PROSTATE CANCER

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Learning Objectives:

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for patients with prostate cancer.
2. Discuss short- and long-term treatment goals, including post-therapy and survivorship, with a patient with prostate cancer and his caregiver.
3. Select relevant information and guidance for the public regarding prostate cancer-related issues (e.g., risk factors, prevention, screening).

PROSTATE CANCER

Patient Case #1: DR is a 40-year-old Caucasian male with a past medical history of seasonal allergies. His primary care physician checked a PSA which resulted at 9 ng/ml and he had an abnormal digital rectal exam (DRE). Further imaging and biopsy reveal a very low risk prostate adenocarcinoma. He prefers a treatment strategy that minimizes adverse effects. **What is the most appropriate treatment option for DR at this time?**

A. Active surveillance
B. Radical prostatectomy + short term androgen deprivation therapy
C. Radiation therapy + short term androgen deprivation therapy
D. Observation

I. Genomics, Etiology and Pathogenesis

A. Dysregulation of signaling pathways areis involved in initiation and progression of prostate cancer;, however, the exact genes and pathways are not fully understood. Altered expression of NKX3.1, Forkhead box A1 (FOXA1), the androgen receptor (AR) and Myc are involved in early stage prostate cancer.[1]

1. AR: Most well studied receptor involved in prostate cancer. Understood to be reactivated in disease that progresses despite castrate levels of testosterone. The term androgen-independent is no longer used. Castration resistant prostate cancer (CRPC) is the appropriate nomenclature. Several mechanisms for reactivation of AR are noted below and thought to be the mechanisms of resistance to hormonal manipulations.[1]

2. Intratumoral androgen synthesis (autocrine androgen production): CYP17A1 and HSDD3B2 are key enzymes in conversion of cholesterol to androgen precursors. These enzymes have been found to be 10-fold higher in metastatic prostate cancer cells. SRD5A1/2 codes for 5-alpha-reductase and is responsible for conversion of testosterone to dihydrotestosterone, which is also elevated in metastatic prostate cancer cells.[1]

B. Family history plays a large role in prostate cancer risk. Prostate cancer is associated with Hereditary Breast and Ovarian Cancer (HBOC) syndrome, due to germline mutations in homologous recombination repair mutations (HRRm), as well as Lynch syndrome, due to germline mutations in DNA mismatch repair genes.[1]

C. Tumor cells may have mutations in MLH1, MSH2, MSH6 or PMS2 resulting in microsatellite instability (MSI) or deficient mismatch repair (dMMR). The incidence of MSI-high tumors has been reported to be around 3% in studies of prostate cancer patients.[2] This may be due to germline mutations (as described above) or more often, due to somatic mutations. NCCN Clinical Practice Guidelines (NCCN®) state that somatic MSI/dMMR testing could be considered for regional or castrate sensitive metastatic disease and is recommended in metastatic castrate resistant disease (if not conducted previously).[3]

D. Prostate cancer is also associated with somatic HRRm (mutations found in tumor DNA rather than germline). Mutations in HRR genes may be somatic or germline and the prevalence in the metastatic castrate-resistant setting has been reported up to 33%.[4] Knowledge of germline mutations can impact family genetic screening, prognosis (BRCA1/2 germline mutations known to have increased risk of progression on local therapy and decreased overall survival), and potential implications for treatment in advanced disease.[5]

1. NCCN Guidelines® recommend germline testing for all high-risk, very high-risk, regional, or metastatic prostate cancer (regardless of family history) as well as those with prostate cancer and a positive family history, or Ashkenazi Jewish ancestry. Germline testing may also be considered in patients with intermediate-risk prostate cancer and intraductal histology or those with personal history of prostate cancer and a second cancer (exocrine pancreas, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary, or small intestine). NCCN strongly recommends somatic tumor testing for all patients with metastatic prostate cancer, and notes that it can be considered for regional prostate cancer.
2. Mutations known to directly or indirectly impact HRR include: BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L.[6]

I. Screening & Prevention[3, 5]

A. Screening

1. Screening for prostate cancer continues to be controversial with several organizations making different recommendations based on current data.
2. Must balance the benefits of screening to prevent mortality in an often-indolent malignancy versus the harms of over-diagnosis and over-treatment.
3. Screening generally refers to periodic PSA ± digital rectal examination (DRE) evaluations in asymptomatic men. Most organizations endorse a detailed discussion of the risks and benefits between provider and patient prior to the start of screening.
4. Prostate Specific Antigen[3,5]
    a. PSA is a glycoprotein produced by epithelial cells of the prostate. It is a kallikrein-like serine protease which liquefies seminal secretions.
    b. PSA is specific to the prostate, but not specific for cancer. In conjunction with DRE, PSA is the most common test used to screen for prostate cancer, but can be affected by other factors.
        1) Increased by: prostatic manipulation, prostate biopsy, transurethral resection of the prostate (TURP), benign prostatic hyperplasia (BPH), and prostatitis
        2) Decreased by: finasteride [5]

Factors Affecting the PSA[7]

Factor	Effect on PSA	Interpretation
Finasteride, dutasteride	50% decrease in PSA (although may vary from 40-60%) within 6-12 months	Note use and duration; Consider doubling PSA (due to variability and over estimating PSA and unreliable cancer)
Saw palmetto	Unpredictable	Record in history
Androgen receptor blockers	Variable, but usually increase	Record in history
Ejaculation	Increase	Abstain for 48 hours prior to getting PSA drawn
Prostatic manipulation, biopsy or DRE	Increase, however, not clinically significant – not specified to when to perform	Measure PSA prior or immediately post DRE[8]

c. Total PSA measurements are used widely for prostate cancer screening in the United States.

1) The normal range for total PSA is ≤ 4 ng/mL and this cut-off is primarily based on a prospective study by Gann and colleagues, which demonstrated that a single PSA level > 4.0 ng/mL had a sensitivity of 73%, with a specificity of 91% in detecting prostate cancer within 4 years.[7]

2) It is estimated that there is a greater than 67% chance of prostate cancer for PSA levels > 10 ng/mL. PSA elevations between 4 and 10 ng/mL cannot distinguish between BPH and prostate cancer and it is estimated that 15% of men with PSA <4ng/mL and a normal DRE will have biopsy-confirmed prostate cancer.[9]

d. PSA velocity may be another predictor of prostate cancer risk.

1) Carter and colleagues found men with an initial PSA of < 4 ng/mL but with a PSA velocity > 0.35 ng/mL per year had a higher relative risk of prostate cancer death as compared to men with a PSA velocity of ≤ 0.35 ng/mL per year (RR = 4.7, 95% CI = 1.3 to 16.5; p = 0.02).[10]

2) Based on these results, some experts recommend further work-up for individuals with a PSA < 4 ng/mL, if their PSA velocity is > 0.35 ng/mL per year. This decision should be made in conjunction with other factors such as age, comorbidity, ethnicity and family history. Of note, PSA velocity is not useful in patients with high PSA (> 10 ng/ml) and prostatitis may cause a dramatic increase in PSA confounding PSA velocity as well.

5. US Preventive Services Task Force (USPSTF) does not recommend screening. As of May 2018, the USPSTF recommends against utilizing PSA for screening based on lack of evidence that PSA test saves lives. PSA screening may result in over-diagnosed prostate cancer, which may not otherwise cause clinical problems in men's lifetime. It may lead to unnecessary testing and treatment.[11]

a. In May of 2018, USPSTF provided a supplement to their earlier statements to individualize decision-making about prostate cancer screening for men ages 55 to 69, including informing each man about the potential benefits and harms of screening.

b. The USPTF continues to recommend against screening men 70 years and older. They concluded that evidence was insufficient to make specific recommendations regarding earlier screening discussions for higher-risk groups: African-American men and those with a family history of prostate cancer.

c. American Society of Clinical Oncology (ASCO) published a provisional clinical opinion paper on PSA screening in 2012. They recommend against general screening in men with a life expectancy < 10 years. For men with a > 10- year life expectancy, ASCO recommends patient-physician discussion about the benefits vs. harms of PSA screening. They also recommend literature written in lay language be provided to the patient prior to ordering PSA tests.[12]

d. For patients choosing screening, when to initiate further workup for abnormal PSA is debated. General agreement is that a PSA > 4ng/mL should require further workup. However, some would argue a cutoff PSA > 2.5 ng/mL based on the Goteborg study which illustrated reduction in prostate cancer related death of Swedish men through screening and included PSA > 2.5 ng/mL.[13]

6. Harms vs benefits

a. Harms: Complications from biopsy (hematuria, hematochezia, hematospermia, dysuria, urinary retention, infection, pain). Estimated that 1/3 of patients will have some type of complication from biopsy and 4% may be hospitalized. Over-diagnosis and over-treatment: American Urological Association (AUA) estimates 1 in 4 are over-diagnosed. Over-treatment leads to complications of surgery and/or radiation including urinary complications, erectile dysfunction, infections, bleeding, and death.[14]

b. Benefits: Lower stage and grade of cancer at diagnosis; possible reduction in prostate cancer mortality; limit morbidity from advanced disease such as bladder outlet obstruction, hematuria, bone pain.[14]

7. Prostate-cancer screening guidelines summary

a. Screening guidelines as well as treatment are often determined by a patient's life expectancy. Life expectancy may be estimated by using the Minnesota Metropolitan Life Insurance calculator or the Social Security Administration Life Insurance calculator. It may then be adjusted for individual patients by adding or subtracting 50% if the patient is in the healthiest quartile or the unhealthiest quartile, respectively.

Screening Recommendations

Recommendation	AUA, ASCO[14]	NCCN® v.1.2022[3]	USPSTF[11]	ACS[15]
Shared decision between patient and clinician	Yes	Yes	Yes	Yes
Age to begin screening		For those who choose to be screened	For those who choose to be screened	For those who choose to be screened
Average-risk patient (years old)	55	45	55	50 (begin discussion)
High-risk patient* (years old)	Consider at 40-54	Consider at age 40	No firm stance	40-45 (begin discussion)
Screening test	PSA only - don't recommend DRE or %PSA, etc (not as primary screening)	PSA +/-DRE	PSA only for age 55-69 for those who choose to be screened	PSA +/- DRE
Frequency of screening	Every 2 years or more	Every 1-4 years depending on baseline PSA	Every 2-4 years	PSA < 2.5 ng/ml, every 2 years PSA ≥ 2.5 ng/ml, annually
Discontinue screening / Do not offer	Age < 40 or ≥70 years or life expectancy <10-15 yr	Life expectancy < 10 yr OR up to 75 y/o (unless little to no comorbidities)	Age ≥ 70 years	Life expectancy < 10 yr

**High Risk: African American, men with first-degree relative diagnosed with prostate cancer at age <65 years.*
AUA: American Urological Association; NCCN®: National Comprehensive Cancer Network; ASCO: American Society of Clinical Oncology; USPSTF: United States Preventative Services Task Force; ACS: American Cancer Society

B. Prevention

1. Chemoprevention

    a. Interest in preventing prostate cancer exists and several large chemoprevention trials are sponsored and ongoing by the National Cancer Institute.

    b. Currently, there is a lack of data supporting the use of vitamins or dietary supplements for the prevention of prostate cancer.

    c. 5-alpha reductase inhibitors

        1) Prostate Cancer Prevention Trial (PCPT)

            a. The first large chemoprevention trial in prostate cancer. It began in 1994 and randomized 18,882 men older than 55 years with a low risk of prostate cancer (PSA </= 3.0 ng/mL and normal DRE) to receive 5 mg finasteride daily or placebo for 7 years to determine if inhibition of dihydrotestosterone synthesis in the prostate for a prolonged period would lead to a decreased incidence of prostate cancer.[16]

            b. Finasteride demonstrated a 24.8% reduction in prostate cancer prevalence during the 7-year period.

            c. For all men in whom prostate cancer developed during the study period, the treated group had a higher Gleason score, suggesting more aggressive disease compared to the placebo group for all men in whom prostate cancer developed during the study period.

            d. The 18- year follow up data confirmed a reduction in the risk of prostate cancer (10.5% of men receiving finasteride vs 14.9% of men receiving placebo were diagnosed. P<0.001). High-grade cancer was diagnosed in 3.5% of finasteride group versus 3.0% in placebo (RR 1.17; 95% CI 1.0-1.37, p=0.05). The 15 year overall survival rate was 78% and 78.2% for finasteride and placebo, respectively.[17]

            e. A number of biases in cancer detection caused by finasteride have been proposed, including improved detection of overall and high-grade prostate cancer, increased sensitivity of DRE, and increased sensitivity of biopsy for high-grade cancer detection.

        2) The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) Trial[18]

            a. Phase III trial of dutasteride versus placebo in over 8000 men with PSA between 2.5-10 ng/mL and a negative biopsy.

            b. There was a 22.8% risk reduction of prostate cancer in the dutasteride arm (p<0.001). A non-significant increase in high-grade tumors was seen in the dutasteride group (p=0.81).

            c. There was a significant increase in high-grade tumors detected during years 3 and 4 in the dutasteride group (p=0.003).

        3) The American Society of Clinical Oncology and the American Urological Association published a joint practice guideline for prostate cancer chemoprevention.[19]

a. In men who are taking dutasteride or finasteride for benign conditions such as BPH, the potential benefits and risks of dutasteride or finasteride should be discussed.

b. The guideline does not recommend the use of finasteride or dutasteride for prostate cancer chemoprevention.

c. The higher incidence of high-grade cancer in the finasteride group seen in the PCPT is most likely related to bias. Cancer induction or promotion by finasteride cannot be excluded with certainty.

4) Neither finasteride nor dutasteride is FDA approved for preventing or reducing risk of prostate cancer.

I. Treatment

A. Treatment determined by risk stratification rather than solely based on stage.

Management of Prostate Cancer with Low and Intermediate Recurrence Risk[3]

Recurrence Risk		Expected Survival	Initial Therapy
Very Low cT1c, Grade Group 1, PSA < 10, < 3 Bx cores (+) and ≤ 50% cancer in each core, PSA density < 0.15 ng/ml/g		< 10 y	Observation
		10-20y	Active Surveillance (AS)
		≥ 20 y	AS (preferred), EBRT or brachytherapy, or RP (± EBRT ± ADT if adverse features[a])
Low cT1-2a, Grade Group 1, PSA < 10		< 10 y	Observation
		≥ 10 y	AS (preferred), EBRT or brachytherapy, or RP (± EBRT ± ADT if adverse features)[a]
Intermediate ≥1 intermediate risk factors (IRF): cT2b-cT2c Grade group 2-3 PSA 10-20 ng/ml	**Favorable** Meets all of: 1 IRF, Grade Group 1-2, < 50% Bx cores (+)	< 5 y	Observation[c]
		5- 10 y	Observation (preferred), or EBRT or brachytherapy
		> 10 y	AS, EBRT or brachytherapy, or RP ± PLND (± EBRT ± ADT if adverse features or positive lymph nodes)[a,b]
	Unfavorable Has one or more of: 2-3 IRF, Grade group 3, ≥ 50% Bx cores (+)	< 5 y	Observation[c]
		5- 10 y	Observation, or EBRT + ADT, or EBRT + brachytherapy ± ADT
		> 10 y	RP + PLND (± EBRT ± ADT if adverse features or positive lymph nodes)[a,b], or EBRT + ADT, or EBRT + brachytherapy ± ADT

a adverse features: positive margin(s); seminal vesicle invasion; extracapsular extension; detectable PSA; b If lymph node metastasis ADT (category 1) ± EBRT (category 2B) or observation. If adverse features only EBRT± ADT (6 months) or observation ADT=Androgen deprivation therapy, c for asymptomatic patients with life expectancy <5 years, no imaging or treatment indicated until patient becomes symptomatic (then ADT should be given); AS=Active surveillance; Bx=Biopsy; RP=Radical prostatectomy; EBRT= External beam radiation therapy; PLND = pelvic lymph node dissection

B. Localized Disease (T1a-c, T2a-c, N0M0): Treatment will depend primarily on the stage and grade, but also takes into consideration the patient's age, general health and preferences.

1. Observation[3]

a. Preferred for those with low-risk prostate cancer with life expectancy less than 10 years

1) Expectation to deliver palliative therapy if necessary (symptomatic or symptoms are imminent; PSA > 100 ng/mL or change in exam)

2) Monitor with PSA no more than every 6 months.

3) Repeat prostate biopsy not recommended

1) Advantage: avoid immediate morbidity associated with treatment

2) Disadvantage: Risk of disease complications such as urinary retention or pathologic fracture without symptoms

2. Active surveillance (AS): Based on the premise that prostate cancer is a benign and indolent disease[3]

    1) Preferred in those with very-low risk disease and life expectancy at least 20 years and for low risk and life expectancy of at least than 10 years

    2) Expectation to deliver potentially curative therapy upon progression of disease

    3) Involves actively monitoring the disease.

        i. PSA no more often than every 6 months unless clinically indicated

        ii. DRE no more often than every 12 months unless clinically indicated

        iii. Repeat prostate biopsies no more than every 12 months unless clinically indicated, and

        iv. MRI no more than every 12 months unless clinically indicated

3. Radiation Therapy (RT): External Beam (EBRT) or Brachytherapy[3]

    a. Appears equivalent to surgery in outcome, although the only head- to- head comparison has been greatly criticized for bias

        1) Option for patients who are not surgical candidates

        2) Benefits versus surgery: less bleeding, avoids risks of anesthesia, low risk of urinary incontinence and stricture, short term preservation of erectile function

        3) Disadvantages versus surgery: treatment course of 8-9 weeks; 50% have temporary bowel or bladder symptoms during therapy, erectile dysfunction increases over time, radiation proctitis

    b. External Beam (EBRT)[3]

        1) 3D conformational or IMRT (intensity modulated radiation therapy) should be employed in preference to standard techniques

        2) High risk cancers: may also have pelvic lymph nodes irradiated and the addition of adjuvant ADT for 1-3 years (4-6 months of ADT if only 1 high-risk factor).

        3) Intermediate risk cancers: may have pelvic lymph node irradiation and 4-6 months of ADT

        4) Low risk cancer: no pelvic lymph node irradiation or ADT

    c. Brachytherapy[3]

        1) Traditionally an option for -low-risk prostate cancers. However, new advancements may increase use in intermediate to high-risk cancers.

        2) Low dose rate (LDR) brachytherapy

            i. Permanent seed implantation

            ii. Allows delivery of radiation to prostate and limits exposure of bladder and rectum

iii. Monotherapy in -low-risk patients; combined with EBRT ± ADT for intermediate risk; used as a "boost" of radiation

iv. Advantages: 1 day therapy, control rates comparable to surgery for -low-risk tumors, minimal risk for incontinence, erectile function preserved in short term

v. Disadvantages: requires general anesthesia, acute urinary retention

vi. Avoid in patients post-transurethral resection of the prostate (TURP)

3) High dose rate (HDR) brachytherapy

i. Temporary insertion of radiation source to provide "boost" radiation

ii. Used in addition to EBRT in patients at high risk for recurrence

4. Radical Prostatectomy (RP) ± Pelvic lymph node dissection (PLND)[3]

a. RP appropriate if tumor confined to prostate and is definitive curative therapy

b. Significant perioperative morbidity, therefore, reserved for those with life expectancy ≥10 years. The PIVOT trial compared radical prostatectomy to observation in 731 men with localized prostate cancer. No significant difference was found in overall mortality or prostate cancer specific mortality through 20 years of follow up. However, 21% of patients undergoing surgery had an adverse event within 30 days of surgery.[20, 21]

c. 85% of men with disease confined to the prostate are cured at 10 years

d. PLND

1) Indicated if probability of lymph node involvement is >2%

2) Extensive PLND is preferred and includes removal of all lymph node bearing tissue from the area.

e. Complications

1) Early mortality (0.3%)

2) Bladder contracture (1-22%)

3) Incontinence (0-17%)

4) Impotence (63% retain potency with bilateral nerve sparing procedure)

5. Androgen Deprivation Therapy (ADT)[3]

a. Goal of therapy is to induce castrate levels of testosterone

1) Surgical castration: orchiectomy

2) Medical/chemical castration: Luteinizing hormone-releasing hormone (LHRH) agonist or antagonist

3) Goal serum testosterone <50 ng/dl after 1 month of therapy

b. Combination with RT in low and intermediate risk disease

1) D'Amico et al. evaluated 206 patients with T1b to T2b disease, a PSA ≥ 10 ng/ml, Gleason of at least 7, or evidence of extraprostatic disease. Patients were randomized to RT in

combination with 6 months of ADT vs. RT alone. Five-year survival was 88% in the RT + ADT group vs. 78% in the RT alone group (p=0.04).[22]

2) RTOG 94-08 Trial: Eligible patients had T1b, T1c, T2a, or T2b prostate cancer, and PSA of 20 ng/mL or less and were randomized to RT alone or RT + 4 months of ADT. The androgen suppression was started 2 months before radiation therapy. In the study of 1979 evaluable patients combined radiation therapy with androgen suppression had significantly better 10-year overall survival compared with radiation alone (62% vs. 57%; P=0.03). The re-analysis according to recurrence risk suggested overall and disease-specific mortality rate benefit primarily in intermediate-risk patients.[23]

c. No role for adjuvant ADT after prostatectomy in -low-risk patients. Use after prostatectomy in patients with positive lymph nodes has shown mixed results.

Patient Case #1, Answer:

Correct answer = A (active surveillance). BF is classified as very low risk and has life expectancy >20 years. Active surveillance is the preferred option for this risk category/life expectancy. Active surveillance minimizes toxicity of treatment. Observation is not appropriate for a young healthy patient. Adjuvant radiation is not indicated in very low risk disease.

Management of Prostate Cancer with High and Very High Recurrence Risk

Recurrence Risk	Expected Survival	Initial Therapy
High Risk One high risk feature (HRF) : T3a or Grade 4 or 5 or PSA > 20	≤ 5 years and asymptomatic	Observation or ADT or EBRT
	>5 years or symptomatic	EBRT + 1.5-3y ADT (Category 1) ± Abiraterone (very high risk only)
Very High Risk One or more of: cT3b-cT4, Primary Gleason pattern 5, or >4 cores with Grade Group 4 or 5, 2-3 HRF		EBRT + brachytherapy + 1-3y ADT (ADT Category 1)
		RP + PLND (± EBRT ± ADT if adverse features or positive lymph nodes)[a,b]
Regional Any T, N1, M0	≤ 5 years and asymptomatic	Observation or ADT
	>5 years or symptomatic	ADT + EBRT + abiraterone (preferred)
		ADT + EBRT
		ADT ± abiraterone
		RP + PLND (± EBRT ± ADT if adverse features or positive lymph nodes)[a,b]

a adverse features: positive margin(s); seminal vesicle invasion; extracapsular extension; detectable PSA

b If lymph node metastasis ADT (category 1) ± EBRT (category 2B) or monitoring/observation. If adverse features only EBRT± ADT (6 months) or monitoring/observation

ADT=Androgen deprivation therapy; AS=Active surveillance; Bx=Biopsy; RP=Radical prostatectomy; EBRT=External beam radiation therapy; PLND = pelvic lymph node dissection

C. Treatment of High- Risk, Locally Advanced Disease, or Very High Risk (T3 and T4)[3]

1. External Beam Radiation Therapy + Neoadjuvant/Adjuvant/Concurrent Hormonal Therapy

a. Multiple studies have evaluated the combination of ADT with EBRT in patients with -high-risk disease compared with either therapy alone. Studies have also compared short term ADT to long term ADT in -high-risk patients. Results are summarized in the table below.

b. A recent meta-analysis evaluated hormonal therapy after primary therapy of radiation or prostatectomy for men with locally advanced prostate cancer. ADT with EBRT improved 5-year overall survival, clinical disease-specific survival, and biochemical disease-free survival. No significant difference in overall survival in the prostatectomy groups was observed.[24]

c. ADT usually starts prior to radiation, continues during radiation and for 2-3 years after radiation. Optimal duration of neoadjuvant therapy for those with high recurrence risk is 2-3 years.

Summary of studies including EBRT and ADT in high-risk patients

	Inclusion	Randomized Arms	Findings
RTOG 85-31[25] n=977	T3 or N1	Arm 1: RT + ADT indefinitely Arm 2: RT -> ADT at progression	-10-year survival rate was improved with Arm 1 (49% vs 39%, p=0.002) -10-year local failure rate was better for Arm 1 (23% vs 38%, p<0.0001) -Secondary analysis found ADT > 5 years was associated with improved survival and disease-free survival[26]
RTOG 92-02[27, 28] n=1521	T2c-T4	4 months of ADT with RT then randomized to: Arm 1: no further ADT Arm 2: ADT x 2 years	At 10 years, -DFS improved with Arm 2 (13.2% vs 22.5%, p<0.0001) -distant metastases improved with Arm 2 (22.8% vs 14.86%, p<0.0001) -biochemical failure improved with Arm 2 (68.1% vs 51.9%, p≤ 0.0001) -Overall survival was no different (51.6% vs 53.9%, p=0.36) -Subgroup of patients with Gleason 8-10 found improvement in overall survival with Arm 2 (31.9% vs 45.1%, p=0.0061) At median 19.6 years, DFS, OS, and biochemical failure all favored the longer duration ADT arm across the entire cohort. Relative reduction for OS was 12% (p=0.03).
EORTC 22961[29] n=970	pT1c to pT2a-b + pN1 to pN2 + M0 or cT2c to cT4 + cN0 to cN2 + M0	6 months of ADT with RT then randomized to: Arm 1: no further ADT Arm 2: ADT x 2.5 years	-Noninferiority study -5-year overall mortality was 15.2% for Arm 2 and 19% for Arm 1 (p=0.65 for noninferiority)
EORTC 22863[30] n=415	T1-2 and grade 3 Or T3-4	Arm 1: RT alone Arm 2: RT + ADT x 3 years	-10-year overall survival was improved for Arm 2 (39.8% vs 58.1%, p=0.0004) -10-year prostate cancer mortality was improved in Arm 2 (30.4% vs 10.3%, p<0.0001)
NCIC CTG PR.3/MRC UK PR07 Trial[31] n=1205	T2 and PSA >40 or PSA>20 and Gleason ≥8; T3-4	Arm 1: ADT indefinitely Arm 2: ADT + RT	-7-year overall survival was improved for Arm 2 (66% vs 74%, p=0.033)

EBRT: External Beam Radiation therapy; ADT: androgen deprivation therapy; DFS: disease free survival

2. Radical Prostatectomy with pelvic lymph node dissection +/- Neoadjuvant/Adjuvant/Concurrent Hormonal Therapy[3]

    a. Currently, neoadjuvant and adjuvant hormonal therapy are not recommended in combination with prostatectomy. Use is restricted to where positive lymph nodes are found, although there are mixed results with this approach. Clinical trials are ongoing.

Patient Case #2: LB is a 60-year-old male with history of myocardial infarction 3 months ago and low risk prostate cancer treated with external beam radiation 6 months ago. He follows up with his oncologist regularly and his PSA has doubled in the last four months. He presents today to discuss recent imaging which shows no sites of metastatic disease. He is not a candidate for further local treatment and is hesitant to purse androgen deprivation therapy due to fear of adverse cardiac effects. **Which of the following options is most appropriate for LB?**

A. Continuous ADT with leuprolide
B. Intermittent ADT with relugolix
C. Intermittent ADT with leuprolide
D. Treatment is not indicated at this time

D. Androgen Deprivation Therapy

1. Androgen Deprivation Therapy (Bilateral orchiectomy or LHRH Agonist or Antagonist)

    a. Bilateral Orchiectomy (removal of the testes)

        1) Immediate drop in testosterone levels

        2) Previous gold standard

        3) Benefits of adding antiandrogen to surgical castration is unclear

        4) Side effects: Impotence, hot flashes

        5) Recent evidence suggests bilateral orchiectomy may have fewer long term adverse effects than LHRH agonists[32]

            i. Population based cohort of 3295 men with metastatic prostate cancer treated with orchiectomy vs. LHRH agonist (from 1995 to 2009)

            ii. Decreased risk of fracture [(HR], 0.77; p = 0.01), peripheral arterial disease (HR, 0.65; p = 0.004), and cardiac-related complications (HR, 0.74; p = 0.01)

            iii. No difference in incidence of diabetes, or cognitive disorders

    b. Luteinizing hormone-releasing hormone (LHRH) agonists

Luteinizing hormone-releasing hormone agonists[33]

Agents	Dosing	Adverse Events
Goserelin (Zoladex®)	3.6 mg SQ every 4 weeks 10.8 mg SQ every 12 weeks	Acute events: Tumor flare, gynecomastia, hot flashes, edema, injection site reaction, erectile dysfunction, shrinkage of testes and penis, fatigue, depression, etc. Long-term: Osteoporosis, clinical fracture, obesity, decreased muscle mass, insulin resistance, alteration in lipids, increased risk of diabetes and CV events See Supportive Care section for more information
Leuprolide (Lupron®, Eligard®)	7.5 mg IM/SQ every month 22.5 mg IM/SQ every 3 months 30 mg IM/SQ every 4 months 45 mg IM/SQ every 6 months	
Triptorelin (Trelstar®)	3.75 mg IM every 4 weeks 11.25 mg IM every 12 weeks 22.5 mg IM every 24 weeks	

1) LHRH agonists are a reversible method of androgen ablation and are as effective as orchiectomy in treating prostate cancer. Also referred to as gonadotropin-releasing hormone (GnRH) agonists.

2) Several randomized trials have demonstrated that leuprolide and goserelin are effective agents when used alone in patients with advanced prostate cancer. Response rates around 80% have been reported, with a lower incidence of adverse effects compared with estrogens.

3) No direct comparative trials but a recent meta-analysis reported that there is no difference in efficacy or toxicity between triptorelin, histrelin (recently discontinued by manufacturer), leuprolide, and goserelin. Therefore, the choice between the four agents is usually made based on institution formulary, cost and patient and physician preference for a dosing schedule.[34]

4) Disease flare with LHRH agonist is thought to be caused by initial induction of luteinizing hormone (LH) and follicle stimulating hormone (FSH) by the LHRH agonist and manifests clinically as either increased bone pain or increased urinary symptoms. This flare reaction usually resolves after 2 weeks and has a similar onset and duration pattern for the depot LHRH agonists.

5) Antiandrogen therapy (with first generation anti-androgen such as bicalutamide, flutamide, nilutamide) should precede LHRH agonist and be continued in combination for at least 7 days for patients with overt metastasis to attenuate the tumor flare.

6) In practice, antiandrogen therapy is often started seven days prior to GnRH agonist initiation for men at high risk of flare symptoms, or concurrently for asymptomatic patients. Antiandrogen therapy is then continued for two to four weeks.

c. LHRH antagonist: Degarelix (Firmagon®)

1) Loading dose: 240 mg SubQ as two 120 mg injections

2) Maintenance dose: 80 mg SubQ every 28 days

3) The major advantage of degarelix over LHRH agonists is the speed at which it can achieve the drop in testosterone levels with no surge of LH or FSH levels; castrate levels are achieved in 7 days or less with degarelix, compared to 28 days with leuprolide, eliminating the tumor flare seen and need for antiandrogens.

4) In a trial of 610 men with advanced prostate cancer, degarelix was shown to be equivalent to leuprolide in lowering testosterone levels for up to one year and is approved by the FDA for the treatment of advanced prostate cancer.[35]

5) Degarelix has not been studied in combination with antiandrogens and routine use of the combination cannot be recommended. Currently, degarelix can be considered in first-line setting where tumor flare up from LHRH agonist is a major concern (i.e. spinal cord injury compression concern).

6) Recent studies have evaluated the cardiovascular effects of LHRH agonists vs. antagonists.

   i. Initially, a pooled post-hoc analysis of 6 phase III trials comparing LHRH agonists (leuprolide, goserelin) to LHRH antagonist (degarelix) evaluated differences in death from any cause or cardiac events. The authors found no difference in patients with no pre-existing cardiac history. However, in those with history of cardiac event, the incidence of death or cardiac event was significantly lower (HR: 0.44, p = 0.002) for those treated with the LHRH antagonist.[36]

   ii. This prompted a prospective phase II study in patients with history of cardiac events, comparing LHRH agonists vs. LHRH antagonist (n = 80). While the primary outcome of endothelial function at 12 months was not statistically different, the secondary outcome of a new cardiovascular event was higher in those randomized to receive the LHRH agonist (33.3% vs. 4.8%; p = 0.001).[37]

   iii. A large phase III study comparing degarelix to LHRH agonists in men with concomitant atherosclerotic cardiovascular disease was terminated prematurely due to slow enrollment and a smaller than expected number of primary outcome events. .[38]

      1. No major difference in cardiovascular events at 1 year was observed.

7) Disadvantage: Must be given monthly and more local site reactions.

d. Oral LHRH Antagonist: Relugolix (Orgovyx®)[40]

   1) Drug information:

      i. Mechanism of Action: Oral GnRH antagonist (competitive pituitary GnRH receptor such antagonist →↓LSH + FSH→↓testosterone)

      ii. Dosing: 360mg orally (3 tablets) x 1 day, then 120mg orally (1 tablet) daily (reload if interrupted ≥ 7 days)

      iii. Adverse Effects: Similar to other ADT, diarrhea

         1. Lower risk of major cardiovascular events compared to LHRH agonists

      iv. Drug-drug Interactions: CYP2C8 (minormajor substrate), CYP3A4 (minor substrate), PGP/ABCB1 (major substrate)

v. Pearls: Has not been adequately studied with other prostate cancer therapies (should not be used in combination; studies are still ongoing); adherence >99% in trial (consider patient compliance, testosterone monitoring)

2) HERO Phase III Trial:[41]

i. Enrolled men with advanced adenocarcinoma of the prostate who were candidates for at least one year of ADT (biochemical or clinical relapse after primary intervention, newly diagnosed m1CSPC, advanced localized disease unlikely to be cured with primary intervention), n = 622

1. Randomized 2:1 to relugolix 360mg x1 then 120mg PO daily OR leuprolide 22.5mg IM every 3 months

ii. Primary outcome: sustained testosterone suppression through 48 weeks: 96.7 vs. 88.8% ($p<0.001$)

iii. Safety:

1. Adverse effects similar between arms

2. Diarrhea: 12.2% vs. 6.8%

3. Can cause QTc prolongation

4. Major cardiovascular adverse events (MACE): 2.9% vs. 6.2% across all patients (HR 0.46)

a. With history of MACE: 3.6% vs. 17.8%

3) Limitations:

i. Most outcomes related to fast on and off-set of testosterone suppression. No published data related to overall or progression free survival endpoints available.

ii. Study reported >99% compliance for both arms – difficult to replicate in real world setting and important considering fast off-set of action (consider monitoring testosterone, carefully consider compliance when choosing appropriate patients).

iii. No drug-drug interaction studies with other prostate cancer therapies (abiraterone, docetaxel, enzalutamide, apalutamide, etc.). At progression, patients could add docetaxel or enzalutamide per protocol – data on these patients not yet available. Not recommended to use in combination at this time. Concerns

4) Benefits: offers an oral agent with fewer cardiac risks and fast on/off-set of action for patients who need treatment with ADT alone. Ideal properties for intermittent ADT.

e. Antiandrogens: Flutamide (Eulexin®), Bicalutamide (Casodex®), Nilutamide (Nilandron®)

1) Antiandrogens have been used as monotherapy in previously untreated patients, but a recent meta-analysis determined that monotherapy with antiandrogens is less effective than LHRH agonist therapy and is not currently recommended to be used alone (unless patient had orchiectomy).

2) Bicalutamide is generally preferred due to better toxicity profile.

3) For advanced prostate cancer, all currently available antiandrogens are indicated only in combination with androgen-ablation therapy; flutamide and bicalutamide are indicated

in combination with an LHRH agonist, and nilutamide is indicated in combination with orchiectomy.

4) The most common antiandrogen-related adverse effects are listed in the table below. In the only randomized comparison of bicalutamide plus an LHRH agonist versus flutamide plus an LHRH agonist, diarrhea was more common in flutamide-treated patients.

Comparison of the Antiandrogens[33]

Drug	Half-life	Dose	Adverse Effects
Flutamide	9.6 hours	250 mg PO TID	Diarrhea 12-26% (all grades) Hematuria
Bicalutamide	1 week	50 mg PO daily	Diarrhea 2-12% (all grades) Hematuria 12% (all grades)
Nilutamide	41-49 hours	300 mg PO daily x 1 month, then 150 mg PO daily	Diarrhea 2% Disulfiram-like reaction Decreased visual accommodation 13% Interstitial pneumonia 2%

f. Combined androgen blockade (CAB) LHRH + anti-androgen (AA)

1) Although up to 80% of patients with advanced prostate cancer will respond to initial hormonal manipulation, almost all patients will relapse within 2 to 4 years after initiating therapy.

2) Two mechanisms have been proposed to explain this tumor resistance. The tumor could be heterogeneously composed of cells that are hormone-dependent and hormone-independent, or the tumor could be stimulated by extratesticular androgens that are converted intracellularly to DHT.

3) A meta-analysis of 21 trials compared monotherapy (orchiectomy or LHRH agonist) to combination therapy (orchiectomy or LHRH agonist plus an antiandrogen). It found a statistically significant difference in -5-year survival with CAB (HR 0.871; 95% CI 0.805-0.942). The good prognosis subgroup had no difference in survival. Adverse events causing withdrawal from therapy occurred more in the CAB group.[42]

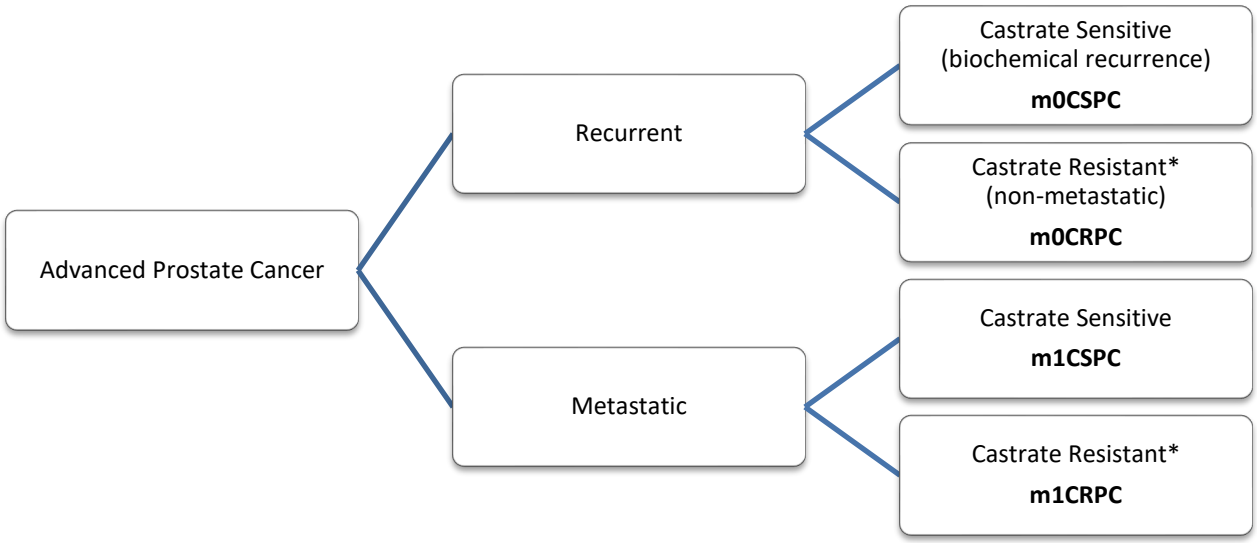
4) Other trials and meta-analyses have reported no advantage to CAB.

5) CAB is associated with more adverse events leading to withdrawal from therapy.

6) Although some investigators now consider CAB to be the initial hormonal therapy of choice for newly diagnosed patients, the clinician is left to weigh the costs of combined therapy against potential benefits in light of conflicting results in the randomized trials and the modest benefit seen in the meta-analysis.

7) CAB may be most beneficial for improving survival in patients with minimal disease and for preventing tumor flare, particularly in those with advanced metastatic disease. All other patients may be started on LHRH monotherapy, and an antiandrogen may be added after several months if androgen ablation is incomplete.[3]

E. Treatment of Recurrent or Metastatic Disease[3]



**Castrate Resistant (progression despite testosterone <50ng/dL)*

1. Biochemical Recurrence (m0CSPC)
    a. Need to distinguish between a PSA recurrence and overt metastatic disease. Those with a PSA recurrence alone may not need to immediately start ADT. PSA velocity, toxicity of ADT and patient wishes are taken into consideration with treatment decisions. Consider intermittent ADT in this clinical setting. In patients with long PSA doubling time (PSADT; >10 months) or older age, observation may be appropriate. Those with the following criteria may be considered for initiation of ADT:
        1) Rapid PSA velocity and short PSADT (<10 months)
        2) Long life expectancy
    b. Intermittent androgen deprivation (IAD)
        1) With IAD, patients are started on either an LHRH analog alone or on combined androgen blockade. They are monitored and when PSA has returned to a pre-specified baseline (typically <=4 ng/mL) androgen suppression is discontinued. PSA is monitored while the patient is off androgen ablation therapy and therapy is re-started at a pre-defined PSA (typically 10-20 ng/mLdL) as described below.
            i. Advantages of IAD include decreased cost and potentially decreased adverse effects.
            ii. Crook et al. evaluated intermittent ADT compared to continuous ADT in men with a rising PSA after primary or salvage RT (no distant metastases). Intermittent ADT consisted of 8-month treatment cycles. ADT was held if no evidence of disease progression and PSA was <4ng/ml. PSA was then monitored every 2 months until it was >10ng/ml at which time ADT was reinitiated. The study randomized 1386 men and found that intermittent ADT was noninferior to continuous ADT with regards to overall survival with median overall survival of 8.8 years in the intermittent group versus 9.1 years in the continuous group (HR 1.02;95% CI 0.86-1.21). Intermittent

ADT was associated with better quality of life scores for hot flashes, desire for sexual activity, and urinary symptoms.[43]

iii. Hussain et al. conducted a noninferiority trial (SWOG 9346) that compared IAD to continuous androgen deprivation (CAD) in 1535 newly diagnosed metastatic prostate cancer patients. Patients received 7 months of an LHRH agonist and an antiandrogen. Those with a PSA of $\leq$ 4 ng/ml at 7 months were randomized to CAD or IAD. ADT was resumed for an additional 7 months in the IAD group once the PSA was $\geq$ 20ng/ml (or over baseline for those with PSA < 20 ng/ml at enrollment). Median survival was 5.8 years in the CAD group versus 5.1 years in the IAD group. However, the findings were statistically inconclusive as the CI exceeded the upper boundary for noninferiority. IAD was associated with better erectile function and mental health.[44]

iv. Niraula et al. conducted a systematic review of 9 trials including 5508 men comparing IAD to CAD in men with relapsing, locally advanced or metastatic disease. The pooled HR for overall survival of IAD compared with CAD was 1.02 (95% CI 0.94-1.11) and PFS was 0.96 (95% CI 0.76-1.20). There tended to be more prostate cancer specific deaths in the IAD group but more deaths not related to prostate cancer in the CAD group. IAD had less treatment related adverse effects such as hot flashes, sexual dysfunction, and impaired physical function.[45]

v. An additional critical review of IAD versus CAD was published evaluating 7 phase 3 trials. The evaluation found that most patients spent more time on ADT rather than off. It also confirmed that in metastatic cases, IAD and CAD have similar results with HR for overall survival ranging from 0.98-1.08. Treatment related adverse effects tended to be improved for IAD, however the overall quality of life benefit for IAD was minimal.[46]

vi. Summary: For men with biochemical relapse only, consider IAD since no difference in overall survival was observed and the largest trial was inconclusive. Close monitoring and follow up are required, especially during off treatment periods.

Patient Case #2, Answer:

Correct answer = B (Intermittent ADT with relugolix). LB has a biochemical recurrence (castrate sensitive). Appropriate treatments include ADT and active surveillance. Due to his short doubling time, ADT is a good choice for him. Intermittent ADT is an option for biochemical recurrence. With regard to cardiac events, relugolix showed a benefit over leuprolide in the HERO trial, making it preferable for this patient. It is also a good option for intermittent ADT because of its short half-life.

Patient Case #3: RC is a 62-year-old that presents to your clinic with a history of high risk prostate cancer status post EBRT, currently on adjuvant leuprolide. Six months prior PSA level was 2.4 ng/mL and testosterone levels less than 20ng/dL. Three months prior PSA of 4.7ng/ml. Today's lab values are within normal limits except PSA level of 25 ng/ml and testosterone less than 20ng/dL. CT scan shows no metastatic disease. **Which is the most appropriate change in RC's treatment at this time?**

A. Stop leuprolide, start docetaxel + prednisone
B. Stop leuprolide, start relugolix
C. Continue leuprolide, add darolutamide
D. Continue leuprolide, add abiraterone + prednisone

2. Non-metastatic Castrate Resistant Prostate Cancer (m0CRPC)
    a. Treatment based upon PSA doubling time
        1) If doubling time greater than 10 months, observation or secondary hormonal therapy recommended
    b. Apalutamide[47]
        1) NCCN® Category 1 for M0 castration-resistant prostate cancer and PSADT ≤10 mo
        2) SPARTAN trial
            i. Phase III International, double-blind, randomized, placebo controlled
            ii. N = 1207 patients with m0CRPC at high risk to develop metastatic disease, PSADT ≤10 months
            iii. Randomly assigned in a 2:1 ratio to apalutamide 240 mg per day or placebo. All patients continued ADT.
            iv. Median metastasis-free survival was 40.5 months in the apalutamide group versus 16.2 months in the placebo group (HR 0.28; 95% CI 0.23 to 0.35; P<0.001).
            v. Time to symptomatic progression was significantly longer with apalutamide than with placebo (HR 0.45; 95% CI 0.32 to 0.63; P<0.001)
            vi. Final overall survival, published in 2021, favored apalutamide at 73.9 vs. 59.9 months (HR 0.784, p value 0.016).[48, 49]
    c. Enzalutamide
        1) NCCN® Category 1 for M0 castration-resistant prostate cancer and PSADT ≤10 mo
        2) PROSPER trial[50]
            i. Phase III, international, double-blind, randomized, placebo controlled.
            ii. 1401 patients with m0CRPC on ADT and no evidence of metastatic disease, PSADT ≤10 months
            iii. Randomized in a 2:1 ratio to receive enzalutamide 160 mg daily or placebo.
            iv. Median metastasis-free survival was 36.6 months vs 14.7 months (HR 0.29; 95% CI, 0.24-0.35; P<0.001).
            v. The time to first antineoplastic agent was longer 39.6 vs. 17.7 months.
            vi. 2020 Final mOS update: 67 vs. 56.3 months (HR 0.73; p = 0.001)[51]
    d. Darolutamide
        1) NCCN® Category 1 for M0 castration-resistant prostate cancer and PSADT ≤10 mo
            i. Approved in July 2019 for the treatment of non-metastatic, castration resistant prostate cancer
            ii. AR antagonist. Darolutamide also inhibits nuclear translocation and transcription.
            iii. Novel structure versus enzalutamide and apalutamide; may have fewer CNS adverse effects and drug-drug interactions

2) ARAMIS trial[52, 53]

i. Phase III, international, randomized, double blind, placebo controlled

ii. N = 1509 with m0CRPC, PSADT ≤10 months

iii. Randomized 2:1 to receive ADT + darolutamide 600mg PO BID or ADT + placebo

iv. Median metastasis-free survival was 40.4 months (95% CI: 34.3, not reached) for patients treated with darolutamide compared with 18.4 months (95% CI: 15.5, 22.3) for those receiving placebo (hazard ratio 0.41; 95% CI: 0.34, 0.50; p<0.001). OS data were not mature.

v. Final 2020 OS update: median OS not reached in either arm but HR for death 0.69, p = 0.003

e. The three second-generation antiandrogens have not been compared head- to- head, but there are differences in side effect profile, CYP drug interactions, and administration (i.e. with food) between enzalutamide/apalutamide vs. darolutamide that are summarized below.

Comparison of 2nd Generation Antiandrogens

	Enzalutamide	**Apalutamide**	**Darolutamide**
Indications	m1CSPC, m1CRPC, m0CRPC	m1CSPC, m0CRPC	m0CRPC, m1CSPC (in combination with docetaxel)
Dosing	160mg daily	240mg daily	600 mg BID with food
Adverse Effects* (vs. placebo, %)	Fatigue (33 vs. 14), falls + fracture (17 vs 8), hypertension (12 vs 5), seizure (0.3)	Rash (23.8 vs 5.5), fracture (11.7 vs 6.5), fatigue (30.4 vs 21.1) hypothyroidism (8 vs 2), hypertension (24.8 vs. 19.8), seizures (0.2)	Fatigue (12.1 vs. 8.7), hypertension (6.6 vs. 5.2) rash (2.9 vs. 0.9), seizures (0.2 vs. 0.2)
Pearls			Renal dose adjustment (300mg BID if CrCl 15-29, has not been studied with CrCl <15), hepatic dose adjustment (300mg BID for moderate impairment), poor blood-brain barrier penetration

*adverse effects taken from the m0CRPC trials (SPARTAN, PROSPER, and ARAMIS) to better compare among similar patient populations
** SPARTAN and PROSPER trials excluded patients with seizure history or predisposition to seizures, whereas ARAMIS trial did not

Common Drug-Drug Interactions with 2nd Generation Antiandrogens

	Enzalutamide	Apalutamide	Darolutamide
Substrate	CYP3A4/5, CYP2C8	CYP3A4, CYP2C8	CYP3A4, P-gp
Inhibits	CYP2C8 (weak) P-gp	CYP2B6, CYP2C8, (moderate) CYP3A4 (weak) CYP2C9, CYP2C19	BCRP
Induces	CYP3A4 (strong), CYP2C9, CYP2C19, CYP2D6 (moderate), CYP1A2 (weak)	CYP3A4, CYP2C19 (strong), OATP1B1, CYP2C9 (weak), UGT, P-gp, BCRP	CYP3A4 (weak)
Common drug-drug interactions	Statins, direct-acting oral anticoagulants (DOACs), warfarin, calcium channel blockers, opioids, PPIs, losartan, citalopram	Statins, DOACs, clopidogrel, warfarin, calcium channel blockers, opioids, PPIs, citalopram	Rosuvastatin

f. Second Line Hormonal Therapy (not a *preferred* option in NCCN guidelines)

1) Antiandrogen withdrawal (for those treated with ADT + antiandrogen)

i. 20-30% respond from androgen withdrawal alone. Generally short duration of response.

ii. Mechanism unknown, but potentially new mutations and androgen receptor changes over time that make the tumor cells resistant to antiandrogen therapy.

iii. Half-life of the antiandrogen will determine the time to response.

2) Corticosteroids[3]

i. Dexamethasone or prednisone

ii. Mechanism of action: Suppression of ACTH and subsequently adrenal androgens

iii. Dose: Prednisone 5-10mg, Dexamethasone PO 0.5-1.5 mg daily

3) Ketoconazole[3]

i. Inhibits androgen synthesis in the testes and the adrenal gland and it has rapid onset of action

ii. Dose: 400 mg PO q 8h

iii. Adverse effects: Nausea and vomiting (33%), impotence, gynecomastia, dry skin, increased LFTs, and rarely, hepatitis

iv. Drug interaction with cytochrome p450s

v. Corticosteroid replacement with hydrocortisone is recommended due to potential adrenal insufficiency induced by ketoconazole. The typical hydrocortisone dose is 20 mg PO every morning and 10 mg PO every evening.

Patient Case #3, Answer:

Correct answer = C (Continue leuprolide, add darolutamide). Based on laboratory and imaging data, RC has non-metastatic castration resistant prostate cancer. Darolutamide is indicated in this setting, supported by data from the ARAMIS trial. Docetaxel and abiraterone are indicated in the metastatic setting but not in the M0 setting. ADT should be continued despite progression to castration-resistant disease. Relugolix is an alternative to leuprolide for ADT but is not indicated after progression on leuprolide as a single agent.

Patient Case #4:

A. AC is a 65-year-old male with history of hypertension (controlled with amlodipine). After initially presenting with back pain, imaging and biopsy revealed prostate cancer metastatic to the liver and spine. Current ECOG performance status is zero. All lab values are within normal limits except for a PSA of 87ng/dl. In addition to starting ADT, **which of the following is the most appropriate treatment option for AC at this time**? Abiraterone + prednisone
B. Lutetium-177 PSMA
C. Docetaxel + darolutamide
D. Docetaxel + enzalutamide
E.

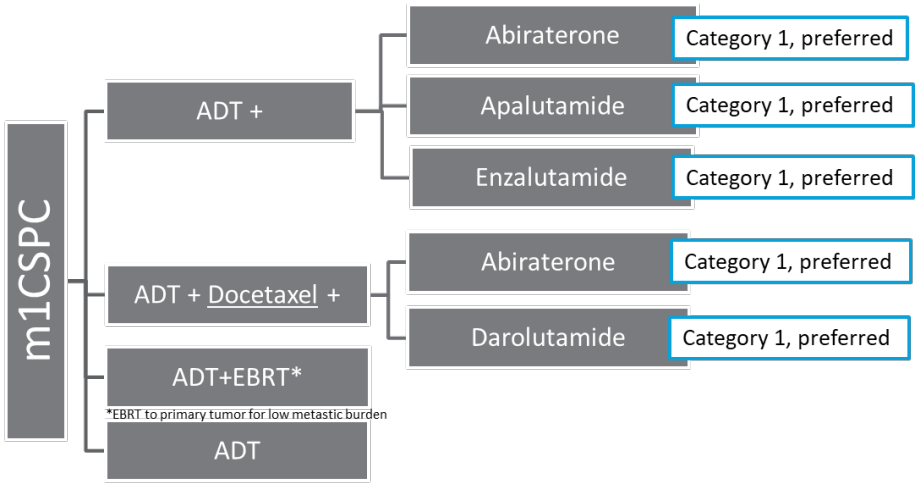
3. Metastatic Castrate Sensitive Prostate Cancer (m1CSPC)

a. ASCO guidelines published in 2021[54] establish four options (in combination with ADT) for m1CSPC, consistent with the preferred, Category 1 options from NCCN guidelines[3]:

1) Docetaxel
2) Abiraterone + prednisone
3) Enzalutamide
4) Apalutamide

b. However, based on recently published trials, NCCN released new guidelines in 2022 removing ADT+ docetaxel as a treatment option. Instead, ADT + Docetaxel + Abiraterone + prednisone or ADT + Docetaxel + Darolutamide are options for men with high-volume disease m1CPSC.

c. Treatment overview: m1CSPC



d. Docetaxel + ADT

1) NCCN® Category 1 for M1 castration-naïve prostate cancer (recommended in combination with abiraterone or darolutamide for high-volume disease); ASCO guidelines recommend only for patients with high volume disease

    i. High volume disease: defined as visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column

2) Prednisone is not a required part of the docetaxel regimen when used for metastatic hormone sensitive disease (referred to as castrate sensitive disease in NCCN Guidelines® as patients are not on ADT at time of progression).

3) Sweeney et al conducted a phase 3 trial (ECOG 3805; CHAARTED trial) comparing ADT alone to ADT + docetaxel for 6 cycles in 790 men with metastatic hormone sensitive prostate cancer (ADT-naïve). There was a significant improvement in OS with the addition of docetaxel. Median time to development of castration resistant prostate cancer was significantly improved as well.

    i. Docetaxel was associated with additional toxicities including fatigue, diarrhea, stomatitis and neuropathy. Approximately 6% of patients developed neutropenic fever.[55]

    ii. Subgroup analysis showed survival benefit was greater in patients with high volume disease. Survival benefit was uncertain in patients with low volume disease.

Outcomes of ECOG 3805 – CHAARTED Trial[55, 56]

	ADT + Docetaxel 75mg/m^2 IV every 3 weeks x 6 cycles	**ADT**	**HR; 95% CI**
Median overall survival	57.6 mo	44 mo	0.61; 0.47-0.80 (p<0.001)
Median OS in high-volume disease	49.2 mo	32.2 mo	0.60; 0.45-0.81 (p<0.001)
Median time to development of castration-resistant prostate cancer	20.2 mo	11.7 mo	0.61; 0.51-0.72 (p<0.001)

*ADT: androgen deprivation therapy; HR: hazard ratio; CI: confidence interval; mo: month

4) Kyriakopoulos et al published the phase III matured data from the CHAARTED trial confirming OS benefit in high-volume disease with a median OS of 51.2 months ADT + docetaxel versus months vs 34.4 months in ADT alone. For those with low volume disease no OS benefit was observed (HR 1.04; p =0.86).[57]

5) James et al conducted Phase 2/3 trial known as the STAMPEDE trial that confirmed the survival advantage seen in the CHAARTED trial. Overall survival of 5.4 years in ADT + docetaxel versus 3.6 years in ADT only arm. However, the extent of disease (high vs low volume) was not evaluated.[58]

6) A meta-analysis of CHAARTED + GETUG-AFU15 compared overall survival for ADT + docetaxel vs. ADT alone and found a benefit for high volume disease (HR=0.68; p<0.001) but no benefit for low volume disease (HR=1.03)[59]

7) ARASENS Trial: ADT+ Docetaxel + Darolutamide[60]

i. FDA approved in July 2022

ii. Based on the Phase III ARASENS Trial

1. Enrolled 1,306 men with m1CSPC, ECOG 0-1 with no prior chemotherapy, immunotherapy, or ADT

a. 86% had de-novo metastatic disease, ~17% had visceral metastases

2. Background therapy:

a. ADT (investigator's choice) – started within 12 weeks prior to start of study drug

b. Docetaxel 75mg/m^2 IV every 3 weeks x 6 cycles (started within 6 weeks of start of study drug)

3. Study drug:

a. Randomized 1:1 to:

i. Darolutamide 600mg twice daily with food

ii. Matching placebo twice daily with food

4. Efficacy:

a. Median OS: NR vs. 48.9 months (HR 0.68; p<0.001)

b. Time to CRPC: NR vs. 19.1 months (HR 0.36; p<0.0001)

5. Safety:

a. Serious adverse events: 44.8% vs. 42.3%

b. No significant difference in fatigue, falls, fractures, mental impairment, rash, hypertension, and cardiovascular events

8) PEACE-1 Trial: ADT+ Docetaxel + Abiraterone + Prednisone[61]

i. Phase III trial published in 2022; enrolled 1173 men with de novo m1CSPC

1. More than half of patients had high burden of metastatic disease (as defined by Sweeney, et al.)[55] and around 10-12% of patients had visceral metastases.

2. Patients were randomized 1:1:1:1 to the following arms:

a. ADT ± docetaxel

b. ADT ± docetaxel + radiotherapy

c. ADT ± docetaxel + abiraterone

d. ADT ± docetaxel + radiotherapy + abiraterone

3. Treatment notes:

a. Patients receiving abiraterone started within 6 weeks of ADT and received prednisone 5mg by mouth twice daily (accrual started prior to publication of LATTITUDE and STAMPEDE which used prednisone 5mg daily in the castrate sensitive setting)

b. Patients receiving docetaxel started at least 6 weeks after initiation of ADT. Primary growth factor prophylaxis was recommended until a protocol amendment made it mandatory for all patients mid-way through the trial

c. Patients receiving radiotherapy did initiated that 3 to 8 weeks after completion of docetaxel

4. When comparing all patients who received abiraterone (n = 583) to those who did not, radiographic PFS (HR 0.54; p <0.0001) and OS (HR 0.82; p=0.003) both favored abiraterone. When comparing all patients who received docetaxel (n=355) to those who did not, radiographic PFS (HR 0.5; p<0.001) and OS (HR 0.75; p=0.017) both favored docetaxel.

   a. Median overall survival with vs. without docetaxel separated by volume of disease:

      i. High-volume disease: 5.1 vs. 3.5 years (HR 0.72; 0.55 to 0.95)

      ii. Low-volume disease: NR vs. NR (HR 0.83; 0.5-1.39)

5. When looking specifically at patients who received docetaxel as standard of care, the addition of abiraterone improved overall survival (NR vs. 4.43 years (HR 0.75; 0.59-0.95; p=0.017)) in the total population.

      i. High-volume disease: 5.14 vs. 3.47 years (HR 0. 72; p=0.019)

      ii. Low-volume disease: data not mature

6. Adverse events

   a. No significant increase in docetaxel-related adverse events was seen with the addition of abiraterone.

      i. Grade 3 neutropenia: 10 vs. 9%

      ii. Grade 3 peripheral neuropathy: 1 vs. 2%

   b. The incidence of adverse events with the addition of abiraterone was consistent with known side effect profile (increased hypertension, hepatotoxicity).

e. Abiraterone Acetate + ADT

   1) NCCN® Category 1 for M1 castration-naïve prostate cancer[3]; ASCO 2021 Guidelines recommend only for use in patients with de novo metastatic disease[54]

   2) Approval based on the results of two trials

      i. LATITUDE: men that were high risk, metastatic, castration naïve randomized ADT with abiraterone 1000mg + prednisone 5mg once daily or ADT + placebo. 95% of patients had de-novo metastatic disease.

         1. 3-year OS 66% versus 49%. HR, 0.62; 95% CI, 0.51-0.76; P<0.001

         2. 2020 update:

            a. Median OS 53.3 vs 36.5 months; HR 0.66, p<0.0001

3. Time until pain progression, next subsequent prostate cancer therapy, initiation of chemotherapy, and prostate-specific antigen progression also improved

4. Adverse events included hypertension, hypokalemia, edema, LFT elevation, cardiovascular disorder, fatigue, hot flushes.[62]

ii. STAMPEDE: 1,917 patients that were de-novo metastatic, high risk with multiple risk factors. The study also permitted those with non-metastatic, nodal and metastatic disease. Patients were randomized to ADT alone or ADT plus abiraterone 1000mg + prednisolone 5mg daily

1. 3-year OS 83% versus 76% HR, 0.63; 95% CI, 0.52-0.76; P<0.0001

2. 2021 update:

a. Median OS: 6.6 vs. 3.8 years; HR 0.6, p<0.0001

i. Low risk: HR 0.66 (p=0.041)

b. High risk: HR 0.54 (p<0.001)

3. Adverse events included hypertension, endocrine, fatigue and cardiovascular disorders. [63]

3) Note on corticosteroid with abiraterone:[64]

i. Abiraterone (the active metabolite of abiraterone acetate) is CYP17A1 inhibitor, responsible for blocking androgen biosynthesis. Other downstream effects of blocking this enzyme include a reduction in serum cortisol and compensatory increase in adrenocorticotropic hormone (ACTH). This ultimately results in mineralocorticoid-related adverse events such as hypokalemia, edema, and hypertension. Administration of glucocorticoid replacement compensates for the reduction in cortisol and compensatory increase in ACTH, therefore decreasing the incidence of these adverse effects.

ii. In the castrate-resistant setting, abiraterone is approved with prednisone 5mg PO BID, while the studies in the castrate-sensitive setting used a dose of 5mg once daily. Additionally, the fine-particle abiraterone formulation was approved with methylprednisolone 4mg twice daily. Various glucocorticoid replacement strategies have been utilized and may be effective, but should be prescribed as they were studied and FDA approved.

iii. Available data suggests that the low doses of glucocorticoids used with abiraterone do not result in immunosuppression seen at higher doses, however long-term use of glucocorticoids does come with inherent risks. It is important to consider patient-specific factors when choosing an initial regimen for management of prostate cancer.

f. Enzalutamide + ADT

1) NCCN® Category 1 for M1 castration-sensitive prostate cancer; ASCO 2021 guidelines recommend for all m1CSPC patients (although survival benefit after docetaxel treatment in castrate sensitive setting is unclear)

1) ENZAMET trial, open-label, randomized phase III trial[65]

i. N = 1125, castrate sensitive prostate cancer (up to 12 weeks of prior ADT allowed and after protocol amendment, prior docetaxel allowed)

1. 45% were planned to received prior docetaxel

ii. ADT + Enzalutamide 160 mg PO daily vs ADT + first generation antiandrogen

iii. Primary end point was OS met at first analysis HR for death, 0.67; 95% CI, 0.52-0.86; *P* = 0.002

iv. Secondary end points

1. PSA PFS (defined as 25% increase in PSA from nadir value), 174 and 333 events, respectively; HR, 0.39; *P* <0.001

2. Clinical PFS, 167 and 320 events, respectively; HR, 0.40; *P* <0.001

v. Subgroup analysis

1. With prior docetaxel, PFS was improved (HR 0.48; 95% CI 0.37-0.62) but OS was not at this time (HR 0.9; 95% CI 0.62-1.31)[66]

2) ARCHES trial, double-blind, randomized phase III trial[67]

i. N = 1,150, metastatic castrate sensitive prostate cancer (prior ADT and up to 6 cycles of docetaxel were allowed)

ii. Enzalutamide 160mg PO daily + ADT vs. placebo PO daily + ADT

iii. Primary endpoint was radiographic PFS; median rPFS: NR vs. 19 months (HR 0.39, p <0.001)

iv. Secondary endpoints all favored enzalutamide – time to PSA progression, time to initiation of new antineoplastic therapy, objective response rate, PSA undetectable rate

v. Subgroup analysis

1. In those with prior docetaxel, radiographic PFS was improved (HR 0.52; 95% CI 0.3-0.89), OS not reported

g. Apalutamide + ADT[68]

1) NCCN® Category 1 for M1 castration-naïve prostate cancer; recommend for all m1CSPC patients (although survival benefit after docetaxel treatment in castrate sensitive is unclear)[3, 54]

2) TITAN trial double-blind, phase 3 trial

i. ADT + Apalutamide 240 mg PO daily vs ADT + placebo

ii. OS end point met at first analysis, with 24-month OS: 82.4% vs 73.5%; HR, 0.67 (p= 0.005)

iii. 2021 OS Update: 48--month OS: 65% vs. 52%; HR 0.65 (p<0.001)

iv. rPFS end point met at first analysis, with rPFS 68.2% vs 47.5% at 24 months; HR 0.48; p <0.001

v. In a subgroup analysis, patients who received prior docetaxel had median rPFS of NR vs. 22.1 months; HR 0.47 (95% CI 0.22 to 1.01)

h. Note: see section on m0CRPC for comparison of second generation androgen antagonist agents

Patient Case #4; Answer:

Correct answer = C (Docetaxel + darolutamide). This patient has m1CSPC – treatment options include docetaxel + abiraterone, docetaxel + darolutamide, abiraterone + prednisone, apalutamide or enzalutamide. Lutetium-177 PSMA is not approved for m1CSPC. Docetaxel + enzalutamide has not been approved as a combination regimen in any setting. This patient has high volume disease, making a docetaxel-containing regimen preferred. Additionally, he is having pain from his cancer, making docetaxel an attractive option to provide quick relief of his pain. He is otherwise healthy with minimal comorbidities making him a good candidate for docetaxel.

Patient Case #5:

AB is a 60-year-old male with castration resistant prostate cancer that was initially treated with ADT + docetaxel x 6 cycles and at progression started on ADT + abiraterone + prednisone. He did well for 2 years with this regimen and then presented with a rising PSA (14ng/ml, then 20ng/ml, over 3 months) and increased back pain. Today, his PSA is 35ng/ml and imaging shows progression of skeletal metastases and several new small liver metastases. His ECOG PS is 0. In addition to continuing ADT, **what is the most appropriate next line of treatment for AB?**

A. Enzalutamide
B. Radium-223
C. Mitoxantrone + prednisone
D. Cabazitaxel + prednisone

4. Metastatic Castrate Resistant Prostate Cancer (m1CRPC)

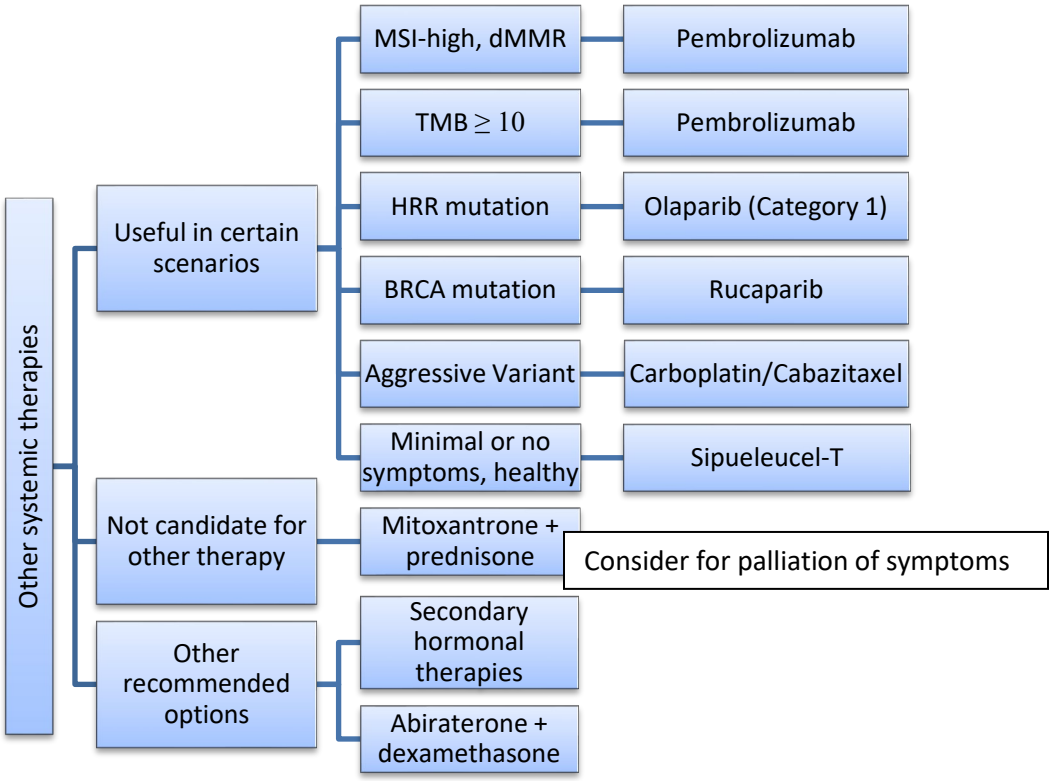
a. NCCN® Recommendations[3]

1) Continue ADT and maintain castrate testosterone suppression

Summary of NCCN preferred recommendations for treatment of metastatic castrate-resistant prostate cancer based on prior therapies[3]

Prior ADT only •Docetaxel (Category 1) •Abiraterone (Category 1) •Enzalutamide (Category 1)	**Prior hormonal therapy only** •Docetaxel (Category 1)
If bone-only metastases: Radium-223 (Category 1)	
Prior docetaxel (T) only •Abiraterone (Category 1) •Enzalutamide (Category 1) •Cabazitaxel	**Prior docetaxel and hormonal therapies** •Cabazitaxel (Category 1) •Lu-177-PSMA-617 (If PSMA+, Category 1) •Docetaxel rechallenge *(if no prior progression)*

NCCN guidelines recommendations for subsequent therapeutic options for CRPC following progression[3]



b. Docetaxel + Prednisone

1) TAX 327: Over 1,000 patients with metastatic CRPC were randomized to 1 of 2 regimens of docetaxel/prednisone or mitoxantrone/prednisone. The initial and updated follow up showed a significant improvement in median survival for patients receiving docetaxel q3 weeks/prednisone compared to mitoxantrone/prednisone.[69, 70]

2) The benefit of docetaxel/prednisone is seen in patients with and without symptoms. Per NCCN®, this regimen may be considered for rapid progression or visceral metastases despite lack of symptoms

Results of TAX 327 Study[70]

	Initial median survival[70] (months)	Follow up median survival[69] (months)	Toxicity (%)
Docetaxel 75 mg/m^2 every 3 weeks + prednisone 5 mg (n=332)	18.9	19.2	Neutropenia: 32% Febrile Neutropenia: 3% Septic Death: 0 Neuropathy: 30% Diarrhea: 32%
Docetaxel 30 mg/m^2 every week + prednisone 5 mg (n=330)	17.4	17.8	Neutropenia: 1.5% Febrile Neutropenia: 0% Septic Death: 0.3% Neuropathy: 24% Diarrhea: 34%
Mitoxantrone 12 mg/m^2 every 3 weeks + prednisone 5 mg (n= 335)	16.5	16.3	Neutropenia: 22% Febrile Neutropenia: 2% Septic Death: 0.3% Neuropathy: 7% Diarrhea: 10%

c. Abiraterone

1) Should be given with corticosteroid (see note on corticosteroids with abiraterone in castrate-sensitive section above)

i. In this setting, approved with prednisone 5mg BID

2) COU-AA-302 Trial: Randomized, phase III, double-blind trial of 1,088 patients with castration-resistant prostate cancer who **had not** received any previous chemotherapy. Patients were eligible if they were asymptomatic or mildly symptomatic. Patients were randomized to receive abiraterone plus prednisone or placebo plus prednisone. The median radiographic progression free survival was 16.5 months with abiraterone compared with 8.3 months with placebo (HR 0.53, 95% CI 0.45-0.62; p<0.001).

i. At interim analysis of 22 months follow-up period, median overall survival was not reached for abiraterone, but it was 27.2 months for the placebo (HR 0.75), however the boundary for statistically significance was not met.

ii. In the final analysis, after a median of 49 months of follow-up, overall survival was significantly improved with abiraterone plus prednisone despite 44% of the placebo group receiving abiraterone as crossover per protocol or as subsequent therapy (34.7 months v 30.3 months; hazard ratio 0.81 [95% CI 0.7-0.93]; p=0.0033).[71]

1. Overall, patients receiving abiraterone had longer time to initiation of chemotherapy, initiation of opiates for cancer-related pain, greater time to PSA progression and greater time to decline in performance status.[71, 72]

3) COU-AA-301 Trial: A phase III, randomized, double-blind, placebo-controlled trial abiraterone plus prednisone was evaluated in 1,195 patients with prostate cancer who

had received previous docetaxel therapy. Abiraterone significantly improved median overall survival (14.8 vs. 10.9 months, p<0.001) compared with placebo. At the preplanned interim analysis, there was a 35.4% reduction in risk of death (HR 0.65; 95% CI, 0.54-0.77; p<0.001).

i. In addition, abiraterone showed significant improvements in time to PSA response rate, PSA progression time and progression free survival.

ii. Abiraterone had significant higher incidence mineralocorticoid-related adverse events of fluid retention, hypertension and hypokalemia compared with placebo. Patients also had muscle discomfort, hot flashes, diarrhea, and urinary tract infection.[73]

4) STAAR trial: Phase 2 trial of 53 men with metastatic CRPC not treated with abiraterone, enzalutamide, radium-223 or chemotherapy except docetaxel for metastatic CRCP at least 1 year prior to enrollment. Patients were randomized to 500mg PO daily of fine-particle abiraterone with 4mg of methylprednisolone PO twice daily or the originator formulation plus 5mg of prednisone PO twice daily regardless of food

i. Bioequivalence was confirmed based on PSA response, testosterone levels and abiraterone pharmacokinetics

ii. Rates of adverse grade 3/4 adverse effects were similar only musculoskeletal and connective tissue disorders occurring more frequently.[74]

5) Abiraterone + Dexamethasone

i. In patients with asymptomatic PSA progression on abiraterone + prednisone, a switch from prednisone 10mg/day to dexamethasone 0.5mg/day has shown to induce PSA stabilization or decrease in some studies. While corticosteroids are used to prevent the mineralocorticoid excess induced by abiraterone, they also have an antitumor effect through inhibition of ACTH production (and therefore adrenal androgen synthesis). The exact mechanism explaining why switching steroids would induce a response is unclear, however possible mechanisms include differences in effect on glucocorticoid receptor (and development of resistant mutations), differences in pharmacokinetic properties of the two drugs, and differences in effect on cellular growth factors.[75]

ii. The Phase II, single arm, SWITCH study evaluated 26 patients with mCRPC who had been on abiraterone + prednisone for at least 12 weeks with limited radiographic, asymptomatic progression were eligible for enrollment.[76]

1. The primary endpoint was PSA decline of at least 30% at 6 weeks: 46.2%

2. Time to PSA progression: 5.3 months; Time to radiographic progression: 11.8 months

iii. A single center, retrospective analysis evaluated 48 patients on abiraterone + prednisone with asymptomatic PSA progression who were switched to abiraterone + dexamethasone 0.5mg/day.[77]

1. 56.25% of patients experienced a stabilization or decline in PSA after the switch.

2. Median time to PSA progression: 8.94 months

3. Factors associated with response to switch: long hormone-sensitivity duration (>5 years), low PSA at time of switch (<50ng/mL), and short time to PSA progression on abiraterone + prednisone (<6 months).

iv. Switching steroids may be a cost-effective option with limited toxicity in patients experiencing an asymptomatic progression on abiraterone + prednisone, however large, randomized trials need to be done to confirm a survival benefit.

d. Enzalutamide

1) PREVAIL trial: Phase 3 trial of 1,717 patients with asymptomatic or minimally symptomatic metastatic CRPC who had not received cytotoxic chemotherapy or abiraterone. Patients could have visceral metastases but were excluded if they had history of seizures. Patients were randomized to enzalutamide 160mg po daily or placebo. Co-primary end points were radiographic PFS and overall survival.

i. Radiographic PFS at 12 months was 65% in enzalutamide versus 14% in placebo. There was an 81% risk reduction of radiographic progression or death (HR 0.19; 95% CI, 0.15-0.23) and a 29% reduction in risk of death (HR 0.71; 95% CI, 0.60-0.84).

ii. Median OS was estimated at 32.4 months in enzalutamide versus 30.2 months in placebo. At 18 months, 82% of enzalutamide patients were alive versus 73% of placebo patients.

iii. Median time to PSA progression (11.2 months v 2.8 months), PSA decline at least 50% (78% v 3%), and soft tissue response (59% v 5%) were all significantly improved in the enzalutamide group.[78]

2) AFFIRM Trial: Randomized, phase III, double-blind, placebo-controlled trial comparing enzalutamide to placebo in 1,199 men with castration-resistant prostate cancer who were previously treated with docetaxel. Patients with history of seizure activity or risk of seizure were excluded. Overall survival was the primary end point. The median number of previous docetaxel cycles given was 8 in each group.

i. Study showed significantly longer median overall survival of 18.4 months with enzalutamide compared with 13.6 months with placebo (HR 0.63, 95% CI 0.53-0.75, p<0.001).

ii. PSA response (54% vs 2%) and time to PSA progression (8.3 vs 3.0 months) was significantly improved with enzalutamide. Radiographic progression free survival was 8.3 vs. 2.9 months and time to first skeletal related events was 16.7 vs. 13.3 months.

iii. Fatigue, diarrhea, hot flashes musculoskeletal pain and headache were more common in the enzalutamide receiving patients. Seizure was reported in 0.6% of patients receiving enzalutamide.[79]

3) TERRAIN Trial: Randomized, phase II, double blind trial comparing enzalutamide to bicalutamide in 375 asymptomatic or minimally symptomatic men with CRPC with disease progression on ADT. Primary endpoint of PFS.

i. The enzalutamide group had improved median PFS of 15.7 months vs 5.8 months (HR 0.44, 95% CI 0.34–0.57, p<0.0001) in the bicalutamide group. Median time to PSA progression 19.4 months (95% CI 16.6–not reached) for patients assigned to

enzalutamide and 5.8 months (5.6–8.3) for patients assigned to bicalutamide (HR 0.28, 95% CI 0.20–0.39; p<0.0001).

ii. The adverse events occurring in a higher proportion of patients who received enzalutamide were fatigue, back pain, hot flashes, hypertension, diarrhea, weight loss, and pain in the extremities. Seizure was reported in 1% (n=2) of enzalutamide arm.[80]

4) STRIVE Trial: Randomized, phase II, double-blind trial comparing enzalutamide to bicalutamide in 396 men with CRPC with disease progression on ADT. Exclusion criteria included previous chemotherapy, brain metastasis, or a history of seizure. Primary end point was PFS.

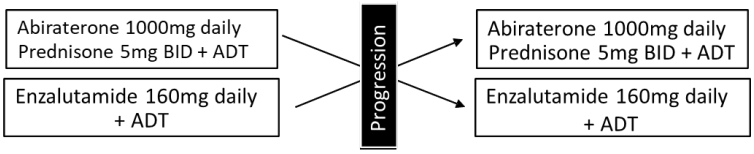
i. The enzalutamide group had a reduction in risk of progression or death by 76% compared with bicalutamide (HR, 0.24, 95% CI, 0.18 to 0.32, P< 0.001). Median PFS was 19.4 months with enzalutamide and 5.7 months with bicalutamide.

ii. Median time to PSA progression (HR, 0.19, 95% CI, 0.14 to 0.26, P<0.001); proportion of patients with ≥50% PSA response (81% v 31% P<0.001), and radiographic PFS in metastatic patients (HR, 0.32; 95% CI, 0.21 to 0.50, P<0.001).[81]

e. Sequencing of hormonal therapies

1) Phase II trial of 202 newly diagnosed m1CRPC[82]

i. Randomized patients to either:



ii. Patients crossed to second line treatment at progression (defined as PSA increase, radiation to symptomatic bone metastases, or unacceptable toxicity)

iii. Efficacy endpoints:

	Time to PSA Progression 2	PSA response (>30%) 2	Time to PSA Progression 1	PSA response (>30%) 1	Median OS
Group A	19.3 months	36%	11.2 months	68%	28.8 months
Group B	15.2 months	4%	10.2 months	82%	24.4 months
	HR 0.66; p=0.036	**p<0.0001**	HR 0.95; p=0.78	**p=0.023**	HR 0.79; p=0.23

iv. Time to first PSA progression was similar between the two groups (11.2 vs. 10.2 months HR 0.95; p=0.78), indicating similar efficacy in the first line setting. This led the authors to conclude that the overall benefit from sequencing therapies was derived from the improved response to enzalutamide in the second-line setting. The authors theorize this may be due to difference in mechanism of action between the two drugs and mechanisms of resistance.

2) Further studies are needed to confirm a survival benefit from sequencing therapies as this study was not powered to detect a difference in mOS and the 4 month benefit was not statistically significant.

f. Cabazitaxel (Jevtana®)

1) Not indicated in the first line setting

2) TROPIC Trial: Phase III, randomized, open-label, multi-center trial in 755 patients with metastatic CRPC who had received prior docetaxel therapy. Patients were randomized to receive cabazitaxel 25 mg/m^2 or mitoxantrone with daily prednisone every 3 weeks up to total of 10 cycles.

   i. Study showed median PFS of 2.8 months with cabazitaxel vs. 1.4 months with mitoxantrone ($p<0.0001$). The median OS was significantly better with cabazitaxel at 15.1 vs. 12.7 months ($p<0.0001$).

      1. There were significantly higher incidences of severe neutropenia, diarrhea and febrile neutropenia (8%) in the cabazitaxel arm. Another side effect of concern is the 30-day mortality after last dose of drug of 4.9% in cabazitaxel group compared with 2% in mitoxantrone. It is more likely due to higher incidences of neutropenia and diarrhea.[83]

3) PROSELICA Trial: Phase III, noninferiority trial assessed 20mg/m^2 vs 25mg/m^2 in post docetaxel patients with metastatic CRPC[84]

   i. Confirmed efficacy and noninferiority of 20mg/m^2 in post-docetaxel patients

   ii. PFS, prostate-specific antigen (PSA) response favored 25mg/m^2

   iii. Health-related quality of life, and safety favored 20mg/m^2

   iv. Dosing 20 mg/m^2 every 3 weeks in combination with prednisone recommended

   v. . It is important to pre-medicate patient with an antihistamine, a corticosteroid, and an H2 antagonist[84] to prevent hypersensitivity reaction

4) FIRSTANA Trial:[85] Phase III superiority trial comparing cabazitaxel to docetaxel for mCRPC. Randomized 1,168 patients 1:1:1 to cabazitaxel 20mg/m^2 (C20) to cabazitaxel 25mg/m^2 (C25) to docetaxel 75mg/m^2 (D75) IV every 3 weeks plus prednisone.

   i. Primary endpoint: median OS (C20 vs. C25 vs. D75)

      1. 24.5 vs. 25.2 vs. 24.3 months (no difference between either cabazitaxel regimen and D75)

   ii. Median PFS was not different between the groups. Tumor response rate was numerically higher with C25 vs. D75 (41.6 vs. 30.9%, p =0.37)

   iii. Adverse effects:

      1. Rate of grade 3 or 4 AE: 41.2%, 60.1%, and 46.0% (C20 vs. C25 vs. D75)

      2. D75 had higher rates of peripheral neuropathy, edema, and nail disorders. C25 had higher rates of febrile neutropenia, diarrhea and hematuria.

   iv. In first line setting, cabazitaxel is not superior to docetaxel. Only FDA approved after treatment with docetaxel-containing regimen.

5) CARD Trial[86]:

i. Phase III, open label, randomized 225 men with mCRPC previously treated with docetaxel and one novel hormonal therapy (abiraterone or enzalutamide) randomized to:

1. Cabazitaxel 25mg/m^2 IV every 3 weeks + prednisone + WBC growth factor
2. The alternate novel hormonal therapy (abiraterone or enzalutamide)

ii. Primary outcome: median radiographic PFS: 8 vs. 3.7 months (HR 0.54; $p < 0.001$)

iii. Median OS: 13.6 vs. 11 months (HR 0.64; $p = 0.008$)

iv. PSA response: 35.7 vs. 13.5% ($p<0.001$)

v. Limitations: Study done in Europe where 25mg/m^2 is still standard of care, in US – 20mg/m^2 dose is used based on PROESLICA trial above. If giving higher dose, must use growth factor. Previous studies showed rates of febrile neutropenia 8-9.3%, with growth factor in the CARD trial incidence was 3%. Consider patient selection and performance status.

vi. Based on this trial, if a patient is a candidate for chemotherapy, it may be preferred over a second novel hormonal therapy in the castrate resistant setting.

Patient Case #5: Answer = D (Cabazitaxel).
Mitoxantrone has no overall survival benefit and should be reserved for patients with no other appropriate treatment options. Radium-223 is only indicated for pts with bone-only mets. Cabazitaxel and alternate novel hormonal therapy were compared in this setting in the CARD trial and cabazitaxel had superior survival benefit. Therefore, cabazitaxel is preferred over enzalutamide for this patient.

Patient Case #6: GC has metastatic castration resistant prostate cancer with no other comorbidities. He was initially treated with leuprolide and apalutamide and when he progressed, he was started on docetaxel. His most recent PSMA PET scan shows numerous sites of progressing disease in the lung and bones. In addition to continuing his leuprolide, **which of the following is the most appropriate next line of treatment for AB?**

A. Enzalutamide
B. Radium-223
C. Mitoxantrone + prednisone
D. Lutetium-177 PSMA

g. Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617)

1) Novel radiopharmaceutical FDA approved in 2022 for treatment of PSMA-positive m1CRPC

i. Approved for patients with at least one PSMA-positive lesion and/or metastatic disease that is primarily PSMA-positive (with no dominant PSMA-negative lesions) and have been treated with at least two prior therapies (one novel hormonal therapy and one taxane-based therapy)

2) Prostate-Specific Membrane Antigen (PSMA) is a transmembrane protein that is present on the cell surface. It is expressed in normal prostate tissue but is known to have increased expression in prostate cancer tissue. Over 90% of prostate cancers are thought to over-express PSMA. Androgen deprivation leads to upregulation of PSMA.[87]

i. Levels of PSMA expression are thought to correlate with cancer aggressiveness and inversely with prognosis.

ii. PSMA-targeted PET imaging was initially approved by the FDA and used as a more sensitive imaging test for metastatic disease compared to the standard fluciclovine-based PET scans. Currently there are three FDA approved products for PSMA PET imaging.[88, 89]

3) VISION trial[90]

i. Open-label, international phase III trial

1. Enrolled 831 patients with PSMA-positive castrate-resistant metastatic prostate cancer who had received at least one prior novel hormonal therapy and one prior taxane

a. Around 40% had two prior novel hormonal therapies

2. Randomized 2:1 to Lu-PSMA-617 + Standard Care vs. Standard Care Alone

a. Standard Care allowed androgen deprivation, bisphosphonates/denosumab, novel hormonal therapies

i. Excluded chemotherapy, immunotherapy, radium-223, and other investigational drugs

b. Lu-PSMA was given every 6 weeks x 4-6 cycles (cycles 5 and 6 at discretion of investigator based on response)

i. Median 5 cycles given; 17.6% require dose delay and 5.7% required dose reduction

3. Primary endpoints:

a. Imaging-based PFS: 8.7 vs. 3.4 months (HR 0.4, p <0.001)

b. Median OS: 15.3 vs. 11.3 months (0.62, p<0.001)

4. Safety endpoints:

a. Grade 3/4 in 52.7% vs. 38%

i. 23.4% bone marrow suppression, 3.4% renal effects

b. Adverse effects of all grades that occurred in >30% of patients: fatigue, dry mouth, nausea, anemia

4) Phase II TheraP Trial:[91]

i. N = 200 m1CRPC, PSMA positive, previously treated with docetaxel (could also be treated with prior novel hormonal therapy, which 90% had)

ii. Randomized patients 1:1 (open label)

1. Lutetium-177 PSMA 6-8.5GBq IV every 6 weeks up to 6 cycles

2. Cabazitaxel 20mg/m^2 IV every 3 weeks up to 10 cycles

iii. Efficacy:

1. Primary endpoint was PSA response (defined as a 50% reduction in PSA)

a. 66 vs. 37%; p =0.0016

2. Progression free survival:

a. Kaplan Meier curves cross around 6 months for the two groups. Median PFS was 5.1 months in each arm but hazard ratio favored Lutetium-177 PSMA (0.63). 12 month PFS was 19% vs. 3%

5) Lutetium-177 PSMA (Pluvicto®)[92]

i. Mechanism of action:

1. Radiopharmaceutical: Lutetium-177 bound to PSMA-617

2. Selectively delivers beta-particle radiation to PSMA-positive cells and surrounding microenvironment

ii. Indication: m1CRPC (PSMA-positive) previously treated with one taxane-based therapy and one androgen-receptor pathway inhibitor

iii. Dosing: 7.4 GBq (200 mCi) IV every 6 weeks (up to 6 doses)

iv. Toxicities: fatigue, dry mouth, nausea/vomiting, decreased appetite, and constipation/diarrhea, renal toxicity, myelosuppression, infertility

v. Drug-drug interactions: Not evaluated

vi. Pearls: Patient precautions (avoid close contact for 3-7 days); antiemetic pre-medications recommended; dose reduce for dry mouth, GI toxicity, renal toxicity, myelosuppression

Patient Case #6: Answer = D (Lutetium-177 PSMA). The patient meets criteria to receive this agent, as he has PSMA-positive disease that has progressed through a taxane and a novel hormonal therapy. Enzalutamide is not appropriate after progression on apalutamide. Radium-223 is not recommended with visceral disease. Mitoxantrone does not provide a survival benefit in this setting.

h. Radium-223 – for patients with symptomatic bone only disease

1) Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) Trial: A phase III, double-blind, randomized trial comparing radium-233 to placebo in 921 patients with CRPC and symptomatic bone metastases and no visceral metastases. Approximately 60% had received previous docetaxel therapy and 13% were ECOG $\geq$2. Approximately 30% of the patients had >20 bone metastases, 45% had 6-20 bone metastases and 15% had < 6 bone metastases. Patients were randomized to receive 6 injections of radium-223 given 1 injection every 4 weeks or placebo. Patients also received other standard of care prostate cancer therapy. [93]

i. At the interim analysis, radium-223 not only delayed time to first skeletal related events, but showed survival advantage (only seen when all 6 injections were given).

ii. The median overall survival was 14 months compared with 11.2 months in placebo group (P = 0.002). The updated analysis confirmed the survival benefit (14.9 months vs 11.3 months, p<0.001).

iii. Median time to first skeletal related events was 15.6 months vs. 9.8 months (p<0.001). Median time to PSA progression was 3.6 mo v 3.4 mo (p<0.001).

iv. There was also a significant improvement in quality of life by FACT-P score associated with radium 223.

v. Grade 3 or 4 toxicities of radium-223 are anemia 10%, neutropenia 2%, and thrombocytopenia 4%.

2) NCCN® Category 1 for patients with symptomatic bone metastases and **no known visceral metastases** prior to and after docetaxel therapy.[3]

3) Not approved to be used in combination with docetaxel or any other chemotherapy due to potential of additive myelosuppression. Prior to initial dose, ANC should be ≥1,500/mm^3, platelets ≥100,000/mm^3, and hemoglobin ≥10 g/dL; prior to subsequent doses, ANC should be ≥1,000/mm^3 and platelets ≥50,000/mm^3. Neutrophils and platelet nadirs typically occurred 2 to 3 weeks after administration; recovery generally occurred ~6 to 8 weeks after administration. If recovery does not occur within 6 to 8 weeks from the last dose (despite supportive care), treatment should be discontinued.

4) Should not be used with any therapy other than ADT and bone-directed therapies (denosumab, zoledronic acid). Studies in combination with abiraterone showed no benefit with respect to skeletal event-free survival and an increase in risk of fracture.[94]

i. Sipuleucel-T– For asymptomatic or minimally symptomatic patients

1) IMPACT Trial: Phase III, randomized, double-blind, placebo-controlled trial in patients with metastatic CRPC who were asymptomatic or minimally symptomatic. Patients had a ≥ 6 month life expectancy and PSA ≥ 5 ng/ml without visceral metastases. 341 patients received sipuleucel-T and 171 placebo.[95]

i. There was a 22% relative reduction in risk of death (HR 0.78; 95% CI, 0.61-0.98). Median overall survival was 25.8 months in patients receiving sipuleucel-T compared with 21.7 months in patients receiving placebo (P=0.03).

ii. Median time to disease progression was not significantly different between the 2 groups (14.6 weeks v 14.4 weeks, p=0.63).

2) Sipuleucel-T is not recommended for patients with small cell/neuroendocrine prostate cancer.

3) Sipuleucel-T should be considered for patients with metastatic CRPC and have the following:[3]

i. No or minimal symptoms or requiring opioids

ii. Good performance status

iii. ≥ 6 months life expectancy

iv. No visceral disease

j. Mitoxantrone/Prednisone – generally for symptomatic patients who are not candidates for docetaxel therapy as there is no difference in overall survival[3]

k. Cabazitaxel + Carboplatin[96]

1) This regimen was added to the NCCN guidelines based on a phase 1-2 study (below) and could be considered for select patients with features of aggressive-variant prostate cancer (AVPC) and a good performance status.[3]

2) Phase 1-2 study, open-label, randomized patients with m1CRPC previously treated with docetaxel and one prior novel hormonal therapy

3) Initial phase 1 study enrolled 9 patients with no dose-limiting toxicities.

4) Phase 2 study enrolled 160 patients and randomized 1:1 to:

   i. Cabazitaxel 25mg/m^2 + carboplatin AUC 4 IV every 3 weeks + prednisone 10mg daily + WBC growth factor

   ii. Cabazitaxel 25mg/m^2 + prednisone 10mg daily + WBC growth factor

5) Patients were stratified based on presence of AVPC clinicopathologic features (AVPC-C) or molecular findings suggestive of AVPC (AVPC-MS) in an attempt to identify an androgen-indifferent subtype:

   i. AVPC-C:

      1. Small cell histology, exclusively visceral metastases, predominantly lytic bone metastases, bulky lymphadenopathy or Gleason ≥ 8 at diagnosis, PSA≤10 + high volume (≥20) bone metastases, elevated LDH or CEA, ≤ 6 month response to ADT

   ii. AVPC-MS:

      1. Defect in 2 of 3 tumor suppressor genes (TP53, RB1, and PTEN) on ctDNA or immunohistochemistry

      2. Only available in 56 patients

6) Median PFS:

All patients	AVPC-C	AVPC-MS (post-hoc)
7.3 vs. 4.5 months	NR	6 vs 2.2 months
HR 0.69; p =0.018	HR 0.58; p=0.013	HR 0.35; p=0.00033

7) Median OS:

All patients	AVPC-C	AVPC-MS (post-hoc)
18.5 vs. 17.3 months	NR	17.4 vs. 9.9 months
HR 0.89; p=0.5	NR	HR 0.39; p=0.0024

Note: NCCN guidelines recommend lower cabazitaxel dosing of 20mg/m^2 (in combination with carboplatin AUC 4 and WBC growth factor)

Patient Case #7: RC is a 65-year- old male with metastatic prostate cancer and tumor mutation testing revealed BRCA1 mutation. His previous lines of therapy include leuprolide + abiraterone + prednisone, leuprolide + Radium-223, and leuprolide + docetaxel + prednisone. He has received 3 cycles of docetaxel and his PSA has been increasing over the 2 months. Repeat staging scans show worsening bone and liver metastases. He now requires scheduled morphine for bone pain. His ECOG performance status is 1. **In addition to continuing ADT, which of the following is the most appropriate treatment option for RC at this time?**

A. Olaparib
B. Sipuleucel T
C. Mitoxantrone
D. Pembrolizumab

l. Olaparib

1) PROFOUND Trial: Phase III open label trial. Enrolled 387 men with mCRPC who had progressed on either abiraterone or enzalutamide and had one of 15 prespecified HRR mutations. Patients were randomized 2:1 to olaparib 300mg PO BID or physician's choice of abiraterone or enzalutamide (all patients continued ADT).[6]

   i. Of note, 2,792 had tumor tissue screened for HRRm and 28% had a mutation in 1 of the 15 prespecified genes. Of these, 387 met criteria for enrollment. The most common mutations were BRCA2, ATM, and CDK12.

   ii. Patients were separated into 2 cohorts. Cohort A included patients with BRCA1, BRCA2, or ATM mutations. Cohort B included the 12 remaining pre-specified HRRm.

      1. Approximately 18% of patients in control arm had received both abiraterone and enzalutamide in the past. Around over 60% of patients had received a prior taxane.

   iii. Primary endpoint was imaging-based PFS

      1. Cohort A: 7.4 vs. 3.6 months (HR 0.34, p <0.001)

      2. Cohort A + B: 5.8 vs. 3.5 months (HR 0.49, p <0.001)

      3. Not reported for cohort B alone. Unclear how much the benefit across all groups is driven by Cohort A (specifically BRCA2 mutation).

      4. In subgroup analysis, patients with PPP2R2A mutation, HR for progression or death significantly favored the control arm (6.61; 95% CI 1.41 to 46.41). NCCN recommends against use in these patients.

   iv. Overall Survival Update:[97]

      1. mOS in Cohort A: 19.1 vs. 14.7 months (HR 0.69, p = 0.02)

      2. mOS in Cohort B:

         a. 14.1 vs. 11.5 months (HR 0.96; 95% CI 0.63 – 1.495.98) before adjusting for crossover

         b. Post-hoc analysis excluding PPP2R2A from cohort B:

            i. mOS 14.2 vs. 10.8 months (HR 0.79; 95% CI 0.5-1.25)

      3. mOS in total population:

a. 17.3 vs. 14 months (HR 0.79; 95% CI 0.61-1.03)

v. FDA approved for mCRPC with any germline or somatic HRRm after progression on either abiraterone or enzalutamide.

m. Rucaparib

1) FDA approved for m1CRPC with germline or somatic BRCA1/2 mutation and prior treatment with taxane and androgen-receptor directed therapy.

2) TRITON 2, an ongoing single-arm phase II trial of rucaparib 600mg PO BID in mCRPC with any HRRm after progression on 1 prior taxane and 1-2 prior androgen-receptor directed therapies.[98]

3) BCRCA1/2 Cohort n = 115

i. Response rate of 43.5% in 66 BRCA2 mutated patients

4) Non-BRCA HRRm cohort (n =78) not reported at this time but authors state limited radiographic or PSA responses.

5) Awaiting confirmatory efficacy and safety results from TRITON3. A randomized trial of rucaparib versus physician's choice of treatment.

Patient Case #7, Answer:
Correct answer = A (Olaparib). Sipuleucel-T is not indicated in this setting. Mitoxantrone has no overall survival benefit and is generally reserved for patients who cannot tolerate any other treatment option. This patient has a homologous recombinant repair mutation making him a candidate for a PARP inhibitor. Olaparib is FDA indicated for any HRRm (and NCCN guidelines recommend for any HRRm except PPP2R2A). Pembrolizumab is only indicated for dMMR or MSI-high cancers. Olaparib is the most appropriate option for the patient based on available evidence.

Patient Case #8:
LL has prostate cancer that progressed during adjuvant ADT with increasing PSA, testosterone <50ng/dL, and bone scans showing new skeletal metastases. His oncologist is planning to add enzalutamide to his ADT at this time. The oncologist asks if there are any other supportive care medications that you would recommend.

What of the following is most appropriate to initiate in LL at this time?

A. Denosumab 120 mg every 4 weeks
B. Calcium plus vitamin D 500mg-400 IU twice daily
C. Alendronate 70 mg every 4 weeks and calcium plus vitamin D 500mg-400 IU twice daily
D. Denosumab 120 mg every 4 weeks and calcium plus vitamin D 500mg-400 IU twice daily

I. Supportive Care and Survivorship

A) Osteoporosis in Prostate Cancer

1. ADT increases the risk for osteoporosis and is associated with a 21%-54% increase in fracture risk. [3]
2. Screening and treatment based on normal population. Calcium 1200mg daily and vitamin D3 800-1000 IU daily are recommended for all men over the age of 50 years.
3. Additional treatment indicated if 10-year probability of hip fracture is $\geq$ 3% or 10-year probability of major osteoporosis related fracture $\geq$ 20%.

4. Fracture risk assessment using FRAX
    a. -10-year risk of fracture based on clinical factors and baseline bone mineral density
5. Baseline DEXA scan prior to initiating therapy for those at risk
6. Bisphosphonates
    a. Zoledronic acid: Randomized, placebo-controlled trial evaluated zoledronic acid 4mg IV x 1 versus placebo in 40 men with non-metastatic prostate cancer on ADT therapy with at T score > -2.5. The mean bone mineral density (BMD) of the lumbar spine decreased by 3.1% in placebo arm and increased by 4% in zoledronic acid arm after 1 year. A significant difference in BMD was also seen in the total hip and trochanter. The study did not assess the impact on fracture rate.[99]
    b. Alendronate: A randomized, double-blind trial evaluated 112 men with non-metastatic prostate cancer on ADT and randomized them to alendronate 70mg PO weekly or placebo. After 1 year, men receiving alendronate had BMD increased by 3.7% at the spine and 1.6% at the femoral neck vs a 1.4% and 0.7% loss in the placebo group, respectively. The study did not assess the impact on fracture rates.[100]
7. Denosumab
    a. A randomized, double-blind trial evaluated denosumab 60mg SQ every 6 months versus placebo in over 1400 men with non-metastatic prostate cancer receiving ADT. Patients had T-score less than -1.0 or history of osteoporotic fracture. At 24 months, bone mineral density was increased by 5.6% in with denosumab compared with loss of 1% in with placebo. Out of 1468 men, 1.5% on denosumab and 3.9% on placebo (P=0.006) had incidence of new vertebral fractures.[101]
8. Current NCCN® recommendations for patients with a fracture risk that warrants drug therapy include zoledronic acid 5mg IV annually, alendronate 70mg PO weekly, or denosumab 60mg SQ every 6 months.[3]

B) Bone Metastasis and Bone Pain in Prostate Cancer

1. Skeletal-related events (SRE) include pathologic fractures (vertebral or non-vertebral), spinal cord compression, surgery to bone, radiation therapy to bone, or change in antineoplastic therapy to treat bone pain.
2. Bisphosphonates: Zoledronic acid is recommended to prevent skeletal related events in men with castration resistant recurrent prostate cancer with bone metastases. It can be given every 3-4 weeks. Overall ideal duration of treatment is unknown. Pamidronate has not been shown to be efficacious compared with placebo in patients with metastatic CRPC.
    a. Over 600 patients with CRPC and bone metastases were randomized to zoledronic acid 4mg, zoledronic acid 8 mg (subsequently reduced to 4mg due to toxicity), or placebo every 3 weeks for 15 months. Zoledronic acid significantly reduced the incidence of SRE and extended the time to first SRE.[102]
        1) A follow up of this study extended treatment out to a total of 24 months. In the 122 patients who completed 24 months, zoledronic acid patients had fewer SRE than those in placebo and no additional toxicity.[103]

b. Castration-sensitive prostate cancer: CALGB 90202 (Alliance): This phase III trial randomized men with castration-sensitive prostate cancer and bone metastases who started ADT within the previous 6 months to zoledronic acid 4mg IV every 4 weeks or placebo. Patients received ADT (bilateral orchiectomies, gonadotropin-releasing hormone agonist, or gonadotropin-releasing hormone antagonist) for ≤ 6 months before randomization and continued ADT throughout the study. After disease progression to CPRC, all patients received open label zoledronic acid. Primary endpoint was time to first SRE.

1) There was no difference in median time to first SRE (31.9 months with zoledronic acid and 29.8 month with placebo; hazard ratio, 0.97; 95% CI, 0-1.17; p=0.39).

2) In men with castration-sensitive prostate cancer and bone metastases, early treatment with zoledronic acid was not associated with lower risk for SREs or adverse events and had no impact on overall survival.[104]

c. Every 3 month dosing: CALGB 70604 (Alliance): Non-inferiority trial.[105]

1) Randomized 1,822 patients with metastatic cancer (breast, prostate, myeloma and other) to zoledronic acid every 3 months versus zoledronic acid monthly for 24 months.

2) Results: zoledronic acid every 3 months was non-inferior to monthly therapy for proportion of SRE. Dose delays were more common in the monthly group.

3) There were also an increased rate of osteonecrosis of the jaw and grade 2-4 creatinine increases in the monthly group.

3. Denosumab 120 mg subcutaneous every 4 weeks[3] (preferred)

a. A non-inferiority, double-blind study of men with CRPC and bone metastases randomized 1904 patients to denosumab 120mg SQ or zoledronic acid 4mg IV every 4 weeks. Median time to first SRE was 20.7 months for denosumab versus 17.1 months for zoledronic acid (p=0.0002; secondary superiority endpoint p=0.008)). There were significantly more grade 3 or 4 adverse events in the denosumab group.[106]

1) ONJ: 2% denosumab vs 1% zoledronic acid

2) Hypocalcemia: 13% denosumab v 6% zoledronic acid

3) Increased risk of hypocalcemia with CrCl <60ml/min

b. Castrate-resistant prostate cancer without bone metastases:[107]

1) Phase III, double-blind, placebo-controlled, randomized trial evaluated denosumab in patients with non-metastatic CRPC at high risk for bone metastases (PSA≥8 ng/ml, PSA doubling time ≤10mo)

2) Denosumab increased the bone metastasis free survival by 4.2 months (median 29.5 vs. 25.2 months; HR 0.85, CI 0.73 – 0.98)

3) No difference in overall survival

4) ONJ in 5% and hypocalcemia in 2% of patients receiving denosumab

4. Patients receiving zoledronic acid or denosumab should be monitored for the development of ONJ. Most cases have occurred after invasive dental procedures. When possible, have dental work completed prior to initiation of therapy.

a. Patients should also receive calcium and vitamin D due to the risk of hypocalcemia and periodic monitoring of serum calcium levels

b. In patients with normal renal function, hypocalcemia occurs twice as often with denosumab than zoledronic acid.

Patient Case #8 Answer:

Correct answer = D (Denosumab 120 mg every 4 weeks and calcium plus vitamin D 500mg-400 IU twice daily). LL now has castrate resistant prostate cancer with bony disease, so it is reasonable to initiate therapy for prevention of a skeletal-related event. Denosumab is a preferred agent for this indication. Alendronate is reasonable to prevent osteoporosis but is not indicated for prevention of skeletal-related events. Denosumab has been shown to delay time to first skeletal related events in patients with bone metastases from prostate cancer. Calcium plus vitamin D should be added to therapy to prevent hypocalcemia.

5. Radiation Therapy[108]

   a. Strontium 89 (Metastron®) and samarium-153 (Quadramet®)

      1) 60-80% analgesic response rates, median duration 3-6 months

      2) Major dose limiting toxicity is myelosuppression due to marrow suppression by the beta particle penetration. Palliative radiation can increase the risk of bone marrow suppression and prevent patients from receiving future systemic chemotherapy.

      3) No advantage in overall survival as seen with Radium 223

   b. External beam radiation

      1) Used to control pain and prevent impending fractures from individual lesions.

      2) Pain relief seen in greater than 90% of patients

      3) Local control rates range from 75-90%

C) Diabetes and Heart Disease in prostate cancer

1. ADT therapy causes physiologic effects such as increased fat mass, decreased lean muscle mass, increased cholesterol and triglycerides, and decreased insulin sensitivity. These events have been linked to diabetes and cardiovascular disease.[3]

2. A population based study of 73,196 patients with locoregional prostate cancer found that use of ADT was associated in an increased risk of diabetes (HR 1.44; p<0.001), coronary artery heart disease (HR 1.16; p<0.001), myocardial infarction (HR 1.11; p=0.03) and sudden cardiac death (HR 1.16; p=0.004).[109]

3. Usual population screening and interventions for diabetes and heart disease are recommended at this time.[3]

D) Sexual and Urinary Dysfunction[110, 111]

1. 90% of prostate cancer survivors report erectile dysfunction (ED)

2. NCCN® recommends asking about sexual function at regular intervals and provides a questionnaire for clinic use[9]

3. The American Cancer Society has published guidelines for prostate cancer survivors[110] that includes sexual and urinary dysfunction

a. Surgery

1) Long-term sexual dysfunction manifested as ED, lack of ejaculation, orgasm changes, and penile shortening

2) Long-term urinary dysfunction manifested as stress incontinence, symptoms of urgency, frequency, nocturia, dribbling and urethral stricture

b. Radiation

1) Long-term sexual dysfunction manifested by progressive ED and decreased semen volume

2) Long-term urinary dysfunction manifested by incontinence, dysuria, urgency, frequency, nocturia, dribbling, hematuria, and urethral stricture

3) Late urinary and sexual dysfunction manifested by urethral stricture, hematuria, and delayed ED 6 to 36 months after therapy

c. ADT

1) Sexual dysfunction manifested by loss of libido and ED

2) Discusses assessment and management of physical and psychosocial long-term and late toxicities

3) Recommends patients with persistent symptoms be referred to a urologist

4. Treatments for ED

a. Modification of risk factors, such as decreasing alcohol consumption, increasing physical activity, smoking cessation, and weight loss

b. PDE-5 (phosphodiesterase type 5) inhibitors early following surgery to improve sexual outcomes post-surgery

i. Contraindicated in patients on nitrates

ii. Start conservatively and titrate to maximum dose if needed

iii. Adequate trial for an agent is defined as 5 separate occasions at maximum dose.

iv. If second-line agent fails, urology referral

5. Treatment of urinary symptoms

a. Anticholinergic medications may be an option in men with urge incontinence, frequency, nocturia, or urgency.

RECOMMENDED READING AND REFERENCES

Recommended Readings

1. Virgo KS, Rumble RB, Wit RD, et al. Initial management of noncastrate advanced, recurrent, or metastatic prostate cancer: ASCO guideline update. *Journal of Clinical Oncology.* 2021; 39(11): 1274-305. https://pubmed.ncbi.nlm.nih.gov/33497248/
2. Sartor O and de Bono J. Metastatic prostate cancer. *N Engl J Med*. 2018; 378(7): 645-57. https://www.ncbi.nlm.nih.gov/pubmed/29412780
3. Sartor O and de Bono J. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med.* 2021; 385:1091-1103. https://pubmed.ncbi.nlm.nih.gov/33581798/
4. Ratta R, Guida A, Scotté F, et al. PARP inhibitors as a new therapeutic option in metastatic prostate cancer: a systematic review. *Prostate Cancer Prostatic Dis*. 2020; 23(4): 549-560. https://pubmed.ncbi.nlm.nih.gov/32367009/

References

1 Schrecengost R and Knudsen KE. Molecular pathogenesis and progression of prostate cancer. *Seminars in oncology.* 2013; 40(3): 244-58.

2 Abida W, Cheng ML, Armenia J et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. *JAMA Oncol.* 2019; 5(4): 471-78.

3 Nccn clinical practice guidelines in oncology (nccn guidelines®) for prostate cancer. V.1.2023, 09/16/2022. *© 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, NCCN IMAGING AUC™, NCCN COMPENDIUM®, NCCN BIOMARKERS COMPENDIUM®, NCCN RADIATION THERAPY COMPENDIUM™, NCCN IMAGING AUC COMPENDIUM™, NCCN TEMPLATES®, NCCN EVIDENCE BLOCKS™, NCCN FRAMEWORK™, NCCN HARMONIZED GUIDELINES™, NCCN FLASH UPDATES™, NCCN TRENDS™ Surveys & Data, Powered by NCCN™, NCCN ONCOLOGY INSIGHTS REPORTS™, and NCCN GUIDELINES FOR PATIENTS® are trademarks ("Marks") of the National Comprehensive Cancer Network, Inc.*

4 Mateo J, Carreira S, Sandhu S et al. DNA-repair defects and olaparib in metastatic prostate cancer. *New England Journal of Medicine.* 2015; 373(18): 1697-708.

5 Nccn clinical practice guidelines in oncology (nccn guidelines®) in prostate cancer early detection. V.1.2022, 02/16/2022. *© 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK.*

6 de Bono J, Mateo J, Fizazi K et al. Olaparib for metastatic castration-resistant prostate cancer. *The New England journal of medicine.* 2020; 382(22): 2091-102.

7 Gann PH, Hennekens CH and Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *Jama.* 1995; 273(4): 289-94.

8 Chybowski FM, Bergstralh EJ and Oesterling JE. The effect of digital rectal examination on the serum prostate specific antigen concentration: Results of a randomized study. *The Journal of urology.* 1992; 148(1): 83-86.

9 Nccn clinical practice guidelines in oncology (nccn guidelines®) in surivorship. V.1.2022, 03/30/2022. *© 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved. NATIONAL COMPREHENSIVE CANCER NETWORK.*

10 Carter HB, Ferrucci L, Kettermann A et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *Journal of the National Cancer Institute.* 2006; 98(21): 1521-7.

11 Force USPST. Screening for prostate cancer: Us preventive services task force recommendation statement. *Jama.* 2018; 319(18): 1901-13.

12 Basch E, Oliver TK, Vickers A et al. Screening for prostate cancer with prostate-specific antigen testing: American society of clinical oncology provisional clinical opinion. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012; 30(24): 3020-5.
13 Hugosson J, Carlsson S, Aus G et al. Mortality results from the göteborg randomised population-based prostate-cancer screening trial. *The Lancet Oncology.* 2010; 11(8): 725-32.
14 Carter HB, Albertsen PC, Barry MJ et al. Early detection of prostate cancer: Aua guideline. *The Journal of urology.* 2013; 190(2): 419-26.
15 Wolf AM, Wender RC, Etzioni RB et al. American cancer society guideline for the early detection of prostate cancer: Update 2010. *CA Cancer J Clin.* 2010; 60(2): 70-98.
16 Thompson IM, Goodman PJ, Tangen CM et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med.* 2003; 349(3): 215-24.
17 Thompson IM, Jr., Goodman PJ, Tangen CM et al. Long-term survival of participants in the prostate cancer prevention trial. *N Engl J Med.* 2013; 369(7): 603-10.
18 Andriole GL, Bostwick DG, Brawley OW et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med.* 2010; 362(13): 1192-202.
19 Kramer BS, Hagerty KL, Justman S et al. Use of 5alpha-reductase inhibitors for prostate cancer chemoprevention: American society of clinical oncology/american urological association 2008 clinical practice guideline. *The Journal of urology.* 2009; 181(4): 1642-57.
20 Wilt TJ, Brawer MK, Jones KM et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med.* 2012; 367(3): 203-13.
21 Wilt TJ, Jones KM, Barry MJ et al. Follow-up of prostatectomy versus observation for early prostate cancer. *New England Journal of Medicine.* 2017; 377(2): 132-42.
22 D'Amico AV, Manola J, Loffredo M et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. *Jama.* 2004; 292(7): 821-7.
23 Jones CU, Hunt D, McGowan DG et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med.* 2011; 365(2): 107-18.
24 Shelley MD, Kumar S, Coles B et al. Adjuvant hormone therapy for localised and locally advanced prostate carcinoma: A systematic review and meta-analysis of randomised trials. *Cancer treatment reviews.* 2009; 35(7): 540-6.
25 Pilepich MV, Winter K, Lawton CA et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase iii rtog 85-31. *International journal of radiation oncology, biology, physics.* 2005; 61(5): 1285-90.
26 Souhami L, Bae K, Pilepich M et al. Impact of the duration of adjuvant hormonal therapy in patients with locally advanced prostate cancer treated with radiotherapy: A secondary analysis of rtog 85-31. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009; 27(13): 2137-43.
27 Horwitz EM, Bae K, Hanks GE et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: A phase iii trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008; 26(15): 2497-504.
28 Lawton CAF, Lin X, Hanks GE et al. Duration of androgen deprivation in locally advanced prostate cancer: Long-term update of nrg oncology rtog 9202. *Int J Radiat Oncol Biol Phys.* 2017; 98(2): 296-303.
29 Bolla M, de Reijke TM, Van Tienhoven G et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med.* 2009; 360(24): 2516-27.
30 Bolla M, Van Tienhoven G, Warde P et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an eortc randomised study. *The Lancet. Oncology.* 2010; 11(11): 1066-73.
31 Warde P, Mason M, Ding K et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: A randomised, phase 3 trial. *Lancet.* 2011; 378(9809): 2104-11.
32 Sun M, Choueiri TK, Hamnvik OP et al. Comparison of gonadotropin-releasing hormone agonists and orchiectomy: Effects of androgen-deprivation therapy. *JAMA Oncol.* 2016; 2(4): 500-7.
33 Lexi-Comp Online. 2019.

34 Seidenfeld J, Samson DJ, Hasselblad V et al. Single-therapy androgen suppression in men with advanced prostate cancer: A systematic review and meta-analysis. *Annals of internal medicine.* 2000; 132(7): 566-77.
35 Klotz L, Boccon-Gibod L, Shore ND et al. The efficacy and safety of degarelix: A 12-month, comparative, randomized, open-label, parallel-group phase iii study in patients with prostate cancer. *BJU international.* 2008; 102(11): 1531-8.
36 Albertsen PC, Klotz L, Tombal B et al. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. *European Urology.* 2014; 65(3): 565-73.
37 Margel D, Peer A, Ber Y et al. Cardiovascular morbidity in a randomized trial comparing gnrh agonist and gnrh antagonist among patients with advanced prostate cancer and preexisting cardiovascular disease. *J Urol.* 2019; 202(6): 1199-208.
38 Lopes RD, Higano CS, Slovin SF et al. Cardiovascular safety of degarelix versus leuprolide in patients with prostate cancer: The primary results of the pronounce randomized trial. *Circulation.* 2021; 144(16): 1295-307.
39 Melloni C, Slovin SF, Blemings A et al. Cardiovascular safety of degarelix versus leuprolide for advanced prostate cancer. *The PRONOUNCE Trial Study Design.* 2020; 2(1): 70-81.
40 Relugolix [package insert]. Brisbane ca; myovant sciences. 2020.
41 Shore ND, Saad F, Cookson MS et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med.* 2020; 382(23): 2187-96.
42 Samson DJ, Seidenfeld J, Schmitt B et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. *Cancer.* 2002; 95(2): 361-76.
43 Crook JM, O'Callaghan CJ, Duncan G et al. Intermittent androgen suppression for rising psa level after radiotherapy. *N Engl J Med.* 2012; 367(10): 895-903.
44 Hussain M, Tangen CM, Berry DL et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med.* 2013; 368(14): 1314-25.
45 Niraula S, Le LW and Tannock IF. Treatment of prostate cancer with intermittent versus continuous androgen deprivation: A systematic review of randomized trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013; 31(16): 2029-36.
46 Sciarra A, Abrahamsson PA, Brausi M et al. Intermittent androgen-deprivation therapy in prostate cancer: A critical review focused on phase 3 trials. *European urology.* 2013; 64(5): 722-30.
47 Smith MR, Saad F, Chowdhury S et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *New England Journal of Medicine.* 2018; 378(15): 1408-18.
48 Small EJ, Saad F, Chowdhury S et al. Final survival results from spartan, a phase iii study of apalutamide (apa) versus placebo (pbo) in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmcrpc). *Journal of Clinical Oncology.* 2020; 38(15_suppl): 5516-16.
49 Smith MR, Saad F, Chowdhury S et al. Apalutamide and overall survival in prostate cancer. *Eur Urol.* 2021; 79(1): 150-58.
50 Hussain M, Fizazi K, Saad F et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *New England Journal of Medicine.* 2018; 378(26): 2465-74.
51 Sternberg CN, Fizazi K, Saad F et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *New England Journal of Medicine.* 2020; 382(23): 2197-206.
52 Fizazi K, Shore N, Tammela TL et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *New England Journal of Medicine.* 2019; 380(13): 1235-46.
53 Fizazi K. Overall survival (os) results of phase iii aramis study of darolutamide (daro) added to androgen deprivation therapy (adt) for nonmetastatic castration-resistant prostate cancer (nmcrpc). *J Clin Oncol.* 2020; 38.
54 Virgo KS, Rumble RB, Wit Rd et al. Initial management of noncastrate advanced, recurrent, or metastatic prostate cancer: Asco guideline update. *Journal of Clinical Oncology.* 2021; 39(11): 1274-305.
55 Sweeney CJ, Chen YH, Carducci M et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med.* 2015; 373(8): 737-46.
56 Kyriakopoulos CE, Chen YH, Carducci MA et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: Long-term survival analysis of the randomized phase iii e3805 chaarted trial. *J Clin Oncol.* 2018; 36(11): 1080-87.

57 Kyriakopoulos CE, Chen Y-H, Carducci MA et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: Long-term survival analysis of the randomized phase iii e3805 chaarted trial. *Journal of Clinical Oncology.* 2018; 36(11): 1080-87.
58 James ND SM, Clarke NW, Mason MD, Dearnaley DP, Spears MR et al. *Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial.* 2016; 387: 1163-77.
59 Gravis G, Boher JM, Chen YH et al. Burden of metastatic castrate naive prostate cancer patients, to identify men more likely to benefit from early docetaxel: Further analyses of chaarted and getug-afu15 studies. *Eur Urol.* 2018; 73(6): 847-55.
60 Smith MR, Hussain M, Saad F et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med.* 2022; 386(12): 1132-42.
61 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; 399(10336): 1695-707.
62 Fizazi K, Tran N, Fein L et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *New England Journal of Medicine.* 2017; 377(4): 352-60.
63 James ND, de Bono JS, Spears MR et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *New England Journal of Medicine.* 2017; 377(4): 338-51.
64 Auchus RJ, Yu MK, Nguyen S et al. Use of prednisone with abiraterone acetate in metastatic castration-resistant prostate cancer. *Oncologist.* 2014; 19(12): 1231-40.
65 Davis ID, Martin AJ, Stockler MR et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *New England Journal of Medicine.* 2019; 381(2): 121-31.
66 Davis I, et al. ANZUP Trial Update - The ENZAMET Trial. In proceedings from Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) Mini Annual Scientific Meeting (ASM). November 2020.
67 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): 2974-86.
68 Chi KN, Agarwal N, Bjartell A et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *New England Journal of Medicine.* 2019; 381(1): 13-24.
69 Berthold DR, Pond GR, Soban F et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: Updated survival in the tax 327 study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008; 26(2): 242-5.
70 Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004; 351(15): 1502-12.
71 Ryan CJ, Smith MR, Fizazi K et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (cou-aa-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *The Lancet. Oncology.* 2015; 16(2): 152-60.
72 Ryan CJ, Smith MR, de Bono JS et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med.* 2013; 368(2): 138-48.
73 de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med.* 2011; 364(21): 1995-2005.
74 Stein CA, Levin R, Given R et al. Randomized phase 2 therapeutic equivalence study of abiraterone acetate fine particle formulation vs. Originator abiraterone acetate in patients with metastatic castration-resistant prostate cancer: The staar study. *Urologic Oncology: Seminars and Original Investigations.* 2018; 36(2): 81.e9-81.e16.
75 Roviello G, Sobhani N, Corona SP et al. Corticosteroid switch after progression on abiraterone acetate plus prednisone. *Int J Clin Oncol.* 2020; 25(2): 240-46.
76 Romero-Laorden N, Lozano R, Jayaram A et al. Phase ii pilot study of the prednisone to dexamethasone switch in metastatic castration-resistant prostate cancer (mcrpc) patients with limited progression on abiraterone plus prednisone (switch study). *British Journal of Cancer.* 2018; 119(9): 1052-59.

77 Fenioux C, Louvet C, Charton E et al. Switch from abiraterone plus prednisone to abiraterone plus dexamethasone at asymptomatic psa progression in patients with metastatic castration-resistant prostate cancer. *BJU Int.* 2019; 123(2): 300-06.
78 Beer TM, Armstrong AJ, Rathkopf DE et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med.* 2014; 371(5): 424-33.
79 Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med.* 2012; 367(13): 1187-97.
80 Shore ND, Chowdhury S, Villers A et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (terrain): A randomised, double-blind, phase 2 study. *The Lancet Oncology.* 17(2): 153-63.
81 Penson DF, Armstrong AJ, Concepcion R et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: The strive trial. *Journal of Clinical Oncology.* 2016; 34(18): 2098-106.
82 Khalaf DJ, Annala M, Taavitsainen S et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: A multicentre, randomised, open-label, phase 2, crossover trial. *The Lancet Oncology.* 2019; 20(12): 1730-39.
83 de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. *Lancet.* 2010; 376(9747): 1147-54.
84 Eisenberger M, Hardy-Bessard A-C, Kim CS et al. Phase iii study comparing a reduced dose of cabazitaxel (20 mg/m2) and the currently approved dose (25 mg/m2) in postdocetaxel patients with metastatic castration-resistant prostate cancer—proselica. *Journal of Clinical Oncology.* 2017; 35(28): 3198-206.
85 Oudard S, Fizazi K, Sengeløv L et al. Cabazitaxel versus docetaxel as first-line therapy for patients with metastatic castration-resistant prostate cancer: A randomized phase iii trial—firstana. *Journal of Clinical Oncology.* 2017; 35(28): 3189-97.
86 de Wit R, de Bono J, Sternberg CN et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *New England Journal of Medicine.* 2019; 381(26): 2506-18.
87 Chang SS. Overview of prostate-specific membrane antigen. *Rev Urol.* 2004; 6 Suppl 10(Suppl 10): S13-S18.
88 Bouchelouche K, Choyke PL and Capala J. Prostate specific membrane antigen- a target for imaging and therapy with radionuclides. *Discov Med.* 2010; 9(44): 55-61.
89 Lenzo NP, Meyrick D and Turner JH. Review of gallium-68 psma pet/ct imaging in the management of prostate cancer. *Diagnostics (Basel).* 2018; 8(1).
90 Sartor O, de Bono J, Chi KN et al. Lutetium-177-psma-617 for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2021; 385(12): 1091-103.
91 Hofman MS, Emmett L, Sandhu S et al. [(177)lu]lu-psma-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (therap): A randomised, open-label, phase 2 trial. *Lancet.* 2021; 397(10276): 797-804.
92 Pluvicto [package insert]. millburn, nj: advanced accelerator applications USA, inc.; 2022.
93 Parker C, Nilsson S, Heinrich D et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013; 369(3): 213-23.
94 Smith M, Parker C, Saad F et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (era 223): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology.* 2019; 20(3): 408-19.
95 Kantoff PW, Higano CS, Shore ND et al. Sipuleucel-t immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010; 363(5): 411-22.
96 Corn PG, Heath EI, Zurita A et al. Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: A randomised, open-label, phase 1-2 trial. *Lancet Oncol.* 2019; 20(10): 1432-43.
97 Hussain M, Mateo J, Fizazi K et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *New England Journal of Medicine.* 2020; 383(24): 2345-57.
98 Abida W, Patnaik A, Campbell D et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a brca1 or brca2 gene alteration. *J Clin Oncol.* 2020; 38(32): 3763-72.

99 Michaelson MD, Kaufman DS, Lee H et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007; 25(9): 1038-42.
100 Greenspan SL, Nelson JB, Trump DL et al. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: A randomized trial. *Annals of internal medicine.* 2007; 146(6): 416-24.
101 Smith MR, Egerdie B, Hernandez Toriz N et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med.* 2009; 361(8): 745-55.
102 Saad F, Gleason DM, Murray R et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *Journal of the National Cancer Institute.* 2002; 94(19): 1458-68.
103 Saad F, Gleason DM, Murray R et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *Journal of the National Cancer Institute.* 2004; 96(11): 879-82.
104 Smith MR, Halabi S, Ryan CJ et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: Results of calgb 90202 (alliance). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014; 32(11): 1143-50.
105 Himelstein AL QR, Novotny PJ, et al. Calgb 70604 (alliance): A randomized phase iii study of standard dosing vs. Longer interval dosing of zoledronic acid in metastatic cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2015; 33(suppl): abstract 9501.
106 Fizazi K, Carducci M, Smith M et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomised, double-blind study. *Lancet.* 2011; 377(9768): 813-22.
107 Smith MR, Saad F, Coleman R et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: Results of a phase 3, randomised, placebo-controlled trial. *Lancet.* 2012; 379(9810): 39-46.
108 Saylor PJ, Armstrong AJ, Fizazi K et al. New and emerging therapies for bone metastases in genitourinary cancers. *European urology.* 2013; 63(2): 309-20.
109 Keating NL, O'Malley AJ and Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006; 24(27): 4448-56.
110 Skolarus TA WA, Erb NL et al. . American cancer society prostate cancer survivorship care guidelines. *CA: A Cancer Journal for Clinicians.* 2014; 64(4): 225-49.
111 Denlinger CS CR, Are M et al. Survivorship: Sexual dysfunction (male). *Journal of the National Comprehensive Cancer Network.* 2014; 12(3): 356-63.

