Overview Of Advanced Prostate Cancer

Aaron D. Berger, MD
VP and Chief Medical Officer
Associated Urological Specialists

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What is "Advanced" Prostate Cancer?

- Can be defined in different ways
  - Locally Advanced
  - Metastatic
  - Recurrent
- In our advanced prostate cancer clinic, patients meet one of two criteria or both
  - Castrate resistant disease
  - Metastatic disease

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Variations in Who Manages Advanced PCa

- In most academic medical centers, advanced prostate cancer is referred to medical oncology
- In many large independent urology practices, these patients stay in the urology group
  - Urologists have often been following these patients since their initial evaluation and diagnosis of prostate cancer
  - Many independent urology groups of in-office dispensaries (IOD) and can provide many of the medications for advanced prostate cancer
  - Many independent urology practices have radiation centers and can therefore provide radiotherapeutics

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Different Stages of Advanced Prostate Cancer

- Locally advanced
- Recurrent cancer after primary treatment
- Castrate sensitive metastatic prostate cancer (mCSPC)
- Non-metastatic castrate resistant prostate cancer (nmCRPC)
- Metastatic castrate resistant prostate cancer (mCRPC)

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Non-metastatic Castrate Resistant PCa (nmCRPC)

- PSA rising despite patients being on androgen deprivation therapy and testosterone at castrate levels (<50 ng/dl)
- Three large trials have shown that second generation anti-androgens improve overall survival and progression free survival in men with nmCRPC compared to ADT alone
  - ARAMIS: Darolutamide (Nubeqa)
  - PROSPER: Enzalutamide (Xtandi)
  - SPARTAN: Apalutamide (Erleada)
- All three studies enrolled patients with PSA doubling time (PSADT) of 10 months or less but this is not a requirement in FDA labeling

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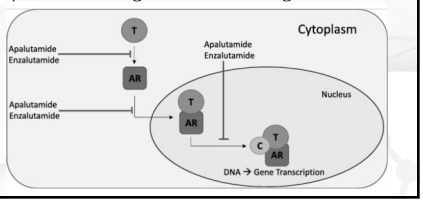
Second Generation Anti-Androgen Mechanism

- Competitive inhibition at 3 points along signalling cascade
  - Blocks testosterone binding to receptor
  - Blocks translocation of T/AR complex into nucleus
  - Blocks T/AR complex from binding to DNA and starting transcription



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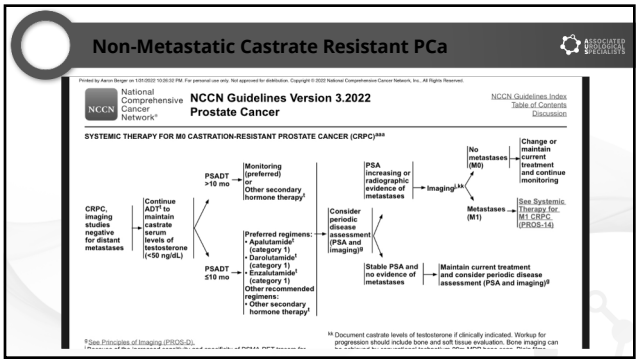
Non-Metastatic Castrate Resistant PCa



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Metastatic Castrate Sensitive Pca (mCSPC)

- Also known as metastatic hormone sensitive or hormone naïve prostate cancer
- Two ways to get to mCSPC:
- Primary recurrent
  - Patients have had primary treatment for localized Pca such as surgery, radiation, or cryoablation
  - During follow-up they are found to have metastasis
  - Not on ADT or just recently started, and are still responding to ADT
- DeNovo
  - Patient have metastatic disease at time of diagnosis
  - Often diagnosed in hospital setting when patients have bone pain, urinary retention, AKI, etc

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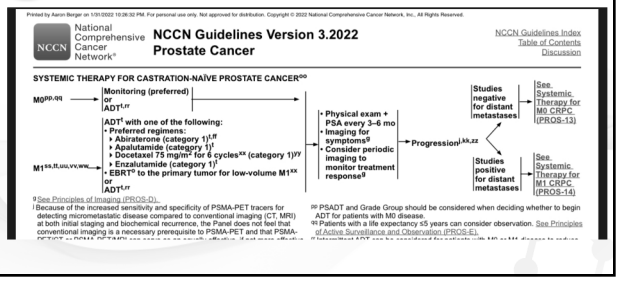
Metastatic Castrate Sensitive Prostate Cancer



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Metastatic Castrate Sensitive PCa

- ADT is still the mainstay of treatment but in most cases, it should not be the only treatment
- Xtandi (enzalutamide), Erleada (apalutamide), abiraterone (fka Zytiga), and chemotherapy (docetaxel) all indicated for mCSPC along with ADT
- Chemotherapy typically indicated for high volume metastatic disease especially in setting of visceral metastases such as long or liver
- Patient with oligometastatic disease can still have benefit from radiation to prostate

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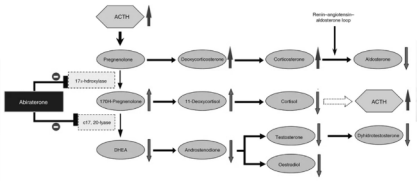
Abiraterone

- Abiraterone inhibits 17 α-hydroxylase
- Leads to decrease in androgen production
- Can increase mineralocorticoids so typically administered with prednisone or prednisolone to minimize side effects



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Abiraterone

- LATITUDE trial showed improvement in OS and rPFS along with ADT in men with mCSPC
- COU-AA-302 trial showed improvement in OS and rPFS along with ADT in men with mCRPC
- Only one of the oral oncolytics for prostate cancer that has a generic form
- Common AE's include: fatigue, arthralgia, edema, hypertension, hypokalemia
- Need to monitor for elevation of LFT's which is rare side effect
  - LFT's every 2 weeks for first 3 months then monthly is recommendation

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Metastatic Castration Resistant PCa (mCRPC)

- On ADT with castrate level of testosterone with rising PSA AND imaging showing metastatic disease
- In addition to continuing ADT, treatment options include
  - Xtandi (enzalutamide)
  - Abiraterone plus prednisone
  - Provenge (Sipeleucel T) immunotherapy
  - Radium 223 (Xofigo)
  - Docetaxel chemotherapy (1st line)
  - Jevtana (cabazitaxel) chemotherapy (2nd line)
  - PARP inhibitors for patients with HRR mutation
    - Lynparza (Olaparib) if no prior chemotherapy
    - Rubraca (rucaparib) if patient had prior chemo
  - Keytruda (pembrolizumab) is MSI high

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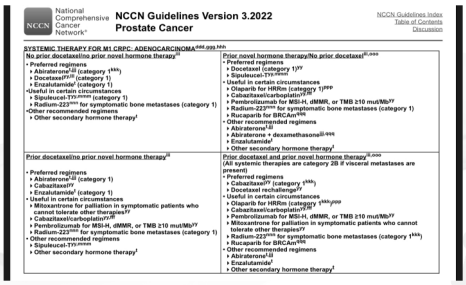
Metastatic Castrate Resistant PCa (mCRPC)



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Prostate Cancer

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Discussion

SYSTEMATIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[ddd,jjj,bbb]

No prior docetaxel/no prior novel hormone therapy[ff]

- Preferred regimens
  - Abiraterone[ddd] (category 1[bbb])
  - Docetaxel[ggg,yy] (category 1)
  - Enzalutamide[i] (category 1)
- Useful in certain circumstances
  - Sipuleucel-T[yy,mmm] (category 1)
  - Radium-223[nnn] for symptomatic bone metastases (category 1)
- Other recommended regimens
  - Other secondary hormone therapy[j]

Prior novel hormone therapy/No prior docetaxel[ff,ggg]

- Preferred regimens
  - Docetaxel (category 1)[yy]
  - Sipuleucel-T[yy,mmm]
- Useful in certain circumstances
  - Olaparib for HRRm (category 1)[ppp]
  - Cabazitaxel/carboplatin[yy,qq]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[yy]
  - Radium-223[nnn] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCAm[kkk]
- Other recommended regimens
  - Abiraterone[dd]
  - Abiraterone + dexamethasone[ddd,eee]
  - Enzalutamide[i]
  - Other secondary hormone therapy[j]

Prior docetaxel/no prior novel hormone therapy[ff]

- Preferred regimens
  - Abiraterone[ddd] (category 1)
  - Cabazitaxel[yy]
  - Enzalutamide[i] (category 1)
- Useful in certain circumstances
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[yy]
  - Cabazitaxel/carboplatin[yy,qq]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[yy]
  - Radium-223[nnn] for symptomatic bone metastases (category 1)
- Other recommended regimens
  - Sipuleucel-T[yy,mmm]
  - Other secondary hormone therapy[j]

Prior docetaxel and prior novel hormone therapy[ff,ggg]
(All systemic therapies are category 2B if visceral metastases are present)

- Preferred regimens
  - Cabazitaxel[yy] (category 1[bbb])
  - Lutetium-177-PSMA[rrr]
- Useful in certain circumstances
  - Olaparib for HRRm (category 1[bbb,ppp])
  - Cabazitaxel/carboplatin[yy,qq]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[yy]
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[yy]
  - Radium-223[nnn] for symptomatic bone metastases (category 1[bbb])
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- Other recommended regimens
  - Abiraterone[dd]
  - Enzalutamide[i]
  - Other secondary hormone therapy[j]

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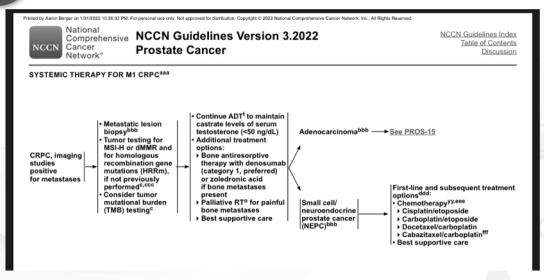
Metastatic Castrate Resistant PCa (mCRPC)



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SYSTEMATIC THERAPY FOR M1 CRPC[bbb]

CRPC, imaging studies positive for metastases →

- Metastatic lesion biopsy[bbb]
- Tumor testing for MSI-H or dMMR and for homologous recombination gene mutations (HRRm), if not previously performed[f,ccc]
- Consider tumor mutational burden (TMB) testing[c]

→

- Continue ADT[i] to maintain castrate levels of serum testosterone (<50 ng/dL)
- Additional treatment options:
  - Bone antiresorptive therapy with denosumab (category 1, preferred) or zoledronic acid if bone metastases present
  - Palliative RT[o] for painful bone metastases
  - Best supportive care

→ Adenocarcinoma[bbb] → See PROS-15

→ Small cell/neuroendocrine prostate cancer (NEPC)[bbb] →

First-line and subsequent treatment options[eee]

- Chemotherapy[yy,eee]
  - Cisplatin/etoposide
  - Carboplatin/etoposide
  - Docetaxel/carboplatin
  - Cabazitaxel/carboplatin[qq]
- Best supportive care

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Provenge (Sipeleucel-T) Immunotherapy

- Provenge is thought to be a tumor vaccine
- Uses patients own immune system to attack prostate cancer cells
- Treatment is done for 3 cycles
  - Step one is patient goes for leukapheresis where some white blood cells are removed
  - Leukapharesis sample sent to company lab in CA for processing
  - Approximately 3 days later patient receives their blood cells back that have now been stimulated to induce immune response against prostate cancer
- Indicated for asymptomatic or minimally symptomatic mCRPC

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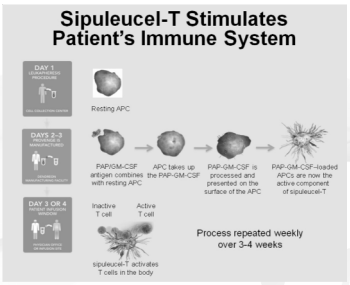
Provenge (Sipeleucel-T) Immunotherapy

- Leukapheresis requires decent venous access so many patients require a temporary port to be placed
- Typically minimal side effects since patients just receiving their own blood products
- Can have mild transfusion reaction like chills, rigors, etc so often pretreat with Tylenol and benadryl



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Provenge (Sipeleucel-T) Immunotherapy

- Provenge did have OS benefit in original studies from more than 10 years ago
- Recent retrospective study showed that adding Provenge at any time for men with mCRPC had OS benefit vs androgen signaling pathway inhibitor (enzalutamide, abiraterone) alone
- Data from the PROCEED registry trial also showed that African-American patients had a better OS benefit from Provenge than did Caucasian patients

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Xofigo (Radium 223) for mCRPC

- Xofigo is an IV form of radiation that preferentially is taken up by bone
- Given as IV infusion, based on patient weight, monthly for 6 doses
- ALSYMPCA trial showed improved overall survival in patients with mCRPC
- Indications is for symptomatic bone metastatis
  - Pain
  - Fatigue
  - Decrease in ADL
- Contraindicated if patient's have visceral metastasis

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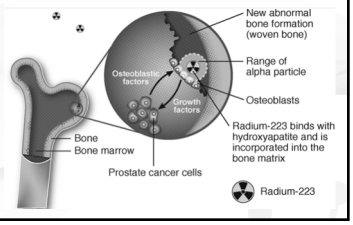
Xofigo (Radium 223) for mCRPC

- Alpha emitter that gets incorporated into bone to destroy osteoblastic metastases

- Main AE's
  - Diarrhea
  - Bone marrow suppression
  - Bone pain
- Typically administered by radiation oncologist or nuclear medicine



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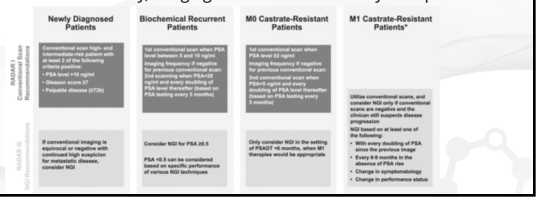
Imaging for Advanced Prostate Cancer

- RADAR Guidelines (Radiographic Assessments for Detection of Advanced Recurrence)
  - Developed to help guide when to image
  - Historically, imaging often done at arbitrary time points



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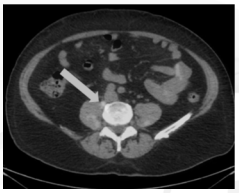
Imaging Modalities

- CT scan and bone scan are the typical "convential imaging" scans and were used in most of the relevant clinical trials for APC treatments
- 18-Fluciclovine (Axumin) PET/CT
  - Can detect metastasis at much lower PSA levels than conventional imaging
  - Fairly widely available and reasonably easy to get coverage for



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Imaging Modalities

- PSMA PET/CT is the newest and most sensitive imaging modality for advanced prostate cancer
  - Prostate specific membrane antigen is highly expressed in prostate cancer cells
  - Some expression in other organs as well such as kidneys and salivary glands
- Pylarify (piflufolastat F-18) currently FDA approved
  - Patients with suspected metastasis who are candidates for definitive therapy
  - Patients with suspected recurrence based on rising PSA levels after treatment
  - Overall broader indication than Axumin so many high risk patients could qualify to see if metastatic prior to surgery or radiation

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Imaging Modalities

- PSMA PET/CT can detect metastases at much lower PSA levels than conventional imaging and likely even lower than Axumin
- Gallium-68 PSMA PET/CT also FDA approved but currently only available at UCLA and UCSF
- PSMA scans still very new so availability and coverage may be an issue in short term but long term could alter treatment landscape substantially

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Bone Health

- Bone health is very important for patients with advanced prostate cancer and often overlooked and/or undertreated
- Patients with advanced prostate cancer often older so can have baseline bone weakness
- Androgen deprivation therapy also can weaken bones and lead to osteopenia or osteoporosis
- All patients who are on ADT should take Calcium and Vit D supplementation
- DEXA scan recommended when starting on ADT as a baseline and then every two years

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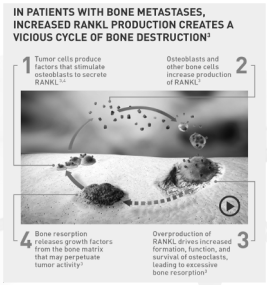
Bone Health

- Patients with bone metastasis qualify for Xgeva (denosumab)
- SC injection given monthly typically that can prevent SRE's (skeletal related events)
- Should be taken along with Ca/Vit D
- Main potential side effect is ONJ (osteonecrosis of jaw)
- For patients with osteopenia or osteoporosis but no mets who are on ADT can get 6 month version (Prolia)



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Genetic Testing

- Two main types of genetic testing
- Germline
  - Reflects genetic mutation that will be present in all patient cells including cancer cells as mutation inherited
  - Can be done with blood or saliva in most cases
  - If patient has germline mutation, genetic counseling for patient and family recommended
  - Estimated that 15-20% of prostate cancer patients have a germline mutation
- Somatic
  - Genetic profile of the cancer cells
  - Can be obtained from tissue (biopsy, RP specimen, metastatic site or from blood (liquid biopsy)
  - Can show mutations almost 50% more frequently

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Genetic Testing: Who Qualifies?

- Any patient with metastatic disease
- Patients with high risk but localized disease
- Patients with family history

PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

Germline testing is recommended *in patients with a personal history of prostate cancer* in the following scenarios:

- By Prostate Cancer Stage or Risk Group (diagnosed at any age)
  - Metastatic, regional (node positive), very-high risk localized, high-risk localized prostate cancer
- By Family History[a] and/or Ancestry
  - ≥1 first-, second-, or third-degree relative with:
    - breast cancer at age ≤50 y
    - colorectal or endometrial cancer at age ≤50 y
    - male breast cancer at any age
    - ovarian cancer at any age
    - exocrine pancreatic cancer at any age
    - metastatic, regional, very-high-risk, high-risk prostate cancer at any age
  - ≥1 first-degree relative (father or brother) with:
    - prostate cancer[b] at age ≤60 y
  - ≥2 first-, second-, or third-degree relatives with:
    - breast cancer at any age
    - prostate cancer[b] at any age
  - ≥3 first- or second-degree relatives with:
    - Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer
  - A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: ***BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, EPCAM***
  - Ashkenazi Jewish ancestry
- Personal history of breast cancer

Germline testing may be considered *in patients with a personal history of prostate cancer* in the following scenarios:

- By Prostate Cancer Tumor Characteristics (diagnosed at any age)
  - intermediate-risk prostate cancer with intraductal/cribriform histology[c]
- By prostate cancer[b] AND a prior personal history of any of the following cancers:
  - exocrine pancreatic, colorectal, gastric, melanoma, pancreatic, upper tract urothelial, glioblastoma, biliary tract, and small intestinal

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Somatic Genetic Testing: NCCN Guideline

SOMATIC TUMOR TESTING

- Pre-test Considerations
  - At present, tumor molecular and biomarker analysis may be used for treatment decision-making, including understanding eligibility for biomarker-directed treatments, genetic counseling, early use of platinum chemotherapy, and eligibility for clinical trials. Clinical trials may include established and/or candidate molecular biomarkers for eligibility.
  - Tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making.
  - Patients should be informed that tumor molecular analysis by DNA sequencing has the potential to uncover germline findings. Confirmatory germline testing may be recommended (see Post-test Considerations, below, and see Tumor Testing in the Principles of Cancer Risk Assessment and Counseling (EVAL-A) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic)
- Testing
  - Tumor testing for alterations in homologous recombination DNA repair genes, such as ***BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2,*** and ***CDK12,*** is recommended in patients with metastatic prostate cancer. This testing can be considered in patients with regional prostate cancer.
  - Tumor testing for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) is recommended in patients with metastatic castration-resistant prostate cancer and may be considered in patients with regional or castration-naive metastatic prostate cancer.
  - TMB testing may be considered in patients with metastatic castration-resistant prostate cancer.
- Tumor Specimen and Assay Considerations
  - The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation. When unsafe or unfeasible, plasma ctDNA assay is an option, preferably collected during biochemical (PSA) and/or radiographic progression in order to maximize diagnostic yield.
  - Caution is needed when interpreting ctDNA-only evaluation due to potential interference from clonal hematopoiesis of indeterminate potential (CHIP), which can result in a false-positive biomarker signal.
  - DNA analysis for MSI and immunohistochemistry (IHC) for MMR are different assays measuring different biological effects caused by dMMR function. If MSI is used, testing using an a next-generation sequencing (NGS) assay validated for prostate cancer is preferred.
- Post-test Considerations
  - Post-test genetic counseling is recommended if pathogenic/likely pathogenic variant (mutation) identified in any gene that has clinical implications if also identified in germline (eg, ***BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2***).
  - Post-test genetic counseling to assess for the possibility of Lynch syndrome is recommended if MSI-H or dMMR is found.

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Role of Chemotherapy

- Prior to the oral novel hormonal agents (enzalutamide, abiraterone, etc) patients with progressive disease or metastatic disease would get chemotherapy
  - This is still thought to be first line by many medical oncologists
  - Many large urology groups however will start patients on an oral therapy along with ADT
- When should chemo be used as first line along with ADT?
  - Younger patients with high volume metastatic disease
  - Patients with visceral mets (lung, liver)
  - Patients with poorly differentiated cancer as they are less likely to respond to hormonal maniupulation

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Role of Chemotherapy

- Docetaxel reasonably well tolerated compared to many other chemo drugs
- Typically infusion every 3 weeks for 6-9 cycles
- If patient is started on oral therapy along with ADT and they then progress, should consider referral to medical oncology to discuss chemo; do not want to wait until patients very advanced
- Jevtana (cabazitaxel) can be used as second line chemotherapy

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PARP Inhibitors

- Patients with either germline or somatic mutations in homologous recombinant repair genes (HRR) are candidates for PARP inhibitors
- 14 different mutations meet FDA indication for currently available PARPi but most common are BRCA1/2
- Two PARPi currently approved for prostate cancer
  - Lynparza (Olaparib) can be used pre-chemotherapy
  - Rubraca (rucaparib) is only post-chemotherapy
- Many new PARPi's coming to market in next year or two

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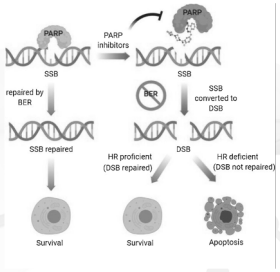
PARPi Mechanism

- Single strand DNA breaks usually repaired by PARP
- With a PARPi, single strand break becomes double strand break
- If patients have HRR gene mutation like BRCA1/2, double strand break not repaired and apoptosis occurs
- Main side effects of PARPi is anemia which can be signficiant



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Immunotherapy

- Keytruda (pembrolizumab) currently used for many cancers and does have indication for prostate cancer
- Somatic genetic testing required to determine eligibility
  - Microsatellite instability high (MSI high)
  - High tumor mutational burden (TMB)
- Given as IV infusion
- Side effects often referred to as the "itis's" like pneumonitis, thyroiditis, gastritis, etc

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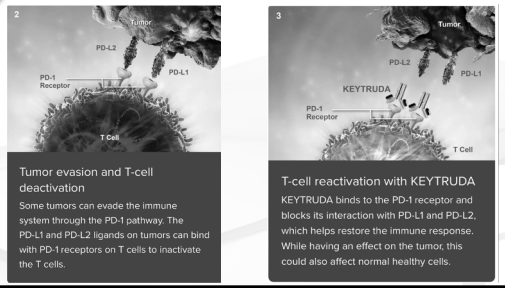
Immunotherapy: Keytruda



Tumor evasion and T-cell deactivation

Some tumors can evade the immune system through the PD-1 pathway. The PD-L1 and PD-L2 ligands on tumors can bind with PD-1 receptors on T cells to inactivate the T cells.

T-cell reactivation with KEYTRUDA

KEYTRUDA binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, which helps restore the immune response. While having an effect on the tumor, this could also affect normal healthy cells.

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PSMA Targeted Therapies

- Multiple treatments in development that attach a radiation particle emitter to a PSMA agent
- Can target any metastatic site unlike Xofigo which only works for bone
- Will likely require that a PSMA scan be performed prior to treatment to make sure there are appropriate treatment targets
- May initially only be approved post-chemotherapy as that is how trials were done

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Treatment Toxicity Concerns

- Many patients now with advanced prostate cancer will get several different therapies and be on multiple agents at same time
- Many drugs can increase risk for cardiovascular events, skeletal related events, bone marrow suppression, and potential increase risk of dementia
- "cardio-oncology" and "neuro-oncology" will likely become more important to understand and minimize risk of long term adverse events with all of these treatments

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Summary

- Many advancements in the diagnosis and treatment of advanced prostate cancer over the last 6-7 years
- Goal that I convey to my patients is to try and treat advanced prostate cancer like a chronic disease like DM or HTN
- Several more new treatment options on the horizon next few years
- New imaging modalities and genetic testing are leading to significant changes in how we manage advanced prostate cancer
- Keeping up with potential adverse effects of these treatments will become increasingly complex but important

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Thank you

Summary

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