Prostate Cancer Highlights from ASCO GU 2021: Cutting-Edge Results

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Apalutamide continues to demonstrate survival benefits in patients with mHSPC and mCRPC

At ASCO Genitourinary (GU) Cancers Symposium 2021, Dr Kim Chi presented the final analysis of the phase III TITAN trial¹, which investigated the efficacy and safety of apalutamide in combination with androgen-deprivation therapy (ADT) versus placebo in patients with metastatic, hormone-sensitive prostate cancer (mHSPC)². After a median follow-up of 44 months, apalutamide plus ADT reduced the risk of death by 35% (HR: 0.65 [95% CI: 0.53–0.79]; $p < 0.0001$). After adjusting for a crossover (~40%), the HR improved to 0.52 [95% CI: 0.42–0.64]; $p < 0.0001$, which translated into a 48%-reduction in the risk of death with apalutamide. This overall survival (OS) benefit was maintained across all prespecified subgroups, including disease volume, baseline lactate dehydrogenase (LDH) level and the presence of visceral disease. Results also showed that health-related quality of life (HRQoL) is maintained with apalutamide and somewhat improved compared with placebo after 2.5 years of treatment. There were no new safety signals. Cardiovascular

events are also a side effect of ADT and augmented by second-generation AR inhibitors. This is a class-specific side effect compared with skin rash, which is rather specific for apalutamide but can be well-managed with the respective care. Taken together, apalutamide is another life-prolonging drug in the treatment armamentarium of mHSPC that facilitates a treatment selection based on patient characteristics and comorbidities.

Positive results were also obtained in the final analysis of the randomized, phase III ACIS trial, which showed that the addition of apalutamide to abiraterone acetate and prednisone (AAP) reduced the risk of radiographic progression or death by 30% in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC).³ In this study, 982 patients underwent 1:1 randomization to receive AAP plus either apalutamide ($n=492$) or placebo ($n=490$). At a median follow-up of 54.8 months, the median radiographic progression-free survival (rPFS) was 24.0 months among patients receiving apalutamide plus AAP and 16.6 months among those receiving

placebo plus AAP (HR: 0.70 [95% CI: 0.60–0.83]). The rPFS benefit with apalutamide plus AAP was sustained across prespecified subgroups, including patients aged ≥ 75 years or the presence of visceral metastasis. Regarding secondary endpoints, there was no significant difference in OS, time to initiation of cytotoxic chemotherapy, pain progression, and chronic opioid use between the two treatment arms. However, there was a trend toward better OS outcomes with apalutamide plus AAP in selected prespecified biomarker subgroups, such as luminal histology or high androgen activity. Results further showed that 79.5% of patients in the apalutamide plus AAP arm had a prostate-specific antigen (PSA) decline of $\geq 50\%$ compared with 72.9% in the control arm ($p=0.015$), with 24.6% versus 19.2% of patients having undetectable PSA (<0.2 ng/mL) at any time during treatment ($p=0.040$). In the final analysis, no new safety signals were reported. About two-thirds of patients treated with apalutamide experienced treatment-emergent adverse events (TEAEs), compared with 56.2% of placebo-treated patients. Grade 3–4 TEAEs that were more common in the apalutamide-based arm compared with the placebo-based arm included hypertension, fatigue and cardiac disorders.

¹⁷⁷Lu-PSMA-617 is a new class of effective therapy for patients with mCRPC

Lutetium-177 (¹⁷⁷Lu)-PSMA-617 (LuPSMA), a radiolabelled small molecule that binds with a high affinity to prostate-specific membrane antigen (PSMA), was used in countries like Germany, Austria or Australia (access granted by specialized clinical programs or individual permissions) over many years but until now, data from randomized trials concerning the efficacy and safety of this therapy were not available. At ASCO GU 2021, Prof. Michael Hofman presented the updated results of the randomized, phase II TheraP trial comparing LuPSMA and cabazitaxel (20 mg/m²) in 200 men with docetaxel-treated metastatic castration-resistant prostate cancer (mCRPC).⁴ Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 and PSA ≥ 20 ng/mL. Of note, patients with low PSMA expression and FDG discordant disease were excluded from the study. The study met its primary endpoint as more patients receiving LuPSMA achieved a higher PSA response, defined by a $>50\%$ reduction from baseline, than patients receiving cabazitaxel (66% vs 37%). LuPSMA versus cabazitaxel also improved both, PFS (HR: 0.63 [95% CI: 0.46–0.86]; $p=0.0028$) and objective response rate (ORR) (49% vs 24%). While grade 1–2 thrombocytopenia, dry mouth and dry eye were more common among LuPSMA-treated versus cabazitaxel-treated patients, LuPSMA was associated with fewer grade 3–4 adverse events (AEs). Surprisingly, cabazitaxel demonstrated a considerably lower rate of neutropenia (grade 1–2: 5%; grade 3–4: 13%) in comparison with our research, which showed that the rate of grade ≥ 3 neutropenia ranges between 40% and 82% and is associated with improved outcome parameters such as PSA response rate, PFS and OS. Several patient-reported outcomes also favored LuPSMA. As stated by Prof. Hofman, the trial was relatively small and lacked OS data, a follow-up and the results of the VISION trial has thus been of great importance.^{5,6} Nevertheless, LuPSMA is an active treatment with a good safety profile, which might soon replace some of the current therapies utilized in clinical practice.

Immune checkpoint inhibitors and prostate cancer: What is new?

KEYNOTE-365 is a phase Ib/II study designed to investigate the safety and efficacy of pembrolizumab in combination with 4 different drug combinations in patients with mCRPC.⁷ At ASCO GU 2021, Dr Leonard Appleman presented new efficacy and safety data from cohort B receiving pembrolizumab plus docetaxel and prednisone, after an additional year of follow-up.⁸ This study included patients who did not respond to or were intolerant to ≥ 4 weeks of abiraterone or enzalutamide in the prechemotherapy mCRPC state and whose disease progressed within 6 months of screening. At data cut-off, both confirmed and unconfirmed PSA response rates (PSA decrease $>50\%$) were 43.7%, while the median radiographic PFS (rPFS) was 8.5 months and the median OS was 20.2 months. Although the authors claimed that survival outcomes and response rates have been encouraging, these results are comparable with those from the TAX 327⁹, SWOG 99-16¹⁰ and FIRSTANA¹¹ trials, which demonstrated a median OS of 20–25 months, exceeding 30 months in the subgroup of patients with severe neutropenia.

In my opinion, these results do not confirm the superiority of this pembrolizumab-based regimen over chemotherapy alone. A similar conclusion can be drawn when interpreting data from arm B of the phase II CHECKMATE 9KD trial, which assessed the efficacy and safety of nivolumab in combination with rucaparib, docetaxel and prednisone in patients with mCRPC.¹² The median PSA change from baseline for all patients (n=81) was 54.6% and more than half of the patients were responders. Notably, slightly better activity was observed in patients without prior exposure to novel antiandrogen therapy (NAT). At a median follow-up of 15.2 months, the median rPFS was 9.0 months and the median OS was 18.2 months. As these results were similar to the KEYNOTE-365 trial, the question remains whether this treatment combination is superior to chemotherapy alone and how to identify the patient achieving the greatest benefit from the addition of ICI.

SARS-CoV-2 and prostate cancer: Has ADT impacted COVID-19 outcomes?

A significantly higher number of men were affected in the first wave of coronavirus disease-2019 (COVID-19). After the discovery that transmembrane protease serine 2 (TMPRSS2) promotes the entry of severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) into the host cells, specialists in the field of prostate cancer discussed whether ADT can down-regulate the TMPRSS2 and decrease the probability of infection or improve the clinical outcomes. At ASCO GU 2021, Dr Daniel Kwon reported no association between the use of ADT and SARS-CoV-2 infection (odds ratio [OR]: 1.18) in a study of a diverse patient population at the University of California Health System medical centers and hospitals.¹³ However, racial or ethnic disparities were observed as African-American and Hispanic patients had a twice as high OR for COVID-19 infection in comparison with Whites.

Similar results were obtained in a study from the CCC19 Prostate Cancer Working Group, which provided evidence that ADT was not associated with improved COVID-19 outcomes.¹⁴ In addition, a high overall mortality rate of 15%, irrespective of the receipt of ADT, was reported. The study also indicated that hydroxychloroquine (HCQ) and remdesivir led to significantly worse outcomes in terms of disease severity (adjusted OR:

8.21 and 5.61), while HCQ considerably increased 30-day mortality (adjusted OR: 5.15). However, these results might be biased as HCQ was most likely given to the extremely critical patients; the high mortality rate might also be related to the side effects of the drug. Furthermore, in a retrospective study, the ADT use in patients with prostate cancer prior to COVID-19 diagnosis did not influence the severity of infection as defined by hospitalization, oxygen utilization, and death.¹⁵ A subgroup analysis also demonstrated that age is the most important predictor of OS (≥ 70 years vs < 70 years; HR: 3.65). Again, no difference in the survival curves was observed in patients with or without ADT.

Role of biomarkers in prostate cancer

A retrospective analysis of the phase III PROSPER trial, which evaluated the safety and efficacy of enzalutamide versus placebo in patients with nonmetastatic CRPC, showed the importance of the depth of response to enzalutamide treatment.¹⁶ About 85% of men receiving enzalutamide had a PSA decline of $\geq 50\%$; of these, 38% of patients achieved PSA reduction $\geq 90\%$ with actual nadir < 0.2 ng/mL, and 27% achieved PSA reduction $\geq 90\%$ with actual nadir ≥ 0.2 ng/mL. Among enzalutamide-treated patients, there was a correlation between increased depth of PSA decline and improved both, OS and metastasis-free survival (MFS). These results suggest that we need more dynamic biomarkers that could help us to adjust treatment during the therapy.

Another study evaluated biomarker associations with rPFS¹⁷ from the phase III IPATential150 trial, which assessed the efficacy and safety of ipatasertib plus abiraterone versus abiraterone alone in patients with treatment-naïve mCRPC¹⁸. Previous data demonstrated an improved rPFS with the combination regimen in the intention-to-treat population as well as in patients with tumors with PTEN loss as assessed by immunohistochemistry (IHC). In the present exploratory analysis, among patients evaluable also for next-generation sequencing (NGS) analysis, there was a good concordance between PTEN loss by IHC and NGS. Notably, stratifying patients by PTEN loss determined by NGS confirmed the rPFS benefit with ipatasertib plus abiraterone, showing that survival outcomes can be significantly improved by the appropriate selection of biomarkers and the most appropriate method for their determination.

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