II SIMPÓSIO INTERNACIONAL

GU - REVIEW 2018 - LACOG

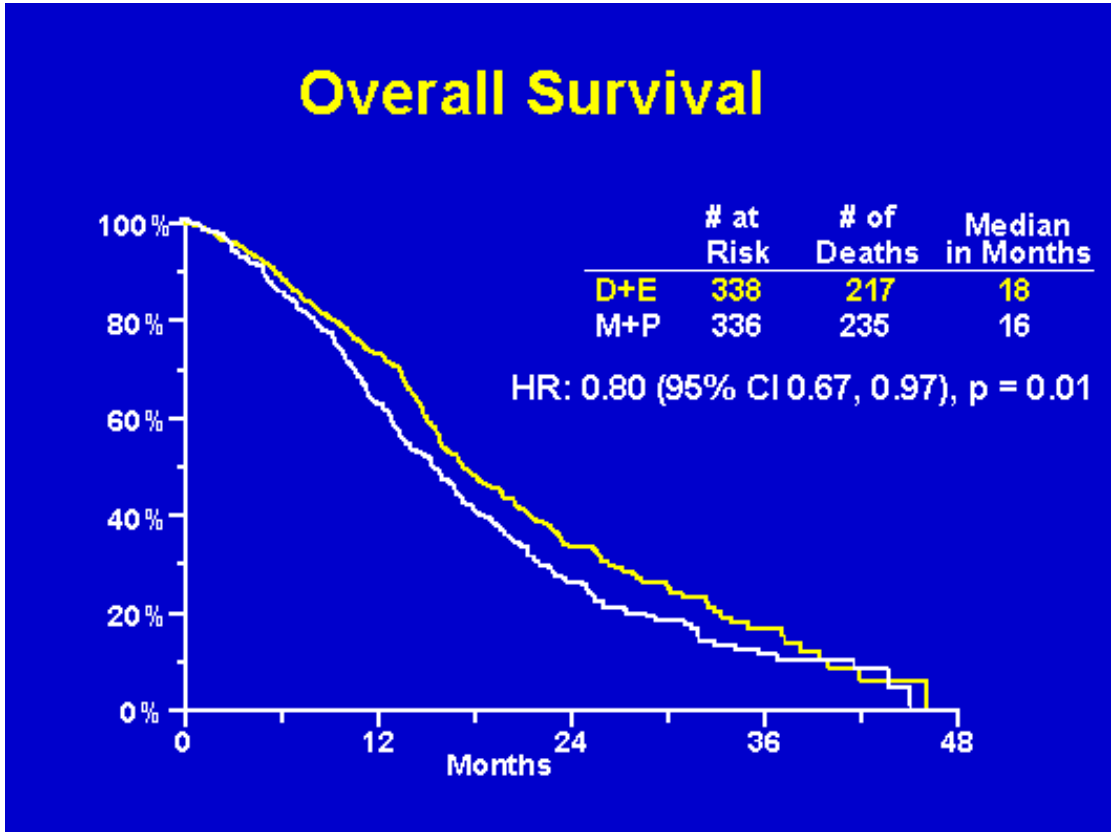
23 E 24 | NOVEMBRO 2018 | HOTEL INTERCONTINENTAL | SÃO PAULO

I Choose Docetaxel

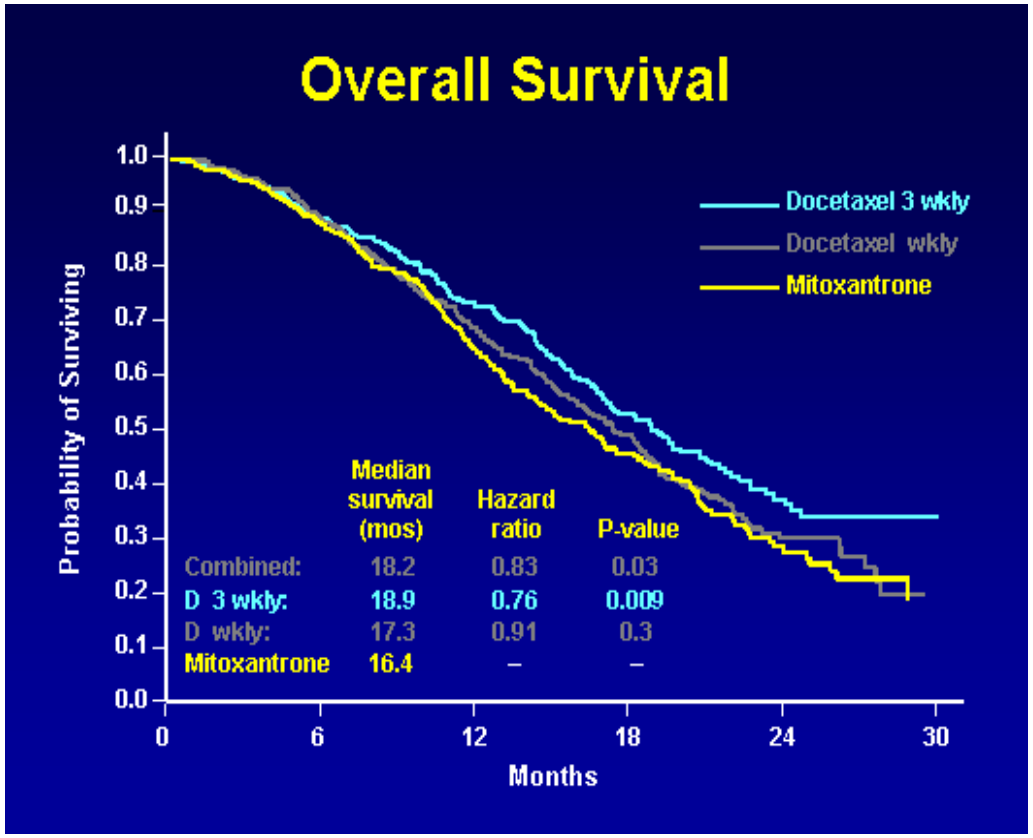
-in metastatic **castration sensitive** prostate cancer in addition to ADT-

Carlos Dzik
Medical Oncologist
Hospital Sírio-Libanês

Docetaxel vs Mitoxantrone in Castration-Resistant Pca



ASCO-2004
SWOG 99-16



ASCO-2004
Aventis Trial
TAX 327

ORIGINAL RESEARCH

Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer

Robert R. Zielinski, MBBS;[*] Arun A. Azad, PhD;[*] Kim N. Chi, MD, FRCSC;[†] Scott Tyldesely, MD, FRCSC[*†]*

[*]BC Cancer Agency, Vancouver Centre, Department of Medical Oncology, British Columbia Cancer Agency, Vancouver BC; [†]BC Cancer Agency, Vancouver Centre, Department of Radiation Oncology, University of British Columbia, Vancouver, BC

Table 1. Baseline and clinical characteristics of patients receiving palliative RT across eras

Characteristic	Pre-DOC era (n = 919)	DOC era (n = 957)	*p* value	Test
Age (median)	75.5	76.7	0.04	t-test
Metastatic disease at diagnosis, N (%)	275 (30)	315 (33)	0.09	Fisher exact
Median time from diagnosis to first palliative RT	3.9 years	3.1 years	0.31	t-test
Received DOC, N (%)	63 (7)	315 (33)	<0.0001	Fisher exact

DOC: docetaxel; RT: radiotherapy.

CUAJ • July-August 2014 • Volume 8, Issues 7-8

Studies	N	M0 vs M1	Rx	Metastatic de novo	mPFS	mOS
GETUG 2004-2008	385	M1 only ECOG 0→ 98%	ADT vs ADT+D x 9	71%	12,9 vs 22,9. HR 0,72 P=0,021	48,6 vs 62,1 HR 0,98 p=0,44
CHAARTED 2006-2013	790	M1 only ECOG 0→ 69%	ADT vs ADT+D x 6	72%	19,8 vs 32,7 HR 0,49 P<0,0001	44 vs 57,6 HR 0,49 P<0,0001
STAMPEDE 2005-2013	1087	M0 & M1 ECOG 0→ 72%	ADT vs ADT+DP x 6	70%	11 vs 22 HR 0,63 P<0,0001	43 x 65 HR 0,73 P=0,002

GETUG – AFU 15

Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial

Gwenaelle Gravis, Karim Fizazi, Florence Joly, Stéphane Oudard, Franck Priou, Benjamin Esterni, Igor Latorzeff, Remy Delva, Ivan Krakowski, Brigitte Laguerre, Fréderic Rolland, Christine Théodore, Gael Deplanque, Jean Marc Ferrero, Damien Pouessel, Loïc Mourey, Philippe Beuzeboc, Sylvie Zanetta, Muriel Habibian, Jean François Berdah, Jerome Dauba, Marjorie Baciuchka, Christian Platini, Claude Linassier, Jean Luc Labourey, Jean Pascal Machiels, Claude El Kouri, Alain Ravaud, Etienne Suc, Jean Christophe Eymard, Ali Hasbini, Guilhem Bousquet, Michel Soulie

Fase 3, multicêntrico
Adenoca próstata M1
KPS >= 70%
TDA início < 2 meses

Randomização

n = 385

TDA
Docetaxel 75mg/m² q 21d x 9

TDA

- EP 1ário: SG
- EP 2ários: SLP clínica, SLP por PSA, qualidade de vida, toxicidades.

Lancet Oncol. 2013 Feb;14(2):149-58
J Clin Oncol 33, 2015 (suppl 7; abstr 140)

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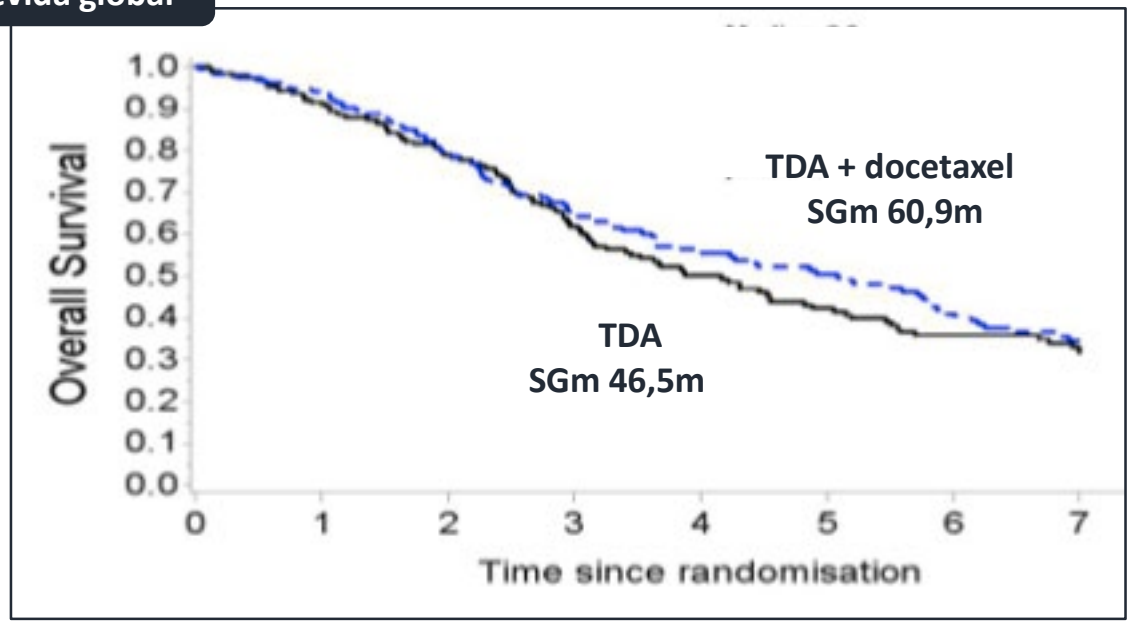
- **Dados de longo prazo: follow-up 82,9meses**

	Docetaxel + TDA	TDA	HR (95% IC)
SLP por PSA	22,9m	12,9m	0,7 (0,6 – 0,9)
SLP clínica	23,5m	15,4m	0,7 (0,6 – 0,9)

Sobrevida global



NEGATIVO

HR 0,9 (0,7 – 1,2)
p = 0,44

Lancet Oncol. 2013 Feb;14(2):149-58

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Retrospective evaluation –Ad Hoc- Stratification by CHAARTED criteria

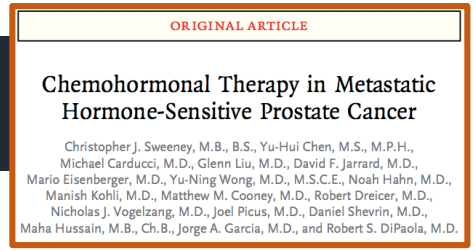
mOS: ADT+Docetaxel → 39,8 mos
ADT alone → 35,1 mos
HR 0.78 p=0.14.

High Risk

ADT+Docetaxel → Not Reached
ADT alone → 83,4 mos
HR 1.02 p=0.9

Low Risk

Survival Curves

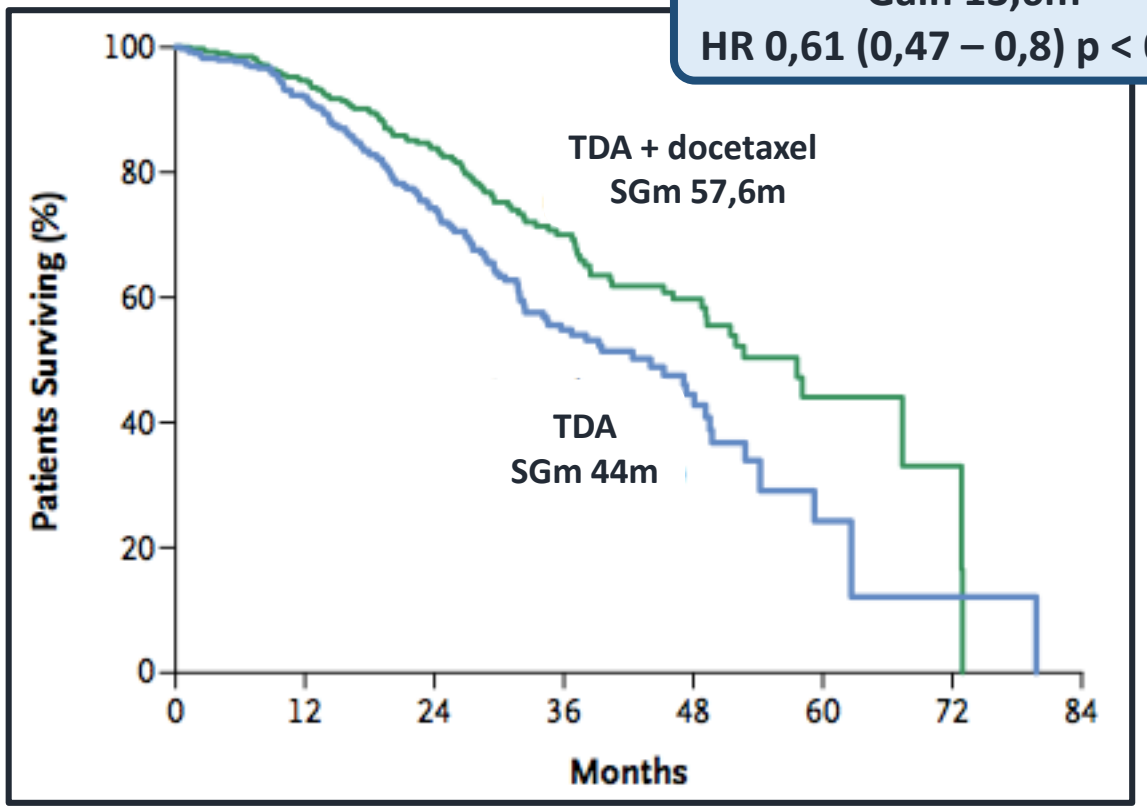

ORIGINAL ARTICLE

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H., Michael Carducci, M.D., Glenn Liu, M.D., David F. Jarrard, M.D., Mario Eisenberger, M.D., Yu-Ning Wong, M.D., M.S.C.E., Noah Hahn, M.D., Manish Kohli, M.D., Matthew M. Cooney, M.D., Robert Dreicer, M.D., Nicholas J. Vogelzang, M.D., Joel Picus, M.D., Daniel Shevrin, M.D., Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.

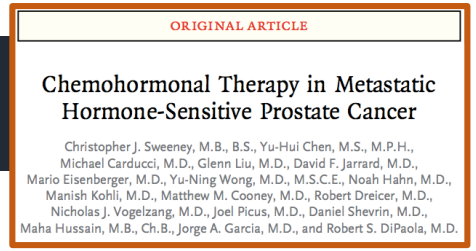
Overal Survival

Gain 13,6m
HR 0,61 (0,47 – 0,8) p < 0,001



CHAARTED TRIAL

Survival Curves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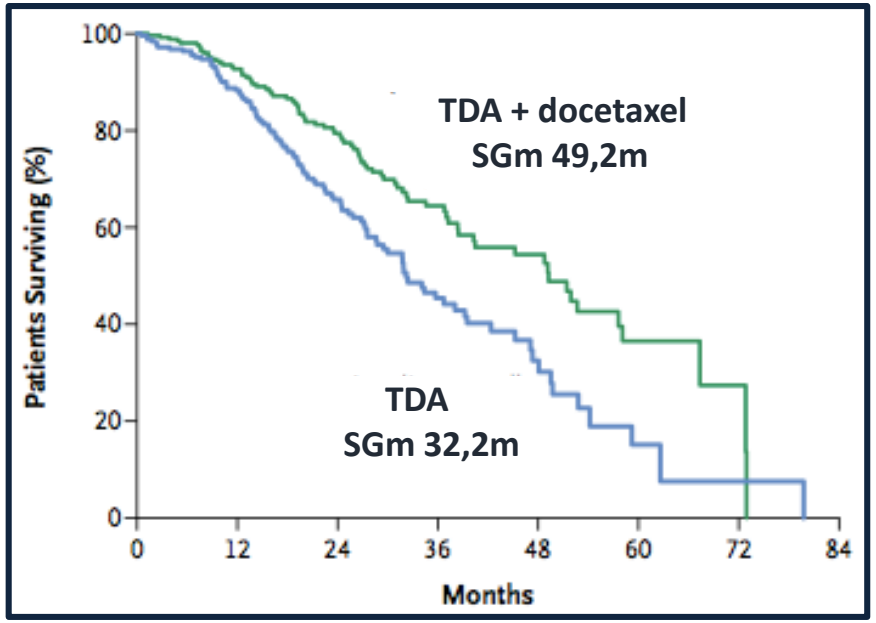
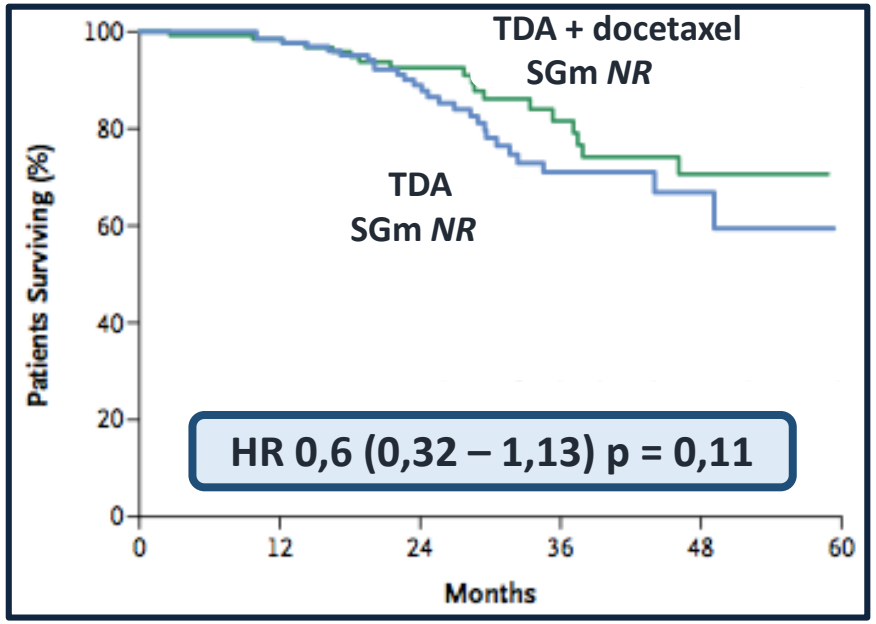
High volume



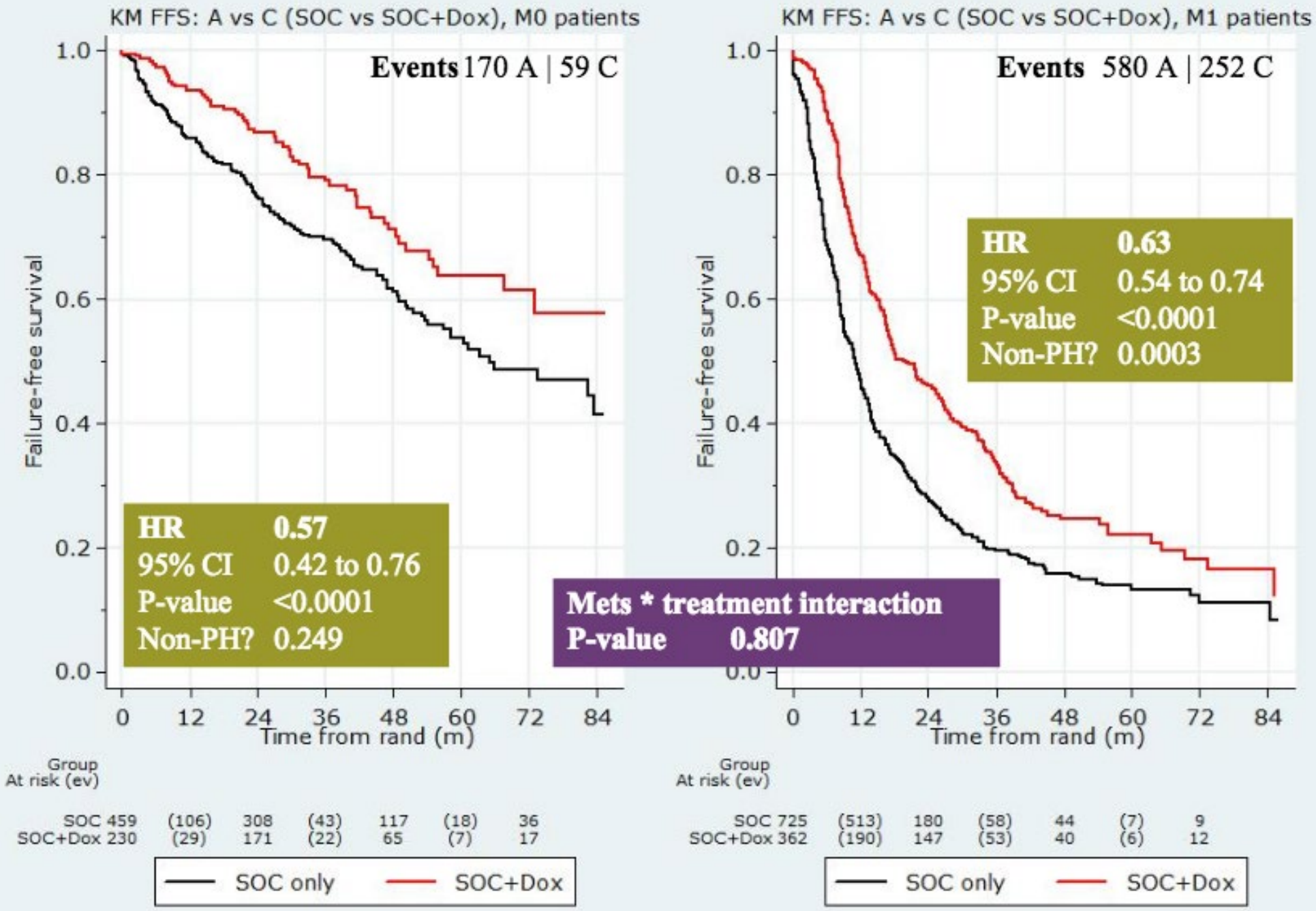
Gain 17m
HR 0,6 (0,45 – 0,81) p < 0,001

Low volume

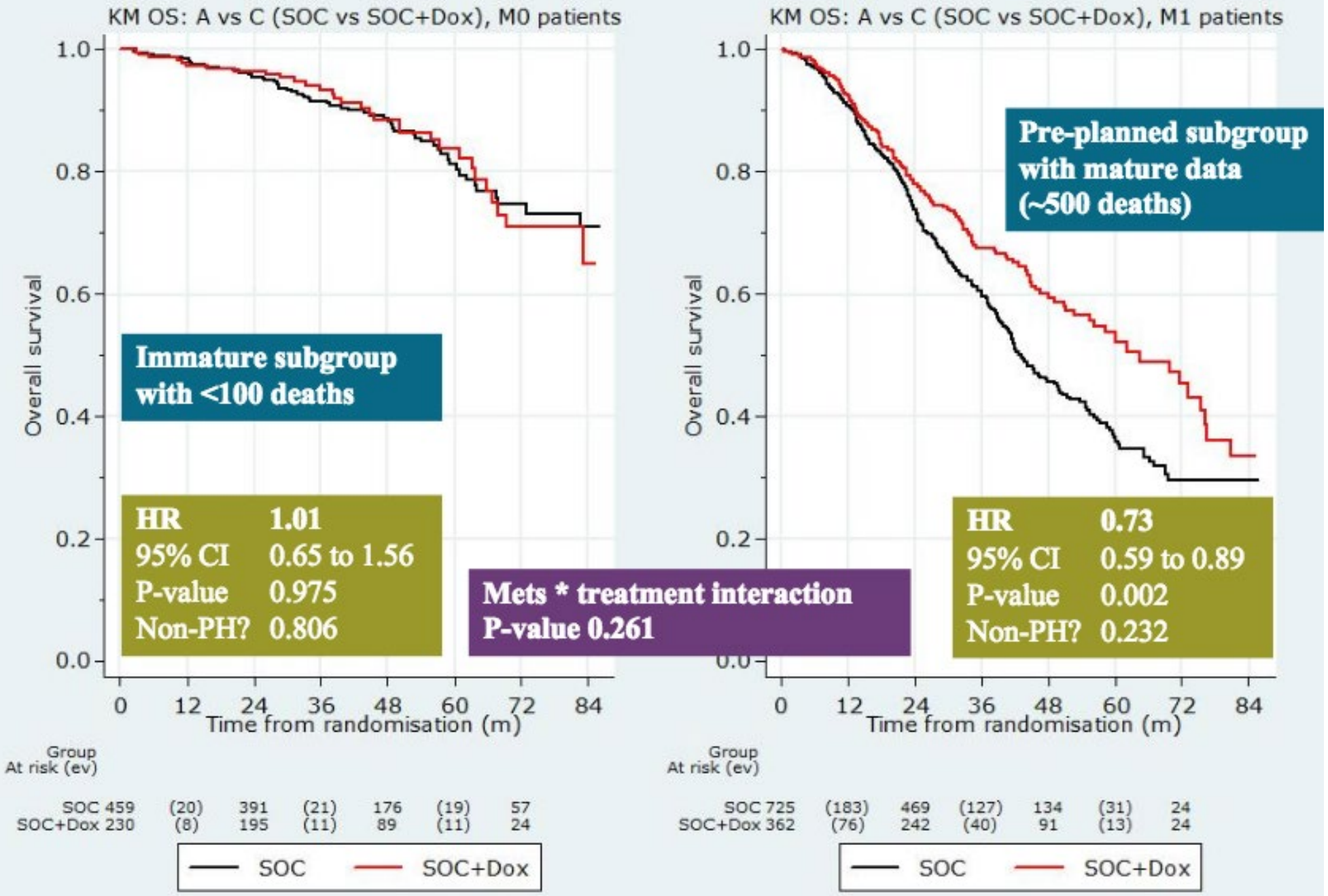


CHAARTED TRIAL

STAMPEDE

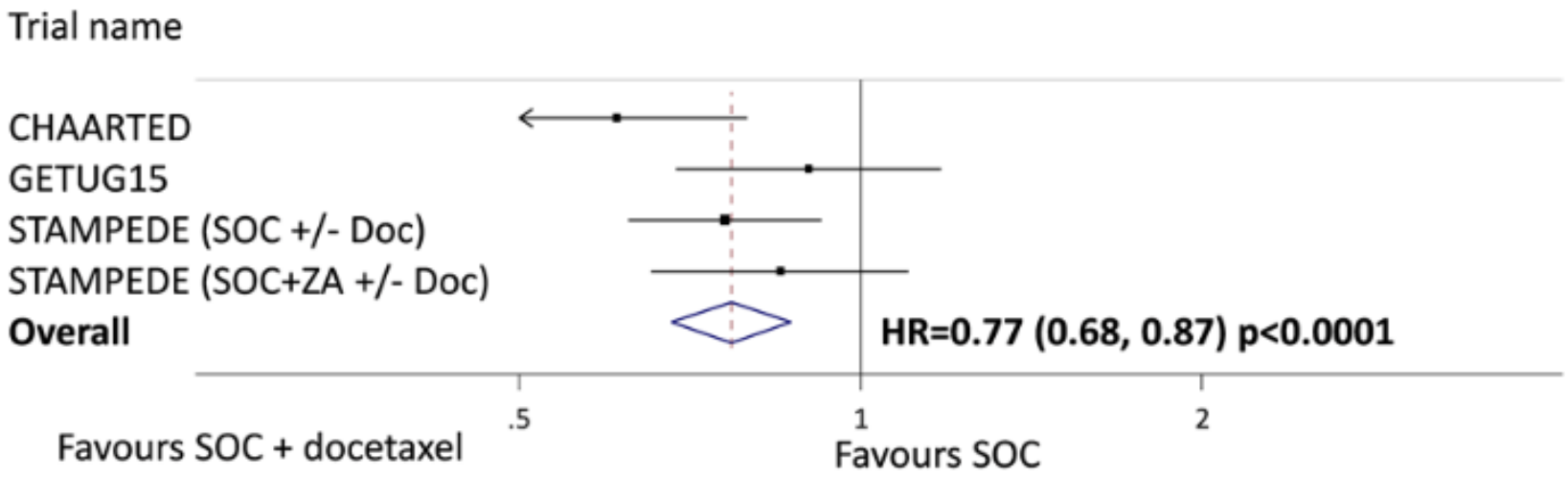

KM FFS: A vs C (SOC vs SOC+Dox), M0 patients
Events 170 A | 59 C
HR 0.57
95% CI 0.42 to 0.76
P-value <0.0001
Non-PH? 0.249
Failure-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0 12 24 36 48 60 72 84
Time from rand (m)
Group
At risk (ev)
SOC 459 (106) 308 (43) 117 (18) 36
SOC+Dox 230 (29) 171 (22) 65 (7) 17
SOC only
SOC+Dox
KM FFS: A vs C (SOC vs SOC+Dox), M1 patients
Events 580 A | 252 C
HR 0.63
95% CI 0.54 to 0.74
P-value <0.0001
Non-PH? 0.0003
Mets * treatment interaction
P-value 0.807
Failure-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0 12 24 36 48 60 72 84
Time from rand (m)
Group
At risk (ev)
SOC 725 (513) 180 (58) 44 (7) 9
SOC+Dox 362 (190) 147 (53) 40 (6) 12
SOC only
SOC+Dox

STAMPEDE


KM OS: A vs C (SOC vs SOC+Dox), M0 patients
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0 12 24 36 48 60 72 84
Time from randomisation (m)
Immature subgroup with <100 deaths
HR 1.01
95% CI 0.65 to 1.56
P-value 0.975
Non-PH? 0.806
Group
At risk (ev)
SOC 459 (20) 391 (21) 176 (19) 57
SOC+Dox 230 (8) 195 (11) 89 (11) 24
SOC
SOC+Dox
Mets * treatment interaction
P-value 0.261
KM OS: A vs C (SOC vs SOC+Dox), M1 patients
Pre-planned subgroup with mature data (~500 deaths)
HR 0.73
95% CI 0.59 to 0.89
P-value 0.002
Non-PH? 0.232
SOC 725 (183) 469 (127) 134 (31) 24
SOC+Dox 362 (76) 242 (40) 91 (13) 24

M1 docetaxel: Survival

Results based on 2993 men / 1254 deaths

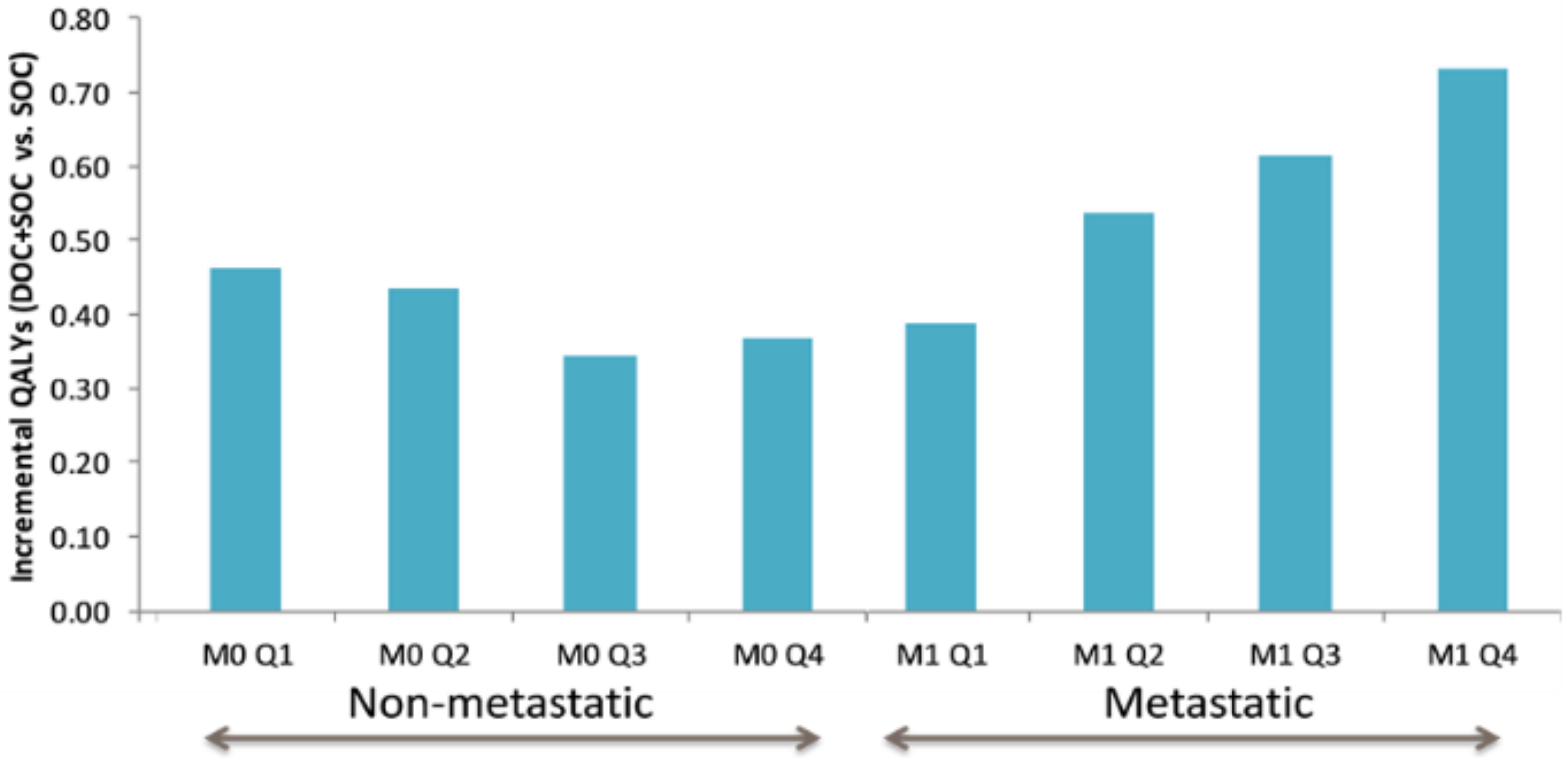


Heterogeneity: χ^2=4.80, df=3, p=0.187, I^2 = 37.5%

10% absolute improvement in survival
(from 40% to 50%) at 4 years

Vale CL, et al. Lancet Oncol. 2016;17(2):243-56

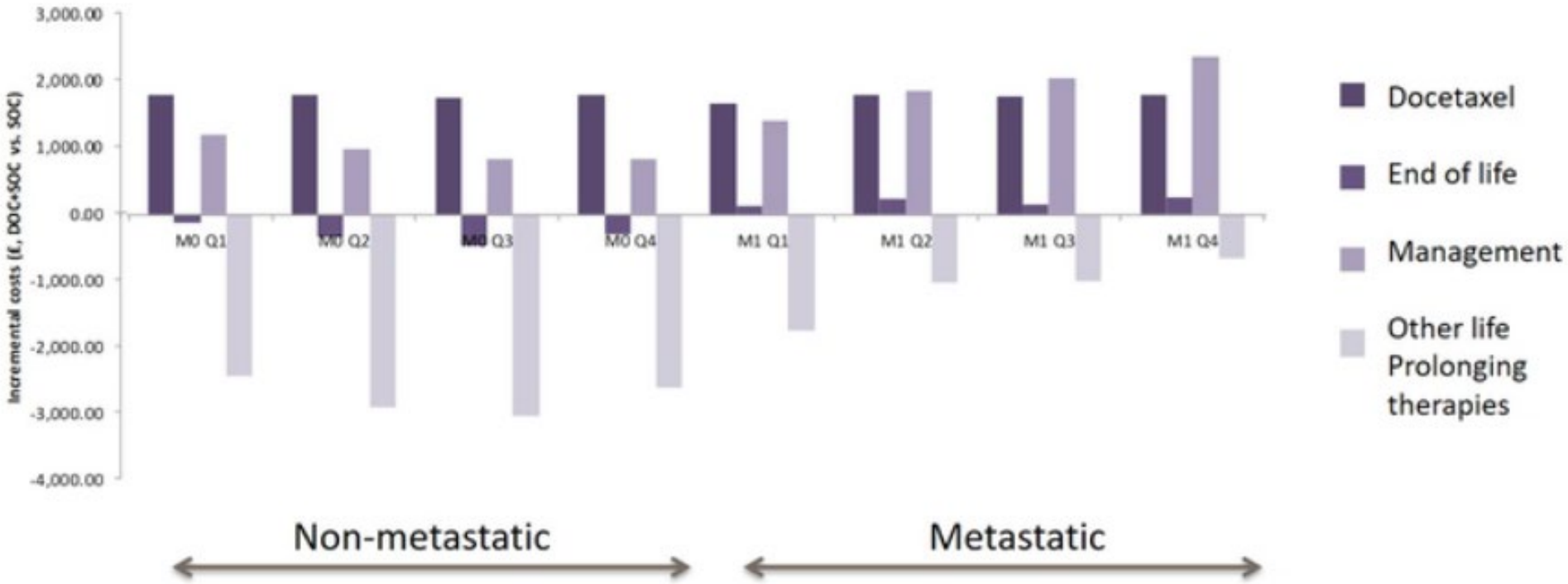
Impact of docetaxel on Quality Adjusted Life Years (QALYs)



- Gains in M1 vary considerably by quartile
- Gains in M0 more homogeneous and lower than in M1
- All groups show a QALY gain

Vale CL, et al. Lancet Oncol. 2016;17(2):243-56

Incremental cost breakdown – modelled to current practice



- Savings in life extending therapies due to shorter period of time spent in CRPC states for patients on DOC+SOC
- Much greater for M0 patients as patients allocated to docetaxel arm spend a much shorter period in CRPC
  - (i.e. extensions to FFS do not fully translate to increased OS)

Life prolonging therapies... Therapies beyond progression

CHAARTED

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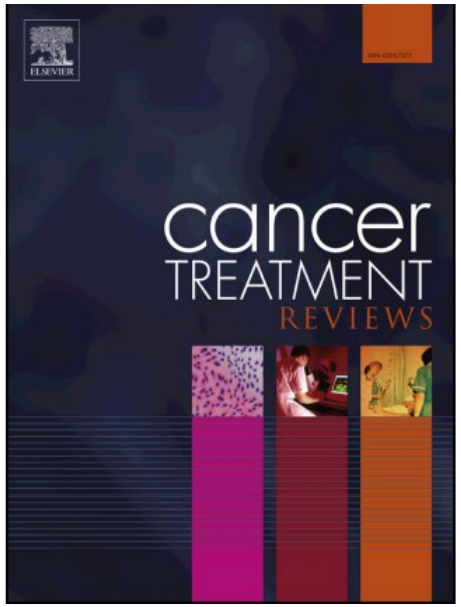
	Docetaxel	Cabazitaxel	Abi or Enza
ADT	48%	12,9%	36%
ADT+Docetaxel	-	23,9	44%

Is this finding responsible for the better survival ?

How About other Prognostic Factors ?



Gleason Score ? No difference !!!

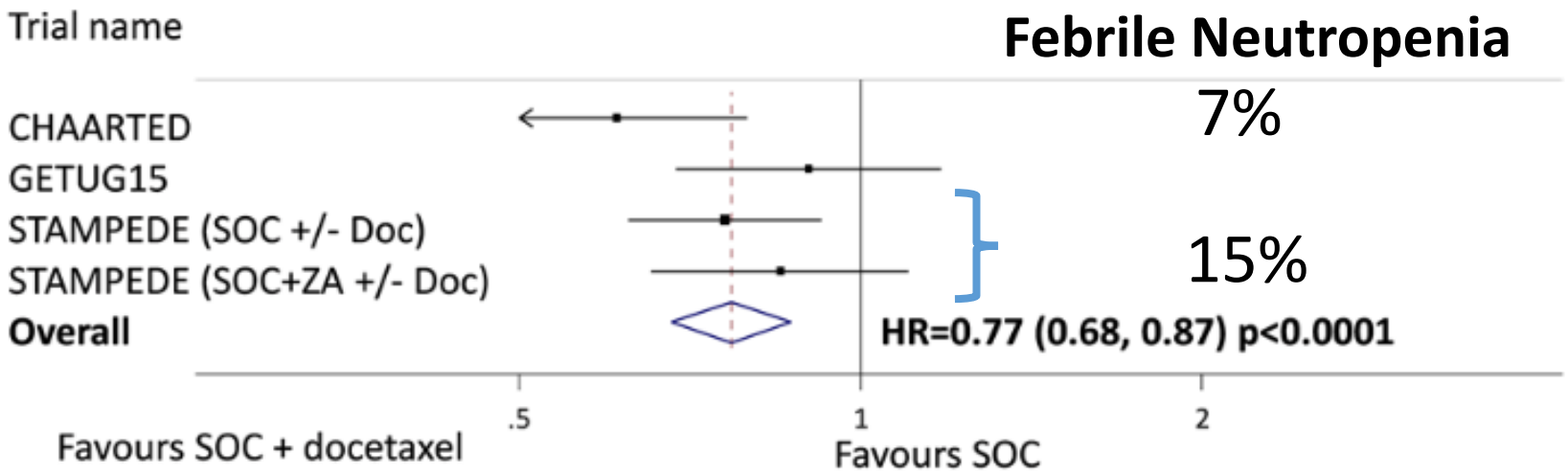
Previous local therapy ? No difference !!!

Age ? No difference !!!

Cancer Treatment Reviews Cancer Treatment Reviews (2016), doi: http://dx.doi.org/10.1016/j.ctrv. 2016.09.008

M1 docetaxel: Survival

A Word of Caution !!!→ **Death related mortality**



TAX 327

3%

16 death cases in the combination arm !!!

Vale CL, et al. Lancet Oncol. 2016;17(2):243-56