Re: Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients with Muscle-invasive Urothelial Bladder Carcinoma (PURE-01): An Open-label, Single-arm, Phase II Study

Necchi A, Anichini A, Raggi D, et al

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Experts' summary:

This prospective, single-arm, phase 2 trial investigated the effect of neoadjuvant checkpoint inhibition (CPI) with three doses of pembrolizumab (200 mg) every 3 wk before radical cystectomy for clinical muscle-invasive bladder cancer with predominantly urothelial histology. Fifty patients were enrolled and evaluated for pathological response as the primary endpoint.

Twenty-one patients (42%) achieved ypT0 stage and an additional six patients had residual non–muscle-invasive (NMIBC) tumors, representing a downstaging rate of 54%. Treatment failure was observed in 10% of patients, who were given additional neoadjuvant chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (four patients owing to lack of radiological response, one patient experienced grade III transaminitis and did not continue CPI therapy).

Response to pembrolizumab was dependent on tumor PD-L1 status. The primary endpoint of ypT0 was achieved in 54.3% of patients with PD-L1-positive tumors, defined according to a combined positive score (CPS) for PD-L1 expression on both immune and tumor cells (CPS $\geq$10 in 35 patients). A pathological complete response was achieved in only 13.3% of patients with CPS $<$10 (n = 15). Similarly, pathological downstaging to NMIBC was observed in 23 patients (65.7%) with CPS $\geq$10 and four patients (26.7%) with CPS $<$10.

Biomarker analyses revealed that tumor mutational burden (TMB) was associated with ypT0 status in a nonlinear fashion and that a pretreatment TMB of $\geq$15 mutations/Mb was predictive of pathological complete response [1].

Experts' comments:

Immune CPIs have recently revolutionized the treatment paradigm for metastatic urothelial bladder cancer, with sustained responses never seen before and relatively minimal side effects resulting in well-tolerated and effective treatment. However, only the minority of patients in unselected cohorts respond to treatment with CPIs in clinical trials. We urgently need predictive biomarkers for better patient selection [2]. Extensive work on PD-L1 has been undertaken to elucidate its role as a predictive biomarker in this setting [3]. The results are not homogeneous and vary according to treatment line, antibody, platform, and scoring system used for PD-L1 evaluation, as well as the compound. Both the European Medicines Agency and the US Food and Drug Administration have recently limited the use of CPIs for first-line treatment of patients with metastatic urothelial carcinoma who are cisplatin-ineligible on the basis of an interim analysis by the data monitoring committees of two ongoing phase 3 clinical trials (IMvigor130 and KEYNOTE-361). After initial hope from early phase 1 trials suggesting potential predictive value of PD-L1 in urothelial carcinoma, this biomarker did not perform as expected. Indeed, the biomarker-driven design of the phase 3 IMvigor211 trial, which evaluated atezolizumab compared to second-line chemotherapy in a PD-L1-enriched cohort, failed [4] largely because of the suboptimal biomarker performance [5].

The heterogeneity in PD-L1 performance is partly due to the difference in assays and scoring systems between clinical trials, which makes comparison between trials impossible. Moreover, PD-L1 status was mostly evaluated using archival tissue, which might also explain the discrepancy in results from the different clinical trials in terms of its predictive value, because of dynamic changes in PD-L1 expression and differential expression between primary tumor and metastatic sites.

The PURE-01 investigators used matched pre- and post-treatment tumor specimens for analyses of biomarkers of response and failure to CPI therapy. The authors reported an impressive pathological complete response rate [1] in a similar range to historic data (if not higher) from trials evaluating the role of cisplatin-based neoadjuvant chemotherapy. Combined with the low adverse event rate, which was comparable to the performance of the drugs in the metastatic setting, these data are not only statistically significant but also clinically highly interesting. There was even strong enrichment of efficacy in patients with PD-L1-positive tumors. A second trial evaluating CPI use in the neoadjuvant setting (ABACUS) is under way, and previously published results from an interim analysis underline the predictive value of PD-L1 in cisplatin-ineligible patients treated with atezolizumab [6].

Both trials build the base for randomized phase 3 trials evaluating the role of CPI and the biomarker PD-L1 in this setting compared to conventional cisplatin-based chemotherapy.

In addition, these trials underline the value of a biomarker-driven approach to systemic treatment of this heterogeneous disease [2,5], which still suffers from ineffective standard chemotherapy. Adjuvant therapeutic approaches may even further improve on these promising successes. Perioperative systemic therapy with CPIs introduces a novel era of individualized medicine for urothelial carcinoma and moves us away from the "one size fits all" approach towards a personalized therapeutic strategy based on precision medicine. We are just entering a new dimension that will have a positive effect on the quantity and quality of life of many patients afflicted by urothelial carcinoma.

Conflicts of interest: Kilian M. Gust has received advisory board fees from Cepheid, Roche, MSD, and Ferring; speaker fees from Astellas, AstraZeneca, BMS, Ipsen, MSD, and Roche; and meeting/travel expenses from Allergan, Astellas, AstraZeneca, Bayer, BMS, Janssen, MSD, Novartis, Pfizer, Pierre Fabre, and Roche. Shahrokh F. Shariat has received advisory board and/or speaker fees from Astellas, AstraZeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Roche, Sanochemia, Sanofi, and Wolff.

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Re: Association of Robotic-Assisted vs Laparoscopic Radical Nephrectomy with Perioperative Outcomes and Health Care Costs, 2003 to 2015

Jeong IG, Khandwala YS, Kim JH, et al

JAMA 2017;318:1561–8

Experts' summary:
Jeong et al. [1] compared the costs of robot-assisted and "straight stick" laparoscopic nephrectomy. Consistent with prior research on robotic surgery costs [2], the authors found longer operating time and higher costs for the robotic surgical approach. Compared with a mean 90-d cost of $19 530 for robot-assisted approaches, laparoscopy averaged $16 851 (difference $2678, 95% CI, $838 to $4519). This was mainly due to higher supply costs as well as longer operating time.

Experts' comments:
Urologists are used to the refrains about the high costs of robot-assisted surgery. While numerous studies have addressed the costs and benefits of robotic surgery, this study is novel in comparing robotic to traditional laparoscopic nephrectomy, a widespread minimally invasive approach. Unlike prostatectomy, for which "straight-stick" laparoscopy is challenging, laparoscopic nephrectomy is within the skill set of many urologists.

Despite the higher costs, the proportion of patients receiving robot-assisted nephrectomy grows every year. Why does the more expensive approach continue to gain ground?

One underappreciated factor in many cost-effectiveness studies is the crucial importance of surgical skill. For a robotically trained surgeon, if you know how to do a robotic prostatectomy or cystectomy, then maybe a robotic approach might be the safest and fastest way to perform a nephrectomy.

In the Premier database, 47.9% of surgeons performed only a single nephrectomy or fewer per year, while 80% performed four or fewer. For a surgeon well versed in robot-assisted approaches, it may be that robotics provides the best opportunity for a safe, minimally invasive nephrectomy. Moreover, in communities without a large number of urologists, a robotic skill set that can be used for many surgeries (from prostatectomies to partial nephrectomies and pyeloplasties) may be more useful and safer than performing occasional laparoscopic nephrectomies.

We would argue that the focus should be on reducing costs for whichever technique is safest and most familiar for an individual surgeon and not on mandating a specific approach. Greater competition (eg, with the entry of new companies to the robotic surgery markets) is one potential route. We have demonstrated that robotic surgery encompasses a wide range of costs [3,4]. Transparency for costs (eg, with surgeon dashboards) may help to shift surgeons towards the low-cost end of the spectrum for robotic approaches [5].

Ultimately it is not the surgical approach that matters, but finding strategies that allow surgeons to perform familiar surgeries safely, and to do so at minimum cost.

Conflicts of interest: Alexander P. Cole has nothing to disclose. Adam S. Kibel reports consulting fees from Janssen and Profound. Pfizer, Blue Earth, Merck and Co. and Insight, outside of the submitted work.

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