CÁNCER DE PRÓSTATA LOCALIZADO DE ALTO RIESGO: CIRUGÍA VS RADIOTERAPIA APALUTAMIDA NEOADYUVANTE

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OBJETIVOS NEOADYUVANCIA

FACILITAR LA RESECCIÓN DEL PRIMARIO

DISMINUIR EL RIESGO DE RECURRENCIA Y AUMENTAR LAS POSIBILIDADES DE SUPERVIVENCIA

PERO PODRÍA

INFORMAR LA TERAPIA ADYUVANTE, DEPENDIENDO DE LA RESPUESTA NEOADYUVANTE

MONITORIZAR LA RESPUESTA DEL TUMOR → TERAPIAS DE DESESCALADA

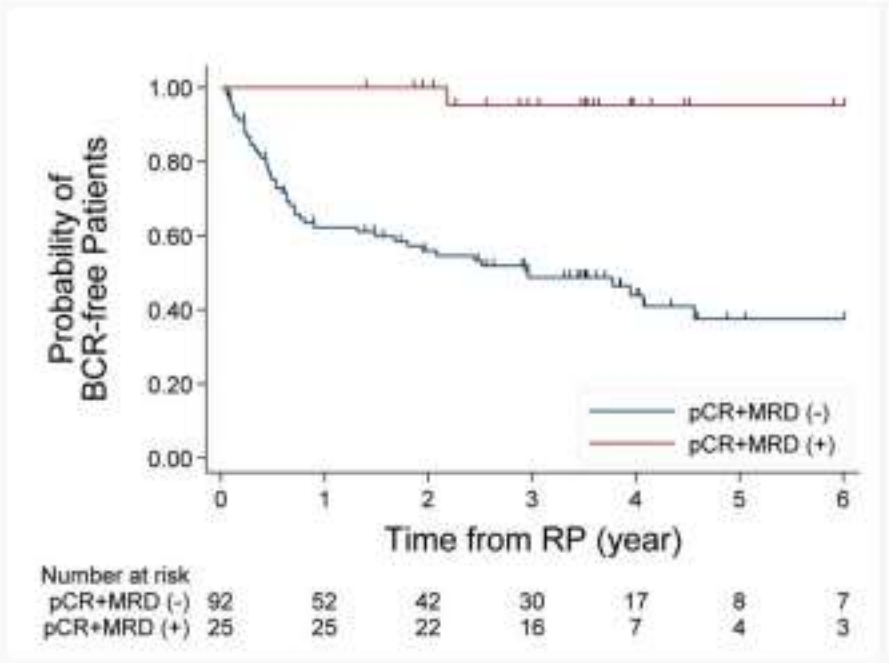
PERMITIR Y FACILITAR LA INVESTIGACIÓN BÁSICA Y TRASLACIONAL.

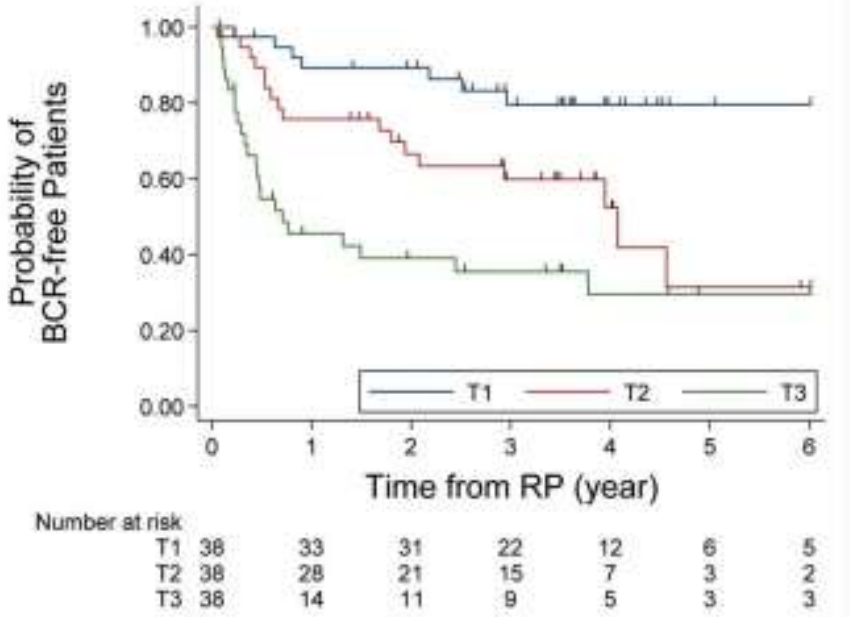
¿Marcadores subrogados?

<u>Pool analyses de 3 ensayos clínicos con ADT:</u> N= 117

Una respuesta patológica “excepcional”

Se asocia con mejor tasa de recurrencia bioquímica



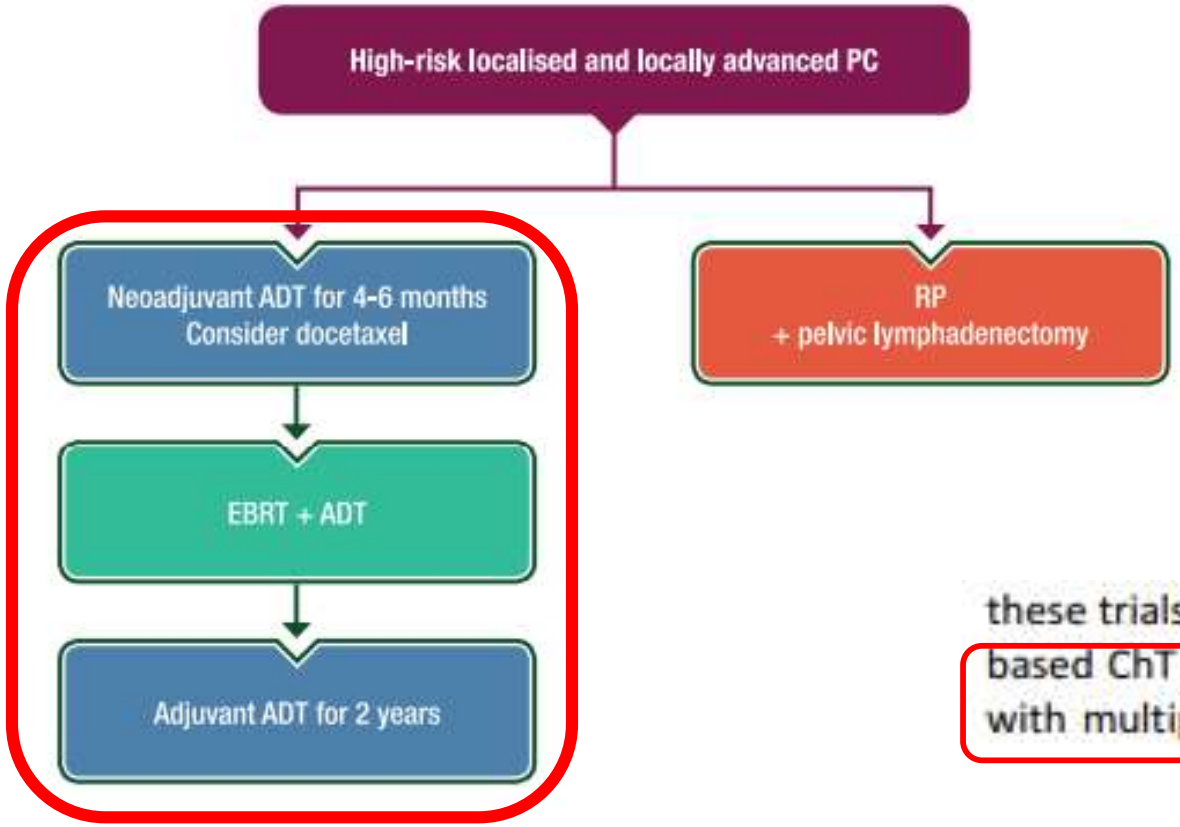


McKay RR, J Urol. 2021;205(6):1689-1697.

SPECIAL ARTICLE

Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

C. Parker[1], E. Castro[2], K. Fizazi[3], A. Heidenreich[4], P. Ost[5], G. Procopio[6], B. Tombal[7] & S. Gillessen[8,9,10], on behalf of the ESMO Guidelines Committee*



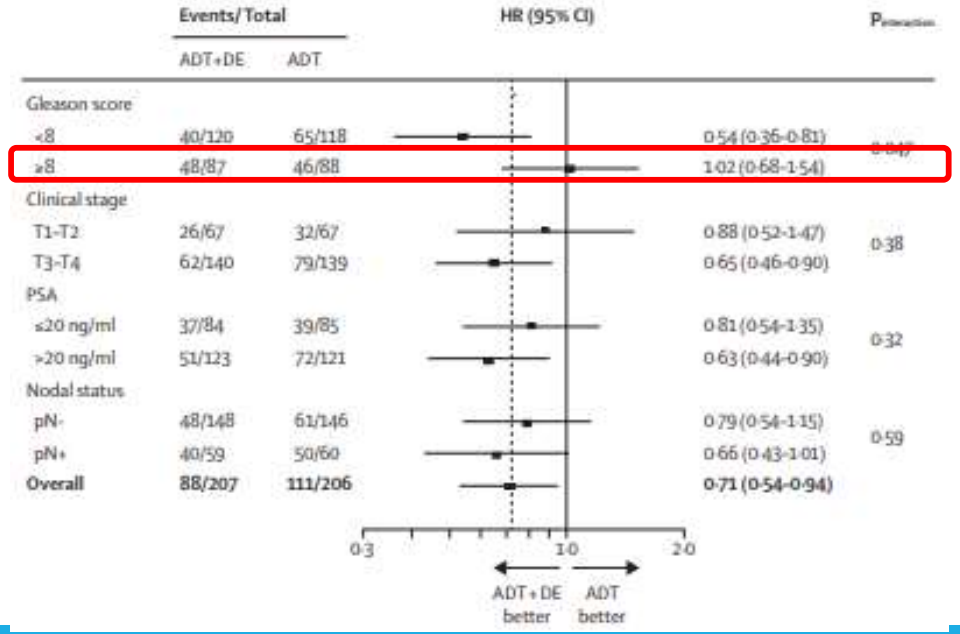
these trials. Based on the available data, offering docetaxel-based ChT may be a reasonable option for younger, fit men with multiple risk factors for recurrence.

Neoadyuvancia pre RADIOTERAPIA DOCETAXEL

GETUG-12. Fase III randomizado: N= 413

RT + ADT 3 años **vs** RT + ADT 3 a +Docetaxel x 4 neoady

RFS HR 0,7 a favor de docetaxel. Clinical RFS (mtx, recaída local o muerte)
→ 13,9 años vs 12,5 muerte. HR 0,75 IC 0,56-1 p= 0,049



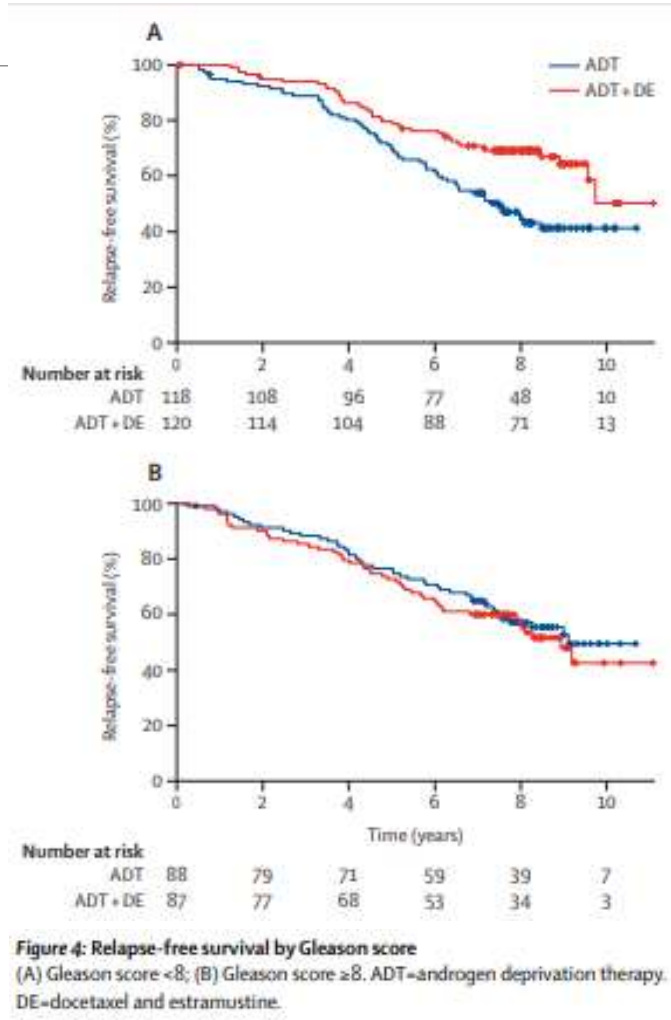


Figure 4: Relapse-free survival by Gleason score
(A) Gleason score <8; (B) Gleason score ≥8. ADT=androgen deprivation therapy. DE=docetaxel and estramustine.

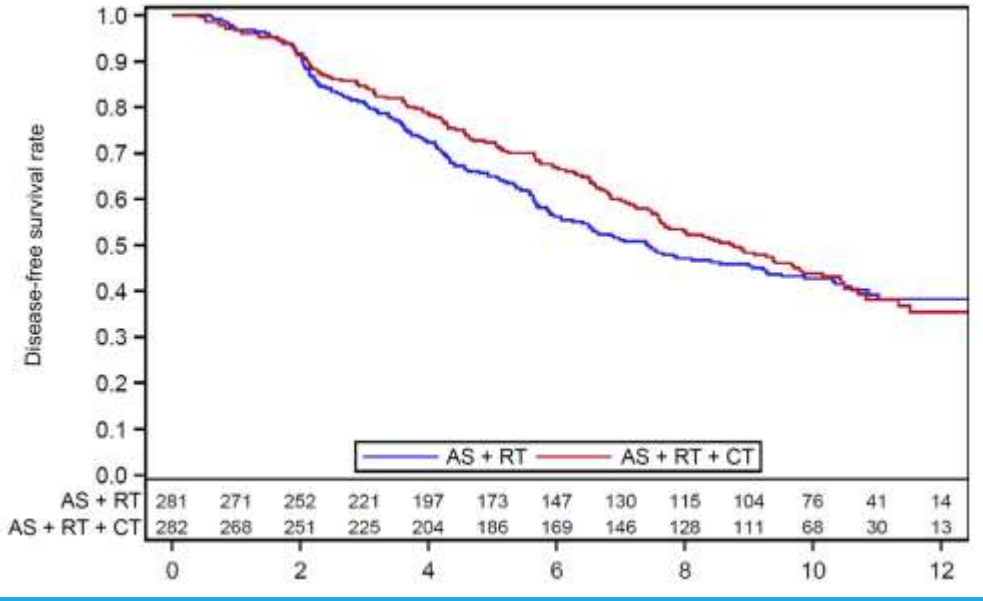
Fizazi K Lancet Oncol. 2015;16(7):787-794.

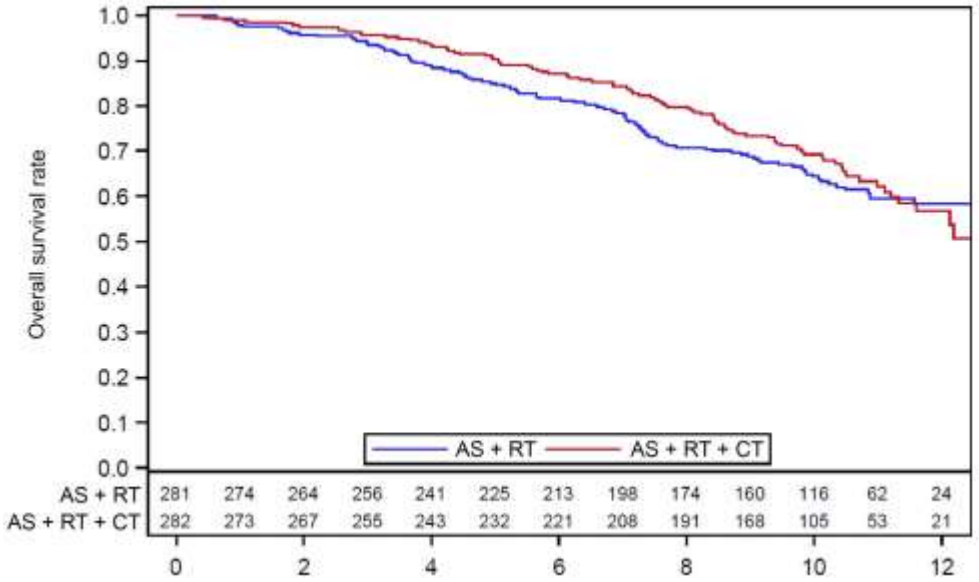
Neoadyuvancia pre RADIOTERAPIA DOCETAXEL

RTOG 0521. Fase III randomizado: N = 612 pts

RT + ADT 2 años **vs** RT + ADT 2 a +Docetaxel x 6 neoady

Seguimiento 10,4 años→ No diferencias estadísticamente significativas en SG



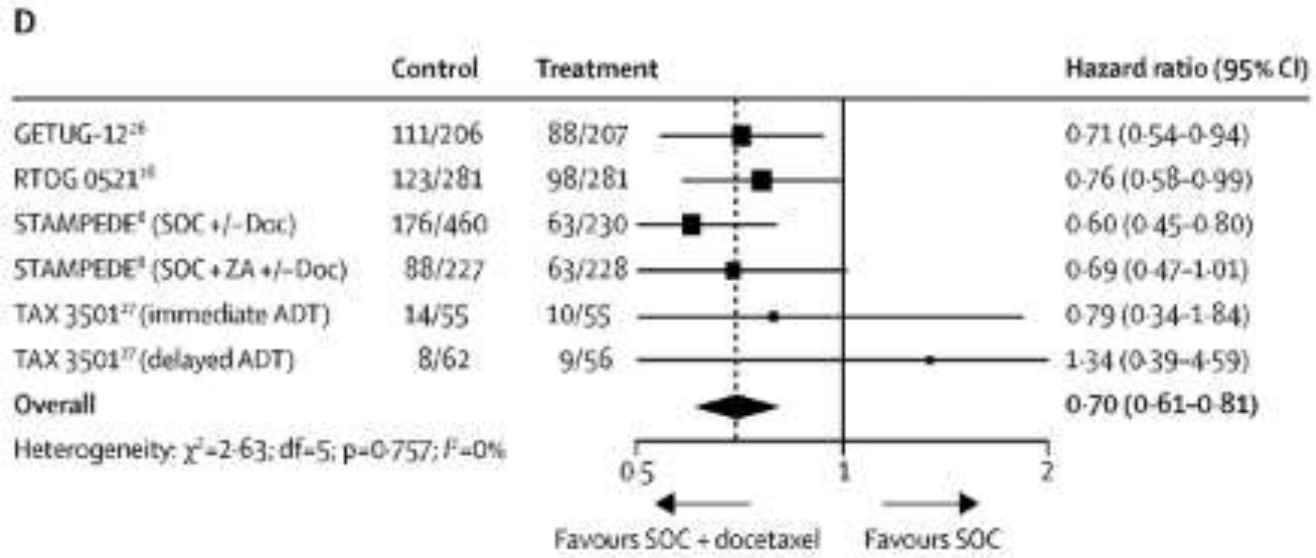


Sartor O, Eur Urol. 2023;84(2):156-163.

Neoadyuvancia pre RADIOTERAPIA DOCETAXEL

Meta-análisis Vale CL, et al

Mejoría RFS (HR 0.70; 95% CI 0.61-0.81; P <0.0001) pero no datos de SG



Vale CL, *Lancet Oncol*. 2016;17(2):243-256..

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SaludMadrid

SPECIAL ARTICLE

Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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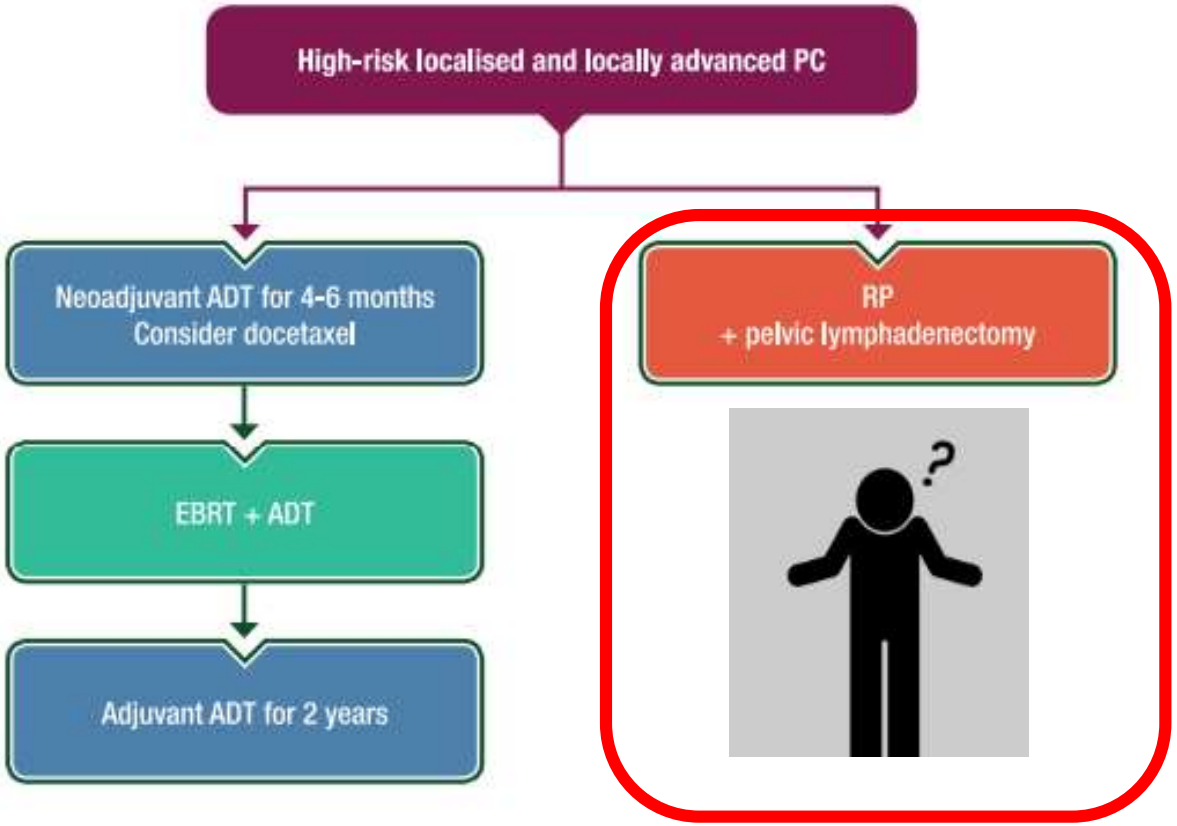

Neoadyuvancia pre PROSTATECTOMÍA TERAPIA HORMONAL

TABLE 1 | Completed, published randomized trials assessing the role of neoadjuvant hormonal or chemohormonal therapy prior to prostatectomy.

Neoadjuvant therapy with Convention Androgen Deprivation therapy agents

Author	Year	Location	n	Abbreviated inclusion criteria	Agent (Duration)	Primary endpoint results
Labrie (26)	1993	Québec, Canada	77	Early stage prostate cancer	Leuprolide + Flutamide (3 Months)	Cancer-positive margins were reduced from 38.5% in control patients to 13.0% in men who received neoadjuvant combination (p = 0.006).
Debruyne (27)	1994	Nijmegen, Netherlands.	65	cT2-3, N0, M0 stages of prostate cancer	Goserelin + Flutamide (3 Months)	Serum PSA levels and prostatic volume decreased from a mean of 12.8 ng/ml and 42.8 cm3 to a mean of 0.8 ng/ml and 29.5 cm3, respectively.
Van Poppel (28)	1995	Leuven, Belgium	65	Stages T2b and T3 prostate cancer	Estramustine + Phosphate (1.5 Months)	For T2b tumors, a significant decrease in positive surgical margins was found compared to the nonpretreated group. This difference was not found for clinical stage T3 tumors.
Dalkin (29)	1996	Tucson, AZ, USA	56	Clinically localized (stages T1C, T2A and T2B) prostatic cancer	Goserelin (3 Months)	No improvement in pathological outcome
Klotz (30, 31)	1999	Toronto, Canada	213	Localized (T1-T2) prostate cancer.	Cyproterone (3 Months)	No difference in risk of biochemical recurrence-free survival. Neoadjuvant group had a lower rate of apical margin involvement than those who did not (17.8 versus 47.8%, respectively, p < 0.0001).
Hugosson (32)	1996	Göteborg, Sweden	56	Prostate cancer (T1b-T3a, N0, M0, G1-3)	Triptorelin, Cyproterone (3 Months)	Neo-adjuvant treatment had a significantly lower frequency of positive margins (41 *vs.* 23%, p = 0.013).
Gleave (33)	2001	Vancouver, Canada	547	T1 or T2 prostate cancer	Leuprolide, flutamide (3 months *vs* 8 months)	Lower pre-operative PSA favored 8 month ADT group (0.052 *vs* 0.12mc/L, P<0.001). Surgical margins favored 8 month ADT group (12% *vs* 23%, p=0.01).
Selli (34)	2002	Pisa, Italy	265	Surgically resectable clinical stage (T2–T3, N0, M0) prostatic cancer	Goserelin, Bicalutamide (3/6 Months)	PSA progression: significant differences between treatment groups.
Prezioso (35)	2004	Naples, Italy	91	Prostatic cancer clinical stage T2b or less	Leuprolide, Cyproterone (3 Months)	Neoadjuvant group: 31% of patients had a decrease in tumor and prostate volume.
Gravina (36)	2007	L'Aquila, Italy	61	Prostate cancer clinical Stage T2-T3a	Bicalutamide (4 Months)	Neoadjuvant treatment had a reduction of positive surgical margins (13.1% versus 34.5%,

Ravi P,. J Urol. 2022;208(4):838-845.

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Neoadyuvancia pre PROSTATECTOMÍA TERAPIA HORMONAL

Neoadjuvant therapy with Novel Antiandrogen agents						
Montgomery (37)	2017	Seattle, WA, USA	25	Surgically resectable, prostate cancer, clinical stage (T1c–T3, N0/NX, M0), Gleason score ≥7 or PSA >10 ng/mL.	Enzalutamide Vs. Enza + Dutasteride + Leu (6 Months)	0 in the Enza arm and 4.3% in the Enza/Dut/LHRHa arm achieved complete pathologic response. Neither treatment arm demonstrated a significantly higher pCR rate compared with the historical control rate of 5%.
McKay (38)	2019	San Diego, CA, USA	50	Prostate cancer, ISUP 3 or greater, PSA greater than 20 ng/mL, or T3 disease (by prostate MRI).	Enzalutamide + leuprolide plus/minus Apalutimide (6 Months)	Complete response or tumor volume reduction rate was numerically higher with additional apalutamide than without, though not significant (30% *vs* 16%, p=0.151)
Efstathiou (39)	2020	Houston, TX, USA	32	Localized (T1-T2), high-risk prostate cancer.	Apalutamide + LHRHa +/- AA (6 Months)	Organ confined disease (sypT2N0) found in 41% APA+LHRHa *vs*. 39% APA+AA+LHRHa treated.

Ravi P,. J Urol. 2022;208(4):838-845.

ARNEO trial

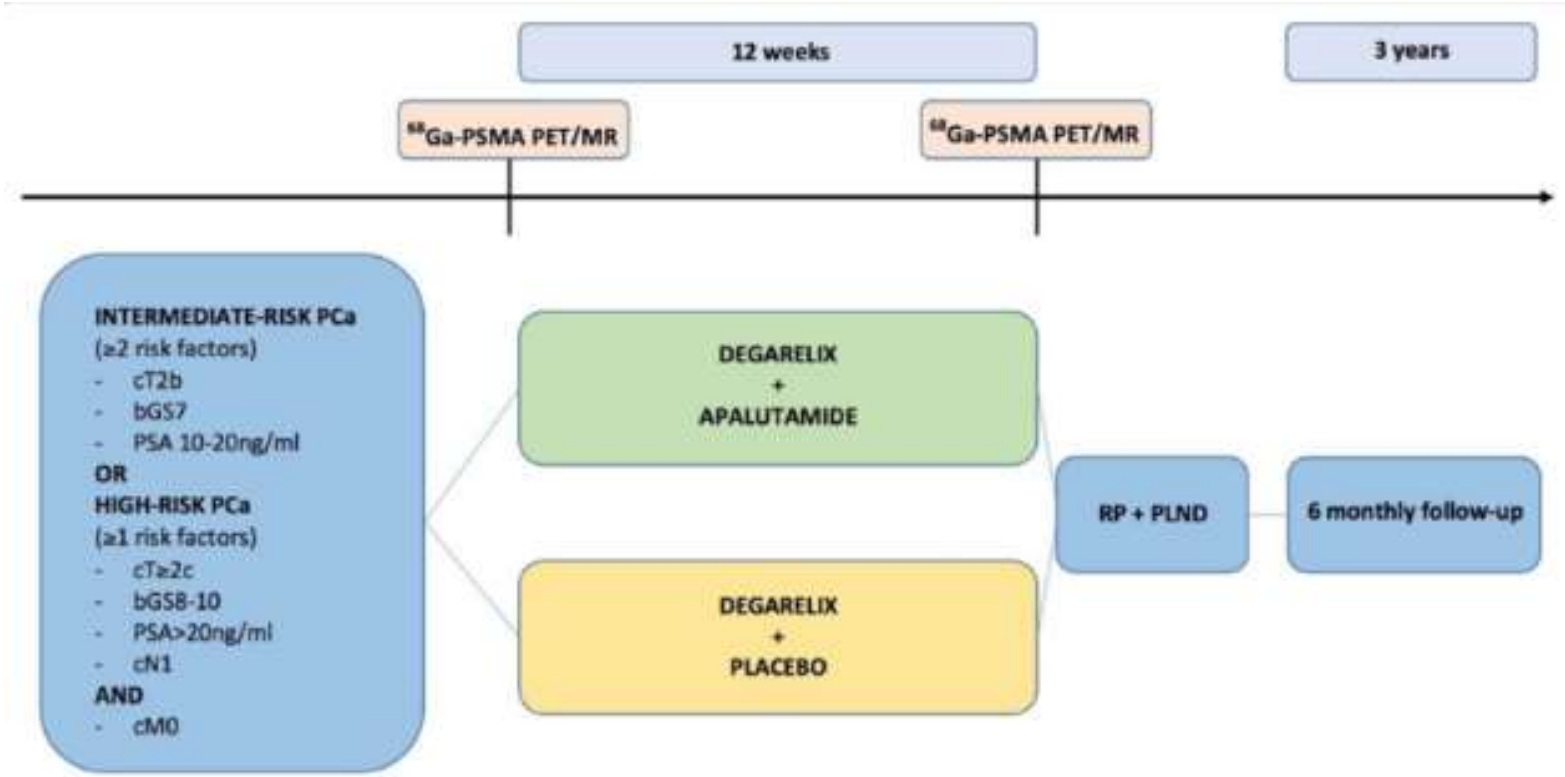

Fig. 1 Flow diagram of ARNEO. Ga: Gallium. bGS: biopsy Gleason score. MR: magnetic resonance. PCa: prostate cancer. PET: Positron Emission Tomography. PLND: pelvic lymph node dissection. PSMA: prostate specific membrane antigen. RP: radical prostatectomy

<u>Objetivo primario</u>: tasa de EMR en ITT

<u>Objetivos secundarios:</u>

Respuesta de PSA

Respuesta patológica (márgenes, afectación ganglionar y estadio quirúrgico)

Cambios en el TNM en el PET-PSMA tras neoady

QoL

Análisis exploratorio: biomarcadores de EMR y RCB (residual cáncer burden)

Devos G, et al. Eur Urol. 2023 Jun;83(6):508-518.

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ARNEO trial

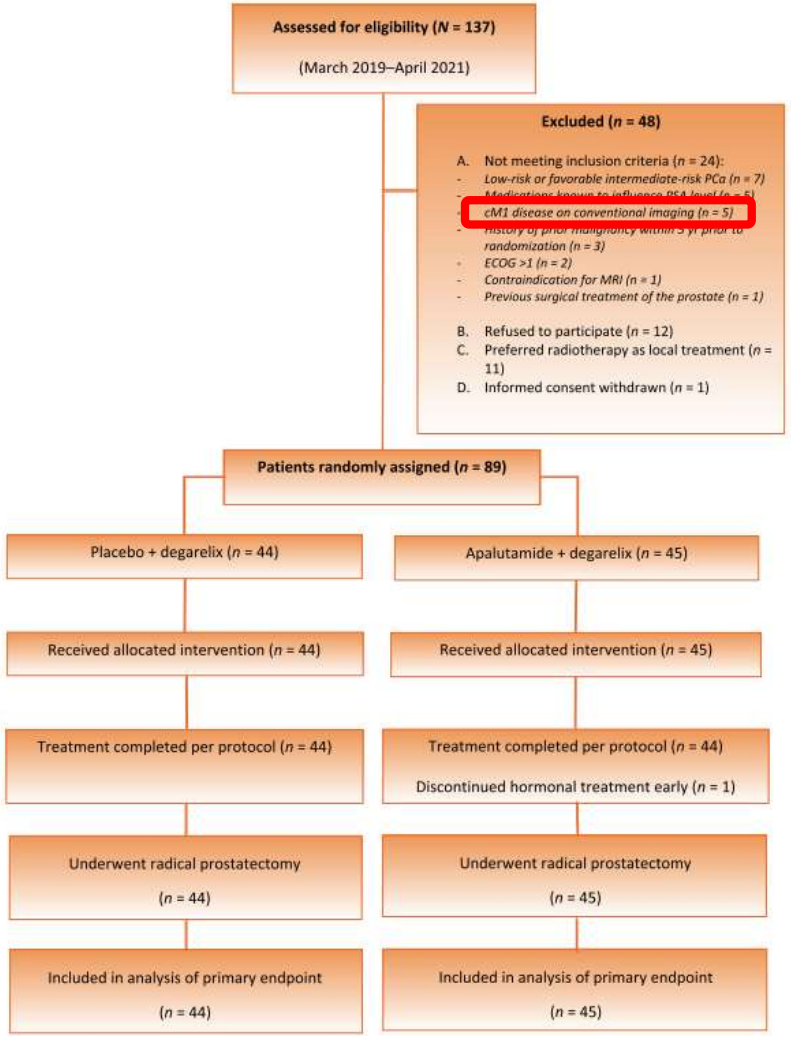

Table 1 – Baseline clinicopathological characteristics

Variable	Degarelix + placebo (n = 44)	Degarelix + apalutamide (n = 45)
Age at time of inclusion (yr), median (IQR)	67 (62–70)	66 (61–70)
ECOG performance status		
0	42 (96)	41 (91)
1	2 (4)	4 (9)
Race		
White	43 (98)	45 (100)
Black	1 (2)	0
PSA at time of biopsy (ng/ml), median (IQR)	11.2 (8.1–19.3)	12.6 (7.8–19.7)
<10 (%)	20 (45)	20 (44)
10–20 (%)	14 (32)	14 (31)
>20 (%)	10 (23)	11 (25)
Clinical T stage (MRI based)		
cT1	1 (2)	1 (2)
cT2	11 (25)	11 (24)
cT3a	20 (46)	18 (40)
cT3b	7 (16)	12 (27)
cT4	5 (11)	3 (7)
Clinical T stage (DRE based)		
cT1	12 (27)	11 (25)
cT2	11 (25)	19 (42)
cT3	20 (46)	13 (29)
NA	1 (2)	2 (4)
Clinical N stage (cross-sectional imaging CT and/or MRI)		
cN1	5 (11)	7 (16)
Biopsy method		
Targeted	13 (30)	13 (29)
Targeted + systematic	22 (50)	25 (55)
Systematic	9 (20)	7 (16)
Biopsy Gleason score		
3 + 4 = 7 (ISUP 2)	3 (7)	5 (11)
4 + 3 = 7 (ISUP 3)	10 (23)	11 (24)
8 (ISUP 4)	17 (39)	10 (22)
9–10 (ISUP 5)	14 (32)	19 (42)
Positive biopsies involved (%), median (IQR)*	46 (37–56)	45 (35–67)
Intraductal growth at biopsy		
Yes	10 (23)	6 (13)
Cribriform pattern at biopsy		
Yes	33 (75)	26 (58)
Risk group		
High risk	43 (98)	44 (98)
Intermediate risk	1 (2)	1 (2)

Devos G, et al. Eur Urol. 2023 Jun;83(6):508-518.

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ARNEO trial

Positive surgical margin		
Yes	8 (18)	8 (18)
Length of positive surgical margin (mm), median (IQR)	3.5 (2.5–8)	1.8 (1–4)
Site of positive surgical margin		
Area of extracapsular extension	7 (16)	5 (11)
Area of capsular violation	1 (2.3)	3 (7)
Pathological complete response	0	0
MRD (RCB <0.25 cm^3)	4 (9)	17 (38)
Overall diameter of remaining tumor <5 mm	2 (4)	2 (4)
Tumor volume (ml), median (IQR)	4.6 (2.3–8.8)	2.7 (0.9–5)
Cellularity (%), median (IQR)	43 (28–67)	20 (10–30)
RCB (cm^3), median (IQR)	1.7 (0.69–5.6)	0.48 (0.080–1.3)

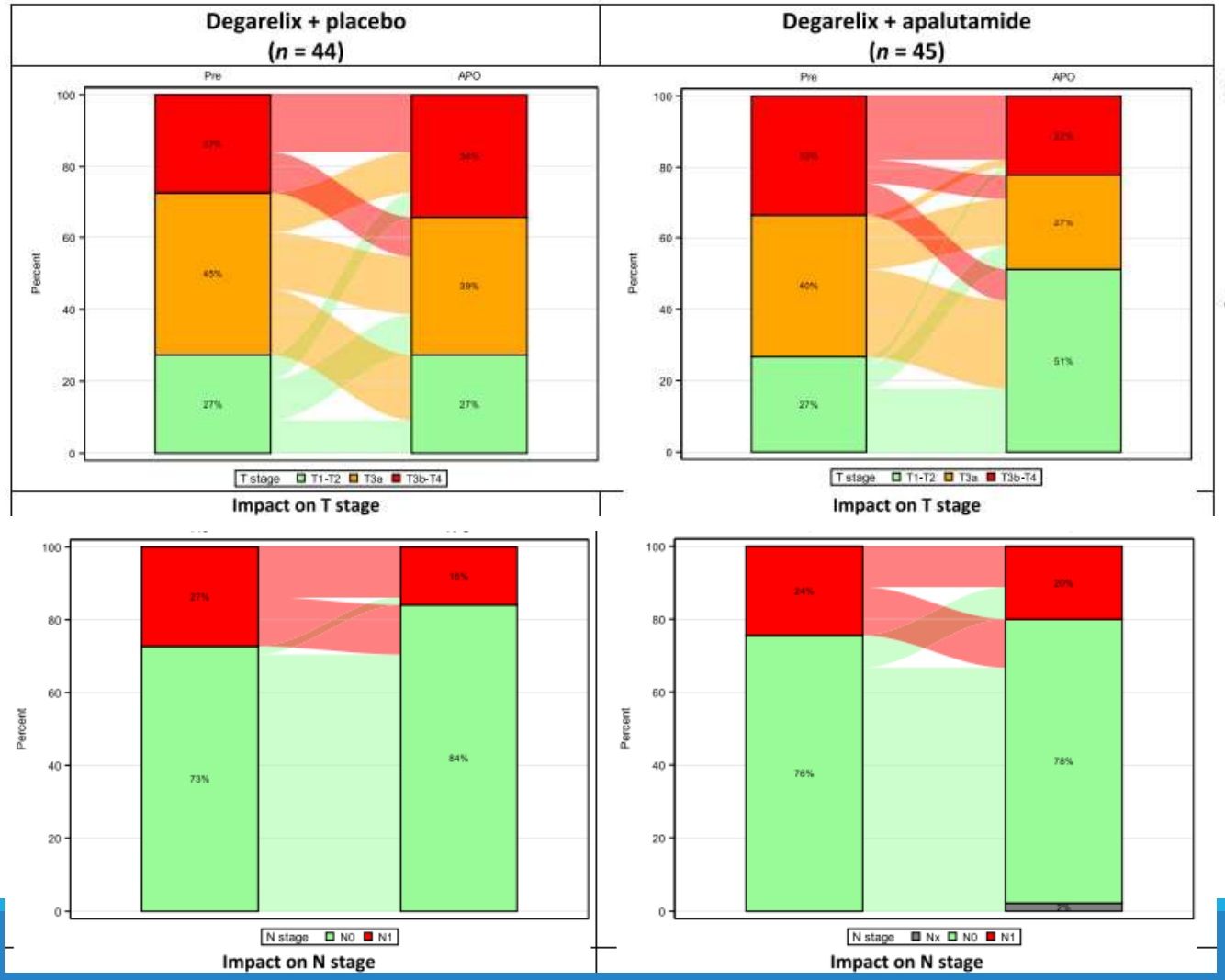
- Los pacientes del grupo de degarelix + apalutamida lograron una tasa significativamente mayor de MRD (38 % frente a 9,1 %; RR [IC del 95 %] = 4,16 [1,52–11,4],

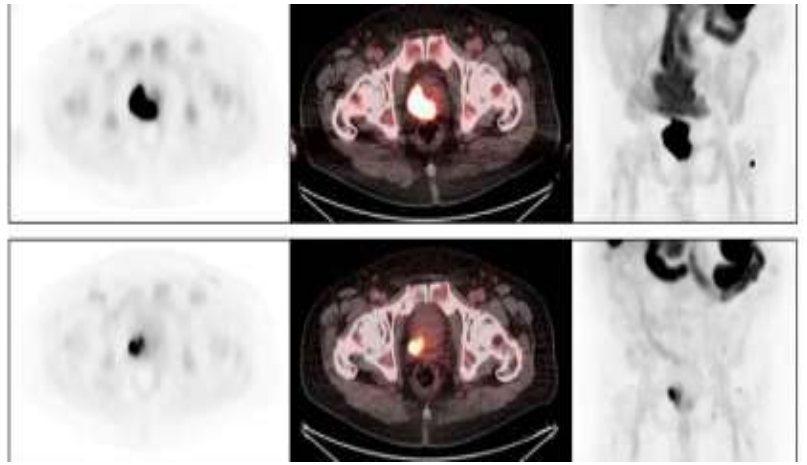
- La mediana de RCB fue significativamente menor en el grupo brazo degarelix + apalutamida (0,48 frente a 1,70 ml; [95% IC] = 1,0 ml (0,48–2,01 ml), p < 0,001

- No diferencias en márgenes quirúrgicos positivos y ganglios linfáticos positivos

Devos G, et al. Eur Urol. 2023 Jun;83(6):508-518.

ARNEO trial





→ PET-PSMA antes del inicio del tratamiento detectó un 7,9% de pacientes metastásicos

→ Downstaging T por PET-PSMA: 40% vs 30%

→ Downstaging N por PET-PSMA 13% en ambas ramas

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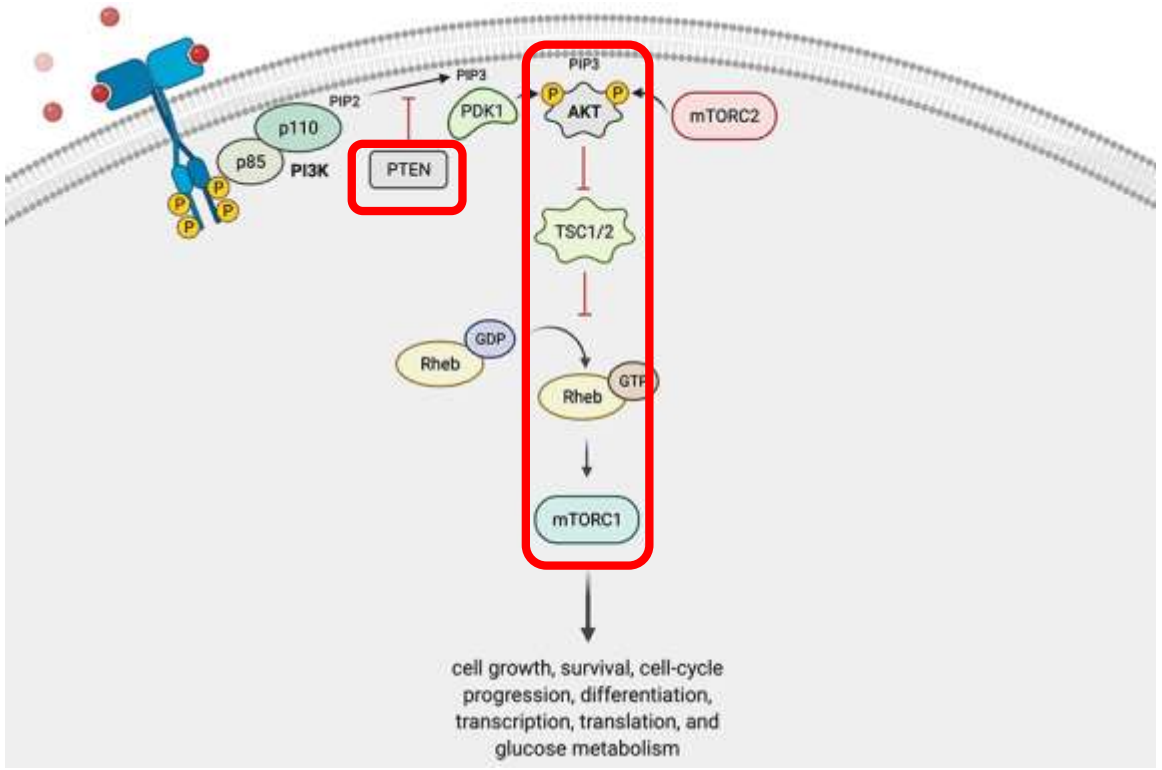
ARNEO trial



→ **PTEN mutado: 40 pacientes (44%)**

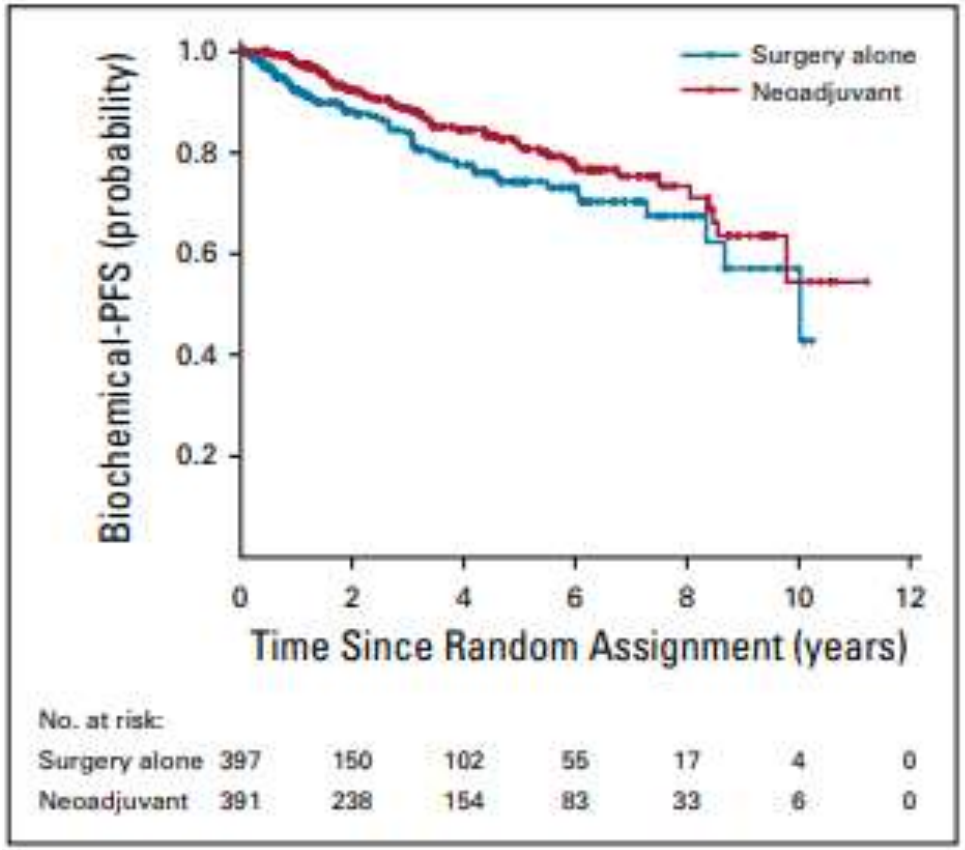
→ PTEN no mutado: 30 pacientes(33%)

Pérdida de expresión de PTEN **asocia menor tasa de MRD** (11% vs 43%, p=0,002) y mayor carga tumoral residual (1,6 vs 0,4 cm3, p<0,001)

Devos G, et al. Eur Urol. 2023 Jun;83(6):508-518.

Neoadyuvancia pre PROSTATECTOMÍA QUIMIOTERAPIA

Neoadjuvant therapy with Chemohormonal therapy						
Eastham (40)	2020	New York, NY, USA	367	Prostate cancer clinical T1-3a disease, serum PSA levels ≤ 100 ng/mL, and no radiographic evidence of metastatic disease	Docetaxel + ADT (4 Months) + RP Versus RP alone	No difference was observed in 3-year BPFS between the neoadjuvant and surgery arms (0.89 v 0.84, respectively.



Eastham JA,. J Clin Oncol. 2020;38(26):3042-3050.

Neoadyuvancia pre PROSTATECTOMÍA LÍNEAS DE INVESTIGACIÓN

Neoadjuvant Androgen Deprivation Therapy Combined With Enzalutamide and Abiraterone Using Multiparametric MRI and 18FDCFPyL PET/CT in Newly Diagnosed Prostate Cancer (NCT03860987)	Bethesda, MD, USA	II	-Intermediate or high risk prostatic adenocarcinoma -cN0/1 -cM0	-Enzalutamide + Abiraterone + GNRH agonist
Neoadjuvant Androgen Deprivation, Darolutamide, and Ipatasertib in Men With Localized, High Risk Prostate Cancer (NCT04737109)	Chicago, IL, USA	II	- Histologically-confirmed diagnosis of localized, untreated prostate cancer with high-risk features. Including: Grade group 4 or higher, OR Stage T3-4, M0 -PTEN loss	- ADT + Ipatasertib + Darolutamide
Genomic Biomarker-Selected Umbrella Neoadjuvant Study for High Risk Localized Prostate Cancer (GUNS) (NCT04812366)	Vancouver, British Columbia, Canada	II	-High-risk localized prostate cancer as defined by: PSA >20, ISUP 4 or greater or high volume Gleason pattern 4 or 5 Participants with oligometastatic (< 3) metastases by PSMA imaging only who are deemed candidates for radical prostatectomy are eligible	-LHRHa + Apalutamide +/- Abiraterone -LHRHa + Abiraterone +/- either Docetaxel or niraparib
Non-fucosylated Anti-CTLA-4 (BMS-986218) + Degarelix Acetate vs. Degarelix Acetate Alone in Men With High-risk Localized Prostate Cancer (NCT04301414)	New York, NY, USA	I	-Prostate Cancer (clinical stage T1c-T3b, N0, M0) and shows at least 2 positive cores and a Gleason sum of ≥4+3	- Non-fucosylated Anti-CTLA-4 (BMS-986218) + Degarelix -Degarelix

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Neoadyuvancia pre PROSTATECTOMÍA LÍNEAS DE INVESTIGACIÓN

TABLE 2 | Current active trials assessing neoadjuvant therapies prior to radical prostatectomy for high-risk, localized disease.

Name (trial number)	Location	Phase	Abbreviated Oncologic Eligibility	Treatment arms
Neoadjuvant Degarelix With or Without Apalutamide Followed by Radical Prostatectomy (ARNEO) (NCT03080116)	Leuven, Belgium	II	-Intermediate risk: at least 2 of the following factors: cT2b, biopsy GS 7, PSA 10-20ng/ml -High risk: cT≥2c and/or biopsy GS≥8 and/or PSA>20ng/ml -cN0-cN1, cM0	-Apalutamide + Degarelix -Placebo + Degarelix
Neoadjuvant Pembrolizumab Plus Androgen Axis Blockade Prior to Prostatectomy for High Risk Localized Prostate Cancer (NCT03753243)	Portland, OR, USA	II	- Any one of the following three high risk features: Gleason grade > 8-10, PSA > 20 ng/ml, cT3a -cM0	-Pembrolizumab + Enzalutamide + GNRH agonist (Single arm)
Neoadjuvant Atezolizumab-Based Combination Therapy in Men With Localized Prostate Cancer Prior to Radical Prostatectomy (NCT03821246)	San Francisco, CA, USA	II	-Only high risk patients in the safety-lead in for each cohort -Intermediate risk patients eligible once safety confirmed on interim analysis -cM0	-Atezolizumab +/- either Tocilizumab OR Etrumadenant (Non-randomized, [illegible])
A Study of Neoadjuvant Hormone Therapy in Patient With Advanced Prostate Cancer Undergoing Radical Prostatectomy. (NCT03971110)	Guangzhou, China	IV	-cT3/4, cN0/1, cM0/1 (with five or fewer extra-pelvic lesions)	-Zoladex + Casodex (Single Arm)
Ibrutinib as Neoadjuvant Therapy in Localized Prostate Cancer (NCT02643667)	San Francisco, CA, USA	II	-Suitable for radical prostatectomy -cM0	-Ibrutinib (Single Arm)
Biomarkers for Neoadjuvant Pembrolizumab in Non-Metastatic Prostate Cancer Positive by 18FDG-PET Scanning (NCT04009967)	Laval, Québec, Canada	II	-Gleason Score ≥ 8, cM0 -Intraprostatic maximum standardized uptake value (SUVmax) ≥4 at 18-FDG-PET/CT exam	-Pembrolizumab (Single arm)
Neoadjuvant Hiltonol® (PolyICLC) for Prostate Cancer (NCT03262103)	New York, NY, USA	I	-Gleason 7 – 10, cT2a - cT3b adenocarcinoma of the prostate with plans for radical prostatectomy and PSA ≥ 4 ng/ml -Tumor visible on multiparametric MRI	Intratumoral injection of Poly-ICLC
177Lu-PSMA-I&T Prior to Radical Prostatectomy for Locally Advanced Disease (NCT04297410)	Petach Tikva, Israel	NA	-cT3/4 and/or Gleason score ≥8 and/or PSA ≥ 20 ng/dl) -Loco-regional prostate cancer (pelvic lymphadenopathy of ≥2 cm on axial imaging) -High PSMA expression: with tracer uptake greater than normal liver (maximal SUV ≥1.5 of liver)	- 177Lu-PSMA-I&T Radionuclide (Single arm)

Ravi P,. J Urol. 2022;208(4):838-845.