Identificación de perfiles moleculares en el CPRC hacia la medicina de la precisión

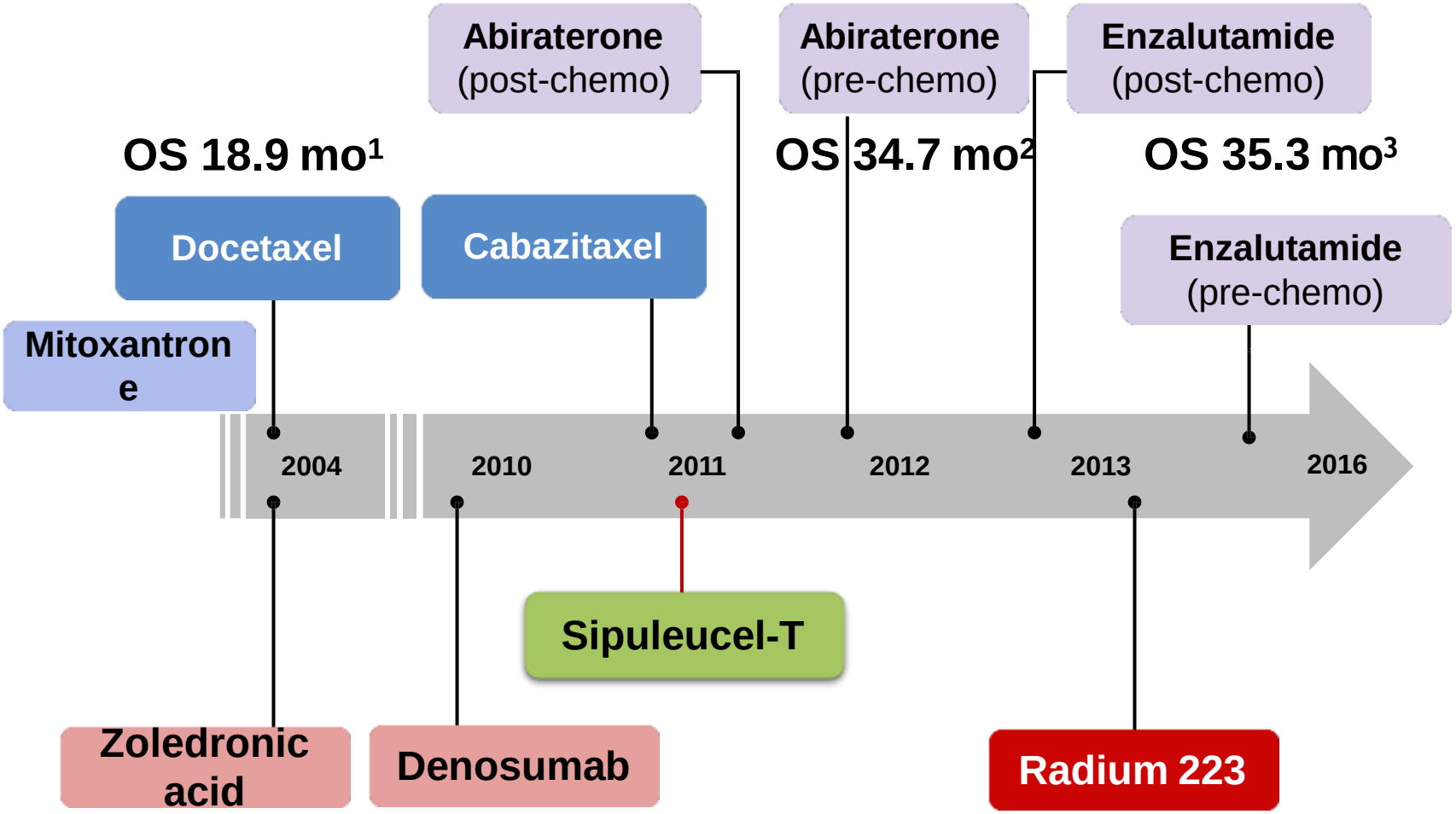
Dr. Antonio Ruiz Fernández

Adjunto Servicio Oncología Medica Área Hospitalaria Zafra-Llerena

INTRODUCCIÓN

- El receptor androgénico como mecanismo clave para la progresión del CPRC
- **El presente**. Las primeras terapias dirigidas al receptor androgénico.
- Principios de Biología Molecular.
- **Presente-Futuro.**
  - ✓ Paneles Genéticos. La búsqueda de Biomarcadores pronósticos y predictivos.
  - ✓ La Biopsia Líquida en la obtención de los Biomarcadores.
  - ✓ La inmunoterapia llega a mCPRC ?
  - ✓ Los primeros biomarcadores. BCRA2. **El tratamiento futuro** hacia la medicina de la precisión.

Cronología aprobación de fármacos en CPRCm



1.Tannock IA et al. N Engl JMed 2004;351:1502-12; 2. Ryan CJet al. Lancet Oncol 2015;16:152–60; 3. Beer TM et al. Eur Urol 2016: doi: 10.1016/j.eururo.2016.07.032 (epub ahead of print)

El receptor Androgénico como mecanismo clave para la progresión del CPRC

Andrógenos: papel que desempeñan en el cáncer de próstata

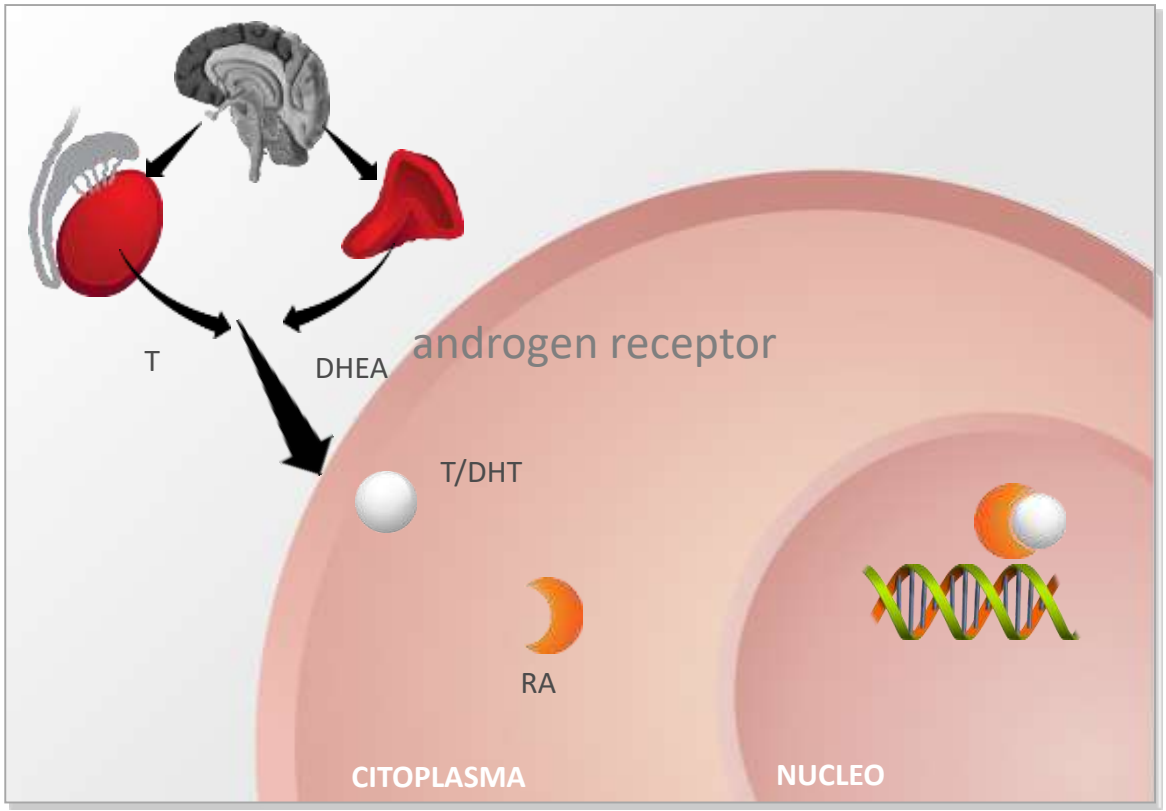
- El cáncer de próstata es un tumor sólido maligno de origen hormonal[1].
- Los andrógenos (testosterona y DHT) son los principales determinantes del crecimiento de las células prostáticas normales y cancerosas[1].
  - Entre el 90 y el 95 % de la testosterona circulante se produce en los testículos.
  - El 5-10 % restante lo sintetizan las glándulas suprarrenales.
- En el cáncer de próstata, los andrógenos y otras moléculas transmiten señales de crecimiento y proliferación a las células malignas[2].
  - Los andrógenos se unen a los RA nucleares activando genes diana que favorecen el crecimiento de las células prostáticas.
  - Por lo tanto, los andrógenos son los principales promotores de la progresión del cáncer de próstata.
- La reducción de los niveles de andrógenos induce la apoptosis de las células prostáticas malignas y normales[2].

RA = receptor androgénico; DHT = dihidrotestosterona.

1. Hou X, Flaig TW. *Adv Urol* 2012 doi:10.1155/2012/9785312.
2. Hu R, *et al. Expert Rev Endocrinol Metab* 2010;5:753-64.

La vía de señalización intracelular del receptor androgénico (RA)

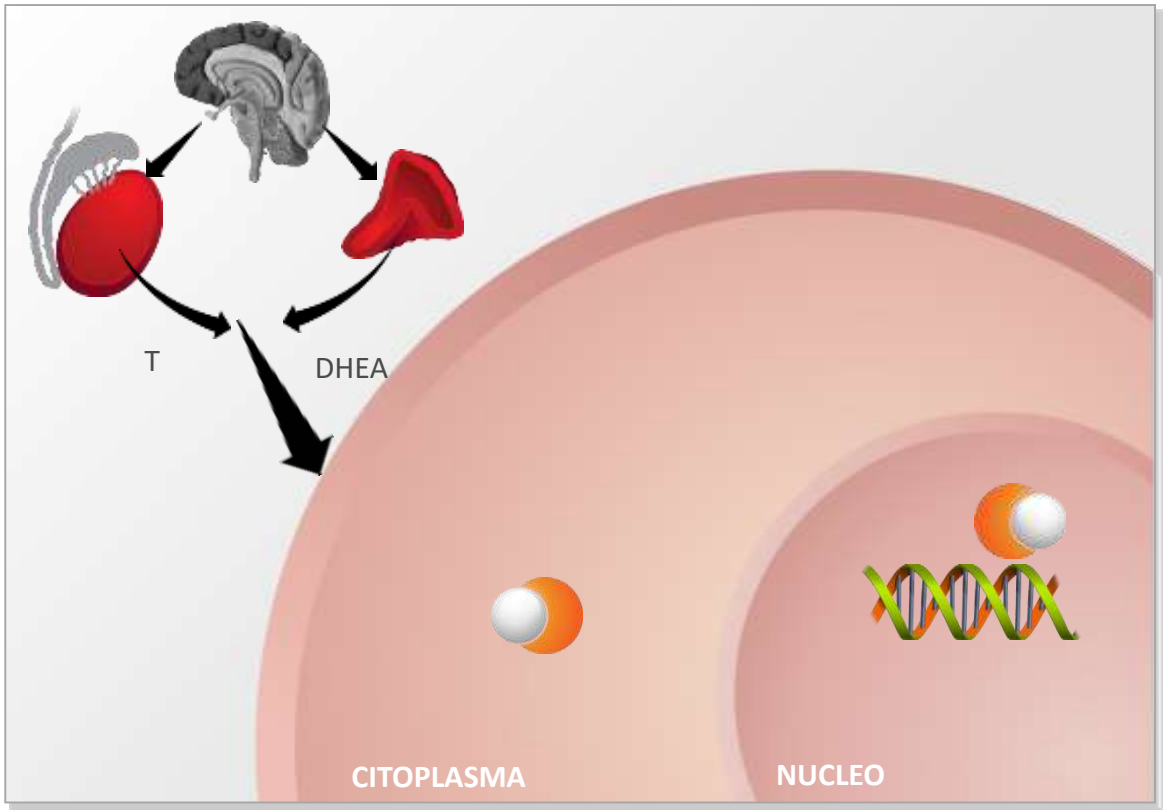
1. Unión Ligando-Receptor Androgénico



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

Heinlein CA, Chang C. *Endocr Rev* 2004;25:276–308.

2. Translocación nuclear del Receptor Androgénico



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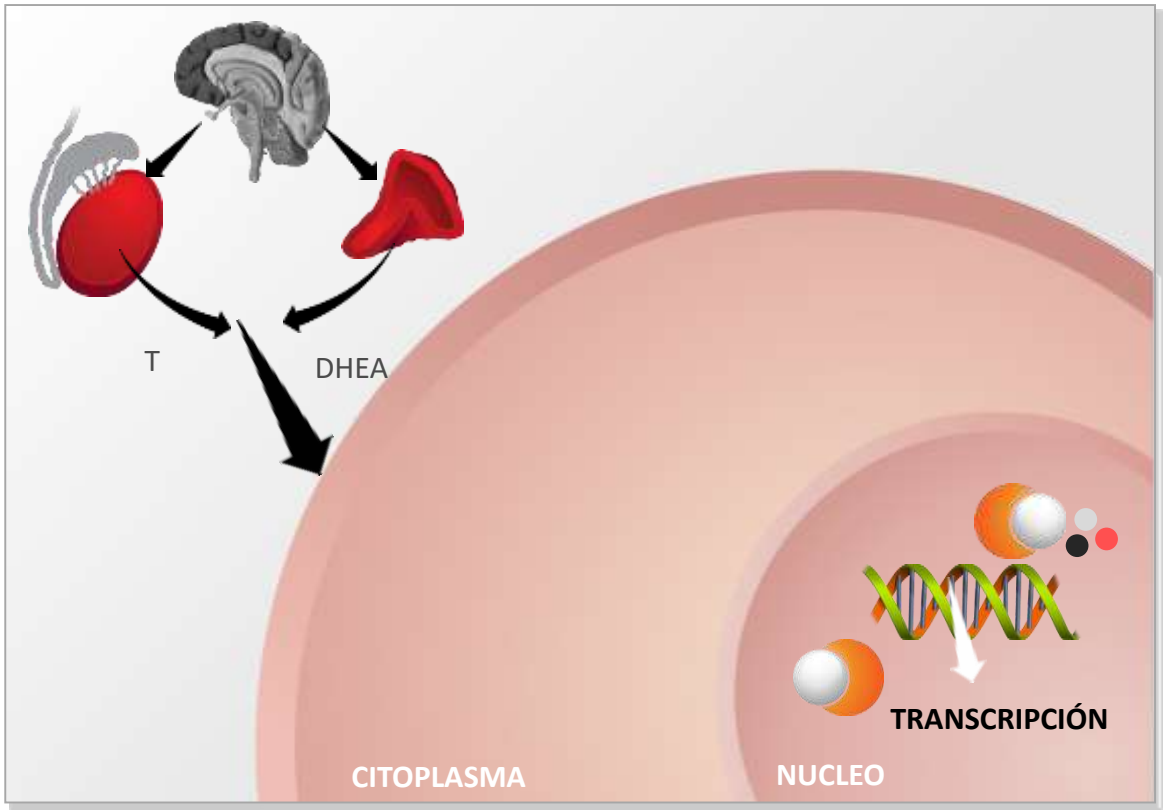
3. Unión Receptor Androgénico y transcripción génica



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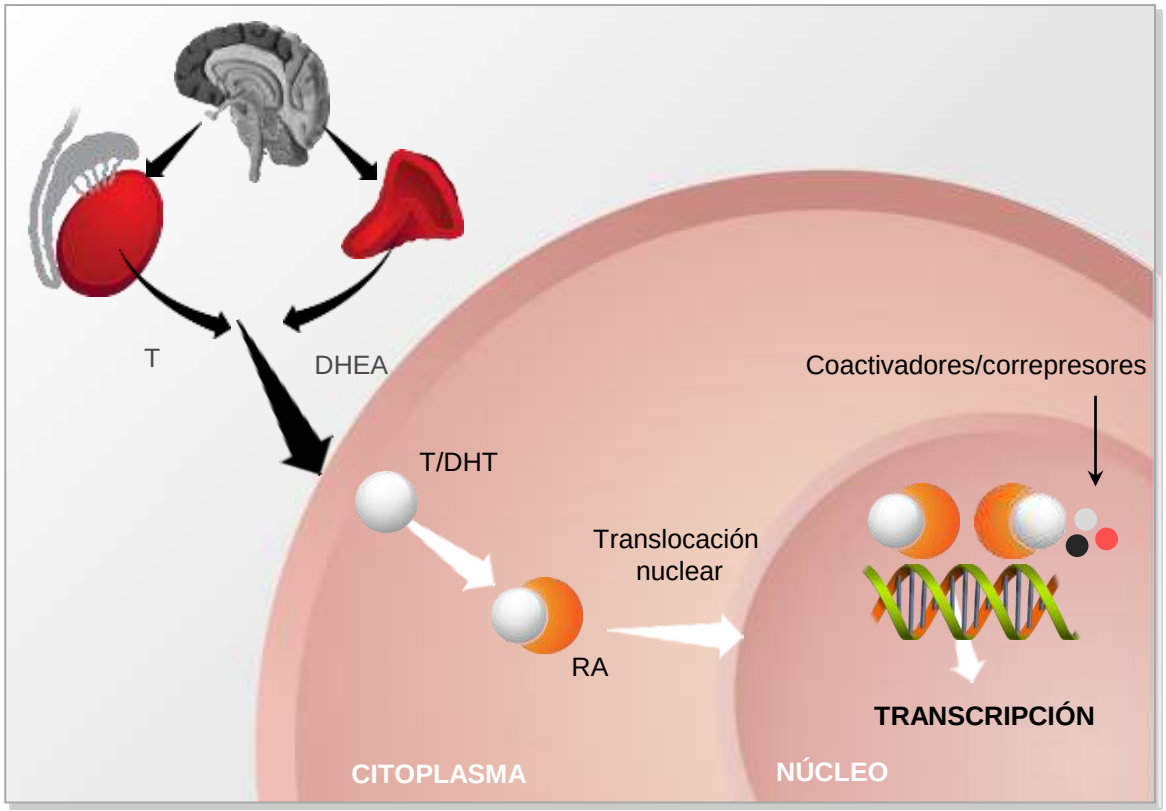

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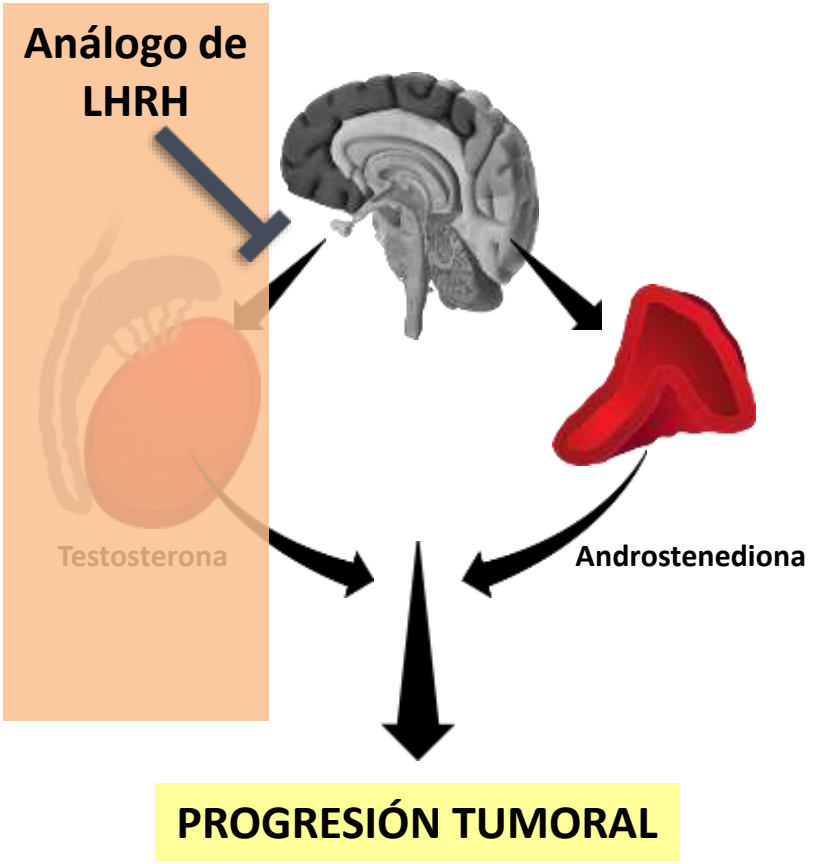
Cáncer de próstata resistente a la castración (CPRC)



- **Progresión del tumor en un ambiente de deprivación de andrógenos**.
  - [Testosterona]p < 50 ng/dl).
  - Maniobra previa de retirada del antiandrógeno.
- **En la mayoría de los pacientes sigue funcionando el mecanismo del RA.**
  - Reactivación de la vía del RA.
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ACTH: corticotropina; LH: hormona luteinizante; LHRH: hormona liberadora de la hormona luteinizante

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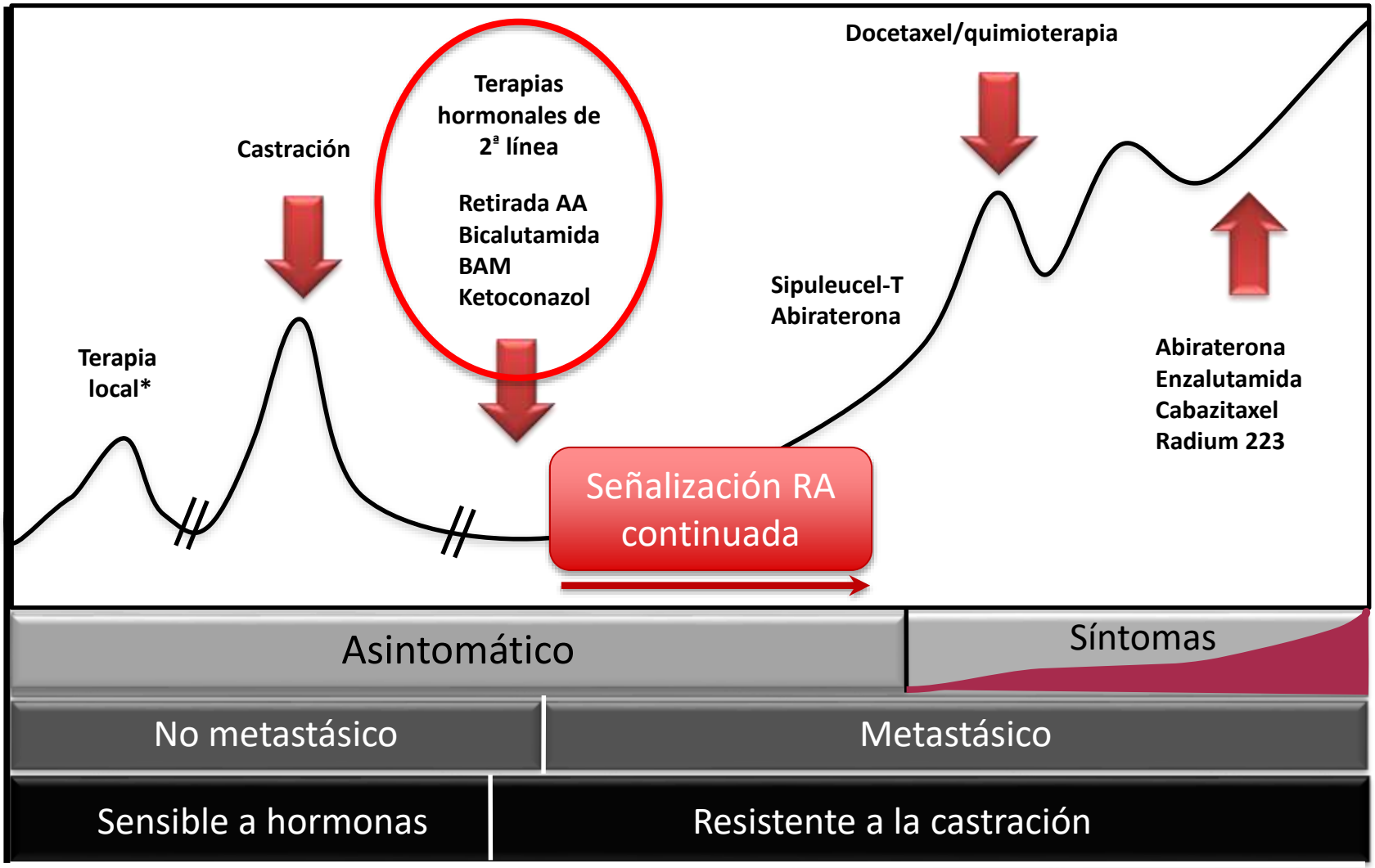
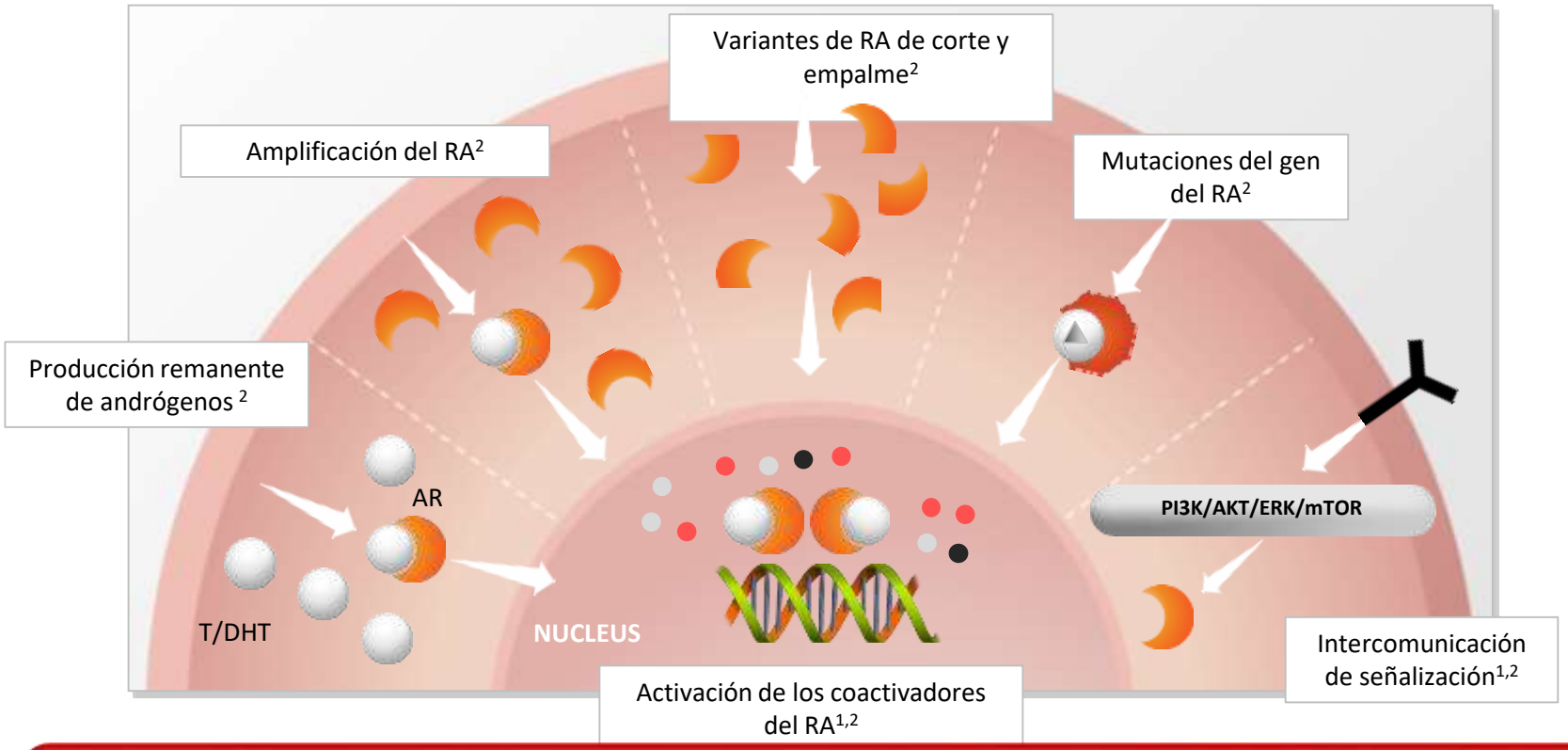
Evolución natural del Cáncer de Próstata



Múltiples procesos moleculares contribuyen a la señalización sostenida del RA :



La señalización del RA es un mecanismo clave en la progresión del CPRC y es una diana lógica del tratamiento.

AR: androgen receptor; DHT: dihydrotestosterone; ERK: extracellular signal-regulated kinase; mTOR: mammalian target of rapamycin; PI3K=phosphatidylinositol-3 kinase; T: testosterone.

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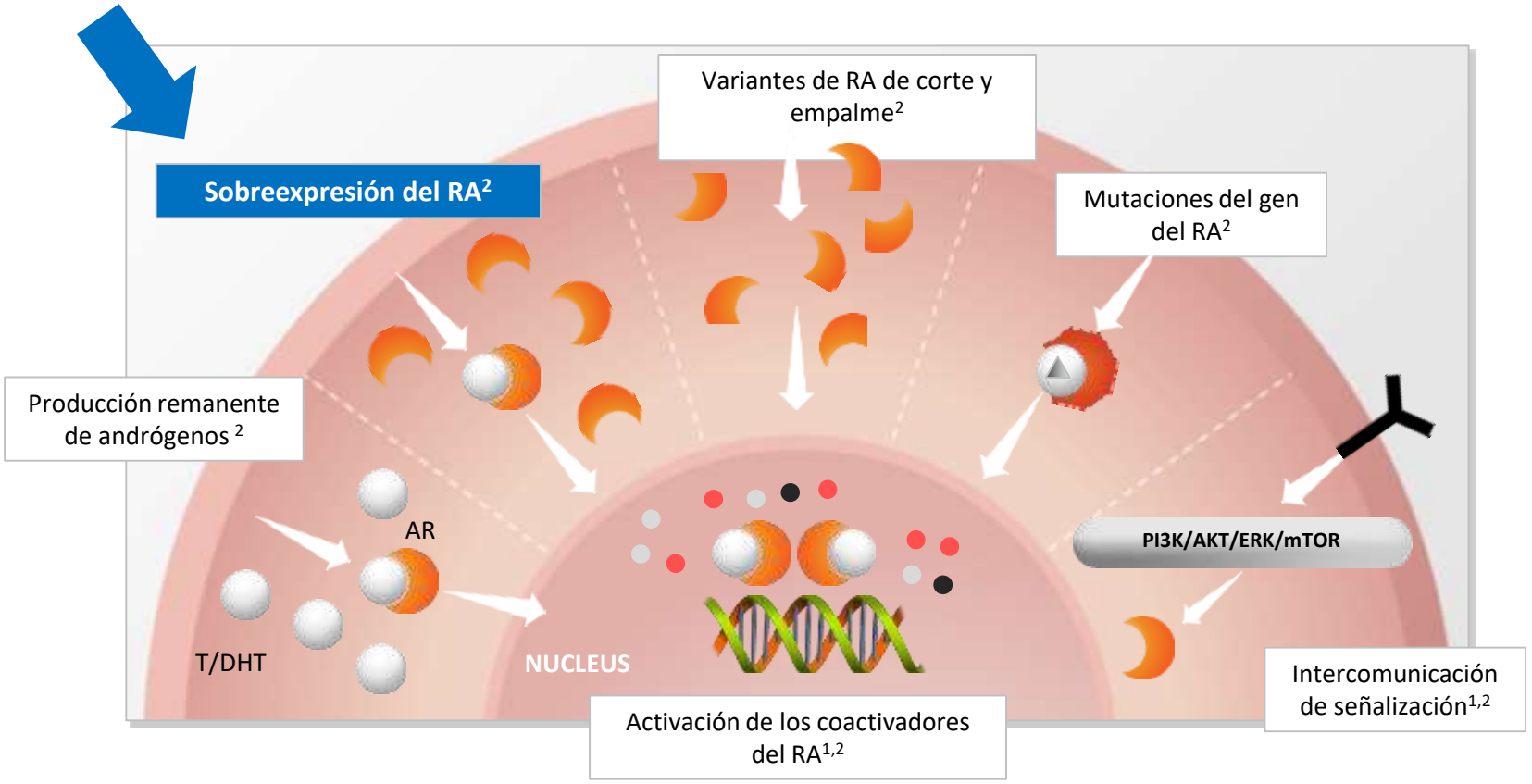

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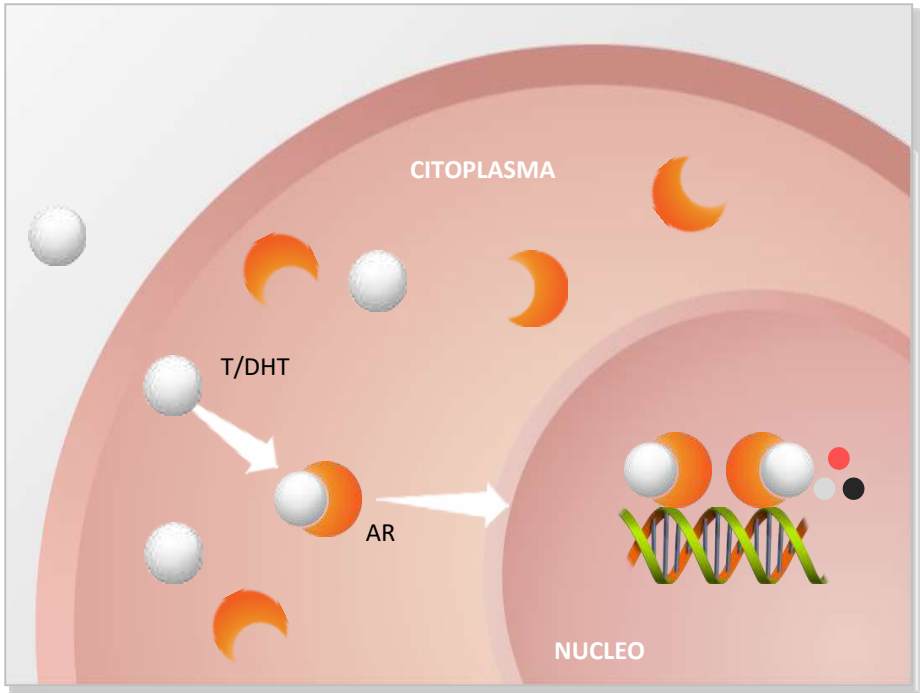
Sobreexpresión del RA

- La amplificación del gen del RA se ha detectado en el 50-85% de los casos de CPRC
- La sobreexpresión del RA lleva a:
  - Aumento de los niveles de proteína del RA
  - Elevada respuesta a bajos niveles de andrógenos.



AR: androgen receptor; CRPC: cáncer de próstata resistente a la castración; DHT: dihidrotestosterona; T: testosterona.
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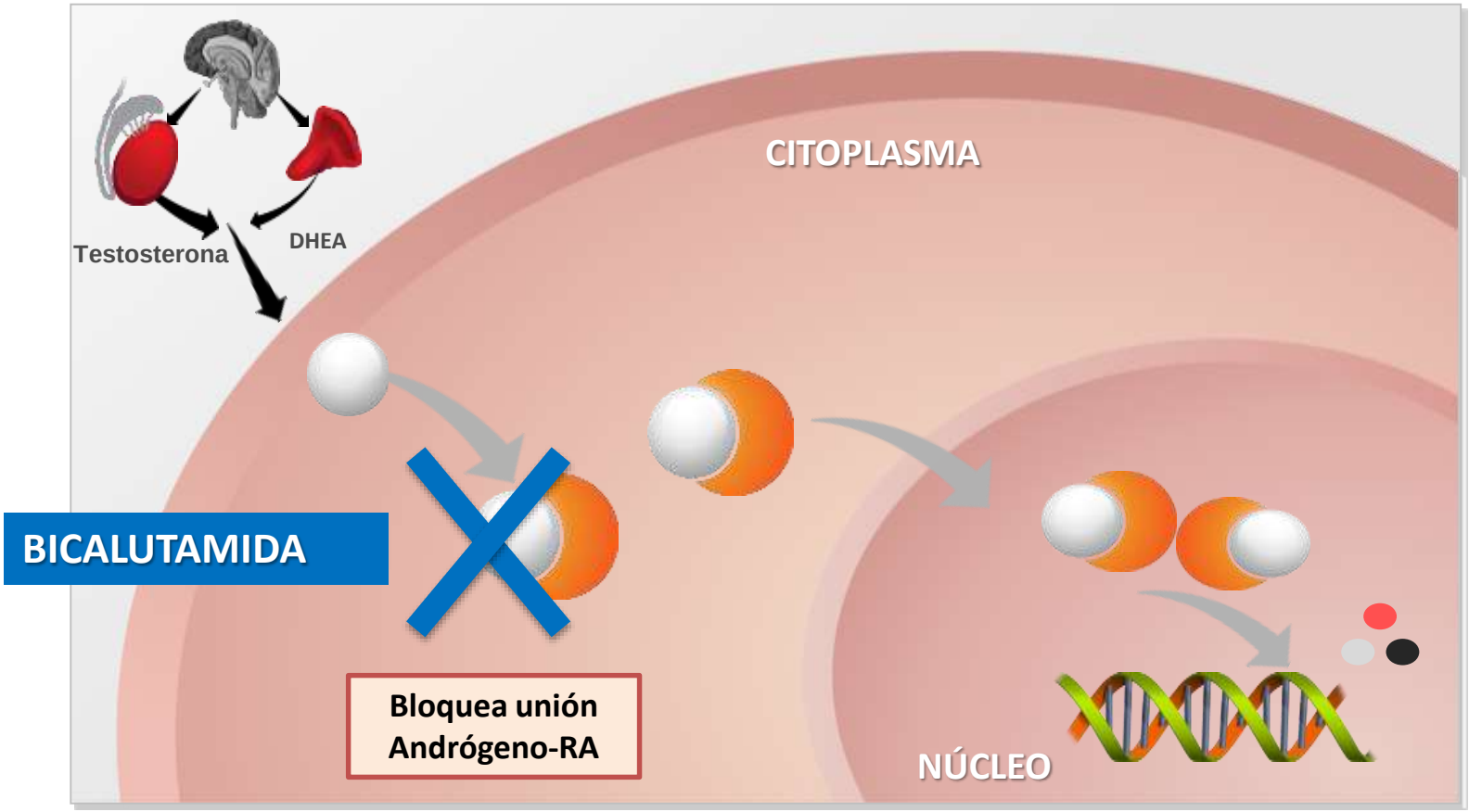
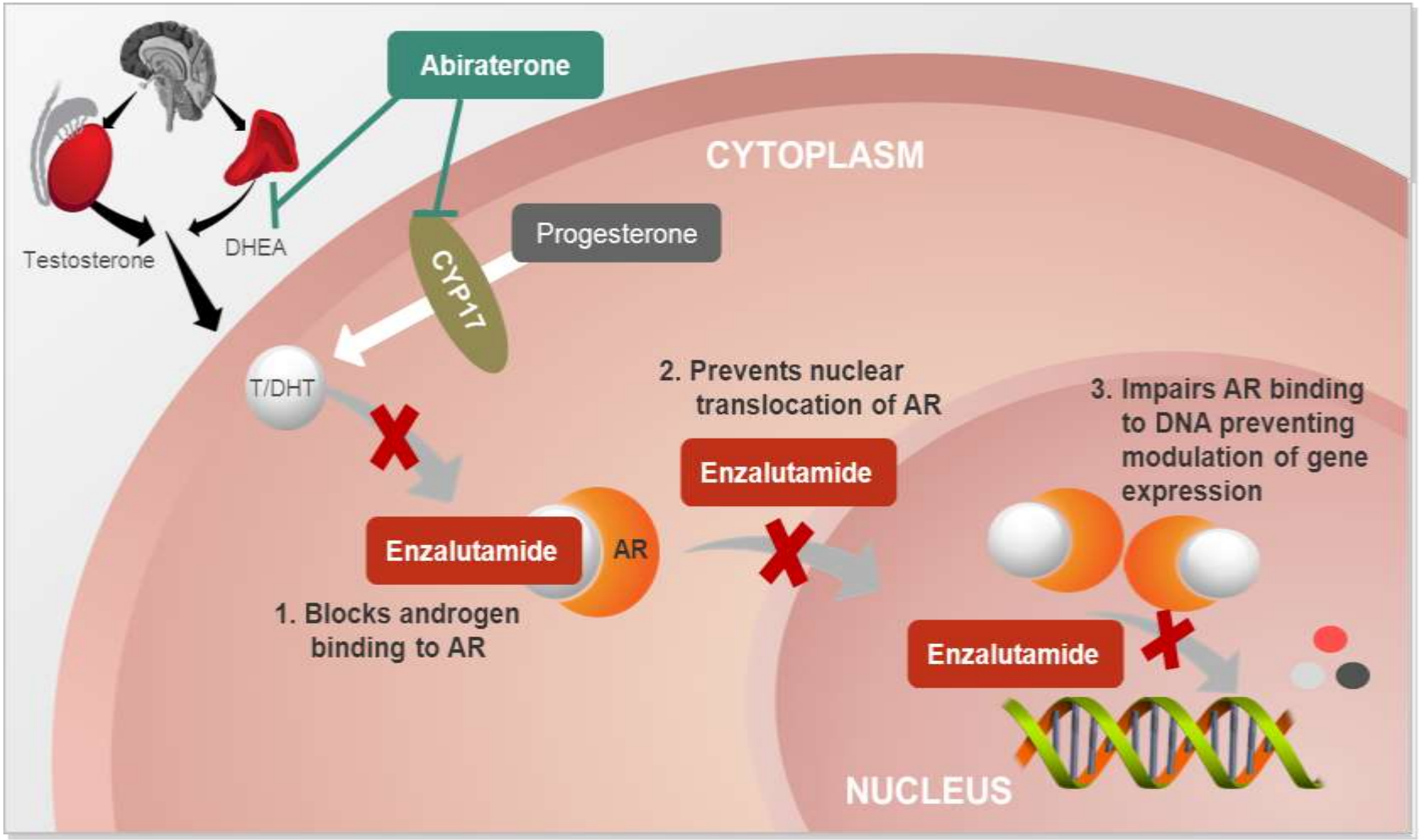
El presente. Las primeras terapias dirigidas al receptor androgénico

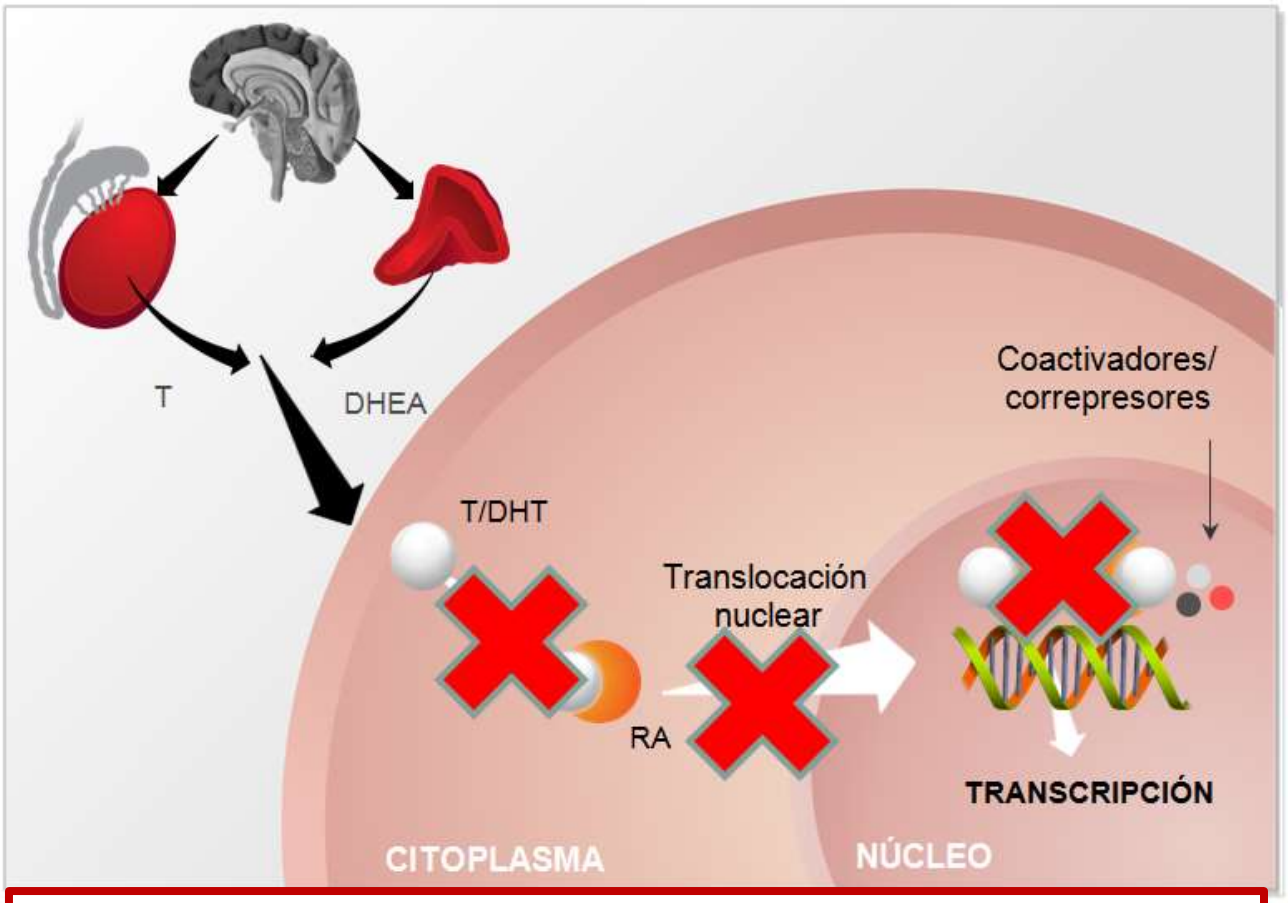
Mecanismo de Acción Antiandrógenos Clásicos



Enzalutamida y abiraterona inhiben la vía de señalización del Receptor Androgénico por mecanismos distintos



Mecanismo de Acción de enzalutamida



Enzalutamida

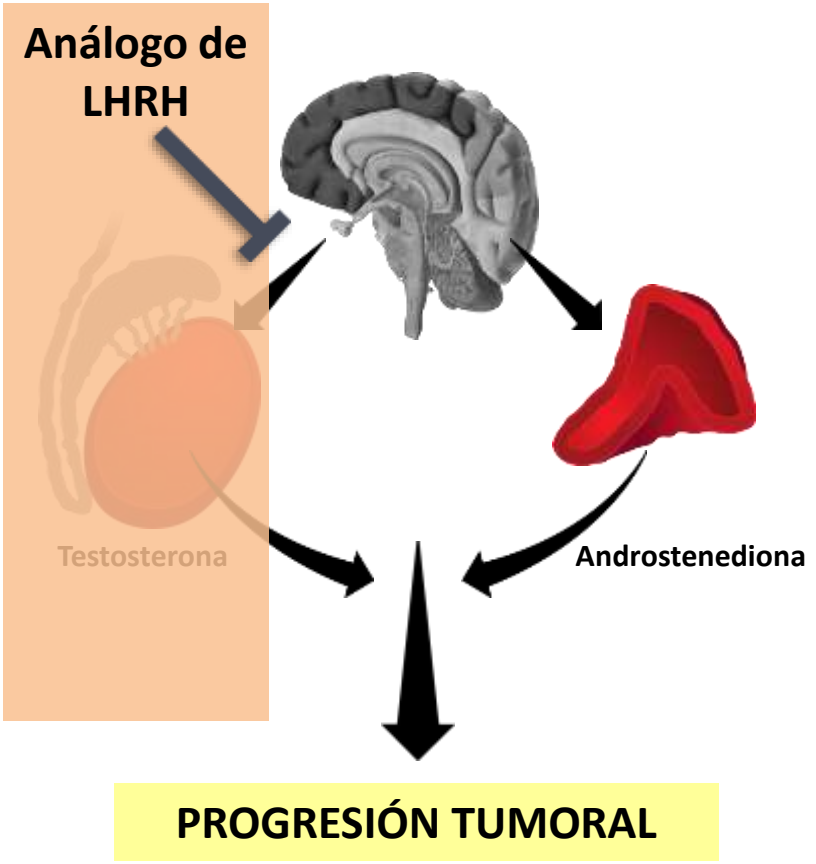
Enzalutamida inhibe la señalización del RA en 3 puntos:

- *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,:testosterone
Ficha Técnica Xtandi

¿RECORDAIS?

Cáncer de próstata resistente a la castración (CPRC)



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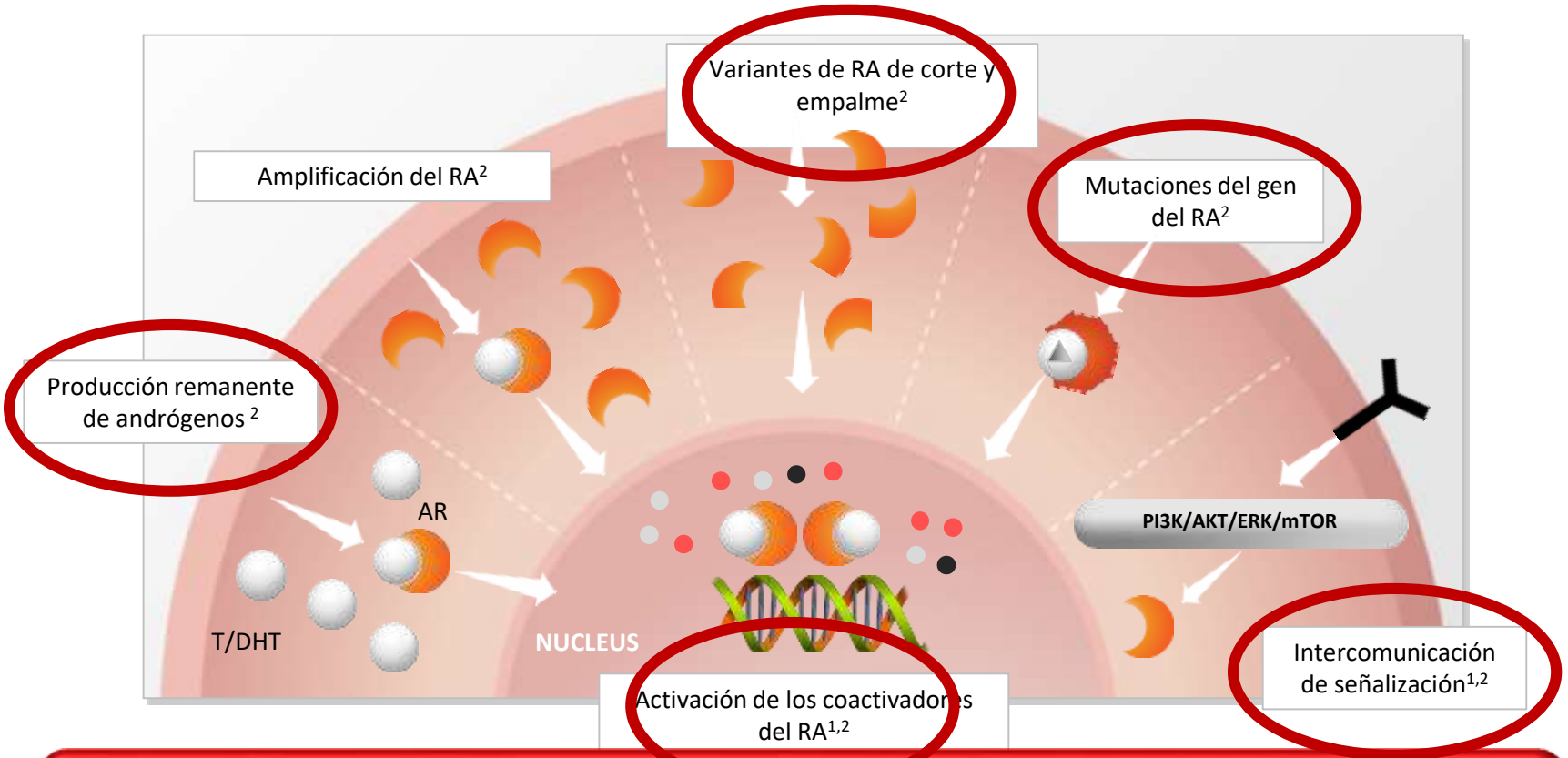

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Principios de Biología Molecular.

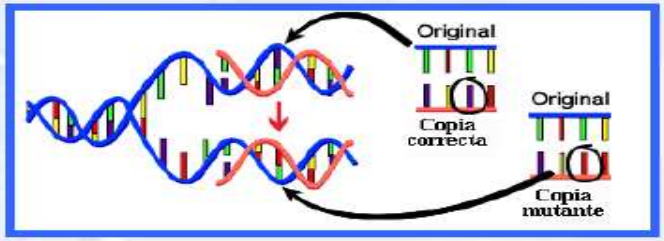
Genoma

- Codificado por ADN.
- El genoma comprende genes y non-coding sequences de ADN
- El ADN codificante se define como aquellas secuencias que se transcriben en mRNA y se traducen en proteínas; estas secuencias ocupan solo una fracción minoritaria del genoma (<2%).
- **ADN no codificante** esta compuesto por secuencias (98% del genoma) que no codifican para proteinas.
- Algunos noncoding DNA contienen genes para moleculas de RNA con funciones biologicas vitales (noncoding RNA, ribosomal RNA y transfer RNA).
- Humanos poseen **3 billones de bases** de información, dividido en 20,000 -22,000 genes, que se distribuyen en **24 cromosomas (22 autosomas mas los sexuales X e Y**.

The complexity of eukaryotic genome https://www.ncbi.nlm.nih.gov/books/NBK9846/

El ADN como material genético

- El material genético debe ser capaz de proporcionar una **fuente de variabilidad** a través del proceso de mutación.
- **Mutación**: cambio que afecta a la composición del ADN que tendrá su reflejo final en la proteína resultante.



- **Mutación línea germinal**: afecta a los gametos, pasará a la descendencia.
- **Mutación somática**: Alteración o cambio en la información genética (ADN) que ocurre después de la concepción.
- Este cambio podrá ser **beneficioso, neutral o perjudicial**.

Tipos de mutaciones

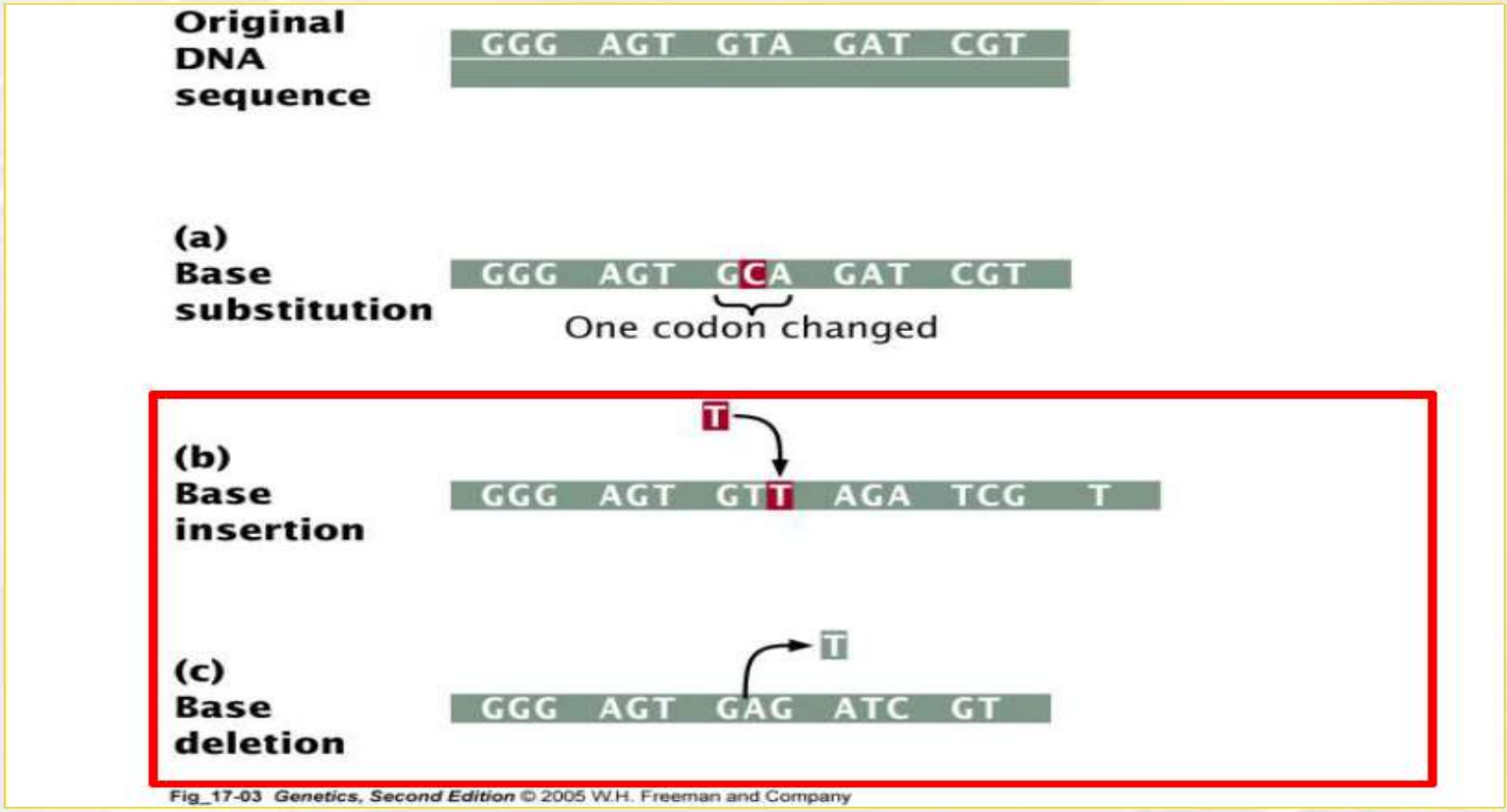
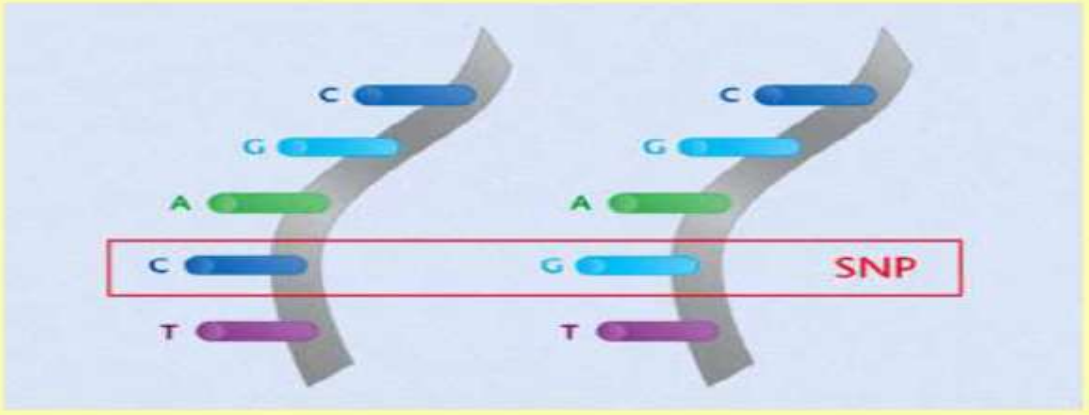


Fig_17-03 *Genetics, Second Edition* © 2005 W.H. Freeman and Company

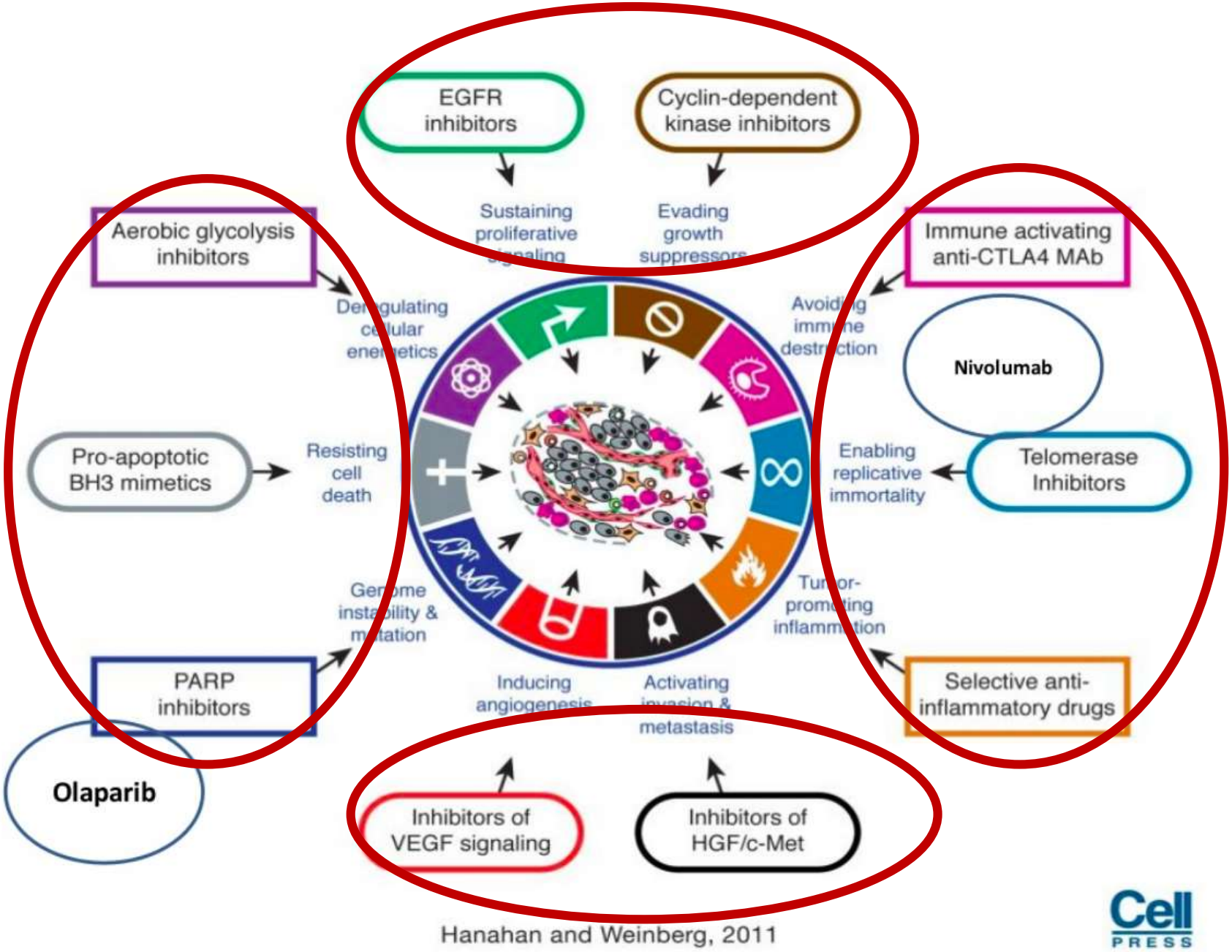
Mutaciones indel: Cambio de la secuencia de codones que debe ser leída durante la traducción, resultando en una proteína completamente diferente, que no suele ser funcional.

SNPs



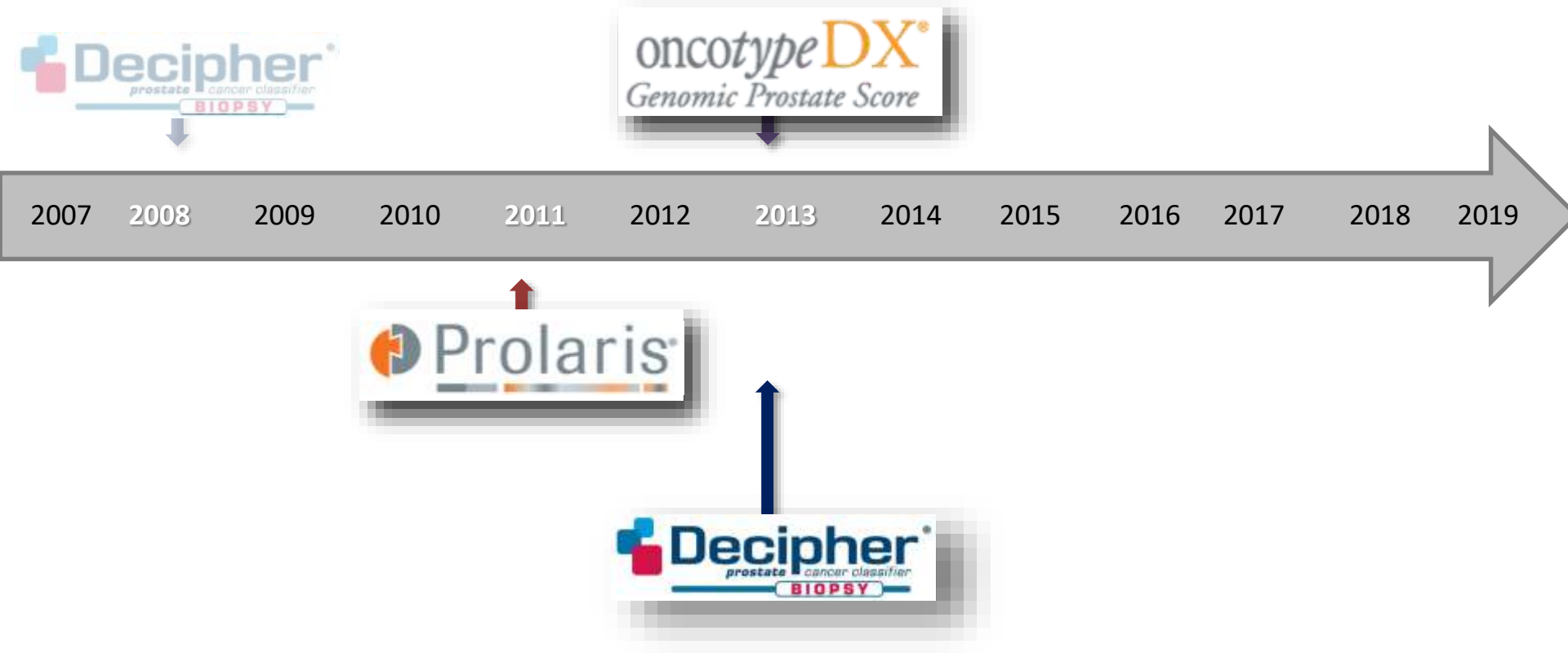
SINGLE NUCLEOTIDE POLYMORPHISM

- Alrededor de 8 millones de SNPs en todo el genoma.
- Algunos pueden producir cambios en proteína:
  - susceptibilidad a padecer enfermedades
  - resistencia a tratamientos específico


EGFR inhibitors
Cyclin-dependent kinase inhibitors
Sustaining proliferative signaling
Evading growth suppressors
Aerobic glycolysis inhibitors
Deregulating cellular energetics
Immune activating anti-CTLA4 MAb
Avoiding immune destruction
Nivolumab
Pro-apoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability & mutation
Tumor-promoting inflammation
PARP inhibitors
Olaparib
Inducing angiogenesis
Activating invasion & metastasis
Selective anti-inflammatory drugs
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met
Hanahan and Weinberg, 2011
Cell PRESS

Paneles Genéticos.
La búsqueda de Biomarcadores pronósticos y predictivos

Paneles genéticos en cáncer de próstata



Paneles genéticos en cáncer de próstata

Predicción de la metástasis precoz, en 5 años.

Resultados:

Table 4. Univariable and multivariable odds Ratios for CC, GC and GCC, and clinicopathologic variables.

	Univariable		Multivariable	
	Odds Ratio (95% CI)	**P**	**Odds Ratio (95% CI)**	**P**
GC	1.42 (1.28–1.60)	p<0.001	1.36 (1.16–1.60)	p<0.001
GCC	1.36 (1.21–1.53)	p<0.001	n.a	n.a
CC	1.35 (1.15–1.59)	p<0.001	n.a	n.a
Pre-operative PSA	0.99 (0.77–1.26)	0.92	0.75 (0.52–1.07)	0.11
Pathologic Gleason Score ≥8	3.02 (1.61–5.68)	p<0.001	1.91 (0.85–4.33)	0.12
Seminal Vesicle Invasion	2.44 (1.30–4.58)	0.01	1.93 (0.79–4.73)	0.15
Tumor Volume	1.02 (0.97–1.06)	0.44	0.97 (0.92–1.04)	0.42
Lymph Node Involvement	1.69 (0.74–3.88)	0.21	1.42 (0.41–4.96)	0.58
Positive Surgical Margins	1.05 (0.57–1.93)	0.87	0.93 (0.40–2.17)	0.87
Extra-capsular Extension	2.01 (1.18–3.73)	0.03	1.00 (0.45–2.20)	0.99

Odd ratios for multivariable classifiers are adjusted as indicated in the Materials and Methods. CC: clinical-only classifier. GC: genomic classifier. GCC: integrated genomic-clinical classifier.

doi:10.1371/journal.pone.0066855.t004

Erho N. PLOS One 2013

DECIPHER
PROSTATE BIOPSY

DECIPHER BIOPSY REPORT

GenomeDx Biosciences Laboratory
10355 Science Center Drive, Suite 240
San Diego, CA 92121
Tel 1.888.792.1601 | Fax 1.855.324.2788
customersupport@genomedx.com | www.genomedx.com

PATIENT DETAILS
Patient Name:
MRN/Patient ID:
Date of Birth: 1
Date of Biopsy:
Pathology Laboratory:
Pathologist:
Address:

ORDER INFORMATION
Order Date:
Specimen Received Date:
GenomeDx Accession ID:
Specimen ID:
Ordering Physician:
Clinic/Hospital Name:
Clinic/Hospital Address:

CLINICAL DETAILS
PSA, Most Recent (ng/mL): 7.1
Specimen Type: **Needle Biopsy**
NCCN Risk Category: **Intermediate Risk**
# of Positive Cores: **11 (11 of 42 Cores)**
Gleason Score: **3+4**
Clinical Stage: **T1c**

YOUR DECIPHER RESULT: GENOMIC LOW RISK

DECIPHER SCORE: 0.23

Risk at RP - Person Lowmost	
High Grade Disease (primary Gleason grade 4 or 5)	12.5%
5-Year Metastasis	1.0%
10-Year Prostate Cancer Specific Mortality	1.9%

INTERPRETATION

Clinical studies have shown that men with a Decipher low risk score have a favorable prognosis. Men considering active surveillance with a Decipher low risk score may be suitable candidates for active surveillance. Men considering a definitive therapy may have excellent outcomes when treated with local therapy alone.[1]

1.0
0.60
0.45
0
DECIPHER SCORE
HIGH RISK
AVG.* RISK
LOW RISK
YOUR DECIPHER SCORE

SAMPLE

Genomic Clasifier
Decipher
BIOPSY

	Manejo sugerido
Decipher Biopsy **Alto Riesgo**	**Pronóstico desfavoreble**- puede no ser un candidato adecuado para vigilancia activa y puede beneficiarse de **intensificación con terapia multimodal.**
Decipher Biopsy **Riesgo Intermedio**	**Pronóstico intermedio**- existe un riesgo clínico y pronóstico intermedio. Dependiendo de esperanza de vida y estado general, pueden beneficiarse de *intensificación con* ***terapia multimodal.***
Decipher Biopsy **Bajo Riesgo**	**Pronóstico favorable**- puede ser un candidato adecuado para **vigilancia activa** y puede tener excelentes resultados cuando se trata sólo con **terapia local,** como cirugía o radioterapia.

PROLARIS® BIOPSY TEST RESULT

ORDERING PHYSICIAN
Bob Doctor MD

123 Grand Ave
Las Vegas, NV 89109

Joe Pathologist MD

CLINICOPATHOLOGIC FEATURES USED FOR ANALYSIS

Patient Age at Diagnosis:	65	% Positive Cores:	25% (3/12)
PSA Prior to This Biopsy:	9.0	Gleason Score:	3+3=6
Clinical T Stage:	T1c	AUA Risk:	Low

SPECIMEN

Specimen Type:	Tissue Block	Sample Received:	Jun 10, 2016
Tissue:	Prostate	Accession Date:	Jun 10, 2016
Biopsy Date:	Mar 13, 2015	Report Date:	Aug 15, 2016
TRF Received:	Jun 10, 2016		

PATIENT

Name:	Patient, Dave	Accession #:	07000106-BLD
Date of Birth:	Oct 26, 1946	Requisition #:	07000106
Patient ID:	12654		
Gender:	Male		

Block(s) Analyzed: 12345546821-8

Less Aggressive
Than Average AUA¹ Low Risk

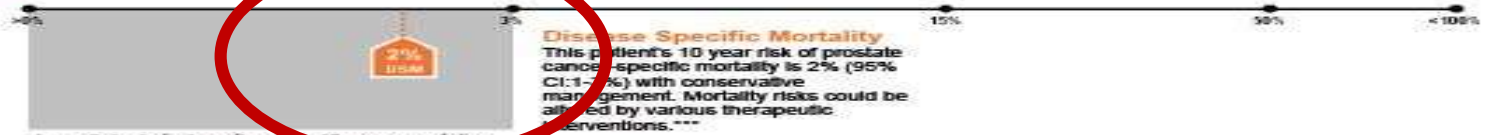
PROLARIS SCORE 2.5

US Distribution Percentile: 9%
(For AUA Low Risk)

Interpretation: 9% of patients in the AUA Low Risk* category have a lower Prolaris Score

Mortality Risk

Mortality Risk: [illegible]% 10-Year Prostate Cancer-Specific



Disease Specific Mortality
This patient's 10 year risk of prostate cancer-specific mortality is 2% (95% CI:1-[illegible]%) with conservative management. Mortality risks could be altered by various therapeutic interventions.***

In a clinical study estimating 10-year prostate cancer-specific mortality risks [illegible] using conservative management, there were no observed prostate cancer deaths in patients with a predefined clinical risk score (CCP combined with CAPRA) corresponding to a 3.2% (95% CI 2.0, 5.2%) prostate cancer-specific mortality risk. **

Prolaris
Myriad Genetic Laboratories, Inc.
320 Wakara Way, Salt Lake City, Utah 84108 | 800.469.7423 | Fax 801.584.3615
prolaris.com

MMM58234

Genomic Health

Genomic Prostate Score

oncotype DX Genomic Prostate Score

Genomic Prostate Score (GPS) Report

oncotype DX Genomic Prostate Score

PATIENT-LAST-NAME, FIRST-NAME I.

Date of Birth: **01-Jan-1950** Gender: **Male** Report Number: **OR000123456-01** Report Date: **22-May-2017**

Ordering Physician: **Dr. First-Name I. Ordering-Physician-Last-Name**

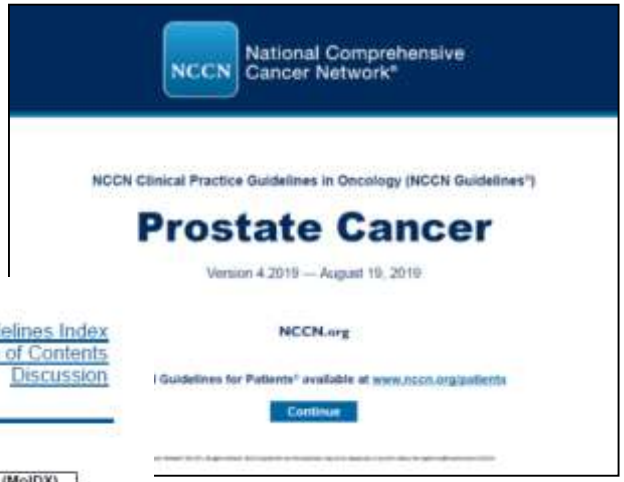
GPS + NCCN®[1] : Very Low Risk

Clinical Interpretation	Clinical Endpoints[†]	Individualized Risk (95% Confidence Interval [CI])
The combination of GPS and clinical features predicts that this patient's risk is consistent with **NCCN Very Low Risk** disease.[‡]	**Prostate Cancer Death Within 10 Years**	<1% (95% CI: <1% - <1%)
In a clinical validation study including patients with NCCN Very Low, Low, and Intermediate Risk, **no patient with a GPS result <20 had metastasis or died** from prostate cancer within 10 years.[†]	**Metastasis Within 10 Years**[§]	1% (95% CI: <1% - 4%)
	Adverse Pathology (Gleason ≥ 4+3 and/or pT3+)	16% (95% CI: 12 % - 21%)

Paneles genómicos en Cáncer de próstata

	Estudio "pivotal"		Validaciones posteriores		¿Costes?[1]
Test	**Tejido**	**Objetivo (predicción)**	**Tejido**	**Objetivo (predicción)**	
Genomic Classifier Decipher®	**Prostatectomía**	• **Metástasis a 5 años**	**Biopsia**	*Vigilancia activa*[2], **SLM, SCE, SG**	***US$ 4250***
			Prostatectomía	*Patología adversa*[2], **SLM, SCE, SG, Respuesta a Radioterapia (adyuvante/rescate), Asociación a MRI, N(+) en PSMA**	
*Panel de **22 genes** implicados en **Proliferación del ciclo celular, Adhesión y movilidad, Inmuno-modulación, y Señalización del RA.***					
Cell-cycle proliferation Prolaris®	**Prostatectomía RTU (WW)**	• **Recidiva bioquímica** • **Muerte**	**Biopsia**	**SLRBª, Patología adversa, MRI**	***US$ 3400***
			Prostatectomía	**SLRBª.**	
*Firma de **46 genes** implicados en exclusiva en la **Proliferación del ciclo celular.***					
Genomic prostate score Oncotype®	**Prostatectomía Biopsia**	• **AP adversa** (pT3 / GG3)	**Biopsia**	**Patología adversa**	***US$ 3825***
			Prostatectomía	**SLM, SCE, MRI,**	
*Panel de **17 genes** implicados en **Respuesta estromal, Organización celular, Proliferación, Epitelio basal, Respuesta al estrés, Y Señalización del RA.***					

[1] Davis JW. Novel commercially available genomic tests for prostate cancer: a roadmap to understanding their clinical impact. BJU Int. 114(3), 320–322 (2014).
[2] Identifican no candidatos a VA por asociar GC a patología adversa, pero el studio lo realizan sobre prostatectomías.



National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Table 1. Available Tissue-Based Tests for Prostate Cancer Risk Stratification/Prognosis

Test	Platform	Populations Studied	Outcome(s) Reported (Test independently predicts)	Selected References	Molecular Diagnostic Services Program (MolDX) Recommendations
Decipher	Whole-transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post radical prostatectomy (RP), adverse pathology/high-risk features	• Metastasis • Prostate cancer-specific mortality • Postoperative radiation sensitivity (PORTOS)	140,143,144,243 ,671,731-743	Cover post-biopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
		Post RP, biochemical recurrence	• Metastasis • Prostate cancer-specific mortality • PORTOS		
		Post RP, adjuvant, or salvage radiation	• Metastasis • Prostate cancer-specific mortality • PORTOS		
		Biopsy, localized prostate cancer post RP or EBRT	• Metastasis • Prostate cancer-specific mortality • Gleason grade ≥4 disease at RP • Adverse pathologic features at RP		
Ki-67	IHC	Biopsy, intermediate- to high-risk treated with EBRT	• Metastasis	744-747	Not recommended
		Biopsy, conservatively managed (active surveillance)	• Prostate cancer-specific mortality		
Oncotype DX Prostate	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls	Biopsy, low- to intermediate-risk treated with RP	• Non-organ-confined pT3 or Gleason grade 4 disease on RP	139,748-751	Cover post-biopsy for NCCN very-low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
Prolaris	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	Transurethral resection of the prostate (TURP), conservatively managed (active surveillance)	• Prostate cancer-specific mortality	135-138,752-754	Cover post-biopsy for NCCN very-low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
		Biopsy, conservatively managed (active surveillance)	• Prostate cancer-specific mortality		
		Biopsy, localized prostate cancer	• Biochemical recurrence • Metastasis		
		Biopsy, intermediate-risk treated with EBRT	• Biochemical recurrence		
		RP, node-negative localized prostate cancer	• Biochemical recurrence		
ProMark	Multiplex immunofluorescent staining of 8 proteins	Biopsy, Gleason grade 3+3 or 3+4	• Non–organ-confined pT3 or Gleason pattern 4 disease on RP	755	Cover post-biopsy for NCCN very-low- and low-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.
PTEN	Fluorescence in situ hybridization or IHC	TURP, conservatively managed (active surveillance)	• Prostate cancer-specific mortality	756-760	Not recommended
		Biopsy, Gleason grade 3+3	• Upgrading to Gleason pattern 4 on RP		
		RP, high-risk localized disease	• Biochemical recurrence		

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

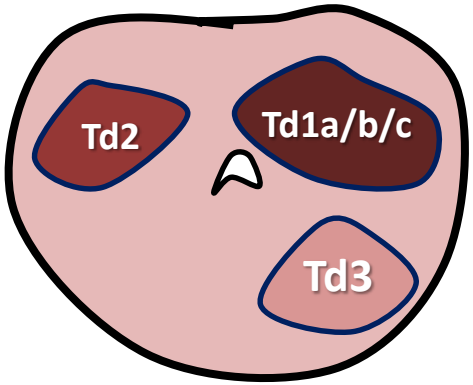
Platinum Priority – Prostate Cancer

Intratumoral and Intertumoral Genomic Heterogeneity of Multifocal Localized Prostate Cancer Impacts Molecular Classifications and Genomic Prognosticators

Lei Wei, Jianmin Wang, Erika Lampert, Simon Schlanger, Adam D. DePriest, Qiang Hu, Eduardo Cortes Gomez, Mitsuko Murakami, Sean T. Glenn, Jeffrey Conroy, Carl Morrison, Gissou Azabdaftari, James L. Mohler, Song Liu, Hannelore V. Heemers

N = 4 p., 26 cilindros

Pieza de prostatectomía,
fijada en parafina



Td1a/b/c:	**Heterogeneidad intratumoral**
Td2/3/4/5:	**Heterogeneidad intertumoral**

Wei L. Eur Urol 2017

DEBILIDADES DE LOS PANELES GENETICOS

Oncotype DX (12 genes)	Prolaris (31 genes)	Decipher (22 genes)
AZGP1	FOXM1	LASP1
KLK2	CDC20	IQGAP3
SRD5A2	CDKN3	NFIB
FAM13C	CDC2	S1PR4
FLNC	KIF11	THBS2
GSN	KIAA0101	ANO7
TPM2	NUSAP1	PCDH7
GSTM2	CENPF	MYBPC1
TPX2	ASPM	EPPK1
BGN	BUB1B	TSBP
COL1A1	RRM2	PBX1
SFRP4	DLGAP5	NUSAP1
	BIRC5	ZWILCH
	KIF20A	UBE2C
	PLK1	CAMK2N1
	TOP2A	RABGAP1
	TK1	PCAT-32
	PBK	GLYATL1P4/PCAT-80
	ASF1B	TNFRSF19
	C18orf24	
	RAD54L	
	PTTG1	
	CDCA3	
	MCM10	
	PRC1	
	DTL	
	CEP55	
	RAD51	
	CENPM	
	CDCA8	
	ORC6L	

Wei L. Eur Urol 2017

Prostate cancer genomics: comparing results from three molecular assays

Syed Alam, MD,[1] Joseph Tortora, MS,[2] Ilene Staff, PhD,[2] Tara McLaughlin, PhD,[1] Joseph Wagner, MD[1]

[1]Urology Division, Hartford Healthcare Medical Group, Hartford Hospital, Hartford, Connecticut, USA
[2]Hartford Hospital Research Program, Hartford Hospital, Hartford, Connecticut, USA

Valoración del Índice Kappa	
Valor de k	**Fuerza de la concordancia**
< 0.20	Pobre
0.21 – 0.40	Débil
0.41 – 0.60	Moderada
0.61 – 0.80	Buena
0.81 – 1.00	Muy buena

TABLE 4. Agreement between each test and results of surgical pathology

Patient	Gleason group	Stage	Margin	Oncotype	Prolaris	Decipher
1	2	T3aN0	Negative	Unfavorable	-	Unfavorable
2	2	T2cN0	Negative	Unfavorable	-	Favorable
3	2	T3bN1	Positive	-	Unfavorable	Favorable
4	2	T2cN0	Negative	-	Favorable	Favorable
5	2	T2cN0	Positive	-	Favorable	Unfavorable
6	2	T3bN0	Negative	-	Favorable	Favorable
7	3	T3bN0	Negative	-	Unfavorable	Favorable
8	4	T3bN0	Positive	-	Unfavorable	Unfavorable

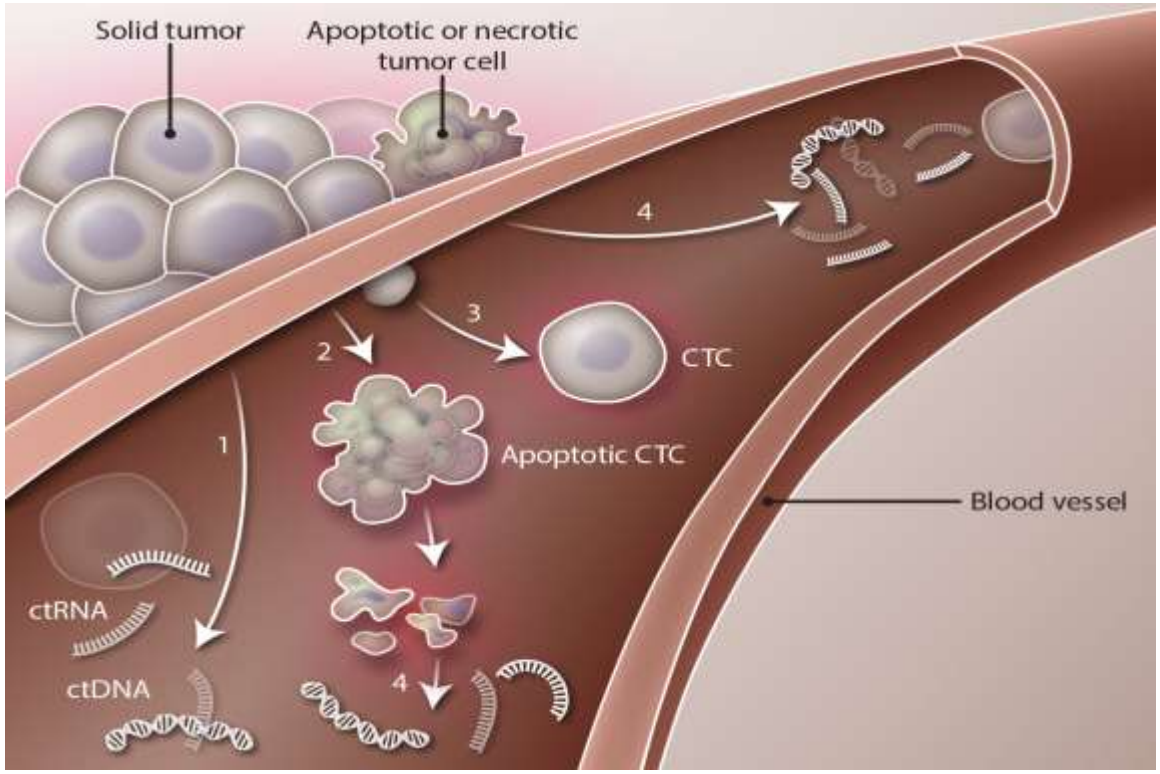
TABLE 3. Agreement between tests

Tests	n	% agree	kappa	p value	Δ Definition favorable test
Decipher vs. Prolaris	12	67%	0.31	0.276	62%
Prolaris vs. Oncotype DX	8	75%	0.39	0.168	89%
Decipher vs. Oncotype DX	2	50%	-	-	50%

Alam S. Can J Urol 2019

La Biopsia Líquida en la obtención de los Biomarcadores

"test <u>minimamente invasivo</u> que se realiza utilizando un fluido corporal (sangre, orina, semen, líquido cefalorraquídeo) y que permite la detección de biomarcadores celulares o moleculares con el fín de obtener informacion ***diagnóstica, pronóstica*** *o* ***predictiva*** *de la enfermedad"*



cfDNA

CTCs

mRNA

Exoxomas

Proteínas

(…)

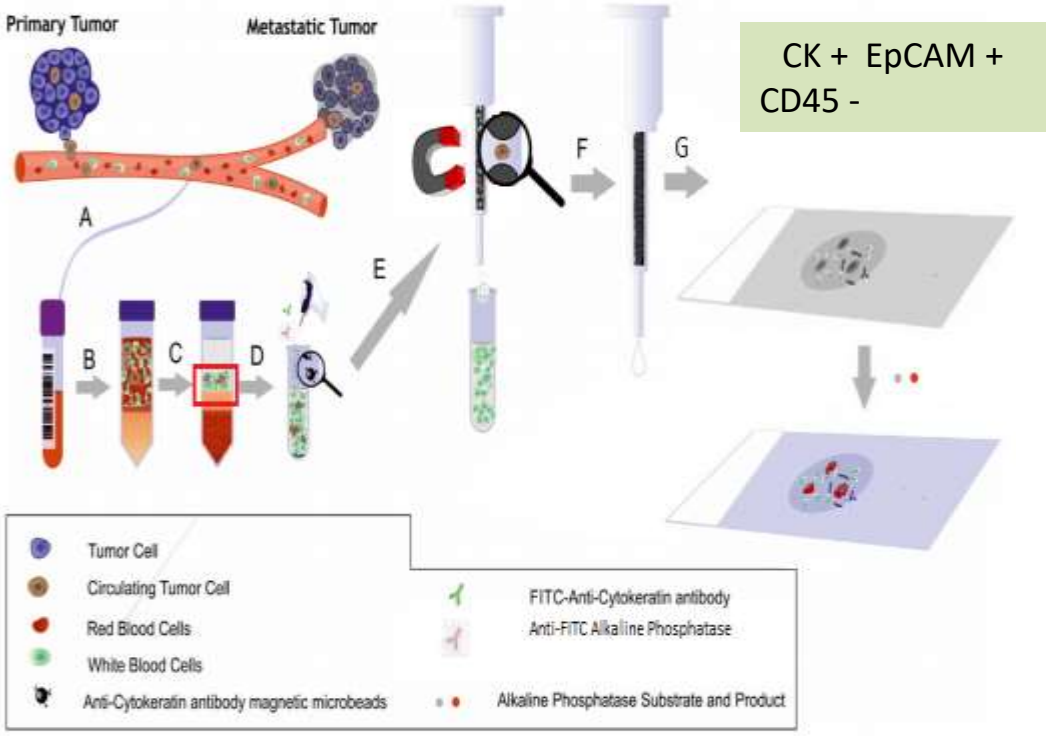
Diaz, L.A & Bardelli, A. *Liquid biopsies: genotyping circulating tumor DNA*. J Clin Oncol. 2014

¿Cómo se detectan las CTCs?

1.- **Fase enriquecimiento** (centrifugado, lavado, conservación)

2.- **Fase aislamiento** (inmunomagnético) CKs y marcadores epiteliales

3.- **Fase selección** (manual, semiautomática, automática)



CK + EpCAM + CD45 -

Marcadores epiteliales

Sistema CellSearch

(Veridex, LLC, Raritan, NJ, USA
FDA approved 2012)

breast cancer:>5 CTCs/7.5 mL
colorectal cancer: >3 CTCs/7.5 mL
prostate cancer: **>5** CTCs/7.5 mL

SLP y SG
en pacientes CPRCm

de Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res. 2008 Oct 1; 14(19): 6302-9
Scher HI, Heller G, Molina A, et al. Evaluation of circulating tumor cell (CTC) enumeration as an efficacy response biomarker of overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC): planned final analysis (FA) of COU-AA- 301, a randomized, double-blind, placebo-controlled phase III study of abiraterone acetate (AA) plus low-dose prednisone (P) post docetaxel. *J Clin Oncol*. 2011;29.

¿Cómo se regula la aprobación de los test de biopsia líquida?

1- Regulación CIENTÍFICO-ADMINISTRATIVA

2- Regulación CIENTÍFICO-TÉCNICA

Estándares metodológicos

3- **Regulación ADMINISTRATIVO-SANITARIA**

Países, Comunidades Autónomas, administraciones locales, hospitales….

SelectMDx™ for Prostate Cancer

Es un algoritmo basado en:

- Niveles ARNm de **HOXC6 y DLX1**
- Edad
- PSA
- Vol próstata
- Tacto rectal
- Antecedentes familiares

EUROPEAN UROLOGY

Eur Urol. 2016 Nov;70(5):740-748. doi: 10.1016/j.eururo.2016.04.012. Epub 2016 Apr 20.

Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score.

Van Neste L[1], Hendriks RJ[2], Dijkstra S[2], Trooskens G[3], Cornel EB[4], Jannink SA[3], de Jong H[3], Hessels D[3], Smit FP[3], Melchers WJ[5], Leyten GH[6], de Reijke TM[7], Vergunst H[8], Kil P[9], Knipscheer BC[10], Hulsbergen-van de Kaa CA[11], Mulders PF[2], van Oort IM[2], Van Criekinge W[12], Schalken JA[13].

Características	Cohorte A *(desarrollo)*	Cohorte B *(validación)*
n (905) *(Pcts a (re)biop por PSA≥3, DRE an)*	519	386
1ª biopsia n (%)	410 (79)	342 (89)
PSAD, ng/ml . ml	[illegible]	[illegible]; 0,10-0,25)
DRE anormal (%)	199 (38,3)	119 (31,3)
Diagnóstico (%)	[illegible]	[illegible]
GS≤6, n (%)	103 (48,6)	91 (50,0)
GS 7, n (%)	58 (27,4)	51 (28,3)
GS 8-10, n (%)	51 (24,1)	39 (21,6)

HOXC6 – DLX1 ctMdx

AUC: 0.76

AUC: 0.86

S: 91%
E: 36%

EVITA en un **53%**
BIOPSIAS INNECESARIAS

VPN

El score de SelectMDx puede estimar:

90% de probabilidad que un paciente NO tiene CaP.
98% de probabilidad que un paciente NO tiene CaP de alto riesgo (Gleason 7 o más)

Caracterización → Factor Predictvo??? **ARV-7**

ARV7 parece un **claro marcador predictivo de respuesta a Enza o Abi**

Controversia: **METODOLOGÍA DE DETECCIÓN**


The NEW ENGLAND JOURNAL of MEDICINE

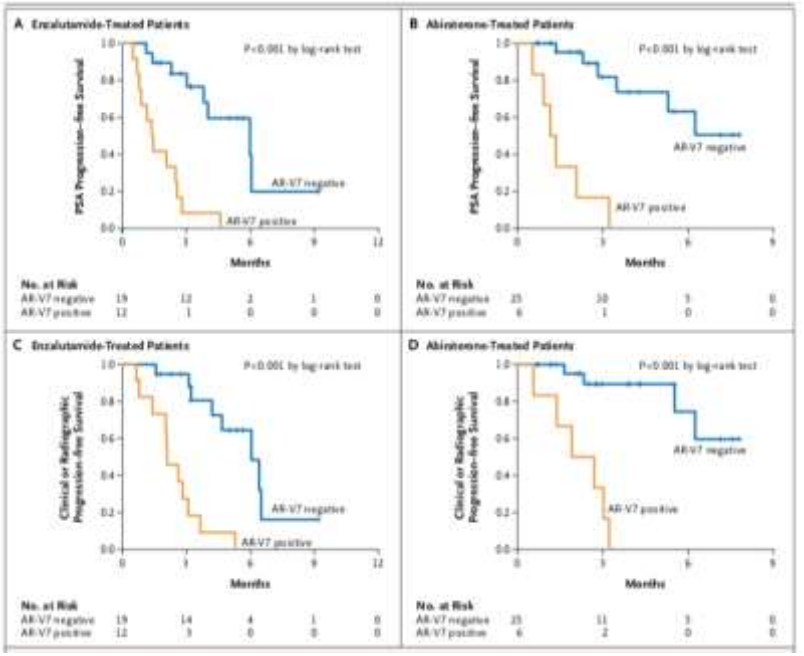
ORIGINAL ARTICLE

AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D.,

62 pacientes
SLP PSA, SLP Rx, SG

ARV7
¿Primer test biopsia líquida
que cambia el manejo terapéutico
del cáncer de próstata avanzado?



qPCR CTCs detectadas por CellSearch

Prostate. 2018 Aug 23. doi: 10.1002/pros.23710. [Epub ahead of print]

Standardization of CTC AR-V7 PCR assay and evaluation of its role in castration resistant prostate cancer progression.

Tommasi S[1], Pilato B[1], Carella C[2], Lasorella A[1,3], Danza K[1], Vallini I[3], De Summa S[1], Naglieri E[2].

Author information

ClinicalTrials.gov identifier: NCT02269982

J Clin Oncol. 2019 May 1;37(13):1120-1129. doi: 10.1200/JCO.18.01731. Epub 2019 Mar 13.

Prospective Multicenter Validation of Androgen Receptor Splice Variant 7 and Hormone Therapy Resistance in High-Risk Castration-Resistant Prostate Cancer: The PROPHECY Study.

Armstrong AJ[1], Halabi S[1], Luo J[2], Nanus DM[3], Giannakakou P[3], Szmulewitz RZ[4], Danila DC[3,5], Healy P[1], Anand M[1], Rothwell CJ[1], Rasmussen J[1], Thornburg B[1], Berry WR[1], Wilder RS[1], Lu C[2], Chen Y[2], Silberstein JL[2], Kemeny G[1], Galletti G[3], Somarelli JA[1], Gupta S[1], Gregory SG[1], Scher HI[3,5], Dittamore R[6], Tagawa ST[3], Antonarakis ES[2], George DJ[1].

118 pacientes

Johns Hopkins University modified-AdnaTest **CTC** AR-V7 mRNA assay

Acuerdo 82%

Epic Sciences CTC nuclear-specific AR-V7 protein assay.

Detection of AR-V7 in CTCs by two blood-based assays is independently associated with shorter PFS and OS with abiraterone or enzalutamide, and such men with mCRPC should be offered alternative treatments.

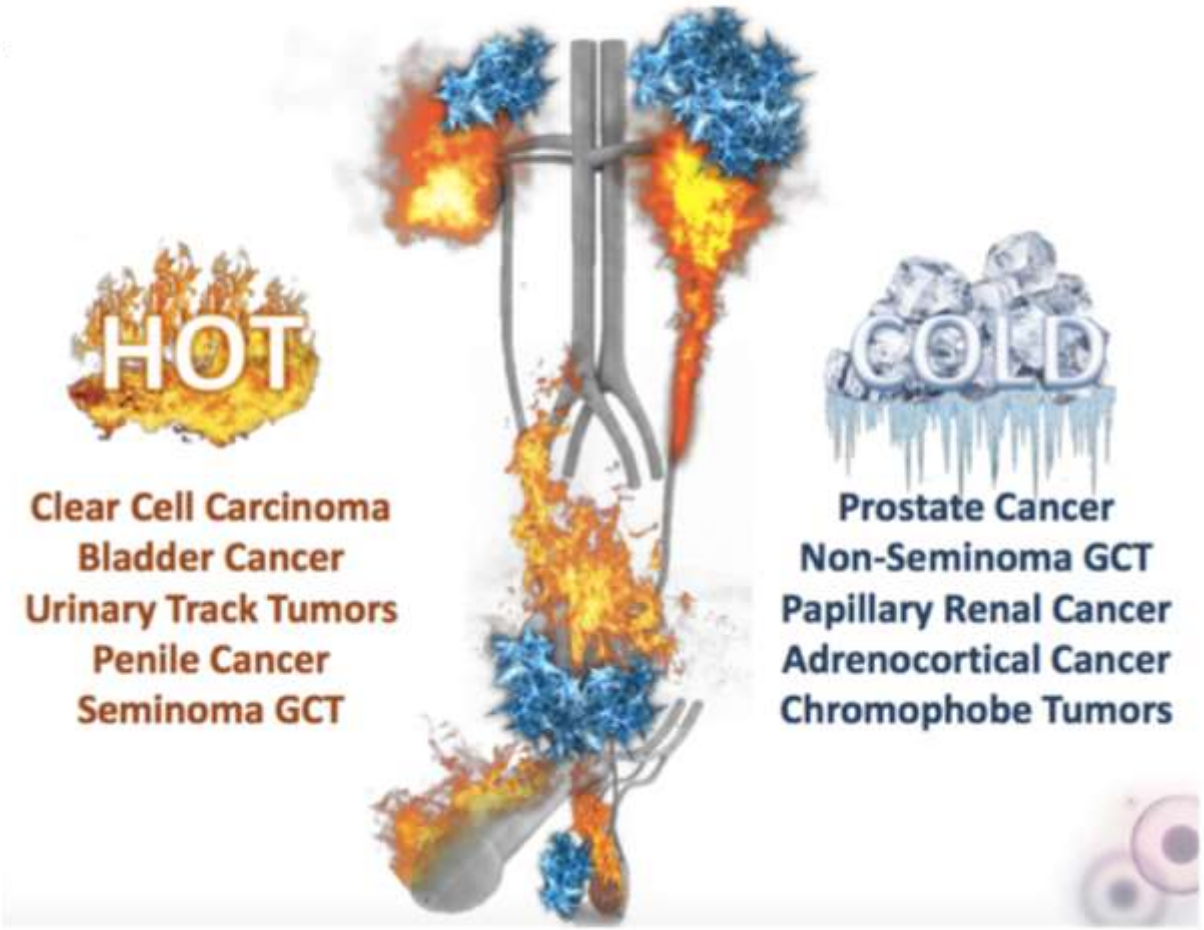
…Vía rápida…

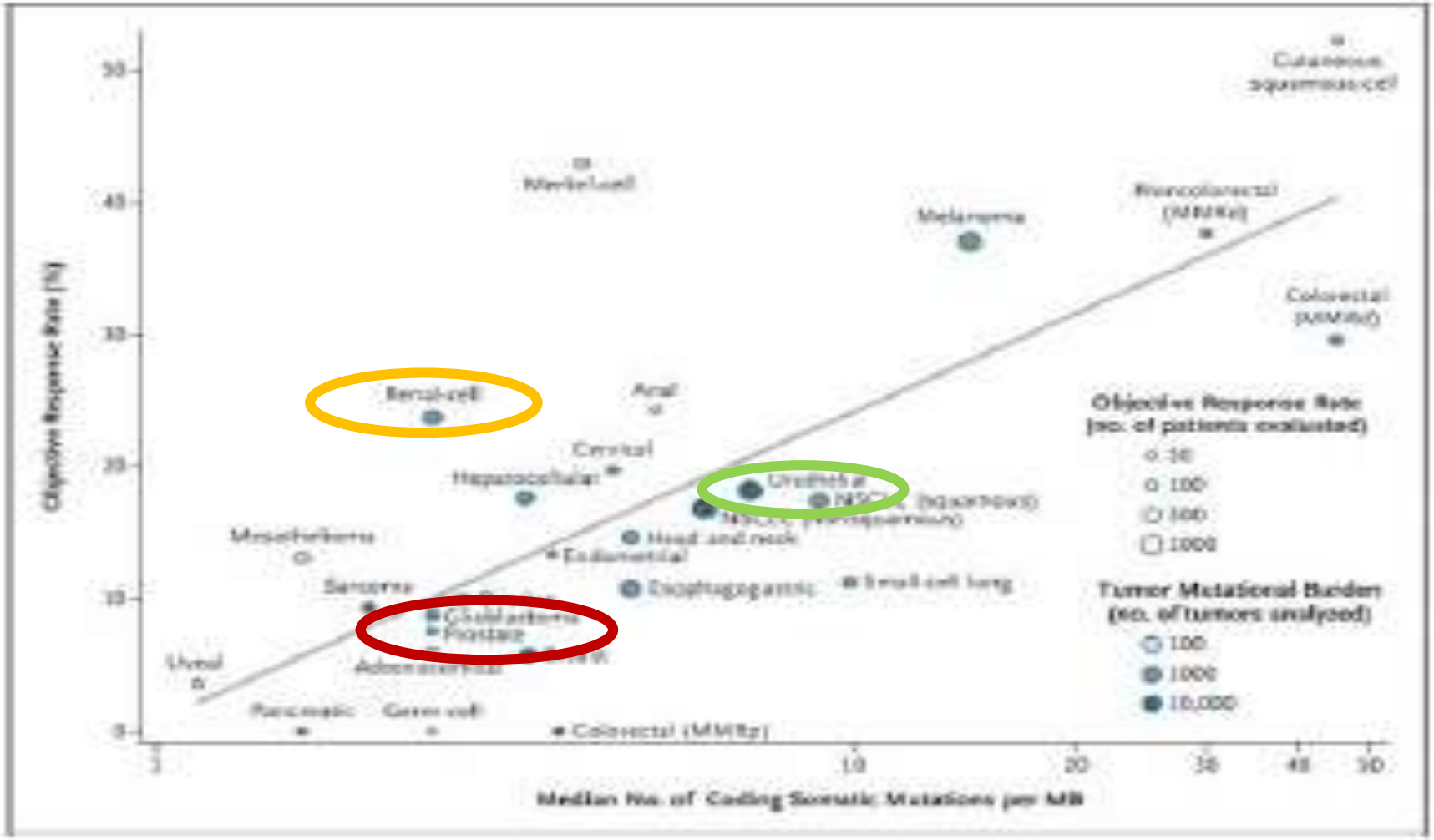
THERANOS

CANCER INTERCEPT DETECT TEST

La inmunoterapia llega al CPRC

Inmunoterapia





Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA WITH VISCERAL METASTASES [xx,bbb]

FIRST-LINE TREATMENT

- Docetaxel[vv] (category 1)
- Enzalutamide[u] (category 1)
- Abiraterone[u] with prednisone
- Abiraterone[u] with methylprednisolone
- Clinical trial
- Mitoxantrone with prednisone[vv,ggg]
- Other secondary hormone therapy[u]

→ Prior therapy enzalutamide/abiraterone[ccc,ddd,hhh] → SECOND-LINE TREATMENT:

- Docetaxel[vv] (category 1)
- If not previously received:
  - Abiraterone[u] with prednisone
  - Abiraterone[u] with methylprednisolone
  - Enzalutamide[u]
  - Cabazitaxel[vv]
- Pembrolizumab for MSI-H or dMMR[vv] (category 2B)
- Clinical trial
- Other secondary hormone therapy[u]
- Best supportive care

→ Prior therapy docetaxel[ddd,hhh] → SECOND-LINE TREATMENT:

- Abiraterone[u] with prednisone (category 1)
- Enzalutamide[u] (category 1)
- Cabazitaxel[vv] (category 1)
- Abiraterone[u] with methylprednisolone
- Pembrolizumab for MSI-H or dMMR[vv] (category 2B)
- Clinical trial
- Docetaxel rechallenge[vv,fff]
- Mitoxantrone with prednisone[vv,ggg]
- Other secondary hormone therapy[u]
- Best supportive care

SECOND-LINE TREATMENT

→

SUBSEQUENT TREATMENT (category 2B)

At progression[ddd,hhh]:
- If not previously received:
  - Enzalutamide[u]
  - Cabazitaxel[vv]
  - Abiraterone[u] with prednisone
  - Abiraterone[u] with methylprednisolone
  - Mitoxantrone with prednisone[vv,ggg]
  - Pembrolizumab for MSI-H or dMMR[vv]
- Clinical trial
- Docetaxel rechallenge[vv,fff]
- Other secondary hormone therapy[u]
- Best supportive care

[u] See Principles of Androgen Deprivation Therapy (PROS-F).
[vv] See Principles of Immunotherapy and Chemotherapy (PROS-G).
[xx] Visceral metastases refers to liver, lung, adrenal, peritoneal, and brain metastases. Soft tissue/lymph node sites are not considered visceral metastases.
[bbb] Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.
[ccc] Consider AR-V7 testing to help guide selection of therapy (See Discussion).
[ddd] Workup for progression should include chest CT, bone imaging, and abdominal/pelvic CT or abdominal/pelvic MRI with and without contrast. Consider metastatic lesion biopsy. See Principles of Imaging (PROS-B) and Discussion.
[fff] Patients who received docetaxel with ADT in the metastatic castration-naive setting can be considered for docetaxel rechallenge in the CRPC setting.
[ggg] Mitoxantrone with prednisone is for palliation in symptomatic patients who cannot tolerate other therapies.
[hhh] Patients treated with systemic therapy for non-visceral metastases (see PROS-17) should proceed to a different subsequent therapy for patients with visceral metastases based on their previous treatment. If small cell neuroendocrine is found, see PROS-16.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable[a]	• Axitinib + pembrolizumab • Pazopanib • Sunitinib	• Ipilimumab + nivolumab • Cabozantinib (category 2B) • Axitinib + avelumab	• Active surveillance[b] • Axitinib (category 2B) • High-dose IL-2[c]
Poor/ intermediate[a]	• Ipilimumab + nivolumab (category 1) • Axitinib + pembrolizumab (category 1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab	• Axitinib (category 2B) • High-dose IL-2[c] • Temsirolimus[d]

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

Preferred regimens	Other recommended regimens	Useful under certain circumstances
• Cabozantinib (category 1) • Nivolumab (category 1) • Ipilimumab + nivolumab	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab (category 3)	• Bevacizumab or biosimilar[e] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[c] (category 2B) • Temsirolimus[d] (category 2B)

[a] See Risk Models to Direct Treatment (IMDC criteria) (KID-D).
[b] Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol 2016;17:1317-1324.
[c] Patients with excellent performance status and normal organ function.
[d] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium greater than 10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281.
[e] Biosimilar options include: bevacizumab-awwb, bevacizumab-bvzr.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY

	First-line systemic therapy for locally advanced or metastatic disease (Stage IV)
Cisplatin eligible	Preferred regimens • Gemcitabine and cisplatin[4] (category 1) • DDMVAC with growth factor support (category 1)[2,8]
Cisplatin ineligible	Preferred regimens • [illegible] and [illegible]platin[11] • Atezolizumab[12] (only for patients whose tumors express PD-L1[a] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) • Pembrolizumab[13] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) Other recommended regimens • Gemcitabine[14] • Gemcitabine and paclitaxel[15] Useful under certain circumstances • Ifosfamide, doxorubicin, and gemcitabine[16] (for patients with good kidney function and good PS)

- The presence of both non-nodal metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.[17]
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
  - Participation in clinical trials of new or more tolerable therapy is recommended.

[a] Atezolizumab: SP142 assay. PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area.
[b] Pembrolizumab: 22C3 antibody assay. Combined Positive Score (CPS) ≥10.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued
References

PRINCIPLES OF SYSTEMIC THERAPY

Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)[c] Participation in clinical trials of new agents is recommended.	
Preferred regimen • Pembrolizumab (category 1)[18]	Other recommended regimens • Paclitaxel[26] or docetaxel[27] • Gemcitabine[14]
Alternative preferred regimens • Immune checkpoint inhibitor ▸ Atezolizumab[19,20] ▸ Nivolumab[21] ▸ Durvalumab[22] ▸ Avelumab[23,24] • Erdafitinib[d,25]	Useful in certain circumstances based on prior medical therapy • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.	
Preferred regimen for cisplatin ineligible, chemotherapy naïve • Gemcitabine/carboplatin	Other recommended regimens • Erdafitinib[d,25] • Paclitaxel or docetaxel[27] • Gemcitabine[14]
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]	Useful in certain circumstances based on prior medical therapy • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15]

[c] If PFS >12 months after platinum (eg, cisplatin or carboplatin), consider re-treatment with platinum if the patient is still platinum eligible.
[d] Only for patients with susceptible *FGFR3* or *FGFR2* genetic alterations.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued
References

ESOU20

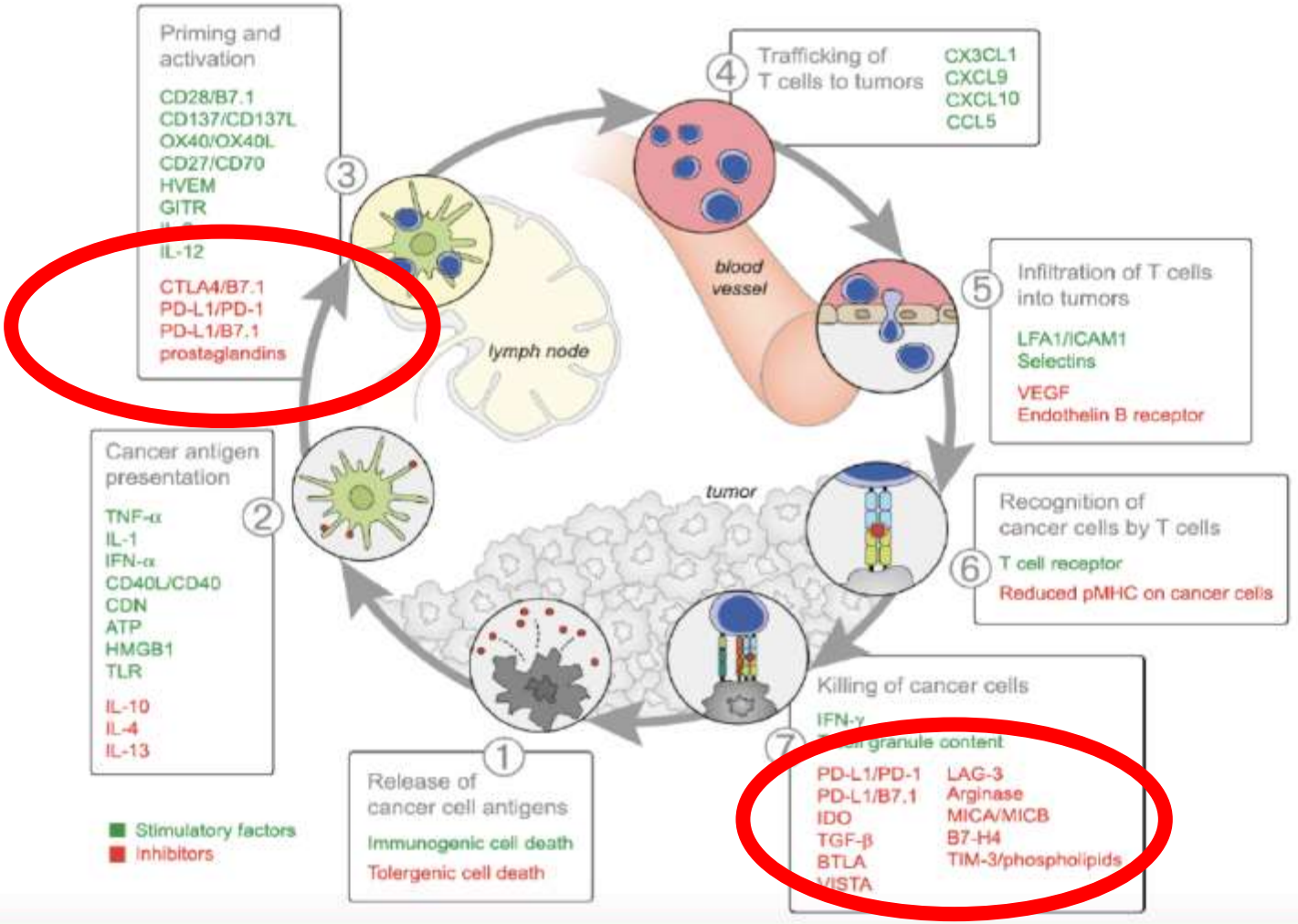
17th Meeting of the EAU Section of Oncological Urology

17-19 January 2020
Dublin, Ireland

Immunotherapy in PCa

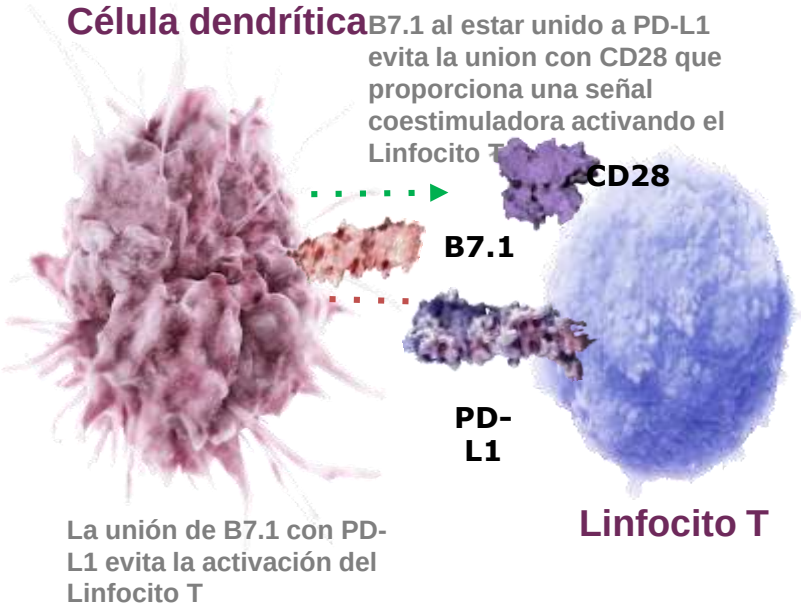
- I do agree with Nicholas: IO is quite disappointing in prostate cancer
- Though, do we have some reasons to expect better outcomes ?

Activatory and Inhibitory Signals



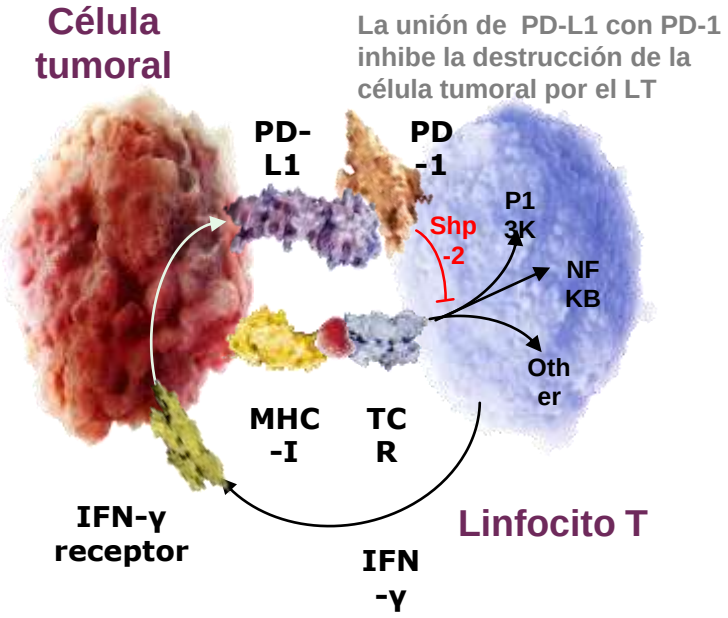
3 Ganglio linfático:

PD-L1 inhibe la activación del LT

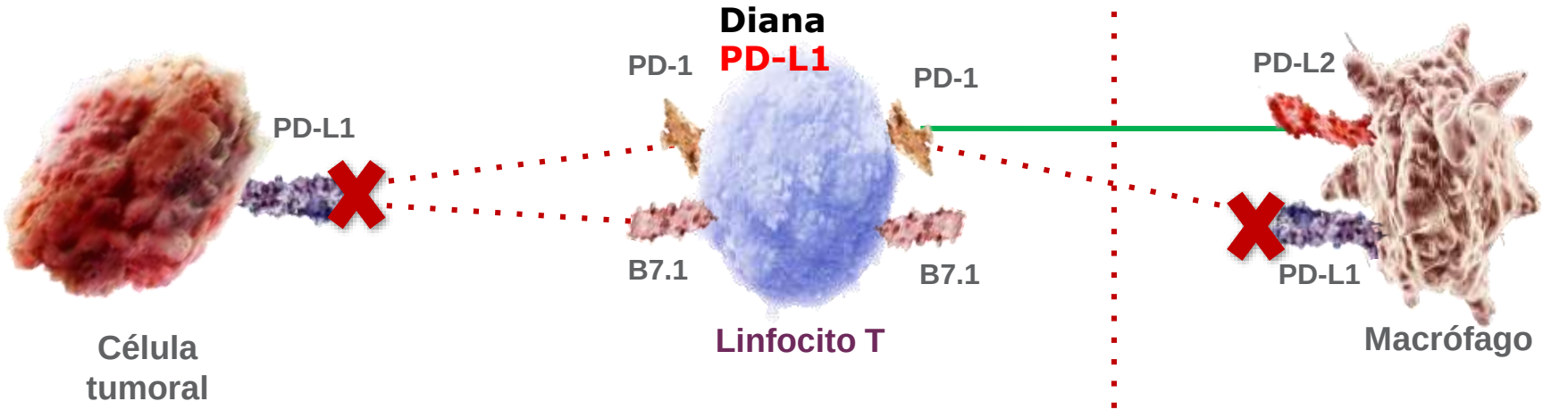


7 Microambiente tumoral:

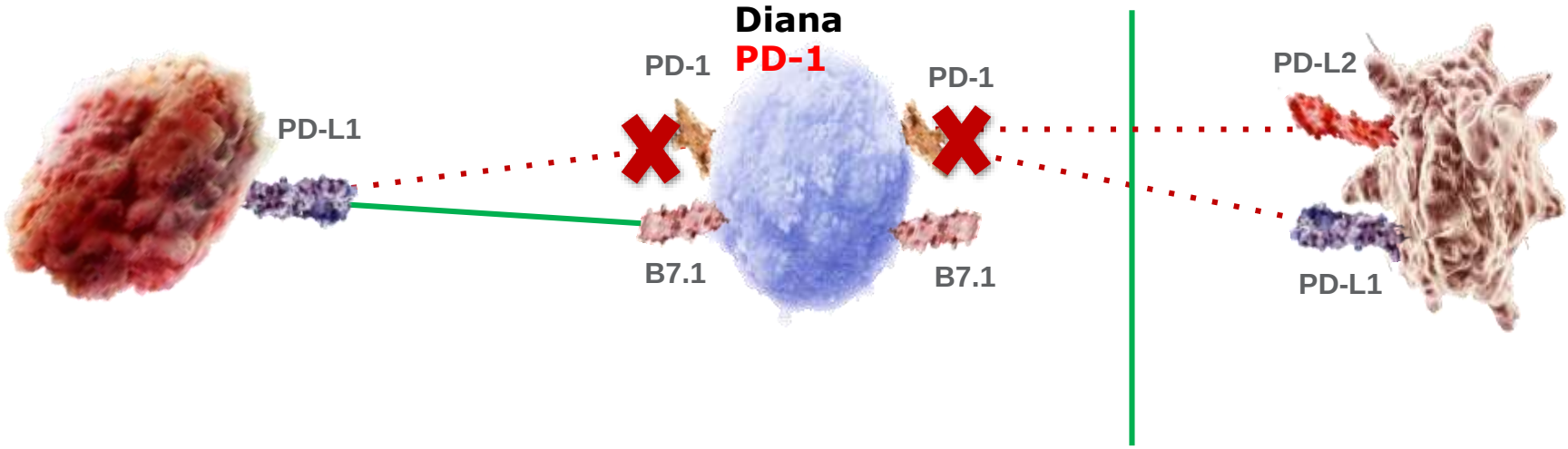
PD-L1 inhibe la destrucción de la célula tumoral por el LT



1.Park, et al. Blood 2010; 2.Paterson, et al. J Immunol 2011
3.Yang, et al. J Immunol 2011; 4. Chen, et al. Clin Cancer Res 2012
LT: Lnfocito T



Los inhibidores PD-L1 and PD-1 tienen diferentes lugares de activación, que generan diferencias en la acticación del linfocito T

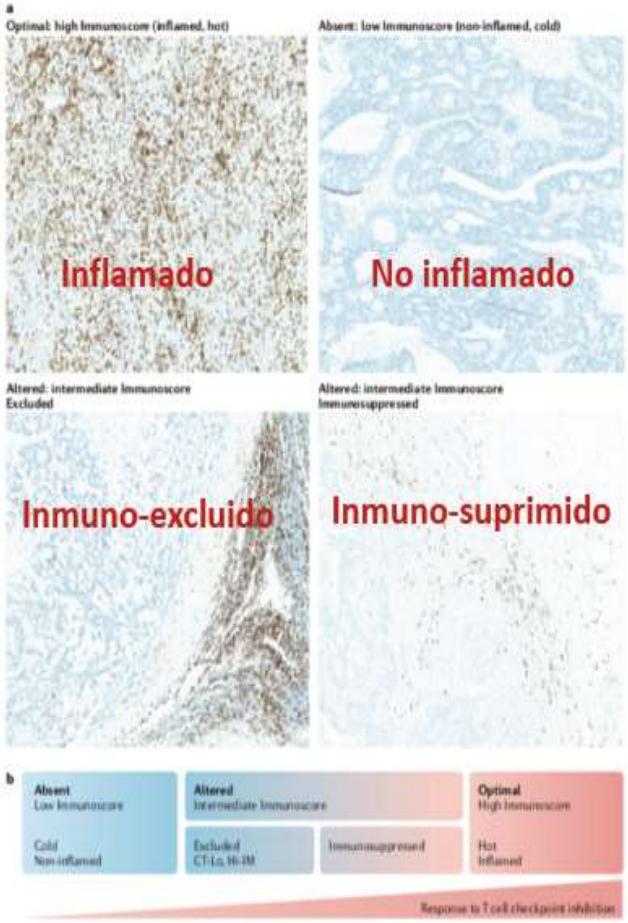


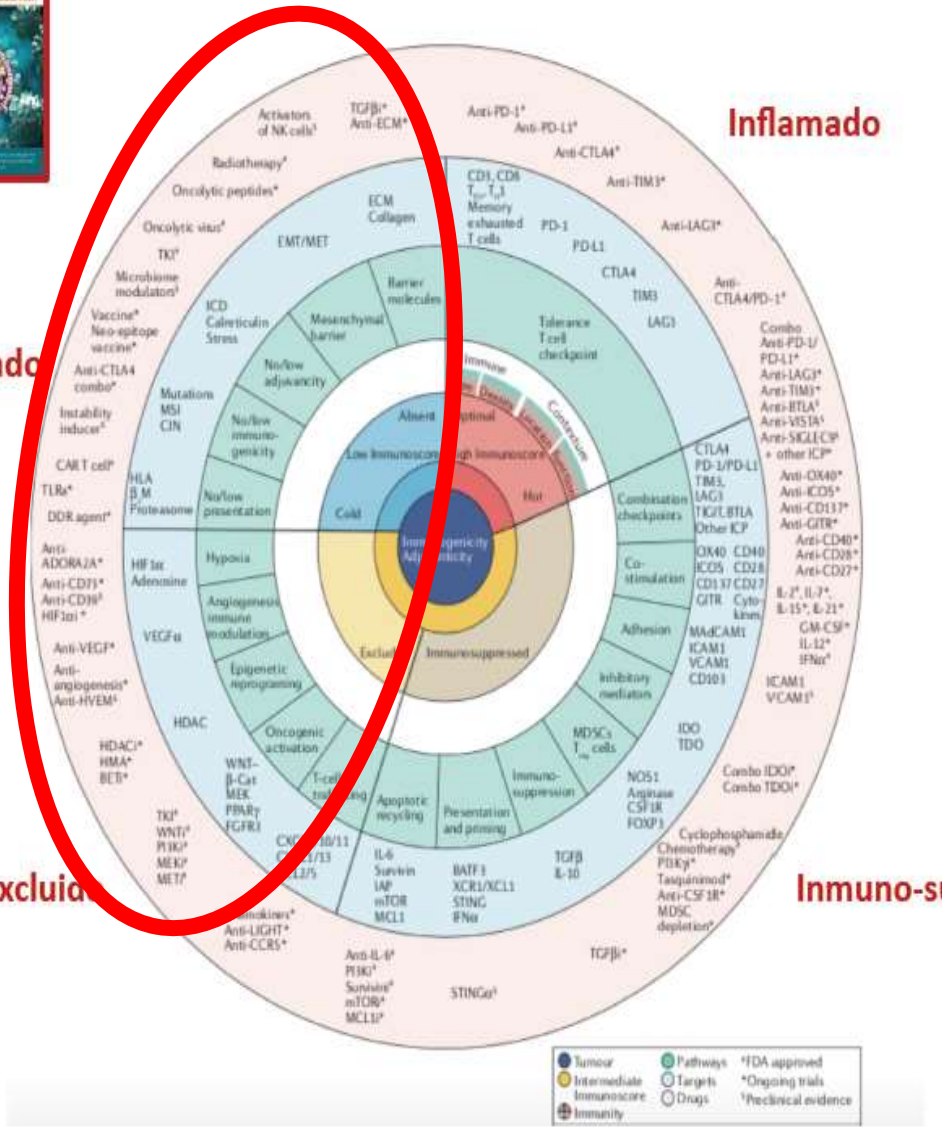
1.Chen, et al. Clin Cancer Res 2012; 2. Paterson, et al. J Immunol 2011; 3.Yang, et al. J Immunol 2011; 4.Brahmer, et al. N Engl J Med 2012

Approaches to treat immune hot, altered and cold tumours with combination immunotherapies

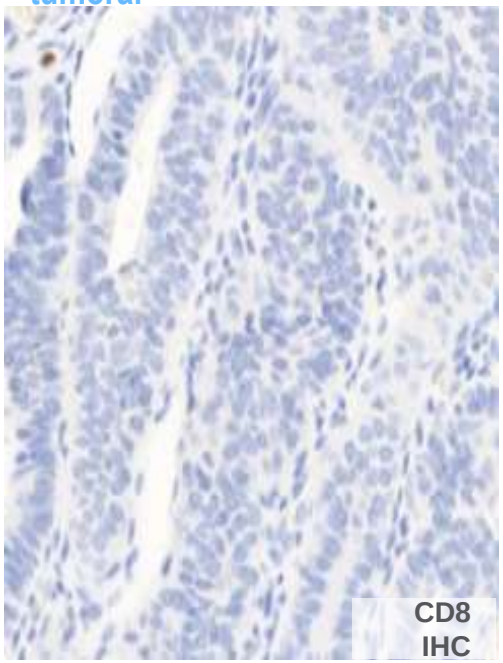
Jérôme Galon * and Daniela Bruni

Galon et al. Nat Rev Drug Discov 2019



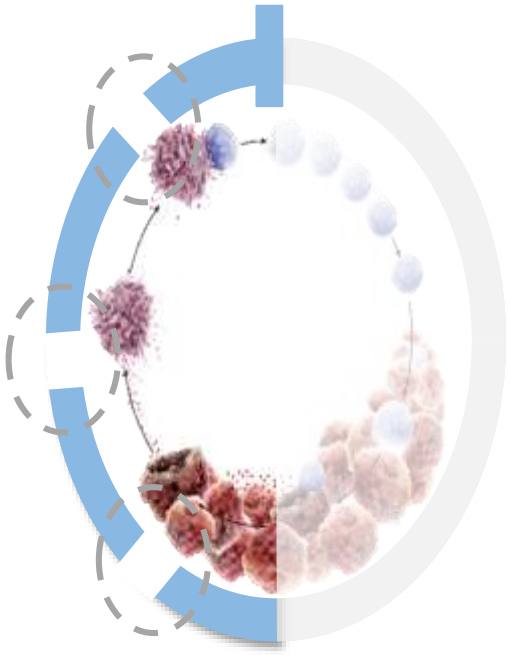


Se caracteriza por una falta de linfocitos T CD8+ en el estroma o parénquima tumoral



Fenotipo No inflamado

Estos tumores suelen tener un defecto en los estadios primarios del ciclo inmune del cáncer (paso 1-3)



Mecanismos asociados con el escape al Sistema inmune que perjudican a la generación de linfocitos T

1. **Escape debido a la baja inmunogenicidad del tumor**
   (ej: carga mutacional del tumor reducida, MHC-I bajo)

2. **Escape debido a la reducida maduración de las células dendríticas**
   (ej: numerosos factores solubles derivados del cáncer o células inmunes inhibitorias)

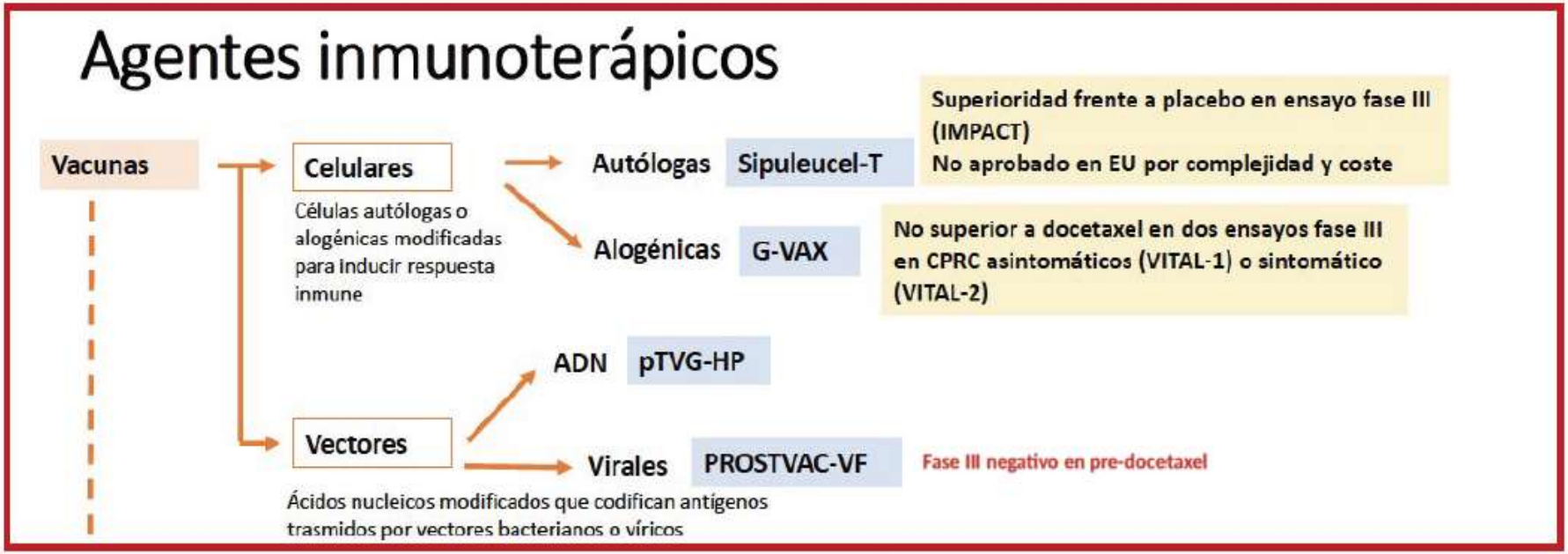
3. **Escape debido a la baja activación de linfocitos T**
   (ej: falta de interacciones coestimuladoras entre las células dendríticas y los linfocitos T, como OX40 o 4-1BB, limitada producción de IL-2 o sobreexpresión de CTLA-4)

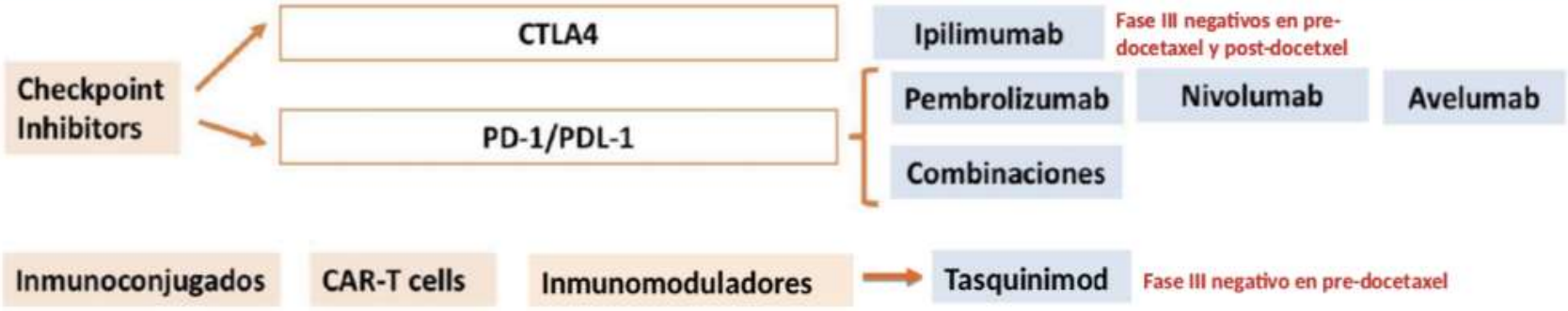
Probablemente debido a fallos en los pasos 1-3 del ciclo inmune del cáncer[4]

1. Gajewski, *et al*. 2013; 2. Herbst, *et al*. 2014; 3. Hedge, *et al*. 2016
Cancer-immunity cycle adapted from Chen & Mellman, 2013.

INMUNOTERAPIA

Agentes inmunoterápicos





Genitourinary Cancers Symposium
February 14–16, 2019 San Francisco
ASCO

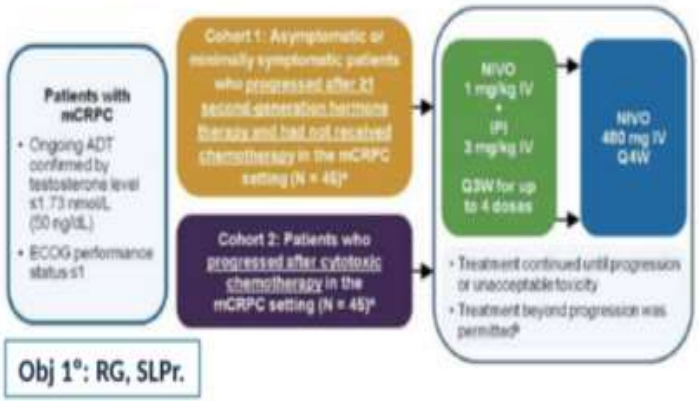
Initial Results From a Phase 2 Study of Nivolumab Plus Ipilimumab for the Treatment of Metastatic Castration-Resistant Prostate Cancer (CheckMate 650)

CPRCm

- Inhibidores de *checkpoint*.
  - Combinaciones.

Nivolumab + Ipilimumab

CA209-650.

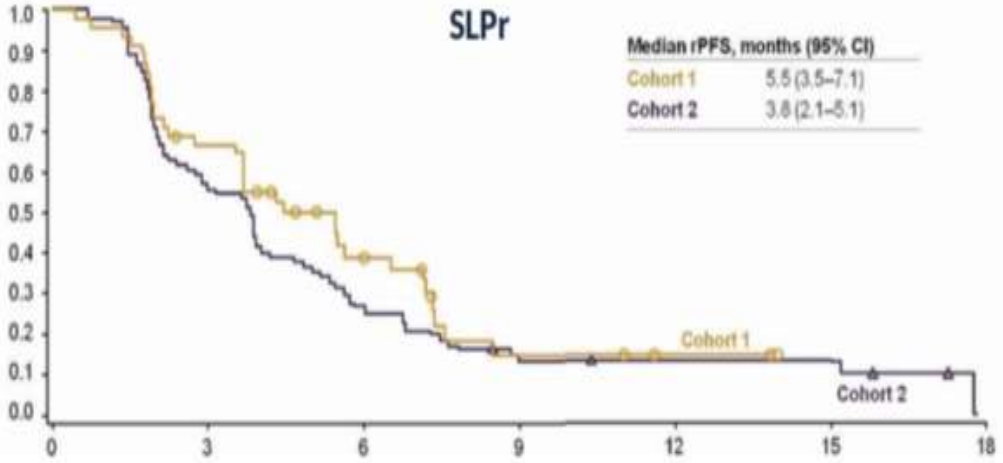


Obj 1º: RG, SLPr.

RG

Objective response (measurable disease only)[a]	Cohort 1 (N = 32)	Cohort 2 (N = 30)
Confirmed ORR, n (%)	8 (25.0)	3 (10.0)
95% CI	11.5–43.4	2.1–26.5
Best overall response, n (%)		
Complete response	2 (6.3)[b]	2 (6.7)
Partial response	6 (18.8)[c]	1 (3.3)
Stable disease	13 (40.6)	11 (36.7)
Progressive disease	9 (28.1)	13 (43.3)
Unable to determine	2 (6.3)	3 (10.0)
Median time to response, months (Q1–Q3)	1.9 (1.9–2.8)	2.1 (1.9–7.4)

SLPr



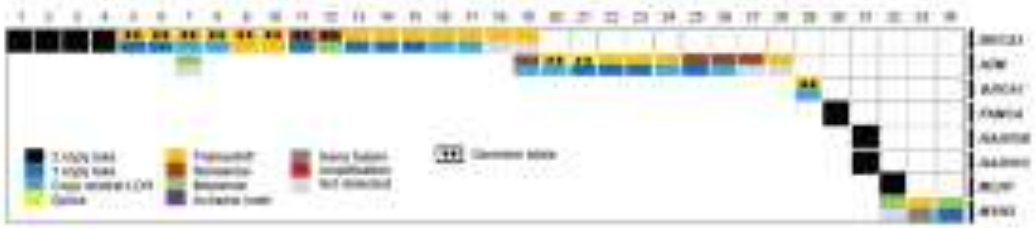
Sharma P, et al. J Clin Oncol 2019; 37(suppl 75;abstr142).

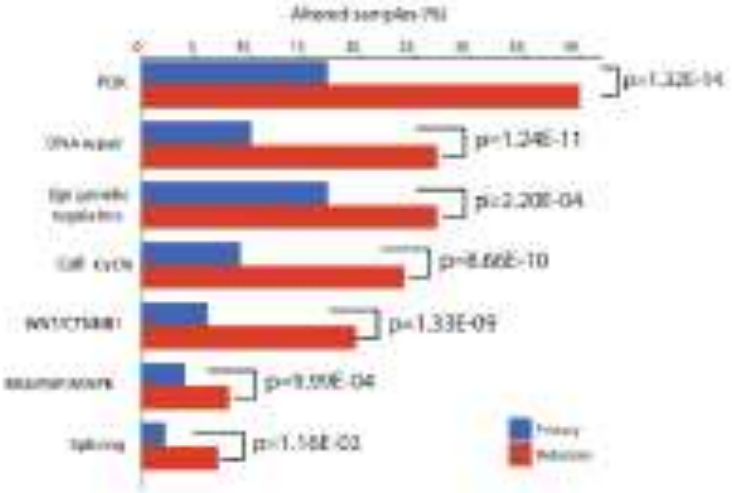
Immunotherapy of prostate cancer combination therapy

Anti-PD-1/ anti-PDL-1	combined with	remarks
nivolumab	Vaccines (eg Prostvac)	
nivolumab	ipilimumab	Neoantigen DNA vaccine, Prostvac, Biomarker driven, Immunogenic signature, enzalutamide
pembrolizumab	Olaparib, docetaxel, enzalutamide	Phase III planned
pembrolizumab	DNA vaccines, Radium-223, ADX531-142, CPI-444	
atezolizumab	Radium-223,Sipuleucel-T, Enzalutamide	Phase III study enzalutamide
avelumab	Sipuleucel-T	
Durvalumab	Tremulimumab	
Regn2810	Ipilimumab (intraprostatic)	+ stereotactic RT

Los primeros biomarcadores. BCRA2.
El tratamiento futuro hacia la medicina de la precisión.

Prevalence of DDR defects in prostate cancer

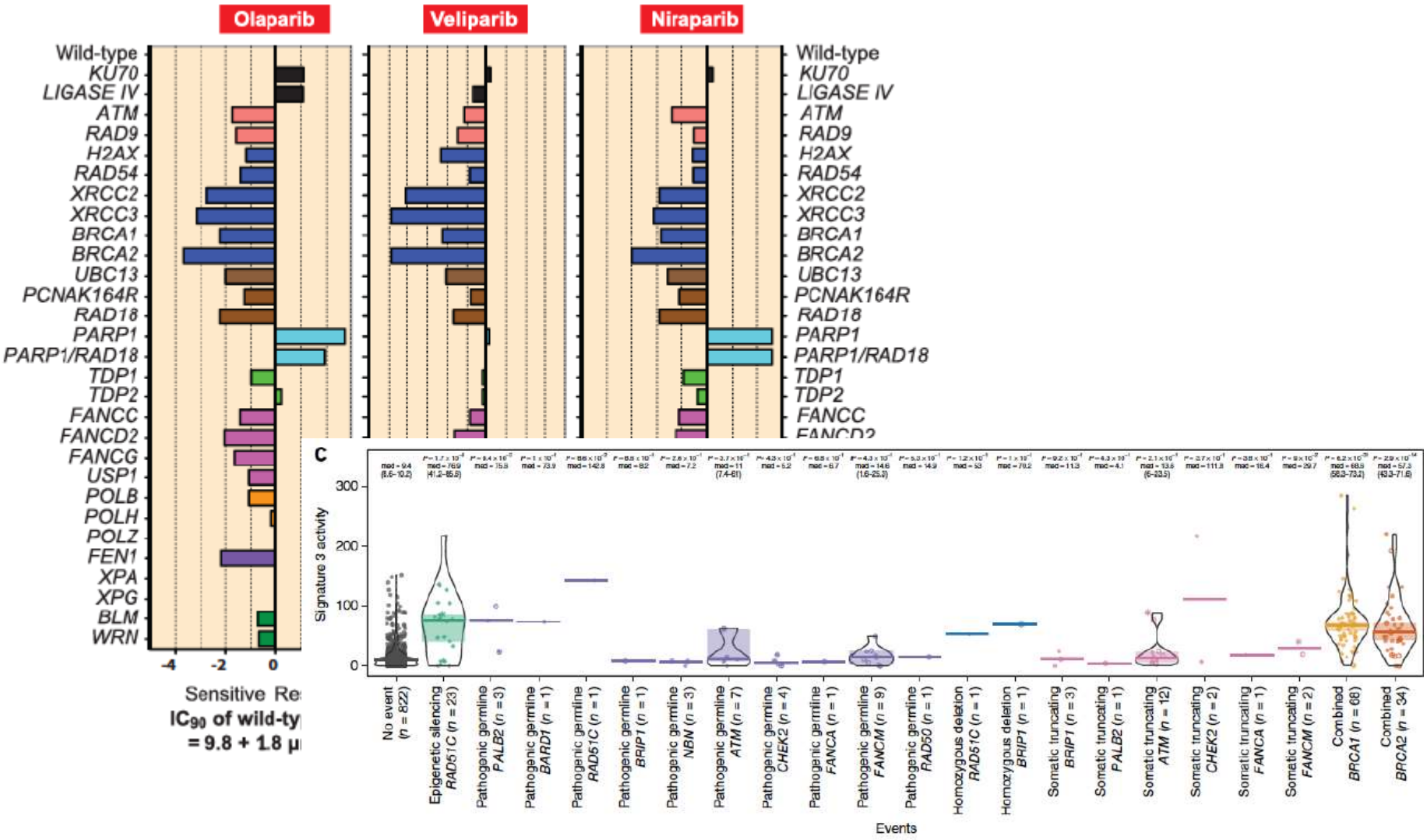




- DNA repair defects identified in 23% of mCRPC
- 8% germline mutations
- 13% BRCA2

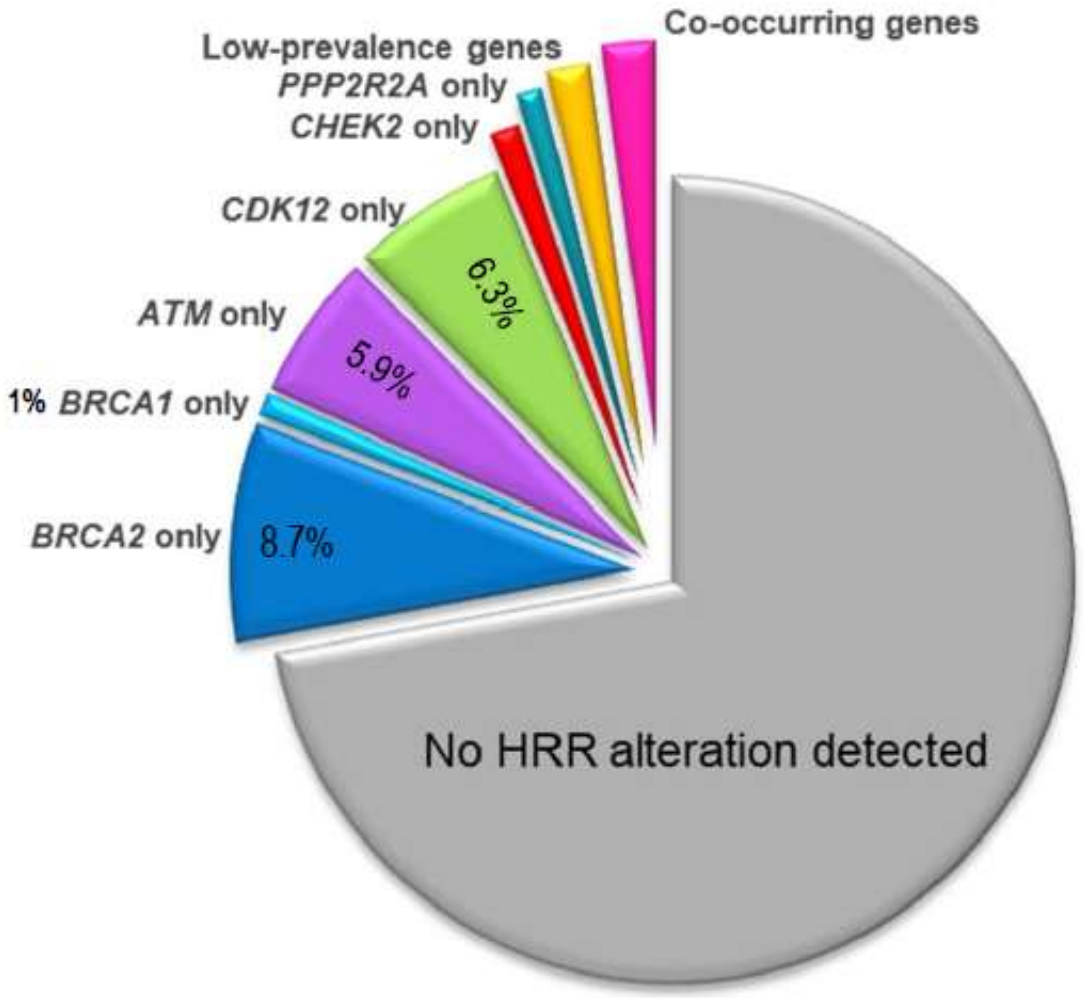
Robinson, Cell, 2015
Armenia, Nat Genet, 2018

PARP inhibitors:
Different magnitude of sensitization



Murai et al, Cancer Res, 2012. Polak et al, Nat Genetics 2017

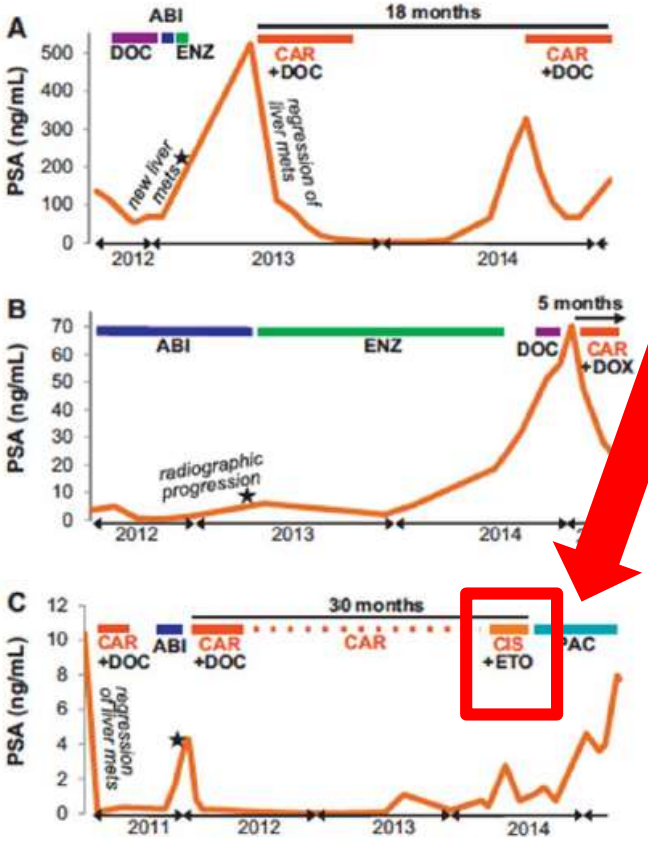
PREVALENCE OF ALTERATIONS IDENTIFIED IN PROFOUND STUDY

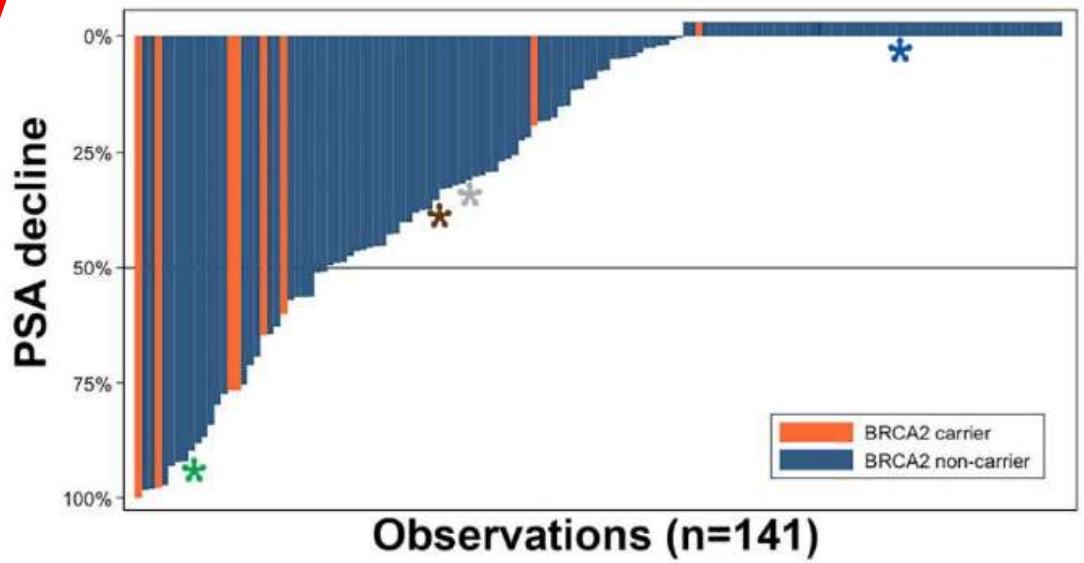


Phase II studies with PARPi presented at ESMO2019

	TRITON 2	GALAHAD
Drug	Rucaparib 600 mg bid	Niraparib 300 mg qd
Study Design	Phase II	Phase II
Population	mCRPC Progression to ARSi and taxane	mCRPC Progression to ARSi and taxane
Primary objective	ORR and PSA response (≥50% decline) in pts with DDR alterations	ORR in patients with Bi-allelic BRCA1/2 alterations
Specimen tested	Plasma or tumor tissue Central/local	Plasma Central
Test used	FoundationOne® FoundationACT® Local	Resolution-HRD®
Genes screened	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*	*ATM, BRCA1, BRCA2, BRIP1, CHEK2, FANCA, HDAC2, PALB2*
Genomic alteration required	Mono- Bi- allelic DDR alterations	Bi-allelic DDR alterations

gBRCA2 mutations and platine-based chemotherapy





Cheng et al, Eur Urol, 2016
Pomerantz et al, Cancer, 2017

CONCLUSIONES

- **La señalización del RA es un mecanismo clave en la progresion del CPRC y es una diana lógica de tratamiento. Asi surgieron las primeras terapias dirigidas contra receptores androgénicos.**
- **Múltiples procesos moleculares contribuyen a la señalización sostenida del RA algunos dependientes del RA y otros independientes.**
- **Es importante el conocimiento de las mutaciones genómicas para identificar nuevas rutas de tratamiento y asi bloquear las diversas vias de escape que presentan las celulas tumorales.**
- **Los paneles genéticos se basan en un conjunto de biomarcadores que tienen como objetivos ser pronosticos y predictivos de la enfermedad y dirigir a tratamientos selectivos individualizados.**
- **La biopsia líquida es un buen procedimiento para la obtención de estos biomarcadores utiles en tumores como el CPRC poco accesibles y que precisan de controles periódicos. Precisa todavía de una regulación cientifico-técnica-administrativa.**
- **El CPRC es un tumor frio, aunque puede existir un futuro prometedor con las combinaciones de inmunoterapia y sobre todo a las combinaciónes de esta con otras terapias dirigidas.**
- **Terapias dirigidas a Biomarcadores como BCRA2, ATM o CDK12 han provocado la aparición de nuevas terapias altamente precisas , dirigidas y que superan a los tratamientos gold standar . Han abierto nuevas expectativas al tratamiento futuro del CPRC**

MUCHAS GRACIAS