VGO NORTE INTERNATIONAL GU DEBATES

Advanced hormone sensitive disease: Is the triplet vs doublet debate over?

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CEU

HOSPITALES CENTRO INTEGRAL ONCOLÓGICO hm CIOCC

START the cure starts here

Disclosures

* *Employment:* HM Hospitales

* *Advisory boards and Consulting* for BMS, Amgen, Novartis, J&J, Pierre-Fabre, Tellix.

* *Speaker honoraria* from Pierre-Fabre, Roche, BMS, Novartis, MSD, J&J, Pfizer, Astra-Zeneca, Astellas, Bayer, Regeneron

* *Travel, accommodations, expenses:* Novartis, BMS, MSD, Pierre-Fabre, J&J

* *Corporate-sponsored research:* Astra-Zeneca, BMS, Amgen, Roche, Novartis, MSD, J&J, Pfizer, Astellas, GSK, PharmaMar, Ipsen, Tesaro, Abbvie, Aprea Therapeutics, EISAI, Bayer, Merck, IOVANCE, Regeneron, Immunocore, Eikon Therapeutics, iOmx Therapeutics, IDEAYA Biosciences, Gilead Science, Synnovation Therapeutics, Genmab, Samsung Bioepis, Rondo Therapeutics, Janux Therapeutics.

* *IDMC member:* J&J

Metastatic Androgen Pathway Modulation-Sensitive (APMS) disease:
Is the triplet vs doublet debate over?

Beyond triplet versus doublet:

no one-size-fits-all winner, only patient-centered treatment choices

Table 2 | Phase III trials evaluating ARPIs in patients with metastatic hormone-sensitive prostate cancer[a]

Trial	Interventions (number of patients)	Docetaxel use	Median follow-up	Median OS; landmark OS[b]	Incidence of grade≥3 adverse events	Refs.
LATITUDE	ADT+abiraterone+prednisone (*n*=597) versus ADT+dual placebo (*n*=602)	Not allowed	52 months	53.3 versus 36.5 months; not reported (HR 0.66, 95% CI 0.56–0.78; *P*<0.0001)	63% versus 48%, including more hypertension (20% versus 10%), hypokalaemia (11% versus 1%) and serum aminotransferase elevations (ALT and AST increases in 5% versus 1% and 4% versus 1%, respectively) in the abiraterone group	46,59
STAMPEDE (Arm G)	ADT+abiraterone+prednisone (*n*=502) versus ADT (*n*=501)	Not allowed	96 months	79 versus 46 months; 5-year OS 60% versus 41% (HR 0.60, 95% CI 0.50–0.71; *P*<0.0001)	47% versus 33%, including more hypertension (5% versus 1%), serum aminotransferase elevations (7% versus 1%) and respiratory disorders (5% versus 2%) in the abiraterone group	47,56
TITAN	ADT+apalutamide (*n*=525) versus ADT+placebo (*n*=527)	Prior docetaxel (11%)	44 months	NR versus 52.2 months; not reported (HR 0.65, 95% CI 0.53–0.79; *P*<0.0001)	42% versus 40%, including more rash (6% versus 1%) in the apalutamide group; grade 2 hypothyroidism (6.5% versus 1%) was also more common in the apalutamide group	48,61
ENZAMET	ADT+enzalutamide (*n*=563) versus ADT+non-steroidal antiandrogen (*n*=562)	Concurrent docetaxel (45%)	98 months	95 versus 70 months; 5-year OS 67% versus 57% and 8-year OS 50% versus 40% (HR 0.73, 95% CI 0.63–0.81; *P*<0.001)	57% versus 43%; including more fatigue (6% versus 1%), syncope (4% versus 1%) in the enzalutamide group; seizures of any grade were also more common in the enzalutamide group (1.2% versus 0%)	49,65,66
ARCHES	ADT+enzalutamide (*n*=574) versus ADT+placebo (*n*=576)	Prior docetaxel (18%)	61 months	NR versus NR; 5-year OS 65% versus 53% (HR 0.70; 95% CI 0.58–0.85; *P*=0.0003)	24% versus 26%; more cognitive/memory impairment of any grade (4.5% versus 2.1%) was observed in the enzalutamide group	69,70,132
ARANOTE	ADT+darolutamide (*n*=446) versus ADT+placebo (*n*=223)	Not allowed	25 months	NR versus NR; not reported (HR 0.81, 95% CI 0.59–1.12)	36% versus 36%, including more arthralgia (1% versus 0%) in the darolutamide group; any-grade urinary tract infection was also more common in this group (14% versus 8%)	50
ARASENS	ADT+docetaxel+darolutamide (*n*=651) versus ADT+docetaxel+placebo (*n*=655)	Included as standard of care in both groups	43 months	NR versus 48.9 months; 4-year OS 62.7% versus 50.4% (HR 0.68, 95% CI 0.57–0.80; *P*<0.001)	70% versus 67%, including more hypertension (grade≥3 in 6.4% versus 3.2%, any grade in 13.7% versus 9.2%) as well as any-grade rash (16.6% versus 13.5%) in the darolutamide group	44
PEACE-1	ADT ± docetaxel+abiraterone+prednisone (*n*=583) versus ADT±docetaxel (*n*=589)	Concurrent docetaxel (60%)	53 months	Overall population: 68.6 versus 56.6 months (HR 0.82, 95.1% CI 0.69–0.98; *P*=0.030) ADT+docetaxel population (*n*=355 in each arm): NR versus 53 months (HR 0.75, 95.1% CI 0.59–0.95; *P*=0.017)	63% versus 52% in the ADT+docetaxel safety population, including more hypertension (22% versus 13%) and hepatotoxicity with increased aminotransferases (6% versus 1%) in the abiraterone group 66% versus 41% in the ADT without docetaxel population, including more hypertension (29% versus 16%) and hepatotoxicity with increased aminotransferases (6% versus 1%)	45

MA Cilento et al. Nat Rev Clin Oncol. 2026 Feb;23(2):121-136.

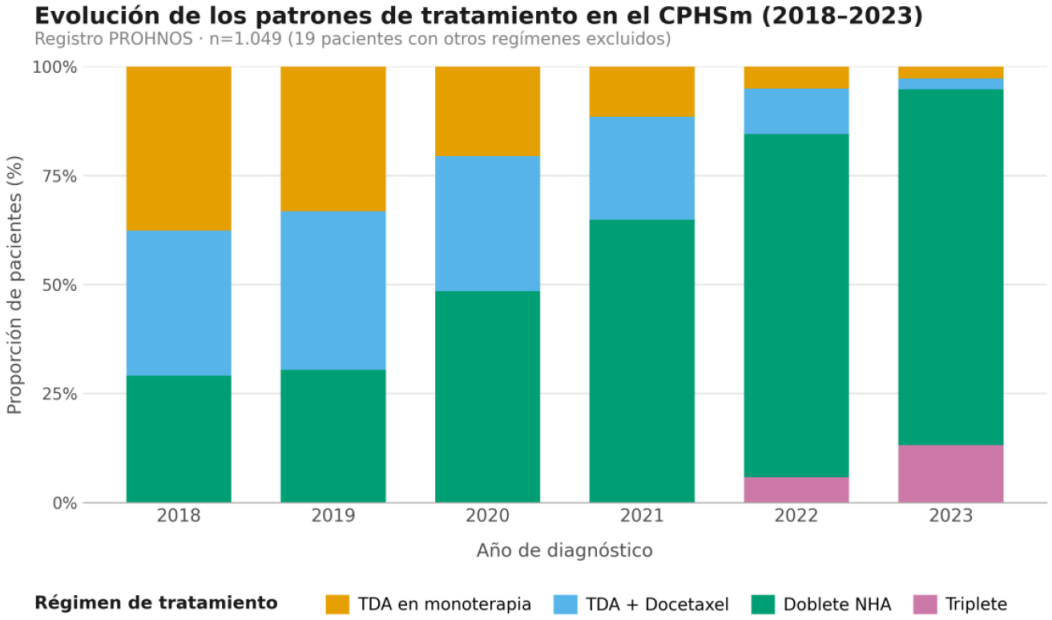
CONGRESO 2026

MADRID
29 - 30 SEPTIEMBRE
1 - 2 OCTUBRE

GONORTE
Grupo Oncológico

Registro PROHNOS

Tratamiento intensificación

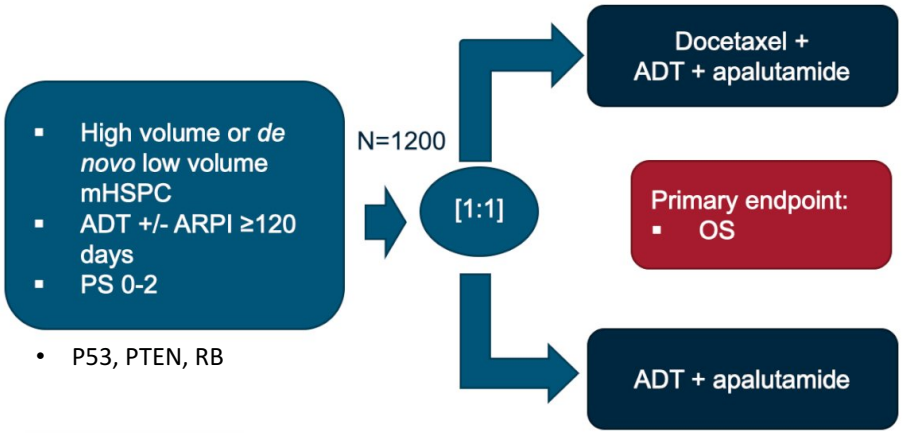


N Lainez et al. SEOM Annual Meeting 2026

What is the optimal use of docetaxel in mHSPC?

What is the optimal use of docetaxel in mHSPC?

* Is triplet therapy really necessary?



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ASPIRE

Positive or Negative…..??:

- Which subgroups derive meaningful benefit from docetaxel?
- What about other molecular subgroups? (HRD, SPOP, Decipher)
- Specific clinical scenarios: "high need for response", visceral disease, bulky nodal disease

What is the optimal use of docetaxel in mHSPC?

* After more than 8.500 patients enrolled…What have we learned?

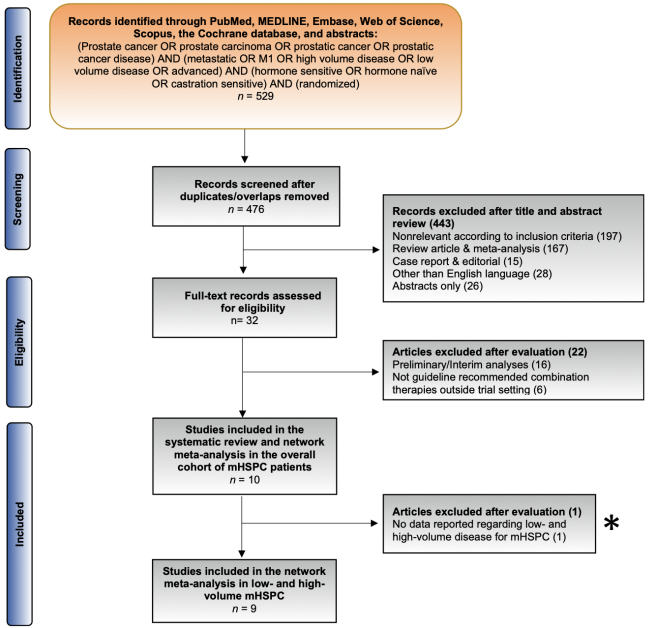


Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart depicting the studies and abstracts included in the meta-analysis of overall survival (OS) in metastatic hormone-sensitive prostate cancer (mHSPC).

Network Meta-analysis

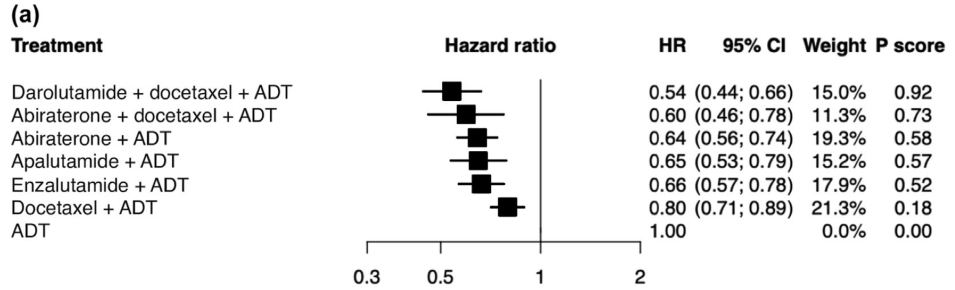
To rank therapy options
Doublet versus triplet therapy
Stratification according to volume tumor burden

- Transitivity assumption
- NMA do not make different trial populations comparable. They rely on the assumption that they are comparable enough for indirect comparisons to be valid.
- Random-effects models account for heterogeneity. They do not eliminate it.

Mandel P. et al. Eur Urol Focus. 2023;9(1):96-105.
Hoeh B. et al. Eur Urol Focus. 2023;9(5):838-842

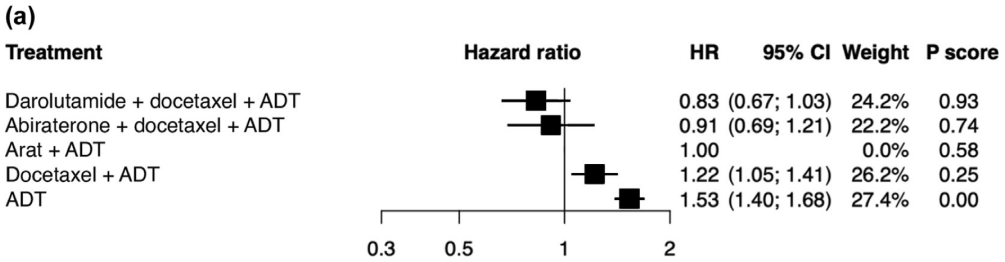
What is the optimal use of docetaxel in mHSPC?

* After more than 8.500 patients enrolled…What have we learned?



OS (overall cohort)

- ADT alone no longer represents a valid treatment option for mHSPC.
- Similar considerations apply to doublet therapy with docetaxel + ADT



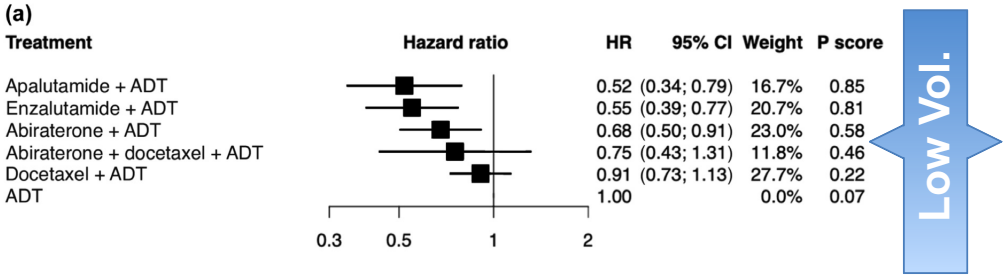
OS (overall cohort pooled ARPI comparison)

- Both triplet therapies failed to demonstrate an statistically significant OS benefit in comparison with ARPI+ADT

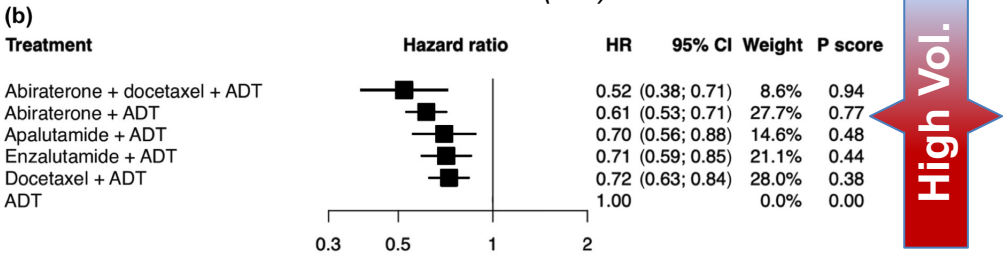
Mandel P. et al. Eur Urol Focus. 2023;9(1):96-105.
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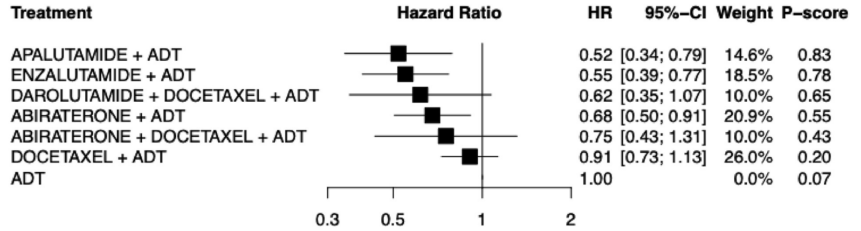


Mandel et al. (OS)

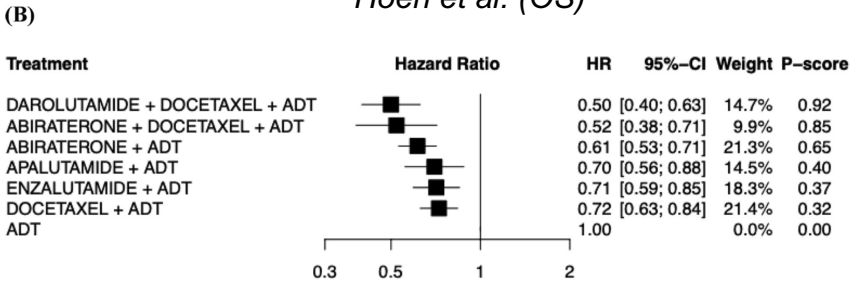


Low Vol.

High Vol.



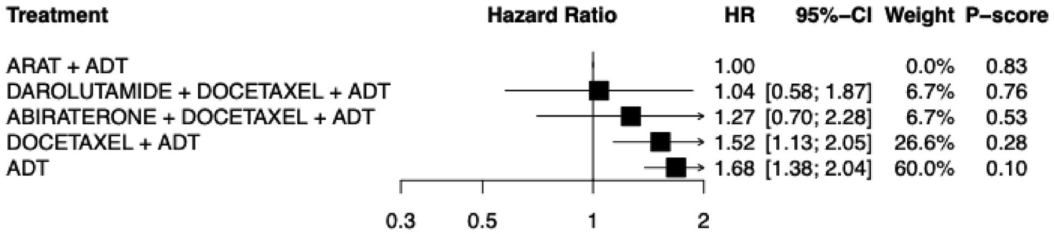
Hoeh et al. (OS)



Mandel P. et al. Eur Urol Focus. 2023;9(1):96-105.
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What is the optimal use of docetaxel in mHSPC?

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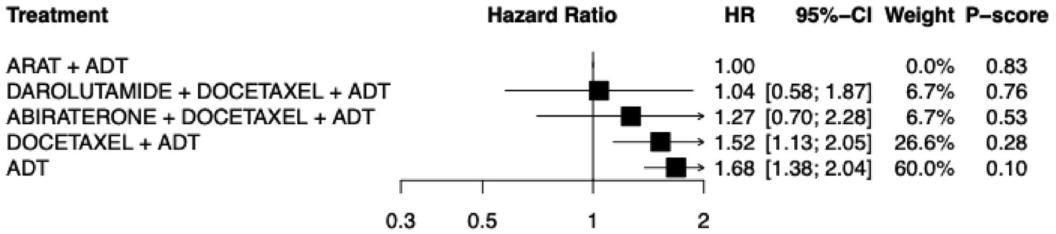
OS (Low Vol. cohort pooled ARPI comparison)

- Available analyses are underpowered and cannot exclude a benefit in selected low-volume patients.

Fizazi K. et al. Lancet. 2022;399:1695-1707.
Mandel P. et al. Eur Urol Focus. 2023;9(1):96-105.
Hoeh B. et al. Eur Urol Focus. 2023;9(5):838-842

What is the optimal use of docetaxel in mHSPC?

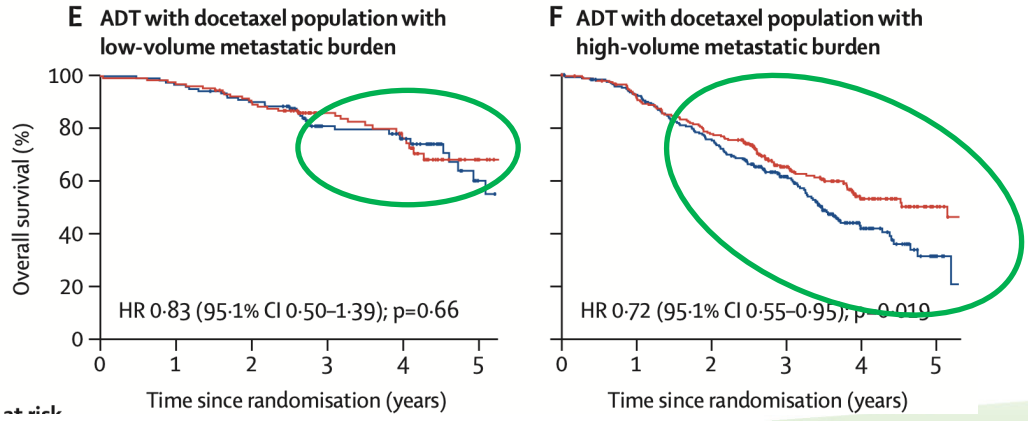
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PEACE-1

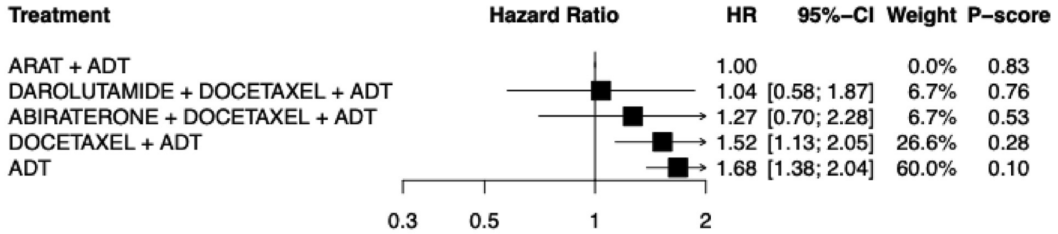


MADRID 2026 ESMO congress

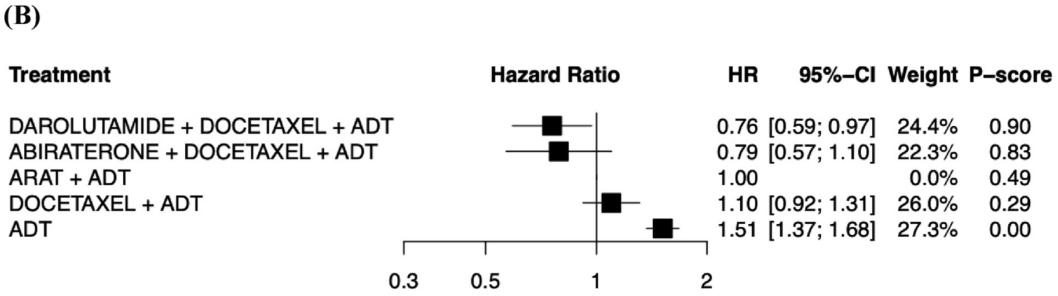
Fizazi K. et al. Lancet. 2022;399:1695-1707.
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What is the optimal use of docetaxel in mHSPC?

* After more than 8.500 patients enrolled…What have we learned?



OS (Low Vol. cohort pooled ARPI comparison)



OS (High Vol. cohort pooled ARPI comparison)

- Available analyses are underpowered and cannot exclude a benefit in selected low-volume patients.
- Although only the darolutamide-based triplet achieved statistical significance, the effect estimates for ARASENS and PEACE-1 were nearly identical (HR 0.76 vs 0.79), suggesting a difference in precision rather than magnitude of benefit.

Mandel P. et al. Eur Urol Focus. 2023;9(1):96-105.
Hoeh B. et al. Eur Urol Focus. 2023;9(5):838-842

What is the optimal use of docetaxel in mHSPC?

* Lessons from Docetaxel-based doublets

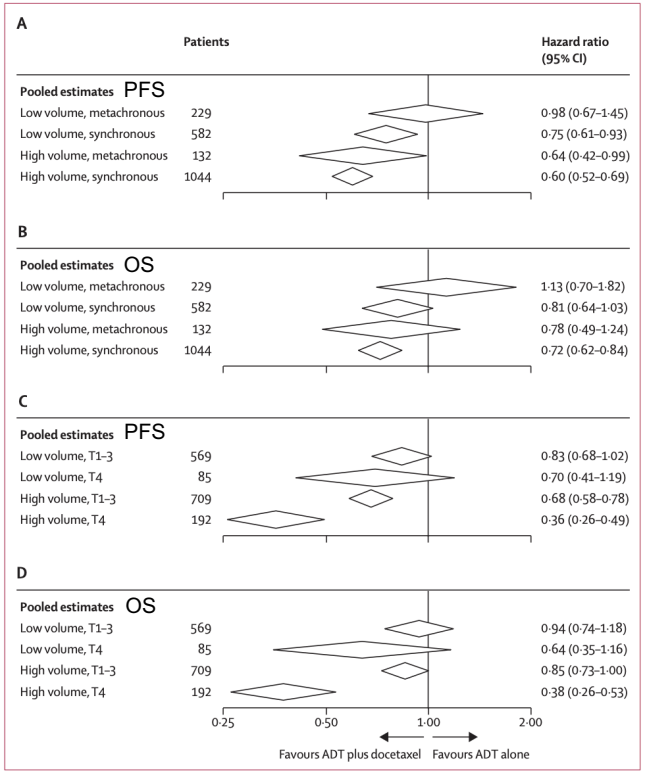
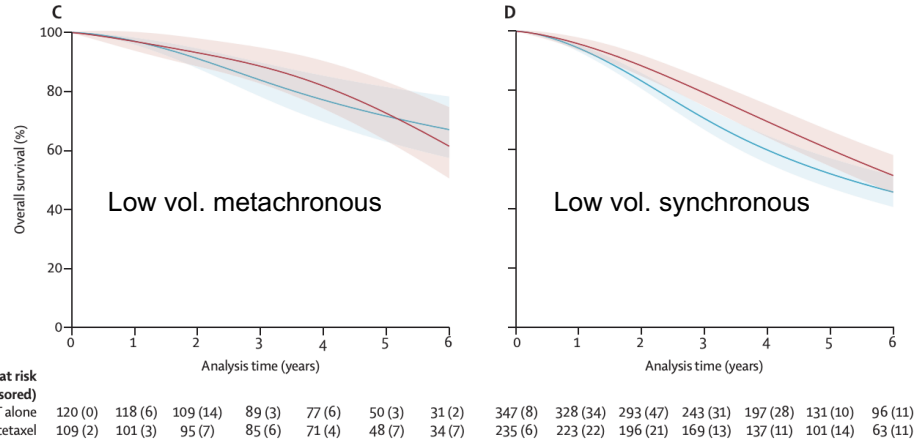


Figure 2: **Effect of docetaxel on progression-free survival and overall survival by volume and timing of metastatic disease diagnosis and by volume and clinical T stage**

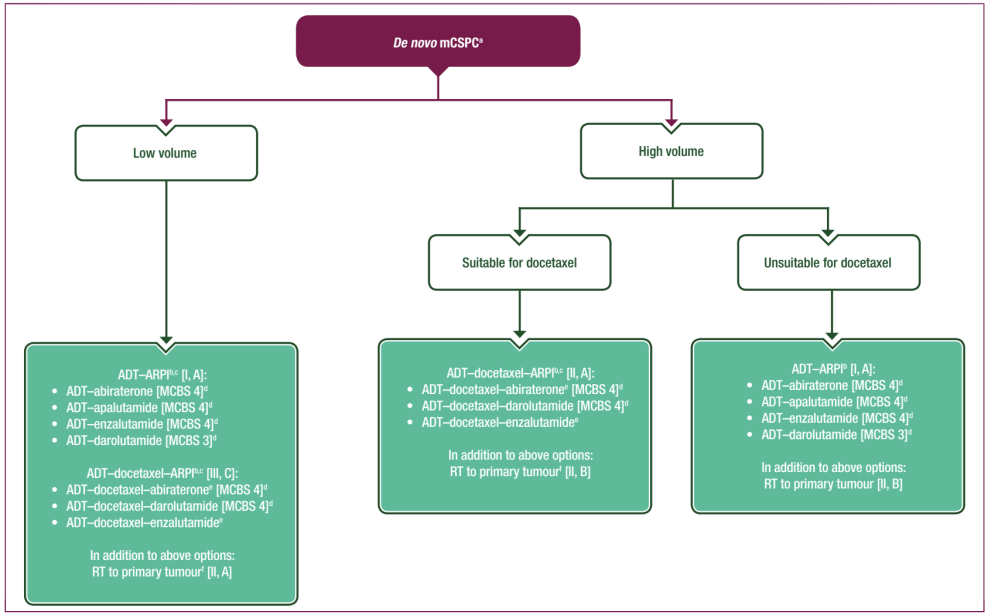
Effects of docetaxel on OS and PFS are modified by **volume** of metastases, **timing** of metastatic disease diagnosis, and clinical **T stage**.

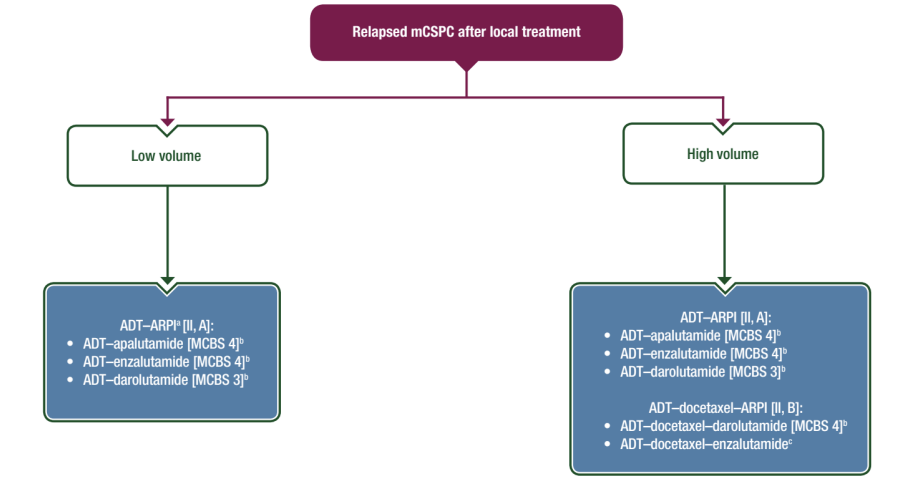


Burdett S. et al. STOPCAP M1 collaborators. Lancet Oncol. 2023;24(7):783-797

What is the optimal use of docetaxel in mHSPC?

* What Do Current Guidelines Recommend?





K.Fizazi et al. ESMO Guidelines Committee. https://doi.org/10.1016/j.annonc.2026.01.015

What is the optimal use of docetaxel in mHSPC?

* APCCC?

Table 1 | Current state of personalized treatment intensification for mHSPC based on timing and volume of metastases

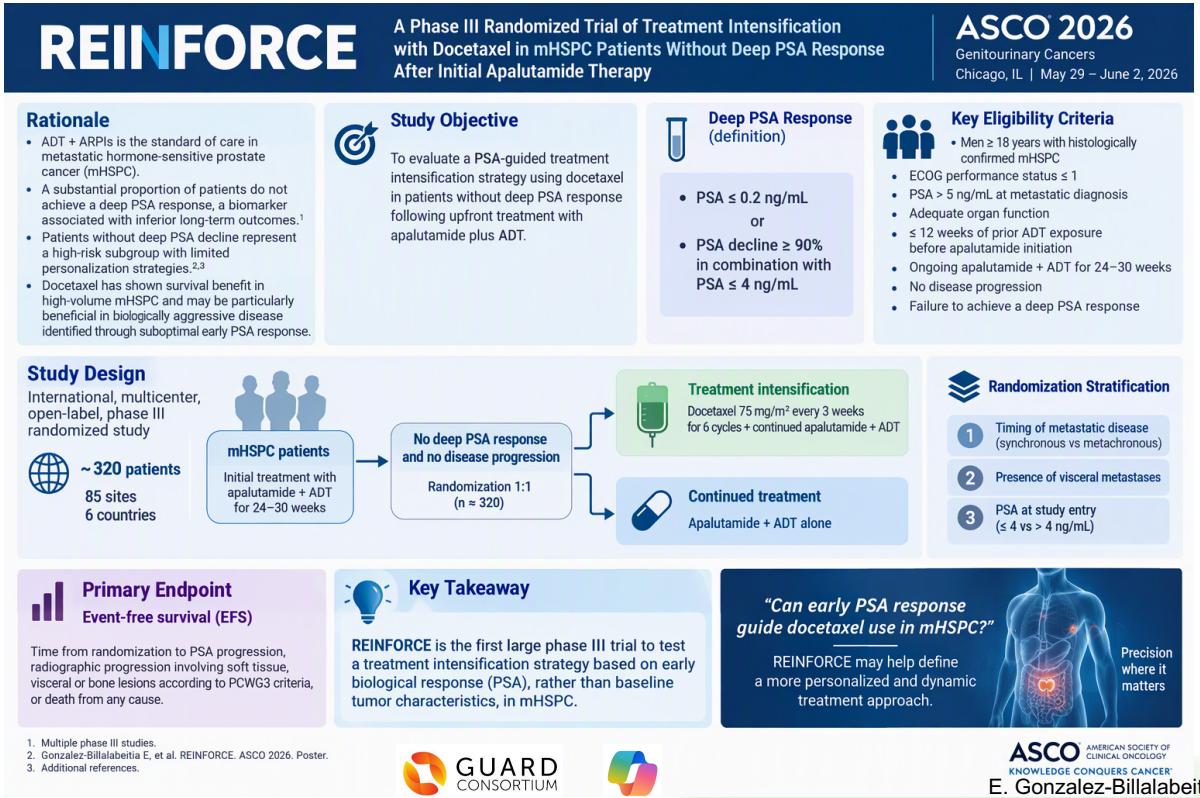
Systemic therapy backbone	Timing of metastases	Number of metastases[a]	Intensification approach	Advanced Prostate Cancer Consensus Conference votes in favour[b]
All patients: ADT + ARPI (abiraterone, apalutamide, enzalutamide or darolutamide) or ADT alone for those with a very short life expectancy owing to age or comorbidities	Metachronous	≤3 bone metastases (±non-regional lymph node metastases)	Stereotactic ablative radiotherapy to metastases	68% (91% of respondents chose ADT + ARPI doublet as preferred systemic therapy)
		≥4 bone metastases (visceral metastases rare)	Docetaxel (for patients deemed fit for chemotherapy)	84% (34% recommend the ADT + ARPI + docetaxel triplet for the majority of patients with ≥4 metachronous bone metastases, and 50% recommend this approach for selected patients)
	Synchronous (de novo)	≤3 bone metastases (±non-regional lymph node metastases)	Prostate radiotherapy and stereotactic ablative radiotherapy	82%
		≥4 bone metastases or any liver metastasis	Docetaxel (for patients deemed fit for chemotherapy)	94% (54% recommend ADT + ARPI + docetaxel triplet for the majority of patients with ≥4 synchronous bone metastases, and 40% recommend this approach for selected patients)

ADT, androgen-deprivation therapy; ARPI, androgen receptor pathway inhibitors. [a]Detectable on conventional imaging with CT (including CT as part of prostate-specific membrane antigen PET–CT) and technetium-99m whole-body bone scintigraphy; future refinements to be made based on prostate-specific membrane antigen PET and molecular biomarkers. [b]Advanced Prostate Cancer Consensus Conference votes in favour combines votes for 'in the majority of patients' and 'in selected patients'[131].

MA Cilento et al. Nat Rev Clin Oncol. 2026 Feb;23(2):121-136.

What is the optimal use of docetaxel in mHSPC?

* Use guided by PSA Response

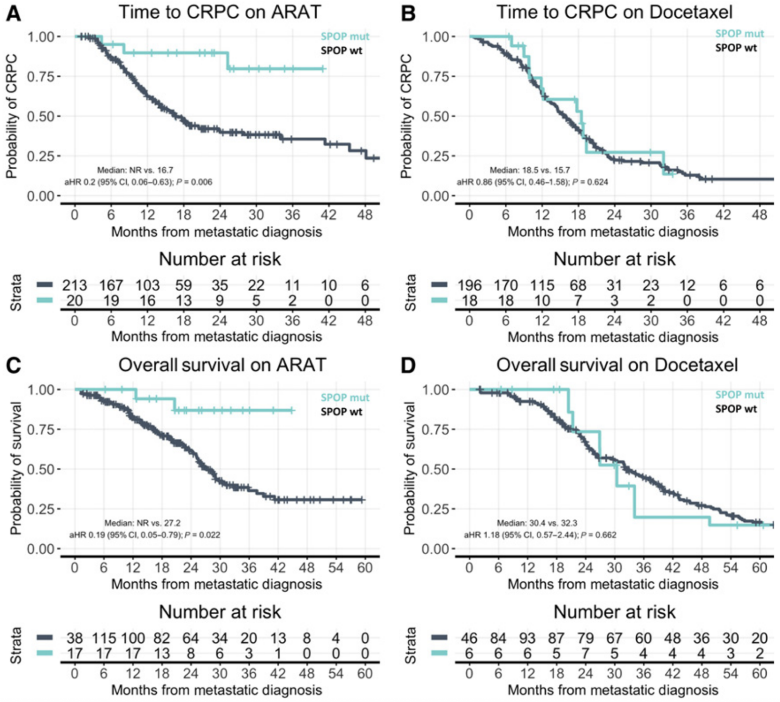


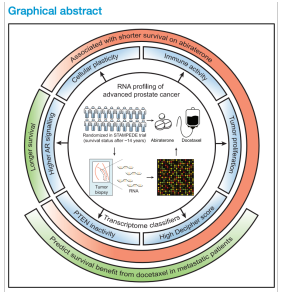
E. Gonzalez-Billalabeitia et al. ASCO Annual Meeting 2026

What is the optimal use of docetaxel in mHSPC?

* Use guided by Biomarkers





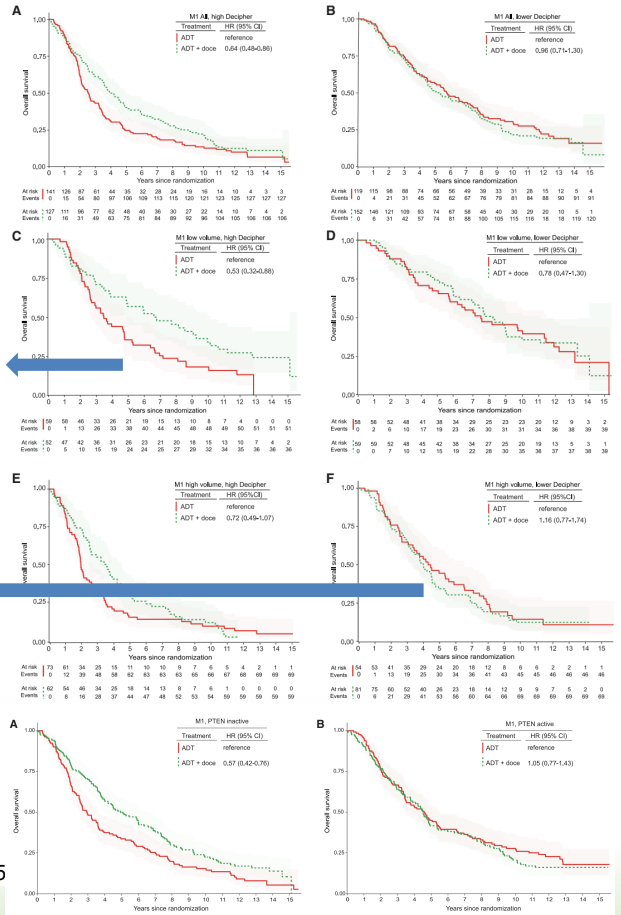


Impact of Decipher® classifier on benefit (OS) from docetaxel, independent of volumen of disease

Necesidad de intensificación?

Sobretratamiento?

PTEN



J Swami et al. Clin Cancer Res 2022;28:4917–25
E Grist et al. 2025, Cell 188, 5717–5734

What is the optimal use of docetaxel in mHSPC?

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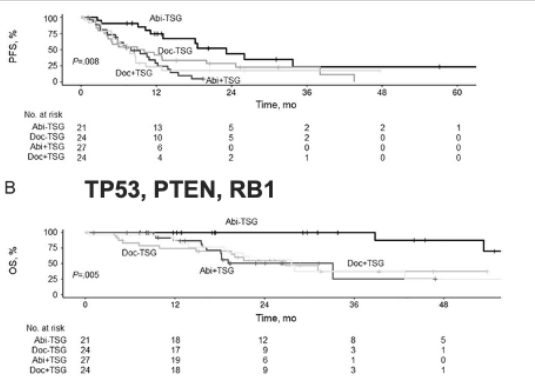
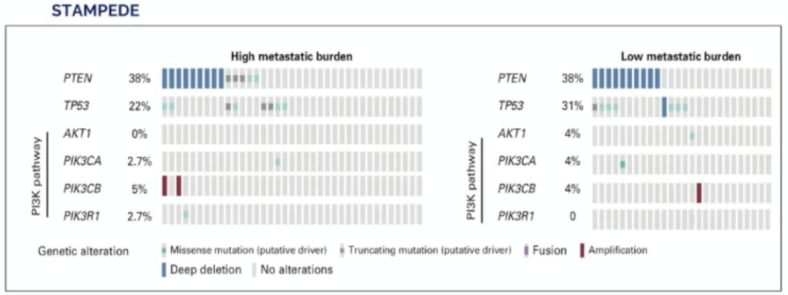
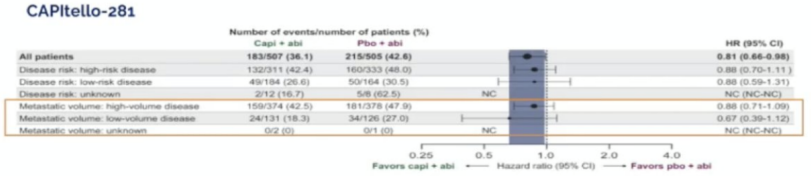
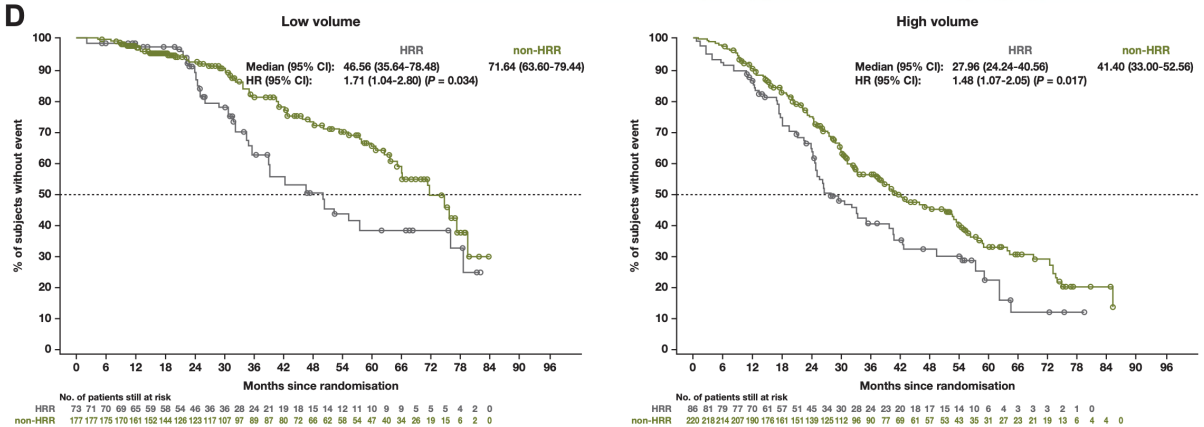


Fig. 3 Progression-Free Survival (PFS) and Overall Survival (OS) by First-Line Treatment and Tumor Suppressor Gene Alteration (TSG-alt) Status. Kaplan–Meier curves showing PFS (**A**) and OS (**B**) for patients with (+TSG) and without (−TSG) TSG-alt treated with abiraterone acetate (Abi) or docetaxel (Doc).







MG Velez et al. Prostate Cancer Prostatic Dis 2022 Sep;25(3):479-483.
Fizazi K et al. Ann. Oncol. doi.org/10.1016/j.annonc.2025.10.004 (2025).
D. Olmos et al. https://doi.org/10.1016/j.annonc.2025.05.534

What is the optimal use of docetaxel in mHSPC?

* Use guided by Patient Fitness and other clinical characteristics

- “Real” volume of disease

- Cancer-related symptoms
- PSA, LDH, FA, …
- Gleason, histology,…

- Age
- Frailty
- Comorbidities
- Bone health
- Cognitive function
- Patient preferences
- Lifestyle

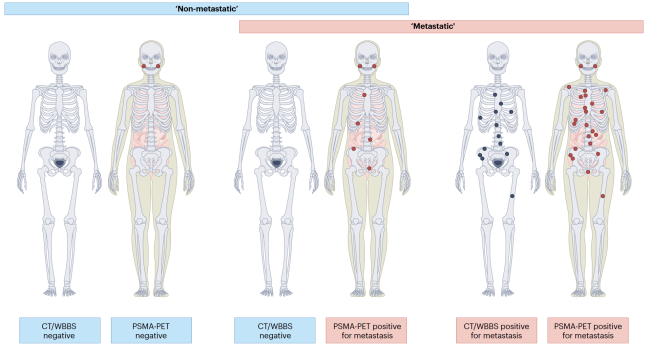


Figure 2 Effects of ARPIs on OS by class of ARPI agent and by age group

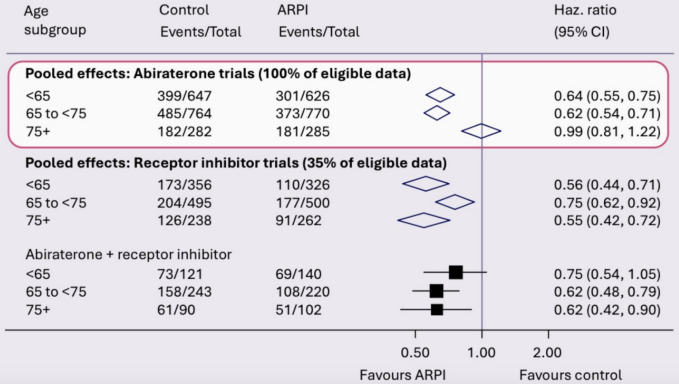
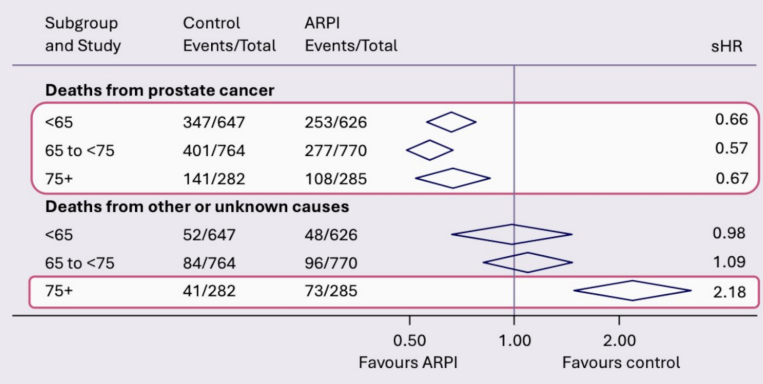


Figure 3 Effect of abiraterone on causes of death



MA Cilento et al. Nat Rev Clin Oncol. 2026 Feb;23(2):121-136.
D. Fisher et al. STOPCAP M1 collaborators APCCC 2026

What is the optimal use of docetaxel in mHSPC?

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- "Real" volume of disease

- Cancer-related symptoms
- PSA, LDH, FA, …
- Gleason, histology,…

- Age
- Frailty
- Comorbidities
- Bone health
- Cognitive function
- Patient preferences
- Lifestyle



Perfil de seguridad

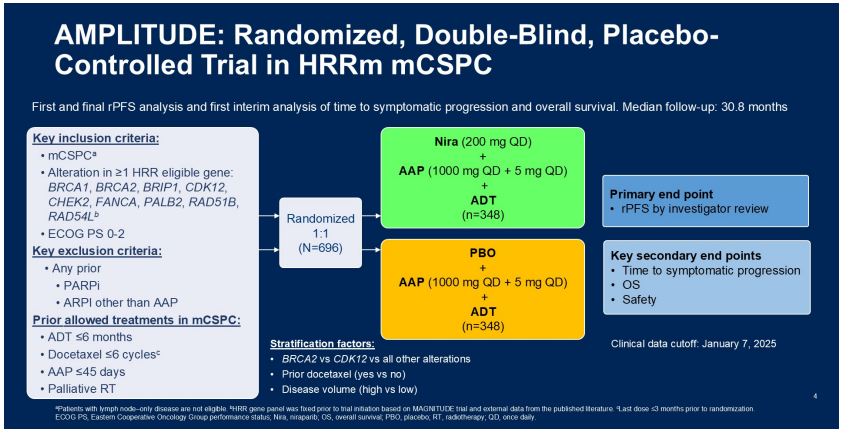
- **24,7% interrumpió el tratamiento de intensificación**

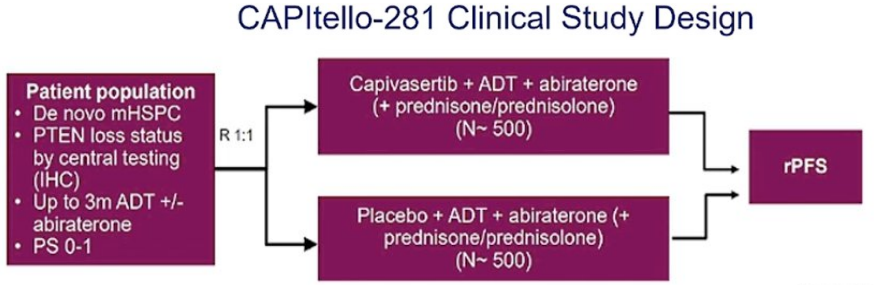
  Con el porcentaje más alto en el grupo triplete (32,2%);

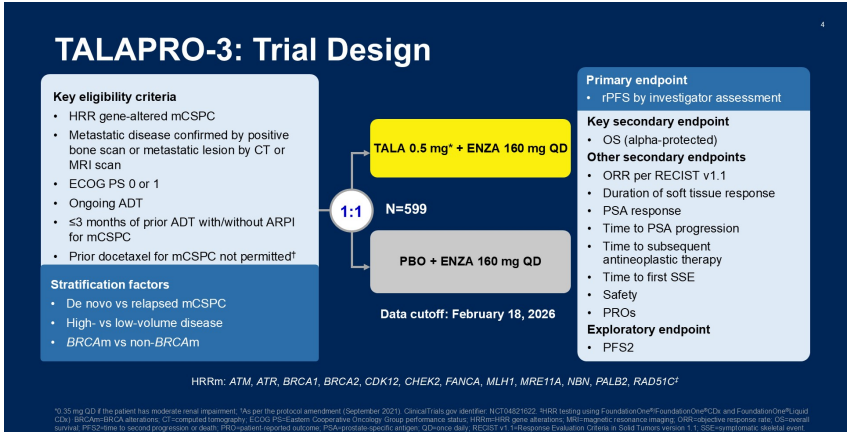
  La toxicidad más frecuente que llevó a interrupción

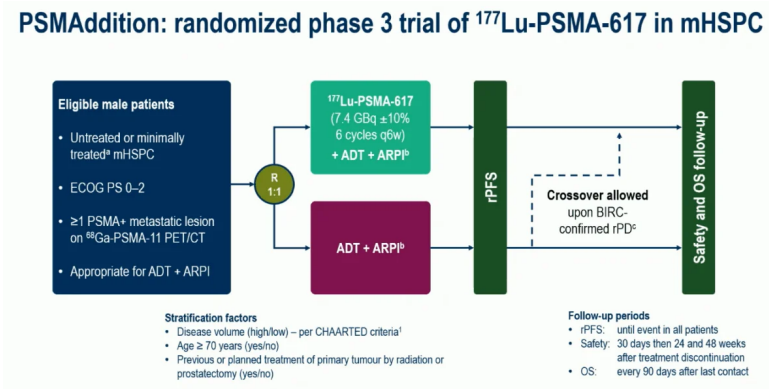
  - TDA + docetaxel → Neutropenia febril 26,7%
  - Doblete → Astenia/fatiga 23,9%
  - Triplete → Neutropenia febril 63,6%

But the future is,…which triplet should you choose?









G Attard et al. Nat Med (2025). https://doi.org/10.1038/s41591-025-03961-8
N. Agarwal et al. DOI: 10.1056/NEJMoa2604126
Fizazi K et al. Ann. Oncol. doi.org/10.1016/j.annonc.2025.10.004 (2025).
ST Tagawa et al. Lancet 2026; 408: 793–807

Metastatic Androgen Pathway Modulation-Sensitive (APMS) disease:
Is the triplet vs doublet debate over?

Beyond triplet versus doublet:

no one-size-fits-all winner, only patient-centered treatment choices

VGO NORTE INTERNATIONAL GU DEBATES

Thank you for your attention!

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