GU MALIGNANCIES

Bruce J. Roth, M.D.
Clinical Trials: Medivation, Oncogenix

PROSTATE CANCER

1) Alpharadin (Ra223) in CRPC with bone metastases
2) Enzalutamide (MDV-3100) in CRPC and prior docetaxel
3) Abiraterone in chemo-naïve CRPC
4) Intermittent androgen deprivation in androgen-sensitive PCa

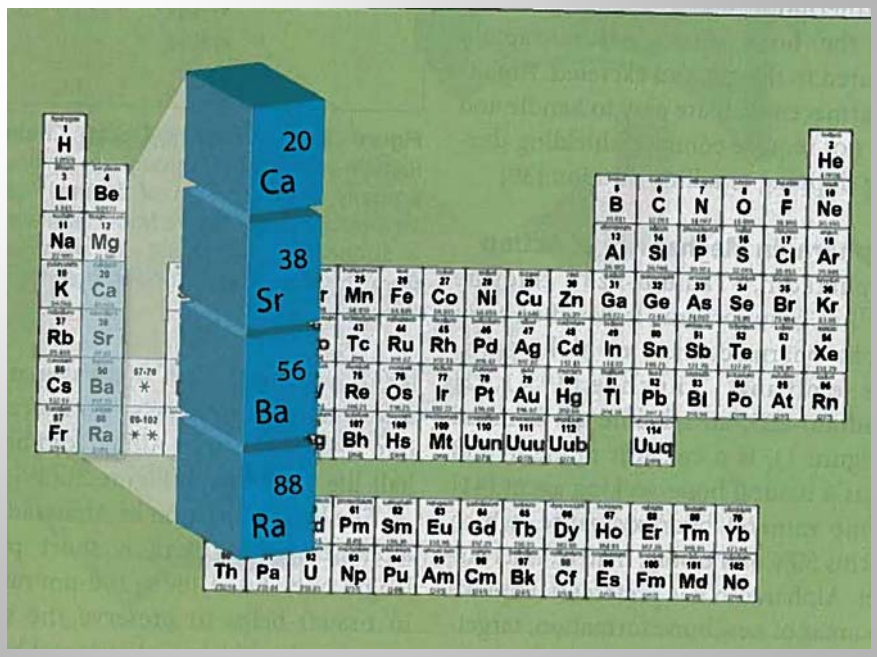
UPDATED ANALYSIS OF THE PHASE III, DOUBLE-BLIND, RANDOMIZED MULTINATIONAL STUDY OF RADIUM-223 CHLORIDE IN CASTRATION-RESISTANT PROSTATE CANCER (CRPC) PATIENTS WITH BONE METASTASES (ALSYMPCA)

Parker C, et al.

LBA4512

ALPHA PARTICLES AS RADIOPHARMACEUTICALS

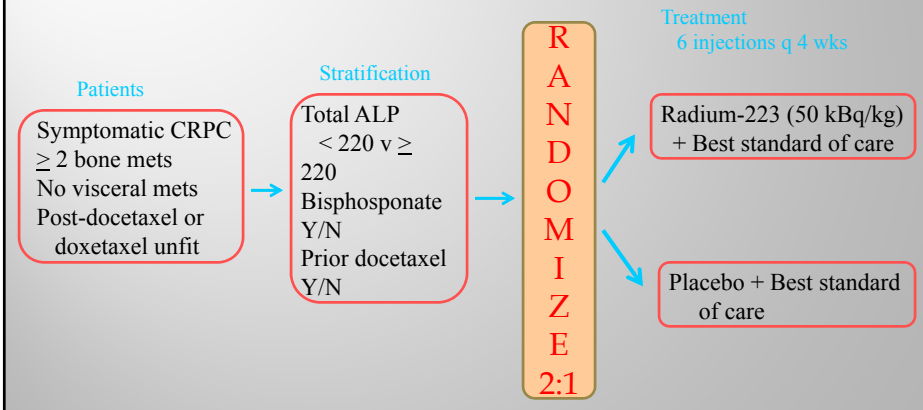
- Differ from beta particles in terms of energy, tissue range, linear-energy transfer, and number of DNA hits needed to kill a cell
- Deliver and intense and highly localized radiation dose (range 2-10 cell diameters)
- Double-stranded DNA breaks (does not require cycling cells)
- Less irradiation of healthy bone marrow



ALPHARADIN: CHARACTERISTICS

- Calcium-mimetic, forms complexes with hydroxyapatite, incorporated into bony matrix
- Preferential uptake in areas of new bone formation, targeting tumor cells in close proximity to areaas of new bone growth surrounding metastases
- Path length of only 40 – 100 μm
- Half-life of 11.4 days

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III



N = 922

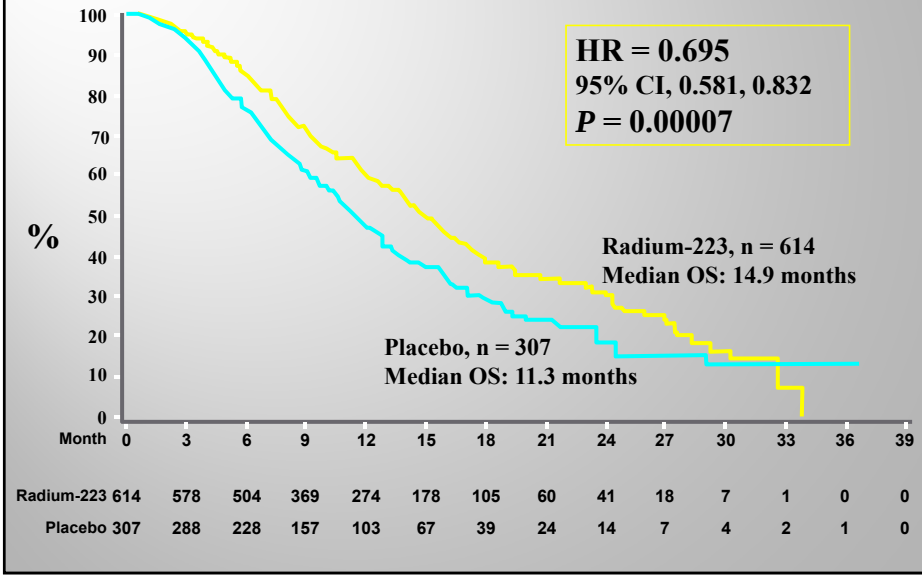
ALSYMPCA: ENDPOINTS

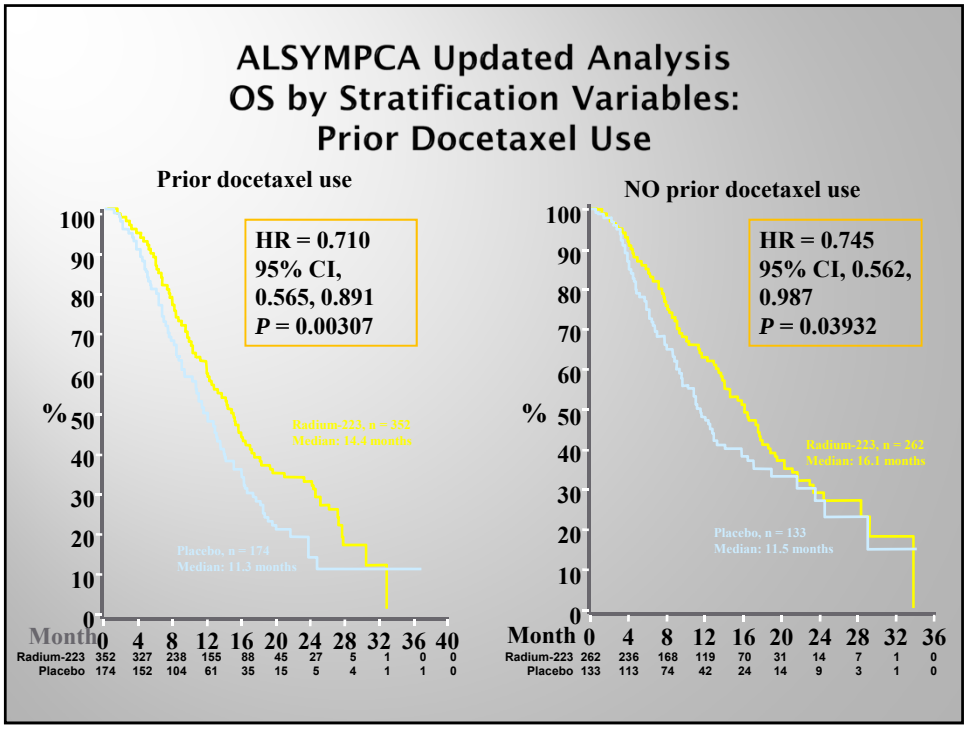
- Primary – overall survival
- Secondary
  - Time to first SRE
  - Time to alk phos progression
  - Total alk phos response
  - Total alk phos normalization
  - Time to PSA progression
  - QOL
  - Safety

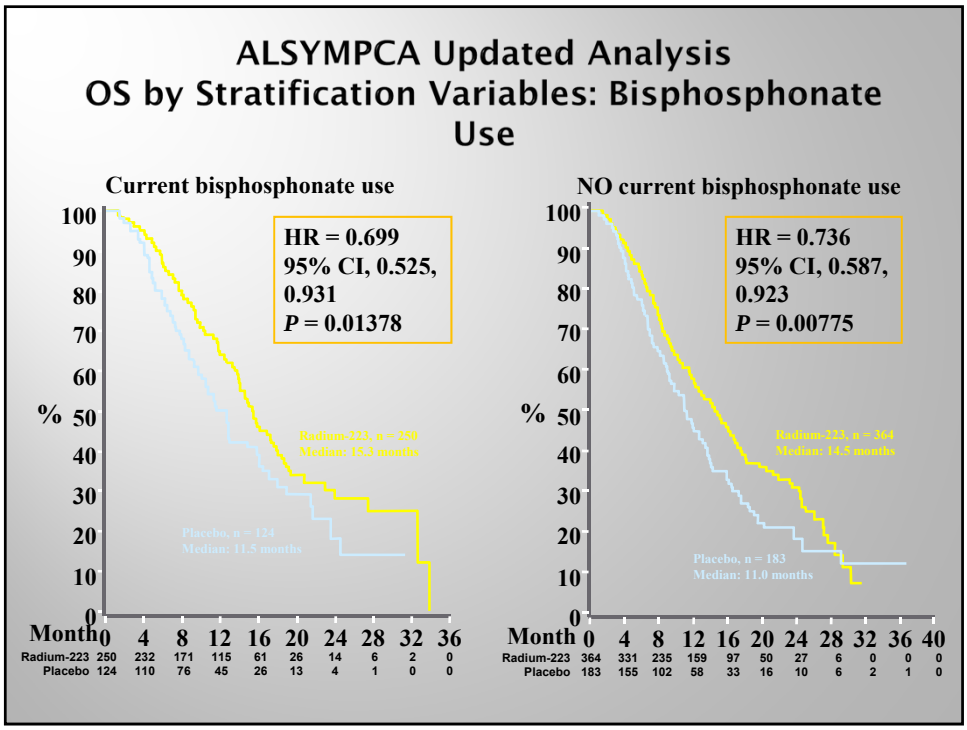
ALSYMPCA Updated Analysis Patient Demographics and Baseline Characteristics (ITT N = 921)

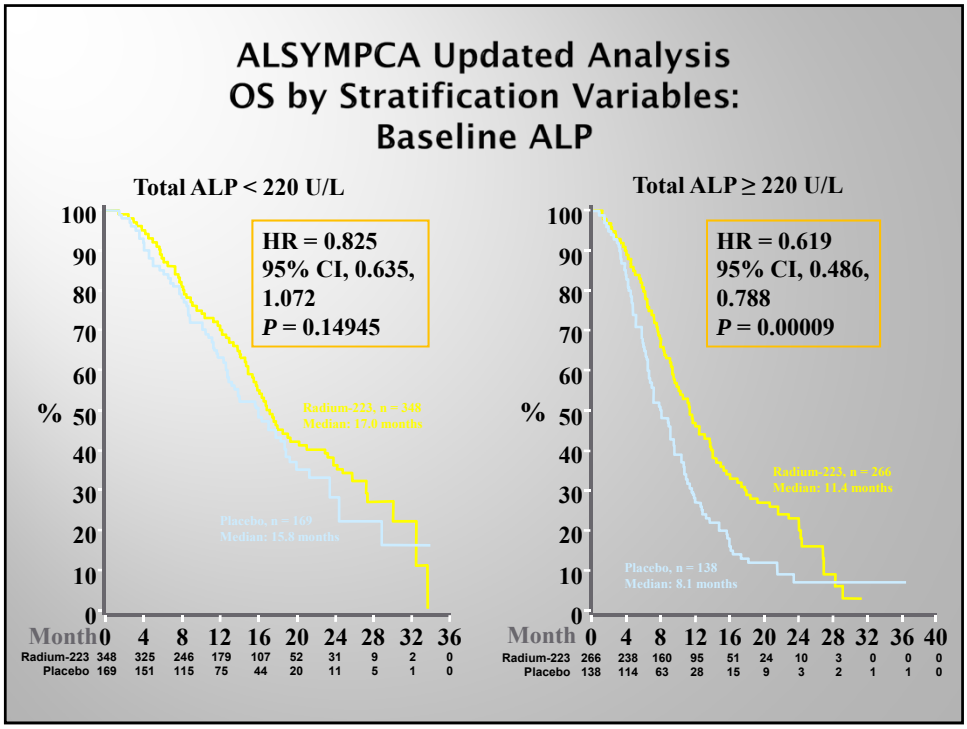
Parameter	Radium-223 n = 614	Placebo n = 307
Age, y		
Mean	70.2	70.8
Race, n (%)		
Caucasian	575 (94)	290 (95)
Baseline ECOG score, n (%)		
≤ 1	536 (87)	265 (86)
2	76 (12)	40 (13)
Extent of disease, n (%)		
< 6 metastases	100 (16)	38 (12)
6–20 metastases	262 (43)	147 (48)
> 20 metastases/superscan	249 (41)	121 (40)
WHO ladder, cancer pain index ≥ 2, n (%)	345 (56)	168 (55)

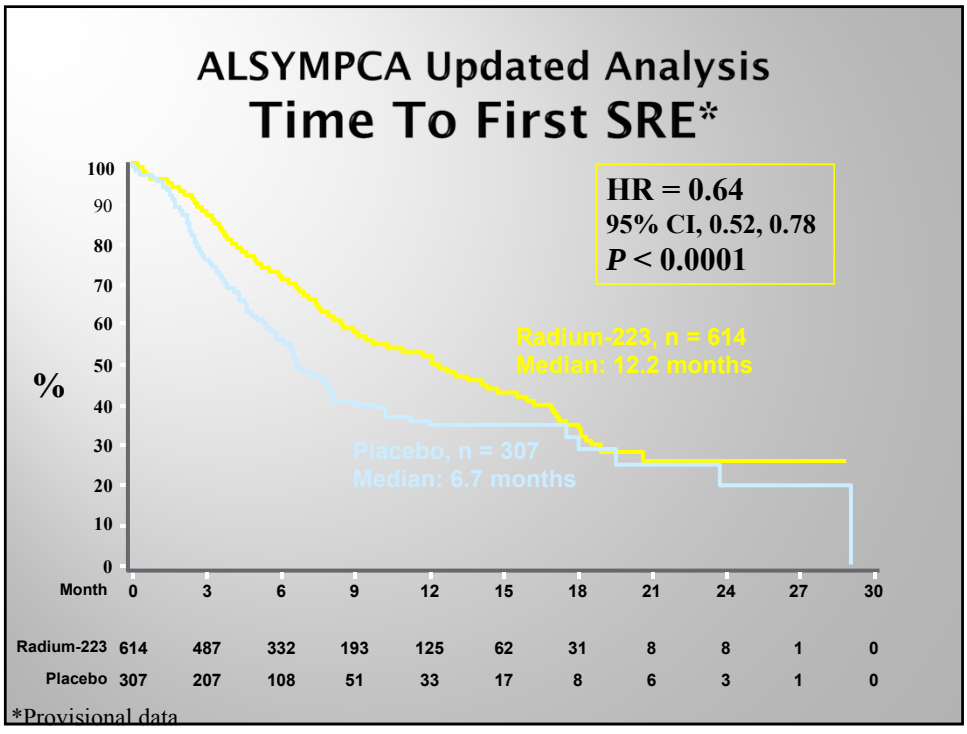
ALSYMPCA Updated Analysis Overall Survival




ALSYMPCA Updated Analysis
OS by Stratification Variables:
Prior Docetaxel Use
Prior docetaxel use
HR = 0.710
95% CI,
0.565, 0.891
P = 0.00307
Radium-223, n = 352
Median: 14.0 months
Placebo, n = 174
Median: 11.3 months
%
Month
Radium-223 352 327 238 155 88 45 27 5 1 0 0
Placebo 174 152 104 61 35 15 5 4 1 1 0
NO prior docetaxel use
HR = 0.745
95% CI, 0.562,
0.987
P = 0.03932
Radium-223, n = 262
Median: 16.1 months
Placebo, n = 133
Median: 11.5 months
Month 0 4 8 12 16 20 24 28 32 36
Radium-223 262 236 168 119 70 31 14 7 1 0
Placebo 133 113 74 42 24 14 9 3 1 0


ALSYMPCA Updated Analysis
OS by Stratification Variables: Bisphosphonate
Use
Current bisphosphonate use
HR = 0.699
95% CI, 0.525,
0.931
P = 0.01378
Radium-223, n = 250
Median: 15.3 months
Placebo, n = 124
Median: 11.5 months
%
Month
Radium-223 250 232 171 115 61 26 14 6 2 0
Placebo 124 110 76 45 26 13 4 1 0 0
NO current bisphosphonate use
HR = 0.736
95% CI, 0.587,
0.923
P = 0.00775
Radium-223, n = 364
Median: 14.5 months
Placebo, n = 183
Median: 11.0 months
Month 0 4 8 12 16 20 24 28 32 36 40
Radium-223 364 331 235 159 97 50 27 6 0 0 0
Placebo 183 155 102 58 33 16 10 6 2 1 0





*Provisional data

ALSYMPCA Updated Analysis
AEs of Interest

	All Grades		Grades 3 or 4	
Patients with AEs n, (%)	**Radium-223 n = 600**	**Placebo n = 301**	**Radium-223 n = 600**	**Placebo n= 301**
Hematologic				
Anemia	187 (31)	92 (31)	77 (13)	39 (13)
Neutropenia	30 (5)	3 (1)	13 (2)	2 (1)
Thrombocytopenia	69 (12)	17 (6)	38 (6)	6 (2)
Non-Hematologic				
Bone pain	300 (50)	187 (62)	125 (21)	77 (26)
Diarrhea	151 (25)	45 (15)	9 (2)	5 (2)
Nausea	213 (36)	104 (35)	10 (2)	5 (2)
Vomiting	111 (19)	41 (14)	10 (2)	7 (2)
Constipation	108 (18)	64 (21)	6 (1)	4 (1)

CONCLUSIONS: (Author's)

- Radium-223 compared with placebo in CRPC patients with bone metastases:
  - Significantly prolonged median OS by 3.6 months (HR = 0.695; *P* = 0.00007)
    - 30.5% reduction in risk of death
  - Significantly prolonged median time to first SRE by 5.5 months (HR = 0.64; *P* < 0.0001)
- Further follow-up in all randomized patients continues to show highly favorable safety profile

Radium-223, a first-in-class alpha-emitter, may provide a new standard of care for the treatment of CRPC patients with bone metastases

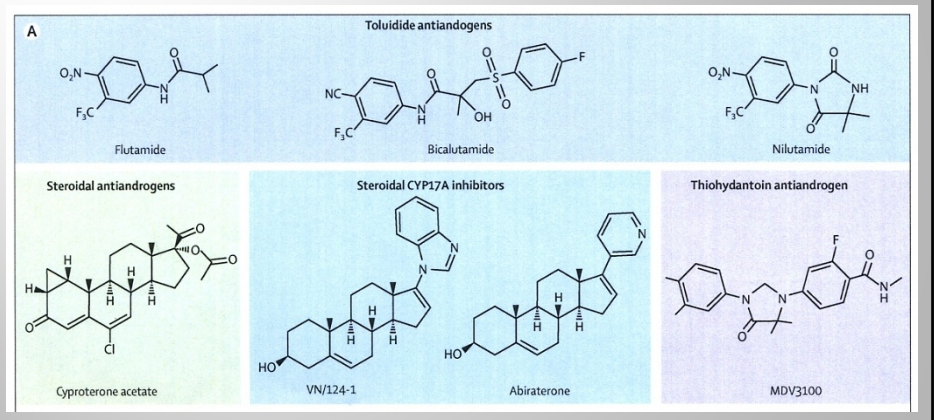
CONCLUSIONS: (Mine)

- What "standard of care" is this replacing?
  - samarium? cabazitaxel? bisphosphonates? denosumab?
- Let's wait for additional info
  - Peer-reviewed publication
  - ODAC deliberation
  - Package insert
- That being said, this is a first-in class compound with unexpectedly good results

PHASE III TRIAL (AFFIRM) OF ENZALUTAMIDE (MDV3100), AN ANDROGEN RECEPTOR SIGNALING INHIBITOR: PRIMARY, SECONDARY, AND QUALITY-OF-LIFE ENDPOINT RESULTS

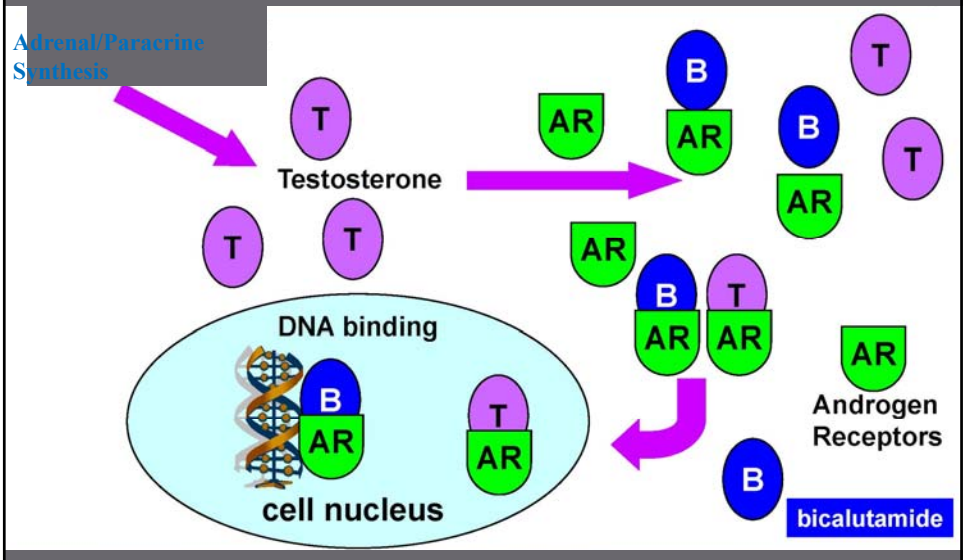
De Bono J, et al.
LBA 4519

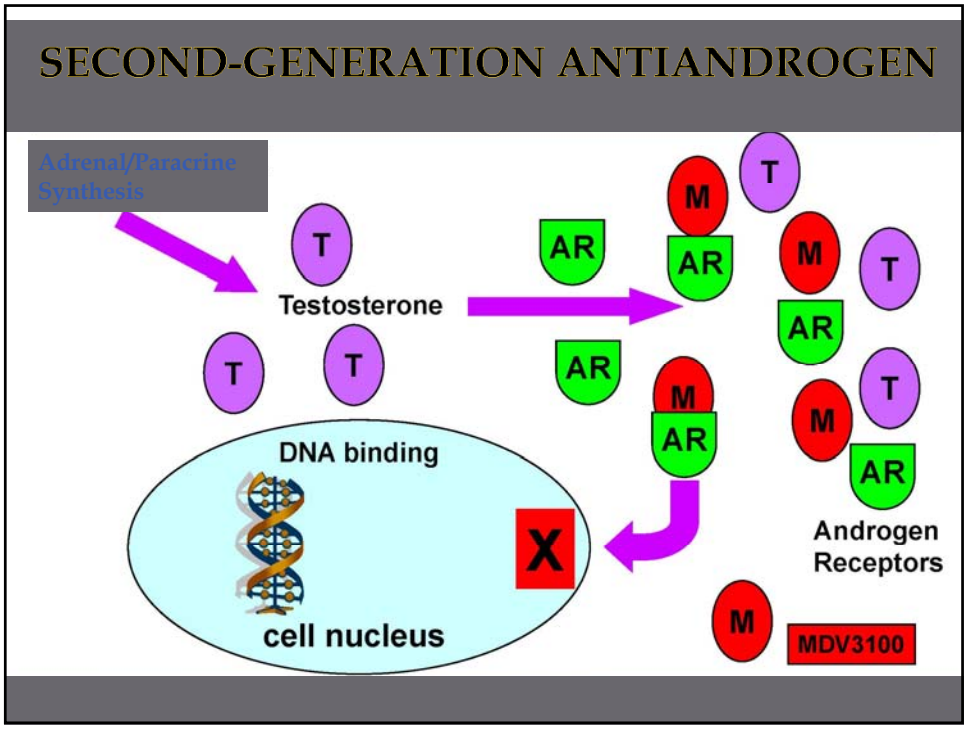
ANTIANDROGENS

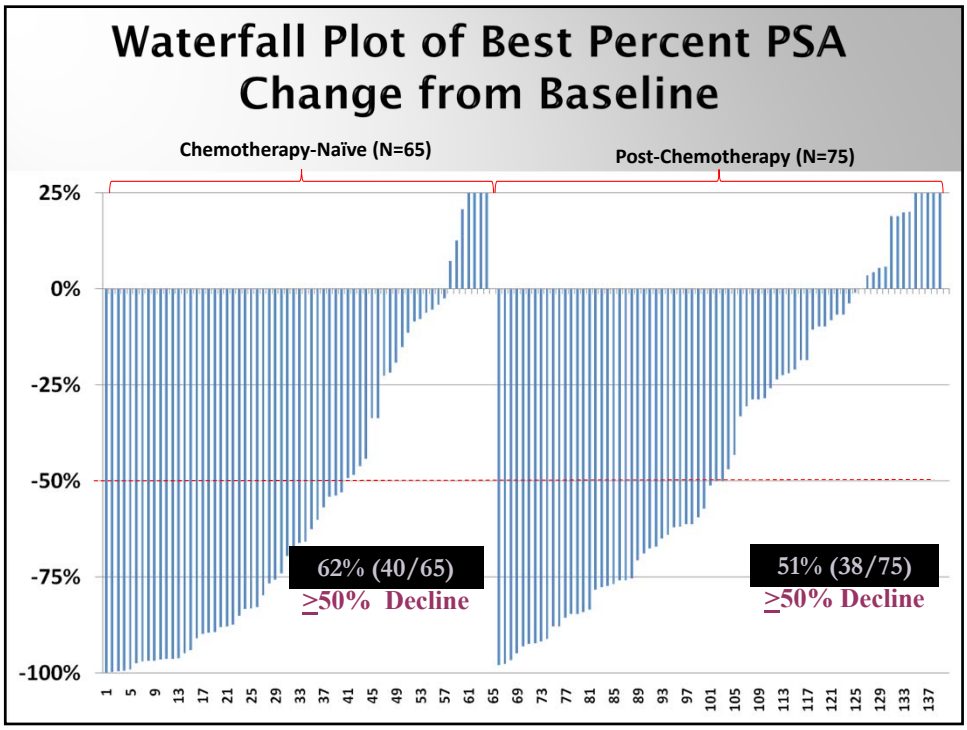


Chen Y, et al. Lancet Oncol 10:981-989, 2009

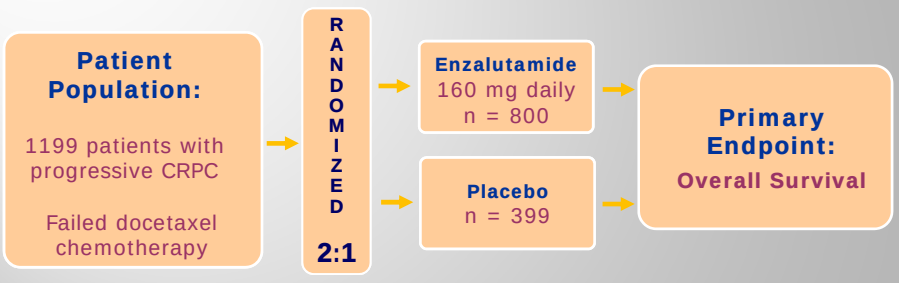
ADDITION OF AN ANTIANDROGEN




SECOND-GENERATION ANTIANDROGEN
Adrenal/Paracrine Synthesis
T
Testosterone
T
T
AR
AR
AR
M
M
M
T
T
T
AR
AR
AR
DNA binding
X
cell nucleus
Androgen Receptors
M
MDV3100

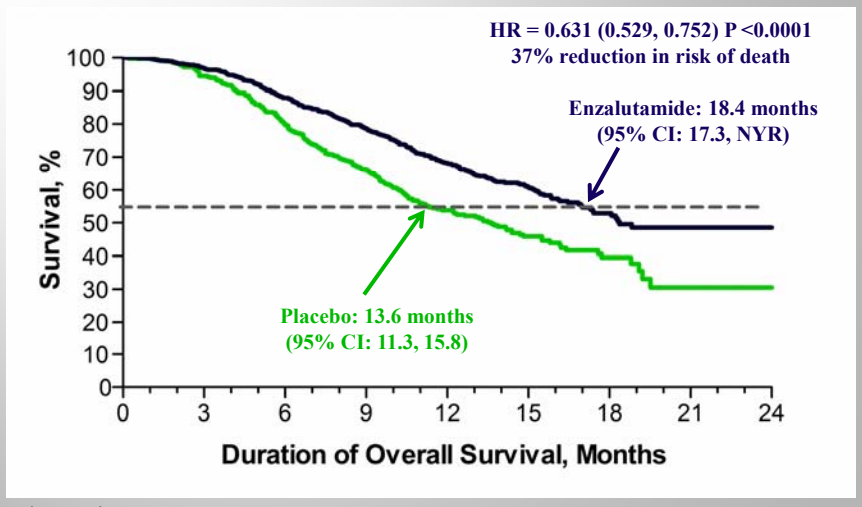

Waterfall Plot of Best Percent PSA Change from Baseline
Chemotherapy-Naïve (N=65)
Post-Chemotherapy (N=75)
25%
0%
-25%
-50%
-75%
-100%
62% (40/65)
≥50% Decline
51% (38/75)
≥50% Decline
1 5 9 13 17 21 25 29 33 37 41 45 49 53 57 61 65 69 73 77 81 85 89 93 97 101 105 109 113 117 121 125 129 133 137

AFFIRM Trial Design



2-sided alpha – 0.05; 90% power to detect 24% reduction in mortality (HR=0.76)
Solitary planned interim analysis at 520 events – DSMC called for halting/unblinding the study

OVERALL SURVIVAL



Enzalutamide	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0

SECONDARY ENDPOINTS

- PSA response
  - ≥ 50%: E - 54%; P - 2% ($p < 0.0001$)
  - > 90%: E - 25%; P - 1% ($p < 0.0001$)
- PSA PFS
  - E – 8.3 mths; P – 3.0 mths (HR 0.248, $p < 0.0001$)
- RECIST Response
  - CR + PR: E – 28.9%; P – 3.8% ($p < 0.0001$)

SECONDARY ENDPOINTS (cont.)

- Radiographic PFS
  - E – 8.3 mths; P – 2.9 mths (HR 0.404, $p < 0.0001$)
- Time to First SRE
  - E – 16.7 mths; P – 13.3 mths (HR 0.621, $p < 0.0001$)
- QOL Responses (FACT-P) (10-pt increase in score)
  - E – 43.2%; P – 18.3% ($p < 0.0001$)

Adverse Events of Special Interest

	All Grades		Grade ≥ 3 Events	
	Enzalutamide (n = 800)	Placebo (n = 399)	Enzalutamide (n = 800)	Placebo (n = 399)
Fatigue	33.6%	29.1%	6.3%	7.3%
Cardiac Disorders	6.1%	7.5%	0.9%	2.0%
Myocardial Infarction	0.3%	0.5%	0.3%	0.5%
LFT Abnormalities	1.0%	1.5%	0.4%	0.8%
Seizure	0.6%	0.0%	0.6%	0.0%

Seizure Cases

CASE	1	2	3	4	5
Time on Study	**2 months**	**10 months**	**2 months**	**5 months**	**10 months**
On study drug?	Yes	Yes	Yes	Off trial drug for 26 days	Yes
Seizure type	Focal onset	Generalized	Complex partial status	Focal onset	Unknown, fall not witnessed
Recurrence	No	No	No	No	No
Potential confounding factors	Large 5 x 4 cm temporal lobe brain metastases	IV Lidocaine inadvertentl y given just before seizure*	Atrophy and leukoariosis on MRI brain; nil else	Multiple CNS metastases: Eye, meninges, cerebellar	Alcohol excess; started on haloperidol 7 days prior

*40 mgs IV lidocaine (lignocaine); patient also on Na+ channel modulator: propafenone (flecainide like antidysrhythmic).

CONCLUSIONS

- Enzalutamide, a once a day oral Androgen Receptor Signaling Inhibitor, is well tolerated and prolongs survival in men with CRPC by almost 5 months.
- Enzalutamide improved secondary measures of antitumor activity including health-related quality of life, response, time to SRE and time to disease progression.
- The androgen receptor remains a valid therapeutic target for treating CRPC following chemotherapy.

ENZALUTAMIDE – FUTURE DIRECTIONS

- FDA approved 8/31/2012
- Pre-chemotherapy phase III trial has completed accrual – results likely available in 2013
- STRIVE – phase III enzalutamide versus bicalutamide as second-line hormonal therapy (both non-metastatic and metastatic) just opening to accrual

INTERIM ANALYSIS RESULTS OF COU-AA-302, A RANDOMIZED PHASE III STUDY OF ABIRATERONE ACETATE IN CHEMOTHERAPY-NAÏVE PATIENTS WITH METASTATIC, CASTRATION-RESISTANT PROSTATE CANCER

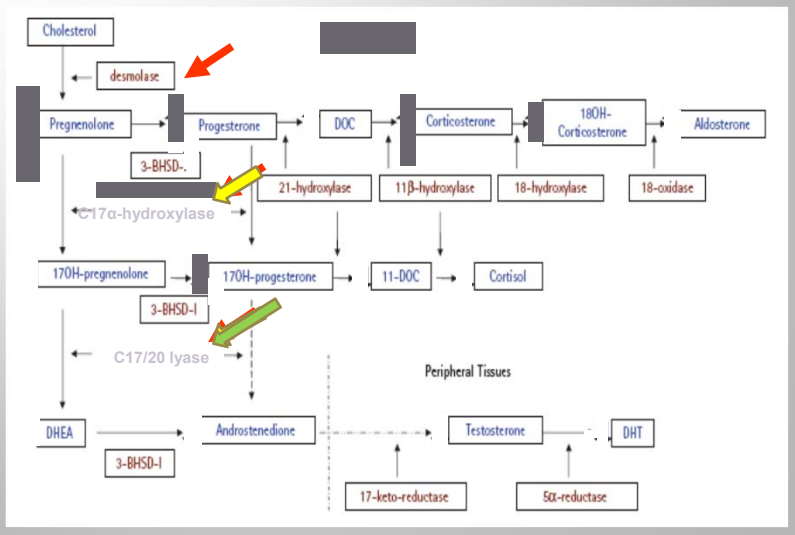
Ryan, CJ et al
LBA 4518

SOURCES OF ANDROGEN FOR THE PROSTATE CANCER CELL

- Testicle
- Adrenal
- Intracrine

→ Androgen synthesis inhibition

Androgen Synthesis Pathway



Ketoconazole Abiraterone Tak-700

Phase III Registration Trial of Abiraterone Acetate in Post-Chemotherapy Setting

Abiraterone 1000 mg daily
Prednisone 10 mg daily

Randomization 2:1

Placebo daily
Prednisone 10 mg daily

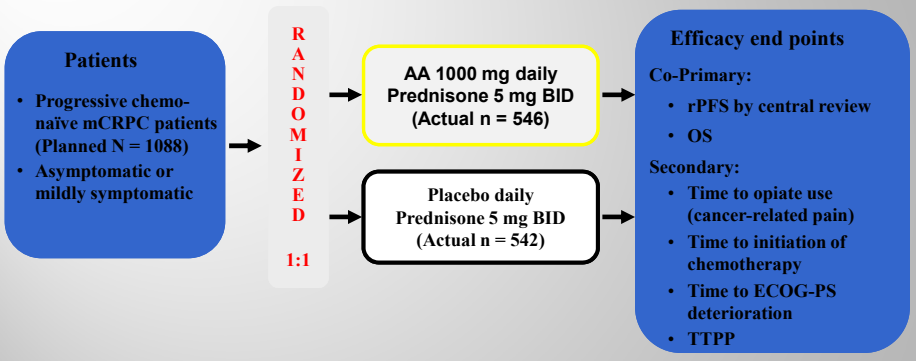
Primary Endpoint: 25% survival increase (12 – 15 mos)
Secondary Endpoints: TT PSA progression, PFS, PSA response rate

Phase III Abiraterone Post-Chemotherapy – Results

- 1195 pts (abiraterone 797: placebo 398); median f/u 12.8 mths: data unblinded at interim analysis
- OS: abiraterone 14.8 mths: placebo 10.9 mths (HR .65 (95% CI 0.54 - 0.77; P<0.001)
- TT PSA progression: abi 10.2 v placebo 6.6 mths
- PFS: abi 5.6 v placebo 3.6 mths
- PSA RR: abi 29% v placebo 6% (P< 0.001)

deBono JS, et al: NEJM 364:1995-2005, 2011

Overall Study Design of COU-AA-302



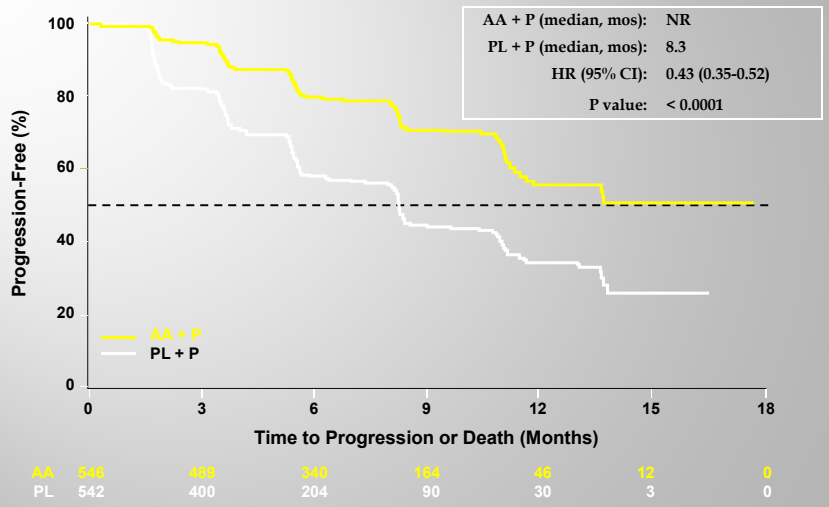
- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Stratification by ECOG performance status 0 vs 1

COU-AA-302: rPFS Definition

- Progressive disease (PD) by bone scan: Adapted from Consensus Criteria[1]
  - Blinded central radiologist review
  - < 12 weeks after randomization
    - ≥ 2 new bone lesions plus 2 additional at confirmation ("2+2")
  - ≥ 12 weeks after randomization
    - ≥ 2 new bone lesions with subsequent confirmation
- PD (soft tissue lesions) by CT or MRI by modified RECIST criteria
- Death from any cause

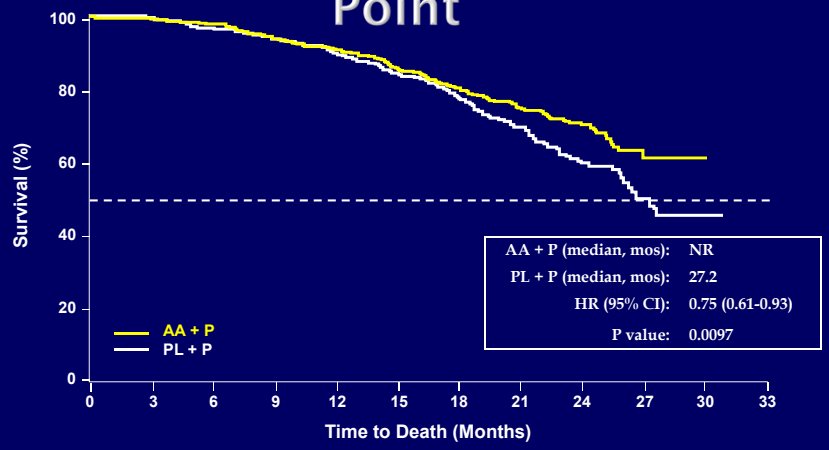
1. Scher H, *J Clin Oncol.* 2008;26:1148-1159.

Statistically Significant Improvement in rPFS Primary End Point



Data cutoff 12/20/2010.
NR, not reached; PL, placebo.

Strong Trend in OS Primary End Point



Data cutoff 12/20/2011.
Pre-specified significance level by O'Brien-Fleming Boundary = 0.0008.

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ASCO Annual '12 Meeting

Serologic and Clinical Responses

	AA + P (n = 546)	Placebo + P (n = 542)	RR (95% CI)	P Value
PSA decline ≥50%	62%	24%	NA	<0.0001
	N=220	N=218		
RECIST: Defined objective response	36%	16%	2.273 (1.591, 3.247)	<0.0001
Complete response	11%	4%		
Partial response	25%	12%		
Stable disease	61%	69%		
Progressive disease	2%	15%		

Statistically Significant Improvement in All Secondary End Points

	AA + P	Placebo + P		
	Median (months)	Median (months)	HR (95% CI)	P Value
Time to opiate use (cancer related pain)	NR	23.7	0.69 (0.57, 0.83)	0.0001
Time to chemotherapy initiation	25.2	16.8	0.58 (0.49, 0.69)	<0.0001
Time to ECOG PS deterioration	12.3	10.9	0.82 (0.71, 0.94)	0.0053
Time to PSA progression	11.1	5.6	0.49 (0.42, 0.57)	<0.0001

Note: All secondary end points remain significant after adjusting for multiplicity testing

Patient Reported Outcomes favored AA +P vs Placebo +P
Full data to be reported

Data cut off 12/20/2011.

Summary

- In patients with asymptomatic and mildly symptomatic, chemotherapy-naïve mCRPC, treatment with abiraterone acetate plus prednisone:
  - Delays disease progression
  - Increases survival
  - Extends time with minimal or no symptoms
  - No new important safety signals
  - Granted accelerated review for expanded indication by FDA

INTERMITTENT VERSUS CONTINUOUS ANDROGEN DEPRIVATION IN HORMONE SENSITIVE METASTATIC PROSTATE CANCER PATIENTS: RESULTS OF SWOG 9346 (INT-0162) AN INTERNATIONAL PHASE III TRIAL

Hussain M, et al

4

BACKGROUND

- Continuous androgen deprivation is the standard approach to advanced disease
- Preclinical data suggested that intermittent therapy might prolong the time to development of castrate resistant state
- Smaller clinical trials have confirmed a better QOL for patients receiving intermittent therapy, but have been underpowered to conclude anything regarding overall survival

S9346 (INT-0162): Objectives

Primary

- Determine if survival with IAD is Not Inferior to survival with CAD.
- QOL*: To compare 3 treatment-specific symptoms (Impotence, Libido, Energy/Vitality) and physical and emotional functioning between arms

Secondary:

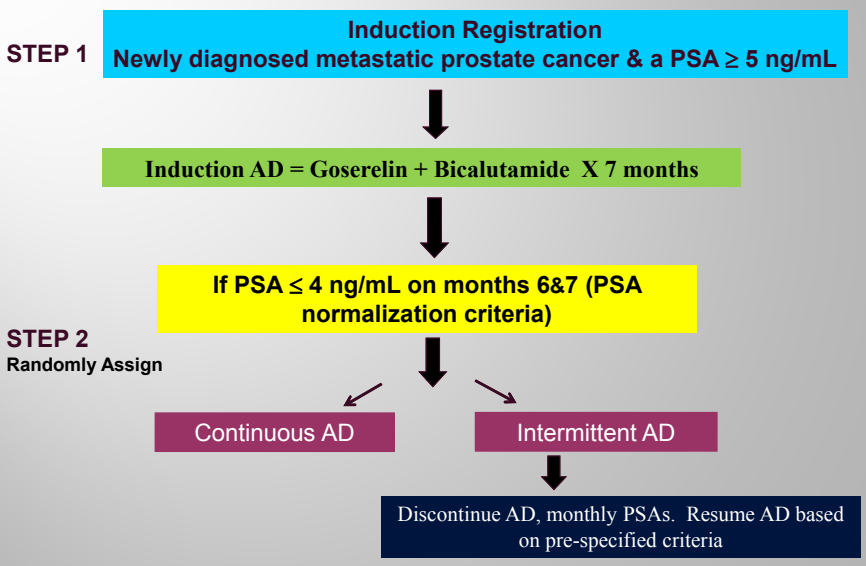
-More general QOL measures
-PSA dynamics between arms, and correlations with other endpoints

**Moinpour et-al, Abstract # 4571 describes results for QOL*

ELIGIBILITY AND STRATIFICATION

- Eligibility
  - Newly diagnosed metastatic prostate cancer
  - PSA ≥ 5 ng/ml
  - PS 0-2
- Stratification
  - PS (0-1 v 2)
  - Extent of disease
    - Minimal (spine, pelvis +/- nodal disease)
    - Extensive (ribs, long bones +/- visceral disease)
- Prior hormonal tx
  - neoadjuvant therapy v finsteride v neither

Study Design



IAD Arm: Subsequent Therapy Cycles

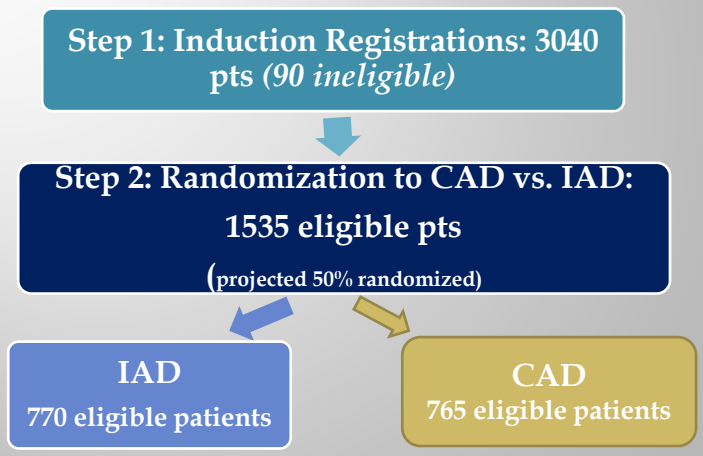
- Therapy was reinitiated when PSA increased to 20 ng/ml (or returned to baseline for patients who had pre-registration baseline value < 20 ng/ml) or for symptoms.
- If the PSA after another 7 months induction course met the PSA normalization criterion then the patients started another observation period.
- If the PSA at either months 6 or 7th of an induction course was greater than 4 ng/ml then the patients received continuous therapy until progression.

Statistical Methods

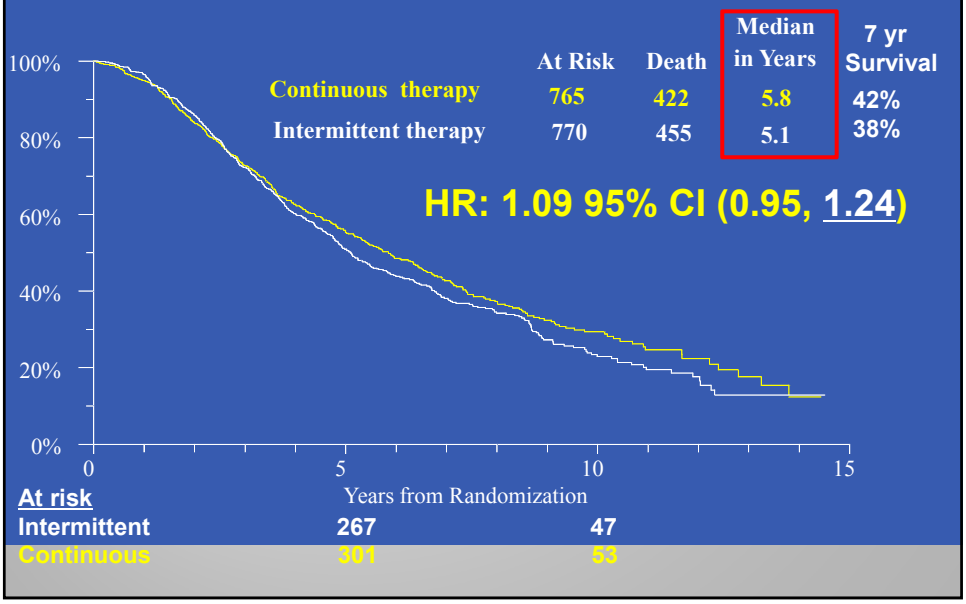
- **Primary outcome:** Survival post-randomization
  - Hypothesis: "**IAD is NOT inferior to CAD"**
- **Design specifications:**
  - **Survival with IAD is not inferior if the 95% confidence interval for the hazard ratio (IAD vs. CAD) excludes 1.2,** α=0.05, power=90%, adjusting for stratification factors in proportional hazards model.
- **Assumptions:** post-randomization median survival for CAD = 3 years:
  - Sample size: 1500 eligible, randomized patients
  - accrual: 6.25 yrs. + 2 additional yrs. of follow-up.

S9346 Study Information

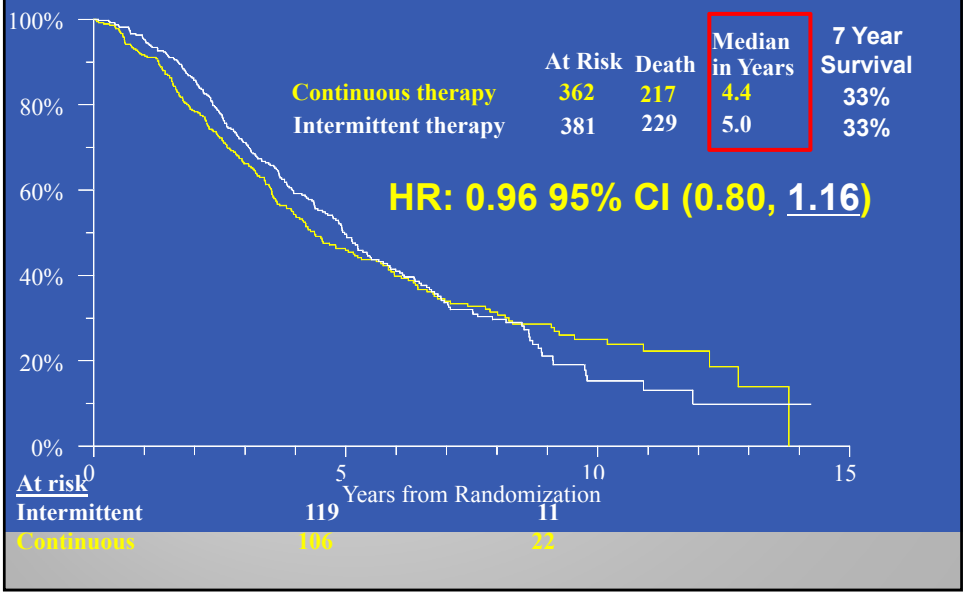
Activated: 5/15/1995 **Closed**: 9/1/2008



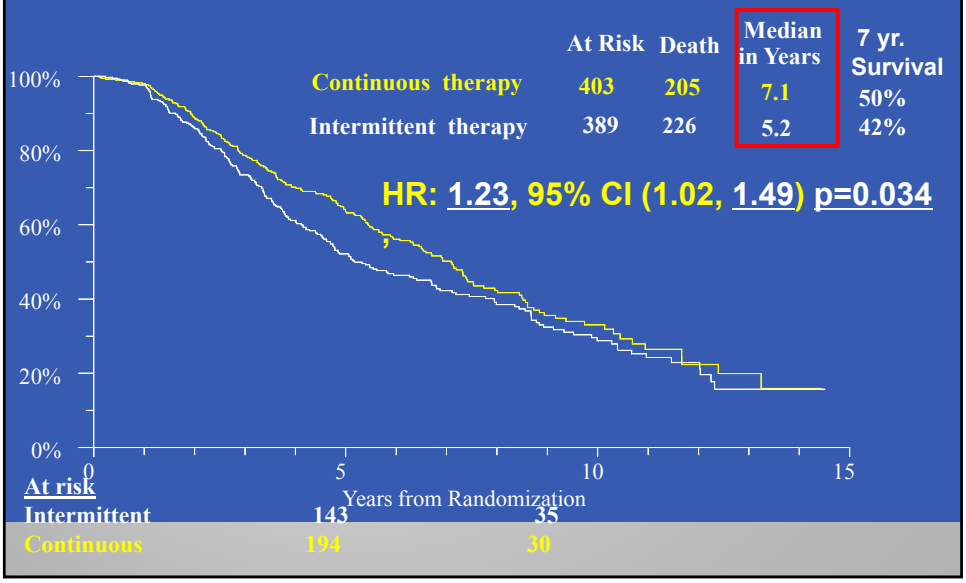
Overall Survival: Intermittent Therapy is Inferior Compared to Continuous Therapy



Overall Survival for Patients with Extensive Disease by Treatment Arm



Overall Survival for Patients with Minimal Disease by Treatment Arm



Conclusions

In this international phase III trial in patients with metastatic hormone sensitive prostate cancer :

1. IAD was inferior to CAD based on our pre-specified definition of survival comparability [HR: 1.09, 95% CI (0.95, 1.24)]. Therefore, CAD continues to be the standard of care.
2. In a secondary analysis:
   - IAD was not-inferior to CAD in patients with extensive disease. [HR: 0.96 95% CI (0.80, 1.16)].
   - IAD was inferior in patients with minimal disease & CAD was statistically significantly superior [HR: 1.23, 95% CI (1.02, 1.49), p=0.034].
   - These observations suggest inherent biological differences and warrant further mechanistic evaluation.

INTERPRETATION

- Huge debate at the meeting regarding the definitions of minimal v extensive metastatic disease
- Even bigger debate regarding the statistical implications of a therapy being "not non-inferior"

AXIOM #1

- If the results of a trial validate your pre-existing bias, then you are willing to overlook some statistical aberrations
- If the results are contrary to your bias, then you attack the statistics unmercifully

TAKE HOME

- Intermittent androgen deprivation is absolutely superior in terms of QOL
- But, the assumption that survival is equivalent with this approach is not supported by this trial
- A patient may still choose IAD based on QOL issues, but the survival differences observed in this study need to be discussed with the patient