Informed Prostate Cancer Support Group Inc.
"A 501 C 3 CORPORATION ID # 54-2141691"

DECEMBER 2023 NEWSLETTER

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Friday, December 22, 2023

Volume 16 Issue 12

Next Meeting Saturday, January 20, 2024 IPCSG—10:00am—Noon PDT.

- ***No meeting in December***
- **In January, Dr. A. J. Mundt MD, UCSD Radiation Oncology will be introducing the other members of his team who will speak on their specialties and will also give an introductory overview of radiation oncology as it relates to prostate cancer.**
- As always, spouses/partners and caregivers are welcome and encouraged to attend!
- After the meeting a light lunch will be served in the foyer outside the meeting room
- **For links to further Reading: https://ipcsg.blogspot.com/ (includes member suggested links)**
- **If you have Comments, Ideas or Questions,** email Newsletter@ipcsg.org
- **For more information, please send email to bill@ipcsg.org or call Bill at (619) 591-8670 or Gene at (619) 890-8447**

Sam Denmeade, M.D. - Bipolar Androgen Therapy (BAT)

November 2023 IPCSG Presentation - Summary

Testosterone as a Treatment for Prostate Cancer

Dr. Denmeade discusses the use of testosterone as a treatment for prostate cancer, presenting an alternative approach to the typical deprivation of testosterone to combat the disease. The discussion delves into the role of androgens in male biology, the synthesis of hormones, the historical paradigm of prostate cancer treatment, and the evolution of hormonal therapies. He also addresses the side effects associated with androgen deprivation therapy and the challenges of resistance to sequential treatments. Overall, the focus is on the complexities of utilizing testosterone in prostate cancer treatment and the implications for patient outcomes.

Testosterone Manipulation as a Potential Prostate Cancer Treatment

Dr. Mark Scholz discusses the potential of using testosterone manipulation as a treatment for prostate cancer. He explains that by first administering hormone treatment to shock the cancer cells used to a certain level of testosterone and then suddenly taking it away, the cancer cells are not

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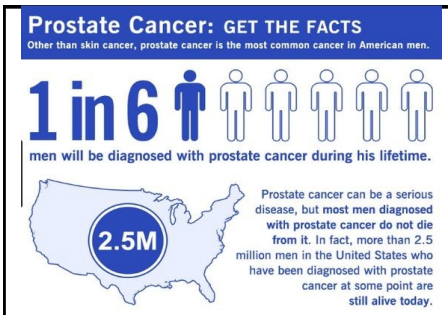

Organization

a 501c3 non-profit organization - all positions are performed gratis

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NEWSLETTER
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PROSTATE CANCER—*2 WORDS, NOT A SENTENCE*

What We Are About

Our Group offers the complete spectrum of information on prevention and treatment. We provide a forum where you can get all your questions answered in one place by men that have lived through the experience. Prostate cancer is very personal. Our goal is to make you more aware of your options before you begin a treatment that has serious side effects that were not properly explained. Impotence, incontinence, and a high rate of recurrence are very common side effects and may be for life. Men who are newly diagnosed with PCa are often overwhelmed by the frightening magnitude of their condition. Networking with our members will help identify what options are best suited for your life style.

Join the IPCSG TEAM

If you consider the IPCSG to be valuable in your cancer journey, realize that we need people to step up and HELP. Call **President** Bill Lewis @ (619) 591-8670 "bill@ipcsg.org"; or **Director** Gene Van Vleet @ 619-890-8447.

From the Editor

In this issue:

A summary of Dr. **Sam Denmeade's talk on** current work and planned trials on Binary Androgen Therapy is provided. For further articles see the blog at https://ipcsg.blogspot.com/ . Some apparently important optimistic items of interest this month:

1. From BPH to male LUTS: a 20-year journey of the EAU guidelines—how European Association of Urology (EAU) try to provide consistent clinical practice guidelines to maximize patient quality of life.
2. Impact of medical treatment on storage and voiding LUTS, nocturia, and quality of life in men at risk for progression | Prostate Cancer and Prostatic Diseases
3. Major adverse cardiovascular events of enzalutamide versus abiraterone in prostate cancer: a retrospective cohort study | Prostate Cancer and Prostatic Diseases—(zytiga) abiraterone may be worse for your heart than (Xtandi) enzalutamide.
4. 177Lu-Prostate-Specific Membrane Antigen Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer and Prior 223Ra (RALU Study) | Journal of Nuclear Medicine— PSMA PET/CT is a valuable imaging biomarker after ARPI treatment initiation in mCRPC patients

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ready to handle the change, resulting in many of them dying. However, some cancer cells survive and enter an adaption phase, where they start making more of the androgen receptor, allowing them to grow again. He introduces the concept of bipolar androgen therapy, which involves taking men from low testosterone to high testosterone levels over a treatment cycle, making the cells vulnerable at both extremes. Dr. Scholz also presented findings from a trial where patients showed significant responses to testosterone treatment, including decreases in PSA levels and tumor shrinkage, demonstrating the potential of this approach as a prostate cancer treatment.

Effectiveness and Side Effects of Hormone Treatments in Prostate Cancer Patients

Dr. Denmeade discusses the side effects and effectiveness of hormone treatments, specifically testosterone and anti-testosterone (enzalutamide) in prostate cancer patients. He highlights that while both treatments showed similar efficacy in terms of disease progression and PSA response, testosterone treatment resulted in better quality of life, including improved sexual function, libido, and energy levels. Moreover, the cost of testosterone treatment is significantly lower compared to anti-testosterone treatment. Additionally, the segment emphasizes the potential of testosterone treatment to reverse metabolic effects of hormone therapy and its role in re-sensitizing patients to subsequent treatments, potentially improving survival and delaying the need for more toxic treatments like chemotherapy. The study also indicates promising results in combination treatments involving testosterone and immune therapy, showing potential for enhancing the immune environment of cancer. The findings suggest that the sequence of hormone treatments, particularly involving testosterone, could be key to optimizing treatment outcomes for prostate cancer patients.

New Treatment Approach for Prostate Cancer: Testosterone Therapy and Resensitization to Hormone Treatments

Dr. Denmeade, MD discusses a new treatment approach for prostate cancer involving testosterone therapy and re-sensitization to hormone treatments. This approach aims to re-sensitize the cancer to hormone treatments, leading to tumor shrinkage and decreased PSA levels, while also improving patients' quality of life. The study is being conducted at multiple locations, with three arms exploring different treatment variations. Additionally, the research team is also looking into combining testosterone therapy with other drugs to further enhance its efficacy. Furthermore, they have observed promising results in reducing the level of a gene called Mick, which drives cancer growth, through testosterone therapy. This has led to a proposed study, Cosmic, to further investigate this finding. Another significant observation is the impact of testosterone therapy on metabolic changes within cancer cells, leading to the design of the Apex trial to combine testosterone with the drug dfmo. This trial, aimed at studying the effects of combining testosterone with dfmo and its potential impact on the immune system, has recently opened and holds promise for further advancements in prostate cancer treatment.

BAT Treatment for Prostate Cancer and its Potential Impact in Africa

Dr. Denmeade discussed the lack of funding for BAT, as a treatment for prostate cancer and the potential interest from groups in Africa due to the affordability and lack of access to other drugs. He discussed the possibility of conducting a trial in Africa before the United States due to the prevailing conditions. Additionally, he highlighted the involvement of various individuals and the need for advocacy and support for the treatment. Furthermore, the Q&A session addressed concerns about androgen deprivation resistance, potential involvement in upcoming summits, and the appropriateness of BAT treatment for localized cancers.

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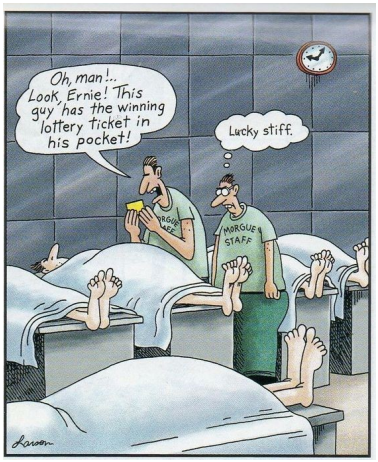
Prostate-Specific Antigen (PSA) and Prostate Health

He discussed the role of prostate-specific antigen (PSA) in prostate health and its implications for diagnosing prostate conditions. PSA is a protein produced by the prostate and is found in semen, with small amounts also present in the blood. Elevated levels of PSA in the blood may indicate prostate cancer, while prostatitis, a prostate inflammation, could also influence PSA levels. The conversation emphasizes the significance of monitoring PSA levels and the potential need for a biopsy to rule out prostate cancer in cases of elevated PSA, providing insights into the diagnosis and management of prostate health issues.

The video is available on YouTube at https://youtu.be/R2CIx4mcS6c

On the Lighter Side



Items of Interest

From BPH to male LUTS: a 20-year journey of the EAU guidelines | Prostate Cancer and Prostatic Diseases

nature.com

Kaplan, Steven A.

Over the past three decades, there has been a concerted effort by many medical organizations to create clinical practice guidelines (CPGs) across a wide spectrum of conditions and diseases. Ultimately, CPGs are designed to maximize patient quality of life and outcomes and to minimize adverse events and patient burden. Guidelines are not mandates or commandments nor should they be interpreted as absolutes. Nevertheless, they can augment clinical expertise in delivery of more optimal results.

The authors herein review the journey undertaken by the European Association of Urology (EAU) in the initial creation of, modification and adoption of CPG's for men with voiding symptoms. Most significantly, terms evolved from benign prostatic hyperplasia (BPH) to male lower urinary tract symptoms (LUTS) and finally adding the modifier 'non-neurogenic". These iterations were designed in part to provide a more robust data repository which accurately reflects the multifactorial nature of LUTS as men age. This is contrast to the American Urological Association (AUA) guidelines (full disclosure: I have been a member of the AUA BPH Guidelines Committee for over 15 years) which have maintained the term BPH since 1994. While arguments can be made on either side of the Atlantic on terminology, for the most part there is significant overlap in analysis and recommendations.

Moreover, despite advances in science and technology, the health care delivery system fails to consistently provide QUALITY medical care to patients. How do we assess quality? What outcomes are important when defining quality? And ultimately, do CPGs help or matter? Finally, there are numerous internal barriers including awareness, familiarity and agreement.

The challenge in creating CPGs is the quality of evidence that is analyzed. Ultimately, it's what you put into the data blender that determines the quality of the guideline recommendations. In a recent study, it appears that the strength of evidence correlated with recommendation levels [1]. Of 939 statements across 29 AUA guidelines in 2021, the levels of evidence were: Grade A: 39 (4.2%), Grade B: 188 (20%), Grade C: 297 (31.6%), Clinical Principle: 185 (19.7%) and Expert Opinion: 230 (24.5%). Oncology has more Grade A and less Grade C; diagnosis and evaluation more likely based on Clinical Principle, strong recommendations more likely supported by high – grade evidence and most of the evidence for AUA Guidelines in NOT high grade.

In summary, the EAU should be commended for their focus and long-standing commitment to the creation of meaningful CPG's. As in the AUA CPG process, lots of time, effort and focus is spent in the creation and modification of CPG's with the hope of continued improvement in urologic care. Looking into the future, use of technology and remote care / diagnosis will help in improving access and hopefully improve long term care in the management of men with LUTS and BPH.

Reference

Du C, Harandi AA, Hwang K, Hill J, Adler HL. Analysis of the AUA Guidelines: Strength of Evidence Correlates With Recommendation Levels. Urol Pract. 2023;10:116.

Impact of medical treatment on storage and voiding LUTS, nocturia, and quality of life in men at risk for progression | Prostate Cancer and Prostatic Diseases

nature.com

Spatafora, Pietro

Prostate enlargement is a very common pathologic condition [1]: male aging process is associated with a continuous worsening of both storage and voiding urinary symptoms, the development of nocturia, with the consequent decline of quality of life (QoL) and the risk of urinary retention and need of surgery.

Drugs are the first line of treatment to prevent the risk of progression. Several compounds, acting through different pathways are now available for both general practitioners and urologists. All these drugs are indicated – according to current literature [2] – to treat patients with moderate to severe LUTS, but there is poor evidence that can help both healthcare professionals and patients in making more aware personalized, data-driven decisions based on individual baseline parameters and risk factors.

The study from Gravas et al. [3] was designed to create a predictive analytics model to better understand how placebo, dutasteride, tamsulosin, or combination therapy impact on urinary symptoms (storage, voiding, QoL, nocturia, preventing disease progression), in different profiles of patients with BPE at risk of worsening, as defined by their baseline characteristics. Data were extrapolated by more than 9000 patients included in the CombAT study and placebo-controlled dutasteride monotherapy studies.

Several interesting results were reported in the manuscript. First of all, Gravas et al. confirmed what has been previously indicated both in Mtops and Combact studies: alpha-blockers and 5alpha reductase inhibitors act on different pathways within the prostatic gland and the bladder neck and their combinations allow to achieve higher improvement of all lower urinary tract symptoms as compared to monotherapy. Furthermore, this study also underlines that there is no specific patient profile that present better outcomes as compared to the other ones, even if in real life, only a few patients use combination therapy while in the majority of cases monotherapy is the first line of treatment.

Moreover, Gravas et al. identify age, use of Alpha blocker and Qmax as significant predictors of clinical outcomes. This is in accordance with a cross sectional study of Shao WH et al. where IPSS score, PSA, PV, and PVR significantly increased with age [4]. The risk predictors of BPH progression were positively correlated with age after 61 years, while PVR found to be determinant in storage and voiding scores. A systematic analysis of expert opinion in 2005 by Lowe FC et al., which included a panel of 12 urologists from 8 different countries, assessed the appropriates of common treatments for LUTS/BPH [5]. 243 different patient scenarios were based on the permutation of values of clinical variables (total I-PSS, PV, PSA, Qmax and PVR) which were valued for the risk of disease progression. Authors concluded that symptom severity (total I-PSS 20–35), maximum flow rate (Qmax < 10 ml) postvoid residual PVR (>150 ml), are the most dominant factors of increased risk of disease progression focused on the impact of several "unfavorable" combinations rather than the impact of a single risk factor [5].

Another critical point evaluated by Gravas et al. was nocturia. Authors showed that PVR, age, Qmax and nocturia are predictors of change in nocturia and underline the role of treating disease mechanism, reinforcing therefore the value of 5 alpha reductase inhibitors. Gravas predicted the noteworthy benefit of the long-term effects of 5ARI-based treatment regarding nocturia and storage symptoms. According to Oelke et al [6], an analysis of 4-year CombAT data showed that combination treatment led to a significant nocturia improvement in terms of number of nocturnal voiding episodes over either monotherapy. Despite that LUTS/BPE is rarely life-threatening, nocturia on the other hand has been linked to increase mortality in men [7].

Finally regarding to QoL, the baseline covariates of total IPSS, Qmax, PVR and previous use of alpha blocker were the main predictors of QoL change. In particular, higher scores at baseline were predictive of greater improvement in QoL (IPSS-Q8) with CT as with monotherapy. This outcome is in agreement with data reported by Roehrborn et al. [8]: in a post hoc analysis of CombAT study, where CT showed greater improvement in IPSS at 48 months in comparison with tamsulosin, across all baseline subgroups and significantly improved Qmax compared to tamsulosin, but not compared to dutasteride as monotherapy. Therefore, even if all 3 therapies (CT, tamsulosin and dutasteride) have shown an improved Qmax to a different extent, most remarkable improvement is provided by CT. Previous use of alpha blockers appeared as a significant predictor of several outcomes. The changes in IPSS and Qmax regarding previous treatment of a blocker was also described by Roehrborn C et al. extracting a 2-year data from the CombAT study, where the effect of CT therapy was superior to tamsulosin and dutasteride in naïve and previously treated men [9].

In conclusion, predictive results indicate superiority of CT compared to any monotherapy, regarding all baseline parameters, even if pharmacoeconomic evaluations, and the increased risk of sexual related adverse event should be considered before prescription [10].

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Major adverse cardiovascular events of enzalutamide versus abiraterone in prostate cancer: a retrospective cohort study | Prostate Cancer and Prostatic Diseases

nature.com

Ng, Chi Fai

Abstract

Background

While the cardiovascular risks of androgen receptor pathway inhibitors have been studied, they were seldom compared directly. This study compares the risks of major adverse cardiovascular events (MACE) between enzalutamide and abiraterone among prostate cancer (PCa) patients.

Methods

Adult PCa patients receiving either enzalutamide or abiraterone in addition to androgen deprivation therapy in Hong Kong between 1 December 1999 and 31 March 2021 were identified in this retrospective cohort study. Patients who switched between enzalutamide and abiraterone, initiated abiraterone used without steroids, or experienced prior cardiac events were excluded. Patients were followed-up until 30 September 2021. The primary outcomes were MACE, a composite of stroke, myocardial infarction (MI), Heart failure (HF), or all-cause mortality and a composite of adverse cardiovascular events (CACE) not including all-cause mortality. The secondary outcomes were individual components of MACE. Inverse probability treatment weighting was used to balance covariates between treatment groups.

Results

In total, 1015 patients were analyzed (456 enzalutamide users and 559 abiraterone users; mean age 70.6 ± 8.8 years old) over a median follow-up duration of 11.3 (IQR: 5.3–21.3) months. Enzalutamide users had significantly lower risks of 4P-MACE (weighted hazard ratio (wHR) 0.71 [95% confidence interval (CI) 0.59–0.86], $p < 0.001$) and CACE (wHR 0.63 [95% CI: 0.42–0.96], $p = 0.031$), which remained consistent in multivariable analysis. Such an association may be stronger in patients aged ≥65 years or without diabetes mellitus and was independent of bilateral orchidectomy. Enzalutamide users also had significantly lower risks of MI (wHR 0.57 [95% CI: 0.33–0.97], $p = 0.040$) and all-cause mortality (wHR 0.71 [95% CI: 0.59–0.85], $p < 0.001$).

Conclusion

Enzalutamide was associated with lower cardiovascular risks than abiraterone in PCa patients.

177Lu-Prostate-Specific Membrane Antigen Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer and Prior 223Ra (RALU Study) | Journal of Nuclear Medicine

jnm.snmjournals.org

Kambiz Rahbar, Markus Essler, Matthias Eiber, Christian la Fougère, Vikas Prasad, Wolfgang P. Fendler, Philipp Ras-

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sek, Ergela Hasa, Helmut Dittmann, Ralph A. Bundschuh, Kim M. Pabst, Milena Kurtinecz, Anja Schmall, Frank Verholen and Oliver Sartor

Journal of Nuclear Medicine December 2023, 64 (12) 1925-1931; DOI: https://doi.org/10.2967/jnumed.123.266125

Abstract

223Ra-dichloride (223Ra) and 177Lu-prostate-specific membrane antigen (PSMA) are approved treatments for metastatic castration-resistant prostate cancer (mCRPC). The safety and effectiveness of sequential use of 223Ra and 177Lu-PSMA in patients with mCRPC are not well described. This study aimed to evaluate 177Lu-PSMA safety and efficacy in patients with mCRPC previously treated with 223Ra.

Methods: The radium→lutetium (RALU) study was a multicenter, retrospective, medical chart review. Participants had received at least 1 223Ra dose and, in any subsequent therapy line, at least 1 177Lu-PSMA dose. Primary endpoints included the incidence of adverse events (AEs), serious AEs, grade 3–4 hematologic AEs, and abnormal laboratory values. Secondary endpoints included overall survival, time to next treatment/death, and change from baseline in serum prostate-specific antigen and alkaline phosphatase levels.

Results: Data were from 133 patients. Before 177Lu-PSMA therapy, 56% (75/133) of patients received at least 4 life-prolonging therapies; all patients received 223Ra (73% received 5–6 injections). Overall, 27% (36/133) of patients received at least 5 177Lu-PSMA infusions. Any-grade treatment-emergent AEs were reported in 79% (105/133) of patients and serious AEs in 30% (40/133). The most frequent grade 3–4 laboratory abnormalities were anemia (30%, 40/133) and thrombocytopenia (13%, 17/133). Median overall survival was 13.2 mo (95% CI, 10.5–15.6 mo) from the start of 177Lu-PSMA.

Conclusion: In this real-world setting, 223Ra followed by 177Lu-PSMA therapy in heavily pretreated patients with mCRPC was clinically feasible, with no indication of impairment of 177Lu-PSMA safety or effectiveness.

PSMA PET/CT for Response Assessment and Overall Survival Prediction in Patients with Metastatic Castration-Resistant Prostate Cancer Treated with Androgen Receptor Pathway Inhibitors | Journal of Nuclear Medicine

Journal of Nuclear Medicine December 2023, 64 (12) 1869-1875;

DOI: https://doi.org/10.2967/jnumed.123.265874

Abstract

We aimed to evaluate the role of prostate-specific membrane antigen (PSMA) PET/CT for response assessment and outcome prediction in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with androgen receptor pathway inhibitors (ARPIs), including abiraterone acetate or enzalutamide.

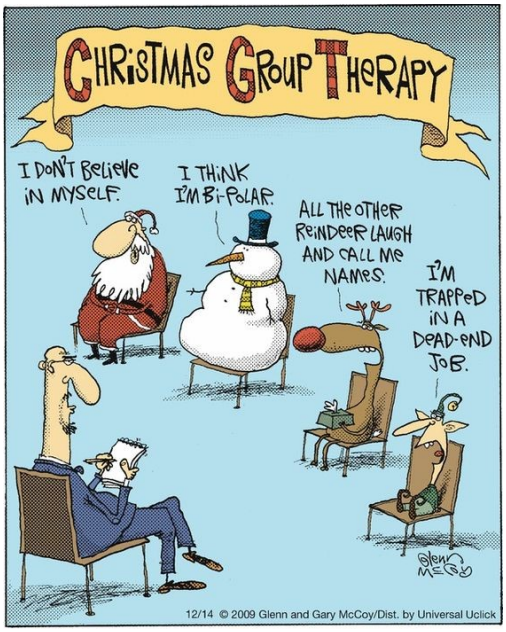
Methods: We retrospectively analyzed 30 ARPI-treated mCRPC patients who underwent 68Ga-PSMA-11 PET/CT within 8 wk before (baseline) and 12 ± 4 wk after treatment initiation. Total PSMA tumor volume was calculated using the fixed threshold method (SUV ≥ 3). Patients were categorized as PSMA responders (PSMA-Rs) or PSMA nonresponders (PSMA-NRs) on the basis of both European Association of Urology/European Association of Nuclear Medicine (EAU/EANM) criteria and Response Evaluation Criteria in PSMA PET/CT (RECIP) 1.0. PSMA-R included patients with a complete response, a partial response, or stable disease, and PSMA-NR included those with progressive disease. On the basis of prostate-specific antigen (PSA), patients were classified as biochemical responders

if PSA decreased by at least 50% and as nonresponders if it did not. The Φ-coefficient was used to evaluate the correlation of PSMA- and PSA-based responses. Survival analysis was performed using the Cox regression hazard model and the Kaplan–Meier method. Predictive accuracy was tested for both response criteria.

Results: On the basis of PSMA PET/CT, 13 (43%) patients were PSMA-NR according to the EAU/EANM criteria and 11 (37%) patients were PSMA-NR according to RECIP 1.0. Significant correlations were observed between PSMA- and PSA-based responses for both criteria ($\Phi = 0.79$ and 0.66, respectively). After a median follow-up of 25 mo (interquartile range, 21–43 mo), the median overall survival was significantly longer for PSMA-R than PSMA-NR (54 vs. 22 mo) for both the EAU/EANM criteria and RECIP 1.0, with hazard ratios of 6.9 (95% CI, 1.9–26; P = 0.004) and 5.6 (95% CI, 1.69–18.26, P = 0.005), respectively. No significant difference in predictive accuracy was found between the 2 criteria (C-index, 0.79 vs. 0.76, respectively, P = 0.54). Flare phenomena at the second PSMA PET study were not observed in our cohort.

Conclusion: Our results demonstrate that PSMA PET/CT is a valuable imaging biomarker for response assessment and overall survival prediction when performed at 3 mo after ARPI treatment initiation in mCRPC patients. Both proposed PSMA response criteria (EAU/EANM and RECIP 1.0) seem to perform equally well. No PSMA flare was observed. Prospective validation of these findings is strongly needed.

On the Lighter Side



NETWORKING

Please help us in our outreach efforts. Our speakers bureau consisting of Gene Van Vleet and Bill Lewis is available to speak to organizations of which you might be a member. Contact Gene 619-890-8447 or gene@ipcsg.org or Bill 619-591-8670 (bill@ipcsg.org) to coordinate.

Member John Tassi is the webmaster of our website and welcomes any suggestions to make our website simple and easy to navigate. Check out the Personal Experiences page and send us your story. Go to: https://ipcsg.org/personal-experience

FINANCES

We want to thank those of you who have made special donations to IPCSG. Remember that your gifts are tax deductible because we are a 501(c)(3) non-profit organization.

We again are reminding our members and friends to consider giving a large financial contribution to the IPCSG. This can include estate giving as well as giving in memory of a loved one. You can also have a distribution from your IRA made to our account. We need your support. We will, in turn, make contributions from our group to Prostate Cancer researchers and other groups as appropriate for a non-profit organization. Our group ID number is 54-2141691. Corporate donors are welcome!

DIRECTIONS TO MEETINGS

Directions to Sanford-Burnham-Prebys Auditorium
10905 Road to the Cure,
San Diego, CA 92121

- Take I-5 (north or south) to the Genesee exit (west).
- Follow Genesee up the hill, staying right.
- Genesee rounds right onto North Torrey Pines Road.
- **Do not turn into the Sanford-Burnham-Prebys Medical Discovery Institute or Fishman Auditorium**
- Turn right on Science Park Road. Watch for our sign here.
- Turn Left on Torreyana Road. Watch for our sign here.
- Turn Right on Road to the Cure (formerly Altman Row). Watch for our sign here.