Focus sulla malattia metastatica ormonosensibile (mHSPC)
ADT e Chemioterapia: quando e a chi ?

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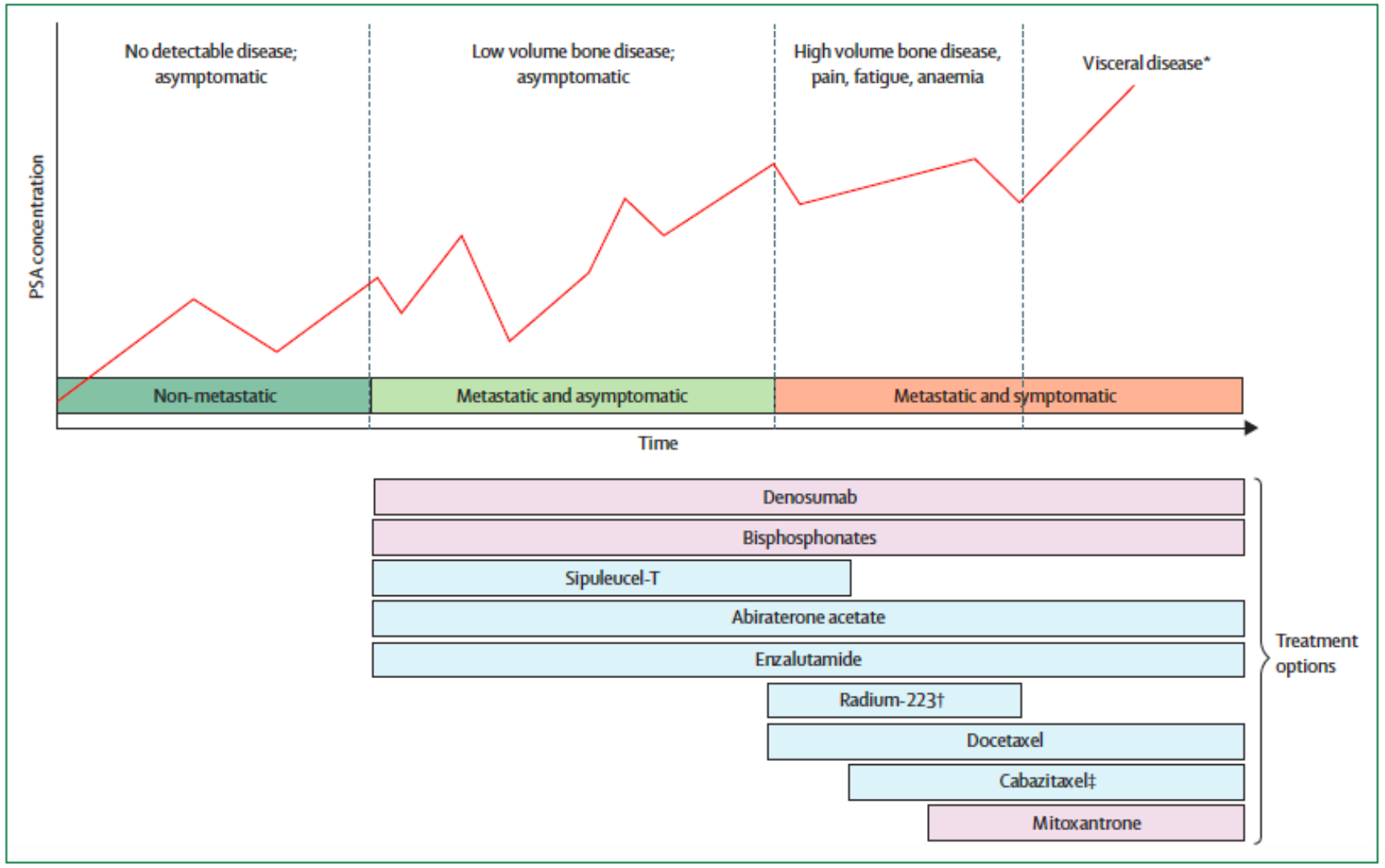
Gestione ottimale del paziente con carcinoma della prostata - Milano, 25-26.09.18

Disclosures

- No pertinent C.O.I. with this presentation
- Advisory Boards/Honoraria/Consultant for:
  - Astellas
  - BMS
  - Janssen
  - Merk
  - Pfizer
  - Roche

Progress in Management of PCa



Modified by Lorente D, Lancet Oncology 2015; 16: e279–92

Progress in Management of PCa

- mCRPC – 2011 paradigm shift
  - Novel AR-targeted agents pre-chemotherapy
- mHSPC – 2014 paradigm shift
  - ADT + Docetaxel in newly diagnosed M1 disease
- mHSPC – 2017
  - ADT + Abiraterone in newly diagnosed M1 disease

EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer 2018 (http://uroweb.org)

Why choose to candidate the patient for chemotherapy?

Rationale

- Mature results with a robust clinical benefit (at least in high-volume disease)

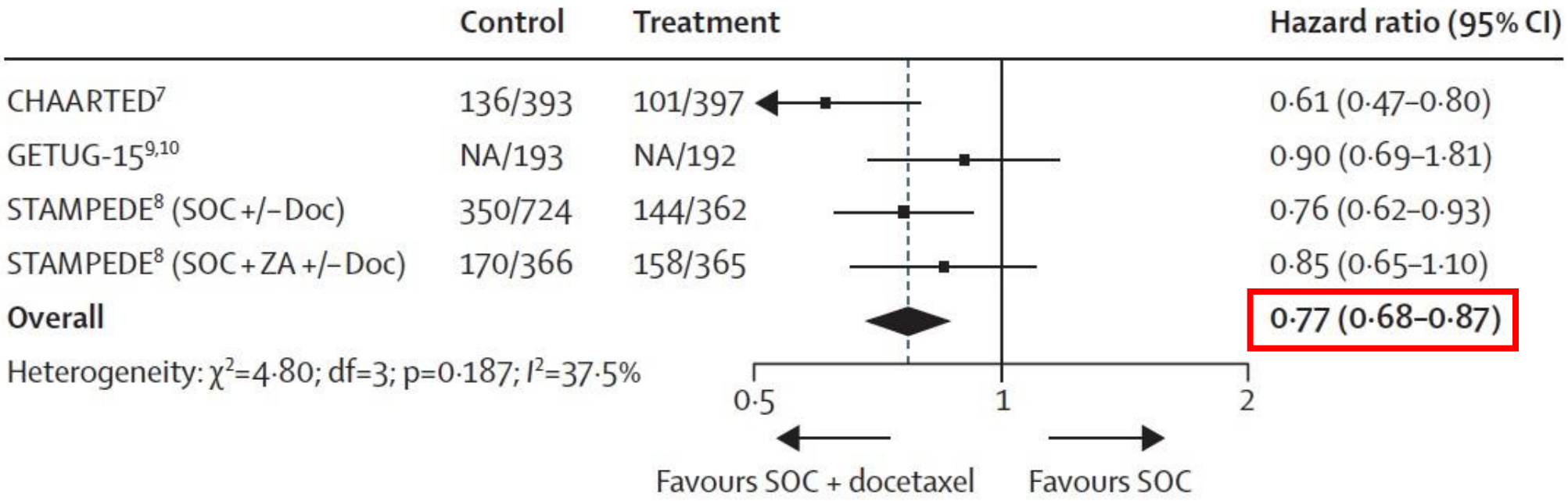
Phase III Studies in mHSPC

Study	Agents	N	Median FU (Months)	Median OS (Months)
CHAARTED[1]	DOC vs ADT	790	53.7	57.6 vs 47.2
STAMPEDE[2]	DOC/P vs ADT	1,086	43	60 vs 45
GETUG 15[3]	DOC vs ADT	385	83	62.1 vs 48.6
LATITUDE[4]	ABI/P vs ADT	1,199	30.4	Not reached vs 34.7
STAMPEDE[5]	ABI/P vs ADT	1,002	40	Not reached

1. Kyriakopoulos C, et al. J Clin Oncol. 2018;doi:10.1200/JCO.2017.75.3657; 2. James ND, et al. Lancet. 2016;387:1163-77; 3. Gravis G, et al. Eur Urol. 2016;70:256-62; 4. Fizazi K, et al. N Engl J Med. 2017;377:352-60; 5. James ND, et al. N Engl J Med. 2017;377:352-60.

ADT + Docetaxel in M1 HSPC

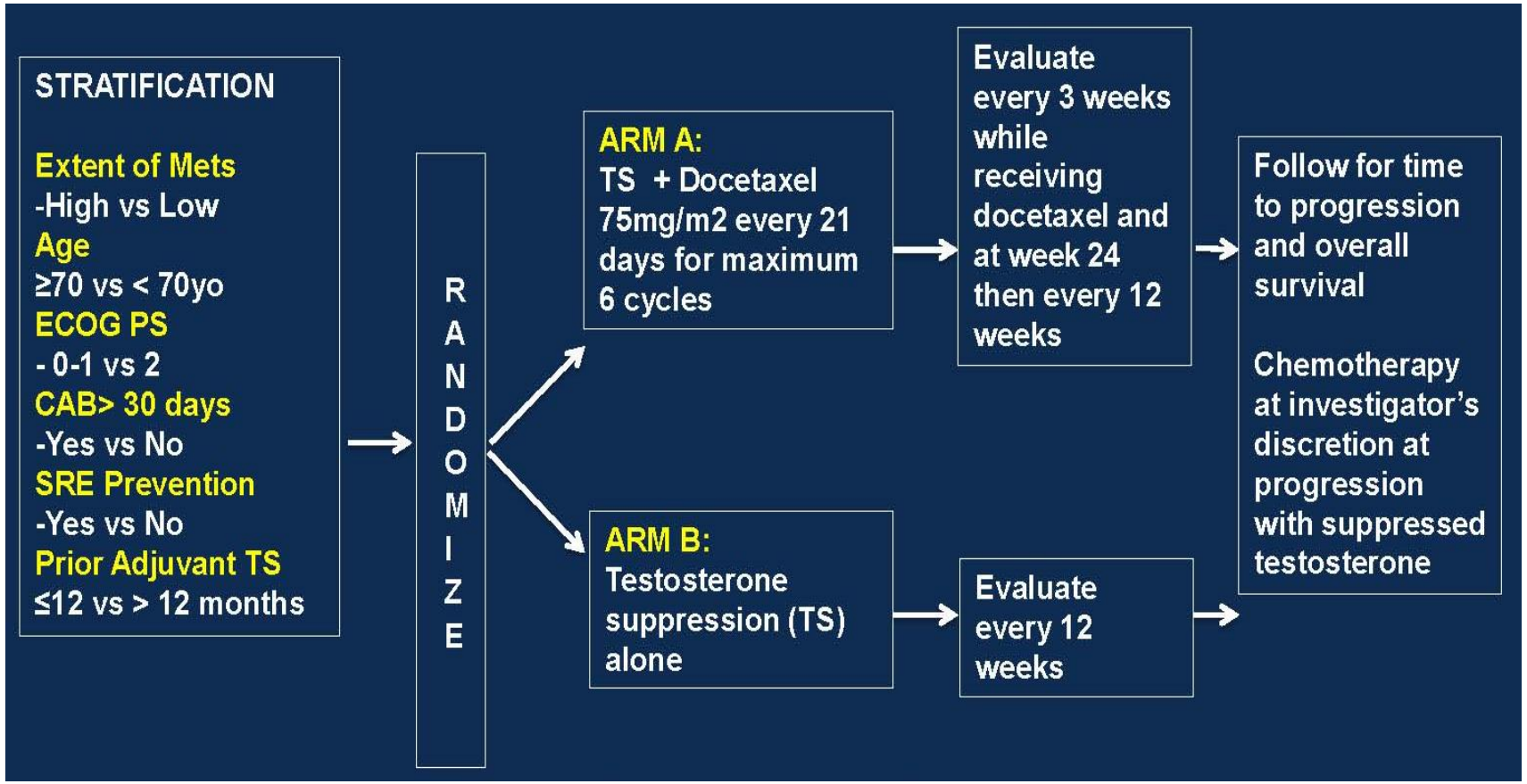
Results based on 2,993 men / 1,254 deaths



Absolute 9% OS benefit at 4 years
Most men with newly diagnosed PCa

Vale CL, et al. Lancet Oncol. 2016;17:243-56.

CHAARTED – ADT+DOC in M1 HNPC

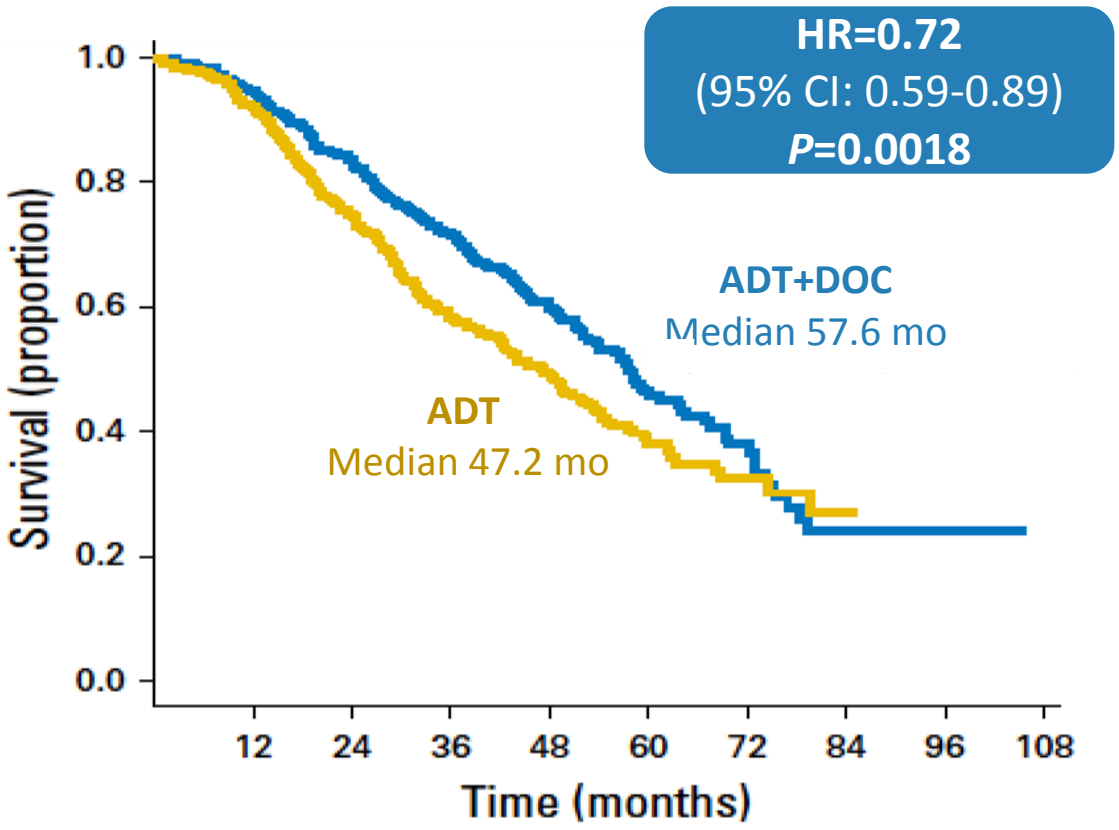


High volume:

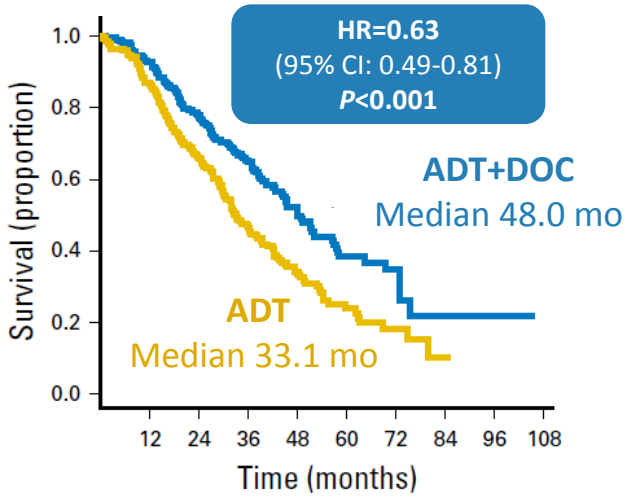
- presence of visceral metastases or
- ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis

Sweeney C, et al. N Engl J Med, 2015;373:737-46;

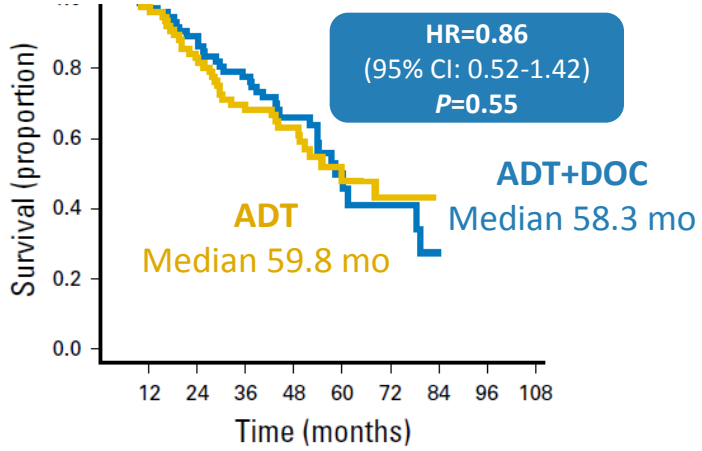
CHAARTED Updated – ADT+DOC in M1 HNPC
Primary Endpoint: OS



High-volume* (N=421)

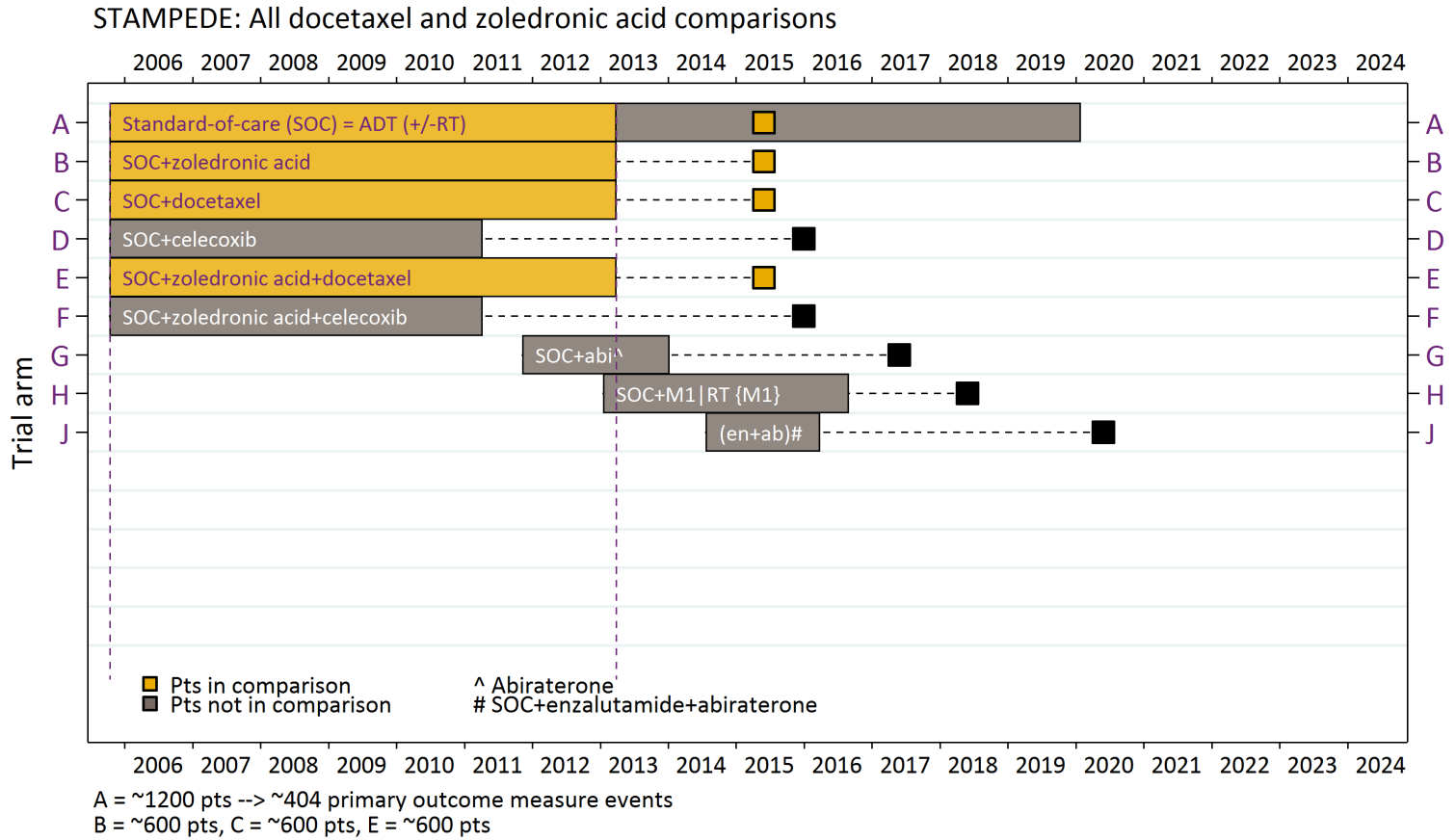


Low-volume (N=154)



Sweeney C, et al. N Engl J Med, 2015;373:737-46;
Kyriakopoulos C, et al. J Clin Oncol, 2018;doi:10.1200/JCO.2017.75.3657.

Chemotherapy - Docetaxel - STAMPEDE



Relapsing after previous RP or RT with ≥1 of:

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

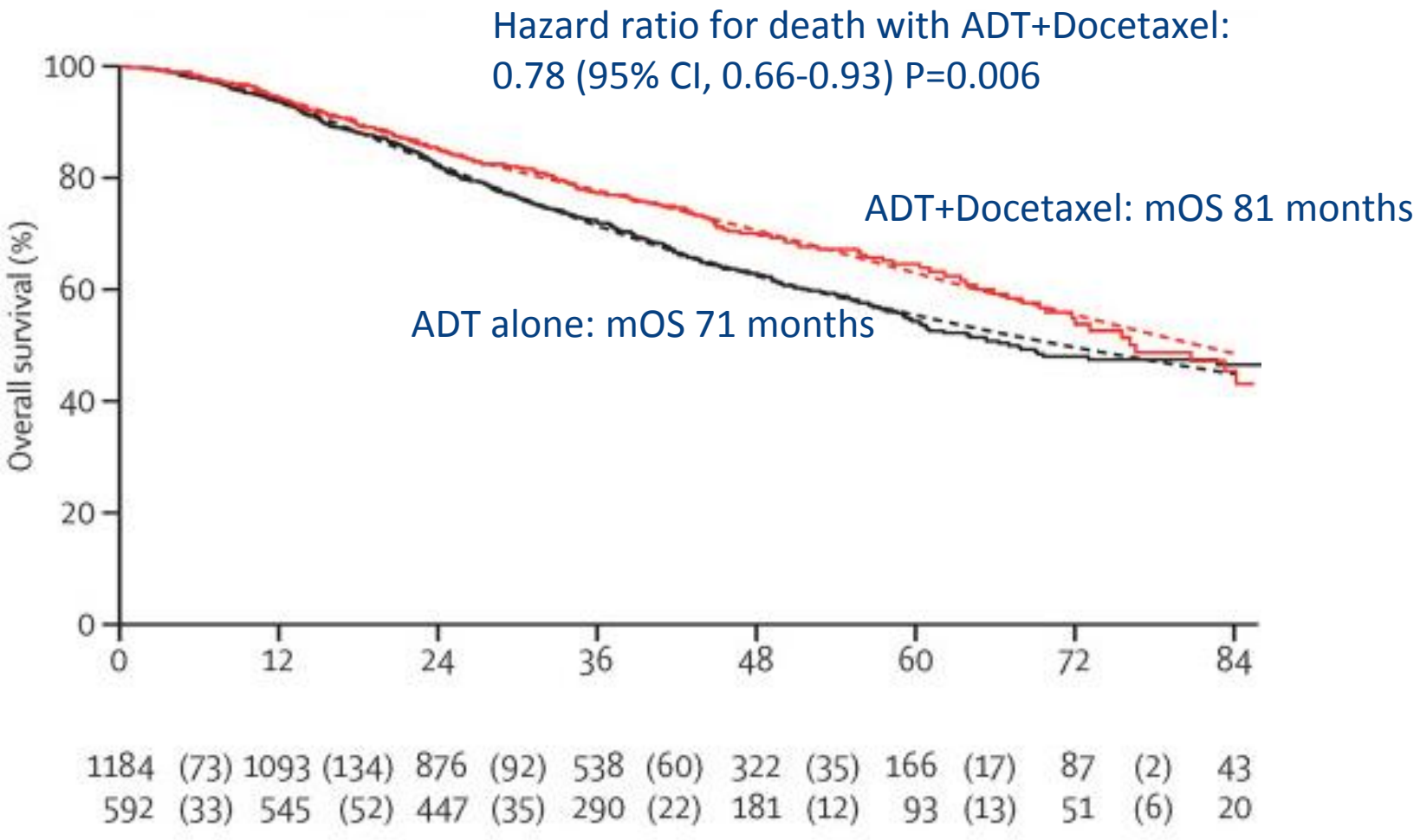
Newly-diagnosed

Any of:

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

James ND et al. Lancet 2016 Mar 19;387(10024):1163-77.

Chemotherapy - Docetaxel - STAMPEDE



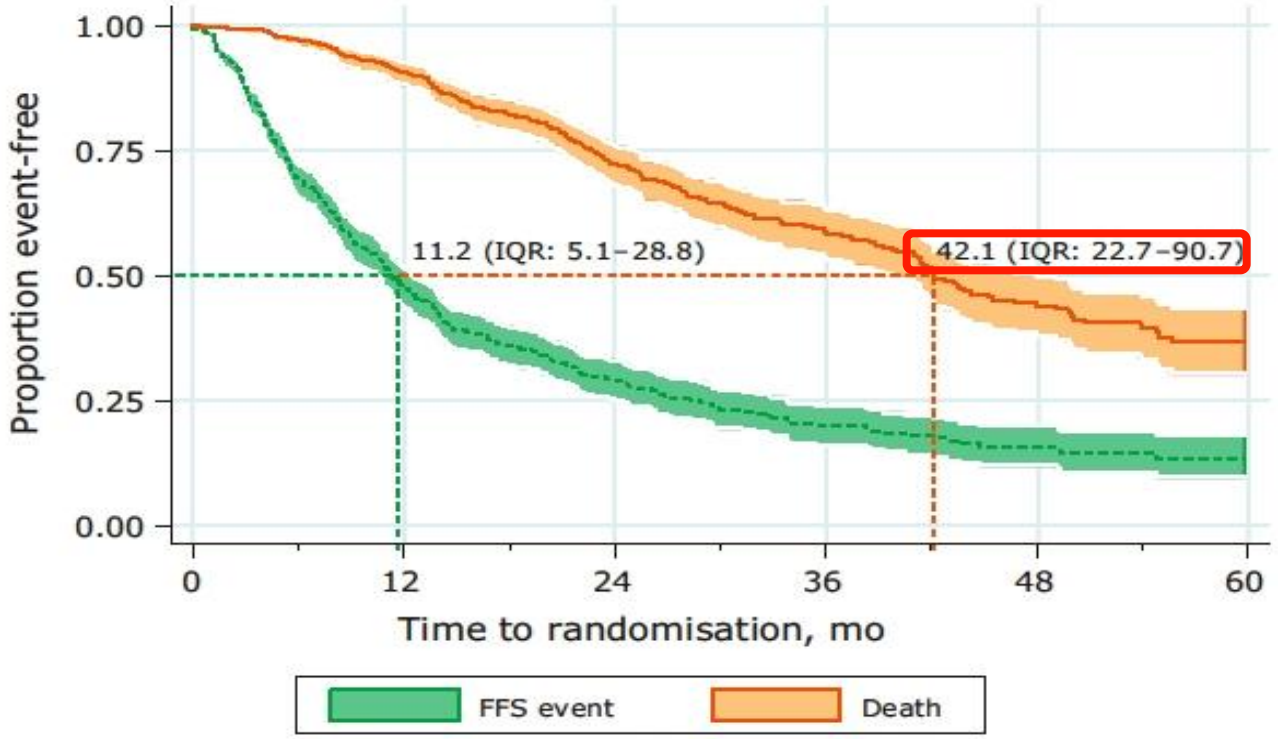
James ND et al. Lancet 2016 Mar 19;387(10024):1163-77.

Rationale

- Mature results with a robust clinical benefit (at least in high-volume disease)
- Patients with newly diagnosed M1 disease have a poor prognosis → They may not be fit to receive DOC after ABI

De Novo M1 HNPC Has a Poor Prognosis

- 917 patients with de novo M1 HNPC (2005-2014) treated by ADT alone (STAMPEDE randomized trial control arm)
- Median OS from diagnosis: 42 months

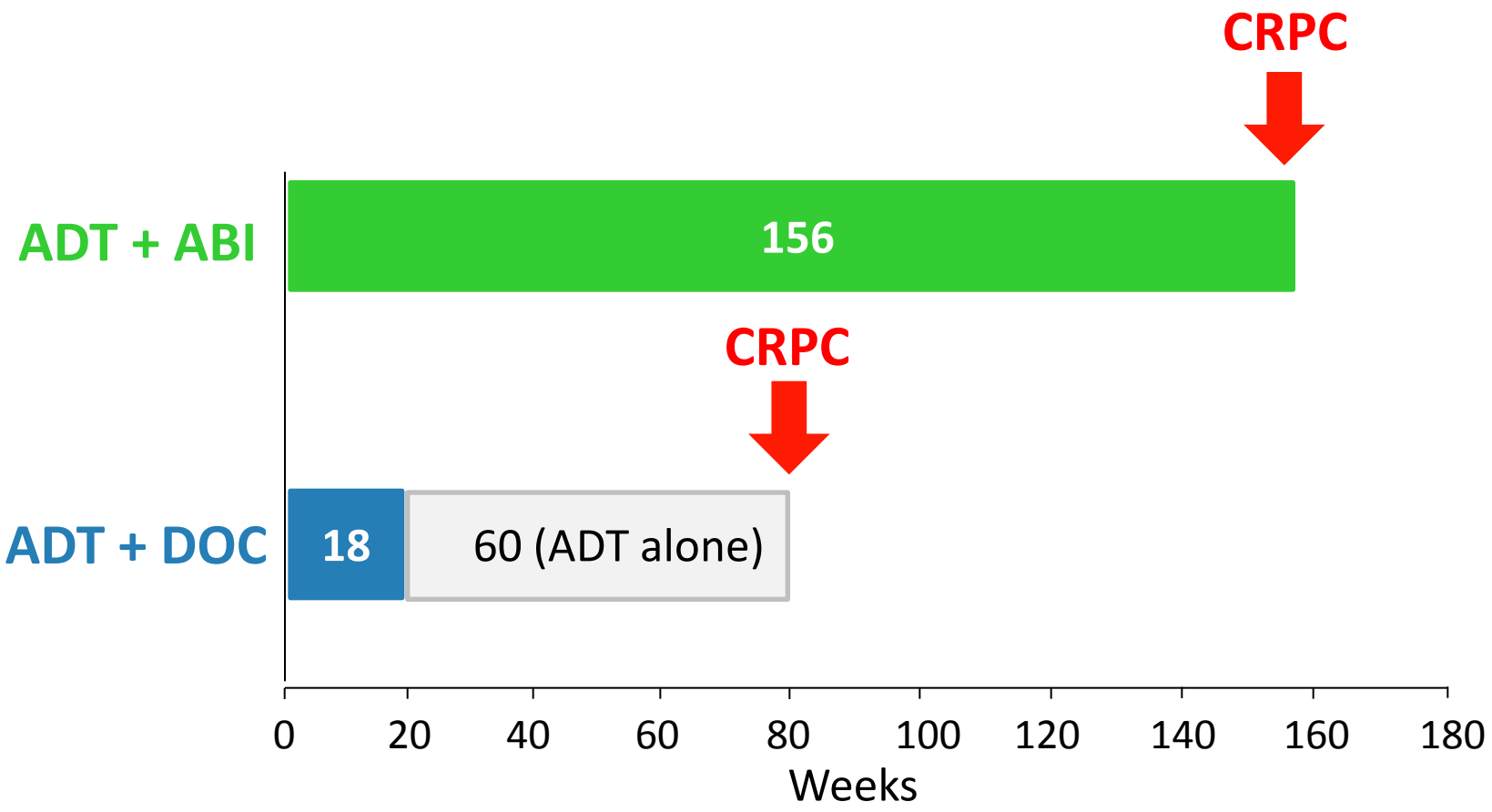


James ND, et al. Eur Urol. 2015;67:1028-38.

Rationale

- Mature results with a robust clinical benefit (at least in high-volume disease)
- Patients with newly diagnosed M1 disease have a poor prognosis → They may not be fit to receive DOC after ABI
- Brief exposure

Median Treatment Duration (Weeks)



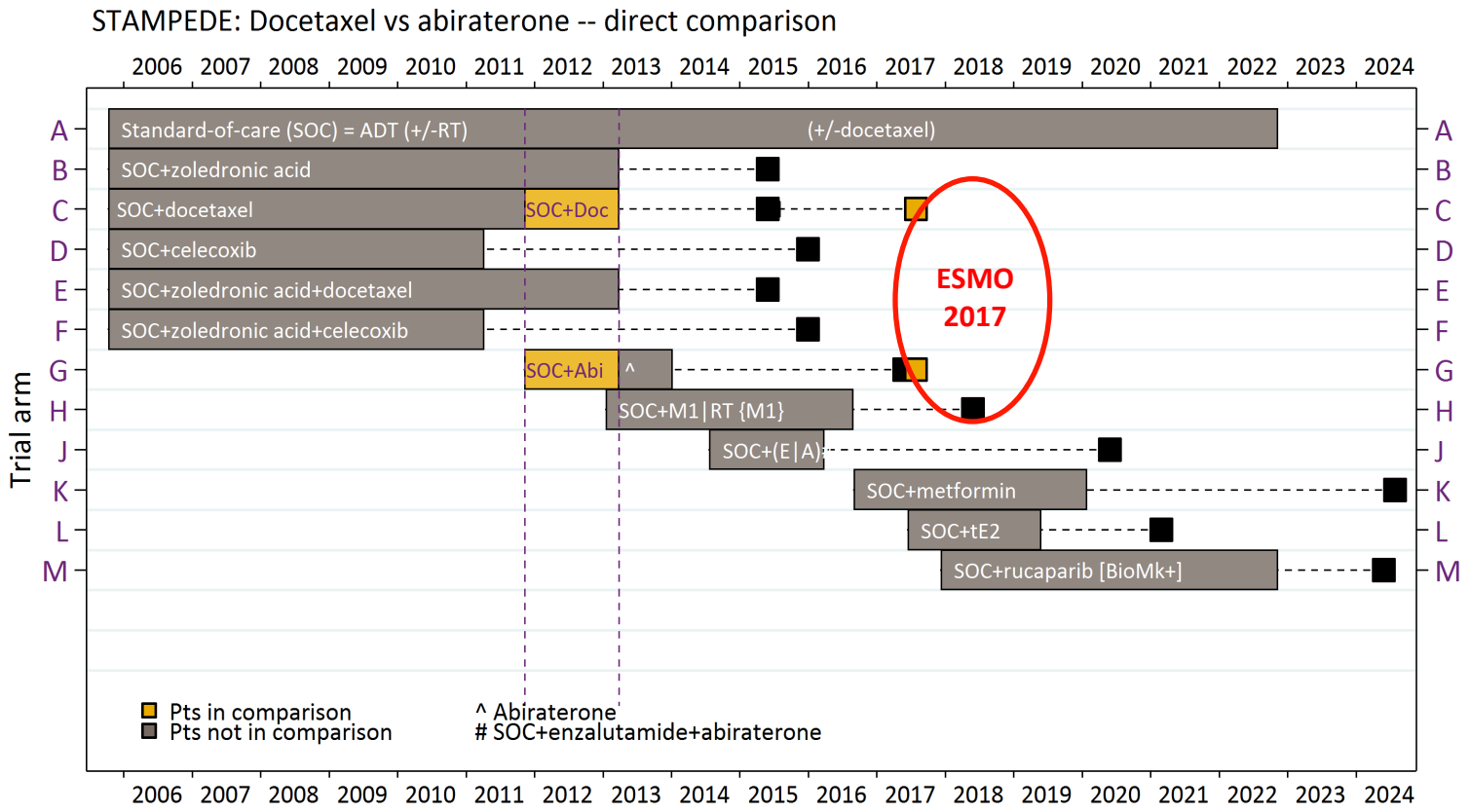
Estimations based on CHAARTED (high volume)[1] and LATITUDE[2] results

1. Kyriakopoulos C, et al. J Clin Oncol. 2018;doi:10.1200/JCO.2017.75.3657;
2. Fizazi K, et al. N Eng J Med. 2017;377:352-60 (Figure S5 supplementary appendix).

Rationale

- Mature results with a robust clinical benefit (at least in high-volume disease)
- Patients with newly diagnosed M1 disease have a poor prognosis → They may not be fit to receive DOC after ABI
- Brief exposure
- Similar efficacy in strong endpoints

STAMPEDE: SOC+ABI/P vs SOC+Doc/P

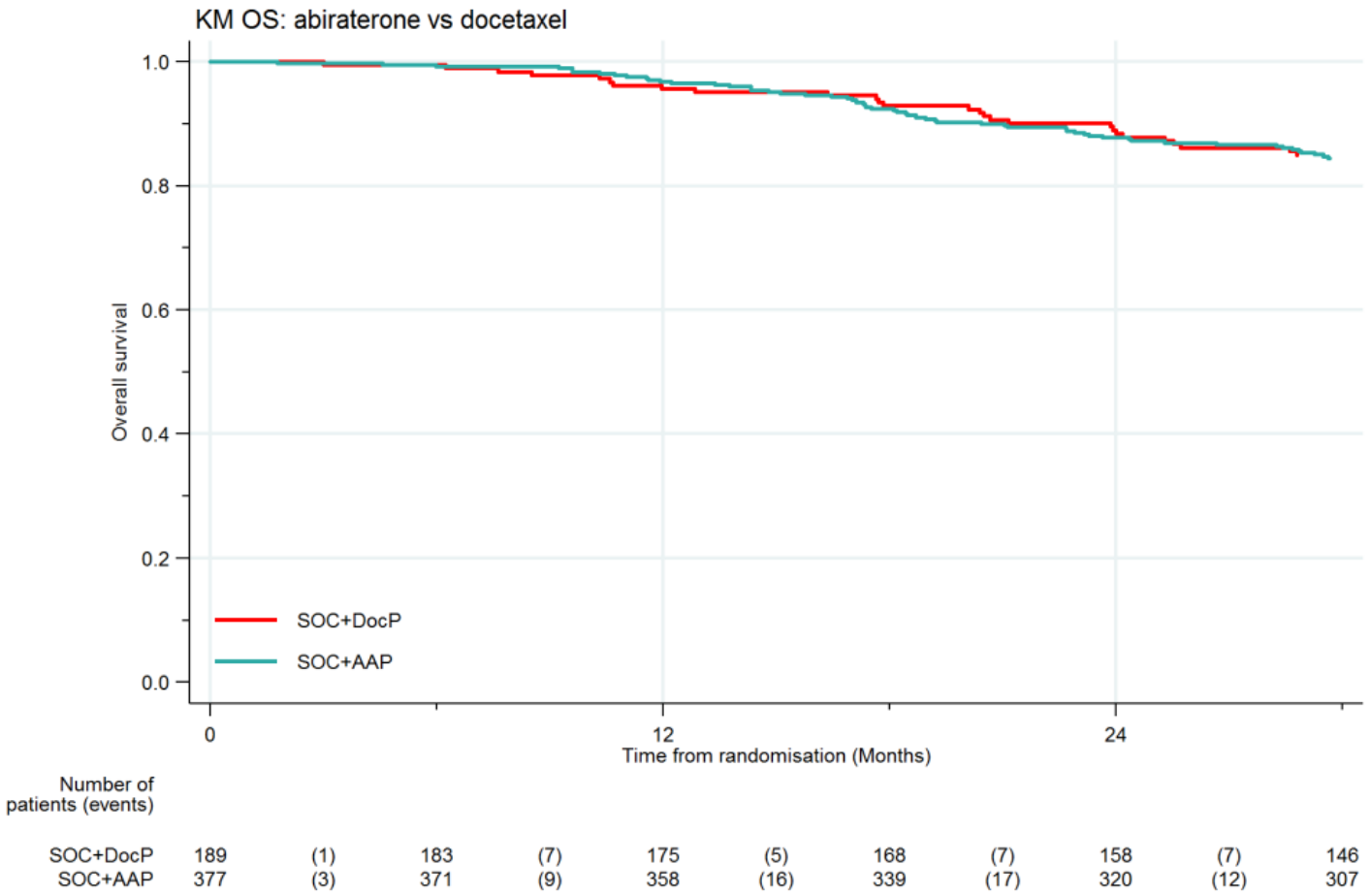


- ABI/P and DocP may work in quite different ways
- Evidence about whether to give both is pending
- From Nov 2011 to March 2013, 566 patients randomised contemporaneously to either research arm
  - 189 SOC+Doc/P
  - 377 SOC+ABI/P

Sydes MR, et al. ESMO 2017 (podium presentation); Sydes MR, et al. Ann Oncol. 2018

STAMPEDE: SOC+ABI/P vs SOC+Doc/P

OS (primary end-point)



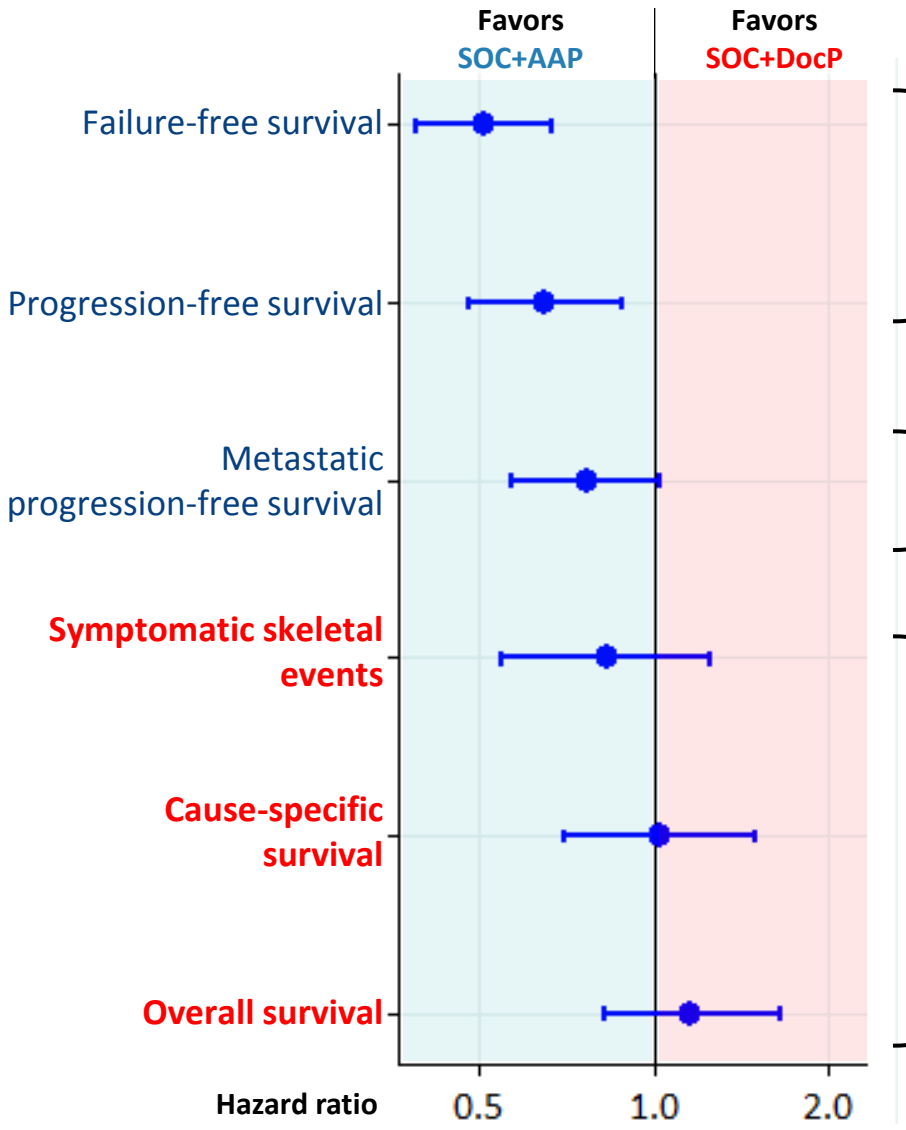
Cause specific survival

Status	SOC+DocP		SOC+ABI/P	
	N	%	N	%
Alive	145	77%	272	72%
Dead	44	23%	105	28%
PCa Death	40	21%	86	23%
Other cause	4	2%	19	5%

	Sub-HR (95%CI)	P-val
All	**1.02** (0.70 to 1.49)	0.92

Sydes MR, et al. ESMO 2017 (podium presentation); Sydes MR, et al. Ann Oncol. 2018

Summary of Endpoints



Head-to-head data in 566 pts (Nov-2011 to Mar-2013)

Strong evidence favoring AAP

Weak evidence favoring AAP

No good evidence of a difference

→ Proportionately different time spent in each disease state

Toxicity profiles quite different and well known

Sydes MR, et al. ESMO 2017 (podium presentation); Sydes MR, et al. Ann Oncol. 2018

But Undertreatment of LATITUDE Control Arm

LATITUDE[1] Subsequent therapies

N (%)	ADT+ABI/P (n=597)	ADT+Pbos (n=602)
N patients eligible	314	469
DOC, %	34%	40%
ENZA, %	10%	16%
ABI/P, %	3%	11%
CABA, %	4%	6%
Radium-223, %	4%	6%

CHAARTED[2] Subsequent therapies

N (%)	ADT+DOC/P (n=397)	ADT (n=393)
N patients eligible	238	287
DOC, %	22.7%	48%
ABI/P or ENZA, %	44.1%	36.2%
Sipuleucel-T	9.2%	6.6%
CABA, %	23.9%	12.9%
Radium-223, %	0	0

Double-blind study!!
Tested early ABI vs no ABI

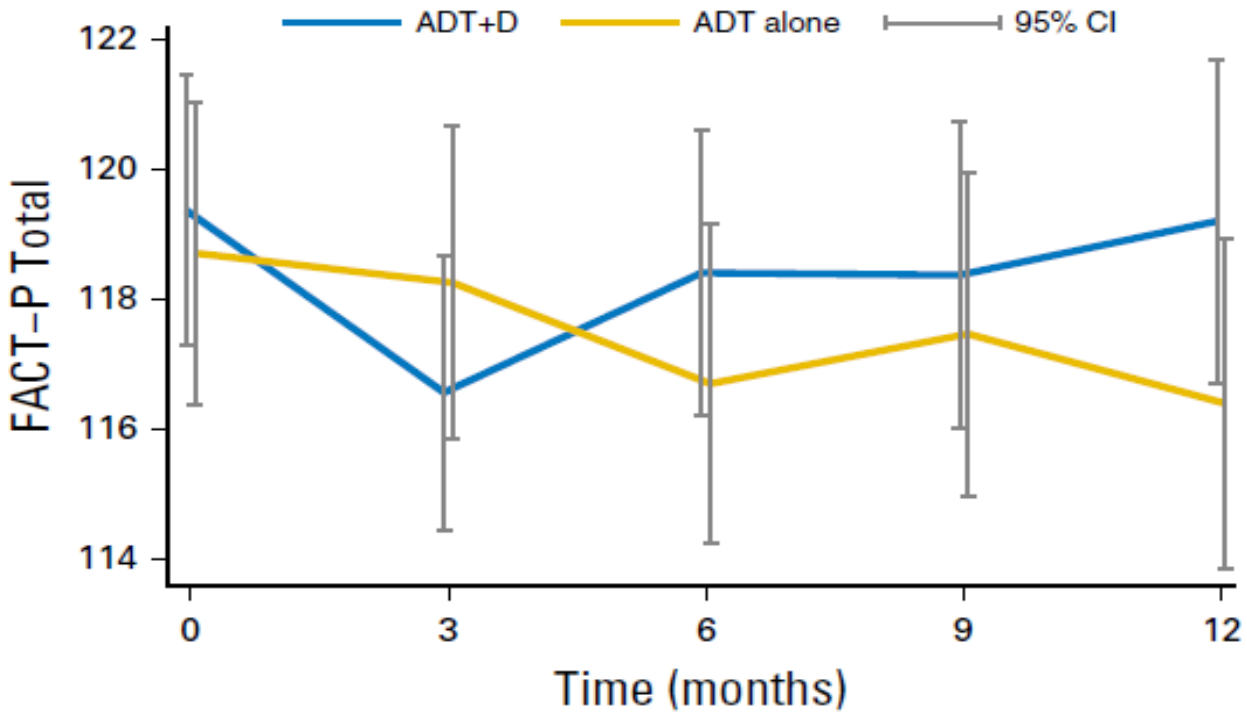
1. Fizazi K, et al. N Eng J Med. 2017;377:352-60; 2. Gravis G, et al. Cancer Treat Rev. 2017; 55:211-217.

Rationale

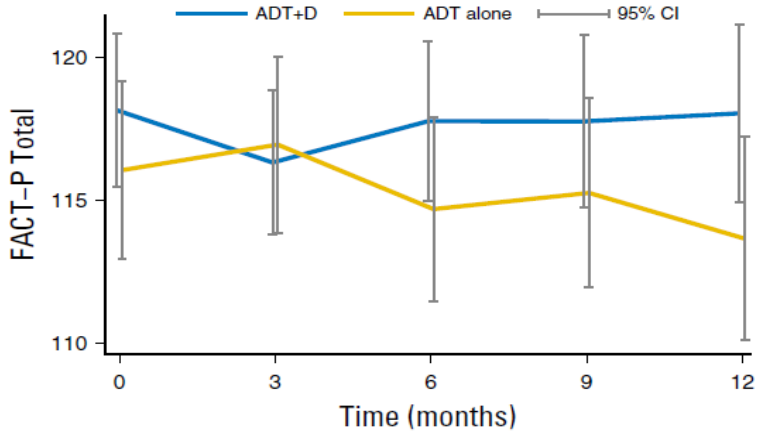
- Mature results with a robust clinical benefit (at least in high-volume disease)
- Patients with newly diagnosed M1 disease have a poor prognosis → They may not be fit to receive DOC after ABI
- Brief exposure
- Similar efficacy in strong endpoints
- Improved quality of life at 1 year and no prolonged toxicity

CHAARTED – Quality of Life

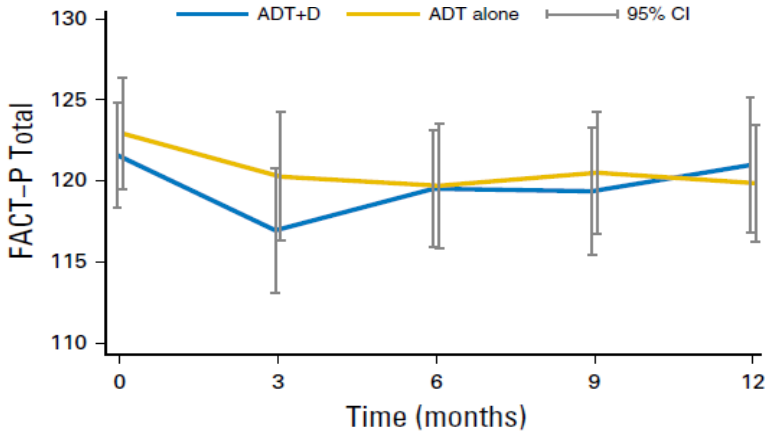
All patients



High volume



Low volume



Morgans AK, et al. J Clin Oncol. 2018;doi:10.1200/JCO.2017.75.3335.

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- Improved quality of life at 1 year and no prolonged toxicity
- Similar grade ≥ 3 adverse events

Adverse Events – Worst Toxicity Ever

Safety population	**ADT+DOC/P**	**ADT+ABI/P**
Patients included in adverse event analysis	172 (91%)	373 (>99%)
Grade 1+ AE	172 (100%)	370 (99%)
Grade 3+ AE	86 (**50%**)	180 (**48%**)
Grade 3+ AEs by category (*incl. expected AEs*)		
Endocrine disorder (*incl. hot flashes, impotence*)	15 (9%)	49 (13%)
Febrile neutropenia	29 (**17%**)	3 (1%)
Neutropenia	22 (**13%**)	4 (1%)
Musculoskeletal disorder	9 (5%)	33 (9%)
Cardiovascular disorder (*incl. hypertension, MI, cardiac dysrhythmia*)	6 (3%)	32 (**9%**)
Gastrointestinal disorder	9 (5%)	28 (8%)
Hepatic disorder (*incl. increased AST, increased ALT*)	1 (1%)	32 (**9%**)
General disorder (*incl. fatigue, oedema*)	18 (10%)	21 (6%)
Respiratory disorder (*incl. breathlessness*)	12 (7%)	11 (3%)
Renal disorder	5 (3%)	20 (5%)
Lab abnormalities (*incl. hypokalaemia*)	9 (5%)	11 (3%)

Sydes MR, et al. Ann Oncol. 2018.

Rationale

- Mature results with a robust clinical benefit (at least in high-volume disease)
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- Brief exposure
- Similar efficacy in strong endpoints
- Improved quality of life at 1 year and no prolonged toxicity
- Similar grade ≥ 3 adverse events
- Efficacy of subsequent therapies not affected post-DOC

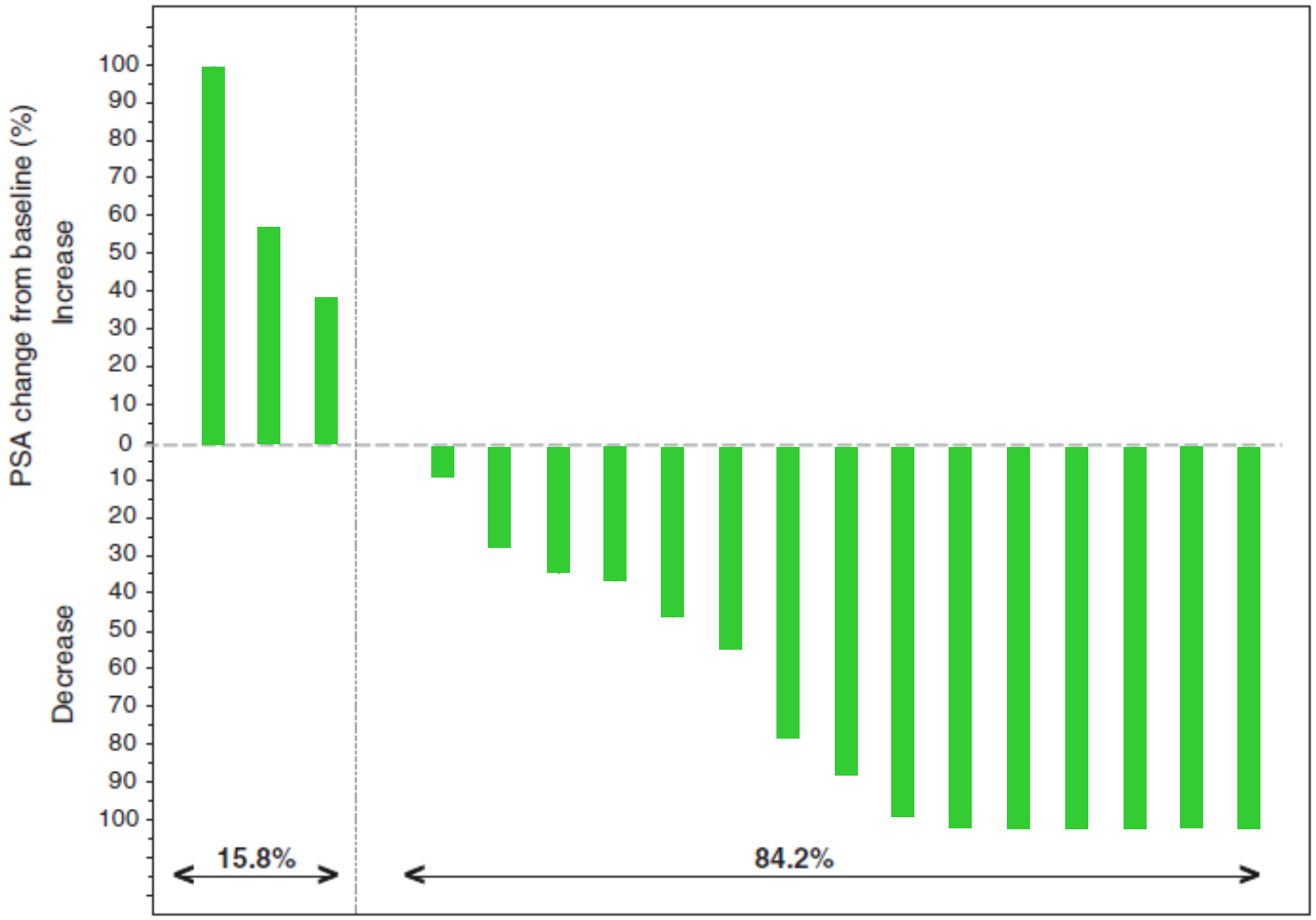
DOC Possibly Diminished Activity After ADT+ABI

	FIRSTANA[1] DOC/Pbo N=391	de Bono[2] ABI→DOC N=35	Schweizer[3]		Azad[4] ABI→DOC N=86	de Bono[5] (COU-AA-302) ABI→DOC N=100
			DOC N=95	ABI→DOC N=24		
Therapy line	1	2	1	2	2	2
Visceral mets	YES	YES	YES	YES	YES	NO
↓ PSA ≥50%	68.5%	25.7%	63.0%	38.0%	35.0%	27%
Median PSA-PFS (month)	8.3	4.6	6.7	4.1	4.0	7.6
OS, median	24.3	12.5	-	-	11.7	NA

[2-5] trials are retrospective studies in small number of patients

1. Oudard S, et al. J Clin Oncol. 2017;35(28):3189-3197; 2. Mezynski J, et al. Ann Oncol. 2012;23:2943-7;
3. Schweizer, MT et al. Eur Urol. 2014;66:646-52; 4. Azad AA, et al. Prostate. 2014;74:1544-50; 5. De Bono J, et al. Eur Urol. 2017;71:656-64

ABI or ENZA Likely to Work After ADT + DOC

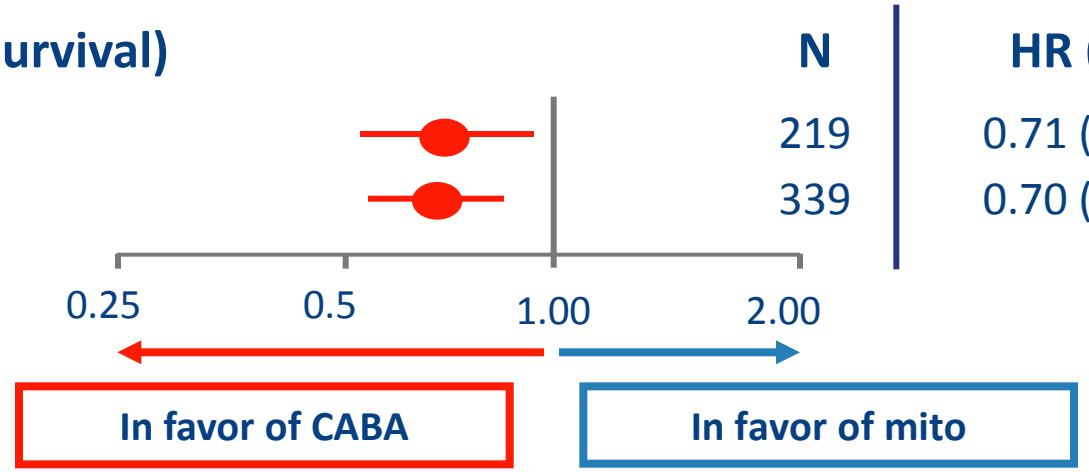


- Retrospective data from GETUG 15 trial (ADT vs ADT+DOC in M1 HNPC)
- 19 men treated with ABI or ENZA after ADT+DOC
- PSA decrease ≥50% in 10/19 (53%) patients

Lavaud P, et al. Eur Urol. 2017

CABA Is Effective in Patients Progressing During or Rapidly After Last DOC Cycle

TROPIC trial[1-2]



1. De Bono J, et al. Lancet. 2010;376:1147-54; 2. Oudard S, et al. Future Oncol. 2011;7:497-506

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- Brief exposure
- Similar efficacy in strong endpoints
- Improved quality of life at 1 year and no prolonged toxicity
- Similar grade ≥ 3 adverse events
- Efficacy of subsequent therapies not affected post-DOC
- Cheap (ABI 10-fold more expensive)

COST OF TREATMENT OF ABIRATERONE OR DOCETAXEL IN MHSPC: IMPACT ON ECONOMIC HEALTH

Cost from my hospital at the **Georges Pompidou center**, Paris, France

	Abiraterone[1,2]	Docetaxel[3,4]
Price of drugs	3071 € (one month)	14 € (for 160 mg) per cycle
Price G-CSF for 3-5 days	NA	97 € (per cycle)
Cost for daily hospital	NA	1364 €
Cost for one cycle	NA	710.8 €
Average duration of TT	33 months	18 weeks (6 cycles)
Cost of hospitalization if case of toxicity* (3 nights)	NA	1644 € per night
Total cost of care	101,355 €	10,265 €

* 10% of patients if no G-CSF prophylaxis

Courtesy of Hail Aboudagga

1. Fizazi K. NEJM 2017; 377:352-60; 2. James ND. NEJM 2017; 377: 338-51;
3. Sweeney C. NEJM 2015;373:737-46; 4. James ND Lancet 2016;387:1163-77

Presented by S Oudard at ESMO 2017. Discussant for Abstr 788PD, LBA33, LBA34 and 789PD.

Conclusions

- CHAARTED mature results & robust benefit by 6 cycles DOC; only in high-volume patients
- STAMPEDE benefit in M1 patients, tumor volume unknown; benefit high vs low volume?
- Brief exposure (18 weeks) by DOC
- QoL after 6-9 months similar to ADT in low volume, but better than ADT in high volume (benefit)
- Post ADT+DOC: all existing treatmenr options remain
- Cheap!

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