Carcinoma prostatico localmente avanzato e metastatico ormono sensibile

Carcinoma metastatico ''in evoluzione''

Francesco Massari

Oncologia Medica

Azienda Ospedaliero – Universitaria di Bologna

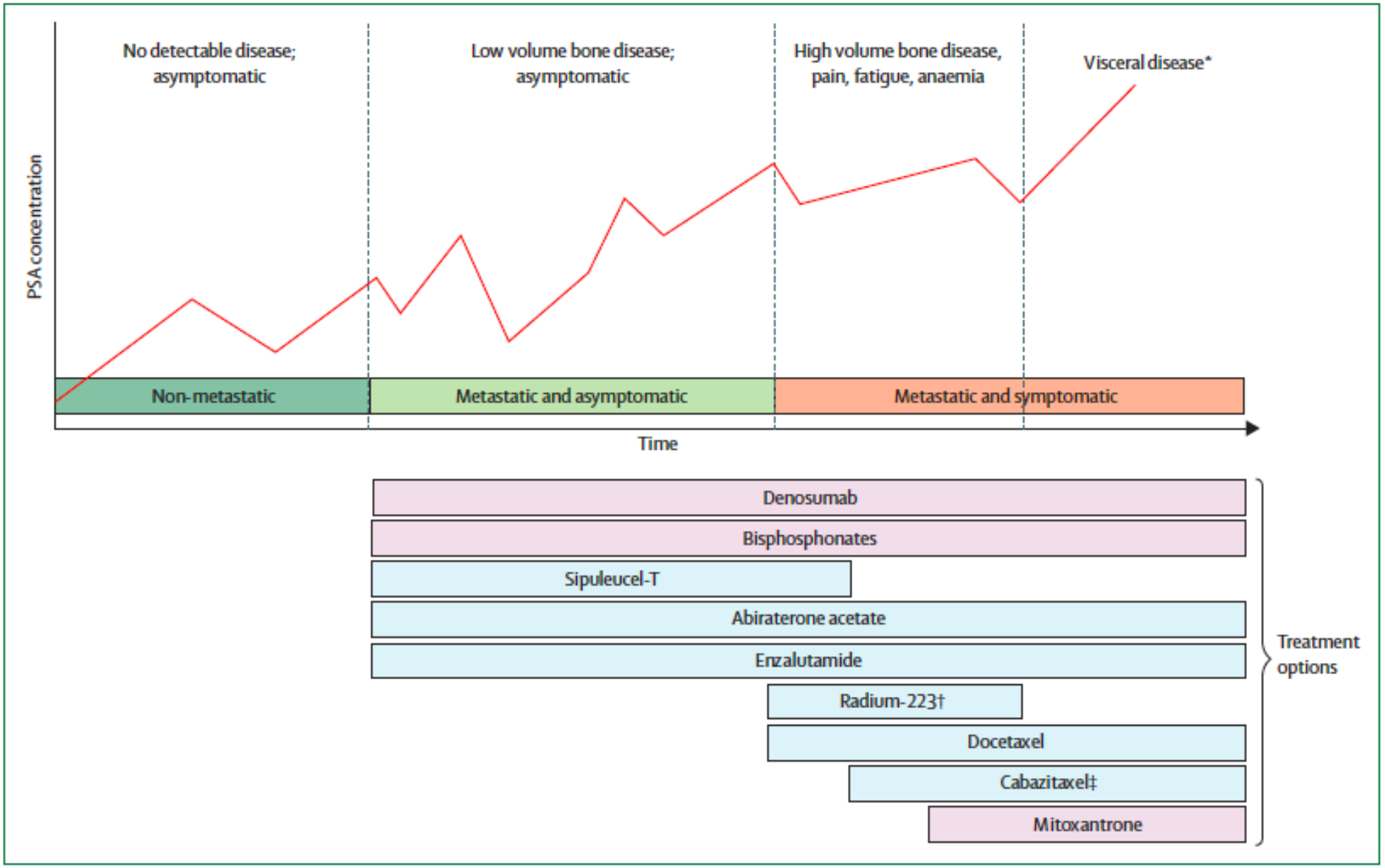
Policlinico S. Orsola-Malpighi

Il team interdisciplinare nel carcinoma della prostata – Negrar 07.12.2019

Disclosures

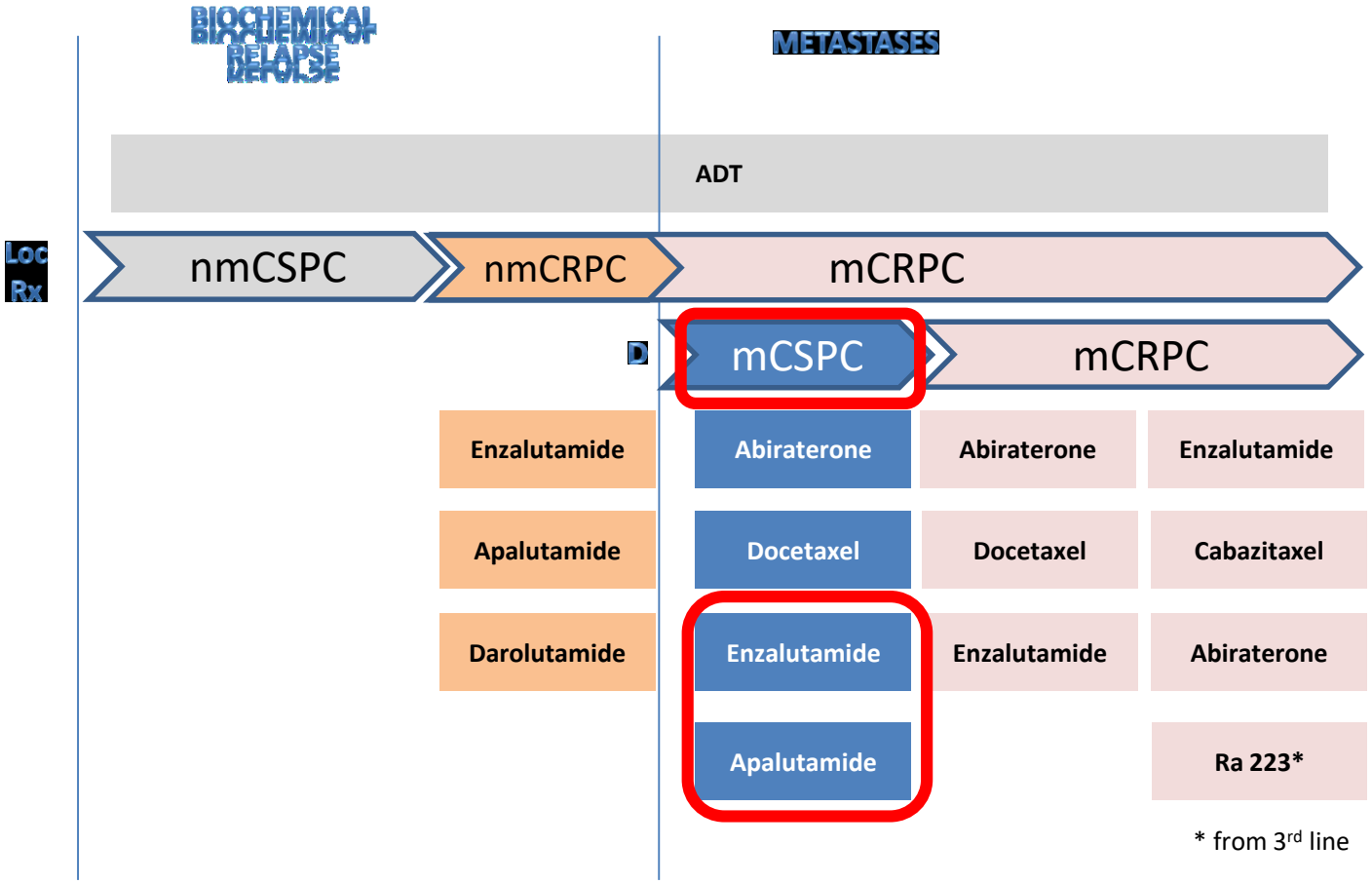
- No pertinent C.O.I. with this presentation
- Advisory Boards/Honoraria/Consultant for:
  - Astellas
  - BMS
  - Janssen
  - Ipsen
  - MSD
  - Pfizer

Progress in Management of PCa



Modified by Lorente D, Lancet Oncology 2015; 16: e279–92

Progress in Management of PCa



Modified by Caffo O

Progress in Management of mHSPC

- 2015 paradigm shift → Docetaxel upfront
  - ADT + Docetaxel in newly diagnosed M1 disease (CHAARTED[1], STAMPEDE[2])
- 2017 → Abiraterone acetate upfront
  - ADT + Abiraterone in newly diagnosed M1 disease (LATITUDE[3], STAMPEDE[4])
- 2019 ASCO GU and ASCO → Apalutamide, Enzalutamide
  - TITAN: Apalutamide[5]
  - ARCHES: Enzalutamide[6]
  - ENZAMET: Enzalutamide[7]

EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer 2018 (http://uroweb.org)

1. Sweeney et al NEJM 2015; 373:737
2. James et al Lancet 2016; 387:1163
3. Fizazi et al NEJM 2017; 377:352
4. James et al NEJM 2017; 377:338
5. Chi et al NEJM 2019
6. Armstrong et al ASCO GU abstr#687
7. Davis et al NEJM 2019

TITAN

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

Kim N. Chi, M.D., Neeraj Agarwal, M.D., Anders Bjartell, M.D., Byung Ha Chung, M.D., Andrea J. Pereira de Santana Gomes, M.D., Robert Given, M.D., Álvaro Juárez Soto, M.D., Axel S. Merseburger, M.D., Mustafa Özgüroğlu, M.D., Hirotsugu Uemura, M.D., Dingwei Ye, M.D., Kris Deprince, M.D., Vahid Naini, Pharm.D., Jinhui Li, Ph.D., Shinta Cheng, M.D., Margaret K. Yu, M.D., Ke Zhang, Ph.D., Julie S. Larsen, Pharm.D., Sharon McCarthy, B.Pharm., and Simon Chowdhury, M.D., for the TITAN Investigators*

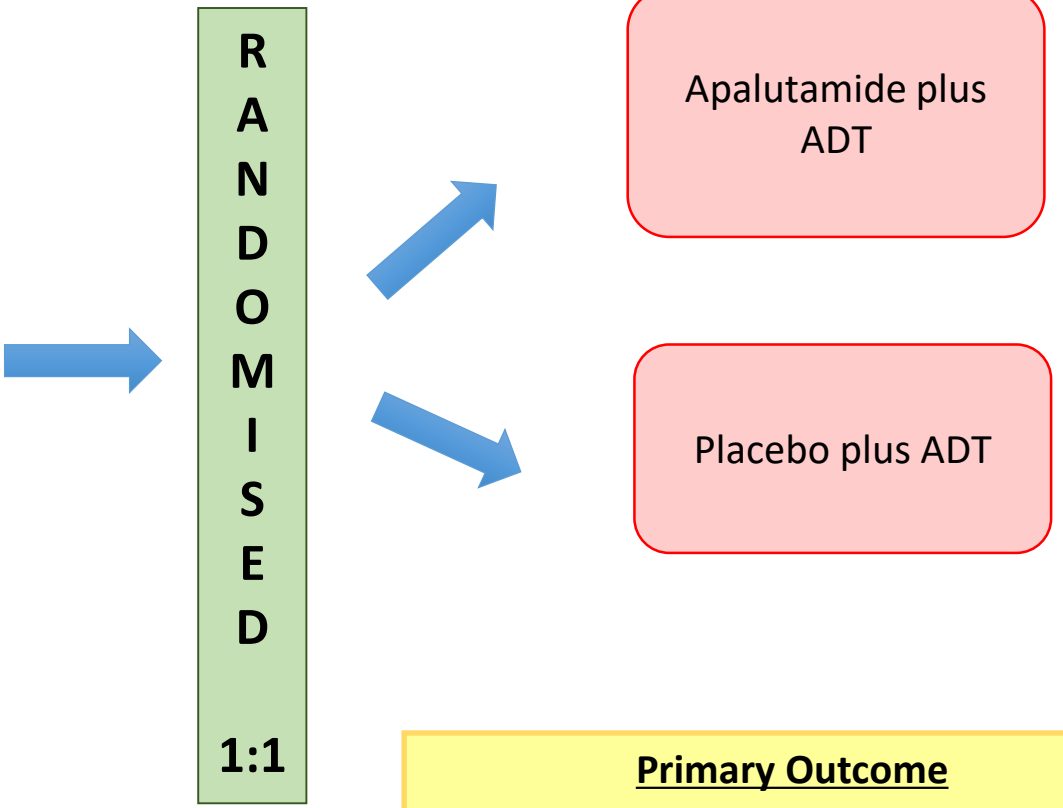
Chi et al NEJM 2019

Next-generation androgen receptor (AR) antagonist - APALUTAMIDE

TITAN: STUDY DESIGN

Study population:
(estimated 1000 pts)

- Diagnosis of prostate adenocarcinoma.
- Metastatic disease documented by >= 1 bone lesions.
- ECOG PS grade of 0 or 1
- Permitted previous docetaxel treatment: maximum of 6 cycles, last dose <=2 months, stable disease or better
- Other allowed prior treatment for mHSPC: a) Maximum of 1 course of radiation or surgical intervention; radiation therapy for metastatic lesions must be completed prior to randomization; b) Less than or equal to (<=) 6 months of ADT
- Allowed prior treatments for localized prostate

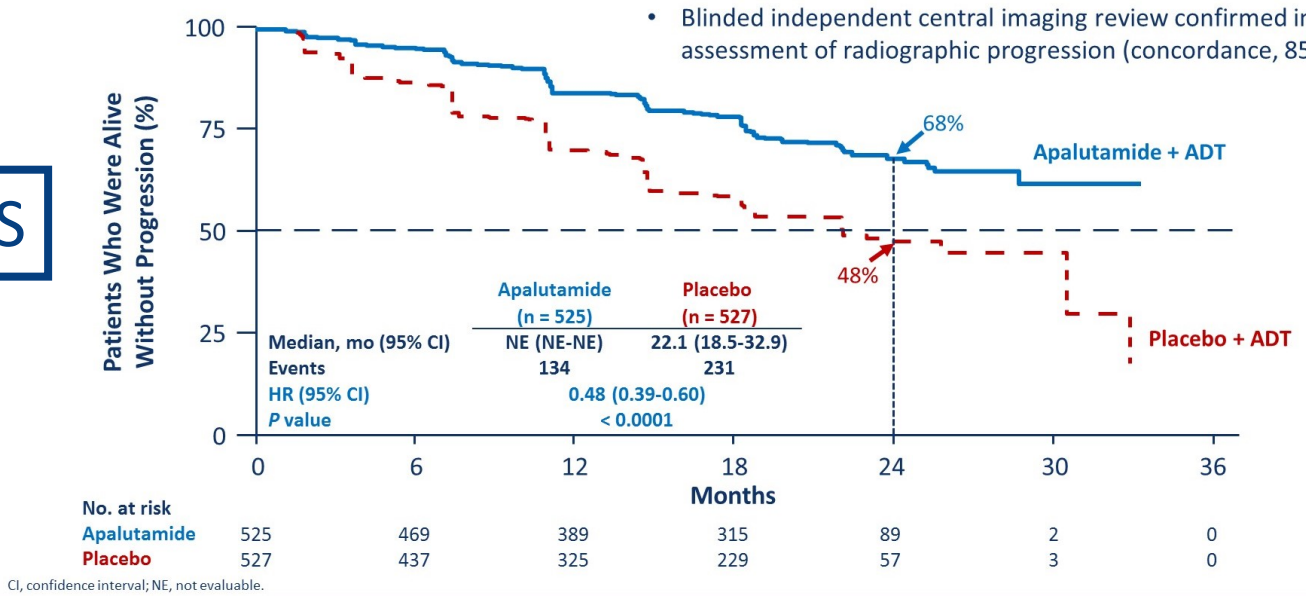


Primary Outcome

- Radiographic Progression-Free Survival
- Overall Survival

TITAN – Results

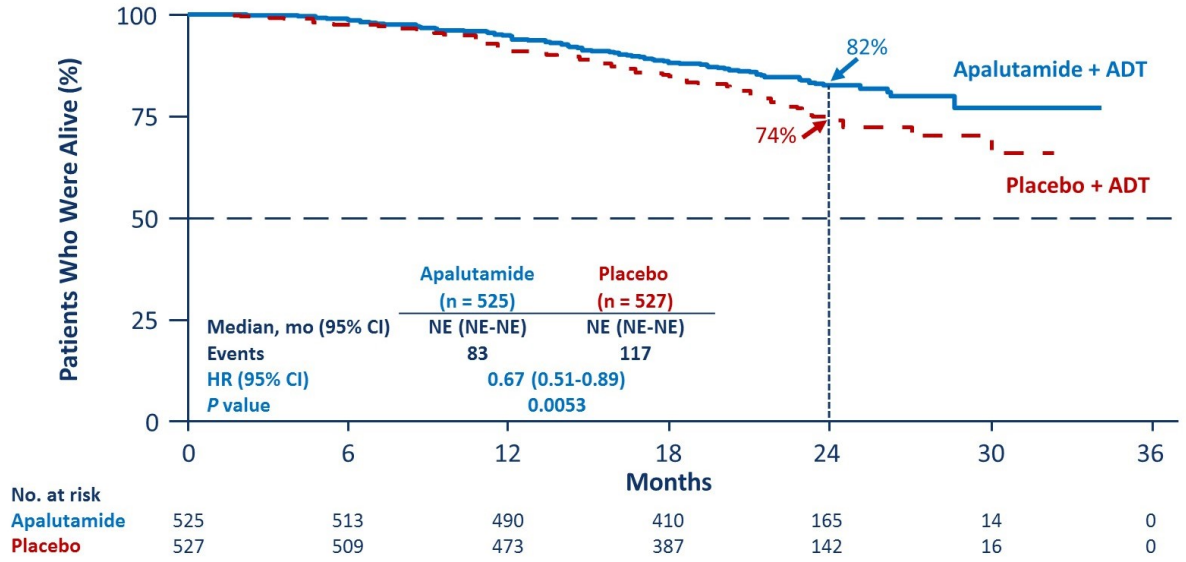
rPFS



CI, confidence interval; NE, not evaluable.

Apalutamide significaIntly reduced risk of rPFS or death by 52%

OS



Apalutamide significaIntly reduced risk of death by 33%

Modified By Kim Chi at 2019 ASCO Annual Meeting

TITAN – Conclusions

- In patients with metastatic castration-sensitive prostate cancer, the addition of apalutamide to ADT significantly improved survival
  - rPFS: 52% reduction in risk of radiographic progression or death (HR: 0.48; 95% CI: 0.39-0.60; *P* < .0001)
  - OS: 33% reduction in risk of death (HR: 0.67; 95% CI: 0.51-0.89; *P* = .0053)
- Apalutamide was well tolerated with adverse events consistent with previously reported data
- Results support the addition of apalutamide to ADT for patients with metastatic castration-sensitive prostate cancer

ENZAMET

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer

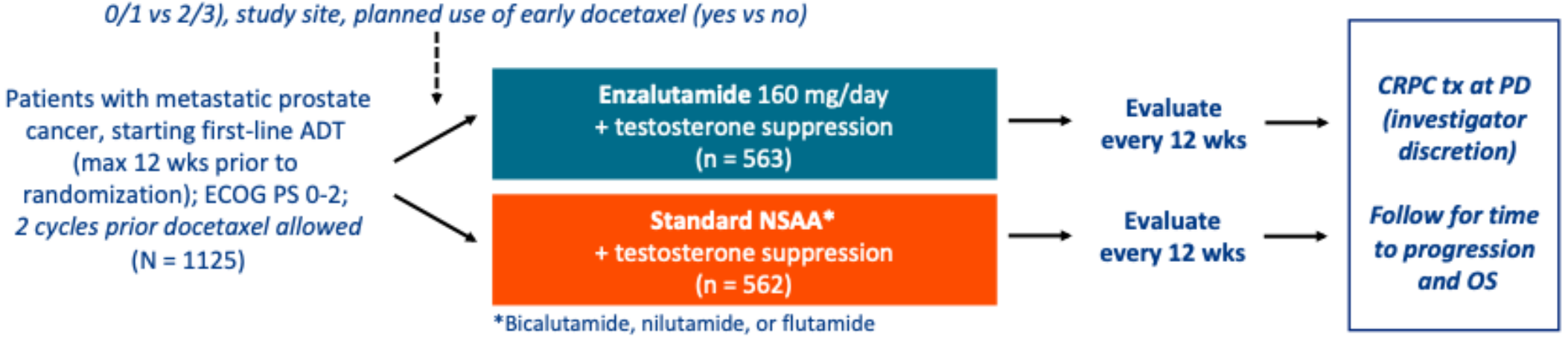
I.D. Davis, A.J. Martin, M.R. Stockler, S. Begbie, K.N. Chi, S. Chowdhury, X. Coskinas, M. Frydenberg, W.E. Hague, L.G. Horvath, A.M. Joshua, N.J. Lawrence, G. Marx, J. McCaffrey, R. McDermott, M. McJannett, S.A. North, F. Parnis, W. Parulekar, D.W. Pook, M.N. Reaume, S.K. Sandhu, A. Tan, T.H. Tan, A. Thomson, E. Tu, F. Vera-Badillo, S.G. Williams, S. Yip, A.Y. Zhang, R.R. Zielinski, and C.J. Sweeney, for the ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group*

Davis et al NEJM 2019

ENZAMET – Study Design

- Phase III, randomized, open-label, multicenter clinical trial

Stratified by volume of metastases (high vs low), antiresorptive therapy (yes vs no), ECOG PS (0/1 vs 2), comorbidities (ACE-27: 0/1 vs 2/3), study site, planned use of early docetaxel (yes vs no)



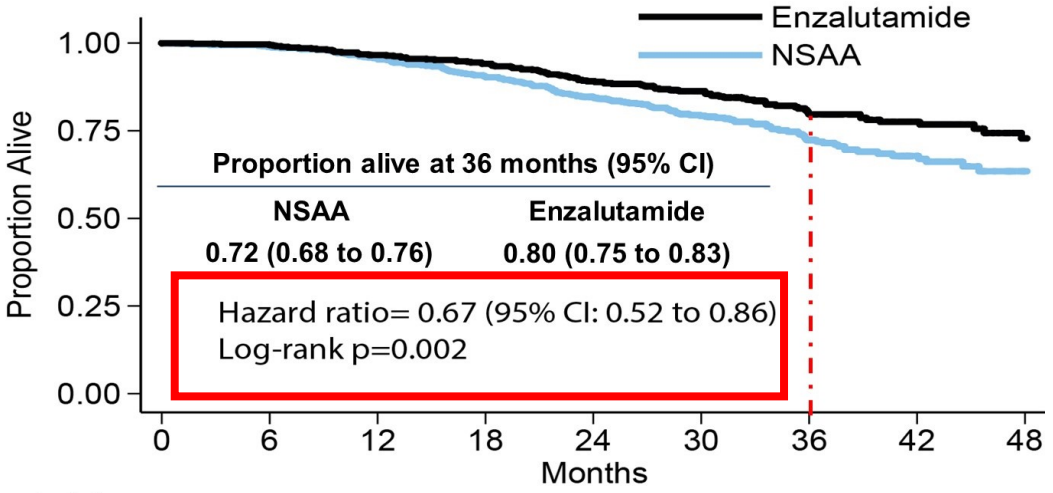
*Bicalutamide, nilutamide, or flutamide

- Primary endpoint: OS
- Secondary endpoints: PSA PFS (including clinical progression if occurring first), clinical PFS, AEs, HRQoL

Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

ENZAMET – Results

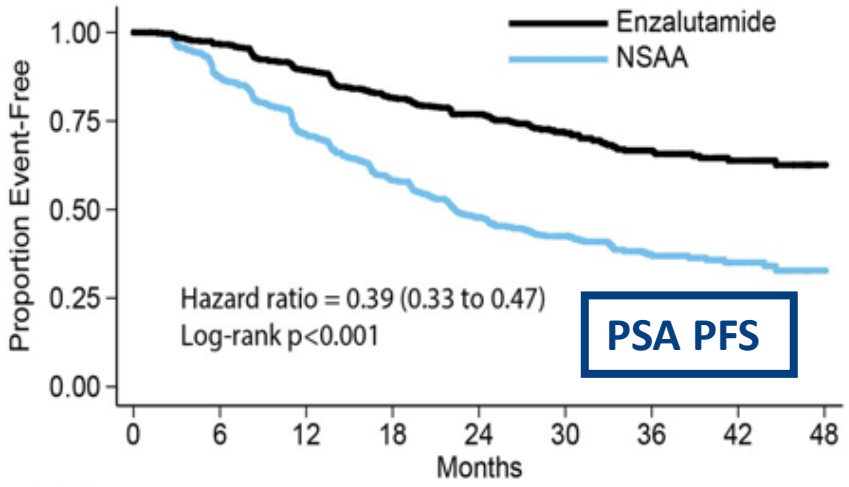
Primary endpoint: OS



Number at risk

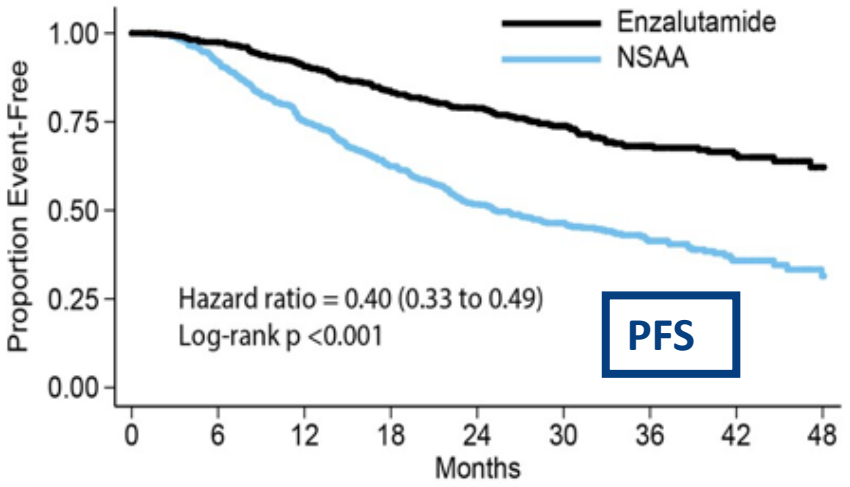
NSAA	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45

Secondary endpoint: PFS (PCWG2)



Number at risk

NSAA	562	486	395	322	249	161	78	44	17
Enzalutamide	563	543	500	455	411	269	146	77	34

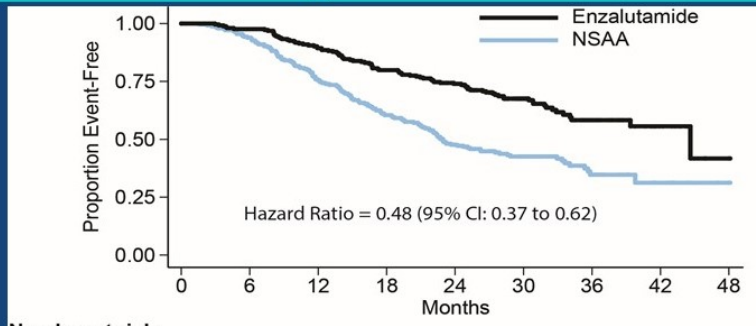
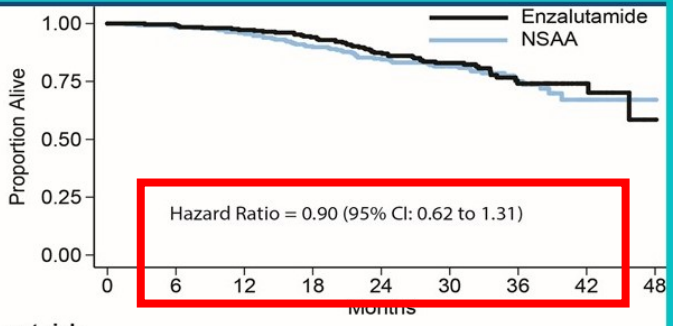
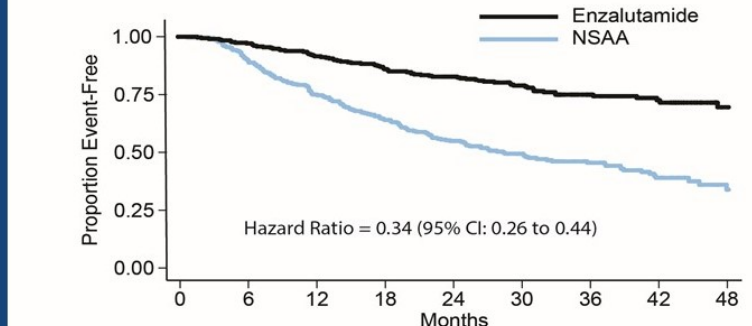
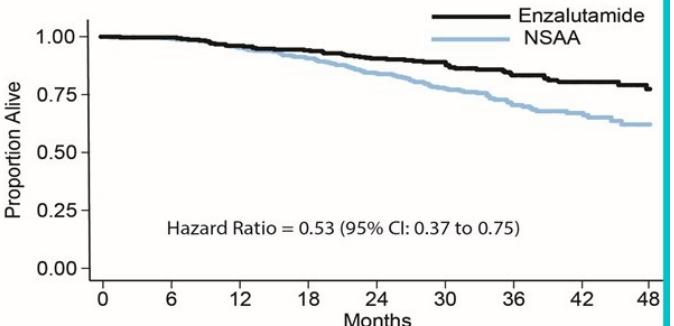


Number at risk

NSAA	562	512	418	346	272	182	96	50	17
Enzalutamide	563	547	507	468	424	284	156	84	36

Modified By Christopher Sweeney at 2019 ASCO Annual Meeting

ENZAMET – Concurrent Docetaxel

	Clinical Progression-Free Survival	Overall Survival
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

Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

ENZAMET – Conclusions

- Enzalutamide demonstrated improved survival compared with standard NSAA in patients with mHSPC
  - 36-mo OS: 80% for enzalutamide vs 72% for NSAA (HR: 0.67; *P* = .002)
  - Similar OS benefit in patients with low and high volume of metastases
- Increased toxicity was shown with the addition of enzalutamide, as expected
  - Patients who were also treated with docetaxel experienced more chemotherapy-related toxicity
- The study investigators concluded that enzalutamide is an appropriate option for men with mHSPC starting on ADT

Davis et al NEJM 2019
Sweeney C 2019 ASCO Annual Meeting

ENZALUTAMIDE - ARCHES

original report

ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer

Andrew J. Armstrong, MD, ScM[1]; Russell Z. Szmulewitz, MD[2]; Daniel P. Petrylak, MD[3]; Jeffrey Holzbeierlein, MD[4]; Arnauld Villers, MD[5]; Arun Azad, MBBS, PhD[6]; Antonio Alcaraz, MD, PhD[7]; Boris Alekseev, MD[8]; Taro Iguchi, MD, PhD[9]; Neal D. Shore, MD[10]; Brad Rosbrook, MS[11]; Jennifer Sugg, MS[12]; Benoit Baron, MS[13]; Lucy Chen, MD[12]; and Arnulf Stenzl, MD[14]

Journal of Clinical Oncology®

Armstrong et al, JCO 2019

ENZALUTAMIDE - ARCHES

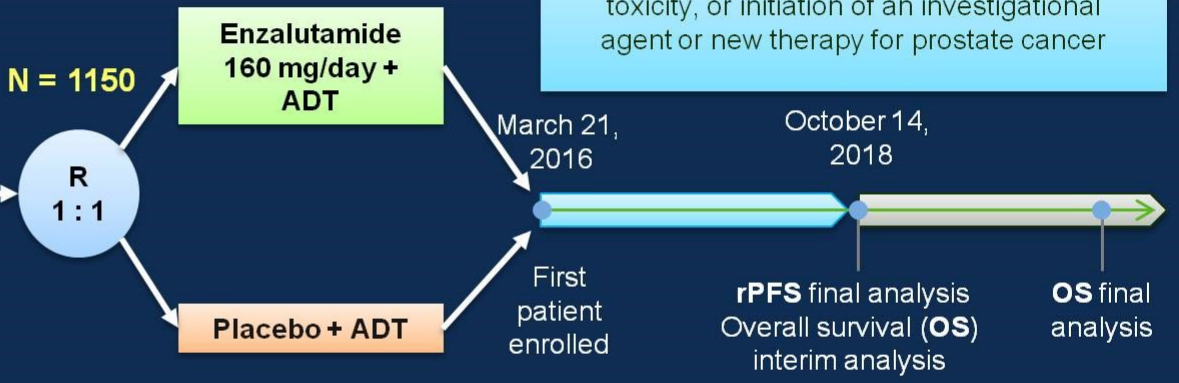
ARCHES study design

Key eligibility criteria

- mHSPC (confirmed by bone scan, CT, or MRI), histologically confirmed adenocarcinoma
- ECOG Performance Status 0 to 1
- Current ADT duration ≤3 months unless prior docetaxel, then ≤6 months

Stratification factors

- Volume of disease (low vs. high*)
- Prior docetaxel therapy for mHSPC (none, 1–5, or 6 cycles)



Key discontinuation criteria

Radiographic progression, unacceptable toxicity, or initiation of an investigational agent or new therapy for prostate cancer

Primary endpoint

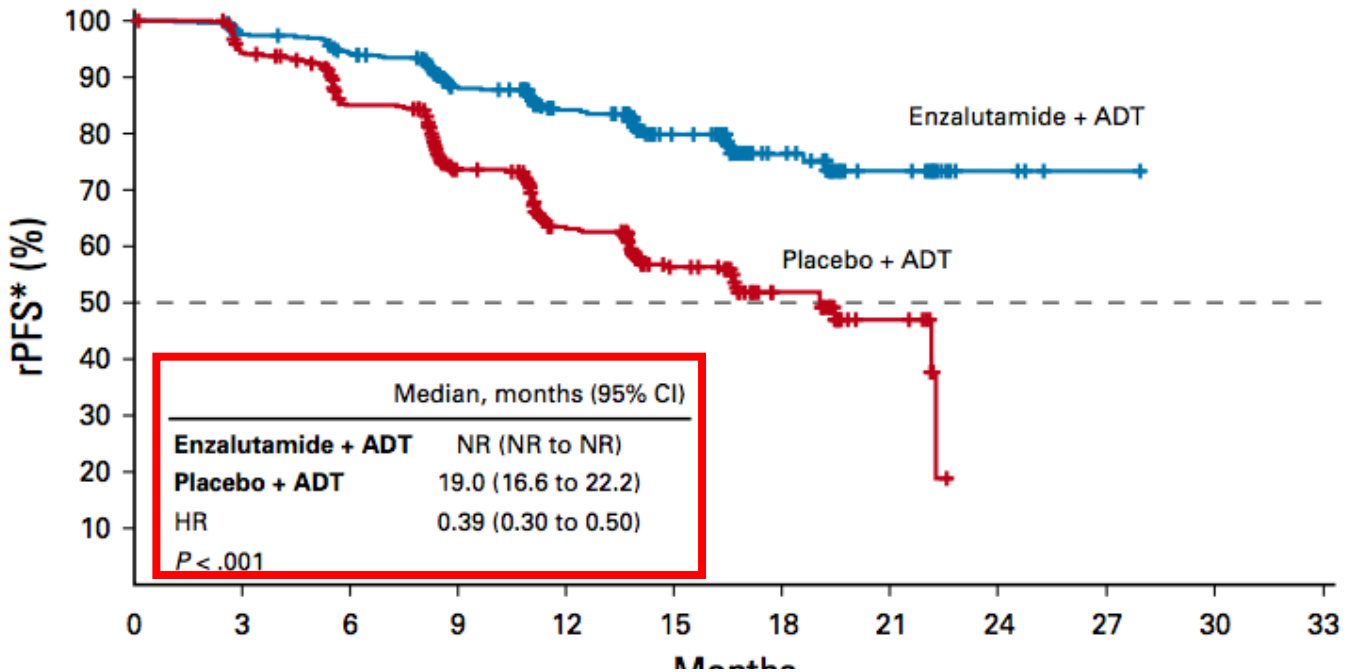
- rPFS: time from randomization to first objective evidence of radiographic progression assessed centrally, or death from any cause within 24 weeks of treatment discontinuation, whichever occurs first
  - Radiographic disease progression was defined by RECIST 1.1 criteria for soft tissue disease or by appearance of ≥2 new lesions on bone scan compared to baseline (at week 13) or vs. best response on treatment (week 25 or later). New bone scan lesions observed at week 13 required confirmation of ≥2 additional new bone lesions on subsequent scans

*Defined as metastases involving the viscera or, in the absence of visceral lesions, ≥4 bone lesions, ≥1 of which must be in a bony structure beyond the vertebral column and pelvic bone

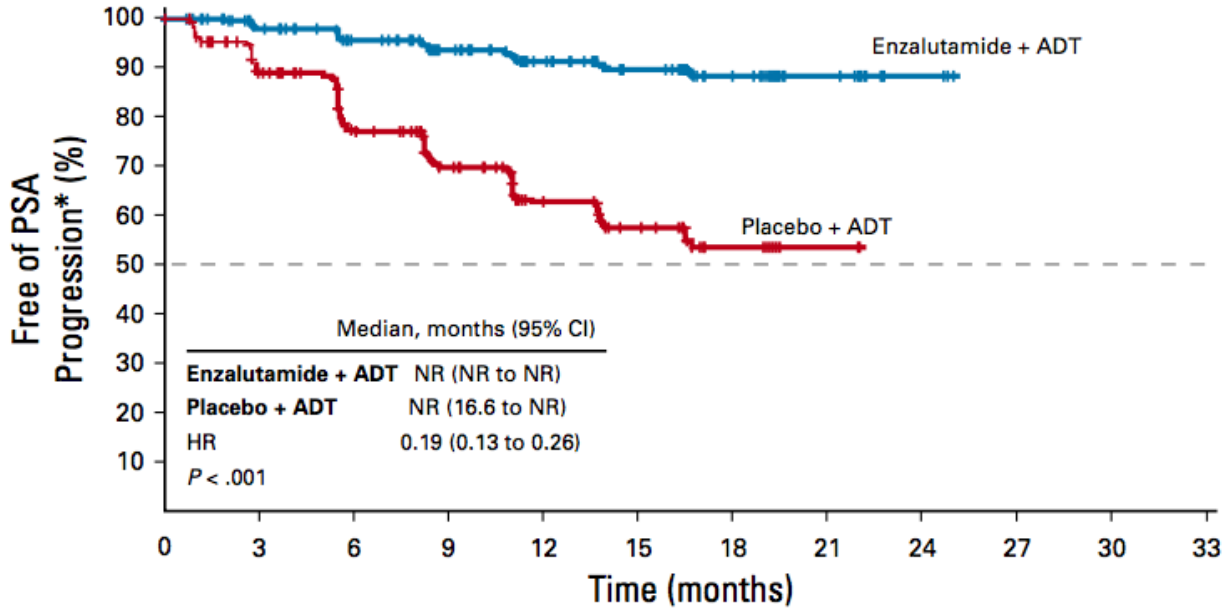
Armstrong ASCO GU 2019

ENZALUTAMIDE - ARCHES

rPFS



PSA PFS



Armstrong et al, JCO 2019

ADVERSE EVENTS OF SPECIAL INTEREST

ARCHES

Event, n (%)	Enzalutamide + ADT (n = 572)		Placebo + ADT (n = 574)	
Any AE of special interest*	324 (56.6)		291 (50.7)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Convulsion	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Hypertension	49 (8.6)	19 (3.3)	36 (6.3)	12 (2.1)
Neutrophil count decreased	5 (0.9)	2 (0.3)	4 (0.7)	2 (0.3)
Cognitive / memory impairment	26 (4.5)	4 (0.7)	12 (2.1)	0
Ischemic heart disease	10 (1.7)	3 (0.5)	8 (1.4)	6 (1.0)
Other selected cardiovascular events	13 (2.3)	6 (1.0)	9 (1.6)	5 (0.9)
Posterior reversible encephalopathy syndrome	0	0	0	0
Fatigue	138 (24.1)	10 (1.7)	112 (19.5)	9 (1.6)
Fall	21 (3.7)	2 (0.3)	15 (2.6)	1 (0.2)
Fractures	37 (6.5)	6 (1.0)	24 (4.2)	6 (1.0)

TITAN

	Apalutamide + ADT (n = 524)		Placebo + ADT (n = 527)	
Adverse Event, n (%)	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Rash[a]	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[b]	34 (6.5)	0	6 (1.1)	0
Fracture[c]	33 (6.3)	7 (1.3)	24 (4.6)	4 (0.8)
Seizure[d]	3 (0.6)	1 (0.2)	2 (0.4)	0

ENZAMET

	TS + NSAA N=558		TS + ENZA N=563	
Serious AE rate per yr of Rx exposure	0.33	95% CI: 0.28-0.39	0.34	95% CI: 0.29-0.40
AEs of Interest	N	%	N	%
Hypertension: Gde 3	24	4%	43	8%
Gde 2	30	5%	60	11%
Fatigue: Gde 3	4	1%	31	6%
Gde 2	80	14%	142	25%
Falls: Gde 3	2	<1%	6	1%
Gde 2	8	1%	28	5%
Syncope	7	1%	20	4%
Concentration Impairment: Gde 1/2	6	1%	24	4%
Any Seizure	0	0%	7	1%

HOW TO CHOOSE BETWEEN UP-FRONT TREATMENTS IN mHSPC

	DOCETAXEL	ABIRATERONE	ENZALUTAMIDE APALUTAMIDE
Duration of treatment	➢ Short term treatment	➢ Long term treatment	➢ Long term treatment
Toxicities	➢ Peripheral neuropathy, hair loss	➢ Liver enzymes, electrolytes	➢ CNS (seizure), falls
Corticosteroids	➢ Use of corticosteroids	➢ Use of corticosteroids	➢ No use of corticosteroids
Setting	➢ High volume	➢ Any	➢ Any

TREATMENT OPTIONS IN mHSPC

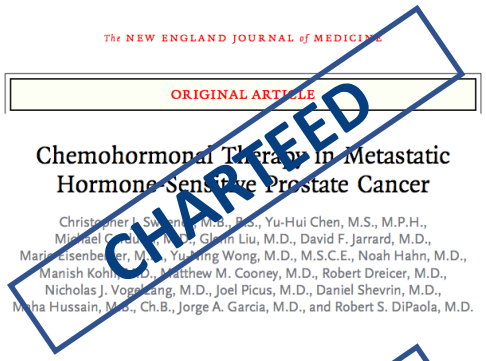
DOCETAXEL

ABIRATERONE

ENZALUTAMIDE

APALUTAMIDE

2015


The NEW ENGLAND JOURNAL of MEDICINE

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., Marie 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.

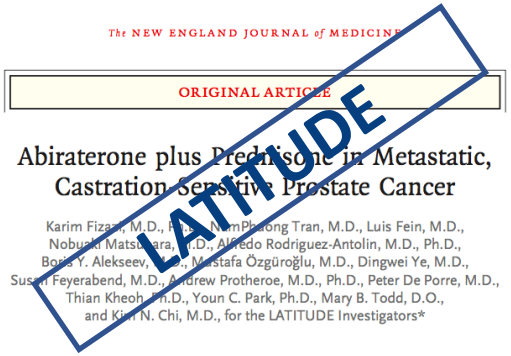
CHARTFEED


Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

*Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie, Christopher C Parker, Martin Russell, Gerhardt Attard, Johann de Bono, William Cross, Rob J Jones, George Thalmann, Claire Amos, David Matheson, Robin Millman, Mymoona Alzouebi, Sharon Beesley, Alison J Birtle, Susannah Brock, Richard Cathomas, Prabir Chakraborti, Simon Chowdhury, Audrey Cook, Tony Elliott, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Laing, Fiona McKinna, Duncan B Matheson, Joe M O'Sullivan, Omi Parikh, Clive Peedell, Andrew Protheroe, Angus J Robinson, Narayanan Srihari, Rajaguru Srinivasan, John Staffurth, Santhanam Sundar, Shaun Tolan, David Tsang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE Investigators**

STAMPEDE

2017


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., Nam Phung Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., Youn C. Park, Ph.D., Mary B. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators*

LATITUDE


The NEW ENGLAND JOURNAL of MEDICINE

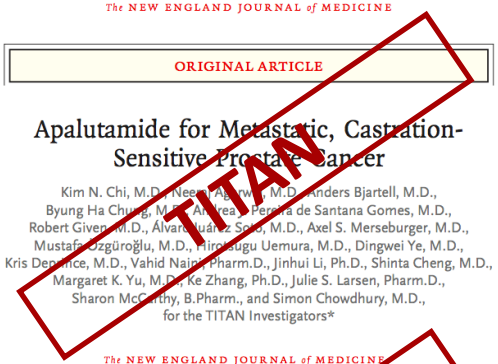
ORIGINAL ARTICLE

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

N.D. James, J.S. de Bono, M.R. Sydes, N.W. Clarke, M.D. Mason, D.P. Dearnaley, A.W.S. Ritchie, C.C. Amos, C. Gilson, R.J. Jones, D. Matheson, R. Millman, G. Attard, S. Chowdhury, W.R. Cross, S. Gillessen, C.C. Parker, J.M. Russell, R.R. Begum, S. Bhalla, M. Cawkwell, F. Adab, S. Aung, A.J. Birtle, J. Bowen, S. Brock, P. Chakraborti, C. Ferguson, J. Gale, E. Gray, M. Hingorani, P.J. Hoskin, J.F. Lester, Z.I. Malik, F. McKenna, N. McPhail, J. Money-Kyrle, J. O'Sullivan, O. Parikh, A. Protheroe, A. Robinson, N.N. Srihari, C. Thomas, J. Wagstaff, J. Wylie, A. Zarkar, M.K.B. Parmar, and M.R. Sydes, for the STAMPEDE Investigators*

STAMPEDE

2019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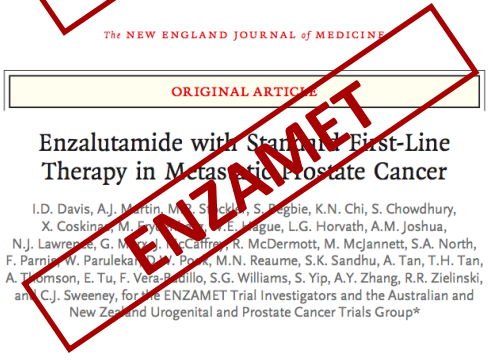
TITAN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ENZAMET

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