

August 27, 2011

Caleb Briggs, Pharm.D.
Center for Drug Evaluation and Research
Food and Drug Administration

Dear Dr Briggs,

Upon learning of an ODAC review on prevention of bone metastases in prostate cancer I felt it was important for me to share some thoughts regarding this topic which is of significant importance to patients in my practice. I am a urologic oncologist and who dedicates about 80% of my time to clinical practice and research in the area of prostate cancer. Since I am unable to attend the meeting in person I will summarize some of the key points around this issue in writing.

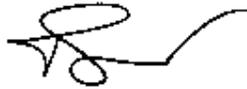
Please allow me first to introduce myself. I am Professor and Chair of the Division of Urology at the University of Montreal Hospital Center in Montreal Canada. I also have the privilege of chairing the National Cancer Institute of Canada (NCIC) Genito-Urinary (GU) site group and the Canadian Uro Oncology Group (CUOG) in Canada. Over the last 20 years I have been involved in both the design of studies and patient recruitment to clinical trials in the area of advanced prostate cancer. Treatment and prevention of bone metastases is one of my main research interests. I am pleased with the progress we have made in the treatment of metastatic prostate cancer over the last few years but am still frustrated by the number of trials that have failed in this area. Over the last 2 decades, we as researchers have agreed that delaying the appearance of bone metastases is a clinically significant endpoint that may further improve on the limited success we have had in treating metastatic prostate cancer. Many of us believe that this endpoint is a clinically relevant surrogate for an overall survival advantage. This endpoint has been used in almost all the randomized controlled studies I have been involved in that have studied non-metastatic high risk patients. Unfortunately it has been very frustrating to observe the number of successive trials that have failed to delay the appearance of bone metastases in patients at risk. I, as a researcher and clinician, was very pleased that for the first time a randomized placebo controlled was successful in delaying the appearance of bone metastases. The study using denosumab demonstrated a significant delay in the appearance of bone metastases in patients with non-metastatic castration resistant prostate cancer.

In terms of clinical relevance of delaying metastases I can say with conviction that in the clinical setting delaying the appearance of metastases is important to both patients and physicians. For patients it is clear that the psychologic and physical impact of bone metastases is very significant. The risk of bone complications increases dramatically and survival diminishes significantly. The indications (and need) for systemic therapy begin when metastases appear. With the appearance of metastases both cost and side effects related to systemic therapy increase enormously. The most recent example demonstrating that bone metastasis free survival is a valid endpoint comes from one of the largest ongoing intergroup studies in prostate cancer. Given the significance related to the appearance of bone metastases the large randomized clinical study ``RADICALS`` has

changed the primary endpoint of the study to bone metastases free survival instead of cancer specific survival. The RADICALS study is addressing the role of radiotherapy following surgery. The study is led by MRC (UK) and NCIC (Canada) and all involved agreed that delaying bone metastases as an endpoint was a robust surrogate for the survival endpoint and that delaying metastases would lead to a change in clinical practice.

In summary it is clear to me that bone metastases free survival is a valid and robust endpoint for clinical studies and is a clinically useful objective to aim for in our management of patients with prostate cancer.

Respectfully submitted

A handwritten signature in black ink, appearing to be 'Fred Saad', with a stylized flourish at the end.

Fred Saad MD FRCS
Professor and Chief of Urology
Director of Urologic Oncology
U of M Endowed Chair in Prostate Cancer
University of Montreal Hospital Center
Chairman, NCIC-CTG G-U Group and CUOG
Tel. 514-890-8000 ext 27466
Fax 514-412-7620
fredsaad@videotron.ca

Caleb Briggs, Pharm.D.
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
WO31-2428
Silver Spring, MD 20993-0002
Phone: 301-796-9001
Fax: 301-847-8533
E-mail: ODAC@fda.hhs.gov

Dear Dr. Briggs:

Unfortunately, I am unable to attend today's ODAC, September 14 2011 meeting; nonetheless, I am writing now because of my commitment to the both clinical research and present day therapy for patients with advanced prostate cancer, specifically for patients with metastatic castrate resistant prostate cancer. As the Medical Director of Carolina Urologic Research Center, we have participated for the last decade in many phase II/III trials for mCRPC protocols which have led to FDA approval and with several still in clinical trial accrual (as examples, denosumab, abiraterone, MDV3100, OGX-11, Tasquinimod, Cabazitaxel, Sipuleucel-T). Additionally, I am the Managing Partner of Atlantic Urology Clinics, a 16 physician Urology practice in Myrtle Beach, SC, where we care for and provide therapies for a large population of men with all stages of prostate cancer.

I would respectfully offer my thoughts on the following issues which may be germane to your hearing today:

1: Prostate cancer can manifest as a very heterogeneous disease, regarding clinical as well as molecular pathways of progression. Simplistically, we oftentimes bifurcate disease states as either androgen sensitive versus insensitive. Androgen deprivation is the cornerstone of therapy upon failure of localized therapeutic options (surgery, radiation, thermal ablation), and this remains a tenet of care both for the androgen sensitive/insensitive patient, e.g. M0/M1 CRPC. There is clearly no benefit, and in fact probable deleterious effect will ensue, if a CRPC patient is allowed to have his serum testosterone rise, which would result potentially with stimulation and progression of androgen sensitive cell lines, potentially exacerbating pain and cachexia of his existing disease, certainly macrometastatic and even theoretically micrometastatic as well. Hence, there is no literature or level one evidence, which I am aware of, which has ever supported cessation of ADT for the mCRPC patient.

2: While I completely applaud and agree with the importance of avoiding overt treatment with ADT, as either primary therapy or in certain cases of PSA relapse alone, and recognize that ADT assuredly has systemic side effects which must be carefully monitored and managed; the pace of progressive disease for the mCRPC patient is entirely different from the aforementioned examples. The patient with mCRPC,

who is not confounded by significant other medical co-morbidities which would reduce survival expectation, must assuredly continue on ADT despite the known side effects of testosterone reduction, as all trials to date which have manifested either progression or survival efficacy have mandated and required testosterone suppression.

3: Today, we face a sudden “embarrassment of riches” with respect to newly approved agents and extremely promising clinical trials for patients with mCRPC. Clearly, this is a very welcomed event, given our historical paucity of therapies prior to 2004 and the approval of docetaxel. Nevertheless, as we attempt to trial therapies to prevent progression of disease (e.g., bone metastases) and prolongation of survival (OS), we are confronted by the dilemma of patient therapeutic crossover to multiple approved therapies and very appealing clinical trial enrollment. Subsequently, our currently established endpoint of overall survival may be more difficult to achieve with statistical significance due to the frequency of crossover therapies, requiring increasingly larger population pools for adequate trial analysis. Hence, other appropriate and validated endpoints must be sought and implemented where academic consensus can be discerned. In addition to overall survival, the endpoint of prevention of SREs has been accepted, resulting in approvals of zoledronic acid and denosumab. Preventing bone metastasis is another time-to-event end point that is a direct clinical benefit in its own right, as has been well articulated by H. Scher et al. in *Journal Clinical Oncology*, August 22, 2011.

Thank you very much for reading and reviewing this written communication.

Respectfully yours,

Neal Shore, MD, FACS, CPI

Carolina Urologic Research Center

Atlantic Urology Clinics

823 82nd Parkway

Myrtle Beach, SC 29572