Comparison of Docetaxel- and Vinca Alkaloid–Based Chemotherapy in the First-line Treatment of Advanced Non-small Cell Lung Cancer: A Meta-analysis of Seven Randomized Clinical Trials

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Introduction: To compare the impact on overall survival (OS) of docetaxel-based chemotherapy versus vinca alkaloid–based regimens for first-line therapy of advanced non-small cell lung cancer.

Methods: A meta-analysis of all randomized, controlled trials comparing docetaxel- and vinca alkaloid–based chemotherapy was undertaken using MEDLINE, CANCERLIT, MEDSCAPE, Google Scholar, the Cochrane Library, the National Institutes of Health randomized, controlled trials register, and conference proceedings, supplemented by information from clinical study reports. All published and unpublished randomized, controlled trials (in any language) were included. Analysis was based on pooling individual logarithms of the hazard ratio for OS and the odds ratio (OR) for safety.

Results: From eight potentially eligible trials, seven were selected (n = 2867). Docetaxel was administered with a platinum agent (three trials), with gemcitabine (two trials), or as monotherapy (two trials). Vinca alkaloid (vinorelbine [six trials] and vindesine [one trial]) was administered with cisplatin (six trials) or alone (one trial). The pooled estimate for OS showed an 11% improvement in favor of docetaxel (hazard ratio = 0.89; 95% confidence interval: 0.82–0.96; p = 0.004). Sensitivity analyses considering only vinorelbine as a comparator or only the doublet regimens showed similar improvements. Grade 3/4 neutropenia and grade 3/4 serious adverse events were less frequent with docetaxel- versus vinca alkaloid–based regimens (OR = 0.59; 95% confidence interval: 0.38–0.89; p = 0.013 and OR = 0.68; 95% confidence interval: 0.55–0.84; p < 0.001, respectively).

Conclusion: According to this meta-analysis, docetaxel is superior to vinca alkaloid–based regimens in terms of OS and safety for first-line therapy of advanced non-small cell lung cancer.

(J Thorac Oncol. 2007;2: 939–946)

Lung cancer is the leading cause of cancer and cancer-related deaths worldwide, with 1.2 million deaths annually.¹ Non-small cell lung cancer (NSCLC), which accounts for approximately 80% of lung cancer cases, presents as local disease in 20% to 30% of patients and as advanced metastatic disease (stage IIIB/IV) in 40% to 50%.² Platinum-based doublet regimens are considered the standard first-line treatment for advanced NSCLC.³–⁵

Newer, so-called third-generation chemotherapy agents, including docetaxel, paclitaxel, vinorelbine, and gemcitabine, have improved outcomes in advanced NSCLC compared with older agents.⁶ Vinorelbine was the first agent to show a survival benefit when combined with cisplatin⁷ and consequently became a standard regimen for the first-line treatment of NSCLC.⁸

Combinations of a vinca alkaloid (vinorelbine and vindesine) and cisplatin have yielded response rates from 19% to 43% and median survival times from 8 to 10 months.⁷–¹² Several randomized trials and one meta-analysis have attempted to compare the different third-generation chemotherapy agents.⁸,⁹,¹³–¹⁷ Among these comparative studies of docetaxel- and vinca alkaloid–based chemotherapy, some have suggested that differences in activity may exist between the treatments, particularly in terms of survival. However, a cross-trial comparison of these studies is not possible because of differences in trial design, dose regimens, and patient characteristics and thus may not provide reliable conclusions. Furthermore, some trials may be underpowered to detect differences between treatment groups in survival and safety outcomes if they are powered for surrogate endpoints such as tumor response or time to progression. To provide a more statistically powerful method of cross-trial
comparison and detecting treatment differences, a meta-analysis was performed. Data from docetaxel- and vinca alkaloid–based regimens were compared for the first-line treatment of advanced NSCLC using all relevant published and unpublished randomized, controlled trials (RCTs).

MATERIALS AND METHODS

Literature Search and Study Identification

Our aim was to identify all relevant published and unpublished RCTs comparing docetaxel- and vinca alkaloid–based chemotherapy regimens for the first-line treatment of advanced NSCLC. An exhaustive literature search, both manual and computer assisted, was performed without any restriction on language or dates.

The computer-assisted search was carried out on electronic databases (MEDLINE, CANCERLIT, MEDSCAPE, Google Scholar, the Cochrane Library, and the National Institutes of Health RCT register [clinicaltrials.org]) using the terms non-small cell lung cancer or NSCLC; phase II, phase III, randomized, controlled, or meta-analysis; docetaxel or Taxotere, in combination with generic and trade names of the vinca alkaloids. In addition, conference proceedings from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology, and the European Cancer Conference were searched for abstracts of relevant trials. We manually searched the bibliographies of journal articles to find additional studies. Particular attention was given to duplicate reports, and, when studies were published both in abstract form and as an original article, only the article was referenced. If more than one article was published for a single study, all citations were included.

Study Selection

We selected randomized trials evaluating the effect of docetaxel compared with a vinca alkaloid as first-line chemotherapy for advanced NSCLC. All trials had to include one or more treatment arm with docetaxel alone, or combined with either a platinum agent (cisplatin or carboplatin) or gemcitabine, and one or more vinca alkaloid–based treatment arm. Studies including the administration of granulocyte colony-stimulating factor (G-CSF) were considered. When a trial was deemed eligible, all investigators and sponsors were systematically contacted and asked to provide the protocol and clinical and statistical study reports because detailed statistical information (i.e., log of the hazard ratio [HR] and the variance) is required for meta-analyses of survival outcomes.

Assessment of Study Quality

The methodologic quality of each trial was classified according to the Jadad score. This score incorporates assessments of randomization, proper generation and concealment of the treatment allocation sequence, blinding of patients and investigators, and completeness of follow-up (based on information for withdrawals and dropouts). To be included in this analysis, studies had to achieve a Jadad score >2, in effect excluding trials that did not involve proper randomization procedures (i.e., studies without concealment of randomization). Because all studies were open-label trials, as is common in oncology, the blinding items were systematically not filled in.

Data Extraction

Predefined data from individual trials were extracted independently by two of the authors (M.C., S.L.). A concordance meeting was held, and, in case of a discrepancy in either study selection or data extraction, agreement was reached. The following data were extracted: name of the first author and study acronym, year(s) of publication, number of randomized patients, study design, study quality (Jadad score), treatment regimens, duration of follow-up, and efficacy and safety endpoints (overall survival [OS]; grade 3/4 neutropenia; febrile neutropenia; grade 3/4 serious adverse events [SAEs]; SAEs leading to discontinuation of the drug; and SAEs leading to death). Data were directly extracted from the protocol and clinical and statistical reports.

Statistical Analysis

The efficacy analysis was performed on an intent-to-treat basis. Analysis of survival was based on the pooling of individual logarithms of the HR. Summary data were pooled by the inverse-variance weighting method. The results were generated using the fixed-effects model unless otherwise stated. When there was evidence of significant statistical heterogeneity (and in the absence of a clear explanation for heterogeneity), a random-effects model was employed, generating a more conservative estimate.

A funnel plot of treatment effect versus study precision was created for the primary endpoint to detect publication bias. Such a technique is potentially helpful in determining whether additional small studies may have been conducted but not published because of unfavorable or negative results and therefore not identified for the meta-analysis.

Subgroup analyses were performed for the combination of docetaxel with a platinum agent or gemcitabine, or as monotherapy. Sensitivity analyses (planned a priori) were performed to further establish the robustness of the results for the primary endpoint—first, when considering only docetaxel-based regimens versus the vinorelbine comparator and, second, when considering only docetaxel-doublet regimens. An additional a posteriori sensitivity analysis was performed, generating a more conservative estimate.
performed when considering only trials comparing docetaxel with vinca alkaloid administered via matching regimens (both alone or both with the same concomitant chemotherapy).

Finally, to identify any study that may have exerted a disproportionate influence on the summary treatment effect, we deleted studies one at a time from the analysis. Statistical analyses were performed using the computer program easyMA (Department of Clinical Pharmacology, Cardiological Hospital, Lyon, France).

RESULTS

Study Selection

Eight RCTs were identified as potentially eligible for inclusion.14–16,26–30 One trial comparing docetaxel plus carboplatin versus vinorelbine plus carboplatin in 60 patients was excluded30 because we did not have access to the study protocol or randomization schedule, resulting in a Jadad score <2. However, a print version of all individual case report forms (CRFs) was provided by the principal investigator and an additional sensitivity analysis was performed including this trial. The inclusion and exclusion criteria, study design, and principal outcomes for each study included in the meta-analysis are shown in Table 1. Finally, the reports for all the remaining trials were available to extract the data on survival and safety outcomes.

Study Design

Seven trials were available, including 2867 patients (Table 1). The largest trial was carried out mainly in the United States, Canada, and Europe. Two trials were performed in Japan, two in France, one in Greece, and one in Europe (mainly in Eastern Europe [Russia and the Czech Republic]). The age range of patients included in all studies was 22 to 87 years. One trial was performed in elderly patients (median age, 76 years). Of the enrolled populations, the proportion of males ranged from 66% to 88%.

One of the studies was a three-arm trial.14 In the absence of a clear methodologic consensus, the two comparisons derived from this trial were considered separately without in-trial adjustment of the alpha risk for multiplicity. Four comparisons were available for docetaxel plus a platinum agent (cisplatin or carboplatin), two for docetaxel plus gemcitabine, and two for docetaxel alone (restricted either to elderly patients or to a population selected based on the presence of a potential biologic marker). One trial comparing docetaxel plus carboplatin versus vinorelbine plus carboplatin in 60 patients was excluded because we did not have access to the study protocol or randomization schedule, resulting in a Jadad score <2. However, a print version of all individual case report forms (CRFs) was provided by the principal investigator and an additional sensitivity analysis was performed including this trial. The inclusion and exclusion criteria, study design, and principal outcomes for each study included in the meta-analysis are shown in Table 1. Finally, the reports for all the remaining trials were available to extract the data on survival and safety outcomes.

Study Quality and Publication Bias

All the trials were open label. Appropriate methods were used to generate the randomized treatment allocations, which appeared to be adequately concealed in all studies. Withdrawals and dropouts were available for five trials, yielding a Jadad score of 3. The funnel plot of effect size was symmetrical, with a similar number of studies on either side of the summary treatment effect (data not shown), indicating a lack of major publication bias.

Overall Survival

The HR for each trial and the corresponding confidence intervals (CIs) for OS are shown in Figure 1. Individual HRs ranged from 0.75 to 1.00. The pooled estimate for OS showed a significant 11% improvement in favor of docetaxel (HR = 0.89; 95% CI: 0.82–0.96; p = 0.004) (Figure 1). No significant heterogeneity was found between the trials for OS. The results for all drug combinations favored docetaxel, with an HR of 0.87 (95% CI: 0.79–0.96) for docetaxel combined with a platinum agent; 0.89 (95% CI: 0.82–0.96) for non-platinum-based docetaxel regimens; 0.96 (95% CI: 0.81–1.13) for docetaxel combined with gemcitabine; and 0.87 (95% CI: 0.69–1.09) for docetaxel monotherapy.

OS benefit was similar when considering only vinorelbine trials (HR = 0.91; 95% CI: 0.83–0.98), only doublet regimens (HR = 0.89; 95% CI: 0.82–0.97), or only trials with matching regimens14–16,26 (HR = 0.82; 95% CI: 0.73–0.92). Any uncertainty about the effect of excluding the Rubio and Sahagun trial due to the lack of access to the study protocol was ruled out by the secondary evaluation, which showed no change from the original results. Finally, removing individual studies from the analysis did not alter the result: for example, when excluding the largest trial (Fossella et al.), the result for the primary endpoint (OS) remained significant (HR = 0.88; 95% CI: 0.79–0.98).

Neutropenia

All individual study results for grade 3/4 neutropenia favored docetaxel except for the Kudoh et al. trial,16 which compared single-agent docetaxel with a vinorelbine monotherapy regimen with a rather low-dose intensity schedule. Thus, heterogeneity between trials was observed (heterogeneity test p = 0.005). After exclusion of the Kudoh et al. study, the results consistently favored docetaxel, irrespective of which combination was used. Finally, a random-effects model was used to calculate the overall estimate including all trials. A significant reduction in grade 3/4 neutropenia was observed in favor of docetaxel, with a significant 41% reduction in the number of events versus the vinca alkaloid comparator (OR = 0.59; 95% CI: 0.38–0.89; p = 0.013) (Figure 2A).

Similar results were observed for febrile neutropenia, with a significant 43% reduction in the number of events in favor of docetaxel compared with vinca alkaloids (OR = 0.57; 95% CI: 0.35–0.94; p = 0.028) (Figure 2B).

Serious Adverse Events

When considering grade 3/4 SAEs, the results favored docetaxel, with a significant 32% reduction in the number of events versus the vinca alkaloid (OR = 0.68; 95% CI: 0.55–0.84; p < 0.001; Figure 3). There was both a reduction in SAEs leading to study drug discontinuation (OR = 0.61; 95% CI: 0.34–1.10; p = 0.10) and in SAEs leading to death with docetaxel (OR = 0.76; 95% CI: 0.48–1.21; p = 0.25) (Figure 3).
<table>
<thead>
<tr>
<th>Study Ref.</th>
<th>Trial Duration</th>
<th>No. of Patients</th>
<th>Median Age, y</th>
<th>PS</th>
<th>Disease Stage</th>
<th>Sponsor/Country</th>
<th>Docetaxel Regimen and Dose</th>
<th>Vinca alkaloid Regimen and Dose</th>
<th>Primary Endpoint</th>
<th>Jadad Score</th>
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<tr>
<td>Fossella et al.</td>
<td>Jul 1998–Jan 2000</td>
<td>1218</td>
<td>60</td>
<td>4% KPS 70</td>
<td>33% IIIb, 67% IV</td>
<td>Aventis/US</td>
<td>DC: D, 75 mg/m² day 1; C, 75 mg/m² day 1 q 3 wk × 6DCb: D, 75 mg/m² day 1; Cb AUC 6 mg/mL · min day 1 q 3 wk × 6</td>
<td>VC: V, 25 mg/m² days 1, 8, 15, + 22; C, 100 mg/m² day 1 q 4 wk × 6</td>
<td>OS</td>
<td>3</td>
</tr>
<tr>
<td>Douillard et al.</td>
<td>May 1998–Mar 2000</td>
<td>233</td>
<td>58</td>
<td>15% WHO PS 2</td>
<td>100% IV</td>
<td>Aventis/France</td>
<td>DC: D, 75 mg/m² day 1; C, 100 mg/m² day 1 q 3 wk × 6</td>
<td>VC: V, 30 mg/m² days 1 + 8; C, 100 mg/m² day 1 q 3 wk × 6</td>
<td>ORR</td>
<td>3</td>
</tr>
<tr>
<td>Kubota et al.</td>
<td>Apr 1998–Mar 2000</td>
<td>311</td>
<td>63</td>
<td>4% ECOG PS ≥2</td>
<td>100% IV</td>
<td>Aventis/Japan</td>
<td>DC: D, 60 mg/m² day 1; C 80 mg/m² day 1 q 3 or 4 wk × ≥2 cycles</td>
<td>VindC: Vind, 3 mg/m² days 1, 8, + 15; C, 80 mg/m² day 1 q 4 wk × ≥2 cycles</td>
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<td>Georgoulas et al.</td>
<td>Apr 1999–Sep 2002</td>
<td>413</td>
<td>63</td>
<td>11% WHO PS 2</td>
<td>37% IIIb, 63% IV</td>
<td>CABR/Greece</td>
<td>DG: D, 100 mg/m² day 8; G 1000 mg/m² days 1 + 8 q 3 wk × 6</td>
<td>VC: V, 30 mg/m² days 1 + 8; C 80 mg/m² day 8 q 3 wk × 6</td>
<td>OS</td>
<td>3</td>
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<tr>
<td>Pujol et al.</td>
<td>Sep 1999–Apr 2001</td>
<td>311</td>
<td>59</td>
<td>8% KPS 70</td>
<td>18% IIIb, 82% IV</td>
<td>Eli Lilly/France</td>
<td>DG: D, 85 mg/m² day 8; G, 1000 mg/m² days 1 + 8 q 3 wk × 8</td>
<td>VC: V, 30 mg/m² days 1, 8, 15, + 22; C, 100 mg/m² day 1q 4 wk × 6</td>
<td>PFS</td>
<td>3</td>
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<tr>
<td>Kudoh et al.</td>
<td>May 2000–Sep 2003</td>
<td>180 elderly</td>
<td>76</td>
<td>4% ECOG PS 2</td>
<td>37% IIIb, 63% IV</td>
<td>Aventis/Japan</td>
<td>D: 60 mg/m² day 1 q 3 wk × 4</td>
<td>V: V, 25 mg/m² days 1 + 8 q 3 wk × 4</td>
<td>OS</td>
<td>3</td>
</tr>
<tr>
<td>Monnier et al.</td>
<td>Mar 2000–Mar 2001</td>
<td>201 normal AAG</td>
<td>61</td>
<td>10% WHO PS 2</td>
<td>34% IIB, 66% IV</td>
<td>Aventis/Europe</td>
<td>D: 100 mg/m² day 1 q 3 wk × 6</td>
<td>VC: V, 25 mg/m² days 1, 8, 15, + 22; C, 100 mg/m² day 1q 4 wk × 6</td>
<td>ORR</td>
<td>2</td>
</tr>
</tbody>
</table>

AAG, α1 acid glycoprotein; AUC, area under curve; C, cisplatin; CABR, Cretan Association for Biomedical Research; Cb, carboplatin; D, docetaxel; ECOG, Eastern Cooperative Oncology Group; G, gemcitabine; KPS, Karnofsky performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; V, vinorelbine; Vind, vindesine; WHO, World Health Organization.
Dose Intensity and G-CSF Use

Median dose intensities varied from 75% to 98% for docetaxel, from 65% to 90% for the vinca alkaloids, and from 74% to 100% for cisplatin (Table 2). The use of G-CSF was comparable between groups (Table 2).

DISCUSSION

The results of this meta-analysis (2867 patients from seven RCTs) show that docetaxel-based regimens statistically significantly improve survival compared with vinca alkaloid regimens for first-line therapy of advanced NSCLC. This benefit in OS for docetaxel was accompanied by an improved safety profile compared with vinca alkaloids, with a significant reduction in grade 3/4 SAEs and febrile neutropenia. The improvements in safety were obtained without increasing the use of G-CSF or decreasing the dose intensity in the docetaxel arm compared with the vinca alkaloid arm.

Improvements in OS and safety might have been expected to be associated with an improvement in overall quality of life. Unfortunately, only some of the trials in this meta-analysis included a formal quality-of-life assessment, and when a quality-of-life assessment was included, the scales used were different and hence the data could not be pooled.

Several points associated with the methodology used in this meta-analysis are worth noting. First, the absence of significant heterogeneity between trials in terms of OS led to consistent results, as the benefit in OS was always in favor of docetaxel-based regimens compared with vinca alkaloids. Second, the sensitivity analyses confirmed the consistent results in favor of docetaxel whether comparing docetaxel with vinorelbine-based regimens, considering only docetaxel administered in doublet regimens, or including only trials with matching regimens. In 1997, ASCO recommendations advocated that chemotherapy for NSCLC patients should consist of a platinum-based combination regimen. The ASCO recommendations were revised in 2003 to include nonplatinum-containing chemotherapy regimens as an alternative to platinum-based regimens for first-line treatment, and single-agent chemotherapy in elderly patients or patients with an Eastern Cooperative Oncology Group performance status of 2. These guidelines are currently the standard of care for NSCLC in the United States and Europe, where similar recommendations have been adopted. Considering some of the different treatment options for patients with advanced NSCLC, this meta-analysis shows that OS was significantly improved with docetaxel plus a platinum agent (HR = 0.87; 95% CI: 0.79–0.96) as well as with nonplatinum-based docetaxel regimens (HR = 0.89; 95% CI: 0.82–0.96).

To minimize publication bias in this meta-analysis, data from published and unpublished trials were included. Although the risk of publication bias exists in any meta-analysis, whether based on individual patient data or not, the symmetrical funnel plot indicated that this was not a major concern in our study. Furthermore, as the use of third-generation agents for NSCLC is a fairly recent development, the risk of omitting data was reduced.

Although this meta-analysis was not performed on individual patient data, neither was it solely based on published data. The quality of data was improved by obtaining clinical and statistical reports from the authors or sponsors of all included trials. As the primary aim of the study was to assess the robust clinical endpoints of OS and safety, it is unlikely that individual patient data would have provided additional value. However, further investigations using individual patient data are warranted to provide more detailed...
analyses in specific subgroups of patients and to examine additional endpoints. Following the exhaustive research of data, a mix of phase II and III RCTs has been considered here. Although the phase II studies may have been too small to produce reliable survival data, no significant heterogeneity was observed in OS among the trials included in the analysis. This result supports the decision to include all randomized phase II or III trials with prospectively recorded survival data.

During the past 10 years, several NSCLC meta-analyses have been published. As the NSCLC Group meta-analysis published in 1995 has demonstrated, the contribution of meta-analyses to the treatment of patients with NSCLC has been very important in illustrating the impact of chemotherapy on survival. Such studies have helped to define a two-drug platinum-based regimen as the gold-standard treatment for NSCLC. Recently, in the meta-analysis published by Le Chevalier et al., gemcitabine plus platinum regimens resulted in a 7% reduction in overall mortality versus other third-generation drugs combined with a platinum compound. No data on safety were analyzed in this meta-analysis of gemcitabine trials. However, the comparison between gemcitabine-based platinum regimens and docetaxel-based platinum regimens has not been assessed by any meta-analysis as yet, and further studies are required to analyze the benefit:risk ratio of docetaxel with that of other comparators.

Our meta-analysis shows that some significant benefits exist for docetaxel- versus vinca alkaloid– based regimens for first-line therapy of advanced NSCLC, including a survival benefit. Docetaxel-based regimens were also associated with...
a more favorable safety profile than vinorelbine- or vindesine-based combination regimens. These findings may be helpful when choosing an appropriate therapy for advanced NSCLC, with the aim of improving survival without increasing the toxicity profile. The improved efficacy and safety profile of docetaxel-based regimens compared with vinca alkaloid-based regimens is very encouraging, and such regimens may provide a potential platform on which to add targeted therapies for first-line treatment in the future.

Since the present analysis was performed, two additional trials were presented at ASCO 2007 as posters. One phase III from the Hellenic Oncology Research Group compared a combination of oral vinorelbine-gemcitabine with docetaxel-gemcitabine in 254 patients. The results show no difference on survival but a trend in favor of the docetaxel-gemcitabine arm. The second study also from the same group in elderly patients evaluated the use of vinorelbine versus docetaxel as single agents in 112 patients in a phase II setting. No statistical difference was observed in survival, with again a trend in favor of docetaxel. Less myelosuppression was seen with docetaxel. These two additional trials show results in the same direction that our meta-analysis favoring the use of docetaxel but were underpowered to reach their objectives.

In conclusion, docetaxel-containing regimens provided a statistically significant reduction in the risk of death and toxicity for patients with advanced NSCLC when compared with vinca alkaloid–containing regimens.

ACKNOWLEDGMENTS

Research supported by Sanofi-Aventis. The authors sincerely thank Sanofi-Aventis for providing data for the Fossella et al., Kubota et al., Douillard et al., and Monnier et al. trials; Eli Lilly for providing data for the Pujol et al. trial; the West Japan Thoracic Oncology Group for the Kudoh.

REFERENCES


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**TABLE 2.** Median Dose Intensity and Frequency of G-CSF Use for Individual Studies by Treatment Group

<table>
<thead>
<tr>
<th>Study Ref.</th>
<th>Dose Intensity</th>
<th>G-CSF Use</th>
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<tr>
<td></td>
<td>Docetaxel Group</td>
<td>Vinca Alkaloid Group</td>
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<tr>
<td>Fossella et al.</td>
<td>D 97% + C 97%; D 97% + Cb 94%</td>
<td>V 68% + C 93%</td>
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<tr>
<td>Douillard et al.</td>
<td>D 98% + C 98%</td>
<td>V 88% + C 90%</td>
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<td>Kubota et al.</td>
<td>D 75% + C 74%</td>
<td>V 70% + C 100%</td>
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<td>Georgoulias et al.</td>
<td>D 93% + G 93%</td>
<td>V 90% + C 85%</td>
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<td>Pujol et al.</td>
<td>D 93% + G 96%</td>
<td>V 65% + C 95%</td>
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<td>Kudoh et al.</td>
<td>D 91%</td>
<td>V 83%</td>
</tr>
<tr>
<td>Monnier et al.</td>
<td>D 98%</td>
<td>V 70% + C 98%</td>
</tr>
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</table>

C, cisplatin; Ch, carboplatin; D, docetaxel; G, gemcitabine; G-CSF, granulocyte colony-stimulating factor; NA, not available; V, vinorelbine; Vind, vindesine.

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**FIGURE 3.** Pooled safety results by outcome, showing 95% CIs. An OR < 1 (on the left of the black line) corresponds to results in favor of docetaxel. CI, confidence interval; OR, odds ratio; SAEs, serious adverse events.


