Prostate Cancer: Advanced and Metastatic Disease

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1. Introduction

- Prostate cancer is the second most common cancer and second leading cause of cancer deaths among men in the United States.
- While most cases are localized, the number of men presenting with and progressing to metastatic disease is increasing[1-2]
- Most prostate cancer deaths occur in men with the most advanced stage of the disease, namely metastatic castration-resistance prostate cancer (mCRPC)
- Advanced prostate cancer can be diagnosed in two cohorts of men: (1) those presenting with de novo metastatic disease and (2) those progressing to advanced disease therapy with curative intent
- Advanced prostate cancer in men following localized therapy can be further characterized into four disease states:
  - **Biochemical recurrence onl**y without evidence of clinical metastatic disease based on cross-sectional imaging with axial computed tomography (CT) or magnetic and technetium bone scan (BS)
  - **Metastatic castration-sensitive prostate cancer (mCSPC)**
  - **Non-metastatic CRPC (nmCRPC)**
  - **Metastatic CRPC (mCRPC)**
- Historically, the median survival of men with mCRPC was less than 2 years, but with the advent of novel agents and introducing them earlier in the disease process, the r
- Androgen deprivation therapy (ADT) has been the mainstay of therapy for advanced prostate cancer. However, it was not until the introduction of the cytotoxic chemothe 2004, that treatment options with survival benefit began to emerge
- The AUS/ASTRO/SUO 2020 Guidelines on **Advanced Prostate Cancer** provides a comprehensive review of the evaluation, counseling and treatment of men within eac disease state
  - **GU Podcast (2020): Advanced Prostate Cancer: AUA/ASTRO SUO Guideline Podcast Part 1**
  - **GU Podcast (2020): Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline Podcast Part 2**
- Current challenges in the management of advanced prostate cancer include:
  - the role of the next generation of imaging modalities such as positron emission tomography (PET)-CT imaging in defining metastatic disease[4]
  - Timing and sequencing of these agents

1.1 Androgen deprivation therapy (ADT)

- ADT is the foundation of all treatments in men with advanced prostate cancer
  - The dependence of prostate cancer cells on testosterone was established by Huggins and Hodges[5]
- **Testosterone suppression or castration in advanced prostate cancer is associated with prolonged time to disease progression and improved survival**[6-7-8-9]
- **Castration is typically defined as a testosterone level less than 50 ng/dL**; however, there are many proponents for lowering this threshold to 20 ng/dL due to the imp survival, cancer-specific survival and overall survival observed below this testosterone level[9-10]
- In comparison to various forms of chemical castration, **bilateral orchiectomy is associated with a testosterone level of 15 ng/dL**[11]
- **Dihydrotestosterone is the principal androgen found in the prostate** and is at least 10 times more potent than testosterone in stimulating the androgen receptor (AR
- Inhibition of androgen signaling is based on three strategies:
  - **Suppression of the testosterone production via hypothalamic-pituitary-gonadal axis** (e.g. luteinizing hormone releasing hormone (LHRH) agonists and antag
    - Pulsatile release of LHRH from the hypothalamus results in the release of LH from the pituitary gland which stimulates receptors on Leydig cells in the testes
    - Disruption of LHRH pulsatile release through either continuous circulatory exogenous LHRH (agonist) or blockage of the LHRH receptors on the pituitary (ant testosterone production
  - **Inhibition of enzymes involved in androgen biosynthesis**:
    - Testosterone biosynthesis begins with the substrate **cholesterol** and involves a number of enzymes including 17a hydroxylase and c-17,20 lyase which are t 17A1 inhibitors, e.g., abiraterone[12]
  - **Inhibiting AR** (e.g. bicalutamide, enzalutamide, apalutamide, darolutamide):
    - Testosterone activity is mediated through activation of the AR
    - AR resides in the cytoplasm of prostate cancer cells and can be activated by any number of other ligands, most commonly, dihydrotestosterone[12]
    - Once activated, AR translocates to the nucleus where it binds to the androgen response element on the DNA to promote the transcription of AR target genes cell growth and survival
- ADT and localized prostate cancer
  - Adjuvant ADT is recommended in men with intermediate and high risk localized prostate cancer treated with external beam radiation or external beam radiation and
  - May be used in men with low risk or favorable intermediate risk prostate cancer with large prostate glands (>60 mL) who opt for **brachytherapy**[14]
- ADT may be considered for men with lymph node positive prostate cancer after radical prostatectomy.
- ADT and advanced prostate cancer (4 cohorts)
  - Biochemical recurrence only
    - Men with non-metastatic biochemical relapse are treated with observation (recommended). In select patients with non-metastatic biochemical relapse, treatm ADT such as an LHRH agonist or antagonist, either continuously or in an intermittent fashion.[15]
    - Clinical presentation and patients' priorities regarding quality of life dictate ADT initiation in these scenarios.
  - Androgen receptor blockade alone with such drugs as bicalutamide is **not** a standard-of-care option for men with biochemical recurrence or beyond, although it ma scenarios based on risk and patient preferences.[16]
  - No definitive level 1 evidence exists to support use of early ADT in regard to an overall survival benefit, although a recent underpowered trial (TOAD) suggested ea
  - The addition of an antiandrogen to LHRH therapy is an option but is controversial with no single trial proving a significant benefit to such a maneuver with a noted ir
  - mCSPC
    - In cases where patients present with metastatic prostate cancer and are naïve to ADT, they are generally considered to be mCSPC but following a period of A

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ADT, the disease will

eventually develop into mCRPC.
- Data from the control arm of the STAMPEDE trial demonstrates that median failure free survival (FFS) for men with newly diagnosed mCSPC treated with AD 2-year FFS of 29%. Median OS was 42 mo; 2-yr OS was 72% (95% CI, 68-76). Survival time was associated with performance status, age, Gleason score, a Median survival after FFS event was 22 mo.[19]
- Prior to the development of castration resistance, ADT in combination with other agents are recommended (discussed below)

- mCRPC
  - **The median survival of CRPC is 15-36 months based on the extent of the presenting disease burden at the time of diagnosis with initial ADT resist**
  - It remains unclear why prostate cancer progresses to castration resistance. However, several mechanisms of resistance have been identified.[21]
  - **Mechanisms of castration resistance include**:
    - The ability of prostate cancer cells to utilize intracellular androgens via de novo synthesis or obtain it exogenously from the adrenal glands and tumor m
    - Increased androgen receptor (AR) expression
    - AR gene mutations that allow the receptor to be activated by other ligands other than androgens such as glucocorticoids
    - Alterations of AR signaling to promote tumor growth
    - Synthesis of AR variants such as **AR-V7** that are constitutively active even in the absence of ligands.[21]

- **ADT has a number of side-effects including:**
  - **Vasomotor symptoms**
  - **Weight gain**
  - **Bone density loss**
  - **Metabolic syndrome**
  - **Sexual dysfunction**
  - **Fatigue**
  - **Muscle mass loss**
  - **Cognitive decline**
  - **Depression**
  - **Increased risk of suicidality**
- **Strategies to mitigate those symptoms include:**
  - **Bone-directed agents such as denosumab or zolendronic acid, calcium and vitamin D, exercise**
  - **Medications such as venlafaxine, gabapentin and medroxyprogesterone**.[22]
  - Intermittent ADT may help with sexual dysfunction. The utilization of intermittent ADT is controversial and is often limited to patients with biochemical recurrence on patients.[23]
- **Baseline and periodic bone density testing (e.g., DEXA Scan) should be performed for any patient receiving ADT**.
- Selecting the correct sequence and type of systemic treatment in advanced prostate cancer must account for prostate cancer heterogeneity and identification of potential example, identifying CRPC patients with AR-V7 variants known to be associated with primary or acquired resistance to second line ADT agents such as abiraterone and the selection of more likely effective therapeutic regimens. [24]

25,26,27

2. Treatment Strategies for Metastatic Castration-Sensitive Prostate Cancer

- ADT as monotherapy had been the mainstay of treatment for men with metastatic prostate cancer for decades until clinical trials with **combination therapies including** overall survival in this population (**Table 1**)
- **Combination docetaxel and ADT was shown to improve survival in men with mCSPC as compared to ADT in two clinical trials (CHAARTED, STAMPEDE). The a statistically significant difference in survival with combination docetaxel and ADT versus ADT alone but there was a trend favoring improved overall surviva treatment in men with high volume disease.**
- Combination antiandrogens (abiraterone, enzalutamide and apalutamide) and ADT were also shown to improve survival as compared to ADT alone.
- Given the variety of treatment options for this disease, patient selection, disease severity, and treatment-related side effects have emerged as important factors that infor
  - Patient selection:
    - Identifying patients who harbor metastatic disease will be influenced by improved detection with emerging imaging modalities such as prostate specific memb emission tomography (PSMA-PET)
    - Definition of castrate sensitivity may change as the biology of castration resistance is better understood
  - Disease severity:
    - Clinical trials have introduced terms such as disease volume (CHAARTED) and disease risk (LATITUDE) as important parameters to determine who is likely t treatments
  - Treatment-related side effects
- In addition to these systemic treatment options, there is emerging evidence for a beneficial role for localized treatments (radiation) in select patients[28] with oligometastatic
- Radical prostatectomy for patients with metastatic prostate cancer is considered investigational and is the subject of several ongoing clinical trials.
  - Retrospective single-arm data from large registries has demonstrated safety and feasibility of treatment of the primary tumor in patients with metastatic prostate car associated with improved survival.[29]
  - Several clinical trials seeking to address this issue are currently accruing, including SWOG 1802, a Phase III Randomized Trial of Standard Systemic Therapy (SST Therapy plus Definitive Treatment (Surgery or Radiation) of the Primary Tumor in Metastatic Prostate Cancer.
- Salvage lymphadenectomy following radical prostatectomy is an additional ongoing area of clinical interest, particularly as novel imaging modalities such as PSMA PET r oligometastatic lesions, including pelvic lymph nodes.
  - Retrospective data suggests salvage lymph node dissection may be associated with prolonging biochemical relapse-free survival in appropriately selected patients.
  - **Salvage lymph node dissection can be considered as a component of a multi-modal approach; however, data have yet to clearly demonstrate cancer-sp benefit.[30]**
- Managing patients with mCSPC must be based on adequate imaging to correctly ascertain the presence and burden of metastatic disease, tailoring systemic and localize on disease volume, and limiting treatment related side effects.
- Also see:
  - GU Podcast (2020): Advanced Prostate Cancer: AUA/ASTRO SUO Guideline Podcast Part 1
  - GU Podcast (2020): Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline Podcast Part 2
  - **Metastatic Hormone Sensitive Prostate Cancer - Expert Guidance For Urologists**

2.1 ADT Plus Docetaxel

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- Several large phase III trials evaluated docetaxel chemotherapy in combination with ADT for men with metastatic prostate cancer (recurrent or de novo).
  - **CHAARTED TRIAL - ECOG 3805**
    - 790 men with newly diagnosed mCSPC were randomized to ADT alone vs. ADT plus 6 cycles of docetaxel. At median follow-up of 53.7 months, the median O 57.6 months in favor of the ADT + docetaxel arm (HR 0.72, (0.59-0.89), P=0.0018).[31-32-33]
    - **Further analysis showed the benefit was seen in men with high-volume disease (defined as > 4 bone metastases with at least one outside of the ax metastasis), but not in those with low-volume disease**.
    - Among the men with high-volume disease, the median OS in the chemo-hormonal group was 51.2 months vs 34.4 months in the ADT alone group (HR, 0.63; .001).[33]
  - o **STAMPEDE Trial**
    - Multi-arm, multi-stage trial of close to 3000 men, wherein the addition of docetaxel to ADT improved OS. In the subset of 1086 men with metastatic disease, tl undergoing ADT alone was 45 months compared to 60 months in the ADT plus docetaxel arm (HR 0.76 (0.62-0.92), P=0.005).[34]
    - **Long-term data on 1086 participants with mCSPC showed a significant reduction in risk of death in the ADT plus docetaxel arm (HR 0.81 (0.69-0.95** difference in docetaxel effect between low-volume and high-volume disease (P interaction=0.827).[35]
  - o **GETUG-AFU 15 Trial**
    - Randomized, open-label phase 3 study of 385 patients that did **not** demonstrate statistically significant improvement in survival with the addition of docetaxel months in the ADT with docetaxel group, and 54.2 months in the ADT alone group (HR 1.01, 95% CI 0.75-1.36).[36]
    - Based on results of other similar studies, a post hoc analysis of GETUG-AFU 15 was done evaluating potential differences between low-volume and high-volu **the high-volume group, a non-significant 20% reduction in risk of death was noted in the docetaxel group, leading authors to conclude that chemo discussed with these patients.**[37]
    - **Meta-analysis of CHAARTED and GETUG-AFU15, showed no benefit of docetaxel in patients with low-metastatic burden.** For patients with high-volur improved survival was observed in patients receiving docetaxel (HR 0.68 ([95% DI 0.56-0.82]; p<0.001).[38]

2.2 ADT Plus Antiandrogen Therapies

- **ADT plus Abiraterone**
  - Two large phase III trials have evaluated the use of abiraterone acetate in addition to ADT at the time of diagnosis of either de novo mCSPC or those with high-risk cancer.
  - In the **LATITUDE** study, 1,199 men with de novo metastatic prostate cancer and with 2 of 3 high risk features (visceral disease, Gleason score of ≥ 8, presence of were randomized to ADT with abiraterone or placebo. **Interim analysis showed a marked benefit in the abiraterone plus ADT group with a prolongation of ra progression-free survival and a 38% reduction in the risk of death compared to ADT and placebo**.[39] A follow-up report was subsequently published confirmin abiraterone. At a median follow-up of 51.8 months, OS was 53.3 months (48.2-not reached) in the abiraterone plus ADT arm, and 36.5 months (33.5-40) in the ADT **hazard ratio (HR) of 0.66 (95% CI, 0.56-0.78, P<0.0001)**.[40]
  - Similarly, although in a more heterogeneous population (52% metastatic, 20% node positive non-metastatic, and 28% very high risk localized or biochemically recu demonstrated that at a median follow-up of 40 months, abiraterone in addition to ADT led to an OS benefit in a group of 1,917 men. A 37% relative improvement in **of 0.63 (95% CI, 0.52-0.76, P < 0.0001)**.[41]
- **ADT Plus Enzalutamide**
  - Enzalutamide is a novel androgen receptor signaling inhibitor that has previously shown effectiveness in CRPC and is now also approved for the treatment of mCS
  - The recently published **ENZAMET** trial randomized 1125 mCSPC patients to receive ADT plus standard nonsteroidal anti-androgens or ADT plus enzalutamide. Th the enzalutamide group and 72% in the control group. At a median follow-up of 34 months, the **HR for death was 0.67 (95% CI 0.52 -0.86, P=0.002)** in favor of th However, a higher proportion of patients in the enzalutamide group experienced **adverse events (AEs)**, especially by patients who also received docetaxel.[42]
  - In the **ARCHES** trial, 1150 men received ADT and were randomized to enzalutamide or placebo. **Risk of radiographic progression and death were reduced in group** .[43]
- **ADT Plus Apalutamide**
  - Apalutamide is a nonsteroidal anti-androgen that is approved for the treatment of mCSPC.
  - The phase 3 **TITAN** randomized trial of 1052 men compared ADT plus apalutamide to ADT plus placebo. **An interim analysis showed OS at 24 months was 82 compared to 73.5% in the placebo arm. The HR for death was 0.67 (95% CI 0.51-0.89, P=0.005).** The rate of AEs was similar in the apalutamide and placebo a
- Optimal treatment
  - To date, there has been no head-to-head analysis comparing all four options.
  - **In the STAMPEDE trial, with a median follow up of 4 years, an indirect comparison of arm C (docetaxel) and arm G (abiraterone) did not reveal any differ metastasis-free survival, cancer-specific survival or symptomatic skeletal events** .[45]
  - Several analyses have indirectly compared all 4 options and concluded that there is no treatment option with a better overall survival benefit as compared to the oth **antiandrogens have a better safety profile compared to docetaxel**.[46-47]
- **ADT Plus External Beam Radiation to the primary tumor**
  - Two completed trials (STAMPEDE arm H and HORRAD) evaluated the benefit of external beam radiation to the primary tumor and ADT versus ADT alone in men
  - The **STAMPEDE** randomized trial **arm H** included a comparison of **ADT vs ADT plus external beam radiotherapy in 2061 men with newly diagnosed metasta** Three-year survival was noted to be 81% with radiotherapy and 73% in the control group among men **with low volume metastatic disease burden by CHAARTE 0.52-0.90, P=0.007)**. An improvement in failure-free survival was noted for the radiotherapy group as a whole (including low and high-volume disease) (HR 0.76, 95 **without a survival benefit for all comers**.[28]
  - The phase III HORRAD trial randomized 432 patients with PSA >20 ng/mL and primary bone metastases on bone scan between 2004 and 2014 to ADT with exter (EBRT) or ADT alone. The median PSA was 142 ng/mL with 67% of the patients having ≥ 5 bone metastases. With a median follow up of 47 months, there was no overall survival (45 months in EBRT + ADT group and 43 months in the ADT group (p=0.4). There was an improvement in PSA progression in the radiotherapy grou 0.63-0.97m p=0.02[29].
  - The PEACE-1 trial (NCT01957436) randomized men with de novo mCSPC to one of four arms: ADT + docetaxel, ADT + docetaxel + abiraterone, ADT + docetaxel docetaxel + abiraterone + radiotherapy in a 1:1:1:1 ratio. The estimated primary completion date was August 2021 and study completion date is December 2032.
  - **A recent STOPCAP Systemic Review and Meta-analysis incorporating data from each of these three clinical trials demonstrated no overall improvement addition of radiotherapy to ADT. However, there was improvement in biochemical progression and failure free survival rates with radiotherapy.**[49] **The co that radiotherapy may be offered to men with mCSPC and concomitant low metastatic burden.**

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Table 1. Treatment options for mCSPC

ADT plus	Mechanism of Action	Dosing	Clinical Trials	Low volume	High volume *
Docetaxel	Microtubule inhibitor	75 mg/m2/dose IV x 1 on day 1 of 21-day cycle; 6 cycles	CHAARTED STAMPEDE GETUG-AFU15	+	+
Abiraterone	Nonsteroidal inhibitor of CYP17A1	1,000 mg PO daily; use with prednisone 5 mg PO daily	LATITUDE STAMPEDE	+	+
Apalutamide	Nonsteroidal anti-androgen	240 mg PO daily	TITAN	+	+
Docetaxel, Abiraterone	Microtubule inhibitor Nonsteroidal inhibitor of CYP17A1	75 mg/m2/dose IV x 1 on day 1 of 21-day cycle; 6 cycles 1,000 mg PO daily; use with prednisone 5 mg PO BID	PEACE-1		+/-
Enzalutamide	Androgen receptor signaling inhibitor	160 mg PO daily	ENZAMET ARCHES	+	+
Radiation	DNA damage	2.75 Gy x 20 Fx	STAMPEDE arm H HORRAD PEACE-1	+	

* High volume defined as any visceral mets, >4 bone mets with at least 1 outside of pelvis or spine

3. Treatment Strategies for Non-Metastatic Castrate Resistant Prostate Cancer (nmCRPC)

- **nmCRPC is defined as the patient with a rising PSA despite castrate levels of testosterone following androgen deprivation therapy and no radiographic evide conventional imaging with CT or MRI abdomen/pelvis and bone scan**
- **The goal of treatment is to delay the development of metastatic disease**
- The use of PET-CT imaging is redefining this patient cohort[51]
- **Men with a rapidly rising PSA are at high risk for metastases**.
  - Men are routinely followed with PSA every 3 to 6 months. A PSA doubling time (PSADT) of <10 months is associated with disease progression[52,53]
- Historically, these men were managed with observation if the PSADT >10 months and with hormone therapy when PSADT <10 months
- However, **three randomized controlled Phase III clinical trials, PROSPER, SPARTAN and ARAMIS demonstrated a survival advantage over placebo for combin deprivation therapy with enzalutamide, apalutamide, and darolutamide, respectively (Table 2)**.
- **Bicalutamide** was evaluated against enzalumatide in 2 trials, STRIVE and TERRAIN and found to be inferior and thus **is no longer recommended** for nmCRPC treatm
- Abiraterone plus prednisone is also not recommended as no Level 1 evidence exist for this agent in this specific disease state.

3.1 Enzalutamide

- In PROSPER, a total of 1401 patients with nmCRPC and a PSA doubling time of 10 months or less (mean PSA doubling time 3.7 months) were randomized 2:1 to receiv placebo plus ADT. The median metastasis-free survival (**MFS**) was 36.6 months in the enzalutamide group versus 14.7 months in the placebo group (**HR 0.29, CI 0.24-0.** first use of a subsequent antineoplastic therapy was longer with enzalutamide treatment than with placebo (39.6 vs. 17.7 months; HR 0.21, p<0.001). **The time to PSA p enzalutamide than with placebo** as well (37.2 vs. 3.9 months; HR 0.07; p<0.001).[56] In a follow-up report on the final analysis of overall survival, as of October 15, 2019 enzalutamide group and 38% in the placebo group had died.[57] Median overall survival was 67 months (95% CI, 64 to not reached) in the enzalutamide group and 56.3 mo (HR for death 0.73; 95% CI 0.61 to 0.89, p=0.001). **This corresponded to a 27% lower risk of death in the enzalutamide group**. The exposure adjusted rate of adver higher was 17/100 patient-years and 20/100 patient-years in the enzalutamide and placebo groups respectively. Fatigue and musculoskeletal events were the most repo enzalutamide group.[57]

3.2 Apalutamide

- **In SPARTAN**, a total of 1207 patients with nmCRPC and a PSA doubling time of 10 months or less were randomized 2:1 to receive apalutamide plus ADT or placebo plu primary analysis, median **MFS** was 40.5 months in the apalutamide group as compared with 16.2 months in the placebo group (**HR for metastasis or death 0.28, 95% C** to symptomatic progression was significantly longer with apalutamide than with placebo (HR 0.45, 95% CI 0.32-0.63; p<0.001). The rate of AEs leading to discontinuatior 10.6% in the apalutamide group and 7% in the placebo group (most notably rash).[58] The final overall survival results were recently reported.[59] Given that the study had ac of improved metastasis-free survival with apalutamde, study participants were unblinded and 76 patients in the placebo arm that did not progress were crossed over to th follow-up at time of data cut-off was 52 months with the median duration of treatment lasting longer in the apalatumide arm (32.9 vs 11.5 months for placebo). **The media longer in men treated with apalutamide versus placebo (73.9 vs 59.9 months)** . **This corresponded to a relative risk reduction of 21.6% in the risk of death (HR**

3.3 Darolutamide

- In **ARAMIS**, a total of 1509 patients with nmCRPC, PSA doubling time of 10 months or less, baseline PSA level of 2 ng/mL and an Eastern Cooperative Oncology Group of 0 or 1 were randomized 2:1 to receive oral darolutamide 600 mg twice daily vs. placebo while continuing ADT. Median follow-up was 17.9 months. The median MFS w darolutamide compared to 18.4 months with placebo (**HR 0.41, 95% CI 0.34 to 0.50; p<0.001**). **Risk of death** was lower with the darolutamide group **HR 0.71, 95% CI 0.5** to pain progression was longer in the darolutamide group (median 40.3 months vs 25.4 months); HR 0.65; 95% CI 0.53 to 0.79, p<0.001. Time to first cytotoxic chemothe darolutamide group and was 38.2 months in the placebo group (HR 0.43 95% CI 0.31 to 0.60; p<0.001). Darolutamide treatment was superior to placebo with respect to skeletal event (HR 0.43 95% CI 0.22 to 0.84; p =0.01). Additional exploratory end points favored darolutamide over placebo including for progression-free survival, time t first prostate cancer-related invasive procedure and time to initiate subsequent anti-neoplastic therapy. Serious AEs occurred in 15.8% patients in the darolutamide group group. The percentage of patients who discontinued treatment due to AEs were similar between the two groups at 8.9% for darolutamide and 8.7% for placebo.[60]

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PSA progression, time to
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Table 2. Treatment options for nmCRPC

ADT Plus	Mechanism of Action	Dosing	Clinical Trials	Specific P
Enzalutamide	Androgen receptor signaling inhibitor	160 mg PO daily	PROSPER	PSA doubli
Apalutamide	Androgen receptor signaling inhibitor	240 mg PO Daily	SPARTAN	PSA doubli
Darolutamide	Androgen receptor signaling inhibitor	600 mg PO BID	ARAMIS	PSA doubli

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4. Treatment Strategies for Metastatic Castration-Resistant Prostate Cancer (mCRPC)

- **Castration resistance is defined by serum testosterone level < 50 ng/dl or 1.7 nmol/L plus one of the following definitions of progression**:
  - **Biochemical progression: 3 consecutive rises in PSA at least one week apart, resulting in 25% increases over the nadir, and PSA greater than 2 ng/mL**
  - **Radiographic progression: The appearance of new lesions: Either 2 or more new bone lesions on a bone scan and confirmed by other imaging modality ambiguous or a soft tissue lesion measurable using RECIST criteria**[61,62]
- mCRPC requires the presence of radiographic bone or soft tissue lesions.
- Choice of therapy in this setting will be dependent, in part, on prior therapy.
- Level 1 evidence exists for the use of:
  - **Abiraterone acetate plus prednisone**,[63,64,65,66] **enzalutamide**,[67,68] **docetaxel**,[69,70,71,72] **sipuleucel-T**,[73,74] **cabazitaxel**,[75], **Radium-223**[76,77], **and** ^{177}**Lu-PSMA-617**[78] **in the f 3)**
  - Germline testing for *BRCA1, BRCA2, ATM, PALB2* and *CHEK2* mutations in men with metastatic prostate cancer[79,80,81,82,83]
  - Germline & somatic tumor testing for *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2*, and *CDK12* in men with metastatic prostate cancer[84,85,86]
  - **Olaparib for treatment of mCRPC patients following androgen receptor-directed therapy with a pathogenic mutation (germline and / or somatic) in homo (HR)-mediated repair genes: *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D OR RAD54L***[86,87,
  - **Rucaparib for treatment of mCRPC associated with a pathogenic *BRCA1* or *BRCA2* mutation (germline and / or somatic) following treatment with both a therapy and taxane-based chemotherapy**[89,90]
  - Use of bone-protecting agents in men with mCRPC and bone metastases to prevent skeletal related complications[91,92,93]
  - Routine testing for microsatellite instability to determine eligibility for pembrolizumab[79]
- Also see **AUA Update Series Vol. 38, Lesson 26, 2019**[94]

4.1 Novel Hormonal Therapy - Abiraterone Acetate

- **Abiraterone acetate is an inhibitor of androgen biosynthesis** approved for use either prior to or after chemotherapy for mCRPC.
  - **COU-AA-301** was a multinational, phase 3, double-blind placebo-controlled study of 1195 patients with metastatic prostate cancer **previously treated with docetа** according to the criteria of the prostate cancer working group 2 (PCWG2) or radiographic disease progression in soft tissue or bone, ongoing ADT with a castrate le randomized in a 2:1 manner to 1000 mg of abiraterone versus placebo both given with oral prednisone 5 mg twice daily. At the preplanned interim analysis, **abirat reduction in the risk of death** compared with placebo (**HR 0.65; 95% CI 0.54–0.77; p< 0.001**). Median overall survival was 14.8 vs 10.9 months in favor of abirate advantage was consistent across all subgroups (**HR 0.66; 95% CI 0.55-0.78; P less than 0.001**). All secondary endpoints, including PSA response rate, objective re RESIST criteria, time to PSA progression and PFS were statistically improved with abiraterone. The most common AE was fatigue; others included back pain, naus and arthralgia[66]
  - In **chemotherapy-naïve patients**, abiraterone acetate was evaluated in comparison to placebo, both with prednisone, in 1088 men with mCRPC and progression b or radiographic progression;[95] in the phase 3 trial **COU-AA-302** trial.[65] With a median follow up of 22.2 months, abiraterone afforded a significant improvement in rPF months; **HR 0.53; p<0.001**) and the trial was unblinded, with 44% of those initially receiving placebo crossed over to receive abiraterone. The final analysis, with m months, revealed a clinically and **statistically significant improvement in OS for abiraterone** vs placebo (34.7 vs 30.3 months, **HR 0.81 (95%CI 0.70-0.90), p=0** grade 3-4 AEs were cardiac disorders (8% in the abiraterone vs 4% placebo), increased alanine aminotransferase (6% vs < 1%, respectively) and hypertension (5%

4.2 Novel Hormonal Therapy - Enzalutamide

- **Enzalutamide**, an oral **androgen receptor inhibitor** therapy, was initially approved in 2012 for the treatment of mCRPC patients who had previously received docetaxel approved for men with mCRPC who are chemotherapy naïve.[67]
  - **AFFIRM**: Phase 3 double-blind, placebo-controlled study of enzalutamide in men with mCRPC who had been **previously treated with one or 2 chemotherapy re** which contained docetaxel. 1199 patients were randomized in 2:1 fashion to enzalutamide or placebo respectively. At the time of prespecified interim analysis, ther **the risk of death** for enzalutamide compared with placebo (**HR 0.63; 95% CI 0.53-0.75; p< 0.001**). mOS was 18.4 months for enzalutamide versus 13.6 months fo was seen in all patient subgroups including the stratified according to age ECOG performance status, extent of disease on diagnostic imaging, biochemical measur adjustment for baseline factors. The IDMC recommended the study be halted and unblinded, with eligible patients in the placebo group offered treatment with enza incidence in the enzalutamide arm included fatigue, diarrhea, hot flashes, musculoskeletal pain and headache[68]
  - **PREVAIL**: Phase 3, double-blind, placebo-controlled study of enzalutamide in 1717 men with mCRPC who were **chemotherapy naïve**. An interim analysis of 540 significant benefit for enzalutamide over placebo, with a **30% reduction in risk of death (HR 0.70 (95% CI: 0.59-0.83); p< 0.0001)** and an 81% reduction in risk of **0.19 (95% CI: 0.15-0.23); p< 0.0001**). The IDMC recommended stopping the study and crossing placebo patients to enzalutamide.[67] Final analysis revealed a medi enzalutamide vs 5.4 months in the placebo arm. Median OS was 35.3 months (95% CI 32.2-not yet reached) in the enzalutamide arm and 31.3 month (95% CI 28.8 At the time of the OS analysis, 167 patients in the placebo arm crossed over to receive enzalutamide. The most common AEs with enzalutamide or fatigue, back pa arthralgia.[95,96,97]

4.3 Chemotherapy - Mitoxantrone

- **Mitoxantrone is an anthracycline chemotherapy** that acts during multiple phases of the cell cycle to **disrupt DNA synthesis and DNA repair**.
  - **In a randomized trial assessing** palliation of cancer related pain, mitoxantrone plus prednisone was shown to be superior to prednisone alone in overall palliative **p=0.01**)[98] in a randomized trial of symptomatic mCRPC patients with a primary endpoint of decreased pain.[98]
  - A subsequent study, CALGB 9182 did not reveal a survival benefit of mitoxantrone + hydrocortisone vs hydrocortisone alone.[99]
  - Given the palliative benefit, mitoxantrone plus prednisone was utilized as a control arm in later studies assessing docetaxel first line for mCRPC[70,71] and cabazitaxel
  - **There is currently no role for mitoxantrone in the treatment of mCRPC.**

4.4 Chemotherapy - Docetaxel

- **Docetaxel is a second-generation taxane** chemotherapy that **inhibits microtubule assembly** into the mitotic spindle, thus **arresting the cell cycle during G2/M phas** increase apoptosis by **downregulation of the BCL2 gene**, which tends to be over-expressed in cancer cells.
  - **TAX 327**: Phase 3 trial consisting of 1006 men randomized to mitoxantrone plus prednisone vs weekly docetaxel plus prednisone vs q3 week docetaxel plus predn statistically significant **survival advantage for every 3 week docetaxel** vs mitoxantrone plus prednisone with median OS 18.9 months vs 16.5 months, respectivel **0.62-0.94, p=0.009**), but not for weekly docetaxel vs mitoxantrone plus prednisone with median OS 17.4 months vs 16.5 months, respectively (**HR 0.91, 95% CI 0.7** updated analysis confirmed 19.2 vs 16.3 months (**HR 0.79, p=0.009**) survival advantage for docetaxel every 3 weeks.[72]
  - **SWOG 9916**: Phase 3 trial randomizing 674 eligible patients to docetaxel plus estramustine or to mitoxantrone plus prednisone. **Docetaxel plus estramustine** pro median OS than mitoxantrone plus prednisone (17.5 months vs 15.6 months, p=0.02, **HR 0.80 [95% CI 0.67 to 0.97]**).[71]
  - **Docetaxel re-challenge**: While commonly used in the early years after the approval of docetaxel for mCRPC and prior to the development of cabazitaxel or the ne docetaxel re-challenge is rarely attempted now. However, a retrospective study evaluated 62 patients who had previously received docetaxel-based chemotherapy

r (e.g., CT or MRI) if

reatment of mCRPC (Table

logous recombination
[88]
ndrogen receptor-directed

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based on PCWG2 definition
S (median 16.5 vs 8.2
edian follow up of 49.2
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with docetaxel. 61% of patients were eligible for re-challenge with a second docetaxel sequence and 35% were eligible for a third docetaxel sequence. The study sl re-challenge could be effective in improving OS in those with treatment free intervals > 3 months and a partial PSA response at re-challenge.[100]

4.5 Chemotherapy - Cabazitaxel

- **Cabazitaxel is a second-generation taxane** with a broader range of cytotoxicity, high potency that **remains cytotoxic for docetaxel-resistant cell lines** due to **gp-1 o** blood-brain penetration than docetaxel.
  - **TROPIC**: Phase 3 study of 755 docetaxel pretreated mCRPC patients randomized to mitoxantrone plus prednisone or to cabazitaxel plus prednisone. The dose of q 21 days. The **median OS was significantly in favor of cabazitaxel** at the first interim analysis, with 30% decreased risk in dying (15.1 vs 12.7 months, **HR = 0.** analyses indicated the highest survival advantage in the most heavily pretreated patients.[75] Subsequently updated data from TROPIC revealed an ongoing > 2 year versus 16%.[101]
  - **FIRSTANA**: Randomized study evaluating cabazitaxel vs docetaxel for first line mCRPC. Due to toxicity of cabazitaxel, FIRSTANA assessed cabazitaxel at 20 mg/ mg/ml (C25) compared to docetaxel 75 mg/m^2. The primary endpoint was overall survival. The study enrolled 1168 patients and results indicated **no superiority o** chemotherapy-naïve mCRPC (**HR 1.01 and 0.97, respectively**). While tumor response was higher with C25, pain PFS was improved with docetaxel. Overall, there compared with C25. [69]
  - **PROSELICA**: Phase 3 randomized non-inferiority trial of 1200 docetaxel pretreated mCRPC patients evaluating cabazitaxel 20 mg/m2 (C20) plus prednisone versu (C25) plus prednisone. C20 was found to be non-inferior in docetaxel-pretreated patients in comparison to C25 for the primary endpoint of overall survival (**13.4 vs** Secondary endpoints were in favor of the C25 arm: PSA50 response rates C20 29.5% vs C25 42.9% (**p < 0.001**); median time to PSA progression C20 5.7 months **1.195**).[102]
  - **CARD:** Phase 3 randomized trial of cabazitaxel 25 mg/m2 (European label) versus abiraterone or enzalutamide in 255 mCRPC patients with prior docetaxel treatm 12 months of receiving either abiraterone or enzalutamide. Imaging-based progression-free survival was the primary endpoint, and secondary endpoints included C radiographic and pain response, time to 1st SRE and safety. With a median follow up of 9.2 months, **median imaging-based PFS was 8 months vs 3.7 months, fa 0.54; p<0.001**], with benefit seen across all pre-specified subgroups. Likewise, **overall survival was superior for cabazitaxel** (**13.6 vs 11.0 months, HR 0.64; p=** 50% was achieved in 35.7 vs 13.5% (P<0.001) of patients in the cabazitaxel vs androgen-signaling-targeted inhibitor arm. Radiographic tumor response was also s vs 12% with androgen-signaling-targeted inhibitor (P=0.004). **Superiority of cabazitaxel persisted regardless of the androgen-signaling-targeted-inhibitor rec**
  - **Cabazitaxel re-challenge:** A multi-institutional, retrospective analysis was performed evaluating the impact of cabazitaxel rechallenge on overall and progression-f pretreated mCRPC patients who underwent 3 or more courses of treatment with varied doses and schedules of cabazitaxel. **mOS was 105 months from mCRPC d initiation of cabazitaxel was 11.8 months for 1st use, 9.6 months for 1st re-challenge and 5.6 months in 2nd re-challenge**. **ORR was 50, 45.5 and 20% for the re-challenges, respectively**. 60-80% of patients at each re-challenge achieved PSA decrease > 50%. Median PFS ranged from 10.2 to 5 months with each subse median overall survival ranged from 43.5 down to 19 months. There were no new safety signals and the authors concluded that multiple cabazitaxel re-challenge in without increased toxicity and can extend mOS.[103]

4.6 Other Considerations – Germline and Somatic Genetic Testing

- Research has indicated that aggressive prostate cancers may be linked to inherited mutations in ***BRCA1***, ***BRCA2***, ***ATM***, ***PALB2*** **and** ***CHEK2***. Germline and/or somatic a repair genes occur in **15-25% of men with mCRPC**.
- Furthermore, a small subset of advanced prostate cancer patients may carry germline and/or somatic mutations in DNA mismatch repair genes, where mutations in ***MSH*** **are found in <5% of mCRPC**.[104]
- The role of somatic versus germline, and mono-allelic versus bi-allelic mutations, is not currently clear.[80-82]
- **Germline genetic testing is recommended for newly diagnosed men with NCCN® high-risk, very high-risk, regional, or metastatic prostate cancer.**[83]
- **Additionally, germline testing is recommended for prostate cancer patients with Ashkenazi Jewish ancestry, family history of a known high-risk germline mut strong family history of prostate cancer, or multiple family members with cancers suggesting possible hereditary breast and ovarian cancer syndrome (breas Lynch syndrome (colorectal, endometrial, gastric, ovarian, pancreatic, small bowel, urothelial, renal or bile duct cancers).**
- The NCCN® also recommends somatic tumor testing for **HR-mediated repair mutations and microsatellite instability (MSI) or mismatch repair deficiency (dMMR)** regional spread or distant metastatic prostate cancer.
- Testing of mCRPC patients may inform therapeutic options as follows:
  - Genetic counseling, surveillance and cascade testing of patient and family members
  - Early use of platinum-based chemotherapy
  - Eligibility for treatment with Poly-ADP ribose polymerase (PARP) inhibitors.[82-88]
  - Eligibility for treatment with pembrolizumab.[79]
- Also see:
  - **GU Podcast (2020): Genetic Testing And Personalized Medicine In Prostate Cancer**
  - **Genomic Testing in Prostate Cancer**

4.7 Poly(adenosine diphosphate-ribose) Polymerase Inhibitor (PARPi) Therapy

- **Poly(adenosine diphosphate-ribose) polymerases (PARPs)** are a large family of 18 proteins which are responsible for facilitating DNA repair caused by either single- repair pathways. Cancer cell survival is dependent upon the ability to replicate DNA and repair DNA replicating errors. **PARP inhibitors cause genomic instability and** inability to repair damaged DNA.
- **Olaparib**
  - **TOPARP-A**: Phase 2 open-label, single-arm, two-stage study evaluated olaparib 400 mg p.o. B.I.D in 50 PARP inhibitor naïve patients, unselected for DNA damag with mCRPC progressing after one or two chemotherapy regimens. The primary endpoint was overall response rate. 16 (33%) patients had DRR mutations; 7 were ATM aberrations, 1 was BRCA1 and FANCA deletion, 1 was CHEK2 and FANCA, 1 PALB2 deletion and 1 HDAC2 aberration. Results included **overall response and median OS was 10.1 months**. Notably, those with DDR mutations had improved ORR, as well as improved median PFS and OS compared to patients without **6%; mPFS 9.8 vs 2.7 months, p<0.001; mOS 13.8 vs 7.5 months, p=0.05**).[86]
  - **TOPARP-B**: Randomized phase 2 study comparing olaparib 300 mg p.o. BID vs olaparib 400 mg p.o. B.I.D in pretreated mCRPC patients with up to 2 prior taxane tumors had a putatively pathogenic mutation or homozygous deletion in a DDR gene associated with sensitivity to PARP inhibition therapy. The primary endpoint w response, by second consecutive assessment no earlier than 4 weeks later and defined as any the following: radiological objective response by RECIST 1.1; a 50% PSA; conversion of circulating tumor cell count from > 5 cells/7.5 ml blood to < 5 cells/7.5 ml blood. Of 592 patients with evaluable tissue samples, 161 (27%) had D next generation sequencing (NGS); most commonly BRCA2 (7%), ATM (7%) and CDK12 (6%), and 92 were evaluable for primary endpoint. Overall **confirmed co** improved, but not significantly, in favor of the 400 mg BID dose (**54.3 vs 39.1%, p=0.14**); however, this met the predefined criteria for success. **Median PFS** ranged depending upon DDR mutation, with BRCA1/2 mutations representing the longest mPFS.[87]
  - **PROFOUND**: 2:1 randomized phase 3 trial evaluating olaparib vs treating physician choice of enzalutamide or abiraterone in patients with mCRPC who had diseas either enzalutamide or abiraterone. All patients carried at least one qualifying alteration in prespecified HR-mediated repair genes (BRCA1, BRCA2, ATM, BRIP1, E

CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L). Cohort A included those with at least 1 alteration in BRCA1, BRCA2 or ATM while with alterations in any of the 12 other prespecified genes. The primary end point was imaging-based PFS, assessed by independent review committee, in cohort A, the overall population was a secondary endpoint. The trial randomized 387 patients: 162 in Cohort A and 94 in Cohort B. For Cohort A, olaparib resulted in a statisti **imaging-based PFS vs control** (7.4 vs 3.6 months; **HR 0.34; p<0.001**). **Confirmed ORR** was also significant in favor of olaparib (**33 vs 2%, p<0.001**). Olaparib re 36% in an interim survival analysis vs control (**HR 0.64; p=0.02**). For the overall population, there was a significantly longer median imaging-based PFS (**HR 0.49;** control group.[88]

- **Rucaparib**
  - **TRITON2**: Phase 2 study of rucaparib, 600 mg p.o. B.I.D., in 115 patients with mCRPC and disease progression following androgen receptor-signaling directed the taxane-based chemotherapy who also had a somatic or germline mutation in one or more prespecified homologous recombination genes (*BRCA1, BRCA2, ATM, B CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51D or RAD54L*). 3 cohorts were defined: Cohort A had BRCA1/2 or ATM mutation and measurable viscera Cohort B had BRCA1/2 or ATM mutation without measurable or nodal disease; Cohort C had a mutation in any of the other HR genes with or without measurable d each cohort was response rate; ORR based on RECIST 1.1 criteria for cohorts A & C and PSA response (> 50% decrease) in cohort B. At a median duration of foll **and ORR in BRCA mutated patients were 53.6% and 40%**, respectively. Accelerated FDA approval was granted based on ORR 44% and duration of response 1 assessed in the 62 patients with measurable disease.[90] **TRITON3**: Ongoing phase 3 randomized trial evaluating rucaparib compared to physician's choice of therapy patients with mCRPC and specific gene alterations including BRCA and ATM who have progressed on one prior androgen-receptor targeted therapy. The primary e progression free survival (rPFS).[89]

4.8 Immunotherapy - Pembrolizumab

- In 2017, pembrolizumab was granted accelerated FDA approval for treatment of advanced solid tumors, including prostate cancers, that were microsatellite instability-hig deficient (dMMR) following progression on prior therapies and for which there are no alternative therapy options. In 2020, the FDA extended the accelerated approval to i mutational burden (TMB) greater than 10 mutations per megabase.
  - Approval was based on the outcomes of 5 uncontrolled, open-label, multi-cohort and multi-center single arm trials of pembrolizumab enrolling 149 patients with MS (KEYNOTE-016, -164, -012, -028, and -158). Prostate cancer was significantly underrepresented in these trials. Primary endpoint was ORR, and DOR was a secor MSI-H and dMMR population across all 5 trials, the ORR was 39.6% (7.4% CR and 32.2% PR, SD not reported). DOR was not reached (1.6+, 22.7+ months); how response last at least 6 months.[95]
  - **KEYNOTE-028:** multicenter, phase 1b open-label study of pembrolizumab in patients with PD-L1 positive (>1% of tumor or stromal cells) advanced solid tumors. **2 positive mCRPC** were enrolled and treated with pembrolizumab 10 mg/kg IV q2 weeks. Co-primary endpoints were ORR, CR and PR, and secondary endpoints in and OS. PSA response was exploratory. At median follow up of 7.9 months (1.4 – 30.3 months), 22 (95.7%) patients had discontinued therapy for progressive disea (4.3%) or due to patient or physician decision (26.1%). **Median ORR was 17.4% (all PR),** with DCR 30.4%. Median time to response was 2.7 months (1.8 – 5.7 mo **13.5 months** (6.5 – 14.2 months). **Median PFS was 3.5 months** (1.7 – 6.5 months) and **median OS 7.9 months** (6.5 – NR). 13% of patients experienced grade 3 discontinuing therapy due to toxicity. The authors concluded that pembrolizumab showed activity in heavily pretreated patients with PD-L1 positive mCRPC.[106]
  - **KEYNOTE-199:** 5 cohort, open-label phase 2 study of pembrolizumab, 200 mg IV q3 weeks for up to 35 cycles, in patients with treatment-refractory mCRPC, previ targeted endocrine therapy and 1 or 2 chemotherapy regimens, including docetaxel. Cohort 1 included patients with PD-L1 positive (CPS > 1) measurable disease, patients with PD-L1 negative measurable disease and cohort 3 included patients with bone-predominant metastasis (PD-L1 positive or negative). The primary endp and 2 separately and combined. Secondary endpoints included DCR; radiographic PFS; PSA response rate; OS in cohorts 1 and 2 combined, cohorts 1, 2 and 3 co separately; DOR for cohorts 1 and 2 combined and separately; safety and tolerability. **260 patients** were enrolled (cohort 1 = 133; cohort 2 = 65; cohort 3 = 59). Pe PCWG3-modified RECIST v1.1, **ORR for cohorts 1 (5%) and 2 (3%) was 5%.** Using **RECIST v1.1**, **DCR was 12% for combined cohort 1 (10%), 2 (9%) and 3 (2 PCWG3-modified RECIST v1.1**, **DCR was 20% for combined cohort 1 (13%), cohort 2 (18%) and cohort 3 (39%)**. **PSA response was 6% cohort 1, 8% coho** however, PSA50 was 9% and PSA90 was 5%. **Median DOR was 16.8 months for combined** cohort 1 (NR, 1.9 - >21.8 months) and 2 (10.6, 4.4 – 16.8 months). **PCWG3-modified RECIST v1.1** ranged from 2.1 to 3.7 (2.0 -4.2) months, and **median OS** ranged from 7.9 to 14.1 (5.9 – 17.6) months among all cohorts.[107]

4.9 Immunotherapy Therapy - Sipuleucel-T

- **Sipuleucel-T** is an immunotherapy product that contains patient-specific autologous dendritic cells loaded ex vivo with a **recombinant fusion protein** consisting of pros **linked to a granulocyte-macrophage colony stimulating factor (GM-CSF)** designed to break immune tolerance to normal tissue antigen PAP.[108]
  - Initial phase 1 and phase 2 studies revealed that sipuleucel-T was reasonably well tolerated with fever as the most common AE (14.7%) after 15 infusions. All patie responses to the recombinant fusion protein used to prepare the vaccine and 38% developed immune responses to PAP. Of 31 patients enrolled, 3 patients had a PSA and another 3 patients had a 25% to 49% decline in PSA. The time to disease progression correlated with development of an immune response to PAP with th received.[109]
  - In **2010, sipuleucel-T was granted FDA approval in the US for the treatment of asymptomatic or minimally symptomatic mCRPC** based on **IMPACT**, a phas placebo-controlled study of sipuleucel-T revealed a survival benefit in 512 patients with asymptomatic or minimal symptomatic mCRPC. Median OS was 25.8 mont 21.7 months in the placebo arm (**HR 0.78; p = 0.03**) after a median of 34 months follow up. **There was no PSA decline and there was no difference in PFS in ei** cytokine related toxicity was increased in the sipuleucel-T group; however, grade 3-4 toxicity was similar in both groups.[99]

4.10 Radium-223

- **Radium-223** is an isotope of radium that emits a low level of **alpha particle radiation** with an affinity for sites of bone metastases. It has a half-life of 11.4 days and worl double-stranded DNA breaks.
  - **ALSYMPCA**: Phase 3 randomized in 2:1 manner, double-blind, placebo-controlled study of 921 men with mCRPC and bone metastases who had received, refused docetaxel. At an interim analysis of 809 patients, RAD-223 significantly **improved OS** vs placebo (mOS 14 vs 11.2 months, **HR 0.70, p=0.002**). The **final analysis** (14.9 vs 11.3 months, **HR 0.70, p<0.001**). Radium has been approved for treatment of mCRPC patients with symptomatic bone metastases and is not indicated for metastases.[77]
  - **ERA 223 Trial**: Randomized Phase 3 trial of Radium-223 plus abiraterone and prednisone vs abiraterone and prednisone alone; however, the trial was closed early **fractures and death** on the combination arm.[110]
  - **There is currently no role for combining Radium-223 with other systemic therapies outside a clinical trial**.

4.11 Lutetium-177

- **Lutetium-177 (^{177}Lu)-PSMA-617** is a radioligand that delivers **beta-particle radiation selectively to PSMA-expressing** cells and their surrounding microenvironment.
- **PSMA (Prostate-specific transmembrane antigen), a transmembrane glutamate carboxypeptidase, is highly expressed on prostate cancer cells, with high exp independent biomarker of poor prognosis in both early- and late-stage disease.**
- High expression of PSMA has been correlated independently with decreased survival in metastatic castrate-resistant prostate cancer.[111,112]
  - Early-phase studies of ^{177}Lu-PSMA-617 in subjects with progressive mCRPC revealed encouraging biochemical and radiographic response rates along with improv toxicity following standard therapies.[113,114]

- **VISION Trial:** Phase 3 randomized 2:1 trial of ^{177}Lu-PSMA-617 every 6 weeks x 4 cycles plus protocol permitted SOC vs SOC alone in 831 patients with ^{68}Ga-PSM no PSMA-negative lymph node, visceral organ or bone lesions with soft tissue components meeting RECIST 1.1 measurable disease criteria and previously treatec receptor pathway inhibitors *and* 1 or 2 taxane chemotherapy regimens. Protocol-permitted SOC therapy *excluded* chemotherapy, immunotherapy, radium-223 and investigational at the time of VISION study design. Initial primary endpoint was overall survival; however, after an early high drop-out rate in the SOC control arm, ir free survival was added as an alternate end point following discussion with the FDA. Secondary end points included ORR and DCR. Overall survival analysis incluc whereas, due to the high early dropout rate, imaging-based PFS and key secondary endpoints were analyzed in subjects randomized after the amendment in prima met all eligibility and were randomized. At time of presentation at ASCO 2021, **mOS was 15.3 months in the ^{177}Lu-PSMA-617 group vs 11.3 months** in the contro **p<0.001]**. **Imaging-based PFS** was superior in the ^{177}Lu-PSMA-617 group at **8.7 vs 3.4 months [HR 0.40; 0.29-0.57; p<0.001]**. Overall, there was a low incidence leading to dose reduction, interruption, or discontinuation in the ^{177}Lu-PSMA-617 group.[78]
- In a post-hoc exploratory analysis presented at the ASCO 2022 meeting, VISION investigators presented data on the consistency of treatment effect in subgroups c concomitant cancer-directed therapies. **Consistent benefit for overall survival and imaging-based PFS with ^{177}Lu-PSMA-617 was observed whether patients androgen receptor pathway inhibitor, bone health agents, or radiation therapy.** Similarly, consistent benefit for overall survival and imaging-based PFS was ol therapies including androgen receptor pathway inhibitors, taxane and non-taxane chemotherapy, immunotherapy, bone health agents, radium-223, or PARP inhibit
- In a second VISION sub-study presented at ASCO 2022, overall response, PSA response, imaging-based progression, and overall survival were analyzed as a fun standardized uptake value (SUV) parameters such as tumor load and tumor volume as well as location of PSMA-positive lesions. When divided into quartiles and te analysis, higher whole-body mean SUV was associated with improved imaging-based PFS and overall survival. The absence of PSMA-positive lesions in bone and decreased risk of imaging-based progression and death, as well as higher odds of radiographic response to ^{177}Lu-PSMA-617.
- **TheraP trial:** Phase 2 unblinded, randomized 1:1 trial of ^{177}Lu-PSMA-617 every 6 weeks for up to 6 cycles vs cabazitaxel 20 mg/m^2 every 3 weeks for up to 10 cycl ^{68}Ga-PSMA-11 PET/CT avid mCRPC, no discordant ^{18F}FDG PET positive but ^{68}Ga-PSMA negative lesions at site of measurable disease, and adequate organ func should have received docetaxel and be suitable for cabazitaxel chemotherapy. The initial primary endpoint was the proportion of patients with PSA response, defin least 50% from baseline. Secondary objectives included overall survival, objective response rate per RECIST v1.1 criteria, progression by radiographic or PSA or p life. In the intention to treat analysis, **PSA response occurred in 66% of ^{177}Lu-PSMA-617 treated patients and 37% of cabazitaxel treated patients [difference p<0.001].** Grade 3-4 adverse events occurred in 33% of ^{177}Lu-PSMA-617 treated patients and 53% of cabazitaxel treated patients. ^{177}Lu-PSMA-617 treated patients experienced dry mouth (grade 1-2), dry eyes (grade 1-2), thrombocytopenia (grade 3-4), and less diarrhea, and neutropenia compared to cabazitaxel treated patier presented updated PFS and OS data after a median follow-up of 3 years at ASCO 2022. **^{177}Lu-PSMA-617 treatment significantly delayed radiographic and PS restricted mean survival time for PFS with ^{177}Lu-PSMA-617 treatment was 7.1 months vs 5.0 months for cabazitaxel [HR 0.62, 95% CI 0.45-0.85, p=0.0028 survival was detected between the two treatment arms, with restricted mean survival time of 19.1 months with ^{177}Lu-PSMA-617 treatment and 19.6 montl 0.97, 95% CI 0.70-1.4, p=0.99]**.[117] Notably patients who screen failed due to discordant lesions that were positive by ^{18F}FDG PET scan but negative by ^{68}Ga-PSMA worse overall survival compared to either treatment arm.
- There is interest in combining ^{177}Lu-PSMA-617 with other agents including immunotherapy, with the goal of boosting the otherwise very low activity of immune chec prostate cancer. Investigators from the phase 1 PRINCE trial presented PSA response data from the combination of ^{177}Lu-PSMA-617 and pembrolizumab in 37 pat similar eligibility criteria to the TheraP trial (except docetaxel not required). The PSA response rate, defined as at least 50% PSA response from baseline, was 76% evaluated in subsequent trials.

- On June 16, 2021, ^{177}Lu-PSMA-617 was granted a Breakthrough Therapy Designation by the FDA for the treatment of patients with mCRPC[119], and on March 23, 2022 it treatment of men with PSMA-positive mCRPC following treatment with androgen receptor pathway inhibition and taxane-based chemotherapy.
- There are two available radioligands for **PSMA PET/CT imaging**: ^{68}Ga-PSMA-11 (Illuccix) and ^{18}F-DCFPyl (Pylarify). The initial FDA approval was based on eligibility as ^{68}Ga-PSMA-11 PET/CT imaging.

4.12 Other Considerations - Bone Protective Agents (BPA)

- **90% of metastatic prostate cancer patients will have skeletal involvement**,[120] which leads to skeletal related events (SRE), including severe bone pain, requirement pathologic fracture, or spinal cord compression.
- While prostate cancer bone metastases are predominantly osteoblastic in appearance, there is data to support the idea that **excess osteoclastic activity induces bone**
- **The use of BPA is vital to prevent SREs in prostate cancer patients with bone metastases**.
  - **Bisphosphonates blocks bone destruction**. Early bisphosphonate studies showed no benefit vs placebo in rate of SREs or bone PFS.[121,122] Subsequently, zoled randomized double-blinded study using doses of 4mg, 8mg or placebo every 3 weeks x 15 months in 643 men with CRPC and bone metastases.[91] During the study acid was removed and those patients transferred to the 4mg arm due to increased nephrotoxicity on the higher dose. **The rate of SRE in placebo arm was signifi those receiving 4mg of zoledronic acid (44.2% vs 33.2%, p=0.021)**.[93] **Dosage may need to be decreased for renal function**.
  - **Denosumab is a human monoclonal antibody against RANK ligand (RANKL), acting to inhibit RANKL**, the main driver of osteoclast formation, function and s activity in a placebo-controlled trial,[123] denosumab was studied in a large phase 3 study of 1904 men with mCRPC and no prior bisphosphonate therapy to denosun placebo vs 4 mg zoledronic acid IV plus SQ placebo. **Median time to first SRE was 20.7 months vs 17.1 months in favor of denosumab (p=0.008 for superior** arm had AEs, with serious AEs in 63% denosumab and 60% zoledronic acid. Hypercalcemia occurred slightly more than 2x the rate in zoledronic acid (13% to 6%) infrequent in both arms.[124]

Table 3. Treatment options for mCRPC

Mechanism of Action	Agent	Clinical Trial	Specific Population (if indicated)
Androgen receptor-directed therapies	Abiraterone	**COU-AA-301** **COU-AA-302**	mCRPC
	Enzalutamide	**AFFIRM** **PREVAIL**	
Immune-modulating therapy	Sipuleucel-T	**IMPACT**	Asymptomatic/minimally sympotmatic, no live metastases
Chemotherapy agents	Docetaxel	**TAX 327**	mCRPC
	Cabazitaxel	**TROPIC** **FRISTANA** **PROSELICA** **CARD**	
Poly (adenosine diphosphate-ribose) Polymerase Inhibitor (PARPi)	Olaparib	**TOPARP-A** **TOPARP-B** **PROFOUND**	• DDR mutation following androgen receptor-directed thera
	Rucaparib	**TRITON2** **TRITON3**	• BRCA 1/2 mutation following androgen receptor directed taxane-based chemotherapy
Radioactive / Radioligand therapy	Radium-223	**ALSYMPICA**	• Symptomatic bone metastases
	^{117}Lu-PSMA-617	**VISION**	• PSMA-expressing metastases • FDA breakthrough therapy designation for PSMA-positive
Immunotherapy: PD-L1 inhibitor to induce anti-tumor response	Pembrolizumab	**KEYNOTE-028** **KEYNOTE-199**	Unresectable or metastatic tumor with • Microsatellite instability-high (MSI-H) or • Tumor Mutational Burden-high (TMB ≥ 10 mut/Mb)

5. Metastasis-Directed Therapy

- The role of metastasis-directed therapy (MDT) in oligometastatic prostate cancer continues to evolve with growing evidence from phase II trials in the absence of level 1 e trials are ongoing.
- The **hypothesis of MDT is that the treatment of metastatic lesions could prevent the development of other metastatic lesions and improve survival in those wi**
  - One multicenter, phase II trial (STOMP) of 62 patients with biochemical recurrence after primary definitive treatment with 1-3 documented metastases on non-PET- randomized to observation alone or MDT. MDT could either be surgery or stereotactic body radiotherapy (SBRT). With a median follow-up of 3 years, MDT was ass survival with a median of 21 months compared to 13 months alone. [125] Five-year results were presented in 2020, demonstrating that 5-year ADT-free survival was 8 versus 34% in the MDT group.[126]
  - In studies using novel molecular imaging, one trial included 72 patients with biochemical recurrence after definitive local therapy and negative conventional imaging prostate-specific membrane antigen (PSMA)-PET/CT. Thirty-eight patients were found to have PSMA-detected oligometastatic disease that was felt to be amenabl nodal only (92%) while the rest were bone lesions. Thirty-seven patients agreed to undergo MDT. Ten and 27 patients underwent surgery and SBRT, respectively. 15.9 months, 22% normalized their PSA values (and were effectively biochemical 'no evidence of disease').[127]
  - The use of SBRT as an effective tool for MDT was demonstrated in the SABR-COMET trial.[128] This phase II study included 99 patients with various different primary primary prostate cancer) and were randomized 2:1 to receive standard-of-care therapy plus SBRT to all metastatic lesions or standard-of-care therapy alone. With a months, adding SBRT to standard-of-care therapy resulted in an improvement in five-year overall survival (42% versus 18%, p=0.006).
  - To establish feasibility within prostate cancer specifically, a single-institution study enrolled 33 prostate cancer patients with either castrate-sensitive or castrate-resi (3 or fewer sites of nodal or bony metastases as detected by NaF PET scan) to receive a single fraction of 20 Gy SBRT to each lesion.[129] The 1- and 2-year local co overall, respectively. In 22 patients who had hormone-sensitive disease, freedom from ADT at 24 months was 48%. These data suggest that SBRT to multiple meta feasible, and can potentially delay time to systemic therapy.
  - This was further established in the Observation versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer (ORIOLE) trial. This phase II study rand recurrent, hormone-sensitive oligometastatic prostate cancer (defined as ≤3 lesions by conventional imaging) to either observation or SBRT.[130] Six months post-ran (defined as PSA increase, radiographic progression on conventional imaging, or symptomatic decline) occurred 19% of SBRT patients and 61% of observed patien improved median progression-free survival (not reached versus 5.8 months). Separately, SBRT-assigned patients underwent PSMA-PET/CT at baseline and at 6 m total consolidation of PSMA radiotracer-avid disease, the risk of new lesions was decreased at 6 months (16% versus 63%, p=0.006).
  - There are multiple ongoing, phase II and III trials that will clarify the role of SBRT for oligometastatic prostate cancer (NCT04115007; NCT03449719; NCT0350334
  - Finally, there are trials recruiting patients with oligometastatic prostate cancer to assess combinations of MDT and advanced systemic therapies. One phase II stud therapy (leuprolide, apalutamide, and abiraterone) plus SBRT (NCT03902951). The POSTCARD study will determine the effect of durvalumab in addition to MDT (I evaluate the combination of darolutamide plus SBRT (NCT04641078). An ongoing phase III trial is evaluating the role of apalutamide alone or in combination with M hormone-sensitive prostate cancer patients (NCT04423211).

Presentations

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