MOVEMBER

NUOVE PROSPETTIVE DI CURA PER IL PAZIENTE CON CARCINOMA PROSTATICO AVANZATO

22-23 NOVEMBRE 2018

MILANO

HILTON MILAN
via L. Galvani 12

SIU
Società Italiana di Urologia
dal 1908

Come sta cambiando il trattamento del Ca prostatico metastatico, stato dell'arte

Giario Conti

Direttore U.O. Urologia

Ospedale S.Anna, Como

PC: epidemiology

Second most frequent tumour among men

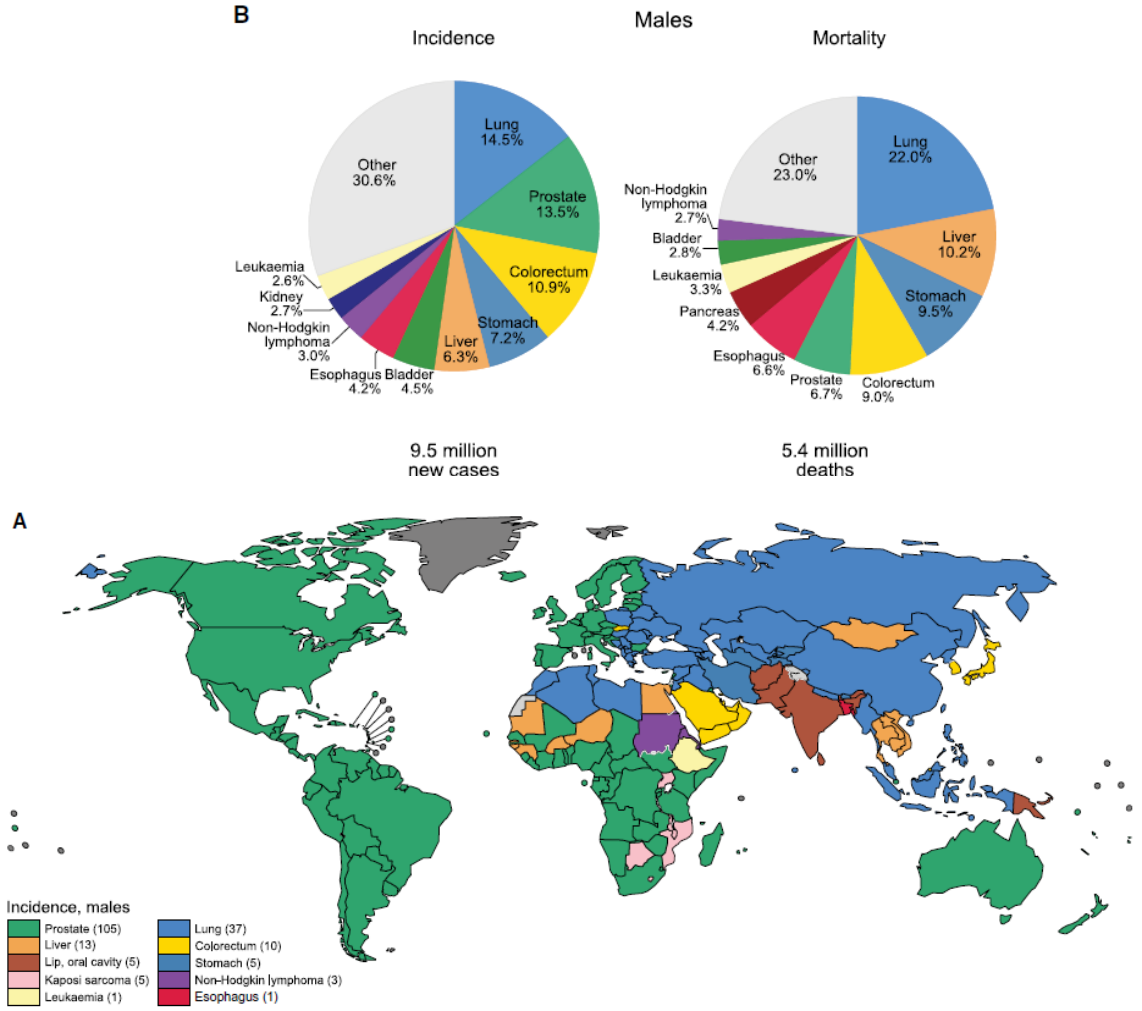
New diagnoses in 2018:

1,280,000

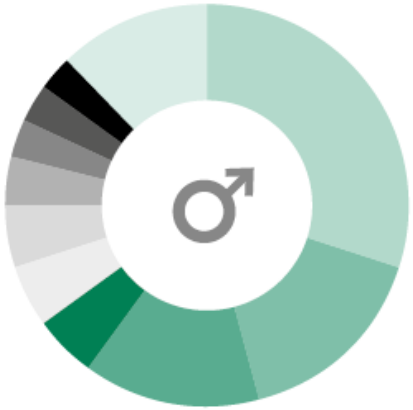
5th leading cause of cancer death in men

Deaths in 2018:

360,000



Bray F, et al. CA Cancer J Clin. 2018 Sept 12 [Epub ahead of print].



	Tumore	N.	%
	Prostata	457902	30
	Colon-retto-ano	244046	16
	Vescica	212326	14
	Rene, vie urinarie	81603	5
	Linfoma n. H.	73570	5
	Cute (melanomi)	73076	5
	Polmone	67405	4
	Testicolo	51062	3
	Leucemie	45198	3
	Tiroide	44582	3
	Altri	180388	12

Tumore della prostata

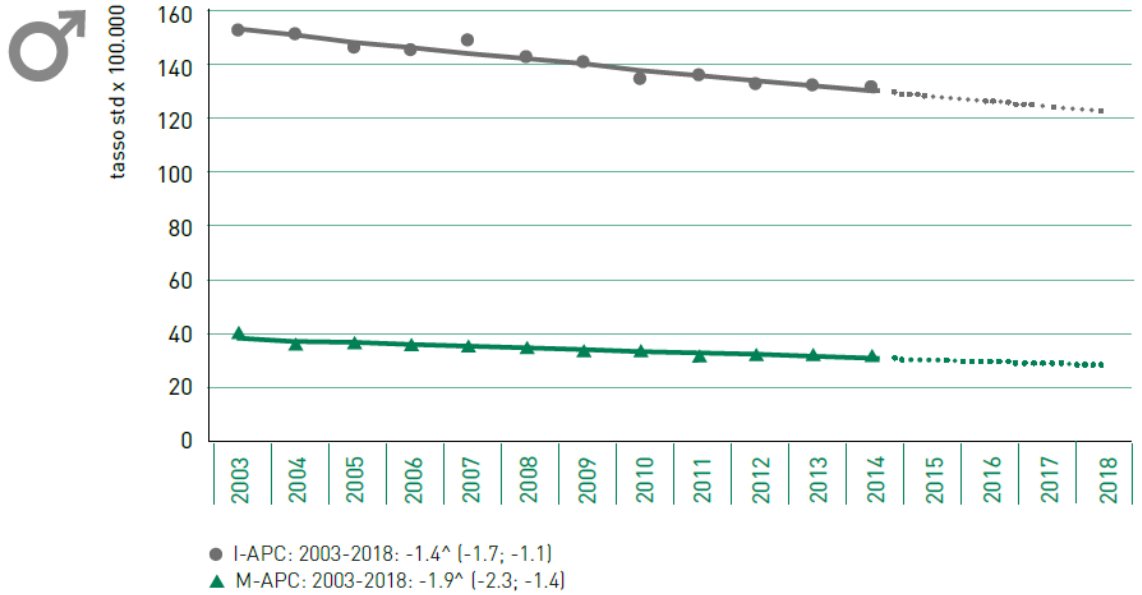


FIGURA 27. Tumore della prostata. AIRTUM: stima dei trend tumorali di incidenza e mortalità 2003-2018. Tassi standardizzati nuova popolazione europea 2013

APC = Annual Percent Change (variazione percentuale media annua), I = incidenza, M = mortalità.

Rango	Maschi	Femmine	Tutta la popolazione
1°	Prostata (18%)	Mammella (29%)	Mammella (14%)
2°	Colon-retto (15%)	Colon-retto (13%)	Colon-retto (14%)
3°	Polmone (14%)	Polmone (8%)	Polmone (11%)
4°	Vescica* (11%)	Tiroide (6%)	Prostata (9%)
5°	Fegato (5%)	Utero corpo (5%)	Vescica* (7%)

TABELLA 6. Primi cinque tumori più frequentemente diagnosticati e proporzione sul totale dei tumori (esclusi i carcinomi della cute) per sesso. Stime per l'Italia 2018

* Comprende sia tumori infiltranti sia non infiltranti.
** Comprende rene, pelvi e uretere.

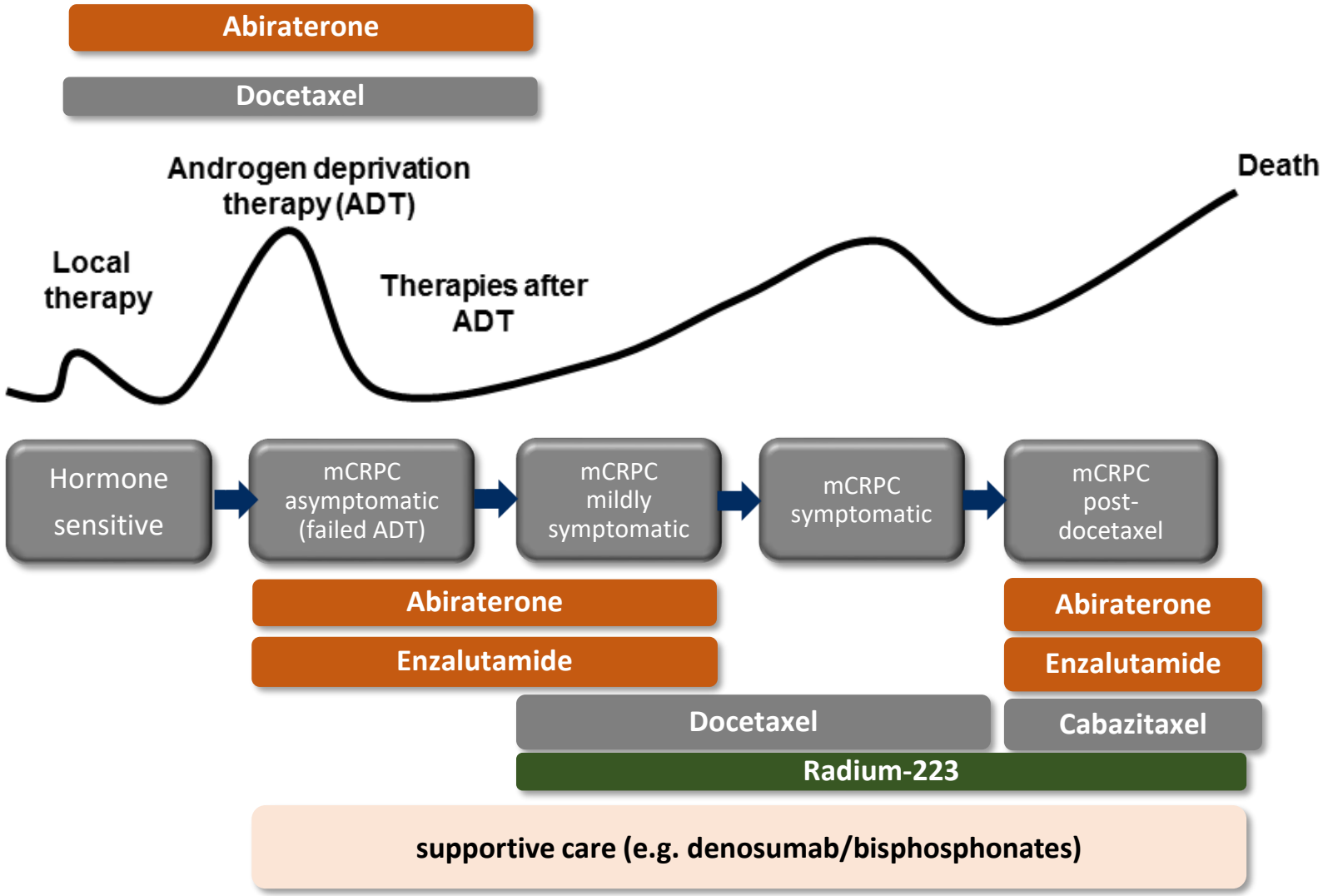
Rango	Maschi			Femmine		
	Età			Età		
	0-49	50-69	70+	0-49	50-69	70+
1°	Testicolo (12%)	Prostata (22%)	Prostata (19%)	Mammella (41%)	Mammella (35%)	Mammella (22%)
2°	Cute (melanomi) (9%)	Polmone (14%)	Polmone (17%)	Tiroide (15%)	Colon-retto (11%)	Colon-retto (16%)
3°	Tiroide (8%)	Colon-retto (12%)	Colon-retto (14%)	Cute (melanomi) (7%)	Polmone (7%)	Polmone (8%)
4°	LNH (7%)	Vescica* (11%)	Vescica* (12%)	Colon-retto (4%)	Utero corpo (7%)	Pancreas (6%)
5°	Colon-retto (7%)	Vie aerodigestive superiori** (5%)	Stomaco (5%)	Utero cervice (4%)	Tiroide (5%)	Stomaco (5%)

TABELLA 7. Primi cinque tumori in termini di frequenza e proporzione sul totale dei tumori incidenti (esclusi i carcinomi della cute) per sesso e fascia di età. Pool AIRTUM 2010-2014

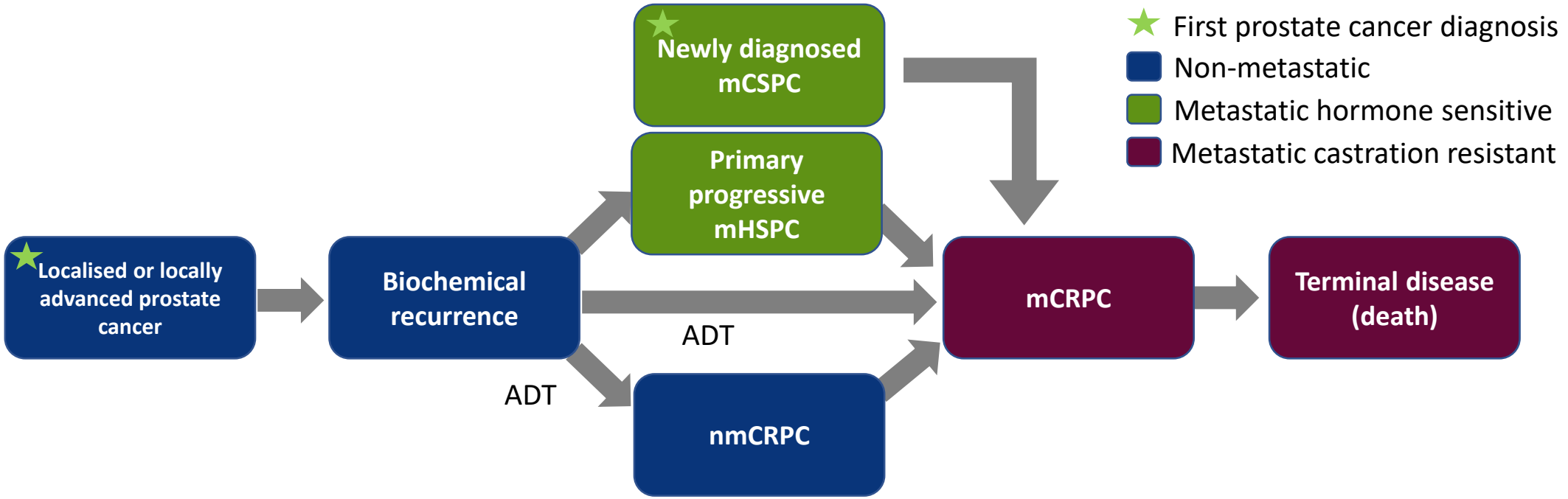
* Comprende sia tumori infiltranti sia non infiltranti.

** Comprende lingua, bocca, orofaringe, rinofaringe, ipofaringe, faringe NAS, laringe.

Current Treatment Paradigm is Evolving



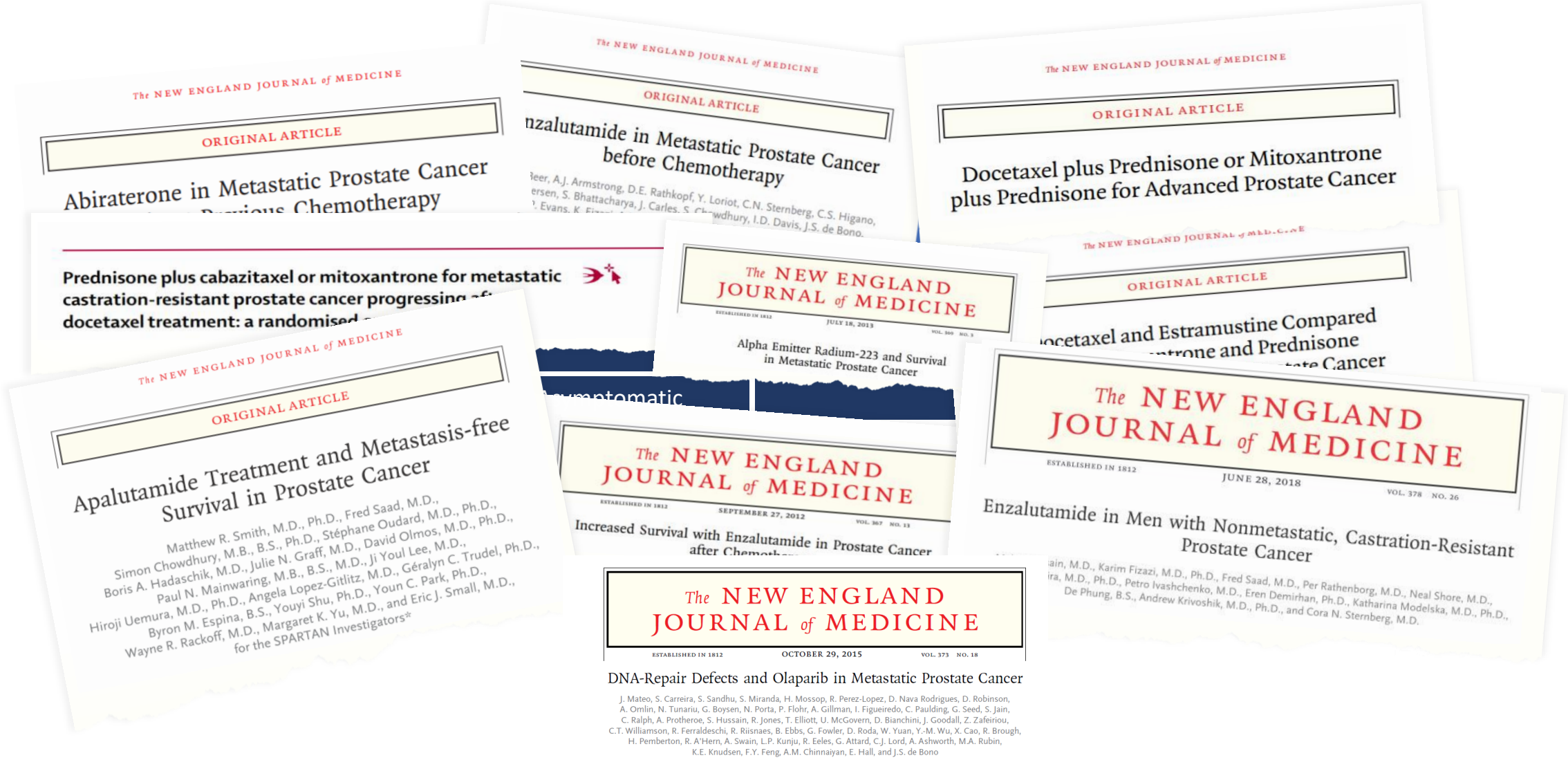
The PC landscape



mCRPC, metastatic castration-resistant prostate cancer;
mCSPC, metastatic hormone-sensitive prostate cancer;
nmCRPC, non-metastatic castration-resistant prostate cancer.

Hong JH, Kim IY. Korean J Urol. 2014;55:153-60.
Mottet N, et al. EAU/ESTRO/ESUR/SIOG Guidelines on Prostate Cancer 2017. Available from: http://uroweb.org/guideline/prostate-cancer. Accessed February 2018.
Adapted from: Scher HI, et al. J Clin Oncol. 2016;34:1402-18.

2010 onwards: a new era in PC treatment



2014 onwards: advances in mHSPC and nmCRPC treatment

ASCO GU 2015
GETUG-AFU 15

ASCO 2015
STAMPEDE (Doc)

ASCO GU 2018
SPARTAN (APA)
PROSPER (ENZA)

ASCO 2014
CHAARTED

ASCO 2017
LATITUDE
STAMPEDE (AAP)

AAP, abiraterone acetate plus prednisone;
ASCO, American Society of Clinical Oncology;
ASCO GU, ASCO Genitourinary Cancers Symposium.

Fizazi K, et al. N Engl J Med. 2017;377:352-60. Gravis G, et al. Eur Urol. 2016;70:256-62. James ND, et al. Lancet. 2016;387:1163-77. James ND, et al. N Engl J Med. 2017;377:338-51. Sweeney CJ, et al. N Engl J Med. 2015;373:737-46.

Median OS gain in Advanced Prostate Cancer

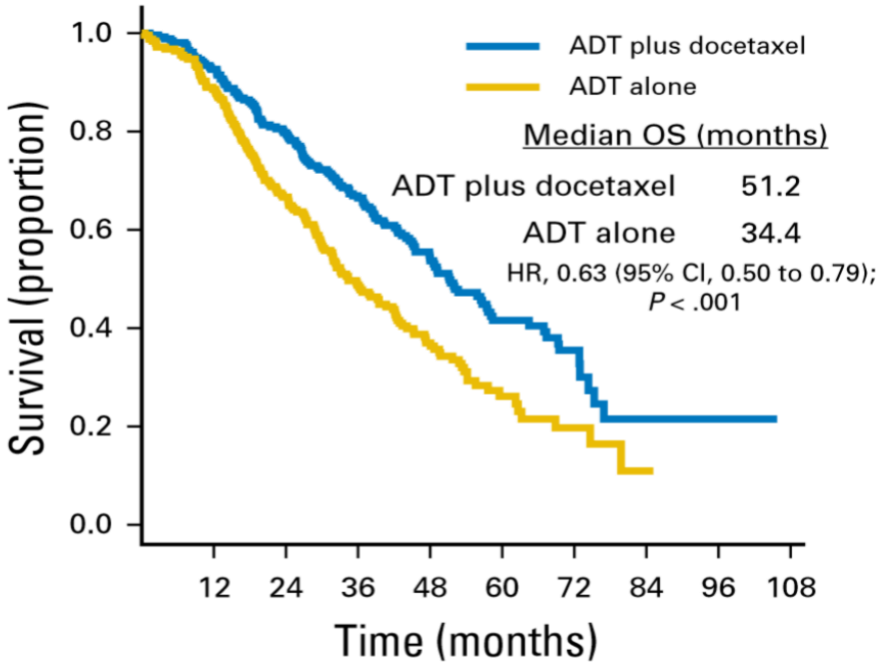
2004	TAX327 (DOC/P – mCRPC):	**2.7** mo[2]
2010	TROPIC (DOC/P → CAB/P – mCRPC):	**2.4** mo[3-4]
2011	COU-AA-301 (DOC/P → ABI/P – mCRPC):	**4.6** mo[5]
2013	COU-AA-302 (ABI/P pre-DOC – mCRPC):	**4.4** mo[6]
2014	PREVAIL (ENZA pre-DOC – mCRPC):	**4.0** mo[7]
2015	STAMPEDE – M1 (DOC/P + ADT – mHSPC):	**15.0** mo[8]
2016	CHAARTED – M1 De Novo (DOC/P + ADT – mHSPC):	**15.0** mo[9]
2017	LATITUDE & STAMPEDE (ABI/P +ADT –mHSPC):	**not yet reached**
2018	PROSPER – M0 CRPC (ENZA)	**not yet reached**
2018	SPARTAN –M0 CRPC (APA/P)	**not yet reached**

1. Kantoff PW. *J Clin Oncol*. 1999;7:2506–13; 2. Tannock IF. *N Engl J Med*. 2004;351:1502–12; 3. de Bono JS et al. *Lancet*. 2010;376:1147–54; 4. Sartor O. *J Clin Oncol*. 2011;29(S15):abstract 4525 (podium presentation); 5. Fizazi K . *Lancet Oncol*. 2012;13:983–92 (supplementary appendix); 6. Ryan CJ. *Lancet Oncol*. 2015;16:152–60; 7. Beer TM. *Eur Urol*. 2017;71:151–54; 8. James ND et al. *Lancet*. 2016;387:1163–77; 9. Sweeney C et al. Ann Oncol. 2016;27(suppl 6):

Docetaxel in mHSPC
OS is greater when doce is used at diagnosis

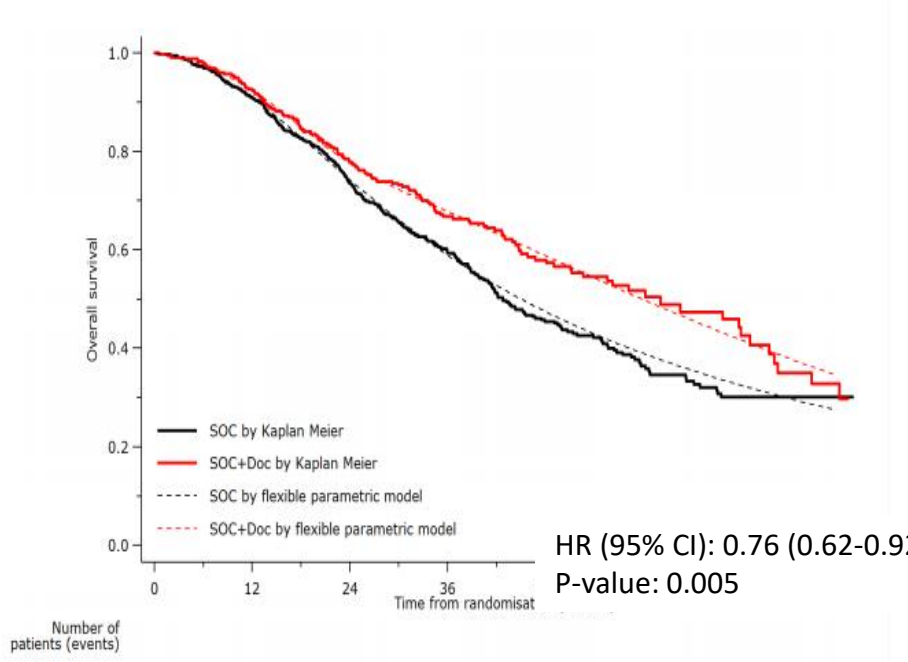
Riduzione del rischio di morte del 37%

Chaarted high volume de novo



Riduzione del rischio di morte del 24%

Stampede M1 whole population



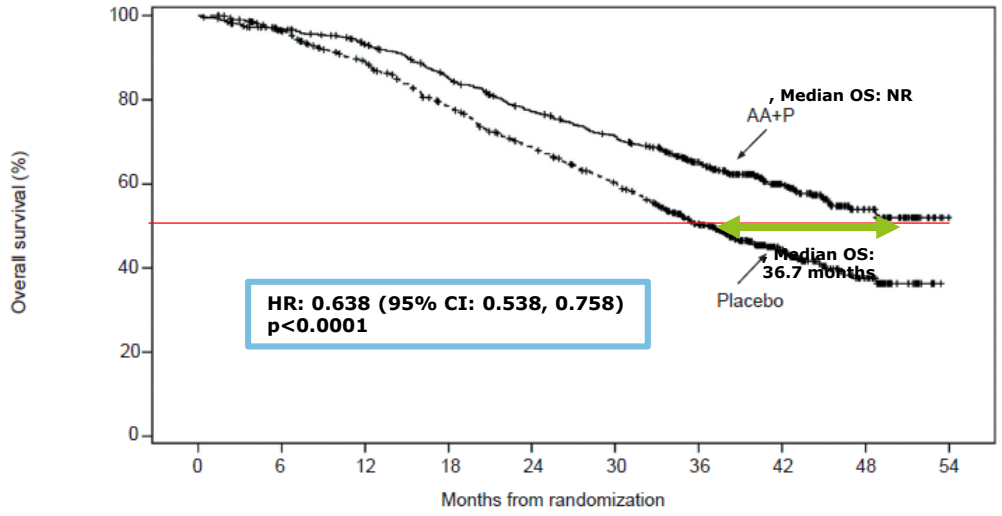
HR (95% CI): 0.76 (0.62-0.92)
P-value: 0.005

Kyriakopoulos CE, et al. J Clin Oncol. 2018;36:1080-7
James ND, et al. Lancet. 2016;387:1163-77

Abiraterone in mHSPC
OS is greater when abiraterone is used at diagnosis

LATITUDE high risk de novo[1]

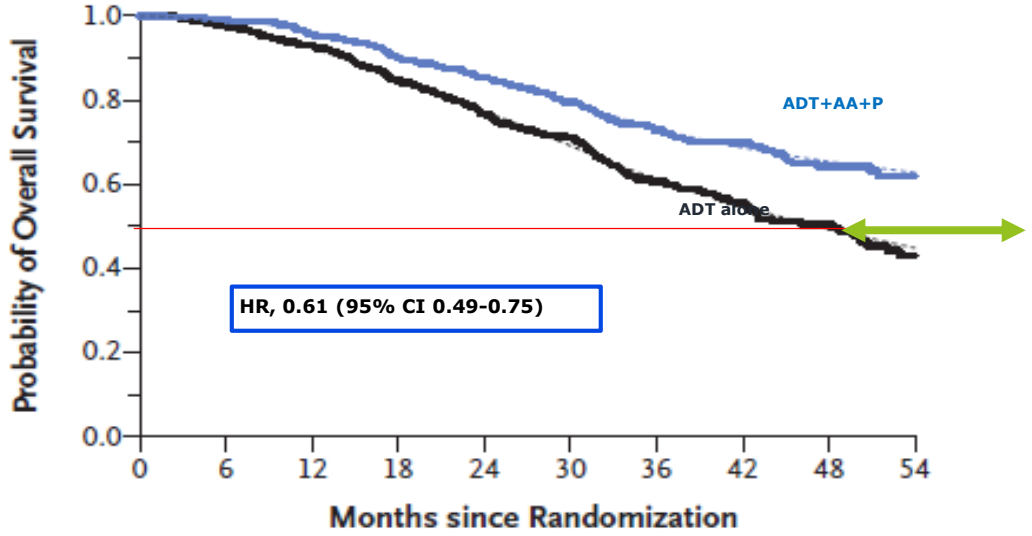
Riduzione del rischio di morte del 36 %



Follow up 41 months

STAMPEDE - M1 Disease[2,3]

Riduzione del rischio di morte del 39 %



Follow up 40 months

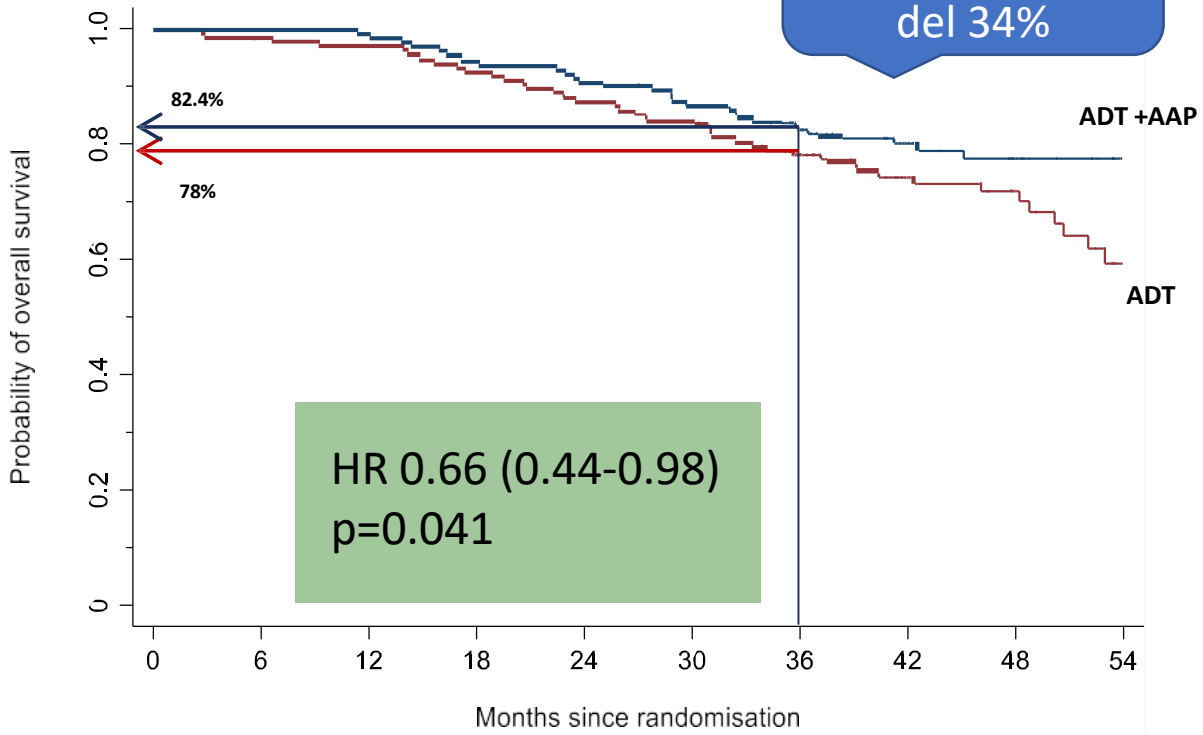
Gl. Score 8 or more, at least 3 bone lesions, presence of measurable visceral met (2 out of 3)

Fizazi K, et al. N Engl J Med. 2017 Jul 27;377(4
James ND et al, N Engl J Med. 2017 Jul 27;377(4)

Overall Survival nello studio Stampede
Vantaggio per abiraterone
sia nei pazienti a basso che ad alto rischio

Low Risk

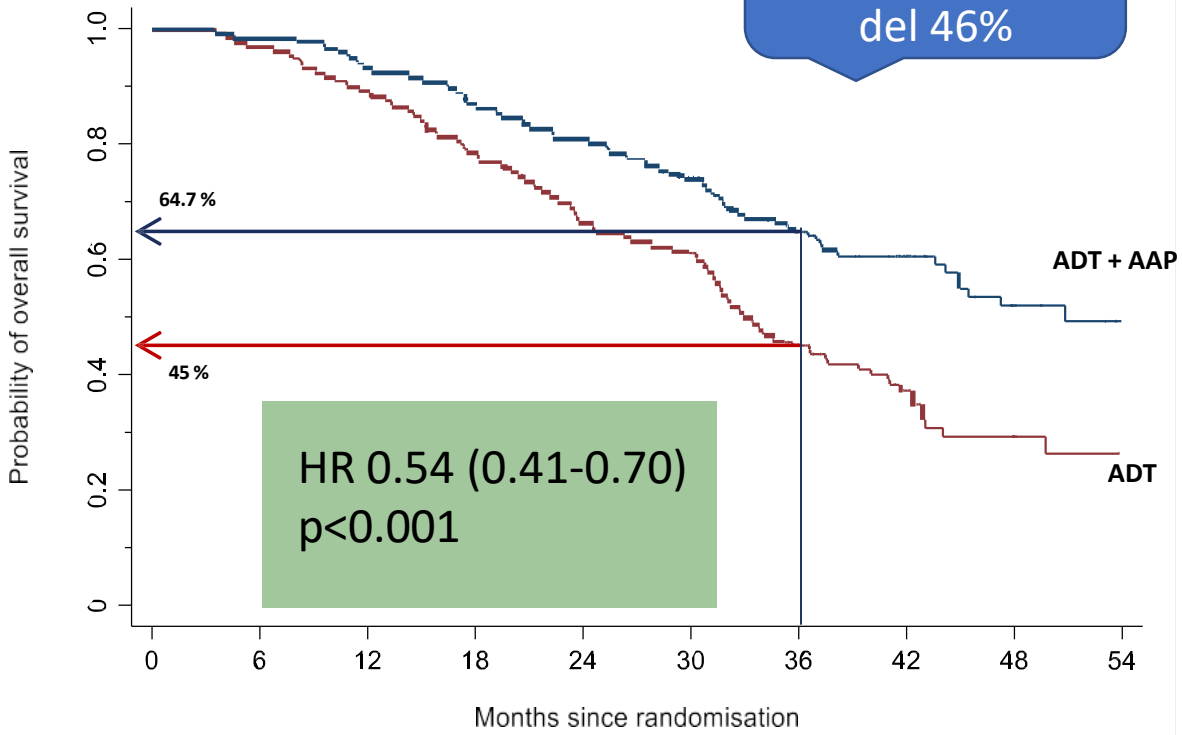
Riduzione del rischio di morte del 34%



No. of patients (Events)

High Risk

Riduzione del rischio di morte del 46%



No. of patients (Events)

Hoyle ESMO 2018 Presidential Symposium

STAMPEDE trial: SOC+ABI/P vs SOC+Doc/P

Adverse Events

Safety population	**ADT+DOC/P**	**ADT+ABI/P**
Patients included in adverse event analysis	172 (91%)	373 (>99%)
Grade 1+ AE	172 (100%)	370 (99%)
Grade 3+ AE	86 (**50%**)	180 (**48%**)
Grade 3+ AEs by category (*incl. expected AEs*)		
Endocrine disorder (*incl. hot flashes, impotence*)	15 (9%)	49 (13%)
Febrile neutropenia	29 (**17%**)	3 (1%)
Neutropenia	22 (**13%**)	4 (1%)
Musculoskeletal disorder	9 (5%)	33 (9%)
Cardiovascular disorder (*incl. hypertension, MI, cardiac dysrhythmia*)	6 (3%)	32 (**9%**)
Gastrointestinal disorder	9 (5%)	28 (8%)
Hepatic disorder (*incl. increased AST, increased ALT*)	1 (1%)	32 (**9%**)
General disorder (*incl. fatigue, oedema*)	18 (10%)	21 (6%)
Respiratory disorder (*incl. breathlessness*)	12 (7%)	11 (3%)
Renal disorder	5 (3%)	20 (5%)
Lab abnormalities (*incl. hypokalaemia*)	9 (5%)	11 (3%)

Sydes MR, et al. Ann Oncol. 2018 May 1;29(5):1235-1248.

Sequencing of Taxanes and New Androgen-targeted Therapies in Metastatic Castration-resistant Prostate Cancer: Results of the International Multicentre Retrospective CATS Database

CATS International Database

- Retrospective analysis of 669 consecutive patients treated with DOC, CABA and one ART in 34 centers in 8 countries (France, Austria, Greece, Italy, Israel, Denmark,Spain, UK)

669 mCRPC pts treated with DOC, CABA and ART

DOC → CABA →ART (N=158)

DOC → ART → CABA (N=456)

ART → DOC → CABA (N=55)

Doc: docetaxel; CABA: Cabazitaxel; ART: Androgen Receptor–Targeted agent

Delanoy N et al. Eur Urol Oncol 2018 (In press)

Sequencing of Taxanes and New Androgen-targeted Therapies in Metastatic Castration-resistant Prostate Cancer: Results of the International Multicentre Retrospective CATS Database

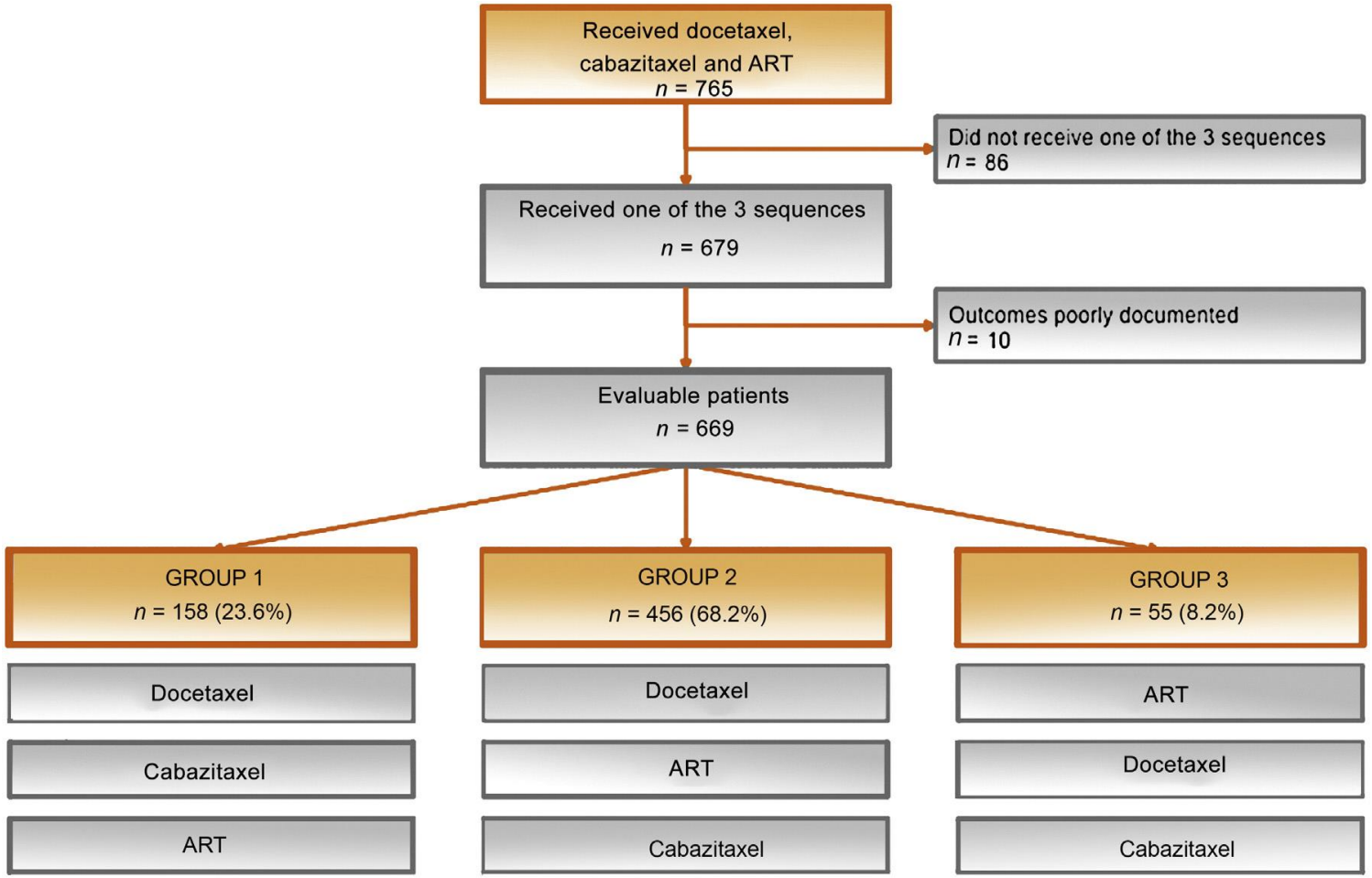


Fig. 1 – Selection of patients for inclusion in the study. Data for patients treated with docetaxel, cabazitaxel, and one next-generation androgen receptor–targeted therapy (ART; abiraterone acetate or enzalutamide) between November 2012 and October 2016 were retrospectively collected.

Doc: docetaxel; CABA: Cabazitaxel; ART: Androgen Receptor–Targeted agent ; LET: first life-extending

Delanoy N et al, Eur Urol Oncol 2018 (In press)

Sequencing of Taxanes and New Androgen-targeted Therapies in Metastatic Castration-resistant Prostate Cancer: Results of the International Multicentre Retrospective CATS Database

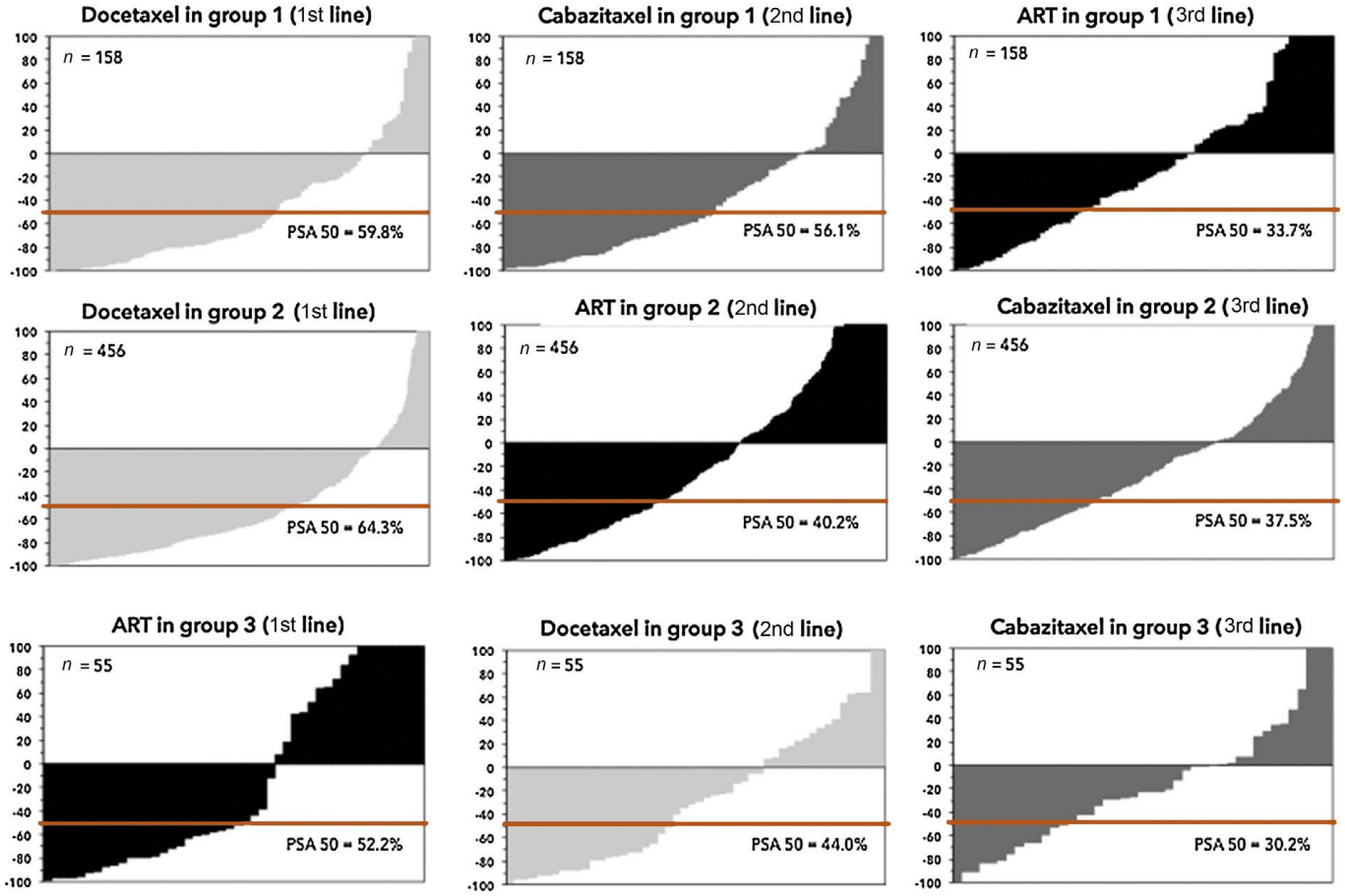


Fig. 2 – prostate-specific antigen (PSA) response in patients with metastatic castration-resistant prostate cancer according to treatment sequence. Group 1: patients received DOC before CABA and then ART; group 2: patients received DOC before ART and then CABA; group 3: patients received ART before DOC and then CABA. ART = novel androgen receptor–targeted therapy (abiraterone acetate or enzalutamide); CABA = cabazitaxel; DOC = docetaxel; PSA 50 = decrease in PSA from baseline of ≥50%.

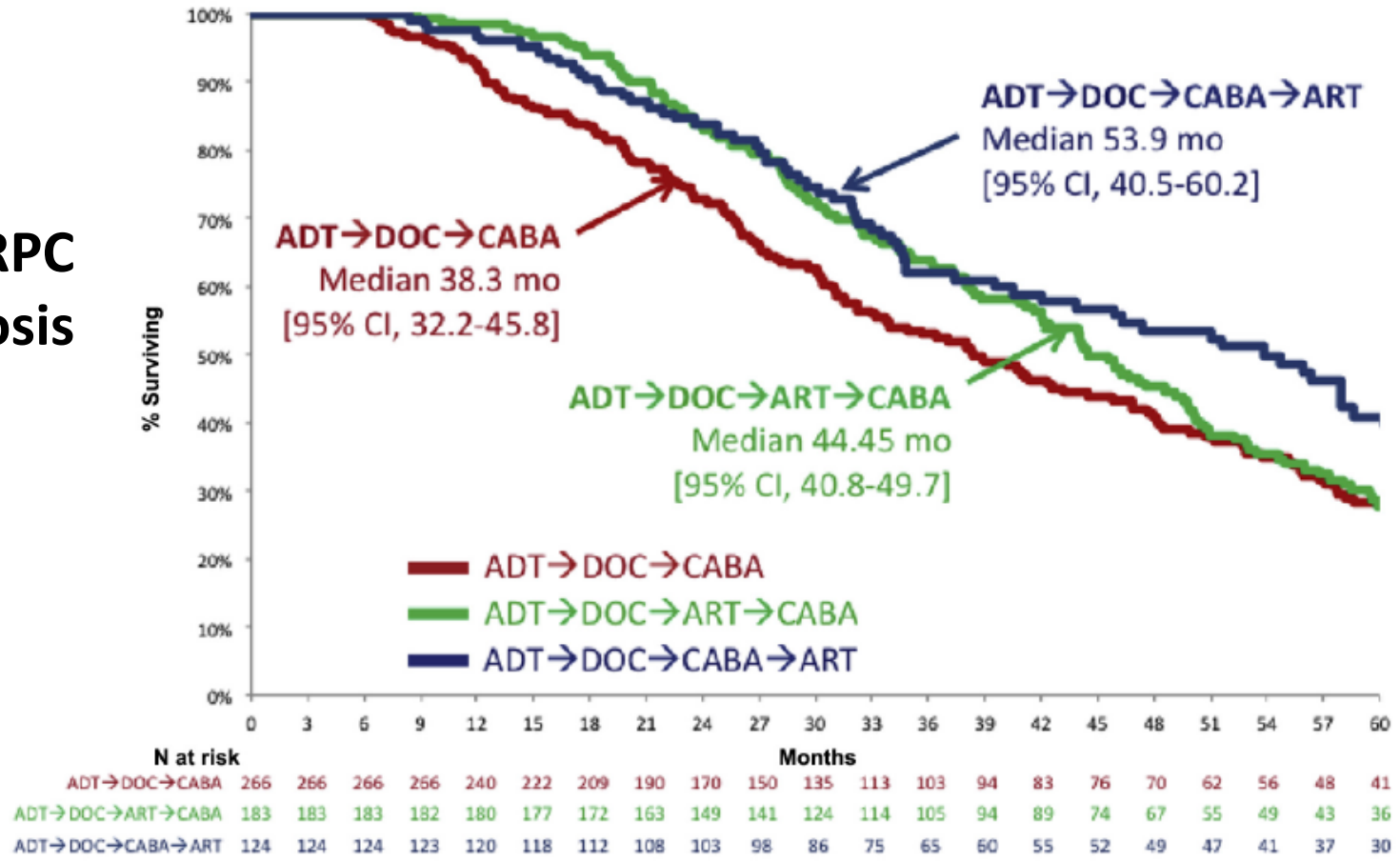
Doc: docetaxel; CABA: Cabazitaxel; ART: Androgen Receptor–Targeted agent ; LET: first life-extending

Delanoy N et al, Eur Urol Oncol 2018 (In press)

FLAC Retrospective Registry in mCRPC (N=573)

2 taxanes (DOC, CABA) and 1 ART better than 2 taxanes (DOC, CABA) without ART

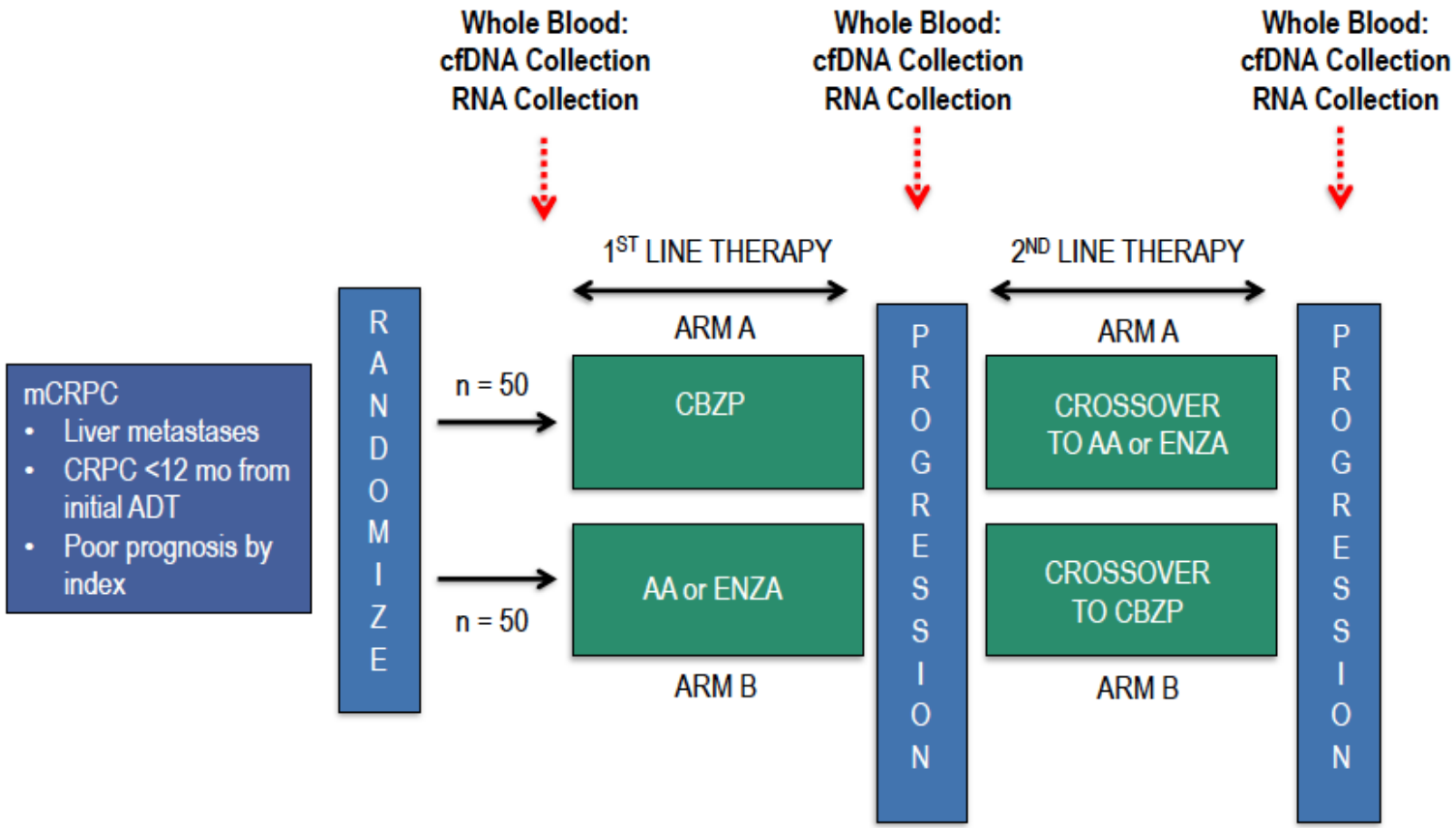
OS from mCRPC diagnosis



Angelergues et al. Clin GU Cancer. 2018 (epub ahead of print).

Cabazitaxel vs. Abiraterone or Enzalutamide in Poor-Prognosis mCRPC

OZM-054: A phase 2, randomized, multicenter study



CBZP: cabazitaxel; ENZA: enzalutamide
ClinicalTrials.gov: NCT02254785

The PROPHECY trial: Multicenter prospective trial of circulating tumor cell (CTC) AR-V7 detection in men with mCRPC receiving abiraterone (A) or enzalutamide (E).

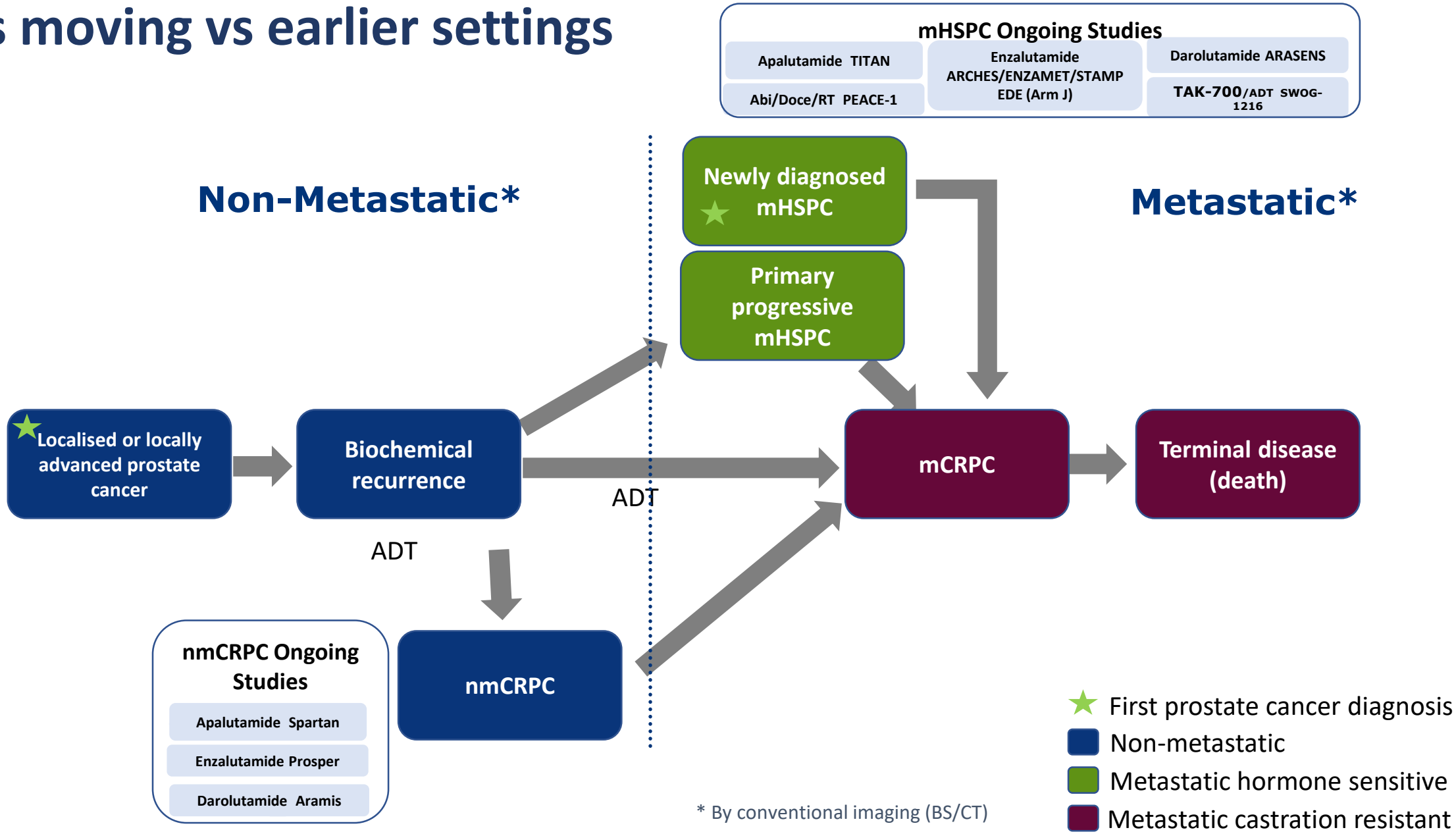
Andrew J. Armstrong, Susan Halabi,.

Presented Monday, June 4, 2018

Outcome	AR-V7 (JHU n = 116) (+) n = 28 (24%) / (-) n = 88 (66%)	AR-V7 (Epic n = 105) (+) n = 11 (10%) / (-) n = 94 (90%)
Median PFS (mo)	3.1 / 7.3	3.1 / 6.0
p-value	0.0003	0.007
HR* (95% CI)	2.4 (1.6-3.8)	2.4 (1.3-4.6)
HR˚(95% CI)	2.4 (1.4-3.9)	2.2 (1.0-4.9)
Median OS (mo)	11.5 / 25.5	8.4 / 25.5
HR*(95% CI)	3.9 (2.1- 7.3)	4.5 (2.1-9.8)
HR˚ (95% CI	4.6 (2.3-9.2)	3.6 (1.5-8.6)
≥ 50% confirmed PSA decline	11% / 28%	0% / 26%
Odds Ratio (95% CI)	0.31 (0.09-1.12)	Not estimable

*univariate, ˚adjusted for Cellsearch CTC enumeration, PSA, Alk Phos, Hgb

Clinical Reserach is moving vs earlier settings



Phase 3 Ongoing Combination Therapy Trials in HSPC

Study	Identifier	Study Drugs	Pts (N)	Primary End Point	Status/Read Out
LATITUDE	NCT01715285	ADT ± **AA**	1209	rPFS, OS	ASCO 2017
STAMPEDE (Arm G)	NCT00268476	ADT ± **AA**	1800	OS	LBA ASCO 2017
PEACE-1	NCT01957436	ADT ± DOC vs ADT + **AA** ± DOC (± local RT)	916	PFS, OS	Recruiting/2020
STAMPEDE (Arm J)	NCT00268476	ADT ± **AA + ENZ***	1800	OS	Closed-will report in 2-3 yrs
SWOG-1216	NCT01809691	ADT + **TAK-700** vs ADT + BIC	1304	OS	Recruiting/2027
ENZAMET	NCT02446405	ADT + **ENZ** vs ADT + antiandrogen	1100	OS	Recruiting/2020
TITAN	NCT02489318	ADT ± **APA (ARN 509)**	1000	rPFS, OS	Recruiting/ 2021
ARCHES	NCT02677896	ADT ± **ENZ**	1100	rPFS	Recruiting/ 2023
ARASENS	NCT02799602	ADT + DOC ± **ODM-201**	1300	OS	Recruiting/2022

*Includes upfront Doc

Modified from and courtesy of K. Fizazi

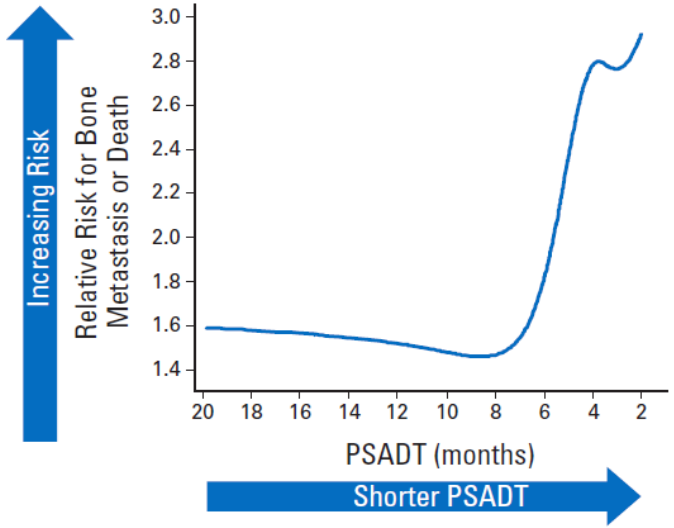
Non Metastatic Castration Resistant: the new therapeutic opportunity

M0 CRPC definition:

Biochemical progression while on ADT **PSA ≥ 2 ng/dl**	+	**Serum testosterone levels below 50 ng/mL**	+	**No evidence of metastasis** **By CT/bone scan**

HIGH Risk
PSA DT <10 months

- Patients with **high-risk nmCRPC have a shorter PSADT** and a higher risk of metastasis[4,5]



Adapted from: Scher HI et al. J Clin Oncol. 2016;34(12):1402-1418; Mottet, N, et al. (2017). EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer. Available from: http://uroweb.org/guideline/prostate-cancer/ (Access Date: August 2017); Hong JH, Kim IY. Korean J Urol. 2014 Mar;55(3):153-60

Benefit of delaying metastases

Delaying metastases, or extending metastasis-free survival, may delay:[1-3]

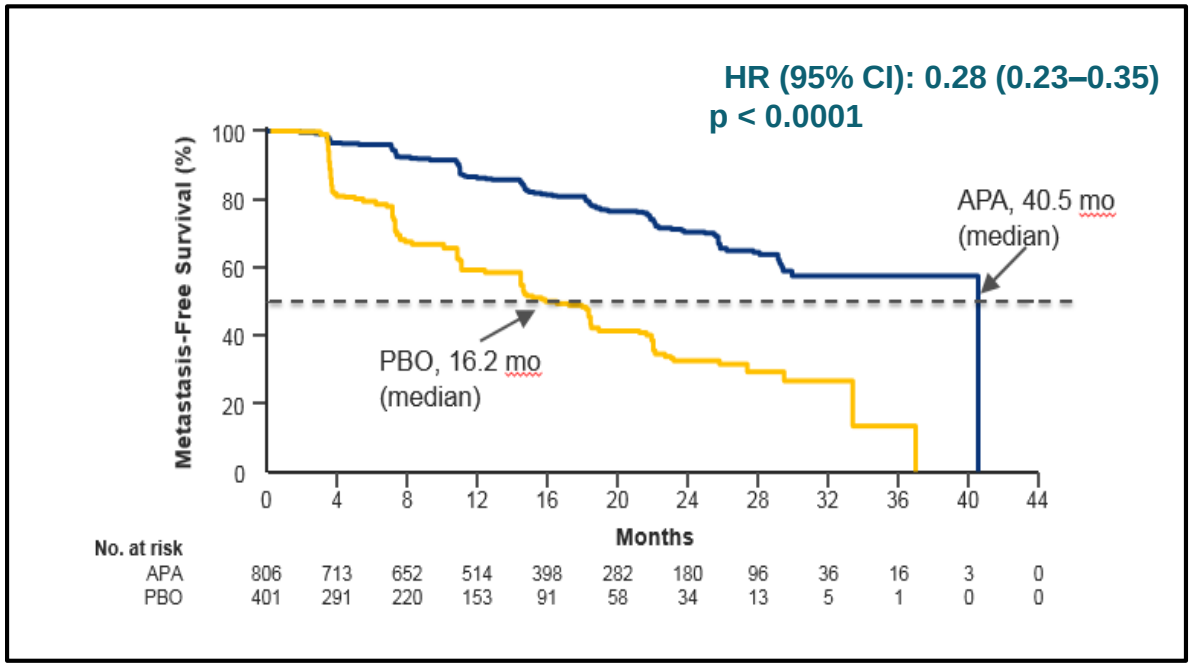
- Symptomatic progression
- Morbidity
- Mortality
- QoL impairment
- Healthcare resource utilization

- Metastatic disease is a turning point in CRPC[1-3]
- Therefore, it has become as a major challenge to delay as long as possible this health state by delaying the onset of the first bone metastasis[4]

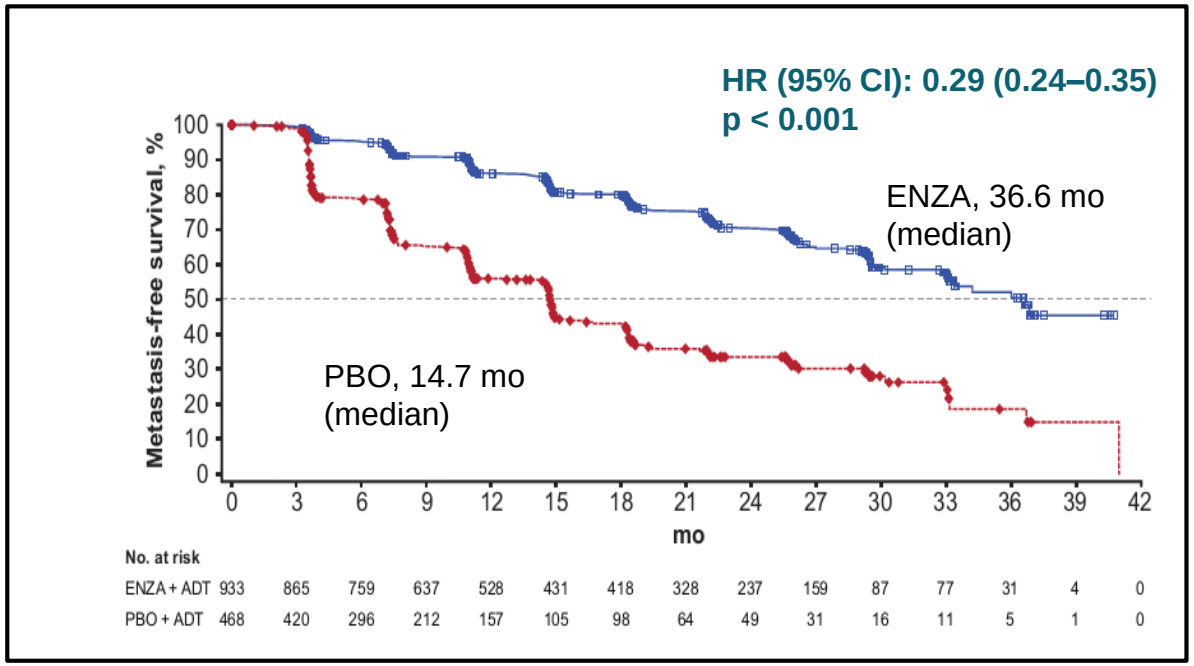
1. Luo, et al. Oncology (Williston Park). 2016 Apr;30(4):336-44; 2. Li TT et al. Cancer. 2017;123(18):3591-3601; 3. Li T, et al. ASCO-GU 2016. Abstract (and poster) E10; 4. Tombal B. Ann Oncol. 2012 Sep;23 Suppl 10:x251-8

nmCRPC: Metastasis Free Survival (MFS)

SPARTAN[1]



PROSPER[2]



- Median MFS: APA 40.5 vs PBO 16.2 months
- **24-month additional MFS benefit with APA**

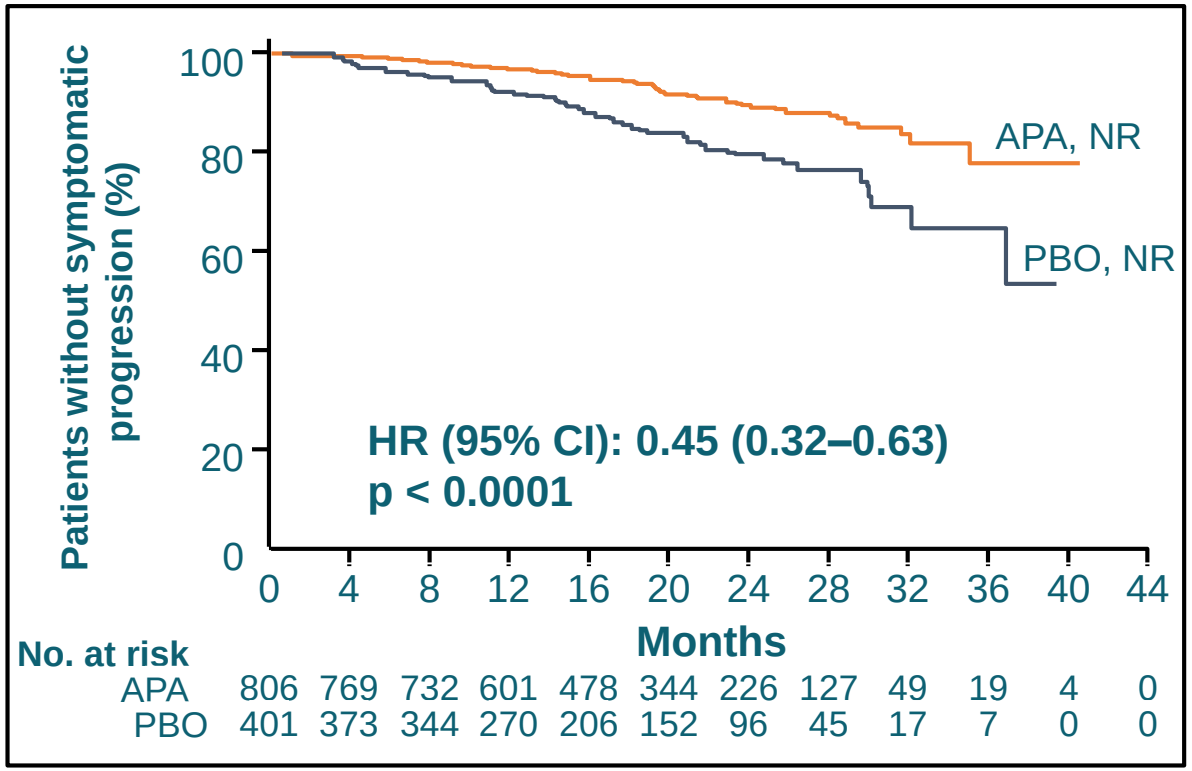
- Median MFS: ENZA 36.6 vs PBO 14.7 months
- **22-month additional MFS benefit with ENZA**

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18.

2. Hussain M, et al. N Engl J Med. 2018;378:2465-74.

nmCRPC: Time to symptomatic progression

SPARTAN[1]



PROSPER[2]

Not Evaluated

55% risk reduction with APA

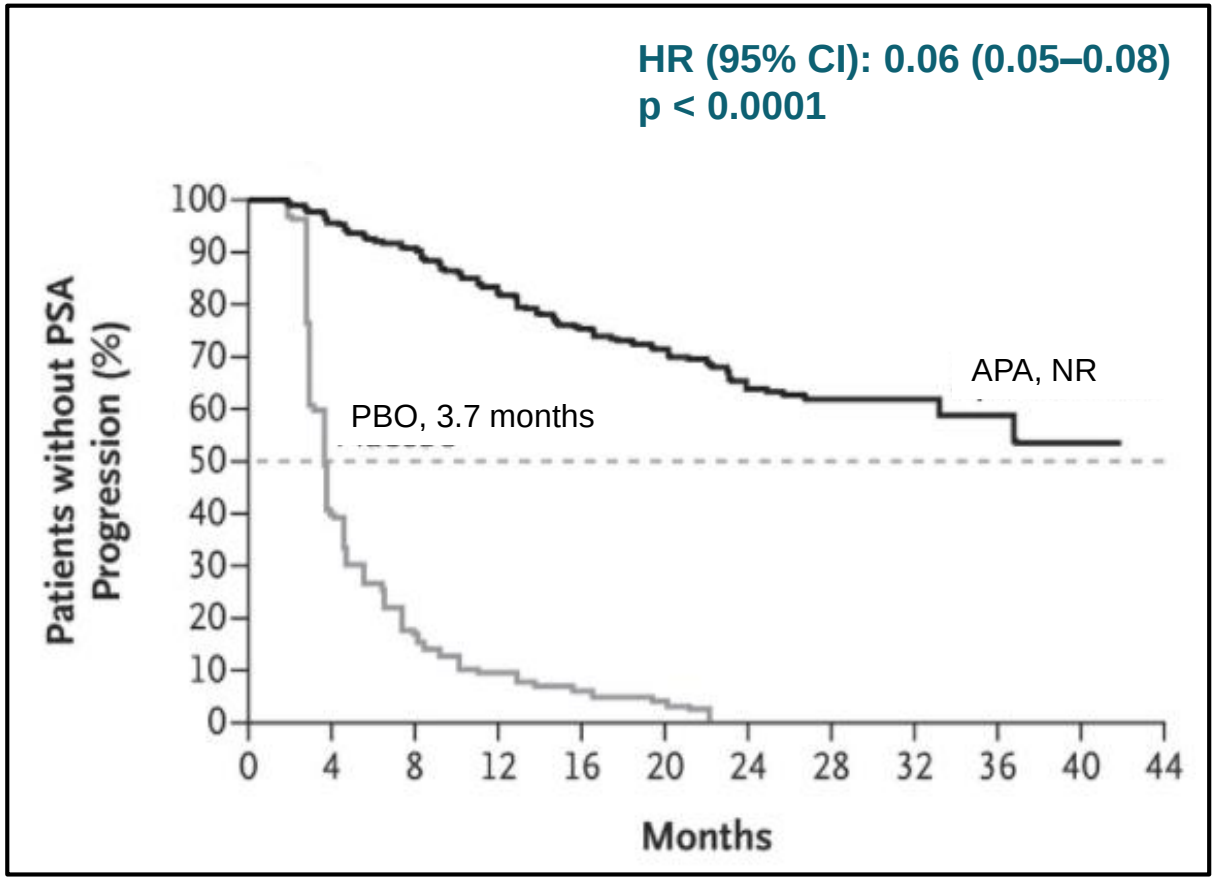
NR, not reached.

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18.

2. Hussain M, et al. N Engl J Med. 2018;378:2465-74

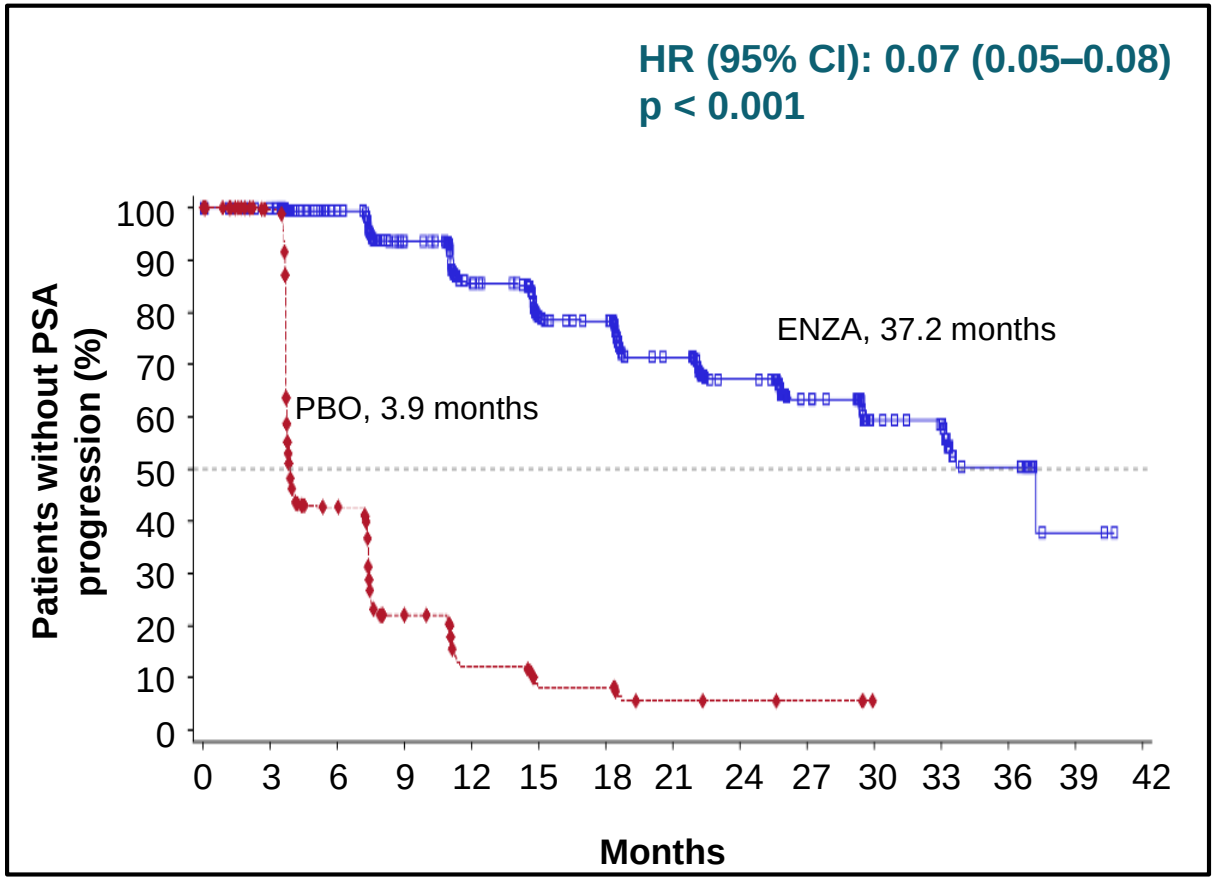
nmCRPC: Time to PSA progression

SPARTAN[1]



- 94% risk reduction in PSA progression

PROSPER[2]



- 93% risk reduction in PSA progression

NR, not reached.

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18.

2. Hussain M, et al. N Engl J Med. 2018;378:2465-74.

nmCRPC: AEs of interest

	SPARTAN[1]		PROSPER[2]	
	APA (n = 803)	PBO (n = 398)	ENZA (n = 930)	PBO (n = 465)
Safety	AE reporting every 4 weeks		AE reporting every 4 months	
AEs (all grades), %				
Fatigue	30.4	21.1	33.0	14.0
Hypertension	24.8	19.8	12.0	5.0
Rash	23.8	5.5	0	0
Falls	15.6	9.0	11.0	4.0
Mental impairment disorders	5.1	3.0	5.0	2.0
AEs (grade 3 and 4 only), %				
Fatigue	0.9	0.3	3.0	1.0
Hypertension	14.3	11.8	5.0	2.0
Rash	5.2	0.3	0	0
Falls	1.7	0.8	1.0	1.0
Mental impairment disorders	0	0	<1	0
Seizures	0.2	0	0.3	0
Major CV event	1	1	5.0	3.0
AEs leading to discontinuation, %	11.0	7.0	9.0	6.0
AEs leading to death, n (%)	10 (1.2)	1 (0.3)	32 (3.4)	3 (0.7)

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18.

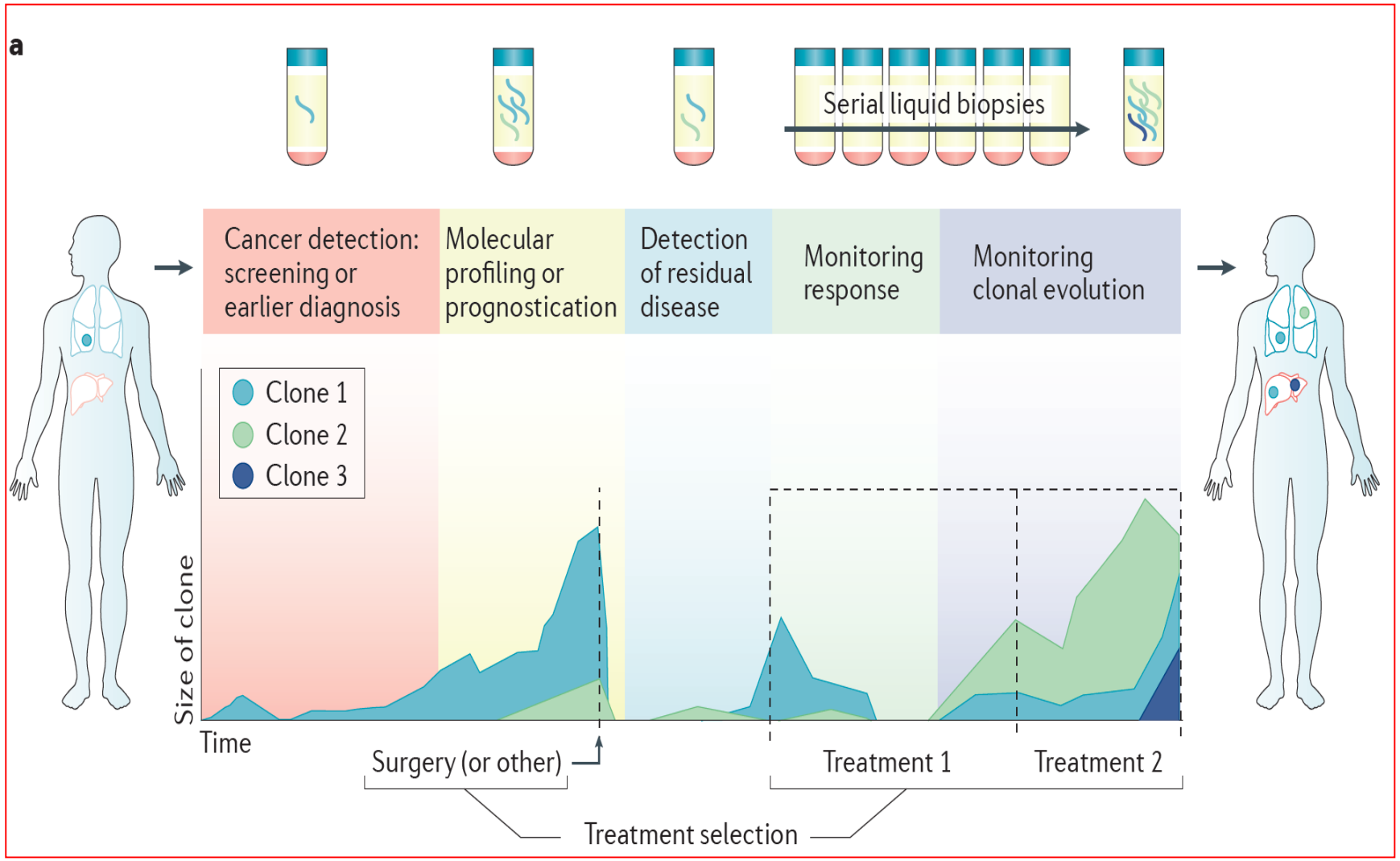
2. Hussain M, et al. N Engl J Med. 2018;378:2465-74.

AE, adverse event; CV cardiovascular.

Prostate cancer:
what should we expect in the near future?

- New drugs (PARP-i, Immuno, Teranostic…)
- New tools (BRCA1, BRCA2, Splice variants, liquid biopsies…)
- Sequences/combinations

The near future?



Courtesy of M. Tucci

Prostate cancer:
what should we expect in the near future?

- The therapeutic landscape is rapidly changing
- The early use of new treatments leads to a greater clinical benefit
- Stop ADT manipulation
- The clinical research is increasing in the early disease settings
- High risk non metastatic CRPC has an elevated medical need
- The nmCRPC patient can be offered apalutamide within a named patient program

The Challenge for the Uro-oncologist in mCRPC

- **To identify disease progression on 1L therapy at an early time point**
  … and to offer subsequent therapy before performance status deteriorates
- **To pro-actively manage adverse events of new treatment options**
  … to optimize treatment outcomes (quality of life, survival)
- **Multidisciplinary care a key to success!!**