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NEWS AND VIEWS

Adjuvant checkpoint inhibition after cystectomy – why, when, and for whom?

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Context: Adjuvant systemic treatment after radical cystectomy is only recommended within trials, although clinical praxis is adjuvant cisplatin-based combination chemotherapy in patients not receiving neoadjuvant chemotherapy. The recently published CheckMate 274 trial investigated adjuvant checkpoint inhibition (nivolumab) after radical surgery with or without neoadjuvant chemotherapy for urothelial carcinoma.

News: The interim analysis of the CheckMate 274 trial suggests longer median disease-free survival after adjuvant nivolumab during 12 months after radical surgery compared to placebo (HR 0.70 (0.55–0.90)). In the subgroup of patients receiving neoadjuvant chemotherapy prior to radical surgery, the effect size of the intervention was even larger (HR 0.52 (0.38–0.71)). Toxicity grade 3 or above occurred only in 18% of the patients compared to 7% in the placebo arm, and health-related quality of life assessed with EORTC QLQ-C30 did not show any relevant difference in quality of life between the treatment arms. Thus, the study outcome differs from negative results reported from the first published phase III trial on adjuvant checkpoint inihibition after radical surgery for urothelial carcinoma, where adjuvant atezolizumab for 12 months did not improve disease-free survival compared to observation [1]. For patients with upper tract urothelial carcinoma where adjuvant chemotherapy is the new standard of care [2], the CheckMate 274 data have no immediate impact on postoperative treatment after nephroureterectomy. However, after radical cystectomy with adverse pathology in the cystectomy-specimen the questions why, when and for whom should adjuvant nivolumab be considered are highly relevant.

Views: Obviously, data on overall survival are eagerly awaited, albeit only three treatment-related deaths occurred in the experimental trial arm (two patients with pneumonitis and one with bowel-perforation). However, the hypothesis-generating finding in the subgroup analysis of patients treated with cisplatin-based neoadjuvant chemotherapy appears to have been driving the overall benefit of adjuvant nivolumab. Thus, that currently not give adjuvant nivolumab in this clinical setting while awaiting approval from authorities in patients with a high risk of treatment failure with adverse prognostic findings in the cystectomy specimen after neoadjuvant chemotherapy and radical cystectomy, is a clinical dilemma. The recently reported large effect-size on overall survival when sequencing chemotherapy and checkpoint inhibition in the metastatic setting was compared to treatment with avelumab at progression (HR 0.69 (0.56–0.86)) [3], is also in line with the survival data in CheckMate 274 in chemotherapy pretreated patients. Altogether, this raises the question whether to implement adjuvant nivolumab for patients with pT3/pT4 and/or N + after neoadjuvant chemotherapy and radical cystectomy despite that data on overall survival according to intention-to-treat are immature.

Another question is for whom this treatment is indicated, given that the subgroup of 401 patients without preoperative chemotherapy did not seem to have any effect of adjuvant nivolumab (0.91 (0.69–1.21)). Other predictive markers than PD-L1-expression are needed, as long-term responses after checkpoint inhibition occurs also in PD-L1 negative tumors. When the IMvigor 211 trial investigating atezolizumab in the metastatic setting did not meet it is primary endpoint, tumors in the preceding phase II trial (IMvigor 210) were subjected to extensive molecular characterization [4]. Findings suggested that TGF-beta signaling and lack of CD8 T-effector cells in the tumor attenuated the response, whereas tumors with genomically unstable subtype (Lund Taxonomy) responded favourably. Recently, applying ctDNA-positivity as a marker for molecular residual disease identified patients with benefit from atezolizumab in the negative randomized IMvigor 010 trial [5], a concept currently evaluated in a randomized setting after cystectomy (NCT04138628).

Still, it is my belief that based on the current data from Checkmate274 we need to consider offering patients with pT3/pT4 and/or N + after neoadjuvant chemotherapy and radical cystectomy adjuvant nivolumab for a year after surgery, while awaiting overall survival data to mature.

Disclosure statement

The author has no relevant conflict of interest to declare.

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Social media promotion: Time for adjuvant nivolumab after neoadjuvant chemotherapy and RC

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