Editorial

Immunotherapy, checkpoint inhibitor advance to frontline non-small cell lung cancer

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For many years, immune-based therapies have been explored in a selected array of cancers traditionally considered "immunogenic", namely melanoma, prostate, renal cell, non-Hodgkin's lymphoma, bladder cancer, and renal cell carcinoma. Until recently, lung cancer has not been considered part of this group. Indeed, the designation "immunogenic" has essentially been ex post facto descriptive. However, our increased understanding of dynamic molecular immunology, including the multifarious immune editing process, and an expanded array of technologic tools now allow for a mechanistic classification with regard to immunogenicity. So yes, in non-small cell lung cancer (NSCLC) there can be impaired peptide transport and MHC-peptide affinity, a lack of effective MHC-peptide:TCR binding, intratumoral cytokine and microenvironmental cytokine and cellular [both stromal and tumor infiltrating lymphocytes (TIL)] immune suppressors and, in counter-response to an endogenous or exogenous elicited adaptive immune response, the development of adaptive immune resistance. Determining the tumor/host specific mechanism(s) rendering NSCLC "non-immunogenic" in an individual patient allows the opportunity for mechanism-specific therapeutic intervention (1). Prior to the clinical use of the FDA approved checkpoint inhibitors (nivolumab and pembrolizumab), vaccine success in NSCLC was limited at best [i.e., belagenpumatucel-L (2), L-BLP 25 (3), GVAX (4), EP2101 (5) and MAGE-3 vaccines (6)].

Having elucidated, in part, the endogenous and adaptive immune resistance role of immune checkpoint inhibitors along with the availability of a variety of PD-L1 assays (as yet to be standardized), some remarkable immune mediated responses in NSCLC have been described. In previous phase II/III studies of Pembrolizumab 2 *vs.* 10 mg/kg *vs.* docetaxel 75 mg/m^2 every 3 weeks in patients with 2nd/3rd line advanced NSCLC, those with greater than 50% membranous expression of PD-L1 (at both dose levels) achieved a statistically significant progression free survival (PFS) and overall survival (OS) compared to those receiving docetaxel (7,8). In the current publication, Reck *et al.* (9) present the results of a phase III study of front-line therapy in 305 NSCLC patient comparing Pembrolizumab 200 mg every 3 weeks (n=154) to standard of care (pathology specific) chemotherapy (n=151) which not only confirms a significant improvement in PFS (10.3 *vs.* 6 months) but also a significant survival advantage (P=0.005). The OS results are all the more impressive insofar as 43.7% of the chemotherapy comparator group crossed over to Pembrolizumab treatment after disease progression. It would be of interest to have a breakdown of the crossover and non-crossover groups. The limited number of non-smokers (10) precludes any conclusion in this group with a lower mutational burden (11). These results strongly support the mechanism of action of the human IgG4κ monoclonal antibody against PD-1 as well as the "immunogenicity" of NSCLC. But despite these results, the objective response rate to Pembrolizumab was only 44.8% and the achievement of a "cure" is rare. Furthermore,

although a higher rate of response to PD-L1/PD-1 inhibitors is seen in PD-L1 expressing tumors, responses are not infrequently seen in PD-L1 negative patients (12). In part, this may be due to both dynamic temporal changes in PD-L1 expression as well as intrapatient expression discordance (13). Thus, the need and opportunity to pursue more effective biomarkers related to mechanisms of primary and secondary resistance with thought towards use of rational combinatorial therapeutic regimens is an increasingly appropriate focus of clinical management.

A recent meta-analysis (14) (using random effects modeling) of patients with advanced NSCLC comprising 6,756 patients enrolled in 18 randomized controlled trials reported a clinical advantage for "tumor vaccines" and "cellular immunotherapies" compared to protocol-specific best supportive care, placebo, or matched chemotherapy. Immunotherapy was associated with an OS advantage of 5.43 months (P=0.005) and a PFS difference of 3.24 months (P=0.005). Excluded from analysis were studies of immune checkpoint blockade therapy, autologous tumor vaccines and biologic response modifiers. The significant benefits derived from first generation immunotherapeutics as suggested by this meta-analysis combined with current insight into immune molecular mechanisms support the exploration of "combination" immunotherapy field as envisioned almost 10 years ago (15).

So are there other biomarkers for targeted immunotherapy in addition to the non-exclusionary predictive PD-L1?

Recent preclinical testing (16) in immune competent models reveals a correlation between high nonsynonymous tumor mutation burden (TMB) and both response and survival following immunotherapy with PD-L1/PD-1 axis checkpoint inhibitor therapy. Rizvi *et al.* (10) showed that a higher clinical benefit rate (PR/CR or SD >6 mo) to Pembrolizumab correlates with TMB in NSCLC patients. PFS was also improved in high *vs.* low TMB patients (14.5 *vs.* 3.7 mo, P=0.01). Interestingly, the analysis of mutational patterns in patients with high TMB revealed a response correlation with mutations involving DNA repair genes (i.e., POLD1, POLE, MSH2). Rizvi *et al.* addressed the underlying mechanism by hypothesizing (as others have) that recognition of tumor specific neoantigens, not subject to central processing, formed as a consequence of somatic mutations (predominantly missense), 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 have a higher probability of processing and presenting neoantigens recognizable by T cells (17). For example, Rosenberg showed that the TH1 cell clone responsible for clinical response in a patient with metastatic cholangiocarcinoma treated on an adoptive T cell protocol was a single unique mutation in ERBB2 (18). Schreiber, using genomic and bioinformatic approaches, identified autologous tumor specific mutation antigens responsible for anti-PD-1 mediated rejection of an aggressive sarcoma in a mouse model (19) and Verdegaal (20) ascribed the significant tumor responses to adoptive autologous cell transfer in two advanced stage melanoma patients to unique tumor neoantigens. However, insofar as these neoantigens elicit antitumor immune responses, they also have the potential to induce off-setting counter responses including CTLA4, PD-1, and PD-L1, i.e., adaptive immune resistance. This would explain the benefit shown to be derived from checkpoint inhibitors. It stands to reason that the presence of both cytotoxic T-cells (CTLs) (as a subset of TIL) and an operative and dominant PD-1/PD-L1 checkpoint in the tumor and/or TIL would provide the optimal scenario for effective PD-1/PD-L1 axis inhibition. Given that CTL PD-1/PD-L1 expression can be induced following TCR activation and tumor PD-L1 expression induced following IFNγ and STAT3 stimulation (21), it would account for the finding that quantitative TIL and PD-L1 expression appear to be conjoint predictors of response to PD-1/PD-L1 pathway inhibition.

For the above reasons, a rational combination strategy would be to pair a PD-1/PD-L1 inhibitor (e.g., avelumab) with a treatment strategy that attracts TIL and enhances tumor (neo)antigen processing and presentation particularly in the presence of a low TMB (22). There is evidence of enhanced activated T-cell infiltration into tumor in response to adaptive immunotherapy. A recent study demonstrated PD-L1 IHC positivity in 12.5% (3 of 25) of resected specimens from unvaccinated patients with pancreatic cancer (23). Two weeks following autologous GVAX vaccine, specimen membranous PD-L1 expression was increased to 25% (10 of 40), and was found in vaccine induced intratumoral tertiary nodules in >80% of patients. In the same report, cyclophosphamide + GVAX treatment of Panc02 xenografts in C57B16 mice elicited an 11% cure rate which was increased to 30% with the addition of monoclonal antibody targeting PD-L1. Further, the combination of cyclophosphamide/GVAX + monoclonal antibody targeting PD-1 significantly increased the

percentage of IFNγ-producing T cells within TILs as well as greater CD8+ T cell IFNγ secretion compared to either cyclophosphamide/GVAX or anti-PD-1 alone.

Vigil (24) is an autologous whole tumor cell vaccine, which incorporates a non-viral plasmid vector to simultaneously drive GMCSF production (via rhGMCSF transgene) and TGFβ1 and β2 knockdown (via bifunctional shRNA^{furin}). It provides patient-specific, tumor-specific antigenic matrix (including neoantigens and cancer-testis antigens, when present) capable of activating CD8+ T-cell antigen-specific effector function and T-cell effector memory acquisition. It is one of the combinatorial therapeutic pathways in development that would obviate the necessity of identifying tumor specific neoantigens that appears to be required for optimizing peptide-based vaccines. 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 and II trials (24,25) demonstrated safety, confirmed transgene product expression, and effectively activated T-cells (IFNγ-ELISPOT conversion) against autologous tumor cells that correlated with survival and time to relapse in a range of tumor types (24,25). Vigil is currently being evaluated in combination with avelumab in a phase I trial.

Reck and colleagues have expanded the role of immunotherapeutics by demonstrating the effectiveness of single agent pembrolizumab as first-line therapy in NSCLC. Immunotherapy can now be added to surgery, radiation, chemotherapy and targeted therapy as standards of care in this second most commonly diagnosed malignancy with 224,390 new cases and 158,080 deaths expected this year.

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Footnote

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

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