

Intégration des Traitements dans le Cancer de la Prostate **Oligo- métastatique**

**Vers une approche multimodale
personnalisée**

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What is oligometastatic cancer?

- An intermediate state of cancer spread between localized disease and widespread metastases
- Proposed as a distinct clinical state by S Hellman and R Weichselbaum

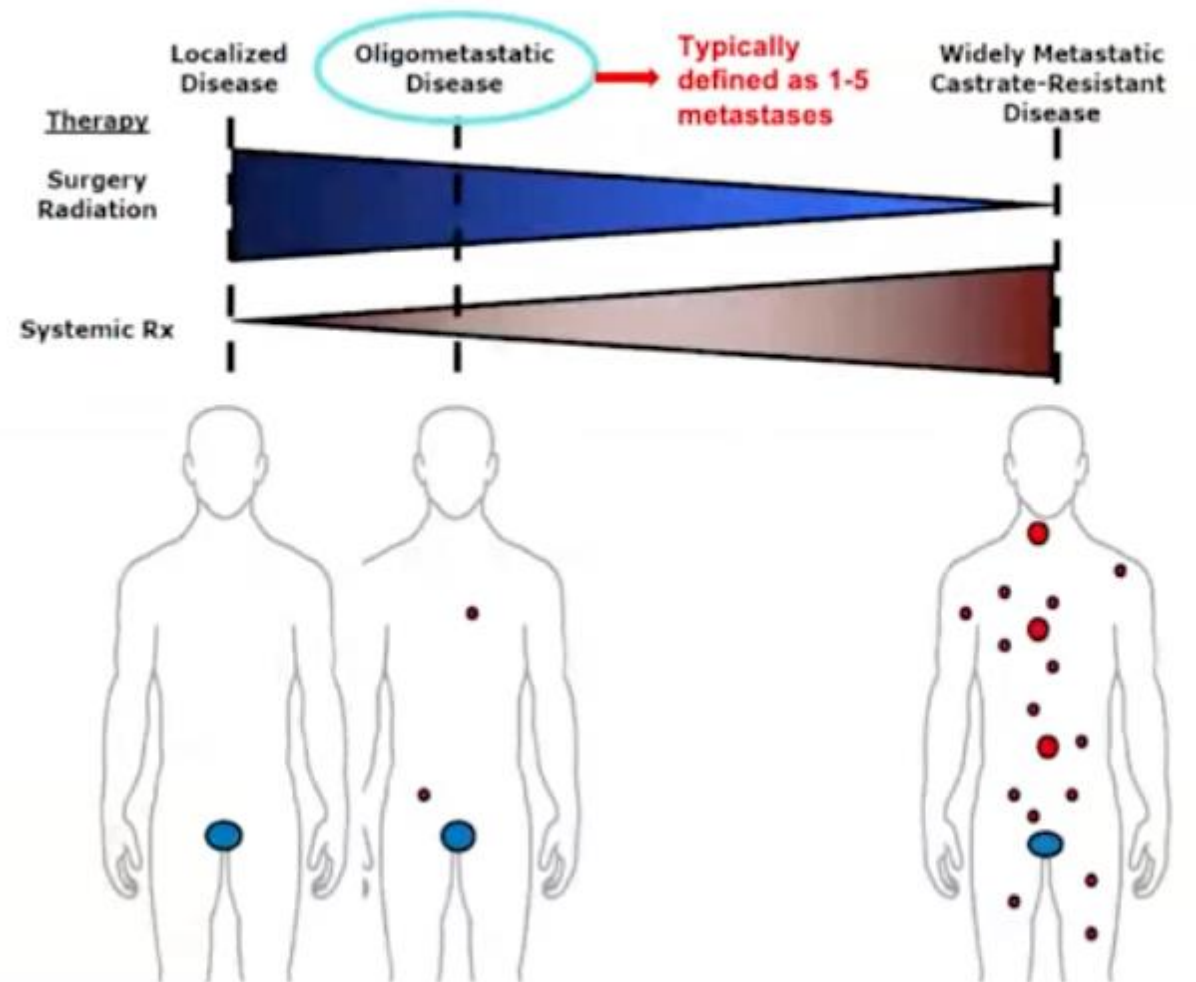
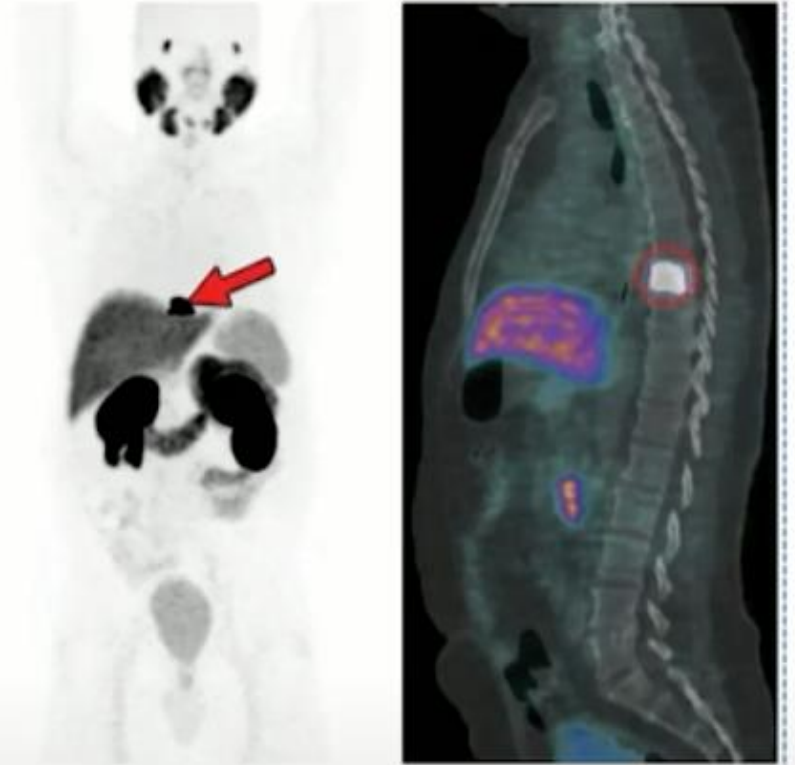


Figure courtesy of Phuoc Tran



What is oligometastatic prostate cancer?

- Metastatic disease limited in extent and number (≤ 5) of metastatic sites.
 - Hellman and Weichselbaum defined 1995 and revisited 2011
- Hypothesis: Metastasis-directed therapy (MDT) may be effective for these patients
- Growing clinical dilemma with PSMA PET/CT



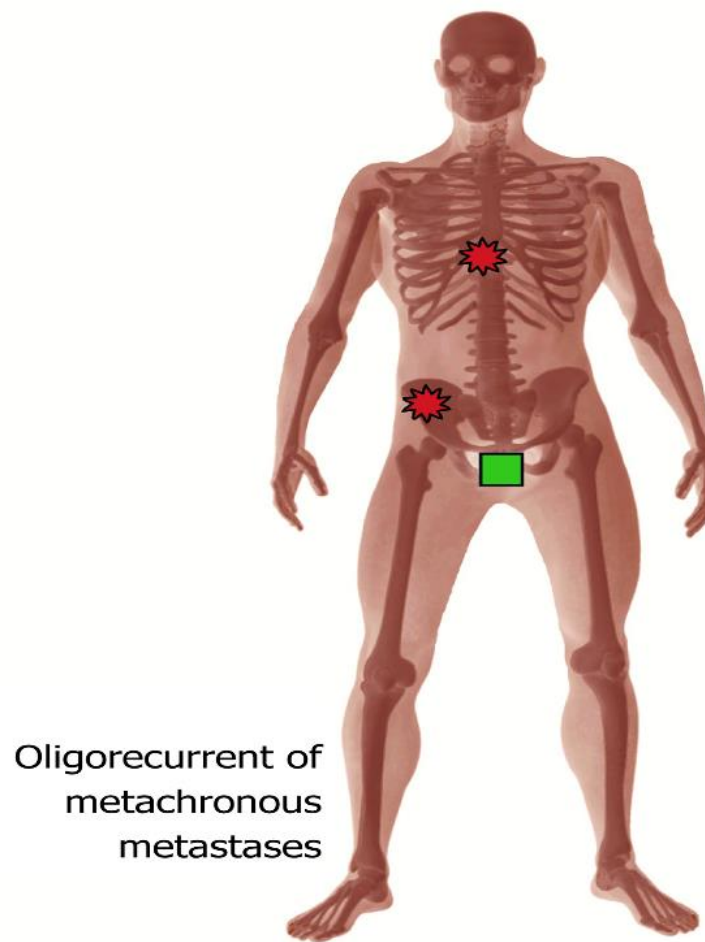
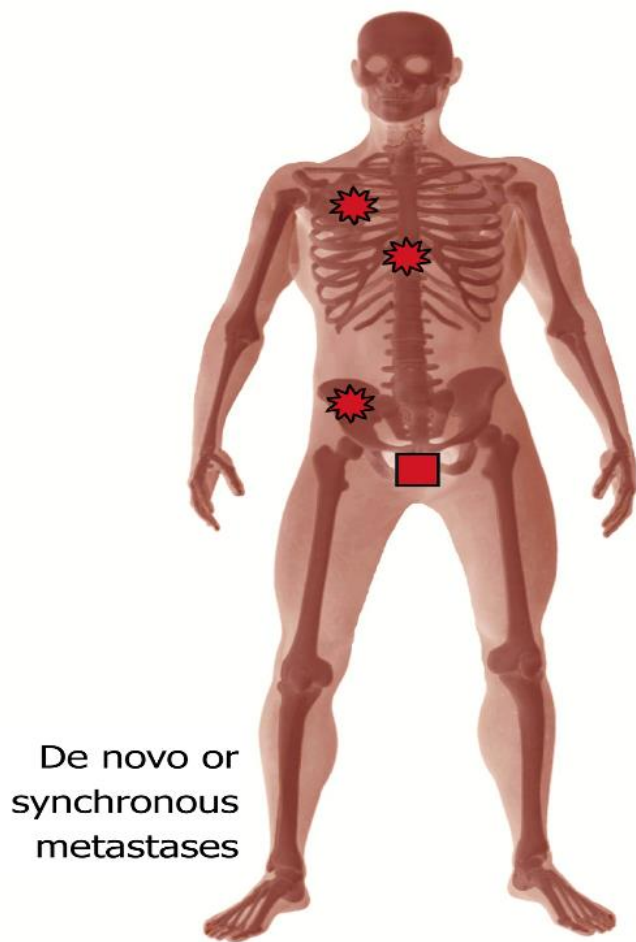
Number of lesions vs. biology

- Number of lesions does not define survival or outcome with MDT
 - Is 4 mets different than 6?
- Increased sensitivity of imaging changes number of lesions but not biology.
- Other cancers prove “seed” + “soil” define outcome

Determinants of survival and therapeutic approach

- De novo, synchronous or metachronous after prior local therapy
- Genomic alterations: germline and somatic DNA
- Host co-morbidities

Types of oligometastasis

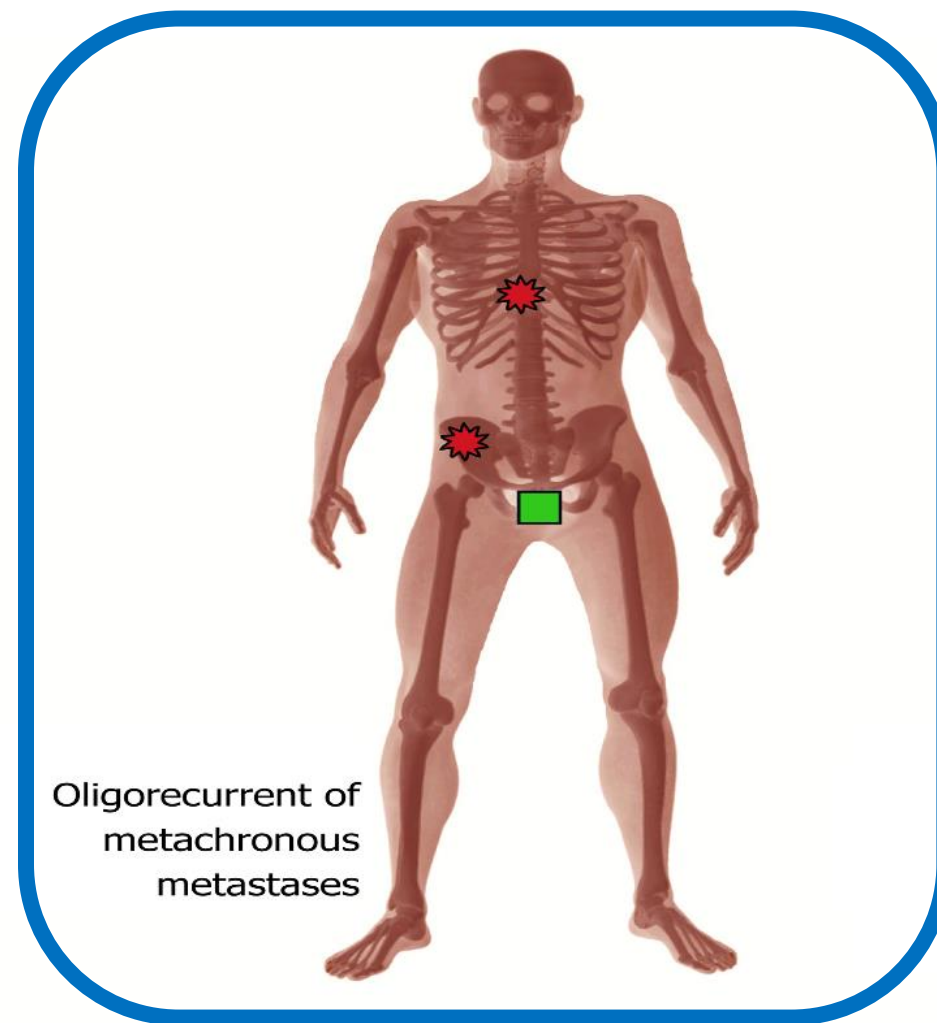
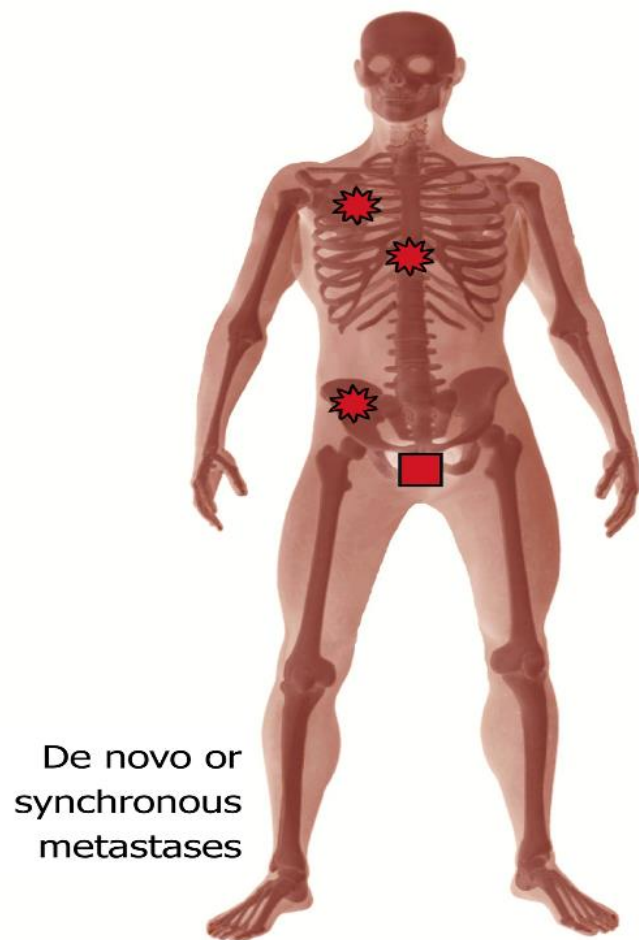


■ Primary tumor uncontrolled

■ Primary tumor controlled

★ Lesion uncontrolled

Types of oligometastasis

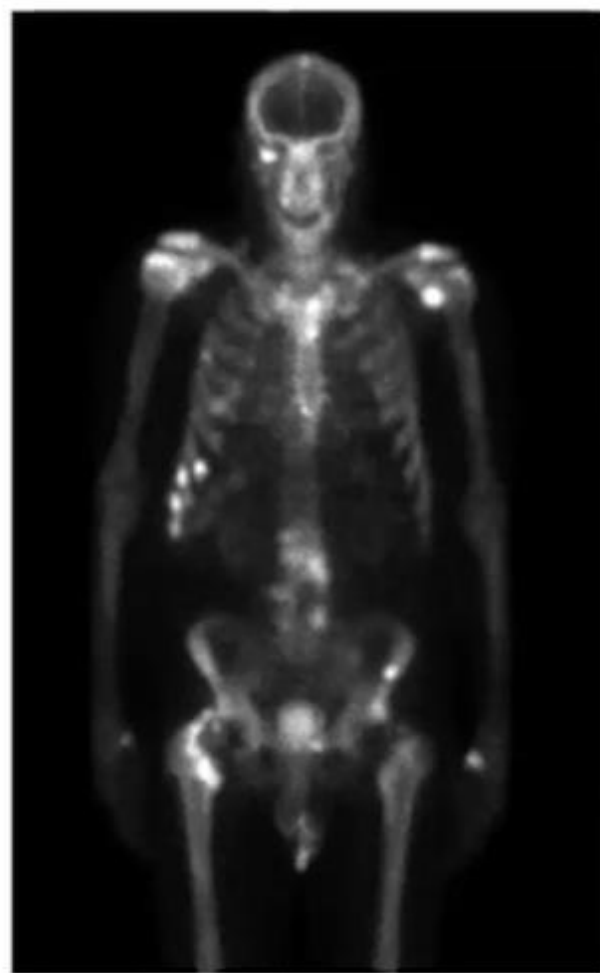


■ Primary tumor uncontrolled

■ Primary tumor controlled

★ Lesion uncontrolled

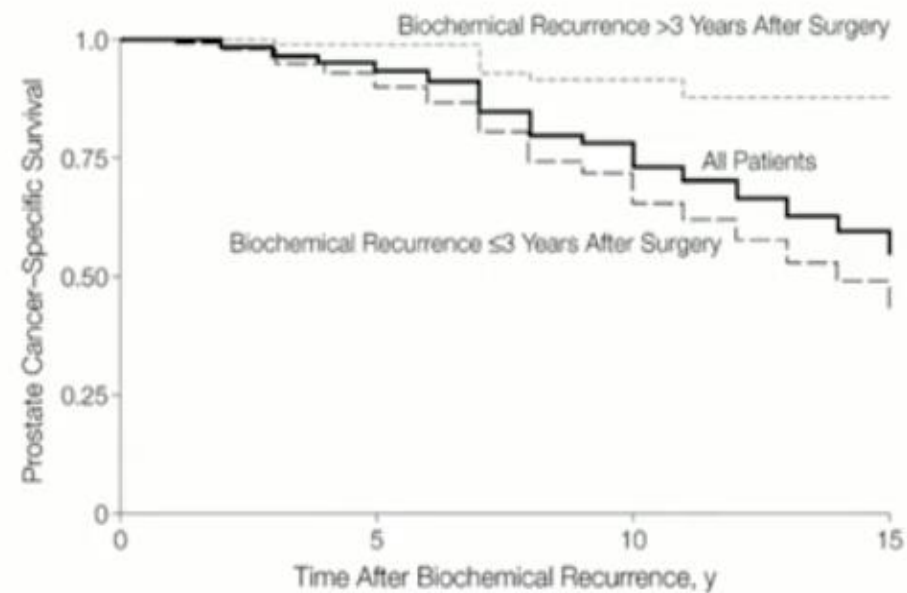
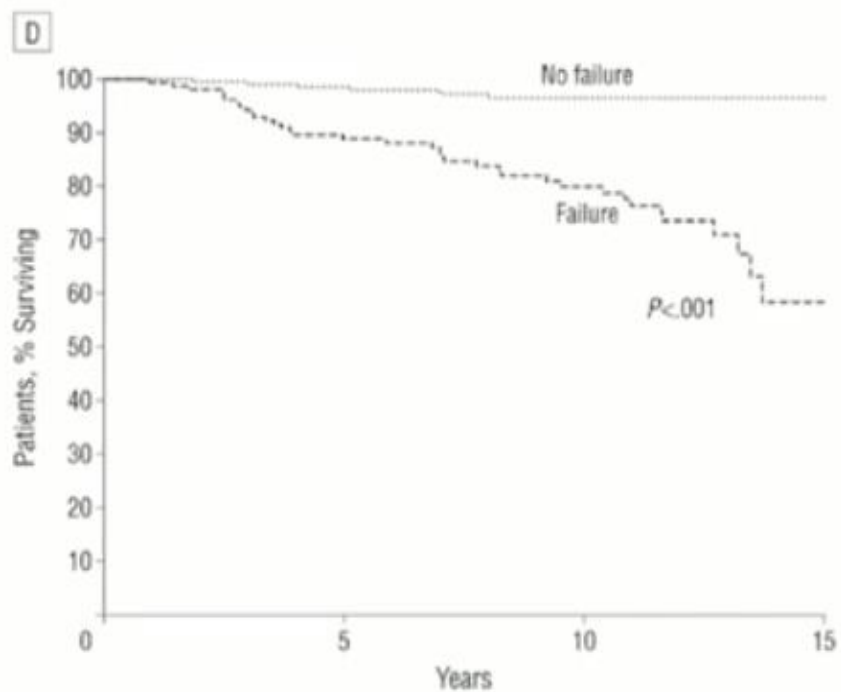
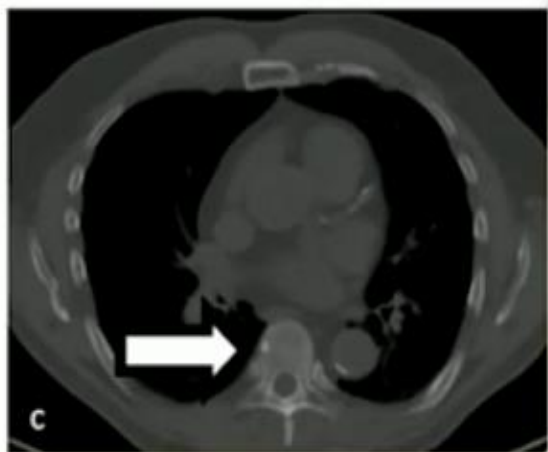
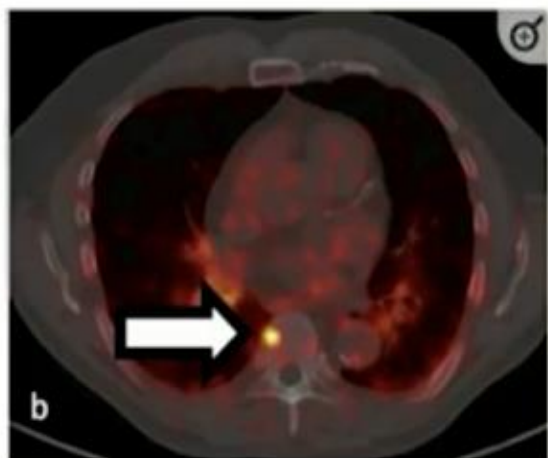
Imaging is getting better



≠



PSMA (+), CI (-) = BCR



Un seuil au PSMA pour différencier haut et bas volume en imagerie de nouvelle génération ?

- Barbato et al, JNM 2021

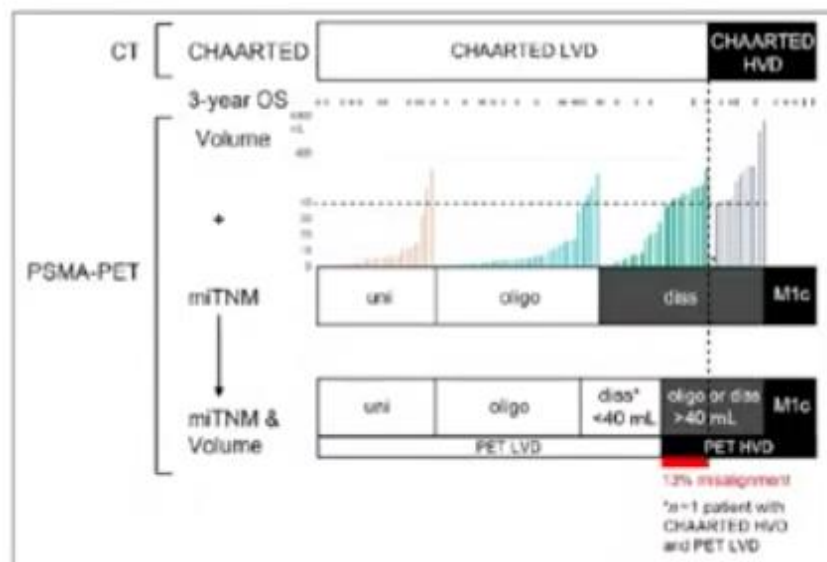


FIGURE 1. mHSPC disease extent as stratified by CT using CHAARTED criteria and PET using tumor volume and miTNM. Criteria for combined (miTNM and volume) PET volume-of-disease assessment are shown. Dashed line indicates area under curve for approximate 40-cm³ cutoff between PET LVD and PET HVD. Three-year overall survival is given for 40 patients (□ = alive; † = died; all others alive and 3 y after PET not yet reached). diss = disseminated, oligo = oligometastatic; uni = unifocal.

Problèmes posés par la migration de stade (plus de métastases visualisées)

1. Les indications de traitement reposent actuellement sur le bilan conventionnel : haut vs bas volume
2. Besoin de trouver une correspondance PSMA/Imagerie conventionnelle
3. Proposition de seuil à 40 mL de volume métabolique au PSMA

Stereotactic body radiation therapy (SBRT)

- Used for primary cancers
- Oligometastases
- Precise, image-guided, high dose radiation in 5 or fewer treatments



Histology	Trial Name/1st author	Intervention	Benefit
NSCLCC	Gomez	Radical RT/SABR or Surgery	OS, PFS
	Iyengar	SABR	PFS
	SINDAS/Wang	SABR	OS, PFS
Prostate	STOMP/Ost	SABR or Surgery	ADT-free survival
	ORIOLE/Philips	SABR	PFS
	EXTEND/Tang	SABR	PFS
	ARTO/Francolini	SABR	PFS (CRPC)
	*RADIOSA/Marvaso	SABR	PFS
Colorectal	EORTC40004/Ruers	RFA-Liver	OS, PFS
	PULMICC/Treasure	Surgery-Lung	No benefit
Esophagus	Liu	SABR, Surgery or Thermal ablation	OS, PFS
Pancreas	*EXTEND/Ludmir	SABR	PFS
Breast	BR-002/	SABR or Surgery	No benefit
Various	SABR-COMET/Palma	SABR	OS, PFS
	*CORE/Khoo	SABR	PFS
	CURB/Tsai	SABR	PFS
	*STOP/Schefferberg	SABR, TA or Surgery	No benefit

* from abstract only

RCT: Addition of Metastasis-Directed Therapy to Intermittent Hormone Therapy for Oligometastatic Prostate Cancer

POPULATION

87 Men



Adults with oligometastatic prostate cancer at ≤ 5 metastatic sites

Median age, 67 y

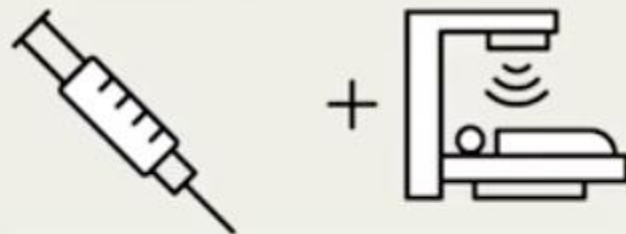
SETTINGS / LOCATIONS



3 Tertiary care centers in US

INTERVENTION

87 Participants randomized



44 Hormone therapy alone

Intermittent hormone therapy

43 Combined therapy

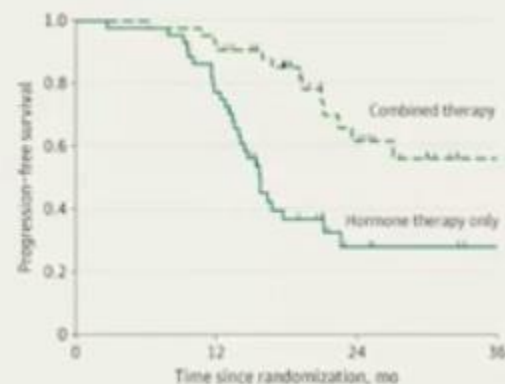
Metastasis-directed therapy combined with intermittent hormone therapy

PRIMARY OUTCOME

Progression-free survival (PFS), defined as time from randomization to radiographic progression per RECIST 1.1 criteria, clinical progression, increasing prostate-specific antigen level, or death

FINDINGS

PFS was significantly improved with combined therapy compared with hormone therapy alone



Hazard ratio, 0.25 (95% CI, 0.12-0.55)

Median PFS: hormone therapy alone, 15.8 mo; combined therapy, median PFS not reached

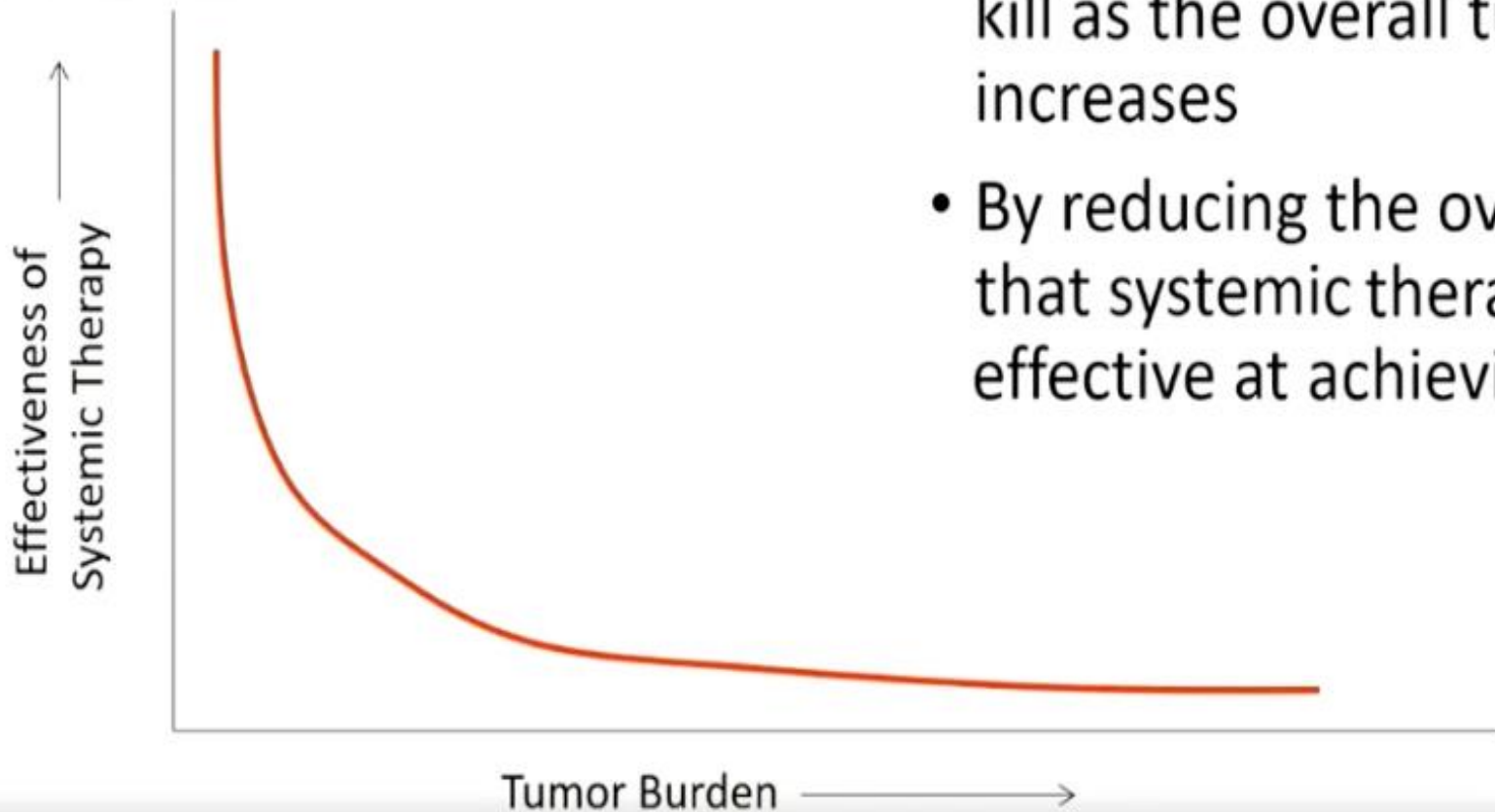
Tang C, Sherry AD, Haymaker C, et al. Addition of metastasis-directed therapy to intermittent hormone therapy for oligometastatic prostate cancer: the EXTEND phase 2 randomized clinical trial. *JAMA Oncol*. Published online April 6, 2023. doi:10.1001/jamaoncol.2023.0161

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The Norton-Simon Hypothesis Revisited

Larry Norton^{1,*} and Richard Simon²

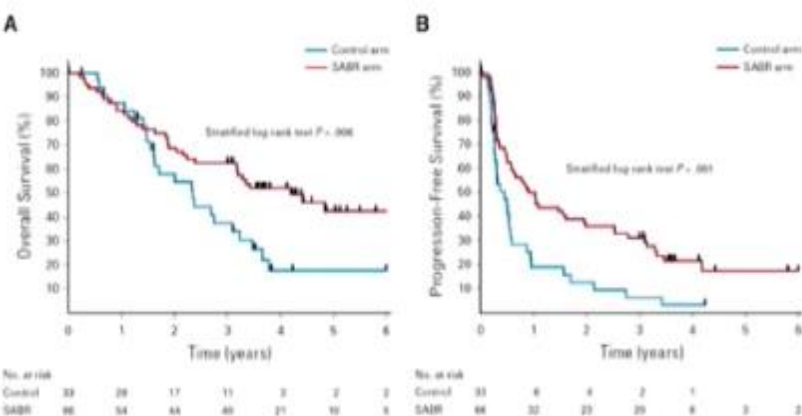
Norton and Simon 1970



- A given system therapy, at a given dose, is less effective in terms of cell kill as the overall tumor burden increases
- By reducing the overall tumor burden that systemic therapy will be more effective at achieving cell kill.

COMET : Phase IIR

Survie globale
1 à 5 méta (No PET)
IL ?

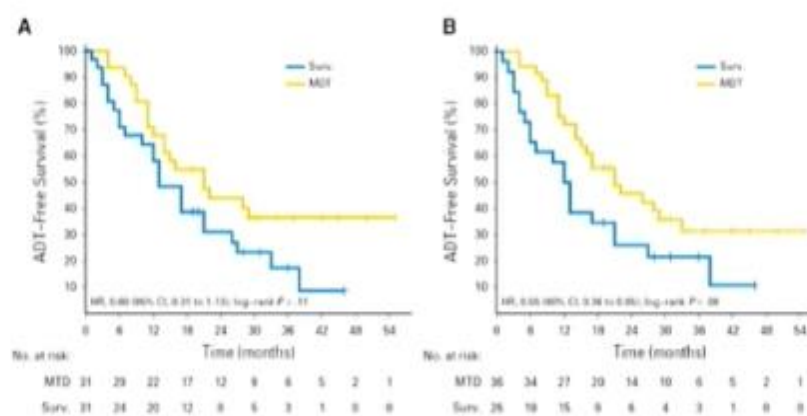


HR= 0.47 (95% CI, 0.27 to 0.81); p= .006

Palma D, JCO 2020

STOMP : Phase IIR

Survie sans hormones
1 à 3 méta (PET choline)
IL > 1mois

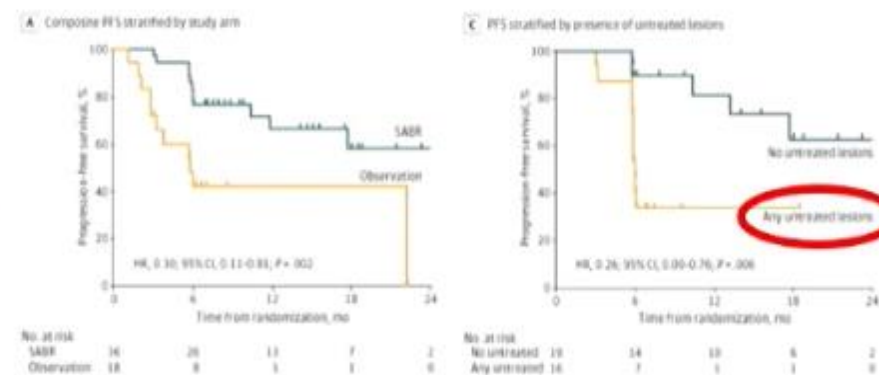


HR= 0.64 (80%CI, 0.42 to 0.96); p = .16

Ost P, JCO
2017

ORIOLE : Phase IIR

Survie sans progression
1 à 3 méta (No PET)
IL > 6mois



HR= 0.30; (95% CI, 0.11-0.81); P = .002

Phillips R, JAMA Oncol
2020

Local consolidative Therapy (LCT) :

- Decreased ctDNA burden
- Fewer detected mutations
- Decreased average variant allele frequency (VAF)

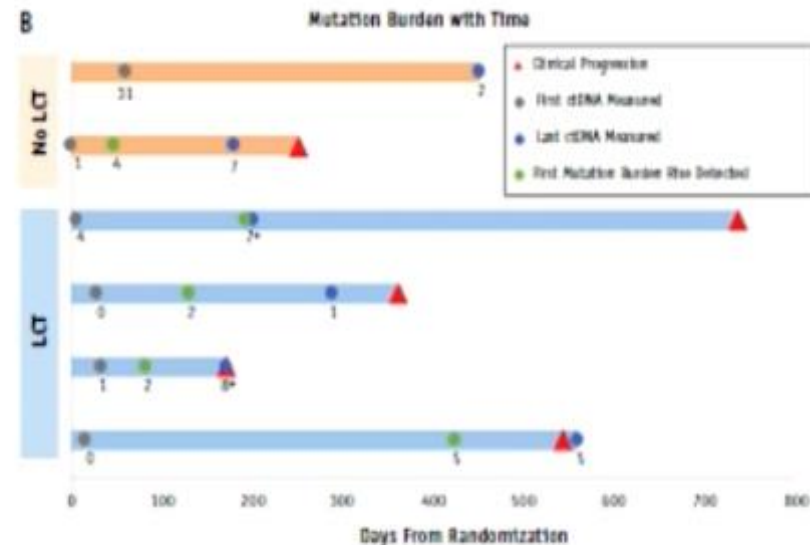
Rise in ctDNA preceded clinical progression by 6.7 months

International Journal of
Radiation Oncology
biology • physics

Clinical Investigation

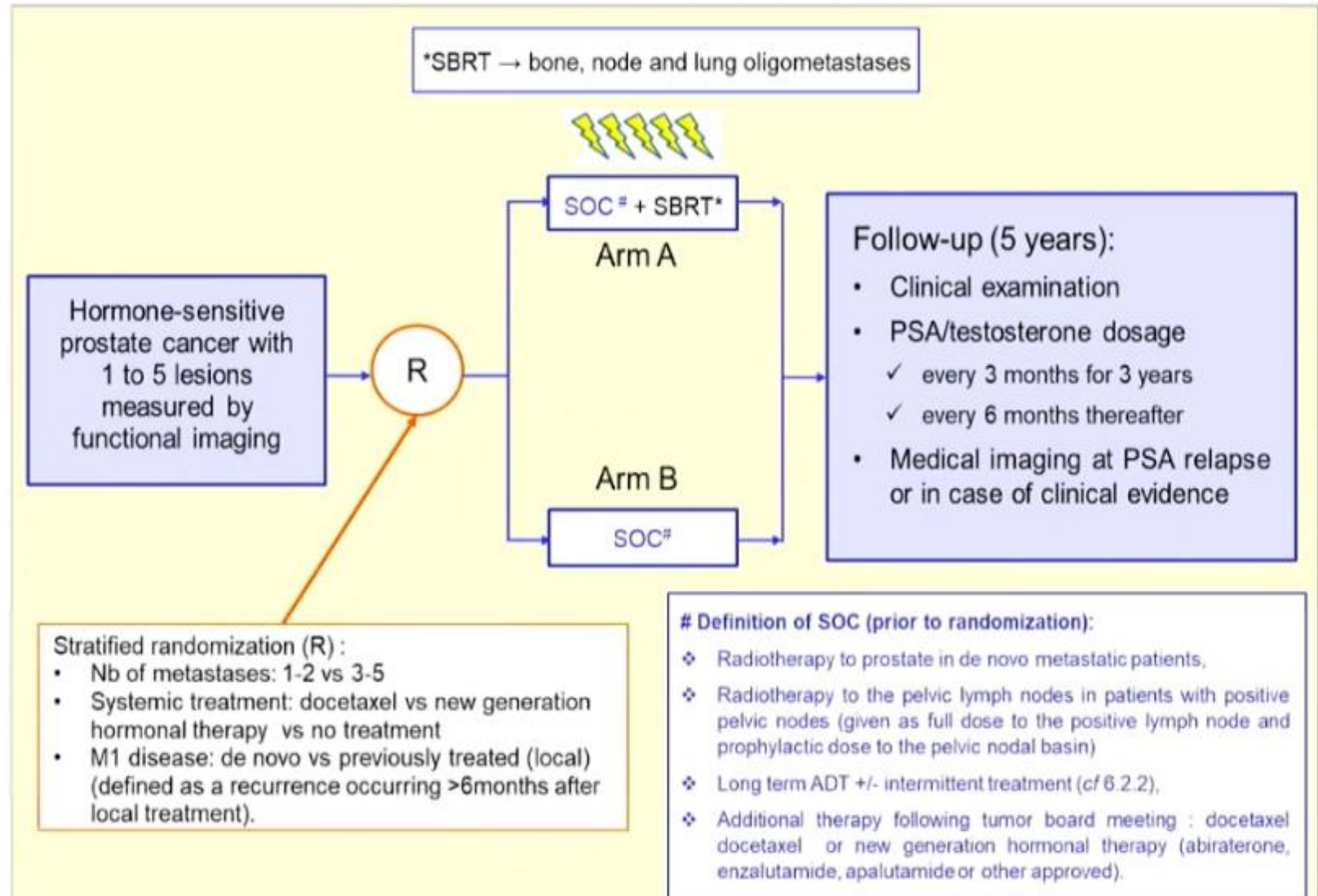
Immune and Circulating Tumor DNA Profiling After Radiation Treatment for Oligometastatic Non-Small Cell Lung Cancer: Translational Correlatives from a Mature Randomized Phase II Trial

Chad Tang, MD,^{*,†} Won-Chul Lee, PhD,^{1,§} Alexandre Reuben, PhD,[§]



Peace6(OligoPRESTO)

- ≤ 5 lésions TEP
(N ou Os)
- Obj principal =
SS Progression Clinique
- N = 350
- HR = 0.6

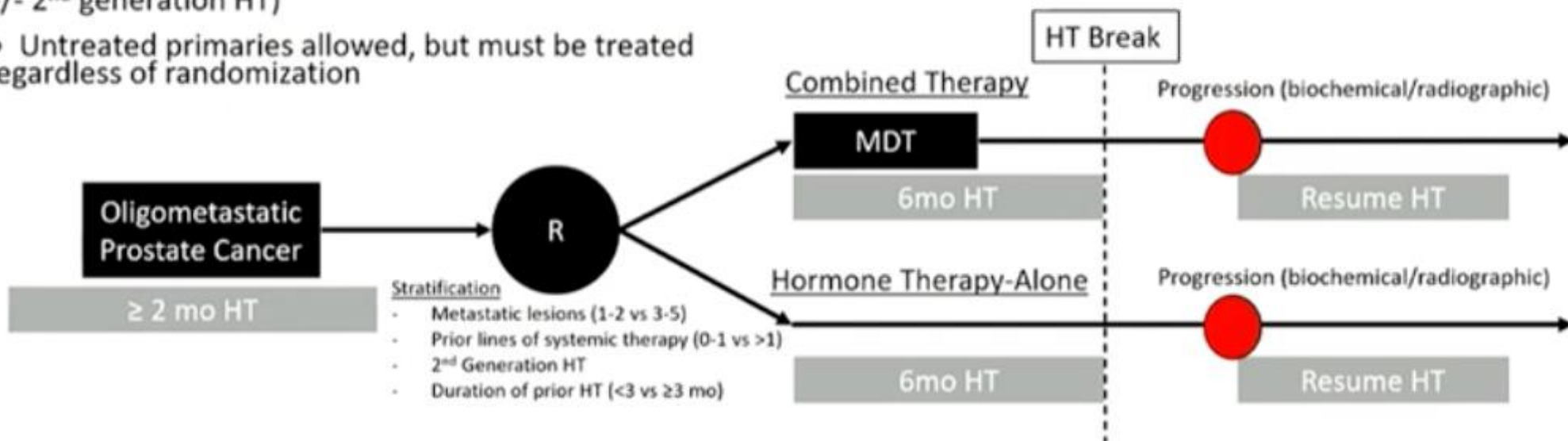


The EXTEND Trial IIR: MDT pour allonger l'hormonosensibilité

Seulement 28% oligométastatiques d'emblée

Major Inclusion Criteria

- Histologic diagnosis of prostate cancer
- ≤5 metastases
- ≥2 months of prior HT (either GNRH agonist/antagonist +/- 2nd generation HT)
- Untreated primaries allowed, but must be treated regardless of randomization

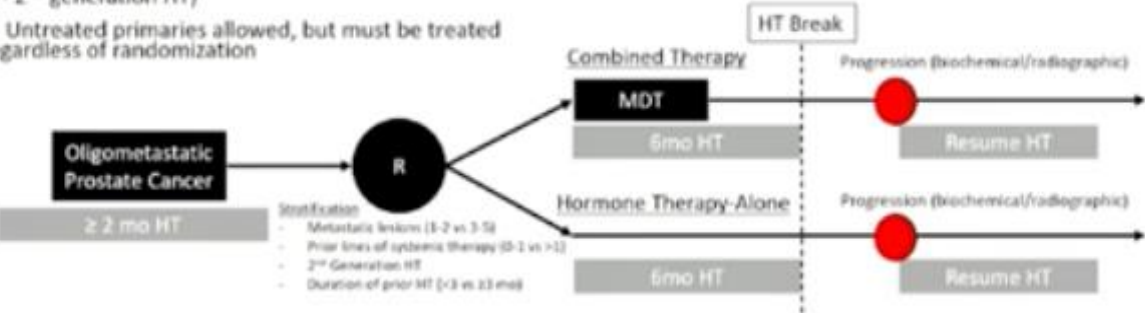


MDT pour allonger l'hormonosensibilité

EXTEND intermittent prostate cancer

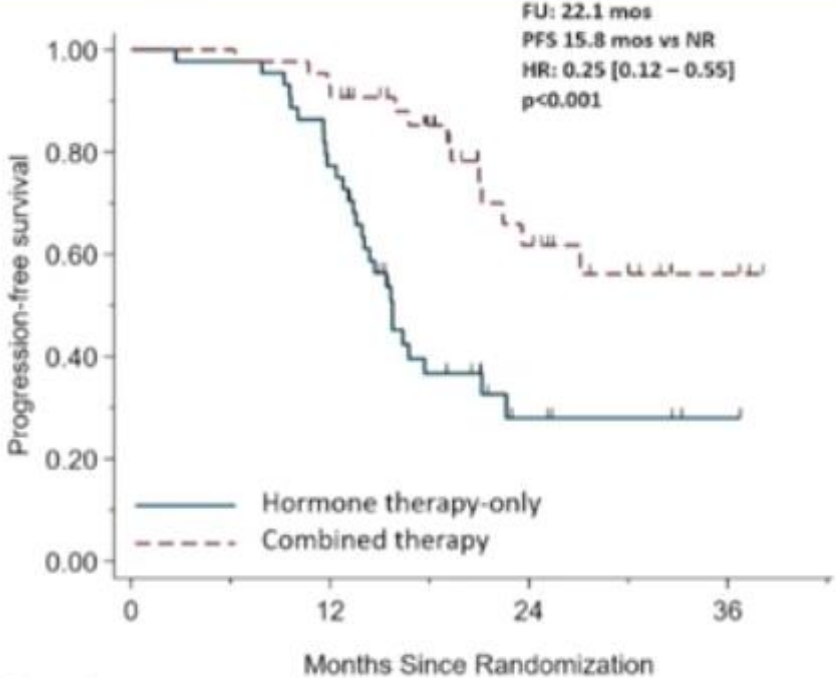
Major Inclusion Criteria

- Histologic diagnosis of prostate cancer
- ≤5 metastases
- ≥2 months of prior HT (either GNRH agonist/antagonist +/- 2nd generation HT)
- Untreated primaries allowed, but must be treated regardless of randomization



Stratification

- Metastatic lesions (1-2 vs 3-5)
- Prior lines of systemic therapy (0-1 vs >1)
- 2nd Generation HT
- Duration of prior HT (<13 vs ≥13 mo)



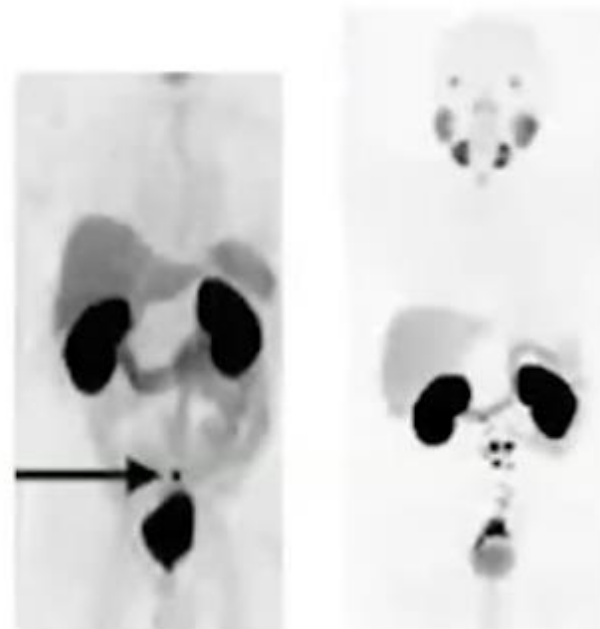
	0	12	24	36			
N at risk (Events)							
Hormone therapy-only	44	(10)	34	(18)	5	(0)	1
Combined therapy	43	(3)	40	(9)	15	(1)	3

Seuls 28% sont oligométastatiques d'emblée...

Adding Systemic (Hormonal) Therapy to Radiation Therapy in Oligometastatic Prostate Cancer : Type and Duration

PSMA PET was first FDA approved in 12/2020 so there are very few completed clinical trials using PET imaging.

Consequently, we frequently need to extrapolate from clinical trials undertaken in the pre-PSMA PET era.



The type and duration of hormonal therapy falls along a spectrum, based on:

- Characteristics at diagnosis (PSA level, Gleason Score, Stage, Decipher Score)
- Current Characteristics (number and location of PSMA positive spots)

Adding Systemic (Hormonal) Therapy to Radiation Therapy in Oligometastatic Prostate Cancer : Type and Duration

	Low Risk ←————→ High Risk			
PET Scan Findings	Single pelvic LN	Multiple pelvic LN	LN outside pelvis	Bone
Characteristics of Cancer at Diagnosis	GS 6,7 Organ confined Decipher score low PSA <4	T3	Node +	GS 8-10 Bone Decipher score high PSA > 20
Current Cancer Characteristics	PSA < 1 PSADT >12 mos			PSA > 5-10 PSA DT < 6 mos

Adding Systemic (Hormonal) Therapy to Radiation Therapy in Oligometastatic Prostate Cancer : Type and Duration

	Low Risk ←————→ High Risk			
PET Scan Findings	Single pelvic LN	Multiple pelvic LN	LN outside pelvis	Bone
Type and Duration of Hormonal Therapy	No ADT	6 months of single agent ADT		24 months of "intensified ADT"

Goals of therapy:

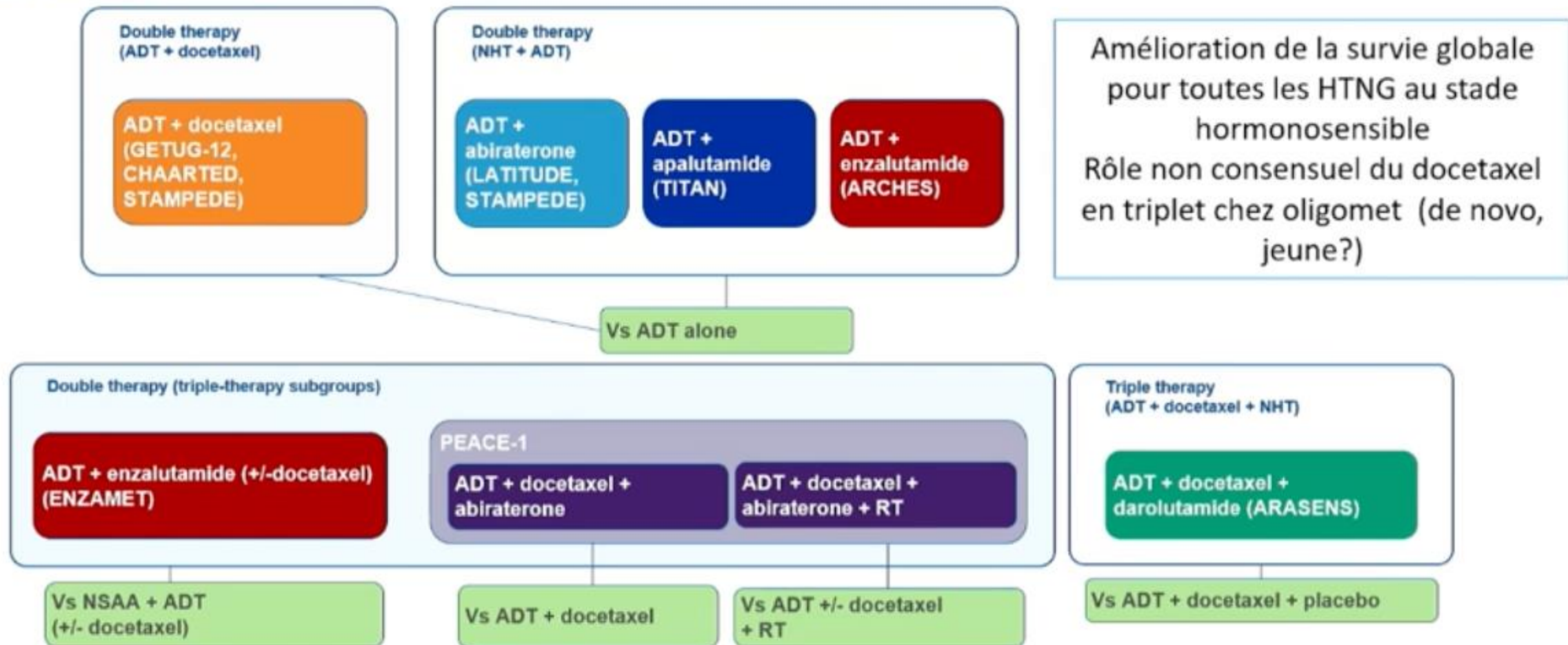
- Avoid systemic therapy
- Delay time until next therapy ("kicking the can down the road")
- Delay time until disease progression
- Eliminate risk of recurrence (cure)

Measuring outcomes:

Requires waiting until completion of the hormonal therapy, recovery of testosterone levels, and tracking ultra-sensitive PSA.

Repetitive PSMA PET scans and repeat targeted radiation upon PSA climb is often feasible!

Traitement systémique actuel pour les cancers de prostate métastatiques hormonosensibles ?



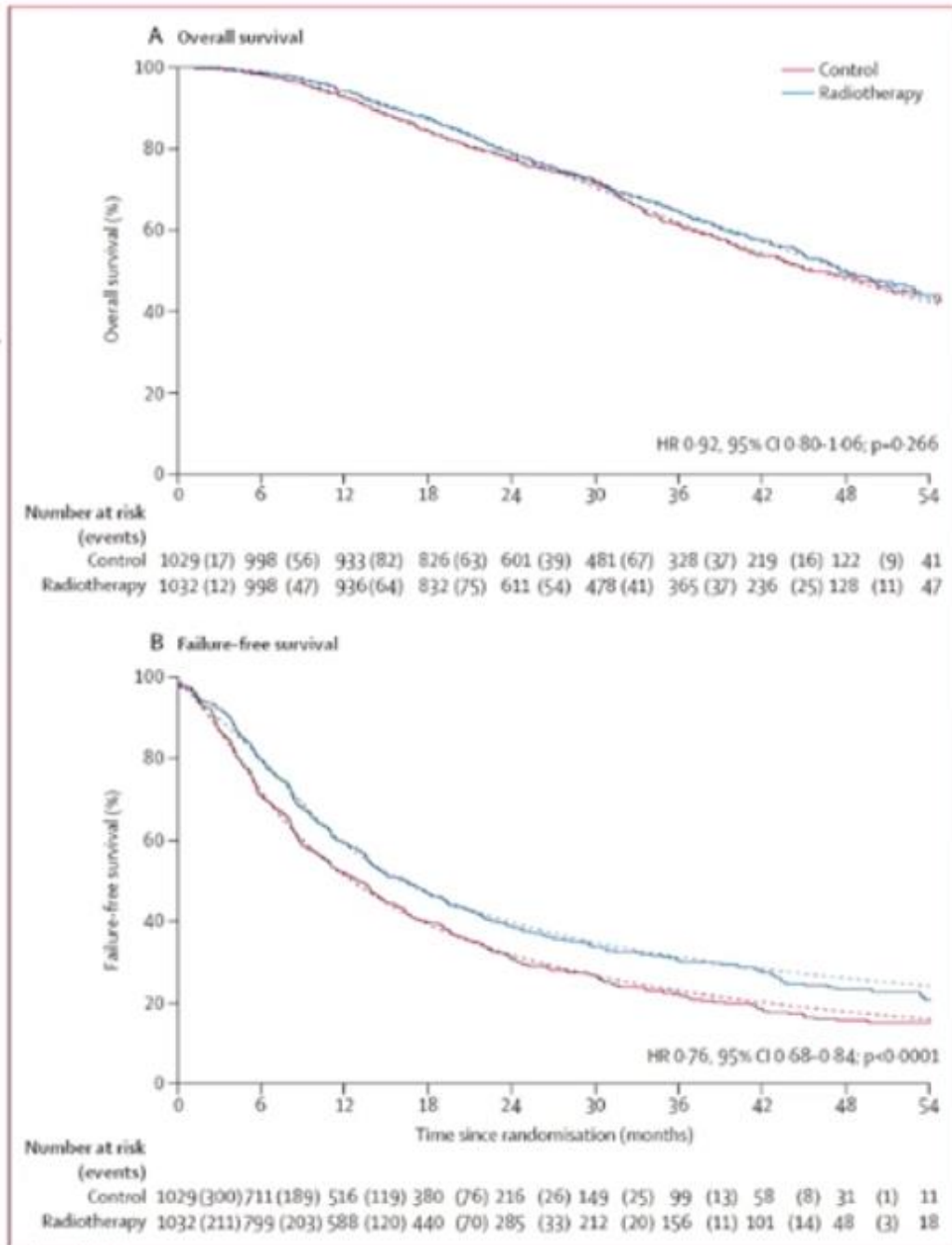
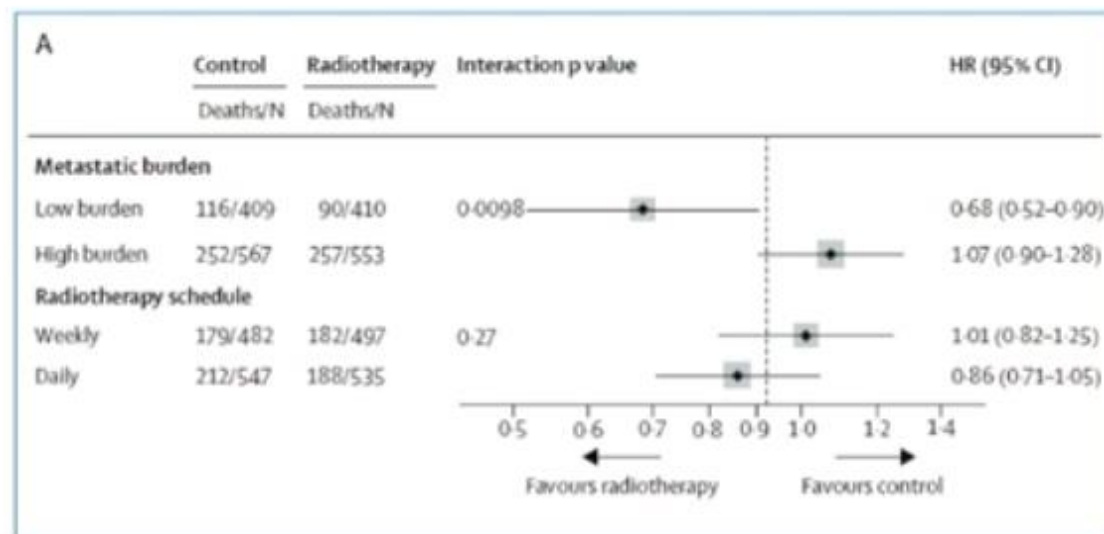
Amélioration de la survie globale pour toutes les HTNG au stade hormonosensible
Rôle non consensuel du docetaxel en triplet chez oligomet (de novo, jeune?)

Bénéfice de l'intensification de l'ADT avec HTNG qq soit le volume métastatique

Essai	Population globale OS, HR (95% CI)	Population haut volume OS, HR (95% CI)	Population bas volume OS, HR (95% CI)
LATITUDE AAP + ADT vs PBO + ADT (100% <i>de novo</i> ; N=1199)	0.66 (0.56, 0.78)	0.62 (0.52, 0.74)	0.72 (0.47, 1.10)
STAMPEDE AAP AAP + SOC vs SOC (94% <i>de novo</i> ; N=1003)	0.62 (0.53, 0.73)	0.54 (0.43, 0.69)	0.55 (0.41, 0.76)
ENZAMET ENZA + ADT vs NSAA + ADT (45% concurrent DOC; N=1125)	0.70 (0.58, 0.84)	0.79 (0.63, 0.98)	0.54 (0.39, 0.74)
TITAN APA + ADT vs PBO + ADT (10% prior DOC; N=1052)	0.65 (0.53, 0.79)	0.70 (0.56, 0.88)	0.52 (0.35, 0.79)
ARCHES ENZA + ADT vs PBO + ADT (18% prior DOC; N=1150)	0.66 (0.53, 0.81)	0.66 (0.52, 0.83)	0.66 (0.43, 1.03)
ARASENS DARO + ADT + DOC vs PBO + ADT + DOC (100% DOC; N=1306)	0.68 (0.57, 0.80)	0.69 (0.57, 0.82)	0.68 (0.41, 1.13)

Traitement local

Stampede-RT – résultats



Design of PEACE-1

Key Eligibility Criteria

De novo mCSPC

Distant metastatic disease: ≥ 1 lesion on bone scan and/or CT scan

ECOG PS 0 -2

On-Study Requirement

Continuous ADT

Permitted

ADT ≤ 3 months

Stratification

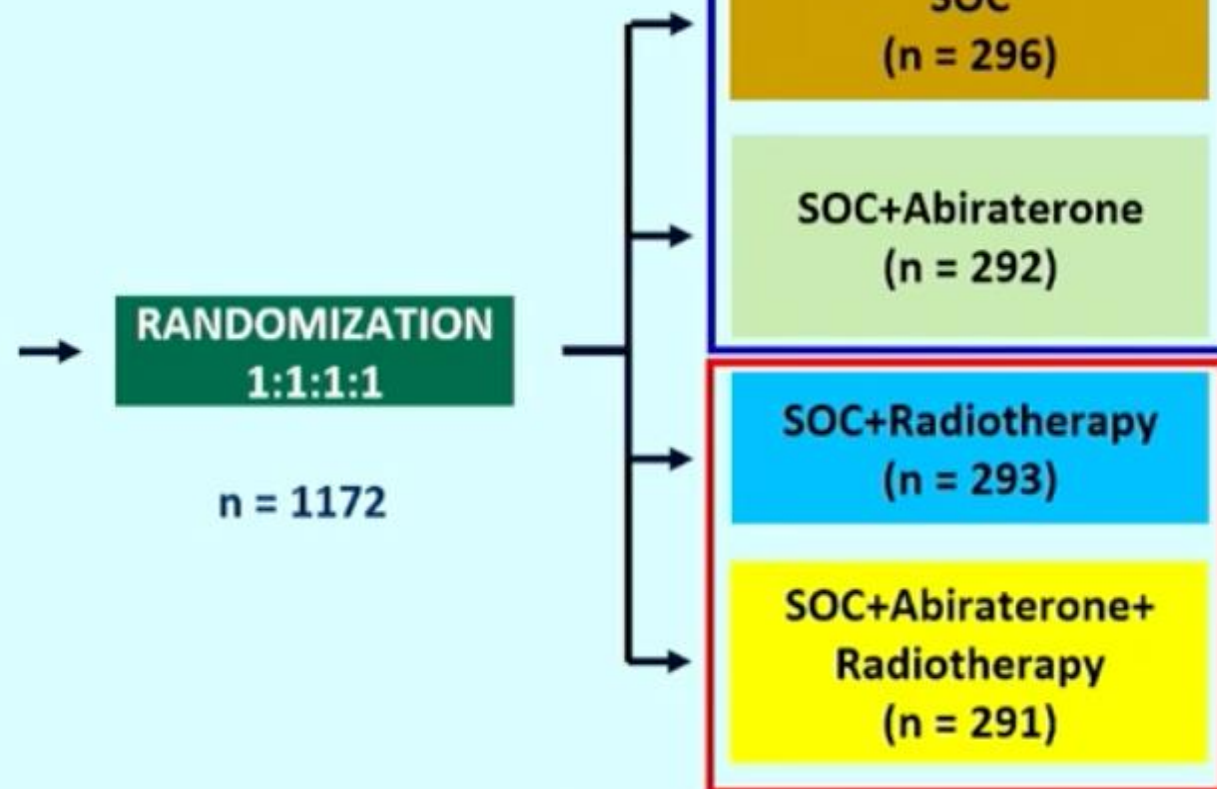
ECOG PS (0 vs 1-2)

Metastatic sites (LN vs bone vs visceral)

Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)

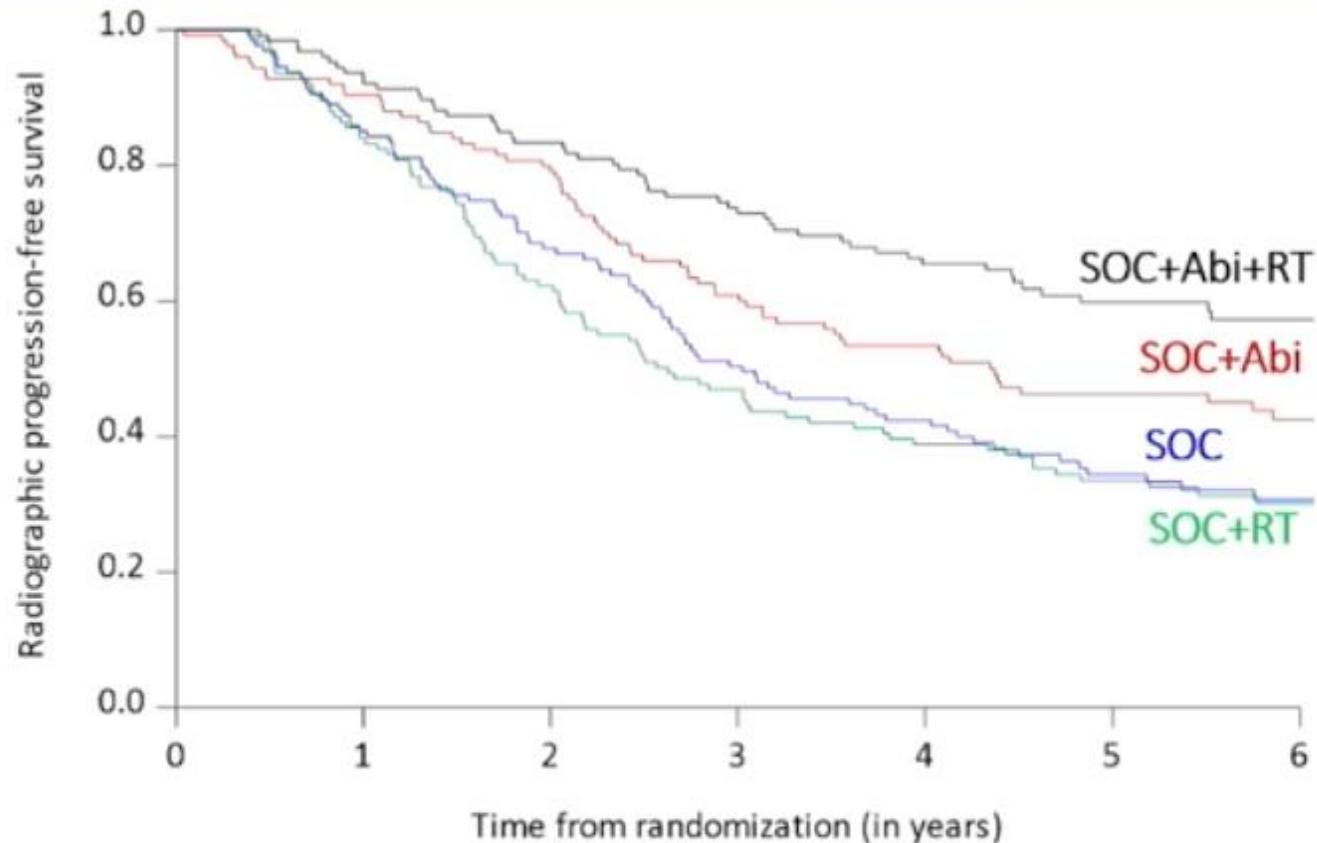
Docetaxel (yes vs no)

Nov 2013 – Dec 2018



ECOG PS, Eastern Cooperative Oncology Group performance status

rPFS (low volume population)



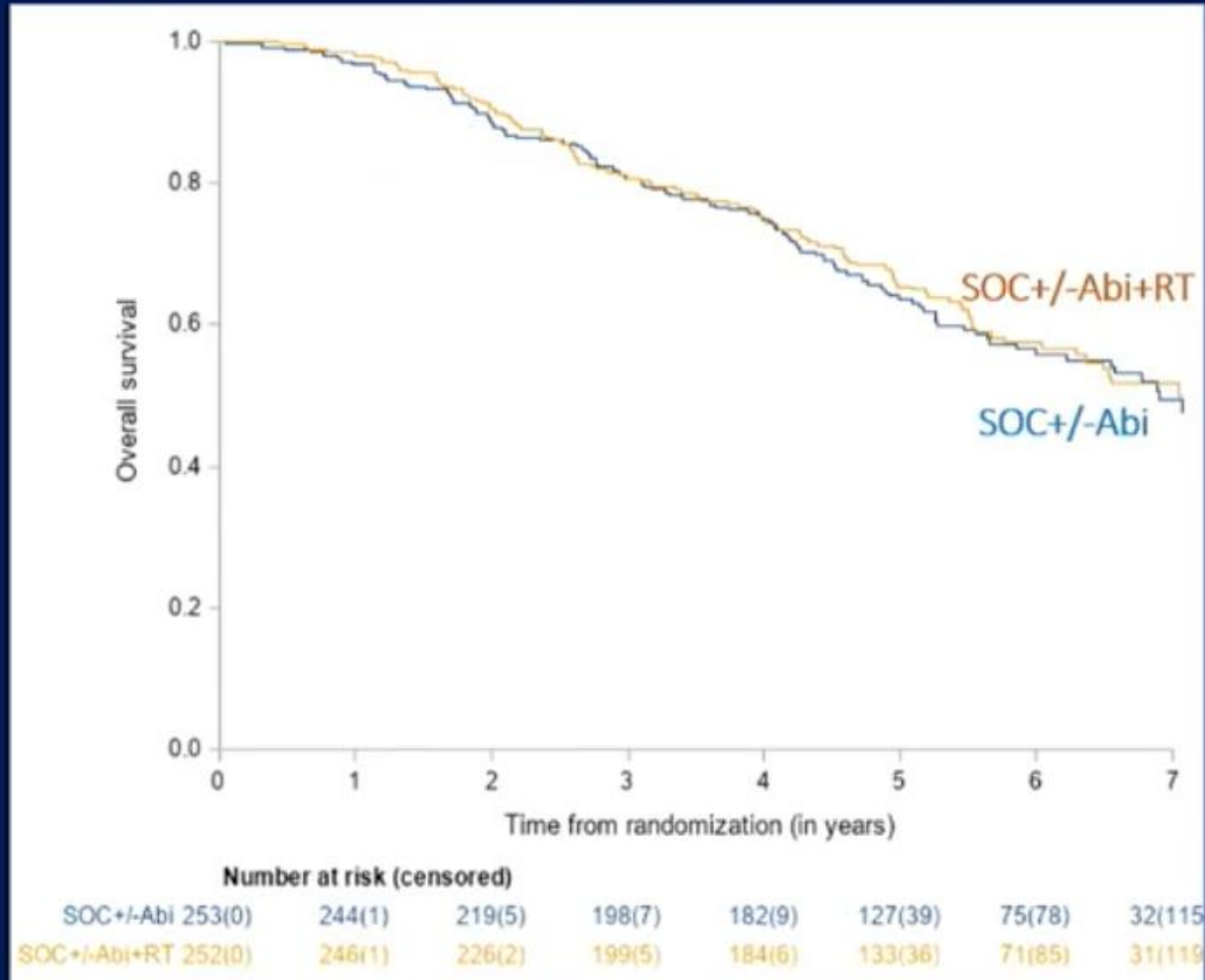
Number at risk (censored)

	0	1	2	3	4	5	6
SOC 127(0)	108(0)	86(0)	64(0)	53(1)	34(11)	20(22)	
SOC+Abi 126(0)	113(1)	96(4)	73(5)	64(5)	46(15)	31(27)	
SOC+RT 126(0)	105(1)	77(2)	58(2)	48(2)	36(8)	23(18)	
SOC+Abi+RT 126(0)	116(0)	105(0)	89(3)	79(4)	60(17)	34(41)	

	SOC (n=127)	SOC+RT (n=126)	SOC+Abi (n=126)	SOC+Abi+RT (n=126)
Median, ys. (99.9% CI)	3.0 (2.3-4.8)	2.6 (1.7-4.6)	4.4 (2.5-7.3)	7.5 (4.0-NE)
Events, n.	87	89	74	55
HR (99.9%CI)*	Ref	1.11 (0.67-1.84)	0.76 (0.45-1.28)	0.50 (0.28-0.88)
Global p-value	<0.0001			
HR (99.9% CI)*	Ref	1.08 (0.65-1.80)	Ref	0.65 (0.36-1.19)
P-values arms w/wo Abi	0.61		0.02	

*Adjusted on stratification factors (PS, type of castration, docetaxel)

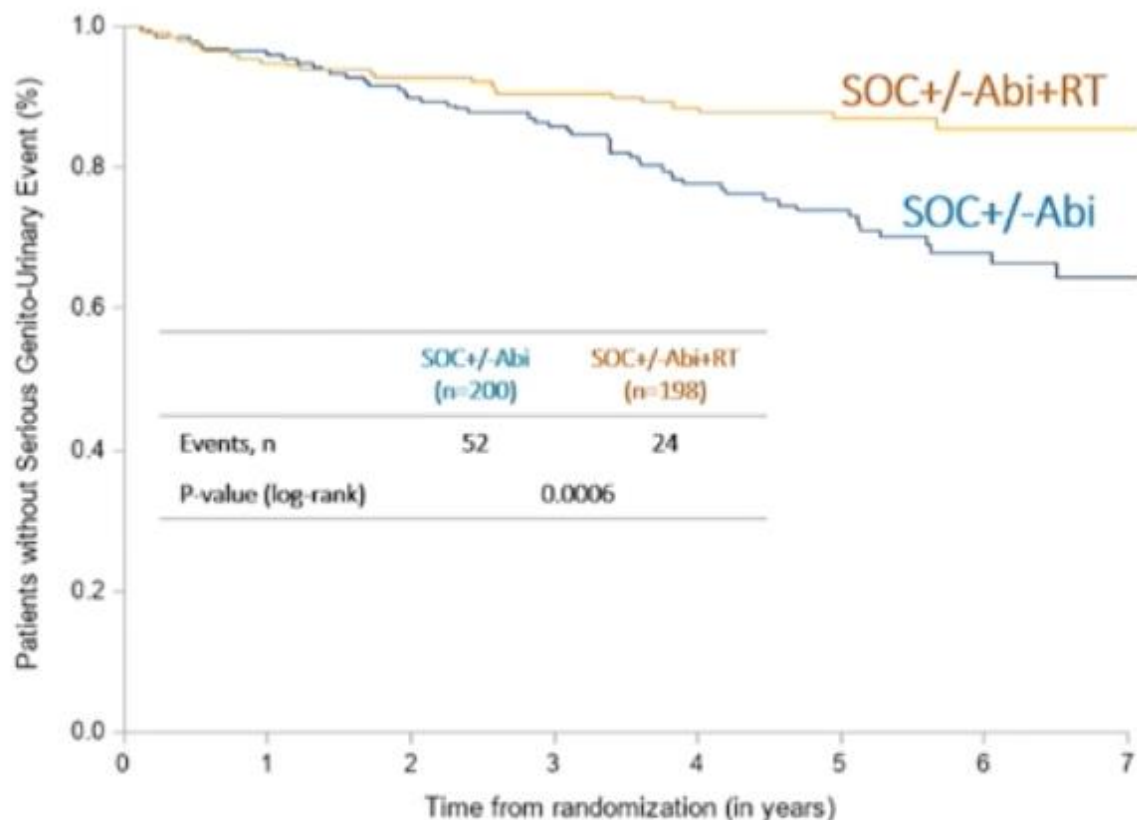
OS (low volume population)



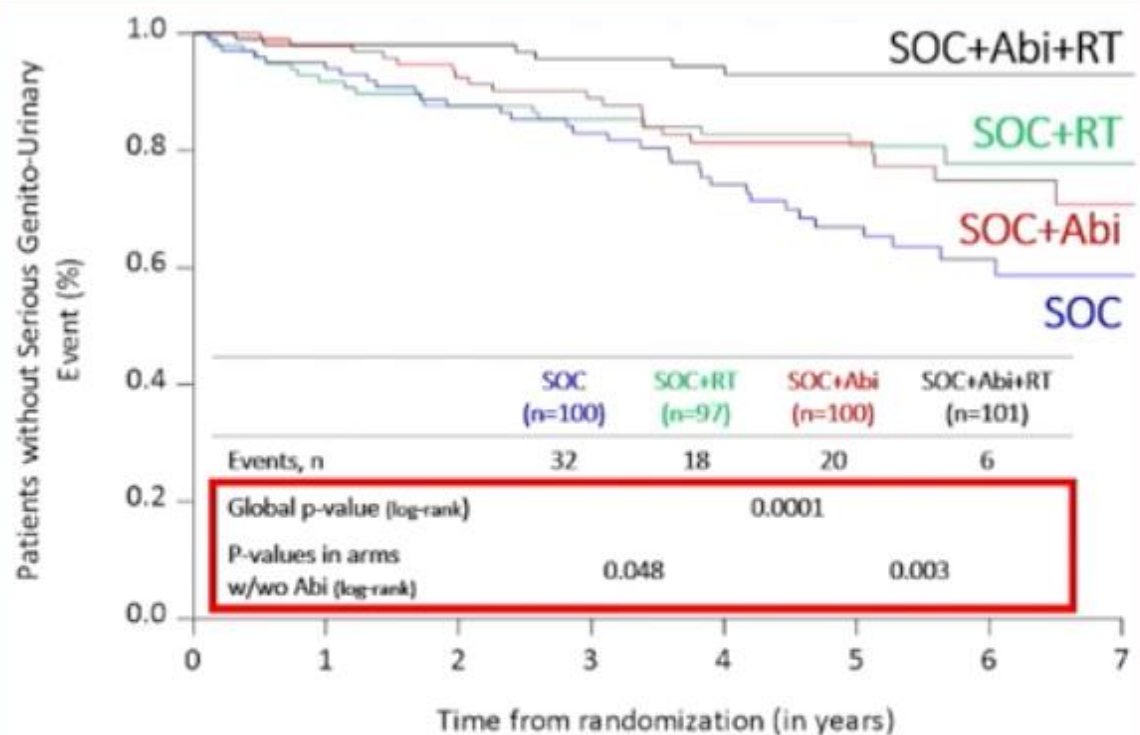
	SOC+/-Abi (n=253)	SOC+/-Abi+RT (n=252)
Median, ys. (95.1% CI)	6.9 (5.9-7.5)	7.5 (6-NE)
Events, n	111	104
HR*	Ref	0.98 (0.74-1.28)
p-value	0.86	

*Adjusted on Abiraterone and stratification factors (PS, type of castration, docetaxel)

Time to Serious Genito-Urinary events (low volume pop.)

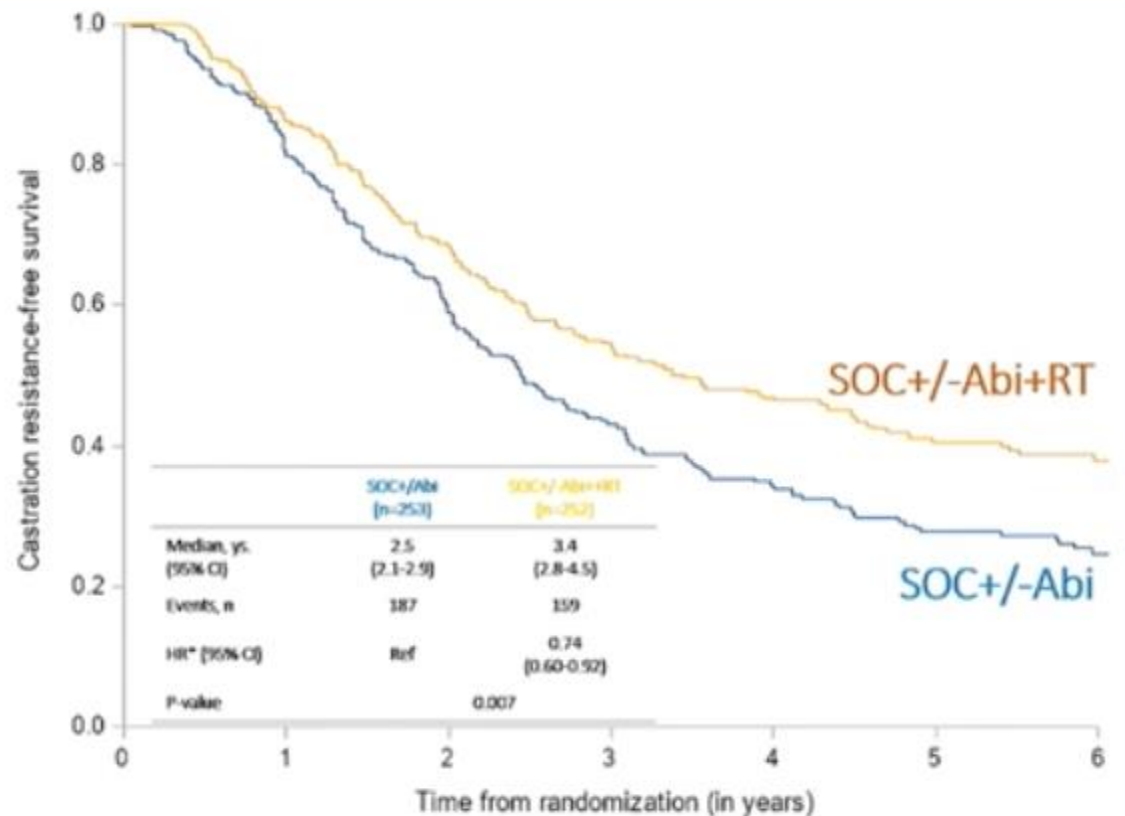


	0	1	2	3	4	5	6	7
Number at risk (censored)								
SOC+/-Abi 200(0)	185(7)	162(19)	140(34)	119(42)	86(70)	46(104)	19(129)	
SOC+/-Abi+RT 198(0)	184(4)	167(17)	145(35)	132(45)	95(80)	54(120)	24(150)	

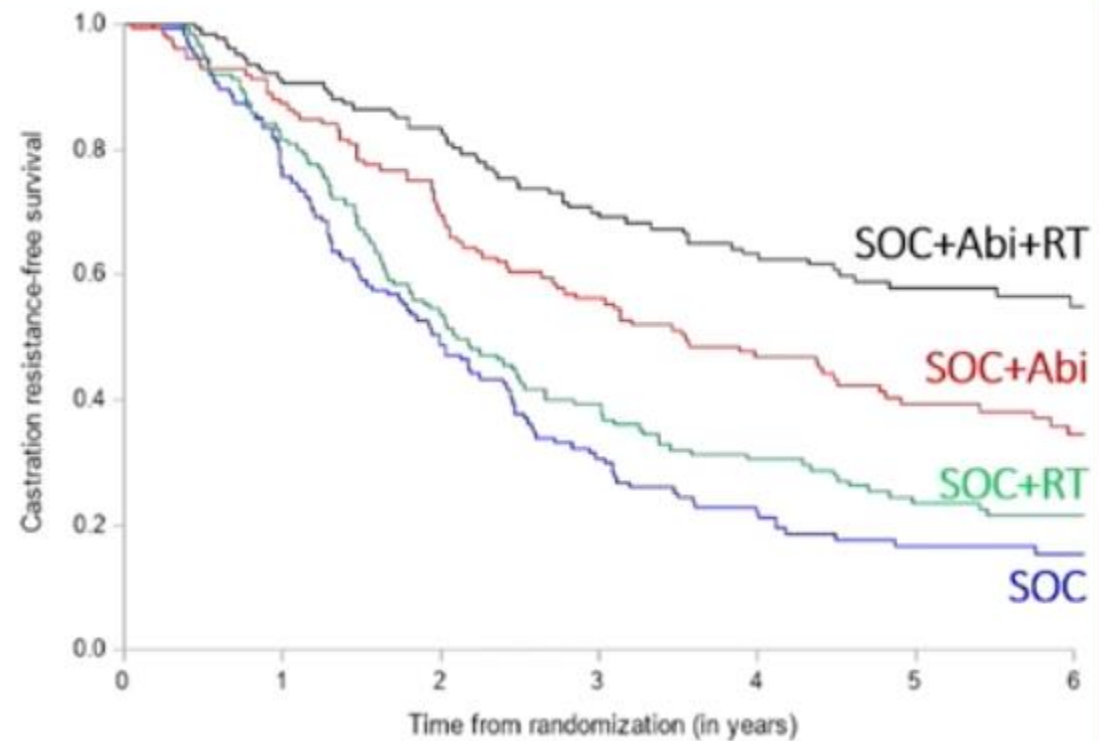


	0	1	2	3	4	5	6	7
Number at risk (censored)								
SOC 100(0)	91(3)	79(9)	68(16)	58(19)	43(29)	22(47)	8(60)	
SOC+Abi 100(0)	94(4)	83(10)	72(18)	61(23)	43(41)	24(57)	11(69)	
SOC+RT 97(0)	89(0)	82(3)	69(14)	61(20)	39(41)	22(57)	12(67)	
SOC+Abi+RT 101(0)	95(4)	85(14)	76(21)	71(25)	56(39)	32(63)	12(83)	

Castration Resistance Free-Survival (low volume pop.)



	0	1	2	3	4	5	6
SOC+/-Abi 253(0)	206(1)	146(4)	106(5)	83(6)	56(19)	37(33)	
SOC+/-Abi+RT 252(0)	216(1)	172(1)	134(3)	115(4)	84(21)	51(50)	



	0	1	2	3	4	5	6
SOC 127(0)	97(0)	62(0)	39(0)	27(1)	16(6)	11(10)	
SOC+Abi 126(0)	109(1)	84(4)	67(5)	56(5)	40(13)	26(23)	
SOC+RT 126(0)	102(1)	67(1)	49(1)	38(1)	26(5)	18(11)	
SOC+Abi+RT 126(0)	114(0)	105(0)	85(2)	77(3)	58(16)	33(39)	

interaction p-value = 0.15

*Adjusted on abiraterone and stratification factors (PS, type of castration, docetaxel)

MDT dans les cancers de prostate oligoM+

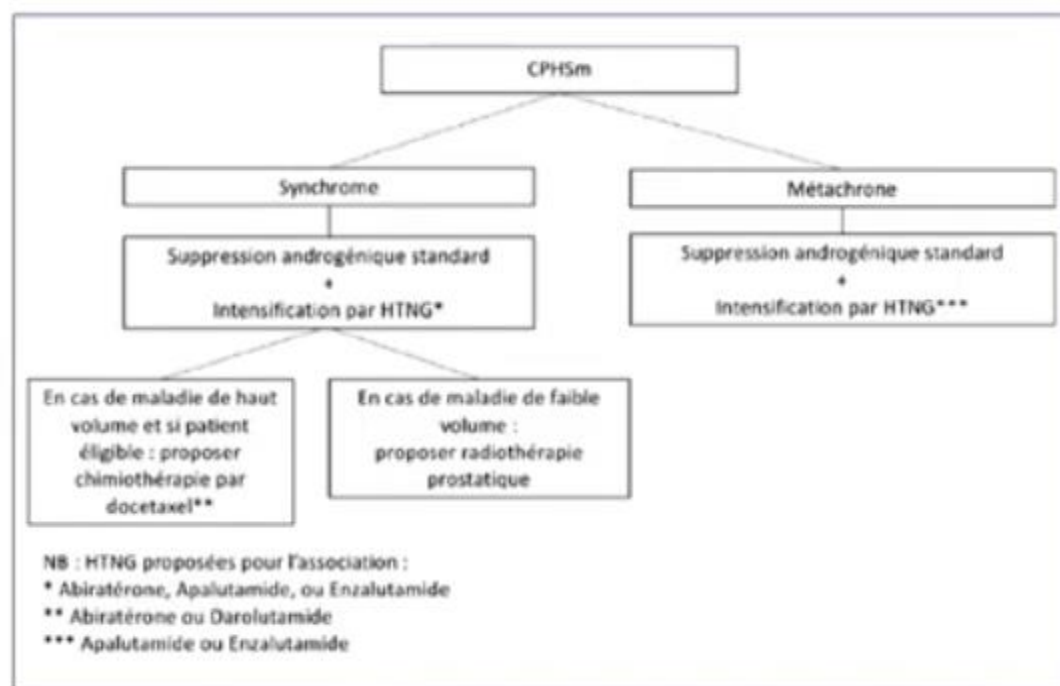
Essais en cours

Trial characteristics	PLATON (CCTG PR20) NCT03784755	PRESTO (GETUG-PEACE 6) NCT04115007	STARPORT (VA) NCT04787744	STAMPEDE 2 OLIGOMETS	START-MET NCT05209243
Disease status	De novo + recurrent	De novo + recurrent	Recurrent	De novo	De novo + recurrent
Imaging	Bone scan and CT scan	F- or C-PET/CT, PSMA PET/CT, or whole-body MRI scan	Abdomen/pelvis CT/MRI, F- or C- PET/CT, bone scan, or PSMA PET/CT scan	Bone scan and CT/MRI scan	Bone / CT scans + Choline or PSMA PET/CT
Oligomets definition	M1 disease with ≤ 5 metastases (including ≤ 3 metastases in any non-bone organ system)	M1 disease with ≤ 5 metastases (including ≥ 1 bone or pulmonary lesion)	≤ 5	$\leq 3^1$	≤ 5
ADT	Yes, continuous	Yes, continuous or intermittent	Yes, continuous	Yes, continuous	yes, continuous
Primary endpoint	FFS	CRPC-free survival	CRPC-free survival	OS	rPFS
Sample size	410	550	464	1939	266

PRESTO: >500 patients inclus à ce jour

Conclusions : recommandations EAU/AFU

CCAFU 2022

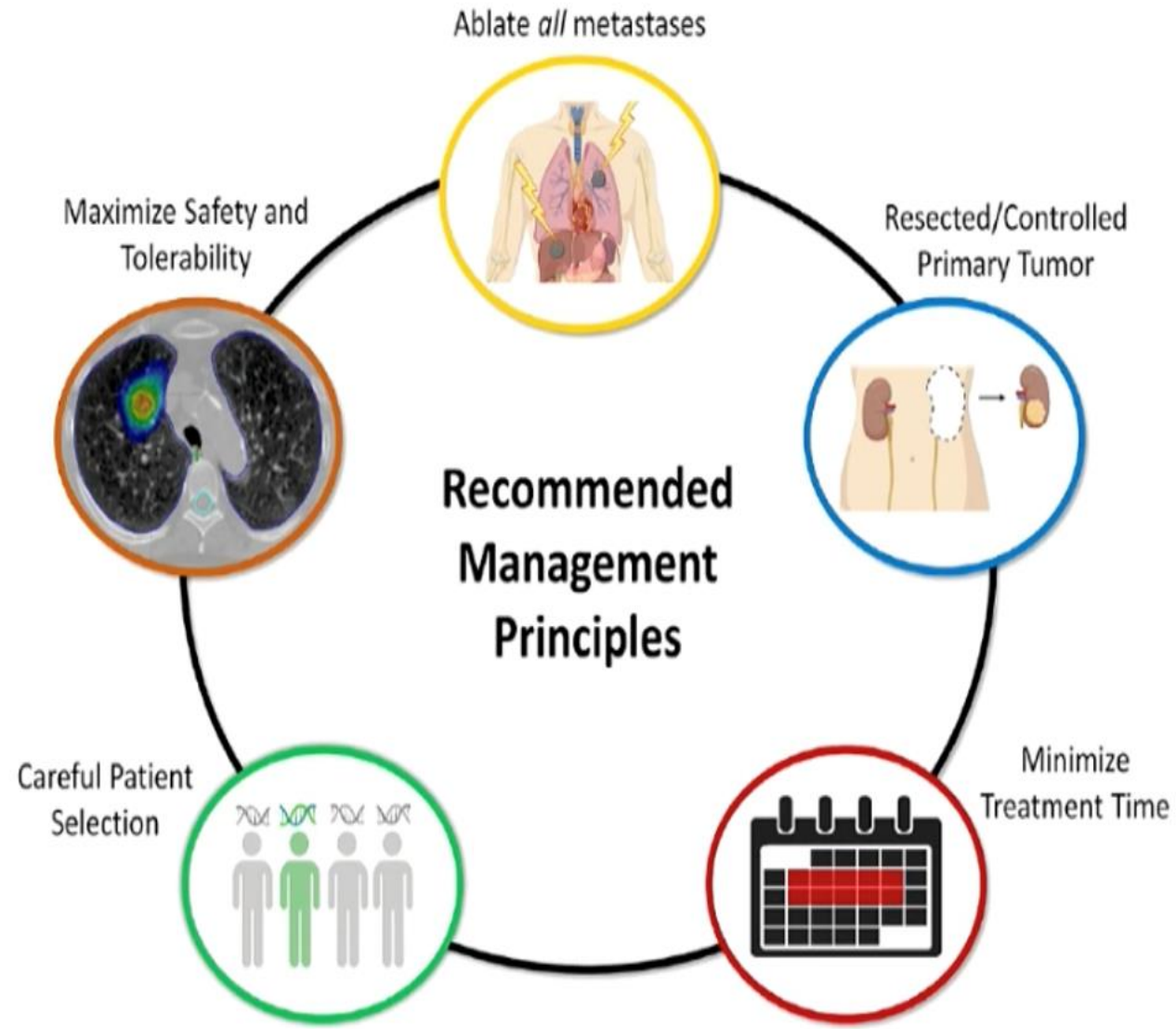


La radiothérapie dirigée sur les métastases (en dehors du contexte symptomatique) n'a pas fait preuve de son efficacité oncologique et doit être proposée dans le cadre d'essais cliniques

Fort

EAU 2023

Recommendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
At the start of ADT offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy to patients with impending clinical complications such as spinal cord compression or bladder outlet obstruction.	Strong
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contra-indications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients with M1 disease who are fit for the regimen.	Strong
Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease who are fit for docetaxel.	Strong
Offer ADT combined with prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHARTED criteria.	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or a well-designed prospective cohort study.	Strong



Take home messages

- Le cancer de la prostate oligo-métastatique est une entité récente à l'origine d'un dilemme clinique grandissant marqué par la migration de stade d'où l'importance du PET PSMA
- De Novo VS métachrone dirige le traitement plus que la notion de nombre de métastases
- Place centrale du traitement systémique en plus de la castration (TNG +++)
- RTH du primitif pour les bas volumes, et SBRT en cours d'évaluation (de novo)
- Rôle de la SBRT comme MDT+LH-RH+TNG pour une durée définie
- Rôle de la concertation pour la sélection des patients (éviter le surtraitement pour les CI(-))