Title of Research
Baseline Neutrophil-to-Lymphocyte Ratio and Benefit from Ipilimumab

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Summary of Research
In recent years, peripheral blood cell markers of systemic inflammation have been recognized as prognostic factors for cancer patients. Recently, we have analyzed the prognostic relevance of hematological parameters of metastatic melanoma patients receiving ipilimumab, and we have shown that pre-therapy neutrophil counts (ANC), neutrophil-to-lymphocyte ratio (NLR), and derived NLR (dNLR) are associated with patient outcome.

Briefly, in the first study (Ferrucci et al, Br J Cancer, 2015), we showed that patients presenting with an elevated pre-therapy NLR had a 2.6-fold increased risk of progression (HR2.63, 95%CI1.51–4.55, p=0.0006) and a 4-fold increased risk of mortality (HR4.17; 95%CI2.17–7.69, p<0.0001) compared with patients with lower NLR, independently of age, sex, performance status, and lactic acid dehydrogenase (LDH) levels. In the second study (Ferrucci et al, Ann Oncol, 2016), we analyzed data from 720 patients who participated in the Italian expanded access program for ipilimumab, and we showed that baseline ANC and dNLR were significantly associated with outcomes of ipilimumab-treated melanoma patients, in terms of disease progression and death (p<0.0001 for all). Moreover, patients with both elevated pre-therapy ANC and dNLR had a significantly increased risk of death (HR5.76; 95%CI 4.29–7.75) and of progression (HR4.10; 95%CI 3.08–5.46) compared with patients with both lower ANC and dNLR, independently of other known prognostic factors. Strikingly, the 1-year and 2-year survival rates were 2% and 0%, respectively, for patients with elevated ANC and dNLR, and 43% and 24%, respectively, for patients with both lower ANC and dNLR. Taken together, our findings showed that although lower ANC, NLR, or dNLR were not sufficient to warrant ipilimumab efficacy, they were associated with greater survival. It is noteworthy that these markers are measured before therapy initiation. Unfortunately, the design of both studies (which lacked a proper control arm population not receiving ipilimumab) did not allow us to establish whether ANC, NLR, and dNLR are general prognostic markers or predictive markers for response to ipilimumab.

More recently, we have analyzed the prognostic relevance of hematological profiles (including the NLR) in 127 metastatic melanoma patients included in our institutional tumor registry (Gandini et al, Int J Cancer, 2016, in press). Most of these patients (115/127, 90%) were treated before the advent of ipilimumab. Our preliminary results show that in this cohort, an elevated NLR is once again significantly associated with poorer overall survival, although with a less increased risk of death (HR2.87; 95%CI 1.75–4.70).

These observations lead us to hypothesize that baseline NLR, ANC, and dNLR might be predictive markers for benefit from ipilimumab. The aim of this proposal is to address this issue.

Melanoma is a potentially fatal type of skin cancer that can frequently spread to other parts of the body despite chemotherapy. Ipilimumab is a novel agent that has been shown to be quite effective in treating patients with melanoma. However, despite its effectiveness, many patients with melanoma do not respond adequately to ipilimumab and experience progression of disease and eventually death. This study hopes to assess if simple findings on routine blood tests could be used to predict how patients will respond to treatment with ipilimumab.

Our group has previously shown that the pre-treatment ratio of two different types of white blood cells, neutrophils and lymphocytes, and the total number of neutrophils, can predict which patients with melanoma being treated with ipilimumab are more likely to do poorly. However, these findings are limited in the sense that they cannot confirm if these blood tests can be used to predict how well patients will respond to ipilimumab since we did not assess their significance in patients who were getting a placebo drug or some alternate treatment.

Study Design
With this proposal, we ask Bristol-Myers Squibb to share clinical data from two sponsored trials: NCT00094653 and NCT00324155.We will test the hypothesis that baseline NLR is a predictive biomarker for benefit from ipilimumab treatment in advanced melanoma patients. We would need information on baseline clinical characteristics of patients, baseline hematology (full blood cell count with differential count and LDH levels), and patient outcomes (overall survival, progression-free survival, response to treatments).In this study, using data from two sponsored trials by Bristol-Myers Squibb, a global biopharmaceutical company, we will analyze whether blood tests can accurately predict how patients enrolled in these clinical trials respond to ipilimumab. We will acquire history and information about these patients from before the start of treatment, including their neutrophil to lymphocyte ratio (NLR), their absolute neutrophil count (ANC) and other relevant information and assess if this data can be used to predict patients most or least likely to benefit from being treated with ipilimumab.

Study Population
Patients randomized in the two phase 3 trials NCT00094653 and NCT00324155

Funding Source of Research
No funding resources and no need for funding

Conflicts of Interests
Pier Francesco Ferrucci: BMS advisory boards participation, consultancies, travelling.

Requested Studies
CA184-002 (NCT00094653): A Randomized, Double-Blind, Multicenter Study Comparing MDX-010 Monotherapy, MDX-010 in Combination With a Melanoma Peptide Vaccine, and Melanoma Vaccine Monotherapy in HLA-A2*0201-Positive Patients With Previously Treated Unresectable Stage III or IV Melanoma

CA184-024(NCT00324155): A Multi-Center, Randomized, Double-Blind, Two-Arm, Phase III Study in Patients With Untreated Stage III (Unresectable) or IV Melanoma Receiving Dacarbazine Plus 10 mg/kg Ipilimumab (MDX-010) vs. Dacarbazine With Placebo