

The CONs of treating non-metastatic (nm) CRPC: Important considerations to take into account

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What is the definition of nmCRPC?

Standard definition:

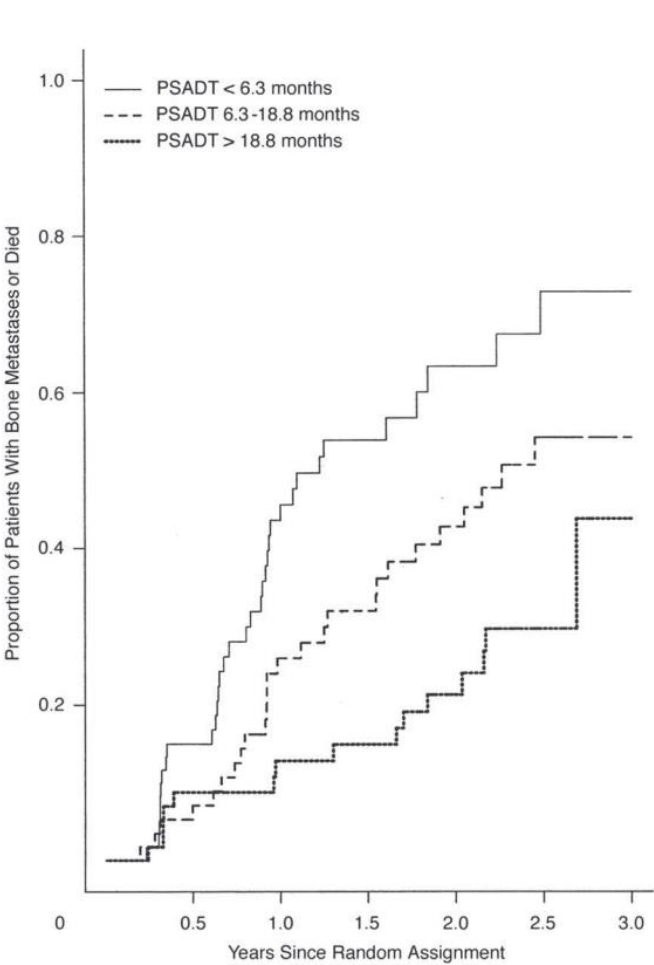
- Serial rising PSAs despite a castrate level of testosterone
- No evidence of metastatic disease by conventional imaging:
Technetium bone scan, CT chest, abdomen, pelvis

Inclusion criteria for clinical trials included only “high risk” nmCRPC

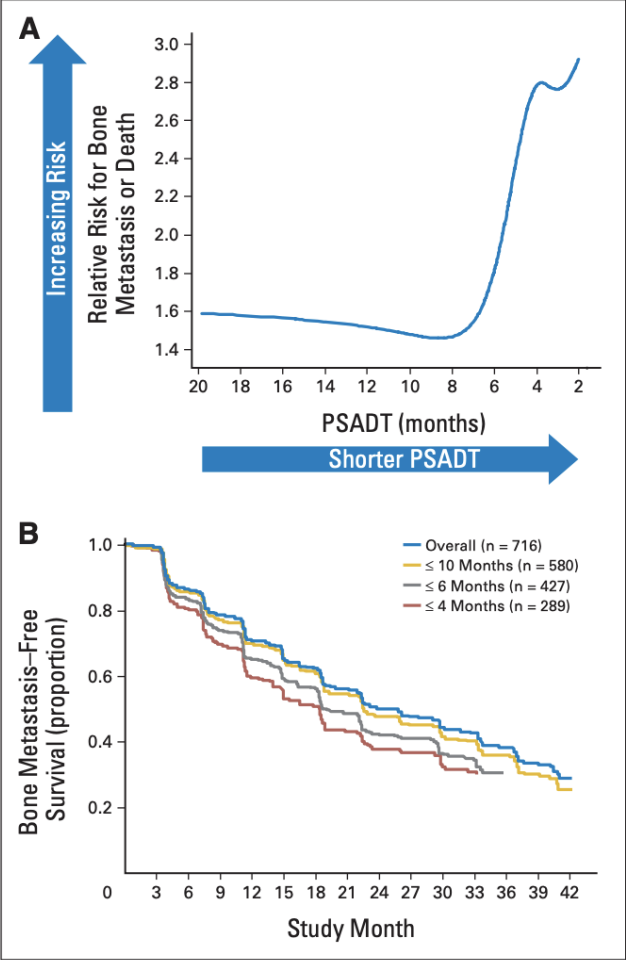
- PSA DT \leq 10 months *and*
- PSA 2 or greater

It is important to understand that FDA label does not restrict use of 2nd gen AA to high risk populations even though lower risk patients were not included

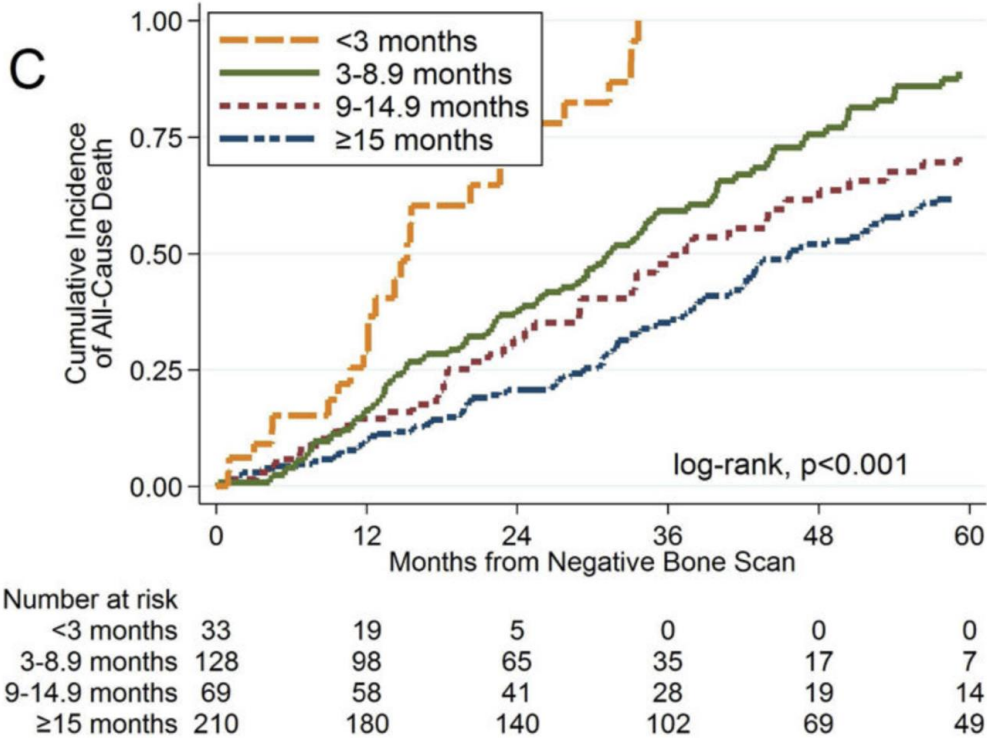
Risk of bone metastases or death for men with nmCRPC based on PSA-DT



Smith et al, JCO 2005



Smith et al, JCO 2013



Howard et al, BJU Int 2017

Overview metastases free survival

Agent (trial)	Active	Placebo
	Median MFS (months)	
Apalutamide (SPARTAN)	40.5	16.2
Enzalutamide (PROSPER)	36.6	14.7
Darolutamide (ARAMIS)	40.4	18.4

First time this magnitude of difference seen in trials in this population

Very substantial difference

Even without OS data, difference in delaying time to metastasis is meaningful to patients...as long as they do not experience substantial toxicity...

And can afford the price, sometimes up to \$10,000/month

Specific toxicities of concern

Adverse event	Apalutamide (SPARTAN)	Enzalutamide (PROSPER)	Darolutamide (ARAMIS)
	Tx vs PBO (%)	Tx vs PBO (%)	Tx vs PBO (%)
Grade 5 AE (death)	1.2 vs 0.3	3 vs 1	3.9 vs 3.2
Fatigue, any	30 vs 21	33 vs 14	12.1 vs 8.7
Fatigue, gr 3-4	0.9 vs 0.3	3 vs 1	0.4 vs 0.9
Asthenia	NR	9 vs 6	NR
HTN, any	24.8 vs 19	12 vs 5	6.6 vs 5.2
HTN, gr 3-4	14.3 vs 11.8	5 vs 2	3.1 vs 2.2
Falls, any	15.6 vs 9	11 vs 4	NR
Falls, gr 3-4	1.7 vs 0.8	1 vs 1	NR
Fracture, any	11.7 vs 6.5	Falls and fractures 17 vs 8	NR
Fracture, gr 3-4	2.7 vs 0.8		NR

No head to head comparison data

- Regarding toxicities and tolerance
- Impact on QOL and other functional measures
- How underlying co-morbidities are affected
 - Cardiovascular disease
 - Hypertension
 - History of falls or seizure
 - Frailty
 - Impact on osteoporosis or osteopenia/fracture

What do we know about the proportion of high vs low risk nmCRPC based on PSA-DT

VA patients with nm CRCP (2000-2015)¹

PSA-DT	N=440 (%)
< 3 months	33 (7.5)
3-8.9 months	128 (29.1)
9-14.9 months	69 (15.7)
≥ 15 months	210 (77.1)

Canadian cohort (2011)²

PSA-DT	N=1188
< 8 months	712/1188 (60)

- Obviously the proportion of lower risk patients is extremely variable
- Treating all patients with nmCRPC with 2nd gen ART could expose a significant number to longer durations of therapy and thus more potential for toxicity

How many nmCRPC patients have metastases by PSMA-PET imaging?

200 men with nmCRPC by conventional imaging had PSMA-PET imaging

- M1 disease in 55%
61% had PDA-DT ≤ 10 months
- M0 disease in 46%
43% had PSA-DT ≤ 10 months

Fendler et al, (in press)

Clearly, PSMA-PET imaging will identify more patients with nmCRPC who have very early M1 CRPC.

Questions:

Should the “M1” nmCRPC patient be treated with therapy for mCRPC or should they be treated with 2nd gen AA? (no prospective data)?

Can PSMA-PET imaging +/- PSA-DT be used to identify patients who could delay systemic therapy and perhaps be treated with SBRT or other salvage approaches?

What are the cons of using 2nd line ART for nmCRPC?

There is definitely toxicity at the individual patient level that we don't yet understand: who will have it and how reversible is it?

Long term effect on natural history of mCRPC is unknown: will the more aggressive disease phenotype develop earlier in mCRPC due to longer exposure to ARTs during nmCRPC.

Treating men with nmCRPC and longer PSA-DT has a significant risk of doing more harm than good.

Safe choice of agent and monitoring of these agents requires urologists to practice internal medicine.

There can be significant financial toxicity for those who do not qualify for assistance programs (in US, can be \$10,000/month).

Going forward

I realize that these 3 trials are strongly positive and that these agents should be used in appropriate men, but I do not believe all nmCRPC patients are suitable candidates for therapy.

We will need a better understanding in the post-market setting about the toxicities of these agents relative to each other.

Are there genetic, pharmacogenomic, or other biomarkers that can predict these patient specific toxicities?

Need to consider the role of conventional imaging in concert with molecular imaging to better characterize the different subtypes of nmCRPC in clinical trials and to determine the role of salvage approaches guided by PSMA-PET in nmCRPC.

