Systemic Therapy for Prostate Cancer: Advances in Context

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Presenter Disclosure

- I have no commercial or financial conflicts of interest to disclose

Mitigating Potential Bias

- Not applicable

Learning Objectives

1. Understand the general approach to treatment of advanced prostate cancer
2. Recognize that limitations in trial design can impede our ability to make true progress
3. Appreciate common toxicities of primary treatment classes

Some context…

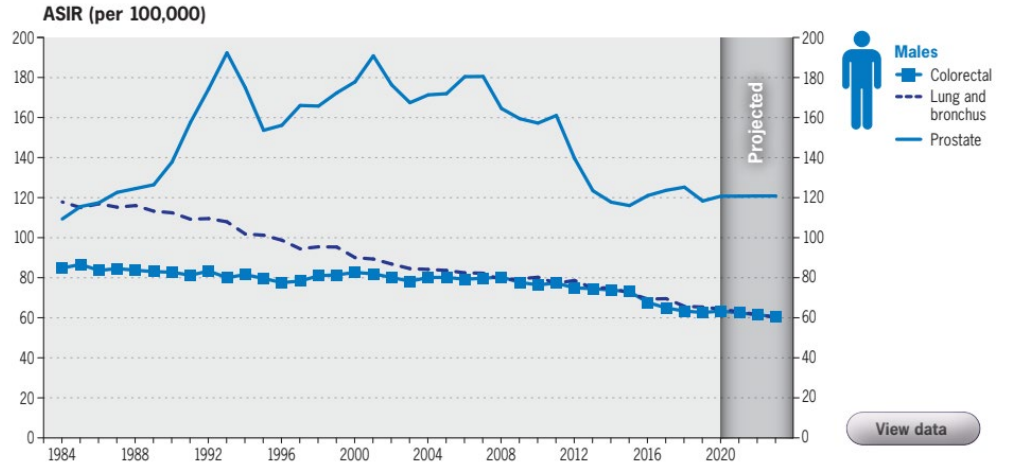
Males
124,200
new cases

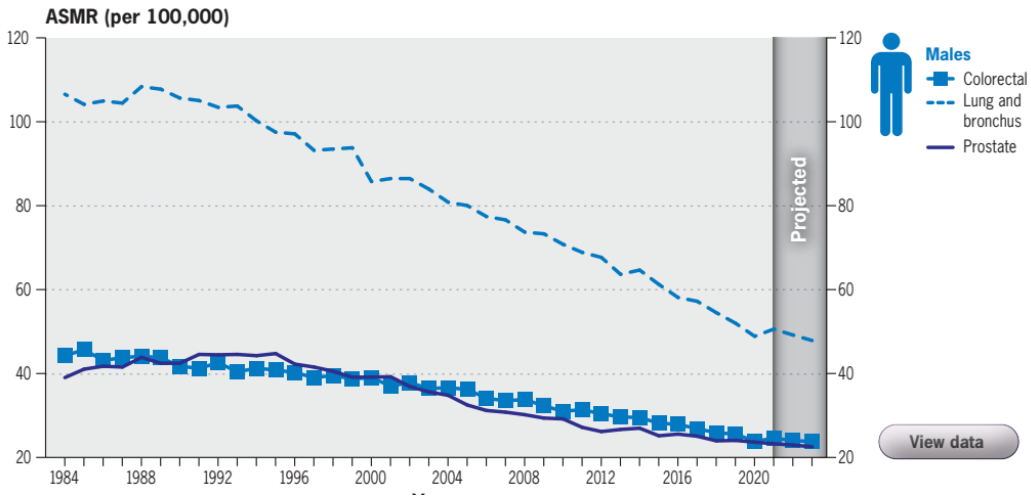
Prostate	20.8%
Lung and bronchus	12.3%
Colorectal	10.9%
Bladder	8.2%
Non-Hodgkin lymphoma	4.9%
Head and neck	4.7%
Kidney and renal pelvis	4.5%
Melanoma	4.5%
Pancreas	3.2%
Leukemia	3.2%
Liver and intrahepatic bile duct	2.6%
Stomach	2.2%

Males
46,500
Deaths

Lung and bronchus	23.2%
Colorectal	11.2%
Prostate	10.5%
Pancreas	6.7%
Liver and intrahepatic bile duct*	4.7%
Esophagus	4.0%
Bladder	4.0%
Leukemia	3.9%
Non-Hodgkin lymphoma	3.9%
Head and neck	3.3%
Brain/CNS	3.1%
Stomach	2.7%

MB 2024:
890 Cases
200 Deaths



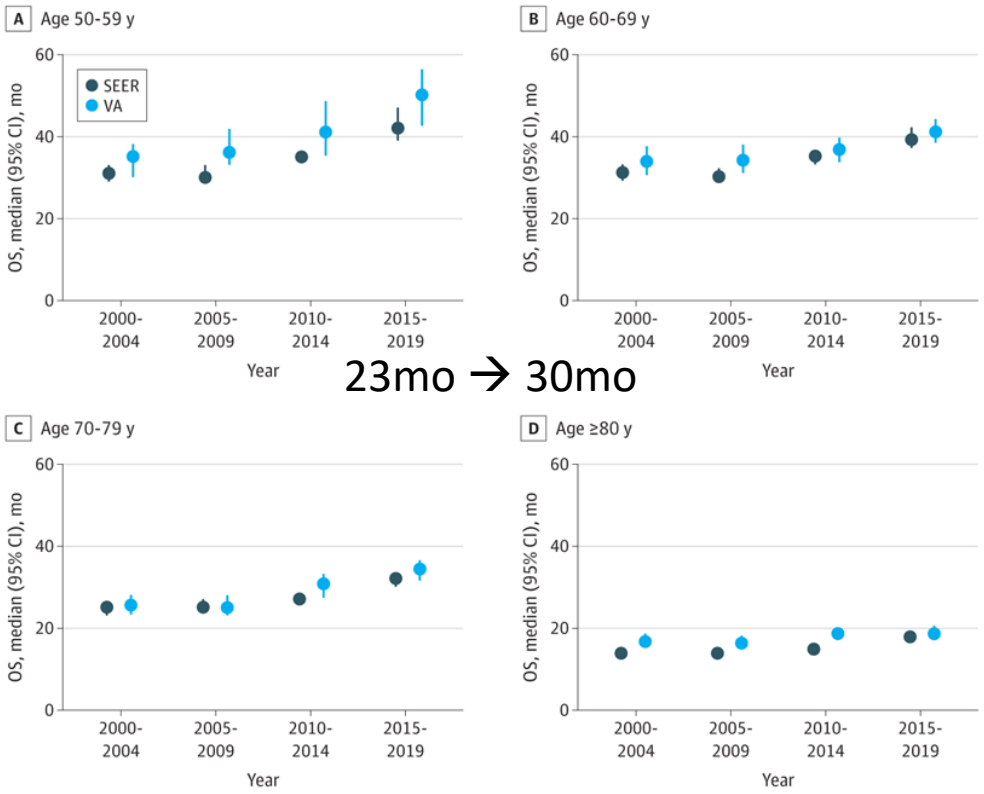


Canadian Cancer Society (2023)

Landmark trials 1L mCRPC

Author (year)	Intervention	mOS (95% CI)
Tannock (2004)	Docetaxel	19 (17-21)
Ryan (2015)	Abiraterone	35 (33-37)
Armstrong (2020)	Enzalutamide	36 (34-38)

Real World Outcomes: mCSPC



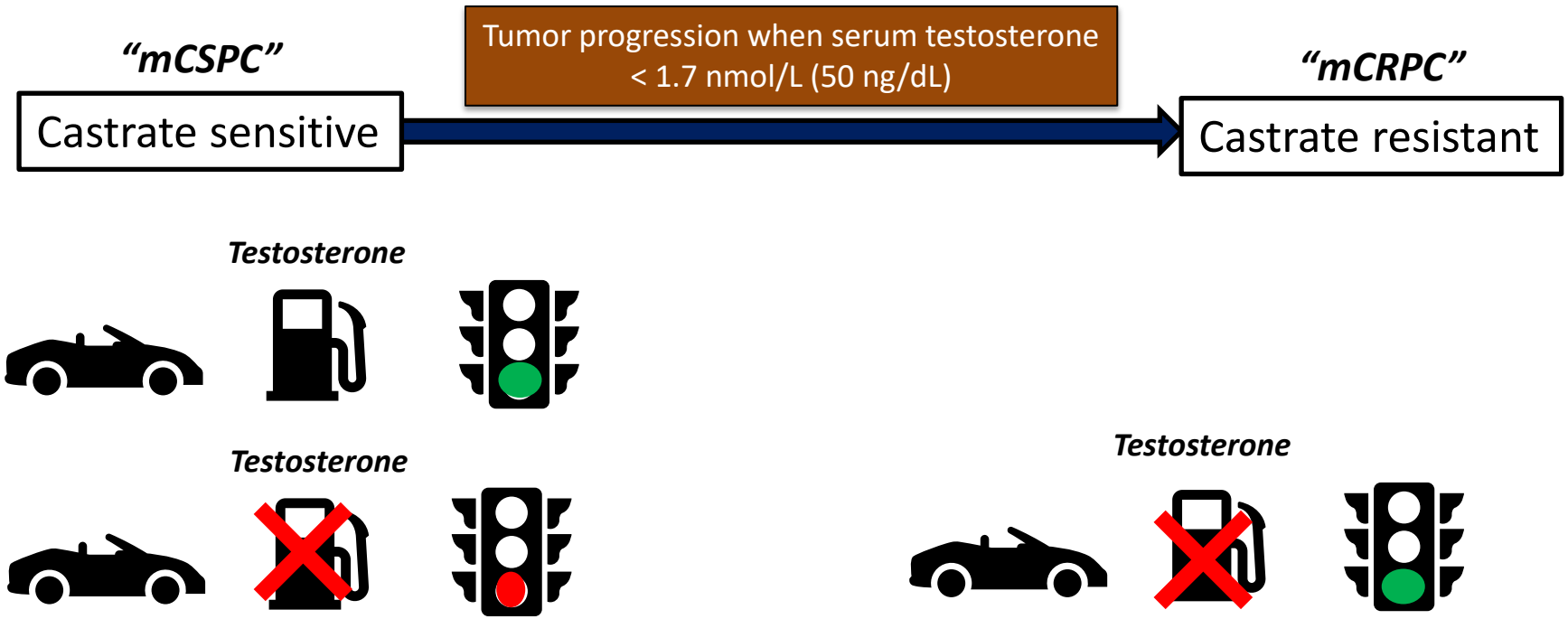
23mo → 30mo

Schoen et al. JAMA Net Open (2024)

Take Home #1:

Prostate Cancer is common with stable incidence. Outcomes are improving.

Metastatic Prostate Cancer: The Basics



Summary: mCSPC RCT's

Trial (Year)	Intervention (ADT+)	Control	Patient population	mOS (mo)	HR (P value)
CHAARTED (2018)	Docetaxel	ADT	"High volume"	51.2 v. 34.4	0.63 (<0.001)
LATITUDE (2019)	Abi/Pred	ADT	"High risk"	53.3 v. 36.5	0.66 (<0.001)
TITAN (2021)	Apalutamide	ADT	≥ 1 bone met	NR v. 52.2 4yr: 65 vs. 52%	0.65 (<0.001)
ARCHES (2022)	Enzalutamide	ADT	Any met dz	NR v. NR 4yr: 71 v. 57%	0.66 (<0.001)
PEACE-1 (2022)	Abi/pred + Docetaxel	ADT + docetaxel	*De novo* met dz	NR v. 53.2 'high volume': 61.7 v. 41.6	0.75 (0.02)
ARASENS (2022)	Darolutamide + Docetaxel	ADT + docetaxel	Met Dz *De novo* = 86%	NR v. 48.9 4yr: 63 vs 50%	0.68 (<0.001)

High risk (2+ of): Gleason 8+, 3+ bone mets, visceral mets
High volume: visceral mets or 4+ bone mets, 1 outside spine/pelvis

ADT PLUS…Analysis Paralysis in mCSPC

High vol/risk

Docetaxel + Darolutamide / Abiraterone	→ Triplet > ADT+NHA ???
Enzalutamide / Apalutamide / Abiraterone	→ Which agent?
Docetaxel	→ Decreasing role on its own

Low vol/risk

Enzalutamide / Apalutamide / Abiraterone	→ Which agent?
RT to Prostate (if de novo)	→ ?delay systemic tx
ADT alone	→ Pt preference, frailty, etc.

Summary: mCRPC RCT's

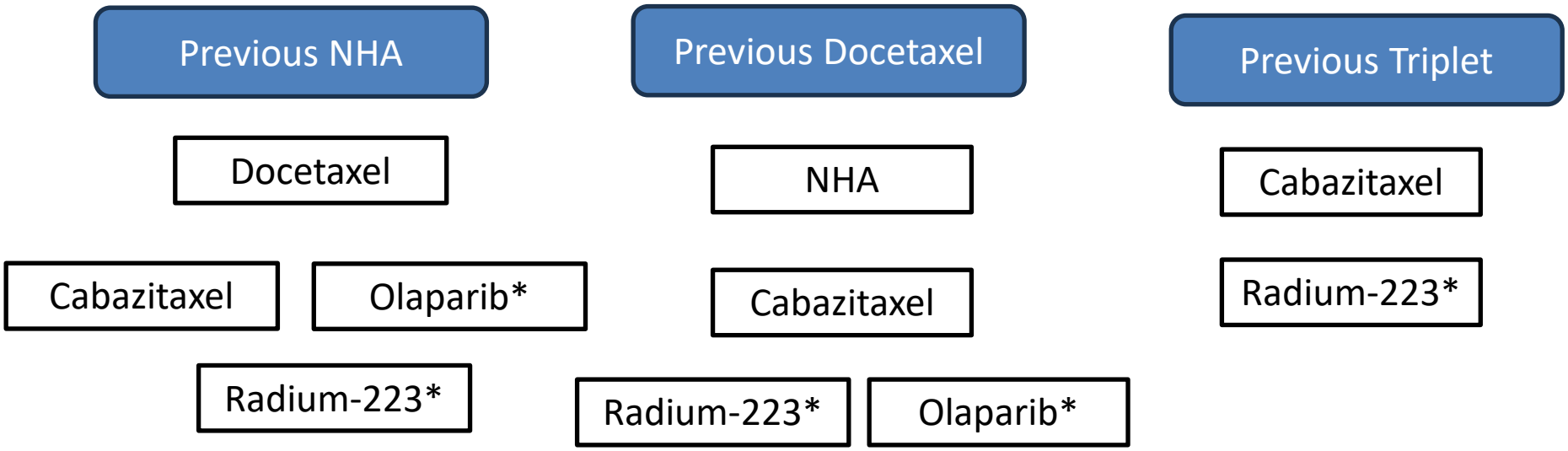
Trial (Year)	Intervention (ADT+)	Control	Patient population	mOS (mo)	HR (P value)
TAX327 (2004)	Docetaxel	Mitoxantrone	1L	18.9 v. 16.5	0.76 (<0.01)
COU-AA-302 (2015) COU-AA-301 (2012)	Abi/Pred	Pred	No prior docetaxel Prior docetaxel	34.7 v. 30.3 15.8 v. 11.2	0.81 (<0.01) 0.74(<0.001)
PREVAIL (2020) AFFIRM (2012)	Enzalutamide	Placebo	No prior docetaxel Prior docetaxel	36 v. 31 18.4 v. 13.6	0.83 (<0.001) 0.63 (<0.001)
CARD (2019)	Cabazitaxel	Alternative NHA	Prior NHA + Docetaxel	13.6 v. 11.0	0.64 (<0.01)

Summary: mCRPC RCT's

Trial (Year)	Intervention (ADT+)	Control	Patient population	mOS (mo)	HR (P value)
ALSYMPCA (2013)	Radium 223	Placebo	2+ bone mets, +/- prev docetaxel	14.9 vs. 11.3	0.70 (<0.01)
PROFOUND (2020)	Olaparib	Alternative NHA	BRCA 1/2, ATM mut. Prior NHA	19.1 vs. 14.7	0.69 (0.02)
VISION (2021)	Lutetium 177 PSMA*	Invest. Choice	PSMA+, previous NHA, taxane	15.3 vs. 11.3	0.62 (<0.001)

*Pending Availability in MB

mCRPC: Unclear post mCSPC



THE OPTIMAL SEQUENCE IS UNKNOWN!

Take Home #2:

ADT, NHA and chemotherapy are the backbones of treatment for Stage IV Prostate CA. Optimal sequences unknown.

Interlude: Barriers to Change

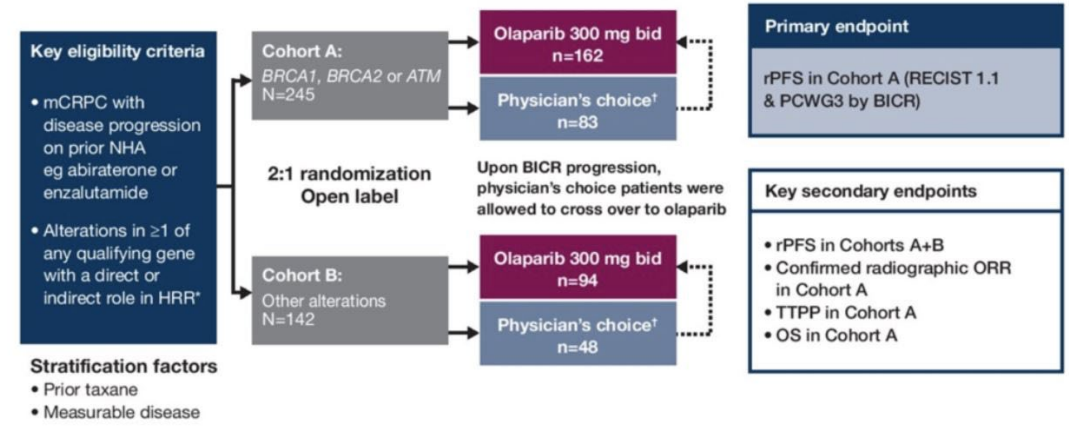
Despite progress, most trials provide “options” without definitively advancing best practice

RCT must have:

- Endpoints that matter (OS, QOL)
- Control arms that you would give to your loved one
- Adequate post-protocol therapy (i.e. do they get standard of care after the study?)

Ex: Olaparib in mCRPC

Figure 1. PROfound study design



BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L; †Either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid]). BICR, blinded independent central review; ORR, objective response rate; OS, overall survival; qd, once daily; TTPP, time to pain progression

A) Endpoints that matter (OS, QOL): Mostly! OS for Cohort A as secondary endpoint

B) Control arms that you would give to your loved one: No. Alternative NHA in pt already receiving. 30% no prior docetaxel. ~80% no prior cabazitaxel.

C) Adequate post-protocol therapy (i.e. do they get standard of care after the study?) No. 25% received nothing further. ~70% of those who did received Olaparib. Very few receiving taxane chemotherapy (standard of care)

Would this ~4 month OS benefit exist if the trial was run differently?

What endpoints truly matter?

1) Overall Survival: “Will I live longer?”

- Primary endpoint in <30% of cancer trials in major oncology journals from 2010-2020 (versus ~50% in 1994-2004) *Del Paggio et al. JAMA Onc (2021)*

- Instead, ‘surrogate’ endpoints: response rate, progression-free survival, etc. These are not strongly correlated with OS in most disease settings, but may be evidence of PFS in mCSPC *Halabi et al. JCO (2024)*

- OS benefit demonstrated in only ~50% of cancer drugs recommended for reimbursement w/ in Canadian framework – median gains ~3.5mo *Meyers et al. JAMA IM (2021)*

2) Quality of Life: “Will I live better?”

- Not included as endpoint, or absent from published results in 50+% of Phase III trials in prostate cancer *Marandino et al. Clin Gen Cancer (2019)*

- Only ~3% of cancer trials capture QOL until the end of the patient’s life *Haslam et al. JAMA Net Open (2020)*

- Most common primary endpoint (PFS) has a weak association with global QOL, or any specific domain within QOL *Hwang et al. Int J. Cancer (2018)*

Take Home #3:

Despite our progress, many clinical trials have fundamental flaws that make interpretation/application to patients difficult.

Key Toxicities - ADT

↓ libido/sexual dysfunction

Gynecomastia

Hot flashes

Weight gain

Metabolic syndrome

Mood change

Bone Loss

Tx / Monitoring:

A1C, Lipids and BP q6-12 mo

BMD q1-3 years → Tx w/ bisphosphonates per guidelines for OP

Daily Vit D, Calcium

SNRI / SSRI / Gabapentin for vasomotor symptoms

NCCN guidelines. Version 4.2019, 9/5/19. www.nccn.org
Kokorovic et al Can Urol Assoc J (2021)

Key Toxicities - NHA

Abiraterone	**Enzalutamide**	**Apalutamide**	**Darolutamide**
HTN	HTN	HTN	HTN
Edema	Fatigue	Rash	Cardiac Isch.
Liver injury	Cognitive Imp.	Fatigue	Fatigue
Hypokalemia	?Seizure (<1%)	HypoThyroid	CHF
Cardiac Isch.	QT	QT	Liver injury

+pred side effects

*****ALWAYS CHECK DRUG INTERACTIONS*****

CancerCare Ontario Drug Formulary (2024)

Key Toxicities – Chemotherapy

	Docetaxel (%)	Cabazitaxel (%)
Any AE (Gr3+)	97 (46)	96 (60)
AE Leading to d/c	15	20
Diarrhea (Gr3+)	37 (2)	50 (6)
Nausea (Gr3+)	32 (1)	23 (1)
Hematuria (Gr3+)	4 (0)	25 (4)
Neuropathy (Gr3+)	25 (2)	12 (0)
Feb Neut (Gr 3+)	8 (8)	12 (12)

Oudard et al. JCO (2017)

Take Home #4:

All systemic therapies for prostate cancer have potential toxicity to be considered w/ patient context and preferences.

Take home messages

1. Prostate Cancer is common with stable incidence. Outcomes are improving.
2. ADT, NHA and chemotherapy are the backbones of treatment for Stage IV Prostate CA. Optimal sequences unknown.
3. Despite our progress, many clinical trials have fundamental flaws that make interpretation/application to patients difficult.
4. All systemic therapies for prostate cancer have potential toxicity to be considered w/ patient context and preferences

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