Title: Neutrophil-to-lymphocyte ratio in castration-resistant prostate cancer patients treated with daily oral corticosteroids.

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Key words: corticosteroids, prednisolone, dexamethasone, NLR, castration-resistant prostate cancer, CRPC

Abbreviations

ACTH, adrenal corticotrophin-releasing hormone

BL, baseline

CI, confidence interval

CRPC, castration-resistant prostate cancer

D, Dexamethasone

ECOG, Eastern Cooperative Oncology Group

HPA, hypothalamic-pituary axis

IQ, interquartile

MDSC, myeloid-derived suppressor cell

MVA, multivariate analysis

NLR, neutrophil-to-lymphocyte ratio

P, Prednisolone

PSA, prostate-specific antigen

Treg, regulatory T-cell

UVA, univariate analysis

Wk(s), week(s)

MicroAbstract

Concerns exist that low-dose corticosteroids may adversely affect outcome in patients with castration-resistant prostate cancer (CRPC), due to its tumour-promoting and immunosuppressive characteristics. An increased neutrophil-lymphocyte ratio (NLR), an indirect measure of tumour-inflammation, associated with a shorter PSA progression-free interval and a shorter overall survival, in 75 treatment-naïve CRPC patients treated with low-dose corticosteroids in a prospective clinical trial.

Clinical Practice Points

Corticosteroids enjoy widespread use in patients with castration-resistant prostate cancer (CRPC). Mounting concerns have arisen that corticosteroids fuel tumour growth by promiscuous activation of the androgen receptor (AR) and through glucocorticoid receptor (GR) signalling, leading to AR-independent CRPC progression and an array of immunosuppressive effects. These include inhibition of leukocyte trafficking, apoptosis of immature T-cells, polarisation of T-cells into cells with a regulatory phenotype, and accumulation of myeloid-derived suppressor cells and tolerogenic dendritic cells. Corticosteroids may adversely impact outcome in mCRPC patients supported by data from the COU-AA-301, AFFIRM, and TROPIC trials. In addition, steroid withdrawal has been linked to biochemical responses. NLR, a ratio of systemic neutrophil-lymphocyte levels, has been proposed as a biomarker of a cancer-promoting systemic inflammation, and is now a well established biomarker of poor prognosis. Previous reports suggested corticosteroid therapy itself may induce NLR rises, which indeed was the case, however the timing and extent strongly varied between patients. Our findings indicate that treatment-naïve CRPC patients with a high baseline NLR, treated with low-dose corticosteroids, show a more rapid biochemical progression and have a shorter overall survival, than those with low baseline values. Those patients showing a strong and rapid increase in NLR during the first 6 weeks had a shorter benefit and lower odds of biochemical respons, suggesting corticosteroids or an induced systemic inflammatory response may adversely affect outcome. Whether corticosteroids unequivocally drive prostate cancer progression in patiens with high NLR tumours has not been demonstrated, as the trial lacked a control arm. Our results nevertheless implicate potentially adverse effects of low-dose corticosteroids; we particulary advocate caution in the use of therapeutic or palliative low-dose corticosteroids in patients with a high NLR and recommend discontinuation of supportive corticosteroid regimens following tumour progression.

Abstract

Objective: The neutrophil-lymphocyte ratio (NLR) is highly prognostic across many tumour types, predictive of treatment outcome in advanced prostate cancer (PCa), and a indirect measure of tumour-associated inflammation. We evaluated the impact of low-dose steroids on NLR in castration-resistant PCa (CRPC).

Patients and methods: The NLR was evaluated in a prospective phase II RCT comparing daily prednisolone 10mg and dexamethasone 0.5mg administered to 75 chemotherapy and abiraterone/enzalutamide-naïve CRPC patients. NLR was examined at baseline (BL), after 6- and 12-weeks of corticosteroid treatment; associations with >50%PSA response, time to PSA progression; TTPSAPD) and OS were tested using regression analyses.

Results: The median NLR for all evaluable patients was 2.6 at BL; 2.9 at 6-wks; and 4.0 at 12-wks. Following low-dose corticosteroid, 46 patients had a decline in PSA with 24 confirmed responders. BL-NLR(log10) associated with PSA response (OR=34.6;95%CI=2.0-589.1;P=0.014), and with extent of PSA decline (P=0.009). A favourable BL-NLR (<median) associated with 5.5- higher odds of PSA>50% response (95%CI=1.3-23.9;P=0.02). Higher BL-NLR(log10) associated with TTPSAPD (HR=9.5;95%CI=2.3-39.9;P=0.002). In MVA BL-NLR associated with TTPSAPD (HR=3.5;95%CI=1.5-8.1;P=0.003). NLR at 6-weeks associated with duration of benefit; in the favourable NLR category TTPSAPD was 10.8mo, converters to unfavourable (>median) category 4.5mo, those remaining in a unfavourable category 1.5mo (95%CI=0.5-2.5;P=0.003). OS was 33.1mo (95%CI=24.2-42.0) and 21.9mo (95%CI=19.3-24.4) for those with favourable and unfavourable BL-NLR, respectively.

Conclusion: Treatment-naïve CRPC patients with high-BL or on-treatment NLR appear not to benefit from low-dose corticosteroids. The immunological implications of unfavourable NLR, and whether corticosteroids drive PCa progression in patients harbouring high-NLR warrant further study.

Introduction

Corticosteroids are widely used in the management of patients with metastatic castration-resistant prostate cancer (mCRPC)(1). Incontrovertible evidence exists that corticosteroids suppress the adrenocorticotrophic hormone (ACTH) axis, thereby decreasing levels of the peripheral adrenal androgens dihydrotestosterone and testosterone(2). Even though corticosteroids induce PSA responses(3), circulating tumour cell (CTC) falls(4) and objective responses(5,6), prolonged use suggests no survival advantage in the CRPC state. Concerns are also emerging that the widespread and sustained use of these agents in mCRPC may not be beneficial to all, due to pleiotropic effects on multiple signalling pathways impacting tumor-promoting inflammation, as well as promoting an immunosuppressive environment(6–9).

Corticosteroid alter cellular differentiation programs that result in the accumulation of regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSC)(11,12), known to drive tumour growth and affect outcome(13–15). Corticosteroids may additionally decrease peripheral lymphocyte and increase granulocyte counts, increasing the NLR(8). A high NLR has been reported to represent an adverse prognostic factor in over 40,000 cancer patients with different tumor types(16). In patients with mCRPC, a high baseline (BL) NLR also is associated with a lower rate of response to abiraterone(17), enzalutamide(18) and cabazitaxel chemotherapy(19). BL-NLR and on-treatment NLR have not been studied in relation to response, duration of response and survival in CRPC patients treated with low-dose corticosteroids.

We hypothesized that a high NLR reflects an immune contexture that promotes tumour growth through: (I) the secretion of cytokines by inflammatory cells recruited to the tumour microenvironment, (II) reduced immune-surveillance due to the generation and expansion of myeloid-derived suppressor cells, regulatory T-cells (Tregs) and suppression of cytotoxic T-lymphocytes, and (III) senescence evasion and metastases promotion through direct and indirect actions of MDSCs. These concepts are substantiated by a good correlation between peripheral blood MDSC levels and NLR (20,21).

Studies on the impact of corticosteroids on the anti-prostate cancer immune response are therefore warranted. This led us to evaluate the impact of low-dose corticosteroids on the NLR in treatment-naïve CRPC patients treated on a prospective investigator-initiated randomized phase II trial (Prednisolone or Dexamethasone, POD trial) comparing low dose prednisolone 5mg twice-daily versus low dose dexamethasone at 0.5mg once-daily versus intermittent high-dose dexamethasone at 8mg for three days on a 3 week schedule(3). As corticosteroids increase the NLR, we hypothesized that patients with a high BL or on-treatment NLR, indicative of a high intratumoral and systemic

inflammatory state, would have a shorter PSA progression-free interval and a shorter time of benefit, compared to those with a low NLR. Corticosteroids are frequently used as supportive treatment in the latter stages of the disease where a high NLR is commonly seen; therefore it is of clinical significance to medical oncologists to ascertain whether NLR assessments may be utilized to select for patients that may have benefit or even have detriment from corticosteroid therapy, due to an induced increase in tumor-promoting inflammation driving prostate cancer growth(18).

Methods

Patients

All patients and healthy volunteers provided written informed consent prior to blood sampling. The local National Health Service research ethics committee approved the initial protocol on the single-centre, randomised, open-label, phase 2 trial of daily prednisolone versus daily dexamethasone versus intermittent dexamethasone in patients with CRPC (POD trial)(3). We conducted an unplanned retrospective analysis to study BL-NLR and NLR changes following the initiation of corticosteroid treatment in the POD trial. The inclusion and exclusion criteria are reported in the original publication, and comprise patients with CRPC (defined as having testosterone levels <2 nmol/l on androgen deprivation therapy or following bilateral orchidectomy) and progressive disease (PSA progression using three serum PSA measurements at least 7 days apart). In brief, patients were randomised in a 1:1:1 ratio among intermittent oral dexamethasone (8 mg twice daily for 3 days every 3 weeks), daily oral dexamethasone (0.5 mg once-daily), and oral prednisolone (5 mg twice-daily), until biochemical progression or unacceptable toxicity. Randomisation to the intermittent dexamethasone arm was stopped early because of lack of antitumor activity, and the analyses in this manuscript are restricted to the 75 patients randomised to the other two arms of the trial. Patient BL investigations included medical history, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, serum PSA (within 7 days of randomisation), serum testosterone, and routine haematology and biochemistry tests. The NLR was defined as the quotient of absolute peripheral neutrophil count (cells/mm3) by absolute peripheral baseline lymphocyte count (cells/mm3). The neutrophil and lymphocyte counts were collected from the electronic patient record. In the POD trial haematological assessments were used from time of screening to the first day of treatment. All assessments in the POD trial were performed at 6-week intervals, and included physical examination, serum PSA, haematological and biochemistry testing. The primary endpoint was PSA response, defined as the first timepoint with a 50% decline in serum PSA which is confirmed more than 4 weeks later, and secondary endpoints included time to PSA progression. In PSA nonresponders, progression was defined as a 25% increase over the nadir value (provided the rise was a minimum of 5 ng/ml) and confirmed by a second value at least 1 wk later. In PSA responders, progression was defined as a 50% increase over the nadir value (provided the rise was a minimum of 5 ng/ml) and confirmed by a second value at least 1 wk later. Patient survival was updated to 1 February 2015.

Statistical considerations

All results are presented as the median with interquartile (IQ) ranges for continuous variables. For non-normally distributed data, the Spearman rank-order correlation (*r*) was used to test for

associations, the Mann-Whitney test was used to test for differences between two groups, and the Wilcoxon signed-rank test was used for paired samples with repeated measurements following treatment. Lactate dehydrogenase (LDH), baseline PSA, alkaline phosphatase (ALP) and NLR were $\log_{10}$ transformed prior to testing in regression analysis. The relationship between continuous and dichotomized variables (at the median) and response were analysed using logistic regression models, with linear univariate regression model testing the relationship between BL-NLR and extent of PSA decline. Prognostic factirs tested in univariate analyses included metastatic disease, ECOG performance status, baseline PSA, categorised baseline testosterone, lactate dehydrogenase, haemoglobin, albumin, alkaline phosphatase and trial randomisation arm. All variables with a $P<0.10$ in UVA were selected for further testing in multivariate (MVA) regression analysis. Median OS and progression-free survival (PFS) were estimated using the Kaplan-Meier method with comparison between groups using the log-rank test. Additionally survival analyses were performed at the 6 and 12-week landmarks as previously reported(22). Boxplots where depicted using the Tukey method for plotting the whiskers and outliers. A Bonferroni correction was applied for multiple testing at BL, week 6 and week 12. All P values <0.05 were considered significant (and <0.025 or <0.017 with Bonferroni correction, for 2 or 3 time points tested). SPSS Statistics for Macintosh, Version 22.0 (IBM Corp, Armonk, NY) and GraphPad Prism version 6.0 for Macintosh (GraphPad Software, La Jolla, California) were used for the statistical analyses and figures.

Results

NLR following the initiation of low dose corticosteroids

We evaluated BL-NLR and the change in NLR after initiation of continuous low-dose corticosteroid treatment on this trial. The median NLR for all evaluable patients was 2.6 at BL; 2.9 at 6-weeks; and 4.0 at 12-weeks **(Supplementary table S1)**, with no significant differences between the two randomization arms at BL. When testing paired samples following corticosteroid treatment initiation the increase observed from BL to week-6 and weeks-12 was statistically significant (Wilcoxon paired rank-test, n=50, P<0.001 and n=48, P<0.001, respectively). In the prednisolone arm the NLR increased from a BL of 2.6 (IQ range of 2.0-3.4) to 3.7 at 6-weeks (IQ range of 2.8-5.9) to 4.1 at 12-weeks (IQ range of 2.8-7.2). In the dexamethasone arm the NLR increased by a lesser extent from a BL of 2.6 (IQ range of 2.0-3.5) to 2.7 at 6-weeks (IQ range of 1.9-4.0) and 4.0 at 12-weeks (IQ range of 2.0-5.4). There was a significantly lower NLR at week-6 for the patients on dexamethasone (P=0.02). The median granulocyte counts at BL, 6- and 12-weeks were 4.0 (IQ range 3.4-5.1, n=69), 5.4 (IQ range 4.1-6.8, n=55), and 5.7x10^9 cells (IQ range 4.5-7.2, n=51), respectively. The median lymphocyte counts were 1.5 (IQ range 1.2-1.9, n=70), 1.7 (IQ range 1.2-2.1, n=56) and 1.5 x10^9 cells (IQ range 1.2-1.8, n=51), respectively (**Figure 1**). The increased NLR was due to an increase in granulocytes at the 6- and the 12-week time point (in 42 out of 50, and in 41 out of 48 patients, respectively; both with P<0.01), without any statistically significant overall decrease in lymphocyte counts (P=0.09 and p=0.20, respectively).

Baseline NLR and response to corticosteroids

Of the evaluable 73 patients, 46 patients had a decline in PSA from BL following corticosteroid treatment initiation, with a confirmed PSA>50% response in 24 patients. No responses were witnessed in the arm with intermittent oral dexamethasone (8 mg twice daily for 3 days every 3 weeks), suggesting an anti-tumour activity of daily single-agent low-dose corticosteroids. Relationships between NLR and response could be evaluated in 69 (94.5%) patients with a documented BL-NLR. In univariate logistic regression analyses, BL-NLR associated with a PSA>50% response (odds ratio=34.6, 95% confidence interval [CI]=2.0-589.1, P=0.014), and with the extent of PSA decline in those patients that responded (P=0.009). A favourable BL-NLR (<2.6 or median) associated with a 5.5-fold higher odds of a PSA>50% response than those in the unfavourable (≥2.6 or median) BL-NLR category (95%CI=1.9-15.8; P=0.001, n=69). At the 6-week time point, 50 (72.5%) patients were evaluable with both a documented BL and 6-week NLR. In 68% of evaluable patients the NLR remained unchanged (30.0% remained NLR<median; 38.0% remained NLR≥median), however there were some conversions from low to high (28.0%), and from high to low (4.0%). Patients remaining in the favourable NLR category

at 6-weeks showed a 10.3-fold higher odds of a PSA>50% response compared to those that remained in the unfavourable category (95%CI=2.1-50.5; P=0.002, n=34). Patients that converted from a favourable to a unfavourable NLR showed a trend for a decreased response rate (P=0.086, n=16). Furthermore, the PSA progression-free interval was longer in patients with a low BL-NLR; as a continuous variable BL-NLR associated with the duration of PSA response (95%CI 2.3-39.9, P=0.002). Patients with a BL-NLR<median had a PSA progression-free interval of 6.1 months (95%CI 5.3-7.0), while patients with a BL-NLR≥median had a median interval of 3.3 months (95%CI 2.8-4.2, difference in median PFS of P=0.003; **Figure 2A**. These results indicate that a higher BL-NLR associates with reduced CS antitumour activity and a shorter duration of response.

After 6 weeks of treatment, patients that remained in the favourable NLR category were more likely to benefit from low-dose corticosteroids than those in the unfavourable category. Even though 6 patients that converted to an unfavourable NLR category still showed a PSA>50% response, the duration of responses were brief. The median time to PSA progression for those in the favourable NLR category was 8.5 months (95% CI 5.2-14.8), those converting to unfavourable category 4.5 (95% CI 2.8-6.2) and those remaining in a unfavorable category only 1.5 months (95% CI 0.5-2.5; P=0.003; results for favourable and unfavourable NLR shown in **Figure 2B**). Univariate and multivariate analyses (MVA) are shown in **Table 1.** In MVA BL-NLR was independently associated with the PSA progression-free interval (hazard Ratio [HR] 3.5; 95% CI 1.5-8.1, p=0.003). Prognostic factors that retained significance in multivariate testing were BL-PSA and randomization arm (D versus P), with a borderline significance for BL-testosterone.

Baseline NLR and overall survival.

The median overall survival (OS) of all 75 evaluable patients was 25.6 months (95% CI 14.9-42.0), with no significant difference between the two steroid regimens (P=0.15). As a continuous variable BL-NLR was significantly associated with OS (HR 5.5 with 95%CI of 1.3-24.0, P=0.024); patients in the favourable NLR category showed median OS estimates of 33.1 months (95% CI 24.2-42.0), and 21.9 months (95% CI 19.3-24.4) for patients with an unfavourable NLR (P=0.006; **Figure 3**). On-treatment NLR was not prognostic for OS at 6-weeks (HR 1.7 with 95%CI of 0.6-5.2) and not prognostic at 12-weeks (HR 2.2 with 95%CI of 0.6-8.3). In MVA, only ECOG≥2, LDH and haemoglobin retained significance, with borderline significance for BL-NLR (HR 2.0 with 95%CI of 1.0-4.0, P=0.062; **Supplementary Table S2**).

Discussion

Parallel to an increasing insight into the molecular mechanisms of glucocorticoid's anti-inflammatory effects(7), mounting concerns have arisen regarding the prolonged use of corticosteroids in mCRPC (9). Corticosteroids have an array of effects that dampen the inflammatory response by creating a immune-suppressive environment that may support tumor growth through the evasion of immune surveillance(23). These include inhibition of leukocyte trafficking and multiple effects on the degree of adaptive immunity by altering cellular differentiation programs(8). Studies on the impact of therapeutic and supportive corticosteroid treatment on the immune response in prostate cancer patients are therefore now urgently required.

We identified a strong relation between NLR in chemotherapy/ abiraterone/ enzalutamide-naïve patients and benefit from low-dose corticosteroid therapy, suggesting little or no benefit from single-agent corticosteroids in patients with high NLR. These results indicate that steroids simply may be insufficient as a therapeutic option in those patients with a high NLR, or may even suggest that in patients with a cancer-induced systemic inflammatory response, corticosteroid treatment may even be detrimental.

Most of the immunosuppressive and anti-inflammatory actions of corticosteroids are directly or indirectly attributable to transcriptional effects on GR. GR signaling induces apoptosis in immature double-positive $CD4^+$ $CD8^+$ T-cell in the thymus(24); monocytic precursors are also blocked in their pathway of maturation and cells with an anti-inflammatory MDSC phenotype accumulate(11,12,25); dendritic cell (DC) maturation is also suppressed and turn into tolerogenic semi-mature DCs(26) that polarize T-cell differentiation towards a regulatory T-cell profile (Tregs (25,27)). These immunomodulatory cells shape the tumor microenvironment by creating an immune-suppressive *milieu interieur* that impairs functional effector T and natural killer (NK) cell function. Corticosteroids also directly reduce T-cell functionality by numerous mechanisms, including enhancing PD-1 expression(28) and repressing transcription of pro-inflammatory cytokines (e.g. IL-2, IFN-γ and TNF- α) and chemokines that decrease migration and survival. Our results indicate that a high NLR rise is mainly caused by a corticosteroids-induced neutrophilia, of which cancer-associated neutrophils are known to support cancer growth. Recent immunophenotyping data from a prospective cohort of mCRPC patients indicates a positive correlation between NLR and peripheral blolod MDSC levels in patients on long-term corticosteroid treatment(21,29). In addition to an association between NLR and circulating MDSCs, significantly higher tumour-infiltrating MDSCs were detected in CRPC biopsies of patients with high versus low NLR(30). This in part may explain the

impact of BL- corticosteroid treatment on outcome in mCRPC patients, with inferior OS in patients with a higher NLR in the COU-AA-301, AFFIRM and TROPIC trials (31–33). In addition to these immunomodulatory effects, adverse effects of GR signaling have also been reported to act directly on cancer cells, and indicate that corticosteroids may interfere with the therapeutic efficacy of anti-cancer therapy. These include AR-independent CRPC progression through GR signaling with corticosteroids driving resistance of second-generation AR-antagonists (34), and point mutations in the ligand domain of AR including L701H, L702H, H875Y and T877A variants that are activated by iatrogenic corticosteroids (35,36) and drive resistance to abiraterone(37).

As concomitant corticosteroid treatment may drive resistance, cancer progression and adversely impact OS, more caution is now warranted when using supportive corticosteroids in high-NLR mCRPC. These data need validated in further prospective cohorts but could change daily management of CRPC in urological oncology practices. The strength of our study originates from the uniqueness of studying NLR in a completed randomized phase II trial of low-dose corticosteroids in CRPC. Critique may be given on the fact that the trial did not include a placebo arm, therefore all our findings of NLR need be taken with caution as all patients were treated with corticosteroids, and the effects of NLR as determinant of outcome required additional analysis in other datasets. It must be noted that the intermittent corticosteroid arm did not induce any PSA responses and if not terminated early, may have been used as a control arm. Given the array of life-prolonging therapeutic options in CRPC, such as the taxanes docetaxel and cabazitaxel, the oral hormonal agents abiraterone and enzalutamide, as well as radium-223 and sipuleucel-T, we recommend limited use of single-agent steroids as no survival advantage has been demonstrated. With regard to our findings, we advocate caution in the use of low-dose corticosteroids in patients with a high NLR, pending other prospective studies.

In conclusion, in patients with a high BL and on-treatment NLR, no apparent benefit from low-dose corticosteroid is witnessed. A pro-inflammatory environment in high NLR tumours may explain these findings, wherein corticosteroid treatment tips the scales in favor of the adverse effects that include accumulation and trafficking of immunoregulatory cells such as MDSCs and Tregs, decreased functional antigen presenting cells and effector T-lymphocytes, resulting in a tolerogenic tumour microenvironment supporting tumour growth, treatment resistance and an adverse outcome.

Acknowledgments

This work was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research. DL is supported by a 2-year grant from the Spanish Medical Oncology Society (SEOM) "Beca SEOM para la Investigación Traslacional en el Extranjero". We would like to thank the patients and their families that participated in the study.

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Figure 1 Assessment of Neutrophil to Lymphocyte Ratio (NLR) in the POD (Prednisolone or Dexamethasone) Trial. Box and Whisker Plot for NLR (A) and Neutroophils and Lymphocytes (B) at Baseline (BL) and After Initiation of Corticosteroid Treatment in the POD Trial. The Increase Observed in NLR and Neutrophils From BL to 6- and 12-Week Time Points and at End of Treatment (EOT) Was Statistically Significant. Also Paired Testing Revealed Significant Increases at Both Time Points (Both P<.001, Wilcoxon Paired Rank Test n [50 and n[48). Depicts Significance at the *P<.05; **P<.01; ***P<.001; and ****P<.0001 level

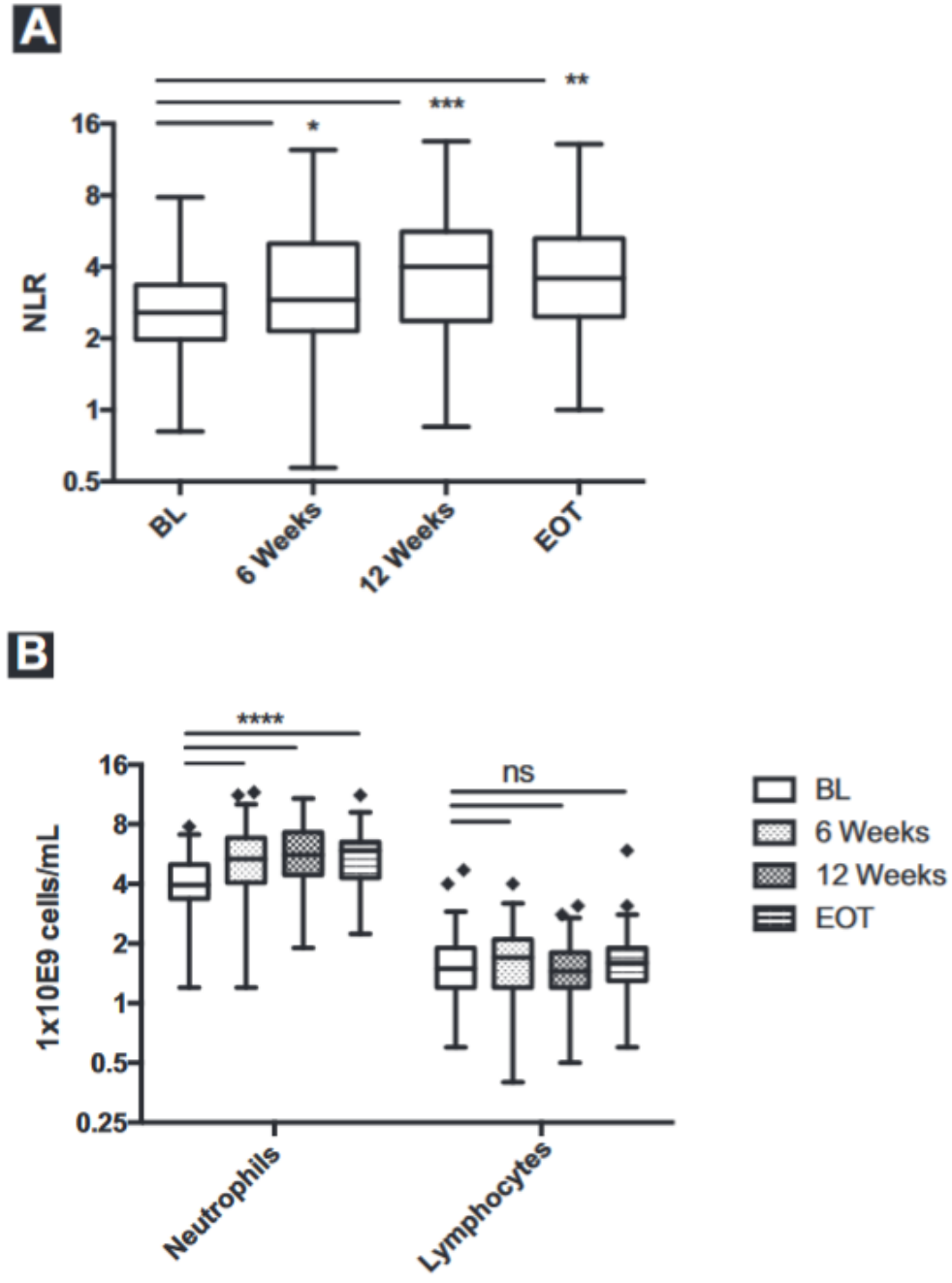

Figure 2. Time to Prostate-Specific Antigen (PSA) Progression (TTPSAPD) in Patients With Unfavorable Neutrophil to Lymphocyte Ratio (NLR; ‡2.6 or Median) and Favorable NLR (<2.6 or Median). The Median TTPSAPD in Patients With Unfavorable or Favorable NLR at Baseline (A) Was 3.3 Months (95% CI, 2.8-4.2) and 6.1 Months (95% CI, 5.3-7.0), Respectively. The Median TTPSAPD in Patients With an Unfavorable or Favorable NLR in the Landmark Analysis at 6 Weeks (B) Was 2.7 Months (95% CI, 2.4-4.7) and 8.5 Months (95% CI, 5.2-14.8), Respectively.

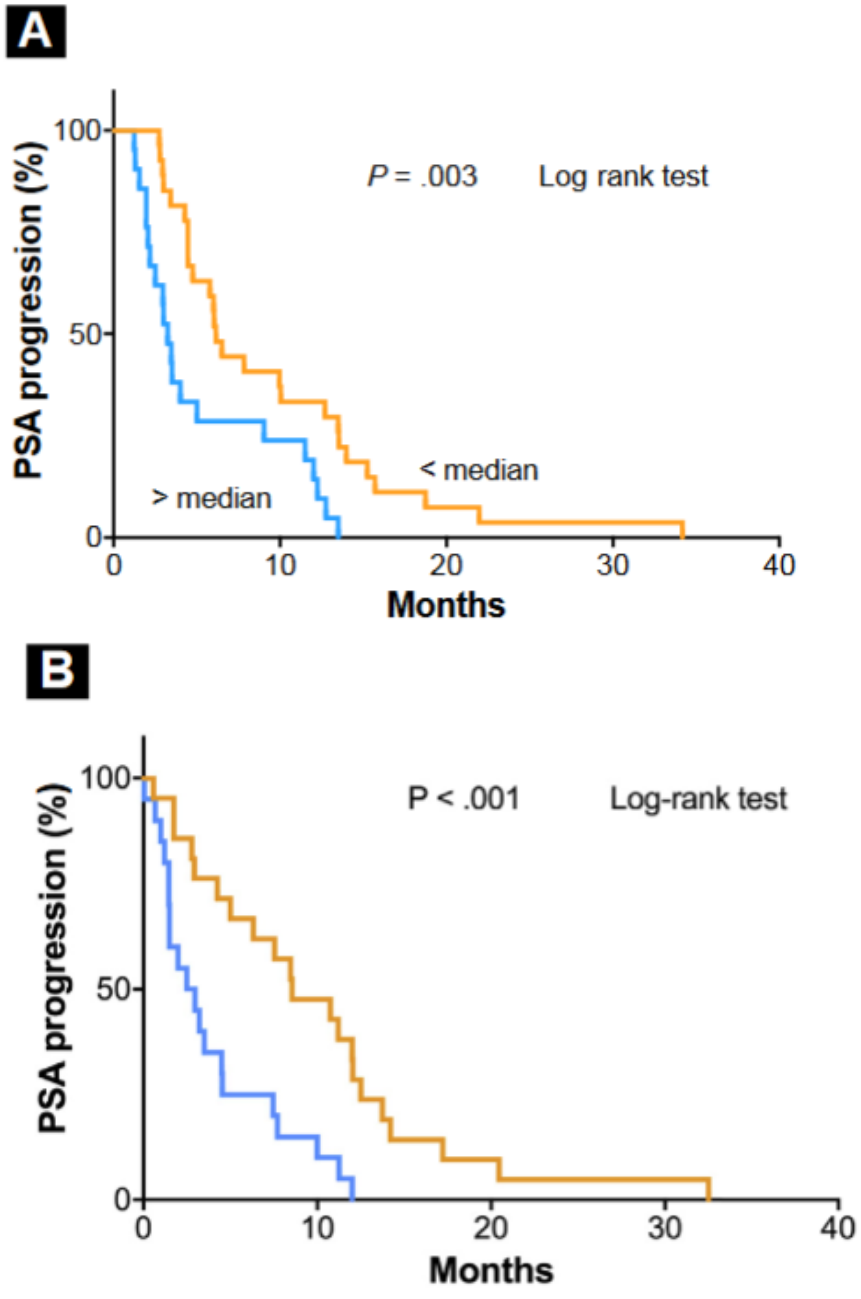

Figure 3 Overall Survival (OS) in Patients With Neutrophil to Lymphocyte Ratio (NLR) ‡ 2.6 (Median) and NLR <2.6 (Median). The Median OS in Patients With High or Low NLR at Baseline Was 21.9 Months (95% CI, 19.3- 24.4) and 33.1 Months (95% CI, 24.2-42.0), Respectively.

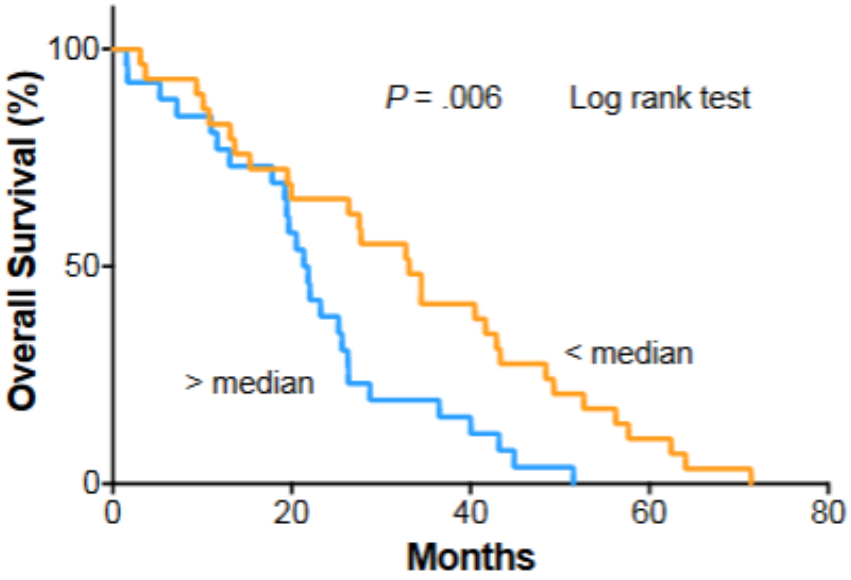

Table 1 Univariate and Multivariate Cox Model of the Association Between Clinicopathological and Prognostic Factors and the Time to PSA Progression.

	Univariate			Multivariate		
Parameter	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Metastatic Disease (Categorical)						
Yes	1.1	0.4-2.8	.83			
No	Ref	Ref				
Alkaline Phosphatase (Continuous; Log10)	2.1	0.8-5.6	.15			
Lactate Dehydrogenase (Continuous; Log10)	2.6	0.3-23.9	.40			
Hemoglobin (Continuous)	0.4	0.1-3.3	.44			
Albumin (Continuous)	1.0	0.9-1.0	.17			
ECOG Performance Status (Categorical)						
0	Ref	Ref				
1	1.1	0.6-2.0	.90			
2 and 3	2.3	0.7-7.4	.15			
Baseline PSA (Continuous; Log10)	2.0	1.2-3.1	.004	2.5	1.2-5.1	.014
Randomization Arm (Categorical)						
Prednisolone	Ref	Ref		Ref	Ref	
Dexamethasone	0.6	0.3-1.0	.056	0.4	0.2-0.8	.011
Baseline Testosterone (Categorical)						
<0.35	Ref	Ref		Ref	Ref	
≥0.35	0.5	0.2-0.9	.03	0.6	0.3-1.2	.057
NLR						
BL-NLR (Continuous; Log 10)	9.5	2.3-39.9	.002			
BL <median	Ref	Ref		Ref	Ref	
BL ≥median	2.3	1.3-4.3	.008	3.5	1.5-8.1	.003

BL-NLR as a dichotomous variable was most significantly associated with the time to PSA progression, and was selected for further testing in multivariate analysis.
Abbreviations: BL = baseline; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NLR = neutrophil to lymphocyte ratio; PSA = prostate-specific antigen; Ref = reference.

Supplementary Table 1. The NLR Values of Patients in the Combined Corticosteroid Treatment Arm and for Prednisolone and Dexamethasone

	Combined		Prednisolone		Dexamethasone	
NLR	**Median (n)**	**IQR**	**Median (n)**	**IQR**	**Median (n)**	**IQR**
Baseline	2.60 (69)	2.00-3.39	2.57	2.00-3.43	2.63	1.97-3.46
6 Weeks	2.94 (55)[a]	2.17-5.00	3.74[b]	2.81-5.85	2.70	1.90-3.98
12 Weeks	4.00 (51)[a]	2.93-5.60	4.11[b]	2.77-7.20	3.96[b]	2.00-5.39
EOT	3.58 (57)[a]	2.46-5.27	4.00[c]	2.63-5.34	3.56[b]	1.96-5.33

There were significant increases in all 3 groups after the initiation of corticosteroid treatment, except for at the 6-week time point in the dexamethasone group (Wilcoxon rank test for paired sample testing). In a comparison of differences between the 2 randomization arms (prednisolone and dexamethasone), there was a significant difference at the 6-week time point only.
Abbreviations: EOT = end of treatment; IQR = interquartile range; NLR = neutrophil to lymphocyte ratio.
[a] $P < .001$, NLR from BL to specified time point.
[b] $P < .01$, NLR from BL to specified time point.
[c] $P < .05$, NLR from BL to specified time point.

Supplementary Table 2. Univariate and Multivariate Cox Regression Analysis of the Association Between Clinicopathological and Prognostic Factors and Overall Survival

	Univariate			Multivariate		
Parameter	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Metastatic Disease (Categorical)						
Yes	1.1	0.5-2.5	.87			
No	Ref	Ref				
Alkaline Phosphatase (Continuous; Log10)	4.3	1.8-10.4	.001	4.2	0.9-19.3	.066
Lactate Dehydrogenase (Continuous; Log10)	33.9	6.0-192.4	<.001	41.4	2.0-852.0	.016
Hemoglobin (Continuous)	0.8	0.7-0.9	.009	0.04	0.0-0.9	.043
Albumin (Continuous)	0.92	0.9-1.0	.008	1.1	1.0-1.2	.095
ECOG Performance Status (Categorical)						
0	Ref	Ref		Ref	Ref	
1	1.5	0.8-2.8	.17	1.1	0.5-2.5	.84
2 and 3	3.0	1.1-8.0	.026	2.6	0.8-8.2	.10
Baseline PSA (Continuous; Log10)	1.7	1.0-2.8	.035	1.2	0.6-2.4	.52
Randomization Arm (Categorical)						
Prednisolone	Ref	Ref				
Dexamethasone	0.7	0.4-1.2	.15			
Baseline Testosterone (Categorical)						
<0.35	Ref	Ref				
≥0.35	0.9	0.5-1.7	.76			
NLR						
BL-NLR continuous (log10)	5.5	1.3-24.0	.024			
BL <median	Ref	Ref		Ref	Ref	
BL ≥median	2.1	1.2-3.7	.013	2.0	1.0-4.0	.062

BL-NLR as dichotomous variable was most significantly associated with overall survival, and was selected for further testing in MVA.
Abbreviations: BL = baseline; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NLR = neutrophil to lymphocyte ratio; PSA = prostate-specific antigen; Ref = reference.