Reviewer's report

Title: A word of caution: Do not wake sleeping dogs. Micrometastases of melanoma suddenly grew after progesterone treatment.

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Reviewer: mario santinami

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Mordoh, J et al present in their manuscript the case of a young woman with a histopathologic diagnosis of a stage IIB primary cutaneous melanoma undergone to a wide excision and without evidence of regional node metastases after a sentinel lymph-node biopsy, the patient entered into a randomized Phase II/III clinical study comparing the CSF470 vaccine plus BCG plus GM-CSF versus IFN-alpha 2b and she was assigned to the vaccine arm. After two years of negative follow up, the patient was treated her with three cycles of 200mg progesterone/day for ten days for ovary dysfunction and three month after an ultrasound exam revealed multiple, large melanoma metastases in the liver. The authors support the hypothesis that the administration of progesterone and the relapse of disease could be related.

The skin expresses estrogen, progesterone, and androgen receptors. In the presence of steroid hormones, such as those contained in oral contraceptives, the skin likely responds to hormonal signals that control the cell cycle, apoptosis, DNA replication, and other cellular functions. Some estrogen-responsive pathways have the potential to promote tumor development, including the augmentation of epidermal growth factor signaling, the expression of proto-oncogenes, and inhibition of apoptosis. The question of whether progesterone increases the risk for the development of skin cancer, particularly melanoma, is still an area of concern. The most of the available studies on this topic suggest that while the skin responds to estrogens, progestins, and androgens, these responses do not significantly increase the risk of developing skin cancer when estrogen exposure is not excessive.

This manuscript could be of interest for the melanoma community in order to evaluate and to discuss whether an higher dose of progesterone could support a role in the development of skin cancer in and particularly of melanoma and could be considered for publication

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.