

Supplementary materials

Table S1 – Randomized controlled trials included in the network meta-analyses

Inclusion criteria for the systematic review of randomized controlled trials	<ul style="list-style-type: none">• Randomized controlled trials• Patients with advanced or metastatic NSCLC (stage IIIB or stage IV)• Investigating the efficacy and/or safety of any of the induction comparators stated above• English language• Reporting hazard ratios for OS or PFS, Kaplan–Meier plots or response rate
Inclusion criteria for the systematic review of published meta-analyses	<ul style="list-style-type: none">• Meta-analyses• Patients with advanced or metastatic NSCLC (stage IIIB or stage IV)• Comparators: doublets of third-generation chemotherapy agents specified above, comparisons with platinum-based triplets of bevacizumab and cetuximab and comparisons with erlotinib and gefitinib monotherapy• English language• All outcomes included
Exclusion criteria	<ul style="list-style-type: none">• Animal or <i>in vitro</i> studies• Publications without an abstract• Studies not conducted specifically in patients with advanced or metastatic NSCLC with stage IIIB or stage IV or which included patients with earlier stages of the disease• Studies investigating efficacy and/or safety of interventions provided beyond first-line and induction/maintenance settings

	(second-line or more of therapy) <ul style="list-style-type: none">• Studies conducted in patients undergoing radiotherapy, with or without chemotherapy
--	---

Studies included in induction NMAs (14 in total): PFS and OS

Chen Y-M, Perng R-P, Shih J-F, Tsai C-M, Whang-Peng J. A randomized phase II study of docetaxel or vinorelbine in combination with cisplatin against inoperable, chemo-naive non-small-cell lung cancer in Taiwan. *Lung Cancer*. 2007;56(3):363–9.

Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol*. 2003;21:3016–24.

Niho S, Kunitoh H, Nokihara H, et al. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. *Lung Cancer*. 2012;76(3):362–7.

Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet*. 2009;373:1525–31.

Reck M, von PJ, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol*. 2010;21:1804–9.

Rosell R, Gatzemeier U, Betticher DC, et al. Phase III randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: a cooperative multinational trial. *Ann Oncol*. 2002;13:1539–49.

Rosell R, Robinet G, Szczesna A, et al. Randomized phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/vinorelbine alone as first-line therapy in EGFR-expressing advanced non-small-cell lung cancer. *Ann Oncol*. 2008;19:362–9.

Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.[Erratum appears in *N Engl J Med.* 2007;356(3):318]. *N Engl J Med.* 2006;355(24):2542–50.

Sandler A, Yi J, Dahlberg S, Kolb MM, et al. Treatment outcomes by tumor histology in Eastern Cooperative Group Study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer. *J Thorac Oncol.* 2010;5:1416–23.

Scagliotti GV, De MF, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol.* 2002;20:4285–91.

Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008;26:3543–51.

Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med.* 2002;346:92–8.

Smit EF, Van Meerbeeck JPAM, Lianes P, et al. Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer: A phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group – EORTC 08975. *J Clin Oncol.* 2003;21(21):3909–17.

Treat JA, Gonin R, Socinski MA, et al. A randomized, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer. *Ann Oncol.* 2010;21(3):540–7.

Studies included in maintenance NMAs (8 in total): PFS and OS

Belani CP, Waterhouse DM, Ghazal H, Ramalingam SS, Bordoni, Greenberg R. Phase III study of maintenance gemcitabine (G) and best supportive care (BSC) versus BSC, following standard combination

therapy with gemcitabine-carboplatin (G-Cb) for patients with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2010;28(15s):abstract 7506. Available from:

http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=51201.

Accessed September 19, 2011.

Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol.* 2010;11(6):521–9.

Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for on-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet.* 2009;374 (9699):1432–40.

Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. *J Clin Oncol.* 2009;27(4):591–8.

Paz-Ares L, de Marinis F, Dedi M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): A double-blind, phase 3, randomised controlled trial. *Lancet Oncol.* 2012;13:247–55.

Perol M, Zalcman G, Monnet I, et al. Final results from the IFCT-GFPC 0502 phase III study: Maintenance therapy in advanced NSCLC with either gemcitabine (G) or erlotinib (E) versus observation (O) after cisplatin-gemcitabine induction chemotherapy (CT), with a predefined second-line treatment. *Ann Oncol.* 2010; 21(Suppl 8): viii124 [Abstract 370PD]. Available from:

http://annonc.oxfordjournals.org/content/21/suppl_8/viii122.full.pdf+html. Accessed November 8, 2016. Surmont VF, Gaafar

RM, Scagliotti GV, et al. A double-blind, randomized, placebo-controlled phase III study of gefitinib (G) versus placebo (P) in patients (PTS) with advanced NSCLC, non progressing after first-line platinum-based chemotherapy (EORTC 08021 - ILCP). *Ann Oncol.* 2010; 21(Suppl 8):viii124 [Abstract 368PD].

http://annonc.oxfordjournals.org/content/21/suppl_8/viii122.full.pdf+html. Accessed November 8, 2016.

Westeel V, Quoix E, Moro-Sibilot D, et al. Randomized study of maintenance vinorelbine in responders with advanced non-small-cell lung cancer. *J Natl Cancer Inst.* 2005;97:499–506.

NMA = network meta-analysis; NSCLC = nonsmall cell lung cancer; OS = overall survival; PFS = progression-free survival

Table S2 Induction doses, cycle length and average cycles

Comparator	Component	Dose	Frequency per cycle	Cycle length (days)	Mean/median cycles	Source
Cisplatin+gemcitabine	Gemcitabine	1000 mg/m ²	2	28	4.37	Dose, frequency & cycle length – FDA
	Cisplatin	75 mg/m ²	3			Mean/median cycles – Scagliotti et al. 2008
Cisplatin+docetaxel	Docetaxel	75 mg/m ²	1	21	5	Dose, frequency & cycle length – EMA
	Cisplatin	75 mg/m ²	1			Mean/median cycles – Fossella et al. 2003
Cisplatin+pemetrexed	Pemetrexed	500 mg/m ²	1	21	4.35	Dose, frequency & cycle length – EMA
	Cisplatin	75 mg/m ²	1			Mean/median cycles – Scagliotti et al. 2008
Cisplatin+vinorelbine	Vinorelbine	30 mg/m ²	2	21	3.58	Dose, frequency & cycle length – FDA
	Cisplatin	80 mg/m ²	1			Mean/median cycles – Treat et al. 2010
Bevacizumab+cisplatin+gemcitabine	Bevacizumab	7.5 mg/kg	1	21	4.94	Dose, frequency & cycle length – EMA
	Gemcitabine	1250 mg/m ²	2			Mean/median cycles – Reck et al. 2010
	Cisplatin	80 mg/m ²	1			

Pemetrexed	Pemetrexed	500 mg/m ²	1	21		EMA
Cisplatin+paclitaxel	Cisplatin	80 mg/m ²	1	21	4.28	Dose, frequency & cycle length – EMA
	Paclitaxel	175 mg/m ²	1			Mean/median cycles – Rosell et al. 2002
Carboplatin+paclitaxel	Carboplatin	400 mg/m ²	1	21	3.70	Dose, frequency & cycle length – Treat et al. 2010
	Paclitaxel	225 mg/m ²	1			Mean/median cycles – Treat et al. 2010
Bevacizumab+carboplatin+paclitaxel	Bevacizumab	8 mg/m ²	1	21	6.00	Dose, frequency & cycle length – EMA
	Paclitaxel	400 mg/m ²	1			Mean/median cycles – Johnson et al. 2004
	Carboplatin	200 mg/m ²	1			

References

EMA - <http://www.ema.europa.eu>. 2012.

FDA - <http://www.access.fda.gov/>. 2012.

Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol.* 2003;21:3016–24.

Johnson D, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol.* 2004;22(11):2184–91.

Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol.* 2010;21(9):1804–9.

Rossell R Gatzemeier U, Betticher DC, et al. Phase III randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: a cooperative multinational trial. *Ann Oncol.* 2002;13:1539–49.

Scagliotti GV Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol.* 2008;26(21):3543–51.

Treat JA, Gonin R, Socinski MA, et al. A randomized, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer. *Ann Oncol.* 2010;21:540–7.

Table S3 Results of a re-run of the cost-effectiveness model excluding carboplatin-based regimens and using vinorelbine+cisplatin→BSC as the referent plus cost-effectiveness acceptability frontier (CEAF) analysis

Comparator	Median PFS (months)*	Median OS (months)*	Total LYs	Total QALYs	Total costs	Incremental LYs gained	Incremental QALYs gained (compared to referent)	Incremental costs (compared to referent)	Fully incremental ICER/QALY gained†,‡
Vinorelbine 30 mg/m ² +cisplatin 80 mg/m ² →BSC	4.37	9.66	0.99	0.64	€13,200	Referent	Referent	Referent	Referent
Gemcitabine 1000 mg/m ² +cisplatin 75 mg/m ² →BSC	4.83	10.12	1.04	0.68	€13,285	0.05	0.04	€86	€2120
Docetaxel 75 mg/m ² +cisplatin 75 mg/m ² →BSC	4.37	9.20	0.94	0.61	€13,573	-0.05	-0.03	€373	Dominated

Pemetrexed 500 mg/m ² +cisplatin 75 mg/m ² →BSC	5.29	11.50	1.22	0.80	€23,134	0.22	0.16	€9935	€80,656
Vinorelbine 30 mg/m ² +cisplatin 80 mg/m ² →pemetrexed 500 mg/m ²	5.52	10.81	1.17	0.78	€26,557	0.18	0.14	€13,357	Dominated
Docetaxel 75 mg/m ² +cisplatin 75 mg/m ² →pemetrexed 500 mg/m ²	5.75	10.35	1.11	0.74	€27,571	0.12	0.10	€14,371	Dominated
Gemcitabine 1000 mg/m ² +cisplatin 75 mg/m ² →pemetrexed 500 mg/m ²	5.98	11.50	1.23	0.84	€28,580	0.24	0.20	€15,381	Extendedly dominated
Gemcitabine 1250 mg/m ² +cisplatin 80 mg/m ² +bevacizumab	5.52	10.12	1.06	0.70	€30,638	0.07	0.06	€17,438	Dominated

7.5 mg/kg→bevacizumab 7.5 mg/kg									
Pemetrexed 500 mg/m ² +cisplatin 75 mg/m ² →pemetrexed 500 mg/m ²	5.98	12.88	1.37	0.93	€35,617	0.38	0.28	€22,417	€102,179

*Rounded to nearest week (0.23 months) due to cycle length of 1 week

[†]Fully incremental analysis is conducted by comparing regimens to the next most cost-effective option

[‡]Due to the rounding of these values it may not be possible to precisely recreate these results

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-years

The removal of carboplatin has made minimal difference – apart from in the case of gemcitabine+cisplatin→BSC, where the ICER has fallen to €2120/QALY. This is because the referent treatment is no longer paclitaxel+carboplatin→BSC. The other ICERs for pemetrexed+cisplatin→BSC and pemetrexed+cisplatin→pemetrexed have not changed because this is a fully incremental analysis – so the ICERS are calculated based on the next most effective comparator (and dominated results are removed). This means that

pemetrexed+cisplatin→BSC is still compared with gemcitabine+cisplatin→BSC and pemetrexed+cisplatin→pemetrexed is still compared with pemetrexed+cisplatin→BSC.

The probability of cisplatin plus pemetrexed induction followed by pemetrexed maintenance being the most cost-effective treatment sequence is approximately 33.8% at a willingness-to-pay threshold of approximately €106,000 (Figure).

CEAF

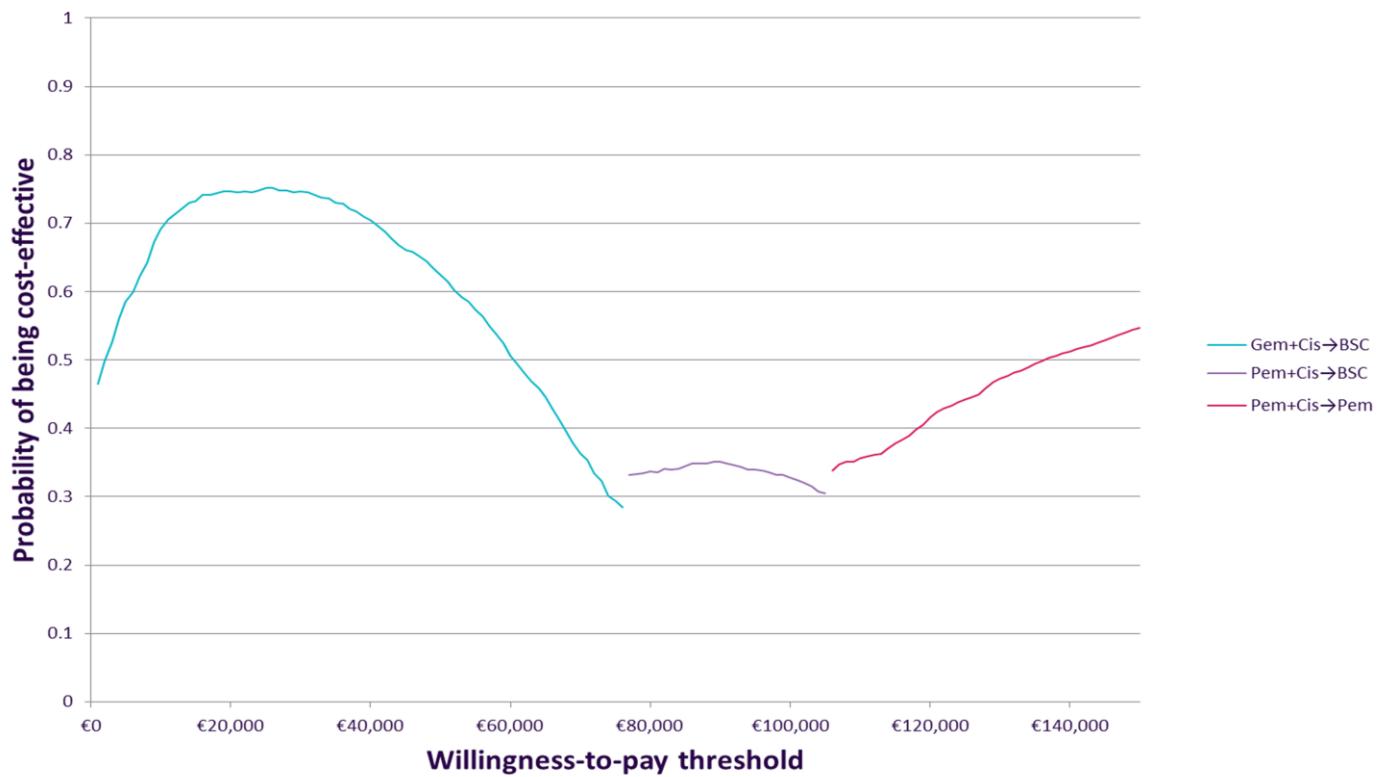


Figure S1 Cost-effectiveness acceptability frontier (CEAF) following a re-run of the cost-effectiveness model omitting the carboplatin-based regimens. For details of the regimens refer to Table S2.

Abbreviations: BSC, best support care; Cis, cisplatin; Gem, gemcitabine; Pem, pemetrexed.