Editorial

PD1/PD-L1 inhibitor treatment for late stage non-small cell lung carcinoma, sometimes…does more harm than good!

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Despite the major advances in treatment of lung carcinomas, in particular of advanced or metastatic non-small cell lung carcinomas (NSCLC) with immunotherapies, a high number of patients do not benefit from this effective treatment. These patients either do not express a sufficient level of biomarkers of companion or complementary tests [PD-L1 and tumor mutational burden (TMB)] for anti-PD1/PD-L1 treatments, or, do not respond to immunotherapies and even worse have a rapid progression of their tumor. The patients who are treated with immunotherapy with a poor clinical presentation with rapid and fatal consequences enter into the group of hyperprogressors (1-5). Recent studies have attempted to better characterize this population of patients by determining their clinical and biological parameters but so far the number of patients that have been studied is quite low (2,6,7).

The study by Ferrara *et al.* describes a large series of advanced stage or metastatic NSCLC patients with hyperprogressive tumors that develop following immunotherapy (8). This study included characterization of hyperprogressors treated with chemotherapy too, a population considered as a control (8). The radiological images of this multi centric French study were centralized and examined by two experts of the Gustave Roussy Institut (Villejuif, France) (8). The criteria for defining a hyperprogressor were based on the radiology and the tumor growth rate (TGR), represented by the sum of the diameters of the tumor before and after treatment for two months with immunotherapy. Evaluation was performed according to Response Evaluation Criteria in Solid Tumours (version 1.1) (RECIST) criteria. The same approach was applied to a population of patients treated with chemotherapy. Among the 406 patients treated with immunotherapy, 13.8% showed radiological criteria corresponding to a hyperprogressive tumor (8). It is noteworthy that before treatment these patients showed at least two metastatic sites in comparison to treated non hyperprogressor patients (8). As in other studies the survival time of hyperprogressors was very short, on average two months (2,8). In contrast, the epidemiological parameters described recently in the study of Champiat *et al.* were not detected with this new series of patients (2,8). Particularly, there were no additional hyperprogressors among the patients older than 65 years. The study by Ferrara *et al.* also analyzed a control population treated with chemotherapy (8). This population included 59 patients amongst whom 3 patients showed hyperprogressive tumors (8). Even if the number of patients in this group was low it is certain that the hyperprogressive phenotype is more frequent in patients treated with immunotherapy compared to patients treated with chemotherapy.

The study by Ferrara *et al.* holds a number of limitations, some of which are greatly underlined by the authors themselves (8). In fact the majority of patients (more than 70%) were not evaluated for the PD-L1 status by immunohistochemistry before administration of

immunotherapy using as second-line treatment nivolumab. In addition, analysis of the TMB was not performed. So no potential correlation between hyperprogressive tumors and the status of two biomarkers of strong interest analyzed alone or in combination was obtained. In addition, the study only analyzed patients treated with second-line and not first-line immunotherapy. It would have been interesting to compare the frequency and profile of the patients presenting with hyperprogressive tumors in these two populations of treated patients. Likewise, very few patients in this study received a combination of nivolumab and ipilimumab (8). Most cases had adenocarcinomas (more than 70%) rather than epidermoid carcinomas, which makes difficult comparative analyses between the different histological types. Moreover, analysis of genetic or immunopathological biomarkers was not performed. More specifically, no DNA from tissue or blood was analyzed by high throughput sequencing to look for genomic alterations that are predictive of response to immunotherapy. Thus, the pathophysiological mechanisms behind the frequency of hyperprogression among the studied patients were not discussed. Finally, it would have been interesting to use this large cohort of patients to compare the RECIST (version 1.1) criteria with the ir (immune-related) RECIST criteria and the iRECIST (9,10).

The symptoms of hyperprogressive disease of patients treated with immunotherapy urgently merit identification and compilation to perform studies comparing tissue and blood biomarkers. As underlined in the study of Ferrara *et al.* and, by other series, the prognosis of patients with this syndrome is very poor and, considering the exponential increase in the number of patients receiving first- and second-line immunotherapy, a biological indicator identified prior to treatment that predicts the progress of patients is strongly needed (2,8). Of course this is applicable to all patients, but even more to populations of fragile patients, in particular the elderly for whom it is more difficult to propose immunotherapy (11). Distinction of pseudoprogression may be difficult from a radiological standpoint but favorable progression of this latter syndrome allows the difference to be made (10,12). The frequency of the hyperprogressive syndrome varies according to the type of solid tumor and correlation with biomarkers that differ among pathologies must be obtained. Some studies have shown amplification in *MDM2* or certain mutations in *EGFR* that may be associated with a hyperprogression syndrome in patients presenting with metastatic lung cancer but the number of published cases is too low to validate these genomic biomarkers in clinical routine practice. Other biological indicators may also tend toward genetic predisposition and research into genes of susceptibility is certainly a domain to be rapidly explored. Recently, Lo Russo *et al.* showed that in patients who develop hyperprogressive tumors the majority of macrophages have an M2 phenotype (CD163+/CD33+ and PD-L1+) (13). Using a murine xenograft model of lung carcinoma the authors showed that a mechanism of macrophage reprogramming associated to the tumor occurred subsequent to immunotherapy-induced recruitment of the Fc receptor (13).

Even if the tumor hyperprogressive syndrome has not yet been described in early stage NSCLC patients receiving neoadjuvant immunotherapy it is possible that this may occur in the near future. This underlines too the need to better understand the pathophysiology of this syndrome and to rapidly find tissue and/or blood predictive biomarkers. The progress made into the knowledge of biological mechanisms associated to immunotherapy, considering the respective impact of the host and the tumor, should certainly help in the near future to stratify therapeutic decisions, in particular using algorithms that integrate prediction of hyperprogressive tumors (14).

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Footnote

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