Highlights in Genitourinary Cancer

Commentary by Daniel George, MD

Erdafitinib Improves Overall Survival vs Chemotherapy in *FGFR*-Altered Advanced Urothelial Carcinoma

Erdafitinib (Balversa, Janssen) significantly improves overall survival (OS) compared with chemotherapy in patients with *FGFR*-altered advanced or metastatic urothelial carcinoma (UC) who have received a checkpoint inhibitor, according to an interim analysis of the THOR study. Erdafitinib currently has accelerated approval for patients with *FGFR*-altered advanced or metastatic UC who have received platinum-based chemotherapy.

For the study, Dr Yohann Loriot and colleagues enrolled 266 patients with advanced or metastatic UC who had selected *FGFR2/3* mutations or fusions, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and progression after 1 of 2 lines of prior systemic therapy that included an anti–programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) agent. Patients were randomly assigned in a 1:1 ratio to receive erdafitinib (uptitrated from 8 to 9 mg) each day or investigator's choice of chemotherapy (docetaxel or vinflunine) every 3 weeks until disease progression or intolerable toxicity. The primary endpoint was OS.

At a median follow-up of 15.9 months, median OS was significantly longer in the erdafitinib group than the chemotherapy group, at 12.1 vs 7.8 months (hazard ratio [HR], 0.64; 95% CI, 0.47-0.88; *P*=.005). Based on this finding, the study was halted, and patients in the chemotherapy group were given the opportunity to switch to erdafitinib. The OS benefit continued across all subgroups. Erdafitinib also surpassed chemotherapy in median progression-free survival (PFS), at 5.6 vs 2.7 months, respectively (HR, 0.58; 95% CI, 0.44-0.78; *P*=.0002), and in objective response rate (ORR), at 45.6% vs 11.5%, respectively (relative risk, 3.94; 95% CI, 2.37-6.57; *P*<.001). No new safety signals were seen. Serious treatment-related adverse events (TRAEs) occurred in 13.3% of patients on erdafitinib and 24.1% of those on chemotherapy, and grade 3 or 4 TRAEs occurred in approximately 46% of patients in both groups. TRAEs leading to death were reported in 1 patient on erdafitinib and 6 patients on chemotherapy. Central serous chorioretinopathy occurred in 17% of the erdafitinib patients.

"The phase 3 THOR study supports the clinical efficacy of erdafitinib as the standard of care option for patients with metastatic urothelial carcinoma with *FGFR* alterations after immune checkpoint inhibitor treatment," said Dr Loriot.

Loriot Y, Matsubara N, Park SH, et al. Phase 3 THOR study: results of erdafitinib (erda) versus chemotherapy (chemo) in patients (pts) with advanced or metastatic urothelial cancer (mUC) with select fibroblast growth factor receptor alterations (*FGFRalt*) [ASCO abstract LBA4619]. *J Clin Oncol.* 2023;41(17)(suppl).

Commentary: Results from the THOR study validate the clinical efficacy of erdafitinib in patients with *FGFR*-altered metastatic UC, and should replace chemotherapy as the preferred SOC for previously treated patients. Further studies are warranted in earlier disease settings. Systematic screening for *FGFR* alterations should be the SOC to identify patients who will benefit from this precision medicine.

Addition of Atezolizumab to Cabozantinib Fails to Improve Outcomes in Pretreated Renal Cell Carcinoma

The addition of atezolizumab (Tecentriq, Genentech) to cabozantinib (Cabometyx, Exelixis) does not improve clinical outcomes and increases toxicity in patients with renal cell carcinoma (RCC) that has progressed despite prior checkpoint inhibitor treatment, according to the results of the CONTACT-03 trial. This is the first randomized, phase 3 trial to examine the benefit of checkpoint inhibitor rechallenge by direct addition to a control arm, said presenter Dr Toni K. Choueiri, and the results should prompt caution when considering this approach for other cancers.

The trial enrolled 522 patients with inoperable, locally advanced, or metastatic clear cell (cc) or non-cc RCC that had progressed on or after checkpoint inhibition. Patients were randomly assigned in a 1:1 ratio to atezolizumab at 1200 mg intravenously every 3 weeks plus cabozantinib at 60 mg orally daily (n=263) or cabozantinib alone (n=259). The primary efficacy endpoints were PFS by blinded independent central review (BICR) and OS.

At a median follow-up of 15.2 months, median PFS by BICR was not significantly longer in the atezolizumab group than in the cabozantinib-alone group, at 10.6 vs 10.8 months, respectively, and subgroup analysis failed to identify any subset of patients who benefited from the combination. Median OS also was not significantly different between the atezolizumab group and the cabozantinib-alone group, at 25.7 months vs not estimable at the interim analysis. The confirmed ORR was approximately 41% in both arms and the duration of response was not significantly different between the atezolizumab group and the cabozantinib-alone group, at 12.7 vs 14.8 months, respectively. Grade 3 or 4 TRAEs occurred in

55.3% of the atezolizumab patients and 47.3% of the cabozantinib-alone patients who were evaluable for safety. Deaths due to TRAEs occurred in 1.1% and 0% of patients, respectively, and serious TRAEs occurred in 24.0% and 11.7% of patients, respectively.

The results of CONTACT-3 were simultaneously published in the *Lancet*. The authors concluded that "these results should discourage sequential use of immune checkpoint inhibitors in patients with renal cell carcinoma outside of clinical trials."

Choueiri T, Albiges L, Tomczak P, et al. Efficacy and safety of atezolizumab plus cabozantinib vs cabozantinib alone after progression with prior immune checkpoint inhibitor (ICI) treatment in metastatic renal cell carcinoma (RCC): primary PFS analysis from the phase 3, randomized, open-label CONTACT-03 study [ASCO abstract LBA4500]. *J Clin Oncol.* 2023;41(17)(suppl).

Commentary: CONTACT-03, which is the first phase 3 trial to test sequential checkpoint inhibition in patients with metastatic RCC, failed to demonstrate any signal of efficacy in favor of the combination. Cabozantinib alone revealed improved efficacy in this setting beyond its label, with the longest median PFS, OS, and ORR of any single-agent tyrosine kinase inhibitor in patients previously treated with immunotherapy.

AI-Derived Pathology Biomarker Predicts Benefits of Long-Term Hormonal Therapy in High-Risk Localized Prostate Cancer

An artificial intelligence (AI)-derived clinical and histopathologic biomarker called ArteraAI LT-ADT can predict which men with high-risk localized prostate cancer receiving radiotherapy (RT) benefit from long-term vs short-term androgen deprivation therapy (ADT), according to research by Dr Andrew J. Armstrong and colleagues from the National Radiotherapy Group (NRG).

The researchers began by digitizing pretreatment prostate biopsy slides from 6 phase 3 NRG/RTOG randomized trials of men receiving RT with or without ADT for prostate cancer. The AI-derived biomarker was trained by having AI analyze the relationship between the slides, the use of long-term ADT, and the rate of distant metastasis (DM) in 2641 men from 5 trials: RTOG 9408, 9413, 9902, 9910, and 0521. After establishing the biomarker, it was validated using data from 1192 men from the phase 3 RTOG 9202 trial, in which patients were randomly assigned to RT plus either short-term ADT (4 months) or long-term ADT (28 months). The median follow-up was 17.2 years, and most patients (80%) had at least 1 high-risk or very high–risk feature.

As expected, the use of long-term ADT significantly improved the rate of DM in the validation cohort. AI biomarker–positive men (66%) were less likely to experience DM if they had long-term ADT (subdistribution HR, 0.55; 95% CI, 0.41-0.73; $P<.001$), whereas AI biomarker–negative men (34%) experienced no benefit with the same treatment (subdistribution HR, 1.06; 95% CI, 0.61-1.84; $P=.84$). The 15-year DM rate was 19% with long-term ADT and 33% with short-term ADT in the AI biomarker–positive group, representing an absolute difference of 14%, whereas it was 11% for both long-term ADT and short-term ADT in the AI biomarker–negative group, showing no benefit from long-term ADT in these patients. The interaction P value was .04, which indicates a predictive utility for ADT duration in this setting. Similar outcomes were observed for the endpoint of death with DM.

Based on the results of the validation study, the authors concluded that the AI biomarker could identify the 29% of high-risk men who could skip long-term ADT in favor of short-term ADT, which would reduce the duration of side effects. In addition, the AI biomarker was able to identify the 43% of intermediate-risk men who might benefit from treatment intensification to long-term ADT owing to a higher risk of DM with short-term ADT.

Armstrong AJ, Liu VY, Selvaraju RR, et al. Development and validation of an AI-derived digital pathology-based biomarker to predict benefit of long-term androgen deprivation therapy with radiotherapy in men with localized high-risk prostate cancer across multiple phase III NRG/RTOG trials [ASCO abstract 5001]. *J Clin Oncol.* 2023;41(16)(suppl).

Commentary: Results from this NRG discovery and validation analysis of pretreatment digital pathology from 6 historical phase 3 trials demonstrate that AI can predict which patients benefit from long-term hormonal therapy and which ones could be spared. Although the results generally align with clinical prognostic features, there were differences. These results suggest that AI could be used to improve our precision in selecting patients for long-term hormonal therapy in addition to RT.

RT Improves Outcomes in Some Men With Castration-Sensitive Prostate Cancer

The addition of primary tumor radiotherapy (RT) to androgen deprivation therapy (ADT) plus abiraterone and prednisone improves radiographic PFS (rPFS) and castration-resistant prostate cancer (CRPC)-free survival in men with de novo metastatic castration-sensitive prostate cancer (mCSPC) and low metastatic burden, according to a second analysis of the phase 3 PEACE-1 trial. In a previous analysis of the trial, ADT plus abiraterone and prednisone improved OS and rPFS in patients with high-volume disease.

PEACE-1, which was presented by Dr Alberto Bossi, is a multicenter, international trial with a 2 × 2 design. A total of 1172 patients with de novo mCSPC and an ECOG performance status of 0 to 2 were randomly assigned in a 1:1:1:1 ratio to 1 of 4 treatment groups: SOC, which consisted of ADT with or without docetaxel; SOC plus abiraterone and prednisone; SOC plus RT; or SOC plus abiraterone and prednisone plus RT. Although SOC initially consisted of continuous androgen deprivation therapy (ADT) with or without docetaxel, docetaxel became required starting in 2017. Docetaxel was administered at 75 mg/m² every 3 weeks for 6 cycles, and abiraterone was dosed at 1000 mg/day and prednisone at 10 mg/day until disease progression or intolerance. The co-primary endpoints were rPFS and OS.

Although the addition of RT to SOC plus abiraterone and prednisone did not improve OS, it did improve rPFS and CRPC-free survival in men with low-burden, de novo mCSPC. The use of RT had a minimal effect on toxicity, with grade 3 to 5 gastrointestinal disorders occurring in 5% of the non-RT group and 3% of the RT group, and grade 3 to 5 rectal hemorrhage occurring in 0% of the non-RT group and 1% of the RT group. The addition of RT also led to a significant decrease in the time to serious genitourinary events in both the low-volume population and the overall population.

Dr Bossi emphasized that PEACE-1 is the first trial to establish a role for RT in the prevention of serious genitourinary events, regardless of metastatic burden. In addition, he said that a triplet of ADT, abiraterone, and prostate RT "should be considered a standard of care" for men with de novo, low-burden mCSPC. Finally, he added that RT "may be considered" for selected men with de novo, high-burden mCSPC.

Bossi A, Foulon S, Maldonado X, et al. Prostate irradiation in men with de novo, low-volume, metastatic, castration-sensitive prostate cancer (mCSPC): results of PEACE-1, a phase 3 randomized trial with a 2x2 design [ASCO abstract 5000]. *J Clin Oncol.* 2023;41(17)(suppl).

Commentary: Results from the PEACE-1 trial reveal that consolidative treatment of the primary tumor with RT is beneficial to patients with limited metastatic disease. These important, practice-informing results should fine-tune our management of these patients, particularly those with urinary symptoms or large primary tumors.

Addition of Talazoparib to Enzalutamide Increases PFS in mCRPC with HRR Gene Alterations

The addition of talazoparib (Talzenna, Pfizer) to enzalutamide (Xtandi, Astellas) increases rPFS in patients with mCRPC and homologous recombination repair (HRR) gene alterations, according to results from the phase 3 TALAPRO-2 study. This study was the first to evaluate talazoparib plus enzalutamide as first-line treatment for mCRPC, according to presenter Dr Karim Fizazi.

The trial enrolled 399 patients with untreated mCRPC and HRR deficiency who had an ECOG performance status of 0 to 1 and were receiving ADT. Patients were randomized in a 1:1 ratio to receive enzalutamide at a dose of 160 mg once daily plus either talazoparib at 0.5 mg or placebo. Randomization was stratified by prior treatment with abiraterone or docetaxel for CSPC and by HRR gene alteration status. The primary endpoint was rPFS by BICR.

After a median follow-up of 16.8 to 17.5 months, median rPFS by BICR was not reached in the talazoparib group and was 13.8 months in the placebo group, for an HR of progression or death of 0.45 (95% CI, 0.33-0.61; $P<.001$). The rPFS benefit was greater in patients with *BRCA*-mutated disease (HR, 0.20; 95% CI, 0.11-0.36; $P<.001$) than in those with non–*BRCA*-mutated disease (HR, 0.72; 95% CI, 0.49-1.07; $P=.10$). The most common grade 3 or 4 treatment-emergent AE was anemia, and no new safety signals were identified. The use of talazoparib vs placebo also increased the time until deterioration in the Global Health Status/Quality of Life scale, from 19.3 to 27.1 months, respectively (HR, 0.69; 95% CI, 0.49-0.97). OS data were immature, but there was a trend toward improved OS in patients with HRR gene alterations.

Dr Fizazi concluded that based on these data, "talazoparib plus enzalutamide, if approved, should become a standard of care" for patients with mCSPC and HRR gene alterations, especially in those with *BRCA* alterations.

Fizazi K, Azad A, Matsubara N, et al. TALAPRO-2: phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) harboring homologous recombination repair (HRR) gene alterations [ASCO abstract 5004]. *J Clin Oncol.* 2023;41(16)(suppl).

Commentary: New results from the TALAPRO-2 study reveal that patients with HRR-mutated tumors derive a clinically significant doubling in their time to radiographic progression or death with the addition of talazoparib to enzalutamide. The benefit is greater in patients with *BRCA2*-mutated tumors but is still robust in patients with non–*BRCA*-mutated tumors, with an improvement of nearly 30%. These results represent meaningful benefits for patients with limited life expectancy and nonchemotherapy treatment options, and further require us to genetically screen all advanced-stage prostate cancer for HRR mutations.

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