
بسم الله الرحمن الرحيم

20th Congress of Iranian Society of Medical Oncology & Hematology

بیستمین کنگره سراسری انجمن هماتولوژی و انکولوژی پزشکی ایران (سال ۱۴۰۰)

PROSTATE CANCER PANEL

ESFAHAN UNIVERSITY

15-17 DAY 1400

DR VALIOLLAH MEHRZAD

HEMATOLOGIST AND ONCOLOGIST

Prostate cancer

- What do you do for screening of prostate cancer?
- Age of beginning?
- With PSA or DRE or others

- A 59-y-old married man presented to his physician in 2012 with dysuria and other symptoms that were attributed to a urinary tract infection

- The symptoms continued over 2 y, despite antibiotic treatment In 2014, the patient approached a urologist for a second opinion, and his prostate-specific antigen (PSA) level was 9.8 ng/ ml

- what's your opinion?

- Trans rectal biopsy confirmed a diagnosis of clinically localized prostate cancer (cT2, Gleason score 9 (4 þ 5), 4/ 8 cores affected)

- How do you interpret this pathology?

- What is your decision about this patient ?
- PROSTECTOMY or RADIOTHERAPY?
- What does evaluation you suggest?
- MRI(what kind),CTSCAN,BONE SCAN,PET CTSCAN

- After discussion of the treatment options (radical prostatectomy, brachytherapy, and external-beam radiotherapy), the patient opted to undergo surgery
- Histopathologic restaging revealed extensive disease within the prostate, with positive surgical margins (pT3)
- Postoperatively, the PSA level remained at 0.5 ng/ml, and within 3 months started to rise

- Please interpret pathology?
- What's your decision about adjuvant therapy?

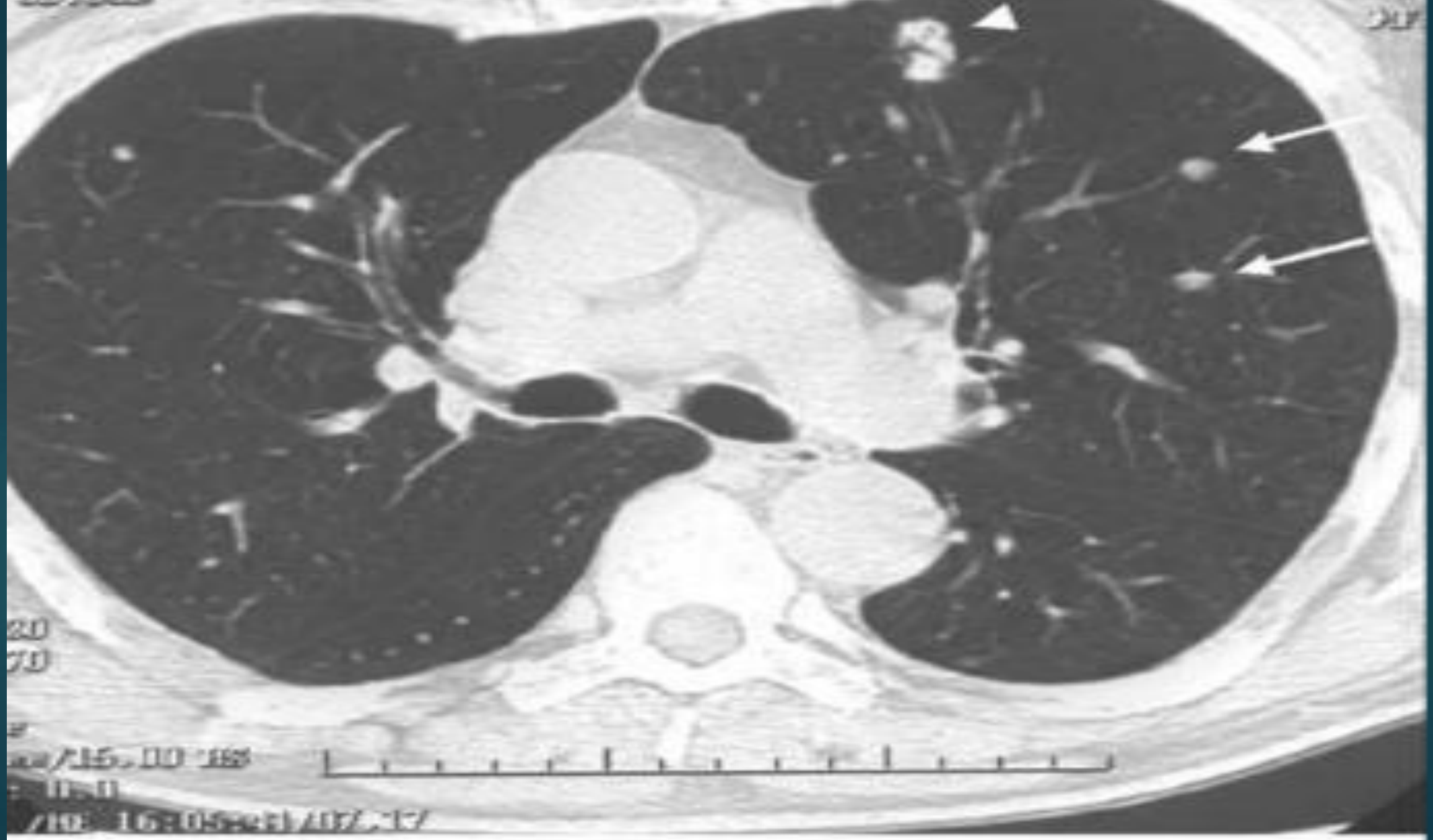
- Upon second-line radiotherapy (70 Gy over 6 weeks), preceded by a 3-month depot injection of goserelin (‘Zoladex’), the PSA level was stable for 2 y at <0.2 ng/ml before rising again

- When the PSA level reached >1 ng/ml, hormonal therapy was discussed; the patient elected to receive monotherapy with the nonsteroidal antiandrogen bicalutamide (‘Casodex’) 150 mg to avoid the side effects of castration

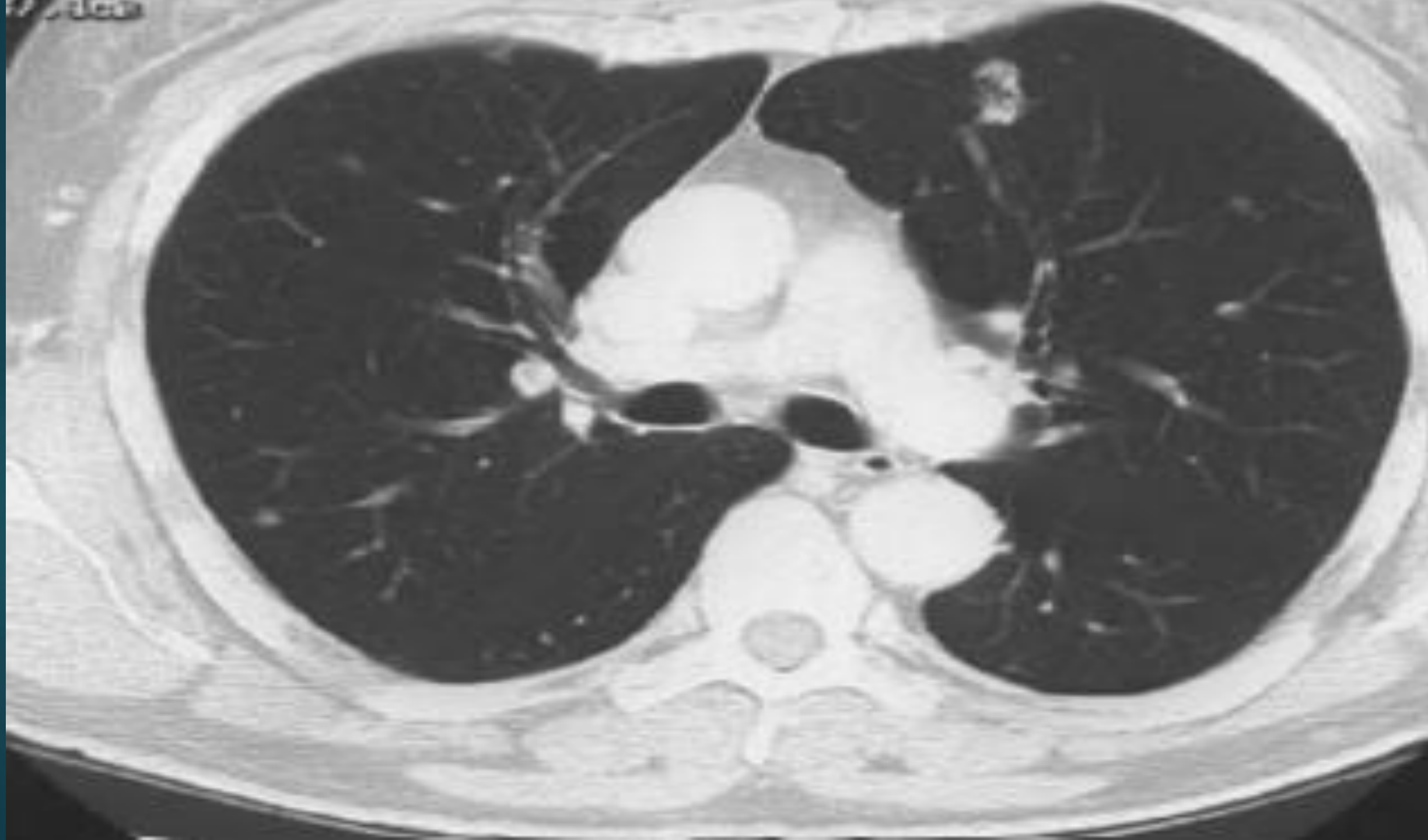
- Within 3 months, the PSA level fell to 0.1 ng/ ml; however, after 2 y of bicalutamide treatment, the patient decided to discontinue therapy after developing gynecomastia, which he found embarrassing

- Subsequently, the PSA level gradually increased to 23 ng/ml and, in 2017, the patient developed breathlessness and hemoptysis

- A computed tomography scan and bone scan revealed pulmonary metastases, but no bone and other soft tissue metastases



- A lung biopsy revealed moderately differentiated metastatic adenocarcinoma
- Is it need to biopsy?
- Is it different biopsy from prostate and metastatic site?



- The patient still wished to avoid castration, and elected to restart bicalutamide 150 mg monotherapy
- the PSA level had fallen to 2.7 ng/ml and there was marked regression of the pulmonary metastases

- Although the outcome following radical prostatectomy is generally favorable, up to one-third of men will experience PSA progression within 10 y
- 1 Such patients are at increased risk of developing metastases
- 2 and should be considered for second-line radiotherapy and/or hormonal therapy

- Prostate cancer metastases are most commonly skeletal; pulmonary metastases are usually only seen after bone or lymph node involvement.3
- The present case, in which pulmonary metastases developed without detectable disease in the bones or other soft tissue sites, is very rare

- The mainstay of treatment for men with advanced prostate cancer is hormonal therapy
- Recent American Society of Clinical Oncology (ASCO) guidelines recommended bilateral orchiectomy or medical castration with an LH-RH agonist as initial treatments
- Nonsteroidal antiandrogen monotherapy may be discussed as an alternative to castration
- Steroidal antiandrogens should not be offered as monotherapy, since they have a smaller time to disease progression relative to LH-RH agonists
- Combination therapy, that is, castration combined with a nonsteroidal antiandrogen, is a further treatment option

- This patient wished to avoid the side effects of castration, and opted to receive bicalutamide 150 mg monotherapy. Nonsteroidal antiandrogens have an improved side-effect profile compared with castrationbased therapy, particularly in terms of maintaining sexual interest and physical capacity and avoiding loss of bone mineral density
- However, these benefits in favor of nonsteroidal antiandrogen monotherapy need to be balanced against the available comparative efficacy data from randomized trials in patients with metastatic disease, which show mixed results
- It should be noted that there are currently no randomized trial data on the use of any hormonal therapies in patients with rising PSA

- Among the nonsteroidal antiandrogens, bicalutamide 150 mg offers an attractive monotherapy option in terms of its risk of side effects, with a low incidence of nonpharmacologic complications
- In contrast, flutamide carries a higher risk of gastrointestinal effects and hepatotoxicity than the other nonsteroidal antiandrogens, and nilutamide is associated with delayed adaptation to darkness, alcohol intolerance, and interstitial pneumonitis
- With all nonsteroidal antiandrogens, the most frequent side effects are mild-to-moderate gynecomastia and breast pain

Case no 2

- a 66-year-old man, a former smoker who suffers from hypertension, with moderate urinary obstructive symptoms
- He was found to have a prostate-specific antigen (PSA) of 32 ng/mL, and a suspicious digital rectal examination (DRE) suggestive of clinical T3a disease

- Biopsy revealed 10/12 positive cores with Gleason 4+3 = 7 pattern and a tertiary Gleason 5 pattern

- What does evaluation you suggest?(before surgery or other treatment)
- MRI(what kind),CTSCAN,BONE SCAN,PET CTSCAN

- Abdominal CT showed no adenopathy, but one suspicious bone lesion
- That bone lesion was confirmed by 18F-PSMA-PET/CT scan
- The overall diagnosis for this patient was M1b hormone-sensitive prostate cancer with a low metastatic burden

- The first question was regarding preferred systemic treatment options:
- (1) androgen deprivation therapy (ADT) alone
- (2) ADT + docetaxel
- (3) ADT + enzalutamide or apalutamide
- (4) ADT + abiraterone

Given these options, the discussants proposed various considerations for how to decide on treatment

Treatment considerations for mHSPC

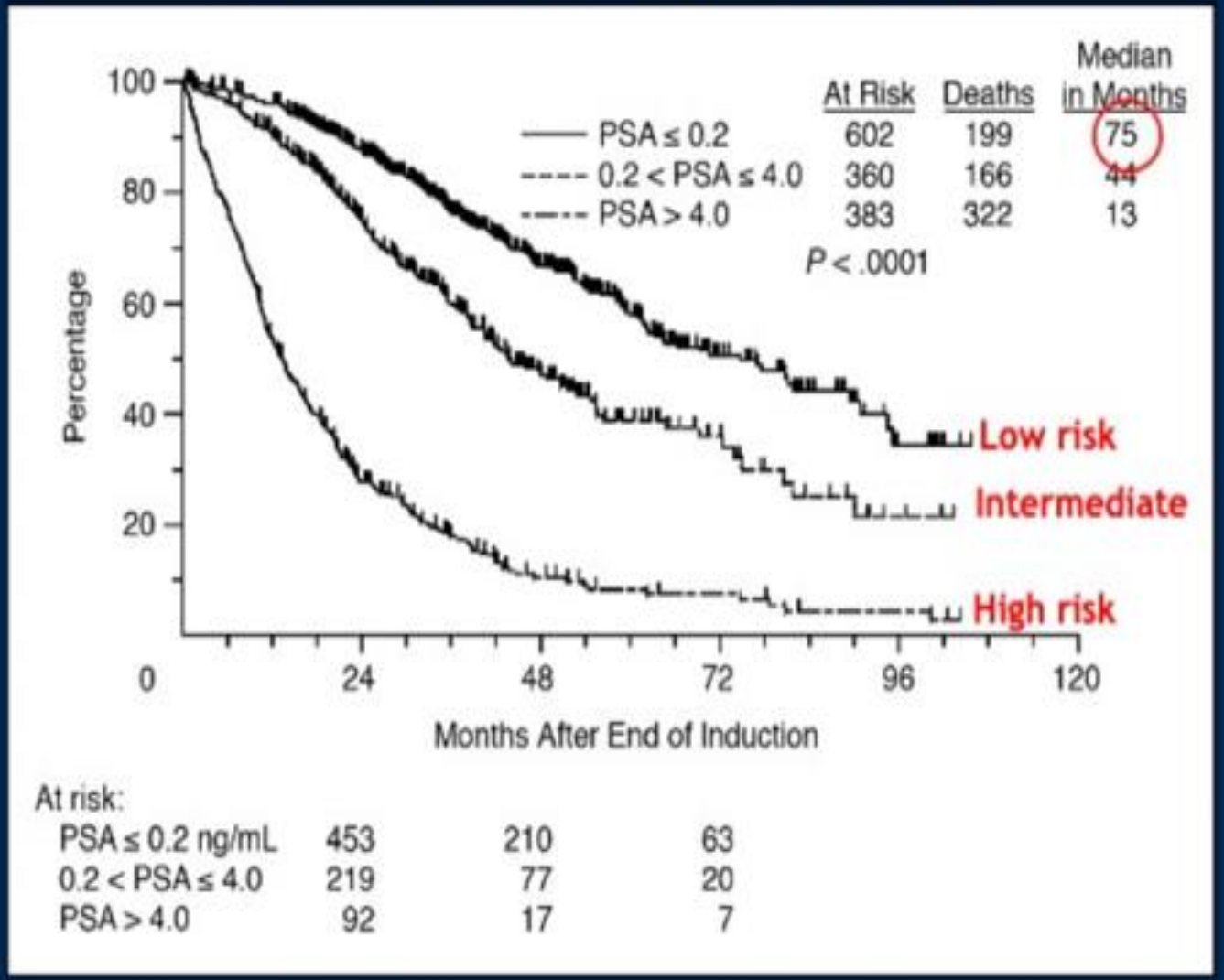
- De novo versus recurrent disease at presentation
- Volume of disease
- Co-morbidities
- Side effect profiles
- Patient preferences
- Cost
- Availability of drugs

- For this patient with “low volume” metastatic hormone-sensitive prostate cancer, there are multiple treatment options including ADT alone, ADT + anti-androgen
- the addition of radiation therapy to the primary

ADT alone? (!)

- Can response to ADT alone be used to make treatment decisions in low volume disease?

Overall survival by PSA status after 7 months ADT alone (SWOG 9346)

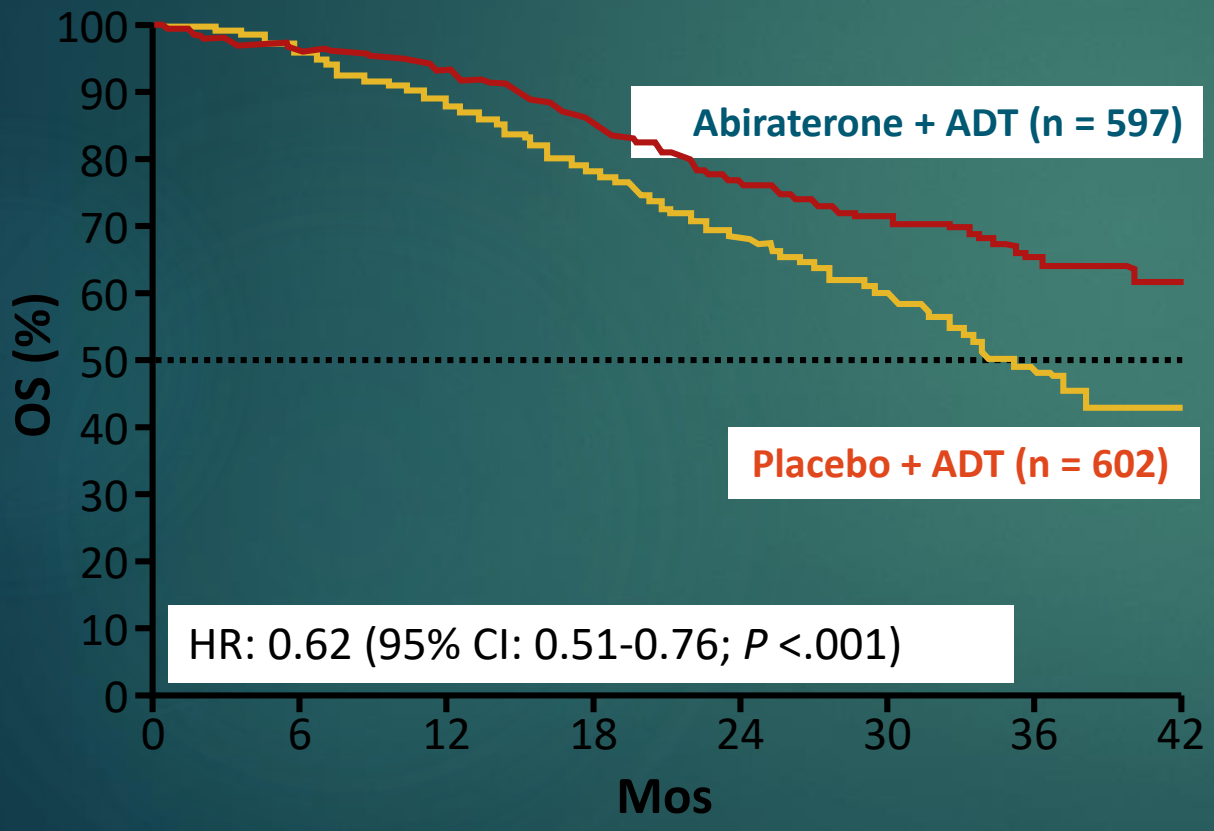


- For this patient with “low volume” metastatic hormone-sensitive prostate cancer, there are multiple treatment options including ADT alone, ADT + anti-androgen

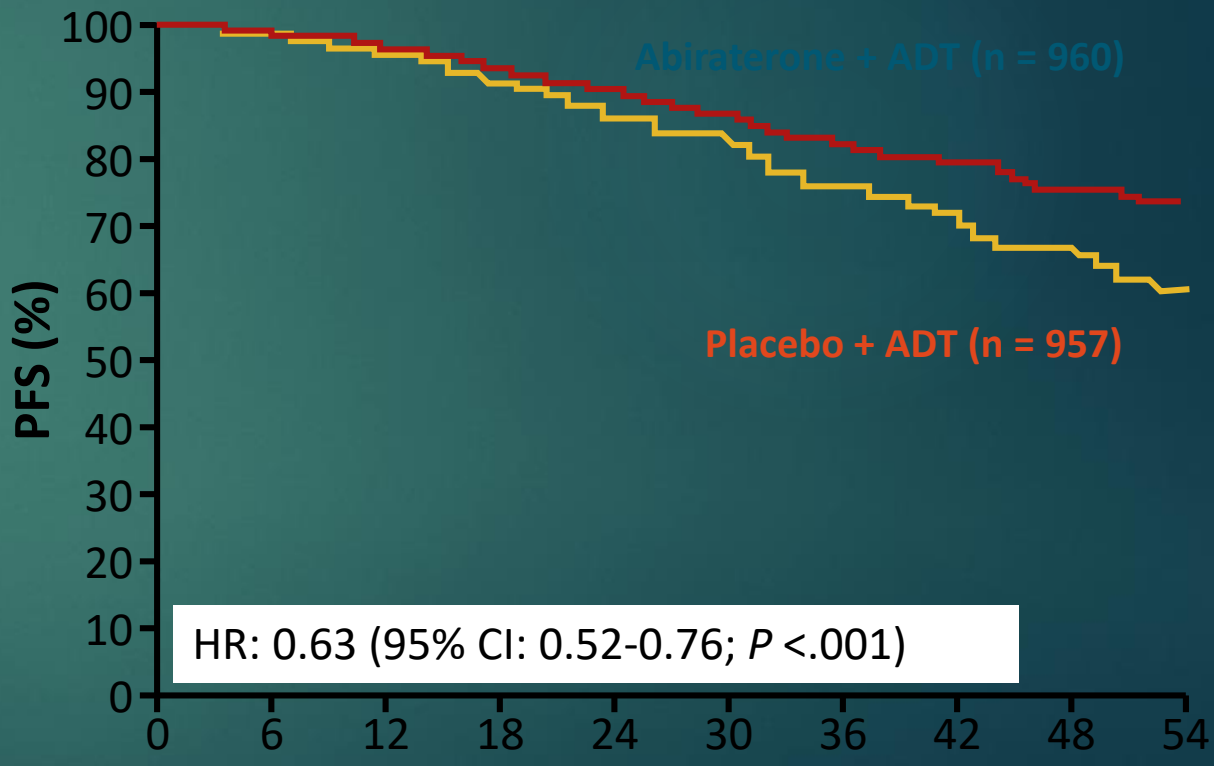
- What's your opinion about radiotherapy to prostate and metastatic site at low volume met patient?

Abiraterone Acetate

- LATITUDE: randomized, double-blind phase III trial of abiraterone acetate + ADT vs placebo + ADT in patients with newly diagnosed mHSPC (N = 1199)



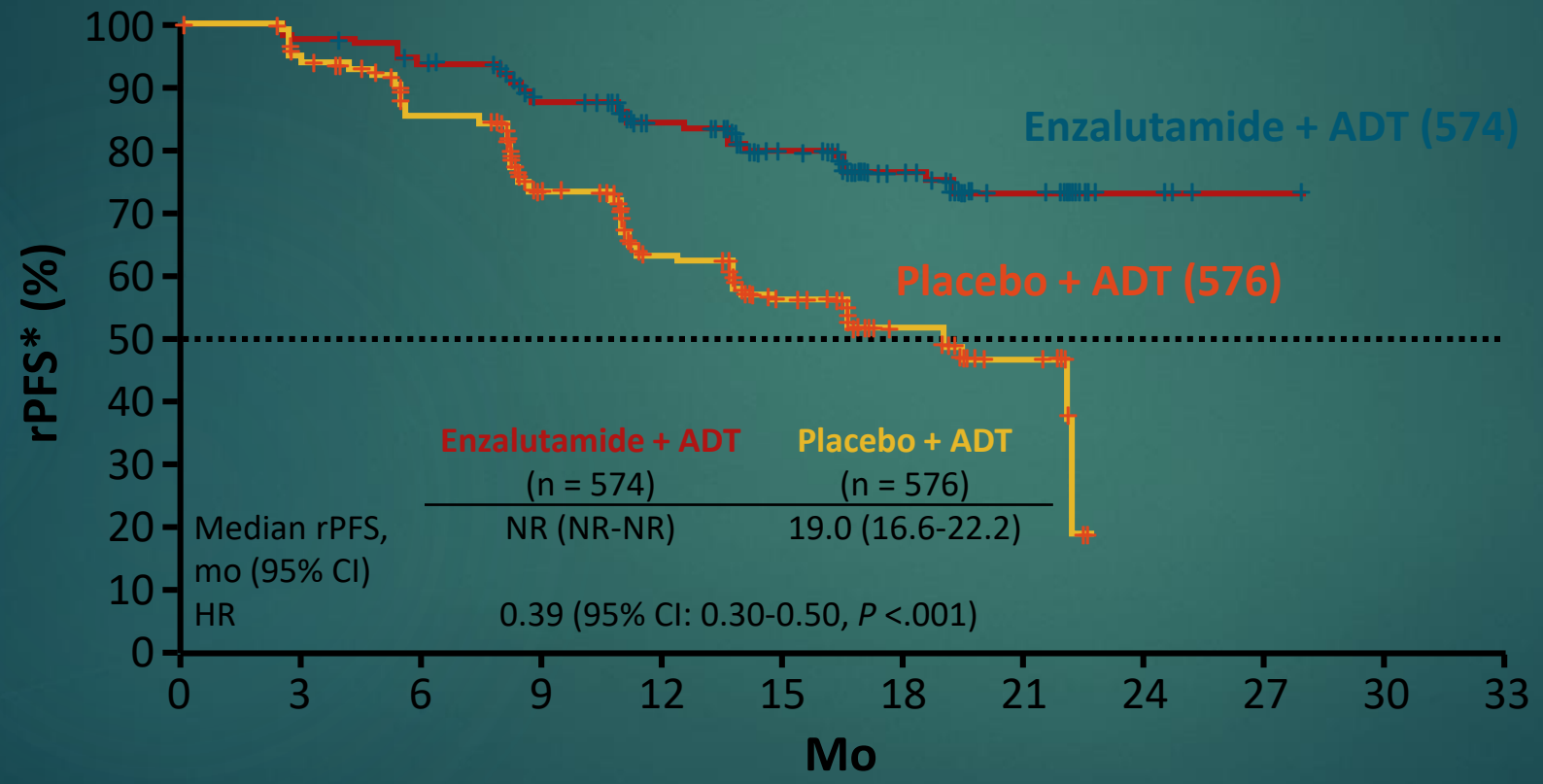
- STAMPEDE: randomized, open-label, multiarm, multistage phase II/III trial (N = 1917)



Fizazi. NEJM. 2017;377:352. James. NEJM. 2017;377:338.

ARCHES: Enzalutamide + ADT vs Placebo + ADT in mHSPC

- International, double-blind, randomized phase III trial of enzalutamide 160 mg/day + ADT vs placebo + ADT for patients with mHSPC (N = 1150)



- Overall survival: HR 0.81 (95% CI: 0.53-1.25); *P* = .3361; however, survival data were immature with only 14.4 mo median follow-up and 84 deaths

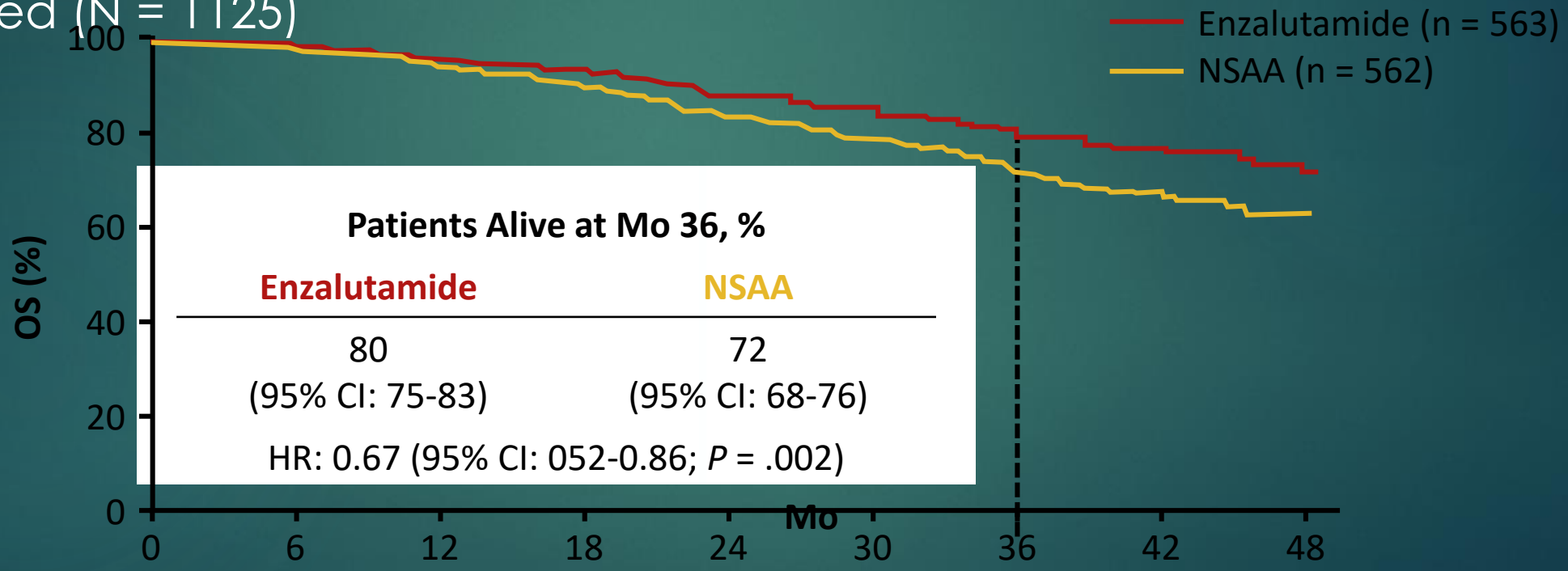
*Included only patients with no documented progression event and censoring at the date of the last radiologic assessment prior to the cutoff date.

Armstrong. JCO. 2019;37:2974.

Slide credit: clinicaloptions.com

ENZAMET: Enzalutamide + ADT vs NSAA + ADT in mHSPC

- Randomized, open-label phase III trial of enzalutamide + testosterone suppression vs standard NSAA*+ testosterone suppression for patients with metastatic prostate cancer, starting first-line ADT; 2 cycles prior docetaxel allowed (N = 1125)



*Bicalutamide, nilutamide, or flutamide.

Davis. NEJM. 2019;381:121.

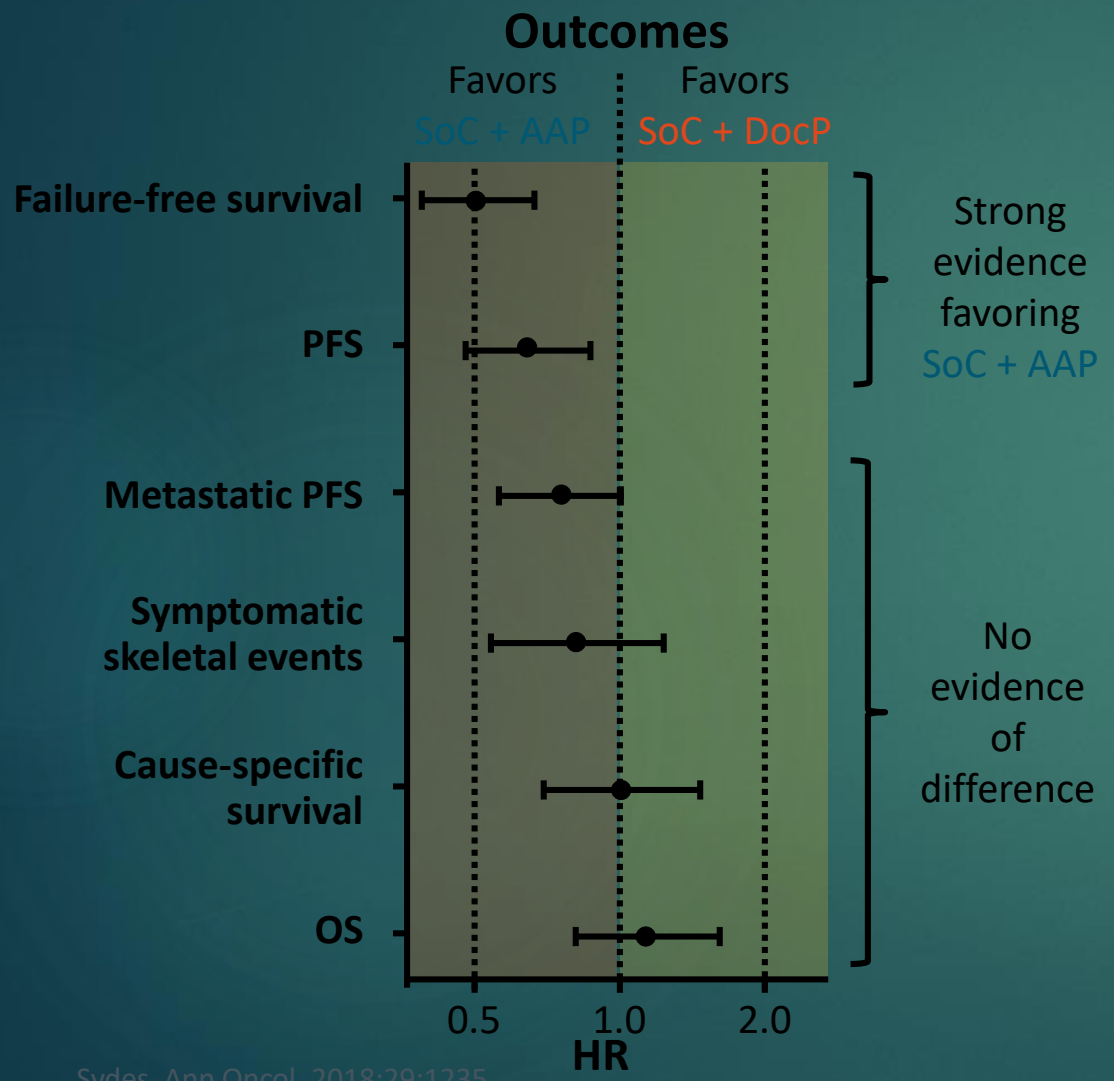
Slide credit: clinicaloptions.com

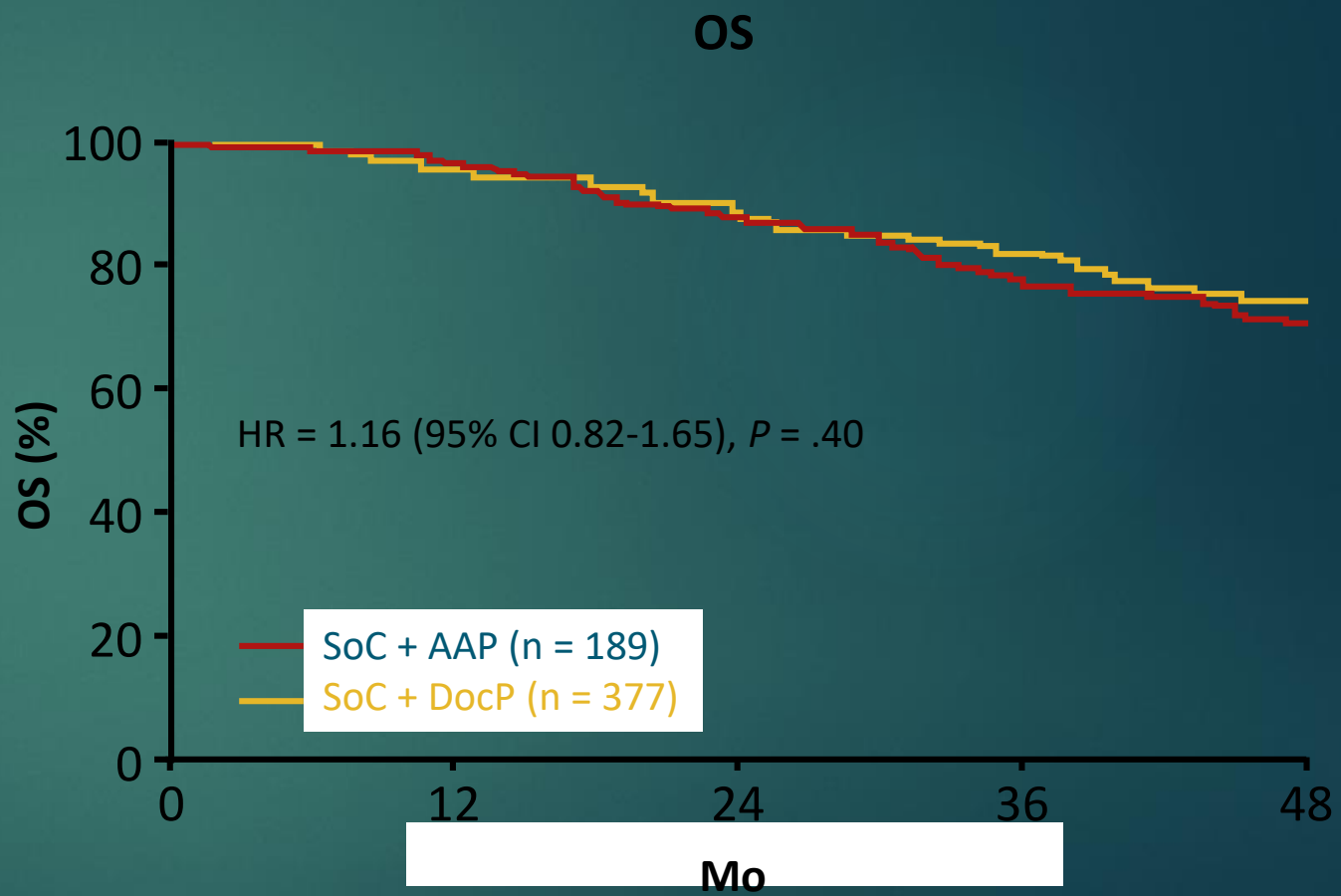
ENZAMET: Select Docetaxel-Relevant AEs

AE in First 6 Mo, n (%)	Enzalutamide + Docetaxel (n = 254)	NSAA + Docetaxel (n = 246)	Enzalutamide No Docetaxel (n = 309)	NSAA No Docetaxel (n = 312)
Neutropenic fever	35 (14)	32 (13)	1 (<1)	0
Sensory neuropathy				
▪ Grade 2	24 (9)	7 (3)	0	2 (<1)
▪ Grade 3	3 (1)	1 (<1)	0	0
Motor neuropathy				
▪ Grade 2	4 (2)	1 (<1)	0	0
▪ Grade 3	0	0	1 (<1)	0
Nail discoloration	25 (10)	13 (5)	0	0
Grade 1/2 watery eyes	52 (20)	15 (6)	0	0
Grade 2 fatigue	52 (20)	35 (14)	32 (10)	9 (3)

Sweeney. ASCO 2019. Abstr LBA2. Davis. NEJM. 2019;381:121.

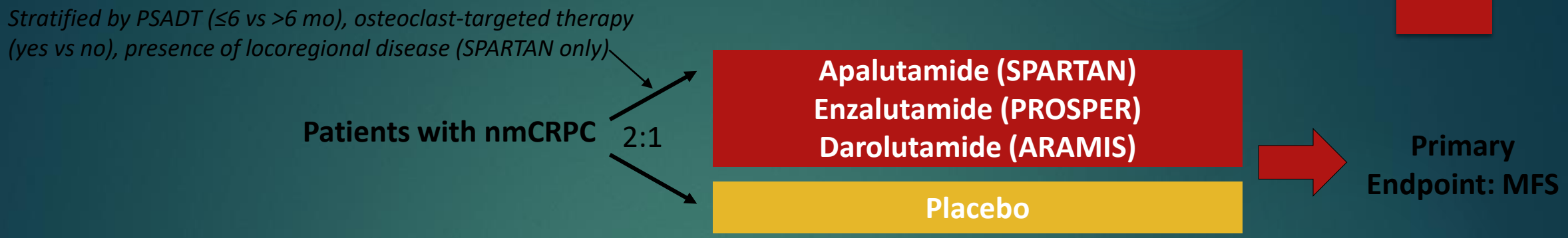
STAMPEDE: Docetaxel vs Abiraterone Comparison





Sydes. Ann Oncol. 2018;29:1235.

Current Clinical Trials in Nonmetastatic CRPC



Criterion	SPARTAN (Apalutamide)[1-3]	PROSPER (Enzalutamide)[4-7]	ARAMIS (Darolutamide)[8,9]
Seizure history	Excluded, including predisposing conditions	Excluded, including predisposing conditions	Allowed, including predisposing conditions
LN involvement	Pelvic LN progression *not* considered MFS event	Pelvic LN progression *was* considered MFS event	Pelvic LN progression *not* considered MFS event
Bone targeting/sparing agent	Apalutamide: 10.2% Placebo: 9.7%	Enzalutamide: 10.2% Placebo: 10.4%	Darolutamide: 3% Placebo: 6%
PSA blinding	Yes	Yes	No
Secondary endpoints	Time to mets, PFS, TTP, OS, time to first new chemotherapy	Time to PSA progression, PSA RR, time to first neoplastic therapy, QoL, OS, safety	OS, time to pain progression, time to chemotherapy, time to first symptomatic SRE
Crossover unblinding	76 patients (19%) continued open-label apalutamide	87 pts (19%) continued open-label enzalutamide	170 patients (31%) continued open-label darolutamide

1. Small. ASCO 2020. Abstr 5516. 2. NCT01946204. 3. Smith. NEJM. 2018;378:1408. 4. NCT02003924. 5. Sternberg. NEJM. 2020;382:2197.
6. Hussain. NEJM. 2018;378:2465. 7. Sternberg. NEJM. 2020;382:2197. 8. Fizazi. ASCO 2020. Abstr 5514. 9. Fizazi. NEJM. 2019;380:1235.

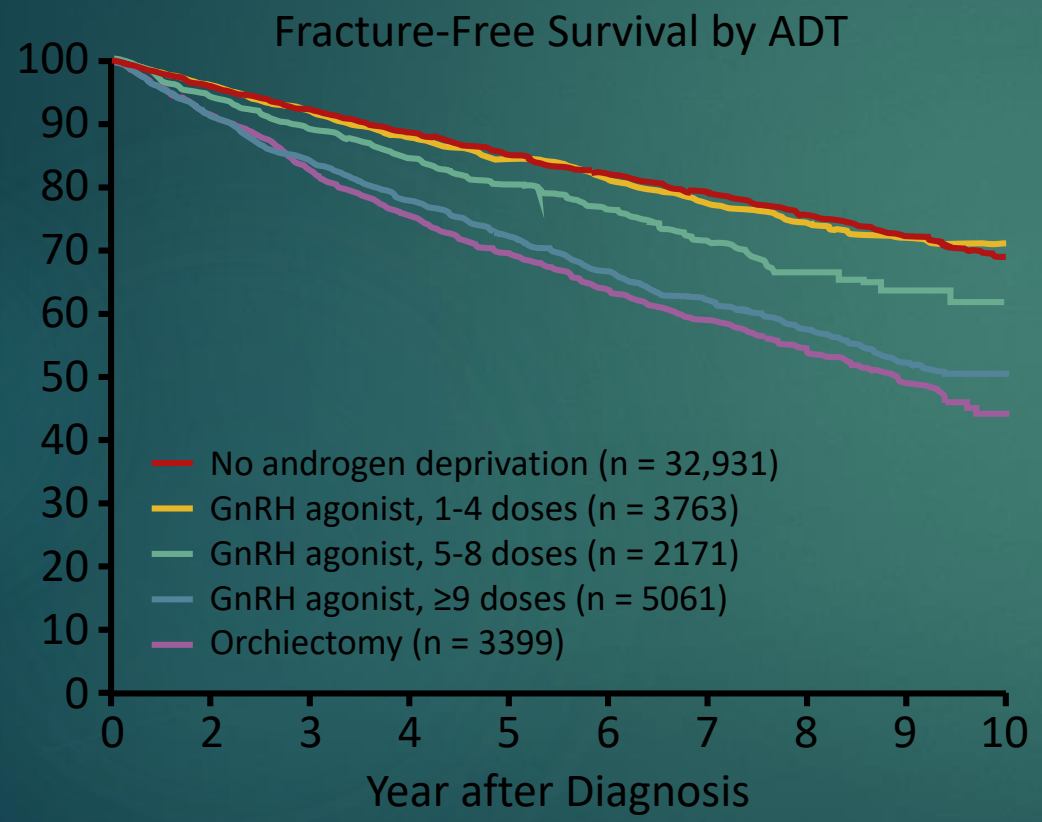
nmCRPC: Conclusions From SPARTAN, PROSPER, and ARAMIS

- Apalutamide, enzalutamide, and darolutamide all significantly improved OS vs placebo in men with nmCRPC
  - SPARTAN: 22% reduction of risk of death (HR: 0.78; *P* = .016)[1]
  - PROSPER: 27% reduction of risk of death (HR: 0.73; *P* = .001)[2]
  - ARAMIS: 31% reduction of risk of death (HR: 0.69; *P* = .003)[3]
- AEs leading to study drug discontinuation
  - SPARTAN: apalutamide (14.9%) vs placebo (7.3%)[1]
  - PROSPER: enzalutamide (17.0%) vs placebo (9.0%)[2]
  - ARAMIS: darolutamide (8.9%) vs placebo (8.7%)[3]

1. Smith. Eur Urol. 2021;79:150. 2. Sternberg. NEJM. 2020;382:2197. 3. Fizazi. NEJM. 2019;380:1235.

Fracture Risk Associated With ADT in Prostate Cancer

- Retrospective analysis of 50,613 men in SEER-Medicare database diagnosed with prostate cancer between 1992-1997



Risk of Fracture by ADT (Multivariate Analysis)

Variable	RR, Fracture (95% CI)	RR, Hospitalization (95% CI)
ADT		
▪ None	1.00	1.00
▪ GnRH agonist		
▪ 1-4 doses	1.07 (0.98-1.16)	0.98 (0.82-1.17)
▪ 5-8 doses	1.22 (111-1.35)	1.51 (1.26-1.80)
▪ ≥9 doses	1.45 (1.36-1.56)	1.66 (1.47-1.87)
▪ Orchiectomy	1.54 (1.42-1.68)	1.70 (1.48-1.96)
Age (in 5-yr categories)	1.21 (1.19-1.24)	1.45 (1.40-1.50)

Curves begin at 12 mo post diagnosis; ADT was started within 6 mo post diagnosis.

Shahinian. NEJM. 2005;352:154.

Take-home Messages

- Some patients with nmCRPC will benefit from novel androgen receptor inhibitors
  - PSADT of less than 10 mo is a good tool to determine which patients to treat
- All 3 AR inhibitors are effective
  - Differences in side effect profiles and patient preferences will drive treatment choice
  - Cardiovascular conditions may factor heavily in decision-making as well
- Bone health is an important consideration for men on ADT
  - Vitamin D may be helpful
  - Patients should be screened for osteoporosis
  - There are effective agents to treat bone loss in these patients

Guideline Recommendations: 2021 Treatment Options for mHSPC

ADT

ADT plus:

Abiraterone

Apalutamide

Enzalutamide

Docetaxel

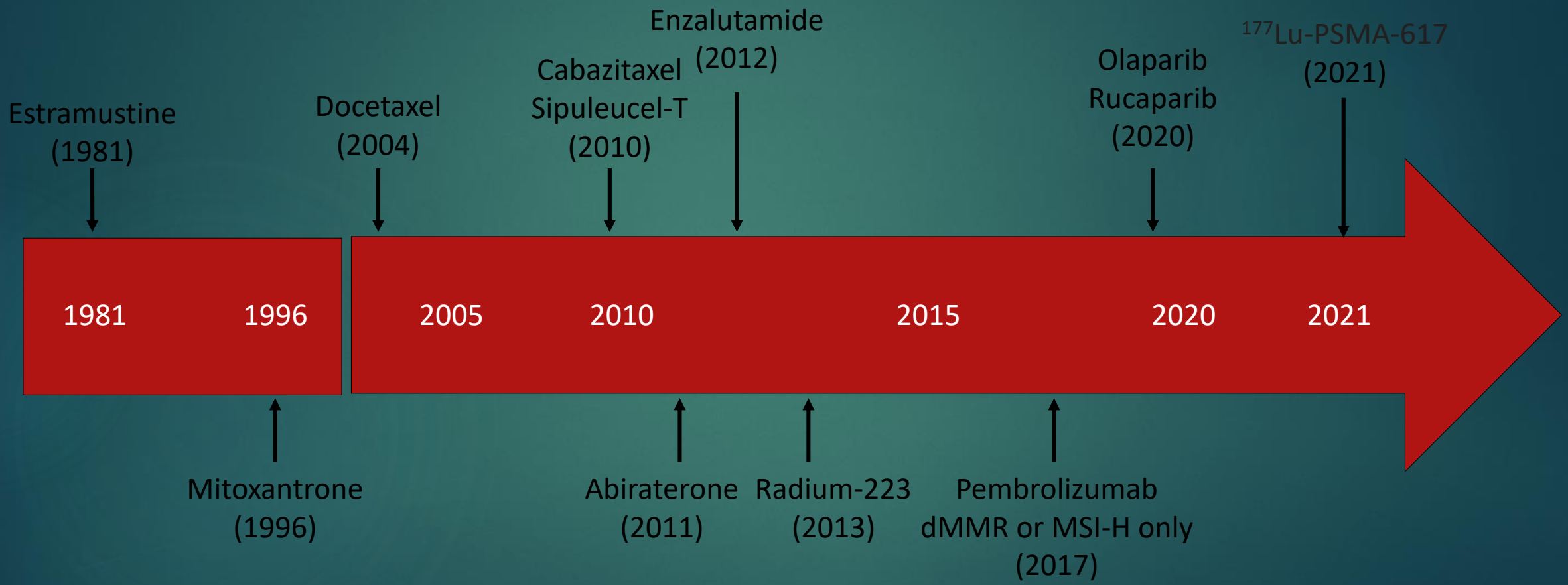
ADT plus EBRT to primary tumor (for low-volume disease)

NCCN. Clinical practice guidelines in oncology: prostate cancer. v2.2021.

Overall Conclusions

- Treatment intensification with docetaxel or an AR-targeted therapy is the new standard of care for mHSPC
  - ADT alone is no longer the standard of care for the vast majority of men
- Treatment intensification is preferred regardless of how fast or far PSA falls
- Quality of life and patient preferences should be considered when choosing treatment
  - Shared decision-making can help match a patient with the right treatment for him

FDA-Approved Agents for mCRPC



- Dates are for initial approvals

Abiraterone PI. Enzalutamide PI. Docetaxel PI. Cabazitaxel PI. Mitoxantrone PI. Estramustine PI. Sipuleucel-T PI. Pembrolizumab PI. Radium-223 PI. Olaparib PI. Rucaparib PI.

Therapeutic Decision-Making for Patients With mCSPC Based Upon Disease State and Clinical Factors[1]

Clinical Factors	Low-Volume Disease (Chemotherapy Appropriate)	High-Volume Disease (Chemotherapy Appropriate)
• Fitness for chemotherapy • Fitness for AR inhibitor (frailty and comorbidities) • Fitness for abiraterone (blood sugar, cardiac history, and liver disease) • Prior therapy (eg, AR inhibitor in nmCRPC) • Non-AR phenotype (poor PSA expressor and presence of hepatic metastases)	• Evidence for AR inhibitor • Evidence for abiraterone • Less compelling data for docetaxel	• Evidence for AR inhibitor • Evidence for abiraterone • Evidence for docetaxel

1. VanderWeele DJ et al. *J Clin Oncol*. 2019;37:2961-2967.

با تشکر از صبر وحوصله همگی