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Editorial

Multifactorial, Biomarker-Based Predictive Models for Immunotherapy Response Enter the Arena

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The PURE-01 trial studied preoperative treatment with the anti-PD-1 monoclonal antibody pembrolizumab in patients with muscle-invasive bladder cancer planned for cystectomy (1). Patients were enrolled regardless of eligibility for standard cisplatin-based neoadjuvant therapy, with the goal of developing a less toxic perioperative treatment. Cisplatin-based chemotherapy has shown an overall survival benefit compared with surgery alone (2), so it is imperative, therefore, that any alternative neoadjuvant treatment demonstrates comparable efficacy. PURE-01, in fact, demonstrated robust clinical activity for pembrolizumab: complete pathologic response (pT0N0) was achieved in 37.5% of patients and downstaging to less than pT2 in 58% (1,3). In spite of these favorable outcomes, 42% of patients were defined as treatment failures based on residual T2 or greater disease or radiographic progression. These patients might have been better served by neoadjuvant cytotoxic chemotherapy or immediate surgery. Accurate, practical predictive biomarkers are essential to distinguish between responders and nonresponders to optimize treatment across the population.

In this issue of the Journal, Bandini et al. (3) used data from 105 patients to construct a model to predict pT0N0 in response to pembrolizumb. pT0N0 has been validated as a surrogate marker for overall survival in the case of cisplatin-based chemotherapy (4); however, it is not known whether pT0N0 has the same association with overall survival after neoadjuvant immunotherapy. Longer follow-up and additional clinical trials in the neoadjuvant space will hopefully elucidate the association between pT0N0 and overall survival for patients treated with neoadjuvant immune checkpoint inhibitor therapy prior to cystectomy.

The predictive model that was developed in the current article incorporates pretreatment clinical T stage and 2 biomarkers that had been prespecified candidates at study inception: programmed cell-death ligand (PD-L1) protein expression, in both tumor and infiltrating immune cells, measured as a continuous variable by the combined positive score with the DAKO 22C3 antibody and tumor mutational burden (TMB) measured as a continuous variable. Predictive biomarkers in cancer medicine are often targets of the therapeutic agent: HER2 for trastuzumab in breast and gastric cancer (5), mutated estimated glomerular filtration rate in non-small cell lung cancer for erlotinib and other small molecule inhibitors of this kinase (4), and fibroblast growth factor receptors 2 and 3 mutations or fusionsfor the inhibitors of those receptor kinases. In some cases, the predictive marker is not the direct target of the drug but a component of the same pathway [BRAF + MEK inhibitors for BRAF-mutated melanoma (6)] or a component of a pathway with a synthetic lethal relationship with the target [poly(ADP-ribose) polymerase inhibitors for tumors with loss of function of homologous recombination DNA repair components such as *BRACA1* and *2* (7)]. Biomarkers can be tumor intrinsic or derived from the microenvironment. It is noteworthy that the 2 molecular biomarkers, PD-L1 and TMB, that form the basis of the PURE-01 predictive model are linked to the proposed mechanism of action for pembrolizumab. TMB is tumor intrinsic, whereas the combined positive score for PD-L1 is derived from both tumor and infiltrating cell expression.

The PURE-01 investigators also used broad-based screening to identify novel candidate predictive biomarkers and signatures. More than 400 genes known to be mutated or rearranged in cancer were sequenced in tumor specimens using the commercially available FoundationOne platform (8). None of these selected genes were predictive of pT0N0. In a separate publication, the PURE-01 investigators showed that immune gene expression signatures were correlated with pT0N0 (9). Of interest, this association was not seen in a separate cohort of patients treated with neoadjuvant platinum-based chemotherapy. Study of the genes contained within the immune signature panels may lead to target discovery for future immunotherapeutic approaches. The FoundationOne genomic mutation and the gene expression panels each contain a limited number of genes. Whole-exome and whole-genome sequencing could identify additional genes whose expression or mutation might be incorporated into predictive models of checkpoint inhibitor response and could lead to target discovery.

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High TMB is thought to facilitate immune checkpoint inhibitor response via the generation of neoantigen peptides presented to T lymphocytes (10). TMB predicted response to immune checkpoint inhibitors in PURE-01 as well as in other studies and tumor types. However, total TMB may not be the most accurate measure of neoantigen load. There are data that frameshift mutations generate more plentiful and potent neoantigens than point mutations (11). A more qualitative assessment of TMB and neoantigen content could one day surpass the predictive power of the total TMB in predicting response to checkpoint inhibitor therapy.

The predictive model presented by Bandini et al. (3) performed well, with a concordance statistic (C index) of 0.77 (95% confidence interval = 0.68 to 0.86). The authors have helpfully included an Excel spreadsheet tool for modeling pT0N0. This calculator is freely available as an online web resource at https://marco-bandini-md-sanraffaele.shinyapps.io/pure01/.
The neoadjuvant ABACUS study of the PD-L1 monoclonal antibody atezolizumab, with a design similar to PURE-01, observed a comparable pT0N0 rate of 31% (12). However, there was no statistically significant association between PD-L1 expression (either on tumor cells or infiltrating cells) and outcomes, and TMB failed to predict response (12). It is not clear why these biomarkers did not perform as they had in PURE-01 and in studies of metastatic urothelial cancer. In ABACUS, the presence of activated T-effector cells (dual CD8+/granzyme B staining) was predictive for pT0N0 (12).It would be interesting to correlate the abundance of these activated effector T cells with pathologic response in the PURE-01 dataset.

Landmark studies like PURE-01 have established the feasibility of using novel treatment approaches in the neoadjuvant setting, and in the article by Bandini et al. (3), predicting response using biomarkers. We are in a new area of bladder cancer care, where we have several different modalities: cisplatin-based chemotherapy, anti-PD-1/PD-L1 checkpoint inhibitors, the antibody-drug conjugate enfortumab vedotin (13), and erdefitinib for fibroblast growth factor receptors 2 and 3 mutated or rearrangedtumors (14). The optimal use and timing of these agents in the perioperative and metastatic setting are not established and will need to be elucidated by a series of carefully performed and adequately powered phase III studies. In fact, several clinical trials of cisplatin-based chemotherapy in combination with PD-1 and PD-L1 antibody treatment are ongoing at this time, as are studies adding novel agents to chemotherapy or to anti-PD-1 and PD-L1 in the neoadjuvant space. The use of predictive biomarkers will be critical to this effort and the optimal use of these agents across the population of patients with muscle-invasive and metastatic urothelial cancer. Chemotherapy or other treatments may alter the tumor microenvironment and the predictive power of biomarkers (15).

The challenge for the worldwide community of investigators is to work together to apply these new and emerging treatments most effectively. Predictive biomarkers are essential components to this effort to get the right drug to the right patient at the right time. The PURE-01 study and the predictive model described in the Bandini et al. (3) article are important steps toward these goals.

Notes

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References

1. Necchi A, Anichini A, Raggi D, et al. 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. *J Clin Oncol*. 2018;36(6_suppl):TPS534.
2. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med*. 2003;349(9):859–866.
3. Bandini M, Ross J, Raggi D, et al. Predicting the pathologic complete response after neoadjuvant pembrolizumab in muscle-invasive bladder cancer. *J Natl Cancer Inst*. 2021;113(1):48–53.
4. Yoneda K, Imanishi N, Ichiki Y, et al. Treatment of non-small cell lung cancer with EGFR-mutations. *J UOEH*. 2019;41(2):153–163.
5. Pernas S, Tolaney SM. HER2-positive breast cancer: new therapeutic frontiers and overcoming resistance. *Ther Adv Med Oncol*. 2019;11:175883591983351.
6. Broman KK, Dossett LA, Sun J, et al. Update on BRAF and MEK inhibition for treatment of melanoma in metastatic, unresectable, and adjuvant settings. *Expert Opin Drug Saf*. 2019;18(5):381–392.
7. Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. *Science*. 2017;355(6330):1152–1158.
8. Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nat Biotechnol*. 2013;31(11):1023–1031.
9. Necchi A, Raggi D, Gallina A, et al. Impact of molecular subtyping and immune infiltration on pathological response and outcome following neoadjuvant pembrolizumab in muscle-invasive bladder cancer. *Eur Urol*. 2020;70:701–710.
10. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med*. 2017;377(25):2500–2501.
11. Turajlic S, Litchfield K, Xu H, et al. Insertion-and-deletion-derived tumour-specific neoantigens and the immunogenic phenotype: a pan-cancer analysis. *Lancet Oncol*. 2017;18(8):1009–1021.
12. Powles T, Kockx M, Rodriguez-Vida A, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. *Nat Med*. 2019;25(11):1706–1714.
13. Rosenberg JE, O'Donnell PH, Balar AV, et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. *J Clin Oncol*. 2019;37(29):2592–2600.
14. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2019;381(4):338–348.
15. Yi M, Jiao D, Xu H, et al. Biomarkers for predicting efficacy of PD-1/PD-L1 inhibitors. *Mol Cancer*. 2018;17(1):129.