IPOGONADISMO,
PATOLOGIA PROSTATICA
E DISFUNZIONI SESSUALI:

Endocrinologo ed Urologo a confronto

28 SETTEMBRE 2018
MILANO
Starhotel Echo
Viale Andrea Doria

Terapia ormonale del carcinoma della prostata ormonosensibile e resistente alla deprivazione androgenica: razionale, indicazioni e protocolli.

Paolo Andrea Zucali
Dipartimento di Oncologia
HUMANITAS CANCER CENTER
Rozzano - Milano

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AGENDA

- **Rational**
- mHSPC: pharmacological options
- mCRPC: pharmacological options

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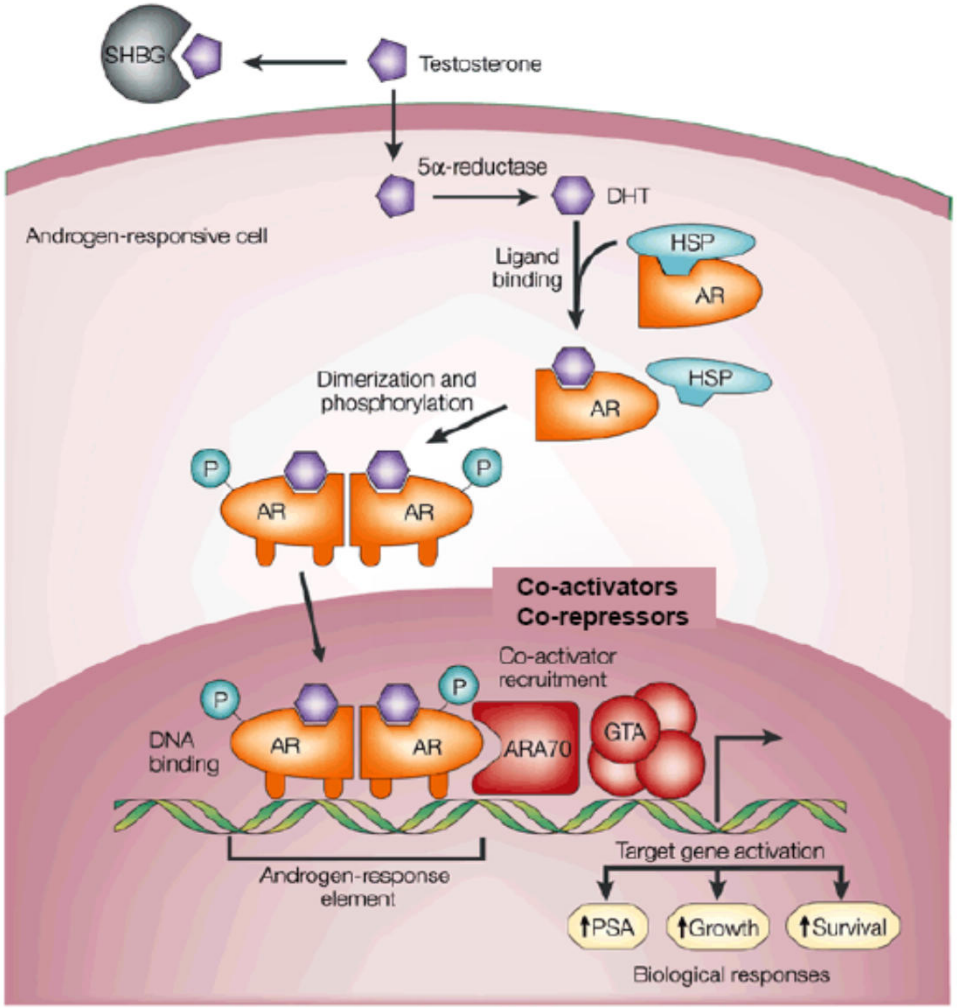
AR pathway

Androgens: Mechanism of action

- Testosterone converted to DHT
  - More potent AR agonist
- AR normally bound in a complex with multiple chaperones (HSPs)
- After binding of DHT (or other androgens), AR changes its conformation leading to:
  - Phosphorylation and dimerisation
  - Nuclear translocation
  - Binding to ARE in promoter and enhancer regions of target gene
- Co-activators or co-repressors initiate or inhibit transcription



AR: Androgen receptor. ARE: Androgen response element.
DHT: Dihydrotestosterone. HSP: Heat-shock protein.
SHBG: sex hormone-binding globulin

Feldman BJ. *Nat Rev Cancer* 2001;1:34–44

Prostate cancer tumour progression

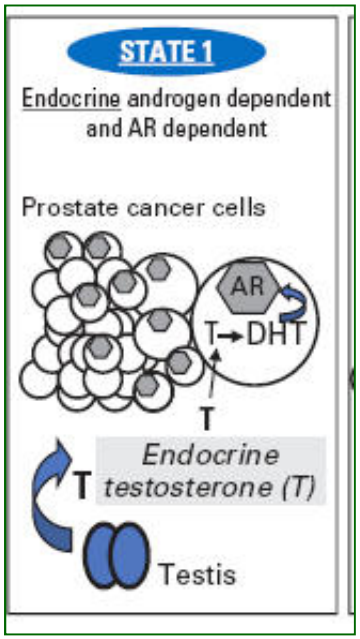
HSPC

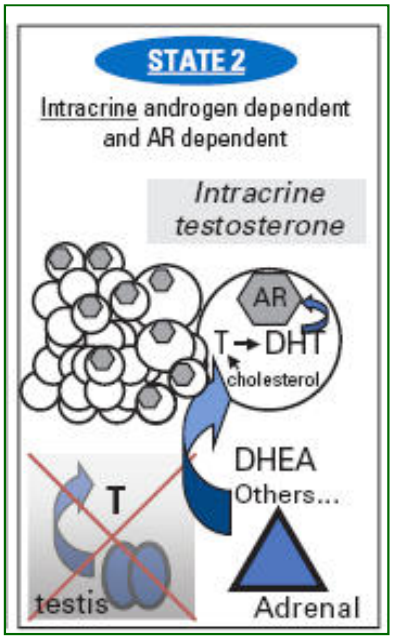
CRPC

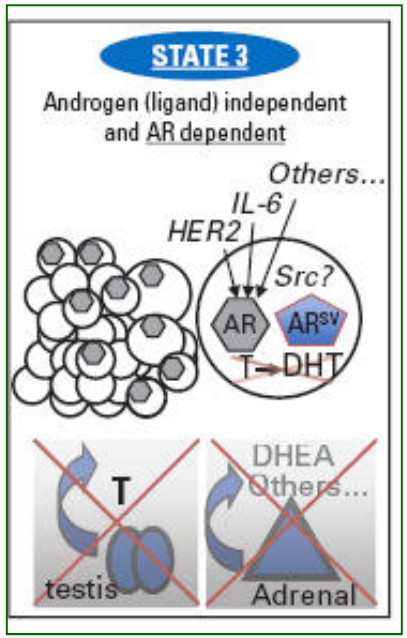
Totally circulating testosterone dependent

Intracrine androgen and AR dependent

Aspecific AR activation

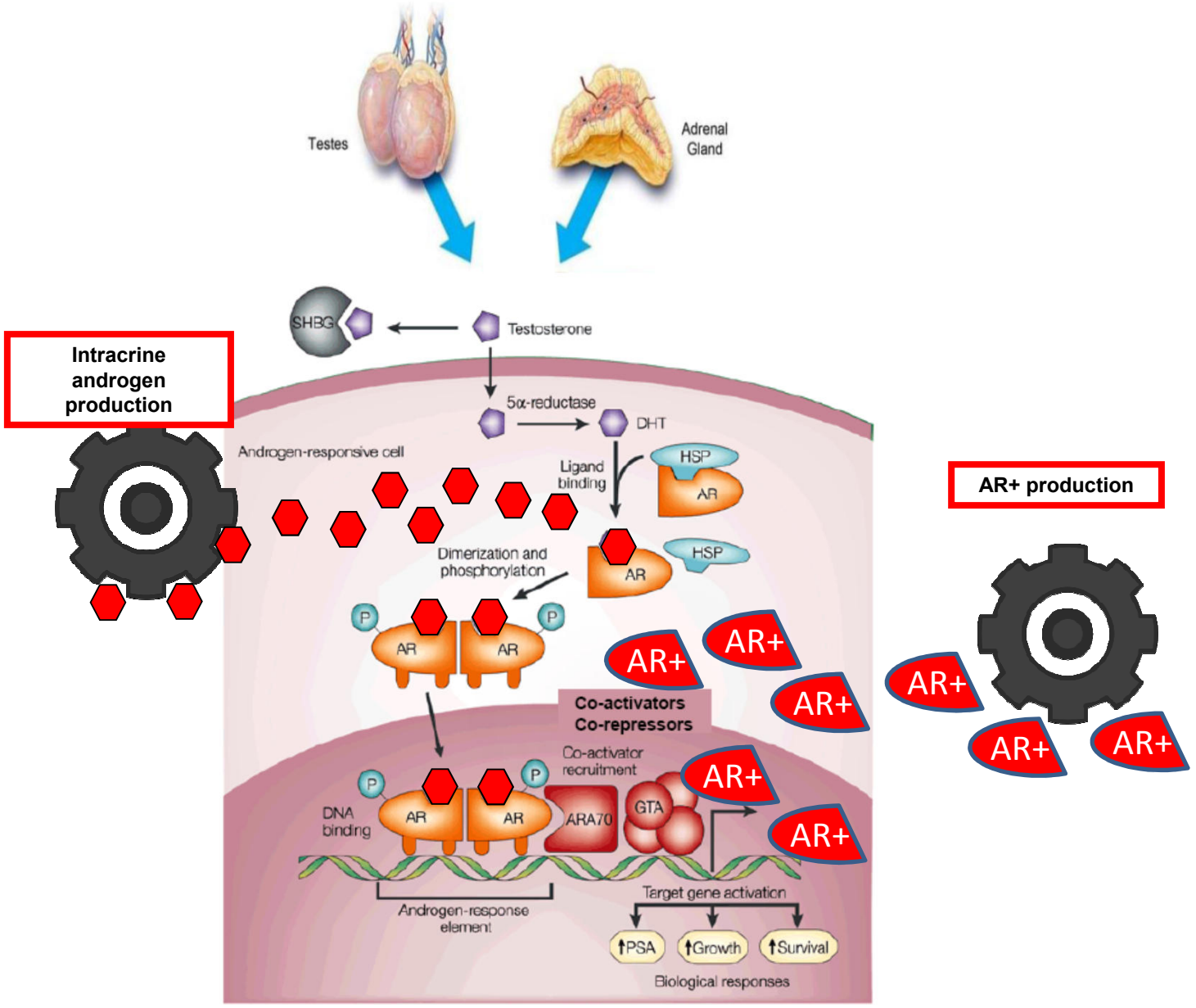






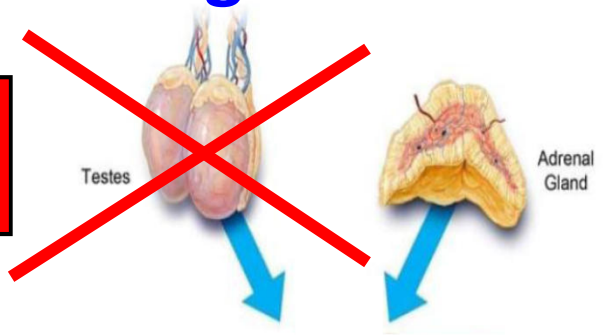
Elaborazione grafica da Nelson et al, J Clin Oncol 2012

Castration Resistant Prostate Cancer

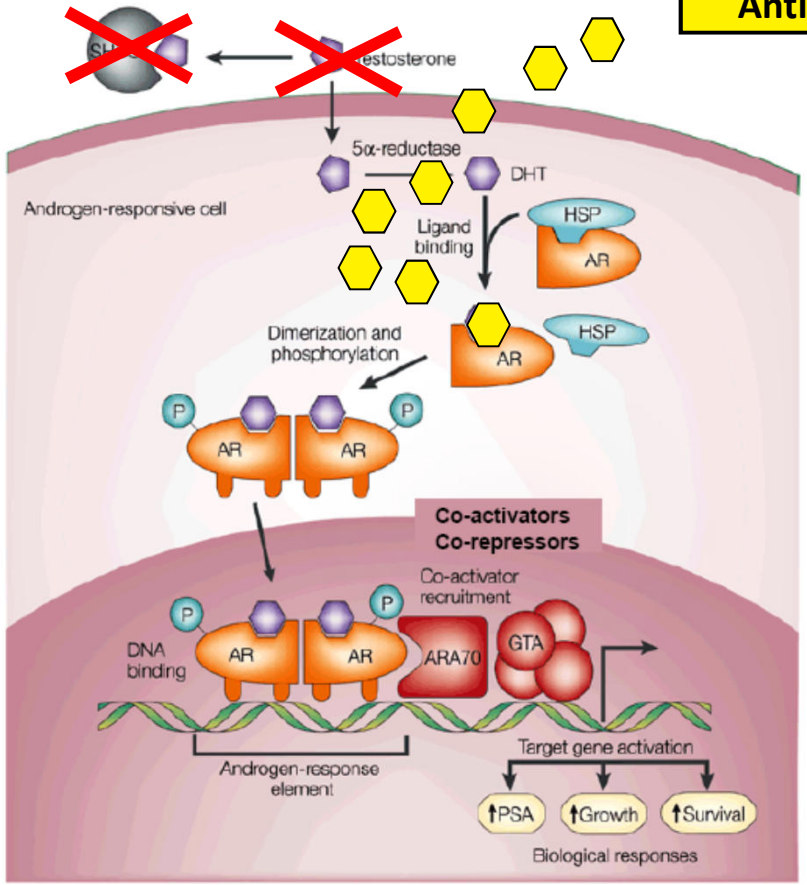


HSPC: Androgen ablation therapy

Surgical or pharmacological androgens depletion

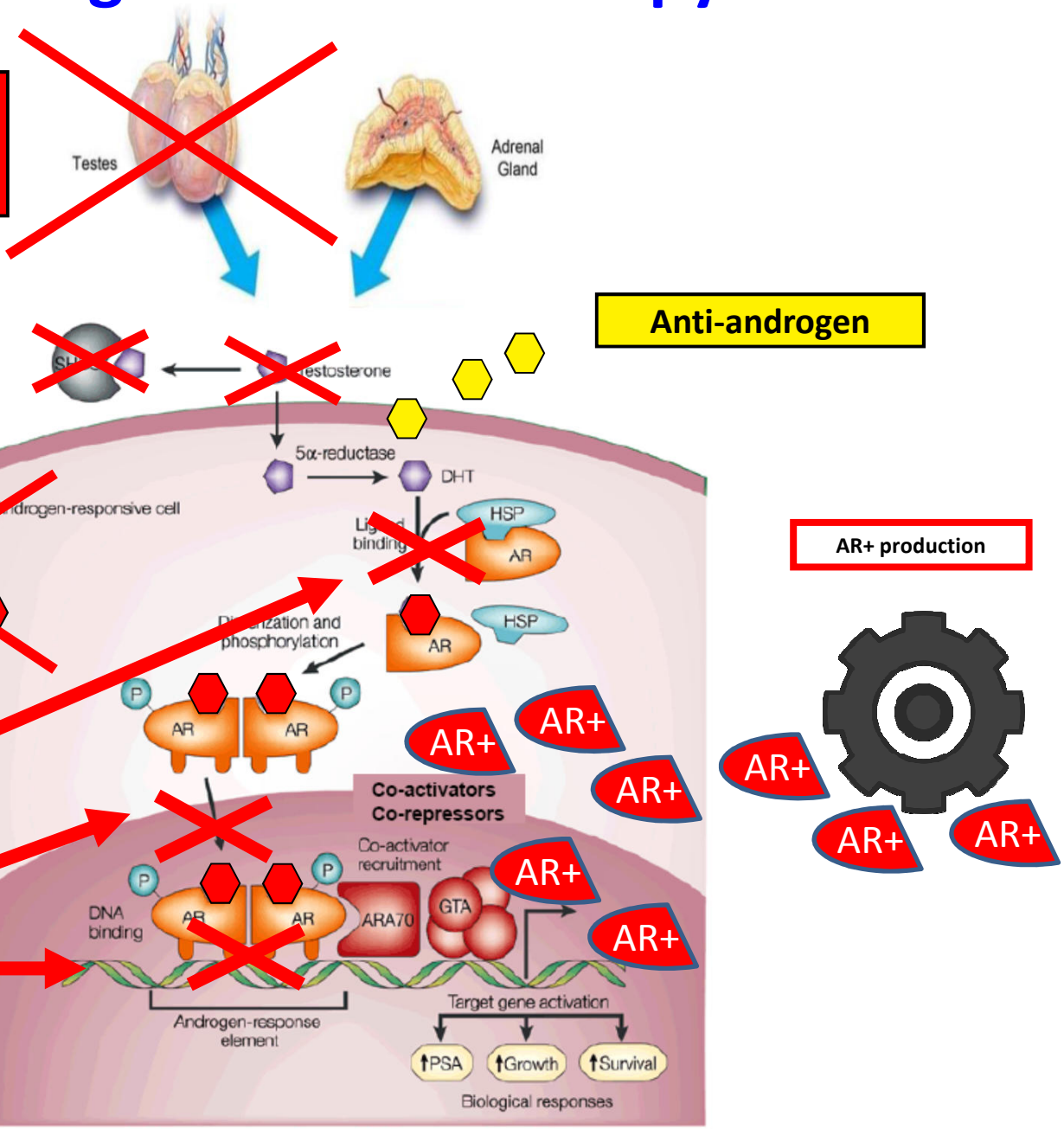


Anti-androgen



Androgen ablation therapy

Surgical or pharmacological androgens depletion



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Androgen ablation therapy

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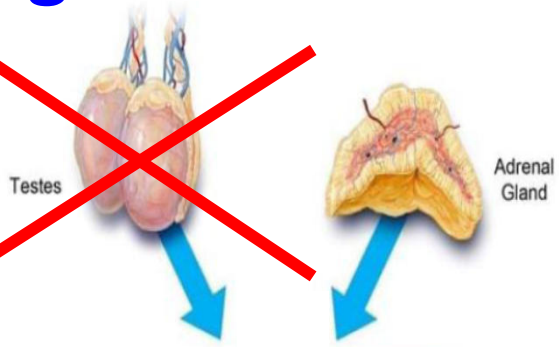
Surgical or pharmacological androgens depletion

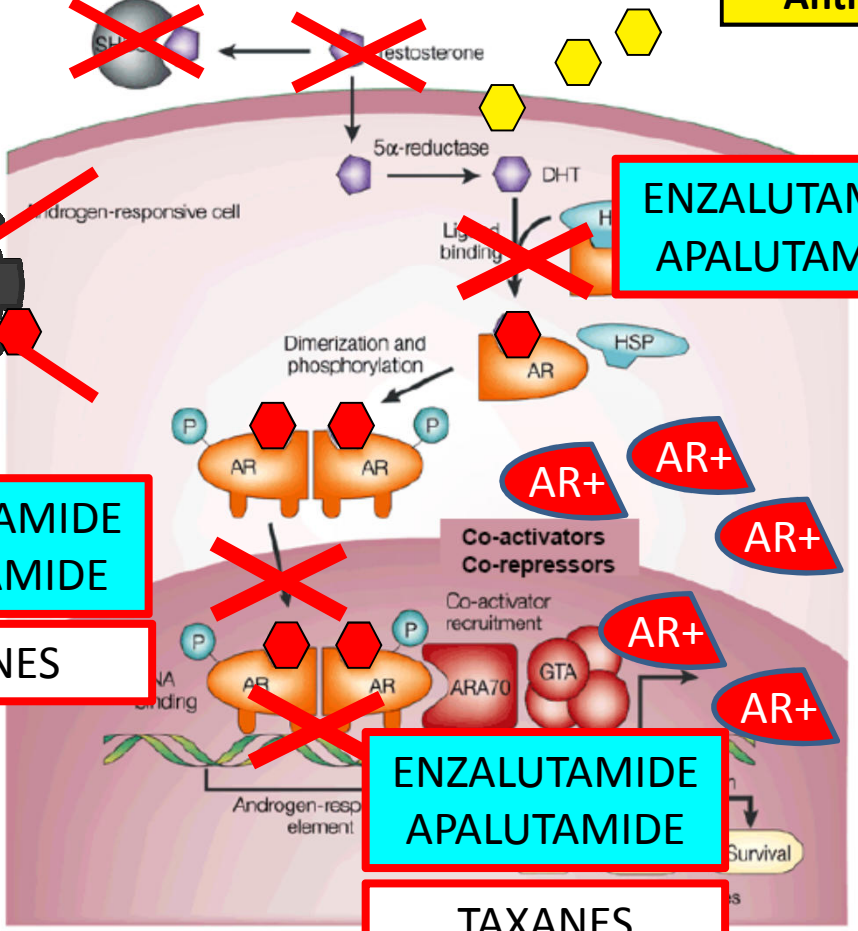


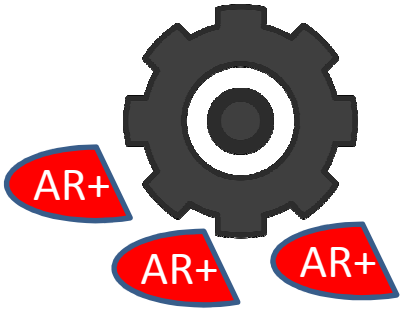
Anti-androgen

ABIRATERONE

ENZALUTAMIDE
APALUTAMIDE

AR+ production





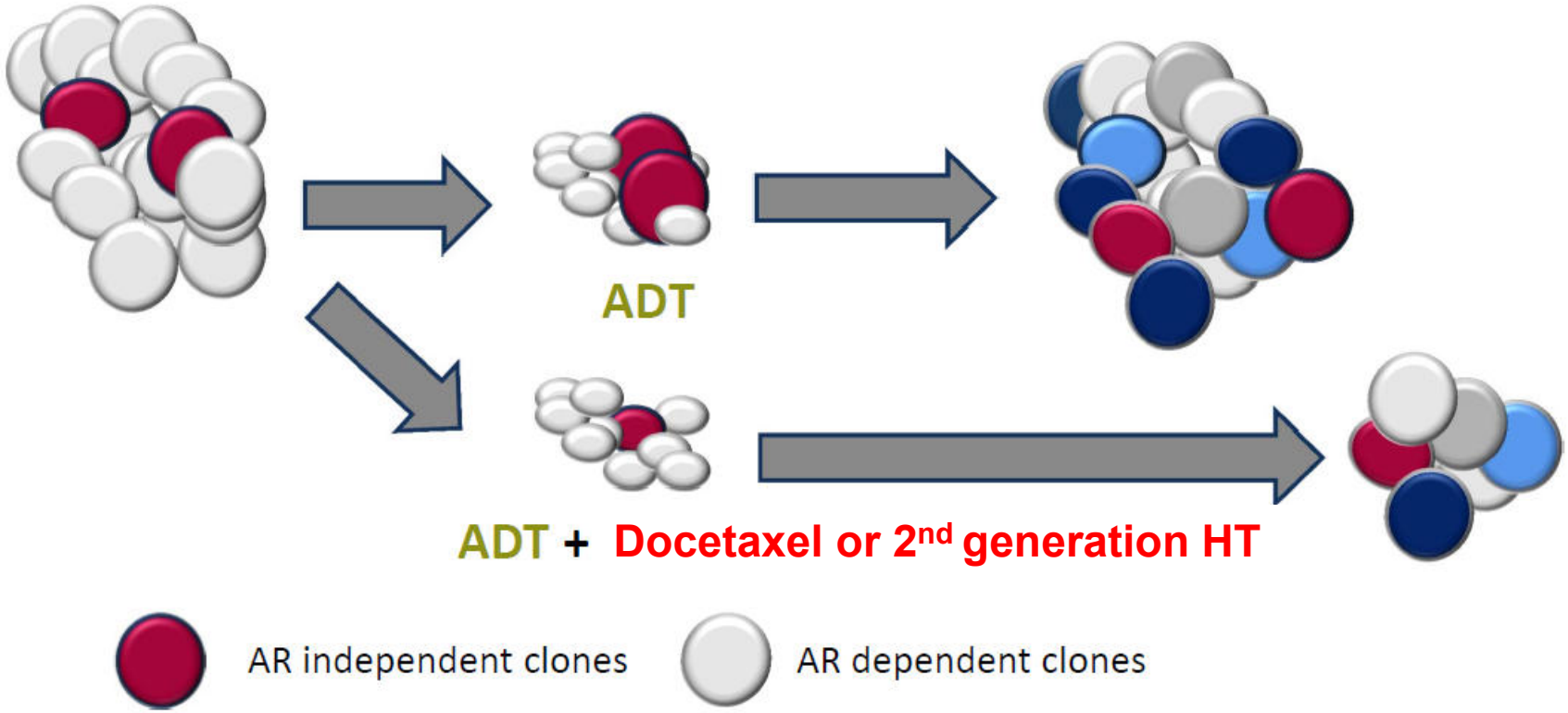
ENZALUTAMIDE
APALUTAMIDE

TAXANES

ENZALUTAMIDE
APALUTAMIDE

TAXANES

The role of CT or 2nd generation HT in HSPC:
Rational



Sweeney C et al. J Clin Oncol 2014;32(June 20 suppl):abstract LBA2
ADT: Androgen Deprivation Therapy; AR: androgen receptor

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AGENDA

- Rational
- **HSPC: pharmacological options**
- CRPC: pharmacological options

Evolution of Hormone Blockade in PCa

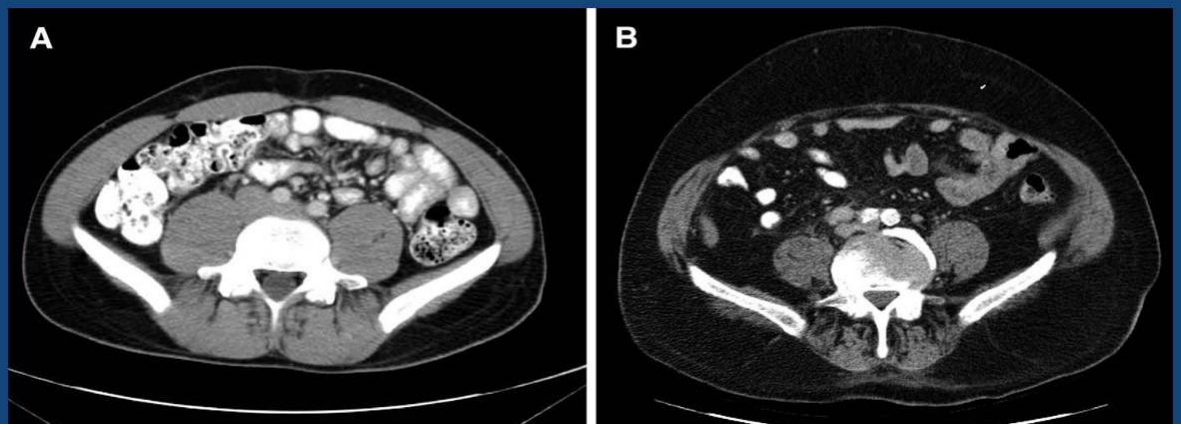
GnRH agonist/antagonist:
efficacy in clinical setting

• PSA reduction:	> 90%
• Clinical Response:	70-80%
• Early progression:	< 5%
• PSA progression-free at 1 year:	80-85%
• PFS	18-36 months
• OS	> 4-5 years

Klotz. BJU Int 2008; Kienle, et al. Urol Int 1996; Trachtenberg, et al. J Urol 2002

Medical Complications of ADT

- Sarcopenia
- Weight gain
- Decline in bone mineral density
- Increased fracture risk
- Increased risk of DM
- Increased risk of CVD
- Psychological Effects
- Cognitive Change



Morgans A, ASCO 2018

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mHSPC:
ROLE OF 2nd generation HT

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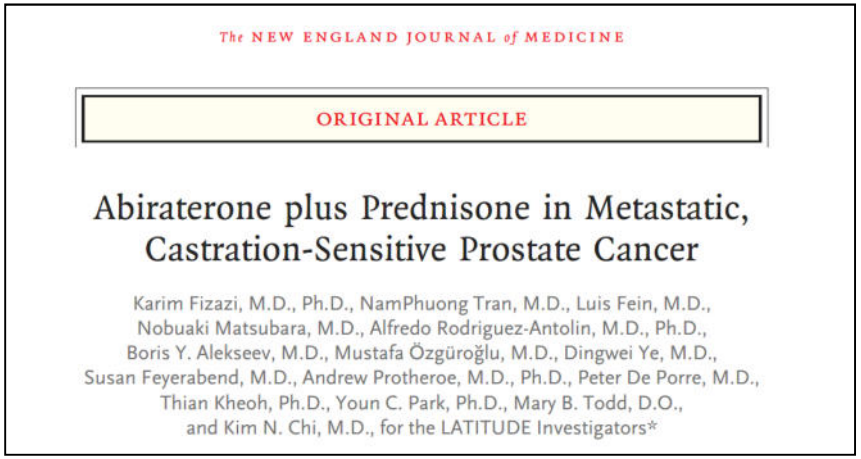
Hormone Sensitive Prostate Cancer

LATITUDE STUDY

***N Engl J Med*. 2017 June 4**



The NEW ENGLAND JOURNAL of MEDICINE

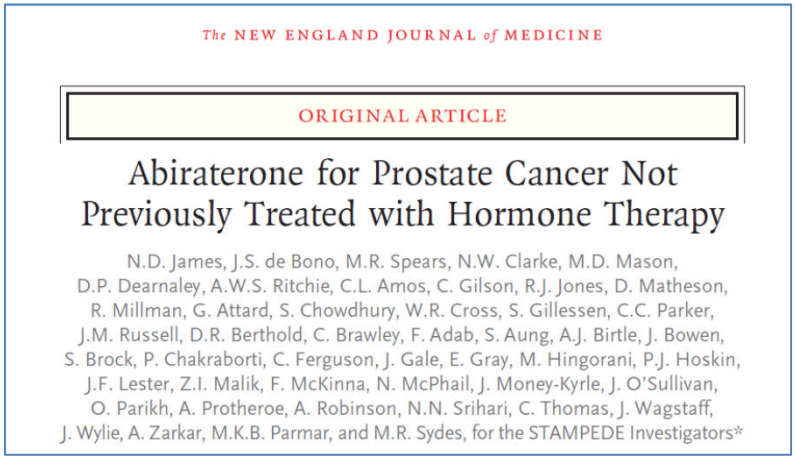
ORIGINAL ARTICLE

Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., Youn C. Park, Ph.D., Mary B. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators*

STAMPEDE STUDY

***N Engl J Med*. 2017 June 3**



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

N.D. James, J.S. de Bono, M.R. Spears, N.W. Clarke, M.D. Mason, D.P. Dearnaley, A.W.S. Ritchie, C.L. Amos, C. Gilson, R.J. Jones, D. Matheson, R. Millman, G. Attard, S. Chowdhury, W.R. Cross, S. Gillessen, C.C. Parker, J.M. Russell, D.R. Berthold, C. Brawley, F. Adab, S. Aung, A.J. Birtle, J. Bowen, S. Brock, P. Chakraborti, C. Ferguson, J. Gale, E. Gray, M. Hingorani, P.J. Hoskin, J.F. Lester, Z.I. Malik, F. McKinna, N. McPhail, J. Money-Kyrle, J. O'Sullivan, O. Parikh, A. Protheroe, A. Robinson, N.N. Srihari, C. Thomas, J. Wagstaff, J. Wylie, A. Zarkar, M.K.B. Parmar, and M.R. Sydes, for the STAMPEDE Investigators*

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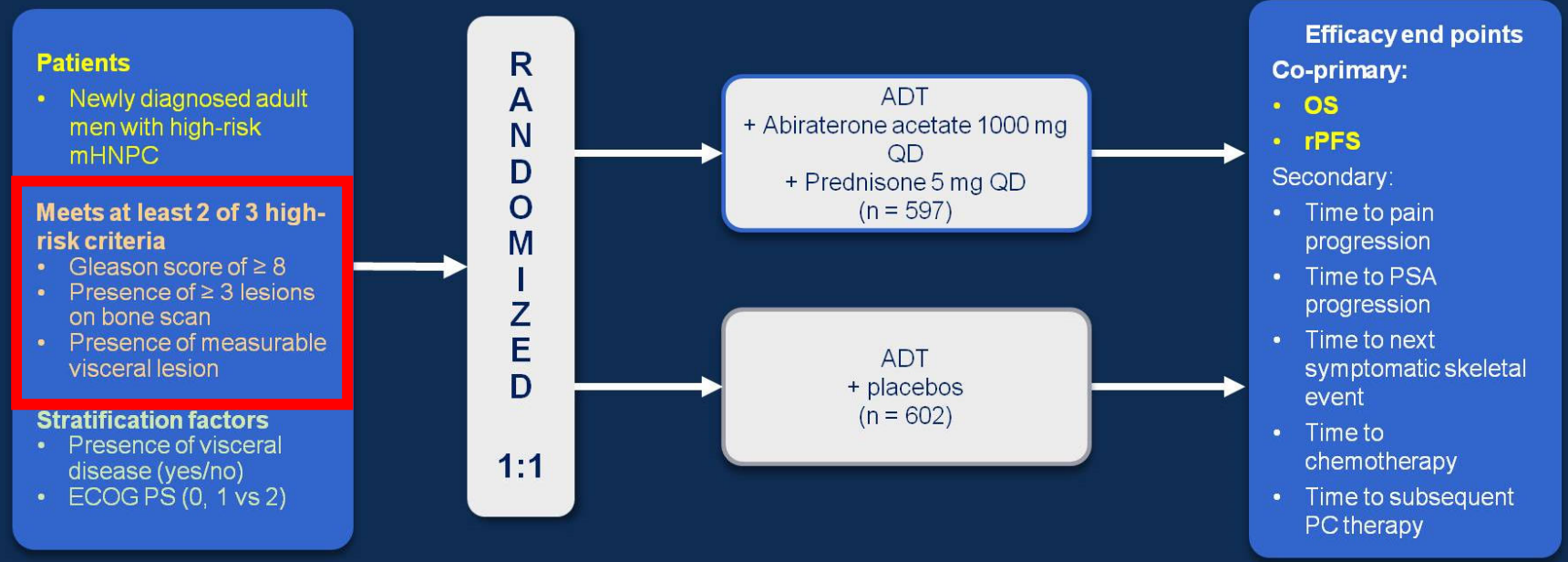
The role of 2nd generation HT in mHSPC

Study design of LATITUDE



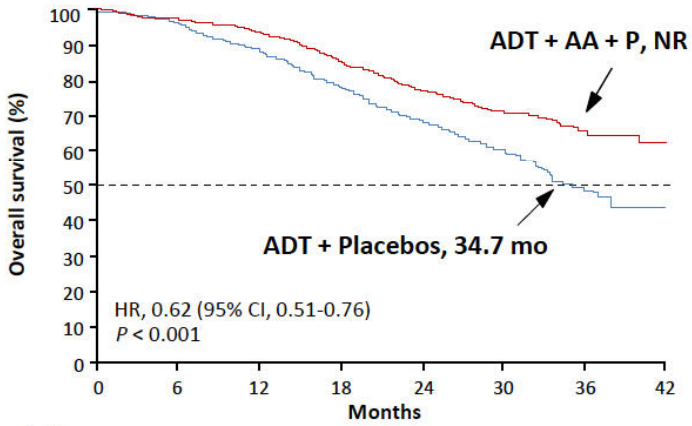
- **Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada**

From Fizazi et al, ASCO 2017

The role of 2nd generation HT in mHSPC

LATITUDE: Co-primary End Points

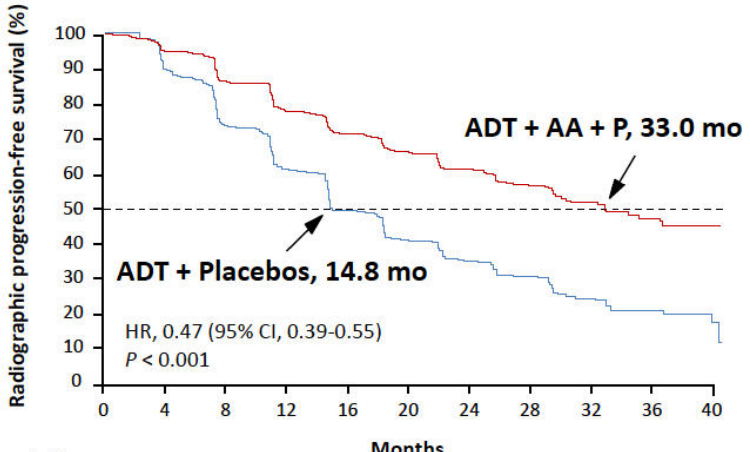
38% Risk Reduction for Death



Patients at risk

ADT + AA + P	597	565	529	479	388	233	93	9
ADT + Placebos	602	564	504	432	332	172	57	2

53% Risk Reduction for rPFS



Patients at risk

ADT + AA + P	597	533	464	400	353	316	251	177	102	51	21
ADT + Placebos	602	488	367	289	214	168	127	81	41	17	7

Figures included with permission, from Fizazi K, et al. *N Engl J Med*. 2017;377:352-360. CI, confidence interval; HR, hazard ratio; NR, not reached; rPFS, radiographic progression-free survival.

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LATITUDE
AEs of special interest

Adverse Events	ADT + AA + P (n = 597)		ADT + placebos (n = 602)	
	Grade 3	Grade 4	Grade 3	Grade 4
	%		%	
Hypertension	20	0	10	0.2
Hypokalemia	10	0.8	1	0.2
ALT increased	5	0.3	1	0
AST increased	4	0.2	1	0
Hyperglycemia	4	0.2	3	0
Bone pain	3	0	3	0
Cardiac disorder	3	0.8	1	0
Anemia	2	0.5	4	0.2
Back pain	2	0	3	0
Fatigue	2	0	2	0
Spinal cord compression	2	0	1	0.5

Fizazi K, NEJM 2017

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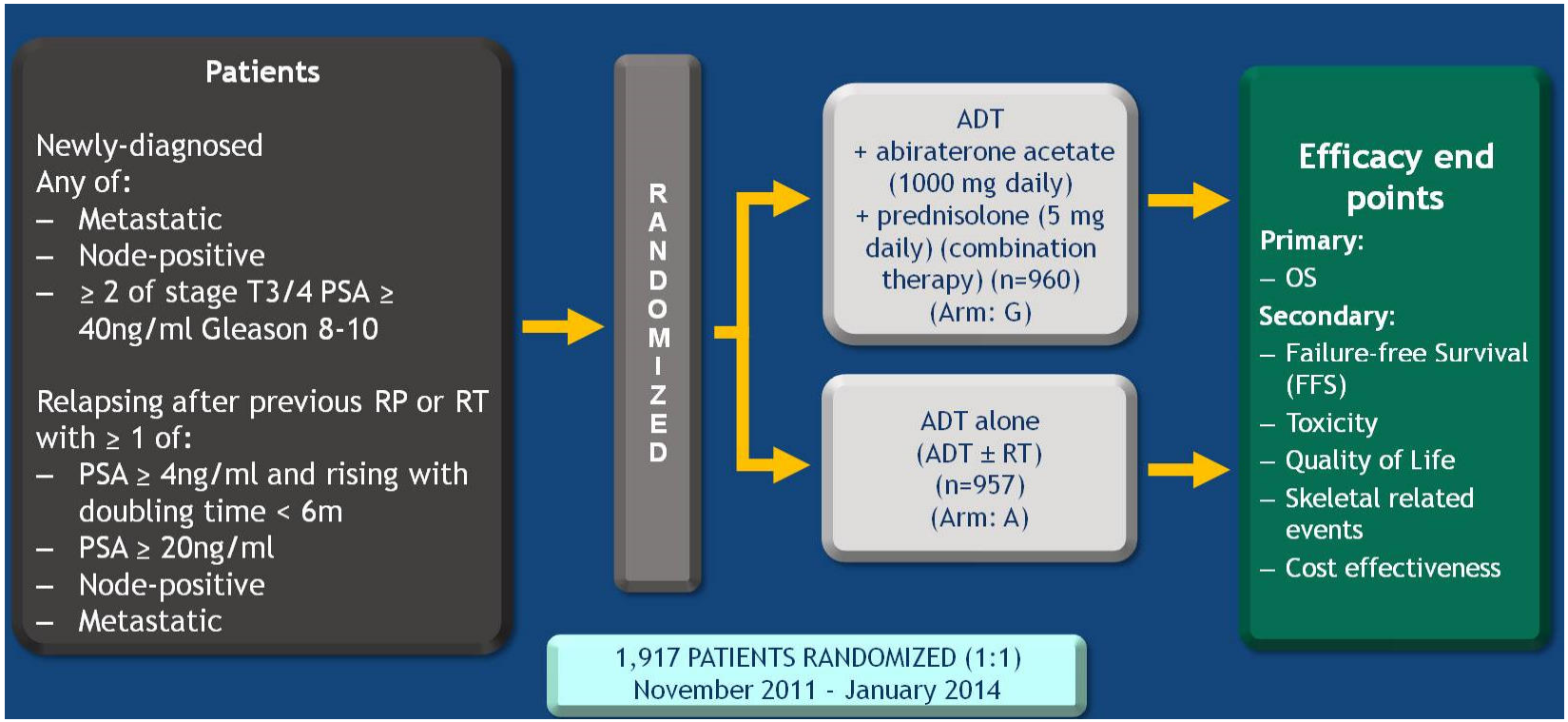
The role of 2nd generation HT in mHSPC

STAMPEDE. Multi-Arm Multi-Stage platform design



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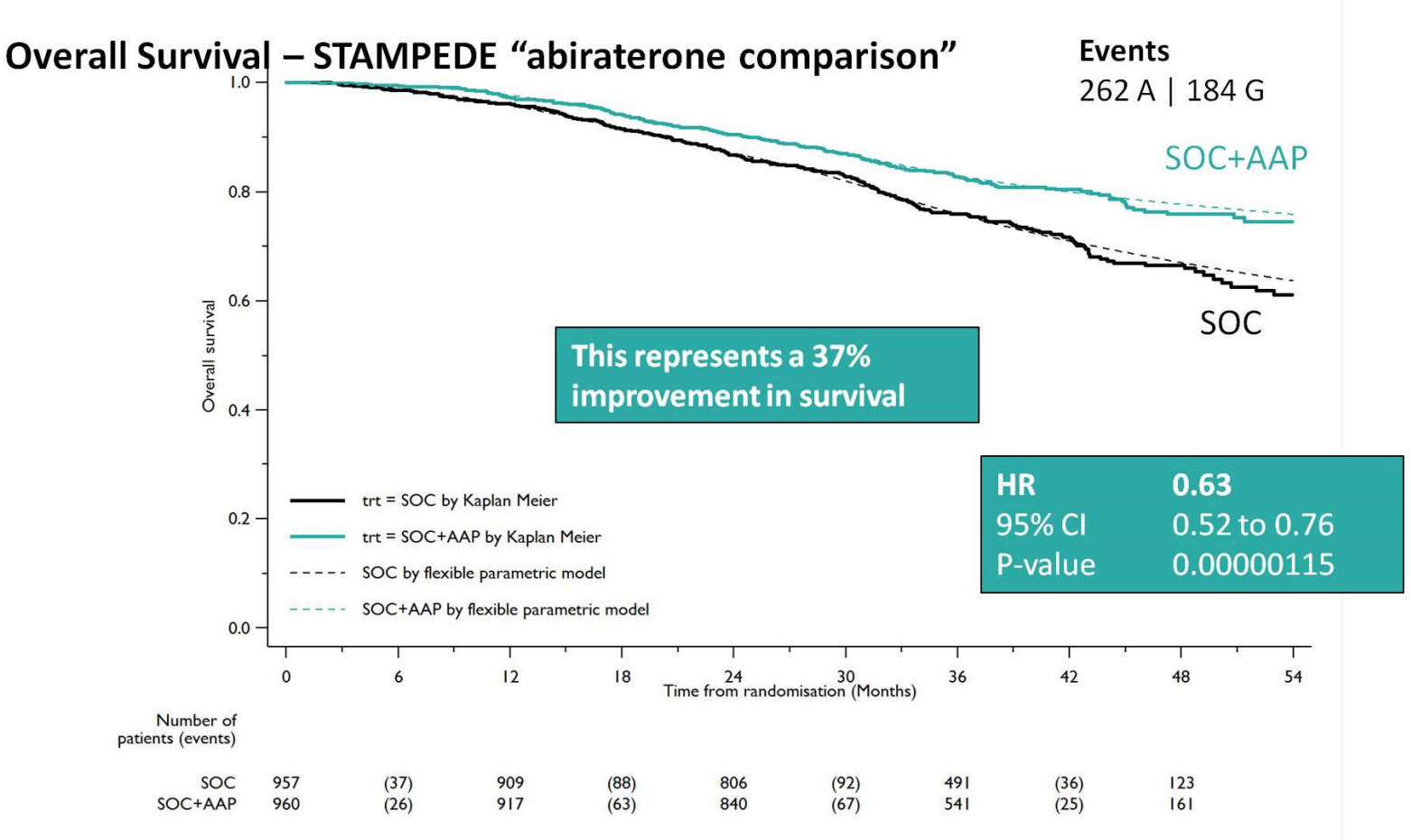
The role of 2nd generation HT in mHSPC

Abiraterone in STAMPEDE



James N, ASCO 2017

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Hormone Sensitive Prostate Cancer
ABI vs DOCE

Study	Agents	N	Median FU (Months)	Median OS (Months)
CHAARTED	DOC vs ADT	790	**53.7**	**57.6 vs 47.2**
STAMPEDE	DOC/P vs ADT	1,086	**43**	**60 vs 45**
GETUG 15	DOC vs ADT	385	**83**	**62.1 vs 48.6**
LATITUDE	ABI/P vs ADT	1,199	41	NR vs 36.7
STAMPEDE	ABI/P vs ADT	1,002	40	NR

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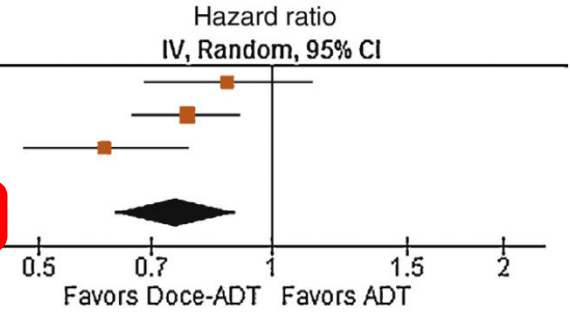
Comparison of Abiraterone Acetate and Docetaxel with Androgen Deprivation Therapy in High-risk and Metastatic Hormone-naïve Prostate Cancer: A Systematic Review and Network Meta-analysis

Christopher J.D. Wallis[a,†,], Zachary Klaassen[a,b,†], Bimal Bhindi[c], Hanan Goldberg[a,b], Thenappan Chandrasekar[a,b], Ann M. Farrell[d], Stephen A. Boorjian[c], Girish S. Kulkarni[a,b], Robert Jeffrey Karnes[c], Raj Satkunasivam[a,e]*

A

Study or subgroup	log[Hazard ratio]	SE	Doce-ADT Total	ADT Total	Weight	Hazard ratio IV, Random, 95% CI
Gravis 2016	−0.1278	0.1315	192	193	28.9%	0.88 [0.68, 1.14]
James 2016	−0.2485	0.0852	592	1184	42.7%	0.78 [0.66, 0.92]
Sweeney 2015	−0.4943	0.133	397	393	28.5%	0.61 [0.47, 0.79]
Total (95% CI)			**1181**	**1770**	**100.0%**	**0.75 [0.63, 0.91]**

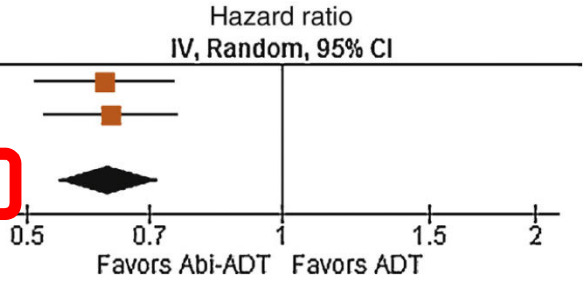
Heterogeneity: Tau² = 0.01; χ^2 = 4.07, df = 2 (p = 0.13); I^2 = 51%
Test for overall effect: Z = 3.00 (p = 0.003)



B

Study or subgroup	log[Hazard ratio]	SE	Abi-ADT Total	ADT Total	Weight	Hazard ratio IV, Random, 95% CI
Fizazi 2017	−0.478	0.0996	597	602	49.1%	0.62 [0.51, 0.75]
James 2017	−0.462	0.0979	960	957	50.9%	0.63 [0.52, 0.76]
Total (95% CI)			**1557**	**1559**	**100.0%**	**0.63 [0.55, 0.72]**

Heterogeneity: Tau² = 0.00; χ^2 = 0.01, df = 1 (p = 0.91); I^2 = 0%
Test for overall effect: Z = 6.73 (p < 0.00001)



Wallis, Eur J Urol 2017

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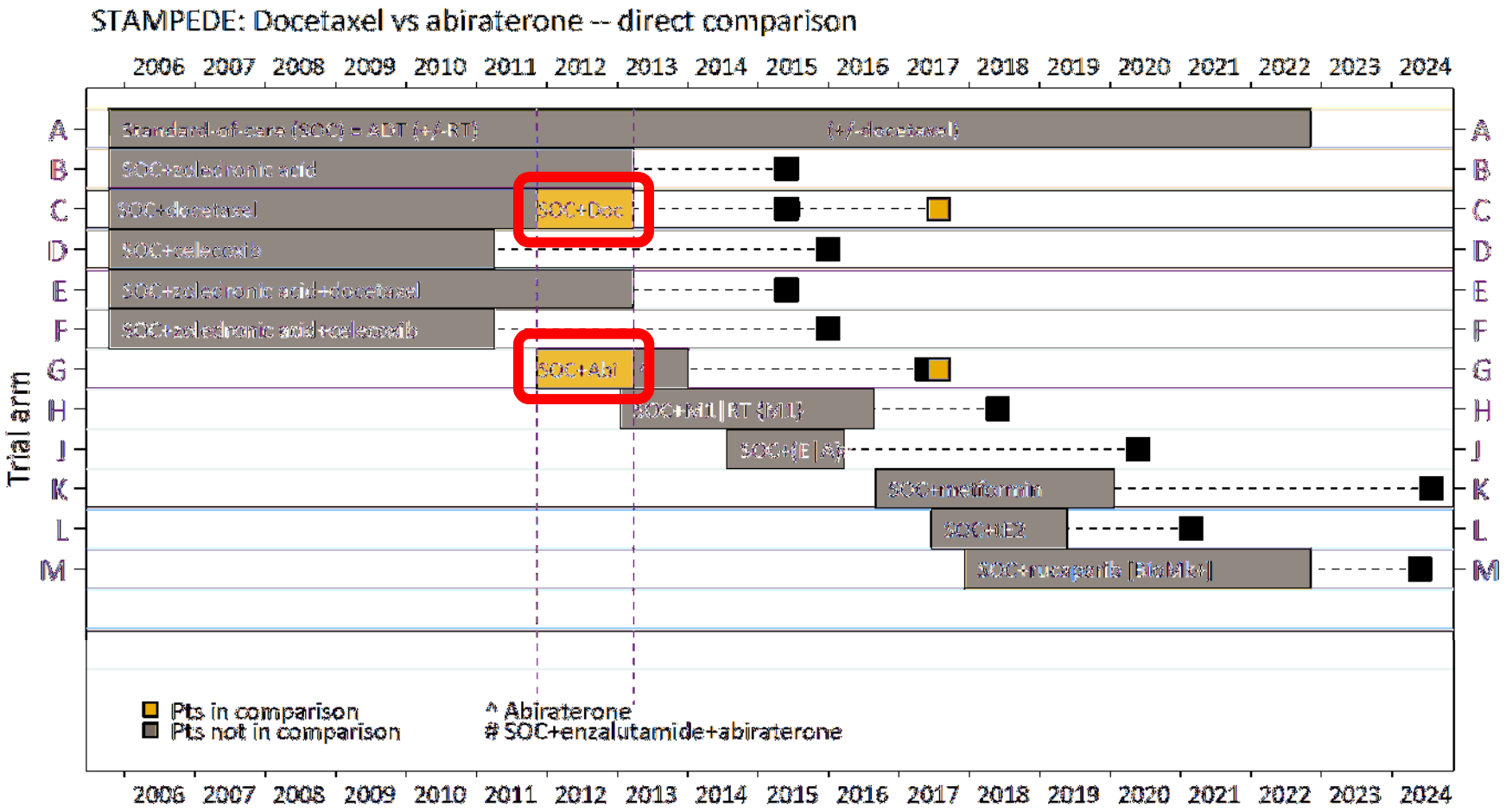
The role of CT or 2nd generation HT in mHSPC:

STAMPEDE: ADT+AA+P vs ADT+DOC (377 vs 189)



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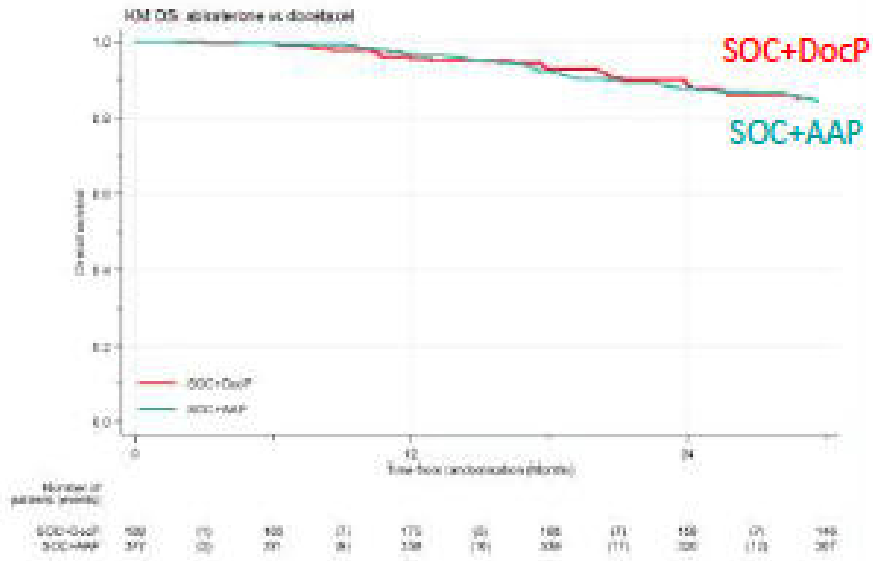
The role of CT or 2nd generation HT in mHSPC:

STAMPEDE

Overall survival [primary outcome measure]



	HR (95%CI)	P-val	*Interact^n test*
All	1.16 (0.82 to 1.65)	0.40	
M0	1.51 (0.58 to 3.93)	0.40	*0.69*
M1	1.13 (0.77 to 1.66)	0.53	

	SOC+DocP		SOC+AAP	
	Events	Pts	Events	Pts
All	44	189	105	377
M0	6	74	16	150
M1	38	115	89	227

Key:
HR<1 favours SOC+AAP
HR>1 favours SOC+DocP

Interact^n = test for interaction (heterogeneity of treatment effect)

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The role of CT or 2nd generation HT in mHSPC:

STAMPEDE

Adverse events – worst toxicity ever

Safety population	SOC+DocP	SOC+AAP
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%)

DocP

AAP

Sydes M, ESMO 2017

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AGENDA

- Rational
- HSPC: pharmacological options
- **CRPC: pharmacological options**

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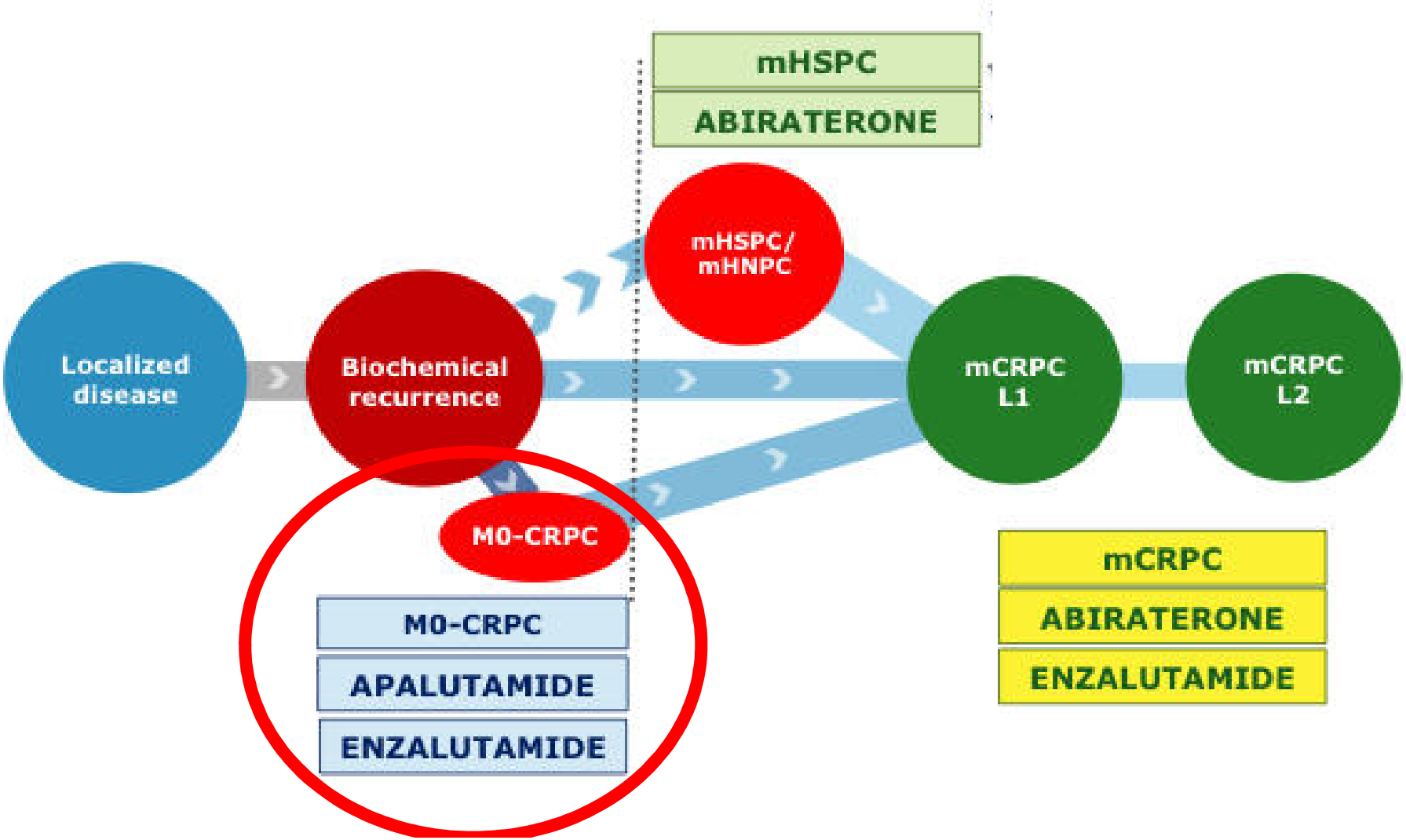
The different stages of prostate cancer



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M0-CRPC

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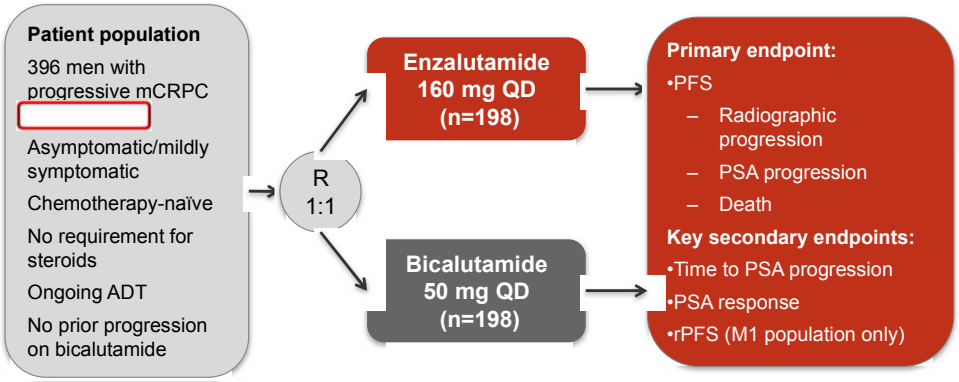
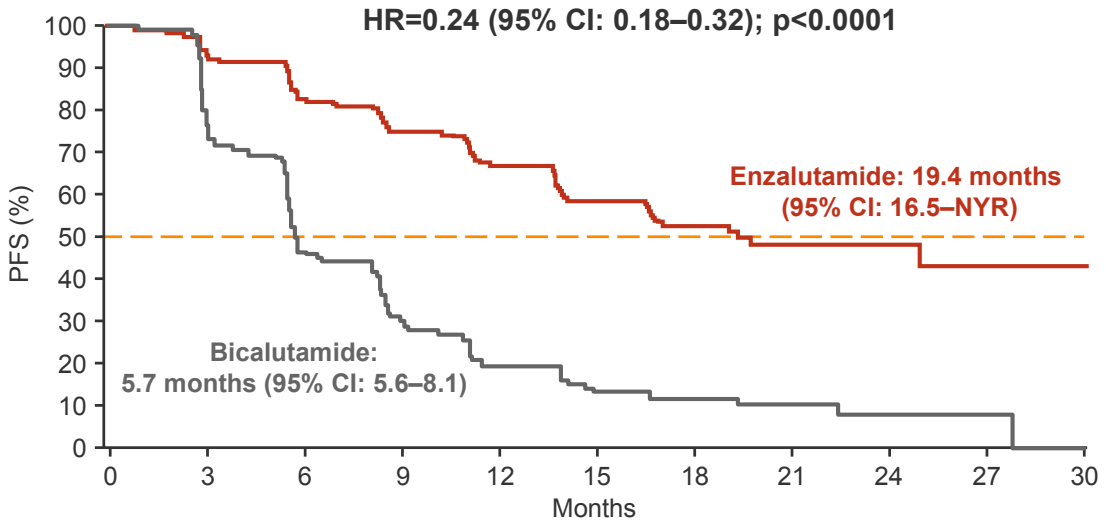
STRIVE: Study design

- A multicentre, Phase 2, randomised, double-blind, efficacy and safety study in asymptomatic or mildly symptomatic patients with progression despite primary ADT





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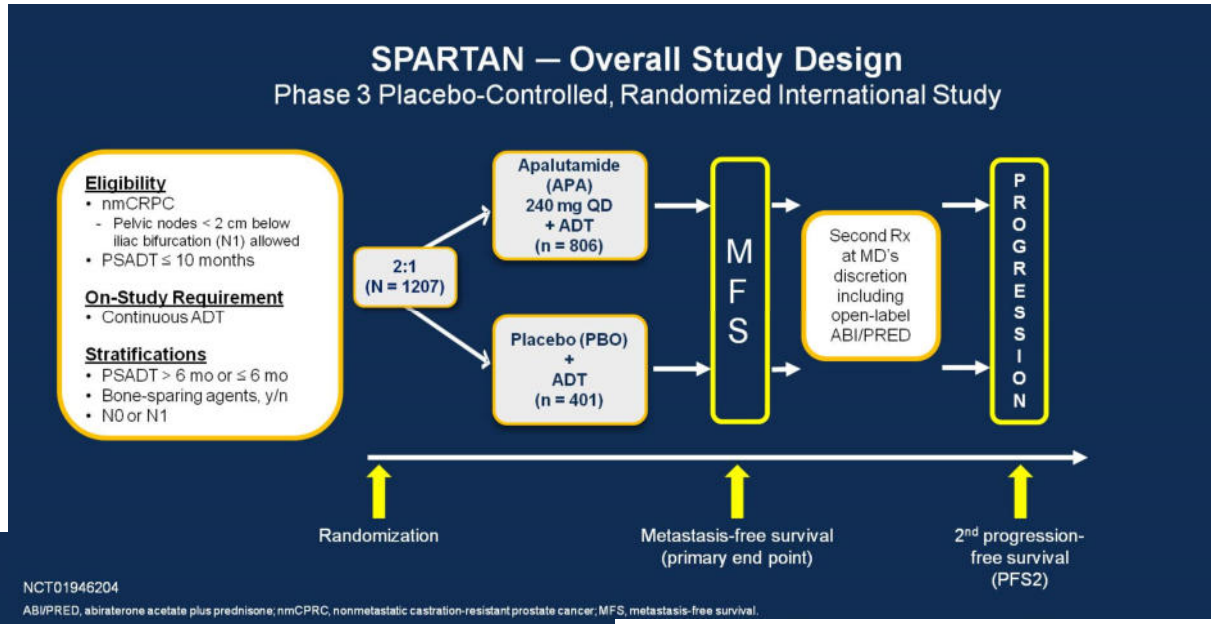
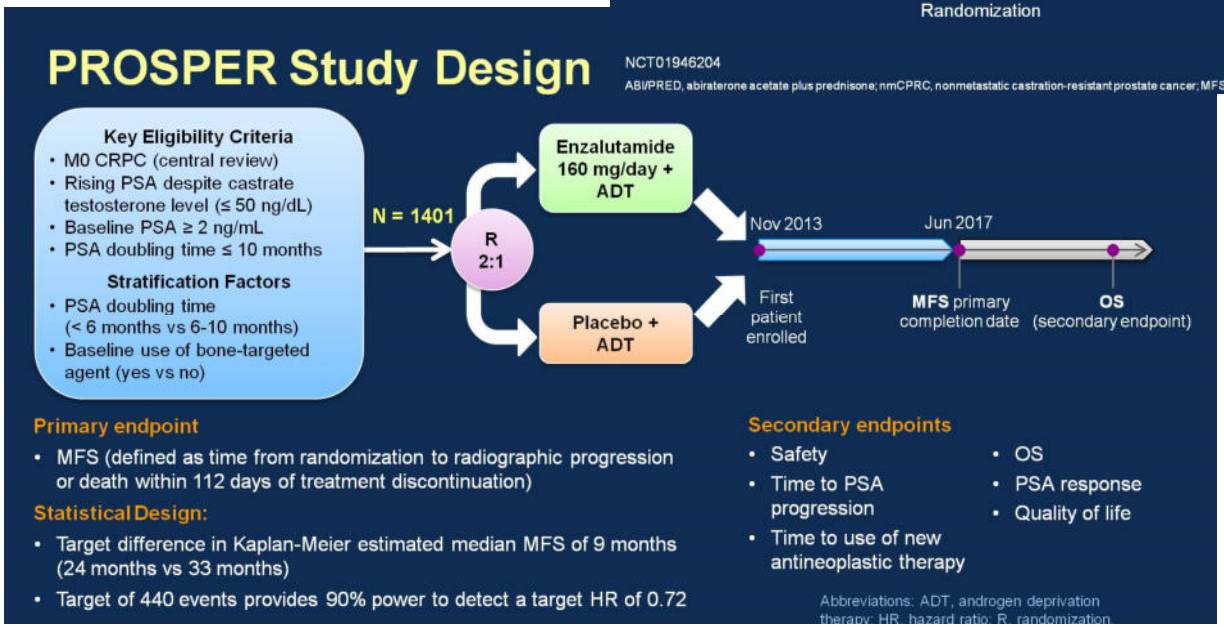
M0-CRPC





Husain M, ASCO 2018
Small E, ASCO 2018

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M0-CRPC

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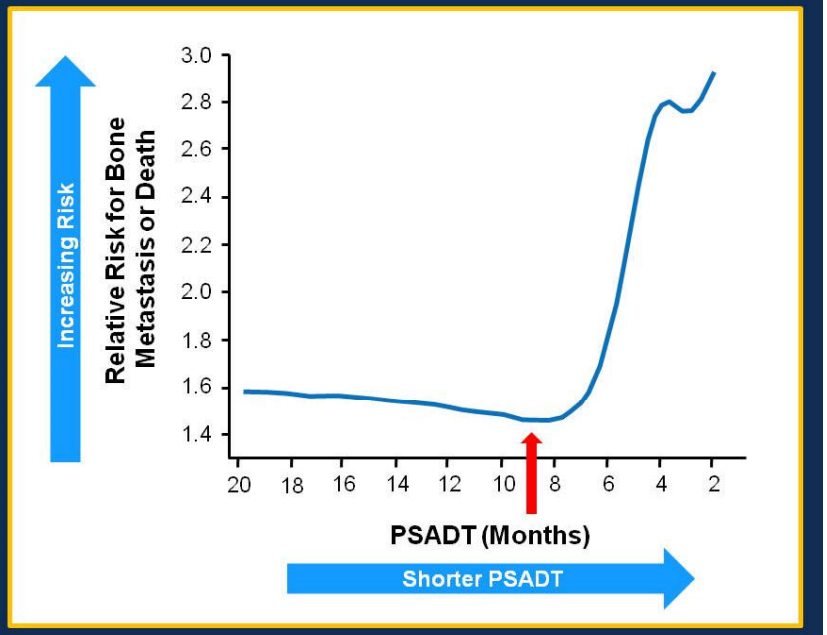
Background

- Men with nmCRPC with a prostate-specific antigen doubling time (PSADT) of < 8-10 months are at significant risk for metastatic disease and prostate cancer–specific death[1]
- Metastases are a major cause of morbidity and mortality[2,3]
- There are no approved treatments for patients with nmCRPC
- Prevention of metastases represents an important unmet medical need in these patients



1. Smith MR, et al. *J Clin Oncol*. 2013;31:3800-3806.
2. Scher HI, et al. *PLoS One*. 2015;10:e0139440.
3. Gartrell BA, et al. *Nat Rev Clin Oncol*. 2014;11:335-345.

Husain M, ASCO 2018
Small E, ASCO 2018

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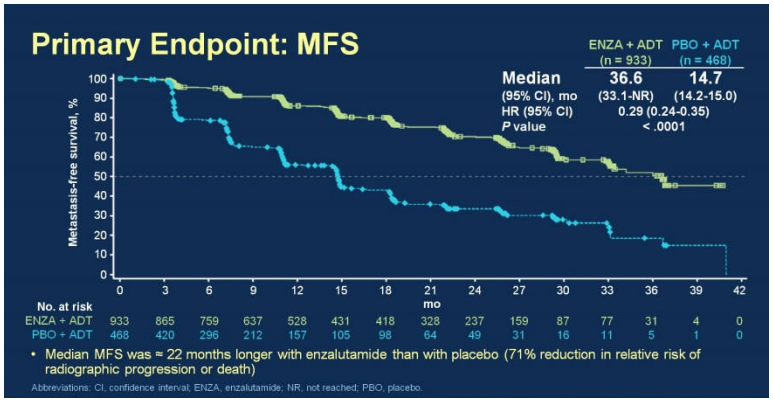
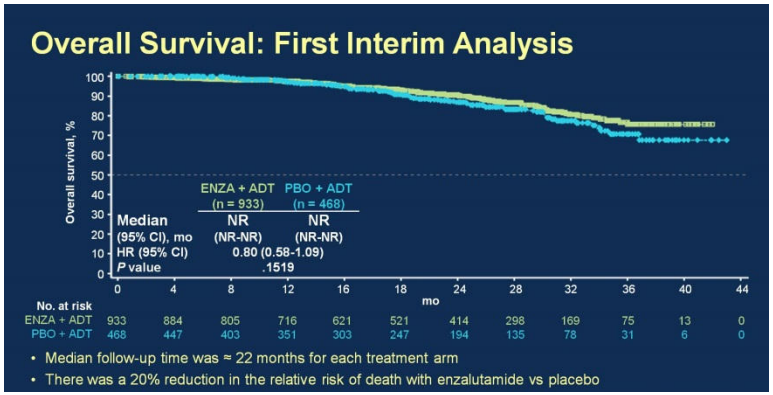
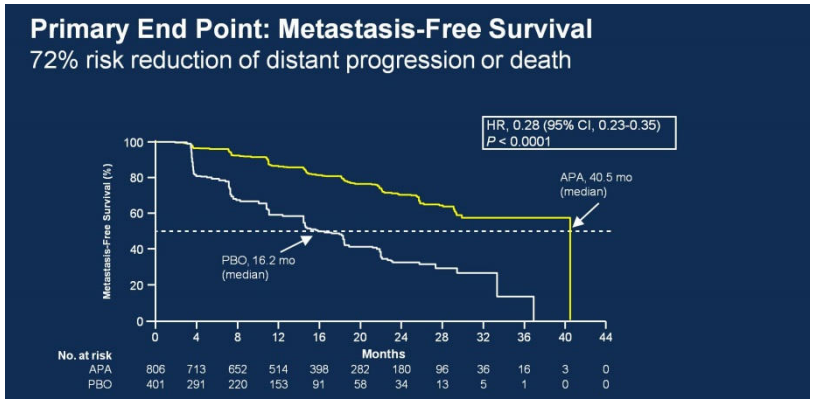
M0-CRPC

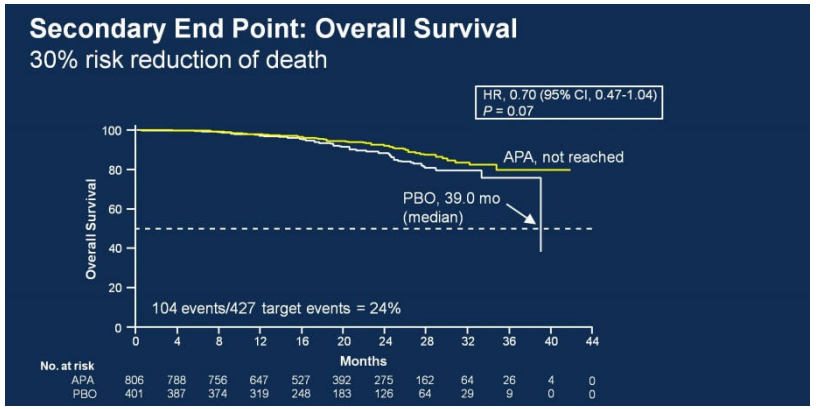
PROSPER TRIAL





SPARTAN TRIAL





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PROSPER TRIAL

Adverse Events of Special Interest*

Any Grade Event, No. (%)	Enzalutamide + ADT (n = 930)	Placebo + ADT (n = 465)
Hypertension†	114 (12%)	25 (5%)
Major adverse cardiovascular event‡	48 (5%)	13 (3%)
Mental impairment disorders§	48 (5%)	9 (2%)
Hepatic impairment	11 (1%)	9 (2%)
Neutropenia	9 (1%)	1 (< 1%)
Convulsion	3 (< 1%)	0
Posterior reversible encephalopathy syndrome	0	0

In both arms the incidence of major adverse cardiovascular events was higher in patients with:

- Baseline history of cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, or age ≥75 years

*Adverse events were collected up to 30 days after the last dose of study drug.
†Includes increased blood pressure.
‡Includes acute myocardial infarction, hemorrhagic cerebrovascular conditions, ischemic cerebrovascular conditions, and heart failure.
§Includes memory impairment, disturbance in attention, cognitive disorders, amnesia, dementia Alzheimer's type, senile dementia, mental impairment, and vascular dementia.

SPARTAN TRIAL

Results: Treatment Associated Adverse Events

	APA (n = 803)		PBO (n = 398)	
	All	Gr 3/4	All	Gr 3/4
Fatigue	30.4%	0.9%	21.1%	0.3%
Rash	23.8%	5.2%	5.5%	0.3%
Weight loss	16.1%	1.1%	6.3%	0.3%
Arthralgia	15.9%	0	7.5%	0
Fall	15.6%	1.7%	9.0%	0.8%
Fracture	11.7%	2.7%	6.5%	0.8%
Hypothyroidism	8.1%	0	2.0%	0
Seizure	0.2%	0	0	0

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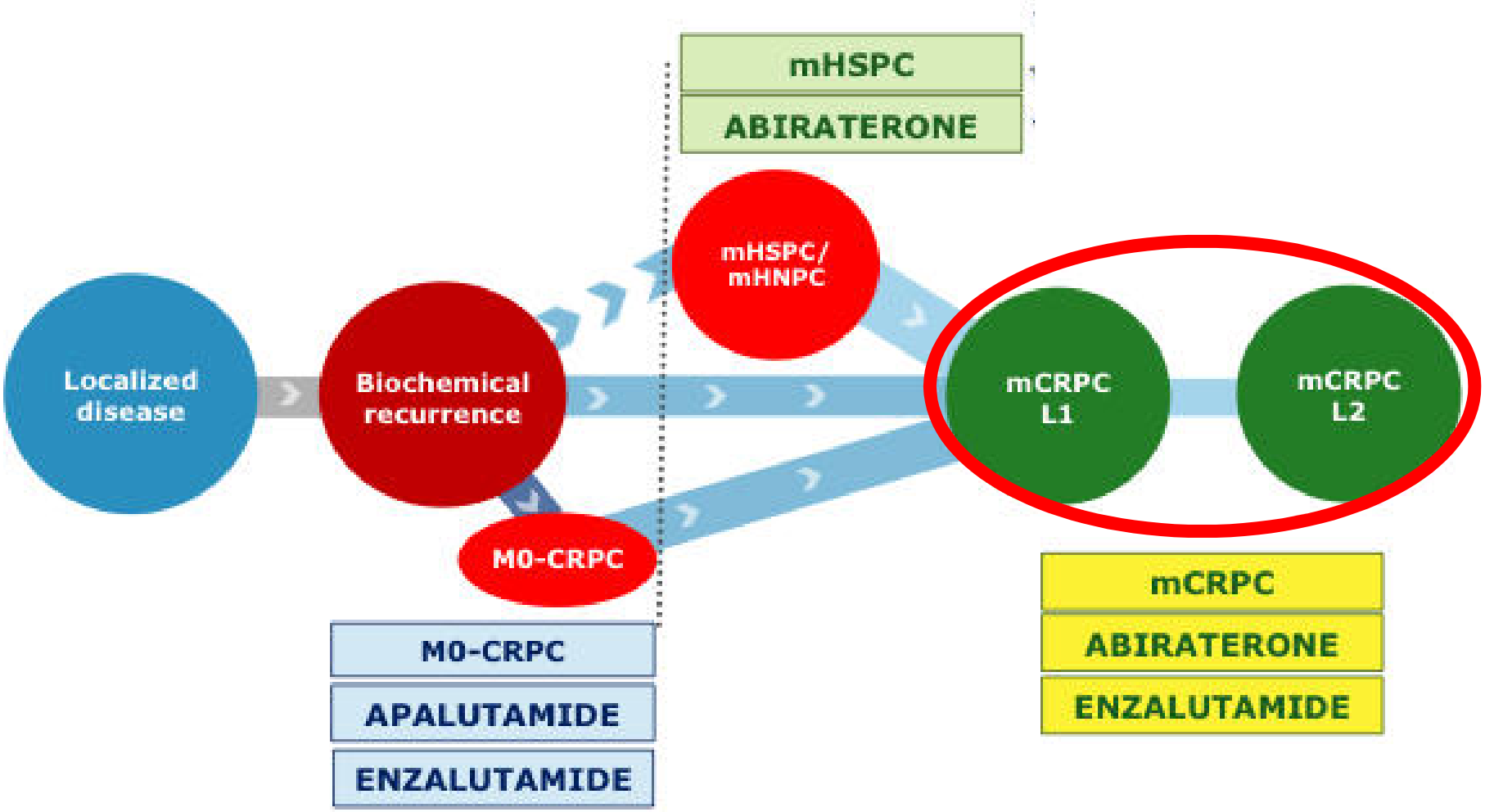
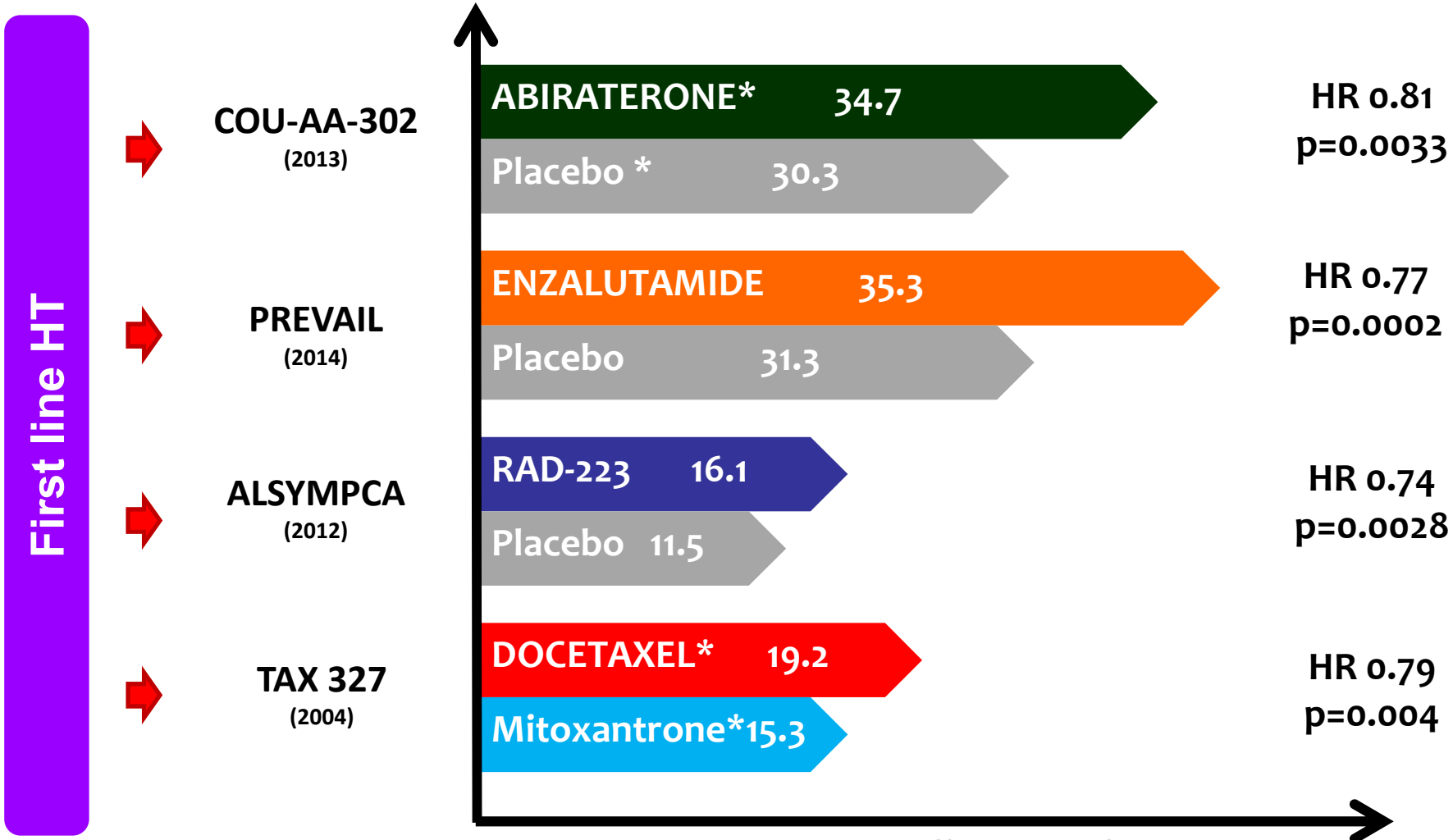
The different stages of prostate cancer

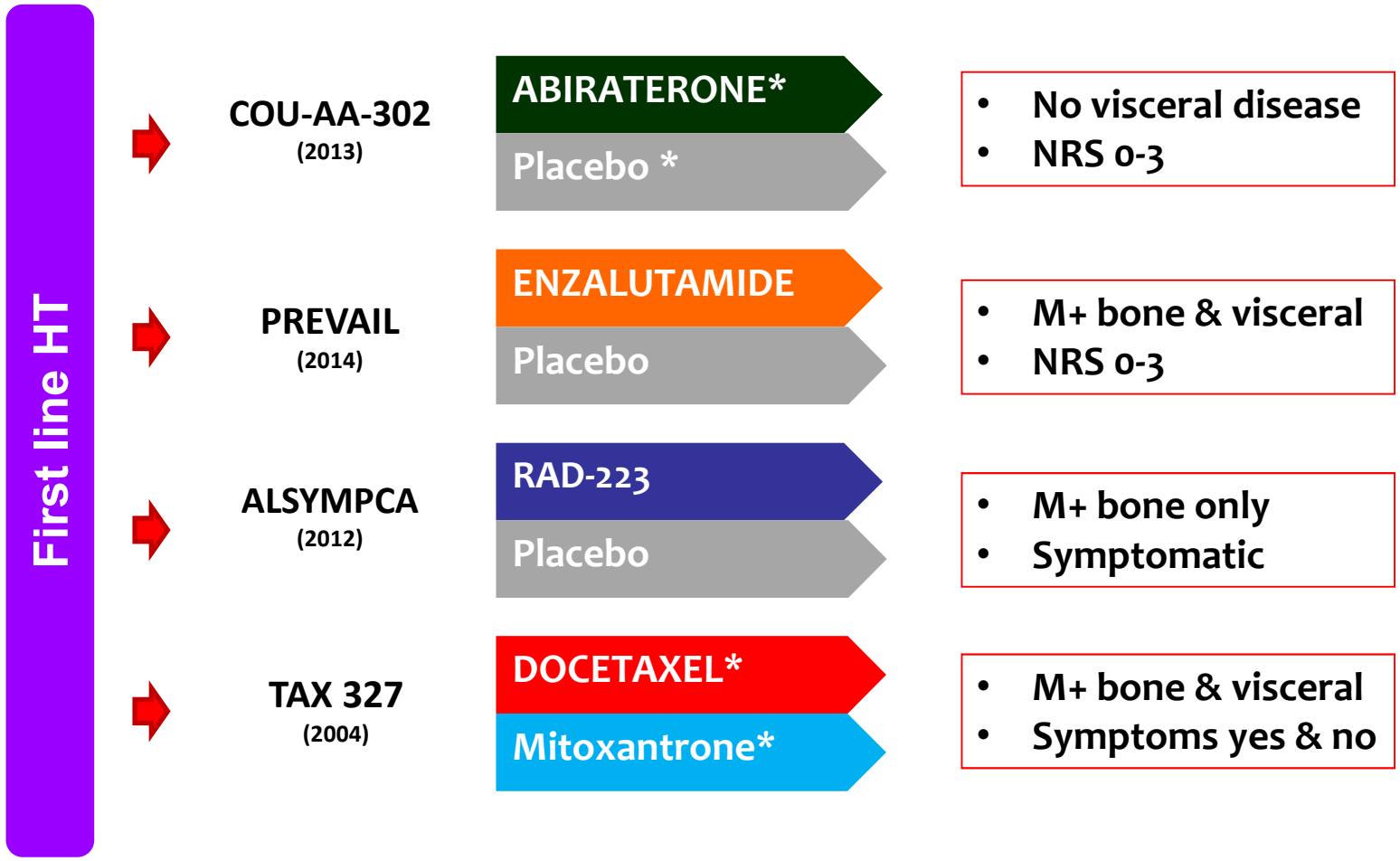


Summary of mCRPC therapy: chemo-naive pts



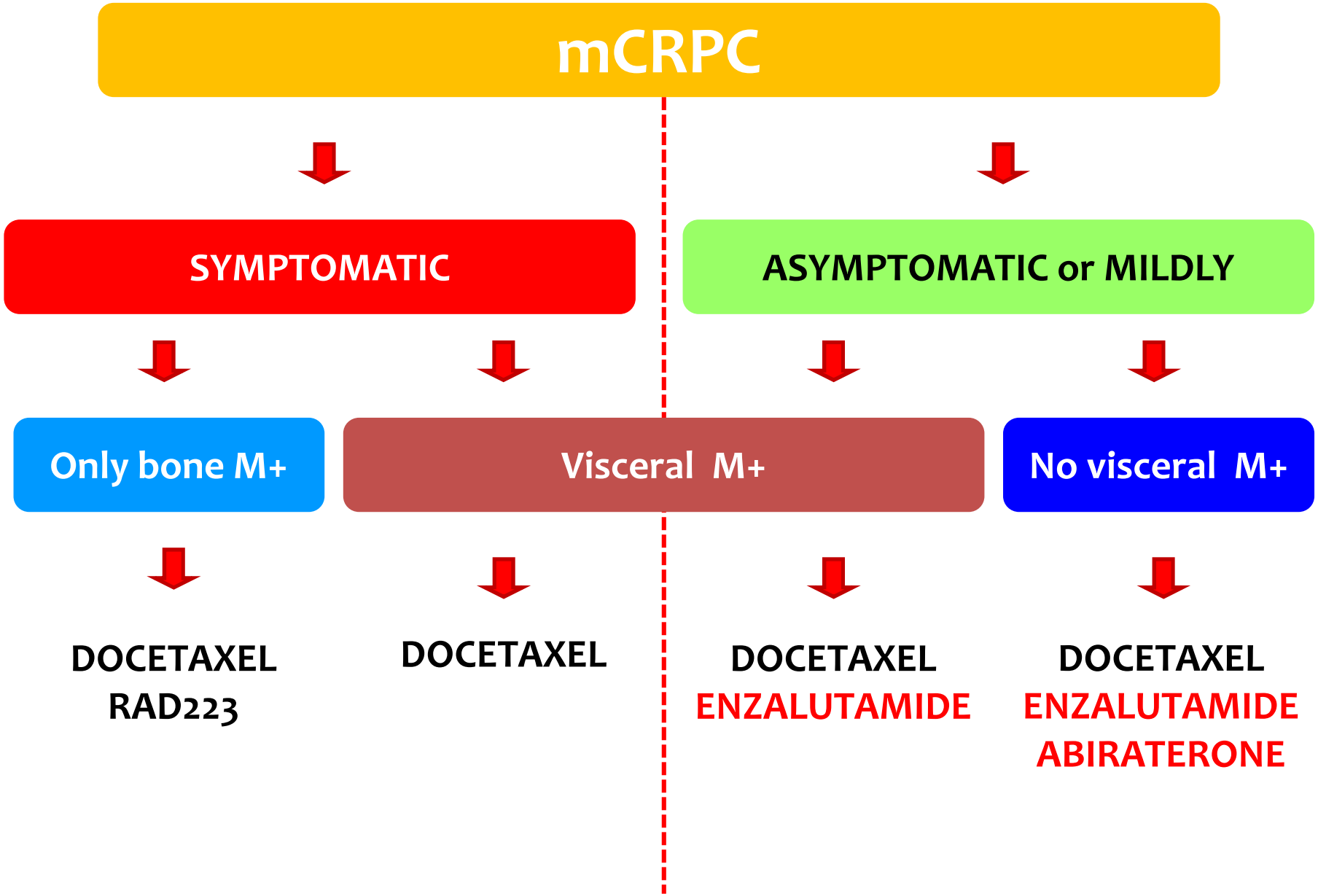
* Plus Prednisone

Summary of mCRPC therapy: chemo-naive pts

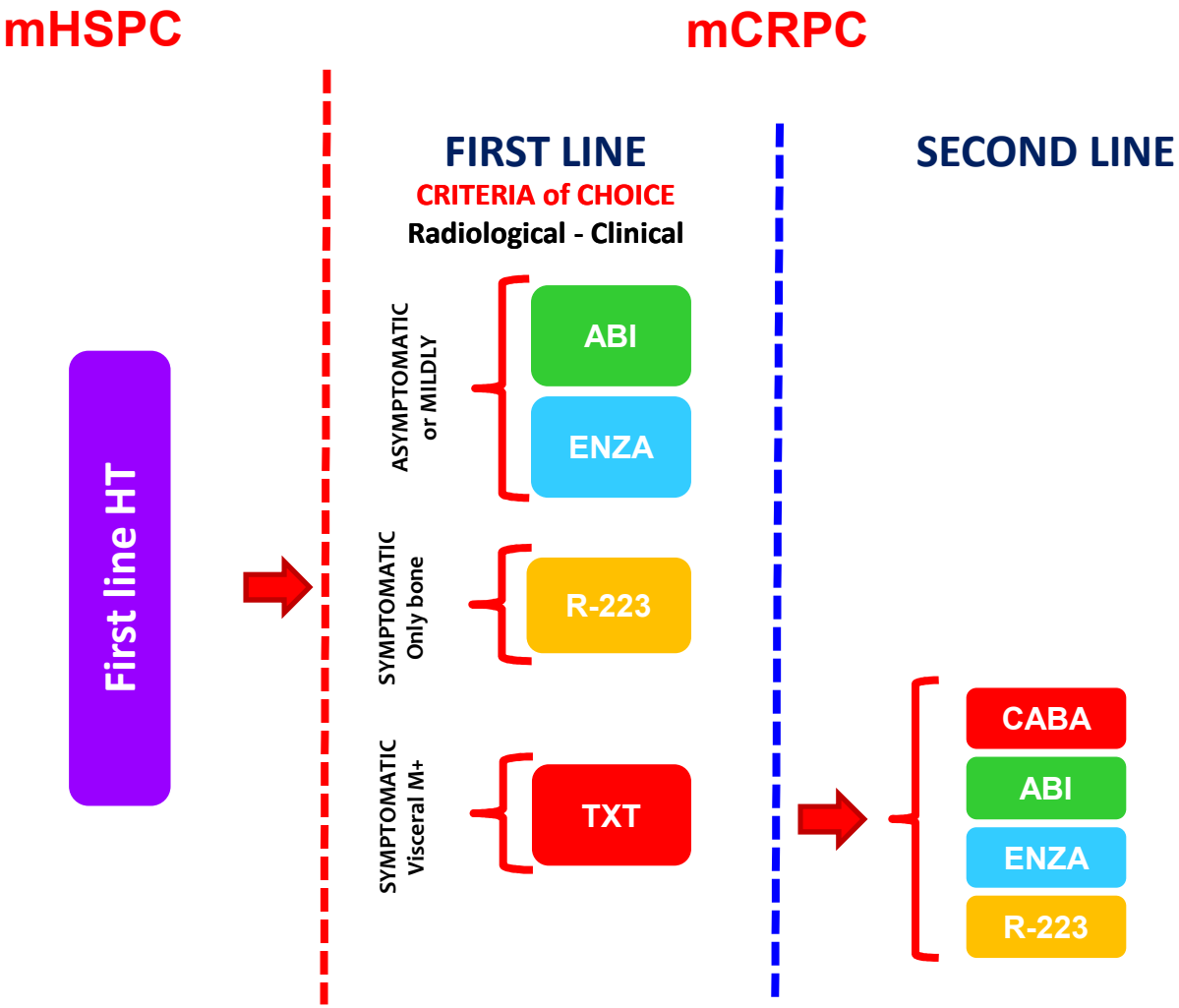


* Plus Prednisone

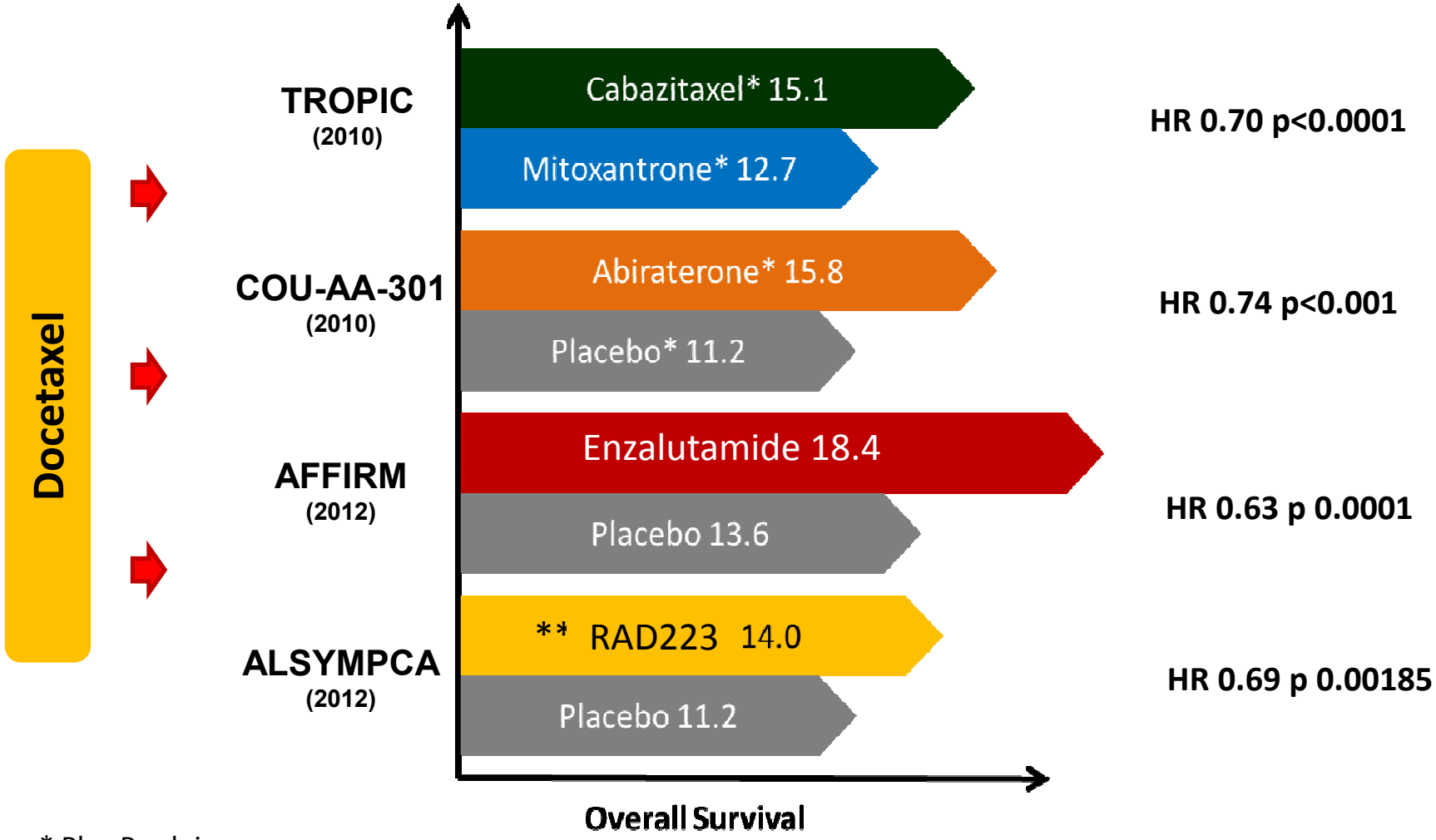
Therapeutic options for mCRPC 2016



Summary of mCRPC therapy



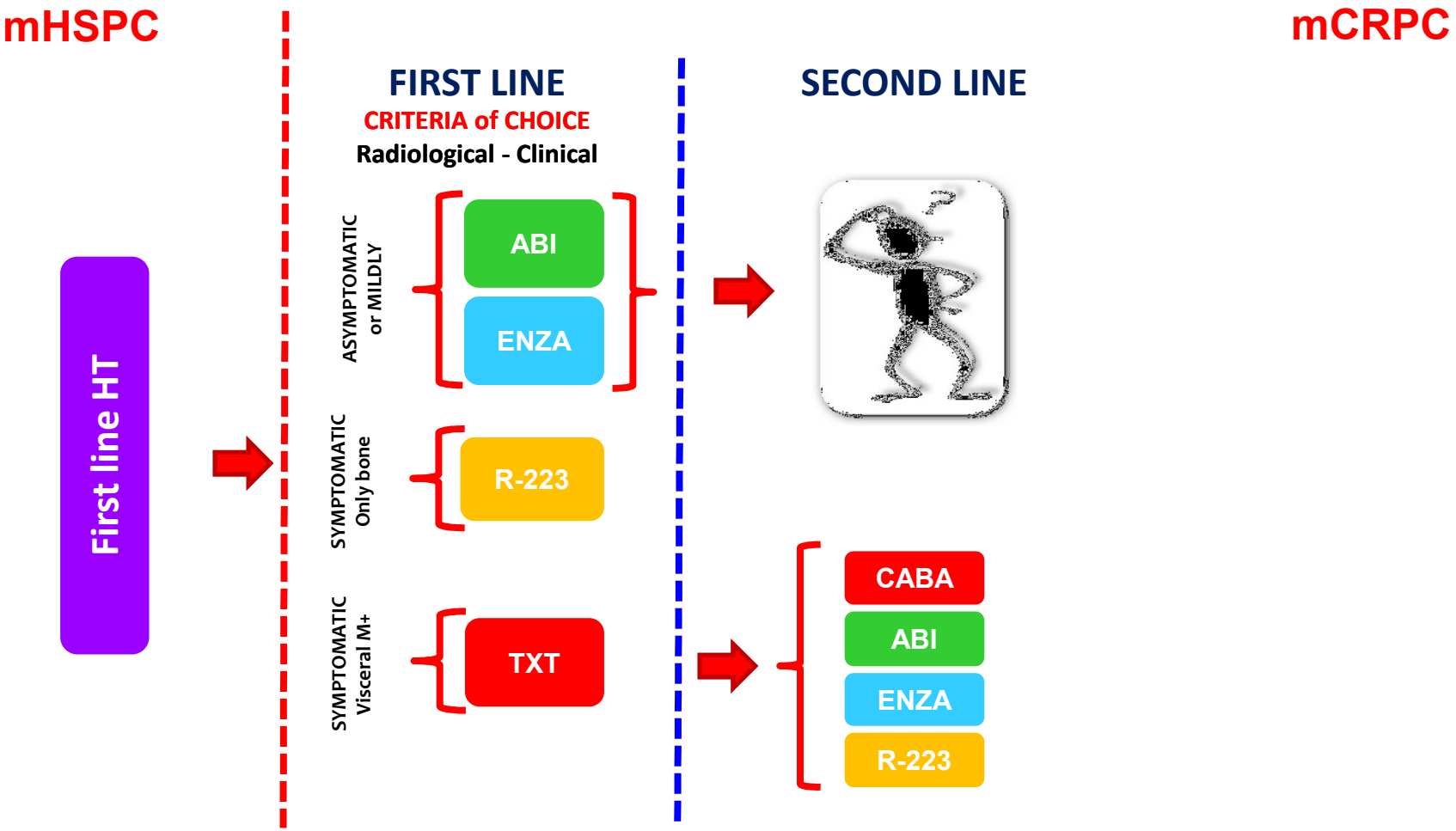
Summary of mCRPC therapy after docetaxel



* Plus Prednisone

** 2 or more bone M+ mCRCP symptomatic; no visceral disease.
pts who had received, were not eligible to receive, or declined docetaxel

Summary of mCRPC therapy

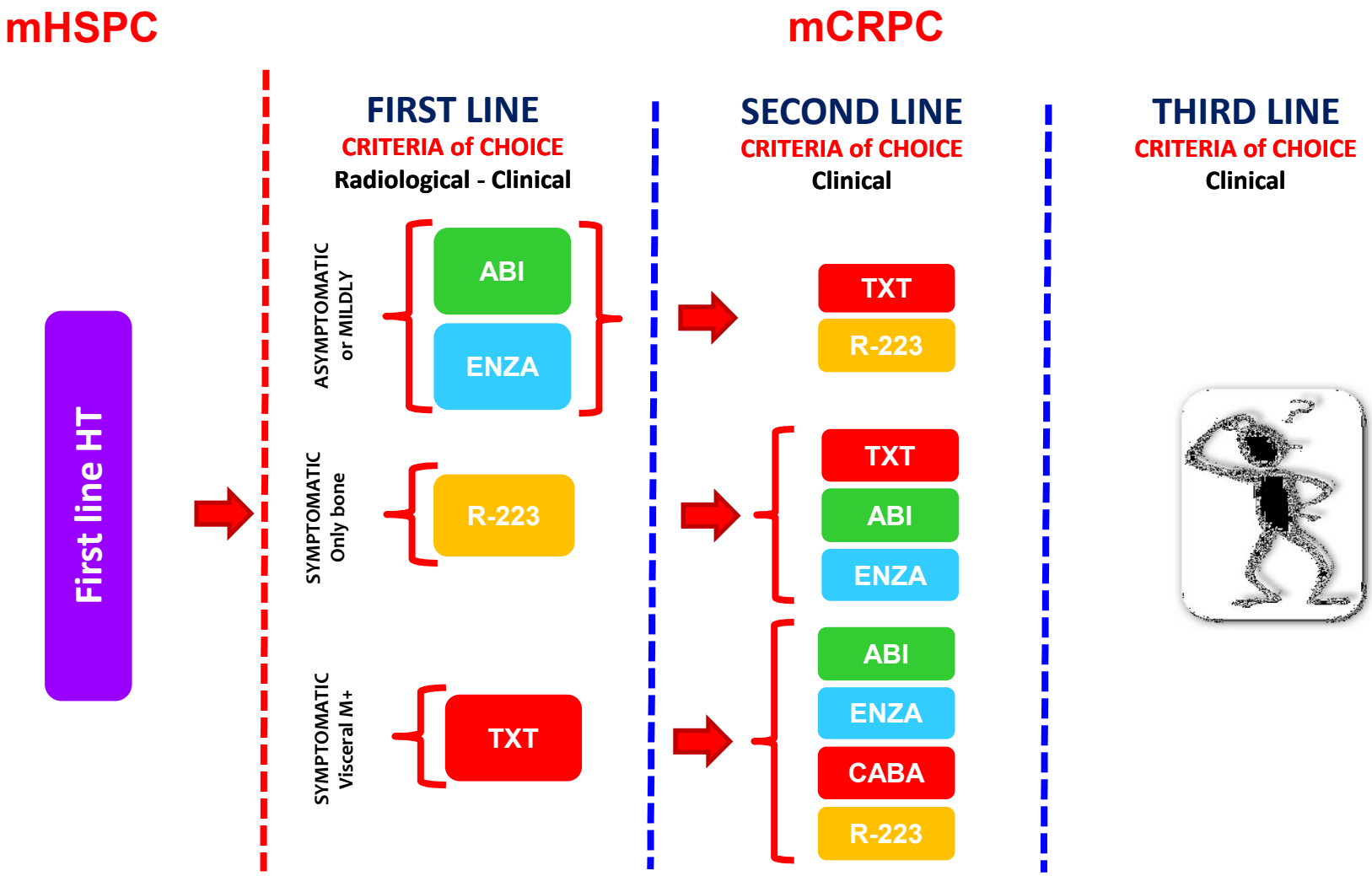


Cross-resistance between abiraterone and enzalutamide

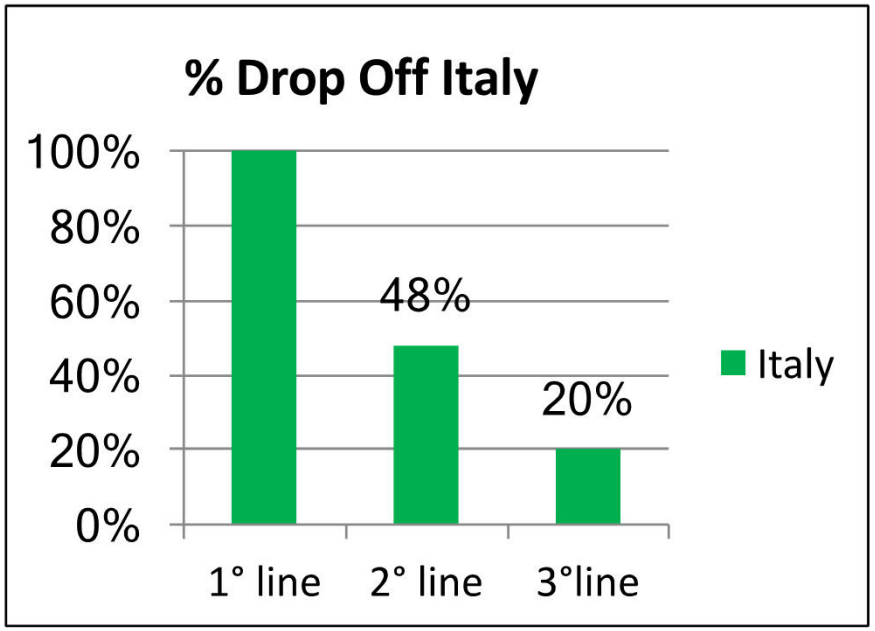
Author	Year published	N pts	Duration of 2nd treatment	↓ PSA ≥ 50%	Median PFS
ENZ → ABI					
Loriot et al.	2013	38	3 mo	8%	2.7 mo
Noonan et al.	2013	30	13 wks	3%	3.6 mo
ABI → ENZ					
Schrader et al.	2013	35	4.9 mo	29%	-
Badrising et al.	2014	61	3 mo	21%	-
Bianchini et al.	2014	39	2.9 mo	23%	-
Schmid et al.	2014	35	2.8 mo	10%	-
Brasso et al.	2014	137	3.2 mo	18%	-

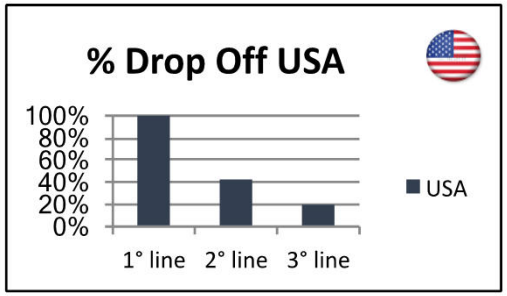
Zhang T et al. Expert Opin Pharmacotherap 2014;16:1-9

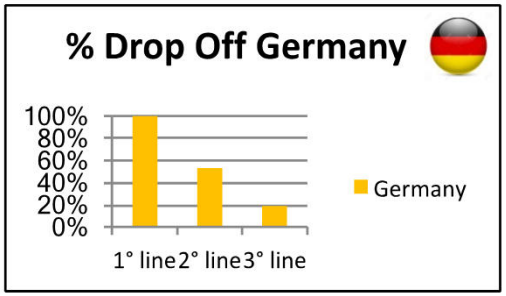
Summary of mCRPC therapy

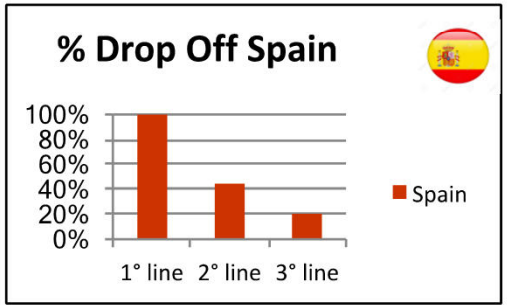


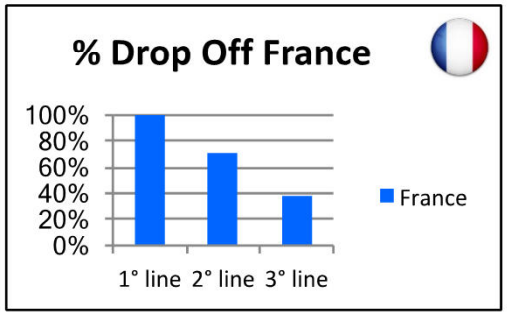
Drop off in daily clinical practice



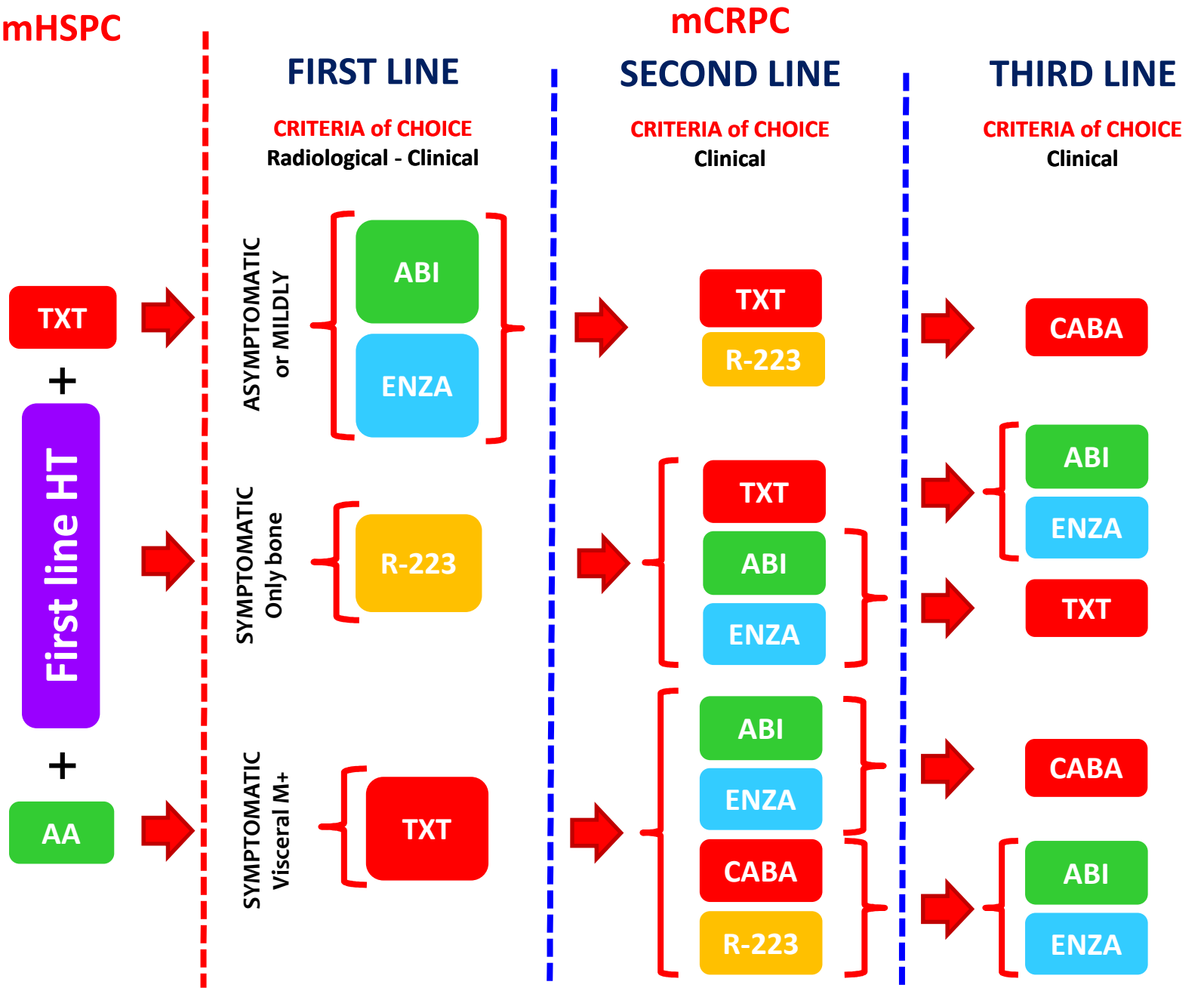








Summary of mCRPC therapy



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Conclusions

(HSPC pts)

- Biochemical or surgical castration represent the standard of care

- ABIRATERONE SHOULD BE DELIVERED:
  - Metastases at diagnosis: synchronous disease.
  - High risk disease (both high and low volume)

- CHEMOTHERAPY SHOULD BE DELIVERED:
  - Metastases at diagnosis: synchronous disease.
  - High volume disease (Visceral metastases or $\geq$ 4 bone lesions with at least one beyond the vertebral bodies and pelvis [Charteed criteria]).

Conclusions

(CRPC pts)

1. In case of M0CRPC, ADT + ENZALUTAMIDE or APALUTAMIDE showed a statistically significant improve of MFS.

2. The therapeutic choice should be driven by radiological visceral presence/absence of M+ and clinical presence/absence of symptoms.

3. ABIRATERONE/ENZALUTAMIDE significantly improve survival outcomes of pts with asymptomatic/mildly symptomatic M+ disease.

4. Cross-resistance between AA and ENZA (20% responders)


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paolo.zucali@humanitas.it