IL2, originally isolated and described as a T-cell growth factor, is a cytokine that engages the high-affinity IL2 receptor (IL2R) on T-effector, natural killer (NK), and T-regulatory (Treg) cells (1). When given at high doses and intravenously to patients with metastatic renal cell carcinoma (RCC) or melanoma, a subset of patients achieves complete and durable responses that can last decades (2, 3). On the basis of this remarkable efficacy, albeit for a small minority of patients, high-dose IL2 (HD IL2) was approved by the FDA to treat metastatic RCC and melanoma in 1992 and 1998, respectively. However, the toxicity of HD IL2, which is characterized by a capillary leak syndrome that leads to cardiac, pulmonary, neurologic, and renal toxicity, traditionally restricted this therapy to a limited number of highly specialized centers and was contraindicated in patients with underlying comorbidities and/or advanced age (4). Furthermore, the activation of Treg cells by HD IL2, through the engagement of the alpha-subunit of the IL2 receptor (CD25), was a proposed mechanism for the rather limited therapeutic benefit (1). The final limitation on the use of IL2 is that it immune checkpoint inhibitors, including antagonistic mAbs against CTLA4, PD-1, and PD-L1, have revolutionized the management of RCC, melanoma, and many other malignancies, and made IL2, with its high toxicity and limited efficacy, seemingly obsolete (5).

NKTR-214 (bempegaldesleukin) is a pegylated IL2 with, on average, six releasable polyethylene glycol sites which purportedly release in such a manner as to lead to preferential binding of the IL2R beta-gamma subunit (CD122) as opposed to the alpha subunit, thereby promoting IL2 effects on T-effector and NK cells as opposed to Treg cells. In preclinical models, this led to a significant expansion of these effector elements, without increases in Treg cells, and tumor control. In this issue of Cancer Discovery, Bentebibel and colleagues report the phase I clinical trial results of NKTR-214 in patients with advanced solid tumors (6). In all, 28 patients were enrolled to five dose levels (ranging from 0.003 mg/kg to 0.012 mg/kg every 2–3 weeks). A dose-dependent increase in toxicity was seen, with the one patient treated with the highest dose level (0.012 mg/kg) having developed syncope related to hypotension. Yet in general, NKTR-214 at the other dose levels was well tolerated, with IL2-related symptoms like hypotension and edema common, but typically low grade 1–2 and manageable with outpatient intervention. The MTD was defined as 0.009 mg/kg every 3 weeks and the recommended phase II dose was 0.006 mg/kg every 3 weeks. With regard to efficacy, no confirmed responses were seen, although two patients remained on treatment for over a year with stable disease prior to developing disease progression. Despite a paucity of clinical efficacy, the correlative data from blood and tumor analysis of patients enrolled to this phase I trial demonstrated findings supporting combinatorial therapy with NKTR-214 and immune checkpoint inhibitor therapy.

In the peripheral blood, NKTR-214 led to increases in proliferation, as defined by the percentage of cells expressing the marker Ki67, of CD4+, CD8+, and CD56+ cells, the latter a representative marker on NK cells. Furthermore, changes consistent with activation of these cells were shown, including increases in inducible T-cell costimulator (ICOS) and PD-1 expression. Importantly, Treg cells hallmarkmed by the following characteristics, CD4+, CD25hi, FOXP3+, and CD56+, were markedly increased in the peripheral blood on day 8 of cycles 1 and 2 and had increased evidence of proliferation (Ki67%) and activation (ICOS%, CTLA4%). Finally, the pharmacodynamic effects of NKTR-214, specifically on soluble CD25 levels and absolute lymphocyte count, persisted for the duration of therapy, leading to metronomic increases in response to ongoing doses. Importantly, all of these findings were seen across all dose levels tested. Critically, serial biopsies were performed on a significant percentage of patients enrolled to this dose-escalation study. This allows for more nuanced understanding of the potential benefits of NKTR-214 on the tumor microenvironment that goes beyond the modest clinical efficacy described above. In all, 14 patients were evaluable for flow cytometry.
analysis of tumors obtained prior to and on therapy and 12 patients had serial time points available for NanoString analysis using the 770 gene Human PanCancer Immune Profiling panels. On flow cytometry, the major findings were that, in general, increases in CD8+ and CD56+ cells were seen in the tumor microenvironment, with only a modest increase in CD4+CD25hiFOXP3hi Treg cells. Importantly, only 4 of 14 patients had a clear increase in Treg cells (quantified as a % of CD3+ cells) and 6 of 11 evaluable patients had a clear increase in CD8/Treg ratio. This data, though not overly compelling, is at least suggestive that there is preferential upregulation of effector cells compared with regulatory cells in the immune microenvironment that might predict more efficacy as a single agent than high-dose IL2. More revealing, at least with respect to combinatorial approaches utilizing NKTR-214, was the gene-expression data. Not surprisingly, given the known effects of IL2, marked elevation of certain immune-related genes were seen on-treatment compared with baseline. However, the list of the 62 most statistically significant differentially expressed genes (shown in Supplementary Table S4) between baseline and on-treatment reads as a “who’s who” list of relevant immunotherapy-related genes associated with benefit and/or resistance to immune checkpoint inhibitor therapy. Among these genes associated with T-cell activation and coinhibition (ICOS, PD-1, TIGIT, CTLA4, LAG3), immune cell–mediated cytotoxicity (perforin 1 and granzymes B, A, and K), the PD-1 ligands PD-L1 and PD-L2, NK cell–regulated genes, and CD8 and Th1-associated genes (CD8A, IFNG, CXCR3, EOMES, TBX21), as well as genes associated with recently described effector memory cells associated with response to anti–PD-1 therapy (TCF7, IL7R, GZMK, CD8A, LTB; ref. 7). These findings support the exploration of a number of combinatorial approaches as simple as combined NKTR-214 with anti–PD-1/PD-L1 antibodies, taking advantage of the favorable immune microenvironment changes that predict benefit to anti–PD-1/PD-L1 therapy, as well as combinations with alternative checkpoint inhibitors cotargeting one or more of the following: TIGIT, ICOS, CTLA4, and LAG3.

In summary, the phase I trial of NKTR-214 presented here by Bentebibel and colleagues is emblematic of a modern early-phase trial of an immunotherapeutic. From an efficacy standpoint, this trial did not demonstrate a clear signal yet did present illustrative correlative data supporting significant clinical development paths forward. A number of these are ongoing (NCT03138889, NCT03635983, NCT03785925), and more data than has previously been presented will be necessary to understand the impact of NKTR-214 plus immune checkpoint inhibitor therapy. However, what is absolutely clear is that there again is excitement about rediscovering the “original immunotherapy” that provided the modern proof of concept that the immune system, if manipulated properly, can be weaponized powerfully against cancer. What also is clear is that NKTR-214 is not the only game in town, as other approaches evaluating the utility of unmodified IL2 or other engineered versions of IL2 are also ongoing (NCT03861793, NCT03875079, NCT03476174, NCT02989714, NCT02964078). This is remarkable news for an agent that had been, at least in the abstract, consigned to the dustbin of history.

Disclosure of Potential Conflicts of Interest

R.J. Sullivan is a consultant/advisory board member for Bristol-Myers Squibb, Merck, Array Biopharma, Replimmune, Amgen, CompuGen, Novartis, Syndax, and Takeda.

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Back to the Future: Rethinking and Retooling IL2 in the Immune Checkpoint Inhibitor Era

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