

# ASCO | Guidelines

## Data Supplement

### **2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer**

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## Stage IV NSCLC Focused Update

### Data Supplements

**Data Supplement 1. EFFICACY OUTCOMES EVIDENCE TABLE**

Trial	Median # of cycles	# Pts Followed		PFS		HR (95% CI)	p value	OS		HR (95% CI)	p value
		Maintenance	Comparator	Maintenance	Comparator			Maintenance	Comparator		
				Time period (95% CI)	Time period (95% CI)			Months (95% CI)	Months (95% CI)		
Fidias et al. <sup>2</sup> immediate docetaxel vs. delayed docetaxel	6 vs. 4	153	256	5.7 (4.4-6.9) months	2.7 (2.6-2.9) months	NR	0.0001	12.3 (10.4-15.2)	9.7 (8.4-12.5)	NR	0.0853
Ciuleanu et al. <sup>3</sup> pemetrexed/BSC vs. placebo/BSC	5 vs. 3.5	441	222	4.3 (4.1-4.7) months	2.6 (1.7-2.8) months	0.50 (0.42-0.61)	<0.0001	13.4 (11.9-15.9)	10.6 (8.7-12)	0.79 (0.65-0.95)	0.012
Cappuzzo et al. <sup>4</sup> erlotinib vs. placebo after 4 cycles platinum-based chemotherapy	N/A	483	451	12.3 weeks	11.1 weeks	0.71 (0.62-0.82)	<0.0001	12	11	0.81 (0.70-0.95)	0.0088
Johnson et al. <sup>5</sup> carboxyaminoimidazole (CAI) vs. placebo	2 vs. 3	94	92	2.8* months	2.4* months	N/A	0.5	11.4	10.5	N/A	0.54
Takeda et al. <sup>6</sup> platinum doublet 6 cycles vs. platinum doublet 3 cycles, then gefitinib until DP	N/A	297	298	4.3 months	4.6 months	0.68 (0.57-0.80)	<.001	12.9	13.7	0.86 (0.72-1.03)	0.11
Perol et al. <sup>7</sup> gemcitabine or erlotinib vs. observation (after 4 cycles	N/A	G: 154 E: 155	155	G: 3.8 months E: 2.9	1.9 months	G: 0.55 (0.43-0.7) E: 0.82	G: <0.0001	NR	NR	G: 0.86 (0.66-1.12) E: 0.91	NR

cisplatin/gemcitabine)				months		(0.73-0.93)	E: 0.002			(0.80-1.04)	
Kabbinavar et al. <sup>9</sup> /Miller et al. <sup>8</sup>  bevacizumab vs. bevacizumab/erlotinib after 4 cycles of bevacizumab/chemotherapy	N/A	370 (PFS)	373 (PFS)	4.8 months <sup>8</sup>	3.7 <sup>8</sup>	0.722 (0.592-0.881) <sup>8</sup>	0.0012 <sup>8</sup>	15.9 <sup>9***</sup>	13.9 <sup>9***</sup>	0.90 (0.74-1.09) <sup>9***</sup>	0.2686 <sup>9***</sup>
		768 (for survival)**									

Abbreviations: BSC, best supportive care; DP, disease progression; N/A, not available; NR, not reported; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval

\*Time to Progression

\*\*# per arm N/A

\*\*\* from 6/19/2009, posthoc analysis

**Data Supplement 2. ADVERSE EVENTS EVIDENCE TABLE**

Trial	Adverse Events
Fidias et al. <sup>2</sup>  Immediate docetaxel versus delayed docetaxel	Grade 3/4 AE - % neutropenia 27.6 vs. 28.6 thrombocytopenia 0 vs. 0 febrile neutropenia 2.8/0.7 vs. 1.0/1.0 anemia 0.7/0 vs. 0
Ciuleanu et al. <sup>3</sup>  pemetrexed/BSC vs. placebo/BSC	Grade 3/4 AE - % neutropenia 3 vs. 0, P=0.006 anemia 3 vs. <1 leukopenia 2 vs. <1 fatigue 5 vs. <1, p<0.001 infection 2 vs. 0
Cappuzzo et al. <sup>4</sup>  erlotinib vs. placebo after 4 cycles platinum-based chemotherapy	Grade ≥3 AE - % skin 9 vs. 0 diarrhea 2 vs. 0 infection 1 vs. 0
Johnson et al. <sup>5</sup>  carboxyaminoimidazole (CAI) vs. placebo	Grade 3 AE - % fatigue 7.8 vs. 3.3 ataxia 11.1 vs. 3.3 neuro-sensory 8.9 vs. 0 hematologic AEs, difference NS (both ≤2%)  Grade 5 AE - n CAI: 2 pulmonary, 1 arrhythmia placebo: ischemia/infarction, arrhythmia, pulmonary
Takeda et al. <sup>6</sup>  platinum doublet 3 cycles, then gefitinib until DP vs. platinum doublet 6 cycles	Grade 3/4 AE - % anemia 13.3 vs. 21.8, P=.006 AST/ALT elevation > in Arm B, P=.002 leukopenia 37 vs. 39.9, NS neutropenia 70.6 vs. 75.8, NS

	febrile neutropenia 12.8 vs. 12.8, NS fatigue 7.3 vs. 9.7, NS thrombocytopenia 6.3 vs. 10.7, P=0.54
Perol et al. <sup>7</sup>  gemcitabine or erlotinib vs. observation (after 4 cycles cisplatin/gemcitabine)	Grade 3/4 AE - % anemia 2.6 vs. 1.3 vs. 0.6 neutropenia 21 vs. 0.6 vs. 0.6 thrombocytopenia 6.5 vs. 0 vs. 0 rash 0 vs. 9 vs. 0
Miller et al. <sup>8</sup>  bevacizumab/erlotinib vs. bevacizumab	Grade 3/4 AE - % Thrombocytopenia 0.3 vs. 0.5 Neutropenia 0.5 vs. 1.1 Hypertension 5.4 vs. 5.7 VTE 1.1 vs. 2.7 Rash 10.4 vs. 0.5 Diarrhea 9.3 vs. 0.8

Abbreviations: AE, adverse event; NS, non-significant; BSC, best supportive care; DP, disease progression

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### **Data Supplement 3. GUIDELINE CLINICAL QUESTIONS**

#### ***First-Line Chemotherapy***

- 1. Clinical question.* Which patients with stage IV (as defined by the International Association for the Study of Lung Cancer Lung Cancer Staging Project<sup>2</sup>) NSCLC should be treated with chemotherapy? (Note: In this document, the term “chemotherapy” refers to any anticancer drug, regardless of its mechanism of action [ie, cytotoxic and biologic drugs included] unless otherwise specified.)
- 2. Clinical questions.* What is the most effective first-line chemotherapy for the treatment of patients with stage IV NSCLC? What are the benefits, with respect to OS, PFS, toxicity, and QOL/symptom relief, in the treatment of stage IV NSCLC with chemotherapy?
- 3. Clinical question.* What is the best chemotherapy for treatment of patients with PS 2 with stage IV NSCLC?
- 4. Clinical question.* What is the best chemotherapy for treatment of elderly patients with stage IV NSCLC?
- 5. Clinical question.* Is cisplatin more effective than carboplatin in the first-line treatment of stage IV NSCLC?
- 6. Clinical question.* What is the optimal duration of first-line chemotherapy for stage IV NSCLC?
- 7. Clinical question.* What are the benefits, with respect to OS, PFS, toxicity, and QOL/symptom relief, in the treatment of stage IV NSCLC with targeted therapies?

#### ***Second-Line Chemotherapy***

- 1. Clinical questions.* Is there an optimal second-line treatment for stage IV NSCLC? Is there evidence to support the use of combination biologic therapy as second-line therapy? Is there an optimal schedule of administration in second-line treatment for stage IV NSCLC?
- 2. Clinical question.* What is the optimal second-line treatment for elderly patients with stage IV NSCLC?

#### ***Third-Line Chemotherapy and Beyond***

- 1. Clinical question.* Is there a role for third-line therapy in the treatment of stage IV NSCLC?

#### ***Use of Molecular Markers to Select Therapy***

- 1. Clinical question.* For the purposes of prescribing chemotherapy what is the relevance of molecular analysis of tissue?

## Data Supplement 4

2011 Focused Update search strategy (PUBMED)

From January 2008 – June 2010

### NSCLC search string

((Carcinoma, Non-Small-Cell Lung[MH] OR ((cancer[TIAB] OR neoplasm[TIAB] OR neoplasms[TIAB] OR tumor[TIAB] OR tumors[TIAB] OR tumour[TIAB] OR tumours[TIAB] OR malignant[TIAB] OR malignancy[TIAB] OR malignancies[TIAB] OR carcinoma[TIAB] OR carcinomas[TIAB] OR carcinomatosis[TIAB] OR carcinomatoses[TIAB] OR adenocarcinoma[TIAB] OR adenocarcinomas[TIAB] OR oncology[TIAB]) AND (Lung[MH] OR non-small-cell lung[TIAB])) OR NSCLC[TIAB] OR Adenocarcinoma, Bronchiolo-Alveolar[MH]) AND (advanced[TIAB] OR unresectable[TIAB] OR stage IV[TIAB] OR metastatic[TIAB] OR incurable[TIAB])) AND (Drug Therapy[mh] OR drug therapy, combination[mh] OR Antineoplastic protocols[mh] OR Antineoplastic Agents[mh] OR Antineoplastic combined chemotherapy protocols [mh] OR Tarceva[TIAB] OR erlotinib[NM] OR vinorelbine[NM] OR Navelbine[TIAB] OR Paclitaxel[mh] OR Taxol[TIAB] OR Alimta[TIAB] OR pemetrexed[NM] OR bevacizumab[NM] OR Avastin[TIAB] OR docetaxel[NM] OR taxotere[TIAB]) NOT radiotherapy[all fields] AND english [LA]) AND human [MH]) AND ("2008/01/01"[PDat]: "2010/06/11"[PDat])

### RCT search string

AND (((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR clinical trials as topic[mh] OR controlled clinical trials as topic[mh] OR randomized controlled trials as topic[mh] OR clinical trials, phase II as topic[mh] OR clinical trials, phase III as topic[mh] OR clinical trials, phase IV as topic[mh] OR clinical trial, phase II[pt] OR clinical trial, phase III[pt] OR clinical trial, phase IV[pt] OR random allocation[mh] OR "random allocation"[tiab] OR "randomly allocated"[tiab] OR double-blind method[mh] OR single-blind method[mh]) OR ((random[tiab] OR randomly[tiab] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab]) AND (clinical[tiab] OR control[tiab] OR controlled[tiab] or control groups[mh])) OR ((single[tiab] OR single-[tiab] OR double[tiab] OR double-[tiab] OR triple[tiab] OR triple-[tiab] OR multi[tiab] OR multi-[tiab] OR evaluator[tiab] OR assessor[tiab] OR interviewer[tiab]) AND (mask[tiab] OR masked[tiab] OR masking[tiab] OR blind[tiab] OR blinded[tiab] OR blinding[tiab])) OR ((placebos[mh] OR placebo[tiab] OR placebos[tiab] OR random[tiab] OR randomly[tiab] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomization[tiab]) AND (research design[mh] OR "comparative study"[tiab] OR comparative study[pt] OR evaluation studies as topic[mh:noexp] OR evaluation studies[pt] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR validation studies as topic[mh] OR follow-up studies[mh] OR "follow-up study"[tiab] OR "follow up study"[tiab] OR "follow-up studies"[tiab] OR "follow up studies"[tiab] OR prospective studies[mh] OR prospective[tiab] OR epidemiologic research design[mh] OR epidemiologic methods[mh] OR epidemiologic study characteristics as topic[mh] OR epidemiologic studies[mh] OR intervention studies[mh] OR cross-over studies[mh])) NOT (clinical trial, phase I[pt] OR clinical trials, phase I as topic[mh]) NOT (animals[mh] NOT humans[mh]) NOT (case

reports[pt] OR case report[tiab] OR editorial[pt] OR editorial[tiab] OR letter[pt] OR newspaper article[pt]))

### **Meta-analyses, guidelines, evidence-based medicine search string**

AND ((meta-analysis[pt] OR meta-analysis as topic[mh] OR "meta-analysis"[tiab] OR "meta analysis"[tiab] OR "meta-analyses"[tiab] OR "meta analyses"[tiab] OR "meta-analyzed"[tiab] OR "meta-analysed"[tiab] OR "meta analyzed"[tiab] OR "meta analysed"[tiab] OR (meta[tiab] AND analysis[tiab]) OR (meta-[tiab] AND analysis[tiab])) OR ((critical[tiab] OR critically[tiab] OR systematic[tiab] OR systematical[tiab] OR systematically[tiab] OR evidence-based[tiab] OR "evidence based"[tiab]) AND (review[pt] OR review[tiab] OR reviews[tiab] OR reviewed[tiab] OR appraise[tiab] OR appraises[tiab] OR appraised[tiab] OR appraisal[tiab] OR assess[tiab] OR assesses[tiab] OR assessed[tiab] OR assessment[tiab] OR evaluate[tiab] OR evaluates[tiab] OR evaluated[tiab] OR evaluation[tiab] OR critique[tiab] OR critiques[tiab] OR analysis[tiab] OR analyses[tiab] OR analyzed[tiab] OR analysed[tiab])) OR ((evidence-based[tiab] OR "evidence based"[tiab]) AND (guideline[tiab] OR guidelines[tiab] OR recommendation[tiab] OR recommendations[tiab] OR consensus[mh] OR consensus[tiab] OR consensuses[tiab])) OR (review literature as topic[mh] OR consensus development conference[pt] OR consensus development conference, NIH[pt] OR consensus development conferences as topic[mh] OR consensus development conferences, NIH as topic[mh] OR "consensus development"[tiab] OR health planning guidelines[mh] OR guideline[pt] OR practice guideline[pt] OR practice guidelines as topic[mh] OR "practice guideline"[tiab] OR "practice guidelines"[tiab] OR health planning guidelines[mh] OR "standard of care"[tiab] OR "evidence-based medicine"[tiab] OR "evidence based medicine"[tiab] OR "evidence-based care" OR "evidence-based practice"[tiab] OR cochrane database syst rev[ta] OR acp j club[ta] OR health technol assess[ta] OR clin evid[ta])) NOT (clinical trial, phase I[pt] OR clinical trials, phase I as topic[mh]) NOT (animals[mh] NOT humans[mh]) NOT (case reports[pt] OR case report[tiab] OR editorial[pt] OR editorial[tiab] OR letter[pt] OR newspaper article[pt])

## Data Supplement 5

### QUOROM Diagram

#### Exclusions and Inclusions of Publications Identified for Systematic Review for this Focused Update

Literature Search Date Parameters: January 01, 2008 to June 11, 2010

