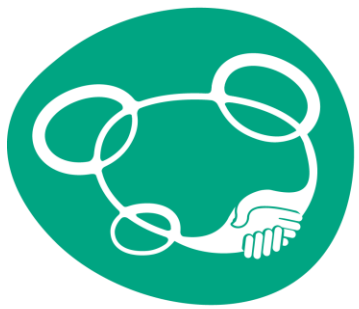

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TREATMENT SEQUENCING FOR mCRPC: PROVIDING CRUCIAL SUPPORT TO THE PATIENT

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mCRPC, metastatic castration-resistant prostate cancer

DISCLAIMER AND DISCLOSURES

Please Note: The views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author's institute or the rest of the GU Nurses CONNECT group.

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INTRODUCTION

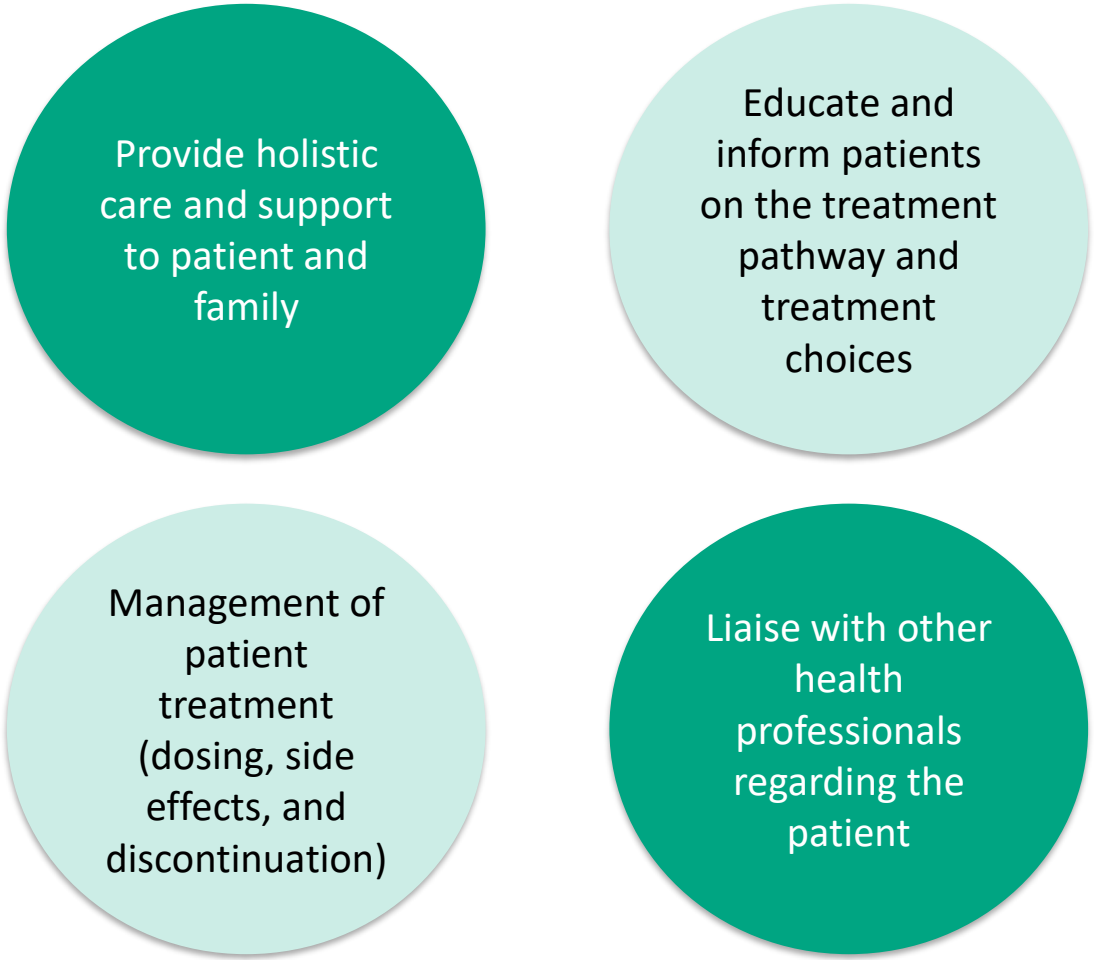
- Over the past few years, the number of treatment options available to patients with metastatic castration-sensitive prostate cancer (mCSPC) has increased significantly
- Androgen receptor targeted agents (ARTAs) along with androgen deprivation therapy (ADT) are increasingly used at the mCSPC disease stage; as a result, most metastatic castration-resistant prostate cancer (mCRPC) patients have already received treatment with an ARTA
- Prior treatments, including those for mCSPC, influence future treatment decisions when the patient progresses to mCRPC
- Cross-resistance occurs with ARTAs; therefore, it is preferable to select subsequent therapies with a different mechanism of action
- There are several different treatments available for patients with mCRPC, and individualisation of treatment is important, considering patient preference and quality of life
- Genitourinary (GU) nurses play an integral role in supporting mCRPC patients during treatment sequencing decisions

NCCN Guidelines Version 3.2020, Prostate Cancer

THE ROLE OF THE GU NURSE

KEY RESPONSIBILITIES OF SPECIALIST GU NURSES

- **GU nurses play an integral role in supporting mCRPC patients during treatment-sequencing decisions by:**
  - Helping patients understand the available treatments and mechanisms of action
  - Explaining treatments and potential side effects in a language that patients and care givers can understand
  - Listening and answering patient questions

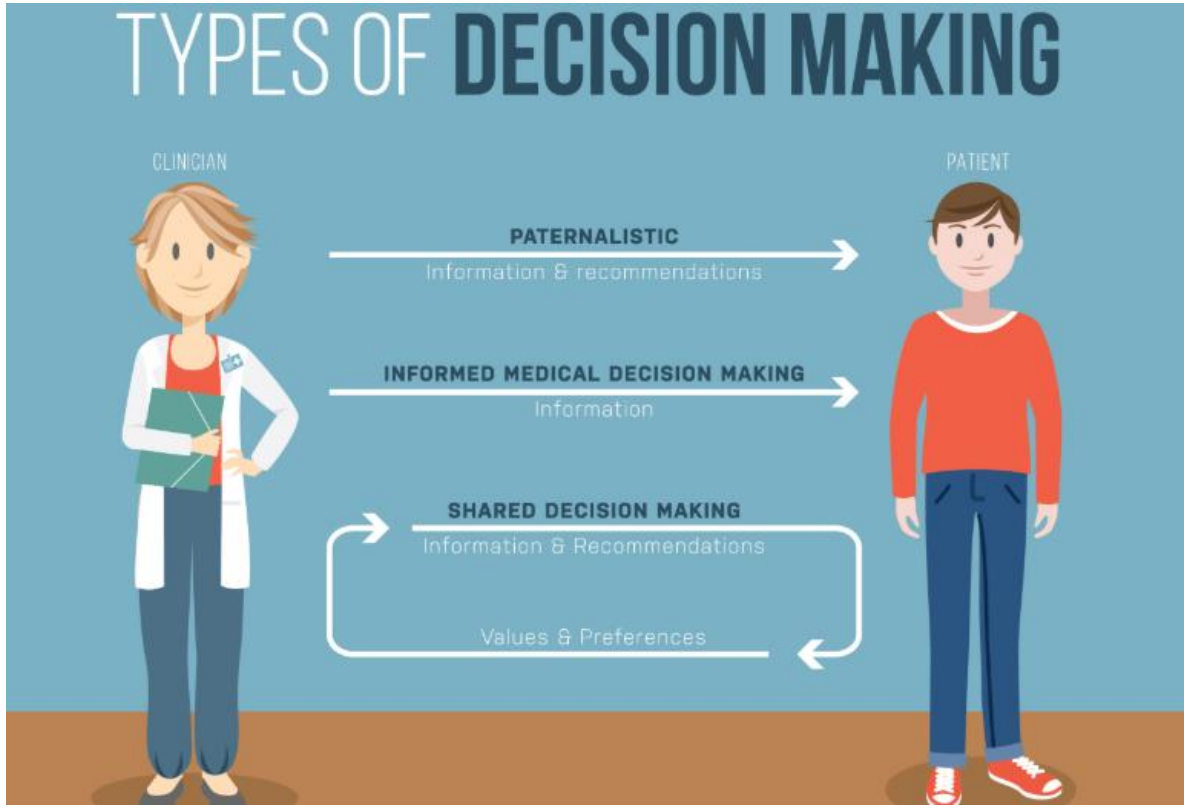


GU, genitourinary; mCRPC, metastatic castration resistant prostate cancer

Basketter V, et al. Br J Nurs 2018; 27(4 Suppl 2): S1-8

SHARED DECISION MAKING

- Support patients to articulate their understanding of their condition and of what they hope treatment will achieve
- Discuss options for treatment
- Discuss benefits and potential risks
- Discuss potential risk regarding existing medical conditions
- Ask patient their preferences
- Answer their questions

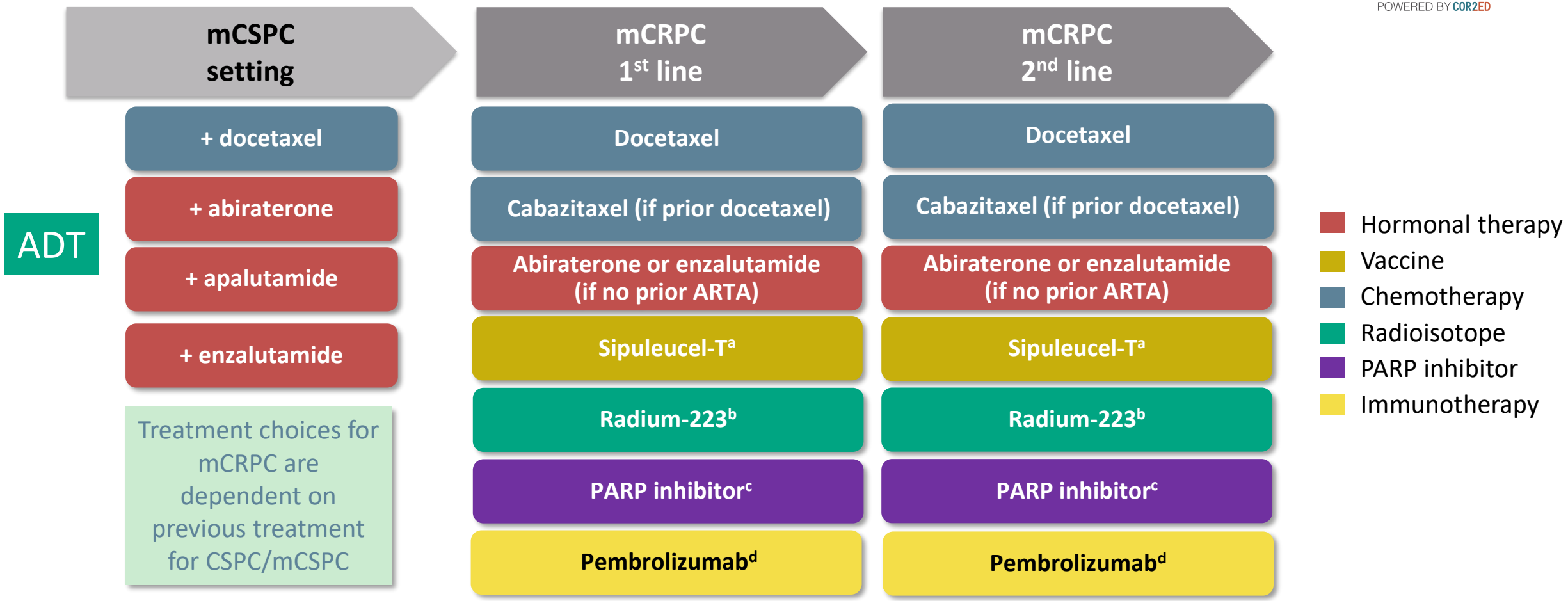


"Tell me and I forget. Teach me and I remember. Involve me and I learn" – Benjamin Franklin

www.therapeuticassociates.com/shared-decision-making/

UNDERSTANDING THE THERAPEUTIC OPTIONS FOR mCRPC

THERAPEUTIC OPTIONS IN mCRPC



Treatment options vary depending on local approvals and treatment guidelines

[a] Not recommended if visceral metastases are present; [b] For patients with symptomatic bone metastasis and no known visceral metastasis (in the EU, radium-223 should be restricted for use in patients who have had two previous treatments for metastatic prostate cancer or who cannot receive other treatments); [c] PARP inhibitor as per FDA indication: olaparib for men with *HRR* mutations, after ARTA, before or after taxane; rucaparib for men with *BRCA1* or *BRCA2* mutations after ARTA and taxane. Mutations can be germline or somatic; [d] FDA-approved for men with tumours identified as having high microsatellite instability (MSI high)

ADT, androgen deprivation therapy; ARTA, androgen receptor targeted agent; (m)CSPC, (metastatic) castration-sensitive prostate cancer; FDA, food and drug administration; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly (ADP-ribose) polymerase

Adapted from Birtle A. Women for Mankind Symposium. ESMO 2018

Product Prescribing Information; NCCN Clinical Practice Guidelines in Oncology – Prostate Cancer, Version 3.2020. Accessed 28-Jan-2021; Cornford P, et al. European oncology 2021; 79: 263-282 (EAU prostate cancer guidelines)

KEY PHASE 3 TRIALS IN mCRPC

OVERALL SURVIVAL RESULTS

Study	Treatments	N	Population	HR	95% CI; p value
TAX 327[1]	Docetaxel[a]/prednisone vs mitoxantrone/prednisone	1,006	mCRPC	0.76	0.62-0.95; p=0.009
TROPIC[2]	Cabazitaxel/prednisone vs mitoxantrone/prednisone	755	mCRPC (post docetaxel)	0.70	0.59-0.83; p<0.0001
COU-AA-301[3]	Abiraterone/prednisone vs prednisone	1,195	mCRPC (post docetaxel)	0.74	0.64-0.86; p<0.0001
COU-AA-302[4]	Abiraterone/prednisone vs prednisone	1,088	mCRPC (pre docetaxel)	0.81	0.70-0.93; p=0.0033
PREVAIL[5]	Enzalutamide vs placebo	1,717	mCRPC (pre docetaxel)	0.71	0.60-0.84; p<0.001
AFFIRM[6]	Enzalutamide vs placebo (or prednisone)	1,199	mCRPC (post docetaxel)	0.63	0.53-0.75; p<0.001
ALSYMPCA[7]	Radium-223 vs placebo	921	mCRPC	0.70	0.58-0.83; p<0.0001
IMPACT[8]	Sipuleucel-T vs placebo	512	mCRPC (pre chemotherapy[b])	0.78	0.61-0.98; p=0.03
CARD[9]	Cabazitaxel vs ASTI[c]	255	mCRPC (post docetaxel and post abiraterone or enzalutamide)	0.64	0.46-0.89; p=0.008
PROfound[10]	Olaparib vs ASTI[c]	387	mCRPC with HRR mutations (post abiraterone or enzalutamide and post chemotherapy[d]	0.69[e]	0.50-0.97; p=0.02

[a] 3-weekly docetaxel cycle; [b] 18.2% had received previous treatment with chemotherapy; [c] abiraterone or enzalutamide; [d] approximately 65% of patients had previously progressed on taxanes; [e] Results for cohort A of study: patients with alterations in *BRCA1, BRCA2, ATM*

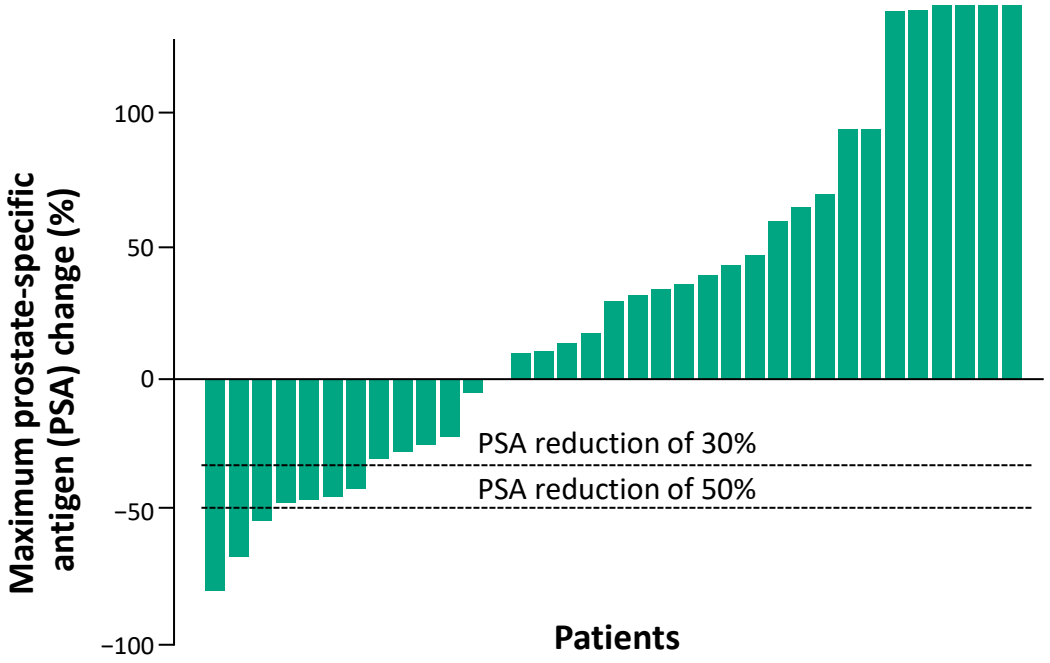
ASTI, androgen signaling targeted inhibitor; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer

1. Tannock IF, et al. N Engl J Med. 2004;351:1502-12; 2. de Bono JS, et al. Lancet. 2010;376:1147-54; 3. Fizazi K, et al. Lancet Oncol. 2012;13; 983-92; 4. Ryan C, et al. Lancet Oncol. 2015;16:152-60; 5. Beer TM, et al. N Engl J Med. 2014;371:424-33; 6. Scher HI, et al. N Engl J Med. 2012;367:1187-97; 7. Parker C, et al. N Engl J Med. 2013;369:213-23; 8. Kantoff PW, et al. N Engl J Med. 2010;363:411-22; 9. de Wit R, et al. N Engl J Med. 2019;381:2506-189; 10. Hussain M, et al. N Engl J Med. 2020;383:2345-357

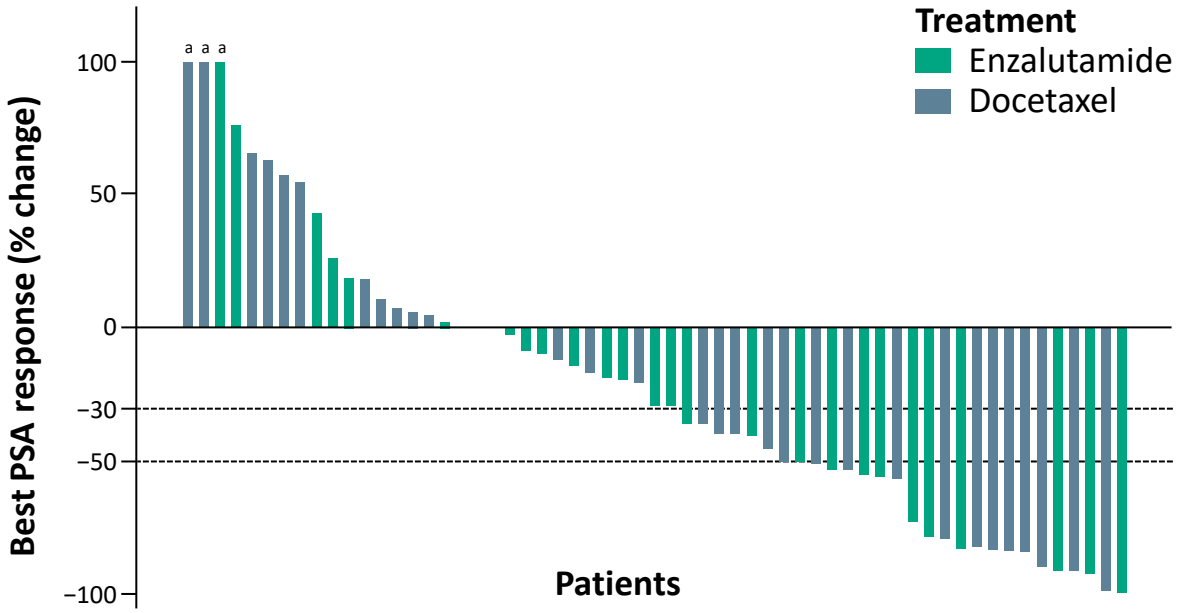
LIMITED BENEFIT TO SEQUENCING ANDROGEN RECEPTOR-TARGETED THERAPIES

- Different mechanisms of action are important!

RESPONSE TO ABIRATERONE AFTER TREATMENT WITH ENZALUTAMIDE[1]



ENZALUTAMIDE VS DOCETAXEL IN MEN WITH mCRPC PROGRESSING ON ABIRATERONE[2]



[a] Bar is truncated because of a PSA increase >100%.

CRPC, castration-resistant prostate cancer

1. Loriot Y, et al. Ann Oncol. 2013;24:1807-12; 2. Suzman DL, et al. Prostate. 2014;74:1278-85.

UNDERSTANDING TREATMENT SIDE EFFECTS AND APPROPRIATE MANAGEMENT

SECOND-GENERATION ARTAs FOR mCRPC: FAST FACTS

ABIRATERONE ACETATE 1,000 MG OD AND PREDNISONE 5 MG BID[1,2]

- Abiraterone must be taken on an empty stomach; prednisone to be taken with food
- **Most common side effects (≥10%):** fatigue, arthralgia, hypertension, nausea, oedema, hypokalaemia, hot flush, diarrhoea, vomiting, upper respiratory infection, cough, headache
- **Most common lab abnormalities (>20%):** anaemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolaemia, hyperglycaemia, hypokalaemia
- **Recommended monitoring**: transaminases, bilirubin, blood pressure, serum potassium, signs/symptoms of fluid retention or adrenocortical insufficiency
- **Managing side effects:** use of corticosteroids for adrenal insufficiency; dose modification or discontinuation for hepatotoxicity

ENZALUTAMIDE 160 MG OD[3,4]

- May be taken with or without food
- **Most common side effects (≥10%):** asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhoea, hypertension
- **Recommended monitoring**: complete blood count (CBC) with differential and liver function tests; additional international normalized ratio monitoring (if on warfarin); blood pressure. Monitor for signs/symptoms of ischaemic heart disease, posterior reversible encephalopathy syndrome, and seizure; evaluate fall and fracture risk
- **Managing side effects:** treat with bone-targeting agents

BID, twice daily; OD, once daily

1. Abiraterone Prescribing Information (October 2020); 2. Abiraterone acetate (June 2020). www.drugs.com/ppa/abiraterone-acetate.html. Accessed 4 January 2021; 3. Enzalutamide Prescribing Information (October 2020); 4. Enzalutamide (May 2020). www.drugs.com/mtm/enzalutamide.html. Accessed 4 January 2021

PARP INHIBITORS FOR *HRR*-MUTATED PROSTATE CANCER

OLAPARIB 300 MG BID OR RUCAPARIB 600 MG BID[1-4]

- **Most common side effects:**[a]
  - Anaemia
  - Fatigue
  - Nausea and vomiting
  - Diarrhoea
  - Decreased appetite
  - Thrombocytopenia
  - Cough (olaparib)
  - Dyspnoea (olaparib)
  - ALT/AST increased (rucaparib)
  - Rash (rucaparib)
  - Constipation (rucaparib)

[a] ≥10% for olaparib and ≥20% for rucaparib

- **Recommended monitoring:**
  - Monitor CBC testing at baseline and monthly thereafter
  - For prolonged haematological toxicities, monitor blood counts weekly and interrupt therapy until recovery
- **Managing side effects:**
  - Encourage gentle exercise with rest periods
  - Stay hydrated with caffeine-free liquids
  - Anti-emetics as needed
  - Antidiarrhoeal medications
  - Small frequent calorie-dense snacks
  - Consider a dosing holiday and/or dose reduction

ALT, alanine transaminase; AST, aspartate transaminase; BID, twice daily; CBC, complete blood count; OD, once daily

1. Olaparib Prescribing Information (December 2020); 2. Olaparib (August 2020). www.drugs.com/ppa/olaparib.html. Accessed 4 January 2021; 3. Rucaparib Prescribing Information (October 2020); 4. Rucaparib (April 2020). www.drugs.com/ppa/rucaparib.html. Accessed 4 January 2021

CHEMOTHERAPY: FAST FACTS

DOCETAXEL 75 MG/M² EVERY 21 DAYS WITH PREDNISONE 5 MG BID

- **Premedication:** dexamethasone 8 mg BID the day prior, day of, and day after
- **Recommended monitoring:**
  - Monitor CBC for anaemia, thrombocytopenia, neutropenia
  - Monitor chemistries (transaminases, bilirubin, alkaline phosphatase)
  - Monitor for fluid retention
  - Monitor for peripheral neuropathies
- **Managing side effects:**
  - Anti-emetics for nausea and vomiting
  - Antidiarrhoeals
  - Dose reduction to 60 mg/m^2 if required
- **Most common side effects:**
  - Neutropenia, febrile neutropenia, thrombocytopenia
  - Anaemia
  - Hypersensitivity
  - Neuropathy, myalgia
  - Dysgeusia, mucositis
  - Dyspnoea
  - Constipation
  - Nausea, diarrhoea, vomiting
  - Anorexia
  - Nail disorders, alopecia, skin reactions
  - Fluid retention
  - Asthenia
  - Pain

BID, twice daily; CBC, complete blood count

Docetaxel Prescribing Information (November 2020)

CHEMOTHERAPY: FAST FACTS

CABAZITAXEL 20 MG/M² EVERY 21 DAYS WITH PREDNISONE 5 MG BID

- Indicated following prior taxane therapy
- **Premedication (30 mins prior to cabazitaxel administration; intravenous):**
  - **Antihistamine** (dexchlorpheniramine 5 mg/diphenhydramine 25 mg)
  - **Corticosteroid** (dexamethasone 8 mg)
  - **H_2 antagonist** (ranitidine 50 mg)
- **Recommended monitoring:**
  - Monitor CBC for anaemia, thrombocytopenia, neutropenia
  - Monitor chemistries (transaminases, bilirubin, alkaline phosphatase)
  - Monitor for peripheral neuropathies
- **Most common side effects (≥10%):**
  - Neutropenia
  - Anaemia
  - Diarrhoea, constipation
  - Nausea, vomiting
  - Fatigue
  - Asthenia
  - Haematuria
  - Decreased appetite,
  - Back pain, abdominal pain
- **Managing side effects:**
  - Anti-emetics for nausea and vomiting
  - Antidiarrhoeals
  - Treatment with G-CSF (e.g. pegfilgrastim)
  - Dose modification if required

BID, twice daily; CBC, complete blood count; G-CSF, granulocyte-colony stimulating factor

Cabazitaxel Prescribing Information (December 2020)

IMMUNOTHERAPY AND PROSTATE CANCER

SIPULEUCEL-T (3 DOSES AT 2-WEEK INTERVALS)[1]

- Autologous activated cellular immunotherapy
- **Premedication:** with oral acetaminophen and an antihistamine such as diphenhydramine
- **Most common side effects (≥15%):** chills, fatigue, fever, back pain, nausea, joint ache, headache
- **Managing side effects:**
  - To manage infusion reactions, decrease the infusion rate or stop the infusion and administer appropriate medical treatment such as acetaminophen, intravenous H_1 and/or H_2 blockers, or low-dose intravenous meperidine

PEMBROLIZUMAB (200 MG EVERY 3 WEEKS/400 MG EVERY 6 WEEKS)[2]

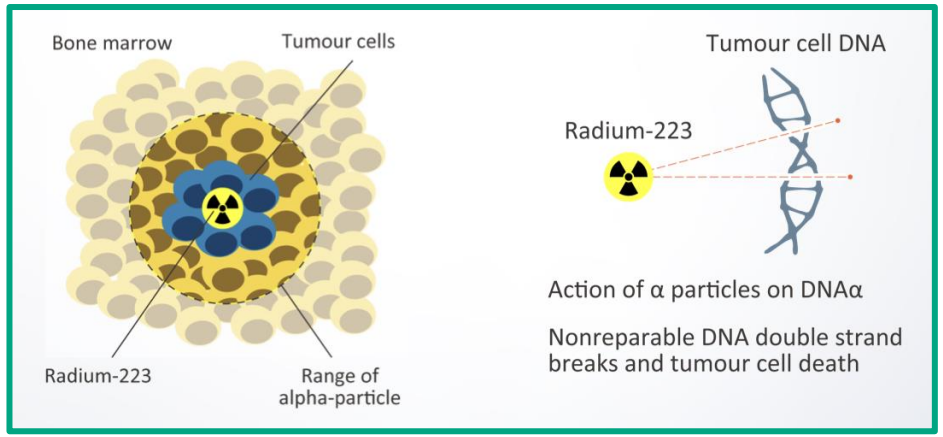
- MSI high or mismatch repair deficient cancer
- **Immune-related adverse reactions:** hepatitis, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, solid organ transplant rejection
- **Most common side effects (≥20%):** fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhoea, nausea, rash, pyrexia, cough, dyspnoea, constipation, pain, abdominal pain
- **Managing side effects:** withhold or permanently discontinue treatment based on severity and type of reaction
- **Recommended monitoring:** monitor chemistries (transaminases and bilirubin)

MSI high, high microsatellite instability

1. Sipuleucel-T Prescribing Information (July 2017); 2. Pembrolizumab Prescribing Information (November 2020)

RADIOPHARMACEUTICALS

RADIUM-223 (55 kBq/KG BODY WEIGHT OR 1.49 MICROCURIE/KG BODY WEIGHT)



- Indicated for **mCRPC with symptomatic bone metastases** (no visceral metastases)
- Administered as a 1-minute injection every 4 weeks; total of 6 injections
- Alpha particle-emitting isotope **radium-223** (as radium-223 dichloride); **mimics calcium and forms complexes with the bone mineral** hydroxyapatite at areas of increased bone turnover, such as bone metastases

- **Most common side effects (≥10%):** diarrhoea, nausea, vomiting, peripheral oedema
- **Most common haematological laboratory side effects (≥10%):** anaemia, lymphocytopenia, leukopenia, neutropenia, thrombocytopenia
- **Recommended monitoring:** CBC/differential blood count prior to each dose
- **Recommended monitoring:** Bone Marrow Suppression: Measure blood counts prior to treatment initiation and before every dose. Discontinue Radium-223 if haematologic values do not recover within 6-8 weeks after treatment. Monitor patients with compromised bone marrow reserve closely. Discontinue treatment in patients who experience life-threatening complications despite supportive care measures.

CBC, complete blood count; kBq, kilobecquerel; mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate specific membrane antigen

1. Radium-223 Prescribing Information (December 2019)

Figure adapted from: Deshayes E, et al. Drug Des Devel Ther. 2017;11:2643-51.

SUMMARY

- The range of treatment options for patients with mCRPC has dramatically increased during the past decade
- Sequencing treatments in mCRPC is evolving with the variety of available treatment options:
  - 2nd-generation ARTAs, PARP inhibitors, immunotherapy, chemotherapy, and radiolabelled isotopes
- Choice of treatment for mCRPC patients is influenced by:
  - **Prior treatments** the patient may have received for their prostate cancer
  - **Novel mechanism of action** important due to treatment resistance
  - **Clinical factors and patient preferences** guide treatment choice
- **GU nurses play an integral role in supporting patients during treatment sequencing decisions**

GU, genitourinary; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly (ADP-ribose) polymerase

https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Access date: 16 Jan 2020

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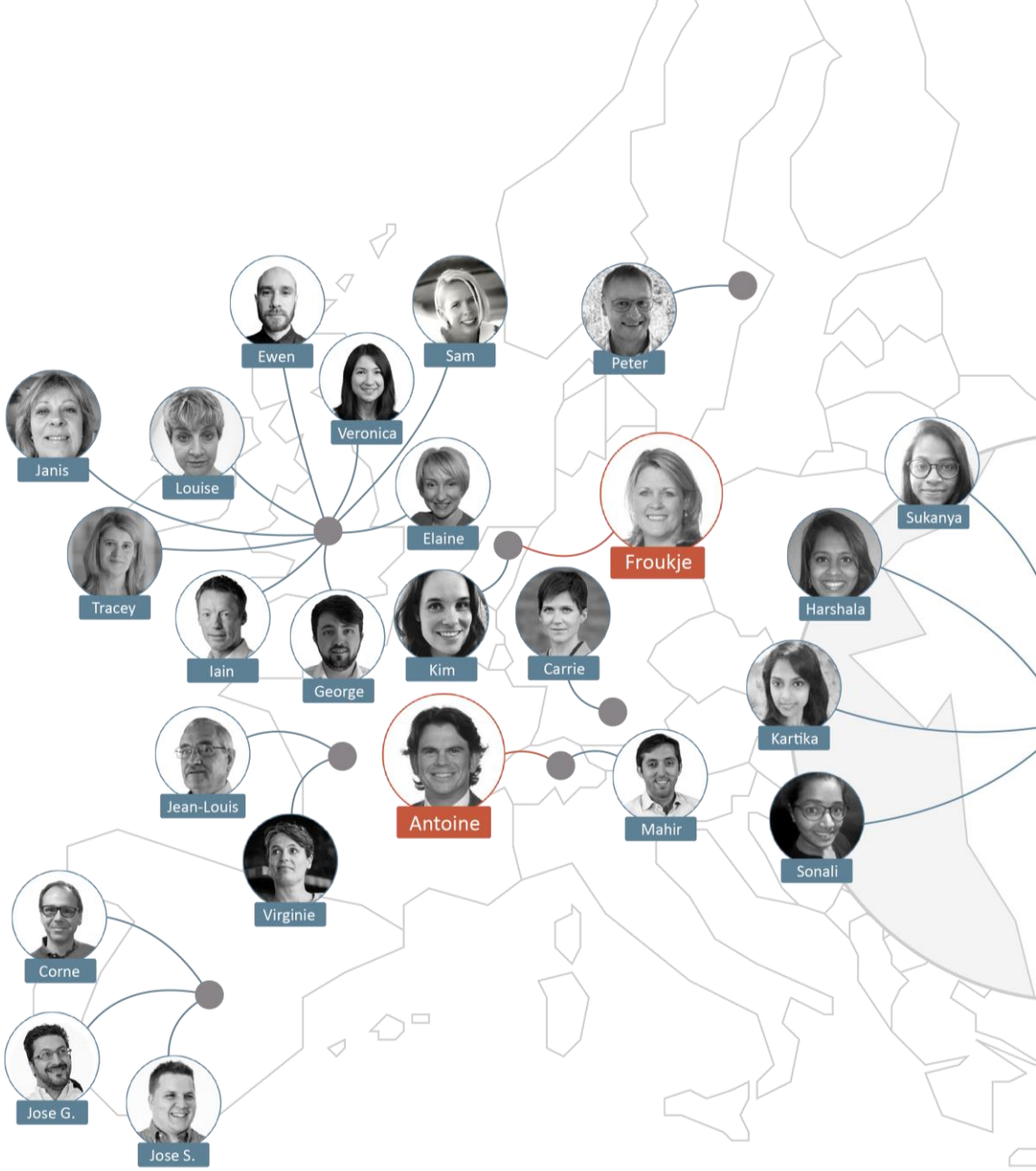

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