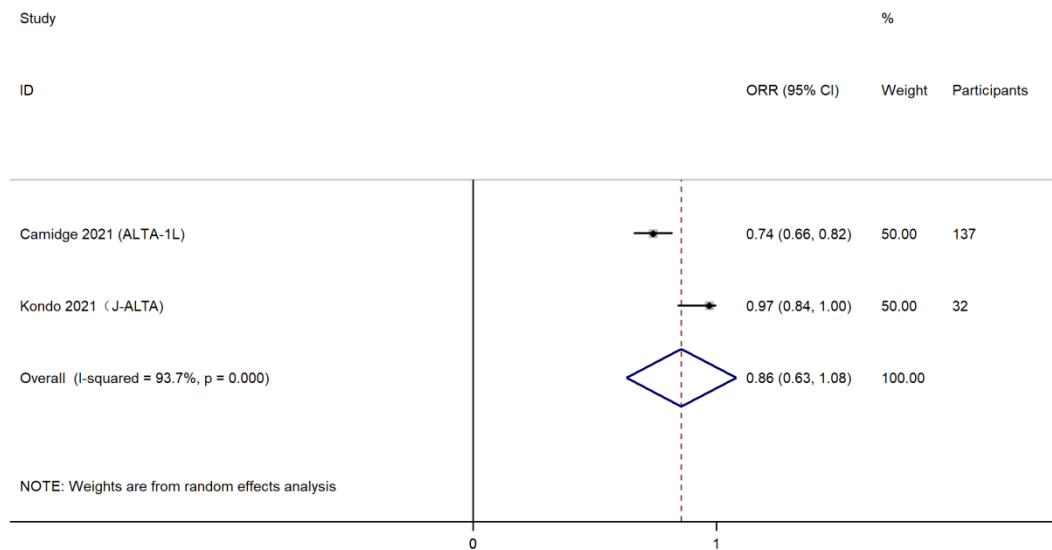
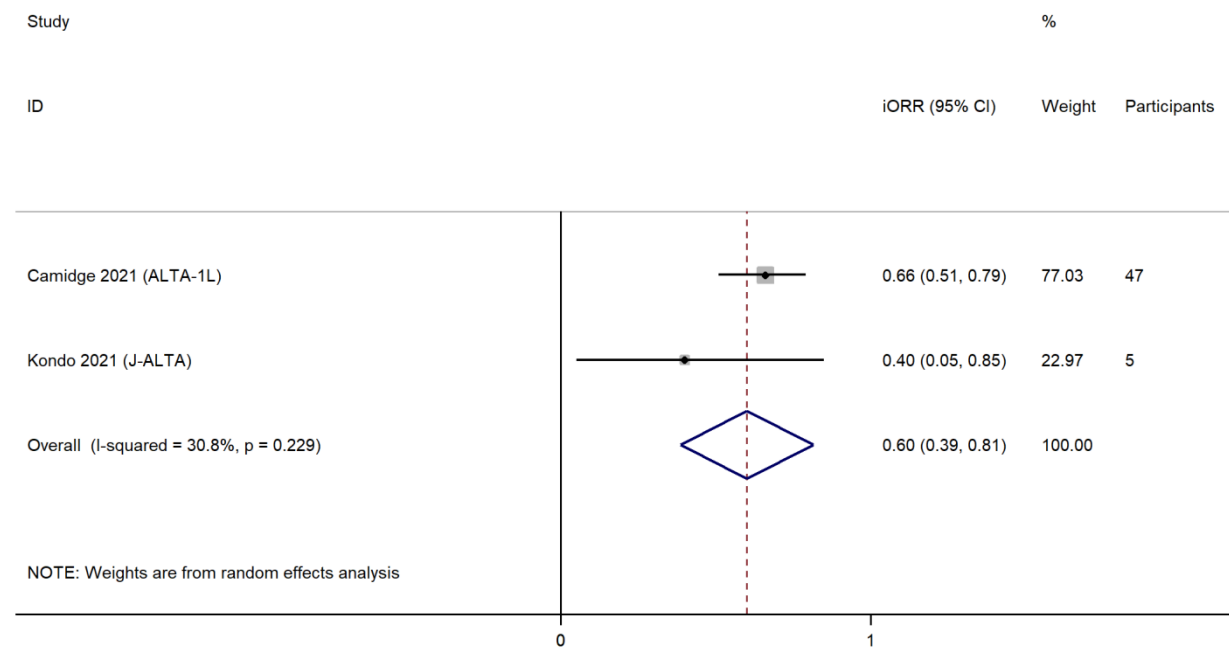


Supplementary Material

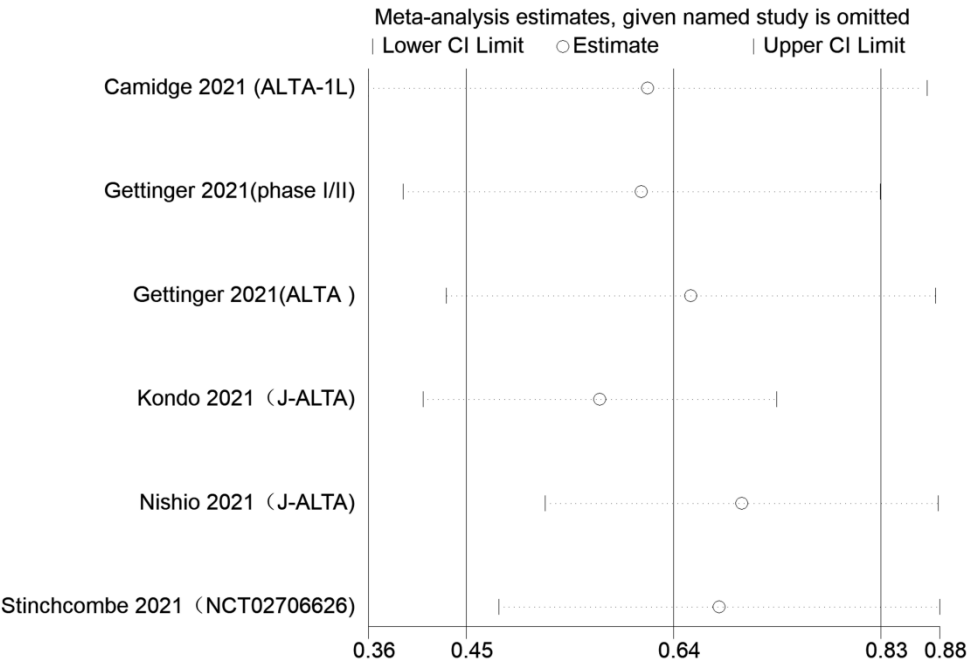


Supplemental Figure 1. Forest plot of objective response rate (ORR) among patients who received brigatinib as first-line treatment.

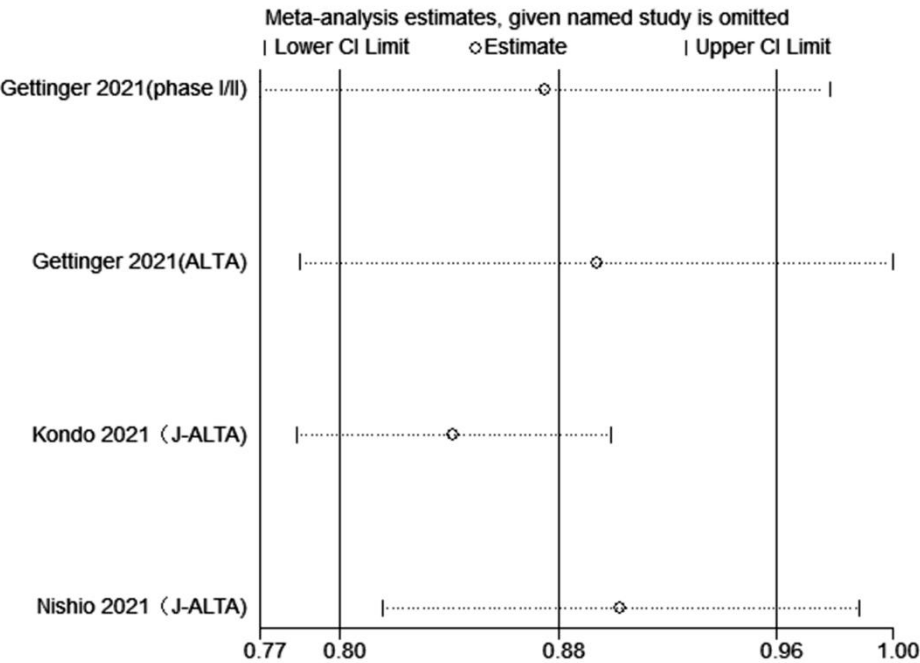


Supplemental Figure 2. Forest plot of intracranial objective response rate (iORR) among patients who received brigatinib as first-line treatment.

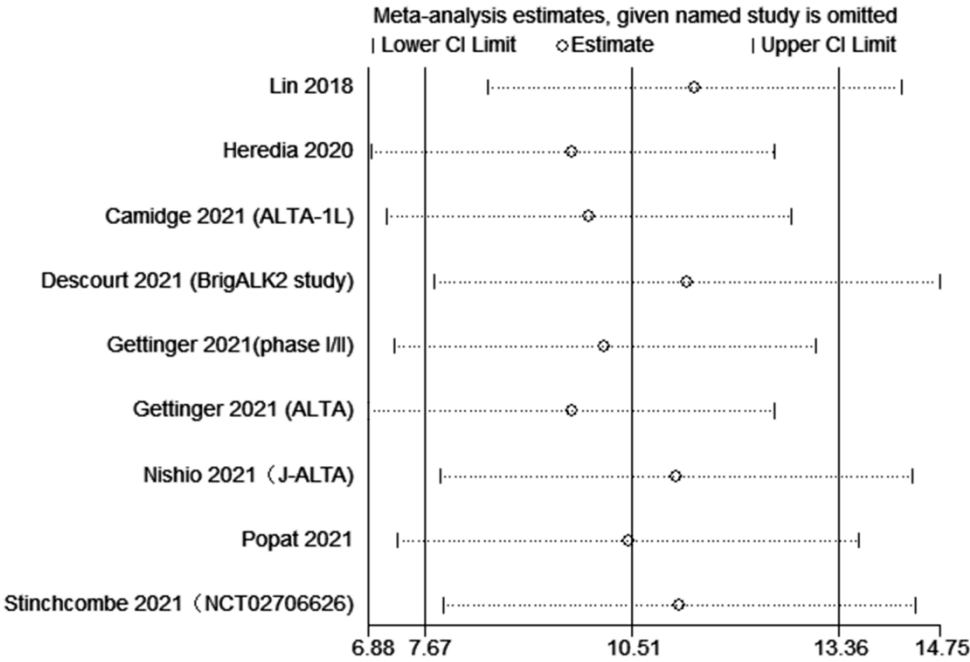
(3A)



(3B)

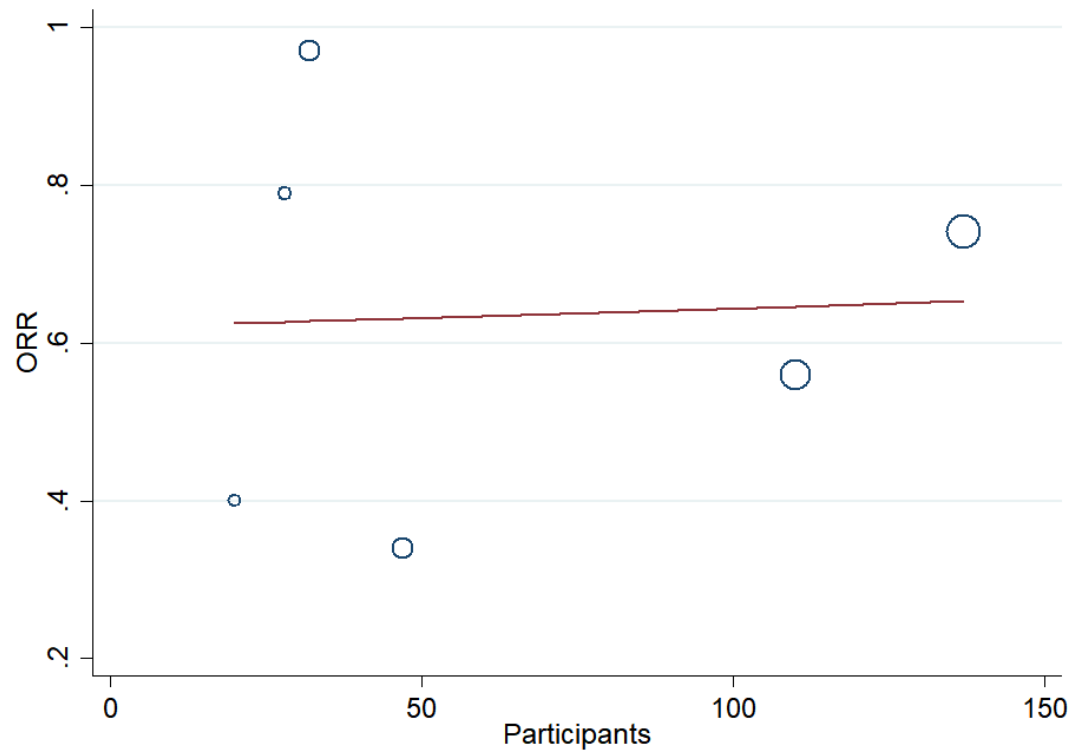


(3C)



Supplemental Figure 3. A, Sensitivity analysis of objective response rate (ORR); B, Sensitivity analysis of disease control rate (DCR); C, Sensitivity analysis of progression free survival (PFS).

(4A)

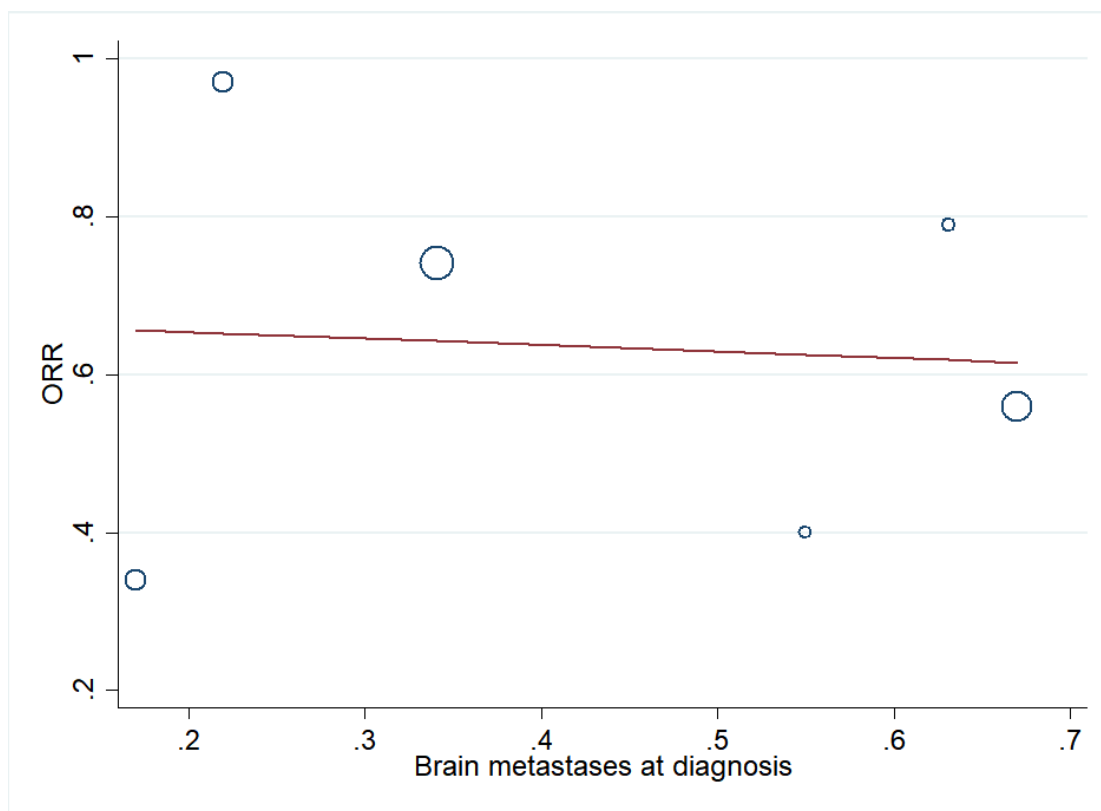


Meta-regression
REML estimate of between-study variance
 % residual variation due to heterogeneity
 Proportion of between-study variance explained
With Knapp-Hartung modification

Number of obs = **6**
 tau2 = **.06782**
 I-squared_res = **93.41%**
 Adj R-squared = **-28.18%**

orr	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
participants	.0002471	.0024537	0.10	0.925	-.0065654	.0070595
_cons	.6192675	.1924284	3.22	0.032	.0850005	1.153535

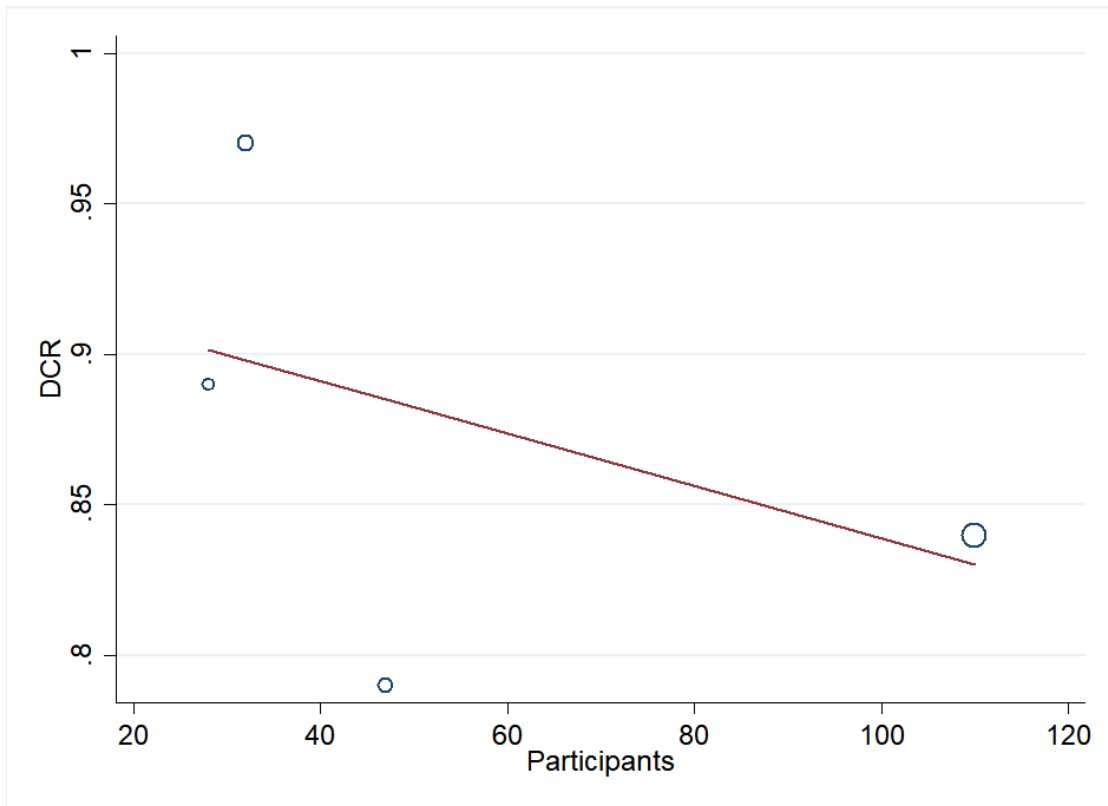
(4B)



Meta-regression	Number of obs	=	6			
REML estimate of between-study variance	tau2	=	.06733			
% residual variation due to heterogeneity	I-squared_res	=	93.21%			
Proportion of between-study variance explained	Adj R-squared	=	-27.24%			
With Knapp-Hartung modification						
orr	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
brainmetastasesatdiagnosis	-.0821656	.5592249	-0.15	0.890	-1.634823	1.470492
_cons	.670191	.2628434	2.55	0.063	-.0595793	1.399961

Supplemental Figure 4. A, Meta-regression analysis for heterogeneity of objective response rate (ORR) regarding sample size; B; Meta-regression analysis for heterogeneity of objective response rate (ORR) regarding brain metastases.

(5A)



Meta-regression

REML estimate of between-study variance

% residual variation due to heterogeneity

Proportion of between-study variance explained

With Knapp-Hartung modification

Number of obs = 4

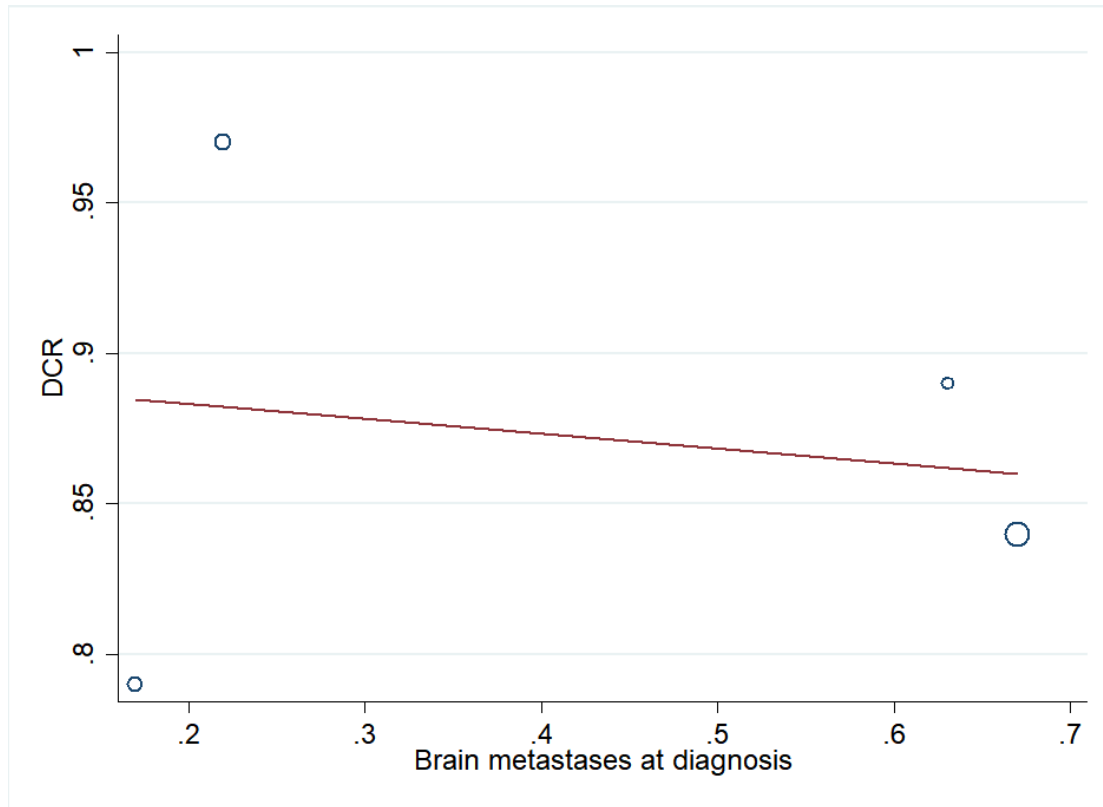
tau2 = .002547

I-squared_res = 27.81%

Adj R-squared = -96.14%

dcr	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
participants	-.0008715	.0011434	-0.76	0.526	-.0057913	.0040483
_cons	.9260117	.0836344	11.07	0.008	.566162	1.285861

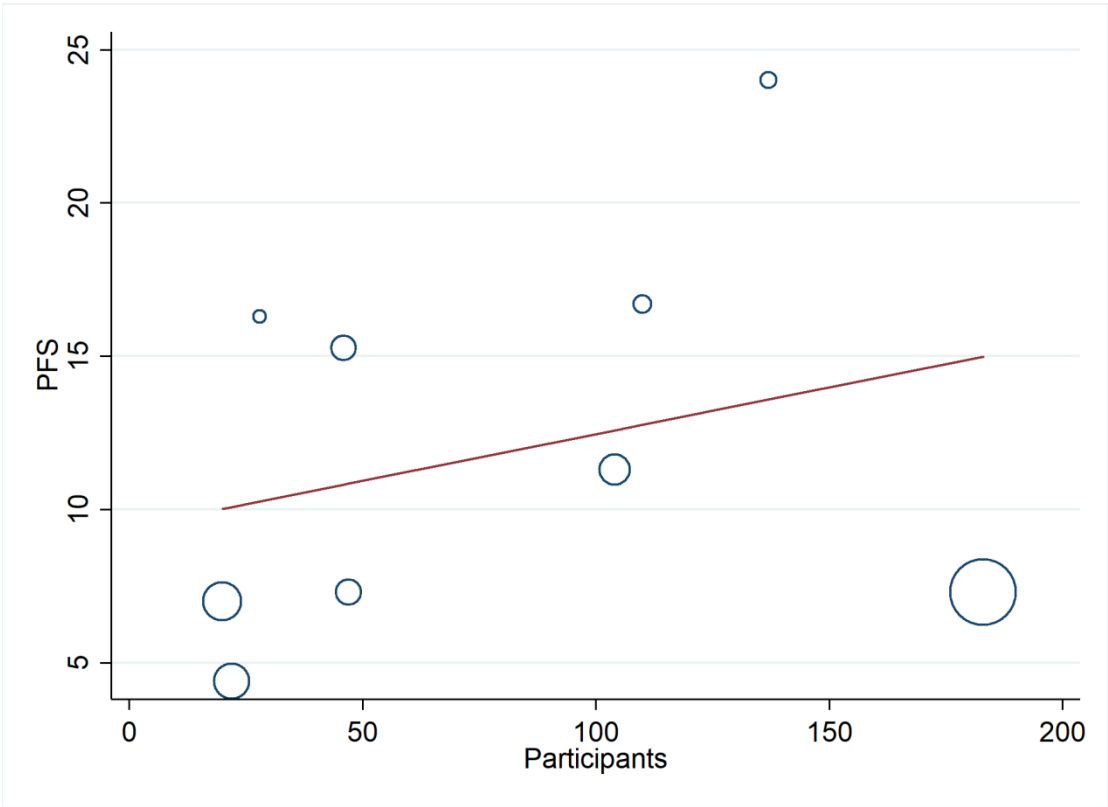
(5B)



Meta-regression	Number of obs	=	4			
REML estimate of between-study variance	tau2	=	.003883			
% residual variation due to heterogeneity	I-squared_res	=	43.41%			
Proportion of between-study variance explained	Adj R-squared	=	-199.04%			
With Knapp-Hartung modification						
dcr	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
brainmetastasesatdiagnosis	-.0495535	.1985982	-0.25	0.826	-.9040524	.8049454
_cons	.8931612	.0989432	9.03	0.012	.4674429	1.318879

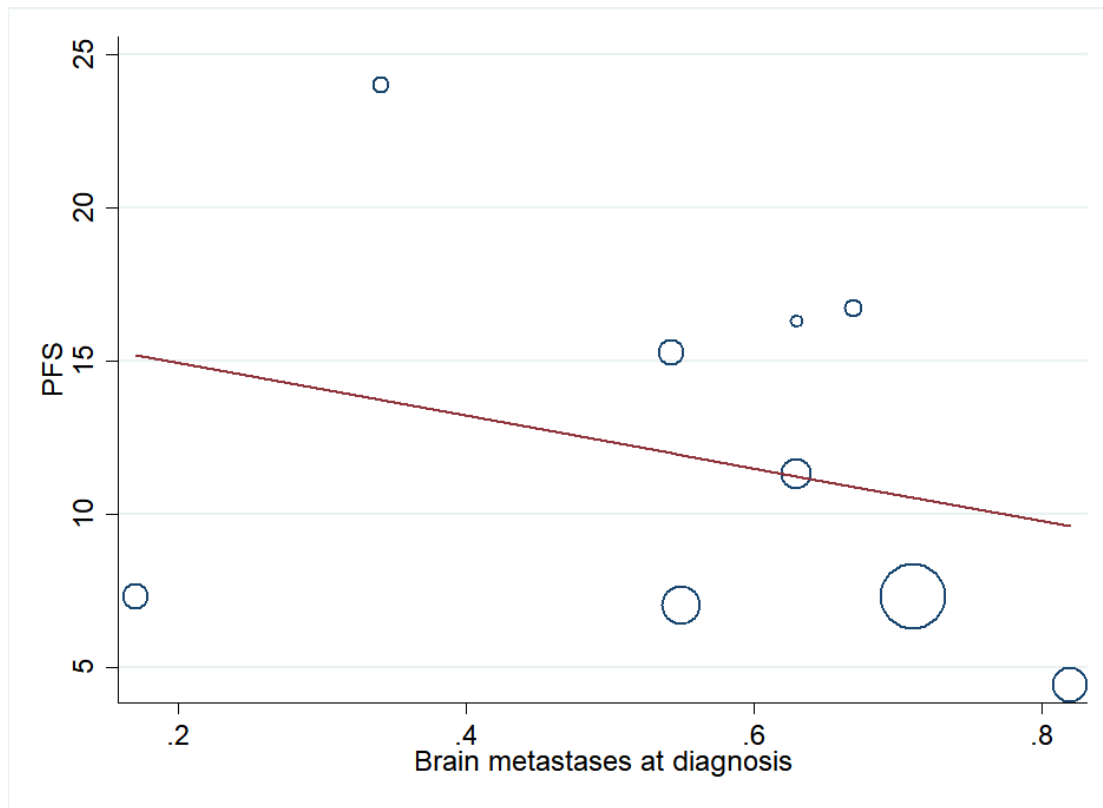
Supplemental Figure 5. A, Meta-regression analysis for heterogeneity of disease control rate (DCR) regarding sample size; B; Meta-regression analysis for heterogeneity of disease control rate (DCR) regarding brain metastases.

(6A)



Meta-regression					Number of obs	=	9
REML estimate of between-study variance					tau2	=	36.35
% residual variation due to heterogeneity					I-squared_res	=	90.75%
Proportion of between-study variance explained					Adj R-squared	=	-7.53%
With Knapp-Hartung modification							
pfs	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]		
participants	.0304864	.0382823	0.80	0.452	-.0600367	.1210096	
_cons	9.406849	3.669978	2.56	0.037	.7287293	18.08497	

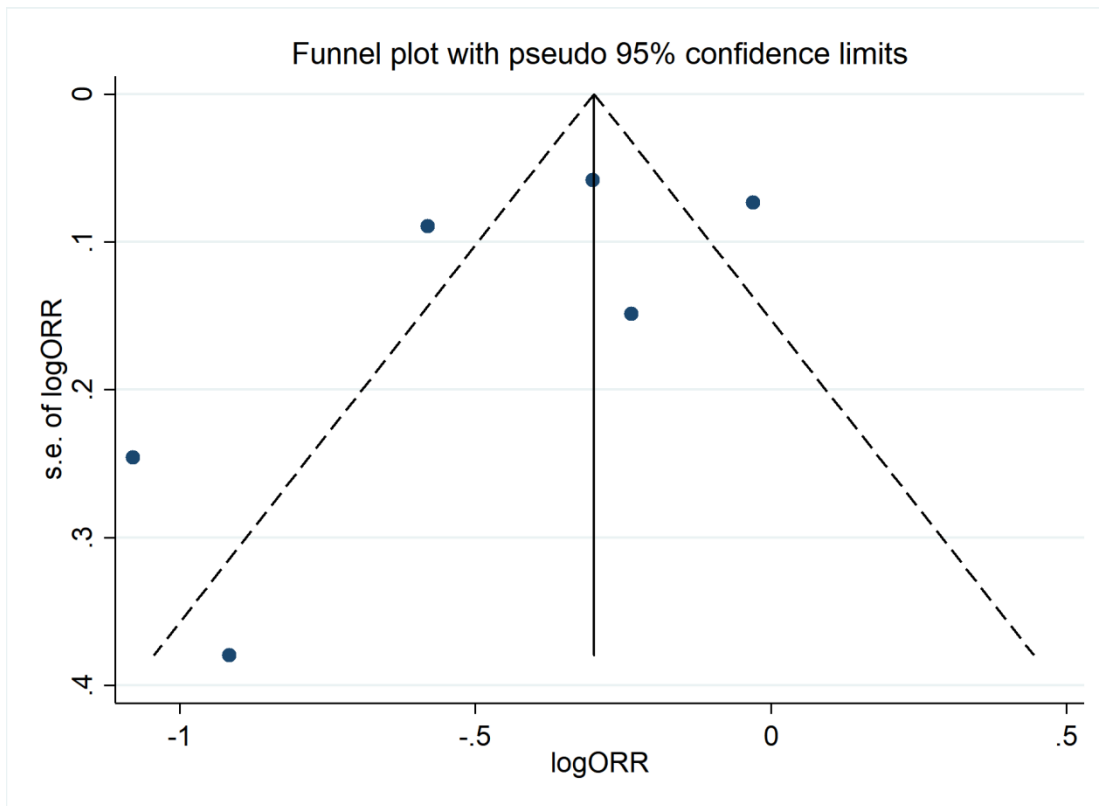
(6B)



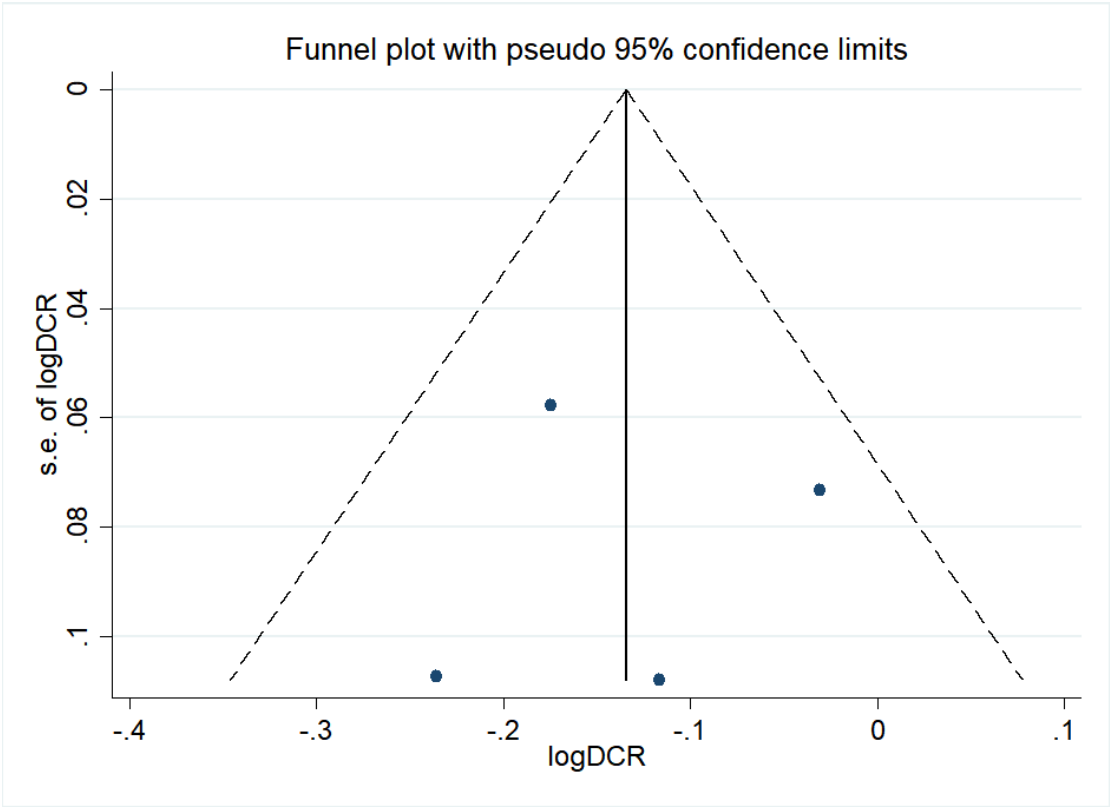
Meta-regression			Number of obs = 9		
REML estimate of between-study variance			tau2 = 36.17		
% residual variation due to heterogeneity			I-squared_res = 89.32%		
Proportion of between-study variance explained			Adj R-squared = -7.00%		
With Knapp-Hartung modification					
pfs	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
brainmetastasesatdiagnosis	-8.580177	11.43503	-0.75	0.478	-35.61973 18.45937
_cons	16.63752	6.815945	2.44	0.045	.5203719 32.75467

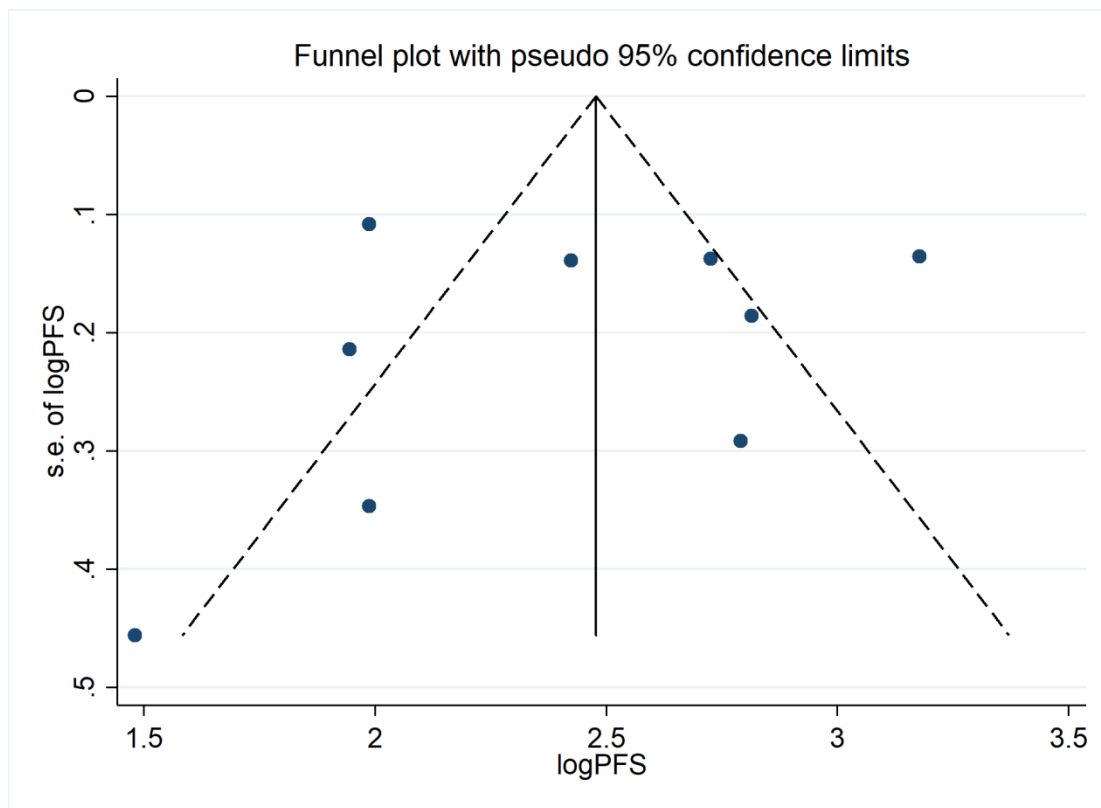
Supplemental Figure 6. A, Meta-regression analysis for heterogeneity of progression free survival (PFS) regarding sample size; B; Meta-regression analysis for heterogeneity of progression free survival (PFS) regarding brain metastases.

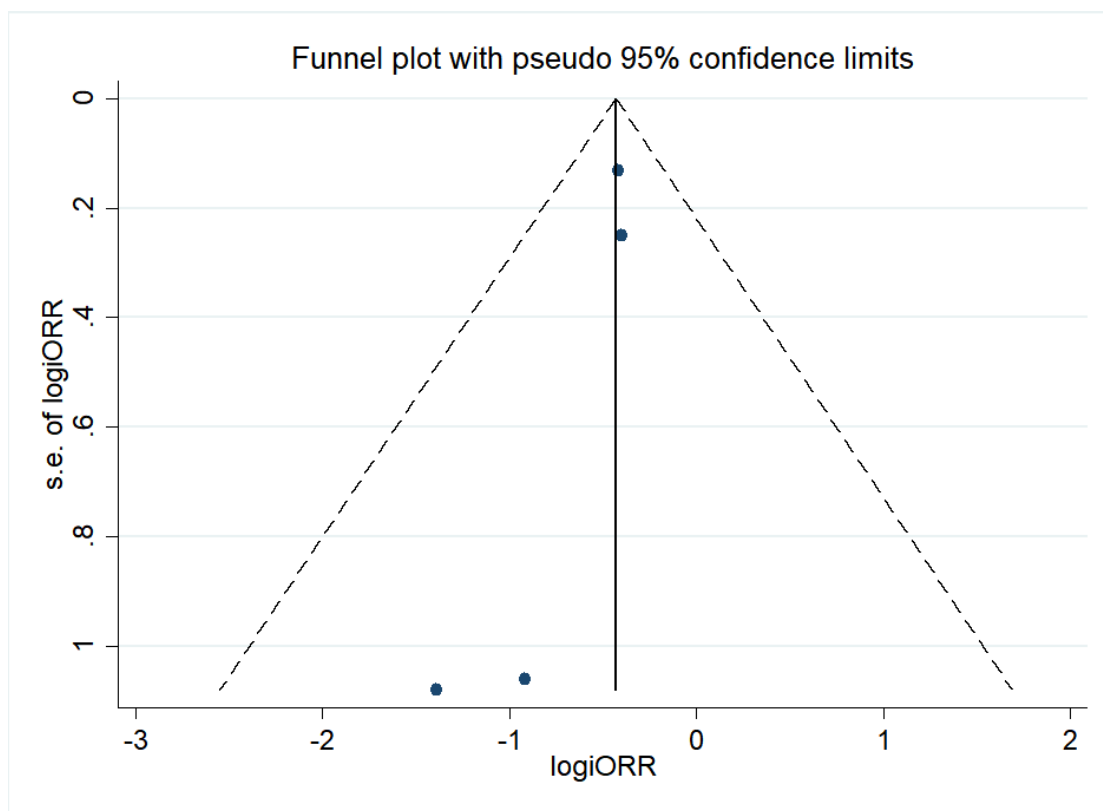
(7A)



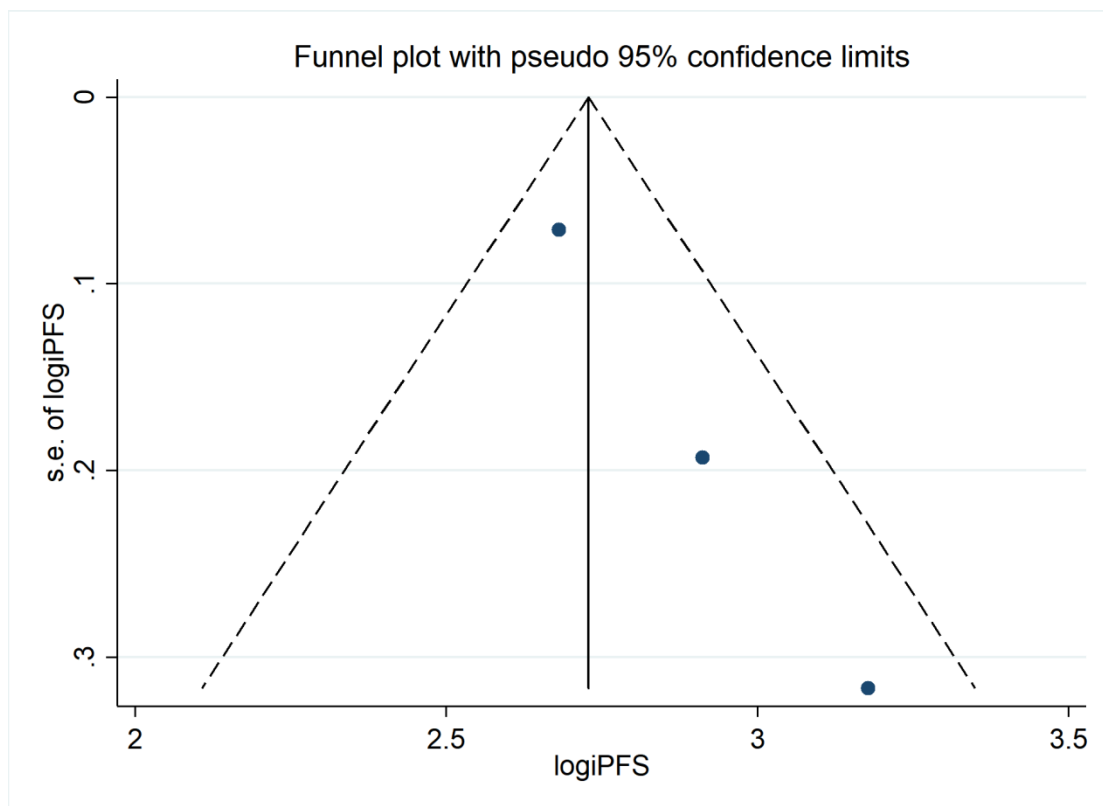
(7B)



(7C)**(7D)**



(7E)



Supplemental Figure 7. A, Funnel plot of objective response rate (ORR); B, Funnel plot of disease

control rate (DCR); C, Funnel plot of progression free survival (PFS); D, Funnel plot of intracranial objective response rate (iORR); E, Funnel plot of intracranial progression free survival (iPFS).

Supplemental Table 1. Treatment line and number of patients for included studies.

Study	Treatment line	Number of patients
Camidge 2018 (phase I/II)	1L, 2L post-crizotinib	46
Lin 2018	2L post-alectinib	22
Heredia 2020	≥2L	46
Descourt 2021 (BrigALK2 study)	≥2L	183
Camidge 2021 (ALTA-1L)	1L	137
Nishio 2021 (J-ALTA)	≥2L post alectinib±crizotinib	47
Stinchcombe 2021 (NCT02706626)	≥2L	20
Popat 2021	≥2L	104
Gettinger 2021 (phase I/II)	1L, 2L post-crizotinib	28 (1L, n=3; 2L post-crizotinib, n=25)
Gettinger 2021 (ALTA)	2L post-crizotinib	110
Kondo 2021 (J-ALTA)	1L	32

Supplemental Table 2. Publication bias based on Begg's test and Egger's test

Comparisons	Begg's test		Egger's test	
	Z	P	t	P
ORR	0.38	0.707	-1.27	0.273
iORR	1.70	0.089	-2.64	0.118
PFS	0.94	0.348	-0.31	0.763
iPFS	1.04	0.296	29.46	0.022
DCR	-0.34	1.000	-0.09	0.938