The role of early hormonal manipulation and immunotherapy in CRPC

Open questions

Open questions

The trials used conventional imaging approach, with CT scans and bone scans: could more recent imaging techniques (fluciclovine PET, PSMA PET) potentially able to earlier detect metastases, shrink the population of men with nmCRPC?

32% of patients enrolled had metastatic disease at the time of screening for the study

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J Urol. 2012 July ; 188(1): 103–109. doi:10.1016/j.juro.2012.03.008.

Detection of Previously Unidentified Metastatic Disease as a Leading Cause of Screening Failure in a Phase III Trial of Zibotentan Versus Placebo in Patients with Nonmetastatic, Castration Resistant Prostate Cancer

Evan Y. Yu[*], Kurt Miller[*], Joel Nelson, Martin Gleave, Karim Fizazi[*], Judd W. Moul[†], Faith E. Nathan[*], and Celestia S. Higano[‡,*]

Purpose—Understanding the extent of disease in asymptomatic patients with castration resistant prostate cancer is important when making treatment decisions and designing clinical trials. The ENTHUSE M0 (ENdoTHelin A USE) trial (NCT00626548) was a large phase III study comparing the endothelin A receptor antagonist zibotentan with placebo in patients with nonmetastatic, castration resistant prostate cancer. The study was stopped prematurely after early efficacy review indicated that it was unlikely to meet its co-primary objectives of improved overall and progression-free survival vs placebo. Screening failed in an unexpectedly high number of patients. We investigated this screening failure rate to promote better classification of patients thought to have nonmetastatic castration resistant prostate cancer and inform the design of future clinical trials in this setting.

Results—Of 2,577 patients enrolled in a total of 350 hospital based centers in 39 countries screening failed in 1,155 (45%). The most common reason for screening failure was the detection of metastatic disease in 32% of all screened patients and in 71% of those in whom screening failed. The leading reasons for failed screening did not differ between investigator specialties overall or by geographic region.

Conclusions—The high frequency of asymptomatic metastasis in men thought to have nonmetastatic, castration resistant prostate cancer highlights the importance of periodic staging assessments for the condition. Optimal treatment modalities may differ for metastatic and nonmetastatic disease.

Challenges and Recommendations for Early Identification of Metastatic Disease in Prostate Cancer

E. David Crawford, Nelson N. Stone, Evan Y. Yu, Phillip J. Koo, Stephen J. Freedland, Susan F. Slovin, Leonard G. Gomella, E. Roy Berger, Thomas E. Keane, Paul Sieber, Neal D. Shore, Daniel P. Petrylak, and the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group

UROLOGY 83: 664–669, 2014.

Considering the cost-effectiveness when implementing new techniques/strategies for bone and soft tissue imaging, the RADAR Group recommended 99mTc bone scintigraphy and abdomen/pelvis/chest CT as the imaging modalities for initial testing.

Additional tests recommended
were plain radiography, MRI, and NaF PET to be
conducted at the physician's discretion when necessary.

Nonmetastatic Castration-resistant Prostate Cancer: A Modern Perspective

Madeline Cancian and Joseph F. Renzulli II

UROLOGY ■■: ■■–■■, 2018. © 2018 Elsevier Inc.

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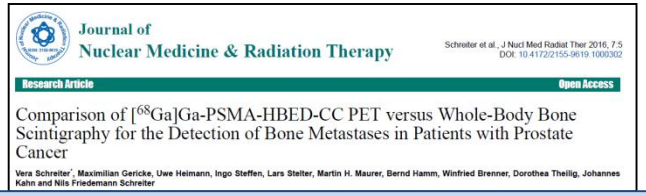
Nonmetastatic castration-resistant prostate cancer (nmCRPC) presents a challenge to urologists as currently there are no Food and Drug Administration-approved therapies. However, there are new imaging modalities, including fluciclovine positron emission tomography-computed tomography and Ga-PSMA (prostate specific membrane antigent) positron emission tomography computed tomography, which are improving accuracy of diagnosis. With improved imaging, we are better able to target therapy.



Journal of Nuclear Medicine & Radiation Therapy

Schreiter et al., J Nucl Med Radiat Ther 2016, 7:5
DOI: 10.4172/2155-9619.1000302

Research Article | Open Access

Comparison of [^{68}Ga]Ga-PSMA-HBED-CC PET versus Whole-Body Bone Scintigraphy for the Detection of Bone Metastases in Patients with Prostate Cancer

Vera Schreiter*, Maximilian Gericke, Uwe Heimann, Ingo Steffen, Lars Stelter, Martin H. Maurer, Bernd Hamm, Winfried Brenner, Dorothea Theilig, Johannes Kahn and Nils Friedemann Schreiter

Conclusion: [68Ga]Ga-PSMA-HBED-CC PET could detect significantly more bone metastases in prostate cancerthan (99m)Tc-DPD bone scintigraphy.

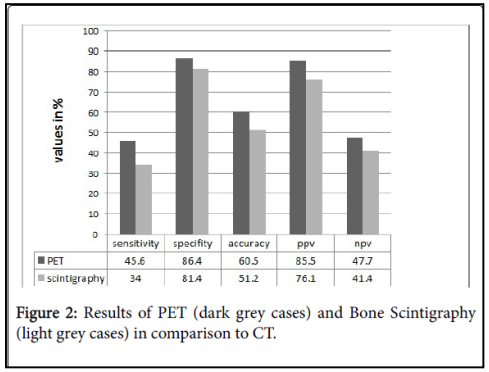


Figure 2: Results of PET (dark grey cases) and Bone Scintigraphy (light grey cases) in comparison to CT.

New imaging modalities are allowing for earlier identification of metastatic disease that will allow for more targeted therapy.

Open questions

Is PSA a reliable predictor of disease progression during APA/ENZ treatment?

Does the impact on PSA suggest that these agents may alter the biology of nmCRPC?

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Challenges and Recommendations for Early Identification of Metastatic Disease in Prostate Cancer

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UROLOGY 83: 664—669, 2014.

The RADAR Group considered PSADT to be the best and the most consistent predictor and useful in different patient groups. Limited data showed that acceleration or slow down of PSADT correlated with outcomes (eg, time to metastasis).

PD10-04
A POPULATION-BASED STUDY OF THE ASSOCIATION OF PROSTATE-SPECIFIC ANTIGEN DOUBLING TIME (PSADT) WITH METASTASIS-FREE SURVIVAL (MFS) AND OVERALL SURVIVAL (OS) IN NONMETASTATIC CASTRATION-RESISTANT PROSTATE CANCER (NMCRPC) PATIENTS (PTS)

Fred Saad, Montreal, Canada; Maneesha Mehra, Raritan, NJ; Eric J. Small, San Francisco, CA; Joe Lawson, Raritan, NJ; Anandaroop Dasgupta, New York, NY; Boris A. Hadaschik, Essen, Germany; Hiroji Uemura, Yokohama, Japan; Matthew R. Smith, Boston, MA*

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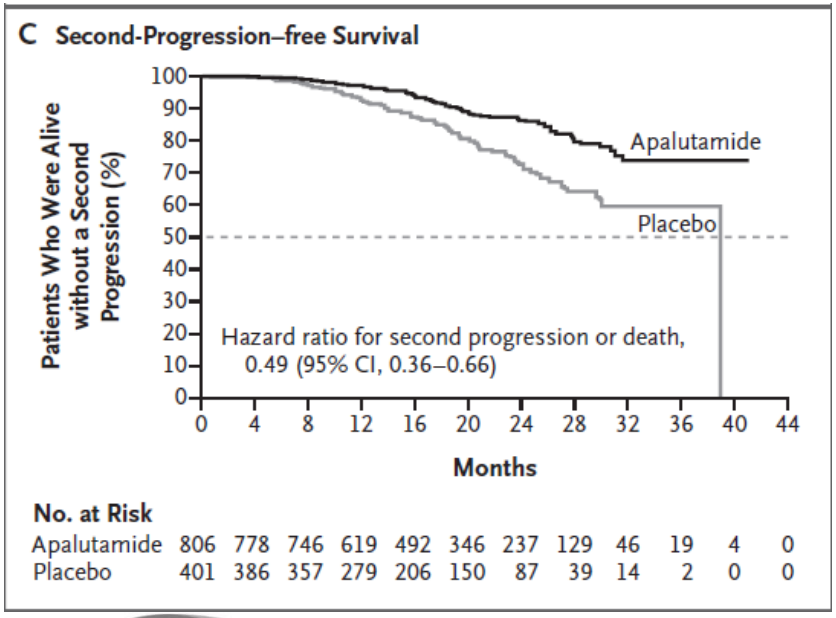
CONCLUSIONS: These population-based data confirm prior observations that PSADT in nmCRPC pts is associated with outcomes. In particular, PSADT $\leq$ 10 mos was associated with shorter MFS and OS. These data also indicate that approximately 30% of nmCRPC pts in a population-based analysis are in a high-risk group as defined by PSADT, and that baseline PSA level is a potential factor for predicting outcomes.

Open questions

Is PSA a reliable predictor of disease progression during APA/ENZ treatment?
Does the impact on PSA suggest that these agents may alter the biology of nmCRPC?

The SPARTAN trial also has exploratory endpoints such as a second PFS (PFS2) that measured the PFS after patients received second treatment at physician's choice including abiraterone or enzalutamide .

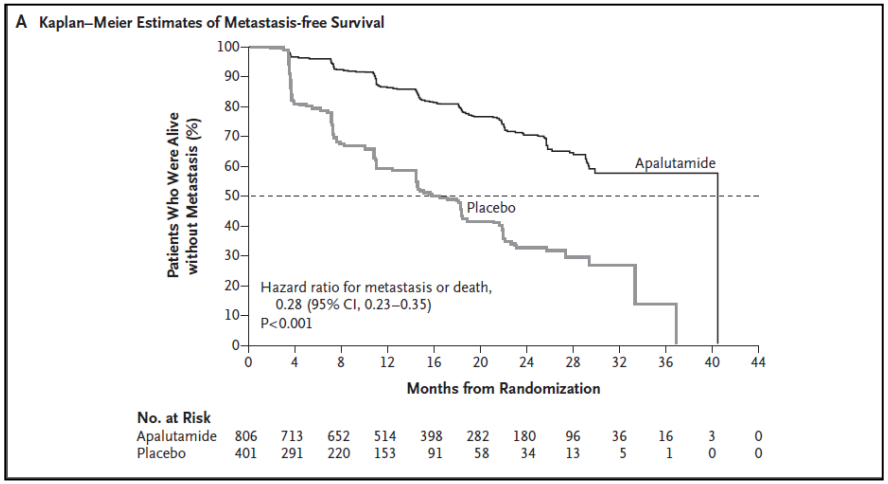
48% of patients who discontinued apalutamide (145/314) and 68% (189/279) who discontinued treatment in the placebo arm received either abiraterone or enzalutamide in subsequent treatment. For these patients who received subsequent drug, the PFS2 from the apalutamide arm was not reached, while it was 39.0 months in the placebo arm **(HR=0.49, p<0.0001)**, showing a **51% risk reduction of secondary progression.**

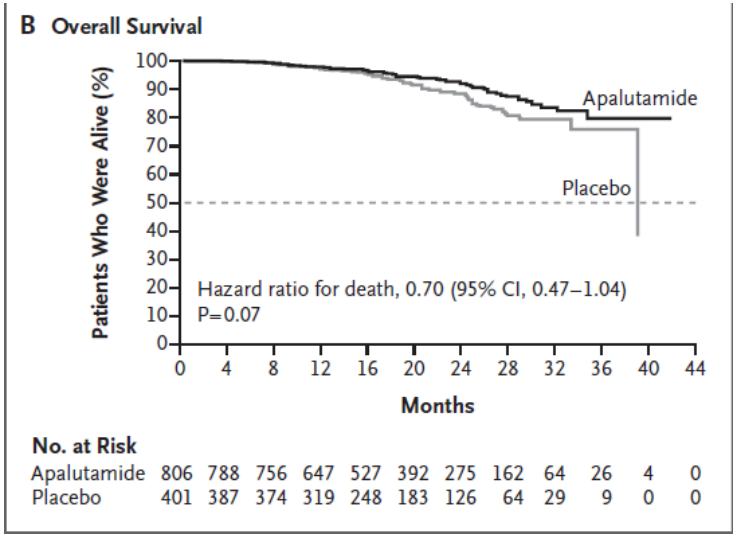


Open questions

Is MFS an appropriate endpoint?

The argument could be made whether MFS is an appropriate surrogate for OS. In fact, at the interim analyses of the aforementioned trials, both agents (when added to ADT) had numerical trends for OS improvement that were not statistically significant, although the OS data were immature.

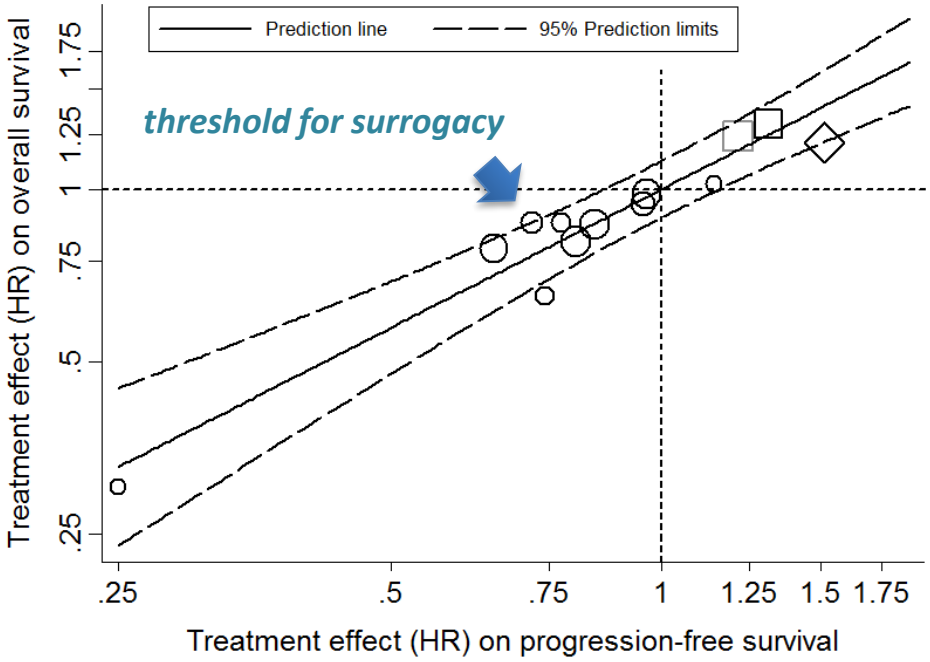




Prentice's Criteria

- To be a direct substitute for a clinical benefit endpoint on inferences of superiority and inferiority
  - The surrogate endpoint must be correlated with the clinical outcome
  - The surrogate endpoint must fully capture the net effect of treatment on the clinical outcome

TRIAL LEVEL CORRELATION BETWEEN EFFECTS



Burzykowski and Buyse, Pharmaceutical Statist 2006;5:173

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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer

Wanling Xie, Meredith M. Regan, Marc Buyse, Susan Halabi, Philip W. Kantoff, Oliver Sartor, Howard Soule, Noel W. Clarke, Laurence Collette, James J. Dignam, Karim Fizazi, Wendy R. Paruleker, Howard M. Sandler, Matthew R. Sydes, Bertrand Tombal, Scott G. Williams, and Christopher J. Sweeney, on behalf of the ICECaP Working Group

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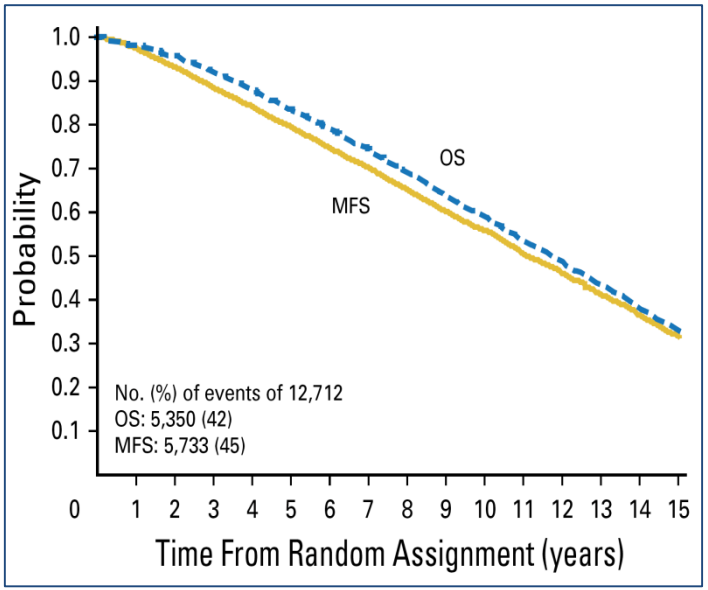
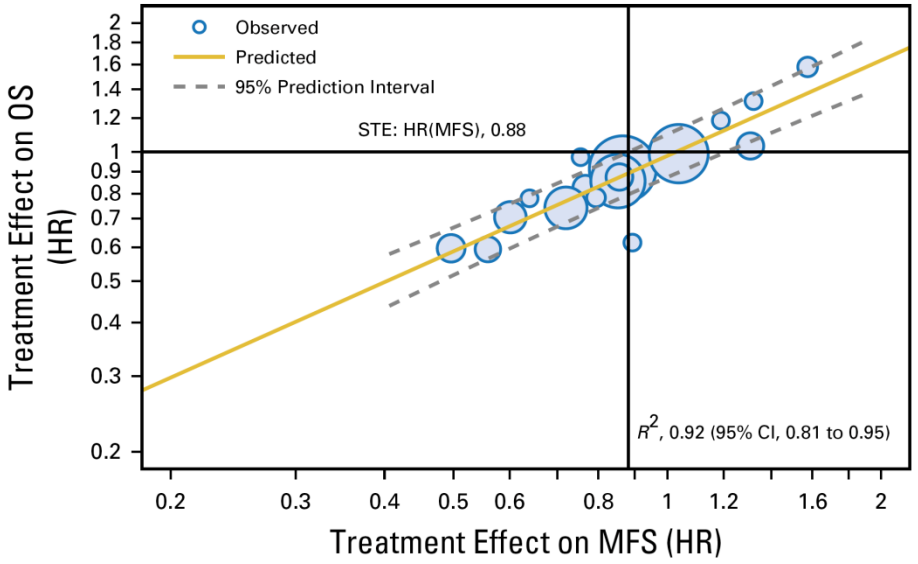
At the individual patient level, the correlation with OS was 0.91 (95% CI, 0.91 to 0.91) for MFS, as measured by Kendall's tau





VOLUME 33 · NUMBER 12 · APRIL 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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Radiographic Progression-Free Survival As a Response Biomarker in Metastatic Castration-Resistant Prostate Cancer: COU-AA-302 Results

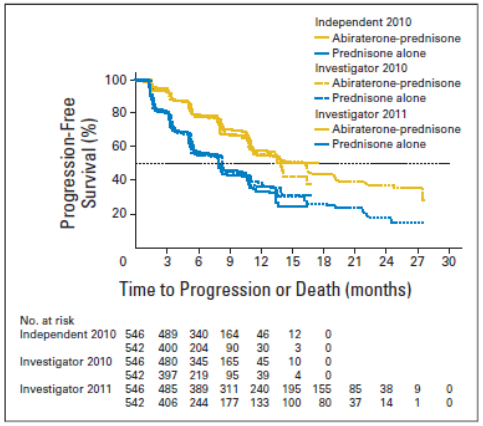

Fig 2. Radiographic progression-free survival as assessed by blinded independent review (December 2010), blinded independent and investigator review (December 2010), and blinded independent and investigator review (December 2011).

Conclusion

rPFS was highly consistent and highly associated with OS, providing initial prospective evidence on further developing rPFS as an intermediate end point in mCRPC trials.

Table A2. rPFS Positively Associated With OS, Overall and Within Both Treatment Groups

Group	Spearman's Correlation Coefficient	95% CI	Kendall's Tau Statistic	95% CI
Overall	0.71	0.65 to 0.77	0.52	0.47 to 0.58
Abiraterone plus prednisone	0.82	0.75 to 0.88	0.63	0.56 to 0.70
Prednisone alone	0.60	0.50 to 0.69	0.43	0.35 to 0.51

NOTE. Total of 1,064 observations from 10 countries analyzed.
Abbreviations: OS, overall survival; rPFS, radiographic progression-free survival.