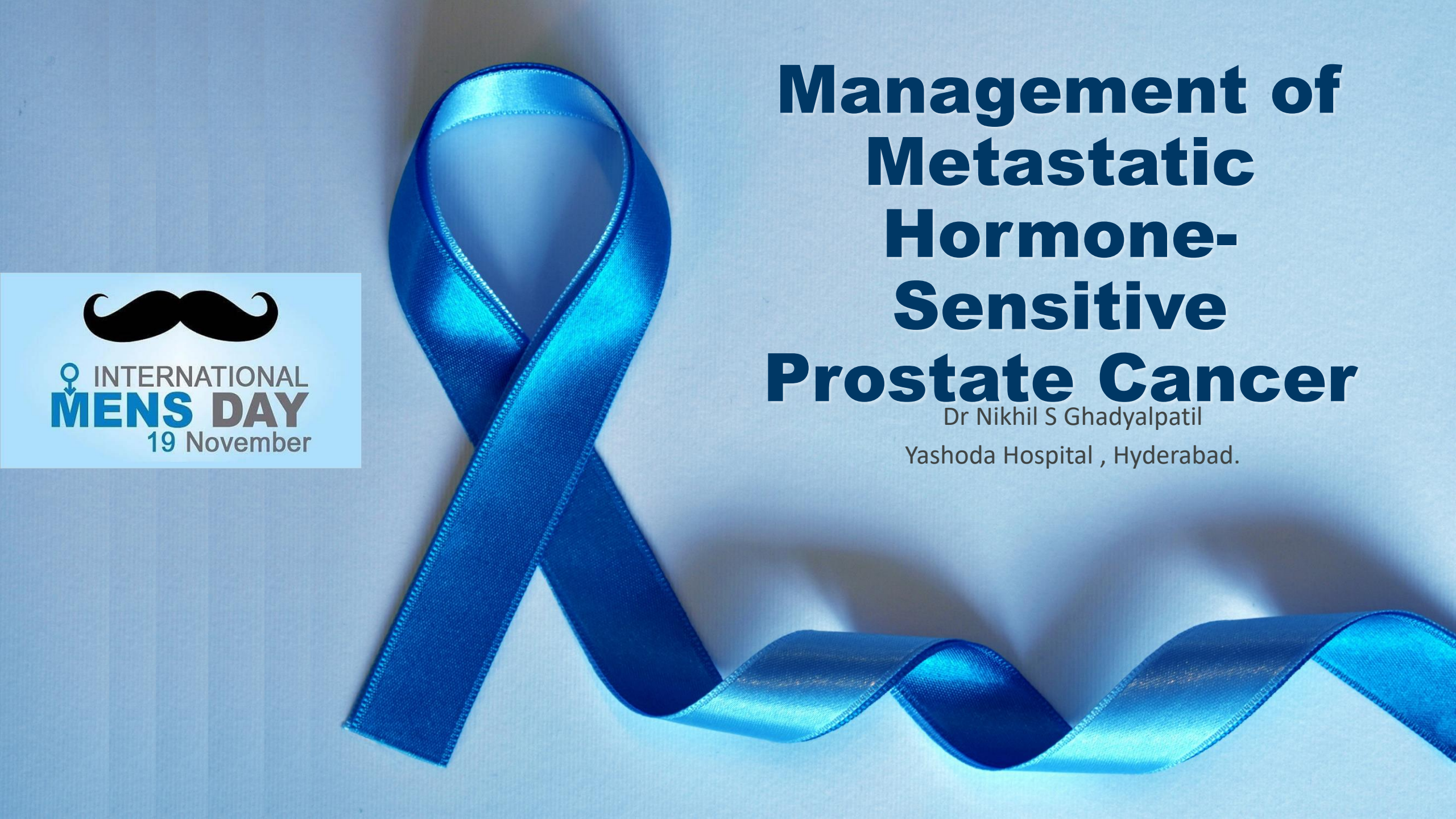



# Management of Metastatic Hormone-Sensitive Prostate Cancer

Dr Nikhil S Ghadyalpatil

Yashoda Hospital , Hyderabad.

# Why is it important to treat mHSPC?

Around 15% of patients with prostate cancer have metastases at the time of diagnosis[1]

Around 40% of prostate cancer deaths arise in patients presenting with primary mHSPC[1]

Prostate cancer patient

Mortality in patient with mHSPC

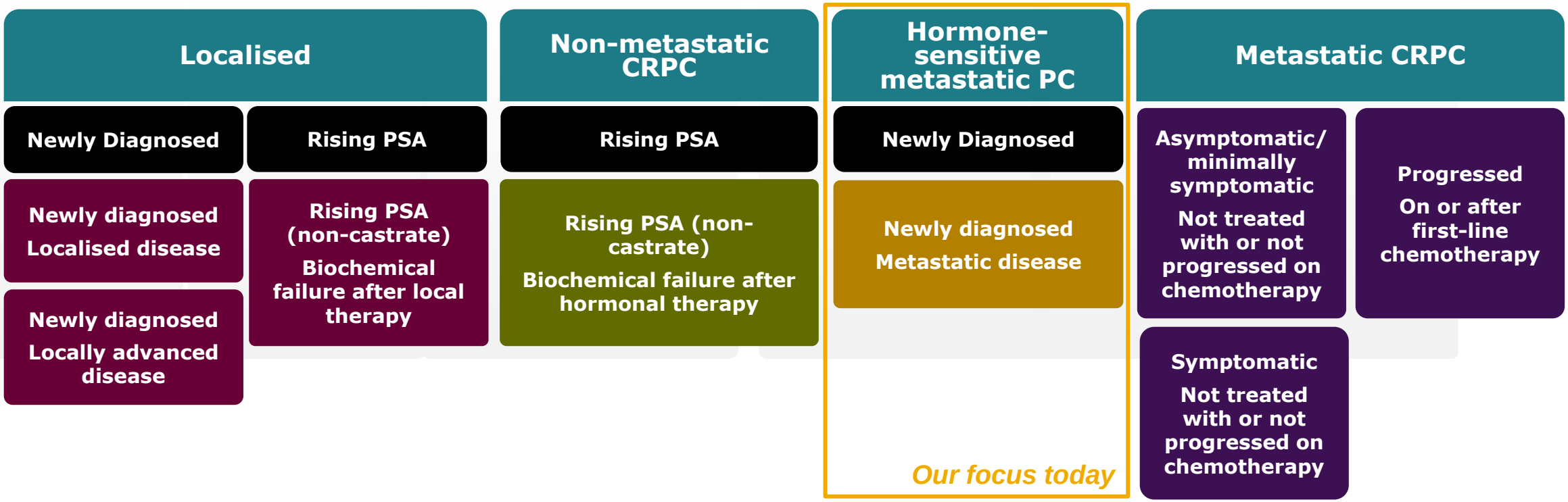
Metastases at diagnosis

Patients respond to androgen deprivation therapy in around 90% of cases; **however, most cases will progress to CRPC after 2–3 years**[2]

CRPC=castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer

1. National Prostate Cancer Audit. Annual Report 2017. https://www.npca.org.uk/content/uploads/2018/02/NPCA-2017-Annual-Report_final_211117.pdf. Accessed September 3, 2019; 2. Karantanos T et al. Oncogene. 2013;32:5501–5511.

# Prostate cancer is comprised of multiple disease states




CRPC, castrate-resistant prostate cancer; PSA, prostate-specific antigen.

Adapted from Scher HI, Solo K, Valant J, Todd MB, Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLOS ONE. 2015 Oct 13;10(10):e0139440.

# Defining mHSPC

- M1 prostate cancer that (still) responds to ADT
- Not necessarily ADT naive (could have been exposed to ADT as part of primary therapy)
- Equivalent to metastatic castration-sensitive prostate cancer or castration-naive prostate cancer
  - NCCN uses castration naive “even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy, provided that they have recovered testicular function”

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

# Treatment decision making in patients with advanced prostate cancer is influenced by multiple different factors[1-3]

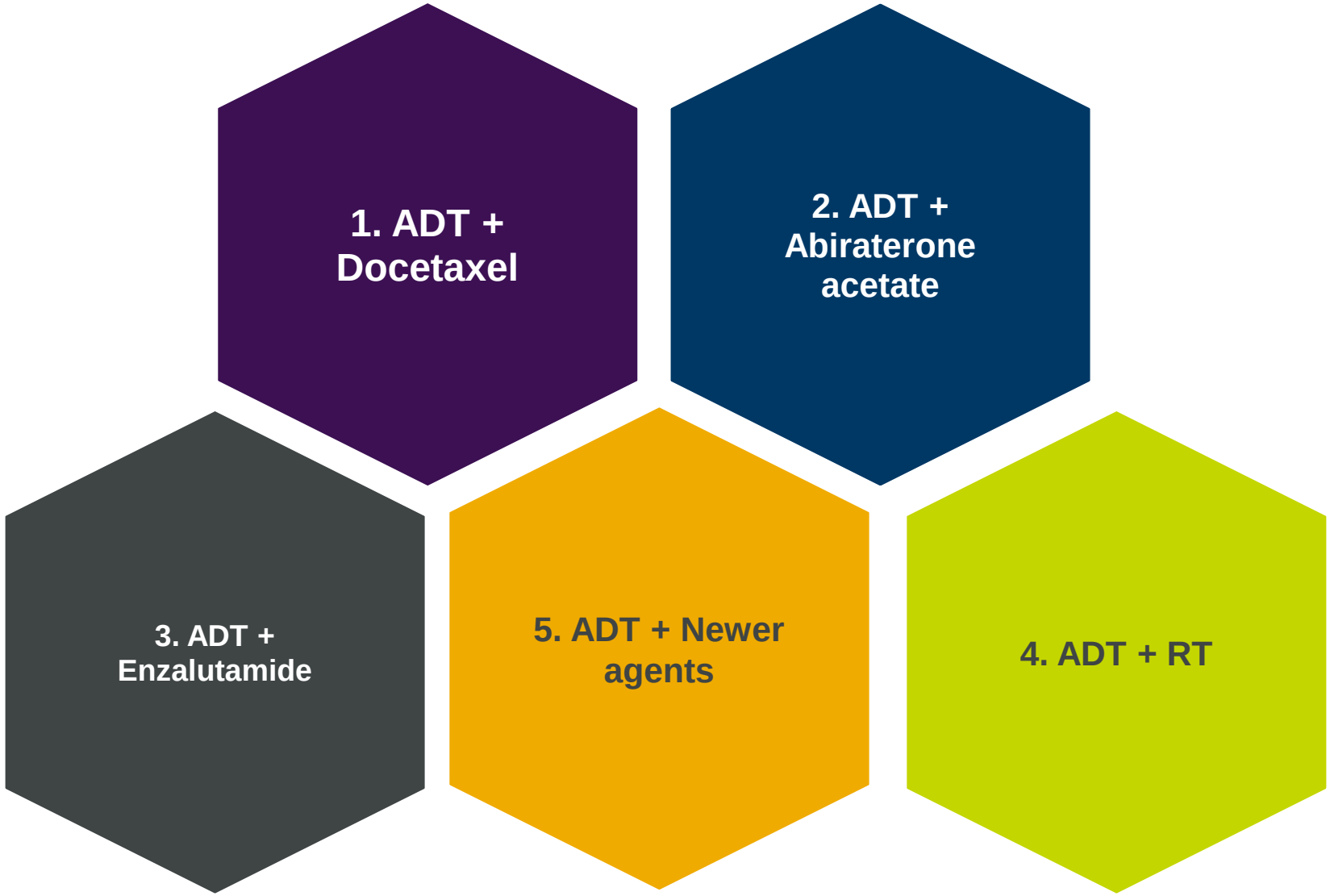
| Disease factors | Treatment resistance | Prior treatments | Patient factors |
|---|---|---|---|
| Extent of disease (low- vs high-volume) | Primary resistance | Impacts sequence options (trial data and reimbursement) | Patient fitness for therapy |
| Distribution of metastases | Acquired resistance | Impact on subsequent line therapies (trial data and reimbursement) | Therapy tolerance and co-morbidities |
| Symptomatic vs non-symptomatic disease | | | Genetic mutations and their functional consequences |
| Other disease characteristics (e.g. tumour histology, rate of change of disease burden) | | | |

**There are very limited prospective sequencing and head-to-head studies to guide treatment choice in mHSPC[3]**

mCRPC=metastatic castration-resistant prostate cancer

1. Aggarwal RR et al. Oncology (Williston Park). 2017;31:467-474; 2. Burt LM et al. Adv Radiat Oncol. 2018;3:170–180. 3. Maragkouli E. Presented at: ESMO Annual Congress; October 19-23, 2018; Munich Germany.

# ADT remains the mainstay of treatment given along with all systemic agents in mHSPC



# ADT

- Surgical Castration
- Medical:

1. GnRH Agonists
2. GnRH Antagonists

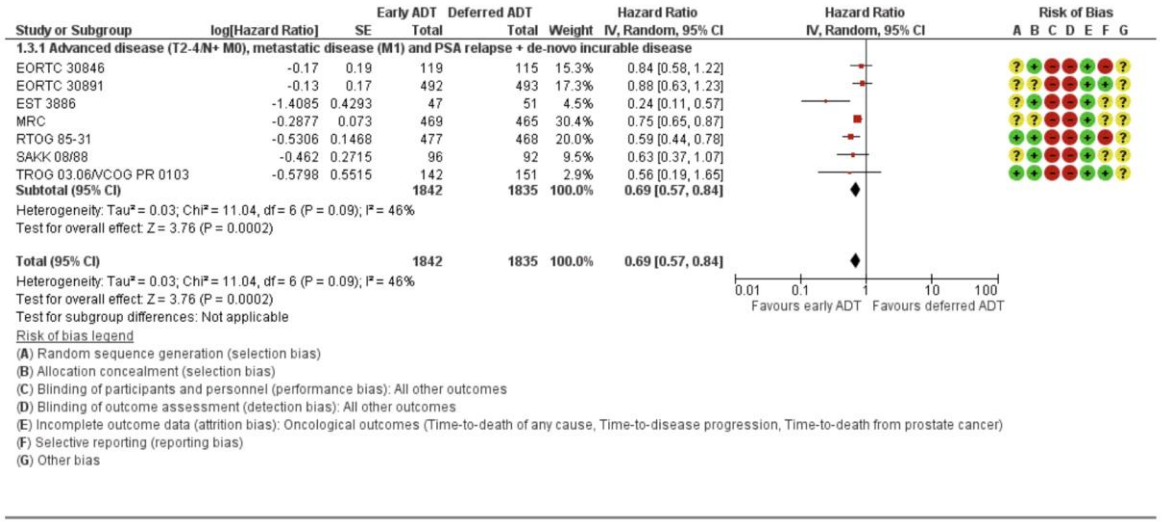
Flare Phenomenon

Symptomatic versus Asymptomatic

Early versus Late ADT

Intermittent versus continuous ADT

Cochrane 2019;Early Vs Late ADT

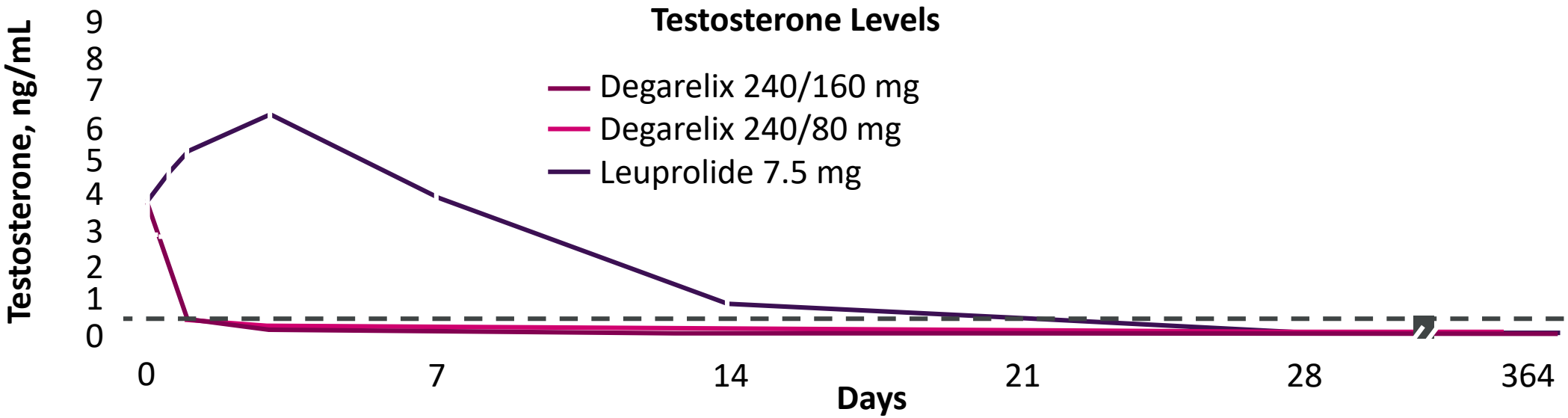


# ADT for Metastatic Castration-Sensitive Disease

- **ADT with treatment intensification is preferred** for most patients with metastatic prostate cancer. ADT alone is appropriate for some patients.
- Treatment options for patients with M1 castration-sensitive disease are:
  - **ADT alone** (orchiectomy, LHRH agonist, LHRH agonist plus first generation antiandrogen, or LHRH antagonist)
    - ◊ LHRH agonists: Goserelin, leuprolide, or triptorelin
    - ◊ First-generation antiandrogens: Nilutamide, flutamide, or bicalutamide
    - ◊ A first-generation antiandrogen must be given with LHRH agonist for ≥7 days to prevent testosterone flare if metastases are present in weight-bearing bone
  - **Orchiectomy plus abiraterone, enzalutamide, or apalutamide**
  - **Orchiectomy plus docetaxel and abiraterone or darolutamide**
  - **LHRH agonist (as above) plus abiraterone, enzalutamide, or apalutamide**
  - **LHRH agonist (as above) plus docetaxel and abiraterone or darolutamide**
  - **Degarelix plus abiraterone, enzalutamide, or apalutamide**
  - **Degarelix plus docetaxel and abiraterone or darolutamide**
- Abiraterone should be given with concurrent
- When EBRT to primary is given with ADT in low metastatic burden M1, the options are LHRH agonist, LHRH antagonist, and orchiectomy.
  - Close monitoring of PSA and testosterone levels and possibly imaging is required when using intermittent ADT, especially during off-treatment periods, and patients may need to switch to continuous ADT upon signs of disease progression.

# Degarelix vs Leuprolide for Prostate Cancer

- Randomized, open-label, phase III trial of degarelix 80 mg or 160 mg SC QM* vs leuprolide 7.5 mg IM QM for 1 year in patients with prostate cancer who were indicated for ADT (N = 610)



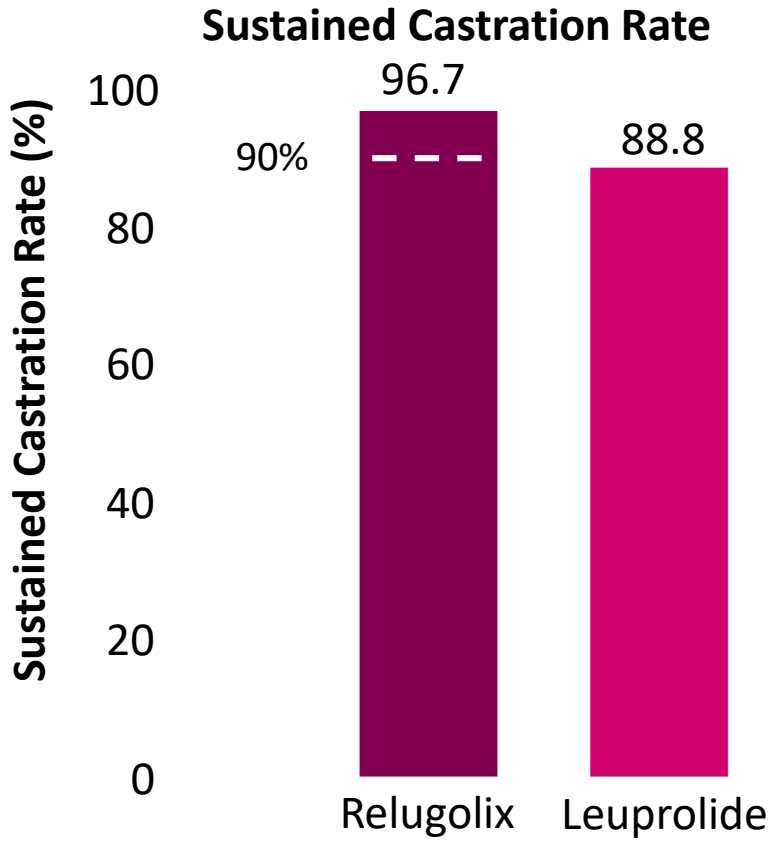

- Cumulative probability of testosterone <50 ng/dL from Days 28 to 364: degarelix 80 mg, 97%; degarelix 160 mg, 98%; leuprolide, 96%
- Similar overall rates of TEAEs; CV events: degarelix, 9%; leuprolide, 13%

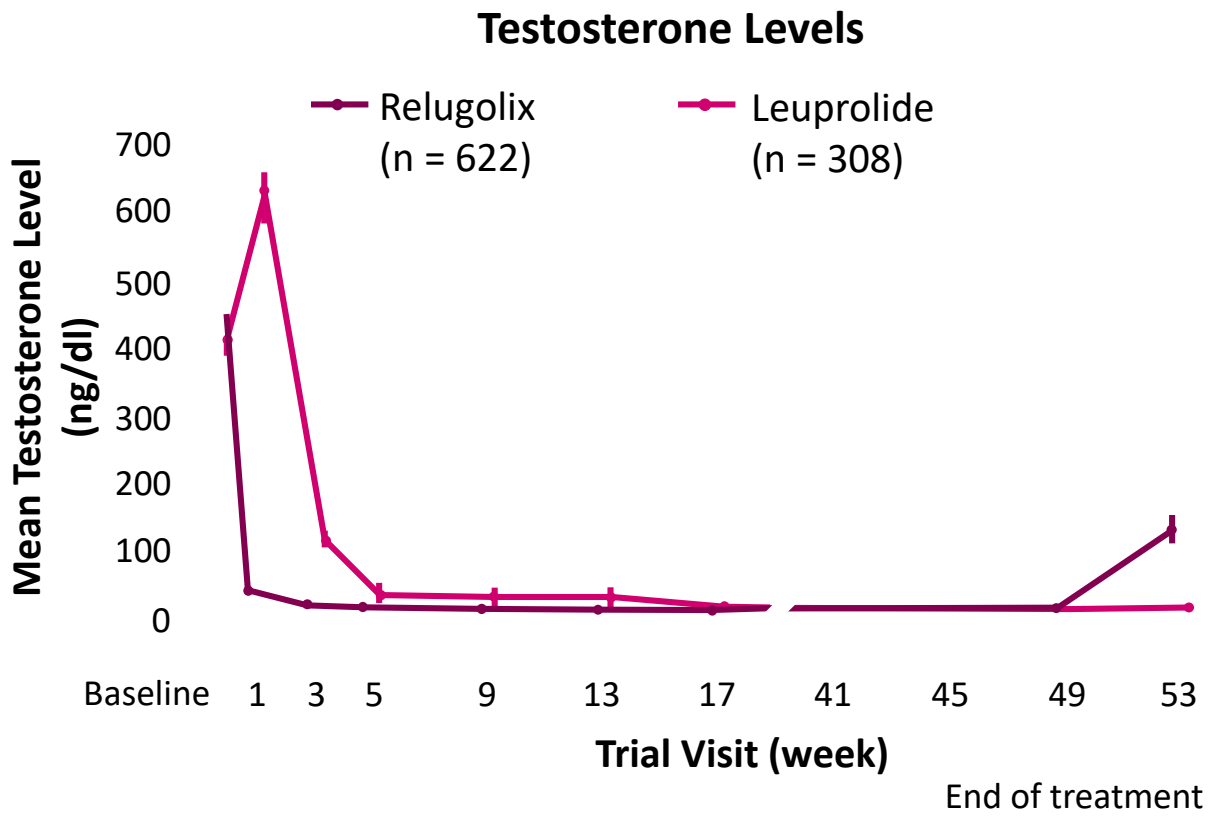
*After a loading dose of 240 mg.

Klotz. BJU Int. 2008;102:1531.

# HERO: Relugolix vs Leuprolide for Prostate Cancer

- Randomized, open-label, phase III trial of relugolix 120 mg PO QD* vs leuprolide 11.25/22.5 mg IV QM for 48 weeks in patients with prostate cancer who were candidates for ADT (N = 930)



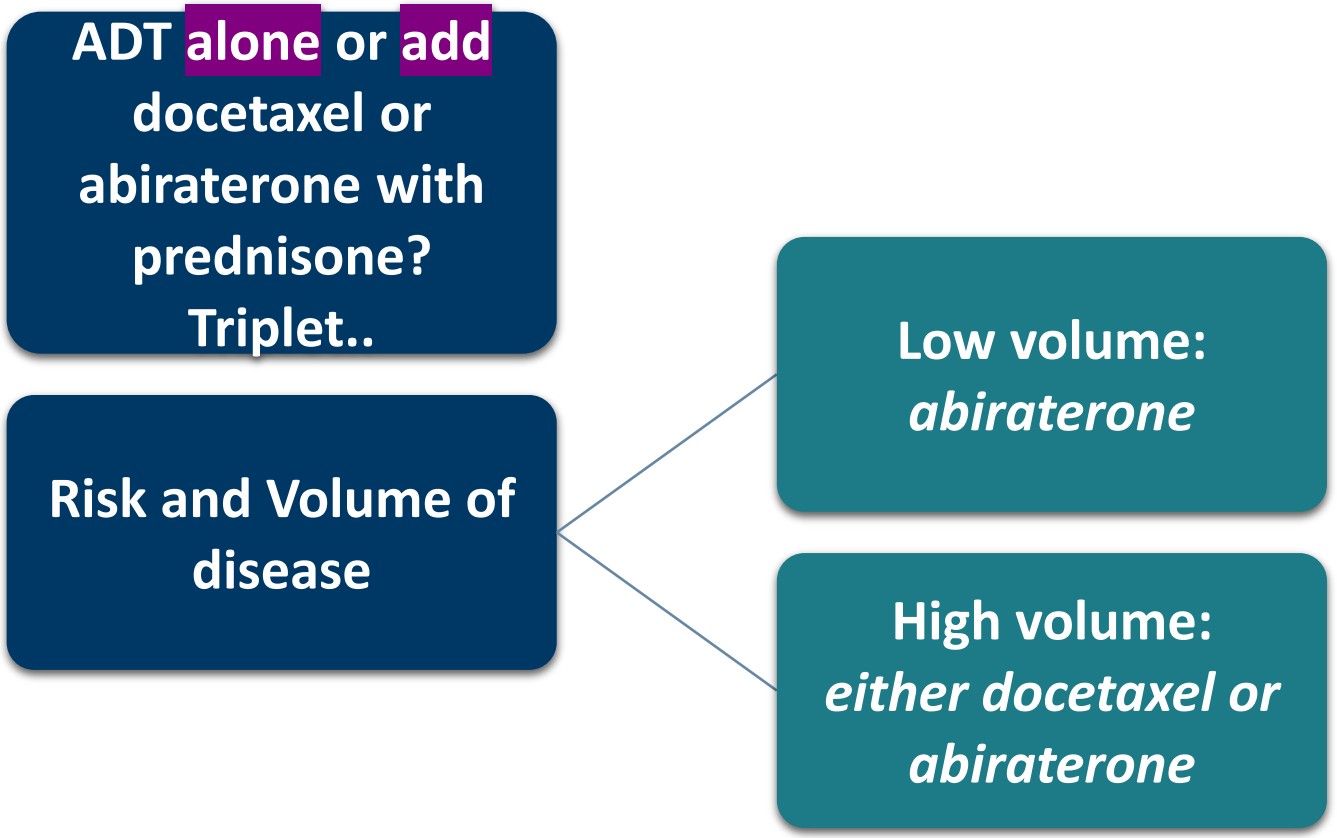

Shore. NEJM. 2020;382:2187.

# Defining Oligometastatic (Low Volume) vs Polymetastatic (High Volume) mHSPC

- High volume definition:
  - ≥4 bone metastases and/or visceral metastases
  - ≥1 metastasis beyond pelvis or vertebral column
- Volume of disease has significant therapy-related implications

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

# Considerations in the Treatment of mHSPC



# Considerations in the Treatment of mHSPC

- ADT alone or add docetaxel or abiraterone with prednisone?
  - Practical considerations
    - Patient comorbidities, eg, cardiovascular or bone disease
    - Adverse event profiles
    - Duration of therapy
    - Administration
    - Financial toxicity
  - No data for sequencing abiraterone before/after previous docetaxel

# Key studies in mHSPC

| Study | Investigational arm | Comparator arm |
|---|---|---|
| **Docetaxel studies** | | |
| GETUG-AFU-15[1] | Docetaxel + ADT | ADT |
| CHAARTED[2] | Docetaxel + ADT | ADT |
| STAMPEDE[3] | Docetaxel + ADT | ADT |
| **NHA studies** | | |
| STAMPEDE[3] | Abiraterone + ADT + prednisolone | ADT + dual placebo |
| LATITUDE[4] | Abiraterone + ADT + prednisone | ADT + dual placebo |
| TITAN[5] | Apalutamide + ADT | ADT |
| ENZAMET[6] | Enzalutamide + ADT | ADT |
| ARCHES[7] | Enzalutamide + ADT | ADT |
| AREMIS | Darolutamide | ADT |
| **Radiotherapy studies** | | |
| STAMPEDE[3] | Radiotherapy + SOC | SOC |

ADT=androgen deprivation therapy; SOC=standard of care

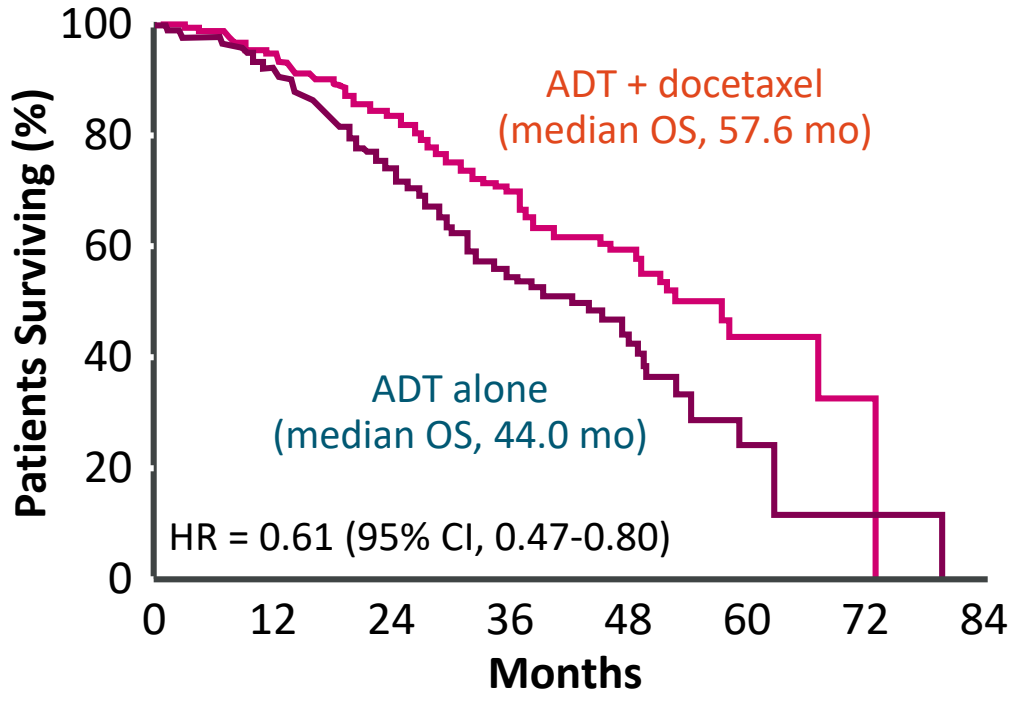
1. Gravis G *et al. Lancet Oncol* 2013;14:149–158; 2. Kyriakopoulos CE et al. *J Clin Oncol.* 2018;36:1080–1087;3. James ND et al. *Lancet.* 2016;387:1163–1177; 4. Fizazi K et al. *N Engl J Med.* 2017;377:352-360; 5. Chi KN, et al. Presented at ASCO 2019; Chicago. Abstract 5006; 6. Sweeney C, et al. Presented at ASCO 2019; Chicago. Abstract LBA2; 7. Armstrong AJ, et al. Pres
ASCO 2019; Chicago. Poster 5048

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

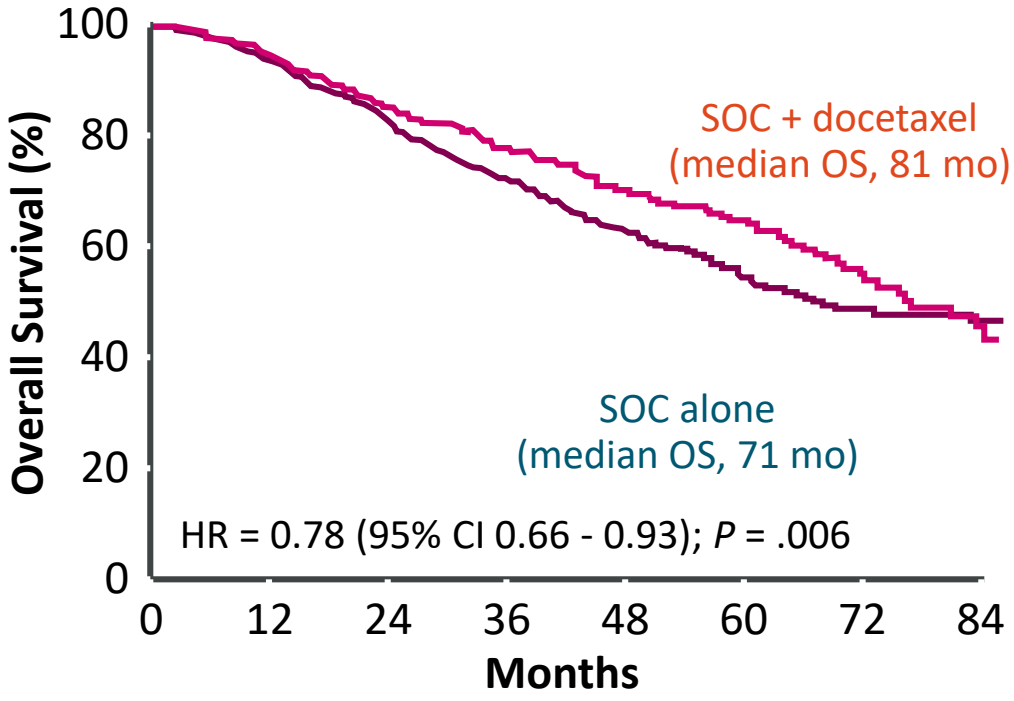
CHAARTED: randomized phase III trial of docetaxel + ADT vs ADT alone for pts with mHSPC with elevated PSA (N = 790)




THE LANCET

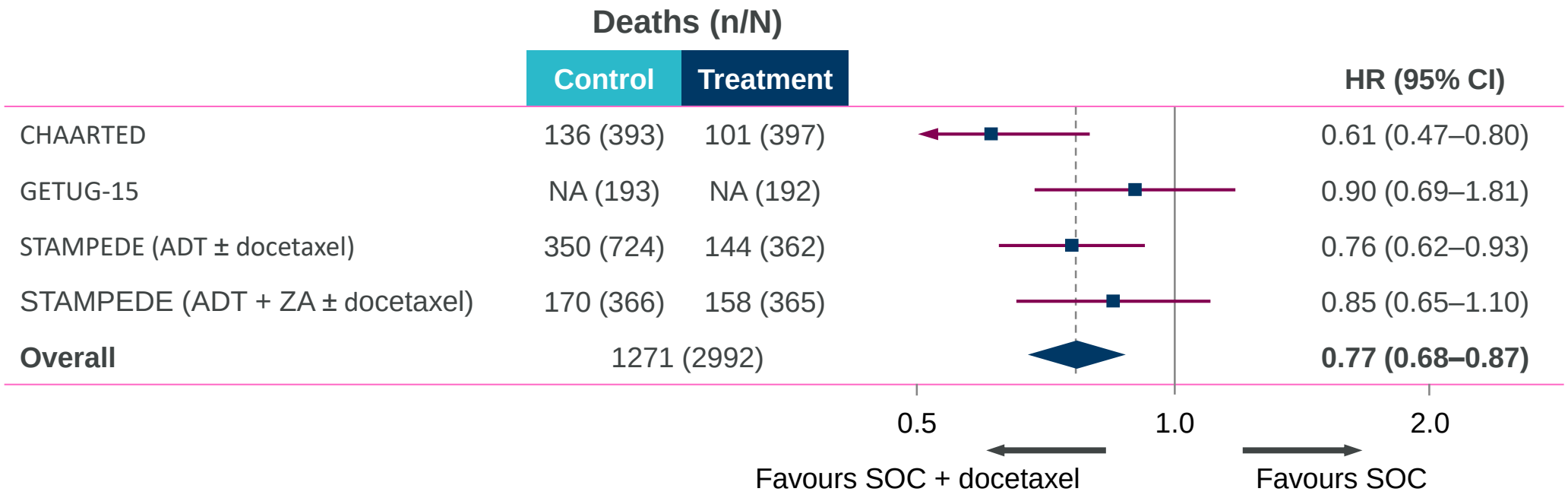
**Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial**

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




Sweeney. NEJM. 2015;373:737. James. Lancet. 2016;387:1163.

# Overall, a meta-analysis confirmed that the addition of docetaxel to ADT improved survival in men with mHSPC



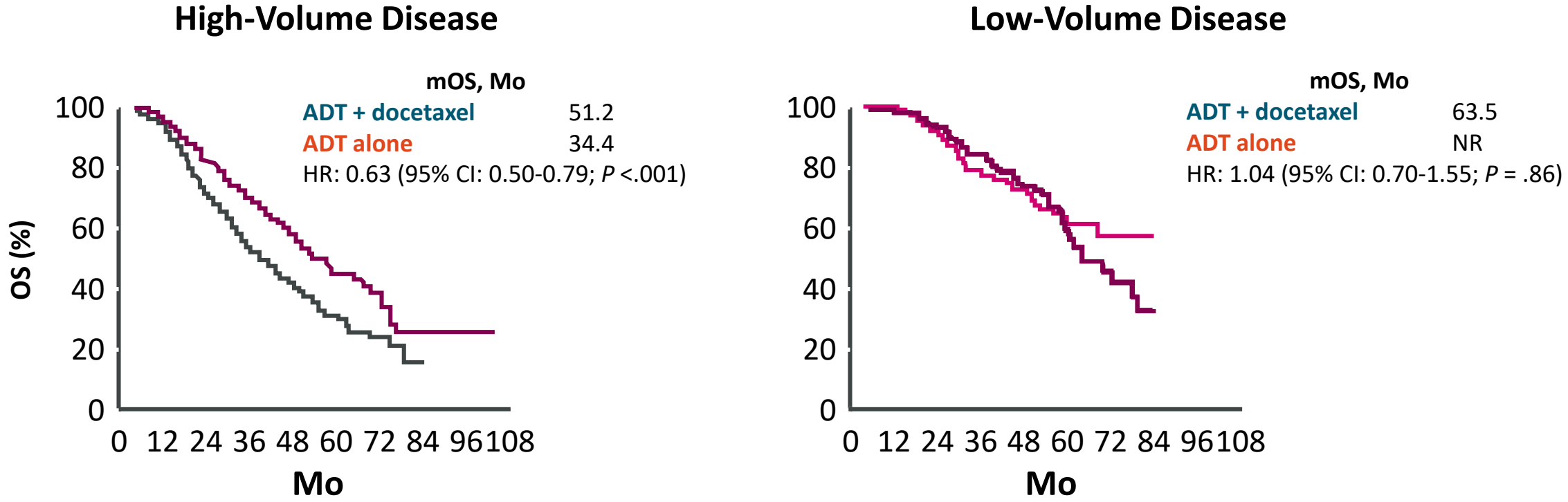

ADT=androgen deprivation therapy; CI=confidence interval; HR=hazard ratio; mHSPC=metastatic hormone-sensitive prostate cancer; NA=not available; SOC=standard of care; ZA=zoledronic acid

Vale CL et al. *Lancet Oncol.* 2016;17:243–256

This study was a combined analysis of multiple studies

# CHAARTED: High-Volume vs Low-Volume Disease

- Median follow-up of 53.7 mo in patients with metastatic hormone-sensitive prostate cancer randomized to ADT + docetaxel vs ADT alone (N = 790)




Kyriakopoulos. JCO. 2018;36:1080.

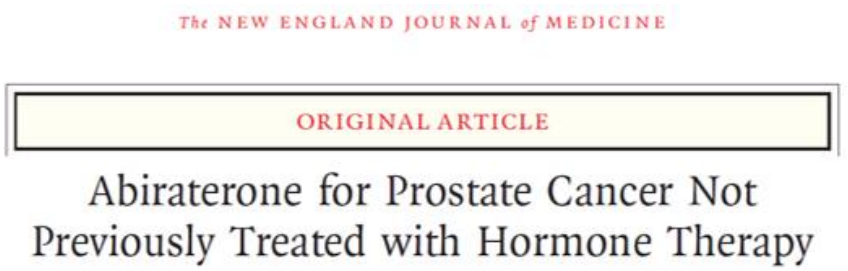
# Abiraterone Acetate: LATITUDE and STAMPEDE Trials in Advanced Prostate Cancer


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

- LATITUDE: randomized, double-blind phase III trial of abiraterone acetate + ADT vs placebo + ADT in patients with newly diagnosed mHSPC (N = 1199)
- High risk = at least 2 of the following 3 features: Gleason score ≥8, measurable visceral metastasis, ≥3 bone lesions


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

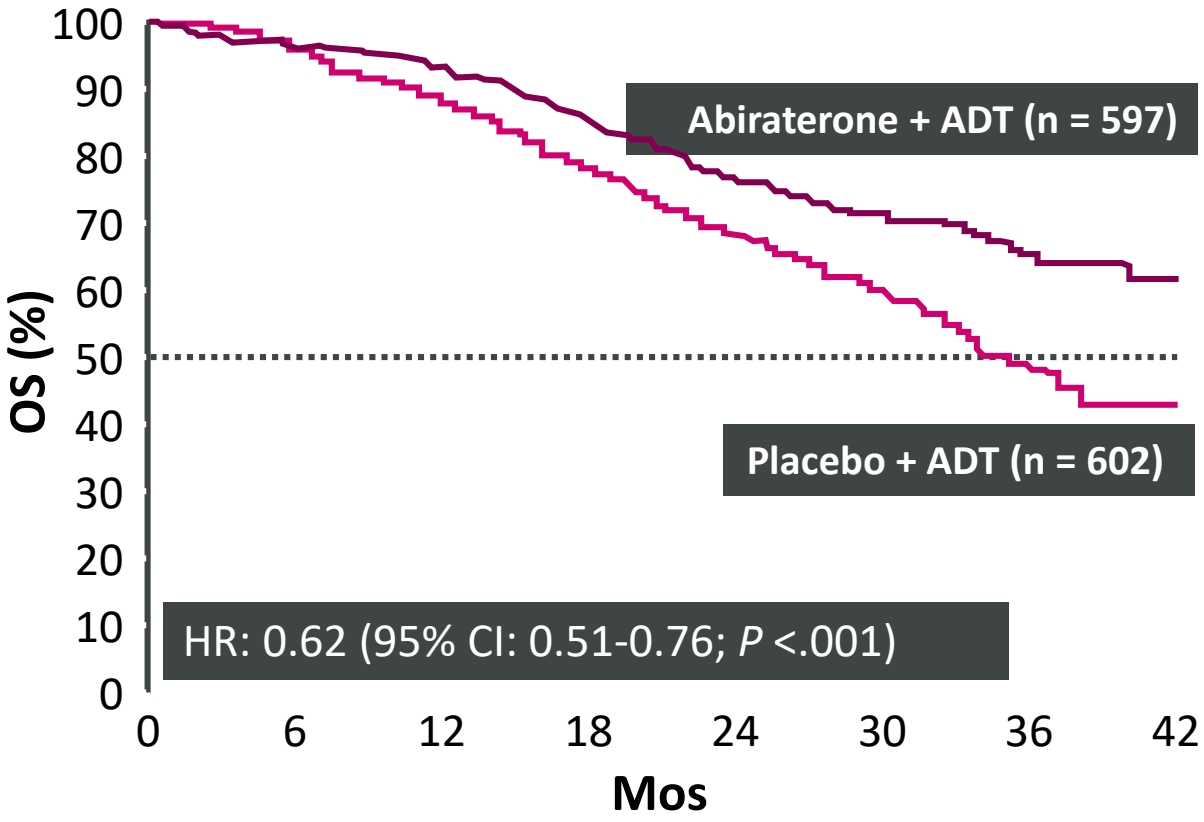
Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

- STAMPEDE: randomized, open-label, multiarm, multistage phase II/III trial (N = 1917)
- Newly diagnosed metastatic disease that was pelvic node–positive or high-risk locally advanced with ≥2 high-risk features (Gleason score 8-10, T3-T4, PSA ≥40 ng/mL)
- Relapsing after local therapy with high-risk features: PSA >4 ng/mL with doubling time <6 mo, PSA >20 ng/mL, metastatic or nodal relapse, <12 mo of total ADT including interval >12 mo without treatment

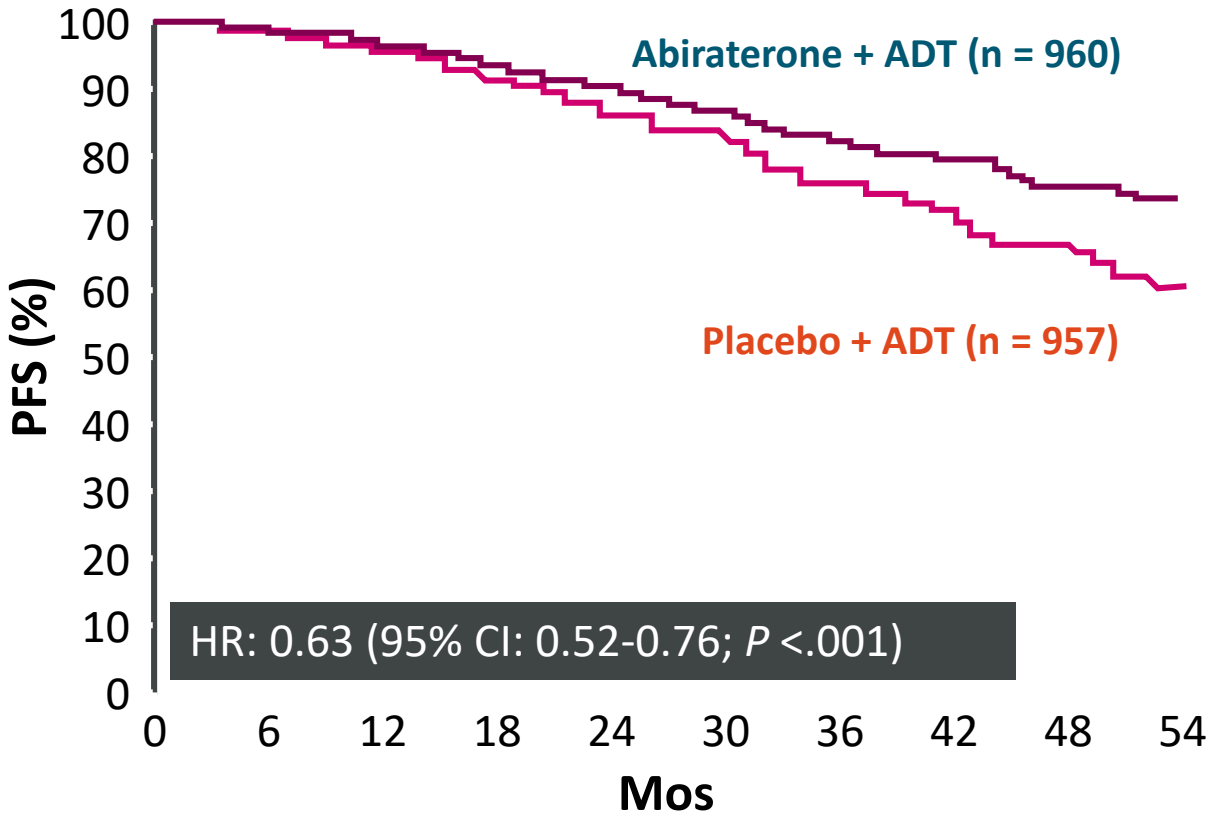
Fizazi. NEJM. 2017;377:352. James. NEJM. 2017;377:338.

# Abiraterone Acetate

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



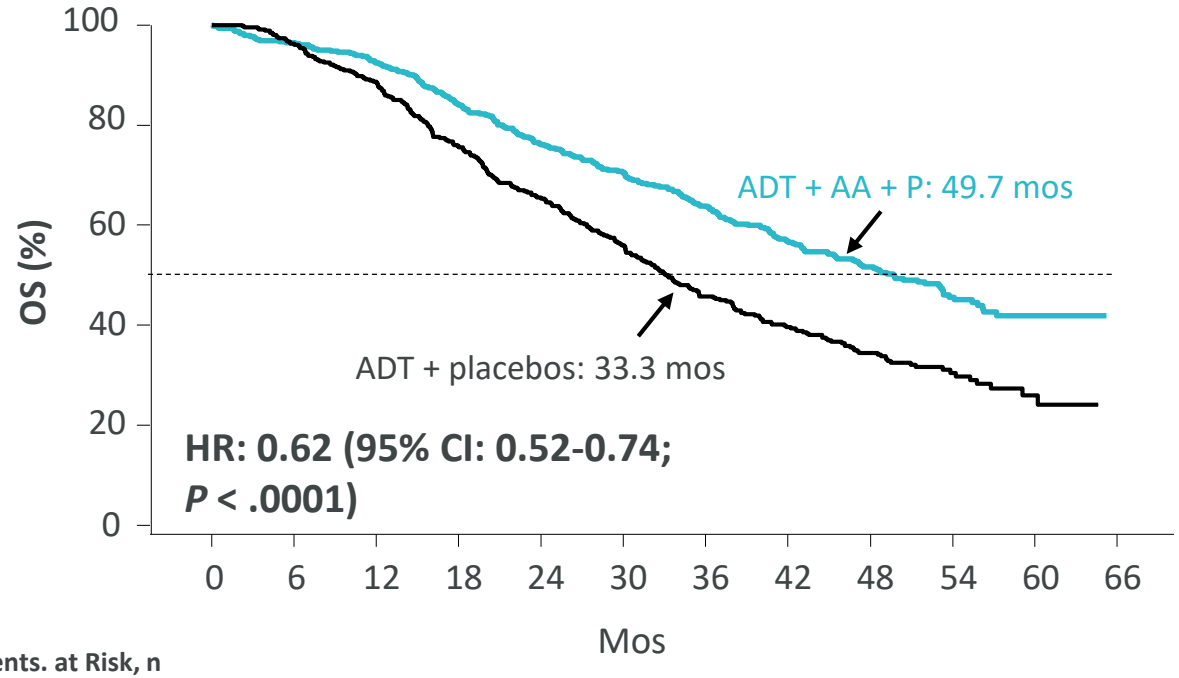

STAMPEDE: randomized, open-label, multiarm, multistage phase II/III trial (N = 1917)




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

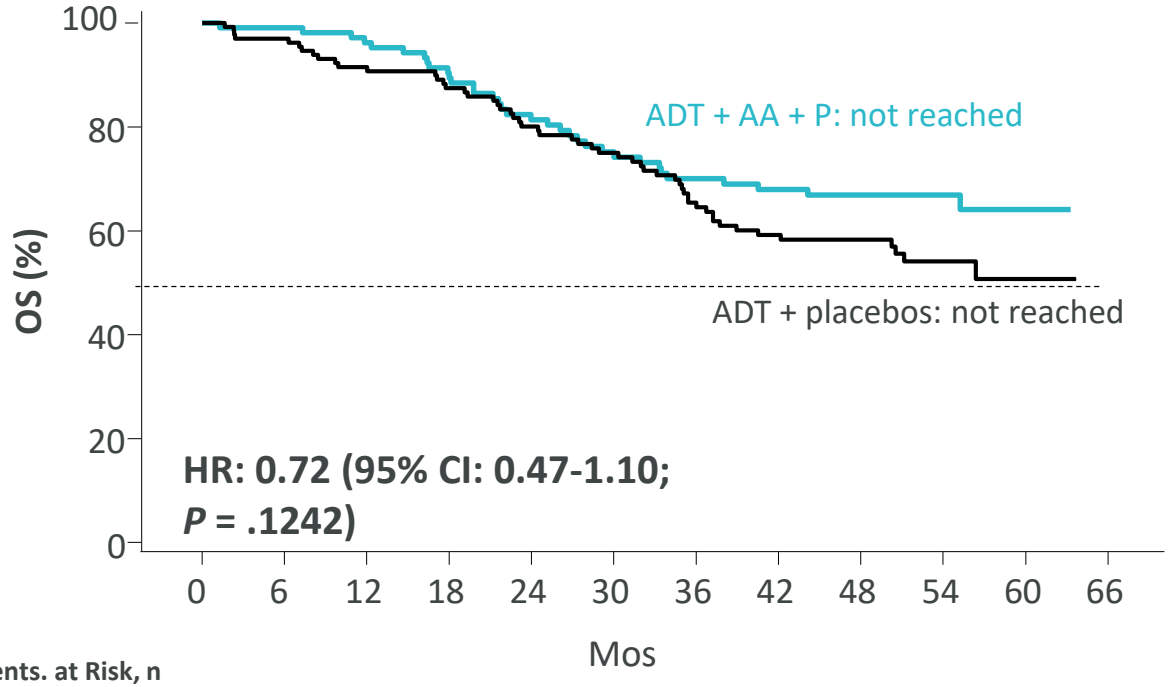
# LATITUDE: OS in High and Low Volume Disease*

## High Volume Disease




| Patients. at Risk, n | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ADT + AA + P | 487 | 460 | 429 | 386 | 345 | 317 | 283 | 246 | 188 | 97 | 31 | 0 |
| ADT + placebos | 468 | 438 | 389 | 323 | 270 | 266 | 181 | 154 | 113 | 46 | 14 | 0 |

## Low Volume Disease




| Patients. at Risk, n | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ADT + AA + P | 110 | 105 | 100 | 93 | 80 | 72 | 68 | 65 | 52 | 27 | 9 | 0 |
| ADT + placebos | 133 | 125 | 115 | 108 | 97 | 88 | 74 | 66 | 52 | 23 | 9 | 0 |

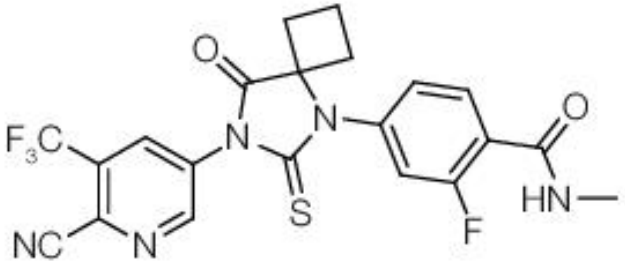
*By CHAARTED definition of high and low volume: high volume = visceral metastases and/or ≥ 4 bone lesions with at least 1 outside the vertebral column or pelvis



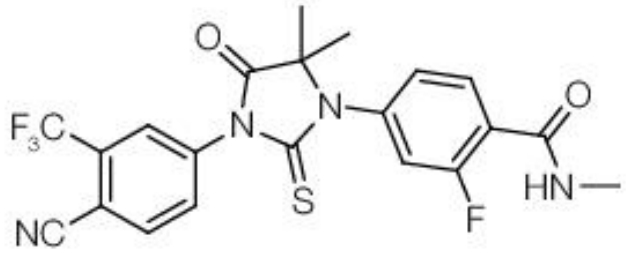
Fizazi. Lancet Onc. 2019;[Epub].

# Next-Generation Androgen Receptor Inhibitors

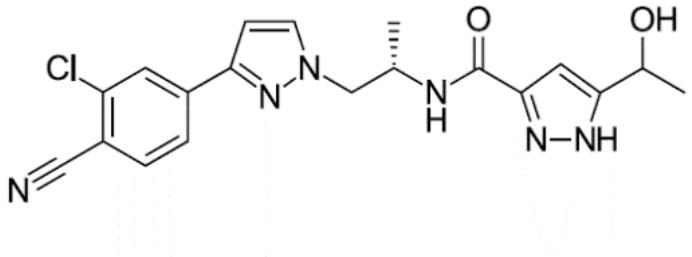
**Apalutamide[1]**



**Enzalutamide[1]**



**Darolutamide[1]**

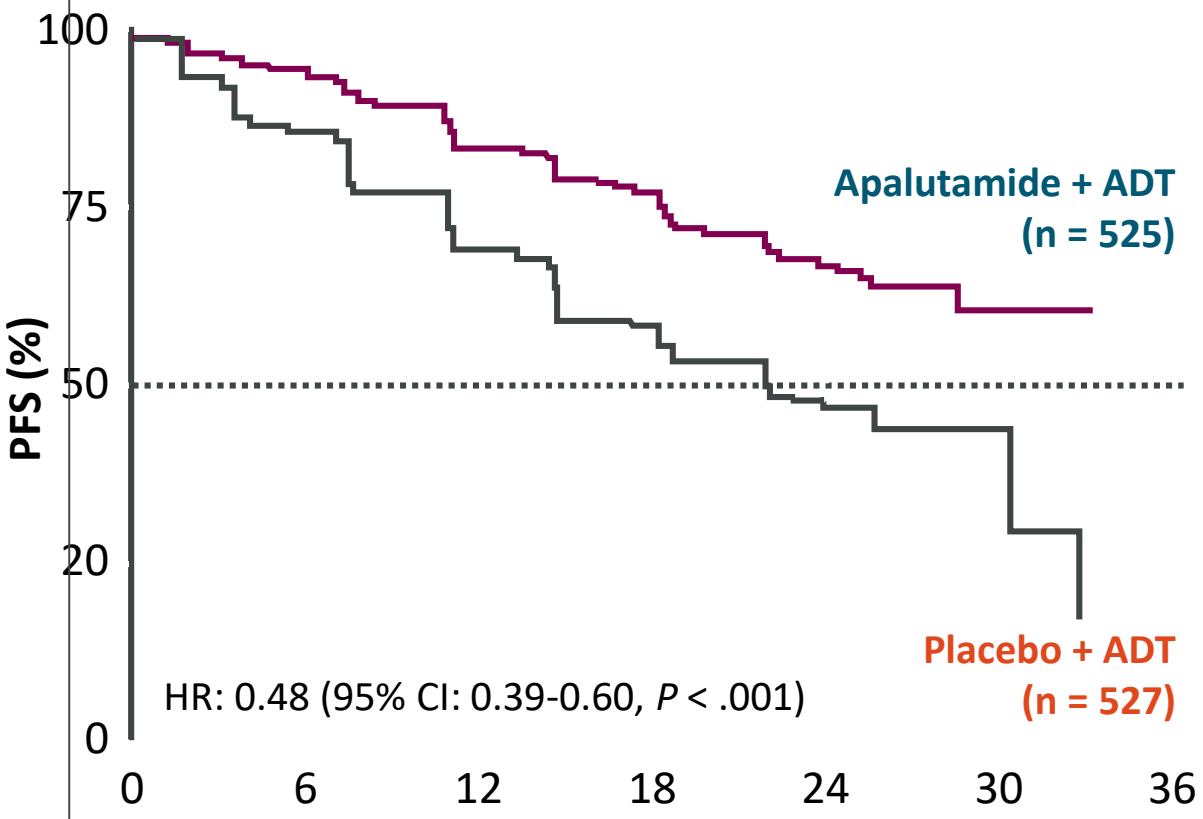


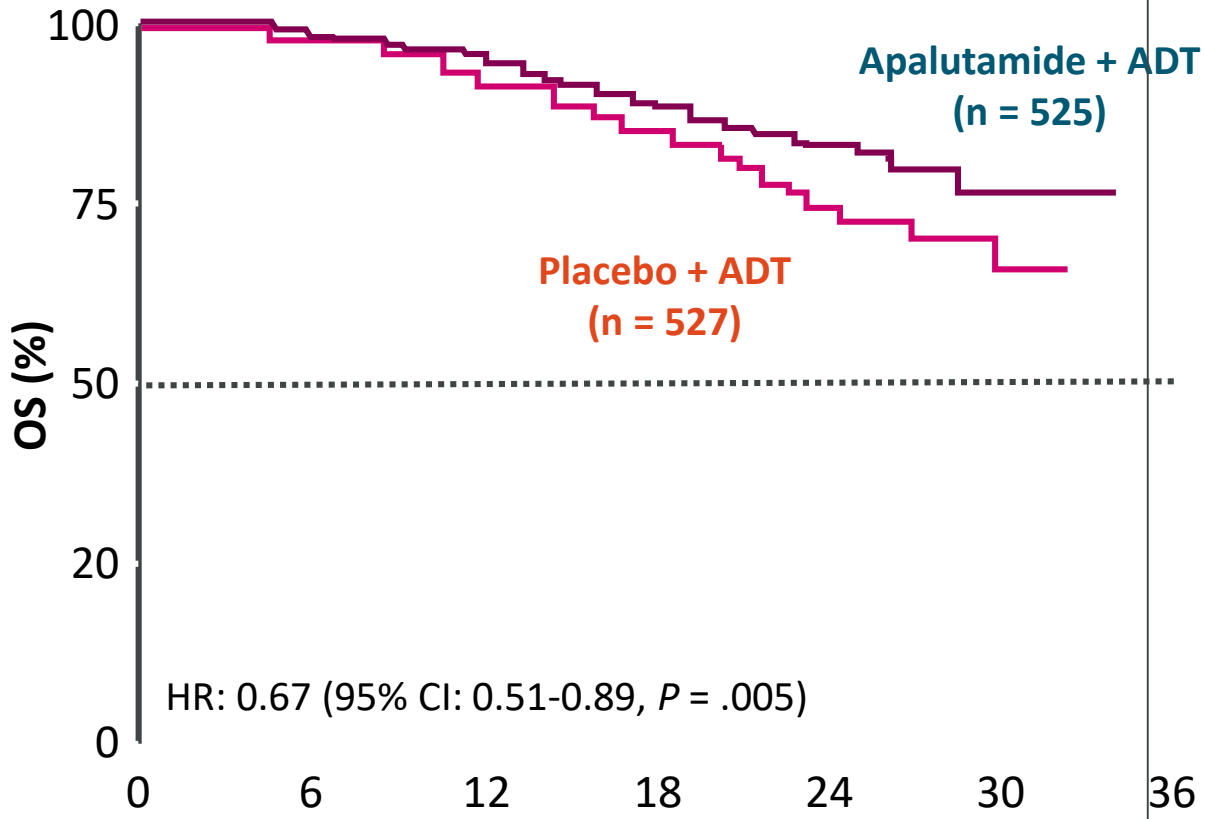
- Apalutamide and enzalutamide have similar structures[2]
- Darolutamide is structurally distinct from apalutamide and enzalutamide, characterized by low blood–brain barrier penetration and may have improved tolerability[2]

1. Higano. Nat Rev Urol. 2019;16:335. 2. Lavaud. Ther Adv Med Oncol. 2020;12:1758835920978134.

# TITAN: Apalutamide + ADT vs Placebo + ADT in mHSPC

Randomized, double-blind phase III trial of apalutamide + ADT vs placebo + ADT for patients with mHSPC (N = 1052)

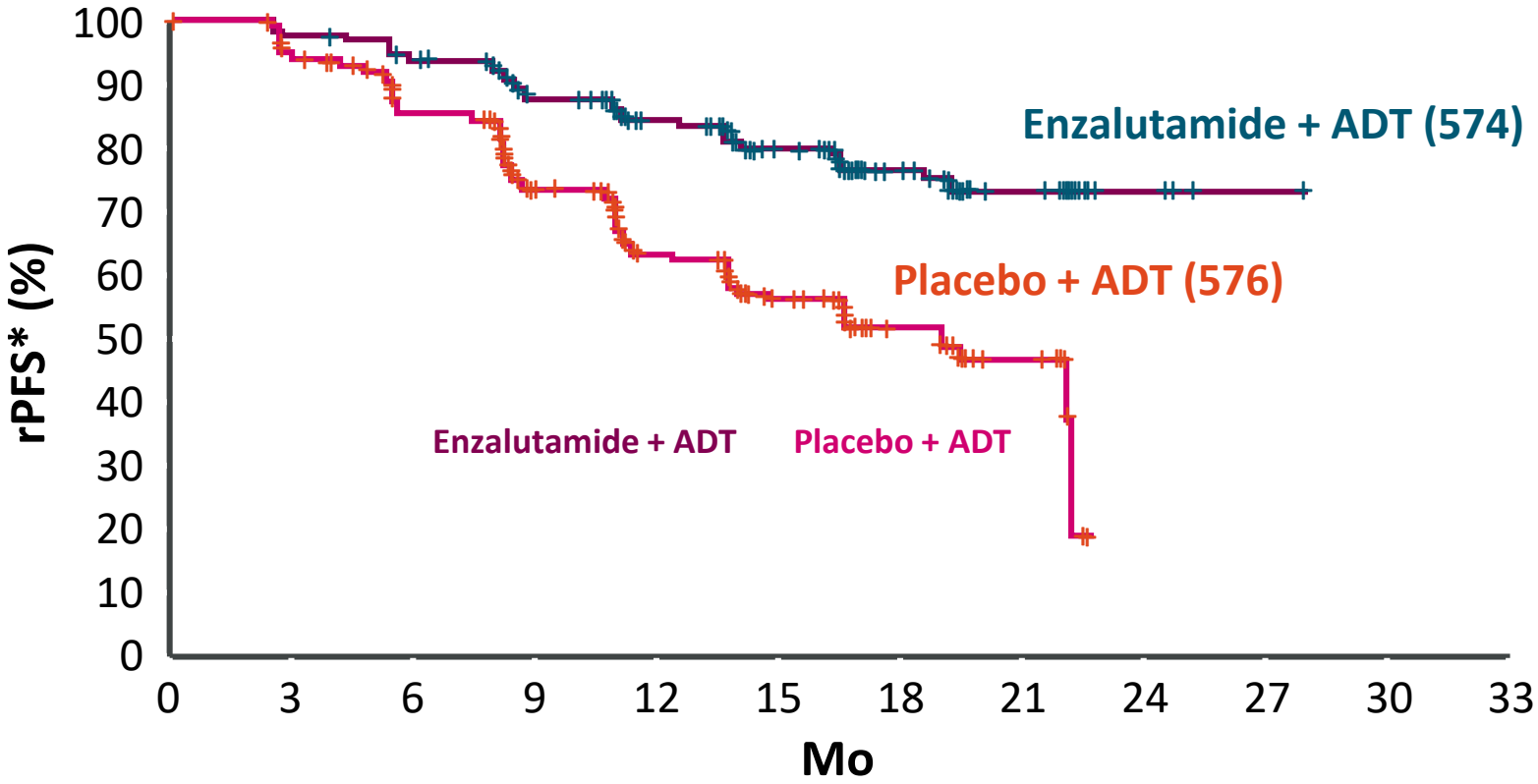



Chi. NEJM. 2019;381:13.

# 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)



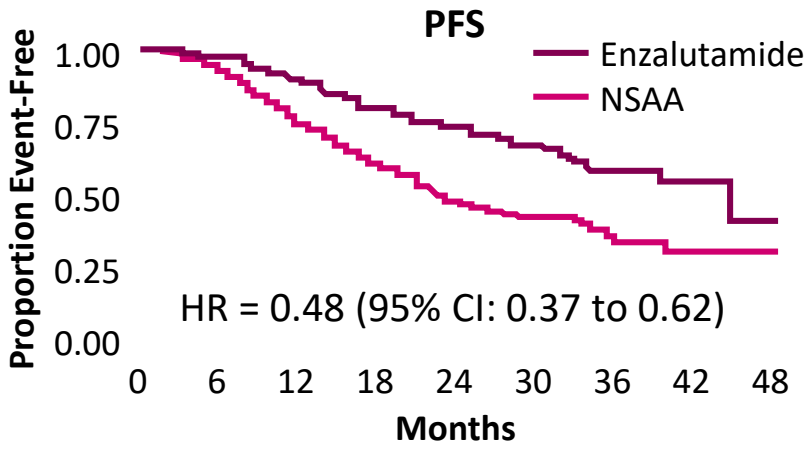

- Overall survival: HR 0.81 (95% CI: 0.53-1.25); *P* = .3361; however, survival data were immature with only 14.4 mo median follow-up and 84 deaths

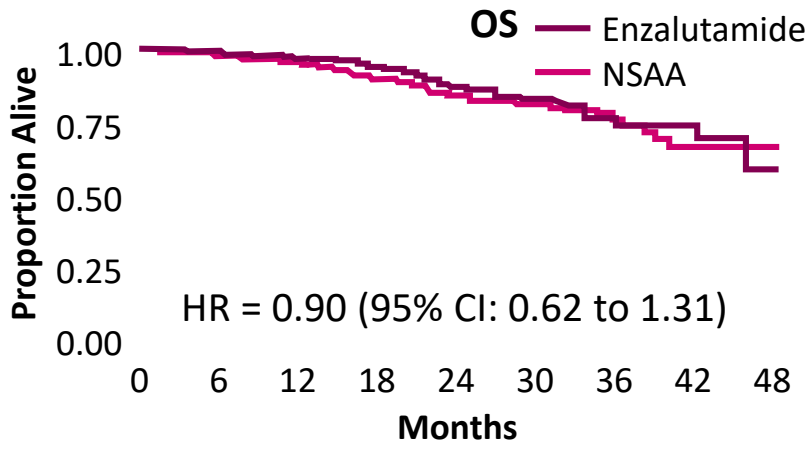
*Included only patients with no documented progression event and censoring at the date of the last radiologic assessment prior to the cutoff date.

Armstrong. JCO. 2019;37:2974.

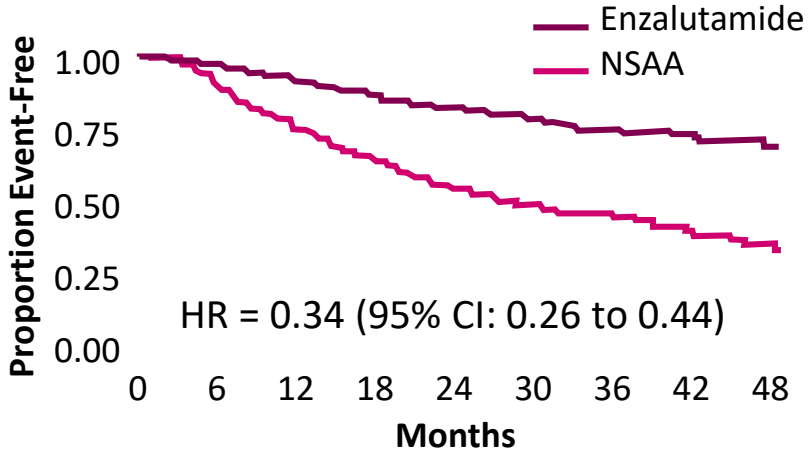
# ENZAMET: PFS and OS With Concurrent Docetaxel

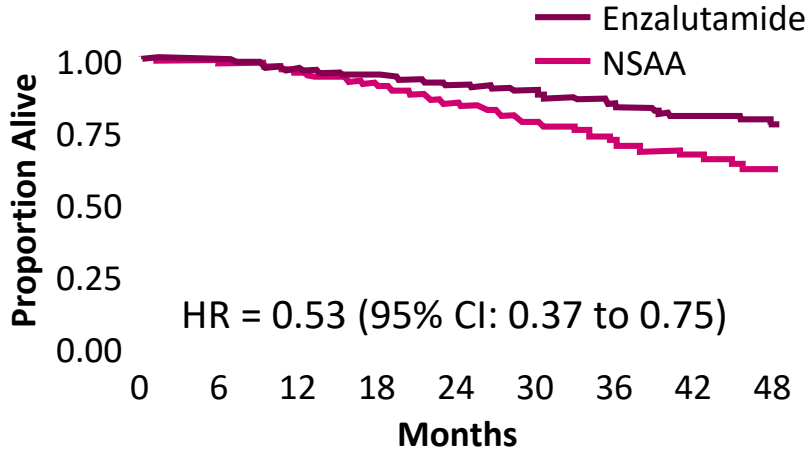
**Testosterone Suppression + Docetaxel (n = 503; 71% high volume)**




**Testosterone Suppression + No Docetaxel (n = 622; 37% high volume)**

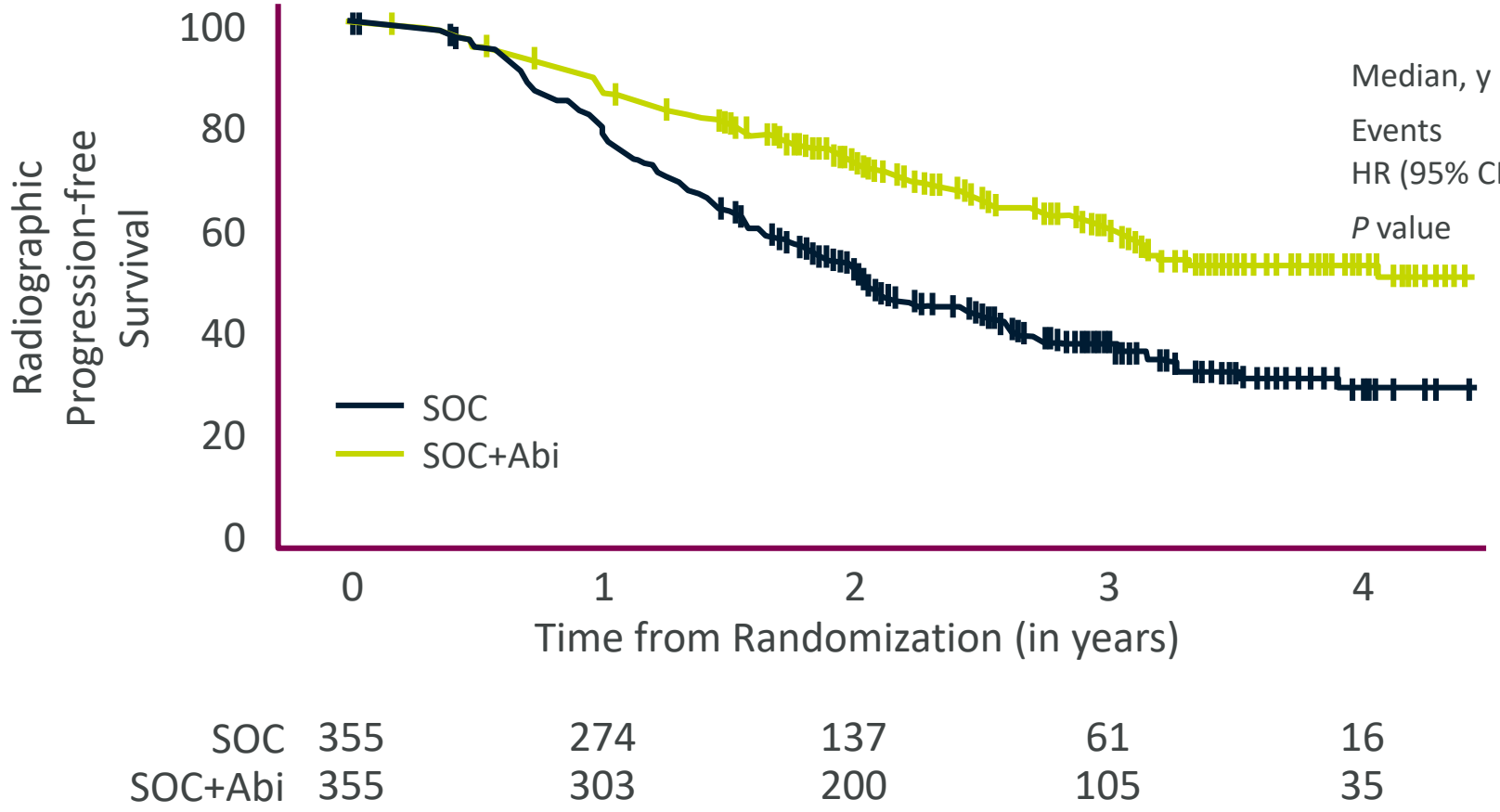



Davis. NEJM. 2019;381:121.

Slide credit: clinicaloptions.com

# PEACE-1: Radiologic PFS With Abiraterone in ADT + Docetaxel Population (± Radiotherapy)

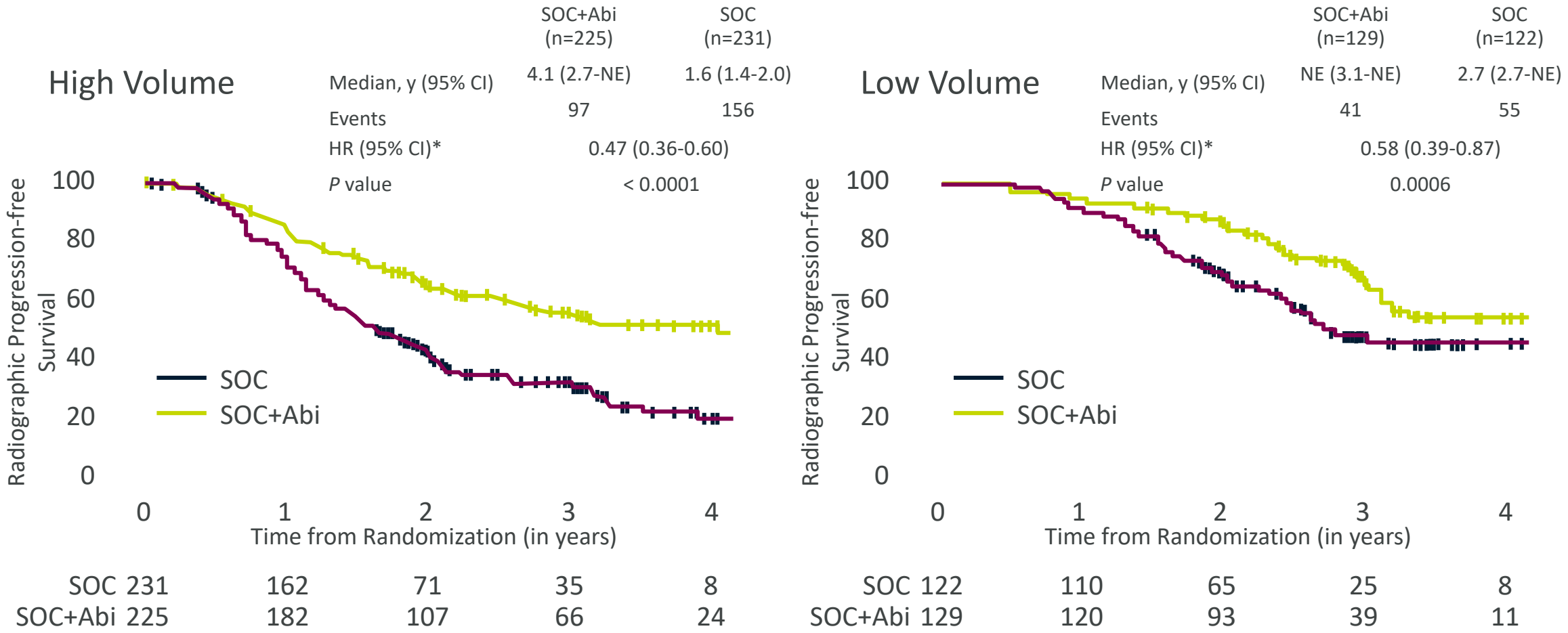



| | SOC+Abi (n=355) | SOC (n=355) |
|---|---|---|
| Median, y (95% CI) | 4.5 (3.1-NE) | 2.0 (1.8-2.3) |
| Events | 139 | 211 |
| HR (95% CI)* | 0.50 (0.40-0.62) | |
| *P* value | < 0.0001 | |

*Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden)

Fizazi. ESMO 2021. Abstr LBA5. Reproduced with permission.

# PEACE-1: Radiologic PFS With Abiraterone in ADT + Docetaxel (± RXT) Population by Metastatic Burden




*Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden)

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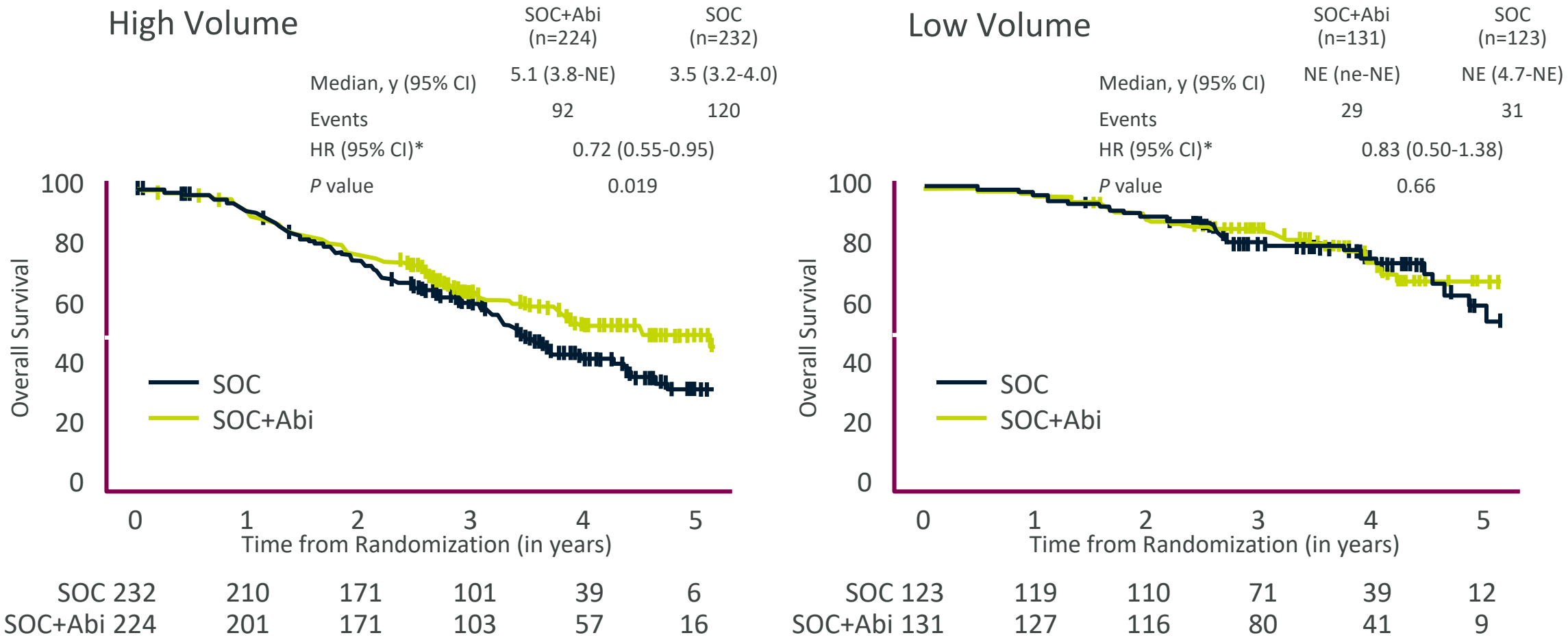
# PEACE-1: OS With Abiraterone in ADT + Docetaxel Population (± Radiotherapy) by Metastatic Burden

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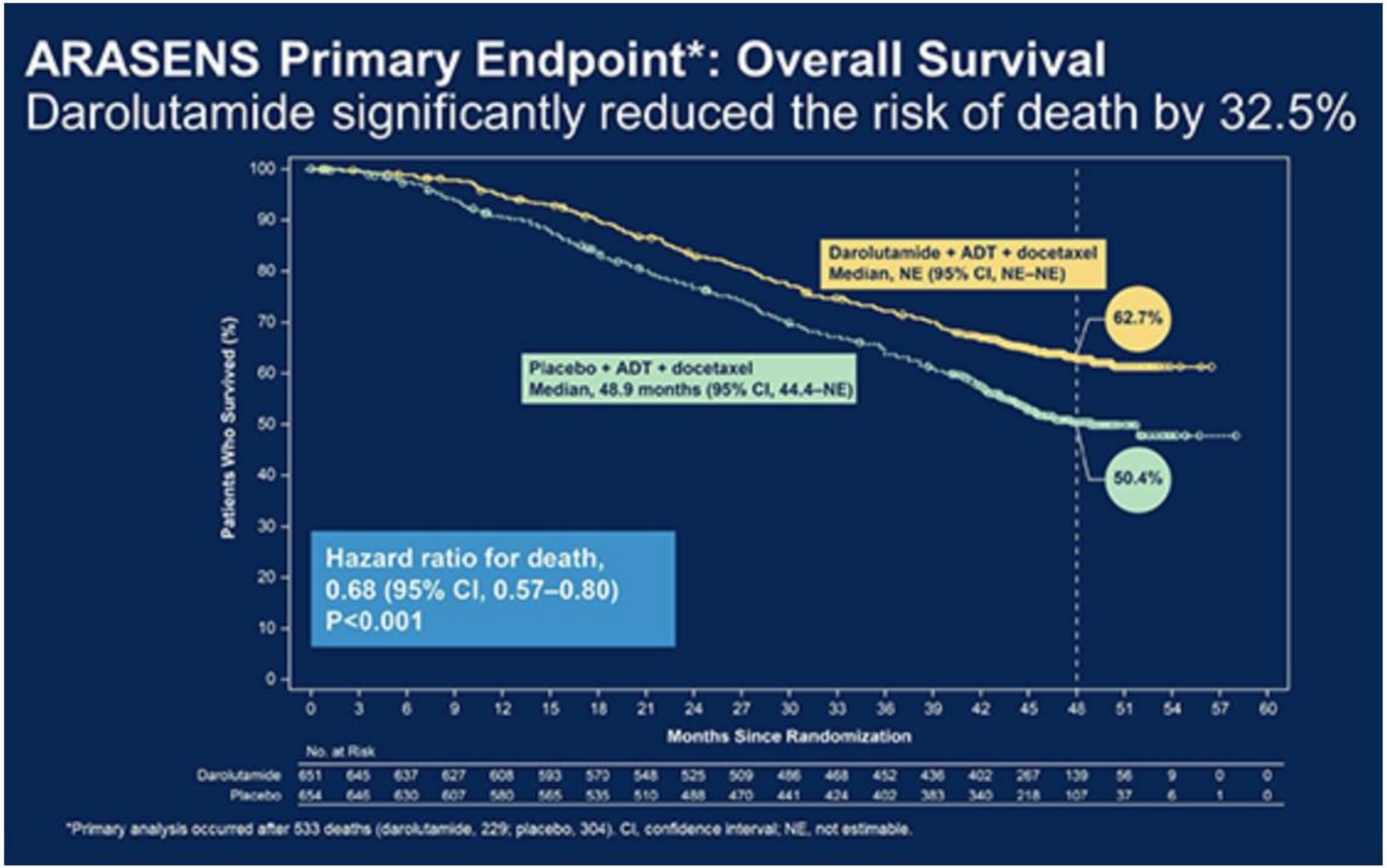
ADT and Docetaxel in Patients With mHSPC



# Efficacy in metastatic disease similar with all agents!!!

| | HR for OS |
|---|---|
| Docetaxel | 0.61 |
| Abiraterone | 0.62 |
| Enzalutamide | 0.67 |
| Apalutamide | 0.67 |
| Darolutamide | 0.68 |

- **No significant difference in OS.**
- **Other Secondary end points similar**

***FFS, PFS, rPFS, time to clinical progression, time to CRPC, PSA complete response, QoL***

***No clear evidence of superiority of one agent over the others***
***No direct inter-agent comparison***

OS- Overall Survival.FFS- Failure free survival, CRPC- Castrate Resistant Prostate Cancer RPFS- Radiographic Progression free survival, PFS- Progression free survival

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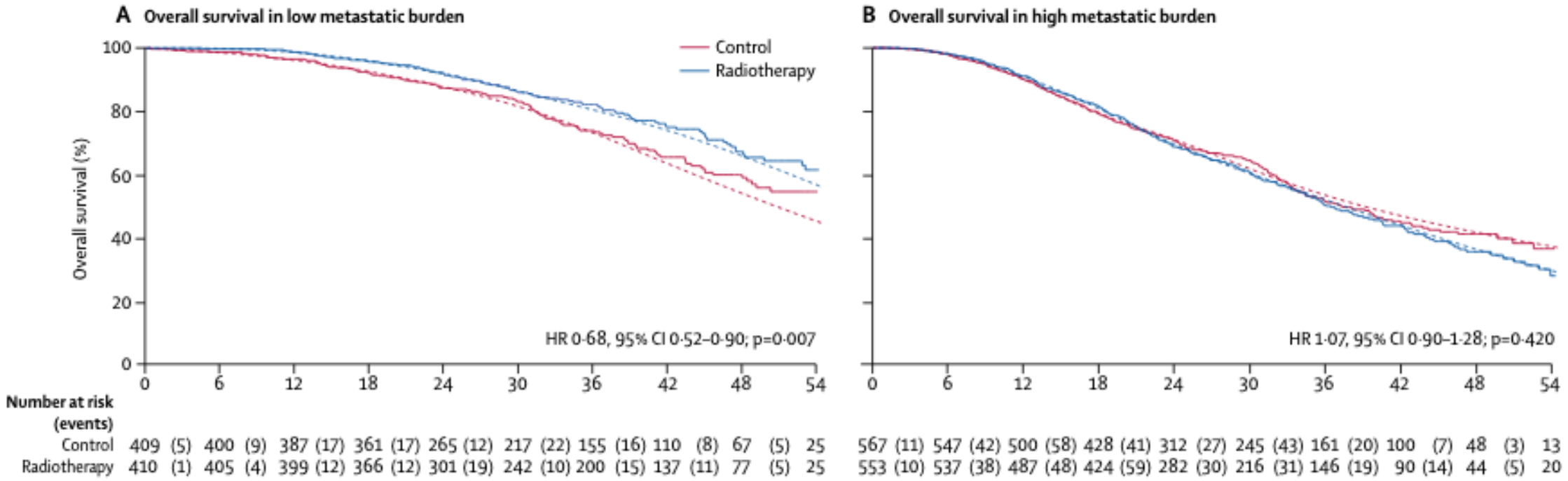
# Prostate radiotherapy improves OS for men with metastatic prostate cancer who have a low metastatic burden, but not for unselected patients/those with a high metastatic burden




**Safety summary**

- Radiotherapy was well tolerated
- The proportion of patients reporting at least one serious AE was similar between treatment groups

AE=adverse event; CI=confidence interval; HR=hazard ratio; mHSPC= metastatic hormone sensitive prostate cancer; OS=overall survival

1. Parker CC et al. *Lancet*. 2018;392:2353-2366

# Summary

- **Key docetaxel + ADT studies in mHSPC include: GETUG-AFU-15,[1] CHAARTED[2] and STAMPEDE[3-5]**
- **Key NHA studies in mHSPC include: STAMPEDE,[3-5] LATITUDE,[6] TITAN,[7] ENZAMET,[8] ARCHES[9]**
- **STAMPEDE[3-5] in the key study in mHSPC demonstrating the benefit of adding radiotherapy of the primary tumour to standard of care in patients with oligometastatic disease**

- **Docetaxel has demonstrated a significant PFS and OS benefit vs control in men with mHSPC[2,3]**
- **In men with mHSPC, the addition of docetaxel to ADT improved overall survival, while addition of NHA to ADT improved both rPFS and OS[2-9]**
- **In the STAMPEDE trial, the addition of radiotherapy of the primary tumour to SOC translated to a positive OS benefit amongst patients with oligometastatic disease[10]**
- **In the ENZAMET study, no additional benefit of docetaxel + enzalutamide was observed in the subgroup analysis. However, further studies will assess the role of combinations in this setting[8]**
- **Triplet combination options**

ADT=androgen deprivation therapy; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; NHA=novel hormonal agent; OS=overall survival; rPFS=radiographic progression-free survival; SOC=standard of care

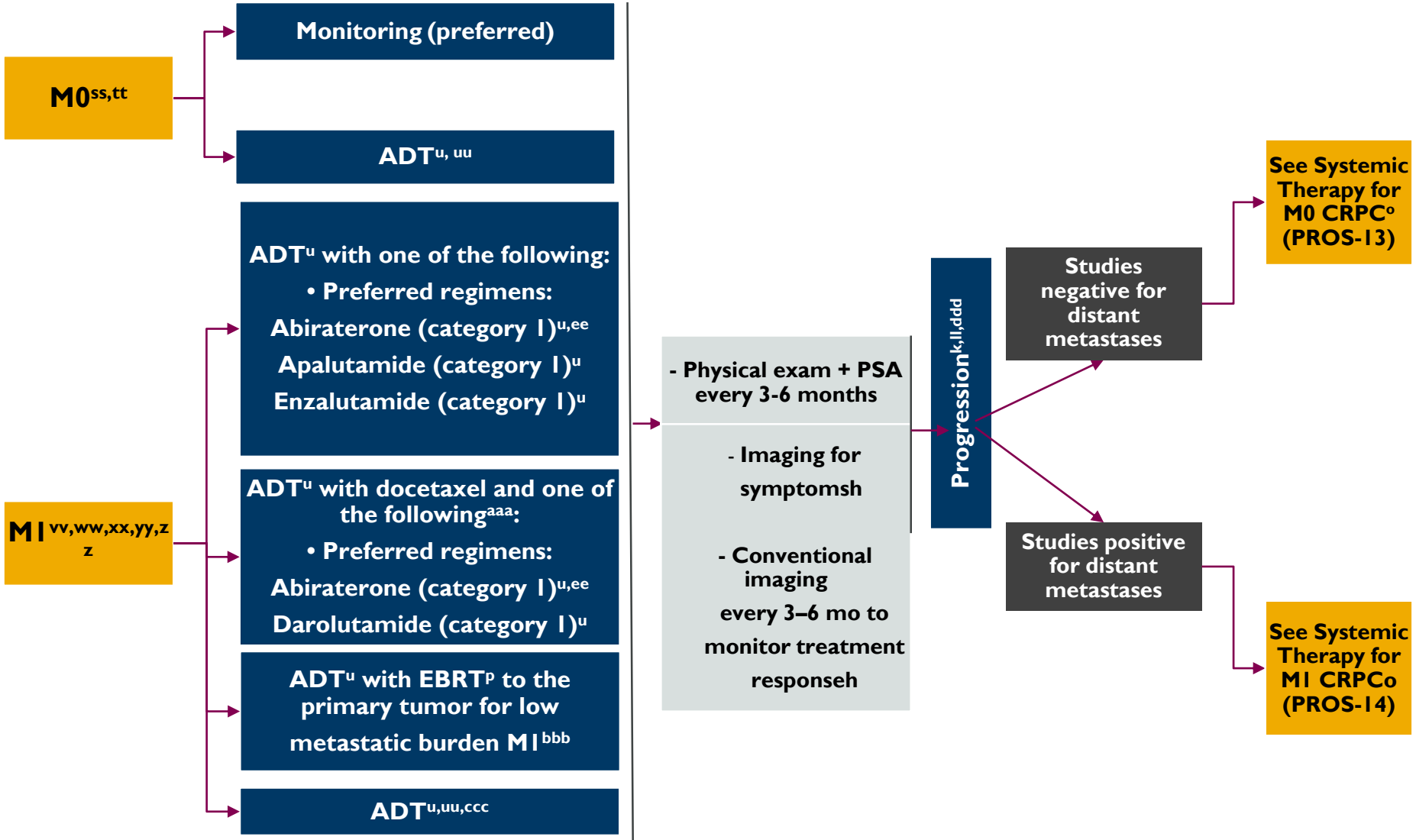
1. Gravis G *et al. Lancet Oncol* 2013;14:149–158; 2. Kyriakopoulos CE et al. *J Clin Oncol*. 2018;36:1080–1087; 3. James ND et al. *Lancet*. 2016;387:1163-1177; 4. James N et al. Presented at: ASCO GU Congress: February 8-10, 2018; San Francisco, CA; 5. James ND et al. *N Engl J Med*. 2017; 377:338-351; 6. Fizazi K et al. *N Engl J Med*. 2017;377:352-360; 7. Chi KN, et al. Presented at ASCO 2019; Chicago. Abstract 5006; 8. Sweeney C, et al. Presented at ASCO 2019; Chicago. Abstract LBA2; 9. Armstrong AJ et al. Presented at: ASCO Annual Congress. May 31-June 4, 2019; Chicago, IL; 10. Parker CC et al. *Lancet*. 2018;392:2353-2366.

# Treatment strategy will depend upon

- Extent of disease / disease burden
- Pts comorbidities
- Duration of response to ADT
- Cost and availability of therapy

- ✓ **High volume disease: Docetaxel or Abiraterone or Enzalutamide (?)**
- ✓ **Low volume disease: Abiraterone or Enzalutamide**
- ✓ **High risk disease: (Gleason >8, visceral metastasis, neuroendocrine): Chemotherapy preferred over abi/enza**
- ✓ **Severe symptomatic (esp pain): Docetaxel**
- ✓ **Mild or no symptoms: Abiraterone or enzalutamide**
- ✓ **Impending disease related emergencies: Docetaxel**
- ✓ **Bone Health**

# NCCN: Management options for castration-naïve prostate cancer




ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; LHRH = luteinizing hormone releasing hormone; M0 = no distant metastases; M1 = distant metastases; PSA = prostate-specific androgen.

1. NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES®) PROSTATE CANCER VERSION 1.2023

# 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