Genomic alterations in plasma DNA from patients with metastasized prostate cancer receiving abiraterone acetate plus prednisone or enzalutamide

Jelena Belic[1], Peter Ulz[1], Thomas Bauernhofer[2], Yauheniya Cherkas[3], Ricarda Graf[1], Julie Waldispuehl-Geigl[1], Sam Perakis[1], Michael Gormley[3], Jaymala Patel[3], Weimin Li[3], Jochen B. Geigl[1], Denis Smirnov[3], Ellen Heitzer[1], Mitchell E. Gross[4], Michael R. Speicher[1]

1: Institute of Human Genetics, Medical University of Graz, Austria; 2: Division of Oncology, Medical University of Graz, Austria; 3: Janssen Oncology Therapeutic Area, Janssen Research and Development, LLC, USA; 4: Lawrence J. Ellison Institute for Transformative Medicine of USC, University of Southern California, Los Angeles CA , USA

Purpose: Novel agents targeting the androgen-receptor (AR) pathway, such as abiraterone or enzalutamide, have improved the outcome in metastatic castration-resistant prostate cancer (CRPC). Here, we investigated somatic alterations detectable in circulating tumor DNA (ctDNA) and analyzed their association with resistance. In addition, we sought determinants of ctDNA detection in CRPC patients.

Patients and Methods: To identify determinants of ctDNA detection we analyzed two cohorts of subjects with 94 plasma samples from 25 patients and 334 plasma samples from 125 patients, respectively. We conducted whole-genome sequencing (plasma-Seq) for genome-wide profiling of somatic copy number alterations (SCNAs) and targeted sequencing of 31 prostate cancer-associated genes.

Results: The combination of plasma-Seq with targeted AR analyses identified significant genomic alterations in 16 of 25 (64%) subjects in the first cohort. We also evaluated determinants of ctDNA detection in an independent cohort of patients due to the wide variability of ctDNA levels. In 150 patients and 428 plasma samples from both cohorts, we identified increased lactate dehydrogenase (LDH) to be the strongest independent predictor of ctDNA release. Furthermore, in contrast to previous reports, we show that AR amplification alone is unreliable to predict abiraterone and enzalutamide therapy outcome. In patients treated with abiraterone, low ctDNA levels at baseline were a significant determinant of progression-free survival.

Conclusion: Analyses of ctDNA in two independent cohorts of subjects have provided insights into unique patterns of response and the emergence of resistance to abiraterone and enzalutamide. ctDNA measures contain additional information that has the ability to guide clinical decision making and significantly contribute to precision oncology.

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