Supplementary

Table S1 Study characteristics of included trials of ALK inhibitors in treatment-naïve patients with *ALK* rearranged advanced non-small cell lung cancer

Study name (author, year)	Intervention arm (no. of patients)	Comparator arm (no. of patients)	Median age, years (intervention arm *vs.* comparator arm)	Gender (male), % (intervention arm *vs.* comparator arm)	Brain or CNS metastases, % (intervention arm *vs.* comparator arm)	ORR,% (intervention arm *vs.* comparator arm)	IRC PFS, HR (95% CI)	IA PFS, HR (95% CI)	OS, HR (95% CI)	Ref.
PROFILE 1014 (Solomon, 2014; Solomon 2018)	Crizotinib N=172	Chemotherapy N=171	52 *vs.* 54	40 *vs.* 37	26 *vs.* 27	74 *vs.* 45	0.45 (0.35–0.60)	–	0.76 (0.55–1.05)	(2,12)
PROFILE 1029 (Wu, 2018)	Crizotinib N=104	Chemotherapy N=103	48 *vs.* 50	48 *vs.* 42	20 *vs.* 31	88 *vs.* 46	0.40 (0.29–0.57)	–	0.90 (0.56–1.45)	(13)
J-ALEX (Hida, 2017; Nakagawa, 2020; Yoshioka 2021)	Alectinib N=103	Crizotinib N=104	61 *vs.* 60	40 *vs.* 39	14 *vs.* 28[†]	92 *vs.* 79	0.31 (0.17–0.57)[‡]	–	–	(17-19)
ALEX (Peters, 2017; Mok, 2020)	Alectinib N=152	Crizotinib N=151	56 *vs.* 54	45 *vs.* 42	42 *vs.* 38	83 *vs.* 76	0.50 (0.36–0.70)	0.43 (0.32–0.58)	0.67 (0.46–0.98)	(14,15)
ASCEND-4 (Soria, 2017)	Ceritinib N=189	Chemotherapy N=187	55 *vs.* 54	46 *vs.* 39	31 *vs.* 33	73 *vs.* 27	0.55 (0.42–0.73)	0.49 (0.37–0.64)	0.73 (0.50–1.08)	(23)
ALESIA (Zhou, 2019)	Alectinib N=125	Crizotinib N=62	51 *vs.* 51	51 *vs.* 55	35 *vs.* 37[†]	91 *vs.* 77	0.37 (0.22–0.61)	0.22 (0.13–0.38)	0.28 (0.12–0.68)	(16)
ALTA-1L (Camidge, 2020; Camidge, 2021)	Brigatinib N=137	Crizotinib N=138	58 *vs.* 60	50 *vs.* 41	29 *vs.* 30	74 *vs.* 62	0.50 (0.35–0.73)[§]	–	–	(20,21)
CROWN (Shaw, 2020; Solomon, 2022)	Lorlatinib N=149	Crizotinib N=147	59 *vs.* 56	44 *vs.* 38	26 *vs.* 27	76 *vs.* 58	0.28 (0.19–0.41)	0.21 (0.14–0.31)	0.72 (0.41–1.25)	(25,26)
eXalt3[¶] (Horn, 2021)	Ensartinib N=121	Crizotinib N=126	54 *vs.* 53	50 *vs.* 52	33 *vs.* 40	74 *vs.* 67	0.45 (0.30–0.66)	–	0.91 (0.54–1.54)	(24)

[†], presence of brain or CNS metastases based on independent review. [‡], subgroup of patients in first-line setting (alectinib n=66; crizotinib n=67). [§], subgroup of patients with no prior chemotherapy (brigatinib n=101; crizotinib n=101). [¶], using modified intent-to-treat (mITT) patient population. CI, confidence interval; CNS; central nervous system; HR, hazard ratio; IA, investigator assessed; IRC, independent review criteria; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

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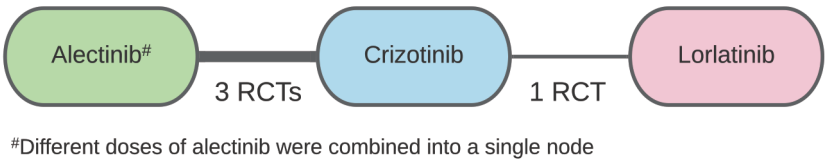

Figure S1 Evidence network for the network meta-analysis of progression-free survival by investigator assessment in treatment-naïve patients with *ALK* rearranged advanced non-small cell lung cancer. Colours represent first-generation (blue), second-generation (green) and third-generation (pink) ALK TKI. RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor.

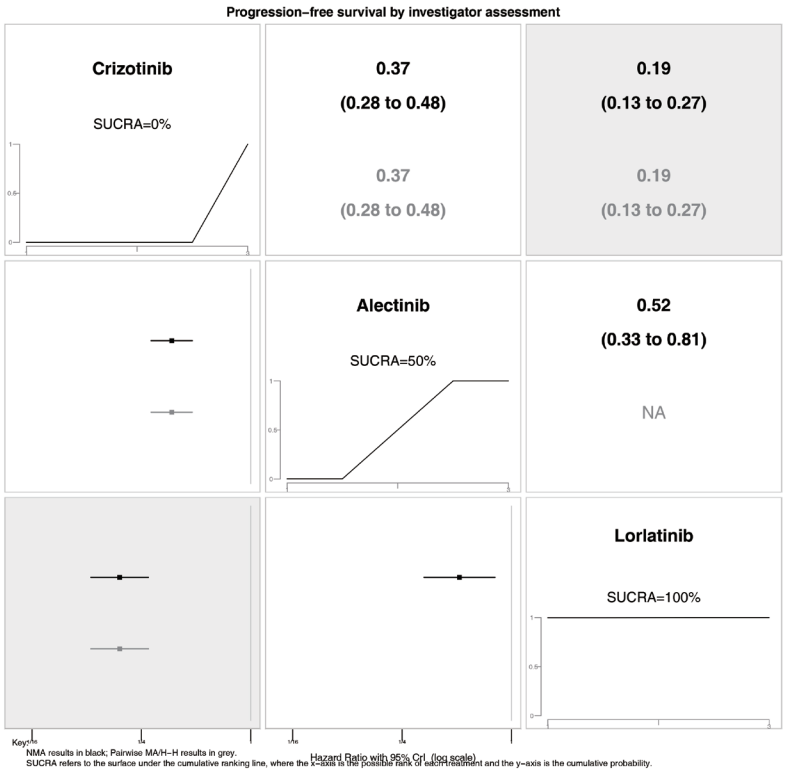

Figure S2 Network meta-analysis of hazard ratios for progression-free survival by investigator assessment for individual ALK inhibitors in treatment-naïve patients with *ALK* rearranged advanced non-small cell lung cancer. Significant results in bold. CrI, credible interval; H-H, head-to-head; MA, meta-analysis; NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve.

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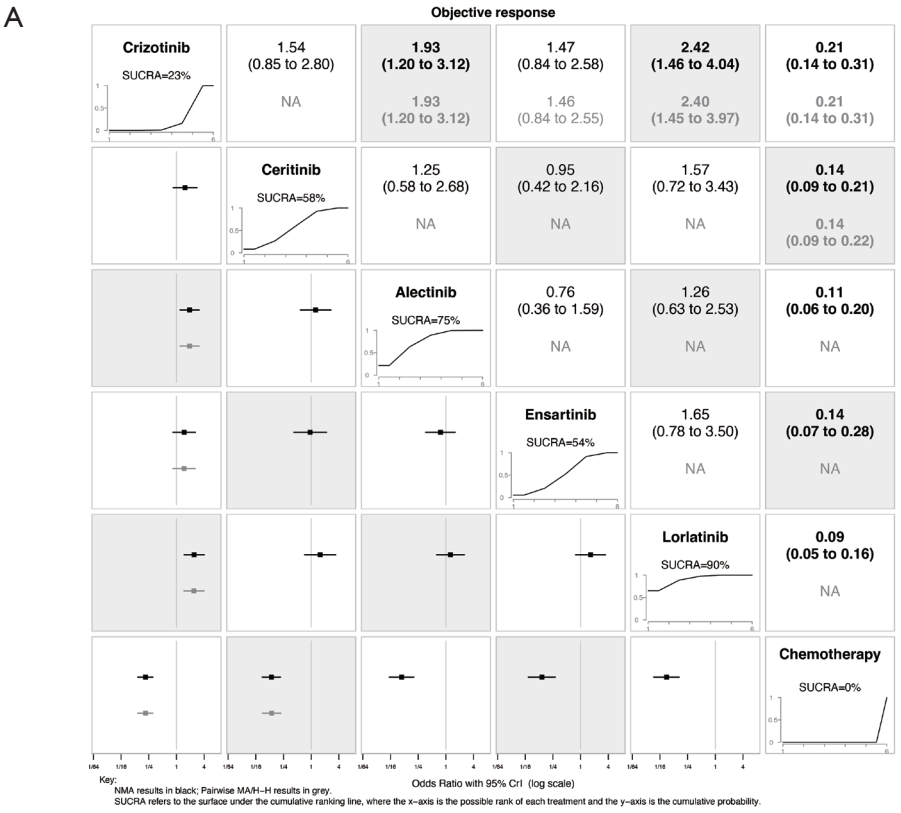

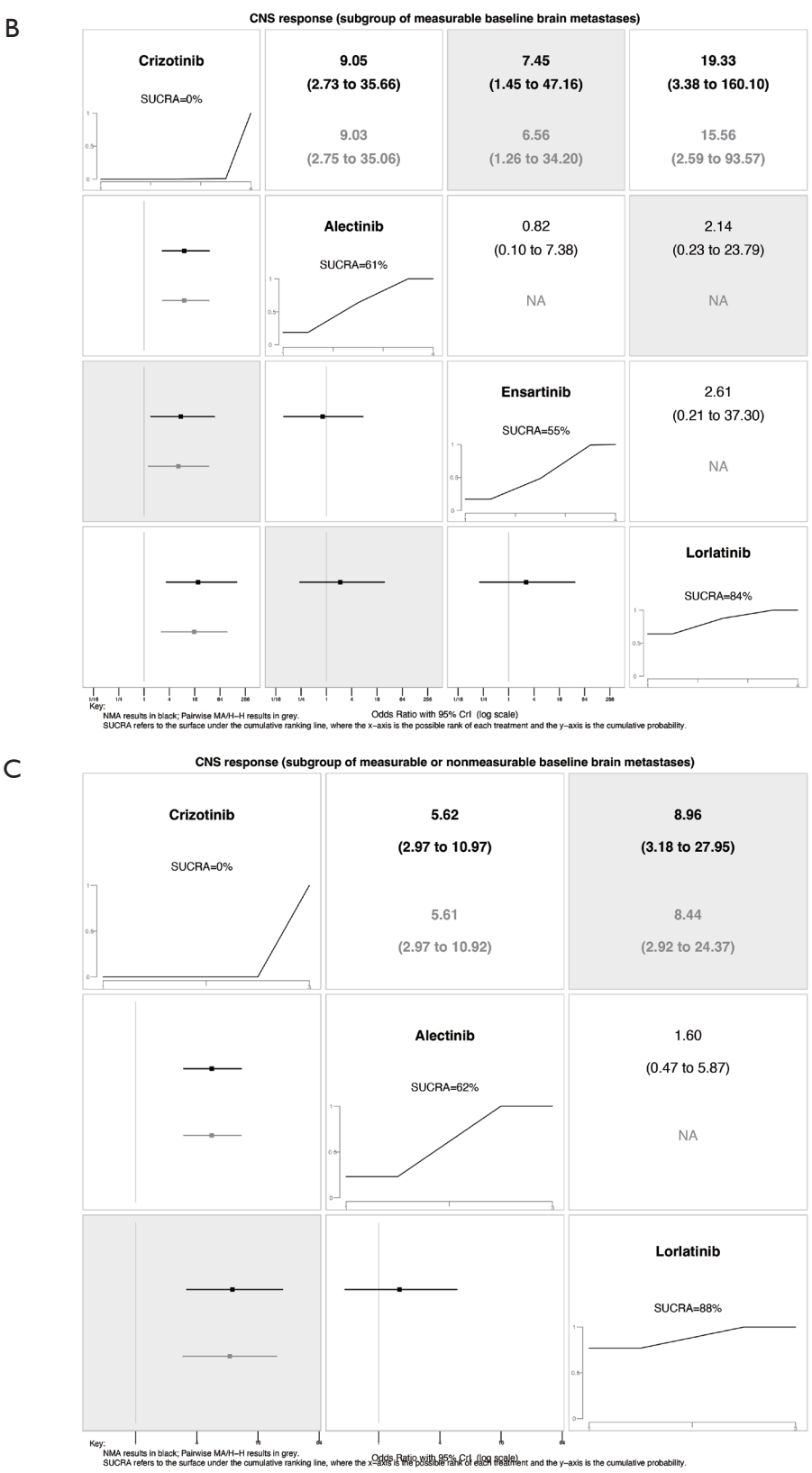

Figure S3 Network meta-analysis of odds ratios for response rate by independent review criteria according to the presence of baseline brain metastases for individual ALK inhibitors in treatment-naïve patients with *ALK* rearranged advanced non-small cell lung cancer. (A) Objective response rate; (B) CNS response rate in patients with measurable brain metastases at baseline; (C) CNS response rate in patients with measurable and non-measurable brain metastases at baseline. Significant results in bold. CNS, central nervous system; CrI, credible interval; H-H, head-to-head; MA, meta-analysis; NA, not available; NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve.

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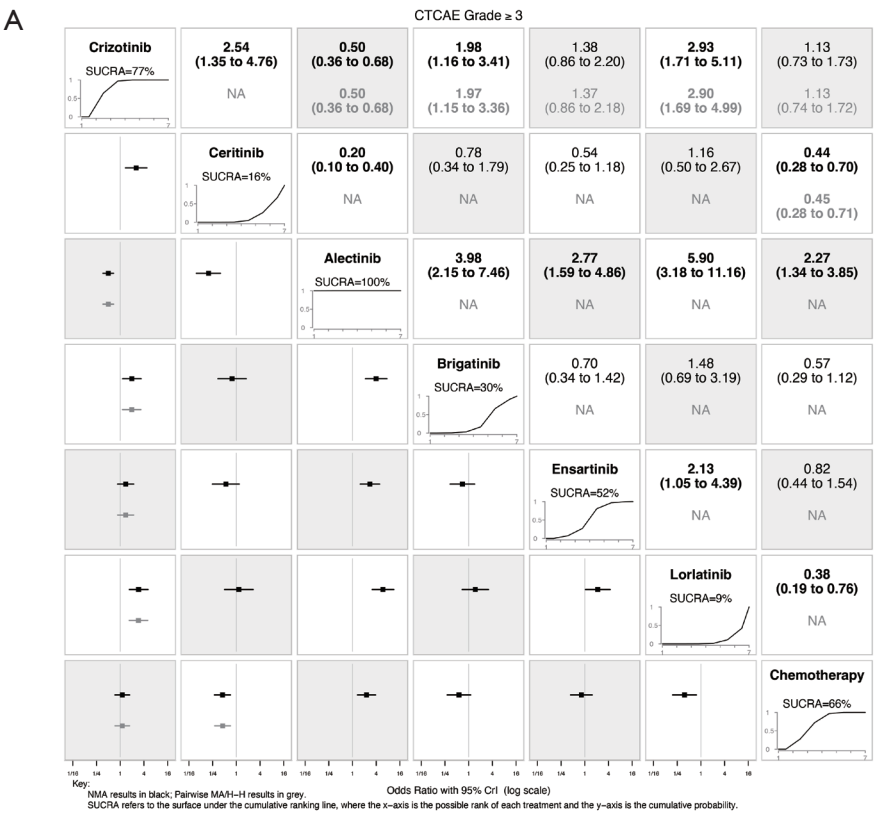

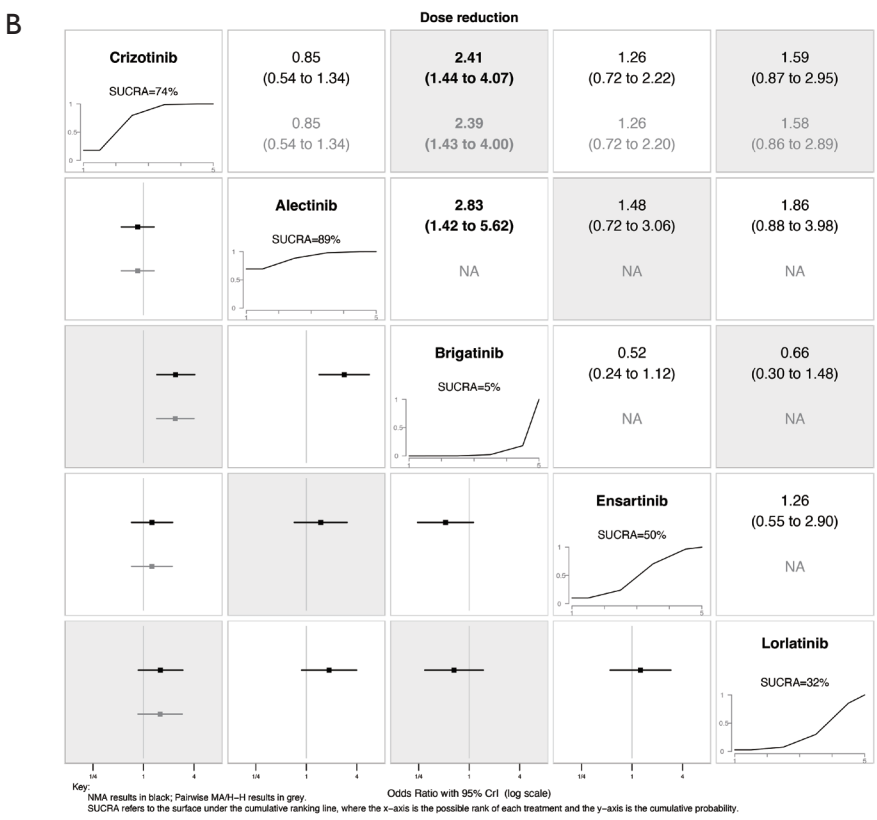

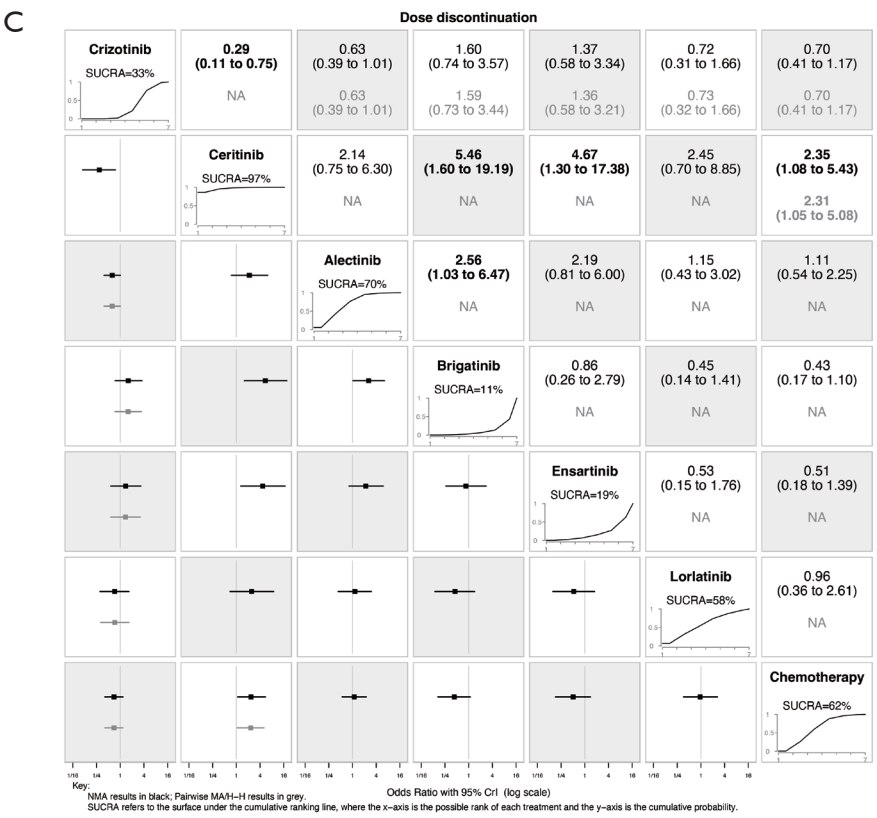

Figure S4 Network meta-analysis of odds ratios for toxicity and safety evaluation for individual ALK inhibitors in treatment-naïve patients with *ALK* rearranged advanced non-small cell lung cancer. (A) Proportion of patients with CTCAE grade 3 or higher all-cause adverse events; (B) dose reduction due to adverse events; (C) dose discontinuation due to adverse events. Significant results in bold. CrI, credible interval; CTCAE, Common Terminology Criteria for Adverse Events; H-H, head-to-head; MA, meta-analysis; NA, not available; NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve.

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Table S2 Toxicity outcomes of included trials of ALK inhibitors

Study name (author, year)	Intervention arm (no. of patients)	Comparator arm (no. of patients)	Dose reduction (n, intervention arm *vs.* comparator arm)	Dose discontinuation (n, intervention arm *vs.* comparator arm)	CTCAE grade 3 or higher adverse events (n, intervention arm *vs.* comparator arm)	Ref.
PROFILE 1014 (Solomon, 2014; Solomon 2018)	Crizotinib N=169	Chemotherapy N=171	NR	20 *vs.* 24	86 *vs.* 90	(2,12)
PROFILE 1029 (Wu, 2018)	Crizotinib N=104	Chemotherapy N=101	NR	19 *vs.* 4	NR	(13)
J-ALEX (Hida, 2017)	Alectinib N=103	Crizotinib N=104	NR	9 *vs.* 21	27 *vs.* 54	(17)
ALEX (Peters, 2017)	Alectinib N=152	Crizotinib N=151	24 *vs.* 31	17 *vs.* 19	63 *vs.* 76	(14)
ASCEND-4 (Soria, 2017)	Ceritinib N=189	Chemotherapy N=175	152 *vs.* 78	10 *vs.* 20	148 *vs.* 108	(23)
ALESIA (Zhou, 2019)	Alectinib N=125	Crizotinib N=62	30 *vs.* 14	9 *vs.* 6	36 *vs.* 30	(16)
ALTA-1L (Camidge, 2018)	Brigatinib N=136	Crizotinib N=137	60 *vs.* 34	18 *vs.* 12	106 *vs.* 88	(22)
CROWN (Shaw, 2020; Solomon, 2022)	Lorlatinib N=149	Crizotinib N=142	32 *vs.* 21	11 *vs.* 14	123 *vs.* 88	(25,26)
eXalt3 (Horn, 2021)	Ensartinib N=143	Crizotinib N=146	34 *vs.* 29	13 *vs.* 10	72 *vs.* 62	(24)

CTCAE, Common Terminology Criteria for Adverse Events; NR, not reported.

Table S3 Relative toxicity of treatments on commonly reported specific adverse events for ALK inhibitors and chemotherapy

Treatment	SUCRA (%)													
	AST/ALT elevation	Nausea	Constipation	Vomiting	Fatigue	Anaemia	Oedema	Diarrhoea	Dizziness	Dysgeusia	Headache	Loss of appetite	Vision disorder	Rash
Crizotinib	33	28	16	17	50	98	29	24	19	9	23	34	0	90
Ceritinib	7	1	68	0	20	72	NR	0	NR	NR	61	1	NR	NR
Alectinib	76	98	37	100	90	15	60	84	85	81	83	94	65	67
Brigatinib	39	68	99	63	61	NR	98	36	56	69	16	61	91	25
Ensartinib	22	36	4	54	25	62	31	NR	12	12	NR	NR	NR	1
Lorlatinib	77	84	71	79	89	41	1	60	41	50	29	85	25	67
Chemotherapy	97	35	56	36	15	11	82	96	87	80	88	25	69	NR

Treatments with the lowest SUCRA for specific adverse events are shaded grey. ALT, alanine aminotransferase; AST, aspartate aminotransferase; NR, not reported; SUCRA, surface under the cumulative ranking line.

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Table S4 Risk of bias assessment

Study name	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding, subjective outcomes	Blinding, objective outcomes	Incomplete outcome data	Selective reporting	Other threats	Ref.
PROFILE 1014	Low	Low	High	High	Low	Low	Low	Unclear	(2,12)
PROFILE 1029	Unclear	Unclear	High	High	Low	Low	Low	Unclear	(13)
ALEX	Low	Low	High	High	Low	High	Low	Unclear	(14,15)
ALESIA	Low	Low	High	High	Low	Low	High	Unclear	(16)
J-ALEX	Low	Low	High	High	Low	Low	Unclear	Unclear	(17,18)
ALTA-1L	Unclear	Unclear	High	High	Low	Low	High	Unclear	(20,21)
ASCEND-4	Low	Low	High	High	Low	Low	Low	Unclear	(23)
CROWN	Unclear	Unclear	High	High	Low	Low	Low	Unclear	(25)
eXalt3	Unclear	Unclear	High	High	Low	Low	Low	Unclear	(24)

Table S5 Summary of risk of bias assessment

Grade	Random sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding, subjective outcomes	Blinding, objective outcomes	Incomplete outcome data	Selective reporting	Other threats
Low	56%	56%	0%	0%	100%	89%	67%	0%
Unclear	44%	44%	0%	0%	0%	0%	11%	100%
High	0%	0%	100%	100%	0%	11%	22%	0%

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Table S6 Certainty of the evidence

Outcomes	Certainty of the evidence (GRADE)
Progression-free survival (PFS) by independent review criteria (IRC)	High
PFS IRC (patients without brain metastases)	High
PFS IRC (patients with brain metastases)	High
Objective response rate	High
Overall survival	High
CTCAE grade 3 or higher adverse events	Low[1]
Dose discontinuation	High

[1], as trials were unblinded and adverse events can be a subjective outcome. CTCAE, Common Terminology Criteria for Adverse Events.

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