SOLUBLE PROGRAMMED DEATH LIGAND 1 AS PROGNOSTIC BIOMARKER IN NON-SMALL CELL LUNG CANCER RECEIVING IMMUNE CHECK-POINT INHIBITORS – APPLICABILITY AND POTENTIAL CAVEATS

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Background Immune checkpoint inhibitors against programmed death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) have improved the survival of non-small cell lung cancer (NSCLC) patients. A number of studies have analyzed the level of soluble PD-L1 (sPD-L1) as a prognostic marker, but the results are divergent and call for further investigations. We addressed this by looking at sPD-L1 in baseline samples of such patients. Moreover, we studied the dynamics of sPD-L1 in serum collected prior to the three subsequent cycles of treatment to determine if anti-PD-L1 therapy and anti-PD-1 treatments instigate changes in the level of sPD-L1.

Methods 79 patients with advanced or recurrent NSCLC were enrolled at the Department of Oncology, Vejle Hospital, Denmark. The patients were treated with pembrolizumab (n=73), nivolumab (n=3), and atezolizumab (n=3). Blood samples were collected at baseline and before the following three cycles of treatment. sPD-L1 was measured using the Simoa® PD-L1 Discovery Kit and the Simoa® HD-1 analyzer (Quanterix). The study was approved by the Regional Committee on Health Research Ethics for Southern Denmark, approval number S-20170063.

Results In baseline samples the median concentration of sPD-L1 was 52 pg/mL (95% CI=49-57). Based on baseline sPD-L1 level the cohort was divided in three groups: sPD-L1(low) (n=24, median 38 pg/mL), sPD-L1(medium) (n=31, median 53 pg/mL), and sPD-L1(high) (n=24, median 79 pg/mL). The median overall survival was 26 months in sPD-L1(low), 15 months in sPD-L1(medium), and 9 months in sPD-L1(high). The difference between these was statistically significant (p=0.04, logrank test). The dynamics of sPD-L1 differed between patients receiving anti-PD-1 and anti-PD-L1 treatment. In patients receiving anti-PD-1 therapy, the level of sPD-L1 remained stable from the baseline sample and over the course of three cycles. Notably, in patients treated with anti-PD-L1, sPD-L1 rose by 50-fold following the first cycle and the concentration remained at the same high level in the subsequent samples. However, spiking atezolizumab in serum from healthy donors and anti-PD-1 treated patients showed that atezolizumab did not result in assay interference, but caused lower levels of sPD-L1 as one would expect.

Conclusions sPD-L1 has potential as a prognostic marker in NSCLC receiving anti-PD-1 and anti-PD-L1 therapy. Moreover, the data imply that continuous measures of this antigen in patients in anti-PD-L1 therapy need to be interpreted with caution, as it is undecided whether the elevated levels observed are accurate. Currently, experiments are conducted in our lab to solve this issue.

Ethics Approval The study was approved by the Regional Committee on Health Research Ethics for Southern Denmark, approval number S-20170063. All participants provided written informed consent.