SUPPLEMENTARY INFORMATION S1

Immunomonitoring

Immune reactivity, in particular the adaptive immune response and the inflammatory nature of the tumour immune microenvironment, are two recently recognized hallmarks of cancer. Hence, it is logical to assume that appropriate immune-related biomarkers should i) Provide a rationale for the choice of immunotherapeutic agents and combinations thereof; ii) Reflect the in vivo activity of the used compound(s) based on the mechanism of action, and iii) Correlate with clinical outcome after treatment so that for each and every patient the right choice for a reasonable price is made. This requires the use of immunological assays to identify and validate such biomarkers. Most of these assays will reflect immunological processes and many will be related to T cells and myeloid cells since the immune-based cancer therapies primarily target these components of the immune system. The challenges and requirements for optimal monitoring have been described elsewhere.

An important guidance for immunomonitoring is found in two overlapping immune signatures: 1) the immune contexture, encompassing the type, density and functional orientation of T cells in tumours, which is similar among patients with different types of cancers displaying an increased likelihood to respond to therapy or undergo complete regressions, and 2) the immunological signature of rejection, which is associated with the phenomenon of immune-mediated tissue-specific destruction as observed in autoimmunity, allograft-rejection and infections. These features are associated with a Th1 signature (IFNγ, STAT1, IL-12, IRF1, T-bet), T cell cytotoxicity (perforin, granzymes, caspases, TIA1), T cell attraction (CXCR3 and CCR5 with CXCL9, CXCL10 and CCL5), and T cell adhesion (MADCAM1, ICAM1, VCAM1). The presence of (parts of) this signature before treatment may indicate pre-existing immune activation and thus active immune signalling mediated by the tumour. The induction of these components in the response to treatment may serve as biomarkers for potentially successful therapy, and the immunomonitoring strategy may focus on capturing as many of these components as possible. The quantification of T cells expressing co-inhibitory receptors may also serve as indicators of immune reactivity as they identify the tumour-reactive T cell repertoire and are associated with better prognosis, at least in HPV-associated diseases. A simple but effective way to understand which types of immunotherapy might be needed for a particular patient might be to screen the patient's tumour with respect to T cell infiltration. This may also provide clues to what is needed for vaccination to succeed. Many tumours have successfully developed mechanisms to prevent recruitment of T cells to tumour site through deregulation of chemokine circuits. In addition, T cells may fail to deeply penetrate tumours because of suppressed transmigration of cells through the tumour endothelial barrier, mediated by type and quantity of adhesion molecules preventing T cell adhesion and infiltration of the tumour or the expression of molecules such as FasL and TRAIL involved in killing immune cells. In case a tumour comprises many TILs, this would indicate that the induction of tumour-specific T cells by APC and the homing of these T cells are not
strongly impaired. In these patients one might focus on increasing the activation of T cells through checkpoint blocking and vaccination, thereby turning tumour observing cells into tumouricidal cells. Alternatively, when tumours are only scarcely infiltrated by T cells one might want to focus on the relief of immune suppression preventing the expansion or homing of tumour-specific T cells.

The internationally coordinated harmonization efforts of the Cancer Immunotherapy Immunoguiding program (CIP) and the Cancer Immunotherapy Consortium (CIC) over the last 10 years have led to high standards for the implementation of antigen-specific T cells assays within clinical settings \cite{11} and more recently for the development of reference cell samples \cite{12, 13} and a consensus position regarding the measurement of regulatory T cells \cite{14}. Harmonization of the monitoring of macrophages and MDSCs is under development but suffers from the great plasticity of these cells reflected in a large number of subsets of these cells detectable both in tumours and in peripheral blood \cite{15, 16}.

References

