ASCO GU 2025- Docetaxel Rechallenge Versus Cabazitaxel in Patients Previously Treated with Docetaxel for Metastatic Castrate-Resistant Prostate Cancer (mCRPC)

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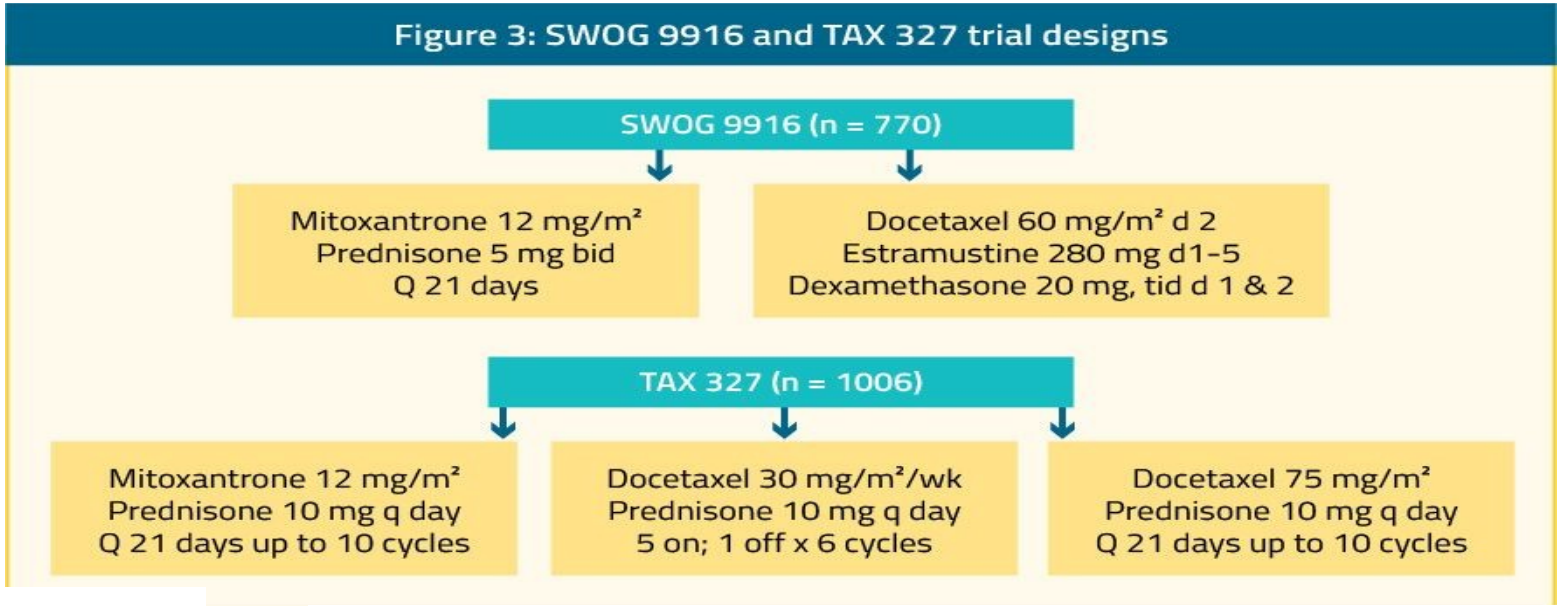
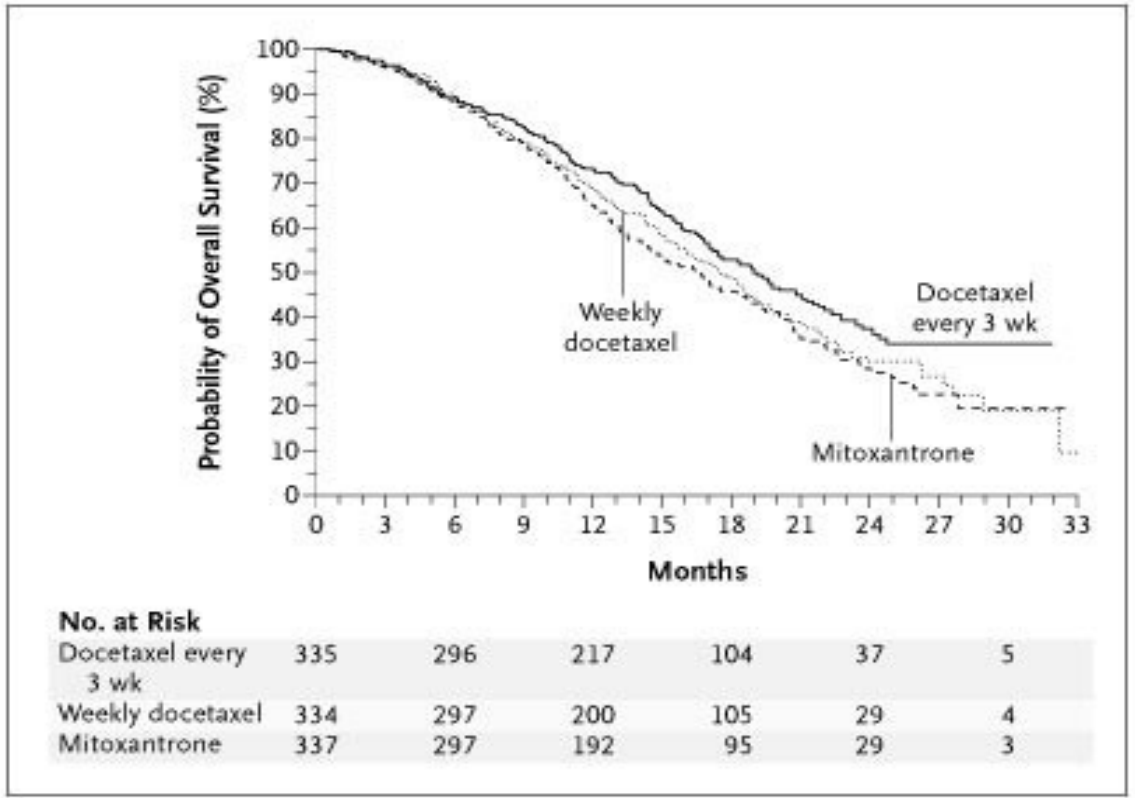
Background- Docetaxel in castration resistant prostate cancer

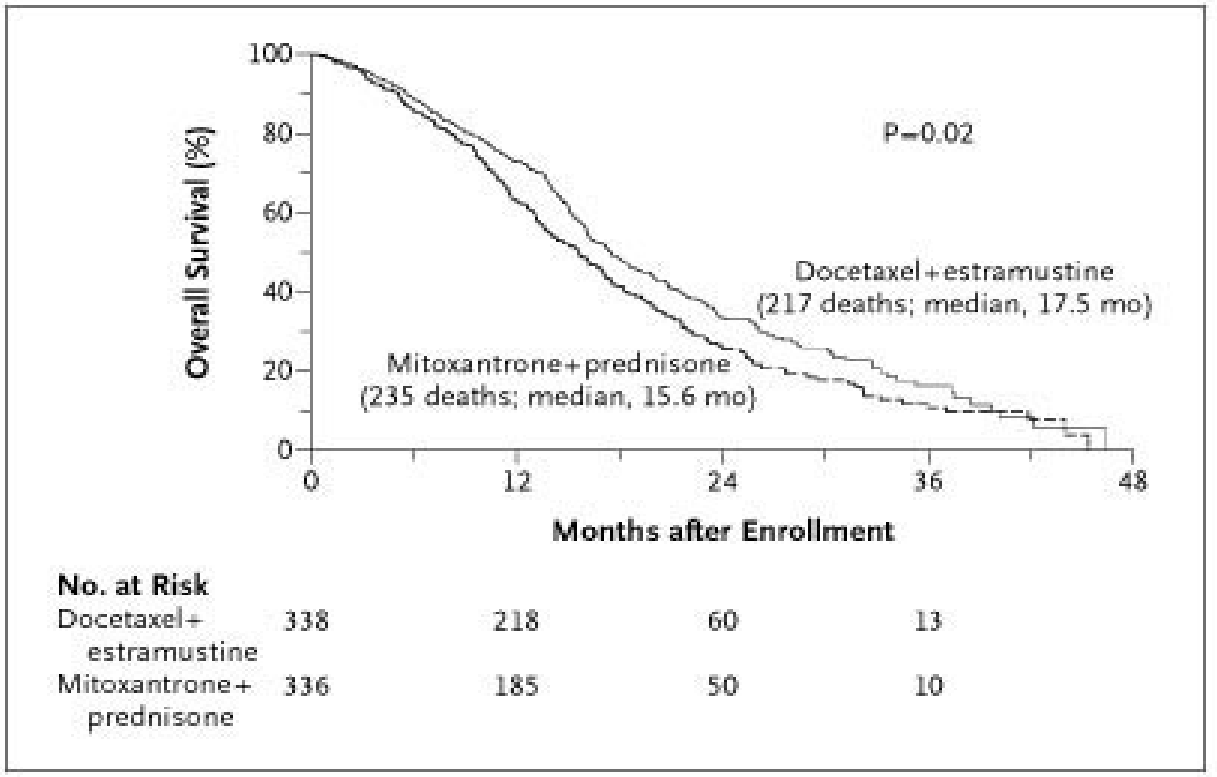
- In 2004, Docetaxel was approved for the treatment of mCRPC patients, based on the results of the TAX-327 trial that demonstrated improved overall survival outcomes with docetaxel plus prednisone therapy with ADT vs ADT alone

- In 2004, we also had the results of the SWOG 9916 trial, which showed that in mCRPC, Docetaxel + Estraumustine +Prednisolone significantly improved survival compared to Mitoxantrone and Prednisolone

TAX 327 and SWOG 9916 trials- graphic representations





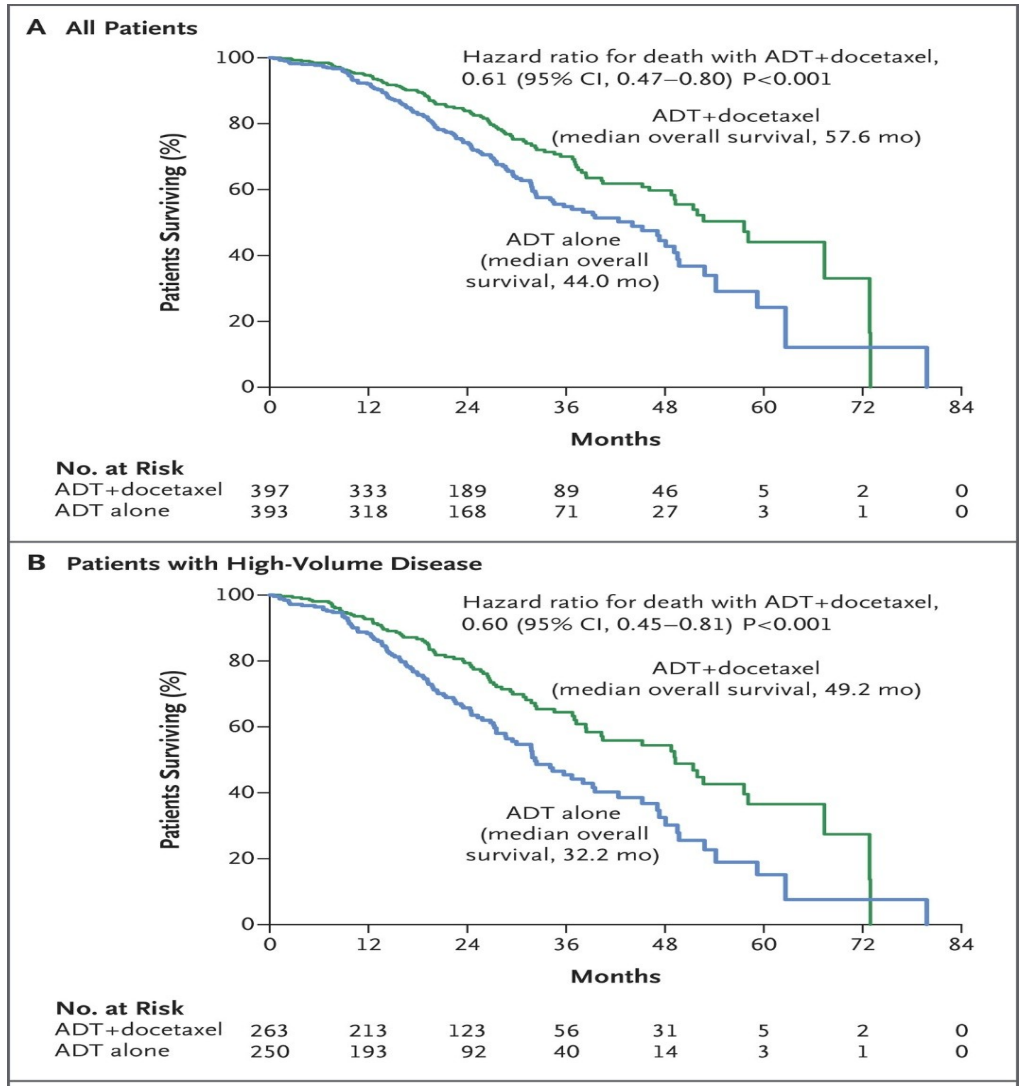


Docetaxel use then moved to mHSPC

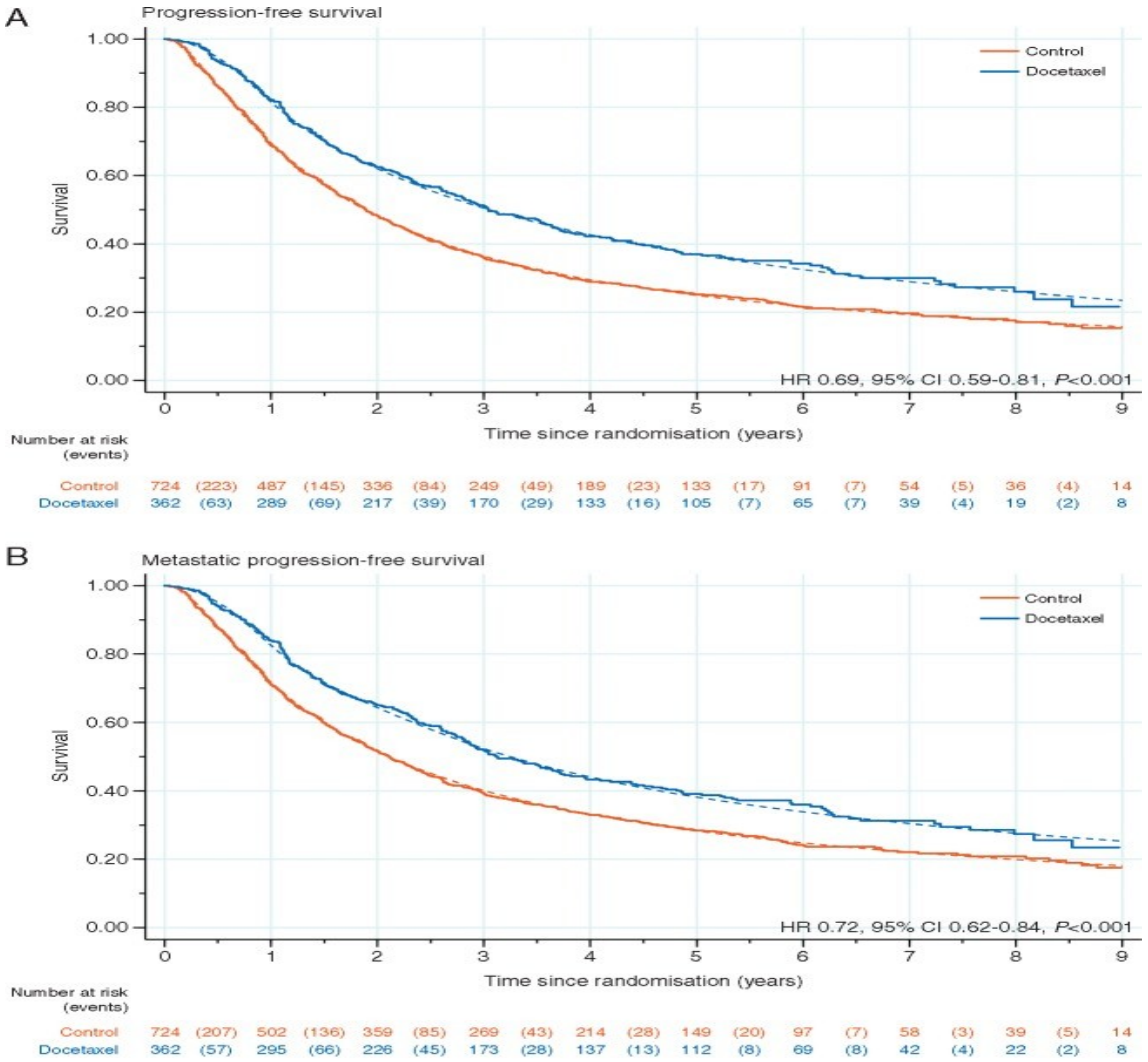
The use of Docetaxel then moved to the setting of metastatic castration sensitive prostate cancer, based on the results of the CHAARTED, STAMPEDE and GETUG AFU trials

- CHAARTED trial- ADT + Docetaxel vs ADT alone, Docetaxel improved OS
- STAMPEDE trial- a multi arm trial, it also showed that ADT + Docetaxel improves OS compared to ADT alone
- GETUG AFU trial- ADT + Docetaxel improved PSA PFS and radiographic PFS but not OS compared to ADT alone
- Finally, after PEACE 1 trial, Docetaxel + ADT + Abiraterone (triplet therapy) has become standard of care for mHSPC

CHAARTED trial



STAMPEDE trial



Cabazitaxel in mCRPC

- In 2010, cabazitaxel was approved in 2010 for mCRPC patients previously exposed to docetaxel, based on the results of the TROPIC trial

- Men with mCRPC, ECOG PS 0–2, who had prior hormone therapy, chemotherapy, and radiotherapy, but had PD during or after Docetaxel (cumulative dose ≥225 mg/m^2) were randomized to 10 mg/day of prednisone with either mitoxantrone 12 mg/m^2 (MP) or Cabazitaxel 25 mg/m^2 (CbzP), both administered 3-weekly

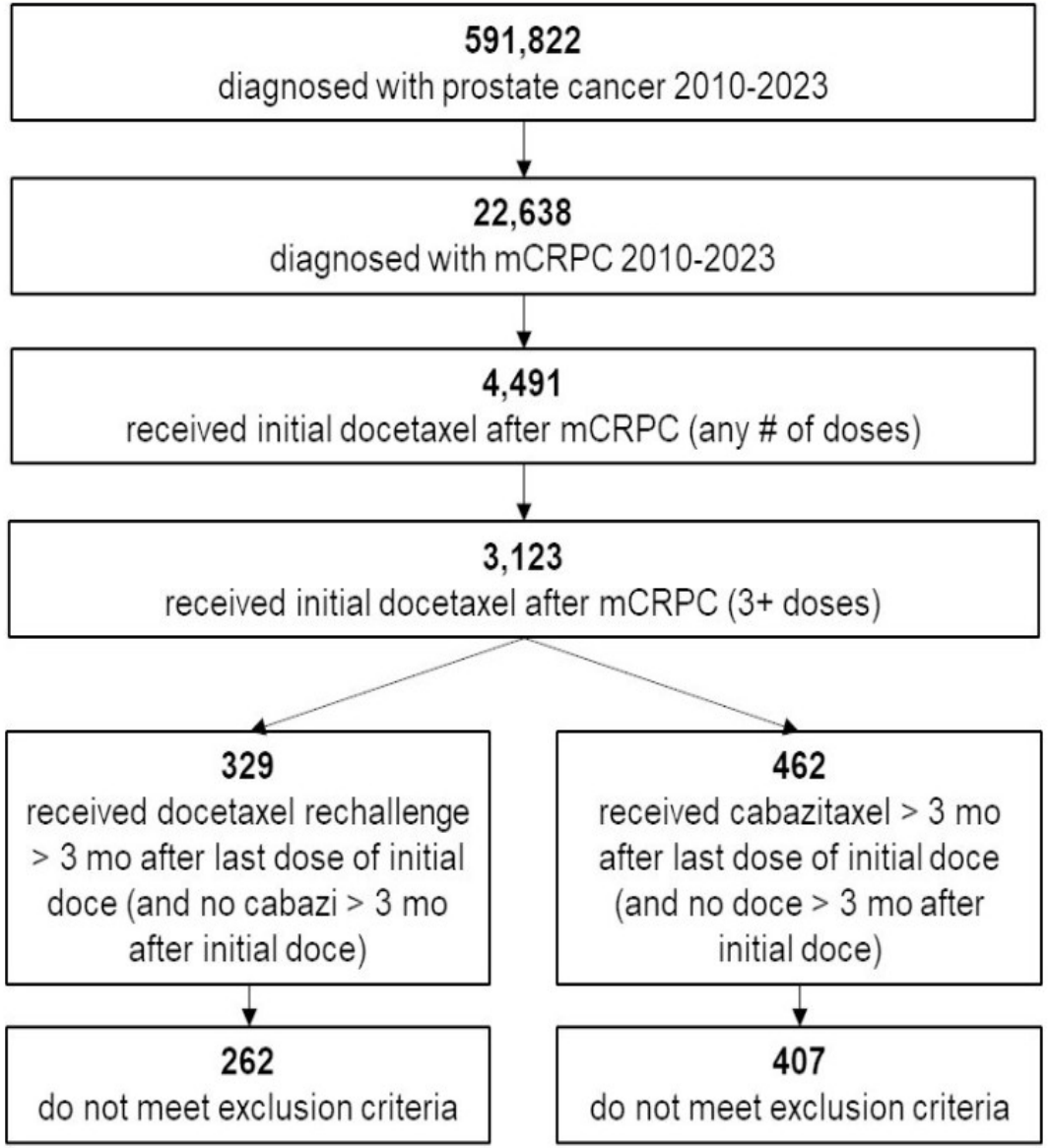
- Cabazitaxel improved OS compared to Mixotantrone

Why this study?

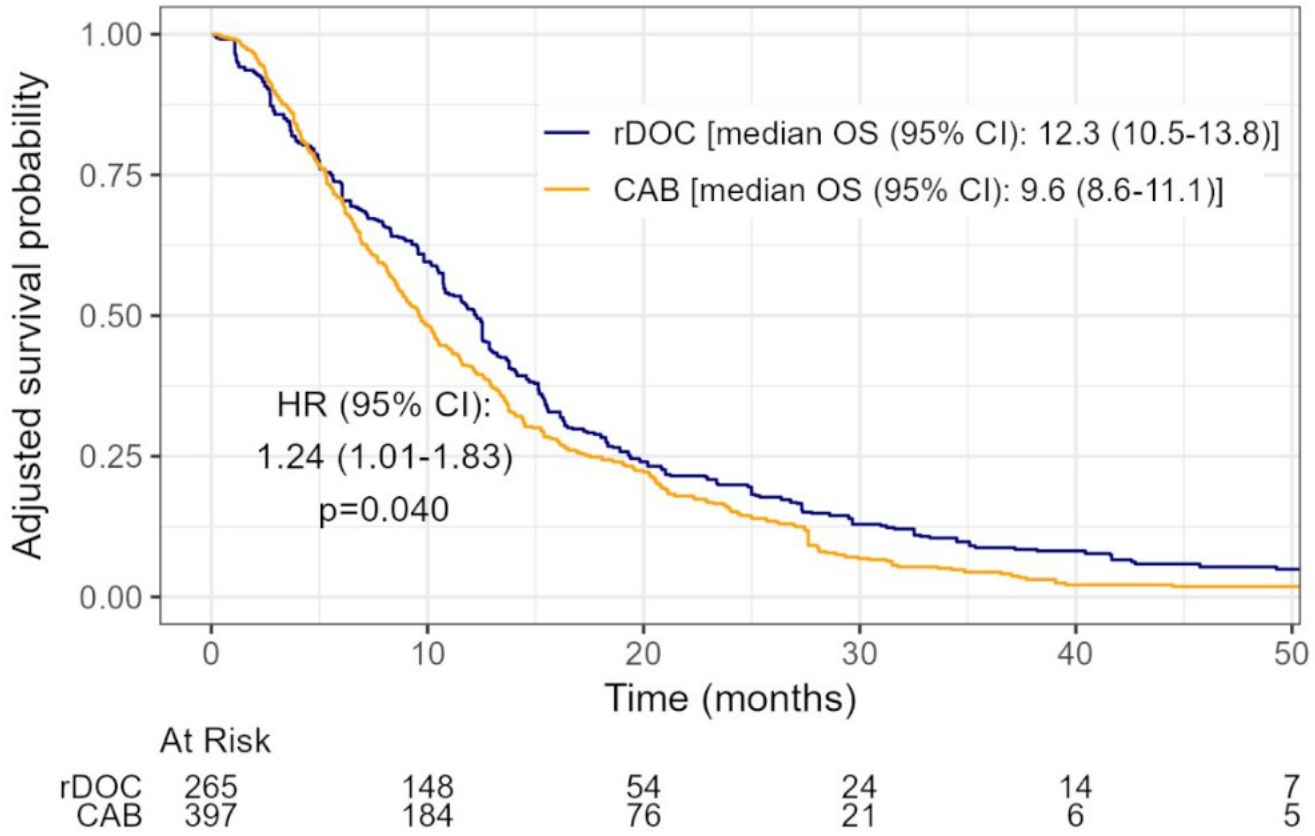
- Prostate cancer is a disease of remissions and relapses, with most patients experiencing long term survival in years
- Hence sequencing of therapy has become very important
- Most patients are now initially exposed to Docetaxel in the first line mHSPC setting as part of triplet therapy
- For patients previously treated with docetaxel, it is unclear whether docetaxel rechallenge or switch to Cabazitaxel is a better option

Methods

- This was a retrospective cohort analysis
- Use of the nationwide VA healthcare system database
- Included patients who received initial docetaxel for mCRPC, subsequently discontinued docetaxel for a reason other than disease progression, and who later received a docetaxel re-challenge or cabazitaxel switch
- Patients were eligible for inclusion if they received at least 3 cycles of DOC and at least 90 days later received a second course of DOC or CAB. The index date was the date of the start of the second course of taxane treatment
- Time-to-event analyses were performed, with the date of docetaxel re-challenge or cabazitaxel switch marking the start of follow-up (i.e., T0)
- Inverse probability of treatment weighting (IPTW) was used to control for potential confounders


591,822
diagnosed with prostate cancer 2010-2023
22,638
diagnosed with mCRPC 2010-2023
4,491
received initial docetaxel after mCRPC (any # of doses)
3,123
received initial docetaxel after mCRPC (3+ doses)
329
received docetaxel rechallenge > 3 mo after last dose of initial doce (and no cabazi > 3 mo after initial doce)
462
received cabazitaxel > 3 mo after last dose of initial doce (and no doce > 3 mo after initial doce)
262
do not meet exclusion criteria
407
do not meet exclusion criteria

Overall Survival Curve



PSA responses

Table 1. Weighted PSA responses in patients treated with rDOC versus CAB

	rDOC	CAB	p
n	265.2	397.2	
PSA Maximum Decline (%)			
>= 30% decline	102.8 (42.0)	119.6 (32.5)	0.057
>= 50% decline	65.9 (26.9)	77.8 (21.1)	0.134
>= 90% decline	23.9 (9.8)	11.2 (3.0)	0.001
Stable	73.7 (30.1)	122.3 (33.2)	0.538
No Decline	68.4 (27.9)	126.6 (34.4)	0.159

Patient characteristics

- Median age 72
- 29% Black
- 39% CKD
- 8% DM2

- For the first instance of docetaxel, patients received a median of 6 (IQR: 4-10) cycles with a PSA50 = 20%, PSA90 = 3% and a median of 1 (IQR: 0-1) additional systemic treatment prior to subsequent taxane

- At the time of the initiation of the second taxane, 73% of patients had bone and 18% visceral metastases and median initial PSA of 75

Compared to Cabazitaxel, rechallenge Docetaxel showed-

1- Higher PSA90 (11% vs 3%, p 0.001)

2- Longer OS (12.5 vs 9.6 months, p 0.001)

3- Numerically longer time to next systemic treatment (16.4 vs 12.4 months, p=0.2)

4- Shorter time on treatment (2.1 vs. 2.6 months, p=0.56)

5- Similar PSA50 (8% vs 9%, p=0.31)

The use of platinum (9% vs 6%, p=0.15), immunotherapy (2 vs 1%, p=0.79) and PARP inhibitors (6% vs 5%, p=0.67) after the second instance of a taxane was not statistically different between groups

Investigators' conclusions

- They opined that a docetaxel re-challenge was associated with superior survival outcomes and deeper PSA responses, compared to a cabazitaxel switch, in docetaxel pre-treated mCRPC patients who discontinued docetaxel for a reason other than disease progression

- They also opine that the findings of this large-scale study provide guidance for making well-informed, cost-effective decisions regarding the sequential use of taxanes for the treatment of mCRPC patients.

Other studies of Docetaxel vs Cabazitaxel

CANTATA trial

- Prospective, two-arm, open-label, phase II study
- Patients of mCRPC who had previously been treated with Docetaxel but not had PD during Docetaxel
- Randmomized to 1-Docetaxel or 2-Cabazitaxel

- 15 patients were enrolled
- Study was halted due to slow accrual
- The median clinical PFS time in the Cabazitaxel group was 6.2 months compared with 8.4 for the Docetaxel group

Other studies of Docetaxel vs Cabazitaxel
Pobel et al study

- 22 CRPC patients who have received Docetaxel and hormonal therapy
- Received multiple rechallenges of Cabazitaxel 25 mg per m2 (reduced doses at subsequent rechallenges)
- The median number of Cabazitaxel cycles was 7 at first Cabazitaxel treatment, 6 at first rechallenge, and 5 at subsequent rechallenges

- Median progression-free survival at first rechallenge was 9.6 months and 5.6 months at second rechallenge.
- Median overall survival was 50.9 months from the first cabazitaxel dose, 114.9 months from first life-extending therapy initiation in mCRPC, and 105 months from mCRPC diagnosis.
- There was no cumulative grade ≥3 neuropathy or nail disorder and one case of febrile neutropenia.

Other studies of Docetaxel vs Cabazitaxel

Thibault et al study

- A total of 69 patients were rechallenged with Cabazitaxel
- For 1–10 (median 6) cycles
- Median radiological or clinical PFS with CABA rechallenge was 7.8 months and 11.9 months with initial CABA therapy
- OS was 13.7 months from the first CABA rechallenge cycle, 59.9 months from the first life-extending therapy in mCRPC and 78.3 months from mCRPC diagnosis
- Best clinical benefit was improved (34.3%) or stable (47.8%).
- Lack of response to rechallenge occurred in 17.9% of patients (3.1% with initial CABA)

Docetaxel rechallenge in metastatic castration-resistant prostate cancer

Seonggyu Byeon et al

- Out of 227 patients who received Docetaxel in first line, 22 were rechallenged with Docetaxel
- With docetaxel rechallenge, PSA response was 35%

- Median PFS was 4.5 months
- Median OS was 24.3 months
- Grade 3 or more adverse events were manageable- anemia (8.7%), neutropenia, thrombocytopenia, leukopenia, diarrhea, and nausea (4.3% each)

Conclusion

- Docetaxel rechallenge appears to offer better outcomes compared to Cabazitaxel in mCRPC patients who have previously received Docetaxel

- Given the chronic nature of the disease, both drugs have their place in the treatment armametrium

- Given modest responses with both Docetaxel rechallenge and Cabazitaxel, better, more durable and less toxic therapies are the need of the hour in later lines of prostate cancer