



US009410205B2

(12) **United States Patent**
Bogunovic et al.

(10) **Patent No.:** **US 9,410,205 B2**
(45) **Date of Patent:** **Aug. 9, 2016**

(54) **METHODS FOR PREDICTING SURVIVAL IN METASTATIC MELANOMA PATIENTS**

(75) Inventors: **Dusan Bogunovic**, New York, NY (US);
Nina Bhardwaj, West Orange, NJ (US);
David O'Neill, New York, NY (US)

(73) Assignee: **New York University**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 603 days.

(21) Appl. No.: **12/932,068**

(22) Filed: **Feb. 17, 2011**

(65) **Prior Publication Data**

US 2011/0275089 A1 Nov. 10, 2011

Related U.S. Application Data

(60) Provisional application No. 61/305,870, filed on Feb. 18, 2010.

(51) **Int. Cl.**
G01N 33/574 (2006.01)
C12Q 1/68 (2006.01)

(52) **U.S. Cl.**
CPC **C12Q 1/6886** (2013.01); **G01N 33/5743** (2013.01); **C12Q 2600/106** (2013.01); **C12Q 2600/118** (2013.01); **C12Q 2600/158** (2013.01); **G01N 2800/52** (2013.01)

(58) **Field of Classification Search**
USPC 435/7.23, 6.14
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

7,615,349 B2 11/2009 Riker et al.
2008/0113360 A1 5/2008 Riker et al.
2008/0118462 A1 5/2008 Alani et al.
2010/0076691 A1 3/2010 Palucka et al.

OTHER PUBLICATIONS

Niezabitowski et al. (Journal of Surgical Oncology 1999, 70:150-160).*

Fecher et al., "Toward a molecular classification of melanoma", J Clin Oncol, 2007, vol. 25, pp. 1606-1620.

Balch et al., "Predicting outcomes in metastatic melanoma", J Clin Oncol, 2008, vol. 26, pp. 168-169.

Haqq et al., "The gene expression signatures of melanoma progression", Proc Natl Acad Sci USA, 2005, vol. 102, pp. 6092-6097.

Jaeger et al., "Gene expression signatures for tumor progression, tumor subtype, and tumor thickness in laser-microdissected melanoma tissues", Clin Cancer Res, 2007, vol. 13, pp. 806-815.

John et al., "Predicting clinical outcome through molecular profiling in stage III melanoma", Clin Cancer Res, 2008, vol. 14, pp. 5173-5180.

Piras et al., "The predictive value of CD8, CD4, CD68, and human leukocyte antigen-D-related cells in the prognosis of cutaneous malignant melanoma with vertical growth phase", Cancer, 2005, vol. 104, pp. 1246-1254.

Sato et al., "Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer", Proc Natl Acad Sci USA, 2005, vol. 102, pp. 18538-18543.

Galon et al., "Type, density, and location of immune cells within human colorectal tumors predict clinical outcome", Science, 2006, vol. 313, pp. 1960-1964.

Clemente et al., "Prognostic value of tumor infiltrating lymphocytes in the vertical growth phase of primary cutaneous melanoma", Cancer, 1996, vol. 77, pp. 1303-1310.

Mihm et al., "Tumor infiltrating lymphocytes in lymph node melanoma metastases: A histopathologic prognostic indicator and an expression of local immune response", Lab Invest, 1996, vol. 74, pp. 43-47.

Dave et al., "Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells", N Engl J Med, 2004, vol. 351, pp. 2159-2169.

Attis et al., "Mitotic rate in melanoma: A reexamination", Am J Clin Pathol, 2007, vol. 127, pp. 380-384.

Francken et al., "The prognostic importance of tumor mitotic rate confirmed in 1317 patients with primary cutaneous melanoma and long follow-up", Ann Surg Oncol, 2004, vol. 11, pp. 426-433.

Liu et al., "Correlation of subjective self-reported melanoma growth rate with objective tumor proliferation markers", Arch Dermatol, 2008, vol. 144, pp. 555-556.

Reddy et al., "Cell proliferation markers in predicting metastases in malignant melanoma", 1995, J Cutan Pathol, vol. 22, pp. 248-251.

Agarwala, "Current systemic therapy for metastatic melanoma", Expert Rev Anticancer Therapy, 2009, vol. 9, pp. 1-18.

Yang et al., "The history and future of chemotherapy for melanoma", Hematol Oncol Clin N Am, 2009, vol. 23, pp. 583-597.

Bhatia et al., "Treatment of metastatic melanoma: An overview", Oncology, 2009, vol. 23, pp. 488-496.

Mouawad et al., "Treatment for metastatic malignant melanoma: Old drugs and new strategies", Critical Reviews in Oncology/Hematology, 2010, vol. 74, pp. 27-29.

Bhardwaj et al., "TLR Agonists: Are they good adjuvants?", Cancer J, 2010, vol. 16, pp. 382-391.

Rosenberg et al., "Adoptive cell therapy for the treatment of patients with metastatic melanoma", Curr Opin Immunol, 2009, vol. 21, pp. 233-240.

(Continued)

Primary Examiner — Yan Xiao

(74) Attorney, Agent, or Firm — Klauber & Jackson LLC

(57) **ABSTRACT**

Cellular and genetic signatures and methods of using same for subcategorizing stage III melanoma tumors are described herein. The signatures and methods are particularly useful with regard to establishing more distinct criteria on which basis to differentiate stage IIIB and IIIC melanoma patients. Assessment of the cellular and genetic signatures of a melanoma sample using methods described herein yields information on which basis differential survival duration and sensitivity to various cancer therapies can be predicted for a Stage IIIB or Stage IIIC melanoma patients. As described herein, gene expression profiling, determination of mitotic index (MI), and quantification of tumor infiltrating leukocytes (TILs) and CD3+ cells in metastatic lesions may be utilized to predict or assess drug response, drug sensitivity, and clinical outcome in metastatic melanoma patients.