Cisplatin (Cis) + etoposide (VP16) vs. cis + irinotecan (CPT11) in extensive stage small cell lung cancer (E-SCLC): Updated pharmacogenomic (SWOG 0124) and comparative toxicity analysis (JCOG 9511 & SWOG 0124)

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Introduction: S0124 is a recently completed North American phase III trial designed to confirm the results of J9511 which previously showed a significant survival benefit for Cis/CPT11 over Cis/VP16 in Japanese patients (pts). S0124 employed the same J9511 treatment protocol. One hypothesis is that toxicities would differ between North American & Japanese pts due partly to differences in the proportion of genetic polymorphisms involved in chemotherapy metabolism in these populations.

Methods: Patient level toxicity data were compared among 706 pts enrolled in J9511 & S0124 receiving common treatment using a logistic model adjusted for age, sex, and performance status (PS). Select polymorphisms of the UGT1A1, ABCB1, OATP, & GSTP1 genes in genomic DNA were evaluated in 142 pts in S0124 (67 Cis/CPT1 & 75 Cis/VP16). Associations between toxicity & genotype within each arm were assessed using logistic regression.

Results: Pt demographics for J9511 & S0124, respectively: Mean age - 61 & 62 years; Male sex - 131 (86%) & 315 (57%); PS 0 - 19 (13%) & 173 (31%); PS>0 - 133 (87%) & 372 (68%). Comparative hematologic toxicities (> grade 3) are summarized below.

<table>
<thead>
<tr>
<th></th>
<th>Cis/CPT11 (n=75)</th>
<th>Cis/VP16 (n=278)</th>
<th>J9511 (n=77)</th>
<th>S0124 (n=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>49 (65%)**</td>
<td>88 (32%)</td>
<td>71 (92%)*</td>
<td>182 (66%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>20 (27%)**</td>
<td>48 (17%)</td>
<td>41 (53%)**</td>
<td>92 (33%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>21 (28%)**</td>
<td>16 (6%)</td>
<td>25 (32%)**</td>
<td>36 (13%)</td>
</tr>
<tr>
<td>Platelets</td>
<td>4 (5%)</td>
<td>10 (4%)</td>
<td>14 (18%)</td>
<td>42 (15%)</td>
</tr>
</tbody>
</table>

*P<0.0001
**P<0.01
***P=0.02

There were no significant differences in grade 3+ non-hematologic toxicities between studies. Polymorphism frequencies in S0124 pts: ABCB1*1236 (C/C 39%; T/C 61%; T/T 0%); *3435 (C/C 31%; C/T 46%; T/T 24%); 2627 (G/G 57%; T/G 43%; T/T 0%); UGT1A1*28 (6/6 38%; 6/7 59%; 7/7 4%); *3156 (A/A 10%; A/G 49%; G/G 41%); OATP-C*521 (m/m 2%, w/m 36%, w/w 61%); ABCBq3*3435 T/T was associated with an increased risk of CPT11 grade 3+ diarrhea (p=0.04) vs. C/C and C/T. UGT1A1*3156 A/A was associated with increased risk of CPT11 neutropenia (p=0.009) & leukopenia (p=0.05). No gene tested was associated with VP16 toxicity.

Conclusions: Significant differences in treatment-related myelosuppression exist between J9511 and S0124 pt populations. Certain polymorphisms in genes involved in CPT11 metabolism are significantly associated with CPT11 toxicities in S0124 pts. These results support the hypothesis that toxicities may be associated with distribution of genetic polymorphisms. Updated outcomes data from S0124 will be presented.

D1-05
Irinotecan, carboplatin, and bevacizumab in untreated extensive-stage small-cell lung cancer

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Background: Bevacizumab’s role in the treatment of small-cell lung cancer is unknown. A multicenter phase II trial with bevacizumab and chemotherapy was conducted in patients with untreated extensive-stage small-cell lung cancer.

Methods: The primary objective of this trial was to improve the historical median time to progression (TTP) of 6 months by 40%. Eligibility criteria included: no prior chemotherapy for small-cell lung cancer, no active brain metastases, normal organ function, no hemoptysis, ECOC PS 0-1, measurable disease, and signed informed consent. Treatment consisted of: irinotecan 60mg/m² IV days 1, 8, 15, carboplatin AUC=4 IV day 1, and bevacizumab 10 mg/kg IV days 1 and 15 every 28 days. Restaging studies were performed every 2 cycles (8 weeks). If there was no evidence of progressive disease after 4-6 cycles of combination therapy, patients went on to receive maintenance bevacizumab for 6 months.

Results: 44 pts have been enrolled from 2/06 to 3/07 (n=50 planned), with a median follow-up of 9 months. Baseline features included: median age 66 years (range 46-81); male/female, 57%/43%; 3 patients (7%) with previously treated brain metastases; 89% current or former smokers; and ECOC PS 0/1, 32%/68%. The objective response rate was 72% (95% CI 55%-85%), including 2 complete responses and 21 partial responses. 7 patients (22%) had stable disease and 2 patients had progressive disease at restaging. 12 patients were not evaluable due to: comorbidity (off study), 2 patients; being too early for restaging, 10 patients. TTP and overall survival data are not mature at the time of this analysis. Grade 3/4 toxicity has been limited: diarrhea (26%), fatigue (13%), and neutropenia (13%). There has been no significant bleeding to date.

Conclusions: Bevacizumab can be safely added to carboplatin and irinotecan in the first-line treatment of extensive-stage small-cell lung cancer. Analysis of TTP will soon be mature to better estimate bevacizumab’s role in this setting. Ultimately, randomized trials will best assess bevacizumab’s efficacy in small-cell lung cancer treatment.