CHEMOTHERAPY IN PROSTATE CANCER

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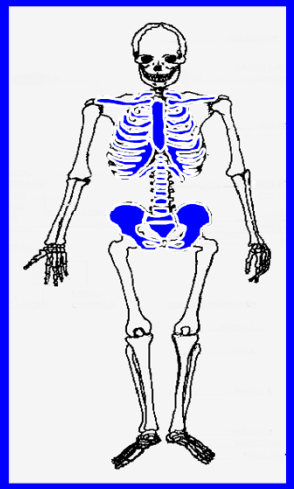
Important Specific Issues for Prostate Cancer

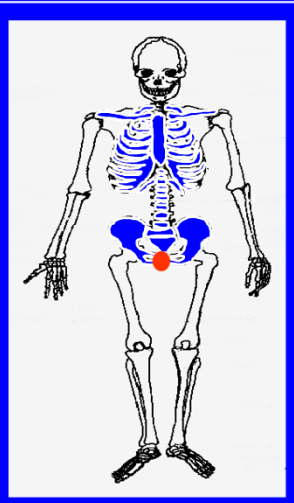
- Potentially long natural history – 10+ years
- Elderly patients
  - intercurrent disease
  - deaths from competing risks
- Variable clinical manifestations – the “states” model
  - Advanced “conventional” disease – clinical metastases
  - Hormone treated – relapsed, resistant, refractory
  - New imaging techniques used more actively → earlier stage
  - PSA-only disease after treatment
- Stage migration
  - Changes in imaging
  - PSA and other tumor markers
  - Quality of life measurement – new indices
- Changing surrogate measures of outcome

OBJECTIVES BY CLINICAL STATE



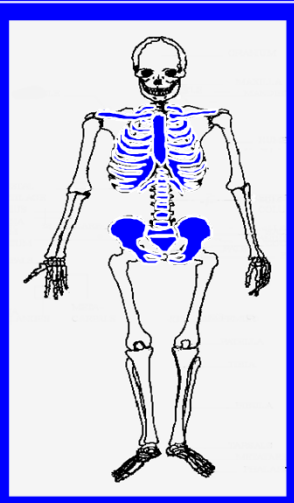
INITIAL EVALUATION: NO CANCER DIAGNOSIS

PREVENTION



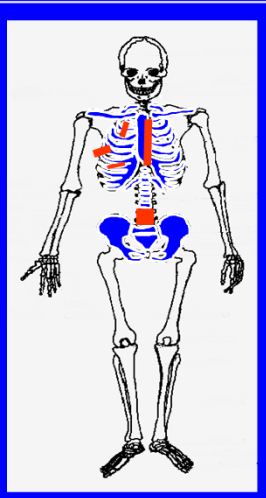
LOCALIZED DISEASE

MINIMIZE MORBIDITY/ MAXIMIZE CURE

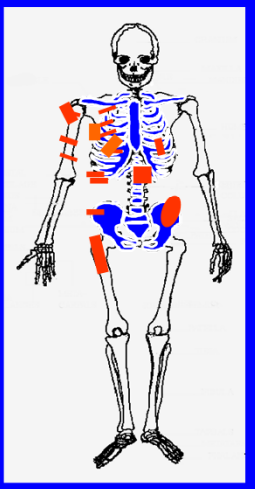


RISING PSA

PREVENT METASTASES



CLINICAL METASTASES: NON-CASTRATE



CLINICAL METASTASES: CASTRATE

ELIMINATE / PREVENT SYMPTOMS

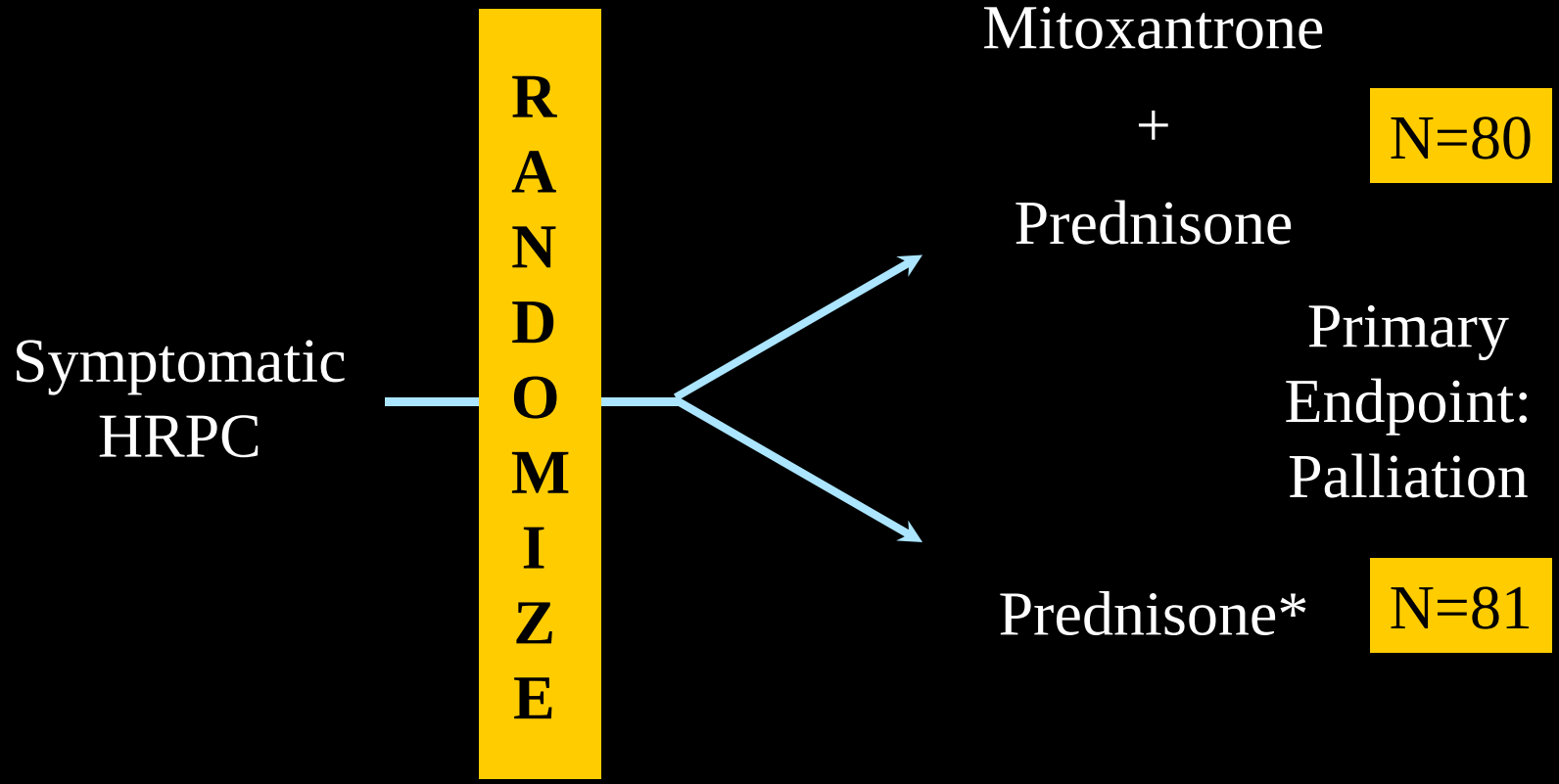
DEATH OF DISEASE

EARLY CHEMOTHERAPY ERA.....

HORMONE REFRACTORY PROSTATE CANCER

- PRIOR TO MAY 2004
- MITOXANTRONE- advanced PC (FDA approved in 1996)
- no evidence of a survival benefit
- one-third of symptomatic patients experienced improvement in pain (QOL)

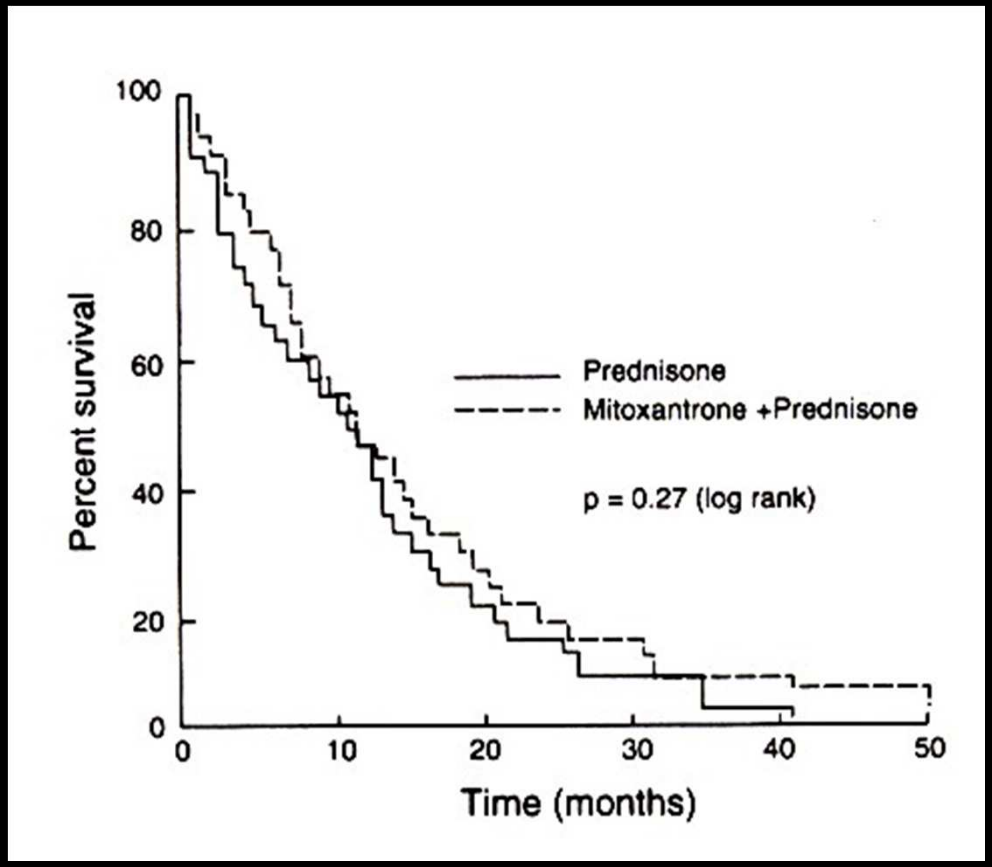
Mitoxantrone Phase III Canadian Trial: Study Design



*Crossover on progression (N=50)

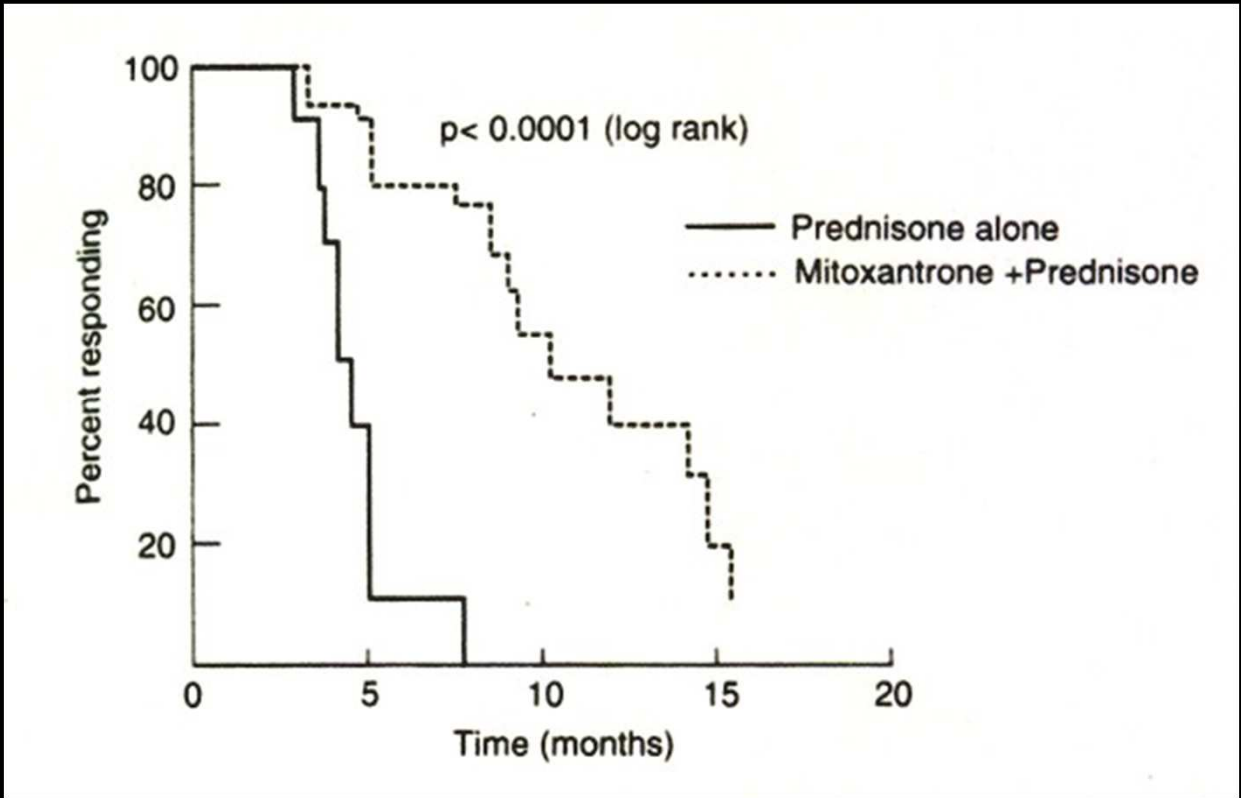
Tannock, et al. *J Clin Oncol.* 1996;14:1756-1764.

Mitoxantrone for Advanced Prostate Cancer: Overall Survival



Tannock et al, J. Clin. Oncol., 1996

Mitoxantrone for Advanced Prostate Cancer: Quality of Life



Tannock et al, J. Clin. Oncol., 1996

- 2003, FDA approved ZOLENDRONIC ACID for metastatic HRPC with bone metastasis
- QOL – pain relief

- October 2004, the New England Journal of Medicine reported on two studies using docetaxel in advanced PC

  .....

- ‘DOCETAXEL ERA’

- TAX 327
- 1006 PATIENTS
- RCT: docetaxel plus prednisone vs. mitoxantrone plus prednisone.
- MEDIAN SURVIVAL : 18.2 months compared with 16.4 months

- SWOG 9916
- 770 men
- docetaxel and estramustine compared with mitoxantrone and prednisone
- overall survival favored docetaxel (18.9 months compared with 16 months for mitoxantrone).

- THUS CAME FDA APPROVAL TO DOCETAXEL IN 2004

- ‘DEFINITE SURVIVAL BENEFIT’

Chemotherapy for Prostate Cancer: "Why Bother?"

DIFFERENCE IN SURVIVAL ONLY 2-21/2 MONTHS

- MARK TWAIN:
- FAMOUS QUIB ABOUT PRACTICE OF LYING:- 3 TYPES:
- “lies”, “damned lies”, and “statistics”

- Several points should be made about the survival analysis in these studies

1. both studies crossed over (to docetaxel) men who initially received mitoxantrone and did not respond

2. MEDIAN SURVIVAL: analysis includes all patients, not only those who respond, but also those that do not respond.

3. median survival analysis says little about patients on the right side of the survival curve (the men who respond to treatment, despite a poor prognosis).

- The existence of a small group of survivors far past the “median” point, even in cancers with a dire prognosis such as advanced PC, should provide real hope even when the prognosis is bleak.

Summarize effects of Docetaxel

- Survival improved
- Pain relief much superior
- greatest benefit was in “quality of life” issues (area of weight loss, appetite, pain, physical comfort, and bowel and genitourinary function)

What About Chemotherapy in Earlier Stages of PC?

- SUBSET OF “high-risk” PC(> 50% chances of disease recurrence) :

- PSA > 20
- Gleason score of 8 or higher
- Clinical Stage of T3 or higher determined by a digital rectal exam (tumor is already extending outside of the prostate gland).
- PSA doubling time (< 6 months)

COMBINING CHEMOTHERAPY WITH NOVEL AGENTS IN ADVANCED PROSTATE CANCER

- metastatic HRPC is the ‘HETEROGENOUS’ disease
- means that there are several or multiple forms or clones of PC cells existing within one patient
- the combination of chemotherapy with a novel or innovative agent takes advantage of our evolving understanding of advanced PC biology.

Table 1. Selected Novel New Agents in Early Clinical Trials
(many in combination with chemotherapy) **for Metastatic Hormone Refractory Prostate Cancer**

Target	Agent(s)
Microtubule	Epotholones, halichondrin, B analog, SB 715992
VEGF, VEGFR, Integrine	Bevacizumab, EMD121974, PTK787, SU11248
Histone deacetylase	SAHA, aplidine
EGFR, PDGF, HER-2	Sorefanib, imatinib, trastuzumab
AKT, mTOR	CCI779, RAD001
Endothelin receptor	Atrasentan
Immune modulation	Vaccines (GVAX, APC8105), lenalidomide, Revamid, Prostavac-VF, Provenge
Apoptotic pathway	Gossypol, Bcl-2 antisense, anti-clusterin
Proteosome Inhibition	bortezomib
Antiangiogenic	thalidomide

RECENT TRIALS ……HORMONE REFRACTORY STATES

GM-CSF and Anti-CTLA4 in Hormone-Refractory P Ca

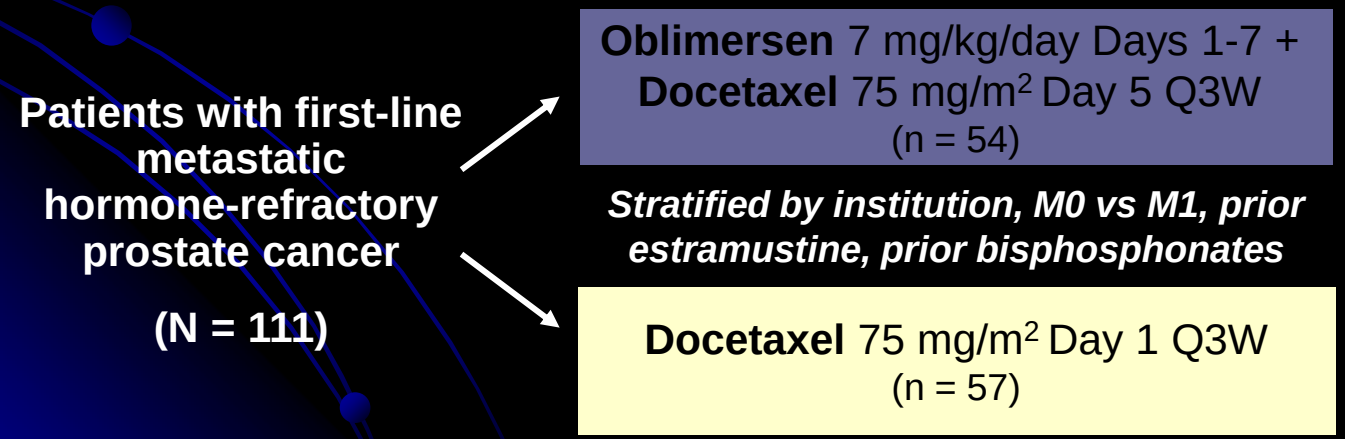
- CTLA4 transmits an inhibitory signal to activated T cells
  - Anti-CTLA4 augments T-cell responses and antitumor immunity in animal models

- Phase I study of GM-CSF 250 μg/m^2/day SC on Days 1-14 every 28 days with escalating doses of anti-CTLA4 Abipilimumab
(0.5-3.0 mg/kg)

Small EJ, et al. 2007 ASCO Prostate Cancer Symposium. Abstract 49.

Oblimersen + Docetaxel in Hormone-Refractory P Ca

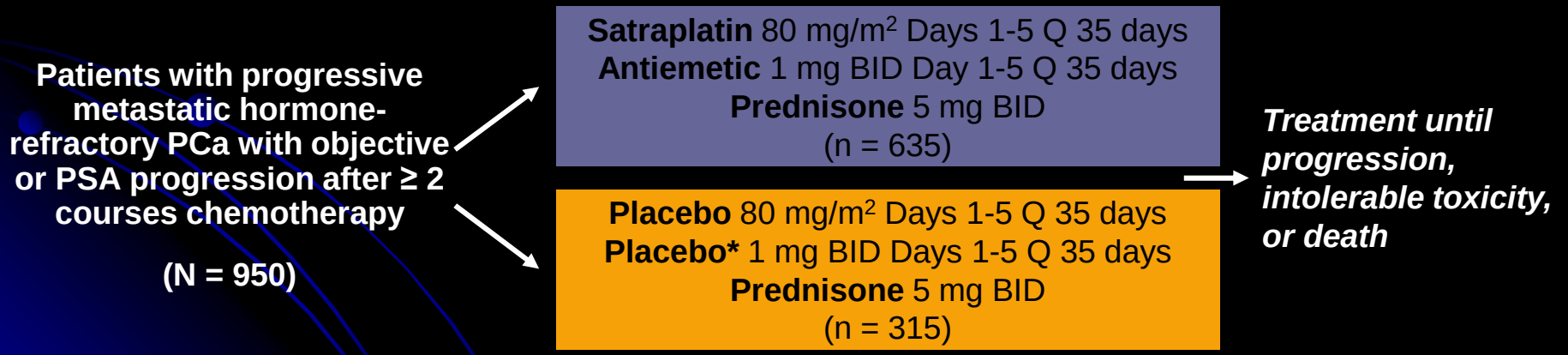
- Bcl-2 regulates apoptosis, contributes to docetaxel resistance
- Oblimersen sodium: DNA antisense oligonucleotide that prevents Bcl-2 protein production
- Phase II study evaluated benefit of adding oblimersen to docetaxel



Sternberg CN, et al. 2007 ASCO Prostate Cancer Symposium. Abstract 144.

Satraplatin + Prednisone in Hormone-Refractory P Ca

- Satraplatin: novel oral platinum compound
  - Associated with significant PFS improvements in chemotherapy-naive patients with hormone-refractory PCa[1]
- SPARC: phase III, randomized, placebo-controlled trial[2]



*Placebo antiemetic.

1. Sternberg CN, et al. Oncology. 2005;68:2-9.
2. Petrylak DP, et al. 2007 ASCO Prostate Cancer Symposium. Abstract 145.

Efficacy of Satraplatin + Prednisone in Hormone-Refractory PCa

- PFS significantly longer with satraplatin + prednisone vs prednisone
- Median PFS: 11.1 vs 9.7 weeks
- Median PFS among patients with prior docetaxel (n = 487): 10.1 vs 9.1 weeks
- Greater proportion of satraplatin-treated patients received ≥ 5 treatment cycles (40% vs 20%)

Petrylak DP, et al. 2007 ASCO Prostate Cancer Symposium. Abstract 145.

Atrasentan in Nonmetastatic, Hormone-Refractory PCa

- Atrasentan: oral selective endothelin A receptor antagonist
- Phase III randomized, controlled study of 941 patients with nonmetastatic, hormone-refractory PCa and rising PSA
- Trend toward higher rate of new skeletal lesions with placebo vs. atrasentan (44.3% vs. 36.2%)

Nelson JB, et al. 2007 ASCO Prostate Cancer Symposium. Abstract 146.

Isotope Therapy + Docetaxel for Castrate Metastatic PCa

- Phase I study of docetaxel + ^{153}Sm-lexidronam (Samarium-153) in patients with progressive CMPC (N = 15)
- Escalating trial of docetaxel (65-75 mg/m^2) and Samarium-153 (0.5-1.0 mCi/kg) every 6 weeks
- Dose-limiting toxicity not reached at 75 mg/m^2 docetaxel and 0.75 mCi/kg Samarium-153

Gignac J, et al. 2007 ASCO Prostate Cancer Symposium. Abstract 231.

NITI RAIZADA, CHEMOTHERAPY CA PROSTATE

SUMMARY

- Survival has been the standard
- Surrogates under evaluation
  - Quality of Life and Patient Reporting
  - PSA response
  - PSA time dependent kinetics
  - Markers of bone turnover
- New agents that cause cytostatic effects
  - Need for new parameters?
  - Are they really useful?

THANK YOU…..