Management of de novo metastatic prostate cancer

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Trillium Health Partners

September 7, 2019

Princess Margaret Cancer Centre Uro-Oncology Dialogue

Disclosures

- Speaking honorarium – Pfizer

- I will discuss indications for pharmaceutical products which do not have Health Canada approval.

Objectives

- Review systemic therapy options for de novo metastatic prostate cancer
- Discuss emerging data for combination systemic therapy and local therapy mCSPC
- Raise awareness for ongoing clinical trials in mCSPC

Wine List

- ADT + docetaxel
- ADT + abiraterone
- ADT + NSAA
- How to choose?
- Is more better?
- Summary

Cases

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Case 1

- 73M presents with fatigue, low back pain
- CT scan shows bone, LN, and liver mets
- PSA 289
- Biopsy shows adeno with neuroendocrine differentiation

Case 2

- 73M presents after annual PSA with GP was 36. Some mild fatigue and low back pain.
- Bone scan shows 5 bone mets in lumber spine and pelvis. No other mets.

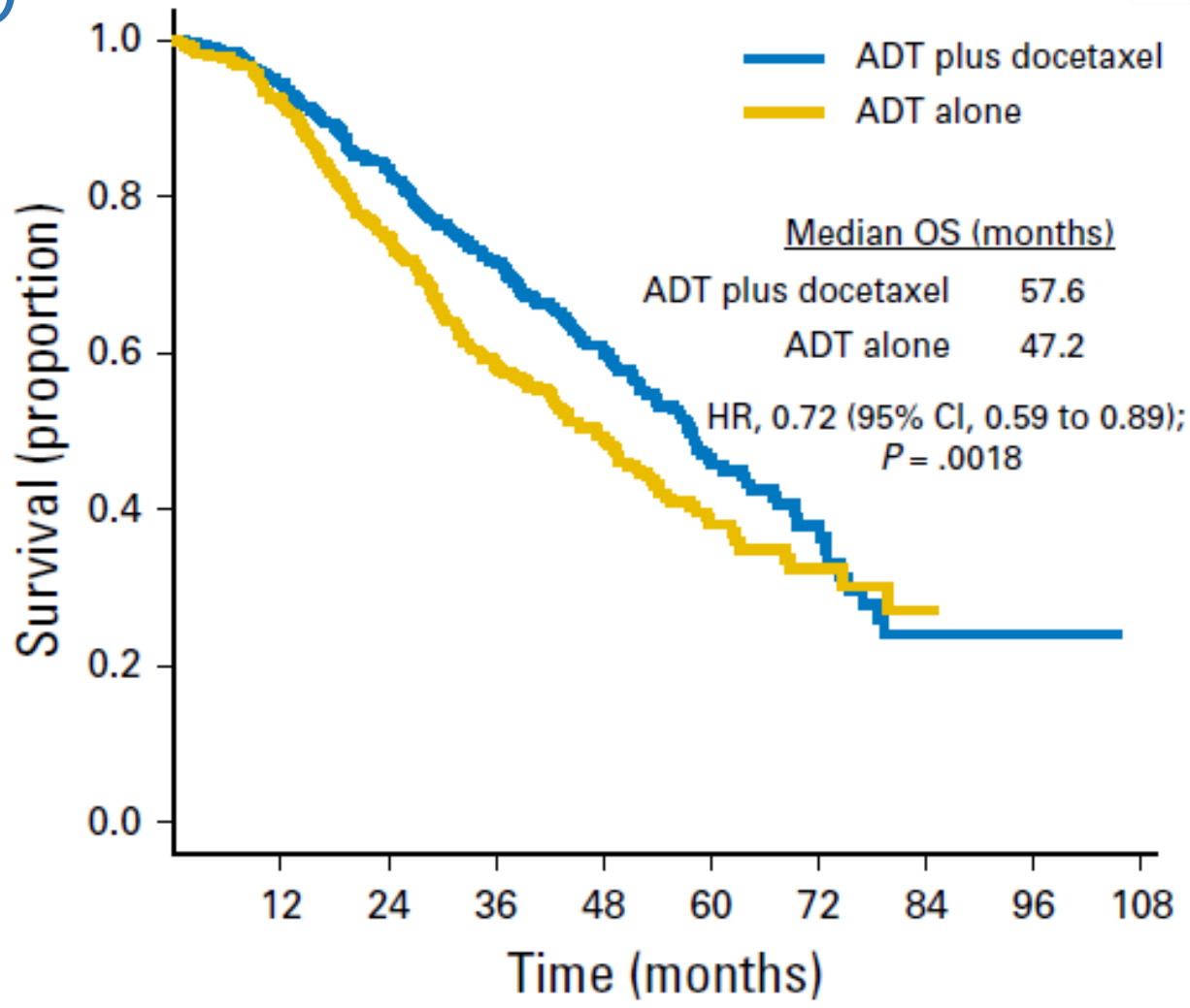
Case 3

- 73M admitted for NSTEMI. Poor mobility, socially isolated. In hospital imaging shows numerous bone mets.
- PSA 54.

ADT vs ADT + docetaxel

- 3 phase 3 trials: CHAARTED, STAMPEDE, GETUG-AFU 15
- Trial populations were slightly different in terms of de novo vs recurrent, high vs low volume
- Compared ADT to ADT + docetaxel x 6-9 cycles

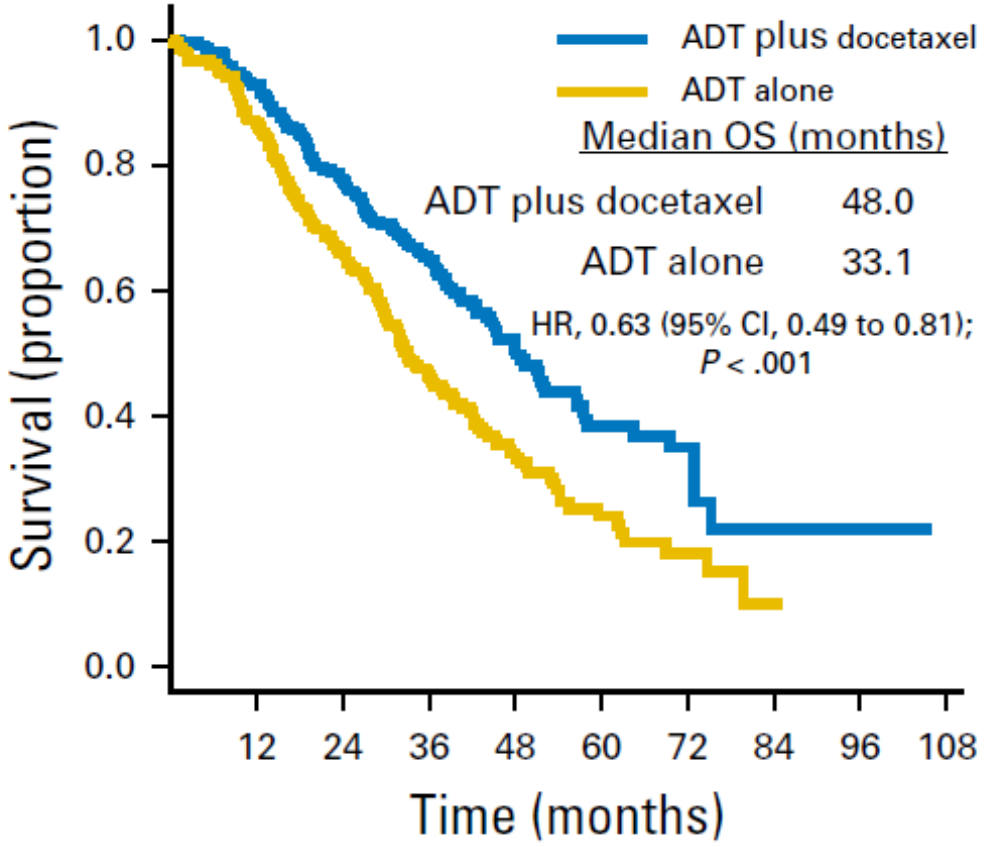
CHAARTED



No. at risk:										
ADT plus docetaxel	397	366	314	245	155	67	28	7	2	0
ADT alone	393	352	278	198	126	45	21	2	0	0

CHAARTED

HIGH VOLUME DE NOVO METASTATIC



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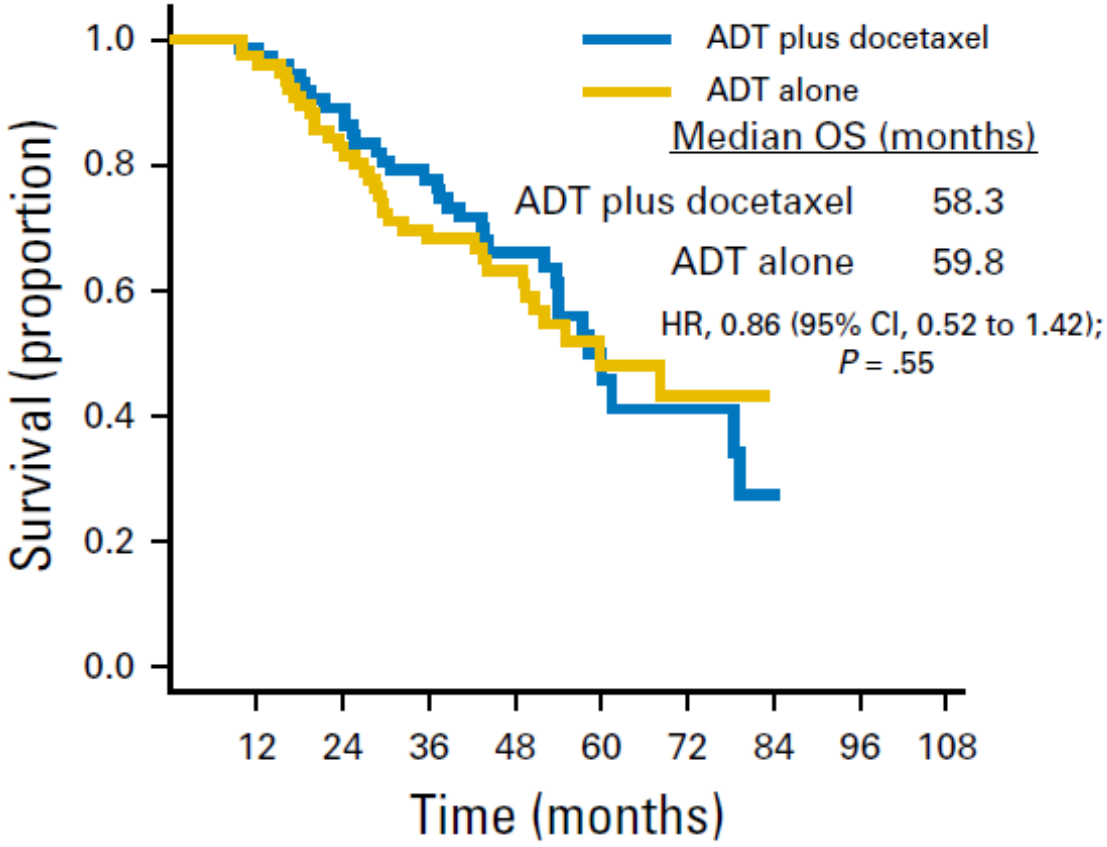
LOW VOLUME DE NOVO METASTATIC



No. at risk:										
ADT plus docetaxel	75	73	63	52	31	13	7	2	0	0
ADT alone	79	75	63	48	32	11	7	0	0	0

ADT vs ADT + docetaxel

- CHAARTED and STAMPEDE both showed a significant OS advantage to ADT + docetaxel compared to ADT alone
- GETUG-AFU 15 did not show a significant difference in OS
- Subgroup analysis from all three trials showed a greater benefit for high-volume disease compared to low-volume disease
- No significant difference between recurrent or de novo metastatic disease

Docetaxel toxicity

- Expected docetaxel toxicity profile
  - 6-15% febrile neutropenia
  - <1% treatment-related death

ADT vs ADT + docetaxel

- Docetaxel improves overall survival for patients with metastatic castrate sensitive prostate cancer
- Greatest benefit for patients with high-volume disease
- Survival advantage for both de novo and recurrent metastatic disease

ADT vs ADT + abiraterone

- Two phase 3 trials: LATITUDE and STAMPEDE
- Studies used a different patient populations
  - LATITUDE = M1 high-risk
  - STAMPEDE = M0 high-risk, N+ and M1
- No prior docetaxel
- Compared ADT to ADT + abiraterone 1000mg daily + prednisone

LATITUDE

Median OS:

ADT + placebo = 36.5mo

ADT + abiraterone+prednisone = 53.3mo

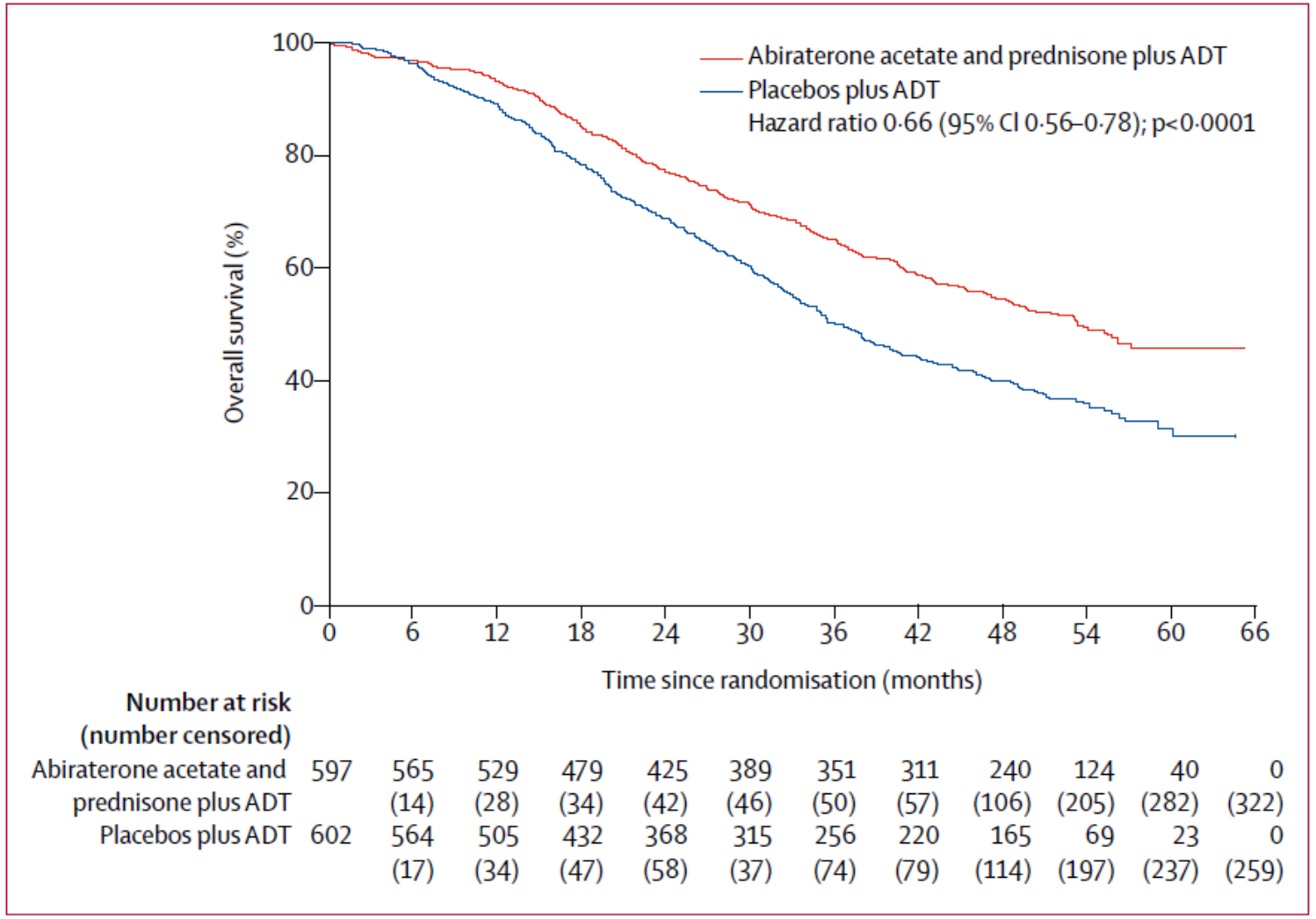


Figure 2: **Kaplan-Meier curve of overall survival in the intention-to-treat population**
ADT=androgen deprivation therapy.

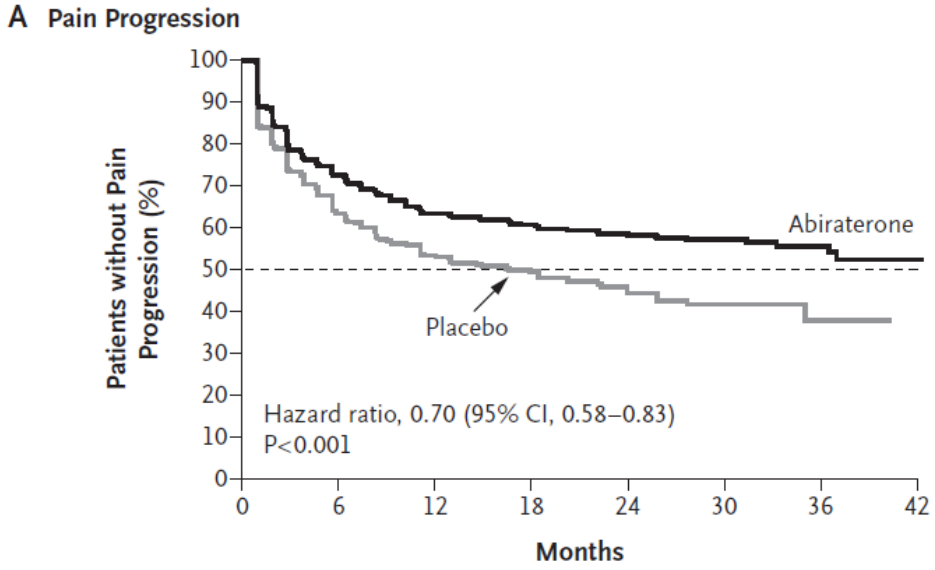
ADT vs ADT + abiraterone

- Both trials showed significant improvement in overall survival
- Significant benefit seen in subgroup of de novo metastatic disease (recurrent population quite small)
- Unclear of the interaction with disease volume

Abiraterone HR-QOL

- Addition of abiraterone improved time to skeletal related events

- Addition of abieraterone improved proportion living without pain



Abiraterone toxicity

- Expected side-effect profile as seen in CRPC setting

- Grade 3-4:
  - hypertension = 20%
  - Hypokalemia = 11%
  - Transaminitis = 4-7%

ADT vs ADT + abiraterone

- Abiraterone + prednisone improves overall survival for patients with metastatic castrate sensitive prostate cancer

- Abiraterone + prednisone reduces proportion living with pain and time to skeletal-related events

ADT vs ADT + NSAA

** neither apalutamide nor enzalutamide have Health Canada indications for castrate-sensitive prostate cancer **

- Three phase 3 trials: TITAN (apalutamide vs placebo), ARCHES (enzalutamide vs placebo), ENZAMET (enzalutamide vs 1st Gen NSAA)
- All M1 CSPC
- 10-25% of patients received prior docetaxel

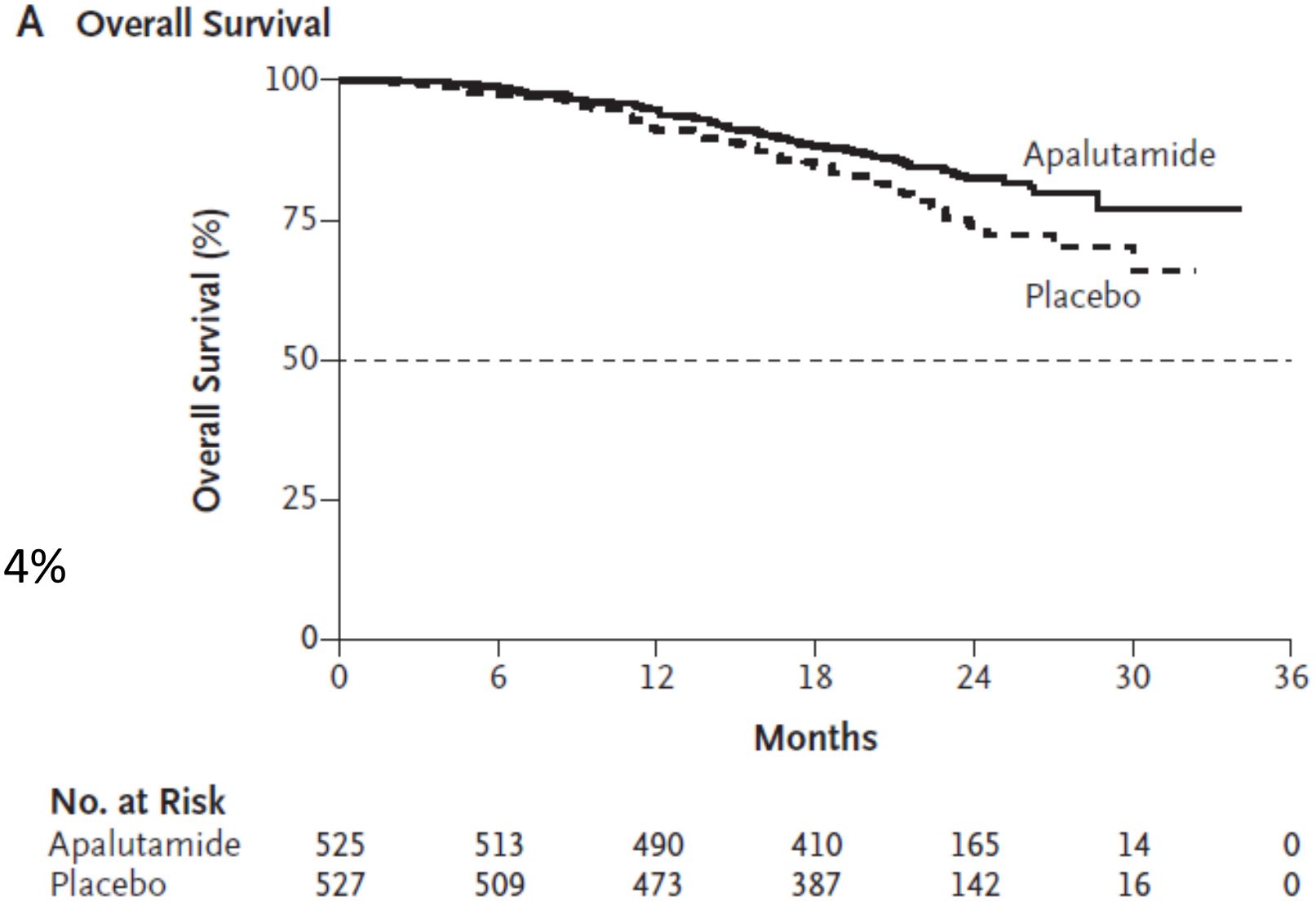
TITAN

2y OS:

ADT + placebo = 73.5%

ADT + apalutamide = 82.4%

HR 0.67, 95% CI 0.51-0.89

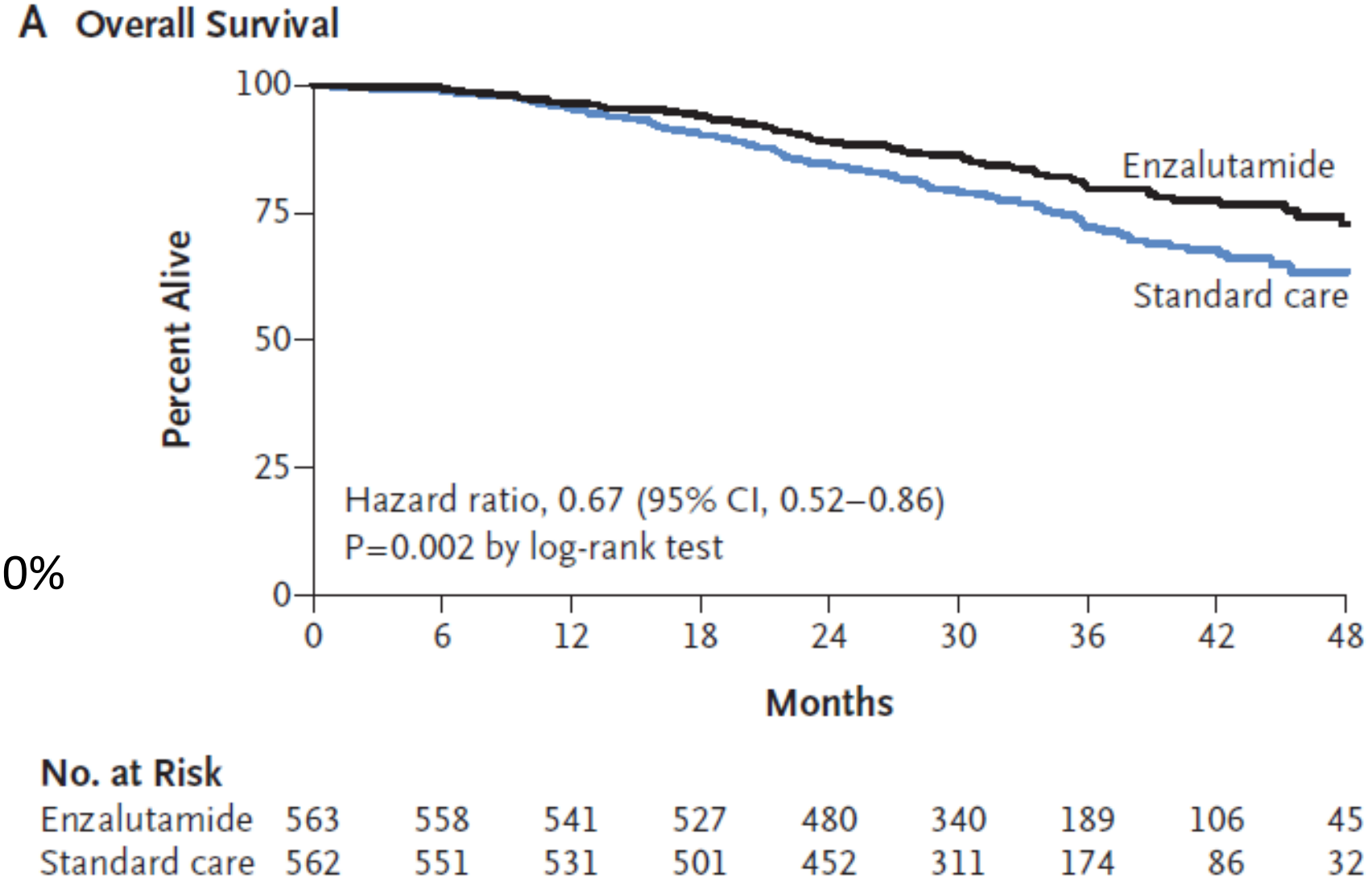


ENZAMET

3y OS:

ADT + placebo = 72%

ADT + enzalutamide = 80%



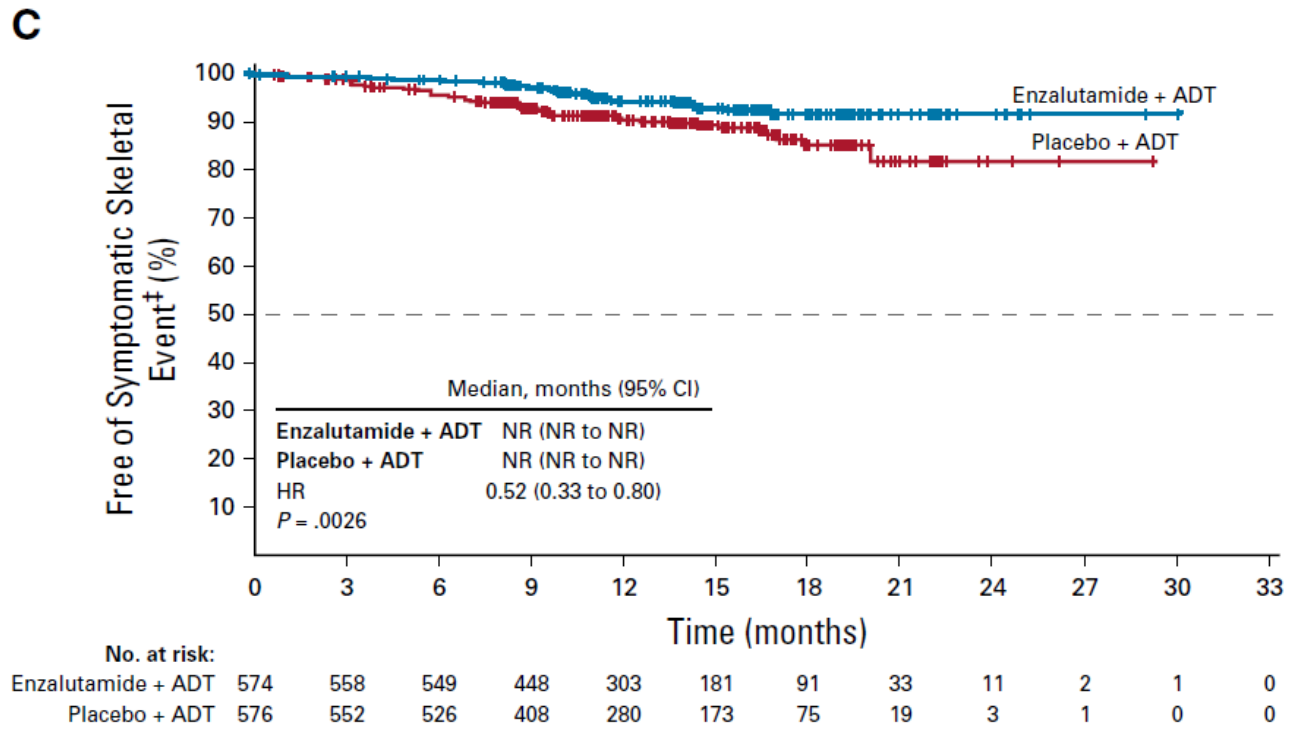
ADT vs ADT + NSAA

- TITAN and ENZAMET have shown improvement in OS for addition of NSAA
- Both trials showed improvement in OS for low and high-volume disease
- Improvement in OS for both de novo and recurrent metastatic disease

NSAA HR-QOL

- Addition of NSAA reduced time to symptomatic skeletal event and time to clinical progression

- Most QOL data is not mature



NSAA Toxicity

- Apalutamide:
  - Rash 27% (Grade 3-4 = 6%)
  - Hypothyroid 6% (Grade 3-4 = 0%)

- Enzalutamide
  - As seen with CRPC
  - Seizure 2% (Grade 3-4 = <1%)
  - Fatigue (Grade 3-4 = 6%)
  - Hypertension (Grade 3-4 = 8%)

ADT vs ADT + NSAA

- Addition of NSAA to ADT improves OS for de novo metastatic prostate cancer
- Improvement in OS for both de novo and recurrent mCSPC
- Improvement in OS for both low and high-volume disease
- QOL data is early but some improvement in time to symptomatic skeletal events and time to clinical progression

How to choose?

- STAMPEDE direct comparison of docetaxel and abiraterone arms did not show any significant difference in survival
  - Worst toxicity profile was similar between two arms but different

- Network meta-analysis (GETUG, CHAARTED, STAMPEDE, LATITUDE) showed no significant difference in survival, suggests slightly better QOL data for abiraterone

- No comparison trials between docetaxel and NSAA or abiraterone and NSAA

Sydes Ann Oncol 2018, Feyerabend Eur J Oncol 2019

Why choose - add more?

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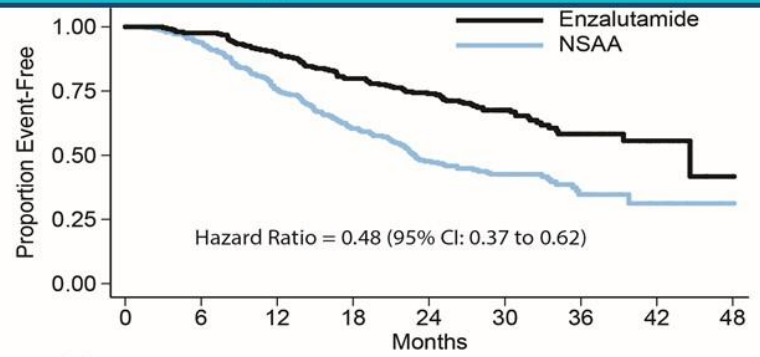
Concurrent Docetaxel: Prespecified Subgroup of Interest (Biology and Treatment Implications)

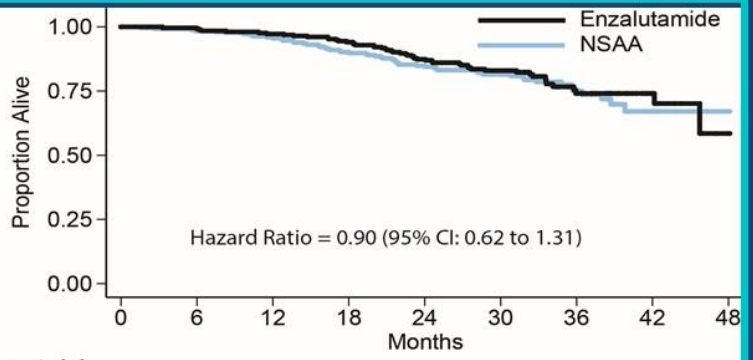
Clinical Progression-Free Survival

Overall Survival

Testosterone Suppression + Docetaxel N=503 (71% High Volume)

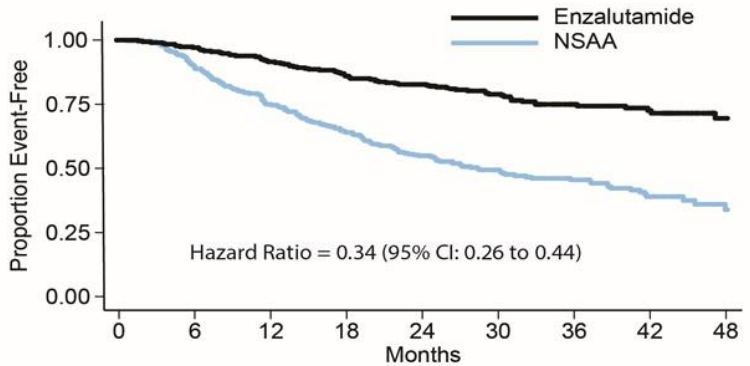


Number at risk									
NSAA	249	230	185	148	112	73	21	6	1
Enzalutamide	254	248	226	202	178	109	35	12	2

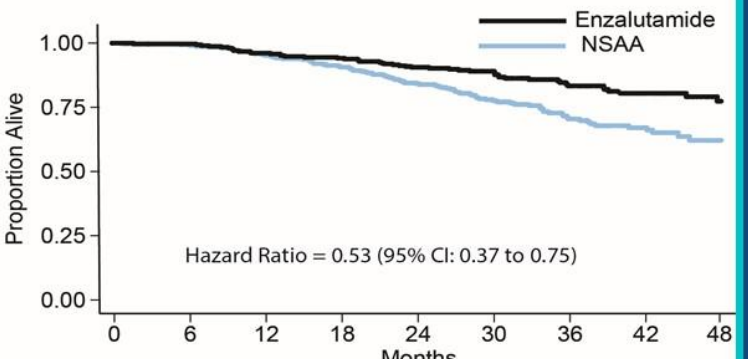


Number at risk									
NSAA	249	241	235	220	203	135	56	13	2
Enzalutamide	254	252	246	238	210	139	54	19	3

Testosterone Suppression + No Docetaxel N=622 (37% High Volume)



Number at risk									
NSAA	313	282	233	198	160	109	75	44	16
Enzalutamide	309	299	281	266	246	175	121	72	34



Number at risk									
NSAA	313	310	296	281	249	176	118	73	30
Enzalutamide	309	306	295	289	270	201	135	87	42

ADT vs ADT + docetaxel + NSAA

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- Subgroup analysis of TITAN and ENZAMET did show significant difference in OS for NSAA in patients with prior docetaxel but there was an improvement in PFS

- Ongoing studies:
  - ARASENS – mCSPC treated with ADT+docetaxel +/- darolutamide
  - PEACE-1 trial – mCSPC ADT+docetaxel +/- abiraterone +/- radiotherapy

Treatment of the primary

- STAMPEDE population randomized to radiotherapy or no radiotherapy to the primary tumour
  - Prior docetaxel (18%) but no abiraterone

- Whole population:
  - Improvement in failure free survival but not overall survival (HR 0.92, 95% CI 0.80-1.06)

- Low-volume disease
  - Improvement in 3yr OS (81% vs 73%, HR 0.68, 95% CI 0.52 to 0.90)

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- PSA 54.

Summary

- ADT-alone, docetaxel and abiraterone are treatment options for selected patients with de novo metastatic prostate cancer

- Recent trial data show promising results for addition of NSAA to ADT in this patient population.

- Further data is needed understand role of abiraterone or NSAA for patients who received docetaxel.

Thank you

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Go Bianca!

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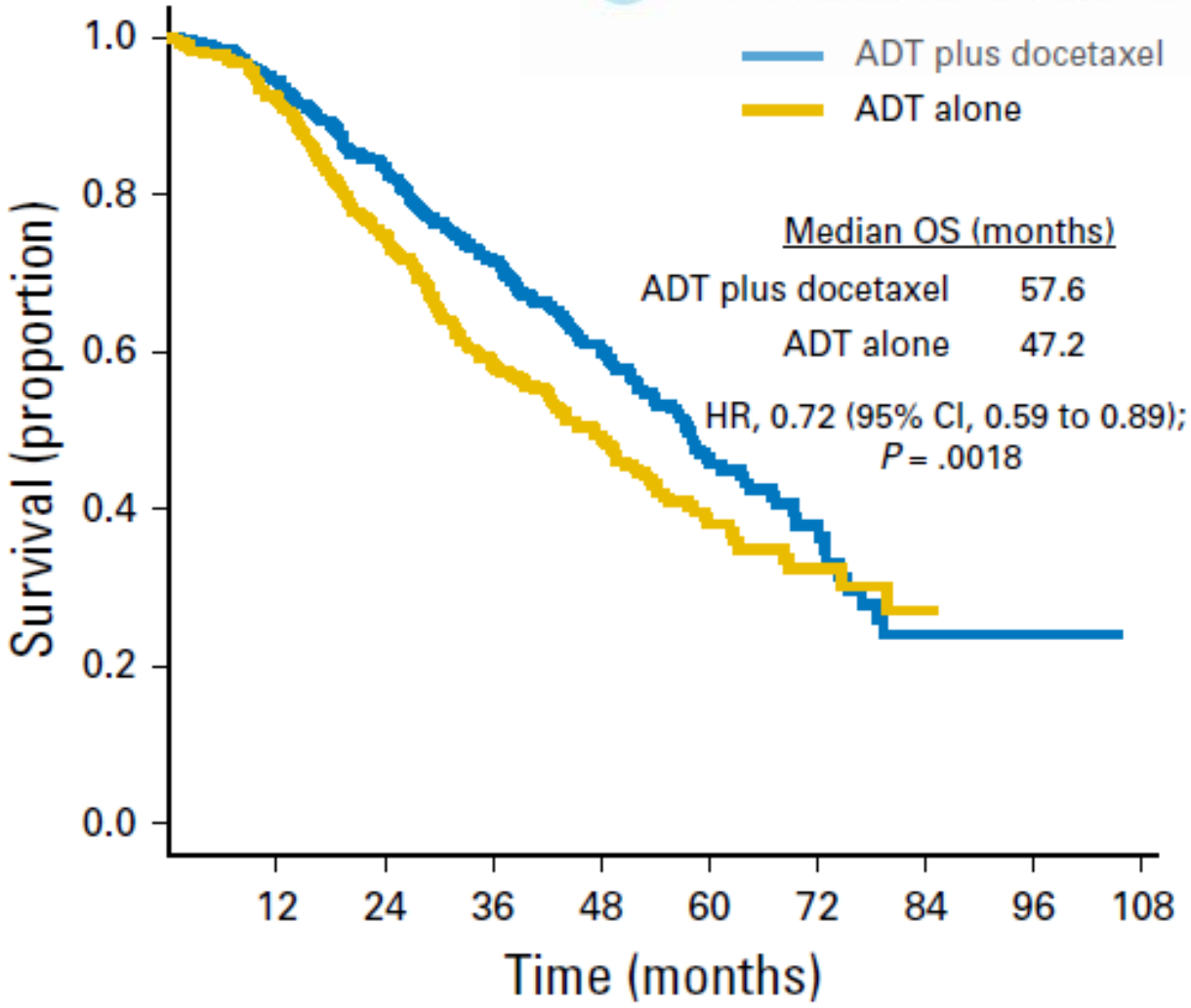
CHAARTED

- Newly diagnosed metastatic (M1) CSPC
  - Median age 64
  - De novo metastatic 72.8%

- Arm A: ADT
- Arm B: ADT + docetaxel x 6 cycles



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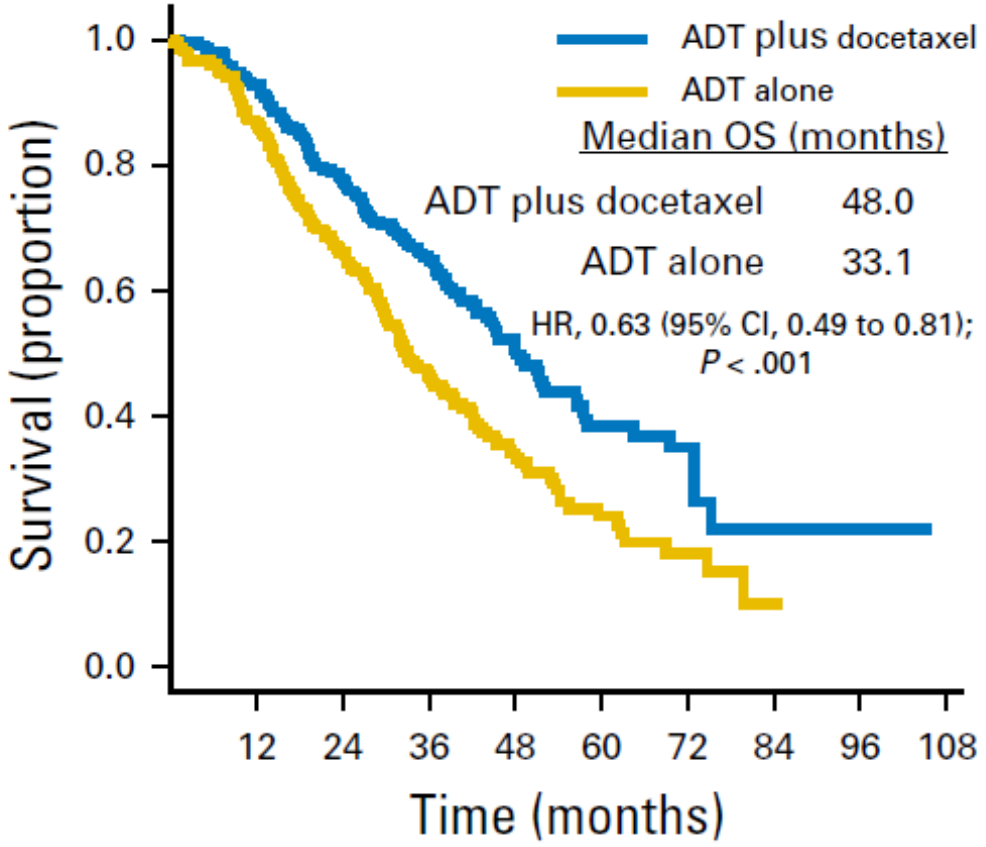

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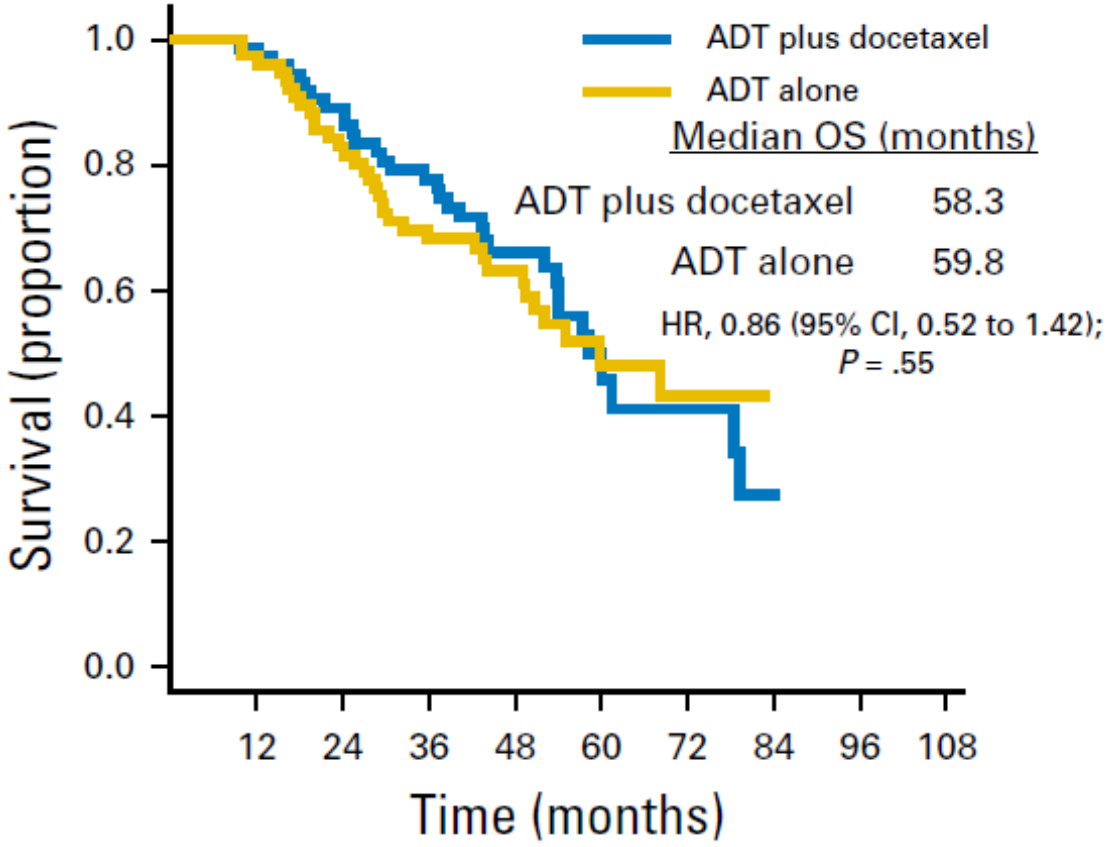

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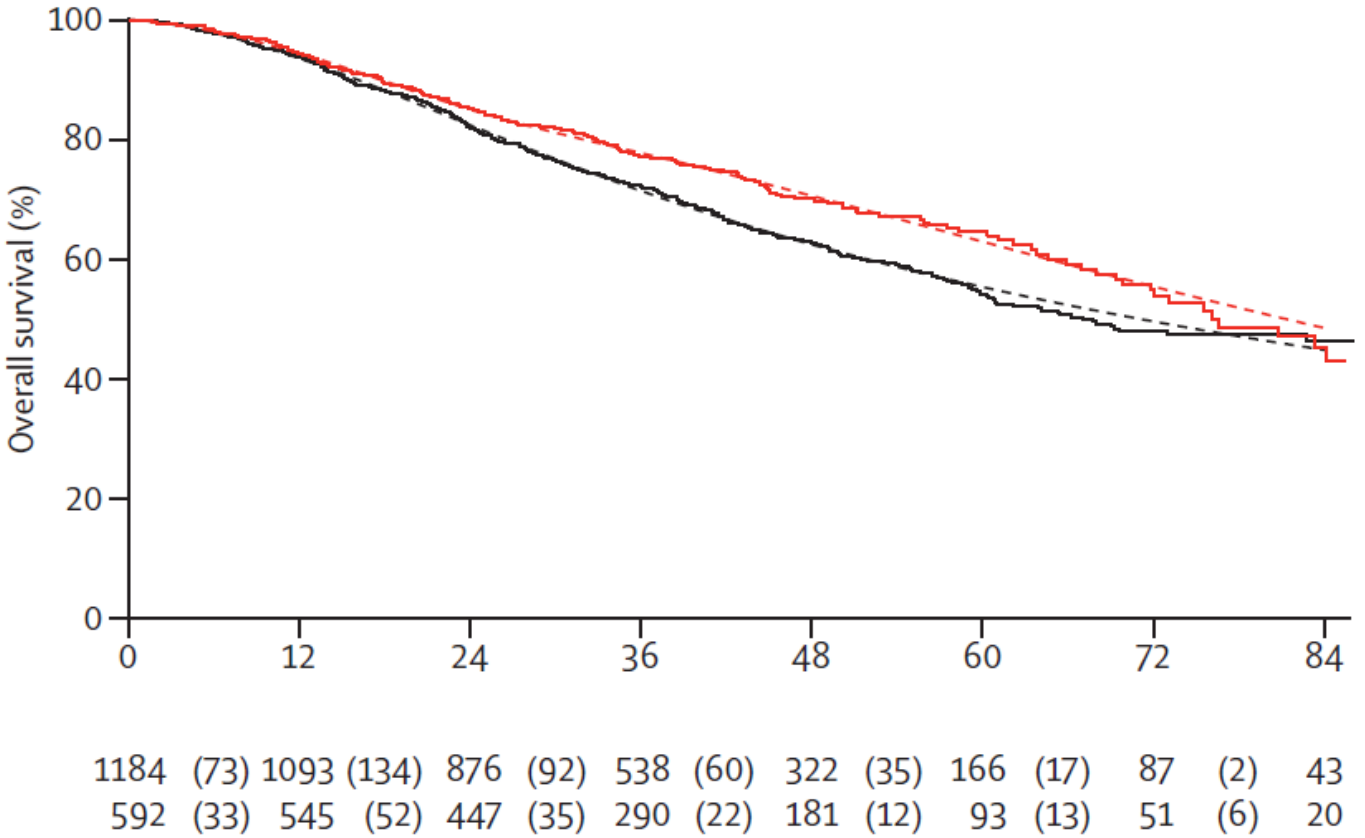
STAMPEDE

- Advanced prostate cancer
  - Recurrent (3%)
  - M1 (59%) and/or
  - N+ (15%) and/or
  - high-risk locally advanced (22%) defined as 2 of 3: (i) T3-4, (ii) Gleason 8-10, (iii) PSA $\geq$ 40
  - Median age 65
- Arm A: Standard of care
- Arm B: Standard of care + docetaxel + prednisone x 6 cycles



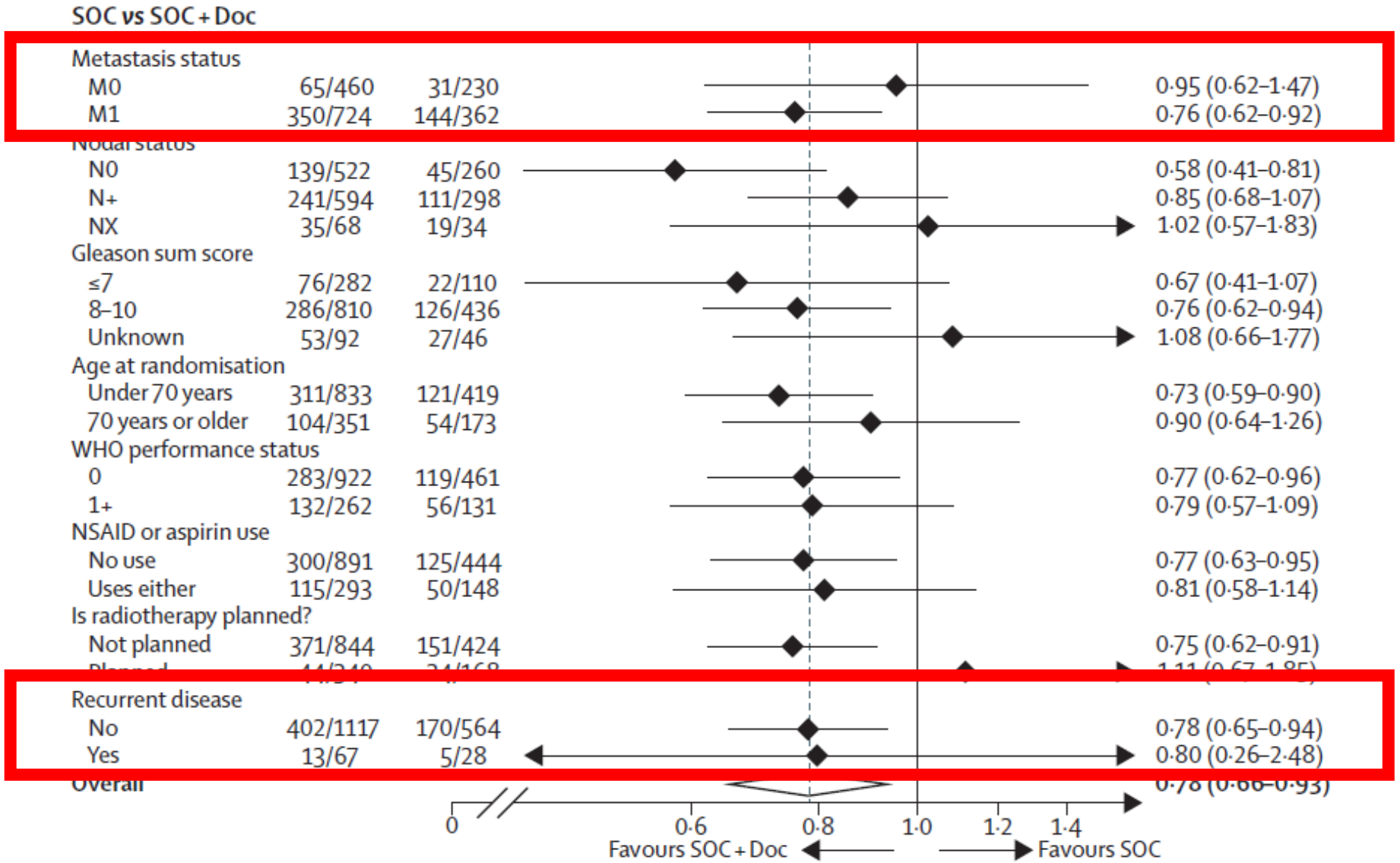
Median OS:

SOC = 71mo

SOC+Doc = 81mo

HR 0.78, 95% CI 0.66-0.93

STAMPEDE


SOC vs SOC + Doc
Metastasis status
M0 65/460 31/230 0·95 (0·62–1·47)
M1 350/724 144/362 0·76 (0·62–0·92)
Nodal status
N0 139/522 45/260 0·58 (0·41–0·81)
N+ 241/594 111/298 0·85 (0·68–1·07)
NX 35/68 19/34 1·02 (0·57–1·83)
Gleason sum score
≤7 76/282 22/110 0·67 (0·41–1·07)
8–10 286/810 126/436 0·76 (0·62–0·94)
Unknown 53/92 27/46 1·08 (0·66–1·77)
Age at randomisation
Under 70 years 311/833 121/419 0·73 (0·59–0·90)
70 years or older 104/351 54/173 0·90 (0·64–1·26)
WHO performance status
0 283/922 119/461 0·77 (0·62–0·96)
1+ 132/262 56/131 0·79 (0·57–1·09)
NSAID or aspirin use
No use 300/891 125/444 0·77 (0·63–0·95)
Uses either 115/293 50/148 0·81 (0·58–1·14)
Is radiotherapy planned?
Not planned 371/844 151/424 0·75 (0·62–0·91)
Recurrent disease
No 402/1117 170/564 0·78 (0·65–0·94)
Yes 13/67 5/28 0·80 (0·26–2·48)
Overall
0·78 (0·66–0·93)
0
0·6
0·8
1·0
1·2
1·4
Favours SOC + Doc
Favours SOC

GETUG-AFU 15

- Newly diagnosed metastatic (M1) CSPC
  - Median age 64
  - De novo metastatic 72.0%
- Arm A: ADT
- Arm B: ADT + docetaxel x 9 cycles

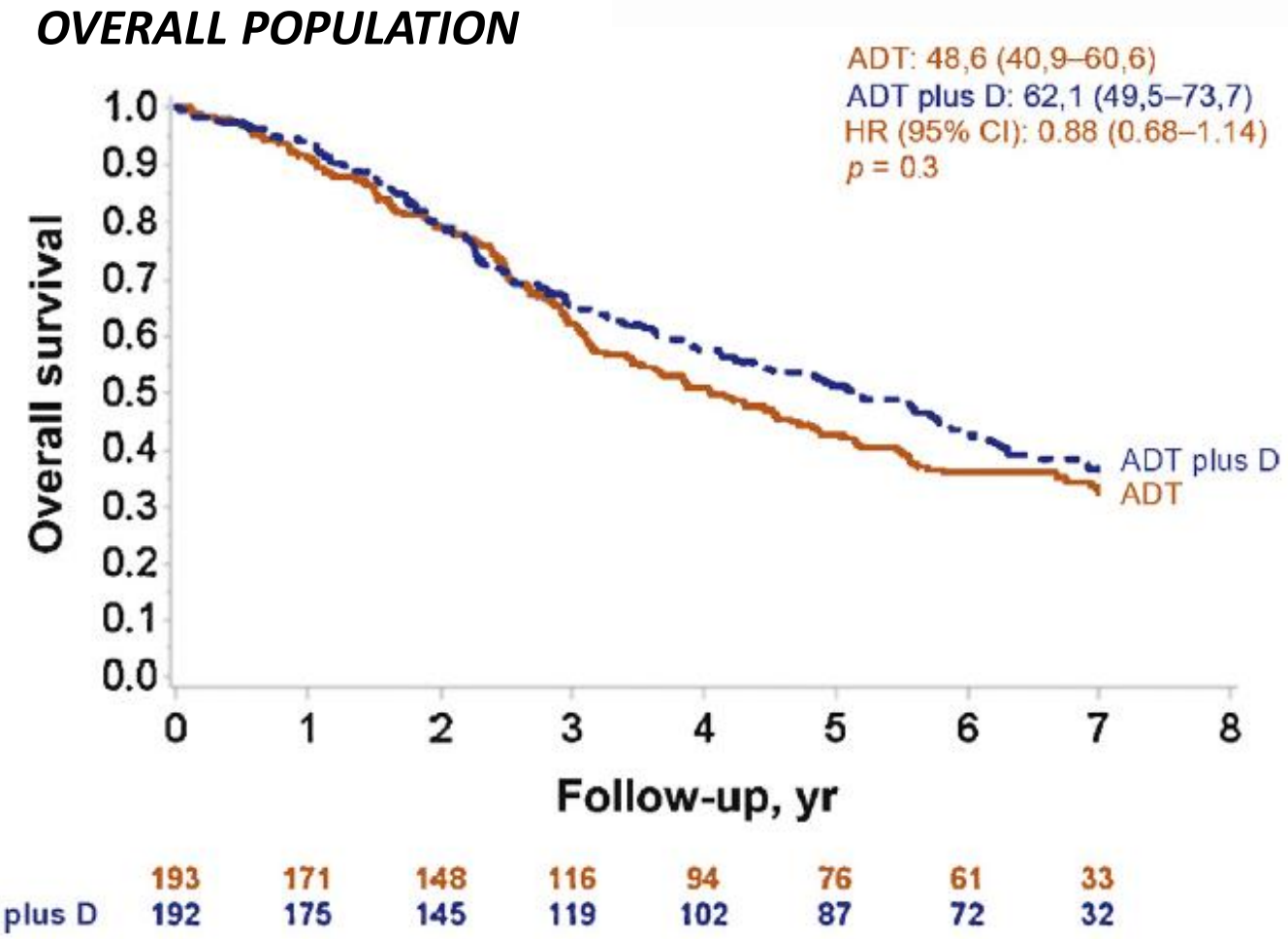


Fig. 1 – Overall survival in the overall population.
ADT = androgen-deprivation therapy; CI = confidence interval; D = docetaxel; HR = hazard ratio.

GETUG-AFU 15

- Similar HR to CHAARTED and STAMPEDE but not statistically significant

HIGH VOLUME DISEASE POPULATION

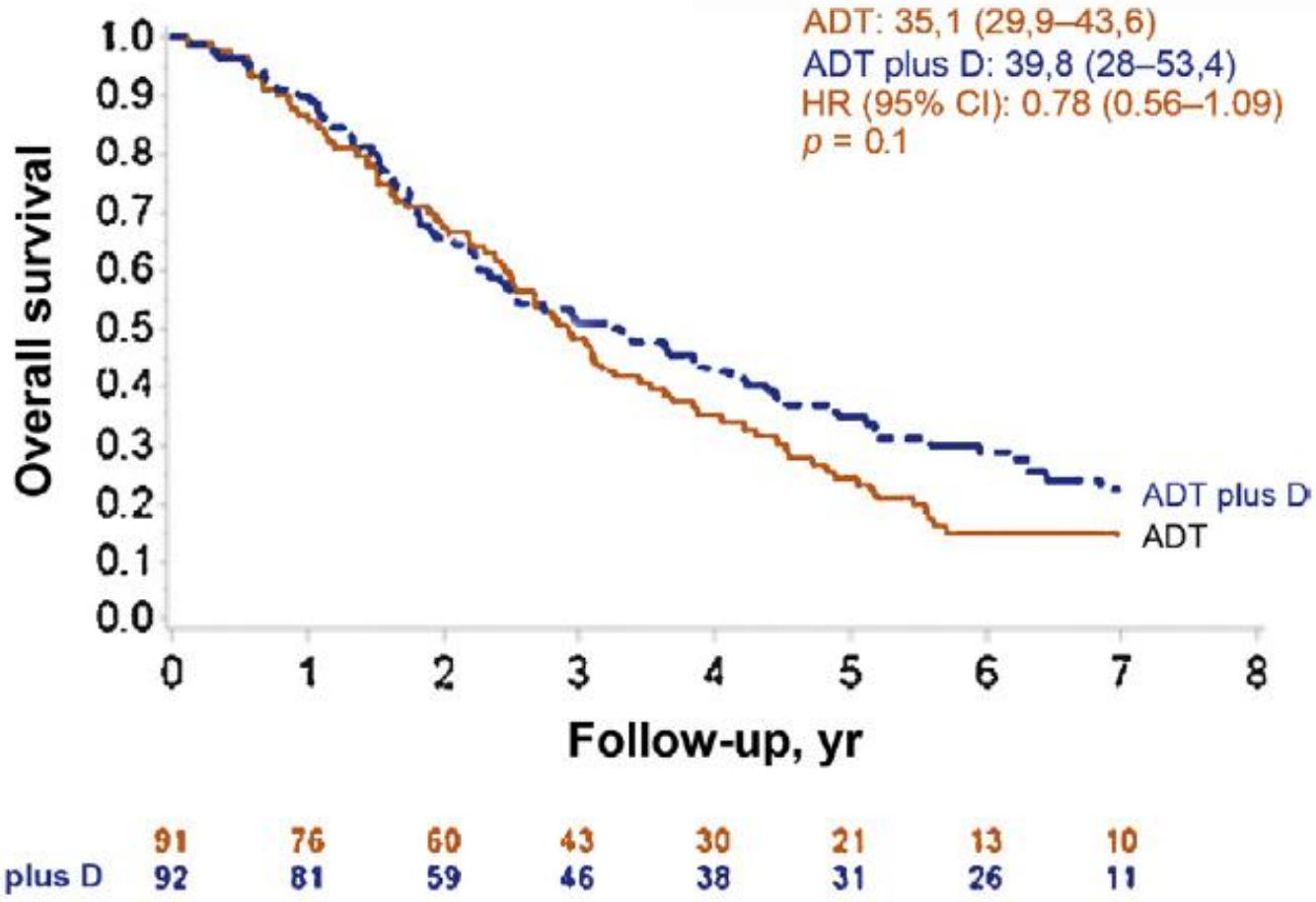


Fig. 2 – Overall survival for patients with high-volume disease. ADT = androgen-deprivation therapy; CI = confidence interval; D = docetaxel; HR = hazard ratio.

LATITUDE

- Newly diagnosed high-risk M1 prostate cancer
  - 2 of 3:
    - Gleason ≥ 8
    - ≥ 3 bone mets
    - ≥1 visceral met
  - Prior docetaxel = none
  - Median age 67
  - De novo NR%

- Arm A: ADT + placebo
- Arm B: ADT + abiraterone + prednisone

Median OS:

ADT + placebo = 36.5mo

ADT + abiraterone+prednisone = 53.3mo

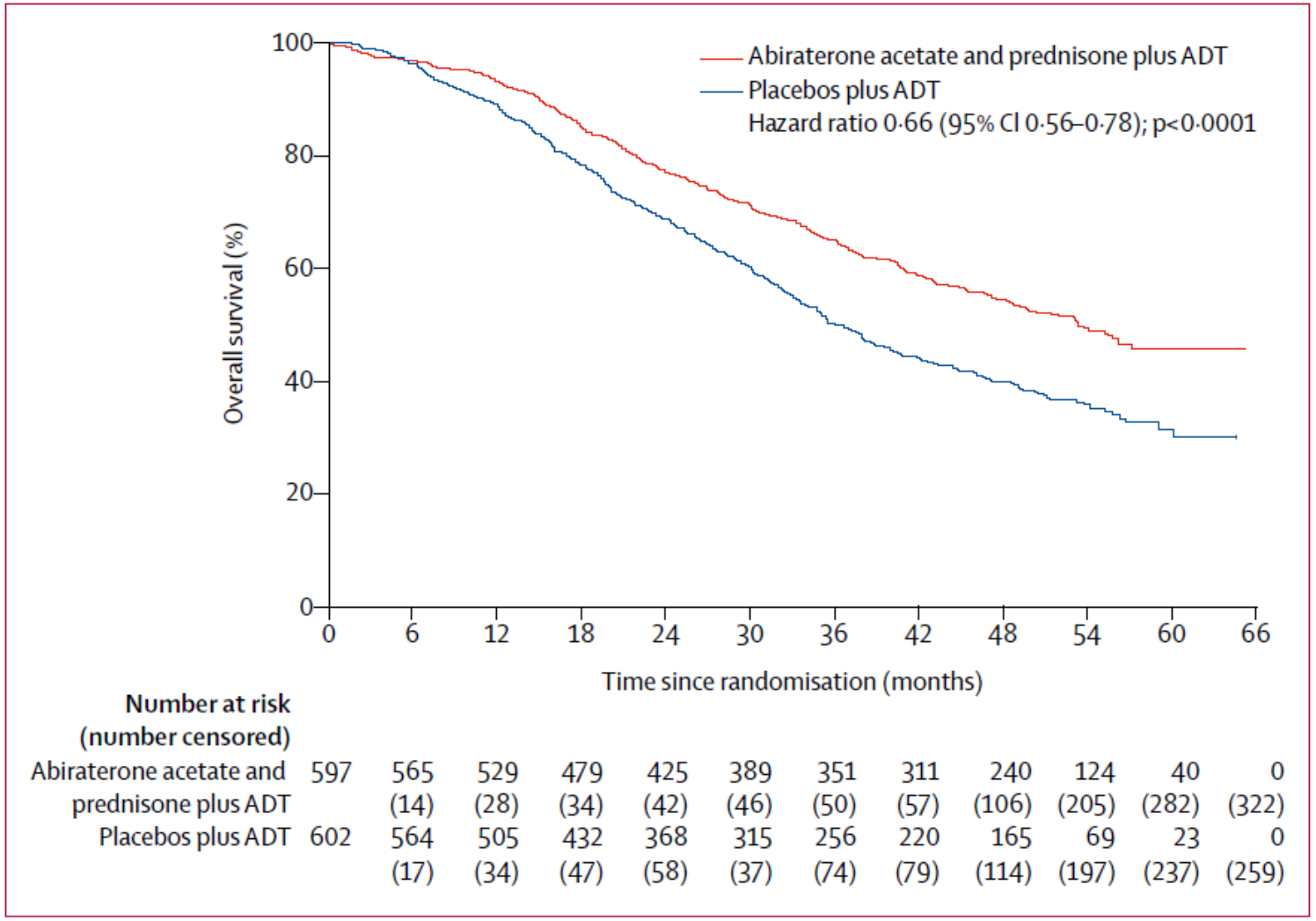


Figure 2: **Kaplan-Meier curve of overall survival in the intention-to-treat population**
ADT=androgen deprivation therapy.

STAMPEDE

Median OS (not reported):
SOC = ~ 42mo
SOC + abiraterone+prednisone = NR

HR 0.61

- Advanced prostate cancer
  - Recurrent (4%)
  - M1 (49%) and/or
  - N+ (20%) and/or
  - high-risk locally advanced (27%) defined as 2 of 3: (i) T3-4, (ii) Gleason 8-10, (iii) PSA ≥ 40
  - Prior docetaxel = none
  - Median age 67

- Arm A: Standard of care
- Arm B: Standard of care + abiraterone + prednisone