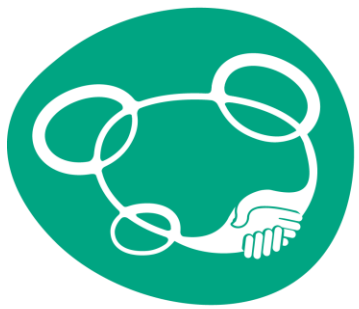

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PRACTICAL CONSIDERATIONS WHEN SEQUENCING TREATMENTS FOR mCRPC PATIENTS IN CLINICAL PRACTICE

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AUGUST 2021

mCRPC, metastatic castration-resistant prostate cancer

DISCLAIMER AND DISCLOSURE

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Joanne Chien does not have any relevant financial relationships to disclose.

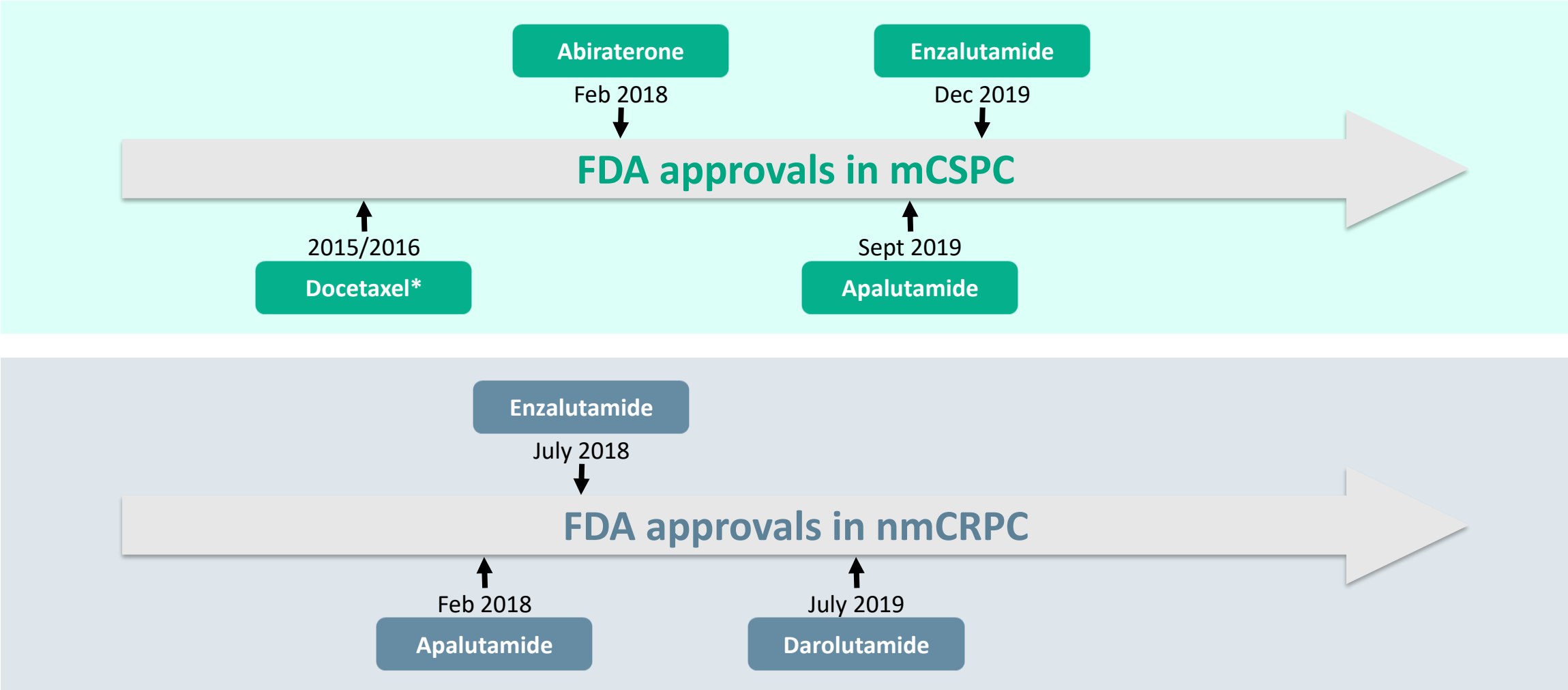
INTRODUCTION

- Treatment options for metastatic castration-resistant prostate cancer (mCRPC) have increased dramatically over recent years
- Prior treatments during metastatic castration-sensitive prostate cancer (mCSPC) and non-metastatic castration-resistant prostate cancer (nmCRPC) impact future treatment decisions
  - mCRPC patients may have already received treatment with an androgen-receptor pathway inhibitor (ARPI)
- Sequencing is evolving: numerous studies ongoing to develop new therapies, optimise sequencing and/or combination therapies
- Cross-resistance can occur with ARPIs so it is preferable to select subsequent therapies with a different mechanism of action
- Real-world findings provide valuable information, including data in patients with comorbidities

ARPI, androgen receptor pathway inhibitor; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer

1. Lowrance W, et al. Advanced Prostate Cancer: AUA/ASTRO/SUO guideline. Available from https://www.auanet.org/guidelines/advanced-prostate-cancer. Accessed Jul 30, 2021; 2. NCCN Clinical Practice Guidelines in Oncology – Prostate Cancer, version 2.2021. Accessed Jul 30, 2021

APPROVED TREATMENTS FOR mCSPC AND nmCRPC



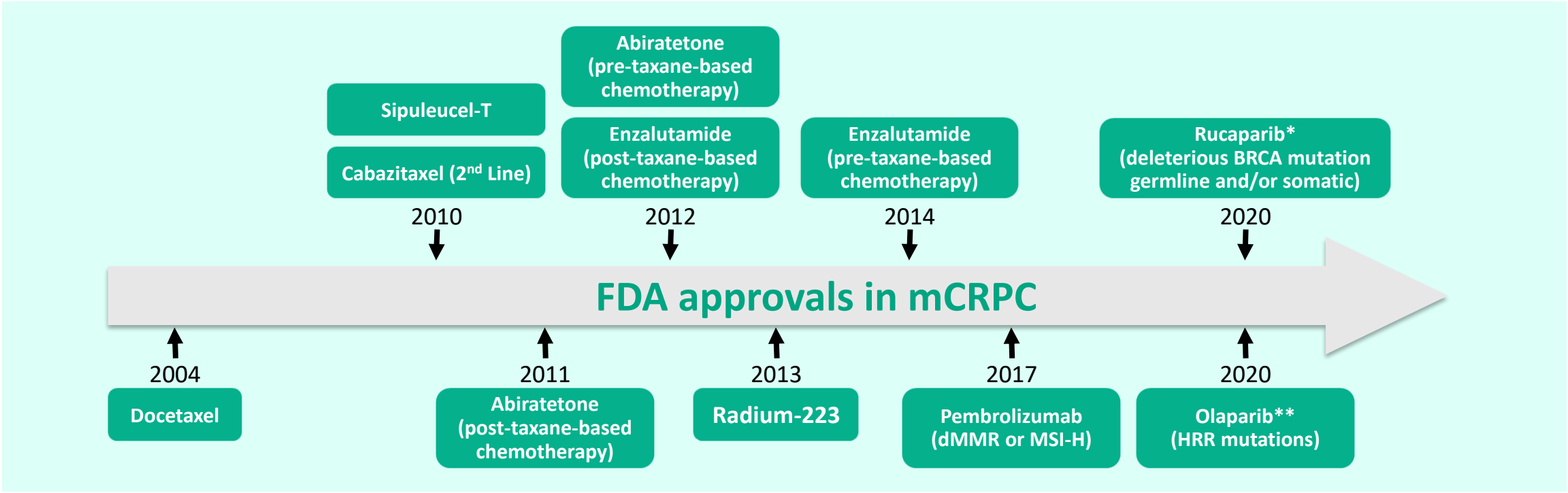
*Level-1 evidence, no SNDA filed

FDA, Food & Drug Administration; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; SNDA, supplementary new drug application

www.fda.gov

APPROVED TREATMENTS FOR mCRPC

- Treatment choice for mCRPC is dependent on prior treatments received during mCSPC (doce, abi, enza, apa) or nmCRPC (apa, enza, daro)



*Progressed following androgen-axis targeted treatment and taxane-based chemotherapy; **Progressed following treatment with enzalutamide or abiraterone
abi, abiraterone; apa, apalutamide; BRCA, breast cancer; daro, darolutamide; dMMR, deficient DNA mismatch repair; doce, docetaxel; enza, enzalutamide; FDA, Food & Drug Administration; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; MSI-H, microsatellite instability-high. www.fda.gov

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Prostate Cancer

NCCN Guidelines Index
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Discussion

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[zz,ccc,ddd,eee]

No prior docetaxel/no prior novel hormone therapy[fff]	Prior novel hormone therapy/No prior docetaxel[fff,lll]
• Preferred regimens ▸ Abiraterone[t,ggg] (category 1[hhh]) ▸ Docetaxel[aaa,iii] (category 1) ▸ Enzalutamide[t] (category 1) •Useful in certain circumstances ▸ Sipuleucel-T[aaa,jjj] (category 1) ▸ Radium-223[kkk] for symptomatic bone metastases (category 1) •Other recommended regimens ▸ Other secondary hormone therapy[t]	• Preferred regimens ▸ Docetaxel (category 1)[aaa] ▸ Sipuleucel-T[aaa,jjj] • Useful in certain circumstances ▸ Olaparib for HRRm (category 1)[mmm] ▸ Cabazitaxel/carboplatin[aaa,nnn] ▸ Pembrolizumab for MSI-H or dMMR[aaa] ▸ Radium-223[kkk] for symptomatic bone metastases (category 1) ▸ Rucaparib for BRCAm[ooo] • Other recommended regimens ▸ Abiraterone[t,ggg] ▸ Abiraterone + dexamethasone[ggg,ppp] ▸ Enzalutamide[t] ▸ Other secondary hormone therapy[t]
Prior docetaxel/no prior novel hormone therapy[fff]	Prior docetaxel and prior novel hormone therapy[fff,lll]
• Preferred regimens ▸ Abiraterone[t, ggg] (category 1) ▸ Cabazitaxel[aaa] ▸ Enzalutamide[t] (category 1) • Useful in certain circumstances ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[aaa] ▸ Cabazitaxel/carboplatin[aaa,nnn] ▸ Pembrolizumab for MSI-H or dMMR[aaa] ▸ Radium-223[kkk] for symptomatic bone metastases (category 1) • Other recommended regimens ▸ Sipuleucel-T[aaa,jjj] ▸ Other secondary hormone therapy[t]	(All systemic therapies are category 2B if visceral metastases are present) • Preferred regimens ▸ Cabazitaxel[aaa] (category 1[hhh]) ▸ Docetaxel rechallenge[aaa,eee] • Useful in certain circumstances ▸ Olaparib for HRRm (category 1)[hhh,mmm] ▸ Cabazitaxel/carboplatin[aaa,nnn] ▸ Pembrolizumab for MSI-H or dMMR[aaa] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[aaa] ▸ Radium-223[kkk] for symptomatic bone metastases (category 1[hhh]) ▸ Rucaparib for BRCAm[ooo] • Other recommended regimens ▸ Abiraterone[t,ggg] ▸ Enzalutamide[t] ▸ Other secondary hormone therapy[t]

BRCAm, breast cancer mutated; dMMR, deficient DNA mismatch repair; HRRm, homologous recombination repair mutated; MSI-H, microsatellite instability-high

TREATMENT PATTERNS IN PATIENTS WITH mCRPC IN A REAL-WORLD CLINICAL PRACTICE SETTING IN THE UNITED STATES

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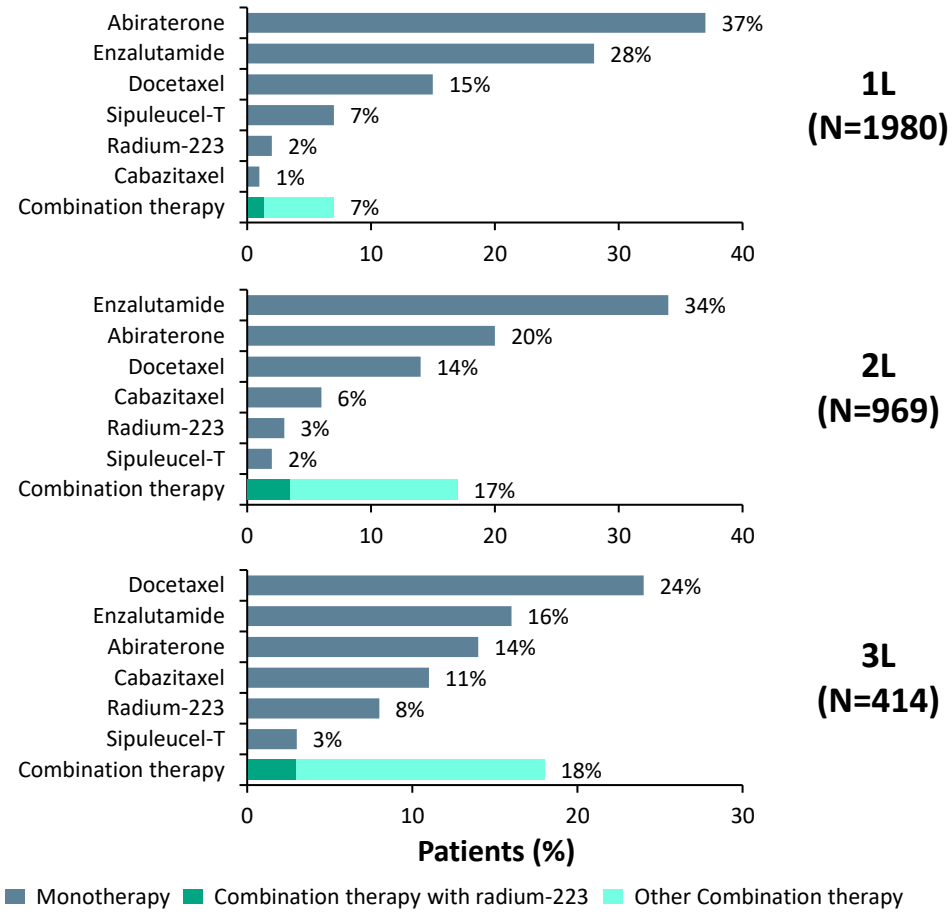
Duration of mCRPC treatment by line of therapy for 1L, 2L and 3L therapies

Treatment	Treatment duration, months[a]					
	1L		2L		3L	
	N	Median (min-max)	N	Median (min-max)	N	Median (min-max)
Docetaxel	293	4.6 (0.03-28.9)	137	3.8 (0.03-37.2)	101	4.1 (0.03-20.8)
Abiraterone	742	5.4 (0.03-47.5)	193	4.8 (0.03-53.4)	59	4.2 (0.3-17.5)
Enzalutamide	552	5.8 (0.03-48.6)	326	5.4 (0.03-36.5)	68	4.0 (0.03-27.2)
Other combination	107	4.7 (0.27-28.6)	112	4.3 (0.03-24.0)	51	4.9 (0.03-28.4)
Sipuleucel-T	140	3.5 (0.03-51.4)	16	2.5 (0.03-6.8)	14	2.8 (0.03-13.2)
Cabazitaxel	22	2.2 (0.03-6.3)	61	2.6 (0.03-26.3)	46	3.1 (0.03-24.5)
Radium overall	94	6.0 (0.03-34.4)	85	5.0 (0.03-22.7)	56	4.4 (0.03-13.1)
Radium-223	47	4.7 (0.03-16.1)	32	4.9 (0.03-13.3)	33	5.1 (0.03-11.0)
Radium combination	47	7.3 (0.7-34.4)	53	5.2 (0.4-22.7)	23	4.1 (0.8-13.1)
Other	30	1.9 (0.03-18.4)	39	1.9 (0.03-22.9)	19	1.7 (0.4-12.9)

[a]In cases in which patients were treated with combination therapy, the duration of therapy was defined as the period between the first and last administration of any agent(s) in the combination

Patients with mCRPC receiving various life-prolonging therapies in the 1L, 2L and 3L settings



1L, first line; 2L, second line; 3L, third line; mCRPC, metastatic castration-resistant prostate cancer

George D, et al. Clinical Genitourinary Cancer. 2020;18:284-94

TREATMENT PATTERNS IN PATIENTS WITH mCRPC IN A REAL-WORLD CLINICAL PRACTICE SETTING IN THE UNITED STATES

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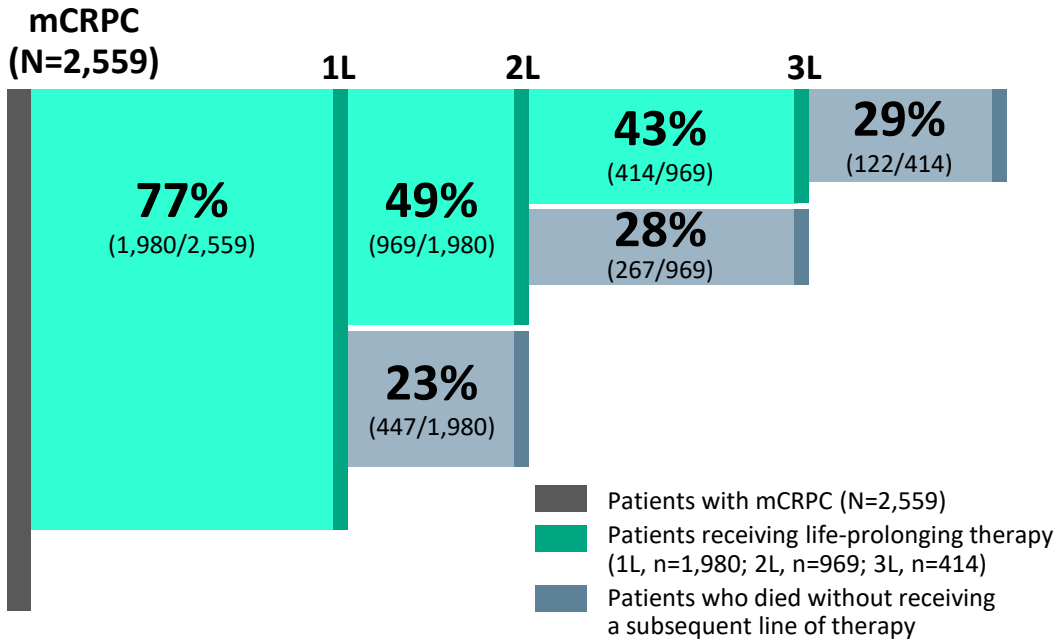
THE PROPORTION OF PATIENTS WITH mCRPC RECEIVING LIFE-PROLONGING ANTICANCER THERAPIES IN THE 1L, 2L AND 3L SETTINGS



A total of 23%, 28% and 29% of patients did not receive a subsequent line of therapy after 1L, 2L and 3L therapy, respectively. In this Sankey diagram, a node to the right illustrates patients with mCRPC (grey) transitioning to a subsequent line of therapy (green) or death without receiving a subsequent line (blue).

- The median OS was longer in patients who received life-prolonging therapies (23.7 months; 95% CI: 22.3-25.1 months) than in those who did not (10.1 months; 95% CI: 9.1-11.5 months)
- Underutilisation of life-prolonging treatment
- Most common therapies per line: abiraterone/prednisone (1L), enzalutamide (2L), docetaxel (3L)
- Back-to-back use of abiraterone/prednisone and enzalutamide was common despite known cross-resistance
- The results suggested an underutilisation of radium-223 and BHAs

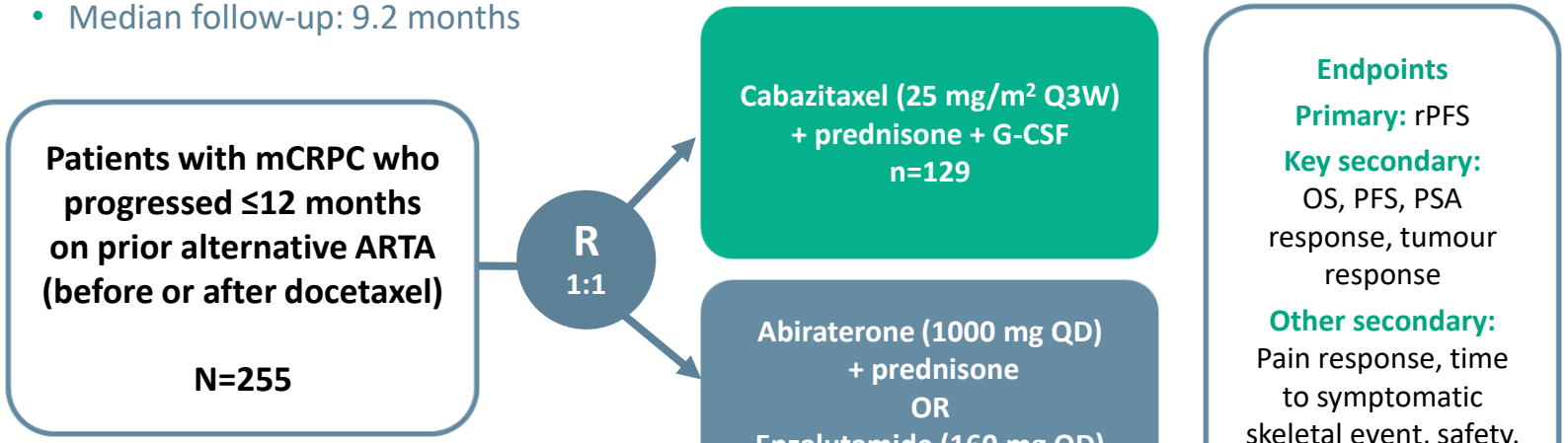
1L, first line; 2L, second line; 3L, third line; BHAs, bone health agents; CI, confidence interval; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival

George D, et al. Clinical Genitourinary Cancer. 2020;18:284-94

CARD STUDY DESIGN

- Phase 4 trial of cabazitaxel vs. abiraterone or enzalutamide in previously treated mCRPC patients

  - Multicenter, randomised, open-label study
  - Enrolment: Nov 2015 – Nov 2018
  - Median follow-up: 9.2 months



Stratification factors:

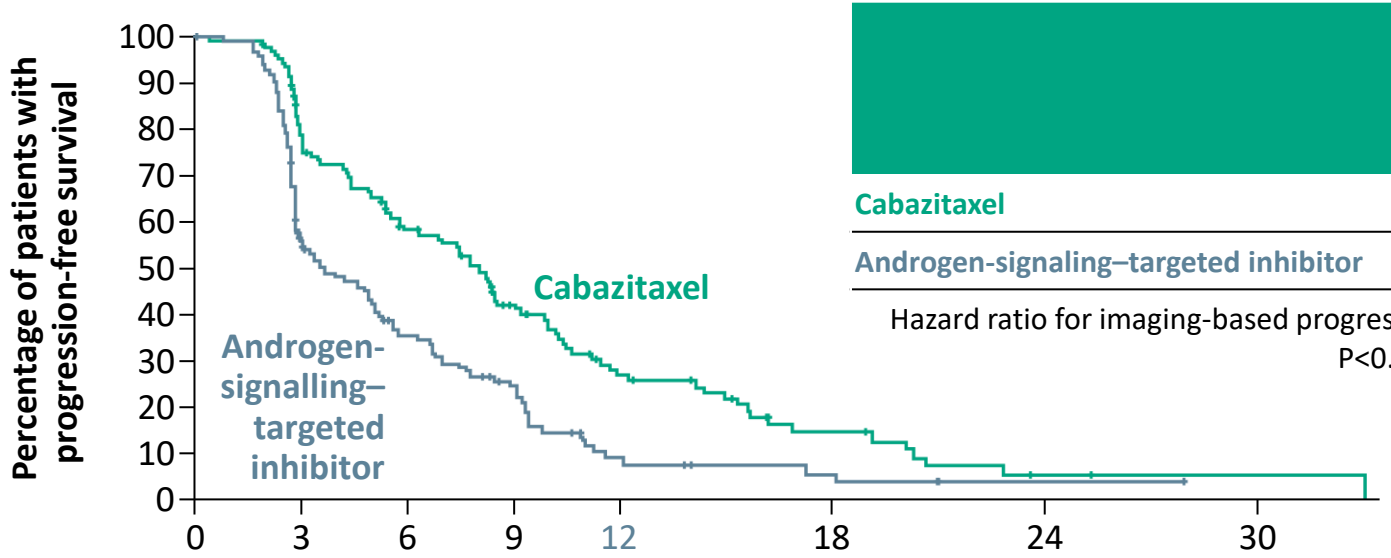
- ECOG PS (0/1 vs 2)
- Time to progression on prior alternative ARTA (0–6 vs >6–12 months)
- Timing of ARTA (before vs after docetaxel)

ARTA, androgen receptor-targeted agents; ECOG PS, eastern cooperative oncology group performance status; G-CSF, granulocyte colony stimulating factor; HRQoL, health-related quality of life; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; Q3W, every three weeks; QD, once daily; (r)PFS, (radiographic) progression free survival; PSA, prostate-specific antigen

1. de Wit R, et al. Ann Oncol. 2019;30(suppl_5):v851-v934; 2. de Wit R, et al. N Engl J Med. 2019;381:2506-18.

CARD STUDY: PRIMARY ENDPOINT

RADIOGRAPHIC PROGRESSION-FREE SURVIVAL



	No. of patients	Median imaging-based progression-free survival (95% CI) *mo*
Cabazitaxel	129	8.0 (5.7-9.2)
Androgen-signaling–targeted inhibitor	126	3.7 (2.8-5.1)

Hazard ratio for imaging-based progression or death, 0.54 (95% CI, 0.40-0.73)
P<0.001

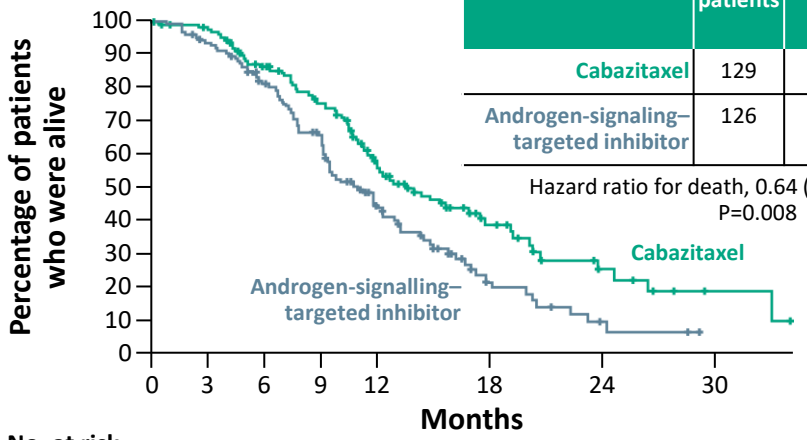
No. at risk								
Cabazitaxel	129	91	64	41	23	9	2	1
Androgen-signalling–targeted inhibitor	126	61	36	22	7	3	1	0

CI, confidence interval

de Wit, R et al. N Engl J Med. 2019;381:2506-18

CARD STUDY: SECONDARY ENDPOINTS

OVERALL SURVIVAL

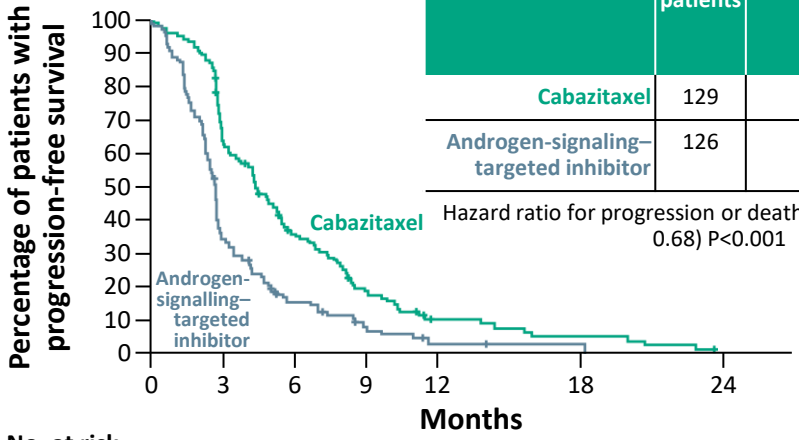


	No. of patients	Median overall survival (95% CI) *mo*
Cabazitaxel	129	13.6 (11.5-17.5)
Androgen-signaling–targeted inhibitor	126	11.0 (9.2-12.9)

Hazard ratio for death, 0.64 (95% CI, 0.46-0.89) P=0.008

No. at risk								
Cabazitaxel	129	122	96	77	51	21	8	2
Androgen-signalling–targeted inhibitor	126	116	88	64	39	11	3	0

PROGRESSION-FREE SURVIVAL



	No. of patients	Median progression-free survival (95% CI) *mo*
Cabazitaxel	129	4.4 (3.6-5.4)
Androgen-signaling–targeted inhibitor	126	2.7 (2.4-2.8)

Hazard ratio for progression or death, 0.52 (95% CI, 0.40-0.68) P<0.001

No. at risk							
Cabazitaxel	129	82	39	20	8	4	0
Androgen-signalling–targeted inhibitor	126	42	16	7	2	1	0

- Chemotherapy with cabazitaxel was superior to the alternate NHA:
  - Improved OS, PFS, PSA response, tumour response, pain response, time to SSE
- No new safety signals were observed
- Improved QOL favouring cabazitaxel
- Cabazitaxel should be offered prior to 2nd NHA

CI, confidence interval; NHA, novel hormonal agents; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen, SSE, symptomatic skeletal event; QOL, quality of life

1. de Wit, R et al. N Engl J Med. 2019;381:2506-18; 2. Fizazi K, et al. Lancet Oncol. 2020:21:1513-25

REAL-WORLD EVIDENCE FOR PATIENTS WITH mCRPC TREATED WITH CABAZITAXEL

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COMPARISON WITH THE RANDOMISED CLINICAL STUDY CARD

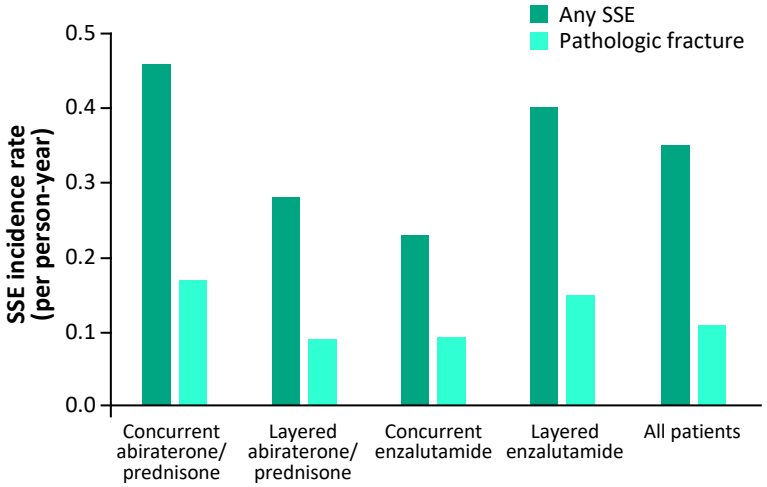
	CARD-like cohort cabazitaxel (N=452)	CARD study cabazitaxel (N=129)
Treatment duration		
Median duration of treatment exposure, weeks (range)	12.9 (1.0-117.4)	22.0 (3.0-88.0)
Treatment with first ARTA, weeks (range)		
≤12 months	21.6 (1.0-117.4), n=136	23.9 (3.0-87.9)
>12 months	25.9 (1.0-108.6), n=297	21.6 (6.0-51.7)
Median number of cycles, n (range)	6 (1-15)[b]	7.0 (1.0-29.0)
Treatment reduction		
Patients with ≥1 cycle administered at reduced dose, n (%)	250 (55.3)	27 (21.4)
Treatment discontinuation		
Patients who discontinued treatment, n (%)	452 (100)	120 (95.2)
Reasons for discontinuation		
Disease progression	293 (64.8)	55 (43.7)
Adverse event	–	25 (19.8)
Investigator decision	–	21 (16.7)
Patient request	39 (8.6)	12 (9.5)
Other reason	29 (8.6)	7 (5.6)
To improve quality of life	24 (5.3)	–
Not reported	57 (12.6)	0

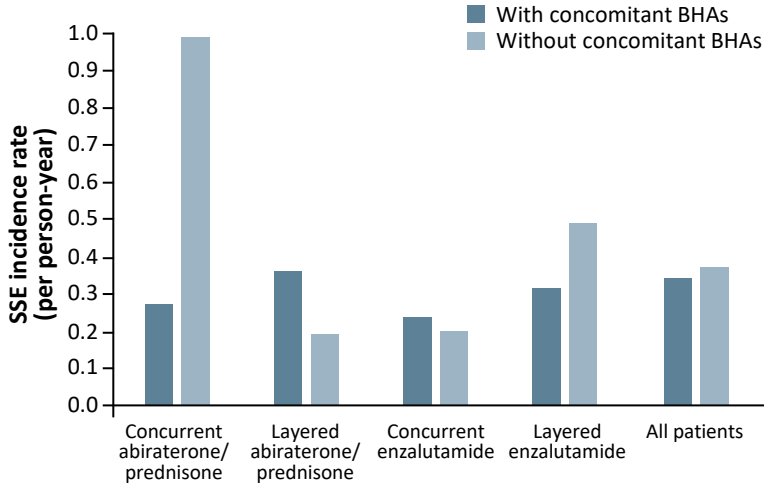
- More patients received both abi and enza before cabazitaxel despite evidence of cross-resistance
- More patients received lower dose; however, duration of treatment was comparable to the CARD study despite poorer ECOG and more aggressive disease features
- Treatment with ARTA beyond PSA progression is common
- Reflective of the CARD study population

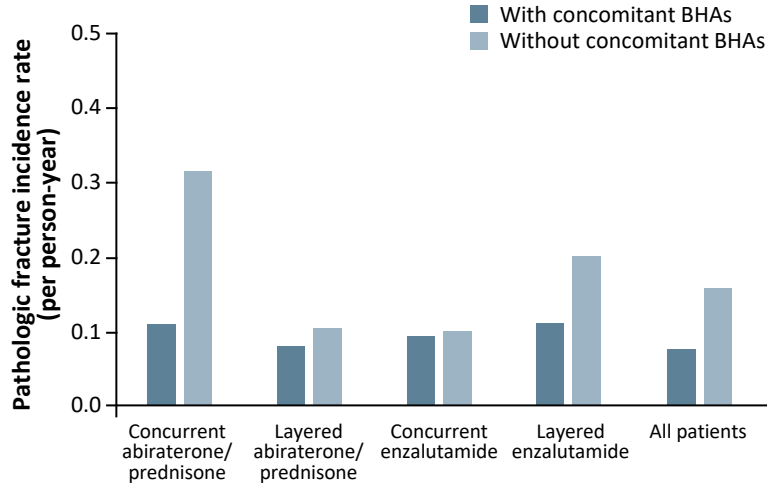
Abi, abiraterone; ARTA, androgen receptor-targeted agent; ECOG, Eastern Cooperative Oncology Group; enza, enzalutamide; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen

de Wit R, et al. Ann of Oncol. 2020:31(suppl_4):S518 (ESMO 2020 poster)

CONCURRENT OR LAYERED TREATMENT WITH RADIUM-223 AND ENZALUTAMIDE OR ABIRATERONE/PREDNISONE







SUMMARY OF OVERALL SURVIVAL

	Radium-223 + abiraterone/prednisone (N=136)		Radium-223 + enzalutamide (N=167)		All patients (N=625)
	Concurrent (n=39)	Layered (n=97)	Concurrent (n=44)	Layered (n=123)	
Median follow-up time, months (range)	13 (0-40)	10 (0-42)	12 (1-40)	10 (0-32)	9 (0-46)
Median OS from mCRPC diagnosis, months (95% CI)	28.3 (18.4-NR)	34.5 (25.9–50.9)	28.1 (16.7-NR)	26.9 (25.0-34.4)	28.1 (25.7-30.4)
Median OS from radium-223 initiation, months (95% CI)	22.1 (14.7-NR)	19.3 (11.3-27.5)	19.1 (12.3-NR)	15.2 (11.6-16.3)	15.2 (13.2-16.3)

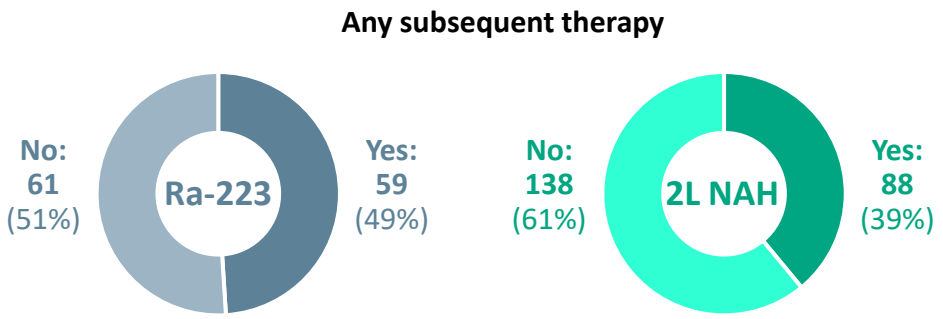
- Combination of radium-223 with either abiraterone/prednisone or enzalutamide was common in the US clinical setting
  - Layered approach (≥30 days) was more common than concurrent (within 30 days)
- Lower incidence of pathological fracture in patients receiving BHAs
  - BHAs were underutilized

BHA, bone health agent; CI, confidence interval; mCRPC, metastatic castration-resistant prostate cancer; NR, not reached; OS, overall survival; SSE, symptomatic skeletal event

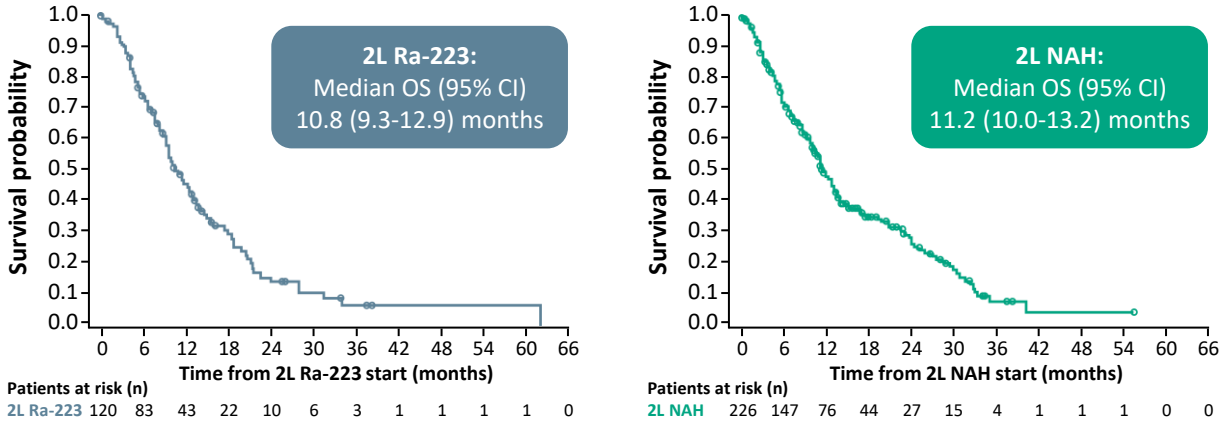
Shore N, et al. Prostate Cancer and Prostatic Dis. 2020;23:680-8

PHENIX REAL-WORLD STUDY: SEQUENTIAL NAH OR RA-223 AFTER PROGRESSION ON 1L NAH

SUBSEQUENT LIFE-PROLONGING THERAPY AFTER 2L RA-223 OR 2L NAH



OVERALL SURVIVAL FROM START OF 2L THERAPY



- Patients on 2L Ra-223 had similar rates of subsequent life-prolonging therapies as patients on 2L NAH (49% vs 39%)
- The rate of SSEs after 2L start was similar in both cohorts

SYMPTOMATIC SKELETAL EVENTS

Patients with SSEs after 2L start, n/N (%)

	All patients	Patients with prior SSEs before 2L start
2L Ra-223	32/120 (27)	18/61 (30)
2L NAH	49/226 (22)	23/75 (31)

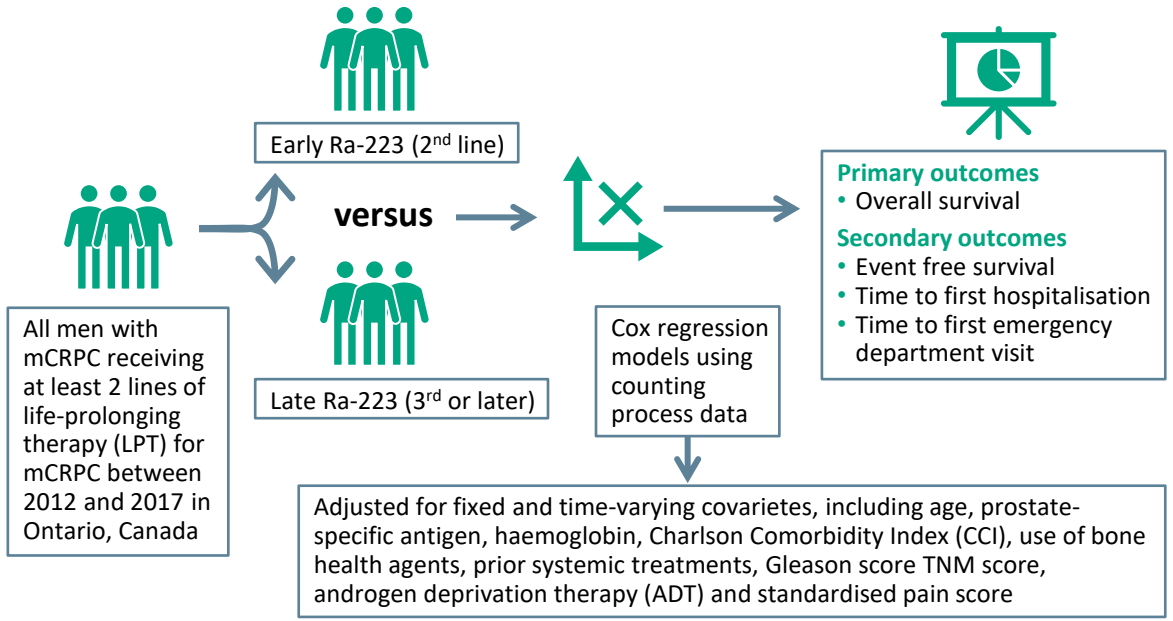
- 57% of the 2L Ra-223 cohort and 58% of the 2L NAH cohort were taking bone health agents (mostly denosumab) at start of 2L therapy

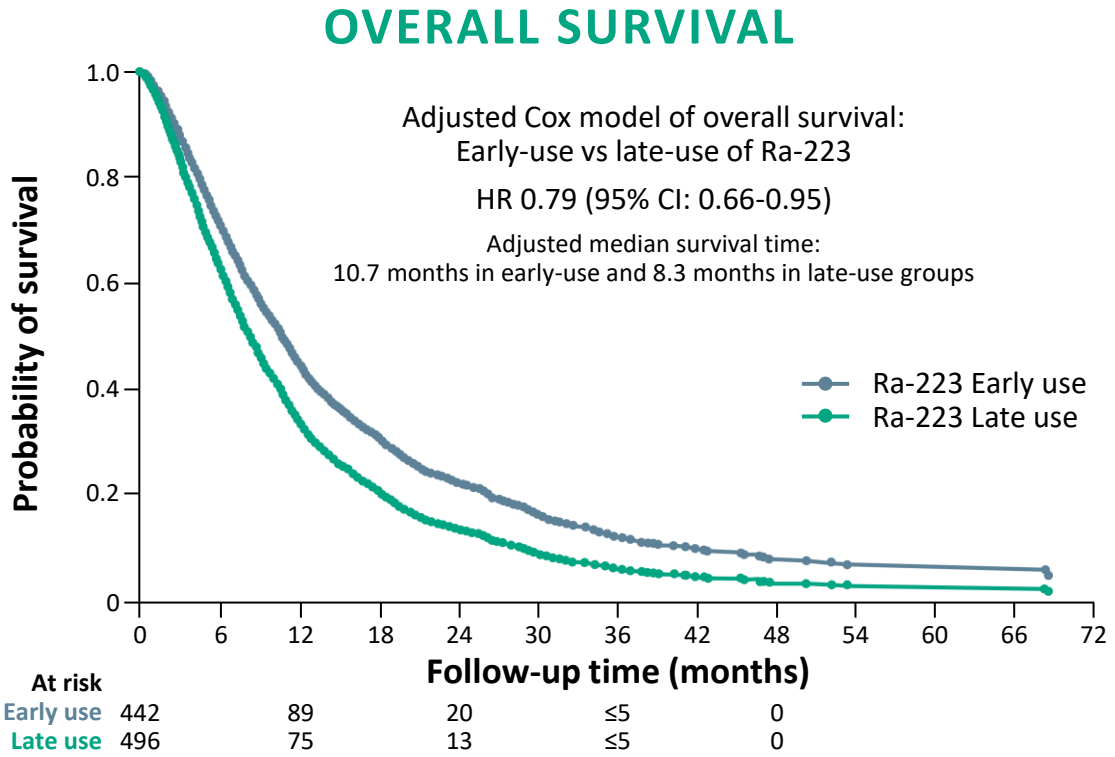
2L, second line; BHA, bone health agents; CI, confidence interval; NAH, novel antihormone; Ra-223, radium-223; OS, overall survival; SSE, symptomatic skeletal event

Sartor O, et al. J Clin Oncol. 2021;39(suppl_6):abstract 48 (ASCO GU 2021 poster)

Ra-223 EARLY VS LATE IN THE TREATMENT SEQUENCE REAL-WORLD DATA

- Patients who received Ra-223 in second-line versus third-line or later had better outcomes
- Patients who received Ra-223 early received less chemotherapy, but had better survival
- EFS was better in the early vs late Ra-223 cohort (HR 0.71, 95% CI 0.58-0.86)





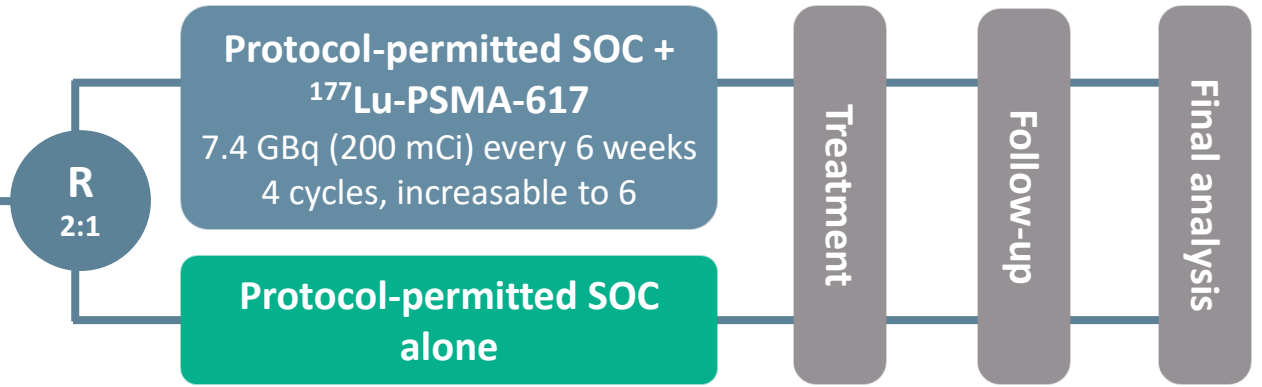
ADT, androgen deprivation therapy; CCI, Charlson Comorbidity Index; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; LPT, life-prolonging therapy; mCRPC, metastatic castration-resistant prostate cancer; Ra-223, radium-223; TNM, tumour, node, metastasis

Mbuagbaw L, et al. J Clin Oncol. 2021;39(suppl_6):abstract 136 (ASCO GU 2021 poster presentation)

VISION TRIAL: LUTETIUM-177-PSMA-617 FOR mCRPC

Eligible patients:

- Previous treatment with **both**
  - ≥1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomisation
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0-2
- Life expectancy >6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11



Randomisation stratified by:

- ECOG status (0-1 or 2)
- LDH (high or low)
- Liver metastases (yes or no)
- Androgen receptor pathway inhibitors in SOC (yes or no)

CT/MRI/bone scans:

- Every 8 weeks (treatment)
- Every 12 weeks (follow-up)
- Blinded independent central review

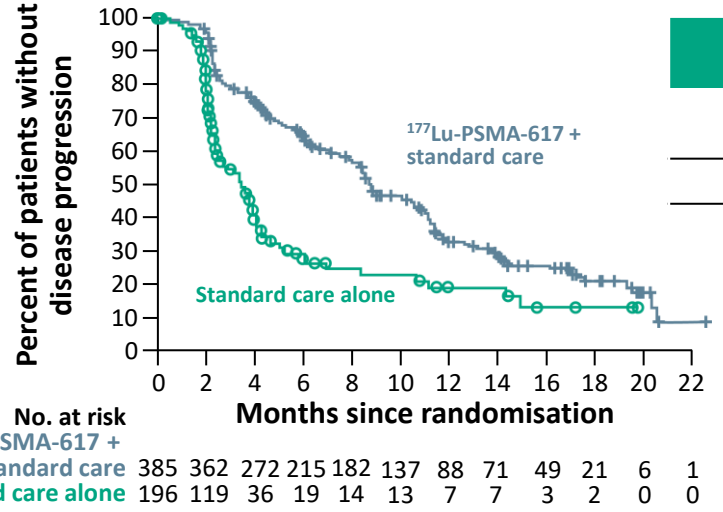
CT, computerised tomography; ECOG, Eastern Cooperative Oncology Group; Ga, gallium; GBq, gigabecquerel; LDH, lactate dehydrogenase; Lu-177, lutetium-177; mCi, millicurie; mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging PET, positron emission tomography; PSMA, prostate-specific membrane antigen; SOC, standard of care

Sartor O, et al. N Engl J Med. 2021. DOI: 10.1056/NEJMoa2107322 (ASCO 2021 oral presentation)

VISION TRIAL: LUTETIUM-177-PSMA-617 FOR mCRPC

ALTERNATE PRIMARY ENDPOINTS

Imaging-based progression-free survival

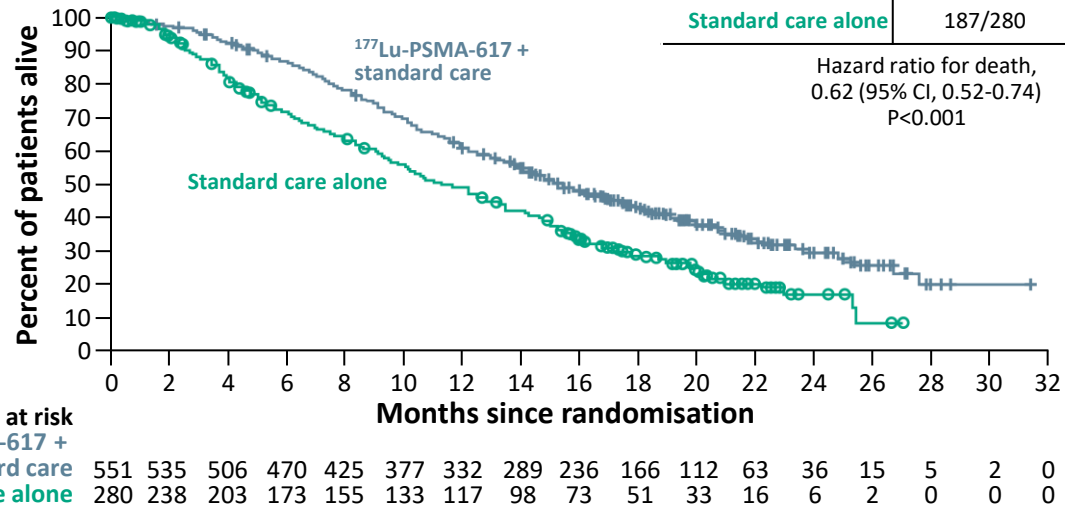


	No. of events/ No. of patients	Median *mo*
^{177}Lu-PSMA-617 + standard care	254/385	8.7
Standard care alone	93/196	3.4

Hazard ratio for progression or death, 0.40 (99.2% CI, 0.29-0.57) P<0.001

- Lu177 + SOC significantly improved PFS and OS vs SOC alone
- Potential new treatment option in mCRPC post both ARI and taxane chemotherapy

Overall survival



	No. of events/ No. of patients	Median *mo*
^{177}Lu-PSMA-617 + standard care	343/551	15.3
Standard care alone	187/280	11.3

Hazard ratio for death, 0.62 (95% CI, 0.52-0.74) P<0.001

ARI, androgen receptor inhibitor; CI, confidence interval; Lu-177, lutetium-177; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; PSMA, prostate-specific membrane antigen; SOC, standard of care; QOL, quality of life

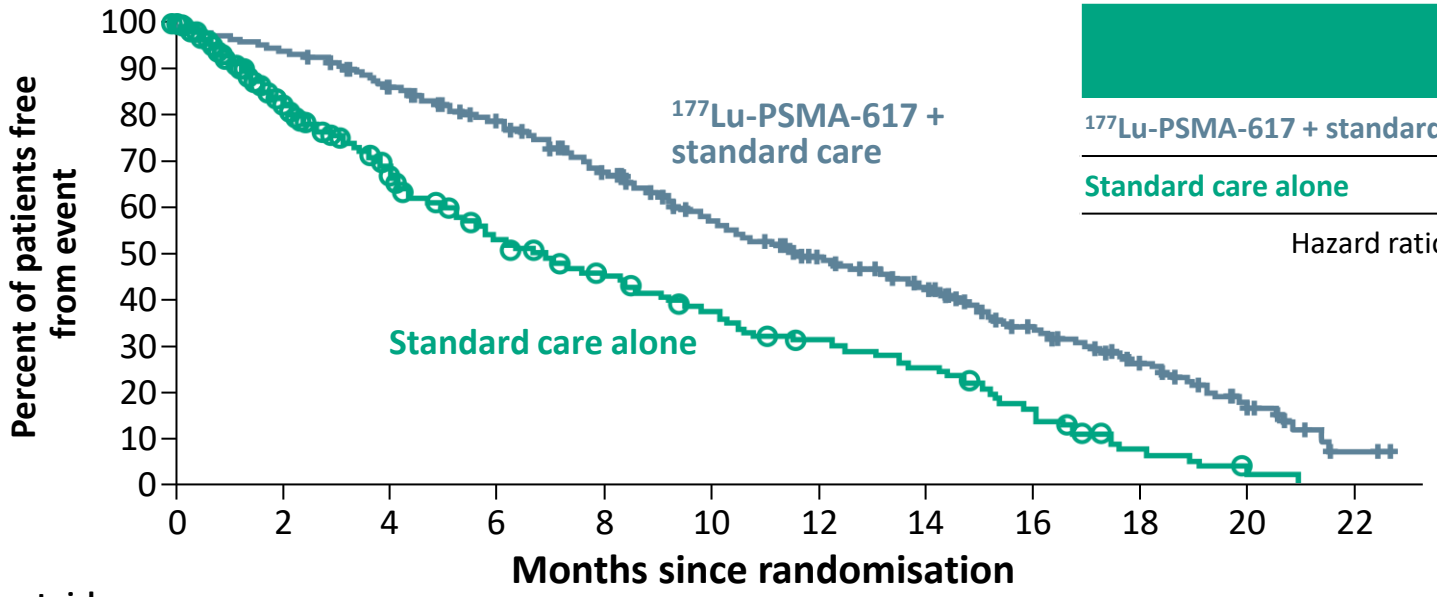
Sartor O, et al. N Engl J Med. 2021. DOI: 10.1056/NEJMoa2107322

VISION TRIAL: LUTETIUM-177-PSMA-617 FOR mCRPC

SECONDARY ENDPOINT

- Lu-177 prolonged time to symptomatic skeletal events compared with SOC

Time to first symptomatic skeletal event



	No. of events/ No. of patients	Median *mo*
^{177}Lu-PSMA-617 + standard care	256/385	11.5
Standard care alone	137/196	6.8

Hazard ratio, 0.50 (95% CI, 0.40-0.62)
P<0.001

No. at risk												
^{177}Lu-PSMA-617 + standard care	385	363	329	290	240	189	153	117	73	34	12	2
Standard care alone	196	141	104	75	61	48	36	29	15	6	2	0

CI, confidence interval; Lu-177, lutetium-177; mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen; SOC, standard of care

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SUMMARY

- Practical considerations when sequencing mCRPC treatments:
  - Consider prior therapies and sandwich therapies of different mechanism of actions or consider combination therapy
  - Consider sites of metastases (visceral vs. bone disease)
  - Is the patient symptomatic vs. asymptomatic?
  - Presence vs. absence of genomic/germline mutations indicates suitability for PARPi, immunotherapy, clinical trials
  - Patient preferences: oral vs. IV; side effects of therapies; goals of care; quality of life
  - Supportive care (BHA for mCRPC, managing side effects)
- Goal is to choose the right therapy at the right time, deliver all effective life-prolonging therapies and balance quality of life

BHA, bone health agents; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; PARPi, Poly (ADP-ribose) polymerase inhibitors

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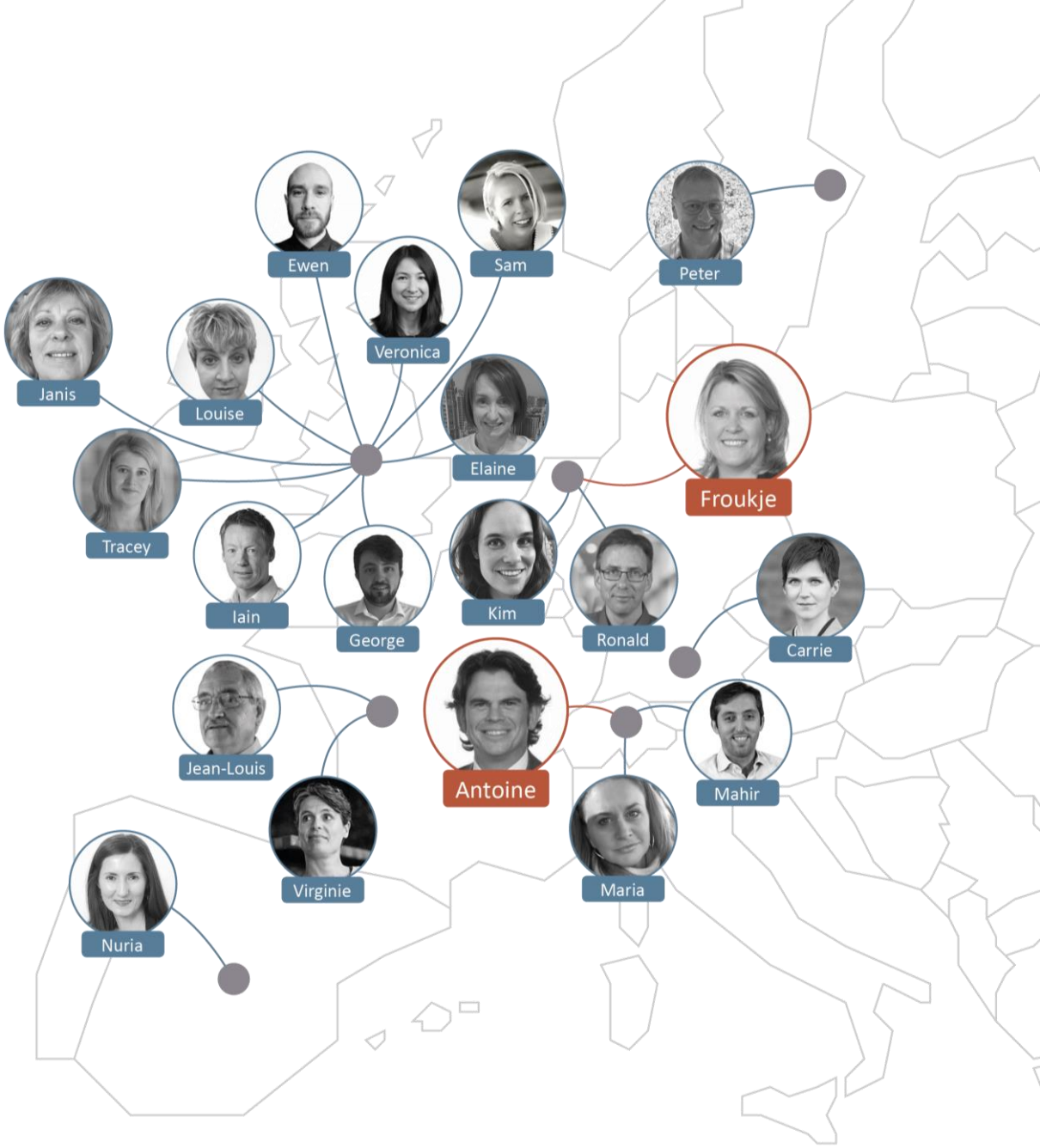

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