ACTUALIZACION EN EL TRATAMIENTO DEL CPRC

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En los últimos 7 años hemos asistido a una verdadera revolución en el tratamiento del Ca de próstata.

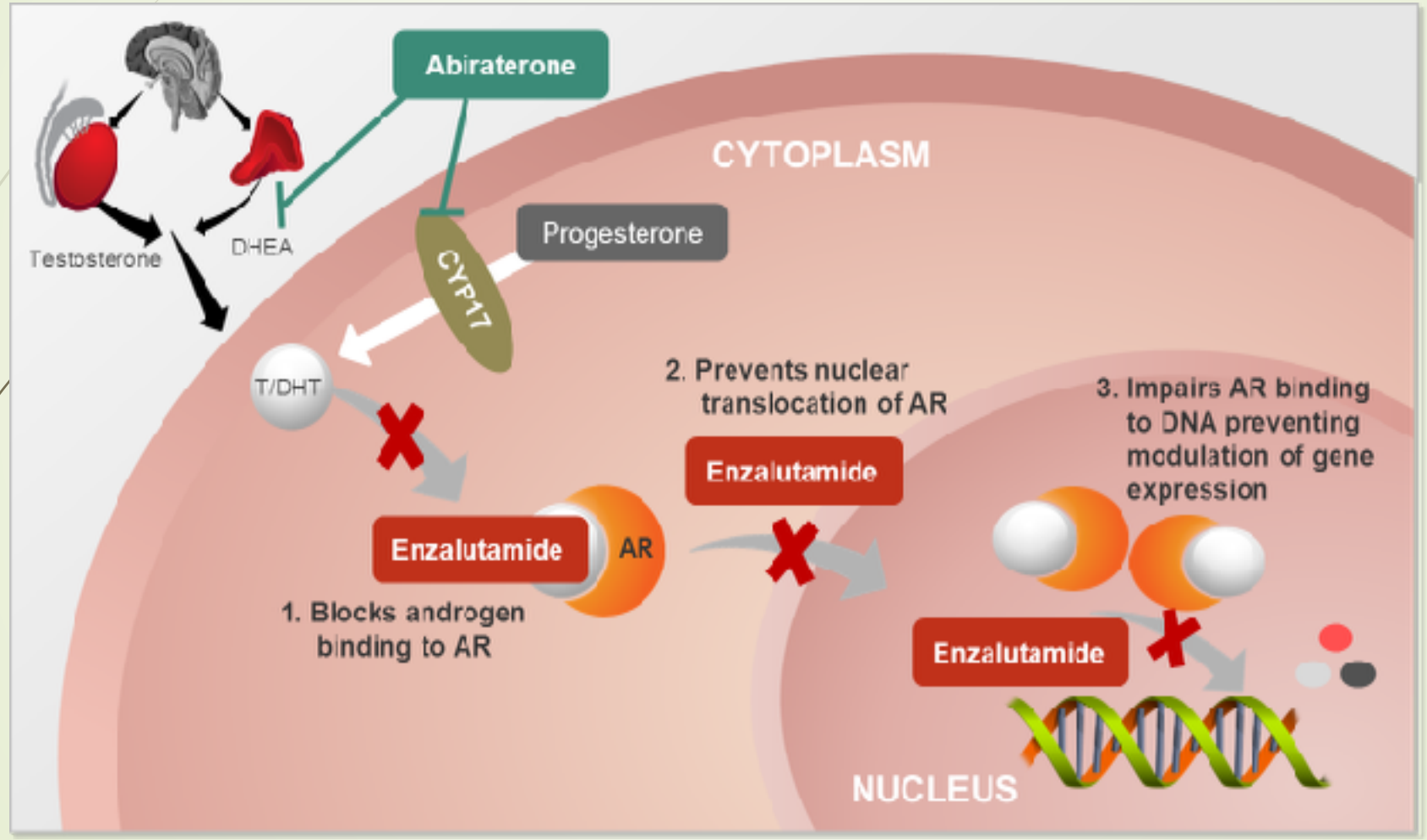
En el año 2013 se publica el resultado del estudio COU-AA-302

En el año 2014 el estudio Prevail pone a nuestro alcance el tratamiento con Enzalutamida para aquellos pacientes con CPRC M+

Table 1: Study characteristics of eight randomized controlled trials for a network meta-analysis

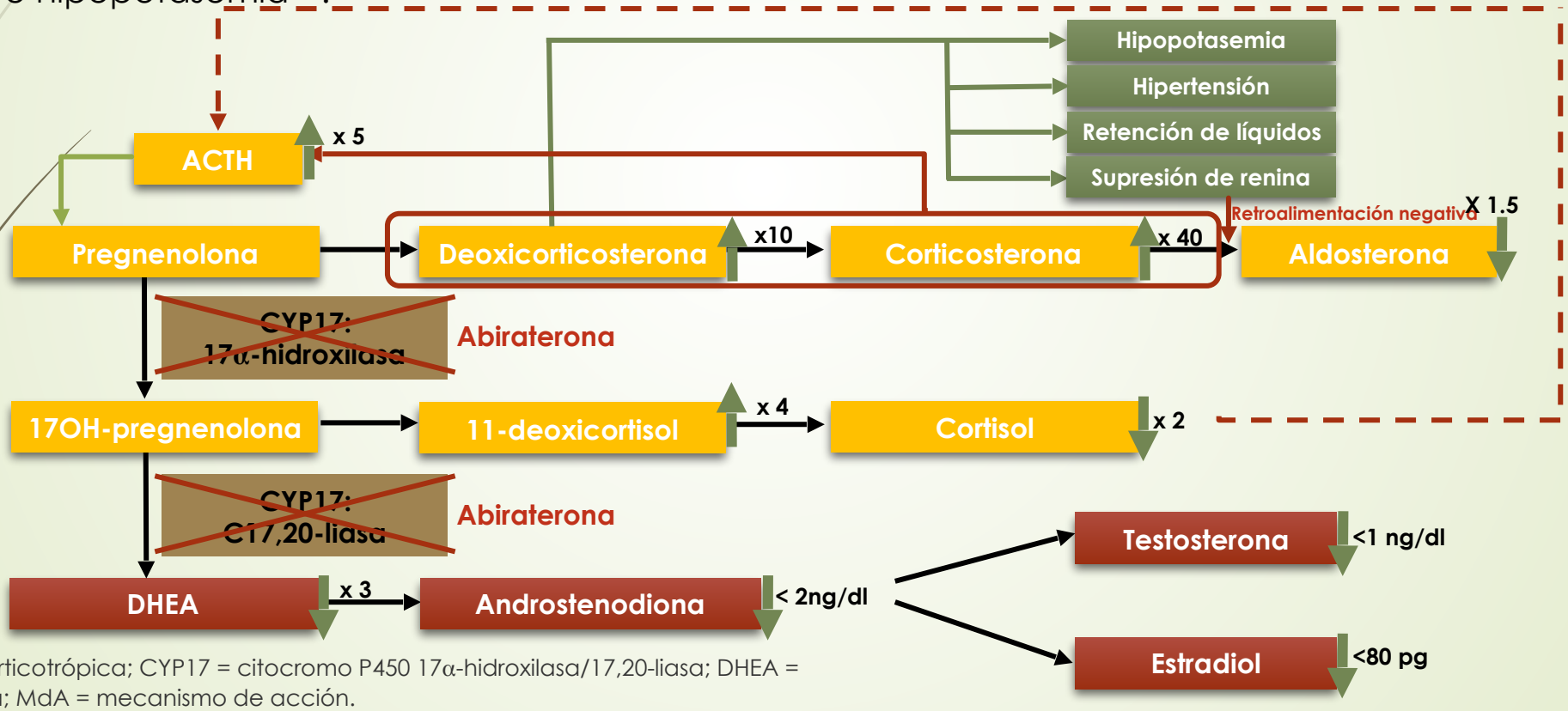
Author [Reference]	Study name	Year	Journal	Treatment arm (N)	Control arm (N)	Treatment setting	Primary endpoint	Median OS (mos)	Median F/U duration (mos)
de Bono [8]	COU-AA-301	2011	NEJM	Abiraterone plus PD (797)	PD (398)	Post-chemotherapy	OS	15.8	20.2
Ryan [10]	COU-AA-302	2013	NEJM	Abiraterone plus PD (545)	PD (542)	Pre-chemotherapy	OS radiographic PFS	34.7	49.2
Scher [9]	AFFIRM	2012	NEJM	Enzalutamide (800)	Placebo (399)	Post-chemotherapy	OS	18.4	14.4
Beer [11]	PREVAIL	2014	NEJM	Enzalutamide (872)	Placebo (845)	Pre-chemotherapy	OS radiographic PFS	32.4	31
Saad [12]	ELM-PC 4	2015	Lancet Oncology	Orteronel plus PD (781)	PD (789)	Pre-chemotherapy	OS radiographic PFS	31.4	20.7
Fizazi [13]	ELM-PC 5	2015	JCO	Orteronel plus PD (734)	PD (365)	Post-chemotherapy	OS	17	10.7
Shore [20]	TERRAIN	2016	Lancet Oncology	Enzalutamide (183)	Bicalutamide (189)	Pre-chemotherapy	PFS	Not reported	20
Penson [21]	STRIVE	2016	JCO	Enzalutamide (198)	Bicalutamide (198)	Pre-chemotherapy	PFS	Not reported	Not reported

ENZALUTAMIDA Y ABIRATERONA INHIBEN LA VÍA DEL SEÑALIZACIÓN DEL RA POR MECANISMOS DISTINTOS.



MECANISMO DE ACCIÓN DE ABIRATERONA

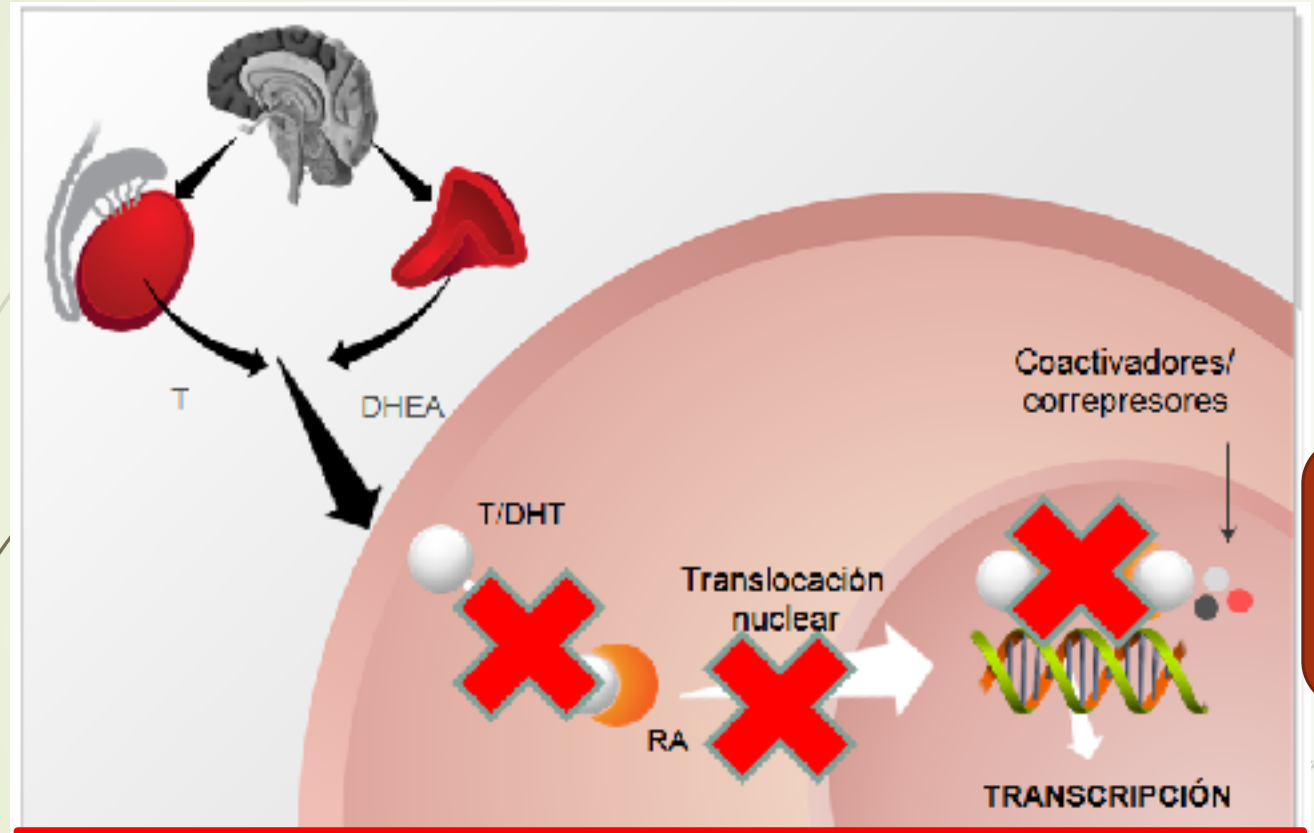
- La inhibición de CYP17 :
  - reduce la síntesis del cortisol y de andrógenos suprarrenales produciendo un **aumento de la hormona estimuladora ACTH[1,2].**
  - El aumento de ACTH puede generar un **exceso de mineralocorticoides**, con síntomas como retención de líquidos, hipertensión e hipopotasemia[1,2].



ACTH = hormona adrenocorticotrópica; CYP17 = citocromo P450 17α-hidroxilasa/17,20-liasa; DHEA = dehidroepiandrostenodiona; MdA = mecanismo de acción.

1. Attard G, *et al. J Clin Oncol* 2008;26:4563–571.
2. Ang JE, *et al. Br J Cancer* 2009;100:671-5.

MECANISMO DE ACCIÓN DE ENZALUTAMIDA



Enzalutamida

- RA como eje del tratamiento.
- NO necesario el uso de **corticoides**

Enzalutamida inhibe la señalización del RA en 3 puntos:

- *Bloquea la unión del andrógeno al receptor*
- *Impide la translocación nuclear*
- *Bloquea la unión y activación al DNA*

RA, receptor androgénico; DHEA, dehidroepiandrosterona; DHT, dihidrotestosterona; T, testosterona

DIFERENCIAS EN LOS CRITERIOS DE ELEGIBILIDAD DE LOS ESTUDIOS COU-AA-302 Y PREVAIL

Categoría	COU-AA-302[1]	PREVAIL[2]
Enfermedad Visceral	**Excluidos**	**Permitidos**
Tensión arterial	Permitidos pacientes con tensión arterial **<160/95**	Permitidos pacientes con tensión arterial **<170/105**
Insuficiencia Cardiaca Congestiva (ICC)	**Excluidos** pacientes con ICC **clase 2**, **3 y 4** según la NYHA (**leve, moderada, grave**).	**Permitidos** pacientes con ICC **clase 3 y 4** según NYHA **(moderada, grave)** si FEVI ≥ 45%
Fibrilación Auricular y cualquier arritmia que requiere tratamiento	**Excluidos**	**Permitidos**

1. Ryan CJ, *et al. N Engl J Med* 2013;368:138-48.
2. Beer TM, et al. N Engl J Med 2014; DOI:. 10.1056/NEJMoa1405095

Asian Journal of Andrology (2016) 18, 1–7

www.asiandrs.com; www.ajandrology.com

Open Access

ORIGINAL ARTICLE

Prostate Disease

Indirect comparison between abiraterone acetate and enzalutamide for the treatment of metastatic castration-resistant prostate cancer: a systematic review

Wei Zhang[1,*], Teng-Yun Wu[2,*], Qi Chen[2], Xiao-Lei Shi[1], Guang-An Xiao[1], Lin Zhao[1], Chuan-Liang Xu[1], Tie Zhou[1], Ying-Hao Sun[1]

Table 1: Summary of adverse events of RCTs

Clinical trial	Study	Subgroup, n	Adverse events, n (%)								
			All grades	Grade 3/4	Fatigue	Liver function abnormalities	Cardiac disorders	Hypertension	Fluid retention	Hypokalemia	Seizures
COU-AA-301	Fizazi *et al.*[15]	All subjects (791)	781 (99.1)	478 (60.4)	372 (47.0)	89 (11.3)	126 (15.9)	88 (11.1)	261 (33.0)	143 (18.1)	-
	Mulders *et al.*[19]	Aged >75 years (218)	218 (100)	132 (60.6)	104 (47.7)		43 (19.7)	20 (9.2)	77 (35.3)	39 (17.9)	
		Aged <75 years (573)	566 (98.8)	346 (60.4)	268 (46.8)	-	83 (11.0)	56 (9.8)	135 (23.6)	104 (18.2)	-
AFFIRM	Scher *et al.*[11]	All subjects (800)	785 (98.1)	362 (45.3)	269 (33.6)	8 (1.0)	49 (6.1)	53 (6.6)	-	-	5 (0.6)
	Sternberg *et al.*[17]	Aged >75 years (199)	198 (99.5)	101 (50.8)	79 (39.7)	-	-	-	44 (22.1)	-	2 (1.0)
		Aged <75 years (601)	587 (97.7)	261 (43.4)	190 (31.6)	-	-	-	75 (12.5)	-	3 (0.5)
COU-AA-302	Ryan *et al.*[18] Ralikopl *et al.*[16]	All subjects (542)	541 (99.8)	290 (53.5)	215 (39.7)	60–65 (11.1–12.0)	126 (23.2)	129 (23.8)	167 (30.8)	101 (18.6)	-
PREVAIL	Beer *et al.*[20]	All subjects (871)		376 (43.1)	310 (35.6)	8 (0.9)	88 (10.1)	117 (13.4)	92 (10.6)		1 (0.1)

RCTs: randomized controlled trials

Table 1. Comparison of common and grade 3 adverse events of enzalutamide and AA in Phase III trials in pre-chemotherapy (PREVAIL and COU-AA-302) and post-chemotherapy (AFFIRM and COU-AA-301) settings, with limitations of extrapolations between the Phase III studies.

	Abiraterone acetate + prednisone		Prednisone		Enzalutamide		Placebo	
	Any grade N (%)	Grade ≥ 3 N (%)	Any grade N (%)	Grade ≥ 3 N (%)	Any grade N (%)	Grade ≥ 3 N (%)	Any grade N (%)	Grade ≥ 3 N (%)
Pre-chemotherapy								
Fatigue	212 (39%)	n/a	185 (34%)	n/a	310 (36%)	16 (2%)	218 (26%)	16 (2%)
Fluid retention/ edema	150 (28%)	4 (< 1%)	127 (24%)	9 (2%)	92 (11%)	2 (< 1%)	69 (8%)	3 (< 1%)
Hypokalemia	91 (17%)	13 (2%)	68 (13%)	10 (2%)	n/a	n/a	n/a	n/a
Hypertension	118 (22%)	21 (4%)	71 (13%)	16 (3%)	117 (13%)	59 (7%)	35 (4%)	19 (2%)
ALT increased	63 (12%)	29 (5%)	27 (5%)	4 (< 1%)	8 (1%)	2 (< 1%)	5 (1%)	1 (< 1%)
Any cardiac	102 (19%)	31 (6%)	84 (16%)	18 (3%)	88 (10%)	24 (3%)	66 (8%)	18 (2%)
Atrial fibrillation	22 (4%)	7 (1%)	26 (5%)	5 (< 1%)	16 (2%)	3 (< 1%)	12 (1%)	5 (1%)
Seizures	0	0	0	0	1 (0.1%)	1 (0.1%)	1 (< 1%)	0
Post-chemotherapy								
Fatigue	346 (44%)	66 (9%)	169 (43%)	39 (10%)	269 (34%)	50 (6%)	116 (29%)	29 (7%)
Diarrhea	139 (18%)	5 (1%)	53 (14%)	5 (1%)	171 (21%)	9 (1%)	70 (18%)	1 (< 1%)
Hot flash/ pyrexia	71 (9%)	3 (< 1%)	35 (9%)	5 (1%)	162 (20%)	0	41 (10%)	0
Fluid retention/ edema	241 (31%)	18 (3%)	88 (22%)	4 (1%)	n/a	n/a	n/a	n/a
Hypokalemia	135 (17%)	30 (4%)	33 (8%)	3 (1%)	n/a	n/a	n/a	n/a
Any cardiac	106 (13%)	26 (3%)	42 (11%)	7 (2%)	49 (6%)	7 (1%)	30 (8%)	8 (2%)
Atrial fibrillation	16 (2%)	n/a	4 (1%)	n/a	n/a	n/a	n/a	n/a
Seizures	0	0	0	0	5 (< 1%)	5 (< 1%)	0	0

AA: Abiraterone acetate.

Zhang et al.Expert Opin. Pharmacother. (2015) 16(4):473-485

SEGURIDAD EN ESTUDIO ENZA VS ABI (ASCO 2017)

	Abiraterone (N=101)		Enzalutamide (N=101)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Hypertension	39 (39%)	21 (21%)	31 (31%)	12 (12%)
Hypokalemia	19 (19%)	1 (1%)	3 (3%)	0 (0%)
Peripheral edema	31 (31%)	0 (0%)	35 (35%)	0 (0%)
Elevated ALT	8 (8%)	5 (5%)	0 (0%)	1 (1%)
Elevated AST	11 (11%)	4 (4%)	0 (0%)	1 (1%)
Fatigue	62 (61%)	5 (5%)	78 (77%)	2 (2%)
Seizure	0 (0%)	0 (0%)	1 (1%)	0 (0%)

Kim N. Chi et al, JCO 2017

HOSPITALIZACIONES POST ABI O ENZA

- BACKGROUND: ENZA and ABI are approved to treat mCRPC in chemotherapy-naïve patients; few real-world analyses exist to compare HA pre- and post-treatment. This study characterized and compared incidence and incidence rate ratios (IRRs) of HA pre/post initiation of ENZA or ABI in chemotherapy-naïve mCRPC patients in the US.
- METHODS: 1603 patients (ENZA, 656; ABI, 947) jan 2014-dec 2015
- RESULTS: IRRs of HA (any position) due ypokalemia, liver toxicity and pneumonia were significantly higher f ents (IRR [95% CI]: 1.63 [1.22–2.17], 1.90 [1.21–2.98], 3.13 [1.46–6.71] -4.10]). IRRs of HA (any position) due to cardiac disorder, dyspnea and y lower in the ENZA cohort than ABI cohort (1.02 vs 1.63, 0.84 vs 1.90, 0
- **CONCLUSIONS:** Incidence rate ratios (IRRs) were significantly lower for ENZA vs ABI treated patients for multiple HA.

MAS HOSPITALIZACIONES POR DESORDENES CARDIACOS, DISPNEA Y HIPOPOTASEMIA CON ABI QUE CON ENZA

Hospital admissions (HA) among chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) patients newly treated with enzalutamide (ENZA) or abiraterone (ABI). J Clin Oncol 35, 2017 (suppl; abstr e16524)

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2017

Published: May 09, 2017

Comparing the clinical efficacy of abiraterone acetate, enzalutamide, and orteronel in patients with metastatic castration-resistant prostate cancer by performing a network meta-analysis of eight randomized controlled trials

Minyong Kang[1], Chang Wook Jeong[2], Cheol Kwak[2], Ja Hyeon Ku[2,*], Hyeon Hoe Kim[2,*]

- **No se ha alcanzado un consenso sobre cual de los tres nuevos antiandrógenos proporcionaría mejores resultados oncológicos favorables.**
- **El objetivo de este estudio es comparar la eficacia de Enzalutamida, Abiraterona y Orteronel en pacientes con CPRCm**

  - Metanálisis de 8 estudios randomizados (COU-AA-301/2, AFFIRM, PREVAIL, TERRAIN, STRIVE, ELM-PC 4/5)

  Objetivo primario: **SG**

  Objetivos secundarios:

  - ✓ **SLP**
  - ✓ **Respuesta de PSA**
  - ✓ **Tiempo hasta progresión de PSA**
  - ✓ **Tiempo hasta el 1er evento óseo**

Kang et al. Oncotarget 2017

with improved OS compared with control arms. Enzalutamide was ranked as the most efficacious agent for improving OS (hazard ratio [HR] = 0.71), and abiraterone appeared to be the second-most efficacious drug for this purpose (HR = 0.78). Enzalutamide improved PFS in comparison with control groups (HR = 0.36), but abiraterone and orteronel were not significantly associated with PFS improvements. Enzalutamide (HR = 0.20) and abiraterone (HR = 0.56) were significantly associated with prolonged times to PSA progression as compared with control groups. However, only orteronel was associated with an increased risk of AEs as compared with control groups. In summary, our study can help to guide treatment selection, especially because AR-targeted agents have not been compared directly in head-to-head trials.

- **Enzalutamida se clasificó como el agente mas eficaz en mejorar la SG, HR = 0,71; Abiraterona en segunda posición, HR = 0,78**
- **Enza y Abi** se asociaron significativamente a prolongación del **Tiempo de Progresión de PSA**
- **Orteronel** se asoció a un incremento del **riesgo de AEs**

Kang et al. Oncotarget 2017

A randomized phase II cross-over study of abiraterone + prednisone vs enzalutamide for patients with metastatic, castration-resistant prostate cancer

Kim N. Chi, Matti Annala, Katherine Sunderland, Daniel Khalaf, Daygen Finch, Conrad D. Oja, Joanna Vergidis, Muhammad Zulfiqar, Kevin Beja, Gillian Vandekerkhove, Martin Gleave, Alexander W. Wyatt

British Columbia Cancer Agency, Vancouver, BC; Institute of Biosciences and Medical Technology, Tampere, Finland; BC Cancer Agency - Vancouver Centre, Vancouver, BC; BC Cancer Agency - Centre for the Southern Interior, Kelowna, BC; British Columbia Cancer Agency, Fraser Valley Centre, Vancouver, BC; British Columbia Cancer Agency, Vancouver Island Centre, Victoria, BC; BC Cancer Agency, Abbotsford, BC; Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC; Vancouver Prostate Centre, University of British Columbia, Vancouver, BC

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Presented By Kim Chi at 2017 ASCO Annual Meeting

Background

- Abiraterone + prednisone and enzalutamide are indicated as first-line therapy for mCRPC
  - Have not been directly compared
  - Optimal treatment sequencing not evaluated prospectively
  - Need for predictive biomarkers

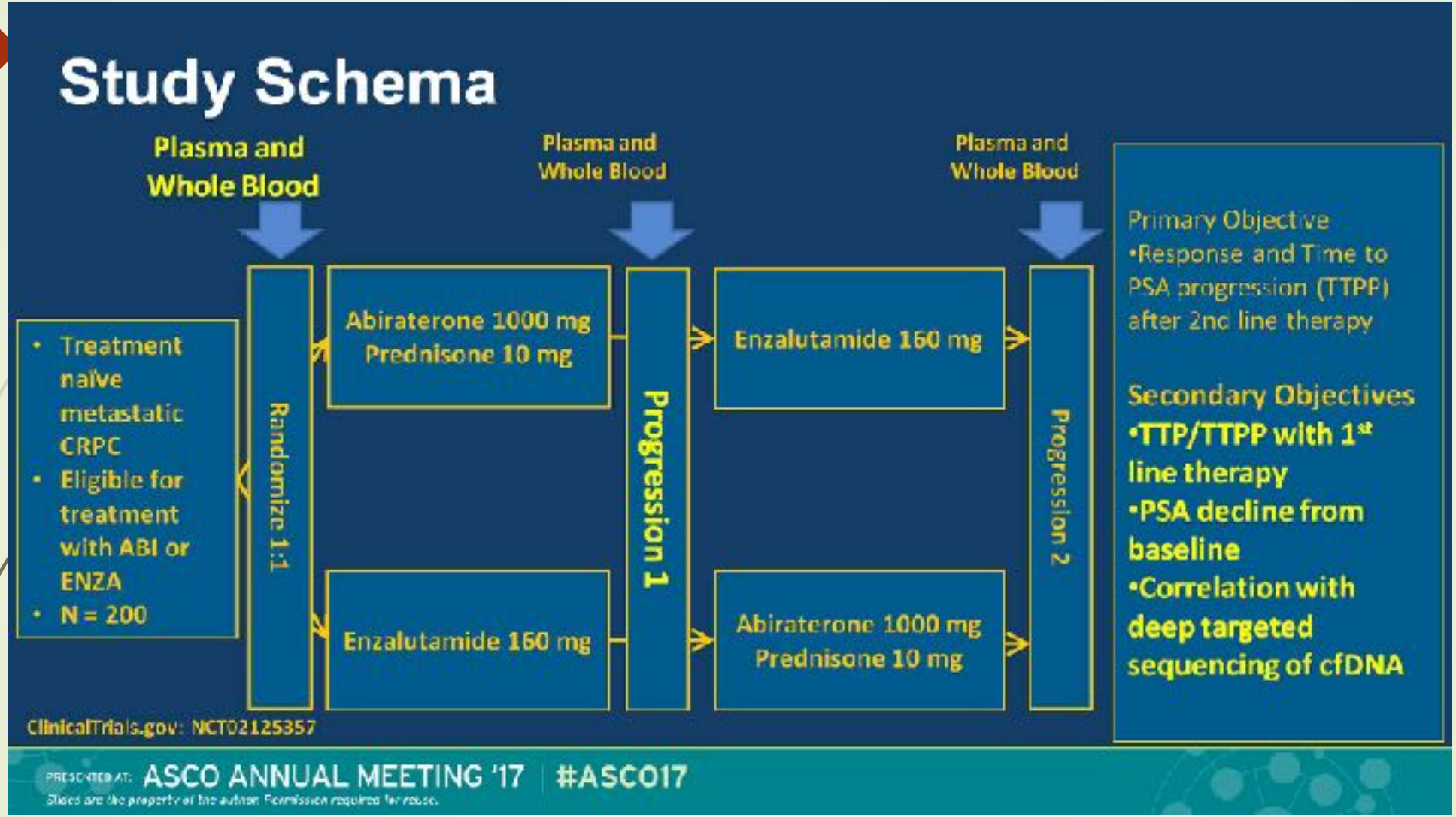
Background

- ctDNA in metastatic CRPC
  - Abundant
    - Median ctDNA fraction of 29% (0 - 95%)
    - Over 75% of patients have >2% ctDNA

      SU2C/PCF Dream Team study, AW Wyatt et al, In Press
  - Representative of the mutational landscape
    - 100% of driver mutations in matched tissue biopsies also identified in ctDNA

      SU2C/PCF West Coast Dream Team study, AW Wyatt et al, In Press
  - Detection of AR and non-AR genomic aberrations has been correlated with outcomes in cohorts of CRPC patients treated with abiraterone and enzalutamide

    AW Wyatt, JAMA Oncol 2016, 2 1598, AA Azad et al, Clin Cancer Res 2015, 21 2315, A Romanel, Sci Transl Med 2015, 7 312re10



Presented By Kim Chi at 2017 ASCO Annual Meeting

Methods: Circulating Tumor DNA

- Targeted sequencing: all patients
  - Plasma cell free DNA and germline (WBC)
  - 73 CRPC-related genes (all exons) including
    - Prostate cancer drivers (e.g. AR, SPOP, NKX3.1, FOXA1)
    - Cell cycle (e.g. TP53, RB1, CDKN1B, CDKN2A)
    - DNA repair (e.g. BRCA1/2, FANC family genes, ATM, MSH2/6)
    - PI3K pathway (e.g. PIK3CA, PTEN, AKT1)
- AR gene sequencing (exons, introns, flanking regions) to detect AR gene rearrangements
- Whole exome sequencing in patients with >20% ctDNA

Baseline Characteristics

Characteristic	1st-Line Abiraterone + P N = 101	1st-Line Enzalutamide N = 101	P-value
Median Age, years (range)	72.9 (51.3 - 93.3)	77.6 (49.3 - 94.1)	0.01
ECOG PS			0.09
0-1	89 (88%)	79 (78%)	
2	12 (12%)	22 (22%)	
Median PSA, ug/L (range)	35.0 (2.2 – 2817)	37.0 (1.7 – 1060)	
Median Hemoglobin, g/L (range)	130 (89 – 155)	130 (89 – 165)	1.0
Alkaline Phosphatase > ULN	34 (34%)	35 (35%)	1.0
LDH > ULN	17 (17%)	22 (22%)	0.38
Site of Metastases			0.82
Lymph Node	38 (38%)	44 (44%)	
Bone	96 (95%)	83 (82%)	
Liver and/or Lung	12 (12%)	15 (15%)	
cfDNA yield, ng/ml (range)	12.4 (1.5 – 258)	13.3 (1.5 – 3871)	0.42
ctDNA quantifiable ≥2%	56 (55%)	59 (58%)	0.84

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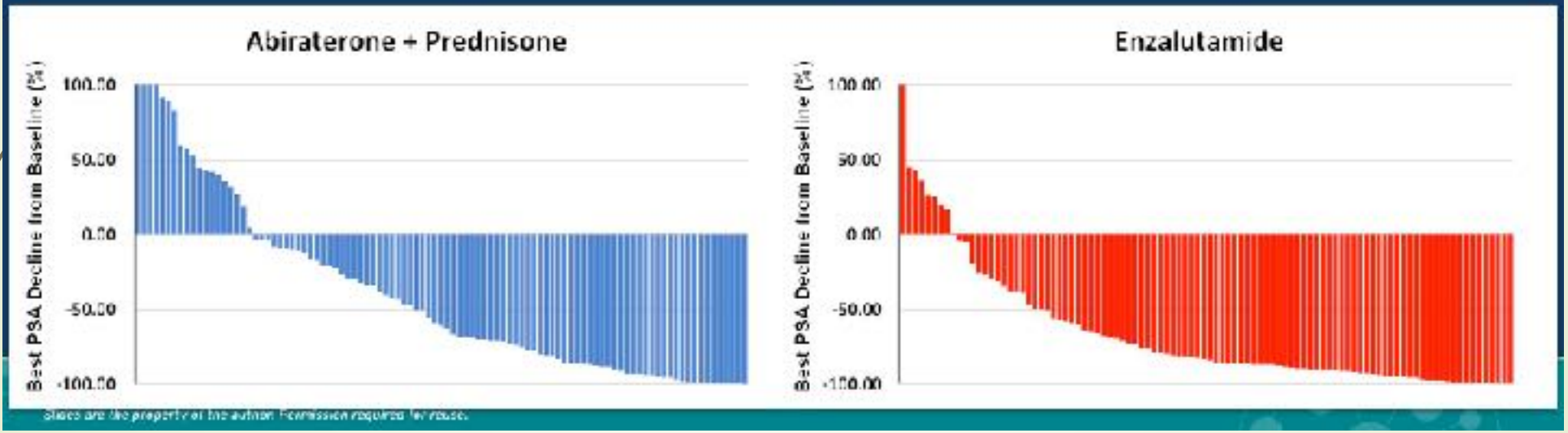
Best PSA decline: 12 weeks

	Abiraterone + P N=99	Enzalutamide N=98	P-value
PSA Decline ≥ 30%	64 (65%)	83 (85%)	0.0012
PSA Decline ≥ 50%	54 (55%)	75 (77%)	0.0012
No PSA Decline	20 (20%)	10 (10%)	0.0501



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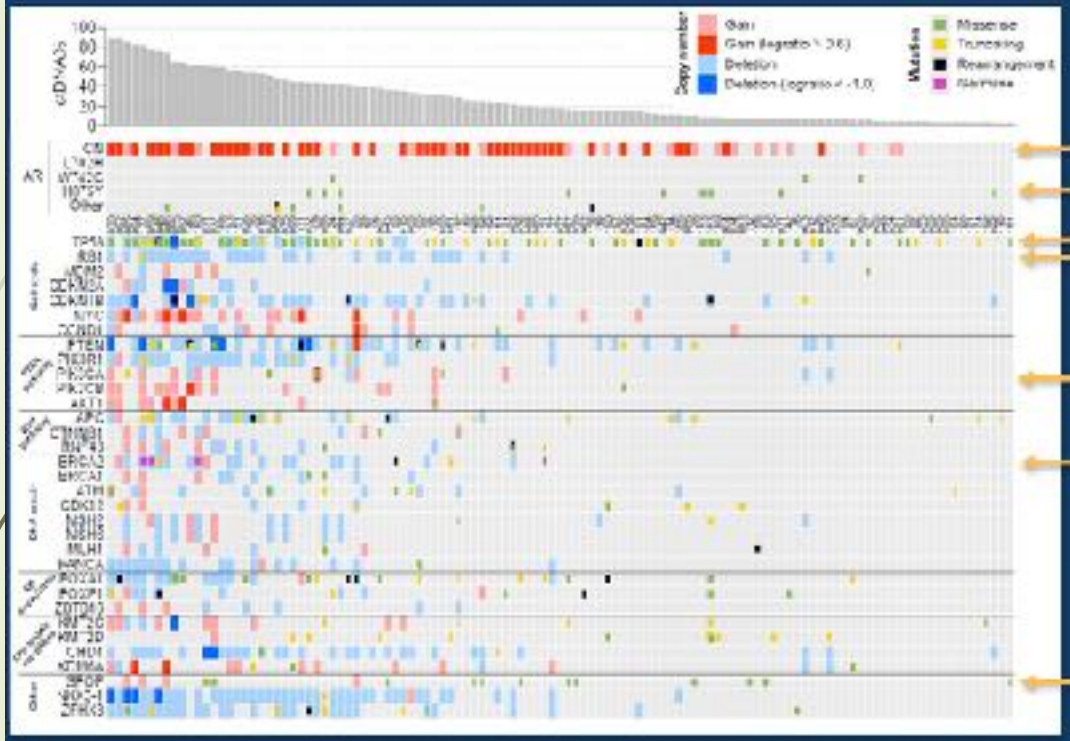
Genomic Landscape at Baseline

Somatic landscape among patients with quantifiable ctDNA (n=115) was consistent with previous studies



***AR* amplification = 56.5%**

***AR* mutation = 12.2%**

***TP53* mutation/rearrangement/deletion = 58.5%**

***RB1* mutation/rearrangement/deletion = 28.7%**

PI3K pathway = 49.6%
(PTEN deletion or truncation/PIK3R1 deletion or truncation/PIK3CA hotspot mutation/AKT1 hotspot mutation)

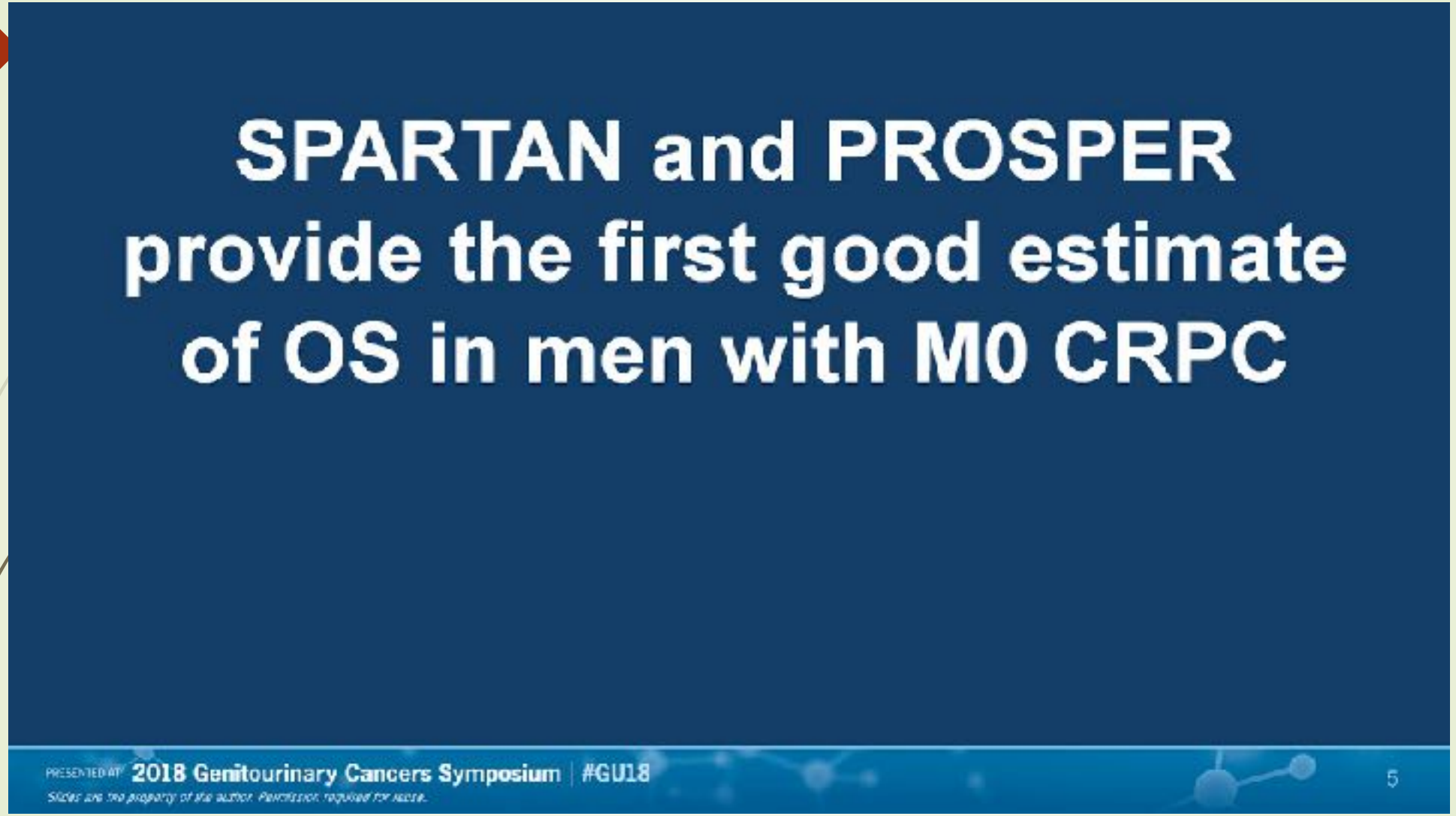
***BRCA2* or *ATM* *somatic* truncating mutation = 5.2%**
***BRCA2* or *ATM* *germline* truncating mutation = 4%**
(8 of 202 patients)

***SPOP* mutations = 10.4%**

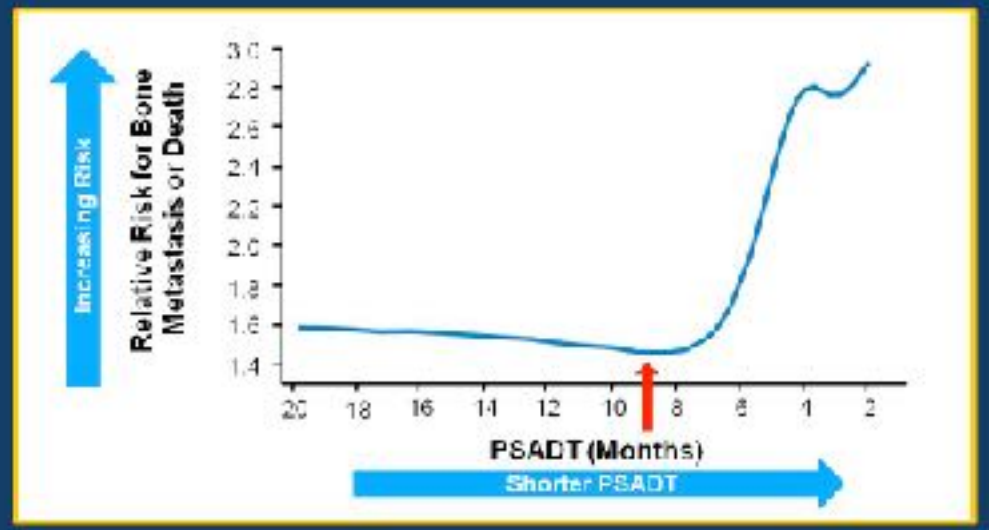
Presented By Kim Chi at 2017 ASCO Annual Meeting

Conclusions

- Higher PSA response with enzalutamide compared to abiraterone + prednisone but with no difference in time to progression or time to PSA progression
- Detection of ctDNA was associated with measures of tumour burden and poor outcomes
- Genomic alterations in *BRCA2/ATM*, *TP53*, PI3K pathway, *RB1*, and *AR* were associated with earlier progression and primary resistance
- In multivariate analyses including clinical factors, *BRCA2/ATM*, *TP53* and *PI3K* pathway alterations remained significantly associated with shorter TTP
- *AR* genomic structural rearrangements encoding for truncated AR are detectable in ctDNA from treatment naïve mCRPC and may identify primary resistant disease


SPARTAN and PROSPER provide the first good estimate of OS in men with M0 CRPC
PRESENTED AT 2018 Genitourinary Cancers Symposium | #GU18
5

We know that men who have a more rapid PSADT develop metastases sooner



In SPARTAN (71%) and PROSPER (77%) had PSADT <6 months therefore patients rapidly progressing

PSADT (%)			
≤ 6 mos	71	71	S
> 6 mos	29	29	

PSADT (%)			
< 6 mos	77	77	P
≥ 6 mos	23	23	

Smith et al J. Clin Onc 2013

Presented By Philip Kantoff at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

SPARTAN, a Phase 3 Double-Blind, Randomized Study of Apalutamide vs Placebo in Patients With Nonmetastatic Castration-Resistant Prostate Cancer

Eric J. Small,[1] Fred Saad,[2] Simon Chowdhury,[3] Boris A. Hadaschik,[4] Julie N. Graff,[5] David Olmos,[6] Paul N. Mainwaring,[7] Hiroji Uemura,[8] Angela Lopez-Gitlitz,[9] Géralyn C. Trudel,[9] Byron M. Espina,[9] Youyi Shu,[9] Youn C. Park,[9] Wayne R. Rackoff,[9] Margaret K. Yu,[9] Matthew R. Smith,[10] on behalf of the SPARTAN Investigators

[1]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [2]Centre Hospitalier de l'Université de Montréal, Université de Montréal, Montréal, Québec, Canada; [3]Guy's, King's and St. Thomas' Hospitals, Great Maze Pond, London, UK; [4]University of Duisburg-Essen, Essen, Germany; [5]VA Portland Health Care System, Portland, and Knight Cancer Institute, Oregon Health & Science University, Portland, OR; [6]Spanish National Cancer Research Centre (CNIO), Madrid, and Hospitales Universitarios Virgen de la Victoria y Regional de Málaga, Málaga, Spain; [7]Centre for Personalised Nanomedicine, University of Queensland, Brisbane, Australia; [8]Yokohama City University Medical Center, Yokohama, Japan; [9]Janssen Research & Development, Los Angeles, CA; [10]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA

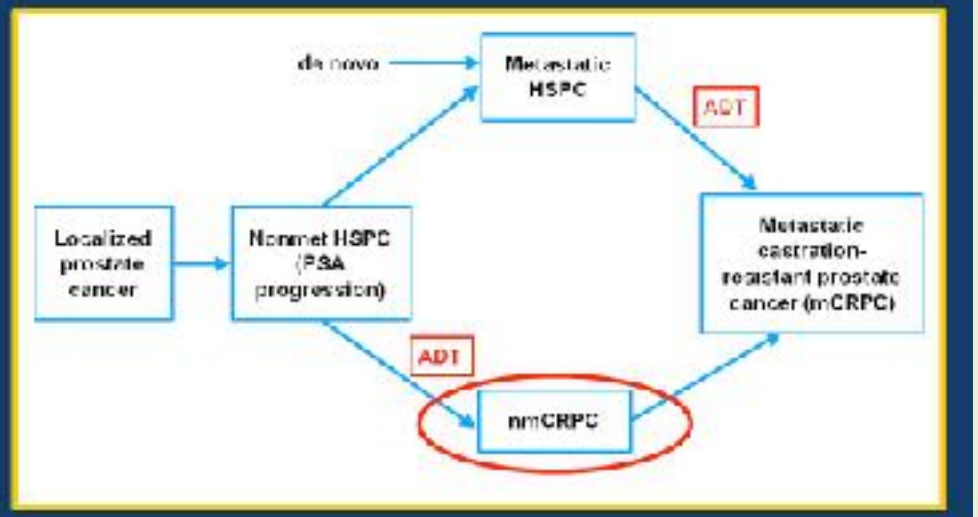
PRESENTED AT: 2018 Genitourinary Cancers Symposium | #GU18

Presented by: Eric Small, MD, FASCO

Presented By Eric Small at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

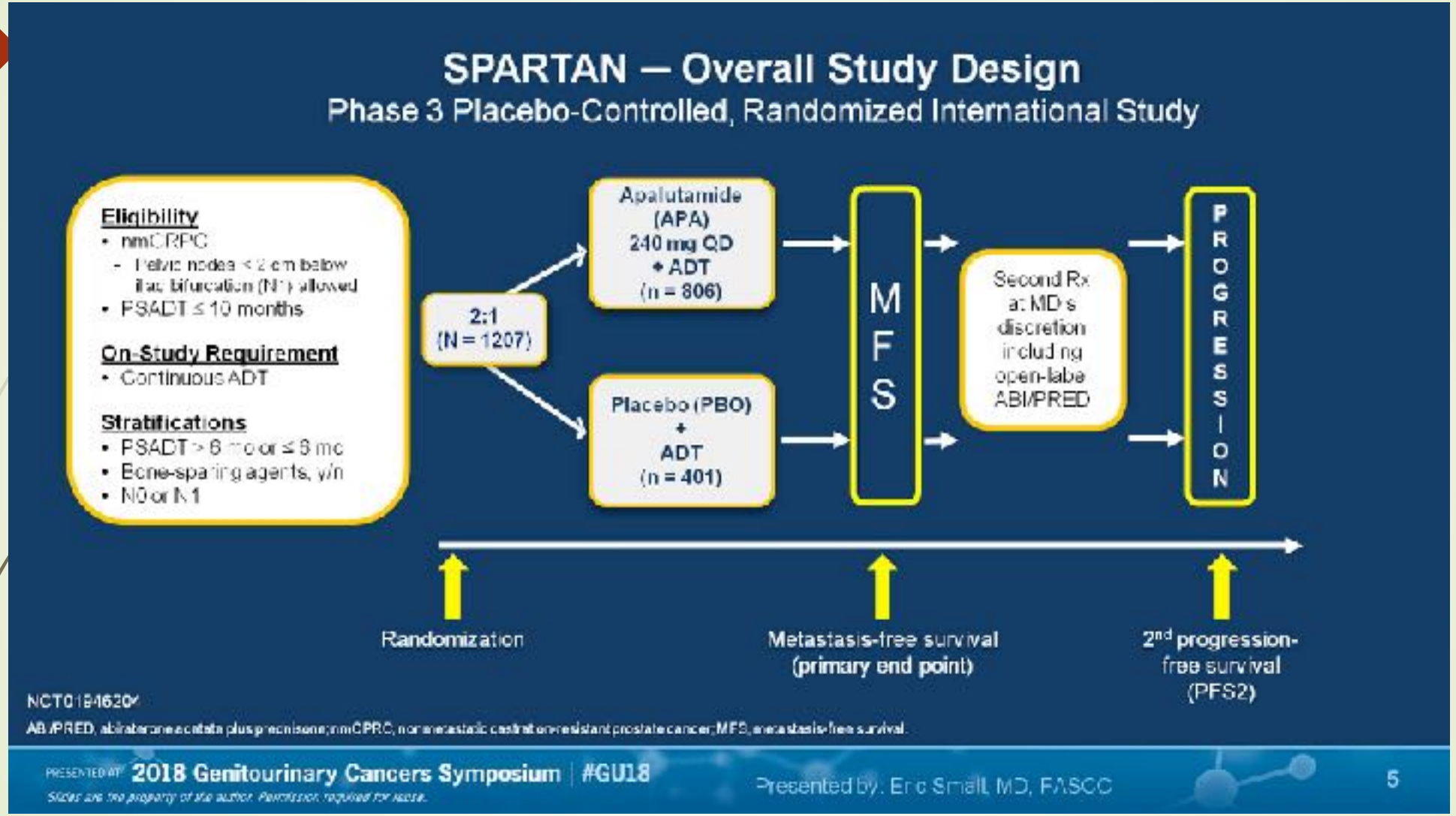
Background

- Metastatic castration-resistant prostate cancer (mCRPC) is a uniformly fatal disease, with a median survival of ~2.5 years[1]
- mCRPC can develop from:
  - a) Metastatic hormone-sensitive prostate cancer (HSPC) that has developed resistance to androgen deprivation therapy (ADT)
  - b) Nonmetastatic prostate cancer that has developed resistance to ADT, termed nmCRPC[2]



1. Ryan CJ. Lancet Oncol. 2015;16:152-160.
2. Dai C, et al. Cold Spring Harb Perspect Med. 2017;7:pii:a030452.

Presented By Eric Small at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care



Presented By Eric Small at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

Primary End Point: Metastasis-Free Survival

72% risk reduction of distant progression or death

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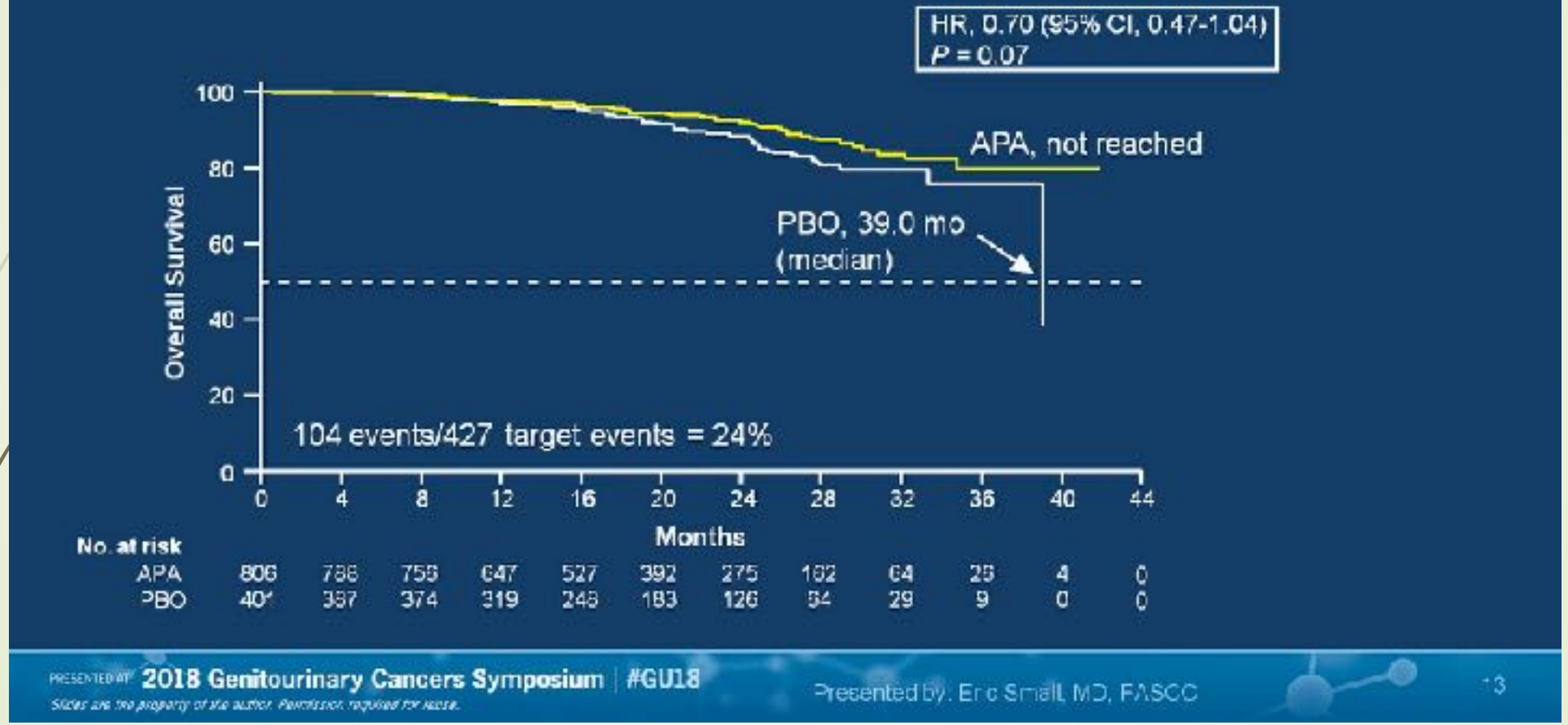
Secondary End Point: Overall Survival

30% risk reduction of death



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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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Conclusions

- Apalutamide decreased the risk of metastasis or death by 72%, and prolonged the median MFS by more than 2 years in men with high-risk nmCRPC
- The MFS benefit was consistently seen across all subgroups
- These results are supported by consistent improvement across all evaluable end points
  - Time to metastasis
  - Progression-free survival
  - Time to symptomatic progression
  - Time to PSA progression
  - PSA decline

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Conclusions

- Apalutamide was associated with a 30% reduction in risk of death at this early interim analysis for survival (p = NS)
- The majority of placebo patients received an approved second therapy
- Apalutamide resulted in a 51% risk reduction in PFS2 even in the face of a high rate of secondary ASI use in the placebo arm
- The addition of apalutamide to ADT was well tolerated, with maintained HRQoL
- Overall, these data suggest that apalutamide should be considered as a new standard of care for men with high-risk nmCRPC

NS, non-significant

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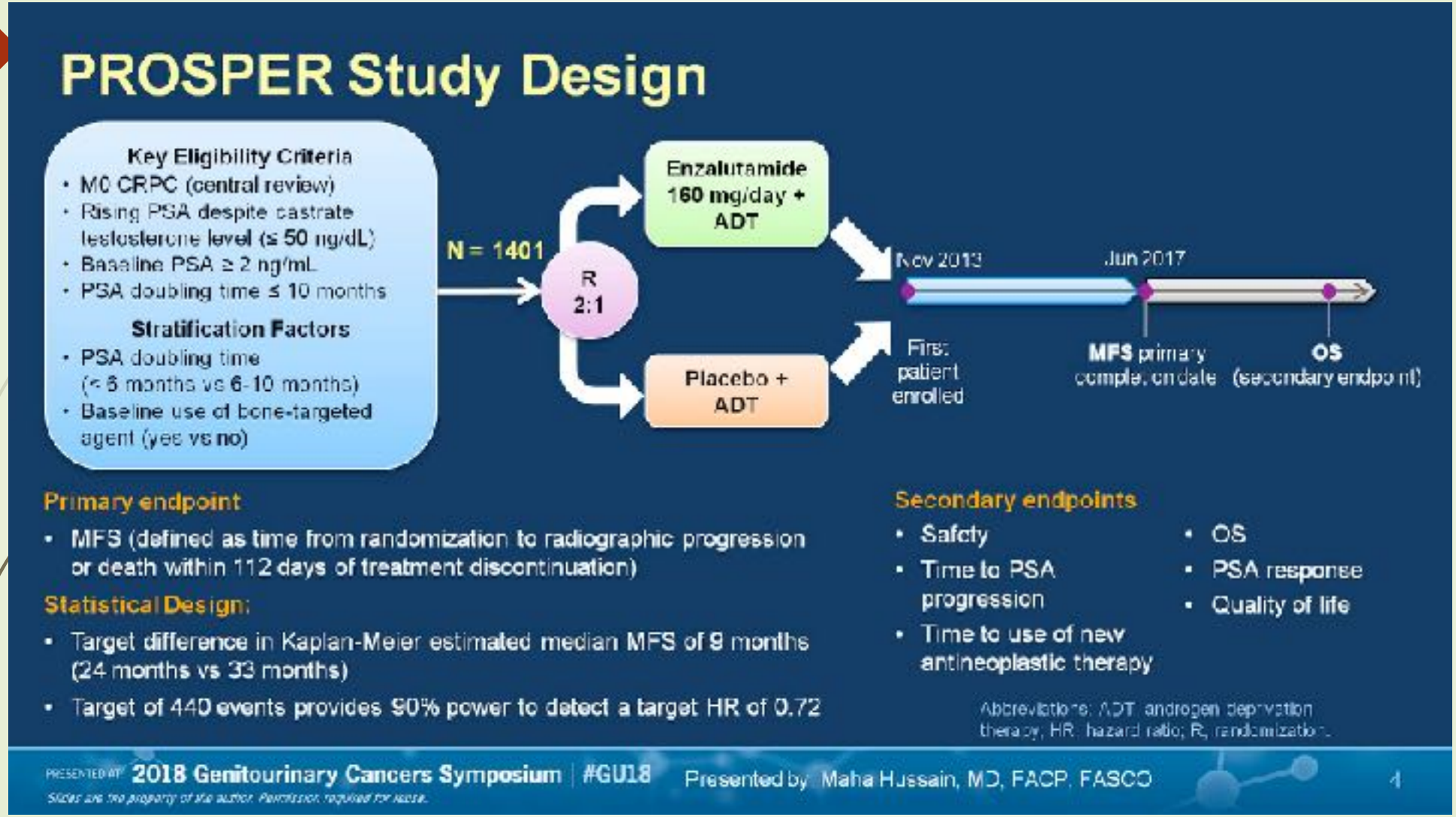

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Baseline Patient Characteristics (N = 1401)

Characteristic	Enzalutamide + ADT (n = 933)	Placebo + ADT (n = 468)
Median age (range), y	74 (50-95)	73 (53-92)
ECOG PS, no. (%)		
0	747 (80%)	382 (82%)
1	185 (20%)	85 (18%)
Median serum PSA (range), ng/mL	11.1 (0.8-1071.1)	10.2 (0.2-467.5)
Median PSA doubling time (range), mo	3.8 (0.4-37.4)	3.6 (0.5-71.8)
PSA doubling time category, no. (%)		
< 6 mo	715 (77%)	361 (77%)
≥ 6 mo	217 (23%)	107 (23%)
Baseline use of bone targeting agent, no. (%)		
No	828 (89%)	420 (90%)
Yes	105 (11%)	48 (10%)

- Median duration of therapy was 18.4 (range, 0-41.9+) months for enzalutamide and 11.1 (range, 0-42.8+) months for placebo
- Patients on treatment as of 28 June 2017 (cutoff date): 534 patients (68%) on enzalutamide and 176 patients (38%) on placebo

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status

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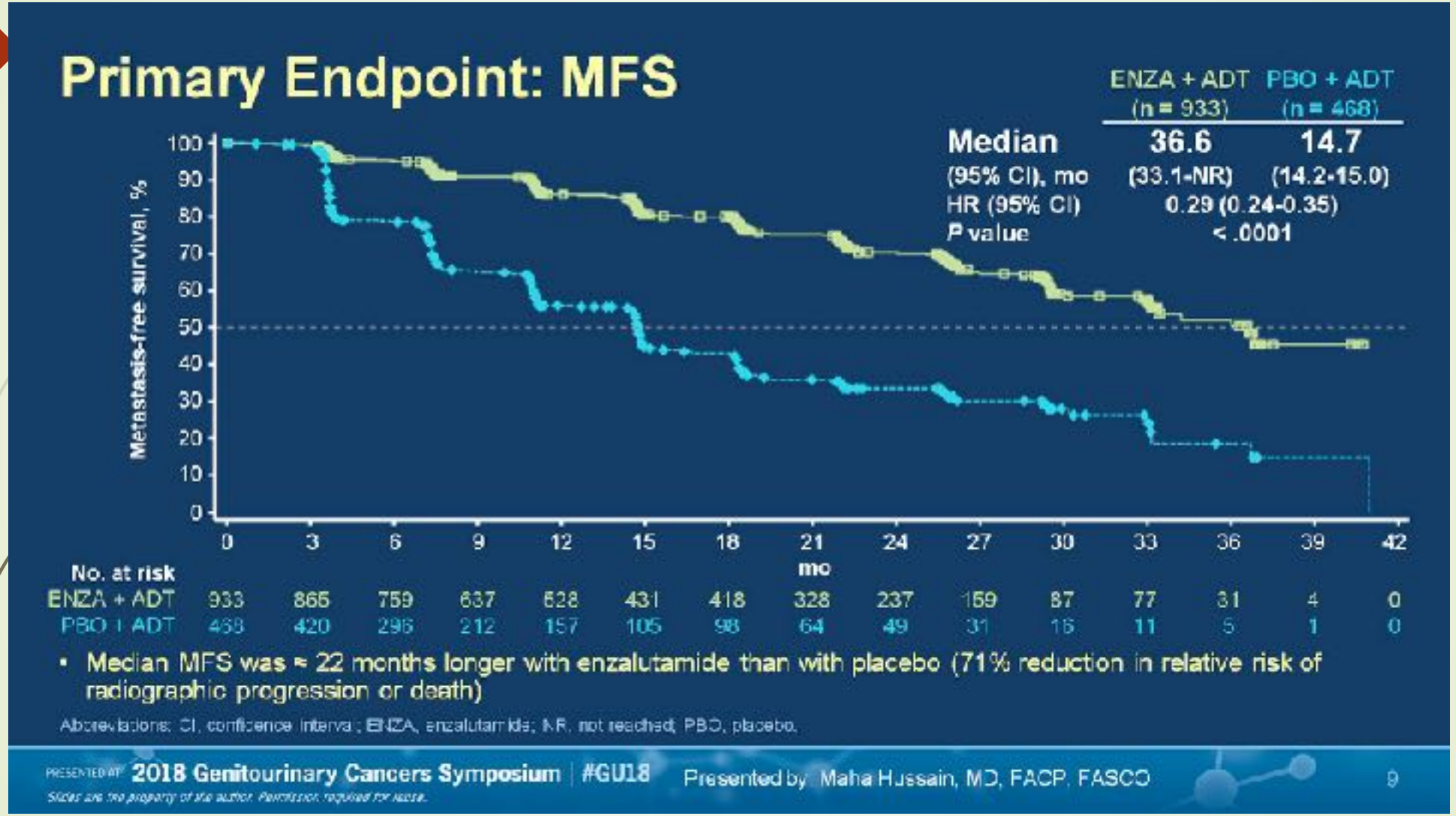

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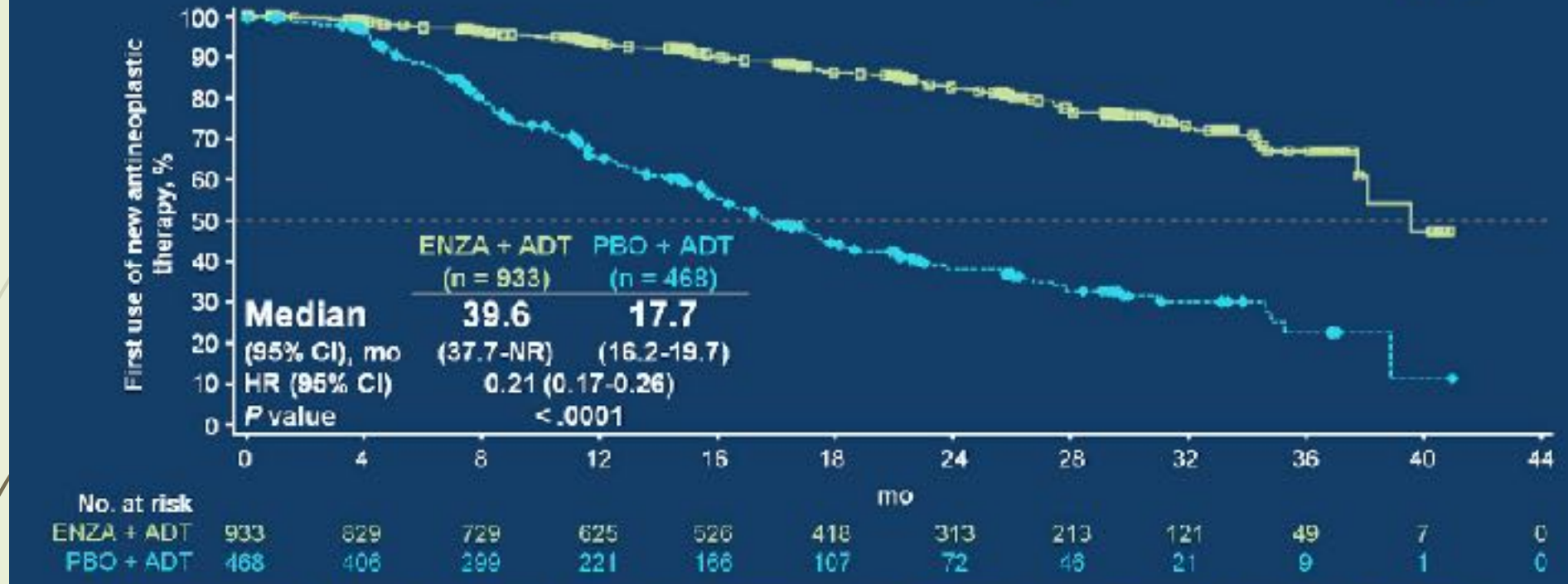
Time to First Use of New Antineoplastic Therapy



- Median time to first use of new antineoplastic therapy was ≈ 22 months longer with enzalutamide than with placebo (79% relative risk reduction)

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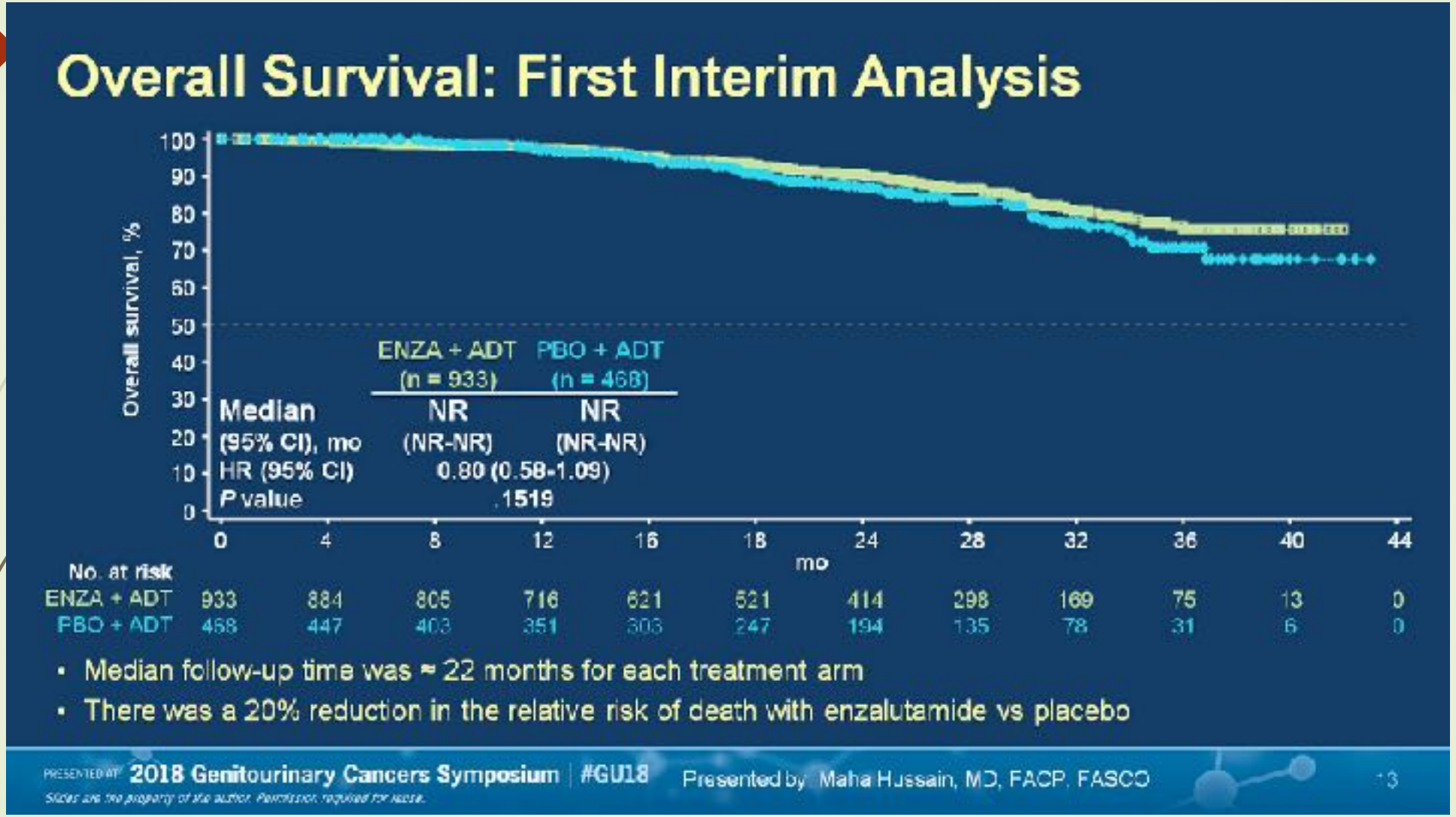
Overall Survival: First Interim Analysis



- Median follow-up time was ≈ 22 months for each treatment arm
- There was a 20% reduction in the relative risk of death with enzalutamide vs placebo

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Progression Event by Type

Event, No. (%)	Enzalutamide + ADT (n = 933)	Placebo + ADT (n = 468)
All progression events*	**219 (23%)**	**228 (49%)**
Radiographic progression†	187 (85%)	224 (98%)
New bone metastases	71 (32%)	79 (35%)
New soft-tissue metastases	109 (50%)	132 (58%)
Concurrent new bone and soft-tissue metastases	7 (3%)	13 (6%)
Death without documented radiographic progression within 112 days of study treatment discontinuation‡	32 (15%)	4 (2%)

- The proportion of progression events in the enzalutamide arm was 50% less than that of the placebo arm

*Event percentages are based on total number of patients randomized in each arm (enzalutamide + ADT, n = 933; placebo + ADT, n = 465).
†Partition of event percentages are based on total number of events in each arm (enzalutamide + ADT, n = 219; placebo + ADT, n = 228).

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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.

Conclusions

- In men with M0 CRPC and rapid PSA doubling time (median 3.7 months), enzalutamide resulted in a clinically meaningful and statistically significant 71% reduction in the relative risk of developing M1 CRPC
  - Median MFS was 36.6 months with enzalutamide vs 14.7 months with placebo (HR, 0.29; $P < .0001$)
- Therapy was well tolerated; adverse events were generally consistent with those reported in prior clinical trials in men with CRPC
- Secondary endpoints (time to PSA progression, time to first use of new antineoplastic therapy) were also significantly longer with enzalutamide than with placebo
- Median OS was not reached in either group in the first interim analysis
  - There was a 20% lower relative risk of death in the enzalutamide group than in the placebo group

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RESULTADOS TRATAMIENTO CON ABIRATERONA Y ENZALUTAMIDA

HOSPITAL GENERAL VIRGEN DE LA LUZ

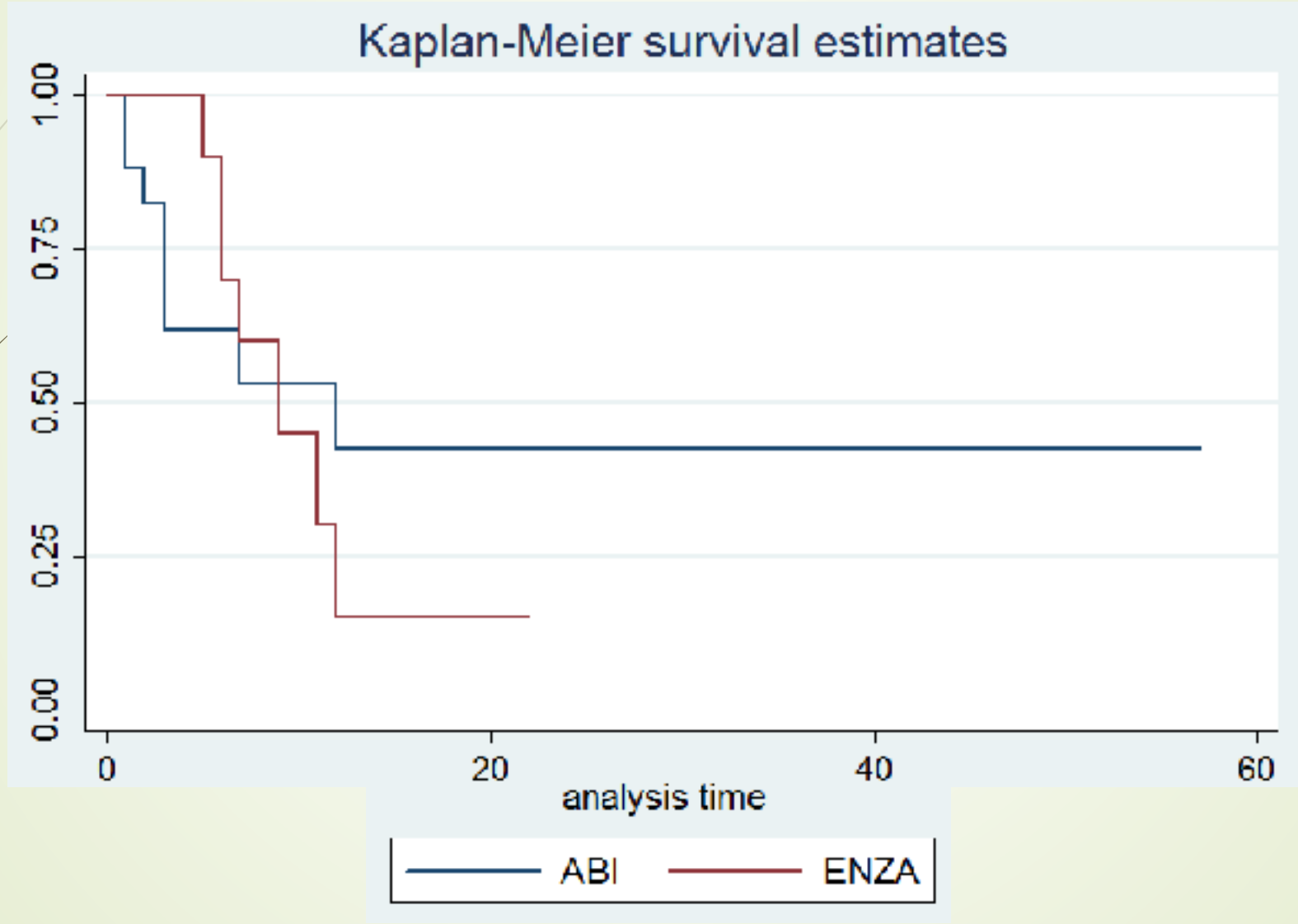
COMPARACIÓN INICIAL DE LOS PACIENTES

	ABIRATERONA (N=20)	ENZALUTAMIDA (N=14)	P
EDAD al dx CPRC(años)	78.5	79.5	0.16
PSA al dx CPRC (ng/dl)	52.4	60.9	0.71
Tº duplicación PSA (meses)	3.33	5.89	0.41
% Gleason >7	33% (6/18)	22% (2/9)	0.68
% metastásico al dx CaP	30% (6/20)	43.9% (6/14)	0.64
% Tto local al dx (sólo RT)	45% (9/20)	35.7% (5/14)	0.71
Tº desde dx hasta CPRC (meses)	52.9	61.4	0.64
% sólo ganglionar en CPRC	25% (5/20)	7.1% (1/14)	0.19
% afectación visceral en CPRC	5% (1/20)	7.1% (1/14)	0.66
Nº lesiones óseas	5.8	7.2	0.35
ECOG al inicio del tto	0.6	1.2	0.07
Nº comorbilidades	1.4	1.4	0.93
Tº seguimiento (meses)	17.1	8.8	0.08

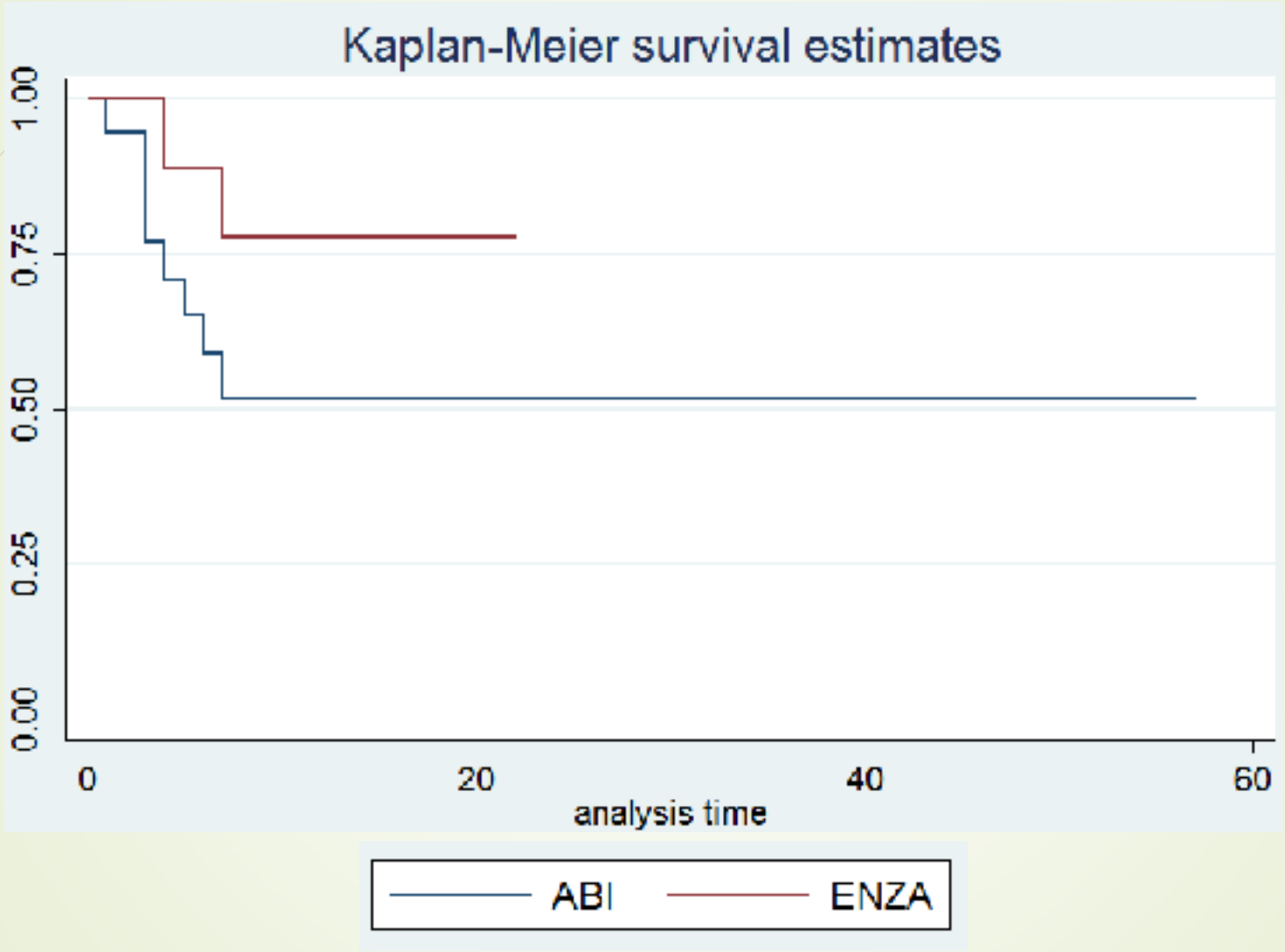
RESULTADOS DEL TRATAMIENTO

	ABIRATERONA (N=20)	ENZALUTAMIDA (N=14)	P
Tº progresión PSA (meses)	6	9,8	0.02
Tº progresión rx (meses)	8.2	10	0.13
Tº progresión clínica (meses)	10	12	0.88
% muerte CaP	38.9% (7/18)	14.3% (2/14)	0.95
% muerte otros	11.1 % (2/18)	28.6% (4/14)	0.21
% suspensión tratamiento por efecto 2º	10% (2/20)	7.1% (1/14)	0.63

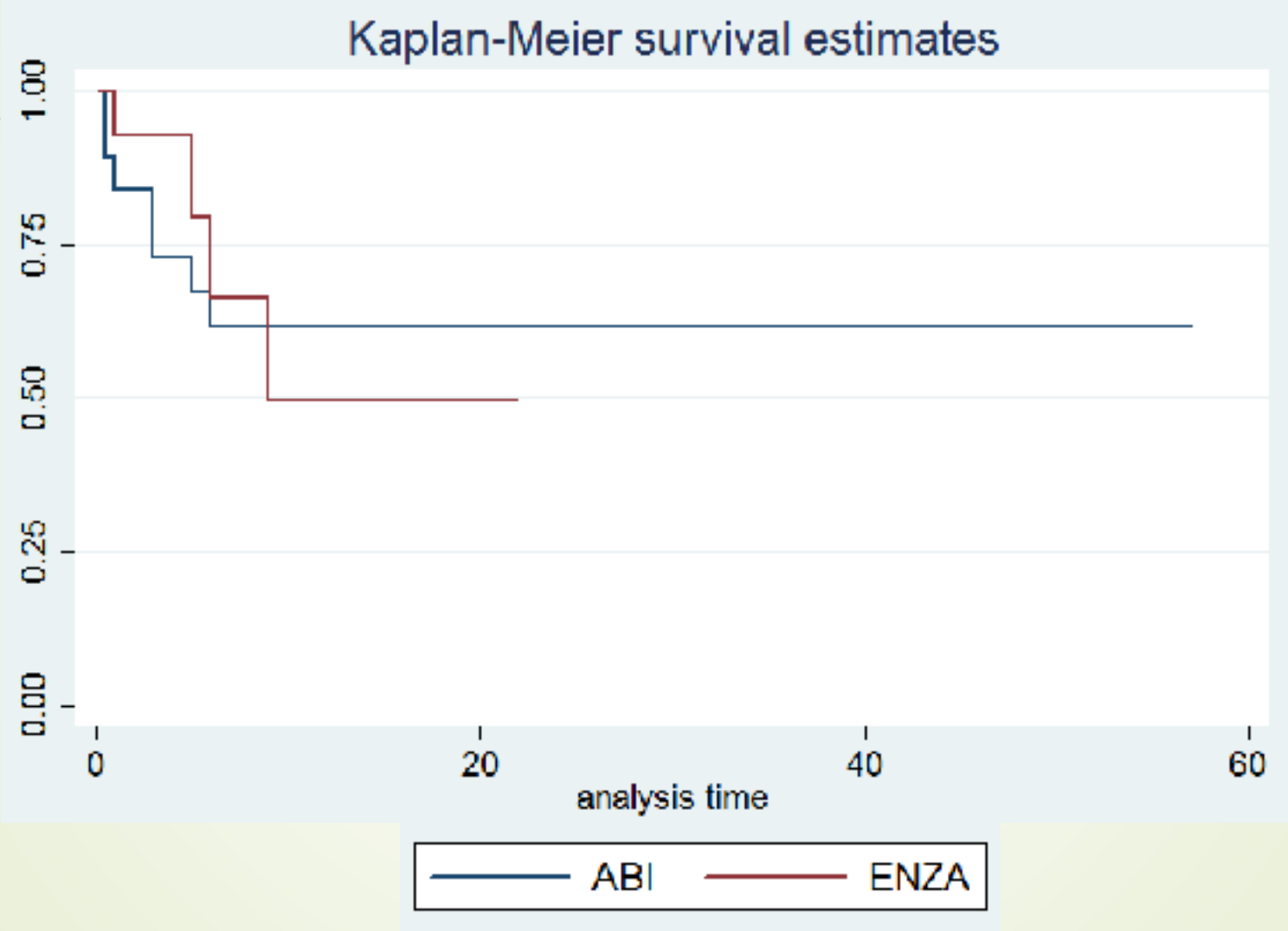
Progresión de PSA



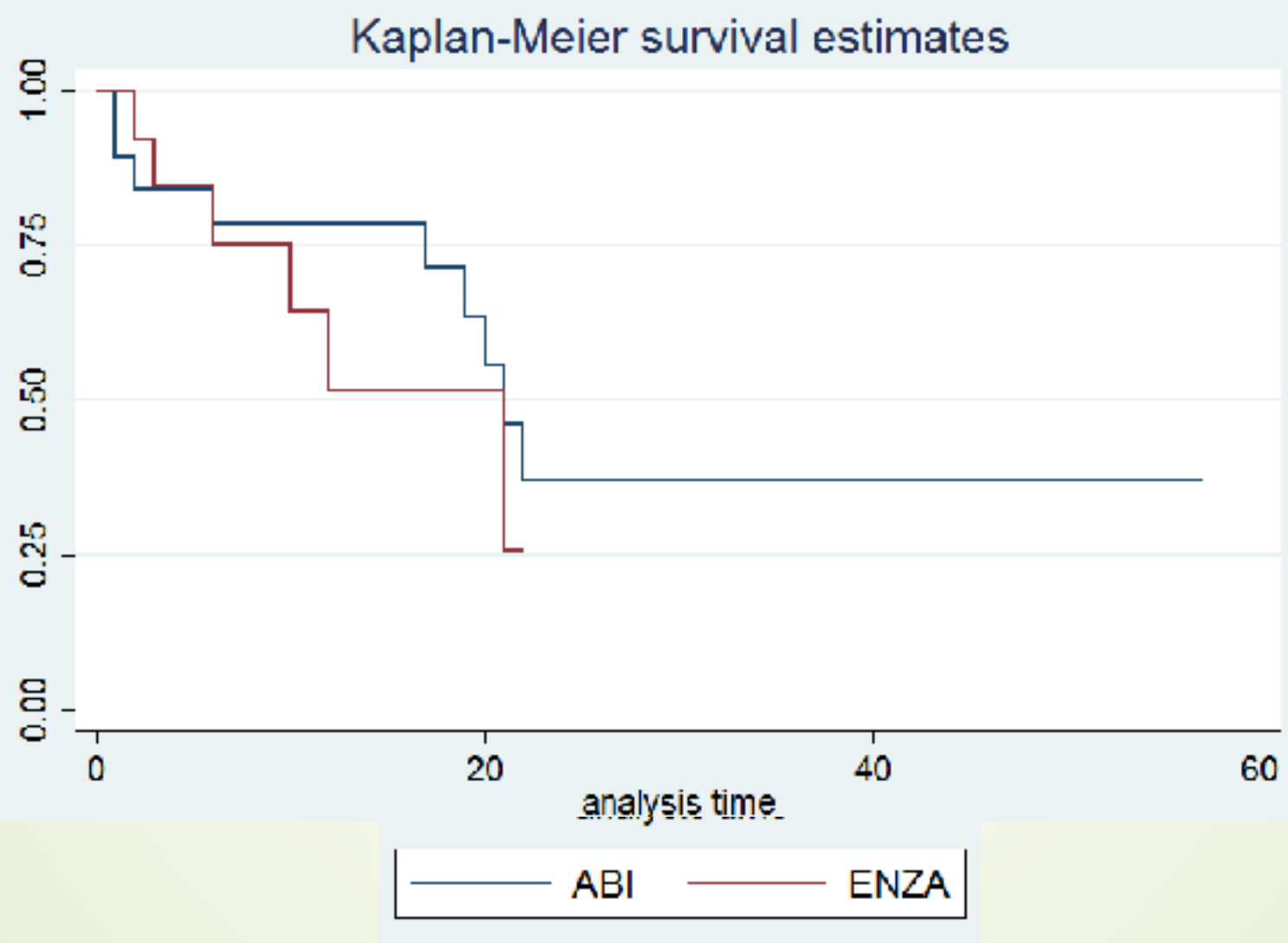
Progresión radiológica



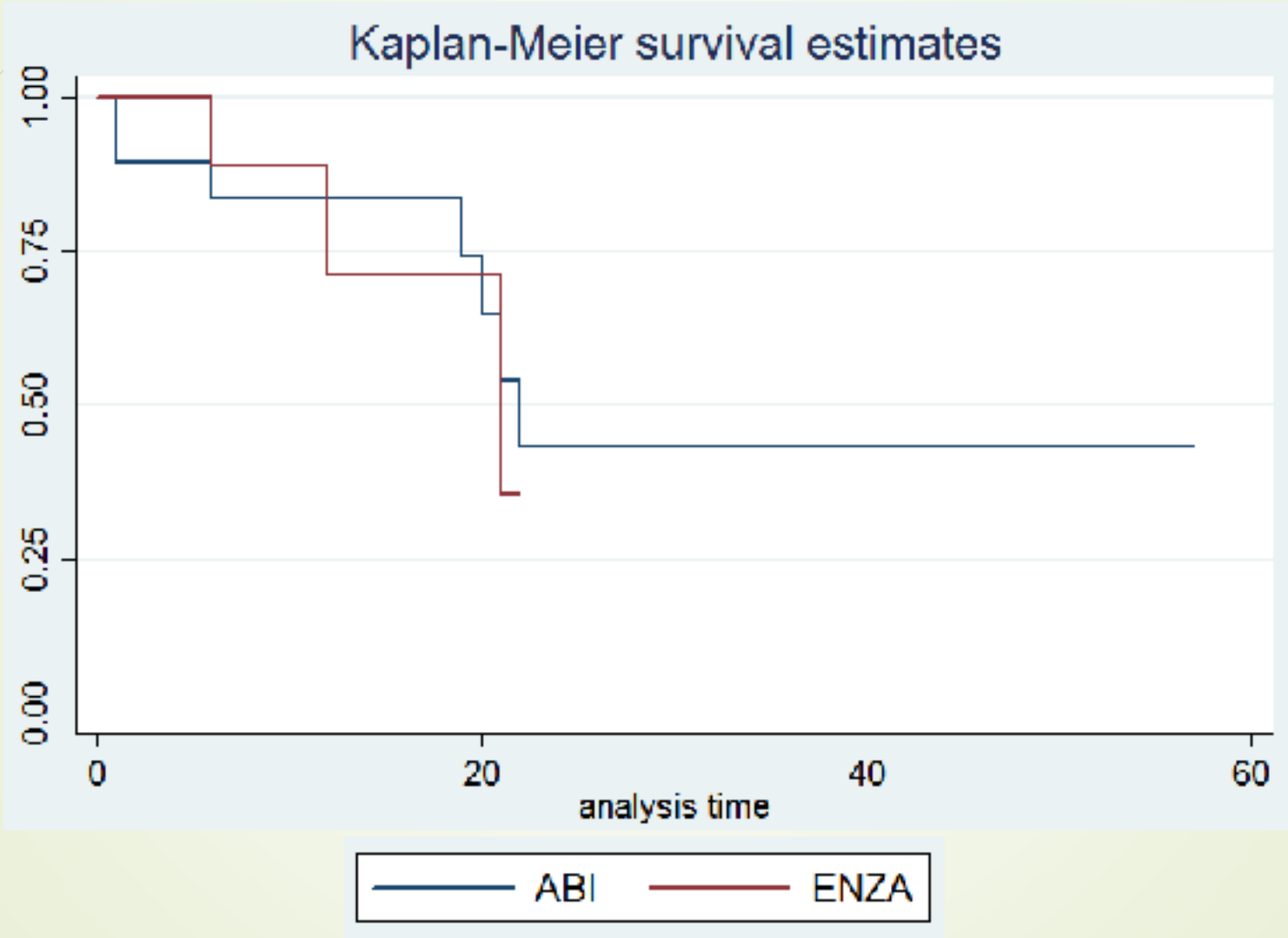
Progresión clínica



Muerte global



Muerte por cáncer de próstata



TRATAMIENTOS DE SEGUNDA LÍNEA