Θεραπεία Μεταστατικής Ευνουχοευαίσθητης νόσου

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«Ερρίκος Ντυνάν Hospital Center»

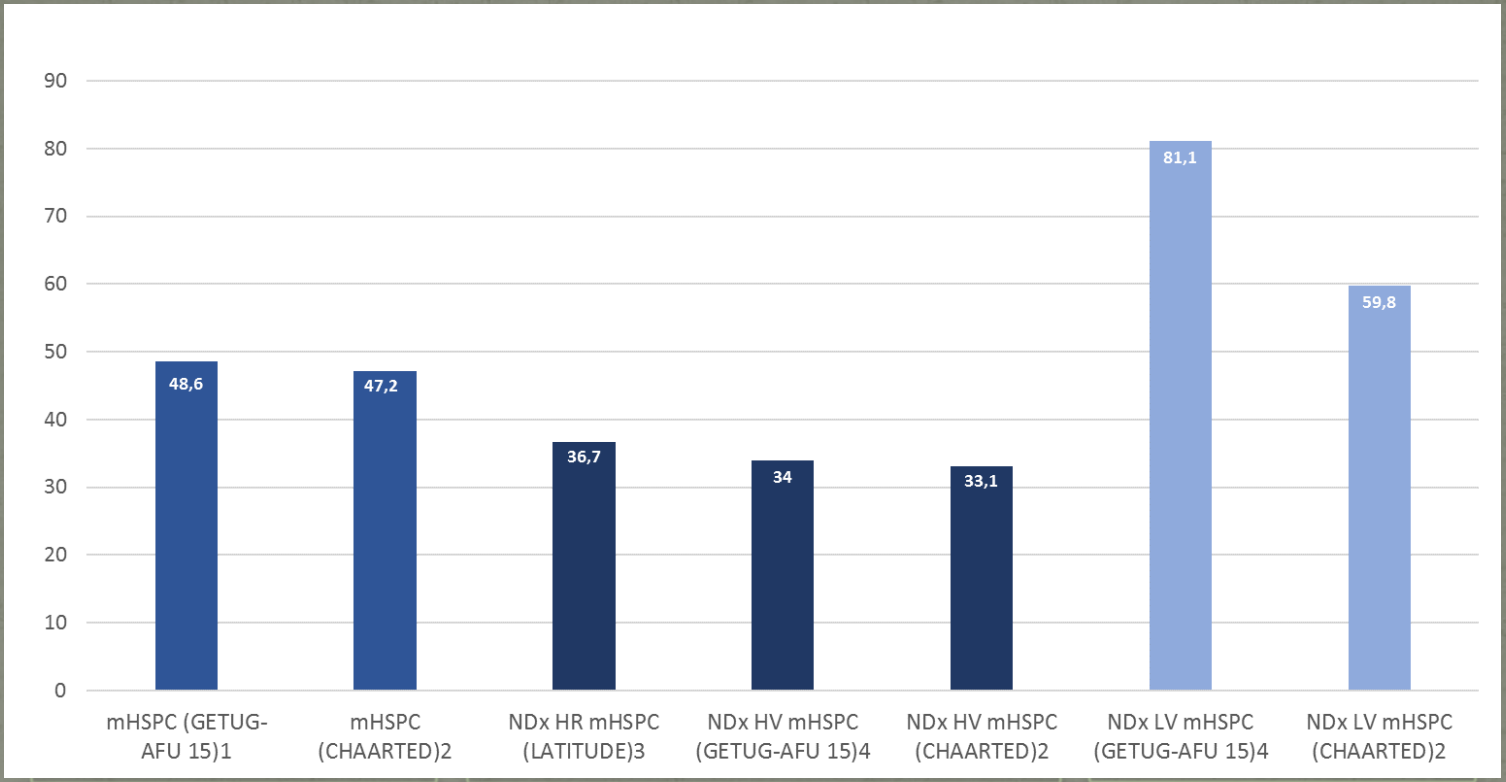
Δήλωση Συμφερόντων

ουδέν

Disease volume impacts outcomes in mHSPC

Median OS

Data from the control arm (ADT) of phase III trials in pts with mHSPC



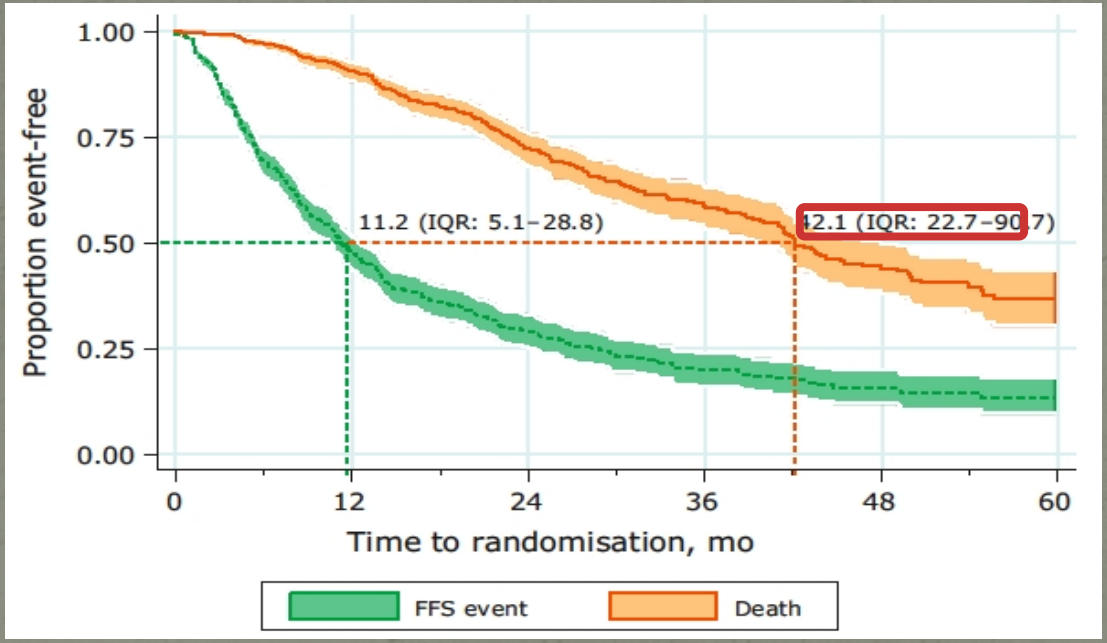
mHSPC | **high risk/high volume mHSPC** | **low volume mHSPC**

Median OS in patients with HR/HV mHSPC receiving ADT is less than 3 years

1. Gravis G, et al. Eur Urol. 2016 Aug;70(2):256-62; 2. Kyriakopoulos CE, et al. J Clin Oncol. 2018 Apr 10;36(11):1080-1087; 3. Fizazi K, et al. Poster presented at ASCO 2018, Abstract 5023; 4. Gravis G, et al. ASCO-GU 2017. Abstract 136 (and poster)

De novo M1 hormone-sensitive prostate cancer (HSPC) has a poor prognosis

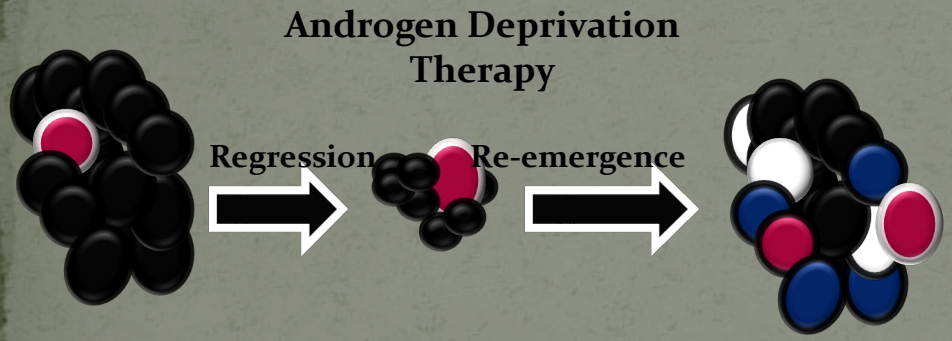
- 917 patients with *de novo* M1 HSPC (2005-2014) treated by ADT alone (STAMPEDE randomized trial control arm)
- **Median OS from diagnosis: 42 mo**



ADT: androgen deprivation therapy; FFS: failure-free survival; HSPC: hormone-sensitive prostate cancer; OS: overall survival

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

Early other treatment+ADT: A debate in one slide



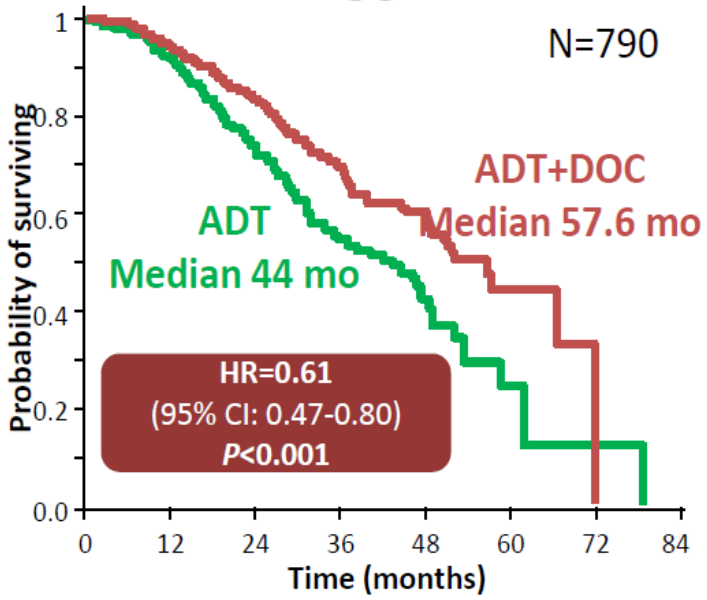
- **Pro**
  - Attack de-novo testosterone independent clones early - allow ADT to keep PrCa in remission longer
  - Some patients at the time of progression are too frail for chemo.

Presented by: Christopher J. Sweeney, MBBS

Συνδυασμός ADT και Taxanes σε mHSPC

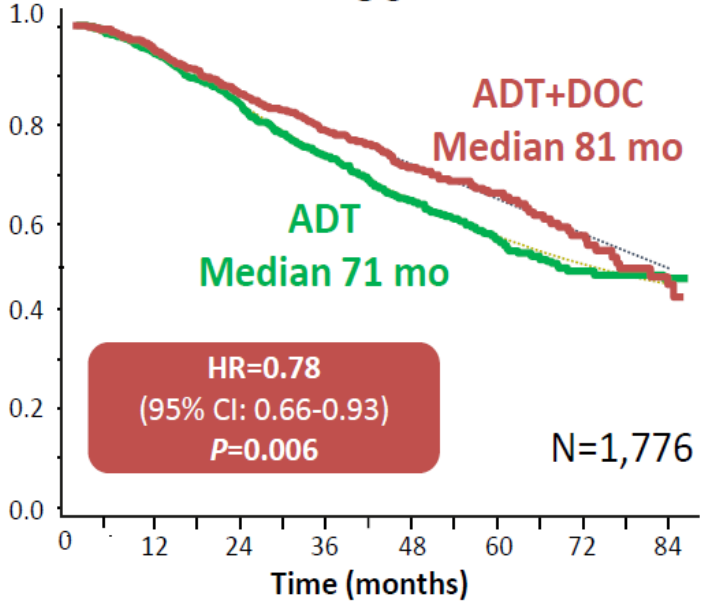
Combining ADT and Taxanes in mHNPC

CHAARTED (M1)[1]
OS



Phase III randomized trial in M1 HNPC (72.8% newly diagnosed M1[3]) – Primary endpoint: OS

STAMPEDE (M0/M1)[2]
OS



Phase III randomized trial in M0/M1 HNPC (61% newly diagnosed M1[3]) – Primary endpoint: OS

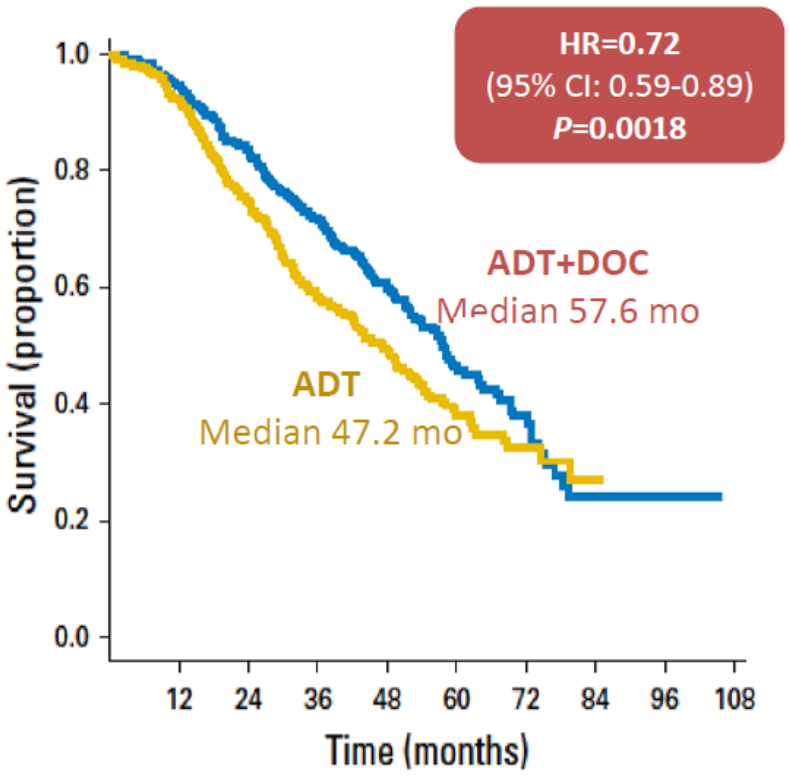
DOC/P is registered for the treatment of patients with mCRPC

ADT, androgen deprivation therapy; CI, confidence interval; DOC, docetaxel 75 mg/m² every 3 weeks; HR, hazard ratio; M0/M1 nonmetastatic/metastatic; mHNCP, metastatic hormone-naive prostate cancer; OS, overall survival; P, prednisone

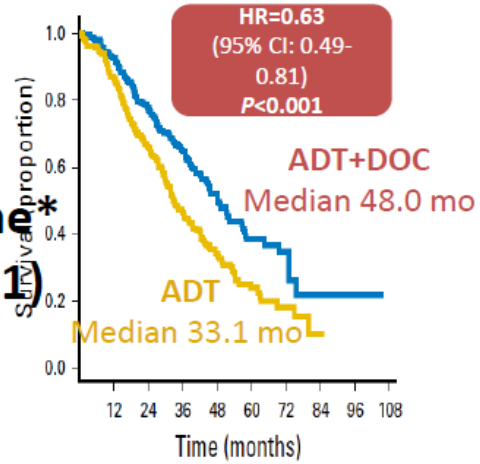
1. Sweeney C, et al. N Engl J Med. 2015;373:737-46; 2. James ND, et al. Lancet. 2016;387:1163-77; 3. Gravis G, et al. Cancer Treat Rev.

nonmetastatic/metastatic; mHNCP, metastatic hormone-naive prostate cancer; OS, overall survival; P, prednisone
1. Sweeney C, et al. N Engl J Med. 2015;373:737-46; 2. James ND, et al. Lancet. 2016;387:1163-77; 3. Gravis G, et al. Cancer Treat Rev.

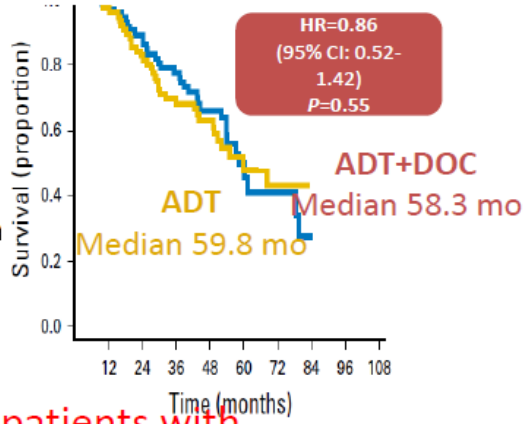
CHAARTED Updated – ADT+DOC in M1 HNPC
Primary Endpoint: OS



High-volume* (N=421)



Low-volum (N=15

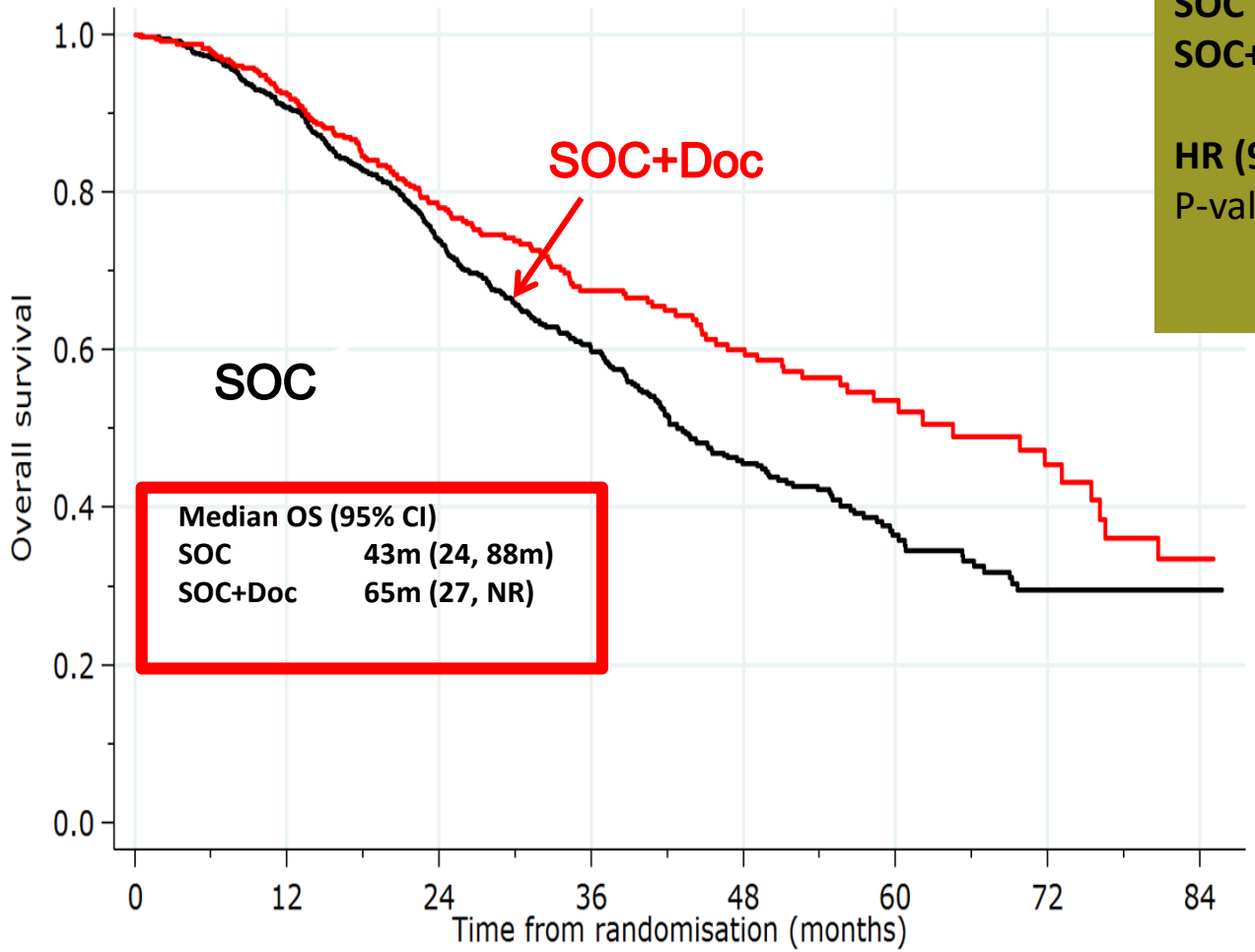


DOC/P is registered for the treatment of patients with hormone-refractory metastatic PCa

ADT, androgen deprivation thearpy; CI, confidence interval; DOC, docetaxel; HR, hazard ratio; HNCP, hormone-naive prostate cancer; NA, not available; M1, metastatic; OS, overall surviva; P, prednisone; PCa, prostate cancer

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.

Docetaxel: Survival – M1 Patients- STAMPEDE



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

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

Non-PH p-value 0.23

Restricted mean OS time

SOC	49.3m
SOC+Doc	56.1m
Diff (95%CI)	6.8m (2.8, 11.0m)

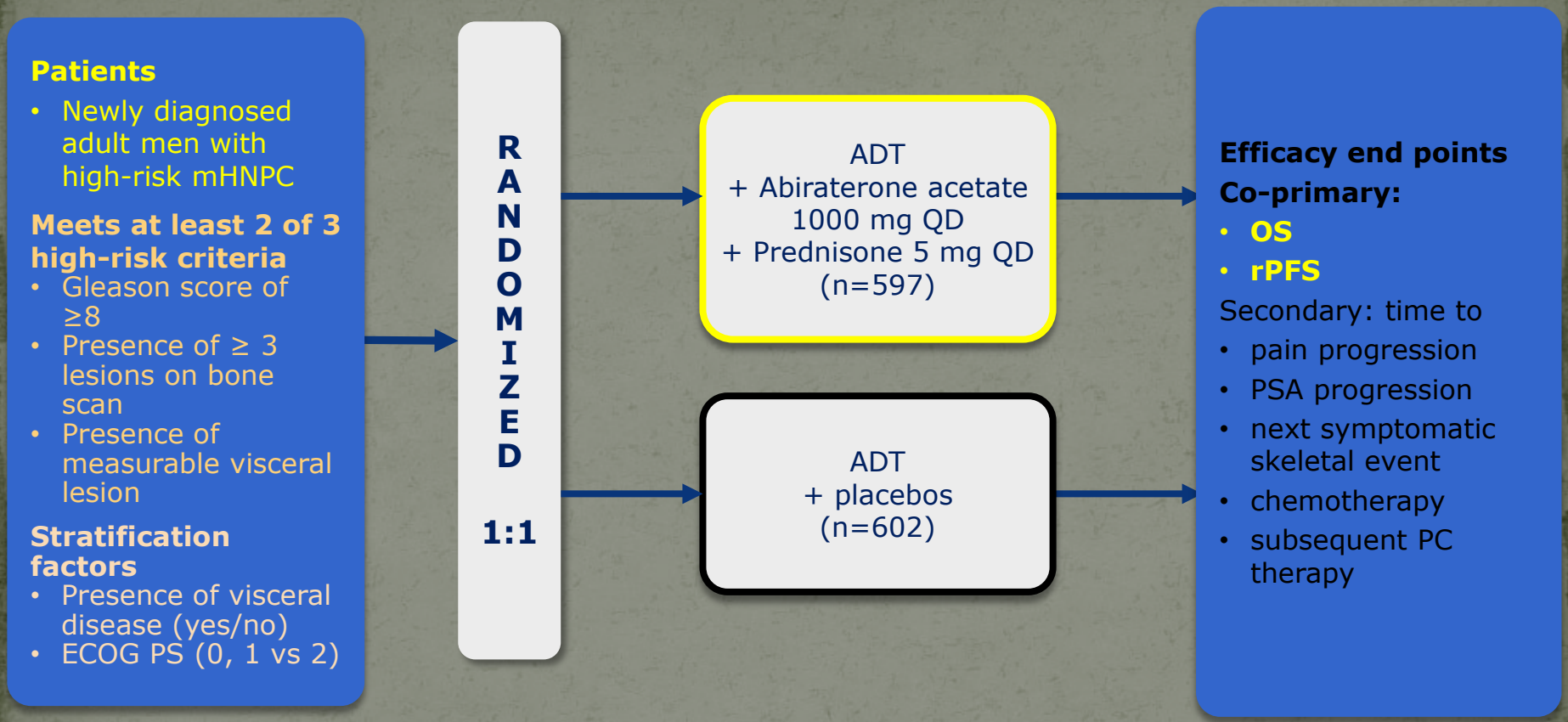
Συνδυασμός ADT και Abiraterone acetate+ Prednisone σε mHSPC

Rationale for AA + P added to ADT in mCNPC

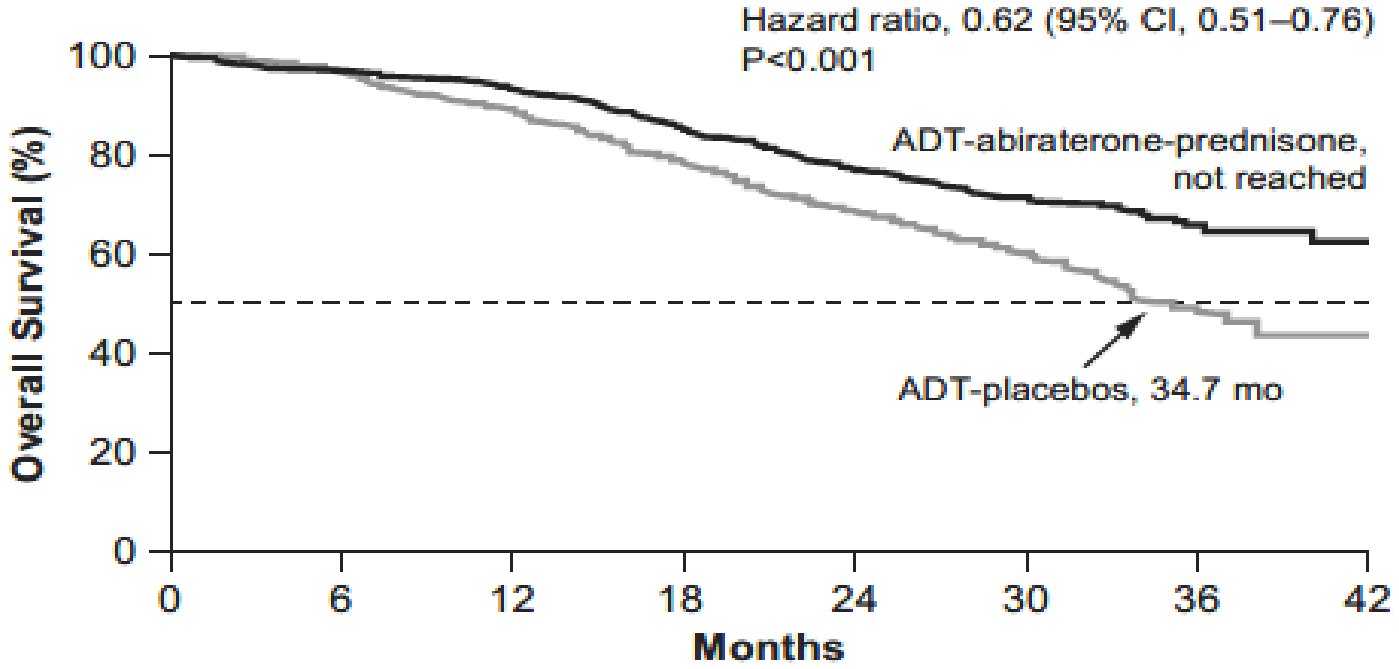
- Mechanisms of resistance to ADT may develop early[1-3]
- ADT alone does not inhibit androgen synthesis by:
  - adrenal
  - prostatic cancer cells
- AA + P:
  - improves OS in mCRPC[4,5]
  - reduces tumor burden in high-risk, localized PC[6,7]
- These data suggest a potential role for inhibiting extragonadal androgen biosynthesis ***prior to the emergence of castration resistance***

1. Gravis G, et al. *Eur Urol*. 2016:70:256-262. 2. Sweeney C, et al. *N Engl J Med*. 2015;373:737-746. 3. James N, et al. *Lancet*. 2016;387:1163-1177. 4. de Bono JS, et al. *N Engl J Med*. 2011;364:1995-2005. 5. Ryan CJ, et al. *Lancet Oncol*. 2015;16:152-160. 6. Taplin ME, et al. *J Clin Oncol*. 2014;32:3705-3715. 7. Efstathiou E, et al. *J Clin Oncol*. 2015;33(suppl):15s. Abstract 5061.

Study Design (LATITUDE)



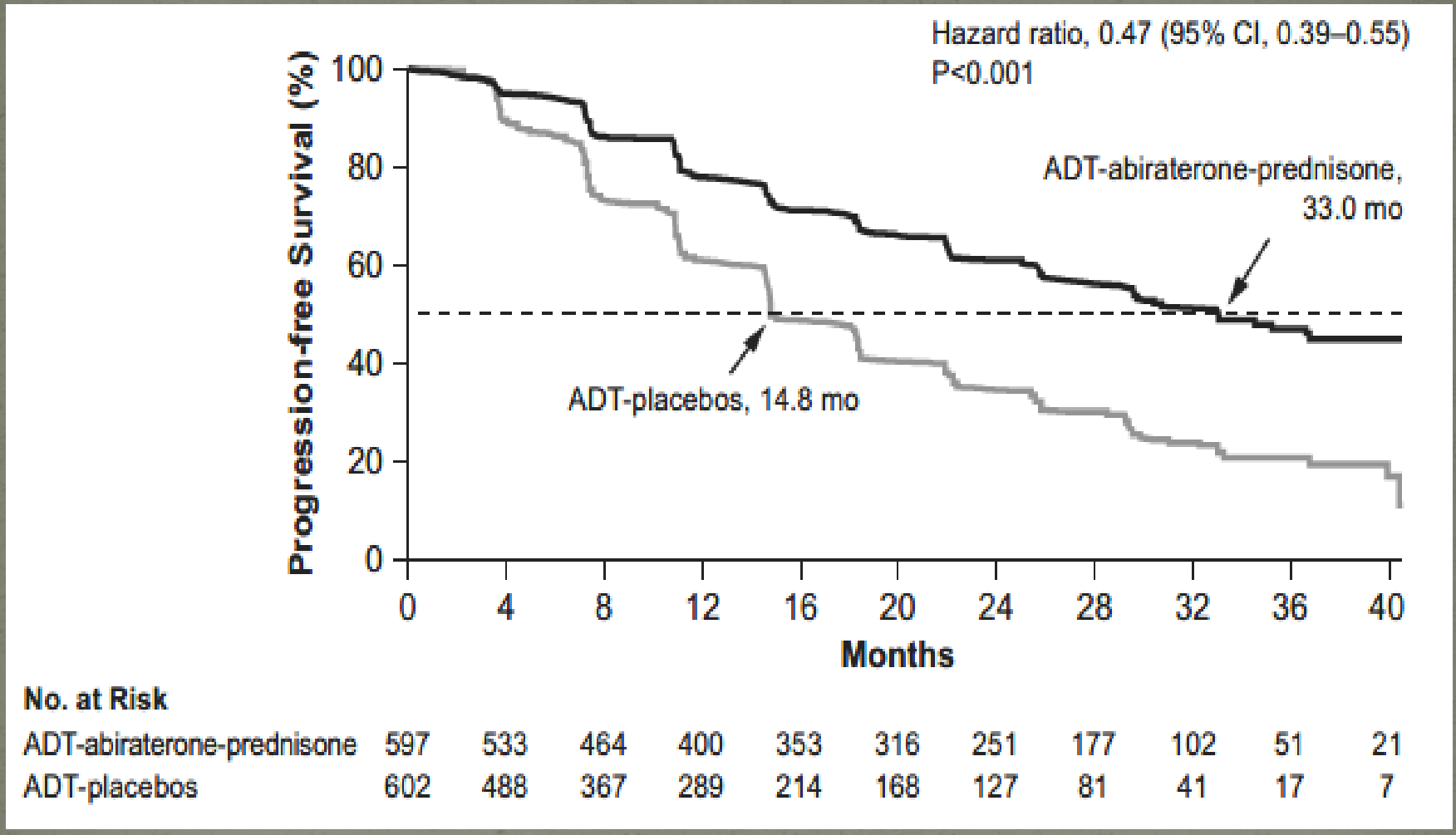
Overall Survival



No. at Risk								
ADT-abiraterone-prednisone	597	565	529	479	388	233	93	9
ADT-placebos	602	564	504	432	332	172	57	2

- At a median follow-up of 30.4 months (48% of total deaths), the addition of abiraterone acetate and prednisone to ADT significantly improved OS, with a 38% reduction in the risk of death
- The 3-year OS rate was 66% in the ADT-abiraterone-prednisone group compared with 44% in the ADT-placebos group

Radiographic Progression-free Survival



No. at Risk

ADT-abiraterone-prednisone	597	533	464	400	353	316	251	177	102	51	21
ADT-placebos	602	488	367	289	214	168	127	81	41	17	7

- **Patients in the ADT-abiraterone-prednisone group had a 53% reduction in the risk of radiographic progression or death compared with patients receiving ADT plus placebos**

Inclusion criteria- STAMPEDE

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

Primary outcome measure

Overall survival

Secondary outcome measures

Failure-free survival (FFS)

Toxicity

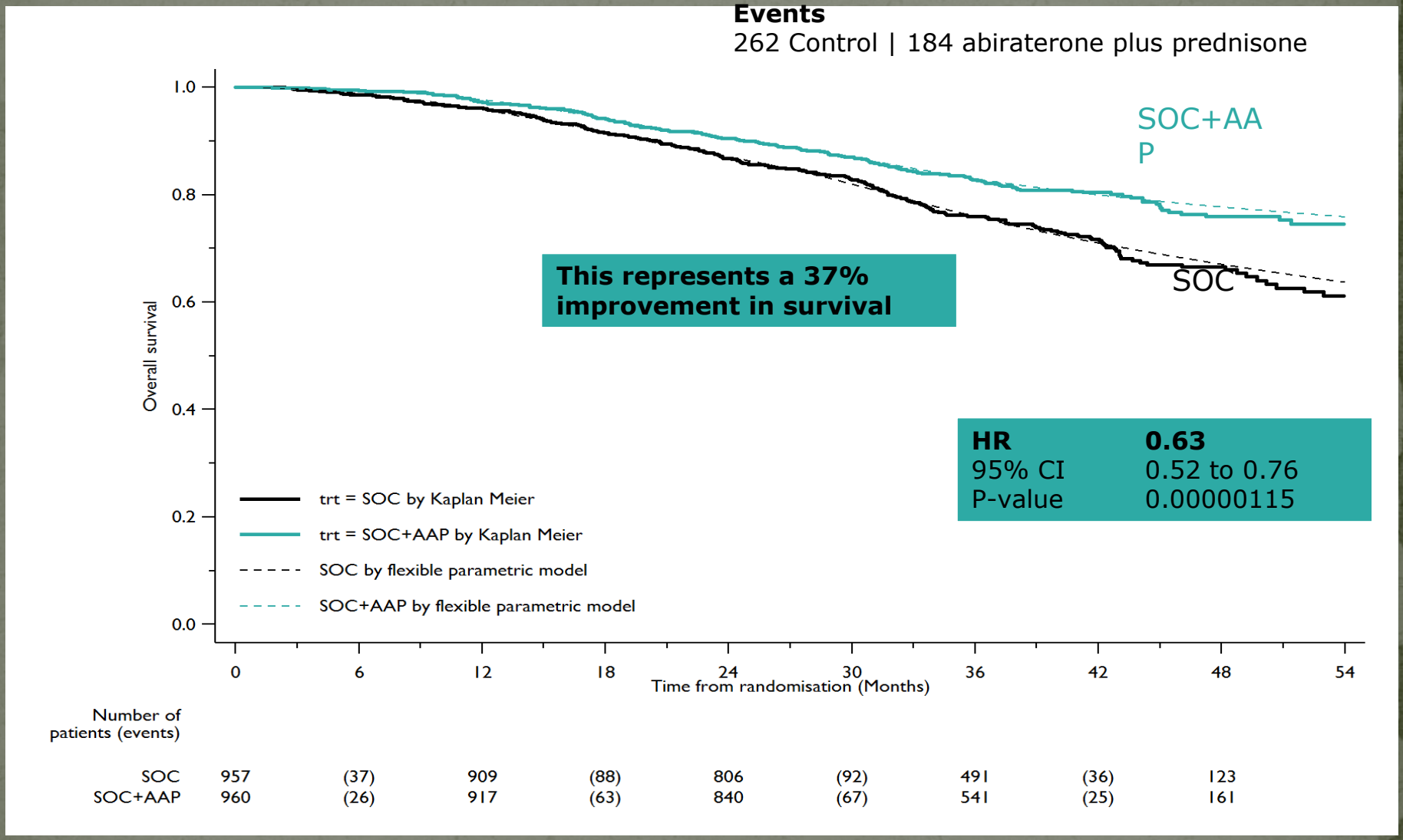
Quality of life

Skeletal-related events

Cost effectiveness

James N, et al. ASCO 2017. LBA5003 and Oral Abstract Session

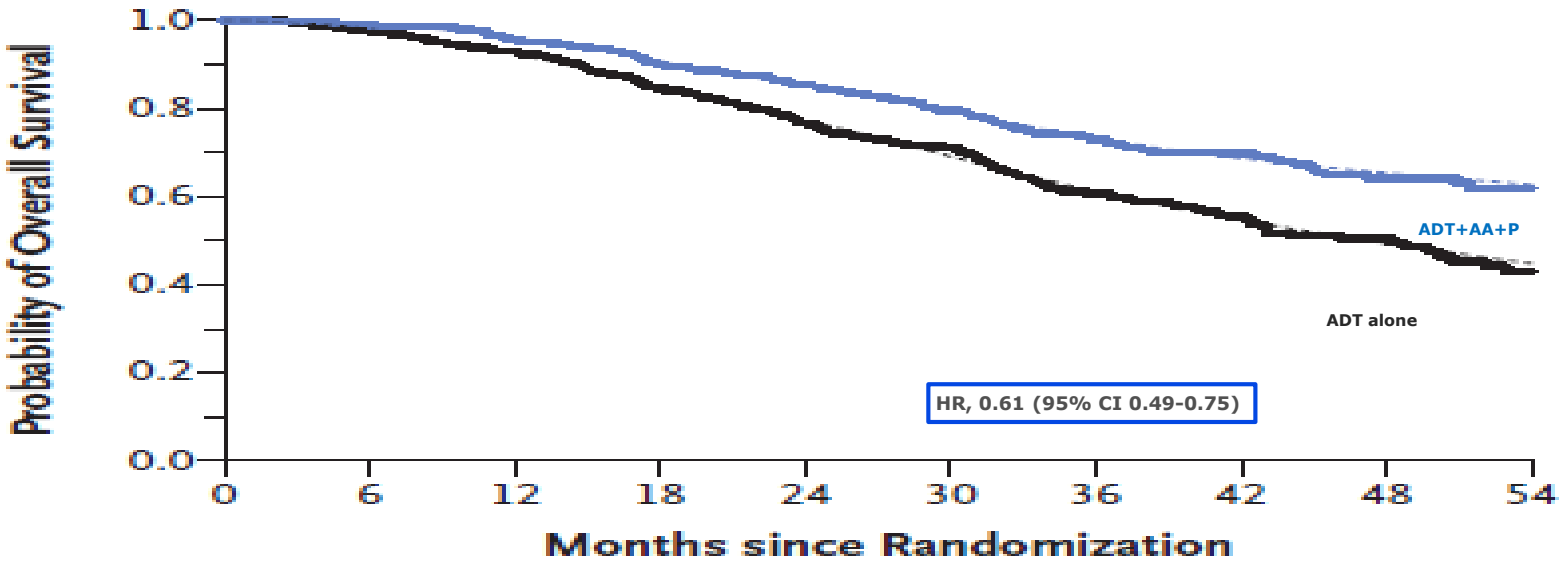
OS – STAMPEDE "abiraterone plus prednisone comparison" 83% 3-year OS vs 76%



James N, et al. ASCO 2017. LBA5003 and Oral Abstract Session

STAMPEDE : addition of AA+P to ADT significantly improved OS

STAMPEDE - M1 Disease[2,3]



No. of Patients (no. of deaths)									
Combination therapy	500	(22)	469	(50)	41[illegible]				
ADT alone	502	(35)	460	(80)	371	(73)	215	(23)	60

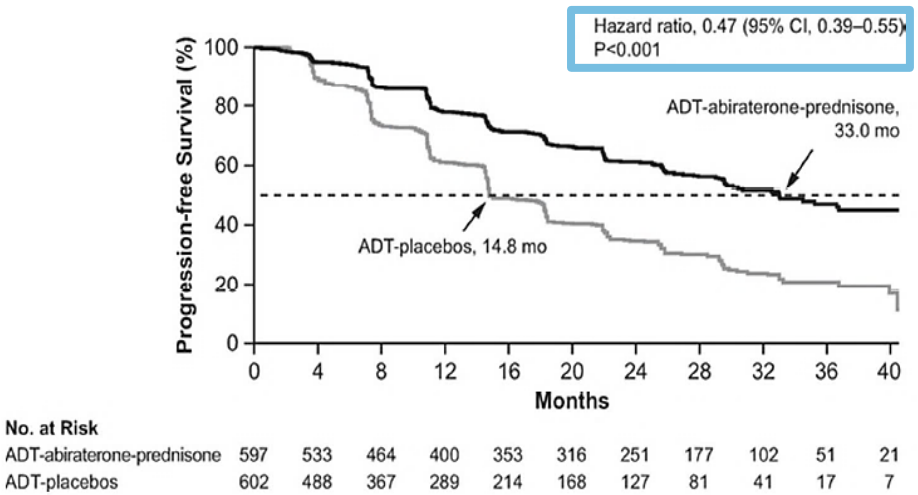
Combination therapy by Kaplan–Meier estimates
ADT alone by Kaplan–Meier estimates
Combination therapy by flexible parametric model
ADT alone by flexible parametric model

- STAMPEDE: **39% reduction in the risk of death** in patients with mHSPC

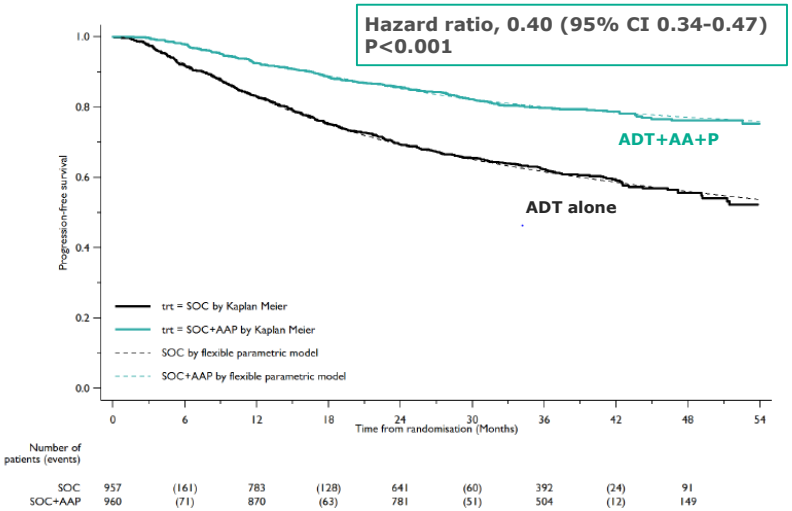
2. James N, et al. ASCO 2017. LBA5003 and Oral Abstract Session; 3. James N, et al. N Engl J Med. 2017 Jul 27;377(4):338-351

In LATITUDE and STAMPEDE addition of AA+P to ADT significantly delayed progression

LATITUDE - rPFS[1]



STAMPEDE – PFS
Overall population (M0+M1 HSPC)[2,3]



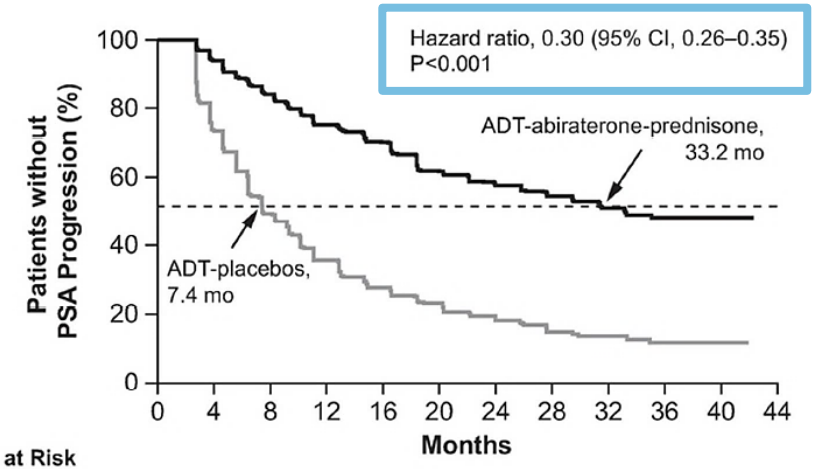
- LATITUDE: **53% reduction in the risk** of radiographic progression or death in patients with NDx HR mHSPC

- STAMPEDE: **60% reduction in the risk** of clinical or radiological progression or death in patients with HSPC

1. Fizazi K, et al. N Engl J Med. 2017 Jul 27;377(4):352-360; 2. James N, et al. ASCO 2017. LBA5003 and Oral Abstract Session; 3. James N, et al. N Engl J Med. 2017 Jul 27;377(4):338-351

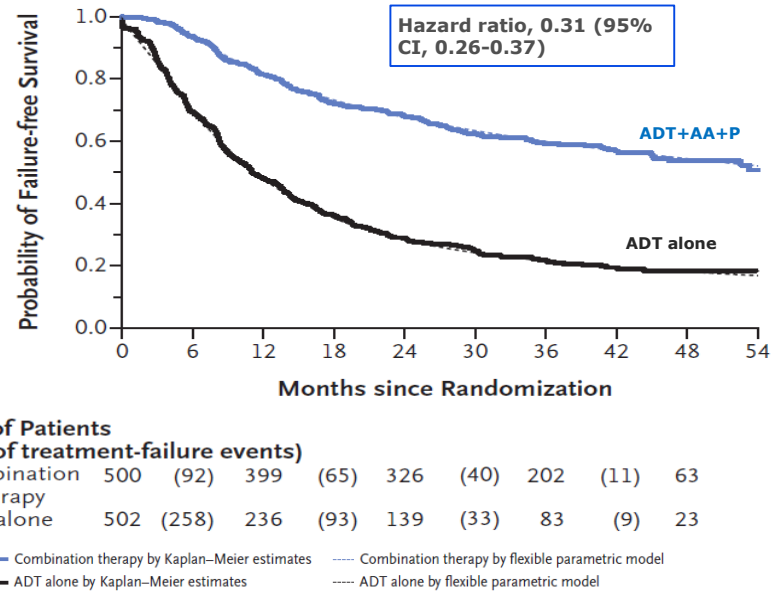
In LATITUDE and STAMPEDE addition of AA+P to ADT significantly delayed time to PSA progression

LATITUDE – time to PSA progression[1]



No. at Risk												
ADT-abiraterone-prednisone	597	520	447	379	340	285	227	162	95	48	18	0
ADT-placebos	602	393	250	172	129	102	65	33	19	8	5	0

STAMPEDE – FFS* – M1 disease[2,3]



No. of Patients (no. of treatment-failure events)									
Combination therapy	500	(92)	399	(65)	326	(40)	202	(11)	63
ADT alone	502	(258)	236	(93)	139	(33)	83	(9)	23

Combination therapy by Kaplan–Meier estimates
ADT alone by Kaplan–Meier estimates
Combination therapy by flexible parametric model
ADT alone by flexible parametric model

- LATITUDE: **70% reduction in the risk** of time to PSA progression in patients with NDx HR mHSPC

- STAMPEDE: **69% reduction in the risk** of FFS in patients with mHSPC

*FFS is driven by PSA failure[4]

1. Fizazi K, et al. N Engl J Med. 2017 Jul 27;377(4):352-360; 2. James N, et al. ASCO 2017. LBA5003 and Oral Abstract Session; 3. James N, et al. N Engl J Med. 2017 Jul 27;377(4):338-351; 4. Sydes M, et al. Abstract LBA31 presented at ESMO 2017

Σύγκριση ADT+AA+P και ADT+DOC σε m HSPC

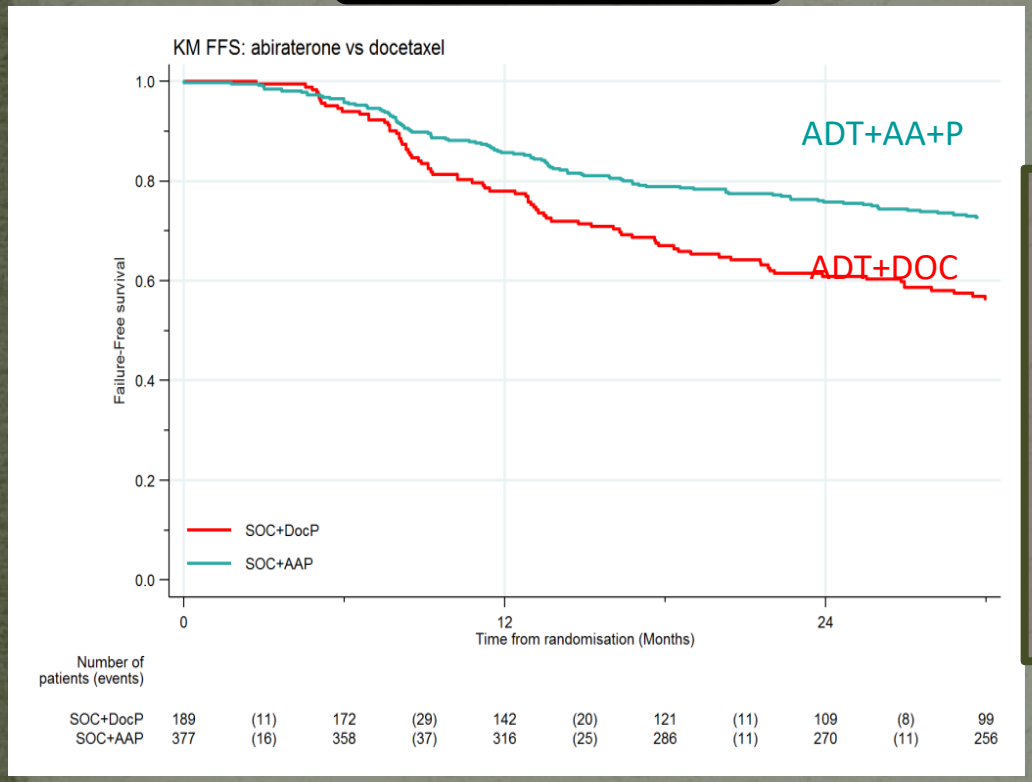
Direct randomised comparison from STAMPEDE (Sydes et al.)

Sydes M, et al. Abstract LBA31 presented at ESMO 2017; Feyerabend S, et al. Poster presented at ESMO 2017. Abstract 803P; Vale C, et al. Poster presented at ESMO 2017. Abstract LBA33

STAMPEDE

Failure-free survival [driven by PSA failure]

FFS: M0 and M1 combined



	HR (95%CI)	P-val	*Interact^n test*
All	**0.51** (0.39 to 0.67)	<0.001	
M0	**0.34** (0.16 to 0.69)	0.003	*0.17*
M1	**0.56** (0.42 to 0.75)	<0.001	

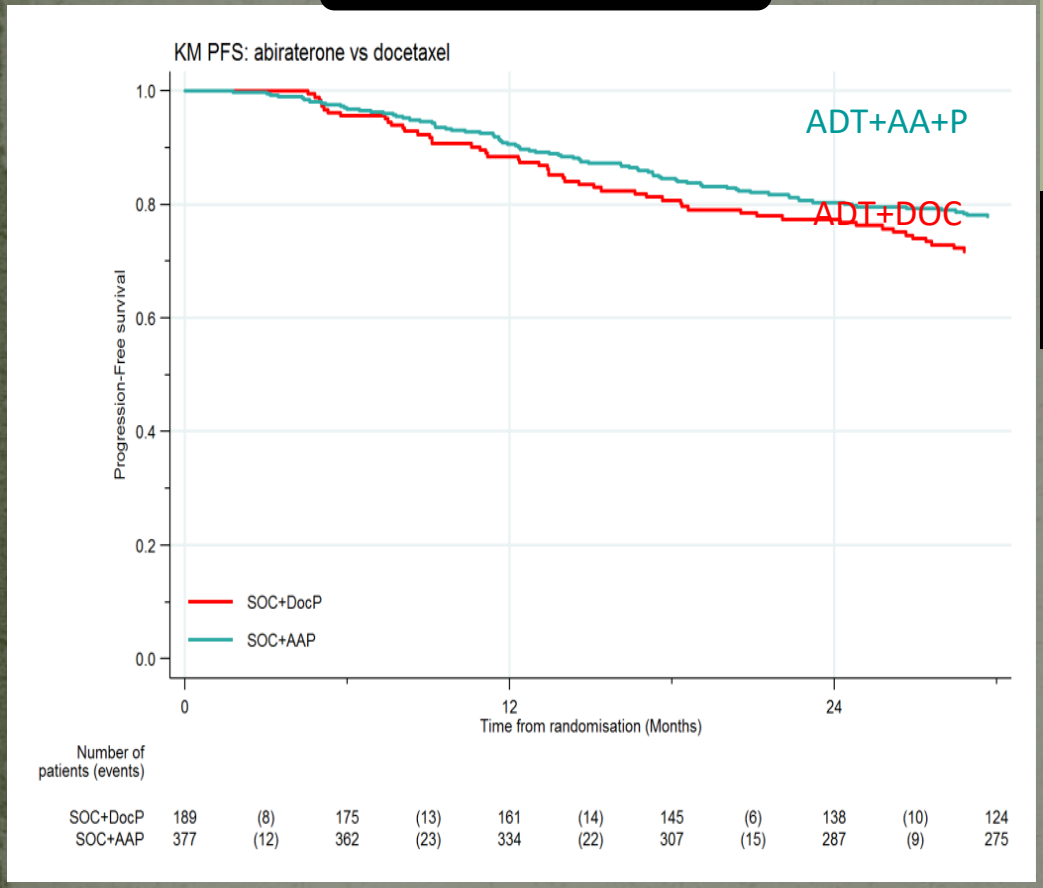
Key:
HR<1 favours ADT+AA+P
HR>1 favours ADT+DOC

Adapted from: Sydes M, et al. Abstract LBA31 presented at ESMO 2017

Progression-free survival

PFS = FFS ignoring PSA failure

FFS: M0 and M1 combined



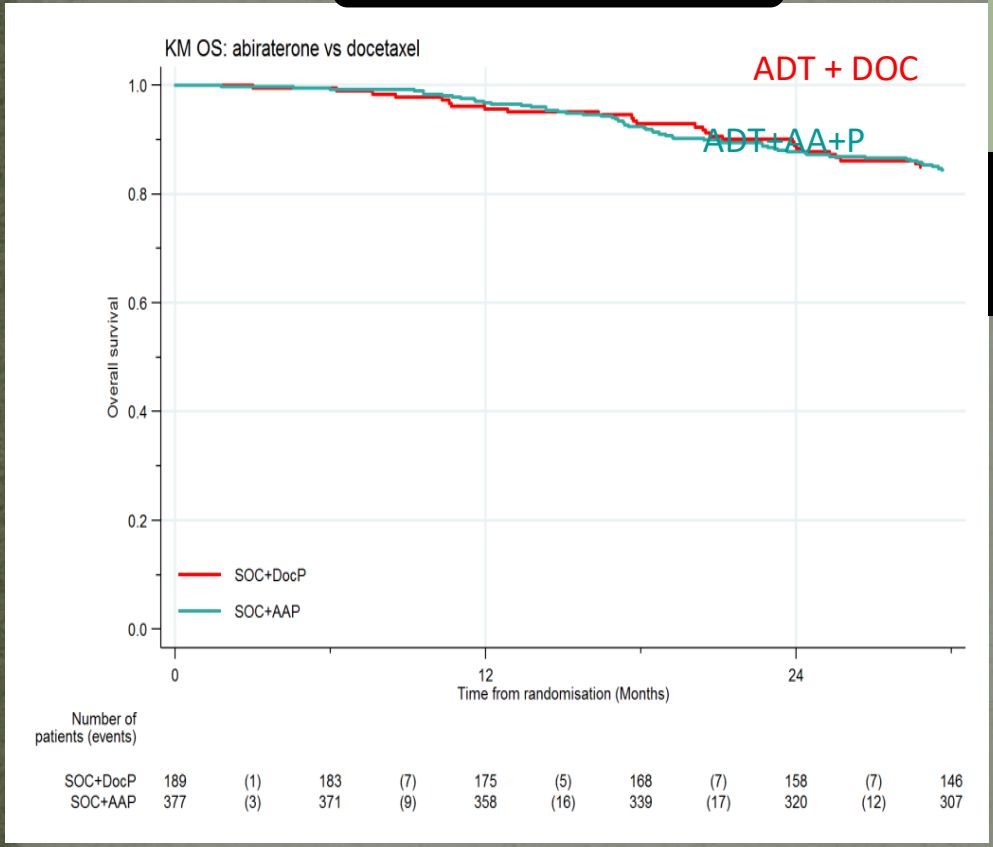
	HR (95%CI)	P-val	*Interact^n test*
All	**0.65** (0.48 to 0.88)	0.005	
M0	**0.42** (0.17 to 1.05)	0.06	0.32
M1	**0.69** (0.50 to 0.95)	0.02	

Key:
HR<1 favours ADT+AA+P
HR>1 favours ADT+DOC

Adapted from: Sydes M, et al. Abstract LBA31 presented at ESMO 2017

Overall survival [primary outcome measure]

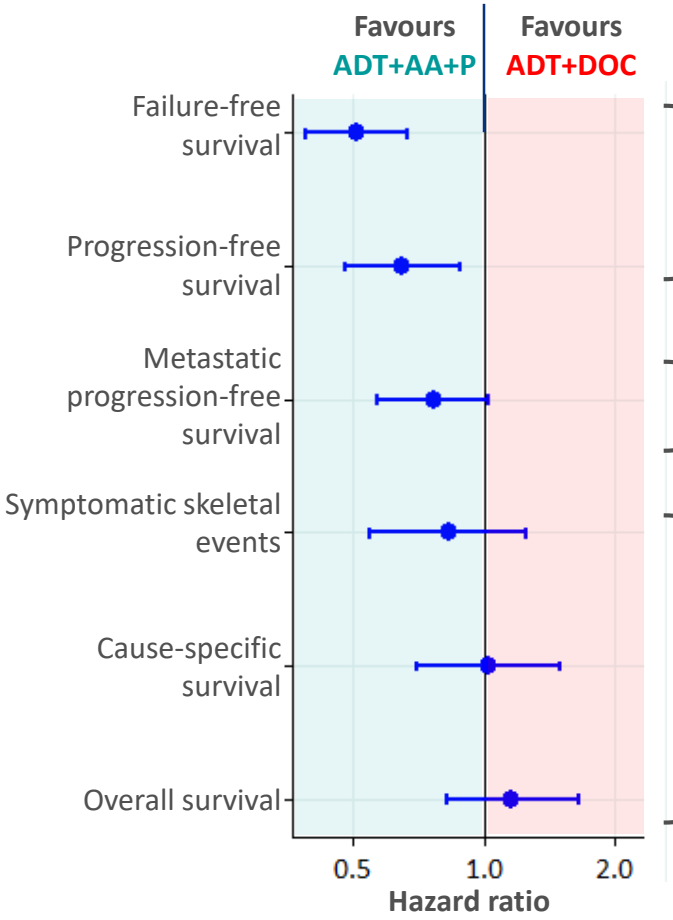
OS: M0 and M1 combined



	HR (95%CI)	P-val	*Interact^n test*
All	**1.16** (0.82 to 1.65)	0.40	
M0	**1.51** (0.58 to 3.93)	0.40	
			0.69
M1	**1.13** (0.77 to 1.66)	0.53	

Key:
HR<1 favours ADT+AA+P
HR>1 favours ADT+DOC

Adapted from: Sydes M, et al. Abstract LBA31 presented at ESMO 2017



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

Strong evidence favouring AA+P

Weak evidence favouring AA+P

No good evidence of a difference

→ Proportionately different time spent in each disease state

Toxicity profiles quite different and well known

AA+P = abiraterone acetate plus prednisone/prednisolone; ADT = androgen-deprivation therapy; DOC = docetaxel

Other studies comparing AA+P+ADT with Doce+ADT in mHSPC - OS

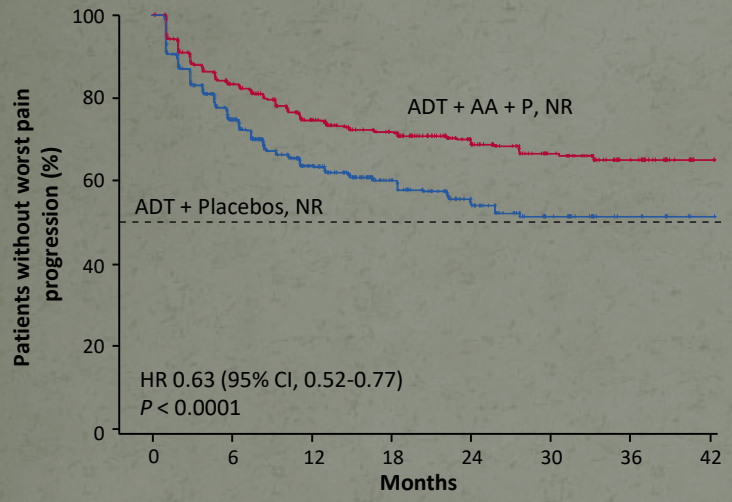
Study	Methodology	Endpoints	Results	Conclusion
Wallis, et al.[1]	Systematic Review and NMA Bayesian approach and SUCRA calculated to rank preference of each treatment option.	OS (ITC)	HR: 0.84, 95% CI: 0.67–1.06	No **statistically significant difference in OS** between these approaches but SUCRA analysis showed that AAP-ADT had **89% probability of being preferred strategy**
		OS (Bayesian)	HR: 0.83, 95% CI: 0.63–1.16	
		OS (SUCRA)	AAP+ADT – 89% probability of being preferred	
Aoun, et al.[2]	NMA using the frequentist approach and generalized pairwise modeling was computed (HR<1 favours AAP+ADT)	OS	HR: 0.79; 95% CI: 0.64–0.99	AAP+ADT resulted in a **survival benefit** compared with docetaxel based regimens
Riaz, et al.[4]	Systematic Review and NMA Bayesian NMA to perform indirect comparison of treatments	OS	HR: 0.81, 95% CI: 0.65-1.01	There is **no difference in OS** using AAP for longer periods in HSPC than a regimen of a limited number of cycles of Doc
Firwana, et al.[1]	**Systematic Review and Meta-Analysis Test for interaction used to determine effect differences in subgroups**	**OS and FFS test for interaction**	**p value for interaction of Doc and AAP subgroups is <0.05 for both OS and FFS, with better outcome leaning towards AAP**	**Test for interaction suggests better outcomes of AAP in comparison to Doc.**
Kassem, et al.[2]	NMA on safety and efficacy. Generalized pair wise modeling for NMA. HR>1 favours	OS	HR= 1.195; 95%CI: 0.98-1.46	There is **no statistically significant OS difference**
Tan, et al.[3]	NMA to generate probabilistic inferences and provide efficacy rankings in terms of posterior hazard ratios with 95% CrI, SUCRA, probability better than competing treatments, and probability best	OS	AAP + ADT suggests improved survival with 97% certainty for a 19% reduction in risk of death compared to docetaxel + ADT (HR: 0.81; 95% CrI: 0.66–1.00).	Addition of **AAP to standard ADT may possibly outperform the addition of docetaxel** in terms of OS

1. Wallis CJD, et al. Eur Urol. 2018 Jun;73(6):834-844; 2. Aoun F, et al. Future Oncol. 2017 Dec;13(30):2785-2790; 3. Sun G, et al. Poster presented at ASCO-GU 2018; abstract 360; 4. Riaz IB, et al. Poster presented at ASCO-GU 2018; abstract 243.

ΜΕ ΟΡΟΥΣ ΠΟΙΟΤΗΤΑΣ ΖΩΗΣ

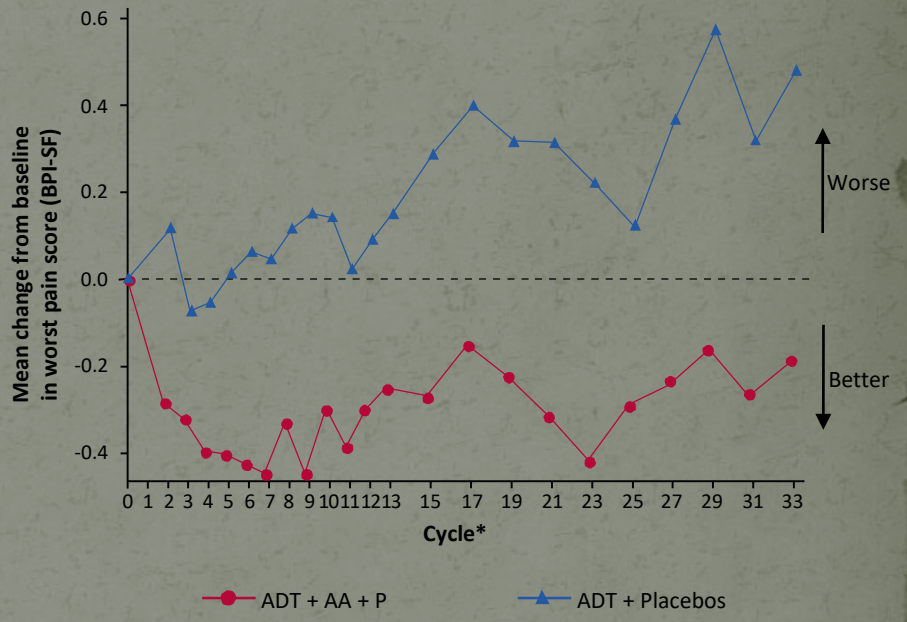
ADT + AA + P Significantly Improved Pain

37% Risk Reduction for Worst Pain Progression



Patients at risk								
ADT + AA + P	597	456	356	299	218	115	47	2
ADT + Placebos	602	387	246	162	99	44	10	1

Mean Change From Baseline Differed From Cycle 2 Onward

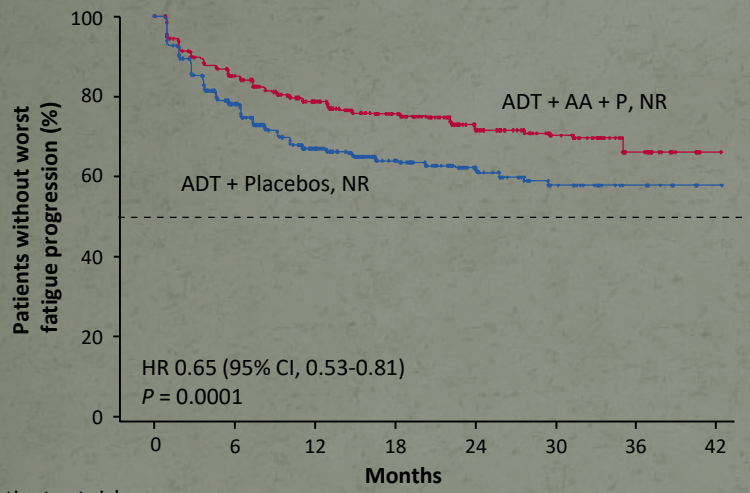


*1 cycle = 28 days.

Chi K, et al. Abstract 783O presented at ESMO 2017

ADT + AA + P Significantly Improved Fatigue

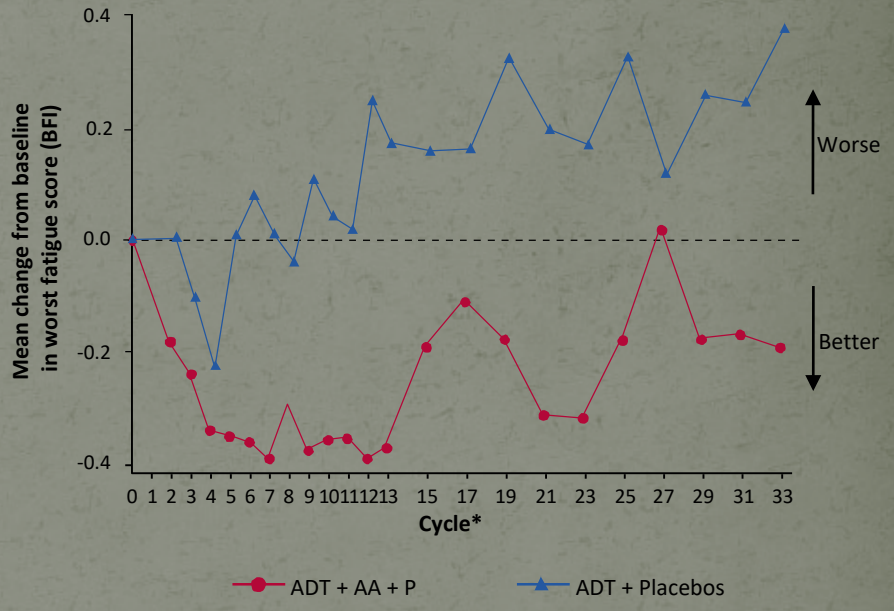
35% Risk Reduction for Worst Fatigue Progression



Patients at risk

ADT + AA + P	597	465	372	305	216	118	44	2
ADT + Placebos	602	407	259	171	106	46	14	1

Mean Change From Baseline Differed from Cycle 5 Onward

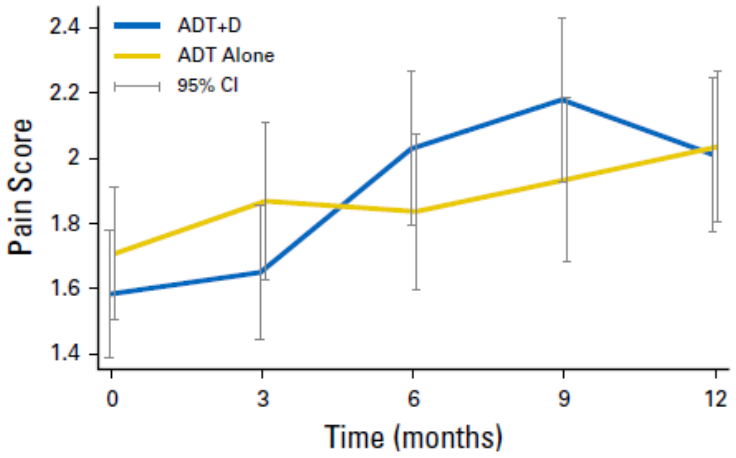


*1 cycle = 28 days.

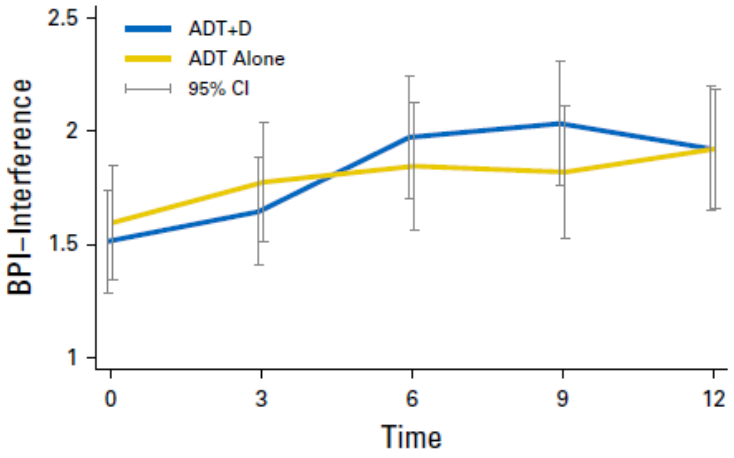
Chi K, et al. Abstract 783O presented at ESMO 2017

In CHAARTED there were no differences in pain comparing ADT+Doce vs ADT

Pain Score



BPI-interference



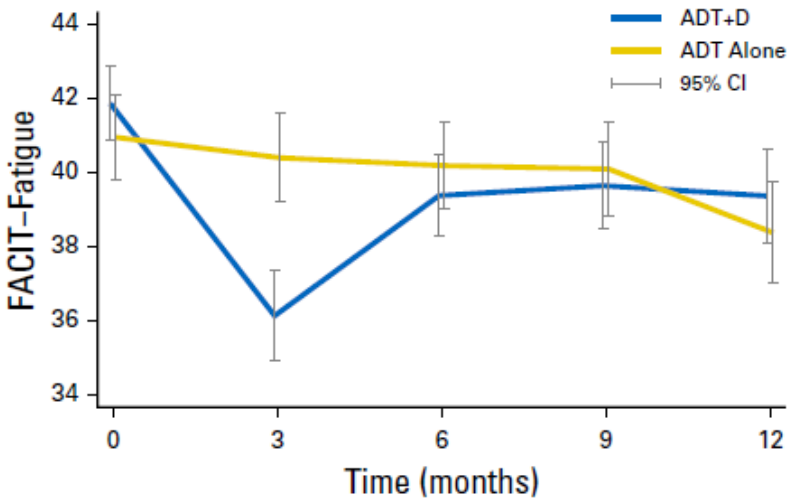
- **No significant difference between arms** in BPI pain intensity or interference scores at any time point.
- Slight pain increase but did not meet the minimal clinically important difference at any time point.

QoL was assessed at 3, 6, 9, and 12 months

Morgans AK, et al. J Clin Oncol. 2018 Apr 10;36(11):1088-1095.

In CHAARTED fatigue was worse at 3 months and similar at baseline and other time points, comparing ADT+Doce with ADT

FACIT-fatigue



- Mean scores for **FACIT-Fatigue were similar between arms** at baseline and at all subsequent time points (**exception of 3 months**)

QoL was assessed at 3, 6, 9, and 12 months

Morgans AK, et al. J Clin Oncol. 2018 Apr 10;36(11):1088-1095.

Results

Primary Endpoint: Overall QOL

Mixed effects model[1] for FACT-P total score difference between Arm A: ADT + Docetaxel and Arm B: ADT

Difference between Arm A and Arm B[2]	Estimate	SE	p-value
Baseline	-1.00	1.28	0.43
3 months	-3.09	1.32	0.02
6 months	0.90	1.34	0.50
9 months	0.29	1.37	0.84
12 months	2.85	1.39	0.04

QOL with early docetaxel compared to ADT:

- Poorer at 3 months (90% RR)
- Not different at 6 months
- Superior at 12 months (69% RR)

1. Adjusted for age (≤ 59 vs. 60-69 v. ≥ 70, disease extent (high v. low), local therapy (Y/N), ECOG PS (0 v. ½), baseline physical well-being (≤ 20 v. 20 < PWB ≤ 25 v. > 25) and baseline pain score (0/1 v. 2/3 vs. ≥ 4)
2. Arm A score - Arm B score

Presented by: Linda Patrick-Miller, Ph.D.

ΜΕ ΟΡΟΥΣ ΑΣΦΑΛΕΙΑΣ - ΤΟΞΙΚΟΤΗΤΑΣ

Adverse Events – Worst Toxicity Ever
Direct Comparison

	SOC+ DOC	SOC+ AAP
Study population	189	377
No. included in analysis	172	373
Patients with an adverse event		
Grade 1-5	172 (100%)	370 (99%)
Grade 3-5	86 (50%)	180 (48%)

Sydes MR et al. Annals of Oncology. 2018, Feb 266[Epub ahead of print]

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%)

ADT, androgen deprivation therapy; ABI, abiraterone; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DOC, docetaxel; MI, myocardial infarction; P, prednisone

Sydes MR, et al. ESMO 2017 (podium presentation); Sydes MR, et al. Ann Oncol. 2018;doi:10.1093/annonc/mdy072.

ΜΕ ΟΡΟΥΣ ΟΙΚΟΝΟΜΙΑΣ - ΚΟΣΤΟΥΣ

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

But is it really that simple and obvious???

G-CSF, granulocyte colony-stimulating factor; TT, total therapy

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

ENZALUTAMIDE IN M1 HSPC

ARCHES: Enzalutamide + ADT vs. Placebo + ADT in mHSPC

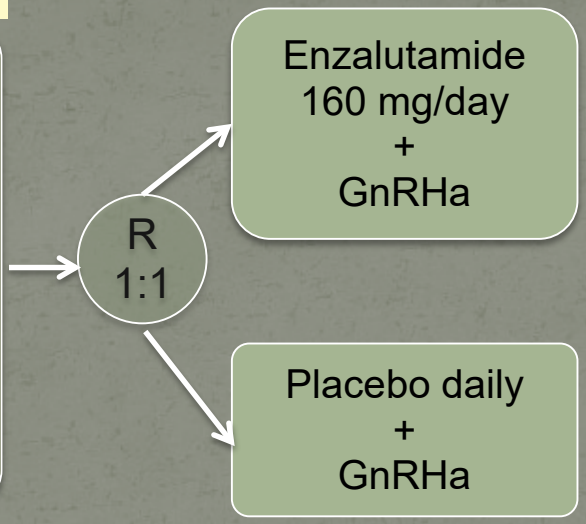
COMPLETED

N = 1100

Patients with mHSPC

ECOG PS 0-1

Prior docetaxel allowed if completed within 2 months prior to Study Day 1 and given ≤ 6 cycles without disease progression during or after therapy



Stratification:

- Volume of disease (low or high*)
- Prior docetaxel (no or 1-5 cycles or 6 cycles)

- Phase 3, multinational, randomized, double-blind, placebo-controlled study

Primary Endpoint

- rPFS

Secondary Endpoints

- Overall survival
- Time to first symptomatic skeletal event
- Time to castration resistance
- Time to initiation of new antineoplastic therapy
- Time to PSA progression
- Rate of undetectable PSA
- Objective response rate
- Quality of life by QLQ-PR25, FACT-P, EQ-5D-5L
- Pain by BPI-SF
- Safety

*High-volume disease = metastases involving viscera or ≥4 bone lesions with at least 1 of which in a bony structure beyond the vertebral column & pelvic bone

ADT = androgen deprivation therapy; BPI-SF = Brief Pain Inventory-Short Form; ECOG PS = Eastern Cooperative Oncology Group performance status; EQ-5D-5L = European Quality of life-5 Dimensions-5 Levels; FACT-P = Functional Assessment of Cancer Therapy-Prostate; GnRHa = gonadotropin releasing hormone analogue (agonist or antagonist) or prior bilateral orchiectomy (medical or surgical castration)

mHSPC = metastatic hormone sensitive prostate cancer; PC = prostate cancer; PSA = prostate-specific antigen; QLQ-PR25 = Quality of Life Questionnaire-Prostate 25; R = randomization; rPFS = radiographic progression-free survival

GUIDELINES mHSPC

New treatment options for mHSPC – European Guidelines

Guideline	Recommendation
ESMO 1,2	• Continuous ADT is recommended as first-line treatment of metastatic, hormone-naïve disease [I, A]. • **ADT plus docetaxel is recommended as first-line treatment** of metastatic, hormone-naïve disease in men fit enough for chemotherapy [1, A]. • **ADT plus abiraterone/prednisone may be considered as first-line treatment** for metastatic, hormone-naïve disease [1, A]
eau 3#	• **Offer castration combined with chemotherapy (docetaxel)** to all patients whose first presentation is M1 disease and who are fit enough for docetaxel. [Strong] • **Offer castration combined with abiraterone acetate plus prednisone** to all patients whose first presentation is M1 disease and who are fit enough for the regimen. [Strong] • Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with docetaxel or abiraterone acetate plus prednisone. [Strong]

1. Parker C, et al. *Ann Oncol*. 2015;26(suppl):v69-v77; 2. http://www.esmo.org/Guidelines/Genitourinary-Cancers/Cancer-of-the-Prostate/eUpdate-Treatment-Recommendation Assessed April-2018; 3. Mottet N, et al. EAU - ESTRO - ESUR -SIOG Guidelines on Prostate Cancer 2018; Accessed April 2018

New treatment options for mHSPC - Guidelines

Guideline	Recommendation
NCCN [1]	Options for men with M1 castration-naïve disease include: 1) Orchiectomy 2) LHRH agonist with or without anti-androgen for at least 7 days to prevent testosterone flare 3) LHRH agonist + antiandrogen 4) LHRH antagonists **5) Continuous ADT and docetaxel* (75 mg/m^2) for 6 cycles (category 1)** **6) ADT and abiraterone with prednisone (category 1)**
ASCO® [2]	Key Recommendations for metastatic Non-Castrate Prostate Cancer: • **Docetaxel and abiraterone are two separate standards of care (SOCs)** for metastatic non-castrate prostate cancer. The use of both standards in combination or in series has not been assessed and therefore cannot be recommended (Type: evidence based, benefits/harms ratio unknown; Evidence quality: no evidence available; Strength of recommendation: strong).

***High-volume disease is differentiated from low volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column.**
Patients with low volume disease have less certain benefit from early treatment with docetaxel combined with ADT.

1. NCCN Guidelines Version 2.2018. Prostate Cancer. https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf**. Accessed 3-May-2018; 2. Morris MJ, et al. J Clin Oncol. 2018;36(15):1521-1539.**

ΑΚΤΙΝΟΘΕΡΑΠΕΙΑ ΣΕ ΜΕΤΑΣΤΑΤΙΚΟ PROSTATE CANCER

ΑΚΤΙΝΟΘΕΡΑΠΕΙΑ ΣΕ ΜΕΤΑΣΤΑΤΙΚΟ PROSTATE CANCER

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

In summary, radiotherapy to the prostate did not improve survival for unselected patients with newly diagnosed metastatic prostate cancer, but, in a prespecified subgroup analysis, *overall survival did improve in men with a low metastatic burden*. Therefore, prostate radiotherapy should be *a standard treatment option for men with a low metastatic burden.*

Lancet. 2018 Dec 1; 392(10162): 2353–2366. doi: 10.1016/S0140-6736(18)32486-3 PMCID: PMC6269599 PMID: 30355464

Ο ΡΟΛΟΣ ΤΗΣ R.P ΣΤΗ ΘΕΡΑΠΕΙΑ N+ PROSTATE CANCER

Ο ΡΟΛΟΣ ΤΗΣ R.P. ΣΤΗ ΘΕΡΑΠΕΙΑ N+ PROSTATE CANCER

cN+ ασθενείς έχουν χειρότερη πρόγνωση από τους pN+

Οι cN+ χρήζουν εξατομικευμένης προσέγγισης , λόγω περιορισμένου αριθμού μελετών που υποστηρίζουν όφελος με την R.P.

TABLE 1 *Studies assessing the effect of Radical Prostatectomy (RP) in high risk and locally advanced prostate cancer*

Study	*n*	Median FU (m)	E or L PLND	Median nodes removed	% of patients with pN+	Adjuvant therapy (% of patients)	CSS (%)	
							5-y	10-y
Cheng et al.	322	75	L	12	100	92	94	83
Tuijer et al.	1,471	69	E	-	100	72	-	-
Kulkarni et al.	208	60	-	-	-	56	79.7	65
Briganti et al.	703	112	E	13.9	100	100	90	82
Spahn et al.	712	77	-	-	-	-	89.8	84.5
Bader et al.	92	40	E	21	25	0	74	62
Zwergel et al.	147	41	L	–	100	92	87	74
Spiess et al.	100	62	L	11	100	30	94	75
Schumacher et al.	122	66	E	22	100	0	85	60

Ο ΡΟΛΟΣ ΤΗΣ R.P. ΣΤΗ ΘΕΡΑΠΕΙΑ N+ PROSTATE CANCER

- Frohmuller et al: βελτίωση της OS, CSS, progression FS σε ριζική προστατεκτομή με εκτεταμένη λεμφαδενεκτομή σε σχέση με την ADT.

Frohmuller HG et al Eur Urol 1995

- Mayo Clinic: R.P.+ ADT OS 60% (vs 30% ADT).

Ghavamian R. et al J Urol 1999

RP *vs.* Conservative Management/RP alone						
Engel et al.	Retrospective, Munich Cancer Registry	5.6	938	(5-year) ADT: 60% RP + ADT: 84% (*p* value unknown)	(5-year relative survival) ADT: 70% RP + ADT: 95% (*p* value unknown)	NA
Frohmuller et al.	Retrospective, single institution	ADT: 4.7 ADT + RP: 4.3	139	(10-year) ADT: 30% RP + ADT: 51% ($p = 0.067$)	(10-year) ADT: 32% RP + ADT: 71% ($p = 0.002$)	(10-year) ADT: 15% RP + ADT: 36% ($p = 0.002$)
Steuber et al.	Retrospective, single institution	8.2	158	NA	(10-year) ADT: 46% RP + ADT: 76% ($p = 0.001$)	(10-year) ADT: 31% RP + ADT: 61% ($p = 0.005$)
ECOG 388610	Randomized	11.9	51	5 years: 75% 10 years: 55%	5 years: 75% 10 years: 55%	NA

Ο ΡΟΛΟΣ ΤΗΣ R.P. ΣΤΗ ΘΕΡΑΠΕΙΑ N+ PROSTATE CANCER

Επιπλοκές RP σε N+ ασθενείς:

- ✓ Ο χειρουργικός χρόνος, στυτική δυσλειτουργία, ακράτεια, λεμφοκήλη, αυξάνουν όσο μεγαλύτερο μέγεθος έχει το καρκινικό φορτίο.
- ✓ Τα λειτουργικά αποτελέσματα σε RP για προχωρημένη νόσο είναι ικανοποιητικά και συγκρίσιμα με αυτά της εντοπισμένης νόσου.

Gontero P. et al: Eur. Urol. 2007 922-929

- ✓ Τα ογκολογικά αποτελέσματα της RP παραμένουν αποδεκτά και σε ολιγομεταστατική νόσο.

Reeves F. et al: BJU Int 2014

Ο ΡΟΛΟΣ ΤΗΣ R.P. ΣΤΗ ΘΕΡΑΠΕΙΑ N+ PROSTATE CANCER

ΣΥΜΠΕΡΑΣΜΑ

- ✓ Η RP στις μελέτες με N+ αφορά σχεδόν αποκλειστικά pN + ασθενείς και για αυτό έχει συγκριτικά καλύτερα αποτελέσματα από την RT+ ADT

- ✓ Η RP ελαττώνει τοπικά συμπτώματα όπως αιματουρία – πόνος- απόφραξη *(Wiegand et al BJU Int 2011)*, παρατείνει την ολική επιβίωση *(Boorjan et al J Urol 2007)* και συνεισφέρει στο να είναι πιο αποτελεσματική η συστηματική θεραπεία

- ✓ 2017 EAU Guidelines: σε cN+ ασθενείς RT+/ADT

ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ