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Serum Markers as predictors for treatment benefit in castration-resistant prostate cancer

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Abstract

Purpose: While most prostate cancer patients initially respond to androgen-deprivation therapy (ADT), they will develop castration-resistance leading to progressing to castration-resistant prostate cancer (CRPC). Different treatment options are available for CRPC, including androgen receptor pathway inhibitors (ARPIs) and docetaxel (DOC). As tissue samples are difficult to access at this stage, blood-based analyses offer a more feasible approach. Therefore, we examined whether serum markers could potentially support treatment decisions in CRPC.

Materials and Methods: Overall survival (OS) was examined in 208 CRPC patients treated with either ARPIs or DOC. Serum markers were chosen to reflect relevant tumor properties: serum thymidine kinase 1 (sTK1) as a proliferation-associated marker, TPS (tissue polypeptide specific antigen) as an epithelial marker, and prostate-specific antigen (PSA).

Results: A median OS (mOS) time of 19.6 (IQR: 9.5–35.4) months was observed for the whole cohort. Patients with $sTK1^{high}/TPS^{high}$ levels treated with ARPIs showed a mOS time of 6.8 (IQR: 4.2–9.5) months, compared to 14.6 (IQR: 8.7–48.9) months for patients receiving DOC ($P = 0.024$). Patients with $sTK1^{low}$ and/or TPS^{low} levels showed similar mOS times irrespective of treatment. Combinations of sTK1 and TPS with PSA yielded similar findings for ARPI-treated patients and longer OS in DOC-treated patients.

Conclusions: This study introduces the concept of identifying proliferating carcinomas using a combination of the serum biomarkers sTK1 and TPS. The results suggest that $sTK1^{high}/TPS^{high}$ CRPC patients derive more benefit from DOC, consistent with known mechanisms of drug action. Further randomized studies will be required to prove the therapy-predictive value of these tumor markers in CRPC.

Keywords: Castration-resistant prostate cancer; Thymidine kinase; TPS; Docetaxel; Enzalutamide; Abiraterone

1. Background

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men, with an estimated incidence of 1.4 million worldwide [1]. Initial treatment for metastatic PCa includes androgen deprivation therapy (ADT) using gonadotropin-releasing hormone (GnRH) agonists, often in combination with androgen receptor pathways inhibitors (ARPIs) or chemotherapy [2]. However, patients on ADT frequently develop disease progression despite having castrate levels of serum testosterone [3]. Intracellular androgen levels are often increased in castration-resistant prostate cancer (CRPC) and the androgen receptor (AR) may be overexpressed. These findings have stimulated the development of compounds that target the androgen axis (ARPIs) such as enzalutamide or abiraterone [2,4,5].

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Approved agents for the treatment of mCRPC in Europe are docetaxel, abiraterone, enzalutamide, cabazitaxel, olaparib, niraparib/abiraterone, talazoparib/ enzalutamide, radium-223 and lutetium (^{177}Lu) PSMA [6,7]. In an expanding therapeutic landscape, it is highly desirable to develop treatment predictive markers. A phase 2 trial including patients with ARPI-naïve mCRPC and poor prognostic features (including liver metastases) demonstrated a higher clinical benefit rate with cabazitaxel *vs.* physician's choice of enzalutamide or abiraterone [8]. Volume of disease as a potential predictor was introduced by the CHAARTED trial, high volume being defined as having visceral metastases, or four or more bone metastases beyond the spine and pelvis [9]. Upfront docetaxel chemotherapy combined with ADT showed a significant survival benefit in the high-volume group but not in the low-volume group [9]. It was recently reported that an elevated tissue Ki-67-positivity rate strongly correlates with unfavorable abiraterone efficacy in men with metastatic PCa, including CRPC [10]. Ki-67 positivity was, however, determined in the primary tumor, not necessarily reflecting the status of CRPC tumors.

Murtola et al. [11] used a serum marker (sTK1, serum thymidine kinase 1) to assess tumor cell proliferation and found that elevated sTK1 was associated with poor outcome in metastatic CRPC treated with ADT or ARPIs. Thymidine kinase 1 (TK1) is an intracellular protein expressed by proliferating cells [12] and is released into the circulation as a consequence of cell death. Serum TK1 (sTK1) levels are elevated in patients with a number of malignant diseases [13], including PCa [11,14].

Keratins (cytokeratins) 8/18/19 are expressed by simple epithelia and by carcinomas derived from simple epithelia. Keratins are released into the circulation from disintegrated tumor cells, either as a consequence of apoptosis or necrosis [15,16]. A number of keratin tumor markers such as TPA (tissue polypeptide antigen), TPS (tissue polypeptide specific antigen), CYFRA 21-1 (cytokeratin-19 fragment), M65 and M30 have been developed [17,18].

Increased levels of both TK1 and TPS in the circulation is expected to indicate the presence of proliferating cells of epithelial origin. Such cells are expected to be sensitive to cell cycle-active therapies. The primary aims the present study was to determine whether double-positivity for serum TK1 and TPS could potentially be helpful for therapy decisions between ARPI and chemotherapy in CRPC. In addition, we also examined the utility of PSA in combination of these markers for this purpose.

2. Material and Methods

2.1. Prostate cancer cohort

Status of castration resistance was defined in accordance with the EAU guidelines [2]. CRPC patients treated at the Department of Urology, Medical University of Vienna or at the Department of Urology, Semmelweis University, Budapest between 2011 and 2022 were included. Serum samples were collected from 208 patients directly before initiation of first-line systemic therapy for CRPC (110 patients received ARPI (abiraterone or enzalutamide) treatment; 98 patients were treated with docetaxel (DOC) chemotherapy). Follow-up was available until August 2022. sTK1 and TPS data were available for 208 patients, PSA for 207. Patients. The study was performed in accordance with the Declaration of Helsinki and the institutional ethics committees approved the study (ECS 1986/2017, SE-RKEB: 33-5/2014). Patients provided informed consent to the study.

2.2. Serum ELISA analyses

Tissue polypeptide specific antigen (TPS) assays were performed as recommended by the vendor (Beckman Coulter Diagnostics, Brea, CA). Serum thymidine kinase was quantified using the TK210 ELISA as described by the vendor (IDL Diagnostics AB, Stockholm, Sweden).

2.3. Statistics

Differences between median values were determined using either the Mann-Whitney U-test or the Kruskal-Wallis test. Correlations were calculated as Spearman rank correlation coefficients (r_s). Univariable survival analyses were done using both Kaplan-Meier curves with log-rank tests and univariable Cox regression analysis. In all tests, P values < 0.05 were considered statistically significant. Statistical analysis was performed using the SPSS 26.0 (IBM, Chicago, IL) software.

3. Results

3.1. Levels of PSA, sTK1 and TPS in CRPC patients

An overall number of 208 patients diagnosed with CRPC were included in the study; 197 men had metastatic disease (178 with bone lesions, 36 had soft tissue lesions, five patients had only lymph node metastases) (Table 1). CRPC patients were either treated with ARPIs (abiraterone (57 patients) or enzalutamide (53 patients)) or with docetaxel (98 patients). The median OS (mOS) was 26.6 months for patients with ≤5 bone lesions and 14.6 months for patients with >10 bone lesions (Table 2). Patients with soft tissue lesions showed a mOS of 13.8 months compared to 20.9 months for patients with no such lesions (P = 0.087) (Table 2). Patients with >10 bone lesions showed a mOS of 14.6 (IQR: 6.8–27.4) months, compared to 26.6 (IQR: 15.5–43.5) months for patients with five of fewer lesions. Differences in OS time between different groups were, however, not statistically significant.

Whereas a significant association was observed between the number of bone lesions and higher PSA levels, no

Table 1
Characteristics of CRPC patients included.

	All patients included	Treatment groups	
		Enzalutamide/Abiraterone	Docetaxel
Number of patients	208	110	98
Median age	71 (IQR: 65–76)	72 (IQR: 68–78)	70 (IQR: 65–74)
PSA	70.8 (IQR: 21.8–312)	70.8 (IQR: 19.2–326)	67.8 (IQR: 26.5–279)
ECOG			
0	117	74	43
1	65	20	45
2	13	3	10
Bone metastasis	181	95	86
Soft tissue lesions	36	18	18

significant association was found between sTK1 or TPS levels and the number of bone lesions (Table 2).

3.2. Correlations between baseline levels of serum biomarkers

Pairwise comparisons of sTK1, TPS and PSA levels were performed. A medium/strong correlation was observed between TPS and sTK1 (r_s: 0.57) (Fig. 1). The correlation between TPS and PSA and between sTK1 and PSA was weaker (r_s 0.29 and r_s = 0.37, respectively). All correlations were statistically significant at $P < 0.00001$.

3.3. Associations between biomarker levels and overall survival

Elevated sTK1, TPS and PSA levels were correlated with shorter OS (Fig. 2). The mOS of patients with TPS, sTK1 or PSA above a median cut-off ranged between 14.6 and 14.8 months, and between 10.5 and 12.6 months, when two of the serum markers were elevated (Supplementary Table 1). Median OS times for patients with various combinations of levels of biomarkers are listed in Supplementary Table 1.

3.4. Associations between biomarker levels and survival in different treatment groups

Median OS times for patients treated with ARPIs or docetaxel are presented in Table 3. Median OS for patients with elevated sTK1 was 10.5 months in the ARPI-treated group, compared to 17.9 months in the docetaxel-treated group ($P = 0.036$). Similar tendencies between mOS in the different treatment groups was observed for TPS and PSA, although these findings were not statistically significant.

When combining two or three serum markers, double-positive and triple-positive patients had shorter OS. Of the double positive groups (sTK1/TPS, sTK1/PSA or TPS/PSA) the shortest OS time (10.5 months) was observed for $sTK1^{high}/TPS^{high}$ patients (observed in 76/208 (37%) patients) (Table 3, Fig. 2). Triple-positive patients (54/207 patients (26%)) had a similarly poor OS with a median of 10.5 months.

When comparing the mOS rates between ARPI vs. DOC treatment in different biomarker groups, we observed that in the high biomarker groups mOS was longer for DOC compared to ARPI treatment. In contrast, no difference in mOS could be observed between DOC vs. ARPI in the low biomarker groups (Table 3). More specifically, the median

Table 2
Biomarker levels in groups differing according to metastasis pattern.

	All CRPC patients	Number of lesions on bone scans			Soft tissue lesions	
		1–5 (n = 51)	6–10 (n = 46)	>10 (n = 81)	Absent (n = 175)	Present (n = 36)
PSA (ng/mL)	70.7 (21.8; 309)[c]	37.0 (14.0; 68.6)	163.5 (44.0; 428)	161 (52.7; 478) $P < 0.00001$[a]	66.1(21.8;317)	97.1 (21.9; 231) N.S.[b]
sTK1 (ng/mL)	0.49 (0.34; 0.83)	0.42 (0.30; 0.65)	0.51 (0.35; 1.89)	0.54 (0.39; 1.12) N.S.[a]	0.47 (0.33;0.73)	0.56(0.39;1.25) N.S.[b]
TPS (Units/L)	98.2 (54.3; 173)	84.7 (43.1; 129)	113.3 (61.4; 208)	118 (69.2; 249) N.S.[a]	91.2 (53.6; 155)	118 (70.8; 210) N.S.[b]
mOS (months)	19.6 (9.5; 35.4)	26.6 (15.5; 43.5)	17.1 (8.6: 30.1)	14.6 (6.8; 27.4) N.S.[a]	20.9 (10.0; 38.1)	13.8 (7.4; 27.8) $P = 0.087$[b]

[a] Kruskal-Wallis test: P-value based on the three groups with different number of bone metastatic lesions, N.S.: $P > 0.1$.
[b] Mann-Whitney U-test: N.S.: $P > 0.1$.
[c] Numbers within parenthesis: IQR, interquartile range.

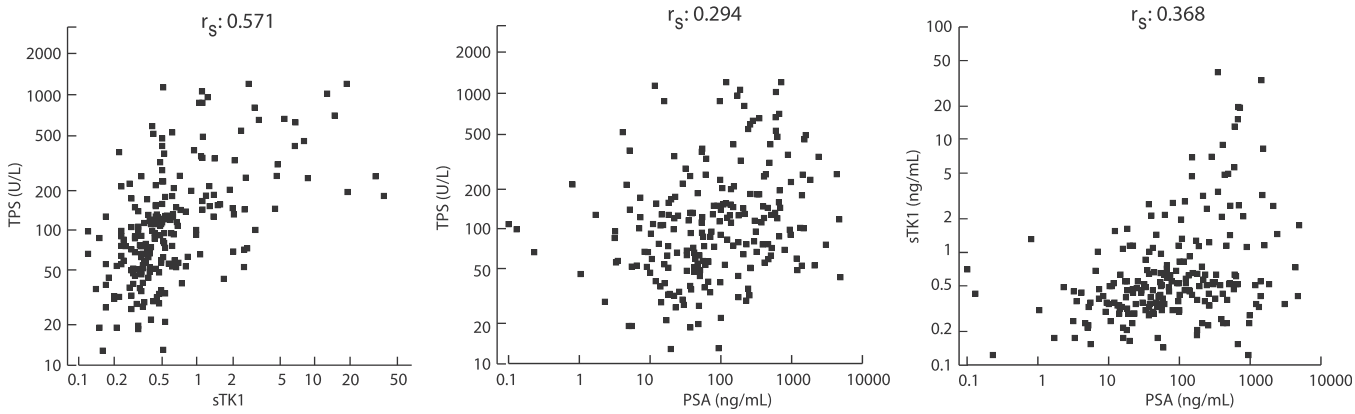

Fig. 1. Pairwise comparisons of sTK1, TPS and PSA levels in sera from 208 CRPC patients. Spearman correlation coefficients (r_S) are displayed on top. All correlations were statistically significant at $P < 0.00001$.

survival of double or triple positive patients was shorter (ranging between 6.7 and 7.9 months) in the ARPI group, compared to 14.6 to 17.1 months in the DOC-treated patients. The difference in mOS times between patients treated with ARPIs or to docetaxel was statistically significant for the $sTK1^{high}/TPS^{high}$ group of patients ($P = 0.024$). No such OS differences between ARPI (mOS range: 25.3−26.9) and DOC (mOS range: 23.7−26.0) could be observed in the biomarker low (non-double and triple positive) biomarker groups.

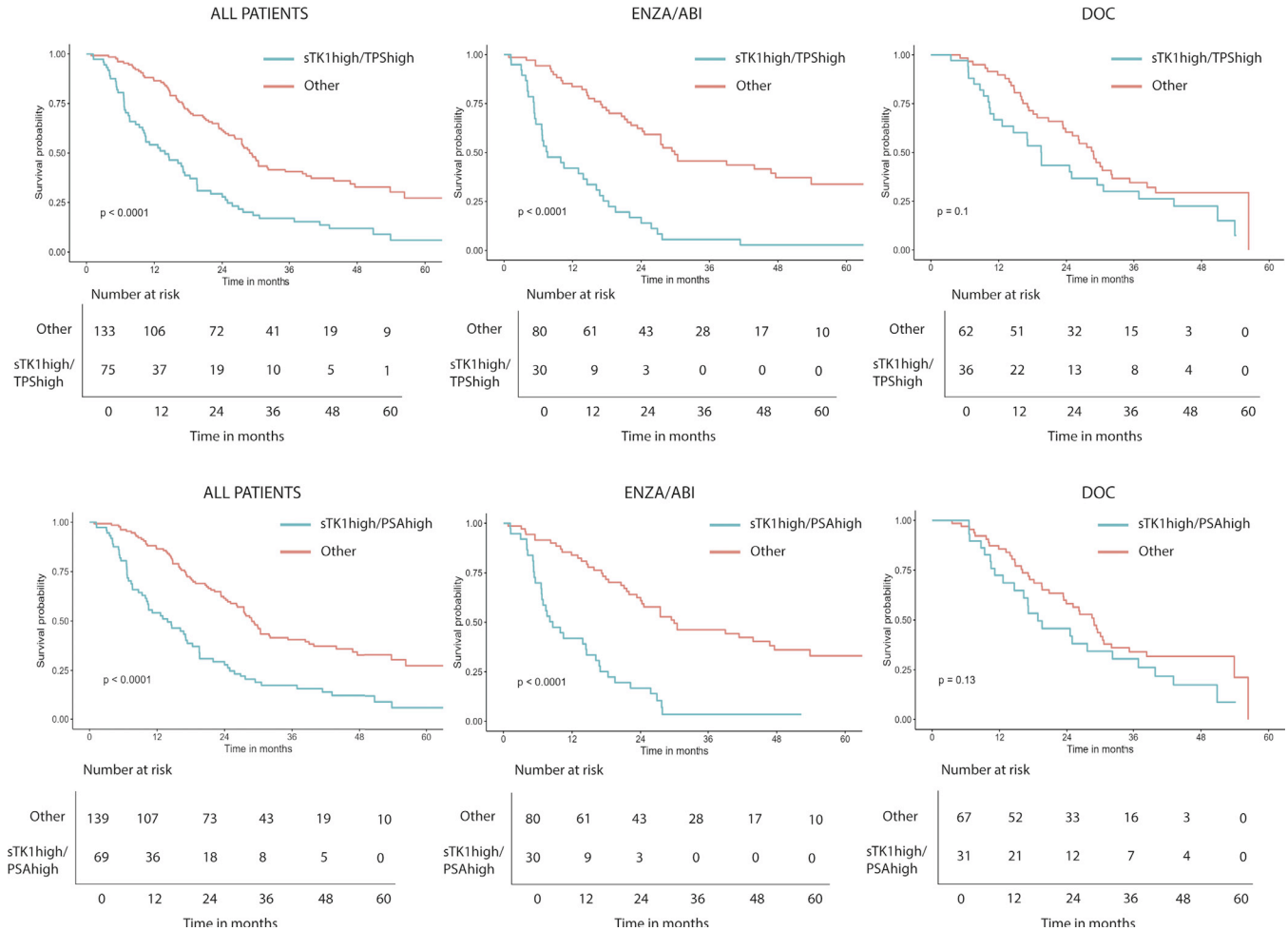

Fig. 2. Overall survival by sTK1, TPS and PSA medians among 208 men with CRPC. $sTK1^{high}$: > 0.49 ng/mL; TPS^{high}: > 98 U/L; PSA^{high}: > 71 ng/mL. Note: PSA values were available for 207 patients.

Table 3
Median survival times of CRPC patients treated with ARPIs or docetaxel (DOC).

	All patients		ARPIs (ENZA/ABI)		DOC	
	No	Survival, months (median; IQR)	no	Survival, months (median; IQR)	No	Survival, months (median; IQR)
All	208	19.6 (9.5; 39.3)	110	18.3 (7.2; 36.9)	98	22.1 (11.9; 35.0)
$sTK1^{high}$	104	14.8 (6.7; 27.8) (N.S.)	56	10.5 (5.3; 22.2)	50	17.9 (9.2; 35.0) ($P = 0.036$)[a]
$sTK1^{low}$	104	25.8 (14.0; 39.7)	57	27.4 (14.1; 50.3)	48	23.7 (14.1; 32.5)
TPS^{high}	106	14.6 (6.6; 27.6) ($P = 0.00036$)[b]	49	9.9 (5.2; 24)	57	17.1 (10.2; 34.3) ($P = 0.12$)K
TPS^{low}	102	25.2 (14.6; 41.5)	61	27.4 (14.4; 47.6)	41	26.0 (15.9; 35.3)
PSA^{high}	104	14.8 (6.7; 27.6)	56	10.1 (5.5; 20.0)	49	18.8 (11.2; 35.3) ($P = 0.11$)[a]
PSA^{low}	103	26.1 (13.9; 40.9)	54	28.7 (17.5; 47.4)	49	23.4 (17.3; 34.3)
$sTK1^{high}/TPS^{high}$	76	10.5 (5.9; 20.0) ($P = 0.016$)[b]	39	6.8 (4.2; 16.6)	35	14.6 (8.7; 48.9) ($P = 0.024$)[a]
$sTK1^{high}/TPS^{low}$ $sTK1^{low}/TPS^{high}$ $sTK11^{ow}/TPS^{low}$	135	26.1 (14.5; 40.3)	71	26.9 (14.5; 47.0)	63	25.8 (14.5; 36.7)
$sTK1^{high}/PSA^{high}$	69	12.6 (6.6; 24.9) ($P = 0.022$)[b]	38	7.9 (8.0; 27.5)	31	17.1 (10.5; 35.0) ($P = 0.062$)[a]
$sTK1^{high}/PSA^{low}$ $sTK1^{low}/PSA^{high}$ $sTK11^{ow}/PSA^{low}$	139	24.8 (13.3; 39.7)	72	26.1 (13.5; 50.0)	67	26.0 (15.1; 39.5)
TPS^{high}/PSA^{high}	66	11.7 (5.6; 24.3) ($P = 0.017$)[b]	38	6.7 (4.5; 15.8)	32	17.1 (10.5; 35.7) ($P = 0.060$)[a]
TPS^{high}/PSA^{low} TPS^{low}/PSA^{high} TPS^{low}/PSA^{low}	142	25.8 (13.7; 40.1)	72	26.1 (14.2; 46.1)	66	23.8 (13.4; 35.3)
$sTK1^{high}/TPS^{high}/PSA^{high}$	54	10.5 (5.7; 18.9) ($P < 0.00001$)[b]	30	6.7 (4.5; 14.4)	24	14.6 (10.4; 34.3) ($P = 0.067$)[a]
$sTK1^{high}/TPS^{low}/PSA^{low}$ $sTK1^{high}/TPS^{high}/PSA^{low}$ $sTK1^{low}/TPS^{low}/PSA^{low}$	154	24.6 (13.6; 39.0)	80	25.3 (13.5; 46.1)	74	23.7 (23.7; 34.6)

$sTK1^{high}$: ≥ 0.49 ng/mL; TPS^{high} ≥ 98 U/L; PSA^{high} ≥ 71 ng/mL.
[a] Mann-Whitney U-test of the significance of the difference between treatment groups (e.g., $sTK1^{high}$ patients treated with ARPIs (ENZA/ABI) or with docetaxel (DOC)).

4. Discussion

The number of therapeutic options is expanding in PCa, increasing the need for development of treatment predictive biomarkers. Most of the predictive markers are based on the analysis of the tumor tissue by using immunohistochemistry [19,20] or more sophisticated methods such as proteomics, transcriptomics and/or genomics [21,22]. In addition to being both specific and sensitive, a biomarker should be easy to use and cost-effective. The proliferation marker Ki-67 was reported to be of prognostic significance for hormone-naïve metastatic PCa patients treated with ADT [23]. Ki-67-positivity was also found to correlate with unfavorable abiraterone efficacy in men with metastatic PCa, including CRPC [10]. In the latter study, Ki-67 positivity was determined in the treatment naive primary tumor tissue, not necessarily representing the biological characteristics of CRPC tumors. Tumor tissue for biomarker analysis is often not available at the time of diagnosis of castration-resistant disease, hampering biomarker analyses. Therefore, routinely available clinical parameters such as "volume of disease" are more frequently considered for treatment prediction [9,24]. Murtola et al. [11] used a serum marker (sTK1, serum thymidine kinase 1) to assess tumor cell proliferation and found that elevated sTK1 was associated with poor outcome in metastatic prostate cancer (mCRPC and mHSPC) treated with ADT or ARPIs.

In the present study, three serum biomarkers were assessed which were considered to reflect properties relevant to treatment decisions for patients with CRPC. PSA is secreted from prostate epithelial cells and its serum levels are correlated with tumor burden [25,26]. Accordingly, we found that PSA levels are correlated with the number of bone lesions (Table 2), in contrast to sTK1 and TPS levels, which did not show similar associations. sTK1 is a proliferation marker, but is not cell type-specific. TPS is a marker of epithelial cells, expressed by most carcinomas, but is expressed by both proliferating and non-proliferating cells. We interpret the correlation between serum levels of sTK1 and TPS levels (Fig. 1), to reflect the release of these proteins from proliferating cells with an elevated apoptosis index. Associations between high apoptotic index and proliferative activity has been reported in a number of human tumors [27–31]. All combinations of sTK1, TPS and PSA levels showed similar levels of association to patients' survival, ranging between 10.5 and 12.6 months (Table 3).

When survival was analyzed separately in the two treatment groups, patients treated with ARPIs had survival rates ranging from 6.7 to 7.9 months, while those treated with docetaxel had survival rates ranging from 14.6 to 17.1 months (Table 3). Docetaxel is a cell cycle-active drug that induces mitotic catastrophe [32,33] and docetaxel sensitivity of tumors is associated with cell cycle progression [34]. The relatively favorable prognosis of docetaxel-treated patients with elevated serum levels of TK1 or TPS, in comparison to patients treated with ARPIs, is therefore consistent with the mechanisms of drug activity.

The baseline serum levels of keratins, TK1 and PSA are elevated in prostate cancer patients [11,14,26,35,36]. A general shortcoming of serum biomarkers is the uncertain origin of the markers. Increased levels of circulating keratins may reflect release from carcinoma cells undergoing apoptosis and/or necrosis [37] but may also be due to liver damage [38,39]. TK1 is expressed by proliferating tumor cells, but is expressed by other proliferating cells such as precursor cells in bone marrow [40]. Using the combination of sTK1 and TPS as an indicator of carcinoma proliferative activity largely overcomes these limitations. In PCa sTK1 and TPS can be combined with PSA to indicate the presence of proliferating tumors. The sTK1/TPS and sTK1/PSA combinations resulted in similar results in terms of estimation of survival in different patients groups.

Recent developments have resulted in recommendations of earlier use of ARPIs and DOC in metastatic hormone sensitive prostate cancer (mHSPC) [41]. It is currently unclear which patients should be treated with a doublet therapy (ADT+ARPI) and which patients would benefit from a more aggressive triplet (ADT+ARPI+DOC) therapy. It is generally stated that “high-volume” mHSPC patients benefit from triplet therapy, while low-volume cases can be adequately treated with a doublet [41]. Our marker-based approach may provide further insights in this regard.

Our study is not without limitations. A major limitation is the nonrandomized inclusion of patients for different treatments which could lead to a selection bias. Therefore, further validation of our results is necessary in a randomized trial or using data where life expectancy and/or comorbidities can be adjusted for.

5. Conclusion

The results suggest that serum biomarkers that indicate the presence of actively proliferating PCa cells may be useful as prognostic markers and also as treatment predictive markers in CRPC and possibly also in mHSPC. The lack of tumor tissue for phenotypic and genotypic examinations at advanced stages makes serum markers a promising alternative.

Declaration of competing interest

Kiran Jagarlamudi is an employee of AroCell AB, Stockholm. Stig Linder is a consultant for AroCell AB, Stockholm. Data analysis has been performed by an independent statistician, Anders Berglund at Statistikakademin, Uppsala, Sweden. The other authors have no conflict of interest.

CRediT authorship contribution statement

Tibor Szarvas: Formal analysis, Validation, Conceptualization, Investigation, Writing – review & editing, Data curation. **Gero Kramer:** Investigation, Writing – review & editing, Validation. **Kiran Jagarlamudi:** Methodology, Writing – review & editing, Investigation. **Johan Styrke:** Writing – review & editing. **Stig Linder:** Validation, Data curation, Writing – review & editing, Investigation, Writing – original draft, Formal analysis, Project administration, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2025.06.018.

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