The status of PD-L1 and tumor-infiltrating immune cells predict resistance and poor prognosis in BRAFi-treated melanoma patients harboring mutant BRAFV600

R. Nassini[1], D. Massi[2], D. Brusa[3], B. Merelli[4], C. Falcone[5], G. Xue[6], A. Carobbio[6], G. Baroni[2], E.Tamborini[7], L. Cattaneo[8], V. Audrito[3], S. Deaglio[3,9], M. Mandalà[4]

[1]Unit of Clinical Pharmacology and Oncology, Dept. of Health Sciences, University of Florence, Firenze
[2]Division of Pathological Anatomy, Dept. of Surgery and Translational Medicine, University of Florence, Firenze
[3]Human Genetics Foundation (HuGeF), Turin
[4]Unit of Medical Oncology, Dept. of Oncology and Hematology, Papa Giovanni XXIII Hospital, Bergamo
[5]Research Foundation, Papa Giovanni XXIII Hospital, Bergamo, Italy
[6]Dept. of Biomedicine, University Hospital of Basel, Basel, Switzerland
[7]Experimental Molecular Pathology, Dept. of Pathology, National Cancer Institute, Milan
[8]Division of Pathological Anatomy, Papa Giovanni XXIII Hospital, Bergamo
[9]Dept. of Medical Sciences, University of Turin, Turin, Italy

At the disseminated stage, melanoma is an incurable disease. For several years the standard of care of metastatic melanoma patients was limited to the administration of a single cytotoxic agent (dacarbazine, temozolomide or fotemustine). The understanding of the genetic heterogeneity underlying melanoma has revolutionized treatment options for metastatic melanoma patients (MMP). The finding of somatic mutations in the BRAF oncogene in ~40-50% of melanoma patients paved the way to the introduction of BRAF inhibitors (BRAFi, vemurafenib and dabrafenib) as a standard treatment in locally advanced or metastatic melanoma patients with BRAFV600 mutation. The oncogenic BRAF contributes to immune evasion, for this reason, BRAFV600 mutation targeting may increase the melanoma immunogenicity (Sumimoto et al., 2006). BRAFi improve survival in metastatic melanoma patients but the duration of clinical benefit is limited by development of drug resistance. Within the first 2 weeks of therapy, the expression of immunomodulatory molecules on the tumor cell surface, such as programmed death ligand 1 (PD-L1 or B7-H1) and programmed death-1 (PD-1) in T lymphocytes, are increased (Frederick et al., 2013). Data in vitro or from animal models propose PD-L1 as a potential mechanism that favors BRAFi resistance through the modulation of host immune responses (Jiang et al., 2013).
Recently, we showed that PD-L1 expression is increased in metastatic melanomas when compared with primary lesions and that PD-L1 expression behaves as a negative prognostic factor in MMP (Massi et al., 2014).
Here, we investigated whether the expression of programmed death-ligand 1 (PD-L1) and the density of tumor-infiltrating mononuclear cells (TIMC) predict the occurrence of resistance, hence affecting the clinical outcome in BRAFi-treated MMP.
PD-L1 expression was analyzed by immunohistochemistry with two different antibodies in 20 BRAFV600-mutated formalin-fixed and paraffin-embedded samples from 80 consecutive MMP treated with BRAFi at a single institution. TIMC were evaluated by conventional hematoxylin and eosin staining. Forty-six and 34 patients received BRAFi, vemurafenib and dabrafenib, respectively. Membranous expression of PD-L1 was detected in 28/80 (35%) of patients. At multivariate analysis, absence of tumoral PD-L1 staining (OR 10.8, 95% CI 2.7–43.3, $P < 0.001$) and the presence of TIMC (OR 6.5, 95% CI 1.7–24.3, $P < 0.005$) were associated with a better response to treatment. Median progression-free survival (PFS) and overall survival were 10 and 15 months, respectively. By multivariate assessment, PD-L1 expression (HR 4.3, 95% CI 2.1–8.7, $P < 0.0001$) and absence of TIMC (HR 2.5, 95% CI 1.4–4.7, $P < 0.002$) correlated with shorter PFS. PD-L1 overexpression (HR 6.2, 95% CI 2.8–14.2, $P < 0.0001$) and absence of TIMC (HR 3.1, 95% CI 1.5–6.5, $P < 0.002$) were independent prognostic factors for melanoma-specific survival.
The results provide the first proof-of-principle evidence for the predictive and prognostic relevance of PD-L1 immunohistochemical expression and density of immune cell infiltration in BRAFV600-mutated MMP treated with BRAFi.

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