2024 RBWH CANCER CARE SERVICES PRECEPTORSHIP
FOR GENERAL PRACTITIONERS

Prostate Cancer Update

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Metro North Health | Queensland Government

Disclosures

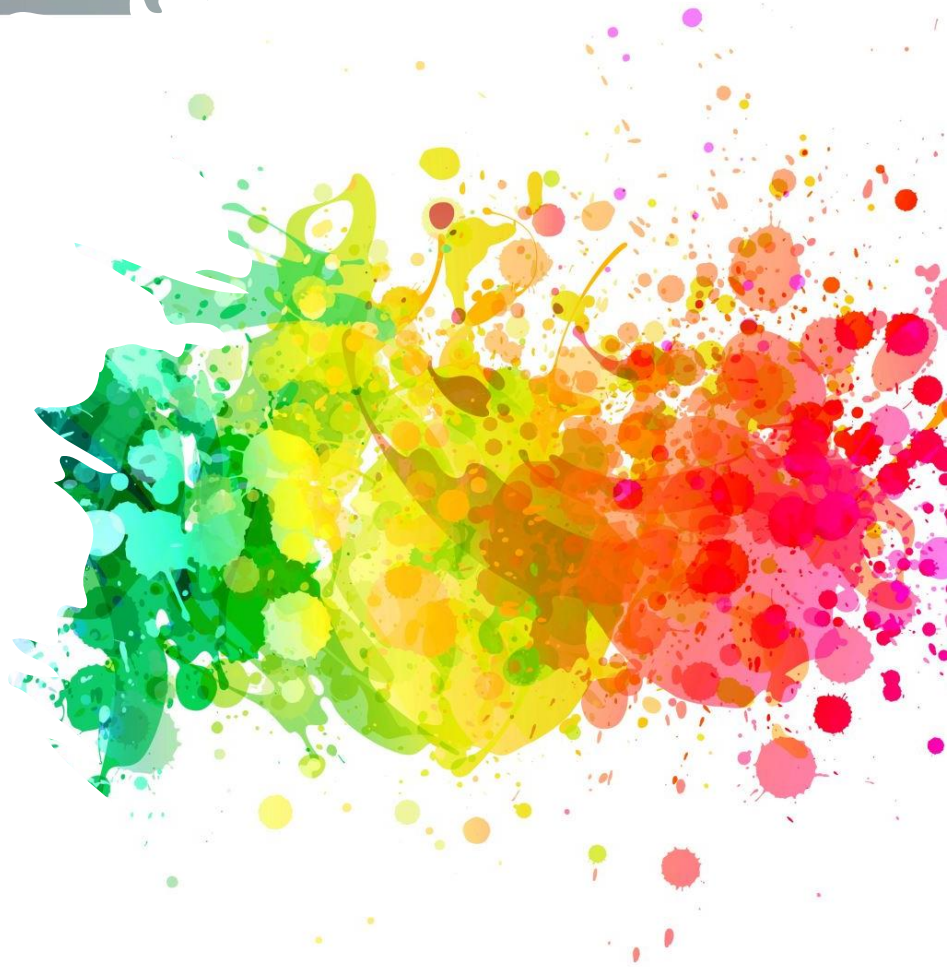
- Travel and accommodation support: Ipsen, Pierre Fabre, Merck
- Honoraria: Ipsen, The limbic, Bayer, Astellas

Objectives

- Prostate cancer incidence and mortality
- Novel androgen receptor pathway inhibitors (ARPI)
- A case of metastatic prostate cancer
- Toxicities management

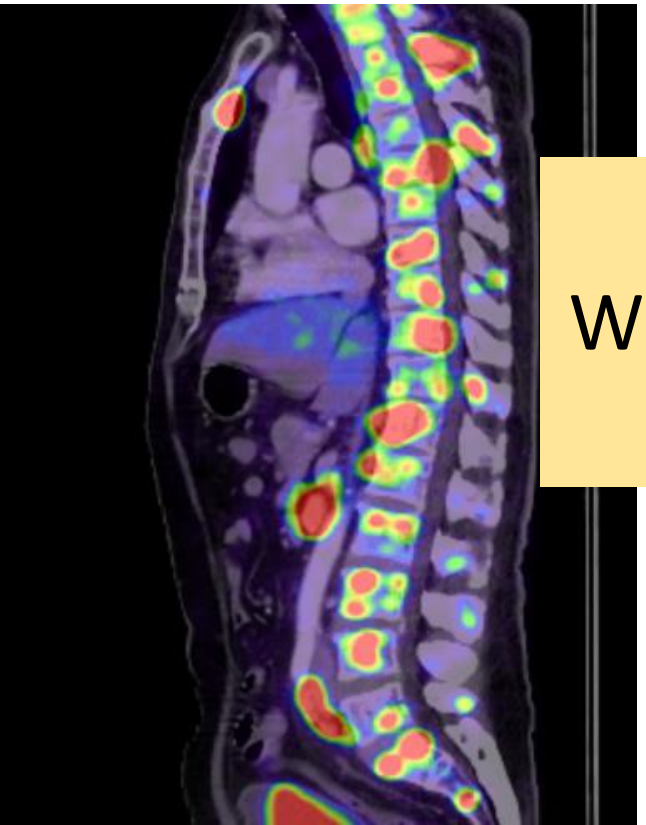
Case 1: 69M referred by radiation oncologist

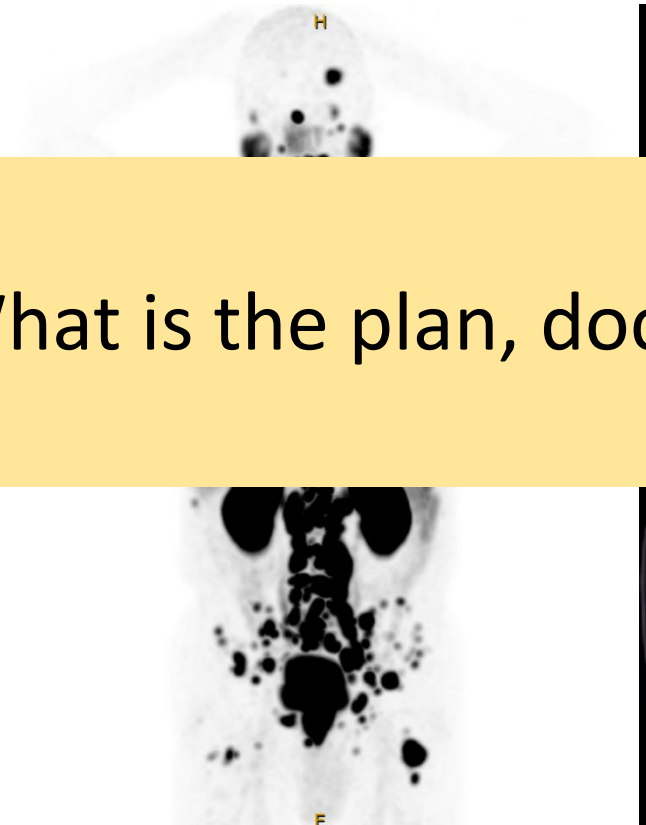
- 3 months history of worsening shoulder pain and LUTS
- PSA 890
- Hypertension
- No family history of prostate cancer
- ECOG 0
- Home with wife, originally from Korea

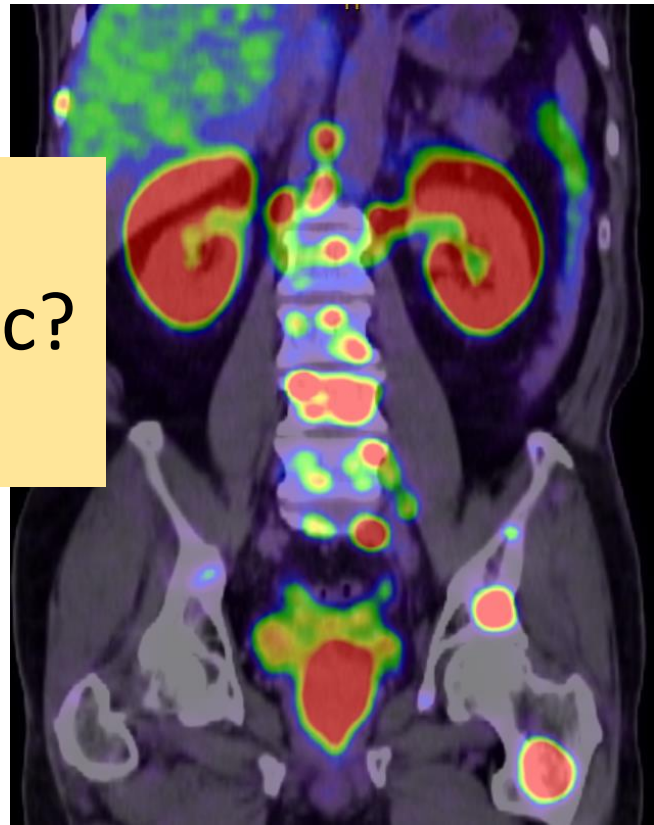


Medication
Perindopril, bicalutamide

PSMA PET







What is the plan, doc?

Genitourological Cancer in Australia

	New Cases (AU)	New Cases (Global)
Prostate	**20,211 (2017)** **1st most common** **5y OS: 96%**	**1,414,259 (2020)** **4th most common**
Kidney	3,891 (2018) 7th most common 5y OS: 81%	431,288 14th most common
Bladder	2,397 (2018) 11th most common 5y OS: 57%	573,278 10th most common
Testicular	898 (2018) 5y OS: 97%	74,458
Penis	174 (2022) 5y OS: 74%	36,068

source: www.canceraustralia.gov.au, www.aihw.gov.au, www.wcrf.org, www.gco.iarc.who.int

Prostate cancer survival rate has improved

In 2014–2018, individuals diagnosed with prostate cancer had a 96% chance of surviving for five years compared to their counterparts in the general Australian population. Between 1989–1993 and 2014–2018, five-year relative survival for prostate cancer improved from 63% to 96%.

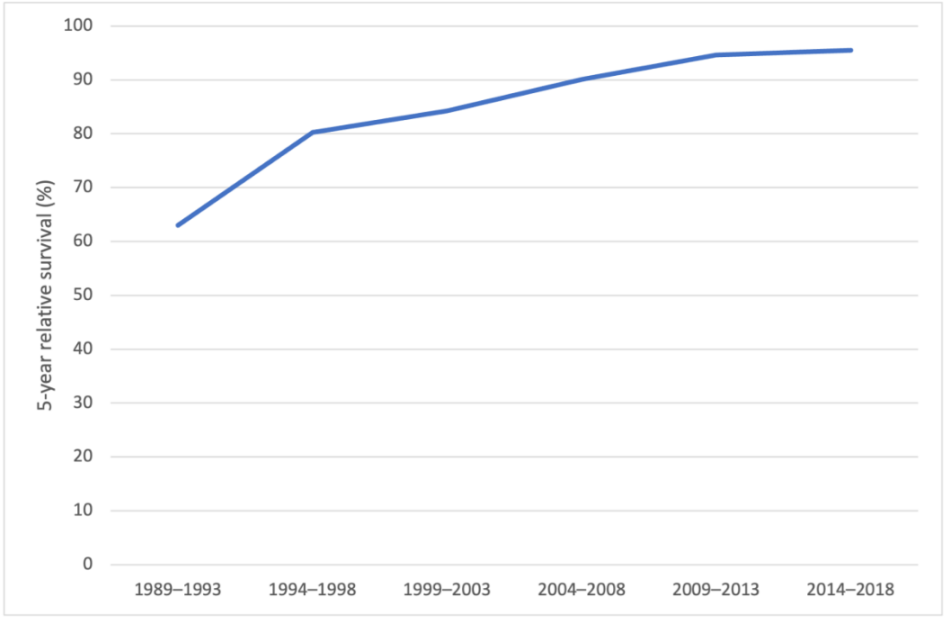
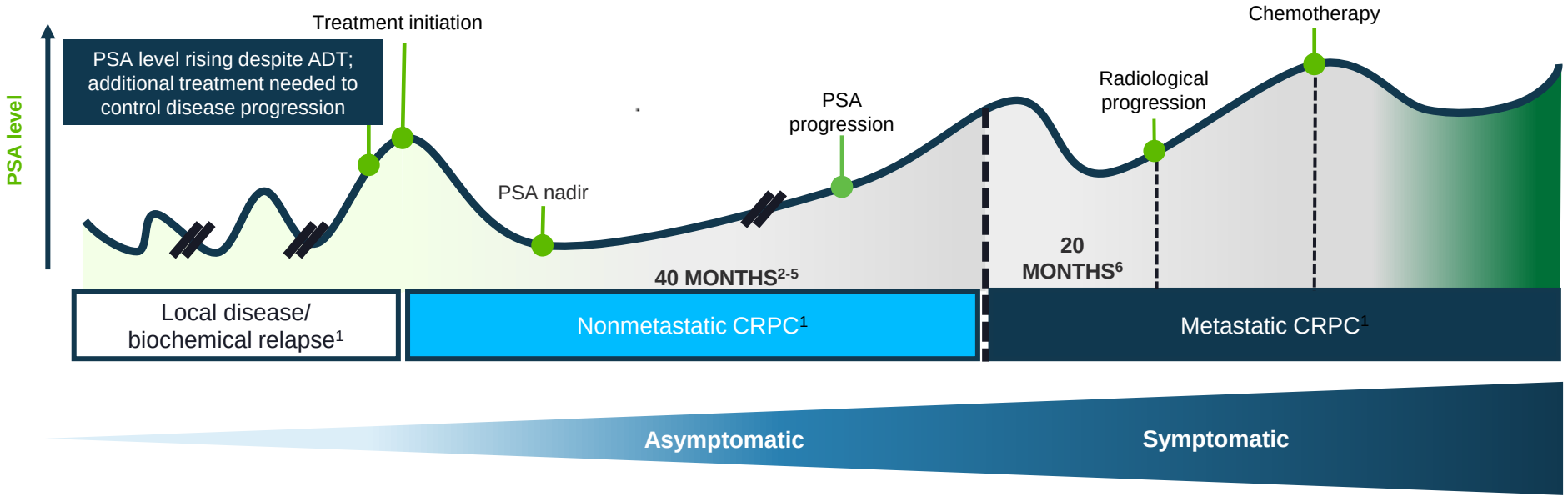


Figure 5. 5-year relative survival for prostate cancer, 1989–1993 to 2014–2018

https://www.canceraustralia.gov.au/cancer-types/prostate-cancer/statistics

Natural History of Prostate Cancer



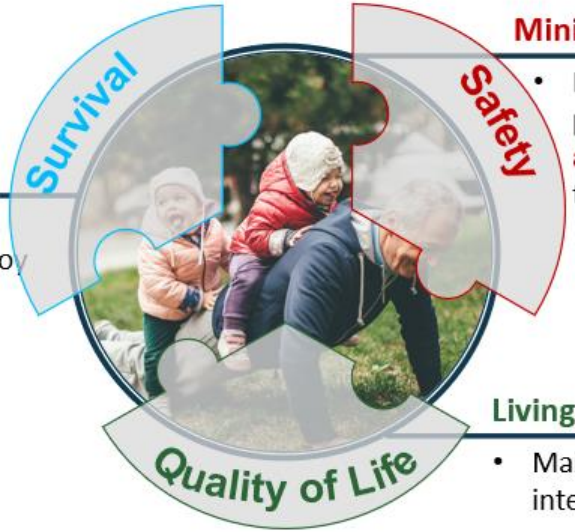
*Not drawn to scale; numbers reported are medians. Figure is for illustrative purposes only.
ADT, androgen deprivation therapy; MFS, metastasis-free survival; nmCRPC, nonmetastatic castration-resistant prostate cancer; OS, overall survival; PSA, prostate-specific antigen; QoL, quality of life.

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)®. Prostate Cancer. v1. 2020. 2. Ryan CJ et al. J Urol. 2018;200:344-352. 3. Fizazi K et al. N Engl J Med. 2019;380:1235-1246. 4. Smith MR et al. N Engl J Med. 2018;378:1408-1418. 5. Hussain M et al. N Engl J Med. 2018;378:2465-2474. 6. Beer TM et al. Eur Urol 2017;71:151-154.. 7. Beer TM et al. N Engl J Med. 2014;371:424-433. 8. Ryan CJ et al. N Engl J Med. 2013;368:138-148; 9. Beer TM et al. N Engl J Med. 2014;371:424-433. 10. Ryan CJ, et al. Lancet Oncol. 2015;16(2):152-160

Treatment for Advanced Prostate Cancer Should Help Achieve Patient Goals

Extending Life

- Improved **overall survival** with treatment allows patients to enjoy more time with loved ones[1,2]



Minimizing Side Effects

- Patients want to focus on future plans without worrying about **adverse events** from cancer treatment[1-3]

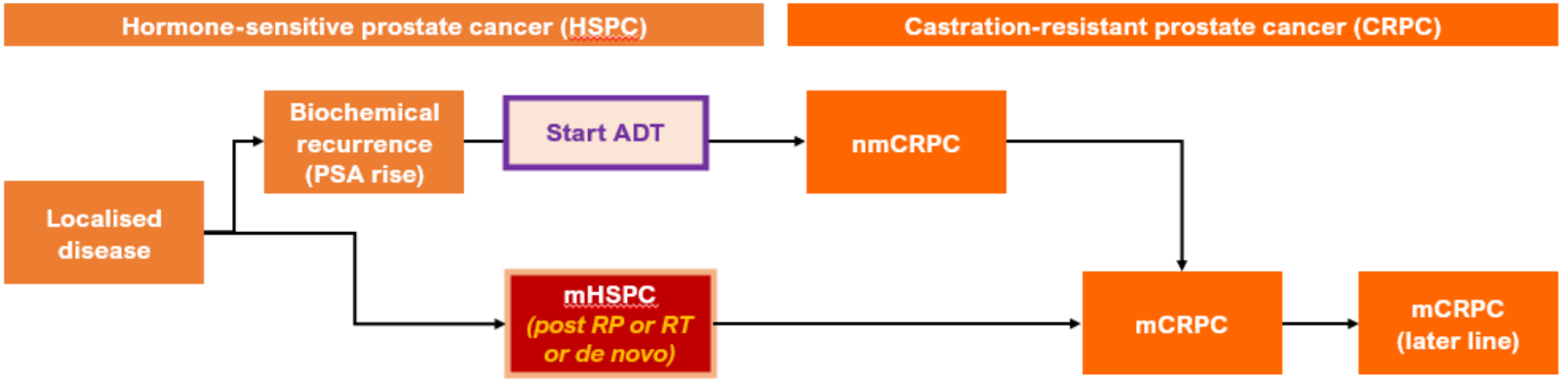
Living Uninterrupted

- Maintaining **QOL** means fewer interruptions to patients' daily life[1,4]

QOL, quality of life.

1. Drudge-Coates L, et al. *Clin Genitourin Cancer.* 2018;16(2):e411-e419. **2.** Al-Batran SE, et al. *Ann Oncol*. 2015; 26(6):1244-1248. **3.** Parker C, et al. *Eur J Cancer.* 2017; 71:1-6. **4.** National Institute on Aging, Cognitive Health and Older Adults. https://www.nia.nih.gov/health/cognitive-health-and-older-adults. Accessed: May 2020.

The Prostate Cancer Spectrum



Treatment Options

- Local therapy
- Active surveillance
- ADT *(Testosterone Suppression)*

In combination with ADT
- Abiraterone
- Apalutamide
- Docetaxel
- Enzalutamide

In combination with ADT and docetaxel
- Abiraterone
- Darolutamide
- Enzalutamide

In combination with ADT
- Apalutamide
- Darolutamide
- Enzalutamide

- Androgen receptor pathway inhibitor + ADT
- Docetaxel + ADT
- Cabazitaxel + ADT
- Radiopharmaceuticals
- Immunotherapies: Vaccine (CPI only for MSI)
- Poly (ADP-ribose) polymerase inhibitors

Trials With Doublet Therapy (ADT + ARPI)

Trial	Experimental arm	Control arm	Number of patients (randomized 1:1)	Population characteristics	Median follow-up (mo)	OS		
						Experimental	Control	HR, 95% CI; P
LATITUDE	Abiraterone + prednisone + ADT	ADT + placebo	1,199	Newly diagnosed mCSPC ≥ 2 of following high-risk factors: Gleason score ≥ 8, ≥ 3 bone lesions, and measurable visceral metastasis	51.8	53.3 mo	36.5 mo	**0.66** [0.56, 0.78]; P < .0001
STAMPEDE	Abiraterone + prednisolone + ADT	ADT	1,917	Newly diagnosed metastatic, node-positive, or high-risk locally advanced (N0M0, ≥ 2 of following: T3 or T4, Gleason score ≥ 8, and PSA ≥ 40 ng/ml), or recurrent disease after local therapy with high-risk features or metastasis	73	OS at 5 years: 60%	OS at 5 years: 41%	**0.60** [0.5, 0.71]; P < .0001
TITAN	Apalutamide + ADT	ADT + placebo	1,052	Newly diagnosed mCPSC	44.0	NR	52.2 mo	**0.65** [0.53, 0.79]; P < .0001
ENZAMET	Enzalutamide + testosterone suppression	Testosterone suppression + standard nonsteroidal antiandrogen therapy	1,125	Newly diagnosed mCPSC	68.0	OS at 5 years: 67%	OS at 5 years: 57%	**0.70** [0.58, 0.84]; P < .0001
ARCHES	Enzalutamide + ADT	ADT + placebo	1,150	Newly diagnosed mCPSC	44.6	NR	NR	**0.66** [0.53, 0.81]; P < .001

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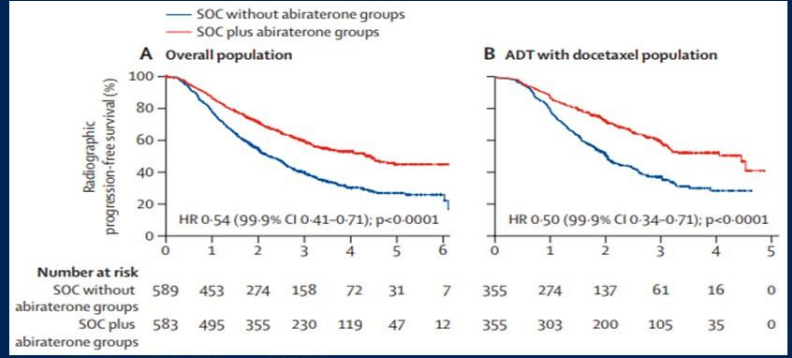
Trials with Triplet Therapy (ADT + Docetaxel+ ARPI)


Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design

*Karim Fizazi, Stéphanie Foulon, Joan Carles, Guilhem Roubaud, Ray McDermott, Aude Fléchon, Bertrand Tombal, Stéphane Supiot, Dominik Berthold, Philippe Ronchin, Gabriel Kacso, Gwenaëlle Gravis, Fabio Calabro, Jean-François Berdah, Ali Hasbini, Marlon Silva, Antoine Thiery-Vuillemin, Igor Latorzeff, Loïc Mourey, Brigitte Laguerre, Sophie Abadie-Lacourtoisie, Etienne Martin, Claude El Kouri, Anne Escande, Alvar Rosello, Nicolas Magne, Friederike Schlurmann, Frank Priou, Marie-Eve Chand-Fouche, Salvador Villà Freixa, Muhammad Jamaluddin, Isabelle Rieger, Alberto Bossi, on behalf of the PEACE-1 investigators**



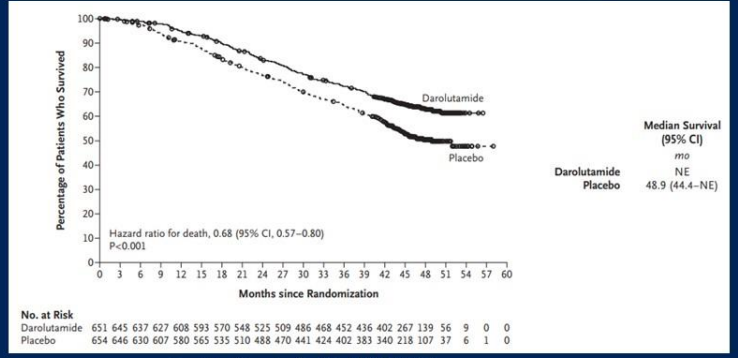
Fizazi K. et al. ***The Lancet*** 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Álvaro Montesa-Pino, M.D., Dingwei Ye, M.D., Francis Parnis, M.B., B.S., Felipe Cruz, M.D., Teuvo L.J. Tammela, M.D., Ph.D., Hiroyoshi Suzuki, M.D., Ph.D., Tapio Utriainen, M.D., Cheng Fu, M.D., Motohide Uemura, M.D., Ph.D., María J. Méndez-Vidal, M.D., Benjamin L. Maughan, M.D., Pharm.D., Heikki Joensuu, M.D., Silke Thiele, M.D., Rui Li, M.S., Iris Kuss, M.D., and Bertrand Tombal, M.D., Ph.D., for the ARASENS Trial Investigators*



Smith M. et al. ***NEJM*** 2022

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Trials With Triplet Therapy (ADT + docetaxel + ARPI)

Trial	Experimental arm	Control arm	Number of patients (randomized 1:1)	Population characteristics	Median follow-up (mo)	OS		
						Experimental	Control	HR, 95% CI; P value
ARASENS	Darolutamide + docetaxel + ADT	ADT + docetaxel	1,306	Newly diagnosed mCSPC (Synchronous disease: 86% High-volume disease: 77%)	43.7	NR	48.9	0.68 [0.57, 0.8]; P < .001
						High-volume disease OS HR: 0.69 (0.57, 0.82)		
						Low-volume disease OS HR: 0.68 (0.41, 1.13)		
						Synchronous disease OS HR: 0.71 (0.59, 0.85)		
						Metachronous disease OS HR: 0.61 (0.35, 1.05)		
PEACE-1	Abiraterone + prednisone + docetaxel + ADT	ADT + docetaxel	710	Newly diagnosed de novo mCSPC (high-volume disease: 64%)	45.6	NR	52.8	0.75 [0.59, 0.95]; P = .017
						High-volume disease OS HR: 0.72 [0.55, 0.95]		
						Low-volume disease OS HR: 0.83 [0.5, 1.39]		

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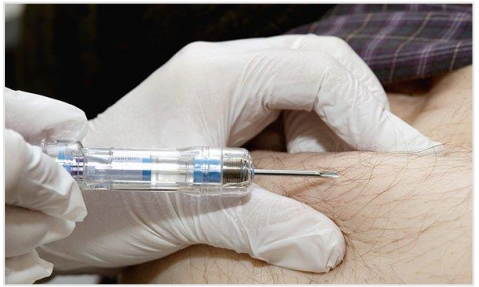
ANDROGEN DEPRIVATION THERAPY (ADT)

- Different types:
  - medications (tablets or injections) that reduce the production of testosterone.
  - Surgical removal of the testes (orchidectomy) to stop the production of androgens.
- ADT injections include:
  - Goserelin (Zoladex®)
  - Leuporelin (Eligard®, Lucrin®)
  - Triptorelin (Diphereline®)
  - Degarelix (Firmagon®)



- Side effects include:
  - Sexual dysfunction: reduction or loss of libido, impotence, infertility.
  - Osteoporosis
  - Hot flushes
  - Fatigue
  - Changes in body appearance, physical strength, mood and cognition
  - Increased risk of heart and endocrinologic disease

eviQ: https://www.eviq.org.au/getmedia/8cd3b382-e0a2-4668-abb9-0b974a9e28fb/3384-ADT-prostate-Nov-2022.pdf.aspx?ext=.pdf.

ANDROGEN RECEPTOR PATHWAY INHIBITORs (ARPI)

- Used in combination with GnRH agonists/antagonists to block the effects of androgens produced by the adrenal gland (doublet therapy) +/- chemotherapy (triplet therapy)
- ARPI include:
  - **Abiraterone (Zytiga®, Yonsa MPred®)**
  - **Apalutamide (Erlyand®)**
  - **Darolutamide (Nubeqa®)**
  - **Enzalutamide (Xtandi®)**
  - Bicalutamide (Cosudex®)
  - Cyrproterone (Androcur®)
  - Nilutamide (Anandron®)

eviQ: https://www.eviq.org.au/getmedia/8cd3b382-e0a2-4668-abb9-0b974a9e28fb/3384-ADT-prostate-Nov-2022.pdf.aspx?ext=.pdf.

ARPI management

- Initiation & education:
  - Baseline assessments: blood pressure, weight, fatigue, memory, ECOG.
  - Drug interactions.
  - Follow-up logistics and medication access.
  - Service contact.
- Clinical assessment & monitoring:
  - Baseline assessments: blood pressure, weight, fatigue, memory & cognition, ECOG.
  - Baseline bloods: FBE, EUC, LFT, Ca, PSA, testosterone.
  - Bone health, cardiovascular health, seizure history.
- Follow-up schedule:
  - Week 3, 6, 12 then every 6-12 weeks when tolerating well.
- PBS approvals:
  - mHSPC: Abiraterone, Apalutamide, Darolutamide, Enzalutamide
  - nmCRPC: Apalutamide, Darolutamide, Enzalutamide
  - mCRPC: Abiraterone, Enzalutamide

ARPI administration

- Food requirement:
  - Enzalutamide, Apalutamide and micronized Abiraterone can be taken with or without food.
  - Abiraterone must be taken without food (2 hours after eating or 1 hour before eating).
  - Darolutamide should be taken with food.

- Significant pill burden:
  - Abiraterone: 2x 500mg tablets (1000mg OD) + 5mg prednisolone OD
  - Micronized abiraterone + methylprednisolone: 4x 125mg OD (500mg) + 4mg methylpred OD
  - Apalutamide: 4x 60mg tablets (240mg OD)
  - Darolutamide: 2x 300mg tablets twice daily (600mg BD)
  - Enzalutamide: 4x 40mg capsules (160mg OD)

Expected s/e of ARPIs

- Fatigue
- Arthralgias
- Nausea
- Hypertension
- Short term memory issues
- Weight gain
- Hot flushes
- Diarrhoea
- Peripheral oedema

Apalutamide – rash, hypothyroidism

Enzalutamide – seizures

Abiraterone – hypertension, arrythmias, electrolyte abnormalities, hepatitis

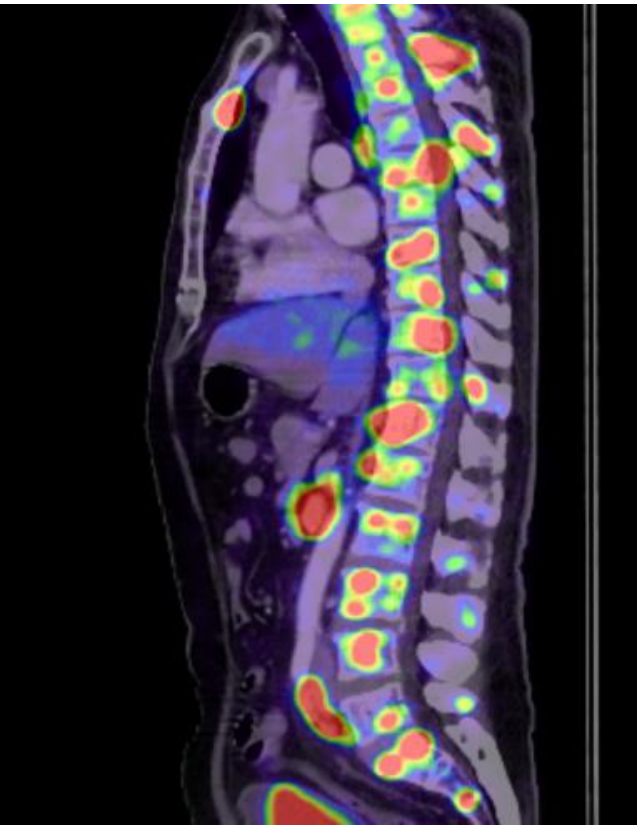
Darolutamide – increased bilirubin

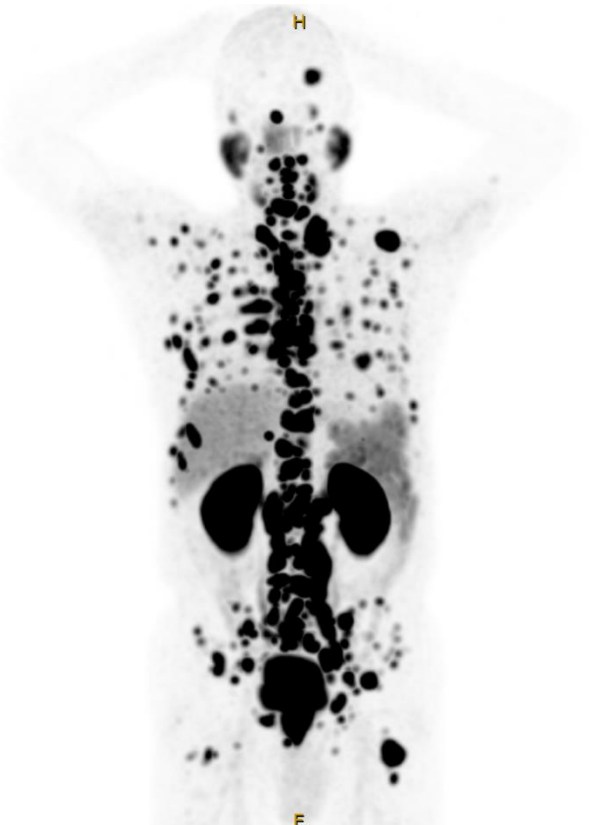
DRUG INTERACTIONS

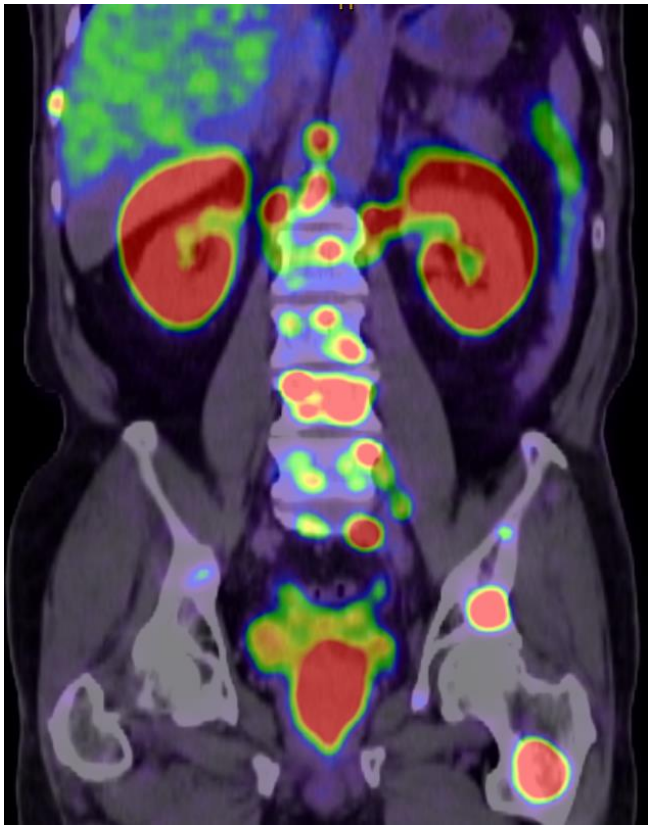
CATEGORY	EXAMPLE	DRUG INTERACTIONS			
		ABI	APA	DARO	ENZA
ANTICOAGULANT	WARFARIN		✓		✓
	CLOPIDOGREL[1]				✓
	DABIGATRAN		✓		✓
	RIVAROXABAN[1]	✓			✓
STATINS	ROSUVASTATIN		✓	✓	
ANTIHYPERTENSIVE	NIFEDIPINE, FELODIPINE, AMLODIPINE		✓		✓
	VERAPAMIL		✓		✓
	DILTIAZEM[1]				✓
DIURETIC	SPIRONOLACTONE	✓			
CARDIAC GLYCOSIDE	DIGOXIN[1]		✓		✓
PPI	OMEPRAZOLE[2]		✓		✓
HYPNOTIC	DIAZEPAM		✓		✓
ANALGESIC	FENTANYL		✓		✓
	OXYCODONE[2]	✓			
ANTIPSYCHOTIC	HALOPERIDOL	✓	✓		✓
ANTIBIOTIC	CLARITHROMYCIN	✓	✓	✓	✓
	RIFAMPICIN	✓	✓	✓	✓
ANTICONVULSANT	CARBAMAZEPINE[1,2]	✓		✓	✓

1. Lennep et al. *Drug Safety*. 2024. 2. **Del re et al**. *Cancer Treatment Reviews*. 2017

69M with newly diagnosed metastatic prostate cancer







69M ECOG 0, no biopsy

High-Volume Disease: CHAARTED Criteria[1]	High-Risk Disease: LATITUDE Criteria[2]
• Visceral metastases and/or • ≥4 bone metastases with ✓ ≥1 beyond the vertebral column/pelvis	• ≥2 risk factors: – Gleason score ≥8 – ≥3 bone metastases[a] ✓ – Visceral metastases

Low-volume and low-risk disease was defined as not meeting the respective high-volume and high-risk criteria.
[a]Including those with diffusely increased skeletal metastases with superscan

High Volume

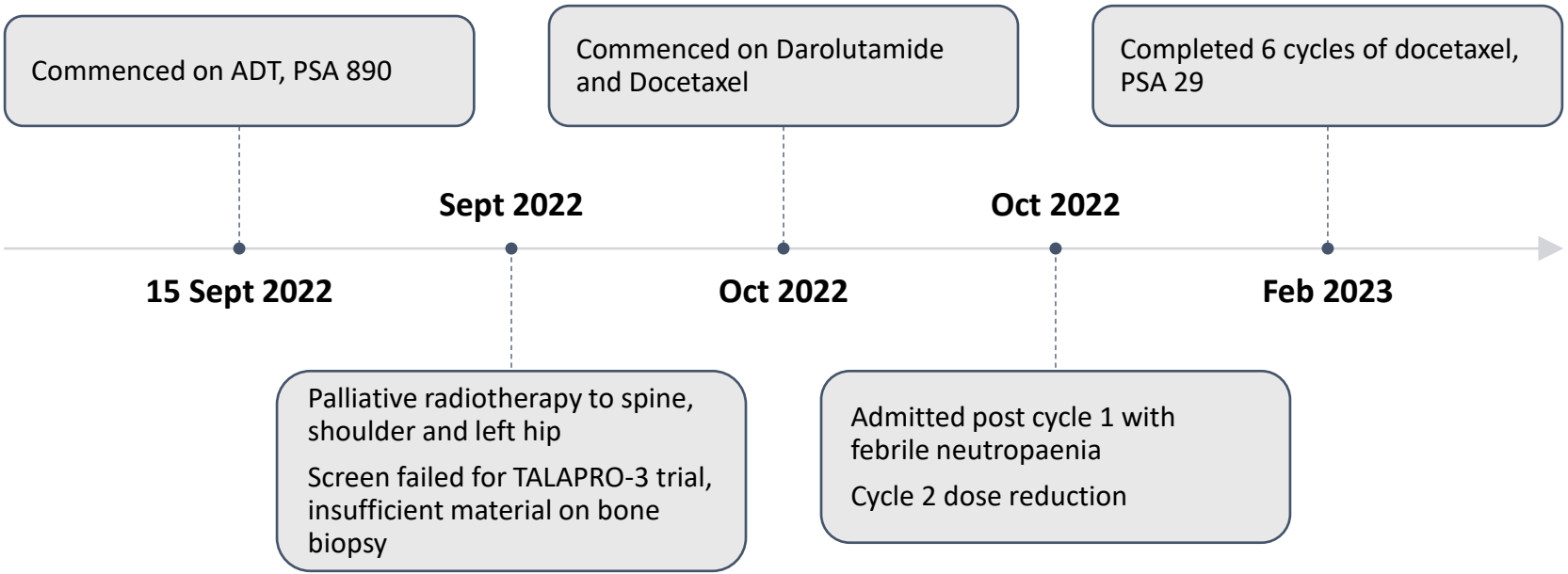
Denovo Metastatic Castration Sensitive Prostate Cancer

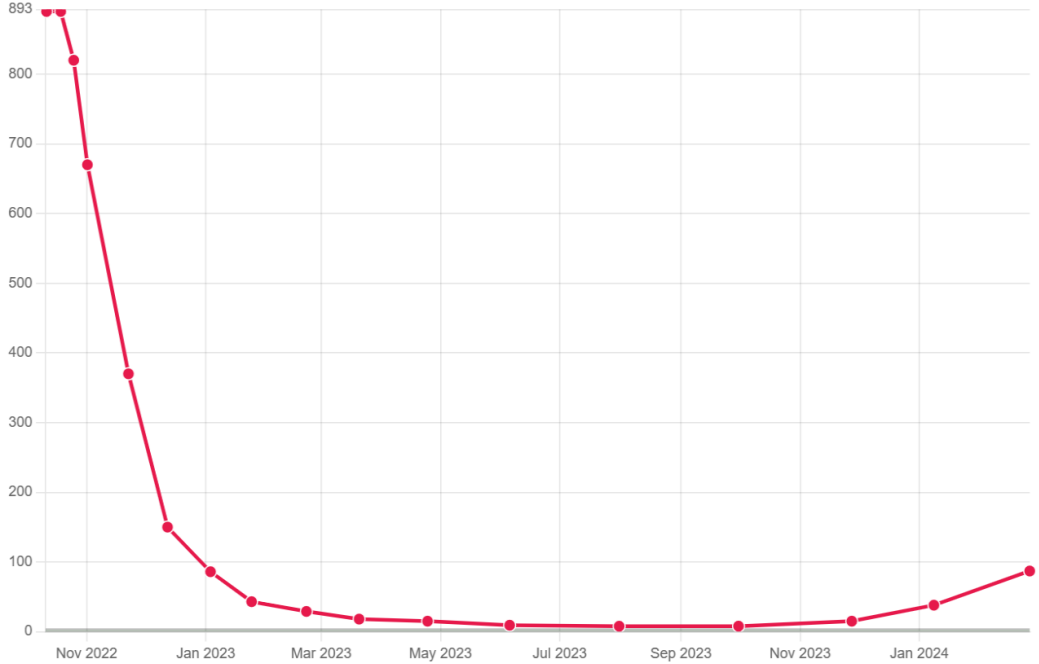
What are the treatment options?

What are the treatment options?

1. ADT alone
2. ADT + ARPI
3. ADT + ARPI + Docetaxel
4. ADT + ARPI + Docetaxel + Prostate RT
5. ADT +ARPI + Docetaxel +/- palliative RT

Progress


Commenced on ADT, PSA 890
15 Sept 2022
Sept 2022
Palliative radiotherapy to spine, shoulder and left hip
Screen failed for TALAPRO-3 trial, insufficient material on bone biopsy
Commenced on Darolutamide and Docetaxel
Oct 2022
Oct 2022
Admitted post cycle 1 with febrile neutropaenia
Cycle 2 dose reduction
Completed 6 cycles of docetaxel, PSA 29
Feb 2023



- Commenced on 2nd line Cabazitaxel chemotherapy
- July 2024: ongoing chemotherapy with reduction in PSA

Thank you

Any Questions?