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Metastatic Hormone Sensitive Prostate Cancer

mHSPC

BSMO-Bordet 22.11.2019

Thierry Gil, MD
Head GU and Sarcoma Medical Oncology Clinic
Institut Jules Bordet
Université Libre de Bruxelles (U.L.B.)

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Disclosure

Consultancy fees and Travel Support

- Sanofi
- BMS
- Janssen
- Ipsen
- Pfizer
- MSD
- Pharmamar
- Bayer
- Amgen

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Summary

- The sooner the better; which one to choose among:
  - Docetaxel (Stampede, chaarted, GETUG)
  - Abiraterone (latitude)
  - Apalutamide (Titan)
  - Enzalutamide (Enzamet, Arches)
- Conclusion (if any)

Taxotère in mHSPC

	GETUG-AFU 15	CHAARTED	STAMPEDE**
Patients, N	385	790	2962
De novo M1	71%	75%	61%
Survival, all patients			
Median survival, months	62.1	57.6	60
Survival benefit	13.5 months (48.6 to 62.1)	13.6 months (44 to 57.6)	15 months*** (45 to 60)
Survival	HR=0.88 P=0.3	HR=0.61 P<0.001	HR 0.76 P=0.005
Survival high-volume metastases			
Survival benefit	4.7 months (35.1 to 39.8)	17 months (32.2 to 49.2)	NE
Survival	HR=0.78 P=0.14	HR=0.60 P<0.001	NE
Survival low-volume metastases			
Surival benefit	- (83,4 to NR)	- (NR / NR)	NE
Survival	HR=1,02 P=0,9 (NS)	HR=0,60 P=0,11 (NS)	NE

*Not head-to-head comparison studies **Includes patients with M0 disease ***M1 61% patients only, no further subgroups
NE, not evaluated

Sweeney et al. N Eng J Med 2015; 378(8): 737-746; Gravis G, et al. Eur Urol. 2016 Aug;70(2):256-62; James et al. Lancet 2016; 387(10024):1163-77

Addition of Docetaxel to AD in low and high burden mHSPC long term survival results from Stampede

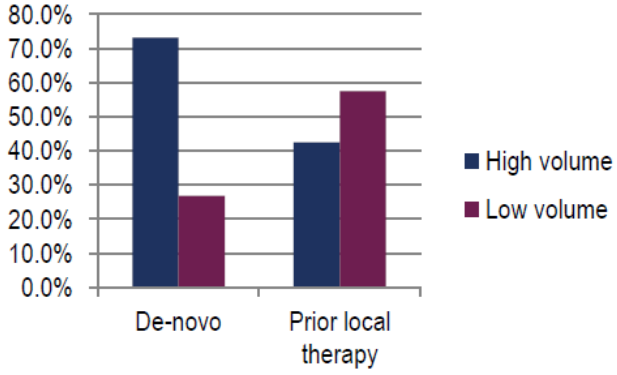
Background

- **Docetaxel improves survival in metastatic hormone naïve prostate cancer** and is an approved first line management option in conjunction with long-term androgen deprivation therapy
- **Controversy** exists over evidence for benefit **in "low metastatic burden"**
- Now report updated survival for the docetaxel arm of STAMPEDE with exploratory analysis by metastatic burden as per CHAARTED
- Impact of metastasis pattern and burden on M1 outcomes

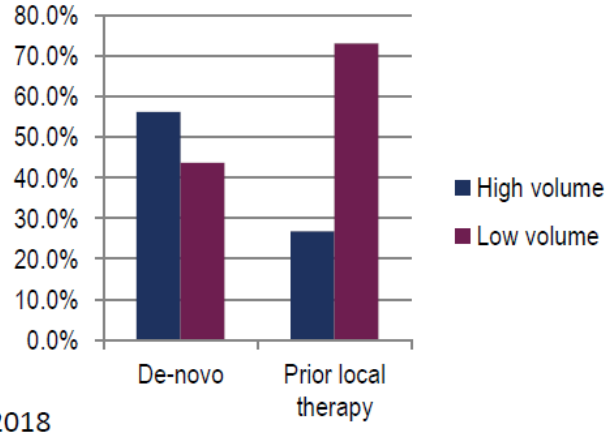
Is there a volume effect in Docetaxel responses ?

- STAMPEDE-docetaxel reported all M1 patients as single group mHSPC
  - Mostly de novo cases
- CHAARTED started as a high volume trial, later added low volume patients
  - Differing proportions of de novo and relapsed in high and low volume groups
  - GETUG-15 similar pattern seen

CHAARTED



GETUG15



Gravis et al Eur Urol 2018
https://doi.org/10.1016/j.eururo.2018.02.001

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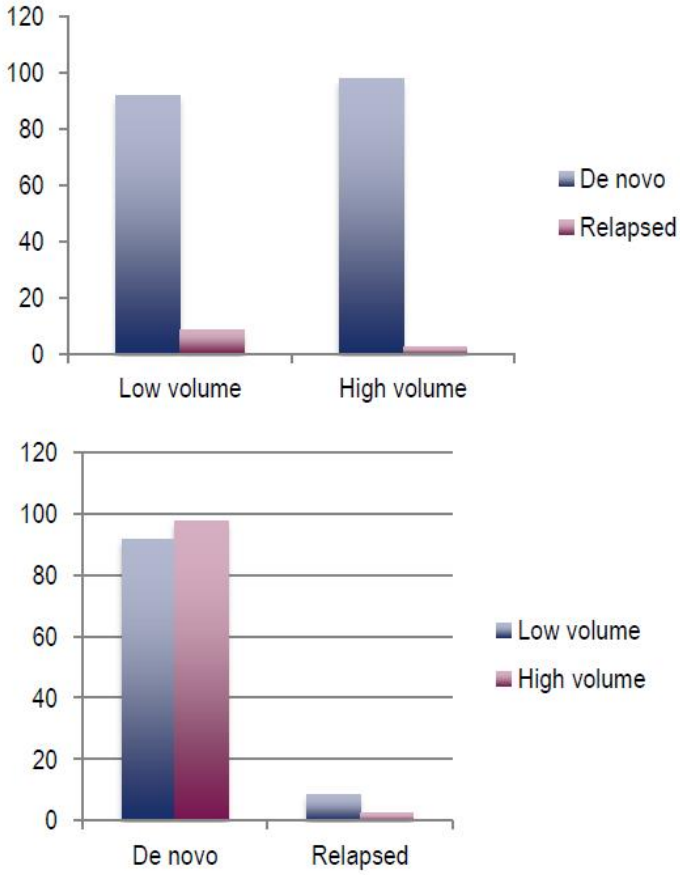
STAMPEDE



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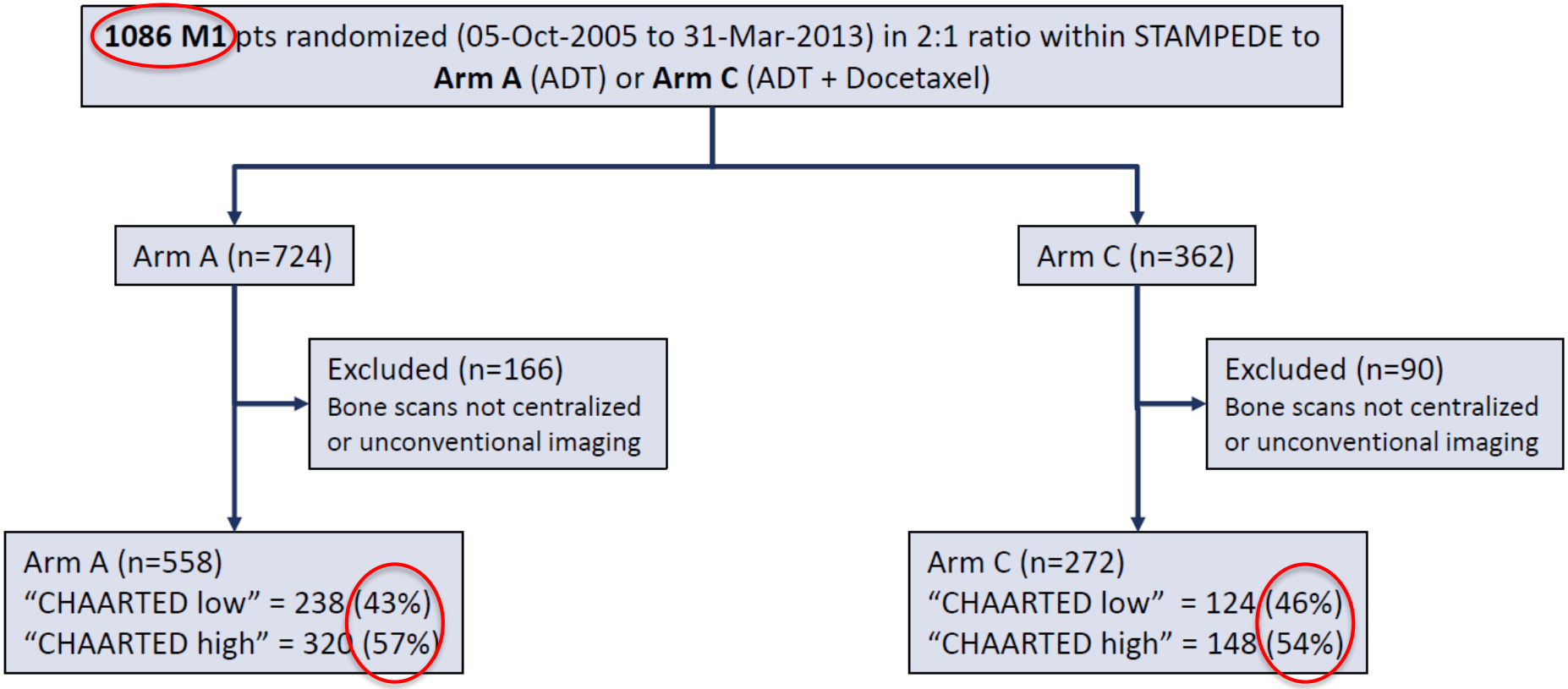
Study design



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Outcome measures

Primary outcome:

Overall Survival

(time from randomisation to death from any cause)

Secondary outcomes:

Failure-Free Survival

(first of biochemical progression, lymph node progression, distant metastases or PCa death)

Progression Free Survival

(first FFS event, excluding biochemical progression)

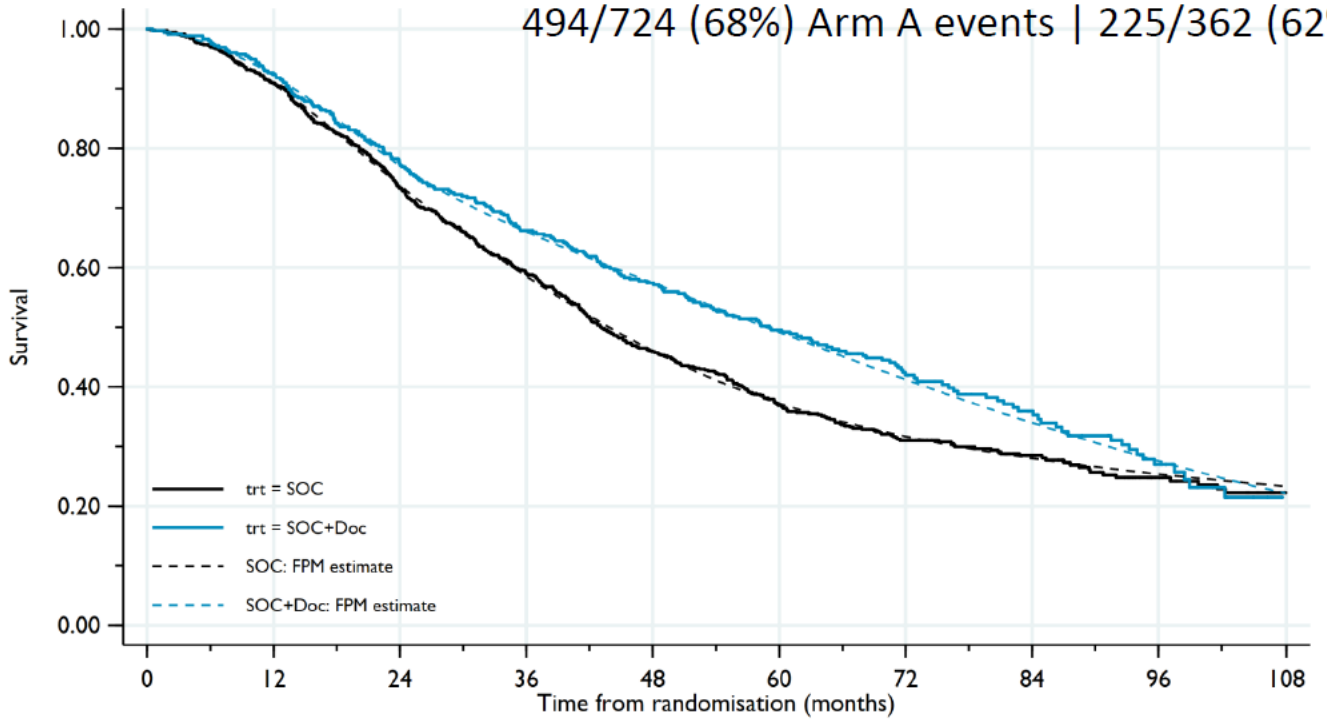
Metastatic Progression Free Survival

(first of new metastases/progression of existing metastases/PCa death)

Prostate Cancer Specific Survival

(death from PCa)

Overall Survival : All Patients



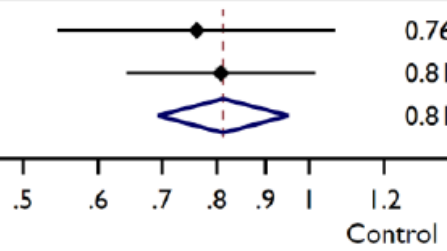
HR 0.81
95% CI 0.69 – 0.95
P = 0.009
Non-PH 0.016

5-yr survival:
A 37%
C 49%

RMST difference at 120 months:
6.0 months
95% CI (0.7-11.4)
P = 0.028

Overall Survival : Subgroup Analysis by Metastatic Burden

Metastatic burden	Control Deaths/N	Docetaxel Deaths/N	Interaction p-value	Haz. Ratio (95% CI)
Low burden	115/238	51/124	0.83	0.76 (0.54, 1.07)
High burden	254/320	106/148		0.81 (0.64, 1.02)
Overall	494/724	225/362		0.81 (0.69, 0.95)



No evidence that the beneficial effect varies by metastatic burden
interaction p-value = 0.827

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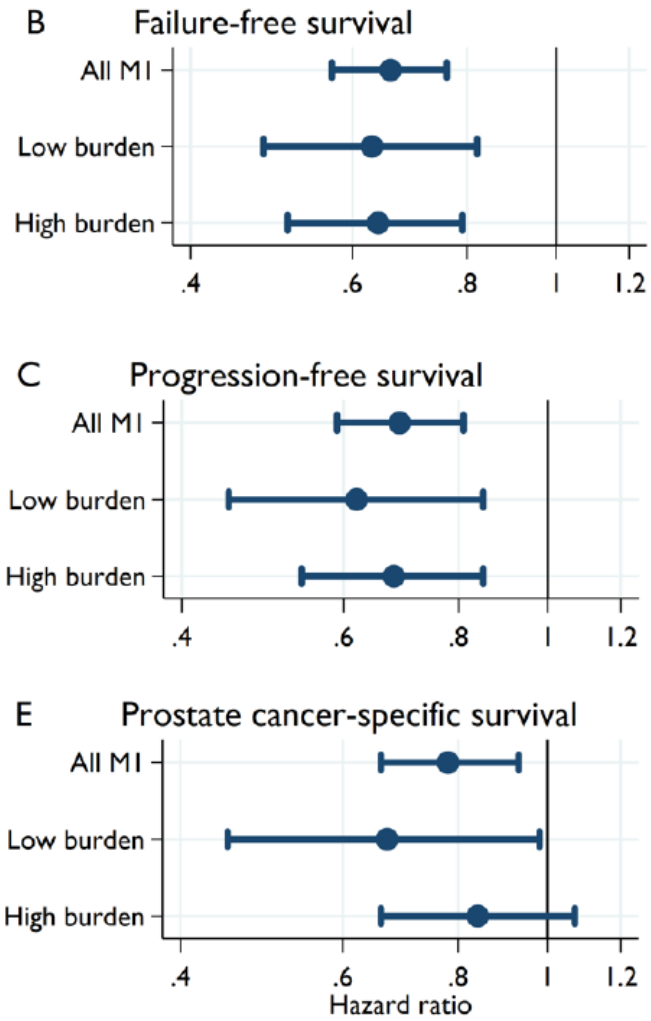
Other Outcomes: Subgroup Analysis by Metastatic Burden



Treatement * metastasis burden interaction:

P=0.792

P=0.855

P=0. 413

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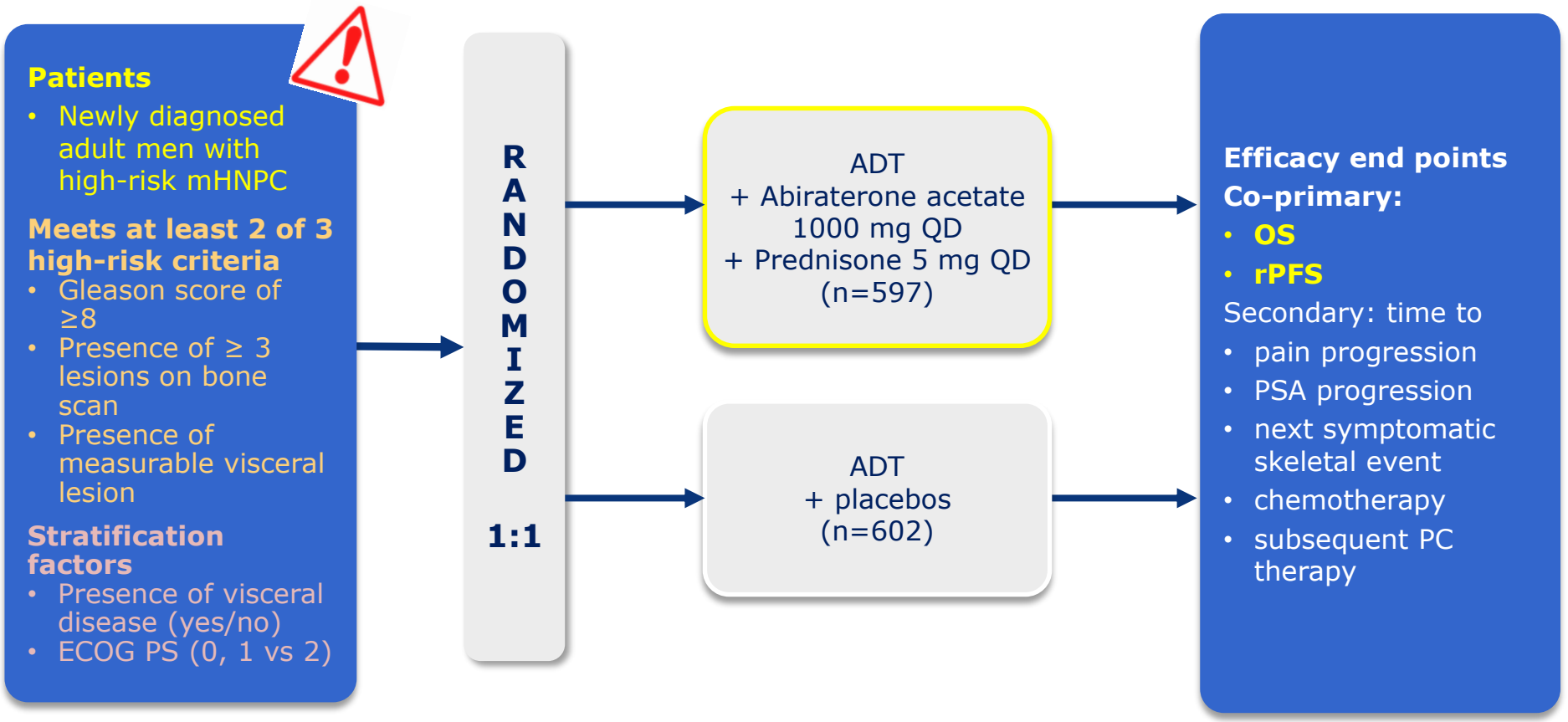
Discussion

- This analysis **does not support the presence of a volume effect on docetaxel effect** in men with newly-diagnosed metastatic prostate cancer
- Metastatic burden is however prognostic
- **STAMPEDE has almost exclusively newly diagnosed patients**
  - Better power to assess effects as homogenous group
  - Suggests differences with GETUG-15 + CHAARTED may relate to high proportions of relapsed patients in low metastatic burden groups in both trials
- **Absolute gains in 5 year survivals**:
  - 57 → 72% for low metastatic burden
  - 24 → 34% for high metastatic burden respectively

Latitude

Abiraterone prednisone + ADT versus ADT + placebo



- Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada
- Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results

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Fizazi K, et al. N Engl J Med. 2017 June 4, DOI: 10.1056/NEJMoa1704174

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mHSPC; High Volume

Definitions

CHAARTED / GETUG-AFU-15 High Volume definition	LATITUDE High Risk definition
• Visceral metastases (extranodal) AND/OR • Bone metastases - At least 4 or more bone lesions - One of which must be outside of the vertebral column or pelvis	Having at least 2 of the following 3 risk factors - Gleason score ≥ 8 - Presence of 3 or more lesions on bone scan - Presence of visceral metastasis

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Sweeney et al. N Eng J Med 2015; 378(8): 737-746

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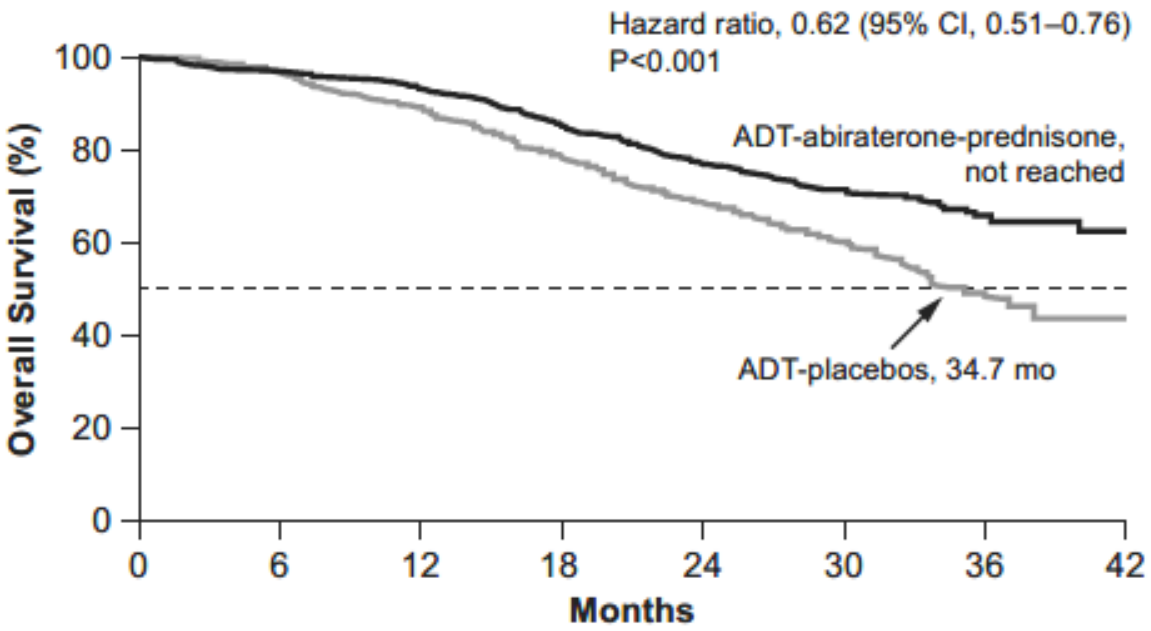
Overall Survival



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

Addition of AA+P to ADT significantly improved OS, with a 38% reduction in the risk of death

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Fizazi K, et al. N Engl J Med 2017; 377:352-360

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5023 – Fizazi K, et al. Longer term preplanned efficacy and safety analysis of AA + P in pts with newly diagnosed high-risk mCNPC from the phase 3 LATITUDE trial

Conclusions:

- This long-term analysis shows the OS benefit of adding AA + P to ADT, with a 36% reduction in the risk of death, although most pts remaining on PBO Tx had crossed over to AA + P
- The secondary endpoints
  - Time to initiation of chemotherapy
  - Time to subsequent therapy for prostate cancer
  - Time to pain progression
  - Time to SRE

continued to favour the AA + P Tx compared with PBO; and no new safety concerns were identified with AA + P Tx

Fizazi K, et al. Poster presented at ASCO 2018; abstract 5023.

TITAN Study Design

"All-comer" patient population

Key Eligibility Criteria
Castration sensitive
Distant metastatic disease by ≥ 1 lesion on bone scan
ECOG PS 0 or 1

On-Study Requirement
Continuous ADT

Permitted
Prior docetaxel
ADT ≤ 6 mo for mCSPC or ≤ 3 yr for local disease
Local treatment completed ≥ 1 yr prior

Stratifications
Gleason score at diagnosis (≤ 7 vs ≥ 8)
Region (NA and EU vs all other countries)
Prior docetaxel (yes vs no)

N = 1052

Dec 2015 – Jul 2017

1:1 RANDOMIZATION

- **Apalutamide 240 mg daily + ADT (n = 525)**
- **Placebo + ADT (n = 527)**

Dual primary end points
- **OS**
- **rPFS**

Secondary end points
- Time to cytotoxic chemotherapy
- Time to pain progression
- Time to chronic opioid use
- Time to skeletal-related event

Exploratory end points
- Time to PSA progression
- Second progression-free survival (PFS2)
- Time to symptomatic progression

ECOG PS, Eastern Cooperative Oncology Group performance status; NA, North America; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

TITAN Demographics and Baseline Characteristics

		Apalutamide + ADT (n = 525)	Placebo + ADT (n = 527)
Median age, yr (range)		69 (45-94)	68 (43-90)
ECOG PS score, n (%)	0 1	328 (63) 197 (38)	348 (66) 178 (34)
Gleason score at initial diagnosis, n (%)	≤ 7 ≥ 8	174 (33) 351 (67)	169 (32) 358 (68)
TNM stage at initial diagnosis, n (%)	M0 or MX M1	114 (22) 411 (78)	86 (16) 441 (84)
Disease volume, n (%)	Low High[a]	200 (38) 325 (62)	192 (36) 335 (64)
Prior docetaxel[b], n (%)		58 (11)	55 (10)
Prior therapy for localized prostate cancer[c], n (%)		94 (18)	79 (15)
Mean baseline BPI-SF pain score[d], n (%)	0 to 3 (none to mild) 4 to 10 (moderate to severe)	393 (75) 110 (21)	407 (77) 106 (20)
Median baseline PSA, µg/L (range)		5.97 (0-2682)	4.02 (0-2229)

BPI-SF, Brief Pain Inventory-Short Form; TNM, tumor, node, metastasis.
[a]High-volume disease included: 1) visceral metastases and ≥ 1 bone lesion, or 2) ≥ 4 bone lesions, with ≥ 1 outside the axial skeleton. [b]27 patients (46.6%) in the apalutamide group and 22 patients (40.0%) in the placebo group were N1 at diagnosis. [c]Prior therapies for localized prostate cancer included prostatectomy and radiotherapy. [d]Scores range from 0 to 10, with lower scores representing lower levels of pain intensity; a change of 2 was the minimally important difference.

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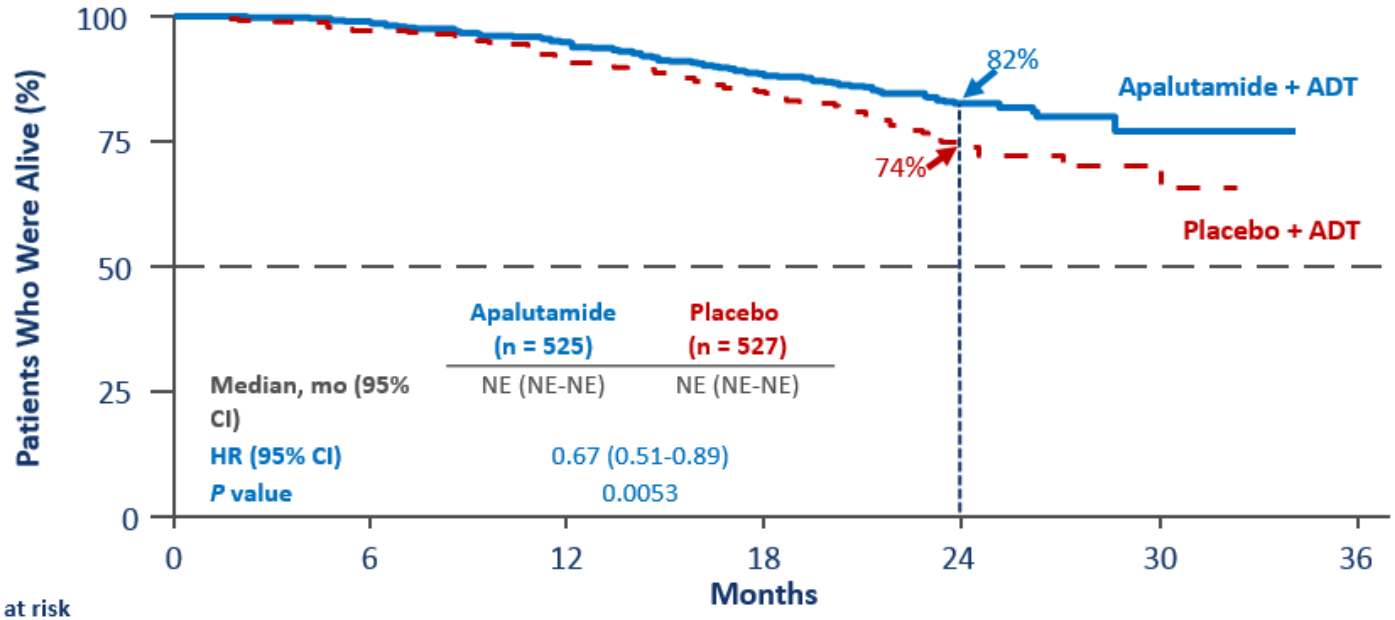
TITAN OS: Apalutamide Significantly Reduced the Risk of Death by 33%1



No. at risk							
Apalutamide	525	513	490	410	165	14	0
Placebo	527	509	473	387	142	16	0

CI, confidence interval; NE, not evaluable.

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TITAN OS Benefit Consistent Across Predefined Subgroups1

Variable		Hazard Ratio (95% CI)	Apalutamide + ADT Events (no./No.)	Placebo + ADT Events (no./No.)
All patients		0.68 (0.51-0.90)	83/525	117/527
Baseline ECOG PS	0	0.71 (0.47-1.05)	41/328	60/348
	1	0.59 (0.40-0.89)	42/197	57/178
Geographic region	EU/NA	0.71 (0.40-1.25)	21/173	29/173
	Other	0.66 (0.48-0.91)	62/352	88/354
Bone metastasis only at baseline	YES	0.47 (0.30-0.75)	28/289	53/269
	NO	0.88 (0.61-1.26)	55/236	64/258
Visceral disease and bone metastasis at baseline	YES	0.99 (0.55-1.77)	20/56	25/72
	NO	0.63 (0.46-0.87)	63/469	92/455
Prior docetaxel use	YES	1.27 (0.52-3.09)	11/58	9/55
	NO	0.63 (0.47-0.85)	72/467	108/472
Age, yr	< 65	0.56 (0.33-0.94)	21/149	43/182
	65-74	0.73 (0.48-1.10)	42/243	51/232
	≥ 75	0.74 (0.41-1.35)	20/133	23/113
Disease volume	High	0.68 (0.50-0.92)	69/325	97/335
	Low	0.67 (0.34-1.32)	14/200	20/192
Metastasis stage at initial diagnosis	M0	0.40 (0.15-1.03)	7/85	11/59
	M1	0.72 (0.53-0.98)	71/411	101/441

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TITAN– safety profile

STUDY	TITAN[1]			
POPULATION	mHSPC "all comers"			
	Apalutamide + ADT (n = 524)		Placebo + ADT (n = 527)	
Any AE	507 (96.8)		509 (96.6)	
Grade 3 or 4 AEs	221 (42.2)		215 (40.8)	
Any SAE	104 (19.8)		107 (20.3)	
Any AE leading to treatment discontinuation	42 (8.0)		28 (5.3)	
AE leading to death	10 (1.9)		16 (3.0)	
Adverse Event, n (%)	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Rash	142 (27.1)	33 (6.3)	45 (8.5)	3 (0.6)
Fatigue	103 (19.7)	8 (1.5)	88 (16.7)	6 (1.1)
Fall	39 (7.4)	4 (0.8)	37 (7.0)	4 (0.8)
Hypothyroidism	34 (6.5)	0	6 (1.1)	0
Fracture	33 (6.3)	7 (1.3)	24 (4.6)	4 (0.8)
Seizure	3 (0.6)	1 (0.2)	2 (0.4)	0

Not head-to-head trials

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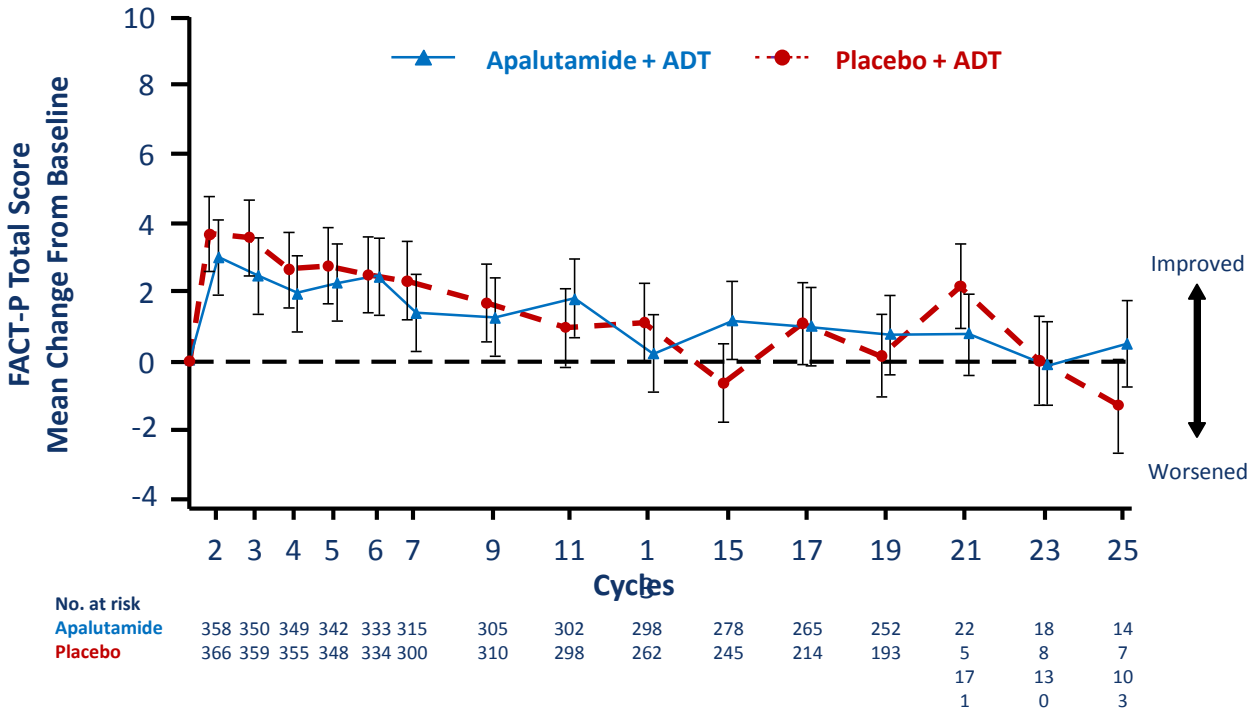
TITAN Health-Related Quality of Life Was Preserved With Apalutamide + ADT and Not Different From Placebo + ADT1



Error bars are standard errors of the mean. Raw FACT-P scores range from 0 to 156, with higher scores indicating more favorable health-related quality of life; a 6- to 10-point change in FACT-P total score would be the minimally important difference. However, this figure presents mean changes in total scores compared with baseline rather than raw total scores.
FACT-P, Functional Assessment of Cancer Therapy-Prostate.

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TITAN Conclusions1

- The TITAN study met its dual primary end points, demonstrating significant benefits with apalutamide + ADT in an all-comer mCSPC population
  - Significant improvement in OS, with a 33% reduction in the risk of death
  - Significant improvement in rPFS, with a 52% reduction in the risk of progression or death
- Secondary and exploratory end points also favored apalutamide
  - Prolonged time to cytotoxic chemotherapy (61% risk reduction), PSA progression (74% risk reduction), and second progression-free survival (PFS2; 34% risk reduction)
- Treatment was tolerable and the safety profile was consistent with the known side effects of apalutamide
- Health-related quality of life was maintained and not different from placebo

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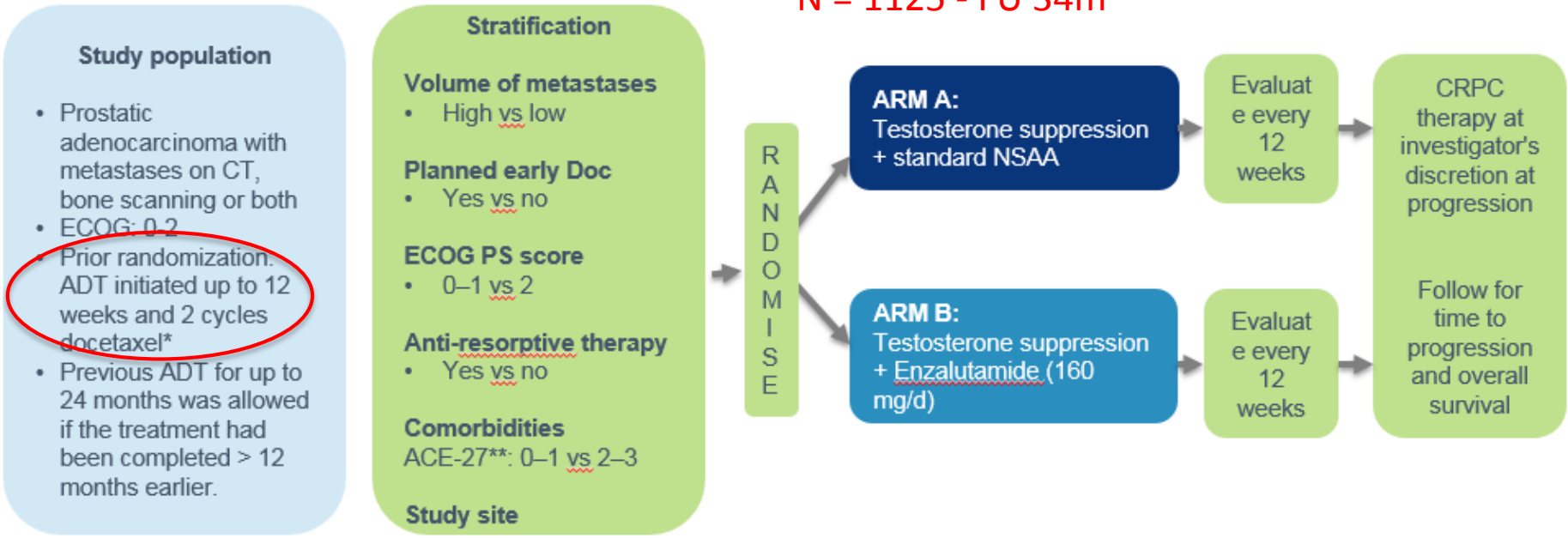
TITAN Conclusions1 (cont'd)

- These results support the addition of apalutamide to ADT for a broad range of patients with mCSPC
  - High or low disease volume
  - Prior docetaxel (?)
  - De novo metastatic disease or relapsed metastatic disease after initial diagnosis of localized disease
  - Prior treatment for localized disease

Enzamet: study design

N = 1125 - $\overline{FU}$ 34m



[a] High volume: Visceral metastases and/or ≥ 4 bone metastases (≥ 1 beyond pelvis and vertebral column).
***After the enrollment of 88 patients, the early administration of docetaxel with testosterone suppression was permitted** in protocol version 2 as a stratification factor before randomization, according to evidence showing improved survival with this approach. The decision to initiate early treatment with docetaxel was left up to the individual patients and their physicians. If docetaxel was administered, the regimen consisted of 75 mg/m^2, without prednisone or prednisolone, given every 3 weeks for a maximum of six cycles. Up to two cycles of docetaxel were permitted before randomization.

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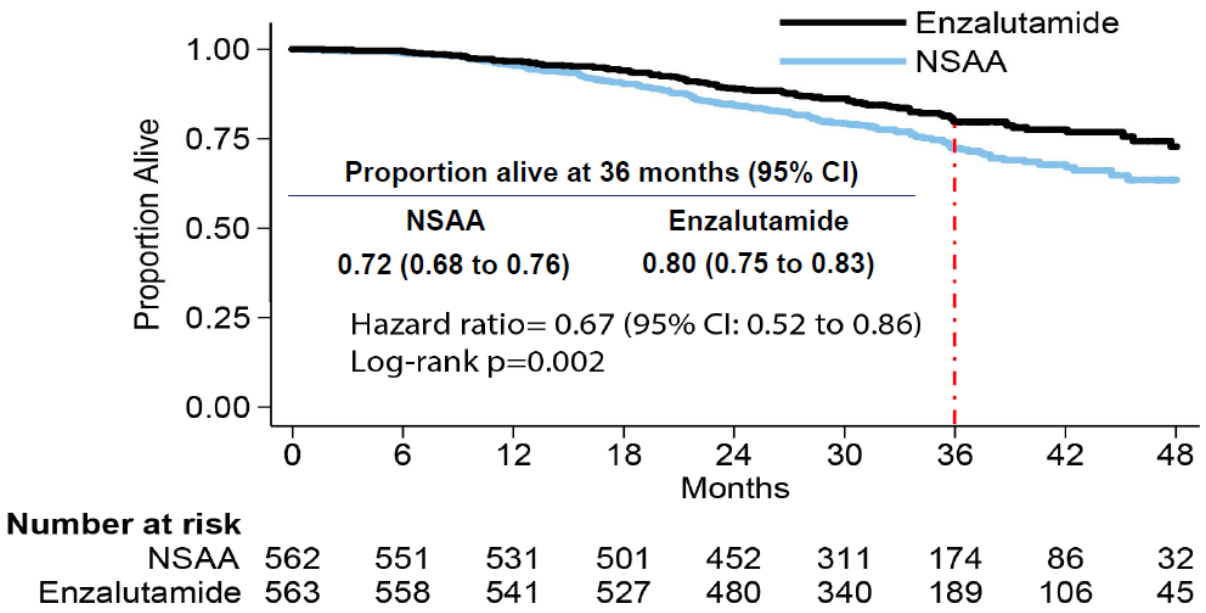
Overall survival: ENZA significantly reduced risk of death by 33%1



- The observed P value of 0.0016 met the rejection boundary of 0.0031 for the null hypothesis that was specified for this IA
- The results that are reported here include a total of 245, after a median follow-up of 34 months.

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Survival at 3 years in predefined subgroups

	TS + NSAA (n = 562)		TS + ENZA (n = 563)	
	3 year OS (%)	95% CI	3 year OS (%)	95% CI
Early docetaxel				
Yes	75	68–81	74	66–80
No	70	64–76	83	78–87
Volume of metastases				
*High	64	58–70	71	64–76
Low	82	75–87	90	84–93

*365 (61%) of 588 HV patients received early docetaxel – OS is better than TS alone in CHAARTED and LATITUDE:~50% 3 year OS

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Conclusions from ENZAMET

- In men with mHSPC receiving testosterone suppression, the addition of **enzalutamide resulted in longer OS, PSA PFS, and clinical PFS** within 3 years than the use of standard NSAA.

- Enzalutamide was associated with some additional toxic effects, including **fatigue** and a small **risk of seizures**.

- Among the patients who also **received early docetaxel** treatment, the addition of enzalutamide was associated with **additional toxic effects** and **longer PFS but not longer overall survival**.

Arches mHSPC

- N = 1150 PS 0-1, current ADT<3m or Prior Docetaxel ≤ 6m
- R : 1:1 Enzalutamide + ADT vs Placebo + ADT
- 1er E.P; rPFS (first objective evidence of radiographic Progression or Death

Results

~ 60% HV, Gleason ≥ 8

~ 90% prior ADT

~ 18% prior Docetaxel

Well balanced

Positive for r PFS p < 0,0001 HR 0,39 84% vs 64% at 12m
Not mature for OS (2nd E, P)

mHSPC
Conclusion 2019

According to toxicity profile patient selection and drug availability

- Castration + Docetaxel for all patients M1 at diagnosis
- Offer Castration
  - + Abiraterone for high risk M1
  - + Apalutamide « all » comers
  - + Enzalutamide (not after Docetaxel)
- Consider RTX on prostate for M1 patients, LV (chaarted criteria)

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