Early Chemotherapy for Metastatic Prostate Cancer

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Disclosure

- Consultant: Sanofi Aventis, Celgene, Pfizer, Merck, Millineum, Dendreon, Johnson and Johnson, Bayer, Medivation, Tyme, Bellicum
- Research Support: Roche, Merck, Dendreon, Progenics, Lilly, Medivation, Novartis
- Team Support: Rangers, Mets, Jets
- AND I AM NOT A PATRIOTS FAN

12th Anniversary of Docetaxel Plenary Presentations

Presented by:

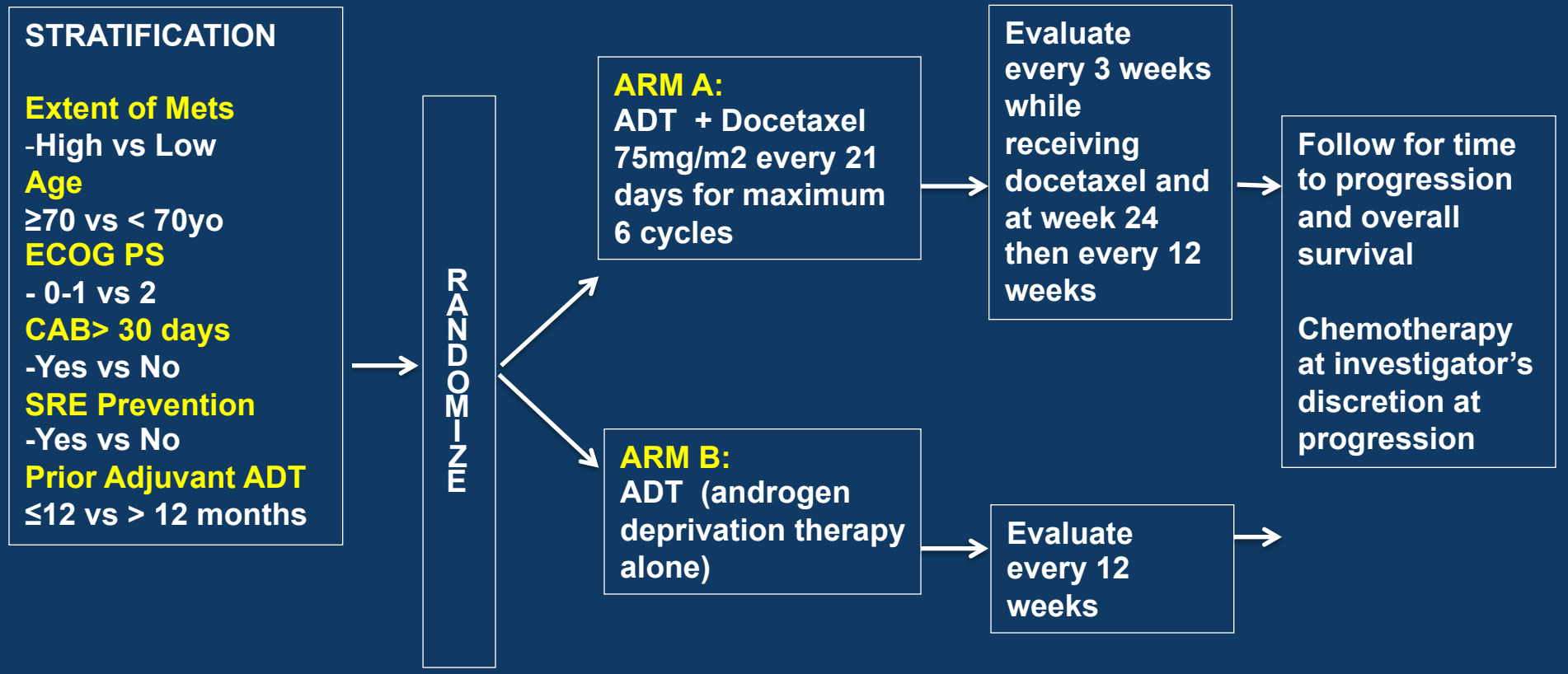
PRESENTED AT:

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Chemotherapy

- Formerly reserved for patients who are
  - Symptomatic
  - Rapidly progressive
  - Visceral disease
- Now should be considered for patients with extensive disease at the initiation of androgen blockade

E3805 – CHAARTED Treatment



- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

Key Eligibility Criteria

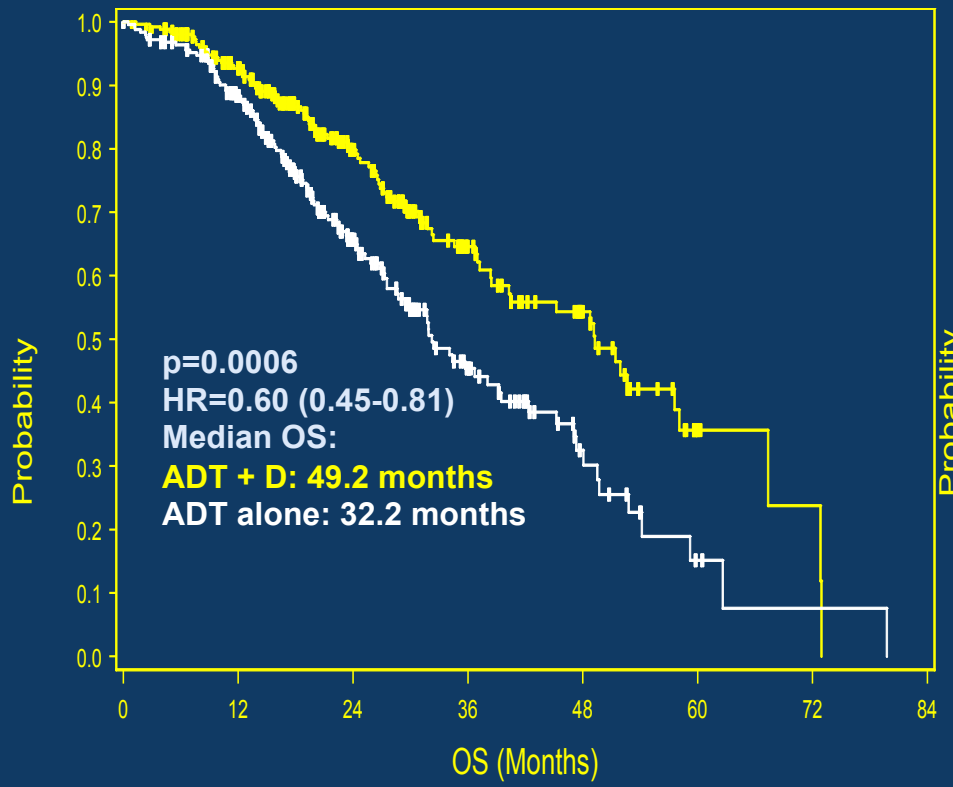
- Metastatic prostate cancer
  - if clinical scenario c/w PrCa can enroll without tissue
- Prior ADT limited to
  - 120 days prior to randomization or adjuvant Rx < 24 months and no progression within 12 months of finish
- ECOG 0-2 (2 only if due to PrCa)
- Liver, bone marrow, renal, cardiac, pulmonary and neurological function suitable for docetaxel
- No prior docetaxel

Results:

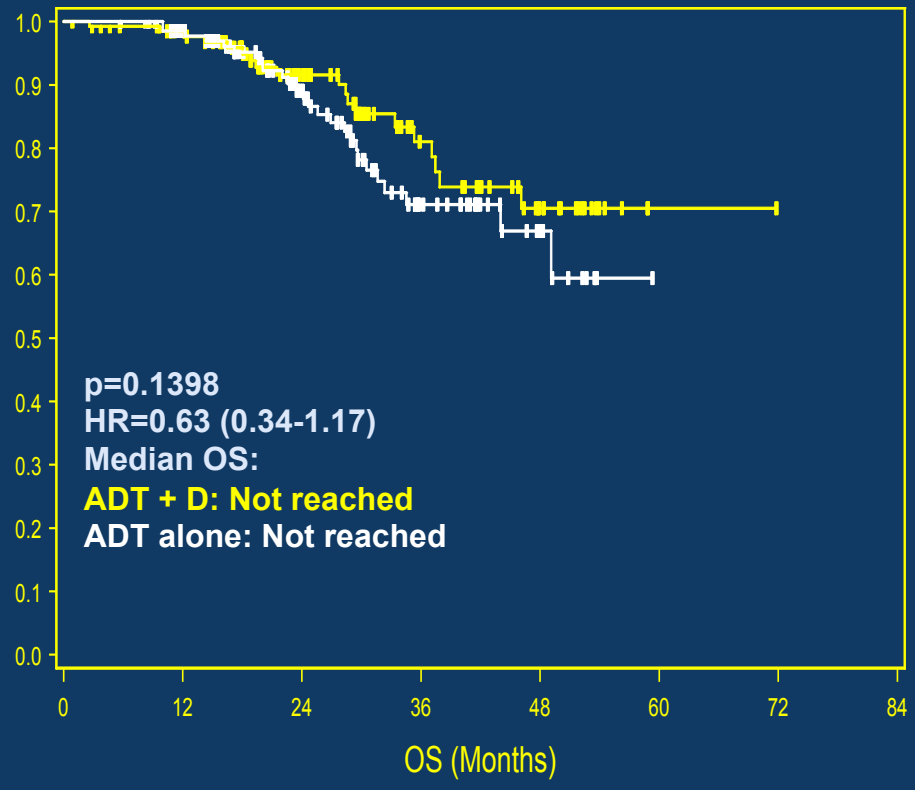
- 790 men accrued 7/28/2006 to 11/21/2012
  - Planned interim analysis at 53% information, Oct 2013 met pre-specified criteria for significance and release of data
  - Jan 16, 2014 median follow-up of 29 months
    - 136 deaths ADT alone vs. 101 deaths ADT+D

OS by extent of metastatic disease at start of ADT

High volume



Low volume



In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months

We projected 33 months in ADT alone arm with collaboration of SWOG9346 team

Presented by: Christopher J. Sweeney, MBBS

Secondary Endpoints

	ADT + Doc (N=397)	ADT alone (N=393)	P-value	Hazard Ratio (95%CI*)
PSA <0.2 ng/mL at 6 months	27.5%	14.0%	<0.0001	
PSA <0.2 ng/mL at 12 months	22.7%	11.7%	<0.0001	
Median time to CRPC - biochemical, symptoms, or radiographic (months)	20.7	14.7	<0.0001	0.56 (0.44, 0.70)
Median time to clinical progression - symptoms or radiographic (months)	32.7	19.8	<0.0001	0.49 (0.37, 0.65)
*CI: confidence intervals				

Therapy beyond progression

	ADT + Docet (N=397) N	ADT alone (N=393) N
Biochem, Sympt, Radiog PD	145	174
Symptom or Radiograph PD	93	133
Docetaxel	49	129
Other Chemotherapy		
Cabazitaxel	43	29
Mitoxantrone &/or Platinum	22	23
Hormonal Therapy		
Abiraterone/Enzalutamide	92	79
Antiandrogen/ketoconazole	87	99
Immunotherapy		
Sipuleucel T	20	18
Radiotherapy	54	67

Presented by: Christopher J. Sweeney, MBBS

Clinical interpretation

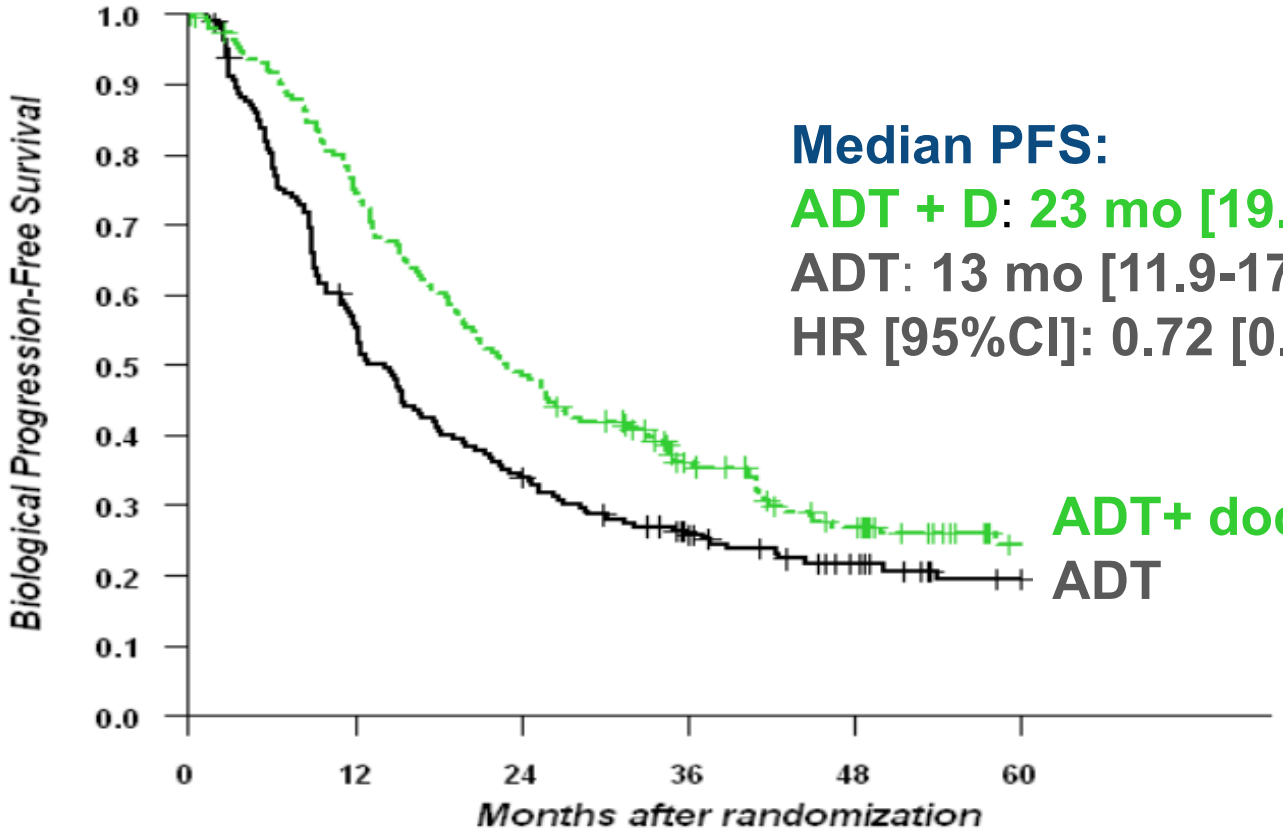
- 6 cycles of docetaxel in addition to ADT represents an appropriate option for men with metastatic prostate cancer commencing ADT who are suitable for docetaxel therapy

- The benefit in patients with a high volume of metastases is clear and justifies the treatment burden
  - longer follow-up is required for patients with low volume metastatic disease

Gravis et al: Androgen Deprivation +/- Docetaxel(D): GETUG-AFU 15

- 385 patients randomized to ADT +/- D (9 cycles); 80% power to detect a HR of 0.62
- Median number of D cycles administered was 8; 48% of D treated patients received 9 cycles
- Neutropenia (21%); febrile neutropenia (3%) neutropenia with infection(1%) were observed in in the ADT + D arm

Biochemical progression free survival



Median PFS:

ADT + D: 23 mo [19.6-28.4]

ADT: 13 mo [11.9-17.7]

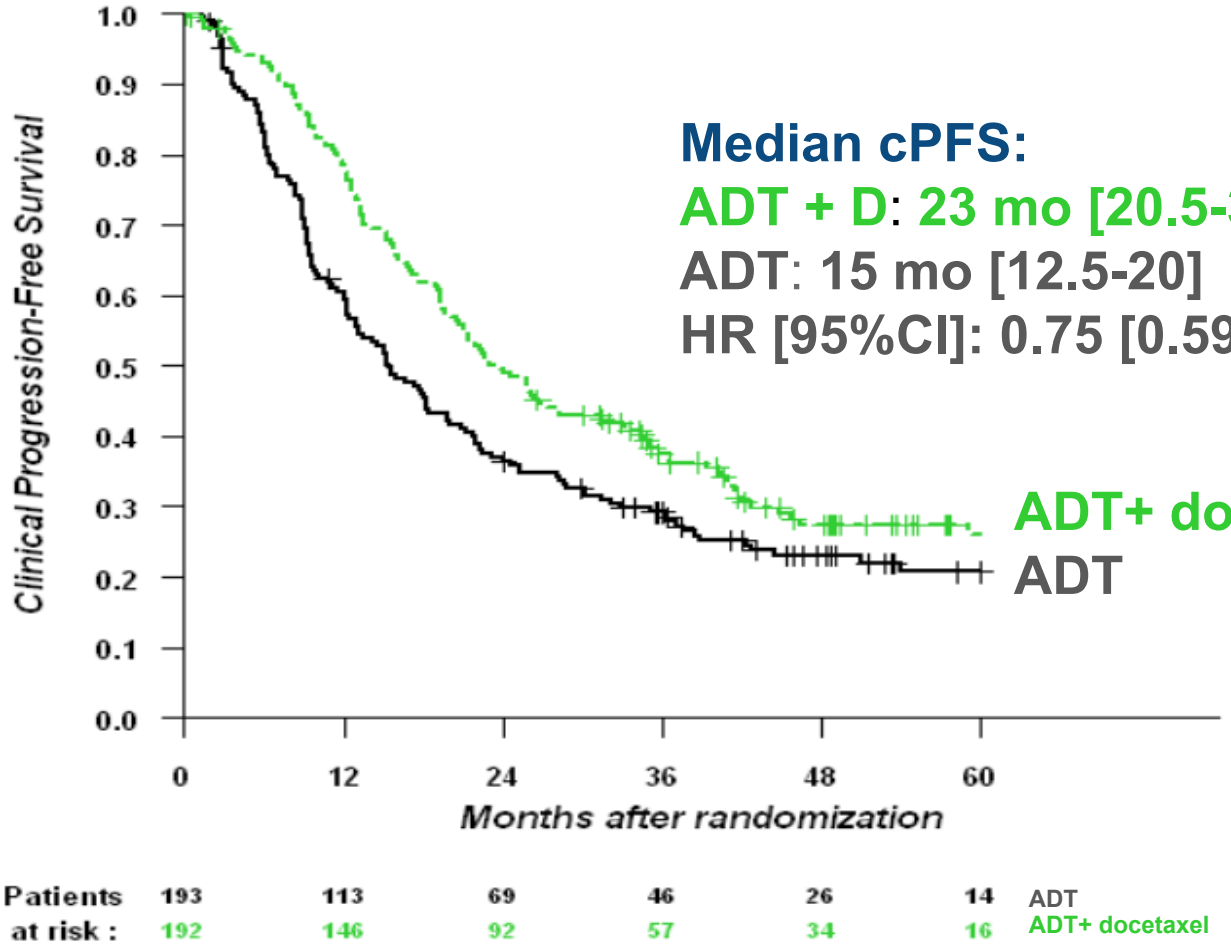
HR [95%CI]: 0.72 [0.57-0.91] p=0.0052

ADT+ docetaxel

ADT

Gravis G, Lancet Oncol 2013

Clinical progression-free survival



Median cPFS:

ADT + D: 23 mo [20.5-32]

ADT: 15 mo [12.5-20]

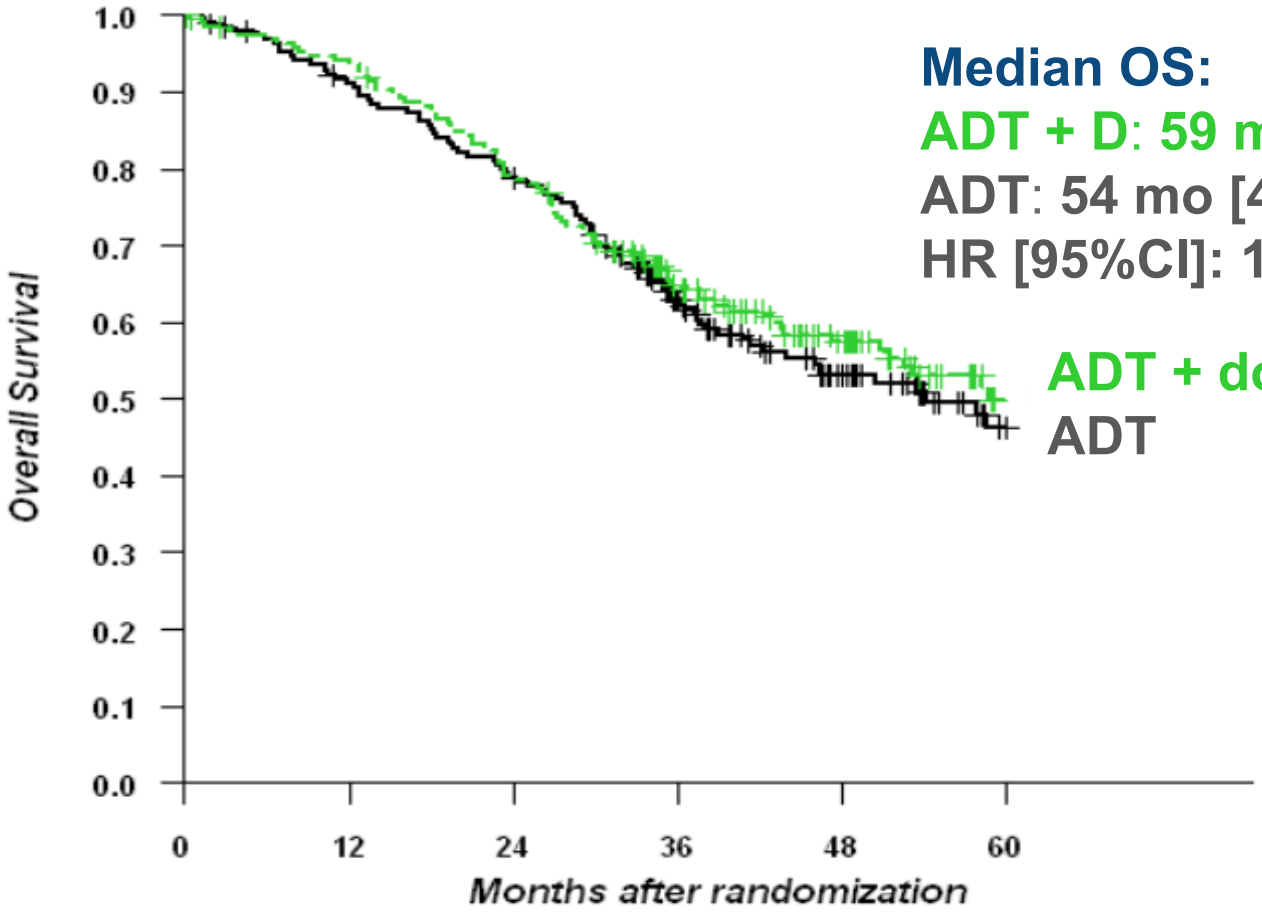
HR [95%CI]: 0.75 [0.59-0.94] p=0.0147

ADT+ docetaxel

ADT

Gravis G, Lancet Oncol 2013

Overall Survival



Median OS:

ADT + D: 59 mo [51-69]

ADT: 54 mo [42-NR]

HR [95%CI]: 1.01 [0.75-1.36] p= 0.95

ADT + docetaxel

ADT

Median follow-up: 50 months [49 - 54]

Gravis G, Lancet Oncol 2013

The GETUG-15-82.9 months of follow-up

	ADT	ADT + D	p-value	Hazard Ratio (95%CI)
Intent to treat Analysis Overall population	**N = 193**	**N = 192**		
Median OS	46.5 [39.1-60.6]	60.9 [46.1-71.4]	0.44	0.9 [0.7-1.2]
Biological PFS	12.9 [11.9-17.7]	22.9 [19.5-28.4]	0.0021	0.7 [0.6-0.9]
High Volume disease * Pts	**N= 91**	**N=92**		
Median OS	35.1 [29.9-44.2]	39 [28-52.6]	0.35	0.8 [0.6-1.2]
Biological PFS	9.2 [8.3-12.2]	15.2 [12-21.2]	0.0039	0.6 [0.5-0.9]
Low Volume disease Pts	**N=102**	**N=100**		
Median OS	NR [61.8-NR]	83.1[69.5-NR]	0.87	1[0.6-1.5]
Biological PFS	22.4 [16.8-37]	40.9 [28.4-62.5]	0.0533	0.7 [0.5-1]

Gravis et al GU ASCO 2015

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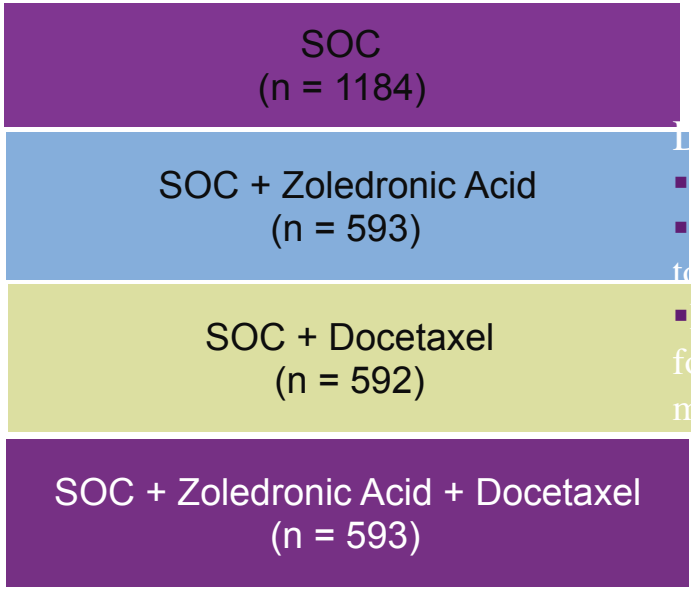
Gravis et al GU ASCO 2015

Why did the European Trial Fail to Show a Survival Benefit?

- Underpowered, half the size of the ECOG trial
- Higher rate of non prostate cancer related deaths.

STAMPEDE: Study Design

- Randomized, controlled, multiarm, multistage trial



- Primary endpoint: OS
- Secondary endpoints: FFS (PSA, local, or lymph node failure; distant metastases; prostate cancer death), toxicity, QoL, skeletal events, cost-effectiveness

James ND, et al. ASCO 2015. Abstract 5001.

STAMPEDE: Significant Improvement in OS, FFS With Docetaxel + SOC vs SOC

Outcome	SOC + Docetaxel (n = 592)	SOC (n = 1184)	*P* Value
Median OS, mos (95% CI)	77 (70-NR)	67 (60-91)	
Deaths, n	165	405	
HR, survival (95% CI)	0.76 (0.63-0.91)		.003
Median FFS, mos (95% CI)	37 (33-42)	21 (18-24)	
FFS events, n	371	750	
HR, FFS (95% CI)	0.62 (0.54-0.70)		$< 1 \times 10^{-9}$

James ND, et al. ASCO 2015. Abstract 5001.g

STAMPEDE: Significant Improvement in OS, FFS With Docetaxel, ZA, SOC vs SOC

Outcome	SOC + ZA + Docetaxel (n = 592)	SOC (n = 1184)	*P* Value
Median OS, mos (95% CI)	72 (63-90)	67 (60-91)	
Deaths, n	181	405	
HR, survival (95% CI)	0.81 (0.68-0.97)		.02
Median FFS, mos (95% CI)	37 (31-42)	21 (18-24)	
FFS events, n	371	750	
HR, FFS (95% CI)	0.62 (0.54-0.71)		$< 1 \times 10^{-9}$

James ND, et al. ASCO 2015. Abstract 5001.

STAMPEDE: No Significant Improvement in OS, FFS With ZA +

Outcome	SOC + Zoledronic Acid (n = 593)	SOC (n = 1184)	*P* Value
Median OS, mos (95% CI)	80 (70-NR)	67 (60-91)	
Deaths, n	197	405	
HR, Survival (95% CI)	0.93 (0.79-1.11)		.44
Median FFS, mos (95% CI)	21 (18-25)	21 (18-24)	
No. of FFS events	371	750	
HR, FFS (95% CI)	0.93 (0.82-1.05)		.26

James ND, et al. ASCO 2015. Abstract 5001.

STAMPEDE: Metastatic Analysis

- Adding docetaxel to SOC showed significant improvement in OS in pts with M1 metastatic status (*P* = .002) but not M0 pts in preplanned analysis

Regimen (+ SOC)	Metastatic Status	Pts, n	OS Events	HR (95% CI)
ZA	M0	686	93	0.96 (0.62-1.48)
	M1	1091	509	0.92 (0.76-1.11)
	Overall	1777	602	0.93 (0.79-1.11)
DOC	M0	689	93	1.01 (0.65-1.56)
	M1	1087	477	0.73 (0.59-0.89)
	Overall	1776	570	0.76 (0.63-0.91)
ZA + DOC	M0	687	91	1.03 (0.66-1.61)
	M1	1090	495	0.78 (0.65-0.95)
	Overall	1777	586	0.81 (0.68-0.97)

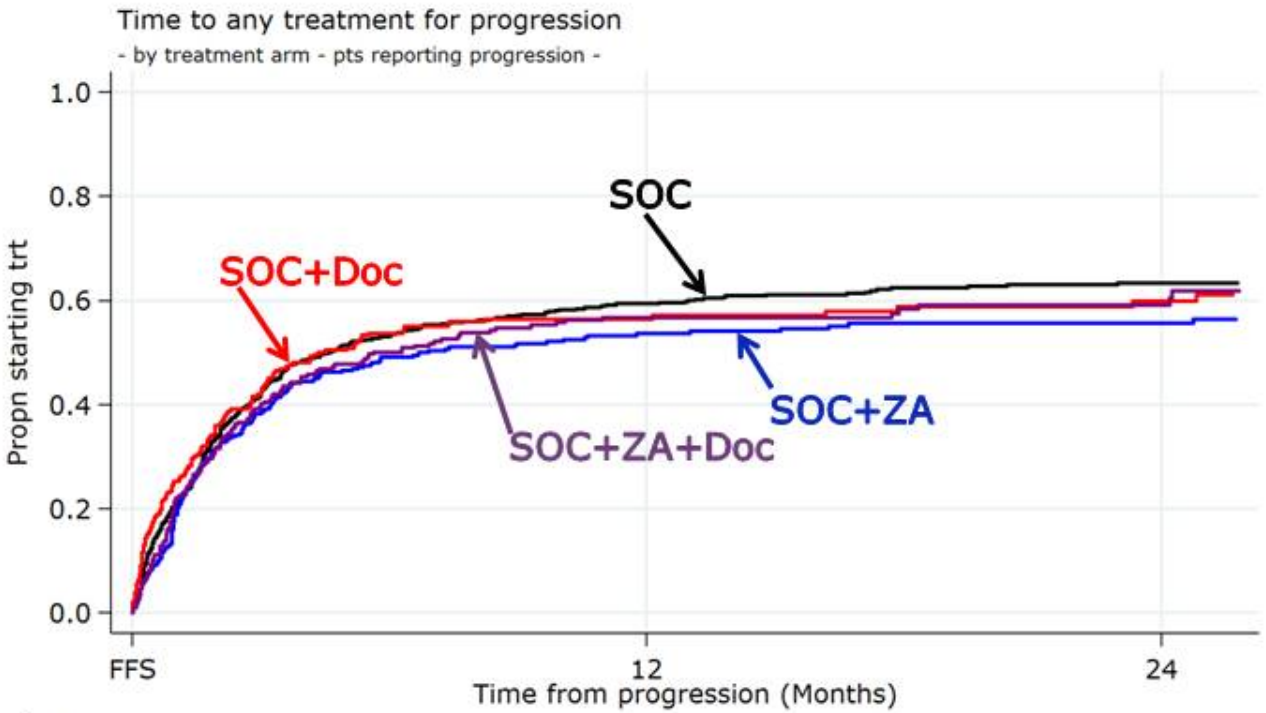
James ND, et al. ASCO 2015. Abstract 5001.

STAMPEDE: Adverse Events

Grade ≥ 3 AEs	SOC (N = 1184)	SOC + ZA (n = 593)	SOC + Docetaxel (n = 592)	SOC + ZA + Docetaxel (n = 593)
Pts with AE data, n	1174	587	579	564
Any grade 3-5 AE, n (%)	363 (31)	185 (31)	291 (51)	294 (52)
Grade 5 AEs, n	3	1	3	7
Endocrine disorder, %	12	12	10	12
Febrile neutropenia, %	1	2	12	12
Neutropenia, %	1	1	12	11
Musculoskeletal disorders, %	5	5	6	8
Gastrointestinal disorders, %	3	3	7	7
Renal disorders	5	4	4	6
Grade ≥ 3 AEs at 1 yr, %	9.7	10.6	10.1	11.3

James ND, et al. ASCO 2015. Abstract 5001.

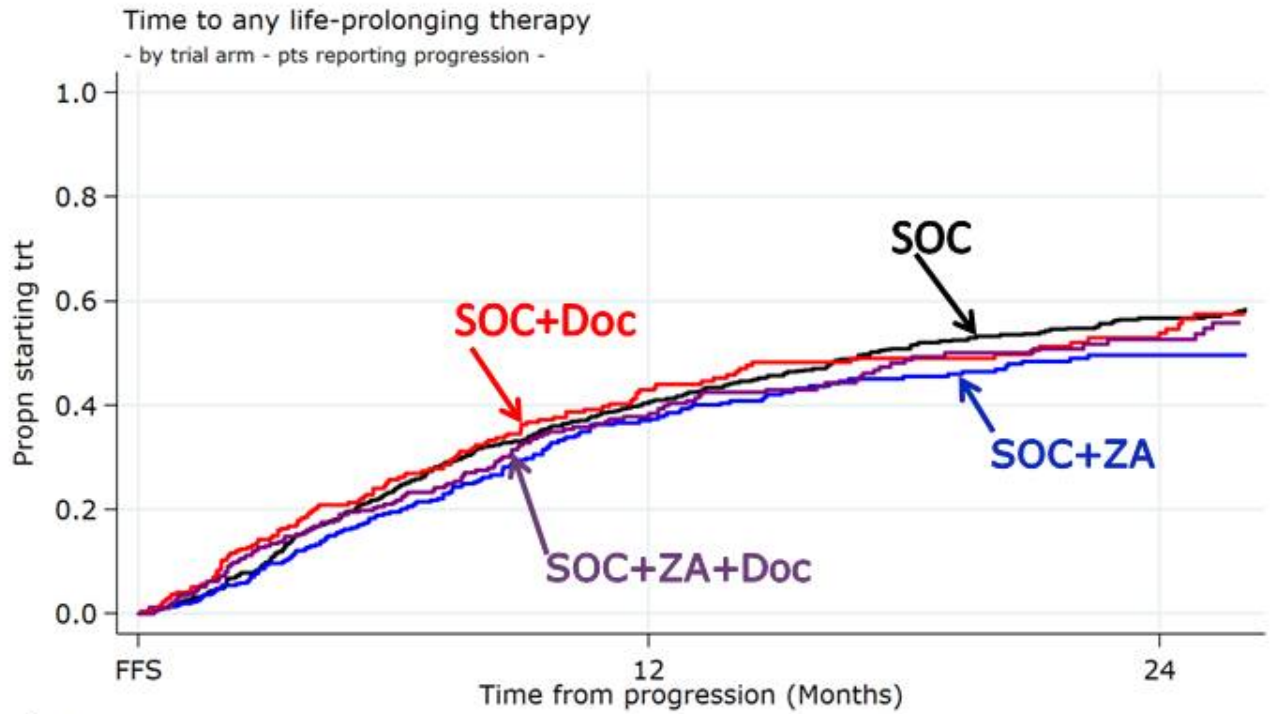
Time to first treatment for failure-free survival event



Group At risk (events)					
SOC	750	(420)	200	(16)	95
SOC+ZA	371	(185)	113	(4)	57
SOC+Doc	311	(159)	67	(4)	35
SOC+ZA+Doc	314	(157)	80	(3)	30

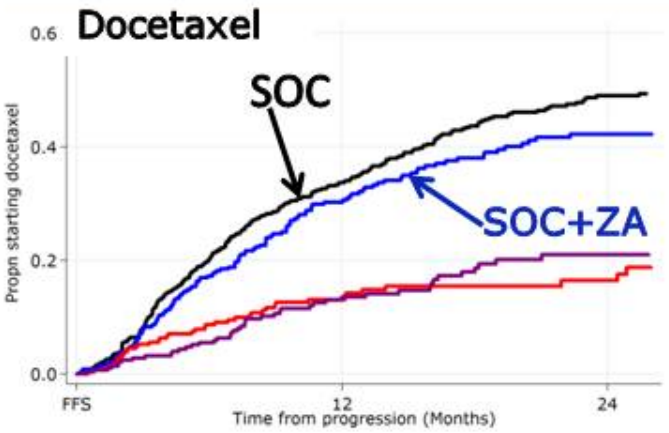
*treatment for progression given at the investigator's discretion

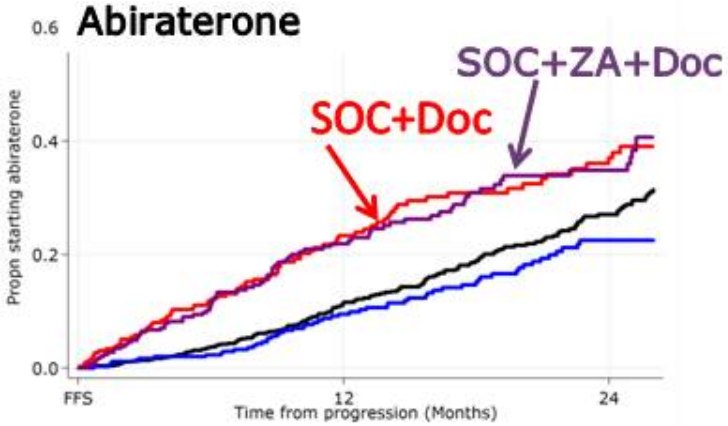
Time to first "life-prolonging therapy" for progression



Group At risk (events)					
SOC	750	(271)	327	(74)	143
SOC+ZA	371	(120)	172	(29)	81
SOC+Doc	311	(109)	105	(16)	53
SOC+ZA+Doc	314	(98)	123	(23)	46

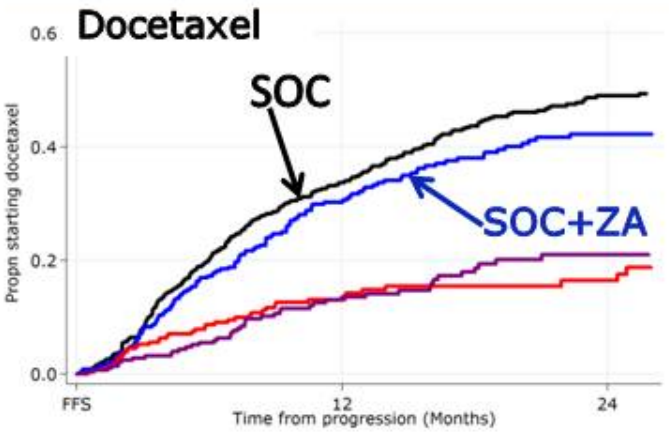
Use of "life-prolonging therapy" for progression

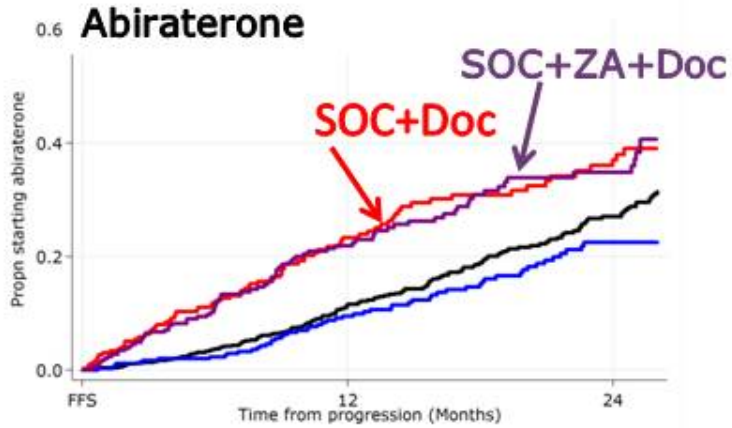




	A *SOC*	B *SOC+ZA*	C *SOC+Doc*	E *SOC+ZA+Doc*
Pts with FFS event (n)	750	371	311	314
Life-prolonging therapy reported ever (n)	372	168	135	130
Docetaxel (%)	41%	36%	14%	15%
Abiraterone (%)	23%	19%	28%	27%
Enzalutamide (%)	7%	4%	7%	7%
Cabazitaxel (%)	3%	3%	6%	9%
Radium-223 (%)	0%	0%	1%	1%

Use of "life-prolonging therapy" for progression





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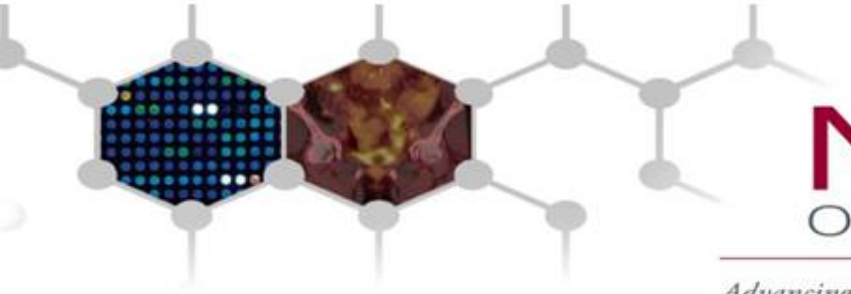

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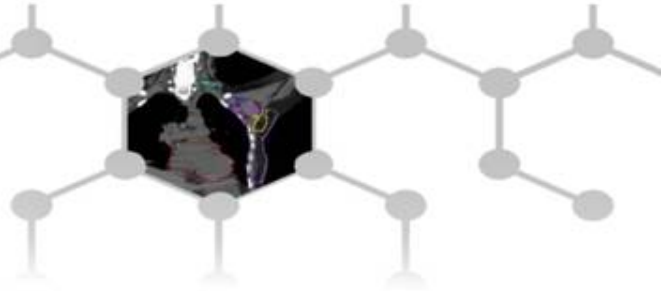

A phase III protocol of androgen suppression and radiotherapy vs AS and RT followed by chemotherapy with docetaxel and prednisone for localized, high-risk prostate cancer (NRG Oncology/RTOG 0521)

Howard Sandler, Chen Hu, Seth Rosenthal, Oliver Sartor, Leonard Gomella, Mahul Amin, James Purdy, Jeff Michalski, Mark Garzotto (SWOG), Nadeem Pervez, Alexander Balogh, George Rodrigues, Luis Souhami, Neil Reaume, Scott Williams, Raquibul Hannan, Eric Horwitz, Adam Raben, Rebecca Paulus, William Shipley

2015 ASCO Annual Meeting May 31, 2015

RTOG 0521

High Risk

Stage	Gleason score	PSA
Any T stage	≥9	<150
	7-8	≥20-150
≥T2	8	<20

Randomize

Arm 1

Androgen Suppression (24 mos)
+
External RT (8 wks)

Arm 2

Androgen Suppression (24 mos)
+
External RT (8 wks)
+
Docetaxel beginning 4 wks after RT (6 cycles)

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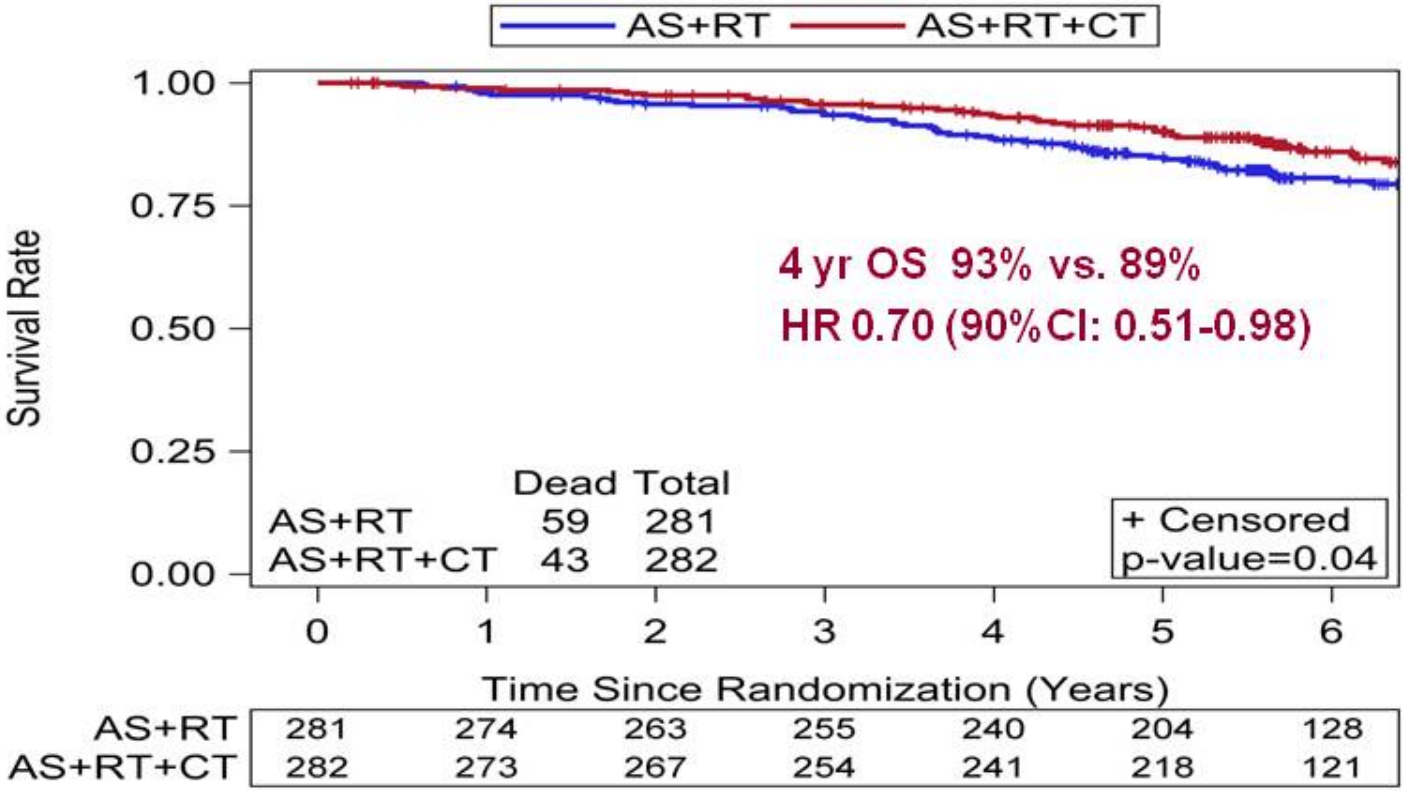
Overall Survival



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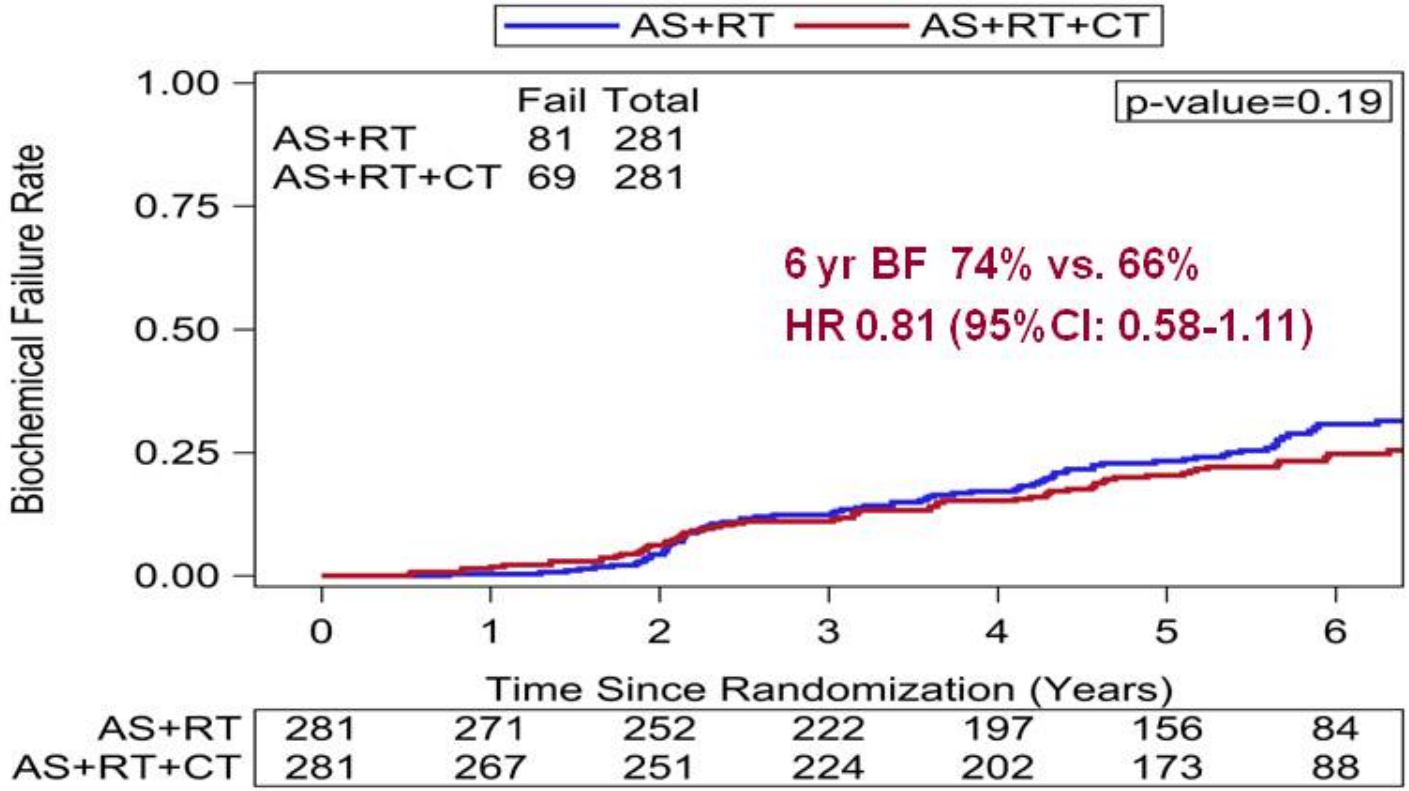
Biochemical Failure



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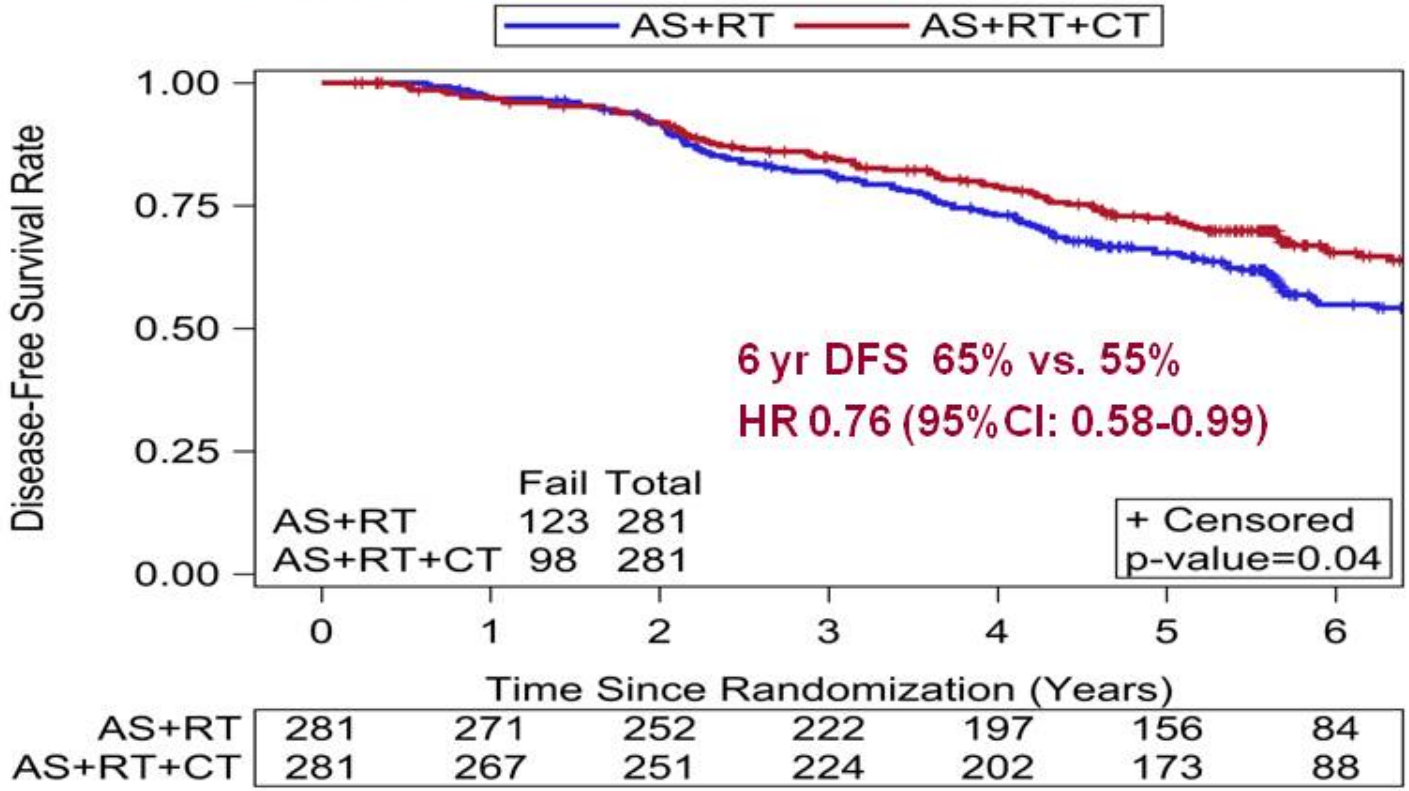
Disease-Free Survival



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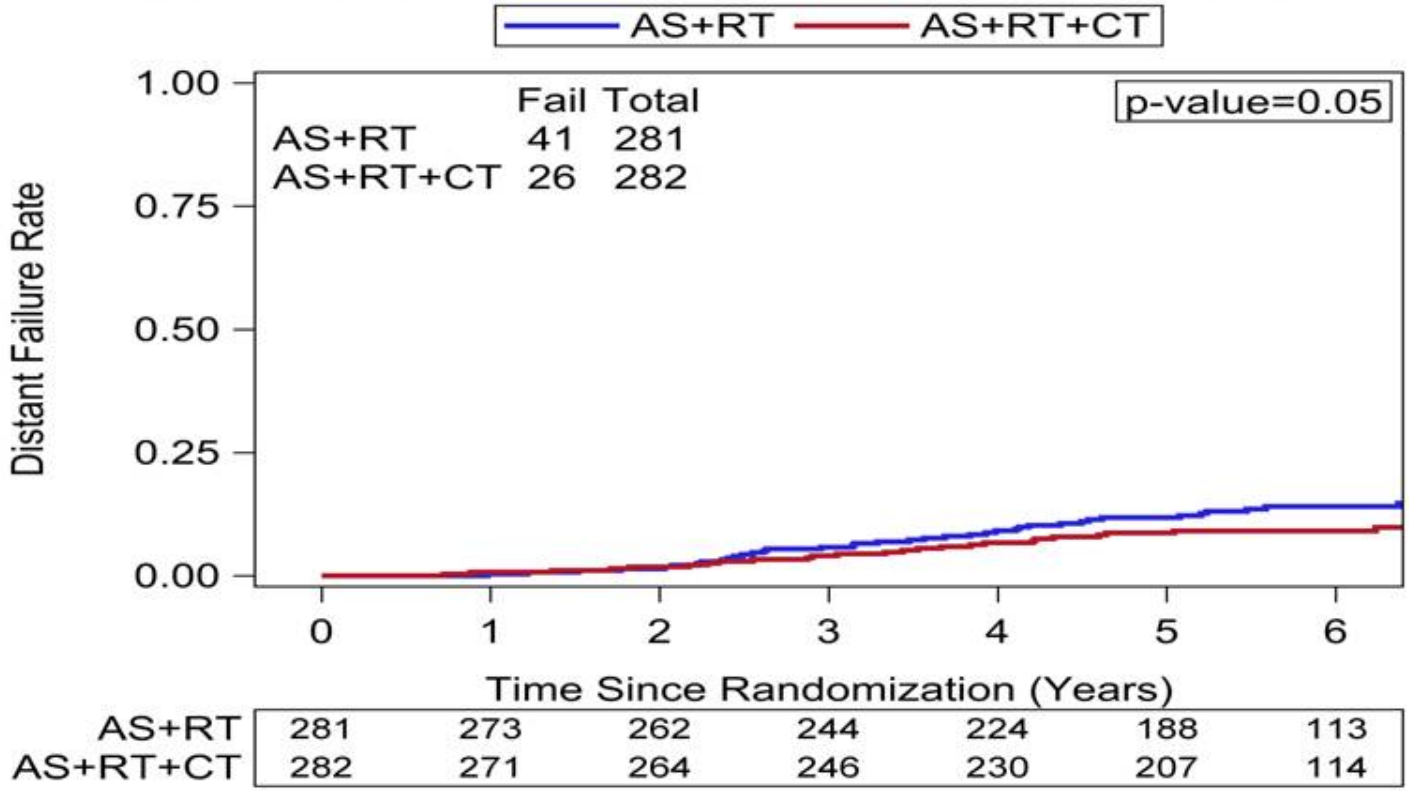
Distant Metastasis at Any Time



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Cause of Death*

	AS+RT (n=59)	AS+RT+CT (n=43)
Death due to cancer under study	23	16
Death due to protocol treatment	0	2
Death due to other cause	24	16
Death due to second primary	12	5
Unknown cause of death	0	4

***Based on central review blinded to treatment arm**

NRG ONCOLOGY™

Phase III Study of Adjuvant Chemotherapy in High-Risk Prostate Cancer: SWOG 9921

T3b, T4 or N1 or
Gleason $\geq$ 8, or
T3a, + margin, and
Gleason 7

RANDOMIZE

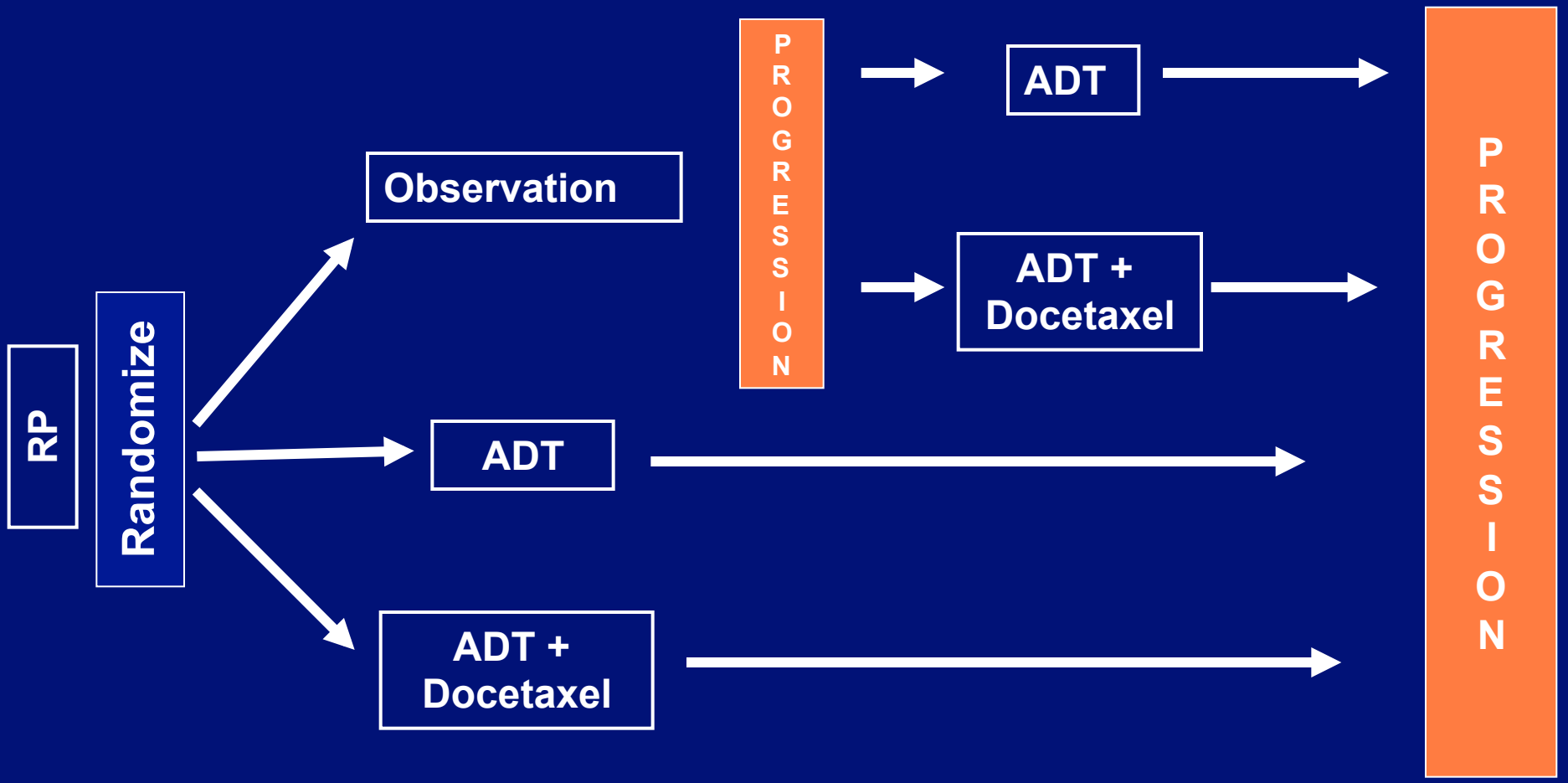
→ CAB X 24 months

→ mitoxantrone 12 mg/m^2 d1
+ prednisone 5 mg BID d1-21
Q 3 Weeks X 6 and
CAB x 24 months

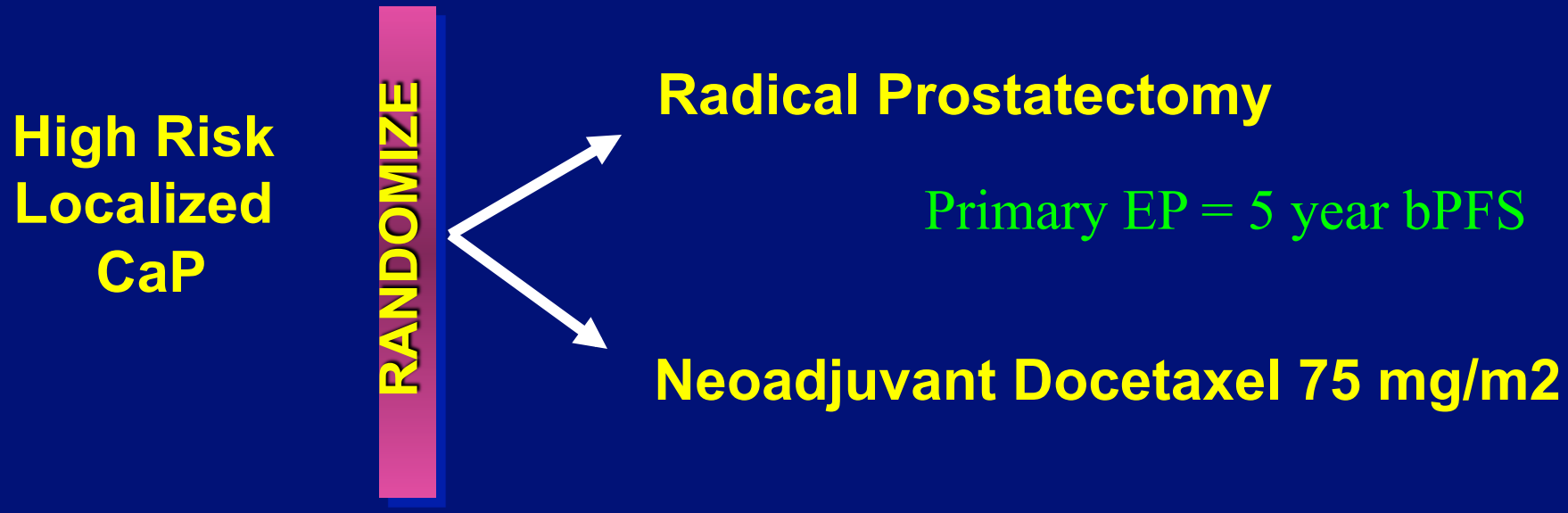
n =1360
(to detect a 30% survival difference)

Closed to Accrual due to toxicity

TAX3501


RP
Randomize
Observation
ADT
ADT + Docetaxel
PROGRESSION
ADT
ADT + Docetaxel
PROGRESSION

CALGB 90203: Phase III Study of Radical Prostatectomy alone vs. Docetaxel in High Risk Localized Prostate Cancer



*Activated

Why?

- ARV7 clones respond to docetaxel
- Biologically different
- More patients are seeing treatment with docetaxel overall

Conclusions

- Androgen blockade + docetaxel is standard of care for first line metastatic prostate cancer
- Unlikely that subsequent therapy significantly impacted outcome, more that 50% of the control patients received effective cytotoxic therapy
- Confirmation was not seen in the European study due to trial design but was seen in STAMPEDE