Advances in the Management of Prostate Cancer: Highlights from the 2014 ASCO Annual Meeting

Editors

Robert Dreicer, MD, MS, FACP, FASCO
Chairman, Department of Solid Tumor Oncology
Taussig Cancer Institute
Cleveland Clinic
Professor of Medicine
Cleveland Clinic Lerner College of Medicine
Deputy Associate Director for Clinical Research
Case Comprehensive Cancer Center
Cleveland, Ohio

Daniel P. Petrylak, MD
Professor of Medicine, Medical Oncology
Director, Prostate and GU Medical Oncology
Co-Director, Signal Transduction Program
Director, Prostate Cancer Translational Research Group
Yale Cancer Center
New Haven, Connecticut
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INTRODUCTION
The 2014 American Society of Clinical Oncology (ASCO) Annual Meeting held in Chicago, Illinois, provided a comprehensive review of key experimental and clinical data. Included in this newsletter are highlights from the conference covering major plenary sessions, key symposia, and targeted oral and poster presentations on the advances in the management of prostate cancer.

EDITORS
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Yale Cancer Center
New Haven, Connecticut

TARGET AUDIENCE
The target audience for this activity is medical oncologists, urologists, hematologist/oncologists, surgeons, radiation oncologists, pathologists, oncology pharmacists, and other allied healthcare professionals caring for patients with prostate cancer.

EDUCATIONAL OBJECTIVES
At the conclusion of this activity, participants should be able to:

• Analyze the benefits and limitations of current treatment strategies for castrate-resistant prostate cancer (CRPC)
• Assess clinical data on emerging treatment strategies for CRPC
• Discuss alternative treatment regimens for prostate cancer patients who have failed docetaxel
• Evaluate future treatment strategies for advancement of therapeutic progress in CRPC
• Recommend specific treatment strategies for patients with different characteristics, based on knowledge of the therapeutic options

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Advances in the Management of Prostate Cancer: Highlights from the 2014 ASCO Annual Meeting

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**ACKNOWLEDGEMENT**
The editors wish to thank Marie N. Becker, PhD, Anne Jacobson, MPH, CCMEP, CMPP, and Sara R. Fagerlie, PhD, CCMEP for assistance in writing this document.

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**ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT**
This activity is supported by an independent educational grant from Teva Oncology.

**CME INQUIRIES**
For further information, please contact:
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INTRODUCTION
The 2014 American Society of Clinical Oncology (ASCO) Annual Meeting, held May 30-June 4 in Chicago, Illinois, featured clinical research with practice-changing implications for patient care and highlighted promising treatment strategies that remain on the horizon. This newsletter focuses on new evidence-informing practice on the roles of chemotherapy, hormonal therapy, bone-targeted agents, and immunotherapy in the management of prostate cancer and other genitourinary cancers.

INTEGRATING CHEMOTHERAPY WITH HORMONE THERAPY
The CHAARTED Trial: Adding Docetaxel to ADT
Representing the US Intergroup, Sweeney and colleagues presented findings from the Eastern Cooperative Oncology Group (ECOG) 3805 trial, also known as the CHAARTED study that has practice-changing implications for the management of patients with metastatic prostate cancer.\(^1\)

Since the 1950s, testosterone suppression via surgical or medical means has been the standard first-line treatment for patients with metastatic prostate cancer. Although androgen deprivation therapy (ADT) has a high initial response rate, the disease almost universally progresses despite castrate levels of testosterone. The beneficial role of cytotoxic chemotherapy with agents such as docetaxel has been demonstrated in the castration-resistant state, with evidence of the potential to improve overall survival (OS) in men with metastatic castrate-resistant prostate cancer (mCRPC).\(^2,3\)

The CHAARTED trial tested the hypothesis that adding docetaxel at the time of initiating ADT would prolong survival in men with hormone-naïve metastatic prostate cancer.\(^1\) The trial included 790 men with newly diagnosed hormone-sensitive metastatic prostate cancer. Patients were randomly assigned to treatment with ADT alone (\(n = 393\)) or ADT plus docetaxel (\(n = 397\)). Patients in the ADT plus docetaxel group received docetaxel dosed at 75 mg/m\(^2\) every 3 weeks for a maximum of 6 cycles within 4 months of starting ADT. The primary endpoint was OS. In contrast to patients treated with docetaxel for mCRPC, prednisone was not administered.

Baseline characteristics were similar in both treatment groups. The majority of patients (\(n = 480\)) had a Gleason score \(\geq 8\). Moreover, approximately two-thirds of patients had high-volume disease at baseline, with visceral disease (\(n = 125\)) and/or extensive bone metastases, defined as 4 or more lesions (\(n = 387\)).

The CHAARTED trial was terminated in January 2014 after an interim analysis showed a statistically significant survival advantage in favor of the ADT/docetaxel regimen. At the 2014 ASCO Annual Meeting, Sweeney and colleagues presented the updated survival analysis.\(^1\) With a median follow-up of 29 months, there were 136 deaths in the ADT alone group and 101 deaths in the ADT plus docetaxel group.

Compared with standard ADT alone, adding docetaxel at the time of ADT initiation prolonged OS by more than 13 months. The median OS was 44.0 months for patients treated with ADT alone, compared with 57.6 months for those treated with the upfront combination of ADT plus docetaxel (HR = 0.61; \(P = 0.0003\)) (Figure 1).
At the time of the analysis, the survival benefit associated with docetaxel was apparent in the subgroup of patients with high-volume metastatic disease at the start of ADT (Figure 2). In this group, the median OS was 32.2 months with ADT alone and 49.2 months with ADT/docetaxel, an improvement of 17 months (HR = 0.60; \( P = 0.0006 \)). For the subgroup of patients with low-volume metastatic disease, the median OS has not yet been reached in either treatment group (HR = 0.63; \( P = 0.1398 \)).

The combination of ADT and docetaxel also provided a significant survival advantage across other patient subgroups defined by age, race, Gleason score, the presence of visceral and/or bone metastases, prior local therapy, the use of combined androgen blockade, and the presence of skeletal-related events.

Starting chemotherapy at the time of ADT initiation also improved several secondary endpoints compared with ADT alone, including:

- Prostate Specific Antigen (PSA) < 0.2 ng/dL at 6 months: 27.5% vs 14.0% (\( P < 0.0001 \))
- PSA < 0.2 ng/dL at 12 months: 22.7% vs 11.7% (\( P < 0.0001 \))
- Median time to castration resistance: 20.7 months vs 14.7 months (HR = 0.56; \( P < 0.0001 \))
- Median time to clinical progression: 32.7 months vs 19.8 months (HR = 0.49; \( P < 0.0001 \))
Investigators also evaluated the choice of therapy at the time of biochemical, symptomatic, or radiographic progression. Among 174 patients who progressed on ADT alone, 129 received docetaxel. This indicates a high rate of crossover (74%) to the ADT/docetaxel combination regimen. By comparison, among patients who progressed with upfront combination therapy (n = 145), 49 received additional docetaxel.

The majority of patients in the ADT/docetaxel group (74%) were able to tolerate treatment without requiring any dose modifications, and 87.5% of patients completed all 6 cycles of treatment. Grade 3/4 adverse events (AEs) included neutropenia (12%), neutropenic fever (6%), sensory neuropathy (1%), and motor neuropathy (1%). One patient died from sudden death due to treatment.

The investigators plan to evaluate additional quality of life outcomes to better define the burden of upfront treatment with ADT plus docetaxel. Additional results with longer follow-up may also clarify the potential role of upfront chemohormonal therapy in patients with low-volume metastatic disease.

**The French Genitourinary Tumor Group GETUG 12**

Following the discovery that docetaxel improves survival in patients with CRPC, several docetaxel-based combinations have been evaluated with the goal of further improving patient outcomes. The phase III Genitourinary Tumor Group (GETUG) 12 trial examined the potential benefit of adding docetaxel/estramustine to standard ADT in patients with localized, high-risk prostate cancer with a primary endpoint of progression-free survival (PFS).

The GETUG 12 trial included 413 previously untreated patients with high-risk disease, defined as the presence of 1 or more of the following risk factors: stage T3 or T4 tumor, Gleason score ≥ 8, PSA ≥ 20 ng/mL, or evidence of lymph node invasion. Patients were randomly assigned to treatment with goserelin 10.8 mg every 3 months for 3 years (ADT arm; n = 206) or goserelin plus 4 cycles of docetaxel 70 mg/m² every 3 weeks and estramustine 10 mg/kg/d on days 1-5 (ADT + DE arm; n = 207). Patients in the ADT + DE arm also received aspirin 300 mg/day or warfarin for thromboprophylaxis. All patients received local therapy at 3 months.

In 2012, investigators reported preliminary findings from the GETUG 12 trial. Local treatment consisted of radiotherapy in 87% of patients, with a median dose of 74 Gy in both study arms. After 3 months of therapy, more patients achieved a PSA response (≤ 0.2 ng/mL) with ADT + DE compared with ADT alone (34% vs 15%; P < 0.0001). The early safety analysis showed a low risk of neutropenic fever (2%), no toxic deaths, and no AEs on quality of life at 1 year in the ADT + DE arm.

At the 2014 ASCO Annual Meeting, investigators presented updated findings with a median follow-up of 7.6 years. Treatment with ADT + DE showed a non-significant trend toward improved 8-year PFS (62%) compared with ADT alone (53%) for the entire study group (HR = 0.75 [95% CI, 0.55-1.01]; P = 0.06). However, a subgroup analysis by baseline stratification factors identified patients who were more likely to benefit from the addition of docetaxel and estramustine. In the subgroup of patients with a Gleason score ≤ 7, treatment with ADT + DE significantly improved the 8-year PFS rate compared with ADT alone (69% vs 51%; HR = 0.55 [95% CI, 0.36-0.84]) (Figure 3). By comparison, for patients with a Gleason score ≥ 8, the Kaplan-Meier curves for PFS largely overlapped.
The analysis of OS showed a similar trend. The 8-year OS rate was 83% for the overall study population, with no difference between treatment groups (HR = 0.94 [95% CI, 0.60-1.49]). However, in patients with a Gleason score ≤ 7, the 8-year OS was 94% for patients in the ADT + DE group and 85% for those treated with ADT alone (HR = 0.40 [95% CI, 0.17-0.91]).

The safety analysis showed no long-term toxicity concerns, including no increased risk of secondary cancers in either treatment group. The cumulative risk of grade ≥ 2 AEs ranged from 18% to 21% and was similar in both treatment arms ($P = 0.61$).

Overall, the addition of docetaxel/estramustine to ADT showed a borderline-significant reduction in the risk of progression or mortality compared with ADT alone, with a more pronounced benefit in patients with stage T3 disease, PSA > 20 ng/mL, and a Gleason score ≤ 7. These findings are consistent with findings from the phase III GETUG 15 trial, where ADT plus docetaxel significantly improved survival compared with ADT alone for patients with a Gleason score ≤ 7 hormone-sensitive prostate cancer ($P = 0.0072$), but not for patients with a Gleason score 8-10 cancers ($P = 0.1617$). The interaction between Gleason score and apparent benefit from chemotherapy warrants further evaluation.

**HORMONE THERAPY UPDATE**

*The ELM-PC 4 Trial*

Orteronel (TAK-700) is an investigational, reversible, and selective inhibitor of 17,20-lyase, an enzyme involved in steroidal hormone biosynthesis and up-regulated in mCRPC. The international, multicenter, randomized phase III ELM-PC 5 trial compared orteronel plus prednisone with prednisone alone in post-docetaxel mCRPC. As reported at the 2014 ASCO Genitourinary Cancers symposium, the ELM-PC 5 trial failed to meet the primary endpoint of improved OS with orteronel. However, there was a significant survival benefit with orteronel/prednisone in non-European/non-North American (NA) countries participating in the
ELM-PC 5 trial, suggesting the potential that the availability of agents such as abiraterone and enzalutamide in the US and Western Europe may have “masked” the true benefit of orteronel. Furthermore, orteronel/prednisone significantly improved the secondary efficacy endpoint of radiographic PFS (rPFS) compared with prednisone alone.

The phase III ELM-PC 4 trial evaluated orteronel earlier in the treatment continuum: chemotherapy-naïve mCRPC refractory to standard hormone therapy. The trial enrolled 1,560 men with mCRPC from 324 treatment centers across 43 countries. All patients were chemotherapy naïve, asymptomatic, and not on opioids at screening. Patients were randomly assigned to treatment with orteronel 400 mg twice daily (n = 781) or placebo (n = 779) in addition to prednisone 5 mg twice daily. Compared with the single efficacy endpoint in the ELM-PC 5 trial, the ELM-PC 4 trial designated 2 co-primary endpoints: rPFS and OS.

Patients were stratified by geographic region and the presence of radiographic disease progression at screening. Approximately half of patients (54%) were from Europe, 22% were from NA countries, and 24% were from non-European/non-NA countries. In both treatment groups, 51% of patients had radiographic disease progression at baseline. In addition, 17-18% of patients had visceral disease at baseline, and 51-52% had a Gleason score ≥ 8. The median duration of treatment was 10.1 months for patients in the orteronel plus prednisone group and 8.9 months for those treated with prednisone alone.

Adding orteronel to prednisone significantly improved the median rPFS by more than 5 months. The median rPFS was 8.7 months for patients treated with prednisone alone and 13.8 months for those treated with orteronel and prednisone (HR = 0.71; P < 0.00001) (Figure 4). The rPFS findings were consistently in favor of orteronel across all patient subgroups, including those defined by baseline PSA, Gleason score, the presence of radiographic disease progression at baseline, and geographic region.

**Figure 4. ELM-PC 4: Radiographic PFS with orteronel and prednisone or prednisone alone in chemotherapy-naïve mCRPC.**

- **Median:** Orteronel + Prednisone 13.8 mo vs Prednisone 8.7 mo
- **Events:** Orteronel + Prednisone 489 vs Prednisone 562
- **P** < 0.0001
- **HR = 0.71 (0.626-0.799)**
Despite the significant 29% improvement in rPFS with orteronel, however, this did not translate to a significant improvement in the second primary endpoint of OS. The median OS was 31.4 months with the orteronel and prednisone group and 29.5 months with prednisone alone (HR = 0.92; \( P = 0.31 \)). A regional subgroup analysis found no survival benefit with orteronel in patients from Europe (\( P = 0.18 \)), NA (\( P = 0.87 \)), or non-European/non-NA regions (\( P = 0.96 \)).

As expected, treatment with orteronel was associated with a rapid reduction in testosterone level, from 7.6 ng/dL at baseline to 0.2 ng/dL (the lower limit of quantification) at week 12 and 24. By comparison, treatment with prednisone alone was associated with a more modest reduction from baseline (7.7 ng/dL) to week 12 (1.9 ng/dL) and week 24 (1.8 ng/dL).

Treatment with orteronel and prednisone also improved several other secondary endpoints compared with prednisone alone, including:

- PSA50 response (≥ 50% decline in PSA) at 12 weeks: 50% vs 28%, respectively (\( P < 0.001 \))
- Circulating tumor cell (CTC) conversion at 12 weeks: 40% vs 25%, respectively (\( P < 0.001 \))
- Median time to any subsequent therapy: 17.2 months vs 13.9 months (\( P < 0.001 \))
- Median time to docetaxel: 23 months vs 19 months (\( P = 0.007 \))

In the safety analysis, patients in the orteronel/prednisone group were more likely than those treated with prednisone alone to develop grade ≥ 3 AEs (67% vs 49%), serious AEs (46% vs 38%), or discontinue treatment due to AEs (26% vs 15%). The most common AEs leading to discontinuation included fatigue, diarrhea, nausea, and vomiting. Based on the disappointing results of the ELM-PC 4 trial, the further clinical development of orteronel in prostate cancer will no longer be pursued.

**CaPSURE Analysis: Immediate vs Deferred ADT**

One of the major challenges in prostate cancer management involves determining the best treatment approach for patients who develop biochemical relapse following curative treatment with surgery or radiotherapy. Although ADT has clear therapeutic advantages in more advanced disease, the risk of treatment-related AEs is daunting for patients who have rising PSA levels but remain clinically asymptomatic. Importantly, there remains no level 1 evidence that earlier introduction of ADT improves patient outcomes. The National Comprehensive Cancer Network guidelines describe the optimal timing of ADT as a “therapeutic dilemma,” while the ASCO guideline states “the critical issue is to determine whether there is benefit – and how large it is – for starting ADT while patients are asymptomatic.”

To address the question of optimal ADT timing, Garcia-Albeniz and colleagues examined the potential benefits and risks of an immediate- versus deferred-ADT strategy in men with a PSA-only relapse after definitive therapy for localized prostate cancer.⁹

Investigators analyzed data from 9,748 men who were participating in the prospective Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry. Of these patients, 2,012 experienced a PSA-only relapse following curative upfront treatment for localized prostate cancer. PSA relapse was defined as PSA ≥ 0.02 ng/mL in patients who were treated surgically or 3 rising PSA measurements 1 month apart among those treated with radiation therapy. Patients in PSA-only relapse had to be asymptomatic and without evidence of metastases.
Two-thirds of patients (68%) underwent prostatectomy with or without radiation therapy as primary treatment for localized prostate cancer, while 32% underwent treatment with radiation therapy alone. In addition, 34% of patients had a Gleason score ≥ 7. The median age at PSA relapse was 69 years, and the median time from primary treatment to PSA relapse was 27 months.

For the survival analysis, patients were grouped according to the timing of ADT:

- Immediate ADT (ie, within 3 months of rising PSA)
- Deferred ADT (ie, ≥ 2 years after PSA-only relapse or at progression)

ADT was defined as the use of any luteinizing hormone-releasing hormone (LHRH) agonists, with or without antiandrogen therapy, or orchiectomy. Progression was defined as short PSA doubling time, the development of severe cancer-related symptoms, or metastasis detected by any imaging technique. The primary endpoint was OS.

The survival analysis included 98,232 person-months of follow up after PSA relapse. There were 185 deaths, including 39 deaths due to prostate cancer. There were no differences in all-cause mortality between the treatment groups (HR, 0.94; 95% CI, 0.51-1.73) (Figure 5). The 5-year OS was 85.1% in the immediate-ADT group and 87.2% in the deferred-ADT group. The 10-year OS was identical in both groups (71.6%).

Prostate-cancer specific mortality was also similar regardless of the timing of ADT (HR, 1.15; 95% CI, 0.33-3.97) (Figure 5). Patients in the immediate-ADT and deferred-ADT groups had similar rates of prostate cancer-specific survival at 5 years (93.3% and 96.0%, respectively) and 10 years (89.4% and 90.2%, respectively).

Figure 5. CaPSURE update. All-cause mortality and prostate cancer-specific mortality with immediate or delayed ADT after PSA-only relapse.
Findings from this observational study suggest that men with PSA-only relapse may be able to delay the start of ADT for at least 2 years, or until clinical progression, without adversely affecting survival outcomes. These results add to the body of evidence that early ADT provides no meaningful improvement in patient outcomes. A prospective, randomized, phase III trial comparing different strategies for ADT timing in patients with PSA-only relapse is currently underway (NCT00110162).

AR-V7: Biomarker of Resistance to Hormonal Therapy

One of the major challenges in cancer treatment involves the selection of optimal therapies for individual patients, as treatment response is often heterogeneous. In the phase III AFFIRM study, for instance, 21% of patients failed to respond to treatment with enzalutamide, while responders benefited from improved survival. The availability of a simple biomarker-based blood test to identify patients with a low likelihood of response would spare patients from unnecessary treatment and steer patients toward alternate therapies.

Multiple factors can contribute to resistance to agents such as enzalutamide and abiraterone, including overexpression of CYP17, activating mutations in the androgen receptor (AR) gene, amplification of AR, and activation of the PI3K/Akt signaling pathway. Another mechanism of treatment resistance involves splice variants of AR. The AR-V7 splice variant is missing the ligand-binding domain of the AR, which serves as the direct target of enzalutamide and abiraterone. AR-V7 protein is constitutively active and has increased expression in CRPC.

At the 2014 ASCO Annual Meeting, Antonarakis and colleagues described the relationship between AR-V7 in CTCs and resistance to enzalutamide and abiraterone in men with mCRPC. Preliminary findings from the study demonstrate the promising role of AR-V7 as a promising biomarker of treatment response.

The prospective study enrolled 62 patients with CRPC who were scheduled to begin treatment with enzalutamide (n = 31) or abiraterone (n = 31). CTC samples were collected at 3 time points during the study: at baseline (pretreatment), at the time of treatment response, and at the development of treatment resistance. AR-V7 status was assessed after CTC enrichment with the Adna Test Prostate Cancer Select followed by AR-V7 detection using custom primers and the Adna Test Prostate Cancer Detect kit. Primary outcomes were PSA response rate, PSA PFS, and PFS.

In the enzalutamide cohort, 12 patients (39%) had detectable AR-V7 in their CTCs, and 19 patients (61%) had AR-V7-negative CTCs. Patients with AR-V7-positive CTCs were more likely than those with AR-V7-negative CTCs to have a history of abiraterone use (92% vs 47%) or docetaxel use (83% vs 53%), and more likely to have visceral metastases (58% vs 16%). The baseline median PSA level was also higher for patients with AR-V7-positive CTCs (144.3 ng/mL) than for patients with AR-V7-negative CTCs (29.8 ng/mL).

The PSA response to enzalutamide differed significantly by AR-V7 status. No patients with AR-V7-positive CTCs responded to enzalutamide (0%), compared with 10 patients with AR-V7-negative CTCs (53%; P = 0.004). Furthermore, AR-V7-positive status was associated with significantly worse PSA PFS (HR, 7.4; P < 0.001) and PFS (HR, 8.5; P < 0.001) (Figure 6).

Patients who started treatment with abiraterone had a lower prevalence of AR-V7-positive CTCs (19.4%) than those in the enzalutamide cohort. However, AR-V7 positivity was similarly prognostic. No patients
AR-V7 is expressed at detectable levels in CTCs in many patients with CRPC. Serial analysis of AR-V7 status is feasible from prospectively collected blood samples in patients with CRPC undergoing treatment with AR-V7-targeted agents. The presence of AR-V7-positive CTCs may indicate both primary and acquired resistance to treatment with enzalutamide and abiraterone.

In the future, validation of these results may help to guide treatment decisions. For instance, patients with detectable AR-V7 in pretreatment CTCs could be offered treatments other than AR-V7-targeted therapies, which have a very low likelihood of response. However, one of the challenges of CTC-based biomarker analysis in earlier settings of mCRPC is the low prevalence of CTCs.
UPDATE ON BONE-TARGETED THERAPY

The TROG 03.04 RADAR Trial

Preliminary findings from the TROG 03.04 RADAR trial demonstrate the importance of individualized patient management, particularly regarding the use of zoledronic acid in patients who are also treated with androgen suppression (AS) therapy.

Adjuvant AS therapy improves outcomes in patients with locally advanced prostate cancer who are treated with radiation therapy (RT). Clinical evidence to date suggests that 28 to 36 months of adjuvant AS is more effective than 3 to 8 months of therapy. However, longer durations of AS (> 24 months) are associated with adverse outcomes, including long-term morbidity.

The TROG 96.01 trial demonstrated the clinical benefits of 6 months of neoadjuvant AS combined with RT for patients with locally advanced prostate cancer. As a follow-up to TROG 96.01, the TROG 03.04 RADAR trial evaluated the use of an additional 12 months of AS following 6 months of neoadjuvant AS, for a total duration of 18 months, as an alternative to 2 or more years of adjuvant AS following RT. The TROG 03.04 trial also examined the role of zoledronic acid in long-term disease control.

Using a 2 x 2 factorial design, 1,071 patients with locally advanced prostate cancer were randomly assigned to 1 of the following 4 treatment groups:

- 6 months of neoadjuvant AS followed by RT (n = 268)
- 18 months of AS, including 6 months of neoadjuvant AS plus 12 months of AS followed by RT (n = 268)
- 6 months of neoadjuvant AS, RT, and 18 months of zoledronic acid (n = 268)
- 18 months of AS (6 months neoadjuvant AS plus 12 months AS), RT, and 18 months of zoledronic acid (n = 267)

The median patient age was 68 years. All patients received AS with leuprolide 22.5 mg IM every 3 months for a total of 2 or 6 cycles. Zoledronic acid 4 mg IV was given every 3 months for 6 cycles. The primary endpoint was prostate cancer-specific mortality.

After a median follow-up of 7.4 years, several significant interactions emerged. Compared with treatment with 6 months of AS alone, treatment with 18 months of AS plus zoledronic acid significantly reduced the risk of PSA progression (HR, 0.71; P = 0.02) and significantly reduced the need for secondary treatment (HR, 0.67; P = 0.02).

The clinical benefit of 18 months of AS plus zoledronic acid, compared with 6 months of AS alone, was even greater in the subgroup of patients with a Gleason score of 8-10 cancers. In this subgroup, treatment with 18 months of AS plus zoledronic acid reduced the risk of PSA progression by 40% compared with 6 months of AS alone (HR, 0.59; P = 0.03). For patients with a Gleason score ≤ 7 cancers, the risk of PSA progression was reduced 35% by 18 months of AS alone compared with 6 months of AS, (HR, 0.65; P = 0.04). The addition of zoledronic acid for 18 months provided no additional benefit.

Results showed important interactions between Gleason score, treatment group, and risk of distant progression. Comparing 6 months of AS alone, treatment with 18 months of AS plus zoledronic acid reduced the risk of distant progression by 46% in patients with a Gleason score of 8-10 cancers (HR, 0.54; P = 0.048). For patients with a Gleason score ≤ 7 cancers, treatment with 6 months of AS plus zoledronic acid showed a trend toward increasing the risk of distant progression compared with 6 months of AS alone (HR, 1.75; P = 0.07).
To better understand these conflicting results, investigators also assessed the risk of bony metastatic progression. This analysis showed that the addition of zoledronic acid in men who received only 6 months of AS increased the risk of bone progression by 85% compared with AS alone (HR, 1.85; \( P = 0.02 \)).

For patients with a Gleason score of 8-10 cancers, all of the efficacy endpoints favored treatment with 18 months of AS plus zoledronic acid compared with 6 months of AS alone (Figure 7A). In contrast, patients with a Gleason score ≤ 7 cancers fared better with treatment with 18 months of AS alone compared with either 18 months of AS plus zoledronic acid or 6 months of AS alone (Figure 7B).

The investigators offered a “unifying hypothesis” to explain the interactions between zoledronic acid, Gleason score, and risk for bony metastases. While zoledronic acid showed activity against a Gleason score of 8-10 cancers, it also appeared to protect bone marrow micro-deposits in patients with a Gleason score ≤ 7 cancers. Bony metastases then increased with testosterone recovery, as observed in patients with a Gleason score ≤ 7 cancers who were treated with 6 months of AS plus zoledronic acid.

All treatment regimens were associated with low rates of treatment-related morbidity. Compared with 6 months of AS alone, all other treatment combinations showed no increased risk of rectal or urinary toxicity, no deterioration in quality of life, and no increase in the risk of vertebral fractures. However, patients who were treated with 18 months of AS alone had an increased risk of non-vertebral fractures during the first 3 years of therapy. Two patients developed osteonecrosis of the jaw.

The primary endpoint of prostate cancer-specific mortality is not yet resolved. Ten-year follow-up data are expected in 2017.

UPDATE ON IMMUNOTHERAPY IN OTHER GENITOURINARY CANCERS

Programmed death 1 (PD-1) is a key immune-checkpoint receptor and a promising target for anticancer therapy. At the 2014 ASCO Annual Meeting, several studies described agents targeting the PD-1 pathway in the treatment of genitourinary cancer.

**Nivolumab in mRCC**

Nivolumab is a fully human monoclonal antibody that restores antitumor T-cell function by selectively blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2. In a phase II trial, Motzer and colleagues examined 3 doses of nivolumab in patients with metastatic renal cell carcinoma (mRCC) who had relapsed after treatment with agents targeting the vascular endothelial growth factor (VEGF) pathway.14

The trial included 168 patients with clear-cell mRCC who had received at least 1 prior antiangiogenic agent and no more than 3 prior systemic therapies. Patients were randomly assigned to intravenous (IV) nivolumab given at a dose of 0.3 mg/kg (n = 60), 2 mg/kg (n = 54), or 10 mg/kg (n = 54) every 3 weeks until disease progression or intolerable toxicity. The primary endpoint was assessing whether a dose-response relationship exists. Secondary endpoints were PFS, objective response rate (ORR), and OS.

At baseline, the majority of patients (82%) had at least 2 metastatic sites, and 25% were considered poor risk according to Memorial Sloan Kettering Cancer Center (MSKCC) criteria. The most common prior systemic therapies in the metastatic setting included sunitinib (74%), everolimus (34%), pazopanib (27%), and interleukin-2 (23%). The duration of follow up was 16 months or longer for all patients.
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Highlights from the 2014 ASCO Annual Meeting

Figures 7A and 7B. The effect of Gleason score (GS) on outcomes after treatment with androgen suppression (AS) for either 6 or 18 months with and without (Z) zoledronic acid treatment for 18 months. Figure 7A. Gleason score greater than 7.

**Figure 7A.** Treatment effects on endpoints for Gleason > 7

18 AS +/- Z vs 6 AS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Groups</th>
<th>n</th>
<th>Events 6 AS</th>
<th>Events 18 AS +/- Z</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>PSA Progression</td>
<td>18 AS v 6 AS</td>
<td>192</td>
<td>42</td>
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<td>Bone Progression</td>
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<td>17</td>
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<td>18 AS+Z v 6 AS</td>
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<td>8</td>
<td>0.56 (0.24, 1.36)</td>
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<tr>
<td>Distant Progression</td>
<td>18 AS v 6 AS</td>
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<td>0.97 (0.57, 1.63)</td>
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<td>16</td>
<td>0.54 (0.29, 1.00)</td>
</tr>
<tr>
<td>STI</td>
<td>18 AS v 6 AS</td>
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<td>0.93 (0.60, 1.44)</td>
</tr>
<tr>
<td></td>
<td>18 AS+Z v 6 AS</td>
<td>178</td>
<td>37</td>
<td>22</td>
<td>0.49 (0.29, 0.83)</td>
</tr>
</tbody>
</table>

**Figure 7B.** Gleason score less than 7.

**Figure 7B.** Treatment effects on endpoints for Gleason ≤ 7

18 AS +/- Z vs 6 AS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Groups</th>
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<th>Events 6 AS</th>
<th>Events 18 AS +/- Z</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
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<tr>
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<td>18 AS+Z v 6 AS</td>
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<td>15</td>
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<td>Distant Progression</td>
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<td>20</td>
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<td>20</td>
<td>0.49 (0.29, 0.84)</td>
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<td></td>
<td>18 AS+Z v 6 AS</td>
<td>357</td>
<td>41</td>
<td>34</td>
<td>0.83 (0.53, 1.30)</td>
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</table>
Nivolumab demonstrated clinical activity across all dose levels, with no significant relationship between PFS and nivolumab dose \((P = 0.9)\). The median PFS in the 0.3 mg/kg, 2 mg/kg, and 10 mg/kg nivolumab dosing groups were 2.7 months, 4.0 months, and 4.2 months, respectively. The ORR was also similar across all dosing groups: 20%, 22%, and 20%, respectively.

Median OS was also similar across all nivolumab dosing groups and ranged from 18.2 months to 25.5 months. When patients were stratified according to baseline MSKCC risk group, there was a trend toward improved OS among patients with more favorable risk profiles \((\text{Figure 8})\). The median OS was 12.5 months in the poor-risk group, 20.3 months in the intermediate-risk group, and not reached in the favorable-risk group. There was also a trend toward prolonged survival among patients who had received just 1 prior treatment (median OS, not reached) compared with patients who received 2 or more prior treatments (median OS, 18.7 months).

\(\text{Figure 8. Overall survival by Memorial Sloan Kettering Cancer Center (MSKCC) risk group and prior treatments in renal cell carcinoma after treatment with nivolumab.}\)

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
Risk Group & Median OS, months (95% CI) \\
\hline
Favorable & NR (24.9, NR) \\
Intermediate & 20.3 (13.4, NR) \\
Poor & 12.5 (8.1, 18.6) \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
Number of Prior Treatments & Median OS, months (95% CI) \\
\hline
1 Prior treatment & NR (19.8, NR) \\
≥ 2 Prior treatment & 18.7 (13.4, 26.0) \\
\hline
\end{tabular}
\end{table}

NR, not reached; Symbols represent censored observations.

Treatment with nivolumab was well tolerated, with 17% or fewer patients in each dosing group experiencing grade 3/4 AEs. The most common grade 3/4 AEs were nausea, pruritus, and arthralgia. No grade 3/4 pneumonitis was reported. Overall, 6% of patients discontinued treatment due to drug-related toxicity.

In summary, nivolumab shows antitumor activity in mRCC, including promising survival results. Indeed, the survival outcomes in this phase II trial compare favorably to findings from recent phase III studies of other targeted therapies in patients with previously treated mRCC, where the median OS ranged from 11 months to 16.6 months.\textsuperscript{15-18}
Further evaluation of nivolumab in patients with mRCC is currently underway. An ongoing phase III study will compare nivolumab with everolimus in patients with relapsed mRCC. In addition, a phase III study will evaluate first-line treatment with nivolumab in combination with ipilimumab.

**PD-L1 Inhibition in Metastatic Urothelial Bladder Cancer**

MPDL3280A is an engineered anti-PD-L1 antibody that blocks PD-L1 from interacting with PD-1 and B7.1, resulting in enhanced T-cell priming and restored T-cell antitumor activity. MPDL3280A was also engineered to leave the interactions between PD-L2 and PD-1 intact, thereby reducing the risk of autoimmunity. In May 2014, MPDL3280A was granted breakthrough therapy designation by the US Food & Drug Administration.

Current treatment options for urothelial bladder cancer (UBC) are limited, particularly for patients with poor renal function who cannot tolerate standard cisplatin-based chemotherapy. Powles and colleagues reported findings from a multicenter, open-label, phase I clinical trial evaluating the safety and efficacy of MPDL3280A in treatment-refractory, metastatic UBC. The expansion cohort included 67 patients evaluable for efficacy, including patients identified as having PD-L1-positive tumors (n = 30) or PD-L1-negative tumors (n = 35) by an investigational PD-L1 diagnostic test. The PD-L1 status was unknown in 2 patients. All patients were treated with IV MPDL3280A every 3 weeks for a maximum of 16 cycles. The median patient age was 65 years (range, 36-86 years). All patients had good performance status (PS) at baseline, defined as ECOG PS 0-1. Most patients (75%) had visceral metastases. Common prior treatments included cisplatin (79%), cystectomy (48%), and carboplatin (34%). For 42% of patients, the last prior chemotherapy regimen had been given within 3 months of study entry.

Treatment with MPDL3280A was well tolerated in the safety-evaluable population (n = 68), which included patients with impaired renal function. Three patients (4%) experienced any grade 3/4 treatment-related AEs, which included asthenia (n = 1), thrombocytopenia (n = 1), and decreased serum phosphorus levels (n = 1). There were no reports of renal toxicity or immune-related toxicities, and no grade 4/5 treatment-related AEs.

After a minimum follow-up of 6 weeks, the ORR was 43% for patients with PD-L1-positive tumors. The ORR increased to 52% in the PD-L1-positive subgroup after a minimum follow-up of 12 weeks. There were 2 complete responses, both in patients with PD-L1-positive tumors. Among patients with PD-L1-negative tumors, the ORR was 11%.

The median time to first response was 42 days (range, 38 to 85 days). The median duration of response had not been reached at the time of data cut-off, suggesting some durability of response. Of 17 responding patients, 16 patients continued to have responsive disease after 12 weeks.

In summary, treatment with MPDL3280A was well tolerated and demonstrated durable antitumor activity in heavily pretreated patients with metastatic UBC. Additional clinical trials of MPDL3280A in a range of cancer types, including UBC, are ongoing.
CONCLUSION
The 2014 ASCO Annual Meeting provided new clinical findings on the optimal use of current and emerging treatments in prostate cancer, mRCC, and UBC. In the area of hormone therapy, the phase III CHAARTED trial showed that the upfront addition of docetaxel to ADT improved survival by more than 13 months in patients with hormone-naïve metastatic prostate cancer – a dramatic improvement with immediate implications for clinical practice. Encouraging observational findings suggest that it may be safe for men with PSA-only relapse to defer the initiation of ADT for up to 2 years, or until disease progression, without any loss of treatment effect compared with immediate ADT. The investigational androgen biosynthesis-inhibitor orteronel improved PFS when added to prednisone, although the lack of a survival advantage in the ELM-PC 4 trial suggests that orteronel may be less active than abiraterone.

Other trials also made incremental advances in defining the optimal use of various combination regimens in prostate cancer. Investigational agents targeting the PD-1 signaling pathway, including nivolumab and MPDL3280A, continue to show promise as next-generation immunotherapies. In the future, biomarker testing may guide the selection of optimal targeted therapies based on the patient’s individual genetic and molecular features.

The 2015 ASCO Annual Meeting will be held May 29-June 2015 in Chicago, Illinois. Additional information can be obtained at http://am.asco.org/future-meetings.

REFERENCES


