Pseudoprogression (PsP) Patterns: Analysis from 2 Independent Phase-2 Studies with Immunotherapy for Recurrent Cervical Cancer

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Background
Pseudoprogression evaluation is from 2 Ph2 studies balstilimab (BAL; anti-PD-1) alone and in combination with zalifrelimab (ZAL; anti-CTLA-4) in Recurrent/Metastatic (RM) Cervical Cancer (CC). Trials NCT03104699 and NCT02495882 as presented at ESMO 2020.

• Pseudoprogression (PsP) may appear in cancer immunotherapy
• Underlying pathogenesis widely unknown and inflammation is the suspected mechanism

Definition
Radiological disease progression as per RECIST 1.1, followed by a significant shrinkage of the measurable lesions OR disappearance of the non-measurable ones OR no further progression for at least two tumor assessments after initial progressive disease (PD).

Challenges of Pseudoprogression
1. Misdiagnosis of PsP as progressive disease leads to discontinuation of potentially beneficial and well tolerated treatment
2. Clinical improvement in setting of radiologic progression
3. Difficulties in diagnosing PsP
  a. Various presentation of PsP
  b. Absence of validated biochemical or clinical marker to support radiological assessment

Method
The analysis performed on cases of 303 evaluable cervical cancer patients who received either BAL 3mg/kg every 2 weeks alone (160 pts) or in combination with ZAL dosed at 1mg/kg every 6 weeks (143 pts).

PsP was divided into 3 categories:
• Early (before or at week 12 of treatment)
• Delayed (after week 12)
• Serial (at least 2 PsP occurrences)

Results

<table>
<thead>
<tr>
<th>PsP</th>
<th>BAL (N=160)</th>
<th>BAL/ZAL (N=143)</th>
<th>PsP location</th>
<th>Target lesion</th>
<th>Non-target lesion</th>
<th>Total lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>7 (8%)</td>
<td>9 (6%)</td>
<td>Nodal</td>
<td>7</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Delayed</td>
<td>1 (1%)</td>
<td>4 (3%)</td>
<td>Extra-nodal</td>
<td>7</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Serial</td>
<td>9 (11%)</td>
<td>1 (1%)</td>
<td>Total</td>
<td>13</td>
<td>10</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 1: PsP observations in cervical cancer patients treated with either BAL alone or in combination with BAL/ZAL.

• Early PsP was observed in 41.8% of patients treated with BAL (N=160) vs 4.9% (N=143).
• Delayed PsP was observed in 1.3% patients experienced delayed PsP (BAL (N=160) vs N=143).
• Serial PsP was observed in 1 patient (BAL).

• In many cases, PsPs were accompanied with clear clinical stabilization/improvements
• 27 nodal involvement seen predominantly in PsP pts (medastinal, lung and thoracic) (tab-2)
• 20 extra nodal lesions were mainly seen in lung, liver, chest, cervix and colon (tab-2)
• Collectively, 21 pts demonstrated PsP with 47 total lesions

Table 2: Pseudoprogression location.

Case study
Case study 55-year-old woman diagnosed with FIGO IVB adenocarcinoma of cervix. BAL was administered after progression on chemotherapy.

• First treatment CT evaluation new metastatic nodes seen (Fig 3)
• Symptomatic symptomatically stable on subsequent scans
• Stable character of nodules with no compressing nature of any adjacent structures
• Complete biopsy showed epithelial and granulomatous granulomas without necrosis, and granuloma.
• Stable per RECIST for additional 42 wks prior to PD
• After radiological was disseminated, surgical resection requested (Fig 4)

PsP: Symptomatic adenopathy seen on first CT evaluation

End of Treatment (Resolution of clinical, symptom progression)
3 months after end of treatment

Fig 4: Sarcoid nodules disappeared post surgical resection.

Discussion and Conclusions
Underlying mechanism of Pseudoprogression may include tumor flare and immune related AEs crucial for treatment optimization

Decision about treatment discontinuation should be supported by both clinical and radiological findings

• This is the first report of PsP in CC population
• PsP has various patterns that could be seen
• PsP can confound radiological evaluation
• Seen in 21/303 (6.9%) recurrent/metastatic CC pts treated with BAL or combination of BAL and ZAL had evidence of PsP

The differentiation of PD and PsP has important consequences
• Significant clinical care and regulatory implications