Mediastinal lymph node clearance and anti-PD-1 induction in resected NSCLC

In locally advanced node-positive non-small-cell lung cancer (NSCLC), neoadjuvant therapy may play a key role because of poor loco-regional control and survival in these patients following surgery alone. However, intensification of induction therapy, e.g. combination of chemotherapy and thoracic irradiation remains questionable based on the results of previous randomized trials.

Recently, Forde et al. [1] reported on the feasibility and efficacy of neoadjuvant nivolumab in patients with resectable Union Internationale Contre le Cancer stage I–IIIA NSCLC. Induction therapy constituted the administration of two infusions and was well tolerated inducing a major primary tumor pathological response rate of 45%. Importantly, in patients' peripheral blood a clonal expansion of neoantigen-specific T cells was documented. Also, a divergence between radiologic (preoperative RECIST) and pathologic primary tumor responses was described in 60% of cases. The authors supposed an extensive immune cell infiltration of the primary tumor and subsequently enlarged tumor volume.

Despite the impressive pathological remission rate of the primary tumor, comprehensive radiologic and pathologic analysis of the achieved mediastinal lymph node clearance (MC) was not described. A prognostic role of MC after induction therapy in resected node positive NSCLC is well established [2–4]. There is also evidence that residual nodal disease after multimodal induction has a negative impact on progression-free and overall survival. In the current trial, a total of one-fourth patients with preoperative N2 disease were down-staged. Furthermore, in the preoperative N0 subgroup (eight patients), there were two patients that were upstaged to ypN1 after resection. In previous studies, MC rate was dependent on therapy modalities. If neoadjuvant chemoradiation was applied, a reported MC rate was relatively high between 33% and 74%.

This finding of possible response discrepancy between primary tumor and involved lymph node compartment after induction with nivolumab in resected NSCLC may be of clinical relevance. An explanation could be a potentially different activity of PD-1 inhibitors in both treated sites. There is a paucity of data demonstrating a potentially different PD-L1 expression in the primary tumor and involved lymph nodes in NSCLC. Additionally, the single-center study from Gettinger et al. [5] investigated clinical features of acquired resistance to PD-1 axis inhibitors in advanced NSCLC and revealed that involved lymph nodes more often appear as a site of resistance.

The risk of divergent pathologic response to nivolumab induction in different compartments (primary tumor versus involved lymph nodes) needs further clarification before integration of anti-PD-1 inhibitors as induction therapy in clinical practice.

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Reply to the letter to the editor 'Androgen deprivation therapy and risk of rheumatoid arthritis in patients with localized prostate cancer' by Yang et al.

We read with great interest the article by Yang et al. [1] first reporting the association between androgen deprivation therapy (ADT), especially for long-term treatment, and the development of rheumatoid arthritis (RA). Interestingly, considering that autoimmunity is more frequent in female sex, this study addressed the possible immunosuppressive action of testosterone, likely responsible of ADT-related autoimmune diseases due to thymic regeneration with an increase of T cells [2]. RA is a chronic autoimmune-inflammatory disease that primarily affects the joints. It is characterized by a complex etiopathogenesis involving autoantibodies against modified self-proteins, stromal and immune cells, circulating pro-inflammatory cytokines/chemokines, and multiple genetic and no-genetic risk factors. Among mechanisms that might contribute to RA development, abnormalities in TP53 and PTEN genes have been demonstrated. Particularly,

downregulated PTEN expression, cooperating with TP53, is a characteristic of activated synovial fibroblast of RA patients displaying a significant role in inflammation and immune response by modulating various cytokines production and T-cell lineage [2]. This aspect of RA pathogenesis makes the article even more interesting because the association of long-term ADT and risk of RA could be due to not only to immunosuppressive action of testosterone, as the authors discussed, but also to PTEN alterations, an early frequent event in prostate carcinogenesis. Genomic studies on tumor tissue from patients developing RA in this work are warranted to better understand RA pathogenesis and potential prognostic-therapeutic implications.

Beyond genomic alterations, the autoimmune-inflammatory response in RA may require, in most cases, a second hit leading to immune-complex formation and complement activation, to induce or increase cytokine production and synovial vascular leakage. Similar events have been extensively described in several chronic inflammatory disorders due to different etiologies. For example, HCV chronic infection sustains B cells clonal expansion and autoantibodies production (i.e. IgM molecules with rheumatoid factor activity), characterizing mixed cryoglobulinemia, a model of autoimmunity, involving immune complexes formation, cytokines and complement activation [3]. Consequently, the knowledge of baseline features as potential triggers of autoimmunity, would have been useful to better characterize the onset and activity of RA, likely also correlated with progression of damage and disability.

Lastly, current findings established a significant relationship among chronic inflammation, metabolic syndrome and prostate cancer [4, 5]. Yang et al. [1] could evaluate the impact of RA development on clinical outcome and probably the detection of autoimmune disease during cancer history might provide a proper management of prostate cancer patients in both early and late disease stages. Recently, our group showed that pre-treatment metabolic syndrome/inflammation status had a negative impact on progression-free/overall survival (PFS/OS) [5]. A subanalysis showed that 23 of 551 (4.2%) castration-resistant prostate cancer patients treated with abiraterone or enzalutamide had an autoimmune condition, of whom 8 (1.5%) was affected by RA. Pre-therapy metabolic/inflammatory alterations were observed in 17 out of these 23 (73.9%) patients ($P = 0.045$) who had a shorter PFS/OS [hazard ratio (HR) = 3.7, 95% confidence interval (CI) 2.9–5.9, $P < 0.0001$ and HR = 5.8, 95% CI 4.0–14.3, $P < 0.0001$, respectively). These evidences confirm the importance of identifying autoimmune disease during ADT not only in localized disease but also in all steps of prostate cancer, especially for the growing number and increasingly early use of new hormonal prolonging-life drugs.

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Treatment of the myeloid/lymphoid neoplasm with *FGFR1* rearrangement with FGFR1 inhibitor

To the Editor,

Myeloid/lymphoid neoplasm with *FGFR1* rearrangement [1] is a rare aggressive disease characterized by myeloid hyperplasia, marked eosinophilia, tendency to rapidly progress to an acute leukemia (AML) and high refractoriness to chemotherapy [2].

The molecular pathogenesis results from a chromosomal translocation involving the *FGFR1* gene at the 8p11 locus with various partner genes causing a constitutive activation of the FGFR1 tyrosine kinase, impacting cell proliferation and survival [3].

Recently, a phase I/II study evaluating a novel, highly selective FGFR kinase inhibitor, INCB054828, in patients with refractory advanced malignancies (ClinicalTrials.gov: NCT02393248) has been initiated [4]. Herein, we present a patient who achieved a complete remission on this highly selective inhibitor.

A 50-year-old male presented with a 5-month history of leukocytosis, fatigue and anorexia. He was found to have leukocytosis with an absolute eosinophilia, anemia, and thrombocytopenia, and bone marrow biopsy revealed hypercellular marrow with eosinophilia consistent with a myeloproliferative neoplasm. Further studies involving conventional cytogenetics, fluorescent in situ hybridization, reverse transcriptase polymerase chain reaction, and Sanger sequencing confirmed t(8; 9)(p11.2; q33) with an *FGFR1* rearrangement leading to an abnormal *CEP110-FGFR1* fusion transcript (breakpoints at exon 38 and 9, respectively) (Figure 1).

After signing informed consent, the patient was enrolled into the clinical trial with INCB054828, 9 mg orally once daily on a 2 weeks-on/1 week-off schedule, in 21 day cycles. The patient achieved rapid response on therapy with complete resolution of