Incorporating an effective and tolerable immunotherapeutic as part of maintenance therapy for unresectable stage III non-small-cell lung cancer (NSCLC) is a potential method of improving overall treatment outcomes (1). Many investigators in the lung cancer community have the research goal of establishing a maintenance therapy that prolongs overall survival by stabilizing disease without significantly decreasing quality of life. Immunotherapy capable of inducing an immune response against a tumor-specific antigen is one such approach anticipated to achieve this goal. The recent publication by Butts et al. of the Stimulating Targeted Antigenic Response To NSCLC (START) trial showed that the primary endpoint of a significant difference in overall survival in the treatment group was not met; however, the predefined subgroup of patients receiving concurrent chemoradiotherapy followed by maintenance therapy with tecemotide, an antigen-specific immunotherapy, received a notable survival benefit (n=806; HR 0.78, 95% CI: 0.64-0.95, P=0.016) (2). The START trial was a randomized, double-blind, placebo-controlled phase III trial investigating tecemotide (L-BLP25), an active immunotherapeutic agent, following chemoradiotherapy for inoperable stage III NSCLC (2). The study was performed to evaluate the effectiveness of tecemotide as a maintenance therapy following either concurrent or sequential chemoradiotherapy. Tecemotide is designed to mount an immune response to the cell-surface glycoprotein, Mucin-1 (MUC1), which is aberrantly glycosylated in various epithelial cell cancers, including NSCLC. When MUC1 in these types of cancers is aberrantly glycosylated, it is more efficiently processed into peptides and loaded onto human lymphocyte antigen (HLA) molecules (3-5). This could yield a tumor-specific epitope repertoire bound to HLA molecules and presented on the surface of neoplastic cells that can be recognized by MUC1-specific cytotoxic T-lymphocytes (CTLs). Upon administration, tecemotide is assumed to be taken up by antigen presenting cells. Its peptide compound is subsequently presented to HLA class I and class II molecules, thus eliciting a T\textsubscript{H}1 immune response which produces MUC1-specific CTLs.

In this international study, the investigators faced many challenges, including a study suspension, which complicated the conduct of the study and made the results difficult to interpret. All histology subtypes of stage III NSCLC were included. A total of 1,513 patients from 33 countries were enrolled and randomized 2:1 using double-blind methods, stratified by stage (IIIA vs. IIIB), response to chemoradiotherapy (stable disease vs. objective response), delivery of chemoradiotherapy (concurrent vs. sequential) and region (North America and Australia, Western Europe, Rest of World). There was no standardization for chemoradiotherapy except that it required only two cycles of platinum-based chemotherapy, along with a minimum of 50 Gy radiation between four and 12 weeks before randomization. There was no standardization of the chemotherapy schedule, dose intensity, or radiation therapy quality or technique. Patients that participated
from North America and Australia almost exclusively received concurrent chemoradiotherapy while most patients from Eastern European sites received sequential chemoradiotherapy. Overall survival was the primary endpoint studied, while secondary endpoints included time to disease progression, time to symptom progression, 1-3 years survival, and safety. The primary endpoint analysis was adjusted for the randomization strata.

Although the results showed no significant survival benefit between tecemotide and placebo treatment groups when analyzing the outcome independently of chemoradiotherapy dose schedule (HR 0.88, 95% CI: 0.75-1.03; \( P=0.123 \)), a sub-group analysis of patients receiving concurrent chemoradiotherapy followed by tecemotide showed a notable overall survival benefit. Median overall survival in this group was 30.8 months compared to 20.6 months in those patients receiving concurrent chemoradiotherapy followed by placebo (HR=0.78, 95% CI: 0.64-0.95; \( P=0.016 \)). The investigators speculated on a number of possible reasons for the difference in tecemotide activity following sequential versus concurrent chemoradiotherapy including initial tumor burden, type of chemotherapy (e.g., taxanes vs. etoposide) and their effect on immunogenic vs. tolerogenic cell death (6), and poorer performance status at the beginning of the trial. However, to confirm the START trial findings and attribute the survival increase to tecemotide maintenance therapy following concurrent chemoradiotherapy, these investigators have initiated a second Phase III study of tecemotide maintenance therapy after concurrent chemoradiotherapy. Additionally, the results of the START trial have led to the modification of an ongoing Phase III study in Asia to exclude sequential therapies and focus solely on concurrent therapy options.

In addition to the new and modified clinical pathways, post-clinical studies using an immune intact human MUC1-expressing lung cancer mouse model (hMUC1. Tg C57BL/6 mice) are also underway with the goal of identifying effective dosing schedules of combination therapy. Using this model, we have previously shown that tecemotide can induce a specific antigen response and produce modest antitumor effects as a single agent. In addition, cisplatin/tecemotide combination therapy results in additive antitumor effects, while therapeutic doses of cisplatin or localized radiation did not interfere with the immune response to tecemotide (7-9). Additional questions we plan to address include the role of cyclophosphamide in enhancing the immune response to tecemotide, and the potential for inducing acquired drug/immune resistance.

Perhaps even more important will be the determination of the factors and timing that result in the development of immune exhaustion following prolonged antigen challenge and methods of reversing immune resistance such as anti-PDL-1 therapy (10,11). In this context, it is essential to monitor the immune response of cancer patients receiving immunotherapy over time and identify parameters that correlate with survival. For instance, it may be worthwhile to investigate an indicator of antigen-specific immune responses to ensure that a given patient is at least exhibiting an immunological response throughout the treatment period.

If the results of the START trial are confirmed, and perhaps further refined with a better understanding of the methods of administering combination therapies while avoiding immune exhaustion and acquired immune resistance, an effective maintenance therapy for patients with unresectable stage III NSCLC is on the horizon.

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