Editorial

Nivolumab as first-line treatment in non-small cell lung cancer patients—key factors: tumor mutation burden and PD-L1 ≥50%

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Although we have new diagnostic equipment, lung cancer is still diagnosed at a late stage (1,2). In the past 5 years, novel targeted therapies with tyrosine kinase inhibitors based on the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B (*BRAF*) and proto-oncogene tyrosine-protein kinase ROS-1 (*ROS-1*) are used for treatment in non-small cell lung cancer (NSCLC) patients (3). Immunotherapy in the past two years brought is considered a breakthrough NSCLC (4). Pembrolizumab can be used as first-line treatment when programmed death-ligand 1 (PD-L1) expression is >50% and as second-line treatment when PD-L1 expression is >2% (4). On the other hand, nivolumab can be used as second-line treatment indifferent of the PD-L1 expression (4). Before commenting on the treatment approach, an observation should be stated that tumor heterogeneity (TH) has been observed in surgical biopsies (5). By TH we do not mean only the different architecture (matrix) of the tumor/lymph node but also the different receptors/genes (EGFR, ALK, *BRAF*, *ROS-1*, PD-L1) that are expressed differently in different parts of the lesion/mass. Therefore, the saying "tissue is the issue" still applies today and also for immunotherapy (6). Most patients are diagnosed with endoscopic procedures which use forceps or biopsy needles. Acquiring samples with biopsy needles from different parts of a lesion/mass/lymph node a better specimen with higher tumor heterogenicity is provided (7-10). Upon diagnosis we have to acquire the best sample possible which means acquiring TH as best possible. It has been observed in paraffin blocks with the same technique, e.g., DAKO, Biocare, that different slices might contain different PD-L1 expression (11). There is the possibility that patients that were included in immunotherapy studies had higher PD-L1 expression that initially diagnosed, a retrospective analysis of the specimens could assist in clarifying this issue. There has been an effort to evaluate nivolumab as first-line treatment in NSCLC. Indeed, in a recent publication by Carbone *et al*. (12), nivolumab was administered versus platinum based chemotherapy. In this study, nivolumab was not associated with significantly longer progression-free survival than chemotherapy among patients with previously untreated stage IV or recurrent NSCLC with a PD-L1 expression level of 5% or more. Overall survival was similar between groups. Nivolumab had a favorable safety profile, as compared with chemotherapy, with no new or unexpected safety signals. Taking a closer look in the study we should make the following observations. Overall survival was similar between groups. A high frequency of patients switching from chemotherapy to nivolumab in

this study may have contributed to the favorable overall survival in the chemotherapy group. It has been previously stated that nivolumab prolongs survival in previously treated patients with advanced NSCLC (13). Moreover; Patients characteristics were in favor of the chemotherapy group (e.g., fewer liver metastasis, smaller tumor burden and higher proportion of women). It has been previously observed that patients with PD-L1 >50% and high tumor burden benefit from nivolumab administration, however; the number of patients with these characteristics were fewer in the nivolumab group (14). In this study, it was observed that tumor mutation burden on its own is a key factor for nivolumab efficacy and longer median progression free survival. In the current study, again it is verified that tumor mutation burden plays the most crucial role for immunotherapy success (15). However; patients with PD-L1 ≥50% and high tumor mutation burden seem to benefit even more with longer median progression-free survival. In conclusion, overall survival with single agent nivolumab was similar to overall survival with platinum doublet chemotherapy. Nivolumab had a favorable safety profile as compared with chemotherapy, and no new safety signals were observed. Pembrolizumab administration could be characterized as targeted immunotherapy since it based strictly on the PD-L1 expression (16). The same should be possibly applied for nivolumab, however; in the case of nivolumab, high tumor burden should be combined with PD-L1 ≥50%. Another issue that has to be addressed is whether radiotherapy treatment prior to immunotherapy administration has a favorable synergistic effect for immunotherapy (17). Indeed, current data indicate that administration of radiotherapy enhance immunotherapy treatment, however, the time and dose of radiotherapy administration are yet to be clarified (18,19). A new focused study with nivolumab with patients with the specific characteristics will clarify the patient population that this immunotherapy should be used.

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Footnote

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