

# Tumor vaccines and cellular immunotherapies

John Nemunaitis, Neil Senzer, Leah Plato

Mary Crowley Cancer Research Center, Dallas, TX, USA

Correspondence to: John Nemunaitis, MD. 12222 Merit Drive, Suite 1500, Dallas, TX 75251, USA. Email: jnemunaitis@marycrowley.org.

Submitted Sep 13, 2016. Accepted for publication Sep 23, 2016.

doi: 10.21037/atm.2016.10.54

View this article at: <http://dx.doi.org/10.21037/atm.2016.10.54>

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, in addition to expansion of the immunotherapy tool box, identification of likely sensitive populations through the use of biomarker enrichment is also a critical necessity for rapid and cost-effective future development. As this new field of cancer management evolves we need to be precise as to who should and should not be treated with monomodal or multimodality combination immunotherapy and, more to

the point, which particular immunotherapy to use.

Rizvi *et al.* (5) recently showed that both the response rate (63% *vs.* 0%;  $P=0.03$ ) and PFS (14.5 *vs.* 3.7 months;  $P=0.01$ ) to pembrolizumab correlates with high *vs.* low tumor mutation burden (TMB) in NSCLC patients. Interestingly, the analysis of mutational patterns in patients with high mutation rates revealed a response correlation with set of DNA repair gene mutations (i.e., POLD1, POLE, MSH2). The authors then addressed the underlying mechanism by hypothesizing (as others have) that recognition of tumor-specific “neoantigens”, formed as a consequence of somatic mutations (particularly missense and frameshift), is important for the activity of anti PD-1 therapy. They then characterized the neoantigen tumor landscape on these same patients and found a direct correlation with TMB ( $P<0.0001$ ). Cancers (regardless of histology type) with a mean mutational load of  $>10$  somatic mutations per Mb of coding DNA are more likely to have a “burden” of neoantigens recognizable by T cells (6,7). 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

**Table 1** Relationship of tumor mutation burden (TMB) to response

Patient	Disease	TMB	Prior treatment	DNA repair defect	Immune treatment	Response
052369	Melanoma	74	Surg, XRT	SF3B1	Vigil (9)	SD >6 months
103884	Uterus cancer	24	Chemo x4, surg	MSH2	Durvalumab (10)	PR >6 months
035096	Unknown primary	40	Chemo x2, surg	PBRM1	TVEC (11)	CR >3 years
137097	Unknown primary	105	Surg, XRT	SF3B1	TVEC (11)	SD >18 months
PW	Melanoma	101	Chemo x2, immune, surg	MSH2	TVEC (11)	PR >2 years
076418	NSCLC	12	Chemo x5, XRT, surg	STK11	Durvalumab (10)	SD >6 months

SD, stable disease; PR, partial response; CR, complete response (RECIST 1.1).

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 shRNA<sup>furin</sup>). The provision of the full patient-specific, tumor-specific antigenic matrix (comprising neoantigens and cancer-testis antigens, when relevant) combined with enhanced CD8<sup>+</sup> 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<sup>+</sup>/PD-L1<sup>+</sup> or type I adaptive immune resistance; TIL<sup>-</sup>/PD-L1<sup>-</sup> or type II immunological ignorance; TIL<sup>-</sup>/PD-L1<sup>+</sup> or type III intrinsic induction; and TIL<sup>+</sup>/PD-L1<sup>-</sup> 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.

## Acknowledgements

None.

## Footnote

*Provenance:* This is a Guest Editorial commissioned by Section Editor Jianrong Zhang, MD (Department of

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.

*Comment on:* Dammeijer F, Lievens LA, Veerman GD, et al. Efficacy of Tumor Vaccines and Cellular Immunotherapies in Non-Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis. *J Clin Oncol* 2016;34:3204-12.

## References

1. Dammeijer F, Lievens LA, Veerman GD, et al. Efficacy of Tumor Vaccines and Cellular Immunotherapies in Non-Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis. *J Clin Oncol* 2016;34:3204-12.
2. Nemunaitis JJ. Are vaccines making a comeback in non-small-cell lung cancer? *J Clin Oncol* 2008;26:1402-3.
3. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* 2015;373:123-35.
4. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540-50.
5. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015;348:124-8.
6. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. *Nature* 2013;500:415-21.
7. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. *Science* 2015;348:69-74.
8. Matsushita H, Sato Y, Karasaki T, et al. Neoantigen Load, Antigen Presentation Machinery, and Immune Signatures Determine Prognosis in Clear Cell Renal Cell Carcinoma. *Cancer Immunol Res* 2016;4:463-71.
9. Nemunaitis J, Barve M, Orr D, et al. Summary of bi-shRNA/GM-CSF augmented autologous tumor cell immunotherapy (FANG™) in advanced cancer of the liver. *Oncology* 2014;87:21-9.
10. Ibrahim R, Stewart R, Shalabi A. PD-L1 blockade for cancer treatment: MEDI4736. *Semin Oncol* 2015;42:474-83.
11. Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. *J Clin Oncol* 2015;33:2780-8.
12. Senzer N, Barve M, Kuhn J, et al. Phase I trial of "bi-shRNAi(furin)/GMCSF DNA/autologous tumor cell" vaccine (FANG) in advanced cancer. *Mol Ther* 2012;20:679-86.
13. Teng MW, Ngiew SF, Ribas A, et al. Classifying Cancers Based on T-cell Infiltration and PD-L1. *Cancer Res* 2015;75:2139-45.

**Cite this article as:** Nemunaitis J, Senzer N, Plato L. Tumor vaccines and cellular immunotherapies. *Ann Transl Med* 2016;4(Suppl 1):S24. doi: 10.21037/atm.2016.10.54