melanoma and other skin tumours

SURVIVAL, RESPONSE DURATION, AND ACTIVITY BY BRAF MUTATION (MT) STATUS IN A PHASE 1 TRIAL OF NIVOLUMAB (ANTI-PD-1, BMS-936558, ONO-4538) AND IPILIMUMAB (IPI) CONCURRENT THERAPY IN ADVANCED MELANOMA (MEL)

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Aim: In a phase 1 trial, concurrent therapy with nivolumab (N) + IPI (N + I) led to an objective response rate (ORR) of 40% and evidence of clinical activity in a further 25% of patients (pts). Tumor regression was generally rapid, with >80% reduction in tumor measurements in 31% of pts. We report updated survival, efficacy and clinical activity by BRAF MT status across all pt cohorts.

Methods: MEL pts (≤3 prior therapies) received concurrent N + I IV Q3W × 4 doses (Table; n = 53) followed by N Q3W × 4 doses. At wk 24, pts without progression by immune-related criteria (iRC) and no dose limiting toxicities could continue N + I Q12W × 8 doses. An additional 41 pts (cohort 8, last pt enrolled Nov 2013) were treated with N + I 1 + 3 mg/kg Q3W × 4 doses, followed by N 3 mg/kg Q2W (selected regimen for phase 2/3 trials). Tumor responses were evaluated by WHO and iRC.

Results: Of the total 94 pts, 53% were stage M1c; 45% had prior systemic therapy. In the initially enrolled cohorts, ORR was 42% (22/53); median duration of response (DOR) not reached (NR); 9/53 (17%) demonstrated confirmed complete response. Fourteen of 22 pts (64%) with an OR had DOR ≥24 wks (range 24.7 + , 105.7+). Clinical activity was similar irrespective of BRAF MT status. Tumor reduction of ≥80% by wk 36 was observed in 22/53 pts (42%). One- and 2-yr OS rates were 85% and 79%, respectively. In cohort 8, ORR was 43% (17/40). For aggregate safety across cohorts, grade 3–4 treatment-related AEs occurred in 58/94 pts (62%); most common: increased lipase (15%), ALT (12%) and AST (11%).

Conclusions: Concurrent N + I demonstrated encouraging survival and a manageable safety profile using standard safety algorithms in advanced MEL pts. Responses were observed regardless of BRAF MT status and were durable in many pts. The preliminary analysis of cohort 8 confirms the activity of N + I observed in the initially enrolled concurrent cohorts.

Table: 1085O

<table>
<thead>
<tr>
<th>Nivolumab (mg/kg) + IPI (mg/kg)</th>
<th>1-yr OS rate, %</th>
<th>Median OS, mo</th>
<th>ACAR, %</th>
<th>ACAR by BRAF MT status,* %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initially enrolled concurrent cohorts</td>
<td>85 (44)</td>
<td>39.7</td>
<td>70</td>
<td>60 (10)</td>
</tr>
<tr>
<td>0.3 + 3 [14]</td>
<td>57 [8]</td>
<td>27.2</td>
<td>57</td>
<td>50 (4)</td>
</tr>
<tr>
<td>1 + 3 [18]</td>
<td>94 [13]</td>
<td>NR</td>
<td>65</td>
<td>50 (2)</td>
</tr>
<tr>
<td>3 + 1 [16]</td>
<td>94 [15]</td>
<td>NR</td>
<td>81</td>
<td>67 (3)</td>
</tr>
<tr>
<td>Cohort 8 [41]</td>
<td>Insufficient</td>
<td>NR</td>
<td>48</td>
<td>58 (7)</td>
</tr>
</tbody>
</table>


*Retrospective analysis.

Disclosure: M. Sznol: Paid consultant and scientific advisory board-Bristol-Myers Squibb, Genentech/Roche, MedImmune, Amgen, Nektar, Symphogen, Merus, Amphivena, NeoStem, Anarenopharma, BerGene, Kyowa-Kirin, Immune Design, Lion Biotechnologies, Seattle Genetics; M. Postow: BMS-consultant advisor, research funding; R. Gordon: BMS remuneration; N.H. Segal: Ad Board-MedImmune, Alkermes Scientific, Imugene; Research Funding BMS, MedImmune, Pfizer; N. Rizvi: Consultant Advisor-BMS; Honoraria-BMS, MedImmune, Genentech/Roche; A. Lesokhin: Consultant/advisor to BMS; Research Funding BMS; M.B. Atkins: Consultant advisor, honoraria-BMS; J. Kirkwood: Consultant advisor-BMS, Merck, GSK, Celgene, Vical, Zopharm; Research Funding Prometheus; W. Feely: BMS-employee, stock; Q. Hong: BMS-employee, stock; S. Krishnan: BMS-employee, stock; J. Wolchok: Consultant/advisor to BMS; Research Funding BMS. All other authors have declared no conflicts of interest.

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