NOVEL MECHANISMS OF TAXANES IN PROSTATE CANCER

"From bench to bedside"

SPYRIDON KARAMPITIANIS, MS6 UNIVERSITY OF ATHENS
IOANNIS ZIOGAS, MS6 UNIVERSITY OF THESSALONIKI
PANAGIOTIS ZOUMPOURLIS, MS5 UNIVERSITY OF ATHENS

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ORIGINAL REPORT

Randomized, Noncomparative, Phase II Trial of Early Switch From Docetaxel to Cabazitaxel or Vice Versa, With Integrated Biomarker Analysis, in Men With Chemotherapy-Naïve, Metastatic, Castration-Resistant Prostate Cancer

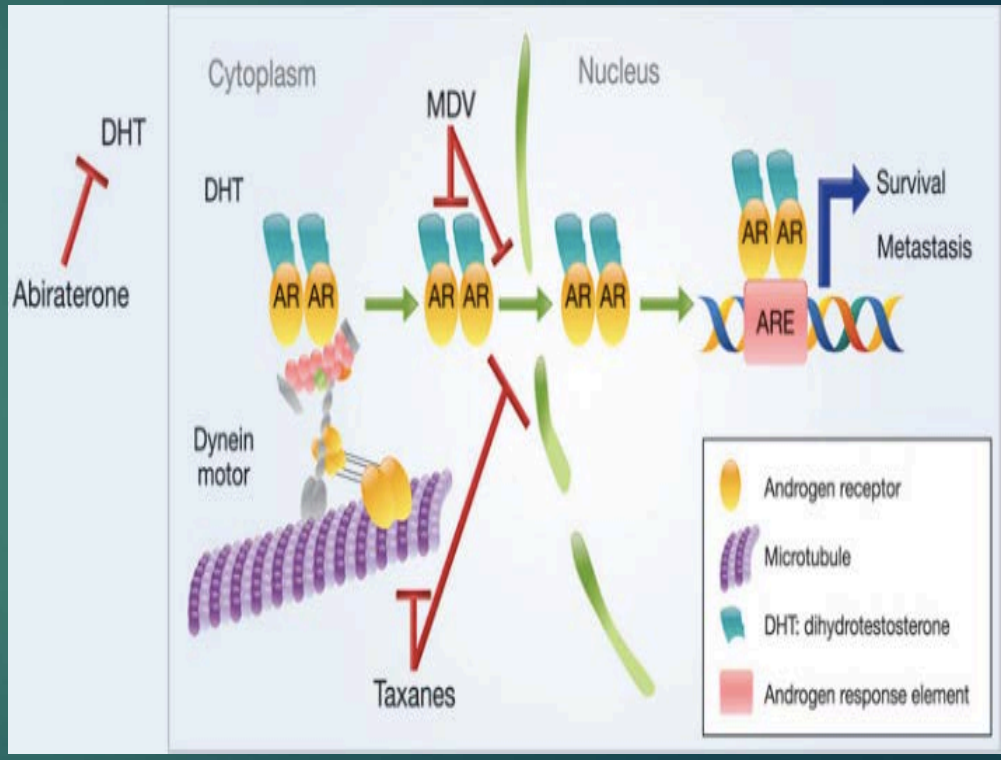
Emmanuel S. Antonarakis, Scott T. Tagawa, Giuseppe Galletti, Daniel Worroll, Karla Ballman, Marie Vanhuyse, Guru Sonpavde, Scott North, Costantine Albany, Che-Kai Tsao, John Stewart, Atef Zaher, Ted Szatrowski, Wei Zhou, Ada Gjyrezi, Shinsuke Tasaki, Luigi Portella, Yang Bai, Timothy B. Lannin, Shalu Suri, Conor N. Gruber, Erica D. Pratt, Brian J. Kirby, Mario A. Eisenberger, David M. Nanus, Fred Saad, and Paraskevi Giannakakou on behalf of the TAXYNERGY Investigators

INTRODUCTION (I)

- Prostate cancer (PC)
  - 1st in incidence (♂)
  - 2nd in mortality (♂)
  - Some patients present with metastatic disease
  - Progression relies on **androgen receptor (AR)** nuclear signaling
  - **Androgen deprivation therapy (ADT)** = backbone of initial therapy (alone or in combination) → chemical castration
  - Disease progression while on ADT → **castration-resistant PC (CRPC)**
  - CRPC continues to be driven by AR signaling due to **AR splice variants (AR-Vs)** lacking the ligand binding domain

INTRODUCTION (II)

- **Taxanes (paclitaxel, DOCETAXEL, cabazitaxel)** extend survival advanced-stage PC
- Taxane-induced microtubule stabilization (termed **drug-target engagement [DTE]**)
  - microtubule bundling (MTB)
  - cytoplasmic sequestration of AR
  - inhibition of AR transcriptional activity
  - inhibition of PC cell growth



INTRODUCTION (III)

- Resistance to taxane therapy is a significant challenge
  - Multiple mechanisms simultaneously – not all of them apply to all taxanes
  - None of them proven until now
- **Cabazitaxel** (recently approved by US FDA – 2nd line) retains activity in many docetaxel-refractory patients with metastatic castration resistant prostate cancer (mCRPC)

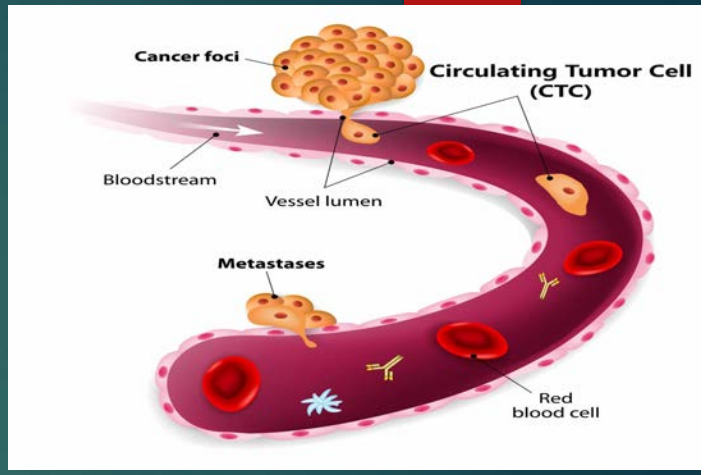
Central clinical hypothesis

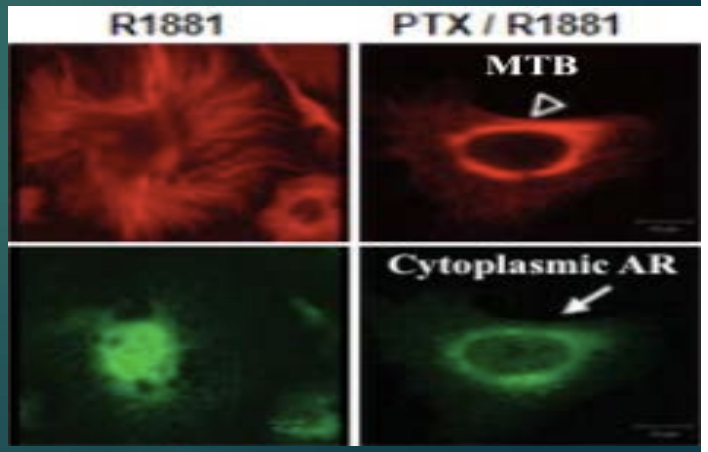
- Some patients with mCRPC with a suboptimal initial prostate-specific antigen (PSA) decline with their first taxane can subsequently achieve a PSA response by an **early switch** to a second taxane before clinical progression

INTRODUCTION (IV)

Central biomarker hypothesis

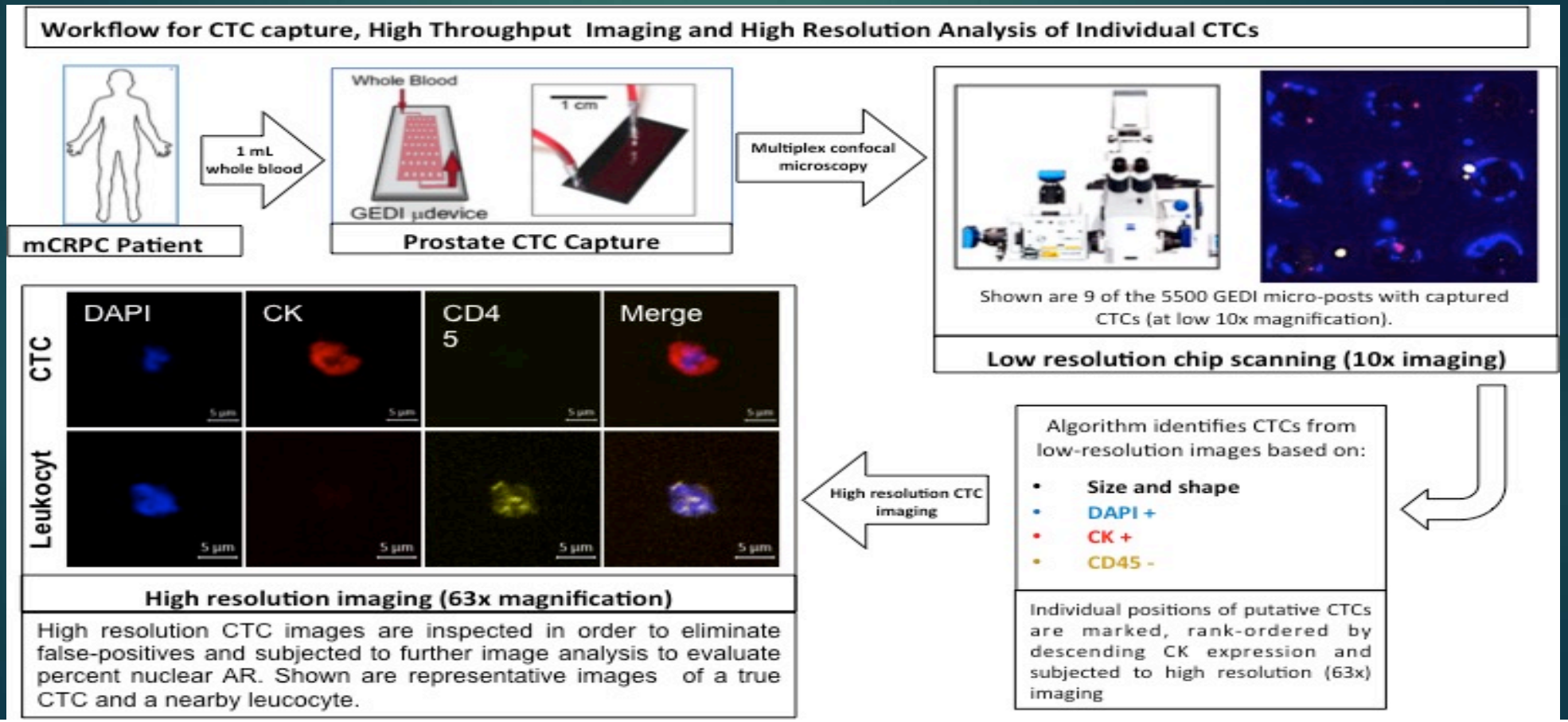
- Liquid biopsy: blood-derived circulating tumor cells (CTCs) from mCRPC patients = biomarkers for taxane sensitivity/resistance
- Evidence of association between CTC-specific DTE and clinical response
  - Microtubule bundling
  - Decrease in AR nuclear localization (ARNL)
- **Absence of evidence of DTE is associated with taxane resistance**





INTRODUCTION (V)

Workflow of CTC isolation and molecular characterization from PC patients



INTRODUCTION (VI)

Objective of TAXYNERGY Trial

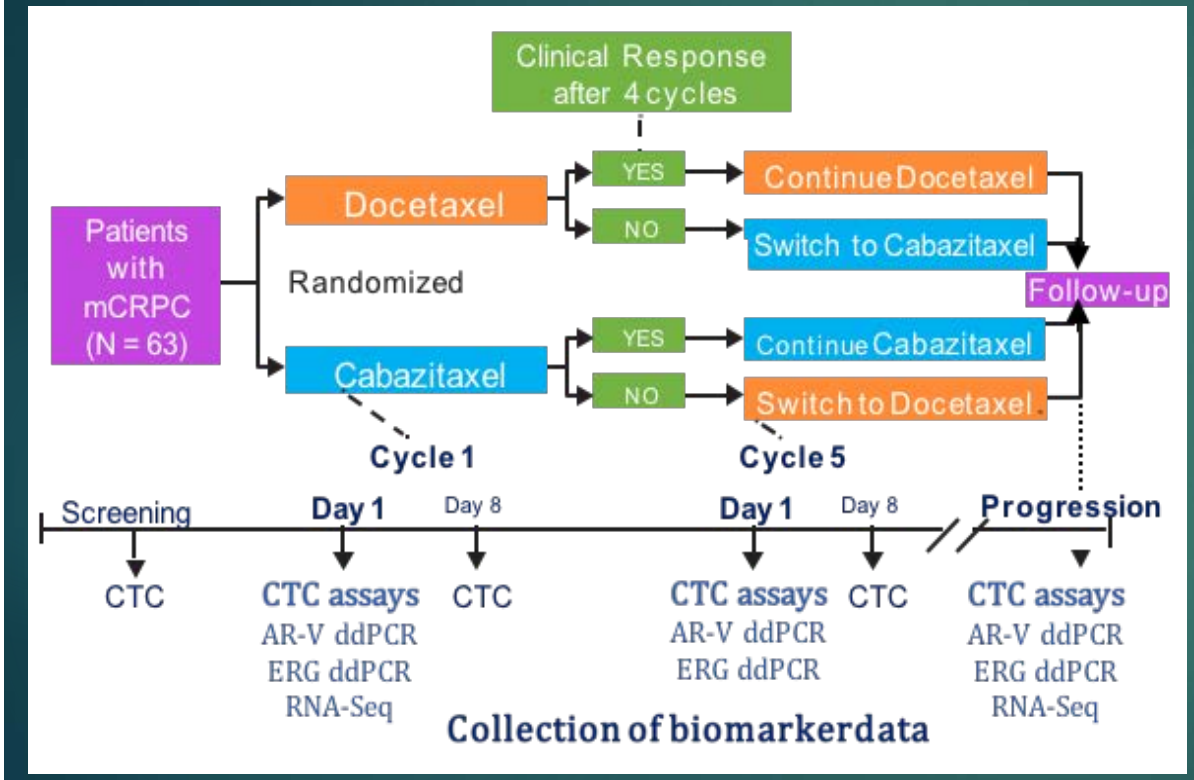
- Prospectively evaluate the benefit of early switch from docetaxel to cabazitaxel or vice versa using early PSA changes (first 12 weeks of therapy)
- Single-cell analysis: CTC-specific DTE → sensitivity to taxane treatment

METHODS (I)

- Population: chemotherapy-naïve patients with progressive mCRPC
  - Eastern Cooperative Oncology Group performance score (ECOG PS) of 0 to 2
  - No prior β isotope therapy, whole pelvic radiotherapy, or radiotherapy to >30% of bone marrow was allowed
  - Patients with neuropathy grade >2 were excluded
  - Prior hormonal therapy and immunotherapy were allowed

- Noncomparative randomized blinded study, 2:1 to docetaxel 75 mg/m^2 or cabazitaxel 25 mg/m^2 every 3 weeks plus daily prednisone 10 mg

METHODS (II)



Primary clinical endpoint:

- **PSA response rate** (≥ 50% decrease from baseline confirmed 3 weeks later, whether a treatment switch occurred)

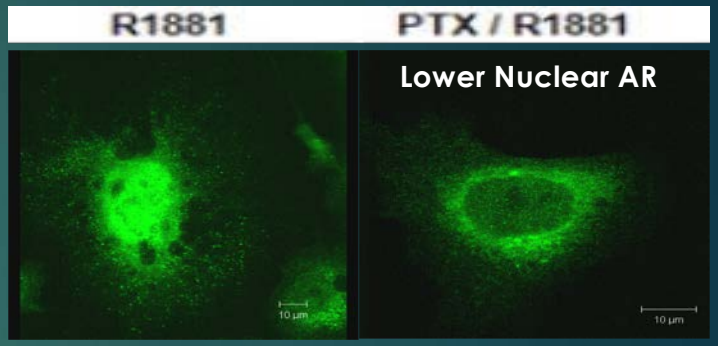
Secondary clinical endpoints:

- Progression-free survival (**PFS**)
- Overall survival (**OS**)

METHODS (III)

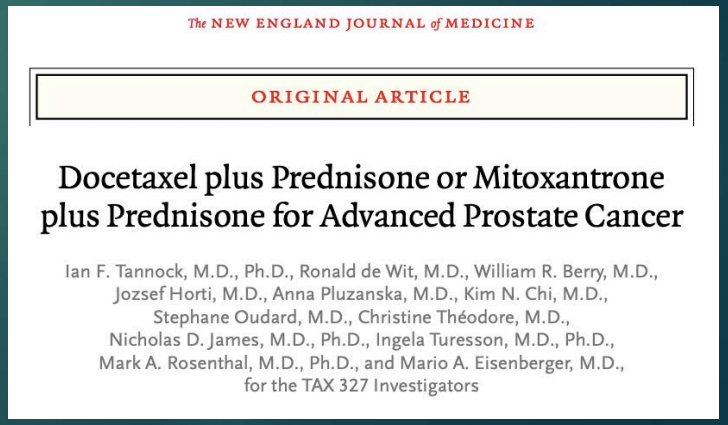
Coprimary (biomarker) endpoint:

- CTCs at baseline (cycle 1 day 1 [**C1D1**]) were compared with CTCs isolated after 1 week of treatment (cycle 1 day 8 [**C1D8**]) for percent ARNL **(%ARNL)**



Statistical considerations

- Sample size determination based on historical PSA response rate 45.4% (intent-to-treat population in TAX327 study)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer

Ian F. Tannock, M.D., Ph.D., Ronald de Wit, M.D., William R. Berry, M.D., Jozsef Horti, M.D., Anna Pluzanska, M.D., Kim N. Chi, M.D., Stephane Oudard, M.D., Christine Théodore, M.D., Nicholas D. James, M.D., Ph.D., Ingela Turesson, M.D., Ph.D., Mark A. Rosenthal, M.D., Ph.D., and Mario A. Eisenberger, M.D., for the TAX 327 Investigators

RESULTS (I)

REMEMBER!!

- Primary endpoint of study = PSA response > 50%

Table 1. Summary of Patients by Treatment and Taxane Switch (treated population)

Switch Status	No. of Patients (%)		
	All Patients (N = 61)	Cabazitaxel (n = 22)	Docetaxel (n = 39)
No taxane switch	46 (75.4)	19 (86.4)	27 (69.2)
No switch after cycle 4	33 (54.1)	13 (59.1)	20 (51.3)
Switch not applicable*	13 (21.3)	6 (27.3)	7 (17.9)
Taxane switch	15 (24.6)	3 (13.6)	12 (30.8)

*Patients who discontinued treatment before cycle 5.

RESULTS (II)

33 (54.1%)
>30% reduction of PSA by C4 → no switch

15 (24.6%)
<30% reduction of PSA by C4 → **switched**

13 (21.3%)
Discontinued therapy before or at C4

7 (46.7%)
Achieved PSA response

RESULTS (III)

Biomarker analysis: nuclear ar localization and tubulin bundling in ctcs

Mechanistic studies: taxanes impair ARNL downstream of microtubule stabilization

Calculation of %ARNL at C1D1 and C1D8.
Is a decrease in %ARNL at C1D8 associated with PSA response?

Captured by geometrically enhanced differential immunocapture

High(76) and low(32) % ARNL (44.0% v 64.1%, respectively; P = .004)

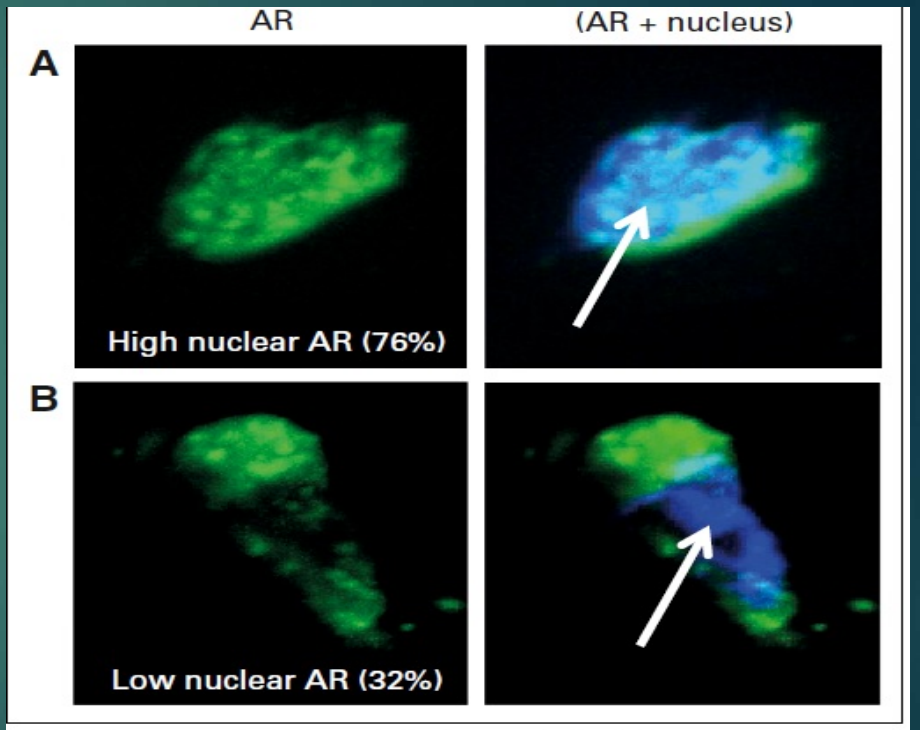


Fig 3. Representative high-resolution images of circulating tumor cells captured by geometrically enhanced differential immunocapture with (A) high and (B) low percent androgen receptor (AR) nuclear localization as assessed by quantitative image analysis. Immunofluorescence staining for AR is indicated in green. 4′,6-Diamidino-2-phenylindole staining for DNA (nucleus) is indicated in blue (arrow).

RESULTS (IV)

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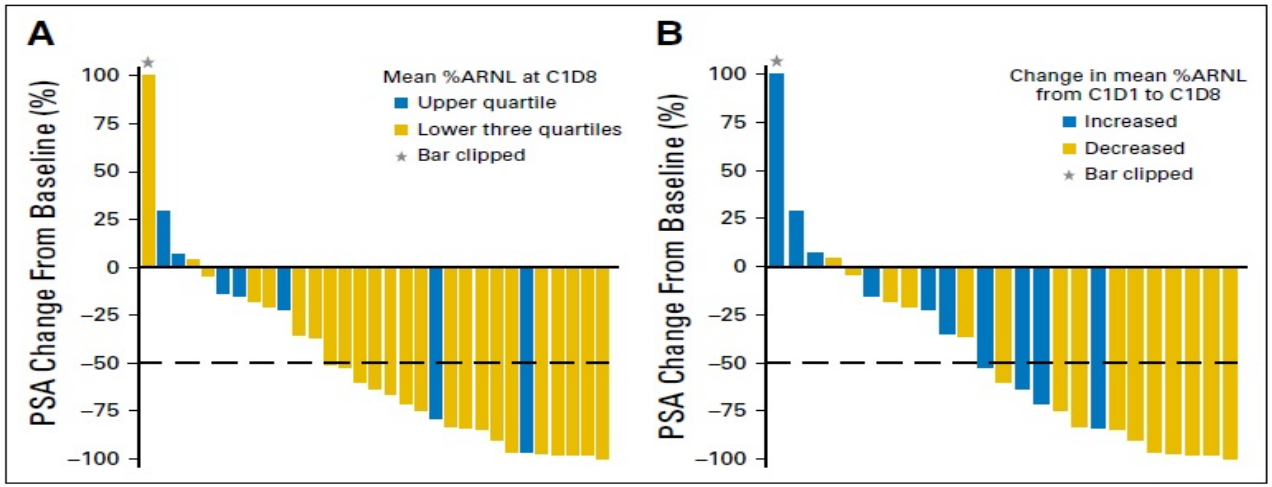


Fig 4. Greatest prostate-specific antigen (PSA) change from baseline at any time on study according to mean percent androgen receptor nuclear localization (%ARNL) at cycle 1 day 8 (C1D8; after 1 week of therapy). (A) Comparison of the lower three quartiles versus the upper quartile of mean %ARNL at C1D8 (n = 31); PSA ≥ 50% decrease from baseline was more common in patients with %ARNL in the lower three quartiles (71%) than in patients with %ARNL in the upper quartile (29%). (B) Comparison of increase versus decrease in %ARNL from cycle 1 day 1 (C1D1) to C1D8 (n = 25); PSA change from baseline was 40% in patients with increased mean %ARNL compared with 67% in patients with decreased mean %ARNL. Thirty-one patients had PSA change and evaluable circulating tumor cells (CTCs) at C1D8; 25 patients had PSA change and evaluable CTCs at both C1D1 and C1D8.

PSA response >50%:
more common in patients with %ARNL at C1D8 that was in the **lower three quartiles** than in patients with %ARNL in the upper quartile

PSA response >50%:
more common in patient with decreased mean %ARNL at C1D8 compared with C1D1
(than in men with increasing mean %ARNL)

RESULTS (V)

35 patients (55.6%) → >50% PSA response.
The lower limit of the 90% one sided CI was 47.5 % which did not overlap the rate of 45.4% in TAX 327

BOTTOM-LINE:
1) There is statistically significant **correlation** between ARNL and PSA
2)There is the possibility to **predict the outcome** of the treatment early on, that is, in the 1st week after treatment

DISCUSSION (I)

Biomarker Hypothesis

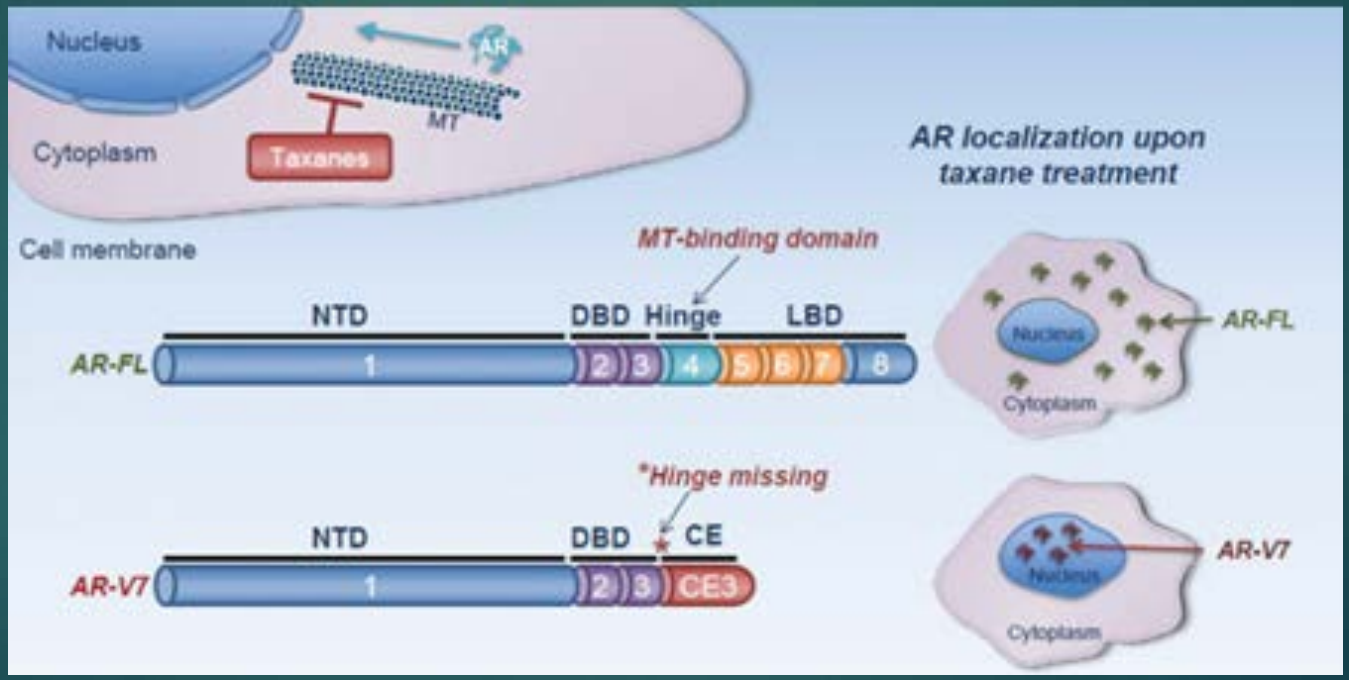
- Based on preclinical data: AR trafficking along the microtubules (dynein)
- First study to report changes in ARNL in CTCs in patients with mCRPC
- The results showed a significant association of %ARNL with sensitivity to taxane therapy.
- Different resistance mechanisms among taxanes remain unclear

DISCUSSION (II)
Taxane resistance

Sensitivity	Resistance	Resistance
MTB (+) and ⬇ ARNL	MTB (-) • P-gp •Tubulin mutation ⬆ ARNL	MTB (+) and ⬆ ARNL •Presence of AR variants

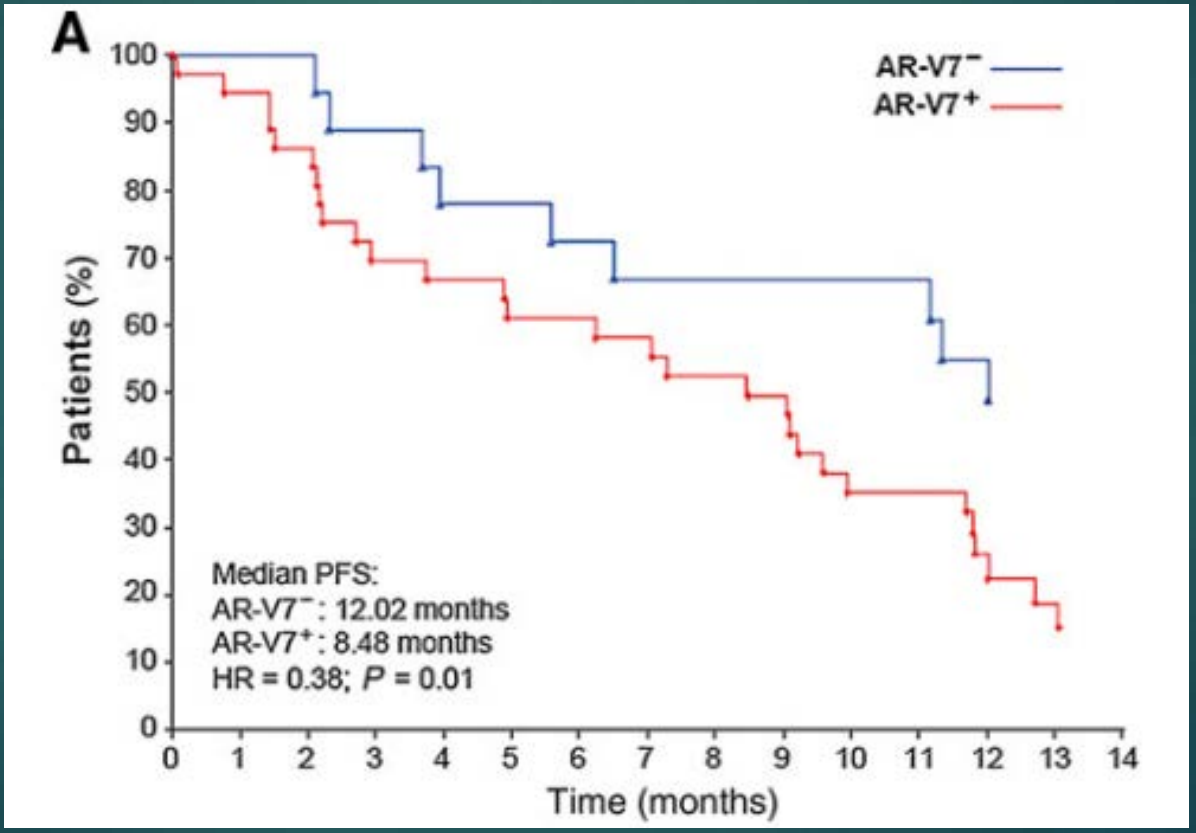
DISCUSSION (III)
Taxane resistance

ARV7



DISCUSSION (IV)

ARV7+ / ARV7- PFS



DISCUSSION (V)

- CTC-specific ARNL observed as early as 1 week after therapy initiation could be a potentially more sensitive and specific biomarker of subsequent clinical response compared to the 12-week PSA changes

DISCUSSION (VI)

Is it enough to change clinical practice?

- TAXYNERGY PSA response rate (55.6%)
- Of all the patients who switched therapy 46.7% subsequently achieved a PSA response >50%
- Worth of investigating this approach in certain patients
- Further studies to determine differences in OS between the standard of car and the early switch strategy proposed in the paper.

DISCUSSION (VII)

Limitations

- Limited sample size (only 15 patients switched)
- Unable to quantify MTB
- Short follow-up did not allow for OS to be reliably calculated or determine whether any biomarker signature was associated with improved survival

THANK YOU!!!