Nektar Therapeutics Announces Publication of Two Manuscripts on Lead Immuno-oncology Candidate, Bempegaldesleukin (Bempeg) in Nature Communications

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Results Show How Bempeg Works Synergistically with Multiple Immune-Based Therapies to Enhance T-Cell-Mediated Tumor Control

SAN FRANCISCO, Feb. 3, 2020 /PRNewswire/ -- Nektar Therapeutics (NASDAQ: NKTR) today announced the publication of preclinical data on its lead immuno-oncology candidate, NKTR-214, bempegaldesleukin (bempeg) in two manuscripts in *Nature Communications*. Bempeg is an investigational CD122-preferential interleukin-2 (IL-2) pathway agonist designed to provide activation and proliferation of cancer-killing immune cells, known as CD8+ effector T cells and natural killer (NK) cells. The published data demonstrate that bempeg, in combination with immune-based therapies including checkpoint inhibition (CPI), antigen-specific vaccination and adoptive cell transfer (ACT) therapy, enhanced T-cell mediated tumor control by selectively expanding effector T cells (Teffs) over T regulatory cells (Tregs) in the tumor microenvironment.

The first manuscript, titled "*Bempegaldesleukin selectively depletes intratumoral Tregs and potentiates T cell-mediated cancer therapy,*" was published online and can be accessed here. The research was conducted by a team at MD Anderson Cancer Center, led by former tenured professor, Willem W. Overwijk, Ph.D., who currently serves as Vice President, Oncology Research at Nektar Therapeutics.

"Using preclinical models, we were able to demonstrate how bempeg potentiates both CPI and vaccination strategies by expanding and maintaining tumor infiltrating T cells and depleting intratumoral Tregs by a novel mechanism of cytokine release to drive efficient intratumoral Treg depletion," said Dr. Overwijk. "Our findings further define the mechanism of action of bempeg and highlight the rationale for its clinical application in combination with immune-based therapies for patients with cancer."

In the study, the activity and mechanism of action of bempeg was evaluated in combination with PD-1 and CTLA-4 CPI therapy and also with antigen-specific vaccination in preclinical animal models. The researchers concluded that bempeg in combination with PD-1 CPI therapy resulted in a higher response rate, prolonged disease control and yielded more complete responses in a variety of preclinical tumor types including colon cancer, melanoma, bladder cancer, lung cancer and breast cancer. In addition, bempeg supported the expansion and long-term maintenance of vaccination-induced anti-tumor Teffs; and bempeg treatment mediated selective depletion of intratumoral but not of peripheral Tregs, suggesting that in patients with cancer, bempeg-containing regimens could increase tumor control without exacerbating systemic inflammation. This preferential depletion of intratumoral Tregs was also observed in a small cohort of patients with renal cell cancer and melanoma receiving bempeg monotherapy, suggesting the results in mice may extend to patients receiving bempeg-based therapies.

Key findings are summarized below:

- Bempeg with anti-PD-1 CPI as combination therapy demonstrated superior efficacy over anti-PD-1 monotherapy in 8 different mouse tumor models.
    - Anti-PD-1 monotherapy did not change TIL frequency or clonality, while addition of bempeg increased both TIL frequency and clonality.
- To delve deeper into the immune-mediated mechanism, the B16 melanoma model was used with gp100 antigen-specific $CD8^+$ (pmel-1) T cells to track T cell numbers and persistence.
    - Combination of gp100 vaccination and bempeg markedly suppressed tumor growth and prolonged mouse survival.
    - Long-term tumor control directly correlated with the magnitude and persistence of vaccination-induced, gp100-specific $CD8^+$ Teff in the circulation. Aldesleukin (IL-2) also synergized with vaccination but did not achieve similar potency of bempeg as measured by tumor control or T cell responses.
    - While bempeg increased systemic and intratumoral levels of melanoma-specific CD8+ T cells, intratumoral numbers of Tregs plummeted.
    - Similar depletion of intratumoral but not systemic Tregs was also observed in patients with renal cell cancer and melanoma treated with bempeg (NCT02869295).
- The authors present data that $CD8^+$ Teff-derived IFN-ɣ and TNF-α synergize to deplete intratumoral Tregs by directly inhibiting local Treg proliferation.

In the second manuscript, published this week in *Nature Communications*, a research team led by Antoni Ribas, Ph.D. at the UCLA Jonsson Comprehensive Cancer Center evaluated bempeg in combination with adoptively transferred T cell therapy (ACT) in melanoma models. The studies found ACT therapy supported by bempeg increases the proliferation, homing and persistence of anti-tumor T cells compared to ACT with IL-2, resulting in superior antitumor activity in the B16 melanoma model.

- Bempeg + ACT showed preferential activation of tumor-specific CD8 T cells over Tregs in spleen and tumors of mice,

increased immune-related gene expression in the tumor microenvironment, and greatly increased animal survival compared to IL-2 + ACT.
- Bempeg + ACT increased tumor-specific T cell polyfunctionality (secreting multiple (>2) cytokines per cell) both intratumorally and peripherally compared to IL-2 +ACT in mice.
- Analysis of peripheral blood samples from patients treated with bempeg monotherapy in a Phase 1 trial (NCT02869295) also showed enhanced polyfunctionality of T cells and NK cells.
- The authors conclude that bempeg may have the potential to improve the antitumor activity of ACT in humans through increased *in vivo* expansion, tumor infiltration and polyfunctionality of the adoptively transferred T cells.

The second manuscript titled *"Persistence of adoptively transferred T cells with a kinetically engineered IL-2 receptor agonist,"* was published online and can be accessed here. The UCLA announcement of the publication can be accessed here.

Bempeg in combination with checkpoint inhibitors and other immune-mediating agents is being evaluated in clinical trials. For more information, visit the Pipeline page on nektar.com.

About Nektar Therapeutics

Nektar Therapeutics is a biopharmaceutical company with a robust, wholly-owned R&D pipeline of investigational medicines in oncology and immunology as well as a portfolio of approved partnered medicines. Nektar is headquartered in San Francisco, California, with additional operations in Huntsville, Alabama and Hyderabad, India. Further information about the company and its drug development programs and capabilities may be found online at http://www.nektar.com.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements which can be identified by words such as: "may," "design," "potential" and similar references to future periods. Examples of forward-looking statements include, among others, statements we make regarding the therapeutic potential of bempegaldesleukin ("bempeg"), the likelihood that results of bempeg-based regimens in the preclinical setting extend to patients in the clinical setting, and the proposed mechanistic properties of bempeg that result in pharmacologic activity in patients. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based only on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, anticipated events and trends, the economy and other future conditions. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict and many of which are outside of our control. Our actual results may differ materially from those indicated in the forward-looking statements. Therefore, you should not rely on any of these forward-looking statements. Important factors that could cause our actual results to differ materially from those indicated in the forward-looking statements include, among others: (i) our statements regarding the therapeutic potential of bempeg are based on preclinical and clinical findings and observations and are subject to change as research and development continue; (ii) bempeg is an investigational agent and its continued research and development is subject to substantial risks, including negative safety and efficacy findings in ongoing clinical studies (notwithstanding positive findings in earlier preclinical and clinical studies); (iii) bempeg and the therapies with which it may be combined are in various stages of clinical development and the risk of failure is high and can unexpectedly occur at any stage prior to regulatory approval; (iv) the timing of the commencement or end of clinical trials and the availability of clinical data may be delayed or unsuccessful due to regulatory delays, slower than anticipated patient enrollment, manufacturing challenges, changing standards of care, evolving regulatory requirements, clinical trial design, clinical outcomes, competitive factors, or delay or failure in ultimately obtaining regulatory approval in one or more important markets; (v) patents may not issue from our patent applications for bempeg, patents that have issued may not be enforceable, or additional intellectual property licenses from third parties may be required; and (vi) certain other important risks and uncertainties set forth in our Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 7, 2019. Any forward-looking statement made by us in this press release is based only on information currently available to us and speaks only as of the date on which it is made. We undertake no obligation to update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.

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