Clinical trial identification: NCT01855477.

Legal entity responsible for the study: Radboud University Medical Center.

Funding: This data and the underlying study have been made possible partly on the basis of the data that Hartwig Medical Foundation and the Center of Personalised Cancer Treatment (CPCT) have made available to the study.

Disclosure: N. Mehra: Advisory board: Janssen; Honoraria: Bayer, Astellas, Janssen. MSD, BMS; Research funding: Astellas, Janssen. M. van der Doelen: Research grant: Bayer, the Netherlands. I. van Oort: Funding: Astellas, Janssen, Sanofi, Bayer. M.J.L. Ligtenberg: Research funds; Consultancy: AstraZeneca. All other authors have declared no conflicts of interest.

798PD | In-depth assessment of metastatic prostate cancer with high tumour mutational burden

N. Mehra1, J. van Riet2, M. Smits3, H. Westdorp4, M. Gorris1, T. van Ee5, M. van der Doelen6, I. van Oort4, S. Meijer3, I. Van de Weerken1, J. Schalken7, I.J.M. de Vries3, M.P. Lolkema8, W.R. Gerritsen1

1Medical Oncology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, 2Department of Cancer Computational Biology Center / Urology, Erasmus Medical Center, Rotterdam, Netherlands, 3Department of Tumour Immunology, Radboud Institute for Molecular Life Sciences, Nijmegen, Netherlands, 4Urology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, 5Center for Molecular Medicine, University Medical Center Utrecht / Hartwig Medical Foundation / Center for Personalized Cancer Treatment, Utrecht, Netherlands, 6Department of Pathology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, 7Department of Pathology / Human Genetics, Radboud University Medical Center Nijmegen, Nijmegen, Netherlands, 8Oncode Institute / Division of Oncogenomics, Netherlands Cancer Institute (NWO-AVL), Amsterdam, Netherlands, 9Division of Oncogenomics and Internal Medicine, Netherlands Cancer Institute (NWO-AVL), Amsterdam, Netherlands, 10Laboratory of Experimental Urology, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands, 11Medical Oncology, Erasmus University Medical Center / Center for Personalized Cancer Therapy, Rotterdam, Netherlands

Background: A comprehensive assessment of biopsies from metastatic prostate cancer (mPCA) patients (pts) may identify a molecular subset of pts susceptible for immune checkpoint (IC) blockade (ICB).

Methods: 148 biopsies and germline DNA from 145 mPCAs pts were whole genome sequenced (WGS) at an average of 11x4 and 38x. Tumour mutational (mut) burden (TMB) was defined as number of somatic single nucleotide variants and InDels per Mb of the genome, known mut signatures (Alexandrov, Nature 2013) extracted by non-negative least squares regression as well as recurrent mutations reported in mismatch repair (MMR) pts (Kim, Cell 2013). Selected pts with high TMB were further evaluated for: (a) MMR proteins expression; (b) multiplex intratumoural (IT) immune cell phenotyping (VICTRA); (c) multiplex IC expression (VICTRA); (d) 8-color flow cytometry blood immune cell phenotyping, with high TMB pts compared with low TMB pts. Pts receiving anti-PD-1 ICB had additional immune phenotyping at C2, C3, C4 and at progression; 3 pts had post-progression biopsies analyzed.

Results: The median TMB was 2.9 (IQR 2.2 – 3.9); 12 pts (8.3%) had high TMB (>10 mut/Mb). In 11/12 pts with high TMB, corresponding MMR deficiency (MMRd) signatures (6, 15, 20 and 21) were identified. Recurrent mut in MMR genes were detected MSH2/MSH6, MSH3, MLH1; other recurrent mut were in POLE, and frameshift mut enriched (p < 0.001) in genes including TGFBR2, CLOCK, RPL22 and JAK1. Immunohistochemistry confirmed MMRd in 6/6 biopsies and in matched primary tissue in 5/5 evaluable pts. Five pts were referred for germline testing without MMR mut. A trend for increased IT CD3+ cells were seen in MMRd (p = 0.06); no relation was found between TMB and tumour PD-L1 expression. Pts were treated with anti-PD-1 ICB, with PSA>50% decline of 57% of hTMB pts (n = 7), and a significant decline in circulating T-cell populations during ICB, including CD4+PD-1+ (p = 0.02) and CD8+PD-1+ (p = 0.007). Response rate, duration of response, genomic and immune correlates will be presented for pts with low and high TMB.

Conclusions: 8% of mPCa pts display a high TMB with recurrent somatic mut in MMR genes and POLE. MMRd appears early in PCa evolution. High TMB pts witness a high response rate to monotherapy anti-PD-1 ICB.