

# Mitotic Rate a Game Changer in Melanoma Tx

BY DOUG BRUNK

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE CALIFORNIA SOCIETY OF DERMATOLOGY AND DERMATOLOGIC SURGERY

SANTA BARBARA, CALIF. – Current American Joint Committee on Cancer melanoma staging criteria incorporate a mitotic rate of 1/mm<sup>2</sup> or greater into the T1b classification, recognizing mitotic rate as an independent prognostic factor in patients with primary melanoma.

This change, which went into effect in January, “is going to have a profound impact in whom we consider eligible for staging with sentinel lymph node biopsy,” Dr. Susan Swetter predicted at the meeting. “The reason is that only about 6%-8% of these T1 tumors (1.0 mm) are ulcerated, but it is estimated that up to 30%-40% will have an elevated mitotic rate of 1.0 or more per square millimeter. This leaves us with a conundrum: Are all of these patients going to be eligible for sentinel lymph node biopsy?”



**‘The new AJCC guidelines incorporate mitotic rate in tumors that are less than or equal to 1.0 mm thick.’**

DR. SWETTER

AJCC melanoma staging criteria are based on data analysis from the 2008 AJCC collaborative melanoma staging database from 14 cancer centers and cooperative oncology organizations worldwide, said Dr. Swetter, professor of dermatology and director of the pigmented lesion and melanoma program at Stanford University Medical Center/VA Palo Alto Health Care System in California.

The criteria are based on prognostic factor analysis of nearly 60,000 patients to validate staging criteria and groupings for the 7th edition of the AJCC Cancer Staging Manual (Springer, New York), which was published in the fall of 2009 and became active in January 2010.

“The concept is that each stage grouping has a uniform risk for survival, and there are a wealth of patients per tumor node metastasis (TNM) categories, with more than 27,000 with stage I and II disease, more than 3,400 with stage III disease, and more than 7,600 with stage IV disease,” Dr. Swetter said.

The newest revision of the AJCC staging for melanoma involves no major changes for TNM and stage grouping criteria, with the exception of mitotic rate.

Other changes involve more advanced disease. For example, “immunohistochemical detection of nodal metastases is now acceptable, whereas only routine histology was used previously,” Dr. Swetter said. “Also, there is no longer a lower limit to designate node-positive disease. The size of the isolated tumor cells is no longer used, although that is quite controversial.”

Thickness of tumors is potentially a marker of duration of growth, with increasing tumor thickness correlating adversely with survival. According to the 2008 AJCC Melanoma Database, patients with tumor thickness of 0.01-0.55 mm have a 10-year survival rate of 95%, while those with a tumor thickness of 4.01-6.0 mm have a 10-year survival rate of 54%.

The most relevant correlate of a mitotic rate increase and its effect on prog-

nosis appears to be in thin tumors, Dr. Swetter said. “This is why the new AJCC guidelines incorporate mitotic rate in tumors that are less than or equal to 1.0 mm thick.”

Survival data from the 2008 AJCC Melanoma Database suggest there is little to no value in promoting sentinel lymph node biopsy in patients who have tumors up to 0.50 mm in depth, regardless of mitotic rate, because the survival

rate in these patients is excellent. Currently, the T1b designation is used for staging in terms of survival. “It is not a criterion in itself to perform sentinel lymph node biopsy,” Dr. Swetter emphasized. “There is some evolving data suggesting that mitotic rate as a continuous variable may be predictive of occult regional nodal disease.”

One published study suggests that sentinel lymph node biopsy is appropriate

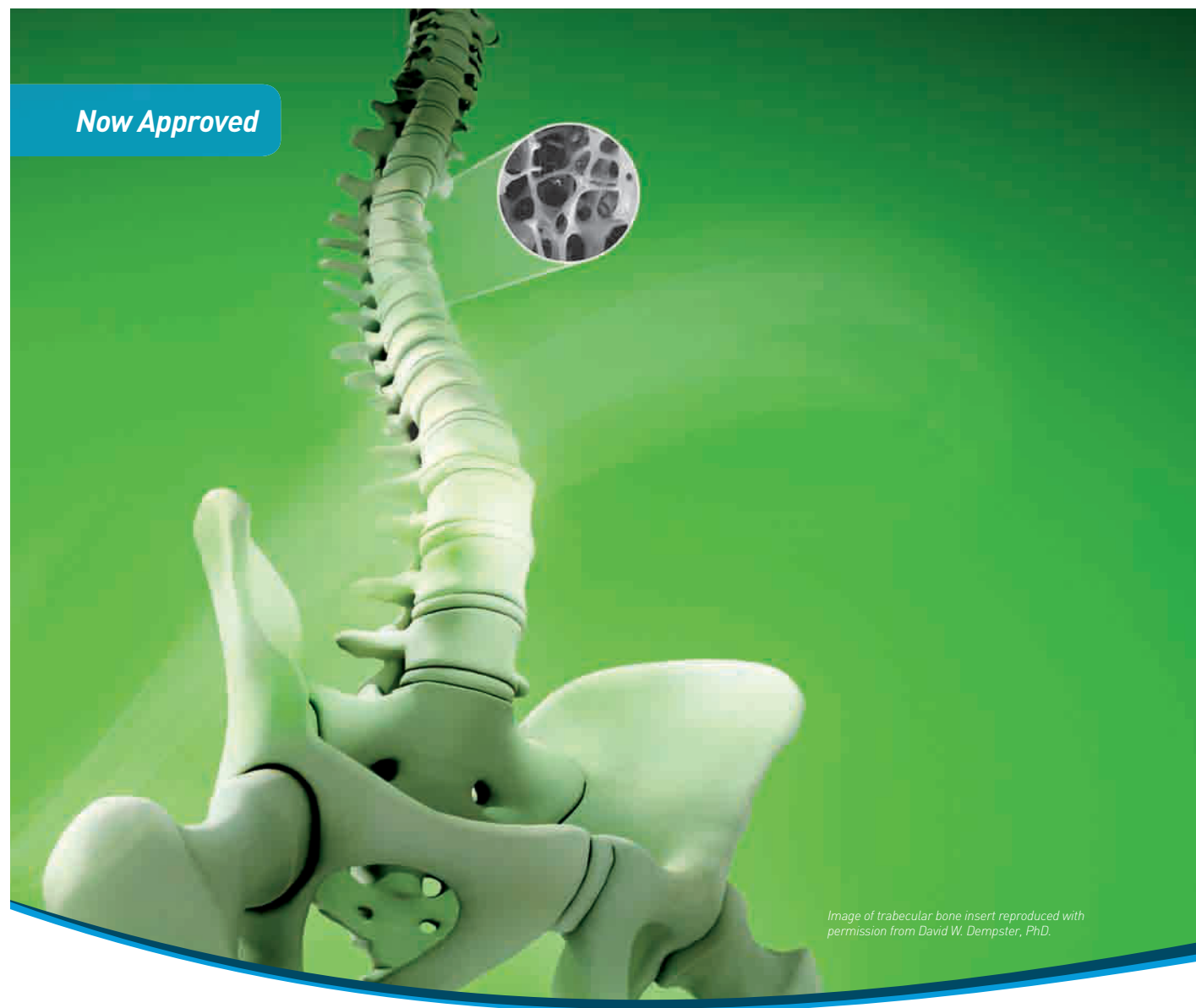


Image of trabecular bone insert reproduced with permission from David W. Dempster, PhD.

## INDICATION

**Prolia™ is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia™ reduces the incidence of vertebral, nonvertebral, and hip fractures.**

## IMPORTANT SAFETY INFORMATION

- ♥ **Hypocalcemia:** Prolia™ is contraindicated in patients with hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating Prolia™. Hypocalcemia may worsen, especially in patients with severe renal impairment. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, clinical monitoring of calcium and mineral levels is highly recommended. Adequately supplement all patients with calcium and vitamin D.
- ♥ **Serious Infections:** In a clinical trial (N = 7808), serious infections leading to hospitalization were reported more frequently in the Prolia™ group than in the placebo group. Serious skin infections, as well as infections of

the abdomen, urinary tract and ear, were more frequent in patients treated with Prolia™. Endocarditis was also reported more frequently in Prolia™-treated subjects. The incidence of opportunistic infections was balanced and the overall incidence of infections was similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. In patients who develop serious infections while on Prolia™, prescribers should assess the need for continued Prolia™ therapy.

- ♥ **Dermatologic Adverse Reactions:** Epidermal and dermal adverse events such as dermatitis, eczema and rashes occurred at a significantly higher rate in the Prolia™ group compared to the placebo group. Most of these events were not specific to the injection site. Consider discontinuing Prolia™ if severe symptoms develop.

- ♥ **Osteonecrosis of the Jaw (ONJ):** ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving Prolia™. An oral exam should

for patients with T1b melanomas, including those defined by mitotic rate (J. Natl. Compr. Canc. Netw. 2009;7:308-17).

"We are now awaiting publication of a larger analysis of patients with thin melanoma," Dr. Swetter said. "Both the National Comprehensive Cancer Network and the AAD [American Academy of Dermatology] melanoma panels are weighing in to establish an appropriate threshold in these T1b patients."

Dr. Swetter, who serves on both of the panels, noted that there is currently "very little enthusiasm from a surgical

perspective to be pursuing sentinel lymph node biopsy on every patient who is T1b by virtue of mitotic rate."

The National Comprehensive Cancer Network recommends that clinicians "discuss and offer" sentinel lymph node biopsy for patients with stage IB and stage II cutaneous melanoma, "recognizing that the sentinel node biopsy is an important staging tool, but its impact on overall survival is unclear," Dr. Swetter said.

The procedure should also be considered for stage IA melanomas with adverse features including positive deep margins, lymphovascular invasion, thickness of

0.75 mm or greater, or younger age.

The decision not to perform sentinel lymph node biopsy can be based on significant patient comorbidities, patient preference, or other factors.

An unresolved question is whether or not sentinel lymph node biopsy is a valid staging technique in older patients. "Older age is associated with worse prognosis, but lower rates of sentinel lymph node positivity," Dr. Swetter said. "The question is, why? One issue is whether there is different biology of melanoma in the elderly, or whether host immune factors come into play. Another [factor]

could be delayed lymphatic spread, or it might be that tumors are more likely to disseminate hematogenously in older patients, compared with younger patients."

In the future, Dr. Swetter predicted the emergence of individualized prognoses based on novel weighted mathematical equations using AJCC staging and other factors. A Web-based predictive tool for prognosis developed by the AJCC Melanoma Database is currently available at [www.melanomaprognosis.org](http://www.melanomaprognosis.org).

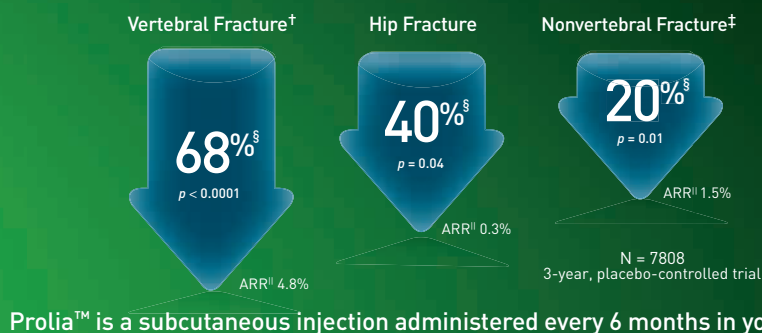
Dr. Swetter stated having no relevant financial conflicts to disclose. ■

In Treating Your Postmenopausal Osteoporosis Patients  
at High Risk for Fracture, Help . . .

## BE A FORCE AGAINST FRACTURE

Prolia™ targets and binds to RANK Ligand, inhibiting osteoclast formation, function, and survival<sup>1</sup>

Prolia™ significantly reduced fracture risk at key sites in a phase 3 trial\*<sup>1,2</sup>



Prolia™ is a subcutaneous injection administered every 6 months in your office<sup>1</sup>



Please see Brief Summary of Prescribing Information on the following page.

be performed by the prescriber prior to initiation of Prolia™. A dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with risk factors for ONJ. Good oral hygiene practices should be maintained during treatment with Prolia™.

For patients requiring invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ should receive care by a dentist or an oral surgeon. Extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia™ should be considered based on individual benefit-risk assessment.

**Suppression of Bone Turnover:** Prolia™ resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment are unknown. Monitor patients for consequences, including ONJ, atypical fractures, and delayed fracture healing.

**Adverse Reactions:** The most common adverse reactions (> 5% and more common than placebo) are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. Pancreatitis has been reported with Prolia™.

The overall incidence of new malignancies was 4.3% in the placebo and 4.8% in the Prolia™ groups. A causal relationship to drug exposure has not been established. Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity.

### Probia™ Postmarketing Active Safety Surveillance Program:

The Prolia™ Postmarketing Active Safety Surveillance Program is available to collect information from prescribers on specific adverse events. Please go to [www.proliasafety.com](http://www.proliasafety.com) or call 1-800-772-6436 for more information about this program.

\* Key sites: vertebral, hip, and nonvertebral.<sup>1,2</sup>

<sup>†</sup> Includes 7393 patients with a baseline and at least one post-baseline radiograph.<sup>1,2</sup>

<sup>‡</sup> Composite measurement excluding pathological fractures and those associated with severe trauma, fractures of the vertebrae, skull, face, mandible, metacarpals, fingers, and toes.<sup>1,2</sup>

<sup>§</sup> RRR = relative risk reduction.

<sup>||</sup> ARR = absolute risk reduction.

References: 1. Prolia™ (denosumab) prescribing information, Amgen. 2. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361:756-765.

For more information, visit [www.ProliaHCP.com/FPI](http://www.ProliaHCP.com/FPI)

NEW  
prolia™  
(denosumab) injection

©2010 Amgen Inc. All rights reserved.  
MC48223 8-10