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EDITORIAL

Bempegaldesleukin (NKTR-214): a CD-122-biased IL-2 receptor agonist for cancer immunotherapy

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1. Introduction

The discovery of immune-checkpoint proteins and the clinical development of antibodies to block these inhibitory pathways has transformed the field of medical oncology over the past 2 decades. Today, there are seven immune-checkpoint–blockade therapies approved by the US Food and Drug Administration (FDA) for more than 14 indications. While these agents can yield remarkable results among a select group of responders, a large majority of patients do not benefit from immune-checkpoint blockade alone. To find strategies to enhance the effectiveness of these immunotherapies, we need to turn back to the historical origins of immuno-oncology to explore other cancer immune pathways that can work synergistically with checkpoint inhibitors to improve outcomes and long-term survival.

Cytokine-signaling pathways, specifically involving interleukin-2 (IL-2), were the focus of some of the earliest research in cancer immunology, and human recombinant IL-2, aldesleukin, was the first cytokine to be approved for the treatment of cancer. Unfortunately, the severe toxicities and unfavorable pharmacokinetic profile of aldesleukin along with its pleiotropic effects on both effector T cells, which identify and kill tumor cells, and regulatory T cells (Tregs), which act to suppress effector T-cell function, have limited its use. However, now that we have a better understanding of the critical nature of the IL-2 pathway in balancing immune activation and suppression, we are revisiting the development of engineered proteins that activate the IL-2 receptor pathway in more pharmacologically productive ways as therapeutic agents with the potential to activate the immune system to eliminate tumor cells.

2. History, promise, and limitations of IL-2 as a cancer therapy

Long before the discovery of checkpoint blockade, cytokines – and specifically IL-2 – were the primary focus of immuno-oncology. Over 40 years ago, researchers in the Laboratory of Tumor Cell Biology at the National Cancer Institute (NCI) in Bethesda, Maryland, led by Robert Gallo, MD, identified and purified human T cell growth factor, now known as IL-2 [1]. The group discovered this immuno-stimulatory cytokine to be important in the regulation of growth, differentiation, and activation of tumor-infiltrating lymphocytes (TILs), including T cells and natural killer (NK) cells. Following the identification of the IL-2 protein, researchers cloned the IL-2 cDNA in 1983 [2], and Cetus (an early biotechnology company) developed a proprietary-purified recombinant version of the cytokine. Steven Rosenberg, MD, PhD, and colleagues at the NCI first evaluated it as an anti-cancer agent in Phase 1 clinical trial in 10 patients with a variety of malignant disorders unresponsive to conventional treatments and demonstrated that high doses given intravenously or intraperitoneally could mediate the regression of cancer in some patients [3]. A subsequent Phase 2 trial of 255 patients with metastatic renal cell carcinoma (RCC) found that multiple cycles of high-dose IL-2 administered every 8 h or as frequently as the patient could tolerate showed a complete response rate of 7% and an overall response rate of 15% [4].

The FDA-approved aldesleukin (PROLEUKIN®) for the treatment of metastatic RCC in 1992 and metastatic melanoma in 1998. While early clinical findings were promising, high-dose IL-2 has major drawbacks that limit its broad use as an effective anti-cancer agent. Because of its short half-life of several minutes, it requires administration at a very high-dose level, resulting in significant and dose-limiting toxicities, including vascular leak syndrome, pulmonary edema, and cardiac toxicities. As widespread use of IL-2 as a treatment modality is restricted, enhancing T-cell and NK-cell function may lead to increased severity of toxicities in some settings, as these are thought to be effector T cell driven [5]. It is also possible that a short half-life might be potentially beneficial from the perspective of toxicity as the cytokine is more easily withdrawn, perhaps leading to more rapid resolution of some toxicities. Importantly, early work has shown that continuous infusion IL-2 (mg for mg) might have more toxicity than high-dose, intermittent boluses of IL-2 [6].

Despite the early enthusiasm for cytokines as cancer therapies, interest from the pharmaceutical industry in researching and developing IL-2 waned given the toxicity of recombinant IL-2 and a lack of understanding of the molecular pathways of IL-2 signaling. Over the subsequent years, some biopharma companies and medical researchers shifted their focus to evaluating the effect of the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and PD-1/PD-L1 axes on immune system

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evasion. As of 2019, seven immune-checkpoint inhibitors have been approved by the FDA, targeting PD-1 (nivolumab, pembrolizumab, and cemiplimab), PD-L1 (atezolizumab, durvalumab, and avelumab) and CTLA-4 (ipilimumab) and target over 14 indications. Although clinical trials have demonstrated that checkpoint inhibitors achieve dramatic results for some patients, with high response rates, most patients do not benefit from checkpoint blockade alone [7,8].

Variable responses and failures encountered during checkpoint blockade are due to several classes of mechanisms of resistance and include tumor-intrinsic (immuno-evasion), tumor-extrinsic (immuno-editing), tumor-microenvironment (TME) factors (immunosuppression/immunoregulation), and host-related factors (gut microbiota), as well as other factors [9], Intrinsic resistance is observed when tumor cells alter processes that are related to immune recognition, cell signaling, and gene expression. Extrinsic resistance occurs external to tumor cells throughout the T-cell activation process [10].

T cells must become initially primed by antigen-presenting dendritic cells, migrate to the tumor bed, recognize tumor cells via MHC-I complexes and overcome potential immunoregulatory mechanisms [9]. Developing tumors often actively inhibit one or more steps in this process in order to evade immune-mediated tumor control. Given that the efficacy of checkpoint inhibitor blockade therapy is driven by T cells, immune evasion can contribute to failures in checkpoint inhibitor blockade treatment.

Failure of immune-checkpoint inhibition to induce clinical responses in the majority of cancer patients is due to exclusion of these dendritic cells from the TME (deficiencies in the cGAS-STING pathway); exclusion of T cells (TILs) from the TME; low tumor mutational burden and low PDL1 expression [9,11]. Various immune cells and factors within the TME can also inhibit the therapeutic activities of immune-checkpoint inhibitors, these include Tregs, myeloid-derived suppressor cells (MDSCs), and indole 2,3-dioxygenase (IDO) activity. Tryptophan is catabolized by the rate-limiting enzyme IDO, expressed in myeloid cells and cancer cells, to yield immunosuppressive metabolites such as kynurenine. The actions of these metabolites, together with the depletion of tryptophan, inhibit the clonal expansion of T cells and can induce T cell anergy and apoptosis [9].

While the pharmaceutical industry was focusing on checkpoint inhibition, the academic sector continued to work on IL-2, ultimately gaining a better understanding of the mechanisms of IL-2 pathway activation and downstream effects that would pave the way for further therapeutic development. Following the identification of IL-2 by Dr. Gallo's lab, immunologists discovered Tregs [12], which had been hypothesized to exist but had not been previously identified. Researchers created a knockout mouse deficient in IL-2 [13], believing that these mice would be unable to mount an immune response and would be susceptible to infections and cancer. Surprisingly, these IL-2-deficient mice developed severe autoimmunity and were found to have a substantially reduced number of CD25+ CD4 + T cells despite a normal number of T cells and a normal composition of CD4+/CD8+ cells. Thus, IL-2 was critical for dampening autoimmune disease through the activation of suppressive Tregs [14].

These results were unexpected given prior work showing the role of IL-2 in CD8 + T-cell growth, survival, and proliferation. Ultimately, researchers determined that IL-2 has pleiotropic effects: at high concentrations, IL-2 causes the expansion and activation of cytotoxic CD8+ effector T cells, while at low concentrations, IL-2 expands and activates Tregs [15]. This dual and seemingly opposing activity was explained through differential binding of IL-2 receptor complexes, consisting of the alpha chain (IL-2Rα), beta chain (IL-2Rβ), and common-cytokine–receptor gamma chain (γ_c).

The low-affinity IL-2 receptor, IL-2Rβγ, tends to be expressed on CD8 + T cells and NK cells, while the high-affinity heterotrimeric IL-2-receptor alpha beta gamma subunits (IL-2Rαβγ) are constitutively expressed by Tregs. This understanding, along with the determination of the molecular structure of the IL-2/IL-2R complex, would lead to a renewed emphasis on engineering a novel biologic based on IL-2 with preferential immune-stimulatory activity [16]. In 2012, the Stanford University lab of Christopher Garcia, PhD, successfully engineered an IL-2 'superkine' to preferentially bind to the IL-2 beta receptor. This rendered it more potent than naturally occurring IL-2 by inducing superior expansion of cytotoxic T cells relative to Tregs, leading to improved anti-tumor responses, while reducing its toxicity [17]. In a recent study, a recombinant IL-2 immunocytokine comprising a tumor-targeting antibody and a 'super mutant IL-2' was successfully constructed, with decreased CD25 binding and increased CD122 binding [18]. The IL-2 immunocytokine, in murine cancer models, significantly enhances anti-tumor activity through tumor targeting and specific binding to cytotoxic T lymphocytes [18]. In another study, a *de novo* computational approach was performed for designing mimics of IL-2 exclusively targeting the IL-2 beta receptor [19]. The experimentally designed crystal structure (Neo-2/15) is very close to the designed model, and has greater therapeutic activity than IL-2 in murine models of cancer, with reduced toxicity and undetectable immunogenicity [19]. These strategies targeting the IL-2 beta receptor serve as preclinical proof of the potential of cytokine engineering to enhance the therapeutic potential of IL-2.

Another strategy taken to improve the therapeutic index is a novel formulation of IL-2. Due to the toxicities associated with systemic IL-2, an aerosolized delivery approach has been developed, which enables localized delivery and a higher local immune cell activation [20].

3. Creation of bempegaldesleukin, a novel IL-2 receptor agonist

Our enhanced understanding of IL-2 biology has fueled further development of an improved and potentially more clinically active version of aldesleukin. Based in part on the discovery that the heterotrimeric IL-2Rαβγ is preferentially expressed on Tregs, we developed bempegaldesleukin, an engineered cytokine designed to improve the efficacy, tolerability, and pharmacokinetics of IL-2. Specifically, we designed it to have an extended half-life, providing controlled and sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2Rβγ) to preferentially activate and expand effector CD8 + T and NK

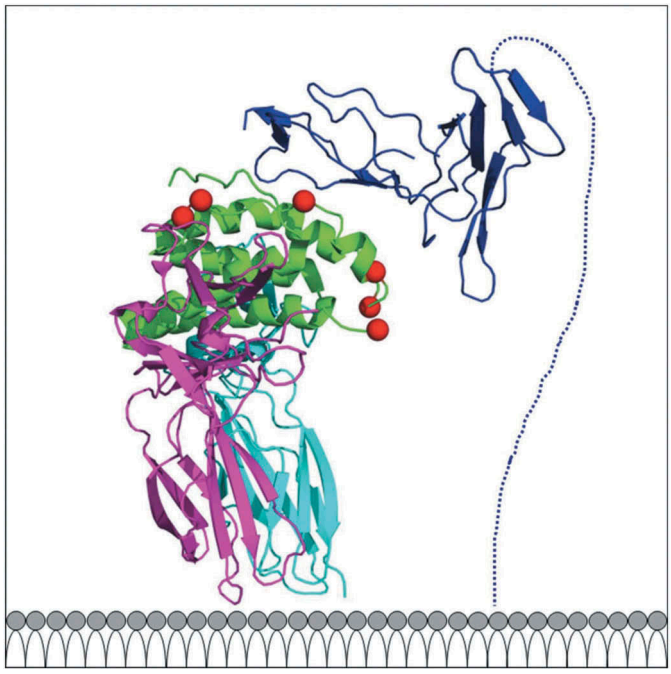

Figure 1. Model demonstrating region of PEGylation sites at IL-2 interface with IL-2Rα. Bempegaldesleukin is aldesleukin at its core (green) bound through surface lysines to six PEG chains per molecule as determined by reverse-phase HPLC quantification of completely released PEG and protein (eight replicates for four lots of bempegaldesleukin). Sites of PEGylation are depicted by red circles. The γ_c receptor is depicted in pink, IL-2Rβ in aqua blue, and IL-2Rα in dark blue. Only peptide 68–94 (VLNLAQSK75NFHLRPRDLISNINVIVLE) and peptide 20–51 (LQMILNGINNYK31NPK34LTRMLTFK42FYMPK47K48ATE) were bound by PEG. The PEGylation results represent six separate experiments, each with two replicates, using three batches of bempegaldesleukin.

Adapted from Wang [16]. Reproduced with permission from AAAS.

cells over Tregs in the tumor microenvironment. A CD122-preferential IL-2 pathway agonist, bempegaldesleukin harnesses the IL-2 pathway to increase endogenous TILs. In clinical and preclinical studies, treatment with bempegaldesleukin has resulted in the expansion of effector T cells and mobilization into the tumor microenvironment.

A biologic that comprises IL-2 protein with multiple covalently attached but releasable polyethylene glycol (PEG) chains (Figure 1), bempegaldesleukin is a prodrug in its dosage form. Unlike aldesleukin or other immediately active cytokines, bempegaldesleukin does not activate T cells in systemic circulation immediately upon infusion, potentially minimizing acute toxicity concerns. When administered in vivo, the PEG chains slowly release, allowing time for tissue distribution of the drug before creating a cascade of increasingly active IL-2 protein conjugates bound by fewer PEG chains (Figure 2) [21]. PEGylation of IL-2 may limit immediate activation of T cells in peripheral blood, potentially reducing its systemic toxicity profile. The 1-PEG-IL-2 and 2-PEG-IL-2 species derived from bempegaldesleukin are the most active conjugated-IL-2 species.

4. Clinical development of bempegaldesleukin

We conducted a Phase 1 dose-escalation study to define the maximum tolerated dose (MTD) of bempegaldesleukin. As a monotherapy, this agent activates the immune system in the tumor and has a favorable safety and tolerability profile with a convenient, outpatient dosing regimen once every 2 or 3 weeks [22]. Results of the Phase 1 study showed that bempegaldesleukin also:

- Promoted proliferation of CD4+, CD8+, and NK cells in peripheral blood;
- Induced CD4 + T cell activation in peripheral blood;
- Increased immune cells, including CD8+ and NK cells in tumors;
- Increased the abundance of proliferating CD8+ and PD-1 + T cells in peripheral blood and tumors; and
- Transiently increased Treg cell frequency in blood but not in the tumor.

Despite the increases in Tregs in the periphery with bempegaldesleukin administration, expansion of these cells was limited or absent in the tumor. Preclinical evidence from mouse tumor models indicates that bempegaldesleukin limits intratumoral Treg proliferation and survival by way of promoting apoptosis, thereby polarizing the TME toward CD8 + T cells and consequently driving a very high CD8+/Treg ratio [21–23]. MDSC and other immunosuppressive immune subsets in the TME, which are likely not affected by bempegaldesleukin, may continue to negatively regulate anti-tumor immune responses.

Bempegaldesleukin has the potential to alleviate or inhibit tumor-mediated TME factors (inhibition of infiltration of dendritic cells and T cells into the TME), setting the stage for immune checkpoint inhibition to induce clinical results. Tumor-intrinsic low mutational burden can also be circumvented with the use of checkpoint inhibition since preexisting quiescent T cells can be activated and expanded as effector

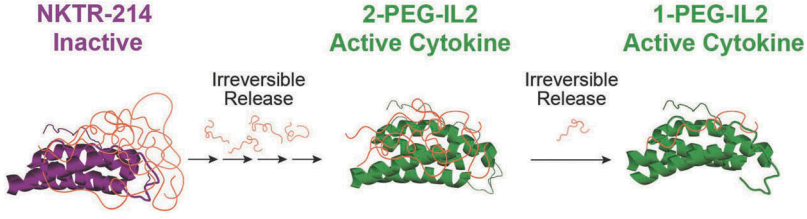

Figure 2. Bempegaldesleukin is a CD122-preferential cytokine agonist conjugated with multiple releasable chains of PEG located at the interface of IL-2 and IL-2Rαβγ. The PEG chains slowly release at physiological pH, creating conjugated-IL-2 species with fewer PEG chains and increased bioactivity.

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Table 1. Ongoing bempegaldesleukin combination clinical trials.

Phase	Combination Agent	Tumor Type	Clinicaltrials.gov
Phase 3	Nivolumab	Melanoma	NCT03635983
Phase 3	Nivolumab	RCC	NCT03729245
Phase 2 (PIVOT-10)	Nivolumab	Urothelial	NCT03785925
Phase 1/2 PIVOT-02	Nivolumab	5 tumor types and 13 indications, including first- and second-line melanoma, first- and second-line RCC, first- and second-line NSCLC, first- and third-line urothelial carcinoma, and first- and second-line TNBC	NCT02983045
Phase 1/2 PROPEL	Atezolizumab or pembrolizumab	Urothelial bladder cancer, melanoma, NSCLC	NCT03138889
Phase 1/2 REVEAL	NKTR-262 (a novel small-molecule agonist of TLR 7/8 administered as an intratumoral injection) [26]	Melanoma, Merkel cell carcinoma, TNBC, RCC, colorectal cancer, SCCHN, sarcoma	NCT03435640
Phase 1b/2	Avelumab (an anti-PD-L1 antibody) and talazoparib (a PARP inhibitor) or enzalutamide (an androgen receptor inhibitor)	SCCHN and mCRPC	NCT04052204

mCRPC, metastatic castration-resistant prostate cancer; NSCLC, non-small cell lung cancer; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; TLR, toll-like receptor; TNBC, triple negative breast cancer.

T cells by bempegaldesleukin. Lastly, tumor PD-L1 expression can be modulated, early data have strongly suggested that the combination of bempegaldesleukin with nivolumab can convert tumors that are PD-L1 negative at baseline to PD-L1 positive status [24].

The clinical activity of bempegaldesleukin was consistent with the biological mechanism of biased IL-2 pathway activation, and its ability to increase TILs and increase PD-1 expression on immune cells provides a sound biological basis for combination with anti-PD1 antibodies. Moreover, comparison of anti-PD1–sensitive and anti-PD1–resistant tumors, which paradoxically both contain CD8 + T cells, has suggested that intratumoral Tregs might be responsible for limiting anti-PD1 antibody efficacy in cases where intratumoral T cell numbers appear sufficient, suggesting that selective expansion of T cells/NK cells over Tregs is a viable approach to overcoming anti-PD1 antibody resistance [9,11].

As we believe the combination of bempegaldesleukin with anti-PD-1 immunotherapy could have the potential to improve response rates and extend survival, we are currently evaluating bempegaldesleukin in combination with nivolumab in our Phase 1/2 PIVOT-02 trial. In this dose-escalation and dose-expansion study, bempegaldesleukin was administered in combination with nivolumab in patients with melanoma, RCC, non-small cell lung cancer (NSCLC), and other tumor types. Preliminary results from 38 previously untreated patients with metastatic stage IV melanoma who were evaluable for efficacy showed the combination therapy was well tolerated with deep and durable responses, including a high rate of complete responses [25]. Clear activation of the IL-2 pathway was demonstrated by an increase in absolute lymphocyte count with activated and proliferating CD4+, CD8+, and NK cells in blood. The combination also demonstrated T cell infiltration and activation in the tumor microenvironment.

The expansion stage of the trial is underway to evaluate the safety and efficacy of combining bempegaldesleukin with nivolumab in patients who are immuno-oncology therapy naïve or anti-PD-1/anti-PD-L1 relapsed/refractory. The expansion cohorts include 5 tumor types and 13 indications, including first- and second-line melanoma, first- and second-line RCC, first and second-line NSCLC, first- and third-line urothelial carcinoma, and first- and second-line triple negative breast cancer (TNBC).

Given the centrality of the IL-2 pathway in the control of adaptive immunity, we continue to evaluate bempegaldesleukin in combination with various other FDA-approved and investigational agents (including checkpoint inhibitors and agents with other mechanisms of action) in a number of ongoing clinical trials (Table 1).

The field of immuno-oncology has advanced significantly since recombinant IL-2 was studied in humans 30 years ago and found to be the first effective immunotherapy for cancer. As we continue to evaluate bempegaldesleukin in this exciting era, we are optimistic that its use in combination with checkpoint inhibitors and other immunotherapies will lead to improvements in the outcomes of patients with advanced, difficult-to-treat cancers, including improved long-term survival with a tolerable safety profile.

5. Expert opinion

Activation of the immune system to fight cancer is the most exciting development in oncology in many years. Among the many discoveries in the field of immuno-oncology, checkpoint inhibition has emerged as the standard backbone of treatment for many tumor types. Yet, despite these advances, many cancer patients still receive no benefit from checkpoint inhibition alone. This is likely due to a combination of factors, including low numbers of TILs, over-activation of Tregs, and limited ability of the immune system to expand new clones over and over as the tumor mutates to evade immune surveillance.

The immune system is highly complex, and targets that control the immune response are frequently transient and context dependent. The system rarely responds effectively to complete, uncontrolled inhibition or activation of single targets, regardless of their function. Multiple medicines that alter the activity of complementary immune pathways in a controlled way will likely provide the best combination of efficacy and tolerability with the fewest side effects.

Activation of the immune system through cytokine therapy is an attractive approach, but it is inherently limited by the activities of native cytokines. Cytokines are not encoded in the

genome to be systemic medicines but, rather, to act locally and transiently in a highly context-dependent way. As a result, they must be engineered to become controlled medicines that could potentially benefit patients.

Bempegaldesleukin is among the most innovative of these next-generation-engineered cytokines. It activates the powerful IL-2 receptor system in a controlled and biased way, tilting the balance in the tumor microenvironment toward effector T cells and away from Treg activity, allowing for activity with limited side effects. Augmenting the potency of T cell/NK cell activity with bempegaldesleukin may circumvent checkpoint blockade resistance, in particular, in settings where intratumoral Tregs might be responsible for limiting anti-PD1 antibody efficacy.

Bempegaldesleukin, as an optimized stimulator of effector T cells, is a prime partner for almost any immune approach to tumor control that relies on effector T cell activity and, as such, may emerge as a central component of many therapeutic regimens.

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Declaration of interest

S. Doberstein is a paid employee and shareholder of Nektar Therapeutics. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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