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Review Article

The Best of the Genitourinary Cancers Symposium (ASCO 2021)

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Abstract

The main World Congress on Genitourinary Tumors is held annually under the auspices of the AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO). This year, due to the effects of the pandemic, it was recently held in virtual format. We have selected what we believe to be the best clinical research articles in three anatomical locations, kidney, bladder and prostate. We summarize the articles, their methodology, results and conclusions.

The congress of the American Society of Oncology on genitourinary tumors, held virtually between February 11 and 13, 2021, is one of the largest congresses on genitourinary neoplasms.

Keywords: Genitourinary tumors, Metastasis, Prostate cancer, Renal cancer

PROSTATE CANCER

Regarding castration-sensitive metastatic prostate cancer (mCPSC), the final analysis of the TITAN study, phase III, has shown that apalutamide (APA) + androgen deprivation therapy (ADT) provides a significant benefit in overall survival (OS) in this group of patients, regardless of the extent of the disease and with a good safety profile [1].

Previously in 2019, it was demonstrated that APA + ADT met the co-primary objectives of OS and radiological progression-free survival (PRS) in patients with mCPSC.

After a median follow-up of 4 years, these results show a statistically significant improvement in OS with PAC, with a 35% reduction in risk of death (HR: 0.65, P <0.0001) compared to ADD alone. This result was similar to the primary analysis, despite the subsequent crossover (40%) from the placebo group to the APA arm. The improvement after adjustment with cross-over patients resulted in a 48% reduction in death (HR: 0.52, P <0.0001).

The benefit was also consistent across the other secondary endpoints, including second progression-free survival (PFS2) (HR: 0.62, P <0.0001) and delay in resistance to castration (HR: 0.34, P <0.0001). The quality of life, safety and tolerability were consistent with what was previously reported.

As has been commented by its authors, the final analysis of TITAN confirms the clear long-term benefit with APA and the adequate safety profile without alteration in the quality of life of these patients.

Darolutamide (DARO) in the ARAMIS study, together with enzalutamide (ENZA) in the PROSPER and apalutamide (APA) in the SPARTAN have shown improvement in metastasis-free survival (MFS) and have been added to the therapeutic options for cancer patients of non-metastatic castration resistant prostate (nmCRPC) since they were presented in 2018. Subsequently, these studies have also shown a significant improvement in overall survival (OS).

In ASCO GU 2021, the results of the analysis of the crossover effect of placebo to darolutamide on OS in the ARAMIS trial have been presented, the original design recruited 1509 patients with mCRPC who were randomized to receive 2: 1, DARO (n=955) or placebo (n=554) and all patients continued ADD. The results of the first analysis showed that DARO significantly prolonged SLM compared to placebo (HR: 0.41; 95% CI, 0.34-0.50; P <.0001).

In the OS analysis, 170 patients crossed over from placebo to DARO (30.7% of those who were randomized to placebo). The final analysis was performed after 254 deaths occurred (15% in patients who received DARO and 19.1% who received placebo). DARO showed a statistically significant OS benefit (HR: 0.69, P = 0.003) and no new toxicities were reported. ACIS is the randomized phase III clinical trial that used the combination of apalutamide + abiraterone (ABI/ pred) (APA 240 mg/day + ABI 1000mg/day- pred 5 mg/BID) vs. ABI / pred (same doses) as the first line of treatment in patients with mCRPC who progressed to ADD and who had

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not been treated with previous systemic therapy (n = 982).

The initial analysis showed that APA + ABI/pred prolongs the PRS vs. ABI / pred in patients with mCRPC not previously exposed to chemotherapy with an absolute difference of 6 months in favor of the combination (22.6 months vs. 16.8 months, 31% reduction in risk of radiological progression or death, P <.001).

An update to 4.5 years showed that APA + ABI/pred continues to maintain a reduction in PFS compared to ABI/pred (24.4 months vs. 16.6 months, respectively; absolute difference of 7.4 months, 30% reduction in risk of radiological progression or death, P <.0001). However, the secondary endpoints were similar in both groups, and there was no significant difference in OS (36.2 months vs. 33.7 months) between both treatment groups. A reduction of PSA ≥ 50% was reported in 79% with the combination vs. 72.9% with ABI / pred. There were no new adverse events than previously reported, but slightly higher rates of adverse events were seen with the combination.

RENAL CANCER

Treatment in patients with metastatic renal cell carcinoma (mCRC) has changed dramatically in recent years. The era of immunotherapy began with the CheckMate 214 study, the combination of nivolumab and ipilimumab (NIVO + IPI) compared with sunitinib (SUN) demonstrated a benefit in survival and increased responses to treatment. However, data on recurrence and disease progression patterns with immuno-oncological agents are still scarce [2].

In this congress, the results of the evaluation by progression patterns with NIVO + IPI vs. SUN. After a minimum follow-up of 4 years, the progression patterns were defined by a growth of ≥20% of the target lesion, uneqivocal progression of the non-target lesions and the appearance of new lesion (s) (LN). Response and progression were assessed by an independent radiological review committee using RECIST v1.1.

Radiological progression was documented in 299/550 (54.4%) patients with NIVO + IPI versus 289/546 (52.9%) with SUN. The pattern of radiological progression differed between the arms: with NIVO + IPI, 106/299 (35.5%) resulted only in NL versus 74/289 (25.6%) with SUN, and this difference was more pronounced in patients with an initial response confirmed (36/71 [50.7%] vs. 23/84 [27.4%]).

Most of the radiological progressions of only LN in the initial responders occurred in a single organ (34/36 [94.4%] for NIVO + IPI; 20/23 [87.0%] for SUN, the most frequent sites being the lymph nodes (11/34 [32.4%]), brain (8/34 [23.5%]) and lung (5/34 [14.7%]) with NIVO + IPI, and lymph nodes (7/20 [35.0%]), brain (4/20 [20.0%]) and adrenal gland (3/20 [15.0%]) with SUN.

This analysis allowed us to observe the differential radiological patterns of tumor relapse and disease progression after long-term follow-up; resulting in that the progression of LN occurred more frequently with NIVO + IPI versus SUN and in a particular way in the subgroup of patients who progressed after having obtained a response with the treatment, reaching these radiological patterns have therapeutic implication.

The JAVELIN Renal 101 trial demonstrated the superiority of avelumab + axitinib (AVE + AXI) compared to sunitinib (SUN) in patients with mCRC; however, the role of the combination of immunotherapy + VEGFR inhibition in elderly patients is still unclear. At this conference, Yoshihiko [3] and his colleagues provide an update of age-stratified efficacy and safety results.

Age stratification was as follows: 271, 138, and 33 patients aged <65, ≥65 to <75, and ≥75 years, respectively, were randomized to receive avelumab + axitinib; while 275, 128 and 41 patients were randomized to receive sunitinib.

The proportion of risk groups according to the International Consortium of mCRC databases (IMDC) was equitable in each age group of both arms; however, in the subgroup aged ≥75 years, the frequency of intermediate-risk patients was slightly higher in the CVA + AXI group, and that of favorable-risk patients was slightly higher in the SUN group. The median follow-up was 19 months in the CVA + AXI group and 16 months in the SUN group. The benefit of the combination was constant in the age groups; especially in terms of objective response rate (ORR) and progression-free survival (PFS). The most common treatment-related adverse events were diarrhea, hypertension, palmar-plantar erythrodysesthesia syndrome, fatigue, and nausea [4].

The combination AVE + AXI shows favorable efficacy in all age groups, including patients older than 75 years.

KEYNOTE

426 is a phase III, randomized, open-label trial studying the combination therapy of pembrolizumab + axitinib (PEMBRO + AXI) that has been shown to significantly improve OS, PFS, and ORT compared to sunitinib (SUN) as first-line therapy line for patients with mCRC.

During this congress, Plimack and collaborators [5] provide us with an update on this study focused on the group of patients who received PEMBRO + AXI and who completed two years of follow-up.

Of 432 patients treated with PEMBRO + AXI, 129 (29.9%) completed 2 years of treatment. 72.1% were men with a median age of 61 years (36-82); 42 (32.6%) and 87 (67.4%) patients had favorable and intermediate / low risk according to the IMDC, respectively. The median follow-up was 31.1 (24.0-37.7) months.

For patients who completed the two years of treatment, the OS rates at 36 months were 93.8% (95% CI, 85.5% -97.4%). The PFS at 24 and 36 months were 72.7% (95% CI, 64.0% -

79.7%) and 57.7% (95% CI, 46.3% -67.5%), respectively. The ORR was 85.3% and the complete response rate was 14.0%. 59.7% of patients experienced grade 3-5 treatment-related adverse events and 8.5% experienced grade 3-5 immune-mediated adverse events.

This analysis allows us to conclude that the proportion of patients who completed 2 years of treatment with combination therapy maintain a clinical benefit with a safe toxicity profile [3].

New analyzes of the Phase III CheckMate 9ER trial, an open label, randomized 1: 1 study of nivolumab + cabozantinib (NIVO + CABOZ) vs. sunitinib (SUN) were presented at this congress. At a median follow-up of 23.5 months, sustained and significant efficacy has been demonstrated in relation to PFS, ORT and OS in favor of the combination for the first-line treatment of patients with mCRC.

In the total population, the combination doubled the PFS (17 months vs. 8.3 months; HR: 0.52; 95% CI, 0.43-0.64). In addition, it showed a 34% reduction in the risk of death compared to sunitinib (HR: 0.66; 95% CI, 0.5-0.87). The disease control rate (complete response, partial response, and stable disease) was 88.2% vs. 68.9%, respectively. The complete response rate for the combination was 9.3% vs. 4.3% with SUN. Regarding adverse effects, of the patients receiving the combination, only 6.6% interrupted doses (9.7% only NIVO and 7.2% only CABOZ).

In the subgroup analysis, of 75 (11.5%) patients with sarcomatoid histology, 34 were randomized to receive combination therapy vs. 41 patients received SUN. After a median follow-up of 18.1 months, the combination was shown to reduce the risk of death by 64% compared to SUN (HR: 0.36; 95% CI, 0.17-0.79), a higher PFS of 10.3 months vs. 4.2 months and an objective response rate of 55.9% versus 22%.

UROTHELIAL CANCER

Regarding adjuvant therapy, an update of the POUT clinical trial was presented. A phase III, open-label, randomized study that included patients at high risk of recurrence after surgery for upper tract urothelial carcinoma. This trial demonstrated a significant improvement in disease-free survival (DFS) (HR: 0.45; 95% CI: 0.30-0.68) post adjuvant chemotherapy with a median follow-up of 30.3 months.

Birtle [6] Presented updated results at a median follow-up of 48.1 months, showing that the benefit is maintained in DFS (HR: 0.52; 95% CI: 0.35 - 0.76; P = 0.0006) and survival metastasis-free (MFS) (HR: 0.52; 95% CI: 0.36-0.77; P = 0.0007)

During follow-up, there were 93/260 (35.8%) patients who died, and chemotherapy conferred a 30% reduction, a result not statistically significant in relation to the relative risk of death (HR: 0.70; 95% CI, 0.46-1.06; P = 0.09)

The 3-year OS rate for observation patients was 67% (95% CI, 58% -75%) and 79% for post-chemotherapy patients (95% CI, 71% -86%). There was no evidence of long-term toxicity associated with chemotherapy, and grade> 2 adverse events were hypertension (10.4%), lethargy (10.4%), and hearing loss (5.4%). There were no significant differences in quality of life at 12 months after treatment.

In relation to metastatic disease, the following studies will be reviewed:

The JAVELIN Bladder 100 study evaluating avelumab maintenance therapy in patients with locally advanced unresectable or metastatic urothelial carcinoma. These patients received induction chemotherapy followed by checkpoint inhibitor maintenance therapy plus best supportive therapy or only best supportive therapy. This study demonstrated that the addition of avelumab improved OS. However, the optimal duration of first-line chemotherapy treatment is unknown and for some patients it is not possible to receive the 6 cycles of chemotherapy [7].

During ASCO GU 2021, an analysis of this study was presented on the efficacy of treatment measured by the duration or number of cycles of first-line chemotherapy. The subgroups were divided into quartiles (Qs) of duration (<Q1 [<15.0 weeks], Q1-Q2 [15.0 to <18.0 weeks], Q2-Q3 [18.0 to <20.1 weeks] and> Q3 [> 20.1 weeks]) or estimated number of cycles (4, 5, or 6) of first-line chemotherapy. The duration of chemotherapy included dosing delays / interruptions, and the decision to discontinue first-line chemotherapy was left to the investigator.

An improvement in OS was observed with maintenance avelumab versus the comparator arm, regardless of the duration or cycles of first-line chemotherapy received prior to trial entry. Additionally, in patients who discontinued first-line chemotherapy before completing the 6 cycles, avelumab maintenance also provided an OS benefit.

Atezolizumab (anti-PD-L1) monotherapy is approved for cisplatin-ineligible patients who have locally advanced or metastatic urothelial cancer, with immune cells expressing PD-L1 in ≥ 5% of the tumor area (IC2/3 per VENTANA trial SP142 IHC).

The IMvigor130 trial, a multicenter, phase III, randomized study with a three-arm design: arm A: atezolizumab + platinum / gemcitabine (plt / gem); arm B: Atezolizumab monotherapy and arm C: placebo (pbo) + plt / gem; addressed atezolizumab monotherapy or in combination as first-line treatment.

The results of this trial were published in May 2020, showing a significant benefit in progression-free survival (PFS) of arm A versus arm C as first-line treatment. The OS results were immature; however, OS in arm B showed efficacy in favor of patients with HF2 / 3.

Galsky and colleagues [8] presented an exploratory analysis at the congress, where the results are evaluated according to the status of PD-L1. OS was calculated using a hierarchical fixed sequencing procedure: arm A vs. arm C in the intention-to-treat population; then, arm B versus arm C in the intention-to-treat population and IC2 / 3 patients. No subgroup analysis was performed. OS and objective response rate (ORR) were descriptively evaluated.

In the results, there were no differences in OS when comparing arm B vs. arm C in the intention-to-treat population (HR: 1.02; 95% CI: 0.83-1.24). Similarly, there was no OS benefit when comparing arm B with arm C in patients with PD-L1 CI2 / 3 (HR: 0.68; 95% CI. 0.43-1.08). However, there was a difference in OS of arm B vs. arm C (HR: 0.53; 95% CI: 0.30-0.94) and a benefit in ORT (arm B 38%, CI 95% 25-53; arm C 33%, CI 95% 19-49) in patients treated with atezolizumab with CI2 / 3 not eligible for cisplatin.

Regarding adverse events related to treatment; was evidenced in 60% of patients in arm B and 96% of patients in arm C. Grade 3-4 treatment-related adverse events occurred in 15% of patients in arm B and 81% of patients in arm C.

The authors conclude that this analysis provides additional evidence of the clinical benefit of atezolizumab as a single agent in addition to an adequately tolerated safety profile other than chemotherapy in these patients.

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