Guest editorial

HIGHLIGHT REPORT: ROLE OF PD-L1 IN NEVER-SMOKERS

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Numerous studies have shown that infiltration of lymphocytes into tumor tissue is associated with better prognosis (Bindea et al., 2013; Lohr et al., 2013; Schmidt et al., 2018; Heimes et al., 2017a, b). This prognostic influence has been seen in many tumor types, including colon (Schmidt et al., 2012), breast (Lohr et al., 2013; Schmidt et al., 2008; Godoy et al., 2014) and lung (Botling et al., 2013; Grinberg et al., 2017; Jabs et al., 2017). With the introduction of programmed death ligand 1 (PD-L1) targeting therapy, immune-inhibitory mechanisms have become a major field of research (Garon et al., 2015; Rizvi et al., 2015a, b; Herbst et al., 2016; Pardoll, 2012; Creelan, 2014; Aguiar et al., 2017). However, the prognostic role of PD-L1 in non-small cell lung cancer (NSCLC) in patients not treated with PD-1 targeting therapies still is unclear. To gain a better understanding, a study recently published in the Journal of Thoracic Oncology immunohistochemically analyzed tissue microarrays of 705 patients with NSCLC and additionally considered publicly available transcriptomics data of 1724 patients (Edlund et al., 2019). Key findings of this study in patients without PD-1 targeting therapies are: (1) Infiltration of T-, B- and plasma cells is associated with better prognosis, similar to previous studies; (2) This association is strongest in highly proliferative tumors; (3) PD-L1 is not associated with prognosis in the total cohort of NSCLC patients; (4) However, a significant association of PD-L1 positivity with shorter survival was obtained in the never-smokers. This association was validated in independent patients on the RNA level.

This result is of relevance, because it shows that immune modifiers have different roles in NSCLC of smokers and non-smokers. It will be important to consider this difference in therapy studies targeting the PD-1/PD-L1 axis. Predicting prognosis and response to therapy remains a challenging task (Hellwig et al., 2016; Lohr et al., 2015; Weisner et al., 2019) with many modifying factors, e.g. proliferation (Siggelkow et al., 2012), antioxidative status (Cadenas et al., 2010, 2014, 2019) and metabolism (Marchan et al., 2017; Stewart et al., 2012) playing an important role. The present study of Edlund and colleagues helps to gain an overview which key factors modify the prognostic role of tumor infiltrating lymphocytes.

Conflict of interest

The author declares no conflict of interest.

REFERENCES

Aguiar PN Jr, De Mello RA, Hall P, Tadokoro H, Lima Lopes G. PD-L1 expression as a predictive biomarker in advanced non-small-cell lung cancer: updated survival data. Immunotherapy. 2017;9:499-506.

Bindea G, Mlecnik B, Tosolini M, Kirilovsky A, Waldner M, Obenauf AC, et al. Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. Immunity. 2013;39:782-95.

Botling J, Edlund K, Lohr M, Hellwig B, Holmberg L, Lambe M, et al. Biomarker discovery in non-small cell lung cancer: integrating gene expression profiling, meta-analysis, and tissue microarray validation. Clin Cancer Res. 2013;19:194-204.

Cadenas C, Franckenstein D, Schmidt M, Gehrmann M, Hermes M, Geppert B, et al. Role of thioredoxin reductase 1 and thioredoxin interacting protein in prognosis of breast cancer. Breast Cancer Res. 2010;12(3): R44.

Cadenas C, van de Sandt L, Edlund K, Lohr M, Hellwig B, Marchan R, et al. Loss of circadian clock gene expression is associated with tumor progression in breast cancer. Cell Cycle. 2014;13:3282-91.

Cadenas C, Vosbeck S, Edlund K, Grgas K, Madjar K, Hellwig B, et al. LIPG-promoted lipid storage mediates adaptation to oxidative stress in breast cancer. Int J Cancer. 2019 Jan 17. doi: 10.1002/ijc.32138. [Epub ahead of print].

Creelan BC. Update on immune checkpoint inhibitors in lung cancer. Cancer Control. 2014;21:80–9.

Edlund K, Madjar K, Mattsson JSM, Djureinovic D, Lindskog C, Brunnström H, et al. Prognostic impact of tumor cell programmed death ligand 1 expression and immune cell infiltration in NSCLC. J Thorac Oncol. 2019;14:628-40.

Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372: 2018-28.

Godoy P, Cadenas C, Hellwig B, Marchan R, Stewart J, Reif R, et al. Interferon-inducible guanylate binding protein (GBP2) is associated with better prognosis in breast cancer and indicates an efficient T cell response. Breast Cancer. 2014;21:491-9.

Grinberg M, Djureinovic D, Brunnström HR, Mattsson JS, Edlund K, Hengstler JG, et al. Reaching the limits of prognostication in non-small cell lung cancer: an optimized biomarker panel fails to outperform clinical parameters. Mod Pathol. 2017;30:964-77.

Heimes AS, Madjar K, Edlund K, Battista MJ, Almstedt K, Elger T, et al. Subtype-specific prognostic impact of different immune signatures in node-negative breast cancer. Breast Cancer Res Treat. 2017a;165: 293-300.

Heimes AS, Madjar K, Edlund K, Battista MJ, Almstedt K, Gebhard S, et al. Prognostic significance of interferon regulating factor 4 (IRF4) in node-negative breast cancer. J Cancer Res Clin Oncol. 2017b; 143:1123-31.

Hellwig B, Madjar K, Edlund K, Marchan R, Cadenas C, Heimes AS, et al. Epsin family member 3 and ribosome-related genes are associated with late metastasis in estrogen receptor-positive breast cancer and long-term survival in non-small cell lung cancer using a genome-wide identification and validation strategy. PLoS One. 2016;11(12):e0167585.

Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, 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(10027):1540-50.

Jabs V, Edlund K, König H, Grinberg M, Madjar K, Rahnenführer J, et al. Integrative analysis of genome-wide gene copy number changes and gene expression in non-small cell lung cancer. PLoS One. 2017;12(11): e0187246.

Lohr M, Edlund K, Botling J, Hammad S, Hellwig B, Othman A, et al. The prognostic relevance of tumour-infiltrating plasma cells and immunoglobulin kappa C indicates an important role of the humoral immune response in non-small cell lung cancer. Cancer Lett. 2013;333:222-8.

Lohr M, Hellwig B, Edlund K, Mattsson JS, Botling J, Schmidt M, et al. Identification of sample annotation errors in gene expression datasets. Arch Toxicol. 2015;89:2265-72.

Marchan R, Büttner B, Lambert J, Edlund K, Glaeser I, Blaszkewicz M, et al. Glycerol-3-phosphate acyltransferase 1 promotes tumor cell migration and poor survival in ovarian carcinoma. Cancer Res. 2017;77: 4589-601.

Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12: 252–64.

Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, et al. Activity and safety of nivolumab, an anti–PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non–small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015a;16:257–65.

Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer. Science. 2015b;348:124–8.

Schmidt M, Böhm D, von Törne C, Steiner E, Puhl A, Pilch H, et al. The humoral immune system has a key prognostic impact in node-negative breast cancer. Cancer Res. 2008;68:5405-13.

Schmidt M, Hellwig B, Hammad S, Othman A, Lohr M, Chen Z, et al. A comprehensive analysis of human gene expression profiles identifies stromal immunoglobulin κ C as a compatible prognostic marker in human solid tumors. Clin Cancer Res. 2012;18:2695-703.

Schmidt M, Weyer-Elberich V, Hengstler JG, Heimes AS, Almstedt K, Gerhold-Ay A, et al. Prognostic impact of CD4-positive T cell subsets in early breast cancer: a study based on the FinHer trial patient population. Breast Cancer Res. 2018;20(1):15.

Siggelkow W, Boehm D, Gebhard S, Battista M, Sicking I, Lebrecht A, et al. Expression of aurora kinase A is associated with metastasis-free survival in node-negative breast cancer patients. BMC Cancer. 2012;12: 562.

Stewart JD, Marchan R, Lesjak MS, Lambert J, Hergenroeder R, Ellis JK, et al. Choline-releasing glycerophosphodiesterase EDI3 drives tumor cell migration and metastasis. Proc Natl Acad Sci U S A. 2012;109: 8155-60.

Weisner J, Landel I, Reintjes C, Uhlenbrock N, Trajkovic-Arsic M, Dienstbier N, et al. Preclinical efficacy of covalent-allosteric AKT inhibitor Borussertib in combination with Trametinib in KRAS-mutant pancreatic and colorectal cancer. Cancer Res. 2019;79: 2367-78.