

## **Supplementary material “Systematic evaluation of the efficacy-effectiveness gap of systemic treatments in metastatic NSCLC”**

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## APPENDIX 1 Literature search

### PubMed; search on September 1, 2017

#### 1. Cisplatin pemetrexed

((cisplatin\*[tiab] OR "Cisplatin"[Mesh]) AND ("Pemetrexed"[Mesh] OR pemetrexed[tiab])) AND ("carcinoma, non-small-cell lung"[MeSH Terms] OR non small cell lung ca\*[tiab] OR NSCLC\*[tiab] OR lung adenocarcinom\*[tiab]) AND ("Neoplasm Metastasis"[Mesh] OR "secondary"[Subheading] OR stage IV[tiab] OR stage 4[tiab] OR stage IIIB[tiab] OR stage 3B[tiab] OR metastatic[tiab] OR metastas\*[tiab] OR advanced[tiab]) AND ("mortality" [Subheading] OR "Mortality"[Mesh] OR "Survival"[Mesh] OR "Survival Analysis"[Mesh] OR mortality[tiab] OR death\*[tiab] OR survival[tiab]) NOT ("animals"[mesh] NOT "humans"[mesh]) AND ("Clinical Trial, Phase III"[pt] OR phase III[ti] OR phase 3[ti] OR (("controlled clinical trial"[pt] OR controlled clinical trial[ti] OR randomized controlled trial[ti] OR randomized clinical trial[ti] OR randomised controlled trial[ti] OR randomised clinical trial[ti] OR rct[ti]) NOT ("Clinical Trial, Phase II"[pt] OR phase II[ti] OR phase 2[ti]))) AND english[la]

#### 2. Cisplatin gemcitabine

((cisplatin\*[tiab] OR "Cisplatin"[Mesh]) AND (gemcitabin\*[tiab] OR "gemcitabine" [Supplementary Concept])) AND ("carcinoma, non-small-cell lung"[MeSH Terms] OR non small cell lung ca\*[tiab] OR NSCLC\*[tiab] OR lung adenocarcinom\*[tiab]) AND ("Neoplasm Metastasis"[Mesh] OR "secondary"[Subheading] OR stage IV[tiab] OR stage 4[tiab] OR stage IIIB[tiab] OR stage 3B[tiab] OR metastatic[tiab] OR metastas\*[tiab] OR advanced[tiab]) AND ("mortality" [Subheading] OR "Mortality"[Mesh] OR "Survival"[Mesh] OR "Survival Analysis"[Mesh] OR mortality[tiab] OR death\*[tiab] OR survival[tiab]) NOT ("animals"[mesh] NOT "humans"[mesh]) AND ("Clinical Trial, Phase III"[pt] OR phase III[ti] OR phase 3[ti] OR (("controlled clinical trial"[pt] OR controlled clinical trial[ti] OR randomized controlled trial[ti] OR randomized clinical trial[ti] OR randomised controlled trial[ti] OR randomised clinical trial[ti] OR rct[ti]) NOT ("Clinical Trial, Phase II"[pt] OR phase II[ti] OR phase 2[ti]))) AND english[la]

#### 3. Carboplatin pemetrexed

((carboplatin\*[tiab] OR "Carboplatin"[Mesh]) AND ("Pemetrexed"[Mesh] OR pemetrexed[tiab])) AND ("carcinoma, non-small-cell lung"[MeSH Terms] OR non small cell lung ca\*[tiab] OR NSCLC\*[tiab] OR lung adenocarcinom\*[tiab]) AND ("Neoplasm Metastasis"[Mesh] OR "secondary"[Subheading] OR stage IV[tiab] OR stage 4[tiab] OR stage IIIB[tiab] OR stage 3B[tiab] OR metastatic[tiab] OR metastas\*[tiab] OR advanced[tiab]) AND ("mortality" [Subheading] OR "Mortality"[Mesh] OR "Survival"[Mesh] OR "Survival Analysis"[Mesh] OR mortality[tiab] OR death\*[tiab] OR survival[tiab]) NOT ("animals"[mesh] NOT "humans"[mesh]) AND ("Clinical Trial, Phase III"[pt] OR phase III[ti] OR phase 3[ti] OR (("controlled clinical trial"[pt] OR controlled clinical trial[ti] OR randomized controlled trial[ti] OR randomized clinical trial[ti] OR randomised controlled trial[ti] OR randomised clinical trial[ti] OR rct[ti]) NOT ("Clinical Trial, Phase II"[pt] OR phase II[ti] OR phase 2[ti]))) AND english[la]

#### 4. Carboplatin gemcitabine

((carboplatin\*[tiab] OR "Carboplatin"[Mesh]) AND (gemcitabin\*[tiab] OR "gemcitabine" [Supplementary Concept])) AND ("carcinoma, non-small-cell lung"[MeSH Terms] OR non small cell lung ca\*[tiab] OR NSCLC\*[tiab] OR lung adenocarcinom\*[tiab]) AND ("Neoplasm Metastasis"[Mesh] OR "secondary"[Subheading] OR stage IV[tiab] OR stage 4[tiab] OR stage IIIB[tiab] OR stage 3B[tiab] OR metastatic[tiab] OR metastas\*[tiab] OR advanced[tiab]) AND ("mortality" [Subheading] OR "Mortality"[Mesh] OR "Survival"[Mesh] OR "Survival Analysis"[Mesh] OR mortality[tiab] OR death\*[tiab] OR survival[tiab]) NOT ("animals"[mesh] NOT "humans"[mesh])

AND ("Clinical Trial, Phase III"[pt] OR phase III[ti] OR phase 3[ti] OR (("controlled clinical trial"[pt] OR controlled clinical trial[ti] OR randomized controlled trial[ti] OR randomized clinical trial[ti] OR randomised controlled trial[ti] OR randomised clinical trial[ti] OR rct[ti]) NOT ("Clinical Trial, Phase II"[pt] OR phase II[ti] OR phase 2[ti]))))  
AND english[la]

#### 5. *Bevacizumab carboplatin paclitaxel*

((bevacizumab[tiab] OR "Bevacizumab"[Mesh]) AND (carboplatin\*[tiab] OR "Carboplatin"[Mesh]) AND (paclitaxel[tiab] OR "Paclitaxel"[Mesh]))  
AND ("carcinoma, non-small-cell lung"[MeSH Terms] OR non small cell lung ca\*[tiab] OR NSCLC\*[tiab] OR lung adenocarcinom\*[tiab]) AND ("Neoplasm Metastasis"[Mesh] OR "secondary"[Subheading] OR stage IV[tiab] OR stage 4[tiab] OR stage IIIB[tiab] OR stage 3B[tiab] OR metastatic[tiab] OR metastas\*[tiab] OR advanced[tiab])  
AND ("mortality" [Subheading] OR "Mortality"[Mesh] OR "Survival"[Mesh] OR "Survival Analysis"[Mesh] OR mortality[tiab] OR death\*[tiab] OR survival[tiab])  
NOT ("animals"[mesh] NOT "humans"[mesh])  
AND ("Clinical Trial, Phase III"[pt] OR phase III[ti] OR phase 3[ti] OR (("controlled clinical trial"[pt] OR controlled clinical trial[ti] OR randomized controlled trial[ti] OR randomized clinical trial[ti] OR randomised controlled trial[ti] OR randomised clinical trial[ti] OR rct[ti]) NOT ("Clinical Trial, Phase II"[pt] OR phase II[ti] OR phase 2[ti]))))  
AND english[la]

#### 6. *Carboplatin docetaxel*

((carboplatin\*[tiab] OR "Carboplatin"[Mesh]) AND ("docetaxel"[Supplementary Concept] OR docetaxel[tiab]))  
AND ("carcinoma, non-small-cell lung"[MeSH Terms] OR non small cell lung ca\*[tiab] OR NSCLC\*[tiab] OR lung adenocarcinom\*[tiab]) AND ("Neoplasm Metastasis"[Mesh] OR "secondary"[Subheading] OR stage IV[tiab] OR stage 4[tiab] OR stage IIIB[tiab] OR stage 3B[tiab] OR metastatic[tiab] OR metastas\*[tiab] OR advanced[tiab])  
AND ("mortality" [Subheading] OR "Mortality"[Mesh] OR "Survival"[Mesh] OR "Survival Analysis"[Mesh] OR mortality[tiab] OR death\*[tiab] OR survival[tiab])  
NOT ("animals"[mesh] NOT "humans"[mesh])  
AND ("Clinical Trial, Phase III"[pt] OR phase III[ti] OR phase 3[ti] OR (("controlled clinical trial"[pt] OR controlled clinical trial[ti] OR randomized controlled trial[ti] OR randomized clinical trial[ti] OR randomised controlled trial[ti] OR randomised clinical trial[ti] OR rct[ti]) NOT ("Clinical Trial, Phase II"[pt] OR phase II[ti] OR phase 2[ti]))))  
AND english[la]

#### 7. *Gefitinib*

("gefitinib" [Supplementary Concept] OR gefitinib[tiab])  
AND ("carcinoma, non-small-cell lung"[MeSH Terms] OR non small cell lung ca\*[tiab] OR NSCLC\*[tiab] OR lung adenocarcinom\*[tiab]) AND ("Neoplasm Metastasis"[Mesh] OR "secondary"[Subheading] OR stage IV[tiab] OR stage 4[tiab] OR stage IIIB[tiab] OR stage 3B[tiab] OR metastatic[tiab] OR metastas\*[tiab] OR advanced[tiab])  
AND ("mortality" [Subheading] OR "Mortality"[Mesh] OR "Survival"[Mesh] OR "Survival Analysis"[Mesh] OR mortality[tiab] OR death\*[tiab] OR survival[tiab])  
NOT ("animals"[mesh] NOT "humans"[mesh])  
AND ("Clinical Trial, Phase III"[pt] OR phase III[ti] OR phase 3[ti] OR (("controlled clinical trial"[pt] OR controlled clinical trial[ti] OR randomized controlled trial[ti] OR randomized clinical trial[ti] OR randomised controlled trial[ti] OR randomised clinical trial[ti] OR rct[ti]) NOT ("Clinical Trial, Phase II"[pt] OR phase II[ti] OR phase 2[ti]))))  
AND english[la]

#### 8. *Erlotinib*

("Erlotinib Hydrochloride"[Mesh] OR erlotinib[tiab])  
AND ("carcinoma, non-small-cell lung"[MeSH Terms] OR non small cell lung ca\*[tiab] OR NSCLC\*[tiab] OR lung adenocarcinom\*[tiab]) AND ("Neoplasm Metastasis"[Mesh] OR "secondary"[Subheading] OR stage IV[tiab] OR stage 4[tiab] OR stage IIIB[tiab] OR stage 3B[tiab] OR metastatic[tiab] OR metastas\*[tiab] OR advanced[tiab])

AND ("mortality" [Subheading] OR "Mortality"[Mesh] OR "Survival"[Mesh] OR "Survival Analysis"[Mesh] OR mortality[tiab] OR death\*[tiab] OR survival[tiab])  
NOT ("animals"[mesh] NOT "humans"[mesh])  
AND ("Clinical Trial, Phase III"[pt] OR phase III[ti] OR phase 3[ti] OR ("controlled clinical trial"[pt] OR controlled clinical trial[ti] OR randomized controlled trial[ti] OR randomized clinical trial[ti] OR randomised controlled trial[ti] OR randomised clinical trial[ti] OR rct[ti]) NOT ("Clinical Trial, Phase II"[pt] OR phase II[ti] OR phase 2[ti]))  
AND english[la]

## Embase via Embase.com; search on September 1, 2017

### 1. *Cisplatin pemetrexed*

((cisplatin/exp OR cisplatin\*:ab,ti) AND ('pemetrexed'/exp OR pemetrexed:ab,ti) AND ('non small cell lung cancer'/exp OR 'non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('metastasis'/exp OR 'stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND ('mortality'/exp OR 'survival'/exp OR mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3 clinical trial'/exp OR 'phase III':ti OR 'phase 3':ti OR 'controlled clinical trial'/exp OR 'controlled clinical trial':ti OR 'randomized controlled trial':ti OR 'randomized clinical trial':ti OR 'randomised controlled trial':ti OR 'randomised clinical trial':ti OR rct:ti NOT ('phase 2 clinical trial'/exp OR 'phase II':ti OR 'phase 2':ti)) AND [english]/lim NOT 'conference abstract'/it

### 2. *Cisplatin gemcitabine*

((cisplatin/exp OR cisplatin\*:ab,ti) AND ('gemcitabine'/exp OR gemcitabin\*:ab,ti) AND ('non small cell lung cancer'/exp OR 'non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('metastasis'/exp OR 'stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND ('mortality'/exp OR 'survival'/exp OR mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3 clinical trial'/exp OR 'phase III':ti OR 'phase 3':ti OR 'controlled clinical trial'/exp OR 'controlled clinical trial':ti OR 'randomized controlled trial':ti OR 'randomized clinical trial':ti OR 'randomised controlled trial':ti OR 'randomised clinical trial':ti OR rct:ti NOT ('phase 2 clinical trial'/exp OR 'phase II':ti OR 'phase 2':ti)) AND [english]/lim NOT 'conference abstract'/it

### 3. *Carboplatin pemetrexed*

((carboplatin/exp OR carboplatin\*:ab,ti) AND ('pemetrexed'/exp OR pemetrexed:ab,ti) AND ('non small cell lung cancer'/exp OR 'non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('metastasis'/exp OR 'stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND ('mortality'/exp OR 'survival'/exp OR mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3 clinical trial'/exp OR 'phase III':ti OR 'phase 3':ti OR 'controlled clinical trial'/exp OR 'controlled clinical trial':ti OR 'randomized controlled trial':ti OR 'randomized clinical trial':ti OR 'randomised controlled trial':ti OR 'randomised clinical trial':ti OR rct:ti NOT ('phase 2 clinical trial'/exp OR 'phase II':ti OR 'phase 2':ti)) AND [english]/lim NOT 'conference abstract'/it

### 4. *Carboplatin gemcitabine*

((carboplatin/exp OR carboplatin\*:ab,ti) AND ('gemcitabine'/exp OR gemcitabin\*:ab,ti) AND ('non small cell lung cancer'/exp OR 'non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('metastasis'/exp OR 'stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND ('mortality'/exp OR 'survival'/exp OR mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3 clinical trial'/exp OR 'phase III':ti OR 'phase 3':ti OR 'controlled clinical trial'/exp OR 'controlled clinical trial':ti OR 'randomized controlled trial':ti OR 'randomized clinical trial':ti OR 'randomised controlled trial':ti OR 'randomised clinical trial':ti OR rct:ti NOT ('phase 2 clinical trial'/exp OR 'phase II':ti OR 'phase 2':ti)) AND [english]/lim NOT 'conference abstract'/it

#### 5. *Bevacizumab carboplatin paclitaxel*

(('bevacizumab'/exp OR bevacizumab:ab,ti) AND ('carboplatin'/exp OR carboplatin\*:ab,ti) AND ('paclitaxel'/exp OR paclitaxel:ab,ti)) AND ('non small cell lung cancer'/exp OR 'non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('metastasis'/exp OR 'stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND ('mortality'/exp OR 'survival'/exp OR mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3 clinical trial'/exp OR 'phase III':ti OR 'phase 3':ti OR 'controlled clinical trial'/exp OR 'controlled clinical trial':ti OR 'randomized controlled trial':ti OR 'randomized clinical trial':ti OR 'randomised controlled trial':ti OR 'randomised clinical trial':ti OR rct:ti NOT ('phase 2 clinical trial'/exp OR 'phase II':ti OR 'phase 2':ti)) AND [english]/lim NOT 'conference abstract'/it

#### 6. *Carboplatin docetaxel*

(('carboplatin'/exp OR carboplatin\*:ab,ti) AND ('docetaxel'/exp OR docetaxel:ab,ti)) AND ('non small cell lung cancer'/exp OR 'non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('metastasis'/exp OR 'stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND ('mortality'/exp OR 'survival'/exp OR mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3 clinical trial'/exp OR 'phase III':ti OR 'phase 3':ti OR 'controlled clinical trial'/exp OR 'controlled clinical trial':ti OR 'randomized controlled trial':ti OR 'randomized clinical trial':ti OR 'randomised controlled trial':ti OR 'randomised clinical trial':ti OR rct:ti NOT ('phase 2 clinical trial'/exp OR 'phase II':ti OR 'phase 2':ti)) AND [english]/lim NOT 'conference abstract'/it

#### 7. *Gefitinib*

('gefitinib'/exp OR gefitinib:ab,ti) AND ('non small cell lung cancer'/exp OR 'non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('metastasis'/exp OR 'stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND ('mortality'/exp OR 'survival'/exp OR mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3 clinical trial'/exp OR 'phase III':ti OR 'phase 3':ti OR 'controlled clinical trial'/exp OR 'controlled clinical trial':ti OR 'randomized controlled trial':ti OR 'randomized clinical trial':ti OR 'randomised controlled trial':ti OR 'randomised clinical trial':ti OR rct:ti NOT ('phase 2 clinical trial'/exp OR 'phase II':ti OR 'phase 2':ti)) AND [english]/lim NOT 'conference abstract'/it

#### 8. *Erlotinib*

('erlotinib'/exp OR erlotinib:ab,ti) AND ('non small cell lung cancer'/exp OR 'non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('metastasis'/exp OR 'stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND ('mortality'/exp OR 'survival'/exp OR mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3 clinical trial'/exp OR 'phase III':ti OR 'phase 3':ti OR 'controlled clinical trial'/exp OR 'controlled clinical trial':ti OR 'randomized controlled trial':ti OR 'randomized clinical trial':ti OR 'randomised controlled trial':ti OR 'randomised clinical trial':ti OR rct:ti NOT ('phase 2 clinical trial'/exp OR 'phase II':ti OR 'phase 2':ti)) AND [english]/lim NOT 'conference abstract'/it

### **CENTRAL (Cochrane library); search on September 1, 2017**

#### 1. *Cisplatin pemetrexed*

(cisplatin\*:ab,ti AND pemetrexed:ab,ti) AND ('non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND (mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3':ti OR 'phase III':ti)

#### 2. *Cisplatin gemcitabine*

(cisplatin\*:ab,ti AND gemcitabin\*:ab,ti) AND ('non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND (mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3':ti OR 'phase III':ti)

3. *Carboplatin pemetrexed*

(carboplatin\*:ab,ti AND pemetrexed:ab,ti) AND ('non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND (mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3':ti OR 'phase III':ti)

4. *Carboplatin gemcitabine*

(carboplatin\*:ab,ti AND gemcitabin\*:ab,ti) AND ('non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND (mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3':ti OR 'phase III':ti)

5. *Bevacizumab carboplatin paclitaxel*

(bevacizumab:ab,ti AND carboplatin\*:ab,ti AND paclitaxel:ab,ti) AND ('non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND (mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3':ti OR 'phase III':ti)

6. *Carboplatin docetaxel*

(carboplatin\*:ab,ti AND docetaxel:ab,ti) AND ('non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND (mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3':ti OR 'phase III':ti)

7. *Gefitinib*

(gefitinib:ab,ti) AND ('non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND (mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3':ti OR 'phase III':ti)

8. *Erlotinib*

(erlotinib:ab,ti) AND ('non small cell lung carcinoma':ab,ti OR 'non small cell lung cancer':ab,ti OR NSCLC\*:ab,ti OR 'lung adenocarcinoma':ab,ti) AND ('stage IV':ab,ti OR 'stage 4':ab,ti OR 'stage IIIB':ab,ti OR 'stage 3B':ab,ti OR metastatic:ab,ti OR metastas\*:ab,ti OR advanced:ab,ti) AND (mortality:ab,ti OR death\*:ab,ti OR survival:ab,ti) AND ('phase 3':ti OR 'phase III':ti)

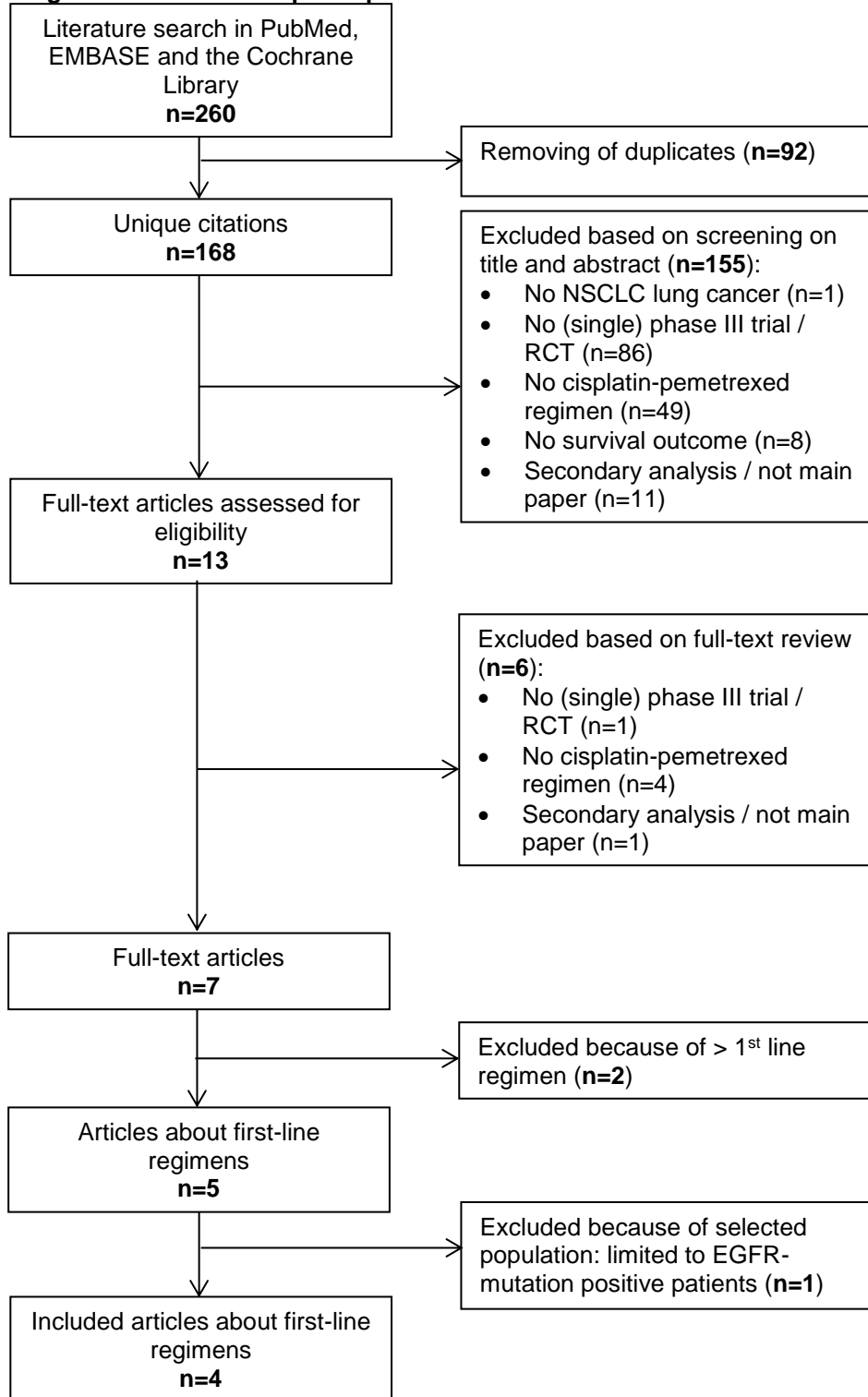
## APPENDIX 2      Flow charts and reference tables clinical trial outcomes

**STable 1. Clinical trial reference outcomes**

<b>Chemotherapy regimen</b>	<b>Median OS clinical trials (months)</b>
1. Cisplatin pemetrexed	10.19
2. Cisplatin gemcitabine	9.88
3. Carboplatin pemetrexed	10.18
4. Carboplatin gemcitabine	8.75
5. Bevacizumab carboplatin paclitaxel	12.57
6. Carboplatin docetaxel	9.52
7. Gefitinib (in EGFR-mutation positive patients)	24.90
8. Erlotinib (in EGFR-mutation positive patients)	22.01
<b>Overall</b>	<b>10.84</b>

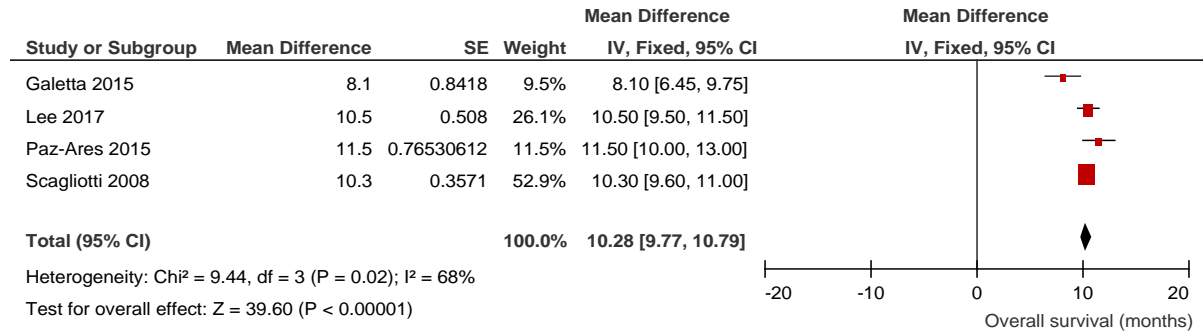
## 1. Cisplatin pemetrexed

**SFigure 1. Flowchart cisplatin-pemetrexed**





**SFigure 2. Forest plot cisplatin-pemetrexed**



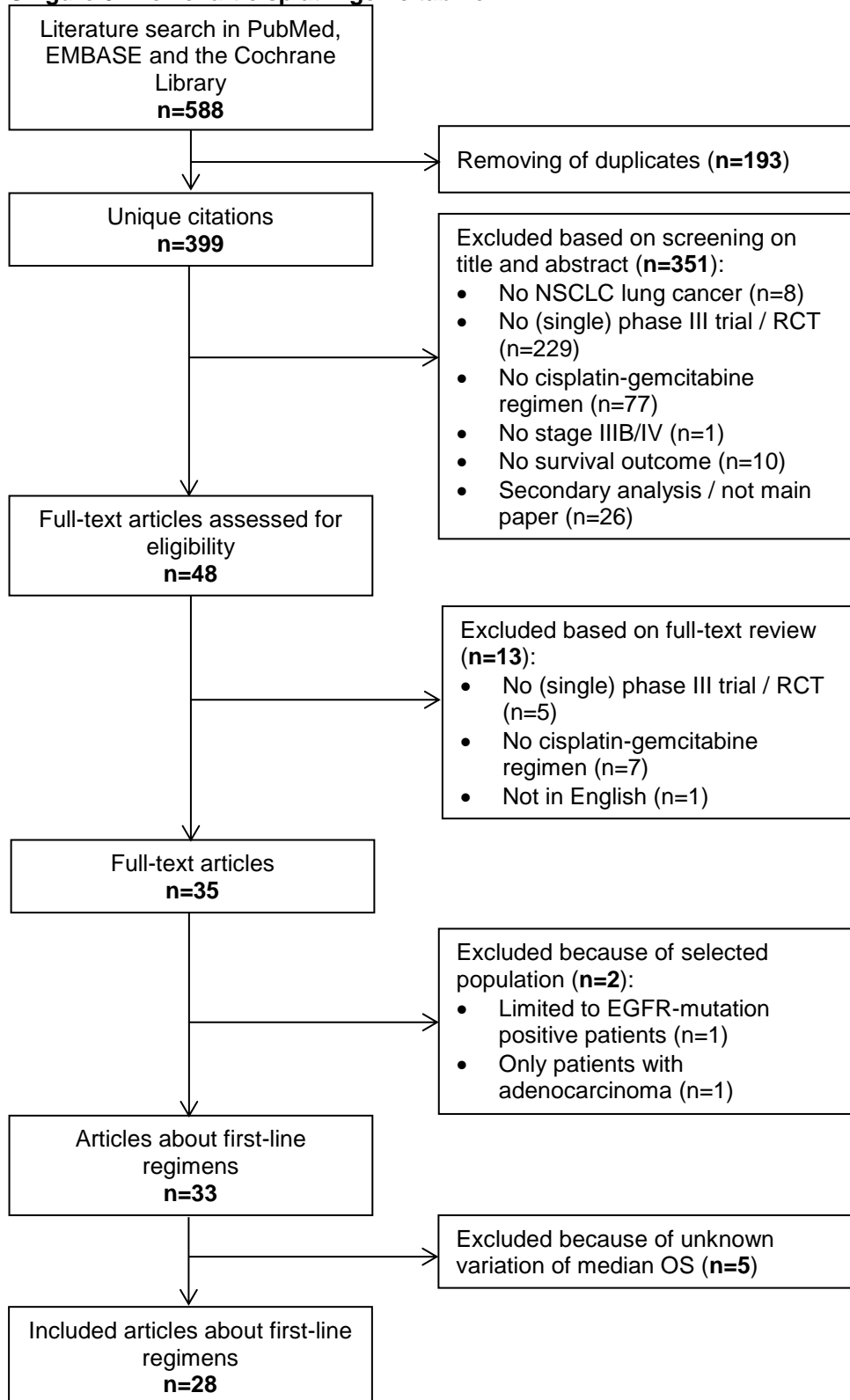
**STable 2. Clinical trial and real-world characteristics regimen cisplatin-pemetrexed**

Characteristic	Clinical trials <sup>a</sup>	Real-world
Total number of patients	1470	347
Overall survival (months)	10.19	8.90
Median age (years)	60.6	59
Male (%)	66.1	49
Stage IV (%)	87.8	100
ECOG Performance Status		
ECOG PS 0-1 (%)	98.5	87
ECOG PS ≥2 (%)	1.5	8
Missing	---	5
Histology		
squamous (%)	9.4	1
adenocarcinoma (%)	79.2	82
large-cell (%)	6.6	4
other or unknown histology (%)	4.8	14

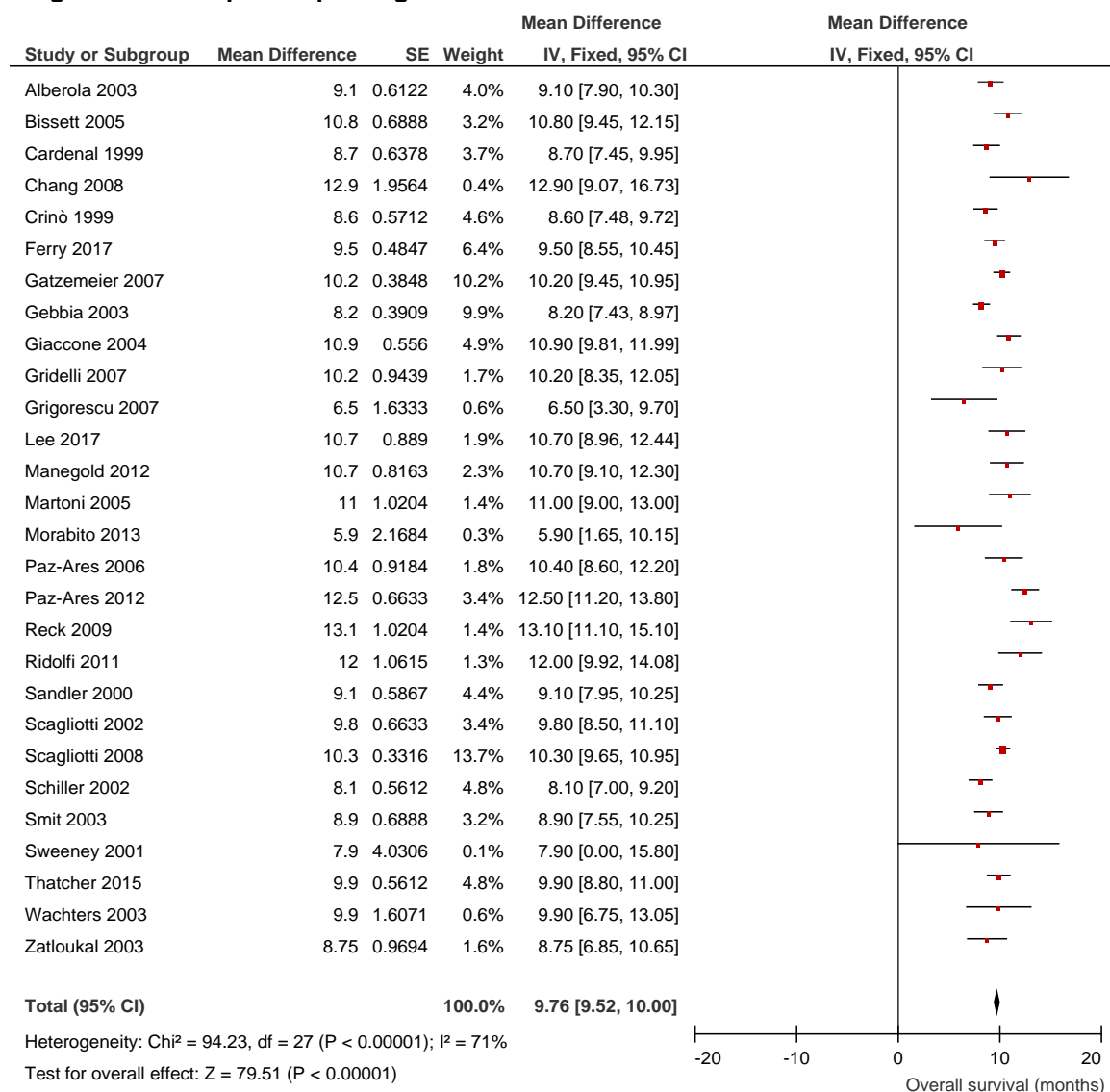
<sup>a</sup>Histology based on 3 references

## 2. Cisplatin gemcitabine

**SFigure 3. Flowchart cisplatin-gemcitabine**



**SFigure 4. Forest plot cisplatin-gemcitabine**



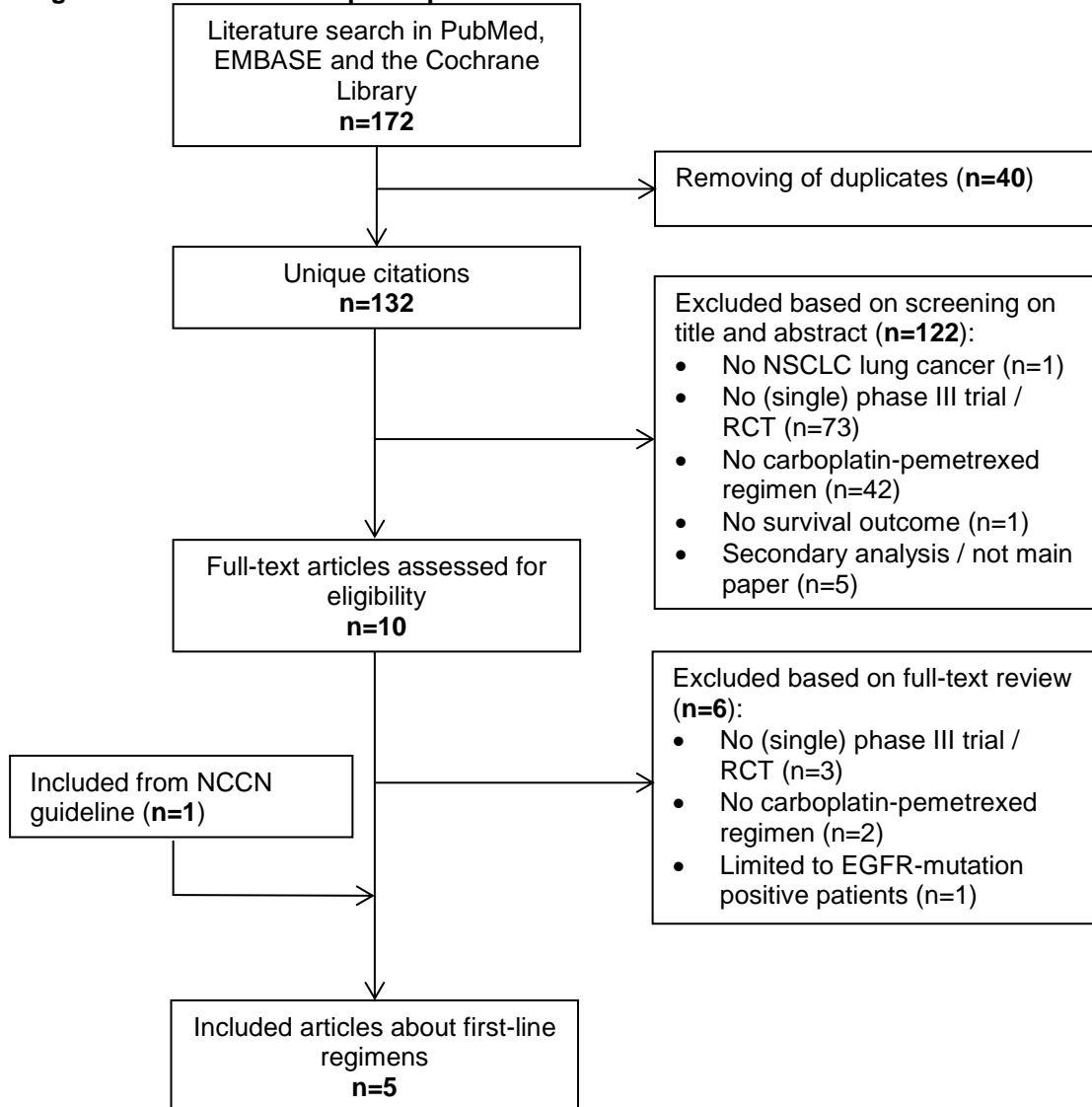
**Stable 3. Clinical trial and real-world characteristics regimen cisplatin-gemcitabine**

Characteristic	Clinical trials <sup>a</sup>	Real-world
Total number of patients	6736	214
Overall survival (months)	9.88	7.90
Median age (years)	61.0	63
Male (%)	74.7	59
Stage IV (%)	72.1	100
ECOG Performance Status		
ECOG PS 0-1 (%)	86.0	86
ECOG PS ≥2 (%)	13.7	6
Missing	---	8
Histology		
squamous (%)	36.6	48
adenocarcinoma (%)	43.3	32
large-cell (%)	7.7	8
other or unknown histology (%)	12.3	12

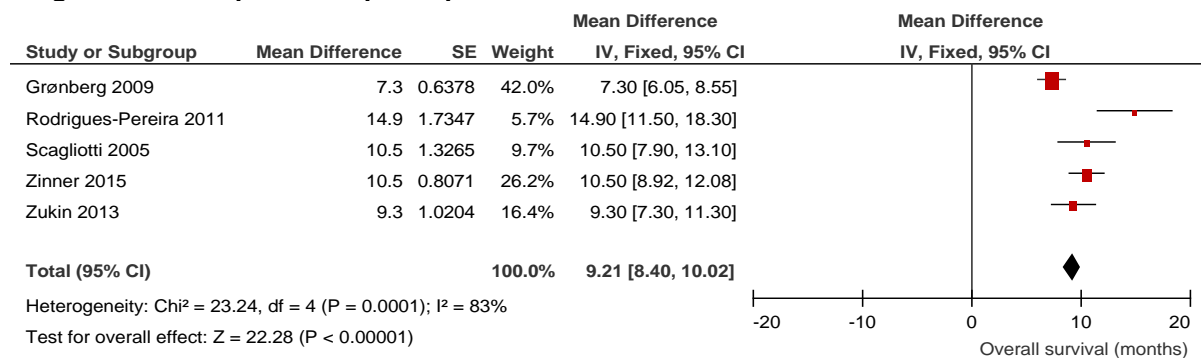
<sup>a</sup>ECOG based on 26 references; Histology based on 25 references

### 3. Carboplatin pemetrexed

**SFigure 5. Flowchart carboplatin-pemetrexed**



**SFigure 6. Forest plot carboplatin-pemetrexed**

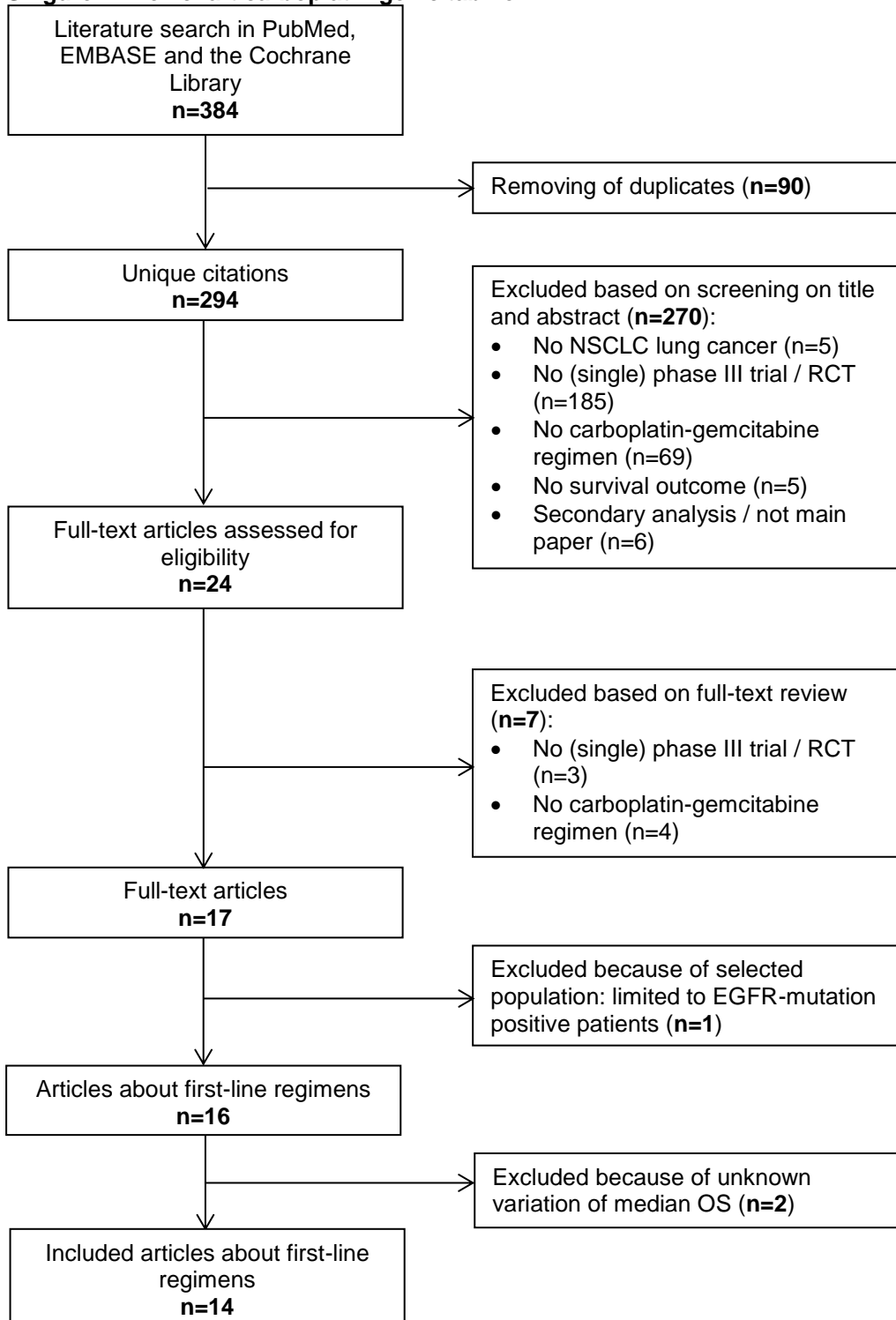


**STable 4. Clinical trial and real-world characteristics regimen carboplatin-pemetrexed**

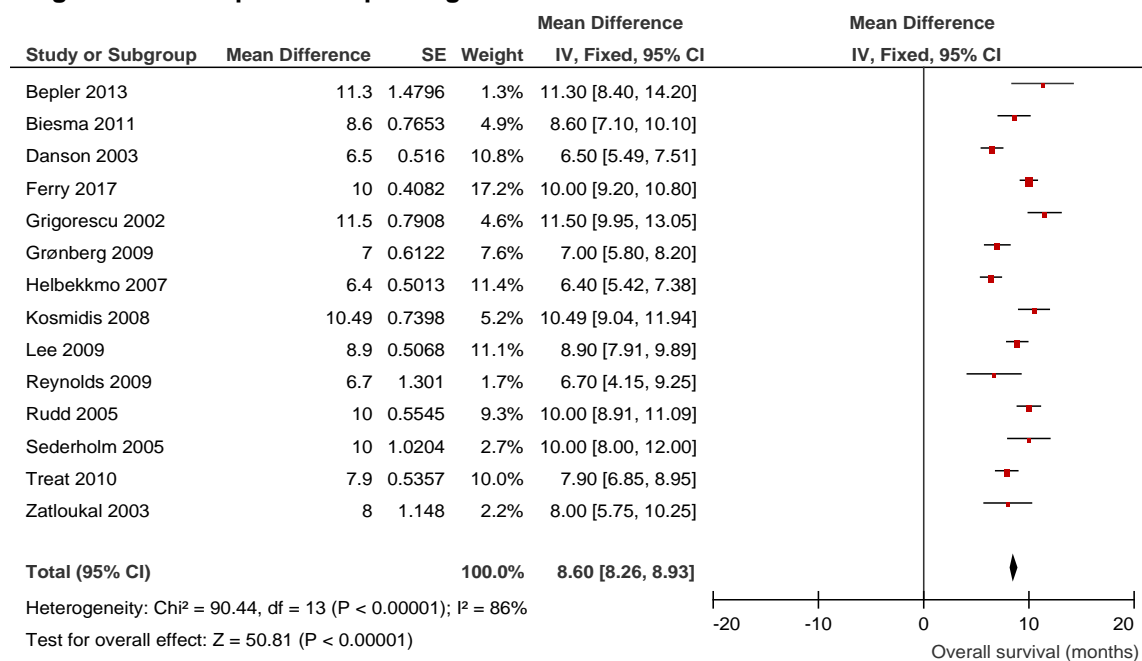
<b>Characteristic</b>	<b>Clinical trials</b>	<b>Real-world</b>
Total number of patients	649	213
Overall survival (months)	10.18	6.51
Median age (years)	64.0	65
Male (%)	63.9	62
Stage IV (%)	82.0	100
ECOG Performance Status		
ECOG PS 0-1 (%)	72.8	81
ECOG PS ≥2 (%)	27.2	16
Missing	---	3
Histology		
squamous (%)	11.9	1
adenocarcinoma (%)	68.4	83
large-cell (%)	3.6	9
other or unknown histology (%)	13.5	8

#### 4. Carboplatin gemcitabine

**SFigure 7. Flowchart carboplatin-gemcitabine**



**SFigure 8. Forest plot carboplatin-gemcitabine**

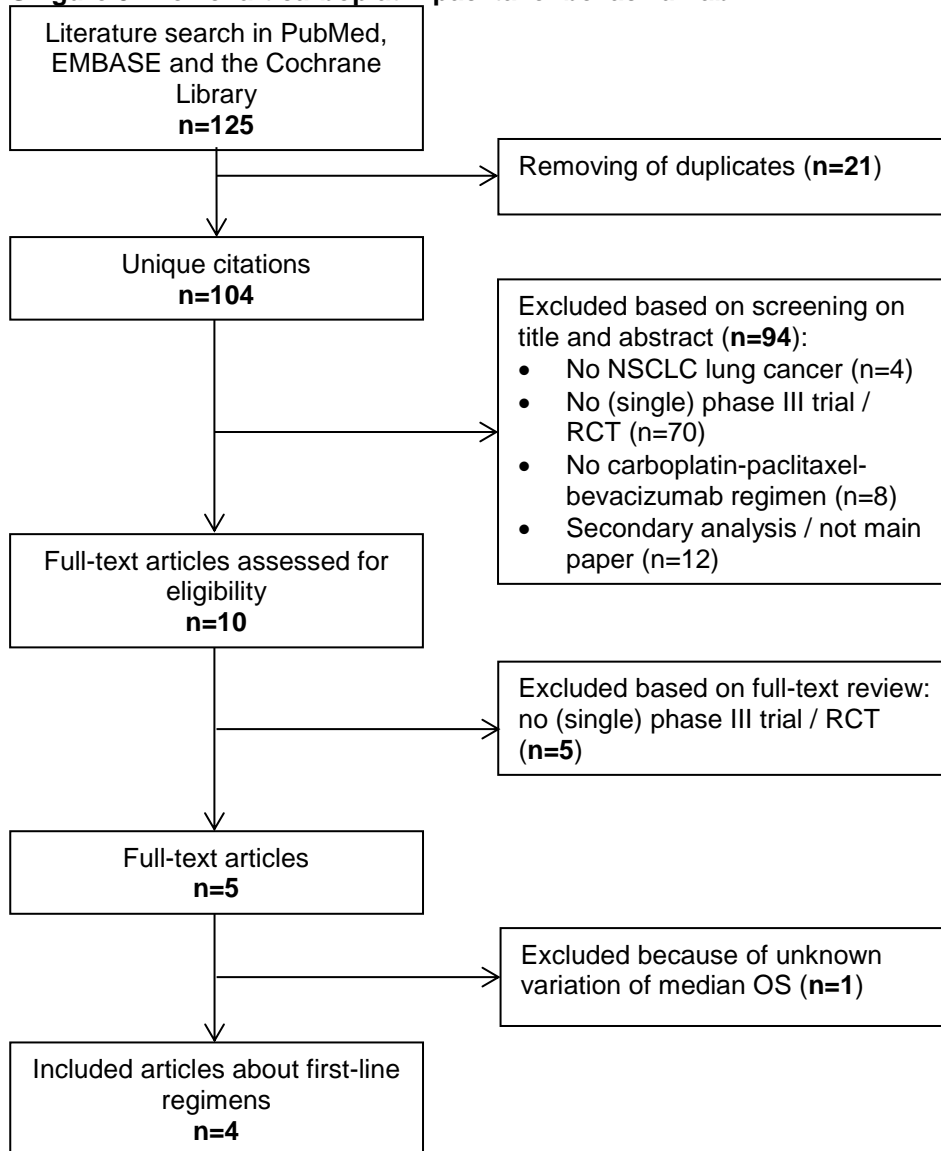


**Stable 5. Clinical trial and real-world characteristics regimen carboplatin-gemcitabine**

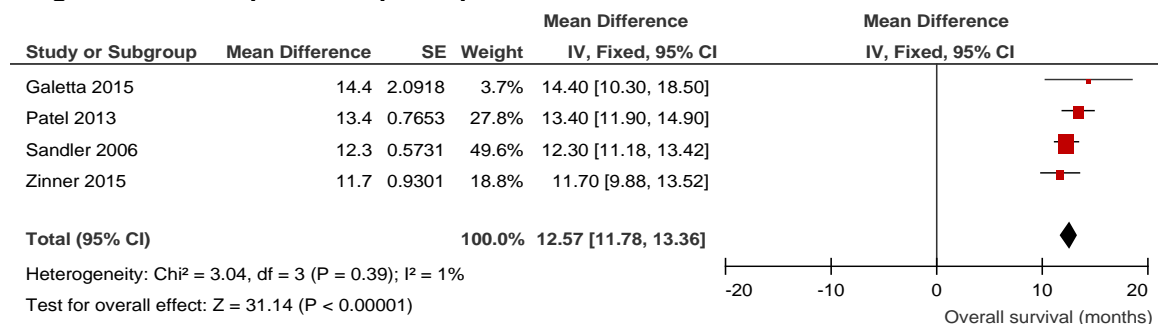
Characteristic	Clinical trials	Real-world
Total number of patients	2857	171
Overall survival (months)	8.75	6.67
Median age (years)	63.1	68
Male (%)	65.2	72
Stage IV (%)	67.9	100
ECOG Performance Status		
ECOG PS 0-1 (%)	77.0	80
ECOG PS $\geq 2$ (%)	22.9	16
Missing	---	4
Histology		
squamous (%)	29.7	40
adenocarcinoma (%)	39.4	30
large-cell (%)	6.1	18
other or unknown histology (%)	24.8	12

## 5. Carboplatin paclitaxel bevacizumab

**SFigure 9. Flowchart carboplatin-paclitaxel-bevacizumab**



**SFigure 10. Forest plot carboplatin-paclitaxel-bevacizumab**



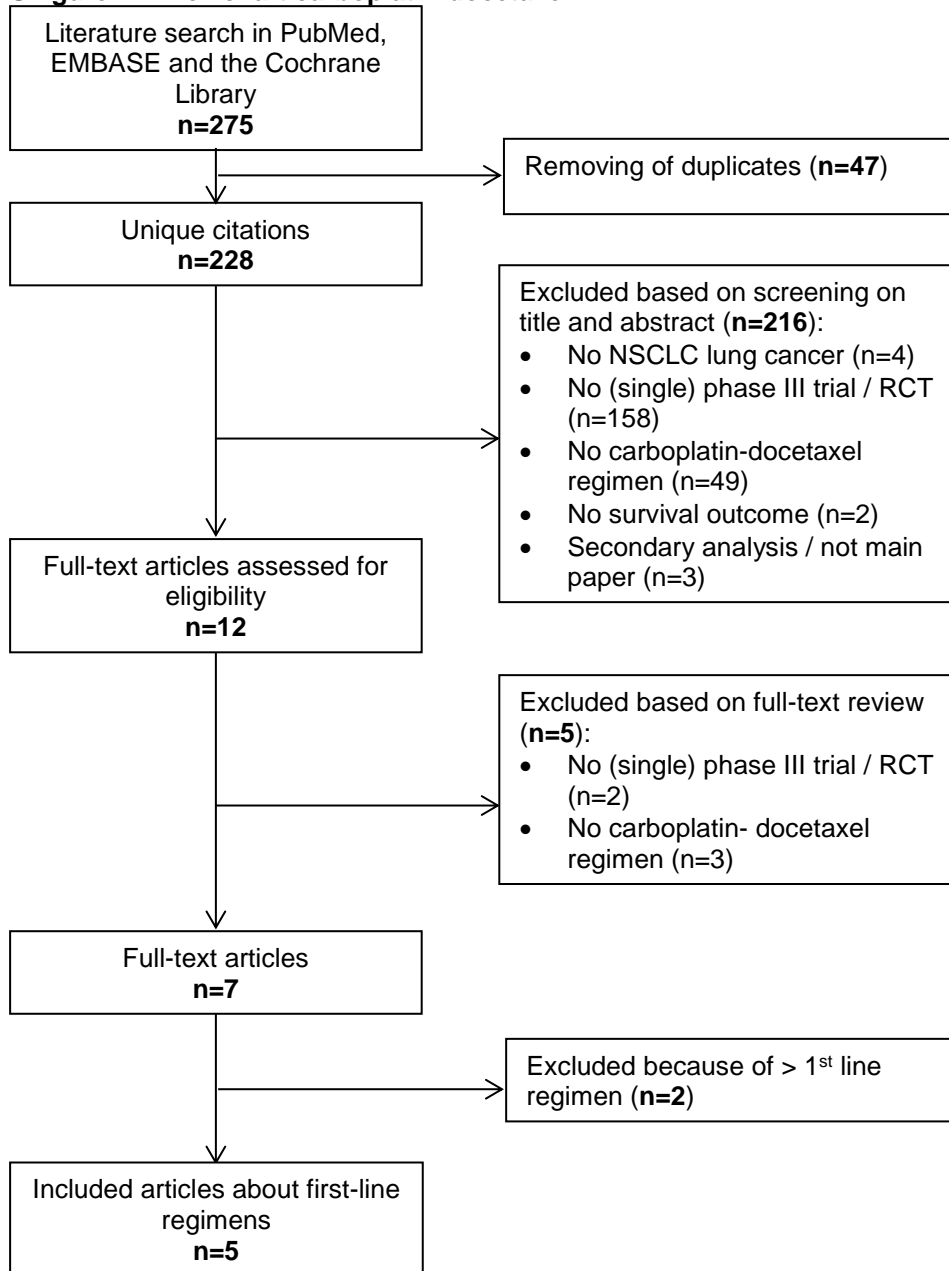


**STable 6. Clinical trial and real-world characteristics regimen carboplatin-paclitaxel-bevacizumab**

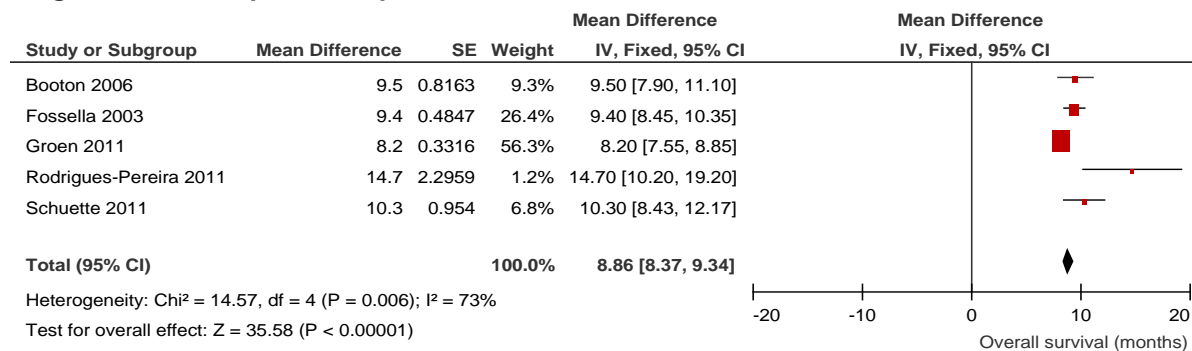
<b>Characteristic</b>	<b>Clinical trials</b>	<b>Real-world</b>
Total number of patients	1121	73
Overall survival (months)	12.57	8.18
Median age (years)	64.9	62
Male (%)	59.9	48
Stage IV (%)	89.3	100
ECOG Performance Status		
ECOG PS 0-1 (%)	100	90
ECOG PS ≥2 (%)	0	7
Missing	---	3
Histology		
squamous (%)	0.0	0
adenocarcinoma (%)	85.7	84
large-cell (%)	3.8	10
other or unknown histology (%)	10.5	7

## 6. Carboplatin docetaxel

**SFigure 11. Flowchart carboplatin-docetaxel**



**SFigure 12. Forest plot carboplatin-docetaxel**



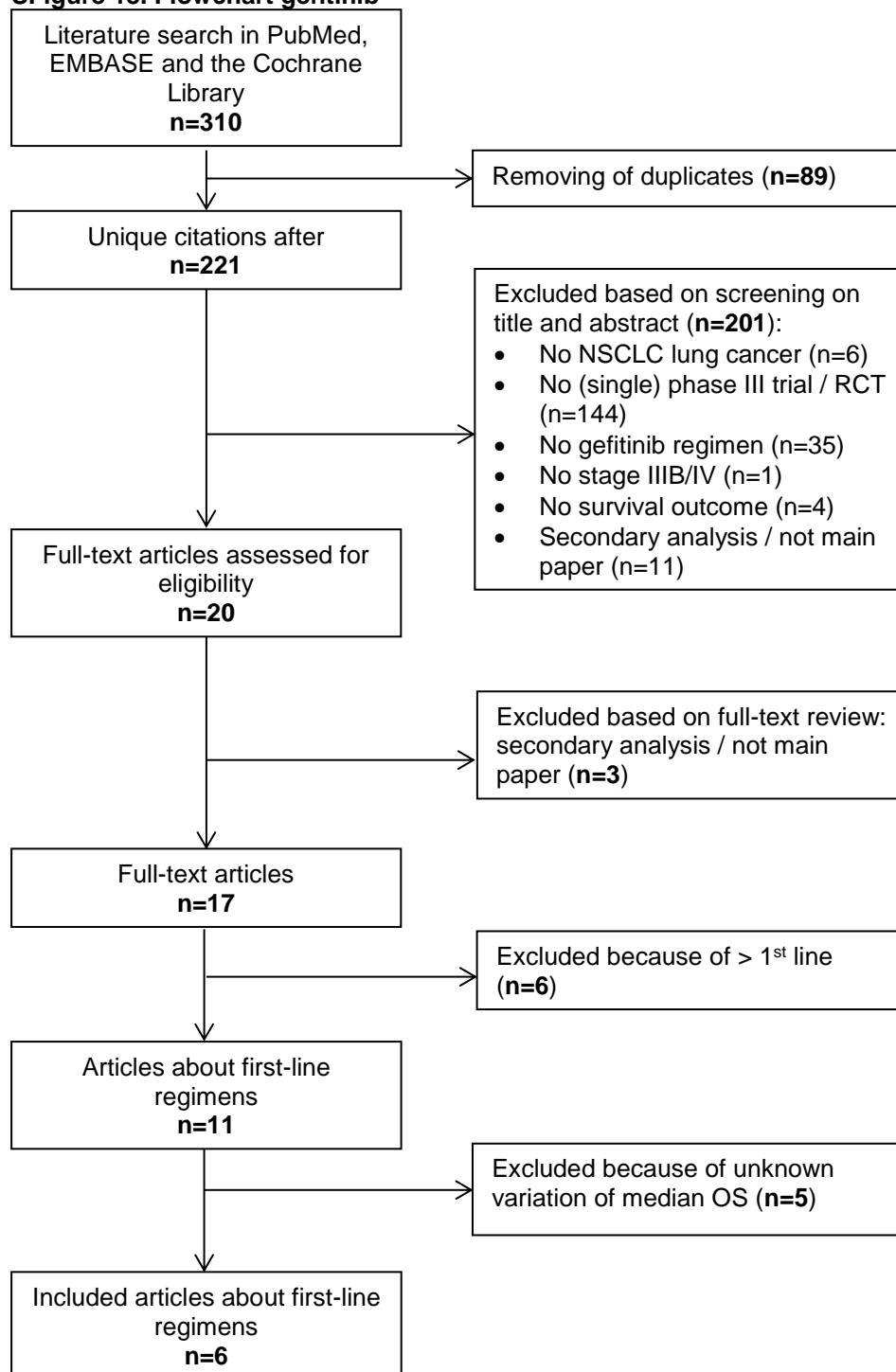
**STable 7. Clinical trial and real-world characteristics regimen carboplatin-docetaxel**

Characteristic	Clinical trials <sup>a</sup>	Real-world
Total number of patients	1100	45
Overall survival (months)	9.52	4.93
Median age (years)	61.0	59
Male (%)	66.6	51
Stage IV (%)	72.0	100
ECOG Performance Status		
ECOG PS 0-1 (%)	87.5	89
ECOG PS ≥2 (%)	12.5	9
Missing	---	2
Histology		
squamous (%)	27.1	9
adenocarcinoma (%)	51.4	51
large-cell (%)	10.5	20
other or unknown histology (%)	11.0	20

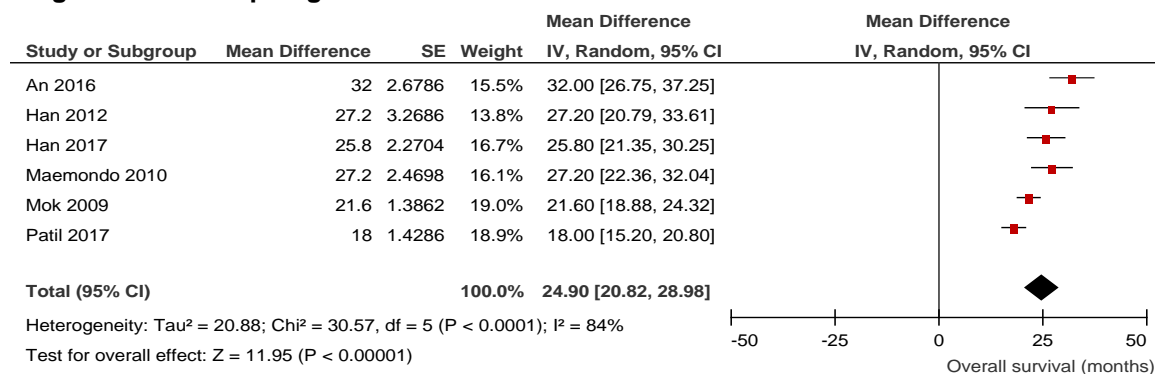
<sup>a</sup>ECOG based on 3 references

## 7. Gefitinib (in EGFR-mutation positive patients)

**SFigure 13. Flowchart gefitinib**



**SFigure 14. Forest plot gefitinib**



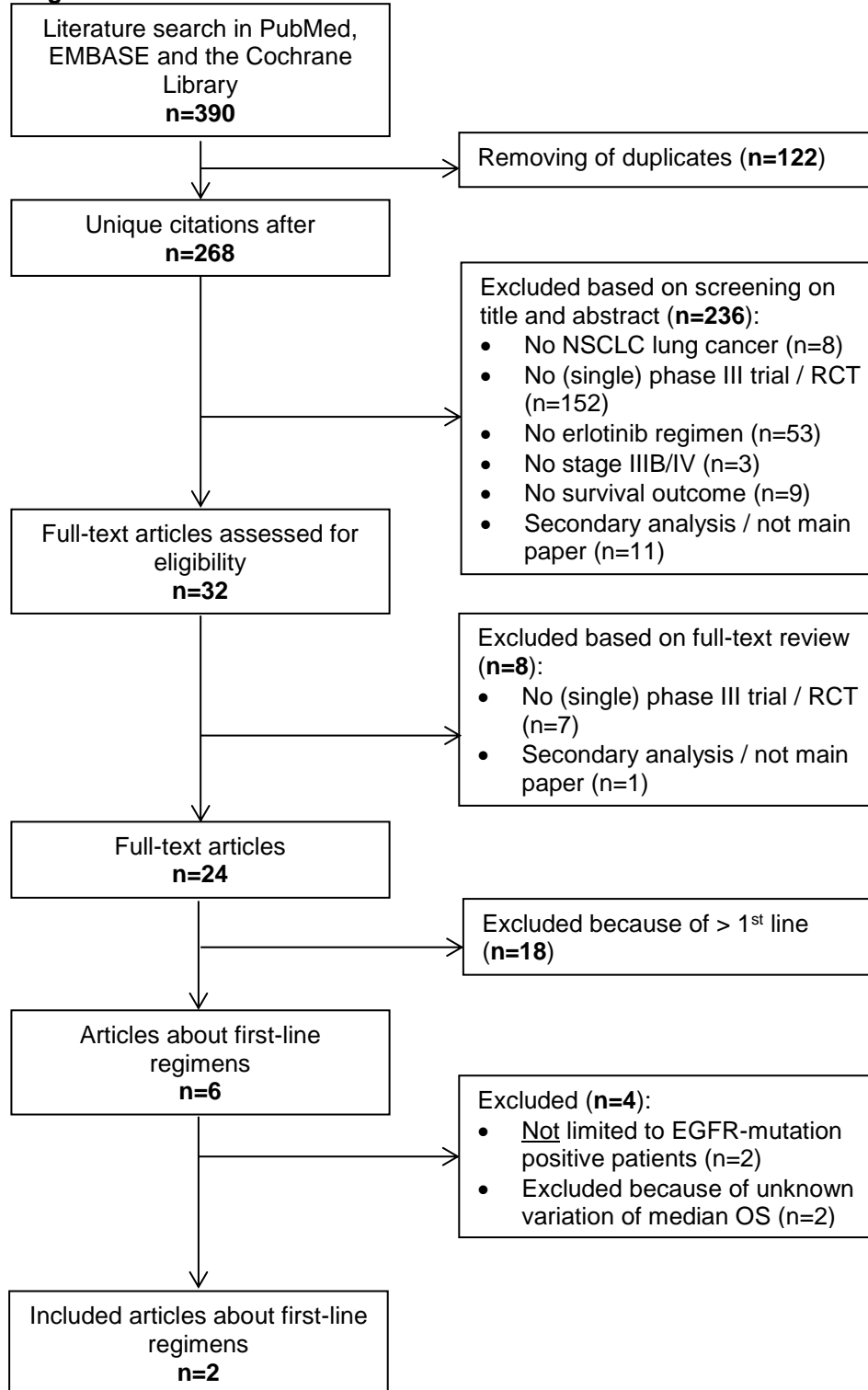
**STable 8. Clinical trial and real-world characteristics regimen gefitinib**

Characteristic	Clinical trials <sup>a</sup>	Real-world
Total number of patients	503	35
Overall survival (months)	24.90	21.19
Median age (years)	63.9	68
Male (%)	45.6	43
Stage IV (%)	87.6	100
ECOG Performance Status		
ECOG PS 0-1 (%)	97.4	89
ECOG PS ≥2 (%)	2.6	11
Missing	---	0
Histology		
squamous (%)	0.4	0
adenocarcinoma (%)	98.2	91
large-cell (%)	0.2	0
other or unknown histology (%)	1.1	9

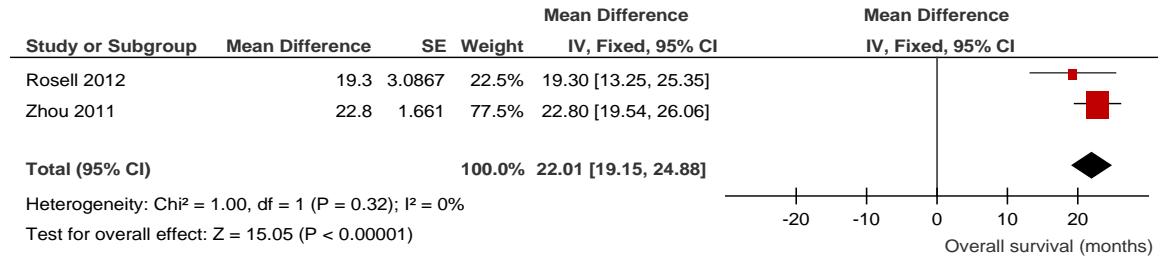
<sup>a</sup>Note: the characteristics from 2 references are based on the whole patient group, not only on the EGFR+ group; ECOG PS based on 3 references

## 8. Erlotinib (in EGFR-mutation positive patients)

**SFigure 15. Flowchart erlotinib**



**SFigure 16. Forest plot erlotinib**

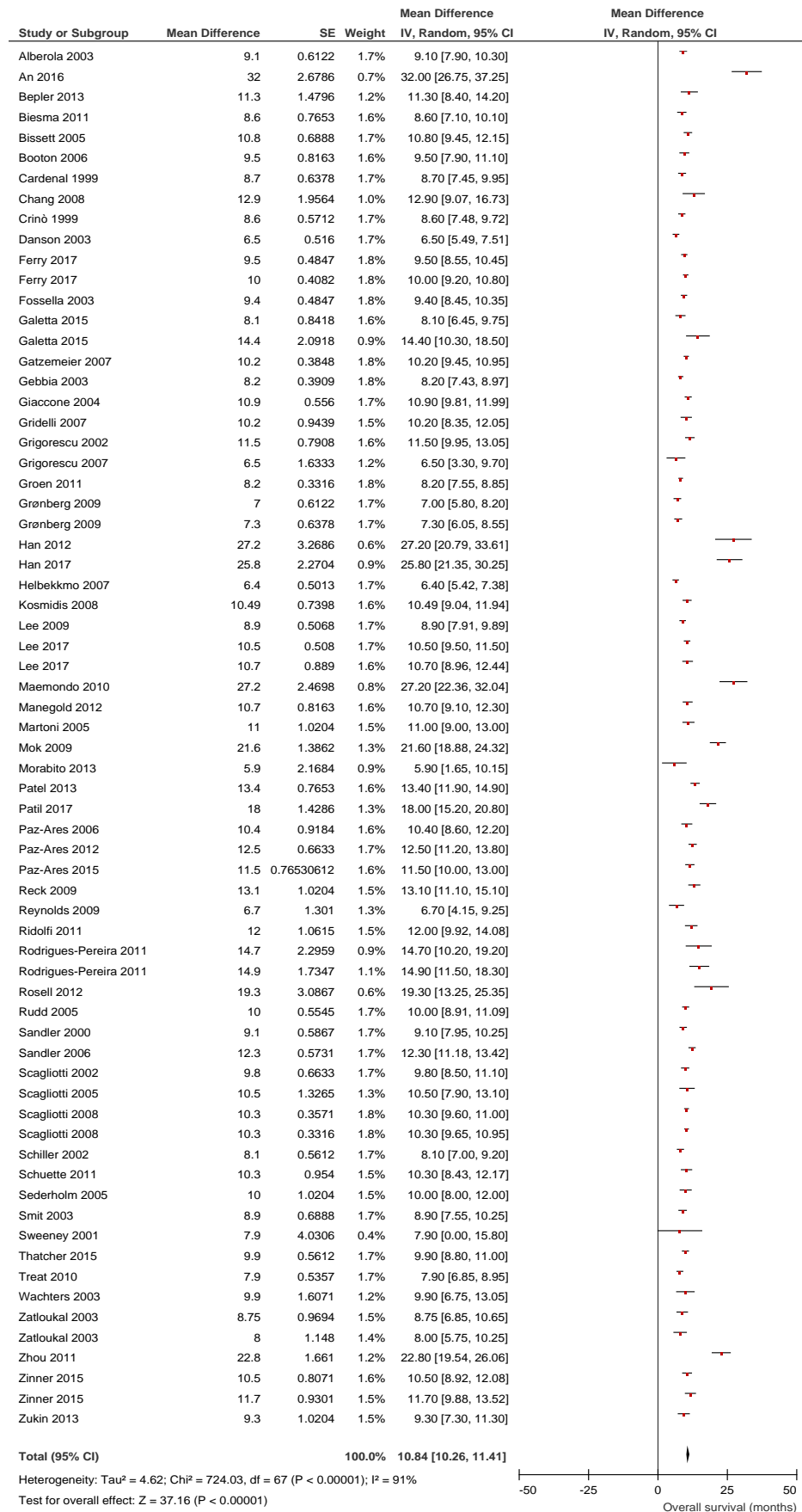


**STable 9. Clinical trial and real-world characteristics regimen erlotinib**

Characteristic	Clinical trials <sup>a</sup>	Real-world
Total number of patients	168	24
Overall survival (months)	22.01	14.32
Median age (years)	61.0	68
Male (%)	37.0	25
Stage IV (%)	89.0	100
ECOG Performance Status		
ECOG PS 0-1 (%)	88.5	75
ECOG PS ≥2 (%)	11.5	17
Missing	---	8
Histology		
squamous (%)	1.0	4
adenocarcinoma (%)	95.0	79
large-cell (%)	3.0	0
other or unknown histology (%)	0.0	17

<sup>a</sup>Histology based on 1 reference

**SFigure 17. Forest plot with overview of clinical trials for reference outcome first-line chemotherapy**





## APPENDIX 3 Proxies for toxicity

**STable 10. Dose reduction and switches to other systemic agents as proxies for toxicity**

	Dose reduction <sup>a</sup>	Switch to other systemic agents <sup>b</sup>
	n (%)	n (%)
Cisplatin pemetrexed	44 (13)	65 (19)
Cisplatin gemcitabine	41 (19)	50 (23)
Carboplatin pemetrexed	38 (18)	2 (1)
Carboplatin gemcitabine	66 (39)	4 (2)
Bevacizumab carboplatin paclitaxel	12 (16)	7 (10)
Carboplatin docetaxel	5 (11)	2 (4)
Gefitinib (in EGFR positive patients) <sup>c</sup>	0	0
Erlotinib (in EGFR positive patients)	3 (13)	1 (4)
<b>Overall</b>	<b>209 (19)</b>	<b>131 (12)</b>

<sup>a</sup>Missing values in 39 patients (3%)

<sup>b</sup>Missing values in 34 patients (3%)

<sup>c</sup>Possible underestimation as data about gefitinib from earlier years was not available in the databases

**STable 11. Co-morbidities in patients with early discontinuation of systemic therapy**

Co-morbidity	Early discontinuation		p-value
	Yes (n=469) n (%)	No (n=653) n (%)	
COPD	92 (20)	108 (17)	0.206
coronary artery disease	64 (14)	75 (12)	0.312
diabetes	54 (12)	60 (9)	0.229
peripheral vascular disease	52 (11)	64 (10)	0.488
other cancer	29 (6)	39 (6)	0.900
cerebrovascular disease	35 (8)	28 (4)	0.025
congestive heart failure	18 (4)	16 (3)	0.217
connective tissue disease	11 (2)	11 (2)	0.514

## **APPENDIX 4      List of included hospitals**

The individual Santeon hospitals include:

- Canisius Wilhelmina Hospital, Nijmegen, the Netherlands
- Catharina Hospital, Eindhoven, the Netherlands
- Martini Hospital, Groningen, the Netherlands
- Medisch Spectrum Twente, Enschede, the Netherlands
- OLVG, Amsterdam, the Netherlands
- St. Antonius Hospital, Nieuwegein/Utrecht, the Netherlands
- Maasstad Hospital, Rotterdam, the Netherlands (member since 2017, not included in this study)

[www.santeon.nl](http://www.santeon.nl)