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EVOLVING THERAPIES (RM BUKOWSKI, SECTION EDITOR)

Pegylated Interleukin-10: Clinical Development of an Immunoregulatory Cytokine for Use in Cancer Therapeutics

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Abstract

Purpose of Review Interleukin-10 (IL-10) is a cytokine with anti-inflammatory properties, which induces activation and proliferation of antigen-activated intratumoral CD8+ T cells. This review discusses the evolution of pegylated IL-10 (pegilodecakin) from preclinical investigation through first-in-human studies in oncology.

Recent Findings Pegilodecakin was evaluated across multiple advanced solid tumors in a large phase 1/1b trial alone and in combination with chemotherapy or anti-PD-1 antibodies. Pegilodecakin monotherapy had immunologic and clinical activity in renal cell carcinoma (RCC) and uveal melanoma. In combination with anti-PD-1 inhibitors, pegilodecakin increased the responses in RCC and lung cancer with efficacy agnostic to PD-L1 status and tumor mutational burden. Pegilodecakin with FOLFOX had activity in pretreated pancreatic cancer, instructing the ongoing randomized phase III trial of the combination versus FOLFOX.

Summary The increased half-life of pegilodecakin enabled compelling preclinical data for IL-10 which has now been confirmed by clinical activity in a variety of cancers. The ability of pegilodecakin to both exert anti-tumor immunity and inhibit tumor-associated inflammation characterizes the uniqueness of this cytokine therapy.

Keywords IL-10 · Pegilodecakin · AM0010 · Cytokine · Immunotherapy

Introduction

IL-10 is a non-covalent homodimeric alpha helical cytokine that is structurally similar to interferon γ (IFNγ). The IL-10 receptor is expressed on hematopoietic cells including CD8+ and FOXp3+ CD4+ T cells, macrophages, and dendritic cells [1, 2]. Importantly, the IL-10 receptor (IL-10R) is upregulated upon T cell receptor (TCR) activation on CD8+ T cells, rendering antigen-recognizing T cells receptive to IL-10 [3]. IL-10 was initially identified as a cytokine that suppresses the secretion of cytokines from T-Helper-1 (Th1) cells [4, 5], but also stimulates the proliferation and cytotoxic activity of CD8+ T cells [6]. IL-10 induces signal transducer and transcription activator (STAT) 1 and STAT3 activation and inhibits several other cytokines, including IL-6, and the common IL-12p40 chain shared by IL-12 and IL-23, thereby reducing macrophage activation and subsequently Th17 T cell responses [7]. In mouse models of endotoxemia, a model to study inflammation in response to bacterial lipopolysaccharides (LPS), IL-10 induction reduces the secretion of IL-12 and IL-23 cytokines from myeloid cells [8]. In addition, mice deficient in IL-10 or its receptor develop inflammatory bowel disease (IBD) [9, 10]. Mutations in genes encoding for IL-10 or the IL-10R subunit proteins have also been identified in patients with very early-onset enterocolitis [10]. This led to the concept that IL-10 has predominantly immune suppressive functions. Yet, IL-10-deficient mice and humans help us to further understand the complexity of this cytokine in disease.

Subsequent to IBD, IL-10 knockout mice develop colon cancer and are sensitized to acquire chemically induced skin cancer [11, 12•]. In addition, chemically induced cancers in IL-10−/− mice progress quickly and die of metastatic disease

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[12•]. Children with IL-10R deficiency develop lymphomas at a young age [13]. IL-10R deficiency predisposes to a subtype of diffuse large B cell lymphoma (DLBCL) with germinal center origin. In contrast to the adult DLBCL patient that is IL-10 proficient, childhood lymphomas arising in IL-10R-deficient children lack infiltration of CD8+ T cells, supporting the role of IL-10 in CD8+ tumor-infiltrating lymphocyte (TIL) activation. The pro-inflammatory phenotype in IL-10 deficiencies suggested a role of IL-10 in inflammation and immune-mediated inflammatory diseases (IMIDs), which lead to the therapeutic rational for using IL-10 in IMID as the first indications for clinical investigation of this cytokine as a therapeutic entity.

Investigation in Inflammatory Disease

Recombinant human IL-10 (ilodecakin) was initially developed for the treatment of inflammatory diseases such as psoriasis, Crohn's disease, and rheumatoid arthritis [14–17]. Clinical responses were seen and ultimately, this agent was studied in pivotal phase 3 trials; however, it failed to reach a level of success worthwhile of drug approval [18]. Administration was often three times a week in these trials, and given the short half-life of 3–4.5 h upon subcutaneous injection, efficacy may have been compromised with the short pulse exposure [15, 19]. In patients with Crohn's disease, efficacy appeared best at intermediate doses. Higher doses of IL-10 induced IFNγ, which was contrary to the treatment of inflammatory conditions [20]. Additionally, in clinical trials of psoriatic arthritis, there was evidence of increased IFNγ producing CD4+ T cells [21]. Even more intriguing was a study in healthy volunteers that demonstrated the upregulation of IFNγ and granzyme B in the serum [8]. Despite inconsistent efficacy results for the treatment of IMIDs, these trials did provide valuable clinical safety data demonstrating tolerability and mild-to-moderate side effects. Most commonly flu-like reactions with fatigue, myalgia, arthralgia, headache, and a mild reduction of red blood cells and thrombocytes were seen [17]. More importantly for the oncologic community, the potential benefit for immune stimulation as an anti-cancer agent surfaced.

Preclinical Data Supporting the Role of IL-10 in Oncology

In addition to study in IMIDs, tumor immunologists were also exploring the cytotoxic properties of IL-10 as an anti-cancer therapy in preclinical tumor models. Treatment of tumors with recombinant IL-10 or the overexpression of IL-10 in the tumor cells transplanted into mice led to the shrinkage and rejection of the tumors [22–24]. However, therapeutic responses were restricted to immune sensitive tumors. In order to create a therapeutic murine IL-10 that would allow for continuous exposure in murine models, a pegylated form (PEG-rMuIL10) was explored. This was essential given the particularly short half-life of IL-10 in mice. PEG-rMuIL10 demonstrated improved efficacy, allowing the reduction and rejection of large and immune-resistant murine tumors [12•]. Potentially most exciting, efficacy was seen in tumors with poor CD8+ T cell infiltration. Tumor control and tumor rejections were also observed in an endogenous Her2 transgenic mouse breast cancer model, which due to the transgenic driver mutation has a low burden of acquired somatic mutations. Mechanistically, treatment with PEG-rMuIL10 increased CD8+ T cells in the tissue and led to robust IFNγ expression and the upregulation of MHC I and II in the tumor [12•]. After 2 weeks of treatment, tumor-specific CD8+ T cell populations had expanded both intratumorally and in the blood [12•]. When mice achieved complete responses, cancer-free mice remained tumor free on observation for up to 8 months. Such mice were re-injected with the same tumor several months later, but they rejected the re-challenge in the absence of further PEG-rMuIL10 therapy, indicating the establishment of long-term immunologic memory in PEG-rMuIL10-treated mice. More than 90% of the reinjected mice rejected the tumor cells upon re-challenge [12•].

PEG-rMuIL10 was able to increase tumor-resident CD8+ T cells even when T cell trafficking to and from the tumor was inhibited, indicating a direct expansion of the tumor-resident T cells. Evaluation of tumor-infiltrating T cells from mice treated with PEG-rMuIL10 showed a three- to fourfold increase in spontaneous secretion of IFNγ and granzyme B. PEG-rMuIL10-treated mice demonstrated activation of T cells in the tumor site and periphery, but interestingly not in secondary lymphatics like the spleen or lymph nodes.

Given the compelling preclinical findings, scientists working on the PEG-rMIL10 studies began the development of the clinical program, which culminated in a large phase 1/1b study.

Phase I Dose Escalation

Overview of Design

The phase I/1b trial (NCT02009449) evaluating PEG-IL10 (AM0010; pegilodecakin) was designed with dose escalation cohorts as monotherapy and in several combinations inclusive of chemotherapy as well as anti-PD-1 inhibitors (Fig. 1). Tumor types included renal cell carcinoma (no restriction on clear cell vs non-clear cell), non-small cell lung cancer (NSCLC), colorectal cancer, melanoma, pancreatic cancer, ovarian cancer, and metastatic castration-resistant prostate cancer. Triple negative breast cancer (TNBC) was later added

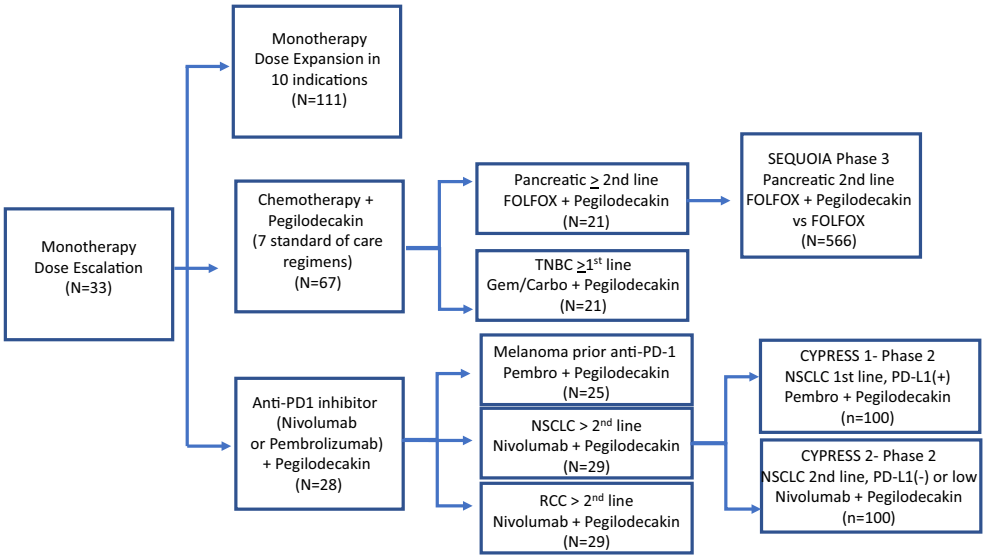

Fig. 1 Study schema of the phase 1/1b trial of pegylated IL-10 in advanced solid tumor malignancies and enrolling phase 2 and 3 trials in progress. This phase 1/1b trial evaluated pegilodecakin as monotherapy and in combination with chemotherapy or anti-PD-1 inhibitors (NCT02009449). Promising results in expansion cohorts have led to phase 2 trials in NSCLC in combination with anti-PD-1 inhibitors (NCT03382899; NCT03382912) and a phase 3 study in pancreatic cancer comparing FOLFOX to the combination of pegilodecakin with FOLFOX (NCT02923921). TNBC, triple negative breast cancer; Gem/Carbo, gemcitabine/carboplatin; pembro, pembrolizumab; NSCLC, non-small cell lung cancer; PD-L1 (+) defined as TPS ≥ 50% using 22c3 assay; PD-L1 (−) or low defined as TPS 0–49% using 22c3 assay

for inclusion in combination cohorts. Analysis of public expression databases aided in the selection of these tumor types for inclusion as they demonstrated (1) IL-10 expression correlated with CD8+ T cells markers, (2) T cell infiltration correlated with survival, and/or (3) IL-10 expression correlated with survival; preclinical data was also generated from tumor-specific cell lines.

All patients were required to have been previously treated with standard of care therapies and have evaluable disease using RECIST. Standard eligibility criteria were used to ensure normal organ function. Patients on anticoagulation with therapeutic doses of coumadin were switched to low molecular weight heparin to safeguard against thrombocytopenia as an expected toxicity that could pose a safety risk in combination with anticoagulation. However, no drug-related bleeding events were observed in the trial. A history of Guillain-Barre or neurologic autoimmune disease was exclusionary as there had been reports of worsening cases of myasthenia gravis on IMID trials; however, other autoimmune diseases such as inflammatory bowel disease were not exclusionary in monotherapy. Tumor assessments using immune-related response criteria (irRC) were performed every 8 weeks, along with immunologic correlates. Biopsies were encouraged, but not required.

AM0010 was self-administered as a daily subcutaneous injection at a flat dose in two dosing brackets. Dosing cohorts of 3–6 patients in dose escalation were evaluated at doses of 1, 2.5, 5, 10, 20, and 40 μg/kg. In order to standardize the dose, patients weighing up to 80 kg administered a flat dose based on 80 kg, and for patients weighing over 80 kg, a flat dose based on 100 kg was used.

In addition to monotherapy, several chemotherapy combinations were explored given the components had shown efficacy in combination with PEG-rMuIL10 in mice. They included combinations with platinum/taxane, FOLFOX, gemcitabine/nab-paclitaxel, capecitabine, paclitaxel, and carboplatin-gemcitabine. Pegilodecakin was also tested in select tumor types in combination with pembrolizumab (melanoma, NSCLC, RCC), nivolumab (RCC, NSCLC), and pazopanib (RCC).

Results from the Phase 1/1b Experience with Pegilodecakin (AM0010)

Monotherapy Experience

This multi-institutional trial is being conducted in the USA and began accrual in 2013 and completed accrual in 2017, with active patients on therapy for as long as 3.5 years. The monotherapy dose escalation portion of the trial enrolled 33 patients using a 3 + 3 design [25•]. The early experience across a variety of tumors identified the safety profile associated with pegilodecakin which differs significantly from both other interleukin therapies such as IL-2, where cytokine release syndrome is common, and checkpoint inhibitors, where autoimmune side effects occur [26]. The most common treatment-related adverse events were thrombocytopenia: grade 1/2 in 13 of 33 (39%) patients and grade 3+ in 1 of 33 (3%) patients. Anemia was also common and grade 1/2 occurred in 12 of 33 (36%) and grade 3+ in 5 of 33 (15%).

Thrombocytopenia was readily reversed with holding of study drug (< 7 days) and did not always require dose reduction. Anemia similarly can improve with holding of drug and dose reduction; patients were allowed transfusions for disease-related anemia. The mechanism of action causing anemia relates to the immune stimulation, as activated macrophages showed an increase in phagocytosis of aging red blood cells and aging thrombocytes [27]. One patient did experience a dose-limiting toxicity (DLT) of drug-related grade 3+ anemia. Mild flu-like reactions (fever, fatigue, myalgias) were seen but did not limit dosing. The recommended phase 2 dose (RP2D) as single agent was identified as 20 μg/kg.

A summary of the reported efficacy data with pegilodecakin is listed in Table 1. Partial responses in monotherapy included a durable response in a uveal melanoma patient and in RCC patients. Of the 5 patients with RCC in dose escalation, there was one partial response (PR) and 2 other patients with mixed responses with some index lesions increasing and others reducing in size. This led to an RCC expansion cohort at 20 μg/kg which demonstrated PRs in 4 of 15 (27%) patients. Histologies in these four responders were clear cell carcinoma [25•].

Cytokines were measured at day 1 and day 29 and identified a dose-dependent increase in IL-18, an immune-activating Th1 cytokine, in all patients as well as increased production of IFNγ, and a reduction in transforming growth factor β (TGFβ) and Th17-related cytokines IL-23 and IL-17. These changes also appeared to persist over time and occurred in multiple tumor types [28•]. Intriguingly, T cell receptor (TCR)–based clonal T cell analysis showed the expansion of T cell clones in the blood, which were not detectable in the patient at the start of therapy, indicating a specific expansion of a new T cell repertoire in response to pegilodecakin. Pegilodecakin also activated LAG3+ PD1+ CD8+ T cells [28•]. The clinical experience has been able to confirm many of the preclinical findings of immune activation (Table 2).

Pegilodecakin in Combination With FOLFOX in Pancreatic Cancer

Pancreatic cancer is associated with a paucity of intratumoral CD8+ T cells and a dominance of a chronic inflammatory tumor microenvironment, rich in macrophages. Hence, there was a strong rationale given the preclinical data which demonstrated increased CD8+ T cell infiltration with PEG-rMuIL10 administration. Checkpoint inhibitors had failed to show clinical benefit in pancreatic disease, and strategies to induce immunogenicity were a high priority. For this reason, the design of the phase 1 dose escalation trial included pancreatic cancer patients who had progressed after at least 1 prior line of therapy; patients were allowed in the dose escalation monotherapy cohorts as well as in the combination of daily pegilodecakin with FOLFOX and in combination with gemcitabine and nab-paclitaxel. Chemotherapy combinations with either 5-fluorouracil (5-FU) or platinum had been explored preclinically with demonstrated synergy. For example, in a colorectal murine model (CT-26), 5-FU synergized with PEG-IL10 to induce complete responses in the majority of tumors.

In 22 pancreatic cancer patients on pegilodecakin monotherapy, objective tumor responses were not observed, but disease control was seen in 53% of patients and 1- and 2-year survival rates were 23% and 15%, respectively [29]. Eight of 12 patients (67%) with serial tumor markers had a decrease in the blood tumor marker CA19-9. Decreases in CA19-9 with treatment are prognostic of progression-free survival (PFS) and overall survival (OS) in some series [30, 31]. The combination of pegilodecakin and FOLFOX has demonstrated clinical activity with a reasonable safety profile. In 19 evaluable patients with pancreatic cancer, there was an overall response rate (ORR) of 15.8% (3 patients), and 2 of whom had a complete response (CR) [29]. The median PFS was 2.6 months with a 1-year OS of 43% and 2-year OS of 28.8%. The disease control rate (CR + PR + SD) was 74%. Interestingly, CA19-9 levels decreased in 75% of patients and by up to 89.9% of baseline. Immune

Table 1 Clinical benefit of pegilodecakin from the reported phase I experience [25•, 29, 32•, 34]

Tumor type	# patients (# evaluable)	Treatment	Dosing (μg/kg)	ORR (%)	DCR (%)	mPFS (mos)	mOS (mos)
Multiple tumors[a]	33 (27)	Monotherapy	1–40	7	NR[b]	NR	NR
Renal Cell	19 (15)	Monotherapy	20	27	100	1.9	9.8
	38 (34)	Anti-PD-1	10–20	41	85	14	NR
NSCLC	7 (9)	Monotherapy	20	–	57	1.8	15.4
	34 (28)	Anti-PD-1	10–20	42.9	82.2	9.4	24.1
Pancreatic	21 (19)	FOLFOX	5	15.8	73.7	2.6	10.2

NR, not reported; *mos*, months; *m*, median

[a] Included pancreatic ($n = 4$), ovarian ($n = 1$), colorectal ($n = 16$), RCC ($n = 6$), metastatic castration-resistant prostate cancer ($n = 1$), NSCLC ($n = 1$), and melanoma ($n = 4$)

[b] NR as DCR, however 2 PR, 1 SD, 5 Mixed responses

Table 2 Immunologic findings in preclinical investigation that have been identified in the phase 1 clinical trial experience

Immunologic event	Preclinical	Clinical
Increase of IFNγ in the serum	√	√
Increase of IL-18 in the serum	√	√
Reduction in TFG beta in the serum		√
Expansion CD8+ T cells in tumor tissue	√	√
Increase of granzyme B (tumor or blood)	√	√
Increase of MHC expression on tumor cells	√	√
Expansion CD8 + T cells in peripheral blood	√	√
Tumor-specific T cell expansion	√	√
Proliferation and expansion of PD-1+ Lag-3+ CD8+ T cells in the blood	√	√
Tumor reduction	√	√

correlates were able to demonstrate that pegilodecakin could increase Th1 cytokines while reducing IL-17 and IL-23 and TGFβ, similar to what had been demonstrated in other tumor types in dose escalation. Evaluation of the TCR repertoire demonstrated an oligoclonal expansion of T cell clones. An increased expansion of previously non-detected T cell clones correlated with increased survival (defined as > 8 months) [29].

During the investigation in this phase 1b cohort of pegilodecakin and FOLFOX, 55% of patients had grade 3 or higher thrombocytopenia, and 45% experienced a grade 3 or higher anemia. Neutropenia was a less common hematologic toxicity, though still occurred in a quarter of patients in this cohort. There were no episodes of febrile neutropenia. The administration was altered from a continuous daily injection of 5 μg/kg daily, to 5 days on/2 days off in order to offset the hematologic toxicity. This alteration reduced the occurrence of grade 3 hematologic toxicity and this regimen is used in the ongoing phase 3 study.

Checkpoint inhibitors as monotherapy have been disappointing in pancreatic cancer, and the promising activity demonstrated in this trial led to fast track status and orphan drug designation for pegilodecakin in pancreatic cancer. A randomized phase 3 trial of FOLFOX versus pegilodecakin with FOLFOX (SEQUOIA trial, NCT02923921) currently is enrolling patients with metastatic pancreatic ductal adenocarcinoma who progressed on a prior gemcitabine-containing regimen. This international trial is planned to enroll 566 patients and has a primary endpoint of OS. Secondary endpoints include PFS and ORR. In the investigational arm, AM0010 (5 μg/kg) is dosed on days 1–5 and days 8–12 SQ plus FOLFOX (400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46-h infusion of 5-FU 2400 mg/m^2) initiated on day 1 of a 14-day cycles until disease progression. The active comparator is the same standard dosing of FOLFOX. The first interim analysis conducted in March 2018 included the first 60 patients with at least 4 months on study and recommended the study continue enrollment as planned, with the second interim analysis anticipated in 2020.

Pegilodecakin in Combination With Anti-PD-1 Inhibitors in RCC and NSCLC

Thirty-eight patients with metastatic RCC (87% clear cell RCC; 13% non-clear cell) received pembrolizumab ($n = 9$) or nivolumab ($n = 29$) in combination with pegilodecakin: 6 (15.8%) at 10 μg/kg and 32 (84.2%) at 20 μg/kg [32•]. Patients had received prior anti-angiogenic therapy and/or ipilimumab, however were anti-PD-1 antibody therapy naïve. Grade 3 anemia was seen in 10 (26.3%) patients and 7 (18.4%) patients experienced grade 3 thrombocytopenia, all at the dose level of 20 μg/kg. Two patients had reversible cytokine release syndrome, and interestingly, both patients also had PRs to therapy.

Of 34 evaluable RCC patients using irRC, there were 14 (41.2%) PRs. Three (8.8%) of those patients had a tumor reduction of 100%. Sixteen (45.7%) had stable disease (SD) as their best response [32•]. Median progression-free survival for pegilodecakin with pembrolizumab or nivolumab was 14.1 months. The median overall survival had not been reached; 1-year overall survival was 89% [32•]. For historic comparison, the reported overall response rate of second-line RCC patients on nivolumab alone is 22% with a 1-year survival of 73% [33].

Thirty-four NSCLC patients received pegilodecakin with nivolumab ($n = 29$) or pembrolizumab ($n = 5$) as their second or later line of therapy. All patients were naïve to immune checkpoint inhibition. Twenty-eight of these patients were evaluable using irRC, and 11 patients (39.3%) had a PR and 1 had a CR (3.6%). Another 11 (39.3%) patients had stable disease [34]. Patients with available archived tissue were evaluated for their PD-L1 status using the 22C3 assay. Twelve of 21 (57%) were PD-L1 < 1%. Four of these 12 PD-L1-negative patients (33.3%) had a PR. Median PFS and OS were 9.4 and 24.1 months [34]. This is encouraging, as studies with anti-PD-1 inhibitors alone report a response rate of 9% in PD-L1-negative patients and 19% in a non-stratified population [35]. The

reported median survival of second-line non-squamous NSCLC on nivolumab alone was 12.2 months [36].

Based on the experience to date with pegilodecakin, there are two ongoing phase 2 trials in anti-PD-1 inhibitor therapy–naïve patients with NSCLC; one for NSCLC patients with PD-L1 expression ≥ 50% comparing pembrolizumab plus pegilodecakin versus pembrolizumab alone (NCT03382899). This study aims to improve the response rates and the overall survival in an immune checkpoint inhibitor–sensitive population which has a historic ORR of 45% to pembrolizumab alone [37]. In the cohort of patients with NSCLC who were PD-L1 ≥ 50% positive and received pegilodecakin plus pembrolizumab in the phase 1 trial, the ORR was 83% (5/6 patients) [38]. In PD-L1 negative and low patients (<1%–49% PD-L1 positive tumor cells), 40% (6/15) of patients responded [38]. Durable responses were also seen in patients with low tumor mutational burden [38], a population with low response rates to checkpoint inhibitor monotherapy. Conclusions are limited based on sample size but are highly encouraging. A second phase 2 study is enrolling NSCLC patients with PD-L1 expression < 50% comparing nivolumab versus the combination of nivolumab with pegilodecakin (NCT03382912). Confirmation of the response and survival data from the phase 1 experience of this combination could place pegilodecakin in a strategic position to fulfill an unmet need for PD-L1 low/negative NSCLC patients which currently receive chemotherapy with anti-PD-1 antibody therapy, due to historically much lower response rates to anti-PD-1 antibody monotherapy.

Conclusion

The pleotropic effects of IL-10 on immune function highlight the dynamic role of this cytokine from its original clinical investigation in immune-mediated inflammatory diseases to its use in cancer immune therapy. The anti-inflammatory properties which had sparked excitement two decades ago are surpassed by the anti-tumor effect demonstrated over the past 5 years utilizing pegilodecakin, a pegylated form of IL-10 that allows for more consistent exposure.

The anti-tumor effects are achieved by increased tumor antigen–specific CD8+ T cell infiltration and the INFγ-mediated induction of antigen presentation, both important requisite steps in generating an effective anti-tumor immune response with long-lasting immunologic memory. Clinical efficacy has been seen with pegilodecakin monotherapy with partial responses in uveal melanoma and RCC, as well as in combination with anti-PD-1 antibodies in RCC and NSCLC, and chemotherapy in other malignancies such as pancreatic cancer. The most common treatment-related adverse events include anemia and thrombocytopenia and have been manageable. There has been a notable absence of the common immune-related adverse events identified with checkpoint inhibitors, which enhances the appeal of pegilodecakin in combination strategies. Many patients have now received pegilodecakin alone or in combination with anti-PD-1 antibody therapies, some for more than 2 years. Ongoing phase 2 and 3 clinical trials will further characterize the potential clinical benefit of this cytokine therapy in the evolving strategies available in immuno-oncology.

Compliance with Ethical Standards

Conflict of Interest Karen Autio has received research funding (paid to her institution) from ARMO Biosciences, Eli Lilly, Pfizer, Merck, GlaxoSmithKline, and CytomX.

Martin Oft is a full-time employee of ARMO Biosciences, a fully owned subsidiary of Eli Lilly and Company.

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