Randomized Phase II Trial of Cisplatin, Etoposide, and Radiation Followed by Gemcitabine Alone or by Combined Gemcitabine and Docetaxel in Stage III A/B Unresectable Non-small Cell Lung Cancer

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Purpose: Southwest Oncology Group 9504 demonstrated the feasibility and potential benefit of docetaxel consolidation after etoposide, cisplatin, and radiotherapy in patients with locally advanced non-small cell lung cancer. Our study assessed consolidation with either gemcitabine alone or with docetaxel after identical chemoradiation as used in Southwest Oncology Group 9504.

Methods: Patients with stage III non-small cell lung cancer and good performance status were included. Treatment consisted of concurrent cisplatin 50 mg/m² on days 1 and 8 plus etoposide 50 mg/m² on days 1 to 5 for two 28-day cycles plus radiotherapy (62 Gy, 2 Gy daily in 31 fractions over 7 weeks), followed by randomization to either gemcitabine 1000 mg/m² on days 1 and 8 (G) or gemcitabine 1000 mg/m² on days 1 and 8 plus docetaxel 75 mg/m² on day 1 (GD) every 21 days for three cycles.

Results: Eighty-three patients were entered, 81 received induction therapy, and 64 were randomized (32 in each arm). Grade 3 or four events, including neutropenia (56.3% vs. 28.1%, \( p = 0.03 \)), anemia (18.8% vs. 3.1%, \( p = 0.05 \)), and fatigue (15.6% vs. 6.3%, \( p = NS \)), were more frequent with GD compared with G. Among all patients, median survival from registration was 20.8 months (95% confidence interval: 16.4–33.8), and 2-year survival was 46.7% (95% confidence interval: 35.6–57.1). From randomization, median progression-free survival was 5.4 months for G and 13.4 months for GD, and median survival was 16.1 months for G and 29.5 months for GD. Two-year survival rates were 40.6% for G and 55.7% for GD.

Conclusion: The doublet, as expected, resulted in more toxicity, particularly myelosuppression and fatigue. Survival associated with the GD treatment arm of this trial exceeds that of previously reported trials.

Key Words: Consolidation, Stage IIIA/B, NSCLC, Docetaxel, Gemcitabine.

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nonrandomized trial produced the best survival reported in stage III NSCLC: median survival of 27 months, a 29% 5-year survival, and a median progression-free survival (PFS) of 16 months. These results were especially favorable compared with SWOG 9019, in which the concurrent chemoradiation regimen was identical, but etoposide and cisplatin were used in lieu of docetaxel during the consolidation period.13

It was a natural step to investigate a modern doublet consolidation regimen in an attempt to improve on SWOG 9504. Preclinical data suggest that gemcitabine (G) and taxanes may act synergistically,14 as the agents have independent mechanisms of action, independent activity in lung cancer, and nonoverlapping toxicities. This randomized phase II study was developed to assess the feasibility and efficacy of consolidation with either single-agent G or combination GD after the same chemoradiation used in SWOG 9504.

PATIENTS AND METHODS

Eligibility Criteria

Patient eligibility was similar to SWOG 9504.12 Key differences from SWOG 9504 were the inclusion of unresectable stage IIIA and IIIB patients and exclusion of Eastern Cooperative Oncology Group performance status in two patients. Patients had histologic or cytologic proof of a single, primary bronchogenic NSCLC. Pathologic diagnosis from involved mediastinal or supraclavicular lymph nodes alone was accepted if a distinct primary lesion was evident on radiographs. Patients with ≥2 distinct parenchymal primary lesions were ineligible. Inoperable stage IIIA disease was determined by the presence of multiple or bulky N2 mediastinal lymph nodes. Stage IIIB disease was determined either by N3 involvement from pathologically documented contralateral mediastinal or by supraclavicular nodes not extending into the cervical region or by T4 invasion of mediastinal structures, including the heart, great vessels, trachea, carina, esophagus, or vertebral body. Patients who had a separate satellite nodule in the same lobe as the primary lesion (T4/Stage IIIB disease) were eligible if the nodule could be encapsulated within a tolerable radiation portal. Initial staging included brain imaging (either computed tomography [CT] or magnetic resonance imaging) and a bone scan. Patients with pleural effusions were eligible only if there was negative cytology or the effusion was inaccessible to thoracentesis. Patients with pericardial effusions or weight loss >10% within the previous 6 months were ineligible.

Patients were required to have measurable disease by chest x-ray or CT scan. Prior chemotherapy or RT for lung cancer was not permitted. Prior exploratory diagnostic surgery was permitted. Pulmonary function requirements included a forced expiratory volume in 1 second (FEV1) >1 liter by spirometry. Organ function requirements included an absolute neutrophil count (ANC) >1500, platelets >100,000, serum bilirubin <1.5 mg/dl, serum glutamic oxaloacetic transaminase (SGOT) <1.5 × institutional upper limits of normal (IULN), unless the abnormality was caused by documented benign disease. Patients with benign disease required a serum glutamic oxaloacetic transaminase <2.5 × IULN and alkaline phosphatase <2.5 × IULN. Patients were also required to have adequate organ and bone marrow function including an estimated creatinine clearance ≥50 milliliters/min (using the modified Cockcroft and Gault formula).15 Patients were required to be ≥18 years of age; patients who were breast feeding, pregnant, or who had serious concomitant disorders were ineligible. The institutional review board of each site approved the protocol before study initiation. This study was performed in compliance with the principles of good clinical practice, the Helsinki Declaration, and federal and institutional guidelines. All participating patients provided written informed consent before undergoing any study procedure or receiving any study therapy.

Study Design

Treatment consisted of concurrent chemoradiation followed by randomization to a consolidation phase of three cycles of G or GD. The concurrent chemoradiation component consisted of cisplatin 50 mg/m2 on days 1 and 8 and etoposide 50 mg/m2 on days 1 to 5 every 4 weeks for two cycles as on SWOG 9504. RT (62 Gy) was delivered over 7 weeks (2 Gy daily in 31 fractions) starting within 24 hours of the first day of chemotherapy. Heterogeneity dose corrections were not used. Weekly complete blood cell counts and chemistries were required during chemoradiotherapy. Specific dose modification criteria were provided for myelotoxicity and renal toxicity, using the National Cancer Institute Common Toxicity Criteria Version 2.0 guidelines.16

The target volume for RT was defined by CT scan, pathologic information, positron emission tomography scan (if available), and clinical evaluation. The treatment volume included the gross tumor and lymph nodes that were pathologically involved, metabolically active, or >1 cm on CT plus up to a 1.5 cm margin (to the block). RT dose was prescribed to a 3-dimensional conformal isodose line that adequately covered the treatment volume. Field orientation was selected to minimize the volume of irradiated lung outside the target volume, especially the contralateral lung.

Normal tissue tolerance criteria were provided as follows: the total lung volume exceeding V20 was ≤30%, mean esophageal dose was ≤34 Gy, maximum spinal cord dose was 48 Gy, and the whole heart was not to exceed 40 Gy (up to 50% of the cardiac silhouette could receive up to 60 Gy). RT did not include elective nodal coverage. RT interruptions were strongly discouraged but were allowed in the circumstances of grade 3 or 4 esophagitis or grade 4 neutropenia with fever.

Patients were restaged at week 10 using CT at a minimum. Patients with evidence of disease recurrence or progression (by RECIST)17 were removed from the study. Patients without evidence of disease progression or distant metastases were then randomized to the consolidation phase of the trial. Consolidation consisted of single-agent G 1000 mg/m2 on days 1 and 8 every 3 weeks for three cycles (G) or combination of G 1000 mg/m2 on days 1 and 8 plus D 75 mg/m2 on day 1 every 3 weeks for three cycles (GD). Before the start of each cycle, G or GD were administered only if ANC was ≥1.5 × 109/liter and platelets ≥100 × 109/liter. On day 8, if ANC was ≤1.0 × 109/liter or platelets were ≤75 × 109/liter, patients received 75% of the planned G...
dose. For ANC ≤0.5 × 10⁹/liter, G was withheld to allow for recovery to minimum acceptable counts. Consolidation dosing was reduced by 50% after any grade 3 nonhematologic event (except nausea, vomiting, or alopecia) and withheld to allow for recovery after a grade 4 event.

### Study Evaluation and Statistical Methods

The primary endpoint of this study was 2-year survival. Assuming 10% of patients would be lost to follow-up, the sample size goal of each treatment arm was 51 patients. This would provide 81% power to test whether the true 2-year survival rate was ≤30% (H₀), versus a true 2-year survival rate of 50% (H₁). Given the 2-year survival rate of 54% observed in SWOG 9504, either regimen would be considered promising if it achieved a 2-year survival of 50% or greater.

OS and PFS were measured from the date of registration to the date of death from any cause or the first date of documented progression. OS and PFS were censored at the date of the last follow-up visit for patients who were still alive or who had not progressed and were analyzed using Kaplan-Meier test. Two-sided 95% confidence intervals (CIs) for tumor response were calculated using exact binomial probabilities. Best tumor response was defined by RECIST criteria. Positron emission tomography was not required for response assessments. Tumor assessments occurred at baseline, at week 10 restaging, within 2 weeks of the last dose of consolidation chemotherapy, and continued at 3-month intervals for the first 2 years. Toxicity was summarized for the consolidation phase of treatment with the modified Medical Dictionary for Regulatory Activities.

### RESULTS

#### Patient Characteristics

Patient disposition is summarized in Figure 1. Between March 14, 2003, and December 31, 2006, 83 patients were entered at 13 sites in the United States, two in China, two in Argentina, and two in Korea. Of these, 82 received induction chemoradiation and 64 were randomized in the consolidation phase of the trial (32 to each treatment group). Baseline demographics of the intent-to-treat (ITT) and randomized populations from the study are summarized in Table 1. The characteristics of patients randomized to G and GD were similar.

TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Primary tumor location, n (%)</th>
<th>Induction Phase</th>
<th>Consolidation (Randomization) Phase</th>
</tr>
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<tbody>
<tr>
<td>Initial stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>23 (27.7)</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>IIIB</td>
<td>56 (67.5)</td>
<td>26 (81.3)</td>
</tr>
<tr>
<td>Unavailable</td>
<td>4 (4.8)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Primary tumor location, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left upper lobe</td>
<td>20 (24.1)</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>Left lower lobe</td>
<td>12 (14.5)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Left lingula</td>
<td>2 (2.4)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Right upper lobe</td>
<td>35 (42.2)</td>
<td>17 (53.1)</td>
</tr>
<tr>
<td>Right middle lobe</td>
<td>6 (7.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Right lower lobe</td>
<td>7 (8.4)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

ECOG, eastern cooperative oncology group; N, number of patients; n, number in group; PS, performance status.
therapy. Of those, eight discontinued because of PD, four because of patient decision, three because of an adverse event, and three because of death. Causes of death were pulmonary embolism, abdominal aortic aneurysm with complicated dissection, and pneumonia. Sixty-four patients (78.0%) proceeded to consolidation therapy, with 32 patients receiving G and 32 receiving GD. Twenty-nine patients (90.6%) received all three planned cycles of G, with two patients receiving one cycle and one patient receiving two cycles. Twenty-two patients (68.8%) received all three planned cycles of GD; two patients received one cycle and eight received two cycles.

Toxicity rates among the 64 patients receiving consolidation therapy are summarized in Table 2. One patient receiving GD died after withdrawal of mechanical ventilation related to radiation pneumonitis and respiratory failure. Grade 3 or 4 hematologic events, including neutropenia (56.3 vs. 28.1%, \( p = 0.03 \)), anemia (18.8% vs. 3.1%, \( p = 0.05 \)), and febrile neutropenia (6.3% vs. 0.0%) were more frequent in the GD arm compared with the G arm. Grade 3 or 4 and febrile neutropenia (6.3% vs. 0.0%) were more frequent in the GD arm compared with the G arm. Grade 3 or 4 febrile neutropenia (6.3% vs. 0.0%) were more frequent in the GD arm compared with the G arm.

Response

Best tumor response to induction therapy is summarized in Table 3. Among all patients, there was 1 CR and 48 PRs, for a response rate of 59.0%. The response rate to induction therapy was slightly greater among patients randomized to the GD treatment group compared with G (68.8% vs. 59.4%). After randomization to consolidation therapy, one patient in the G treatment group and three patients in the GD treatment group achieved previously undocumented CRs, and four patients in the G treatment group and one patient in the GD treatment group achieved previously undocumented PRs. Counting both induction and consolidation phases of the trial, the response rates were 75.0% in the G treatment group (95% CI: 56.6–88.5) and 81.3% in the GD treatment group (95% CI: 63.6–92.8).

### Progression-Free Survival and OS Analysis

Figure 2A summarizes OS for all patients registered in the study. Among the ITT population (including patients who did not proceed to consolidation), median survival from registration was 20.8 months (95% CI: 16.4–33.8, censorship = 35%). One-year survival for the ITT population was 66.7% (95% CI: 57.3–74.5), 2-year survival was 46.7% (95% CI: 35.6–57.1), and 3-year survival was 37.3% (95% CI: 26.3–48.2).

Median follow-up time from randomization was 41.5 months (range: 23.7–67.5) for patients in the G treatment group and 41.3 months (range: 15.5–55.7) in the GD treatment group. At the time of this analysis, 27 patients in the G treatment group (84.4%) and 26 patients in the GD treatment group (81.3%) had experienced disease progression. Figure 2B summarizes PFS for both treatment arms. Median PFS from randomization was 5.4 months in the G treatment group (95% CI: 2.7–7.9) and 13.4 months in the GD treatment group (95% CI: 4.6–23.3).

At the time of this analysis, 20 patients in the G treatment group (62.5%) and 18 patients in the GD treatment group (56.3%) had died. Figure 2C summarizes OS for both treatment groups. Median OS from randomization was 16.1 months in the G treatment group (95% CI: 9.8–34.0) and 29.5 months in the GD treatment group (95% CI: 16.4–52.0). Estimated survival rates from randomization were 65.6% at 1 year (95% CI: 46.9–79.3), 40.6% at 2 years (95% CI: 23.8–56.8), and 30.5% at 3 years (95% CI: 14.2–48.5) for G; and 71.9% at 1 year (95% CI: 52.9–84.3), 55.7% at 2 years (95% CI: 36.8–70.9), and 39.8% at 3 years (95% CI: 22.1–56.9) for GD.

### DISCUSSION

The development of newer chemotherapeutic agents with activity in NSCLC provides the opportunity to explore novel approaches in the treatment of stage IIIIB disease. This study indicates that both G and GD after chemoradiation in locally advanced NSCLC are well tolerated. Consolidation with the doublet, as expected, resulted in more toxicity,

### TABLE 2. Summary of Toxicity

<table>
<thead>
<tr>
<th>Toxicity, n (%)</th>
<th>Gemcitabine (N = 32)</th>
<th>Gemcitabine and Docetaxel (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (3.1)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (15.6)</td>
<td>7 (21.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (12.5)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (3.1)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (3.1)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Radiation pneumonitis*</td>
<td>0 (0.0)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0 (0.0)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1 (3.1)</td>
<td>—</td>
</tr>
</tbody>
</table>

* One patient in the gemcitabine and docetaxel group (3.1%) experienced grade 5 radiation pneumonitis.

N, number of patients; n, number in group.
particularly myelosuppression and fatigue. Consistent with the relative tolerability of each treatment arm, a greater percentage of patients in the single-agent arm received all three planned cycles of consolidation therapy.

The relative tolerability of the treatment arms, however, must be balanced against efficacy. Despite higher toxicity in the GD arm and the greater delivery of the planned three cycles of consolidation in the G arm, survival analysis suggests that doublet chemotherapy is preferred. The possibility that some of the survival difference between arms may have been related to imbalances of stage cannot be ruled out. At the same time, in the chemoradiation setting, stage (IIIA vs. 

### TABLE 3. Summary of Response Rates

<table>
<thead>
<tr>
<th></th>
<th>To Induction Therapy</th>
<th>To Induction and Consolidation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients (N = 83)</td>
<td>Gemcitabine (N = 32)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (1.2)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Partial response</td>
<td>48 (57.8)</td>
<td>18 (56.3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>19 (22.9)</td>
<td>13 (40.6)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8 (9.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (8.4)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%).

### FIGURE 2.

A. Overall survival for the intent-to-treat population (N = 83), measured from registration. B. Progression-free survival for the consolidation population (N = 64), measured from randomization. C. Overall survival for the consolidation population (N = 64), measured from randomization.
IIIB) is typically not a significant predictor of survival. For example, in the Hoosier Oncology Group (HOG) phase III study analysis, IIIA versus IIIB status was not predictive of outcome on either univariate or multivariate analysis.

Table 4 summarizes key studies in stage III NSCLC including this study. Unlike the S9504 trial, which exclusively enrolled stage IIIB patients, 27.7% of patients in this trial were stage IIIA. Median age (59.0) and gender distribution (79.5% male) were similar to studies S9504 and S9019. In this trial and across others, including S9504, approximately 75% of patients receiving chemoradiation were able to proceed to consolidation therapy. Given the heterogeneity of locally advanced disease and the preliminary nature of the results of this study, efficacy comparisons should be made with caution. Despite these limitations, the median survival of 21 months for all patients in this trial (including those who did not proceed to consolidation) was similar to that for all patients in SWOG 0023 (19 months) and HOG 01-24 (21 months), but less than that reported in SWOG 9504 (26 months).

Table 4: Comparison of Results with Similar Trials

<table>
<thead>
<tr>
<th>N</th>
<th>Percentage Proceeding to Consolidation</th>
<th>MS for All Patients (mo)</th>
<th>Consolidation Treatment</th>
<th>Grade 3 or 4 FN During Consolidation</th>
<th>2-yr Survival %</th>
<th>3-yr Survival %</th>
<th>MS by Arm (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 9504</td>
<td>83</td>
<td>78</td>
<td>26</td>
<td>Docetaxel</td>
<td>9%</td>
<td>54</td>
<td>—</td>
</tr>
<tr>
<td>SWOG 0023</td>
<td>571</td>
<td>75.1</td>
<td>19</td>
<td>Docetaxel</td>
<td>5%</td>
<td>42</td>
<td>NR</td>
</tr>
<tr>
<td>HOG 01-24</td>
<td>203</td>
<td>72.4</td>
<td>21</td>
<td>Docetaxel</td>
<td>11%</td>
<td>Between 45–50</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Observation</td>
<td>0%</td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>Current trial</td>
<td>83</td>
<td>77.1</td>
<td>21</td>
<td>Gemcitabine/docetaxel</td>
<td>6%</td>
<td>59</td>
<td>44</td>
</tr>
</tbody>
</table>

This reflects the % of patients receiving chemoradiation who proceeded to the consolidation phase of the trial. All patients in HOG 01-24 who were randomized, including those receiving standard observation, were included in this figure.

Survival in the table is measured from patient registration.

FN, febrile neutropenia; HOG, hoosier oncology group; MS, median survival; NR, not reported; SWOG, southwest oncology group.

As noted by Govindan et al., it seems peculiar that the guidelines suggest four cycles of chemotherapy for stage IV patients but two cycles for stage III patients. To obtain an optimal systemic effect, one would advocate in favor of four or more cycles, as long as there were no untoward delays in initiating RT. Moreover, the combination of two systemic agents together is considered a standard approach concurrent with thoracic RT in stage III disease and as primary therapy in stage IV disease. It makes sense then that two systemic agents together are likely to be more efficacious than single agents in the setting of consolidation therapy after chemoradiation.

This study was terminated before reaching the full sample size of 51 patients per arm of consolidation because of slow accrual. During the duration of the study, an average of 1.4 patients per month received consolidation therapy. At that rate, the study would have required an additional 26 months of accrual to reach the full sample size. This study was not designed to formally test differences between the two treatment arms. However, it is possible that the results associated with the G arm were related to unfavorable patient characteristics at baseline and relatively low accrual numbers.
An ongoing multicenter, randomized phase III trial (NCT00686959) may help to better define the role of consolidation in the locally advanced setting. This trial is expected to randomize approximately 600 patients with nonsquamous histology to receive consolidation with pemetrexed after chemoradiation with pemetrexed plus cisplatin (arm A) or consolidation with any other cytotoxic chemotherapy of individual physician choice after chemoradiation with etoposide plus cisplatin (arm B). Including a unique agent such as pemetrexed that has already demonstrated a potential advantage in PFS in the maintenance setting in stage IV disease is an attractive prospect. However, the impact of this ongoing trial will be limited to defining the role of pemetrexed in patients with nonsquamous histology for locally advanced nonmetastatic disease and its feasibility with concurrent RT. The issue of consolidation chemotherapy in this setting remains still open. Data from this study incorporating D and G indicate that consolidation therapy, as an investigational concept, should be pursued.

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