

# Trial Watch

## Immunostimulatory cytokines

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**Abbreviations:** AML, acute myeloid leukemia; CAF, cytokine and angiogenic factor; CML, chronic myelogenous leukemia; CRC, colorectal carcinoma; CTLA4, cytotoxic T lymphocyte-associated antigen 4; DC, dendritic cell; EGFR, epidermal growth factor receptor; FBP, folate-binding protein; G-CSF, granulocyte colony-stimulating factor; GIST, gastrointestinal stromal tumor; GM-CSF, granulocyte monocyte colony-stimulating factor; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; HNC, head and neck cancer; IFN, interferon; IL, interleukin; MDSC, myeloid-derived suppressor cell; NMR, nuclear magnetic resonance; NSCLC, non-small cell lung carcinoma; NHL, non-Hodgkin's lymphoma; PAP, prostate acid phosphatase; PDGF, platelet-derived growth factor; PF4, platelet factor 4; RCC, renal cell carcinoma; Teff, effector T cell; TGFβ, transforming growth factor β; TKI, tyrosine kinase inhibitor; TLR, Toll-like receptor; TNFα, tumor necrosis factor α; Treg, FOXP3<sup>+</sup> regulatory T cell; USP15, ubiquitin-specific peptidase 15; VEGF, vascular endothelial growth factor

During the past two decades, the notion that cancer would merely constitute a cell-intrinsic disease has gradually been complemented by a model postulating that the immune system plays a relevant role during all stages of oncogenesis and tumor progression. Along with this conceptual shift, several strategies have been devised to stimulate tumor-specific immune responses, including relatively unselective approaches such as the systemic administration of adjuvants or immunomodulatory cytokines. One year ago, in the July issue of *Oncolimmunology*, we described the main biological features of this large group of proteins and discussed the progress of ongoing clinical studies evaluating their safety and therapeutic potential in cancer patients. Here, we summarize the latest developments in this area of clinical research, focusing on high impact studies that have been published during the last 13 mo and clinical trials launched in the same period to investigate which cytokines can be employed as safe and efficient immunostimulatory interventions against cancer.

### Introduction

More than 130 distinct cytokines have been characterized so far, making up a highly pleiotropic signaling system that can operate in an autocrine, paracrine or endocrine fashion.<sup>1-4</sup> Such a pleiotropism at least in part originates from (1) the highly heterogeneous nature of the cytokine family taken as a whole; (2) the fact that cytokines are produced by a wide variety of cell types throughout the body, including immune, epithelial, endothelial and stromal cells; (3) the existence of several receptors and/or receptor isoforms that exhibit different affinity for the same cytokine, which frequently are expressed by distinct cell types; (4) the fact that cytokines are often involved in feedback and feedforward circuitries that control the secretion and release of other biologically active molecules, including additional cytokines; and (5) the fact that the biological activity of a given cytokine is highly context-dependent, that is, it is influenced by several cell-intrinsic and cell-extrinsic variables, first of all the presence of other cytokines.<sup>5-7</sup> Thus, taken together cytokines regulate (in a partially redundant and overlapping fashion) biological functions as diverse as proliferation, differentiation, chemotaxis, inflammation, (innate and adaptive) immune responses and cell death.

Besides controlling physiological processes such as hematopoiesis,<sup>8</sup> cytokines play a critical role in organismal responses to various danger conditions, including infection by pathogens

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and oncogenesis. In this context, specific cytokine cascades have evolved to sequentially promote the neutralization/removal of the triggering stimulus, allow for tissue repair, and—along with the restoration of homeostasis—self-extinguish.<sup>9</sup> In some cases, however, the initial stimulus cannot be efficiently removed and cytokine production becomes chronic, driving (at least some extent of) tissue damage. Such sites of chronic inflammation are particularly relevant for oncogenesis as they represent abundant sources of potentially mutagenic products (e.g., reactive oxygen species) as well as of mitogenic, anti-apoptotic and angiogenic cytokine cocktails.<sup>10–12</sup> Thus, the administration of immunomodulatory cytokines may not only provoke acute toxicities (often mimicking a state of severe infection), but also exert—at least theoretically—bona fide carcinogenic effects. Both these possibilities must be taken under attentive consideration for the development of safe immunotherapeutic regimens based on immunostimulatory cytokines.

Great efforts have been made in this direction during the past two decades, along with the realization that tumors do not merely originate from cell-intrinsic defects but evolve in the context of cell-extrinsic alterations, including (among many others) an ever more permissive immune system.<sup>13–15</sup> Thus, dozens—if not hundreds—of clinical studies have investigated whether the local or systemic administration of immunostimulatory cytokines—most often in combination with conventional chemotherapeutics—would constitute a safe and efficient maneuver to (re)activate tumor-specific immune responses. In spite of such an intense wave of clinical investigation, which we have extensively discussed 1 y ago,<sup>7</sup> only three recombinant cytokines are nowadays licensed by the FDA or other international regulatory agencies for use as immunostimulatory agents to boost anticancer immunity (in patients who are 18 y of age or older): interferon (IFN)- $\alpha$ 2a (also known as Roferon-A<sup>®</sup>), which is indicated for the therapy of hairy cell leukemia and chronic phase, Philadelphia chromosome-positive chronic myelogenous leukemia (CML), upon minimal pretreatment (within 1 y of diagnosis); IFN- $\alpha$ 2b (also known as Intron A<sup>®</sup>), which is employed for the treatment of follicular lymphoma, hairy cell leukemia, AIDS-related Kaposi's sarcoma, multiple myeloma, melanoma, condyloma acuminata and cervical intraepithelial neoplasms; and interleukin (IL)-2 (also known as aldesleukin or Proleukin<sup>®</sup>), which is used in patients affected by metastatic melanoma and metastatic renal cell carcinoma (source [www.fda.gov](http://www.fda.gov)). A few other recombinant cytokines, including granulocyte colony-stimulating factor (G-CSF, also known as filgrastim, lenograstim or Neupogen<sup>®</sup>) and granulocyte monocyte colony-stimulating factor (GM-CSF, also known as molgramostim, sargramostim, Leukomax<sup>®</sup>, Mielogen<sup>®</sup> or Leukine<sup>®</sup>) are currently approved for use in cancer patients, yet are mainly employed (1) to facilitate the reconstitution of the immune system upon transplantation (which is often preceded by lymphodepleting/lymphoablating regimens) or aggressive chemotherapy;<sup>16–18</sup> (2) as a prophylactic measure to minimize chemotherapy-induced neutropenia, in particular in the context of gemcitabine- (a nucleoside analog) and cisplatin- (a DNA-damaging agent) based regimens;<sup>19,20</sup> (3) as a priming stimulus, to recruit possibly quiescent leukemic

cells into the cell cycle and hence increase their chemosensitivity;<sup>21</sup> or (4) to mobilize bone marrow precursors for autologous stem cell transplantation.<sup>22,23</sup>

Along the lines of our monthly Trial Watch series,<sup>7,24–37</sup> here we will summarize the latest advances on the use of cytokines as immunostimulatory agents to re(activate) tumor-specific immune responses, focusing on high impact studies that have been published during the last 13 mo and clinical trials that have been initiated in the same period to assess the safety and efficacy of this immunotherapeutic approach. In line with the objective of this Trial Watch, neither studies investigating the use of cytokines as immunoreconstituting agents [upon hematopoietic stem cell transplantation, to prevent chemotherapy-associated neutropenia, and as a mitogenic support to adoptive cell transfer or dendritic cell (DC)-based anticancer vaccines] nor studies involving FDA-approved immunostimulatory cytokines (i.e., IFN- $\alpha$ 2a, IFN- $\alpha$ 2b and IL-2) employed as “on-label” interventions (see above) will be taken into further consideration here. Along similar lines, we will not discuss further therapeutic strategies that involve the use of potentially cytotoxic cytokines, in particular tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), to directly trigger the demise of malignant cells<sup>38–41</sup> or to damage the tumor vasculature.<sup>42,43</sup>

## Literature Update

During the past 13 mo, results from multiple preclinical and clinical studies have corroborated the notion that cytokines play a critical role not only in the development and progression of a wide array of neoplasms, but also in their capability to elicit therapeutic immunity in response to treatment.

One large branch of clinical research has focused on the potential prognostic/predictive value of the circulating or intratumoral levels of distinct cytokines. Thus, the intra-platelet levels of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and platelet factor 4 (PF4) have been proposed as independent predictors of colorectal carcinoma (CRC),<sup>44</sup> while the bone marrow of pediatric neuroblastoma patients has been shown to exhibit a significant downregulation of CXCL12, as compared with its normal counterpart, as well as to express an IFN-related gene signature.<sup>45</sup> Elevated baseline amounts of circulating CXCL10 have been demonstrated to predict disease relapse and poor overall survival in diffuse large B-cell lymphoma patients.<sup>46</sup> High serum levels of CCL17 have been associated with established clinical risk factors and poor response to treatment in subjects affected by Hodgkin's lymphoma.<sup>47</sup> Specific cytokine and angiogenic factor (CAF) profiles have been linked to the efficacy and toxicity of the multitargeted tyrosine kinase inhibitor (TKI) pazopanib in advanced soft-tissue sarcoma patients,<sup>48</sup> to disease type and general conditions at diagnosis in pediatric non-Hodgkin's lymphoma (NHL) patients,<sup>49</sup> to the propensity of individuals bearing renal cell carcinoma (RCC) to respond to sorafenib, another relatively unselective TKI,<sup>50,51</sup> as well as to the responsiveness of acute myeloid leukemia (AML) patients to the sequential administration of 5-azacytidine (a DNA demethylating agent)<sup>52,53</sup> and lenalidomide (a synthetic chemotherapeutic

with multiple mechanisms of action).<sup>54</sup> High baseline levels of circulating IL-2 and IL-8, but not of hepatocyte growth factor (HGF), IFN $\gamma$  and osteopontin, have been suggested to constitute independent prognostic factors for head and neck cancer (HNC) patients.<sup>55–57</sup> Conversely, high concentrations of TNF $\alpha$  in the serum of HNC patients before treatment have been shown to predict an unfavorable prognosis.<sup>57</sup> Elevated amounts of VEGF and angiopoietin 2 in the serum have turned out to constitute independent predictors of survival (but not of sorafenib sensitivity) among patients with advanced hepatocellular carcinoma (HCC).<sup>58</sup> Reduced levels of the IL-7 receptor as well as high amounts of the IL-12 receptor  $\beta$ 2 on the surface of malignant cells have been associated with improved disease outcome among Stage I lung adenocarcinoma patients.<sup>59</sup> Finally, a single nucleotide polymorphism in the promoter of *IL10* (influencing IL-10 expression) has been suggested to predict survival and disease relapse among non-small cell lung carcinoma (NSCLC) patients subjected to tumor resection.<sup>60</sup> Taken together, these observations are representative of an abundant recent literature (which we cannot exhaustively discuss here owing to space restrictions) demonstrating the critical influence that a large panel of cytokines exerts on the clinical course of cancer.

Alongside, consistent efforts have been devoted to the elucidation of the actual immunostimulatory potential of cytokines in cancer patients, resulting in an equally abundant literature. Some of these clinical reports refer to “on-label” settings, and the underlying studies were intended either to assess the safety and activity profile of FDA-approved cytokines combined with hitherto experimental chemotherapeutic regimens or to generate long-term follow-up data. Thus, Garcia and colleagues have combined GM-CSF with lenalidomide for the treatment of castration-resistant prostate cancer or with IL-2 and IFN- $\alpha$  for the therapy of metastatic RCC, in both cases observing a low incidence of acceptable side effects and modest antitumor activity.<sup>61,62</sup> Tarhini et al. have tested the safety and efficacy of IFN- $\alpha$ 2b combined with tremelimumab, an investigational monoclonal antibody targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4), in patients with Stage IV melanoma.<sup>63,64</sup> In this context, IFN- $\alpha$ 2b plus tremelimumab were associated with low toxicity and promising antitumor effects, which were paralleled by the recovery of effector T-cell (Teff) functions, by a robust downregulation of myeloid-derived suppressor cells (MDSCs), and (less so) by the inhibition of FOXP3<sup>+</sup> regulatory T cells (Tregs).<sup>63,64</sup> IFN- $\alpha$  has also been tested in combination with atrasentan (a selective endothelin A receptor antagonist) or metronomic chemotherapy in metastatic RCC patients,<sup>65,66</sup> and with imatinib (a TKI specific for BCR-ABL, KIT and the PDGF receptor) in CML patients,<sup>67</sup> in all settings being associated with acceptable adverse effects and (at least some extent of) antitumor efficacy. Along similar lines, it has been shown that IL-2 can be safely combined with stereotactic body radiation therapy for the treatment of subjects affected by metastatic melanoma or RCC.<sup>68</sup> Finally, the long-term results of the randomized Phase III trials EORTC 18952 and 18991, comparing the administration of pegylated IFN- $\alpha$ 2b with observation in resected Stage III melanoma patients,<sup>69</sup> have been reported.<sup>70,71</sup> In this setting (mean follow-up: 7.6 y), adjuvant

pegylated IFN- $\alpha$ 2b was found to have a positive impact on relapse-free survival that (1) was more modest than that observed earlier (at a mean follow-up of 3.8 y)<sup>69,71</sup> and (2) was especially pronounced among patients exhibiting ulcerated lesions and low disease burden.<sup>70,71</sup>

A consistent number of clinical studies published in the last 13 mo have investigated the use of immunostimulatory cytokines as “off-label” antineoplastic interventions. Thus, the safety and immunostimulatory potential of IFN- $\alpha$ 2b, combined with either the intraarterial administration of 5-fluorouracil (a nucleoside analog) or a chemoradiotherapeutic regimen involving 5-fluorouracil and cisplatin have been assessed in cohorts of advanced HCC and resected pancreatic carcinoma patients, respectively.<sup>72,73</sup> The pegylated form of IFN- $\alpha$ 2b has been evaluated as a standalone therapeutic intervention in children affected by pontine glioma,<sup>74</sup> or in combination with imatinib in gastrointestinal stromal tumor (GIST) patients.<sup>75</sup> IFN- $\beta$  has been tested for its antineoplastic potential as a maintenance monotherapy for Stage II and III melanoma patients,<sup>76</sup> and as part of a multimodal treatment involving 5-fluorouracil, cisplatin, folic acid and radiotherapy for young HNC patients.<sup>77</sup> In all these settings, IFN- $\alpha$ 2b and IFN- $\beta$  were well tolerated and—in some instances—significantly improved the efficacy of conventional therapeutic regimens. Petrella and colleagues have tested the safety, immunological outcome and antineoplastic activity of IL-21 administered as a standalone therapeutic interventions to metastatic melanoma patients,<sup>78</sup> while Steele et al. have investigated whether this cytokine can be safely administered in combination with cetuximab, a monoclonal antibody specific for the epidermal growth factor receptor (EGFR), to metastatic CRC patients.<sup>79</sup> In both these scenarios, IL-21 was not associated with severe side effects and induced immunological as well as clinical responses, at least in a fraction of patients. In a Phase I clinical trial, Selectikine, i.e., an immunocytokine consisting in an IL-2 molecule fused to a DNA-specific antibody (hence targeting necrotic tumor cells), turned out to be well tolerated by patients with advanced solid tumors, prompting the initiation of a Phase II study.<sup>80</sup> Along similar lines, the systemic administration of h14.18-IL-2 (an immunocytokine comprising IL-2 and a ganglioside GD2-specific monoclonal antibody) to melanoma patients has been associated with an acceptable toxicity, yet also appeared to elicit clinical responses in a limited fraction of individuals.<sup>81</sup> Of note, Pautier and colleagues have reported that IL-2 significantly increases the area under the curve and the maximum concentration of imatinib and its main metabolite CGP74588,<sup>82</sup> suggesting that the antineoplastic and immunostimulatory effects of imatinib<sup>83–85</sup> may be improved by IL-2 via both immunological and pharmacokinetic mechanisms. However, patients receiving IL-2 plus imatinib exhibited mild to moderate adverse effects such as fever, chills, fatigue, nausea and the elevation of hepatic enzymes. Thus, imatinib-associated side effects might also be exacerbated by the co-administration of IL-2.<sup>82</sup> Finally, a few studies have evaluated immunostimulatory cytokines as adjuvants for peptide- and DC-based anticancer vaccines, or as a measure to boost the antineoplastic activity of adoptively transferred T cells, often with encouraging results.<sup>86–91</sup>

Besides such an abundant clinical literature, a number of top quality fundamental reports—unraveling the molecular and cellular cascades whereby cytokines influence oncogenesis, tumor progression and response to therapy—has been published during the last 13 mo. Among major discoveries in the field, (1) TNF $\alpha$  and IFN $\gamma$ , but neither of these T<sub>H</sub>1 cytokines alone, have been shown to promote the senescence of malignant cells in vitro and in vivo;<sup>92</sup> (2) the tumor stroma has been reported to underpin the resistance of melanoma cells to BRAF inhibitor owing to its ability to secrete high levels of HGF;<sup>93,94</sup> (3) HGF has been involved in an autocrine signaling pathway that drives leukemogenesis;<sup>95</sup> (4) the deubiquitinating enzyme ubiquitin-specific peptidase 15 (USP15) turned out to stabilize transforming growth factor  $\beta$  (TGF $\beta$ ) receptor 1, hence promoting the development of glioblastoma via a TGF $\beta$ -dependent mechanism;<sup>96</sup> (5) defects in the intestinal barrier have been linked to colorectal carcinogenesis through a microbial product-driven signaling cascade involving IL-23, T<sub>H</sub>17 cells and IL-17;<sup>97</sup> (6) 5-fluorouracil and gemcitabine have been shown to trigger the activation of the inflammasome<sup>98</sup> in MDSCs, hence initiating an IL-1 $\beta$ -dependent, IL-17-mediated mechanism that eventually promotes chemoresistance;<sup>99</sup> (7) IL-22-binding protein (IL-22BP) has been reported to mediate oncosuppressive functions in the intestine by intercepting available IL-22, in particular during the recovery phase of inflammation;<sup>100</sup> (8) a subset of CD8<sup>+</sup>CTLA4<sup>+</sup> IL-35-secreting Tregs has been suggested to play a central immunosuppressive role in prostate cancer patients treated with a prostate acid phosphatase (PAP)-specific vaccine, suggesting that IL-35-blocking interventions may exert potent immunostimulatory effects (at least in this setting);<sup>101</sup> (9) the administration of IL-2 has been associated with the expansion of naïve CD4<sup>+</sup>CD25<sup>high</sup>FOXP3<sup>+</sup> Tregs in CRC patients;<sup>102</sup> (10) GM-CSF dosing regimens have been shown to influence several immunological parameters in prostate cancer patients, including the abundance and activity of various immune cell subsets as well as the circulating levels of cytokines such as VEGF and TNF $\alpha$ ;<sup>103</sup> (11) a variant of IL-2 that is able to convey robust proliferative signals in the absence of CD25 has been developed;<sup>104</sup> (12) CCL21 gradients have been reported to constitute the major chemotactic drivers of DC migration to lymph nodes in vivo;<sup>105</sup> and (13) the tridimensional structure of human CXCR1, one of the high-affinity receptors for IL-8, has been elucidated by nuclear magnetic resonance (NMR) spectroscopy.<sup>106</sup>

Taken together, these observations suggest that immunostimulatory cytokines continue to attract a consistent amount of interest, both from clinicians and scientists dealing with fundamental research.

### Update on Clinical Trials

When this Trial Watch was being redacted (April 2013), official sources listed no less than 116 clinical trials launched after April 1, 2012, to investigate the safety and therapeutic potential of cytokines in cancer patients (source [www.clinicaltrials.gov](http://www.clinicaltrials.gov)). Of these, 89 trials involved IL-2 or other interleukins (24 studies),

GM-CSF (5 studies), G-CSF (50 studies) and IFNs (10 studies) as fully “on-label” interventions, and therefore will not be discussed further here. Of the remaining 27 clinical trials, 9 aimed at assessing the immunostimulatory potential of IL-2 (as an “off-label” medication) and of other—hitherto investigational—interleukins (i.e., IL-11, IL-15, IL-18 and IL-21); 12 were launched to assess whether GM-CSF might be safely and efficiently used to boost tumor-specific immune responses, most often as induced by anticancer vaccines; and 7 were initiated to test IFN- $\alpha$ 2b and IFN $\beta$ , again in “off-label” oncological settings (Table 1).

In particular, IL-2 is being tested (1) as a single agent, upon intranasal nebulization, for the treatment of patients bearing pulmonary metastases of sarcoma (NCT01590069); (2) in combination with IMAB362 (a monoclonal antibody specific for the gastric differentiation protein claudin 18, splice variant 2)<sup>107</sup> and zoledronic acid (a bisphosphonate), for the therapy of subjects with adenocarcinomas of the stomach, esophagus and gastroesophageal junction (NCT01671774); and (3) in combination with monoclonal antibodies targeting ganglioside GD2 (i.e., ch14.18, ch14.18/CHO and hu3F8), isotretinoin (a retinoid with antineoplastic properties) and GM-CSF (in 1 study), upon intravenous or subcutaneous delivery, for the treatment of neuroblastoma patients (NCT01592045; NCT01662804; NCT01701479). The safety and immunostimulatory potential of IL-15, given s.c. or i.v. as a standalone therapeutic intervention, are being evaluated in a mixed cohort of HNC, NSCLC, RCC and melanoma patients (NCT01727076) as well as in subjects affected by advanced hematopoietic and solid neoplasms (NCT01572493). In addition, IL-18 is being tested in combination with ofatumumab (a monoclonal antibody specific for CD20)<sup>108</sup> in lymphoma patients who have undergone autologous peripheral blood stem cell transplantation (NCT01768338), while the therapeutic activity of intravenous IL-21 plus BMS-936558 (a PD1-blocking monoclonal antibody)<sup>109–111</sup> is being investigated in individuals with advanced or metastatic solid tumors (NCT01629758). All these clinical trials but one (NCT01727076) are currently recruiting participants.

With the exceptions of NCT01592045, NCT01757626, NCT01767194 and NCT01806272, investigating whether GM-CSF can be conveniently combined either with anti-GD2 monoclonal antibodies, alone or together with irinotecan (an inhibitor of topoisomerase 1) and temozolomide (an alkylating agent), or with vitamin B12 for the treatment of neuroblastoma patients or chemoradiation-associated mucositis, respectively, all clinical trials launched during the last 13 mo to test “off-label” applications of GM-CSF involve anticancer vaccines. In particular, GM-CSF is being tested for its ability to boost immune responses as elicited by (1) a Wilms tumor 1 (WT1)-targeting vaccine in patients with multiple myeloma (NCT01827137); (2) a multipetide vaccine in individuals affected by metastatic breast carcinoma (NCT01660529); (3) a telomerase-specific vaccine in subjects with inoperable Stage III NSCLC (NCT01579188); (4) a mixture of four, lethally irradiated melanoma cell lines combined with the bacillus Calmette-Guérin<sup>112</sup> in Stage IIB, IIC and III melanoma patients (NCT01729663); (5) a telomerase-derived synthetic peptide in NSCLC (NCT01789099) and prostate cancer

**Table 1.** Recent clinical trials evaluating the immunostimulatory potential of cytokines for cancer therapy\*

Cytokine	Indication(s)	Status	Phase	Route	Co-therapy	Ref.	
GM-CSF	Breast cancer	Recruiting	n.a.	s.c.	Combined with a multipeptide vaccine	NCT01660529	
	Chemoradiotherapy-associated mucositis	Recruiting	II	Mouthwash solution	Combined with vitamin B12	NCT01806272	
	Melanoma	Recruiting	II/III	n.a.	Combined with CSF470 and BCG	NCT01729663	
	MM	Recruiting	n.a.	s.c.	Combined with WT1 analog peptide	NCT01827137	
	NB		Not yet recruiting	II	i.v.	Combined with ch14.18, irinotecan and temozolomide	NCT01767194
			Recruiting	I	n.a.	Combined with hu3F8	NCT01757626
		NSCLC	Recruiting	I/II	i.v.	Combined with ch14.18, IL-2 and isotretinoin	NCT01592045
			Not yet recruiting	III	s.c.	Combined with a hTERT-derived peptide	NCT01579188
			Recruiting	I/II	s.c.	Combined with a hTERT-derived peptide	NCT01789099
		Ovarian cancer	Recruiting	I	s.c.	Combined with a FBP-derived peptide	NCT01580696
		Prostate cancer	Recruiting	I/II	s.c.	Combined with a hTERT-derived peptide	NCT01784913
		Reproductive tract cancer	Active not recruiting	I	s.c.	Combined with decitabine, PLD and a NY-ESO-1-derived peptide	NCT01673217
	IFN $\alpha$ -2a	Lymphoma	Completed	III	s.c.	Combined with rituximab	NCT01609010
RCC		Recruiting	II	n.a.	Combined with bevacizumab, everolimus and a TKI	NCT01731158	
IFN $\alpha$ -2b	High-grade gliomas	Recruiting	III	n.a.	Combined with radiotherapy and temozolomide	NCT01765088	
	Ovarian cancer	Recruiting	I/II	s.c.	Combined with standard chemotherapy and tocilizumab	NCT01637532	
				n.a.	Combined with gemcitabine and a p53-derived SLP	NCT01639885	
	Solid tumors	Recruiting	II	n.a.	Combined with 5-FU	NCT01658813	
IFN $\beta$	Merkel cell carcinoma	Recruiting	I/II	i.t.	Combined with autologous T-cell transplantation and IL-2	NCT01758458	
IL-2	Gastroesophageal cancer	Recruiting	I	n.a.	Combined with IMAB362 and zoledronic acid	NCT01671774	
	Lung metastases	Recruiting	I/II	Intranasal nebulization	As single agent	NCT01590069	
				s.c.	Combined with hu3F8	NCT01662804	
	NB	Recruiting	I/II	i.v.	Combined with ch14.18, GM-CSF and isotretinoin	NCT01592045	
				s.c.	Combined with ch14.18/CHO and isotretinoin	NCT01701479	
IL-15	HNC Melanoma NSCLC RCC	Not yet recruiting	I	s.c.	As single agent	NCT01727076	
	Solid and hematological tumors	Recruiting	I	i.v.	As single agent	NCT01572493	
IL-18	NHL	Recruiting	I	n.a.	Combined with ofatumumab	NCT01768338	
IL-21	Solid tumors	Recruiting	I	i.v.	Combined with anti-PD1 mAbs	NCT01629758	

5-FU, 5-fluorouracil; BCG, bacillus Calmette-Guérin; FBP, folate-binding protein; GM-CSF, granulocyte macrophage colony-stimulating factor; HNC, head and neck cancer; hTERT, human telomerase reverse transcriptase; IFN, interferon; IL, interleukin; i.t., intra tumorem; i.v., intra venam; mAb, monoclonal antibody; MM, multiple myeloma; n.a. not available; NB, neuroblastoma; NHL, Non-Hodgkin's lymphoma; NSCLC, non-small cell lung carcinoma; PD1, programmed death 1; PLD, pegylated liposomal doxorubicin; RCC, renal cell carcinoma; s.c., sub cutem; SLP, synthetic long peptide; TKI, tyrosine kinase inhibitor; WT1, Wilms tumor 1. \*Limited to trials dealing with investigational cytokines or FDA-approved cytokines employed as "off-label" medications, started after April 1, 2012.

patients (NCT01784913); (6) a folate-binding protein (FBP)-targeting vaccine in ovarian carcinoma patients (NCT01580696); and (7) a NY-ESO-1-derived peptide in subjects with recurrent ovarian epithelial cancer, fallopian tube cancer or peritoneal cancer (NCT01673217). These trials are recruiting participants, with the exception of NCT01579188, NCT01673217 and NCT01767194.

IFN- $\alpha$ 2a in combination with bevacizumab (a monoclonal antibody targeting VEGF) is being tested as a first-line intervention in RCC patients who are allocated to receive either everolimus (an inhibitor of the mammalian target of rapamycin, mTOR)<sup>113</sup> followed by one TKI among sunitinib, sorafenib and pazopanib, or vice versa (NCT01731158). In addition, a clinical trial evaluating subcutaneous IFN- $\alpha$ 2a plus rituximab (a CD20-targeting monoclonal antibody)<sup>114</sup> in subjects with follicular lymphoma or other CD20<sup>+</sup> indolent lymphomas that had originally been registered at www.clinicaltrials.gov on May 29, 2012, (NCT01609010) has already been completed (though results are not yet available). IFN- $\alpha$ 2b is being investigated as an immunostimulatory intervention (1) in patients with newly diagnosed high-grade gliomas (i.e., anaplastic oligoastrocytoma, anaplastic astrocytoma, glioblastoma), combined with temozolomide upon radiotherapy (NCT01765088); (2) in subjects bearing recurrent or chemoresistant ovarian cancer, either in combination with tocilizumab (a monoclonal antibody specific for the IL-6 receptor) and carboplatin-based chemotherapy<sup>115</sup> (NCT01637532), or together with gemcitabine and a p53-derived synthetic long peptide (NCT01639885); and (3) in previously-treated patients bearing metastatic gastrointestinal cancer, NSCLC or RCC, following a 5-fluorouracil-based therapeutic regimen (NCT01658813). Finally, IFN- $\beta$  is being investigated for its ability to boost the antineoplastic activity of autologous T cells genetically manipulated to target tumor cells in individuals affected by metastatic Merkel cell carcinoma, a virus-associated cancer<sup>116</sup> (NCT01758458). With the single exception of NCT01609010, all these studies are currently recruiting participants.

Of note, 21 clinical trials started after January 1, 2008, (which were included in the latest Trial Watch dealing with immunostimulatory cytokines)<sup>7</sup> have been terminated (NCT00819169, for sponsor decision; NCT00724061, due to low accrual), suspended (NCT00923351; NCT01334515) or completed (NCT00602706; NCT00607048; NCT00609076; NCT00619268; NCT00626405; NCT00785122; NCT00796757; NCT00806598; NCT00822770; NCT00836407; NCT00939510; NCT00952237; NCT00990054; NCT01074060; NCT01082887; NCT01107756; NCT01324063) during the last 13 mo (source www.clinicaltrials.gov). Among completed studies, NCT00607048 and NCT00939510 are listed as having results, which however are not yet publicly available.

### Concluding Remarks

Cytokines constitute a highly heterogeneous group of extracellular messengers that—taken as a whole—exerts an incredibly large range of biological effects, de facto regulating virtually all cellular functions.<sup>1–4</sup> In line with this notion, during the past four decades great efforts have been devoted not only to elucidating

the molecular and cellular circuitries that are set in motion by specific cytokines (or cytokine cocktails), but also to understanding whether cytokines can be safely and efficiently used to treat a variety of human conditions, including cancer.<sup>10,117</sup> Nowadays, three distinct cytokines (i.e., IFN- $\alpha$ 2a, IFN- $\alpha$ 2b and IL-2) are approved by the FDA or other international regulatory agencies for use as therapeutic immunostimulants against cancer.<sup>10,117</sup> In addition, cytokines such as G-CSF and GM-CSF are part of the clinical routine as they potently favor immunoreconstitution in transplanted patients or in subjects who underwent aggressive chemotherapy.<sup>8,118</sup>

Arguably, the major obstacle against the clinical use of cytokines stems from their elevated pleiotropism, implying that these proteins may be intrinsically prone to elicit adverse effects, in particular upon systemic administration. For instance, high-dose IL-2 has been associated with tumor regression in a fraction of melanoma and RCC patients,<sup>119,120</sup> yet this regimen also elicits moderate to severe toxicities in some individuals.<sup>121</sup> To circumvent this issue, future efforts will have to focus at narrowing the spectrum of activity of particularly promising cytokines, tipping the balance away from a potentially dangerous pleiotropism and toward a highly specific biological activity. Immunocytokines, i.e., cytokines specifically delivered to target cells by means of monoclonal antibodies, constitute a promising approach in this sense, and some of them, such as Selectikine, have already entered clinical trials.<sup>122,123</sup> In addition, it will be crucial to identify means to expand the clinical benefits of immunostimulatory cytokines—which currently are limited to individuals with highly immunosensitive tumors such as melanoma and RCC—to an ever larger population of cancer patients. Strategies to be pursued in this direction include the development of combinatorial therapeutic regimens involving Toll-like receptor (TLR) agonists,<sup>29,30</sup> immune checkpoint-blocking antibodies<sup>27,28,124,125</sup> or immunogenic chemotherapeutics.<sup>33,34,126</sup> Well designed clinical trials are required to formally identify which of these approaches, if any, will successfully increase the number of cancer patients obtaining a clinical benefit from immunostimulatory cytokines.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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