

# Which systemic therapy for which patient with newly diagnosed metastatic prostate cancer?

**Christopher Sweeney, MBBS**

**Medical Oncologist, Dana Farber Cancer Institute**

**Professor of Medicine, Harvard Medical School**

# Disclosures

	Consultant Compensation	Research Funding
Amgen	X	
Astellas	X	X
Bayer	X	X
Genentech/Roche	X	
Janssen	X	X
Pfizer	X	
Celgene	X	
Sanofi	X	X
Dendreon		X
Lilly	X	

# Which systemic therapy for which patient with newly diagnosed metastatic prostate cancer?

- Goals:
  - High level summary of the 8 recent SYSTEMIC mHSPC trials (docetaxel, new hormones)
  - Highlight the balancing act of choosing which treatment for which patient
    - Co-morbidities vs patient cancer related prognosis vs emerging data vs gaps
    - Focus on overall survival results and QOL and treatment burden
- Working premise in 2019: overall survival is still the most important mHSPC endpoint
  - Accounts for treatment burden (including treatment-related deaths) and treatment benefit (including the impact of salvage systemic CRPC therapy)

# The spectrum of patients starting testosterone suppression for “metastatic” disease

- Some present *de novo* vs some present after prior prostatectomy or radiation
- Some are fit and young, some are frail and elderly
  - and every iteration in between
- Some have minimal disease on conventional scans and some widespread disease
- Some prior adjuvant testosterone suppression with radiation, prostatectomy
  - (+/- abiraterone; +/- docetaxel)

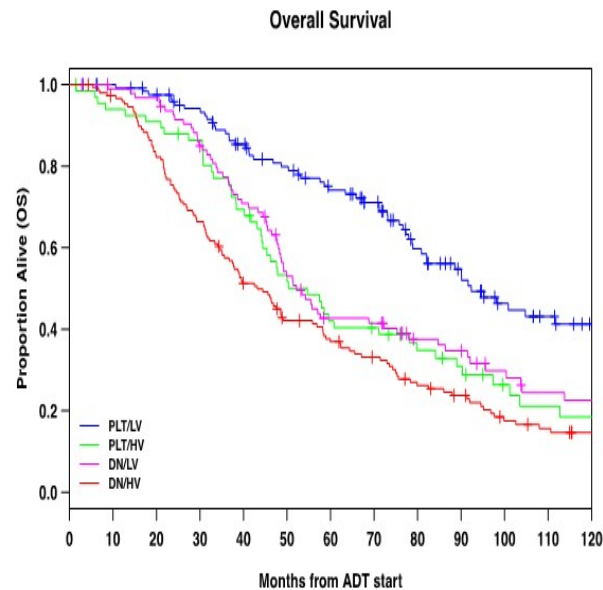
**55 yo with no co-morbidities and high volume *de novo* metastatic disease**

**versus**

**82 yo with CHF and CAD and 2 bone mets 10 year after prostatectomy**

# Patients with mHSPC have variable response to testosterone suppression

CHAARTED & GETUG15	Median OS (years)
Prior local therapy and low volume	~8
PLT and high volume	4.5
De Novo and LV	4.5
De Novo and HV	3



Groups	N (% events)	Median OS yrs (95%CI)
Prior Tx+LV	125 (50)	7.7 (6.7,10.6)
Prior Tx+HV	67 (75)	4.6 (3.7,6.7)
De-novo+LV	96 (70)	4.3 (4,6.5)
De-novo+HV	148 (84)	3.6 (3.1,4.7)

**High volume:** visceral mets and/or 4 or more bone mets  
With at least one beyond vertebra and pelvis)

Francini et al Prostate 2018; Gravis et al Eur Urol 2018

# Limitations of current clinical categorizations

## CHAARTED

- Lung only often indolent
- Large bulky LN may have poor outlook
  - LN only +/- < 4 bone mets
- Does not account for *de novo* vs prior local Rx
- Many pelvic bone and vert mets without spill over (rare)

## LATITUDE

- Lung only often indolent
- Only accounts for *de novo* presentation
- Uses Gleason
  - Some pts Rx on clinical grounds or metastatic biopsy

## SEER analysis by CHRISTIE Clinic Team<sup>1</sup>

- Bone plus non-regional LN using HR(OS): 1.2
- Median OS ~ 3 years c/w both groups being *de novo* metastatic

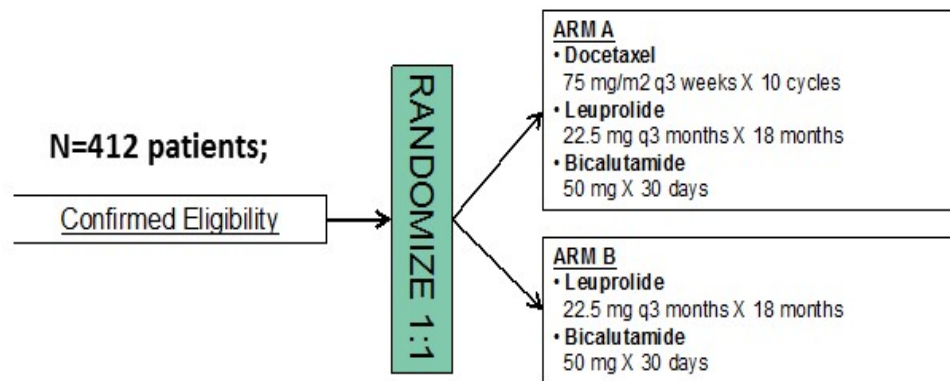
<sup>1</sup> Ali A et al, BJUInt

## **Current Scorecard for mHSPC OS with Docetaxel by Volume of Disease**

## Early Low Volume:

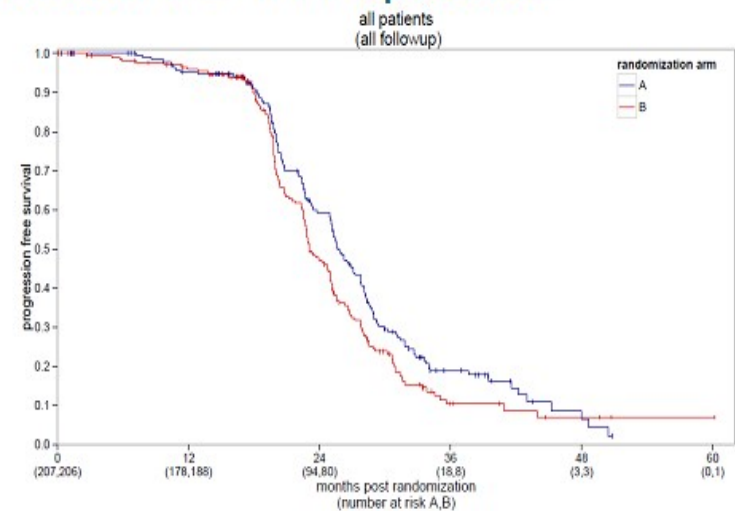
- Biochemical recurrence M0 after RP, XRT
- No disease on CT or Tc-Bone Scan (many PSMA PET positive)
- ADT 18 months +/- docetaxel for 6 cycles

### TAX3503 Study Design



- After 18 months of treatment, patients were followed for at least 18 months or until progression or death.

### Results: PFS- IIT Population

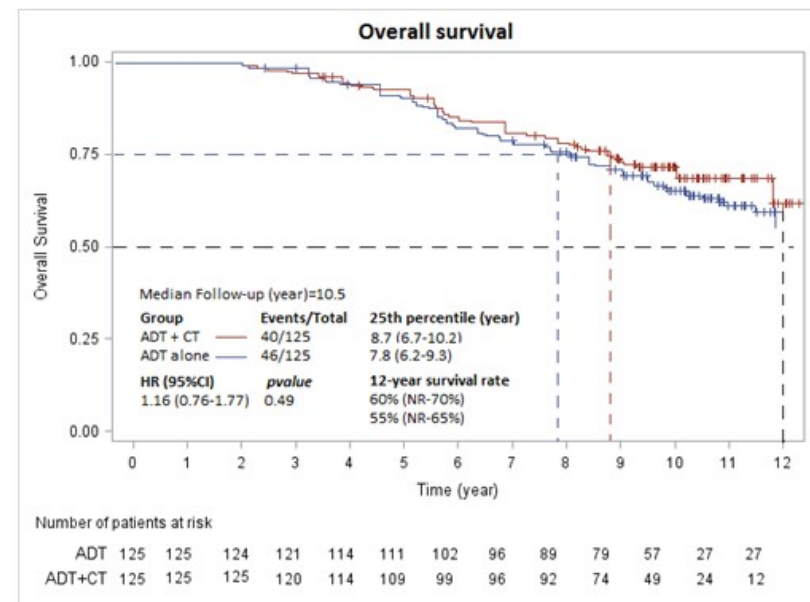
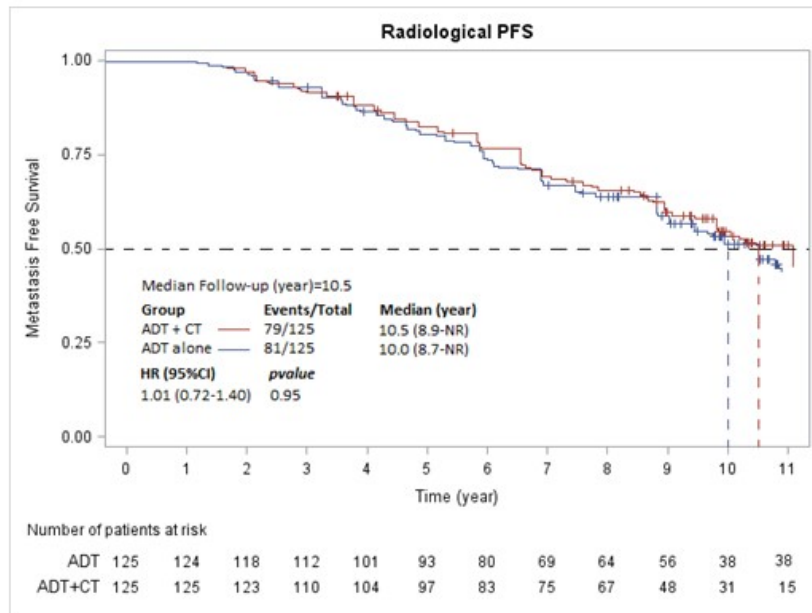


Morris et al ASCO, 2015



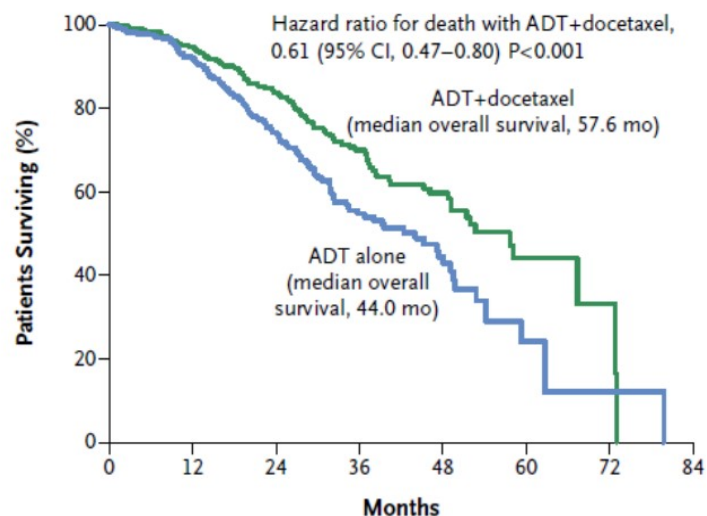
# Early Low Volume

## FrenchM0 HSPC ADT +/- docetaxel: N=250



# What are we learning from long term follow-up of CHAARTED: Overall Population

Median Follow-up  
28.9 months

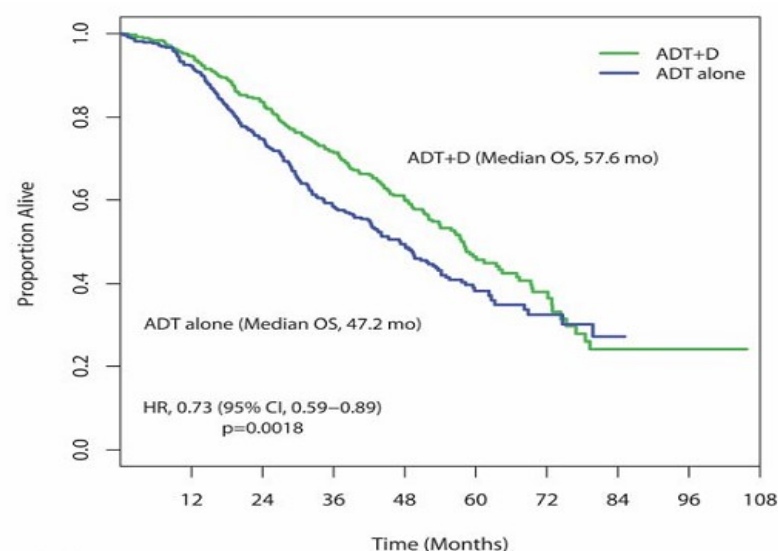


No. at Risk

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

13 months / HR 0.61

Median Follow-up:  
53.7 months



Number at Risk

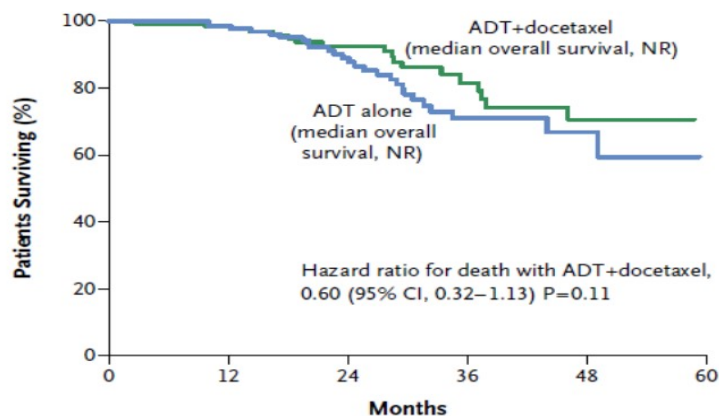
ADT+D	397	366	314	245	155	67	28	7	2	0
ADT alone	393	352	278	198	126	45	21	2	0	0

10 months / HR 0.73

Sweeney et al NEJM 2015, Kyriakopoulos et al JCO Jan 2018;

# What are we learning from long term follow-up of CHAARTED: **Low Volume**

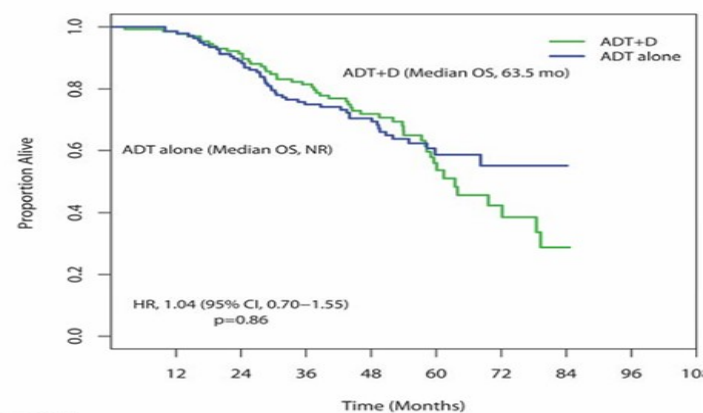
Median Follow-up  
28.9 months



No. at Risk							
		0	12	24	36	48	60
		ADT+docetaxel	134	120	66	33	15
	ADT alone	143	125	76	31	13	0

NR / HR 0.6

Median Follow-up:  
53.7 months



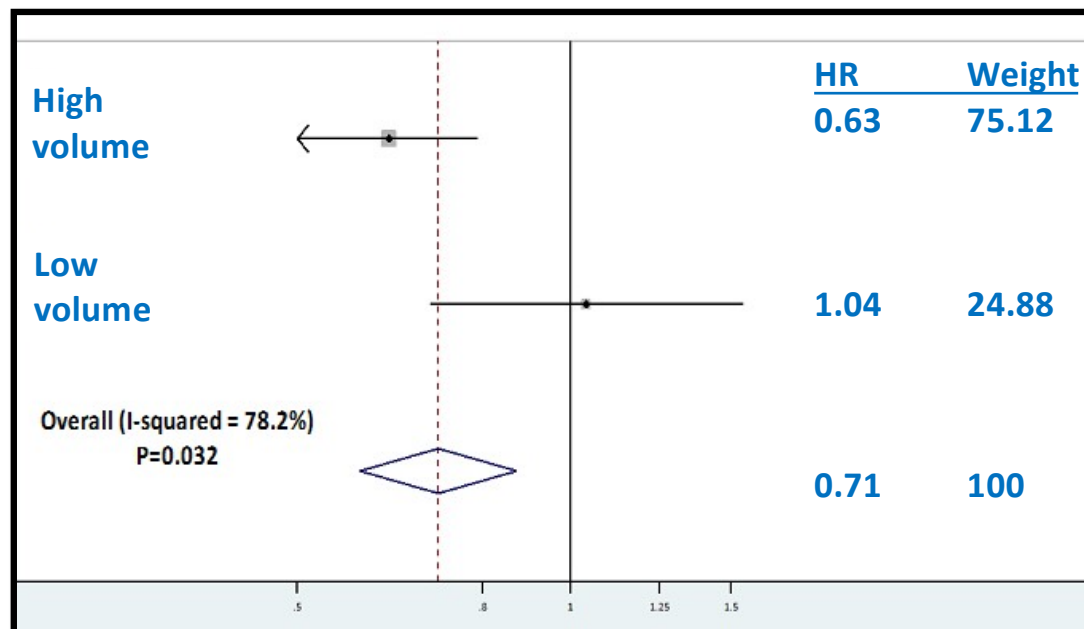
Number at Risk		Time (months)									
		0	12	24	36	48	60	72	84	96	108
ADT+D	134	127	112	94	64	26	12	2	0	0	
ADT alone	143	137	122	94	67	26	12	1	0	0	

0 months / HR 1.0

- Indolent pts dilute long term OS with docetaxel and can not make definitive statements on interim/early results
- Few low volume pts have aggressive disease and benefit from early docetaxel: I do not know who they are and not enough to effect OS of the whole subgroup

Sweeney et al NEJM 2015, Kyriakopoulos et al JCO Jan 2018;

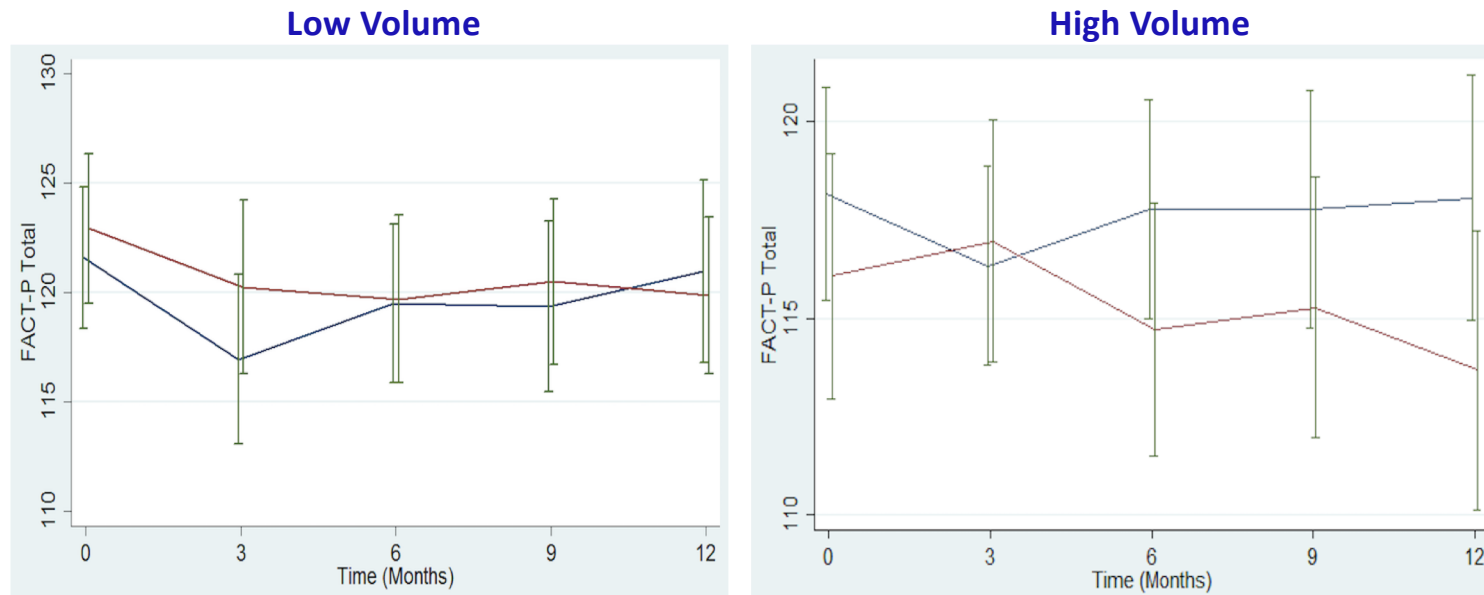
# What are we learning from long term follow-up of CHAARTED: **Test for Heterogeneity**



With long term follow-up low volume and high volume had a differential effect with early docetaxel

Kyriakopoulos et al JCO Jan 2018;

# CHAARTED FACT-P: Quality of Life



ADT alone (**red curves**) in low volume had no change in QOL over 12 months in low volume but decline in high volume (progression of disease – symptoms and progression)

ADT plus docetaxel (**blue curves**) decline in QOL in low vol on chemo  
But no decline and better 12 month QOL in high volume

*Morgans et al J. Clin Oncol 2018*

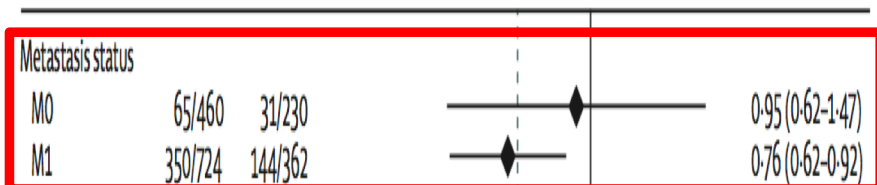
## High level summary of TS + / - docetaxel treatment effect on OS as measured by Hazard Ratio (HR)

Trial	All M1	High Volume /High risk	Low Volume	Median Follow-up (mos)
GETUG15 <sup>1</sup>	HR(OS): 0.88	HR(OS)-HV: 0.78 N=183	HR (OS): 1.02 N=202	83.9
CHAARTED <sup>2</sup>	HR(OS): 0.72	HR(OS)-HV: 0.63 N=513	HR (OS): 1.04 N=277	57.6
CHAARTED/GETUG15 pooled <sup>3</sup>		HR(OS)-HV: 0.68 N=696	HR(OS): 1.03 N=479	Test for heterogeneity: HV and LV differ as HV but not LV benefit (p=0.017)
Test for heterogeneity		CHAARTED/GETUG15 = "homogeneous" HV	CHAARTED/GETUG15 = "homogeneous" LV	
STAMPEDE-Doc <sup>3</sup> (incl Zolendronic acid)	HR(OS): 0.76	N/A; N~720	N/A; N~720 (nearly all are de novo)	43 Update at ESMO 2019

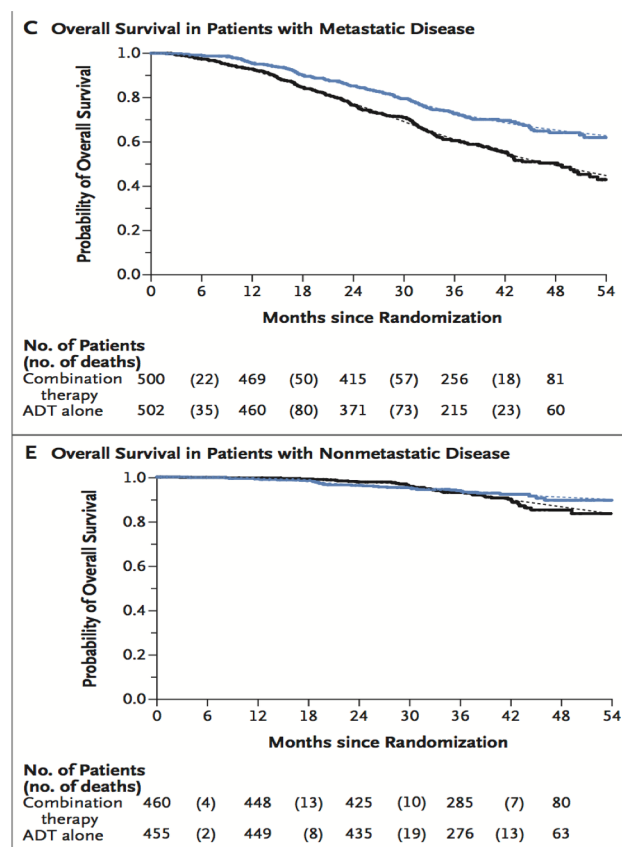
<sup>1</sup>Gravis et al Lancet Oncology 2015; <sup>2</sup>Kyriakopoulos et al JCO 2018; <sup>3</sup>Gravis et al Eur Urol 2018; <sup>4</sup>James et al Lancet 2015;

# STAMPEDE-docetaxel: Test for heterogeneity – M0 vs M1

SOC vs SOC+Doc



- M0 combines
  - High risk localized treated with ADT + XRT
  - Rising PSA post local therapy
- M1 combines
  - Low and High Volume
- Authors conclude LV benefit **based on inference** because no difference on test of heterogeneity bwn M0 and M1



James et al Lancet 2015

# Current Scorecard for Outcome with Docetaxel by Volume of Disease

- Direct overall survival benefit for high volume patients in 2 studies
  - documented improvement in QOL
- Two studies provide DIRECT evidence of no clear OS benefit in low volume disease
  - *For me*: outweighs statistical inferences from vastly different patient groups (M0 vs M1).
  - Await the retrospective volume analysis of STAMPEDE-docetaxel arm
  - Will this translate into routine care (benefit less, toxicity including treatment related deaths worse than in trials<sup>1</sup>)
    - [2.9% OS benefit with NSAA in CAB meta-analysis only 1 of 8 studies used as control<sup>2</sup>]
- Volume is prognostic for outcome on ADT and predictive for docetaxel benefit
  - Does this mean there are different biological diseases in “mHSPC”?

<sup>1</sup>Templeton A, et al ; Annals Onc 2013

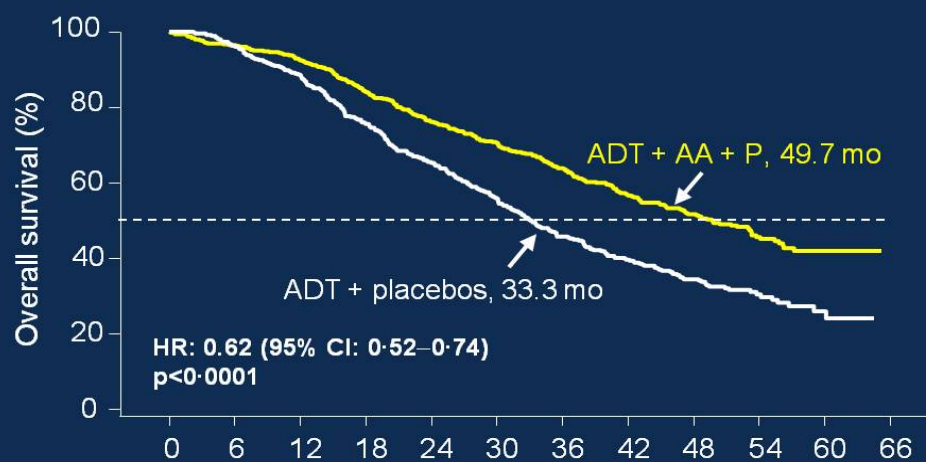
<sup>2</sup> Lancet, 2000 meta-analysis



## **Current Scorecard for mHSPC OS with Abiraterone by Volume of Disease**

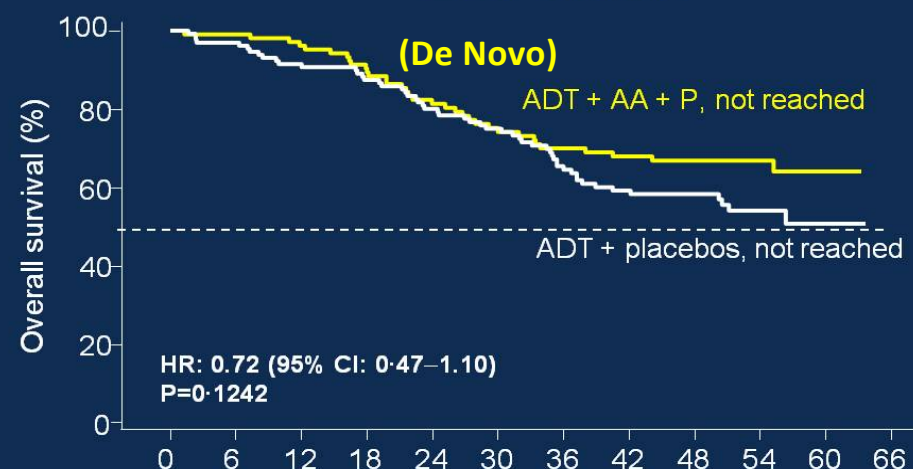
# LATITUDE: Overall Survival in High and Low Volume (CHAARTED definition\*)

## High volume



No. at risk	0	6	12	18	24	30	36	42	48	54	60	66
ADT + AA + P	487	460	429	386	345	317	283	246	188	97	31	0
ADT + placebos	468	438	389	323	270	266	181	154	113	46	14	0

## Low volume



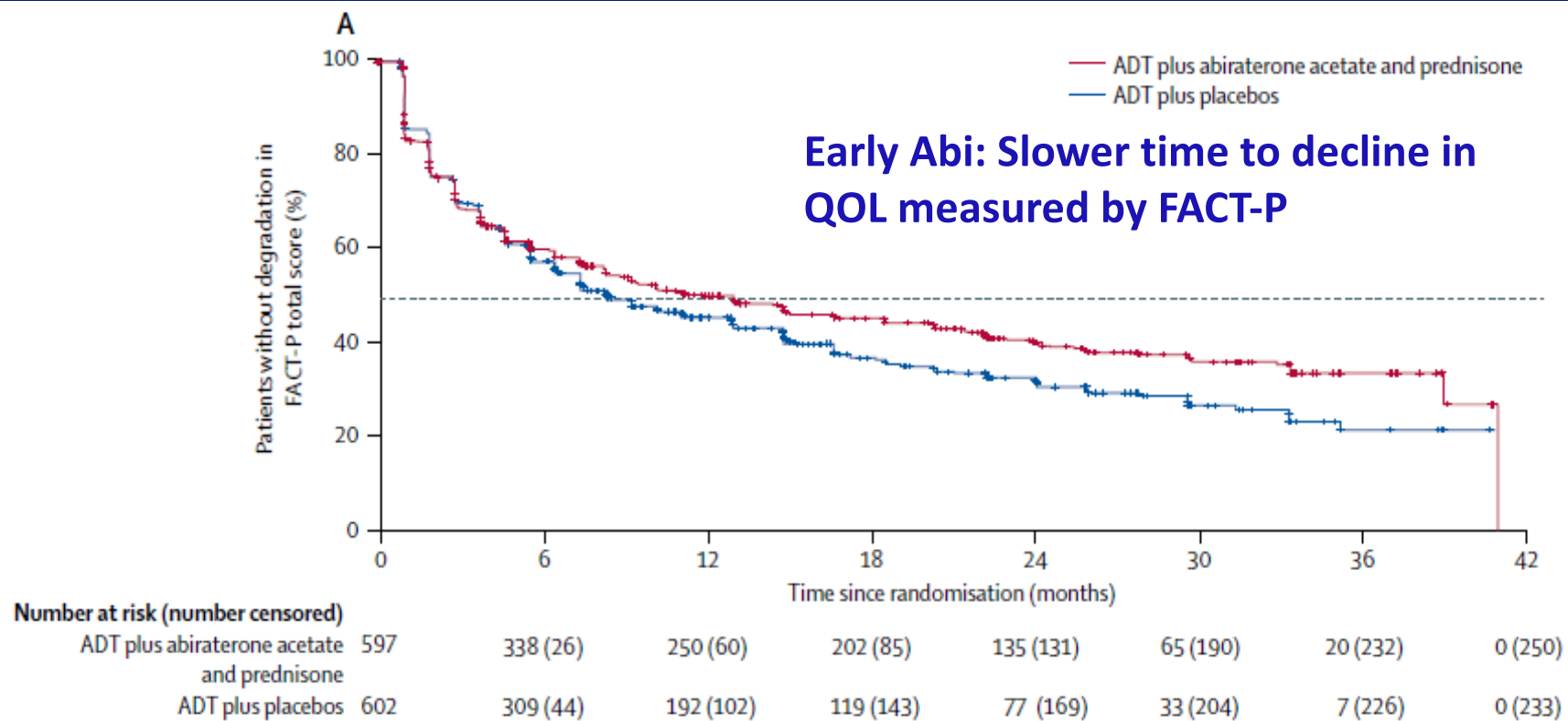
No. at risk	0	6	12	18	24	30	36	42	48	54	60	66
ADT + AA + P	110	105	100	93	80	72	68	65	52	27	9	0
ADT + placebos	133	125	115	108	97	88	74	66	52	23	9	0

CHAARTED Definition of High and Low Volume: \*Presence of visceral metastases and/or  $\geq 4$  bone metastases, with at least one outside the vertebral column or pelvis

PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19

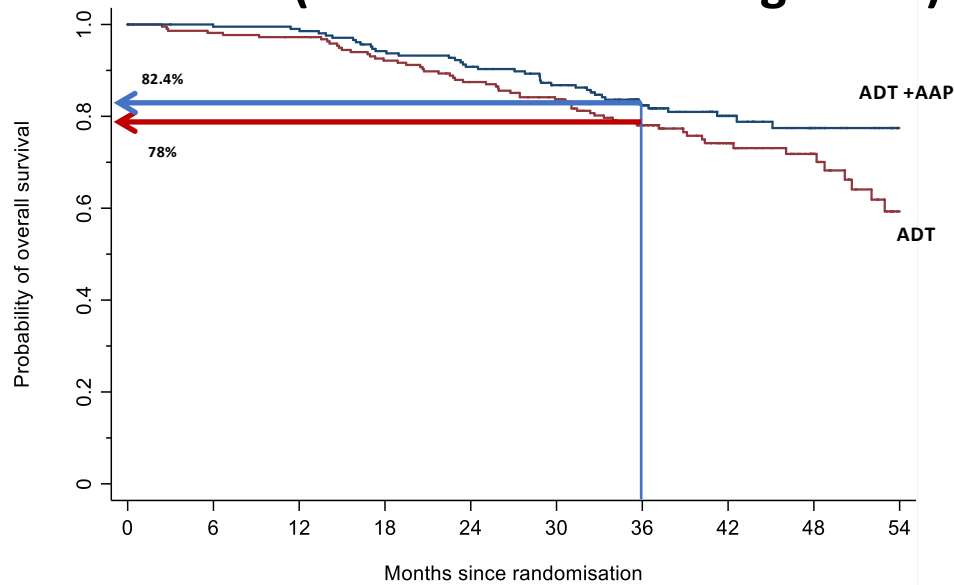
Slides are property of the author. Permission required for reuse.

# LATITUDE: QOL results



# STAMPEDE-Abiraterone: Outcome by Volume of Disease

## Low Risk (ie: not LATITUDE High Risk)



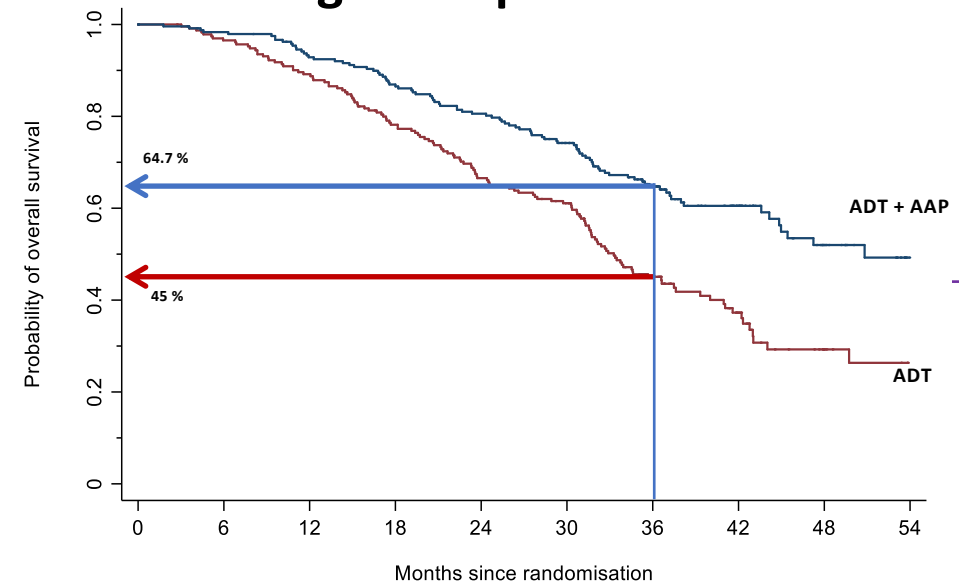
No. of patients  
(Events)

AAP	208	(2)	205	(17)	186	(16)	131	(5)	45
ADT alone	220	(6)	210	(21)	186	(19)	125	(7)	43

**OS - 4.4%**  
HR 0.66 (0.44-0.98)  
p=0.041

Hoyle et al ESMO 2018

## High Risk per LATITUDE



No. of patients  
(Events)

AAP	241	(17)	220	(29)	190	(35)	106	(12)	28
ADT alone	232	(25)	204	(51)	148	(44)	71	(15)	13

**OS - 19.7%**  
HR 0.54 (0.41-0.70)  
p<0.001

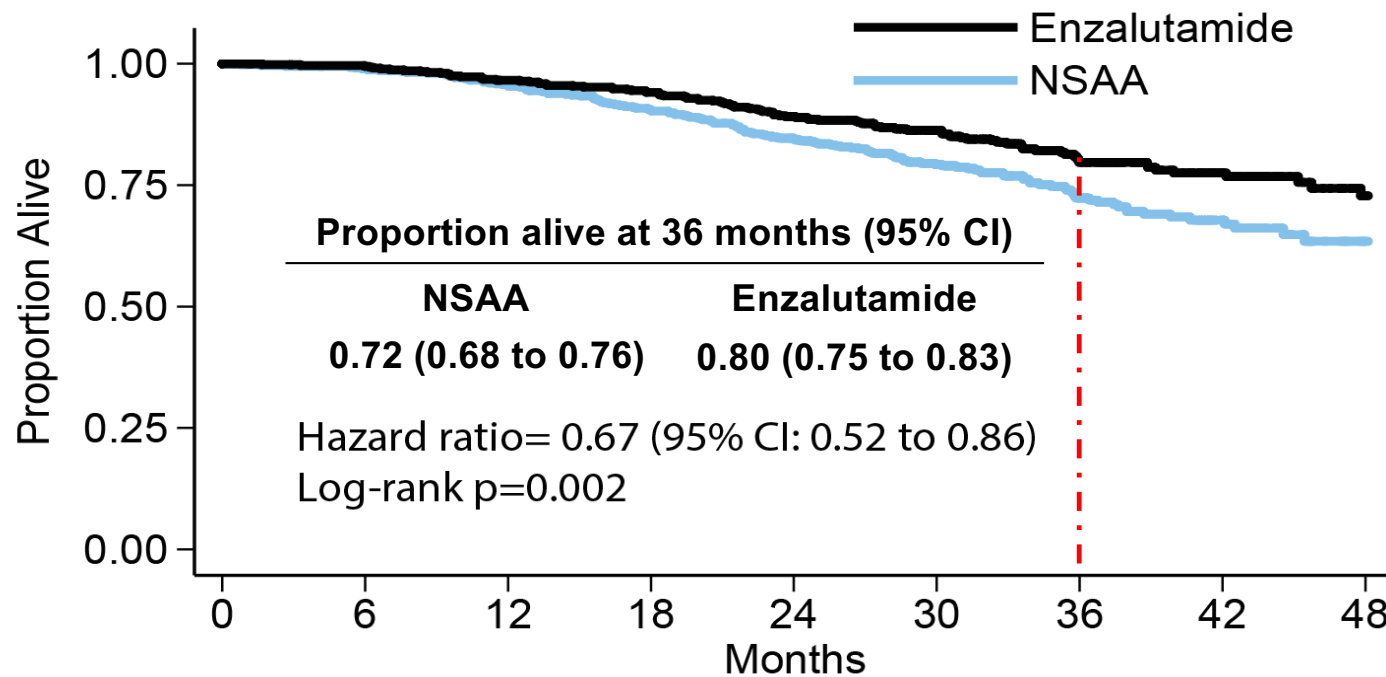
## Current Scorecard for Outcome with Abiraterone by Volume of Disease

- 3 year absolute OS point estimates to help patient counselling
  - Relative risks are less "intuitive" for patients
  - High volume: ~ 20% absolute benefit.
    - Very similar to docetaxel
  - Low volume ~ 5% absolute OS.
- Need longer term OS data to see if OS benefit is greater with early use abiraterone
  - Or are the indolent patients able to be salvaged with addition of abiraterone at CRPC?
- Note: LATITUDE are all de novo and <5% STAMPEDE relapsed after prior local therapy

**Current Scorecard for mHSPC OS with  
“Amides” by Volume of Disease**

# ENZAMET

## Primary Endpoint: Overall Survival

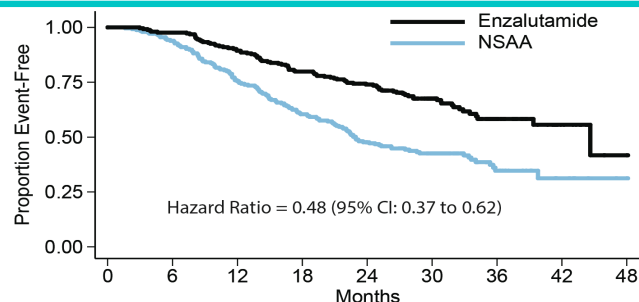


### A Mixed Bag

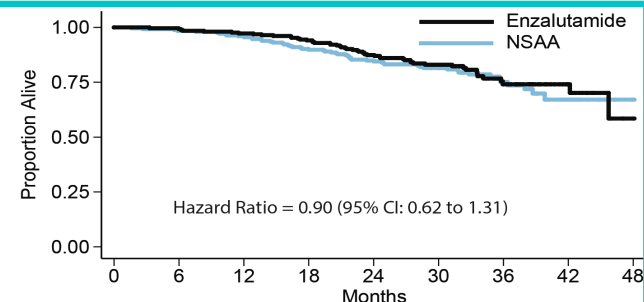
- High and Low Volume
- *De novo* vs Metach Mets
- Concurrent Docetaxel
- Many Permutations

# ENZAMET: Concurrent Docetaxel: Prespecified Subgroup of Interest (Biology and Treatment Implications)

**Testosterone  
Suppression  
+  
Docetaxel  
N=503  
(71% High Volume)**

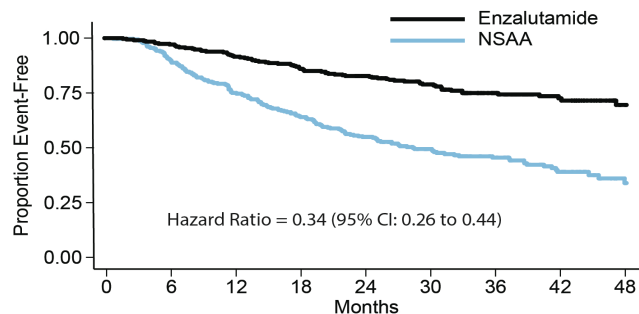


Number at risk									
NSAA	249	230	185	148	112	73	21	6	1
Enzalutamide	254	248	226	202	178	109	35	12	2

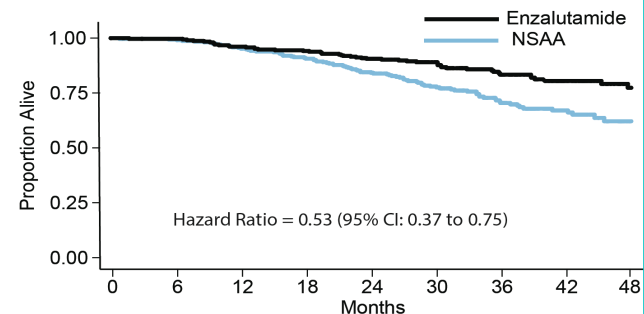


Number at risk									
NSAA	249	241	235	220	203	135	56	13	2
Enzalutamide	254	252	246	238	210	139	54	19	3

**Testosterone  
Suppression  
+  
No Docetaxel  
N=622  
(37% High Volume)**



Number at risk									
NSAA	313	282	233	198	160	109	75	44	16
Enzalutamide	309	299	281	266	246	175	121	72	34



Number at risk									
NSAA	313	310	296	281	249	176	118	73	30
Enzalutamide	309	306	295	289	270	201	135	87	42



# ENZAMET: 3 year OS point-estimates in biologically and clinically relevant predefined subgroups

		TS + NSAA (N=562)		TS + Enzalutamide (N=563)	
		3 year OS (%)	95% CI	3 year OS (%)	95% CI
<b>Early Docetaxel</b>					
Yes		75	68 to 81	74	66 to 80
No		70	64 to 76	83	78 to 87
<b>Volume of Metastases</b>					
*High		64	58 to 70	71	64 to 76
Low		82	75 to 87	90	84 to 93

*\*356 (61%) of 588 high volume patients received early docetaxel - OS is better than testosterone suppression alone in CHAARTED and LATITUDE: ~50% 3 year OS*

# ENZAMET: Total Treatment Exposure in Patients With Clinical Progression

	TS + NSAA (N=320)	TS + ENZA (N=167)
<b>Docetaxel when starting testosterone suppression</b>	<b>139 (43%)</b>	<b>88 (53%)</b>
<b>One or more life prolonging CRPC therapy</b>	<b>271 (85%)</b>	<b>112 (67%)</b>
<b>Enzalutamide</b>	<b>141 (44%)</b>	<b>0 (0%)</b>
<b>Abiraterone</b>	<b>113 (35%)</b>	<b>46 (28%)</b>
<b>Docetaxel</b>	<b>69 (22%)</b>	<b>45 (27%)</b>
<b>Radium-223</b>	<b>22 (7%)</b>	<b>14 (8%)</b>
<b>Sipuleucel-T</b>	<b>2 (&lt;1%)</b>	<b>0 (0%)</b>
<b>Cabazitaxel</b>	<b>64 (20%)</b>	<b>34 (20%)</b>
<b>Died without further CRPC therapy</b>	<b>13 (4%)**</b> <b>[3 pts early docetaxel]</b>	<b>28 (17%)</b> <b>[13 pts early docetaxel]</b>

*\*\*10 of the 320 pts (4%) assigned early NSAA who progressed and died, did not receive additional life prolonging therapy docetaxel for mHSPC or CRPC, or other life prolonging CRPC Rx*

# Scorecard of other trials of potent direct AR inhibitors in mHSPC

Potent Direct Androgen Receptor Inhibitors				rPFS	OS
<b>ADT + Placebo</b>	<b>ADT + Enzalutamide</b> - ARCHES (Astellas) (Armstrong A, et al J. Clin Onc 2019)	<b>Stratify by prior docetaxel</b>	<b>N=1150 (2016-2018)</b> <ul style="list-style-type: none"><li>• Med Follow-up: 14.4 mos</li><li>• 2/3<sup>rd</sup> High Volume</li><li>• 17% prior docetaxel</li><li>• 25% prior RP/XRT</li></ul>	<b>HR: 0.39</b> <ul style="list-style-type: none"><li>- Prior Doc: 0.52</li><li>- HV: 0.43</li><li>- LV: 0.25</li></ul> <b>18 mo PFS</b> <ul style="list-style-type: none"><li>- 50% (P)</li><li>- 75% (A)</li></ul>	<b>HR: 0.81</b> <ul style="list-style-type: none"><li>- Too immature</li></ul>
<b>ADT + Placebo</b>	<b>ADT + Apalutamide</b> - TITAN (Janssen) (Chi K, et al NEJM 2019)	<b>Stratify by Prior docetaxel</b>	<b>N=1052 (2015-2017)</b> <ul style="list-style-type: none"><li>• Med Follow-up: 22.7 mos</li><li>• 2/3<sup>rd</sup> High Volume;</li><li>• 10% prior docetaxel</li><li>• 17% prior RP/XRT</li></ul>	<b>HR: 0.48</b> <ul style="list-style-type: none"><li>- Prior Doc: 0.47</li><li>- HV: 0.53</li><li>- LV: 0.36</li></ul> <b>2y PFS</b> <ul style="list-style-type: none"><li>- 48% (P)</li><li>- 68% (A)</li></ul>	<b>HR: 0.67</b> <ul style="list-style-type: none"><li>- Prior Doc: 1.27</li><li>- HV: 0.68</li><li>- LV: 0.67</li></ul> <b>2 yr OS</b> <ul style="list-style-type: none"><li>- 74% (P)</li><li>- 82% (A)</li></ul>

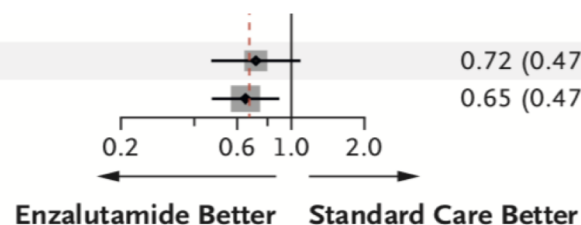
# Very Limited OS Data-sets of Outcome by Presenting with Metastases versus not at First Diagnosis of PrCa

- Patients with metastases after prostatectomy or radiation with curative intent are generally identified by PSA rise and have low volume disease

## ENZAMET, Forest Plot, Davis et al NEJM 2019

Previous local treatment

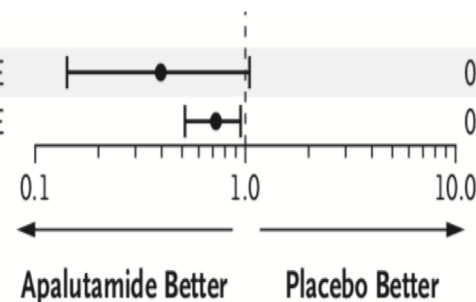
Yes	39/238	49/235			0.72 (0.47–1.09)
No	63/325	94/327			0.65 (0.47–0.89)



## TITAN Forest Plot, Chi et al NEJM 2019

Metastasis stage at initial diagnosis

M0	7/85	11/59	NE	NE	0.40 (0.15–1.03)
M1	71/411	101/441	NE	NE	0.72 (0.53–0.98)



# A brief word on zoledronic acid and denosumab in mHSPC: - skeletal related events

- Data shows NO data to support monthly SRE dosing in mHSPC
  - STAMPEDE-Zoledronic Acid (+/- docetaxel): HR(OS)~0.95<sup>1</sup>
  - CALGB 90202-zoledronic acid: HR(OS): 0.88<sup>2</sup>
  - No studies with denosumab completed
  - ? First line mHSPC therapy is effective for most in preventing SRE / bone turnover
- But maybe if pt with poor cancer control with pain and will declare CRPC soon
  - Possible benefit but not shown
  - Low risk of ONJ when outlook is poor and limit dosing for 2 years
  - Consider add on with first line CRPC with rising PSA or fail to suppress PSA “well”
  - No data on benefit of adding on BTT if bone turnover markers not suppressed

<sup>1</sup>James et al Lancet 2015; <sup>2</sup>Smith et al

# A brief word on zoledronic acid and denosumab in mHSPC: - Osteoporosis management

- Completely different conversation
- Vitamin D3 and Calcium and weight bearing exercises:
  - Calcium no harm unless renal stones or primary hyperparathyroidism
- Less reliability of DEXA given bone mets
  - Maybe rely more on forearm
  - *Vert bodies and hip: more likely to get mets (occult to CT and bone scan)*
- But .... Low volume patient managed with long term abiraterone with super low androgens and prednisone
  - If in deep remission, monitor closely and starting osteoporosis per guidelines given risk substantial and outlook long

**Score-card of *direct* evidence of *some*  
overall survival treatment benefit in mHSPC  
(as of Aug 2019; not treatment recommendations<sup>1</sup>)**

Patient co-morbidity	Burden and Presentation of Metastatic Disease <sup>2</sup>	Agent to add to testosterone suppression
Chemofit <sup>3</sup>	High volume	Docetaxel / Abiraterone / Apalutamide/ Enzalutamide
Not Chemofit	High volume	Abiraterone / Apalutamide / Enzalutamide
Chemofit and Not Chemofit	Low volume / <i>De-Novo</i> Metastatic	Abiraterone / Apalutamide / Enzalutamide Or Radiate primary ( <i>Docetaxel: TBD</i> ) <sup>5</sup>
Chemofit and Not chemofit	Low volume / Prior local therapy <sup>6</sup>	Apalutamide <sup>7</sup> / Enzalutamide <sup>7</sup> ( <i>too few pts in abiraterone studies</i> )

<sup>1</sup> Choice based on patient-physician discussion and availability/affordability; <sup>2</sup>CHAARTED definition; <sup>3</sup>Able to tolerate 75mg/m<sup>2</sup> of docetaxel every 3 weeks; <sup>4</sup>Unknown if docetaxel or new hormonal therapies add to radiation or radiation adds to docetaxel or new hormonal therapies; <sup>5</sup>Data to be presented at ESMO 2019; <sup>6</sup>Prior prostatectomy or radiation with curative intent; <sup>7</sup>Very immature and incomplete.

# Conclusions and Next Steps

## Balancing Act

- Look for patterns in available data to make decisions for individual patients
- Disease burden vs Co-morbidities vs Treatment Benefit vs Treatment Risk

## Harmonize and improve clinical definitions

- More accurate prognostication and prediction (*STOPCaP, Halabi/Sweeney, PCF award*)
- More granular data on burden of metastatic disease, account for *de novo* vs prior local therapy

## Need to revisit treatment breaks

- > 60% of patients are on abiraterone + prednisone, enzalutamide, apalutamide > 3 years

## Biomarkers

- >3,000 pts with blood and tumor specimens CHAARTED, STAMPEDE-abi and STAMPEDE-doc, ENZAMET
- Determine underlying biology to guide therapy and prevent emergence of CRPC