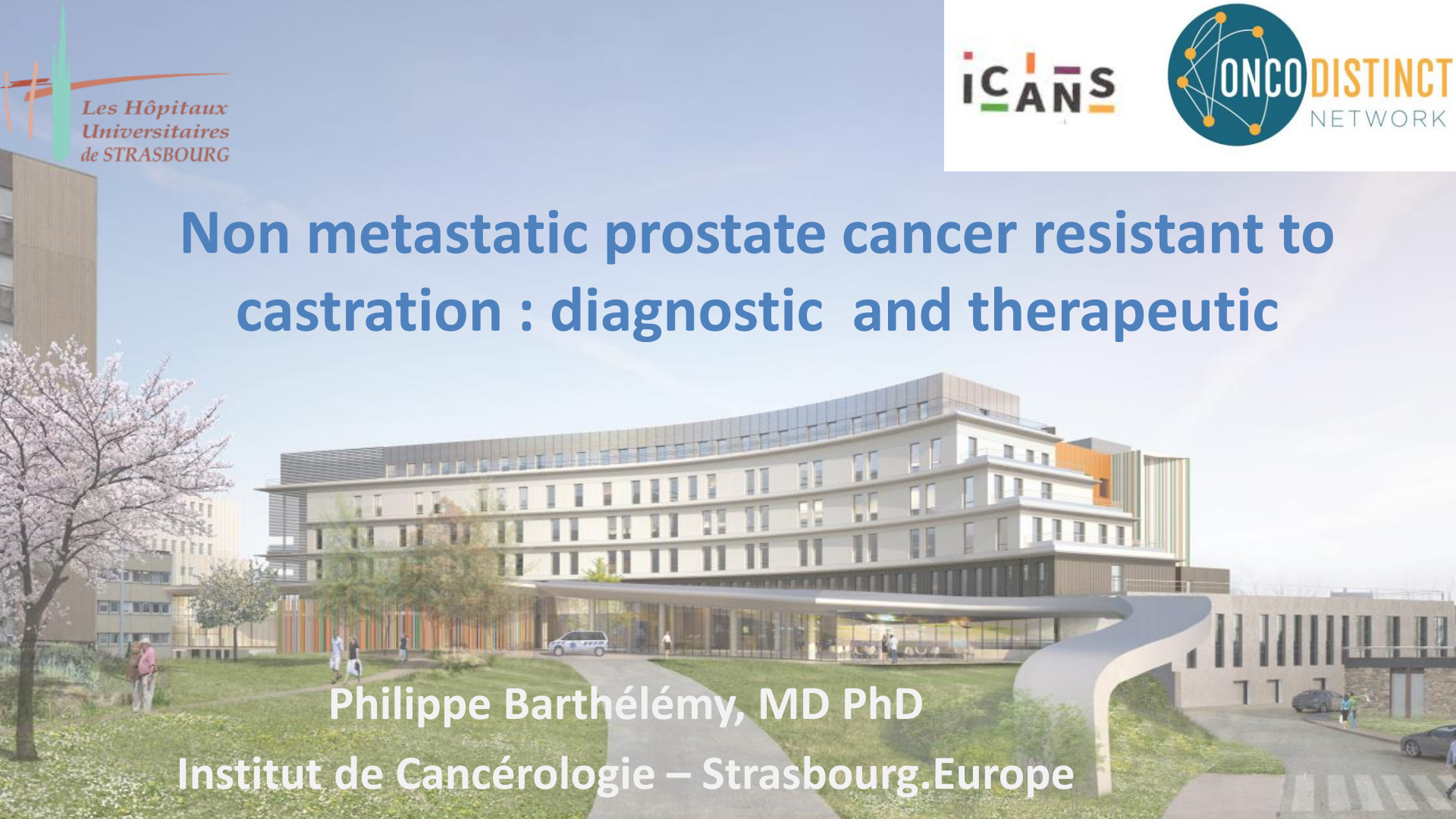
Non metastatic prostate cancer resistant to castration : diagnostic and therapeutic



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Disclosures

- **Advisory Board , Consulting**
  - IPSEN, BMS, ROCHE, MSD, PFIZER, NOVARTIS, EUSAPHARMA
  - JANSSEN CILAG, ASTELLAS, AMGEN, SANOFI
- **Honoraria : Speaker**
  - SANOFI, BAYER

Outline : nmCRPC

1. Definition : What are we talking about ?
2. Who needs a treatment ?
3. How to treat patients ?
4. Remaining questions: Metabolic imaging

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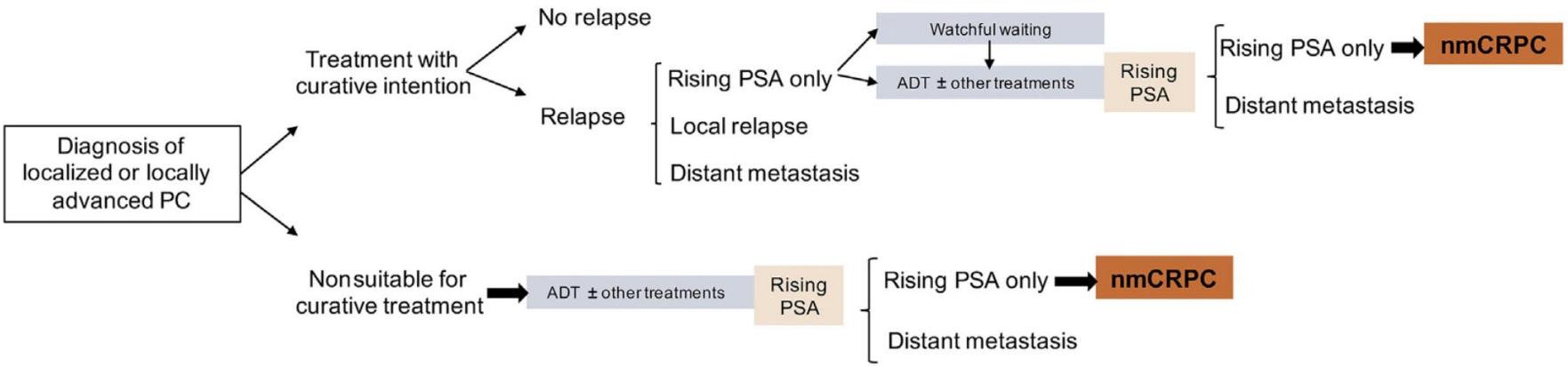
Definition :



Biochemical progression while on ADT + **Serum testosterone levels below 50 ng/dL** + **No evidence of metastasis**

On conventional Imaging
CT scan
Bone Scan

Mateo et al Eur urol 75:285, 2019

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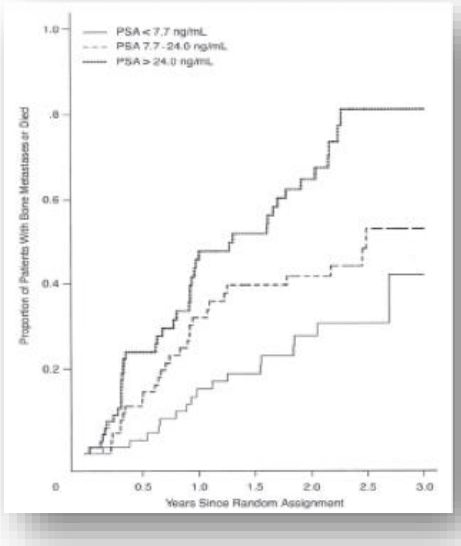
Prognostic factors : PSA level and doubling time

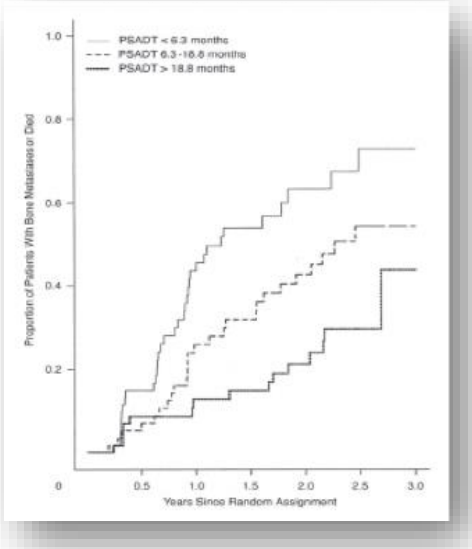
- Men (N=201) with non-metastatic prostate cancer and rising PSA despite ADT were followed for 48 months to assess development of metastatic disease and survival

Time to bone metastases or death by PSA level



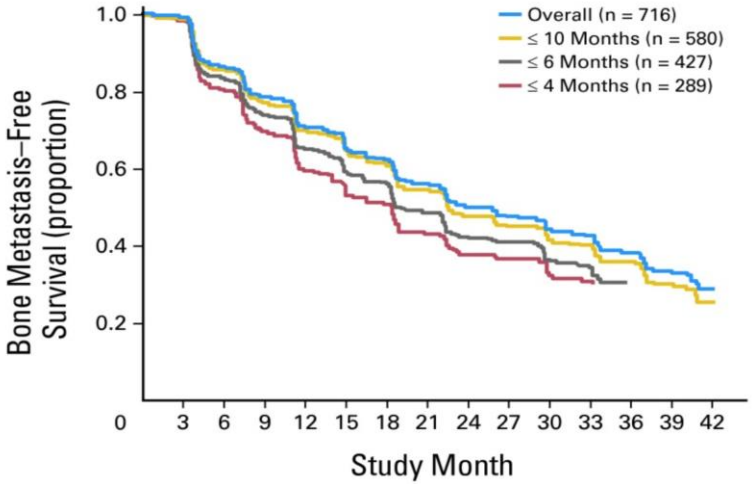
MFS

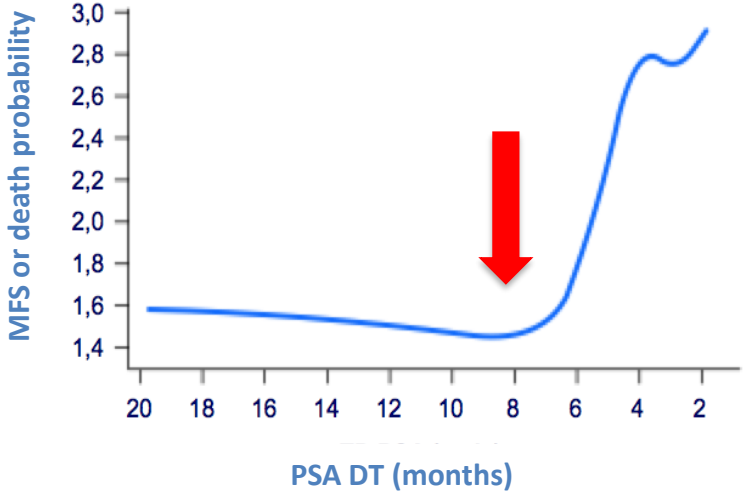
Time to bone metastases or death by PSA Doubling Time (PSADT)



Smith M et al. J Clin Oncol. 2005;23:2918-2925.

More recent trials : PSA DT in placebo arm





High risk nmCRPC

PSA doubling time (DT) < 8 or 10 months

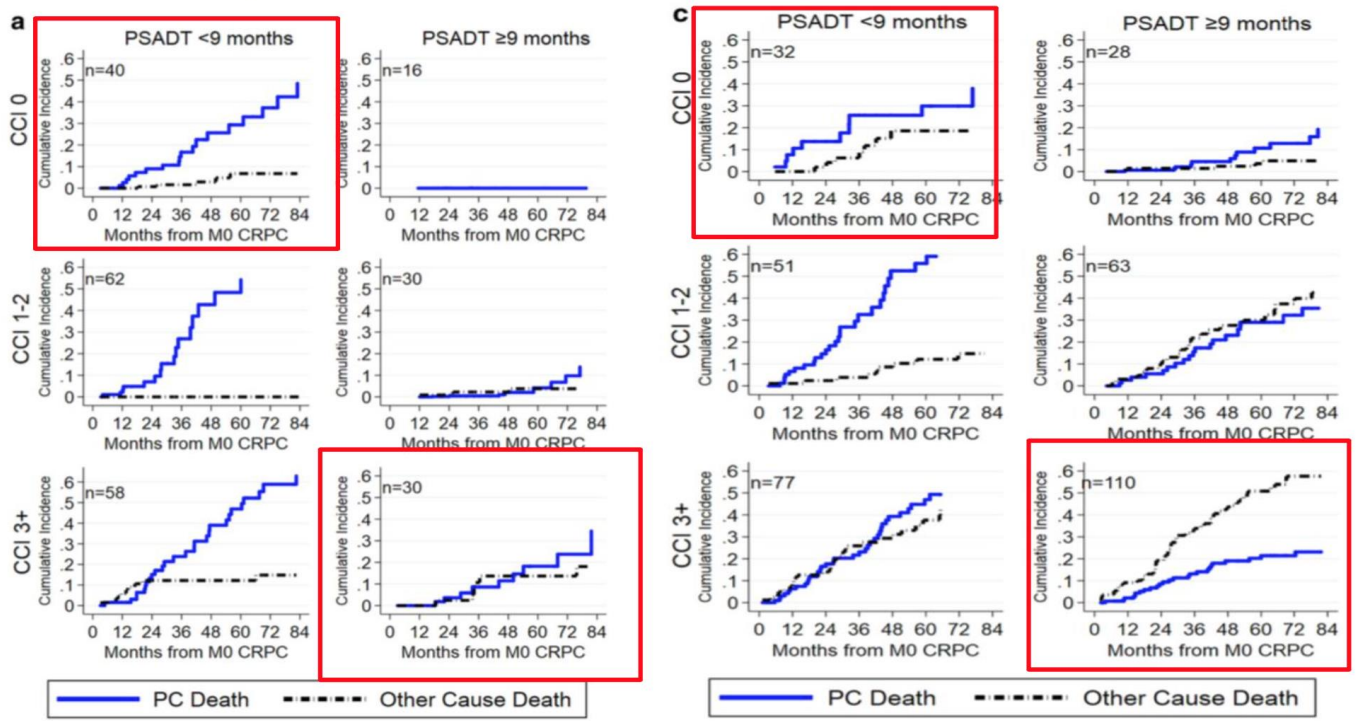
PSA > 2ng/mL

Smith et al, J Clin Onc 31:3800 2013

Other key factors: Age, comorbidies

Age <70 Years

Age >80 Years



Whitney et al. Prostate Cancer Prostatic Diseases 22:252, 2019

CCI : Charlson Comorbidity Index

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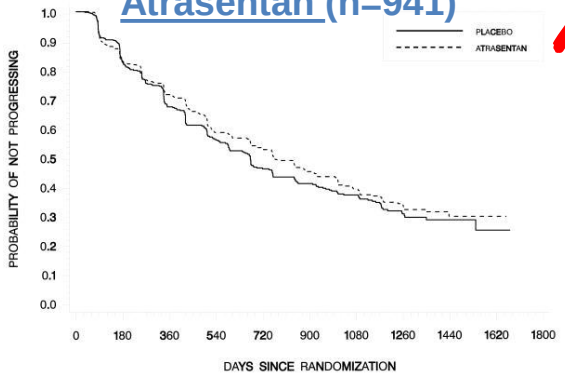
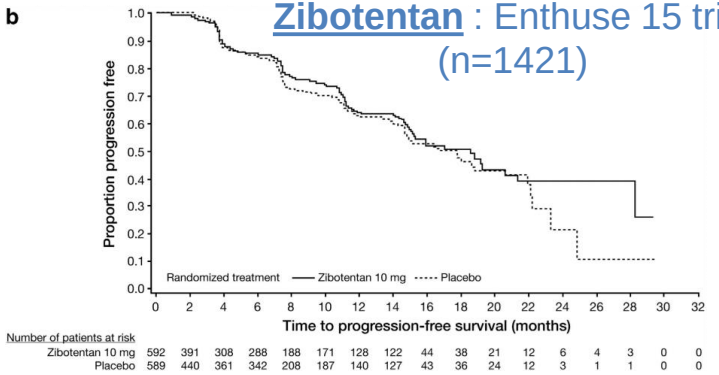
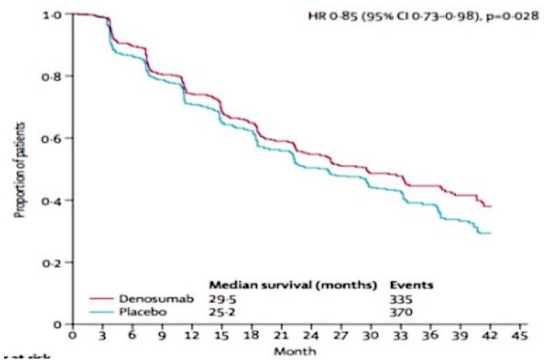
Previous Phase III trials in nmCRPC

Atrasentan (n=941) ✗



Zibotentan : Enthuse 15 trial (n=1421) ✗





Denosumab (n=1432)

B-MFS : HR= 0.85 ; 4.2 months improvment ✓

OS : HR 1.1, 95% CI 0.85-1.20, p=0.91 ✗

Miller K, Prostate Cancer Prostatic Dis 2013; 16: 187-92 ; Nelson JB, Cancer 2008; 113:2 478-87 ; Smith MR, Lancet 2012; 379: 39-46

Next generation AR targeted agents in nmCRPC

SPARTAN [1]
n= 1207

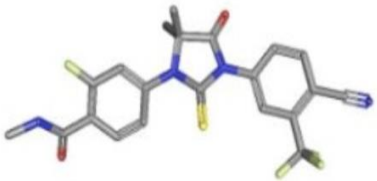
Apalutamide
240 mg/day + ADT

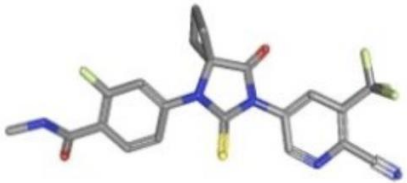
PROSPER [2]
n = 1401

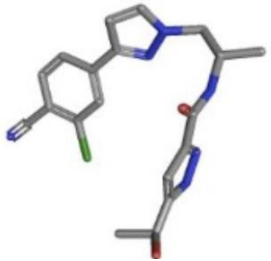
Enzalutamide
160 mg/day + ADT

ARAMIS [3]
n=1509

Darolutamide
1200 mg (600 mg x 2/D) + ADT

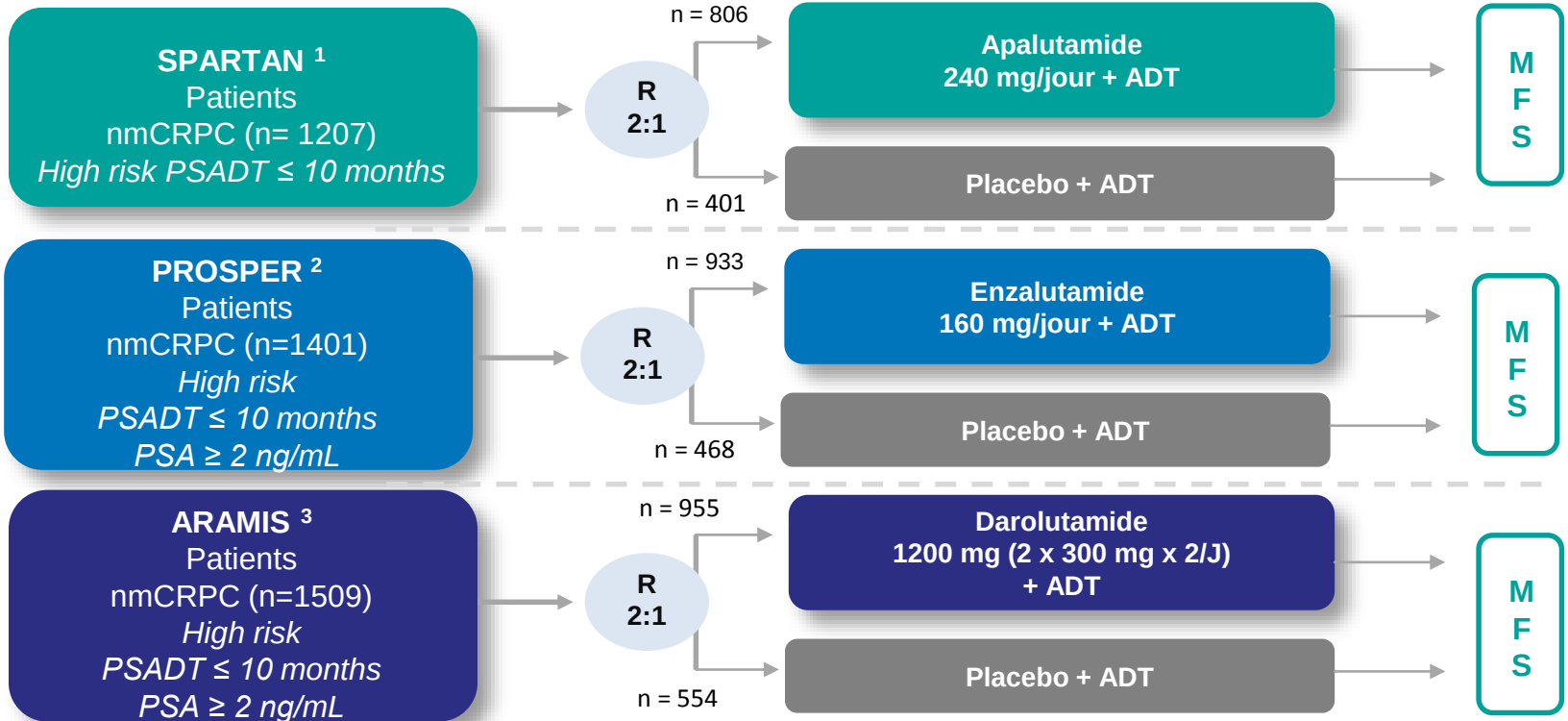






1. Smith MR, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med. 2018;378(15):1408-18.
2. Hussain M, et al. Enzalutamide in Men with Non metastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018 Jun 28;378(26):2465-2474.
3. Fizazi K, et al. Darolutamide in Nonmetastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2019 Feb 14. doi: 10.1056/NEJMoa1815671. [Epub ahead of print]

Phase 3R trials : Design + Endpoints



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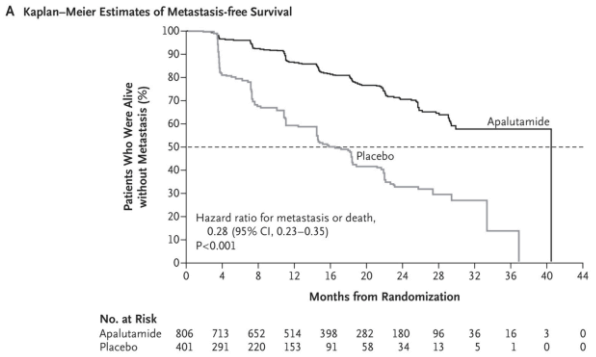
Primary Endpoint : MFS

SPARTAN



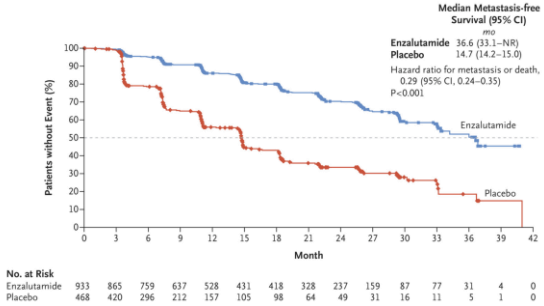
72% median MFS :

APA 40,5 vs PBO 16,2 months

MFS gain: **24,3 months**

Smith MR et al. N Engl J Med 2018;378(15):1408-1418

PROSPER



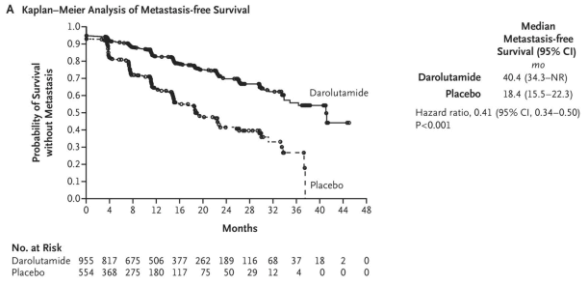
71% median MFS :

ENZA 36,6 vs PBO 14,7 months

MFS gain: **21,9 months**

Hussain M et al. N Engl J Med 2018;378(26):2465-2474

ARAMIS



59% median MFS :

DARO 40,4 vs PBO 18,4 months

MFS gain: **22 months**

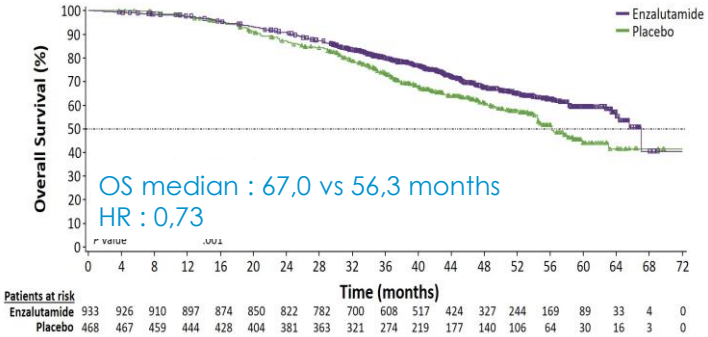
Fizazi K et al. N Engl J Med 2019;380(13):1235-1246

SSM: survie sans métastases

Overall Survival

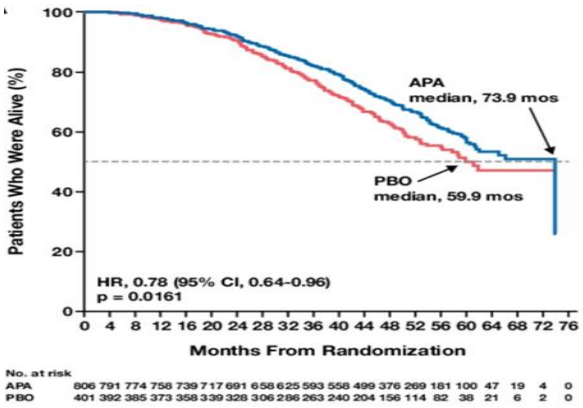
PROSPER (Sternberg et al. NEJM 2020)

OS



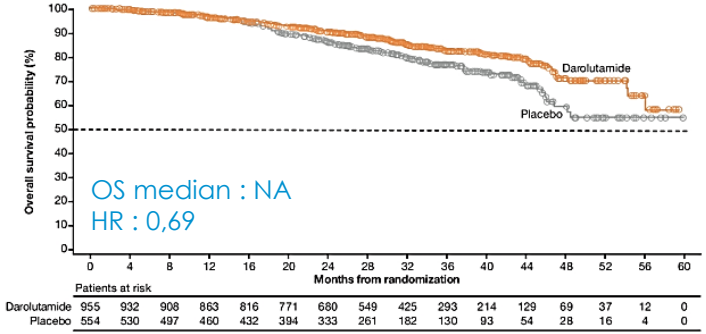
SPARTAN (Smith Eur Urol 2020)

OS



ARAMIS (Fizazi et al. #NEJM 2020)

OS



Adverse events : Toxicity profile

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	4,2 vs 4,7
Falls, gr 3-4	1.7 vs 0.8	1 vs 1	0,8 vs 0,9
Fracture, any	11.7 vs 6.5	Falls and fractures 17 vs 8	4,2 vs 3,6
Fracture, gr 3-4	2.7 vs 0.8		0,9 vs 0,9

Smith MR, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med. 2018;378(15):1408-18.
Hussain M, et al. Enzalutamide in Men with Non metastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018 Jun 28;378(26):2465-2474.
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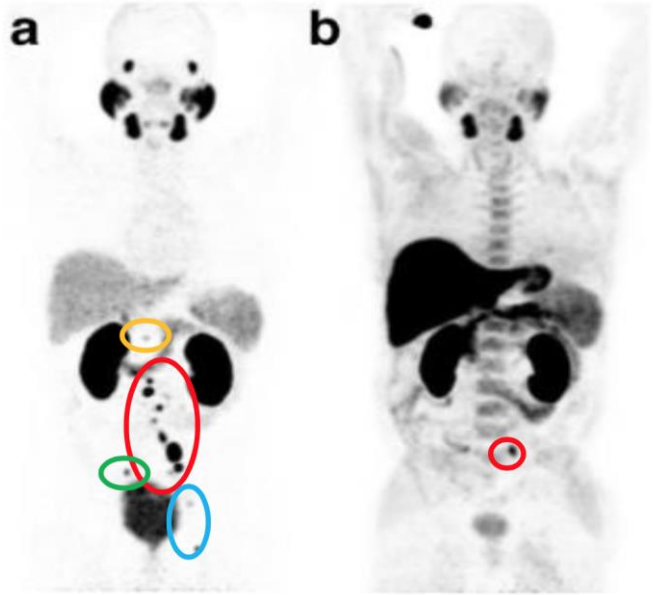
Metabolic Imaging



^{68}Ga-PSMA ^{18}F-Choline

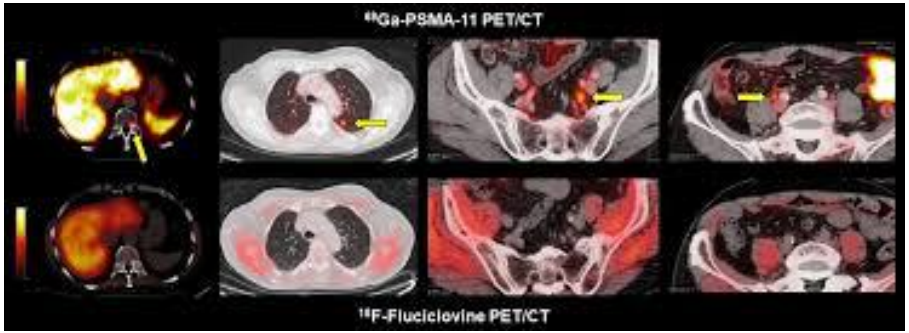
PET-(^{11}C/^{18}F)Choline

- >> Conventional imaging
- Limited sensitivity for low PSA level

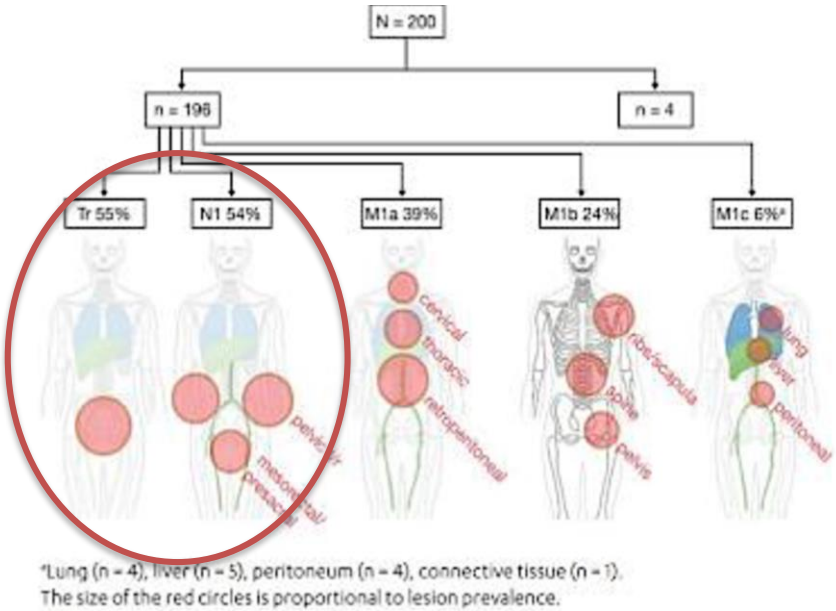
PET-^{68}GaPSMA :

Biochemical relapse

CPRC M0??



nmCRPC : localized or locally advanced disease



[a]Lung (n = 4), liver (n = 5), peritoneum (n = 4), connective tissue (n = 1).
The size of the red circles is proportional to lesion prevalence.

- N=200 pts
- Spartan inclusion criteria
- PSA DT<10 months
- Conventional Imaging
- PET Choline : 98% positivity
- 55% poly-metastatic

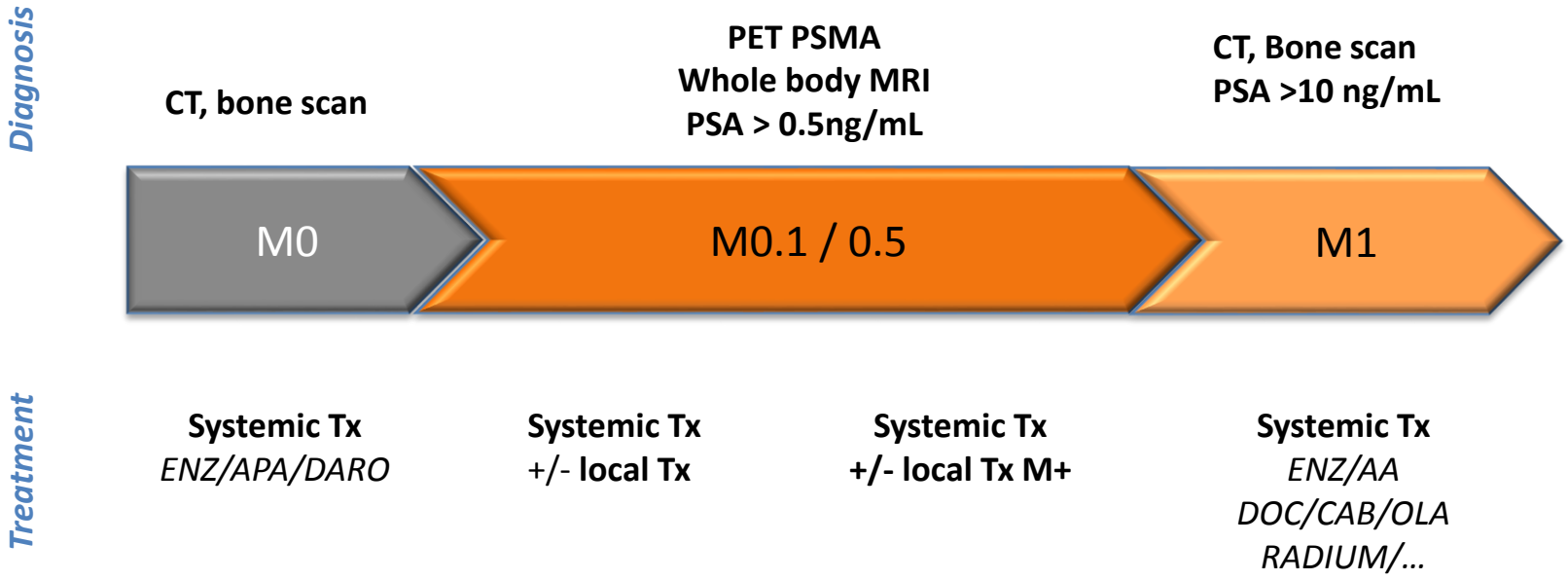
25% Local progression

25% Locally advanced (N+)

Treatment of the primary +/- pelvis

Fendler et al SUO, 2018

Toward a new classification ??



Remaining questions

- **How should we monitor these patients**
  - Baseline imaging, every 3-6 months, at PSA progression
- **When should we change treatment**
  - PSA alone, radiological/clinical progression?
- **Intermittent use of second generation HT ?**

Conclusion : nmCRPC

- Quite rare situation
- Even rarer if next generation imaging is used
- Three agents: Apa -, Enza-, Darolutamide
  - Clear and meaningful improvement of MFS and OS
  - Acceptable toxicity, some issues though (fall, fractures, CV)
  - Cost
- New strategies should be assessed
  - Treatment of oligometastatic disease
  - Intermittent use of AR targeted agents
  - Monitoring strategies

Thanks for your attention

Urologie
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