Chemotherapy in Castrate Resistant Prostate Cancer: The Game is Changing….FAST

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Disclosures

- Consultant to Algeta, Bavarian-Nordic, Bayer, Sanofi, JNJ, Bellicum, BMS, Dendreon, Algeta, Pfizer, Oncogenex, Medivation, Takeda, TEVA, and Exelixis
- Investigator for Algeta, Bayer, Sanofi, Takeda, Algeta, Exelixis, Cougar, JNJ

Cancer cells, like plants, adapt to harsh environments by clever adaptations

Where we have been…..FDA Regulatory Approvals in Metastatic CRPC

- Estramustine-1981 Ancient History
- Strontium^{89}-1993 Reduction in new onset of painful bone lesions after XRT + isotope
- Mitoxantrone + prednisone-1996 Reduction in pain
- Samarium^{153}-1997 Reduction in bone pain
- Zoledronic acid-2002 Skeletal related event reduction
- Docetaxel + prednisone-2004 Prolonged survival
- Sipuleucel-T-2010 Prolonged Survival
- Cabazitaxel + prednisone-2010 Prolonged Survival
- Denosumab-2010 Skeletal related event reduction
- Abiraterone + prednisone-2011 Prolonged Survival
- Enzalutamide-2012 Prolonged Survival

Categorization of mCRPC Options Today

- **Androgen axis manipulations**
  - **Antiandrogens (nilutamide/enzalutamide, etc.)**
  - **Androgen synthesis inhibitors (ketoconazole/abiraterone)**
  - **Corticosteroids (dexamethasone, etc,)**
  - **Estrogens (Estradiol patches, DES, etc.)**
- **Radiation**
  - **External beam, alpha emitters (radium-223) and beta-emitters (samarium-153 EDTMP, strontium-89, etc.)**
- **Immune Therapies**
  - **Sipuleucel T**
- **Chemotherapies**
  - **Taxanes (docetaxel, cabazitaxel), mitoxantrone, etc.**
- **Osteoclast targeted**
  - **Zoledronic acid, denosumab**

TRIAL	FRONT LINE	HR	Survival (months)
TAX 327	Docetaxel/prednisone vs mitoxantrone/prednisone	0.76	18.9 vs 16.5
IMPACT	Sipuleucel-T vs Control	0.78	25.8 vs 21.7
COU-AA-302	Abiraterone/prednisone vs Placebo/prednisone	0.75	NR vs. 27.2
	POST-DOCETAXEL		
TROPIC	Cabazitaxel/prednisone vs mitoxantrone/prednisone	0.70	15.1 vs 12.7
COU-AA- 301	Abiraterone/prednisone vs Placebo/prednisone	0.65	14.8 vs 10.9
AFFIRM	Enzalutamide vs Placebo	0.63	18.4 vs 13.6
	POST-DOCETAXEL or UNFIT or REFUSE		
ALSYMPCA	Radium-223/supportive care vs placebo/BSC	0.70	14.0 vs 11.2

"Post-Docetaxel" Space: Some Comments

- How many men actually receive docetaxel?
- The "post-docetaxel" setting is a regulatory distinction…..is it also a biologic distinction?
- How much cross-resistance between taxanes and the AR axis targeted drugs?
- It is obvious that none of the new agents have been compared to one another
- The "post-abiraterone" and "post-enzalutamide" setting is becoming more important every day
- Abiraterone is moving up quickly in the "pre-doctaxel" space….COU-302 data and pending action at the FDA

What is the optimal sequence in CRPC?

- Great question but nobody knows!
  - Reasonable to use less toxic therapies first
  - For today, stop debating the “best” choice. Treat your patients with a sense of urgency and try multiple therapies before the patient dies!
  - Which drug for which patient is a tremendously important research question…….
- Until we get smarter…..patients should have exposure to as many “active” drugs as possible
- Do not let the patient deteriorate too far, that limits future options….follow patients closely!

If abiraterone is moving up….We better start thinking about the post-abiraterone space

- Potential mechanisms of resistance
- Patterns and timing of progressive disease
- Activity of therapies post-abiraterone

Resistance to CYP17A1 Inhibition with Abiraterone in Castration-Resistant Prostate Cancer: Induction of Steroidogenesis and Androgen Receptor Splice Variants

Elahe A. Mostaghel[1,3], Brett T. Marck[4], Stephen R. Plymate[3,4], Robert L. Vessella[5], Stephen Balk[6], Alvin M. Matsumoto[3,4], Peter S. Nelson[1,2,3], and R. Bruce Montgomery[3,4]

Does progression occur post-abiraterone with new ligands or ligand independent AR activation?

Effects of Abiraterone Acetate on Androgen Signaling in Castrate-Resistant Prostate Cancer in Bone

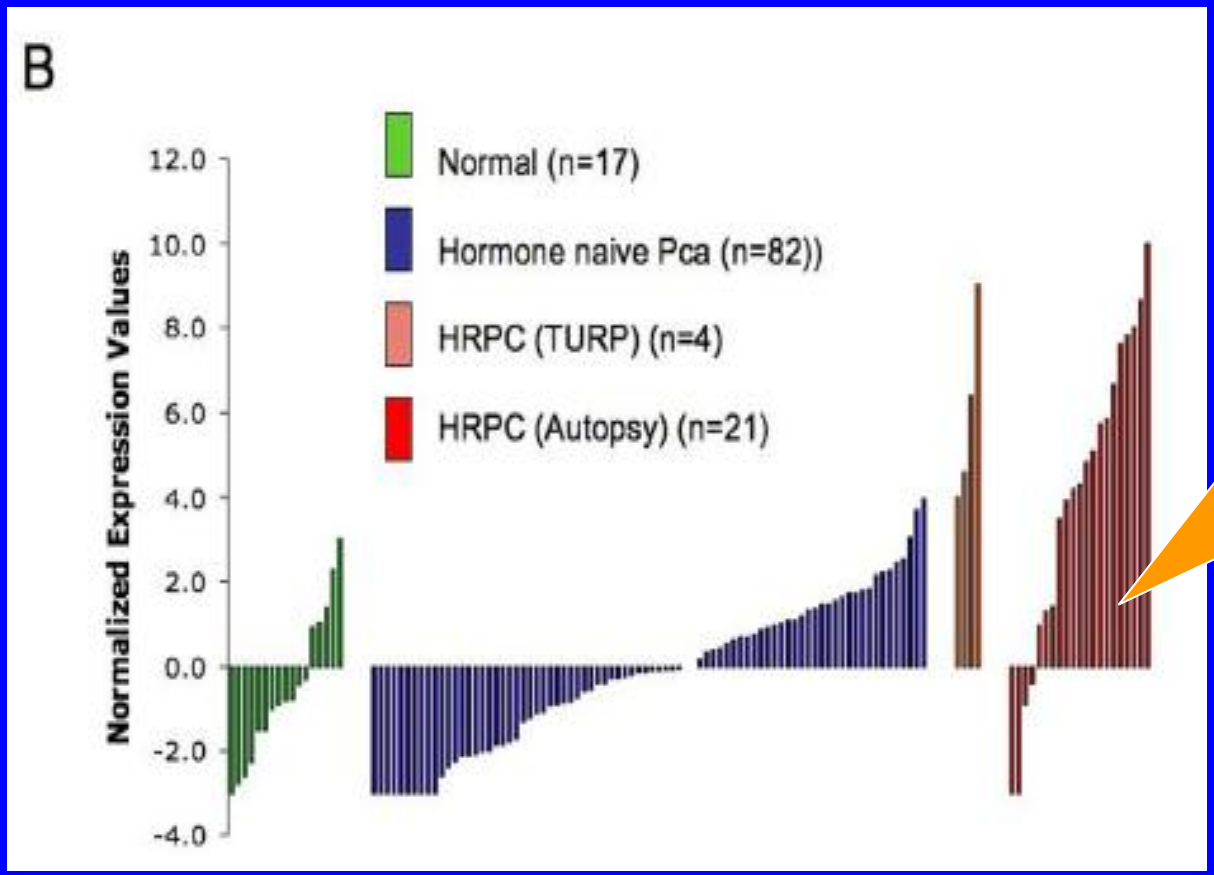
Eleni Efstathiou, Mark Titus, Dimitra Tsavachidou, Vassiliki Tzelepi, Sijin Wen, Anh Hoang, Arturo Molina, Nicole Chieffo, Lisa A. Smith, Maria Karlou, Patricia Troncoso, and Christopher J. Logothetis

"Blood and bone marrow aspirate testosterone concentrations declined to <pg/ml levels and remained suppressed at progression."

Are spice variants responsible for abiraterone resistance and ligand independent AR activation?

AR Splice Variants are Readily Detected in Human Tumors

Hu et al. Cancer Research 69:16-22, 2009



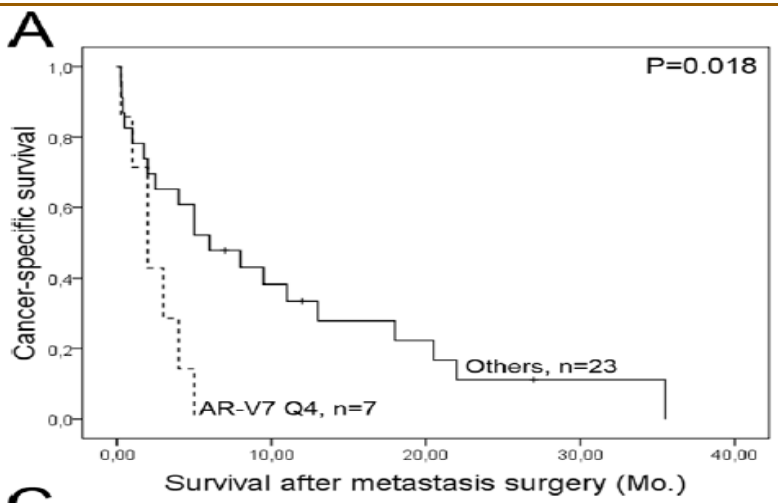
AR Splice variants readily detected in CRPC tissue

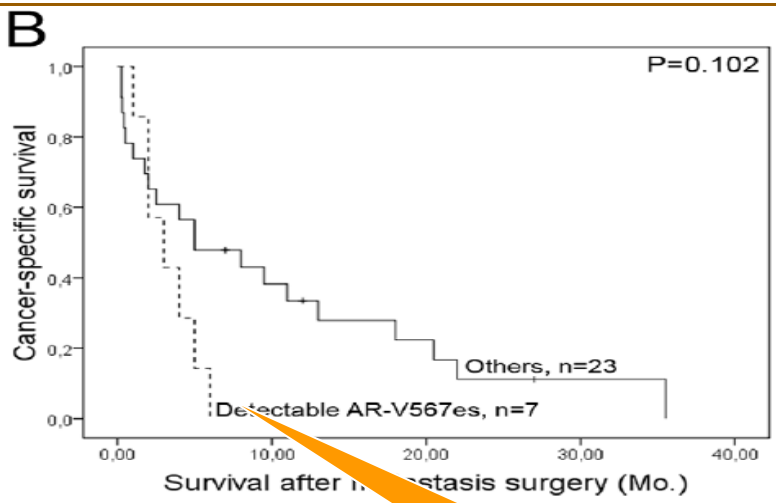
OPEN ACCESS Freely available online

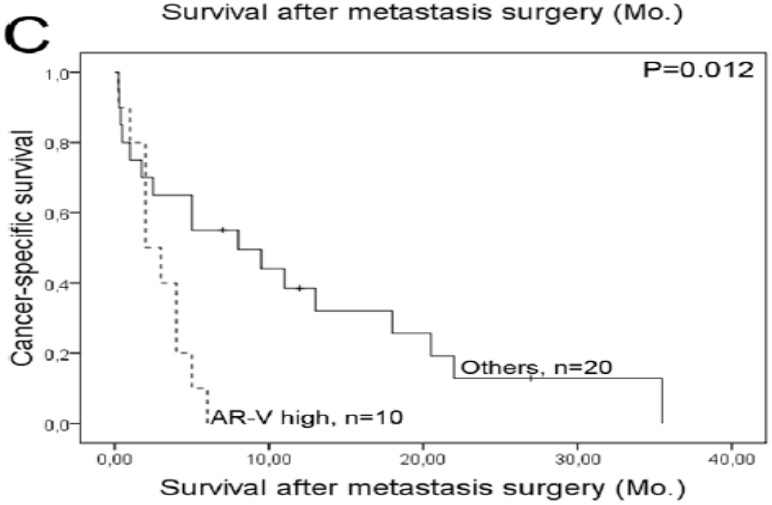
PLoS one

Expression of Androgen Receptor Splice Variants in Prostate Cancer Bone Metastases is Associated with Castration-Resistance and Short Survival

Emma Hörnberg[1], Erik Bovinder Ylitalo[1], Sead Crnalic[2], Henrik Antti[3], Pär Stattin[2], Anders Widmark[4], Anders Bergh[1], Pernilla Wikström[1]*







Survival dramatically compromised

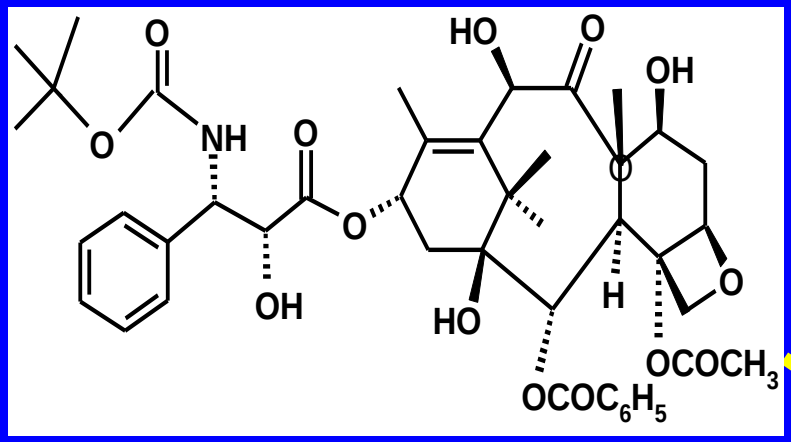
Implications of progression in a ligand independent AR world

- Sequential CURRENT hormonal agents will not add much…..
  - The early data seem to support that concept
  - High degree of cross-resistance to the current androgen-axis targeted therapies
- What about taxanes?

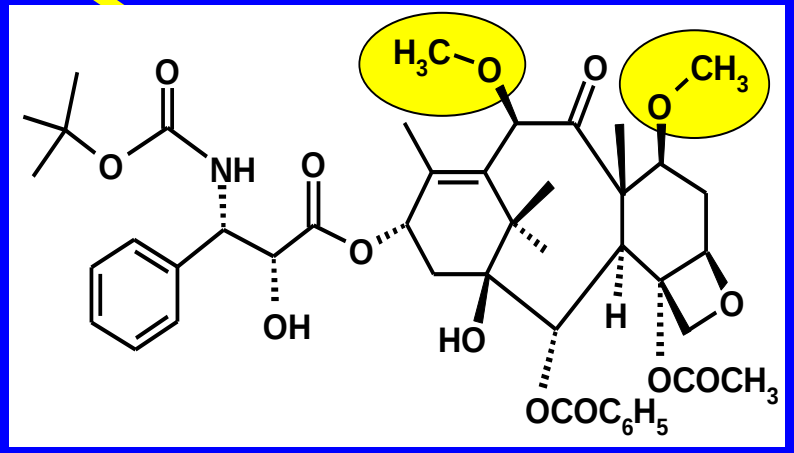
Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance?

J. Mezynski, C. Pezaro, D. Bianchini, A. Zivi, S. Sandhu, E. Thompson, J. Hunt, E. Sheridan, B. Baikady, A. Sarvadikar, G. Maier, A. H. M. Reid, A. Mulick Cassidy, D. Olmos, G. Attard*,‡ & J. deBono‡

- In 26% of patients, docetaxel resulted in PSA decline of at least 50%, with a median time to PSA progression of 4.6 months.
- Eight patients without a PSA decline on abiraterone were docetaxel-refractory.

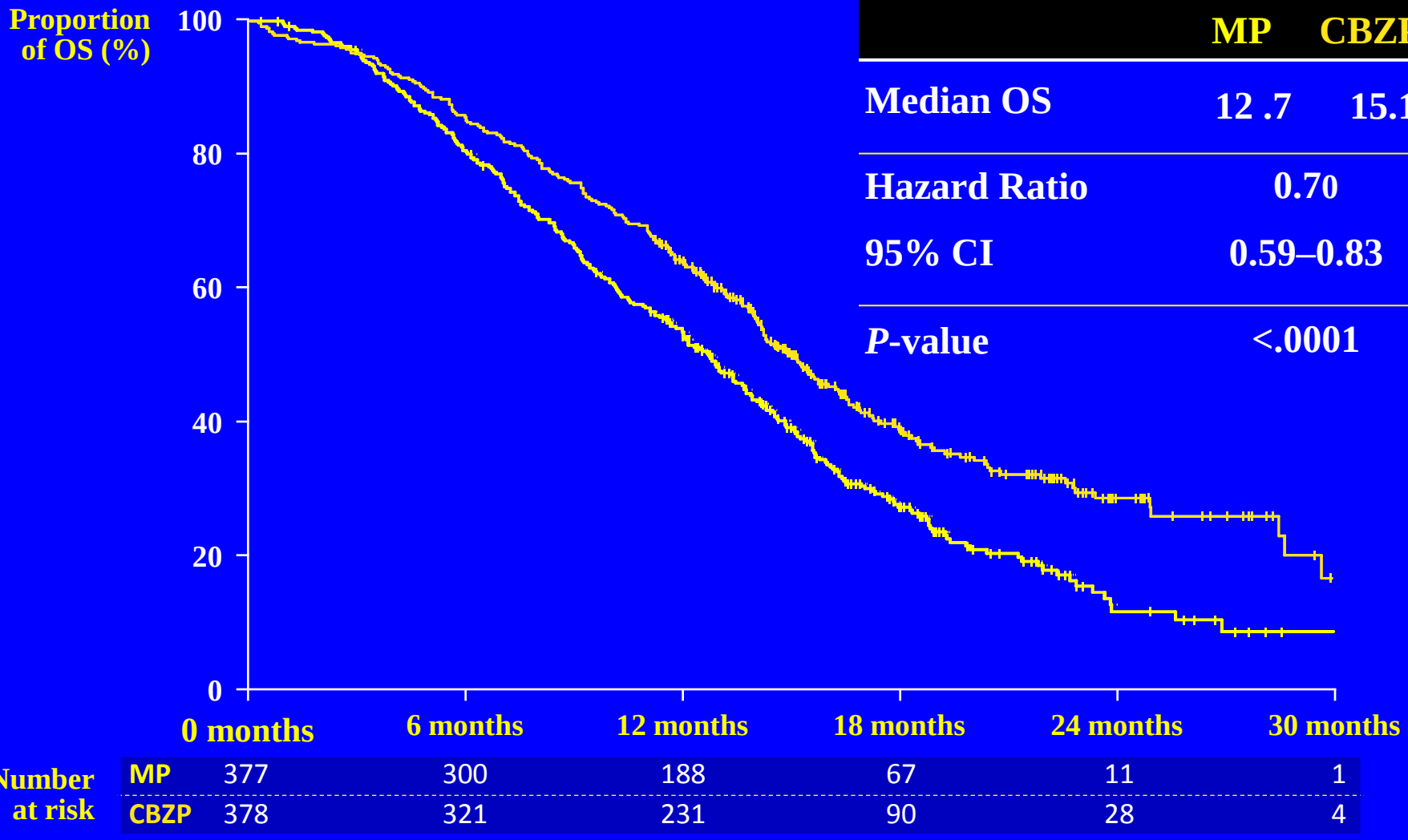


Docetaxel



Cabazitaxel

Cabazitaxel: Overall Survival Post-Docetaxel



	MP	CBZP
Median OS	12 .7	15.1
Hazard Ratio	0.70	
95% CI	0.59–0.83	
P-value	<.0001	

de Bono et al. Lancet, 376:1147-54, 2010

Does Cabazitaxel have Activity in the Post-Abiraterone Space?

Abstract: 951

REPONSE TO CABAZITAXEL IN THE POSTCHEMOTHERAPY SETTING IN CRPC PATIENTS PREVIOUSLY TREATED WITH DOCETAXEL AND ABIRATERONE ACETATE

L. Albiges[1], S. Le Moulec[2], Y. Loriot[1], M. Gross Goupil[3], T. De La Motte Rouge[4], A. Guillot[5], K. Fizazi[6], C. Massard[7]

"Of 32 patients with PSA data available, 18 (56%) have had a 50% or greater PSA decline."

Cabazitaxel: Is it better than docetaxel? Is the 25 mg/M2 dose optimal?

- FIRSTANA: Cabazitaxel/prednisone at doses of 20 and 25 mg/M2 compared to docetaxel/prednisone for first line mCRPC

- PROSELICA: Cabazitaxel/prednisone at doses of 20 and 25 mg/M2 compared in post-docetaxelmCRPC

What about combining taxanes with other novel agents?

- The docetaxel-combination graveyard is big!
  - DN-101, GVAX, bevacizumab, atrasentan, zibotentan, lenalidomide, aflibercept
  - So far, we have done a poor job of selecting agents to go forward in clinical trials

- The “hopefuls” in phase III
  - Dasatinib
  - Custirsen
  - Strontium-89

What taxane combinations are novel and being explored?

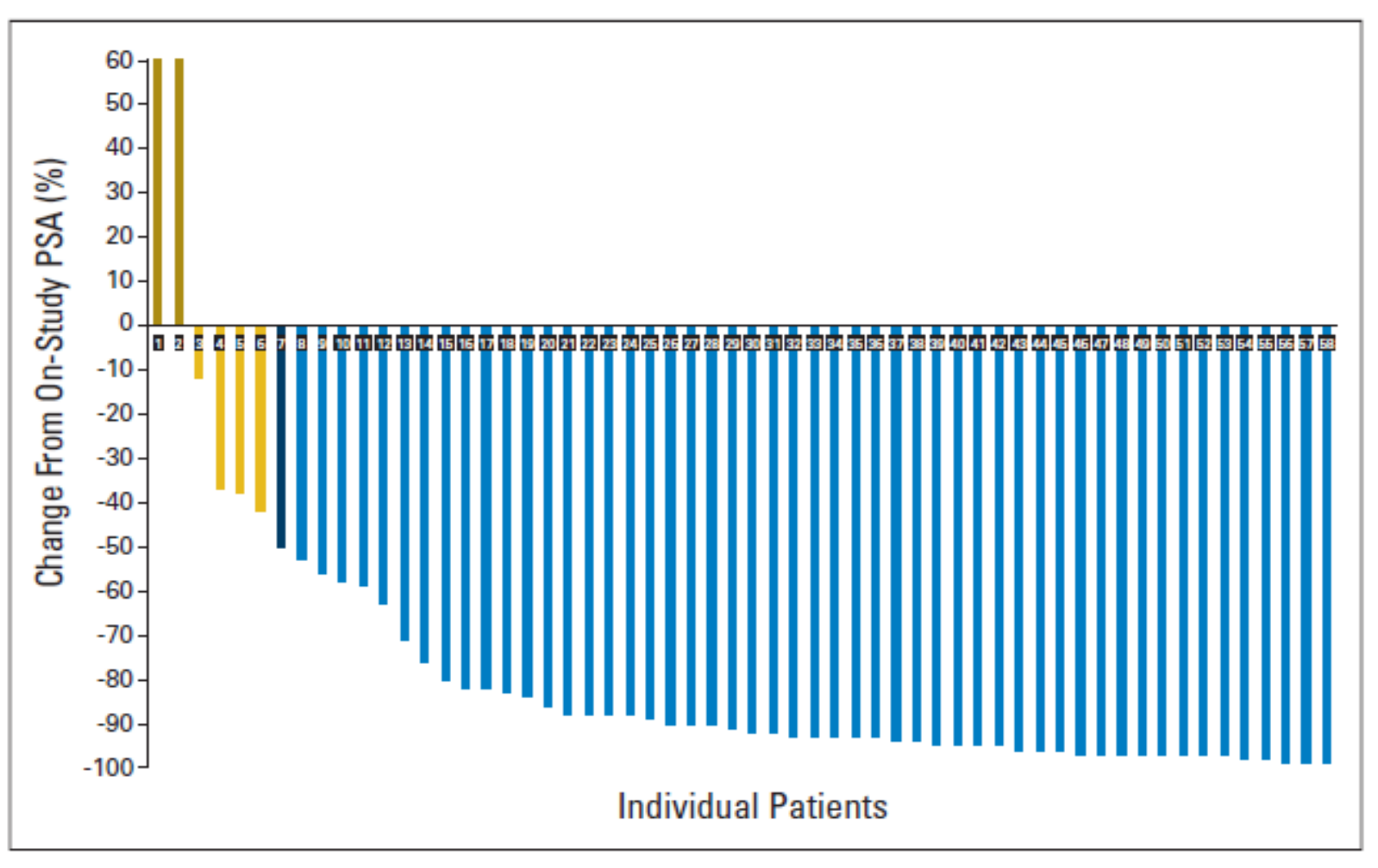
- Docetaxel + abiraterone
- Docetaxel + TAK-700
- Docetaxel + radium-223

Novel chemotherapies of interest?

- Survey of this meetings abstracts demonstrate a remarkable void
- Aurora kinase inhibitors…..

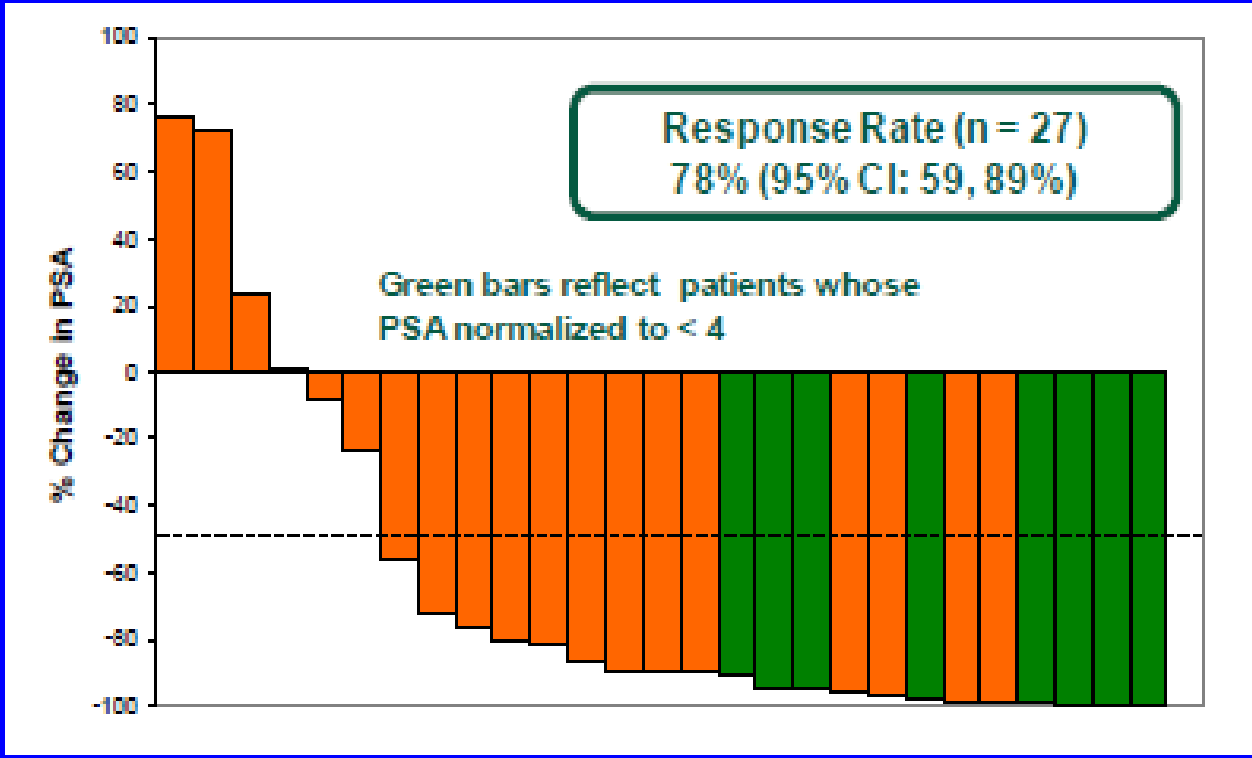
Docetaxel/Bevacizumab/Thalidomide/Zoledronate

Dahut et al. JCO 28:2070-76, 2010



Platins + Docetaxel

Dejager et al. J Clin Oncol 27:15s, 2009 (suppl; abstr 5140)



Is there a subset that really benefits from platinums?

Low PSA/neuroendocrine/small cell variants……

Antibody Drug Conjugates
Proof of Principle in Other Diseases

- Can we now target cytotoxics better? Breast and Hodgkins for sure……

- What about prostate?

- PSMA antibody drug conjugates?
- SLC44A4 antibody drug conjugates?

Where do we go from here?

- Taxanes are a critical component in our armamentarium……
- Can we do a better in terms of ensuring that we choose the best drug for an individual patient?
- Will combinations prove to be effective or will we remain in a sequential world?
- Antibody drug conjugates may point a way forward…..
- How are we going to afford it all?

Cancer cells, like plants, adapt to harsh environments by clever adaptations