



The power of immunotherapy plus platinum–based chemotherapy for locally advanced or early stage non-small cell lung cancer

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Immunotherapy alone or combined with chemotherapy has drastically reconfigured first-line treatment of patients with non-small cell lung carcinoma (NSCLC) (1,2). Until recently, treatment concerned stage IIIB/IV tumors showing no *EGFR*, *ALK*, *ROS1*, *BRAF* or *NTRK* genomic alterations (1).

The treatment of locally advanced initially non surgically resectable tumors [stage IIIA (T1–T4, N0–N2)] is complex and depends on mediastinal lymph node staging. The goal of the different therapeutic strategies, intended as a permanent cancer cure, was to provide patients with thoracic surgery. So, until recently the gold standard treatment of these tumors was platinum-based chemotherapy or radio-chemotherapy prior to surgery, sometimes in association with adjuvant radiotherapy or radio-chemotherapy in case of a residual tumor. For stage IIIB (N3) non resectable tumors, radio-chemotherapy, chemotherapy or immunotherapy alone or combined immunotherapy and chemotherapy are proposed for first-line treatment of NSCLC wild-type for the genes cited above.

Following the positive result of the PACIFIC clinical trial, patients with locally advanced non resectable (stage IIIA) NSCLC wild-type for *EGFR* and *ALK* can be treated with radio-chemotherapy prior to immunotherapy consolidation (durvalumab) (3). This sequential therapy followed by surgical resection of the tumor has been recently approved by the FDA and EMA (4,5). This new therapeutic strategy demonstrated improved overall survival

in comparison of that obtained with chemotherapy or radio-chemotherapy prior to surgery, irrespective of the PD-L1 status (4,5). Different treatments which associate other immunotherapy molecules (notably nivolumab or atezolizumab) and chemotherapy are currently proposed in clinical trials for stage III NSCLC (6,7). More recently, clinical trials using neoadjuvant immunotherapy are ongoing for early stage (stages I-II) NSCLC (8-11). Finally, other clinical trials associating adjuvant immunotherapy alone or in combination with adjuvant chemotherapy or adjuvant radio-chemotherapy are ongoing (7,11).

A recent publication by Hu and colleagues concerned a patient with stage IIIB (T1bN3M0) *EGFR* and *ALK* wild-type lung adenocarcinoma (12). This patient was treated with pembrolizumab and chemotherapy (association of pemetrexed and carboplatin). Complete clinical regression of the metastatic lymph nodes was observed after 4 cycles of treatment giving a cT1bN0M0 tumor (12). Since the disease was stable after these 4 cycles, surgery for complete tumor resection was indicated (12). Post-operative histological analysis showed no residual tumor cells in the 39 resected lymph nodes and a few PD-L1 negative tumor cells associated with massive lymphocytic infiltrates in the primary tumor (12). This attested to a high level of response to the neoadjuvant treatment. Moreover, due to the result of the histological analysis and the absence of some driver mutations, no adjuvant therapy

was administered. No recurrence of the disease was noted at the time of the publication 33 months after surgery (12). Nonetheless, this dramatic result concerned: (I) a small-sized tumor (T1b; >1 cm and <2 cm) corresponding to an *EGFR/ALK* wild-type adenocarcinoma (12); (II) a tumor with 90% PD-L1 positive tumor cells; (III) a tumor with a high tumor mutational burden (TMB) (11 muts/Mb) (12). Thus, this small tumor possessed two positive predictive biomarkers for immunotherapy responsiveness. In the absence of residual tumor cells in the lymph nodes and in the presence of a low percentage of residual tumor cells in the completely resected primary tumor, the decision to not provide adjuvant treatment (immunotherapy and/or chemotherapy) was justified (12). No targeted therapy was justified after surgery since this tumor was *EGFR* and *ALK* wild-type, even if the *ROS1*, *BRAF*, *NTRK*, *MET*, *RET* and *HER2* status was not provided (12).

So, combined neoadjuvant immunotherapy and chemotherapy prior to surgery can be proposed for stage IIIB NSCLC in the absence of any drugable genomic alteration and may lead to complete surgical tumor resection. However, we need to keep in mind that this is a unique case report and that future clinical trials including a larger number of patients are mandatory to confirm the possible benefit of this therapeutic strategy for stage IIIB NSCLC. In this context, different biomarkers should be examined and assessed before proposing this treatment. We may wonder if this therapeutic strategy can be provided only in the case of *EGFR*, *ALK*, *ROS1*, *BRAF* and *NTRK* wild-type NSCLC with more than 50% of tumor cells expressing PD-L1 and with a high TMB. Moreover, the histological results obtained after surgery could suggest or not providing adjuvant therapy, notably adjuvant immunotherapy. In this regard the assessment of the resected specimen needs to be complete and to integrate the different morphological parameters recently described (13,14). One of the main histological criteria to assess is the percentage of residual tumor cells since major response is defined by the presence of less than 10% tumor cells (13,14). However, other biological parameters could allow better prediction of the histological response to neoadjuvant immunotherapy such as the assessment of a higher intra tumoral and blood T cell receptor clonality (15). Besides the histological and the biological parameters, the delay in surgical resection of stage III NSCLC after neoadjuvant immunotherapy needs to be controlled and certainly standardized since this delay can have an impact on overall survival (16). The delay needs to be further established according to the different

neoadjuvant strategies, notably for stages IIIA or IIIB NSCLC.

The development of neoadjuvant immunotherapies requires integrating and combining in the near future several predictive biomarkers of treatment responsiveness, as well as some biomarkers of resistance and of therapeutic toxicity. In this context, PD-L1 immunohistochemistry and the TMB have their limits (17-20). There is an urgent need to clinically validate some other tissue biomarkers but also some new blood biomarkers to better adapt neoadjuvant treatments (21). Thus, to be able to predict effective neoadjuvant immunotherapy leading to a complete surgical resection in NSCLC patients with not only stage I-IIIa but also stage IIIB tumors may be possible.

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