Systemische therapie mHSPC

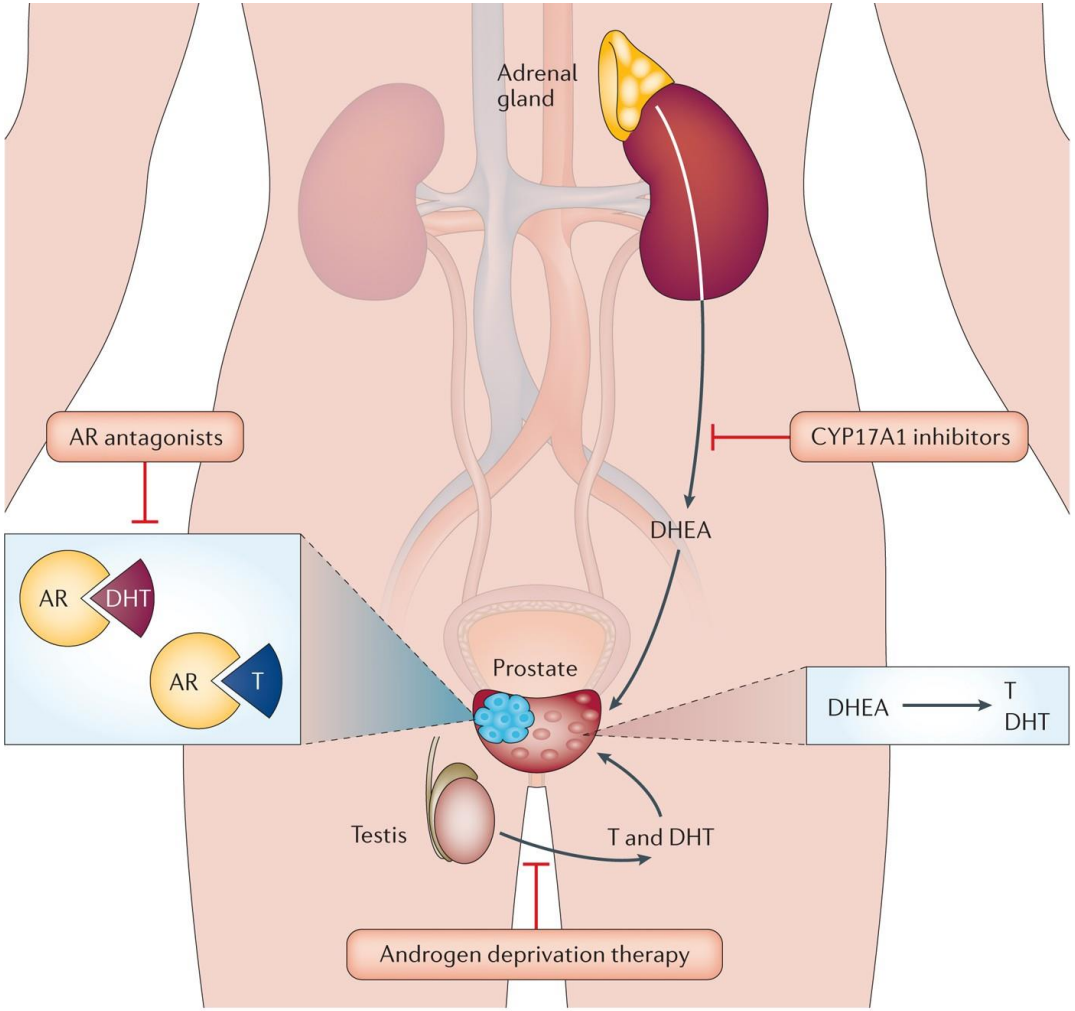
Steve Boudewijns
Internist oncoloog

10-2023

Disclosures

Geen

Inleiding



Nature Reviews Urology **volume 15**, pages191–196 (2018)
Stichting DUOS

10 jaar aan studies

TABLE 1. Summary Data of Completed Trials in Metastatic Hormone-Sensitive Prostate Cancer

Doublet Systemic Therapy

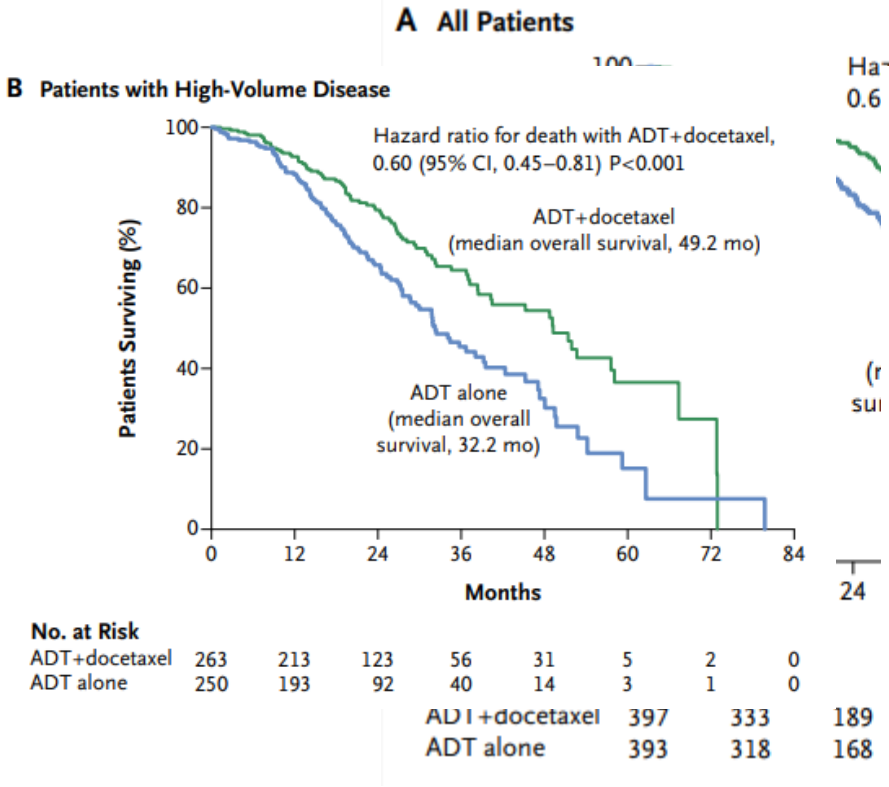
Trial	Patients Enrolled	Intervention Arm	Control Arm	Previous/ Concurrent Docetaxel	Median Follow-Up (months)	Median OS in Intervention Arm (months)	Median OS in Control Arm (months)	Group: HR (95% CI)	*P*
CHAARTED[7]	790	ADT plus docetaxel	ADT	Not allowed	53.7	57.6	47.2	0.72 (0.59 to 0.89)	.0018
STAMPEDE (M1 subgroup)[8]	1,086	ADT plus docetaxel	ADT	Not allowed	78.2	59.1	43.1	0.81 (0.69 to 0.95)	.003
LATITUDE[10]	1,199	ADT plus abiraterone plus prednisone	ADT plus placebo	Not allowed	51.8	53.3	36.5	0.66 (0.56 to 0.78)	<.0001
STAMPEDE[9]	1,917	ADT plus abiraterone plus prednisone	ADT	Not allowed	40	NR	NR	Overall: 0.63 (0.52 to 0.76) M1 subgroup: 0.61 (0.49 to 0.75)	<.001 (overall)
ENZAMET[16]	1,125	ADT plus enzalutamide	ADT plus NSAA	Allowed (concurrent, 45%)	68	NR	NR	Overall: 0.70 (0.58 to 0.84) Early docetaxel: 0.82 (0.63 to 1.06) No early docetaxel: 0.60 (0.47 to 0.78)	<.0001 (overall)
ARCHES[11]	1,150	ADT plus enzalutamide	ADT plus placebo	Allowed (previous, 18%)	44.6	NR	NR	Overall: 0.66 (0.53 to 0.81) Previous docetaxel: 0.74 (0.46 to 1.20) No previous docetaxel: 0.64 (0.51 to 0.81)	<.001 (overall)
TITAN[12]	1,052	ADT plus apalutamide	ADT plus placebo	Allowed (previous, 11%)	44	NR	52.2	Overall: 0.65 (0.53 to 0.79) Previous docetaxel: 1.12 (0.59 to 2.12) No previous docetaxel: 0.61 (0.50 to 0.76)	<.0001 (overall)

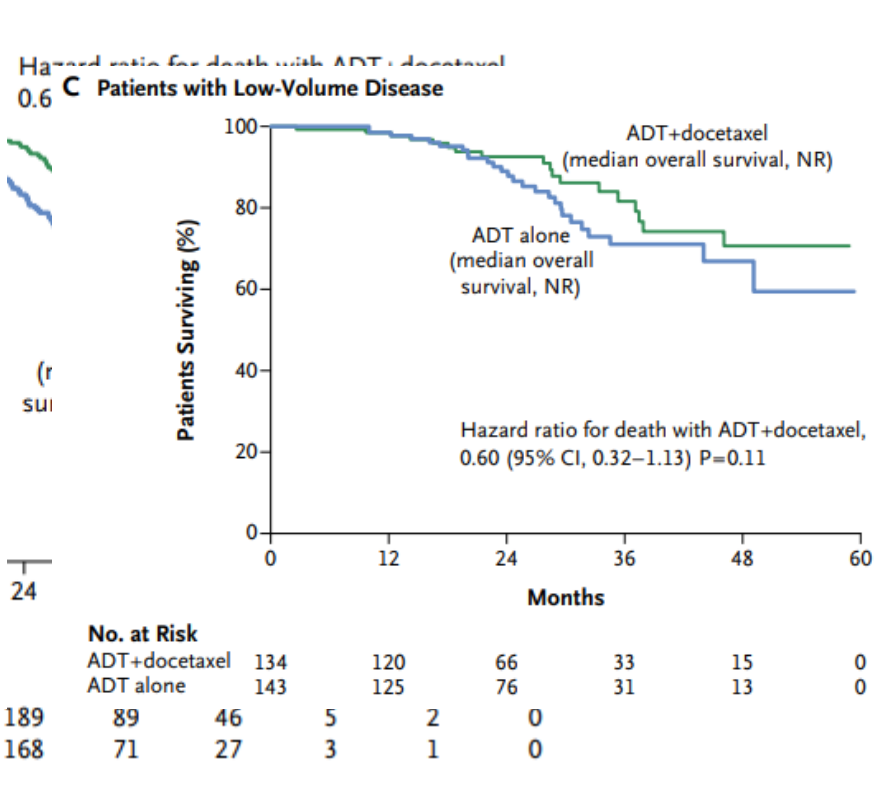
Triplet Systemic Therapy

Trial	Patients Enrolled	Intervention Arm	Control Arm	% Synchronous	% High-Volume	Median Follow-Up (months)	Median OS in Intervention Arm (months)	Median OS in Control Arm (months)	Group: HR (95% CI)
ARASENS[13,14]	1,306	ADT plus docetaxel plus darolutamide	ADT plus docetaxel plus placebo	86	77	43.7	NR	48.9	Overall: 0.68 (0.57 to 0.80) Synchronous + HV: 0.69 (0.57 to 0.85) Synchronous + LV: 0.75 (0.45 to 1.27) Metachronous + HV: 0.69 (0.39 to 1.24) Metachronous + LV: NA
PEACE-1 (docetaxel subgroup)[15]	710	SOC plus abiraterone (with or without RT)	SOC (with or without RT)	100	64	45.6	NR	53.2	Overall (all synchronous): 0.75 (0.59 to 0.95)
ENZAMET (docetaxel subgroup)[16]	503	ADT plus docetaxel plus enzalutamide	ADT plus docetaxel plus NSAA	72	71	68 (overall cohort)	Not reported	Not reported	Synchronous (all): 0.73 (0.55 to 0.99) Synchronous + HV: 0.79 (0.57 to 1.10) Synchronous + LV: 0.57 (0.29 to 1.12) Metachronous (all): 1.10 (0.65 to 1.86)

Hamid et al. *Asco educational book*. e390166

CHAARTED: ADT +/- Docetaxel

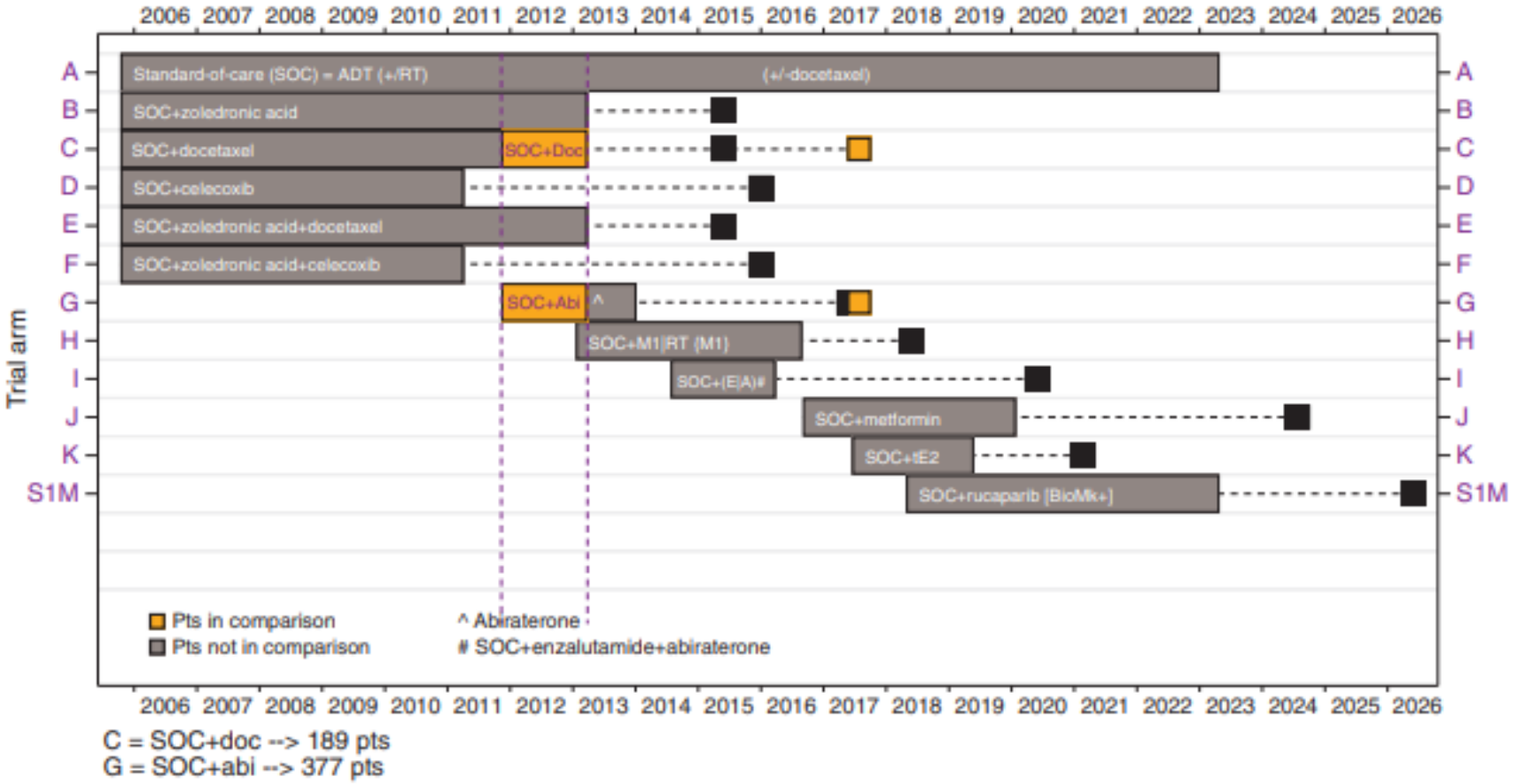




ADT+docetaxel 397 333 189 89 46 5 2 0
ADT alone 393 318 168 71 27 3 1 0

Sweeney CJ et al. *N Engl J Med* 2015;373:737-746.

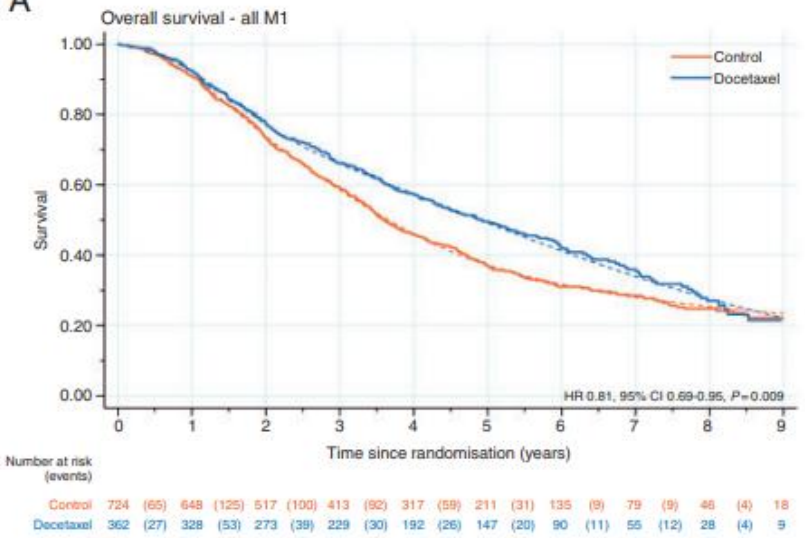
STAMPEDE overzicht



Sydes et al. *Annals of Oncology* 2018

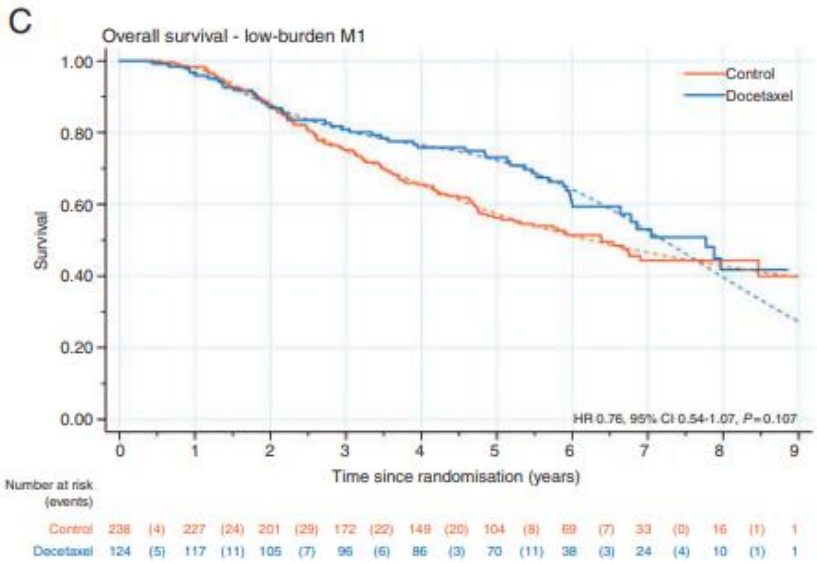
STAMPEDE arm C: ADT +/- Docetaxel

A

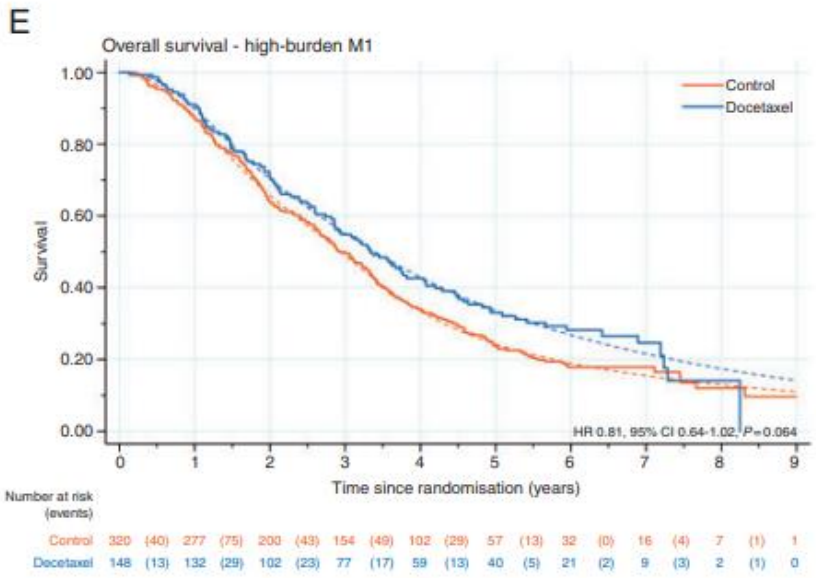


Post-hoc Analyse (CHAARTED)

C

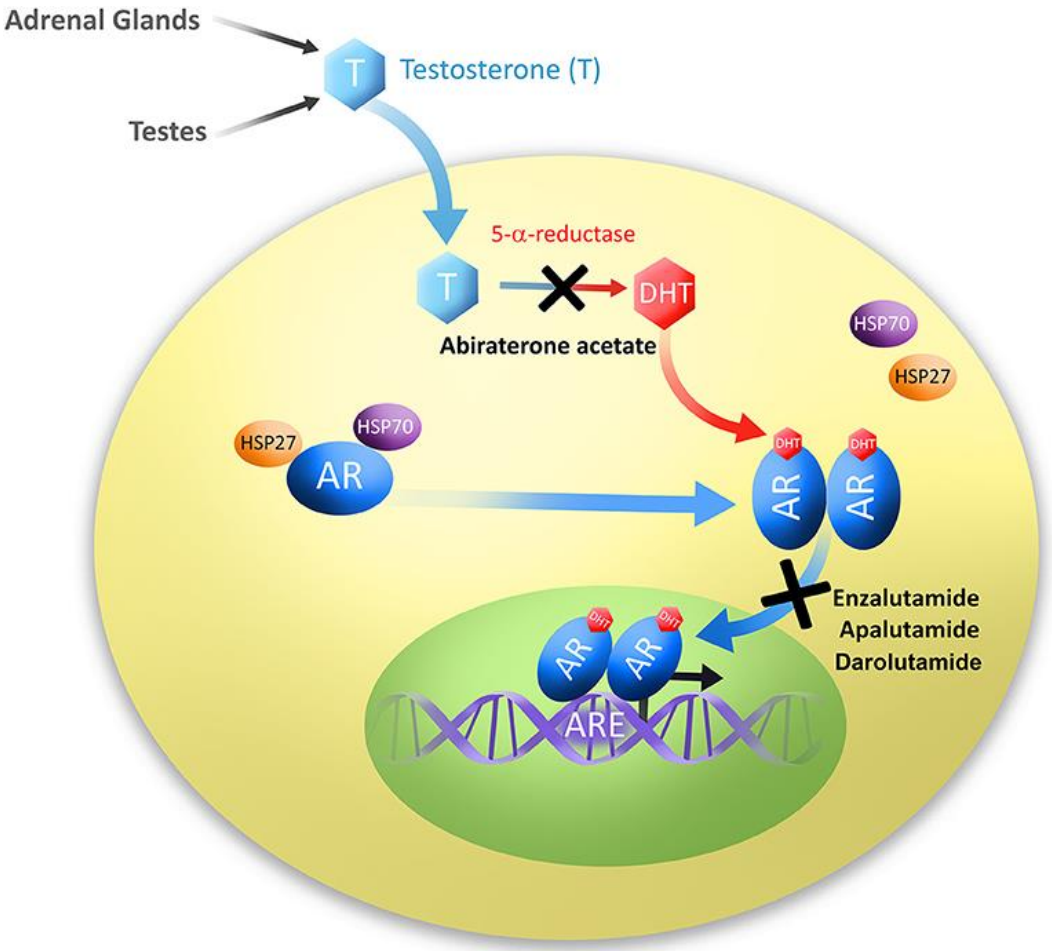


E



Clarke et al. *Annals of Onoclogy 2019*

Upfront androgeen receptor signaal inhibitoren (ARSI's)

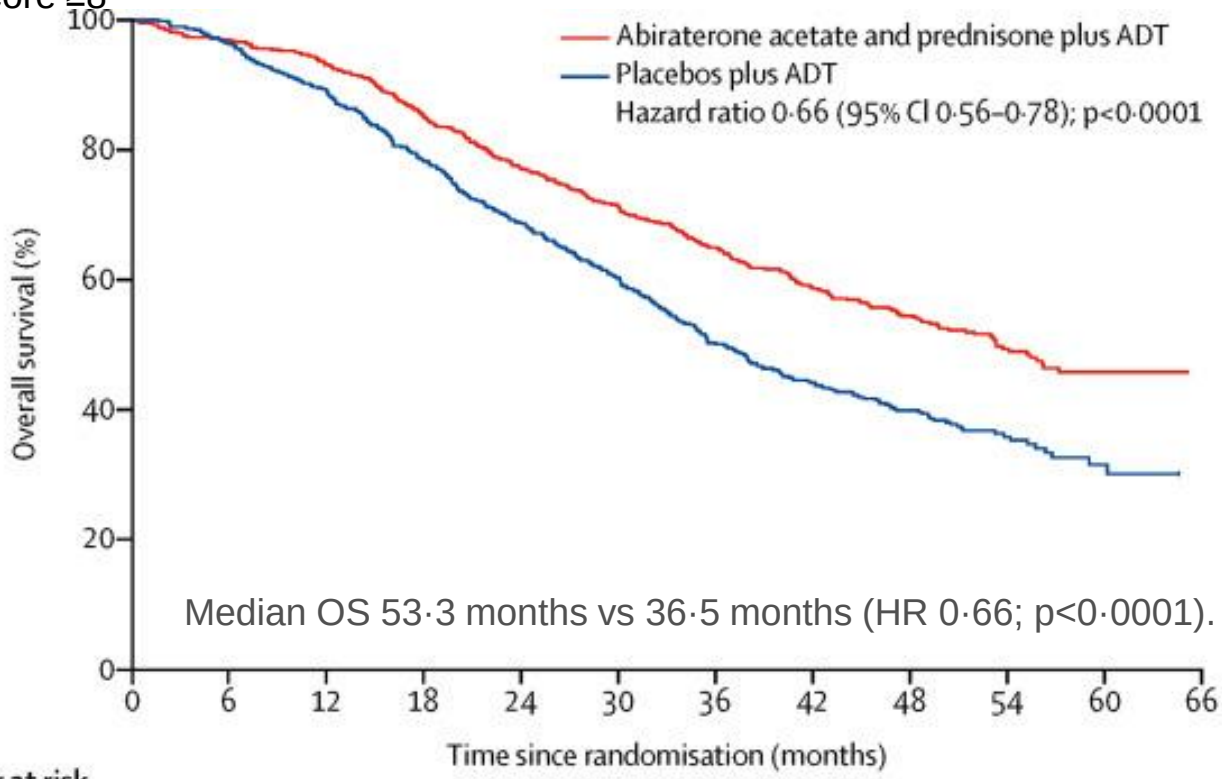


Front. Oncol., 28 August 2019; Sec. Genitourinary Oncology
Volume 9 - 2019

LATITUDE: ADT +/- Abiteteron

Inclusie: de novo mHSPC met minstens 2/3 hoog risico factoren:

- Gleason score ≥8
-
-

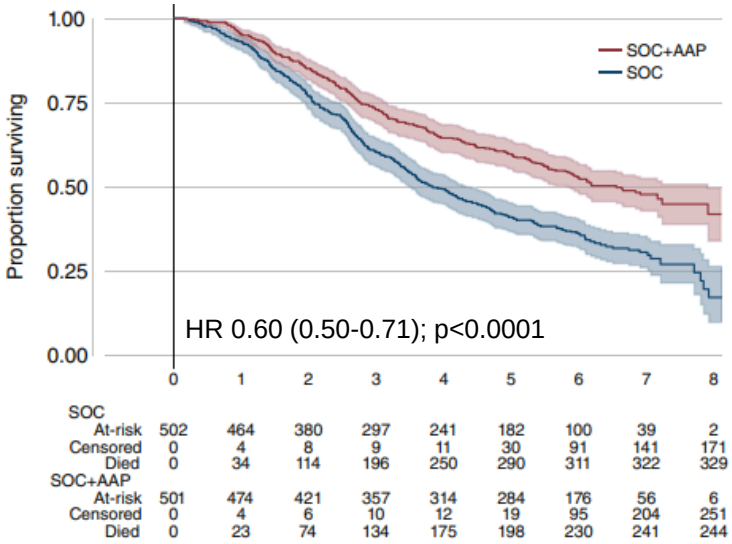


Number at risk (number censored)												
Abiraterone acetate and prednisone plus ADT	597	565 (14)	529 (28)	479 (34)	425 (42)	389 (46)	351 (50)	311 (57)	240 (106)	124 (205)	40 (282)	0 (322)
Placebos plus ADT	602	564 (17)	505 (34)	432 (47)	368 (58)	315 (37)	256 (74)	220 (79)	165 (114)	69 (197)	23 (237)	0 (259)

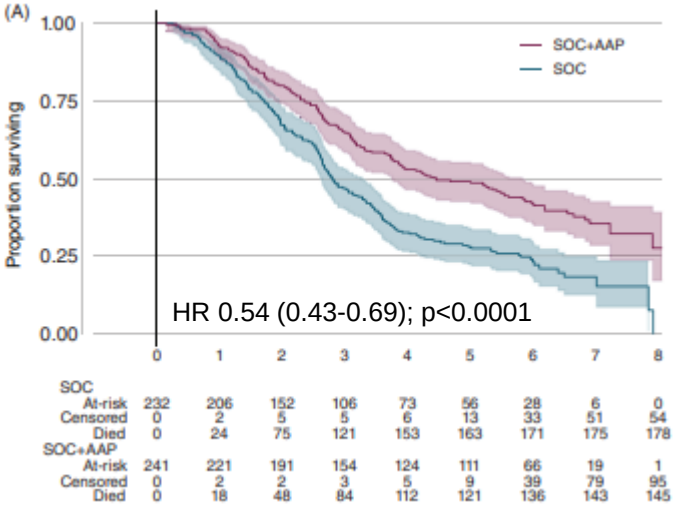
Fizazi et al. *Lancet Oncol.* Volume 20, issue 5, p686-700, May 2019

STAMPEDE arm G: ADT +/- Abirateron

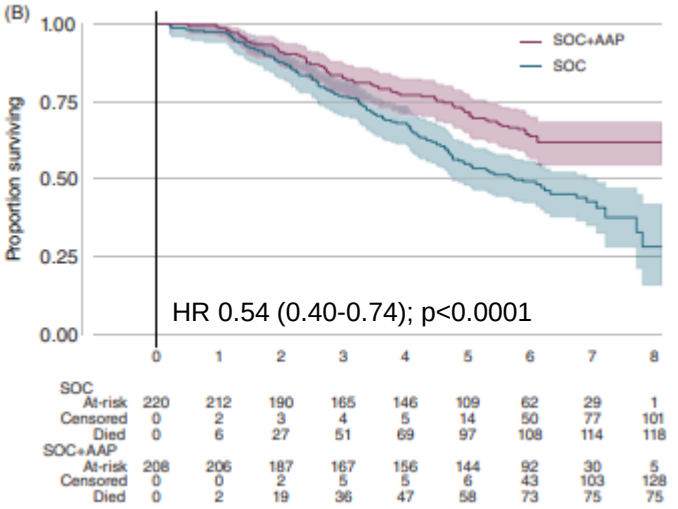
OS totale M1 populatie



Post-hoc Analyse (LATITUDE)



Hoog risico

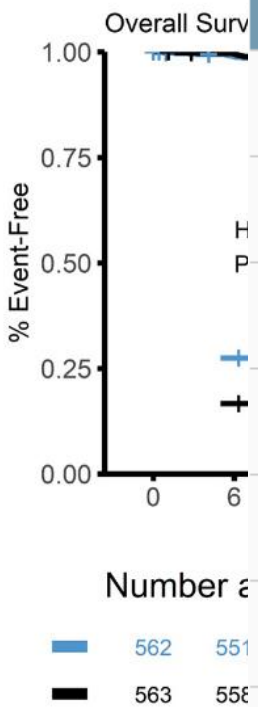


Laag risico

James et al. *Int J Cancer 2022*

ENZAMET: ADT + enzalutamide/NSAA

Enzamet



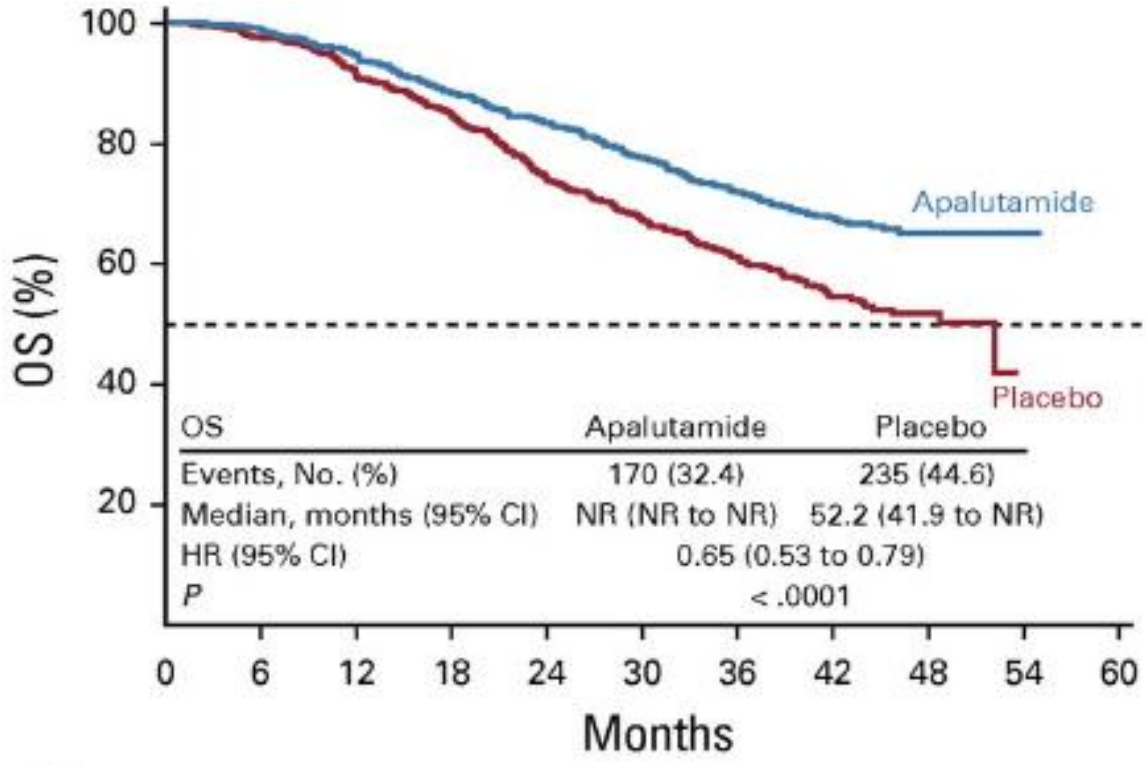
	Enzalutamide		NSAA		HR (95% CI)
	Deaths/Total	5y OS %	Deaths/Total	5y OS %	
All participants	208/563	67	268/562	57	0.70 (0.58 to 0.84)
Concurrent docetaxel					
No	100/310	72	145/312	58	0.60 (0.47 to 0.78)
Yes	108/253	61	123/250	56	0.82 (0.63 to 1.06)
Volume of Disease (Vol)					
Low	59/262	80	97/261	66	0.54 (0.39 to 0.74)
High	149/301	55	171/301	49	0.79 (0 .63 to 0.98)

S:
ISAA): 73.2 mo (64.7 - NR)
nide: NR (NR - NR)

rvival:
ISAA): 57%
nide: 67%

llow-up: 68 months

TITAN: ADT + Apalutamide/placebo



Chi et al. *J Clin Oncol* 39:2294-2303

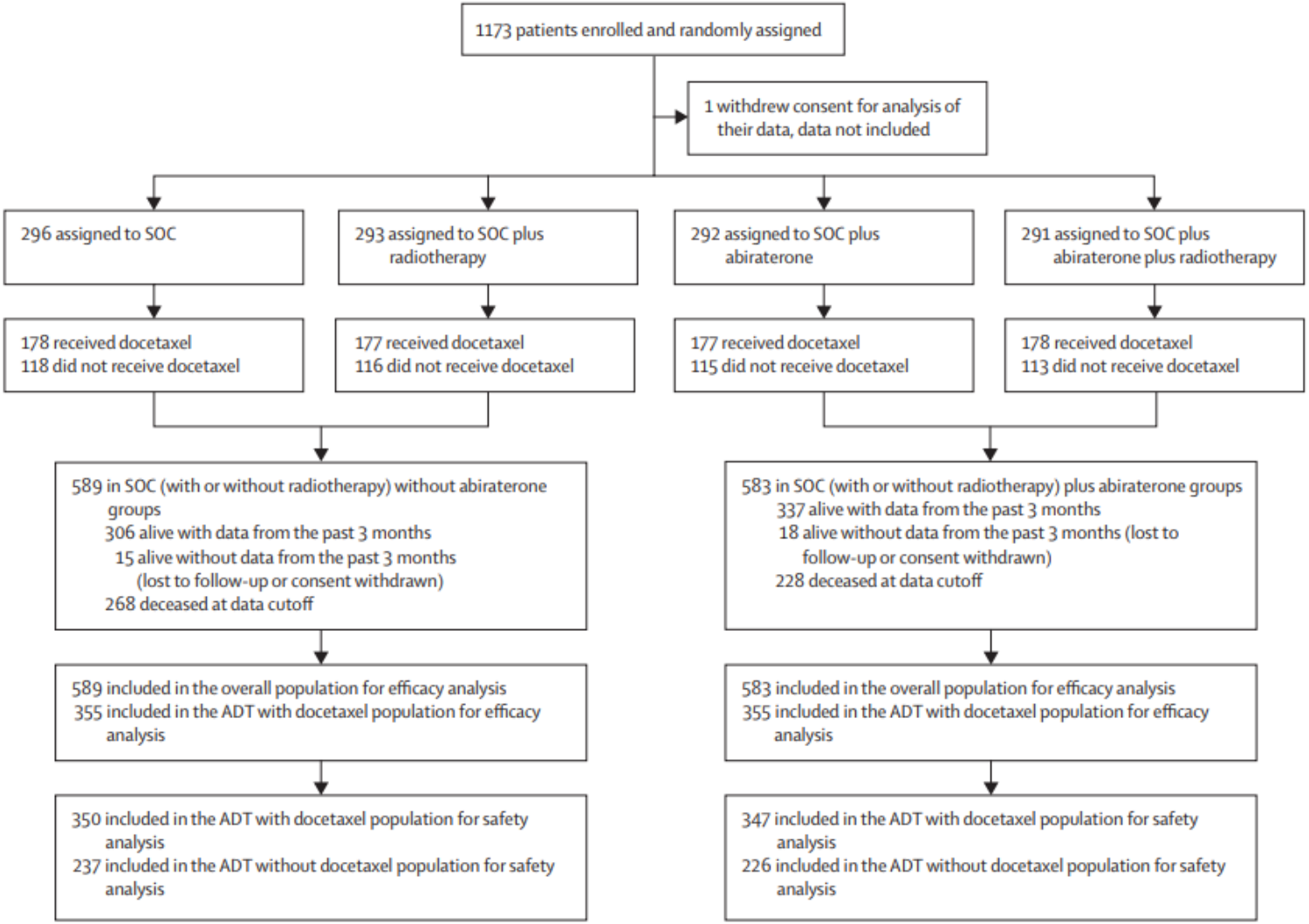
Discussie upfront Docetaxel/ARSI

- Welke beeldvorming gebruiken voor bepalen volume status
- Welke ARSI?
- Verschil bij hoogvolume/laagvolume of hoogrisico/laagrisico
- Duur behandeling
- Plaats van radiotherapie (STAMPEDE arm H)

Outcome measure	Patient group	Adjusted HR[~]	Unadjusted HR[^]	Event free at 5 years[+]		RMST[+]		
				SOC	SOC +RT	SOC	SOC+RT	Difference
OS	All patients	0.90 (0.81 to 1.01)	0.90 (0.81 to 1.01)	42%	45%	52.9	55.5	2.5 (−0.2 to 5.2)
	Low metastatic burden	0.64 (0.52 to 0.79)	0.66 (0.54 to 0.82)	53%	65%	60.6	69.0	8.4 (4.5 to 12.2)
	High metastatic burden	1.11 (0.96 to 1.28)	1.08 (0.94 to 1.25)	35%	30%	47.7	45.5	−2.2 (−5.7 to 1.2)

Parker et al. *PLoS Med* 2022

PEACE 1: ADT + Docetaxel + Abi in de Novo mHSPC



Fizazi et al. *Lancet* 2022; 399: 1695–07

PEACE 1

	Patients assessed, n		Median, years		Median difference, years	Hazard ratio	p value
	SOC with abiraterone groups	SOC without abiraterone groups	SOC with abiraterone groups	SOC without abiraterone groups			
Primary outcomes in the overall population							
Overall survival	583	589	5·7	4·7	0·9 (95·1% CI 0·0–2·0)	0·82 (95·1% CI 0·69–0·98)	0·030
Radiographic progression-free survival	583	589	4·5	2·2	2·1 (99·9% CI 0·7–2·9)	0·54 (99·9% CI 0·41–0·71)	<0·0001
Secondary outcomes in the overall population							
CRPC-free survival	583	589	3·8	1·5	2·3 (95% CI 1·6–3·0)	0·40 (95% CI 0·35–0·47)	<0·0001
Prostate-cancer-specific survival	583	589	NR	5·8	NA	0·75 (95% CI 0·61–0·91)	0·0038
Primary outcomes in the ADT with docetaxel population							
Overall survival	355	355	NR	4·4	NA	0·75 (95·1% CI 0·59–0·95)	0·017
Radiographic progression-free survival	355	355	4·5	2·0	2·2 (99·9% CI 0·6–2·8)	0·50 (99·9% CI 0·34–0·71)	<0·0001
Secondary outcomes in the ADT with docetaxel population							
Overall survival in patients with low-volume metastatic burden	131	123	NR	NR	NA	0·83 (95·1% CI 0·50–1·39)	0·66
Overall survival in patients with high-volume metastatic burden	224	232	5·1	3·5	1·1 (95·1% CI 0·2–1·9)	0·72 (95·1% CI 0·55–0·95)	0·019
Radiographic progression-free survival in patients with low-volume metastatic burden	129	122	NR	2·7	NA	0·58 (99·9% CI 0·29–1·15)	0·0061
Radiographic progression-free survival in patients with high-volume metastatic burden	225	231	4·1	1·6	2·2 (99·9% CI 0·6–3·2)	0·47 (99·9% CI 0·30–0·72)	<0·0001
CRPC-free survival	355	355	3·2	1·4	2·0 (95% CI 1·5–3·1)	0·38 (95% CI 0·31–0·47)	<0·0001
Prostate-cancer-specific survival	355	355	NR	4·7	NA	0·69 (95% CI 0·53–0·90)	0·0062

Fizazi et al. *Lancet* 2022; 399: 1695–07

PEACE 1

	ADT with docetaxel population		ADT without docetaxel population	
	SOC plus abiraterone groups (with or without radiotherapy; n=347)	SOC without abiraterone groups (with or without radiotherapy; n=350)	SOC plus abiraterone groups (with or without radiotherapy; n=226)	SOC without abiraterone groups (with or without radiotherapy; n=237)
Any adverse events	346 (100%)	349 (100%)	226 (100%)	233 (99%)
Severe (grade ≥3) adverse events	217 (63%)	181 (52%)	149 (66%)	97 (41%)
Fatal (grade 5) adverse events	7 (2%)	3 (1%)	8 (4%)	5 (2%)
Frequent severe adverse events				
Hypertension	76 (22%)	45 (13%)	66 (29%)	38 (16%)
Neutropenia	34 (10%)	32 (9%)	0	0
Hepatotoxicity	20 (6%)	2 (1%)	14 (6%)	3 (1%)
Febrile neutropenia	18 (5%)	19 (5%)	2 (1%)	1 (<1%)
Gamma-glutamyl transferase increase	17 (5%)	14 (4%)	6 (3%)	4 (2%)
Erectile dysfunction	7 (2%)	5 (1%)	12 (5%)	13 (5%)
Blood alkaline phosphatase increase	15 (4%)	12 (3%)	6 (3%)	13 (5%)
Other severe adverse events				
Fatigue	10 (3%)	15 (4%)	3 (1%)	0
Peripheral neuropathy	4 (1%)	6 (2%)	1 (<1%)	0

Data are n (%). As the patients were not randomly assigned according to docetaxel prescription, toxicities recorded in the ADT without docetaxel and ADT with docetaxel populations are not directly comparable. Percentages are rounded to the nearest integer. The safety population includes patients who actually received the assigned treatment. Severe adverse events (grade ≥3) were considered frequent if they occurred in at least 5% of patients in either group and are reported in decreasing order of occurrence according to the Medical Dictionary for Regulatory Affairs Preferred Term classification. ADT=androgen deprivation therapy. SOC=standard of care.

Table 3: **Adverse events in the safety population**

Fizazi et al. *Lancet* 2022; 399: 1695–07

ARASENS: ADT + Docetaxel +/- Darolutamide in mHSPC

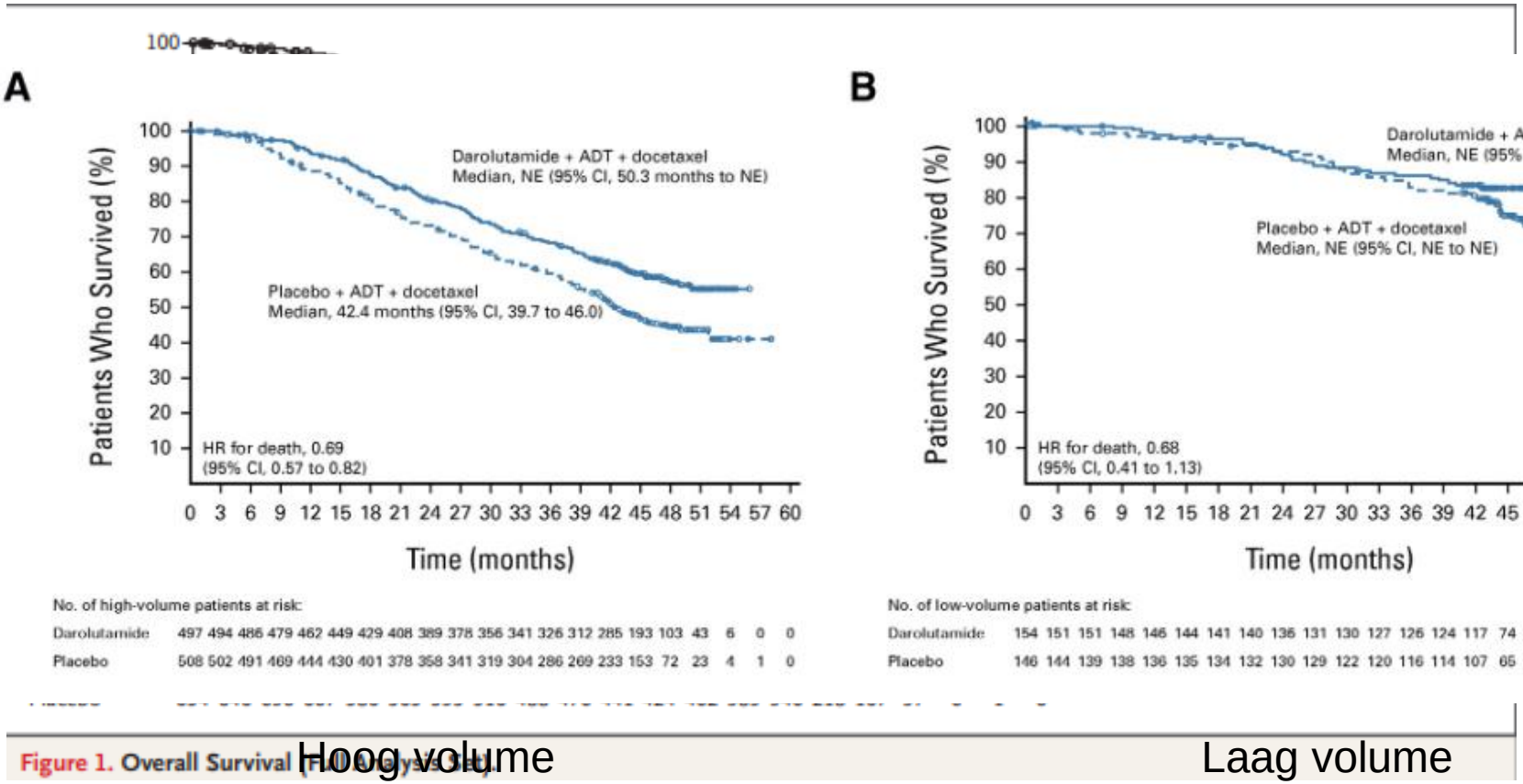


Figure 1. Overall Survival (FAS Analysis Set).

Hoog volume

Laag volume

Smith et al. *N Engl J Med* 2022;386:1132-42
Hussain et al. *J Clin Oncol* 2023

ARASENS trial

Table 3. Adverse Events.*

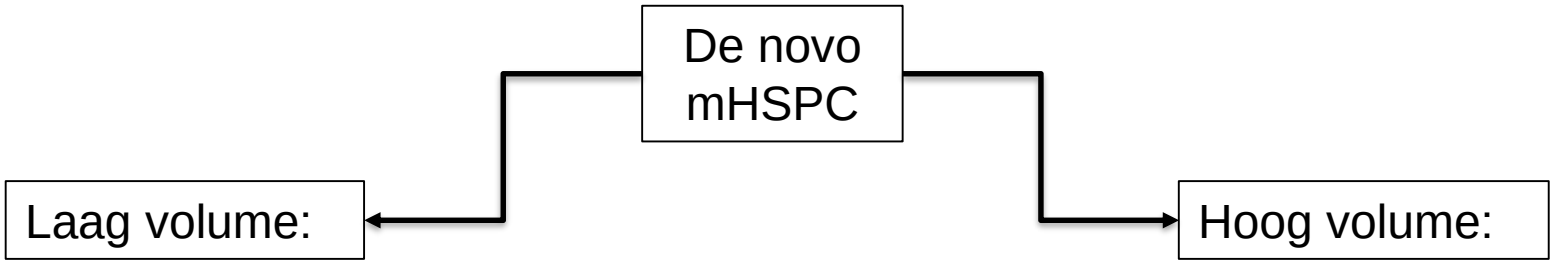
Event	Darolutamide–ADT–Docetaxel (N=652)†	Placebo–ADT–Docetaxel (N=650)†
	number of patients (percent)	
Any adverse event	649 (99.5)	643 (98.9)
Worst grade		
Grade 1	28 (4.3)	35 (5.4)
Grade 2	162 (24.8)	169 (26.0)
Grade 3	248 (38.0)	232 (35.7)
Grade 4	183 (28.1)	181 (27.8)
Grade 5	27 (4.1)	26 (4.0)
Serious adverse event	292 (44.8)	275 (42.3)
Adverse event leading to permanent discontinuation of trial agent		
Darolutamide or placebo	88 (13.5)	69 (10.6)
Docetaxel	52 (8.0)	67 (10.3)
Selected grade 3 or 4 adverse events‡		
Neutropenia§	220 (33.7)	222 (34.2)
Febrile neutropenia	51 (7.8)	48 (7.4)
Hypertension	42 (6.4)	21 (3.2)
Anemia	31 (4.8)	33 (5.1)
Pneumonia	21 (3.2)	20 (3.1)
Hyperglycemia	18 (2.8)	24 (3.7)
Increased ALT level	18 (2.8)	11 (1.7)
Increased AST level	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
Urinary tract infection	13 (2.0)	12 (1.8)

Smith et al. *N Engl J Med* 2022;386:1132-42

Discussie triple therapie

- Opzet PEACE 1 studie
- Docetaxel met abirateron versus abirateron alleen
- Synergistisch effect ARSI en docetaxel?
- Patient reported outcomes/QoL
- Hoe lang door met ARSI in deze vorm van behandeling
- Alle hoog volume patienten triple therapie?

Opties



- Radiotherapie prostaat
- ARSI
- Studiebehandeling

- Docetaxel
- ARSI
- Triple therapie
- Studiebehandeling

Take home messages

- Intensivering behandeling heeft positief effect op overleving
- Moet alles bij iedereen?