Prevalence and clinical impact of PTEN status in patients with *de novo* metastatic hormone sensitive prostate cancer (mHSPC).

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BACKGROUND

- Genomic aberrations of the PTEN tumor suppressor gene are among the most common in prostate cancer[1].
- PTEN loss and subsequent activation of the PI3K/AKT/mTOR pathway has potential clinical and therapeutic value[2].
- To date, the prevalence and clinical significance of PTEN alterations in mHSPC patients are not well characterized.

References:
1. Lee Y-R et al. Nat Rev Mol Cell Biol 2018
2. Jamaspishvili, T, *et al. Nat Rev Urol 2018*

OBJECTIVES

To evaluate the prevalence of PTEN in *de novo* mHSPC patients.

To investigate the clinical outcomes and benefit from standard therapies in *de novo* mHSPC patients based on PTEN status.

METHODS

- A retrospective cohort of *de novo* mHSPC patients with available PTEN expression of tumor specimens was identified across two centers in Europe.
- PTEN expression was assessed by immunoreactivity (IHC) in primary tumor biopsy and loss was defined as absence or weak intensity staining in > 10% cells.
- Patients were not selected on the basis of clinical factors and treatment were given to each center's standard of care.
- Association of PTEN loss on time to castration resistant prostate cancer (TTCRPC) and overall survival (OS) from start of androgen deprivation therapy (ADT) for mHSPC were assessed.

RESULTS

BASELINE CHARACTERISTICS AND TREATMENT EXPOSURE (N=56)

Variable, n (%)	PTEN expression N = 34	PTEN loss N = 22
Median age at diagnosis, years (range)	69 (51-87)	69 (53-85)
Sites of metastatic disease[1]		
- Bone	26 (76%)	18 (82%)
- Lymph nodes	3 (9%)	3 (14%)
- Visceral	5 (15%)	5 (23%)
Volume disease[2]		
- Low volume	6 (18%)	4 (18%)
- High volume	28 (82%)	18 (82%)
Gleason score		
- 6-7	5 (15%)	2 (9%)
- 8	9 (26%)	7 (32%)
- 9	17 (50%)	8 (36%)
- 10	2 (6%)	3 (14%)
- NA[3]	1 (3%)	2 (9%)
Median PSA, ng/mL (range)	48 (7.6-2170)	45 (1.2-1340)
Systemic therapies in mHSPC		
- ADT alone	12 (35%)	4 (18%)
- ADT + docetaxel	14 (41%)	12 (55%)
- ADT + ARTA	5 (15%)	4 (18%)
- ADT + docetaxel + ARTA	3 (9%)	2 (9%)
Local treatment		
- None	25 (73%)	18 (82%)
- Radiotherapy	3 (9%)	2 (9%)
- Surgery	6 (18%)	2 (9%)
Bone targeted therapy[4]		
- None	8 (24%)	4 (18%)
- Yes	26 (76%)	18 (82%)

[1]Can be more than one site; [2]High-volume: visceral metastases and/or ≥ four bone metastases with at least one outside of the vertebral column and pelvis; [3]Not available; [4]Either zoledronic acid or denosumab

PREVALENCE OF PTEN loss

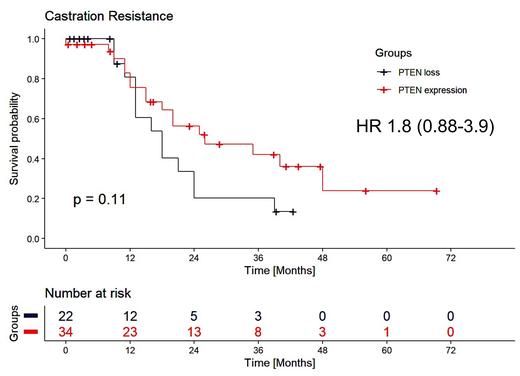
22/56 (39%)

TIME TO EVENT ANALYSES by PTEN STATUS

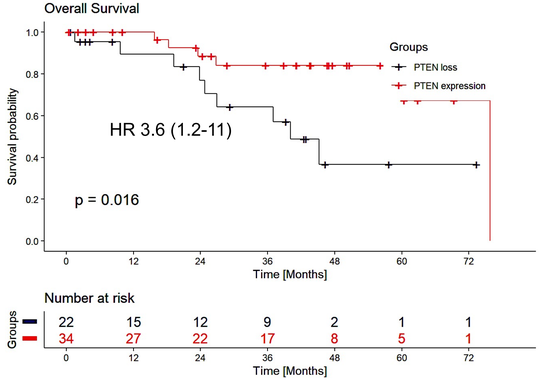
	N	Median TTCRPC (mos)	HR (95%CI)	*p* value	Median OS (mos)	HR (95%CI)	*p* value
OVERALL COHORT	56	21			75.8		
PTEN STATUS							
- Loss	22	26	1.8 (0.88-3.9)	0.11	40.1	3.6 (1.2-11)	0.016
- Intact	34	18			75.8		
DOCETAXEL USE							
- Yes	31	18	1.2 (0.57-2.6)	0.61	NA	0.9 (0.3-2.7)	0.85
- No	25	24			75.8		
SYSTEMIC THERAPIES USE							
- ADT alone	16	18	0.85 (0.4-1.8)	0.69	NA	0.86 (0.27-2.7)	0.79
- ADT + docetaxel or ARTA	40	24			75.8		
VOLUME DISEASE							
- High	46	21	1.2 (0.37-4.1)	0.73	74.8	0.48 (0.13-1.8)	0.26
- Low	10	NA			NA		

- **CRPC occurred in 13 (59%) patients with PTEN loss vs. 17 (50%) patients with intact PTEN expression.**
- **At median follow-up of 28.5 months, PTEN loss was associated with significant shorter survival.**
- **Therapies in first line CRPC setting included ADT + ATRA (n=26/30, 87%), radium-223 (2/30, 7%), docetaxel (1/30, 3%), cabazitaxel (1/30, 3%)**

Kaplan-Meier curve for TTCRPC by PTEN status



Kaplan-Meier curve for OS by PTEN status



CONCLUSIONS

- **In this real-world study of PTEN status assessment, we identified a 39% prevalence among unselected *de novo* mHSPC patients, similar to castration resistant disease.**
- **PTEN loss was associated with deleterious impact on survival in patients treated with conventional therapies.**
- **Support of ongoing prospective studies evaluating targeted therapies in patients harboring PTEN aberrations (e.g. NCT03997123) is warranted to improve clinical outcomes.**

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