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PROSTATE CANCER

PD-L1 expression is common and indicates poor prognosis

> "…PD-L1 expression was an independent prognostic factor of biochemical-recurrence-free survival"

Immunohistochemical assessment of primary prostate cancer samples, using a newly validated antibody, shows that programmed cell death 1 ligand 1 (PD-L1) is expressed in tumours of >50% of patients. In addition, high PD-L1 expression levels were associated with shorter biochemical-recurrence-free survival.

In the new study, Heidrun Gevensleben and colleagues from the University Hospitals in Bonn and Berlin, Germany, for the first time comprehensively investigated the expression of the immune checkpoint marker PD-L1 on primary radical prostatectomy specimens from hormone-treatment-naive patients. "We still have a pressing clinical need for new markers that enable identification of particularly harmless or aggressive prostate cancer cases to optimize therapeutic strategies," senior author Glen Kristiansen told *Nature Reviews Urology*. "In some patients, even a single marker might enable precise estimation of tumour aggressiveness and facilitate deciding between immediate therapy or active surveillance."

The team started their study by validating a commercially available antibody against PD-L1 (specifically, clone EPR1161(2)) in comparison with the current standard reagent, using flow cytometric and western blot analyses. Specificity was evaluated after knockdown of PD-L1 with small interfering RNA, as well as incubation with epitope-specific blocking peptide. "Despite its weaknesses, immunohistochemistry is pivotal to visualize target molecules in their appropriate morphological context, particularly if the target is expressed by tumour and inflammatory bystander cells, as in the case of PD-L1," comments Kristiansen.

In the next step, the researchers evaluated PD-L1 expression in two large, well-characterized sample sets of paraffin-embedded, primary radical prostatectomy specimens, using semiquantitative scoring of staining intensity by two independent assessors who were blinded to patients' clinical outcome. Men in the two cohorts had pT2 or pT3–pT4 disease and mean preoperative PSA levels of around 10 ng/ml. 47.4% and 35.4% of patients in each cohort had a Gleason score <7. In the training set and the validation set, 109 of 209 (52.2%) and 377 of 611 (61.7%) patients had moderate to high levels of PD-L1 expression, respectively. PD-L1 expression was positively correlated with expression of the proliferation marker KI-67, as well as expression of the androgen receptor.

To enable analysis of the relationship between PD-L1 expression and survival, patients were stratified according to median PD-L1 tumour levels, revealing that high PD-L1 expression was associated with significantly shorter biochemical-recurrence-free survival in both cohorts ($P = 0.022$ and $P = 0.009$). Multivariate analysis, including disease status, PSA levels, Gleason score and surgical margins, showed that PD-L1 expression was an independent prognostic factor of biochemical-recurrence-free survival.

"We can only speculate why such findings have not been reported before; maybe methodological differences to previous studies have enabled us to detect PD-L1 in prostate cancer," summarizes Kristiansen. "Further studies to confirm the prognostic value of PD-L1 in cohorts of watchful-waiting patients are underway." Importantly, these findings indicate that treatments targeting the PD-L1 pathway might be useful in men with hormone-naive prostate cancer.

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ORIGINAL ARTICLE Gevensleben, H. *et al.* The immune checkpoint regulator PD-L1 is highly expressed in aggressive primary prostate cancer. *Clin. Cancer Res.* http://dx.doi.org/10.1158/1078-0432.CCR-15-2042