

REVIEW



## Trial Watch: Immunostimulation with recombinant cytokines for cancer therapy

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### ABSTRACT

Cytokines regulate virtually aspects of innate and adaptive immunity, including the initiation, execution and extinction of tumor-targeting immune responses. Over the past three decades, the possibility of using recombinant cytokines as a means to elicit or boost clinically relevant anticancer immune responses has attracted considerable attention. However, only three cytokines have been approved so far by the US Food and Drug Administration and the European Medicines Agency for use in cancer patients, namely, recombinant interleukin (IL)-2 and two variants of recombinant interferon alpha 2 (IFN- $\alpha$ 2a and IFN- $\alpha$ 2b). Moreover, the use of these cytokines in the clinics is steadily decreasing, mostly as a consequence of: (1) the elevated pleiotropism of IL-2, IFN- $\alpha$ 2a and IFN- $\alpha$ 2b, resulting in multiple unwarranted effects; and (2) the development of highly effective immunostimulatory therapeutics, such as immune checkpoint blockers. Despite this and other obstacles, research in the field continues as alternative cytokines with restricted effects on specific cell populations are being evaluated. Here, we summarize research preclinical and clinical developments on the use of recombinant cytokines for immunostimulation in cancer patients.

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## Introduction

Cytokines are a large group of relatively small and generally (but not always) soluble glycoproteins that regulate virtually all biological functions as they elicit autocrine, paracrine or endocrine signaling pathways.<sup>1-6</sup> In particular, cytokines play a key role in (1) the development, maturation and localization of all cellular components of the immune system;<sup>7-12</sup> and (2) the initiation, execution and extinction of innate and adaptive immunity against invading pathogens as well as against malignant cells.<sup>13-21</sup> A detailed description of cytokines, their receptors and their biological activities goes largely beyond the scope of this Trial Watch, and can be found elsewhere.<sup>3-6</sup> For the purpose of the present discussion, however, it should be noted that the cytokine system is characterized by an extreme pleiotropism, and this has major implications for the development of cytokine-based therapeutics.<sup>22-24</sup>

Over the past three decades considerable attention has indeed been attracted by the possibility of using recombinant cytokines as standalone interventions or in combination with other immunotherapeutics to trigger or boost, respectively, clinically relevant anticancer immune responses.<sup>16,19,25,26</sup>

However, only three different agents have been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) so far for the treatment of malignant disorders in humans: recombinant interleukin (IL)-2 (aldesleukin, Proleukin<sup>®</sup>), and two variants of recombinant interferon alpha 2 (IFN- $\alpha$ 2), namely, IFN- $\alpha$ 2a (Roferon<sup>®</sup>-A) and IFN- $\alpha$ 2b (Intron<sup>®</sup>-A). In particular: (1) recombinant IL-2 (generally given at high doses) is licensed for the treatment of some forms of metastatic melanoma and renal cell carcinoma (RCC); (2) recombinant IFN- $\alpha$ 2a is approved for use in patients with hairy cell lymphoma and chronic phase, Philadelphia chromosome-positive chronic myelogenous leukemia (CML) upon minimal pretreatment (within 1 y from diagnosis); and (3) recombinant IFN- $\alpha$ 2b is licensed for the treatment of AIDS-related Kaposi's sarcoma, melanoma, follicular lymphoma, multiple myeloma, hairy cell leukemia, genital warts (*Condyloma acuminata*) and cervical intraepithelial neoplasms (sources [www.fda.gov](http://www.fda.gov) and <http://www.ema.europa.eu/ema/>). Moreover, the use of these agents in the clinics is steadily declining, for at least two reasons. First, the elevated pleiotropism of the system implies that the systemic administration of one cytokine mediates a large

number of biological activities, multiple of which may be unwarranted (including moderate-to-severe side effects) or even detrimental to clinical activity.<sup>27-36</sup> As a standalone example, it is now well known that high-dose IL-2 acts as a mitogen for CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs), which at least in part underlies its therapeutic activity in subjects with melanoma and RCC, but even more so for CD4<sup>+</sup>CD25<sup>+</sup>FOXP3<sup>+</sup> regulatory T (T<sub>REG</sub>) cells, which *de facto* antagonize anticancer immune responses.<sup>37-42</sup> Second, multiple immunotherapeutics with comparatively more specific mechanisms of action and robust clinical activity have been developed, including (but not limited to) immune checkpoint blockers (ICBs).<sup>43-48</sup>

Nonetheless, research on the use of recombinant cytokines as immunostimulants against cancer continues as attention has shifted (1) to molecules with restricted selectivity for one or a few cell types, such as IL12, IL-15 and IL-21<sup>49-52</sup>; and (2) on regimens involving the concomitant or sequential administration of one or more recombinant cytokines with other agents that trigger or boost anticancer immunity,<sup>53</sup> including (but not limited to): ICBs,<sup>54-56</sup> immunostimulatory monoclonal antibodies (mAbs),<sup>57-60</sup> DNA-, dendritic cell (DC)- or peptide-based vaccines,<sup>61-67</sup> chemotherapy with immunogenic cell death inducers,<sup>68-73</sup> radiation therapy delivered according to specific fractionation protocols,<sup>74-76</sup> small molecules targeting the tumor microenvironment,<sup>77-81</sup> adoptively transferred T cells,<sup>82-85</sup> and oncolytic virotherapy.<sup>86-88</sup>

Importantly, at least three other cytokines beyond IL-2, IFN- $\alpha$ 2a and IFN- $\alpha$ 2b are currently licensed by the US FDA and EMA for use in humans, namely, recombinant tumor necrosis factor (TNF), recombinant granulocyte monocyte colony-stimulating factor (GM-CSF, also known as Molgramostim, Sargramostim, Leukomax<sup>®</sup>, Mielogen<sup>®</sup> or Leukine<sup>®</sup>), and recombinant granulocyte colony-stimulating factor (G-CSF, also known as Filgrastim, Lenograstim or Neupogen<sup>®</sup>). However, in the current clinical practice these molecules are employed as oncolytic agents (TNF)<sup>89-100</sup> or immunoreconstituting drugs (GM-CSF, G-CSF).<sup>101-108</sup>

Here, we discuss recent preclinical and clinical advances in the development of recombinant cytokines for use as immunostimulants (rather than oncotoxic and immunoreconstituting agents) in cancer patients.

## Preclinical and translational advances

Since the publication of the latest Trial Watch dealing with this topic (December 2015),<sup>24</sup> a large amount of preclinical and translational work on the role of immunostimulatory cytokines in anticancer immune responses has been released (source <https://www.ncbi.nlm.nih.gov/pubmed>).

Of this abundant scientific literature, we retained the contribution of: (1) Benci and colleagues (from the University of Pennsylvania, Philadelphia, PA, USA), who demonstrated that chronic, low-intensity type I IFN signaling within the tumor microenvironment contributes to the establishment of a multi-genic program of resistance to immune checkpoint blockade<sup>109,110</sup>; (2) Vanpouille-Box and collaborators (from Weill Cornell Medical College, New York, NY, USA), MacKenzie and colleagues (from The University of Edinburgh, Edinburgh, UK) and Harding *et al.* (from the Abramson Family Cancer Research Institute, Philadelphia, PA, USA), who independently

demonstrated that acute, high-intensity type I IFN signaling driven by cyclic GMP-AMP synthase (CGAS)<sup>111-115</sup> and transmembrane protein 173 (TMEM173; best known as STING)<sup>116-119</sup> activation following DNA damage (generally in the context of cellular senescence)<sup>120-123</sup> is paramount for the establishment of anticancer immune responses with systemic activity<sup>124-129</sup>; (3) Gao and colleagues (from The University of Texas MD Anderson Cancer Center, Houston, TX, USA), Ayers and co-workers (from Merck & Co. Inc., Kenilworth, NJ, USA) and Overacre-Delgoffe *et al.* (from St. Jude Children's Research Hospital, Memphis, TN, USA), who provided robust data in support of the notion that an intact IFN- $\gamma$  signaling pathway is required for malignant lesions to respond to ICB-based immunotherapy<sup>130-133</sup>; (4) Ghasemi and collaborators (from Washington University, St. Louis, MO, USA), who demonstrated that selectively targeting IL-2 to natural killer cells expressing killer cell lectin like receptor K1 (KLRK1; best known as NKG2D)<sup>134-137</sup> results in superior tumor control upon as it does not engage T<sub>REG</sub> cells<sup>138,139</sup>; (5) Zhang and colleagues (from Dana-Farber/Harvard Cancer Center, Boston, MA, USA), who showed that the biological activity of IL-1 $\beta$ <sup>140-143</sup> is positively modulated by physiological reactive oxygen species (ROS) levels upon cysteine-S-glutathionylation<sup>144</sup>; and (6) Waghray and co-authors (from University of Michigan, Ann Arbor, MI, USA), who characterized a population of mesenchymal stem cells<sup>145-147</sup> that supports pancreatic tumor progression by releasing GM-CSF.<sup>148</sup>

Moreover, (1) Wagner *et al.* (from Washington University School of Medicine, St. Louis, MO, USA) demonstrated that the potent IL-15 receptor agonist ALT-803<sup>50,149-154</sup> can be used *in vivo* to prime superior antitumor responses by NK cells<sup>155</sup>; (2) Mishra and collaborators (from The Ohio State University, Columbus, OH, USA) proved a critical role for dysregulated IL-15 signaling in the pathogenesis of cutaneous T-cell lymphoma<sup>156</sup>; (3) Hu and coauthors (from the University of Pennsylvania, Philadelphia, PA, USA) showed that CAR T cells engineered to secrete IL-18 mediate superior therapeutic responses in mice with B16F10 melanomas<sup>157-159</sup> as compared to CAR T cells with a wild-type secretory capacity<sup>160</sup>; (4) Seo and co-workers (from Seoul National University, Seoul, Republic of Korea) demonstrated that IL-21<sup>161</sup> can be used to reverse NK cell exhaustion, at least mice, resulting in improved immunity against MHC Class I-deficient neoplasms<sup>162</sup>; (5) Chapius *et al.* (from the Fred Hutchinson Cancer Research Center, Seattle, WA, USA) tested IL-21 primed CTLs transferred in combination with a CTLA4-targeting mAb to a single patient with metastatic melanoma refractory to either intervention alone, demonstrating robust tumor control,<sup>163</sup> mimicking preclinical results from independent investigators;<sup>164</sup> (6) Yin and collaborators (from Academia Sinica, Taipei, Taiwan) showed that the secretion of IL-25<sup>165-167</sup> from cancer-associated fibroblasts<sup>168-172</sup> has direct oncosuppressive effects in preclinical models of breast carcinoma<sup>173</sup>; and (7) Molgora *et al.* (from the Humanitas Clinical and Research Center, Rozzano, Italy) reported that interleukin 1 receptor accessory protein like 1 (IL1RAPL1; best known as IL-1R8), a member of the IL-1 $\beta$  receptor protein family,<sup>174-178</sup> operates as an inhibitory checkpoint in the maturation of and acquisition of effector functions by NK cells.<sup>179</sup>

These and other emerging aspects of the cytokine biology have considerable implications for the immunotherapeutic management of cancer and a plethora of other conditions, including infectious and autoimmune disorders.

### Completed clinical studies

Since December 2015, when the latest Trial Watch dealing with the use of recombinant cytokines as immunostimulants for cancer therapy was published,<sup>24</sup> the results of just a few clinical studies (directly or indirectly) testing this immunotherapeutic paradigms in cancer patients have been released (source <http://www.ncbi.nlm.nih.gov/pubmed>).

NCT01989572 was a Phase III clinical study evaluating yeast-derived GM-CSF *versus* peptide vaccination *versus* GM-CSF plus peptide vaccination<sup>180-183</sup> *versus* placebo in 815 patients with locally advanced or Stage IV melanoma and no evidence of disease after complete surgical resection.<sup>184</sup> In this setting, HLA-A\*02<sup>+</sup> patients were randomly allocated to each of the study arm, while HLA-A\*02<sup>-</sup> individuals were randomized to receive GM-CSF as a stand-alone intervention or placebo. No statistically significant differences in overall survival (OS) or relapse-free survival (RFS) were observed across the groups.<sup>184</sup> These findings are at odds with previous results from prospective Phase II and non-prospective Phase III studies suggesting that recombinant GM-CSF (alone or combined with other immunotherapeutics) provides a clinical benefit to patients with melanoma at high risk for recurrence.<sup>185-191</sup> Of note, it has recently been demonstrated that >90% of melanoma patients receiving adjuvant therapy with GM-CSF develop GM-CSF-targeting antibodies,<sup>192-194</sup> which in >40% of the cases are neutralizing.<sup>195</sup> This may explain, at least in part, the limited therapeutic efficacy of GM-CSF in some clinical settings.

Schijns and colleagues (from the University of Wageningen, The Netherlands) assessed the safety and therapeutic activity of a personalized cell-based cancer vaccine (Gliovac<sup>TM</sup>) administered intradermally in the presence of recombinant GM-CSF to patients with recurrent, incompletely resected, treatment-resistant glioblastoma multiforme (GBM).<sup>196-198</sup> In this context, 9 GBM patients refractory to standard-of-care temozolomide-based chemotherapy,<sup>199</sup> radiation therapy, surgery or targeted therapy with bevacizumab<sup>200,201</sup> received Gliovac plus recombinant GM-CSF following a T<sub>REG</sub>-depleting course of cyclophosphamide,<sup>202</sup> resulting in superior survival rates as compared to historical controls.<sup>203-205</sup> As the treatment was associated with limited toxicity, a Phase II study has been initiated to evaluate this immunotherapeutic approach in a larger cohort of GBM patients including bevacizumab-naïve individuals (NCT01903330). Along similar lines, Rampling and colleagues (from the Beatson West of Scotland Cancer Centre, Glasgow, UK) evaluated a peptide-based vaccine (IMA950)<sup>206,207</sup> plus recombinant GM-CSF along with standard chemoradiotherapy and adjuvant temozolomide for the treatment of patients with newly-diagnosed GBM.<sup>208</sup> In the context of this Phase I clinical study, 45 HLA-A\*02<sup>+</sup> patients who had undergone tumor resection received 11 intradermal injection of IMA950 plus GM-CSF over 24 weeks, beginning either 7-14 day prior to the initiation of chemotherapy or

7 days after. Of 40 evaluable patients, 90% were immunological responders to at least one of the vaccine components, irrespective of therapeutic schedule, and progression-free survival (PFS) rates at 6 mo. and 9 mo. were 74% and 31%, respectively.<sup>208</sup> These findings are in line with previous results demonstrating that GM-CSF can be safely used as an immunostimulant in patients with GBM and other tumors who receive additional (immuno)therapeutic agents.<sup>209-214</sup>

The safety and efficacy of IFN- $\alpha$ 2a in combination with pembrolizumab, an FDA-approved, potent ICB targeting programmed cell death 1 (PDCD1; best known as PD-1),<sup>215-218</sup> was investigated in the context of the KEYNOTE-029 study (NCT02089685).<sup>219</sup> Data from the dose-finding cohort of the study indicate that the maximum tolerated dose is 2 mg/kg pembrolizumab every 3 week plus 1  $\mu$ g/kg pegylated-IFN weekly, a regimen that demonstrated limited antitumor activity.<sup>220</sup> That said, previous findings demonstrated that recombinant IFN- $\alpha$ 2a can be safely administered in combination with: (1) bevacizumab and optionally tyrosine kinase inhibitors, for the treatment of metastatic RCC<sup>221-228</sup>; (2) the FDA approved CD20-targeting agent rituximab,<sup>229-231</sup> for the treatment of lymphoma<sup>232-235</sup>; as well as chemotherapy plus a mAb blocking the IL-6 receptor,<sup>236-239</sup> for the therapy of epithelial ovarian carcinoma.<sup>240</sup>

Interestingly, biomarkers of response amongst patients with advanced RCC have been retrospectively evaluated on data from 12 distinct clinical trials, including NCT00631371, a Phase III study comparing bevacizumab plus recombinant IFN- $\alpha$ 2a with bevacizumab plus the mechanistic target of rapamycin (MTOR) inhibitor temsirolimus,<sup>241</sup> which operates as an anti-proliferative and autophagy-activating agent.<sup>242-247</sup> In this context, an early tumor shrinkage (eTS) above 10% was associated with improved PFS and OS, although the retrospective nature of the analysis constitutes a major limitation of the study.<sup>241</sup>

At the occasion of the 2017 American Society for Clinical Oncology (ASCO) Annual Meeting, Diab and collaborators (from the University of Texas MD Anderson Cancer Center, Houston, TX, USA) reported preliminary findings from an ongoing Phase I-II study testing the safety and therapeutic profile of NKTR-214 (a CD122-biased agonist of the IL-2 system)<sup>248-250</sup> combined with nivolumab (another FDA-approved ICB directed against PD-1)<sup>251-254</sup> in patients with melanoma, non-small cell lung carcinoma (NSCLC), RCC, bladder carcinoma or triple-negative breast cancer (NCT02983045).<sup>255</sup> Amongst 5 patients treated with this regimen, no dose-limiting toxicities and no drug-related or immune-related Grade 3-5 adverse events (AEs) were documented. Moreover, one patient (with melanoma) experienced a mixed radiographic response associated with markers of immune activation, while another patient (also with melanoma) had an unconfirmed complete response per RECIST v. 1.1.<sup>255</sup>

At the same occasion, Tarhini and colleagues (from the University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA) reported the results of a randomized Phase II trial testing the FDA-approved CTLA4-targeting mAb ipilimumab<sup>256-259</sup> at two different doses, alone or in combination with high-dose recombinant IFN- $\alpha$ 2b (NCT01708941).<sup>260</sup> At a median follow-up of 26.4 mo., AEs were consistent with the toxicity profiles of ipilimumab and high-dose IFN- $\alpha$ 2b, including 3 treatment-

related Grade 5 AEs: suicide, lung infection and hemorrhage, and adult respiratory distress syndrome. However, no significant differences in PFS or OS when evaluating ipilimumab-receiving patients *versus* individuals treated with the same dose of ipilimumab and high-dose IFN- $\alpha$ 2b.<sup>260</sup>

The clinical studies discussed here above focused on recombinant cytokines that are already approved for use in humans for anticancer therapy (IL-2, IFN- $\alpha$ 2a) or immune reconstitution (GM-CSF). At least in part, this reflects the well-characterized safety profile of IL-2, IFN- $\alpha$ 2a and GM-CSF. It will be interesting to see the final results of hitherto ongoing clinical trials testing the therapeutic profile relatively poorly investigated cytokines such as IL-12, IL-15 and IL-21 (see below).

### Recently initiated clinical trials

Since the latest Trial Watch dealing with this topic was published,<sup>24</sup> no less than 44 clinical studies have been initiated to assess the therapeutic profile of recombinant cytokines employed as off-label immunostimulants (rather than oncotoxic and immunoreconstituting agents) in cancer patients (source <http://www.clinicaltrials.gov>). Of these studies, (1) nineteen involve recombinant GM-CSF (NCT02623595; NCT02636582; NCT02641782; NCT02663440; NCT02677155; NCT02703714; NCT02728102; NCT02774421; NCT02873819; NCT02946138; NCT02976740; NCT02978222; NCT03012100; NCT03014076; NCT03033303; NCT03189706; NCT03222089; NCT03282188; NCT03363373); (2) fourteen recombinant IFN- $\alpha$  (NCT02576964; NCT02627144; NCT02634294; NCT02737046; NCT02829775; NCT02838342; NCT02948426; NCT02982720; NCT03056599; NCT03066947; NCT0317816; NCT03121079; NCT03253250; NCT03328026); (3) four recombinant IL-2 (NCT02641782; NCT03040401; NCT03222089; NCT03224871); (4) four recombinant IL-12 (NCT02542124; NCT02544724; NCT02994953; NCT03030378); and (5) six additional cytokines including IL-15 (NCT02689453; NCT03388632), IFN- $\beta$  (NCT02584829), IFN- $\gamma$  (NCT02948426; NCT03112590), and fms related tyrosine kinase 3 ligand (FLT3LG)<sup>261,262</sup> (NCT02839265) (Table 1).

In particular, the safety and immunostimulatory activity of recombinant GM-CSF is being investigated: (1) in subjects with neuroblastoma receiving a ganglioside GD2-targeting mAb,<sup>263-267</sup> optionally in the context of multimodal chemotherapy (NCT02641782; NCT03033303; NCT03189706; NCT03363373); (2) in patients with breast cancer, who receive recombinant GM-CSF as an adjuvant to peptide-based vaccination (NCT02636582; NCT03012100; NCT03014076); and (3) in individuals with a panel of other tumors, including biliary cancer (NCT02703714), colorectal carcinoma (NCT03222089), ependymoma (NCT02774421), follicular lymphoma (NCT02677155), GBM (NCT02663440), head and neck cancer (NCT02873819), hepatocellular carcinoma (NCT02946138), lung cancer (NCT02976740; NCT02623595) melanoma (NCT03282188), multiple myeloma (NCT02728102) and ovarian carcinoma (NCT02978222) often in combination with standard-of-care therapy, radiation therapy, or experimental immunotherapy (Table 1).

The therapeutic profile of IFN- $\alpha$ 2a is being assessed: (1) in patients with hepatitis B virus (HBV)-related hepatocellular carcinoma following tumor resection (NCT03253250); (2) in subjects with RCC concomitantly receiving bevacizumab-based therapy (NCT02627144); (3) in individuals with neuroendocrine tumors in the context of chemotherapy with metronomic cyclophosphamide<sup>203,268-271</sup> (NCT02838342); and (4) in patients with advanced tumors previously responding to IFN- $\alpha$ 2a, in the context of maintenance therapy (NCT02829775). The safety and preliminary efficacy of IFN- $\alpha$ 2b are being assessed: (1) in patients with human T-cell lymphotropic virus type I (HTLV-I)-derived adult T-cell leukemia/lymphoma concomitantly receiving belinostat (an FDA-approved histone deacetylase inhibitor)<sup>272,273</sup> and zidovudine (an antiretroviral agent)<sup>274</sup> (NCT02737046); (2) in women with breast cancer in the context of targeted immunotherapy plus metronomic cyclophosphamide (NCT03066947; NCT03328026); (3) in patients with hematological malignancies including CML, as a stand-alone immunotherapeutic intervention for maintenance purposes (NCT03117816; NCT02634294); (4) in individuals with cholangiocarcinoma receiving pembrolizumab (NCT02982720); (5) in subjects with hepatocellular carcinoma receiving capecitabine-based chemotherapy<sup>275,276</sup> (NCT02576964); (6) in patients with soft tissue sarcoma receiving microdosed IFN- $\alpha$ 2b together with multiple other therapeutic agents via a specific delivery device (NCT03056599); and (6) in women with gynecological tumors, as an intraperitoneal infusion combined with recombinant IFN- $\gamma$ <sup>277,278</sup> and autologous monocytes (NCT02948426). Recombinant IFN- $\gamma$  is also being tested in combination with multimodal chemotherapy in women with breast carcinoma (NCT03112590), while recombinant IFN- $\beta$  is being investigated in combination with radiotherapy, the CD274-targeting mAb avelumab<sup>279-283</sup> and optionally adoptive cell transfer in patients with Merkel cell carcinoma (NCT02584829) (Table 1).

Recombinant IL-2 is being investigated: (1) in subjects with CML, as part of a maintenance protocol involving the co-administration of histamine dihydrochloride<sup>284</sup> (NCT03040401); (2) in colorectal carcinoma patients receiving FOLFOXIRI-based chemotherapy (folinic acid plus 5-fluorouracil plus oxaliplatin plus irinotecan)<sup>285,286</sup> and recombinant GM-CSF (NCT03222089); (3) in individuals with neuroblastoma receiving a ganglioside GD2-targeting mAb plus recombinant GM-CSF (NCT02641782); and (4) in subjects with NSCLC receiving radiation therapy plus ICB-based immunotherapy<sup>287-289</sup> (NCT03224871). The safety and therapeutic profile of recombinant IL-12 are being assessed: (1) in lymphoma patients, either in the context of salvage chemotherapy<sup>290</sup> (NCT02544724), or in combination with total skin electron beam therapy<sup>291,292</sup> (NCT02542124); and (2) in subjects with advanced solid tumors, receiving ICB-based immunotherapy (NCT02994953; NCT03030378). Along similar lines, recombinant IL-15 is being investigated: (1) in combination with the CD52-targeting mAb alemtuzumab<sup>293,294</sup> in adults with T-cell leukemia/lymphoma (NCT02689453); and (2) in combination with ipilimumab and/or nivolumab in patients with advanced solid neoplasms (NCT03388632). Finally, the therapeutic profile of recombinant FLT3LG combined with stereotactic body radiation therapy is being assessed in

**Table 1.** Recent clinical trials evaluating recombinant cytokines as immunostimulants in cancer patients.\*

Agent	Indication	Phase	Status	N <sup>o</sup>	Notes	Ref.
FLT3LG	Non-small cell lung carcinoma	II	Recruiting	29	Combined with SBRT	NCT02839265
GM-CSF	Biliary cancer	II	Recruiting	27	Combined with pembrolizumab	NCT02703714
GM-CSF	Breast cancer	I	Completed	30	As adjuvant to peptide-based vaccination, in the context of trastuzumab-based chemotherapy	NCT03014076
GM-CSF	Breast cancer	II	Recruiting	108	Alone or combined with peptide-based vaccination	NCT02636582
GM-CSF	Breast cancer	II	Recruiting	280	As adjuvant to peptide-based vaccination	NCT03012100
GM-CSF	Colorectal carcinoma	II	Not yet recruiting	n.a.	Combined with FOLFOXIRI and IL-2	NCT03222089
GM-CSF	Ependymoma	I	Recruiting	33	Combined with trastuzumab	NCT02774421
GM-CSF	Follicular lymphoma	II	Recruiting	20	Combined with pembrolizumab	NCT02677155
GM-CSF	Glioblastoma multiforme	II	Unknown	41	Combined with HIMRT and temozolomide	NCT02663440
GM-CSF	Head and neck carcinoma	II	Recruiting	n.a.	As adjuvant to peptide-based vaccination	NCT02873819
GM-CSF	Hepatocellular carcinoma	II	Recruiting	44	Combined with carbon ion RT	NCT02946138
GM-CSF	Lung cancer	II	Recruiting	48	Combined with SBRT and thymosin alpha 1	NCT02976740
GM-CSF	Melanoma	I/II	Not yet recruiting	16	Combined with oncolytic virotherapy	NCT03282188
GM-CSF	Multiple myeloma	II	Recruiting	188	Combined with cell-based immunotherapy	NCT02728102
GM-CSF	Neuroblastoma	I	Recruiting	10	Combined with GD2-targeting mAb and multimodal chemotherapy	NCT03189706
GM-CSF	Neuroblastoma	II	Recruiting	59	Combined with GD2-targeting mAb	NCT03033303
GM-CSF	Neuroblastoma	II	Terminated	3	Combined with GD2-targeting mAb and IL-2	NCT02641782
GM-CSF	Neuroblastoma	III	Recruiting	37	Combined with GD2-targeting mAb	NCT03363373
GM-CSF	Non-small cell lung carcinoma	II	Recruiting	60	Combined with SBRT	NCT02623595
GM-CSF	Ovarian cancer	II	Recruiting	120	Alone or combined with peptide-based vaccination	NCT02978222
IFN- $\alpha$ 2a	Neuroendocrine tumors	II	Recruiting	29	Combined with metronomic cyclophosphamide	NCT02838342
IFN- $\alpha$ 2a	Advanced tumors	II/III	Completed	9	As standalone immunotherapeutic agent, potentially pegylated	NCT02829775
IFN- $\alpha$ 2a	Hepatocellular carcinoma	IV	Recruiting	432	Following resection	NCT03253250
IFN- $\alpha$ 2a	Renal cell carcinoma	n.a.	Completed	365	Combined with bevacizumab	NCT02627144
IFN- $\alpha$ 2b	Acute myeloid leukemia	n.a.	Recruiting	29	As standalone intervention to prevent relapse upon ASCT	NCT03121079
IFN- $\alpha$ 2b	Adult T-cell leukemia/lymphoma	II	Recruiting	20	Combined with belinostat and zidovudine	NCT02737046
IFN- $\alpha$ 2b	Breast cancer	I/II	Recruiting	40	Combined with targeted immunotherapy and cyclophosphamide	NCT03066947
IFN- $\alpha$ 2b	Breast cancer	I/II	Recruiting	40	Combined with targeted immunotherapy and ICBs	NCT03328026
IFN- $\alpha$ 2b	Cholangiocarcinoma	II	Recruiting	44	Combined with pembrolizumab	NCT02982720
IFN- $\alpha$ 2b	Chronic myelogenous leukemia	II	Recruiting	214	As standalone immunotherapeutic agent, in pegylated form	NCT03117816
IFN- $\alpha$ 2b	Gynecological tumors	I	Recruiting	40	Combined with IFN- $\gamma$ and adoptively transferred autologous monocytes	NCT02948426
IFN- $\alpha$ 2b	Hematological malignancies	IV	Recruiting	50	As standalone intervention to prevent relapse upon ASCT	NCT02634294
IFN- $\alpha$ 2b	Hepatocellular carcinoma	II	Recruiting	16	Combined with capecitabine-based chemotherapy	NCT02576964
IFN- $\alpha$ 2b	Soft tissue sarcoma	I	Recruiting	12	As standalone therapeutic intervention, in microdoses	NCT03056599
IFN- $\beta$	Merkel cell carcinoma	I/II	Recruiting	20	Combined with RT, avelumab and optionally ACT	NCT02584829
IFN- $\gamma$	Breast cancer	I/II	Recruiting	43	Combined with multimodal chemotherapy	NCT03112590
IFN- $\gamma$	Gynecological tumors	I	Recruiting	40	Combined with IFN- $\alpha$ 2b and adoptively transferred autologous monocytes	NCT02948426
IL-2	Chronic myelogenous leukemia	I/II	Recruiting	15	Combined with histamine dihydrochloride	NCT03040401
IL-2	Colorectal carcinoma	II	Not yet recruiting	n.a.	Combined with FOLFOXIRI and GM-CSF	NCT03222089
IL-2	Non-small cell lung carcinoma	I	Recruiting	30	Combined with RT and ICB-based immunotherapy	NCT03224871
IL-2	Neuroblastoma	II	Recruiting	2	Combined with GD2-targeting antibody and GM-CSF	NCT02641782
IL-12	Advanced solid tumors	I	Recruiting	36	Combined with pembrolizumab	NCT03030378
IL-12	Advanced solid tumors	I	Recruiting	170	Combined with avelumab	NCT02994953
IL-12	Lymphoma	II	Not yet recruiting	n.a.	In the context of salvage chemotherapy	NCT02544724
IL-12	Lymphoma	II	Recruiting	n.a.	In the context of TSEBT	NCT02542124
IL-15	Adult T-cell leukemia/lymphoma	I	Recruiting	30	Combined with alemtuzumab	NCT02689453
IL-15	Advanced solid tumors	I	Recruiting	50	Combined with ipilimumab and/or nivolumab	NCT03388632

Abbreviations: ACT: adoptive cell transfer; ASCT: allogeneic stem cell transplantation; CAR: chimeric antigen receptor; ICB: immune checkpoint blocker; FOLFOXIRI: folinic acid plus 5-fluorouracil plus oxaliplatin plus irinotecan; HIMRT: hypofractionated intensity modulated radiation therapy; n.a.: not available; RT: radiation therapy; SBRT: stereotactic body radiation therapy; TSEBT: total skin electron beam therapy.

\*Initiated between 2015, Dec 1st and 2018, Jan 1st.

subjects with advanced or metastatic NSCLC (NCT02839265) (Table 1).

Of note, a large majority of these studies are ongoing, with three notable exceptions: NCT02627144, NCT02829775 and NCT03014076 (Table 1). NCT02627144 was a non-interventional, multicenter trial to evaluate efficacy and safety of intravenous bevacizumab plus recombinant IFN- $\alpha$ 2a for the first-line treatment of patients with advanced and/or metastatic RCC. The study enrolled a total of 365 individuals, of which 359 were allocated to treatment and 338 could be analyzed for clinical responses. Amongst these 338 subjects, 5.3% experienced a complete response, 21.9% a partial response, and 39.1% disease stabilization; median PFS and OS were 10.2 and 28.7 mo., respectively (source <https://clinicaltrials.gov/ct2/show/results/NCT02627144>). NCT02829775 was a Phase II/III study aimed at enabling patients with CML, melanoma or RCC who previously responded to recombinant IFN- $\alpha$ 2a or pegylated IFN- $\alpha$ 2a in the context of other clinical trials to continue therapy. Of nine patients enrolled in the study, only 5 completed the entire administration schedule (daily or weekly subcutaneous administration until disease progression, withdrawal, or death – up to approximately 3 y.), but all participants achieved a complete response, with a single case of severe AEs (lung infection in one patient) (source <https://clinicaltrials.gov/ct2/show/results/NCT02829775>). NCT03014076 was a Phase I study testing a peptide-based vaccine (GP2) adjuvanted with recombinant GM-CSF plus trastuzumab-based chemotherapy in clinically disease-free patients with breast cancer. Seventeen women were vaccinated, none of whom experienced dose-limiting or severe (Grade 3–5) toxicities.<sup>295</sup> As immunological reactivity was documented in a majority of subjects enrolled in the study, a Phase II trial was launched to evaluate efficacy.<sup>296</sup>

## Concluding remarks

The possibility to employ recombinant cytokines alone or in combination with other immunotherapeutics to elicit or boost, respectively, tumor-specific immune responses in cancer patients has been – and still is being – intensively investigated.<sup>16,19,25</sup> As discussed above, one of the major limitations encountered so far relates to the extraordinary pleiotropism of the system.<sup>22–24</sup> To circumvent (at least in part) this issue, increasing attention is being devoted to cytokines that naturally exhibit a relatively restricted cell specificity, such as IL-12, IL-15 or IL-21.<sup>49,50,52,297</sup> Moreover, efforts are being dedicated at the development of highly targeted cytokine variants aimed at focusing the biological effects of cytokine signaling onto a rather specific cell population.<sup>138,298</sup> Alongside, the panel of immunotherapeutic agents available for inclusion in combinatorial regimens has tremendously expanded over the past few years,<sup>299–301</sup> opening multiple new avenues of clinical investigation.

An interesting cytokine-related approach that is currently being developed in both preclinical and clinical settings involve the use of recombinant IL-4 as a vector to specifically deliver a modified version of exotoxin A from *Pseudomonas aeruginosa* to glioblastoma cells (which express the IL-4 receptor)<sup>302–307</sup> (NCT02858895). Considerable efforts are also being dedicated

to the development of cytokine receptor agonists, such as ALT-803 (which operates as a superagonist of the IL-15 pathway).<sup>50,149–154</sup> No less than twelve different clinical trials have been launched since December 2015 to investigate the safety and therapeutic profile of ALT-803 in multiple oncological indications (source <http://www.clinicaltrials.gov>).

Moreover, increasing attention is being received by the delivery of cytokine-coding genes, especially in the context of CAR T cell-based immunotherapy<sup>308–312</sup> as well as DC-based and cancer cell-based vaccination.<sup>160,313–316</sup> As a matter of fact, the only immunotherapeutic based on myeloid cells currently approved for use in cancer patients, namely, sipuleucel-T (Provenge<sup>®</sup>), relies on the expression of a chimeric protein that encompasses acid phosphatase, prostate (ACPP; best known as PAP) and GM-CSF.<sup>317,318</sup> However, the actual impact of Provenge<sup>®</sup> in the management of prostate cancer patients does not meet the expectations.<sup>319</sup> As it stands, it is difficult to predict which of the aforementioned approaches (if any) will open a clear path to the use of recombinant cytokines as immunostimulants in cancer patients. Additional work on specificity and safety issues is urgently awaited in this sense.

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