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Management of mHSPC

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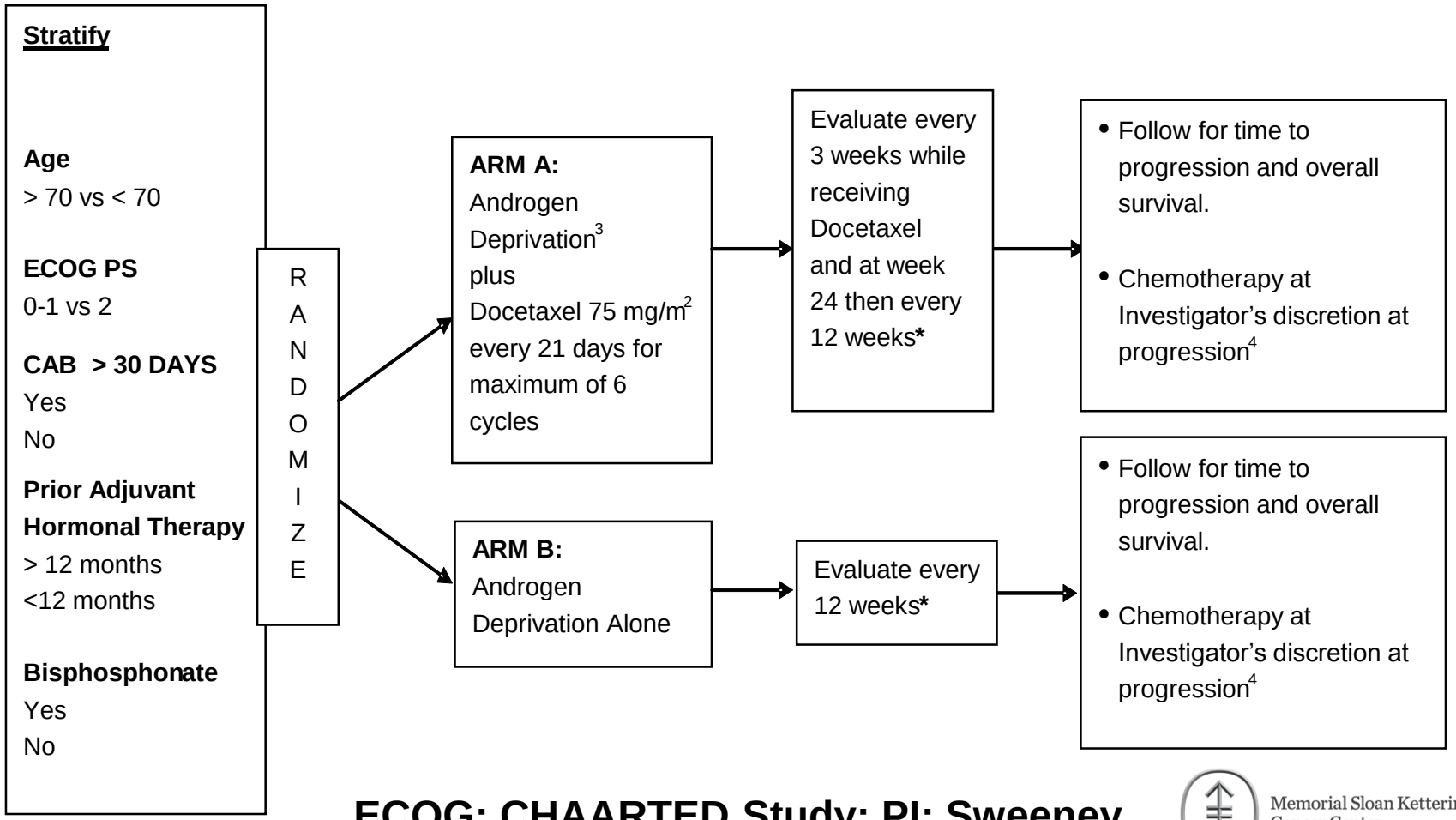
Management of mHSPC-Docetaxel

Metastatic HSPC: CHAARTED



ECOG: CHAARTED Study; PI: Sweeney

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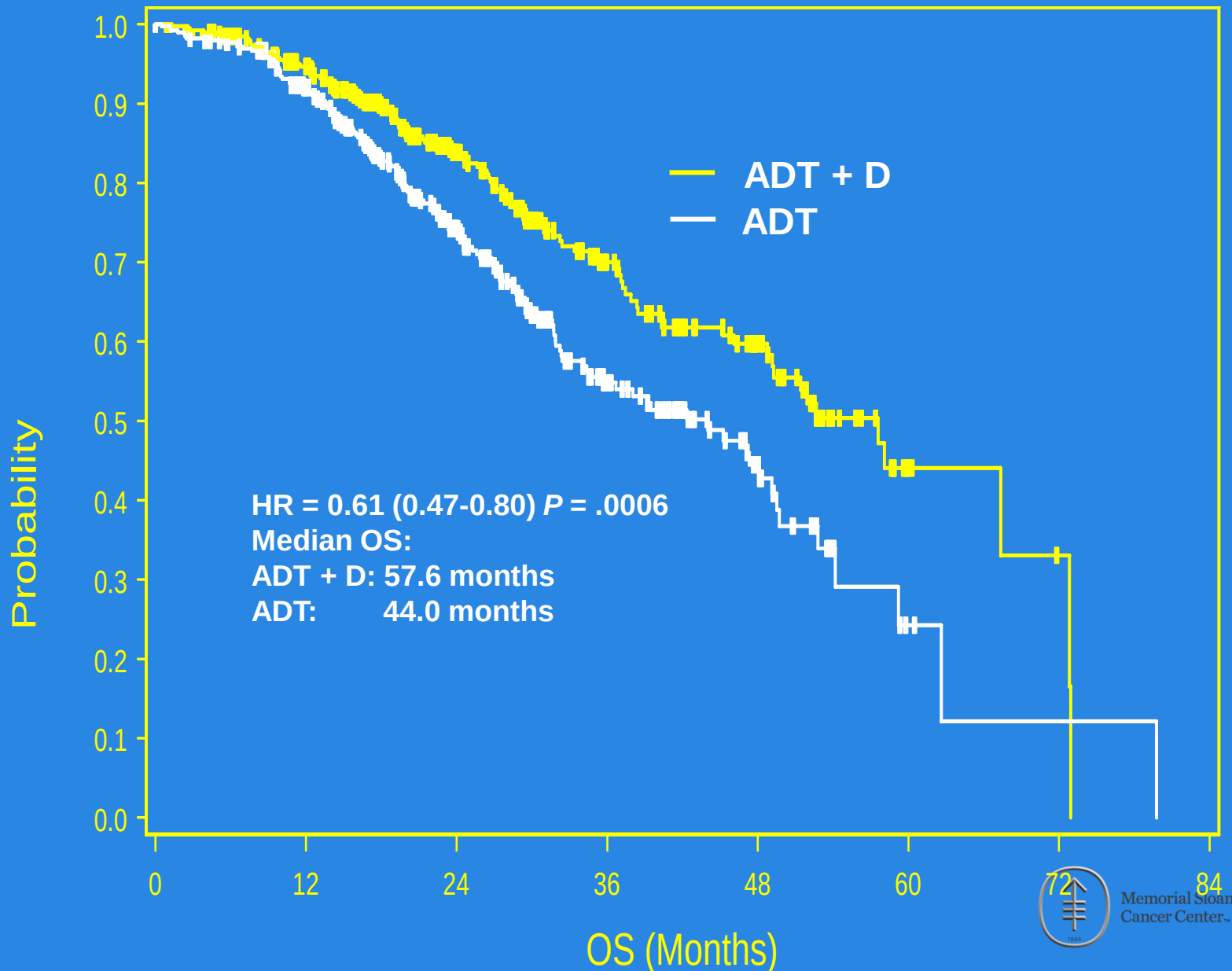
Primary Endpoint: Overall Survival



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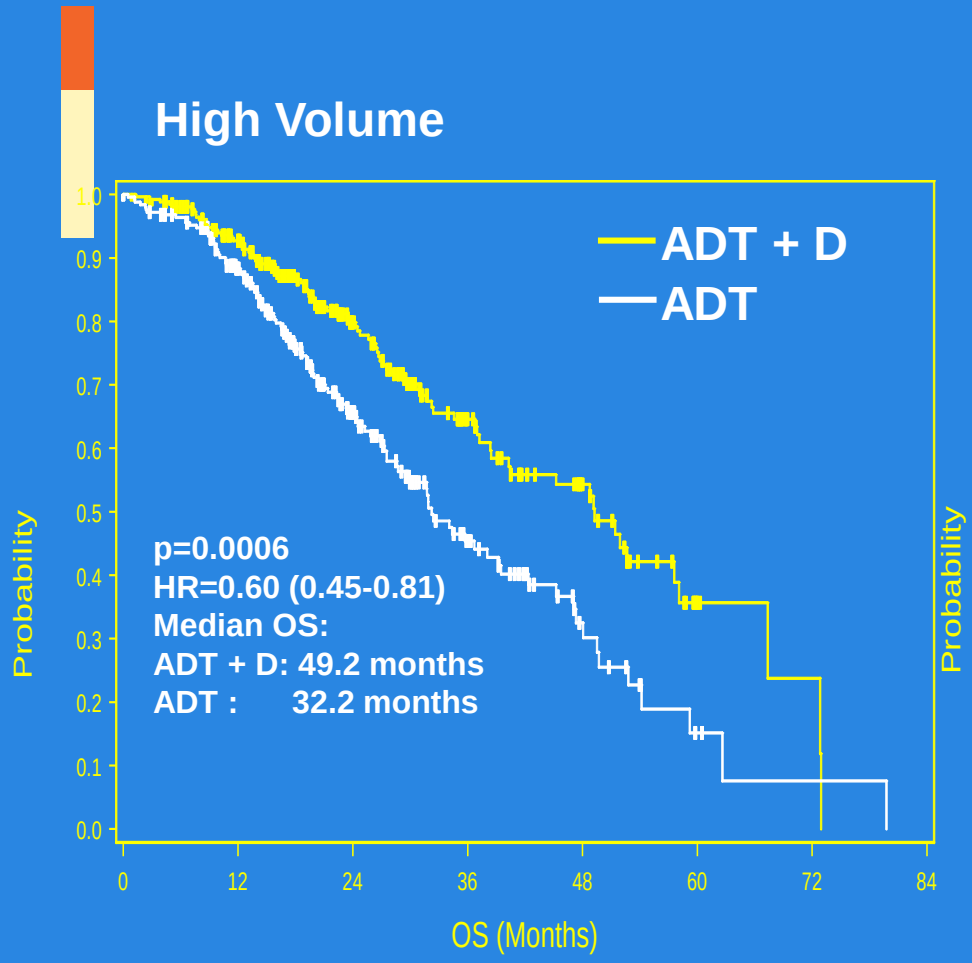
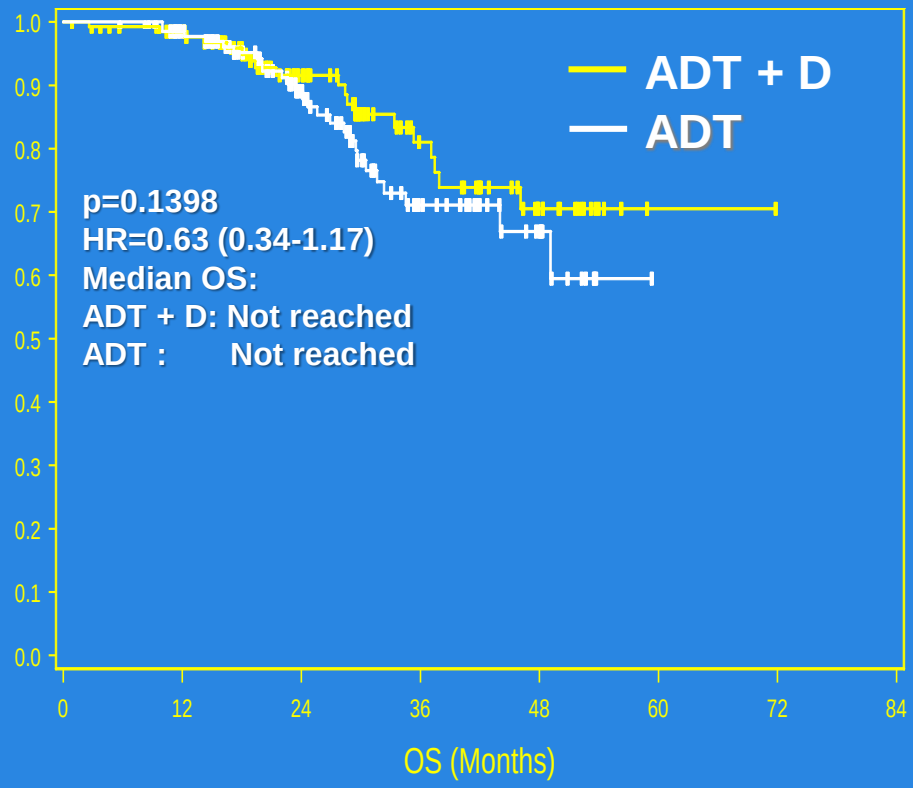
OS by Extent of Metastatic Disease at Start of ADT





High-volume disease: 17 month improvement in median OS 49.2 versus 32.2 months

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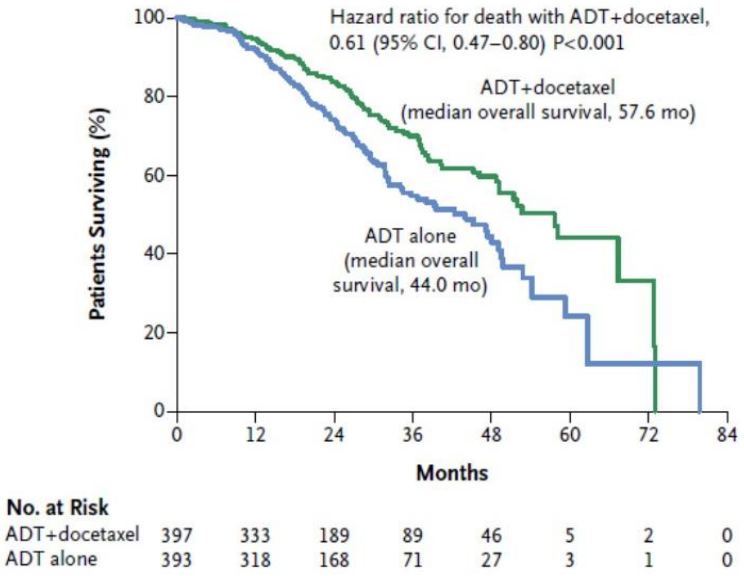
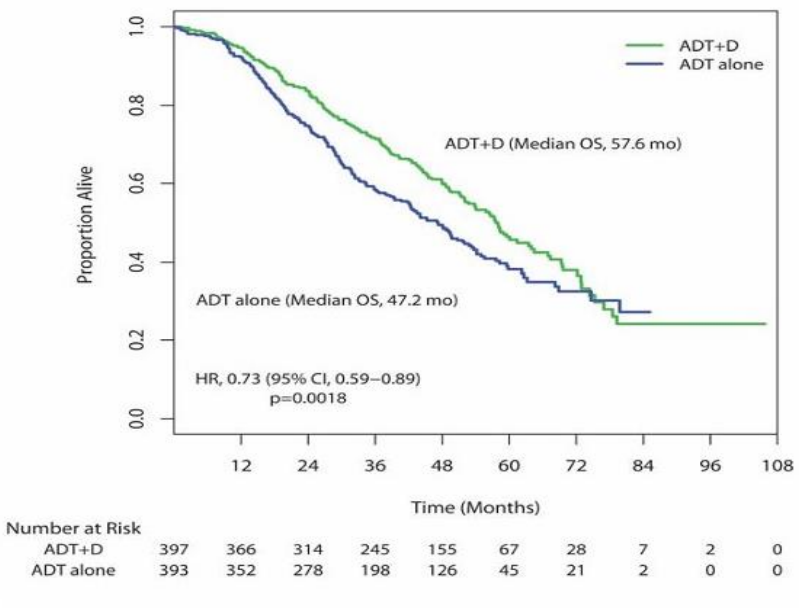
Long term follow-up of CHAARTED: Overall Population

Median Follow-up 28.9 months



13 months / HR 0.61

Median Follow-up: 53.7 months



10 months / HR 0.73

Sweeney et al NEJM 2015, Sweeney et al ESMO 2016

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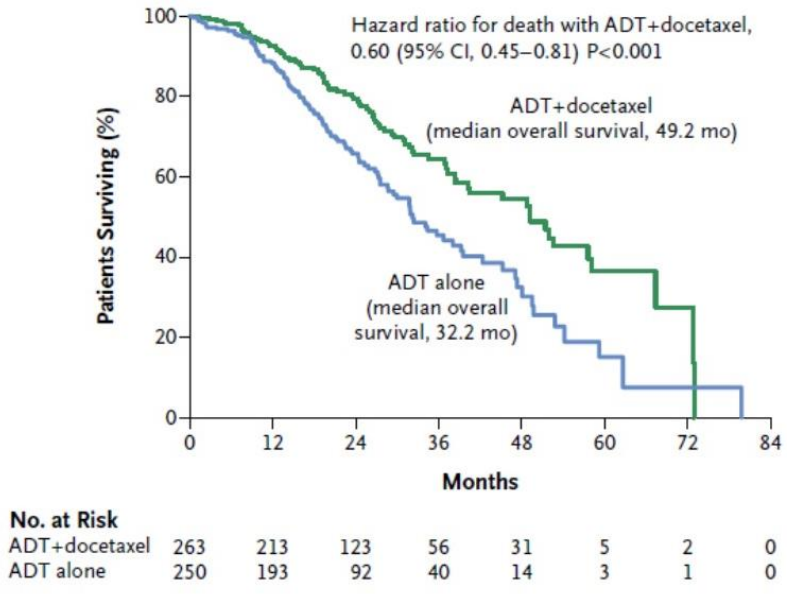
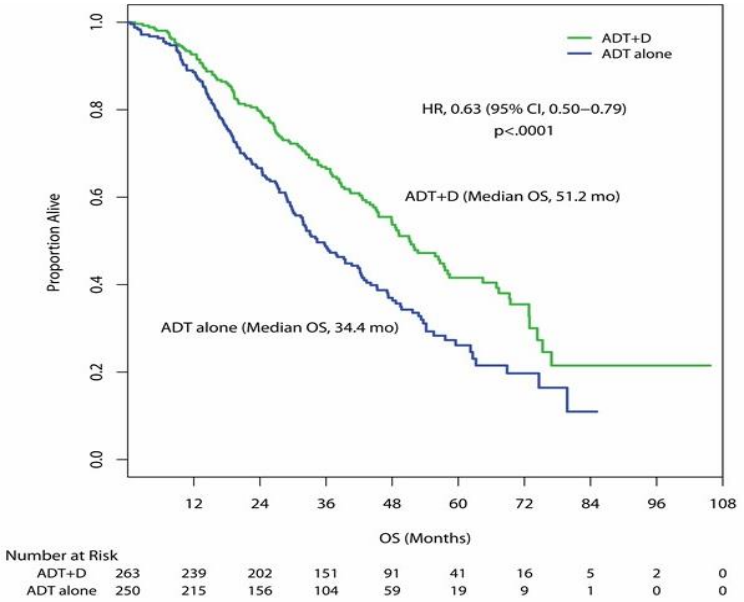
Long term follow-up of CHAARTED: High volume

Median Follow-up 28.9 months



17 months / HR 0.6

Median Follow-up: 53.7 months



17 months / HR 0.6

Sweeney et al NEJM 2015, Sweeney et al ESMO 2016

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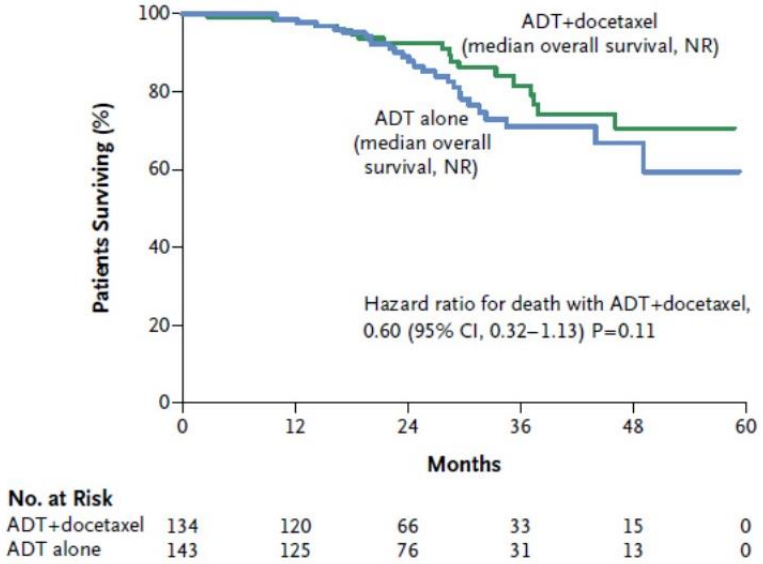
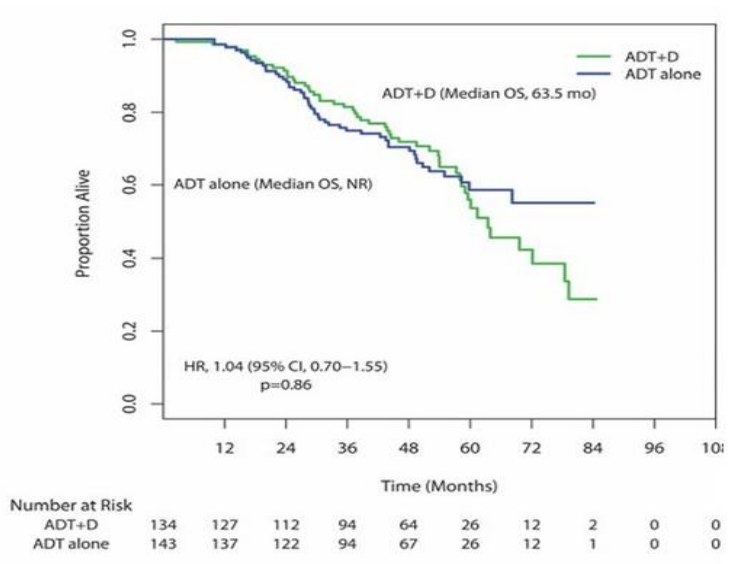
Long term follow-up of CHAARTED: Low volume patients do not benefit

Median Follow-up 28.9 months



Median Follow-up: 53.7 months



NR / HR 0.6

0 months / HR 1.0

(few low volume pts have aggressive disease and benefit from early docetaxel?)

Sweeney et al NEJM 2015, Sweeney et al ESMO 2016

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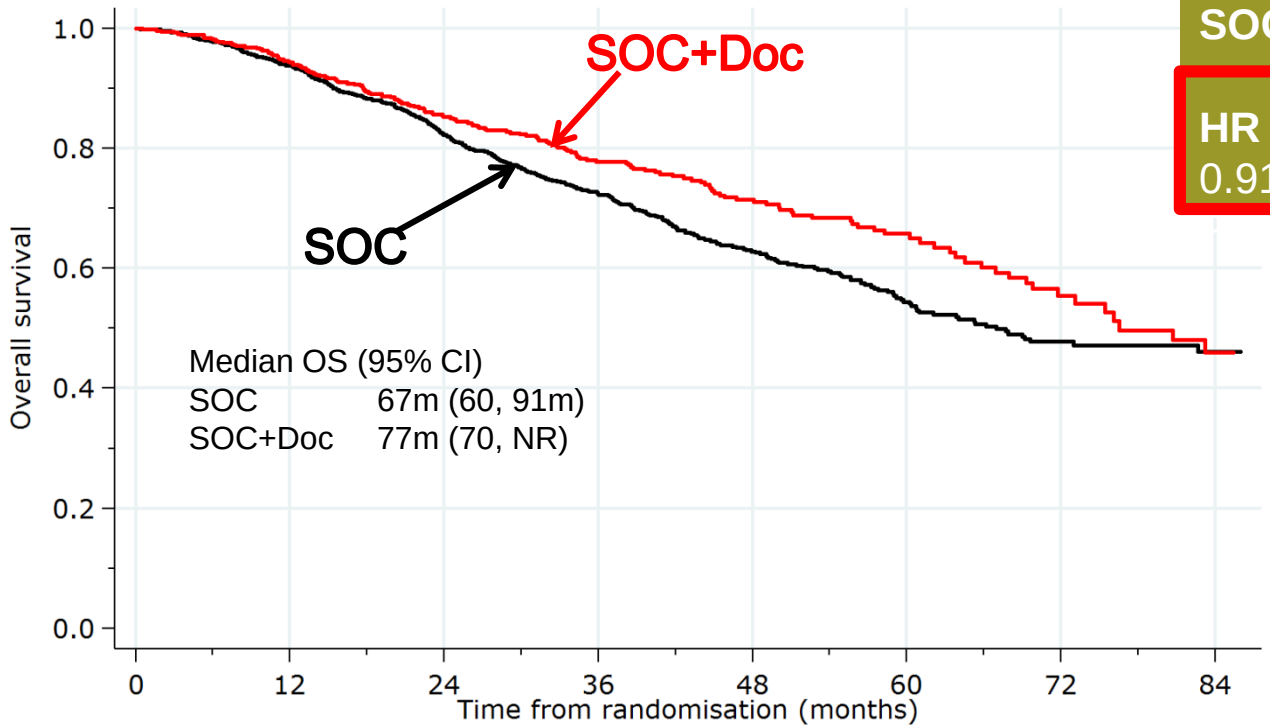
STAMPEDE-docetaxel: Survival



Group
At risk (events)

SOC	1184	(73)	1092	(130)	860	(89)	521	(59)	310	(33)	156	(17)	81	(2)	36
SOC+Doc	592	(33)	545	(51)	437	(32)	283	(19)	180	(12)	91	(12)	48	(6)	18

SOC 405 deaths
SOC+Doc 165 deaths

HR (95%CI) 0.76 (0.63, 0.91)

Non-PH p-value 0.51

Restricted mean OS time

SOC	58.8m
SOC+Doc	63.4m
Diff (95%CI)	4.6m (1.8, 7.3m)

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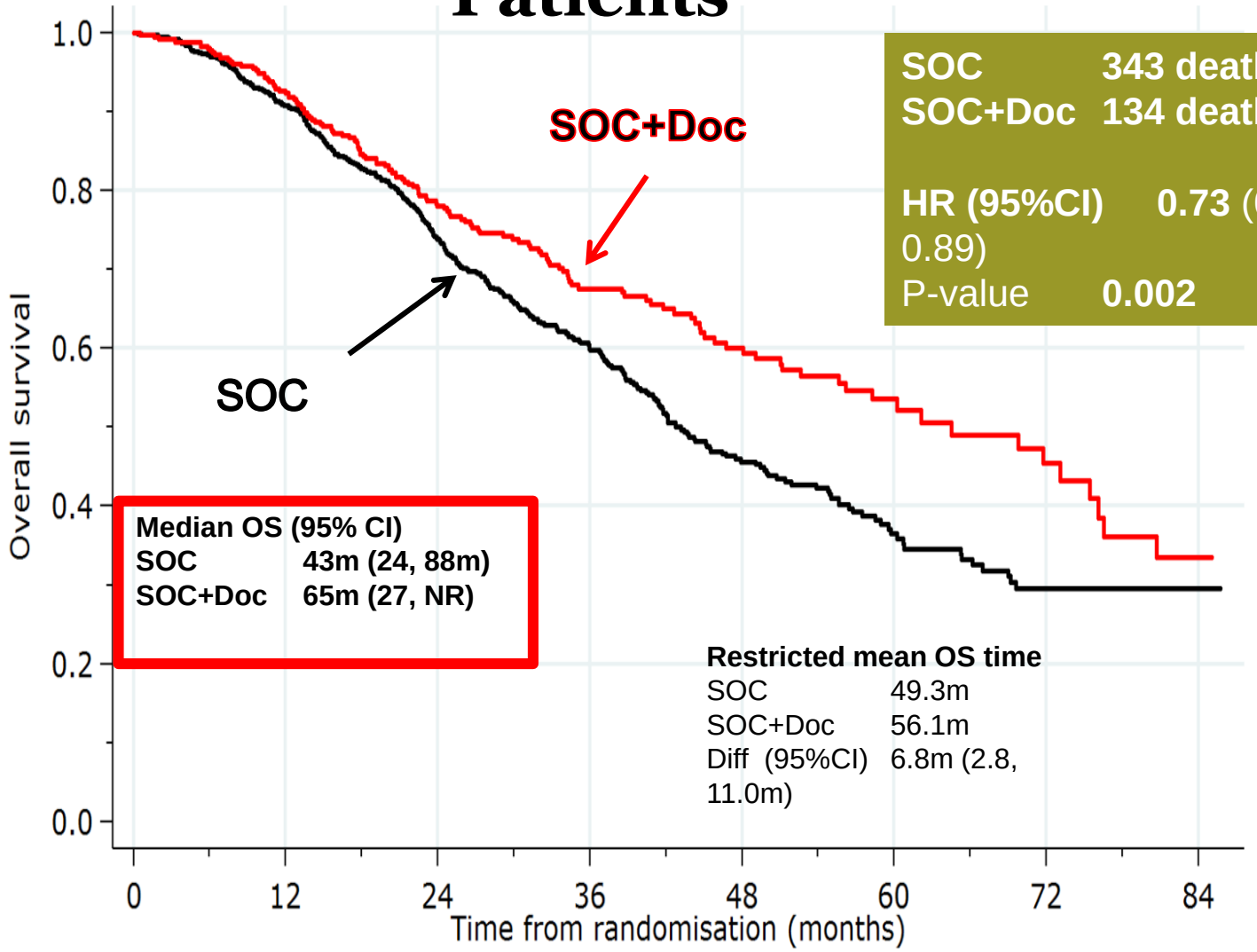
STAMPEDE-docetaxel: Survival-in M1 Patients



SOC	**343 deaths**
SOC+Doc	**134 deaths**
HR (95%CI)	**0.73** (0.59, 0.89)
P-value	**0.002**

Median OS (95% CI)

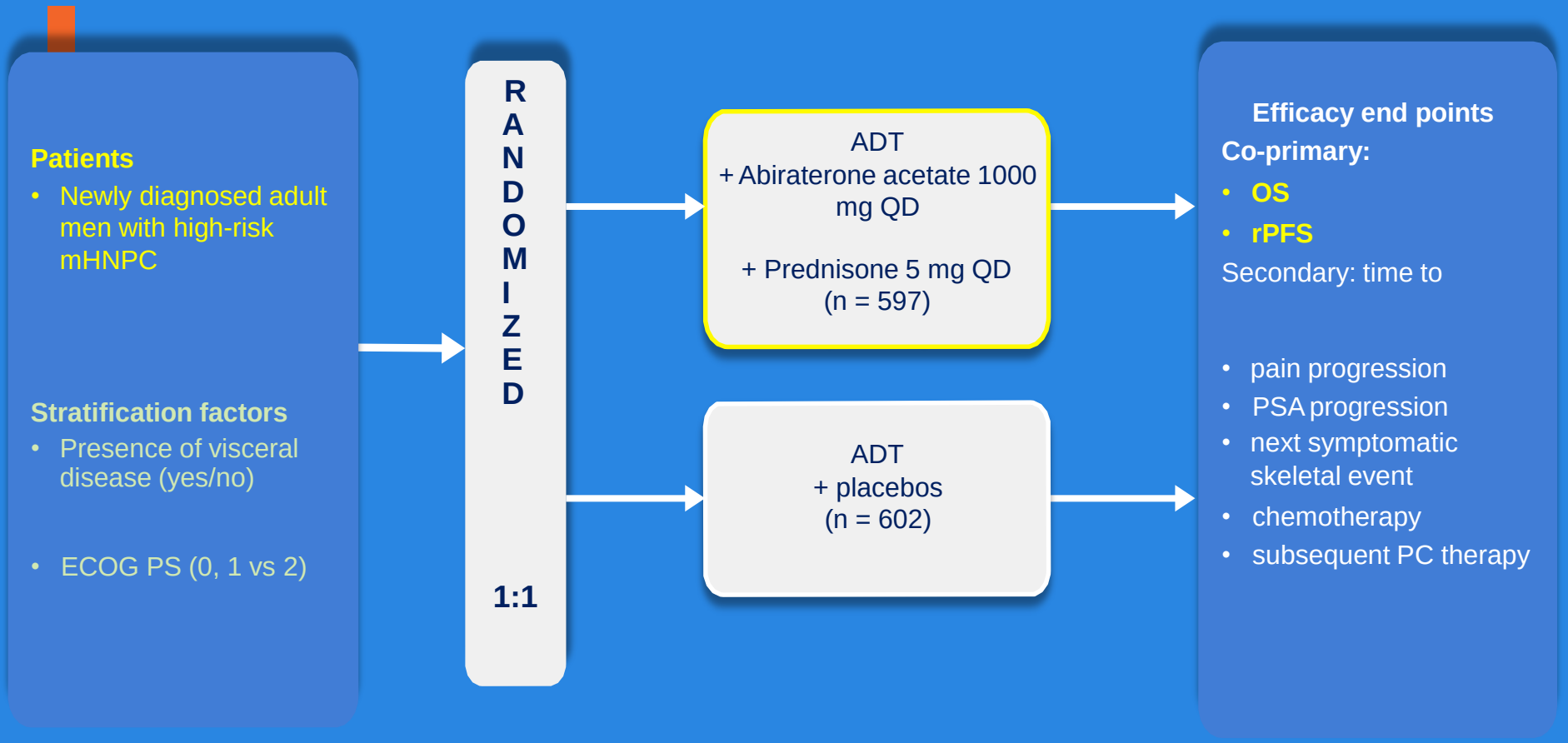
SOC	**43m (24, 88m)**
SOC+Doc	**65m (27, NR)**

Restricted mean OS time

SOC	49.3m
SOC+Doc	56.1m
Diff (95%CI)	6.8m (2.8, 11.0m)

Management of mHSPC-Abiraterone

LATITUDE



- **Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada**
- **Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results**

Fizazi et al NEJM 2017

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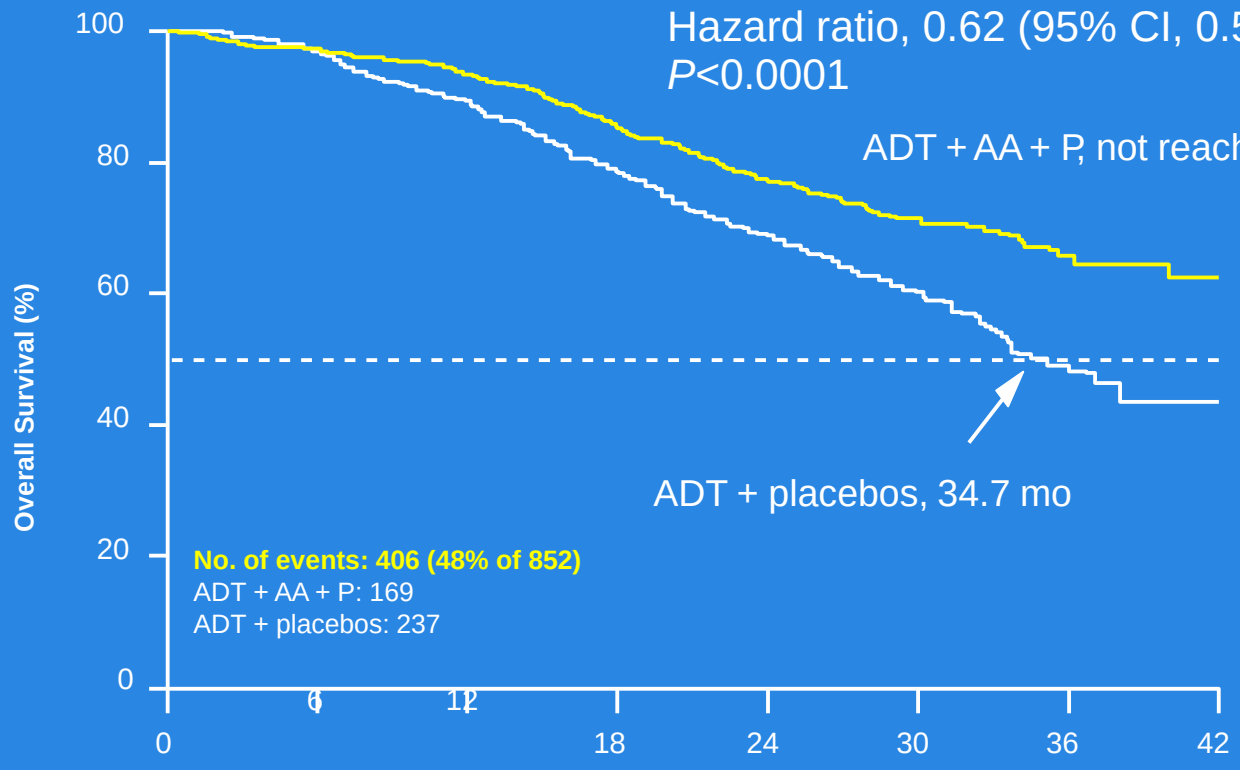
Statistically significant 38% risk reduction of death



OS rate at 3 years:
ADT + AA + P: 66%
ADT + placebos: 49%

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

Fizazi et al NEJM 2017

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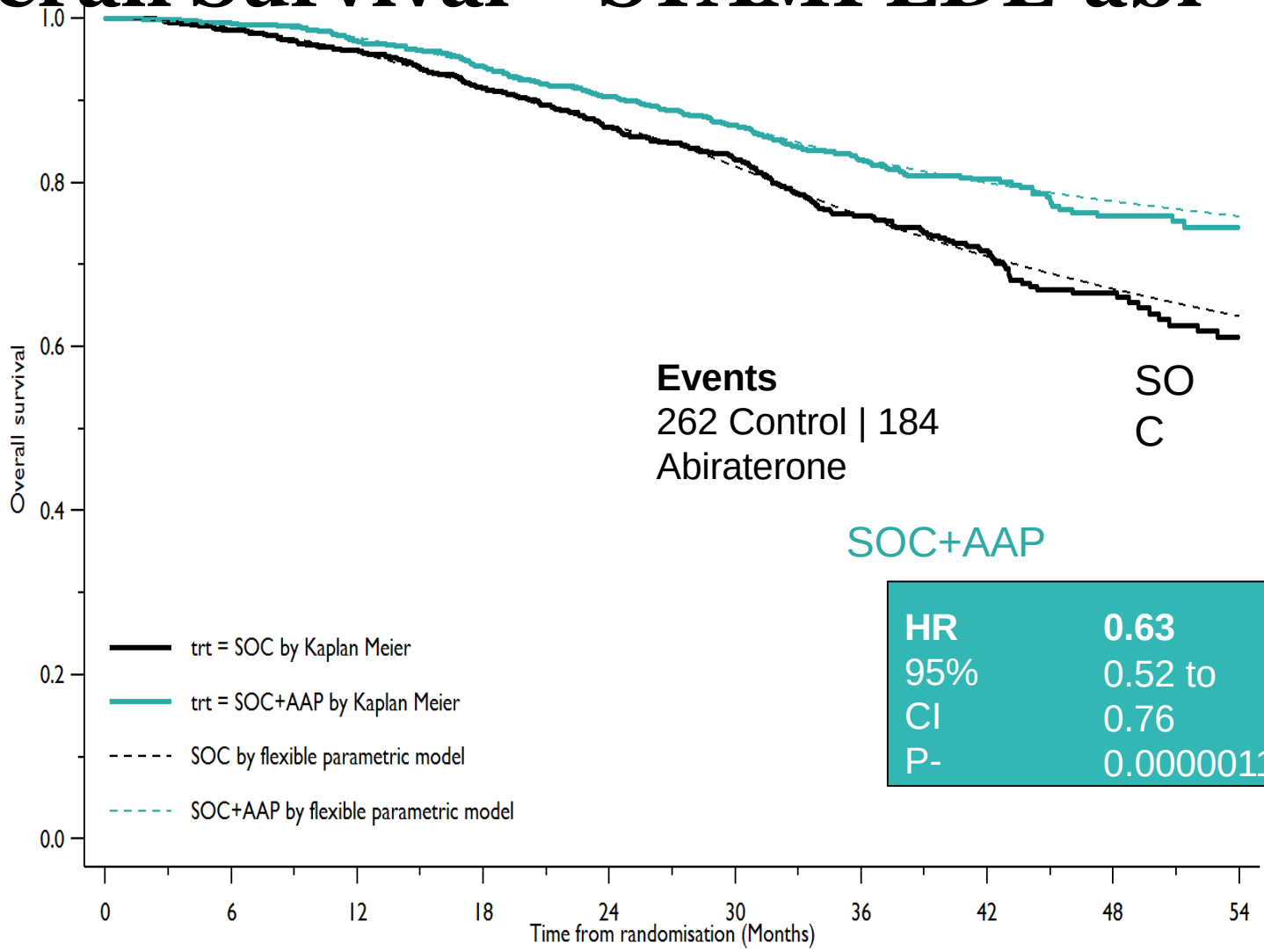
Overall Survival – STAMPEDE-abi



Events
262 Control | 184 Abiraterone

SO
C

SOC+AAP

HR	**0.63**
95% CI	0.52 to 0.76
P-	0.0000011

Number of patients (events)

SOC	957	(37)	909	(88)	806	(92)	491	(36)	123
SOC+AAP	960	(26)	917	(63)	840	(67)	541	(25)	161

James et al NEJM 2017

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What is the prognosis of different subgroups of patients?

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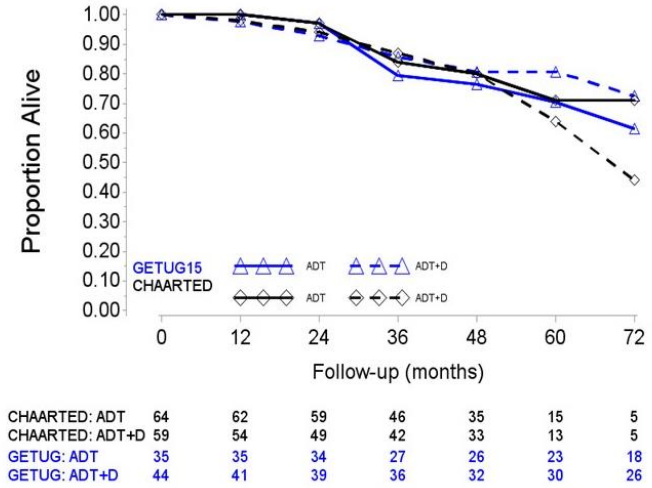
Prognosis of patients with mHSPC

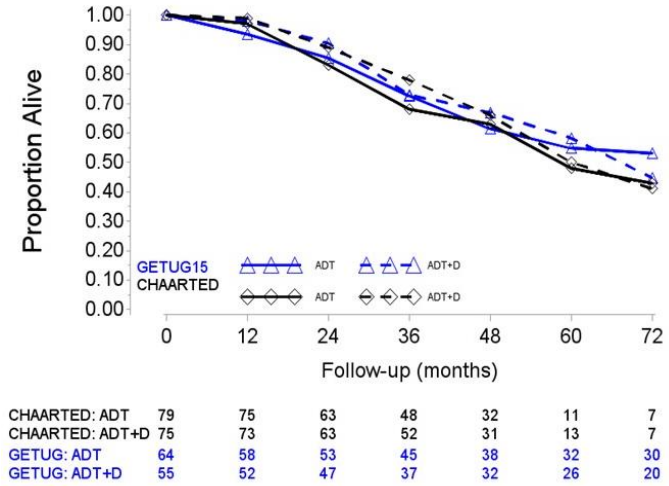
- Patients with high volume disease have a poorer outcome than low volume
    - High volume is 1 risk factor
- Patients with *de novo* metastatic disease have a poorer outcome than those who relapse after local therapy
    - De novo metastatic disease is 1 risk factor
- What is OS if have 0 or 1 or 2 risk factors?

OVERALL SURVIVAL: 1 or 0 risk factors: low volume

Low Volume and Prior Local Therapy	Low Volume and *De Novo* Mets



Median OS ADT: ~ 8 yrs



Median OS ADT: ~ 5 yrs

Gravis et al GUASCO 2017

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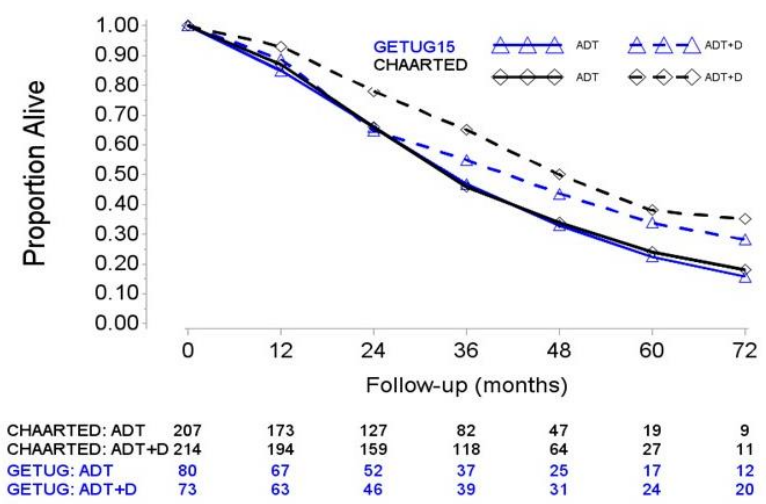
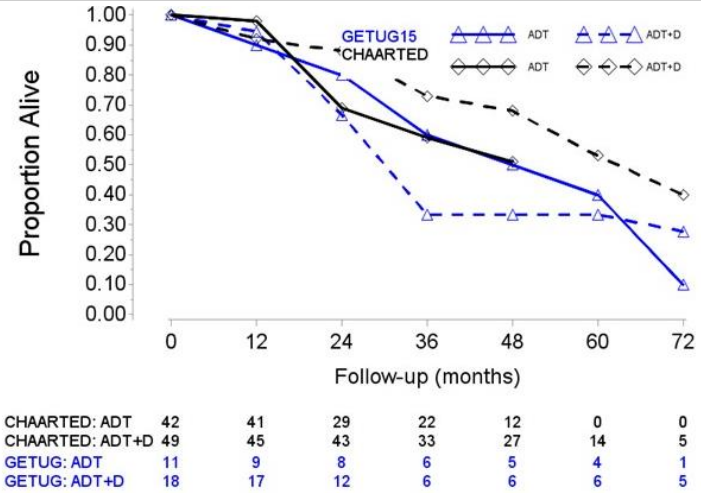
OVERALL SURVIVAL: 1 or 2 risk factors: High volume

High Volume and Prior Local Therapy	High Volume and *De Novo* Mets





Median OS ADT: ~ 4.5 yrs

Median OS ADT: ~ 3 yrs

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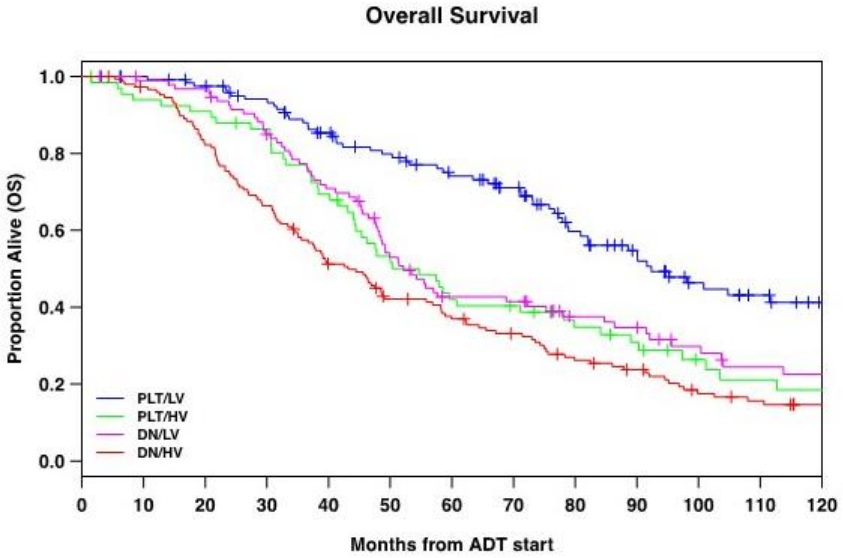
Gravis et al GUASCO2017

Reproducibility in a Hospital-based Registry: DFCI



Groups	N (% events)	Median OS yrs (95%CI)
Prior Tx+LV	125 (50)	7.7 (6.7,10.6)
Prior Tx+HV	67 (75)	4.6 (3.7,6.7)
De-novo+LV	96 (70)	4.3 (4,6.5)
De-novo+HV	148 (84)	3.6 (3.1,4.7)

Francini et al GUASCO 2017

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Abiraterone or docetaxel?

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First questions

- When choosing between docetaxel and abiraterone
  - Is the patient "fit for docetaxel?"
    - Most are
  - Does the patient have a high disease burden or *de novo* disease?

Little apparent benefit from docetaxel in low volume disease

Trial	M1 pt subgps	All M1	High vol. / Poor risk	Low vol.	Median Follow-up (months)
GETUG15	HV & LV	**HR: 0.88 (NS)**	**HR: 0.78 (NS)**	**HR: 1.02**	84
CHAARTED	HV & LV	**HR: 0.73**	**HR: 0.63**	**HR 1.04**	53.7
STAMPED E-Doc	Any M1 (no subgroups)	**HR: 0.76**	**N/A**	N/A	43
LATITUDE	Poor risk only	**N/A**	**HR: 0.62**	Not included	30.4
STAMPED E-Abi	Any M1 (no subgroups)	**HR: 0.63**	**N/A**	N/A	40

Gravis et al Eur Uriol 2016; Sweeney et al ESMO 2016; James et al Lancet 2015; Fizazi et al NEJM 20157 James et al NEJM 2017

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Comparative toxicity

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Grade 3–5 AEs in ≥2% of patients

	CHAARTED[1]			LATITUDE[2]		STAMPED ARM G[3]
	ADT + **Docetaxel** (n=390)			ADT + **Abiraterone** (n=597)		ADT + **Abiraterone** (n=948)
AE, %	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 3–5**
Allergic reaction	1.8	0.3	0	–	–	–
Fatigue	4.1	0	0	2	0	2
Neutropenia	3.1	9.0	0	–	–	–
Febrile neutropenia	3.8	2.3	0	–	–	–
Pulmonary disorder	–	–	0.3	–	–	–
Hypertension	–	–	–	20	0	1
Hypokalaemia	–	–	–	10	1	<1
ALT increased	–	–	–	5	<1	<1
Hyperglycaemia	–	–	–	4	<1	–
AST increased	–	–	–	4	<1	<1
Bone pain	–	–	–	3	0	–
Cardiac disorder	–	–	–	3	1	10
Endocrine disorder	–	–	–	–	–	14
Gastrointestinal disorder	–	–	–	–	–	5
General disorder	–	–	–	–	–	5

The overall safety profile of ADT + abiraterone was consistent with prior studies in mCRPC and favorable in both STAMPEDE and LATITUDE

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1. Sweeney et al. N Engl J Med 2015; 2. Fizazi et al. NEJM 2017; 3. James et al. NEJM 2017

Cost of early docetaxel vs abiraterone

- 100 patients with mHSPC

- **Upfront docetaxel 6 cycles**: visits + infusion + cost of drug: $10,000
  - **Plus add-on abiraterone for rising PSA** at $8,000 per month in USA
  - Median time to progression: 18 months = $144,000 for one person
  - **~$15 million to treat 100 patients**

- **Upfront abiraterone median time to progression: 36 months**
  - [$8K x 36 months x 100 pts] + [$10K x 100] =
  - **~$30 million to treat 100 pts**

Conclusions

- Favor docetaxel for the patient with high volume or *de novo* disease and fit for chemotherapy

- Reasons
  - Docetaxel has more short term adverse events but done in 18 weeks
  - Abiraterone more clinic visits
  - Get docetaxel in before too frail
  - Abiraterone can be added on later more easily if more frail
  - Aim is to get as many therapies in as possible
  - Less cost

Conclusions

- We may develop biomarkers which predict which patients benefit more from docetaxel or abiraterone

- We may learn soon which patients benefit from “triplet” therapy

mHSPC Treatment in Addition to ADT Opinion

Scenario	Option
De novo and/or high volume	Either AA or docetaxel but favor docetaxel
De novo, visceral	Either AA or docetaxel
Non-*de novo* mets	Either AA or docetaxel
Non-high volume *de novo* mets	Either AA or docetaxel