Tumor vaccines and cellular immunotherapies

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A recent meta-analysis (using random effects modeling) of patients with advanced non-small cell lung cancer (NSCLC) comprising 6,756 patients enrolled in 18 randomized controlled trials [Dammeijer et al. (1)] reported a clinical advantage for “tumor vaccines” and “cellular immunOTHERAPIES”. Compared to protocol-specific best supportive care, placebo, or matched chemotherapy, immunotherapy as defined an overall survival (OS) difference of 5.43 months (P=0.005) and a progression free survival (PFS) difference of 3.24 months (P=0.005). Articles on checkpoint blockade therapy and biologic response modifiers were excluded. The tumor vaccines targeted a diverse group of tumor-associated antigens (including over-expressed antigens, cancer-testis antigens, and altered surface glycoproteins), although tumor-specific “neoantigens” do not appear to be represented, and the cellular immunotherapies included cytokine induced killer cells (CIK; mixed T- and natural killer cell-like) or dendritic cells. Autologous tumor vaccine approaches were not included. Overall, the results of this meta-analysis provide further background support for the rapidly developing “combination” immunotherapy field as envisioned almost 10 years ago (2). The combination of the previous generation of immunotherapies reviewed by Dammeijer et al. with the recently FDA approved immune checkpoint inhibitors, particularly the PD-1/PD-L1 axis inhibitors approved for use in NSCLC (3,4), provide an exciting opportunity for future investigations. However, although these neoantigens provide a subset of high-affinity tumor-specific epitopes capable of eliciting antitumor immune responses, those very responses evoke immune counter-responses, e.g., PD-L1 upregulation. The immune checkpoint inhibitors; i.e., inhibitors of CTLA4, PD-1, and PD-L1, have the potential to counter adaptive resistance (8).

At Mary Crowley Cancer Research (MCCR) in collaboration with Foundation Medicine, we have begun to evaluate the role that TMB correlated neoantigens play in response to novel autologous whole tumor cell immunotherapy. TMB was characterized in 266 sequential advanced cancer patients treated at MCCR. Using next generation sequencing (NGS), cancer specimens from 27 heavily pretreated patients who were candidates for phase I trial options showed >10 somatic mutations. Responses
were seen in six of six who received immunotherapy (i.e., RECIST SD >6 months, PR or CR (Table 1) compared to only one of the other 21 patients who did not receive immunotherapy.

One interesting experimental product, Vigil (9,12) is an autologous whole tumor cell immunotherapy incorporating a proprietary non-viral plasmid vector (via electroporation) to simultaneously drive GMCSF production (via rhGMCSF transgene) and TGFβ1 and β2 knockdown (via bifunctional shRNAfurin). The provision of the full patient-specific, tumor-specific antigenic matrix (comprising neoantigens and cancer-testis antigens, when relevant) combined with enhanced CD8+ T-cell antigen-specific effector function and T-cell effector memory acquisition represents an integration of “tumor immunotherapy” and “cellular immunotherapy” as described by Dammeijer et al. (1). Vigil bypasses the necessity of identifying both high-affinity and immune-driver neoantigens required by peptide-based vaccines as well as attenuating immune escape by presentation of multiple antigens. In addition, by incorporating GMCSF and furin mediated TGFβ1/β2 knockdown Vigil drives antigen-presenting cell (APC) recruitment, tumor-associated/specific antigen uptake, processing, maturation, and (cross-) presentation. Results from the Phase I Vigil trial (9,12) demonstrated safety, confirmed effective transgene expression as evidenced by GMCSF production and RNAi knockdown of tumor cell furin and TGFβ1/β2 secretion, and showed T cell activation in the majority of advanced cancer patients in the form of circulating PBMC IFNγ-ELISPOT conversion to positivity using pre-processed autologous tumor cells as antigen source. Preliminary evidence of antitumor effectiveness was reflected in the correlation of IFNγ-ELISPOT conversion with OS in a wide range of cancer patients and prolonged survival based on historical disease-matched comparators.

Although previously regarded with skepticism, cancer immunotherapy has now been accepted as standard of care in a variety of settings and is being evaluated as front line therapy in selected tumor types. Even limiting consideration to PD-1/PD-L1 axis inhibitors given their FDA approval and rapidly expanding evaluation, there remain challenging areas of investigation. Looking at only two PD-1/PD-L1 axis biomarkers, tumor infiltrating lymphocytes (TIL) and PD-L1 expression, Teng et al. (13) have defined four immune subsets; TIL+/PD-L1+ or type I adaptive immune resistance; TIL+/PD-L1- or type II immunological ignorance; TIL-/PD-L1+ or type III intrinsic induction; and TIL-/PD-L1- or type IV tolerance. Each of these subsets requires type specific tailoring of immunotherapeutic approach. For example, we are evaluating the combination of Vigil and PD-1 inhibition in types II and IV. Other tumor intrinsic and immune microenvironment immunosuppressive elements are, likewise, the focus of current and planned investigations, e.g., TIM-3, LAG-3, IDO, TAM, and MDSC.

The Dammeijer meta-analysis is another strut in the framework supporting the incorporation of immunotherapy into the cancer immunotherapeutic tetrad—surgery, radiation, chemotherapy, and targeted therapy. The challenge now, even more complicated than previously, is the integration of multiomic data, cancer evolution dynamics, molecular immunology and pharmacodynamics in order to optimize the use of existing therapies and to develop new therapeutics in a rational, cost-effective manner.

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**Footnote**

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<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease</th>
<th>TMB</th>
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<th>DNA repair defect</th>
<th>Immune treatment</th>
<th>Response</th>
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SD, stable disease; PR, partial response; CR, complete response (RECIST 1.1).
Thoracic Surgery, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease, Guangzhou, China).

**Conflicts of Interest:** The authors have no conflicts of interest to declare.


**References**
