Management of Advanced PCa in Senior Adults: the new mCRPC Landscape

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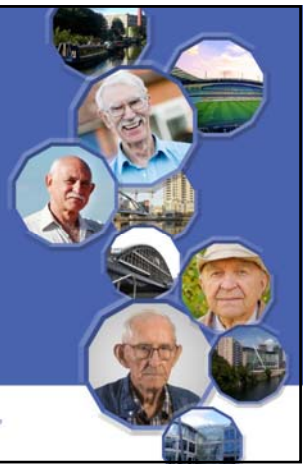


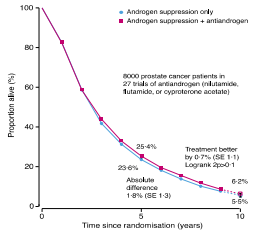
12th meeting of the International Society of Geriatric Oncology
October 25-27, 2012 | Manchester, United Kingdom

Management of advanced PCa: specific considerations for senior adults (1/4)

- First-line androgen deprivation therapy
- First-line chemotherapy
- Progression after first-line docetaxel
- Palliative therapy for bone metastases

Management of advanced prostate cancer: Specific considerations for senior adults (1)

First-line ADT **monotherapy** is the standard of care



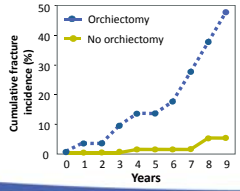
- Maximum androgen blockade results in a small advantage in OS, which is not clinically relevant
- Maximum androgen blockade has significant effects on QoL

Prostate Cancer Trialists Collaborative Group. Lancet 2000;355:1491–8
OS: overall survival. QoL: quality of life

Androgen deprivation therapy: adverse events

- Bone loss with increased risk of fracture[1,2]
  - ❖ Baseline bone density
  - ❖ Prevent risk of osteoporosis
- Increased risk of diabetes[3]
- Increased risk of fatal cardiac events[4–6]

Caution in patients with:
- ❖ History of stroke
- ❖ Chronic heart failure
- ❖ Myocardial infarction



LESS IS BETTER!

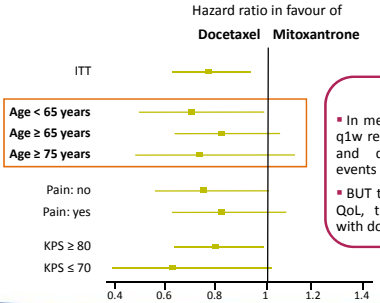
1. Daniell et al. J Urol 1997;157:439–44
2. Shahinian VB et al. N Engl J Med 2005;352:154–64
3. Keating NL et al. J Clin Oncol 2006;27:4448–56
4. D'Amico et al. J Clin Oncol 2007;25:2420–25
5. Hayes et al. BJU Int 2010;106:979–85
6. Nguyen et al. Int J Radiat Oncol Biol Phys 2012;82:1411-6

Management of advanced PCa: Specific considerations for senior adults (2/4)

- First-line androgen deprivation therapy
- First-line chemotherapy
  - ❖ Docetaxel is the standard of care
  - ❖ Provides survival advantage in older men[1]
  - ❖ Weekly regimen for frail patients?[2]
- Progression after first-line docetaxel
- Palliative therapy for bone metastases

1. Berthold D et al. J Clin Oncol 2008;26:242-5
2. Droz JP et al. BJU Int 2010;106:462-9

Docetaxel: survival benefit by age (TAX 327)



ASCO 2011

- In men ≥ 75 years, docetaxel q3w & q1w resulted in more dose reductions and discontinuations for adverse events than mitoxantrone
- BUT trend to better improvement in QoL, tumour response and survival with docetaxel q3w

Tannock IF et al. N Engl J Med 2004;351:1502-12
Seruga B et al. ASCO 2011 (abstract 4530)
QoL: quality of life

MATuRITY: Prospective registry in men aged 70+ with mCRPC

At 6 months	Docetaxel† (N=140)	Non-taxane‡ (N=193)	*P*
OS rate	91%	81%	0.027
PFS	66%	50%	<0.001
Best clinical benefit	60%	36%	<0.001
PSA ↘ ≥ 50%	52.5%	37.4%	0.018

†75mg/m² q3w in 83.9% of cases
‡Hormonal manipulations or non-taxane chemotherapy

Docetaxel Grade ≥3 toxicity	%
Fatigue	17.1%
Nausea/vomiting	14%
Neutropenia Febrile neutropenia	9.8% 2.6%
Sensory neuropathy	9.3%
Diarrhea	8.8%
Anemia	7.8%
Loss of appetite	7.3%
Nail change	6.7%

Droz JP et al. ESMO 2012;Poster 934P

Weekly docetaxel plus prednisolone is superior to prednisolone alone in mCRPC

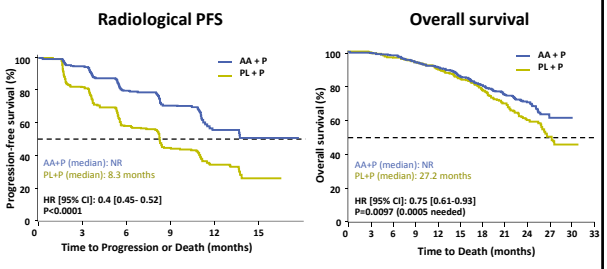
	Docetaxel weekly + Prednisolone	Prednisolone
PFS (median) [95% CI]	11 months [5.8–16.2]	4 months [2.4–5.6]
OS (median) [95% CI]	27 months [19.8–34.2]	18 months [15.2–20.8]
Survival rate (%)		
– 1-year	82%	67%
– 2-year	61%	29%
12-week PSA response rate	69%	36%
QoL improvement		
– Physical function	27%	3%
– Pain	52%	16%
– Fatigue	38%	29%
– Nausea/vomiting	17%	8%
– Global QoL	27%	16%

Toxic outcomes	N
Gastrointestinal: grade ≥2	
Nausea	4
Vomiting	1
Diarrhoea	5
Other/Constitutional: grade ≥2	
Nail changes	27
Alopecia	9
Conjunctivitis/tearing	8
Fatigue/Anorexia	6
Peripheral neuropathy	5
Atrial flutter	4
Fluid retention	4

- **Median age 70 years**
- No cross-over

Fossa SD et al. Eur Urol 2007;52:1691–9
mCRPC: metastatic castrate-resistant prostate cancer; OS: overall survival; PFS: progression-free survival; QoL: quality of life

Abiraterone in chemo-naïve patients: an option if approved by regulatory authorities

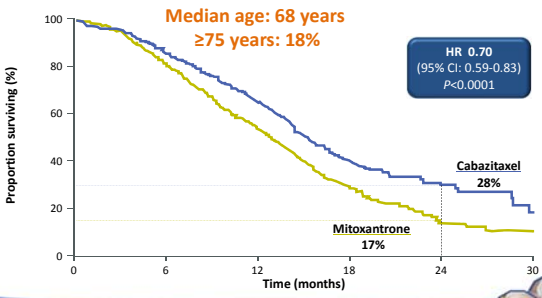


Ryan et al. ASCO 2012;Abstract LBA4518
AA: abiraterone acetate; PL: placebo; P: prednisone; PFS: progression-free survival

Management of advanced PCa: specific considerations for senior adults (3/4)

- First-line androgen deprivation therapy
- First-line chemotherapy
- Progression after first-line docetaxel
- Palliative therapy for bone metastases

Cabazitaxel significantly improves overall survival vs mitoxantrone (TROPIC)



de Bono JS et al. Lancet 2010;376:1147–54

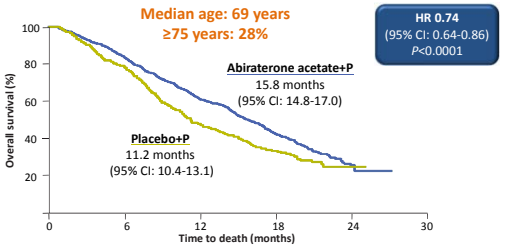
TROPIC: Survival not influenced by age

	N	Favors cabazitaxel / Favors placebo	HR (95% CI)
All randomized patients	755		0.70 (0.59–0.83)
ECOG status: 0,1	694		0.68 (0.57–0.82)
ECOG status: 2	61		0.81 (0.48–1.38)
Measureable disease: no	350		0.72 (0.55–0.93)
Measurable disease: yes	405		0.68 (0.54–0.85)
Number of previous chemotherapies: 1	528		0.67 (0.55–0.83)
Number of previous chemotherapies: ≥2	227		0.75 (0.55–1.02)
Age<65 years	295		0.81 (0.61–1.08)
Age≥65 years	460		0.62 (0.50–0.78)
Pain at baseline: no	314		0.57 (0.43–0.77)
Pain at baseline: yes	310		0.76 (0.59–0.98)
Rising PSA at baseline: no	159		0.88 (0.61–1.26)
Rising PSA at baseline: yes	583		0.65 (0.53–0.80)
Progression during docetaxel treatment	219		0.65 (0.47–0.90)
Progression <3 months after docetaxel	339		0.70 (0.55–0.91)
Progression ≥3 months after docetaxel	192		0.75 (0.51–1.11)

0.25 0.50 1 2

de Bono et al. Lancet 2010;376:1147–54
ECOG: Eastern Cooperative Oncology Group

Abiraterone significantly improves overall survival vs placebo (COU-AA-301)



1195 patients with mCRPC who were previously treated with docetaxel

Fizazi K et al. Lancet Oncol 2012;13(10):983-92
P: placebo; HR: hazard ratio; CI: confidence interval

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COU-AA-301: Survival not influenced by age

Subgroup		AA+P Median (mo)	Placebo+P Median (mo)	HR (95% CI)
Baseline ECOG PS*	0–1	17.0	12.3	0.74 (0.63–0.86)
	2	7.3	7.0	0.77 (0.50–1.17)
Baseline BPI-SF score*	<4	18.4	13.9	0.69 (0.56–0.85)
	≥4	13.3	9.3	0.78 (0.63–0.96)
Number of CT regimens*	1	17.1	11.7	0.71 (0.59–0.85)
	2	14.2	10.4	0.80 (0.61–1.03)
Type of progression*	PSA only	18.3	13.6	0.63 (0.47–0.84)
	Radiographic†	14.8	10.5	0.78 (0.65–0.93)
Age (years)	<65	15.0	11.2	0.69 (0.53–0.91)
	≥65	16.2	11.1	0.76 (0.63–0.90)
	≥75	15.6	9.3	0.64 (0.48–0.85)
Visceral disease at entry	Yes	12.9	8.3	0.79 (0.59–1.05)
	No	17.1	12.3	0.69 (0.58–0.82)
Baseline PSA >median	Yes	13.6	8.8	0.65 (0.53–0.79)
	No	18.2	15.3	0.79 (0.63–0.99)
Baseline LDH >median	Yes	10.4	8.0	0.77 (0.63–0.93)
	No	20.8	18.0	0.75 (0.59–0.96)
Baseline ALK-P >median	Yes	12.4	8.1	0.60 (0.50–0.74)
	No	19.5	18.0	0.88 (0.69–1.12)

Favors AA+P | Favors Placebo+P

Fizazi K et al. Lancet 2012;epub ahead of print
BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; OS: overall survival; PSA: prostate-specific antigen

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Specific considerations for senior adults in patients with VERY advanced disease

Cabazitaxel

- Increased risk of febrile neutropenia (7.5 vs 1.3%)
  - Primary prophylaxis with G-CSF recommended in patients aged > 65 years and/or advanced disease (EORTC guidelines)
- Diarrhoea (6.5 vs 0.3%, grade ≥ 3)
  - Rehydration with antidiarrheals (as needed)

Abiraterone

- Hypokalaemia, hypertension & fluid retention due to mineralocorticoid excess
  - Use with caution in patients with cardiovascular diseases
- Adrenocortical insufficiency
  - Caution after interruption of daily steroids and/or concurrent infection or stress
- Hepatotoxicity
  - Monitor liver function

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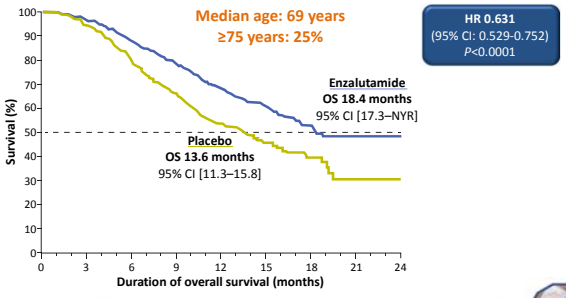
AFFIRM: enzalutamide improves overall survival vs placebo after docetaxel



Scher HI et al. ASCO GU 2012;Abstract LBA1
NYR: not yet reached; OS: overall survival

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AFFIRM: Survival not influenced by age

Subgroup		HR for death (95% CI)	Median OS (months) Enzalutamide/Placebo
All subjects		0.63 (0.53–0.75)	18.4/13.6
Age (years)	<65	0.63 (0.46–0.87)	–/12.6
	>65	0.63 (0.51–0.78)	18.4/13.9
Baseline ECOG PS score	0–1	0.62 (0.52–0.75)	–/14.2
	2	0.65 (0.51–0.78)	10.5/7.2
Baseline mean pain score on BPI-SF	<4	0.59 (0.47–0.74)	–/16.2
	≥4	0.71 (0.54–0.94)	12.4/9.1
Geographic region	North America	0.63 (0.47–0.83)	17.4/12/3
	Other	0.64 (0.51–0.80)	–/14.4
Number of prior chemotherapy regimens	1	0.59 (0.48–0.73)	–/14.2
	≥2	0.74 (0.54–1.03)	15.9/12.3
Type of progression at study entry	PSA only	0.62 (0.46–0.83)	–/19.5
	PSA ±Radiographic	0.64 (0.52–0.80)	17.3/13.0
Baseline value >median value	PSA	0.62 (0.50–0.78)	15.3/10.3
	LDH	0.61 (0.50–0.76)	12.4/8.5

Favors Enzalutamide | Favors Placebo

Scher HI et al. J Clin Oncol 2012;30(Suppl 5):Abstract LBA1 [presented at ASCO]
BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; OS: overall survival; PSA: prostate-specific antigen

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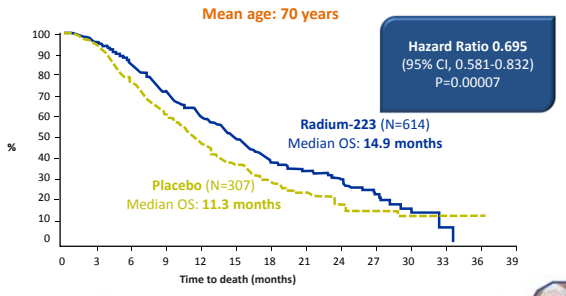
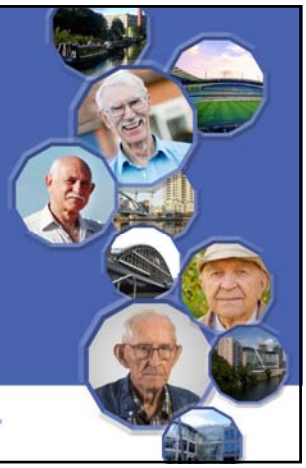
ALFSYMPCA: Radium-223 improves survival vs placebo post-docetaxel



Parker C et al. ASCO 2012 (LBA 4512)

Which drug for which patient?



Short response to first-line ADT predicts poor response to abiraterone & enzalutamide

- 108 mCRPC patients after failure of primary ADT
- Treated with secondary hormonal manipulations: abiraterone, DES, ketoconazole, enzalutamide
- Median duration of response to primary ADT: 16 mo [0-118]

Duration of response to ADT	≥16 mo	<16 mo	*P* value
PSA response	58%	18%	0.01
PFS rate (median)	5 mo	3 mo	<0.043

Loriot Y & Fizazi K. J Clin Oncol 2012;30(Suppl 5):Abstract 213

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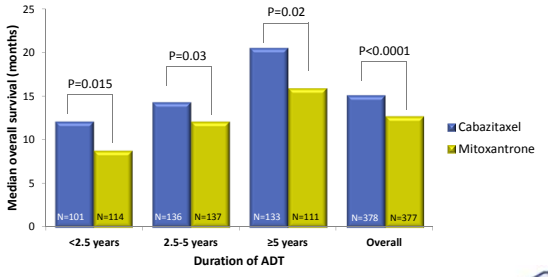
TROPIC: Cabazitaxel improves survival whatever the duration of prior ADT



Oudard S et al. ESMO 2012;Poster 933P

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French ATU: Poor response to abiraterone in patients with high Gleason score

- Abiraterone French ATU program (post-docetaxel setting)
- 408 mCRPC patients enrolled in 19 centers
- Gleason 8-10: 51.2% at diagnosis
- **Independent predictive factors of poor response to Abiraterone:**
  - **Gleason score 8-10**
  - Number of chemotherapy lines (>1)

Azria D et al. J Clin Oncol 2012;30 (Suppl 5):abstract 149
ATU: French 'temporary authorization for use'

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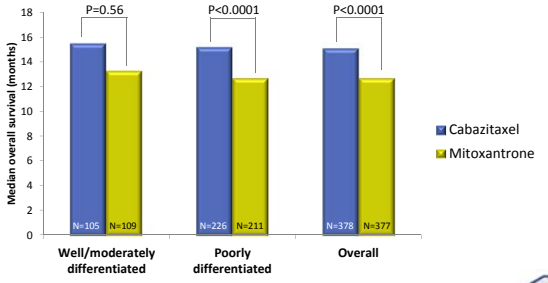
TROPIC: Cabazitaxel improves survival whatever the tumor grade



Oudard S et al. ESMO 2012;Poster 933P

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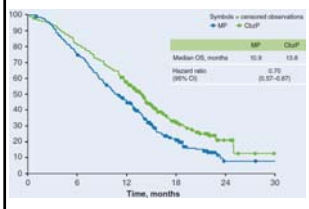
Docetaxel discontinuation for disease progression

Cabazitaxel

Significantly improves OS[1]



Abiraterone

Poorer response[2]?

- 44 mCRPC patients treated with first-line docetaxel followed by abiraterone
- 7/44 patients refractory to docetaxel
- **0/7 had subsequent PSA, radiological or clinical response to abiraterone**

1. de Bono JS et al. Lancet 2010;376:1147–54
2. Muckerjie et al. J Clin Oncol 2012;30(Suppl 5):Abstract 17

mCRPC: metastatic castrate-resistant prostate cancer; OS: overall survival

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Management of advanced PCa: specific considerations for senior adults (4/4)

- First-line androgen deprivation therapy
- First-line chemotherapy
- Progression after first-line docetaxel
- Palliative therapy for bone metastases
  - ❖ Zoledronic acid
  - ❖ Denosumab
  - ❖ Radiation therapy
  - ❖ Experimental radiopharmaceutical: alpharadin

SIOG recommendations for senior adults

1. Droz JP et al. Crit Rev Oncol Hematol 2010;73:61-91
2. Droz JP et al. BJU Int 2010;106:462-9

SIOG recommendations for senior adults

- Treatment recommendations for older men with prostate cancer should be based on:

Health status (mainly driven by co-morbidities)

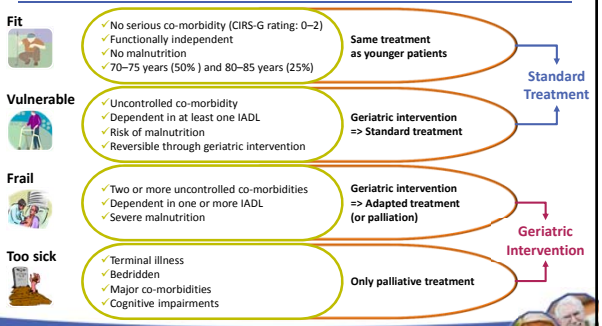
AND

Patient preferences

NOT

Chronological age

Treatment should be adapted to health status



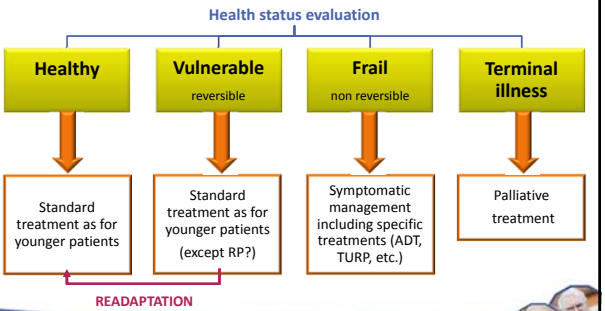
Droz JP et al. Crit Rev Oncol Hematol 2010;73:61–91
Droz JP et al. BJU Int 2010;106:462–9
CIRS-G: cumulative illness rating scale-geriatrics; IADL: instrumental activities of daily living

SIOG recommendations for senior adults with PCa

- The urological approach in senior adults should be the same as in younger patients
- Adapt international guidelines (EAU, ESMO, AUA, etc.) to patient health status
  - ❖ Scientifically established national guidelines are also valid

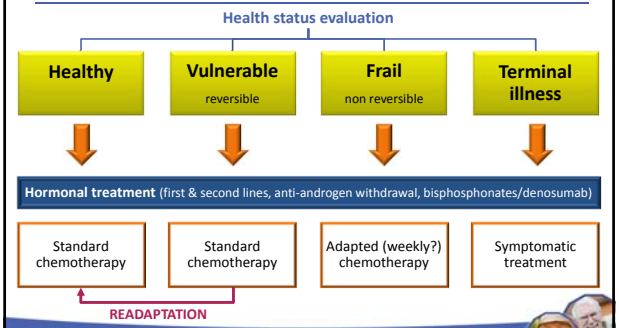
Droz JP et al. Crit Rev Oncol Hematol 2010;73:61–91.
Droz JP et al. BJU Int 2010;106:462–9
PCa: prostate cancer

Guidelines for localized PCa



Droz JP et al. Crit Rev Oncol Hematol 2010;73:61-91
Droz JP et al. BJU Int 2010;106:462-69

Guidelines for advanced PCa



Droz JP et al. Crit Rev Oncol Hematol 2010;73:61-91
Droz JP et al. BJU Int 2010;106:462-69

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Any questions?

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