Monitoring PD-L1 expression on circulating tumor cells (CTCs) and circulating myeloid derived-suppressor cells (MDSC) during anti-PD1 therapy

Myriam Delaunay a,b,d, Nicolas Guibert MD a,b,d, Amélie Lusque e, Nadia Boubekteur b,c, Magali Farella b,c, Isabelle Rouquette MD f, Estelle Clermont f, Aurélien Fortoul b,c, Inge Dormoy a, Pierre Fons, PhD b Michaël Esquerre, PhD b Gilles Favre, PharmD, PhD b,c,d, Anne Pradines PhD b,c, Julien Mazieres MD, PhD a,b,d a Thoracic Oncology Department, Larrey Hospital, University Hospital of Toulouse, France b Institut Claudius Regaud, IUCT-Oncopole, Laboratoire de Biologie Médicale Oncologique, Toulouse, France c Institut Claudius Regaud, IUCT-Oncopole, Bureau des Essais Cliniques, Toulouse, France d Institut Claudius Regaud, IUCT-Oncopole, Laboratoire d'anatomopathologie, IUCT-Oncopole, Toulouse, France e EVOTEC SAS, Toulouse, France

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Purpose:
Inhibitors of the immune checkpoint PD-1/PD-L1 (ICI) have become a care standard in non-small cell lung cancer (NSCLC). To date, neither predictive nor prognostic circulating biomarkers have been identified. We hypothesized that monitoring Myeloid-derived suppressor cells (MDSC) and PD-L1 staining of circulating tumor cells (CTCs) may represent valuable biomarkers.

Experimental Design:
For CTC analysis, blood samples were collected from patients with advanced NSCLC before PD-1 inhibitor treatment, at first follow-up and at progression. CTCs were isolated using a cell size-based technology. PD-L1 expression was assessed by immunofluorescence on CTCs and immunohistochemistry on tissue. For MDSC analysis, percentage of early MDSC: e-MDSC (LIN+/CD14+/CD15+/HLA-DR+/CD33+), monocytic-MDSC: M-MDSC (HLA-DR low+/CD14+/CD15+/CD11b+), polymorphonuclear-MDSC: PMN-MDSC (HLA-DR low+/CD14+/CD15+/CD11b+) were analyzed through flow cytometry at baseline and after one month of treatment.

Results:
96 patients were included for CTC analysis. No correlation between tissue and CTC PD-L1 expression at baseline was observed (r=0.04, p=0.77). Pretreatment CTC number was associated with increased risk of death and progression (HR1.06, p=0.03 for OS; HR1.05, p=0.02 for PFS). The presence of pretreatment PD-L1 expression on CTCs (≥1%) was more frequent High in the “non-responders” group (PFS<6months)(p=0.04), while the persistence of high PD-L1 expression on CTCs (≥10%) at the first follow-up was more frequent in “responders” group (p=0.06). For MDSC analysis 70 patients and 20 healthy donors were included. When compared to healthy donors, patients had significantly higher M-MDSC levels (median: 3.96% (0.08-24.18) vs 2.04% (0.33-4.29), p<0.01). M-MDSC before anti-PD-1 was associated with increased risk of death and progression (HR:1.07 [1.01;1.14], p=0.02 for OS;HR:1.08[1.03;1.15], p<0.01 for PFS). After one month of treatment, median M-MDSC percentage was higher in progressors (PFS<2months) than long-responders (PFS>12months)(4.38% (1.22-11.32) vs 1.85% (0.27-7.02)).

Conclusion:
PD-L1 expression on tissue and CTCs are discordant, CTCs being more likely positive. Pretreatment PD-L1(+) CTCs are associated with poor response, while the persistence of high PD-L1 expression on CTCs at
the first follow-up is associated with benefit. A baseline high level of M-MDSC is associated with poor survival and may be a prognostic biomarker.