MADRID 2014 ESMO congress

E3805: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED)

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A Quick Review of the History of Hormone Sensitive Metastatic Prostate Cancer

- Most patients respond to androgen deprivation therapy (ADT)
  - **1940s testosterone suppression (TS) resulted in prostate cancer regression[1]**
    - Survival benefit of TS vs no therapy is not well documented
    - Improvements over time due to stage migration in PSA era[2]
  - **Patients with higher burden of metastatic disease have shorter survival**
    - Presence of visceral metastases or bone involvement beyond axial skeleton is associated with a poorer outcome[3,4]
  - **Improvements in OS with metastatic castration resistant prostate cancer**
    - Docetaxel first agent to confer an OS benefit (~2 month increase)[5,6]

[1]Huggins and Hodges *Cancer Res*, 1941; [2]Tangen et al *J Urol*, 2012; [3]Millikan et al *J Clin Oncol*, 2008; [4]Eisenberger et al *NEJM*, 1998; [5]Tannock et al *NEJM*, 2004; [6]Petrylak et al *NEJM*, 2004.

Different Definitions of High Volume Disease

- **SWOG: S8894: *NEJM* 1998: Orchiectomy +/- Flutamide**[1]

  Extensive disease: included appendicular skeletal involvement (with or without axial skeletal involvement), visceral (lung or liver) metastasis or both

  Median OS = 27 months

- **MDACC: *J Clin Oncol* 2008; ADT +/KAVE**[2]

  High volume: 3 or more bone mets and / or visceral mets

  Median OS = 37 months

[1]Eisenberger et al *NEJM*, 1998;

[2]Millikan et al *J Clin Oncol*, 2008.

E3805 Definition of High Volume

- **High volume:**
  - visceral metastases

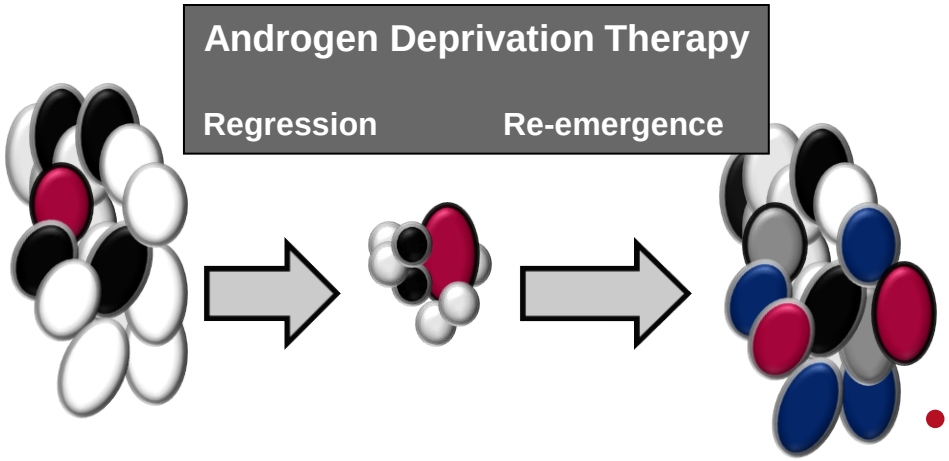
  and/or
  - 4 or more bone metastases with at least 1 beyond pelvis and vertebral column

- At inception, only patients with high volume disease were to be accrued

E3805 Definition of High Volume

- The E3805 definition of high volume disease amalgamated prior classifications
  - All definitions: non-nodal soft tissue visceral disease as a poor risk feature
  - E3805 made use of **sites of** metastases and **number of** metastases
  - Minimize misclassifying patients
    - with oligometastatic disease (3 or less) even if one lesion was beyond vertebrae and pelvis
    - Degenerative changes in spine / pelvic read as cancer and falsely increase number of mets

Early Chemo+ADT: A debate in one slide – a need for a randomized phase 3 trial

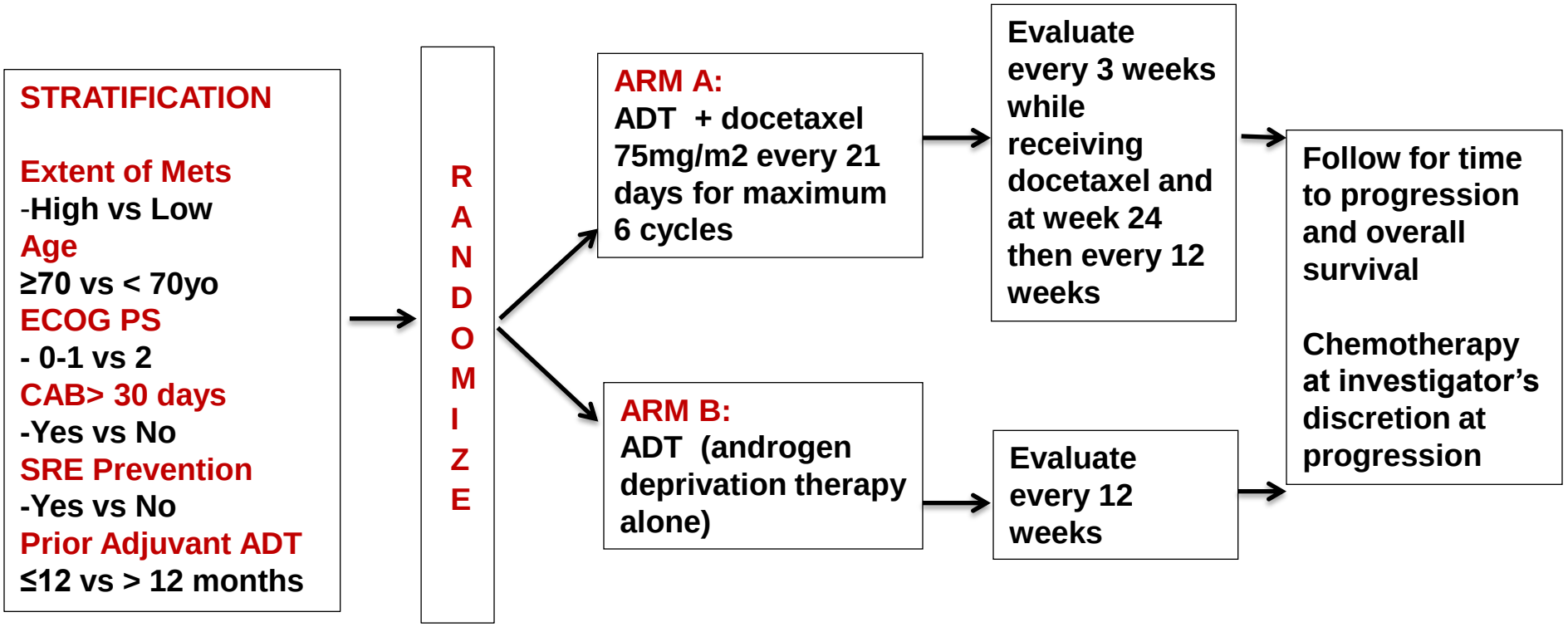


- **Pro**
  - Attack de-novo testosterone independent clones early - allow ADT to keep PrCa in remission longer
  - Some patients at the time of progression are too frail for chemo
- **Con**
  - ADT will take cells out of cycle and be less responsive to cytotoxics
  - Some patients respond for a long time and never need chemo

The CHAARTED Hypothesis

- Docetaxel added at the time of starting androgen deprivation therapy for hormone naïve metastatic prostate cancer will prolong overall survival

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

Study Endpoints

- **Primary Endpoint**
  - Overall survival
- **Secondary Endpoints**
  - Rate of PSA < 0.2 ng/mL at 6 months and 12 months
  - Time to biochemical, radiographic or symptomatic PD
  - Time to radiographic or symptomatic progressive disease (PD)
  - Define adverse event profile and tolerability
  - Quality of life (FACT-P) until 12 months after randomization

Statistical Design: History of CHAARTED

Intent to treat analysis, 80% power 1-sided alpha=2.5% to detect 33% improvement in median OS (with all versions)

	Original Design High volume only	First Revision Allow low volume	Final Design Adjustment of projected OS based on new data (SWOG 9346)
Sample size	568	600	780
Median OS High volume, ADT	24 months	24 months	**33 months** (44 months in C-HT)
Median OS Low volume, ADT	Not enrolled	48 months	67 months (89 months in C-HT)
% with high volume	100% (projected)	50% (projected)	**70% (projected)**

High volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column)

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
  - **514 patients with high volume disease**
  - Jan 16, 2014 median follow-up of 29 months
    - 136 deaths ADT alone vs. 101 deaths ADT+D
    - **110 deaths in 251 HV patients of ADT alone**
    - **82 deaths in 263 HV patients of ADT + docetaxel**

Patient Characteristics: High Volume

	ADT + Docetaxel (N=263)		ADT Alone (N=251)	
	N	%	N	%
Age (year)				
Median	64		63	
Range	42-88		39-91	
Race				
White	224	87.5%	207	87.0%
Other	32	12.5%	31	13.0%
Unknown	7		13	
ECOG PS				
0	169	64.5%	154	61.6%
1	88	33.6%	91	36.4%
2	5	1.9%	5	2.0%
Unknown	1		1	

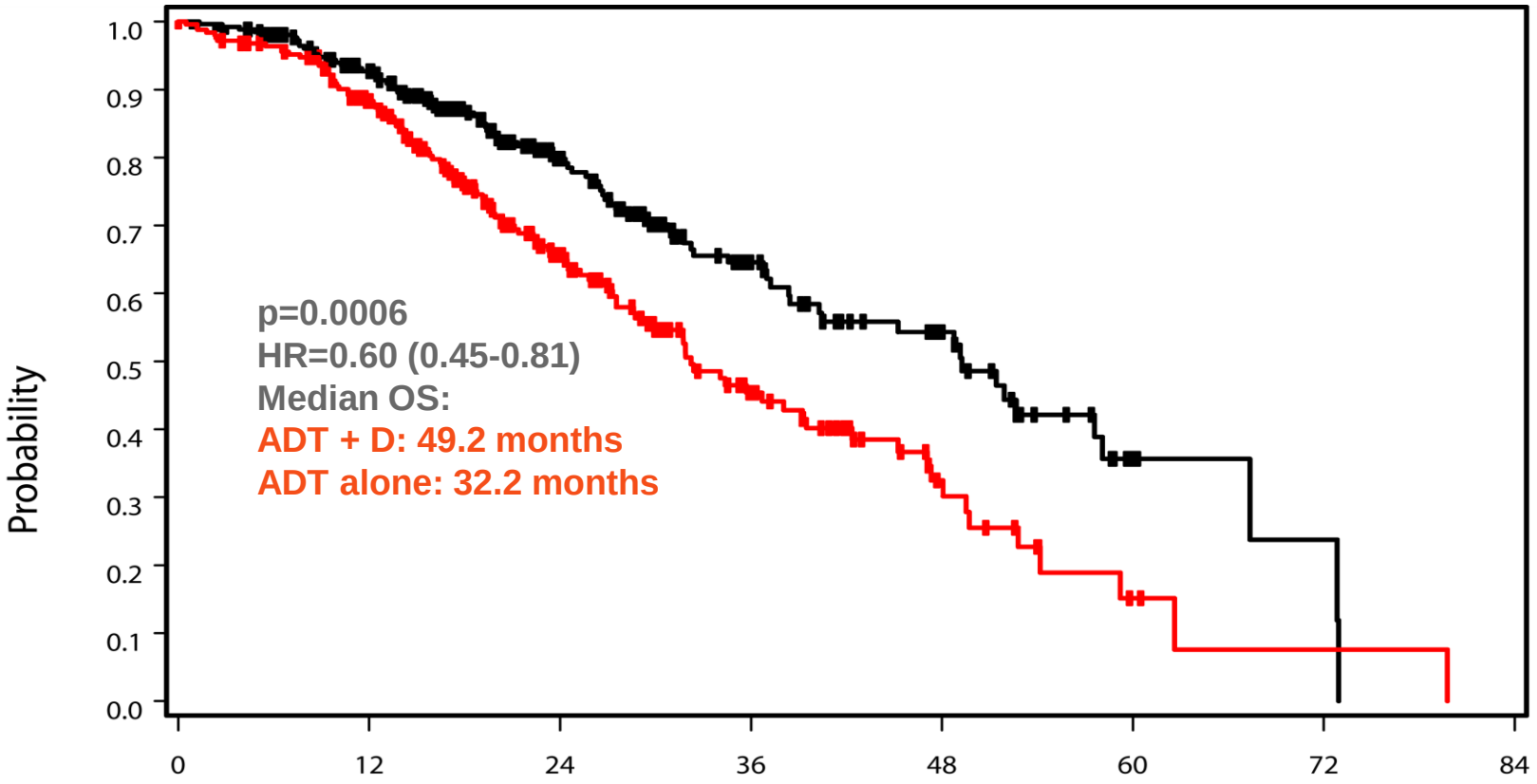
Patient Characteristics: High Volume

	ADT + Docetaxel (N=263)		ADT Alone (N=251)	
	N	%	N	%
Gleason Score				
4-6	12	5.1%	12	5.8%
7	53	22.6%	39	18.8%
8-10	169	72.2%	157	75.5%
Unknown	29		43	
PSA (ng/mL) at Time of ADT Start				
Median	96.1		100.0	
Range	0.4-8540.1		0.3-8056.0	

Patient Characteristics: High Volume

	ADT + Docetaxel (N=263)		ADT Alone (N=251)	
	N	%	N	%
Prior Treatment				
No localized Rx	212	80.6%	209	83.6%
Primary radiation	12	4.6%	13	5.2%
Prostatectomy	39	14.8%	28	11.2%
Missing			1	
Adjuvant ADT	10	3.8%	6	2.4%
Median time from start ADT to randomization				
Months (range)	1.2 (0.03-3.9)		1.2 (0.03-3.9)	
No ADT prior to randomization	30	11.4%	30	12.0%

OS for Patients with High Volume Metastatic Disease at Start of ADT



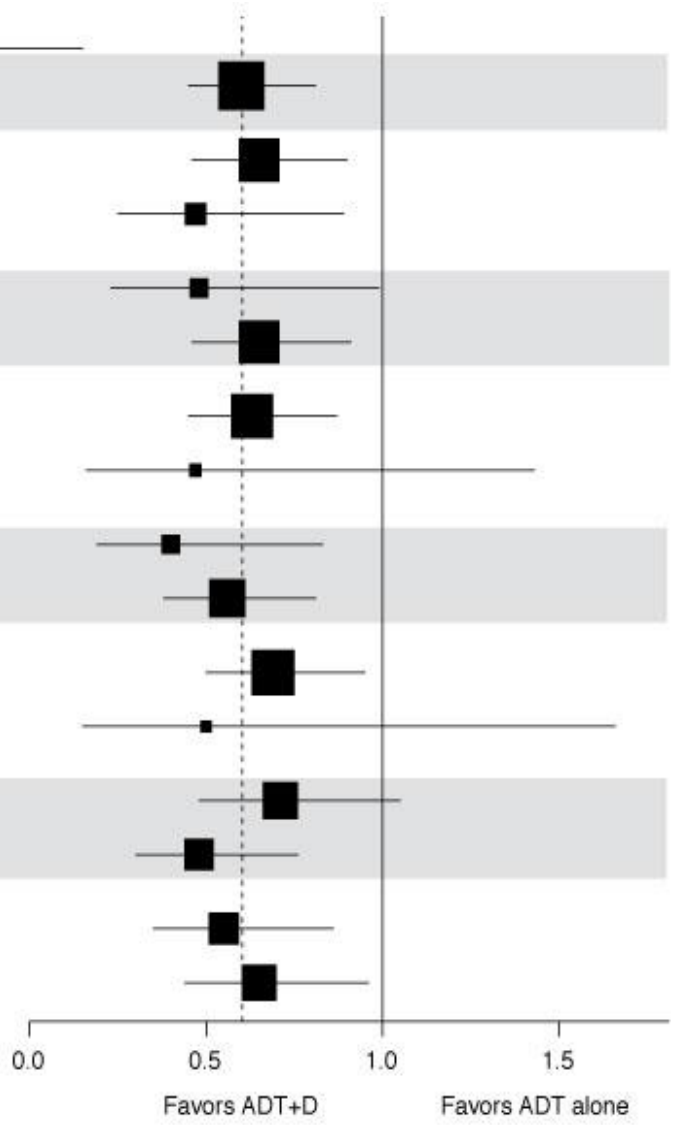
In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months. We projected 33 months in ADT alone arm with collaboration of SWOG 9346 team.

Causes of Death: High volume

	ADT + Docetaxel (N=263)		ADT Alone (N=251)	
	N	%	N	%
Due to prostate cancer	69	84.2	92	84.4
Due to protocol Rx	1	1.2	0	0.0
Other cause	6	7.3	9	8.3
Unknown	6	7.3	8	7.3
Missing	0		1	
Total	82		110	

ADT + docetaxel benefited all subgroups with high volume disease

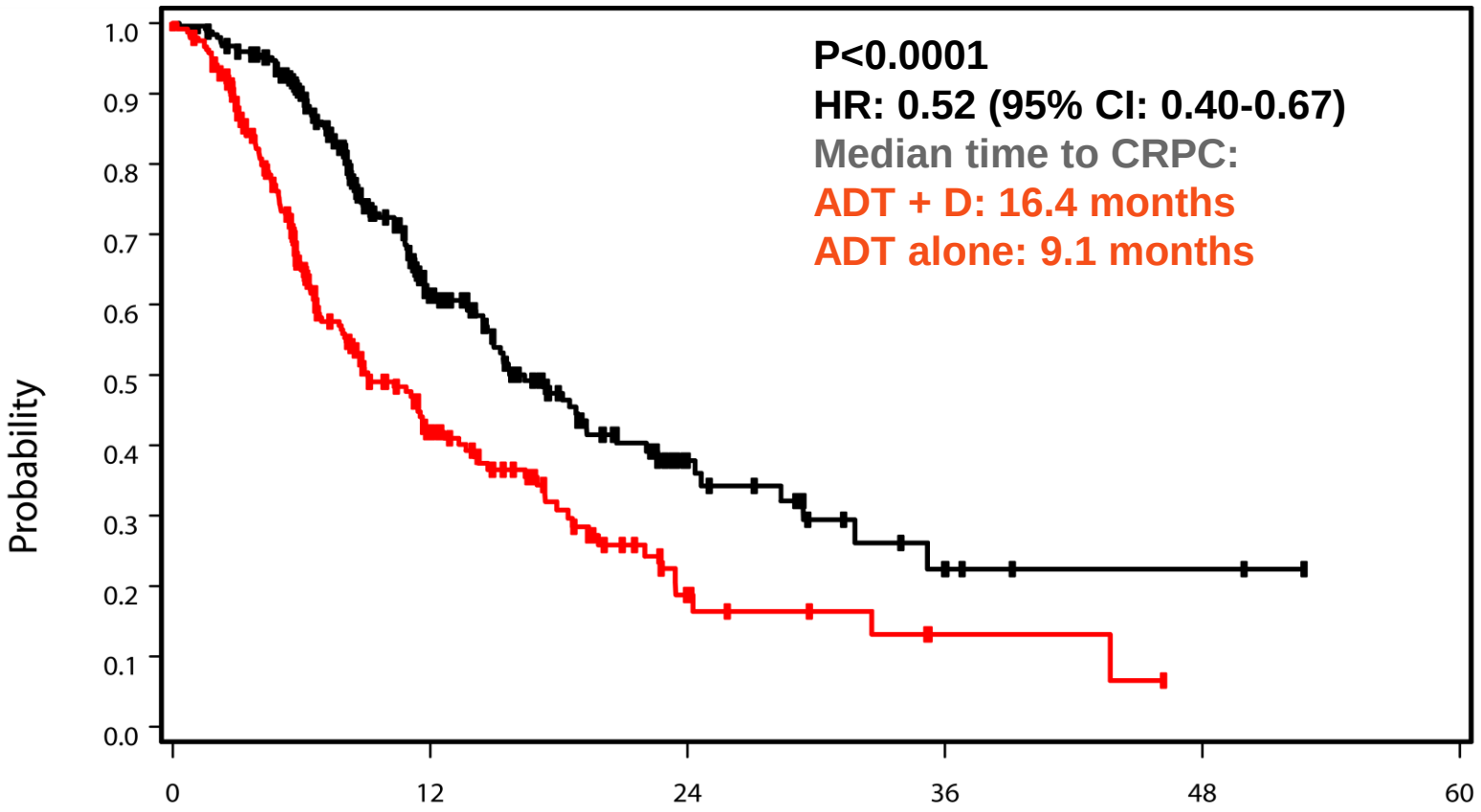
Group	N	HR	95% CI
High Volume Disease Patients	514	0.60	(0.45, 0.81)
Age <70	398	0.65	(0.46, 0.90)
Age >=70	116	0.47	(0.25, 0.89)
Visc Mets +/– Bone Mets (BM)	125	0.48	(0.23, 0.99)
High Volume (BM only)	387	0.65	(0.46, 0.91)
Race – White	431	0.63	(0.45, 0.87)
Race – Other	63	0.47	(0.16, 1.43)
Gleason Score <8	116	0.40	(0.19, 0.83)
Gleason Score >=8	326	0.56	(0.38, 0.81)
Prior Local Therapy – No	421	0.69	(0.50, 0.95)
Prior Local Therapy – Yes	92	0.50	(0.15, 1.66)
CAB >30 Days – No	295	0.71	(0.48, 1.05)
CAB >30 Days – Yes	219	0.48	(0.30, 0.76)
SRE – No	231	0.55	(0.35, 0.86)
SRE – Yes	283	0.65	(0.44, 0.96)



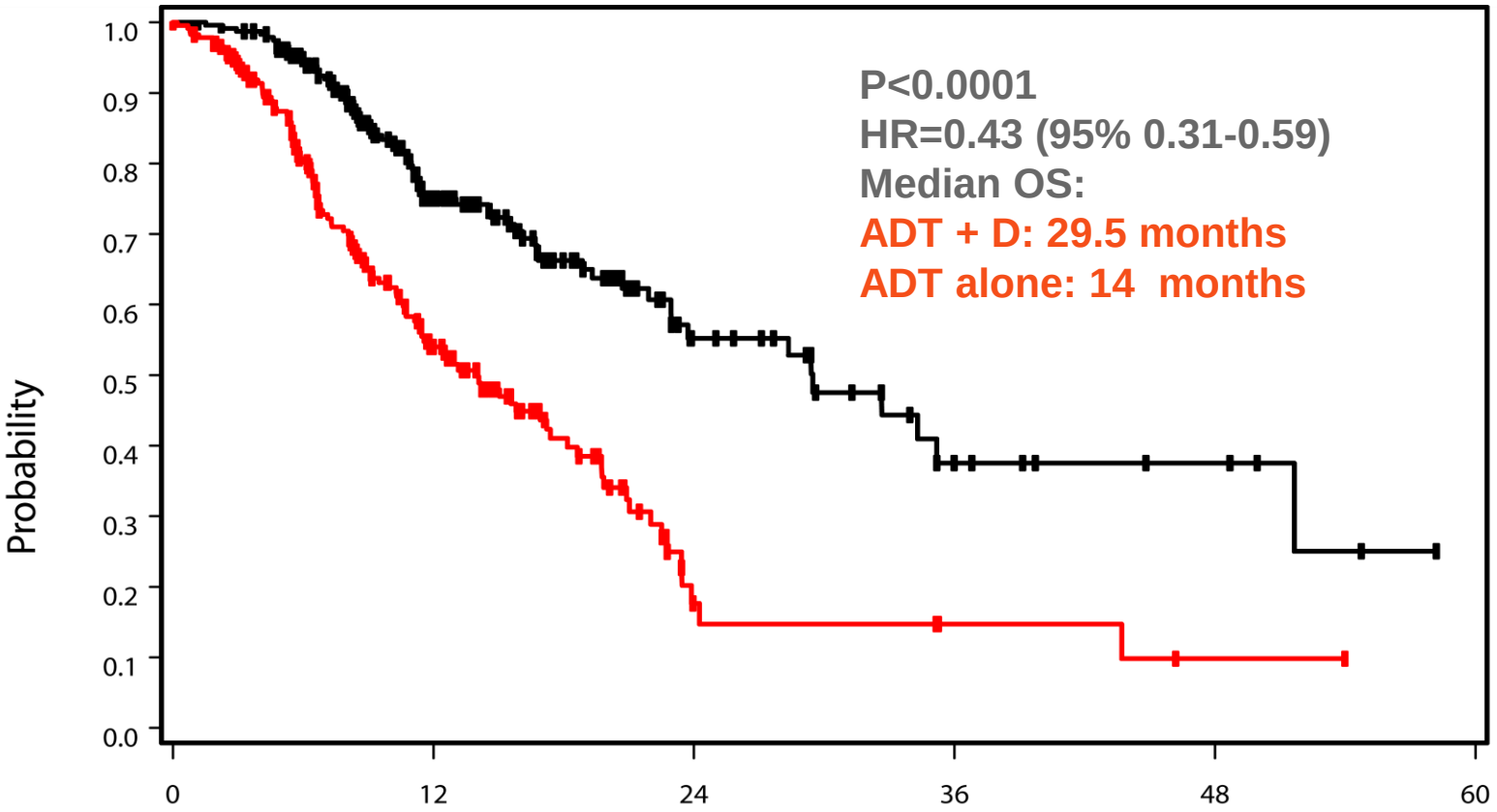
Secondary Endpoints

	ADT + Docetaxel (N=263)	ADT Alone (N=251)	P-value	Hazard Ratio (95%CI*)
PSA <0.2 ng/mL at 6 months	20.5%	6.4%	<.0001	
PSA <0.2 ng/mL at 12 months	16.0%	5.2%	<.0001	
Median time to CRPC - Biochemical, symptoms, or radiographic (months)	16.4	9.1	<.0001	0.52 (0.40-0.67)
Median time to clinical progression - Symptoms or radiographic (months)	29.5	14.0	<.0001	0.43 (0.31-0.59)
*CI: confidence intervals				

Time to castration resistant prostate cancer: PSA, symptoms or radiograph



Time to Clinical Progression - symptomatic or radiographic



Clinical evaluation every 3 months until progression, scans as indicated

Therapy Beyond Progression

	ADT + Docetaxel (N=263)	ADT Alone (N=251)
Biochem, sympt, radiog PD	113	136
Symptom or radiograph PD	70	111
Docetaxel	42	102
Other chemotherapy		
Cabazitaxel	33	23
Mitoxantrone and/or platinum	16	20
Hormonal therapy		
Abiraterone/enzalutamide	69	53#
Antiandrogen/ketoconazole	68	68
Immunotherapy		
Sipuleucel T	14	7
Radiotherapy	40	56

#or placebo in 1 pt

Chemotherapy Doses Given

	ADT + Docetaxel (N=263)	
	Arm A	
Number of cycles	N	%
1	5	2.2
2	6	2.6
3	4	1.7
4	6	2.6
5	8	3.5
6	201	87.4
Total	230	

73% with no dose modifications

* Missing data on 33 pts due to form change (22 pts), never started Rx (4 pts), data missing (7 pts)

Non-Hematologic Toxicity (%)

	ADT + Docetaxel (N=263)		
Grade	**3**	**4**	**5**
Allergic reaction	**2**	-	-
Fatigue	**4**	-	-
Colitis/diarrhea	**1**	-	-
Stomatitis	**1**	-	-
Neuropathy-motor	**1**	-	-
Neuropathy-sensory	**1**	-	-
Thrombo-embolism	-	**1**	-
Sudden death	-	-	-

Hematologic Toxicity (%)

	ADT + Docetaxel (N=263)		
Grade	**3**	**4**	**5**
Anemia	**1**	**<1**	**-**
Thrombocytopenia	**-**	**<1**	
Neutropenia	**4**	**8**	**-**
Febrile neutropenia	**4**	**2**	**-**
Infection with neutropenia	**1**	**<1**	**-**
Worst grade heme and non-heme toxicity per patient	**17**	**11**	**-**

QOL FACT-P to be presented at another time to better define treatment burden

The CHAARTED Conclusion

- The combination of standard ADT and 6 cycles of docetaxel significantly improved overall survival compared to standard ADT alone in men with high volume hormone sensitive prostate cancer

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 and have high volume disease

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