Second Generation Anti-Androgen Agents
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO081

Description
Darolutamide (Nubeqa), apalutamide (Erleada), and enzalutamide (Xtandi) are orally administered androgen receptor inhibitors. Abiraterone (Zytiga, Yonsa) is an androgen biosynthesis inhibitor of CYP17.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
darolutamide (Nubeqa)	Prostate cancer, non-metastatic, castration resistant Prostate cancer, metastatic, castration-sensitive	300 mg tablets	120 tablets/30 days
apalutamide (Erleada)	Prostate cancer, non-metastatic, castration resistant	60 mg tablets	
	Prostate cancer, metastatic, castration-sensitive	240 mg tablets	30 tablets/30 days
enzalutamide (Xtandi)	Prostate cancer, castration resistant	40 mg capsules	120 capsules/30 days
	Prostate cancer, metastatic, castration-sensitive	40 mg tablets	120 tablets/30 days
	Prostate cancer, non-metastatic, castration sensitive	80 mg tablets	60 tablets/30 days
abiraterone (Yonsa)	Prostate cancer, metastatic, castration-resistant, in combination with methylprednisolone	125 mg tablets	120 tablets/30 days
abiraterone (generic Zytiga)	Prostate cancer, metastatic, castration-resistant, in combination with prednisone	250 mg tablets	120 tablets/30 days
	Prostate cancer, metastatic, castration-sensitive, in combination with prednisone	500 mg tablets	60 tablets/30 days
abiraterone (Zytiga)		250 mg tablets	120 tablets/30 days
	Prostate cancer, non-metastatic, castration sensitive, in combination with prednisone	500 mg tablets	60 tablets/30 days

Initial Evaluation

I. **Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga, Yonsa)** may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
   C. The member has **not** previously progressed on darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), OR abiraterone (Zytiga, Yonsa); **AND**
   D. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga, Yonsa) will **not** be used in combination with any other oncolytic medication with the exception of therapies outlined below (e.g., hormone suppression therapy, docetaxel for mCSPC, or PARP inhibitors [i.e., olaparib (Lynparza) and talazoparib (Talzenna)] for mCRPC); **AND**
   E. The member has either had a bilateral orchiectomy OR ongoing hormone suppression (e.g., GnRH therapy) will be used concurrently; **AND**
   F. A diagnosis of one of the following:
      1. **Non-metastatic castration resistant prostate cancer**, defined by evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or a bilateral orchiectomy; **AND**
         i. The member has a PSA-doubling time of 10 months or less during continuous androgen-deprivation therapy or after bilateral orchiectomy; **AND**
         ii. One of the following is prescribed: darolutamide (Nubeqa), apalutamide (Erleada), OR enzalutamide (Xtandi); **OR**
      2. **Non-metastatic castration sensitive prostate cancer; AND**
         i. The member is in the high- or very high-risk group defined by:
            a. Node positive; **OR**
            b. Node negative; **AND**
               i. The member has two of the following:
                  1. Stage T3 or T4 tumor
                  2. Gleason Score ≥ 8
                  3. PSA ≥ 40 ng/mL; **OR**
            c. Experienced PSA doubling time of <6 months or PSA concentration ≥20 ng/mL on androgen deprivation therapy (e.g. GnRH analogs); **AND**
         ii. The request is for generic abiraterone 250 mg tablets and will be used in combination with ALL the following:
            a. External beam radiotherapy (EBRT), unless contraindicated
            b. Androgen deprivation therapy (ADT) (e.g. GnRH analogs)

c. Prednisone; **OR**

iii. The request is for generic abiraterone 500 mg tablets or brand abiraterone (Zytiga, Yonsa); **AND**
   a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **AND**
   b. Treatment will be used in combination with EBRT (unless contraindicated), ADT, and prednisone**; OR**

iv. The request is for enzalutamide (Xtandi); **AND**
   a. Documentation of intolerance or contraindication to generic abiraterone; **OR**

3. **Metastatic castration resistant prostate cancer**, defined by evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or a bilateral orchiectomy; **AND**
   i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
   ii. The request is for generic abiraterone 500 mg tablets; **AND**
      a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
   iii. The request is for brand abiraterone (Zytiga), brand abiraterone (Yonsa); **AND**
      a. Documentation of intolerance or contraindication to generic abiraterone; **AND**
      b. Will be used in combination with prednisone; **OR**
   iv. The request is for enzalutamide (Xtandi); **AND**
      a. Medication will be used as monotherapy **AND**
         i. Documentation of intolerance or contraindication to generic abiraterone; **OR**
      b. Enzalutamide (Xtandi) will be used in combination with talazoparib (Talzenna); **AND**
         i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) alteration in BRCA1 or BRCA2 gene; **AND**
            1. Documentation of intolerance or contraindication to generic abiraterone in combination with olaparib (Lynparza); **OR**
         ii. The member has an alteration in an HRR gene that is not BRCA1 or BCRA2 (e.g., *ATM, ATR, CDK12*, etc.); **OR**

4. **Metastatic castration sensitive or castration naïve prostate cancer; AND**
    i. **For generic abiraterone:**
        a. The member has at least TWO of the following risk factors:
            i. Gleason Score ≥ 7 (Grade Group ≥ 2)
            ii. Bone lesions
            iii. Presence of measurable visceral metastases; **AND**
        b. Abiraterone will be used in combination with prednisone; **AND**
            i. If used in combination with docetaxel, the provider attests that the member has high-volume metastatic burden; **AND**
        c. The request is for generic abiraterone 250 mg tablets; **OR**
            i. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
    ii. **For BRAND abiraterone (Zytiga), apalutamide (Erleada), darolutamide (Nubeqa), or enzalutamide (Xtandi):**
        a. The member has at least TWO of the following risk factors:
            i. Gleason Score ≥ 7 (Grade Group ≥ 2)
            ii. Bone lesions
            iii. Presence of measurable visceral metastases; **AND**
        b. The member must have had an inadequate response, intolerance, or contraindication to generic abiraterone (Note: if criteria is met for generic abiraterone, use of the 250 mg tablets will be required); **AND**
        c. If the request is for abiraterone (Zytiga), it will be used in combination with prednisone; **AND**
            i. If used in combination with docetaxel, the provider attests that the member has high-volume metastatic burden; **OR**
        d. If the request is for darolutamide (Nubeqa), it will be used in combination with docetaxel

II. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), and abiraterone (Zytiga, Yonsa) are considered investigational when used for all other conditions, including but not limited to:
    A. Cushing's Syndrome
    B. Breast cancer
    C. Hepatocellular carcinoma
    D. Fallopian tube, ovarian, or uterine cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. The medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**

IV. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga, Yonsa) will **not** be used in combination with any other oncolytic medication with the exception of docetaxel for mCSPC or PARP inhibitors [i.e., olaparib (Lynparza) and talazoparib (Talzenna)] for mCRPC; **AND**

V. The member has either had a bilateral orchiectomy OR ongoing hormone suppression (e.g., GnRH therapy) will be used concurrently; **AND**

VI. The member has experienced a response to therapy (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**

1. **Non-metastatic castration resistant prostate cancer;**
    i. The request is for one of the following: darolutamide (Nubeqa), apalutamide (Erleada), OR enzalutamide (Xtandi); **OR**
2. **Non-metastatic castration sensitive prostate cancer; AND**
    i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone, EBRT (unless contraindicated), and a GnRH analog; **OR**
    ii. The request is for abiraterone 500mg tablets or brand abiraterone (Zytiga, Yonsa); **AND**
        a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **AND**
        b. Treatment will be used in combination with EBRT (unless contraindicated), ADT, and prednisone**; OR**
3. **Metastatic castration resistant prostate cancer;**
    i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
    ii. The request is for generic abiraterone 500 mg tablets; **AND**
        a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
    iii. The request is for brand abiraterone (Zytiga) plus prednisone OR brand abiraterone (Yonsa) plus methylprednisolone; **AND**

a. The member has an intolerance or contraindication to generic abiraterone (use of 250 mg tablets required); **OR**

iv. The request is for enzalutamide (Xtandi); **OR**

4. **Metastatic castration sensitive prostate cancer;**
   i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
      a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
   ii. The request is for enzalutamide (Xtandi), darolutamide (Nubeqa), or apalutamide (Erleada); **OR**
   iii. The request is for brand abiraterone (Zytiga); **AND**
      a. The member has had inadequate response, intolerance, or contraindication to generic abiraterone (use of 250 mg tablets required); **AND**
      b. Will be used in combination with prednisone

Supporting Evidence

I. Prostate cancer therapies have been evaluated for safety and efficacy in adults. There are multiple treatment modalities with the direction of therapy depending on the manifestations of the disease. The initial and continued approach should be directed by a specialist due to the nuances of treatment, monitoring of disease, treatment safety, evaluation of efficacy, and consideration for patient specific goals.

II. Many treatment options exist, and initial and further line therapy are contingent upon patient specific characteristics. These options include, but are not limited to, radiation therapy, prostatectomy, androgen deprivation pharmacotherapy, bilateral orchiectomy, chemotherapy, abiraterone (Zytiga, Yonsa), or androgen receptor inhibitors (e.g., enzalutamide (Xtandi), darolutamide (Nubeqa), apalutamide (Erleada)). Multi-modal therapy, such as abiraterone or enzalutamide with ADT, is commonly utilized; however, abiraterone and/or androgen receptor inhibitor combinations have not been evaluated for safety and efficacy to date. Continuation of ADT is commonly employed and is recommended as concomitant therapy as discontinuation of GnRH agonists are likely to result in an increase in serum testosterone and disease progression.

III. Use of androgen receptor inhibitor (e.g., darolutamide [Nubeqa], apalutamide [Erleada], enzalutamide [Xtandi]) therapy after disease progression on abiraterone, or vice versa (i.e., abiraterone/androgen receptor inhibitor crossover therapy), has not yet been evaluated for safety and efficacy in quality clinical trials. One retrospective trial evaluating enzalutamide after treatment with abiraterone showed that very few patients (10% or less) had a significant decrease in PSA with enzalutamide therapy. A retrospective case series showed a similar lack of

efficacy in regard to abiraterone after enzalutamide (Xtandi). Additionally, there are studies to suggest cross resistance in switching between second generation anti-androgens. It has been demonstrated that there is a cross-resistance mechanism between darolutamide, apalutamide, enzalutamide, and abiraterone. NCCN guidelines note evidence-based guidance on the sequencing of ADT agents remains limited.

IV. **Non-metastatic castration resistant prostate cancer:** darolutamide (Nubeqa), apalutamide (Erleada), and enzalutamide (Xtandi) are the androgen receptor inhibitors that have been evaluated in this stage of disease. Concurrent treatment with steroids is not required. Patients in the trials for each of these medications had a prostate-specific antigen doubling time of 10 months or less and received GnRH therapy concurrently. Each therapy was evaluated in a double-blind, placebo-controlled trial.

- Darolutamide (Nubeqa) was evaluated in the ARAMIS TRIAL. The primary outcome, metastasis free survival (MFS), showed a statistical significance over placebo (40 vs 18 months, p<0.001). Apalutamide (Erleada) was evaluated in the SPARTAN trial, MFS was statistically significant compared to placebo (40 vs 16 months), and enzalutamide (Xtandi) was evaluated in the PROSPER trial. The MFS was significant compared to placebo (37 months vs 15 months).
- Darolutamide (Nubeqa) does not cross the blood brain barrier; thus, may offer an improved safety profile compared to enzalutamide and even apalutamide (Erleada). There were low rates of fatigue, falls, fractures, and seizures; however, head-to-head trials have not yet been conducted and caution should be used when comparing across trials to make treatment decisions.

V. **Non-metastatic castration sensitive prostate cancer:** abiraterone in combination with androgen deprivation therapy (ADT) (e.g. GnRH analogs) and prednisone, was evaluated in a phase III, randomized, open-label study (STAMPEDE) with 1974 participants with high-risk, non-metastatic prostate cancer. Participants were considered high risk if they are node positive alone, if they are node negative with two factors (stage T3 or T4, Gleason Score >8, or PSA >40), or if there was disease progression on ADT (defined by a PSA ≥ 4ng/mL with a doubling time of <6 months, or PSA ≥ 20 ng/mL). Radiotherapy was required for those participants with node negative and highly encouraged for those that were node positive. A total of 99% of participants with node negative and 77% of participants with node positive disease received radiotherapy (overall 85%). The primary outcome of metastasis-free survival (MFS) was significantly longer in the combination-therapy group versus ADT alone and 6-year MFS improved from 69% in the ADT groups to 82% in the combination therapy groups (HR 0·53, 95% CI 0·44–0·64; p<0·0001). There was a total of 147 deaths in the combination group compared to 236 in the ADT group – overall survival was significantly longer in the combination group vs ADT (not reached, 103–NE; HR 0·60, 95% CI 0·48–0·73, p<0·0001). Prostate-cancer-specific survival was significantly improved in the combination- therapy groups versus ADT alone (HR 0·49, 95% CI 0·37–0·65, p<0·0001).

The most common ADE in combination group versus ADT was hypertension (393 (41%) vs 153 (5%)), aminotransaminases (332 (34%) vs 136 (14%)).

VI. Enzalutamide (Xtandi) received FDA approval for treatment of non-metastatic, castration sensitive prostate cancer, with or without GnRH analog. Enzalutamide in combination with leuprolide, enzalutamide monotherapy and placebo plus leuprolide, was evaluated in a Phase III, randomized, double-blinded, study (EMBARK) with 1068 participants with high-risk, non-metastatic prostate cancer. Participants were considered high risk if they are node positive or had a PSA doubling time less than 9 months after EBRT. The primary outcome of metastasis-free survival (MFS) between the combination group vs leuprolide alone was evaluated. MFS was significantly longer in the combination-therapy group versus placebo and leuprolide (HR 0.42, 95% CI, 0.30-0.61, p<0.0001). The 5-year metastasis-free survival was 87.3% (95% confidence interval [CI], 83.0 to 90.6) in the combination group and 71.4% (95% CI, 65.7 to 76.3) in the leuprolide-alone group. Secondary analysis also demonstrated that enzalutamide monotherapy was also superior to leuprolide alone in delaying metastasis or death (HR 0.63; 95% CI, 0.46-0.87, P=0.005). The most common adverse event leading to discontinuation was fatigue (in 12 patients [3.4%] in the combination group, 4 patients [1.1%] in the leuprolide-alone group, and 8 patients [2.3%] in the monotherapy group).

- NCCN prostate cancer guidelines provide a category 2a recommendation for use of abiraterone acetate in combination with prednisone, EBRT, and ADT in those categorized as high or very high risk, and such combination is listed as the preferred treatment. As of January 2024, NCCN guidelines have not been updated to include enzalutamide (Xtandi)'s new indication.
- Contraindications to EBRT include, but are not limited to preexisting anal fistula, inflammatory bowel disease (e.g. ulcerative colitis, diverticulitis, etc.), unacceptable operative risks or medically unsuitable for anesthesia, history of previous pelvic radiotherapy, and ataxia telangiectasia.

VII. **Metastatic, castration resistant prostate cancer:** enzalutamide (Xtandi) and abiraterone (Zytiga, Yonsa) have been evaluated for safety and efficacy. Enzalutamide (Xtandi) versus placebo was evaluated in those that had previously been treated with chemotherapy and those that were chemotherapy naïve. Overall survival was prolonged in both settings. Abiraterone (Zytiga, Yonsa) plus prednisone has also shown prolonged survival in this setting in those that have been previously treated with chemotherapy and those chemotherapy naïve. Head-to-head trials have not been completed to provide insight to superior therapy between abiraterone (Zytiga, Yonsa) and enzalutamide (Xtandi). Abiraterone (Zytiga, Yonsa) is indicated in combination with prednisone; however, enzalutamide has safety concerns including CNS toxicities and seizures. Additionally, abiraterone (Zytiga, Yonsa) has generic availability.

- The combination therapy of enzalutamide (Xtandi) and talazoparib (Talzenna) was evaluated in the TALAPRO-2 trial. Talazoparib (Talzenna) is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes. A total of 805 patients were randomized 1:1 to

either receive talazoparib/enzalutamide or placebo/enzalutamide. They were further stratified by previous novel hormonal therapy/docetaxel and HRR gene-alteration status. The primary outcome was radiographic progression free survival (rPFS) assessed by blinded independent central review per RECIST 1.1 (soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (bone disease). Treatment with talazoparib/enzalutamide resulted in a 37% lower risk of radiographic progression or death compared to placebo plus enzalutamide (HR 0·63; 95% CI 0·51–0·78; p<0.0001). The most common adverse effects in the treatment group were anemia (66%), neutropenia (36%), and fatigue (34%).

- In a randomized, double-blind, Phase 3 clinical trial (PROpel), the efficacy, safety, and tolerability of olaparib (Lynparza) was assessed versus placebo when given in addition to abiraterone in men with metastatic castration-resistant prostate cancer (mCRPC), who had not received prior chemotherapy or novel hormonal agents (NHAs; e.g., enzalutamide, apalutamide, abiraterone) in the 1st-line metastatic setting. Previous therapy with docetaxel in the neoadjuvant or adjuvant setting, as well as first-generation antiandrogen agents (e.g., bicalutamide, nilutamide) were permitted; however, were not required as part of the inclusion criteria. The primary endpoint, radiographic progression-free survival (rPFS), and secondary endpoints included OS and time to first subsequent anticancer therapy or death. In a predefined interim analysis (as of July 2022), olaparib (Lynparza) in combination with abiraterone reduced the risk of disease progression or death by 34% versus abiraterone alone (based on a hazard ratio [HR] of 0.66; 95% confidence interval [CI] 0.54-0.81; p<0.0001). Median rPFS was 24.8 months for olaparib (Lynparza) plus abiraterone versus 16.6 months for abiraterone alone.
- As of 9/2023, there are no head-to-head trials suggesting superiority of one PARP inhibitor/antiandrogen combination therapy over another. Both olaparib/abiraterone and talazoparib/enzalutamide are categorized as useful in certain circumstances with a Category 1 recommendation per NCCN guidelines. olaparib/abiraterone was FDA approved for this indication in patients harboring a *BRCAm*, while talazoparib/enzalutamide carries a broader FDA approval encompassing all *HRRm*. DNA repair anomalies known as homologous recombination repair gene mutations (HRRm) are identified in approximately 25% of patients with mCRPC. HRR gene mutations can consist of mutations in *ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C*. Approximately 10-15% of patients with mCRPC have the BRCA1/BRCA2 gene mutations. These mutations have been associated with more aggressive disease and poor patient outcomes.

VIII. **Metastatic high-risk castration sensitive prostate cancer:** abiraterone (Zytiga, Yonsa) plus prednisone has been evaluated for safety and efficacy. High risk disease was defined as having

at least two of the following three risk factors: Gleason score eight or greater, presence of three or more bone lesions, evidence of measurable visceral metastases. Overall survival over placebo was shown to be statistically significant for abiraterone (Zytiga, Yonsa).

- NCCN prostate cancer guidelines provide a category 1 recommendation for use of abiraterone acetate in combination with docetaxel and ADT in those with a high-volume metastatic burden who are candidates for chemotherapy. This is based on the findings from the PEACE-1 clinical trial, which evaluated the safety and efficacy of standard of care (SOC) therapy, defined as docetaxel and ADT, against SOC plus abiraterone acetate and prednisone. The co-primary endpoint consisted of radiographic progression free survival (rPFS) and overall survival (OS). The abiraterone group demonstrated statistically significant benefit in rPFS and OS with a hazard ratio (HR) was 0.50 (99.9% CI 0.34-0.71; p<0.0001) and 0.75 (95.1% CI 0.59-0.95; p=0.017), respectively. However, further analysis based on volume of metastatic burden revelated that OS was only statistically significant in the population with high-volume metastatic burden (HR 0.72 [95.1% CI 0.55-0.95]; p=0.019) compared to low-volume metastatic burden (HR 0.83 [95.1% CI 0.50-1.39]; p=0.66). According to NCCN, high-volume disease is differentiated from low-volume disease by visceral metastases and/or four or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. While the addition of docetaxel to abiraterone acetate and ADT did increase overall incidence of adverse reactions, it did not increase the incidence of severe or fatal adverse events and the safety profile is largely the same. Docetaxel is intended to be used at the same time or within a few weeks of starting therapy with darolutamide or abiraterone. In mHSPC, docetaxel is dosed on every 3-week cycles for a total of 6 cycles; completion of docetaxel therapy should reasonably be able to occur within the initial approval period of 6 months.

IX. Although both strengths (250 mg and 500 mg) of abiraterone (Zytiga) are available in generic formulations, the 500 mg tablet remains at a significantly higher cost (40x greater) than the 250 mg tablet. Thus, use of generic abiraterone 250 mg is required over abiraterone 500 mg tablet.

X. Apalutamide (Erleada) was evaluated in the metastatic, castration sensitive prostate cancer setting in combination with ADT versus ADT alone. This was not specifically in high-risk disease; however, 93% of subjects had a Gleason Score of seven or greater, and all subjects had bone metastases. Fifty-five percent of subjects had bone only metastases, and the remaining had additional metastases. Primary outcomes were radiographic progression free survival, which were statistically and clinically significant favoring apalutamide (Erleada). Head-to-head trials against abiraterone (Zytiga) have not occurred in this setting; however, the safety profile of abiraterone is further established at this time.

XI. Enzalutamide (Xtandi) was evaluated in metastatic, castration sensitive, prostate cancer in combination with ADT versus ADT alone. This study was not specifically in high-risk disease;

however, the majority of subjects (> 67%) had a Gleason score of 8 or greater – nearly 85% had bone metastases or bone and other metastases. Progression-free survival was 19 months for placebo plus ADT and was not reached for enzalutamide (Xtandi). Radiographic progression was experienced by 13.8% of those receiving enzalutamide (Xtandi) and 32.6% for placebo plus ADT. Head-to-head trials against abiraterone have not occurred in this setting; however, abiraterone provides a better value for the treatment of mCSPC at this time. Additionally, enzalutamide (Xtandi) was evaluated in a Phase III open-label trial in addition to ADT versus ADE alone in those that were castration naïve. The primary endpoint of OS was statistically significant in a group of 125 subjects (HR for death: 0.67, CI 0.52-0.86, p=0.002).

XII. Darolutamide (Nubeqa) was evaluated in metastatic, castration sensitive, prostate cancer in combination with ADT and docetaxel versus ADT/docetaxel alone. This was not specifically in high-risk disease; however, the majority of subjects (>77%) had a Gleason score of 8 or greater – nearly 80% had bone metastases and all other subjects had visceral or non-regional lymph node metastases. The hazard ratio for death was 0.68 (95% CI, 0.57 – 0.80; p<0.001) with overall survival (OS) at four years reported as 62.7% in the darolutamide group compared to 50.4% in the placebo group, despite a high percentage of patients who received subsequent life-prolonging systemic therapies (primarily a different androgen-receptor pathway inhibitor) among those who entered the follow-up in the placebo group (374 of 495 patients (75.6%). The side effect profile of darolutamide (Nubeqa) was consistent with previous evaluation and a higher incidence of treatment related adverse events was higher during the period when patients received both docetaxel and darolutamide (Nubeqa), and progressively decreased thereafter.

Investigational or Not Medically Necessary Uses

I. Therapies in this policy are being evaluated in other conditions; however, quality data indicating safety and efficacy in the following settings are not yet available:
   A. Cushing's Syndrome
   B. Breast cancer
   C. Hepatocellular carcinoma
   D. Fallopian tube, ovarian, or uterine cancer

References

1. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2019;380(13):1235-1246.
2. National Comprehensive Cancer Network clinical practice guidelines, prostate cancer. Version 4.2023. Updated September 7, 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
3. El-amm J, Aragon-ching JB. The Current Landscape of Treatment in Non-Metastatic Castration-Resistant Prostate Cancer. Clin Med Insights Oncol. 2019;13:1179554919833927.
4. Nubeqa [Package Insert]. 2022. Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ.

5. Xtandi (enzalutamide) [prescribing information]. Northbrook, IL: Astellas Pharma US Inc; November 2023. Erleada [Prescribing Information]. 2019. Janssen Pharmaceuticals Companies. Horsham, PA.
6. Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol. 2013;24(7):1802-7.
7. Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol. 2013;24(7):1807-12.
8. Bianchini D, Lorente D, Rodriguez-vida A, et al. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. Eur J Cancer. 2014;50(1):78-84.
9. Smith MR, Saad F, Rathkopf DE, et al. Clinical Outcomes from Androgen Signaling-directed Therapy after Treatment with Abiraterone Acetate and Prednisone in Patients with Metastatic Castration-resistant Prostate Cancer: Post Hoc Analysis of COU-AA-302. Eur Urol. 2017;72(1):10-13.
10. Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med. 2018;378(15):1408-1418.
11. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018;378(26):2465-2474.
12. Yonsa [Package Insert]. 2011. Sun Pharmaceuticals Industries, Inc. Canbury, NJ.
13. Chi KN., Agarwal N., Bjartell A., et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med. 2019;381(1):13-24.
14. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2019;37(32):2974-2986.
15. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med. 2019;381(2):121-131.
16. Smith MR, Hussain M, Saad F, et al. Darolutamide and Survival in metastatic hormone-sensitive prostate cancer. N Engl Med 2022;386:1132-42.
17. Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. Lancet. 2022 Apr 30;399(10336):1695-1707. doi: 10.1016/S0140-6736(22)00367-1. Epub 2022 Apr 8.
18. Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet. 2022;399(10323):447-460.
19. Zaorsky NG, Davis BJ, Nguyen PL, et al. The evolution of brachytherapy for prostate cancer. Nat Rev Urol. 2017;14(7):415-439.
20. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial [published online ahead of print, 2023 Jun 2]. Lancet. 2023;S0140-6736(23)01055-3. doi:10.1016/S0140-6736(23)01055-3
21. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM Evid. 2022;1(9). doi:10.1056/EVIDoa2200043
22. Freedland SJ, de Almeida Luz M, De Giorgi U, et al. Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer. N Engl J Med. 2023;389(16):1453-1465.

Related Policies

Policy Name	Disease state
olaparib (Lynparza)	Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated

talazoparib (Talzenna)	Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication for Xtandi (enzalutamide) in non-metastatic, castration sensitive prostate cancer upon FDA approval in November 2023. Xtandi was added to existing criteria. Updated step through Lynparza/abiraterone for mCRPC to delineate between patients with BRCAm vs HRRm.	02/2024
Addition of criteria for abiraterone off-label use in non-metastatic, castration sensitive prostate cancer given published meta-analysis, long-term overall survival data from the STAMPEDE trial, and updated NCCN prostate cancer guideline recommendation (category 2a). Addition of pathway to coverage for enzalutamide (Xtandi) in combination with talazoparib (Talzenna) for metastatic castration-resistant prostate cancer given new FDA approved indication. Addition of verbiage to address combination use of olaparib (Lynparza) with abiraterone for mCRPC. Added related policies table.	09/2023
Added 240 mg Erleada tablets to policy	02/2023
Addition of darolutamide (Nubeqa) for metastatic castration-sensitive prostate cancer given new FDA-approved indication; Addition of docetaxel in combination with abiraterone acetate for metastatic castration-sensitive prostate cancer with high volume metastatic burden based on category 1 NCCN recommendation; Changed name of policy to 'Second Generation Anti Androgen Agents'	10/2022
Require clinical rationale for use of generic abiraterone 500 mg instead of generic 250 mg	05/2022
Addition of Grade Group referenced with Gleason Score	05/2021
Additional of newly approved enzalutamide (Xtandi) 40 mg and 80 mg tablets	11/2020
Addition of enzalutamide (Xtandi) for castration sensitive prostate cancer given new FDA-approved indication. Removal of requirement upon renewal to change to generic abiraterone. Consolidation of requirements for agents in the setting of castration sensitive prostate cancer to streamline policy. Formatting updates	12/2019
Darolutamide (Nubeqa) new agent available, criteria converted to policy, and all agents combined into one policy. Requirement of generic abiraterone added unless contraindicated or not tolerated. Addition of use of GnRH therapy in metastatic castration sensitive disease included. Yonsa brand added. Erleada now FDA approved for castration sensitive disease.	08/2019
Generic abiraterone requirement added prior to use of branded 250 mg.	12/2018
Enzalutamide new indication of non-metastatic resistant prostate cancer added. Clinical notes added and appropriate routing through criteria.	08/2018
Apalutamide (Erleada) criteria created	04/2018
Abiraterone new indication of metastatic, high-risk castration sensitive prostate cancer added. LATITUDE trial information incorporated as well.	02/2018
Enzalutamide (Xtandi) criteria created	02/2013
Abiraterone (Zytiga) criteria created	09/2011