AR Targeting in Non-CRPC
Can we do better?

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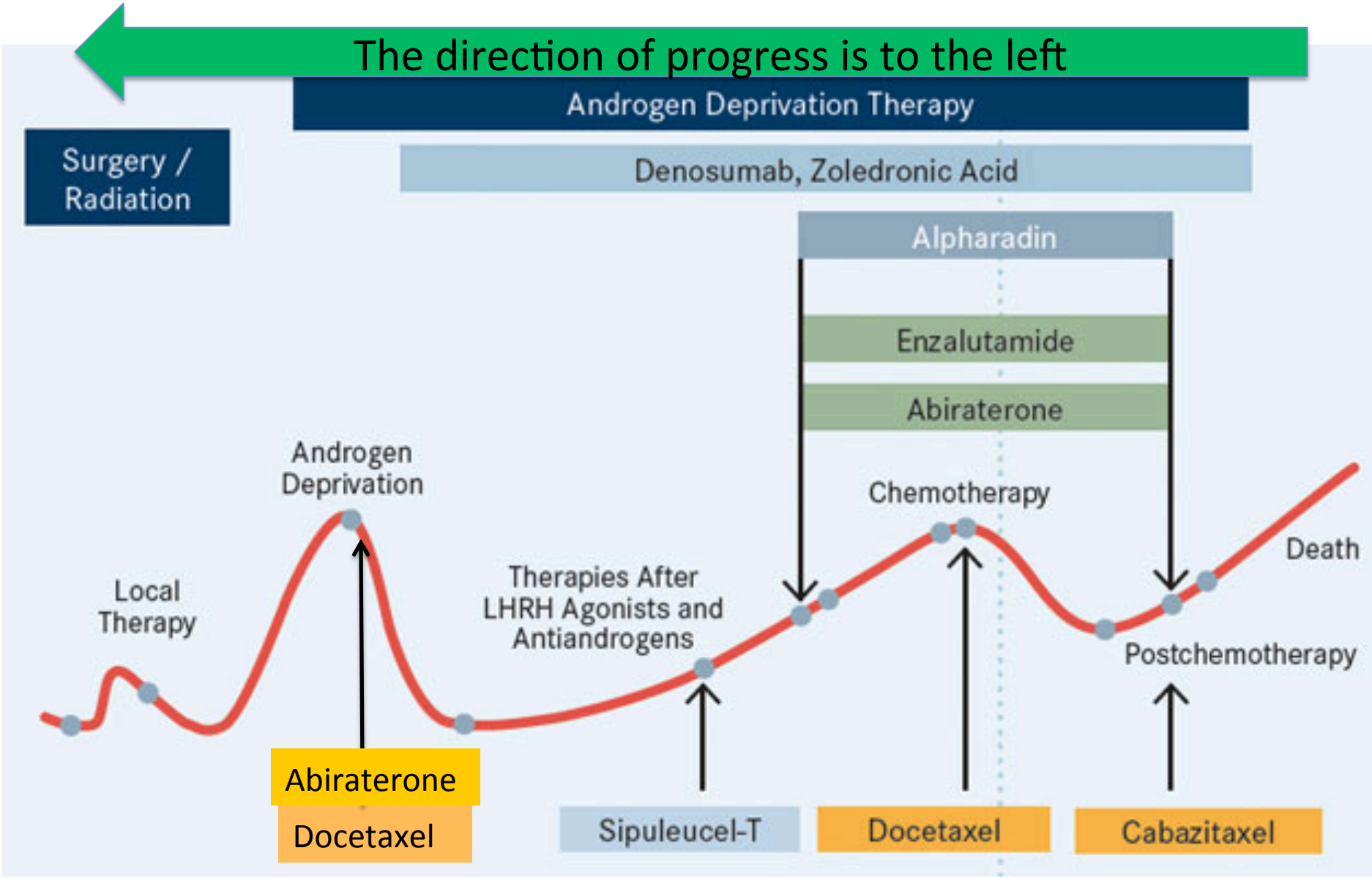
Premise

- AR Targeting is moving “left” from mCRPC to:
  - Nonmet CRPC
  - serologic relapse to:
  - adjuvant.
- Enhanced potency may give the opportunity to delay, avoid or shorten castration.
- Attention to the reduced toxicity and enhanced QOL is key.


The direction of progress is to the left
Androgen Deprivation Therapy
Surgery / Radiation
Denosumab, Zoledronic Acid
Alpharadin
Enzalutamide
Abiraterone
Androgen Deprivation
Chemotherapy
Death
Local Therapy
Therapies After LHRH Agonists and Antiandrogens
Postchemotherapy
Abiraterone
Docetaxel
Sipuleucel-T
Docetaxel
Cabazitaxel

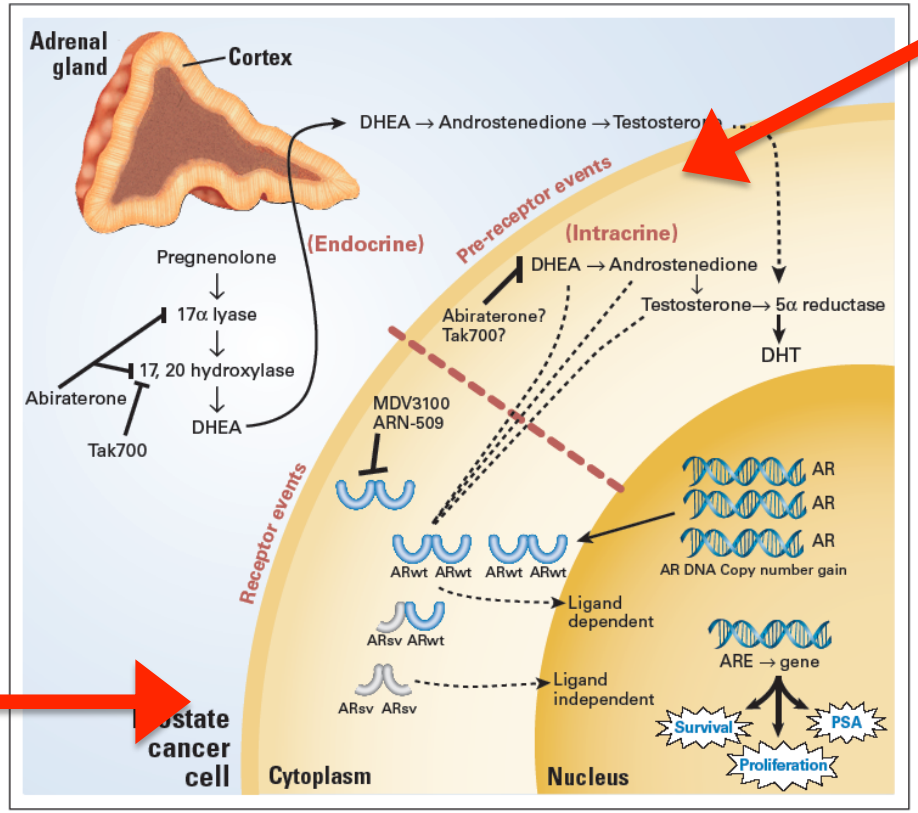
If Rx is going to last for years how can we continue to push efficacy and simultaneously reduce toxicity?

Do we target the ligand, the receptor or both?

Receptor events:

AR Amplification and Mutation

AR Splice Variants



Pre-Receptor Events:

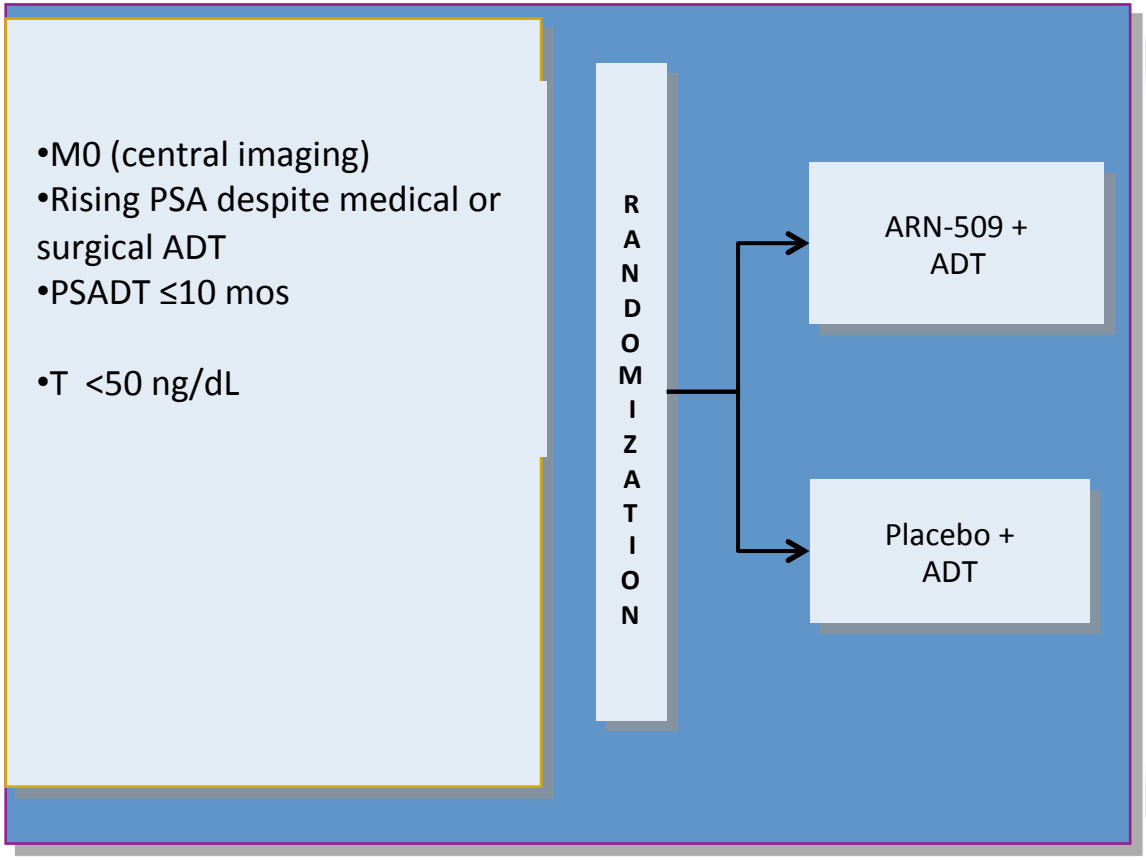
Adrenal Androgen Production And Polymorphisms

Intracrine Androgen Production

Ryan, Tindall Journal of Clinical Oncology 2011

SPARTAN Phase 3 RCT in Non-Metastatic CRPC

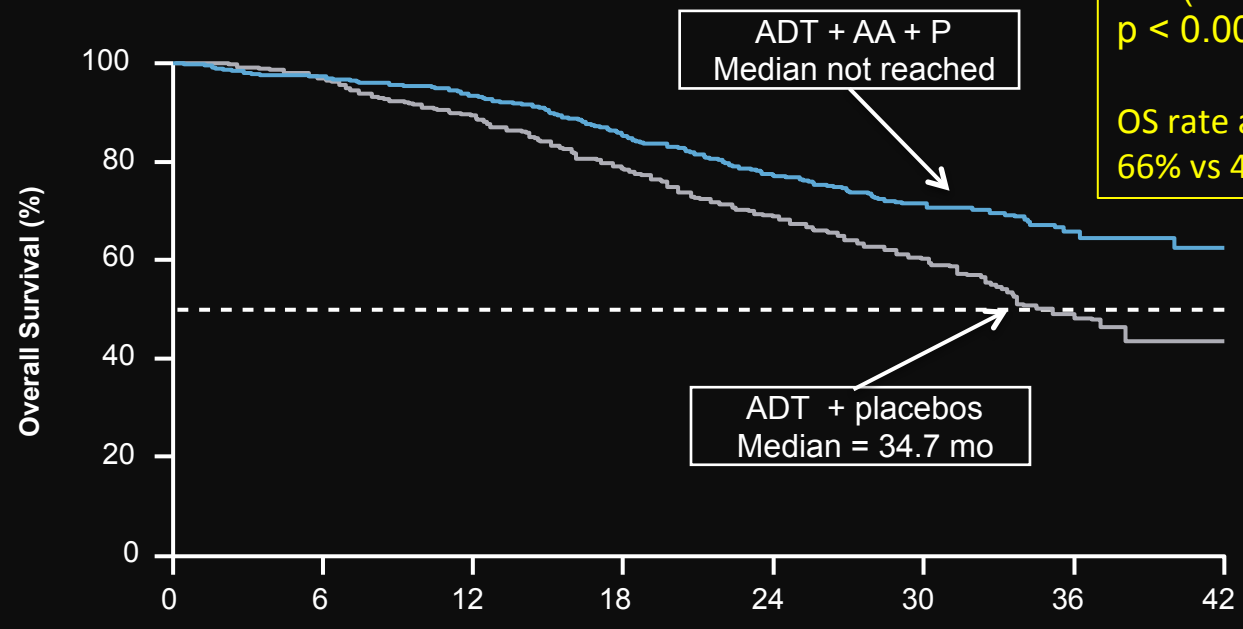
Registration Study for Apalutamide



- **Primary Endpoint: MFS**
- **Key Secondary Endpoint: OS**
- **Other Secondary Endpoints:**
  - TT symptomatic progression
  - TT Chemo
  - rPFS
  - TT mets
  - PROs
  - Safety
  - Pop PK
  - QT sub-study

Global Principal Investigators: Matthew Smith and Eric Small

Latitude: >20% death within 2 years.
AR directed therapy does not benefit all….



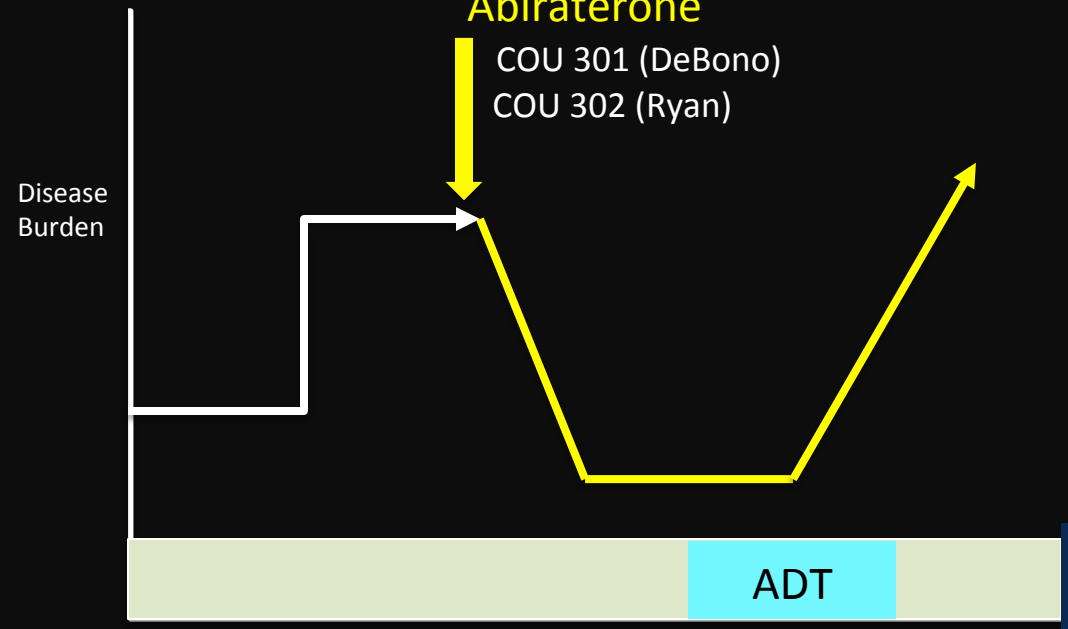
HR (95% CI) = 0.62 (0.51-0.76);
p < 0.001

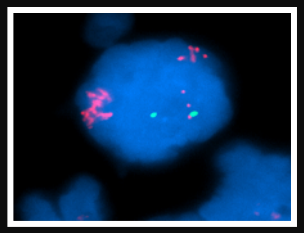
OS rate at 3 years:
66% vs 49%, favoring Abiraterone

No. at risk								
ADT + AA + P	597	565	529	479	388	233	93	9
ADT + placebos	602	564	504	432	332	172	57	2

From Fizazi et al, ASCO 2017

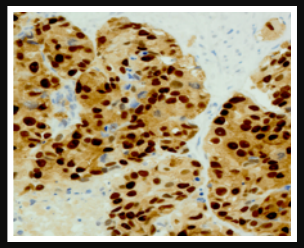
Do the Known Mechanisms of Abiraterone Resistance in Metastatic CRPC Apply in the post Latitude Patient?





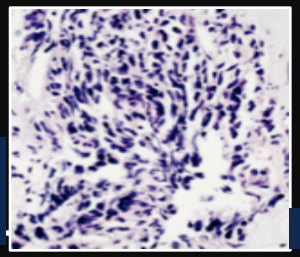
FISH ANALYSIS

- AR probe
- Centromere probe



IHC ANALYSIS

- AR Stain



H & E STAINING

Rx-associated Small Cell/Neuroendocrine Prostate Cancer

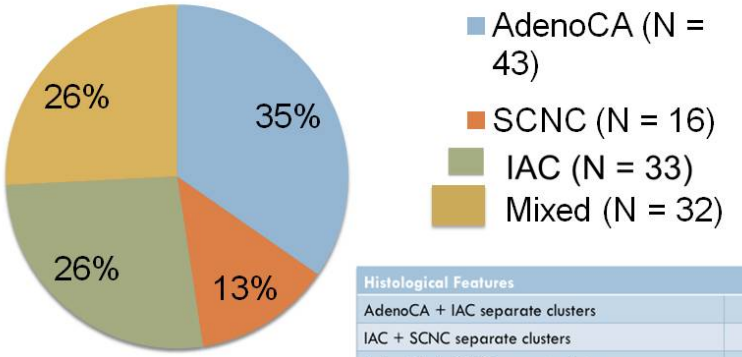
Data from West Coast Prostate Cancer Dream Team

courtesy: Eric J Small, MD

Post Abi/Enza: Non-Adeno is common and has a poor prognosis….in CRPC

Histology of 124 Evaluable Biopsies

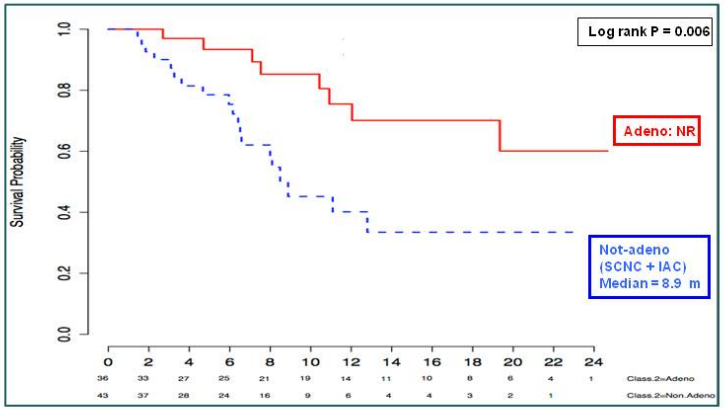
74 % were "pure" with a single histologic subtype (**isolated by LCM)
Remainder (26%) were comprised of mixed populations



Histological Features	Count
AdenoCA + IAC separate clusters	11
IAC + SCNC separate clusters	4
AdenoCA + SCNC separate clusters	1
Non-adenoCA cytology with adenoCA architecture	11

Is the fear of "Inducing" more aggressive post AR Disease Warranted??

Overall survival as function of biopsy pathology
Grouping IAC and SCNC



ENZAMET

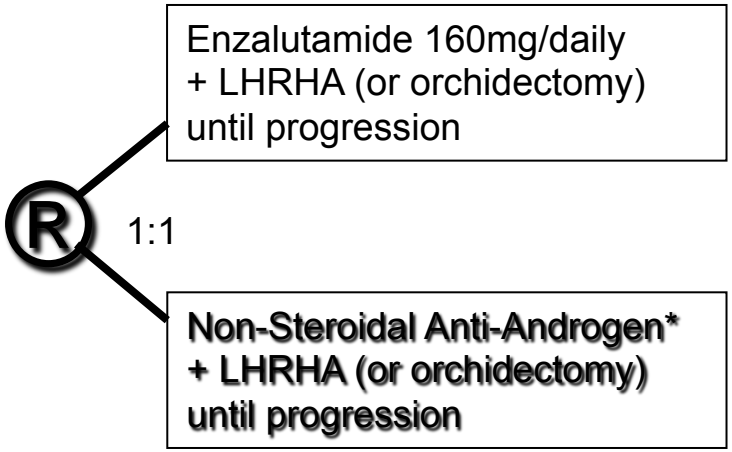
Hypothesis: Earlier use of enzalutamide will increase the longevity of men commencing ADT for hormone sensitive metastatic prostate cancer

Eligibility

Metastatic prostate cancer
Adequate organ function
Starting 1st line ADT

Stratification

Volume of disease
Anti-resorptive therapy
Comorbidities
Study Site
(Docetaxel use -Amendment pending)



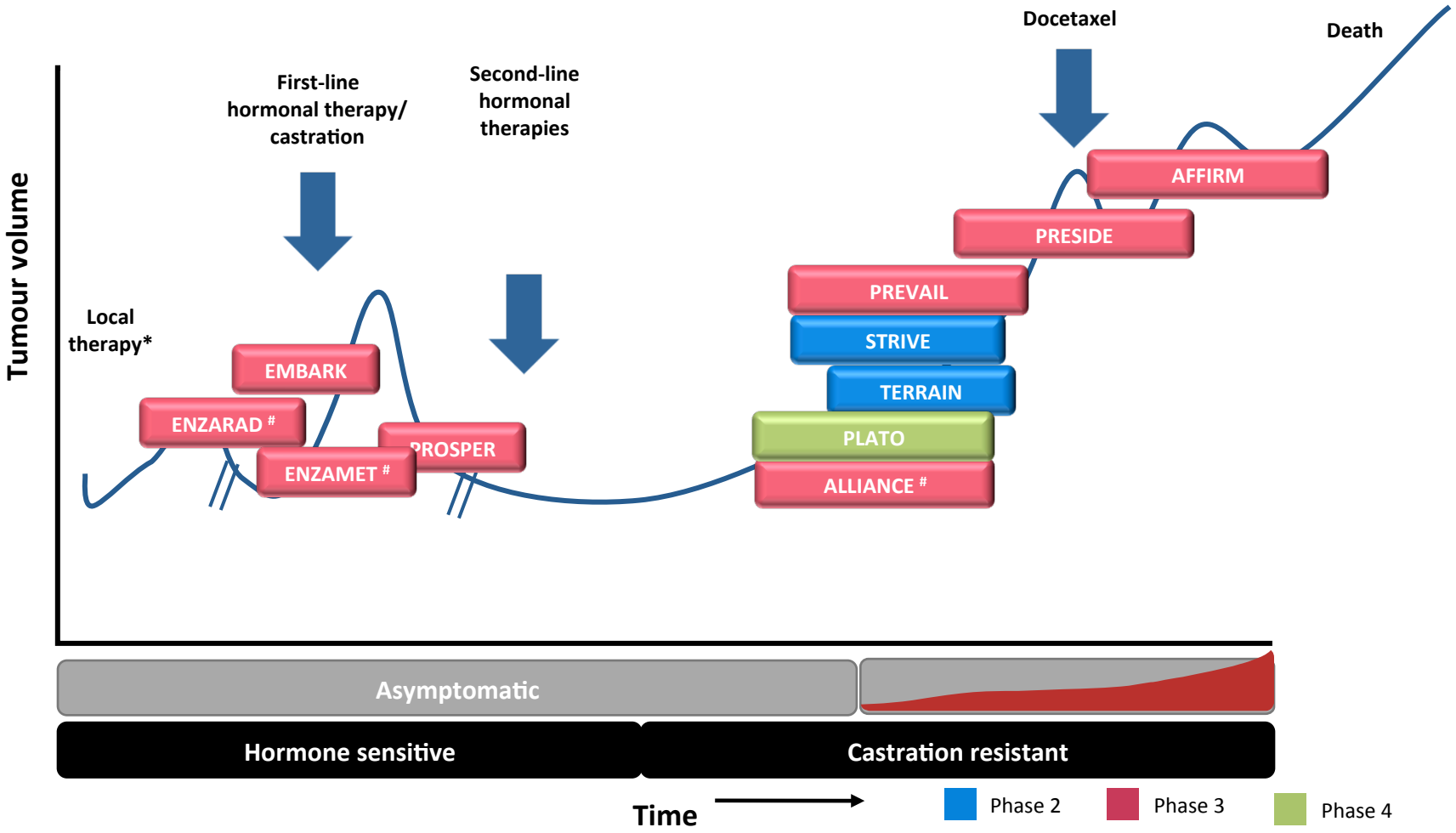
Endpoints

Overall survival (primary)
PSA progression free survival
Clinical progression free survival
Health related quality of life
Adverse events
Incremental cost-effectiveness

1,100 participants
2 years accrual + 3.5 years minimum additional follow-up
80% power to detect 25% reduction in the hazard of death from any cause, assuming an OS rate at 3 years of 65% in the control group

*Conventional Non-Steroidal Anti-Androgens: bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg tid

Select Enzalutamide Prostate Clinical Studies



*For example, surgery, radiotherapy.

Investigator Sponsored Research / COOP Study

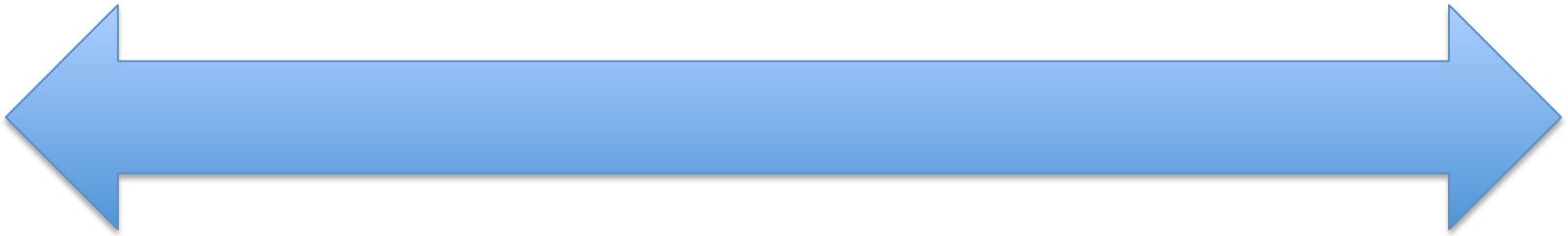
Kohli M, Tindall DJ. *Mayo Clin Proc* 2010;85:77–86.

Serologic Relapse:

Cure

Prevent
Delay

Over Treat

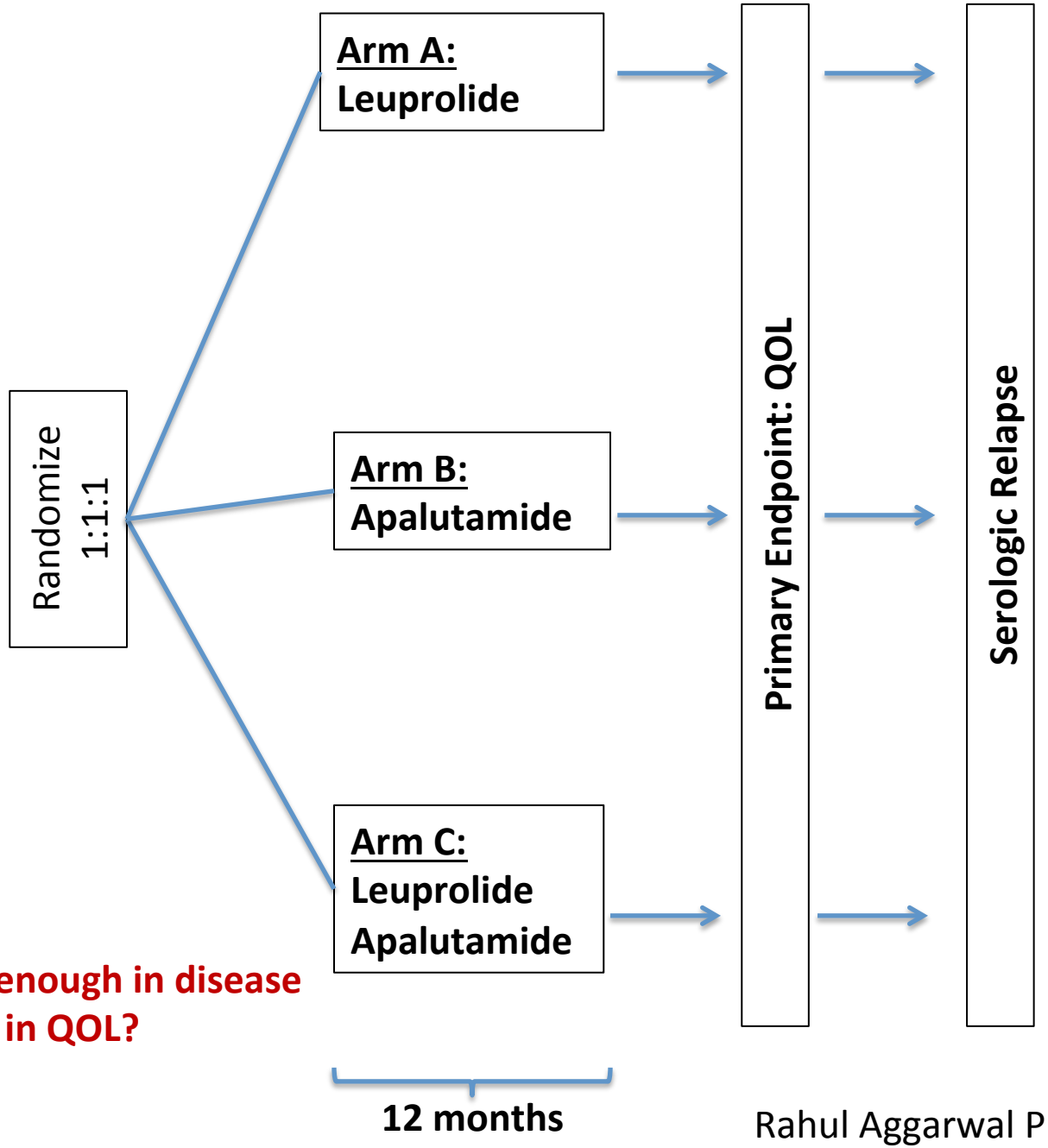


Serologic Relapse: ARN-002 Study: Apalutamide vs LHRH vs combination in Serologic Relapse

ACCRUAL COMPLETE

N = 90

- Prior radical prostatectomy w/RT or RT
- Biochemically relapsed disease with PSADT <= 9 months
- No metastases (abdominal/pelvic nodes < 2 cm allowed)
- No prior ADT for biochemical relapse
- No ADT within 9 months of study entry



Is AR Targeting alone good enough in disease control but better in QOL?

Rahul Aggarwal PI

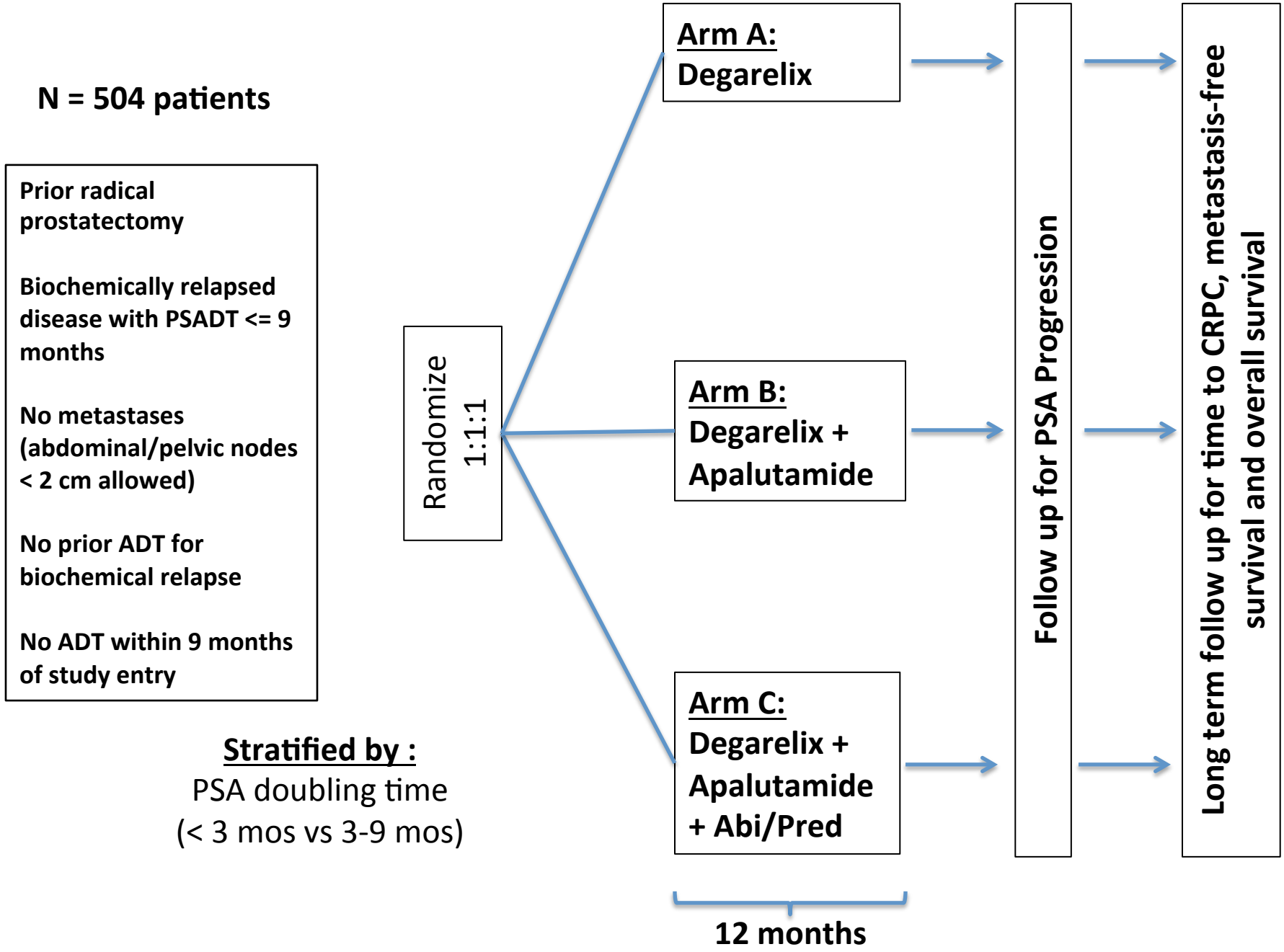
Increased Intensity --- Brief Duration

A Phase 3 Study of Androgen Annihilation in High-Risk Biochemically Relapsed Prostate Cancer

Sponsor: Alliance Foundation
AFT-19
IND #: 131441

Study Chair: Rahul Aggarwal
Correlative Chair: Akash Patnaik
Primary Statistician: Susan Halabi
PROs/Quality of Life: Ron Chen

AFT-19 Phase III Study of Triple Potent AR blockade



Primary endpoint:

- **Median PSA progression-free survival in all randomized pts (ITT population)**
  - On-treatment: Rising PSA confirmed on repeat measurement and absolute value > 25% + 2 ng/ml above nadir/baseline
  - In-follow up: PSA > 0.2 ng/mL confirmed by repeat measurement

Secondary endpoints:

- Median PSA progression-free survival in T-evaluable population
  - T-evaluable defined as recovery of serum T to > 50 ng/dL with follow up PSA measurements sufficient for evaluation
- 36 month PSA progression-free survival rate
- Quality of life (on treatment and in follow up)
- Median time to T recovery to > 50 ng/dL
- Median time to castration-resistance
  - PSA increase > 25% and more than 2 ng/mL above nadir with concomitant T < 50 ng/dL
- Median metastasis-free survival
- Median overall survival

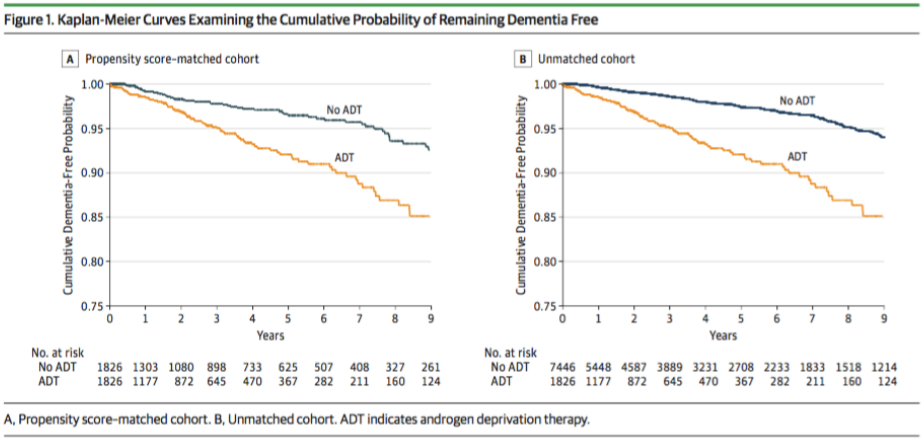
Sample Size Justification

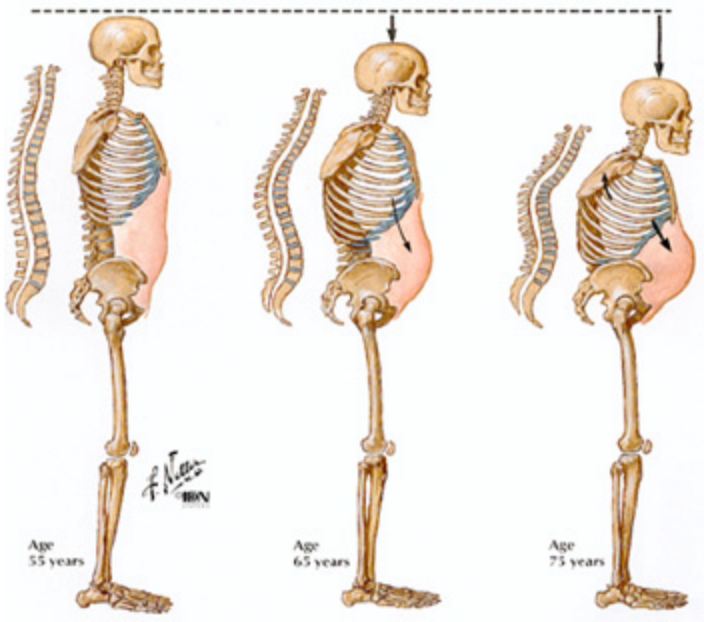
- N = 504 patients (168 pts/arm)
- 205 PFS events required for each comparison
- Study power 85%
- 2 interim analyses at 50% (~ 30 months) and 75% (~ 38 months) of PFS events
- Overall (interim + final analysis) 2 sided alpha = 0.025 for each pair-wise comparison
  - Triplet versus control
  - Doublet versus control

Can we do it without Castration?

As patients live longer, ADT Side effects impact QOL (and DOL?) more…..

ADT And Dementia (of all types)





Nead et al
JAMA Oncology Published online October 13, 2016

Level One Evidence
Targeting the AR alone can impact survival.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 2, 2017 VOL. 376 NO. 5

Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer

W.U. Shipley, W. Seiferheld, H.R. Lukka, P.P. Major, N.M. Heney, D.J. Grignon, O. Sartor, M.P. Patel, J.-P. Bahary, A.L. Zietman, T.M. Pisansky, K.L. Zeitzer, C.A.F. Lawton, F.Y. Feng, R.D. Lovett, A.G. Balogh, L. Souhami, S.A. Rosenthal, K.J. Kerlin, J.J. Dignam, S.L. Pugh, and H.M. Sandler, for the NRG Oncology RTOG*

ABSTRACT

BACKGROUND

Salvage radiation therapy is often necessary in men who have undergone radical prostatectomy and have evidence of prostate-cancer recurrence signaled by a persistently or recurrently elevated prostate-specific antigen (PSA) level. Whether antiandrogen therapy with radiation therapy will further improve cancer control and prolong overall survival is unknown.

METHODS

In a double-blind, placebo-controlled trial conducted from 1998 through 2003, we assigned 760 eligible patients who had undergone prostatectomy with a lymphadenectomy and had disease, as assessed on pathological testing, with a tumor stage of T2 (confined to the prostate but with a positive surgical margin) or T3 (with histologic extension beyond the prostatic capsule), no nodal involvement, and a detectable PSA level of 0.2 to 4.0 ng per milliliter to undergo radiation therapy and receive either antiandrogen therapy (24 months of bicalutamide at a dose of 150 mg daily) or daily placebo tablets during and after radiation therapy. The primary end point was the rate of overall survival.

RESULTS

The median follow-up among the surviving patients was 13 years. The actuarial rate of overall survival at 12 years was 76.3% in the bicalutamide group, as compared with 71.3% in the placebo group (hazard ratio for death, 0.77; 95% confidence interval, 0.59 to 0.99; P=0.04). The 12-year incidence of death from prostate cancer, as assessed by means of central review, was 5.8% in the bicalutamide group, as compared with 13.4% in the placebo group (P<0.001). The cumulative incidence of metastatic prostate cancer at 12 years was 14.5% in the bicalutamide group, as compared with 23.0% in the placebo group (P=0.005). The incidence of late adverse events associated with radiation therapy was similar in the two groups. Gynecomastia was recorded in 69.7% of the patients in the bicalutamide group, as compared with 10.9% of those in the placebo group (P<0.001).

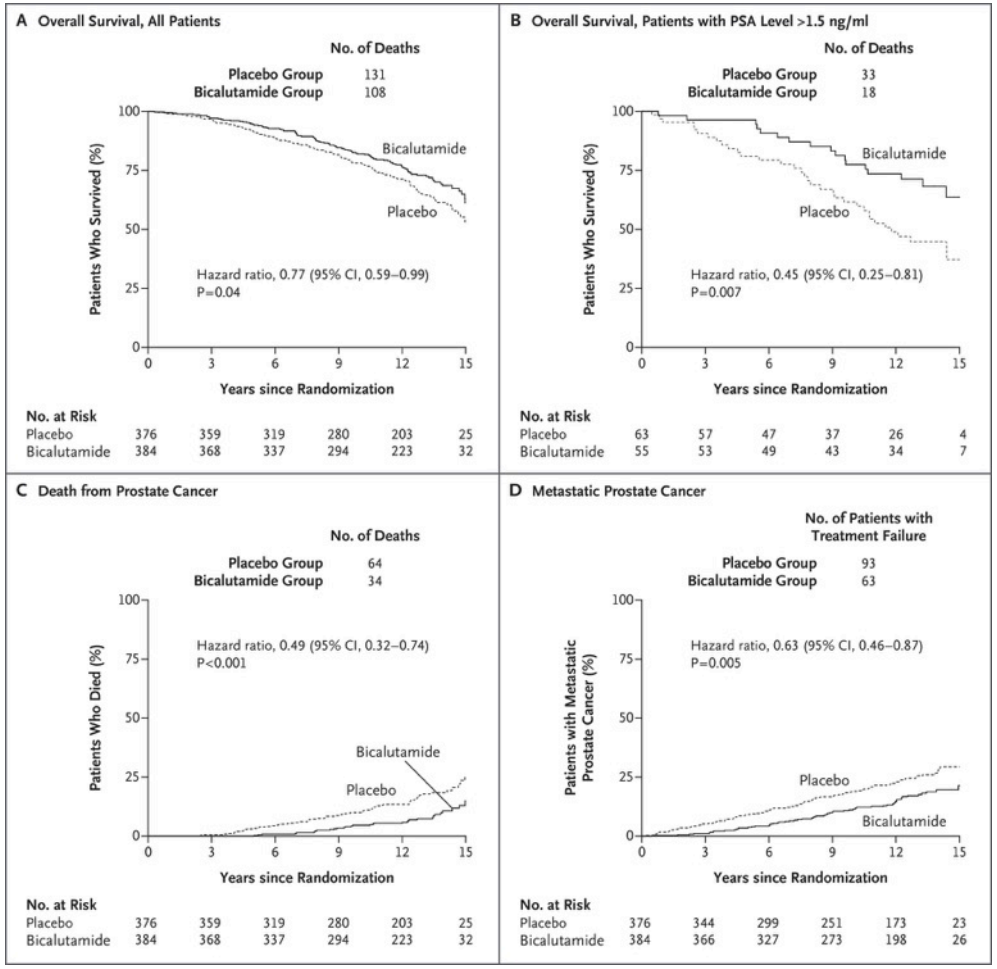
CONCLUSIONS

The addition of 24 months of antiandrogen therapy with daily bicalutamide to salvage radiation therapy resulted in significantly higher rates of long-term overall survival and lower incidences of metastatic prostate cancer and death from prostate cancer than radiation therapy plus placebo. (Funded by the National Cancer Institute and AstraZeneca; RTOG 9601 ClinicalTrials.gov number, NCT00002874.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Shipley at the Department of Radiation Oncology, Massachusetts General Hospital, 55 Fruit St., Cox 3, Boston, MA 02114, or at wshipley@partners.org.

*A complete list of the investigators in the NRG Oncology Radiation Therapy Oncology Group (RTOG) is provided in the Supplementary Appendix, available at NEJM.org.

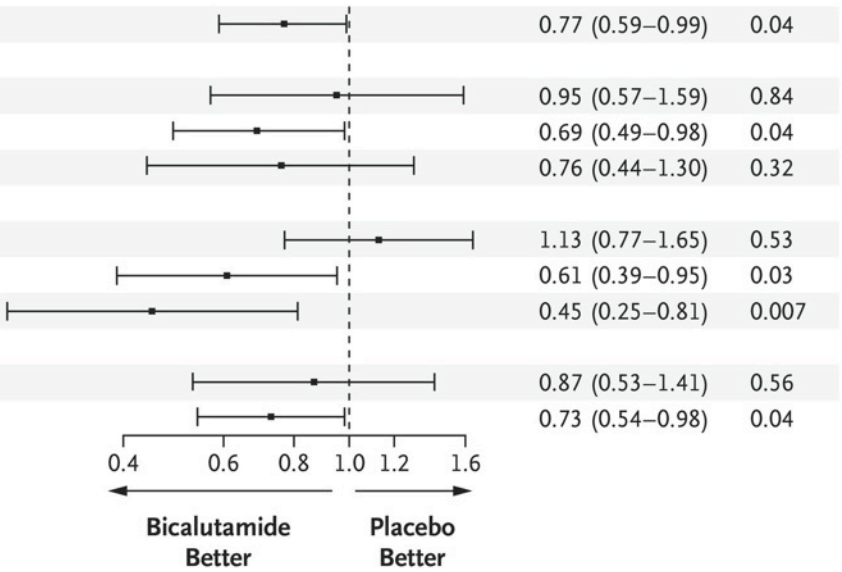
N Engl J Med 2017;376:417-28.
DOI: 10.1056/NEJMoa1607529



The NEW ENGLAND JOURNAL of MEDICINE

Effect of Antiandrogen Therapy with Bicalutamide on 12-Year Overall Survival.

Subgroup	No. of Patients (%)	Bicalutamide Group	Placebo Group	Hazard Ratio (95% CI)	P Value
		12-yr overall survival rate (%)			
Overall	760 (100.0)	76.3	71.3	0.77 (0.59–0.99)	0.04
Gleason score					
2–6	214 (28.2)	79.5	79.2	0.95 (0.57–1.59)	0.84
7	413 (54.5)	78.5	70.9	0.69 (0.49–0.98)	0.04
8–10	131 (17.3)	63.9	58.4	0.76 (0.44–1.30)	0.32
PSA level at trial entry					
<0.7 ng/ml	405 (53.3)	76.8	80.7	1.13 (0.77–1.65)	0.53
0.7–1.5 ng/ml	237 (31.2)	77.0	67.5	0.61 (0.39–0.95)	0.03
>1.5 ngl/ml	118 (15.5)	73.5	48.9	0.45 (0.25–0.81)	0.007
Positive surgical margin					
No	191 (25.1)	73.5	72.9	0.87 (0.53–1.41)	0.56
Yes	569 (74.9)	77.3	70.7	0.73 (0.54–0.98)	0.04



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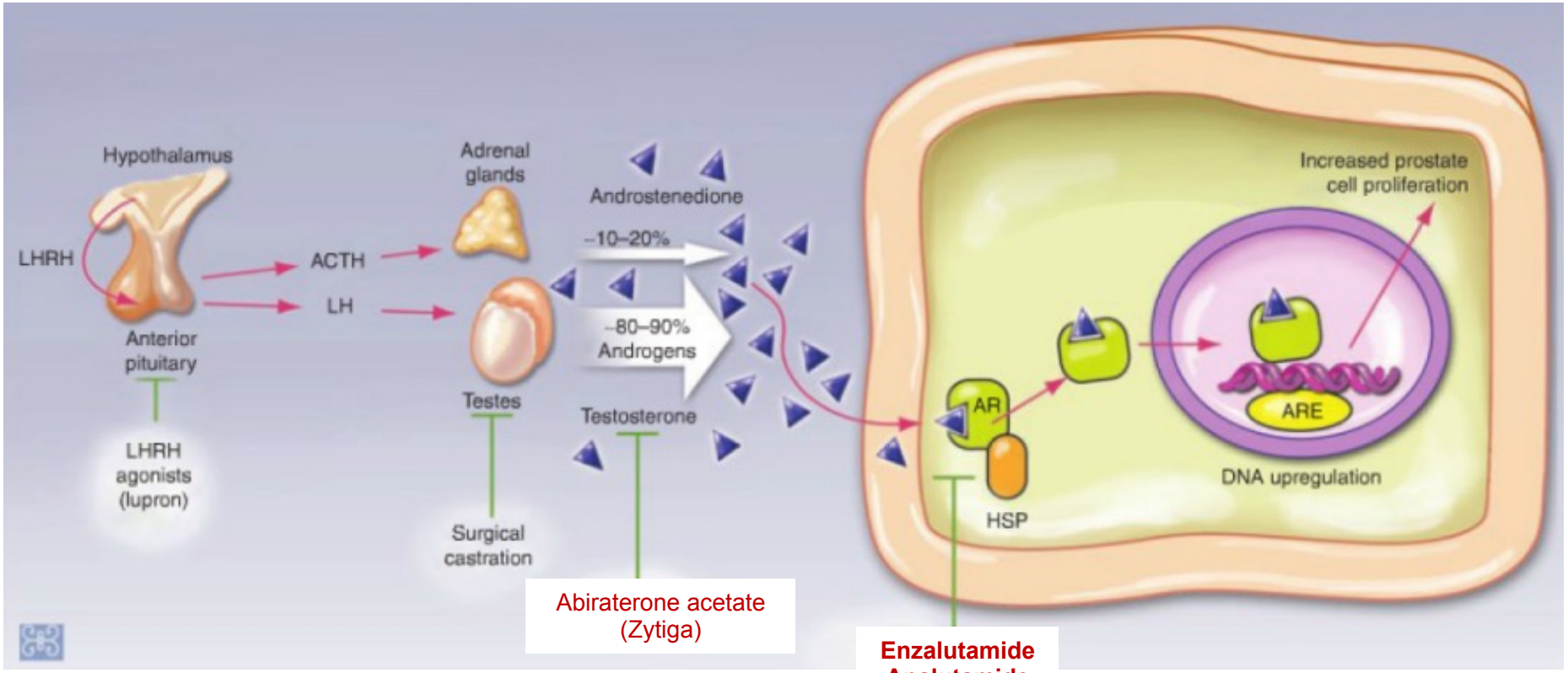
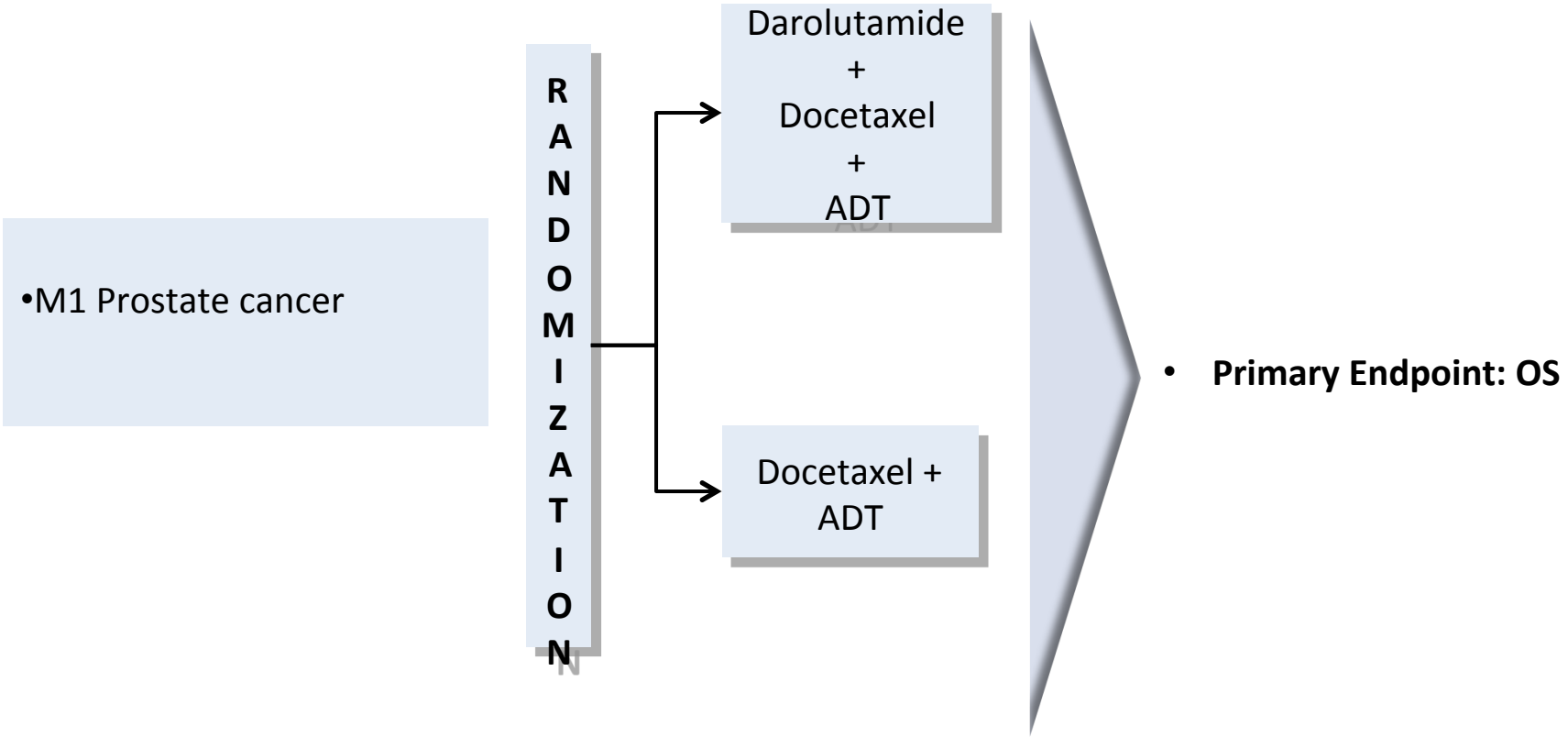
Androgen Receptor (AR) Pathway and Prostate Cancer



Bryce A, Ryan CJ. Clin Pharmacol Ther. 2012;91(1):101-108

A Randomized, Double-blind, Placebo Controlled Phase III Study of ODM-201 Versus Placebo in Addition to Standard Androgen Deprivation Therapy and Docetaxel in Patients With Metastatic Hormone Sensitive Prostate Cancer.

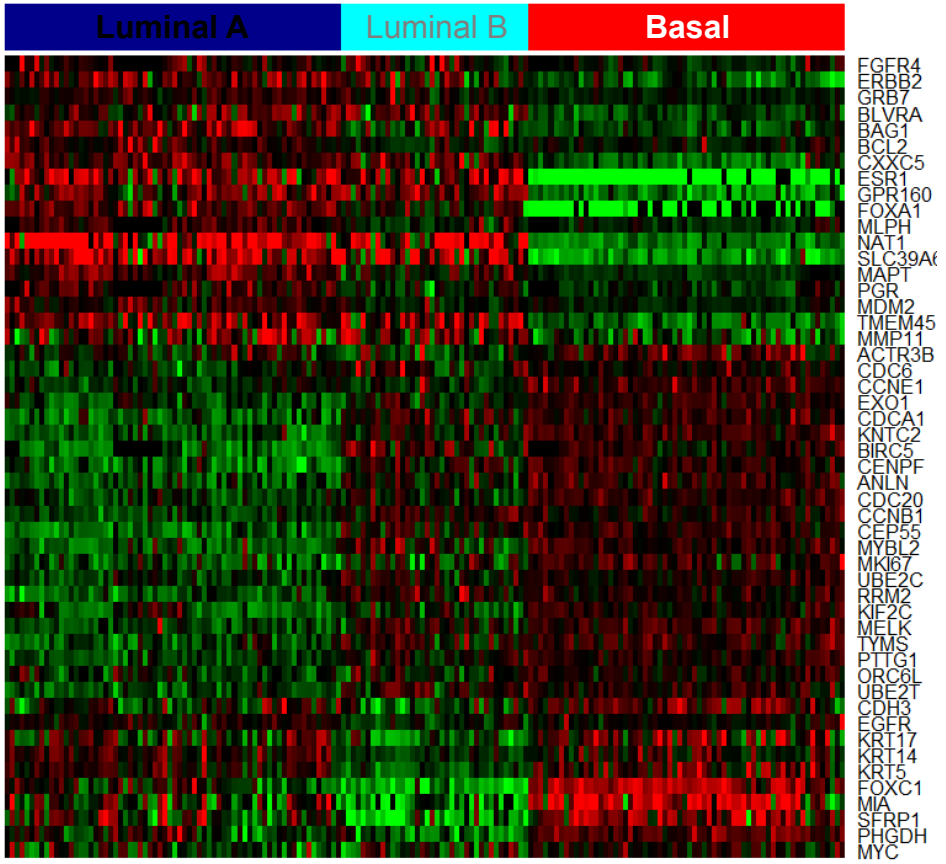
Registration Study for Darolutamide



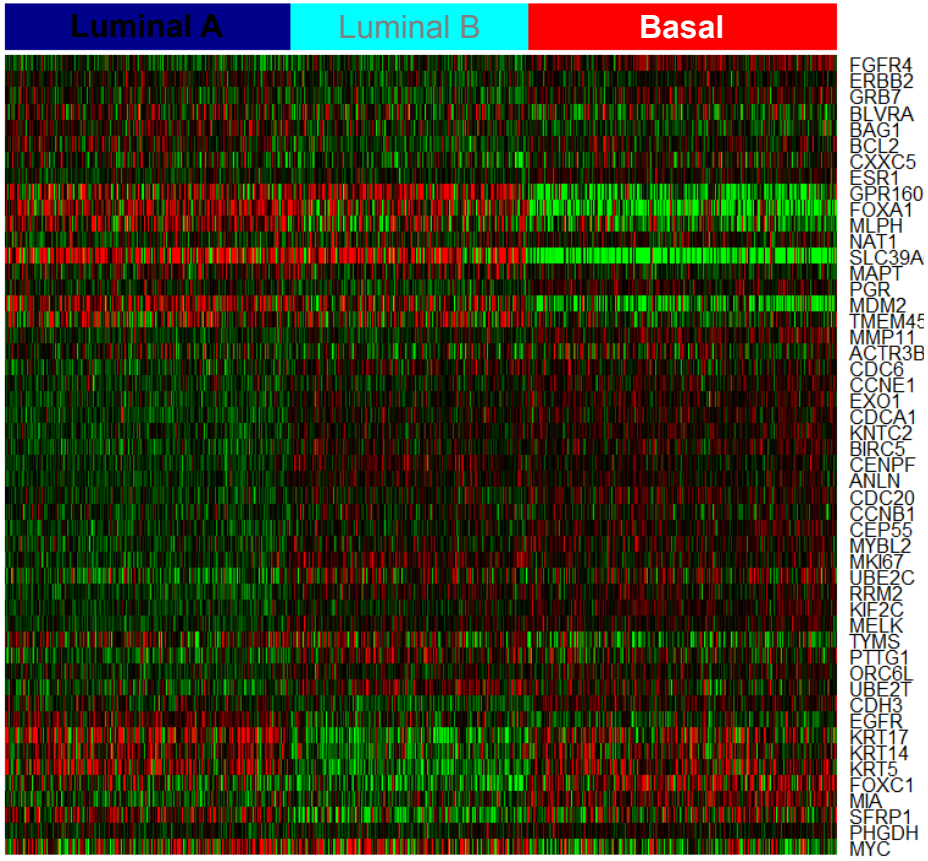
Accruing

The molecular subtypes of prostate cancer are similar to those of breast cancer

Breast Cancer Cohort
(232 patients, Parker et al, JCO)



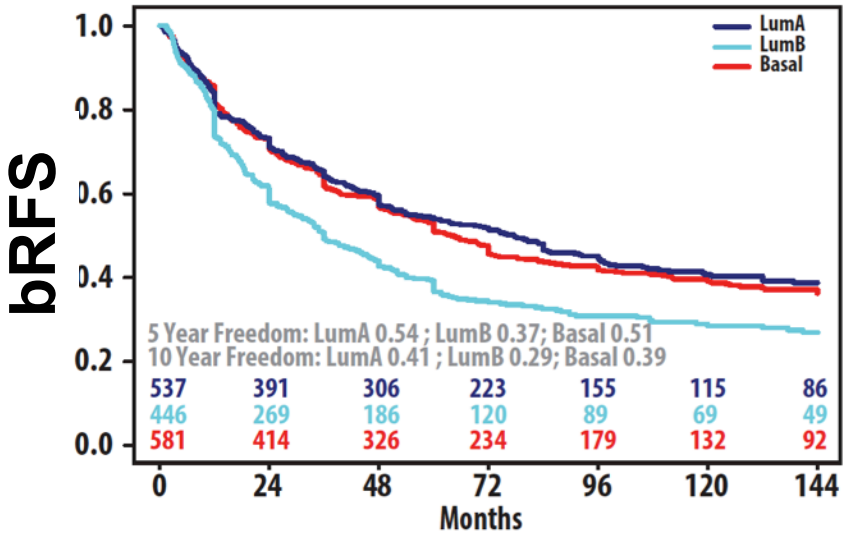
Prostate Cancer Cohort
(1567 patients)

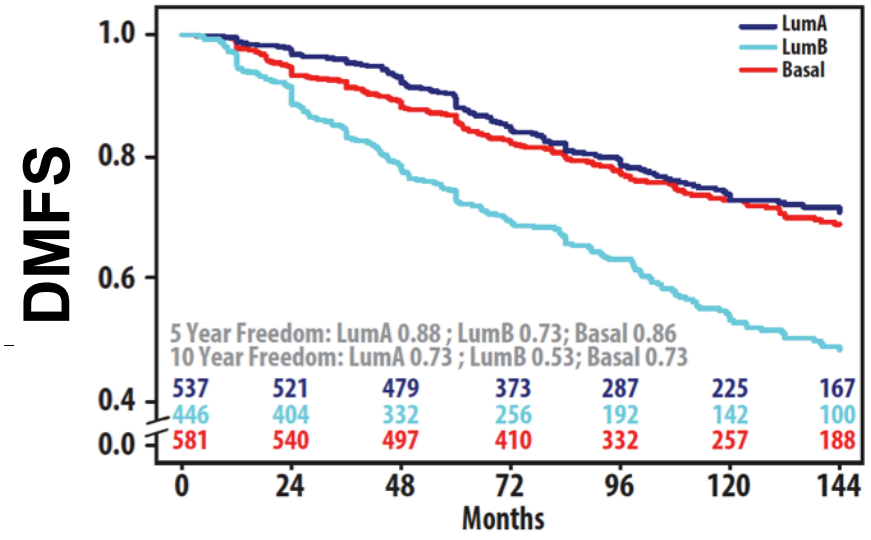


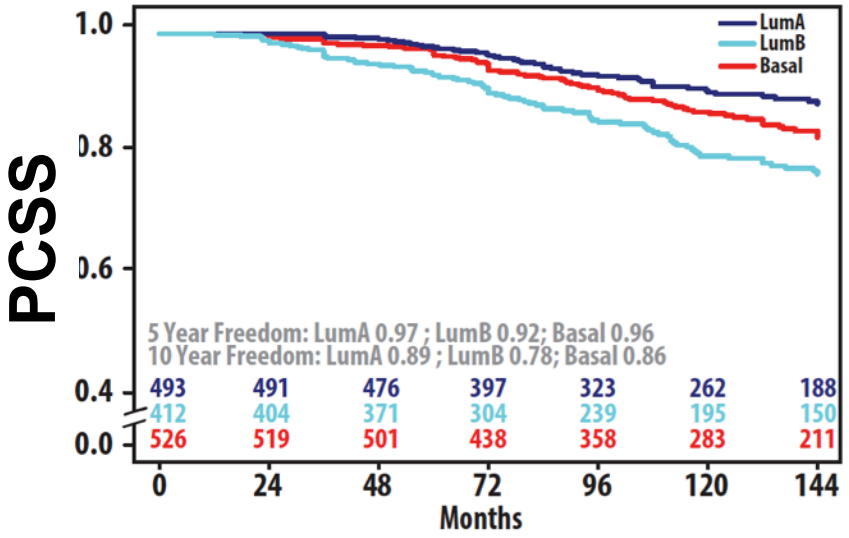
Validated on another 6300 patients with prostate cancer!!

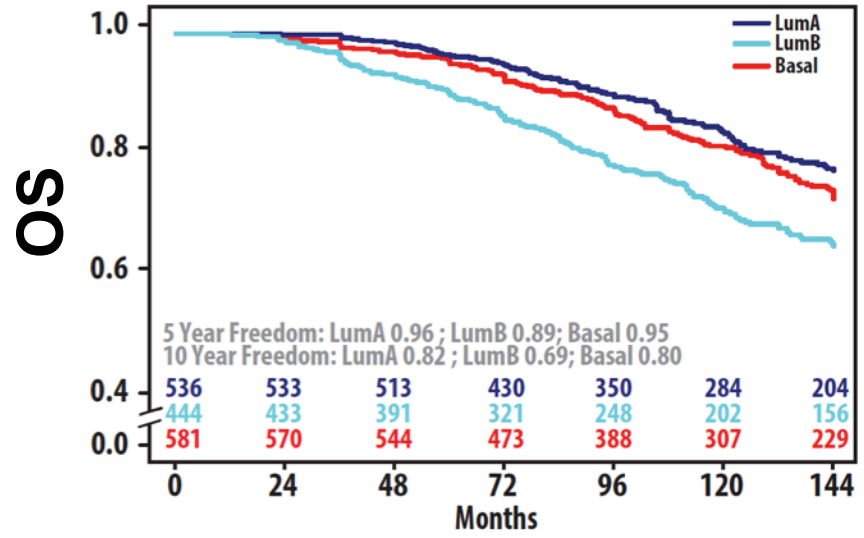
Zhao et al, JAMA Oncology 2017

Luminal B prostate cancers have worse outcomes compared to Luminal A or Basal









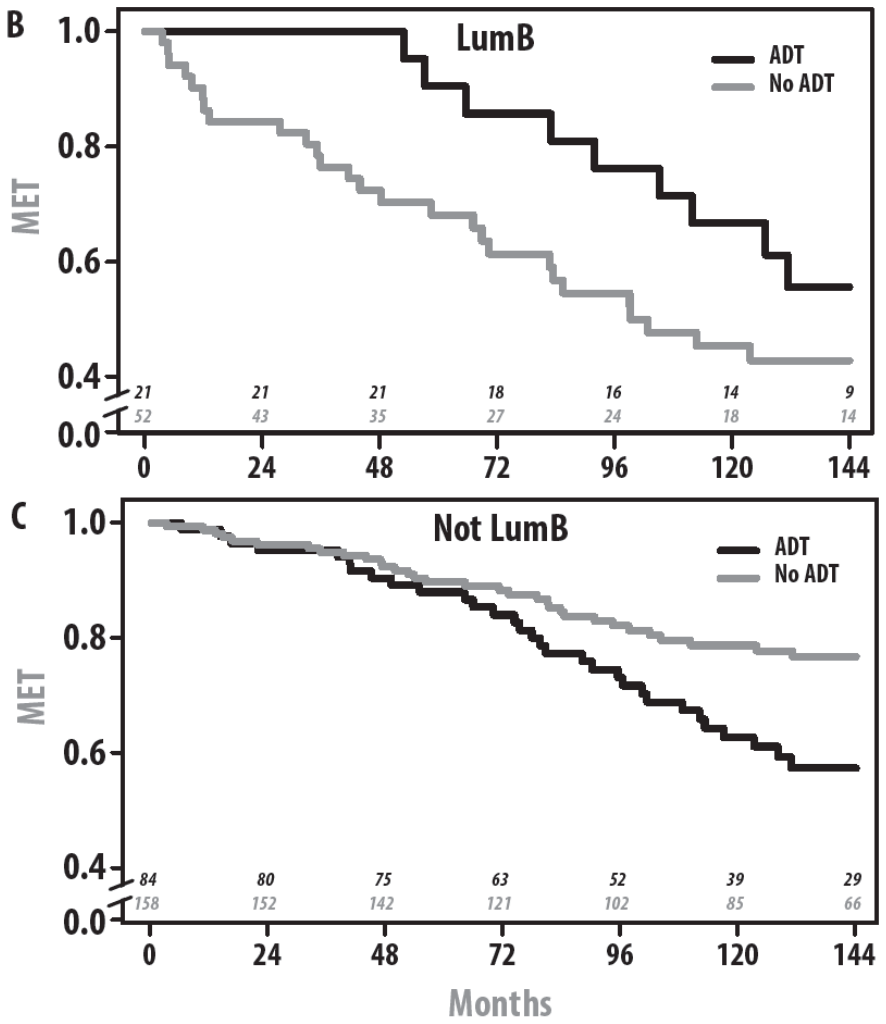
Luminal B prostate cancers exhibit the greatest response to androgen deprivation

Cohorts for Matching N=780

2:1 matching on ADT Covariates: Gleason, PSA, RT, LNI, ECE, SVI, SM

Final Matched Cohort N=315

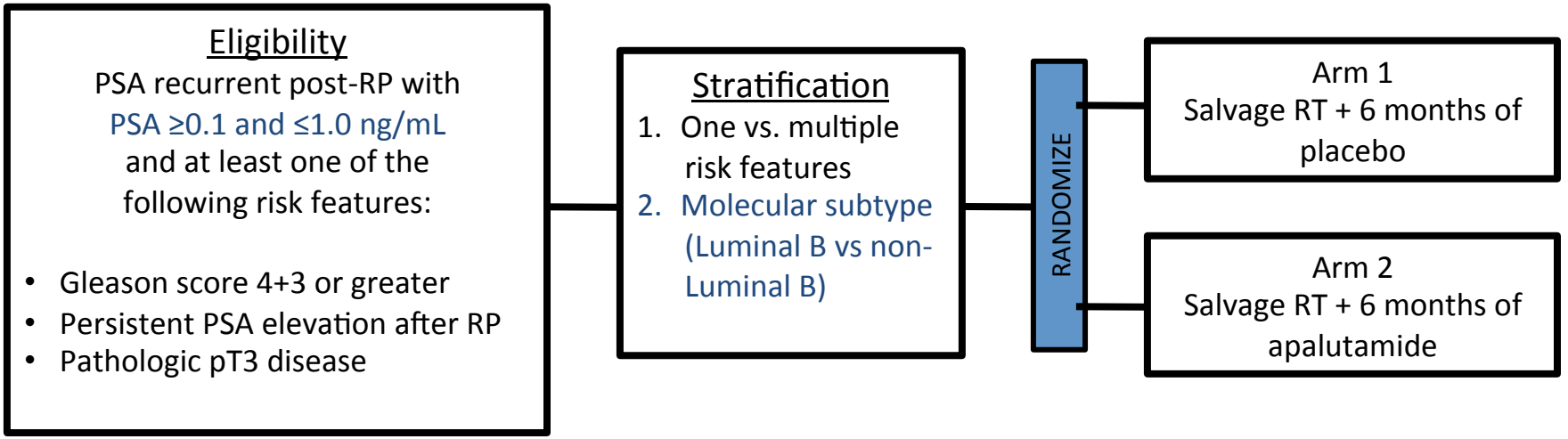
Predict response to post-operative ADT



Zhao et al, JAMA Oncology 2017

Luminal A, B and Basal: The next step: Molecular stratification

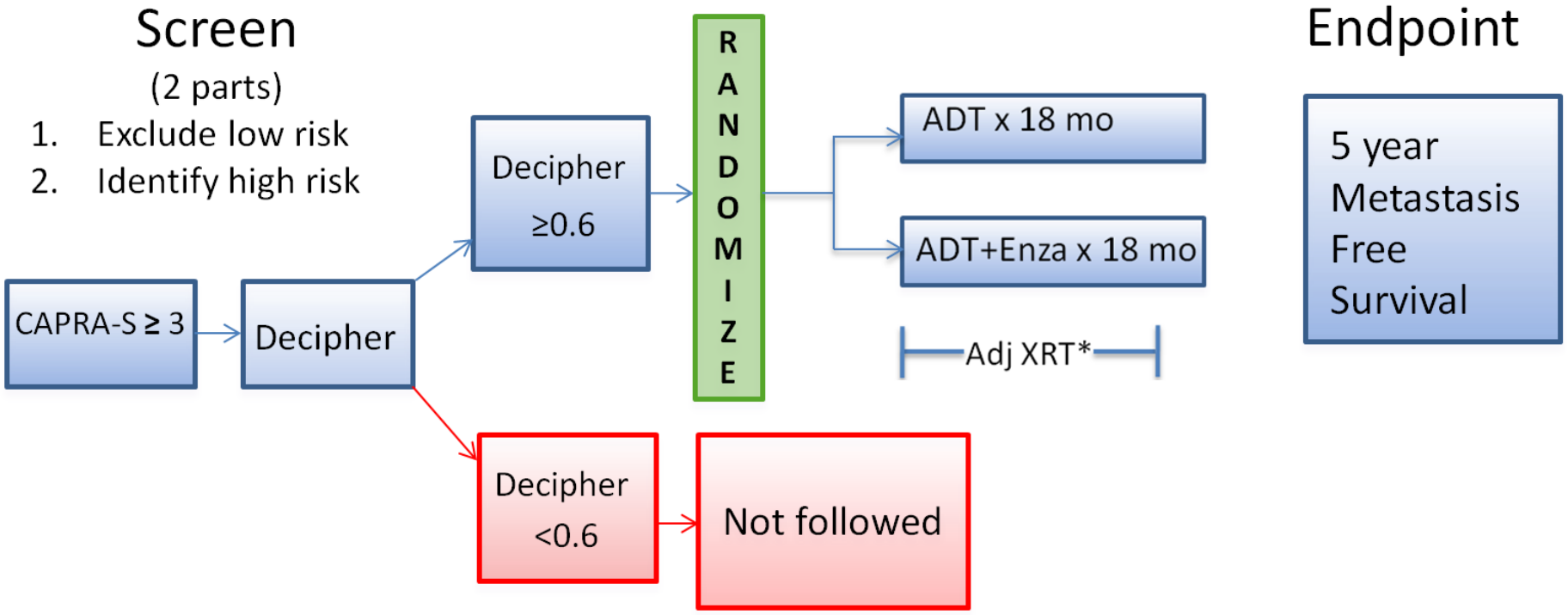
NRG 1614 trial schema:



Trial PIs: F Feng & D Spratt

ERADICATE : ECOG Study in Development

Study Design – Phase II/III



* Can administer adjuvant XRT at any time during the initial 12 months.

Alicia Morgans PI

Summary

- AR Targeting is moving “left” from mCRPC to:
  - Nonmet CRPC
  - serologic relapse to:
  - adjuvant.
- Enhanced potency may give the opportunity to delay, avoid or shorten castration.
- Attention to the reduced toxicity and enhanced QOL is key.