

XV SIMPOSIUM BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

17, 18 Y 19 DE MAYO DE 2023



Visión Actual y Nuevos Retos en el Tratamiento Sistémico del Cáncer de Próstata Avanzado

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Instituto de Investigación Biomédica de Salamanca (IBSAL)



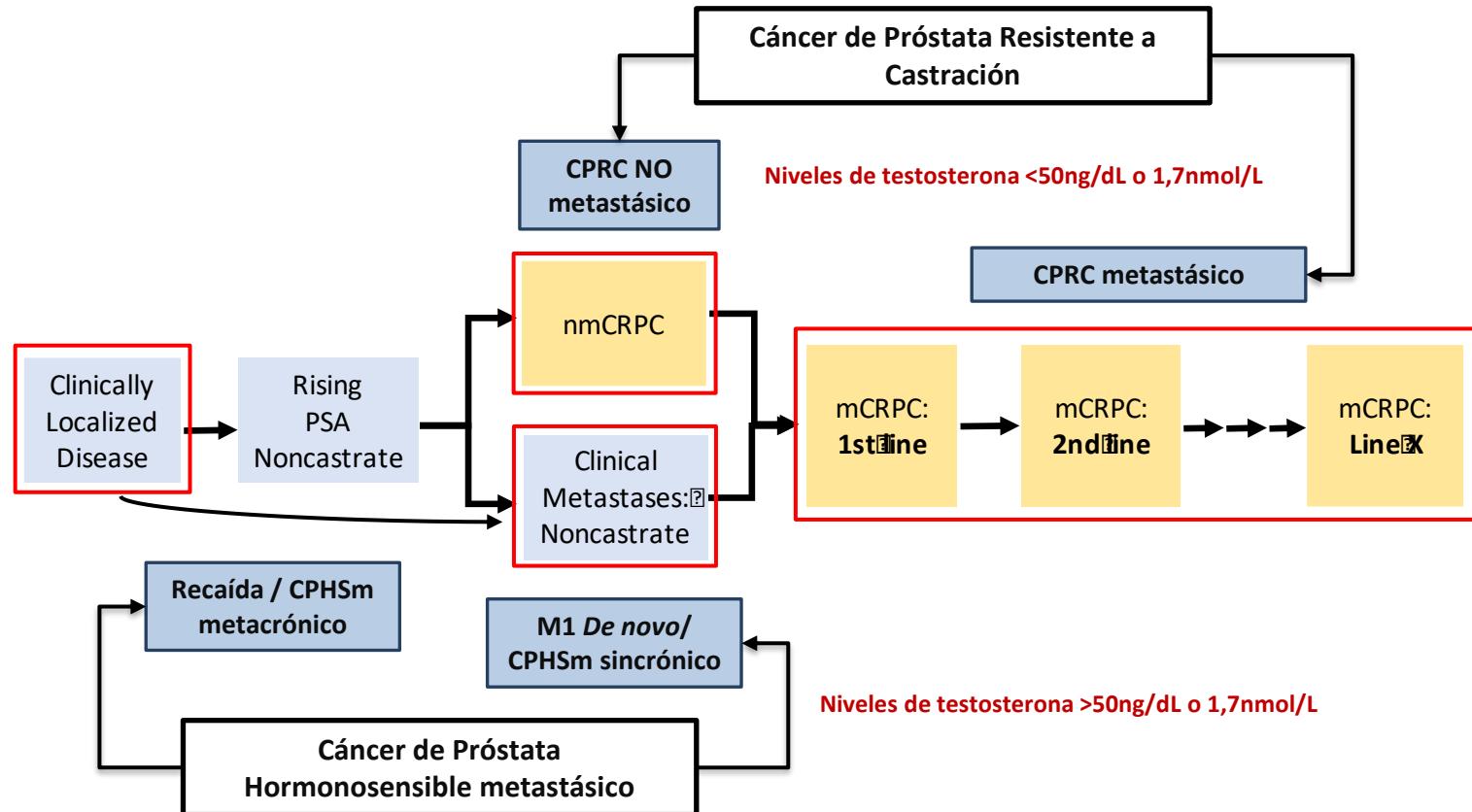


DISCLOSURES

Speaker fees: Janssen, Astellas, Roche, Bayer, Sanofi, IPSEN, AstraZeneca

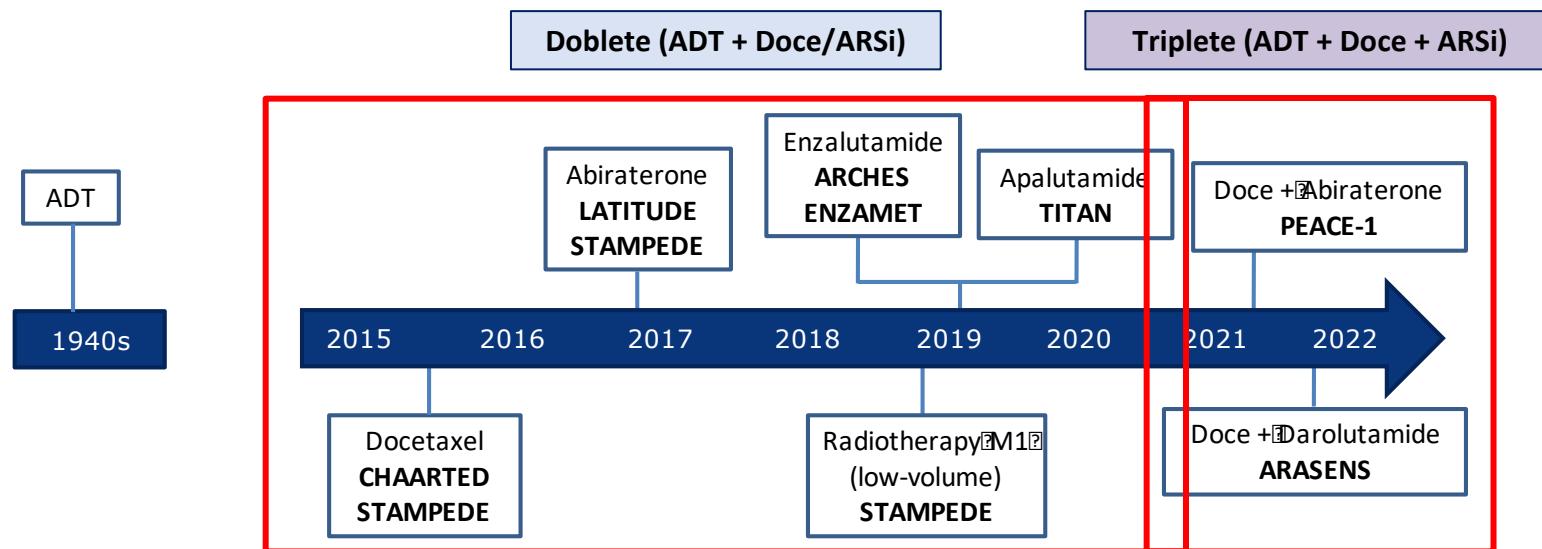
Advisory board: Janssen, Merck/Pfizer, Orion Pharma, Advanced Accelerator Applications (AAA)

Travel/accommodation: Roche, Astellas, Sanofi, Janssen, MSD, BMS, Merck





Cáncer de Próstata Hormonosensible metastásico





	Treatment		Overall survival			
	Experimental	Control	Exp	Control	HR (95% CI)	p-value
CHAARTED	Docetaxel + ADT	ADT	57.6 m	47.2 m	0.72 (0.59-0.89)	0.001
STAMPEDE	Docetaxel + ADT	ADT	59.1 m	34.1 m	0.81 (0.69-0.95)	0.003
STAMPEDE	Abiraterone +ADT	ADT	79.2 m	45.6 m	0.60 (0.50-0.71)	<0.001
LATITUDE	Abiraterone +ADT	ADT	53.3 m	36.5 m	0.66 (0.56-0.78)	<0.001
ARCHES	Enzalutamide + ADT	ADT +/- Doce	NR	NR	0.66 (0.53-0.81)	<0.001
ENZAMET	Enzalutamide + ADT	ADT+AA +/-Doce	NR	73.2 m	0.70 (0.58-0.84)	0.002
TITAN	Apalutamide + ADT	ADT +/- Doce	NR	52.2 m	0.67 (0.51-0.79)	<0.001
PEACE-1	Abi + Doce + ADT	ADT + Doce	NR	52.8 m	0.75 (0.59-0.95)	0.017
ARASENS	Daro + Doce + ADT	ADT + Doce	NR	48.9 m	0.68 (0.57-0.80)	<0.001



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ARASENS	Daro + Doce + ADT	ADT +	NR	48.9 m	0.68 (0.57-0.80)	<0.001

The role of adding docetaxel to ADT + ARSi has NOT been evaluated

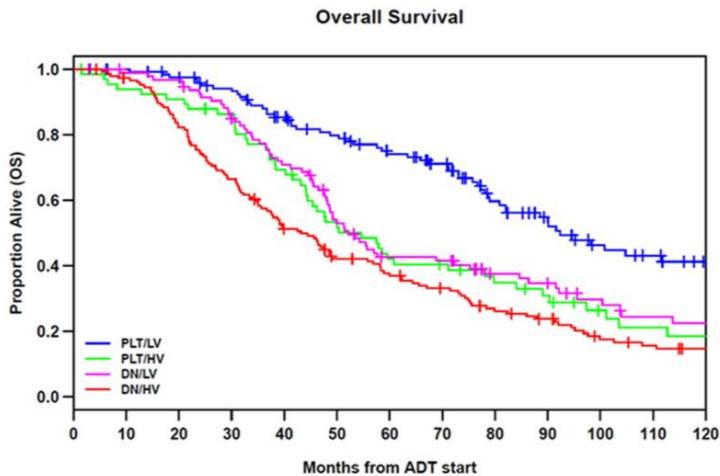


	Treatment		Docetaxel mHSPC	High volume	Visceral mts	Local treatment	de novo M1
	Experimental	Control					
CHAARTED	Docetaxel + ADT	ADT	--	64.9%	15%	27.2%	72.8%
STAMPEDE	Docetaxel + ADT	ADT	--	56%	6%	5%	95%*
STAMPEDE	Abiraterone +ADT	ADT	--	55%	6%	6%	95%†
LATITUDE	Abiraterone +ADT	ADT	--	79%	19%	--	100%
ARCHES	Enzalutamide + ADT	ADT +/- Doce	17.8%	63.2%	??	12-26%	66.6%
ENZAMET	Enzalutamide + ADT	ADT+AA +/-Doce	44%	52.3%	11.5%	42%	60.6%
TITAN	Apalutamide + ADT	ADT +/- Doce	10.7%	62.8%	12.1%	16.4%	80%
PEACE-1	Abi + Doce + ADT	ADT + Doce	100%	64%	13%	--	100%
ARASENS	Daro + Doce + ADT	ADT + Doce	100%	77%	17.5%	13%	86%

*95% of patients with M1 disease at randomization (61% of entire population); †95% of patients with metastatic disease at randomization (50% of entire population)



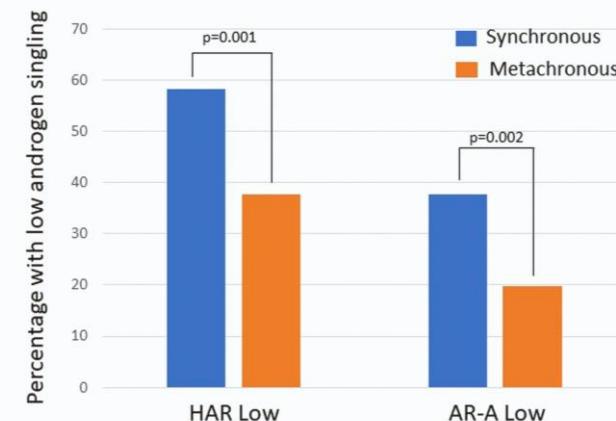
Cáncer de Próstata Hormonosensible metastásico



Bajo volumen – recaída M1 →
Mediana OS ~8 años

Alto volumen – diagnóstico M1 de novo →
Mediana OS ~3 años

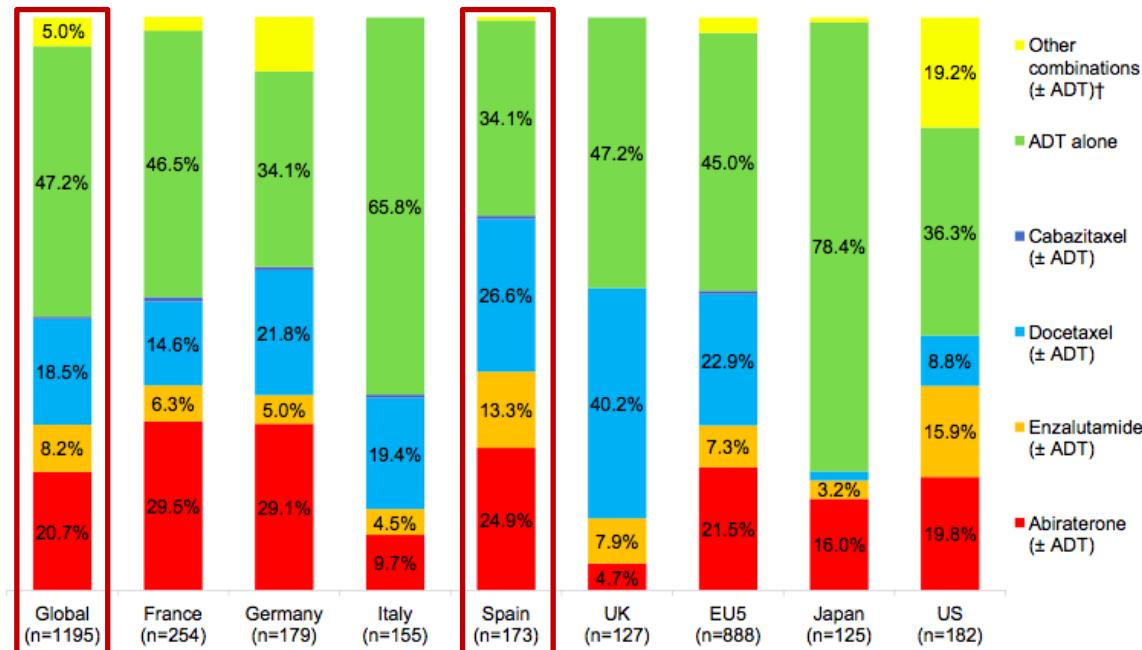
Biologic difference between timing of metastatic disease



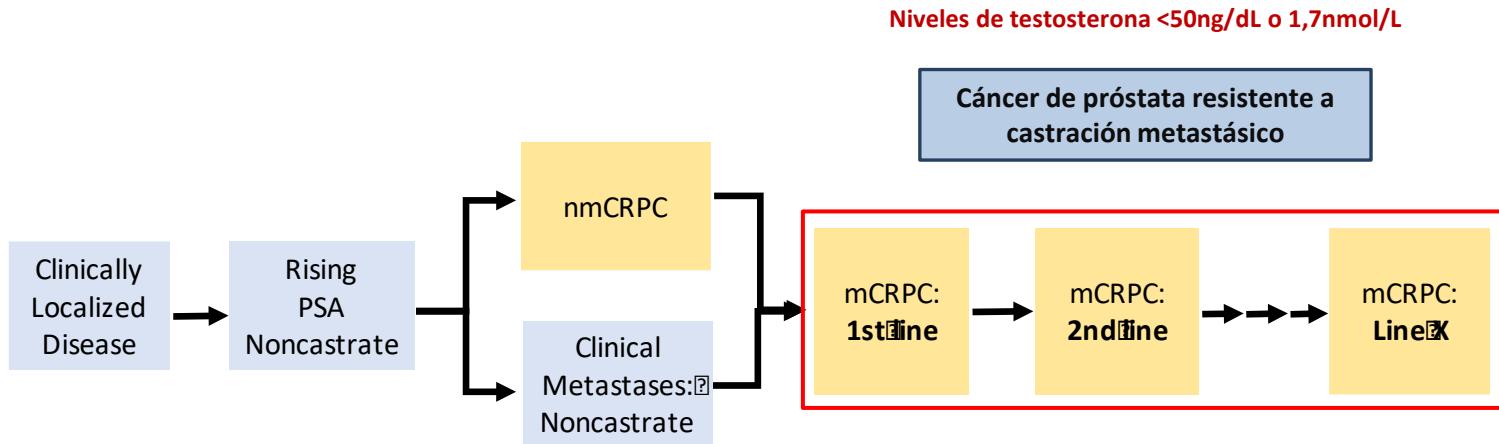
Patients with **synchronous** disease have **lower Androgen Receptor Activity (AR-A)** and **Hallmark Androgen Response (HAR)** gene signature scores in comparison with metachronous disease



REAL-WORL SURVEY



In 2020, ADT alone remained the most common initial mHPSC therapy





Primera línea de CPRCm	N	Supervivencia Global			
		Experim	Control	HR (IC 95%)	p-valor
TAX-327 Docetaxel vs Mitoxantrona	1006	19,2 m	16,3 m	0,79 (0,67-0,93)	0,004
COU-302 Abiraterona/P vs Placebo/P	1088	34,7 m	30,3 m	0,81 (0,70-0,93)	0,003
PREVAIL Enzalutamida vs Placebo	1717	35,3 m	31,3 m	0,77 (0,67-0,88)	<0,001

Segunda línea o

No representan la población actual de pacientes con CPRCm

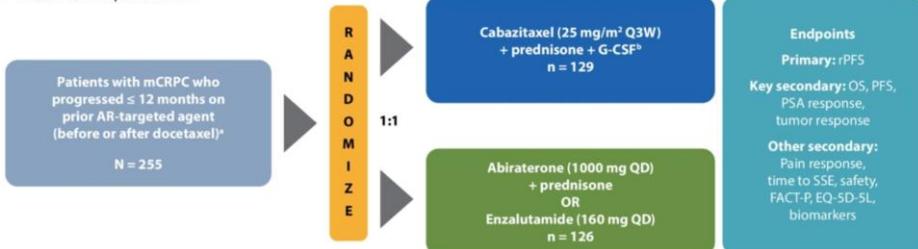
TROPIC Cabazitaxel vs Mitoxantrona	755	15,1 m	12,7 m	0,70 (0,59-0,83)	<0,001
COU-301 Abiraterona/P vs Placebo/P	1195	15,8 m	11,2 m	0,74 (0,64-0,86)	<0,001
AFFIRM Enzalutamida vs Placebo	1199	18,4 m	13,6 m	0,63 (0,53-0,75)	<0,001
ALSYMPCA Radium-223 vs Placebo	921	14,9 m	11,3 m	0,70 (0,58-0,83)	<0,001



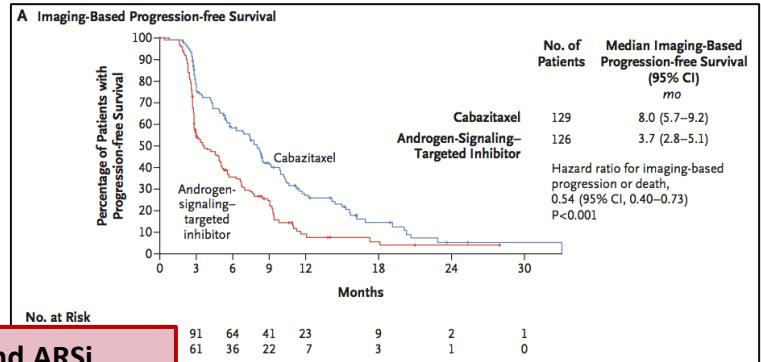
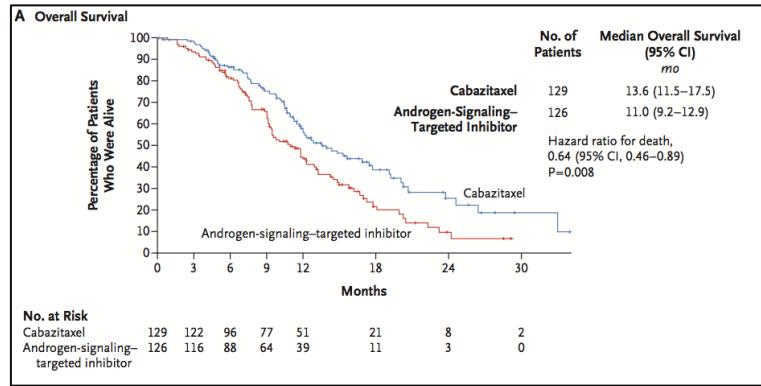
After docetaxel & ARSi...

CARD -STUDY DESIGN-

- Multicenter, randomized, open-label study
- Enrollment: Nov 2015 – Nov 2018
- Median follow-up: 9.2 months



- Stratification factors:**
- ECOG PS (0/1 vs 2)
 - time to disease progression (≤ 6 vs > 6 –12 months)
 - timing of previous alternative AR targeted agent (before vs after docetaxel)



Standard of care after docetaxel and ARSi



Open-label study of protocol-permitted standard of care + ^{177}Lu -PSMA-617 in adults with PSMA-positive mCRPC

Eligible patients
• Previous treatment with <u>both</u>
• ≥ 1 androgen receptor pathway inhibitor
• 1 or 2 taxane regimens
• Protocol-permitted standard of care (SOC) planned before randomization
• Excluding chemotherapy, immunotherapy, radium-223, investigational drugs
• ECOG performance status 0–2
• Life expectancy > 6 months
• PSMA-positive mCRPC on PET/CT with ^{68}Ga -PSMA-11



- Randomization stratified by
 - ECOG status (0–1 or 2)
 - LDH (high or low)
 - Liver metastases (yes or no)
 - Androgen receptor pathway inhibitors in SOC (yes or no)
- CT/MRI/bone scans
 - Every 8 weeks (treatment)
 - Every 12 weeks (follow-up)
 - Blinded independent central review



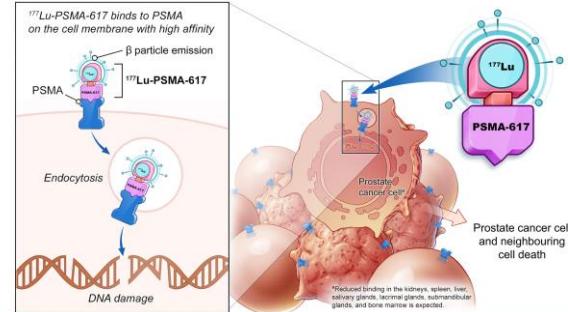
Centrally read PSMA PET imaging criteria

- ≥ 1 PSMA-positive metastatic lesion
 - Positive = ^{68}Ga uptake > liver
- No PSMA-negative metastatic lesions
 - Bone with soft tissue component ≥ 1.0 cm
 - Lymph node ≥ 2.5 cm
 - Solid organ ≥ 1.0 cm



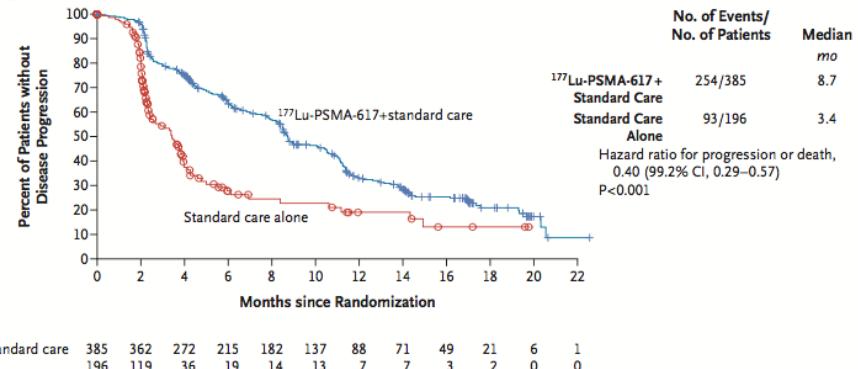
PSMA criteria met	869/1003 (86.6%)
PSMA criteria not met	126/1003 (12.6%)

^{177}Lu -PSMA-617 targeted radioligand therapy

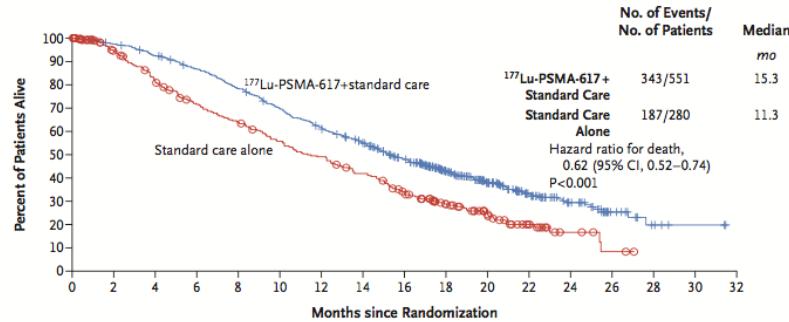




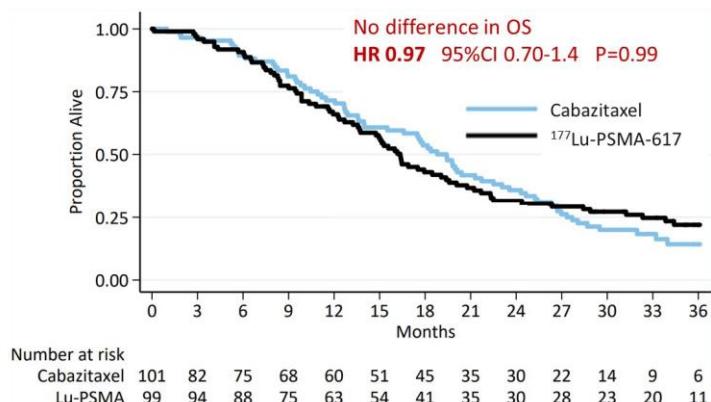
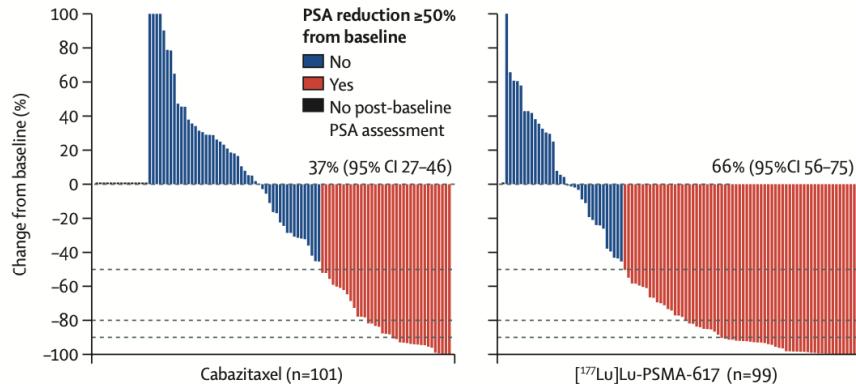
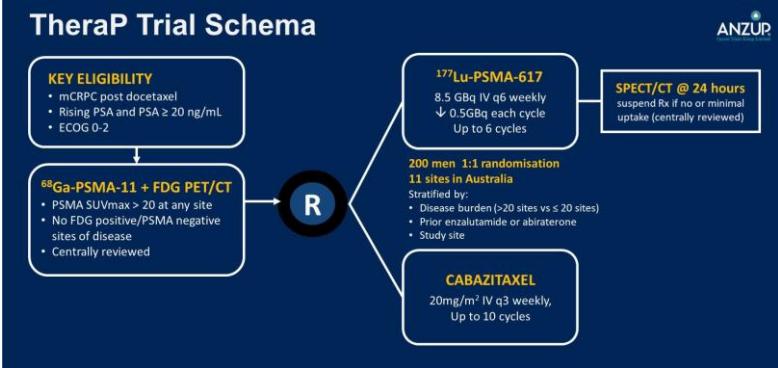
A Imaging-Based Progression-free Survival



B Overall Survival



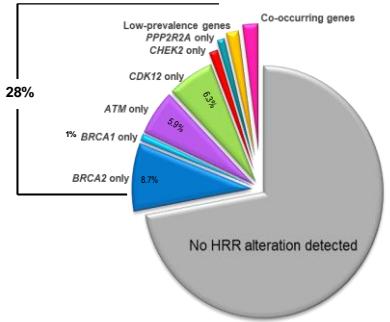
	All Grades	Grade \geq 3
Leukopenia	12.5%	2.5%
Anemia	31.8%	12.9%
Thrombocytopenia	17.2%	7.9%
Dry mouth	39.3%	0%
Nausea & vomiting	39.3%	1.5%
Fatigue	49.1%	7%





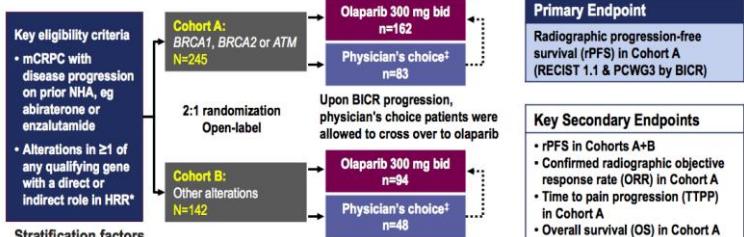
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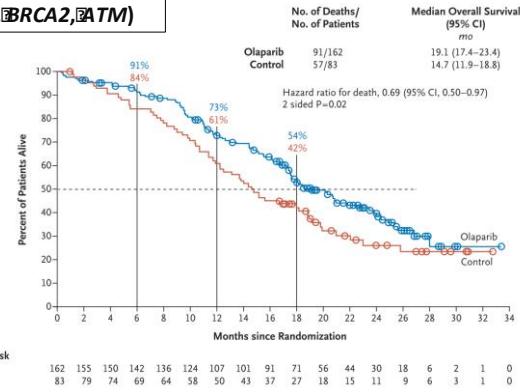
ATM **RAD51B**
BRCA1 **RAD51C**
BRCA2 **RAD51D**
BARD1 **FANCL**
BRIP1 **PALB2**
CDK12 **PPP2R2A**
CHEK1 **RAD54L**
CHEK2

PROfound STUDY DESIGN

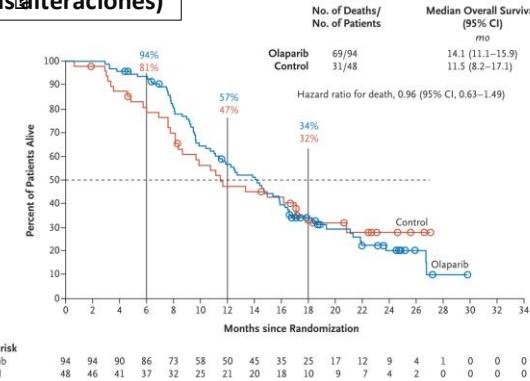


DOCETAXEL → 65%

COHORT A (BRCA1, BRCA2, ATM)

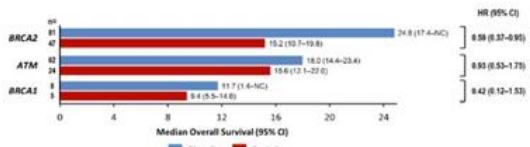


COHORT B (Otras Alteraciones)



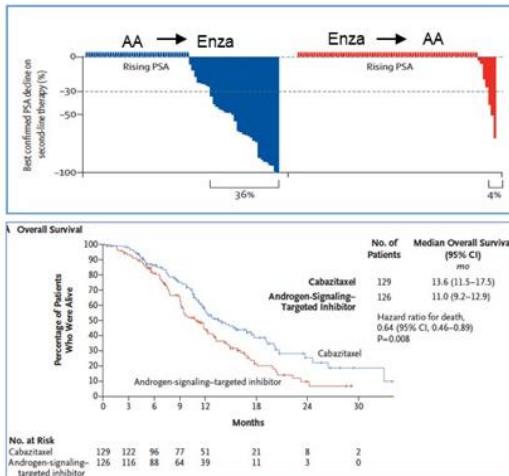


Beneficio mayor en BRCA2



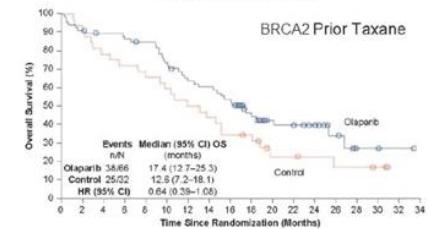
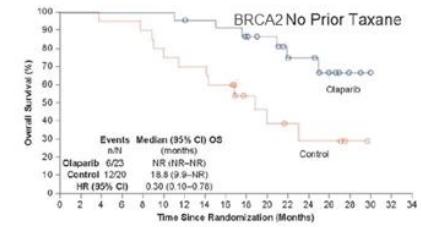
¿Beneficio en ATM?

Brazo control

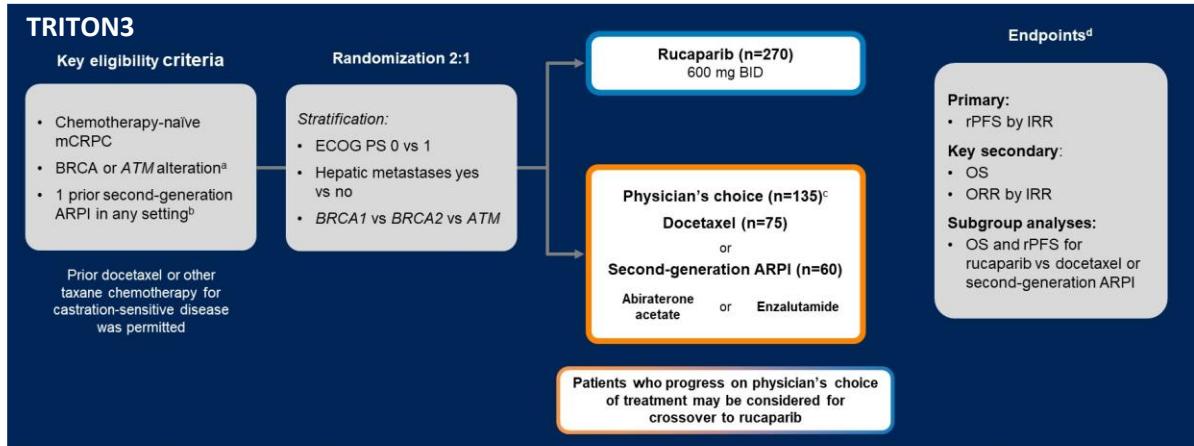


Brazo control → taxanos?

65% docetaxel previo

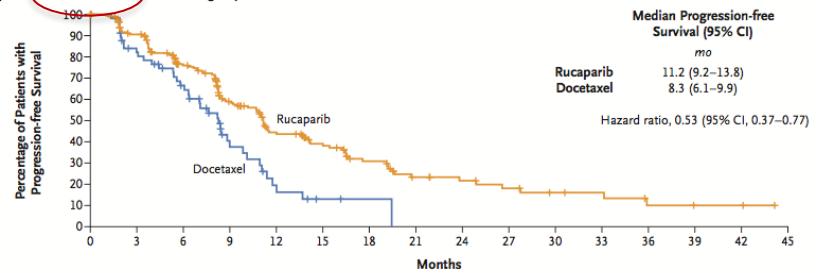


¿iPARP antes o tras taxanos?

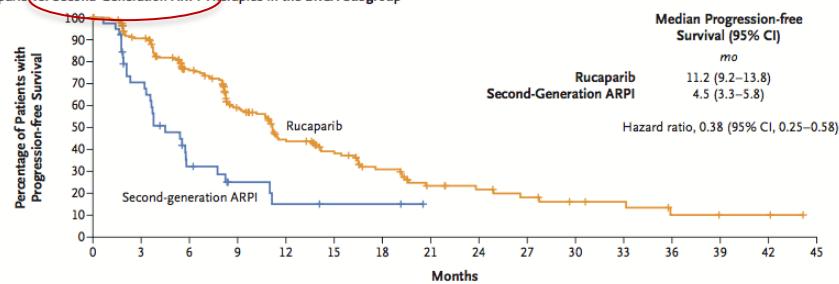




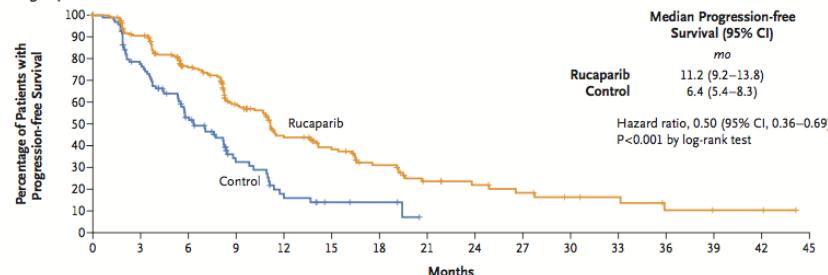
A Rucaparib vs. Docetaxel in the BRCA Subgroup



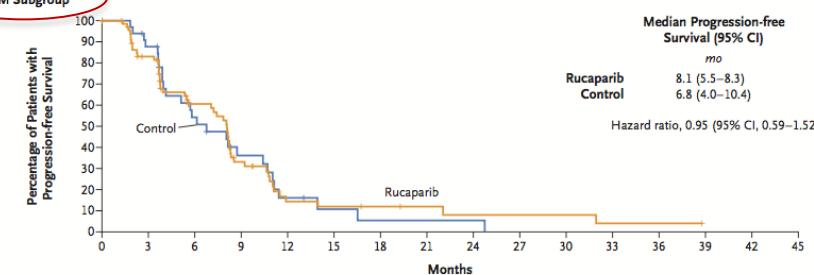
B Rucaparib vs. Second-Generation ARPI Therapies in the BRCA Subgroup



A BRCA Subgroup

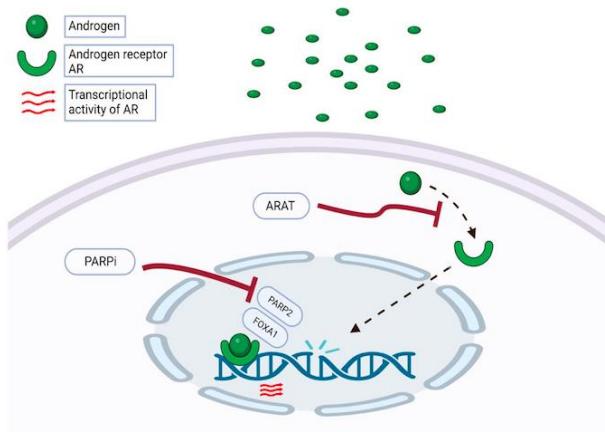


C ATM Subgroup

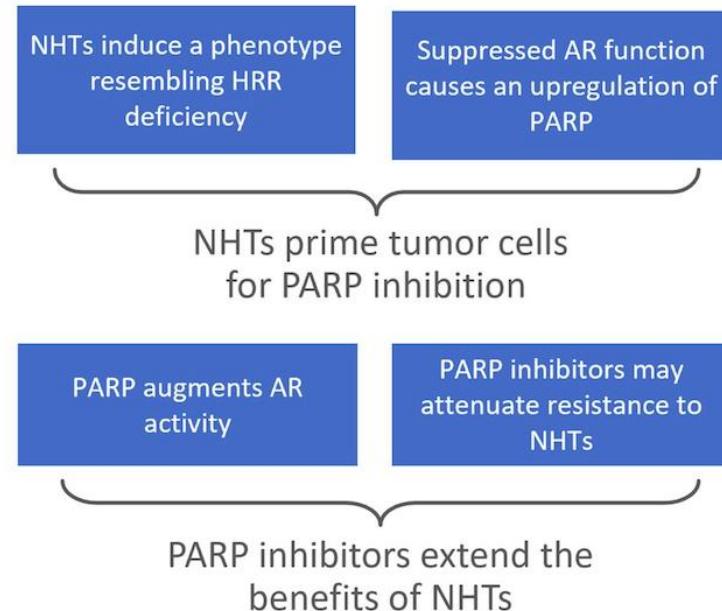




Crosstalk between Androgen Receptor and DDR pathway



The rationale for combining PARPi with NHT





MAGNITUDE

Study start: February 2019

- Patient eligibility
 - L1L mCRPC
 - ≤ 54 months prior AA allowed for mCRPC
 - ECOG PS 0 or 1
 - BPI-SF worst pain score ≤3

- Stratifications
 - Prior taxane-based chemo for mCRPC
 - Prior ARI for nmCRPC or L1L mCRPC
 - Prior AA for L1L mCRPC
 - HRR BM+ cohort only
 - BRCA1/2 vs other HRR gene alterations

Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

Patients were prospectively tested by plasma, tissue and/or saliva/whole blood. Patients negative by plasma only were required to test by tissue to confirm HRR BM= status.

PROpel

- Patient population

- 1L mCRPC
- Docetaxel allowed at mHSPC stage
- No prior abiraterone
- Other NHAs allowed if stopped ≥12 months prior to enrollment
- Ongoing ADT
- ECOG 0-1

- Stratification factors
 - Site of distant metastases: bone only vs visceral vs other
 - Prior taxane at mHSPC: yes vs no

TALAPRO-2

TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study

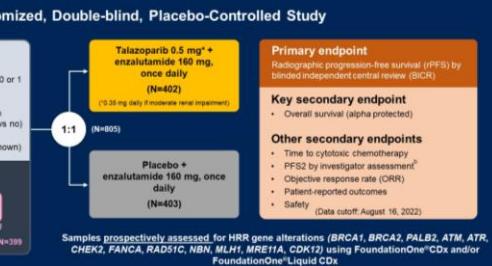
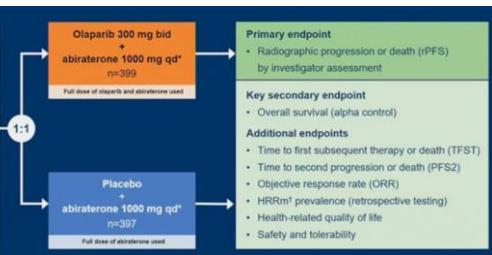
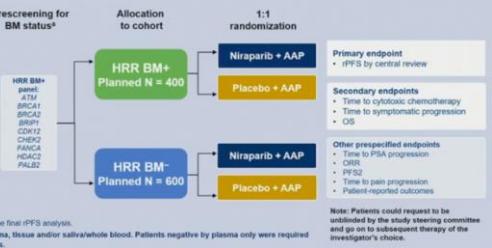
- Patient population
 - First-line mCRPC
 - ECOG performance status (PS) 0 or 1

- Stratification factors
 - Prior abiraterone^a or docetaxel in castration-sensitive setting (yes or no)
 - HRR gene alteration status (deficient or nondisruptive or unknown)

All comers (Chort 1), N=805

Nondisruptive or unknown HRRm N=169 HRRn N=636

HRRm only (Chort 2), N=399



Tratamiento:

iPARP + ARSi vs placebo + ARSi

Población de pacientes:

1L CPRCm

Permitido docetaxel y otros ARSi en CPSHm / CPRCnm

80% de los pacientes incluidos → TDA monoterapia

Diseño del estudio

MAGNITUDE: Pre-screening molecular → HRR+ vs HRR-

PROpel y TALAPRO-2 → población no seleccionada (*all comers*)

Análisis retrospectivo (PROpel) y prospectivo (TALAPRO-2) de alteraciones en genes HRR



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MAGNITUDE

Study start: February 2019

Patient eligibility

- L1 mCRPC
- 54 months prior AAPl allowed for mCRPC
- ECOG PS 0 or 1
- BPI-SF worst pain score <3

Stratifications

- Prior taxane-based chemo for mCRPC
- Prior ARI for nmCRPC or L1 mCRPC
- Prior AAPl for L1 mCRPC
- HRR BM+ cohort only:
 - BRCAl/2 vs other HRR gene alterations

Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

Patients were prospectively tested by plasma, tissue and/or saliva/whole blood. Patients negative by plasma only were required to test by tissue to confirm HRR BM- status.

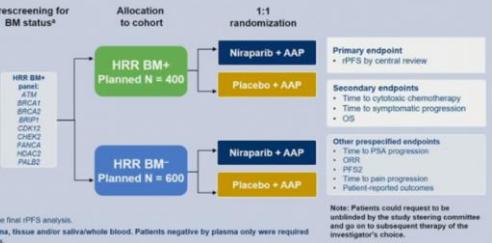
PROpel

Patient population

- 1L mCRPC
- Doxetaxel allowed at mHSPC stage
- No prior abiraterone
- Other NHAs allowed if stopped ≥12 months prior to enrollment
- Ongoing ADT
- ECOG 0-1

Stratification factors

- Site of distant metastases: bone only vs visceral vs other
- Prior taxane at mHSPC: yes vs no



TALAPRO-2

TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study

Patient population

- First-line nmCRPC
- ECOG performance status (PS) 0 or 1

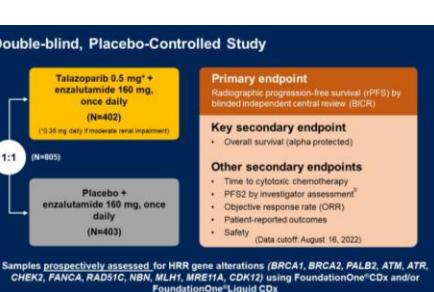
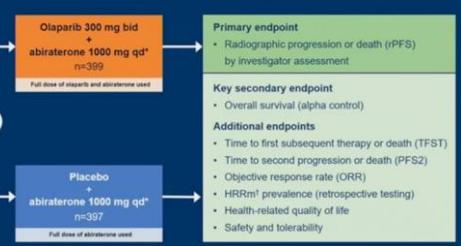
Stratification factors

- Prior abiraterone^a or docetaxel in castration-sensitive setting (yes vs no)
- HRR gene alteration status (deficient vs nondisruptive or unknown)

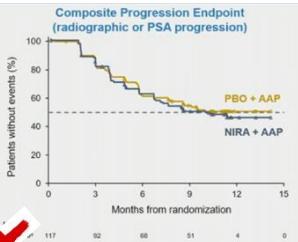
All comers (Cohort 1), N=805

Nondisruptive or unknown HRRm N=169

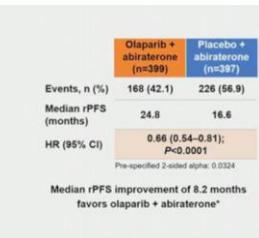
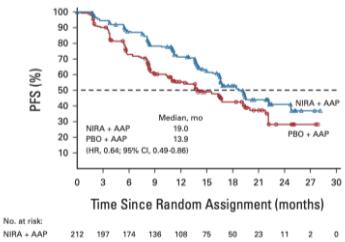
HRRm only (Cohort 2), N=339



HRR Negativo

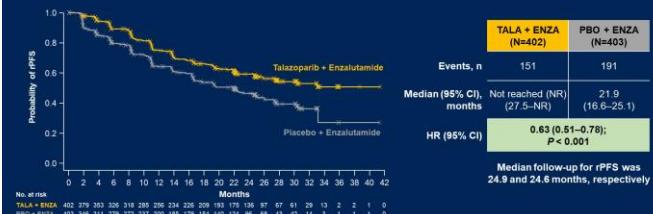


HRR Positivo



TALAPRO-2 Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 37% reduced risk of progression or death



ALL COMERS



XV SIMPOSIUM

BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

Cáncer de Próstata Avanzado

MAGNITUDE

Study start: February 2019

Patient eligibility

- L1 mCRPC
- > 6 months prior AA allowed for mCRPC
- ECOG PS 0 or 1
- BPI-SF worst pain score <3

Stratifications

- Prior taxane-based chemo for mCRPC
- Prior ARI for nmCRPC or L1 CRPC
- Prior AA for L1 mCRPC
- HRR BM+ cohort only:
 - BRCA1/2 vs other HRR gene alterations

Cancer data cut-off was October 8, 2021 for the final rPFS analysis.

Patients were prospectively tested by plasma, tissue and/or saliva/whole blood. Patients negative by plasma only were required to test by tissue to confirm HRR BM+ status.

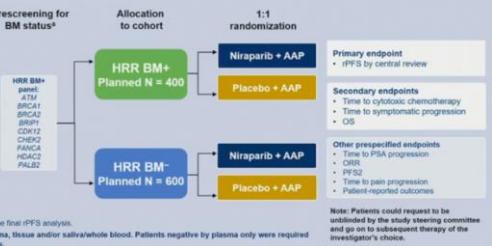
PROpel

Patient population

- 1L mCRPC
- Docetaxel allowed at mHSPC stage
- No prior abiraterone
- Other NHAs allowed if stopped >12 months prior to enrollment
- Ongoing ADT
- ECOG 0-1

Stratification factors

- Site of distant metastases: bone only vs visceral or other
- Prior taxane at mHSPC: yes vs no



^a Note: Patients could request to be unbonded by the study steering committee and go on to subsequent therapy of the investigator's choice.

TALAPRO-2

TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study

Patient population

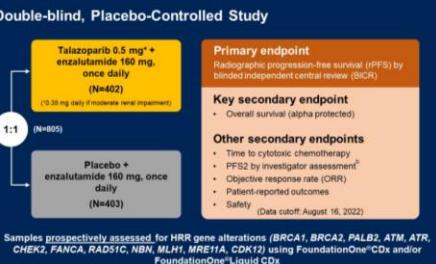
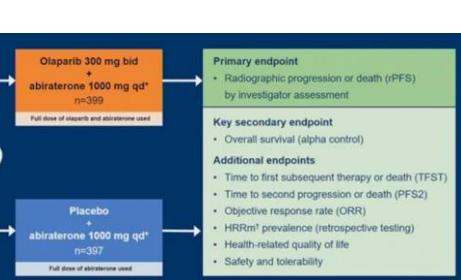
- First-line mCRPC
- ECOG performance status (PS) 0 or 1

Stratification factors

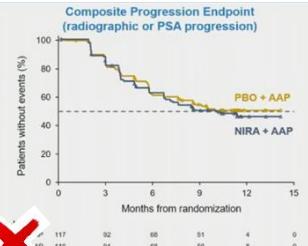
- Prior abiraterone^a or docetaxel in castration-sensitive setting (yes vs no)
- HRG gene alteration status (deficient vs nondisruptive or unknown)

All comers (Cohort 1), N=805

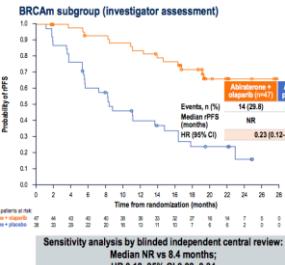
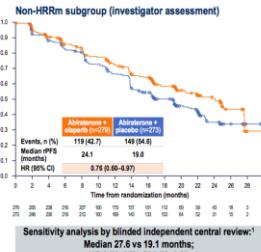
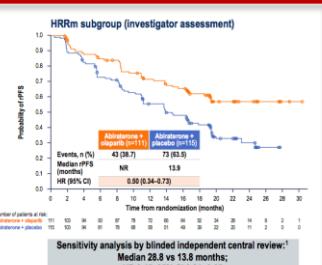
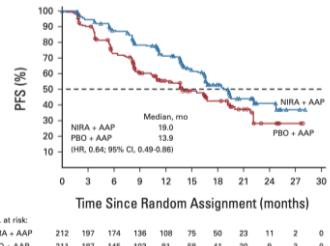
HRRm only (Cohort 2), N=399



HRR Negativo

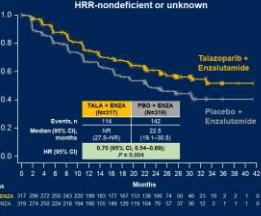
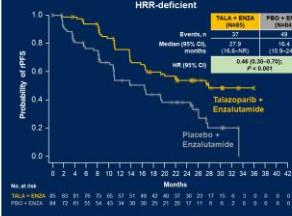


HRR Positivo



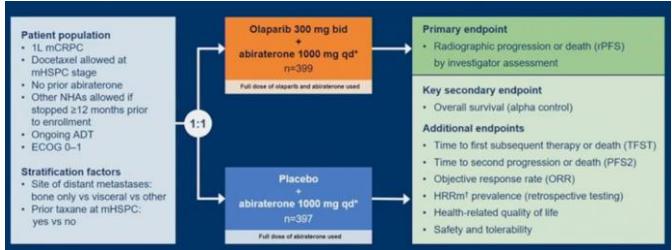
TALAPRO-2: rPFS by BICR by HRR Status

A clinically meaningful reduction in risk of progression or death is seen regardless of HRR status

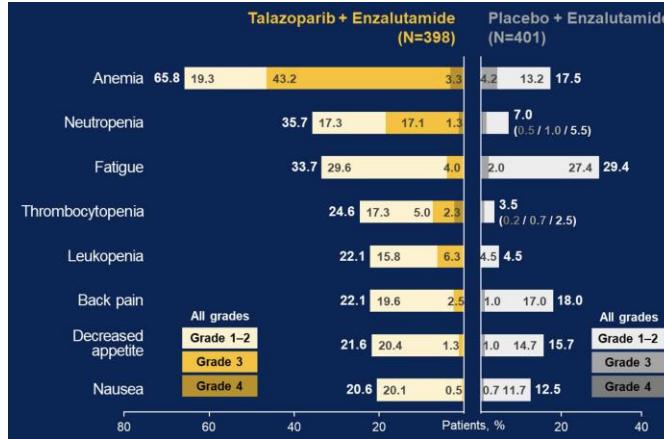
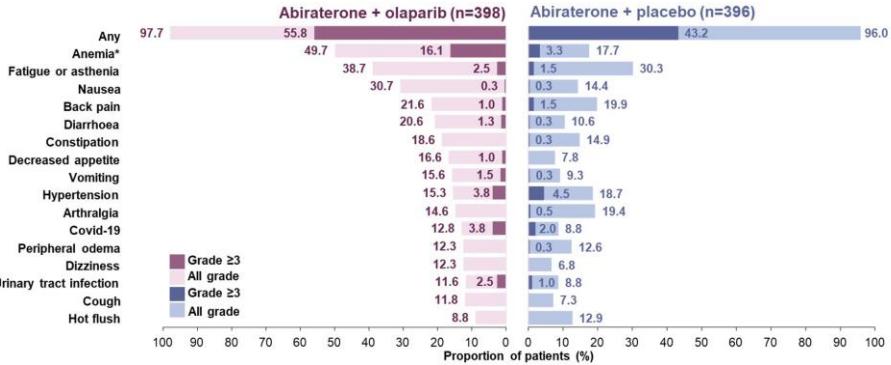
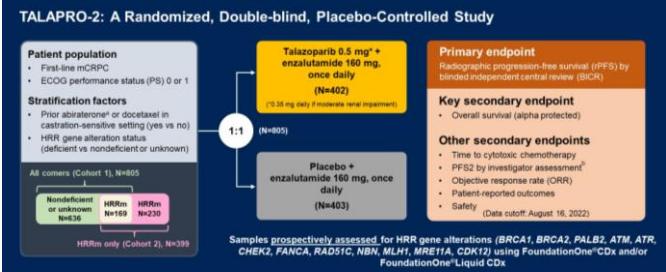




PROpel



TALAPRO-2



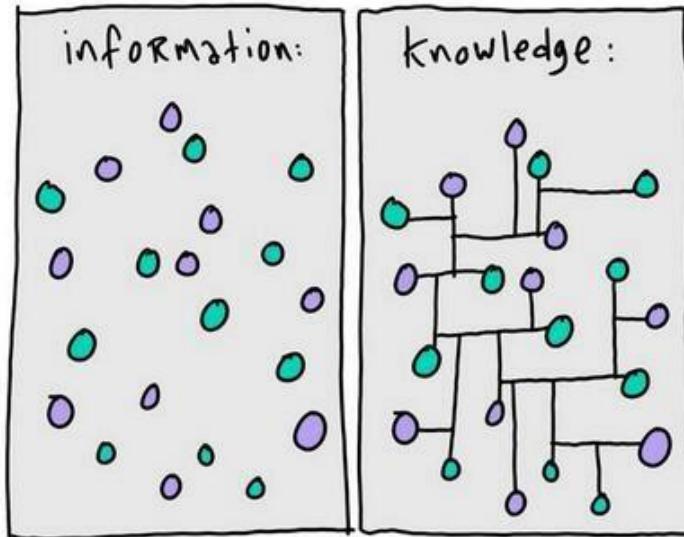


- ❖ En **cáncer de próstata hormonosensible metastásico** → combinación de **TDA + Apalutamida/Enzalutamida/Abiraterona o triplete (TDA + Docetaxel + Abi/Daro)** deben considerarse tratamiento de **elección**.
 - ❖ No comparados → toma de decisiones en base a factores clínicos
- ❖ En **cáncer de próstata resistente a castración metastásico**:
 - ❖ **Cabazitaxel** tras docetaxel / ARSi
 - ❖ **¹⁷⁷Lu-PSMA-617** tras docetaxel / ARSi (PET-PSMA +)
- ❖ Los **inhibidores de PARP** han demostrado beneficio en **supervivencia global** en pacientes con CPRCm portadores de mutaciones en ***BRCA1/2***.
 - ❖ ¿Qué ocurre con otras alteraciones? No beneficio en pacientes con alteraciones en **ATM**
 - ❖ Rucaparib ha demostrado beneficio **independientemente del brazo control** (docetaxel / ARSi)
- ❖ Existe evidencia que demuestra que la **inhibición del RA y PARP** puede ser **sinérgica**, aunque es preciso definir mejor el contexto en el que podemos aplicarlo (más allá de *BRCA2*).
 - ❖ ***BRCA2* >> déficit HRR >> CPRCm no seleccionados >> sin alteraciones en HRR**
 - ❖ El escenario de tratamiento **ha cambiado** → ARSi se emplean en etapas más tempranas (CPHSm / CPRCnm)

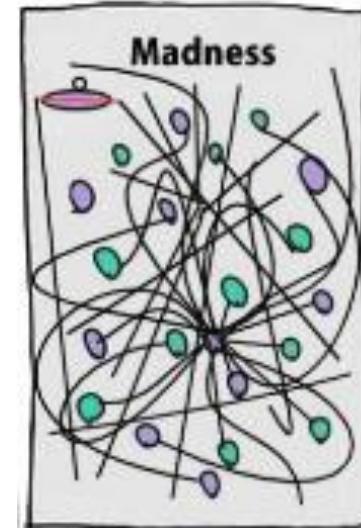


Visión Actual y Nuevos Retos en el Tratamiento Sistémico del Cáncer de Próstata Avanzado

Retos



Visión Actual



XV SIMPOSIUM

BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

17, 18 Y 19 DE MAYO DE 2023



¡Gracias!



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