Single Technology Appraisal (STA)

Afatinib for treating epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer

Dear Helen,

Please find attached our response to the clarification questions regarding the STA of afatinib for treating epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer.

Please note that 'commercial in confidence' information is underlined and highlighted in turquoise, and 'academic in confidence' information is underlined and highlighted in yellow.

In addition to this document, additional attachments (sent in parallel) are:

- B1 and B2.pdf
- B3.rtf
- B4.rtf
- Confidential information checklist - Clarification Questions.pdf
- Inoue et al. 2013.pdf
- Mitsudomi et al 2012.pdf
- Scagliotti 2009.pdf
- Sequist et al 2013.pdf

'B1 and B2.pdf', 'B3.rtf', and 'B4.rtf' are unpublished data and are commercial in confidence.

If you have any further question, please let me know

Kind regards,

[redacted]

Section A: Clarification on clinical effectiveness data

Mixed treatment comparison

The mixed treatment comparison (MTC) presented uses studies of patients with mixed EGFR status. For progression-free survival (PFS), where both independent and local investigator assessments are available, PFS measured by independent assessment has been used. Updated overall survival (OS) data for Mok et al. 2009 and Maemondo et al. 2010 are available in Fukuoka et al. 2011 and Inoue et al 2012 respectively but have not been incorporated. In order to complete the network, the hazard ratio for erlotinib vs. chemotherapy (which can be one of any four combinations of treatment) is replicated four times for the following comparators: (i) erlotinib vs. docetaxel/cisplatin, (ii) erlotinib vs. docetaxel/carboplatin, (iii) erlotinib vs. gemcitabine/cisplatin, (iv) erlotinib vs. gemcitabine/carboplatin.

The OS hazard ratios (HRs) for the IPASS and NEJGSG002 trials have been updated. For clarity, the initial and updated OS HRs along with their associated 95% confidence intervals (CIs) are presented in Table 1.

Table 1: IPASS, NEJGSG002 and WJTOG3405 OS HRs

Trial	Treatment	Comparator	Initial		Updated		Source
			HR	95% CI	HR	95% CI	
IPASS	Gefitinib	Paclitaxel/ Carboplatin	0.78	0.50-1.20			Mok et al., 2009[1]
					1.00	0.76-1.33	Fukuoka et al., 2011[2]
NEJGSG002	Gefitinib	Paclitaxel/ Carboplatin	NR	NR			Maemondo et al., 2010[3]
					0.887	0.634-1.241	Inoue et al., 2013[4]
WJTOG3405	Gefitinib	Docetaxel/ Cisplatin	1.638	0.749-3.582			Mitsudomi et al., 2010[5]
					1.185	0.767-1.829	Mitsudomi et al., 2012[6]

NR: Not reported

The results generated from the network meta-analysis (NMA) by using the updated OS data are presented in Table 2, along with the results that were originally presented in the manufacturer's submission. The updated OS hazard ratios from the IPASS and NEJGSG002 trials have been used in the sensitivity analyses requested in Section A2. The OS hazard ratios for the WJTOG340 trial, originally reported in Mitsudomi et al., 2010[5], have also been updated with more mature data reported in Mitsudomi et al., 2012[6].

Table 2: NMA results from the submitted network

Submitted network							
		fixed effects			random effects		
		HR	l.Cr.I	u.Cr.I	HR	l.Cr.I	u.Cr.I
Gefitinib							
PFS	indep PFS	0.83	0.61	1.10	0.78	0.47	1.20
	inv PFS	0.73	0.54	0.98	0.70	0.43	1.10
OS (original data)		0.84	0.55	1.30	0.83	0.54	1.34
OS (updated data)		0.86	0.60	1.23	0.85	0.57	1.27
Erlotinib							
PFS	indep PFS	0.95	0.67	1.40	0.91	0.53	1.50
	inv PFS	0.84	0.60	1.20	0.82	0.50	1.30
OS (original data)		0.80	0.56	1.14	0.80	0.54	1.18
OS (updated data)		0.80	0.56	1.14	0.79	0.56	1.17

Note: *Green shading indicates values corresponding to base case settings in the cost-effectiveness model*

A1. **Priority Question:** Please clarify the impact of using the hazard ratio derived from the same study (EURTAC) four times within the same network on the results from the MTC.

The EURTAC study, reported in Rosell et al., 2012[7], compares erlotinib with four standard chemotherapies (cisplatin plus docetaxel, cisplatin plus gemcitabine, carboplatin plus docetaxel, and carboplatin plus gemcitabine). The Rosell et al., 2012[7] paper only reports the efficacy of erlotinib versus the chemotherapies as a combined group and does not report the relative efficacy of erlotinib separately versus each specific chemotherapy regimen.

Apart from removing the EURTAC study, which would remove erlotinib from the analysis, there are two possible ways to deal with this in the NMA network. The first is to consider each individual chemotherapy treatment in the comparator arm as a separate element in the network but use the same HRs versus erlotinib for each chemotherapy regimen. The second approach is to consider all platinum/taxol and platinum/nucleoside analog chemotherapy doublets in the network as being the same treatment. We chose the first approach because this allowed the incorporation of more information into the network, which should allow for a more realistic estimation of results.

The impact of using the first approach and incorporating the erlotinib vs chemotherapy HR into the network four times is that the confidence intervals for each of these four comparisons will underestimate the uncertainty around the HR, due to being based on a larger patient population than actually received each chemotherapy combination. However, since none of the PFS and OS HRs for afatinib versus erlotinib and gefitinib used in the base case analysis shows a statistically significant benefit for afatinib the further increase in the variability would not be expected to result in a major re-interpretation of the cost-effectiveness results.

To test this, an exploratory analysis was conducted which investigated the impact of arbitrarily increasing the uncertainty around the HRs from the EURTAC trial used as inputs to the NMA (using

the original network). Uncertainty around the EURTAC input HRs was increased by reducing the lower confidence interval by half and by doubling the upper confidence interval.

For the NMA output HRs used in the base case cost-effectiveness model (independent assessment of PFS, random effects models for PFS and fixed effects models for OS), the HRs produced when exaggerating uncertainty around the EURTAC inputs (shown in Table 3), were comparable to the HRs generated by the network in the original manufacturer's submission (see Table 2). However, a slight increase was observed in the credible interval around the HR for gefitinib PFS (from_0.47 - 1.20 in the submitted network to 0.4291 - 1.303 in the network with exaggerated uncertainty around EURTAC data). A greater increase was observed in the credible intervals around the HR for erlotinib PFS (from 0.53 – 1.50 to 0.395 – 1.965) and OS (from 0.56 – 1.14 to 0.4205 – 1.512).

Table 3: Increasing uncertainty around EURTAC inputs – NMA results

Sensitivity analysis on submitted network							
		fixed effects			random effects		
		HR	l.Cr.I	u.Cr.I	HR	l.Cr.I	u.Cr.I
Gefitinib							
PFS- Exaggerating uncertainty around EURTAC trial	indep PFS	0.8263	0.6066	1.1280	0.7776	0.4291	1.3030
	inv PFS	0.7280	0.5389	0.9838	0.6952	0.4148	1.1090
OS (original data) Exaggerating uncertainty around EURTAC trial		0.8448	0.5538	1.2970	0.8443	0.5308	1.3370
Erlotinib							
PFS- Exaggerating uncertainty around EURTAC trial	indep PFS	0.9233	0.4634	1.8530	0.8861	0.3950	1.9650
	inv PFS	0.8134	0.4097	1.6240	0.7801	0.3623	1.6810
OS (original data)- Exaggerating uncertainty around EURTAC trial		0.7947	0.4205	1.5120	0.7847	0.4058	1.5570

Note: *Green shading indicates values corresponding to base case settings in the cost-effectiveness model*

A2. **Priority Question(s):** Please conduct the following sensitivity analyses for the MTC (using updated OS data, where available):

A3. :

i. Using only data from the population of patients with EGFR mutations (see Table below for full list of studies to be included and excluded) for both PFS and OS.

ii. Excluding EURTAC even if this precludes a comparison with erlotinib. This analysis should be conducted for the current MTC and as in (i).

Non-priority question: Conduct (i) and (ii) using local investigator assessments (where available) instead of independent assessment for PFS

Table of studies to be included and excluded in modified MTC for A2 (iii)

Included	Excluded
LUX-Lung 3	Chang et al. 2001
LUX-Lung 6	Comella et al. 2000
Han et al. 2012 (First SIGNAL)	Fossella et al. 2003
Mitsudomi et al. 2010	Gridelli et al. 2002
Mok et al. 2009 and Fukuoka et al. 2011	Mazzanti et al. 2003
Maemondo et al. 2010 and Inoue et al. 2012	Melo et al. 2002
Rosell et al. 2012 (EURTAC)	Rosell et al. 2002
	Scagliotti et al. 2002
	Scagliotti et al. 2008*
	Schiller et al. 2002
	Smit et al. 2003
	Thomas et al. 2006
	Zatloukal et al. 2003

* This study is referred to as Scagliotti et al. 2009 in the MS but the ERG believe the study being referred to is actually Scagliotti et al. 2008 (Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non–small-cell lung cancer. JCO 26 (21): 3543-3549). Scagliotti et al. 2009 is a retrospective analysis and includes no relevant data,hence Scagliotti et al. 2009 should also be excluded from the MTC

A2i

The NMA network was modified to include only the data from EGFR mutation positive patients, as directed. Results for this network are presented in Table 4, below.

Table 4: Network restricted to EGFR mutation population – NMA results

EGFR mutation positive modified network							
		fixed effects			random effects		
		HR	l.Cr.I	u.Cr.I	HR	l.Cr.I	u.Cr.I
Gefitinib							
PFS	indep PFS	0.5447	0.3061	0.9664	0.5441	0.06891	4.111
	inv PFS	0.5114	0.2909	0.8961	0.4976	0.06342	3.595
OS (updated data)		0.863	0.4596	1.62	0.8725	0.1998	4.323
Erlotinib							
PFS	indep PFS	0.7441	0.4607	1.198	0.7541	0.1021	5.653
	inv PFS	0.6985	0.4393	1.108	0.6858	0.09341	4.816
OS (updated data)		0.9395	0.5478	1.608	0.9429	0.22	4.61

Note: *Green shading indicates values corresponding to base case settings in the cost-effectiveness model*

A2ii

The networks were modified to exclude EURTAC, as directed. Results for the modified networks are presented in Table 5, below.

Table 5: Exclusion of EURTAC from submitted and EGFR mutation network- NMA results

		fixed effects			random effects		
		HR	l.Cr.I	u.Cr.I	HR	l.Cr.I	u.Cr.I
Submitted network- excluding EURTAC							
Gefitinib							
PFS	indep PFS	0.8270	0.6079	1.1280	0.7776	0.4291	1.3030
	inv PFS	0.7284	0.5401	0.9842	0.6973	0.4039	1.1380
OS		0.9144	0.8600	0.6041	1.2330	0.8569	0.5679
EGFR mutation positive modified network- excluding EURTAC							
Gefitinib							
PFS	indep PFS	0.5157	0.2391	1.102	0.5049	0.02332	10.72
	inv PFS	0.4842	0.2263	1.027	0.4821	0.02525	9.572
OS		0.9144	0.4025	2.043	0.914	0.07104	12.03

Note: *Green shading indicates values corresponding to base case settings in the cost-effectiveness model*

Note that the analyses based on both investigator and independent assessments of PFS are presented together in Table 2, Table 3, Table 4, and Table 5 as requested in the non-priority question.

LUX-Lung 3 and LUX-Lung 6 trials

A4. **Priority Question:** In LUX-Lung 3, for each arm of the trial (afatinib and pemetrexed/cisplatin), please provide a breakdown of the baseline characteristics and findings for OS, local investigator assessed PFS, tumour response and adverse events (AEs) for the following two subgroups: (i) Asian and (ii) non-Asian. For AEs, please provide the data in the same format as Table 56 and 57 of the manufacturer's submission.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Sub-group analysis of overall survival by race stratification factor

		Afatinib	Cis/pem	HR* (95% CI)	p value†
Asian patients	Patients died	82 (49.4%)	39 (47%)		
	Median OS (months [95% CI])	30.13 (24.74-37.45)	29.14 (22.90–NE)	0.998 (0.681-1.462)	p=0.9925
	Patients died	34 (53.1%)	20 (62.5%)		

Non-Asian patients	Median OS (months [95% CI])	26.58 (21.06-31.51)	20.73 (16.79-33.51)	0.800 (0.458-1.396)	p=0.4316

* Hazard ratio from Cox proportional hazards model with treatment fitted as the only factor
† P−value from log−rank (two−sided)
OS = overall survival
NE = not estimable

PFS, according to investigator assessment in LUX-Lung 3

- Non-Asian patients: 9.79 (95% CI 6.77 – 13.70) and 5.55 (95% CI 4.01 – 9.46) for afatinib and cis/pem respectively (HR 0.618 [95% CI 0.359-1.064]; p=0.0800).
- Asian patients: 11.30 (95% CI 10.02-13.70) and 6.90 (95% CI 5.49-8.21) for afatinib and cis/pem respectively (HR 0.450 [95% CI 0.327-0.619]; p<0.0001).

Tumour response rates (obtained from the LUX-Lung 3 Clinical Trial Report)

- ORR in Asian patients: 62.7% vs 20.5% for afatinib and cis/pem respectively (OR 6.512; 95% CI 3.507-12.093; p<0.0001)
- ORR in non-Asian patients: 39.1% vs 28.1% for afatinib and cis/pem respectively (OR 1.638; 95% CI 0.653-4.109; p=0.2930)

Adverse Event Data

Asian patients: summary of AEs during the on-treatment period including 28 day post−treatment period

	Afatinib N (%)	Chemotherapy N (%)
Patients	165 (100)	80 (100)
Patients with any AE	165 (100)	79 (98.8)
Drug related[1]	164 (99.4)	78 (97.5)
AEs leading to dose reduction	103 (62.4)	14 (17.5)
AEs leading to a permanent discontinuation	21 (12.7)	11 (13.8)
Drug related AEs leading to permanent discontinuation		
SAEs[2]	48 (29.1)	18 (22.5)
Fatal	7 (4.2)	2 (2.5)
Immediately life-threatening	1 (0.6)	2 (2.5)
Disability/incapacity	0 (0.0)	0 (0.0)
Required hospitalisation	45 (27.3)	14 (17.5)
Prolonged hospitalisation	3 (1.8)	5 (6.3)
Other	2 (1.2)	1 (1.3)
By highest CTCAE grade		
Grade 1	9 (5.5)	10 (12.5)
Grade 2	55 (33.3)	26 (32.5)
Grade 3	86 (52.1)	34 (42.5)
Grade 4	8 (4.8)	7 (8.8)
Grade 5	7 (4.2)	2 (2.5)

[1] As defined by the investigator; [2] A patient may be counted in more than one seriousness criterion
AE = adverse event, SAE = serious adverse event

Non-Asian patients: summary of AEs during the on-treatment period including 28 day post−treatment period

	Afatinib N (%)	Chemotherapy N (%)
Patients	64 (100.0)	31 (100.0)
Patients with any AE	64 (100.0)	30 (96.8)
Drug related[1]	64 (100.0)	28 (90.3)
AEs leading to dose reduction	28 (43.8)	4 (12.9)
AEs leading to a permanent discontinuation	11 (17.2)	6 (19.4)
Drug related AEs leading to permanent discontinuation		
SAEs[2]	18 (28.1)	7 (22.6)
Fatal	6 (9.4)	1 (3.2)
Immediately life-threatening	0 (0.0)	2 (6.5)
Disability/incapacity	0 (0.0)	0 (0.0)
Required hospitalisation	17 (26.6)	6 (19.4)
Prolonged hospitalisation	1 (1.6)	1 (3.2)
By highest CTCAE grade		
Grade 1	3 (4.7)	4 (12.9)
Grade 2	23 (35.9)	6 (19.4)
Grade 3	31 (48.4)	15 (48.4)
Grade 4	1 (1.6)	4 (12.9)
Grade 5	6 (9.4)	1 (3.2)

[1] As defined by the investigator; [2] A patient may be counted in more than one seriousness criterion
AE = adverse event, SAE = serious adverse event

To address this question fully, we are required to provide adverse event data in the same format as table 57 of our submission, which contained drug related AEs with an incidence of >10% in either treatment arm, by treatment arm, for the whole trial population. This data was presented by system organ/class/adverse events. The data we have for related adverse events for Asian and non-Asian patient sub-groups are currently only available by category. Therefore for the purposes of providing consistent data we have provided an updated Table 57 where the drug related AEs are presented by category for the whole trial population and then broken down by sub-group (Asian and non-Asian).

Please note that the HR, 95% CI and p-value from the original table 57 for adverse events of special interest have been removed as they were based on all events, and not on related adverse events.

REVISED TABLE 57

Table 6. Frequency of drug related AEs with an incidence of >10% in either treatment arm, by treatment arm

Adverse event category	Afatinib (n = 229)		Cisplatin/pemetrexed (n = 111)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhoea	218 (95.2)	33 (14.4)	17 (15.3)	0
Rash/acne†	204 (89.1)	37 (16.2)	7 (6.3)	0
Stomatitis†	165 (72.1)	20 (8.7)	17 (15.3)	1 (0.9)
Nail effect†	140 (61.1)	27 (11.8)	0	0
Dry skin	67 (29.3)	1 (0.4)	2 (1.8)	0
Decreased appetite	47 (20.5)	7 (3.1)	59 (53.2)	3 (2.7)
Pruritus	43 (18.8)	1 (0.4)	1 (0.9)	0
Nausea	41 (17.9)	2 (0.9)	73 (65.8)	4 (3.6)
Ocular effect†	41 (17.9)	1 (0.4)	2 (1.8)	0
Fatigue†	40 (17.5)	3 (1.3)	52 (46.8)	14 (12.6)
Vomiting	39 (17.0)	7 (3.1)	47 (42.3)	3 (2.7)
Lip effect†	33 (14.4)	0	2 (1.8)	0
Epistaxis	30 (13.1)	0	1 (0.9)	1 (0.9)
Weight decreased	24 (10.5)	0	10 (9.0)	0
Alopecia	23 (10.0)	0	19 (17.1)	0
Anaemia	7 (3.1)	1 (0.4)	31 (27.9)	7 (6.3)
Constipation	6 (2.6)	0	21 (18.9)	0
Leukopenia	4 (1.7)	1 (0.4)	21 (18.9)	9 (8.1)
Haemoglobin decreased	3 (1.3)	0	12 (10.8)	3 (2.7)
Neutropenia	2 (0.9)	1 (0.4)	35 (31.5)	20 (18.0)

†Group term. Adverse events graded using NCI CTCAE version 3.0

Asian patients: frequency of drug related AEs with an incidence of >10% in either treatment arm, by treatment arm

Adverse event category	Afatinib (n = 165)		Cisplatin/pemetrexed (n = 80)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhoea	158 (95.8)	26 (15.8)	12 (15.0)	0 (0.0)
Rash/Acne†	150 (90.9)	28 (17.0)	6 (7.5)	0 (0.0)
Stomatitis†	140 (84.8)	15 (9.1)	15 (18.8)	1 (1.3)
Nail effect†	115 (69.7)	24 (14.5)	0 (0.0)	0 (0.0)
Dry skin	55 (33.3)	1 (0.6)	1 (1.3)	0 (0.0)
Decreased appetite	43 (26.1)	6 (3.6)	51 (63.8)	3 (3.8)
Pruritus	34 (20.6)	0 (0.0)	1 (1.3)	0 (0.0)
Ocular effect†	33 (20.0)	1 (0.6)	2 (2.5)	0 (0.0)
Vomiting	32 (19.4)	6 (3.6)	38 (47.5)	3 (3.8)
Lip effect†	31 (18.8)	0 (0.0)	2 (2.5)	0 (0.0)
Nausea	28 (17.0)	1 (0.6)	53 (66.3)	3 (3.8)
Fatigue†	27 (16.4)	3 (1.8)	36 (45.0)	7 (8.8)
Epistaxis	24 (14.5)	0 (0.0)	0 (0.0)	0 (0.0)
Weight decreased	23 (13.9)	0 (0.0)	8 (10.0)	0 (0.0)
Alopecia	16 (9.7)	0 (0.0)	12 (15.0)	0 (0.0)
Headache	9 (5.5)	0 (0.0)	9 (11.3)	0 (0.0)
Anaemia	7 (4.2)	1 (0.6)	24 (30.0)	5 (6.3)
Constipation	4 (2.4)	0 (0.0)	17 (21.3)	0 (0.0)
Leukopenia	4 (2.4)	1 (0.6)	19 (23.8)	9 (11.3)
Haemoglobin decreased	2 (1.2)	0 (0.0)	10 (12.5)	3 (3.8)
Neutropenia	2 (1.2)	1 (0.6)	27 (33.8)	15 (18.8)
Blood creatinine increased	1 (0.6)	0 (0.0)	9 (11.3)	0 (0.0)
Hiccups	1 (0.6)	0 (0.0)	10 (12.5)	0 (0.0)

†Group term

Non-Asian patients: frequency of drug related AEs with an incidence of >10% in either treatment arm, by treatment arm

Adverse event category	Afatinib (n = 64)		Cisplatin/pemetrexed (n = 31)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhoea	60 (93.8)	7 (10.9)	5 (16.1)	0 (0.0)
Rash/Acne†	54 (84.4)	9 (14.1)	1 (3.2)	0 (0.0)
Nail effect†	25 (39.1)	3 (4.7)	0 (0.0)	0 (0.0)
Stomatitis†	25 (39.1)	5 (7.8)	2 (6.5)	0 (0.0)
Fatigue†	13 (20.3)	0 (0.0)	16 (51.6)	7 (22.6)
Nausea	13 (20.3)	1 (1.6)	20 (64.5)	1 (3.2)
Dry skin	12 (18.8)	0 (0.0)	1 (3.2)	0 (0.0)
Pruritus	9 (14.1)	1 (1.6)	0 (0.0)	0 (0.0)
Ocular effect†	8 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Alopecia	7 (10.9)	0 (0.0)	7 (22.6)	0 (0.0)
Vomiting	7 (10.9)	1 (1.6)	9 (29.0)	0 (0.0)
Decreased appetite	4 (6.3)	1 (1.6)	8 (25.8)	0 (0.0)
Constipation	2 (3.1)	0 (0.0)	4 (12.9)	0 (0.0)
Anaemia	0 (0.0)	0 (0.0)	7 (22.6)	2 (6.5)
Neutropenia	0 (0.0)	0 (0.0)	8 (25.8)	5 (16.1)

†Group term

A5. For each of the LUX-Lung 3 and LUX-Lung 6 subgroup analyses presented on pages 78 and 87 of the manufacturer's submission, please provide an overall test for interaction.

Comparison of the treatment effect of afatinib vs. pemetrexed/cisplatin on the primary endpoint PFS in the pre-defined subgroups, based on central independent review – LUX-Lung 3:

- Baseline ECOG score interaction between treatment and subgroup: [redacted]
- Gender interaction between treatment and subgroup: [redacted]
- Age group (<65 v >=65) interaction between treatment and subgroup: [redacted]
- EGFR mutation category (Del19/L858R/other) interaction between treatment and subgroup: [redacted]
- EGFR mutation category (common [Del19 or L858R] vs uncommon) interaction between treatment and subgroup: [redacted]
- Race stratification factor (Asian vs non-Asian) interaction between treatment and subgroup: [redacted]
- Smoking history interaction between treatment and subgroup: [redacted]

Comparison of the treatment effect of afatinib vs. gemcitabine/cisplatin on the primary endpoint PFS in pre-defined subgroups, based on central independent review – LUX-Lung 6:

- Baseline ECOG score interaction between treatment and subgroup: [redacted]
- Gender interaction between treatment and subgroup: [redacted]
- Age group (<65 v >=65) interaction between treatment and subgroup: [redacted]
- EGFR mutation stratification factor (Del19/L858R/other) interaction between treatment and subgroup: [redacted]
- EGFR mutation status (common [Del19 or L858R] vs uncommon) interaction between treatment and subgroup: [redacted]
- Smoking history interaction between treatment and subgroup: [redacted]

A6. Page 82 and page 90 of the manufacturer's submission present forest plots for the time to deterioration in coughing, dyspnoea, and pain related items of QLQ-C30 and QLQ-L13 in LUX-Lung 3 and LUX-Lung 6. Here the n value for all analyses is 345 and 364 respectively. Please clarify if this implies a 100% response to these questions.

For the time to deterioration analyses the N usually only indicates the number at risk at the beginning of the study, but not at the individual time points. The number at risk will decline over time as patient's progress and/or deteriorate. The compliance is not included in the N of 345 / 364, but simply states the overall study population.

A7. Page 142 of the manufacturer's submission states the median number of cycles in LUX-Lung 3 was 16 (336 days) but on page 144 this is not reported for LUX-Lung 6 (it just states median 398 days). Please provide the median number of cycles.

The median number of cycles (median number of days divided by 21)

- Afatinib arm: 398/21 = 18.952
- Cis/pem arm: 89/21 = 4.238

Systematic review and mixed treatment comparison

A8. Page 93 of the manufacturer's submission states: "*The systematic review was designed to capture randomized controlled trials, meta-analyses and systematic reviews comparing any licensed chemotherapy and targeted therapies for locally advanced or metastatic NSCLC for either 1st line or 3rd/4th line therapy.*" Please clarify why second line was not included.

The systematic review was designed to identify studies that could be used to compare afatinib in its licensed indication to other potential treatments within the same licensed indication. This would enable a mixed-treatment comparison (MTC) to be undertaken for use in the economic model to provide a quantitative assessment of cost-effectiveness.

At the time the review was conducted, our expectation was that we would have a license for 1st line use and also in patients with prior treatment with a TKI that was either 3rd or 4th line use. This expectation was based on our randomised controlled trail programme (LUX-Lung 1, 3, and 6). The outputs from the systematic review for 1st and 3rd/4th line could be used in the MTC and economic model to estimate cost-effectiveness as there was an active comparator in the afatinib trials (LUX-Lung 1, 3, and 6).

Whilst undertaking the review, we were aware that we could potentially be indicated for 2nd line use in patients who were TKI naive based on the results of LUX-Lung 2. This is now the case and has been confirmed in our license. However, as Boehringer Ingelheim has sole rights to manufacture and license afatinib, and given that when the submission was being prepared afatinib was unlicensed in any indication world-wide, we are certain that no 2nd line RCT data exist where afatinib is a comparator. If a systematic review had been conducted for 2nd line use, the results of the review could not have been used to assess the cost-effectiveness of afatinib, as a robust indirect comparison could not be conducted. Therefore, a systematic review in 2nd line patients would have had little direct relevance to the decision problem.

A9. Page 96 of the manufacturer's submission states that "of the 66 first line studies identified in the systematic literature review, only 8 were conducted in an EGFR mutation positive

population" and implies this is why the other 58 studies were excluded. However, the manufacturer later includes further studies which were not conducted in an EGFR mutation positive population in its MTC. Please list the 58 studies and provide the reasons why they were not considered for the MTC.

The 66 first line NSCLC studies identified are shown in Table 7, starting on the next page. Of these only eight, marked in light green, provided data for an *EGFR* mutation positive tumour population. The remaining 58 studies can be identified as the unshaded rows in Table 7.

Two of the eight *EGFR* mutation positive studies were excluded from the NMA network. Gatzemeier et al., 2007[8] was excluded because erlotinib was not used as a monotherapy. Zhou et al., 2011 (the OPTIMAL trial)[9] was excluded from the base case NMA network because the results reported in this study are notably different from a similar study (EURTAC) therefore raising concerns about the transferability of results. This difference between OPTIMAL and EURTAC may be due to a slightly underperforming comparator arm in OPTIMAL, or a product of better compliance and more aggressive adherence to the maximum possible dose in OPTIMAL, or a product of differences in the ethnic mix of the patients included in each study[10]. Furthermore, the OPTIMAL study has not been accepted by regulatory authorities including the Chinese Authorities and EMA. The EMA's concerns with OPTIMAL were due to the lack of an available clinical study report, and the fact that the database for the trial was not designed for regulatory purposes, which meant that data quality and good clinical practice could not be evaluated [10].

Following the exclusion of 60 trials explained above, six publications, representing five trials (Mok, 2009 and Fukuoka, 2011 both describe IPASS[1;2]), remained. To these, the two afatinib trials, LUX-Lung 3 and LUX-Lung 6 were added to obtain the same basic network of seven trials suggested by NICE in the question for Section A2. However, in this network only one arm of the LUX-Lung 3 trial (afatinib) was connected to the rest of the network. To connect the pemetrexed/cisplatin arm to the rest of the network, the Scagliotti et al., 2009[11] trial was added.

Finally, the network of chemotherapy trials used by Astra Zeneca for the NMA supporting the gefitinib NICE submission was added, to align the afatinib submission's NMA network with this earlier NMA network. The rationale behind this strategy was twofold. Firstly, to provide consistency across the submissions for this indication, in line the NICE guide to the methods of technology appraisal (2013) which states:

"6.2.15 The Appraisal Committee takes account of how the incremental cost effectiveness of the technology being appraised relates to other interventions or technologies currently or potentially applied in the NHS. In addition, as far as possible, the Committee will want to ensure that their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals."

Secondly, to reduce the uncertainty around the HRs estimated in the NMA, by including more data and connections within the network and thereby produce more conservative NMA results. Comparison of the NMA results for the submitted network (in Table 2) with the NMA results for the EGFR mutation positive only network, in Table 4, illustrates that restricting the network to the EGFR mutation positive population does increase the uncertainty around the results, particularly for PFS.

For the PFS network, two of the trials in the gefitinib NICE submission network had already been captured in the systematic literature review, but had previously been excluded due to not reporting data for the EGFR mutation positive population (Scagliotti et al., 2002, and Smit et al., 2003[12;13]).

For the OS network, four of the trials in the gefitinib NICE submission network had already been captured in the systematic literature review, but had previously been excluded due to not reporting data for the EGFR mutation positive population (Fossella et al., 2003, Scagliotti et al., 2002, and Smit et al., 2003, Zatloukal et al., 2003[12-15]). Furthermore, OS HRs from the NEJGSG002 trial were not included in the network, as these weren't published in the initial report by Maemondo et al., 2010[3], and we had not seen the Inoue et al., 2013[4] publication at that time.

Table 7: First line NSCLC studies identified in systematic literature review

	Author, year	Intervention	Comparator	Population
1	Belani et al, 2005[16]	Cisplatin+ Etoposide	Carboplatin+ Paclitaxel	Locally advanced or metastatic NSCLC
2	Bissett et al, 2005[17]	Cisplatin+ Gemcitabine+ Prinomastat	Cisplatin+ Gemcitabine+ Placebo	Locally advanced or metastatic NSCLC
3	Brodowicz et al, 2006[18]	Cisplatin+ Gemcitabine	Cisplatin+ Gemcitabine+ BSC	Locally advanced or metastatic NSCLC
4	Comella et al, 2004[19]	Gemcitabine Paclitaxel Gemcitabine+ Paclitaxel	Gemcitabine+ Vinorelbine	Locally advanced or metastatic NSCLC
5	Danson et al, 2003[20]	Carboplatin+ Gemcitabine	Cisplatin+ Ifosfamide+ Mitomycin or Cisplatin+ Mitomycin+ Vinblastine	Locally advanced or metastatic NSCLC
6	Fidias et al, 2009[21]	Docetaxel (immediate)	Docetaxel (delayed)	Locally advanced or metastatic NSCLC
7	Fossella et al, 2003[14]	Cisplatin+ Docetaxel Carboplatin+ Docetaxel	Cisplatin+ Vinorelbine	Locally advanced or metastatic NSCLC
8	Fournel et al, 2005[22]	Cisplatin+ Vinorelbine+ Radiotherapy	Cisplatin+ Etoposide+ Vinorelbine+ Radiotherapy	Locally advanced or metastatic NSCLC
9	Fukuoka et al, 2011[2]	Gefitinib	Carboplatin+ Paclitaxel	Locally advanced or metastatic NSCLC
10	Gatzemeier et al, 2007[8]	Cisplatin+ Gemcitabine+ Placebo	Cisplatin+ Erlotinib+ Gemcitabine	Locally advanced or metastatic NSCLC
11	Gebbia et al, 2002[23]	Cisplatin+ Vinorelbine	Cisplatin+ Mitomycin+ Vinorelbine	Locally advanced or metastatic NSCLC
12	Georgoulias et al, 2005[24]	Docetaxel+ Gemcitabine	Cisplatin+ rhG-CSF+ Vinorelbine	Locally advanced or metastatic NSCLC
13	Georgoulias et al, 2008[25]	Docetaxel+Gemcitabine	Docetaxel	Locally advanced or metastatic NSCLC
14	Giaccone et al, 2004[26]	Cisplatin+ Gefitinib+ Gemcitabine	Cisplatin+ Gefitinib+ Gemcitabine	Locally advanced or metastatic NSCLC
15	Greco et al, 2007[27]	Carboplatin+ Gemcitabine+ Paclitaxel	Gemcitabine+ Vinorelbine	Locally advanced or metastatic NSCLC
16	Grigorescu et al, 2002[28]	Cisplatin+ Vinblastine	Carboplatin+ Gemcitabine	Locally advanced or metastatic NSCLC
17	Gronberg et al, 2009[29]	Carboplatin+ Pemetrexed	Carboplatin+ Gemcitabine	Locally advanced or metastatic NSCLC
18	Hainsworth et al, 2007[30]	Docetaxel	Docetaxel+ Gemcitabine	Locally advanced or metastatic NSCLC
19	Han et al, 2012[31]	Gefitinib	Cisplatin+Gemcitabine	Locally advanced or metastatic NSCLC
20	Helbekkmo et al, 2007[32]	Carboplatin+ Vinorelbine	Carboplatin+ Gemcitabine	Locally advanced or metastatic NSCLC
21	Karampeazis et al, 2011[33]	Docetaxel	Vinorelbine	Locally advanced or metastatic NSCLC

22	Kodani et al, 2002[34]	Cisplatin+ Vindesine	Cisplatin+ Ifosfamide+ Vindesine	Locally advanced or metastatic NSCLC
23	Kosmidis et al, 2002[35]	Carboplatin+ Paclitaxel	Gemcitabine+ Paclitaxel	Locally advanced or metastatic NSCLC
24	Kosmidis et al, 2008[36]	Gemcitabine+ Paclitaxel	Carboplatin+ Gemcitabine	Locally advanced or metastatic NSCLC
25	Kosmidis et al, 2012[37]	Vinorelbine	Paclitaxel	Locally advanced or metastatic NSCLC
26	Kubota et al, 2008[38]	Docetaxel+ Gemcitabine+Vinorelbine	Carboplatin+ Paclitaxel	Locally advanced or metastatic NSCLC
27	Kudoh et al, 2006[39]	Docetaxel	Vinorelbine	Locally advanced or metastatic NSCLC
28	Langer et al, 2008[40]	Carboplatin+ Paclitaxel Poliglumex	Carboplatin+ Paclitaxel	Locally advanced or metastatic NSCLC
29	Li et al, 2009[41]	Cisplatin+ Vinorelbine+ Surgery	Surgery	Locally advanced or metastatic NSCLC
30	Lilenbaum et al, 2005[42]	Paclitaxel	Carboplatin+ Paclitaxel	Locally advanced or metastatic NSCLC
31	Lissoni et al, 2003[43]	Cisplatin+ Etoposide	Cisplatin+ Etoposide+ Melatonin	Locally advanced or metastatic NSCLC
32	Maemondo et al, 2010[3]	Gefitinib	Carboplatin+ Paclitaxel	Locally advanced or metastatic NSCLC
33	Mitsudomi et al, 2010[5]	Gefitinib	Cisplatin+ Docetaxel	Locally advanced or metastatic NSCLC
34	Mok et al, 2009[1]	Gefitinib	Carboplatin+ Paclitaxel	Locally advanced or metastatic NSCLC
35	O'Brien et al, 2008[44]	Paclitaxel poliglumex	Gemcitabine or Vinorelbine	Locally advanced or metastatic NSCLC
36	Okamoto et al, 2010[45]	Carboplatin+ Paclitaxel	Carboplatin+S-1	Locally advanced or metastatic NSCLC
37	Paccagnella et al, 2004[46]	Cisplatin+ Mitomycin-C+ Vinblastine	Carboplatin+ Mitomycin-C+ Vinblastine	Locally advanced or metastatic NSCLC
38	Paccagnella et al, 2006[47]	Carboplatin+ Paclitaxel	Carboplatin+ Gemcitabine+ Paclitaxel	Locally advanced or metastatic NSCLC
39	Paz-Ares et al, 2006[48]	Cisplatin+ Gemcitabine	Aprinocarson+ Cisplatin+ Gemcitabine	Locally advanced or metastatic NSCLC
40	Pujol et al, 2005[49]	Docetaxel+ Gemcitabine	Cisplatin+ Vinorelbine	Locally advanced or metastatic NSCLC
41	Reck et al, 2010[50]	Cisplatin+ Gemcitabine+ Placebo Bevacizumab+ Cisplatin+ Gemcitabine	Bevacizumab+ Cisplatin+ Gemcitabine	Locally advanced or metastatic NSCLC
42	Reck et al, 2009[51]	Cisplatin+ Gemcitabine+ Placebo Bevacizumab+ Cisplatin+ Gemcitabine	Bevacizumab+ Cisplatin+ Gemcitabine	Locally advanced or metastatic NSCLC
43	Rosell et al, 2012[7]	Erlotinib	Cisplatin+Docetaxel or Cisplatin+Gemcitabine or Carboplatin+Docetaxel or Carboplatin+ Gemcitabine	Locally advanced or metastatic NSCLC

44	Rudd et al, 2005[52]	Carboplatin+Gemcitabine	Cisplatin+ Ifosfamide+ Mitomycin	Locally advanced or metastatic NSCLC
45	Scagliotti et al, 2002[12]	Cisplatin+ Gemcitabine Carboplatin+ Paclitaxel	Cisplatin+ Vinorelbine	Locally advanced or metastatic NSCLC
46	Scagliotti et al, 2009[11]	Cisplatin+ Pemetrexed	Cisplatin+ Gemcitabine	Locally advanced or metastatic NSCLC
47	Schuette et al, 2006[53]	Carboplatin+ Paclitaxel	Carboplatin+ Paclitaxel	Locally advanced or metastatic NSCLC
48	Sederholm et al, 2002[54]	Gemcitabine	Carboplatin+ Gemcitabine	Locally advanced or metastatic NSCLC
49	Sederholm et al, 2005[55]	Gemcitabine	Carboplatin+ Gemcitabine	Locally advanced or metastatic NSCLC
50	Segawa et al, 2010[56]	Cisplatin+ Docetaxel	Cisplatin+ Mitomycin+ Vindesine	Locally advanced or metastatic NSCLC
51	Smit et al, 2003[13]	Paclitaxel Cisplatin+ Gemcitabine	Gemcitabine+ Paclitaxel	Locally advanced or metastatic NSCLC
52	Socinski et al, 2002[57]	Carboplatin+ Paclitaxel	Carboplatin+ Paclitaxel (maintenance)	Locally advanced or metastatic NSCLC
53	Souquet et al, 2002[58]	Cisplatin+ Vinorelbine	Cisplatin+Ifosfamide+Vinorelbine	Locally advanced or metastatic NSCLC
54	Stathopoulos et al, 2004[59]	Carboplatin+ Paclitaxel	Paclitaxel+Vinorelbine	Locally advanced or metastatic NSCLC
55	Stathopoulos et al, 2010[60]	Lipoplatin+ Paclitaxel	Cisplatin+Paclitaxel	Locally advanced or metastatic NSCLC
56	Tan et al, 2005[61]	Carboplatin+ Vinorelbine	Gemcitabine+Vinorelbine	Locally advanced or metastatic NSCLC
57	Tan et al, 2009[62]	Cisplatin+ Vinorelbine	Cisplatin+Docetaxel	Locally advanced or metastatic NSCLC
58	Treat et al, 2010[63]	Carboplatin+ Gemcitabine Gemcitabine+ Paclitaxel	Carboplatin+Paclitaxel	Locally advanced or metastatic NSCLC
59	Vokes et al, 2007[64]	Carboplatin+ Paclitaxel+ Radiotherapy	Carboplatin+ Paclitaxel+ Radiotherapy	Locally advanced or metastatic NSCLC
60	Von Plessen et al, 2006[65]	Carboplatin+ Vinorelbine	Carboplatin+ Vinorelbine	Locally advanced or metastatic NSCLC
61	Wachters et al, 2003[66]	Cisplatin+ Gemcitabine	Epirubicin+ Gemcitabine	Locally advanced or metastatic NSCLC
62	Williamson et al, 2005[67]	Carboplatin+ Paclitaxel+ Tirapazamine	Carboplatin+ Paclitaxel	Locally advanced or metastatic NSCLC
63	Yokomise et al, 2007[68]	Carboplatin+ Paclitaxel+ Radiotherapy	Carboplatin+ Docetaxel+ Radiotherapy	Locally advanced or metastatic NSCLC
64	Zatloukal et al, 2004[69]	Cisplatin+ Gemcitabine	Carboplatin+ Gemcitabine	Locally advanced or metastatic NSCLC
65	Zatloukal et al, 2003[15]	Cisplatin+ Vinorelbine+ Radiotherapy	Cisplatin+ Vinorelbine+ Radiotherapy	Locally advanced or metastatic NSCLC
66	Zhou et al, 2011[9]	Erlotinib	Carboplatin+ Gemcitabine	Locally advanced or metastatic NSCLC

A10. Page 95 of the manufacturer's submission states: "*The three additional records identified through other sources mentioned in the PRISMA diagram, were relevant articles that were published after the systematic search was completed Rosell et al. (2012), Han et al. (2012), and Miller et al. (2012).*" Please clarify how these were identified.

One of these publications (Miller et al., 2012) is a BI-sponsored study so we were aware of its publication. The other two publications are high profile, phase 3 studies which were identified by the medical group at BI, as part of their regular horizon scanning procedures.

A11. Page 234 of the manufacturer's submission states: "*As the systematic literature review was undertaken in March 2012, a literature search was done using the same databases as before. The terms searched for were "EGFR mutation NSCLC," the reference sections for each paper identified were checked to ensure that no articles were missed. The search aimed to identify systematic reviews that had taken place on EGFR mutation positive patients after March 2012*" Please clarify when the additional search was carried out.

The additional search was carried out on 6th August 2013.

Section B: Clarification on cost-effectiveness data

Kaplan Meier analysis results

In order to allow a full validation of the model's accuracy in replicating the trial data, please provide the following:

B1. **Priority Question:** Full Kaplan-Meier analysis results (see example overleaf) showing K-M survival estimates at each event time, for each treatment arm in the LUX-Lung 3 trial for Overall Survival (OS), Progression-Free Survival (PFS) and Post-Progression Survival (PPS). These analyses should use the most recent data cut, be based on local assessment of disease progression, and any patient still at risk at the date of data cut should be censored at the date of data cut, not date of last contact/assessment. These data should be presented separately for the following populations: (i) Asian (ii) non-Asian (iii) All patients.

[redacted]

B2. **Priority Question:** Full Kaplan-Meier analysis results (see example overleaf) showing K-M survival estimates at each event time, for each treatment arm in the LUX-Lung 6 trial for Overall Survival (OS), Progression-Free Survival (PFS) and Post-Progression Survival (PPS). These analyses should use the most recent data cut, be based on local assessment of disease progression, and any patient still at risk at the date of data cut should be censored at the date of data cut, not date of last contact/assessment.

[redacted]

Utility values

B3. **Priority Question**: Please provide PFS utility values (mean and standard error) from the LUX-lung 3 trial for two groups of patients: (i) Asian and (ii)) non-Asian. Two sets of figures should be produced (i) figures including all AEs, and (ii) figures excluding key AEs.

[redacted]

B4. **Priority Question**: Please provide details of compliance with EQ-5D assessments in the LUX-lung 3 trial. Two tables, similar to Table A4 (p119) in the BI HE LUX-Lung 3 report, should be produced: (i) Asian and (ii) non-Asian

[redacted] Please note that during the later time points, only very few patients are still progression-free, so completion is somewhat volatile with one or two questionnaires having a big impact on the completion rate at that time point.

Example from SAS of typical output requested from analyses specified above (B1 and B2)

Product-Limit Survival Estimates						
SURVIVAL		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		0.8548	0.1452	0.0447	9	53
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Section C: Data marked as in confidence

C1. On page 55 of the manufacturer's submission, it is unclear why smoking status and ECOG performance status are highlighted in green; is this intended to be marked as data in confidence? It should also be noted that if so, the values can be determined from the data that is not highlighted.

There are two places in the submission where text is highlighted in green. This is to indicate differences between trails (Table 10) or treatment arms (Table 11) and is in response to the request to highlight any differences between trials (Question 6.3.3) and treatment groups (Question 6.3.4). The items in Table 11 highlighted in green represent differences in these values commented on in the CTR. However, as mentioned, these are not necessarily statistically different as these were not tested. These values are not commercial or academic in confidence.

C2. The PFS data for common mutations presented in Table 15 and marked as being academic in confidence are presented elsewhere in the manufacturer's submission un-marked (PFS events on page 87 and the hazard ratio and confidence intervals in Table 25 on page 106). Please clarify whether these data are academic in confidence.

The PFS in patients with common mutations was presented at the World Conference on Lung Cancer. The reference is:

Sequist LV et al. Comparative safety profile of afatinib in Asian and non-Asian patients with EGFR mutation-positive (EGFR M+) non-small cell lung cancer (NSCLC). Presented at the World Conference on Lung Cancer, 27-30 October 2013. Sydney, Australia (poster presentation).

Therefore this is no longer academic in confidence.

C3. On page 172 and 173 of the manufacturer's submission, the name of the expert clinician with whom the manufacturer consulted is not always marked as being commercial in confidence. Please clarify if the clinician's name should always be marked as in confidence.

The name should always be marked commercial-in-confidence. Therefore, any the references in Table 75 should be underlined and highlighted in blue.

Section D: References

D1. Page 30 of the manufacturer's submission states: "*Afatinib would provide … access to an EGFR TKI with the longest median PFS reported in a 1st line registration study.*" Please provide a reference for this study and ideally also the full document (e.g. PDF) if this has not already been provided.

The reference to these will be from the clinical trials for erlotinib, gefitinib and afatinib. These are Rosell et al. (2012), Mok et al. (2009), and Yang et al (2012a).

D2. As highlighted above, the MTC refers to Scagliotti et al 2009. Please clarify if this is the correct citation.

The correct citation for Scagliotti et al. 2009 should be:

Giorgio Scagliotti, Nasser Hanna, Frank Fossella, Katherine Sugarman, Johannes Blatter, Patrick Peterson, Lorinda Simms and Frances A. Shepherd. The Differential Efficacy of Pemetrexed According to NSCLC Histology: A Review of Two Phase III Studies. The Oncologist. 2009, 14: 253-263.

References

(1) Mok T, Wu Y-L, Thongprasert S, et al. Gefitinib or Carboplatin.Paclitaxel in Pulmonary Adenocarcinoma. N Engl J Med 361[10], 947-957. 3-9-2009.
Ref Type: Journal (Full)

(2) Fukuoka M, Wu Y-L, Thongprasert S, et al. Biomarker Analyses and Final Overall Survival Results From a Phase III, Randomized, Open-Label, First-Line Study of Gefitinib Versus Carboplatin/Paclitaxel in Clinically Selected Patients With Advanced Non-Small-Cell Lung Cancer in Asia (IPASS). J Clin Oncol 29[21], 2866-2874. 20-7-2011.
Ref Type: Journal (Full)

(3) Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or Chemotherapy for Non.Small- Cell Lung Cancer with Mutated EGFR. N Engl J Med 362[25], 2380-2388. 24-6-2010.
Ref Type: Journal (Full)

(4) Inoue A, Kobayashi K, Maemondo M, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Annals of Oncology 24[1], 54-59. 2013.
Ref Type: Journal (Full)

(5) Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncology 2010; 11(2):121-128.

(6) Mitsudomi T, et al. Updated overall survival results of WJTOG 3405, a randomized phase III trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer harboring mutations of the epidermal growth factor receptor (EGFR). J Clin Oncol 30. 2012.
Ref Type: Abstract

(7) Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as fi rst-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 13, 239-246. 2012.
Ref Type: Journal (Full)

(8) Gatzemeier U, Pluzanska A, Szczesna A, Kaukel E, Roubec J, De RF et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. J Clin Oncol 2007; 25(12):1545-1552.

(9) Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncology 2011; 12(8):735-742.

(10) Bagust A, Beale S, Blundell M, Boland A, Dickson R, Dundar Y et al. Erlotinib for the first-line treatment of EGFR-TK mutation positive non-small cell lung cancer. NIHR HTA 11/08. 2011.
Ref Type: Report

(11) Scagliotti GV, Hanna N, Fossella F, Sugarman K, Blatter J, Peterson P et al. The Differential Efficacy of Pemetrexed Accodring to NSCLC Histology: A Review of Two Phase III Studies. The Oncologist 2009; 14:253-263.

(12) Scagliotti GV, De Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 2002; 20(21):4285-4291.

(13) Smit EF, van Meerbeeck JP, Lianes P, Debruyne C, Legrand C, Schramel F 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):3909-3917.

(14) Fossella F, Pereira JR, von PJ, Pluzanska A, Gorbounova V, Kaukel E 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(16):3016-3024.

(15) Zatloukal P, Petruzelka L, Zemanova M, Kolek V, Skrickova J, Pesek M et al. Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial. Lung Cancer 2003; 41(3):321-331.

(16) Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol.[Erratum appears in J Clin Oncol. 2006 Apr 20;24(12):1966]. J Clin Oncol 2005; 23(25):5883-5891.

(17) Bissett D, O'Byrne KJ, von PJ, Gatzemeier U, Price A, Nicolson M et al. Phase III study of matrix metalloproteinase inhibitor prinomastat in non-small-cell lung cancer. J Clin Oncol 2005; 23(4):842-849.

(18) Brodowicz T, Krzakowski M, Zwitter M, Tzekova V, Ramlau R, Ghilezan N et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer 2006; 52(2):155-163.

(19) Comella P, Frasci G, Carnicelli P, Massidda B, Buzzi F, Filippelli G et al. Gemcitabine with either paclitaxel or vinorelbine vs paclitaxel or gemcitabine alone for elderly or unfit advanced non-small-cell lung cancer patients. Br J Cancer 2004; 91(3):489-497.

(20) Danson S, Middleton MR, O'Byrne KJ, Clemons M, Ranson M, Hassan J et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma. Cancer 2003; 98(3):542-553.

(21) Fidias PM, Dakhil SR, Lyss AP, Loesch DM, Waterhouse DM, Bromund JL 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):591-598.

(22) Fournel P, Robinet G, Thomas P, Souquet PJ, Lena H, Vergnenegre A et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95-01 Study. J Clin Oncol 2005; 23(25):5910-5917.

(23) Gebbia V, Galetta D, Riccardi F, Gridelli C, Durini E, Borsellino N et al. Vinorelbine plus cisplatin versus cisplatin plus vindesine and mitomycin C in stage IIIB-IV non-small cell lung carcinoma: a prospective randomized study. Lung Cancer 2002; 37(2):179-187.

(24) Georgoulias V, Ardavanis A, Tsiafaki X, Agelidou A, Mixalopoulou P, Anagnostopoulou O et al. Vinorelbine plus cisplatin versus docetaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III randomized trial. J Clin Oncol 2005; 23(13):2937-2945.

(25) Georgoulias V, Androulakis N, Kotsakis A, Hatzidaki D, Syrigos K, Polyzos A et al. Docetaxel versus docetaxel plus gemcitabine as front-line treatment of patients with advanced non-small cell lung cancer: a randomized, multicenter phase III trial. Lung Cancer 2008; 59(1):57-63.

(26) Giaccone G, Gonzalez-Larriba JL, van Oosterom AT, Alfonso R, Smit EF, Martens M et al. Combination therapy with gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, gemcitabine and cisplatin in patients with advanced solid tumors. Ann Oncol [(Giaccone, Smit, Peters, van der Vijgh) VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, Netherlands;(Gonzalez-Larriba, Alfonso) Hospital Clinico San Carlos, Madrid, Spain;(van Oosterom, Martens) University Hospital Gasthuisberg, Leuven, Belgium;(Smith, Fandi) AstraZeneca, Macclesfield, United Kingdom;(Averbuch) AstraZeneca, Wilmington, DE, United States] 2004 15(5):[831-838]

(27) Greco FA, Spigel DR, Kuzur ME, Shipley D, Gray JR, Thompson DS et al. Paclitaxel/Carboplatin/gemcitabine versus gemcitabine/vinorelbine in advanced non-small-cell lung cancer: a phase II/III study of the Minnie Pearl Cancer Research Network. Clin Lung Cancer 2007; 8(8):483-487.

(28) Grigorescu AC, Draghici IN, Nitipir C, Gutulescu N, Corlan E. Gemcitabine (GEM) and carboplatin (CBDCA) versus cisplatin (CDDP) and vinblastine (VLB) in advanced non-small-cell lung cancer (NSCLC) stages III and IV: a phase III randomised trial. Lung Cancer 2002; 37(1):9-14.

(29) Gronberg BH, Bremnes RM, Flotten O, Amundsen T, Brunsvig PF, Hjelde HH et al. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2009; 27(19):3217-3224.

(30) Hainsworth JD, Spigel DR, Farley C, Shipley DL, Bearden JD, Gandhi J et al. Weekly docetaxel versus docetaxel/gemcitabine in the treatment of elderly or poor performance status patients with advanced nonsmall cell lung cancer: a randomized phase 3 trial of the Minnie Pearl Cancer Research Network. Cancer 2007; 110(9):2027-2034.

(31) Han JY, Park K, Kim SW, Lee DH, Kim HY, Kim HT et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol 2012; 30(10):1122-1128.

(32) Helbekkmo N, Sundstrom SH, Aasebo U, Brunsvig PF, Von PC, Hjelde HH et al. Vinorelbine/carboplatin vs gemcitabine/carboplatin in advanced NSCLC shows similar efficacy, but different impact of toxicity. Br J Cancer 2007; 97(3):283-289.

(33) Karampeazis A, Vamvakas L, Agelidou A, Kentepozidis N, Chainis K, Chandrinos V et al. Docetaxel vs. vinorelbine in elderly patients with advanced non--small-cell lung cancer: a hellenic oncology research group randomized phase III study. Clin Lung Cancer 2011; 12(3):155-160.

(34) Kodani T, Ueoka H, Kiura K, Tabata M, Takigawa N, Segawa Y et al. A phase III randomized trial comparing vindesine and cisplatin with or without ifosfamide in patients with advanced non-small-cell lung cancer: long-term follow-up results and analysis of prognostic factors. Lung Cancer 2002; 36(3):313-319.

(35) Kosmidis P, Mylonakis N, Nicolaides C, Kalophonos C, Samantas E, Boukovinas J et al. Paclitaxel plus carboplatin versus gemcitabine plus paclitaxel in advanced non-small-cell lung cancer: a phase III randomized trial. J Clin Oncol 2002; 20(17):3578-3585.

(36) Kosmidis PA, Kalofonos HP, Christodoulou C, Syrigos K, Makatsoris T, Skarlos D et al. Paclitaxel and gemcitabine versus carboplatin and gemcitabine in patients with advanced non-small-cell lung cancer. A phase III study of the Hellenic Cooperative Oncology Group. Ann Oncol 2008; 19(1):115-122.

(37) Kosmidis PA, Syrigos K, Kalofonos HP, Dimopoulos M-A, Skarlos D, Pavlidis N et al. Vinorelbine versus paclitaxel for patients with advanced non-small cell lung cancer (NSCLC) and a performance status of 2. Anticancer Res [(Kosmidis, Bacoyiannis) Hygeia Hospital, Tsoha 2 and Vas. Sofias Ave, 11521, Athens, Greece;(Syrigos) Sotiria University Hospital, Athens, Greece;(Kalofonos) Patras University Hospital, Patras, Greece;(Dimopoulos) Alexandra University Hospital, Athens, Greece;(Skarlos, Bafaloukos)

Metropolitan Hospital, Piraeus, Greece;(Pavlidis) Ioannina University Hospital, Ioannina, Greece;(Boukovinas) Theageneio Cancer Hospital, Thessaloniki, Greece;(Pectasides) Ippokratio Hospital, Athens, Greece;(Fountzilas) Ahepa University Hospital, Thessaloniki, Greece] 2012 32(1):[175-181]

(38) Kubota K, Kawahara M, Ogawara M, Nishiwaki Y, Komuta K, Minato K et al. Vinorelbine plus gemcitabine followed by docetaxel versus carboplatin plus paclitaxel in patients with advanced non-small-cell lung cancer: a randomised, open-label, phase III study. Lancet Oncol [(Kubota, Nishiwaki) National Cancer Centre Hospital East, Kashiwa, Chiba, Japan;(Kawahara, Ogawara) National Hospital Organisation, Kinki-chuo Chest Medical Centre, Kita, Sakai, Osaka, Japan;(Komuta) Osaka Police Hospital, Tennoji-ku, Osaka, Japan;(Minato) Gunma Prefectural Cancer Centre, Ohta, Gunma, Japan;(Fujita) Dohoku National Hospital, Asahikawa, Hokkaido, Japan;(Teramukai, Fukushima) Kyoto University Hospital, Sakyo-ku, Kyoto, Japan;(Furuse) The Japan-Multinational Trial Organisation, Teramachi-Oike agaru, Nakagyo-ku, Kyoto, Japan] 2008 9(12):[1135-1142]

(39) Kudoh S, Takeda K, Nakagawa K, Takada M, Katakami N, Matsui K et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 2006; 24(22):3657-3663.

(40) Langer CJ, O'Byrne KJ, Socinski MA, Mikhailov SM, Lesniewski-Kmak K, Smakal M et al. Phase III trial comparing paclitaxel poliglumex (CT-2103, PPX) in combination with carboplatin versus standard paclitaxel and carboplatin in the treatment of PS 2 patients with chemotherapy-naive advanced non-small cell lung cancer. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 2008; 3(6):623-630.

(41) Li J, Yu L-C, Chen P, Shi S-B, Dai C-H, Wu J-R. Randomized controlled trial of neoadjuvant chemotherapy with cisplatin and vinorelbine in patients with stage IIIA non-small cell lung cancer in China. Asia-Pac J Clin Oncol [(Li, Chen) Department of Pulmonary Medicine, Hospital of Jiangsu University, No. 438 North Jiefang Road, Zhenjiang 212001 Jiangsu, China;(Yu, Shi) Department of Thoracic Surgery, Hospital of Jiangsu University, No. 438 North Jiefang Road, Zhenjiang 212001 Jiangsu, China;(Dai) Department of Radiation Oncology, Hospital of Jiangsu University, No. 438 North Jiefang Road, Zhenjiang 212001 Jiangsu, China;(Wu) Department of Pathology, Hospital of Jiangsu University, No. 438 North Jiefang Road, Zhenjiang 212001 Jiangsu, China] 2009 5(2):[87-94]

(42) Lilenbaum RC, Chen CS, Chidiac T, Schwarzenberger PO, Thant M, Versola M et al. Phase II randomized trial of vinorelbine and gemcitabine versus carboplatin and paclitaxel in advanced non-small-cell lung cancer. Ann Oncol 2005; 16(1):97-101.

(43) Lissoni P, Chilelli M, Villa S, Cerizza L, Tancini G. Five years survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: a randomized trial. Journal of Pineal Research 2003; 35(1):12-15.

(44) O'Brien ME, Socinski MA, Popovich AY, Bondarenko IN, Tomova A, Bilynsky BT et al. Randomized phase III trial comparing single-agent paclitaxel Poliglumex (CT-2103, PPX) with single-agent gemcitabine or vinorelbine for the treatment of PS 2 patients with chemotherapy-naive advanced non-small cell lung cancer. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 2008; 3(7):728-734.

(45) Okamoto I, Yoshioka H, Morita S, Ando M, Takeda K, Seto T et al. Phase III trial comparing oral S-1 plus carboplatin with paclitaxel plus carboplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer: results of a west Japan oncology group study. J Clin Oncol 2010; 28(36):5240-5246.

(46) Paccagnella A, Favaretto A, Oniga F, Barbieri F, Ceresoli G, Torri W et al. Cisplatin versus carboplatin in combination with mitomycin and vinblastine in advanced non small cell lung cancer. A multicenter, randomized phase III trial. Lung Cancer 2004; 43(1):83-91.

(47) Paccagnella A. Adding gemcitabine to paclitaxel/carboplatin combination increases survival in advanced non-small-cell lung cancer: results of a phase II-III study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006;(4):681-687.

(48) Paz-Ares L, Douillard JY, Koralewski P, Manegold C, Smit EF, Reyes JM et al. Phase III study of gemcitabine and cisplatin with or without aprinocarsen, a protein kinase C-alpha antisense oligonucleotide, in patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2006; 24(9):1428-1434.

(49) Pujol J-L, Breton J-L, Gervais R, Rebattu P, Depierre A, Morere J-F et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: A phase III study addressing the case for cisplatin. Ann Oncol [(Pujol, Quantin) Montpellier University Hospital, Montpellier, France;(Breton) Belfort Hospital, Belfort, France;(Gervais) Caen Cancer Institute, Caen, France;(Rebattu) Lyon Cancer Institute, Lyon, France;(Depierre) Besancon University Hospital, Besancon, France;(Morere) Bobigny Avicenne University Hospital, Bobigny, France;(Milleron) Paris Tenon University Hospital, Paris, France;(Debieuvre) Vesoul Hospital, Vesoul, France;(Castera) Perpignan Saint Pierre Institute, Perpignan, France;(Souquet) Hospices Civils de Lyon, Lyon, France;(Moro-Sibilot) Grenoble University Hospital, Grenoble, France;(Lemarie) Tours University Hospital, Tours, France;(Kessler) Strasbourg Hautepierre University Hospital, Strasbourg, France;(Janicot) Clermont Ferrand University Hospital, Clermont Ferrand, France;(Braun) Briey Hospital, Briey, France;(Spaeth) Nancy Cancer Institute, Nancy, France;(Clary) Nice University Hospital, Nice, France;(Pujol) Montpellier Academic Hospital, Hopital Arnaud de Villeneuve, 34295 Montpellier Cedex 5, France] 2005 16(4):[602-610]

(50) Reck M, von PJ, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V 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):1804-1809.

(51) Reck M, von PJ, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil.[Erratum appears in J Clin Oncol. 2009 May 10;27(14):2415]. J Clin Oncol 2009; 27(8):1227-1234.

(52) Rudd RM, Gower NH, Spiro SG, Eisen TG, Harper PG, Littler JA et al. Gemcitabine plus carboplatin versus mitomycin, ifosfamide, and cisplatin in patients with stage IIIB or IV non-small-cell lung cancer: a phase III randomized study of the London Lung Cancer Group. J Clin Oncol 2005; 23(1):142-153.

(53) Schuette W, Blankenburg T, Schneider CP, von Weikersthal LF, Guetz S, Laier-Groeneveld G et al. Randomized, multicenter, open-label phase II study of gemcitabine plus single-dose versus split-dose carboplatin in the treatment of patients with advanced-stage non-small-cell lung cancer. Clin Lung Cancer 2006; 8(2):135-139.

(54) Sederholm C. Gemcitabine versus gemcitabine/carboplatin in advanced non-small cell lung cancer: preliminary findings in a phase III trial of the Swedish Lung Cancer Study Group. Semin Oncol 2002; 29(3:Suppl 9):Suppl-4.

(55) Sederholm C, Hillerdal G, Lamberg K, Kolbeck K, Dufmats M, Westberg R et al. Phase III trial of gemcitabine plus carboplatin versus single-agent gemcitabine in the treatment of locally advanced or metastatic non-small-cell lung cancer: the Swedish Lung Cancer Study Group. J Clin Oncol 2005; 23(33):8380-8388.

(56) Segawa Y, Kiura K, Takigawa N, Kamei H, Harita S, Hiraki S et al. Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSG 0007. J Clin Oncol 2010; 28(20):3299-3306.

(57) Socinski MA, Schell MJ, Peterman A, Bakri K, Yates S, Gitten R et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-

line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. J Clin Oncol 2002; 20(5):1335-1343.

(58) Souquet PJ TERP. GLOB-1: a prospective randomised clinical phase III trial comparing vinorelbine-cisplatin with vinorelbine-ifosfamide-cisplatin in metastatic non-small-cell lung cancer patients. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2002;(12):1853-1861.

(59) Stathopoulos GP, Veslemes M, Georgatou N, Antoniou D, Giamboudakis P, Katis K et al. Front-line paclitaxel-vinorelbine versus paclitaxel-carboplatin in patients with advanced non-small-cell lung cancer: a randomized phase III trial. Ann Oncol 2004; 15(7):1048-1055.

(60) Stathopoulos GP, Antoniou D, Dimitroulis J, Michalopoulou P, Bastas A, Marosis K et al. Liposomal cisplatin combined with paclitaxel versus cisplatin and paclitaxel in non-small-cell lung cancer: a randomized phase III multicenter trial. Ann Oncol 2010; 21(11):2227-2232.

(61) Tan EH, Szczesna A, Krzakowski M, Macha HN, Gatzemeier U, Mattson K et al. Randomized study of vinorelbine--gemcitabine versus vinorelbine--carboplatin in patients with advanced non-small cell lung cancer. Lung Cancer 2005; 49(2):233-240.

(62) Tan EH, Rolski J, Grodzki T, Schneider CP, Gatzemeier U, Zatloukal P et al. Global Lung Oncology Branch trial 3 (GLOB3): final results of a randomised multinational phase III study alternating oral and i.v. vinorelbine plus cisplatin versus docetaxel plus cisplatin as first-line treatment of advanced non-small-cell lung cancer. Ann Oncol 2009; 20(7):1249-1256.

(63) Treat J. A retrospective analysis of outcomes across histological subgroups in a three-arm phase III trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin for advanced non-small cell lung cancer. Lung cancer (Amsterdam, Netherlands) 2010;(3):340-346.

(64) Vokes EE, Herndon JE, Kelley MJ, Cicchetti MG, Ramnath N, Neill H et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 2007; 25(13):1698-1704.

(65) Von PC, Bergman B, Andresen O, Bremnes RM, Sundstrom S, Gilleryd M et al. Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer. Br J Cancer 2006; 95(8):966-973.

(66) Wachters FM, van Putten JW, Kramer H, Erjavec Z, Eppinga P, Strijbos JH et al. First-line gemcitabine with cisplatin or epirubicin in advanced non-small-cell lung cancer: a phase III trial. Br J Cancer 2003; 89(7):1192-1199.

(67) Williamson SK, Crowley JJ, Lara PN, Jr., McCoy J, Lau DH, Tucker RW et al. Phase III trial of paclitaxel plus carboplatin with or without tirapazamine in advanced non-small-cell lung cancer: Southwest Oncology Group Trial S0003. J Clin Oncol 2005; 23(36):9097-9104.

(68) Yokomise H, Gotoh M, Okamoto T, Yamamoto Y, Ishikawa S, Nakashima T et al. Induction chemoradiotherapy (carboplatin-taxane and concurrent 50-Gy radiation) for bulky cN2, N3 non-small cell lung cancer. Journal of Thoracic & Cardiovascular Surgery 2007; 133(5):1179-1185.

(69) Zatloukal P, Petruzelka L, Zemanova M, Havel L, Janku F, Judas L et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer 2004; 46(1):87-98.