FR		Y (D)			OT	highly probable
19	Substance-induced psychotic disorder	23	M	72	CA		Y (D)			HO	highly probable
20	Panic disorder	89	F		JP	2	Y			OT	probable
21	Hallucination	80	F	69	BE	220	Y (D)			HO	highly probable
22	Nervousness	65	M	73	US		N				probable
23	Hallucination				KW		Y			OT	probable

<b>24</b>	Depersonalisation/derealisation disorder Feeling abnormal Nightmare Psychiatric symptom	79	F	53	JP		Y (D)	prednisolone		OT	possible
<b>25</b>	Anxiety Panic attack	22	M	58	IT		N			OT	probable
<b>26</b>	Feeling of despair	53	F	62	US		Y			HO	probable

\* (D) refers to a verified dechallenge; (R) to a verified rechallenge  
# DE = Death; DS = Disability; HO = Hospitalization; OT = Other serious