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MEDICAL EDUCATION NETWORK

PRIORITY PRESS

39th Annual Congress of the European Society for Medical Oncology (ESMO)

Madrid, Spain / September 26-30, 2014

Survival Data Justify Early Use of Androgen Pathway Inhibitor in Metastatic Castration Resistant Prostate Cancer

Madrid - The final overall survival (OS) results of a phase 3 multicentre trial have confirmed the value of first-line androgen inhibition in metastatic castration resistant prostate cancer (mCRPC). In the study, early use of an androgen pathway inhibitor not only significantly improved OS but exerted a favorable impact on a series of milestones relevant to quality of life over the course of survival, including time to chemotherapy and time to opiate use to control cancer-related pain. These data are important for organizing the expanding number of treatment options that can be applied sequentially to slow progression of mCRPC. Over the course of the long-term follow-up in this phase 3 trial, patients in both arms eventually received a large array of additional treatments, but initial use of an androgen inhibitor was still able to provide a significant OS advantage.

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Compelling evidence of the value of early, first-line inhibition of androgen in patients with mCRPC was drawn from the final OS analysis of the COU-AA-302 trial. The trial compared the androgen pathway inhibitor abiraterone plus prednisone to prednisone alone. Presented in a primary forum for clinically significant studies at the ESMO congress, these along with other data led the ESMO discussant to call for early androgen therapy.

"This study really addresses the very important question of the timing of this agent," explained Dr. Bernard Tombal, Chairman, Division of Urology, Cliniques Universitaires Saint-Luc, Brussels, Belgium. Appointed by ESMO to assess the clinical significance of these data during the session in which they were presented, Dr. Tombal said that due to the design, "the trial really becomes early versus late abiraterone," because patients in both arms eventually received a wide array of the available treatments. The evidence of an early treatment advantage, presented in an early interim analysis and now reconfirmed in this OS analysis, has "profoundly impacted" the approach to mCRPC.

The results of the multinational COU-AA-302 trial, which included centres in Canada, are well known. The study was unblinded after at interim analysis. At that time, abiraterone had achieved a 43% advantage (P<0.001) for the coprimary endpoint of radiologic progression-free survival (rPFS) (Ryan CJ et al. *N Engl J Med* 2013;368:138-48). An OS advantage of 25% (P<0.01) observed at that time was considered preliminary because the prespecified number of events for a final analysis had not been reached.

Study Continues After Unblinding

This most recent final analysis is important because it allows relative OS to be evaluated with an adequate number of events and in the context of subsequent treatments. When presenting these results at the ESMO congress, the principal investigator, Dr. Charles J. Ryan, Genitourinary Medical Oncology, University of California, San Francisco, emphasized that the study was not discontinued when it was unblinded. Rather, the design was amended to allow control patients to switch to abiraterone with the intention to compare OS between arms over an extended period of follow-up. The median is now 49.2 months.

In the final analysis, the hazard ratio (HR) for OS was 0.81 (95% CI 0.70-0.93) favoring abiraterone (P=0.0033). The statistical advantage of this coprimary outcome far exceeded the pre-specified boundary (P=0.0384). This almost 20% reduction in death is similar to that reported at the interim analysis but more statistically robust. In addition, abiraterone demonstrated large and highly clinically significant advantages on all of the pre-specified secondary endpoints including time to initial chemotherapy and time to deterioration of ECOG performance status. The time to opiate use for cancer-related pain was delayed by 1 year (33.4 vs. 23.4 months; HR 0.72; P<0.0001).

The long-term follow-up of COU-AA-302 also permitted confirmation that this agent remains well tolerated and safe over extended periods of treatment. As reported previously, grade 3 or higher adverse effects related to cardiac dysfunction (8% vs. 4%) were more common in the abiraterone arm when compared to the control arm, but the only other grade 3 or higher adverse events found more commonly with initial androgen inhibition were liver enzyme elevations (9% vs. 2%) and hypertension (5% vs. 3%). For lower grade adverse events, those more common on abiraterone included fluid retention (30% vs. 22%), hypertension (19% vs. 11%), and hypokalemia (16% vs. 11%).

Nearly 100% Receive Additional Therapy

The emphasis placed by both Drs. Tombal and Ryan on the timing of abiraterone was based on the fact that 92% of those

in the abiraterone group and 100% of those in the control group received a subsequent therapy for mCRPC. In the control group, more than half received abiraterone or enzalutamide, which is another androgen pathway inhibitor. Approximately 80% of patients in both groups received docetaxel or cabazitaxel. Other treatments, such as sipuleucel-T and radium-223 were less frequently employed, but none of these treatments were available at the time that the COU-AA-302 trial began to enroll patients. This is an important consideration for interpreting these final OS results.

"The management of mCRPC has undergone a sea change in the past decade with regulatory approval of five systemic therapies that have demonstrated clinical benefit," Dr. Ryan explained. Although the subsequent use of these therapies was not considered in the original COU-AA-302 design, Dr. Ryan suggested that "the likelihood that sequential use of these treatments will improve overall prognosis" underscores the importance of determining which therapy to use first. The amendment in the COU-AA-302 design allowed the final OS analysis to evaluate abiraterone efficacy, particularly early use, in the context of these new therapies.

In his remarks, Dr. Tombal emphasized that nearly 50% of the control group eventually received abiraterone, while exposures to other subsequent mCRPC therapies, such as docetaxel (57% vs. 61%), and cabazitaxel (18% vs. 19%) were very similar between the abiraterone and control arms, respectively. Thus, the study suggests that inhibiting androgen as soon as possible after the diagnosis of mCRPC therapy is better than a delay.

Early Androgen Inhibition: Other Data

Early use of androgen inhibition has also been supported by the interim analysis of the PREVAIL trial with enzalutamide (Beer TM et al. *N Engl J Med* 2014;371:424-33). Although the data are less mature, the efficacy of an androgen inhibitor was also evaluated as a first-line therapy in mCRPC. In that trial, which was also terminated at an interim analysis due to efficacy, the comparator arm received placebo rather than an active therapy. Again, the coprimary endpoints were rPFS and OS, both of which favored the androgen inhibitor when the study was unblinded. Enzalutamide was also associated with a favorable impact on several secondary endpoints, such as time to chemotherapy and measures of quality of life.

In clinical practice, it is not uncommon to offer enzalutamide after abiraterone. In COU-AA-302, 16% of patients in the arm that received abiraterone and 10% of those in the control arm received enzalutamide. Both abiraterone, which blocks the cytochrome P450c17 enzyme to prevent testicular synthesis of androgen, and enzalutamide, which blocks the activity of the androgen receptor, are considered androgen pathway inhibitors. The long-term OS data provide an evidence basis for considering abiraterone an established first-line therapy in mCRPC, but ongoing efforts to identify biomarkers of response and resistance may eventually permit individualization of these therapies.

For immediate practice, the results of COU-AA-302 provide an evidence basis for selecting a first-line therapy for mCRPC. According to Dr. Ryan, the early use of abiraterone, when assessed a median four years after treatment initiation, "achieved differences that were not just statistically significant but highly clinically significant."

Conclusion

The final analysis of a multinational trial that randomized more than 1000 mCRPC patients and followed them for a median 49.2 months has confirmed a highly significant OS advantage for abiraterone, an androgen pathway inhibitor. The advantage of abiraterone plus prednisone over the comparator arm of prednisone plus placebo was previously reported for rPFS and OS at the interim analysis, but these final results demonstrate that OS persists for early use of abiraterone even when both groups receive subsequent treatments. These results suggest that early use of androgen inhibition is the most effective strategy to improve long-term outcomes. □

Reflection:

Q1: Does chemotherapy still have a role to play in early treatment of mCRPC in at least some patients?

Q2: Based on available evidence, is it reasonable to offer a second androgen inhibitor after a first in mCRPC when each has a different mechanism?

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