Editorial Commentary

Novel neoadjuvant immunotherapy treatment and surveillance strategies in resectable esophageal cancer: innovation leads to improved outcomes

Kenneth M. Williams[1,2]^, Kian C. Banks[1,2], Jeffrey B. Velotta[1,3,4]

[1]Department of Thoracic Surgery, Kaiser Permanente Northern California, Oakland, CA, USA; [2]Department of Surgery, UCSF East Bay, Oakland, CA, USA; [3]Department of Surgery, UCSF, San Francisco, CA, USA; [4]Department of Clinical Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA, USA

Correspondence to: Kenneth M. Williams, MD. Department of Surgery, UCSF East Bay, 1411 E 31st St, Oakland, CA 94602, USA; Department of Thoracic Surgery, Kaiser Permanente Northern California, 3600 Broadway, Oakland, CA 94611, USA. Email: kenwilliams@alamedahealthsystem.org.

Comment on: Kelly RJ, Landon BV, Zaidi AH, *et al.* Neoadjuvant nivolumab or nivolumab plus LAG-3 inhibitor relatlimab in resectable esophageal/gastroesophageal junction cancer: a phase Ib trial and ctDNA analyses. Nat Med 2024;30:1023-34.

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As our understanding of tumor genetics and biology evolves, novel immunotherapy regimens will continue to play a significant role in combating malignancy. Overexpression of programmed death-ligand 1 (PD-L1)/L2 is fairly common in esophageal cancers and has been associated with suppressive effects on the immune system, decreasing its ability to eliminate cancer cells (1). Studies have shown a survival improvement and favorable safety profile for nivolumab (2), but there exists a continued need to evaluate new combinations of immunotherapy regimens for safety and efficacy.

The study performed by Kelly *et al.* primarily focused on the safety of neoadjuvant nivolumab and chemoradiotherapy (CRT) in combination with relatlimab (anti-LAG-3) as compared to neoadjuvant nivolumab and CRT alone in patients with resectable stage II/III distal esophageal and/or gastroesophageal junction (GEJ) cancer (3). The study duration allowed for the evaluation of pathologic response, recurrence, and short-term survival. Though their initial protocol required augmentation due to adverse events (AEs), the revised protocol does show promise for the addition of relatlimab to neoadjuvant regimens for select patients. The study also makes a compelling case for the promise of circulating tumor DNA (ctDNA) in treatment and surveillance plans.

Kelly *et al.* support the evidence of PD-L1 targeted therapy while providing insight into the potential role of relatlimab in patients with LAG-3 overexpression. Overall, their study demonstrated higher rates of pathological complete response (pCR) when compared with CROSS trial results for adenocarcinoma (30.8% *vs.* 23%) but not for squamous cell carcinoma (SCC) (33.3% *vs.* 49%) (4). This improvement in pCR appears to be driven by the nivolumab control arm with 40% pCR as compared with the treatment arm, with 21.4% pCR. This study was performed in the US and, as such, follows the well-established trends in differences in incidence and mortality between adenocarcinoma and SCC, as seen by the predominance of adenocarcinoma in the study cohort (87.5%) (5). It was surprising to see decreased pCR in the SCC cohort as there have been many studies demonstrating the increased sensitivity to immune checkpoint inhibitor (ICI) treatment in SCC over adenocarcinoma, likely due to the high number of tumor mutations (6). In a recent

^ ORCID: 0009-0009-7180-8246.

meta-analysis, Wang *et al.* [2024] reviewed seven different phase III randomized control trials (RCTs) evaluating nine different primary ICI treatment regimens in SCC patients. They found that nivolumab + chemotherapy and nivolumab + ipilimumab provided improved objective response rates and improved survival when compared with chemotherapy alone (7). Though major pathological response (MPR) is not reported in the CROSS trial data, 50% and 100% for adenocarcinoma and SCC, respectively, align with the aforementioned trends and are also impressive.

Kelly *et al.* sufficiently acknowledge the limits of their study given the context of a phase 1b trial. The change in protocol for arm B (nivolumab + relatlimab) elucidates the possible severity and variability in checkpoint inhibitor side effects. Though considered a therapy with a favorable side effect profile, Kwak *et al.* showed that when observed in clinical practice, the adverse side effects of immunotherapy can be enough to limit treatment completion (8). In a meta-analysis of breast cancer patients by Ji *et al.*, ICI + chemotherapy was associated with higher rates of AEs, serious AEs, and treatment discontinuation (9). Though treatment discontinuation is most feared, treatment interruptions and dose reductions can also significantly negatively impact overall survival (OS) (9). Additionally, findings from the JCOG1109 trial demonstrate this challenge further within esophageal cancer patients (10). Kato *et al.* examined the efficacy and impact of neoadjuvant double (NeoCF) *vs.* triple [NeoCF + docetaxel (D)] *vs.* CRT [NeoCF + radiotherapy (RT)] in patients with locally advanced SCC. They found the highest 3-year OS in the NeoCF + D group and, consequently, the highest rate of grade 3 AEs and rates of treatment discontinuation (10). This distinction between safe and tolerable is one that often obfuscates the generalizability of these treatment profiles but is not limited to immunotherapies. FLOT (fluorouracil plus leucovorin, oxaliplatin and docetaxel) is effective in improving survival when given in the perioperative setting (11) and is used with more regularity in Europe. However, in clinical practice, tolerability and treatment completion, in our experience, remain a challenge. Similar to Becker *et al.* (12), we have experienced poor tumor response from patients on FLOT, evidenced by minimal tumor shrinkage leading to dysphagia and decreased oral intake. Many of these patients require preoperative enteral access to support their nutrition and still enter into the immediate preoperative period with poor nutritional status. Malnutrition in patients receiving chemotherapy has been recognized as a key risk factor for febrile neutropenia (FN). FN is associated with treatment delays, dose reductions, and discontinuation of treatment (13). These regimen changes can have a significant impact on a patient's quality of life and risk of treatment toxicity. Postoperatively, malnutrition is also associated with poorer response to neoadjuvant therapy and worse OS (14). Recent studies have also shown that adequate nutrition, in particular, fatty acids, vitamins, and key nutrients, may also improve the effect of ICIs by reducing inflammation and supporting the overall immune function. Thus, patients suffering from undernutrition and malnutrition would also be missing these notable benefits (15). The combination of the need for an additional procedure superimposed on poor nutritional status places an increased burden of risk for postoperative complications and poor outcomes on these patients. The ESOPEC trial (CROSS protocol *vs.* perioperative FLOT) released some promising initial data earlier this year, but further review of the complete data is needed to address this concern (16).

The study by Kelly *et al.* was well-designed and executed and, importantly, raises interesting questions. First, none of the patients within the non-pCR group that were ctDNA negative after ICI induction recurred, which was not the case among patients within the non-pCR group that were ctDNA positive after ICI. Should pCR still be the goal/target for neoadjuvant treatment, or will ctDNA play more of a role in predicting long-term survival in the near future? These findings raise questions about how clinically impactful pCR and MPR alone are for patients. This was further supported by observing that pCR and MPR less optimally predicted recurrence-free survival (RFS) and OS for the patients for whom ctDNA was evaluated. Future studies to investigate the clinical utility of ctDNA levels pre- and postoperatively will be valuable.

Secondly, undetectable ctDNA levels at earlier points in the treatment continuum were associated with higher rates of RFS. Should ctDNA be used to evaluate the efficacy of treatment? At each measurable point throughout the study, earlier evidence of undetectable ctDNA was associated with increased RFS. It has been shown that the presence of micrometastatic disease in lymph nodes is associated with significantly decreased RFS (17). It is possible that ctDNA levels more effectively measure the burden of micrometastatic disease and, hence, better predict the success of treatment. This may be particularly impactful in cases where a patient's nodal status is negative or unknown. After all, the cause of mortality among GEJ cancer patients is frequently related to distant metastasis rather than local recurrence (18). Kobayashi *et al.* found similar findings

when looking at a cohort of esophageal SCC patients known to be ctDNA positive before neoadjuvant CRT. They found, that of those ctDNA negative after neoadjuvant treatment, 92% were recurrence-free at 36 months compared with 8% of ctDNA positive patients (19). Similarly, there may exist a possibility of ctDNA being used to augment/personalize neoadjuvant or adjuvant treatment modalities to improve patient outcomes. One could envision a protocol approach where, instead of standardized treatment amounts, systemic therapy could be administered with undetectable ctDNA as the endpoint. Thus, allowing for shorter/longer cycles dependent on patient response.

Thirdly, patients who ultimately became ctDNA negative post-operatively, regardless of previous ctDNA status, had improved RFS when compared with those who were ctDNA positive post-operatively. What role can ctDNA play in disease surveillance? This was one of the most interesting findings in this study. These findings raise the possibility of not only evaluating the efficacy of treatment but also continued monitoring for possible early detection of recurrent disease. Current National Comprehensive Cancer Network (NCCN) guidelines for GEJ cancer recommend computed tomography (CT)/positron emission tomography (PET) imaging for surveillance every 6 months for the first two years, then annually thereafter for up to 5 years for all patients who have undergone trimodality treatment (20). There may one day be a paradigm where alongside imaging surveillance, ctDNA could be collected for micrometastatic monitoring postoperatively. This pairing could prove to be quite impactful as a major limitation of current imaging surveillance is the inability to detect micrometastatic disease. Essentially, it could be used similarly to carcinoembryonic antigen (CEA) by our colorectal colleagues when monitoring for colon cancer recurrence and as a trigger for a more robust workup.

Lastly, LAG-3 overexpression was associated with improved benefit from relatlimab therapy. Should LAG-3 testing be used to screen patients for targeted anti-LAG-3 therapy? LAG-3 is an immune checkpoint receptor integral in T cell exhaustion and suppressing immune responses through regulator T cells (Tregs), especially in conditions such as cancer, where there is chronic antigenic activation. LAG-3 inhibitors, such as relatlimab, interrupt this chronic stimulation thus restoring T cell activation, enhancing cytotoxicity, and reducing the suppressive effects of Tregs (21). Combining this with an anti-programmed cell death protein 1 (anti-PD1) inhibitor, such as nivolumab, should produce a synergistic effect, given dual checkpoint blockade, thus enhancing antitumor immunity (21). This was the case in the seminal work done with this combination in metastatic melanoma patients, showing significantly improved progression-free survival in patients treated with the dual blockade combination. This combination was also responsible for increased treatment-related AE's and AE's leading to treatment discontinuation (22). Patients with MPR had higher baseline LAG-3 expression, which was driven by the relatlimab arm. Thus, patients with increased LAG-3 expression benefited more from relatlimab, and given the increased possibility of AEs with relatlimab, widespread use may not be beneficial for all patients. Additionally, patients with LAG-3 expression still benefited from the adjusted protocol (shortened course), suggesting an approach that balances treatment tolerance may still prove effective.

Overall, this elegant study seems to demonstrate an acceptable safety profile with its modified protocol for neoadjuvant nivolumab and relatlimab. Secondarily, it offered evidence for improved pCR and MPR rates when compared with the current standard of care (CROSS trial) while simultaneously bringing into question the importance of pCR/MPR in the future evaluation of treatment efficacy. It opens the floor for an important discussion around the future role of ctDNA in tailoring treatment regimens as well as serving as a tool for high-quality surveillance. It also challenges us to think about the quality of life impact these treatment regimens have on patients, given the understanding that treatment completion is associated with better outcomes (23). This further emphasizes the future in which personalized regimens are tailored to patients based on their specific tumor biology and response to treatments. We look forward to further investigations into novel immunotherapy regimens and ctDNA as possible predictors, prognostic indicators, and/or early detectors.

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Footnote

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