Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

19th Future Directions in Urology Symposium
Directions for the Next Generation of Treatments

Next Generation Anti-Androgen Therapies

August 13, 2018

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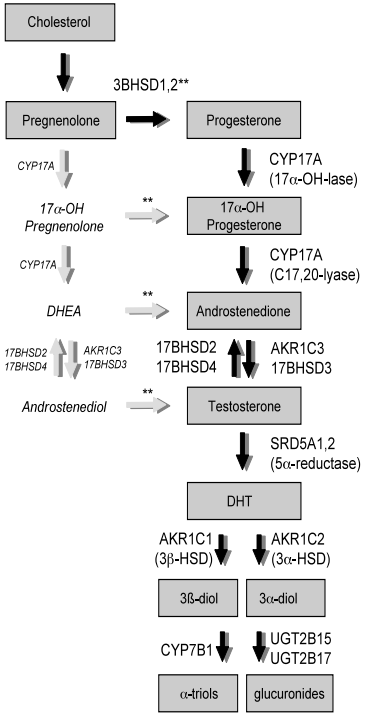
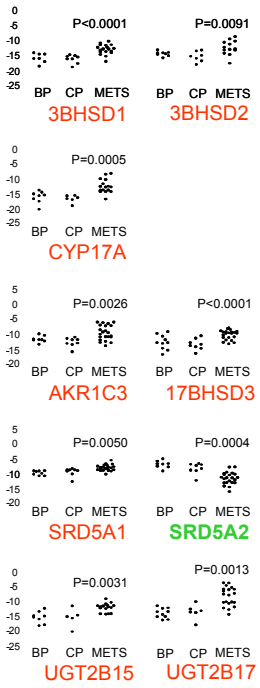
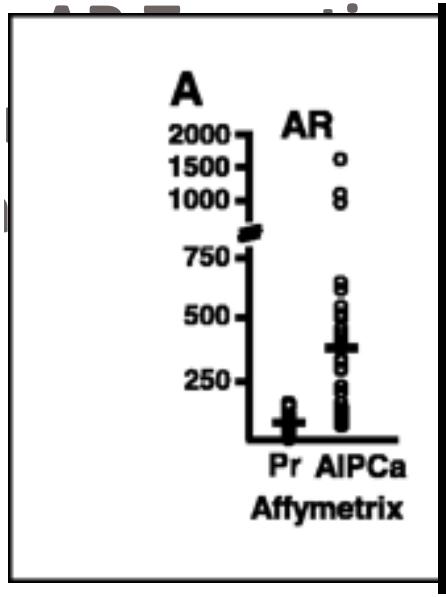
Discussion Topics

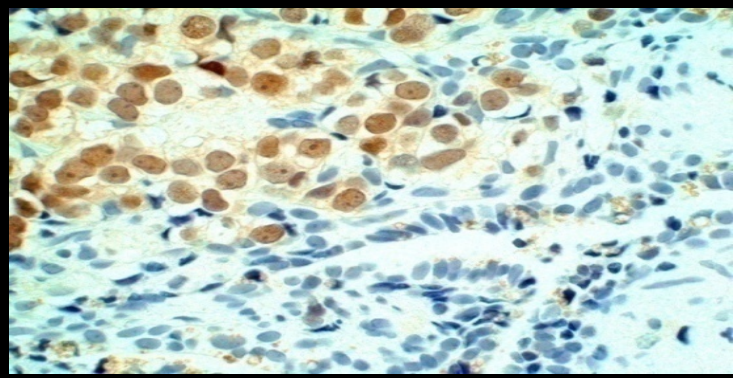
- Metastatic castration-resistant prostate cancer
- Metastatic hormone-sensitive prostate cancer
- M0 castration-resistant prostate cancer – new options
- Biochemical recurrence
- Ongoing trials

Prostate Cancer has the ability to make it's own Androgens and AR is highly expressed









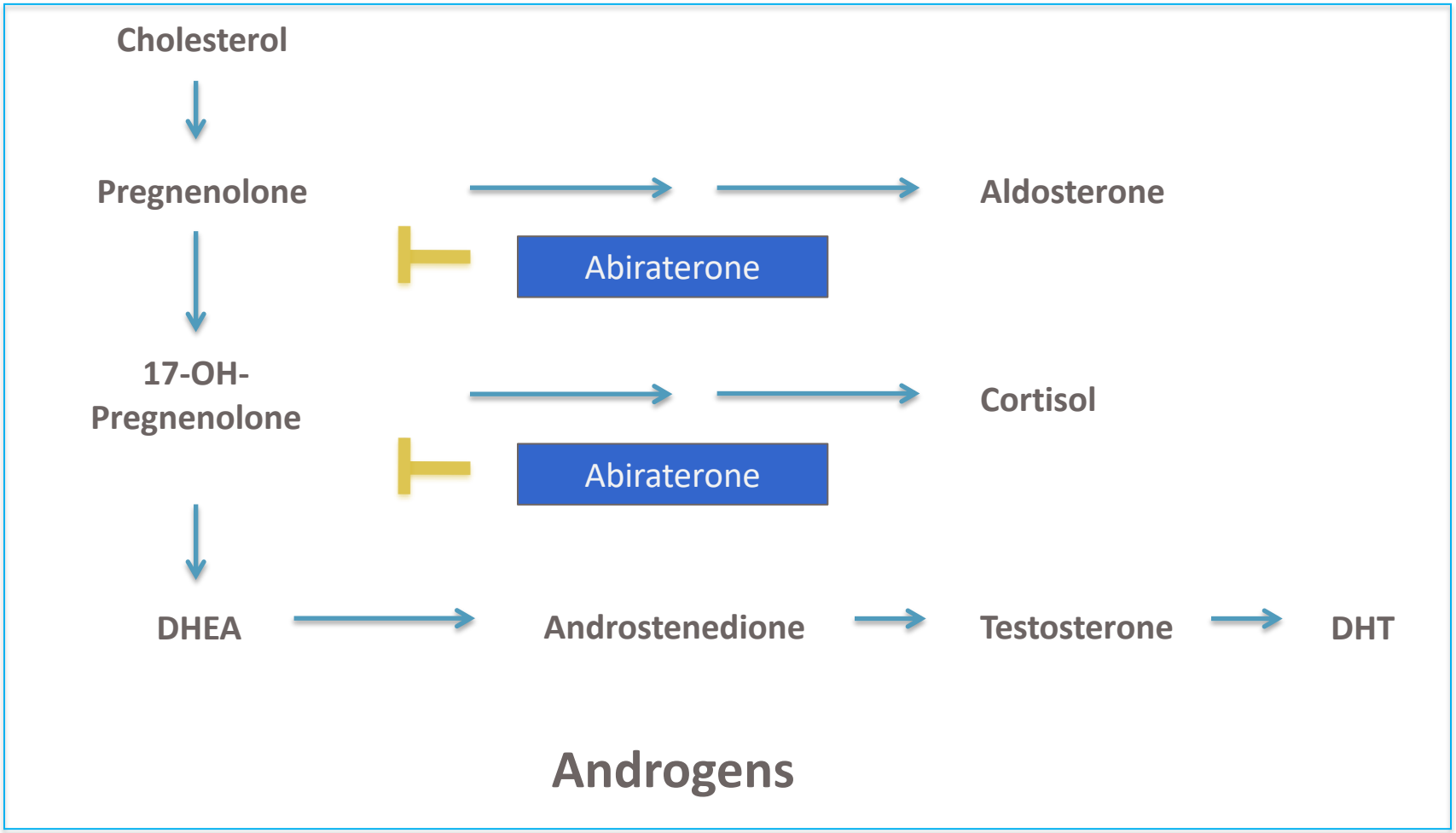
CRPC samples have robust AR expression

Mohler et al

AR, androgen receptor.

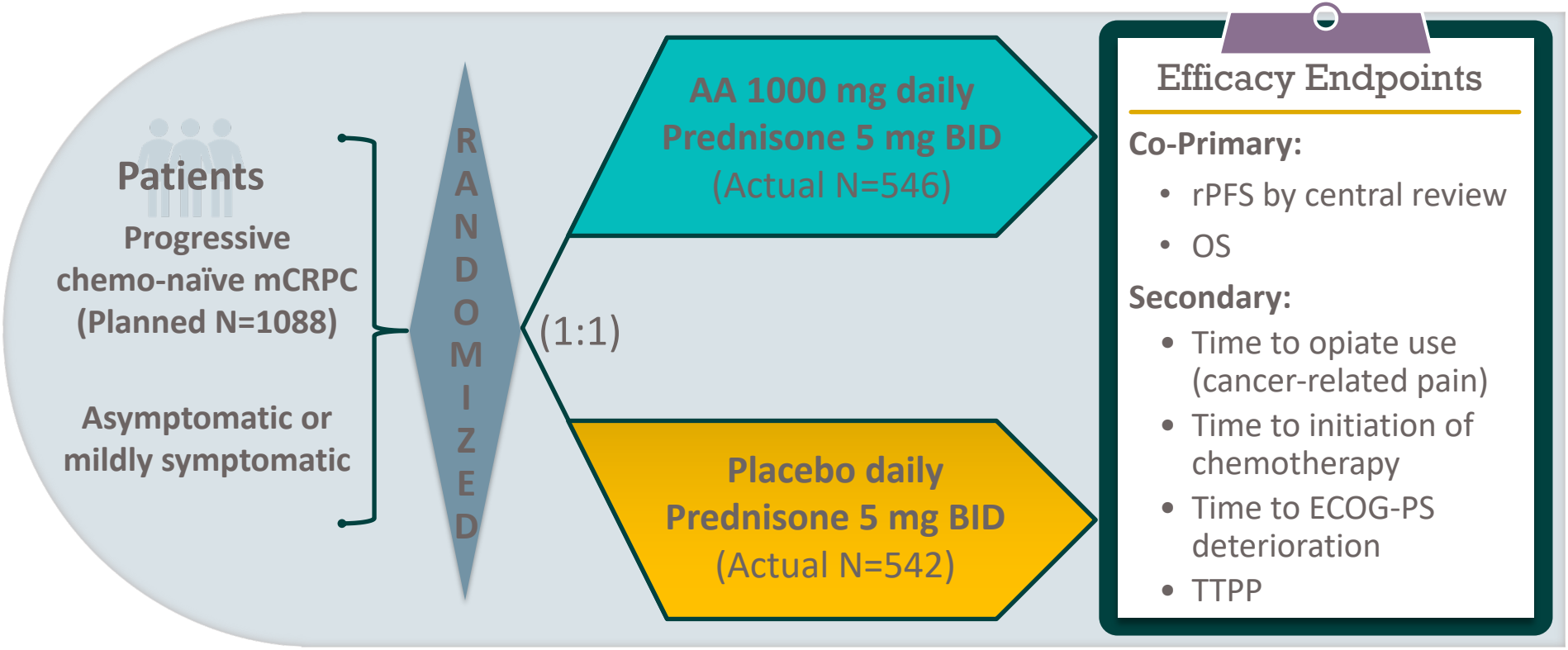
Montgomery RB, et al. *Cancer Res*. 2008;68(11):4447-4454.

Abiraterone Acetate: Mechanism of Action



1. De Bono JS et al. *N Engl J Med*. 2011;26:1995-2005. 2. Ryan et al. 2012 American Society of Clinical Oncology Annual Meeting (ASCO 2012). Abstract LBA4518.

COU-AA-302 Trial Schema

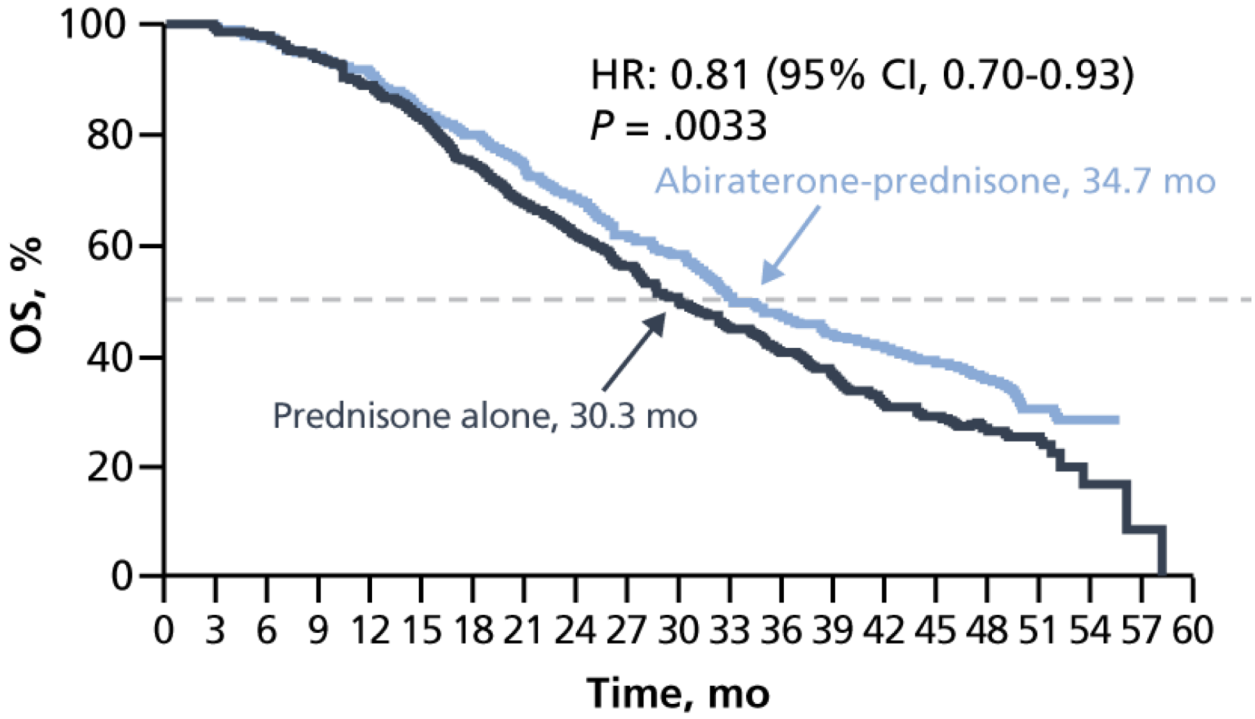


- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Stratification by ECOG performance status 0 vs 1

AA, abiraterone acetate; ECOG-PS, Eastern Cooperative Oncology Group - Performance Status; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; rPFS, radiographic progression-free survival; TTPP, time to PSA progression.

Ryan CJ, et al. *N Engl J Med.* 2013;368:138-148.

COU-AA-302 Overall Survival



No. at Risk

Abiraterone-prednisone	546	538	525	504	483	453	422	394	359	330	296	273	235	218	202	189	118	59	15	0	0
Prednisone alone	542	534	509	493	466	438	401	363	322	292	261	227	201	176	148	132	84	42	10	1	0

OS: overall survival; PFS: progression-free survival.

Ryan CJ et al. *N Engl J Med.* 2013;368:138-148.

Ryan CJ, Smith MR, Fizazi K, Miller K. European Society for Medical Oncology 2014 Congress (ESMO 2014). Abstract 7530.

Enzalutamide is a Pure, Irreversible AR Antagonists

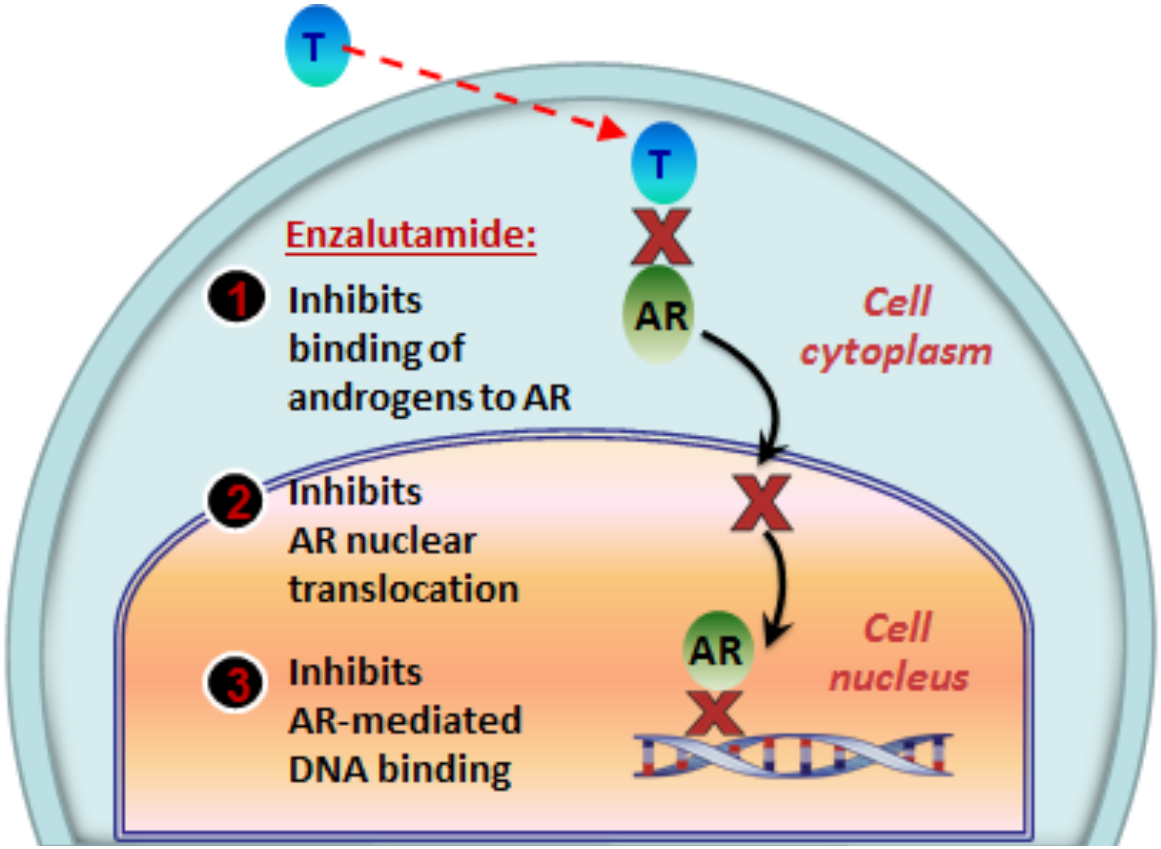
Enzalutamide improved OS and radiographic PFS in patients with mCRPC both pre-[1] and post-docetaxel[2]

1. **AR Binding Affinity**
   - DHT ~ 5nM
   - **Bicalutamide ~160 nM**
   - **MDV3100 ~35 nM**

2. **Nuclear Import**
   - DHT: ++++
   - **Bicalutamide: ++++**
   - **MDV3100: ++**

3. **DNA Binding**
   - DHT: ++++
   - **Bicalutamide: ++**
   - **MDV3100: -**

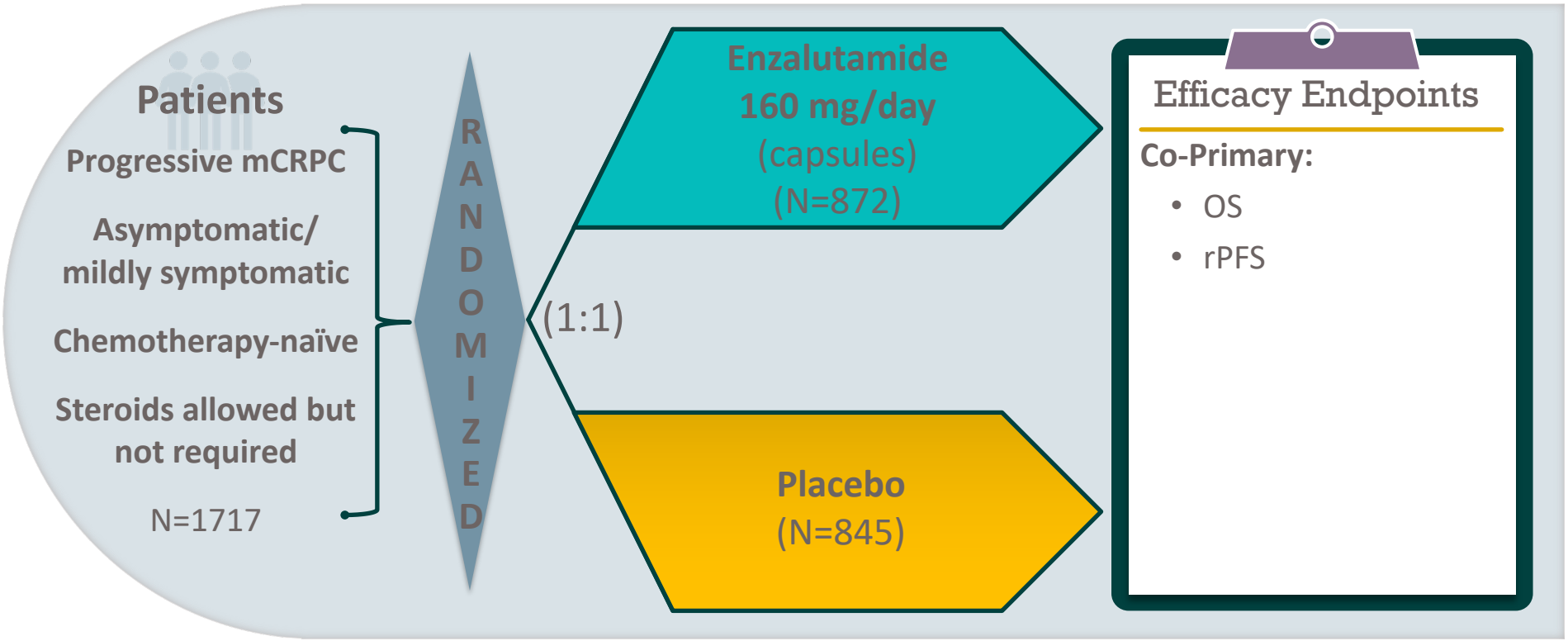
4. **Coactivator recruitment**
   - DHT: ++++
   - **Bicalutamide: ++**
   - **MDV3100: -**



Chen Y et al. *Lancet Oncol*. 2009; 10:981-91.

1. Beer TM et al *N Engl J Med*. 2014;371:424-433.
2. Scher HI et al. *N Engl J Med*. 2012;367:1187-1197.

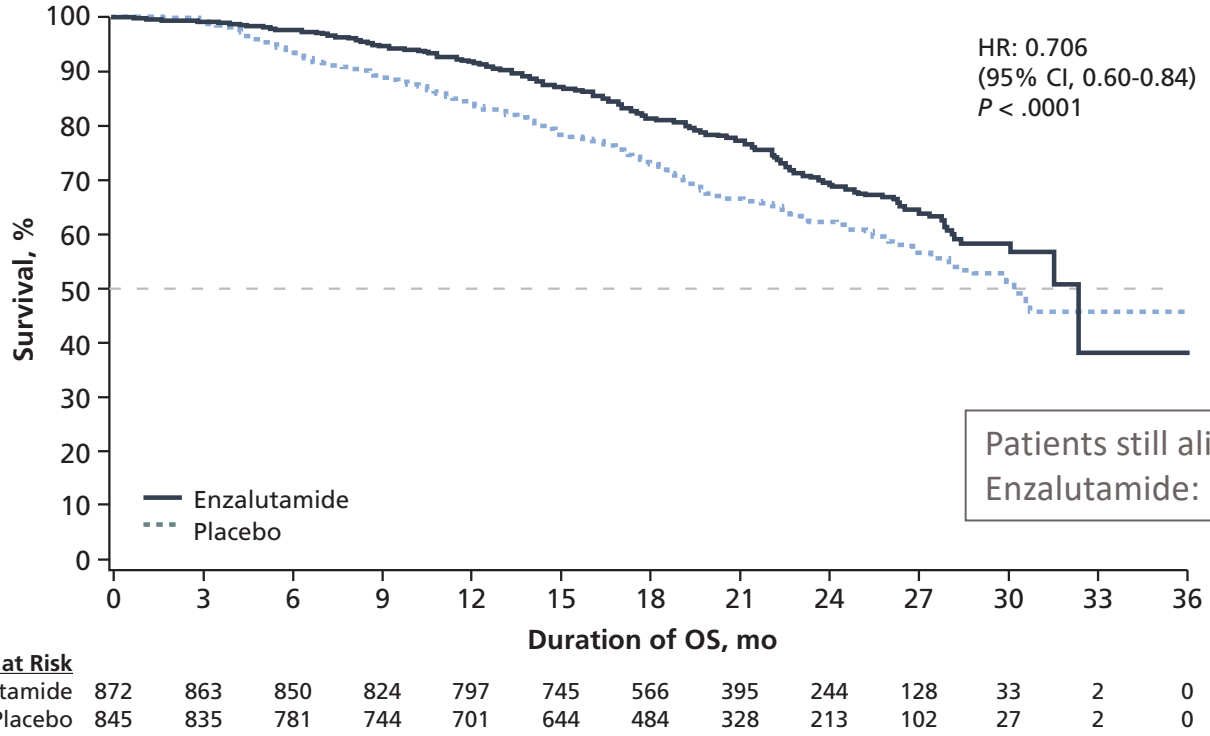
PREVAIL Trial Schema



mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; rPFS, radiographic progression free survival.

Beer TM, et al. *N Engl J Med.* 2014;371:424-433.

PREVAIL Overall Survival



Patients still alive at data cut-off
Enzalutamide: 72%; Placebo: 63%

	Estimated Median OS, mo (95% CI)
Enzalutamide	32.4 (30.1-NYR)
Placebo	30.2 (28.0-NYR)

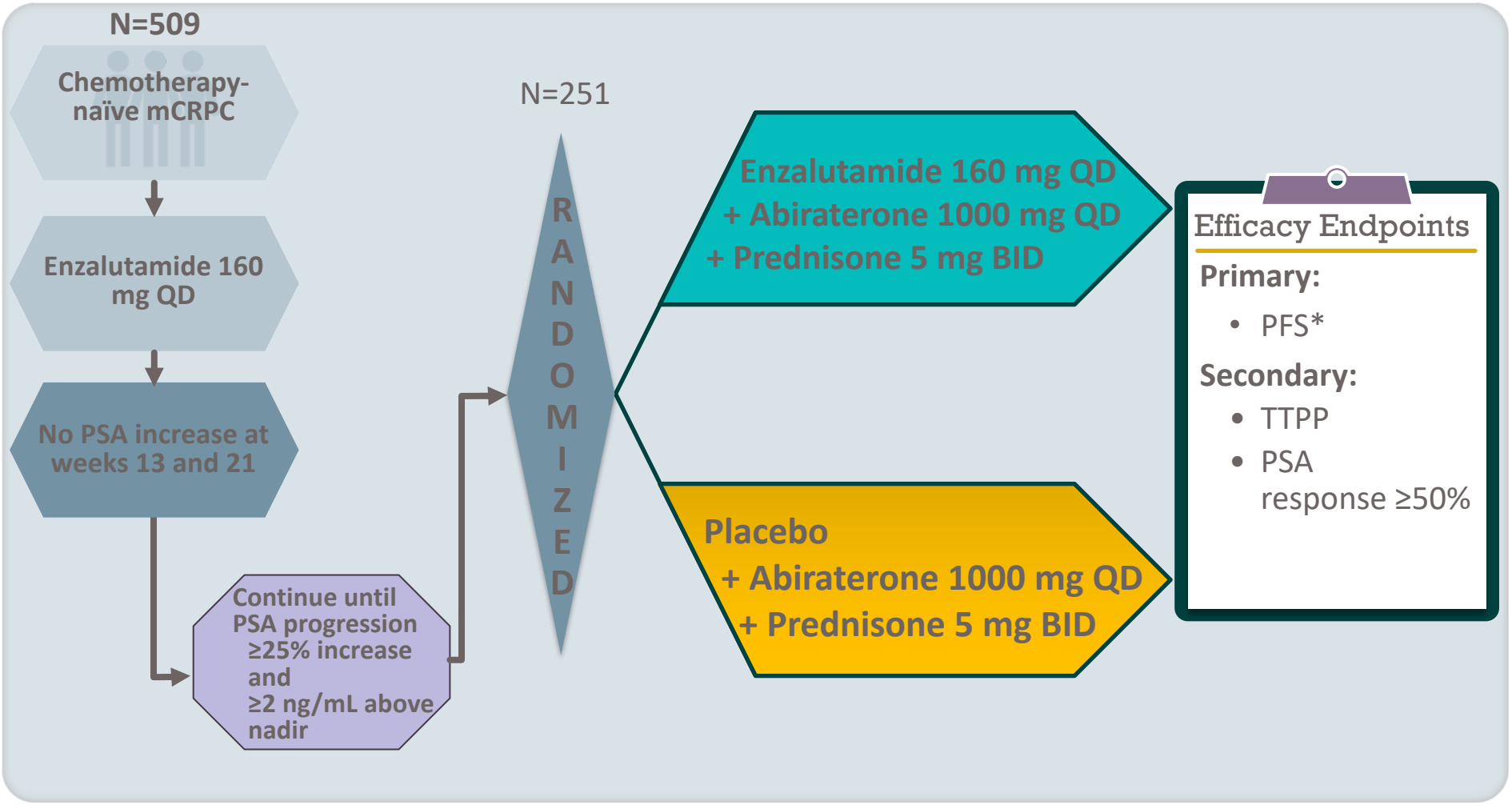
Beer TM et al. *J Clin Oncol*. 2014;32(suppl 4):Abstract LBA1^.

Sequencing of Abiraterone and Enzalutamide

	Prior Docetaxel	N	PSA Decline ≥30%, %	PSA Decline ≥50%, %	Median TTP, mo	Median PFS, mo
Abiraterone after enzalutamide						
Noonan[1]	Y	27	11	4	NR	3.5
Loriot[2]	Y	38	18	8	NR	2.7
Enzalutamide after abiraterone						
Schrader[3]	Y	35	37	29	4.0[a]	–
Bianchini[4]	Y	39	41	13	2.2	2.8
Badrising[5]	Y	61	46	21	4.0	2.8
Cheng[6]	Y	122	39	26	–	–
Azad[7]	Y	68	–	22	4.6	–
Cheng[6]	N	28	40	36	–	–
Azad[7]	N	47	–	26	6.6	–

[a] Responders.
TTP: time to progression.
1. Noonan KL et al. *Ann Oncol*. 2013;24:1802-1807. 2. Loriot Y et al. *Ann Oncol*. 2013;24:1807-1812. 3. Schrader AJ et al. *Eur Urol*. 2014;65:30-36. 4. Bianchini D et al. *Eur J Cancer*. 2014;50:78-84. 5. Badrising S et al. *Cancer*. 2014;12:968-975. 6. Cheng HH et al. *Prostate Cancer Prostatic Dis* 2015; 18:122-7. 7. Azad AA et al. *Eur Urol*. 2015;67:23-29.

PLATO: Enzalutamide Post-PSA Progression in Chemotherapy-Naïve mCRPC Trial Schema



*Radiographic or unequivocal clinical progression or death on study

mCRPC, metastatic castration-resistant prostate cancer; PFS, progression free survival; PSA, prostate specific antigen; TTPP, time to PSA progression.

Attard G, et al. *J Clin Oncol.* 2017;35(18 Suppl): Abstract 5004.

PLATO Results

Endpoint	E+AA+P	Pbo+AA+P	Hazard Ratio (95% CI)
PFS, median	5.7 mos	5.6 mos	0.83 (0.61-1.12)
PFS event rPFS Clinical progression Death	 38% 25% 2%	 55% 18% 1%	
TTPP, median	2.8 mos	2.8 mos	0.87 (0.62-1.24)
PSA response rate	0.8%	2.5%	
rPFS, median	10.0 mos	7.0 mos	0.67 (0.47-0.94)
Adverse Event Back pain Hypertension Nausea Fatigue	 21% 20% 17% 14%	 23% 7% 9% 15%	

Median treatment duration = 5.6 mos

AA, abiraterone acetate; E, enzalutamide; mCRPC, metastatic castration-resistant prostate cancer; mos, months; P, prednisone; Pbo, placebo; PFS, progression free survival; PSA, prostate specific antigen; TTPP, time to PSA progression.

Attard G, et al. *J Clin Oncol*. 2017;35(18 Suppl): Abstract 5004.

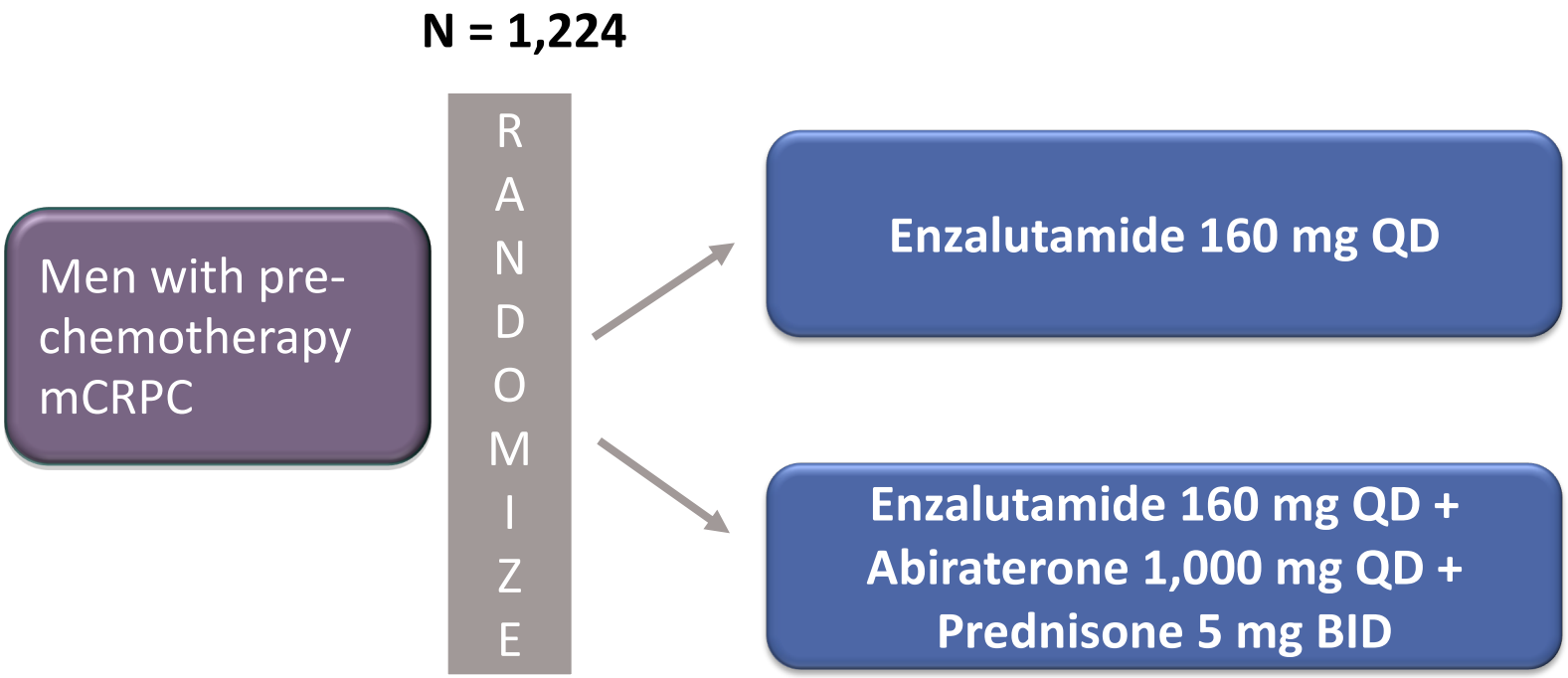
Which Should Go First? 3 Reasons Why I Use Abiraterone Before Enzalutamide – Disclaimer: Evan Yu's Opinion Only

- Response rates to enzalutamide after abiraterone are better than abiraterone after enzalutamide
- Fatigue, depression, falls and hip fractures are more common with enzalutamide
- There are more clinical trials being designed with enzalutamide +/- drug X after abiraterone than the other way around

Do I Sequence Abiraterone and Enzalutamide Back to Back? – Disclaimer: Evan Yu's Opinion Only

- Rarely…if I do I am more apt to try enzalutamide after abiraterone in a patient who strongly desires low toxicity oral therapy
- Never do I sequence back to back in a patient who is symptomatic from his prostate cancer
- Preference to change mechanism of action e.g. radium-223 or docetaxel
- I occasionally will go to the other agent if there has been chemotherapy between the two

Alliance Group A031201: Abiraterone + Enzalutamide vs. Enzalutamide Alone Trial Schema

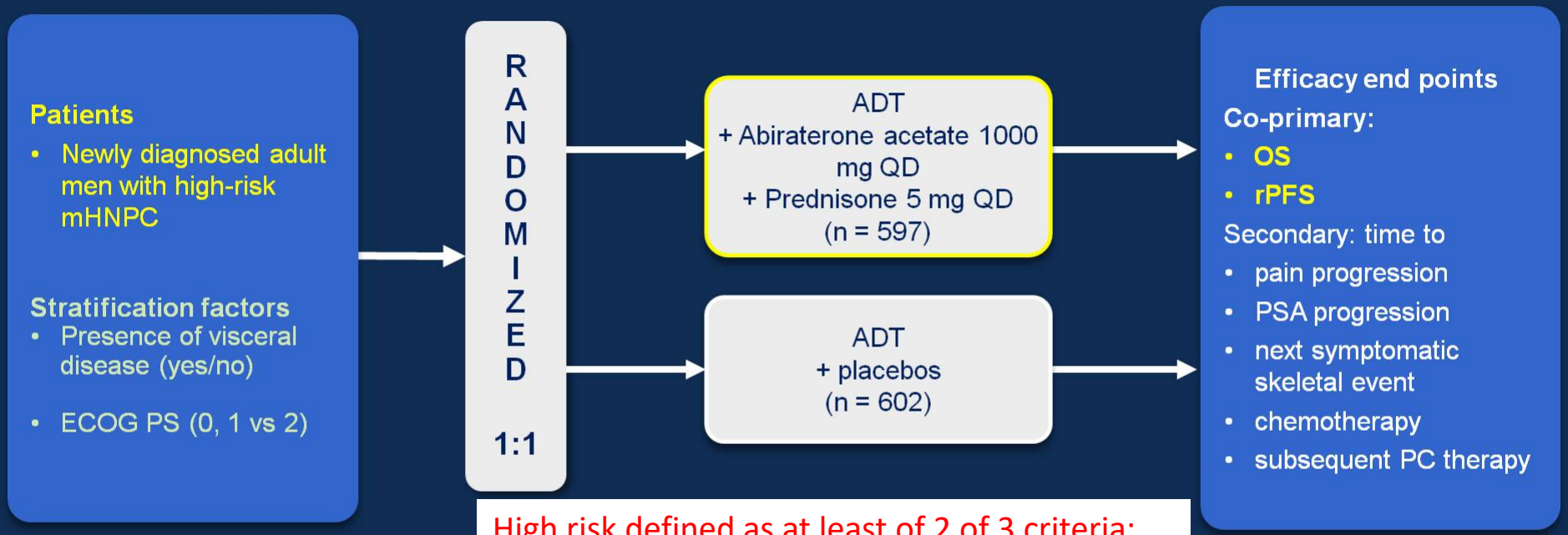


- Endpoints
  - Primary: OS
  - Secondary: PFS, rPFS, ORR, toxicity
- Total of 616 deaths, log-rank statistic 90% power (one-sided type I error rate of 0.025) to detect HR of 0.77 in favor of arm B

ORR: objective response rate.

LATITUDE Trial Schema

Overall study design of LATITUDE

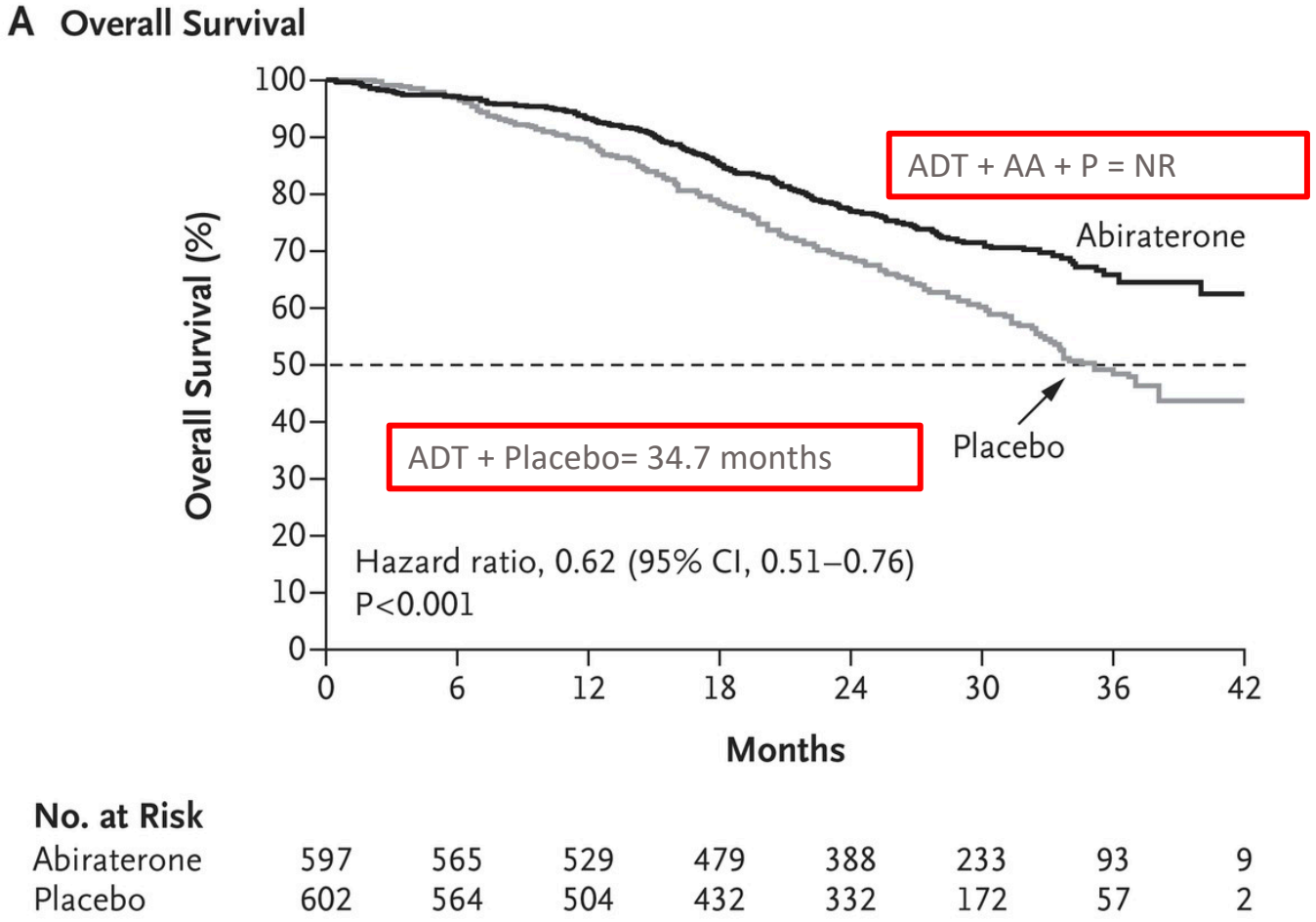


High risk defined as at least of 2 of 3 criteria:
- Gleason score of 8 or more
- Presence of 3 or more lesions on bone scan
- Presence of measurable visceral lesion

- Conducted at 235 sites in … ca, and Canada
- Designed and fully enrolle… results

Fizazi et al. N Engl J Med 2017; June 4, 2017 epub.

LATITUDE – Overall Survival with Abiraterone

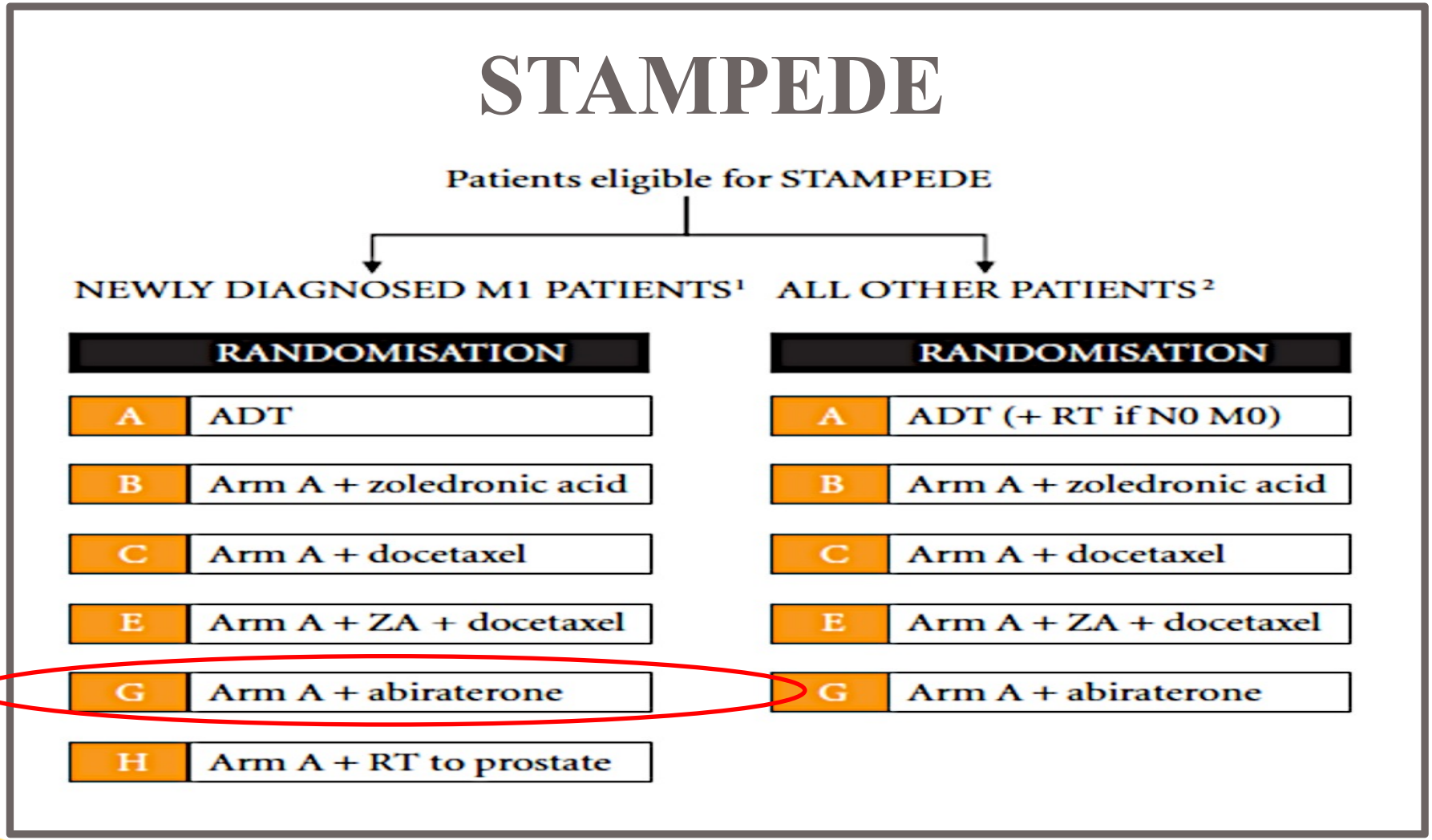


OS rate at three years:
ADT + AA + P: 66%
ADT + placebos: 49%

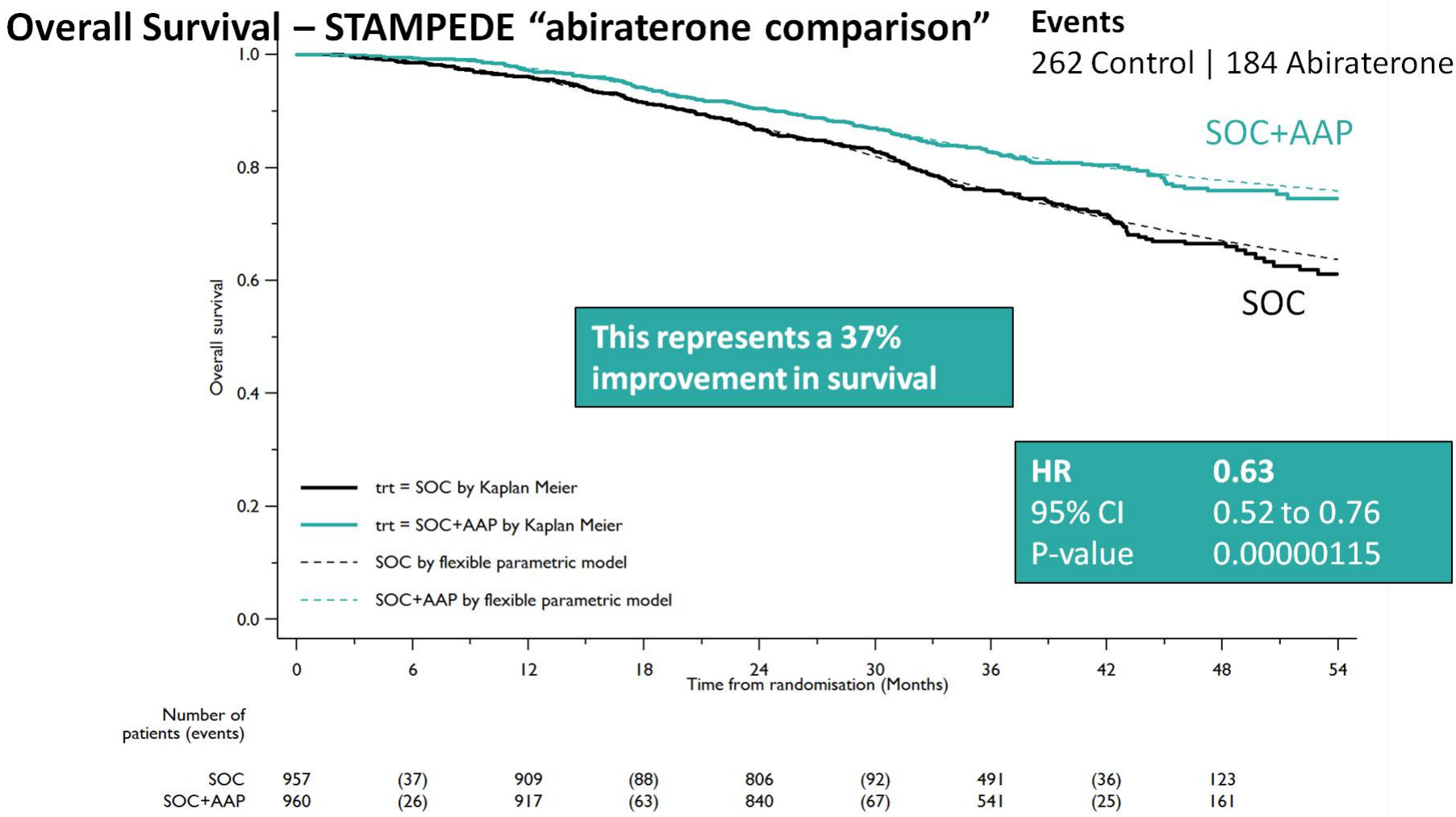
Median follow-up:
30.4 months

Fizazi K et al. N Engl J Med 2017; 377:352-60.

STAMPEDE Trial Schema



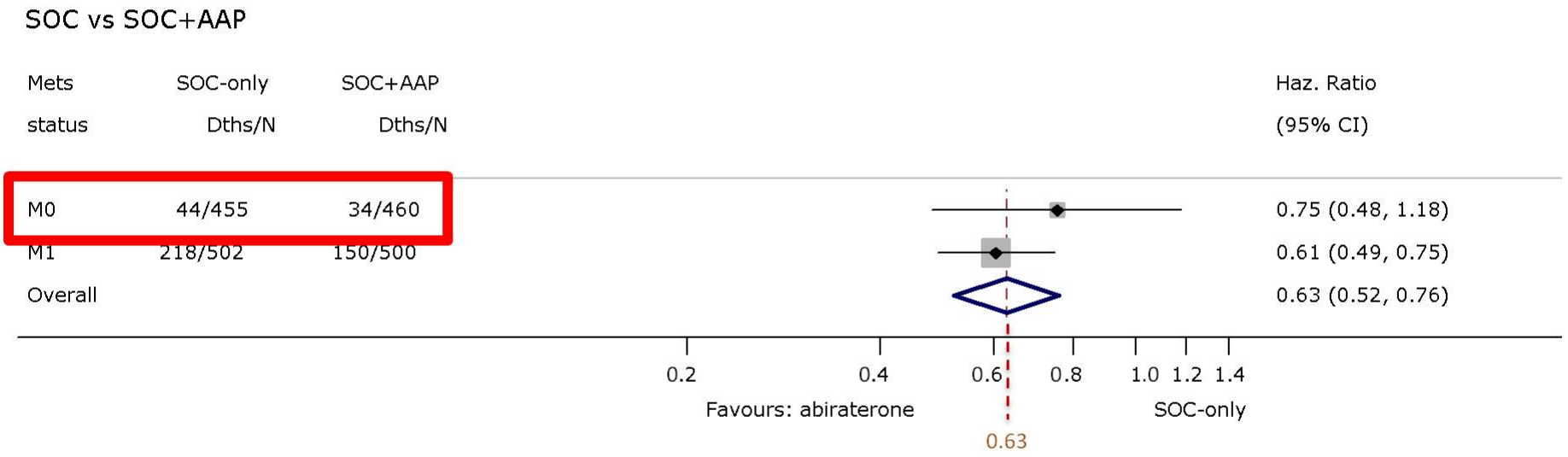
STAMPEDE with Abiraterone – Overall Survival



James ND et al. N Engl J Med 2017; 377:338-53.

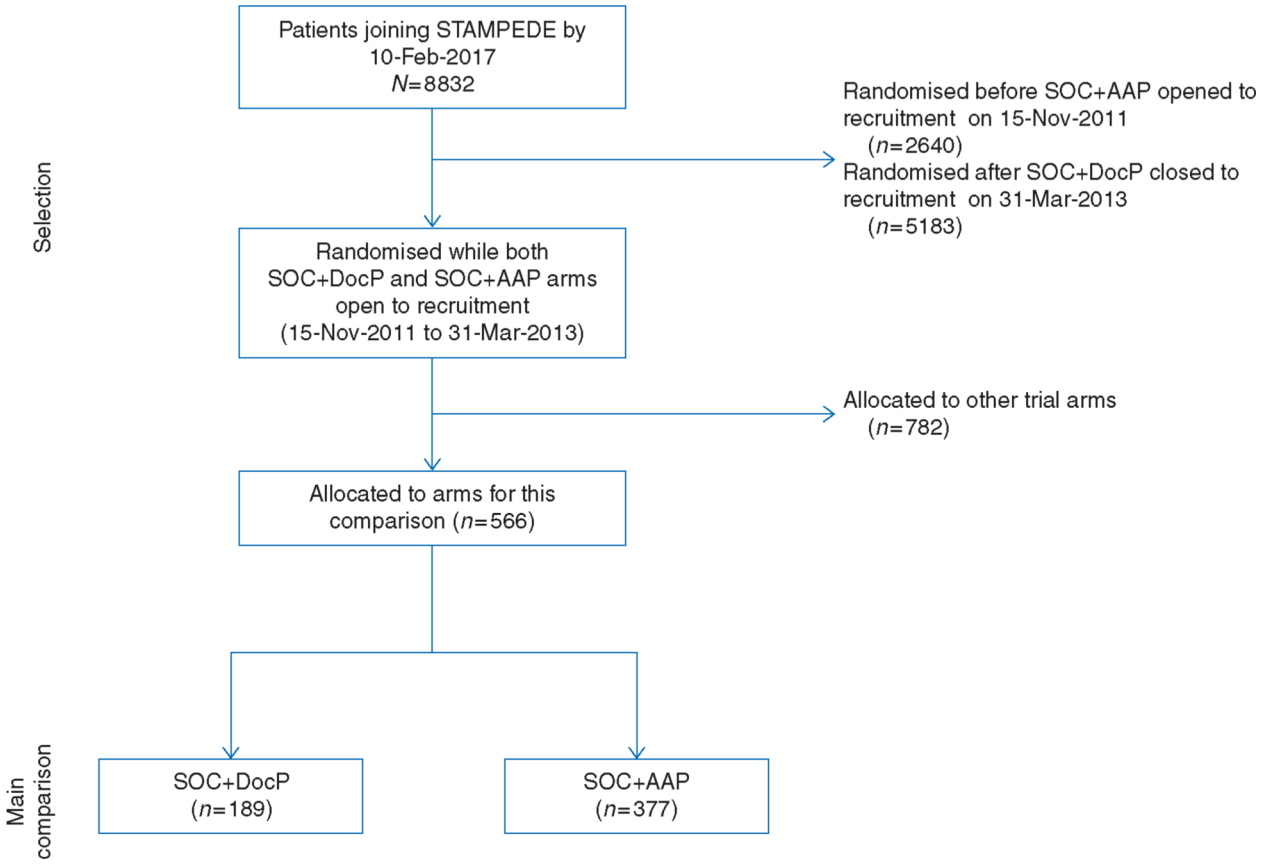
STAMPEDE – What about the M0 Patients?

STAMPEDE "abiraterone comparison"
Overall Survival by metastatic status – pre-planned analysis



James ND et al. N Engl J Med 2017; 377:338-53.

STAMPEDE – Direct Non-randomized Comparison of Docetaxel with Abiraterone



- N=566
- 60% metastatic
- No difference in OS, cancer-specific survival, or skeletal related events between docetaxel and abiraterone
- PFS (driven by PSA) favored abiraterone

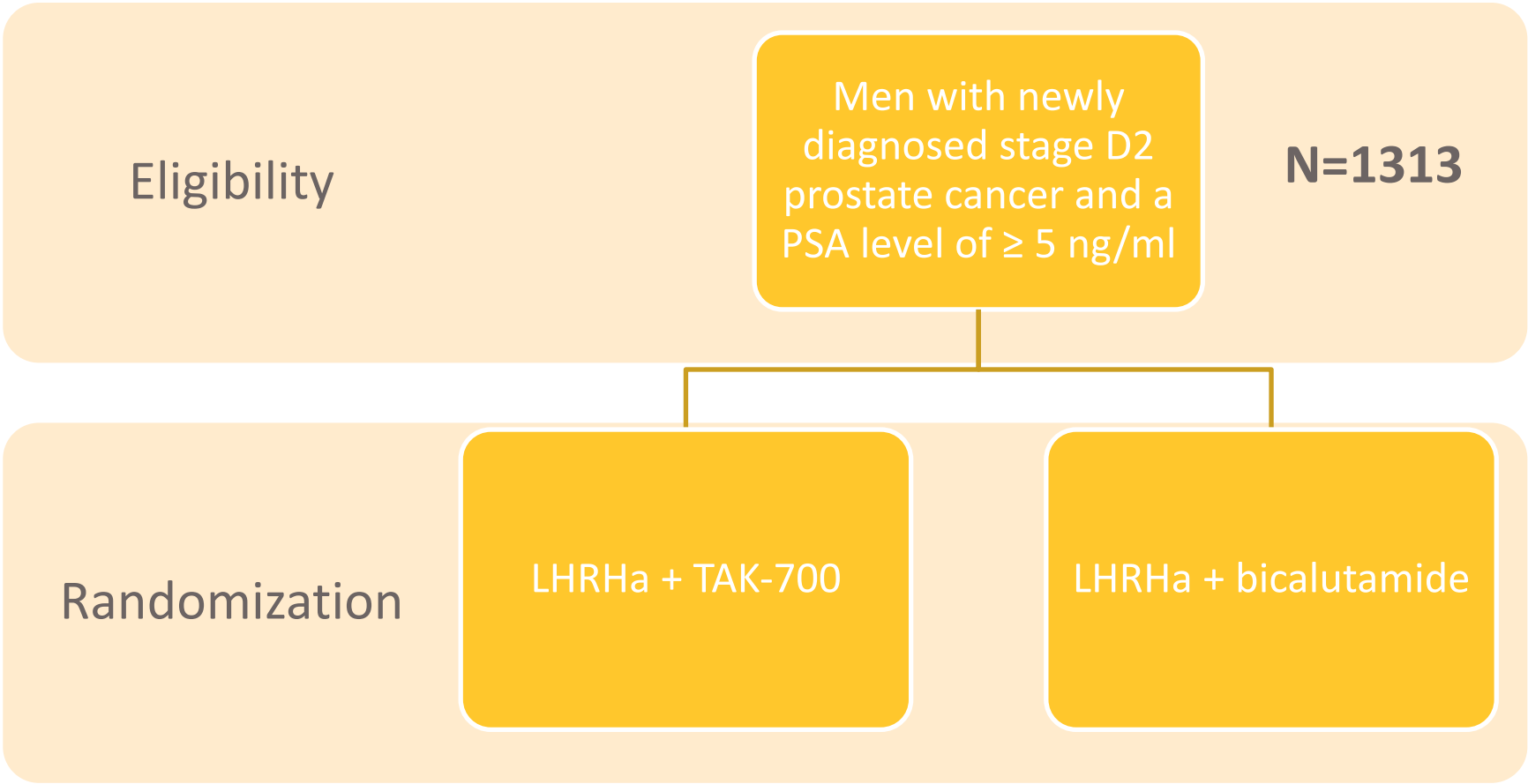
Sydes M et al. Ann Oncol 2018; 29(5):1235–48.

Practical Comparisons Between Docetaxel vs. Abiraterone

Docetaxel	Abiraterone Acetate + P
Limited duration of therapy (18 weeks)	Longer duration of therapy (often years)
Lower cost ($32,000 for a six-dose cycle)	Very expensive (~$10,000 per month or ~$240,000 over two years)
More affordable to patients: no copay for most men (i.e. > 65 years, who are on Medicare)	Less affordable to patients: high copay for most, often hundreds of dollars per month
Higher toxicities (myelosuppression, neuropathy, etc.)	Lower toxicities (hypertension, hypokalemia, edema)
Requires frequent visits to doctor's office for infusions and monitoring	Less frequent visits, no infusions

Adapted from Dr. Neeraj Agarwal, ASCO 2018.

SWOG 1216 Randomized Phase 3 Trial Schema

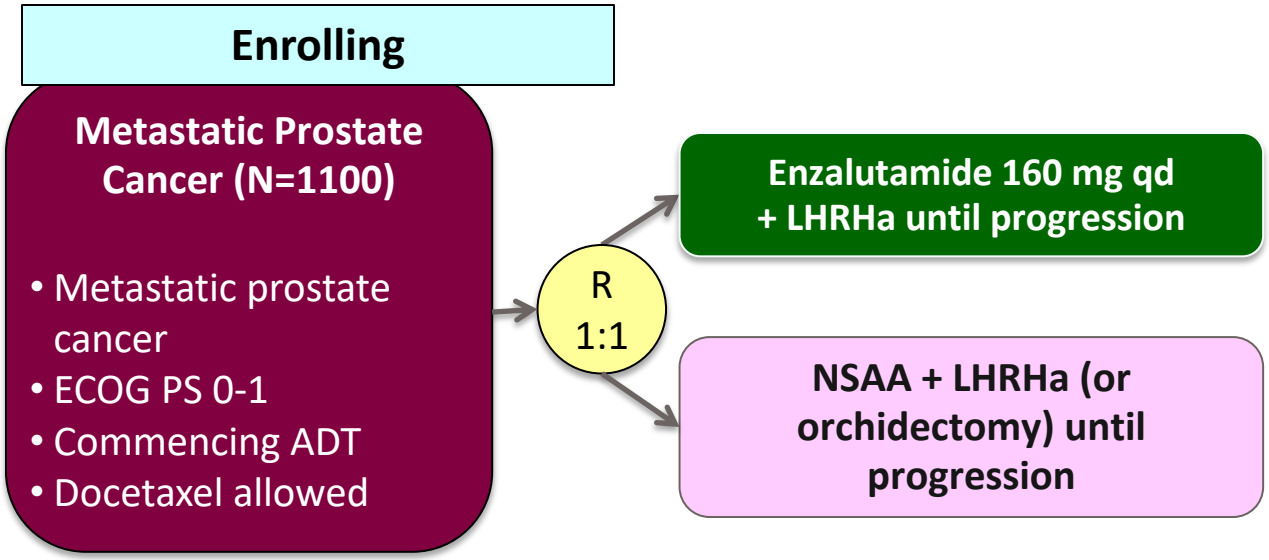


Primary Endpoint: Overall survival

Secondary Endpoints: 7-month PSA ≤ 0.2 ng/ml and PSA of ≥ 4 ng/ml, PFS. Safety, Correlatives

PI: Neeraj Agarwal, University of Utah

ENZAMET Trial: ADT +/- Enzalutamide for Metastatic Prostate Cancer



Planned Evaluations

- OS
- PFS (PSA and clinical)
- AEs
- HRQoL
- Cost effectiveness
- Associations between biomarkers and outcomes

- Stratified by disease volume, antiresorptive therapy, comorbidities and study site
- Primary endpoint: OS

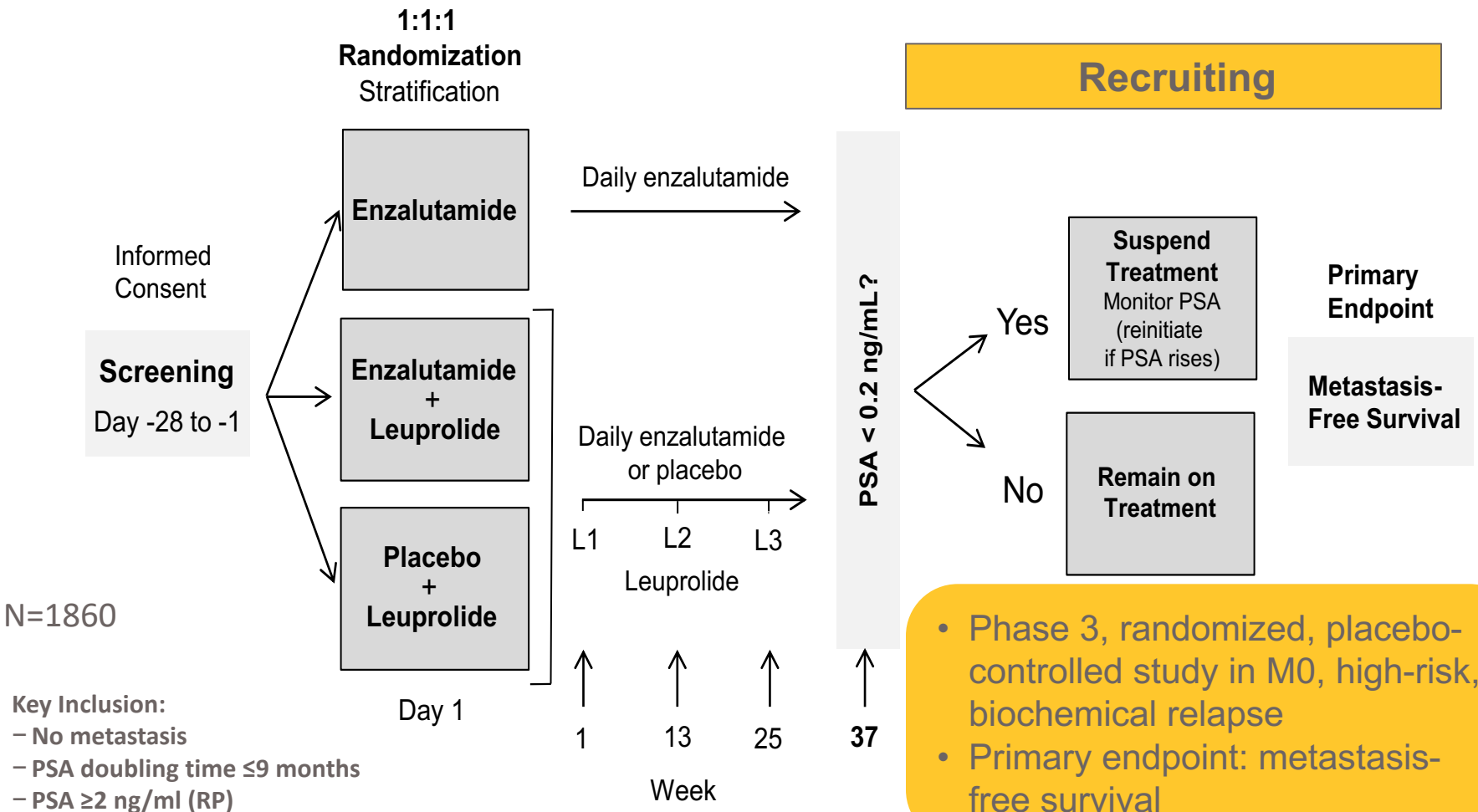
LHRHa= luteinizing hormone-releasing hormone agonist; NSAA= non-steroidal anti-androgen; PFS= Progression Free Survival; HRQoL= Health-Related Quality of Life

www.clinicaltrials.gov (NCT02446405)

What should we do with mHSPC after all this?

- Not certain we should treat M0 patients yet, but might consider abiraterone for select M0 patients with very high risk features (e.g. PSAdt <6 months)
- Treat low volume metastatic disease with abiraterone
- Offer abiraterone or docetaxel for high volume metastatic disease delineating between the two by:
  - Patient comorbidities
  - Side effect profiles
  - Duration of therapy
  - Financial toxicity
- No data for adding abiraterone many months later for a patient already on ADT or after ADT + docetaxel
- Keep enrolling on clinical trials
  - TITAN: ADT +/- apalutamide (allows docetaxel)
  - ARASENS: ADT with docetaxel +/- ODM201

EMBARK Phase 3 Trial Schema

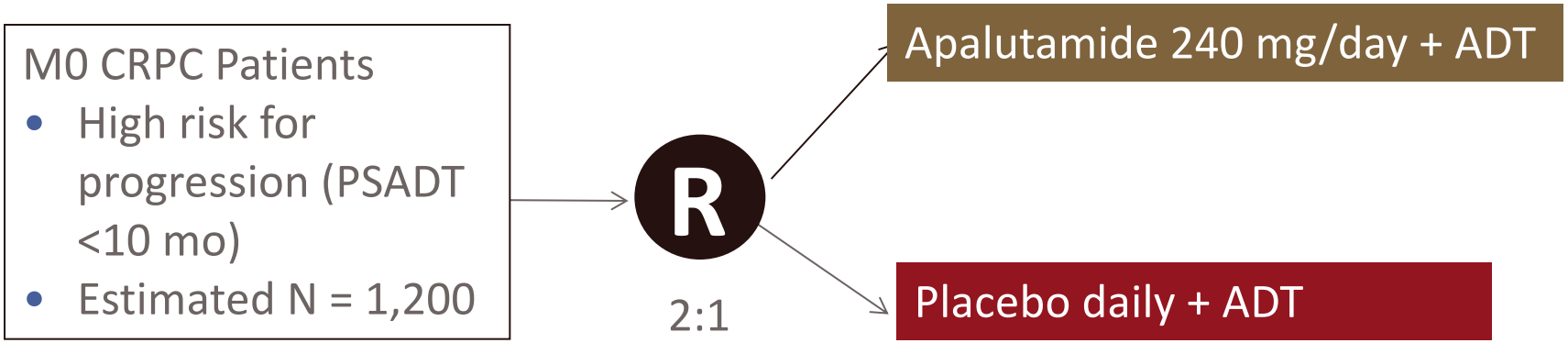


Primary Assessment: Radiographic imaging approximately every 6 months

www.clinicaltrials.gov (NCT02319837)

Phase 3 SPARTAN Trial Design with Apalutamide

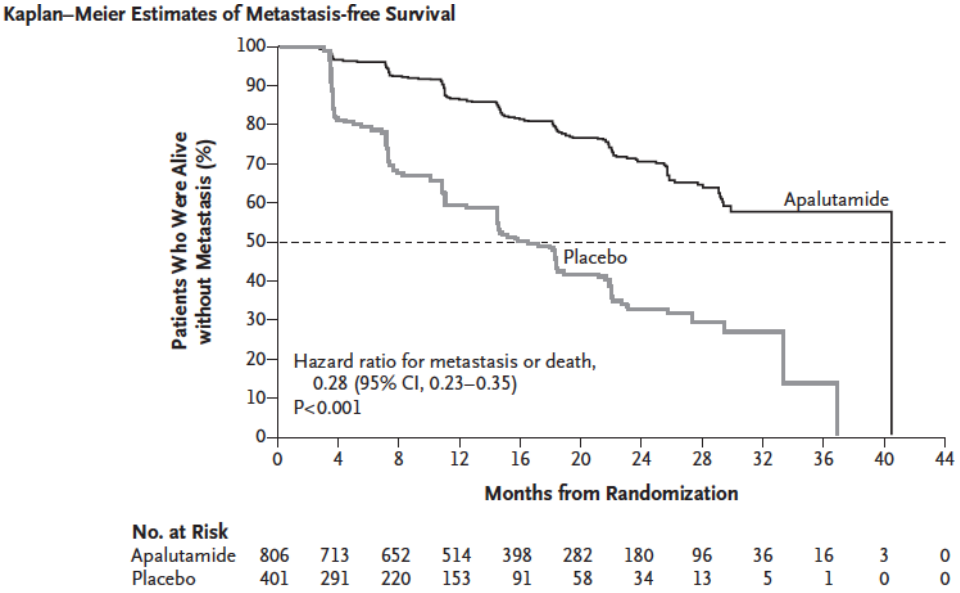
- Multicenter, double-blind, placebo-controlled study

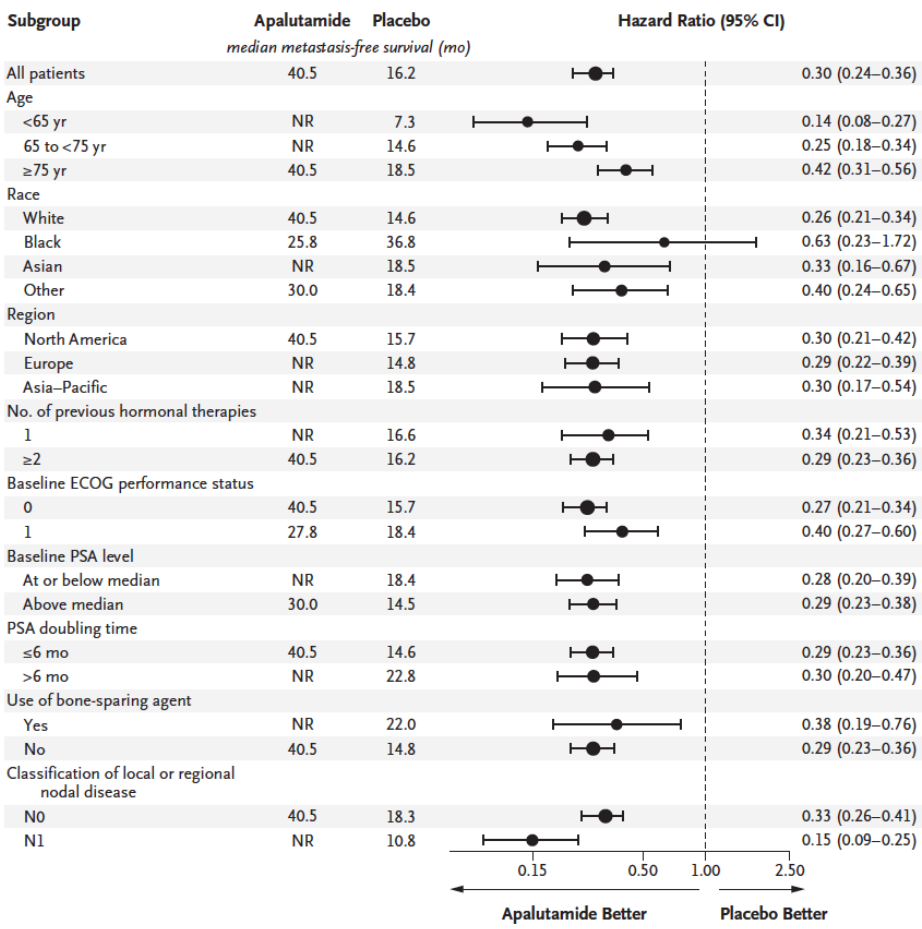


- Primary endpoint: MFS

ADT: androgen deprivation therapy; PSADT: PSA doubling time.
https://clinicaltrials.gov/ct2/show/NCT01946204.

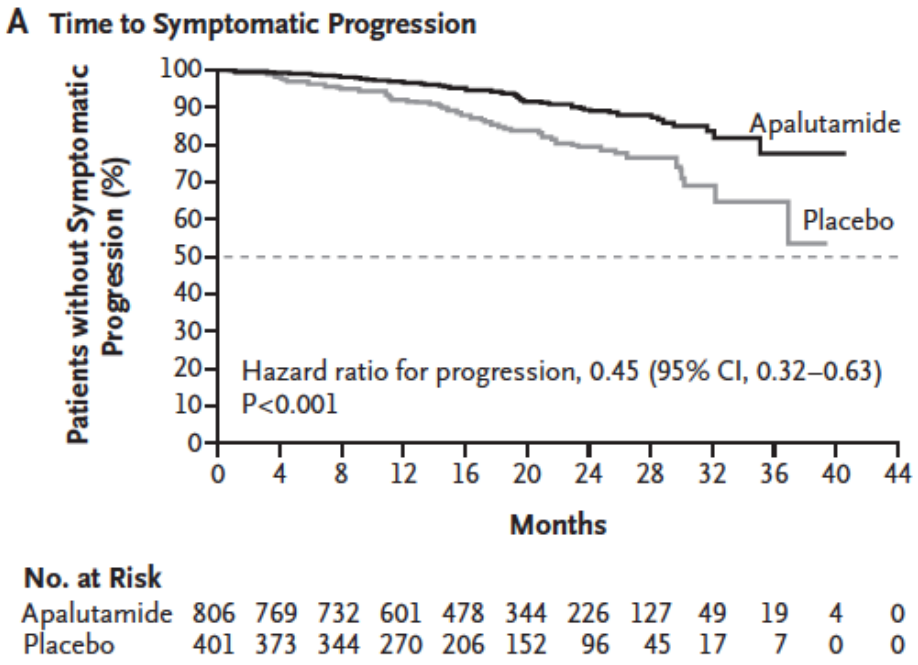
SPARTAN: Apalutamide Improves Metastasis-free Survival for Patients with M0 CRPC

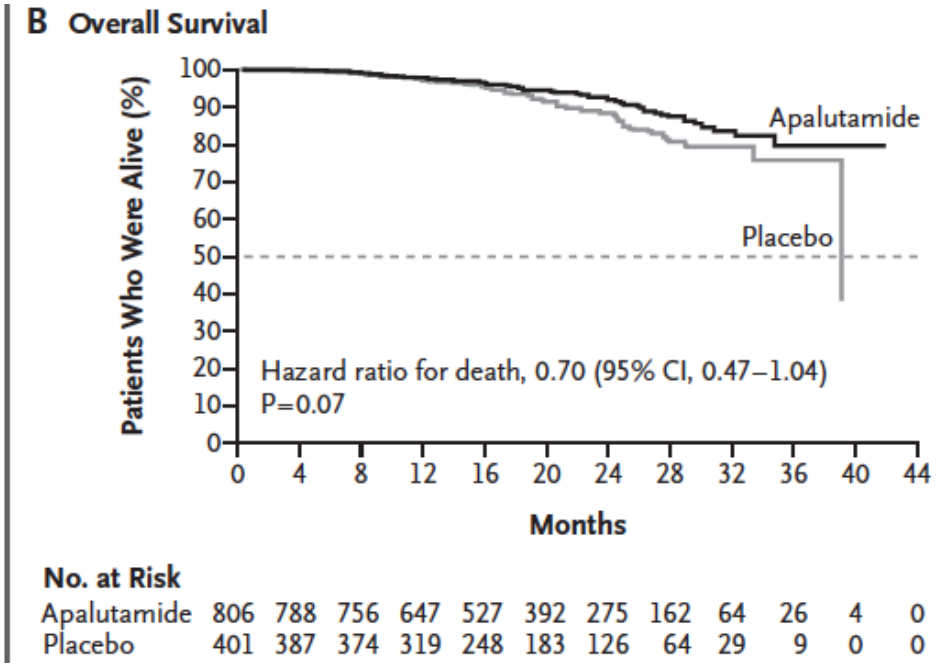




Smith MR et al. N Engl J Med 2018; 378:1408-18.

SPARTAN: Apalutamide Improves Time to Symptomatic Progression for M0 CRPC

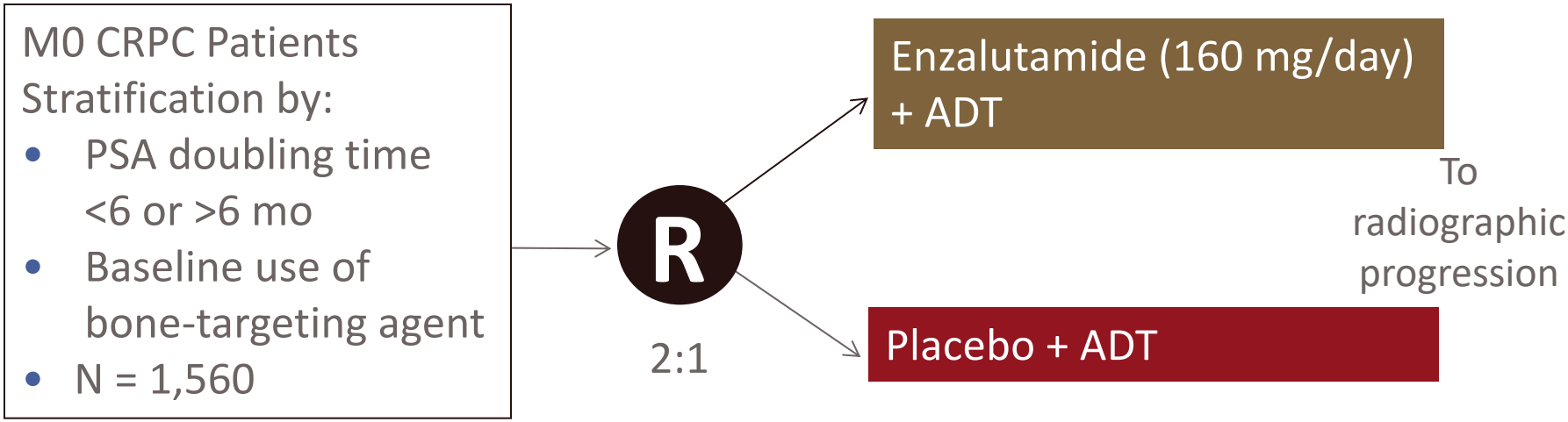




Smith MR et al. N Engl J Med 2018; 378:1408-18.

Phase 3 PROSPER Trial Design with Enzalutamide

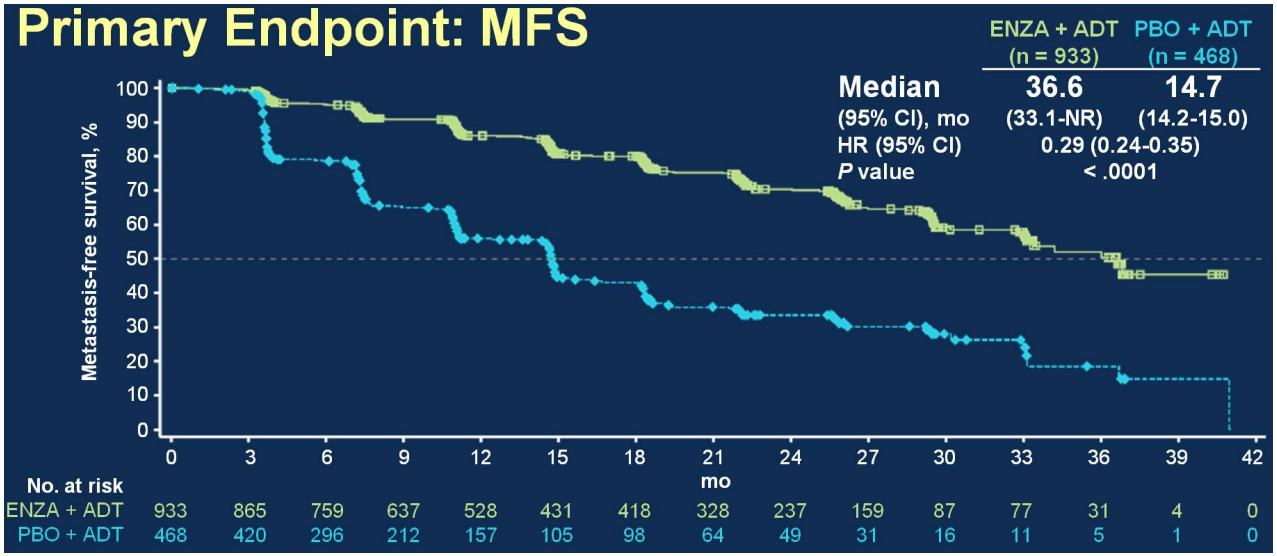
- Randomized, double-blind, placebo-controlled international study

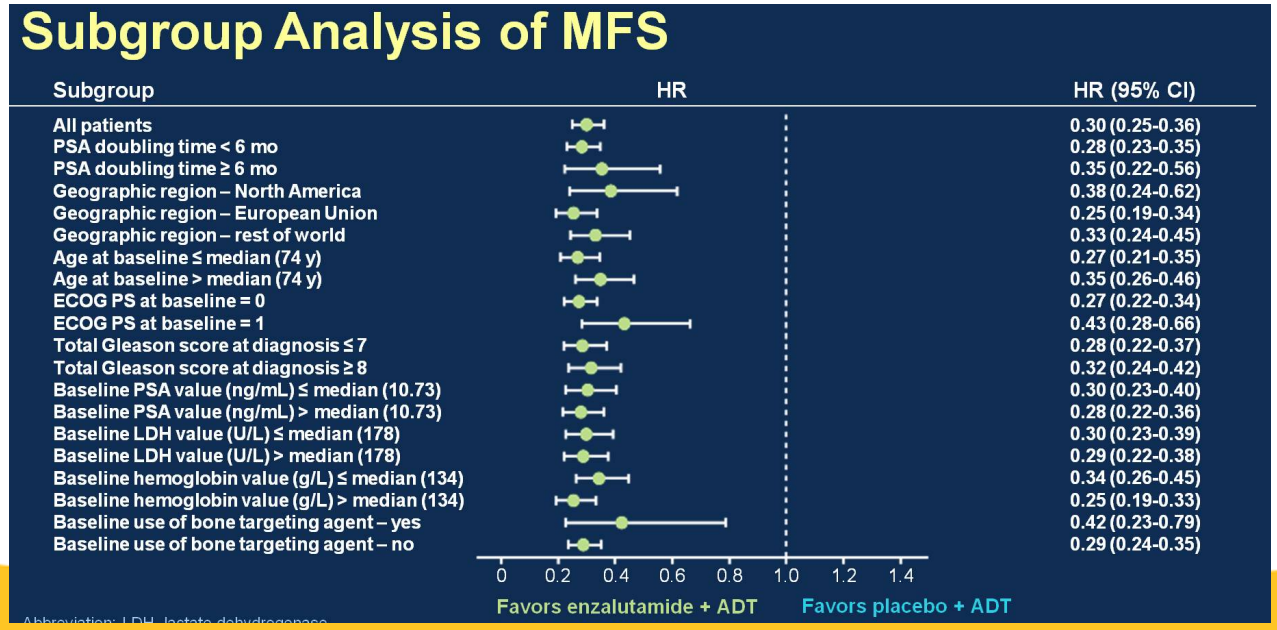


- Primary endpoint: MFS = time to radiographic progression or death on study

https://clinicaltrials.gov/ct2/show/NCT02003924.

PROSPER: Enzalutamide Improves Metastasis-free Survival for Patients with M0 CRPC

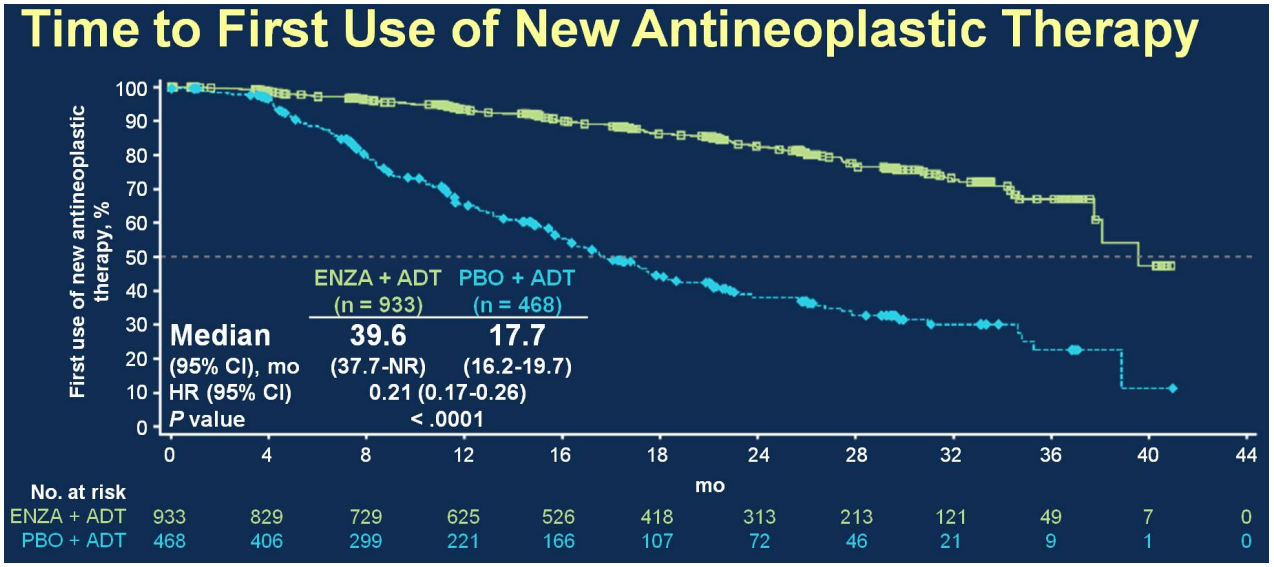


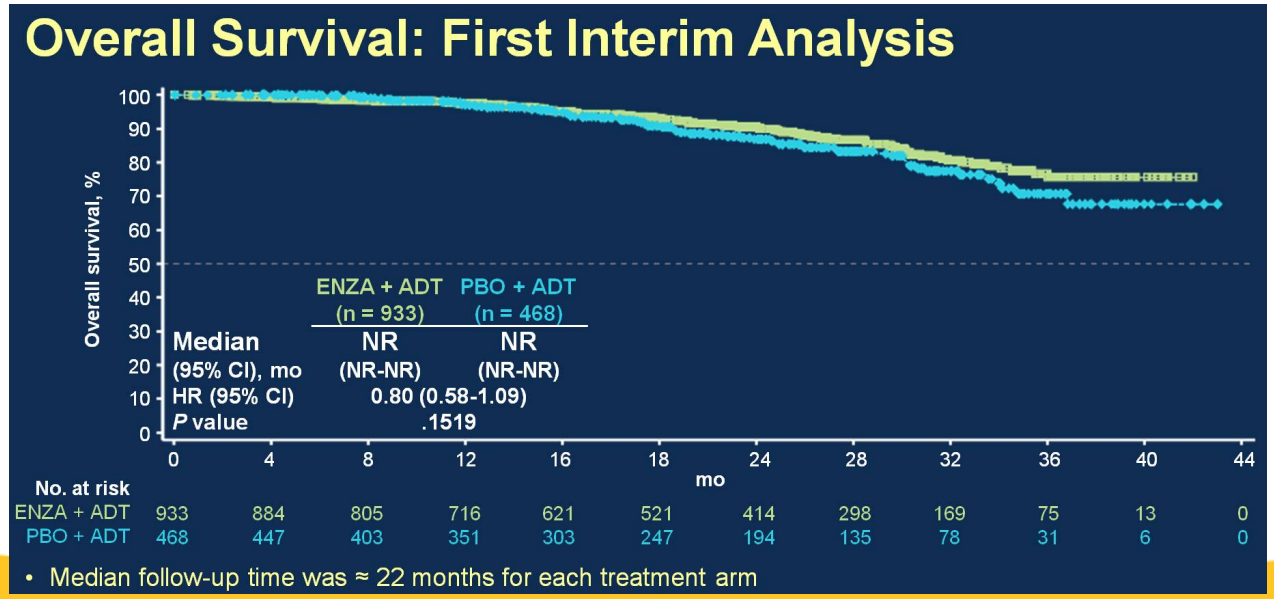


Abbreviation: LDH, lactate dehydrogenase.

Hussain M et al. J Clin Oncol 36, 2018 (suppl 6S; abstr 3).

PROSPER: Other Measures of Efficacy



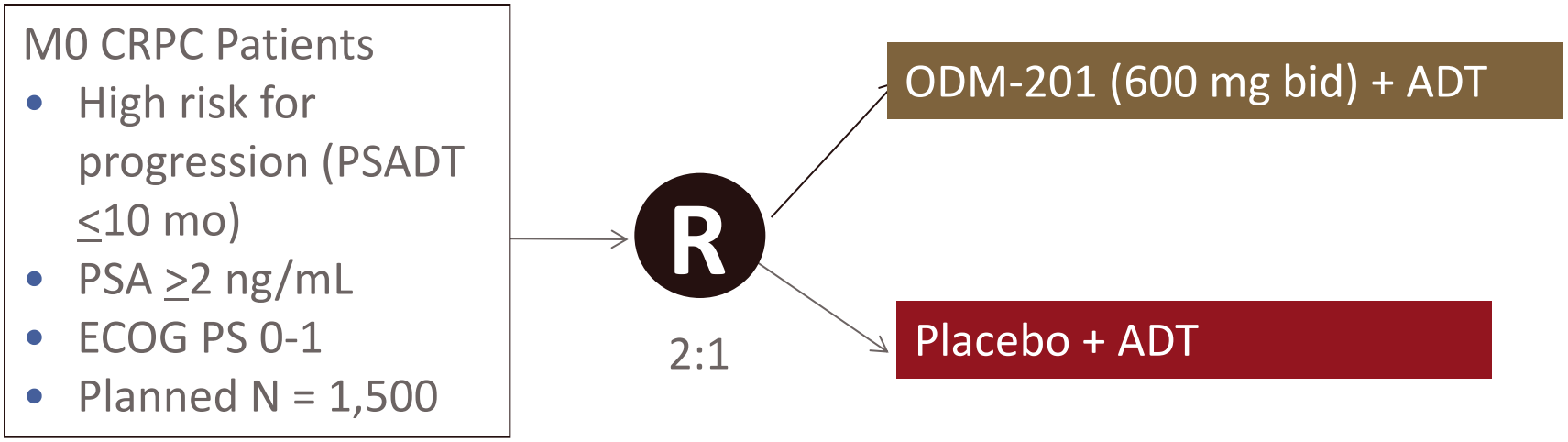


- Median follow-up time was ≈ 22 months for each treatment arm

Hussain M et al. J Clin Oncol 36, 2018 (suppl 6S; abstr 3).

Phase 3 ARAMIS Trial Design

- Randomized, double-blind, placebo-controlled international study



- Primary endpoint: MFS

ADT: androgen deprivation therapy; PSADT: PSA doubling time.
https://clinicaltrials.gov/ct2/show/NCT02200614.

Key Take Home Points

- Sequencing of next generation androgen pathway inhibitors back to back has not led to decent response rates
- Moving our highly efficacious agents for mCRPC earlier in the disease paradigm to mHSPC or M0 CRPC has led to substantially improved outcomes
- Abiraterone offers survival benefit for mHSPC patients and is probably better than docetaxel for low volume disease patients
- Both apalutamide and enzalutamide improve metastasis-free survival for men with M0 CRPC
- Many ongoing trials moving abiraterone, enzalutamide and newer agents earlier and in novel combinations are ongoing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Thank You!
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