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TREATING mCRPC PATIENTS WHO HAVE PROGRESSED ON AR-DIRECTED THERAPY

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INTRODUCTION

- The increased use of potent AR-directed therapies, abiraterone and enzalutamide, in first and second-line treatment of mCRPC has improved patient outcomes but the development of secondary resistance remains a clinical challenge[1]
- Studies show limited benefit to using AR-directed therapies in patients previously treated with these agents[2-6]
- Drugs with different mechanisms of actions are more likely to be beneficial after new hormonal therapies, e.g. docetaxel, cabazitaxel, radium-223 or other agents
- There will be an increasing mCRPC patient population who have received prior treatment with new hormonal therapies (abiraterone, enzalutamide, apalutamide and darolutamide) earlier in their treatment journey

AR, androgen receptor; mCRPC, metastatic castration resistant prostate cancer

1. Chi K, et al. Ann Oncol. 2015;26:2044-56; 2. Attard G, et al. JCO. 2018;36(25):2639-46; 3. Khalaf D, et al. Lancet Oncol. 2019;20:1730-39; 4. Smith MR et al. Eur Urol. 2017;72(1):10-13; 5. Zhang T, et al. Clin Genitourin Cancer. 2015;13:392-9; 6. Azad AA, et al. Eur Urol. 2015;67:23-9

NCCN TREATMENT GUIDELINES FOR mCRPC

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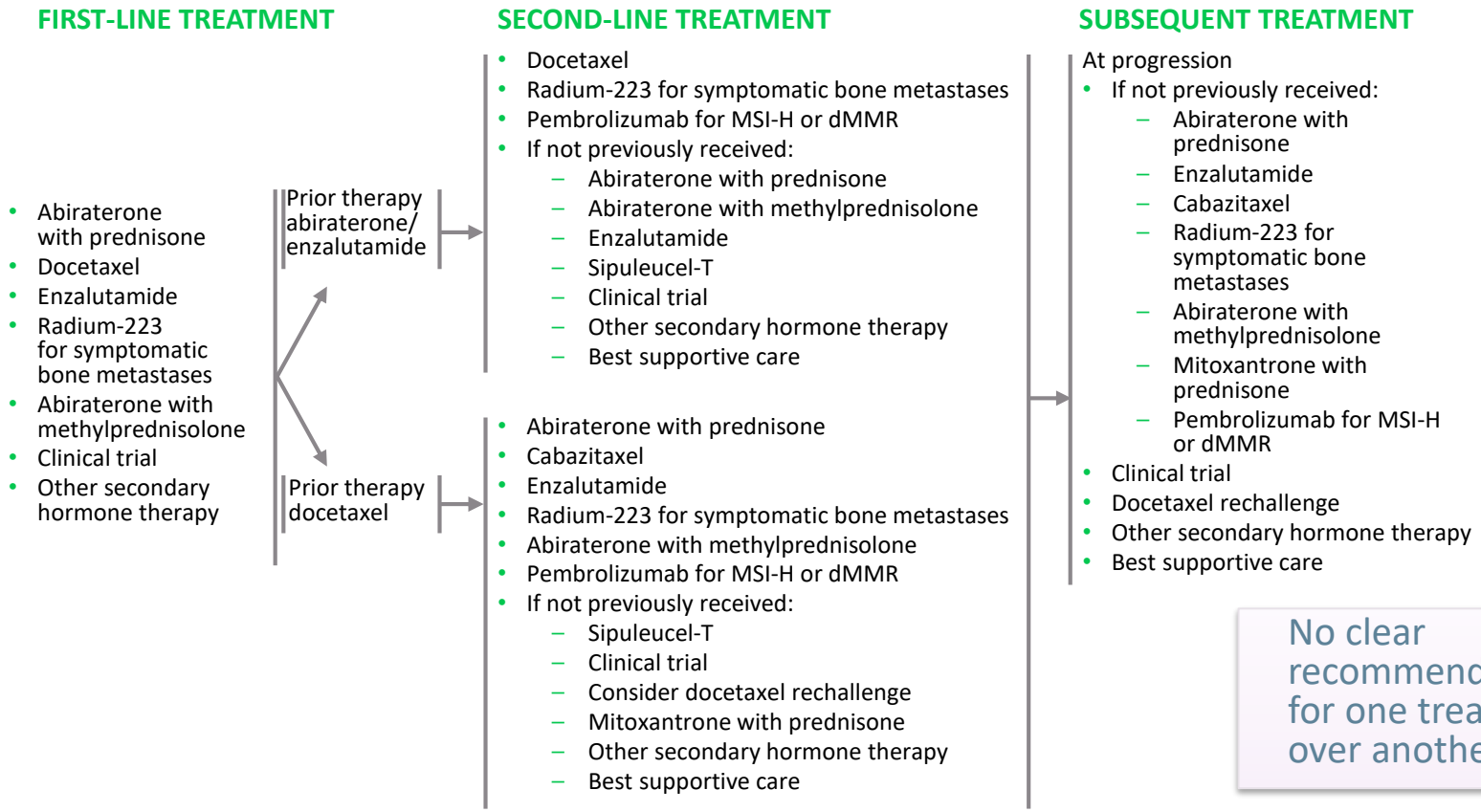
National Comprehensive Cancer Network®

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA WITHOUT VISCERAL METASTASES



No clear recommendation for one treatment over another

CRPC, castrate resistant prostate cancer; dMMR, mismatch repair deficient; M, metastasis; mCRPC, metastatic castrate resistant prostate cancer; MSI-H, microsatellite instability-high; NCCN, national comprehensive cancer network.

NCCN Clinical Practice Guidelines in Oncology (Prostate Cancer) Version 4, Aug 2019. Retrieved from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Access date: 16 Jan 2020.

NCCN TREATMENT GUIDELINES FOR mCRPC

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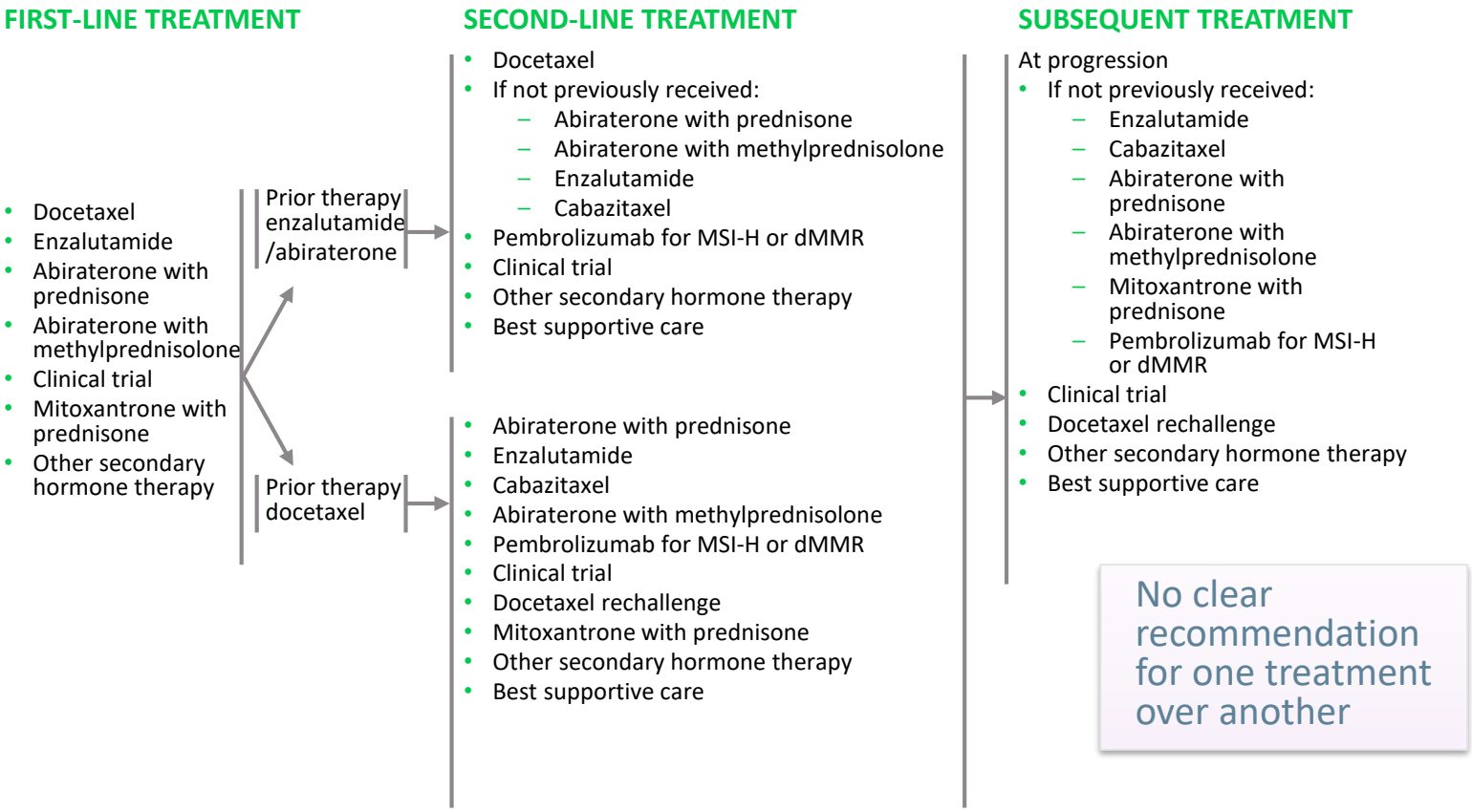

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NCCN Clinical Practice Guidelines in Oncology (Prostate Cancer) Version 4, Aug 2019. Retrieved from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Access date: 16 Jan 2020.

MULTIPLE TREATMENT OPTIONS FOR mCRPC

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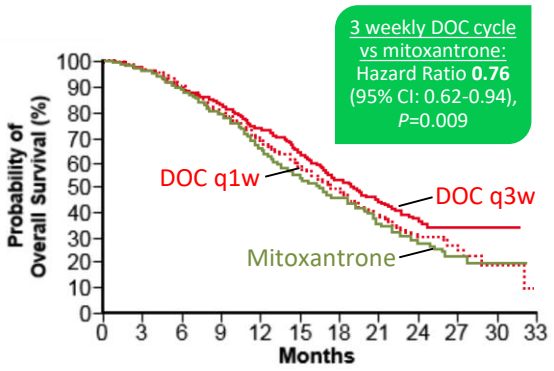
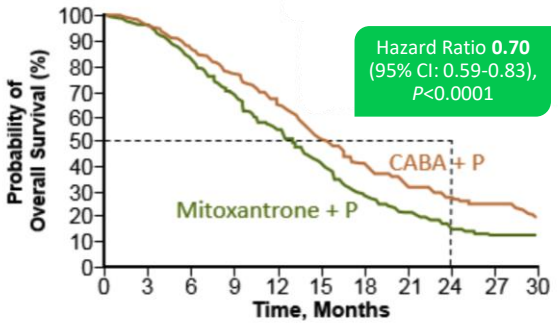
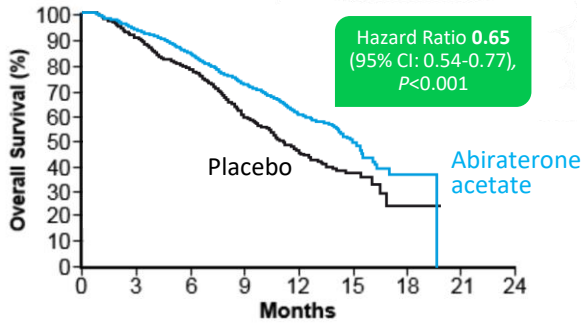
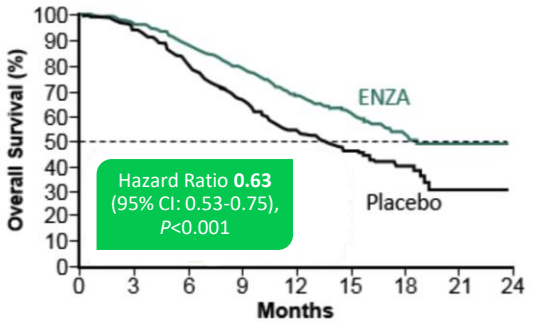
No clear recommendation for one treatment over another

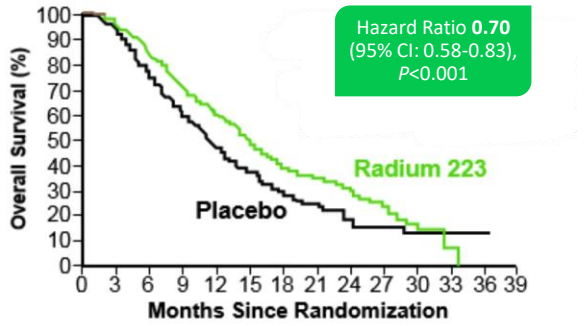
Different mechanism of action critical

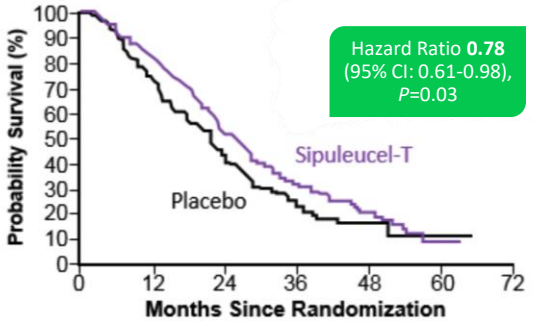










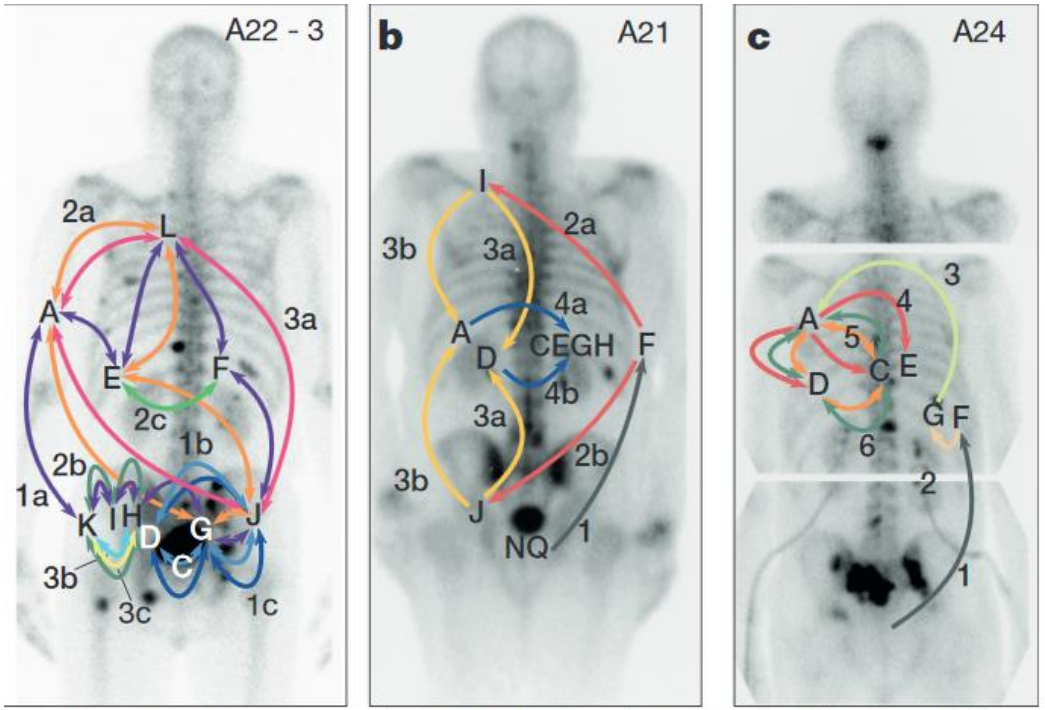


ABI, abiraterone; CABA, cabazitaxel; CI, confidence interval; DOC, docetaxel; ENZA, enzalutamide; mCRPC, metastatic castration resistant prostate cancer; q1w, once a week; q3w, every 3 weeks; P, prednisone.

Tannock IF, et al. NEJM. 2004;351:1502-12; de Bono JS, et al. Lancet. 2010;376:1147-54; de Bono JS, et al. NEJM. 2011;364:1995-2005; Scher HI, et al. NEJM. 2012;367:1187-97; Parker C, et al. NEJM. 2013;369:213-23; Kantoff PW, et al. NEJM. 2010;363:411-22.

NOVEL MECHANISM NEEDED TO TARGET RESISTANCE

- Resistance mechanisms commonly spreads through metastasis-to-metastasis seeding
- Similar resistance patterns often occur in geographic proximity (interclonal cooperativity)

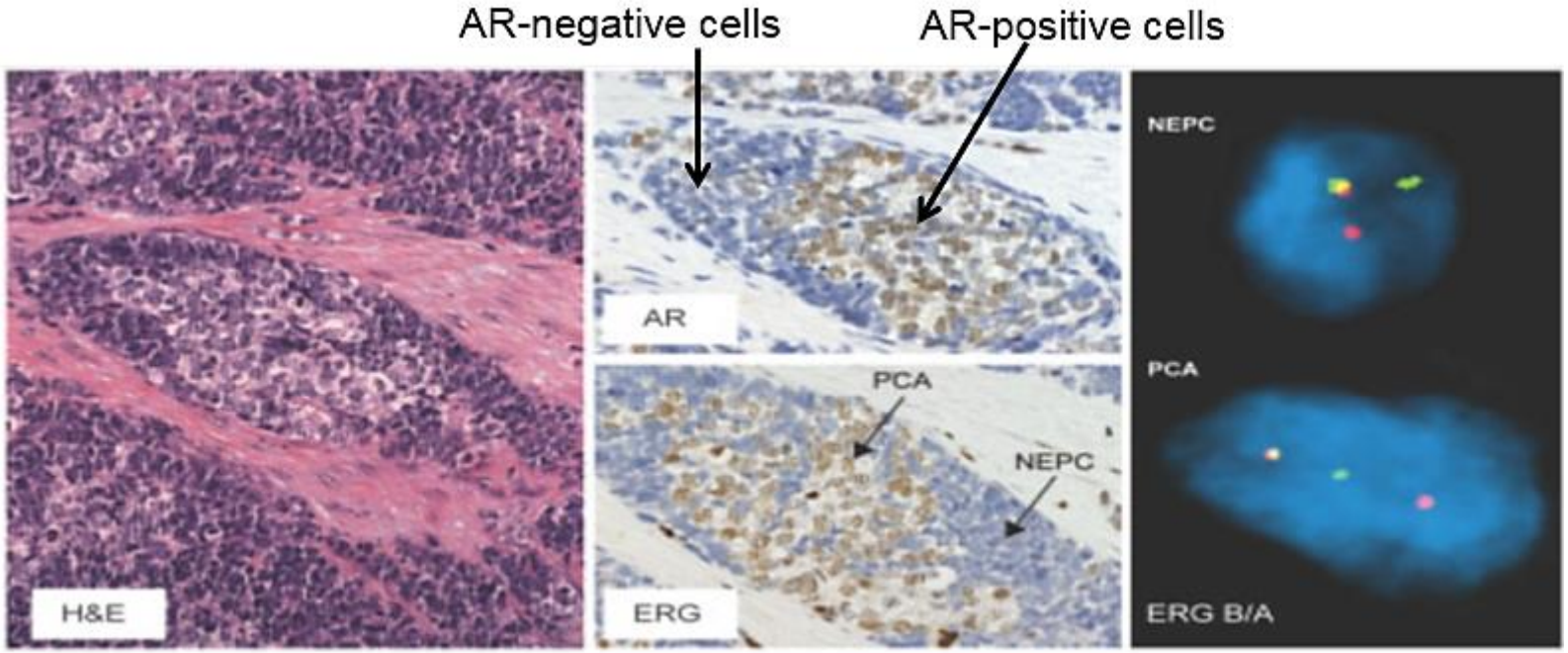


LN, lymph node

Gundem G, et al. Nature. 2015;520(7547):353-7.

NOVEL MECHANISM NEEDED TO TARGET RESISTANCE

- Resistance occurs even within the same site of disease
  - Neuroendocrine features possible adjacent to AR-positive cells



Tumor with mixed features of neuroendocrine PCa and prostate adenocarcinoma

AR, androgen receptor; ERG, E-26 transformation specific-related gene; ERG B/A, ERG break-apart; H&E, hematoxylin and eosin stain; NEPC, neuroendocrine prostate cancer; PCA, prostate adenocarcinoma.

Beltran H, et al. Cancer Discov. 2011;1(6):487-95.

BODY OF EVIDENCE SUGGESTS LIMITED BENEFIT TO SEQUENCING AR TARGETED THERAPIES

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Drug	N	≥50% PSA response	Median PFS (months)	Median OS (months)
Enzalutamide → abiraterone + prednisone				
Attard G et al.[1‡]	125	2%	5.6	Not Reported
Khalaf D et al.[2]	75	4%†	TTPP: 1.7 months*	24.7
Abiraterone + prednisone → enzalutamide				
Smith MR et al.[3]	33	67%	TTPP: 2.8 months	Not Reported
Zhang T et al.[4]	9	11%	3.6	8.5
Azad AA et al.[5]	47	26%	6.6	8.6
Khalaf D et al.[2]	73	36%†	TTPP: 3.5 months*	28.8

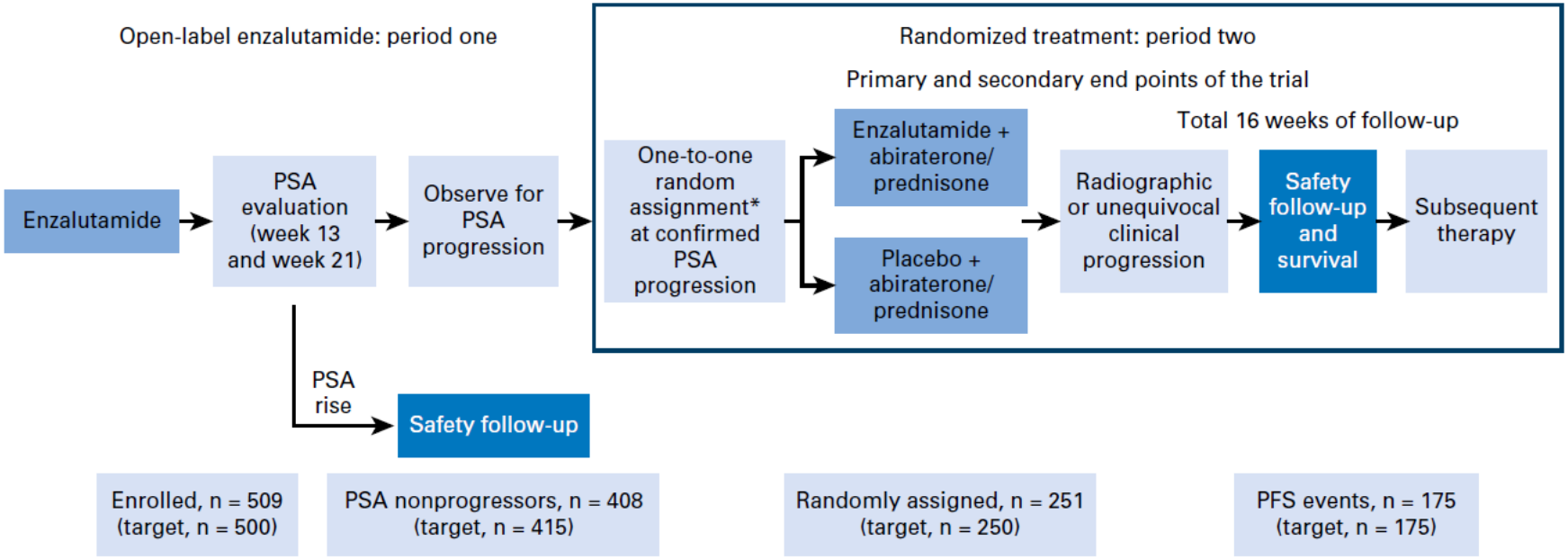
‡Limited benefit of using abiraterone after enzalutamide in the PLATO trial – however was not the primary aim of this trial; †PSA ≥ 30% decline from baseline; *Time to second PSA progression on second therapy

AR, androgen receptor; OS, overall survival; PFS, progression free survival; Prog, progression; PSA, prostate specific antigen; TTPP, time to PSA progression

1. Attard G, et al. JCO. 2018;36(25):2639-46; 2. Khalaf D, et al. Lancet Oncol. 2019;20:1730-39; 3. Smith MR, et al. Eur Urol. 2017;72(1):10-13; 4. Zhang T, et al. Clin Genitourin Cancer. 2015;13:392-9; 5. Azad AA, et al. Eur Urol. 2015;67:23-9.

ABIRATERONE ALONE OR IN COMBINATION WITH ENZALUTAMIDE IN mCRPC WITH RISING PROSTATE-SPECIFIC ANTIGEN DURING ENZALUTAMIDE TREATMENT (PLATO STUDY)

G. Attard, M. Borre, H. Gurney, Y. Loriot, C. Andresen-Daniil, R. Kalleda, T. Pham & M. Taplin on behalf of the PLATO collaborators

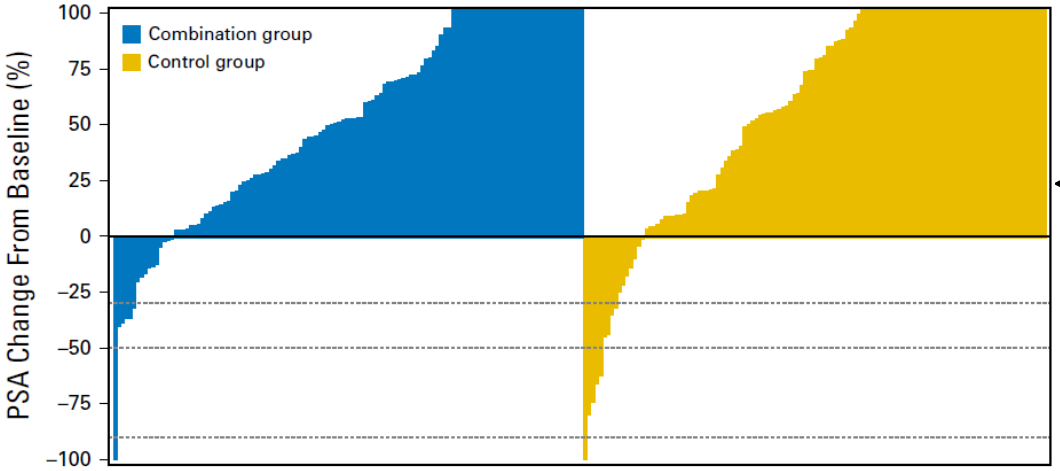


* Random assignment was stratified by confirmed PSA response at week 13 in period one (≥0% to <30% vs ≥ 30%)

mCRPC, metastatic castrate resistant prostate cancer; PFS, progression free survival; PSA, prostate specific antigen.

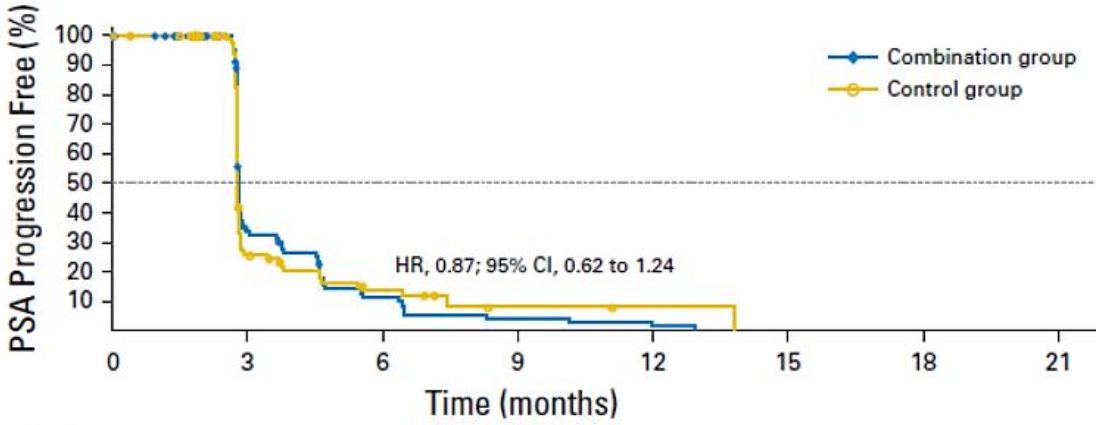
Attard G, et al. JCO. 2018;36(25):2639-46.

PLATO STUDY: PSA ENDPOINTS



Best PSA response

Time to PSA progression



No. at risk:								
Combination group	126	28	8	3	1	0	0	0
Control group	125	22	9	3	1	0	0	0

Primary endpoint of PLATO was not met therefore these endpoints are exploratory; PLATO reported limited benefit with abiraterone after enzalutamide with a low PSA response for both treatment groups

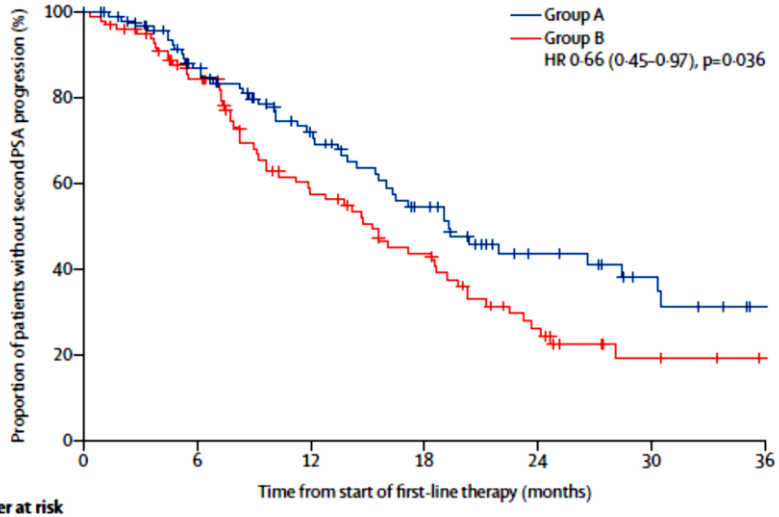
CI, confidence interval; HR, hazard ratio; PSA, prostate specific antigen.

Attard G, et al. JCO. 2018;36(25):2639-46.

CANADIAN CROSS-OVER TRIAL

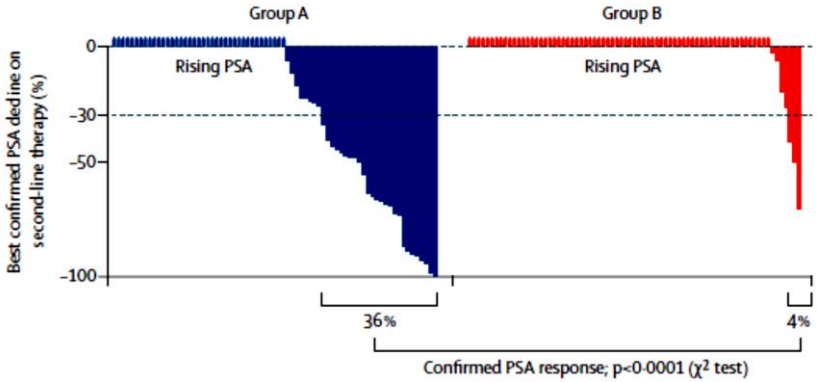
PHASE 2, CROSS-OVER TRIAL OF ENZALUTAMIDE AND ABIRATERONE IN mCRPC PATIENTS

TIME FROM START OF FIRST-LINE THERAPY TO SECOND PSA PROGRESSION



Number at risk (number censored)						
Group A	76 (13)	53 (24)	34 (31)	18 (41)	11 (46)	5 (50)
Group B	75 (11)	43 (22)	30 (25)	15 (29)	6 (35)	3 (38)

BEST CONFIRMED PSA DECLINE DURING SECOND-LINE THERAPY



- This trial demonstrated a benefit to sequencing AR targeted therapies, with enzalutamide after progression on initial abiraterone being the most effective

Group A: abiraterone acetate 1000mg od plus prednisone 5mg bd followed by crossover to enzalutamide 160 mg od upon PSA progression

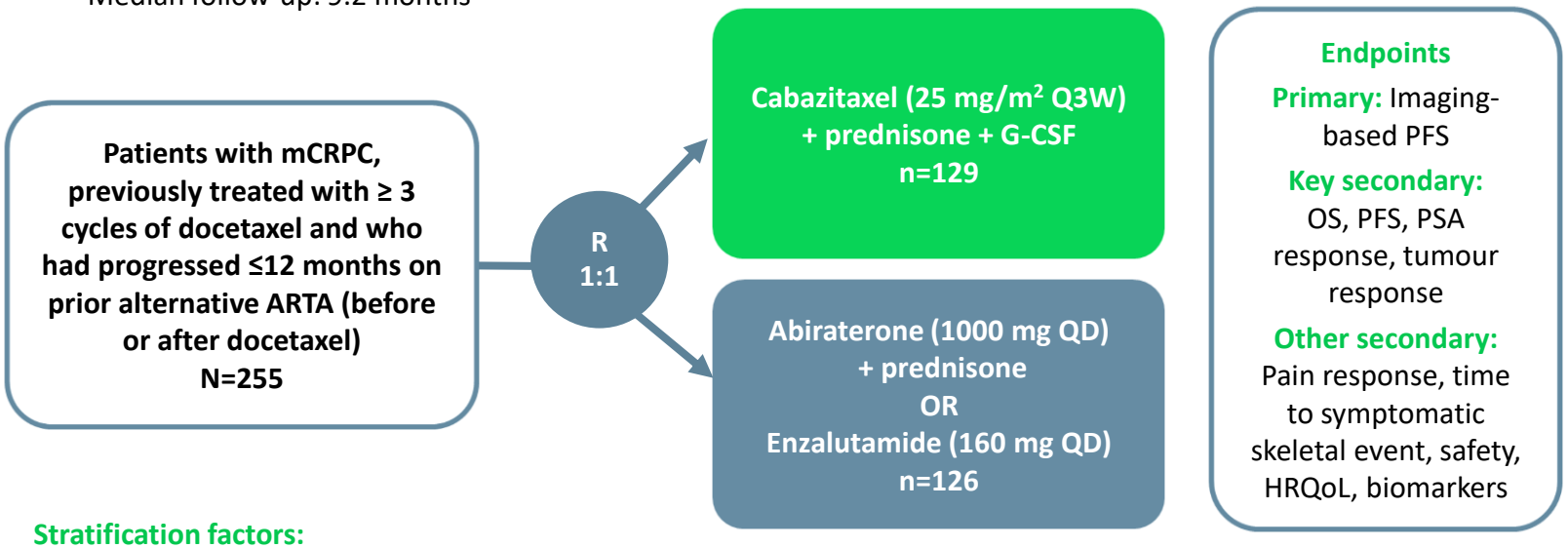
Group B: enzalutamide 160 mg od followed by crossover to abiraterone acetate 1000mg od plus prednisone 5mg bd upon PSA progression

bd, twice daily; HR, hazard ratio; mCRPC, metastatic castrate resistant prostate cancer; od, once daily; PSA, prostate specific antigen

Khalaf D, et al. Lancet Oncol. 2019;20:1730-39.

CARD STUDY DESIGN

- Multicentre, randomised, open-label study
- Enrolment: Nov 2015 – Nov 2018
- Median follow-up: 9.2 months



Stratification factors:

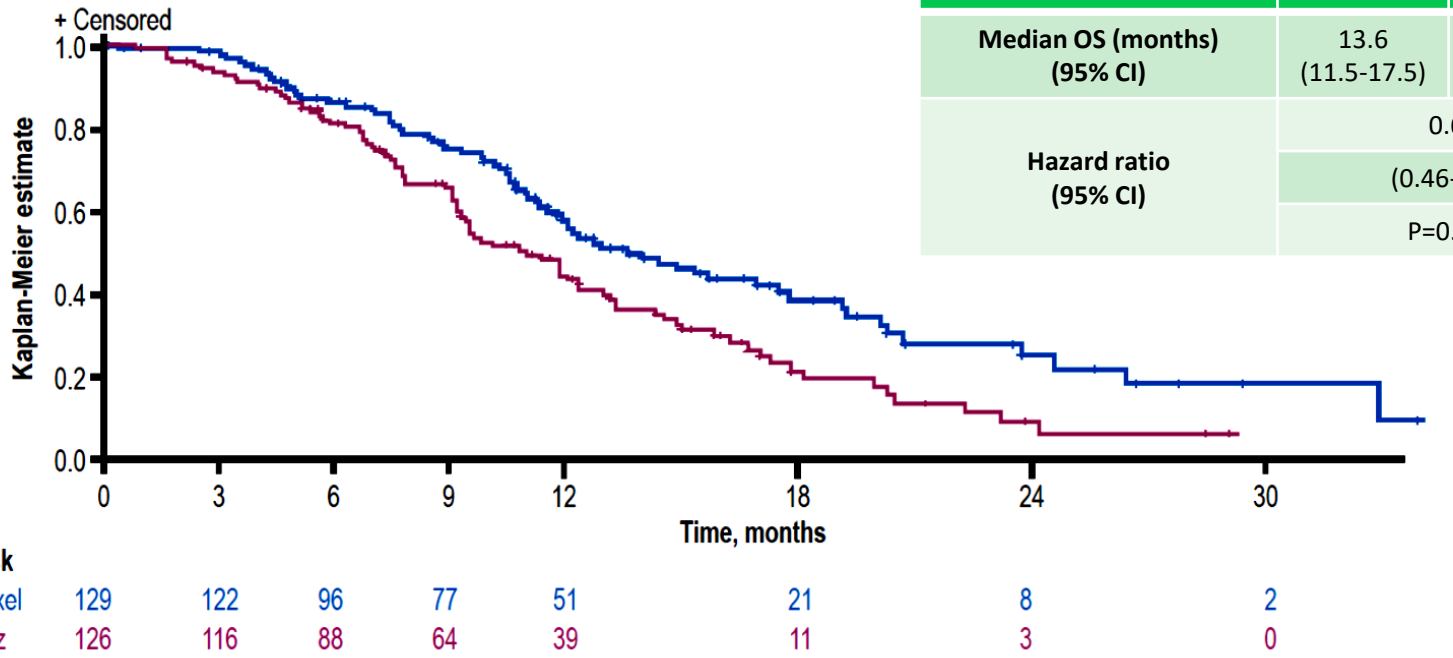
- ECOG PS (0/1 vs 2)
- Time to progression on prior alternative ARTA (0–6 vs >6–12 months)
- Timing of ARTA (before vs after docetaxel)

ARTA, androgen receptor-targeted agents; ECOG PS, eastern cooperative oncology group performance status; G-CSF, granulocyte colony stimulating factor; HRQoL, health related quality of life; mCRPC, metastatic castration resistant prostate cancer; OS, overall survival; Q3W, every three weeks; QD, once daily; PSA, prostate specific antigen

de Wit R, et al. ESMO 2019 Abstract #LBA13; de Wit R, et al. N Engl J Med. 2019;381:2506-18.

CARD STUDY – SECONDARY ENDPOINT

OVERALL SURVIVAL



	cabazitaxel (N=129)	abi/enza (N=126)
Median OS (months) (95% CI)	13.6 (11.5-17.5)	11.0 (9.2-12.9)
Hazard ratio (95% CI)	0.64	
	(0.46-0.89)	
	P=0.008	

- The results of the **CARD trial** are in agreement with those of previous studies that have **shown poor outcomes with a second androgen signaling–targeted inhibitor**[1-5]

Abi, abiraterone; CI, confidence interval; enza, enzalutamide; OS, overall survival

1. Attard G, et al. JCO. 2018;36(25):2639-46; 2. Khalaf D, et al. Lancet Oncol. 2019;20:1730-39; 3. Smith MR, et al. Eur Urol. 2017;72(1):10-13; 4. Zhang T, et al. Clin Genitoruin Cancer. 2015;13:392-9; 5. Azad AA, et al. Eur Urol. 2015;67:23-9; 6. de Wit R, et al. ESMO 2019 Abstract #LBA13; 7. de Wit R, et al. N Engl J Med. 2019;381:2506-18.

USE OF NEW GENERATION ARIs EARLIER IN THE TREATMENT JOURNEY

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RECENT DATA AND REGULATORY APPROVALS

The NEW ENGLAND JOURNAL of MEDICINE

JULY 4, 2019

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

ABSTRACT

FDA approves apalutamide for metastatic castration-sensitive prostate cancer

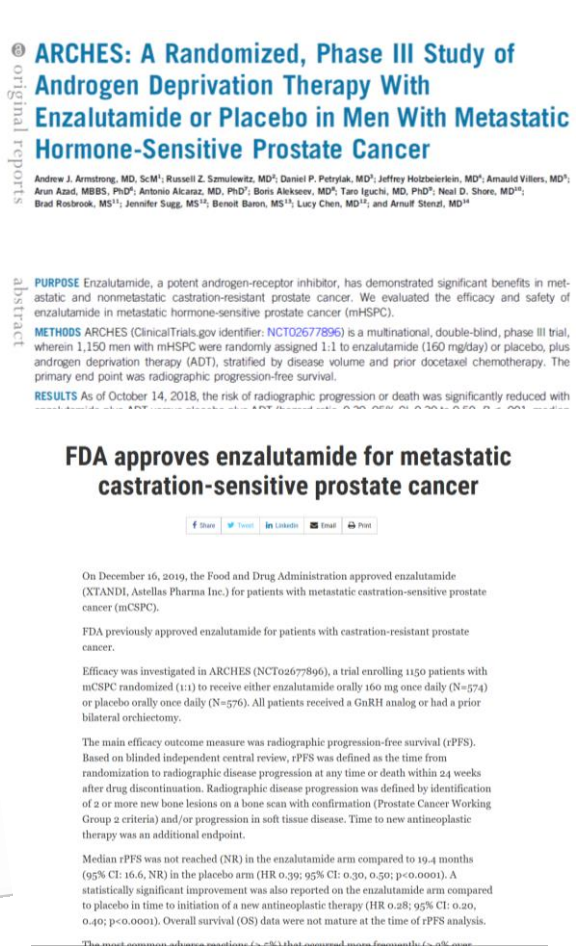
On September 17, 2019, the Food and Drug Administration approved apalutamide (ERLEADA, Janssen Biotech, Inc) for patients with metastatic castration-sensitive prostate cancer (mCSPC). Apalutamide was initially approved in 2018 for patients with non-metastatic castration-resistant prostate cancer.

Efficacy was demonstrated in TITAN (NCT02489318), a randomized, double-blind, placebo-controlled, multi-center clinical trial enrolling 1,052 patients with mCSPC. Patients received either apalutamide 240 mg daily or placebo, orally. All patients received androgen deprivation therapy (ADT)—either concomitant gonadotropin-releasing hormone analog or prior bilateral orchiectomy. Patients with both high- and low-volume disease were enrolled in the study.

Statistically significant improvements in both major efficacy outcomes of overall survival (OS) and radiographic progression-free survival (rPFS) were demonstrated. At the time of a pre-specified interim analysis, the hazard ratio for OS was 0.67 (95% CI: 0.51, 0.89; p=0.0053); however, median OS was not reached in either arm. The hazard ratio for the rPFS improvement was 0.48 (95% CI: 0.39, 0.60; p<0.0001). The median rPFS was not reached for the apalutamide plus ADT arm, and was 22.1 months for the placebo plus ADT arm.

The most common adverse reactions (incidence ≥10%) for patients who received apalutamide were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

The recommended dose of apalutamide is 240 mg (four 60 mg tablets) orally once daily, with or without food. Patients should also receive a gonadotropin-releasing hormone



original reports

ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer

abstract

PURPOSE Enzalutamide, a potent androgen-receptor inhibitor, has demonstrated significant benefits in metastatic and nonmetastatic castration-resistant prostate cancer. We evaluated the efficacy and safety of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC).

METHODS ARCHES (ClinicalTrials.gov identifier: NCT02677896) is a multinational, double-blind, phase III trial, wherein 1,150 men with mHSPC were randomly assigned 1:1 to enzalutamide (160 mg/day) or placebo, plus androgen deprivation therapy (ADT), stratified by disease volume and prior docetaxel chemotherapy. The primary end point was radiographic progression-free survival.

RESULTS As of October 14, 2018, the risk of radiographic progression or death was significantly reduced with

FDA approves enzalutamide for metastatic castration-sensitive prostate cancer

On December 16, 2019, the Food and Drug Administration approved enzalutamide (XTANDI, Astellas Pharma Inc.) for patients with metastatic castration-sensitive prostate cancer (mCSPC).

FDA previously approved enzalutamide for patients with castration-resistant prostate cancer.

Efficacy was investigated in ARCHES (NCT02677896), a trial enrolling 1150 patients with mCSPC randomized (1:1) to receive either enzalutamide orally 160 mg once daily (N=574) or placebo orally once daily (N=576). All patients received a GnRH analog or had a prior bilateral orchiectomy.

The main efficacy outcome measure was radiographic progression-free survival (rPFS). Based on blinded independent central review, rPFS was defined as the time from randomization to radiographic disease progression at any time or death within 24 weeks after drug discontinuation. Radiographic disease progression was defined by identification of 2 or more new bone lesions on a bone scan with confirmation (Prostate Cancer Working Group 2 criteria) and/or progression in soft tissue disease. Time to new antineoplastic therapy was an additional endpoint.

Median rPFS was not reached (NR) in the enzalutamide arm compared to 19.4 months (95% CI: 16.6, NR) in the placebo arm (HR 0.39; 95% CI: 0.30, 0.50; p<0.0001). A statistically significant improvement was also reported on the enzalutamide arm compared to placebo in time to initiation of a new antineoplastic therapy (HR 0.28; 95% CI: 0.20, 0.40; p<0.0001). Overall survival (OS) data were not mature at the time of rPFS analysis.

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer

ABSTRACT

FDA approves darolutamide for non-metastatic castration-resistant prostate cancer

On July 30, 2019, the Food and Drug Administration approved darolutamide (NUBEQA, Bayer HealthCare Pharmaceuticals Inc.) for non-metastatic castration-resistant prostate cancer.

Approval was based on ARAMIS (NCT02200614), a multicenter, double-blind, placebo-controlled clinical trial in 1,509 patients with non-metastatic castration resistant prostate cancer. Patients were randomized (2:1) to receive either 600 mg darolutamide orally twice daily (n=955) or matching placebo (n=554). All patients received a gonadotropin-releasing hormone (GnRH) analog concurrently or had a previous bilateral orchiectomy. Twelve patients with previous seizure histories were treated on the darolutamide arm.

The primary endpoint was metastasis free survival (MFS), defined as the time from randomization to first evidence of distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. The median MFS was 40.4 months (95% CI: 34.3, not reached) for patients treated with darolutamide compared with 18.4 months (95% CI: 15.5, 22.3) for those receiving placebo (hazard ratio 0.41; 95% CI: 0.34, 0.50; p<0.0001). OS data were not mature.

The most common adverse reactions (≥2%) in patients who received darolutamide were fatigue, pain in extremity, and rash. Ischemic heart disease (4.3%) and heart failure (2.1%) were more common on the darolutamide arm. The seizure incidence was similar on the two arms (0.2%).

The recommended darolutamide dose is 600 mg (two 300 mg tablets) administered orally twice daily with food. Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

ARI, androgen receptor inhibitors

Chi KN, et al. N Engl J Med 2019; 381:13-24; Armstrong AJ, et al. J Clin Oncol. 2019 Nov 10;37(32):2974-2986; Fizazi K, et al. N Engl J Med 2019; 380:1235-1246; https://www.fda.gov

CONCLUSIONS

- **Choice of treatment for mCRPC patients** is influenced by[1]:
  - **Prior treatments** the patient may have received for their prostate cancer
  - **Novel mechanism of action important** due to treatment resistance
  - **Clinical factors and patient preferences** guide treatment choice

- **Increased use of new AR-directed therapies earlier in the patient's treatment journey may be expected due to recent drug approvals:**
  - mHSPC: abiraterone, enzalutamide, apalutamide
  - nmCRPC: apalutamide, darolutamide and enzalutamide

- **Sequencing of new hormonal therapies is associated with limited benefit, therefore other life prolonging agents recommended in patients previously treated with these therapies**[2-6]
  - Currently available options include: docetaxel, cabazitaxel *(after previous docetaxel)*, radium-223 *(if symptomatic bone metastases)*[1]
  - Other agents under investigation: such as PARPi, immuno-oncology drugs, new combinations, amongst others

mCRPC, metastatic castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; nmCRPC, non-metastatic castration resistant prostate cancer; PARPi, poly ADP ribose polymerase inhibitors

1. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Access date: 16 Jan 2020; 2. Attard G, et al. JCO. 2018;36(25):2639-46; 3. Khalaf D, et al. Lancet Oncol. 2019;20:1730-39; 4. Smith MR, et al. Eur Urol. 2017;72(1):10-13; 5. Zhang T, et al. Clin Genitourin Cancer. 2015;13:392-9; 6. Azad AA, et al. Eur Urol. 2015;67:23-9.

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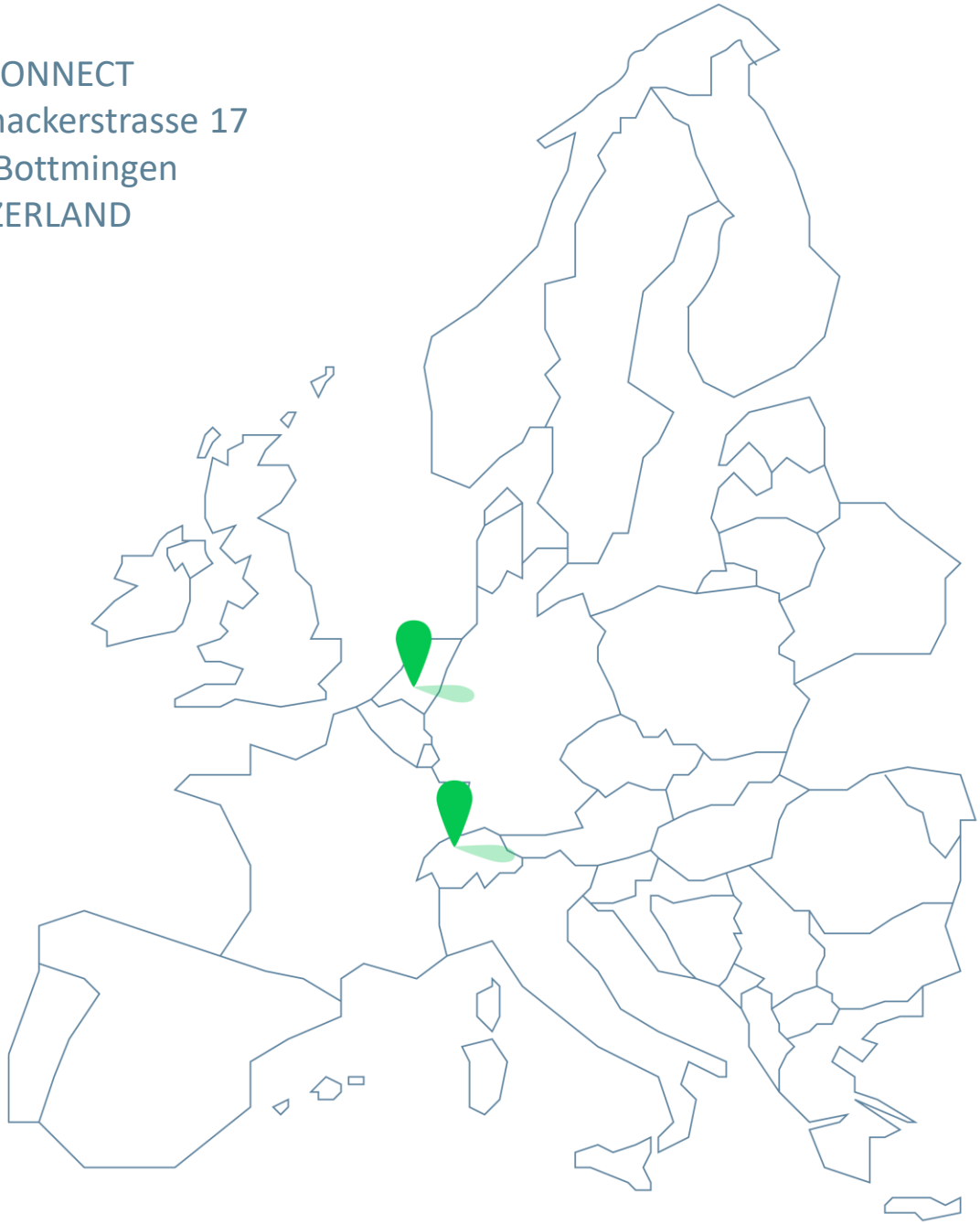

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