Trial watch
Prognostic and predictive value of the immune infiltrate in cancer

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Solid tumors are constituted of a variety of cellular components, including bona fide malignant cells as well as endothelial, structural and immune cells. On one hand, the tumor stroma exerts major pro-tumorigenic and immunosuppressive functions, reflecting the capacity of cancer cells to shape the microenvironment to satisfy their own metabolic and immunological needs. On the other hand, there is a component of tumor-infiltrating leucocytes (TILs) that has been specifically recruited in the attempt to control tumor growth. Along with the recognition of the critical role played by the immune system in oncogenesis, tumor progression and response to therapy, increasing attention has been attracted by the potential prognostic and/or predictive role of the immune infiltrate in this setting. Data from large clinical studies demonstrate indeed that a robust infiltration of neoplastic lesions by specific immune cell populations, including (but not limited to) CD8+ cytotoxic T lymphocytes, Th1 and Th17 CD4+ T cells, natural killer cells, dendritic cells, and M1 macrophages constitutes an independent prognostic indicator in several types of cancer. Conversely, high levels of intratumoral CD4+CD25+FOXP3+ regulatory T cells, Th2 CD4+ T cells, myeloid-derived suppressor cells, M2 macrophages and neutrophils have frequently been associated with dismal prognosis. So far, only a few studies have addressed the true predictive potential of TILs in cancer patients, generally comforting the notion that—at least in some clinical settings—the immune infiltrate can reliably predict if a specific patient will respond to therapy or not. In this Trial Watch, we will summarize the results of clinical trials that have evaluated/are evaluating the prognostic and predictive value of the immune infiltrate in the context of solid malignancies.

Introduction

For a long time, the heterogeneity of solid tumors has been incredibly underestimated and neoplastic lesions have often been regarded as aggregates of relatively disorganized tumor cells

supported by their own vasculature. During the last few decades, this oversimplified view has been challenged by a consistent volume of scientific literature generated from multiple laboratories worldwide. Nowadays, it is generally accepted that cancer cells within neoplastic lesions are highly heterogeneous, exhibiting rather distinct phenotypic, proliferative, differentiative and functional profiles.[1] Two theories have been proposed to account for such a heterogeneity: the clonal evolution and the cancer stem cell model.[2,3] According to the former, a mutant population of cancer cells would, at some stage, acquire a proliferative advantage and hence become the major driver behind tumorigenesis.[2] The latter, which has been proposed much later and for which compelling evidence has accumulated only recently, advocates a hierarchical organization of cancer cells, with a prominent role for a subpopulation of stem-like cells that would sustain tumor growth.[3] In addition, it has nowadays become evident that solid tumors are constituted of multiple cellular components, including bona fide malignant cells as well as endothelial, structural and immune cells.[4,5] Often, such non-malignant cell populations largely outnumber tumor cells, a notion with important pathophysiological and therapeutic implications that has received appropriate attention only recently.[6–8]

Accumulating evidence indicates that malignant cells exert a major control on their non-malignant neighbors. Thus, most cancer cells not only promote angiogenesis to support tumor growth beyond the size limit that would be dictated by a poorly vascularized microenvironment,[9,10] but also activate metabolic circuitries whereby stromal cells are de facto rewired to function as a feeder compartment, generating large amounts of energetic products such as lactate and ketone bodies.[11,12] Cancer-associated fibroblasts (CAFs) are prominent sources of mitogenic and pro-angiogenic factors such as interleukin (IL)-6 and vascular endothelial growth factor (VEGF).[13] Furthermore, cancer cells, either directly or through CAFs, produce a wide array of cytokines including transforming growth factor β (TGFβ) and IL-10 that exert potent immunosuppressive effects.[14] Altogether, these observations demonstrate that during oncogenesis, malignant cells become capable of co-opting the local microenvironment in order to satisfy their own metabolic and immunological needs.

Although part of the immune infiltrate is constituted by immunosuppressive cells that are specifically recruited and/ or instructed by the tumor to maintain an immunoprivileged microenvironment, some tumor-infiltrating leukocytes (TILs) reflect the attempt of the immune system to mount an antitumor response.[7,15,16] Immunosuppressive TILs include (but are not limited to) CD4+CD25+FOXP3+ regulatory T cells (Tregs), T-helper 2 (Th2) CD4+ T cells, myeloid-derived suppressor cells (MDSCs), M2 macrophages and N2 neutrophils. Conversely, CD8+ cytotoxic T lymphocytes (CTLs), T-helper 1 (Th1) and T-helper 17 (Th17) CD4+ T cells, M1 macrophages, N1 neutrophils, natural killer (NK) cells and dendritic cells (DCs) most often promote antitumor responses.[7,15]

Of note, the major role that the immune system plays in oncogenesis, tumor progression and response to therapy has received appropriate credit only during the last decade. Previously, the immune system would be considered as a mere bystander of cancer, incapable of reacting as a result of conventional self-tolerance mechanisms.[17] Now, it has become clear that inflammatory and immune reactions can exert both pro- and anti-tumor effects, depending on the specific context.[17] In particular, the cancer immunoediting hypothesis postulates that the immune system initially can eradicate potentially tumorigenic cells as they develop, a capacity that is progressively lost when transformed cells acquire mutations that sustain immunosubversion and/or immunoevasion.[17] Moreover, accumulating evidence indicates that the success of some anticancer therapies, including conventional cytotoxic compounds, radiotherapy as well as targeted agents, depends (at least partially) on the activation of anticancer immune responses.[8] Along with these conceptual revolutions, increasing interest has been attracted by the possibility that the abundance of specific tumor-infiltrating cell populations might constitute a biomarker for risk stratification (i.e., a prognostic biomarker) or even predict the response of patients to specific therapies (i.e., would constitute a predictive biomarker).[7,18]

Along the lines of our Trial Watch series,[19–25] we will discuss clinical trials that have investigated/are investigating the prognostic and/or predictive value of the immune infiltrate in the context of solid malignancies.

T Lymphocytes

T lymphocytes constitute a diversified group of immune cells sharing the expression of an antigen-specific T-cell receptor (TCR) and a few key signaling molecules, including CD3. T cells develop in the thymus and are locally selected for (1) not recognizing self antigens (negative selection) and (2) being capable to recognize non-self antigens when presented in the context of autologous MHC molecules (positive selection).[26,27] T cells can be grossly subdivided based on the chains that compose their TCR into αβ and γδ cells, the latter constituting a small population that operate at the interface between innate and adaptive immunity.[28] Alternatively, T lymphocytes can be classified based on the expression at the cell surface of either CD8, allowing CTLs to recognize antigenic epitopes presented on MHC Class I molecules, or CD4, allowing helper T cells to recognize antigenic epitopes presented on MHC Class II molecules. According to a perhaps oversimplified model, CD8+ CTLs can specifically recognize (via their TCR) and kill infected or malignant cells, whereas TCR-activated CD4+ T cells secrete stimulatory signals for CTLs as well as for other immune cell populations.[29] In this setting, T-helper (Th) responses can be classified based on the cytokine cocktail that is secreted by activated CD4+ T cells. Thus, while Th1 responses (which promote antiviral and antitumor effects) mainly involve IL-2 and interferon (IFN) γ, their Th2 counterparts develop along with the secretion of IL-4, IL-5, IL-10 and TGFβ, de facto exerting pro-tumorigenic functions.[30] The precise impact of Th17 responses (featuring the secretion of high levels of IL-17) on oncogenesis, tumor progression and response to therapy remains to be elucidated.[31–33] Irrespective of this unresolved issue, a critical class of CD4+ cells is constituted by Tregs, CD4+CD25+FOXP3+ lymphocytes that exert potent and multifaceted immunosuppressive functions.[34]

Of note, activated CD4^{+} and CD8^{+} T lymphocytes can differentiate into central or effector memory T cells, both of which are characterized by a CD45RA^{-}CD45RO^{+} phenotype (the former, but not the latter, also expressing CCR7).[35,36] Memory T cells are important in that they drive secondary immune responses (i.e., immune responses against antigens that have already been in contact with the immune system), de facto underlying the efficacy of vaccination.[35] All naïve (CD45RA^{+}) T cells must be activated by antigen-presenting cells (APCs) such as macrophages or DCs, providing both a TCR-transduced signal (i.e., an antigenic epitope presented in association of self MHC molecules) and a co-stimulatory signal, such as that transduced by the binding of B7 molecules on APCs and CD28 on T cells.[37,38]

Whether tumor infiltration by T cells would influence disease outcome in cohorts of cancer patients was one of the first questions of tumor immunology, formulated even before the actual recognition of oncoimmunology as a self-standing discipline, and has been extensively addressed during the past 15 y.[8] How this question has been approached provides interesting insights into the theoretical and technical advances that have been made in the field since then. Indeed, for a long period extending until today, intratumoral T cells have been quantified based on one or more of their major surface markers, namely CD3, CD4 and CD8. Although this approach may appear relatively gross in view of the extensive functional heterogeneity of T cells, it has generated a sizeable amount of literature demonstrating that high levels of intratumoral T cells generally constitute a positive prognostic factor. Thus, high levels of intratumoral CD3^{+} cells have been associated with improved disease outcomes in cohorts of carcinoma patients receiving neoadjuvant chemotherapy (n = 25);[39] in surgically resected hepatocellular carcinoma (HCC) patients (n = not available), together with DC infiltration;[40] in colorectal cancer patients (n = 160), highlighting a prominent role for the peritumoral infiltrate;[41] in subjects affected by advanced ovarian carcinoma (n = 186); and in prostate cancer patients receiving IL-2-based immunotherapy (n = 24)[42] or not (n = 59).[43] Tumor infiltration by cytotoxic CD3^{+}CD8^{+} CTLs has been attributed a positive prognostic value in cohorts of breast carcinoma patients (n = 1334), positively correlating with tumor grade and inversely correlating with age at diagnosis, estrogen receptor as well as progesterone receptor positivity;[44] differentiated thyroid carcinoma patients (n = 398);[45] subjects affected by oral squamous cell carcinoma (n = 132);[46] glioblastoma patients vaccinated with DC-based immunotherapy (n = 23);[47] subjects affected by esophageal carcinoma (n = 70);[48] non-small cell lung carcinoma (NSCLC) patients (n = 199), highlighting a preponderant prognostic value for T cells infiltrating cancer nests and the tumor stroma;[49] subjects affected by melanoma (n = 264 and n = 285), a setting in which T-cell infiltration appears to convey independent prognostic information;[50,51] surgically resected HCC patients (n = 44);[52] Merkel cell carcinoma patients (n = 146);[53] subjects affected by colorectal carcinoma (CRC) (n = 447, n = 276, n = 41, n = 93, n = 152, n = 97; n = 160 and n = 470);[54–61] ovarian carcinoma patients who underwent surgical resection (n = 70);[62] prostatic adenocarcinoma patients (n = 325);[63] and subjects affected by muscle-invasive urothelial carcinoma (n = 69).[64] Similarly,

increased intratumoral levels of both CD3^{+}CD8^{+} CTLs and not better characterized CD3^{+}CD4^{+} helper T cells have been associated with improved clinicopathological parameters in cohorts of head and neck carcinoma (HNC) patients treated with IRX-2-based immunotherapy (n = 15, n = 42 and n = 27);[65–67] esophageal cancer patients who underwent tumor resection (n = 122 and n = 181), a setting in which NK-cell accumulation also conveyed prognostic information;[68,69] surgically resected NSCLC patients (n = 335), highlighting a prominent prognostic value for CD4^{+} cells accumulating at stromal, as opposed to epithelial, sites;[70] subjects affected by melanoma;[71] surgically resected HCC patients (n = 163);[72] pancreatic adenocarcinoma patients (n = 80), correlating with an intense infiltration by DCs;[73] gallbladder cancer patients treated with curative surgery (n = 110), a setting in which also DC, but not NK-cell, infiltration, conveyed prognostic information;[74] prostate carcinoma patients undergoing radical prostatectomy (n = 188), a setting in which B-cell infiltration also provided prognostic insights;[75] vulval intraepithelial neoplasia patients receiving therapeutic human papillomavirus vaccination combined with the Toll-like receptor (TLR) 7 agonist imiquimod (n = 19),[76] and patients affected by various solid tumors (including breast carcinoma, melanoma and renal cell carcinoma, RCC) undergoing IL-2-based immunotherapy.[77] Of note, CD3^{+} CD4^{+} and CD8^{+} cells (together with CD20^{+} and CD57^{+} cells) have been shown to preferentially accumulate at the margins of breast carcinoma lesions ablated by high intensity focused ultrasound (n = 23 patients), as opposed to similar lesions removed by radical mastectomy (n = 25).[78] Nevertheless, no direct assessments of clinical outcome were performed in this study.

More recently, the identification of intratumoral T cell subsets (and hence the evaluation of their prognostic/predictive value) has been significantly refined, thanks to the implementation of detection techniques that allow for the quantification of T-cell functional markers including proteins related to cytotoxicity (e.g., the granule components granzyme B and TIA-1), proliferative potential (e.g., the nuclear antigen Ki67), helper profile (e.g., intracellular IFNγ, IL-4, IL-10 and IL-17), activation status (e.g., CD69), memory status (e.g., CD45RO) and immunosuppressive capacity (e.g., FOXP3). Thus, tumor infiltration by CD8^{+}granzyme B^{+} cells has been associated with longer survival in cohorts of CRC (n = 131) and ovarian carcinoma (n = not available) patients,[79,80] but with worsened disease outcome in anal squamous cell carcinoma patients (n = 38).[81] The levels of intratumoral CD8^{+}TIA-1^{+} cells inversely correlated with tumor grade, while those of Tregs directly did so, in a cohort of pancreatic ductal adenocarcinoma patients (n = 198),[82] and emerged as a positive prognostic factor among optimally debulked high-grade serous epithelial ovarian carcinoma patients (n = 199).[83] Increased amounts of intratumoral CD8^{+}Ki67^{+} cells have been linked to improved disease outcome in cohorts of RCC (n = 221) and CRC (n = 415 and n = 131) patients,[79,84,85] but not of surgically resected NSCLC patients (n = 178), a setting in which the accumulation of CD8^{+}Ki67^{+} cells in cancer cell nests actually constituted an independent unfavorable prognostic factor by multivariate analysis.[86] High levels of intratumoral CD69^{+} cells have been associated with improved locoregional control of

the tumor and longer survival in melanoma (n = 58) and HNC (n = 84) patients,[87,88] although only in the latter setting additional lymphocytic markers were monitored (i.e., CD4). Robust tumor infiltration by CD8+CD45RO+ cells has been associated with improved disease outcome in large cohorts of CRC patients (n = 415, n = 602, n = 599, n = 87 and n = 768);[85,89–93] NSCLC patients (n = 74), a setting in which T cells were found to stay in close proximity of mature DCs (mDCs) within a so-called "tumor-induced bronchus-associated lymphoid tissue";[94,95] and HCC patients who underwent surgical resection (n = 302).[96]

The development of Th1 responses, alone or linked to the suppression of Th2 responses, has been shown to constitute a positive prognostic marker in cohorts of breast carcinoma patients (n = 112 and n = 1123),[97,98] pediatric medulloblastoma patients (n = 17);[99] subjects awaiting surgery for esophageal cancer (n = 32), correlating with TNM stage;[100] gastric cancer patients who underwent curative gastrectomy (n = 157);[101] CRC patients (n = 103 and n = 125);[102,103] and ovarian carcinoma patients (n = 99 and n = 40).[104,105] The development of Th2 responses has been associated with no prognostic value in a cohort of CRC patients (n = 125), contrarily to Th1 and Th17 responses;[103] with significantly improved disease- and event-free survival in a cohort of Hodgkin Lymphoma patients (n = 87), a setting that is dominated by Th2 immunity,[106] and with worsened outcomes in pancreatic cancer patients (n = 69), correlating with the establishment of an immunosuppressive tumor microenvironment.[107] On a similar note, while circulating CD4+ T cells isolated from healthy donors (n = 23) responded to an antigenic challenge by producing IFNγ and granulocyte macrophage colony-stimulating factor (GM-CSF), their counterparts obtained from prostate cancer patients (n = 44) did so by producing IL-5, thus manifesting a skew toward Th2 immunity.[108] Th17 responses have been given no prognostic value in a cohort of HNC patients (n = 106),[109] shown to constitute positive prognostic factors in cohorts of gastric (n = 192),[110] esophageal (n = 181)[69] and ovarian carcinoma (n = 201) patients,[111] and linked to worsened disease outcome in cohorts of NSCLC (n = 52),[112] HCC (n = 178),[113] and CRC (n = 125 and n = 52) patients.[103,114]

Recently, great efforts have been dedicated to ascertain whether the levels of intratumoral CD4+CD25+FOXP3+ Tregs would have a prognostic or predictive value in cancer patients, with rather heterogeneous results. No significant association with disease outcome has been reported for Treg infiltration in cohorts of glioma (n = 135),[115] glioblastoma (n = 29)[116] and melanoma (n = 58 and n = 97) patients.[87,117] Conversely, high levels of intratumoral Tregs have been associated with worsened disease outcomes in cohorts of breast carcinoma patients (n = 309 and n = 1445);[118,119] subjects affected by gastric cancer (n = 80), highlighting a prominent prognostic valued for Treg localization, rather than absolute abundance;[120] resected NSCLC patients (n = 100 and n = 87);[121,122] individuals affected by melanoma (n = 66, n = 100 and n = 50);[123–125] pancreatic ductal adenocarcinoma patients (n = 198);[82] RCC patients receiving IL-2-based immunotherapy (n = 100);[126] and ovarian carcinoma patients (n = 104).[127] Conversely (and in part surprisingly), tumor infiltration by Tregs has been shown to constitute a positive prognostic

factor in cohorts of HNC patients (n = 84 and n = 56), correlating with a better locoregional control of the tumor and prolonged overall survival;[88,128] individuals affected by multiple types of lymphoma (n = 97 and n = 1019);[129,130] CRC patients (n = 967, n = 57, n = 1420, n = 87, n = 768 and n = 76);[92,93,131–134] cystectomized bladder carcinoma patients (n = 37);[135] and optimally debulked high-grade serous epithelial ovarian carcinoma patients (n = 199).[83] While in some settings, such as CRC, these findings may reflect the very peculiar nature of the oncogenic program, involving a prominent pro-inflammatory component,[136] in others, such as bladder carcinoma, they are not easily reconciled with the current knowledge. One possibility is that studies specifically measuring Treg infiltration are intrinsically prone to imprecise determinations as the intratumoral amounts of Tregs often correlates with the levels of cytotoxic and/or helper T cells.[87] Alternatively, such apparently odd results may reflect the existence of functionally heterogeneous FOXP3+ and FOXP3- cell populations (see below).

To circumvent (at least in part) this issue and obtain a more reliable prognostic/predictive indication, several studies have measured tumor infiltration by both FOXP3+ and CD4+FOXP3- or CD8+FOXP3- cells and integrated such assessments into a combined score (most often represented by the ratio between CD4+FOXP3- or CD8+FOXP3- and FOXP3+ cells). Invariably, tumors that are predominantly infiltrated by effector cells have a better outcome than tumors in which Tregs prevail, as demonstrated in cohorts of breast carcinoma (n = 56, n = 162 and n = 60),[137–139] HNC (n = 106),[109] lymphoma (n = 87),[106] NSCLC (n = 64),[140] HCC (n = 302),[141] and ovarian carcinoma (n = 117, n = 306 and n = not available) patients.[80,142,143]

When this Trial Watch was being redacted (August 2012), official sources listed five clinical studies that would evaluate the predictive/prognostic value of intratumoral T cells in cohorts of cancer patients (**Table 1**). The first one (NCT00854282; current status: recruiting) aims at investigating the impact of intratumoral FOXP3+ cells on the overall survival of ovarian carcinoma patients undergoing surgical resection. The second one (NCT00896922; current status: unknown) intends to evaluate the prognostic significance of FOXP3+ cells (as well as that of CD68+ and CD163+ cells) in follicular lymphoma patients receiving immunochemotherapy. The third one (NCT01513408 current status: recruiting) will investigate if and how intratumoral CD8+ and FOXP3+ cells influence the survival and response to therapy of breast carcinoma patients treated with neoadjuvant therapy. Finally, two trials (NCT00673192; NCT00854269; current status: unknown) will evaluate the predictive/prognostic value of cellular (and humoral) immunity in cohorts of cervical cancer patients, yet the authors do not clearly state how they intend to quantify these parameters (source www.clinicaltrials.gov).

NK and NKT Cells

NK cells are a group of CD3-TCR- large granular lymphocytes that derive from common lymphoid progenitors that also generate B and T lymphocytes, the main anatomical sites for NK-cell differentiation being the bone marrow, spleen, thymus, lymph

Table 1. Current clinical trials involving the prognostic/predictive evaluation of the intratumoral immune infiltrate

Cell type	Setting	Phase	Status	Notes	Ref.
B cells (?) T cells (?)	Cervical carcinoma Surgery	n.a.	Unknown	Not better specified approach and clinicopathological parameters	NCT00673192 NCT00854269
FOXP3⁺ Tregs	Ovarian carcinoma Surgery	n.a.	Recruiting	Not better specified approach Primary outcome: OS Secondary outcome: Severity and progression	NCT00854282
FOXP3⁺ Tregs CD8⁺ T cells	Breast carcinoma Neoadjuvant chemotherapy	n.a.	Recruiting	IHC detection of the CD8⁺/ FOXP3⁺ T-cell ratio Primary outcome: OS Secondary outcome: RFS, pCR and PathIm score	NCT01513408
FOXP3⁺ Tregs TAMs	Follicular lymphoma Immunochemotherapy	n.a.	Unknown	IHC detection of FOXP3⁺, CD68⁺ and CD163⁺ cells Primary outcome: Prognostic significance of FOXP3⁺ Tregs and TAMs	NCT00896922
FOXP3⁺ Tregs T cells	Bladder cancer Immunochemotherapy	n.a.	Ongoing, Not recruiting	Not better specified approach Primary outcome: OS Secondary outcome: Response to therapy	NCT01198808
TAMs	Lung cancer Not specified	n.a.	Unknown	Not better specified detection of M1 vs. M2 TAMs Primary outcome: OS and response to therapy Secondary outcome: Clinical presentation	NCT00690261
TAMs	Wilms' tumor Not specified	n.a.	Unknown	Not better specified IHC approach Primary outcome: Prognostic significance of TAMs	NCT01493817

Abbreviations: IHC, immunohistochemical; n.a., not available; OS, overall survival; PathIm, pathological-immunological; pCR, pathological complete response; TAM, tumor-associated macrophage; Treg, CD4⁺CD25⁺FOXP3⁺ regulatory T cell.

nodes and tonsils.[144] NK cells play a fundamental role in innate immunity. Thus, owing to a diversified set of inhibitory and activating transmembrane receptors, NK cells are capable of specifically recognizing and killing virus-infected and transformed cells well before the initiation of an adaptive immune response.[144,145] In addition, NK cells express the co-stimulatory receptor CD7, the adhesion molecule CD56, the glucuronosyltransferase CD57 (which is also expressed by T cells) and CD16 (FcγRIII), hence sharing with macrophages the ability to detect opsonized material.[146] However, while macrophages respond to the engagement of CD16 by activating the phagocytic program (see below), NK cells mediate the lysis of opsonized cells by releasing perforin- and granzyme B-containing granules.[144,145] Of note, a consistent proportion (~50%) of circulating NK cells expresses CD8, labeling an NK-cell subset that exhibits increased survival upon activation and enhanced effector functions.[147] Along similar lines, NK cells, in particular those found in lymphoid tissues, express CD4, increasing their capacity to secrete cytokines upon activation and conferring them the ability to respond to the chemotactic factor IL-16.[148] Beyond their innate cytotoxic activity against infected and malignant cells, NK cells are also important for adaptive immunity, in particular as they mediate the so-called "DC editing."[149,150] Thus, NK cells are capable of selectively killing DCs that fail to properly mature in response to activation stimuli (often as these cells express low levels of MHC Class I and II molecules), de facto purging the DC repertoire from potentially tolerogenic cells.[149,150] In line with their critical contributions to both the innate and adaptive arms of the immune response, NK cells have been recognized to mediate considerable antitumor effects more than one decade ago.[151–154] In

particular, NK cells appear to underlie the mechanism of immunosurveillance that (at least initially) prevents metastatic colonization.[144,145] Recent data confirm that NK cells are required for the elicitation of potent tumor-specific CTL responses, presumably as they edit, hence optimizing, the DC repertoire.[155]

No statistically significant association between high intratumoral levels of NK cells, most often detected as CD56⁺ or CD57⁺ cells, and clinicopathological parameters has been detected in cohorts of esophageal carcinoma patients (n = 122), a setting in which T-cell infiltration was shown to strongly correlated with prognosis;[68] stage I NSCLC patients (n = 40);[156] and subjects affected by gallbladder cancer (n = 110), at odds with T-cell and DC infiltration.[74] The findings by Cho et al. were disconfirmed by several subsequent studies, linking tumor infiltration by NK cells to improved disease outcomes in (primary resected) esophageal carcinoma patients,[69,157,158] even in settings in which high levels of intratumoral DCs apparently did not correlate with prognosis.[157] Similarly, robust tumor infiltration by NK cells has been associated with improved disease outcomes in cohorts of head and neck squamous cell carcinoma patients receiving intratumoral IL-12 (n = 10);[159] subjects affected by gastric cancer (n = 146 and n = 169), irrespective of DC infiltration;[160,161] HCC patients;[162] and CRC patients who underwent curative colectomy (n = 157 and n = 93), correlating with the intratumoral abundance of T cells.[57,163] Along similar lines, it has recently been demonstrated that parameters reflecting the functional status of circulating NK cells (in particular, IFNγ secreted in response to IL-2 or mDCs) can predict the long-term survival of gastrointestinal stromal tumor patients receiving imatinib mesylate therapy (n = 77).[164,165]

Natural killer T (NKT) cells constitute a lymphocyte subset sharing features of both T and NK cells. On one hand, similar to T lymphocytes, NKT cells are equipped with an αβ TCR and, optionally, with CD4 or CD8 co-receptors. On the other hand, NKT cells express CD16 and CD56, in thus far resembling NK cells.[166] Upon activation, NKT cells produce large amounts of cytokines including IFNγ, IL-4 and GM-CSF, thus exerting potent antiviral and antitumor activity.[166–168] Based on phenotypic markers and functional properties, NKT cells have been classified into three main groups.[168] Type 1, "classical" or "invariant" NKT cells bear TCRs that are far more restricted in diversity than T-cell counterparts, obligatorily involving a Vα24 chain (Vα14 in mice).[169] Type 2, "non-classical" or "diverse" NKT cells significantly resemble their invariant counterparts, with the notable exception that they can count on a non-limited TCR repertoire.[166] Indeed, both these NKT-cell subsets fail to recognize antigenic peptides presented by MHC molecules, yet efficiently react to lipids and glycolipids presented by CD1d, thus playing a prominent role in innate immune responses to infectious agents such as *Mycobacterium tuberculosis*.[170,171] Of note, whereas type 1 NKT cells are reactive against α-galactosylceramide, a component of the cell wall from Gram-negative lipopolysaccharide-negative bacteria, type 2 NKT cells are not.[170,171] Finally, so-called "NKT-like" NKT cells are characterized by a normal TCR repertoire, by the capacity to recognize peptide-MHC complexes and by the expression of CD3 and CD56, de facto constituting the NKT-cell subset that most resembles T cells.[168] Of note, NKT cells appear to mediate potent anticancer effects via multiple mechanisms, among which their capacity to selectively kill a peculiar subset of tumor-associated macrophages as well as MDSCs (see below).[172,173] Moreover, cancer patients exhibit circulating and intratumoral NKT cells that are reduced in number and characterized by prominent functional alterations, perhaps owing to a defective crosstalk with DCs.[174–177] Thus, NKT cells appear to be intimately involved in oncogenesis and tumor progression. In line with this notion, great efforts have recently been dedicated to the development of strategies that would harness the antitumor potential of NKT cells.[178–180]

This said, whether high intratumoral levels of CD3+CD57+ NKT cells are associated with improved clinical outcome remains to be elucidated, and perhaps may be influenced by disease setting and/or other clinicopathological variables. So far, only a few studies have addressed this issue. A high prevalence of intratumoral NKT cells has been associated with poor overall survival and reduced time-to-recurrence in a cohort of HCC patients (n = 42).[181] Along similar lines, elevated levels of circulating CD3+CD57+ NKT cells have been shown to constitute (similar to tumor depth) an independent risk factor in a cohort of advanced (Stage III-IV) gastric carcinoma patients (n = 48).[182] Conversely, robust tumor infiltration by invariant NKT (iNKT) cells has been indicated as an independent favorable prognostic factor in a cohort of CRC patients (n = 103), and has been suggested to predict the outcome of an NKT cell-targeted glycosphingolipid employed for the therapy of several distinct advanced solid tumors (n = 24) in the context of a Phase I clinical trial.[178] Furthermore, the reconstitution of the iNKT-cell compartment appears to be required for the long-term remission of pediatric leukemia patients undergoing HLA-haploidentical stem cell transplantation, as assessed in a cohort of n = 34 individuals.[183]

When this Trial Watch was being redacted (August 2012), official sources listed no clinical studies that would investigate the predictive/prognostic value of NK- and NKT-cell infiltration in cohorts of cancer patients (source www.clinicaltrials.gov).

Dendritic Cells

DCs constitute a relatively small population of myeloid cells exhibiting a peculiar tree-like morphology, after which Ralph Steinman and colleagues originally named them ('dendron' is indeed the Greek term for tree) in 1973.[184] DCs derive from myeloid bone marrow progenitors and can be found in practically all tissues, yet are highly enriched at sites where antigen exposure is most intense (e.g., lymphoid organs, the body surface, internal mucosae).[185,186] In general, tissue-resident DCs are immature, i.e., they are characterized by a high capacity for taking up antigens but a limited potential for releasing cytokines, and they express (1) MHC Class II molecules mostly in the late endosome-lysosomal compartment, (2) low levels of co-stimulatory molecules (e.g., OX40L, CD40, CD70, CD86) and (3) specific chemokine receptors.[187] Following antigen uptake and the obligatory exposure to one among multiple maturation stimuli, including microbe-associated molecular patterns (MAMPs), endogenous damage-associated molecular patterns (DAMPs) and specific paracrine mediators, immature DCs (iDCs) acquire a novel surface phenotype and functional profile.[188] As compared with iDCs, mDCs feature (1) a significantly compromised capacity to capture antigens, (2) increased levels of MHC Class II molecules (including HLA-DR) and other components of the machinery for antigen presentation (e.g., CD1A, CD83, CD208/DC-LAMP, fascin) at the cell surface, (3) the expression of chemokine receptors that are required for their migration to lymphoid organs (e.g., CCR7) and (4) an improved capacity to secrete cytokines/chemokines.[187] Notably, mDCs are highly efficient at eliciting adaptive immune responses, much more than other APCs including macrophages.[189] Conversely, in the absence of maturation signals, iDCs efficiently present antigens to T cells in the context of inhibitory interactions, a response that is critical for the development of peripheral self tolerance.[190]

Multiple subsets of DCs have been described, regulating not only humoral vs. cellular immunity, but also more refined aspects of the latter.[191–193] These include, but are not limited to: (1) human CD14+ dermal DCs, mainly stimulating naïve B cells to differentiate into antibody-producing plasma cells and memory B cells;[194,195] (2) epidermal Langerhans cells, preferentially stimulating CD8+ T-cell responses;[194,195] (3) circulating CD141+ DCs (the human homologs of murine CD8α+ DCs), perhaps constituting the DC subset most efficient at cross-presentation[196–199] and (4) plasmacytoid DCs (pDCs).[200,201] As opposed to their "conventional" counterparts (often indicated with the adjective as "myeloid," improperly, as all DCs have a myeloid origin), pDCs morphologically resemble to antibody-secreting plasma cells and express high levels of endosomal TLR7 and TLR9,[202–204] providing them

with a superior capacity to respond to MAMPs and DAMPs by secreting high levels of type I IFN (in both mice and humans) and IL-12 (only in mice).[205–207] On histological sections, DCs are often identified as they express the Ca²⁺-binding protein S-100, with CD11c (one subunit of CR4, a heterodimeric receptor for the complement component iC3b) and CD123 (the α chain of the IL-3 receptor) being preferentially expressed to high levels by conventional DCs and pDCs, respectively.[208,209] DCs occupy a central position in the immune system, operating as prominent APCs and orchestrating a wide repertoire of responses that span from the development of self tolerance to the induction of potent cellular and humoral immune responses.[190,210] Accordingly, great efforts have been dedicated during the last couple of decades to the development of strategies that would harness the great immunostimulatory potential of DCs against cancer.[19,187]

Elevated intratumoral amounts of DCs have often, but not always, been associated with an improved clinical outcome, most likely owing to the fact that DCs exist in several functionally distinct subsets that cannot be appropriately discriminated by common immunohistochemical approaches. Thus, no statistically significant association between high levels of intratumoral DCs (most often identified as S100⁺ cells) and clinicopathological parameters including disease course has been detected in cohorts of esophageal carcinoma (n = 101) and lung cancer (n = 39) patients.[157,211] Conversely, tumor infiltration by not-better characterized S100⁺ DCs has been associated with improved clinical outcomes in cohorts of nasopharyngeal carcinoma patients (n = 45), correlating with high levels of T cells and macrophages;[212] subjects affected by oral squamous cell carcinoma (n = 132), a setting in which the high levels of intratumoral S100⁺ DCs correlated with the peritumoral accumulation of mDCs and T cells;[46] esophageal cancer patients who underwent surgical resection (n = 88 and n = 203), in one setting correlating with the levels of expression of p53 by tumor cells;[213,214] subjects affected by gastric carcinoma (n = 93; n = 165, n = 123, n = 169 and n = 92);[161,215–218] high-risk melanoma patients receiving GM-CSF-based immunotherapy (n = 42);[219] surgically resected HCC patients (n = 44 and n = not available);[40,52] gallbladder cancer patients treated with curative surgery (n = 110);[74] subjects affected by RCC (n = 69), negatively correlating with lymph node metastasis;[220] and endometrial carcinoma patients (n = 115), upon both uni- and multivariate analyses.[221] Tumor infiltration by mDCs (identified as fascin, CD1A, CD83 or CD208-expressing cells) has been linked to improved clinical outcomes in cohorts of diffuse large B-cell lymphoma patients (n = 48), with a particular propensity of DCs to accumulate within nodal, as opposed to extra-nodal, lesions;[222] subjects affected by esophageal cancer (n = 67), correlating with the accumulation of T cells around tumor nests;[223] breast carcinoma patients (n = 130), a setting in which CD83⁺ (but not CD1A⁺) DCs had an independent prognostic relevance;[224] subjects affected by NSCLC (n = 74);[94,95] melanoma patients (n = 82), again correlating with T-cell infiltration;[225] and RCC patients receiving cytokine-based immunotherapy (n = 25).[226] Along similar lines, tumor infiltration by Langerhans cells has been associated with prolonged overall survival in cohorts of nasopharyngeal carcinoma (n = 119) and NSCLC (n = 74)

patients,[95,227] apparently in contrast with the notion that these cells generally behave as iDCs and hence promote tolerance. Conversely, elevated intratumoral levels of CD208⁺ mDCs have been linked to worsened disease outcomes in cohorts of breast carcinoma patients (n = 152);[228] subjects affected by gastric carcinoma (n = 128);[229] and CRC patients (n = 104).[230] Similar results have been obtained for CD123⁺ pDCs in patients affected by breast carcinoma (n = 152) and melanoma (n = 186).[228,231] In the context of CRC, such a negative correlation between tumor-infiltrating mDCs and clinical outcome is rather expected, in line with the fact that high intratumoral levels of Tregs positively (rather than negatively, as in most other cancers)[8] affect CRC prognosis.[92,93,131–134] This said, the results obtained by Treilleux et al. and Ishigami et al. on cohorts of breast carcinoma and gastric cancer patients, respectively,[228,229] are at odds with several previous studies,[161,215–218,224] raising doubts on the actual prognostic/predictive value of DC infiltration in these settings.

When this Trial Watch was being redacted (August 2012), official sources listed no clinical studies that would evaluate as an endpoint the predictive/prognostic value of DC infiltration in cohorts of cancer patients (source www.clinicaltrials.gov).

Macrophages

Macrophages (literally "big eaters," as from the Greek terms makros "large" and phagein "eat") are tissue-resident myeloid cells generated by the differentiation of circulating monocytes following extravasation.[232] Besides exhibiting a considerable size (Ø = 20–80 μm) and peculiar amoeboid movements, macrophages are characterized by the expression of cell surface markers including, but not limited to: CD14 (the co-receptor for the lipopolysaccharide sensor TLR4), CD16 (FcγRIII), CD31 (also known as PECAM1, a member of the immunoglobulin superfamily involved in phagocytosis), CD40 (a co-stimulatory molecule found on multiple APCs), CD68 (a glycoprotein that binds to low density lipoproteins), CD163 (a member of the scavenger cysteine-rich receptor superfamily involved in the clearance of hemoglobin/haptoglobin complexes), EMR1 (an adhesion molecule, the human ortholog to murine F4/80), lysozime M (a glycoside hydrolase that can damage the bacterial cell wall), MAC-1/CR3 (a CD11b/CD18 heterodimer operating both as a pattern recognition receptor and as a receptor for the complement component iC3b), MAC-3 (a receptor for galectin-3) and the mannose receptor C type 1 (MRC1, also known as CD206).[232–234] Thanks to these and other plasma membrane receptors, macrophages exert prominent phagocytic functions, taking up free as well as opsonized particulate material within intracellular vesicles (endosomes) and ensuring its degradation. Being linked to the activation of the so-called "inflammasome," and hence to the release of pyrogenic IL-1β and IL-18,[235] such a phagocytic activity is particularly relevant as a first line of defense against invading pathogens.[233] Moreover, it constitutes a major mechanism whereby the organism disposes of apoptotic corpses and necrotic debris.[233] Macrophages also operate as bona fide APCs, hence processing internalized antigens and presenting them in the context of MHC Class II molecules to elicit adaptive immune

responses. Alongside, macrophages secrete cytokines that de facto dictate the type of immune response. Thus, whereas "classically" activated (M1) macrophages secreting IL-12 promote protective Th1 responses, "alternatively" activated (M2) macrophages favor the establishment of tolerance, owing to the secretion of multiple cytokines including IL-10.[233,236] Of note, M2 macrophages can be phenotypically discriminated from their M1 counterparts as the former express high levels of CD163 and CD206, while the latter bear on their surface consistent amounts of HLA-DR.[237]

The first studies attempting to correlate intratumoral macrophages with disease outcome generated heterogeneous results, most likely owing to the fact that infiltration was assessed with anti-CD68 antibodies, which do not allow for the discrimination between M1 and M2 macrophage subsets. Thus, no statistically significant association between high levels of CD68^{+} cells within neoplastic lesions and clinicopathological parameters including disease course has been detected in cohorts of nasopharyngeal carcinoma (n = 119) and endometrial cancer (n = 109) patients.[227,238] Tumor infiltration by CD68^{+} macrophages has been linked to worsened disease course in cohorts of breast carcinoma patients (n = 249), in relationship with increased microvessel density and VEGF expression;[239] HNC patients who underwent surgery for the removal of laryngeal lesions (n = 98);[240] patients subjected to potentially curative resection of esophageal cancers (n = 56 and n = 121);[241,242] resected gastric cancer patients (n = 97),[243] subjects with resected HCC (n = 137);[244] lung adenocarcinoma patients (n = 113), again in association with increased local angiogenesis;[245] pleural mesothelioma patients who underwent cytoreductive surgery (n = 52), a setting in which also circulating monocytes correlated with poor survival;[246] melanoma patients (n = 58, n = 202 and n = 190), high macrophage counts being associated with markers of aggressive disease including Breslow thickness, ulceration and mitotic rate;[87,247,248] subjects affected by ovarian carcinoma (n = 67);[249] bladder cancer patients receiving intravesical instillations of the bacillus Calmette-Guérin (BCG) (n = 41);[250] prostate cancer patients treated with hormonal therapy (n = 71), a setting in which macrophage infiltration was shown to predict resistance to treatment;[251] and patients affected by renal pelvis and ureteral transitional cell carcinomas (n = 75).[252] Conversely, tumor infiltration by macrophages (most often detected as CD68^{+} cells) has been correlated with improved disease outcome in cohorts of HNC patients bearing nasopharyngeal lesions (n = 45)[212] or treated with IRX-2-based immunotherapy (n = 27);[67] patients bearing differentiated thyroid carcinoma (n = 398);[45] NSCLC patients who underwent surgical resection (n = 175)[253] or receiving chemotherapy for stage IV lesions (n = 199);[49] gastric cancer patients (n = 84), highlighting a correlation between intratumoral macrophages, intratumoral CD8^{+} T cells and tumor cell apoptosis;[254] HCC patients who underwent surgical resection (n = 302);[96] melanoma patients treated with oral BCG (n = 25);[255] CRC patients (n = 97, n = 70, n = 446 and n = 160), overall suggesting a critical role of macrophages at the tumor invasive margin;[60,256–258] and patients affected by various solid tumors (including breast carcinoma, melanoma and RCC) subjected to IL-2-based immunotherapy.[77] Along similar lines, intense tumor infiltration by CD14^{+}CD40^{+} macrophages

has been shown to constitute an independent prognostic factor in a cohort of CRC patients (n = 31).[259]

Recently, clinical studies based on M2-specific phenotypic markers, most often CD163, have provided more consistent results. Thus, tumor infiltration by elevated amounts of CD163^{+} cells have been associated with poor clinical outcome in cohorts of breast carcinoma patients (n = 144), highlighting a critical role for macrophages located within the tumor stroma, but not tumor nests;[260] subjects affected by lung adenocarcinoma (n = 65), correlating with lymphatic microvessel density;[261] melanoma patients (n = 190), further highlighting the revelance of CD163^{+} cells within the tumor stroma;[248] RCC patients (n = 66), although in this setting the association was statistically significant upon univariate, but not multivariate, analyses;[262] primary leiomyosarcoma patients (n = 149);[263] as well as in subjects affected by Hodgkin's lymphoma (n = 288), among which both CD68 and CD163 positivity were associated not only with poor overall survival but also with the presence of the Epstein-Barr virus within neoplastic cells.[264]

When this Trial Watch was being redacted (August 2012), official sources listed three clinical studies that would evaluate the predictive/prognostic value of intratumoral macrophages in cohorts of cancer patients (**Table 1**). The first one (NCT00690261; current status: recruiting) specifically aims at investigating impact of M1/M2 macrophage polarization on cancer progression and prognosis prediction among lung cancer patients with malignant pleural effusions. The second one (NCT00896922; current status: unknown) intends to evaluate the prognostic significance of CD68^{+} and CD163^{+} cells (as well as that of FOXP3^{+} cells) in follicular lymphoma patients receiving immunochemotherapy. The third one (NCT01493817; current status: active, not recruiting) aims at studying the relationship between tumor-associated macrophages and clinicopathological factors within a large assessment of prognostic/predictive biomarkers in patients affected by Wilms' tumor. (source www.clinicaltrials.gov).

Myeloid-Derived Suppressor Cells

The term MDSCs refers to a heterogeneous population of cells that are defined by their common myeloid origin, relatively immature state and capacity to potently suppress both the innate and the adaptive arms of cellular immunity (i.e., NK-cell, NKT-cell and T-cell responses).[265,266] MDSCs are released from the bone marrow in response to a wide array of signals (including cytokines produced by malignant cells and tumor-associated stromal cells as well as mediators secreted by multiple cells following infection or trauma) and de facto derive from monocytic and granulocytic cell progenitors that would normally differentiate into DCs, macrophages, neutrophils, eosinophils or basophils.[266–270] Accordingly, at least two distinct MDSC subsets can be identified based on morphological features and cell surface markers. Thus, whereas all human MDSCs express CD11b, CD33 (a myeloid lineage-specific lectin also known as SIGLEC-3) and CD124 (the α chain of the IL-4 receptor), granulocytic MDSCs can be discriminated from their myeloid counterparts as the former, but not the latter, express the VEGF receptor 1 (VEGFR1) and (low levels of)

CD16. Conversely, monocytic MDSCs express CD14, low levels of HLA-DR and S100-A9 (a Ca^{2+}-binding protein also known as MRP-14 and calgranulin B) while their granulocytic counterparts fail to do so.[266,271–273] MDSCs can suppress the effector functions of NK, NKT and T cells by a variety of mechanisms including a strong conditioning of the local microenvironment that involves the production of reactive oxygen species, reactive nitrogen species and cytokines as well as the less direct cellular circuitries involving Tregs, NK cells and macrophages.[274–277] Recently, the role of MDSCs in oncogenesis, tumor progression and response to therapy has begun to be unveiled. In particular, it has been shown that intratumoral MDSCs (which, optionally, can differentiate into tumor-associated macrophages) promote tumor growth not only as they exert immunosuppressive functions but also since they promote angiogenesis/lymphangiogenesis, both at the primary tumor site and at distant pre-metastatic niches.[278,279] Of note, the levels of circulating MDSCs are altered in transplanted patients[280] as well as in subjects affected by a large spectrum of tumors, often correlating with disease progression.[266,273,275,281,282] This suggests that MDSCs play a prominent role in the pathogenesis of cancer.

Low levels of circulating MDSCs have been reported to constitute a positive prognostic/predictive factor in cohorts of untreated diffuse large B-cell lymphoma patients (n = 91), indicating a prominent role for the monocytic, rather than the granulocytic MDSC subset;[283] stage II-IIIc breast carcinoma patients receiving neoadjuvant disodium glutathione disulfide-containing chemotherapy (n = 40);[284] treatment-naïve, advanced NSCLC patients (n = 87);[285] subjects affected by gastrointestinal neoplasms (n = 40), correlating with the circulating levels of IL-6 and IL-10;[272] advanced melanoma patients treated with an oncolytic virus encoding GM-CSF (n = 50);[125] RCC patients receiving the broad spectrum tyrosine kinase inhibitor sunitinib (n = 23);[286] bladder carcinoma patients (n = 64), correlating with pathological grade and clinical stage;[287] patients bearing esophageal, gastric or pancreatic neoplasms (n = 131);[288] and patients affected by terminal tumors (n = not available).[289] Conversely, low levels of MDSCs have been reported in high-risk (n = 3) neuroblastoma patients, as compared with their low-risk counterparts (n = 1), correlating with reduced levels of circulating IL-10.[290] However, whether neuroblastoma patients truly benefit from high levels of circulating MDSCs and IL-10 will have to be confirmed in large patient cohorts. Intriguingly, it has been reported that the amount of psychological stress experienced by surgically resected breast carcinoma patients (n = 16) alters the levels of circulating MDSCs. This said, the actual implications of these findings for the therapeutic and psychological management of cancer patients remain to be elucidated.

When this Trial Watch was being redacted (August 2012), official sources listed no clinical studies that would evaluate the predictive/prognostic value of circulating or tumor-infiltrating MDSCs in cohorts of cancer patients (source www.clinicaltrials.gov).

B Cells

B cells are small circulating lymphocytes expressing (at least in the vast majority of cases) a monospecific B-cell receptor (BCR), i.e., a fully rearranged immunoglobulin (most often of the M or D type) inserted in the plasma membrane and associated with a signal transduction machinery involving CD79A and CD79B.[291] In all mammals but rabbits, B cells are generated in the bone marrow, where they progressively mature along with the rearrangement of the immunoglobulin-coding genes.[292] Bone marrow-resident BCR+ immature B cells express high levels of the IL-7 receptor, a phenotypic marker that they lose as they migrate to secondary lymphoid tissues (e.g., spleen, lymph nodes, Peyer's patches).[293] Further surface markers that are routinely used for identifying B cells include CD19, CD20 and CD78, all of which start to be expressed along with the rearrangement of the immunoglobulin heavy chain-coding genes.[294] CD19 (which is also expressed by follicular DCs) has been shown to cooperate with CD21 to form a multimeric receptor for several components of the complement system.[295] Conversely, the functions of CD20 (which is currently employed as a target for monoclonal antibody-based therapies against B cell neoplasms)[22] and CD78 are less characterized, although CD20 appears to required for optimal B-cell responses, in particular against T cell-independent antigens.[296]

B cells that recognize an antigen via their BCR can internalize, process and present it, complexed with MHC Class II molecules, to CD4+ T cells. If the latter react to the same antigen by producing IL-4, B cells expand and mature either into antibody-secreting plasma B cells or into memory B cells. Optionally, prior to reach either of these terminal differentiation stages, B cells can undergo the so-called "class switching," i.e., a further genetic rearrangement that shifts the production of antibodies from one class to another while maintaining specificity.[297] Plasma B cells do not express CD19 and CD20, yet can be identified owing to the presence of CD78, CD38 (a cyclic ADP ribose hydrolase), the receptor for IL-6 and high levels of CD27, a member of the tumor necrosis factor α receptor (TNFR) superfamily.[298] Memory B cells are characterized by the expression the BCR, CD19 and CD27, and—similar to their T-cell counterparts—play a critical role in secondary immune responses.[299,300]

B cells generally resemble T cells also in that they are subjected to multiple control mechanisms for the avoidance of autoimmune responses. Indeed, B cells bearing BCRs that recognize self antigens with high affinity are either driven into apoptotic cell death (clonal deletion), either allowed to rearrange their BCR to generate a new binding specificity (receptor editing), or permanently maintained in an unresponsive status (anergy).[301,302] Finally, it should be noted that not all B cells stimulate immune responses. In particular, so-called regulatory B cells (Bregs) respond to antigens by secreting high amounts of IL-10 and TNFα (which inhibit CD8+ CTLs and favor the differentiation of Tregs) and/or by expressing cell death-inducing molecules such as FASL (to which activated B and T cells are particularly sensitive) on their surface, globally exerting potent immunosuppressive effects.[303–307]

Increased amounts of intratumoral or peritumoral CD20+ B cells (alone or together with other immune cells) have been associated with improved clinical outcome in cohorts of surgically resected HCC patients (n = 163);[72] melanoma as well as superficial bladder carcinoma patients receiving BCG-based immunotherapy (n = 30 and n = 20);[255,308] prostate carcinoma patients undergoing

radical prostatectomy (n = 188), a setting in which T-cell infiltration also provided prognostic insights;[75] and optimally debulked high-grade serous epithelial ovarian carcinoma patients (n = 199).[83] The accumulation of CD20^{+} B cells at the invasive margin, at tumor cell nests or within the tumor stroma has been shown to constitute a good prognostic or predictive biomarker in surgically resected NSCLC patients (n = 335);[70] in subjects affected by melanoma (n = 106)[309] as well as in HNC patients receiving IRX-2-based immunotherapy (n = 27).[67] Increased amounts of circulating CD19^{+} B cells that share clonotypic rearrangements with malignant plasma cells are a relatively common finding among multiple myeloma patients, and have been significantly associated (in a cohort of n = 521 patients) with low (rather than high) stage and longer (rather than shorter) overall survival.[310]

When this Trial Watch was being redacted (August 2012), official sources listed two clinical studies that would evaluate the predictive/prognostic value of humoral (and cellular) immunity in cohorts of cervical cancer patients (NCT00673192; NCT00854269) (**Table 1**). This said, the authors of these trials (current status: unknown) do not clearly state whether they intend to quantify intratumoral B cells or whether other, more direct, measures of humoral antitumor immunity will be employed (source www.clinicaltrials.gov).

Other Immune Cells

Neutrophil granulocytes (also known as polymorphonuclear neutrophils, owing to their peculiar multilobulated nuclear morphology) are the most abundant type of white blood cells in mammals.[311] The term "neutrophil" derives from the fact that on hematoxylin and eosin (H&E) cytological preparations, these cells appear of a neutral pink (as opposed to other granulocytes, see below).[312] In response to chemotactic signals, circulating neutrophils are the first to accumulate at sites of inflammation, where they provide a multipronged contribution to innate immune responses by: (1) secreting cytokines that recruit other immune cells; (2) operating as professional phagocytes, though only toward opsonized material (at odds with DCs and macrophages); (3) releasing pre-formed granules containing a wide spectrum of pro-inflammatory or antimicrobial proteins including myeloperoxidase, bactericidal/permeability-increasing protein (BPI), defensins, lactoferrin, cathelicidin, gelatinase and multiple proteases (e.g., elastase and cathepsins); and (4) liberating so-called neutrophil extracellular traps (NETs), i.e., networks of DNA- and protease-containing fibers that are particularly efficient at capturing and killing extracellular bacteria.[311–313]

Similar to macrophages, neutrophils intensely infiltrate neoplastic lesions.[314,315] However, while the depletion of tumor-associated neutrophils (TANs) normally exacerbates CD8^{+} CTL-mediated antitumor effects, the contrary holds true in condition in which TGFβ is blocked.[315] These observations point to the existence of two functionally distinct subsets of TANs: one with antitumor functions, which is generally repressed by TGFβ (N1 TAN), and one that exerts pro-tumorigenic effects (N2 TANs), which predominates in normal conditions.[315] The surface markers that are routinely employed to identify neutrophils include CD11b, the adhesion molecule CD66 (which is also expressed by epithelial and endothelial cells, but not by other immune cells) and Ly6G, a glycosylphosphatidylinisotol-anchored protein of unknown function that can also be found on a subset of eosinophils, differentiating pre-monocytes, and pDCs.[316,317] So far, no surface markers that would be useful to differentiate between N1 and N2 neutrophils have been reported. Neutrophilia (i.e., an increase in circulating neutrophils) is a normal finding in response to bacterial infection or during acute inflammation (for instance following extensive burns or heart attacks). In addition, neutrophilia is the most prominent hematological manifestation of multiple hematopoietic cancers including chronic myelogenous leukemia (CML), some cases of which are driven by the hyperproliferation of neutrophil progenitors.[318]

High levels of intra- or peritumoral neutrophils have been associated with worsened disease outcomes in cohorts of HCC (n = 238)[319] and melanoma (n = 186)[231] patients, as well as among subjects affected by renal pelvis and ureteral transitional cell carcinoma (n = 75).[252] Along similar lines, tumor infiltration by neutrophils has been shown to predict dismal prognosis in a first cohort of surgically resected advanced gastric carcinoma patients (n = 212),[320] but to constitute a positive prognostic factor (for women only) in a second clinical setting (at least apparently) of the same type (n = 273).[321] This (perhaps only apparent) discrepancy will be clarified by the results of future clinical trials.

Eosinophil granulocytes (also known as polymorphonuclear eosinophils or acidophil granulocytes) account for about 1–6% white blood cells in mammals. The term "eosinophil" (literally "loving eosin," from Greek) stems from the fact that on H&E cytological preparations, these cells acquire the intense brick red staining.[322,323] Eosinophils, which are generated by myeloid precursors in the presence of IL-3, IL-5 and GM-CSF, not only play a prominent role against helminthic and viral infections, but also are involved in the pathogenesis of asthma and allergic responses, as they express (in an inducible fashion) high-affinity receptors for the Fc domain of type E immunoglobulins (FcεRI).[322,323] Activated eosinophils can indeed secrete a wide array of cytokines (e.g., IL-2, IL-4, IL-5, IL-8 and IL-13), growth factors (e.g., TGFβ, VEGF), enzymes (e.g., elastase), lipid mediators (e.g., leukotrienes, prostaglandins) and ROS.[322,323] In addition, eosinophils resemble neutrophils in that they can respond to stimulation by releasing pre-formed granules that contain potentially harmful proteins such as major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO) and eosinophil-derived neurotoxin (EDN).[323,324] Activated eosinophils often express on their surface Ly6G, CD9 and CD44 (two cell-surface glycoproteins involved in cell-to-cell interactions, cell adhesion and migration), as well as CD69 (a lectin also expressed by activated T and NK cells).[325,326] In addition, eosinophils can be detected (upon permeabilization) with antibodies targeting MBP and other granule proteins.[327] Although eosinophils have been proposed to sustain tumor angiogenesis[328] and eosinophilia (i.e., an increase in circulating eosinophils) is a relatively common finding in some types of cancer, the precise role that these cells play in oncogenesis, tumor progression and response to therapy has not yet been fully elucidated.[322,323,328]

Tumor infiltration by eosinophils has been reported to convey no prognostic/predictive information in two distinct cohorts of HNC patients (n = 248 and n = 76),[329,330] a finding that was not confirmed by other studies. Indeed, high levels of intratumoral eosinophils have been associated with poor prognosis in two additional cohorts of HNC patients (n = 31 and n = 87),[331,332] but with improved disease outcome in a third HNC patient group (n = 25), yet only among subjects bearing epidermal growth factor receptor (EGFR)+ lesions.[333] Along similar lines, tumor infiltration by eosinophils has been reported to constitute a positive prognostic indicator in cohorts of gastric carcinoma patients (n = 647 and n = 324),[334,335] glioma patients receiving a combinatorial immunotherapeutic regimen (n = 28),[336] subjects affected by lung adenocarcinoma (n = not available),[337] CRC patients (n = 126),[338] and subjects affected by cervical carcinoma treated with radiotherapy (n = 14).[339]

Basophil granulocytes constitute the least common type of granulocytes, representing less than 1% circulating white blood cells. The term "basophil" (literally "loving basicity," from Greek) reflects the fact that these cells are particularly prone to take up basic dyes, acquiring a dark purple/blue staining on H&E cytological preparations.[340,341] Similar to eosinophils, basophils play a prominent role in the innate immune response against parasites, such as ticks, and contribute to the development of allergic reactions, owing to the fact that they constitutively express high levels of FcεRI.[340,342] On activation, basophils release pre-formed granules that contain large amounts of heparin (an anticoagulant), histamine (a vasodilator) and lytic enzymes (e.g., elastase and lysophospholipase), as well as newly synthesized lipids (e.g., leukotrienes) and cytokines (e.g., IL-4). Altogether, these mediators increase the local blood flow, favor the recruitment of additional immune cells and preferentially drive the production of type E immunoglobulins, de facto contributing to the development of hypersensitivity.[340,342–344] Besides FcεRI, basophils express CD69, CD123, CD49 (the α subunit of the heterodimeric integrin α2β1) and TLR4, but neither CD19 nor other relatively common markers of myeloid cells.[340,341] Basophilia (i.e., an increase in circulating basophils) is relatively rare finding that can be observed in some cases of leukemia and lymphoma.[345] This said, whether basophils modulate oncogenesis, tumor progression and response to therapy remains an open conundrum. Indeed, several studies demonstrate that basophilia is a negative prognostic factor for CML patients.[346–348] Still, in this specific setting, the accumulation of circulating basophils is a manifestation of the disease rather than of an antitumor immune reaction.

Even though they derive from different myeloid progenitors, mast cells (also known as mastocytes) are often considered the tissue-resident counterparts of basophils, for multiple reasons.[349] In particular, mast cells resemble basophils in that they express high levels of FcεRI and respond to activation stimuli by releasing IL-4, leukotrienes as well as pre-formed granules containing heparin and histamine.[349–351] Similar to basophils, mastocytes (in particular those localized at mucosal surfaces) exert potent antiparasitic functions[352] and have been involved in the pathogenesis of allergic reactions and autoimmune diseases.[351] In addition, mast cells are known to promote wound healing and angiogenesis as well as to secrete a wide array of mediators that can profoundly influence immune responses including IL-10, TNFα and TGFβ.[328,353,354] In line with this rather heterogeneous functional profile, mast cells have been proposed to exert either pro- or anti-tumor functions, depending on a variety of parameters including tumor type, presence of additional mediators secreted by other cells and (perhaps with a major influence) intratumoral vs. peritumoral localization.[355,356] The surface of mastocytes presents high amounts of the IL-3 receptor as well as of the tyrosine kinase receptor KIT, which is also expressed by variety of non-hematopoietic cell types, including breast epithelial cells, germ cells and melanocytes.[357,358] Moreover, on tissue sections subjected to immunohistochemistry, mast cells can be detected with antibodies that recognize members of the chymase family of serine proteases.[359] As a note, murine mast cells also express high levels of CD34, a cell-surface sialomucin expressed by hematopoietic stem cells and vascular endothelial cells that regulate homotypic and heterotypic cell-to-cell interactions.[357,360]

Robust tumor infiltration by mast cells has been linked to worsened disease outcomes in cohorts of gastric carcinoma (n = 102),[361] lung adenocarcinoma (n = 180),[362] pancreatic cancer (n = 53 and n = 67),[363,364] and RCC (n = 71) patients,[365] as well as in subjects bearing renal pelvis and ureteral transitional cell carcinomas (n = 75),[252] near-to-invariably correlating with increased tumor angiogenesis and metastatic invasion. Conversely, high intratumoral levels of mastocytes have been reported to constitute a positive prognostic factor in cohorts of breast carcinoma (n = 4444),[366] HNC (n = 50),[367] NSCLC (n = 175),[253] CRC (n = 160)[41] and ovarian carcinoma (n = 44)[368] patients. Whether this apparent discrepancy reflects the differential impact of angiogenesis (which mast cells potently induce) on distinct types of cancer remains an unexplored possibility.

When this Trial Watch was being redacted (August 2012), official sources listed no clinical studies that would evaluate as an endpoint the predictive/prognostic value of tumor-infiltrating and/or circulating neutrophil, eosinophils, basophils and mast cells in cohorts of cancer patients (source www.clinicaltrials.gov).

Concluding Remarks

The results of the clinical studies discussed in this Trial Watch strongly support the contention that the abundance of specific TILs can be translated into reliable prognostic information. Although the number of trials that have specifically addressed this question is relatively low, encouraging results have been obtained also in support of the use of TILs as predictive biomarkers. Of note, at least in some instances, scores based on the type, density and localization of specific TIL populations have been shown to convey a prognostic value that is independent from and superior to that of conventional classifications such as the Duke's stage and the UICC-TNM system.[85,89,90] These observations, which for the most part stem from the pioneer work of Jerome Galon and collaborators,[85,89–91,102,103] strongly suggest that immune scores should be integrated into the clinical practice to ameliorate risk stratification and hence aid in therapy-related decision making.[18,369] As the immunophenotyping of TILs may

provide novel prognostic/predictive information that is likely to influence the therapeutic management of cancer patients, a worldwide task force (including 22 international cancer centers) has recently been instituted for validating a quantitative standardized immune score in routine clinical settings.[369]

One emerging concept in this respect relates to the prognostic and/or predictive value of the exact localization of TILs within and around neoplastic lesions. Infiltration is indeed rather heterogeneous and distinct TIL types accumulate with differential kinetics at the tumor center, at its invasive margin and within tertiary lymphoid structures (TLSs) that are located in the proximity of the lesion.[16,18,94] For instance, granulocytes, macrophages, mast cells and MDSCs often penetrate both tumor cores as well as invasive margins. Conversely, NK cells mainly localize within the tumor stroma, not engaging in direct physical interactions with malignant cells. CD8+ T cells preferentially accumulate at invasive margins, while their naïve and memory counterparts are found within TLSs, which also contain a large number of B cells and mDCs. On the contrary, iDCs are found within the tumor core, both in close contact with neoplastic cells and scattered within stromal components.[7,370] A few reports have already provided evidence supporting the notion that the accumulation of a specific TIL population (e.g., CD83+ DCs) at a specific site (e.g., the invasive margin) conveys prognostic information while the recruitment of the same cells to another location does not.[371] Thus, the clinical implementation of an immune score will have to take into account not only the differential predictive and/or prognostic value of specific TILs, but also that of their intratumoral and/or peritumoral localization. This is further complicated by the fact that the infiltration of immune cells varies quite significantly across cancer types, indicating that the immune system reacts in a relatively specific fashion to distinct neoplasms.[7,372]

Another issue that must be taken into attentive consideration for the clinical implementation of immune infiltrate-based prognostic and/or predictive biomarkers reflects two aspects: (1) the methods whereby TILs are quantified, and (2) our hitherto insufficient knowledge on the phenotypic and functional biology of these cells. Both points are well exemplified by the fact that pioneer studies attempting to evaluate the relevance of intratumoral T cells for disease outcome relied on the immunohistochemical detection of CD3, an invariable component of the TCR signaling complex.[373] Obviously, beyond the intrinsic limitations of immunohistochemistry (which until recently involved an obligate step of visual inspections that, by definition, is prone to operator-dependent bias), such an approach was entirely unreliable in that it quantified a plethora of functionally distinct CD3+ cells, encompassing tumor-reactive CD8+, CD4+ Th1 and Th17 T cells

as well as immunosuppressive CD4+FOXP3+ and Th2 CD4+ Th2 cells.[373] In addition to such relatively gross issues, which are increasingly being resolved along with the discovery of ever more specific surface markers, recent observations indicate that the phenotypic markers that are routinely employed to determine the functional profile of TILs may also be (at least in part) unreliable. Thus, it has recently been shown that a fraction of FOXP3+ cells is not committed to immunosuppressive functions but retain developmental plasticity, being able to differentiate into effector Th cells, in vitro.[374] Along similar lines, some bona fide immunosuppressive FOXP3+ Tregs have been demonstrated to lose FOXP3 expression while retaining their functional profile.[375] Thus, further investigation is warranted to gain deeper insights into the phenotypic and functional profiles of TILs, in turn allowing for the development of detection methods that better reflect the actual role of the immune infiltrate in antitumor responses.

Finally, a mention should be given to immune parameters other than the immune infiltrate that have been shown to influence disease outcome and/or response to therapy in cancer patients. This very large and heterogeneous group of biomarkers includes (but is not limited to) the levels of tumor associated antigen-specific antibodies,[376,377] single-nucleotide polymorphisms in genes coding for factors involved in innate or adaptive immunity such as TLR4 and the purinergic receptor P2RX7,[378–382] the abundance of specific immune cell populations (e.g., MDSCs) in the bloodstream,[282,383,384] the ability of specific immune cell populations (e.g., NK cells) to maintain an elevated production of antitumor cytokines (e.g., IFNγ) in the course of therapy,[165] as well as the expression profile of specific receptors (e.g., NKp30) on the surface of immune cell subsets (e.g., NK cells).[164] The detailed discussion of these biomarkers largely exceeds the scope of this Trial Watch and can be found in refs. 8 and 15. This said, it can be speculated that the prognostic/predictive information conveyed by the abundance, type and localization of TILs (which mainly reflect local immune responses) might be further ameliorated, at least in some instances, by the development of an immune score that would also take into account systemic biomarkers. This possibility will have to be addressed in appropriate clinical settings.

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