Title

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Genomic correlates of PSMA expression and response to ^{177}Lu-PSMA-617: A Retrospective multi-center cohort study

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Abstract

PURPOSE: While ^{177}Lu-PSMA-617 (LuPSMA) is an effective therapy for many patients with metastatic castration-resistant prostate cancer (mCRPC), biomarkers associated with outcomes are not well defined. We hypothesized that prostate cancer mutational profile may associate with clinical activity of LuPSMA. We devised a study to evaluate associations between mCRPC mutational profile with LuPSMA clinical outcomes.

PATIENTS AND METHODS: This was a multicenter retrospective analysis of mCRPC patients with next-generation sequencing (NGS) who received LuPSMA. PSA_{50} response (i.e. ≥50% decline in PSA) rate, PSA progression free survival (PSA PFS) and overall survival (OS) were compared between genetically defined sub-groups.

RESULTS: One hundred twenty-six patients with NGS results who received at least one cycle of LuPSMA were identified. The median age was 73 (IQR: 68 – 78), 124 (98.4%) received ≥1 prior androgen receptor-signaling inhibitor and 121 (96%) received ≥1 taxane-based chemotherapy regimen. Fifty-eight (46%) patients with a DNA damage repair gene mutation (DDR group) and fifty-nine (46.8%) with a mutation in *TP53*, *RB1*, or *PTEN* tumor suppressor genes (TSG group) were identified. After adjusting for relevant confounders, the presence of ≥1 TSG mutation was associated with shorter PSA PFS (HR=1.93; 95% CI 1.05, 3.54; p=0.034) and OS (HR=2.65; 95% CI 1.15, 6.11; p=0.023). There was improved OS favoring the DDR group (HR=0.37; 95% CI 0.14, 0.97, p=0.044) on multivariable analysis. Univariate analysis of patients with *ATM* mutations had significantly higher rates of PSA_{50} response, PSA PFS and OS.

CONCLUSIONS: Outcomes on LuPSMA varied based on mutational profile. Prospective studies to define the clinical activity of LuPSMA in predefined genomic subgroups are justified.

Keywords

177Lu-PSMA-617; ATM; CDK12; DNA damage repair; metastatic prostate cancer; Prostate-specific Membrane Antigen; tumor suppressor gene alterations

Introduction:

While a number of agents have been shown to improve overall survival (OS) for men with metastatic castration-resistant prostate cancer (mCRPC), there remains a great need for more effective targeted therapies[1,2]. Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is highly expressed in most cells of prostatic origin, and has emerged as a selective target for both imaging and therapeutics. Currently, a number of agents directed towards PSMA-expressing cells are in development including radioligands, antibody drug conjugates, and CAR-T constructs[3].

To date, ^{177}Lu-PSMA-617 (LuPSMA) is the only agent approved for the therapeutic targeting of PSMA. It is composed of PSMA-617, a small molecule ligand with specificity for PSMA, conjugated to the beta emitter ^{177}Lu. Its approval was based on the VISION trial, which tested LuPSMA against protocol-permitted standard of care in patients with mCRPC who had PSMA-expressing cancer (determined by PET imaging) and who had previously progressed on an androgen receptor (AR)-signaling inhibitor (ARSI) and taxane chemotherapy[4]. VISION demonstrated improvements in both OS and progression free survival (PFS); however, the clinical activity of LuPSMA was heterogeneous with a median PFS of only 9 months and objective responses in approximately half of patients. As such, additional biomarkers are needed to further refine patient selection strategies and to determine which patients stand to benefit from LuPSMA.

Unsurprisingly, baseline PSMA expression on PET imaging appears to associate with improved clinical outcomes to LuPSMA[5,6]. However, other factors associated with improved outcomes with LuPSMA are poorly defined, including the tumor molecular profile. To that end, only a handful of small, inconclusive studies have evaluated associations between prostate cancer molecular profile and outcomes following LuPSMA therapy[7–9].

A recent study suggested that alterations in a variety of DDR pathway genes may correlate with higher PSMA expression[10]. In addition, DDR gene alterations may also increase sensitivity to radiation-mediated DNA damage[11]. Of note, a prior study has correlated the presences of these mutations with increased sensitivity to the alpha emitter Radium-223[12]. Conversely, loss-of-function mutations in tumor suppressor genes (TSGs) have been associated with neuroendocrine transdifferentiation as well as emergence of AR-null phenotypes, which often do not express PSMA and would therefore not be expected to respond to LuPSMA[13,14]. Loss of TSGs have also been associated with radio-resistance across cancer types and have been shown to mediate resistance to PSMA radioligand therapy in a mouse model[15,16].

Given the limited data correlating genomics with LuPSMA clinical activity, we conducted a multi-institutional retrospective study aimed at addressing this knowledge gap. We

hypothesized that i) patients with DDR gene alterations would have more favorable clinical outcomes to LuPSMA, and ii) loss-of-function mutations in TSGs would be associated with less favorable LuPSMA outcomes.

Methods:

Patients and Methods

Participating centers included University of Washington (UW), University of California San Francisco (UCSF), and University of Colorado (UC). IRB approval was obtained at each site. Patients were included in the primary analysis of outcomes to LuPSMA if they: i) had a diagnosis of mCRPC, ii) received at least one cycle of LuPSMA, and iii) had next-generation sequencing panel (NGS) testing performed on tumor material using a CLIA-approved clinical-grade assay. A germline alteration in a DDR gene was considered sufficient to classify a patient as having a DDR-deficient prostate cancer; however, in the absence of a germline DDR mutation, somatic testing was required for inclusion in this analysis.

A variety of sequencing platforms were used, including UW-OncoPlex, UCSF-500, Foundation One, and Tempus, and mutations reported as pathogenic on the sequencing report were considered for this analysis[17–20]. Tumor DNA analysis was performed on primary samples, metastatic tissue, or cell-free circulating tumor DNA (ctDNA). To avoid false negatives due to low tumor content, we required the presence of an identifiable somatic mutations when ctDNA was sequenced. Cases demonstrating alterations that are commonly attributed to clonal hematopoiesis of indeterminate potential (CHIP) (e.g., *TET2, DNMT3A*) reported at a variant allele frequency less than 1% were not included.

Cases with any pathogenic mutation involved in a DDR pathway, including those involved in homologous recombination repair or mismatch repair (MMR), were included in the DDR-deficient cohort given prior data implicating these pathways in repairing radiation induced DNA damage (supplemental table 1)[21,22]. The commercial sequencing assays used in this study did not consistently report zygosity status of affected DDR pathway genes. If a sequencing report indicated a pathogenic alteration in a DDR pathway was detected, this was considered sufficient for inclusion in the DDR-deficient cohort. However, when a sequencing report explicitly stated that a DDR gene mutation was monoallelic, that case was included in the DDR-intact cohort. Mutations in *TP53*, *PTEN* and/or *RB1* were included in the TSG analyses.

Assessment of PSMA Expression

To explore associations between DDR gene mutational status and PSMA expression, we assembled an additional cohort of mCRPC patients who had undergone sequencing and PSMA PET imaging at UW. PSMA SUV_{mean} was used as a global measure of PSMA expression and was determined using image analysis software (MIM 8.7.11; MIM Software, Cleveland, OH) from baseline PSMA PET images. Lesions with an SUV ≥3 were used to calculate the total tumor volume and determine the PSMA SUV_{mean} as previously described[13]. PSMA-high disease was defined as PSMA SUV_{mean} ≥10 while PSMA-low

disease was defined as a PSMA SUV_{mean} <10 because this threshold is associated with clinical outcomes on LuPSMA[5,6].

Statistical Analyses

Clinical outcomes of interest included PSA_{50} response (i.e. ≥50% decline in PSA from baseline), PSA progression-free survival (PSA PFS), and overall survival (OS) from the time of initiating LuPSMA. PSA progression was defined as PSA ≥2 ng/mL and ≥25% above the nadir on two consecutive lab draws, as recommended by PCWG3[21]. Given inconsistency of repeat imaging and differences in practice patterns, radiographic PFS could not be reliably assessed.

Differences in baseline patient characteristics were compared using the Wilcoxon rank sum - and chi-squared test. PSA PFS and OS were evaluated using the Kaplan-Meier method and compared using the log-rank test. Cox regression analyses were used to evaluate associations between any DDR or TSG status and PSA PFS or OS after adjusting for baseline PSMA SUV_{mean}, prior receipt of PARP inhibitor (PARPi), and presence of liver metastases. Covariates were selected based on observed associations with clinical activity of LuPSMA in univariate analysis and/or prior data suggesting that covariates are associated with outcomes[4–6]. Analyses were performed using R 4.3.1.

Results:

Patient characteristics

A total of 126 patients who had undergone NGS and received at least one cycle of LuPSMA were identified (Supplemental Figure 1, Supplemental Table 2). The median age was 73 years (IQR: 68 – 78), 124 (98.4%) received ≥1 prior ARSI and 121 (96%) received ≥1 taxane-based chemotherapy regimen (Table 1). The PSMA SUV_{mean} was 7.2 for 66 patients at UW who had baseline PSMA PET scans available for analysis. Fifty-eight (46%) patients with a DDR gene mutation (i.e. DDR-deficient) were identified. The cohorts were largely similar when stratified by DDR gene status; however, the DDR-deficient cohort was younger, had higher likelihood of receiving prior PARPi therapy, and were less likely to have ECOG 2 performance status (Supplemental table 3). After excluding six patients with germline only or limited panel sequencing, clinical data on 120 patients were available for analysis based on TSG status. Fifty-nine (49%) patients with a TSG mutation were identified. The TSG-altered cohort was more likely to have lower PSA at diagnosis and to have received more lines of ARSI therapy (Supplemental Table 4).

Mutational Profile and Activity of LuPSMA

Overall, 64 out of 126 patients (50%) achieved a PSA_{50} response. The median duration of follow up was 9.43 months (95% CI: 8.77 – 10.5). Median PSA PFS was 5.72 months (95% CI: 4.76—7.82) and the median OS was 12.5 months (95% CI: 10.2— not reached) for the entire study cohort. There was no significant difference in PSA_{50} response rate between the DDR-deficient vs DDR-proficient cohort (57% vs 46%, P=0.3). The unadjusted survival outcomes between the DDR-deficient vs DDR-proficient groups were similar, with a median PSA-PFS of 6.2 months (95% CI 4.6, 9.1) and 5.8 (95% CI 4.2, 8.4) (p=0.3)

for the DDR-deficient and DDR-proficient cohorts, respectively. The median OS was 23.8 months (95% CI 11.9, not reached) for the DDR-deficient cohort and 10.5 months (95% CI 8.1, not reached) (p = 0.18) for the DDR-proficient cohort (Figure 1).

We did not observe a difference in PSA_{50} response rates for patients whose tumors did vs did not have alterations in *TP53* (53% vs 49%, p= 0.8), *RB1* (50% vs. 51%, p>0.9) or in *PTEN* (58% vs. 50%, p=0.7) (Supplemental Figure 2). We also did not observe any differences in PSA_{50} response rates based on the number of TSG altered (Figure 2, Supplemental Table 3). Unadjusted survival outcomes were similar based on TSG status (Figure 2, Supplemental Figure 2).

A multivariable model including TSG status, DDR gene mutational status, liver metastases, receipt of prior PARPi and baseline PSMA SUV_{mean} was constructed (Table 2). The presence of ≥1 TSG mutation was associated with shorter PSA PFS (HR=1.93; 95% CI 1.05, 3.54; p=0.034) and OS (HR=2.65; 95% CI 1.15, 6.11; p=0.023). While there was no difference in PSA-PFS based on DDR mutational status, OS was improved in the DDR-deficient cohort (HR=0.37; 95% CI 0.14, 0.97, p=0.044) after controlling for relevant covariates. The presence of liver metastases was also independently associated with shorter PSA PFS (HR=3.08; 95% CI 1.34, 7.09; p=0.008) and OS (HR=3.19; 95% CI 1.18, 8.60; p=0.022). A trend was observed for increased PSA PFS (p = 0.13) and OS (p = 0.08) for patients with high (PSMA SUV_{mean} ≥10) vs. low (PSMA SUV_{mean} <10) PSMA expression, although the sample size of this group was limited (N=66) (Supplemental Figure 3). Of note, we did not observe any difference in PSMA expression between DDR-deficient vs. DDR-proficient cohorts (Supplemental Figure 4) or the TSG-mutated vs. unmutated cohorts (Supplemental Figure 5).

Gene-Specific Analyses

Next, we evaluated clinical-genomic associations on an individual gene basis for DDR genes mutated in at least 10 patients (Figure 3, Table 3). We found substantial variation with regards to PSA_{50} responses between sub-groups. Twelve of 14 (86%) patients with an *ATM* alteration achieved a PSA_{50} response, which was significantly higher compared to the 52/112 (46%) PSA_{50} response rate in those without an *ATM* alteration (p=0.01). The PSA PFS for patients with vs. without an *ATM* alteration was also significantly longer, with a median PSA PFS of 9.6 months (95% CI 8.0—not reached) vs. 5.4 months (95% CI 4.1–7.4) (p=0.03). OS was also superior in the *ATM* altered group, where the median OS has not yet been reached compared to 11.9 months (95% CI 8.8, not reached) in the unaltered group (p=0.04). *BRCA2* alterations were not associated with improved clinical outcomes. The PSA_{50} response rate for the *BRCA2* group was 8/15 (53%) compared to 56/111 (50%) (p>0.9) in the unaltered group. There was also no difference in PSA PFS or OS for patients with vs. without a *BRCA2* mutation. Patients with a *CDK12* alteration had inferior outcomes, with 3/13 (23%) exhibiting a PSA_{50} response compared to 61/113 (54%, p = 0.07) for all other patients. These patients also had significantly decreased PSA PFS (p = 0.009) compared to the unaltered group, although OS was similar (p=0.4) between groups. PSMA expression did not vary significantly between genomic subgroups, although analysis was limited by sample size (Supplemental figure 6).

Discussion

To our knowledge, this is the largest study to correlate prostate cancer genomics with clinical outcomes to LuPSMA. After controlling for clinically relevant covariates, we found that mutations in DDR genes were associated with improved OS, while loss of function mutations in TSGs were associated with worse OS. Exploratory gene-by-gene analyses have also identified several clinically relevant subgroups that warrant further study. These include those with *ATM* mutations, who appear to have significantly better outcomes to LuPSMA, and those with *CDK12* mutations, who appear to do worse.

Both clinical and preclinical studies have consistently demonstrated a correlation between PSMA expression and activity of LuPSMA[5,6,22–24]. As such, it is not surprising that loss of function mutations in TSGs, which are associated with the emergence of AR-null phenotypes that lack PSMA expression, would also correlate with poor outcomes to LuPSMA[13,14]. It is worth noting, however, that this association persisted after controlling for the presence of liver metastases and PSMA expression, which would also enrich for AR-null prostate cancers. As such, it is possible that these mutations may also influence the clinical activity of LuPSMA by inducing a radioresistant phenotype. Indeed, clinical data has also suggested that the presence of *RB1* mutations may associate with poor outcomes to the non-PSMA targeted radiopharmaceutical radium-223[25]. Preclinical models have also implicated TSG mutations as a mediator of radio-resistance to PSMA targeted radioligand therapy[15]. It is also worth noting that two recent studies have reported similar genomic features to be associated with poor outcomes to LuPSMA, including TSG mutations and *PI3K* pathway alterations (including *PTEN* deletions)[26,27].

A key challenge facing this, as well as other precision oncology studies, is the broad number of genes involved in DNA damage repair. Given the exploratory nature of this study, we opted for an inclusive approach toward defining our DDR-deficient cohort, including genes directly and indirectly involved in a number of DDR pathways. Overall, we observed improved survival following treatment with LuPSMA for the entire DDR-deficient cohort; however, within this cohort outcomes were heterogenous. While a biologic rationale can be made for why specific associations were observed, it is important to acknowledge that these findings need to be confirmed prospectively.

We observed excellent clinical outcomes in patients with *ATM* mutations who received LuPSMA. This may be explained by this gene's role in mediating cellular response to radiation and is consistent with data showing that *ATM* deficient cells are highly radiosensitive. Some clinic data has also suggested that patients with homozygous germline defects in *ATM* (i.e. ataxia-telangectasia syndrome) are profoundly sensitive to adverse-effects of radiation[28,29]. Of relevance, a recent study found ATM-signaling to be one of the most significantly upregulated kinase pathways in response to LuPSMA therapy[15]. Interestingly, the data supporting *ATM* mutations as a predictive biomarker for response to PARPi monotherapy are conflicting[30–32].

We also found that *CDK12* mutations are associated with poor responses to LuPSMA. Of note, these mutations have not clearly been shown to predict response to PARPi either.

Retrospective data has suggested that patients with *CDK12* mutations appear to have a more aggressive clinical course, and translational work has shown that these alterations are associated with a focal tandem duplicator phenotype rather than the genomic signatures seen in tumors with deficiencies in homologous recombination repair[33–35]. Given the unclear role of *CDK12* in the response to radiation and its association with worse prognosis in general, it is perhaps not surprising that this sub-group had inferior outcomes to LuPSMA. These data further highlight the need to develop new treatment strategies tailored toward this aggressive genomic subgroup.

We also found that outcomes to LuPSMA appeared favorable in patients with MMR deficient (MMRd) prostate cancer, although it is important to note that this group only included seven patients. While these mutations are not predictive for response to DNA damaging cytotoxics and PARP inhibitors, there is data showing that this pathway is involved in responding to DNA damage from ionizing radiation, which could explain the excellent outcomes in this group[36]. Overall, five (71%) of these patients had a PSA_{50} and the median PSA PFS and OS were 12 and 13 months, respectively (Supplemental figure 6). Notably, one patient with an *MSH2* alteration and hypermutation had a complete response and currently off all treatment, including androgen deprivation therapy.

Our study has several important limitations. These include the retrospective nature of the study and small sample size of the analyzed genomic sub-groups. We were also only able to analyze PSMA SUV_{mean} at one site, which limits our ability to form robust conclusions regarding the intersection between genomics, PSMA expression and clinical outcomes to LuPSMA. Another key limitation is the inability to clearly distinguish biallelic versus monoallelic alterations given that this is not consistently reported by most commercial assays – despite the fact that true monoallelic alterations are unlikely to associate with a DDR deficient phenotype[37]. We also note that, while all mCRPC patients should receive germline and tumor somatic genetic testing, this is still not uniformly done, and exclusion of patients who did not have sequencing may have led to selection bias. With these caveats, we believe this hypothesis generating study provides a framework for future work evaluating precision medicine approaches as they pertain to the use of LuPSMA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Context Summary

Key objective:

^{177}Lu-PSMA-617 is a relatively new treatment option for men with metastatic castration resistant prostate cancer. However, about half of patients undergoing this treatment do not achieve objective tumor responses and biomarkers associated with response are lacking. This retrospective, multi-center study assessed 126 patients who had undergone next-generation sequencing as part of standard of care, and explored whether genomic alterations in prostate cancer may correlate with responses to ^{177}Lu-PSMA-617 therapy.

Knowledge generated:

Patients with mutations in the DNA damage repair pathway have improved survival on ^{177}Lu-PSMA-617 compared with those who do not. Exploratory gene-level analysis found that patients with *ATM* mutations appear to do particularly well with ^{177}Lu-PSMA-617 therapy.

Relevance:

Our findings suggest that alterations in certain genes and pathways may hold prognostic significance for patients undergoing therapy with ^{177}Lu-PSMA-617. Further validation in larger cohorts is essential to establish these genomic markers for refining patient selection.

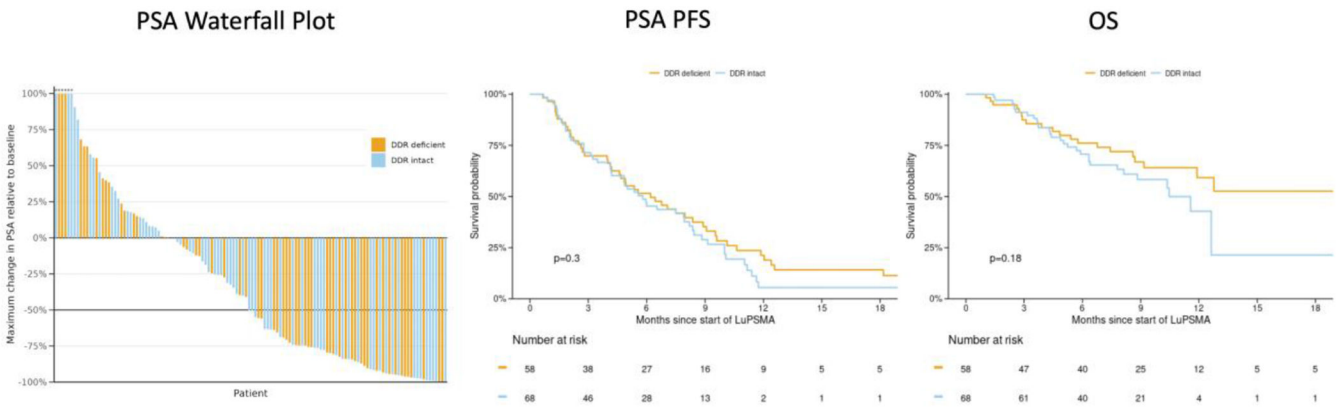

Figure 1:
Unadjusted clinical outcomes for patients with vs. without DNA damage response (DDR) gene mutations.

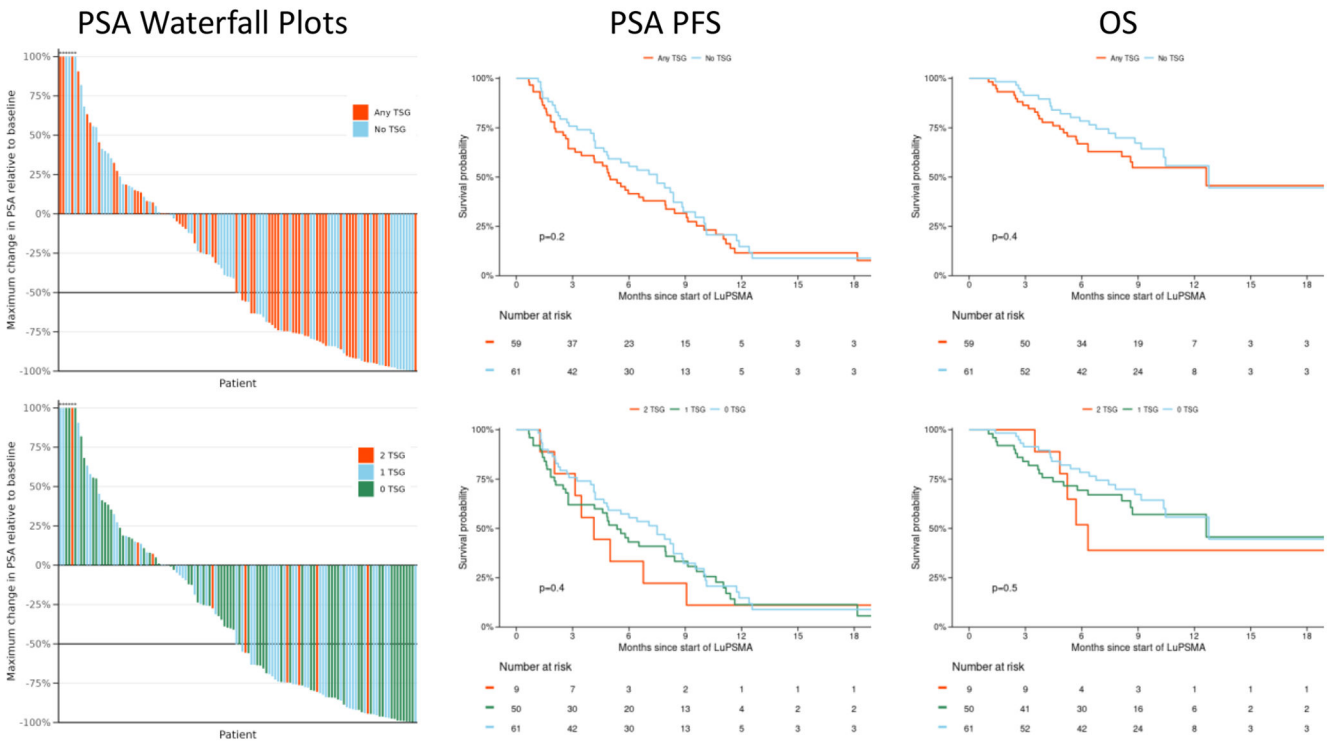

Figure 2:

Unadjusted clinical outcomes based on mutations in tumor suppressor genes (TSG) (i.e. *TP53*, *Rb1*, *PTEN*).

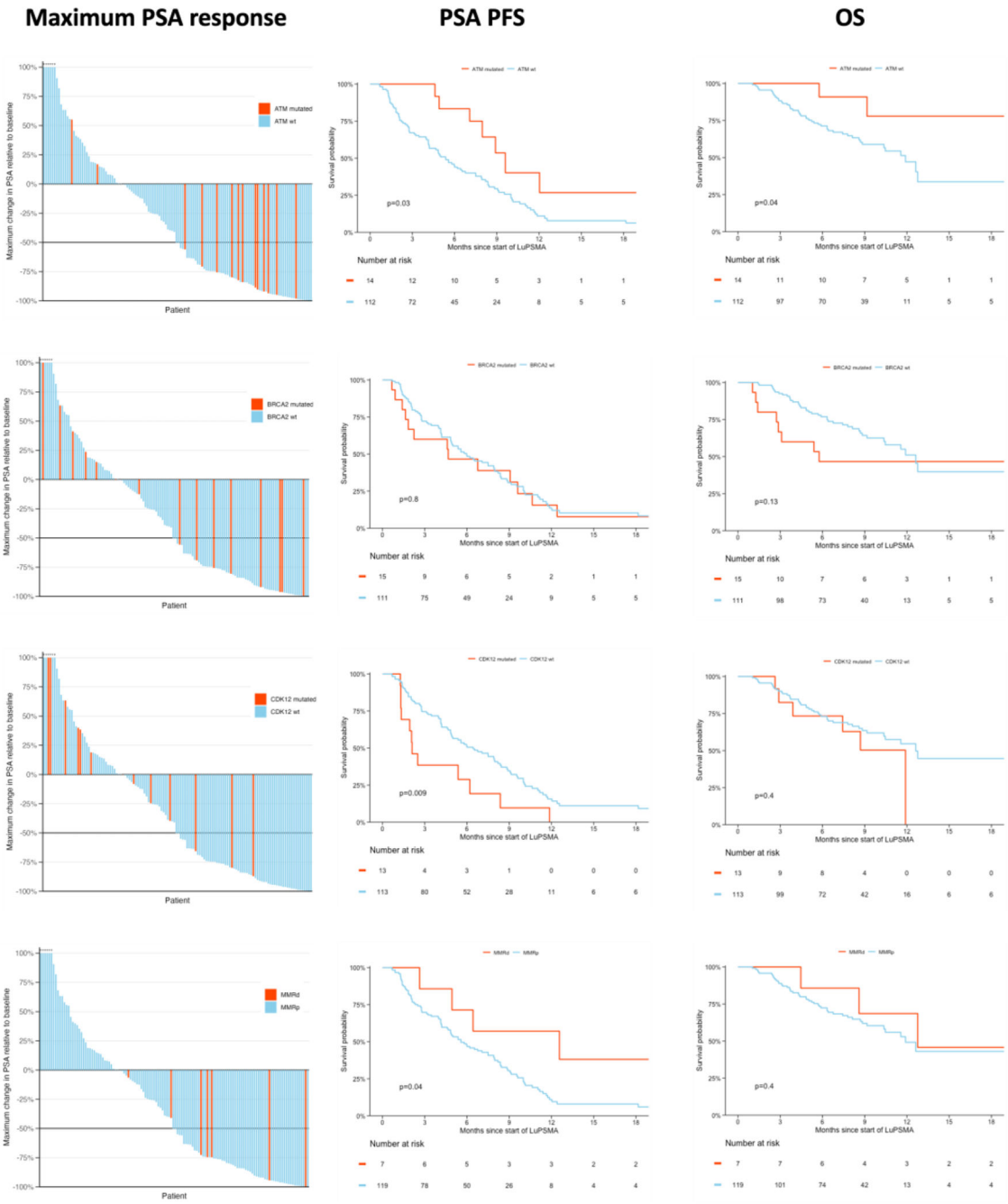

Figure 3:

Waterfall plot of maximum PSA response relative to baseline, PSA progression-free survival (PSA PFS), and overall survival (OS) for individual DNA damage response (DDR) mutations.

Table 1:

Baseline characteristics

Characteristic	N = 126
DDR Status, n (%)	
DDR deficient	58 (46%)
DDR intact	68 (54%)
TSG Status, n (%)	
Any TSG	59 (49%)
No TSG	61 (51%)
Unknown	6
Age, median (IQR)	73 (68, 78)
Race, n (%)	
Asian	5 (4.0%)
Black	5 (4.0%)
Other	8 (6.5%)
White	106 (85%)
Unknown	2
Gleason, n (%)	
<8	26 (24%)
8-10	83 (76%)
Unknown	17
ECOG PS, n (%)	
0	46 (38%)
1	63 (52%)
2	12 (9.9%)
Unknown	5
PSA at Diagnosis, median (IQR)	25 (8, 87)
Unknown	18
De Novo Metastatic, n (%)	56 (44%)
Local Therapy, n (%)	
Radiation	32 (25%)
Surgery	44 (35%)
None	50 (40%)
Liver Metastases, n (%)	20 (16%)
Bone Metastases, n (%)	117 (93%)
Nodal Metastases, n (%)	81 (64%)
Lung Metastases, n (%)	20 (16%)
Lines of ARSI, n (%)	
0	2 (1.6%)
1	37 (29%)
2	87 (69%)
Lines of Taxane, n (%)	

Characteristic	N = 126
0	5 (4.0%)
1	69 (55%)
2	50 (40%)
3	2 (1.6%)
Radium-223 Therapy, n (%)	17 (13%)

Table 2:

Multivariable Cox regression model of PSA progression-free survival and overall survival

	PSA Progression Free Survival			Overall Survival		
Characteristic	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
PSMA SUVmean > 10	0.59	0.25, 1.42	0.2	0.40	0.09, 1.71	0.2
DDR Alteration Present	0.75	0.39, 1.45	0.4	0.37	0.14, 0.97	0.044
Liver Metastases	3.08	1.34, 7.09	0.008	3.19	1.18, 8.60	0.022
PARPi Received	1.44	0.70, 2.97	0.3	1.81	0.66, 4.94	0.2
TSG Alteration Present	1.93	1.05, 3.54	0.034	2.65	1.15, 6.11	0.023

[1]HR = Hazard Ratio, CI = Confidence Interval

Table 3:

PSA response by individual DNA damage response (DDR) alterations.

Alteration	N	PSA50, N	PSA50, %
ATM	10	8	80.00
ATM, CDK12	1	1	100.00
BRCA1	3	2	66.67
BRCA1, ATM	1	1	100.00
BRCA2	13	6	46.15
BRCA2, ATM	2	2	100.00
CDK12	12	2	16.67
CHEK2	3	3	100.00
FANCA	1	1	100.00
PALB2	3	1	33.33
RAD51	1	0	0.00
RAD54L	1	1	100.00
MMRd	7	5	71.42