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What urologists need to know about hormonotherapies, anno 2018.

Peter Schatteman,
L Pauwels, F D'Hondt, G De Naeyer, A Mottrie

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TOPICS

1. **M0 CRPC**
   - Origin
   - What to do
2. **M1 HNPC**
   - High (high risk/high volume)
   - Low (low risk/low volume)
3. **M0 HNPC**
   - Ongoing trials

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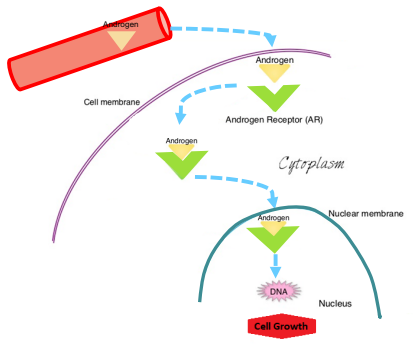
Hormonotherapies



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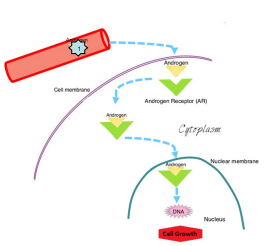

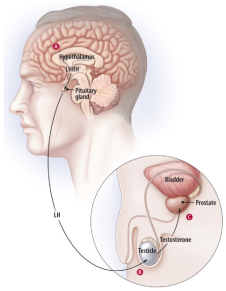

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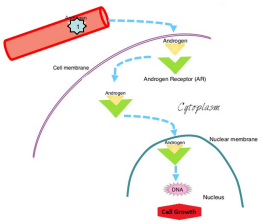

LHRH analogues
- Gosereline
- Triptoreline
- Leuproreline

LHRH antagonists
- Degarelix

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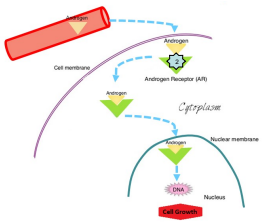

"Old School" Anti-androgens

Non-Steroidal
- Bicalutamide
- Flutamide

Steroidal
- Cyproterone

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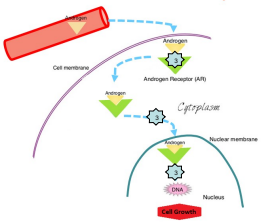

Novel Anti-androgens

Non-Steroidal
- Enzalutamide
- Apalutamide

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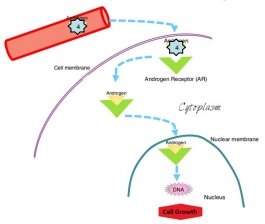

Androgen synthesis inhibitor

- Abiraterone
- (Ketoconazole)

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M0 CRPC : Origin

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M0 CRPC : Origin

→ **ADT for localized prostate cancer**

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M0 CRPC : Origin

VOLUME 32 · NUMBER 13 · MAY 1 2014
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Effectiveness of Primary Androgen-Deprivation Therapy for Clinically Localized Prostate Cancer

Arnold L. Potosky, Reina Haque, Andrea E. Cassidy-Bushrow, Marianne Ulcickas Yood, Miao Jiang, Huei-Ting Tsai, George Luta, Nancy L. Keating, Matthew R. Smith, and Stephen K. Van Den Eeden

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Table 2. Mortality Risk of Primary ADT Versus No Primary ADT Among Men Diagnosed With Clinically Localized Prostate Cancer Not Receiving Curative Intent Therapy Within 12 Months After Diagnosis

Mortality	Total No. of Deaths (n = 15,170)		Deaths According to Receipt of Primary ADT*				Unadjusted Risk Estimates			Conventional Cox Model Adjusted Risk Estimates†			Propensity Score Adjusted Estimates Using Standardized Mortality Ratio Weighting		
			Yes (n = 3,435)		No (n = 11,735)										
	No. of Patients	%	No. of Patients	%	No. of Patients	%	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
All-cause mortality	4,991	33	1,072	31	3,919	33	1.06	1.00 to 1.13	.06	1.04	0.97 to 1.11	.30	0.96	0.91 to 1.00	.06
Prostate cancer-specific mortality	1,049	7	492	14	557	5	2.91	2.67 to 3.18	< .001	1.03	0.89 to 1.19	.67	1.01	0.86 to 1.18	.93
Any cancer mortality	1,932	13	731	21	1,201	10	2.32	2.12 to 2.54	< .001	1.09	0.97 to 1.22	.11	1.02	0.90 to 1.14	.76
Cardiovascular mortality	1,384	9	445	13	939	8	1.81	1.61 to 2.02	< .001	1.11	0.95 to 1.27	.12	1.04	0.88 to 1.20	.57

Abbreviations: ADT, androgen-deprivation therapy; HR, hazard ratio; PSA, prostate-specific antigen.
*Received ADT monotherapy within 12 months of prostate cancer diagnosis.
†Multivariable analysis using a Cox proportional hazards model and imputed data for PSA, Gleason, and T stage. Median follow-up time was 61 months (54 months in primary-ADT group; 64 months in the no-primary-ADT group). HRs are adjusted for age, race-ethnicity, baseline PSA, Gleason score, T stage, sequence of prostate cancer, health plan, and 34 individual baseline comorbid conditions (yes/no) existing up to 2 years before diagnosis (see Appendix for list of these conditions).

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Table 1. Demographic and Clinical Characteristics of 15,170 Men Initially Diagnosed With Clinically Localized Prostate Cancer in Three Health Plans From 1995-2008 Who Did Not Receive Curative Intent Therapy Within 12 Months After Diagnosis

Characteristic	Primary ADT* (n = 3,435) No. of Patients	%	No Primary ADT (n = 11,735) No. of Patients	%	P†
Baseline PSA level, ng/mL					< .001
≤ 4	146	4.3	1,837	15.7	
4-10	857	25.0	6,046	51.5	
10-20	851	24.8	1,966	16.8	
> 20	1,430	41.6	1,194	10.2	
Unknown/missing	151	4.4	692	5.9	
Gleason score at first biopsy					< .001
≤ 6	1,043	30.4	7,313	62.3	
7	1,196	34.8	2,312	19.7	
8	463	13.5	427	3.6	
9-10	421	12.3	368	3.1	
Unknown/missing	312	9.1	1,315	11.2	
Tumor stage, extent					< .001
≤ T2a	1,592	46.4	8,273	70.5	
T2b	375	10.9	650	5.5	
≥ T2c	523	15.2	588	5.0	
Unknown/missing	945	27.5	2,224	19.0	
AUA risk group‡					< .001
Low	306	8.9	4,339	37.0	
Intermediate	957	27.9	3,182	27.1	
High	1,990	57.9	2,054	17.5	
Unknown/missing	182	5.3	2,160	18.4	

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M0 CRPC : Origin

EUROPEAN UROLOGY 53 (2008) 941–949
available at www.sciencedirect.com
journal homepage: www.europeanurology.com
European Association of Urology

Prostate Cancer

Using PSA to Guide Timing of Androgen Deprivation in Patients with T0–4 N0–2 M0 Prostate Cancer not Suitable for Local Curative Treatment (EORTC 30891)

Urs E. Studer[a,*], Laurence Collette[b], Peter Whelan[c], Walter Albrecht[d], Jacques Casselman[e], Theo de Reijke[f], Hartmut Knönagel[g], Wolfgang Loidl[h], Santiago Isorna[i], Subramanian K. Sundaram[j], Muriel Debois[b]
the EORTC Genitourinary Group

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… suggest that patients with a baseline PSA > 50 ng/ml are likely to die of PCa and therefore are good candidates for immediate ADT to prevent or delay complications from progressive disease, although survival is not significantly better than deferring ADT until symptoms occur.

… suggest that in patients with PSA between 8 and 50 ng/ml, ADT should be initiated as soon as PSADT < 12 months.

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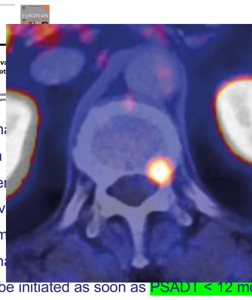

… suggest tha g/ml are likely to die of PCa immediate ADT to preve ssive disease, although surv erring ADT until symptom … suggest tha 50 ng/ml, ADT should be initiated as soon as PSADT < 12 months.

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M0 CRPC : Origin

→ ADT for localized prostate cancer

→ ADT for BCR after local treatment

M0 CRPC : Origin

Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial

Gillian M Duchesne, Henry H Woo, Julie K Bassett, Steven J Bowe, Catherine D'Este, Mark Frydenberg, Madeleine King, Leo Ledwich, Andrew Loblaw, Shawn Malone, Jeremy Millar, Roger Milne, Rosemary G Smith, Nigel Spry, Martin Stockler, Rodney A Syme, Keen Hun Tai, Sandra Turner*

Lancet Oncol 2016; 17: 727–37

Published Online
May 4, 2016

M0 CRPC : Origin

	Group one; PSA relapse (n=261)		Group two; de-novo incurable disease (n=32)	
	Delayed ADT arm (n=137)	Immediate ADT arm (n=124)	Delayed ADT arm (n=14)	Immediate ADT arm (n=18)
Age (years)	70·0 (50·7–85·0)	71·1 (54·0–88·0)	80·0 (76·4–84·9)	78·8 (59·4–88·9)
Previous therapy*				
Radiotherapy alone	88 (64%)	77 (62%)	..	..
Radical prostatectomy with or without radiotherapy	49 (36%)	47 (38%)	..	..
Neoadjuvant ADT	69 (50%)	56 (45%)	..	..
Relapse-free interval				
<2 years	42 (31%)	35 (28%)	..	..
≥2 years	95 (69%)	89 (72%)	..	..
PSA doubling time				
<10 months	57 (42%)	60 (48%)	6 (43%)	12 (67%)
≥10 months	80 (58%)	64 (52%)	8 (57%)	6 (33%)

M0 CRPC : Origin

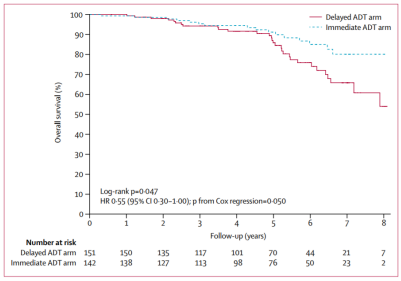

Figure 2: Overall survival
ADT=androgen-deprivation therapy. HR=hazard ratio.

M0 CRPC : Origin

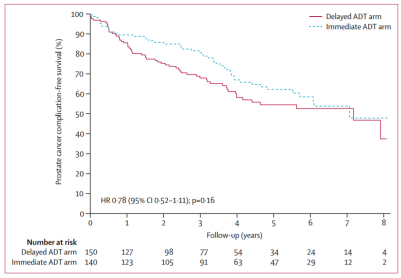

Figure 4: Time to first prostate cancer complication
ADT=androgen-deprivation therapy. HR=hazard ratio.

M0 CRPC : Origin

Mortality and Androgen Deprivation Therapy as Salvage Treatment for Biochemical Recurrence after Primary Therapy for Clinically Localized Prostate Cancer

Alex Z. Fu,* Huei-Ting Tsai, Reina Haque, Marianne Ulcickas Yood, Andrea E. Cassidy-Bushrow, Stephen K. Van Den Eeden,† Nancy L. Keating, Matthew R. Smith, Yingjun Zhou, David S. Aaronson and Arnold L. Potosky

From the Lombardi Comprehensive Cancer Center, Georgetown University Medical Center (AZF, HTT, YZ, ALP), Washington, D.C., Southern California Permanente Medical Group, Kaiser Permanente Research (RH), Pasadena and Kaiser Permanente Northern California (SKVDE, DSA), Oakland, California, Boston University School of Public Health (MUY), Brigham and Women's Hospital and Harvard Medical School (NLK) and Massachusetts General Hospital (MRS), Boston, Massachusetts, and Henry Ford Hospital (AEC-B), Detroit, Michigan

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Printed in U.S.A.
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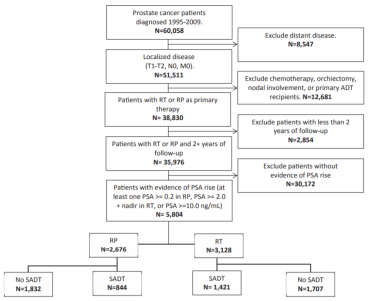

Study cohort. *RP*, radical prostatectomy. *RT*, radiotherapy.

M0 CRPC : Origin

Table 1. *Multivariate analysis of mortality risk of salvage ADT after PSA rise among men with newly diagnosed localized prostate cancer treated with primary prostatectomy or radiotherapy*

	Prostatectomy*				Radiotherapy†			
	All-Cause		Prostate Ca Specific		All-Cause		Prostate Ca Specific	
No. deaths (No./1,000 person-yrs):*	245	(11.3)	83	(3.8)	681	(27.4)	303	(12.2)
Salvage ADT	102	(14.4)	48	(6.8)	357	(30.1)	191	(16.1)
No salvage ADT	143	(9.6)	35	(2.4)	324	(25.0)	112	(8.6)
Unadjusted risk estimates:								
HR (95% CI)	1.71 (1.31–2.22)		3.20 (2.05–5.00)		1.60 (1.36–1.88)		2.49 (1.94–3.19)	
p Value	<0.001		<0.001		<0.001		<0.001	
Adjusted risk estimates:								
HR (95% CI)	0.97 (0.70–1.35)		1.18 (0.68–2.07)		0.84 (0.70–1.01)		1.06 (0.80–1.40)	
p Value	0.857		0.555		0.068		0.699	

Cox proportional hazards model adjusted for age, race/ethnicity, AUA risk group, tumor sequence, Elixhauser score, PSA doubling time, postoperative radiotherapy in prostatectomy group, adjuvant ADT, time from primary therapy to PSA rise, diagnosis year and health plan.
* Total of 844 patients with and 1,832 without salvage ADT.
† Total of 1,421 patients with and 1,707 without salvage ADT.

M0 CRPC : Origin

Table 3. *Subgroup analyses of salvage ADT on all-cause and prostate cancer specific mortality risk*

	All-Cause		Prostate Ca Specific	
	Prostatectomy HR (95% CI)	Radiotherapy HR (95% CI)	Prostatectomy HR (95% CI)	Radiotherapy HR (95% CI)
Age at PSA rise:				
64 or Less	1.66 (0.85–3.22)	1.10 (0.67–1.81)	1.24 (0.45–3.41)	1.30 (0.62–2.75)
65–74	0.72 (0.41–1.28)	1.03 (0.76–1.39)	0.72 (0.26–1.98)	1.00 (0.66–1.52)
75 or Greater	0.72 (0.39–1.34)	0.70 (0.54–0.92)*	1.21 (0.36–4.06)	1.04 (0.66–1.63)
Race:				
White	0.97 (0.65–1.45)	0.74 (0.60–0.91)†	1.08 (0.57–2.07)	0.94 (0.68–1.28)
Black	0.65 (0.31–1.35)	1.10 (0.65–1.86)	1.58 (0.27–9.17)	1.87 (0.78–4.46)
Hispanic	3.13 (0.61–16.15)	1.64 (0.70–3.85)	Limited No. cases‡	1.29 (0.21–7.79)
Elixhauser score:				
0	1.31 (0.74–2.34)	0.88 (0.63–1.22)	0.97 (0.39–2.39)	0.91 (0.56–1.49)
1	1.02 (0.53–1.95)	0.74 (0.53–1.04)	1.08 (0.33–3.54)	0.94 (0.57–1.55)
2+	0.68 (0.38–1.21)	0.97 (0.71–1.33)	1.29 (0.41–4.00)	1.51 (0.93–2.46)
Risk group:				
Low	0.26 (0.06–1.21)	0.89 (0.45–1.78)	Limited No. cases‡	Limited No. cases‡
Intermediate	1.34 (0.82–2.20)	0.76 (0.57–1.00)	3.29 (1.29–8.36)*	1.37 (0.86–2.17)
High	0.87 (0.53–1.42)	0.98 (0.69–1.41)	0.83 (0.25–2.76)	0.78 (0.45–1.37)
PSA doubling time (mos):				
0.0–Less than 9.0	0.35 (0.20–0.63)†	0.62 (0.48–0.80)†	0.43 (0.21–0.91)*	0.65 (0.47–0.90)†
9.0–Less than 15.0	0.32 (0.11–0.92)*	0.91 (0.59–1.42)	Limited No. cases‡	1.25 (0.54–2.89)
15.0–Less than 36.0	1.74 (0.72–4.23)	1.19 (0.79–1.77)	Limited No. cases‡	Limited No. cases‡
36.0+ (no rise)	0.78 (0.21–2.90)	1.08 (0.24–4.82)	Limited No. cases‡	Limited No. cases‡

Each cell represents result of separate Cox proportional hazards model adjusted for age, race/ethnicity, AUA risk group, tumor sequence, Elixhauser score, PSA doubling time, postoperative radiotherapy in prostatectomy group only, adjuvant ADT, time from primary therapy to PSA rise, diagnosis year and health plan
* p <0.05.
† p <0.01.
‡ Model could not converge.

M0 CRPC : Origin

- → **ADT for localized prostate cancer**
- → **ADT for BCR after local treatment**
- → **ADT neo-adjuvant to radiation**
  - Primary, high risk: 36 months
  - Primary, intermediate risk: 6 months
  - Salvage: 6 months

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  - Primary, high risk: 36 months
  - Primary, intermediate risk: 6 months
  - Salvage: 6 months

M0 CRPC : Origin

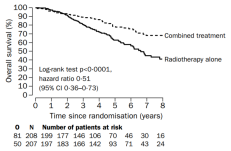
Articles

Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial

Michel Bolla, Laurence Collette, Léo Blank, Padraig Warde, Jean Bernard Dubois, René-Olivier Mirimanoff, Guy Storme, Jacques Bernier, Abraham Kuten, Cora Sternberg, Johan Mattelaer, José Lopez Torecilla, J Rafael Pfeffer, Carmel Lino Cutajar, Alfredo Zurlo, Marianne Pierart

Interpretation Immediate androgen suppression with an LHRH analogue given during and for 3 years after external irradiation improves disease-free and overall survival of patients with locally advanced prostate cancer.

Lancet 2002; **360:** 103–08



M0 CRPC : Origin

EUROPEAN UROLOGY 74 (2018) 432–441

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer – Editor's Choice
Editorial by Wanling Xie and Anthony V. D'Amico on pp. 442–443 of this issue

Duration of Androgen Deprivation Therapy in High-risk Prostate Cancer: A Randomized Phase III Trial

Abdenour Nabid [a,], Nathalie Carrier [a], André-Guy Martin [b], Jean-Paul Bahary [c], Céline Lemaire [d], Sylvie Vass [e], Boris Bahoric [f], Robert Archambault [g], François Vincent [b], Redouane Bettahar [f], Marie Duclos [f], Marie-Pierre Garant [a], Luis Souhami [i]*

[a] Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada; [b] Centre Hospitalier Universitaire de Québec, Québec city, QC, Canada; [c] Centre Hospitalier Universitaire de Montréal, Montréal, QC, Canada; [d] Hôpital Maisonneuve-Rosemont de Montréal, Montréal, QC, Canada; [e] Centre de Santé et Services Sociaux de Chicoutimi, Chicoutimi, QC, Canada; [f] Hôpital Général Juif de Montréal, Montréal, QC, Canada; [g] Hôpital de Gatineau, Gatineau, QC, Canada; [h] Centre Hospitalier Régional de Trois-Rivières, Trois-Rivières, QC, Canada; [i] Centre Hospitalier Régional de Rimouski, Rimouski, QC, Canada; [j] McGill University Health Centre, Montréal, QC, Canada*

M0 CRPC : Origin

Randomization 10/2000 to 01/2008

630 Patients

Arm 1 (310) : ADT* 36 months + RT**
Arm 2 (320) : ADT* 18 months + RT**

*ADT: Bicalutamide 50 mg id x 1 month + Goserelin 10.8 mg q 3 months
**RT: pelvis 44 Gy - 4 ½ weeks, prostate 70 Gy - 7 weeks

Median Follow-up 9.4 years

PRESENTED AT ASCO ANNUAL MEETING '17 #ASCO17 Presented by: A. Nabid
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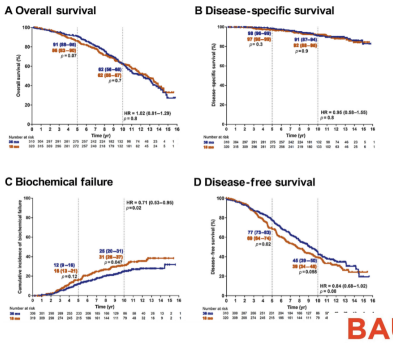
M0 CRPC : Origin



M0 CRPC : Origin

Quality of Life Results	Baseline		End of QoLQ		Overall p-value <0.01
	Arm 1 (n=269)	Arm 2 (n=273)	Arm 1 (n=170)	Arm 2 (n=178)	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Physical	90.4 ± 13.8	91.1 ± 14.5	82.8 ± 19.8	86.0 ± 19.7	0.0008
Trouble to take a long walk (Q2)	75.7 ± 32.3	79.5 ± 31.2	62.2 ± 37.3	68.9 ± 37.4	0.0001
Need to stay in bed or chair (Q4)	95.3 ± 15.3	95.1 ± 15.1	91.7 ± 19.5	92.9 ± 20.0	0.0045
Emotional	81.7 ± 20.9	82.5 ± 20.0	88.2 ± 18.2	88.8 ± 15.1	0.0002
Feel tense (Q21)	81.5 ± 23.6	81.9 ± 23.4	87.5 ± 21.7	88.1 ± 19.2	0.0012
Worry (Q22)	76.2 ± 26.7	77.9 ± 25.8	86.3 ± 23.9	85.9 ± 20.9	0.0005
Feel depressed (Q24)	85.0 ± 24.3	85.2 ± 22.3	90.0 ± 22.3	91.1 ± 16.8	0.0015
Social	93.9 ± 14.8	95.6 ± 12.6	91.8 ± 20.9	94.4 ± 16.4	0.0087
Fatigue	15.6 ± 19.7	14.5 ± 17.9	19.5 ± 22.3	16.9 ± 19.3	0.0025
Felt weak (Q12)	12.8 ± 22.3	11.0 ± 19.4	14.8 ± 24.6	11.2 ± 20.3	0.0003
Need to be closed to a toilet (Q35)	6.5 ± 17.3	6.3 ± 16.7	9.0 ± 21.4	7.0 ± 17.7	0.0008
Blood in stools (Q42)	1.0 ± 6.4	1.2 ± 6.3	2.0 ± 8.8	2.2 ± 9.0	0.0026
Treatment	7.3 ± 9.8	7.8 ± 10.3	10.4 ± 13.0	9.9 ± 11.6	0.0001
Hot flushes (Q44)	8.8 ± 20.8	9.0 ± 20.7	14.3 ± 25.3	13.3 ± 24.4	<.0001
Sore or enlarged nipples or breasts (Q45)	1.1 ± 6.7	1.0 ± 5.7	4.7 ± 14.7	3.7 ± 13.8	<.0001
Sexual active	27.8 ± 27.3	28.4 ± 26.9	12.2 ± 18.6	15.5 ± 23.7	<.0001
Interested in sex (Q50)	34.7 ± 32.2	35.0 ± 32.0	16.1 ± 24.7	19.4 ± 28.9	<.0001
Sexually active (with or without intercourse) (Q51)	20.9 ± 28.4	21.7 ± 27.9	8.3 ± 17.4	11.6 ± 23.7	<.0001
Sex enjoyable (Q52) [*]	60.9 ± 32.2	64.2 ± 29.9	48.5 ± 22.2	59.2 ± 30.7	0.0012

PRESENTED AT ASCO ANNUAL MEETING '17 #ASCO17 Presented by: A. Nabid
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M0 CRPC : Origin

6.2.3.4 *Guidelines for radical treatment of high-risk localised disease*

Recommendation	Strength rating
Radical Prostatectomy (RP)	
Offer RP to patients with high-risk localised PCa and a life expectancy of > ten years only as part of multi-modal therapy.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND in high-risk disease.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapeutic treatments	
In patients with high-risk localised disease, use external-beam radiation therapy (EBRT) with 76-78 Gy in combination with long-term androgen deprivation therapy (ADT) (two to three years).	Strong
In patients with high-risk localised disease, use EBRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (two to three years).	Weak
Other therapeutic options outside surgery and radiotherapy	
Do not offer either whole gland or focal treatment to high-risk patients.	Strong
Do not use ADT monotherapy in asymptomatic patients.	Strong

M0 CRPC : Origin

→ ADT for localized prostate cancer

→ **ADT for BCR after local treatment**

→ **ADT neo-adjuvant to radiation**

- Primary, high risk: 18-24 months
- Primary, intermediate risk: 6 months
- Salvage: 6 months

M0 CRPC : What to do

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M0 CRPC : What to do

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Fred Saad, M.D., Simon Chowdhury, M.B., B.S., Ph.D., Stéphane Oudard, M.D., Ph.D., Boris A. Hadaschik, M.D., Julie N. Graff, M.D., David Olmos, M.D., Ph.D., Paul N. Mainwaring, M.B., B.S., M.D., Ji Youl Lee, M.D., Hiroji Uemura, M.D., Ph.D., Angela Lopez-Gitlitz, M.D., Géralyn C. Trudel, Ph.D., Byron M. Espina, B.S., Youyi Shu, Ph.D., Youn C. Park, Ph.D., Wayne R. Rackoff, M.D., Margaret K. Yu, M.D., and Eric J. Small, M.D., for the SPARTAN Investigators*

N ENGL J MED 378;15 NEJM.ORG APRIL 12, 2018

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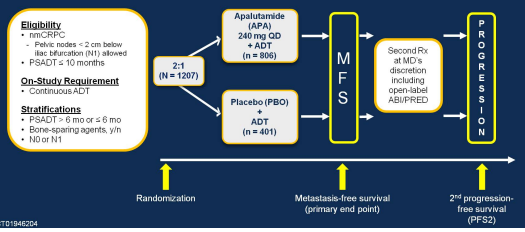
M0 CRPC : What to do

SPARTAN — Overall Study Design

Phase 3 Placebo-Controlled, Randomized International Study



NCT01946204

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M0 CRPC : What to do

Results

Patient Demographics and Disease Characteristics

	APA (n = 806)	PBO (n = 401)
Median age, yrs	74.0	74.0
Median time from initial diagnosis to randomization, yrs	7.95	7.85
Median PSADT, mos	4.40	4.50
PSADT, % ≤ 6 mos > 6 mos	 71 29	 71 29
Bone-sparing agent use, % Yes No	 10 90	 10 90
Nodal status at study entry, % N0 N1	 83 17	 84 16
Prior prostate cancer therapy, % Definitive local therapy Bicalutamide First-generation antiandrogen	 77 27 73	 77 27 72

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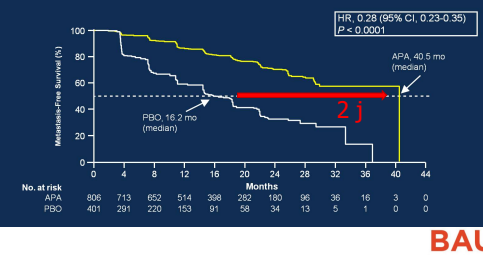
M0 CRPC : What to do

Primary End Point: Metastasis-Free Survival

72% risk reduction of distant progression or death



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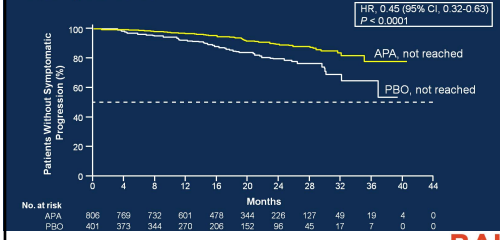
M0 CRPC : What to do

Secondary End Point: Time to Symptomatic Progression

55% risk reduction of SRE, pain progression/worsening sx, clinically significant sx requiring intervention



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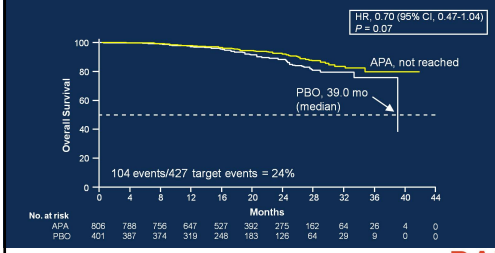
M0 CRPC : What to do

Secondary End Point: Overall Survival
30% risk reduction of death



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M0 CRPC : What to do

Results: Treatment Associated Adverse Events

	APA (n = 803)		PBO (n = 398)	
	All	Gr 3/4	All	Gr 3/4
Fatigue	30.4%	0.9%	21.1%	0.3%
Rash	23.8%	5.2%	5.5%	0.3%
Weight loss	16.1%	1.1%	6.3%	0.3%
Arthralgia	15.9%	0	7.5%	0
Fall	15.6%	1.7%	9.0%	0.8%
Fracture	11.7%	2.7%	6.5%	0.8%
Hypothyroidism	8.1%	0	2.0%	0
Seizure	0.2%	0	0	0

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M0 CRPC : What to do

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 28, 2018 VOL. 378 NO. 26

Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer

Maha Hussain, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Per Rathenborg, M.D., Neal Shore, M.D., Ubirajara Ferreira, M.D., Ph.D., Petro Ivashchenko, M.D., Eren Demirhan, Ph.D., Katharina Modelska, M.D., Ph.D., De Phung, B.S., Andrew Krivoshik, M.D., Ph.D., and Cora N. Sternberg, M.D.

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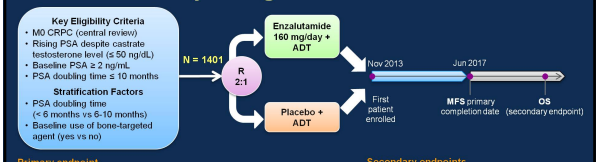
M0 CRPC : What to do

PROSPER Study Design



Primary endpoint
- MFS (defined as time from randomization to radiographic progression or death within 112 days of treatment discontinuation)

Statistical Design:
- Target difference in Kaplan-Meier estimated median MFS of 9 months (24 months vs 33 months)
- Target of 440 events provides 90% power to detect a target HR of 0.72

Secondary endpoints
- Safety
- Time to PSA progression
- Time to use of new antineoplastic therapy
- OS
- PSA response
- Quality of life

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; R, randomization.

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M0 CRPC : What to do

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Enzalutamide Group (N = 933)	Placebo Group (N = 468)
Age — yr		
Median	74	73
Range	50–95	53–92
ECOG performance-status score — no. (%)†		
0	747 (80)	382 (82)
1	185 (20)	85 (18)
Missing data	1 (<1)	1 (<1)
Serum PSA value — ng/ml		
Median	11.1	10.2
Range	0.8–1071.1	0.2–467.5
PSA doubling time		
Median — mo	3.8	3.6
Range — mo	0.4–37.4	0.5–71.8
Distribution — no. (%)		
<6 mo	715 (77)	361 (77)
≥6 mo	217 (23)	107 (23)
Missing data	1 (<1)	0
Use of bone-targeting agent — no. (%)		
No	828 (89)	420 (90)
Yes	105 (11)	48 (10)

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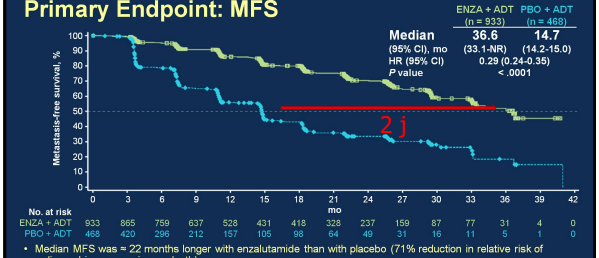
M0 CRPC : What to do

Primary Endpoint: MFS



- Median MFS was ≈ 22 months longer with enzalutamide than with placebo (71% reduction in relative risk of radiographic progression or death)

Abbreviations: CI, confidence interval; ENZA, enzalutamide; NR, not reached; PBO, placebo.

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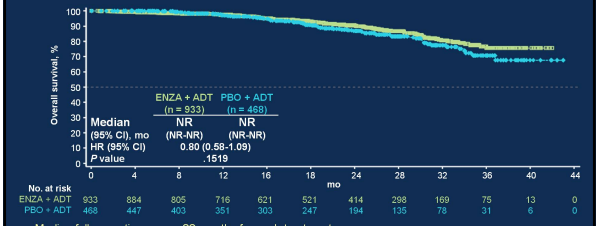
M0 CRPC : What to do

Overall Survival: First Interim Analysis



- Median follow-up time was ≈ 22 months for each treatment arm
- There was a 20% reduction in the relative risk of death with enzalutamide vs placebo

M0 CRPC : What to do

Adverse Events*

Event, No. (%)	Enzalutamide + ADT (n = 930)	Placebo + ADT (n = 465)
Any adverse event	808 (87%)	360 (77%)
Any grade ≥ 3 adverse event	292 (31%)	109 (23%)
Grade ≥ 3 adverse events occurring in ≥ 1% of patients in the enzalutamide group		
Hypertension	43 (5%)	10 (2%)
Fatigue	27 (3%)	3 (1%)
Hematuria	16 (2%)	13 (3%)
Fall	12 (1%)	3 (1%)
Asthenia	11 (1%)	1 (< 1%)
Pneumonia	10 (1%)	2 (< 1%)
Syncope	10 (1%)	2 (< 1%)
Anemia	9 (1%)	6 (1%)
Urinary tract infection	7 (1%)	3 (1%)
Cataract	7 (1%)	2 (< 1%)
Cardiac failure	7 (1%)	1 (< 1%)
Acute myocardial infarction	6 (1%)	2 (< 1%)
Adenocarcinoma of the colon	5 (1%)	2 (< 1%)
Hyperglycemia	5 (1%)	1 (< 1%)
Hyponatremia	5 (1%)	1 (< 1%)
Coronary artery disease	5 (1%)	0

Adverse events as the primary reason for treatment discontinuation:

- Enzalutamide, n = 87 (9%)
- Placebo, n = 28 (6%)

Deaths due to adverse event on trial irrespective of attribution:

- Enzalutamide, n = 32 (3%)
- Placebo, n = 3 (1%)

*Adverse events were collected up to 30 days after the last dose of study drug.

M0 CRPC : What to do

Clinical benefit:

→ Cure :

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M0 CRPC : What to do

Clinical benefit:

→ Cure : Probably not

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M0 CRPC : What to do

Clinical benefit:

→ Cure : Probably not

→ Improving OS

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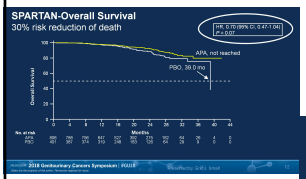
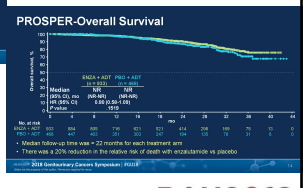
M0 CRPC : What to do





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M0 CRPC : What to do

Clinical benefit:

→ **Cure : Probably not**

→ **Improving OS : Maybe but too early**

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M0 CRPC : What to do

Clinical benefit:

→ **Cure : Probably not**

→ **Improving OS : Maybe but too early**

→ **Improving QoL :**

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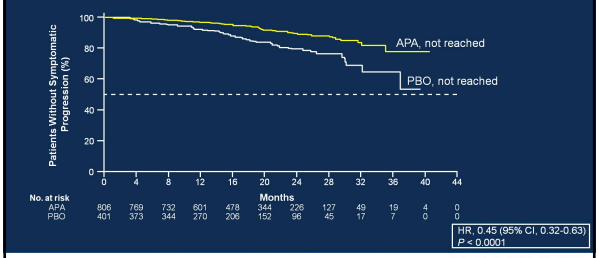
M0 CRPC : What to do

SPARTAN-Time to Symptomatic Progression
55% risk reduction of SRE, pain progression/worsening sx, clinically significant sx



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M0 CRPC : What to do

Clinical benefit:

→ **Cure : Very improbable**

→ **Improving OS : Maybe but too early**

→ **Improving QoL : Delaying Symptoms**

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M0 CRPC : What to do

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M1 HNPC : High/Low

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M1 HNPC : High

Definition		
CHAARTED (volume)	High	Visceral metastases AND/OR ≥4 Bone metastases (≥1 outside vertebral column or pelvis)
LATITUDE (risk)	High	≥2 high risk features • ≥3 Bone metastases • Visceral metastases • ≥Gleason 8

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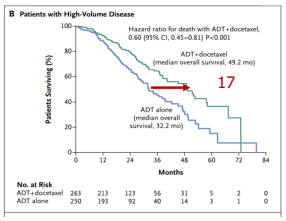
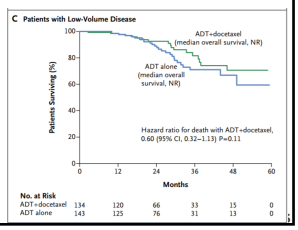
M1 HNPC : High

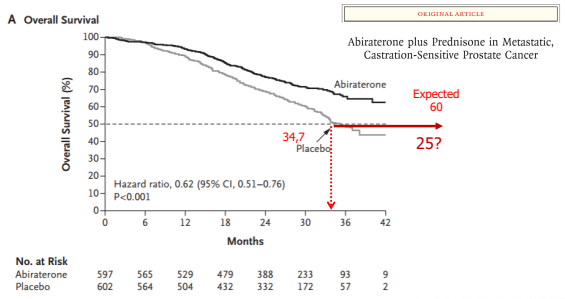


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer



M1 HNPC : High



The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

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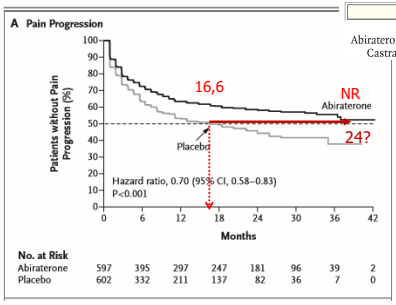
M1 HNPC : High



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Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

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M1 HNPC : High

High volume / High risk metastatic hormone-naive prostate cancer

DO NOT LIMIT TREATMENT TO ADT
GIVE DOC or AA!!

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M1 HNPC : Low

Low volume/ Low risk metastatic hormone-naive prostate cancer

Recommendations	Strength rating
In M1 symptomatic patients, offer immediate systemic treatment to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis).	Strong
Offer luteinizing hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
In M1 asymptomatic patients, offer immediate systemic treatment to improve survival, defer progression to a symptomatic stage and prevent serious disease progression-related complications.	Strong
In M1 asymptomatic patients, discuss deferred castration with a well-informed patient since it lowers the treatment side-effects, provided the patient is closely monitored.	Weak
In M1 patients treated with a LHRH agonist, offer short-term administration of anti-androgens to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer anti-androgen monotherapy for M1 disease.	Strong

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M1 HNPC : Low

Low volume/ Low risk metastatic hormone-naive prostate cancer

⇩

Other systemic treatment?
Local treatment?

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M1 HNPC : Low

Role of Abiraterone Acetate + Prednisolone + ADT in High and Low Risk Metastatic Hormone Naïve Prostate Cancer

Mr Alex Hoyle MBChB MRCS
(Christie GenitoUrinary Research Group Fellow, UK)

Adnan Ali, Nick James, Chris Parker, Adrian Cook, Gert Attard, Simon Chowdhury, Bill Cross, David Dearnaley, Johann de Bono, Clare Gilson, Silke Gillessen, Rob Jones, David Matheson, Malcolm Mason, Alastair Ritchie, Martin Russell, Max Parmar, Matt Sydes, Noel Clarke;
for the STAMPEDE trial

esmo.org

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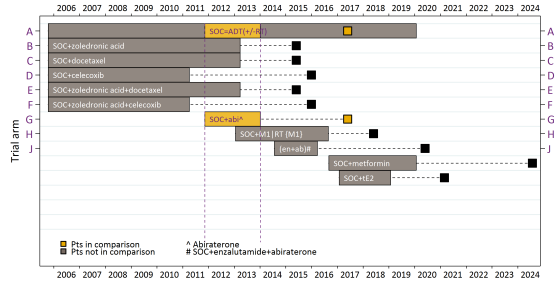
M1 HNPC : Low

STAMPEDE: Abiraterone comparisons



A = ~900 pts --> ~267 primary outcome measure events
G = ~900 pts

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M1 HNPC : Low

PATIENT CHARACTERISTICS

901 patients stratified

LATITUDE criteria

Median Follow up
- **41.5 months**

	Low Risk (n=428)			High Risk (n=473)		
	ADT (n=225)	ADT+AAP (n=203)	p-value	ADT (n=232)	ADT+AAP (n=241)	p-value
Age at randomization Median (Range)	66 (60-84)	66 (45-84)	0.37	67 (39-84)	67 (42-85)	0.79
PSA prior to ADT Median (Range)	51 (0.2-5900)	70 (1.5-4660)	0.14	174 (3.3-8028)	126 (3.0-21460)	0.28
WHO performance status 0 1-2	174 49	158 50	0.44	163 69	177 64	0.44
Gleason Sum <=7 8-10	107 113	102 100	0.93	3 229	2 238	0.62
Primary Tumour stage ≤T2 T3 T4 TX	26 133 54 7	23 125 47 13	0.66	23 116 68 25	21 141 59 20	0.32
Regional node status N0 N+ +++	80 125 15	66 130 12	0.49	78 137 17	84 131 26	0.36
Primary or Progression N+ now Previously treated	202 18	190 18	0.86	220 3	238 3	0.96
Node Bone Visceral Bone + Node Bone + Visceral Visceral + Node Bone + Node + Visceral	47 140 1 32 - - -	55 127 1 24 - - 1	0.55	154 1 60 9 1 7	169 1 52 12 1 7	0.77

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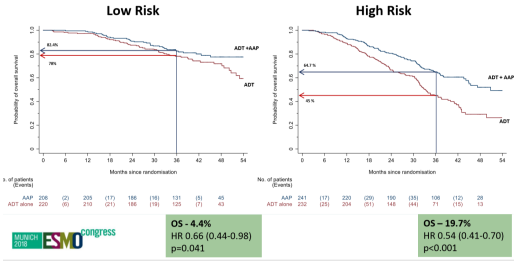
M1 HNPC : Low

RESULTS: OVERALL SURVIVAL



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

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

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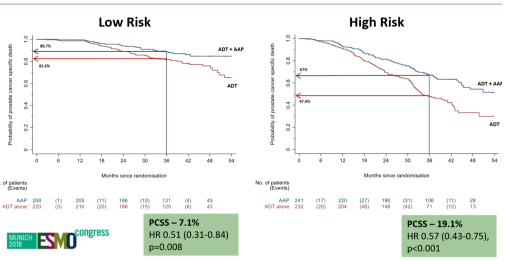
M1 HNPC : Low

RESULTS: PROSTATE CANCER SPECIFIC SURVIVAL



PCSS – 7.1%
HR 0.51 (0.31-0.84)
p=0.008

PCSS – 19.1%
HR 0.57 (0.43-0.75),
p<0.001

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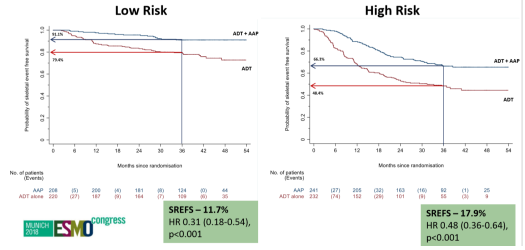
M1 HNPC : Low

RESULTS: SKELETAL RELATED EVENT FREE SURVIVAL



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M1 HNPC : Low

SUMMARY

- Abiraterone + Prednisolone + ADT improves all survival endpoints in mHNPC

Overall	Overall Survival (HR)	p value
STAMPEDE M1 Cohort	**0.61** (0.49-0.79)	p<0.001

- No evidence of subgroup interaction
  - All endpoints
  - Stratification independent

Low	Overall Survival (HR)	p value
STAMPEDE Low Risk	**0.66** (0.44-0.98)	p=0.041
STAMPEDE Low Volume	**0.64** (0.42-0.97)	p=0.034

- Individual risk/volume variation
  - 18.2%

High	Overall Survival (HR)	p value
LATITUDE High Risk	**0.62** (0.51-0.76)	<0.001
STAMPEDE High Risk	**0.54** (0.41-0.74)	<0.001
STAMPEDE High Volume	**0.60** (0.46-0.78)	<0.001

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M1 HNPC : Low

Low volume / Low risk metastatic hormone-naive prostate cancer

"PCa cT2 N0M1 gl 3+4 2 bone mets"

"previously treated Pca with 2 bone mets"

GIVE ADT + AA!!

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M1 HNPC : Low

Low volume / Low risk metastatic hormone-naive prostate cancer

"PCa cT2 N0M1 gl 3+4 2 bone mets"

"previously treated Pca with 2 bone mets"

GIVE ADT + AA!!

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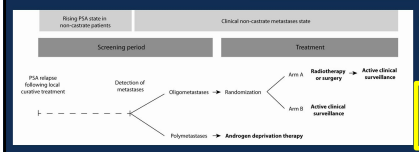
M1 HNPC : Low

STOMP trial

JOURNAL OF CLINICAL ONCOLOGY — ORIGINAL REPORT

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial



Primary endpoint:
- ADT-free survival

Stratification
- PSA DT
- Location of mets

Reason to start ADT
- Symptoms
- Local progression
- Polymetastatic progression

Ost et al, JCO 2017

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M1 HNPC : Low

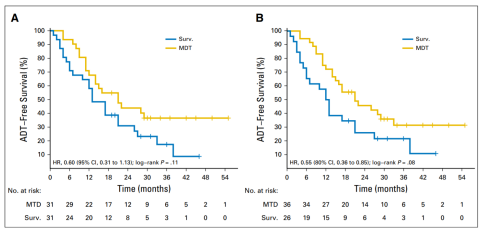

Fig 2. Kaplan-Meier plot comparing androgen deprivation therapy (ADT)-free survival of surveillance versus metastasis-directed therapy (MDT) for (A) the intention-to-treat analysis and (B) the per-protocol analysis. HR, hazard ratio; Surv., surveillance.

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M1 HNPC : Low

Table 2. Indications for Starting Androgen Deprivation Therapy

Indication	Surveillance (n = 31)	Metastasis-Directed Therapy (n = 31)
Not started yet	6 (19)	12 (39)
Polymetastatic progression	16 (55)	19 (61)
Local progression	6 (23)	0 (0)
Symptomatic progression	3 (10)*	0 (0)

NOTE. Data are presented as No. (%).
*Two patients with symptomatic progression also showed local and polymetastatic progression.

81% 61%

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81% 61%
20%

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23%

81% 61%
20%

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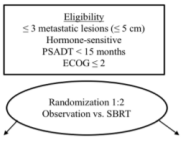
M1 HNPC : Low

STUDY PROTOCOL Open Access

A phase II randomized trial of Observation versus stereotactic ablative RadiatIon for OLigometastatic prostate CancEr (ORIOLE)



Primary endpoint: To radiographically determine the proportion of men who have progressed after 6 months from randomization to observation versus SBRT who have oligometastatic prostate cancer.

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M1 HNPC : Low

Low volume / Low risk metastatic hormone-naive prostate cancer

"previously treated Pca with 2 bone mets"

No ADT and MDT!!

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M1 HNPC : Low

Low volume / Low risk metastatic hormone-naive prostate cancer

"PCa cT2 N0M1 gl 3+4 2 bone mets"

GIVE ADT + AA!!

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M1 HNPC : Low

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

Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attard, Simon Chowdhury, William Cross, David P Dearnaley, Silke Gillessen, Clare Gilson, Robert J Jones, Ruth E Langley, Zafar I Malik, Malcolm D Mason, David Matheson, Robin Millman, J Martin Russell, George N Thalmann, Claire L Amos, Roberto Alonzi, Amit Bahl, Alison Birtle, Omar Din, Hassan Douis, Chinnamani Eswar, Joanna Gale, Melissa R Gannon, Sai Jonnada, Sara Khaksar, Jason F Lester, Joe M O'Sullivan, Omi A Parikh, Ian D Pedley, Delia M Pudney, Denise J Sheehan, Narayanan Nair-Sivhari, Anna T H Tran, Mahesh K B Parmar*, Matthew R Sydes*, on behalf of the Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators†

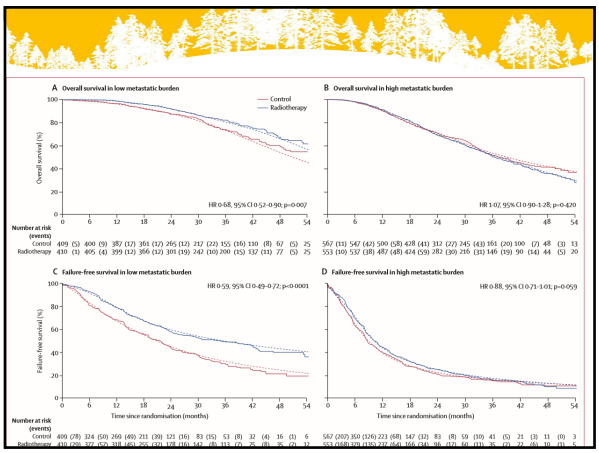
www.thelancet.com Published online October 21, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32486-3

M1 HNPC : Low

	Control (n=1029)	Radiotherapy (n=1032)
Age at randomisation (years)	68 (63-73)	68 (63-73)
Range	37-86	45-87
WHO performance status		
0	732 (71%)	734 (71%)
1-2	297 (29%)	298 (29%)
T category at randomisation		
T0	0 (0%)	2 (<1%)
T1	12 (1%)	12 (1%)
T2	84 (9%)	89 (9%)
T3	585 (62%)	603 (63%)
T4	260 (28%)	246 (26%)
TX	88	80
N category at randomisation		
N0	345 (36%)	344 (36%)
N+	620 (64%)	620 (64%)
NX	64	68
Metastatic burden		
Low	409 (42%)	410 (43%)
High	567 (58%)	553 (57%)
Not classified	53	69

M1 HNPC : Low

	Control (n=1029)	Radiotherapy (n=1032)
(Continued from previous column)		
Sites of metastases		
Bone	919 (89%)	917 (89%)
Liver	23 (2%)	19 (2%)
Lung	42 (4%)	48 (5%)
Distant lymph nodes	294 (29%)	304 (29%)
Other	35 (3%)	33 (3%)
Gleason sum score		
≤7	173 (17%)	172 (18%)
8-10	820 (83%)	810 (82%)
Unknown	36	50
PSA before androgen deprivation therapy (ng/mL)	98 (30-316)	97 (33-313)
Range	1-20 590	1-11 156



M1 HNPC : Low

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

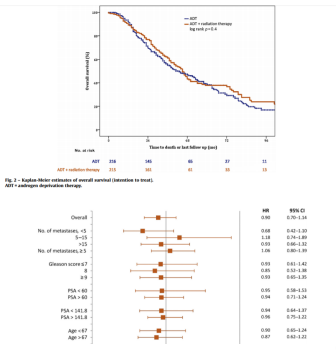
Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial

Liselotte M.S. Boevé[a,b,*], Maarten C.C.M. Hulshof[c], André N. Vis[b], Aeilko H. Zwinderman[d], Jos W.R. Twisk[e], Wim P.J. Witjes[f], Karl P.J. Delaere[g], R. Jeroen A. van Moorselaar[b], Paul C.M.S. Verhagen[h], George van Andel[a]

[a] Department of Urology, OLVG, Amsterdam, The Netherlands; [b] Department of Urology, VU university Medical Centre, Amsterdam, The Netherlands; [c] Department of Radiotherapy, Academic Medical Centre, Amsterdam, The Netherlands; [d] Department of Epidemiology and Biostatistics, Academic Medical Centre, Amsterdam, The Netherlands; [e] Department of Epidemiology and Biostatistics, VU university Medical Centre, Amsterdam, The Netherlands; [f] CuroTrial SMO & Research BV, Arnhem, The Netherlands; [g] Department of Urology, Zuyderland Medical Centre, Heerlen, The Netherlands; [h] Department of Urology, Erasmus Medical Centre, Rotterdam, The Netherlands

M1 HNPC : Low



M1 HNPC : Low

Low volume / Low risk metastatic hormone-naive prostate cancer

"PCa cT2 N0M1 gl 3+4 2 bone mets"

Radiotherapy on the prostate

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M1 HNPC : Low

Low volume / Low risk metastatic hormone-naive prostate cancer

"PCa cT2 N0M1 gl 3+4 2 bone mets"

Surgery on the prostate??

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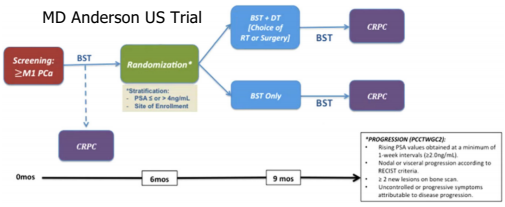
M1 HNPC : Low

MD Anderson US Trial



*Thrombone *g-RAMPP

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M1 HNPC : My opinion

High volume / High Risk

Low volume / Low Risk

- ***Primary unTx***
- ***Primary Tx***

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M1 HNPC : My opinion

High volume / High Risk ***ADT lifelong + Doc/AA***

Low volume / Low Risk

- ***Primary unTx***
- ***Primary Tx***

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M1 HNPC : My opinion

High volume / High Risk ***ADT lifelong + Doc/AA***

Low volume / Low Risk

- ***Primary unTx*** ***ADT 18-24 mnths+ RT Prostate/Pelvis + MDT***
- ***Primary Tx***

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M1 HNPC : My opinion

High volume / High Risk ***ADT lifelong + Doc/AA***

Low volume / Low Risk

- ***Primary unTx*** ***ADT 18-24 mnths+ RT Prostate/Pelvis + MDT***
- ***Primary Tx*** ***MDT***

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Future : M0 HNPC

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Future : M0 HNPC

Enzalutamide in Androgen Deprivation Therapy 24 mths With Radiation Therapy for High Risk, Clinically Localised, Prostate Cancer (ENZARAD)

An Efficacy and Safety Study of JNJ-56021927 (Apalutamide) 24 mths in High-risk Prostate Cancer Subjects Receiving Primary Radiation Therapy: ATLAS

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Hormonotherapies

Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.