The role of chemotherapy as first line treatment

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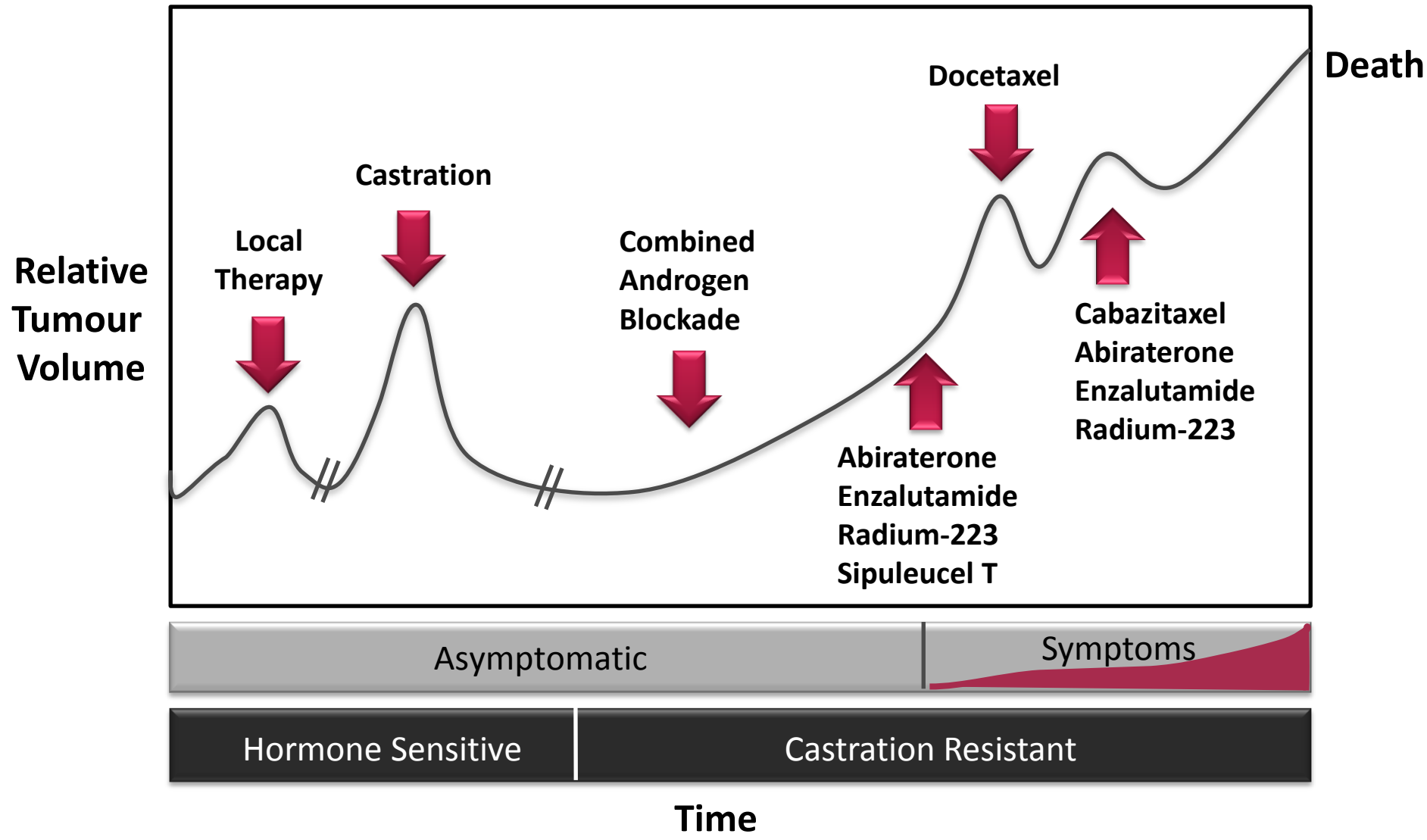
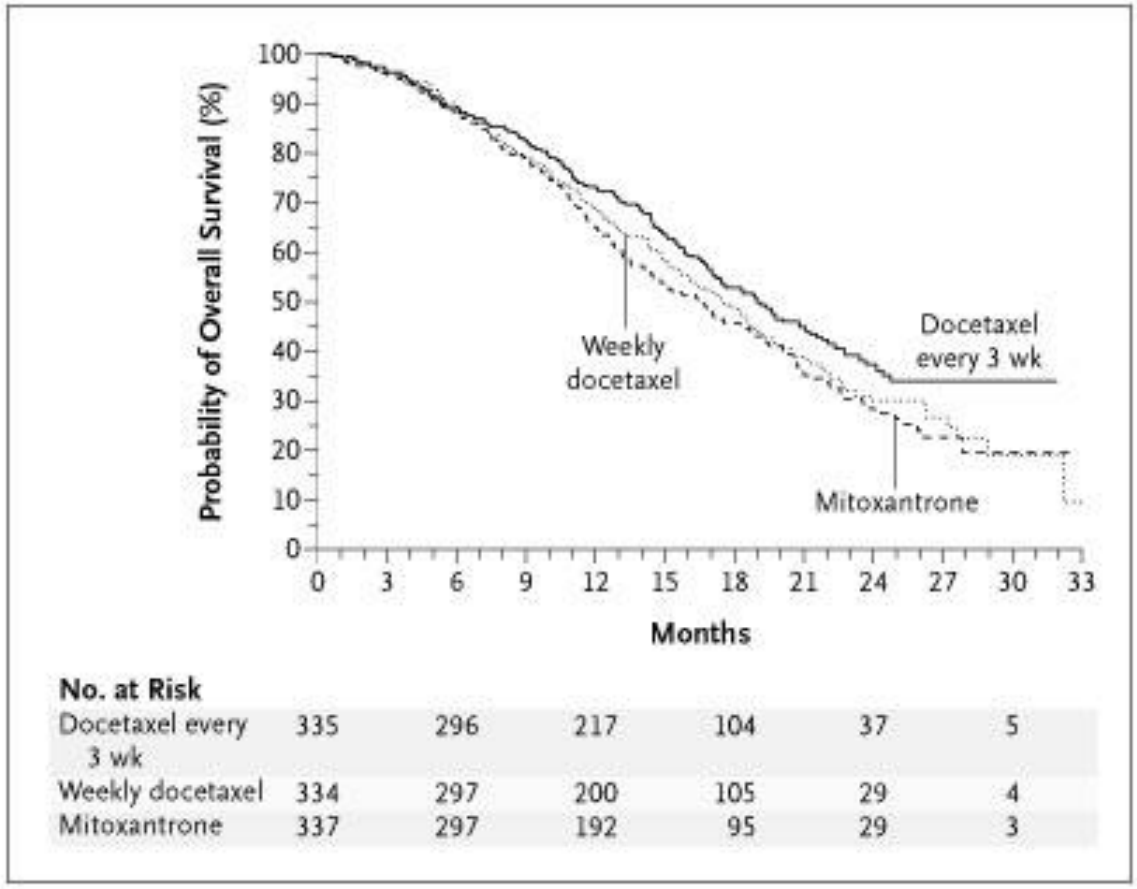
Where we were…



Docetaxel for mCRPC



No. at Risk						
Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

Median survival

- D3 – 19.2 months
- D1 – 17.8 months
- M – 16.3 months

Improvements also in:

- QOL
- Pain
- PSA response

Tannock, N Engl J Med, 2004

‘Up front’ docetaxel?

Pros

- Improved survival
- Prolonged time to clinical progression

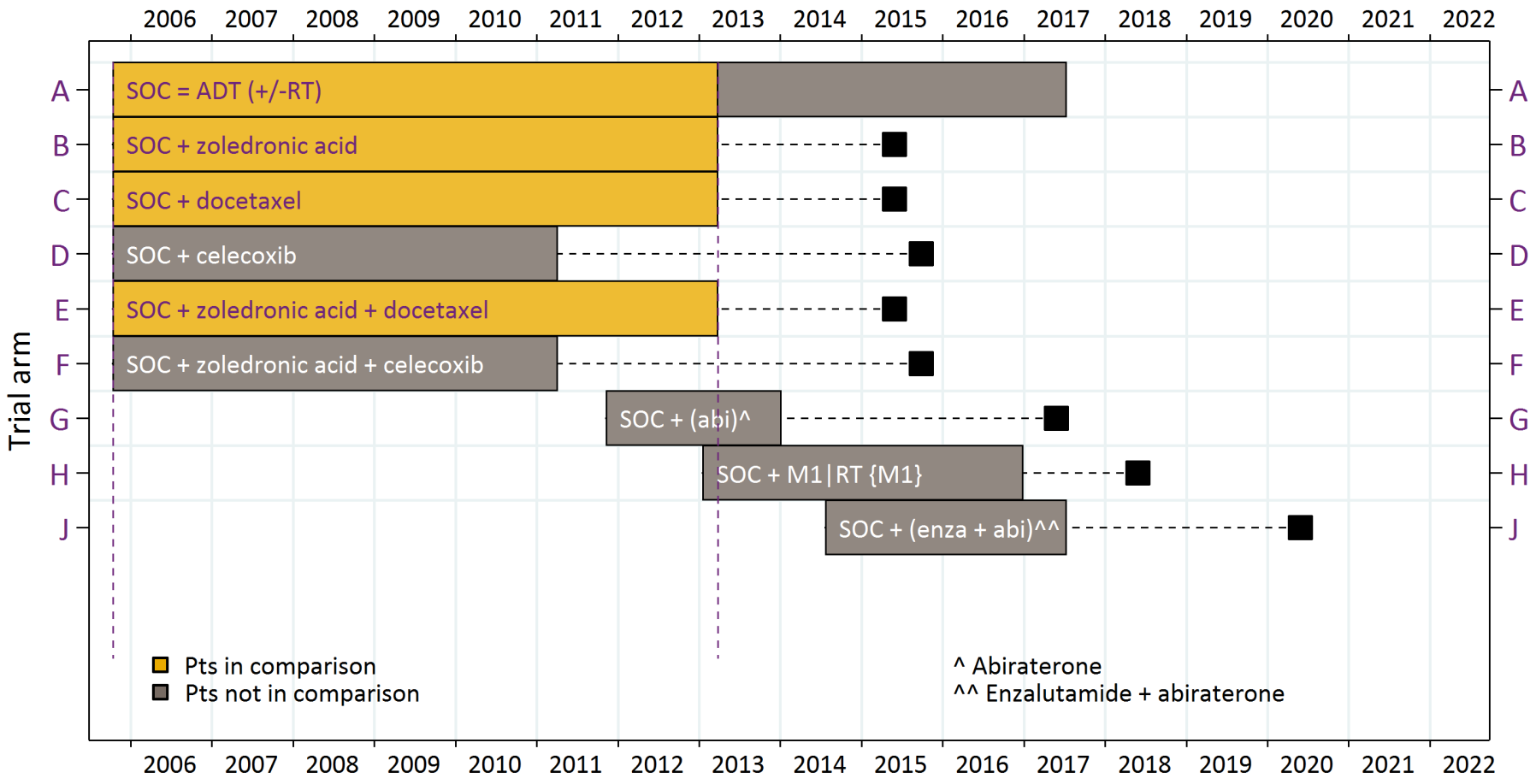
Pros (potentially)

- Improved toxicity profile?
- Quality of life benefit?
- Allow some to benefit that could not do so later due to frailty at progression?
- Cost effectiveness?

Cons (potentially)

- Expose more patients to toxicity
- Some may never ‘need’ chemo
- Cost effectiveness?
- Our data for subsequent management is very limited

STAMPEDE: Comparisons to date



Docetaxel Target Dose: 75mg/m^2, every 3 weeks for 6 cycles (+prednisolone 10mg od)

STAMPEDE slides courtesy of Nick James, ASCO Annual Meeting 2015, abstract 5001

STAMPEDE: Inclusion criteria

Newly-diagnosed

Any of:

- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4
  PSA≥40ng/ml
  Gleason 8-10

Relapsing after previous RP or RT with ≥1 of:

- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/ml
- Node-positive
- Metastatic

All patients

Fit for all protocol treatment

Fit for follow-up

WHO performance status 0-2

Written informed consent

Full criteria and slide set

www.stampedetrial.org

STAMPEDE: Outcome measures

Primary outcome measure

Overall survival

Secondary outcome measures

Failure-free survival (FFS)

Toxicity

Quality of life

Skeletal-related events

Cost effectiveness

FFS definition

First of:

- PSA failure
- Local failure
- Lymph node failure
- Distant metastases
- Prostate cancer death

PSA failure definition

PSA fall >= 50%

→ 24wk nadir + 50% **and**

→ >4ng/ml

PSA fall of <50%

→ failure at t=0

STAMPEDE: Patient characteristics

Comparison

Open:	Oct-2005
Closed:	Mar-2013
Accrual:	2962

Number of patients

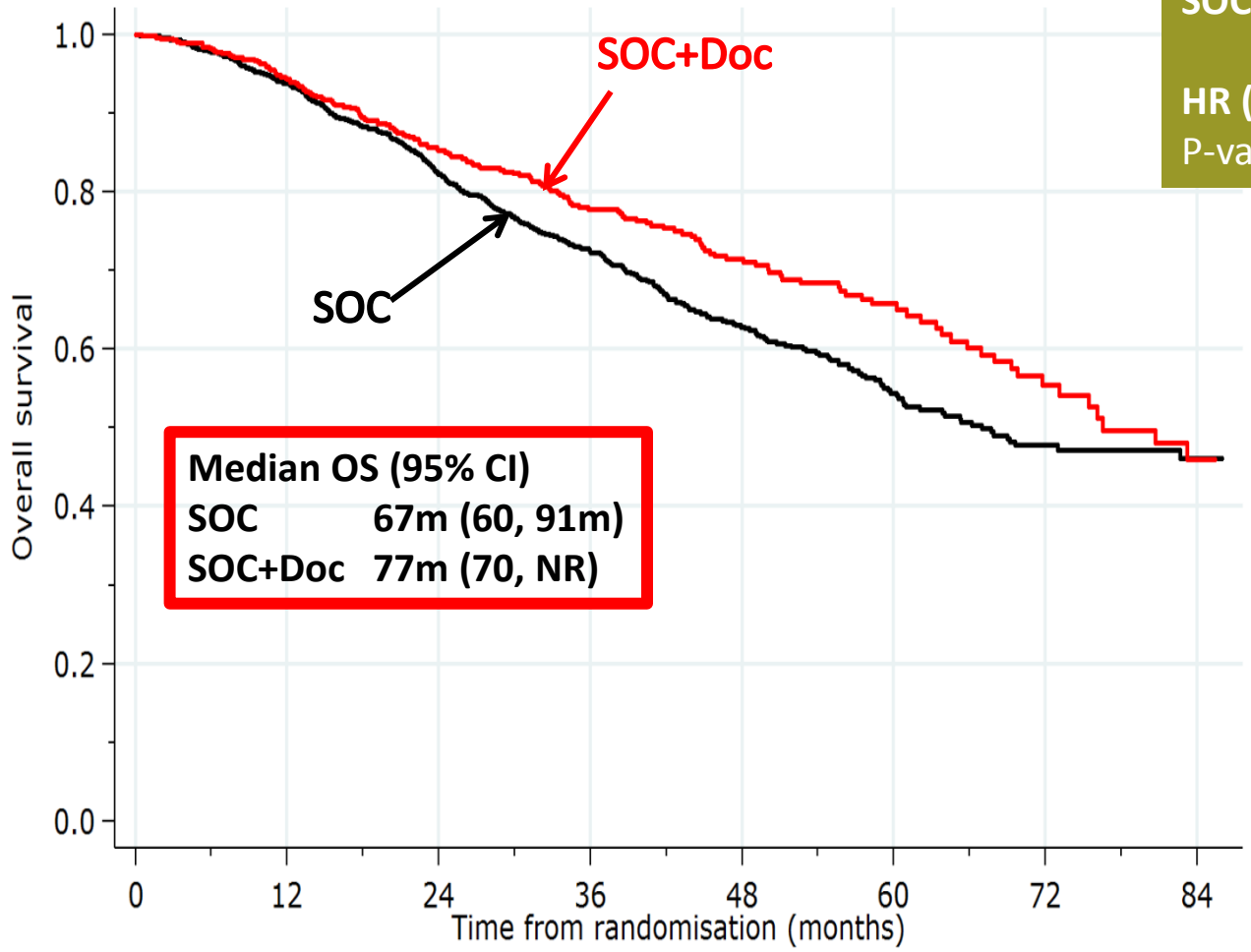
1184	Standard-of-care (SOC)
593	SOC + zoledronic acid
592	SOC + docetaxel
593	SOC + zoledronic acid + docetaxel

1%	WHO PS 2	[s]
21%	WHO PS 1	[s]
65yr	Median age (min 40, max 84)	[s]
61%	Metastatic (85% Bony mets)	[s]
15%	N+M0	
24%	N0M0	
98%	LHRH analogues	[s]
29%	Planned for RT (72% of N0M0 pts)	[s]
6%	Previous local therapy	

Balanced by arm

[s] Stratification factors + hospital + NSAID/aspirin

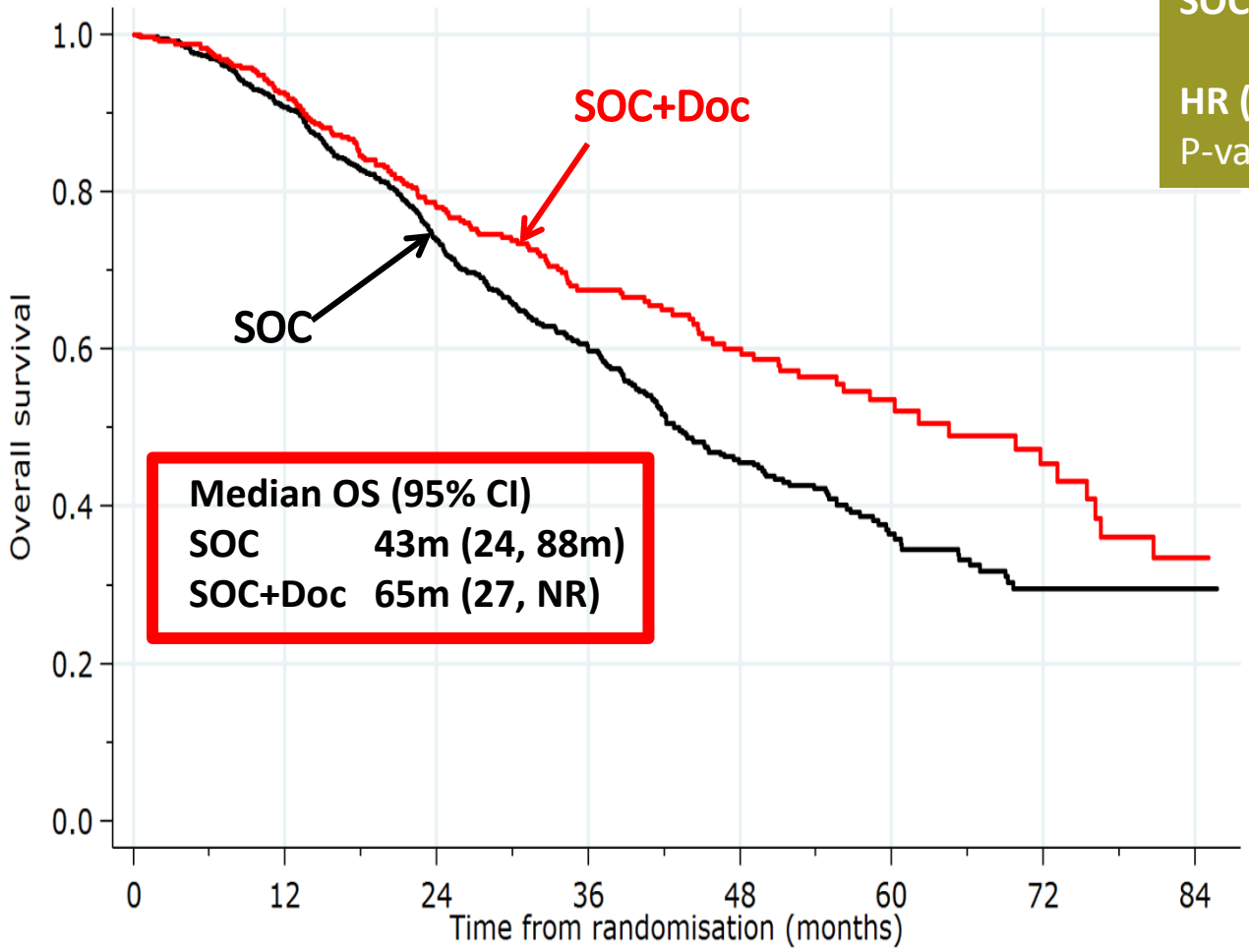
STAMPEDE: Survival +/- docetaxel



SOC	**405 deaths**
SOC+Doc	**165 deaths**
HR (95%CI)	**0.76** (0.63, 0.91)
P-value	**0.003**

STAMPEDE: Survival in M1 Patients +/- docetaxel

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

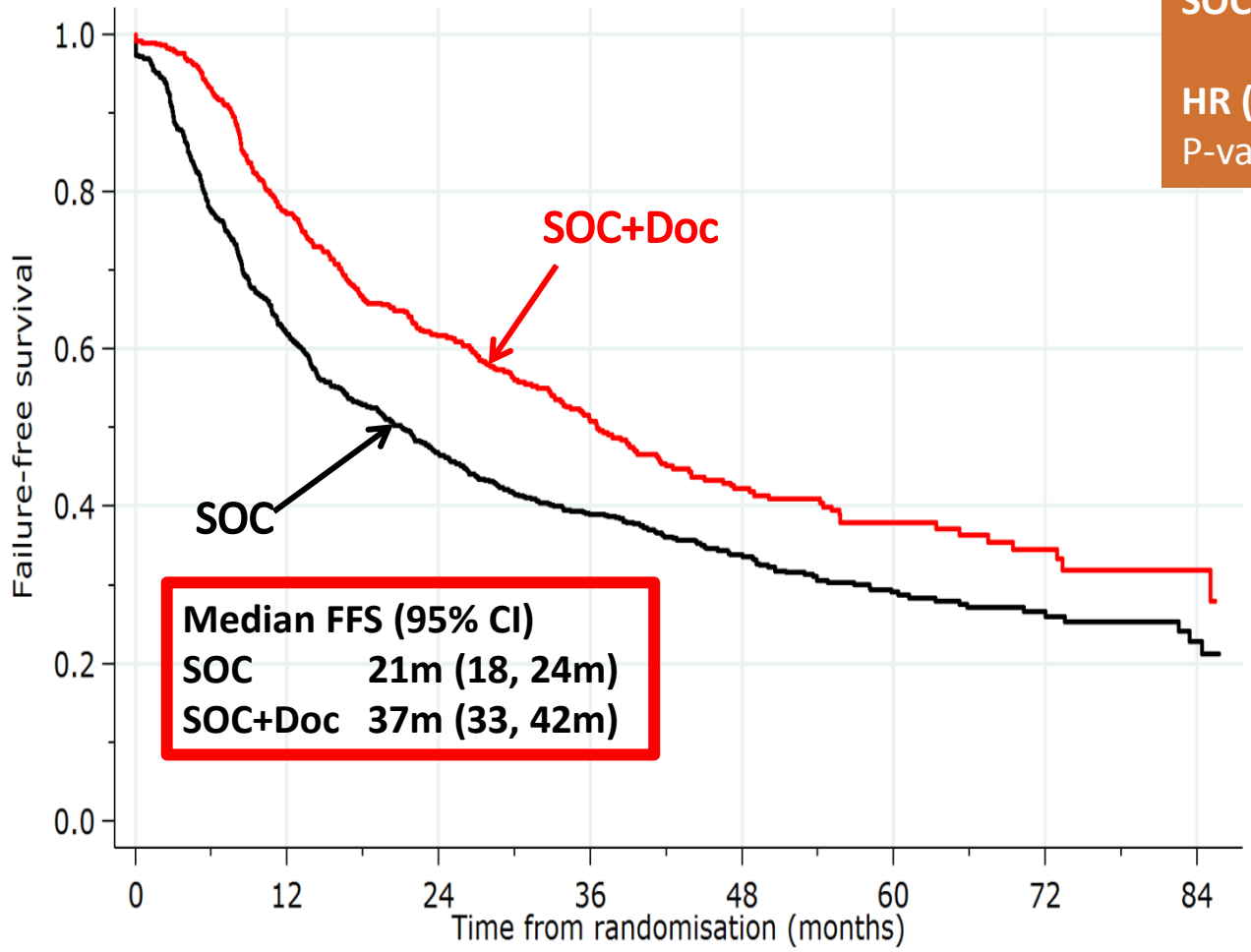


Group
At risk (events)

SOC	725	(66)	645	(117)	469	(75)	254	(52)	134	(21)	58	(10)	24	(0)	10
SOC+Doc	362	(27)	326	(49)	242	(27)	151	(13)	91	(8)	37	(5)	24	(5)	9

STAMPEDE: Failure-free survival +/- docetaxel

SOC	**750 FFS events**
SOC+Doc	**371 FFS events**
HR (95%CI)	**0.62** (0.54, 0.70)
P-value	**<0.0000000001***



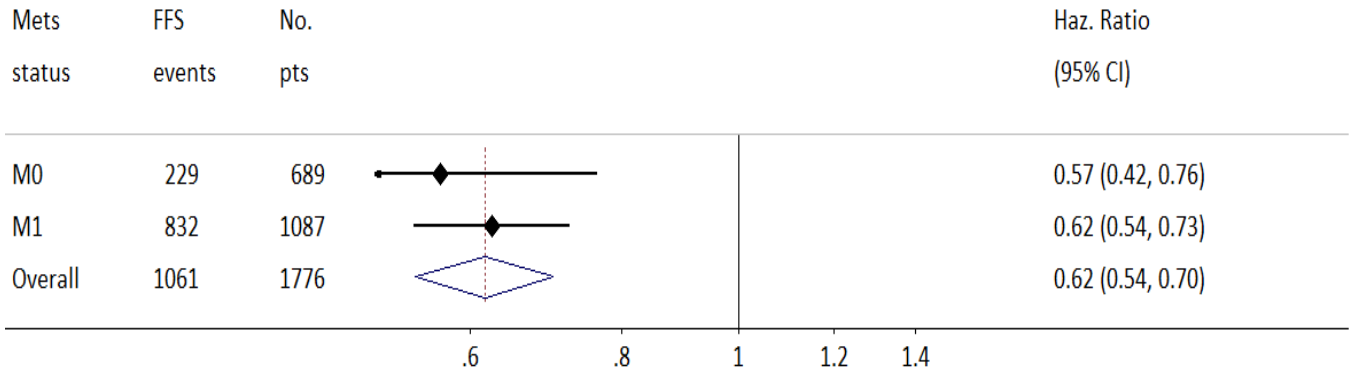
Group
At risk (events)

SOC	1184	(446)	713	(173)	488	(70)	287	(31)	161	(19)	84	(6)	45	(4)	17
SOC+Doc	592	(131)	441	(88)	318	(48)	184	(27)	105	(9)	56	(4)	29	(2)	11

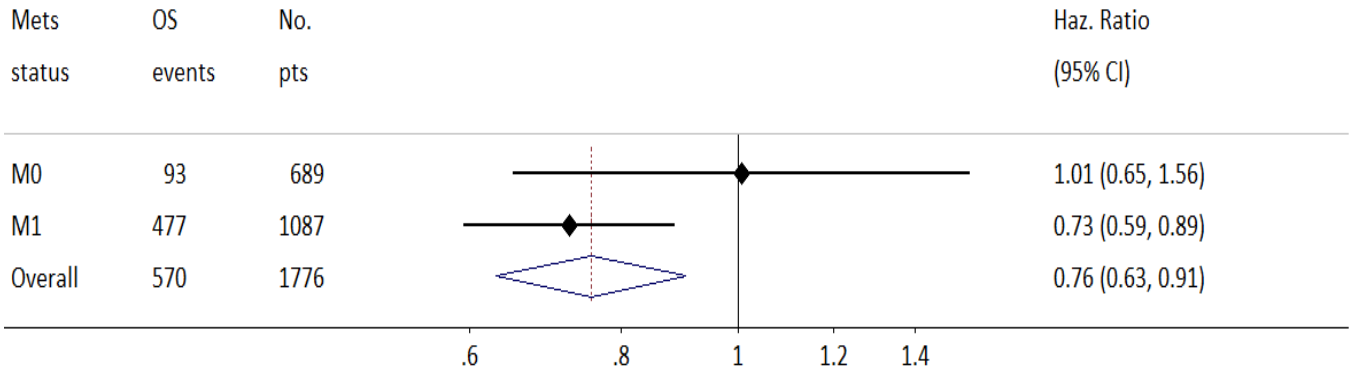
STAMPEDE: Docetaxel effect by metastatic status

Pre-planned analysis

Failure free survival +/- Doc



Overall survival +/- Doc



STAMPEDE: Grade 3+ adverse events ever reported

		A *SOC*	**B** *SOC+ZA*	**C** *SOC+Doc*	**E** *SOC+ZA+ Doc*
Patients randomised		1184	593	592	593
Patients with adverse event data		1174	587	579	564
Grade 3-5 AE (G5)	N	363 (3)	185 (1)	291 (3)	294 (7)
	%	31%	31%	51%	52%
Endocrine disorder		12%	12%	10%	12%
Blood and lymphatic *(febrile neutropenia)*		1%	2%	12%	12%
Blood/bone marrow *(neutrophils)*		1%	1%	12%	11%
General disorder		4%	5%	8%	11%
Musculo-skeletal		5%	5%	6%	8%
Gastrointestinal disorder		3%	3%	7%	7%
Renal		5%	4%	4%	6%

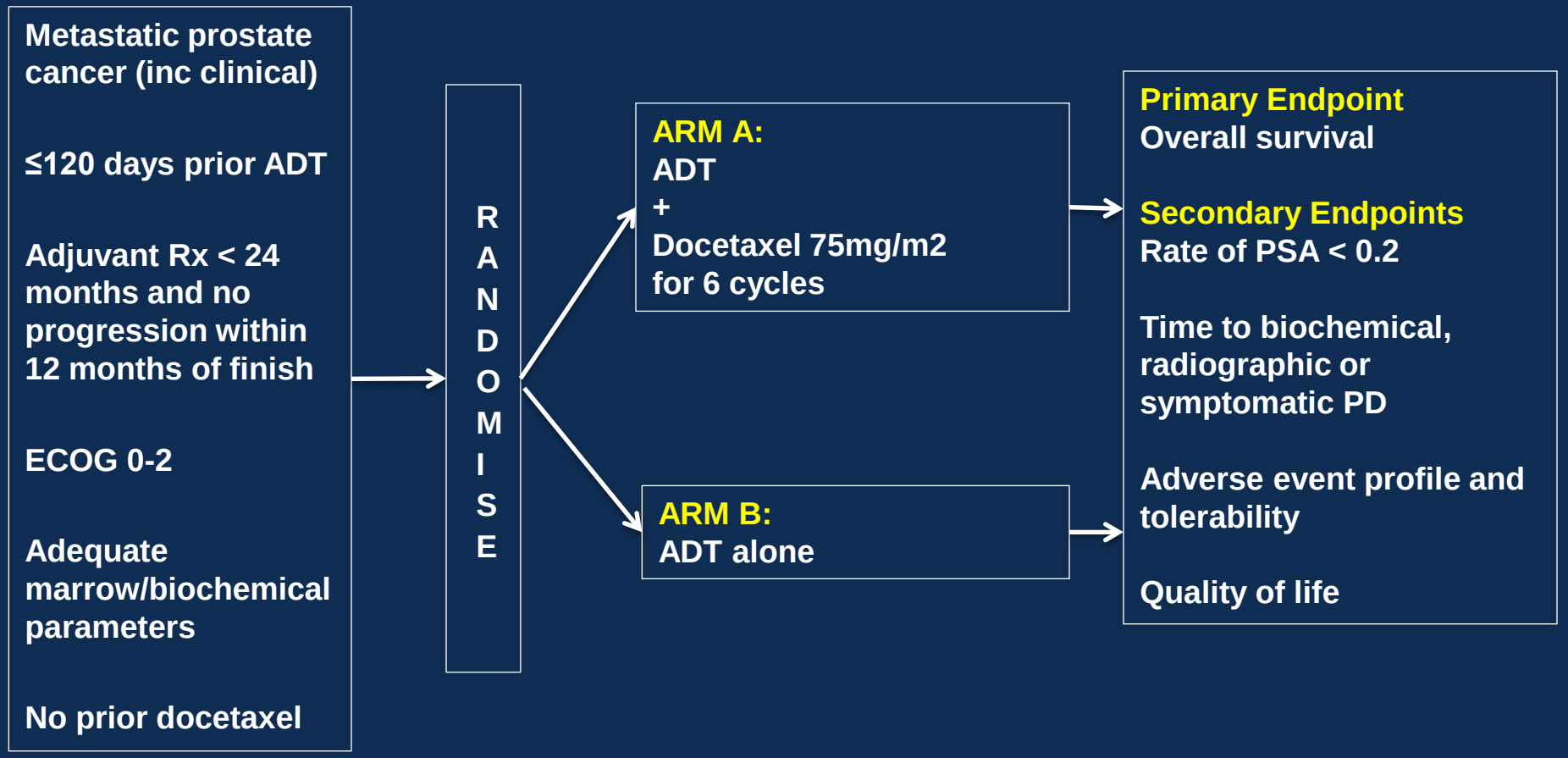
STAMPEDE: Grade 3+ adverse events at 1 year

Treatment	Incidence	Rate	95%CI
SOC	71/732	9.7%	(7.6% to 11.8%)
SOC+ZA	40/377	10.6%	(7.5% to 13.7%)
SOC+Doc	44/437	10.1%	(7.2% to 12.9%)
SOC+ZA+Doc	51/450	11.3%	(8.4% to 14.3%)

Early peak in toxicity during chemotherapy seems to settle by 1 year

CHAARTED

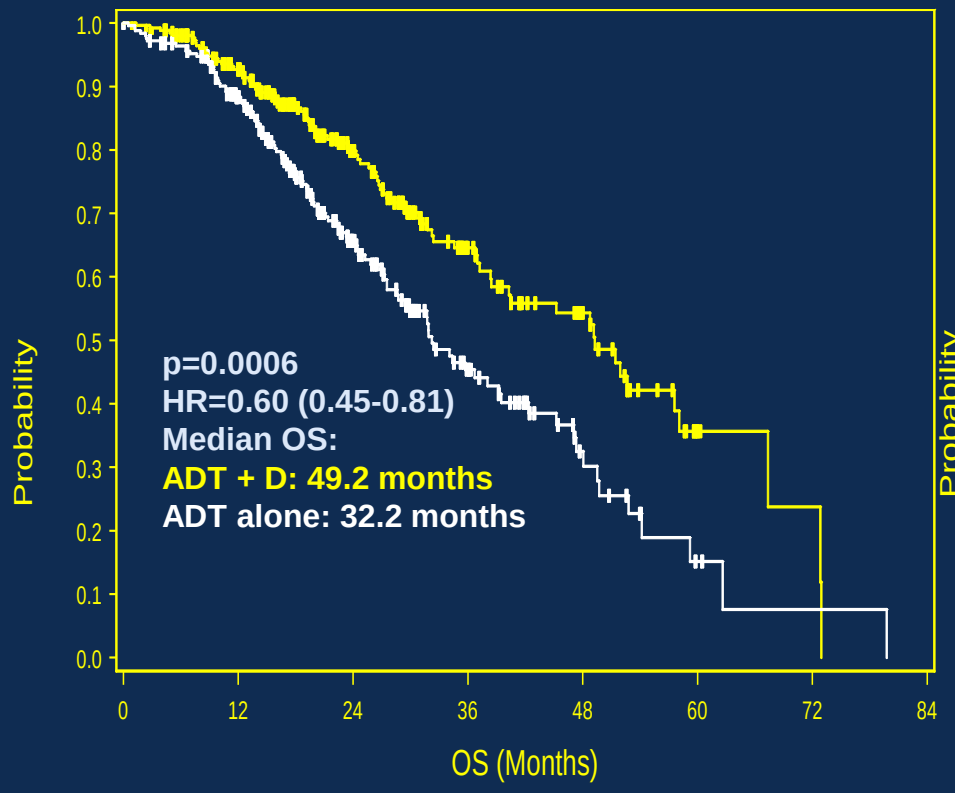
Sweeney et al, N Engl J Med, 2015



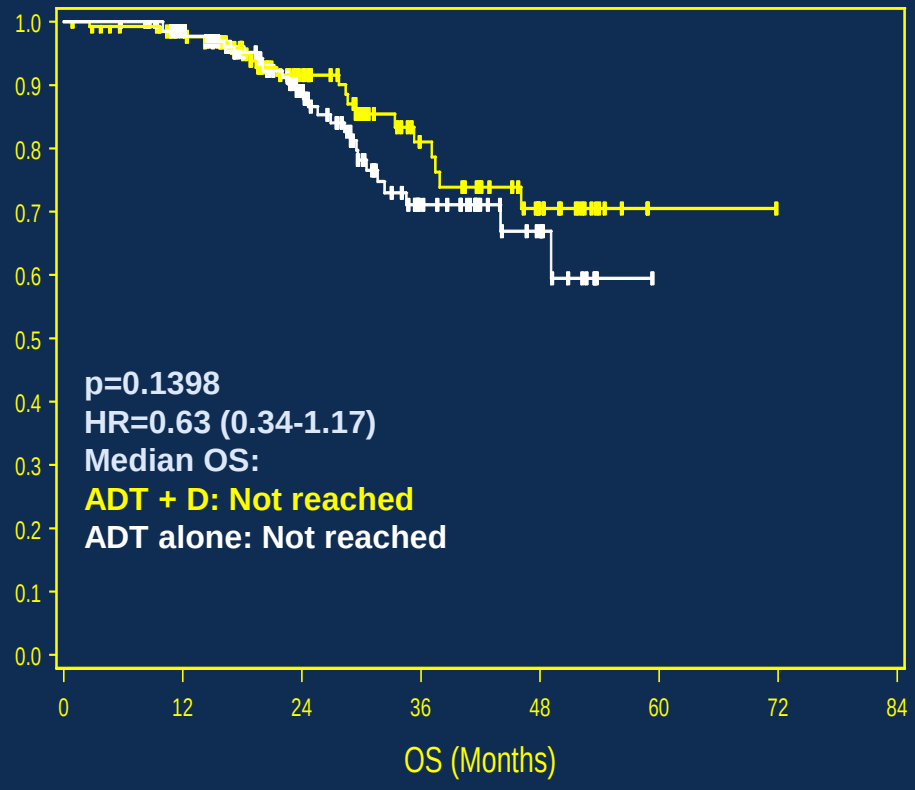
- Intermittent ADT dosing not allowed
- Standard dexamethasone premedication but no daily prednisone
- Treatment at investigator's discretion at progression

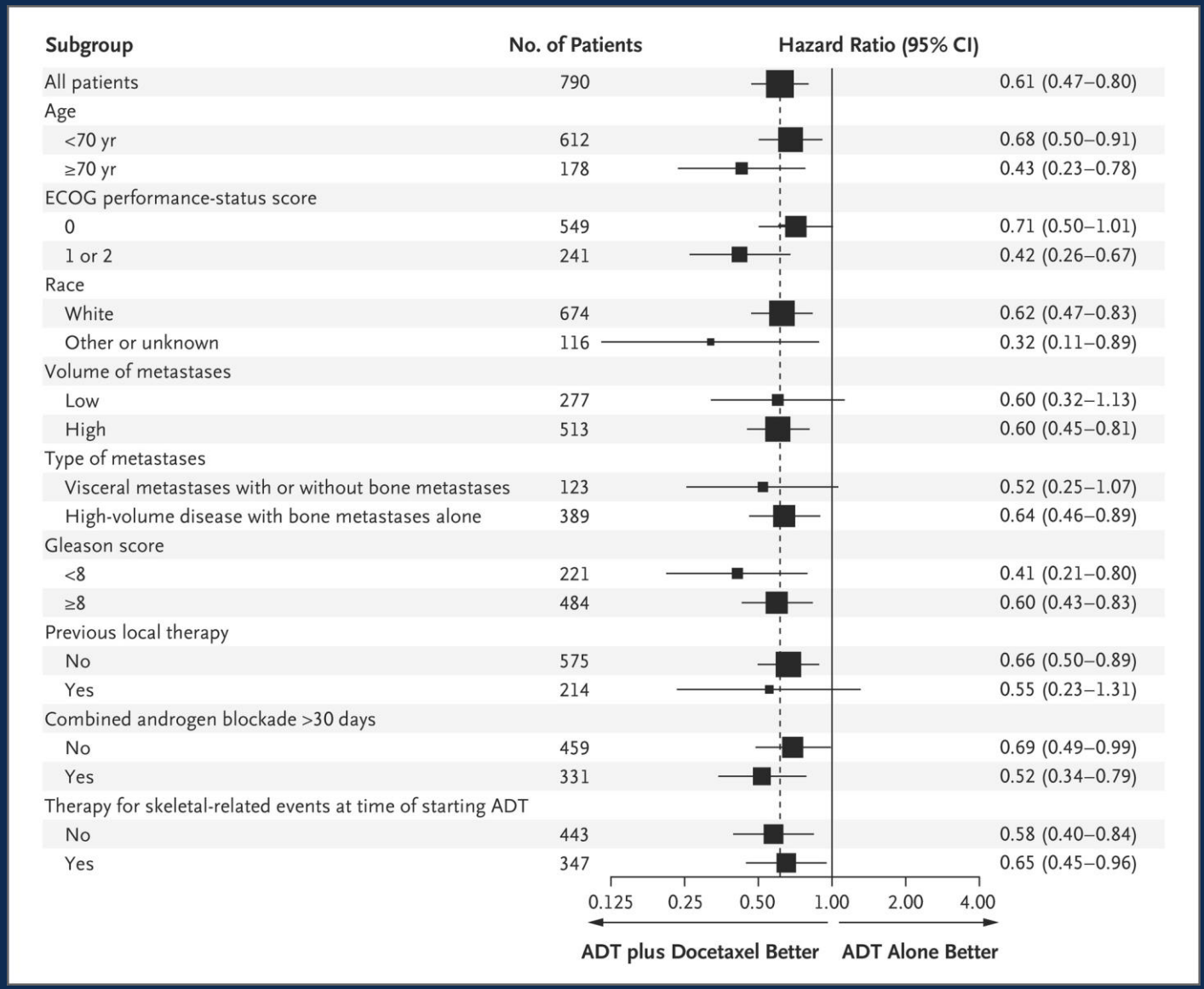
OS by extent of metastatic disease

High volume

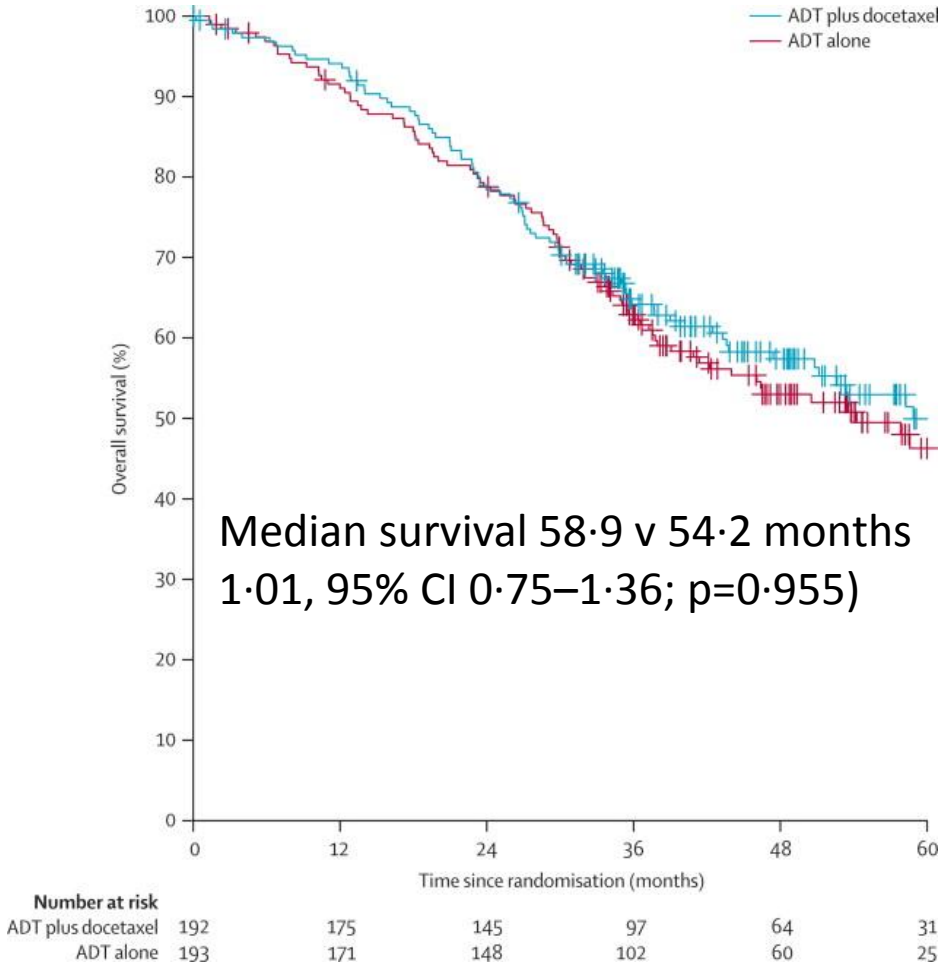


Low volume




Subgroup
No. of Patients
Hazard Ratio (95% CI)
All patients 790 0.61 (0.47–0.80)
Age
<70 yr 612 0.68 (0.50–0.91)
≥70 yr 178 0.43 (0.23–0.78)
ECOG performance-status score
0 549 0.71 (0.50–1.01)
1 or 2 241 0.42 (0.26–0.67)
Race
White 674 0.62 (0.47–0.83)
Other or unknown 116 0.32 (0.11–0.89)
Volume of metastases
Low 277 0.60 (0.32–1.13)
High 513 0.60 (0.45–0.81)
Type of metastases
Visceral metastases with or without bone metastases 123 0.52 (0.25–1.07)
High-volume disease with bone metastases alone 389 0.64 (0.46–0.89)
Gleason score
<8 221 0.41 (0.21–0.80)
≥8 484 0.60 (0.43–0.83)
Previous local therapy
No 575 0.66 (0.50–0.89)
Yes 214 0.55 (0.23–1.31)
Combined androgen blockade >30 days
No 459 0.69 (0.49–0.99)
Yes 331 0.52 (0.34–0.79)
Therapy for skeletal-related events at time of starting ADT
No 443 0.58 (0.40–0.84)
Yes 347 0.65 (0.45–0.96)
0.125
0.25
0.50
1.00
2.00
4.00
ADT plus Docetaxel Better
ADT Alone Better

The French Trial



Median survival 58·9 v 54·2 months
1·01, 95% CI 0·75–1·36; p=0·955)

Gravis, Lancet Oncology, 2013

Conclusions (in my opinion)

- ADT + Docetaxel is now the standard of care for hormone naive M1 prostate cancer in patients fit enough to receive it

- Clinical trials should be offered to all eligible patients as we remain unclear on much (STAMPEDE will allow docetaxel soon)

Open questions

- No cost effectiveness data yet (and access is patchy)
- No QOL data yet
- No data to support a selection strategy
- What to do for M0 patients?
- Should relapsing M1 patients be treated like de-novo M1 patients?
- We have very little data to inform subsequent management decisions if docetaxel is used up front
- How do we modify our MDT practices to incorporate this?
- What is the correct baseline imaging?