The objective of this systematic literature review (SLR) was to explore the clinical efficacy and/or safety of 2LT with antiangiogenic therapy (ramucirumab or bevacizumab) and/or immunotherapy (nivolumab, or pembrolizumab), or chemotherapy (docetaxel, gemcitabine, nab-paclitaxel, paclitaxel, pemetrexed, or vinorelbine) in patients with advanced NSCLC who have characteristics associated with aggressive disease (AD).

Recent randomized clinical trials (RCTs) have explored survival benefits of second-line (2LT) therapy in patients with PD/NE/unknown best response to prior chemotherapy, Adenocarcinoma and PD best response to 1LT/refractory to 1LT, and Asian patients with PD/NE best response to most recent chemotherapy. Predefined subgroup analyses using an exploratory subgroup methodology have been conducted in these trials.

Meta-analyses were searched for studies of interest. The primary outcome was overall survival (OS). The number of number of evaluable patients, censoring, and follow-up varied among studies. Owing to the high level of heterogeneity and wide variances in the meta-analyses, a meta-analysis was not conducted. The results of a meta-analysis cannot be used to make firm conclusions about efficacy, and safety outcomes of 2LT. However, specific characterization of aggressive NSCLC is lacking, and there are important considerations for how best to define these patients. Aggressive Subgroup

<table>
<thead>
<tr>
<th>Aggressive Subgroup</th>
<th>OS</th>
<th>PFS</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma and PD best response to previous chemotherapy</td>
<td>6 months</td>
<td>6 months</td>
<td>25%</td>
</tr>
<tr>
<td>Adenocarcinoma and &lt; 9 months since start of 1LT</td>
<td>6 months</td>
<td>6 months</td>
<td>25%</td>
</tr>
<tr>
<td>Nonsquamous and &lt; 9 months since start of 1LT</td>
<td>6 months</td>
<td>6 months</td>
<td>25%</td>
</tr>
<tr>
<td>Asian patients with PD/NE as best response to most recent chemotherapy</td>
<td>6 months</td>
<td>6 months</td>
<td>25%</td>
</tr>
<tr>
<td>PD/NE/unknown best response to prior chemotherapy</td>
<td>6 months</td>
<td>6 months</td>
<td>25%</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Definitions of AD differ, both across the identified studies of AD and within the predefined categorization, with most defining the third tumor dimension. The best evidence to date suggests that survival benefit from 2LT treatment. Moreover, only a few reported 2LT outcomes data for the same AD subgroups. Future studies should focus on improvement of AD characterization.

With the emerging clinical impact of AD, more standardization of these definitions within RCTs may enter to greater comparison across ADs and self-reported baseline dimensional characteristics of the subgroups.

Address any subgroup data as planned versus post hoc analysis is important for interpretation and should be specified in the study design.

Downloaded and sent to you by: K. Washburn, Global Patient Outcomes Senior Research Scientist, Global Patient Outcomes

References:

1. Takeda et al. (2016)
2. Schuette et al. (2014)
3. TAILOR1
4. LUME-Lung 1
5. ISEL
6. LUME-Lung

Table 1. Subgroup Definitions by Study and AD Characteristic Categorization

| Study | Interventions Investigated | Refractory/Adenosquamous | Refractory/Adenosquamous | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractory/Pemetrexed | Refractor...