Poster # 267

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 (R/M) Cervical Cancer (CC). Trials NCT03104699 and NCT03495882 as presented at ESMO 2020[4]

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

Definition

Radiological disease progression as per RECIST1.1, followed by a significant shrinkage of the measurable lesions OR disappearance of the non-measurable ones[5] OR no further progression for at least two tumor assessments after initial progressive disease (PD) [1]

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) [4]
PsP was divided into 3 categories:

- Early (before or at week 12 of treatment) [2]
- Delayed (after week 12) [2]
- Serial (at least 2 PsP occurrences)[3]

Results

PsP	BAL (N=160)	BAL/ZAL (N=143)
Early	7 (4%)	8 (6%)
Delayed	1 (<1%)	4 (3%)
Serial	1 (<1%)	-
Total	9 (6.3%)	12 (8.3%)

Table 1: PsP observed in cervical cancer patients treated with either BAL (n=160) or in combination with ZAL (n=143)

PsP location	Target lesion	Nontarget lesion	New lesion	Total
Nodal	7	10	10	27
Extra-nodal	7	8	6	20
Total	**13**	**18**	**16**	**47**

Table 2. Pseudoprogression location
Only 13/47 (27%) PsP locations were within target lesions.

- Early PsP was observed in 7(4%) patients treated with BAL and 8(6%) with BAL/ZAL
- 5(4%) patients experienced delayed PsP (BAL (n=1); ZAL(n=4)).
- 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 (mediastinal, 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

References

1. *Rizvi NA et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol 2015*
2. *Ma et al. How to differentiate pseudoprogression from true progression in cancer patients treated with immunotherapy Am J Cancer Res. 2019; 9(8): 1546–1553*
3. *Ozaki et al. Serial pseudoprogression of metastatic malignant melanoma in a patient treated with nivolumab: a case report BMC Cancer (2017) 17:778*
4. *Annals of Oncology (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325*
5. *Park et.al, Incidence of Pseudoprogression during Immune Checkpoint Inhibitor Therapy for Solid Tumors: A Systematic Review and Meta-Analysis, Radiology 2020*

Examples of Pseudoprogression

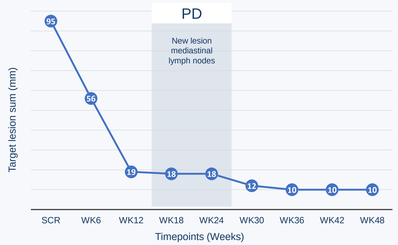

Figure 1: Delayed PsP example
Sum of target lesions reduced from 95mm at screening to 19mm at Wk12. New lesions appeared from Wk18 to Wk24 and disappeared from Wk30 onwards

Visit	TL (mm)	NTL	NL	Responses
Scr	**95** (2 lung, 2 mediastinal LNs)	**Present** (Lumbar Vertebra, Mediastinal LN, Lung)	NA	NA
Wk6	56	NCRNPD	No	PR
Wk12	19	NCRNPD	No	PR
Wk18	18	NCRNPD	Yes Mediastinal LN	PD
Wk24	18	NCRNPD	Yes Mediastinal LN	PD
Wk30	12	NCRNPD	No	PR
Wk36	10	NCRNPD	No	PR
Wk42	10	NCRNPD	No	PR
Wk48	10	NCRNPD	No	PR
Best Overall Response				**PR**

Table 3: Imaging assessments for delayed PsP example
Tp- Timepoints, TL-Target Lesion, NTL-Nontarget Lesion, NL-New Lesion, PD-Progressive Disease, PR-Partial Response, NCRNPD-NonCompleteResponseNonProgressive disease, LN-Lymphnodes , Scr-Screening, Wk-Week, NA-Not Applicable

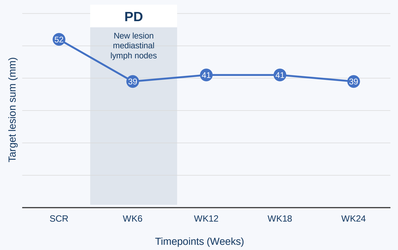

Figure 2: Early PsP example
Sum of target lesions reduced from 52mm at screening to 39mm at Wk6. New lesions appeared from Wk6 to Wk12 and disappeared from Wk18 onwards

visit	TL(mm)	NTL	NL	Responses
Scr	**52** (Paraaortic Lymph Node, Paraaortic Lymph Node, Lung)	**Present** (Lumbar Vertebra, Mediastinal LN, Lung)	NA	NA
Wk6	41	NCRNPD	Yes Mediastinal LN	PD
Wk12	39	NCRNPD	Yes Mediastinal LN	PD
Wk18	41	CR	No	SD
Wk24	39	CR	No	SD
Best Overall Response				**PD**

Table 4: Imaging assessments for early PsP example

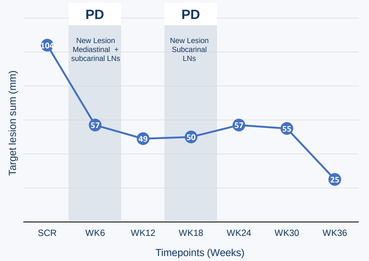

Figure 3: Serial PsP example
Sum of target lesions reduced from 104mm at screening to 57mm at Wk6. New lesions appeared at wWk6 and at Wk18 and disappeared from Wk24 onwards.

visit	TL(mm)	NTL	NL	Responses
Scr	**104** (liver, liver, peritoneal)	**Present** (Retroperitoneal LN and Peritoneal)	NA	NA
Wk6	57	NCRNPD	Mediastinal and subcarinal LNs	PD
Wk12	49	NCRNPD	No	PR
Wk18	50	NCRNPD	subcarinal LNs	PD
Wk24	57	CR	No	PR
Wk30	55	CR	No	PR
Wk36	25	CR	No	PR
Best Overall Response				PD

Table 5: Imaging assessments for serial PsP example

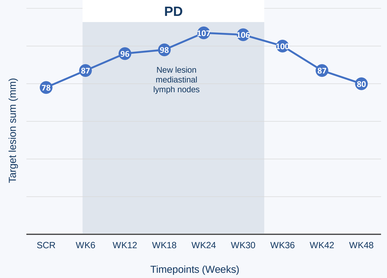

Figure 4: Early PsP with delayed response
Sum of target lesions increased from 78mm at screening to 96mm at Wk21. Disease progression evident until Wk30 and pt showed delayed response after then.

visit	TL(mm)	NTL	NL	Responses
Scr	**78** (Pelvis, paraaortic LN, Thoracic LN)	**Present** (Paraaortic, thoracic and Inguinal LN)	NA	NA
Wk6	87	NCRNPD	No	SD
Wk12	96	PD	No	PD
Wk18	98	PD	No	PD
Wk24	107	PD	No	PD
Wk30	106	PD	No	PD
Wk36	100	PD	No	PD
Wk42	87	NCRNPD	No	PD
Wk48	80	NCRNPD	No	SD
Best Overall Response				PD

Table 6: Imaging assessments for serial PsP example

Case study

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

- First on-treatment CT evaluation new mediastinal nodules seen (fig 5)
- Symmetrical adenopathy appeared stable on subsequent scans
- Stable character of nodes with no compressing nature of any adjacent structures
- Confirmatory biopsy showed epithelial and gigantocellular granulomas without necrosis and tumor cells
- Stable per RECIST for additional 42 wks prior to PD
- After balstilimab was discontinued, sarcoid nodules regressed (fig 6)

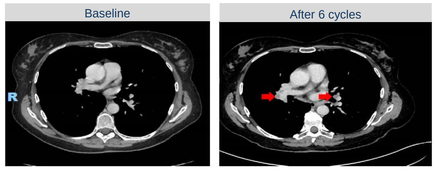

Fig-5: Symmetrical adenopathy seen on first CT evaluation

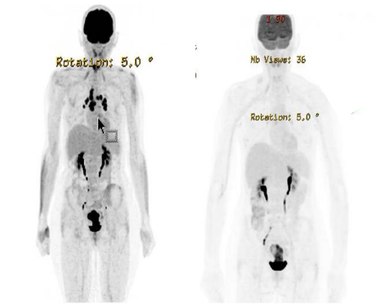

Fig 6: Sarcoid nodules disappeared post balstilimab discontinuation

Discussion and Conclusions

Underlying mechanism of Pseudoprogression may include tumor flare and immune related AEs mimic PD
Further efforts to elucidate the underlying mechanisms to clearly define characteristics of PsP are crucial for treatment optimization
Decision about treatment discontinuation should be supported by both- clinical and radiologic findings

- This is the first report of PsP in CC population
  - *PsP has various patterns that needs to be recognized*
- PsP- confounded 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*