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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Prostate Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Prostate Cancer

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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Prostate Cancer, Version 1.2021

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Prostate Cancer address staging and risk assessment after a prostate cancer diagnosis and include management options for localized, regional, and metastatic disease. Recommendations for disease monitoring and treatment of recurrent disease are also included. The NCCN Prostate Cancer Panel meets annually to reevaluate and update their recommendations based on new clinical data and input from within NCCN Member Institutions and from external entities. This article summarizes the panel's discussions for the 2021 update of the guidelines with regard to systemic therapy for metastatic castration-resistant prostate cancer.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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SYSTEMATIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[zz,ccc,ddd,eee]

First-line treatment
No prior docetaxel/no prior novel hormone therapy[fff]
- Preferred regimens
  - Abiraterone[t,ggg] (category 1[hhh])
  - Docetaxel[aaa,iii] (category 1)
  - Enzalutamide[t] (category 1)
  - ~~Sipuleucel-T (category 1)~~
- Useful in certain circumstances
  - Sipuleucel-T[aaa,jjj] (category 1)
  - Radium-223[kkk] for symptomatic bone metastases (category 1)
  - ~~Mitoxantrone for palliation in symptomatic patients with visceral metastases who cannot tolerate other therapies~~
- Other recommended regimens
  - ~~Fine-particle abiraterone~~
  - Other secondary hormone therapy[t]

Second-line therapy, first-line abiraterone/enzalutamide
Prior novel hormone therapy/No prior docetaxel[fff,lll]
- Preferred regimens
  - Docetaxel (category 1)[aaa]
  - Sipuleucel-T[aaa,jjj]
- Useful in certain circumstances
  - Olaparib for HRRm (category 1)[mmm]
  - Cabazitaxel/carboplatin[aaa,nnn]
  - Pembrolizumab for MSI-H or dMMR[aaa] (~~category 2B~~)
  - Radium-223[kkk] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCAm[ooo]
- Other recommended regimens
  - Abiraterone[t,ggg]
  - Abiraterone + dexamethasone[ggg,ppp]
  - ~~Cabazitaxel[aaa]~~
  - Enzalutamide[t]
  - ~~Fine-particle abiraterone~~
  - Other secondary hormone therapy[t]

Second-line therapy, first-line docetaxel
Prior docetaxel/no prior novel hormone therapy[fff]
- Preferred regimens
  - Abiraterone[t,ggg] (category 1)
  - Cabazitaxel[aaa] (~~category 1~~)
  - Enzalutamide[t] (category 1)
- Useful in certain circumstances
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[aaa]
  - Cabazitaxel/carboplatin[aaa,nnn]
  - ~~Olaparib for HRRm (category 2B)[mmm]~~
  - Pembrolizumab for MSI-H or dMMR[aaa] (~~category 2B~~)
  - Radium-223[kkk] for symptomatic bone metastases (category 1)
  - ~~Rucaparib for BRCAm[ooo]~~
- Other recommended regimens
  - ~~Consider docetaxel rechallenge~~
  - ~~Fine-particle abiraterone~~
  - Sipuleucel-T[aaa,jjj]
  - Other secondary hormone therapy[t]

Subsequent treatment
Prior docetaxel and prior novel hormone therapy[fff,lll]
(All systemic therapies are category 2B if visceral metastases are present)
- Preferred regimens
  - ~~Abiraterone[t,ggg] (category 1[hhh])~~
  - Cabazitaxel[aaa] (category 1[hhh])
  - Docetaxel rechallenge[aaa,eee]
  - ~~Enzalutamide (category 1[ggg])~~
- Useful in certain circumstances
  - Olaparib for HRRm (category 1)[hhh,mmm]
  - Cabazitaxel/carboplatin[aaa,nnn]
  - Pembrolizumab for MSI-H or dMMR[aaa] (~~category 2B~~)
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[aaa]
  - Radium-223[kkk] for symptomatic bone metastases (category 1[hhh])
  - Rucaparib for BRCAm[ooo]
- Other recommended regimens
  - Abiraterone[t,ggg]
  - Enzalutamide[t]
  - ~~Fine-particle abiraterone~~
  - Other secondary hormone therapy[t]

PROS-16

Overview

An estimated 191,930 new cases of prostate cancer were diagnosed in the United States in 2020, accounting for >21% of new cancer cases in men.[1] The age-adjusted death rate from prostate cancer declined by 52% from 1993 to 2017, but the death rate has become stable in recent years.[1] Researchers estimate that prostate cancer accounted for 10.4% of male cancer deaths in the United States in 2020, with an estimated 33,330 deaths. From 2007 to 2014, the incidence of prostate cancer declined, likely in part as a result of decreased detection, attributed to decreased rates of prostate-specific antigen (PSA) screening.[1] After that, incidence rates stabilized and may now be starting to increase as PSA testing is regaining support.[1–4] The comparatively low death rate suggests that increased public awareness with earlier detection and treatment has affected mortality from this prevalent cancer.

Localized prostate cancer represents a spectrum of disease, ranging from indolent disease that does not require treatment (ie, active surveillance), to disease that requires some treatment (eg, radical prostatectomy or radiation), to aggressive disease that requires multimodality treatment (eg, radiation with androgen deprivation therapy [ADT] or radical prostatectomy with postoperative radiotherapy with or without ADT). ADT is also given as primary treatment to men with more aggressive localized prostate cancer and to those with regional and metastatic disease. Most men with advanced disease eventually stop experiencing a response to traditional ADT and are categorized as castration-resistant. Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL).[5]

For men who develop CRPC, ADT with an LHRH agonist or antagonist is continued to maintain castrate serum levels of testosterone (<50 ng/dL). Additional systemic therapies are applied concurrently with ADT and follow a sequential fashion, depending on various patient and disease characteristics. For men with bone metastases and CRPC the addition of bone modifying drugs are recommended.

Sequencing of Systemic Therapy for CRPC

Systemic therapies for patients with CRPC include various secondary hormone therapies, chemotherapies, immunotherapies, radiopharmaceuticals, and/or targeted therapies. Specific options, as delineated in the

FOOTNOTES

[t] See Principles of Androgen Deprivation Therapy (PROS-G).

[zz] Document castrate levels of testosterone if progression occurs on ADT. Workup for progression should include chest CT, bone imaging, and abdominal/pelvic CT with contrast or abdominal/pelvic MRI with and without contrast. Consider metastatic lesion biopsy. If small cell neuroendocrine is found, see PROS-15. See Principles of Imaging (PROS-C) and Discussion.

[aaa] See Principles of Immunotherapy and Chemotherapy (PROS-H).

[ccc] Visceral metastases refers to liver, lung, adrenal, peritoneal, and brain metastases. Soft tissue/lymph node sites are not considered visceral metastases.

[ddd] Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.

[eee] Patients with disease progression on a given therapy should not repeat that therapy, with the exception of docetaxel, which can be given as a rechallenge after progression on a novel hormone therapy in the second- or subsequent-line metastatic CRPC setting ~~if given~~ in men who have not demonstrated definitive evidence of progression on prior docetaxel therapy in the castration-naive setting.

[fff] Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide received for metastatic castration-naïve disease, M0 CRPC, or previous lines of therapy for M1 CRPC.

[ggg] The fine-particle formulation of abiraterone can be used instead of the standard form (other recommended option).

[hhh] The noted category applies only if no visceral metastases.

[iii] Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.

[jjj] Sipuleucel-T is recommended only for asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, and ECOG performance status 0–1. Benefit with sipuleucel-T has not been reported in patients with visceral metastases and is not recommended if visceral metastases are present. Sipuleucel-T also is not recommended for patients with small cell/neuroendocrine prostate cancer.

[kkk] Radium-223 is not recommended for use in combination with docetaxel or any other systemic therapy except ADT and should not be used in patients with visceral metastases. Concomitant use of denosumab or zoledronic acid is recommended. See Principles of Radiation Therapy (PROS-E).

[lll] Consider AR-V7 testing to help guide selection of therapy (See Discussion).

[mmm] Olaparib is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair gene (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D* or *RAD54L*), who have been treated with androgen receptor-directed therapy. Patients with *PPP2R2A* mutations in the PROfound trial experienced an unfavorable risk-benefit profile. Therefore, olaparib is not recommended in patients with a *PPP2R2A* mutations. There may be heterogeneity of response to olaparib for non-BRCA mutations based on which gene has a mutation. (See Discussion).

[nnn] Cabazitaxel 20 mg/m2 plus carboplatin AUC 4 mg/mL per min with growth factor support can be considered for fit patients with aggressive variant prostate cancer (visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of *PTEN*, *TP53*, and *RB1*). Corn et al. Lancet Oncol 2019;20(10):1432-1443.

[ooo] Rucaparib is a treatment option for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. If the patient is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given.

[ppp] ~~de Wit R, de Bono J, Sternberg C, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med 2019; 381:2506-2518.~~

[ppp] Switching from prednisone to dexamethasone 1 mg/d can be considered for patients with disease progression on either formulation of abiraterone. Trials show improved PSA responses and PFS and acceptable safety using this strategy. Romero-Laorden et al. Br J Cancer 2018;119(9):1052-1059 and Fenioux et al. BJU Int 2019;123(2):300-306.

PROS-16A

guidelines for patients with and without distant metastases, are based on a large body of data. However, a limited amount of data informs the optimal sequence for delivery of these agents. Choice of treatments in various lines of therapy is based on patient preferences, prior treatment exposures, the presence or absence of visceral disease, patient symptoms, and potential side effects.

In all cases, patients experiencing disease progression on a given therapy should not repeat that therapy, with the exception of docetaxel, which can be given as a rechallenge in the metastatic CRPC (mCRPC) setting after progression on a novel hormone therapy if given in the castration-naive setting without definitive evidence of progression.

Therapy Selection for mCRPC After Prior Novel Hormone Therapy

During the past few years, the use of second-generation antiandrogens in prostate cancer has expanded beyond the mCRPC setting. For instance, apalutamide was approved by the FDA in February of 2018 for patients with M0 CRPC and in September of 2019 for patients with metastatic castration-naïve prostate cancer.[6] FDA approval for enzalutamide for these same settings occurred in July of 2018 and December of 2019, respectively.[7] Darolutamide was approved in the M0 CRPC setting in July of 2019.[8] The M0 CRPC approvals were based on several trials that showed improvements in metastasis-free survival and overall survival (OS) with use of apalutamide, darolutamide, and enzalutamide.[9–14] The metastatic castration-naïve approvals were based on studies that showed improvements in progression-free survival (PFS) and/or OS.[15–17] These options were all added to previous versions of the NCCN Guidelines.

Abiraterone is also another novel hormone therapy option included in the guidelines for patients with metastatic castration-naïve disease. It was approved in this setting in February of 2018, based on 2 trials that demonstrated improved OS over ADT alone.[18–20]

The panel discussed that, as these hormone therapies began to be used in earlier settings, it became less clear what treatments are appropriate in the mCRPC setting. The panel agreed that patients who receive abiraterone or one of the second-generation antiandrogens for metastatic castration-naïve disease or M0 CRPC (without prior exposure to docetaxel) should receive a therapy from the list that was labeled in the guidelines at that time as 'second-line therapy, first-line

abiraterone/enzalutamide' when they experience progression to metastatic CRPC. The panel further noted that, for patients who received docetaxel for very-high risk, localized prostate cancer who then received a novel hormone therapy for M1 castration-naïve prostate cancer or M0 CRPC, the options that were listed under "subsequent therapy" were most appropriate even though these patients had not yet received treatment of the mCRPC state.

To help clarify these points and help clinicians choose appropriate therapies for their patients, the panel decided to reorganize the treatment recommendations for mCRPC. Instead of organizing the choices as lines of therapy, they included 4 groups of treatments based on prior therapeutic exposures: no prior docetaxel/no prior novel hormone therapy; prior novel hormone therapy/no prior docetaxel; prior docetaxel/no prior novel hormone therapy; and prior docetaxel/prior novel hormone therapy (see PROS-16, page 136). The panel defines novel hormone therapy as abiraterone/enzalutamide/darolutamide/apalutamide given for metastatic castration-naïve disease, M0 CRPC, or previous lines of therapy for M1 CRPC.

Cabazitaxel in Later Lines of Therapy for mCRPC

The panel also discussed results of the multicenter, randomized, open-label CARD study, which compared cabazitaxel with either abiraterone or enzalutamide in 255 patients with metastatic CRPC who had previously received docetaxel and either abiraterone or enzalutamide.[21] Either order of the previously received therapies was allowed, and abiraterone or docetaxel could have been given in the castration-naïve setting. Disease progression on abiraterone or enzalutamide had to have occurred within 12 months for patients to be eligible. Cabazitaxel at 25 mg/m^2 with concurrent steroid improved the primary endpoint of radiographic PFS (8.0 vs 3.7 months; hazard ratio [HR], 0.54; $P<.0001$) and reduced the risk of death compared with abiraterone or enzalutamide in these patients (13.6 vs 11.0 months; HR, 0.64; $P=.008$). Cabazitaxel was also associated with an increased rate of pain response and delayed time to pain progression and skeletal-related events.[22]

Panel consensus was that results of CARD provide level 1 evidence supporting cabazitaxel over abiraterone or enzalutamide in patients who have already received docetaxel and either abiraterone or enzalutamide. Therefore, the panel included cabazitaxel as a category 1, preferred option for patients with prior docetaxel and prior novel hormone therapy in the metastatic CRPC setting (see PROS-16, page 136).

In addition, the panel discussed data suggesting cross-resistance between abiraterone and enzalutamide,[23–26] and the lack of evidence showing that abiraterone extends OS in patients with previous exposure to enzalutamide and vice versa. Although data suggest that AR-V7 testing may help identify patients whose disease will be resistant to abiraterone and enzalutamide,[27–31] the panel agreed that abiraterone/enzalutamide crossover therapy is rarely effective. Overall, the panel agreed that cabazitaxel would be a better option for patients experiencing disease progression on enzalutamide or abiraterone. Therefore, the panel voted to remove the category 1 labels from abiraterone and enzalutamide in this setting and to move those therapies from the list of "preferred regimens" to the list of "other recommended regimens" (see PROS-16, page 136).

Pembrolizumab for MSI-H/dMMR Tumors in mCRPC

The panel received an external request to revisit the recommendation for pembrolizumab in the second-line and subsequent treatment of advanced microsatellite instability–high (MSI-H)/deficient mismatch repair (dMMR) prostate cancer. It was listed as a category 2B recommendation in the 2020 version of the guidelines.

The FDA first approved pembrolizumab, an anti–PD-1 antibody, for treatment of patients with "unresectable or metastatic [MSI-H] or [dMMR] solid tumors that have progressed on prior treatment and who have no satisfactory alternative treatment options" in May of 2017.[32] The indication has since been expanded to include several cancer types, but not prostate cancer specifically.[33] The FDA granted accelerated approval based on the treatment of 149 patients across 5 clinical studies involving MSI-H or dMMR colorectal (n=90) or noncolorectal (n=59) cancer, with an objective response rate (ORR) of 40% (59/149).[32] All patients received ≥1 prior regimen. Among the noncolorectal cohorts, 2 patients had mCRPC: one achieved a partial objective response and the other achieved stable disease for >9 months.

Early studies included few patients with CRPC but show initial evidence of responses in patients with MSI-H or dMMR tumors.[34–36] Data on an increasing number of additional patients with mCRPC treated with pembrolizumab have since been reported.[37–41] Most recently, the multicohort, open-label phase II KEYNOTE-199 study in 258 patients with mCRPC and prior treatment with docetaxel and at least one novel hormone therapy assessed pembrolizumab in patients regardless of MSI status.[42] Cohorts 1 and 2 included patients with PD-L1–positive (n=133) and PD-L1–negative (n=66) prostate cancer, respectively, and cohort 3 included those with bone-predominant disease and positive or negative PD-L1 expression (n=59). The primary endpoint of ORR in cohorts 1 and 2 was 5% (95% CI, 2%–11%) and 3% (95% CI, <1%–11%), respectively. Responses were durable

(range, 1.9 to ≥21.8 months). The most common adverse effects with pembrolizumab were fatigue, pruritus, diarrhea, anorexia, constipation, nausea, rash, fever, cough, dyspnea, and musculoskeletal pain. Pembrolizumab also may be associated with immune-mediated adverse effects, including colitis, hepatitis, endocrinopathies, pneumonitis, and nephritis.

The panel discussed these data and emphasized that the body of evidence on use of pembrolizumab in patients with mCRPC has grown over recent years. Furthermore, many panel members noted that practice patterns have evolved and that they often use pembrolizumab with appropriate patients. A panel vote established pembrolizumab as a category 2A recommendation for patients with MSI-H or dMMR mCRPC whose disease has progressed through docetaxel and/or a novel hormone therapy.

The panel further noted that the prevalence of MMR deficiency in mCRPC is estimated at 2% to 5%,[35,43] and testing for MSI-H or dMMR can be performed using DNA testing or immunohistochemistry. If tumor MSI-H or dMMR is identified, the panel recommends referral to genetic counseling for consideration of germline testing for Lynch syndrome.

New Systemic Therapy Options for CRPC

PARP Inhibitors for Patients With DNA Repair Gene Mutations

Results of early studies suggest that germline and somatic mutations in homologous recombination repair (HRR) genes (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*) may be predictive of the clinical benefit of PARP inhibitors.[44–46] PARP inhibitors are oral agents that exert their activity through synthetic lethality.[47] Currently, 2 PARP inhibitors, olaparib and rucaparib, are FDA-approved for use in prostate cancer.[48,49] The panel discussed the FDA approvals and the data outlined below and voted to add olaparib and rucaparib to the guidelines in recent versions.

Olaparib

Preliminary clinical data on olaparib suggested favorable activity of this agent in patients with HRR gene mutations, but not in those without.[45,46,50] The phase III PROfound study was a randomized trial evaluating olaparib at 300 mg twice daily versus physician's choice of abiraterone or enzalutamide in patients with mCRPC and disease progression on at least one novel hormonal agent (abiraterone or enzalutamide) and up to one prior taxane agent (permitted but not required).[51] Notably, 20% of patients had received both prior abiraterone and enzalutamide and were thus given agents on which they previously experienced progression. Patients had to have a somatic or germline HRR gene mutation, and were allocated to 1 of 2 cohorts: cohort A consisted of patients with *BRCA1/2* or *ATM* mutations, and cohort B consisted of patients with a mutation in at least 1 of 12 other HRR genes (*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*). The primary endpoint of improving radiographic PFS with olaparib versus abiraterone/enzalutamide was met in cohort A (HR, 0.34; 95% CI, 0.25–0.47; $P<.001$), and radiographic PFS was also superior in the entire study population encompassing cohorts A and B (HR, 0.49; 95% CI, 0.38–0.63; $P<.001$). However, in cohort B the primary endpoint was negative but had a statistical interaction with patients in cohort A, indicating that the 12 genes included in cohort B are less likely overall to indicate response to PARP inhibition. More recently, OS was shown to be improved with olaparib versus abiraterone/enzalutamide in cohort A (HR, 0.69; 95% CI, 0.50–0.97; $P=.02$), despite the fact that 86 of 131 patients (66%) crossed over to olaparib after disease progression in the control arm.[52]

Based on data from the PROfound trial, the FDA approved olaparib (300 mg twice daily) in May 2020 for use in patients with mCRPC and deleterious or suspected deleterious germline or somatic HRR gene mutations in at least 1 of 14 genes (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*) and who had previously received treatment with enzalutamide or abiraterone.[48] *PPP2R2A* was excluded due to preliminary evidence showing inferior activity of olaparib in this subset.[51] Of note, the PROfound trial did report minimal activity in patients with *ATM*, *CDK12*, and multiple other HRR gene mutations, consistent with prior trial results (TRITON2 and TOPARP-B).[50,53]

Adverse effects that may occur with olaparib treatment include anemia (including that requiring transfusion), fatigue, nausea or vomiting, anorexia, weight loss, diarrhea, thrombocytopenia, creatinine elevation, cough, and dyspnea. Rare but serious adverse effects may include thromboembolic events (including pulmonary emboli), drug-induced pneumonitis, and a theoretical risk of myelodysplasia or acute myeloid leukemia.[51]

The panel recommends olaparib as an option for men with mCRPC, previous abiraterone or enzalutamide treatment, and an HRR mutation in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L* (category 1). Since prior taxane therapy was not mandated in the PROfound study, panel consensus was that olaparib use might be reasonable in patients with mCRPC before or after docetaxel treatment. The panel noted that patients with *PPP2R2A* mutations in the PROfound trial experienced an unfavorable risk/benefit profile; therefore,

olaparib is not recommended in patients with *PPP2R2A* mutations. The panel also discussed that there may be further heterogeneity of response to olaparib based on which gene has a mutation.

Any commercially available analytically and clinically validated somatic tumor and circulating tumor DNA (ctDNA) assays and germline assays can be used to identify patients for treatment. Careful monitoring of CBC counts and hepatic and renal function, along with type and screens and potential transfusion support and/or dose reductions as needed for severe anemia or intolerance are recommended during olaparib therapy.

Rucaparib

Rucaparib is another PARP inhibitor approved for use in patients with mCRPC.[49] This agent received accelerated FDA approval in May 2020 based on the preliminary favorable data from the TRITON2 clinical trial. In that open-label single-arm phase II trial, patients with mCRPC harboring a deleterious or suspected deleterious germline or somatic *BRCA1* or *BRCA2* mutation and who had previously received therapy with a novel hormonal agent plus one taxane chemotherapy were treated with rucaparib at 600 mg twice daily.[53] The primary endpoint of TRITON2 was ORR in patients with measurable disease, and was 43.5% (95% CI, 31.0%–56.7%) in this *BRCA1/2*-mutated population. Median radiographic PFS, a key secondary endpoint, was 9.0 months (95% CI, 8.3–13.5 months).[53] The TRITON2 investigators have also reported outcomes for patients with non-*BRCA1/2* mutations, and, similar to the PROfound trial, observed minimal to no responses in patients with *ATM* and *CDK12* mutations.[54]

Adverse effects that may occur with rucaparib include anemia (including that requiring transfusion), fatigue, asthenia, nausea or vomiting, anorexia, weight loss, diarrhea or constipation, thrombocytopenia, creatinine elevation, increased liver transaminases, and rash. Rare but serious adverse effects include a theoretical risk of myelodysplasia or acute myeloid leukemia, and fetal teratogenicity.[53,54]

The FDA indication for rucaparib (600 mg twice daily) is for use in patients with mCRPC and deleterious or suspected deleterious germline or somatic *BRCA1* or *BRCA2* mutations, and who had previously received treatment with a novel hormonal agent (enzalutamide or abiraterone) and one taxane-containing chemotherapy. Full FDA approval of rucaparib is contingent upon a favorable efficacy and safety profile for this drug in the phase III TRITON3 study (ClinicalTrials.gov identifier: NCT02975934)—a randomized trial of rucaparib versus physician's choice of therapy (abiraterone, enzalutamide, or docetaxel) in patients with mCRPC and a germline or somatic *BRCA1/2* or *ATM* mutation who previously received a novel hormonal agent but no chemotherapy for mCRPC. Results of this trial are awaited.

The panel discussed results of TRITON2 and the FDA label information. Panel consensus supported a recommendation of rucaparib as an option for men with mCRPC with prior exposure to abiraterone or enzalutamide and a *BRCA1* or *BRCA2* mutation. The panel also agreed that rucaparib should not generally be recommended in patients who have not previously received a taxane agent, but thought an exception could be made for patients who are not fit for chemotherapy. Furthermore, the panel thought rucaparib should not be used in patients with HRR gene mutations other than *BRCA1/2*.[54,55]

The preferred method of selecting patients for rucaparib treatment is somatic analysis of *BRCA1* and *BRCA2* using a ctDNA sample. However, other clinical-grade somatic or germline DNA sequencing assays that include the *BRCA1/2* genes, including germline and somatic tumor tissue and cell-free DNA, can also be used for patient selection. As with olaparib, careful monitoring of CBC counts and hepatic and renal function, along with type and screens and potential transfusion support and/or dose reductions as needed for severe anemia or intolerance, are recommended during treatment with rucaparib.

Cabazitaxel Plus Carboplatin

A randomized, open-label, phase I/II trial sought to determine the maximum tolerated dose and investigator-assessed PFS with combination cabazitaxel + carboplatin in patients with mCRPC.[56] In the phase II part of the trial, 160 patients were randomized to 25 mg/m^2 cabazitaxel or 25 mg/m^2 cabazitaxel + carboplatin at area under the curve (AUC) 4 mg/mL/min. After a median follow-up of 31 months, PFS was improved in the combination arm compared with the cabazitaxel arm (4.5 vs 7.3 months; HR, 0.69; 95% CI, 0.50–0.95; P=.018). Results of a post hoc analysis of patients who did not receive a platinum-containing regimen at progression suggested that the median OS may also have been improved (18.9 vs 12.6 months; HR, 0.68; 95% CI, 0.38–1.22; P=.15).

The investigators performed another post hoc analysis to examine the effect of an aggressive variant prostate cancer phenotype on outcomes with the cabazitaxel/carboplatin combination. Patients were considered to have aggressive variant prostate cancer if their tumor contained defects in at least 2 of 3 tumor suppressors by immunohistochemistry: TP53, RB1, and PTEN. Cancer could also be classified as aggressive variant if certain clinicopathologic criteria were met: the presence of (1) small cell prostate carcinoma,

(2) exclusively visceral metastases, (3) predominantly lytic bone metastases, (4) bulky (>5 cm) lymphadenopathy or Gleason score ≥8 at diagnosis, (5) PSA <10 ng/mL plus ≥20 bone metastases, (6) ≥2 times elevated lactate dehydrogenase (LDH) or CEA level, and/or (7) <6 months interval response to ADT. Evaluable tumor samples from 56 patients were classified as aggressive variant or not. Median PFS for those characterized as having aggressive variant prostate cancer was 1.7 months after treatment with cabazitaxel versus 7.5 months after combination therapy (P=.017). The estimated median OS was 8.5 versus 20.2 months, respectively (P=.0002). Median PFS in patients whose tumors were not identified as aggressive variant was similar for the 2 treatments (6.3 vs 6.5 months; P=.38), and median OS also did not differ in this group of patients based on treatment (21.7 vs 21.5 months; P=.70). The most common grade 3–5 adverse effects with cabazitaxel + carboplatin versus cabazitaxel alone were fatigue (20% vs 9%), anemia (23% vs 4%), neutropenia (16% vs 4%), and thrombocytopenia (14% vs 1%).

After discussing results of this trial, the panel expressed some concerns regarding the toxicity of this combination, but concluded that it could be a good option for some patients with an aggressive variant phenotype. Therefore, the panel consensus was to add this combination at a lower dose of cabazitaxel (20 mg/m^2) as an option for patients with visceral metastases, low PSA level and bulky disease, high LDH level, high CEA level, lytic bone metastases, neuroendocrine histology, and/or unfavorable genomics (defects in at least 2 of *PTEN*, *TP53*, and *RB1*). Growth factor support should be used.

Abiraterone Plus Dexamethasone

The pilot single-arm, open-label, phase II SWITCH study evaluated the efficacy of abiraterone with 0.5 mg dexamethasone daily in 26 patients with mCRPC who experienced disease progression on abiraterone with 5 mg prednisone twice daily.[57] The primary endpoint was the proportion of patients achieving a PSA decline of ≥30% after 6 weeks on abiraterone with dexamethasone, and 46.2% of participants met this criteria. Two patients (7.7%) experienced radiologic responses. Median OS and median time to biochemical and radiologic progression were 20.9, 5.3, and 11.8 months, respectively, and no significant toxicities were reported.

An international, randomized, open-label phase II study also showed that abiraterone with 0.5 mg dexamethasone once daily was safe.[58] The regimen met the prespecified threshold for the primary endpoint of mineralocorticoid excess (grade ≥1 hypokalemia or grade ≥2 hypertension) through 24 weeks of treatment.

Another study that evaluated the approach of switching steroids with abiraterone included 48 consecutive patients with mCRPC who experienced biochemical progression on treatment with abiraterone + prednisone and were asymptomatic.[59] Patients were switched to abiraterone plus 0.5 mg/d dexamethasone until radiologic and/or clinical progression. The primary endpoint of PFS was 10.35 months after the switch occurred, and 56% of the patients experienced improvements or stabilization of PSA levels. Abiraterone + dexamethasone was well tolerated in this study, with no grade 3/4 toxicity reported, and no dose reduction required.

The panel discussed these data and decided that this approach would be an appropriate option for some patients based on improvements in PSA responses and PFS, and acceptable safety.

Conclusions

The list of systemic therapy options for patients with mCRPC has expanded in recent years, with several additions made to the 1.2021 version of the NCCN Guidelines. Treatment options for patients with mCRPC are based mainly on prior treatment exposure, namely to docetaxel and novel hormone therapies that are now often administered in earlier stages of disease. The decision among treatment options is informed by patient preferences, biomarkers, the presence or absence of visceral disease, symptoms, and potential adverse effects. Optimal sequencing of systemic therapies for patients with mCRPC remains challenging, but newer data have helped to support patients and clinicians as they make decisions for first, second, and subsequent lines of therapy in the CRPC setting.

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