Updates in Prostate Cancer

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Disclosures

- Nothing to disclose

Objectives

- Briefly review the pathophysiology of prostate cancer
- Discuss pharmacotherapy options for treatment of prostate cancer
- Review new literature in the treatment of prostate cancer
- Understand updates to NCCN guidelines for treatment of prostate cancer

Overview

- Median age at diagnosis is 66
- 2018 Statistics
  - Estimated 164,690 new cases
  - 19% of new cancer cases in men
  - 9% of male cancer deaths in 2018
- From 1989-2015 age-adjusted death rates from prostate cancer have declined 52%
- Incidence of prostate cancer has declined
  - Decreased prostate specific antigen (PSA) screening

Siegel RL, et.al. Cancer Statistics, 2018. CA Cancer J Clin 2018;68:7-30

Risk Factors

- Race
  - African Americans
- Age
  - Risk increases with age
- Family history
  - 5-10% of cases
  - First degree relative = life time risk 16%
- Genetics
  - BRCA-2 mutations
  - Lynch syndrome

CDC.gov

Screening

- Prostate Specific Antigen (PSA) +/- Digital rectal exam (DRE) and definitive biopsy when warranted
  - Total PSA measurements
    - ≤4 ng/mL, 4-10 ng/mL, >10 ng/mL
  - PSA Density
    - PSA number divided by the prostate volume
    - Better accuracy at predicting prostate cancer compared with PSA > 4 ng/mL
    - Sometimes used for men with large prostate glands to adjust PSA to account for larger size/higher PSA
  - PSA velocity
    - How fast a man's prostate score rises from one test to the next over a period of time
    - PSA <4 ng/mL with PSA velocity > 0.35 ng/mL per year
      - Higher relative risk of prostate cancer death
      - Recommend further work up
      - Not useful in patients with PSA > 10 ng/mL or prostatitis
  - PSA doubling time (PSADT)
    - Number of months it would take PSA to double
    - In non-metastatic castrate resistant prostate cancer (CRPC) a shorter PSADT is associated with shorter time to metastasis or death

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Who Should Be Screened?

Guideline group	Recommendation	Age to start screening	Screening algorithm
ACPM	Insufficient evidence to recommend widespread routine screening	Discussion about screening should occur annually, during the routine periodic examination or in response to a request by the patient	NA
ACS	Informed decision making	40 years for men at highest risk (several first-degree relatives diagnosed with prostate cancer under age 65 years); 45 years for men at high risk (African American or first-degree relative with prostate cancer); 50 years for men at moderate risk with a life-expectancy of more than 10 years	Men who choose to be tested who have a PSA <2.5 ng/ml only need to be retested every 2 years; annual screening for men with PSA ≥2.5 ng/ml
AUA	Informed decision making	40 years for baseline DRE and PSA	Screening intervals based on baseline PSA
EAU	Insufficient evidence to recommend widespread routine screening; opportunistic screening should be offered to all well-informed men	40 years for baseline PSA	Screening interval based on baseline PSA; 8 years generally sufficient for men with initial PSA <1 ng/ml; further PSA testing unnecessary in men >75 years old with baseline PSA <3 ng/ml
NCCN	Informed decision making	40 years for baseline DRE and PSA; 50 years for annual screening	Screening algorithm based on initial PSA and DRE; repeat screening at age 45 years if PSA <1.0 ng/ml
USPSTF	Against screening (grade D)	NA	NA

Abbreviations: ACPM, American College of Preventive Medicine; ACS, American Cancer Society; AUA, American Urological Association; DRE, digital rectal examination; EAU, European Association of Urology; NA, not applicable; NCCN, National Comprehensive Cancer Network; USPSTF, US Preventive Services Task Force.

urotoday.com

Screening

- Early detection can lead to overtreatment
  - Unnecessary side effects
  - Impaired quality of life
  - Increased health care expenditures
- U.S.Preventative Services Task Force (USPSTF)
  - In 2012 recommended against PSA testing
  - Incidence of metastatic disease has increased
  - Rate of prostate mortality has stabilized
  - Updated draft 2017

Negoita S, et. al. Annual report to the Nation on the Status of Cancer, part II: Recent changes in prostate cancer trends and disease characteristics. Cancer 2018

USPSTF Final Statement May 2018

Population	Men aged 55 to 69 y	Men 70 y and older
Recommendation	The decision to be screened for prostate cancer should be an individual one. Grade: C	Do not screen for prostate cancer. Grade: D
Informed Decision Making	Before deciding whether to be screened, men aged 55 to 69 years should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy, overdiagnosis and overtreatment, and treatment complications, such as incontinence and erectile dysfunction. Harms are greater for men 70 years and older. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. Clinicians should not screen men who do not express a preference for screening and should not routinely screen men 70 years and older.	
Risk Assessment	Older age, African American race, and family history of prostate cancer are the most important risk factors for prostate cancer.	
Screening Tests	Screening for prostate cancer begins with a test that measures the amount of prostate-specific antigen (PSA) protein in the blood. An elevated PSA level may be caused by prostate cancer but can also be caused by other conditions, including an enlarged prostate (benign prostatic hyperplasia) and inflammation of the prostate (prostatitis). Some men without prostate cancer may therefore have false-positive results. Men with a positive PSA test result may undergo a transrectal ultrasound–guided core needle biopsy of the prostate to diagnose prostate cancer.	
Treatments	The 3 most common treatment options for men with screen-detected, localized prostate cancer are surgical removal of the prostate gland (radical prostatectomy), radiation therapy (external-beam radiation therapy, proton beam therapy, or brachytherapy), and active surveillance.	

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to https://www.uspreventiveservicestaskforce.org.

U.S. Preventive Services TASK FORCE

JAMA

https://www.uspreventiveservicestaskforce.org
JAMA. 2018;319(18):1901-1913. doi:10.1001/jama.2018.3710

Staging

- Based on five key factors
  - Extent of primary tumor (T)
  - Involvement of lymph nodes (N)
  - Presence of metastases (M)
  - PSA level
  - Grade Groups – includes the Gleason score

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Grade Groups

Grade Group	Gleason Score
1	≤6 (≤3+3)
2	3+4=7
3	4+3 =7
4	8 (4+4, 3+5, 5+3)
5	9-10 (4+5, 5+4, 5+5)

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Staging

Group	T	N	M	PSA (ng/mL)	Grade Group
Stage I	cT1a-c	N0	M0	PSA <10	1
	cT2a	N0	M0	PSA <10	1
	pT2	N0	M0	PSA <10	1
Stage IIA	cT1a-c	N0	M0	PSA ≥10 <20	1
	cT2a	N0	M0	PSA ≥10 <20	1
	pT2	N0	M0	PSA ≥10 <20	1
	cT2b	N0	M0	PSA <20	1
	cT2c	N0	M0	PSA <20	1
Stage IIB	T1-2	N0	M0	PSA <20	2
Stage IIC	T1-2	N0	M0	PSA <20	3
	T1-2	N0	M0	PSA <20	4
Stage IIIA	T1-2	N0	M0	PSA ≥20	1-4
Stage IIIB	T3-4	N0	M0	Any PSA	1-4
Stage IIIC	Any T	N0	M0	Any PSA	5
Stage IVA	Any T	N1	M0	Any PSA	Any
Stage IVB	Any T	Any N	M1	Any PSA	Any

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Life Expectancy

- Critical to informed decision making
- Estimated
  - Social Security Administration Tables
  - Minnesota Metropolitan Life Insurance Tables
  - World Health Organization's Life Tables by country
- Can be adjusted based on clinician's assessment
  - Healthiest quartile – add 50%
  - Unhealthiest quartile – subtract 50%

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Recurrence Risk	Expected Survival	Initial Therapy
Very Low T1c, GS ≤6/Grade group 1, PSA <10 ng/mL, < 3 Bx cores positive ≤50% cancer in any one core, and PSA density <0.15 ng/mL/g	< 10 years	Observation
	10-19 years	Active Surveillance (AS)
	≥20 years	AS, EBRT or brachytherapy or RP±PLND
Low T1-T2a, GS ≤6/Grade group 1, PSA < 10 ng/mL	<10 years	Observation
	≥ 10 years	AS, EBRT or brachytherapy or RP±PLND
Favorable Intermediate T2b-2c or GS 3+4=7/Grade Group 2 or PSA 10-20 ng/mL AND percentage of positive biopsy cores <50%	< 10 years	**Observation or EBRT or brachytherapy alone**
	≥ 10 years	**AS, EBRT or brachytherapy alone or RP± PLND**

GS: Gleason score; EBRT: External beam radiation therapy; RP: radical prostatectomy; PLND: pelvic lymph node dissection; ADT: androgen deprivation therapy; short-term ADT 4-6 months of neoadjuvant/concomitant/adjuvant ADT

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Recurrence Risk		Initial Therapy
Unfavorable Intermediate Same as favorable or GS 4+3=7/Grade group 3 or PSA 10-20 ng/mL	< 10 years	**Observation or EBRT + brachytherapy ± short-term ADT (4-6mo)**
	≥ 10 years	**EBRT± short term ADT (4-6 mo) ± brachytherapy or RP± PLND**
High (>5 years) T3a or GS 8/Grade Group 4 or GS 4+5=9/Grade Group 5 or and PSA > 20 ng/mL **Very High (>5 years)** T3b-T4 OR Primary Gleason pattern 5 or >4 cores with GS 8-10/Grade Group 4 or 5		EBRT+long-term ADT (2-3 yr; category 1), **EBRT+brachytherapy + long term ADT (1-3 yr; category 1),** or RP+PLND *if ≤5 years: observation or ADT or EBRT
Regional (>5 years)		EBRT+ ADT (2-3 yr; Category 1) ± a**biraterone and prednisone** or ADT ± **abiraterone and prednisone**
Regional/Metastatic (≤5 years)		Observation or ADT

GS: Gleason score; EBRT: External beam radiation therapy; RP: radical prostatectomy; PLND: pelvic lymph node dissection; ADT: androgen deprivation therapy; short-term ADT 4-6 months of neoadjuvant/concomitant/adjuvant ADT

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Who should be offered further testing?

Risk group	Molecular testing	Germline testing
Very low	Not indicated	Consider If strong family history
Low	Consider if life expectancy ≥ 10 years	
Favorable intermediate		
Unfavorable intermediate	Not routinely recommended	Consider if strong family history
High		Consider
Very high		
Regional	**Consider tumor testing for MSI-H or dMMR**	
Metastatic		

Strong Family History: brother or father or multiple family members diagnosed with prostate cancer <60 yo; known germline DNA repair gene abnormalities, especially Lynch (MLH1, MSH2, MSH6, or PMS2) or BRCA2 mutation, and/or more than one relative with breast, ovarian, pancreatic (suggests BRCA2), or colorectal, endometrial, gastric, ovarian, pancreatic, small bowel, urothelial, kidney, or bile duct cancer (suggests Lynch) MSI-H – microsatellite instability high; dMMR – deficient mismatched repair

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What is ADT?

- Orchiectomy
- LHRH agonist
  - Leuprolide (Lupron IM, Eligard SQ)
  - Goserelin (Zoladex)
  - Triptorelin (Trelstar)
  - Histrelin (Vantas)
- LHRH antagonist
  - Degarelix (Firmagon)

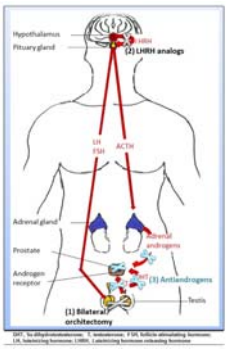


Image: https://doi.org/10.3390/nu6104491

What are Antiandrogens?

- First generation:
  - Flutamide (Eulexin)
  - Bicalutamide (Casodex)
  - Nilutamide (Nilandron)
- Second generation:
  - Enzalutamide (Xtandi)
  - Apalutamide (Erleada)

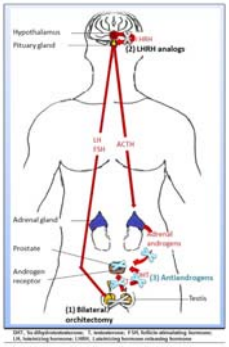
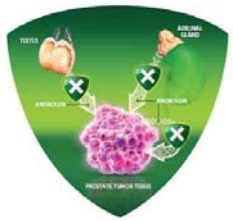


Image: https://doi.org/10.3390/nu6104491

How do androgen synthesis inhibitors work?

- Abiraterone (Zytiga)
  - Combination with pednisone
- Abiraterone (micronized; Yonsa)
  - Combination with methyprednisolone



TREATMENT OF METASTATIC OR NONMETASTATIC CASTRATION-NIAVE

Castration-Naïve Disease

M0	M1
• Orchiectomy • LHRH agonist ± first generation antiandrogen • LHRH antagonist • observation	• Orchiectomy • LHRH agonist ± first generation antiandrogen (≥ 7 days to prevent testosterone flare • LHRH agonist + first generation antiandrogen • LHRH antagonist • **ADT and docetaxel 75 mg/m2 for 6 cycles (category 1)** • **ADT and abiraterone + prednisone** (category 1) • ADT and abiraterone+methylprednisolone (category 2B)

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Castration-Naïve Disease – Secondary Hormone Therapy

M0	M1
• Continue LHRH agonist or antagonist to maintain castrate serum levels of testosterone (< 50 ng/dL) and add: • Second generation anti-androgen: **Apalutamide** or Enzalutamide • First generation antiandrogen: Niluatmide, flutamide, or bicalutamide • Ketoconazole ± hydrocortisone* • Corticosteroids • DES or other estrogen	• Continue LHRH agonist or antagonist to maintain castrate serum levels of testosterone (< 50 ng/dL) and add: • Second generation anti-androgen: Enzalutamide • Androgen metabolism inhibitor • Abiraterone + prednisone • Abiraterone +methylprednisolone • First generation antiandrogen • Ketoconazole ± hydrocortisone* • Corticosteroids • DES or other estrogen

* Should not be used if progression on abiraterone + prednisone

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NEW/UPDATED DATA Castration-Naïve Disease

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial
Kyriakopoulous C, Chen Y, Carducci MA, et al. J Clin Oncol. 2018; 36(11):1080-88

Study Design
Multicenter, randomized, open-label, phase III National Cancer Institute study

Purpose
To present the outcomes of CHAARTED (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) trial with more mature follow up and focus on tumor volume.

Treatment (n=790)
- Metastatic hormone-sensitive prostate cancer
- Equally and randomly assigned
  - ADT+docetaxel 75 mg/m2 for up to 6 cycles
  - ADT alone.

Results*	ADT+docetaxel	ADT alone	P value
Median OS	57.6 mo	47.2 mo	<0.0018
Median OS High volume disease	51.2 mo	34.4 mo	<0.001
Median OS Low volume disease	63.5 mo	NR	0.86

Conclusion
The clinical benefit from chemohormonal therapy in prolonging overall survival (OS) was confirmed for patients with high-volume disease; however, for patients with low-volume disease, no OS benefit was discerned.

*Median follow up at 53.7 months

NCCN 2018 Recommendations

- Originally added docetaxel +ADT+EBRT in 2016
- NCCN in 2018
  - Men with high-volume, ADT-naïve, metastatic disease: considered ADT and docetaxel based on results of ECOG 3805 (CHAARTED) trial
  - Docetaxel should not be offered to men without metastatic disease or to men with low-volume metastatic prostate cancer since this subgroup was not shown to have improved overall survival in either ECOG study or GETUG-AFU 15

LATITUDE : Abiraterone plus Prednisone in Metastatic Castrate-Sensitive Prostate Cancer
Fizazi K, Tran N, Fein L, et al. N Engl J Med 2017; 337:352-60

Study Design
Multinational, double-blind, placebo-controlled, phase III trial

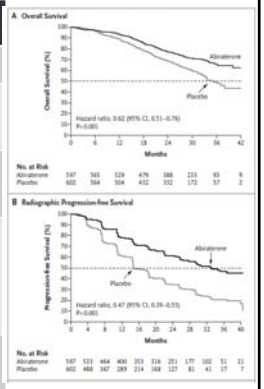
Purpose
Evaluate the addition of abiraterone plus prednisone to androgen-deprivation therapy (ADT), as compared with ADT and dual placebos in men with newly diagnosed, metastatic, castration-sensitive prostate cancer

Treatment (n=1199)
Patients were randomized 1:1 to receive
Abiraterone 1000 mg daily + prednisone 5 mg daily + ADT
Placebos + ADT

Results	Abiraterone	Placebo	P Value
Overall survival	NR	34.7 mo	<0.001
Median length radiographic PFS	33 mo	14.8 mo	<0.001

All secondary endpoints favored abiraterone
High rates of grade 3 hypertension and hypokalemia seen in abiraterone group

Conclusion
The addition of abiraterone acetate and prednisone to androgen-deprivation therapy significantly increased overall survival and radiographic progression-free survival in men with newly diagnosed, metastatic, castration-sensitive prostate cancer.



NCCN Recommendations

- Abiraterone with prednisone 5 mg once daily plus ADT for men with newly diagnosed, M1, castration-naive prostate cancer (category 1).
- For men undergoing curative-intent treatment for N1 disease, abiraterone can be added to EBRT with 2-3 years of neoadjuvant/concurrent/adjuvant ADT or can be given with ADT for castration-naïve disease (without EBRT)
- Insufficient data to recommend abiraterone for men with high-risk of very-high-risk N0 M0 prostate cancer.

TREATMENT OF NON-METASTATIC CRPC

Non-Metastatic Castration Resistant Prostate Cancer (CRPC)

- Continue ADT to maintain castrate serum levels of testosterone (<50 ng/dL)
  - Observation especially if PSADT > 10 months
  - **Apalutamide especially if PSADT ≤ 10 months (category 1)**
  - **Enzalutamide especially if PSADT ≤ 10 months (category 1)**
  - Other secondary hormone therapy especially if PSADT ≤ 10 months
- If PSA increases look to see if metastatic or not
  - No Metastases – change or maintain current therapy
  - Metastases – treat as mCRPC

NCCN v3.2018

NEW DATA
NONMETASTATIC CRPC

SPARTAN Trial: Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer
Smith MR, Saad F, Chowdhury S, et al. NEJM 2018;378:1408-18

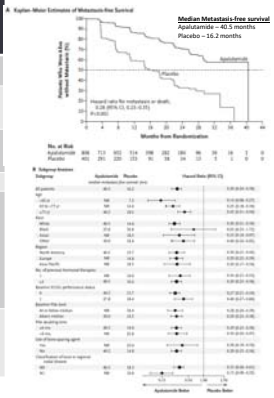
Study Design
Double-blind, placebo-controlled, phase III trial

Purpose
To evaluate efficacy of apalutamide in men with nonmetastatic castration-resistant prostate cancer who are at high risk for development of metastasis.

Treatment (n= 1207)
- Randomly assigned in a 2:1 ratio to apalutamide 240 mg daily or placebo
- All patients continued to receive ADT

Results	Apalutamide	Placebo	P value
Primary			
Median MFS	40.5 mo	16.2 mo	0.001
Secondary (median)			
Time to metastasis	40.5 mo	16.6 mo	<0.001
PFS	40.5 mo	14.7 mo	<0.001
Time to symptomatic progression	NR	NR	<0.001
Overall survival	NR	39 mo	0.07
Time to initiation of chemotherapy	NR	NR	---

Conclusions
Among men with nonmetastatic castration-resistant prostate cancer, metastasis-free survival and time to symptomatic progression were significantly longer with apalutamide than with placebo.



MFS – metastasis-free survival, PFS – progression free survival

NCCN 2018 Update

- Apalutamide was added as a category 1 option for patients with M0 CRPC especially if PSADT ≤ 10 months

NCCN v2018

Apalutamide (Erleada™)

- Second generation anti-androgen
- Dose 240 mg (4 tablets) daily with or without food
- Warnings and precautions:
  - Fall, fractures, and seizures
- Most common adverse reactions (≥10%)
  - Fatigue, hypertension, rash, diarrhea, nausea, decrease in weight, arthralgia, hot flush, decreased appetite, fracture and peripheral edema
- Monitor thyroid function
- Drug interactions
  - Strong CYP2C8 or CYP3A4 inhibitors
  - Apalutamide is a strong inducer of CYP3A4 and CYP2C19 and weak inducer of CYP2C9
  - Use caution if substrates of UGT, P-gp, BCRP, or OATP1B1 must be co-administered

Erleada™ (package insert). Janssen Products, LP, Horsham, PA; February 2018

PROSPER Trial: Enzalutamide in Men with Nonmetastatic, Castration-resistant Prostate Cancer
Hussain M, Fizazi K, Saad F, et al. NEJM 2018; 378(26):2465-74

Study Design
International, double-blind, randomized, placebo-controlled, phase III trial

Purpose
Evaluate the addition of enzalutamide versus placebo to androgen deprivation therapy in delaying the development of metastases in men with nonmetastatic, castration resistant prostate cancer and a rapid PSA doubling time (stratified by PSADT <6 months or ≥6 months; median 3.7 months)

Treatment (n=1401)
Randomized 2:1 to receive enzalutamide 160 mg daily or placebo
All patients continued androgen depravation therapy

Results	Enzalutamide	Placebo	P Value
Metastasis-free survival	36.6 months	14.7 months	<0.001
Time to PSA progression	37.2 months	3.9 months	<0.001
Median time to new therapy	39.6 months	17.7 months	<0.001
Overall Survival	NR	NR	0.15
Confirmed PSA response ≥ 50%	76%	2%	
FACT-P score degradation			
Median time to score degradation	11.1 months	11.1 months	

Conclusion
Among men with nonmetastatic, castration-resistant prostate cancer with a rapidly rising PSA level, enzalutamide treatment led to clinically meaningful and significant 71% lower risk of metastasis or death compared with placebo. Adverse events were consistent with the established safety profile of enzalutamide

NCCN 2018 Update

- In July 2018 the FDA expanded approval for ezalutamide to include men with non-metastatic CRPC
- NCCN: patients with M0 CRPC can be offered enzalutamide, especially if PSADT ≤ 10 months

NCCN v3.2018

TREATMENT OF METASTATIC CRPC

Metastatic Castrate Resistant Prostate Cancer

- **Consider tumor testing for MSI-H or dMMR**
- **Consider genetic counseling and germline testing for homologous recombination gene mutations**
- **Continue ADT to maintain castrate levels of serum testosterone (<50 ng/dL)**
- **Additional treatment options**
  - **Bone antiresorptive therapy**
    - **Zolendronic acid or denosumab (both category-1)**
  - **Immunotherapy with sipuleucel-T (category 1)**
  - **Palliative radiation therapy for painful bone metastases**
  - **Best Supportive Care**

NCCN v3.2018

Metastatic Castration Resistant Prostate Cancer (mCRPC): Initial Treatment

No Visceral Metastases	Visceral Metastases (Adenocarcinoma)*
• Abiraterone + prednisone (category 1) • **Docetaxel** (category 1) • Enzalutamide (category 1) • Radium-223 for symptomatic bone metastases (category 1) • Abiraterone with MP** • Clinical trial • Secondary hormonal therapy (antiandrogen, antiandrogen withdrawal, ketoconazole, corticosteroids)	• Docetaxel (category 1) • Enzalutamide (category 1) • Abiraterone + prednisone /MP • Clinical Trial • Mitoxantrone + prednisone *** • Secondary hormonal therapy (antiandrogen, antiandrogen withdrawal, ketoconazole, corticosteroids)

*Visceral metastases refers to liver, lung, adrenal, peritoneal and brain metastases
**MP = methylprednisolone
***for palliation in symptomatic patients who can't tolerate other therapies
-Abiraterone is not an option for use in combination with docetaxel and should not be co-administered with an antiandrogen
-ketoconazole+/-hydrocortisone should not be used if disease progressed on abiraterone with prednisone

NCCN v3.2018

mCRPC Subsequent Therapy

No Visceral Metastases and prior abiraterone/enzalutamide	No Visceral Metastases and prior docetaxel

• **Docetaxel** (category 1)
• Radium-223 for symptomatic bone mets (category 1)
• **Pembrolizumab for MSI-H or dMMR (category 2B)**
• **If not previously received**:
  • Abiraterone + prednisone/MP
  • Enzalutamide
  • Sipuleucel-T*
• Clinical trial
• Other secondary hormonal therapy (antiandrogen, antiandrogen withdrawl, ketoconazole, corticosteroids, DES or other estrogen)
• Best supportive care
	• Abiraterone+prednisone (category 1)
	• **Cabazitaxel** (category 1)
	• Enzalutamide (category 1)
	• Radium-223 if bone predominate (category 1)
	• **Pembrolizumab for MSI-H or dMMR (category 2B)**
	• **If not previously received:**
	  • Sipuleucel-T*
	• Abiraterone + MP
	• Clinical Trial
	• **Consider** Docetaxel rechallenge**
	• Mitoxantrone + prednisone***
	• Other secondary hormonal therapy
	• Best supportive care

*Only for asymptomatic or minimally symptomatic, no liver metastases, life expectancy > 6 months, ECOG 0-1
** If docetaxel with ADT received in metastatic castration naïve setting they can be considered for re-challenge
***for palliation in symptomatic patients who cannot tolerate other therapies

NCCN v3.2018

mCRPC Subsequent Therapy Visceral Metastasis (Adenocarcinoma)

Visceral Metastases and prior enzalutamide/Abiraterone	Visceral Metastases and prior docetaxel

• Docetaxel (category 1)
• If not previously received:
  • Abiraterone + Prednisone/MP
  • Enzalutamide
  • Cabazitaxel
• **Pembrolizumab for MSI-H or dMMR (category 2B)**
• Clinical trial
• Other secondary hormonal therapy (antiandrogen, antiandrogen withdrawal, ketoconazole, corticosteroids, DES or other estrogen)
• Best supportive care
	• Abiraterone + prednisone (category 1)
	• Enzalutamide (category 1)
	• Cabazitaxel (category 1)
	• Abiraterone + MP
	• **Pembrolizumab for MSI-H or dMMR (category 2B)**
	• Clinical Trial
	• Docetaxel rechallenge
	• Mitoxantrone + prednisone*
	• Other secondary hormonal therapy
	• Best supportive care

NCCN v3.2018

mCRPC Subsequent Therapy Visceral Metastases (Small Cell)

Visceral Metastases

Consider brain MRI with and without contrast
• Chemotherapy
  • Cisplatin/etoposide
  • Carboplatin/etoposide
  • Docetaxel/carboplatin
• Clinical Trial

NCCN v3.2018

NEW DATA Metastatic Castration Resistant Prostate Cancer

GENETIC TESTING

- NCCN recommends in patients with metastatic CRPC testing for
  - MSI-H or dMMR
  - BRCA1/2
  - ATM
  - PALB2
  - FANCA
- Refer to genetic counseling if mutation is found
- For now information can be used for
  - Early use of platinum chemotherapy
  - Use of pembrolizumab in later lines of treatment
  - Eligibility for clinical trials

NCCN v3.2018

Pembrolizumab MSI-H/dMMR Data

- Efficacy of was evaluated in 149 patients across five uncontrolled, open-label, multicohort, multicenter, single-arm trials
- Received FDA approval in May 2017 for solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment

Trial	Description
KEYNOTE-016	Six-site prospective, investigator-initiated trial included patients with CRC (n=28) and non-CRC (n=30) who received KEYTRUDA 10 mg/kg Q2W following ≥2 prior regimens for CRC or ≥1 for non-CRC; tested with local PCR or IHC.
KEYNOTE-164	Prospective, international, multicenter trial of patients with CRC (n=61) who received KEYTRUDA 200 mg Q3W following fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR monoclonal antibody; tested with local PCR or IHC.
KEYNOTE-012	Retrospectively identified patients (n=6) with PD-L1–positive gastric, bladder, or triple-negative breast cancer who received KEYTRUDA 10 mg/kg Q2W following ≥1 prior regimen; tested with central PCR.
KEYNOTE-028	Retrospectively identified patients (n=5) with PD-L1–positive esophageal, biliary, breast, endometrial, or CRC who received KEYTRUDA 10 mg/kg Q2W following ≥1 prior regimen; tested with central PCR.
KEYNOTE-158	Prospective, international, multicenter enrollment of patients with MSI-H/dMMR non-CRC and retrospectively identified patients who were enrolled in specific rare-tumor non-CRC cohorts (n=19) who received KEYTRUDA 200 mg Q3W following ≥1 prior regimen; tested with local PCR or IHC (central PCR for patients in rare-tumor non-CRC cohorts).

Image www.keytruda.com/hcp/msi-h/
Keytruda® [package insert]. Merck & Co., Inc., Whitehouse Station, NJ August 2018

NCCN 2018 Update

- Pembrolizumab may be considered in patients with MSI-H or dMMR mCRPC whose disease has progressed through at least 1 line of systemic therapy for mCRPC
- If MSI-H or dMMR is identified
  - Genetic counseling
  - Germline testing for Lynch syndrome

NCCN v3.2018

PROSELICA: Phase III Study Comparing a Reduced Dose of Cabazitaxel (20 mg/m2) and the Currently Approved Dose (25 mg/m2) in Postdocetaxel Patients with Metastatic Castration-Resistant Prostate Cancer
Eisenberger M, Hardy-Bessard AC, Kim CS, et.al. J Clin Oncol 2017;35(28):3198-3206

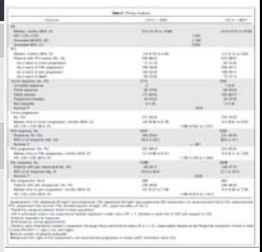
Study Design
Randomized, open label, phase III trial

Purpose
Assess noninferiority of cabazitaxel 20 mg/m2 (C20) versus cabaziaxel 25 mg/m2 (C25) in post docetaxel patients with mCRPC. To claim noninferiority C20 had to maintain ≥ 50% of the OS benefit of C25 versus mitoxantrone in TROPIC.

Treatment (n=1200)
Patients randomly assigned to C25 or C20

Results
- Median OS was 13.4 months for C20 and 14.5 months for C25. The upper boundary of the HR CI was 1.184 (<1.214 noninferiority margin)
- Significant differences were observed in favor of C25 for PSA response and time to PSA progression
- Health related QOL did not differ between C20 and C25
- Rate of grade 3 or 4 adverse events were 39.7% for C20 and 54.5% for C25

Conclusions
The efficacy of cabazitaxel in postdocetaxel patients with mCRPC was confirmed. The noninferiority end point was met. C20 maintained ≥ 50% of the OS benefit of C25 versus mitoxantrone in TROPIC. Secondary endpoints favored C25. Fewer adverse events were observed with C20.



NCCN 2018 Recommendations

- Cabazitaxel at 20 mg/m2 every 3 weeks ± growth factor support is now standard of care for fit patients
- Cabazitaxel at 25 mg/m2 may be considered for healthy men who wish to be more aggressive

NCCN v3.2018

Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomized, double-blind, placebo-controlled, phase 2 trial
Clarke N, Wichno P, Alekseev B, et al. Lancet Oncol 2018; 19:975-86

Study Design
Double-blind, placebo-controlled, phase II trial

Purpose
Aim to assess efficacy of olaparib plus androgen pathway inhibitor abiraterone in patients with metastatic castration-resistant prostate cancer regardless of homologous recombination repair (HRR) mutation status

Treatment (n= 142)
Randomly assigned 1:1 to olaparib 300 mg BID or placebo plus abiraterone 1000 mg daily plus prednisone/prednisolone 5 mg BID

Results	Olaparib	Placebo	Pvalue
Radiographic PFS (n= 142)			
• Intention to treat	13.8 mo	8.2 mo	0.034
• HRR mutation (n=11/10)	17.8 mo	6.5 mo	
• HRR wild type (n= 15/20)	15 mo	5.4 mo	
• Partially characterized	13.1 mo	6.4 mo	
Median OS	22.7 mo	20.9 mo	0.66
Stable disease	48%	21%	
Median duration of response	17.8 mo	12.1 mo	

Conclusion
Olaparib in combination with abiraterone provided clinical efficacy benefit for patients with mCRPC compared with abiraterone alone. More serious adverse events were observed in patients who received olapraib and abiraterone than abiraterone alone. Our data suggest that the combination of olaparib and abiraterone might provide an additional clinical benefit to a broad population of patients with mCRPC

SUMMARY

- Castration-naïve disease
  - Update of CHAARTED confirmed OS benefit of docetaxel in addition to ADT in high volume disease
  - LATITUDE showed addition of abiraterone and prednisone to ADT significantly improved OS and radiographic PFS in men with newly diagnosed, metastatic, castration-sensitive prostate cancer
- Nonmetastatic CRPC
  - SPARTAN - in men with PSADT of 10 months or less apalutamide in combination with ADT was shown to have a significantly longer metastasis-free survival and time to symptomatic progression
  - PROSPER – in men with rapidly rising PSA level, enzalumatide + ADT led to significantly lower risk of death
- mCRPC
  - Pembrolizumab is an option in patients with MSI-H/dMMR with mCRPC who have failed at least one line of therapy; there are several ongoing trials at clinicaltrials.gov
  - PROSELCIA Trial showed noninferority of C20 vs C25, secondary endpoints favored C25 and safety profile favored C20
  - PARP inhibitor olaparib in combination with abiraterone was the first study to show efficacy of a PARP inhibitor independent of homologous recombination repair (HRR) status. There are several ongoing trials at clinicaltrials.gov

Any Questions?