

The combined text and medical subject heading (MeSH) terms used were: “lung cancer”, “necitumumab” and “chemotherapy”.

### PubMed

The database was searched on May 20, 2019, N=53.

Search Strategy:

(Necitumumab [Title/Abstract] OR Portrazza [Title/Abstract]) OR IMC-11F8 [Title/Abstract] OR IMC-11F8 monoclonal antibody [Title/Abstract] )AND (pulmonary neoplasms [Title/Abstract] OR lung neoplasm [Title/Abstract] OR pulmonary neoplasm [Title/Abstract] OR lung cancer [Title/Abstract] OR lung cancers [Title/Abstract] OR pulmonary cancer [Title/Abstract] OR pulmonary cancers [Title/Abstract] OR cancer of the lung [Title/Abstract] OR cancer of lung [Title/Abstract] OR NSCLC [Title/Abstract] OR Lung carcinoma [Title/Abstract] )AND (chemotherapy [Title/Abstract] OR drug chemotherapy [Title/Abstract] OR chemotherapies [Title/Abstract] OR pharmacotherapy [Title/Abstract] OR pharmacotherapies [Title/Abstract]).

### Scopus

The database was searched on May 20, 2019, N=219.

Search Strategy:

(TITLE-ABS-KEY (“necitumumab” OR “Portrazza” OR “IMC-11F8” OR “IMC-11F8 monoclonal antibody”) AND TITLE-ABS-KEY (“pulmonary neoplasms” OR “lung neoplasm” OR “pulmonary neoplasm” OR “lung cancer” OR “lung cancers” OR “pulmonary cancer” OR “pulmonary cancers” OR “cancer of the lung” OR “cancer of lung” OR “NSCLC” OR “Lung carcinoma”) AND TITLE-ABS-KEY (“drug therapies” OR “chemotherapy” OR “chemotherapies” OR “pharmacotherapy” OR “pharmacotherapies”)).

### Web of Science

The database was searched on May 20, 2019, N=83

Search Strategy:

#1: TS=(“pulmonary neoplasms” OR “lung neoplasm” OR “pulmonary neoplasm”

OR “lung cancer” OR “lung cancers” OR “pulmonary cancer” OR “pulmonary cancers” OR “cancer of the lung” OR “cancer of lung” OR “NSCLC” OR “Lung carcinoma”) N=294444

#2: TS=(“Necitumumab” OR “PORTRAZZA” OR “IMC-11F8” OR “IMC-11F8 monoclonal antibody”) N=121

#3: TS=(“drug therapies” OR “chemotherapy” OR “chemotherapies” OR “pharmacotherapy” OR “pharmacotherapies”) N=1542150

#4: #1 AND #2 AND #3 N=83

### Embase

The database was searched on May 20, 2019, N=99

Search Strategy:

(“Necitumumab” OR “PORTRAZZA” OR “IM-11F8” OR “IMC-11F8 monoclonal antibody”): ti, ab, kw AND (“pulmonary neoplasms” OR “lung neoplasm” OR “pulmonary neoplasm” OR “lung cancer” OR “lung cancers” OR “pulmonary cancer” OR “pulmonary cancers” OR “cancer of the lung” OR “cancer of lung” OR “NSCLC”): ti, ab, kw AND (“drug therapies” OR “chemotherapy” OR “chemotherapies” OR “pharmacotherapy” OR “pharmacotherapies”): ti, ab, kw.

### Ovid

The database was searched on May 20, 2019, N=262

Search Strategy:

#1: Necitumumab

#2: Portrazza

#3: IMC-11F8

#4: IMC-11F8 monoclonal antibody

#5: pulmonary neoplasms

#6: pulmonary cancer

#7: pulmonary cancers

#8: cancer of the lung

#9: cancer of lung

#10: Lung carcinoma

#11: Lung neoplasm

#12: NSCLC

#13: drug therapies

#14: chemotherapy

#15: chemotherapies

#16: pharmacotherapy

#17: pharmacotherapies

#18: #1 and #2 and #3 and #4 and #5 and #6 and #7 and #8 and #9 and #10 and #11 and #12 and #13 and #14 and #15 and #16 and #17

## **Cochrane**

The database was searched on May 20, 2019, N=54

Search Strategy:

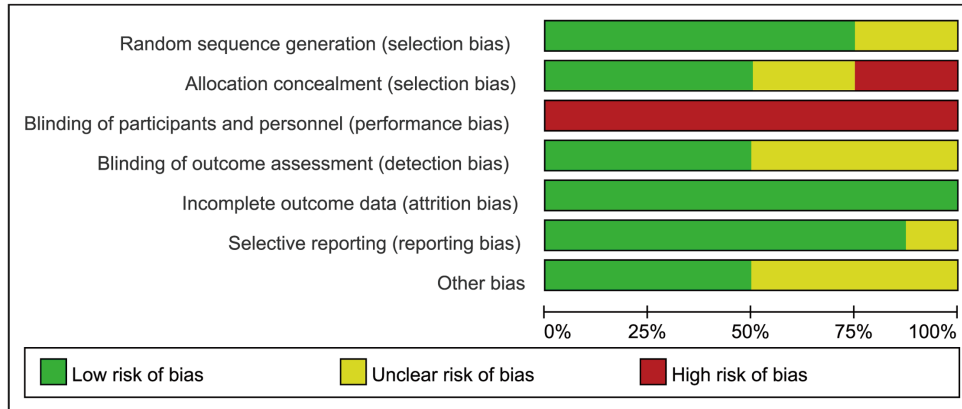
("Necitumumab" OR "Portrazza" OR "IMC-11F8" OR "IMC-11F8 monoclonal antibody"): ti, ab, kw AND ("pulmonary neoplasms" OR "lung neoplasm" OR "pulmonary neoplasm" OR "lung cancer" OR "lung cancers" OR "pulmonary cancer" OR "pulmonary cancers" OR "cancer of the lung" OR "cancer of lung" OR "NSCLC"): ti, ab, kw AND ("drug therapies" OR "chemotherapy" OR "chemotherapies" OR "pharmacotherapy" OR "pharmacotherapies"): ti, ab, kw.

**Table S1** GRADE quality assessment for the outcomes of survival, response rate and toxicity

Primary outcome	No.	No. of participants		Differences <sup>a</sup> (95% CI)	Quality assessment				Publication bias <sup>c</sup>	Quality
		NC	CA		Risk of bias <sup>b</sup>	Inconsistency	Indirectness	Imprecision		
Survival										
OS	4	1,060	1,014	0.93 (0.85–1.01)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
OSR										
0.5-year	4	768/1,060	712/1,014	1.04 (0.94–1.16)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
1-year	4	490/1,060	429/1,014	1.13 (0.94–1.36)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
1.5-year	4	252/1,060	232/1,014	1.07 (0.92–1.25)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
2-year	3	116/950	104/957	1.24 (0.70–2.17)	Serious (-1)	No inconsistency	No indirectness	No imprecision	Unlikely	Medium
PFS	4	1,060	1,014	0.91 (0.84–0.99)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
PFSR										
0.5-year	4	354/1,060	277/1,014	1.22 (0.88–1.69)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
1-year	4	93/1,060	69/1,014	1.28 (0.95–1.73)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
1.5-year	3	39/1,060	29/1,014	1.35 (0.84–2.15)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
2-year	2	14/860	7/866	2.01 (0.82–4.97)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
Response rate										
CR	3	116/1,063	8/1,014	0.14 (0.02–0.79)	Low	Serious (-1)	No indirectness	No imprecision	Unlikely	Medium
PR	4	116/1,064	291/1,014	1.17 (1.03–1.33)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
SD	4	116/1,065	473/1,014	0.99 (0.90–1.09)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
PD	4	116/1,066	121/1,014	0.68 (0.53–0.89)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
ORR	4	116/1,061	299/1,014	1.26 (0.93–1.71)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
DCR	4	116/1,062	772/1,014	1.05 (1.00–1.10)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
Toxicity										
Total AEs	2	324/425	236/375	1.12 (0.97–1.31)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
Grade 3–5 AEs	3	612/963	498/916	1.14 (1.01–1.28)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
Dose reduction	2	465/853	410/853	0.07 (0.02–0.11)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High
Dose discontinuation	3	262/963	194/910	1.30 (1.11–1.53)	Low	No inconsistency	No indirectness	No imprecision	Unlikely	High

<sup>a</sup>, differences: hazard ratio (HR) for OS and PFS; risk ratios (RR) for OSR, PFSR, CR, PR, SD, PD, ORR, DCR, total AEs, grade 3–5 AEs, dose reduction and dose discontinuation; <sup>b</sup>, risk of bias assessed using the Jadad Scale (NOS) for randomized controlled trials; <sup>c</sup>, publication bias was assessed by Egger's and Begg's tests. OS, overall survival; OSR, overall survival rate; PFS, progression free survival; PFSR, progression free survival rate; NC, necitumumab plus platinum-based chemotherapy; CA, platinum-based chemotherapy alone; CI, confidence interval.

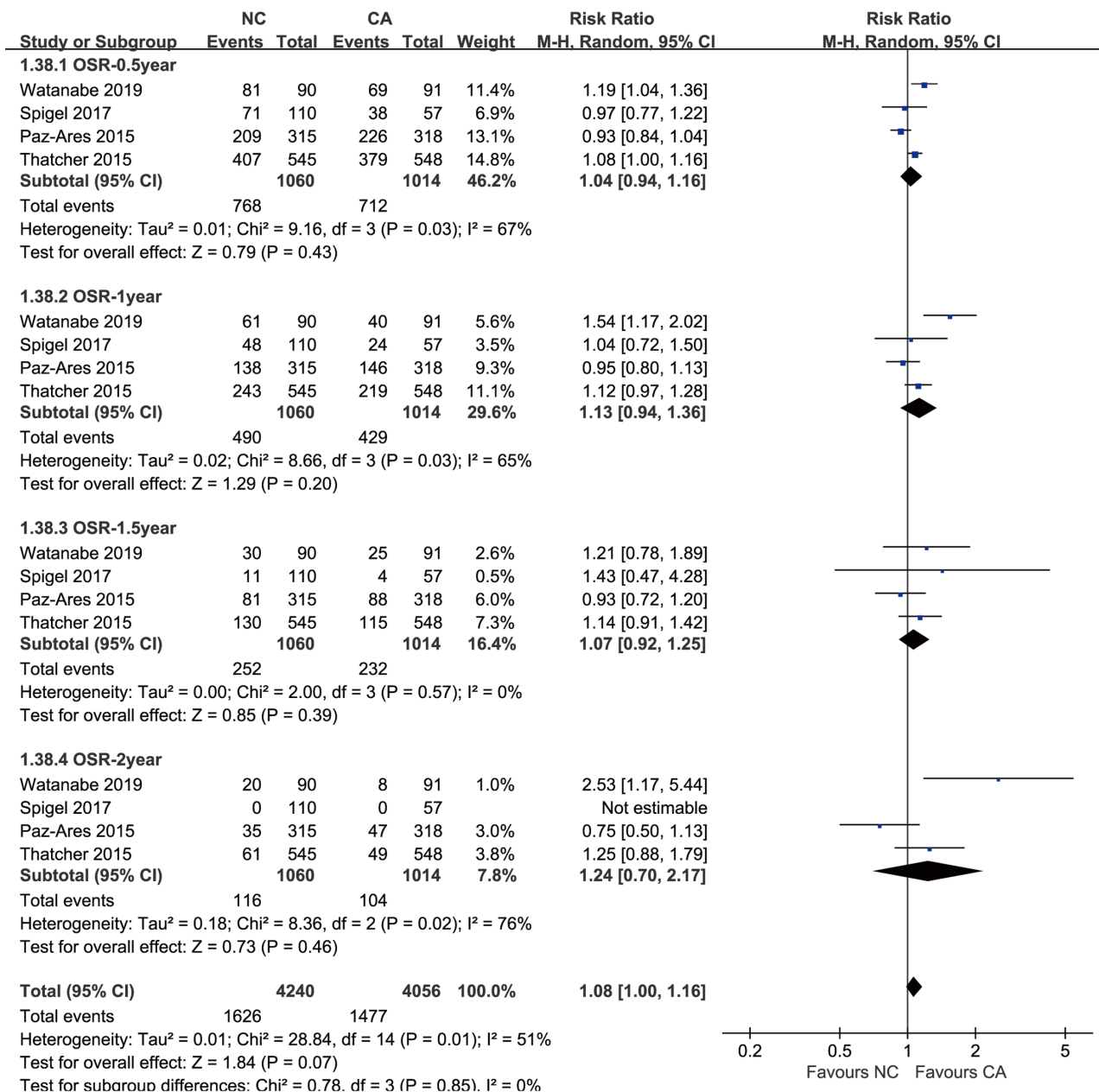
A



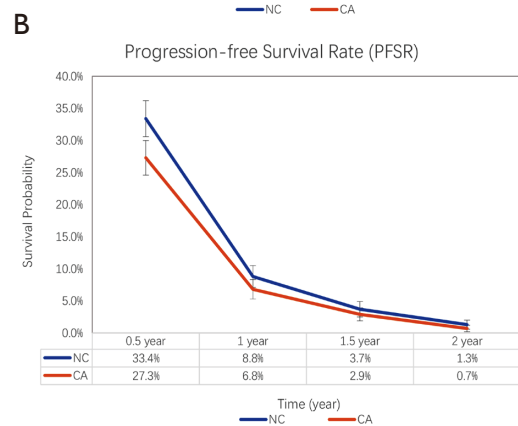
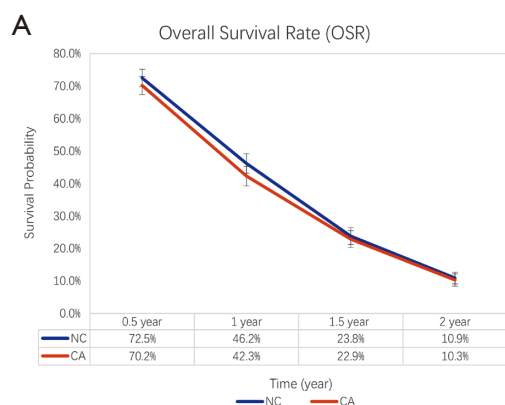
B

Study	Park 2017	Paz-Ares 2015	Paz-Ares 2016	Reck (1) 2016	Reck (2) 2016	Spigel 2017	Thatcher 2015	Watanabe 2019
Random sequence generation (selection bias)	?	?	+	+	+	+	+	+
Allocation concealment (selection bias)	-	-	+	?	?	+	+	+
Blinding of participants and personnel (performance bias)	-	-	-	-	-	-	-	-
Blinding of outcome assessment (detection bias)	+	+	?	+	+	?	?	?
Incomplete outcome data (attrition bias)	+	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+	?	+	+
Other bias	+	+	?	?	?	+	+	?

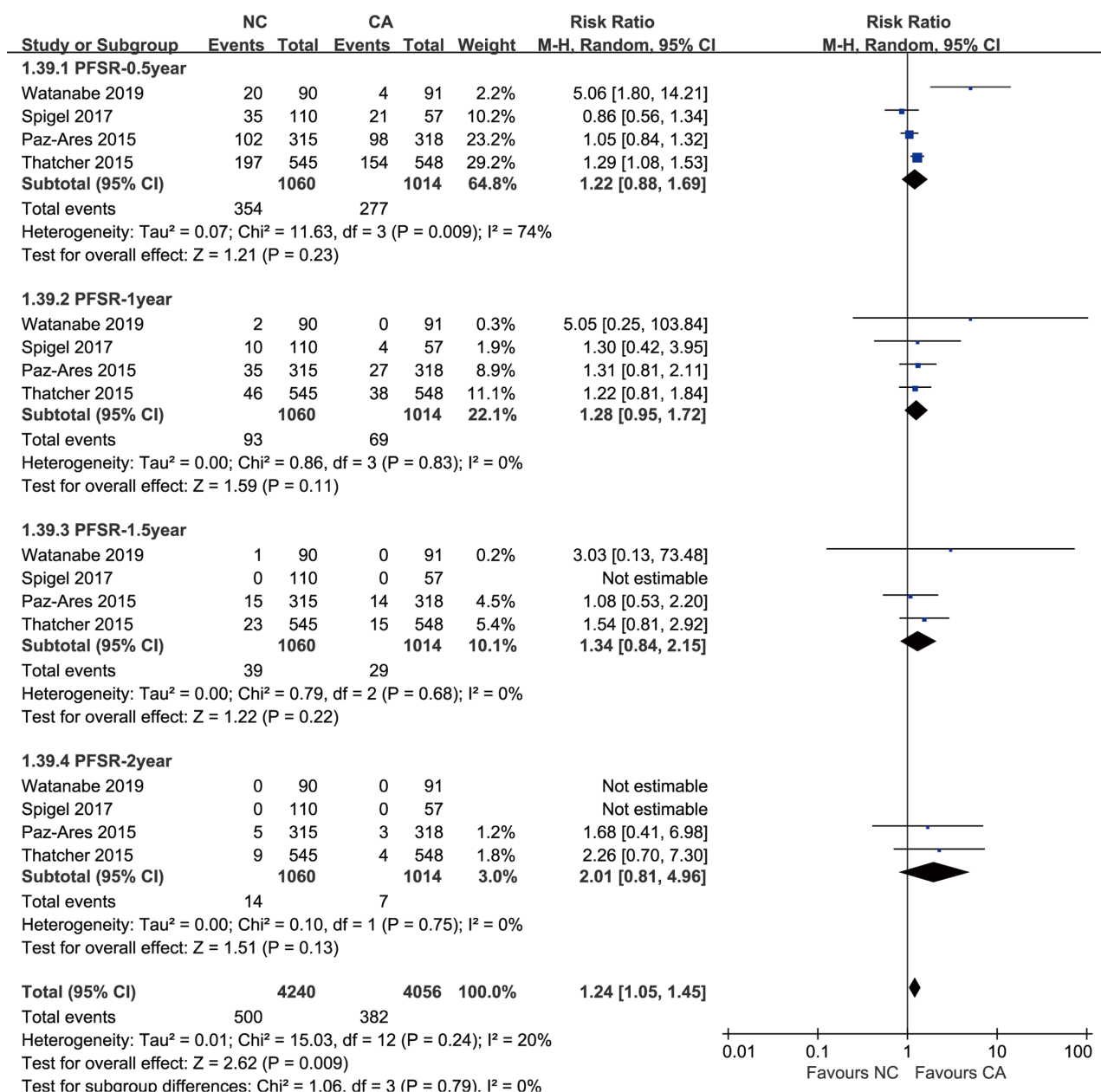
**Figure S1** Cochrane Risk Assessment associated with necitumumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone.



**Figure S2** Forest plots of OSR-0.5y, OSR-1y, OSR-1.5y and OSR-2y associated with necitumumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone. OSR, overall survival rate.

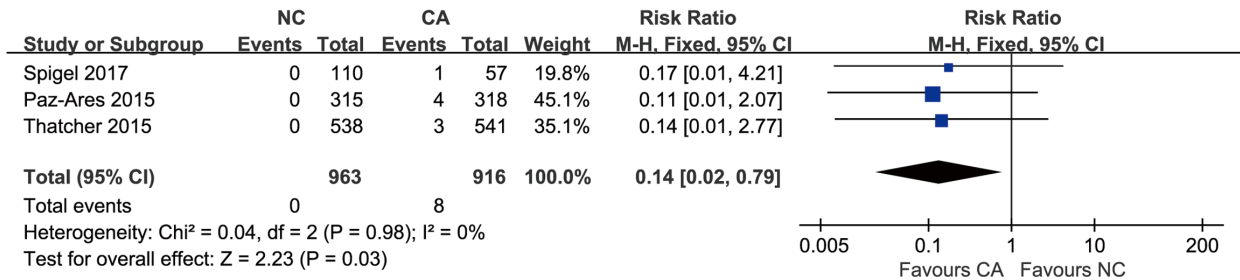


**Figure S3** Trends in the RR of OSR (A) and PFSR (B) over time associated with necitumumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone. RR, risk ratios; OSR, overall survival rate; PFSR, progression free survival rate.

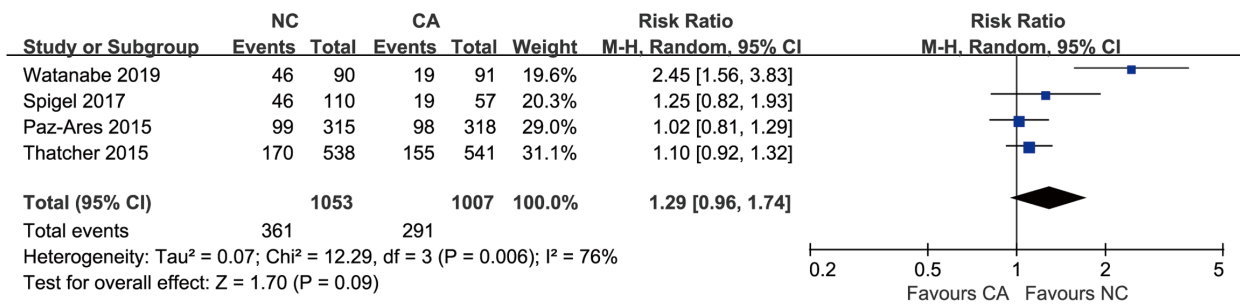


**Figure S4** Forest plots of PFSR-0.5y, PFSR-1y, PFSR-1.5y and PFSR-2y associated with necitumumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone. PFSR, progression free survival rate.

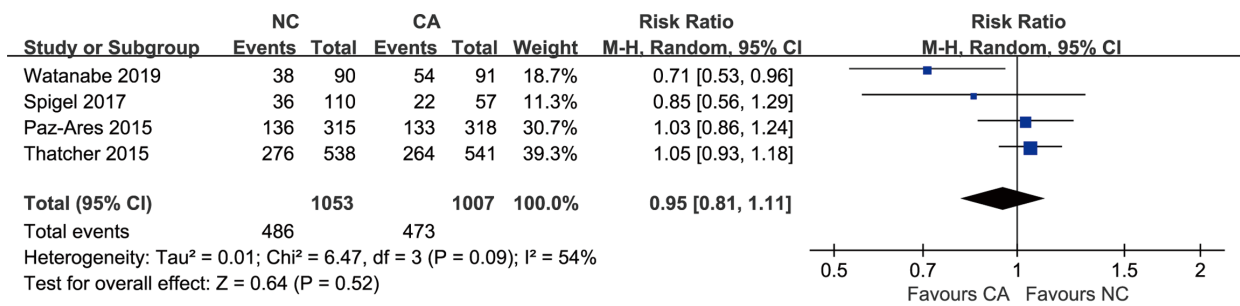
A



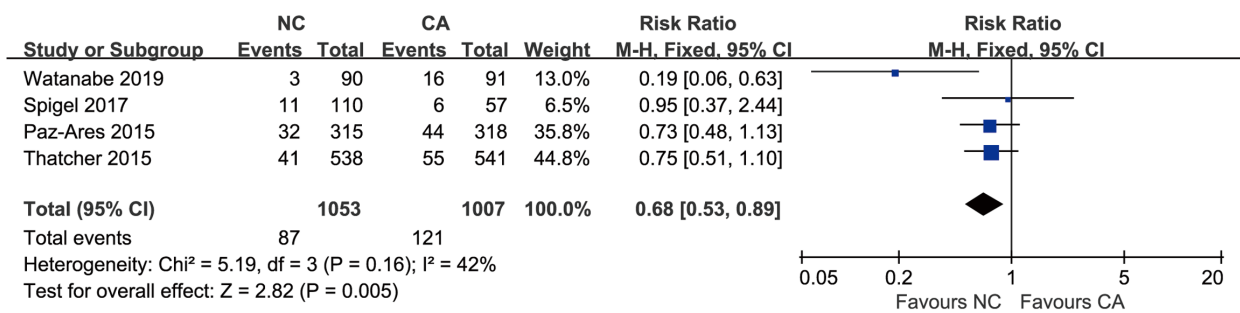
B



C



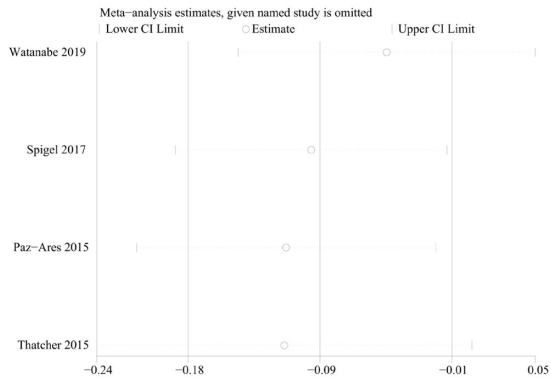
D



**Figure S5** Forest plots of CR (A), PR (B), SD (C) and PD (D) associated with necitumumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone. CR, complete remission; PR, partial remission; SD, stable disease; PD, progression of disease.

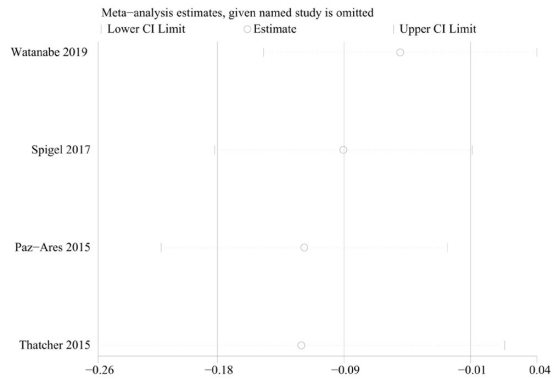


A



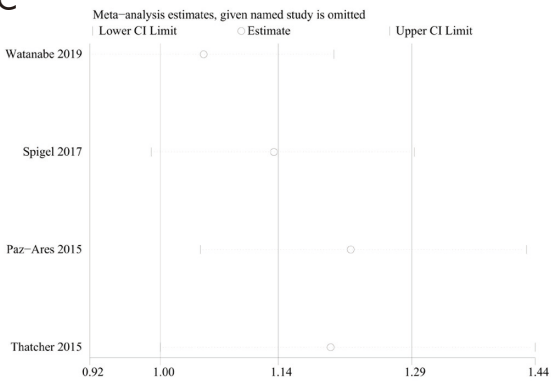
Study omitted	Estimate	[95% Conf. Interval]
Watanabe 2019	-.05052363	-.14645559 .04540832
Spigel 2017	-.09920514	-.18685162 -.01155865
Paz-Ares 2015	-.11541146	-.21192016 -.01890278
Thatcher 2015	-.11658885	-.23771168 .00453397
<b>Combined</b>	<b>-.093498</b>	<b>-.17858606 -.00840994</b>

B



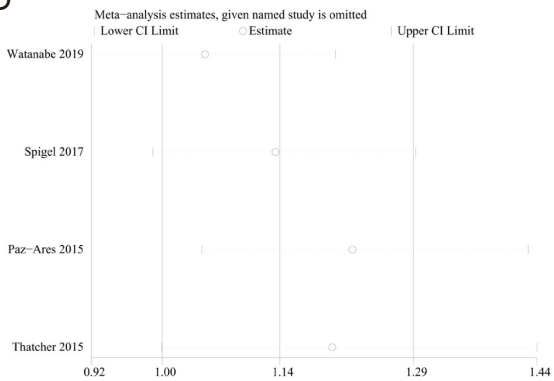
Study omitted	Estimate	[95% Conf. Interval]
Watanabe 2019	-.05528206	-.14783601 .03727189
Spigel 2017	-.0937452	-.18095362 -.00653678
Paz-Ares 2015	-.12032546	-.21732011 -.02333081
Thatcher 2015	-.12221543	-.25990829 .01547744
<b>Combined</b>	<b>-.09334461</b>	<b>-.17917157 -.00751765</b>

C



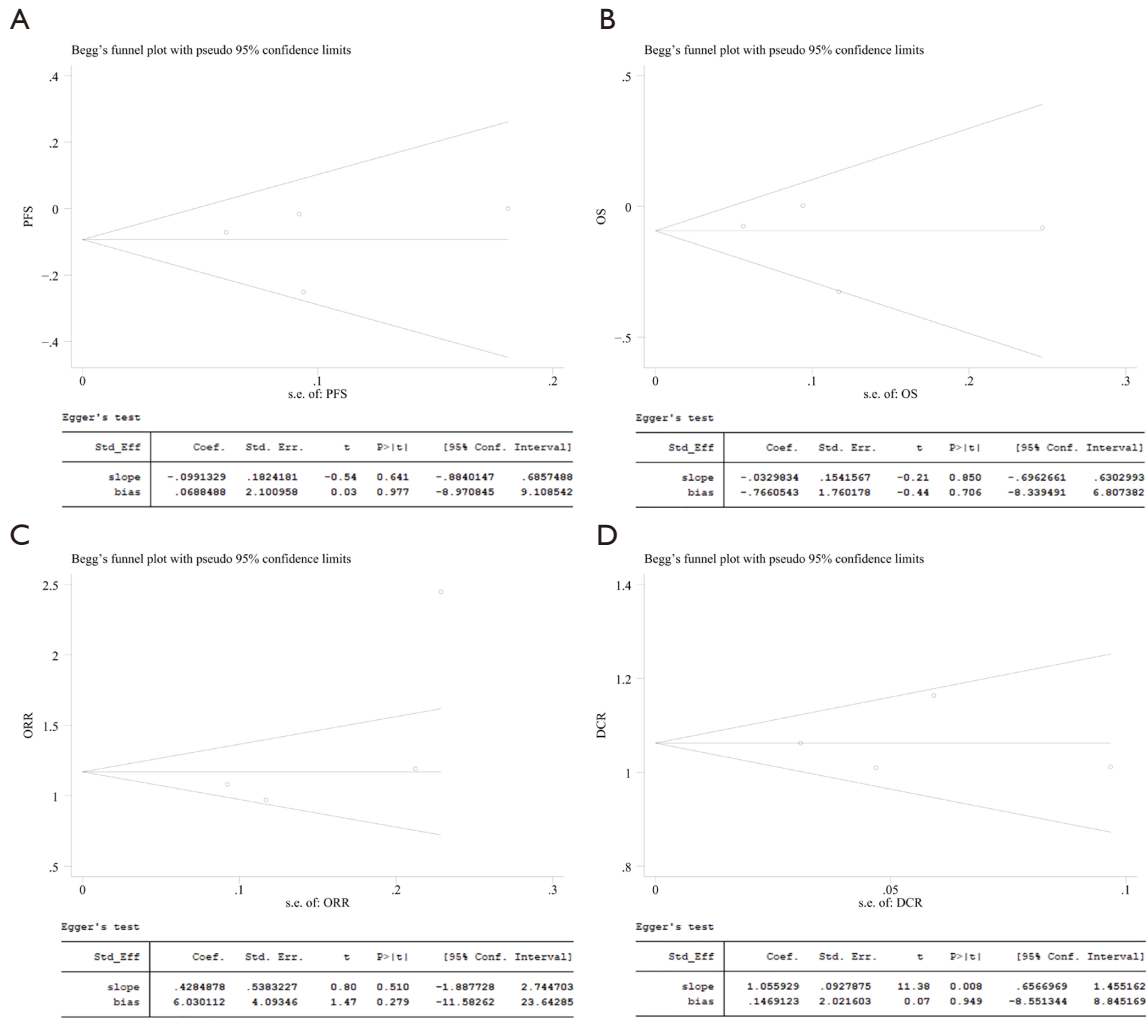
Study omitted	Estimate	[95% Conf. Interval]
Watanabe 2019	1.052209	.9197681 1.2037207
Spigel 2017	1.1338496	.99121994 1.2970028
Paz-Ares 2015	1.2234287	1.0482844 1.4278357
Thatcher 2015	1.2000619	1.001622 1.4378166
<b>Combined</b>	<b>1.1388684</b>	<b>1.0020838 1.294324</b>

D



Study omitted	Estimate	[95% Conf. Interval]
Watanabe 2019	1.052209	.9197681 1.2037207
Spigel 2017	1.1338496	.99121994 1.2970028
Paz-Ares 2015	1.2234287	1.0482844 1.4278357
Thatcher 2015	1.2000619	1.001622 1.4378166
<b>Combined</b>	<b>1.1388684</b>	<b>1.0020838 1.294324</b>

**Figure S6** Sensitivity analysis of PFS (A), OS (B), ORR (C) and DCR (D) associated with necitumumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone. PFS, progression free survival; OS, overall survival; ORR, objective response rate; DCR, disease control rate.



**Figure S7** The publication bias of PFS (A), OS (B), ORR (C) and DCR (D) associated with necitumumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone. PFS, progression free survival; OS, overall survival; ORR, objective response rate; DCR, disease control rate.