Highlights in Prostate Cancer from ASCO GU 2022

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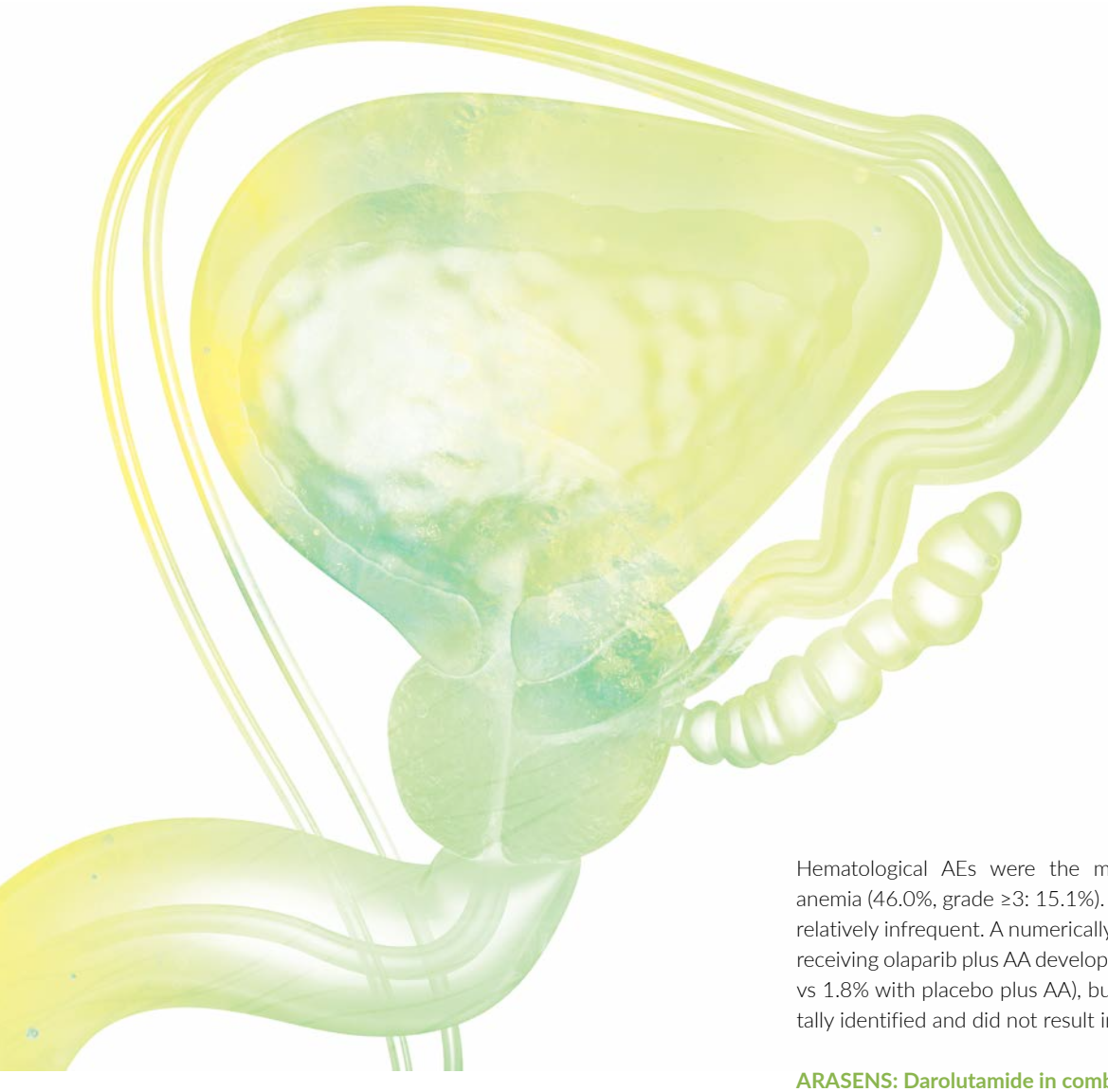
MAGNITUDE: Niraparib plus AAP significantly improved clinical outcomes as first-line therapy for mCRPC with HRR gene alterations

Up to 30% of patients with prostate cancer have defects in the homologous recombination repair (HRR) genes such as *BRCA1/2*, *ATM* and *CHEK2*,[1] rendering these tumors highly sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors (i) like olaparib or niraparib. Blocking androgen receptor (AR) signaling in patients receiving androgen-deprivation therapy (ADT) activates PARP signaling, resulting in synthetic lethality upon PARP inhibition, as demonstrated in preclinical models.[2] Promising results were previously reported from phase II trials on olaparib in combination with abiraterone acetate (AA), as well as niraparib monotherapy, in patients with metastatic castration-resistant prostate cancer (mCRPC).[3,4] Recent data also showed that olaparib yielded improved survival in the phase III PROfound trial in patients with mCRPC who had disease progression while receiving a new hormonal agent (NHA) like enzalutamide or abiraterone.[5,6] Based on these positive results, the MAGNITUDE and PROpel trials have been initiated.

The randomized, double-blind, phase III MAGNITUDE study assessed niraparib plus AA and prednisone (P) in previously untreated patients with mCRPC.[7] After the screening for HRR alterations, patients were allocated to either biomarker-positive or biomarker-negative cohort, with each cohort randomized to either niraparib plus AAP or placebo plus AAP. The primary endpoint was radiographic (r) progression-free survival (PFS), assessed by central review, in the *BRCA1/2* population. At baseline, patient characteristics were generally balanced, except for an increased proportion of patients with baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 and visceral metastases in the niraparib versus placebo arm in the HRR-positive cohort. The HRR-negative cohort was closed early, as prespecified early futility analysis showed no benefit of niraparib plus AAP.

After a median follow-up of 16.7 months, niraparib plus APP versus placebo plus AAP significantly improved rPFS in the *BRCA1/2* subgroup (median, 16.6 months vs 10.9 months; HR: 0.53 [95% CI: 0.36–0.79]; p=0.0014) and in the entire biomarker-positive population (median, 16.5 months vs 13.7 months; HR: 0.73 [95% CI: 0.56–0.96]; p=0.0217).[7] The rPFS benefit with niraparib was maintained across key prespecified subgroups in the HRR-positive cohort. The secondary endpoints including time to cytotoxic chemotherapy, time to symptomatic progression and time to prostate-specific antigen (PSA) progression also favored niraparib over placebo. Overall survival (OS) data were immature at a median follow-up of 18.6 months, showing a numerically prolonged OS in the experimental arm versus the control arm. In the overall HRR-positive cohort, niraparib plus AAP versus placebo plus AAP doubled the overall response rate (ORR) (60% vs 28%), with a complete response rate (CRR) of 22% and 11%, respectively; the CRR magnitude was however lower among *BRCA1/2*-mutant patients (18% vs 14%). Regarding safety, drug-related adverse events (AEs) were more common in patients receiving niraparib plus AAP versus AAP alone (76.4% vs 55.0%), with an increased frequency for dose reduction (19.8% vs 3.3%) and discontinuation (10.8% vs 4.7%). AEs of special interest were cardiovascular events, including hypertension (31.6% with niraparib plus AAP vs 22.3% with placebo plus AAP), arrhythmia (12.7% vs 5.7%) and ischemic heart disease (1.9% vs 3.8%).

Of note, in the safety analysis of phase III PARPi trials in ovarian cancer, cardiovascular events were relatively uncommon.[8-11] With the generally increased cardiovascular risk in prostate cancer patients in conjunction with androgen deprivation and the newly emerging side effects of PARPi treatment, a careful as well as specialized follow-up of patients should be encouraged to timely and effectively manage treatment-emergent cardiovascular complications in these patients.



PROpel: Frontline olaparib plus abiraterone significantly prolongs rPFS in mCRPC, irrespective of HRR status

The phase III PROpel trial investigated the combination of olaparib and AA for the first-line treatment of patients with mCRPC, with several inclusion criteria comparable with MAGNITUDE.[12] However, patients were included regardless of HRR status and were not allocated to certain biomarker-defined cohorts. Baseline patient characteristics were well balanced, with 27.8% and 29.0% of patients with HRR mutations in the olaparib plus AA versus placebo plus AA groups, respectively. Olaparib plus AA significantly improved rPFS in the intention-to-treat population (median, 24.8 months vs 16.6 months with placebo plus AAP), with a 34% reduction in the risk of progression or death (HR: 0.66 [95% CI: 0.54–0.81]; p<0.0001). This rPFS benefit was observed across all prespecified subgroups, with slightly improved outcomes for patients <65 years old or those with mutated HRR. OS data were immature, with a positive trend supporting the use of olaparib plus AA. The ORR also favored olaparib plus AA versus AA alone (58.4% vs 48.1%). The olaparib-containing regimen resulted in a higher rate of AEs, leading to more frequent dose interruption (44.7% vs 25.3%) and discontinuation (13.8% vs 7.8%) of the study drug. Hematological AEs were the most common AEs, including anemia (46.0%, grade ≥3: 15.1%). In general, grade ≥3 AEs were relatively infrequent. A numerically higher proportion of patients receiving olaparib plus AA developed pulmonary embolism (6.5% vs 1.8% with placebo plus AA), but these tended to be incidentally identified and did not result in treatment discontinuation.

ARASENS: Darolutamide in combination with docetaxel and ADT as a potential new standard of care in mHSPC

The phase III ARASENS trial evaluated darolutamide, an androgen receptor inhibitor, versus placebo, in combination with docetaxel and ADT in patients with metastatic hormone-sensitive prostate cancer (mHSPC).[13] The primary endpoint was OS. Overall, baseline demographic and disease characteristics were well balanced. At data cutoff, the median OS was not estimable in the darolutamide-containing arm (n=651) and was 48.9 months in the placebo-containing arm (n=654), with 4-year OS rates of 62.7% and 50.4%, respectively (HR: 0.68 [95% CI: 0.57–0.80]; p<0.001). The OS benefit with darolutamide was observed despite the high frequency of subsequent life-prolonging therapies among patients receiving a placebo-based regimen (75.6% vs 56.8% with a darolutamide-based regimen), including NHAs, radium-223, sipuleucel-T and lutetium-177 prostate-specific membrane antigen (PSMA) therapy. The improvement in the median OS with darolutamide-based therapy was consistent across prespecified subgroups. These included the metastatic stage at initial diagnosis, with HR of 0.71 for *de novo* metastatic disease and HR of 0.61 for recurrent metastatic disease. In terms of safety, the triplet with darolutamide had excellent tolerability and did not lead to an increase in AEs, including grade 3–4 events.

Darolutamide is so far the only second-generation androgen receptor inhibitor that demonstrated a clear survival benefit in a triplet combination with ADT and docetaxel in patients with prostate cancer. In fact, subgroup analyses of the TITAN trial assessing apalutamide plus ADT indicated no improvement in OS outcomes among patients who had received prior docetaxel.[14,15] Similarly, early use of docetaxel in patients treated with enzalutamide plus continuous testosterone suppression in the ENZAMET trial did not yet improve OS outcomes, but it was associated with improved time to clinical progression.[16]

Novel treatment options on the horizon: ODM-208 and ARV-110 for mCRPC

In contrast to abiraterone, which interferes with testosterone biosynthesis by inhibiting CYP17A1,[17] the novel agent ODM-208 acts at the first and rate-limiting stage of steroid hormone synthesis, by blocking CYP11A1 and thus suppressing production not only of androgens and their precursors but also glucocorticoids and mineralocorticoids.[18] This mode of action might benefit especially patients with activating mutations in the AR ligand-binding domain (LBD), as these allow for ligand promiscuity (activation by progesterone and cortisol) and might confer resistance to hormone-based therapies in mCRPC.[19,20] The safety and tolerability of ODM-208 were investigated in heavily pre-treated mCRPC patients in the phase I/II CYPIDES study (n=44).[18] Enrolled patients had previously received at least one line of taxane-based chemotherapy and at least one AR signaling inhibitor. CYPIDES was designed as a classical 3+3 dose-escalation trial with an expansion cohort. Overall, 32% of patients achieved a PSA decline of ≥50%, including a 68% response rate in the AR-LBD mutated subgroup. Responses were durable, with a proportion of patients with AR-LBD mutations continuing treatment beyond 1 year. The most common AE was adrenal insufficiency, leading to hospitalization in 31.8% of patients but was rapidly managed with short-term high-dose glucocorticoid treatment.

Another novel agent presented at the 2022 ASCO Genitourinary Cancers Symposium was ARV-110 (bavdegalutamide), a proteolysis-targeting chimera (PROTAC) protein degrader that is directed against wild-type AR and clinically relevant mutations.[21] PROTAC molecules differ from classical inhibitors in their mode of action as they direct the target to the ubiquitin-proteasome system.[22] They are currently explored as a treatment option in prostate and breast cancer, as well as for non-oncology indications. ARV-110 is being assessed in an ongoing phase II expansion study (ARDENT), which included patients with confirmed mCRPC who had previously received 1–2 NHAs with ≤1 chemotherapy regimen.[21] In the biomarker-evaluable group, 46% of patients with AR T878A/S and/or H875Y mutations (n=28) had best PSA declines ≥50%. Data further showed that PSA declines ≥50% were seen across all subgroups including wild-type and less pretreated patients. Based on these initial results, ARV-110 demonstrated a promising mode of action and might represent an important future therapy in this clinical setting.

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