

# High Responses in Melanoma for Wool Dye/Ocular Stain Rose Bengal

By Walter Alexander

Positive findings in treatment of metastatic melanoma were among the highlights of June's 2010 annual meeting of the American Society of Clinical Oncology (ASCO). For ipilimumab, there was the remarkable achievement of being the first to show a survival advantage in a randomized clinical trial. But whereas ipilimumab is an investigational human monoclonal antibody and a product of the most sophisticated of modern medical technologies, the agent in the second successful metastatic melanoma trial, Rose Bengal, has a more humble pedigree.

The clinical trial of Rose Bengal injections (PV-10, a 10% Rose Bengal solution) revealed a 79% response rate in metastatic melanoma patients, and showed responses in "bystander" lesions that were not injected, suggesting a systemic immune response, according to Sanjiv Agarwala, MD, who is section chief of oncology and hematology at St. Luke's Cancer Center in Bethlehem, Pennsylvania. But for the story of how Rose Bengal evolved in stages over more than 130 years from its original application as a coal tar-derived wool dye, Eric Wachter, PhD, Provectus cofounder and senior vice president, provided a history in an interview at ASCO.

## History of Rose Bengal

In 1882, German patent No. 32584 was granted to Ghnem for a new family of wool dyes. Ghnem took different halogens and added them to fluorescein to produce molecules with different colors. The name, Rose Bengal, arose presumably from the fact that the deep rosy red color was similar to that of the middle-of-the-forehead dot indicating marriage in women of the Bengali region of India. In *Chemistry of the Organic Dyestuffs* (Nietzki R. London, UK: Gurney & Jackson; 1892), the principal constituents of Rose Bengal were identified as iodine derivatives of di- and tetrachlorofluorescein, with those prepared from tetrachlorophthalic acid being the bluest. The original Rose Bengal version combined two iodines, and subsequent modifications through the 1920s adding

two more iodines led to the current form.

It was its color-imparting properties, however, that led to Rose Bengal's predominant medical use; in 1914 Römer, Cobb, and Lohlein reported on its role in combating ocular pneumococcal infections when added to Safranin Victoria Yellow. Kleefeld's discovery, in 1919, that Rose Bengal was an effective stain for visualizing corneal ulcers opened the door to its widespread use as an ocular biological staining agent. As Rosettes and Minims, that use continues today, based on separate improvements over many decades by Sjögren, Norm, and Marsh.

A parallel development of Rose Bengal as an intravenous marker for impaired liver function began in the 1920s through the work of Delprat. In the 1950s, Taplin devised a more sensitive radioisotope labeling with <sup>131</sup>I RB Diagnostic. By the late 1980s, radiolabel-

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ing had been eclipsed and replaced as the preferred diagnostic strategy when direct visualization of the liver was afforded by magnetic resonance imaging and computed tomography scanning.

None of this, of course, suggests anti-neoplastic efficacy. The application of Rose Bengal as a cancer treatment came about indirectly. Wachter and colleagues, all of whom had met working at Oak Ridge National Laboratory, were looking at photodynamic therapy, a process in which agents become cyto-

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toxic when exposed to light (usually from lasers), and in the late 1990s while looking for a candidate agent with anti-neoplastic activity, they hired a commercial data search service that identified several hundred potential substances. Through their own internal screening process they narrowed the candidates to only those agents with powerful effects, and among these was Rose Bengal.

At the same time that the Provectus preclinical tests were showing Rose Bengal to be worthy of deeper study, the researchers stumbled on a three-line sentence in a 1986 journal article (Ito A, et al. *J Natl Cancer Inst.* 1986; 77:277-281) on a study that was, in essence, a failed attempt to show cancer-stimulating properties in Rose Bengal, which was then used in Japan as a food-coloring agent (Red Food No. 105). The Japanese researchers noted no tumorigenicity for Rose Bengal in a strain of particularly tumor-prone mice, but offhandedly mentioned without comment that the higher the concentration of the Rose Bengal solution, the lower the tumor rate.

This further fired the Provectus Rose Bengal investigations and the next test, for Wachter, was giving up on the photodynamic treatment aspect. "I was a laser expert, and I was very psyched about finding this perfect molecule to go with our exciting laser techniques." His cofounders, Craig Dees (a molecular virologist) and Tim Scott (a chemical engineer), were worried that the laser/photodynamic technology was too sophisticated for routine use in the clinic, and that severe phototoxicity, requiring patients to stay not only out of direct sunlight but also away from intense indoor lighting for up to several weeks, would hamper wide acceptance. Dees and Scott, after a few months of modifications and testing, presented Wachter with incontrovert-

ible proof that the laser/photodynamic aspect was unnecessary to the dramatic anticancer effect of Rose Bengal, now in its PV-10 form. Subsequent animal and human studies confirmed that agent's potency and selectivity for ablating cancers.

## Rose Bengal for melanoma

The phase 2 trial presented at ASCO enrolled 80 patients with measurable stage III-IV melanoma, all of whom received initial treatment with PV-10 in up to 20 cutaneous, subcutaneous, or nodal lesions. Investigators were allowed to leave one or two lesions untreated. The primary end point was response rate of injected lesions.

Agarwala reported that among the first 40 subjects to complete the study, 33% achieved complete remission, 28% partial remission, and 20% stable disease in their target lesions. Also, 33% of 21 subjects with evaluable bystander lesions achieved complete remission of these lesions, along with 10% achieving partial remission, and 14% achieving stable disease. Mean progression-free survival for all subjects was 8.5 months. Patients with complete remissions achieved significantly longer progression-free survival (11.1 months) than those with stable disease or progressive disease (2.8 and 2.7 months, respectively).

No grade 4 or 5 adverse events were attributed to PV-10, and overall, adverse events were predominantly mild to moderate.

Agarwala concluded that, "The safety and efficacy profile of PV-10 compares favorably with available and emerging options for this patient population."

Beyond melanoma, PV-10 is currently being evaluated in treatment of primary and metastatic tumors of the liver. Ultimately, systemic administration of PV-10 may be explored for certain indications, Wachter said. ●

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