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# PCa Commentary

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## Clinical Update – New Information on Topics Presented in Earlier Commentaries

### CLINICAL UPDATE: ALPHARADIN

Alpharadin (Radium-223 Chloride) is a soon-to-be FDA approved radiopharmaceutical designed to target prostate cancer metastatic to bone. It was reviewed in full in *PCa Commentary, Vol.74 Mar/Apr 2012*.

In brief, as an alpha radiation emitter, the agent "delivers an intense and highly localized radiation dose (with a range of 2 to 10 cell diameters) to bone surfaces," (Petrylak, *Oncology*, 2012 Apr). This feature minimizes damage to surrounding hemopoietic cells. It is cytotoxic, killing cells directly, and "does not require cells to cycle in order to achieve its antitumor effect" (ibid).

Radium-223 is one of the four natural isotopes of Radium-88. Pharmacologically it mimics calcium in its bone-seeking action. This is the basis of the agent's specific targeting of areas of new bone formation occurring around tumor deposits where it selectively kills cancer cells. The advantage of Alpharadin over earlier radiopharmaceuticals is target specificity and minimal hematopoietic damage.

The agent is administered intravenously in an outpatient setting, has an excellent safety profile, and is usually administered in 4 to 6 monthly doses. It can be repeated.

Alpharadin is currently available through an "expanded access" protocol (<http://clinicaltrials.gov/ct2/show/NCT01516762?term=Alpharadin++expanded+access&rank=1>).

### WHAT'S NEW?

At the 2012 ASCO Genitourinary Conference Dr. Chris Parker presented abstract #8: "Overall survival benefit and safety profile of radium-223 chloride, a first-in-class alpha-pharmaceutical: Results from a phase III randomized trial (ALSYMPCA) in patients with castration-resistant prostate cancer (CRPC) with bone metastases." These results had been reported in September 2011, and based on the significant difference between the treatment and placebo arms the independent monitoring committee closed the trial, allowing the placebo patients to cross over to Alpharadin.

The men were symptomatic from the bony metastases, required pain medication, and had to display  $\geq 2$  sites of disease on a bone scan and no visceral components. Disease progression was an entry requirement based on new bone lesions or PSA rises. Fifty-eight men had progressed through Docetaxel therapy and the remainder were men unfit for chemotherapy. Six injections were given at monthly intervals.

**ALPHARADIN continued:****The Results:**

- The median overall survival for Alpharadin patients (n=615) was 14 months v. 11.2 for men (n=307) on placebo (some of whom were subsequently treated with radium-223).
- The median time to first new bone metastases was 13.6 months (Alpharadin) v. 8.4 months, placebo.
- Safety profile - Radium-223 v. placebo: significant (i.e. grade 3/4) neutropenia 1.8% v.0.8%; and thrombocytopenia, 4% v. 2%.
- Skeletal Related Events: Radium-223 v. placebo: pathologic bone fracture, 4% v. 7%; spinal cord compression, 3% v. 6%; external beam radiotherapy, 23% v. 27%. (as reported in abstract #9 by Dr. Oliver Sartor)

Alpharadin is the first therapy for bone metastases that has shown a survival benefit. Considering the excellent safety profile is it reasonable to envision subsequent retreatment with the agent.

An informative interview with Dr. Chris Parker including data and graphs ("Preview of ASCO GU 2012 Prostate Cancer Data - Biotech Strategy") can be found at <http://biotechstrategyblog.com/2012/01/preview-of-asco-gu-2012-prostate-cancer-data.html>). At this site scroll down to "Abstract #8.

**BOTTOM LINE:** Dr Sartor's abstract concludes: "Radium-223 is an effective therapy with a highly favorable safety profile and may provide a new standard of care for treatment of CRPC patients with bone mets."

## **DEGARELIX: WHAT'S OLD; WHAT'S NEW?**

**WHAT'S ALREADY KNOWN?**

DEGARELIX (Trade name, Firmagon) has been in clinical use since its FDA approval in December 2008 based on the results of a 12 month phase III study of its efficacy and safety as reported by Klotz et al. (BJU Int. 2008 Dec). The trial compared the now standard initial degarelix (D) dose of 240 mg s.c. followed by 80 mg monthly administrations to Lupron (L) 7.5 mg i.m. monthly. The enrollees either had a rising PSA following primary therapy for localized or locally advanced cancer or had metastases. The primary endpoint was the performance of each drug in keeping the testosterone level below 50 ng/dl over 1 year.

*Some major points for the study are cited below:*

**Mechanism of action:** Degarelix, an LHRH blocker, shuts down LH production directly, and in 1-3 days 96.1% of men dropped their testosterone (T) levels to <50 ng/dl (median T level 14 ng/dl). Lupron, which initially stimulates LH production before suppressing LH) was associated with a T increase to about 600 ng/dl in 3 days, a return to baseline in about 7, a further decrease to ~100 ng/dl on day 14. The goal of <50 ng/dl was reached by day 28.

**The Testosterone surge** associated with Lupron, while notable, *was not accompanied by an increase in PSA* and no adverse effects relating to increased bone pain or spinal cord compressions were noted. [This is in keeping with Morgantaler's concept of a testosterone "saturation threshold" which postulated that a T level above ~120 ng/dl does not raise PSA nor promote cancer growth - reviewed in Commentary Vol.70 Jul/Aug 2011.]

**Testosterone suppression:** From day 28 to 364 T was suppressed to below 50 ng/dl in 97.2% of men D v. 96.4% on L.

**%PSA change (median) from baseline:** Degarelix treatment led to about a 40% PSA decrease at 7 days, 60% at 14, 80% at 28, and about 90% at day 56. For Lupron the corresponding (approx.) numbers were: no change, day 7; 20% decrease, day 14; 65% at day 29 and 90% by day 56.

**DEGARELIX continued:**

Anti-androgen requirement: Since D led to no "surge" there was no need for an accompanying antiandrogen. Those men who took an antiandrogen with L had no "surge" and a similar PSA decrease as men on D.

Route of administration: The initial 240 mg dose of D was divided into two 120 mg 3 ml s.c. portions delivered to the abdomen and led to a painful reaction in 40% of men; the maintenance dose of 80 mg was 4 cc s.c. and is also associated with discomfort. Lupron dosage was 1 ml i.m. with <1% site discomfort.

On the basis of this phase III data degarelix was found "non-inferior" to Lupron and currently is in common usage as an alternative.

WHAT'S NEW?

- 1) An additional analysis of the findings in the phase III trial was reported by Tombal et al. (Eur Urol. 2010 May) with the focus on two subgroups: men whose baseline PSA was >20 ng/ml and men with metastases. In the phase III trial the criteria for PSA progression was "two consecutive increases in PSA of 50% compared with nadir *and*  $\geq 5$  ng/ml on two consecutive measurements."

Findings: "Patients receiving degarelix showed a significantly lower risk of PSA progression or death compared with leuprolide (p=0.05). PSA recurrences occurred mainly in patients with *advanced disease* and exclusively in those with *baseline PSA >20 ng/ml.*"

- 2) Additional information regarding the comparison of degarelix and Lupron was presented by Crawford et al. (J Urol. 2011 Sept) based on an additional 27.5 month extension trial following the 1 year phase III trial. This study compared one cohort which continued on degarelix and another group who had been in the Lupron arm of the Phase III trial but were then switched to degarelix in the follow-up study. The primary finding (supporting the results in the Tombal study) was that the increased risk of PSA progression seen in the Lupron group in the Phase III trial was reversed by the switch to degarelix.

The Study Conclusion: "Data support the statistically significant prostate-specific antigen progression-free survival for degarelix over leuprolide seen during" the 1 year phase III trial. The authors recommend moving degarelix to first-line position for androgen deprivation over Lupron and other similar drugs.

- 3) "Incomplete Testosterone Suppression in Prostate Cancer," was the title of an editorial by Drs. Crawford and Rove (N Engl J Med. 2010 Nov) in which they emphasized the need to *monitor* testosterone levels during treatment of men receiving medical androgen suppression with LHRH interfering drugs. As background, they noted that orchiectomy typically yields median T levels of 14 ng/dl.

Crawford cites Morote (J Urol. 2007 Oct) who reported that 25% of men on 3-month Lupron had T levels *above* 50 ng/dl and "only 44% had a level that was consistently below 20 ng/dl". "Breakthrough increases greater than this threshold [i.e. 50 ng/dl] predicted a lower survival free of androgen independent progression."

- 4) In "Testosterone in prostate cancer: the Bethesda consensus," (BJU Int. 2012 Aug), Crawford, Moul et al. noted that "Recently, the 50 ng/dl threshold has been questioned because of reports indicating worse outcomes when [T] levels between 20 and 50 ng/dl were studied." They recommended a target of 20 ng/dl for androgen suppression."

**BOTTOM LINE:** Degarelix and Lupron have many similarities but degarelix has some features that are superior to Lupron. Information about the candidates best served by degarelix is under evaluation.

## MDV3100 - NOW FDA APPROVED.

MDV3100 (trade name, Xtandi; generic name, enzalutamide) was recently approved on the basis of the results of the Phase III AFFIRM study. The trial was carried out on men with castrate-resistant prostate cancer who were progressing after 2 or more courses of Taxotere chemotherapy.

In this trial MDV3100 therapy yielded

- An estimated median overall survival of 18.4 months compared to 13.6 months for placebo and a 37% reduction of risk of death.
- Twenty-five percent of men showed PSA decline of >90%, and 54% had at least 50% decline.
- The first skeletal related event was postponed by 3.4 months, 16.7 v. 13.3 months.
- The median duration of treatment before failure was 8.3 months for MDV3100 patients v. 3 months for men on the placebo. Fatigue was the most common side effect.

Unlike the required use of prednisone with abiraterone, there is no need for the drug with MDV3100.

The FDA approval currently applies to only men with similar characteristics as those in the AFFIRM trial. (MDV3100 was reviewed in full in Vol.74 of the PCa Commentary.) The daily oral dose is 160 mg (tablet content, 40 mg) taken together with or without food. For information on reimbursement support call 855-898-2634.

Xtandi initially will be dispensed only through specialty pharmacies. The retail price is likely to range around \$7,000-\$8,000/month. Prescription authorization will be required from the source of insurance. (In the Capitol Hill area of Seattle Xtandi will be available at the Community Pharmacy, a Walgreens specialty pharmacy, at 1001 Broadway, Suite 1001 Phone 206-324-2335).

An ongoing trial of great clinical importance (NCT01212991) is studying MDV3100 in men with CRPC before chemotherapy. It is closed in the US as a result of sufficient enrollment, but is ongoing in Europe to achieve case balance. The study title is "A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients with Progressive Metastatic Prostate Cancer (PREVAIL)." Androgen deprivation is required.

If MDV3100 in this trial demonstrates effectiveness when compared to a comparator placebo the current paradigm for sequencing prostate cancer therapy is likely to change.

## MRI - An Emerging Role for Selecting Candidates for Active Surveillance.

THE GOAL: "The success of active surveillance as a management strategy for prostate cancer relies primarily on the accurate identification of patients with low-risk disease unlikely to progress" (Vargas, *J Urol*, 2012 Sept). In Vol.78 of the PCa Commentary data was presented supporting MR imaging as a valuable adjunct to standard criteria in choosing optimal candidates for AS. Recent published reports are adding strength to the usefulness of MRI in this role.

The various new studies incorporate several basic principles:

- MRI is the most accurate modality for visualizing the volume of a foci of cancer;
- Increasing tumor volume is related to increasing cancer grade;
- Small foci of biopsied Gleason 6 cancers are visualized poorly by MRI as opposed to more clearly seen tumors of higher grade and volume;
- The 20% of tumors in the distal apex of the prostate, seen well on MRI, are difficult to detect in transrectal ultrasound guided biopsies and can be missed (Nix J, *BJU Int* 2012 Oct).

**MRI continued:**

In the Vargas study, "Magnetic Resonance Imaging for Predicting Prostate Biopsy Findings in Patients Considered for Active Surveillance of Clinically Low Risk Prostate Cancer," T2-weighted MR imaging was interposed between the initial biopsy and a subsequent "confirmatory" biopsy.

The clarity of tumor visualization on MR was graded on a scale from 1 (definitely no tumor), and 2 (probably no tumor), to 5 (definitely tumor) and the size was recorded. Overall 20% of the initial biopsy Gleason scores were upgraded on the subsequent surgical specimen.

**Study Findings and Conclusions:**

"Magnetic resonance imaging scores of 2 or less had a high *negative predictive value* [for upgrading] of 96% and *specificity* of 95% [emphasis mine]. A ... score of 5 was highly sensitive for upgrading on confirmatory biopsy."

"Among patients initially diagnosed with clinically low-risk prostate cancer, those with tumors not clearly visualized on MRI were significantly more likely to demonstrate low risk features, while patients with tumors clearly visualized on MRI were significantly more likely to have disease upgraded on confirmatory biopsy."

Vargus further speculated that when *interpreted by a well-trained radiologist* the MRI may "obviate the need for a confirmatory biopsy in substantial numbers of patients."

Further support for MR imaging is presented by Margel et al, *J Urol. 2012 Apr*: "Impact of multiparametric endorectal coil prostate magnetic imaging on disease reclassification among active surveillance candidates: a prospective cohort study."

Their study evaluated 58 men with biopsied low-risk prostate cancer who then underwent multiparametric endorectal coil MR. A confirmatory biopsy was done within 1 year. The imaging results were stratified:

- "normal" study - meaning that the biopsied cancer was not visible on MR
- the detected lesion was <1 cm; and
- the lesion was >1 cm.

Consistent with many other studies, based on the confirmatory biopsy, 32% of men in the study were reclassified and no longer met the criteria for active surveillance. This included 13 men (22%) whose tumors were >1 cm.

**Results:** "When no cancer was identified on magnetic resonance imaging, only 2 cases (3.5%) were reclassified." "The positive and negative predictive value for MR predicting reclassification were 83% and 81%, respectively."

**BOTTOM LINE:** If the results of this small cohort can be validated with larger studies, the work of both Vargas and Margel will serve to solidify the role of MR as an important adjunct in the selection of men for active surveillance.

### **ASPIRIN: Its Benefits Confirmed**

Aspirin has achieved an excellent record of reducing the incidence and grade of prostate cancer and slowing the progression of the disease once diagnosed. Its many benefits and the contraindications to its use were fully reviewed in Commentary Vol.68, Mar/Apr, 2011. The take-home message was that daily low-dose ASA for 5 years reduced the risk of prostate cancer by 29% with longer usage resulting in the best outcome.

New information offers additional support for the usefulness of daily low-dose aspirin at all stages of the disease. *Four studies will be briefly reviewed.*

**ASPIRIN continued:**

- 1) A major study was reported by D'Amico, Carroll, et al. in the October, 2012, issue of JCO: "Aspirin Use and the Risk of Prostate Cancer Mortality in Men Treated with Prostatectomy or Radiotherapy." Under study were 5955 men with localized prostate cancer from the CaPSURE database. The 37% who were primarily aspirin users (mainly low-dose) were compared to nonusers. The median follow-up was 70 months.

Results at 10 years: The prostate cancer specific mortality (PCSM) for ASA users v. nonusers was 3% v. 8%. For men with high-risk disease the PCSM the results were even more impressive, 4% v. 19%. The risk of disease recurrence (ASA v. nonuse) was 28% v. 36%; and risk for bone metastases 3% v. 6%. There was a nonsignificant difference in PCSM favoring ASA use in men with low-risk disease at 10 years, 2% v. 4%, respectively.

Conclusion: "...use of aspirin was significantly associated with a reduction in PCSM."

- 2) "Aspirin but not ibuprofen is associated with reduced risk of prostate cancer: a PLCO study" (Shebl, et al., from the National Cancer Institute, Br J Cancer. 2012 Jun).

Results showed an 8% decrease in risk of a diagnosis of prostate cancer based on 29,450 men, ages 55-74 using one or more aspirin daily compared to never users.

- 3) Aspirin decreased early biochemical failure after radiotherapy, as concluded by Horwitz et al., from the Fox Chase Cancer Center, (Int J Radiat Oncol Biol Phys. 2012 Sep). This was the largest retrospective study of the issue and involved 2051 men, 36% of whom were taking aspirin.

The primary endpoint was biochemical failure (PSA nadir plus 2 ng/ml) occurring in the interval after treatment of less than 18 months, "which has been shown to be the single strongest predictor of distant metastases, prostate cancer survival, and overall survival after radiotherapy." The median follow-up was 75 months.

Results: The men not taking aspirin were two times more likely to experience PSA recurrence during the 18 month period as compared to nonusers.

- 4) While recognizing that "Epidemiologic and clinical data support a reduced risk of prostate cancer incidence with aspirin use," Stampfer and Giovannucci (Cancer Prevention Research. 2012 Sep) report "There was no association between aspirin use *after a prostate cancer diagnosis* and lethal disease... [Emphasis mine]. Their analysis was based on the 3986 men in the Health Professionals Follow-up Study during 18 years of follow-up.

**BOTTOM LINE:** New information about ASA further supports the beneficial effects of long-term, daily, pre-diagnosis, use of low-dose aspirin in reducing the incidence, progression, and death from prostate cancer.



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