Re: Germline DNA-Repair Gene Mutations and Outcomes in Men with Metastatic Castration-Resistant Prostate Cancer Receiving First-Line Abiraterone and Enzalutamide

E. S. Antonarakis, C. Lu, B. Luber, C. Liang, H. Wang, Y. Chen, J. L. Silberstein, D. Piana, Z. Lai, Y. Chen, W. B. Isaacs and J. Luo

Departments of Oncology and Urology, Johns Hopkins University School of Medicine, Baltimore, Maryland, and Greehey Children's Cancer Research Institute, and Department of Epidemiology and Biostatistics, University of Texas Health Science Center at San Antonio, San Antonio, Texas

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Editorial Comment: It has been suggested that men with castration resistant metastatic prostate cancer germline mutations of DNA repair genes have a shorter time to failure of androgen receptor targeted therapies, indicating that these patients may benefit from earlier second line therapies. In the present study this assertion is challenged by the observation that outcomes with next generation hormonal therapies are improved among men with BRCA/ATM mutations who demonstrate improved progression-free survival and overall survival compared to men with germline mutations of other DNA repair genes. Numbers in this study are small, and thus further validation is needed, particularly since the findings seem to contradict the existing literature. Nonetheless, the secondary observations of a recent trial in which men with somatic mutations of DNA repair genes had improved progression-free survival with abiraterone and prednisone therapy, compared to men without DNA repair genes, suggests that the issue remains unclear.[1] Men with mutations of DNA repair genes warrant special consideration, particularly at more advanced stages of disease, although the correct therapeutic paradigm for all appears indeterminate.

Samir S. Taneja, MD

1. Hussain M, Daignault-Newton S, Twardowski PW et al: Targeting androgen receptor and DNA repair in metastatic castration-resistant prostate cancer: results from NCI 9012. J Clin Oncol 2018; **36:** 991.

Suggested Reading

Taplin ME, Armstrong AJ, Lin P et al: Clinical outcomes of chemotherapy naïve men with metastatic castration resistant prostate cancer and low baseline prostate specific antigen treated with enzalutamide vs placebo. J Urol 2017; **198:** 1324.

Re: Effects of Pathological Upstaging or Upgrading on Metastasis and Cancer-Specific Mortality in Men with Clinical Low-Risk Prostate Cancer

E. Kovac, E. A. Vertosick, D. D. Sjoberg, A. J. Vickers and A. J. Stephenson

Glickman Urological and Kidney Institute, Cleveland Clinic Foundation, Cleveland, Ohio, and Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York

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Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/29802773

Editorial Comment: In this study the authors demonstrate that men whose disease is upgraded from low risk prostate cancer to intermediate risk at radical prostatectomy are not at significantly increased risk for recurrence, metastasis or death compared to men with intermediate risk disease, based on clinical parameters, before prostatectomy. Of men with low risk disease 53% experienced upgrade or upstaging events at radical prostatectomy, although only those with Gleason score 8 or higher, seminal vesical invasion or lymph node involvement (6% overall) exhibited a reduction in 10-year cancer specific survival compared to those without upgrade or upstage.

The relevance of this article comes from the historical observation that men with clinically low risk disease are often discouraged from undergoing active surveillance due to the risk of upgrade/upstage, which has historically been reported to be around 45%, with the majority of cases being upgraded from Gleason score 3 + 3 to Gleason score 3 + 4, as in this study. The observation that after radical

prostatectomy the rates of relapse, metastasis and cancer specific survival are favorable in these men does not actually discount the benefit of prostatectomy, but the previously reported clinical outcomes of active surveillance clearly show the safety of such an approach in men with low risk disease during the course of 15 years.

The findings of this study add further support to the idea that men with clinically low risk disease that is upgraded to higher risk stratiles are distinct from those with clinical evidence of intermediate risk disease. These concepts are evolving with the addition of prebiopsy magnetic resonance imaging, magnetic resonance targeted biopsy and genomic testing for risk segregation to the clinical diagnostic armamentarium.

Samir S. Taneja, MD

Suggested Reading

Tosoian JJ, JohnBull E, Trock BJ et al: Pathological outcomes in men with low risk and very low risk prostate cancer: implications on the practice of active surveillance. J Urol 2013; **190:** 1218.

Conti SL, Dall'era M, Fradet V et al: Pathological outcomes of candidates for active surveillance of prostate cancer. J Urol 2009; **181:** 1628.