Discussion on Sonpavde et al:

Association of PCWG2 defined progression and OS in mCRPC

Gerhardt Attard MD MRCP PhD
Cancer Research UK Clinician Scientist
The Institute of Cancer Research and
the Royal Marsden NHS Foundation Trust

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ICR The Institute of Cancer Research 1909 2009

Financial disclosure

- The inhibitor of androgen synthesis, abiraterone acetate, was developed at The Institute of Cancer Research and is licensed to Cougar Biotechnology/J&J.
- I am included in The ICR co-inventors' reward scheme of abiraterone acetate.
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Better end-points for better clinical studies

- For Phase II trials, we need to discard drugs that are inactive but not miss potentially active agents

- For Phase III trials we need robust, regulatory agency approved surrogates of OS

The challenges

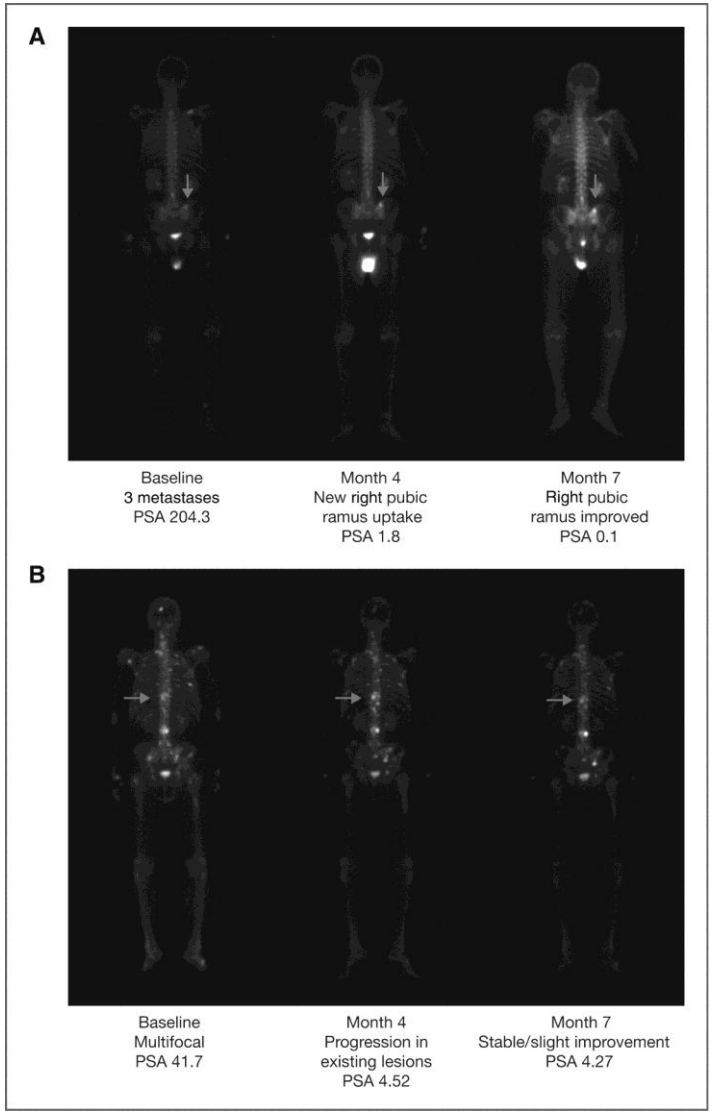
- Most CRPC patients do not have soft tissue disease that is evaluable on CT scan
- Bone scan changes are challenging to interpret
- PSA is not a surrogate of OS
- New drugs with different mechanisms of action can have confounding effects on end-points
- New effective drugs and an increasingly crowded drug development space are making it increasingly difficult to show improvements in OS

Challenges with PSA as a measure of defining activity

- Widely used in clinical practice for treatment decisions

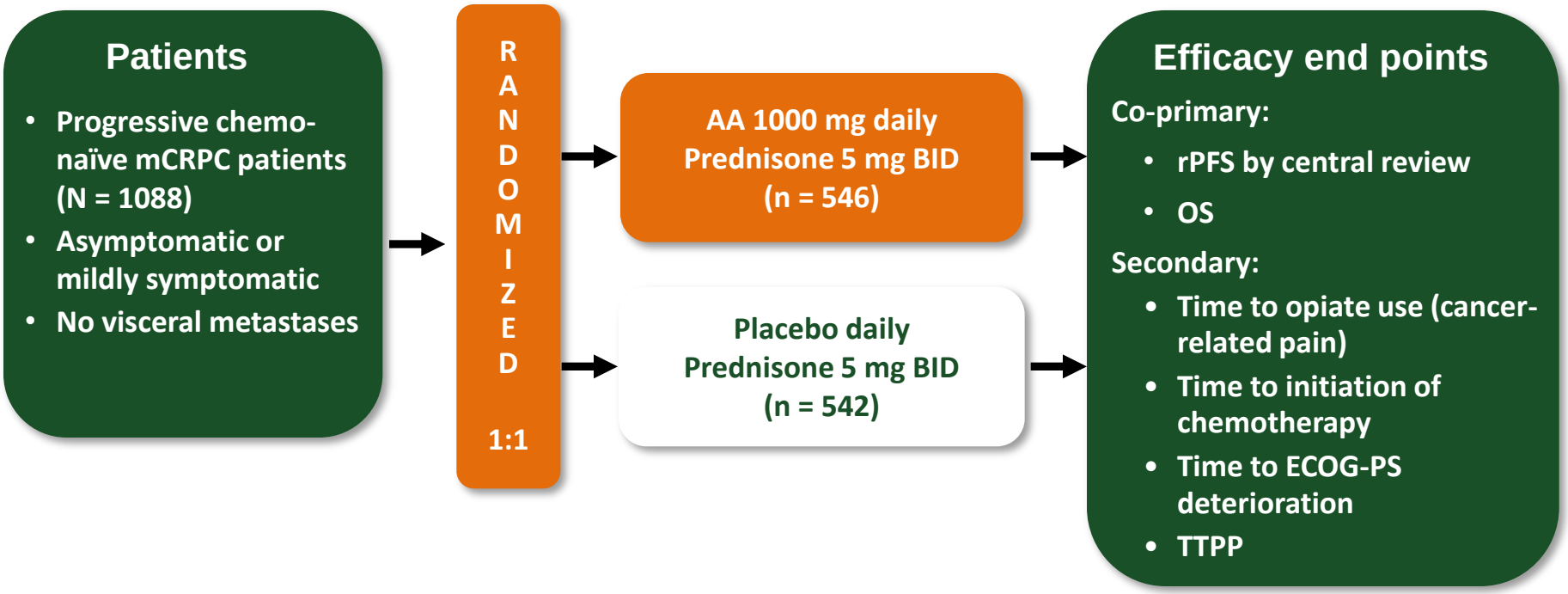
- But
- May represent solely a specific biological effect (activation of AR signalling)
- Changes in the AR signalling axis could result in dissociations between PSA and tumor activity (AR splice variants???)

Bone flare within 3 months of starting abiraterone



Ryan et al, Clin Cancer Res 2011 17(14) 4854-61

Phase 3, Multinational, Randomized, Double-Blind, Placebo-Controlled Study

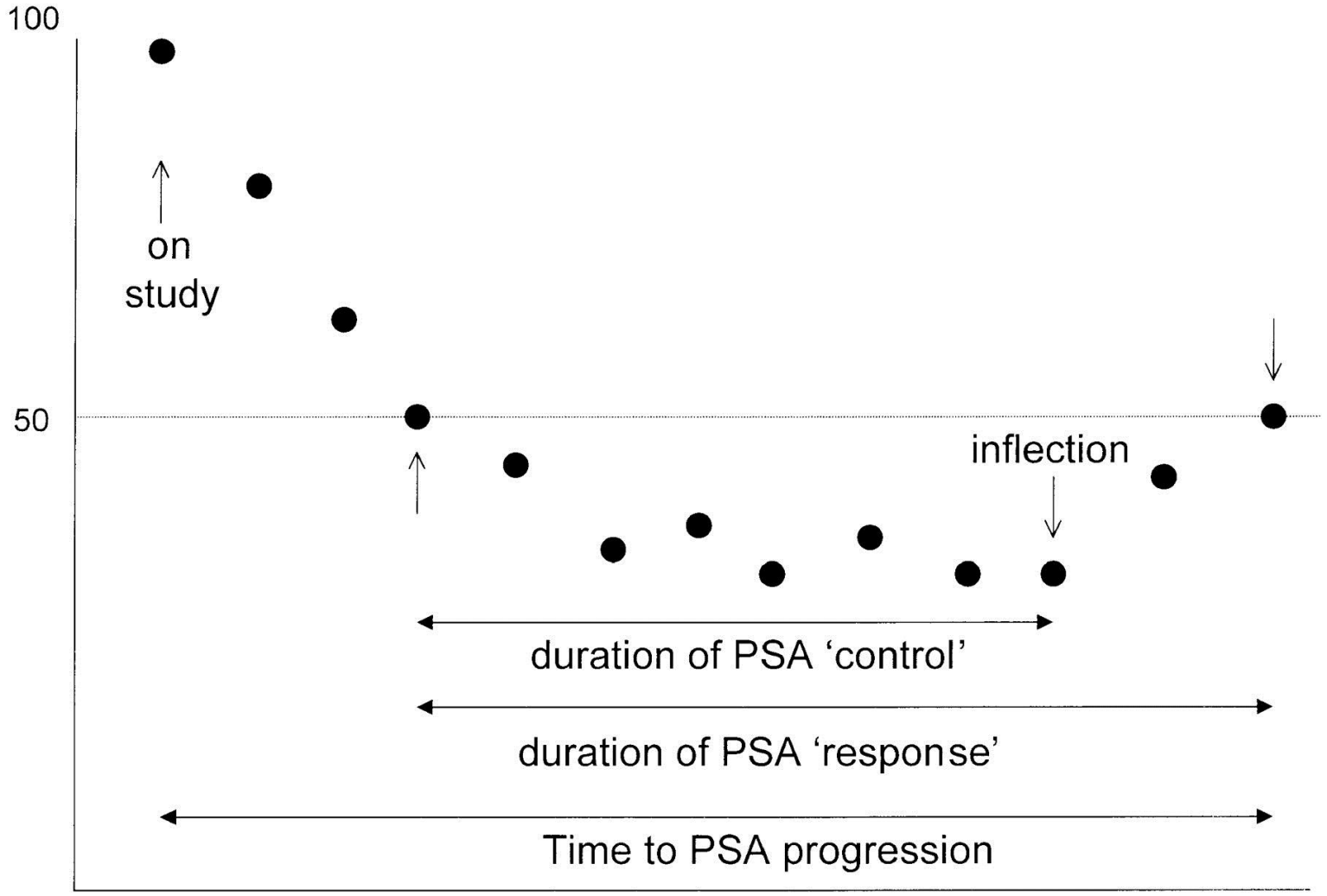


- **Conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada**
- **Stratification by ECOG performance status 0 vs 1**
- **Patients treated until radiographic progression or unequivocal clinical progression**
- ***First use of rPFS adapted from PCWG2 criteria[1] using independent review***

AA, abiraterone acetate; BID, twice daily; ECOG, Eastern Cooperative Oncology Group; TTPP, time to PSA progression.

Ryan et al, Oral session “Genitourinary tumors, prostate II”

PSAWG I recommendations for reporting trial outcomes



Bubley G J et al. JCO 1999;17:3461-3467

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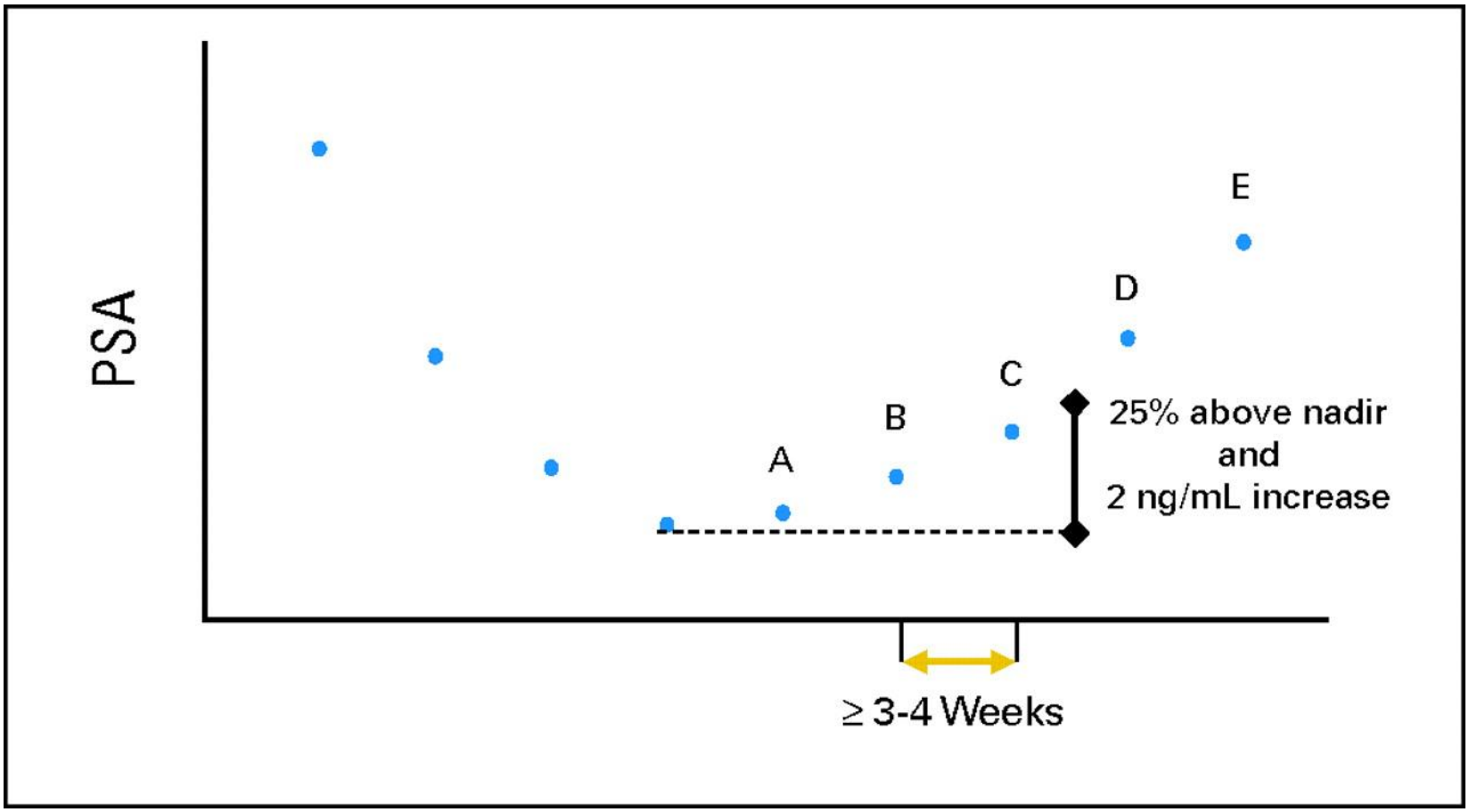
- PCWG2 emphasizes that specific outcomes on which to base the decision to proceed to phase III will depend on the therapeutic objectives and should increasingly be based on time-to-event outcomes.

Scher H I et al. JCO 2008;26:1148-1159

PSA progression as defined by PCWG2



Scher H I et al. JCO 2008;26:1148-1159

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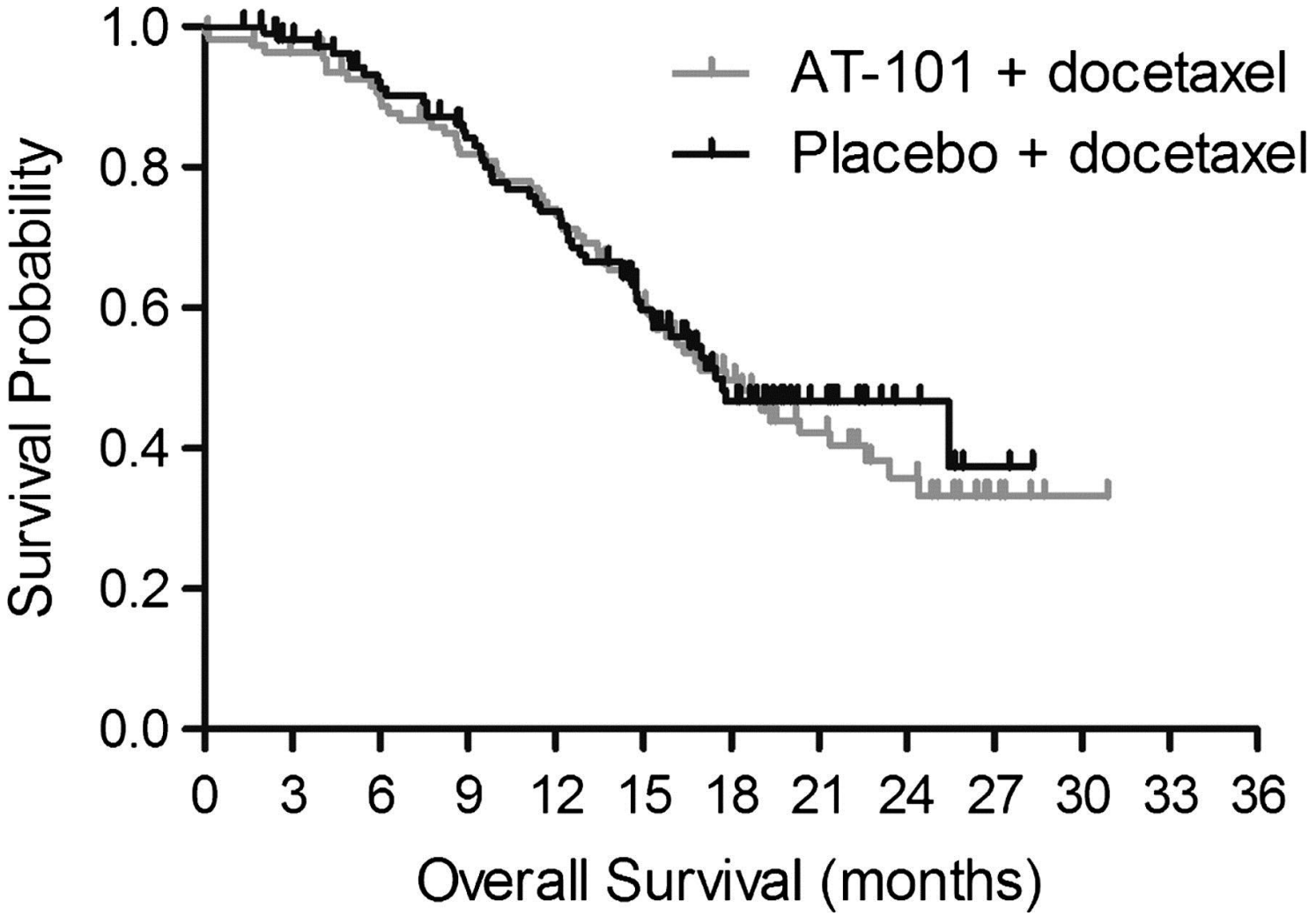
Methods

- Retrospective analysis of 2 randomized trials that used PCWG2 guidelines to define progression and make clinical decisions:

1. The CS-205 trial
   - 220 evaluable patients with chemonaive mCRPC: 110 in each arm (DP + placebo/AT101).

2. The SUN-1120 trial
   - (N=873) compared the combination of prednisone with sunitinib 37.5 mg daily (N=584) or placebo (N=289) for progressive mCRPC following docetaxel-based chemotherapy.

CS-205 trial

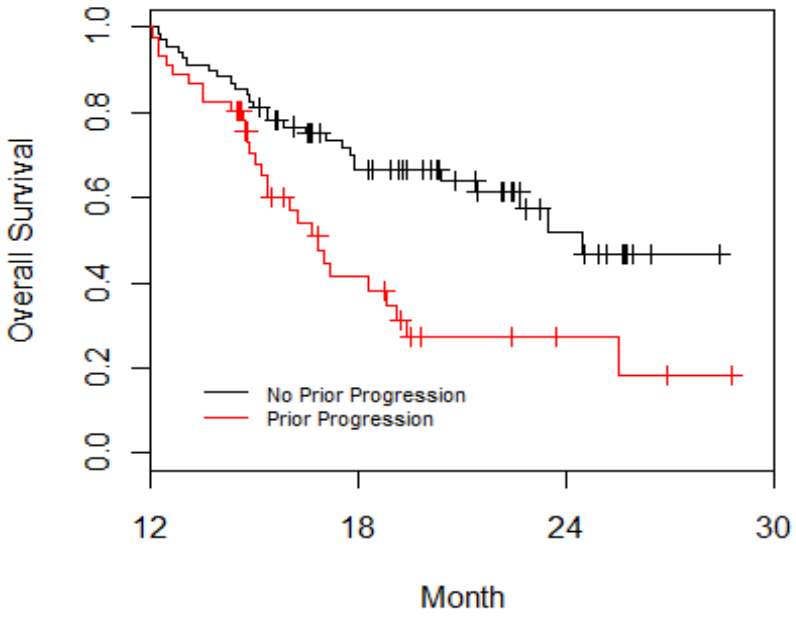


Sonpavde G et al. Ann Oncol 2012;23:1803-1808

Annals of Oncology

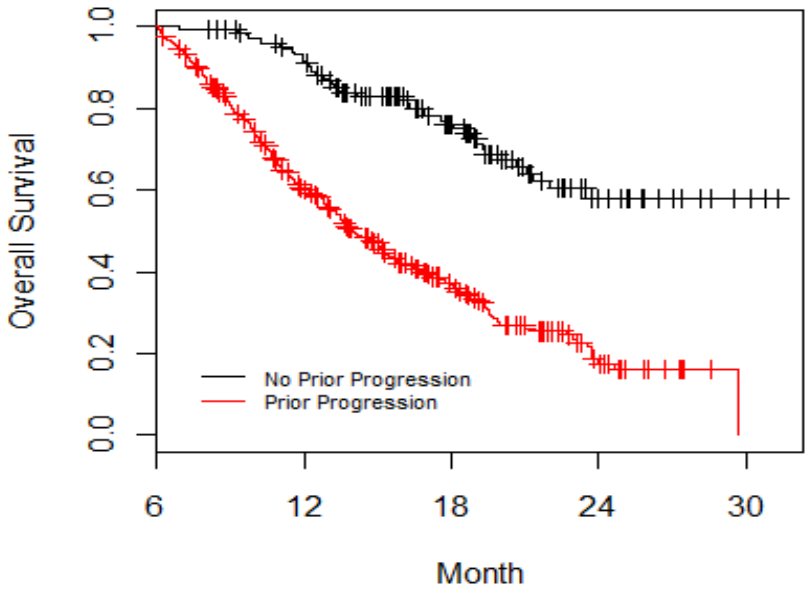
OS based on progression

CS205: Docetaxel-Prednisone + Placebo/AT101



OS based on progression status by 12 months in CS-205 trial (c-statistic=0.596)

SUN1120: Prednisone + Placebo/Sunitinib



OS based on progression status by 6 months in SUN-1120 trial (c-statistic=0.601)

Conclusion

- Progression by PCWG-2 criteria was significantly associated with OS in patients with mCRPC receiving first-line docetaxel-based chemotherapy or post-docetaxel therapy.

How will these data change our current Phase II trial design?

- Composite end-points for assessing activity could be required
  - To evaluate therapeutics with wide range of different actions
  - To assess activity in heterogeneous populations

- Possible candidates in addition to time-to-event:
  - Circulating tumor cell enumeration
  - Multiple modality imaging
  - Circulating tumor nucleic acids

How will these data change our current Phase III trial design?

- a correlate is not necessarily a surrogate
- a surrogate endpoint cannot solely be correlated with clinical outcome (OS), but *must also fully capture the net effect of treatment on the clinical outcome*
- Progression by PCWG-2 criteria cannot replace OS in Phase III trials